Complement is part of innate immunity 2014

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and

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DBM

basel

Immune system

=

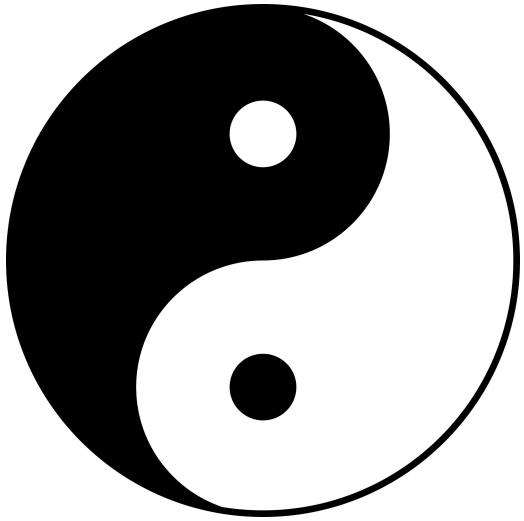
Fitness

Immune system

=

Fitness

=



Inflammation tailored to the needs

Immune system

=

Control system to remove unnecessary / danger elements in the organism

-> internal factors, waste: debris, necrosis, apoptosis (10^{11} neutrophils/day)

-> external factors: foreign body, infectious organisms (not all: e.g. gut microbiome),

Immune system

=

Best inflammatory level :

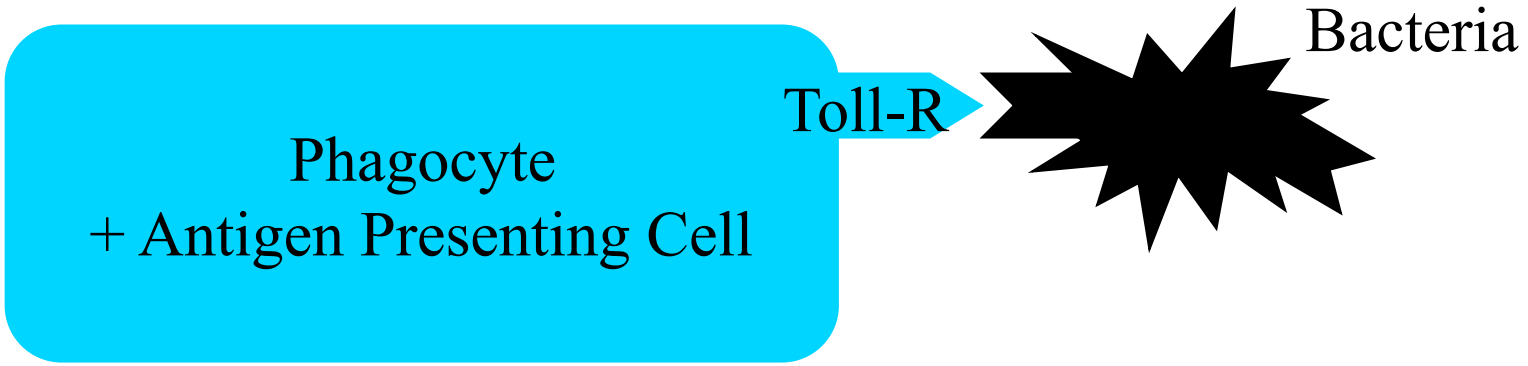
In a non sterile environment ->
be ready to react rapidly (must remain awake)

Signals?

- **internal (low grade autoreactivity against specific patterns (waste)?)**
- **external**

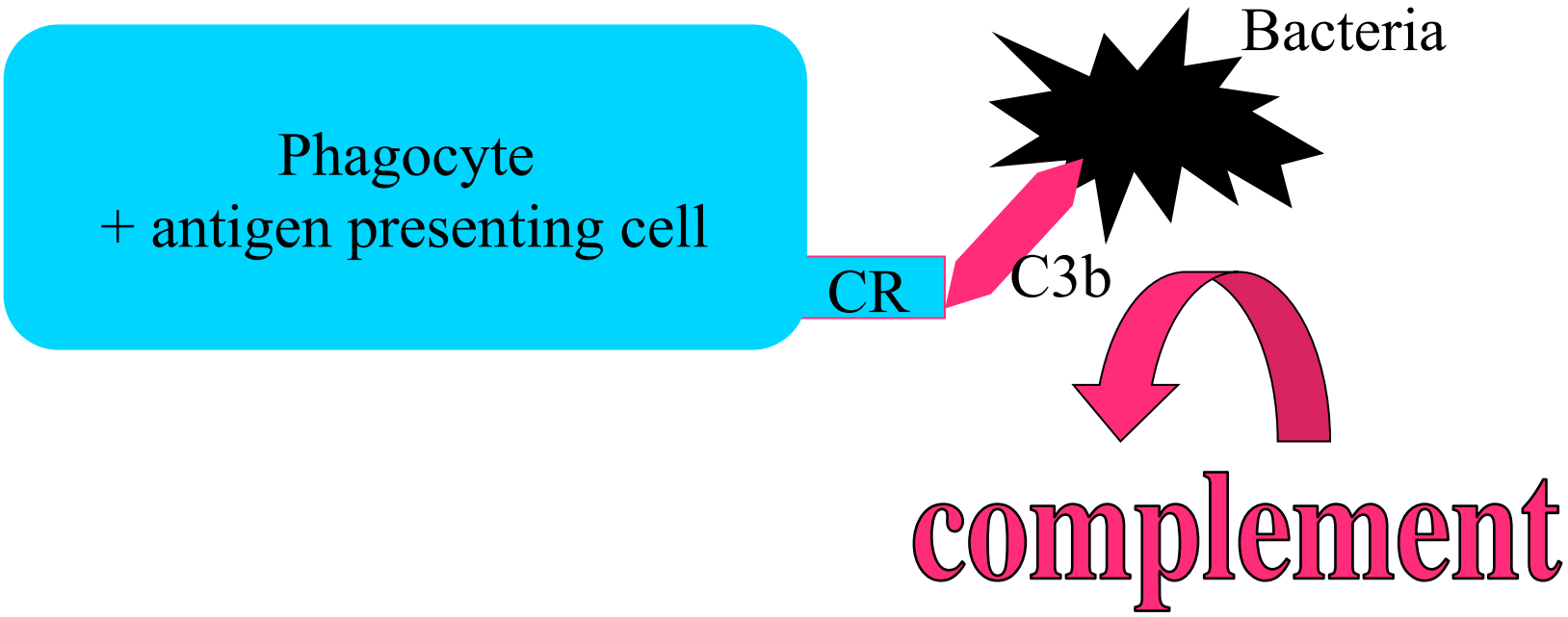
Innate immun system

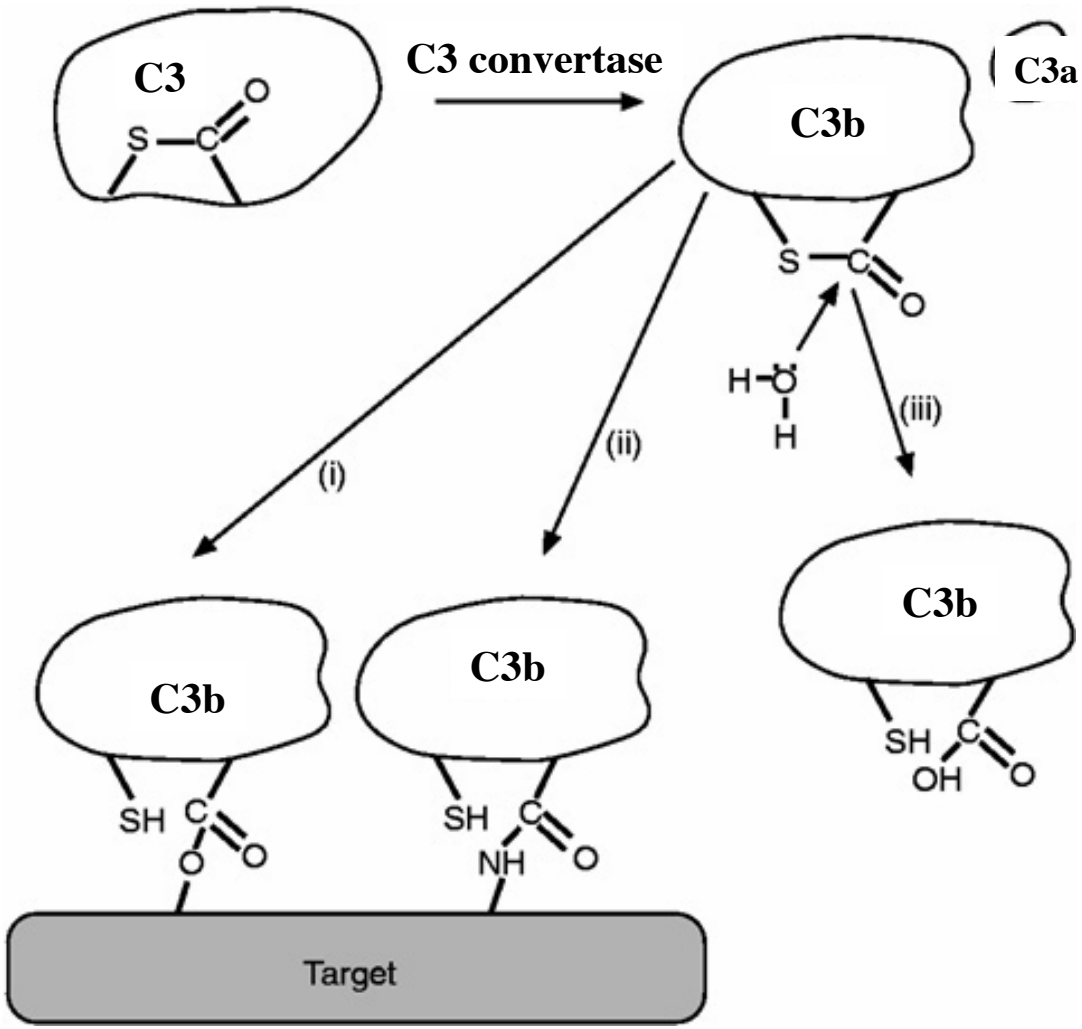
Pattern recognition : Toll-like receptors on <u>cells</u>



Innate immun system

Pattern recognition in the <u>fluid phase</u>:
Complement and complement receptors (CR)

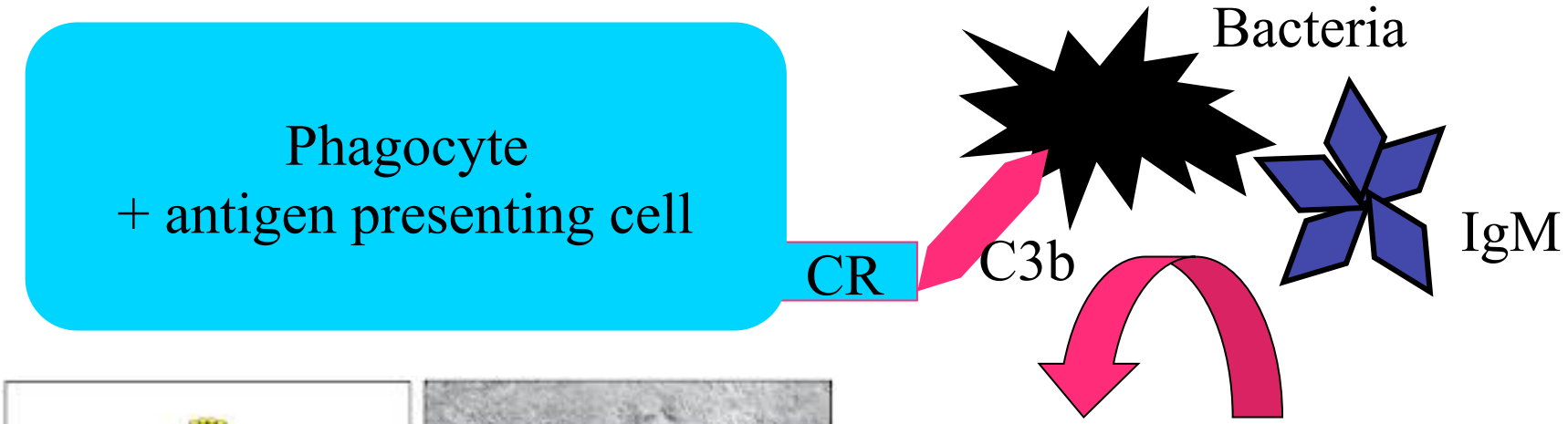


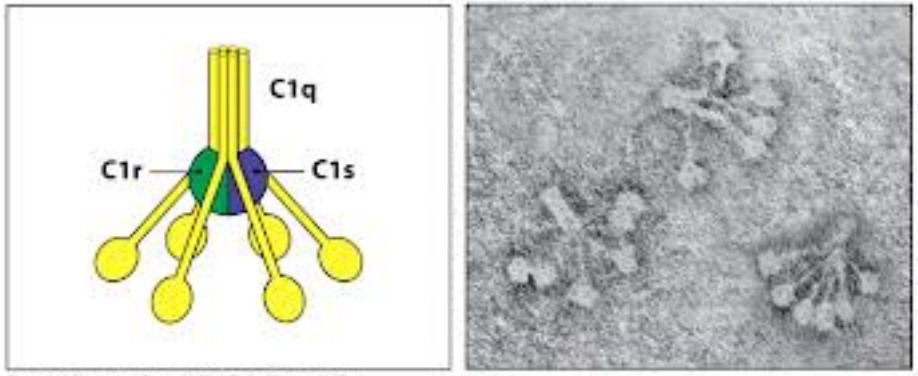


The activation of C4, and covalent binding of C3b. C3 contains an internal thiolester which becomes exposed on cleaveage of C3 by activated C4bC2a or C3bBb. The exposed thiolester may react with OH or NH_2 groups on the surface of the complement activator ((i) and (ii)) or may simply react with water (iii).

Innate immun system

Pattern recognition : Natural IgM Ab + Complement and complement receptors (CR)



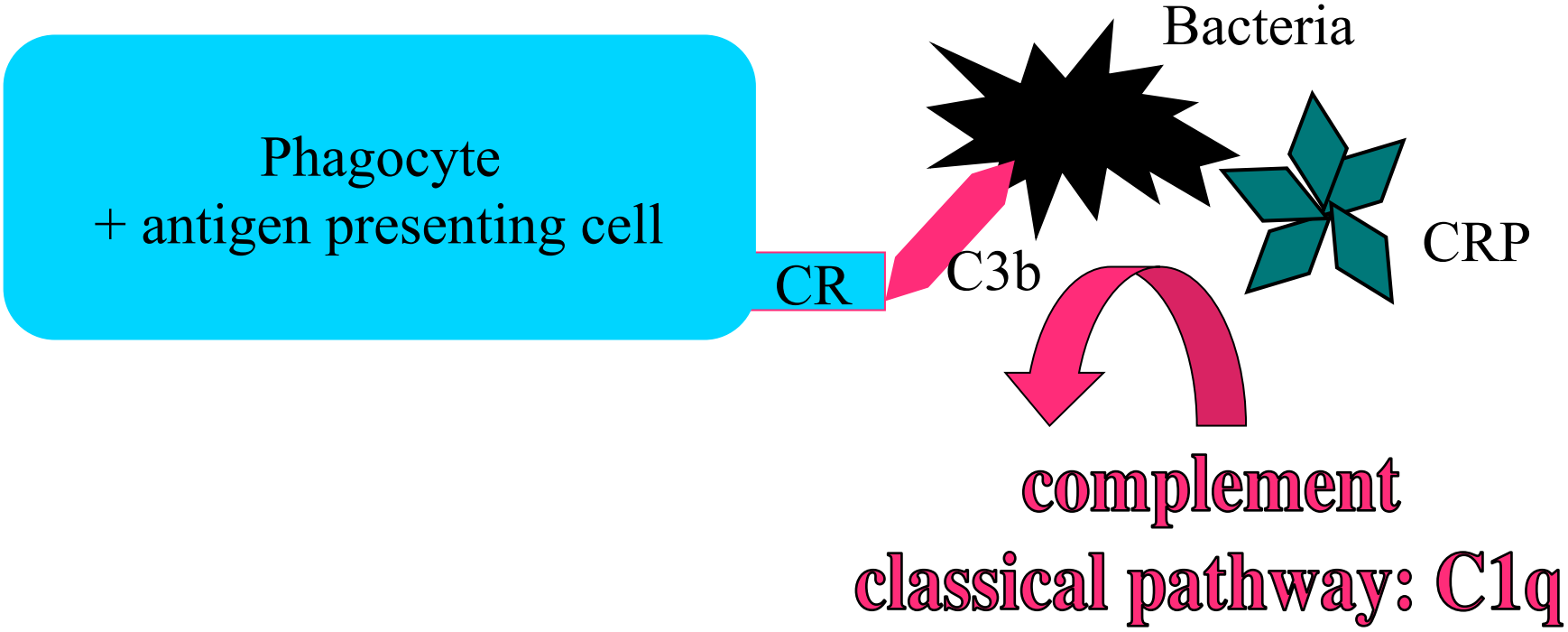


complement

classical pathway: C1q

Innate immun system

Pattern recognition : pentraxine C-reactive protein (CRP) + Complement and complement receptors (CR)

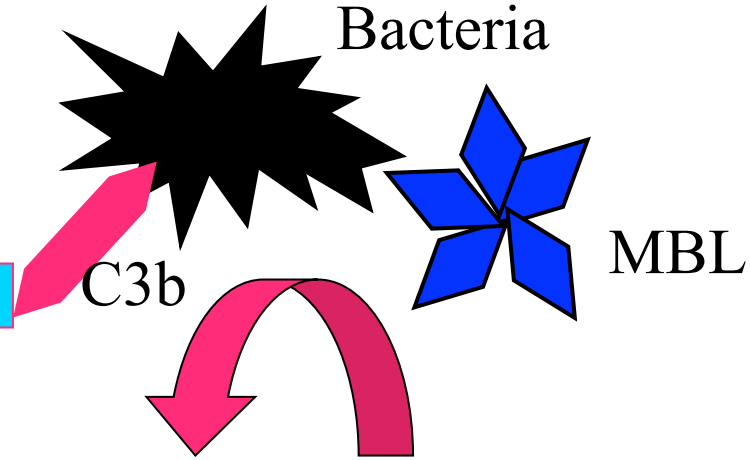


Innate immun system

Pattern recognition : Mannan binding lectin (MBL) + Complement

Phagocyte
+ antigen presenting cell

CR



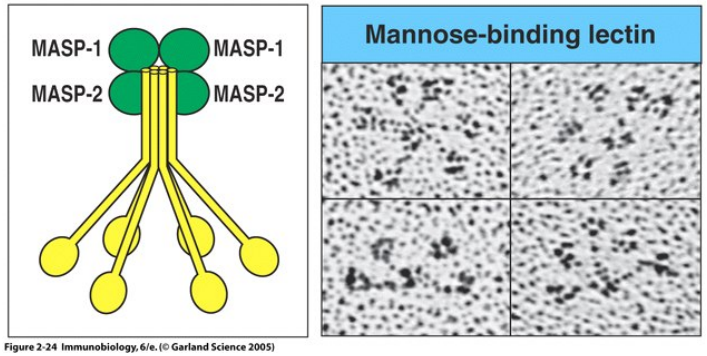
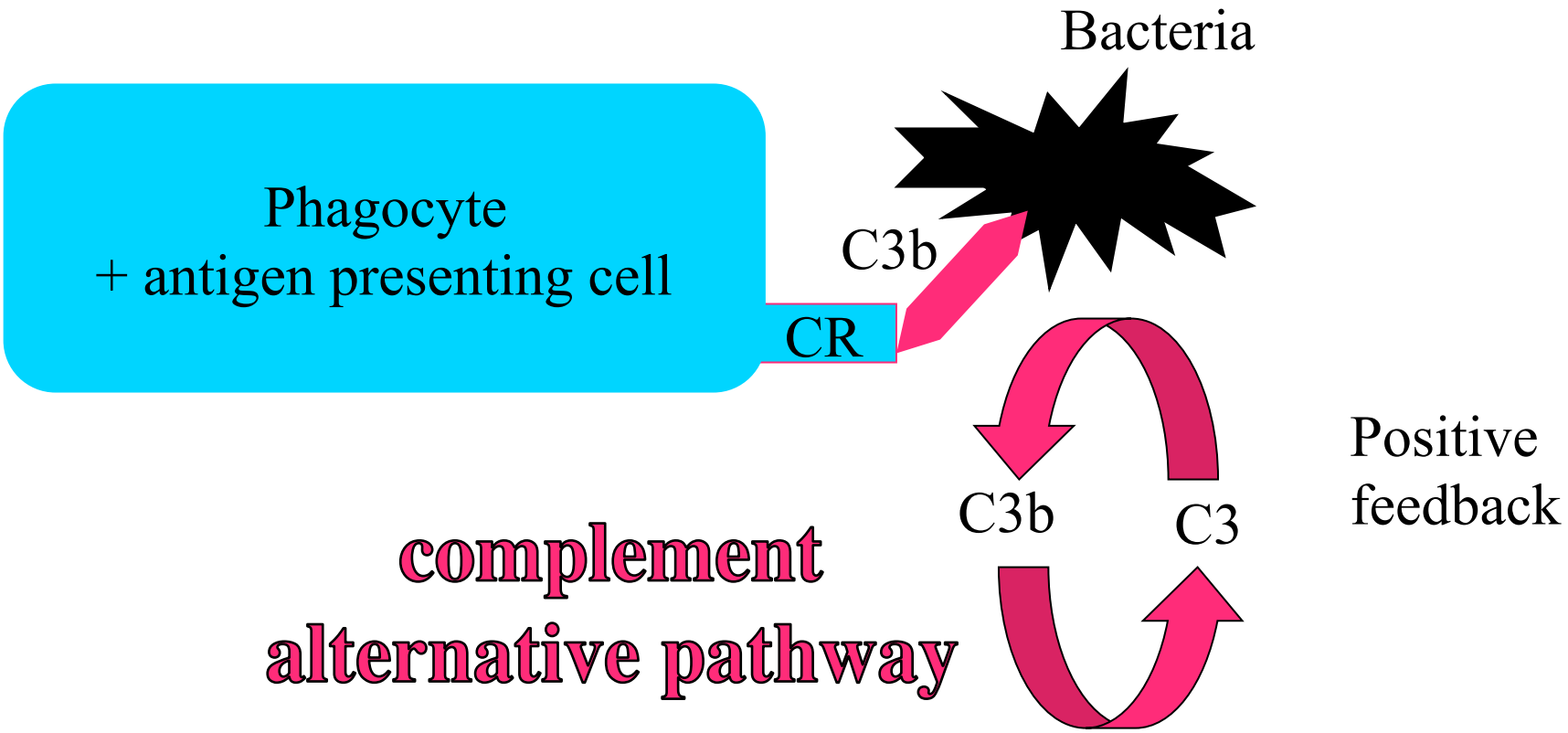


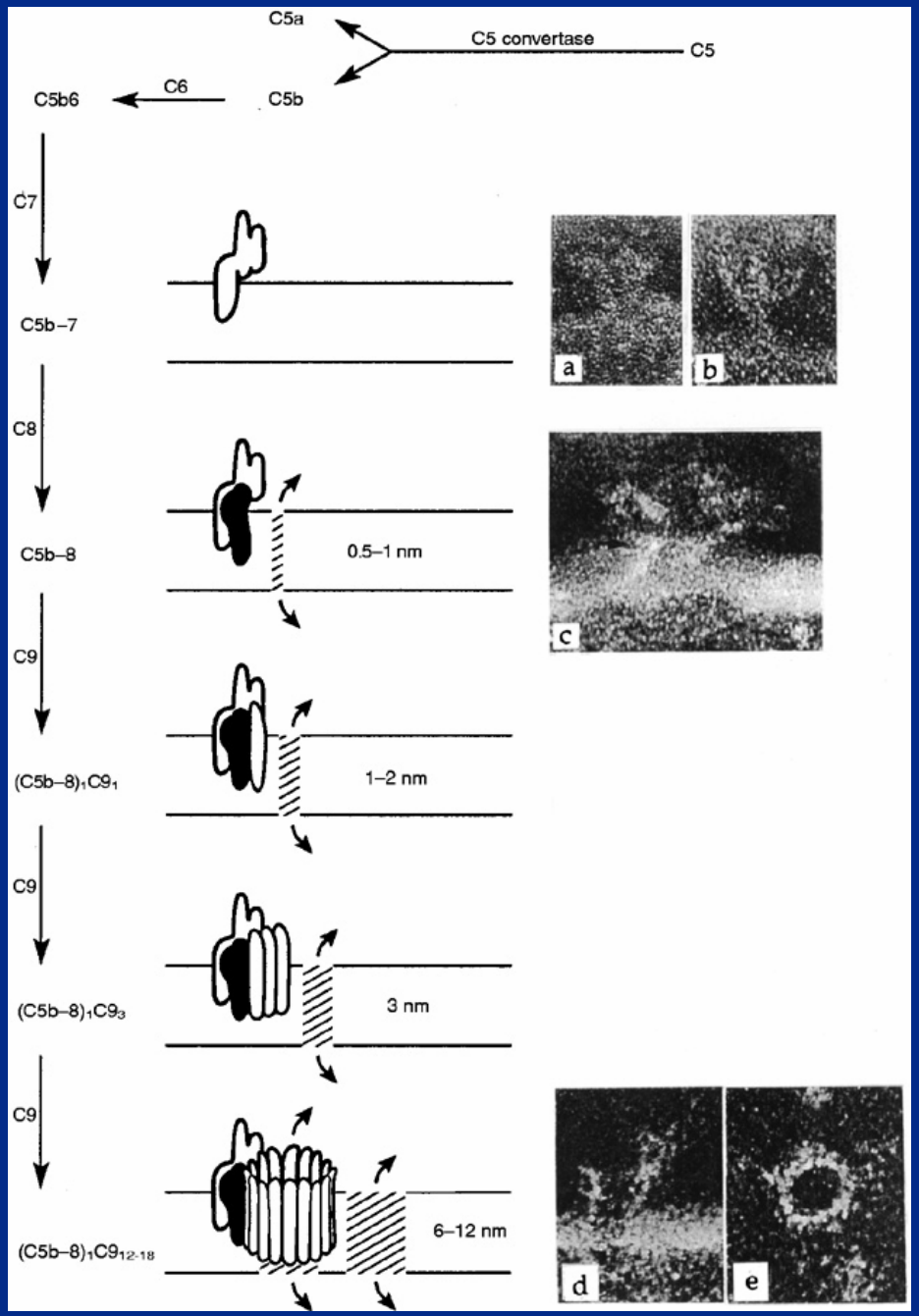
Figure 2-24 Immunobiology, 6/e. (© Garland Science 2005)

complement
MBL pathway

Innate immun system

Activation of complement by lack of inhibition of the alternative pathway

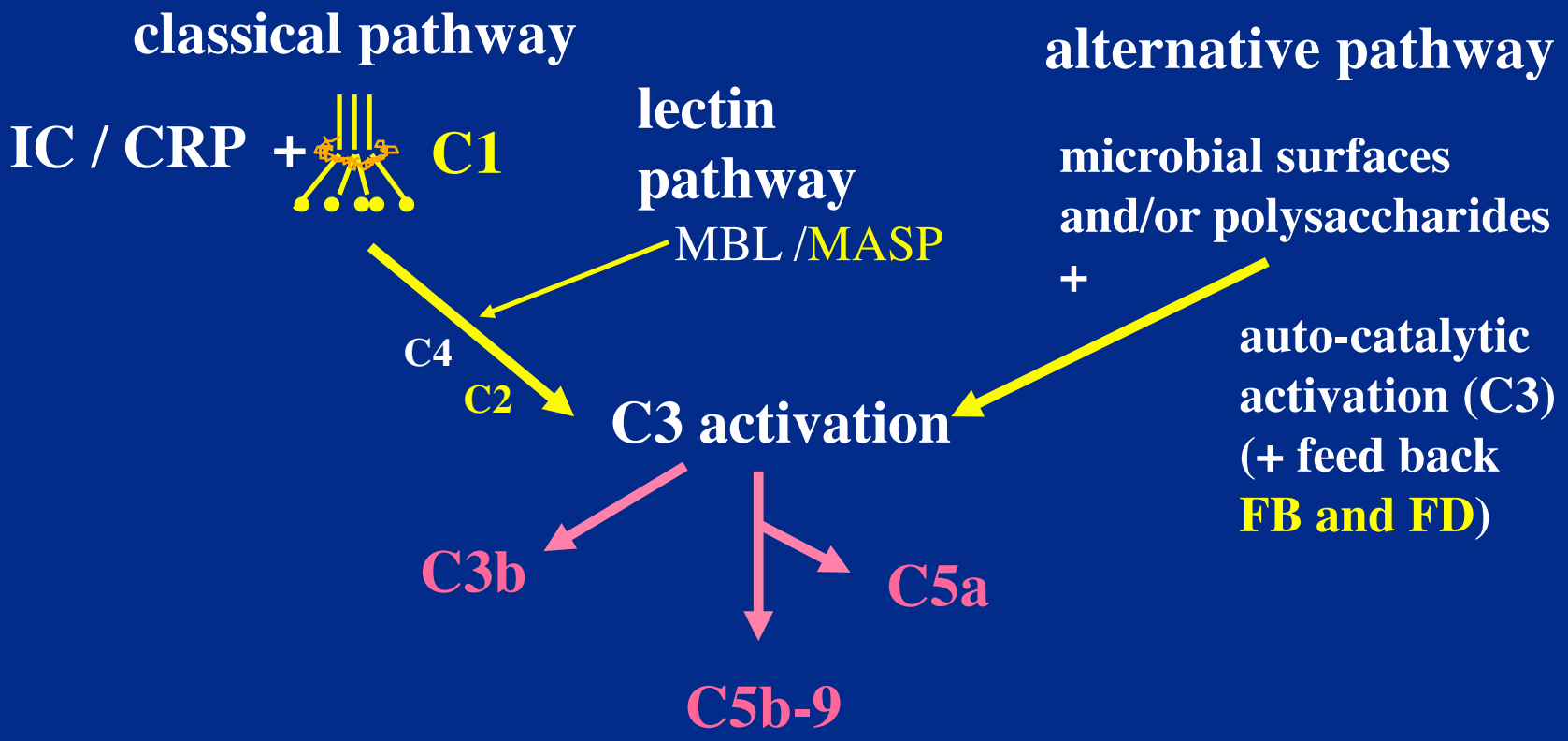




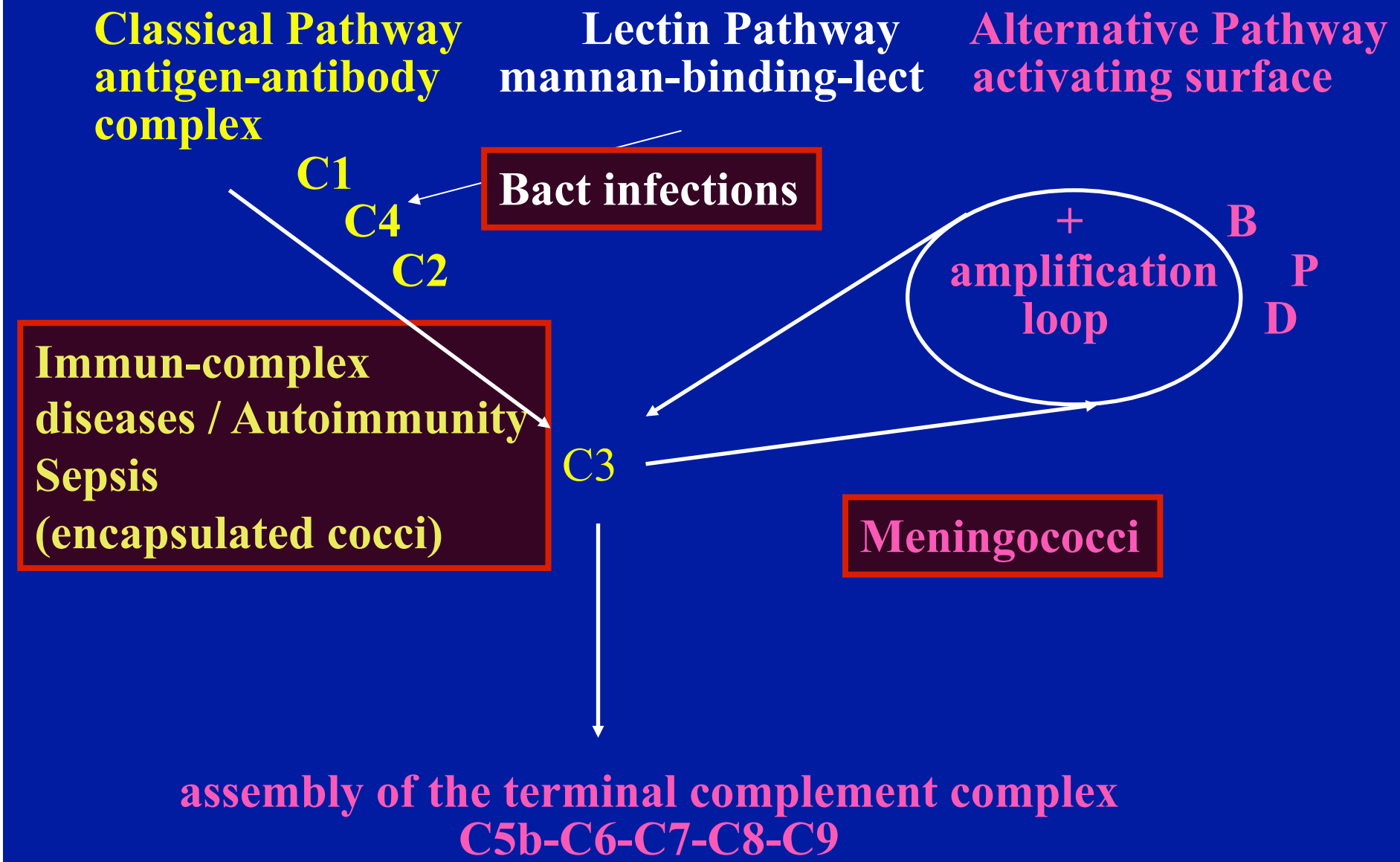
C5a release

formation of the membrane attack complex C5b-C9

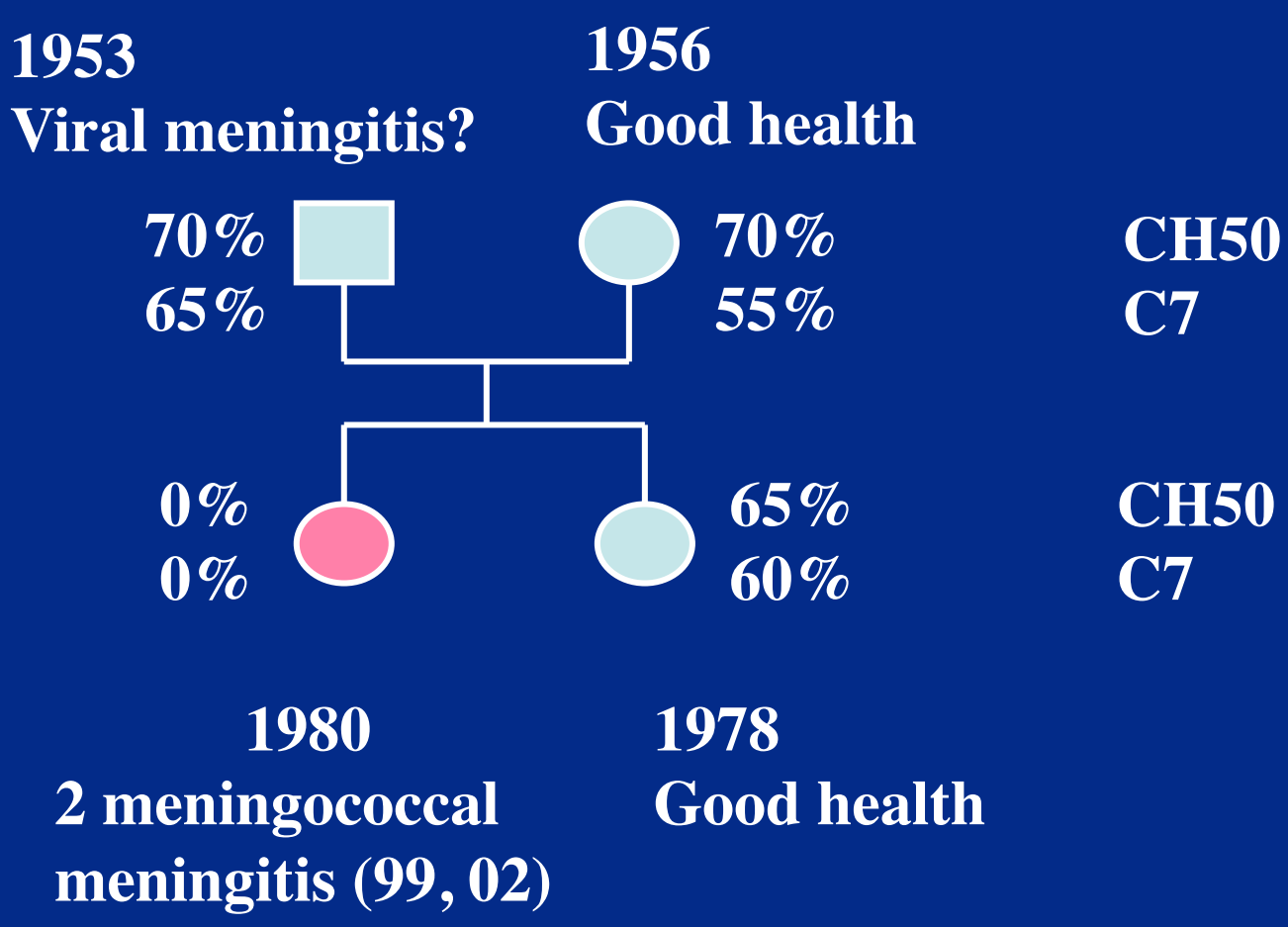
Complement activation cascade

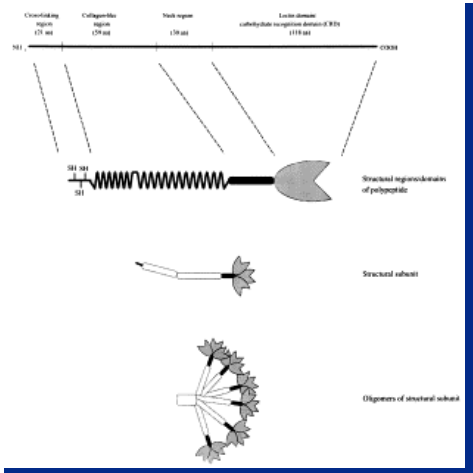


Complement deficiencies



Family Z.


1953
Viral meningitis?
1956
Good health
70%
65%
70%
55%
CH50
C7
0%
0%
65%
60%
CH50
C7
1980
2 meningococcal meningitis (99, 02)
1978
Good health



MBL (L-Ficolin, H-Ficolin) –
associates with MASP2 -->
Cleavage of C4 and C2
(enzymatic activity of MASP2 =C1s)

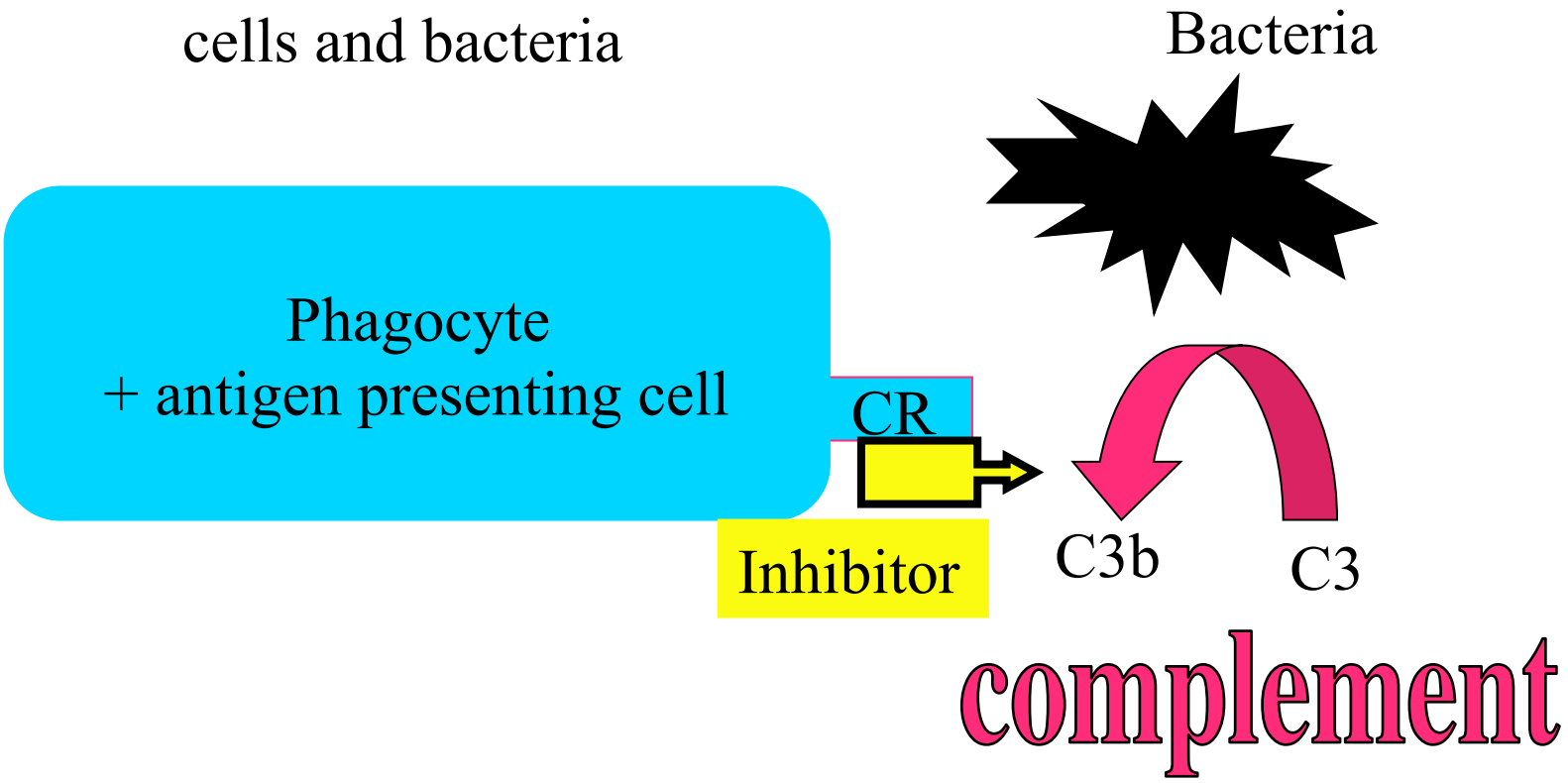
MBL deficiency (partial: 5% of the population!)

- bacterial (pneumoccocal) infections in infants + children
- and even in adults:
meningoccocal infections (1/3 of the cases)
more infections after chemotherapy

Inherited deficiency of MASP 2 -> pneumoccocal infection *NEJM 2003, 349:554*
Inherited deficiency of Ficolin-3 -> bacterial infections *NEJM 2009, 360:2637*

Innate immun system

Blockade of complement
by specific inhibitors expressed by
cells and bacteria



Membrane and fluid phase control proteins in humans

C1inh: ***Angioedema***

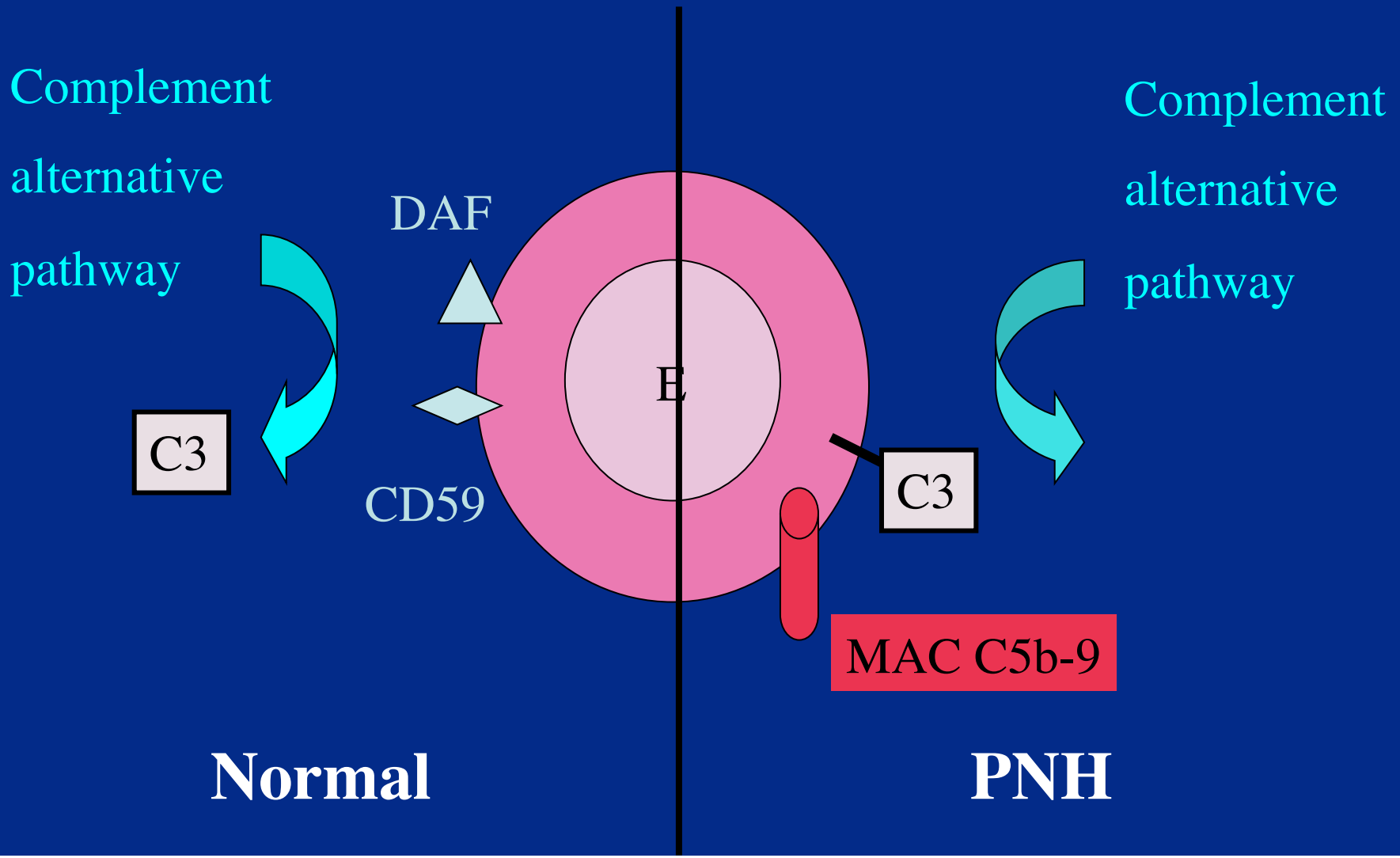
MCP/CD46
CR1/CD35
DAF/CD55
(Factor H?)
CD59

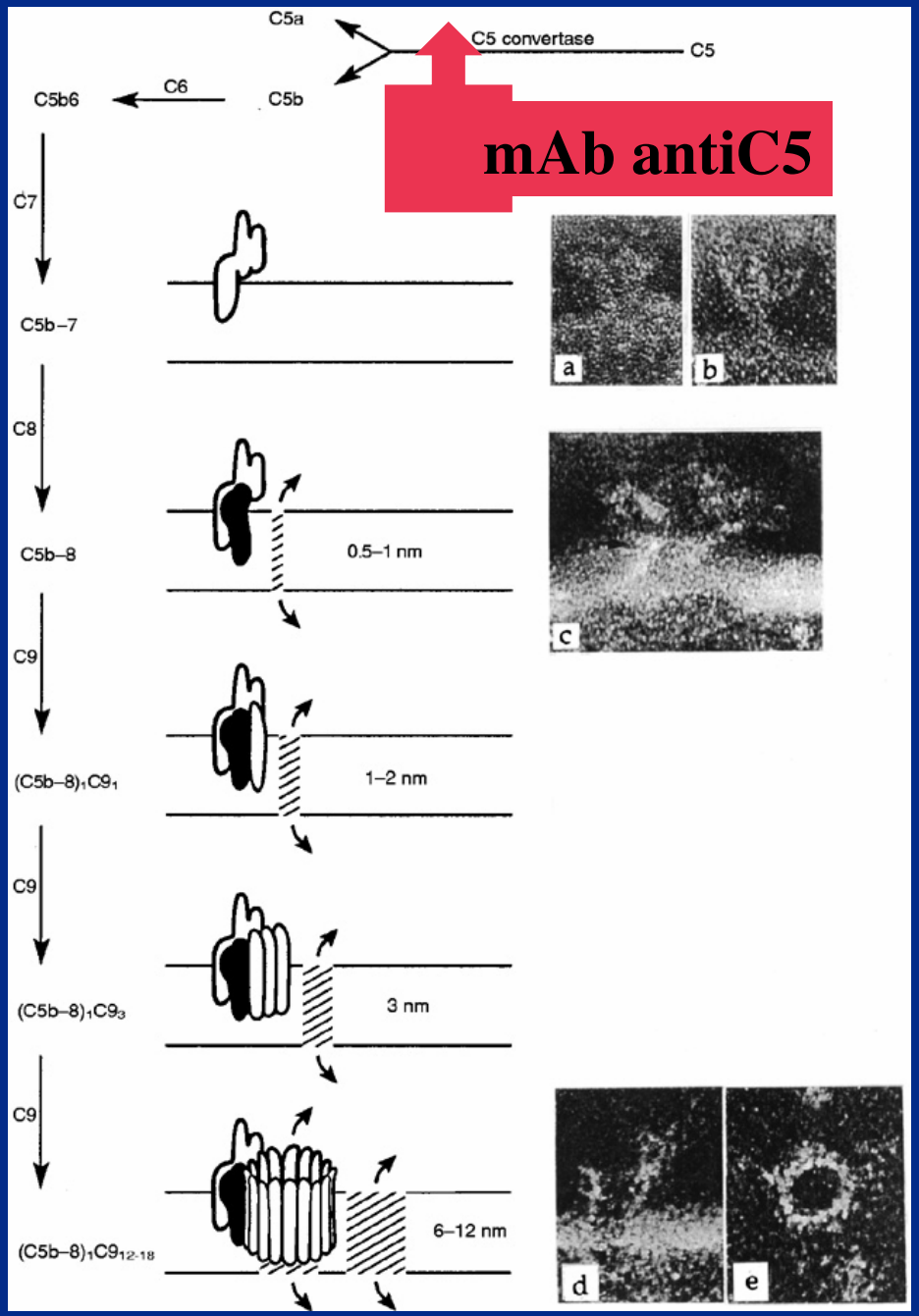
C4bp
Factor H and FH/rel/prot
(Factor I)
Clusterin

CD55 and CD59 deficiency:
paroxysmal nocturnal haemoglobinuria (PNH)

Factor H mutation with loss of binding activity: HUS
MCP mutations: HUS

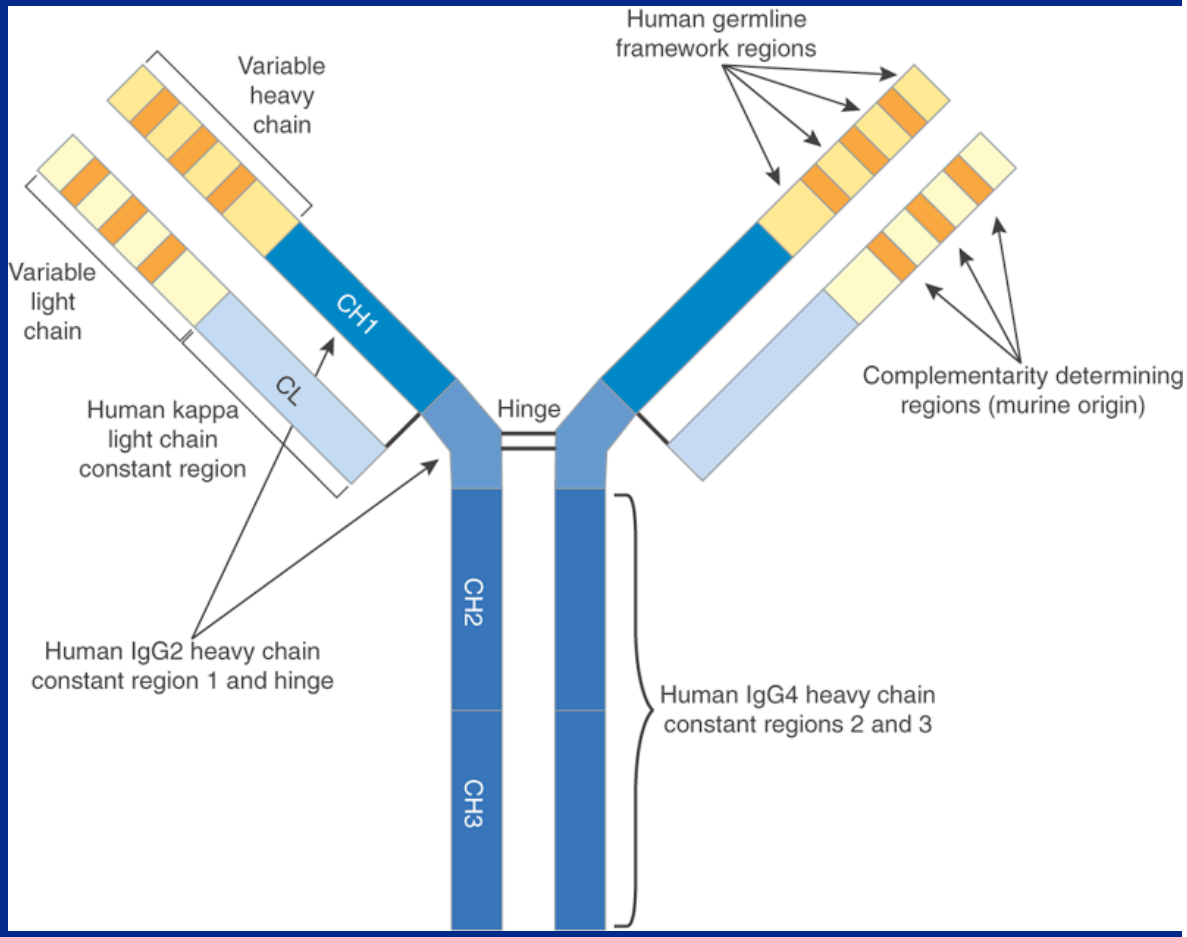
Paroxysmal nocturnal haemoglobinuria (PNH)
CD59 / DAF deficiency





Formation of the Membrane attack complex C5b-C9

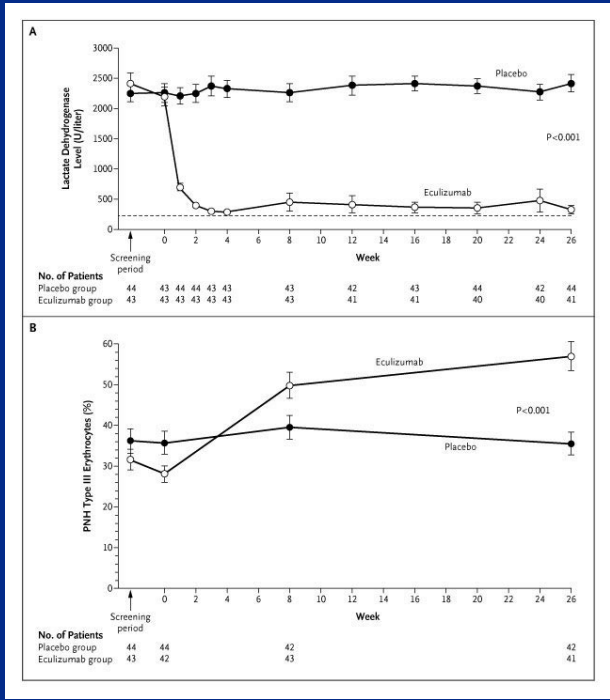
Eculizumab = C5 inhibitor. Russell P et al. Nature Biotechnology 25, 1256 - 1264 (2007)



To minimize immunogenicity, murine complementarity-determining regions was grafted into human heavy and light chain germline antibody framework sequences. Additionally, human IgG2 and IgG4 heavy chain sequences were combined to form a hybrid constant region that is unable to bind Fc receptors or to activate the complement cascade. Eculizumab exhibits high affinity for human C5, effectively blocking its cleavage and downstream proinflammatory and cell lytic properties.

New Engl J Med 370:90-2, 2014: Eculizumab for inherited CD59 deficiency

Levels of Lactate Dehydrogenase and PNH Type III Erythrocytes during Treatment with Eculizumab



Hillmen P et al. N Engl J Med 2006; 355:1233-1243

And:

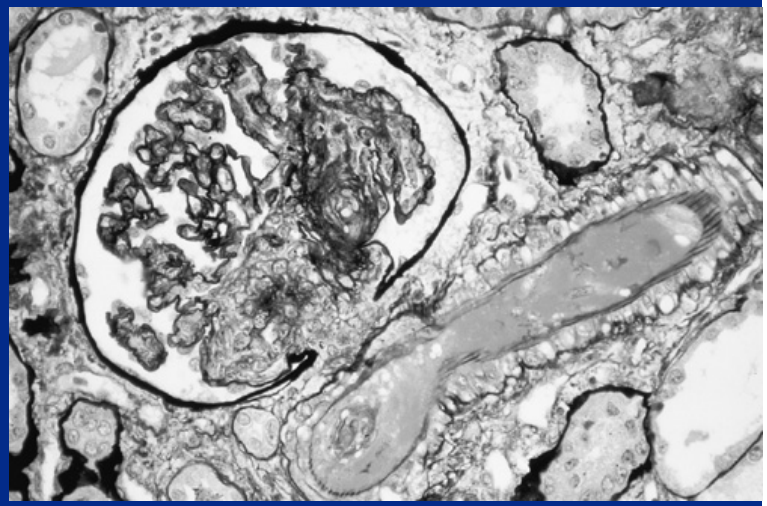
New Engl J Med 370:90-2, 2014:

Eculizumab for inherited CD59 deficiency

The NEW ENGLAND JOURNAL of MEDICINE

Haemolytic uraemic syndrome (HUS)

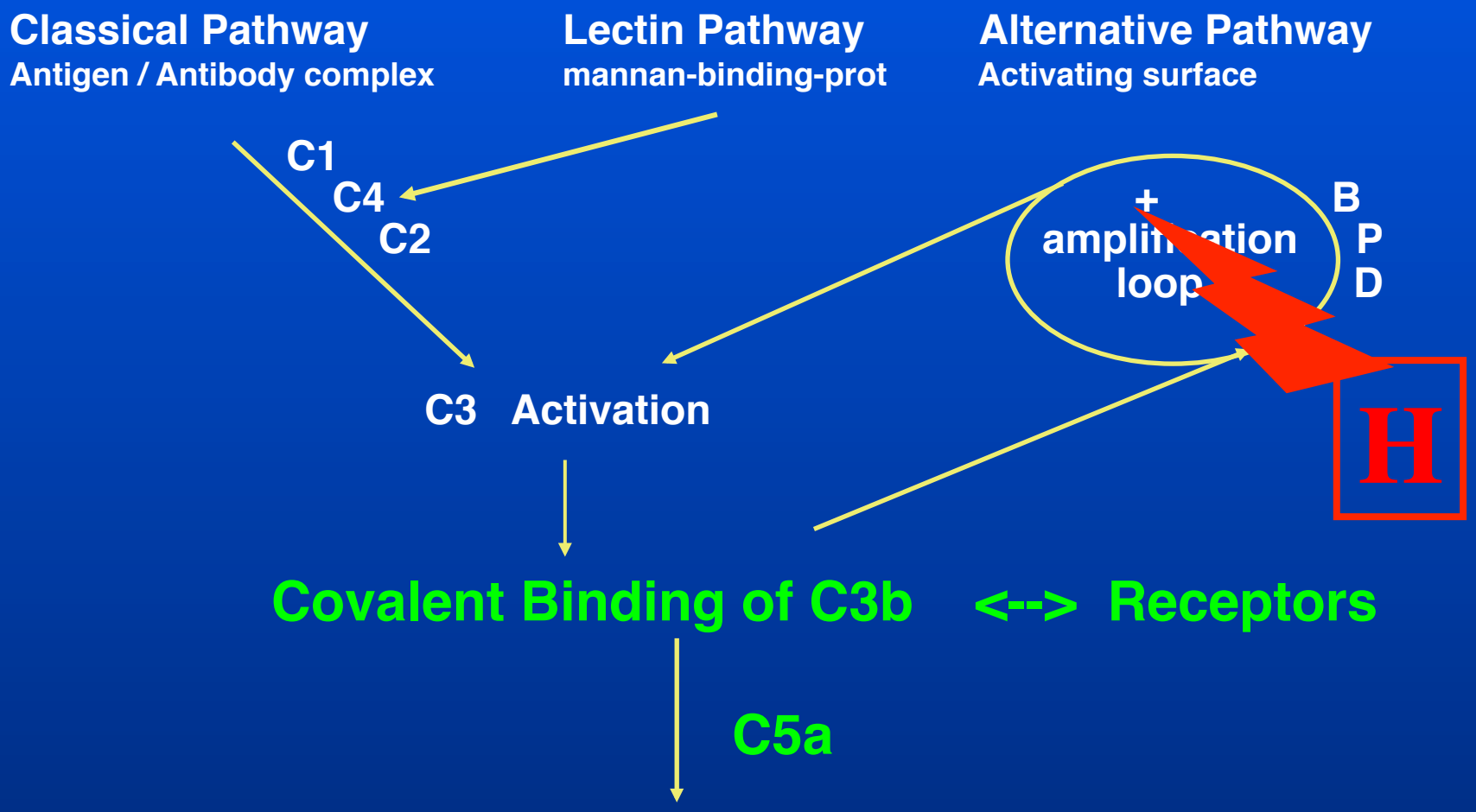
thrombopaenia,
haemolysis,
fragmentocytes,
renal failure (Gasser)

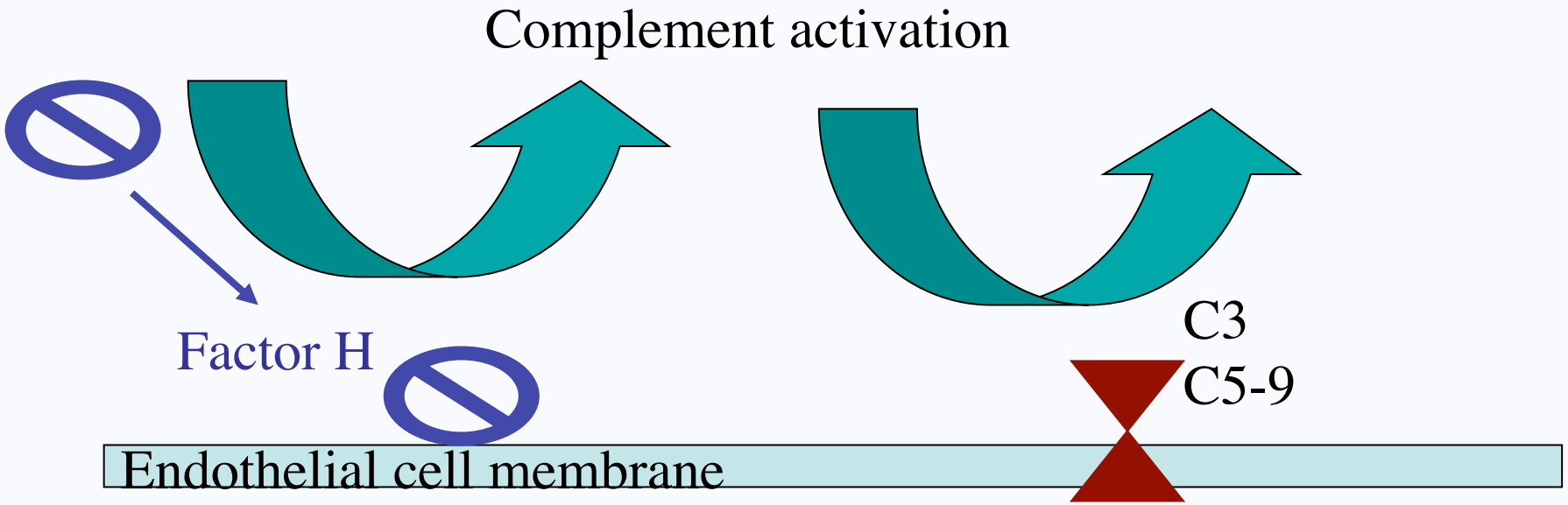


1. Typical (Shiga toxine)
2. Atypical : familial,
   relapsing,
   improved by plasma

==> Mutations of complement proteins Facteur H or MCP

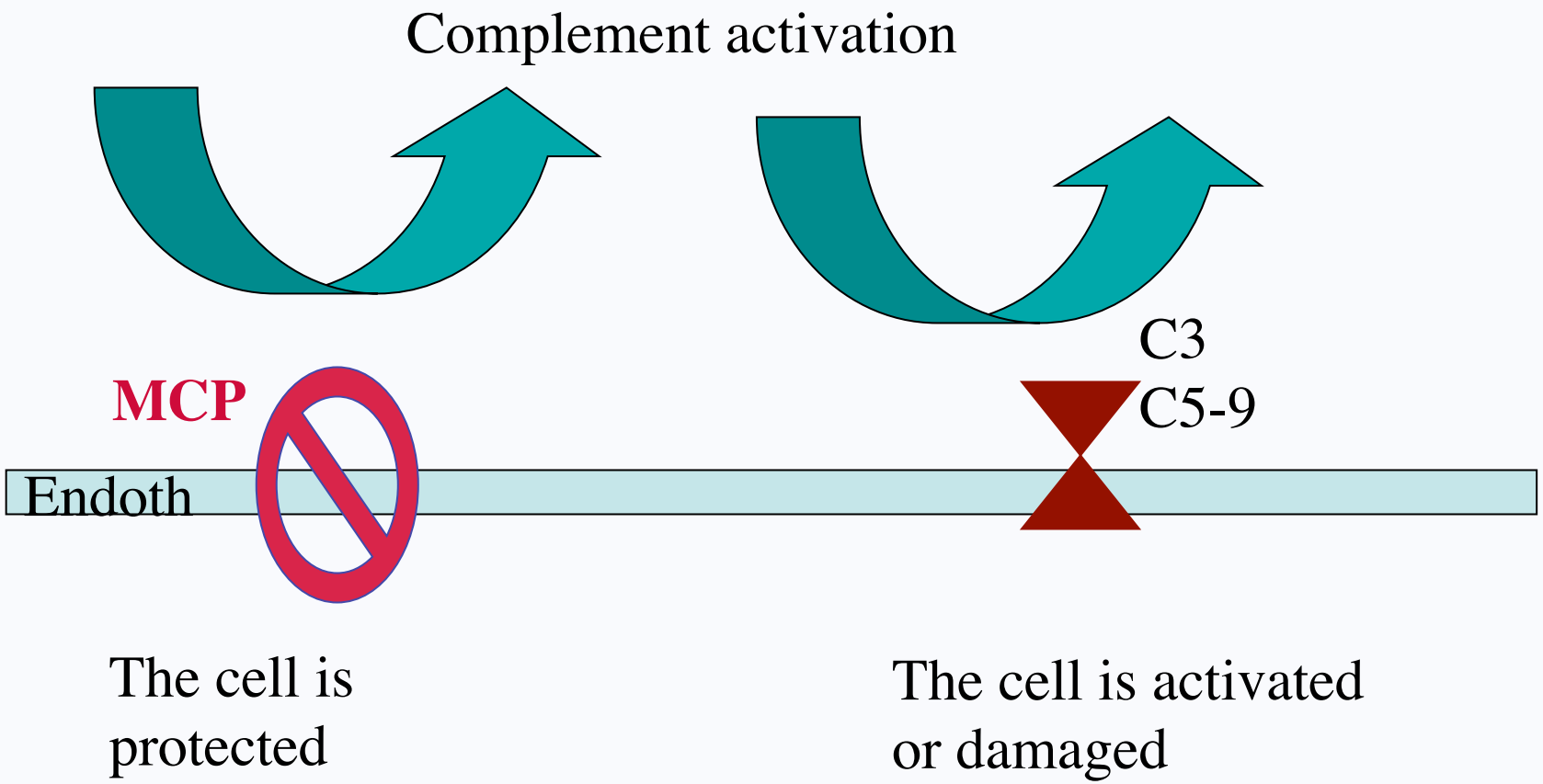
Complement activation





The cell is protected

The cell is activated or damaged


Complement activation
C3
C5-9
MCP
Endoth
The cell is protected
The cell is activated or damaged

HUS and complement mutations

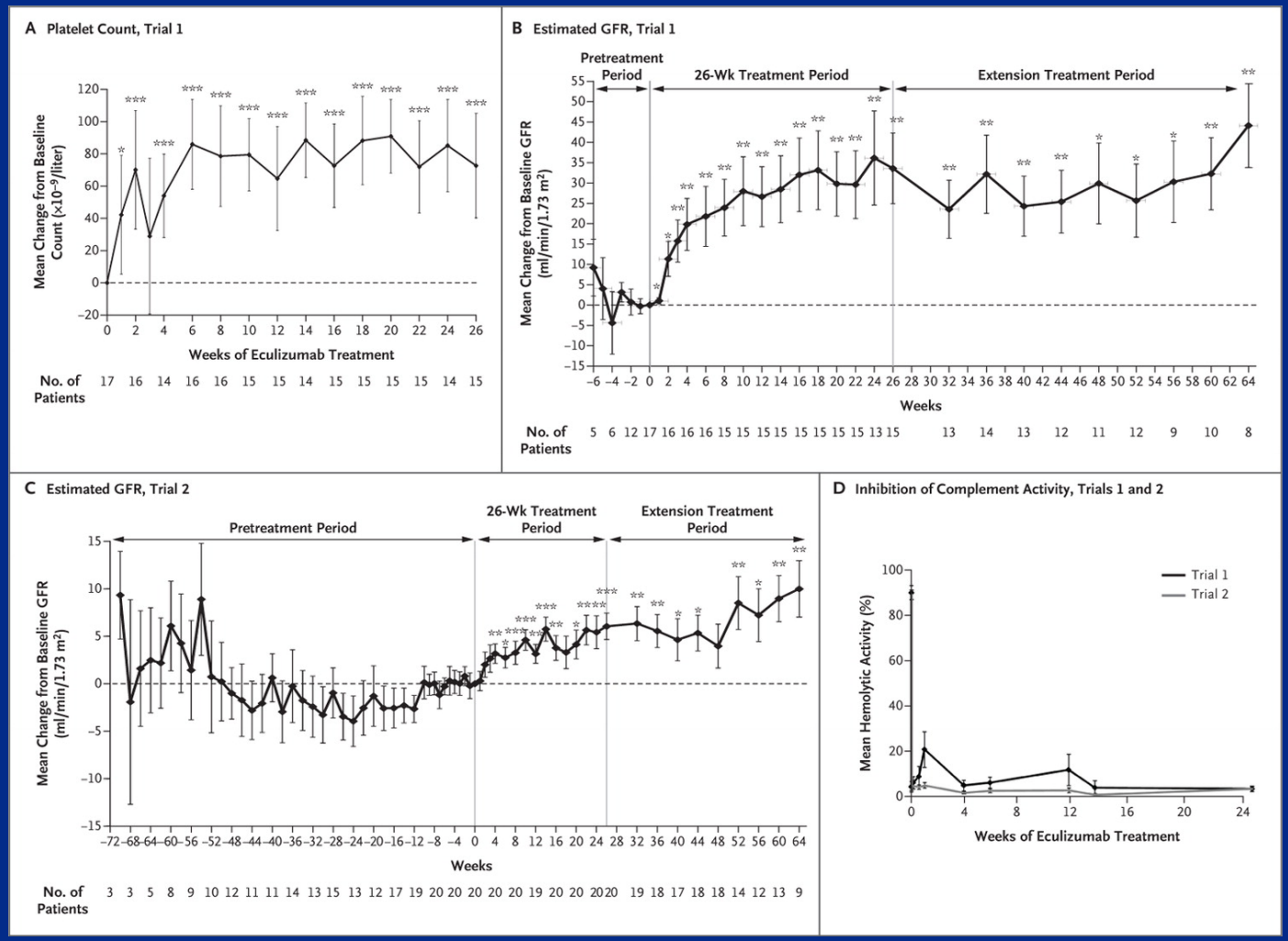
50% mutations in atypical HUS *(Frémeaux Bacchi)*

Loss of inhibition:
Factor H, *AutoAb against FH*
MCP (Membrane Cofactor Protein), Factor I
Others (thrombomodulin: increases activation of prot C))

Gain of function:
Factor B and C3

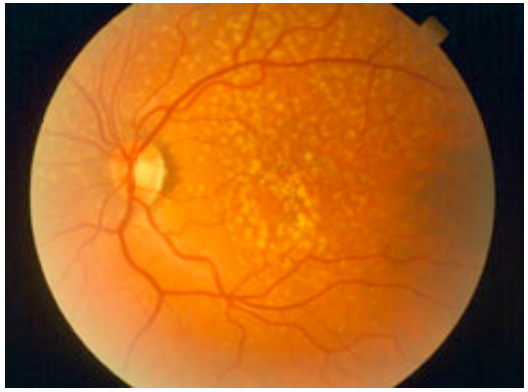
Relevant for therapy ?

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome



Legendre C et al. N Engl J Med 2013;368:2169-2181.

The NEW ENGLAND JOURNAL of MEDICINE



Age-related Macular Degeneration (eye - retina - drusen- blindness)

(drusen = deposits between the retinal-pigmented epithelium and Bruch's membrane)

Risk factor:

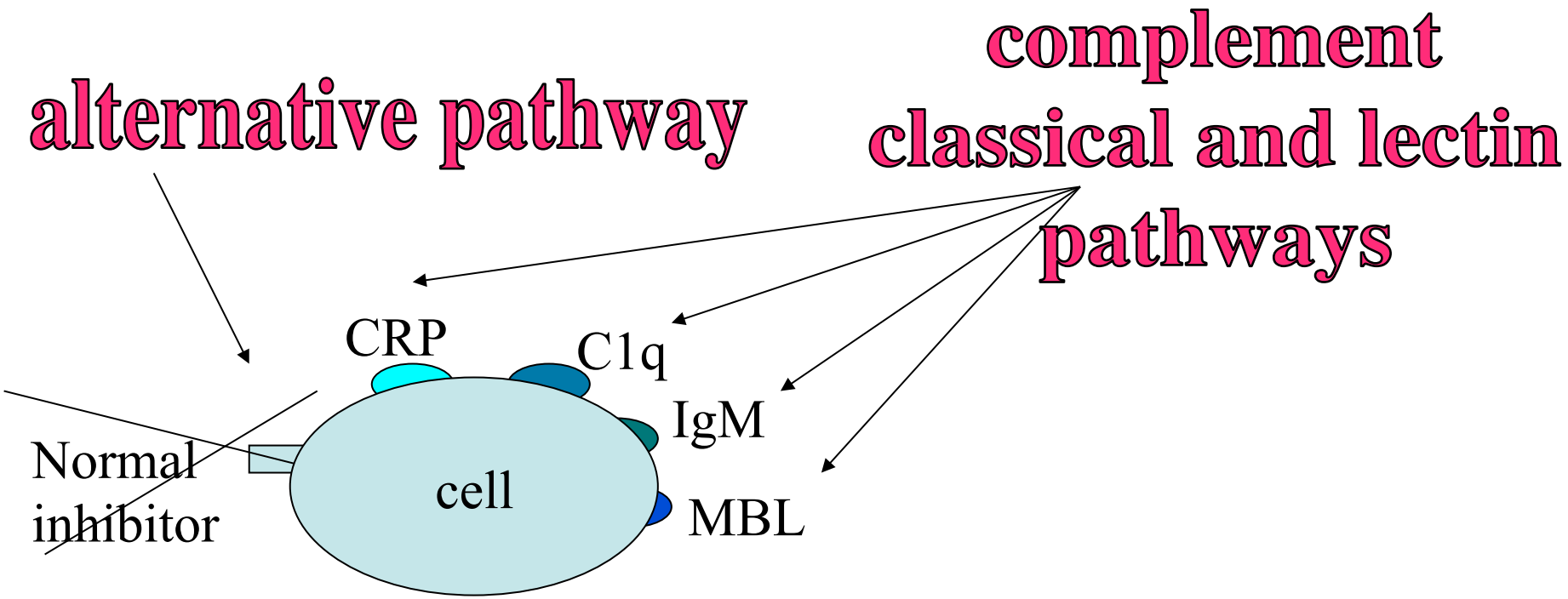
alleles of Factor H *(Science 308:385, 2005)*
and of related proteins (factor B, variant C3)

Associated with:

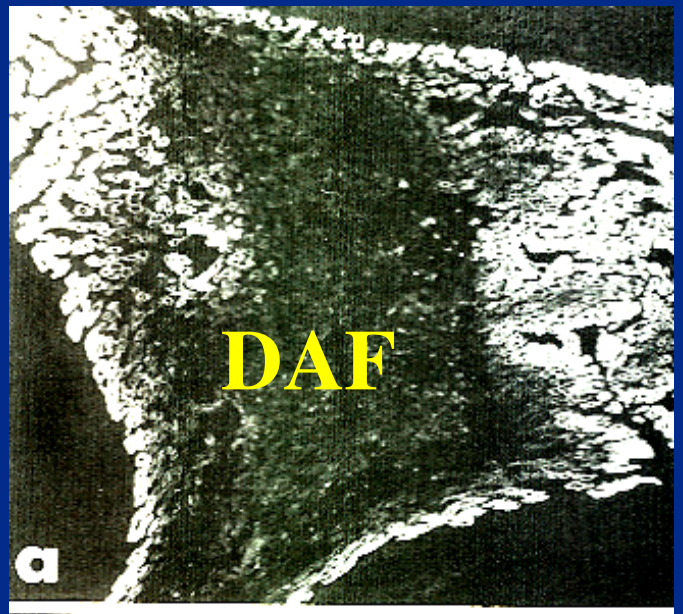
atypical HUS, Membranoproliferative GN/Nef

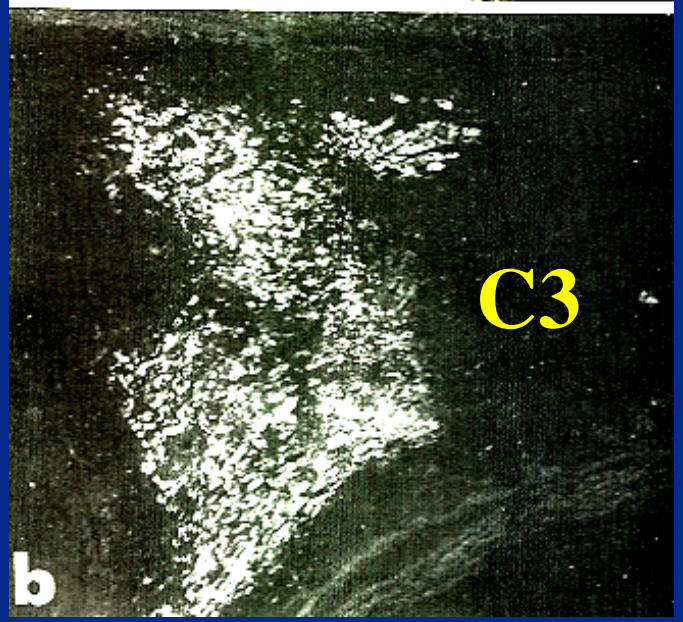
Necrosis - Ischemia-reperfusion injury

(gastrointestinal tract, muscles, myocardium, endothelial cells)



Ischemia => Oxydative damage, necrosis,

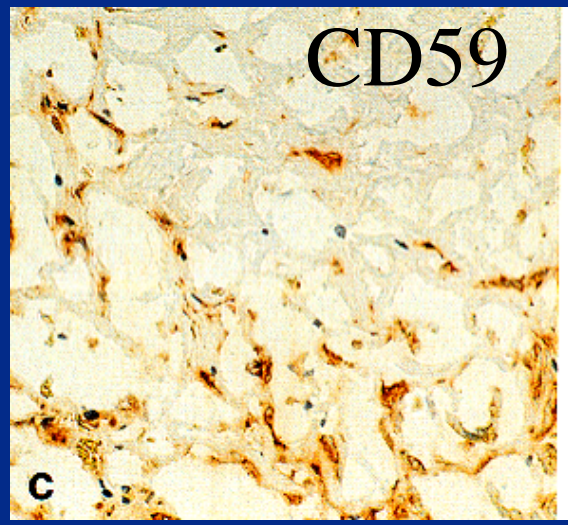


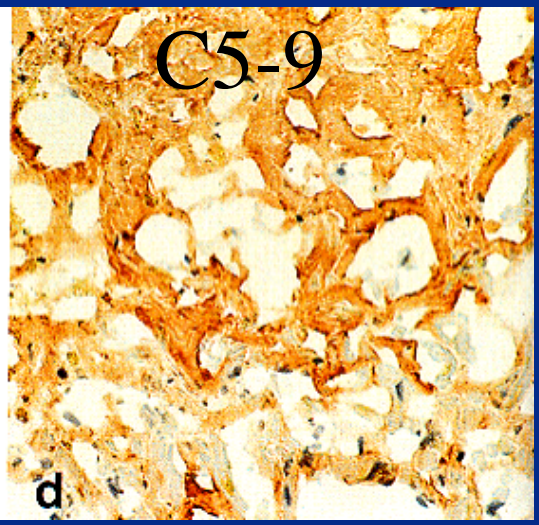


Myocardial infarction

Vakeva et al Am J Pathol 94, 144:1357

Complement deposition and loss of complement inhibitors in the infarcted area





Influence of functional deficiency of complement mannose-binding lectin on outcome of patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

MBL > / < 100 μg/L

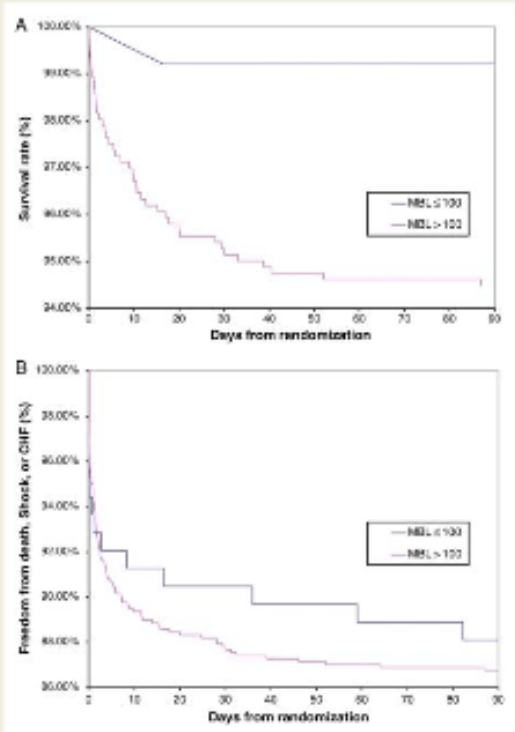
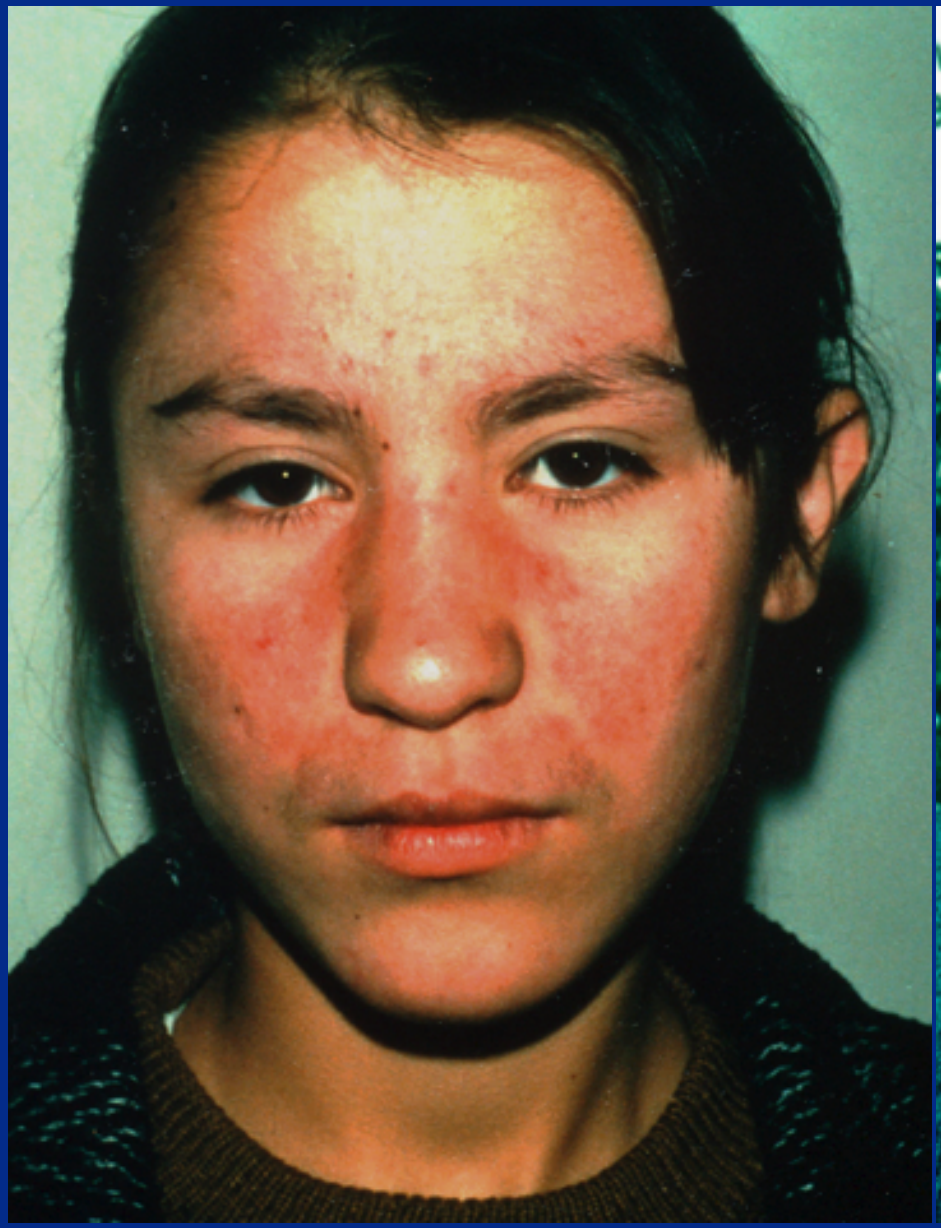
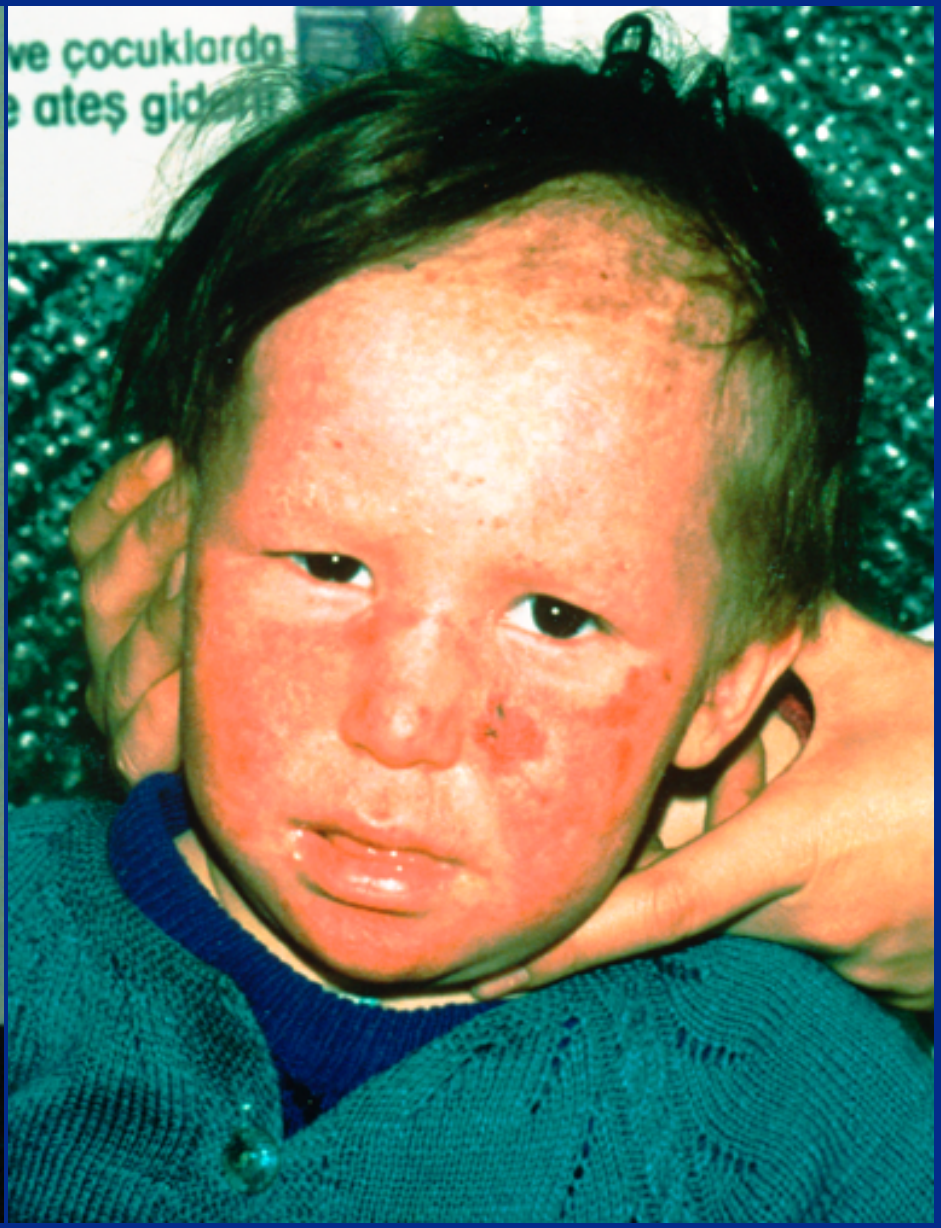


Figure 1 Relationship between serum mannose-binding lectin (MBL) levels and survival rate (*A*) or the combined endpoint of death, shock, and congestive heart failure (CHF) (*B*) in patients with acute ST-elevation myocardial infarction having undergone primary percutaneous coronary intervention. *P*-values were 0.023 and 0.676, respectively.

Marten Trendelenburg
European Heart Journal 2010
31:1181

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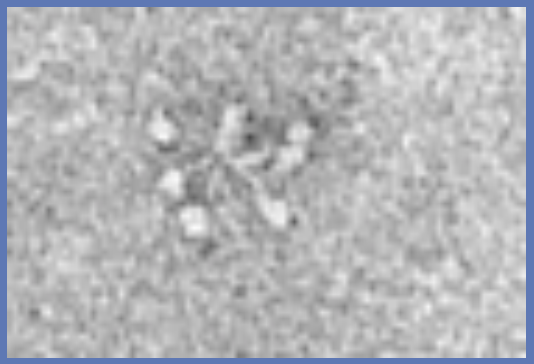
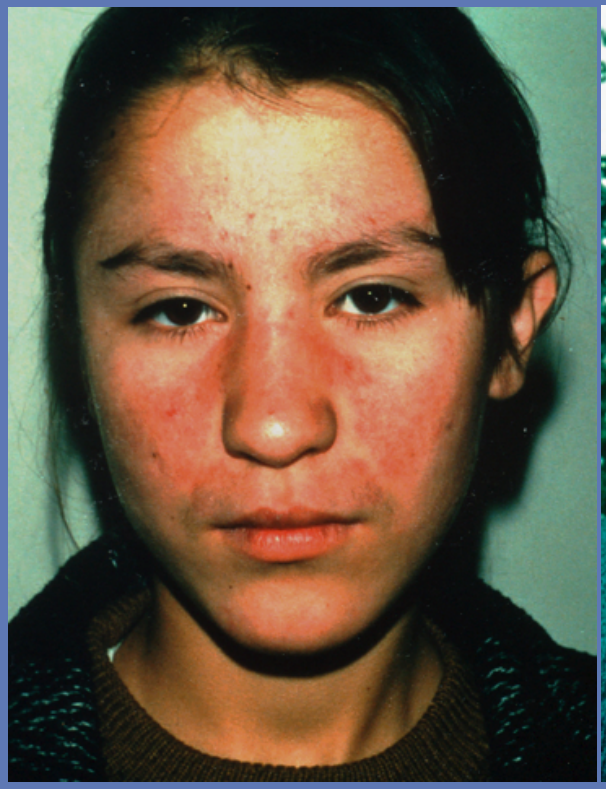
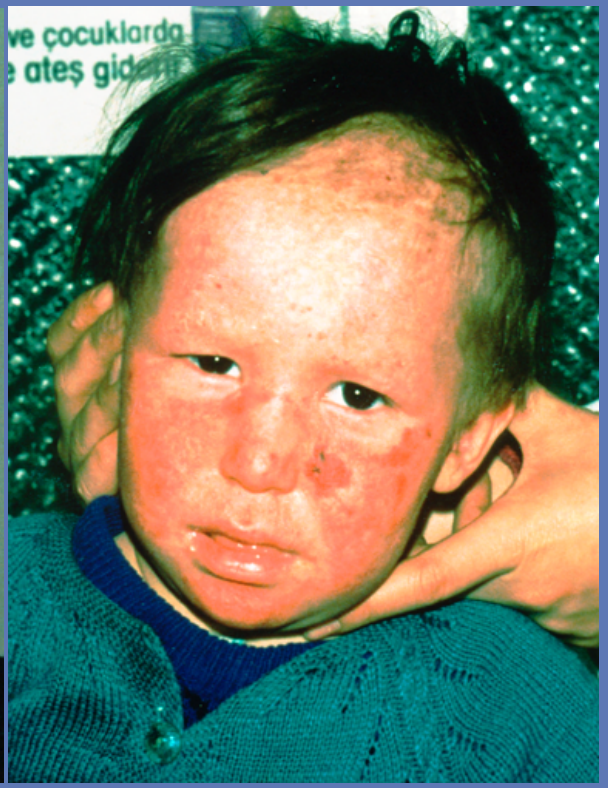


C1q deficiency
SLE





Clearance of Apoptotoc bodies

apoptosis
apoptotic bodies

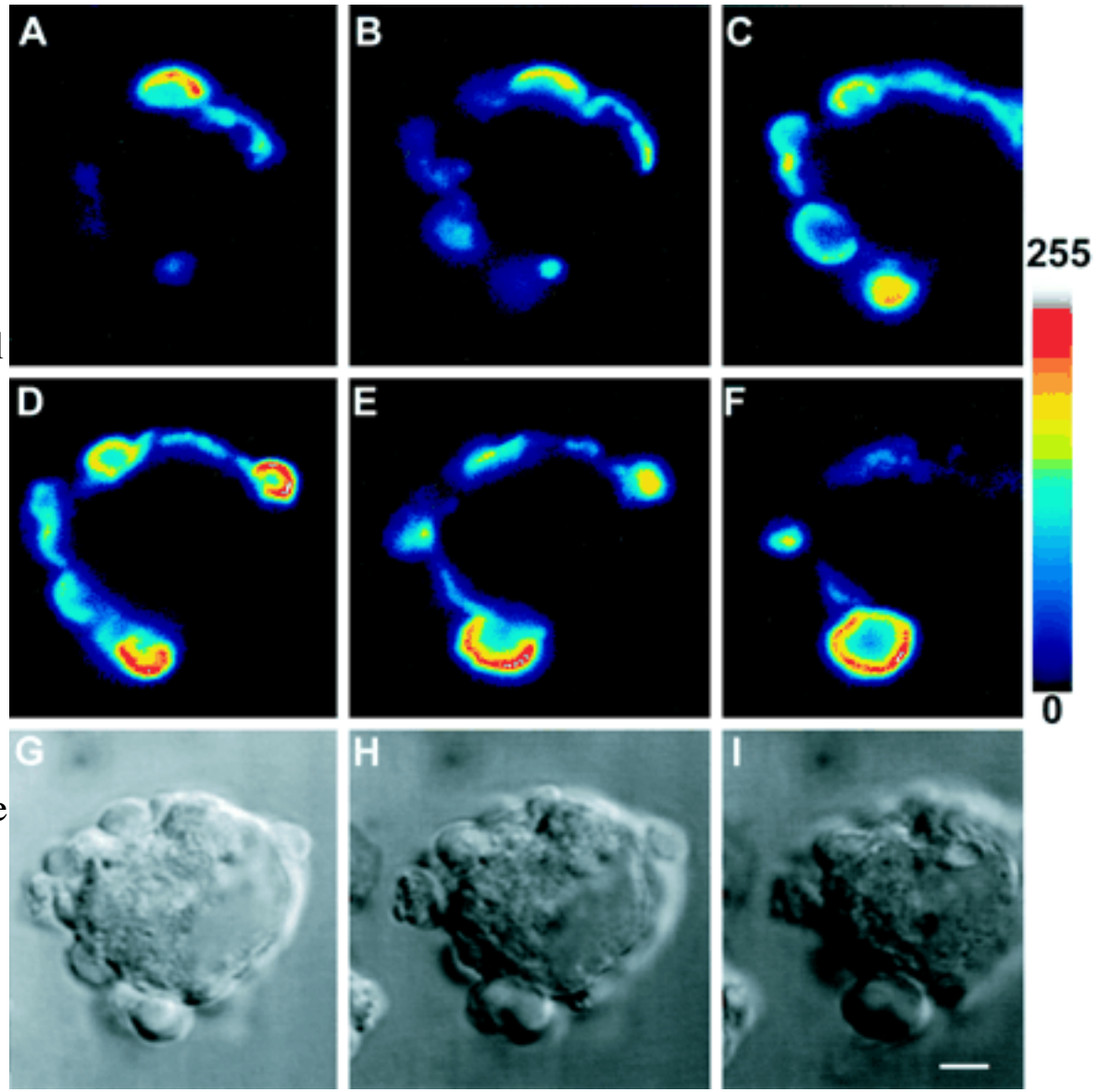
Nucleoproteins
(oxy)phospholipides

C1q -> C4, C3
CRP -> C1q, C4, C3
Other pentraxins
(PTX3, SAP)-> C1q…
nIgM -> C1q….
MBL -> C4, C3

Beta2GP1
Thrombospondin
SP-A
Others…

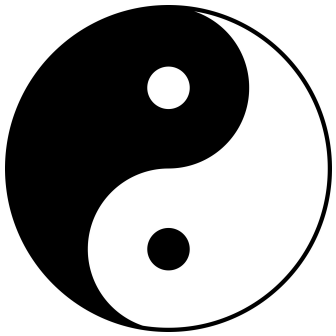
The globular heads of C1q specifically recognize surface blebs of apoptotic vascular endothelial cells.
Navratil JS, Watkins SC, Wisnieski JJ, Ahearn JM.

Confocal analysis of bound C1q on one apoptotic HUVEC. Shown are six consecutive cross-sections through one apoptotic HUVEC stained for the presence of C1q (*A–F*). Bound C1q was detected by indirect immunofluorescence. The fluorescence intensity in this figure is represented by a color scale, with white being the highest intensity and black the lowest. Differential interference contrast images (*G–I*) of the three panels directly above (*D–F*) are shown to visualize morphology of the entire cell



J Immunol 2001 Mar 1;166(5):3231-9

Complement = fitness



➔

Control system to remove unnecessary / danger elements in the organism

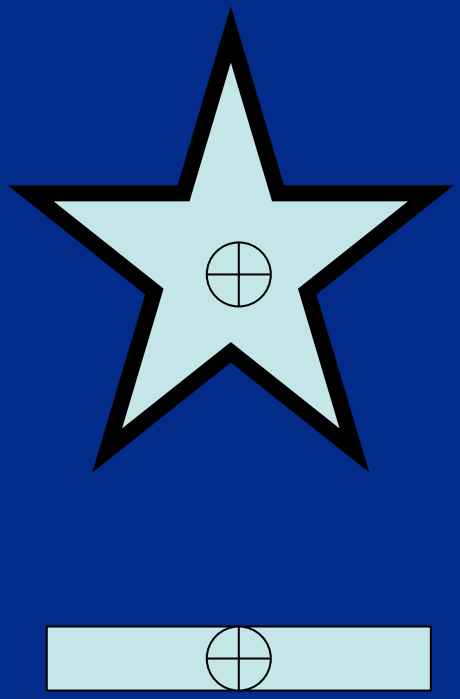
-> internal factors, waste: debris, necrosis, apoptosis (10^{11} neutrophils/day)

-> external factors: foreign body, infectious organisms (not all: e.g. gut microbiome),

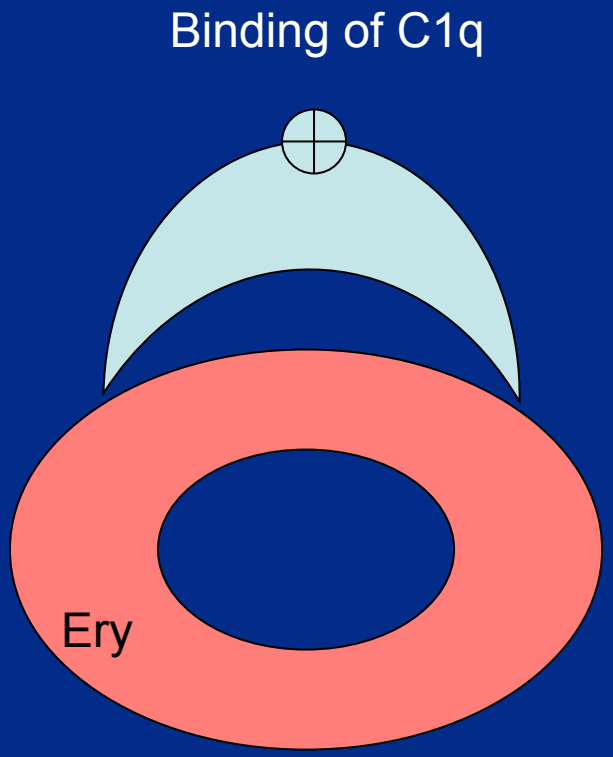
IgM activates Complement on a target

e.g. Blood group transfusion error

In plasma : “seestar”



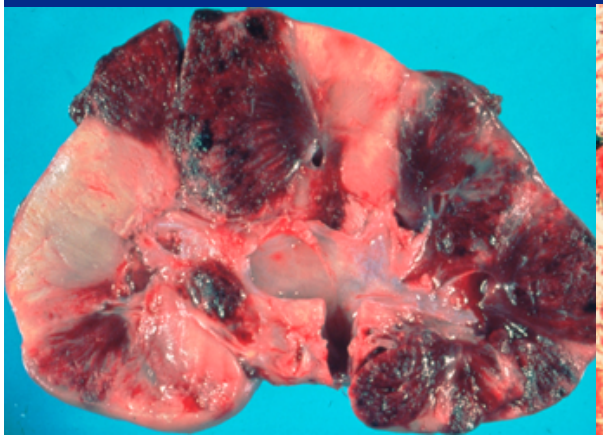
on a target: “spider”

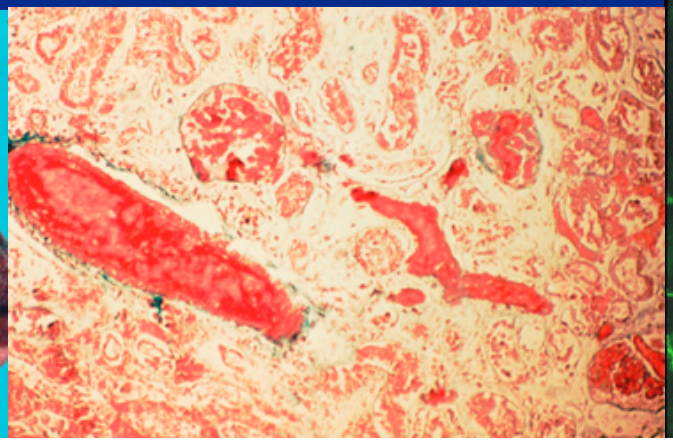


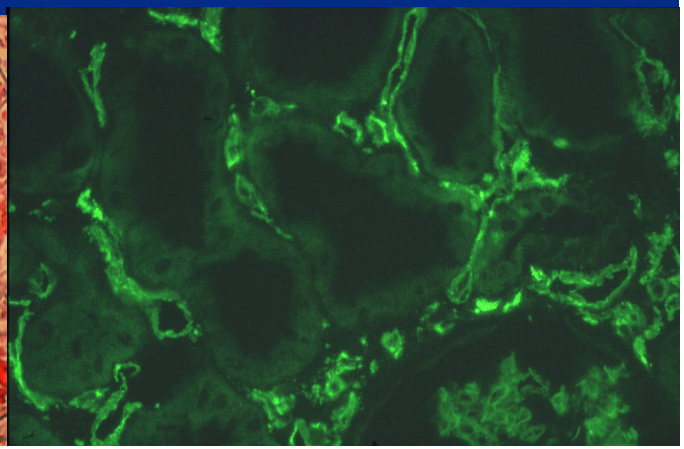
ABO incompatible renal transplantation (+antiC5?)

Endothelial cell +++ for AB Antigen
Immediate hyperacute Rejection

A/B Ag ----> Ac ---> Complement ---> Thrombosis/Bleeding







Systemic Lupus Erythematosus

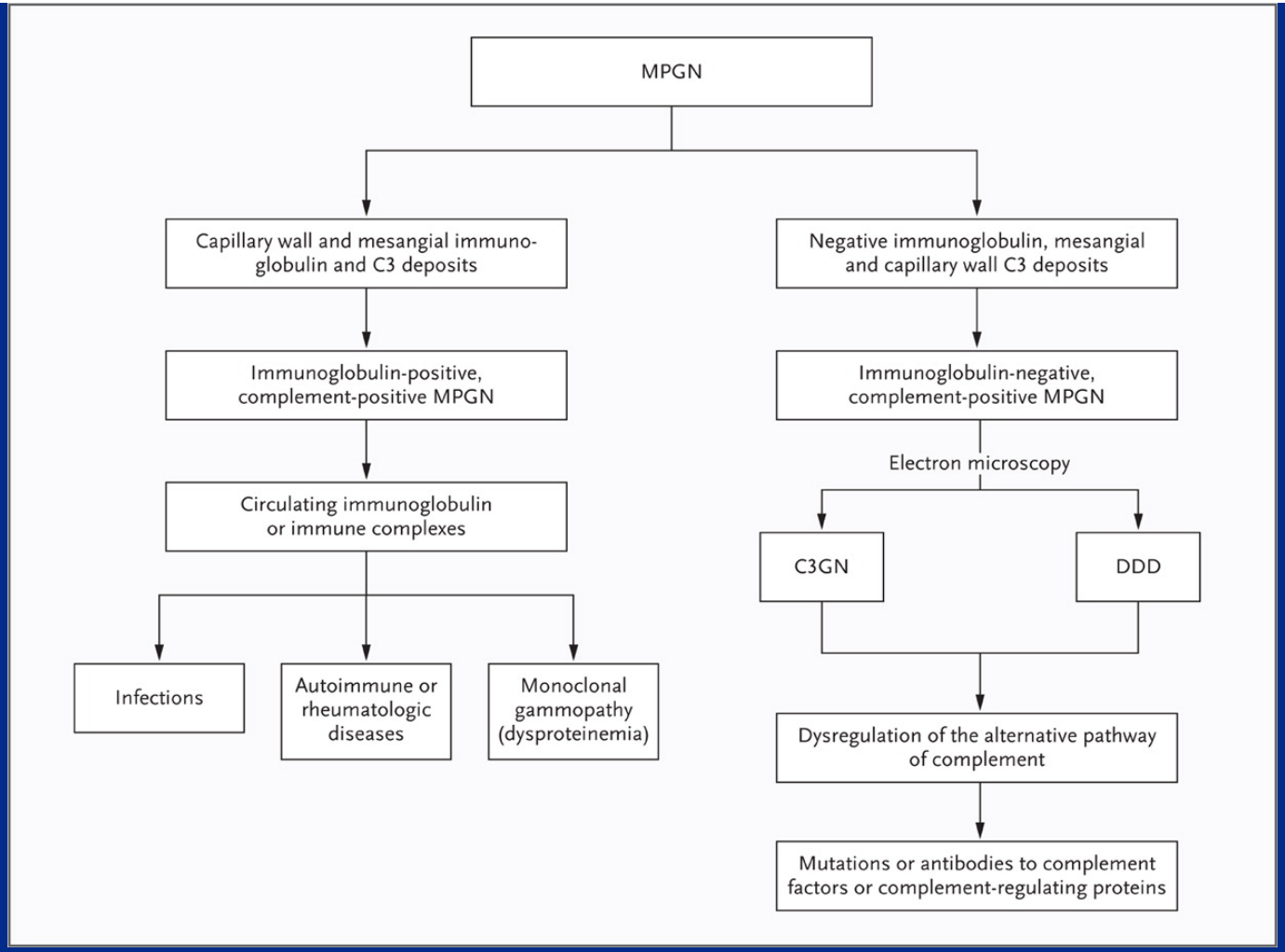
« Immunisation against apoptotic cells (including C1q)

Immune complexes (IC: DNA-antiDNA)

complement activation

low C1q, low C4, low C3 + tissue inflammation (nephritis)

Pathophysiology of MPGN.

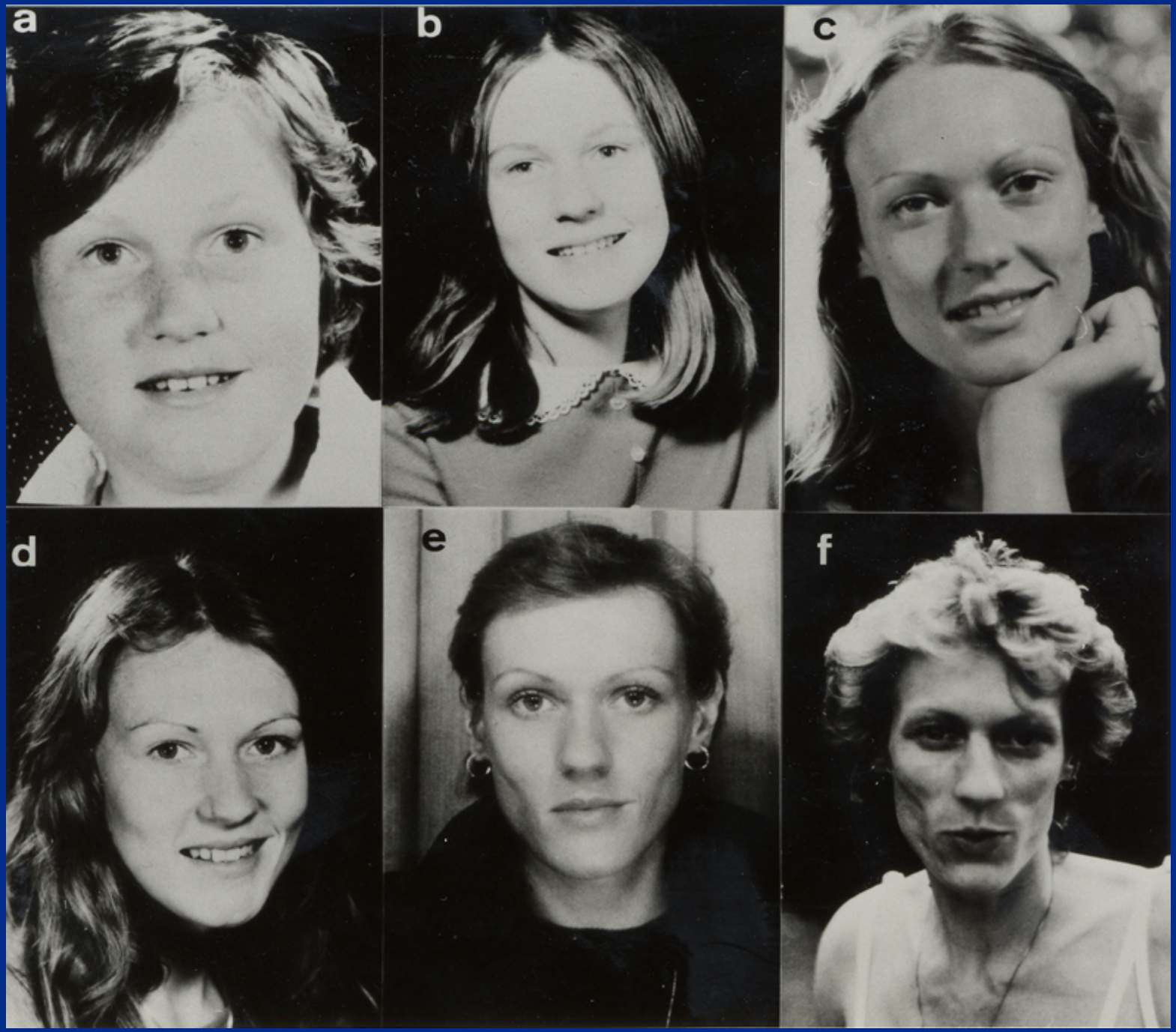


C4 and C3 low
e.g. SLE

Only C3 low
e.g. Nef

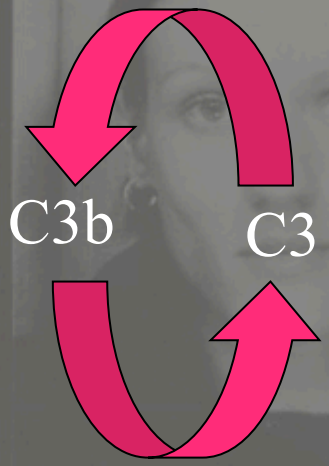
Sethi S, Fervenza FC. N Engl J Med 2012;366:1119-1131.

The NEW ENGLAND JOURNAL of MEDICINE


a
b
c
d
e
f

C3 Nef

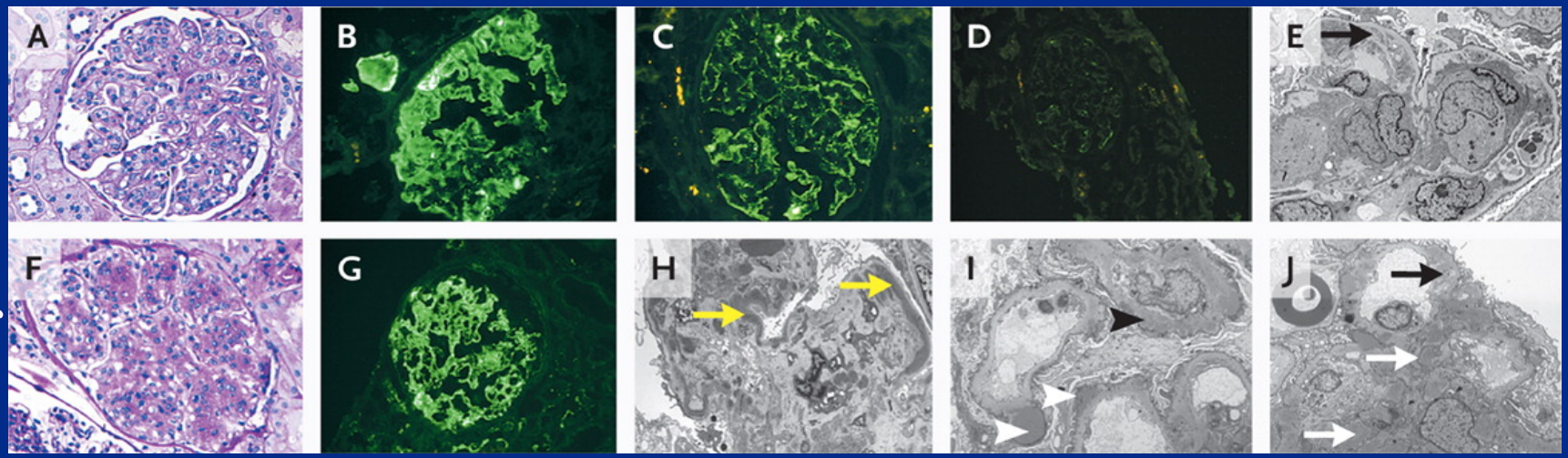
Uncontrolled activation alternative pathway



Positive feedback

C3 nephropathies
Representative Findings on Light, Immunofluorescence, and Electron Microscopy in MPGN.

Nef



C3

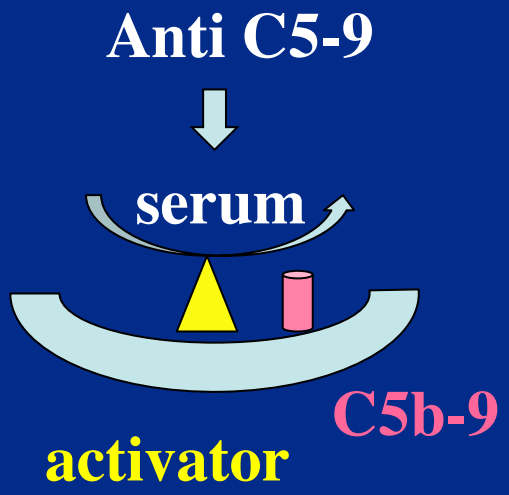
Sethi S, Fervenza FC. N Engl J Med 2012;366:1119-1131.

The NEW ENGLAND JOURNAL of MEDICINE

Complement measurements:

CP
AP
MBLP -> ELISA C5-9

Ag:
(C1q)
C4
C3
C1 inh



Typical Complement measurements:

1) CP and AP = n and MBLP =0

2) CP low, AP very low, C4 norm, C3 low

3) CP very low, AP norm, C4 very low, C3 norm

4) CP = 0, AP = 0, C3 and C4 norm

Typical Complement measurements:

1) CP and AP = n and LP =0

2) CP low, AP very low, C4 norm, C3 low

3) CP very low, AP norm, C4 very low, C3 norm

4) CP = 0, AP = 0, C3 and C4 norm

1) MBL def (MASP def)
2) C3nef, PSGN, def FH or FI
3) C1inh def, Cryoglob,
4) C5,6,7,8 or 9 def

Jürg Schifferli
j.schifferli@unibas.ch

bye bye

Prevalence of antiC1q Ab in SLE nephritis

Multicentric study (Basel, Geneva, Lausanne Madrid, Prag)
M Trendelenburg et al. NDT 2006,21:3115.

38 patients fulfilling at least 4/11 ACR criteria for the diagnosis of SLE were included.
36 patients had proliferative (class II, III or IV) and 2 class V lupus nephritis.

All but one patients with proliferative lupus nephritis were positive for anti-C1q (97.2%).

All patients were positive for glomerular C1q (36/36) and 37/38 patients had glomerular IgG deposits.
Anti-C1q strongly decreased during successful treatment.

CASE 1
A 23-year old women with a nephrotic range proteinuria has following complement measurements:
C4: 70% of normal
C3: 30% of normal
CH50: 70% of normal
The solid phase C1q binding assay for IC is negative
Please discuss and suggest the diagnosis.

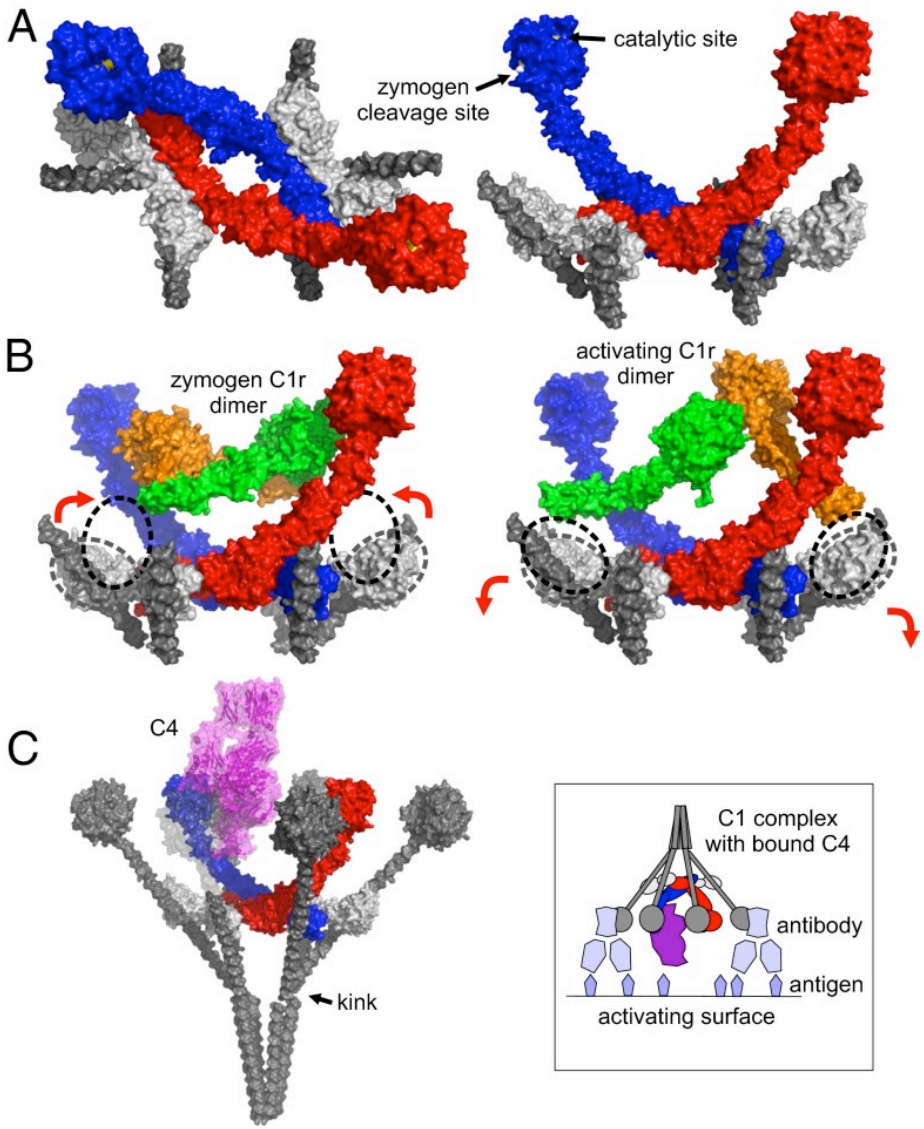
CASE 2
A 60-year old man has 3 attacks of angioedema (tongue and face) in the last year. No familial history of angioedema. He takes no drugs. An MGUS is found (IgGk approx. 3g/L).
what do you expect for
C4
C3
CH50 ?
Additional tests?

CASE 3
A 17 year-old man presents a meningococcal meningitis, which improves after i.v. antibiotic therapy. His personal history reveals that he had already such an infection 12 years previously.
What do you expect for
C4
C3
CH50?
Additional tests?

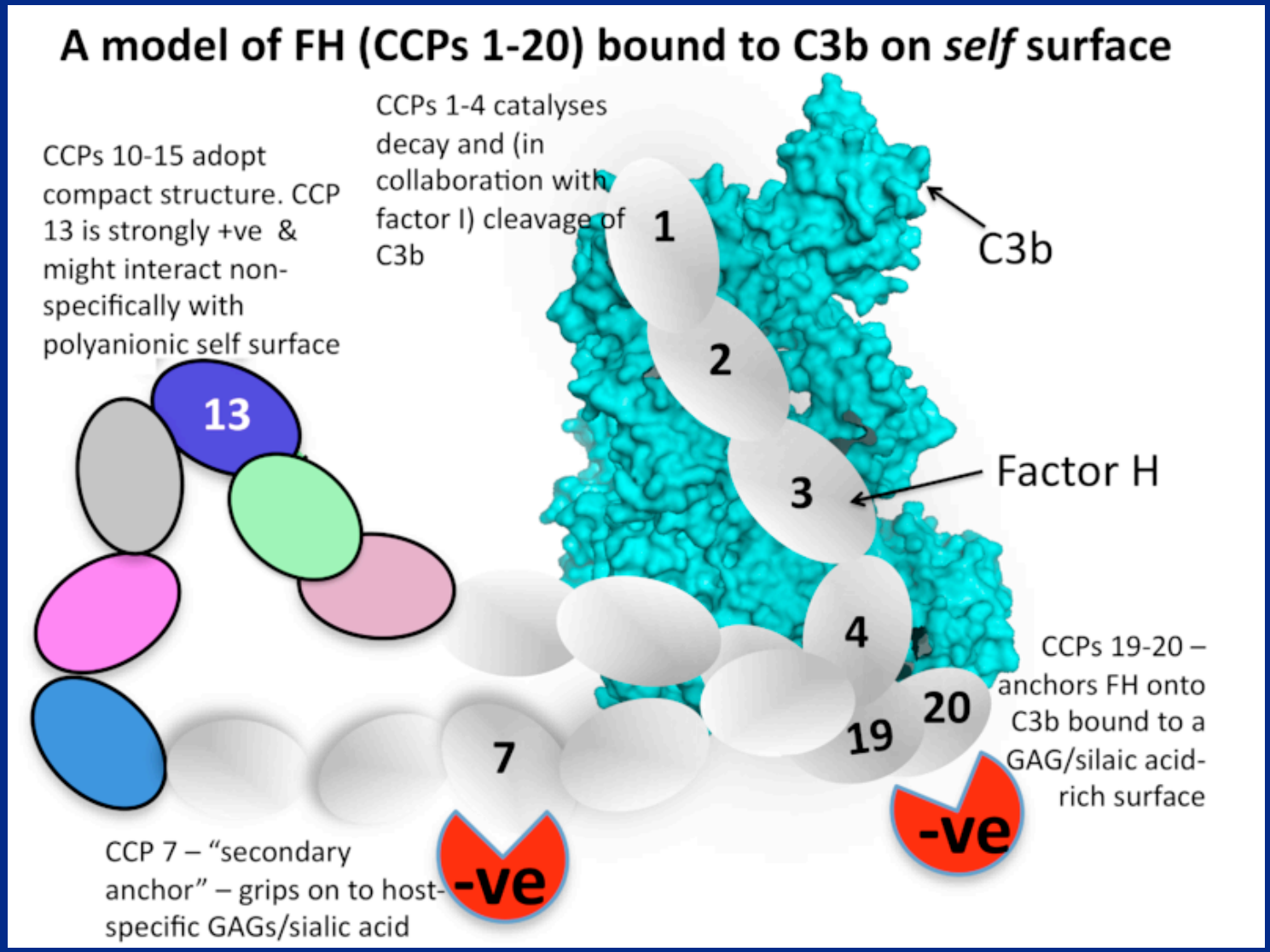
Structural basis of the C1q/C1s interaction and its central role in assembly of the C1 complex of complement activation

Umakhanth Venkatraman Girija et al.

Proc Natl Acad Sci U S A. 2013 August 20; 110(34): 13916–13920.



The 2 functions of FH: inactivation of C3 (with FI) and binding to surfaces



The immune system in plants <-> human
Principles:

Inducer (waste, bact.) e.g.ACAMPs (=altered self: Apoptotic cell associated molecular patterns)
PAMPs (=pathogens associated mol patterns)
->
Sensor e.g PRR= pattern recognition receptors,
->
Mediator e.g. cytokines, chemokines, etc.
->
Effector e.g. neutrophil, enzymes,
membrane attack complex of complement

Innate Immunity

=

A fixed package of sensors that an individual has at birth, which can be modulated in *quantity*: e.g CRP: 1 -> 1000 mg/L

***Qualitative* changes over generations of Individuals : novel package of sensors by rearrangement + mutation of genes (chance), selecting by keeping those producing a survival advantage at a given time and place.**

Innate Immunity

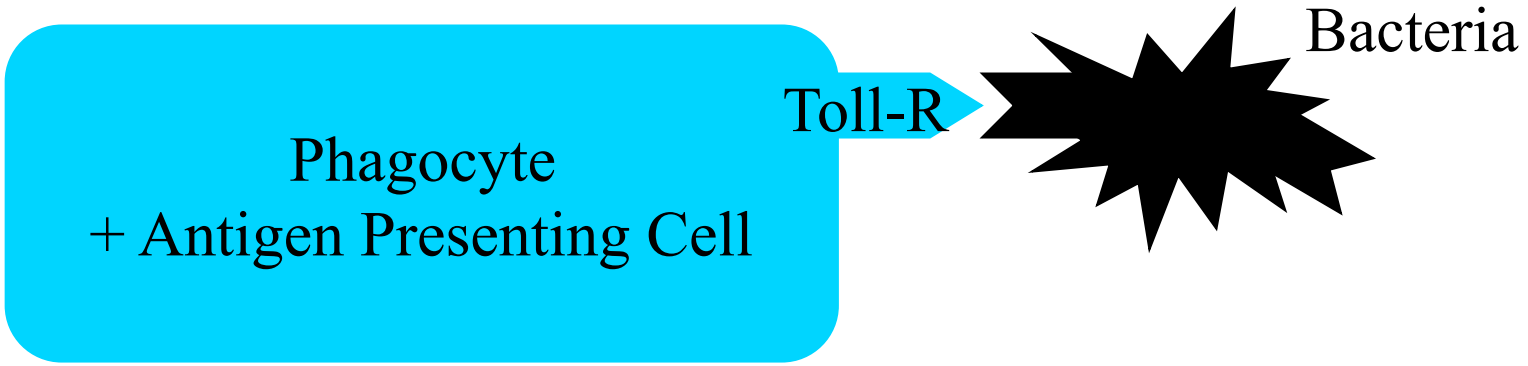
=

Great inter-individual variability (alleles, mutations): -> CCR5 mutation/HIV

Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation
Gero Hütter, M.D., …Eckhard Thiel, M.D.
N Engl J Med 2009; 360:692-698

Innate immun system

Pattern recognition : Toll-like receptors on <u>cells</u>



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Complement measurements:

CP
AP
MBLP -> ELISA C5-9

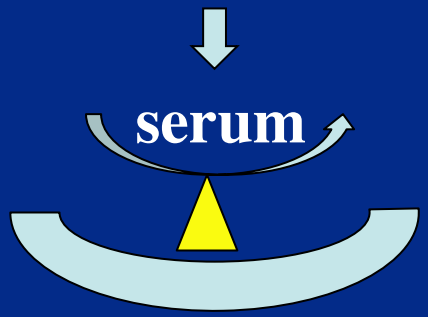
Ag:
(C1q)
C4
C3
C1 inh

activator

Complement measurements:

CP
AP
MBLP -> ELISA C5-9

Ag:
(C1q)
C4
C3
C1 inh



Complement measurements:

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MBLP -> ELISA C5-9

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