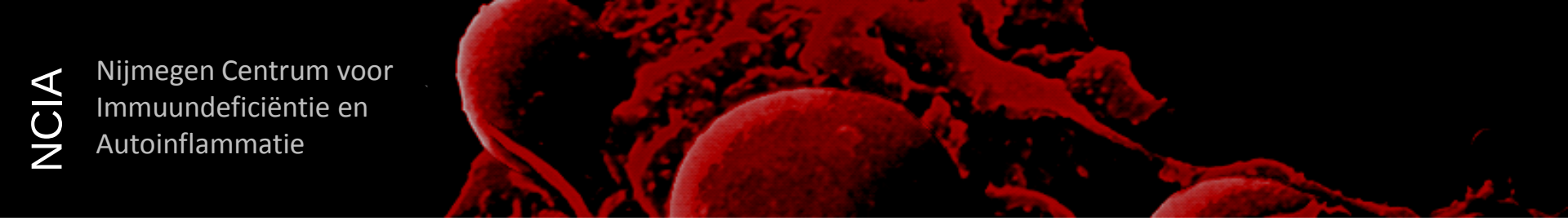



# Complement, ‘een eitje’

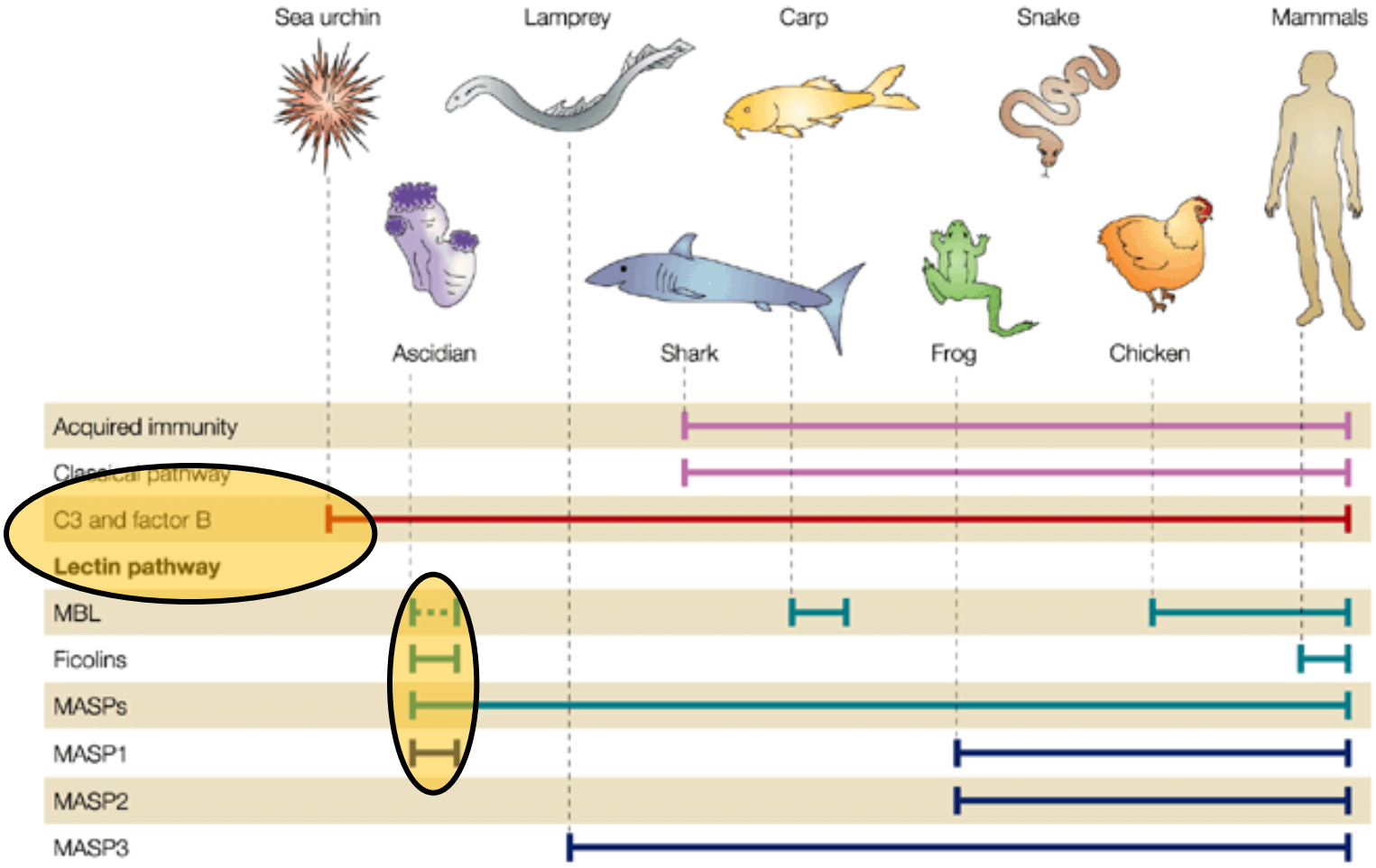
Marcel van Deuren

Afdeling Interne Geneeskunde
Radboudumc

# Roles of complement

- **Action at the right site** ***… Recognize***
- **Clearance of apoptotic cell debris** ***… Remove***
- **Clearance of invasive m.o.** ***…Repell***
- **Orchestrate inflammation** ***… Repair***
- **No action at wrong sites** ***…Regulated!!***

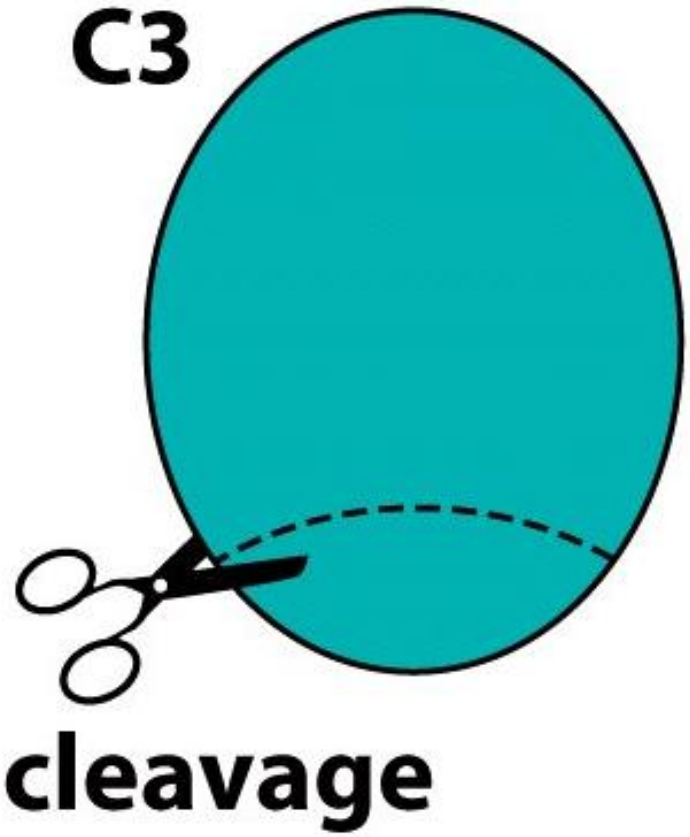
# The fylogenetics of complement



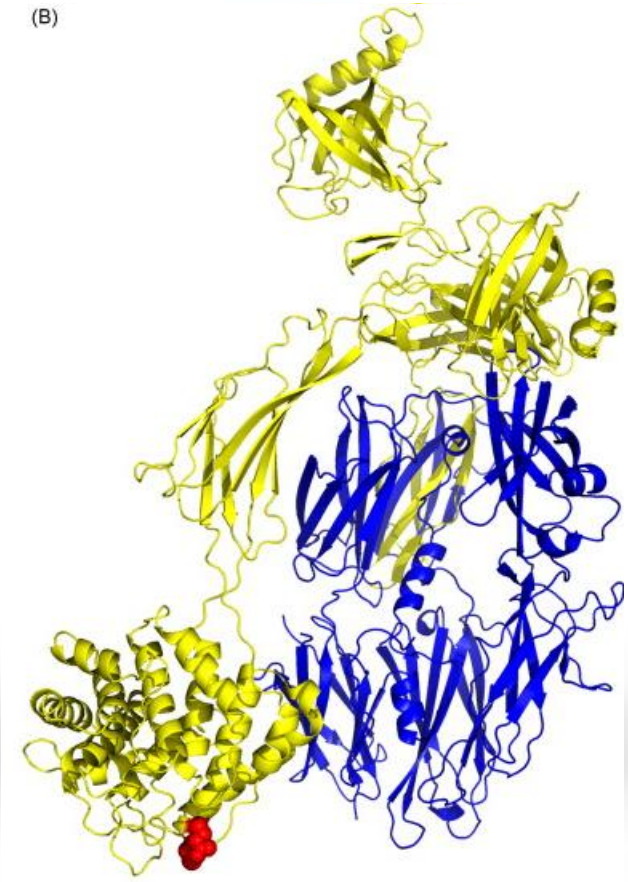

Nature Reviews | Immunology

# Het hele eiereneten…zymogeen (C3)

# Zymogeen: C3 vlgs PARHAM



# Complementfactor C3b



# C3 en C3b vlgs PARHAM

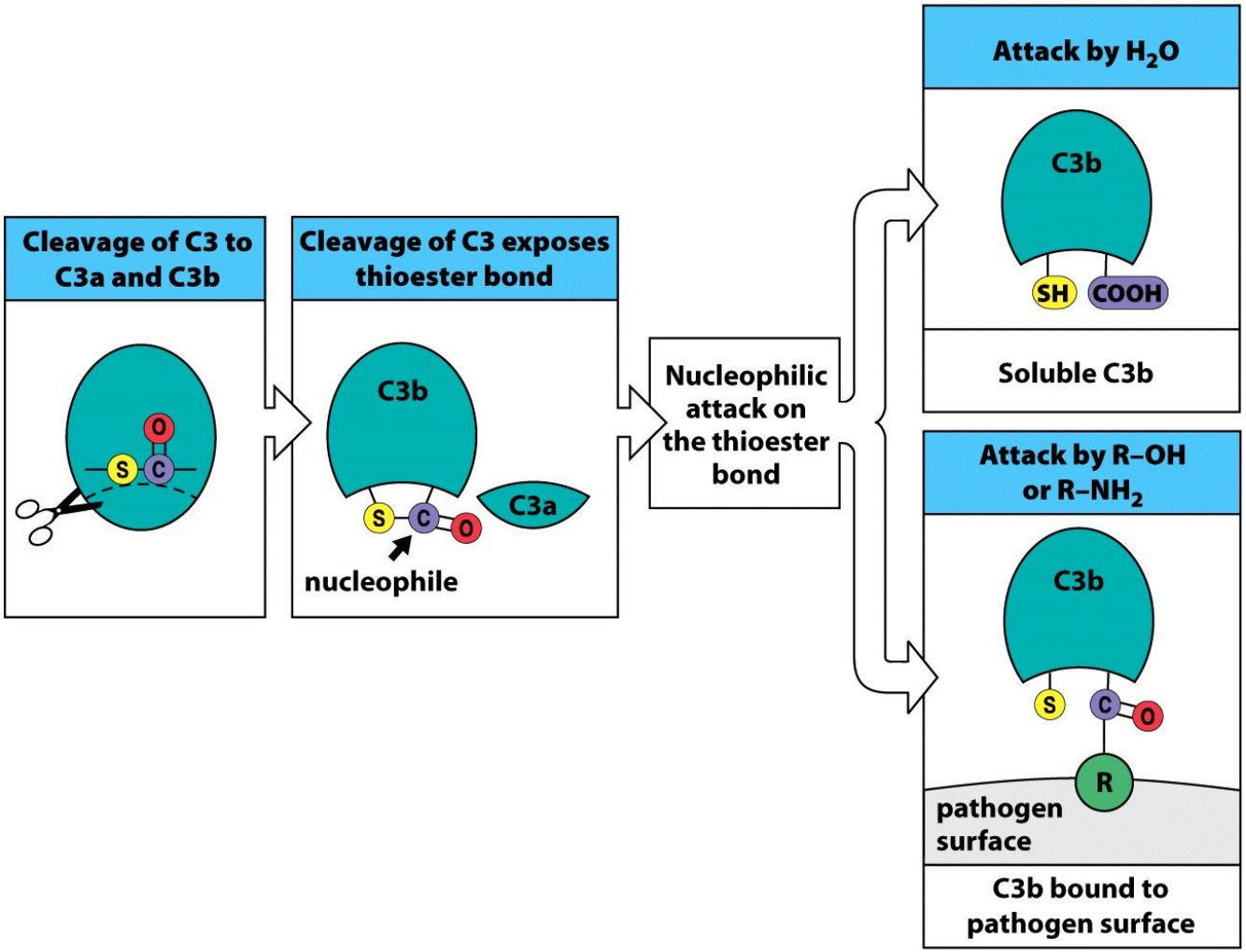
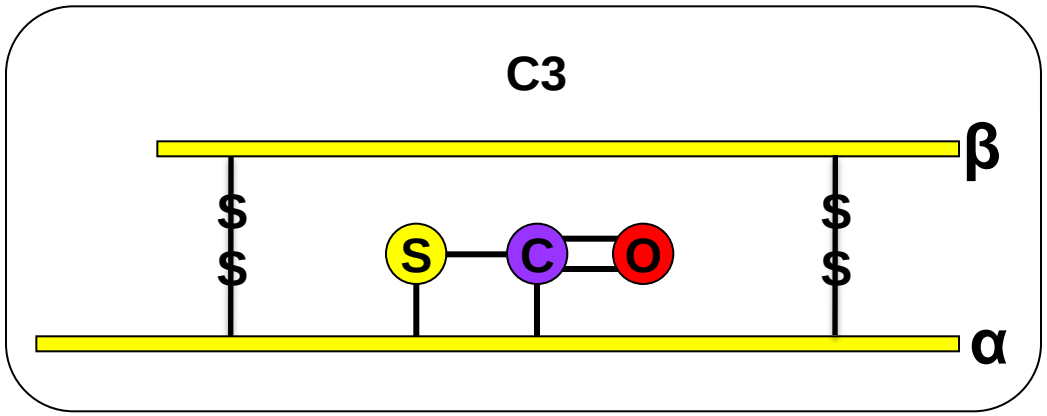



Figure 2.4 The Immune System, 3ed. (© Garland Science 2009)

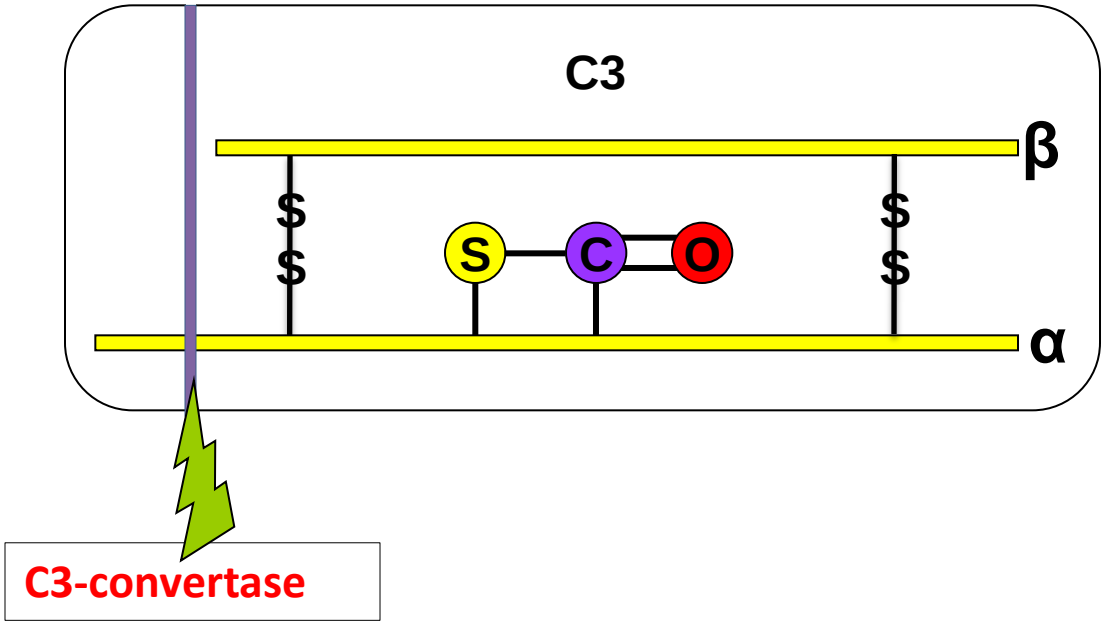
# Het “ei van Columbus”: C3 → C3b

# C3 vlgs MVD

…**C3** is a dipeptide with a hidden reactive thio-esther

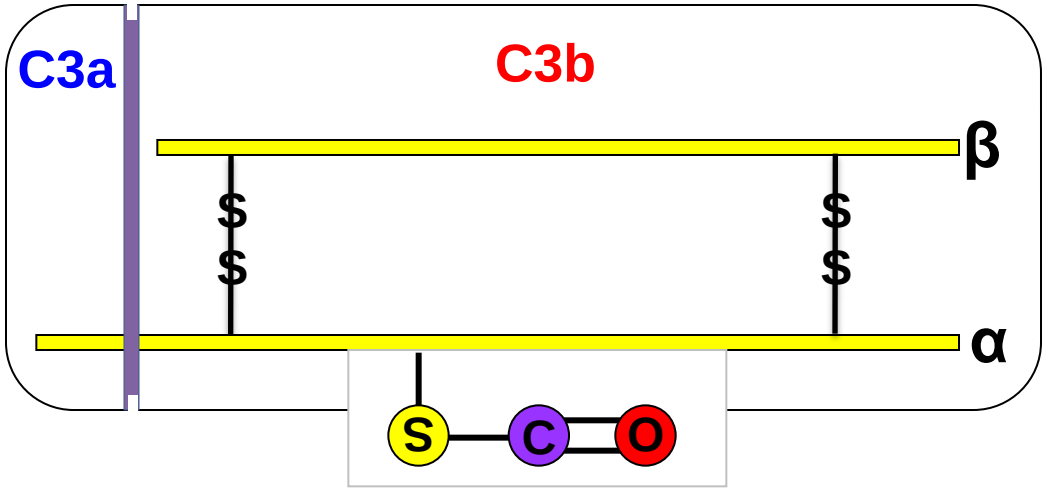


…activation of **C3** by an active **C3-convertase**, cleaves the alpha-chain…

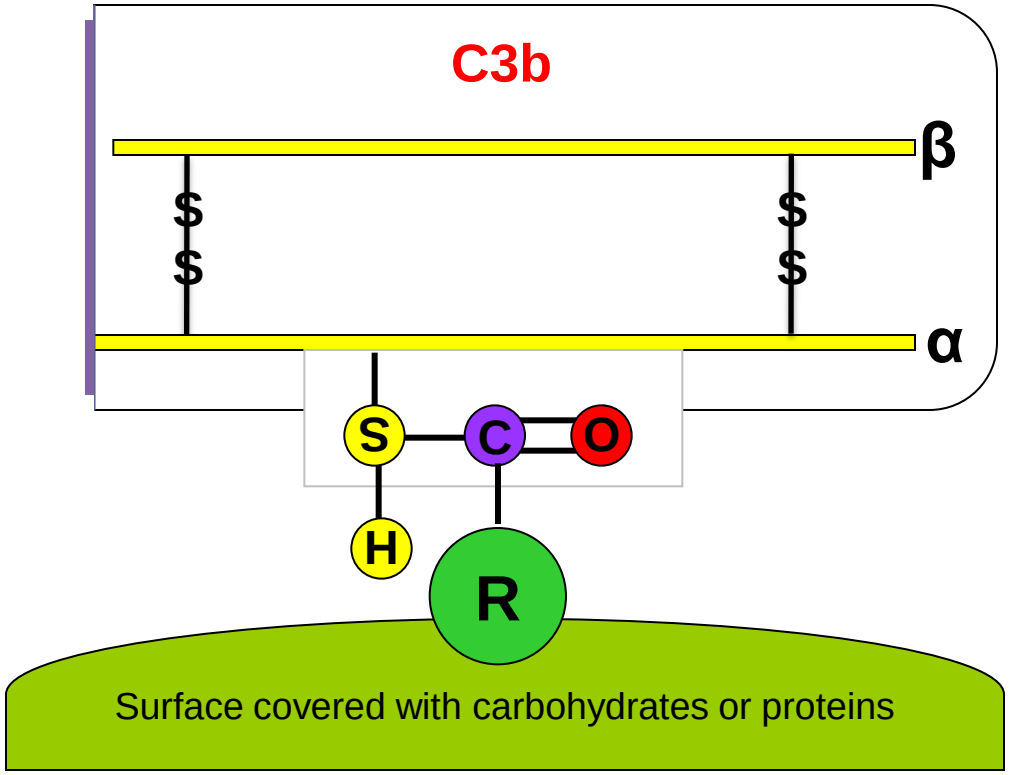


…yielding the anaphylatoxin **C3a** ,

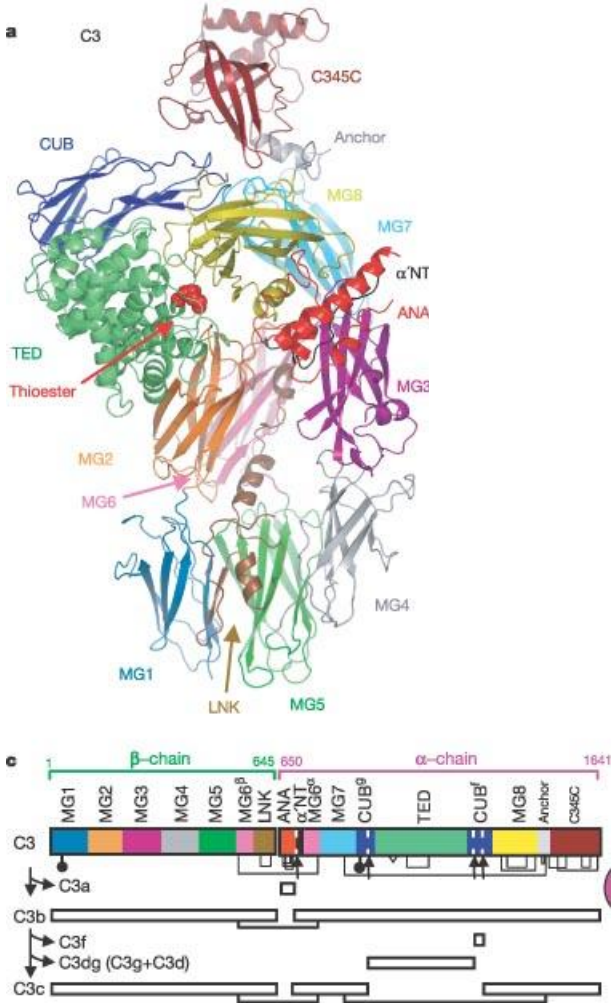
and **C3b**, now with an exposed reactive thio-esther…



…which can bind covalently to OH- or NH2-groups on a ”target” molecules…

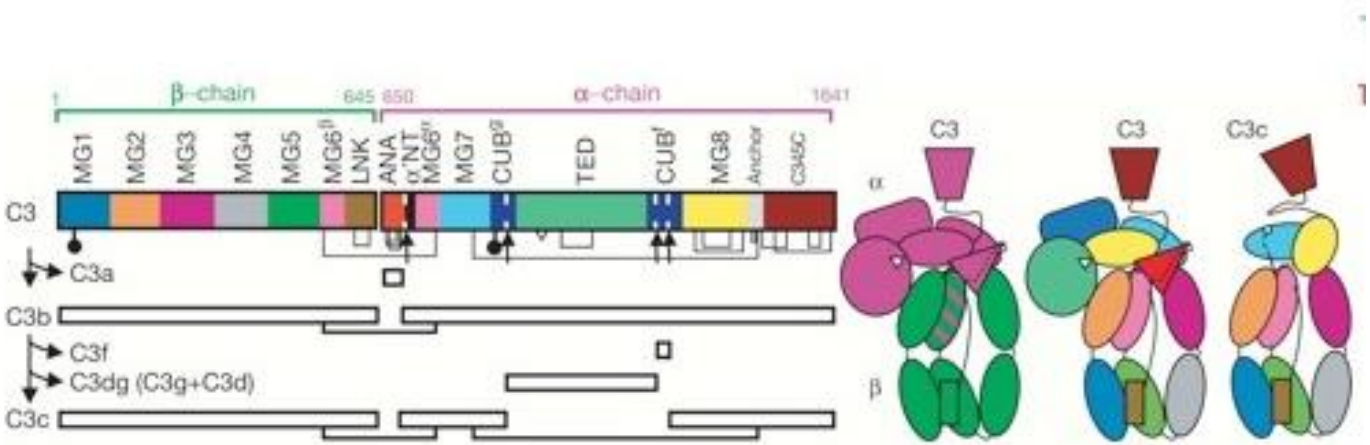


# C3 vlgs JANSSEN & GROS

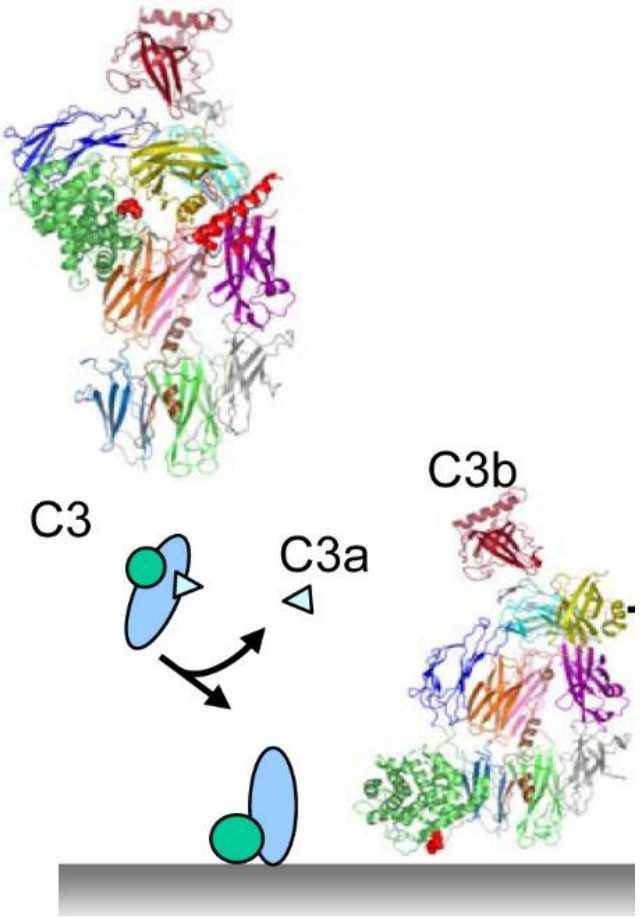




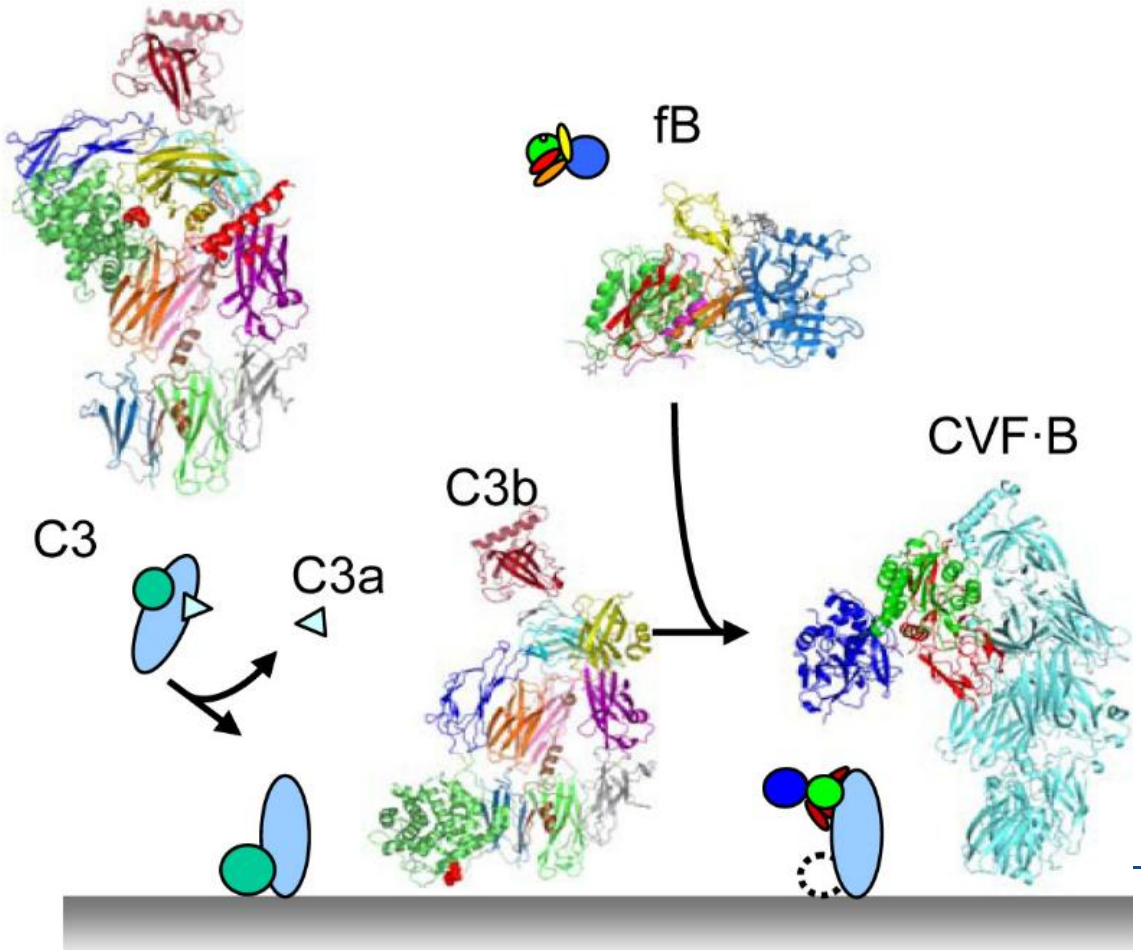

Janssen et al Nature 2005; 437: 505-511




Janssen BJC et al *Nature* **437**:505 (2005)


C3
C3a
C3b

# C3 en Factor B: Alternatieve route



# C3 en Factor B: Alternatieve route C3 convertase vlgs PARHAM

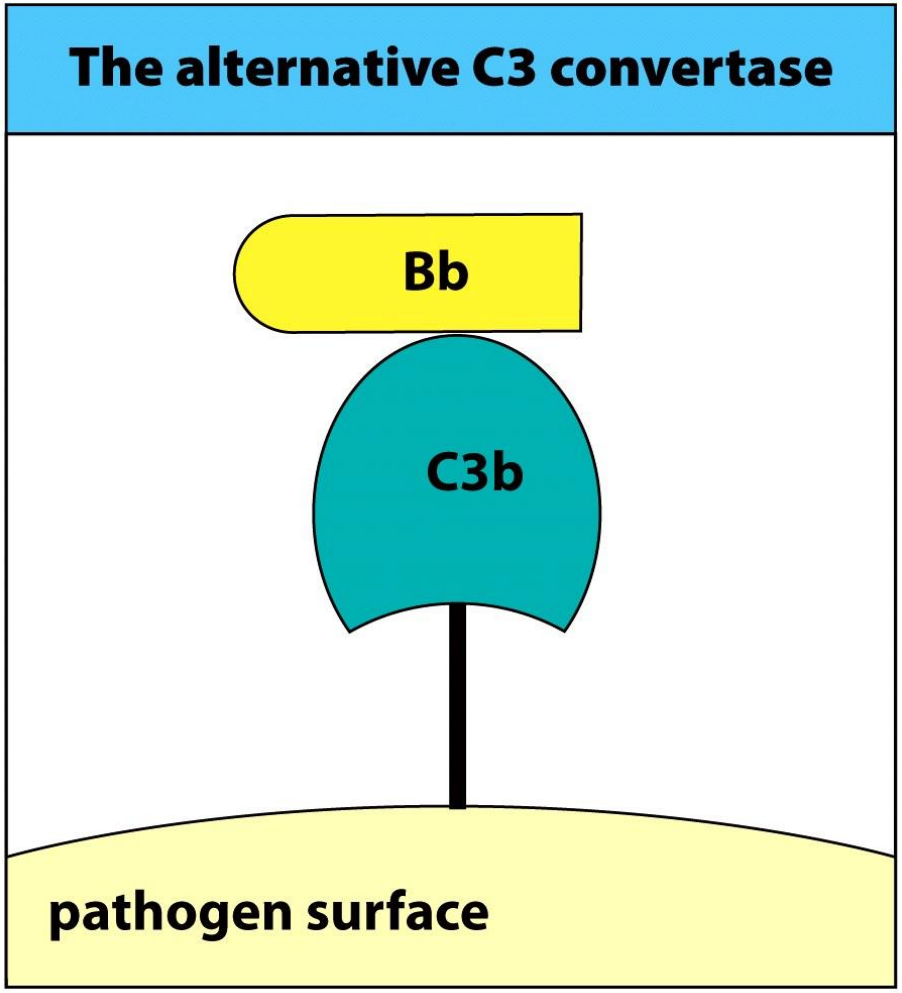
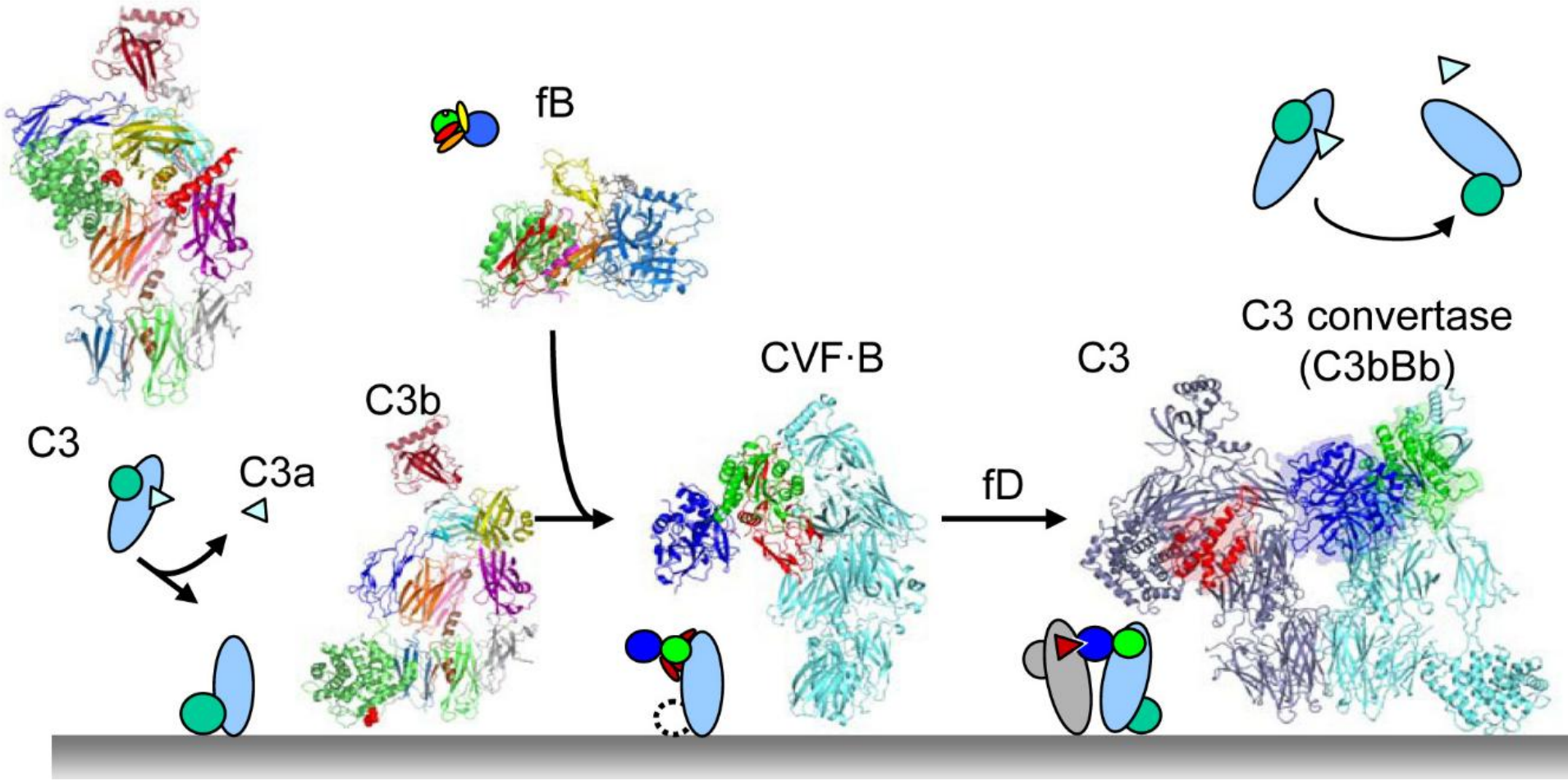



Figure 2.7 The Immune System, 3ed. (© Garland Science 2009)

NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

# C3, FB, en FD → C3bBb: Alternatieve route C3-convertase



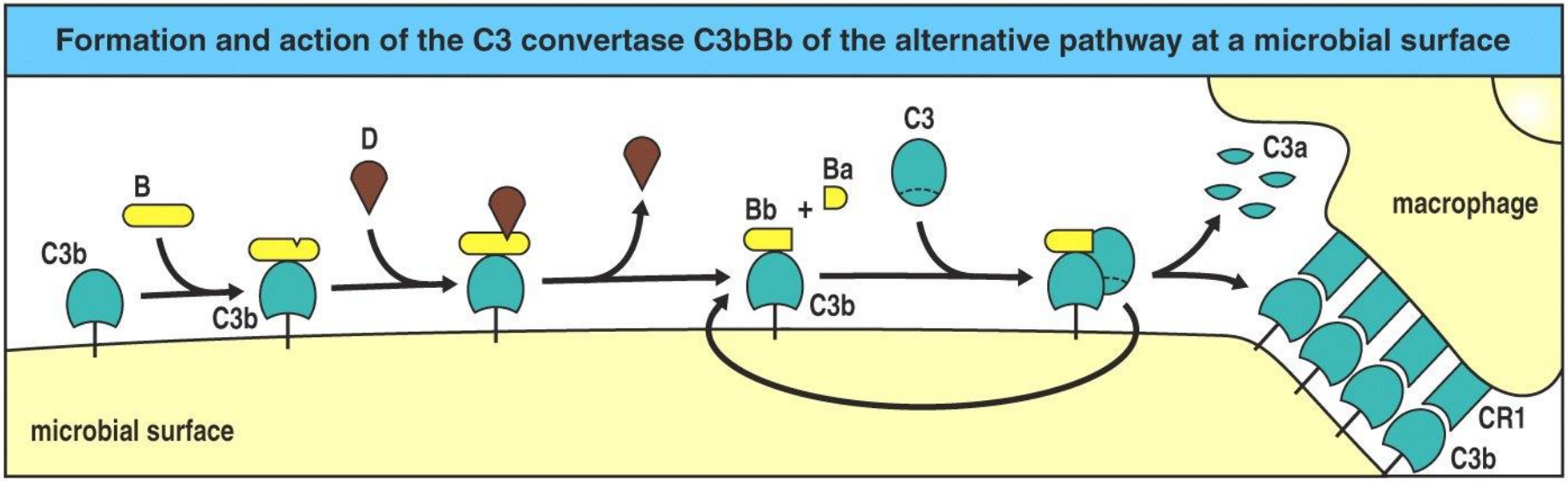
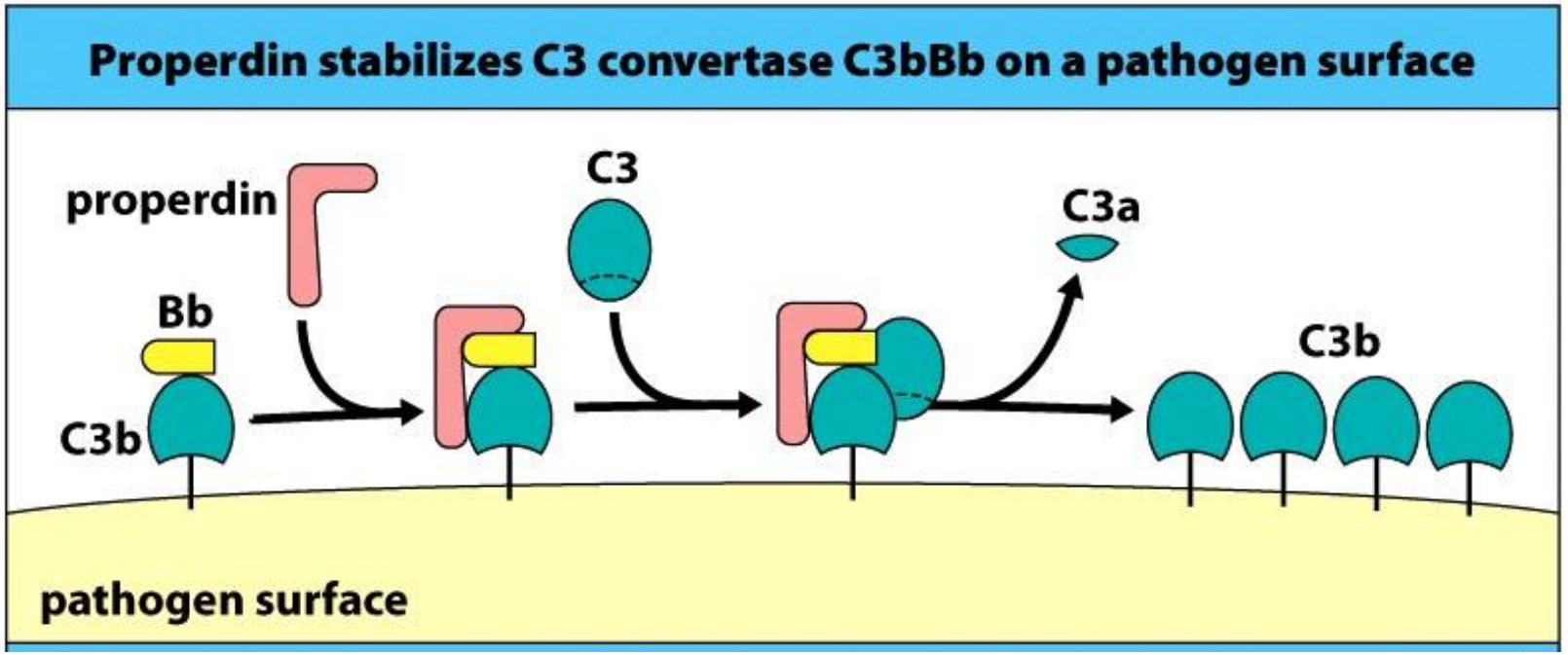
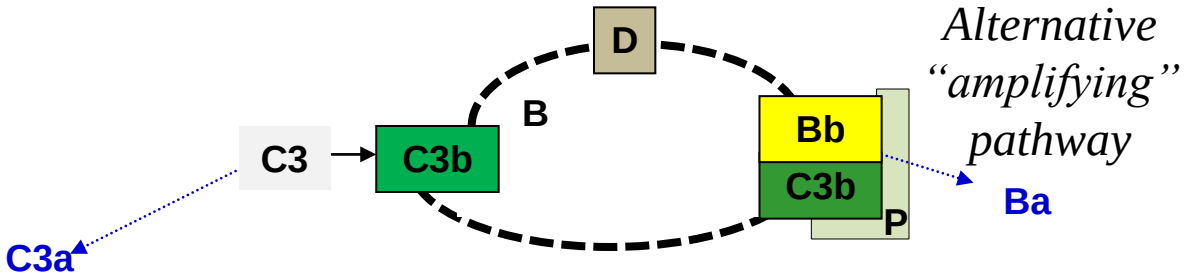
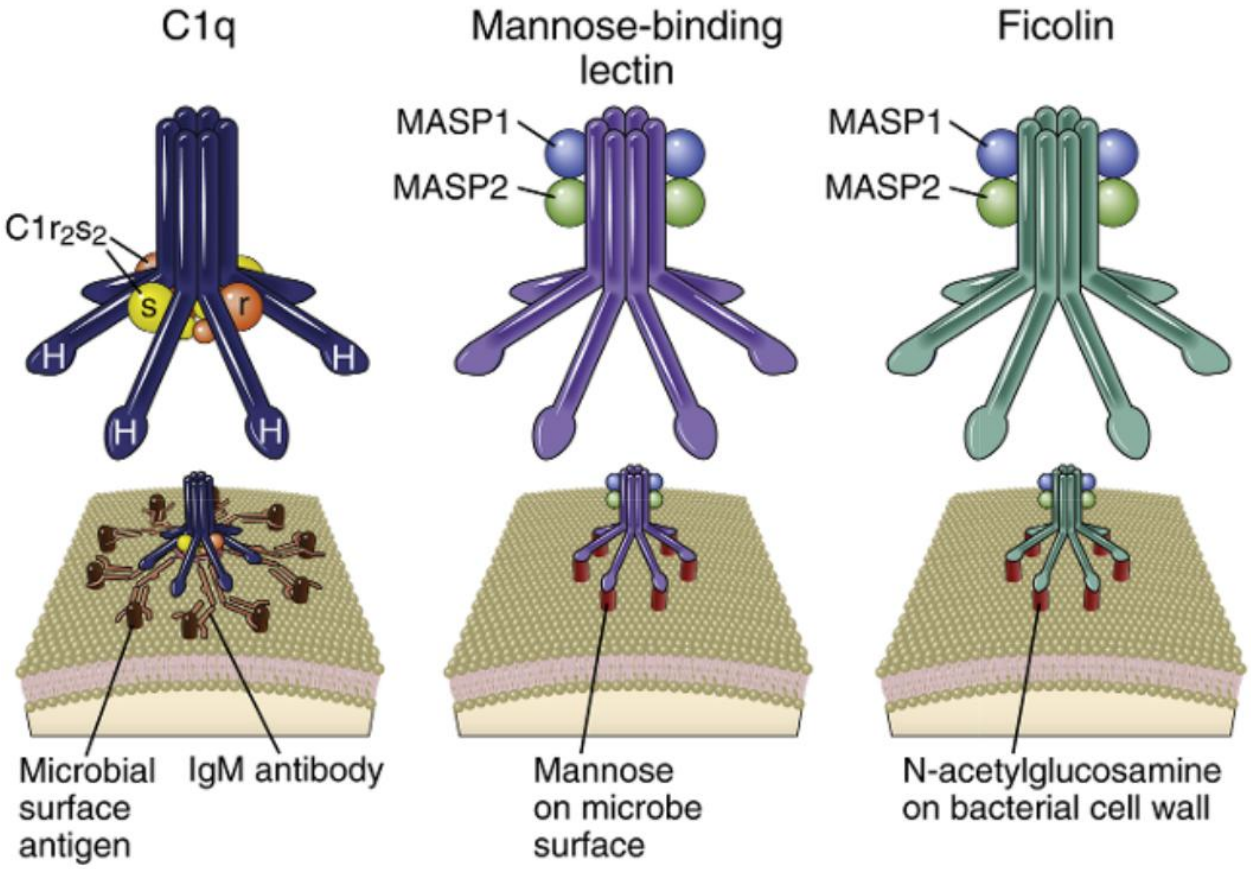


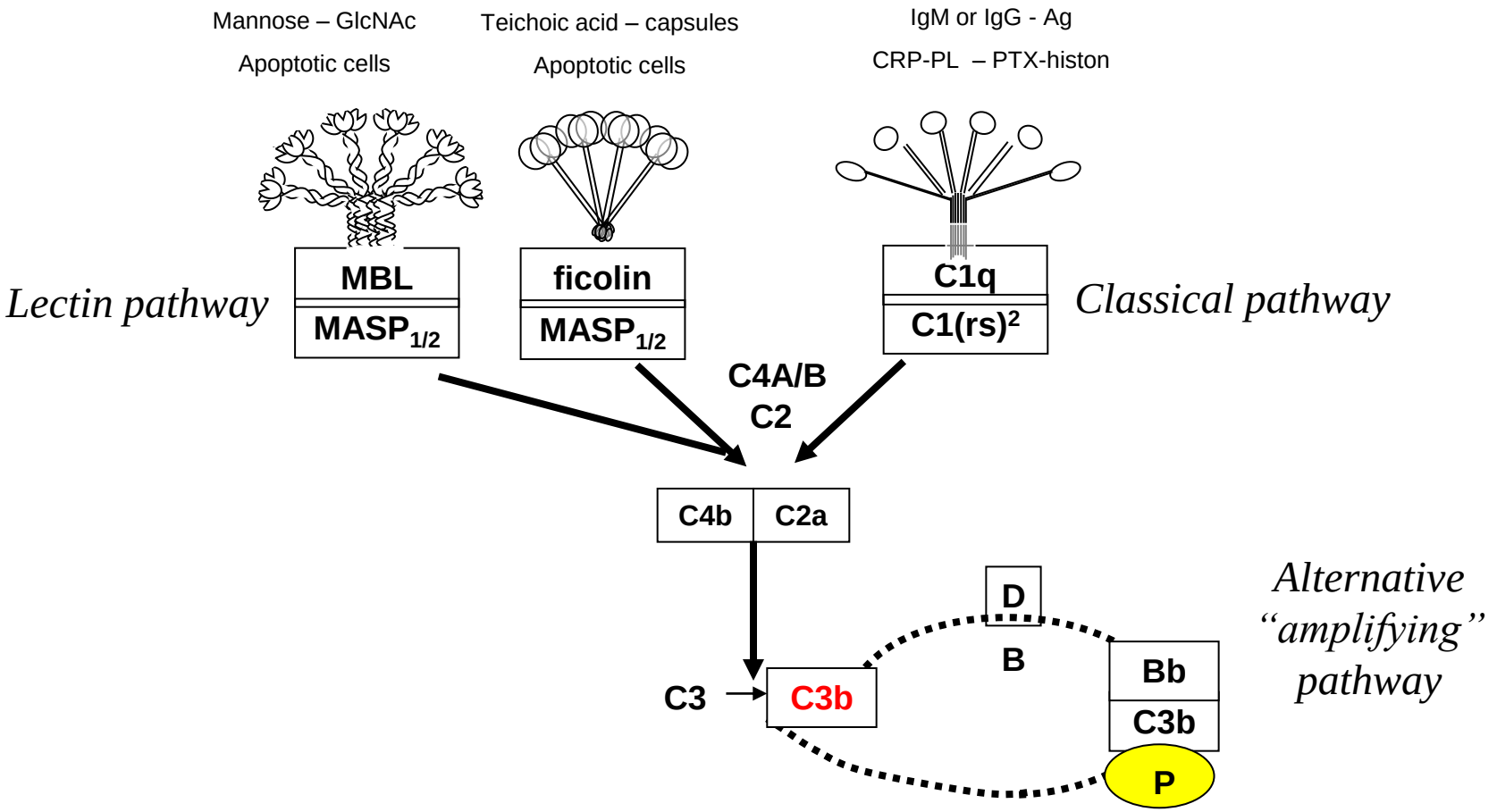

Figure 8-9 The Immune System, 2/e (© Garland Science 2005)

# C3bBb gestabiliseerd door Properdine




D
B
C3
C3b
Bb
C3b
P
C3a
Ba
Alternative
"amplifying"
pathway


C1q
Mannose-binding lectin
Ficolin
MASP1
MASP2
MASP1
MASP2
C1r2s2
s
r
H
H
H
H
Microbial surface antigen
IgM antibody
Mannose on microbe surface
N-acetylglucosamine on bacterial cell wall


Mannose – GlcNAc
Apoptotic cells
Teichoic acid – capsules
Apoptotic cells
IgM or IgG - Ag
CRP-PL – PTX-histon
Lectin pathway
MBL
MASP1/2
ficolin
MASP1/2
C1q
C1(rs)2
Classical pathway
C4A/B
C2
C4b
C2a
D
B
Bb
C3b
C3
C3b
P
Alternative
"amplifying"
pathway

# Start via CP C3-convertase (C4b2a(of b)), amplificatie via AP-C3 convertase (C3bBb)

In Europa wordt het grotere actieve deel van C2, dat bindt aan C4b, ook wel C2b genoemd. Het kleinere restdeel heet dan C2a.

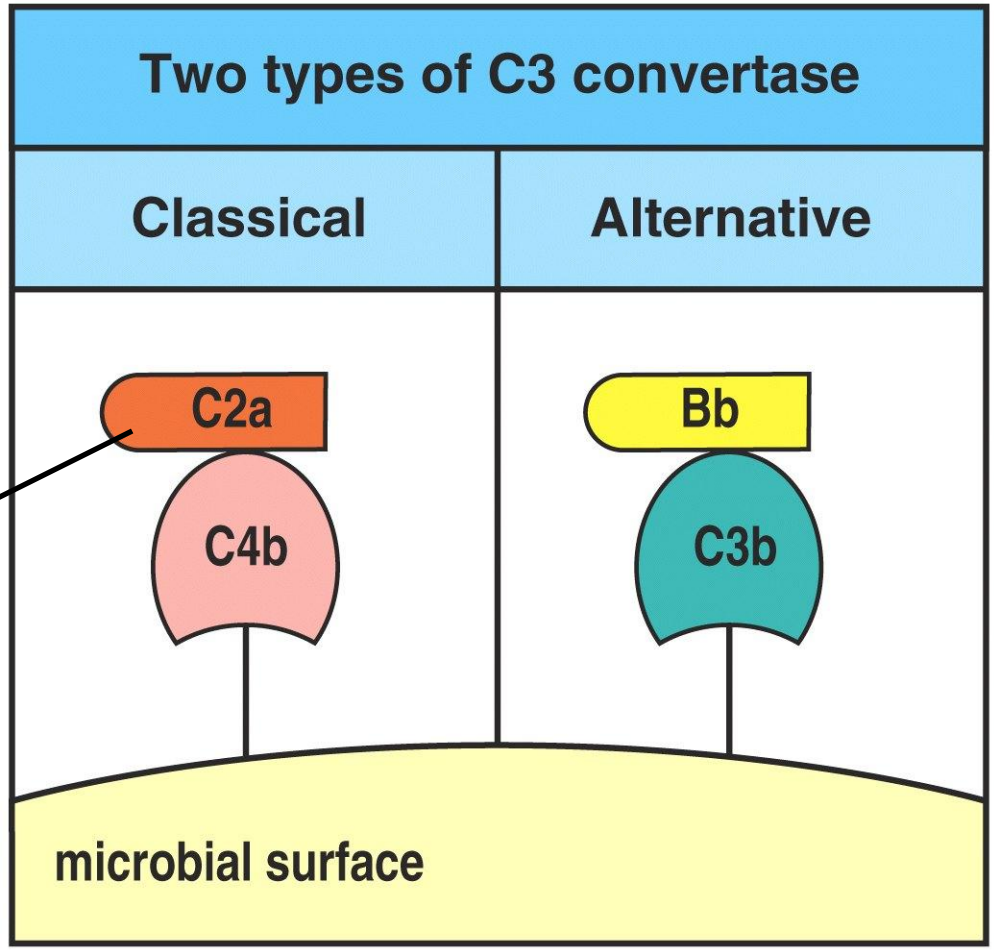



Figure 7-37 The Immune System, 2/e (© Garland Science 2005)

# Start via CP C3-convertase (C4b2a(of b)), amplificatie via AP-C3 convertase (C3bBb)

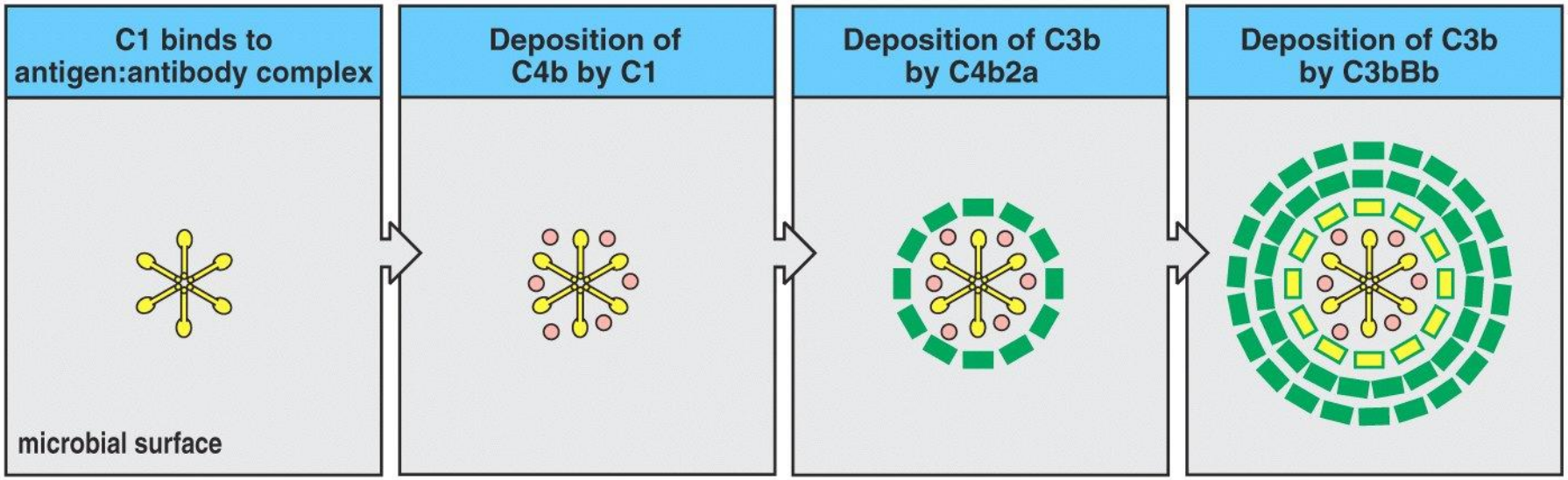
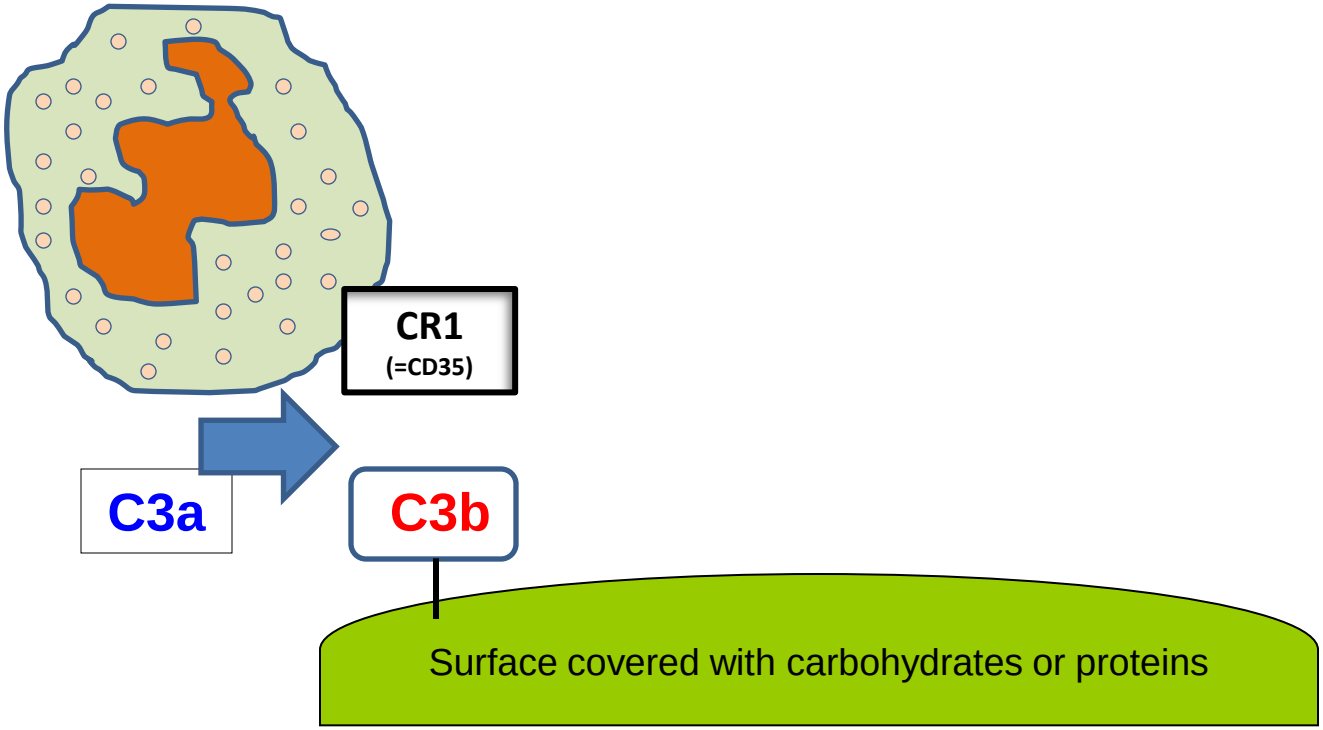
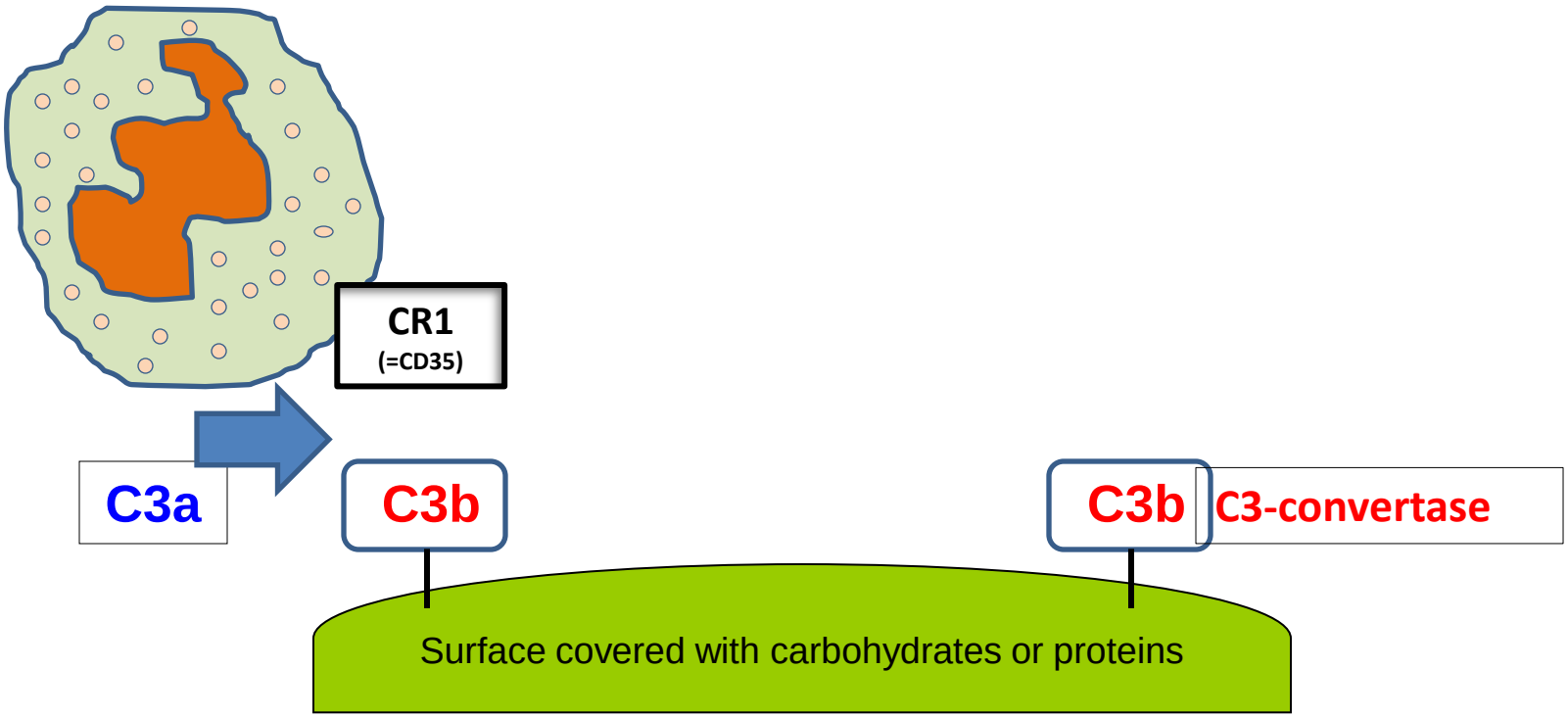



Figure 7-39 The Immune System, 2/e (© Garland Science 2005)

…the fixed **C3b**, acts as an opsonin for fagocytes with C3b-receptors, that are attracted by **C3a** and other anaphylatoxins…



…and/or forms together with its **C3-convertase** a **C5-convertase**…



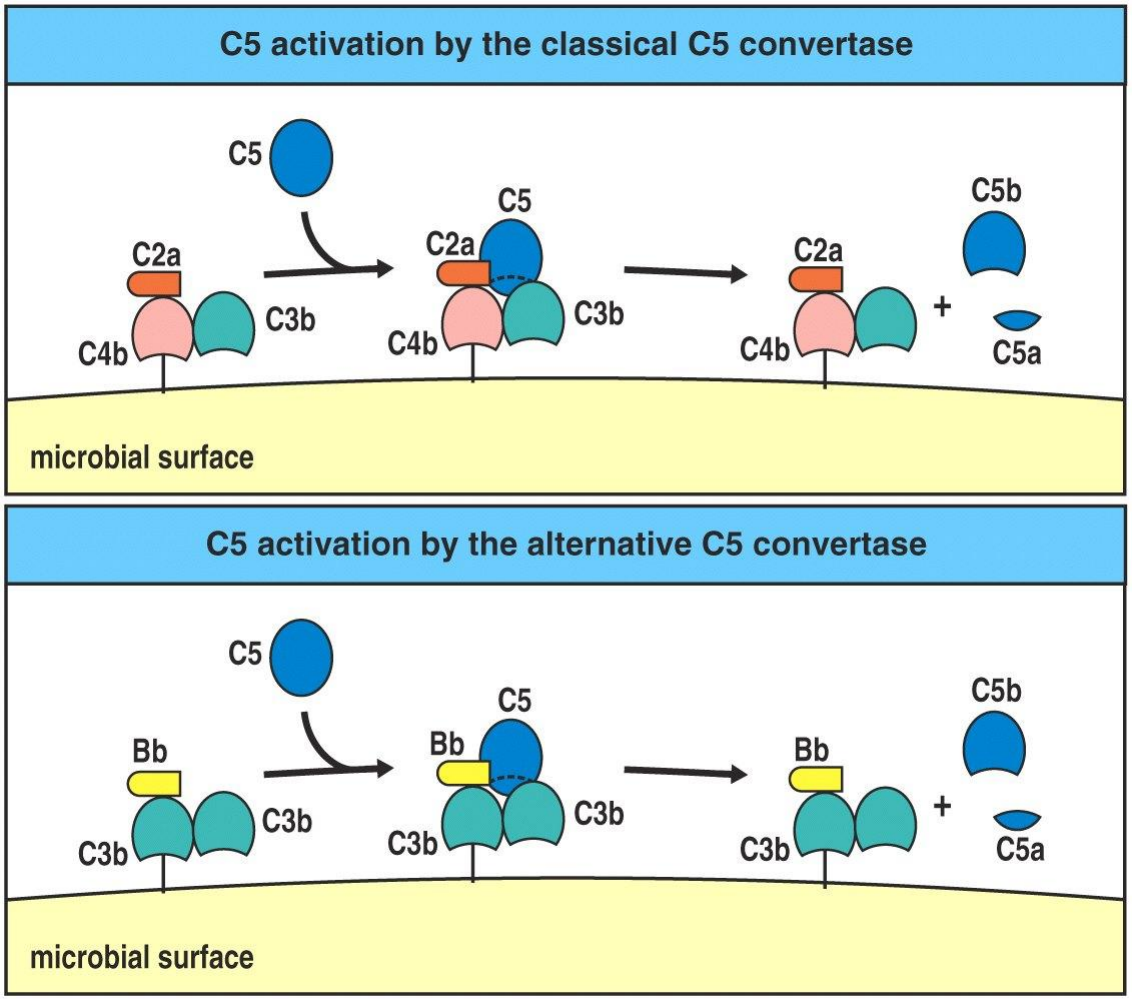
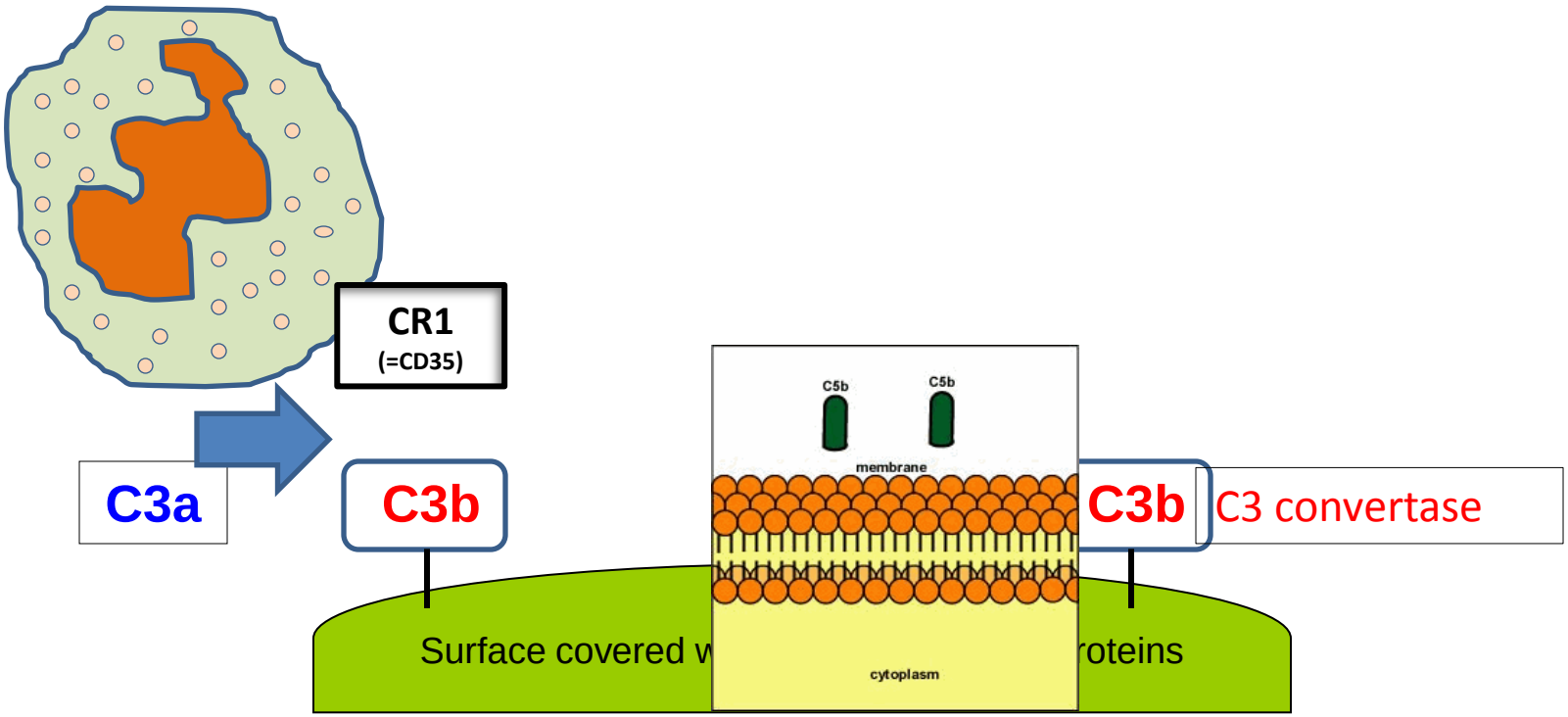


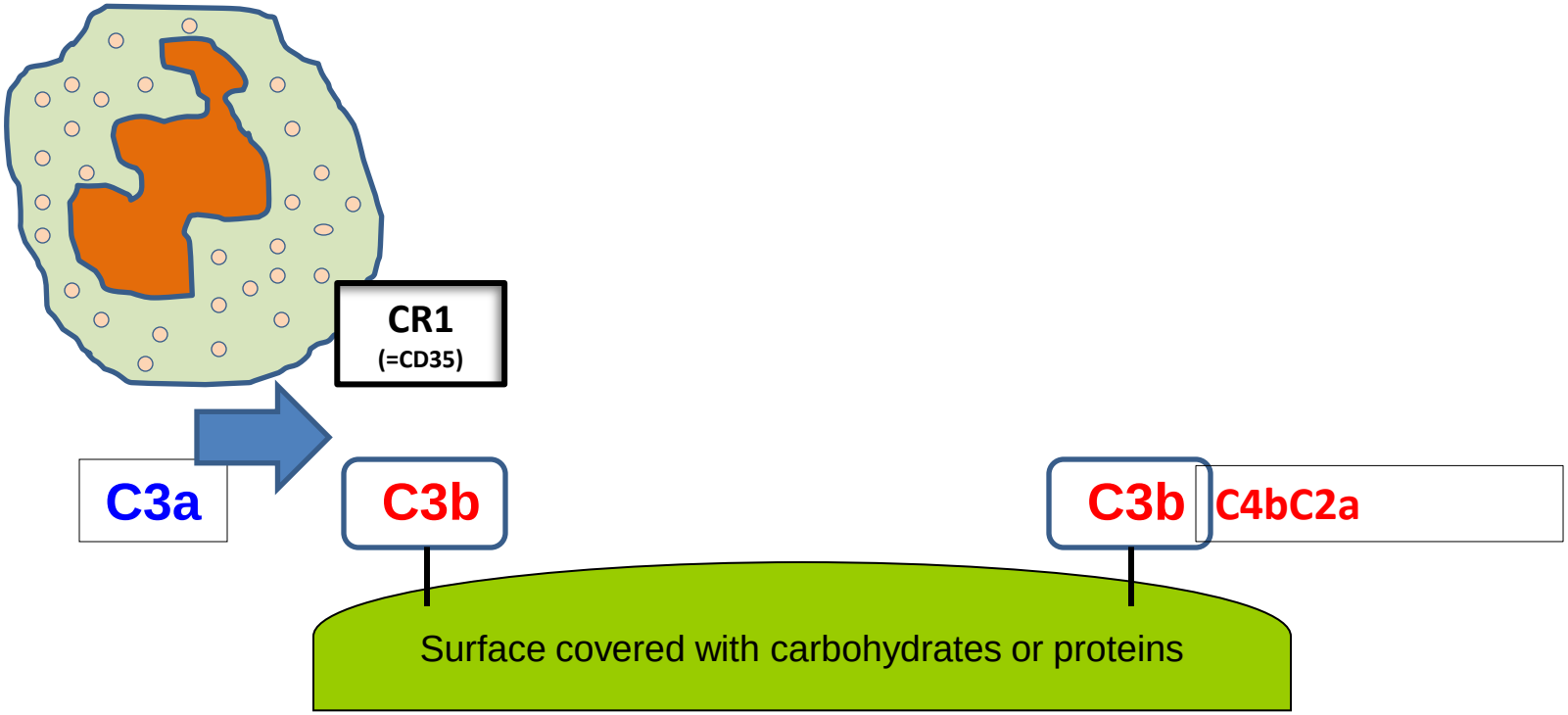

Figure 7-44 The Immune System, 2/e (© Garland Science 2005)

…which starts formation of Membrane Attack Complex and cell-lysis

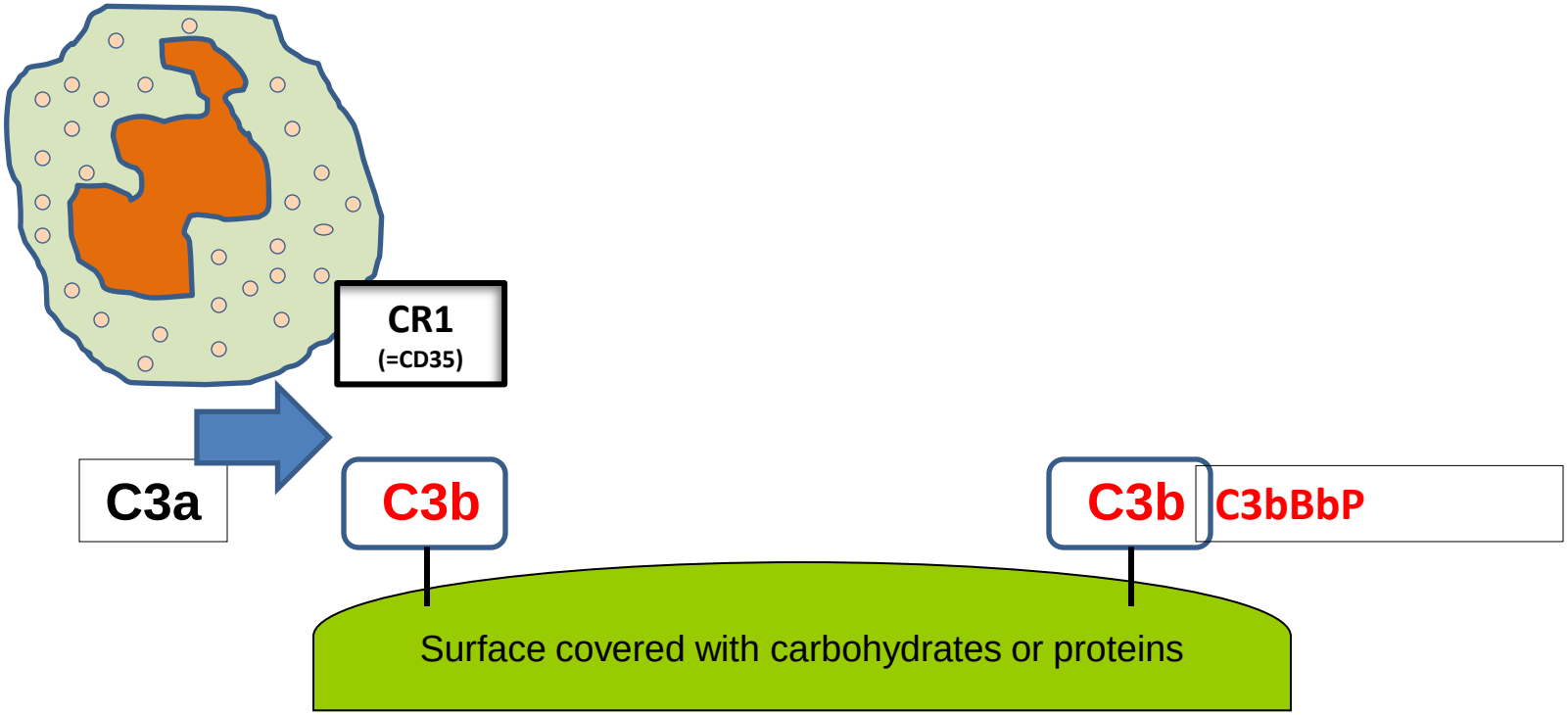


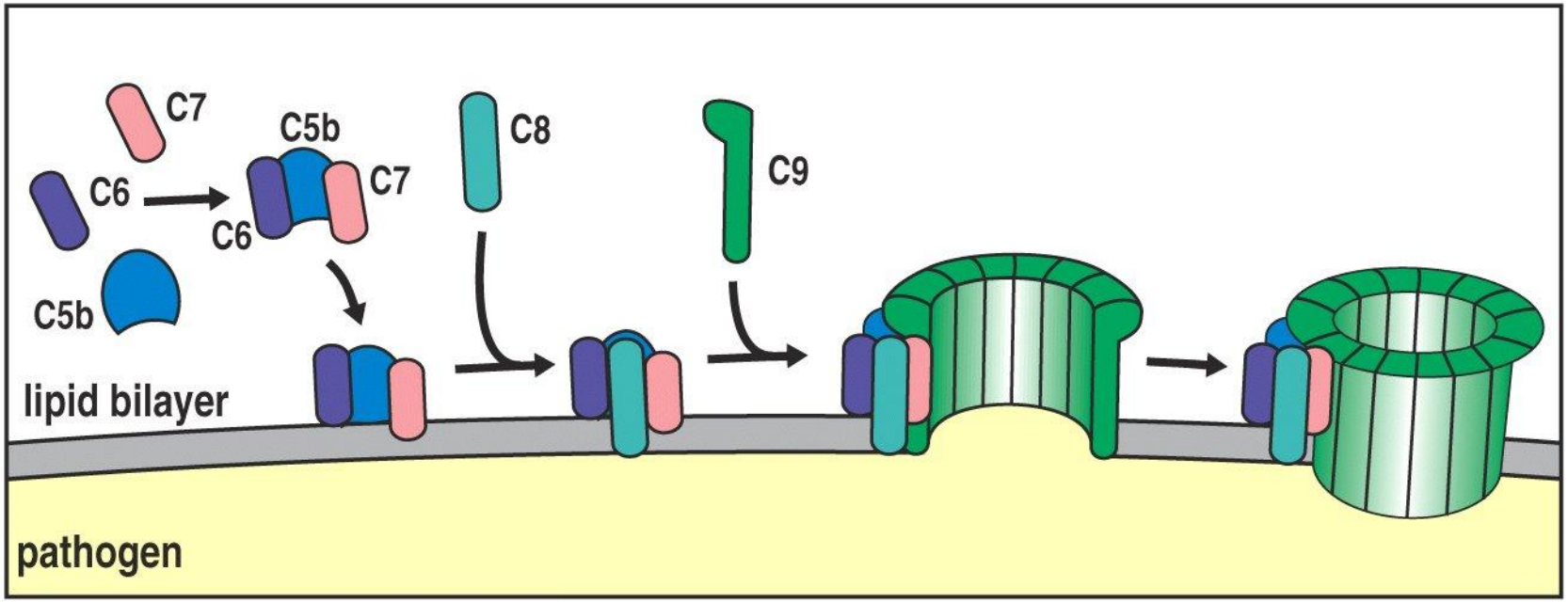
…the **C3-convertase**, being either:

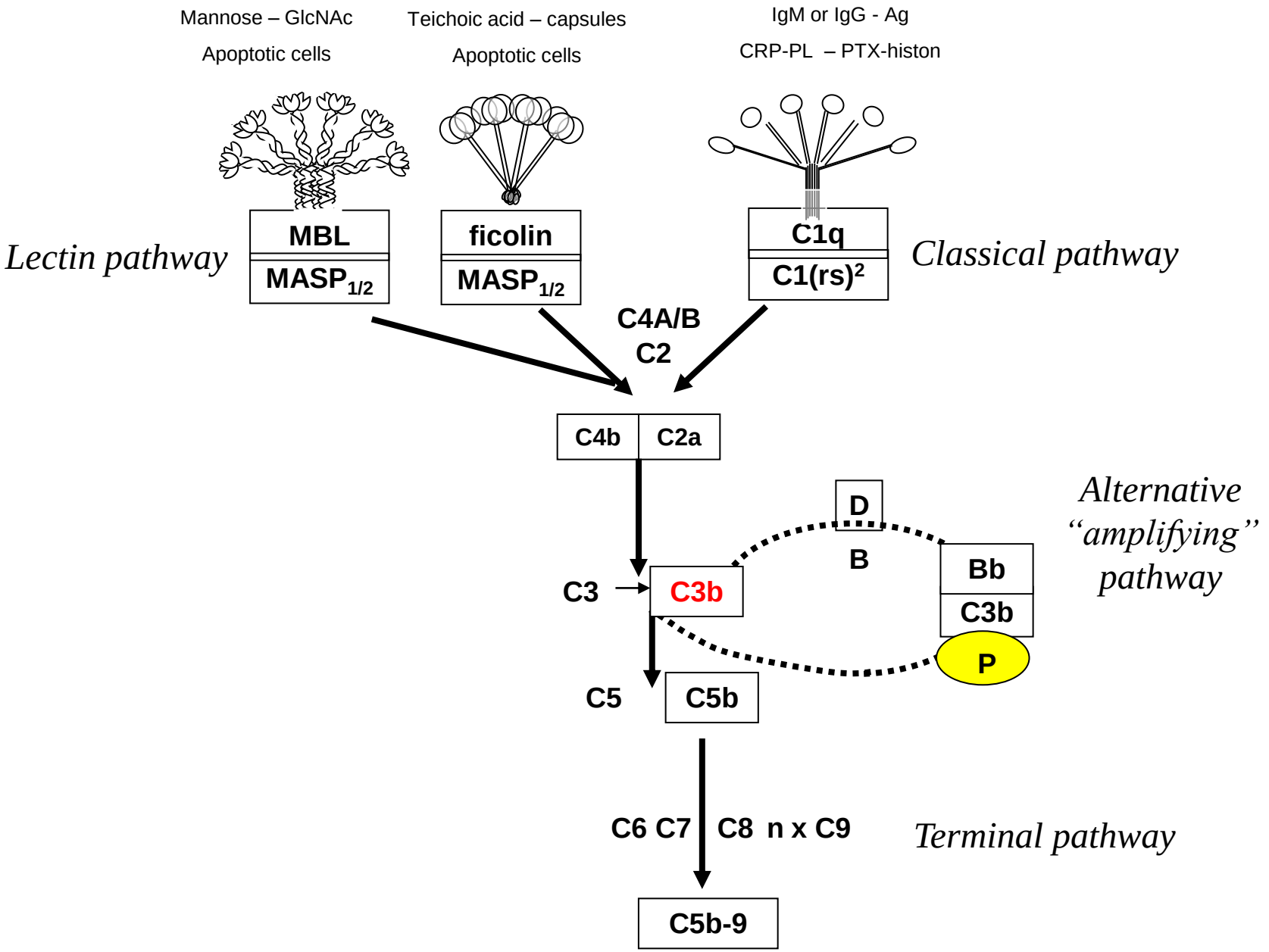
the **classical route C3-convertase** (=**C4bC2a**) or



the **alternative route C3-convertase** (= **C3bBbP**)




C7
C6
C5b
C6
C7
C5b
C8
C9
lipid bilayer
pathogen


Mannose – GlcNAc
Apoptotic cells
Teichoic acid – capsules
Apoptotic cells
IgM or IgG - Ag
CRP-PL – PTX-histon
Lectin pathway
MBL
MASP1/2
ficolin
MASP1/2
C1q
C1(rs)2
Classical pathway
C4A/B
C2
C4b
C2a
D
B
Bb
C3b
C3
C3b
P
Alternative
"amplifying"
pathway
C5
C5b
C6 C7
C8 n x C9
Terminal pathway
C5b-9

# Start via CP C3-convertase (C4b2a(of b)), amplificatie via AP-C3 convertase (C3bBb)

In Europa wordt het grotere actieve deel van C2, dat bindt aan C4b, ook wel C2b genoemd. Het kleinere restdeel heet dan C2a.

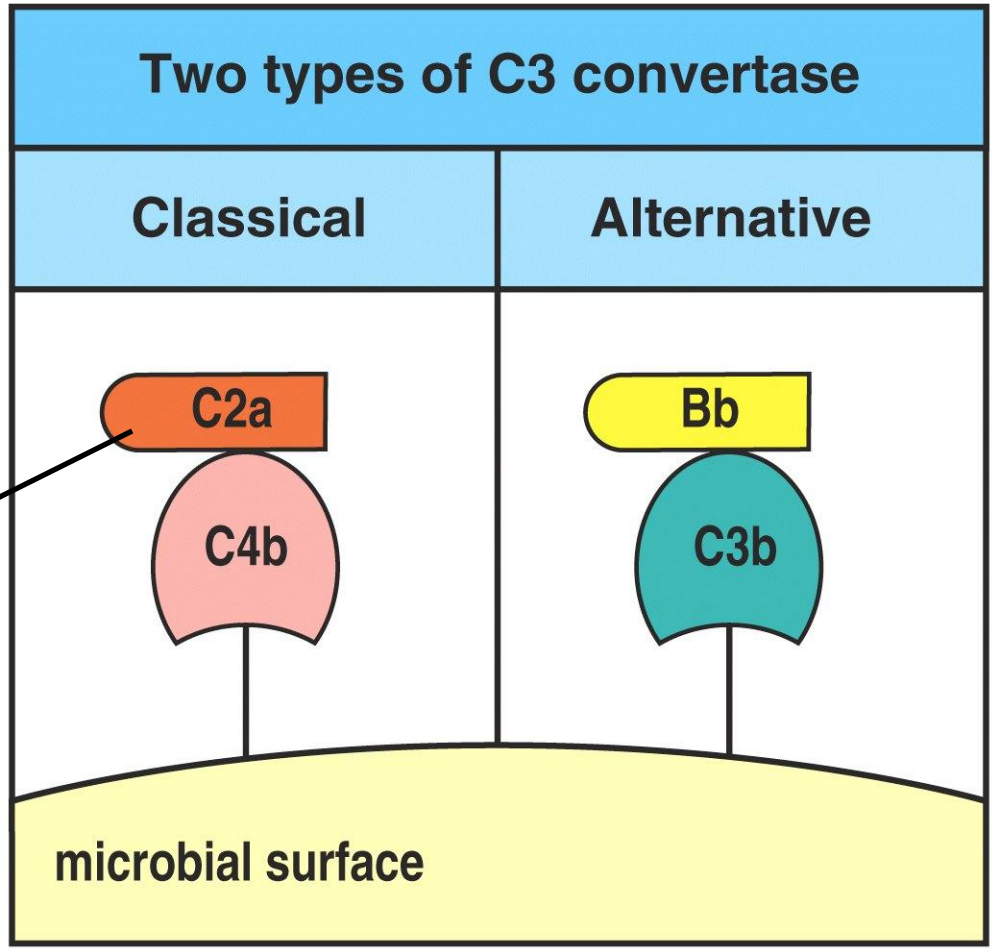



Figure 7-37 The Immune System, 2/e (© Garland Science 2005)

NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

# C4, C2 en Factor B op chrom 6

**article**

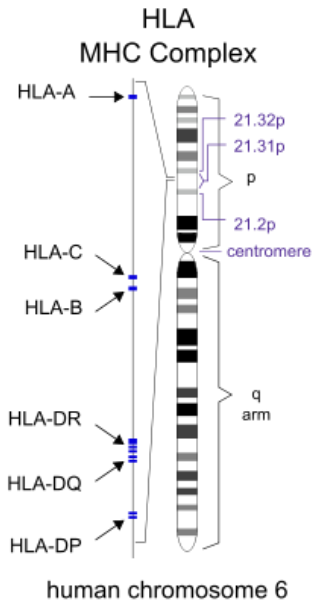
*Nature* **307**, 237 - 241 (19 January 1984); doi:10.1038/307237a0

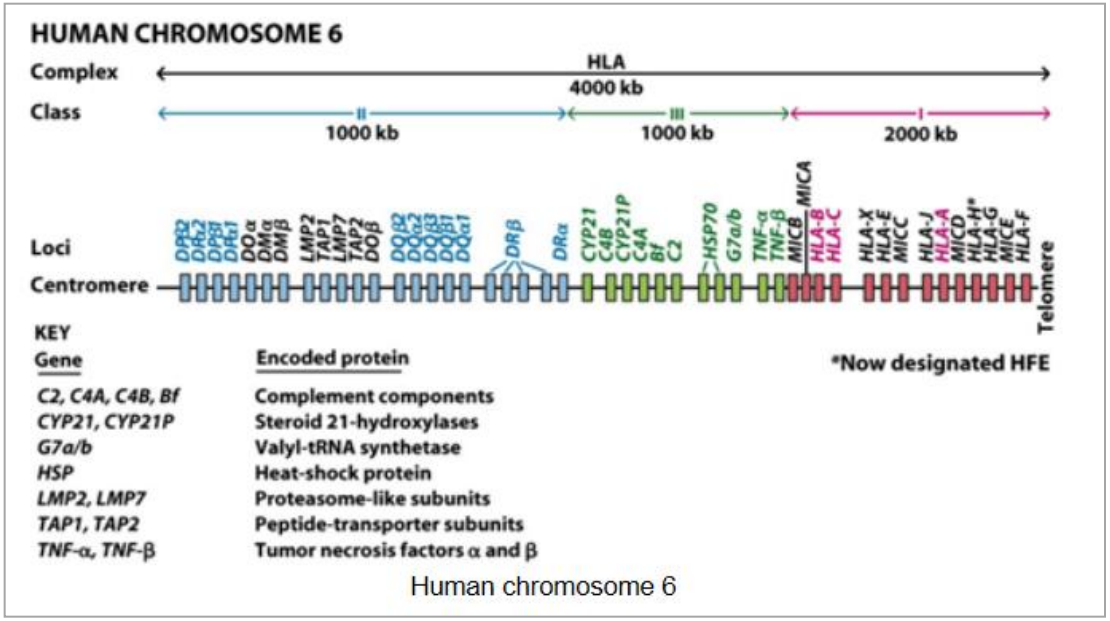
## A molecular map of the human major histocompatibility complex class III region linking complement genes C4, C2 and factor B

MICHAEL C. CARROLL, R. DUNCAN CAMPBELL, DAVID R. BENTLEY & RODNEY R. PORTER

MRC Immunochemistry Unit, Biochemistry Department, Oxford University, South Parks Road, Oxford OX1 3QU, UK

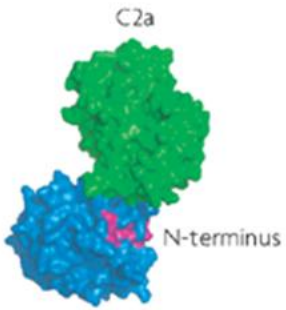
**Four human complement genes, which have previously been mapped between HLA-D and HLA-B on chromosome 6, have now been aligned on a 98-kilobase (kb) section of the chromosome on the basis of four overlapping cosmid clones of genomic DNA. The C2 and factor B genes, less than 2 kb apart, are about 30 kb from two C4 genes separated from each other by about 10 kb.**




Radboudumc

# Start via CP C3-convertase (C4b2a(of b)), amplificatie via AP-C3 convertase (C3bBb)



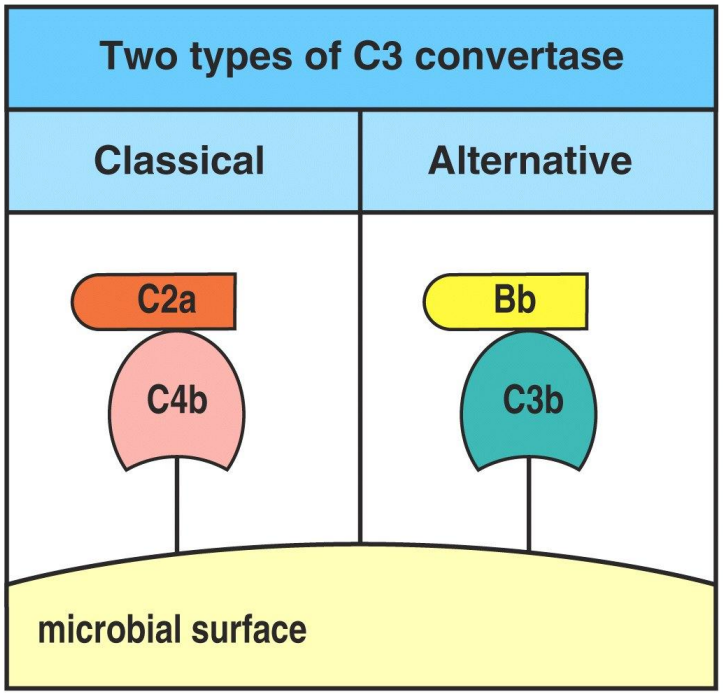
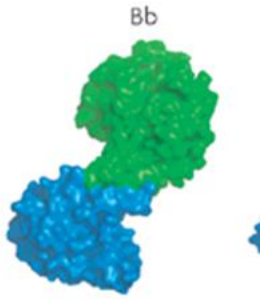
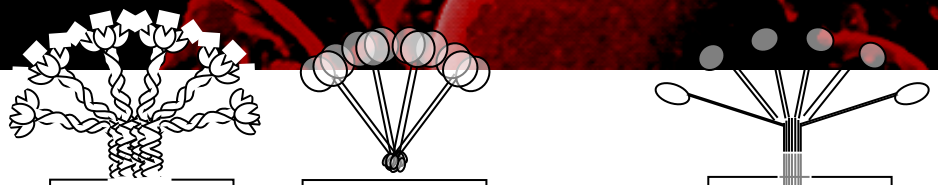




Figure 7-37 The Immune System, 2/e (© Garland Science 2005)





*Lectin pathway*

MBL
$MASP_{1/2}$

ficolin
$MASP_{1/2}$

C1q
$C1(rs)^2$

*Classical pathway*

C4A/B
C2

C4b C2a

C3 → C3b

D
B
Bb
C3b
P

*Alternative "amplifying" pathway*

C5 → C5b

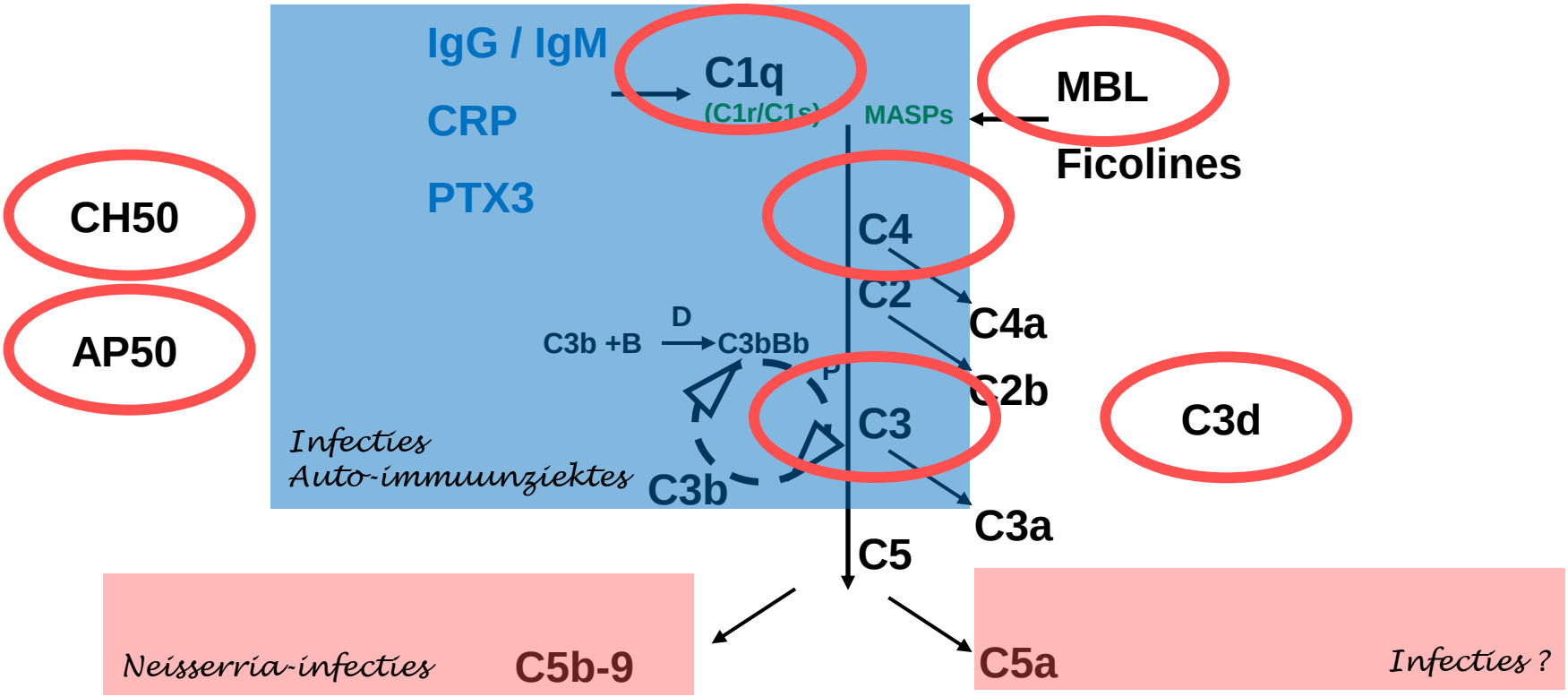
C6 C7 C8 n x C9

*Terminal pathway*

C5b-9

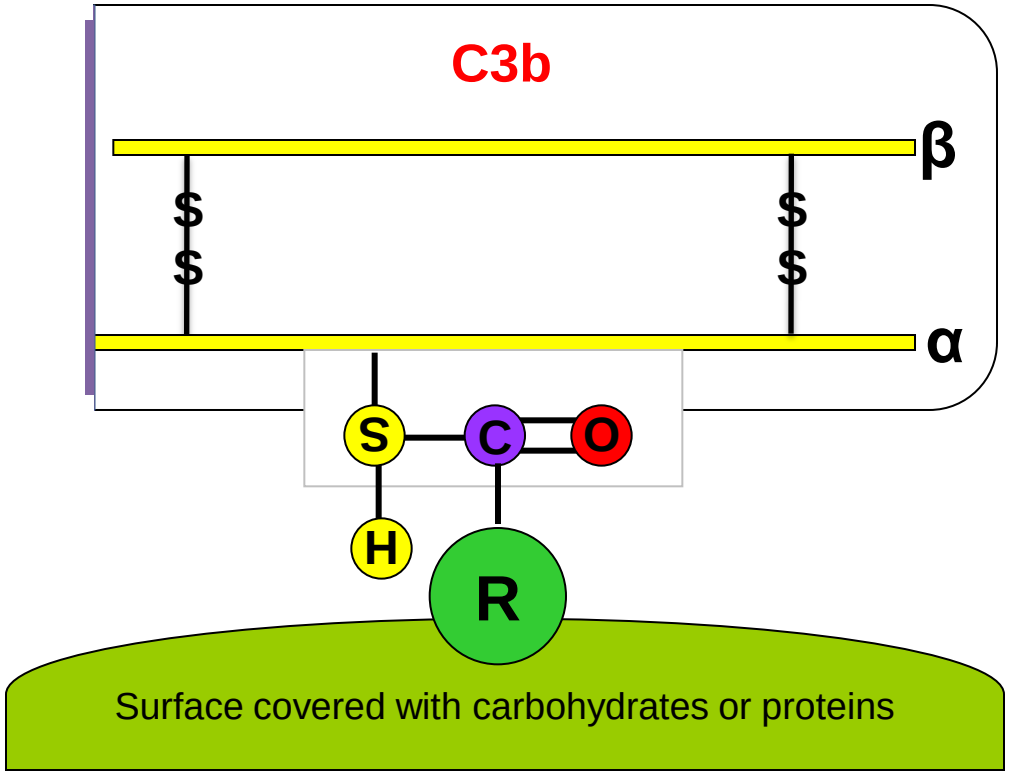
# Eenvoudiger schema:

# Complement-activatie, Ziekte en Lab



# Wat gebeurt er met C3b….?

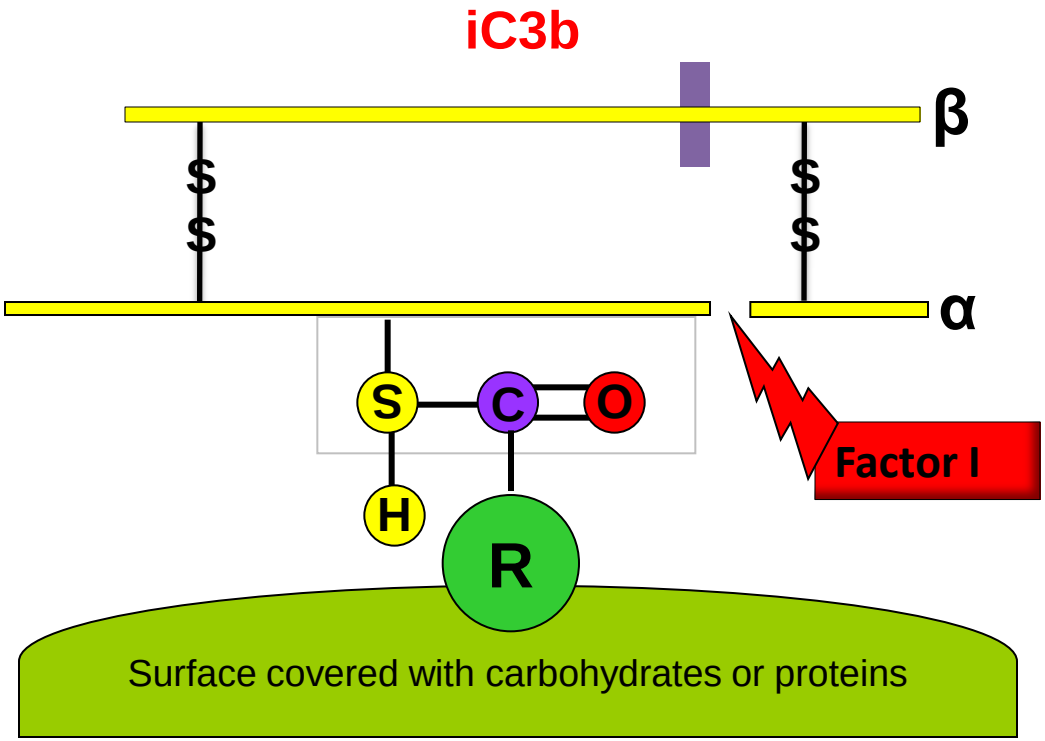
…C3b covalently attached to other molecule…



# Inactivatie (stopt vorming C5-convertase)

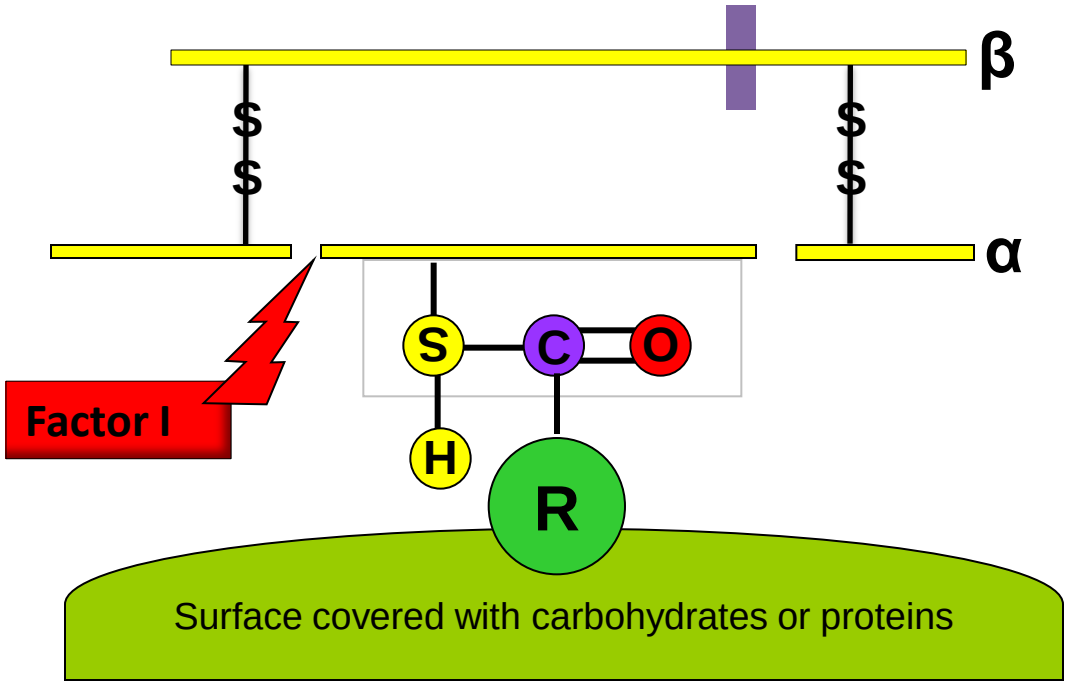
…is inactivated by Factor I (with assistance of a cofactor),

which retains the opsonic activity but blocks C5 activation i.e. terminal pathway



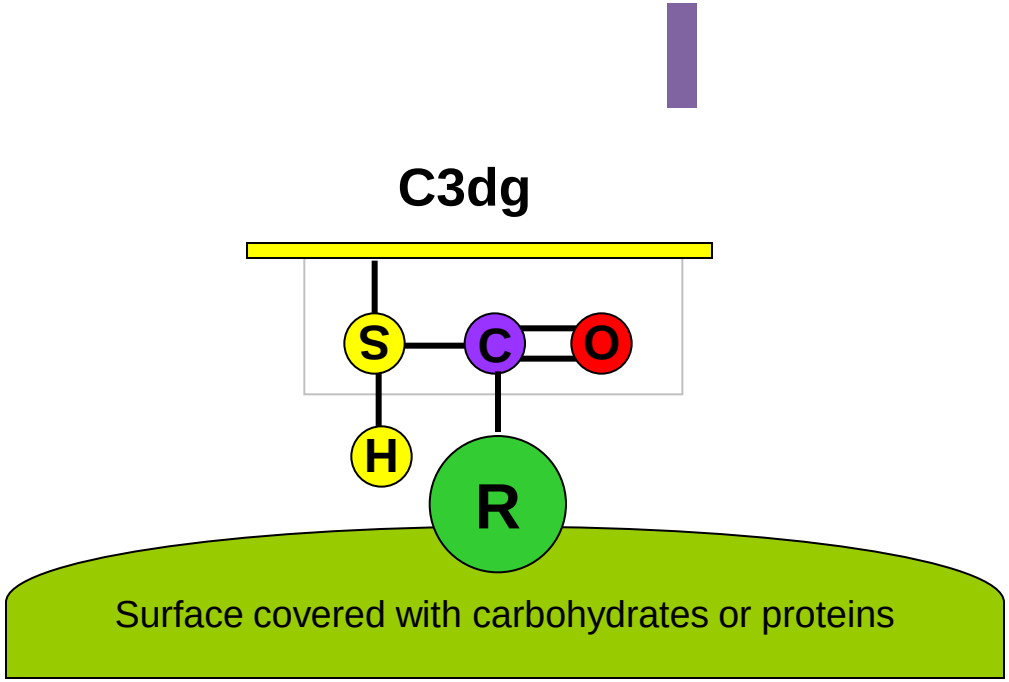
# Verdere afbraak…

…further inactivation of C3b by Factor I (with assistance of a cofactor)…



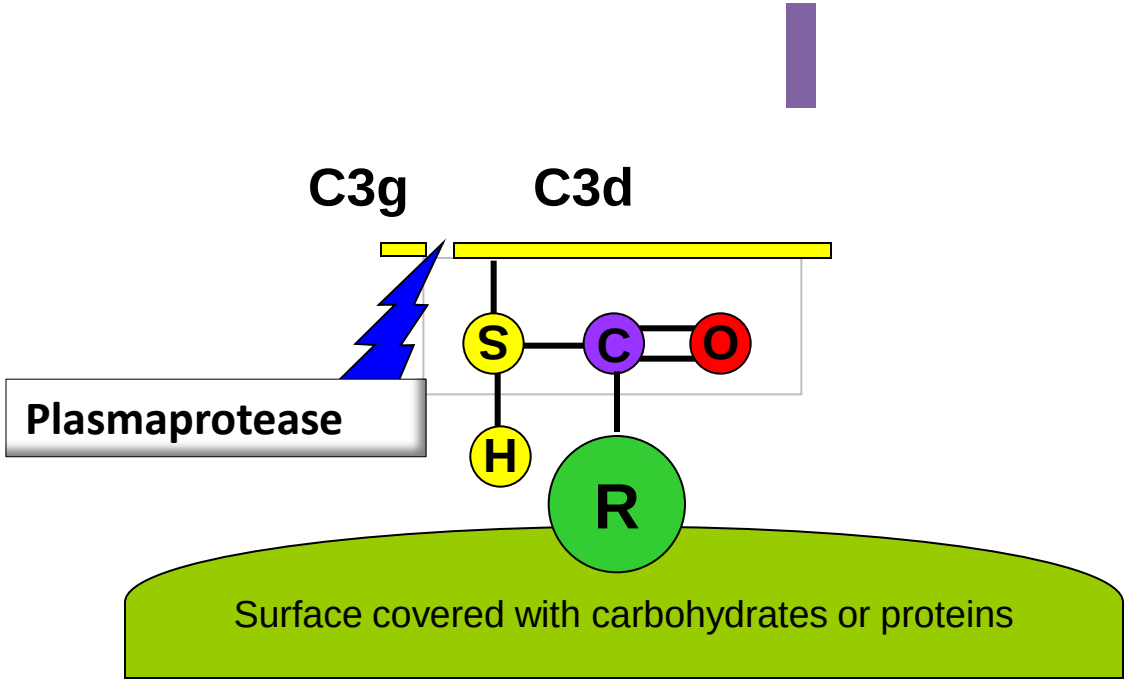
# Nog verdere afbraak…

.. leads to the completely inactive C3dg…

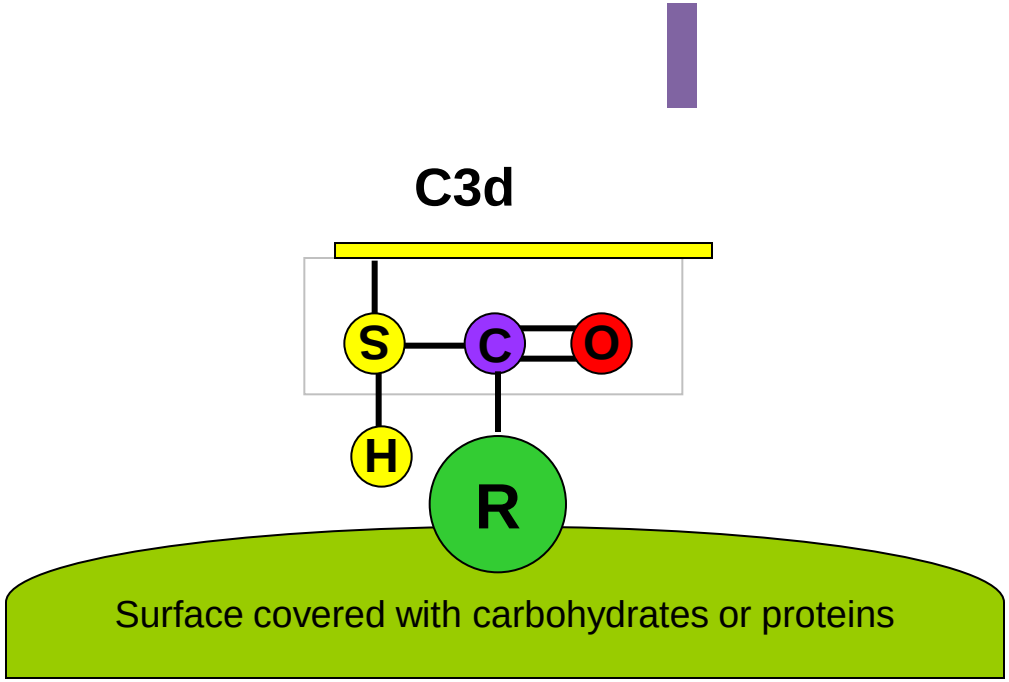


# Tot C3d…

…that after cleavage of a plasmafactor becomes C3d



…which can be measured in plasma of patients with ongoing C3-activation



# Pfff….

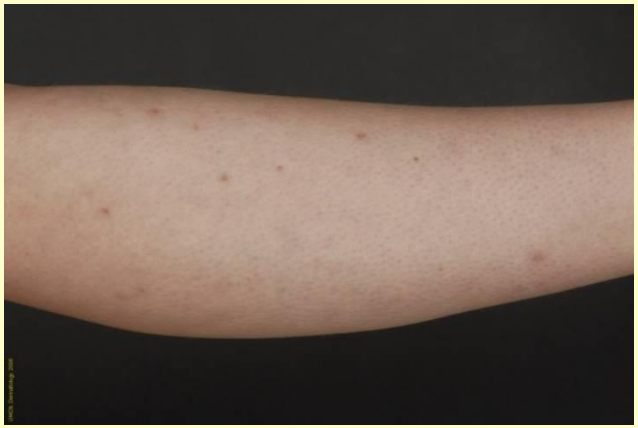
Tot zover complement ‘activatie’ zoals bekend verondersteld….

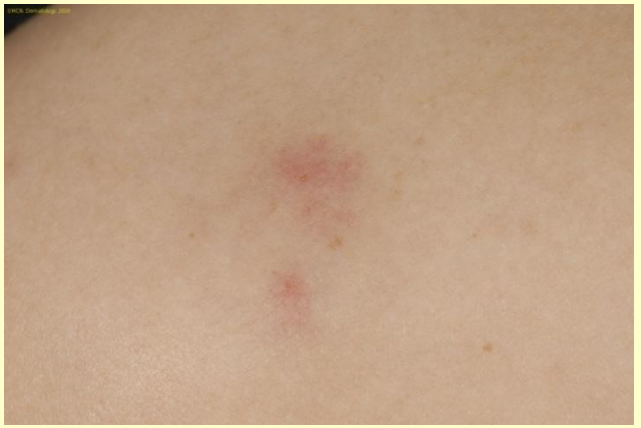
Ziektes door stoornissen in complement-activatie:

- Tekort aan activatie
- Tekort aan regulatie

# Pt 1

Vrouw, 30 jaar, sinds enkele maanden koorts-periodes met huidafwijkingen:





CRP 28 mg/L, dalend naar 5 mg/L.

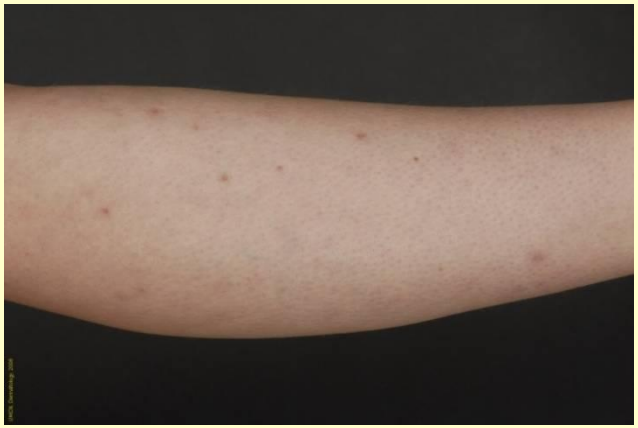
Hb 7.4 mmol/L, Leuko's en thrombo's, leverenzymen, nierfie – normaal, ANA & ANCA neg. U-Sed g.a.

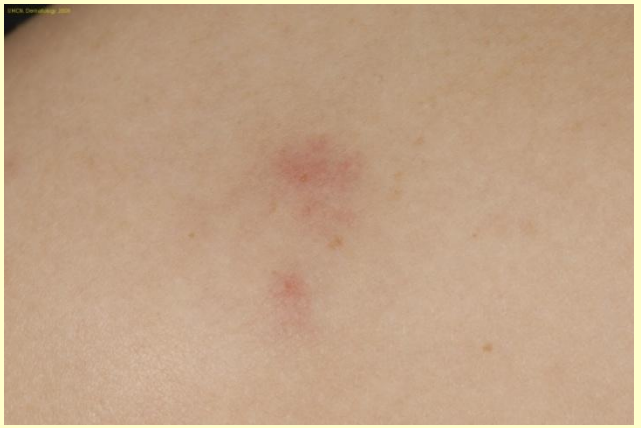
Bloedkweek neg, vagina-kweek N. gonorrhoea neg, keelkweek *N. meningitidis* pos (niet getypeerd)

**C3 en C4 normaal, CH50 < 15%, AP 50 < 15%**

# Pt 1

Vrouw, 30 jaar, sinds enkele maanden koorts-periodes met huidafwijkingen:





CRP 28 mg/L, dalend naar 5 mg/L.

Hb 7.4 mmol/L, Leuko's en thrombo's, leverenzymen, nierfie – normaal, ANA & ANCA neg. U-Sed g.a.

Bloedkweek neg, vagina-kweek N. gonorrhoea neg, keelkweek *N. meningitidis* pos (niet getypeerd)

**C3 en C4 normaal, CH50 < 15%, AP 50 < 15%.** Diagnose: **Volledige complementfactor-C7 deficiëntie**

# Pt 2 (man 24 jaar)

In 2007 op SEH-arts -> consult AIG

Sinds 1 week klachten:

begonnen met spierpijn, “koortsig”, hoofdpijn, koude rillingen, “dacht dood te gaan”

spontaan herstel na 5 dagen

sinds één dag weer spierpijn, transpireren, pijn li-voet; sinds vanmorgen “vlekjes” op benen en armen

student, actief homosexueel, onbeschermd orogenitale contacten

- LO/ Negroïde, 38.8 $^{o}$C, diffuus niet wegdrukbae pijnlijke vlekjes/noduli, Li-knie: flexie, geen hydrops

- Lab/ L 12.0x10$^{9}$/L, CRP 111 mg/L, lever en nierfie g.a., ANA & ANCA neg, BK 2x neg, urine sed g.b.

**Onder differentiaaldiagnose van gedisseminеerde gonorrhoe**: R/ Ceftriaxon, gestart op SEH

# Pt 2 (man 24 jaar)

Op 24-9 PA huidbiopsie: Vasculitis, DD: PAN of microscopische angiitis.

Op 25-9: C3 **1530 mg/L, C4 335 mg/L, MBL < 0.04 mg/L, CH50 < 15%, AP50 < 30%**

Op 24-10 herhaald: **CH50 < 15%, AP50 <15%**

**Diagnose: Volledige complementfactor C6 deficiëntie + MBL-deficientie**

# Pt 3 (vrouw 16 jaar) & 4 (jongen 14 jaar):

Verwezen door haematoloog elders in 2007

Op 2001 (toen 16 jaar) om 12:00 ziek, ijlen, koorts, hoofdpijn, nekstijf, fotofobie:

Rond 15:00 petechiën gezien; rond 16:30 in ZH

Diagnose: **Meningococcen serogroep C meningitis**; restloos herstel. Geen verdere controles nodig.

Broer (toen 14 jaar) rond 08:00 ziek, bleef op bed

's Avonds gegeneraliseerde spierpijn

Rond 03:30 ecchymosen, veel pijn in billen, opvallend helder bewustzijn, geholpen door zus

Om 04:30 ZH opname

Diagnose: **Fulminante meningococcen sepsis;** fataal beloop

Overleden bij aankomst UMCN-retrieval team om 11:00

# Pt 3 & 4:

Vanwege familiair voorkomen meningococcenziekte wendde patiënte zich tot internist/hamatoloog elders

Lab/ **CH50 < 15%, AP50 < 15%, MBL 3.22 mg/L**

**C2 11.7 mg/L ((N 10-80)**

**C5 < 11.0 IE/mL (N 67-125)**

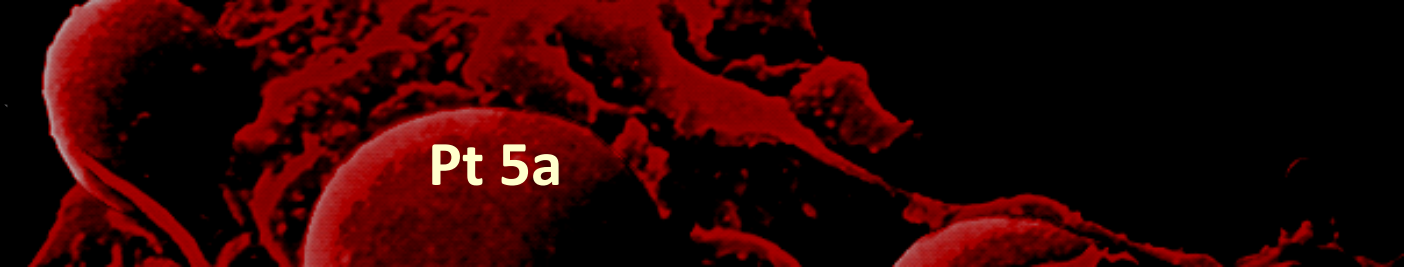
Gen-analyse pte, broer, vader en moeder (lab Peter Garred; Kopenhagen)

P: 4bp-deletie (del AAAC) in exon 11 leidend tot prematuur stopcodon Asp396

M: non-sense mutatie in exon 41, stopcodon Gln1658

Pte en broer zijn beide **C5-deficiëntie door samengestelde heterozygotie**

NB: P en M hebben normale CH50 en AP50



# Pt 5a

9 month-old girl

- Admission to other hospital because of pupura since 2.75 hrs.
- Temp 40 $^{o}$C, poor peripheral circulation, pulse rate 220/min, RR 140/80 mm Hg.
- Lab: CRP 53 mg/L, L 3.9x10$^{9}$/L, T 234x10$^{9}$/L, pH 7.19, BE –15.2 mmol/L.
- CSF: L 20x10$^{6}$/L, gluc 3.8 mmol/L, protein 280 mg/L.
- CSF culture *N. meningitidis* B:P1:15; Blood culture remained sterile.

- Admitted to normal ward: RR dropped to to 79/52, anuria, T dropped to 38x10$^{9}$/L.
- No inotropics; no ventilatory support; no fresh frozen plasma.
- After 36 hrs: Sudden drop in bloodpressure; resuscitated; transfer to our ICU.
- Arrival at ICU in moribund condition; died 11 hrs later.
- No obduction; no remaining blood-samples.



Sprong et al. Blood 2006

# Pt 5b

13 month-old boy, brother of case 5a

- History of recurrent upper and lower resp. tract infections.
- Admitted because of “sudden” onset of fever and petechial rash.
- Temp 39.7 $^{o}$C, decreased refill, pulse rate 180 /min; no nuchal rigidity.
- Lab: CRP 119 mg/L, L 10.9x10$^{9}$/L, T 324x10$^{9}$/L.
- Blood culture *N. meningitidis* B.1.P1-4.
- Admitted to normal ward: telephonic consulation ICU-staff.
- Fluid chalenges, dobutamin, fresh frozen plasma.
- Recovery uneventful.



Sprong et al. Blood 2006

# Pt 5b: Jongen 2 jr

| | 2001 | Normaal |
|---|---|---|
| AP50 (%) | < 5% | 75-125% |
| Factor B (iU/L) | 84 | 75-125 |
| *Factor H (kwalitatief)* | normaal | < 3.3% |
| Properdine (kwal) | normaal | |
| Factor I (kwal) | normaal | |
| | | |

# Pt 5b: Jongen 2 jr

| | 2001 | Normaal |
|---|---|---|
| AP50 (%) | **< 5%** | 75-125% |
| Factor B (iU/L) | 84 | 75-125 |
| *Factor H (kwalitatief)* | normaal | < 3.3% |
| Properdine (kwal) | normaal | |
| Factor I (kwal) | normaal | |
| Factor D (mg/L) | **<0.03** **(undetectable)** | 1.0-2.0 |

# Pt 6 (20 jaar)

In 2001 op SEH bij neuroloog, elders.

In maart één week

- *ziek, koorts, hoofdpijn, misselijk, acustico/photophoba, huidafwijkingen*

Spontaan hersteld, terug naar school, maar…

Eén dag later weer koorts

Sindsdien periodiek, 2-3 dagen durend klachten van

- *vooral koorts, hoofdpijn en huidafwijkingen*

Toevallig op SEH géén klachten meer!

# Pt 6 (20 jaar)

CT-brein

- normaal

Liquor

- Helder
- **Leukocyten 908/3**, 80% PMNs
- **Glucose 2.3 mmol/L**
- Eiwit 416 mg/L

# Pt 6 (20 jaar)

Opname ter observatie op afdeling Neurologie:

- na 3 dagen opnieuw koortspiek met hoofdpijn
- **CRP 102 mg/L**
- Bloedkweek: **Neisseria meningitidis serogroup W-135**

Behandeling:

- Penicillin 6 x 3.000.000 U i.v. gedurende 10 dagen
- Volledig herstel, CRP < 8mg/L

Diagnose bij ontslag:

**Chronische benigne menigococcaemia, N. meningitidis W-135**

# Pt 6 (20-21 jaar)

| | April , 2001 | Juli, 2001 | Herfst, 2002 | Normaal |
|---|---|---|---|---|
| MBL (mg/L) | | | 130 | > 800 |
| C1q (iU/mL) | 122 | 117 | | 81-128 |
| C4 (mg/L) | 340 | 266 | 355 | 150-400 |
| C3 (mg/L) | 100 | 250 | 370 | 900-1800 |
| *C3d (%)* | 19 | | 6 | 0.5-3.1 |
| *C3 nephritic factor* | | | Absent | Absent |
| C5 (iU/mL) | 30 | | 49 | 67-125 |
| Factor B (iU/mL) | 95 | | | 49-129 |
| CH50 (%) | 14 | | 56 | 68-133 |
| AP50 (%) | <17 | <17 | <17 | 67-128 |
| C1-inh (U/mL) | | | 1.14 | 0.76-1.33 |
| Protectine (CD59 (FACS)) | | | Present | Present |
| DAF (CD55(FACS)) | | | Present | Present |

# Pt 6: Verlaagde maar niet afwezige C3 en C5

# normaal C4 and hoog C3d

**Decreased production**

- Genetically determined absent protein

- Liverinsufficiency

**Increased decay or ongoing consumption**

- Gain of function mutation of an activating molecule…

- Loss of function of an inhibitory molecule…

- Ongoing inflammation…Chronic infection, SLE, cryoglobulines, MSC-GN?

- Ongoing loss of an inhibitory molecule…-?

# Pt 6: Verlaagde maar niet afwezige C3 en C5

## normaal C4 and hoog C3d…in 2003…

Suspect for **mesangiocapillary glomerulonephritis**

- Low C3 (high C3d), proteinuria, glomerular erythrocyturia

Refused Renal Biopsy

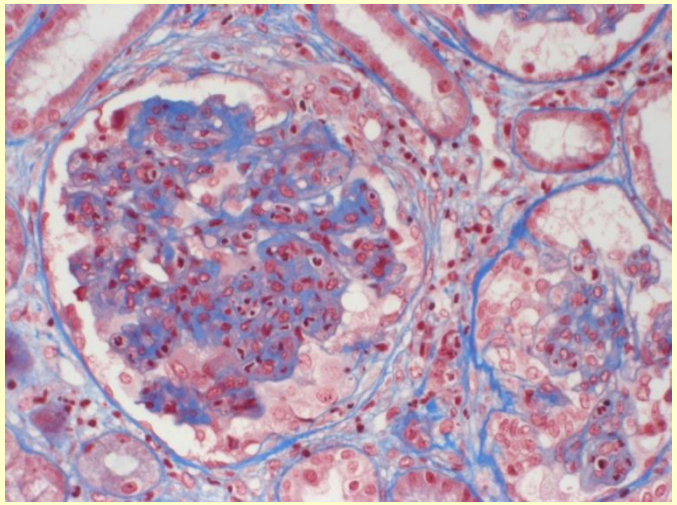
- Start treatment with ACE-inhibition (proteinuria 4.9 → 1.5 g/L)
- Vaccination for Serogroup A,C, W-135 and Y meningococi
- Instruction with respect to possible infections and adequate nephrologic controls
- Controls by nephrologist in local Hospital

# Pt 6:

# …in 2006…

- Serumcreatinin: 100 → 261 µmol/L, **C4 normal, C3 <40 mg/L.**

- Renal biopsy:

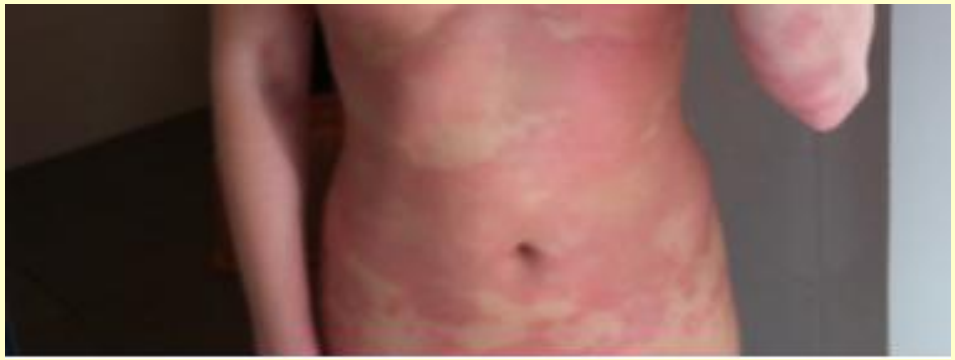


Diagnose: **Mesangiocapillary glomerulonephritis met complementverbruik**

Vermoedelijke oorzaak: **Gain of functie mutatie van Factor B** (p.Lys323Glu)

# Pt 7: 25 jaar

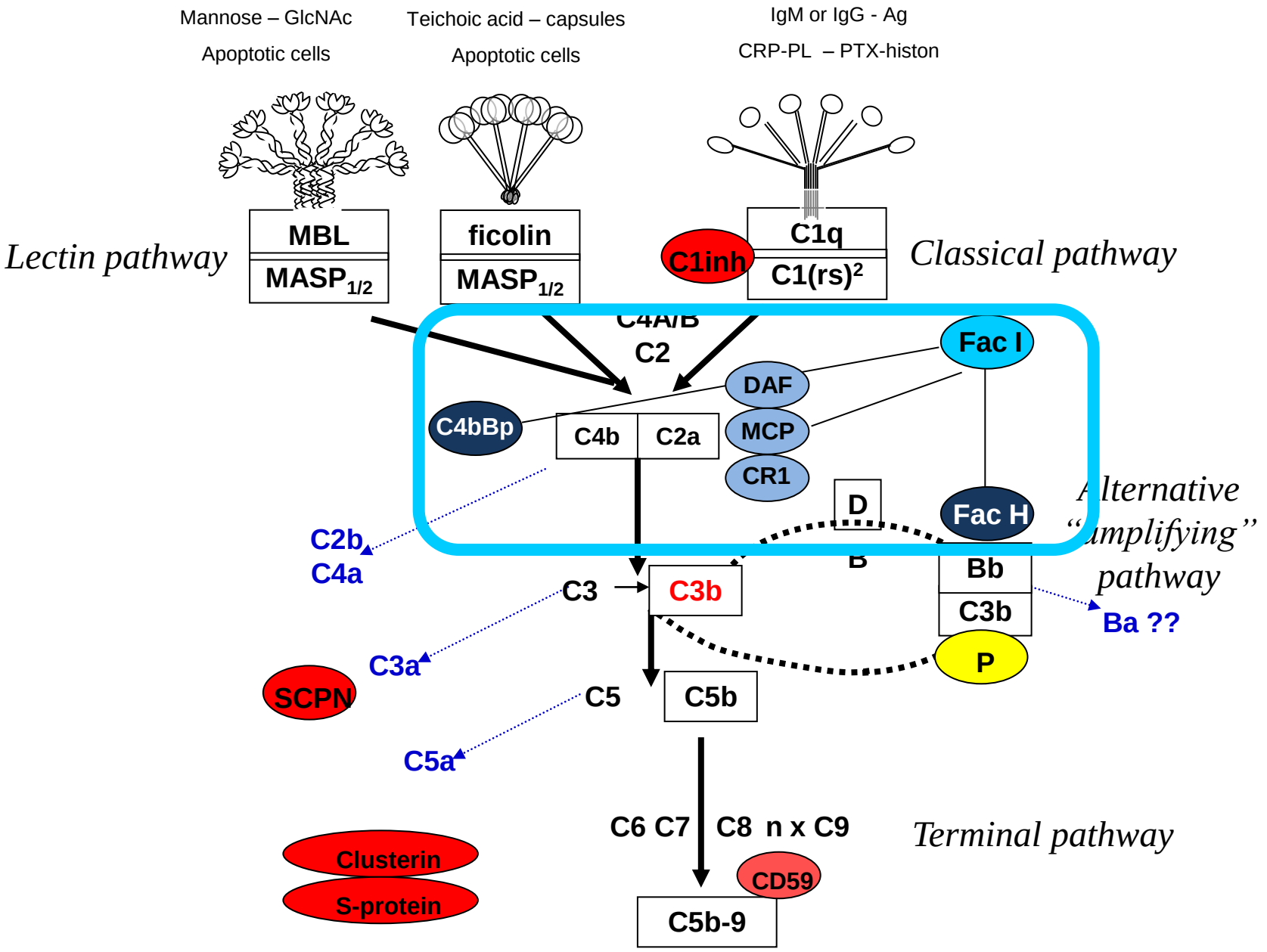
Verwezen door dermatoloog met therapieresistente urticaria



Moeder bekend met HUS, waardoor nier-insufficiënt

# Pt 7: 25 jaar

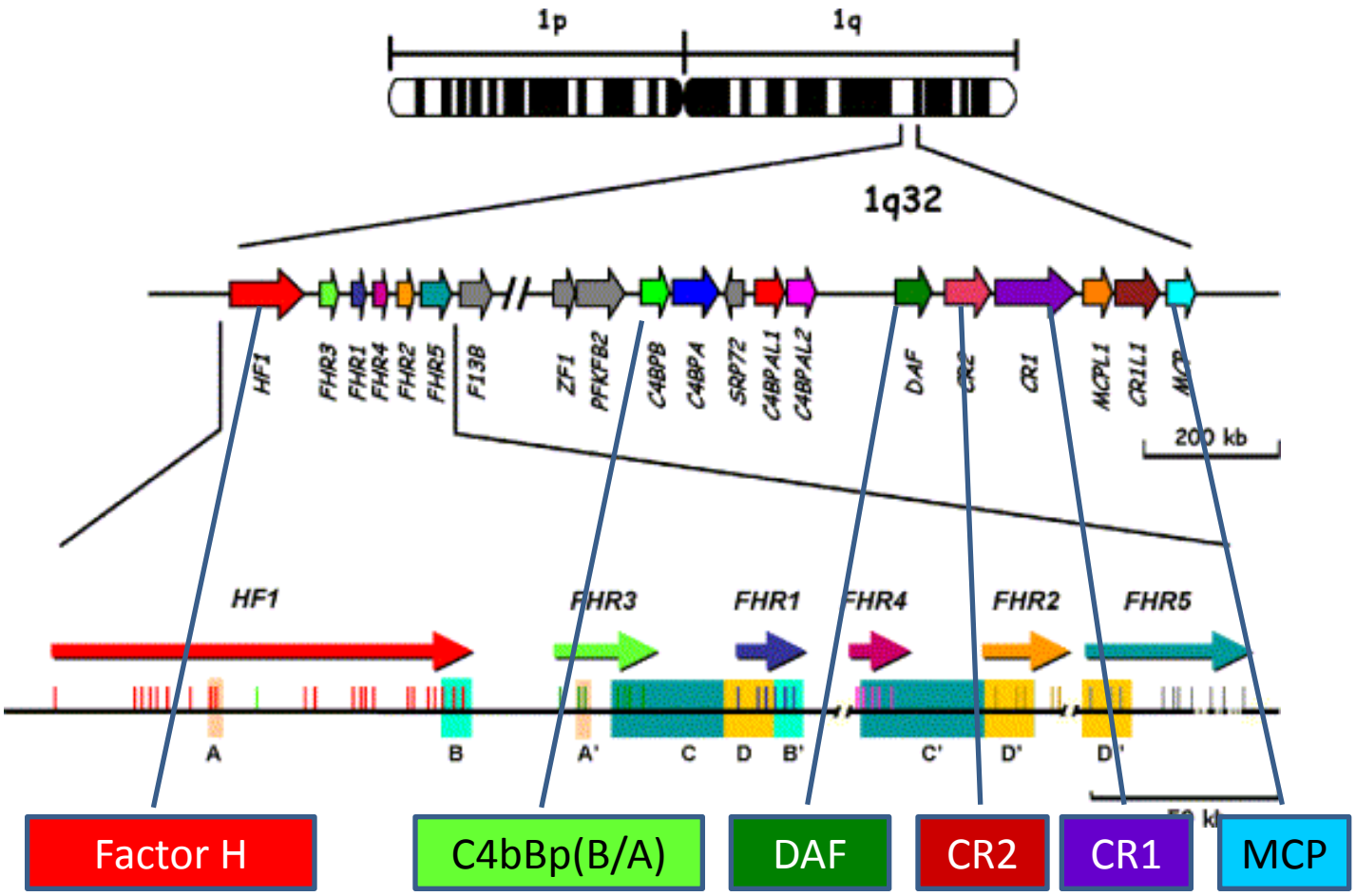
| | April 11, 2001 | Normaal |
|---|---|---|
| C4 (mg/L) | 110 | 100-350 |
| C3 (mg/L) | 776 / 642 | 700-1500 |
| *C3d (%)* | 1.05 | < 3.3% |
| CH50 (%) | **85 /51** | 68-133 |
| AP50 (%) | **47** | 67-128 |
| C1-inh (U/mL) | 1.05 | 0.76-1.33 |


Mannose – GlcNAc
Apoptotic cells
Teichoic acid – capsules
Apoptotic cells
IgM or IgG - Ag
CRP-PL – PTX-histon
Lectin pathway
MBL
MASP1/2
ficolin
MASP1/2
C1inh
C1q
C1(rs)2
Classical pathway
C4A/B
C2
Fac I
DAF
C4bBp
C4b
C2a
MCP
CR1
D
Fac H
Alternative "amplifying" pathway
C2b
C4a
C3
C3b
Bb
C3b
Ba ??
P
C3a
SCPN
C5
C5b
C5a
C6 C7
C8 n x C9
Terminal pathway
Clusterin
S-protein
CD59
C5b-9

NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

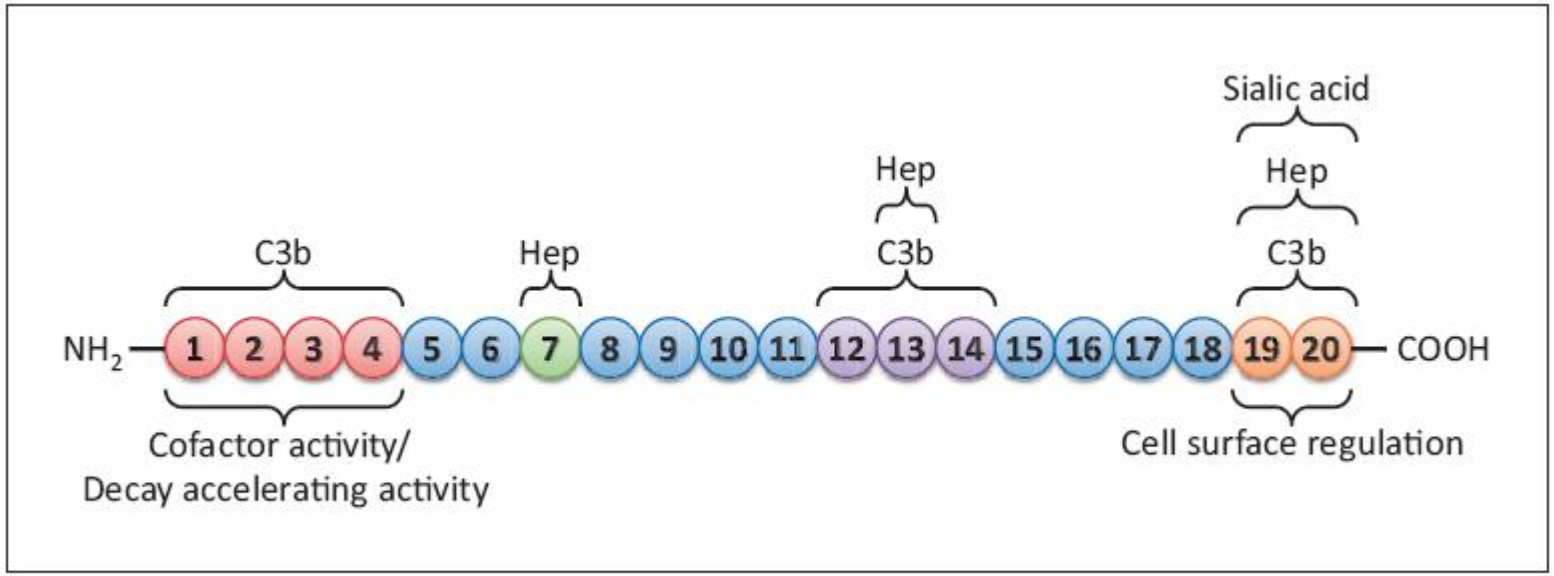
# Regulators of Complement Activation (RCA) gene cluster on Chromosome 1q




Radboudumc

Rodriguez de Córdoba et al. Mol Immunology 2004, 41: 355-67

# Factor H schematically[1)] : "mother" of the RCA family



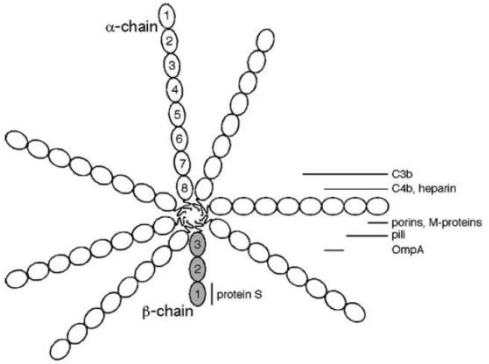

All RCA proteins are polymeres of Complement Control Protein (CCP) domains, or Short Consensus Repeats (SCRs), or sushi domains. They all inhibit C3-convertases either by increasing dissociation of the complex or as a co-factor in the proteolytic degradation of C3b and C4b by Factor I.

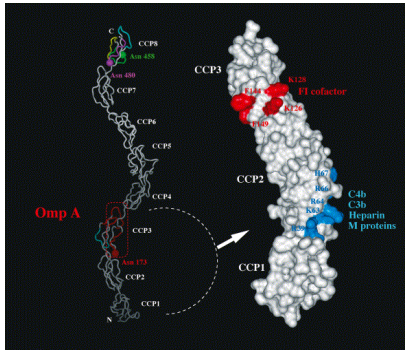
1) In real FH is foulded in a bent-back domain structure, which explains the multiple binding sites for C3b



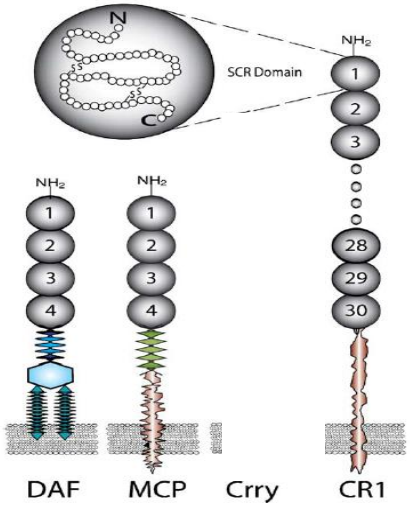
Hirt-Minkowski et al. Nephron Clin Pract 2010, 114:c219-235
1) Aslam and Perkins. J Mol Biol 2001, 309:1117-1138

# Andere leden RCA-familie



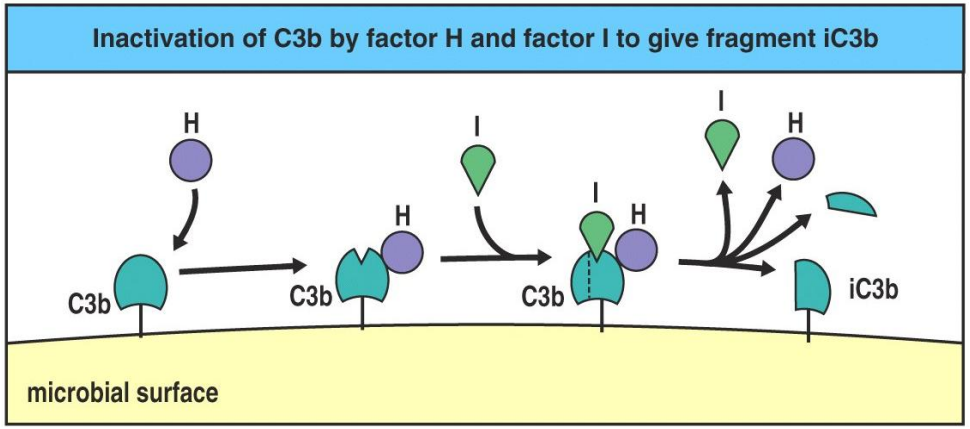



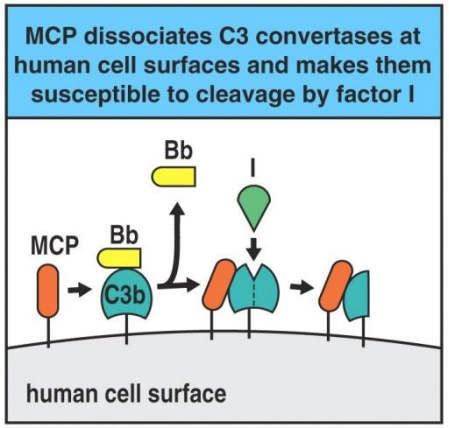

## C4b Binding Protein

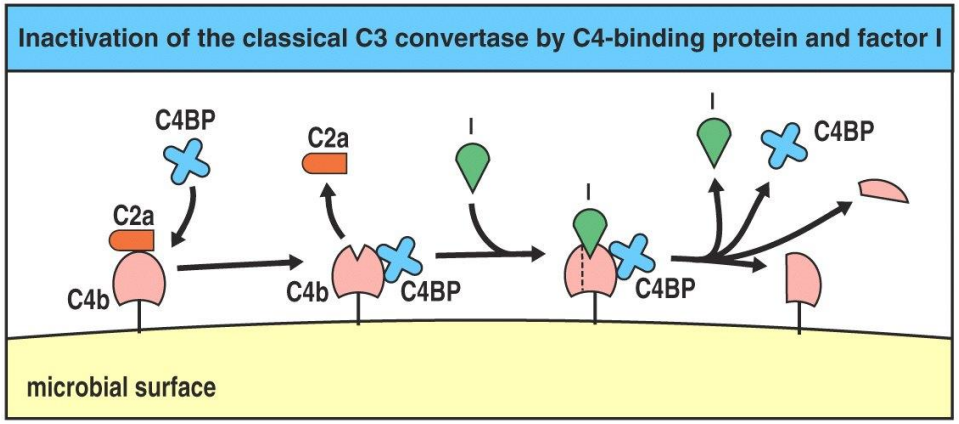


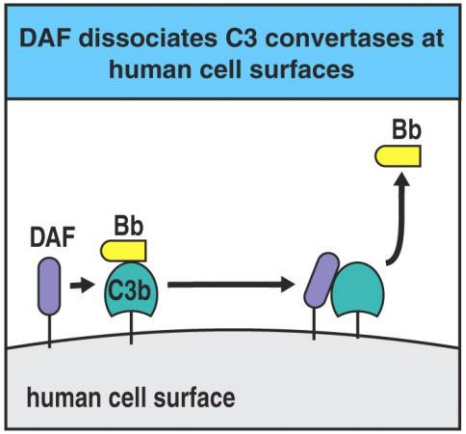

## DAF
## MCP
## CR1

# Remming vorming van, en activiteit van CP- en AP- C3-convertase door FH, C4bBp, MCP, en DAF



# Pt 7: 25 jaar

| | April 11, 2001 | Normaal |
|---|---|---|
| C4 (mg/L) | 110 | 100-350 |
| C3 (mg/L) | 776 / 642 | 700-1500 |
| *C3d (%)* | 1.05 | < 3.3% |
| CH50 (%) | **85 /51** | 68-133 |
| AP50 (%) | **47** | 67-128 |
| C1-inh (U/mL) | 1.05 | 0.76-1.33 |

**Resultaat Factor I-gen analyse: Heterozygotie voor c.454G>A (p.Val152Met) in exon 3 (mogelijk pathogeen)**

# Pt 8:

# …in 2004…

| | |
|---|---|
| 1983 | Coombs positieve anaemie, zwak positeiev ANF, proteïnurie |
| 1996 | Dubieuze cryoglobulinaemie, ANF +, C4 ondetecteerbaar |
| 1997 | ANF +++ |
| 1998 | Type IgGκ paraproteïnaemie |
| 1999 | Ook IgAκ paraproteïnaemie |
| 2004 | Angio-oedeem |

| | 2004 | Normaal |
|---|---|---|
| C1q (iE/mL) | **48** | 81-128 |
| C4 (mg/L) | **< 17** | 100-350 |
| CH50 (%) | **< 15** | 68-133 |
| AP50 (%) | 100 | 67-128 |
| C1-inh (U/mL) | **0.05** | 0.76-1.33 |

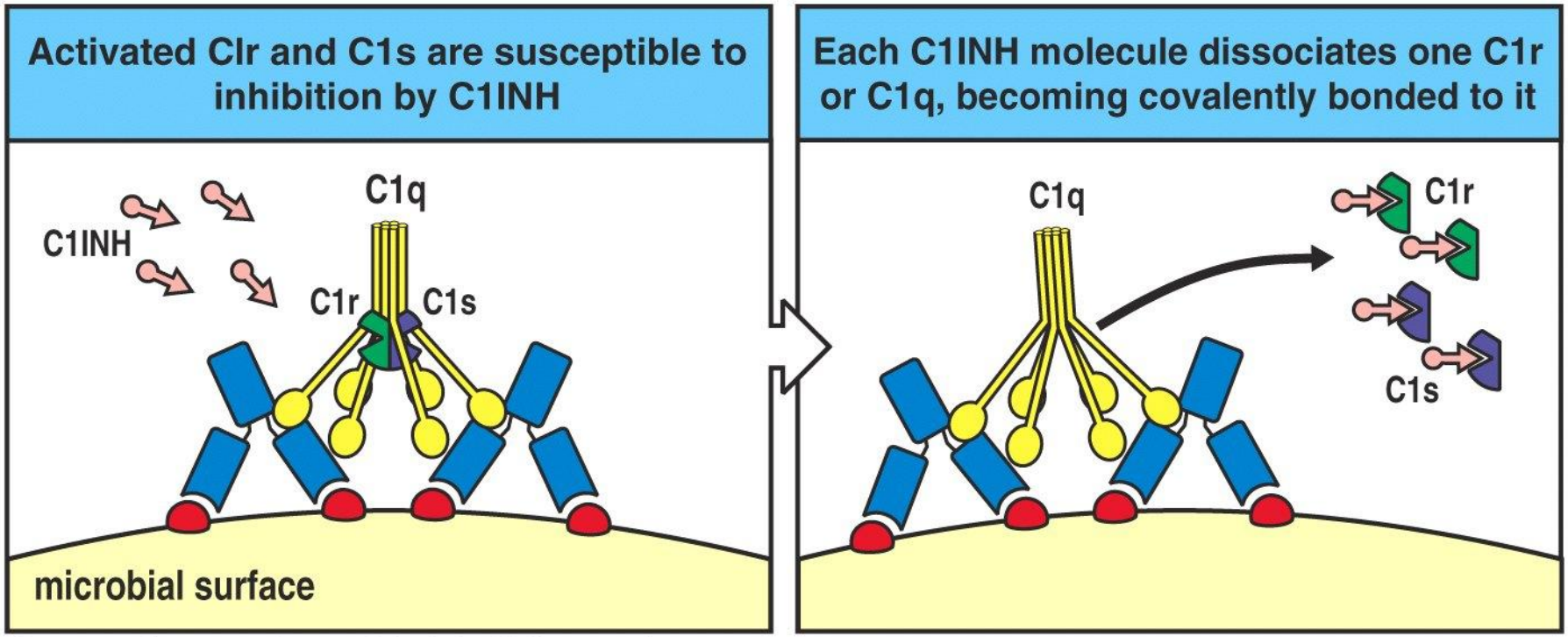



Figure 7-47 The Immune System, 2/e (© Garland Science 2005)

# Pt 8:

# …in 2004…

1983 Coombs positieve anaemie, zwak positeiev ANF, proteïnurie

1996 Dubieuze cryoglobulinaemie, ANF +, C4 ondetecteerbaar

1997 ANF +++

1998 Type IgGκ paraproteïnaemie

1999 Ook IgAκ paraproteïnaemie

2004 Angio-oedeem

| | 2004 | Normaal |
|---|---|---|
| C1q (iE/mL) | **48** | 81-128 |
| C4 (mg/L) | **< 17** | 100-350 |
| CH50 (%) | **< 15** | 68-133 |
| AP50 (%) | 100 | 67-128 |
| C1-inh (U/mL) | **0.05** | 0.76-1.33 |

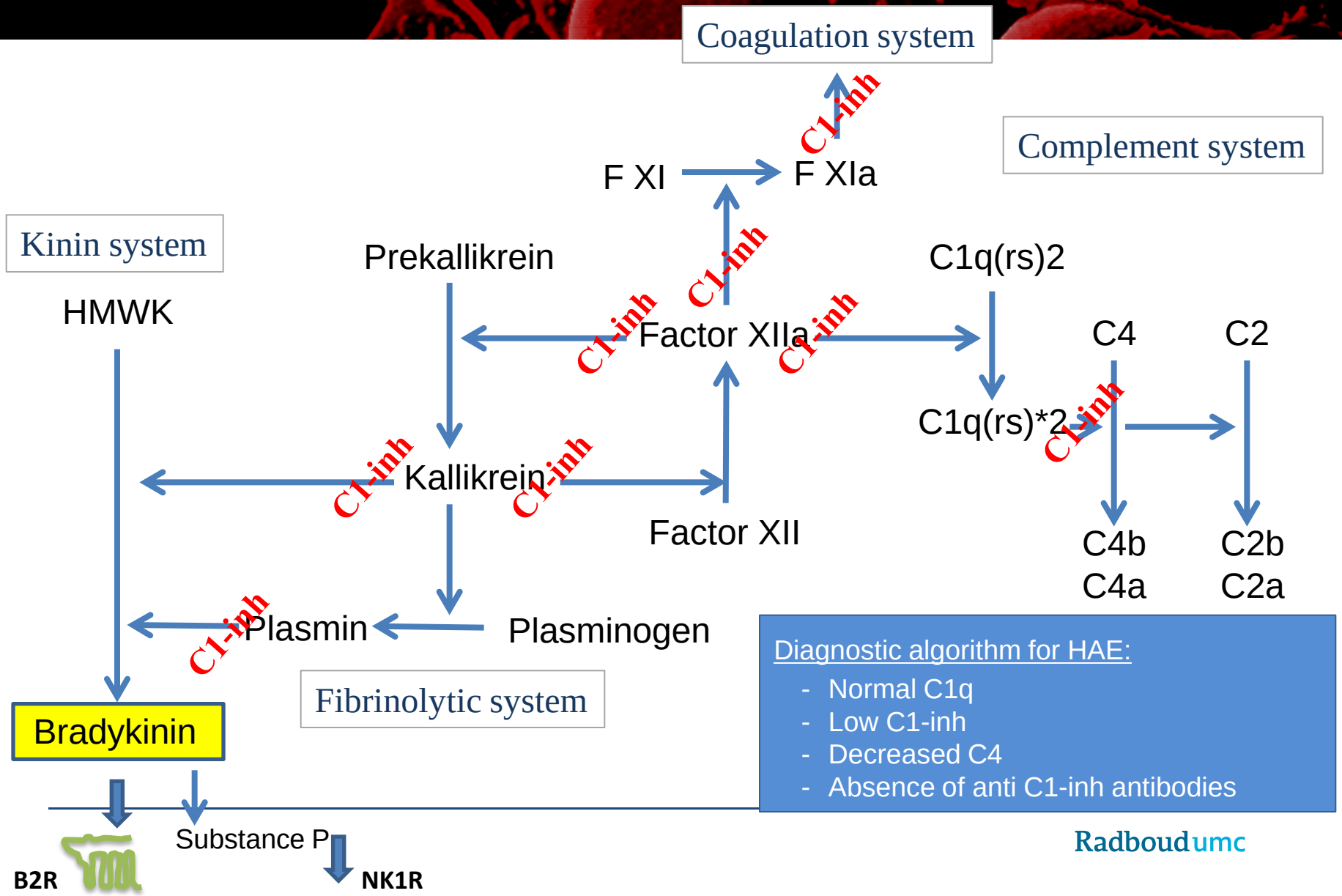
Diagnose: **Laaggradig B-cel lymfoom.**

2005 Rituximab…-> tijdelijk normaliseren complementstatus en verdwijnen angio-oedeem, **maar niet C4**

NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

# Inhibitoire activiteit van C1-inh




Diagnostic algorithm for HAE:

- Normal C1q
- Low C1-inh
- Decreased C4
- Absence of anti C1-inh antibodies

Radboudumc

# Pt 8:
# …in 2004, 2005 en 2014

1983 Coombs positieve anaemie, zwak positeiev ANF, proteïnurie

1996 Dubieuze cryoglobulinaemie, ANF +, C4 ondetecteerbaar

1997 ANF +++

1998 Type IgGκ paraproteïnaemie

1999 Ook IgAκ paraproteïnaemie

| | 2004 | Normaal |
|---|---|---|
| C1q (iE/mL) | **48** | 81-128 |
| C4 (mg/L) | **< 17** | 100-350 |
| CH50 (%) | **< 15** | 68-133 |
| AP50 (%) | 100 | 67-128 |
| C1-inh (U/mL) | **0.05** | 0.76-1.33 |

2004 Angio-oedeem

Diagnose: **Laaggradig B-cel lymfoom.**

2005 Rituximab…-> tijdelijk normaliseren complementstatus en verdwijnen angio-oedeem, **maar niet C4**

NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

# Chromosoom 6

**article**

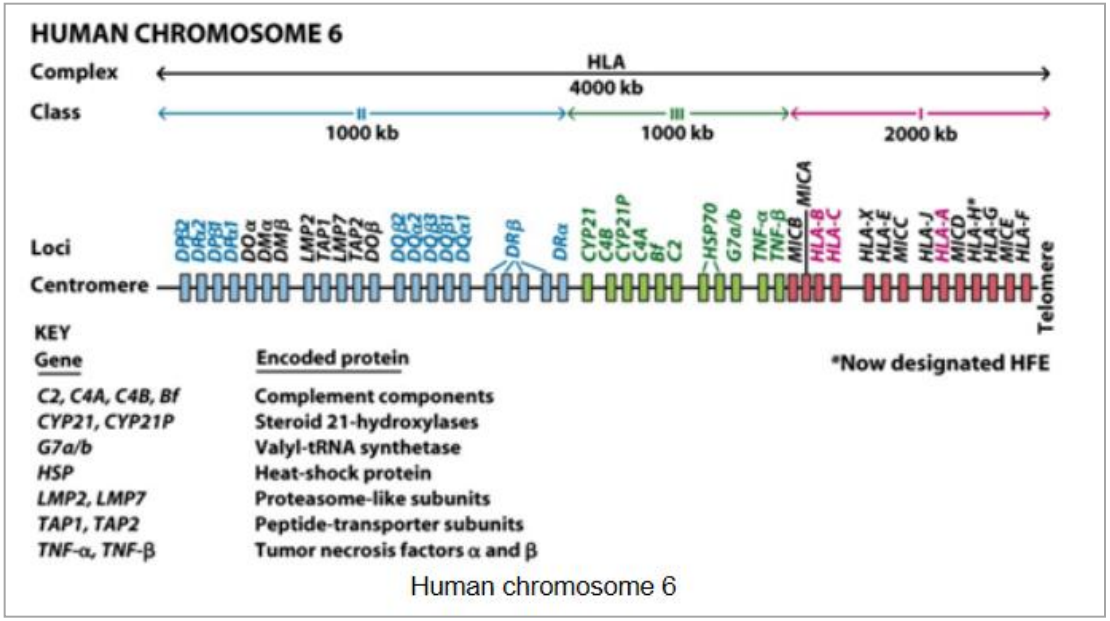
*Nature* **307**, 237 - 241 (19 January 1984); doi:10.1038/307237a0

## A molecular map of the human major histocompatibility complex class III region linking complement genes C4, C2 and factor B

MICHAEL C. CARROLL, R. DUNCAN CAMPBELL, DAVID R. BENTLEY & RODNEY R. PORTER

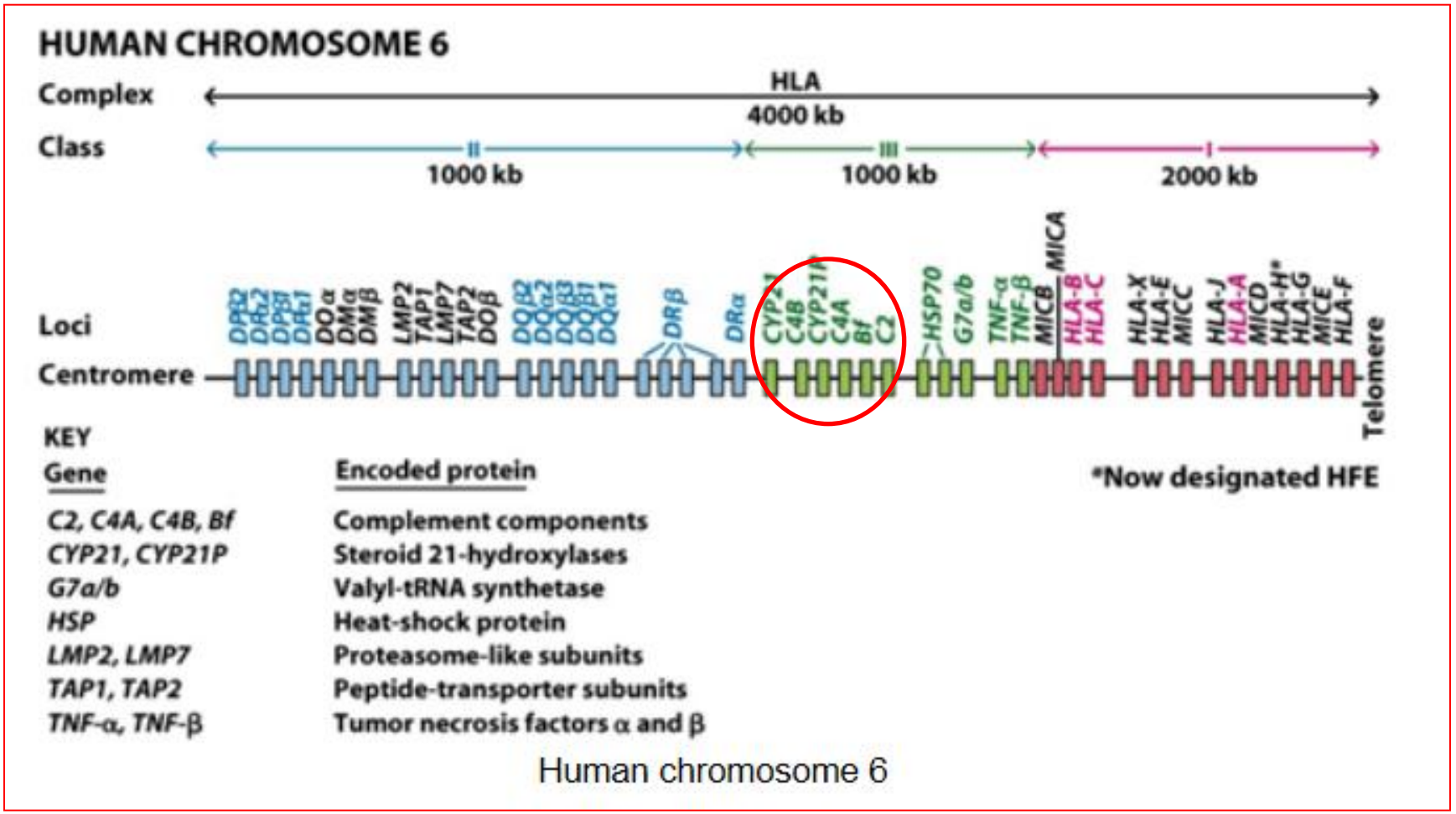
MRC Immunochemistry Unit, Biochemistry Department, Oxford University, South Parks Road, Oxford OX1 3QU, UK

**Four human complement genes, which have previously been mapped between HLA-D and HLA-B on chromosome 6, have now been aligned on a 98-kilobase (kb) section of the chromosome on the basis of four overlapping cosmid clones of genomic DNA. The C2 and factor B genes, less than 2 kb apart, are about 30 kb from two C4 genes separated from each other by about 10 kb.**

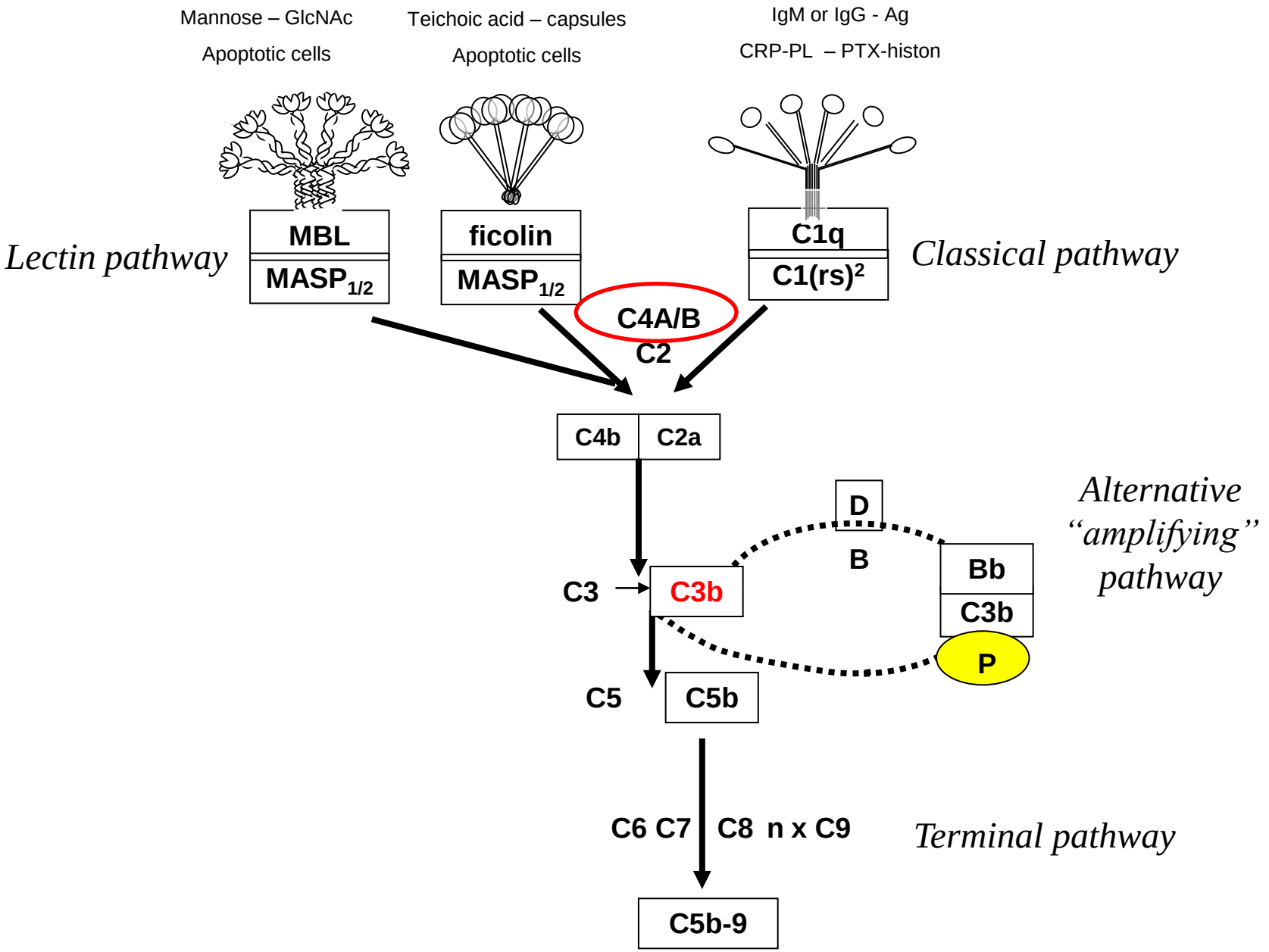



Human chromosome 6

# Er zijn 2 (soms 1, soms 3) *C4*-genen



Human chromosome 6


Mannose – GlcNAc
Apoptotic cells
Teichoic acid – capsules
Apoptotic cells
IgM or IgG - Ag
CRP-PL – PTX-histon
Lectin pathway
MBL
MASP1/2
ficolin
MASP1/2
C1q
C1(rs)2
Classical pathway
C4A/B
C2
C4b
C2a
D
B
Bb
C3b
C3
C3b
P
Alternative
"amplifying"
pathway
C5
C5b
C6 C7
C8 n x C9
Terminal pathway
C5b-9

# C4 bestaat niet; het is C4-null, C4A en/of C4B

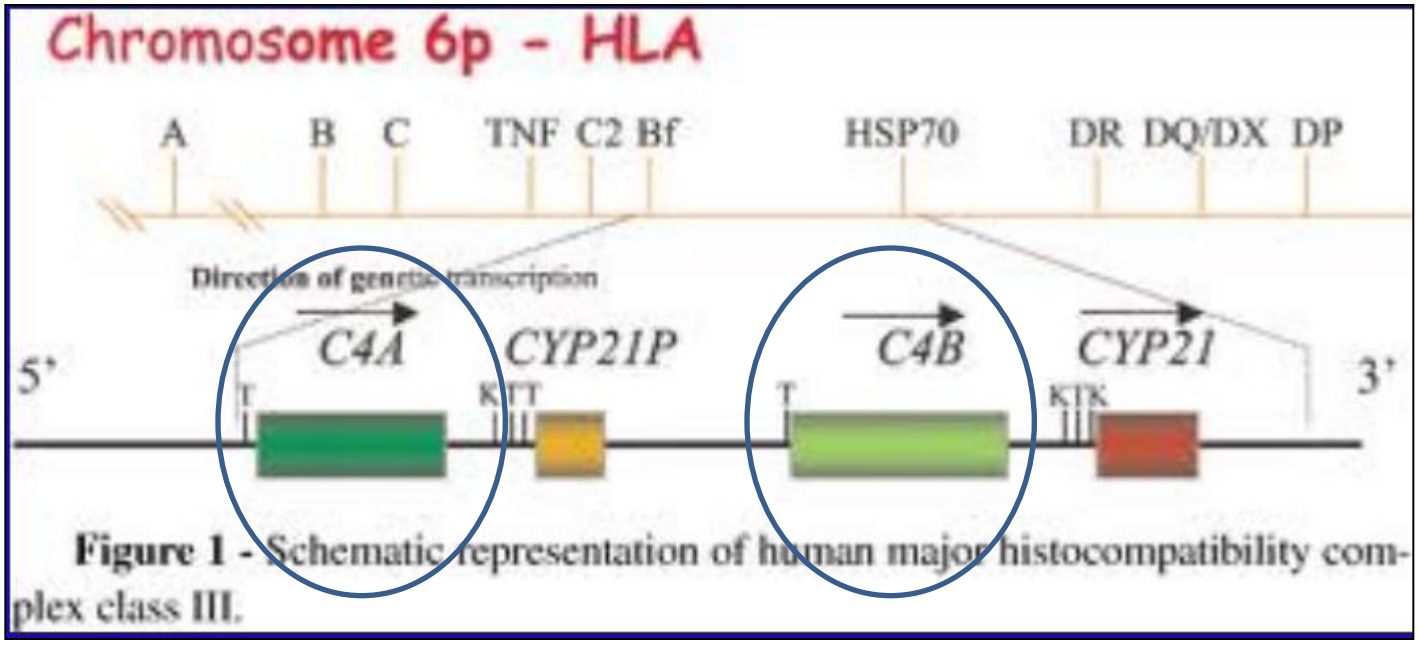
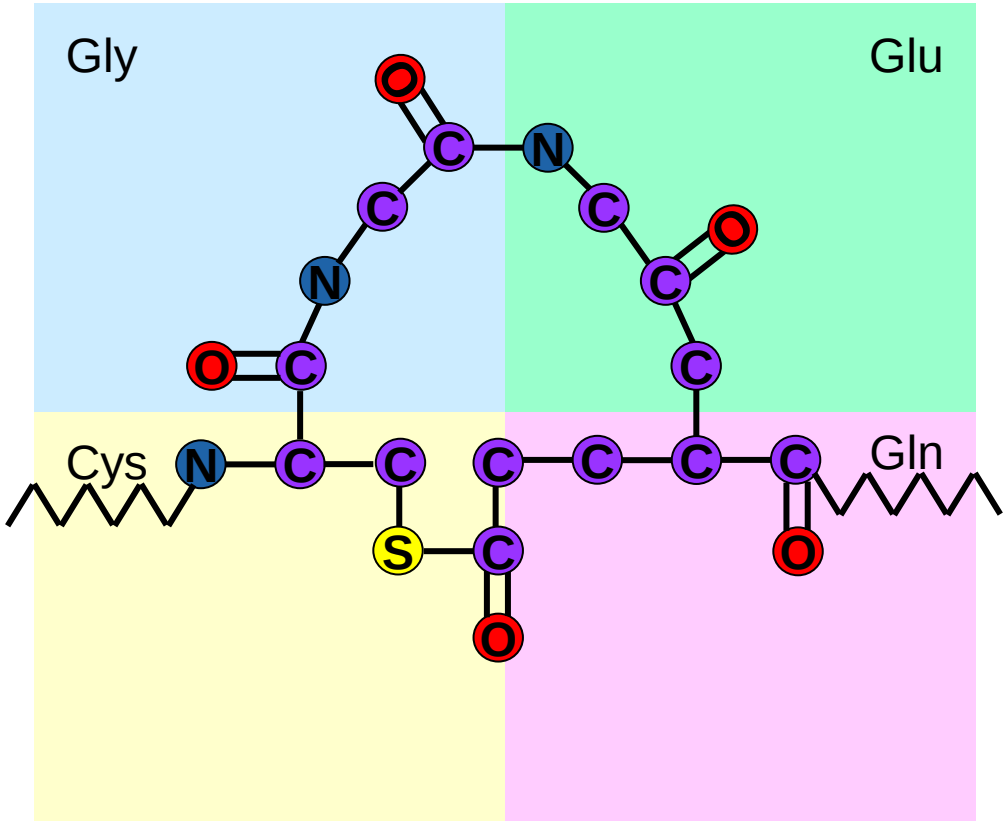



**Figure 1** - Schematic representation of human major histocompatibility complex class III.

**C4A en C4B zijn op ery's herkenbaar als Chido/Rodgers bloedgroep**

# C4 with exposed thio-ester bond



# Pt 8:

# …in 2004, 2005 en 2014…

1983 Coombs positieve anaemie, zwak positeiev ANF, proteïnurie

1996 Dubieuze cryoglobulinaemie, ANF +, **C4 ondetecteerbaar!!!**

1997 ANF +++

1998 Type IgGκ paraproteïnaemie

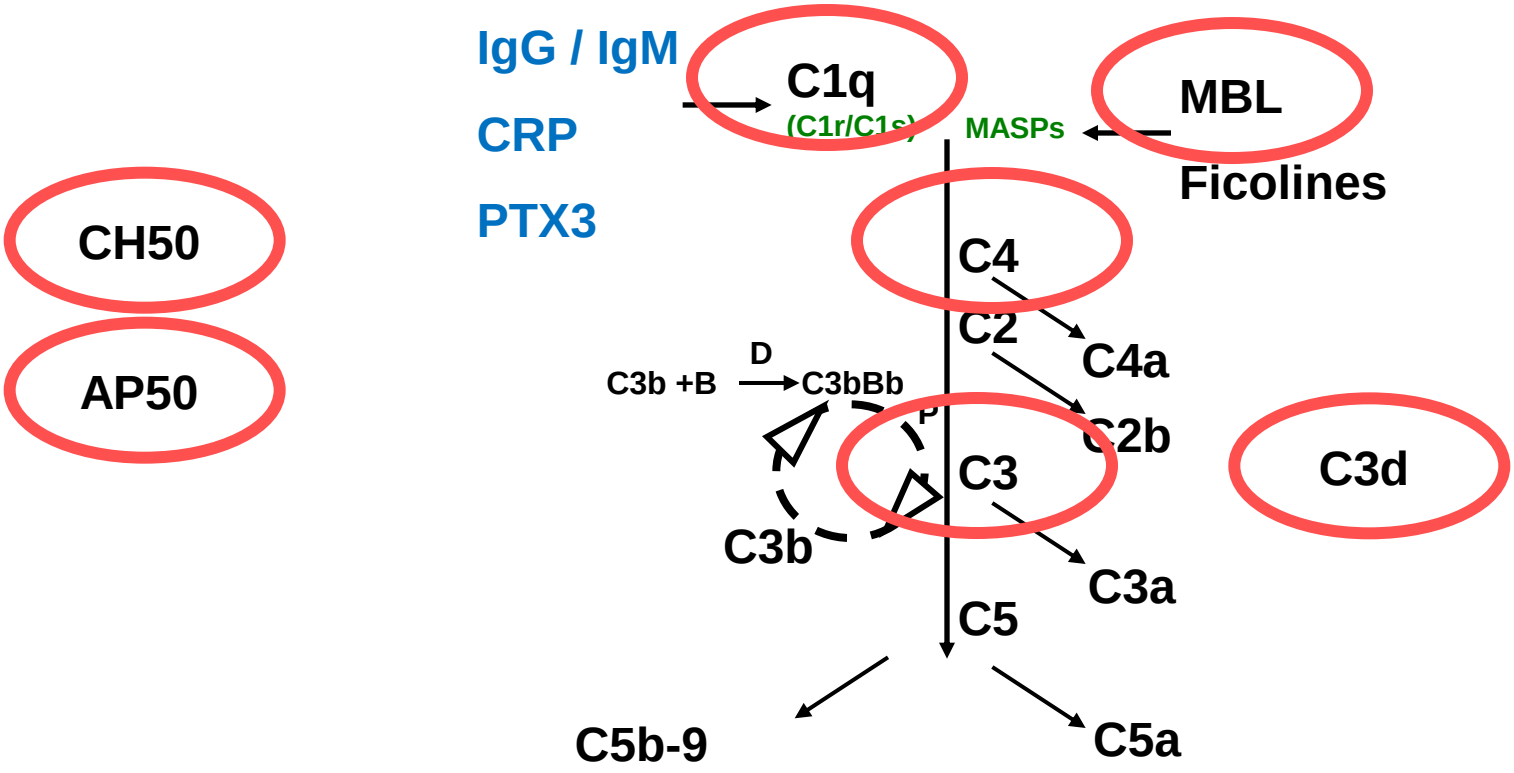
1999 Ook IgAκ paraproteïnaemie

2004 Angio-oedeem

| | 2004 | Normaal |
|---|---|---|
| C1q (iE/mL) | **48** | 81-128 |
| C4 (mg/L) | **< 17** | 100-350 |
| CH50 (%) | **< 15** | 68-133 |
| AP50 (%) | 100 | 67-128 |
| C1-inh (U/mL) | **0.05** | 0.76-1.33 |

2014 **Nog steeds is onbekend of pte C4-null is of dat C4 laag is door activatie….**

# Welke complementmetingen zijn er voor de kliniek beschikbaar



NCIA

Nijmegen Centrum voor Immuundeficiëntie en Autoinflammatie

# Wat missen we bij complement metingen in de kliniek

**Ficoline-assay**

**C4A- en C4B-assays cq gen-bepaling**

**Maat voor alternatieve route overactivatie (C3bBbP)**

**Soluble-TCC**

**C5a (C3a, C4a, C2a)**

**Maat voor activatie van kallikreïne cq bradykinine-vorming**