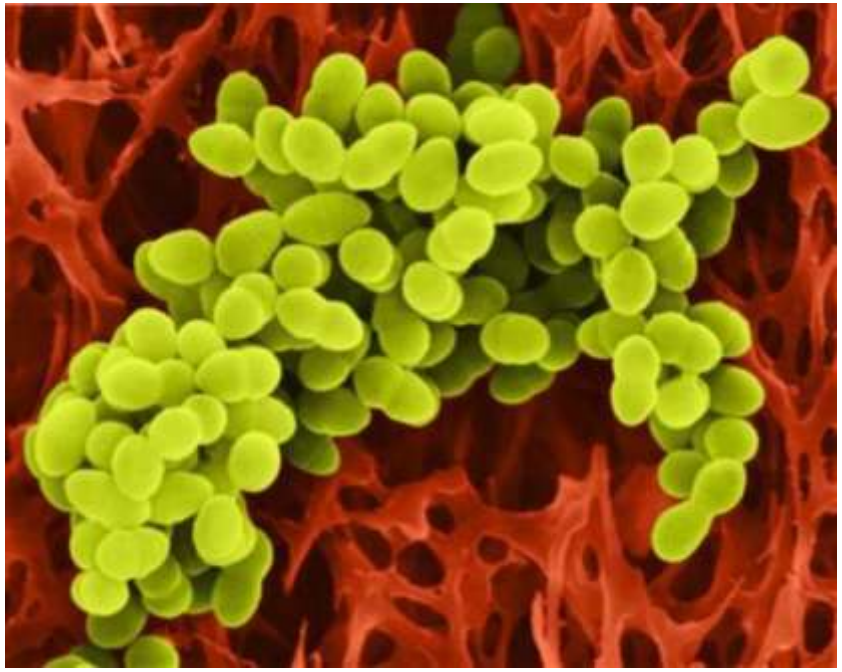
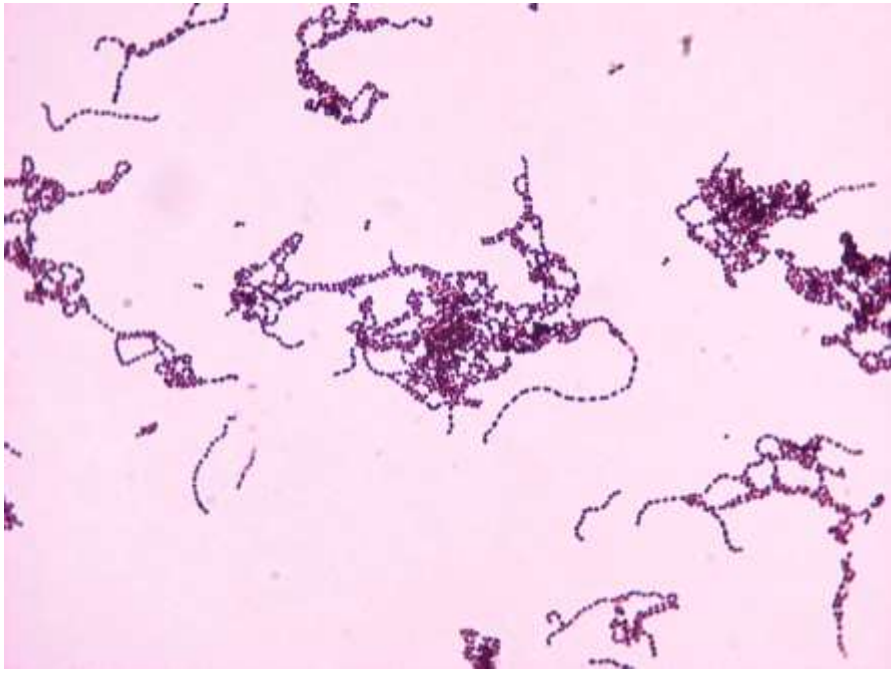




Mechanisms of bacterial pathogenesis

Staph. aureus
Str. pyogenes

Anna
Žlabová
PřF UK

STAPHYLOCOCCUS AUREUS

Type of virulence factors	Selected factors[a]	Associated clinical syndromes
Involved in attachment	MSCRAMMs (e.g., clumping factors, fibronectin-binding proteins, collagen, and bone sialoprotein-binding proteins)	Endocarditis, osteomyelitis, septic arthritis, and prosthetic-device and catheter infections
Involved in persistence	Biofilm accumulation (e.g., polysaccharide intercellular adhesion), small-colony variants, and intracellular persistence	Relapsing infections, cystic fibrosis, and syndromes as described above for attachment
Involved in evading/destroying host defenses	Leukocidins (e.g., PVL and γ-toxin), capsular polysaccharides (e.g., 5 and 8), protein A, CHIPS, Eap, and phenol-soluble modulins	Invasive skin infections and necrotizing pneumonia (CA-MRSA strains that cause these are often associated with PVL) abscesses (associated with capsular polysaccharides)
Involved in tissue invasion/penetration	Proteases, lipases, nucleases, hyaluronate lyase, phospholipase C, and metalloproteases (elastase)	Tissue destruction and metastatic infections
Involved in toxin-mediated disease and/or sepsis	Enterotoxins, toxic shock syndrome toxin-1, exfoliative toxins A and B, α-toxin, peptidoglycan, and lipoteichoic acid	Food poisoning, toxic shock syndrome, scalded skin syndrome, bullous impetigo, and sepsis syndrome
With poorly defined role in virulence	Coagulase, ACME, and bacteriocin	

http://cid.oxfordjournals.org/content/46/Supplement_5/S350.full

Adherence:

MSCRAMMs
(microbial surface components recognizing adhesive matrix molecules)

Cna (Collagen - binding protein)

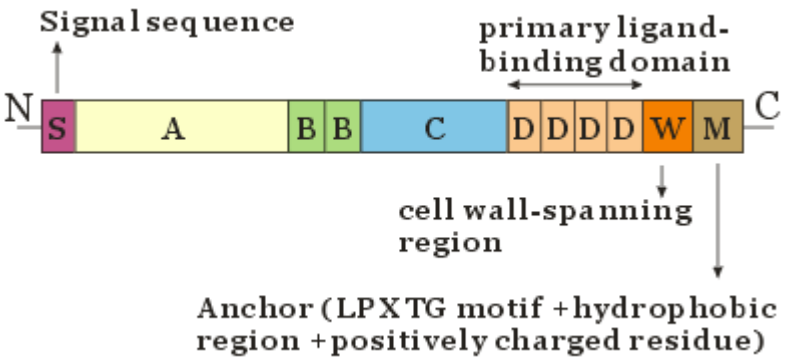
EbpS (elastin-binding proteins)

Intercellular adhesion proteins (icaA; icaB; icaC; icaD; icaR)

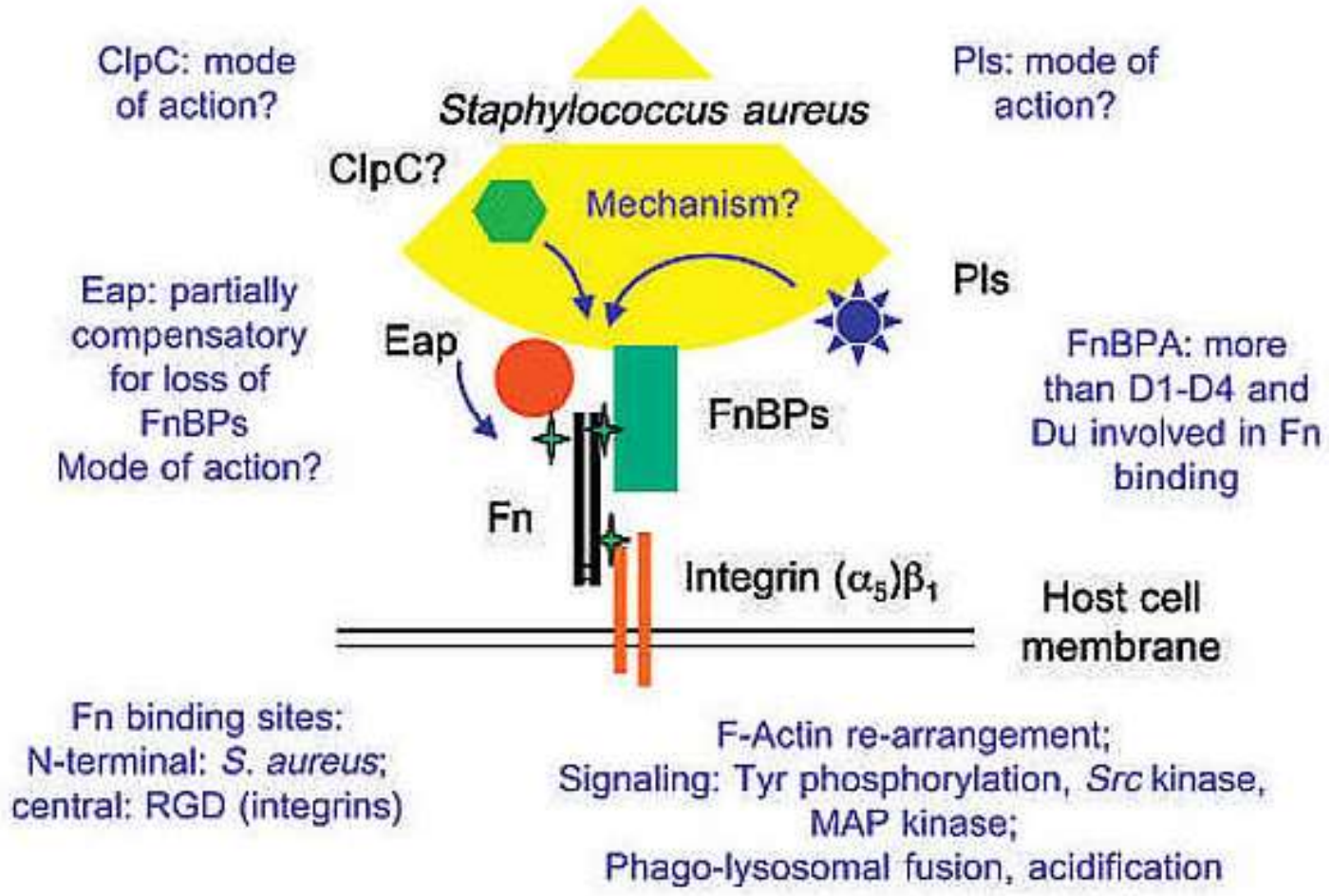
Eap/Map (Extracellular adherence protein/MHC analogous protein)

SDr (Ser-Asp rich proteins - *sdrC*; *sdrD*; *sdrE*)

FnBPs (fibronectin bindings proteins)



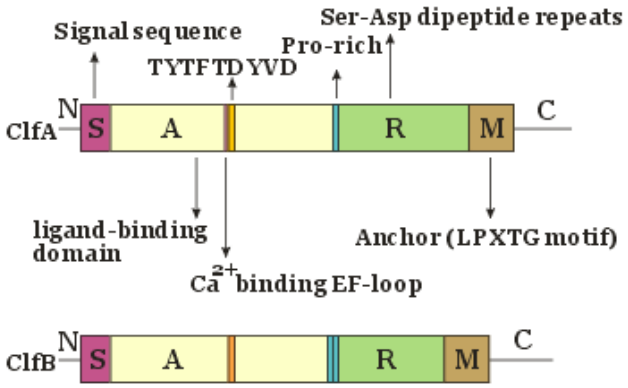
Interaction of *S. aureus* with host cells through FnBP



Invasion:

proteases, lipases, hyaluronide lyase, nuclease, staphylokinase (=fibrinolysin, plasminogen activator), aureolysin

Clumping factor & Plasmacoagulase



Clumping factor A and B

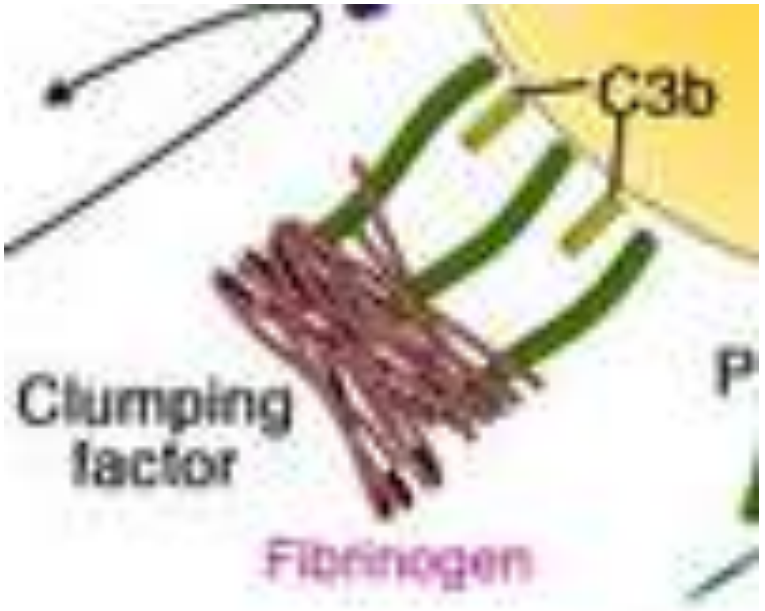
→ **Clf + fibrinogen → fibrin**
Clf + C3b

Tefibazumab

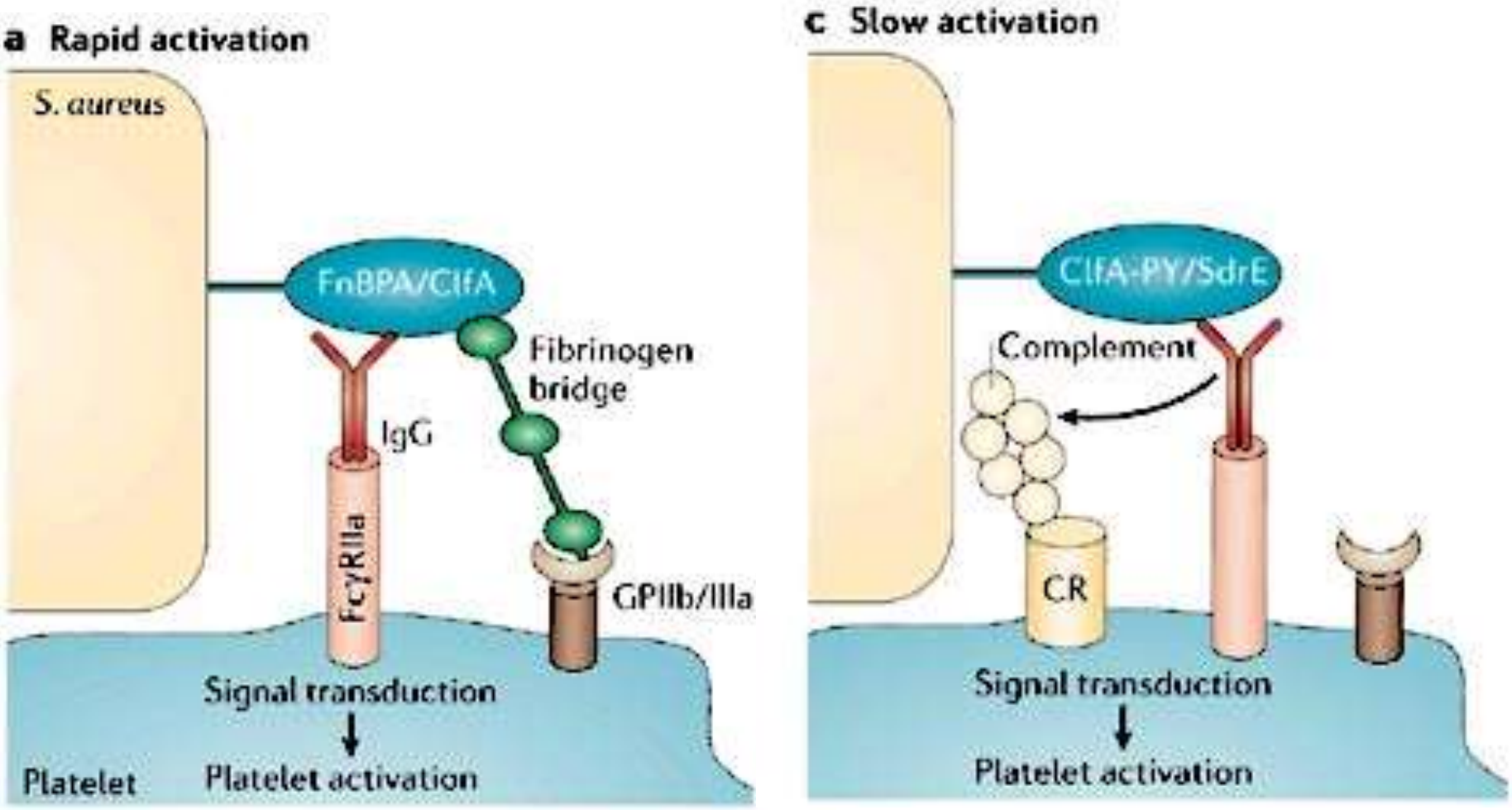
- humanized monoclonal antibody against Clf

Plasmacoagulase

- protrombin → trombin



Trombocytes activation

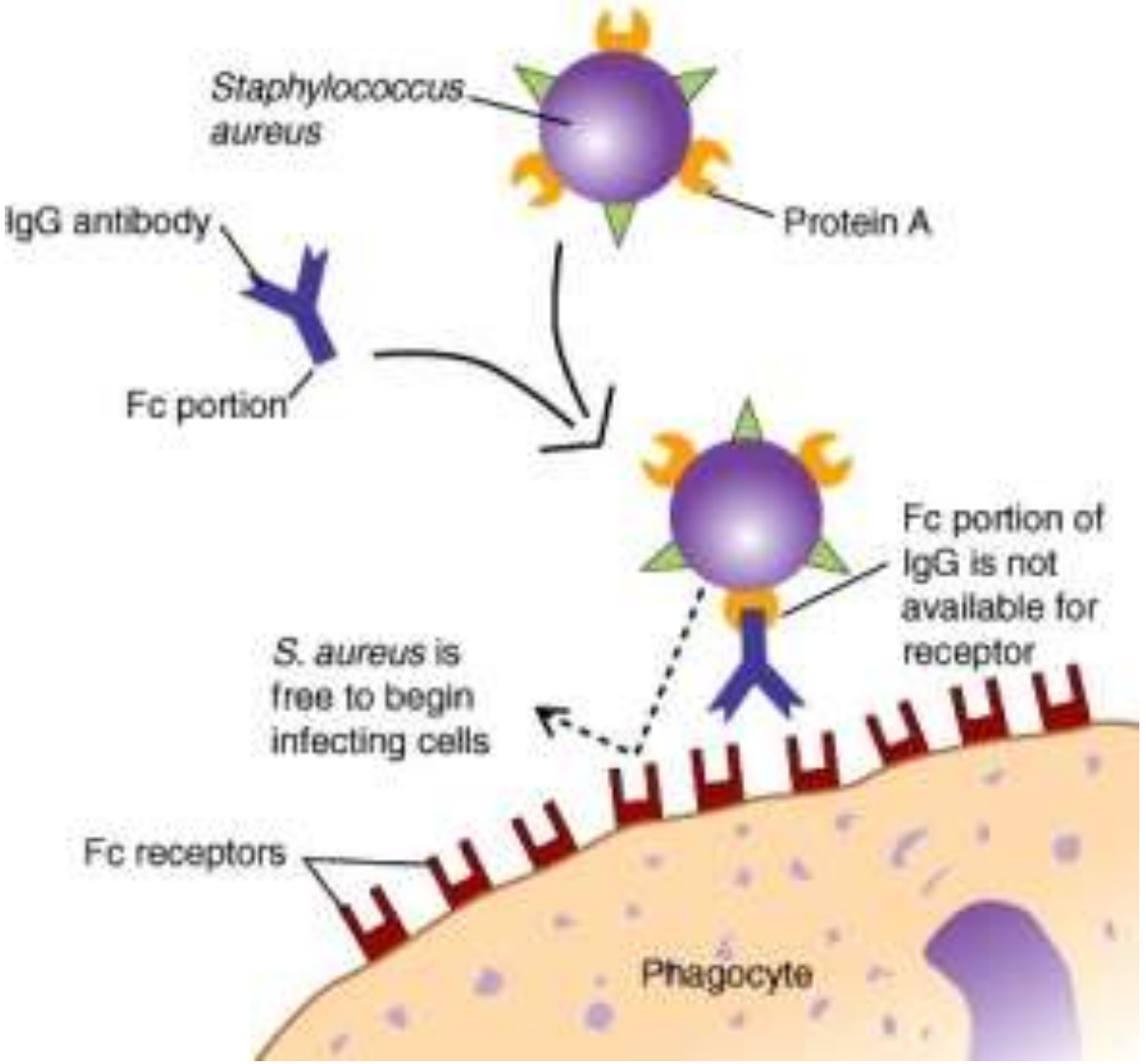


Fitzgerald *et al. Nature Reviews Microbiology* **4**, 445–457 (June 2006) | doi:10.1038/nrmicro1425

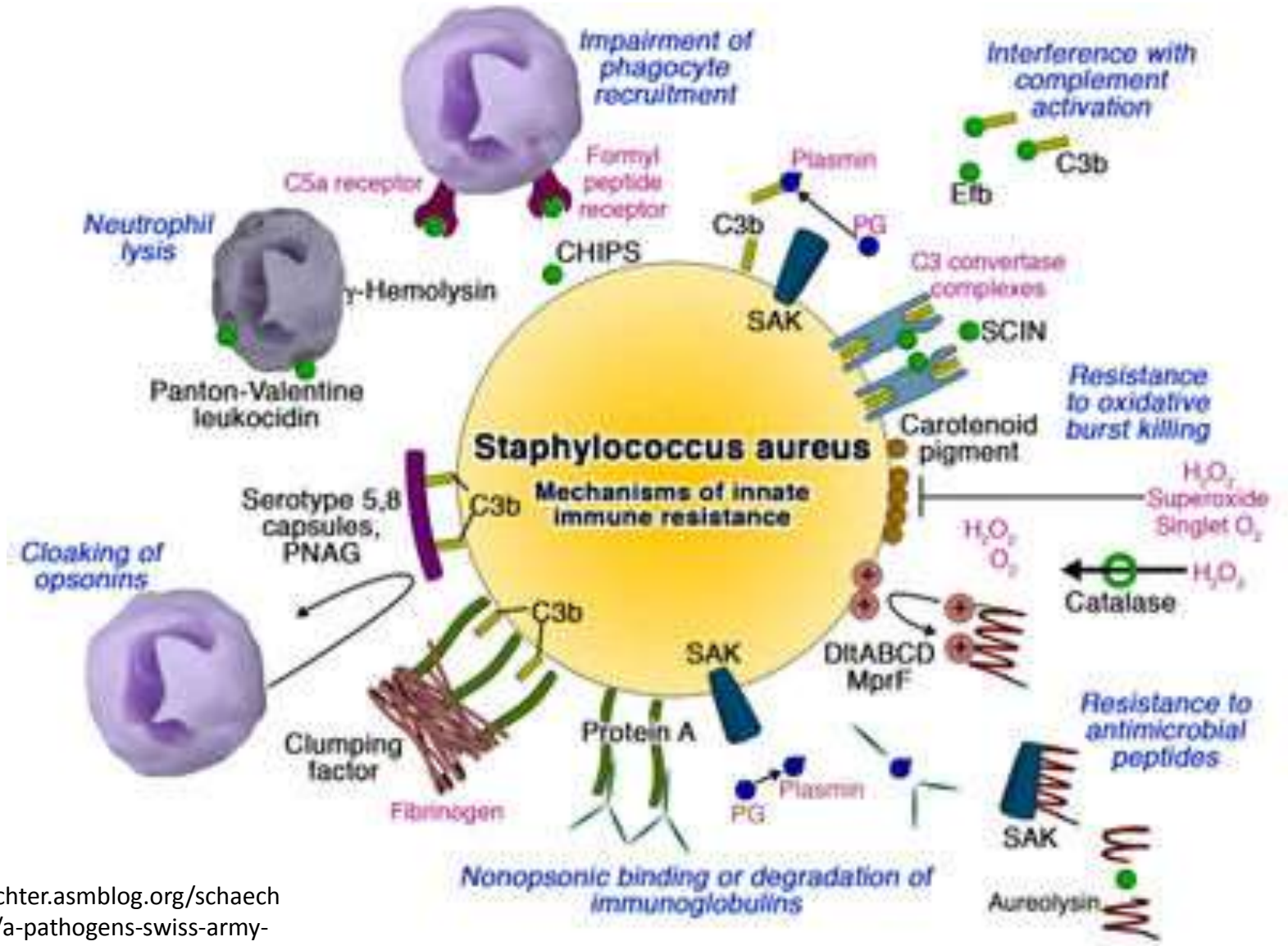
Immune supression

- Leukocidins
- CHIPS (chemotaxis inhibiting protein)
- SCIN (Staphylococcal complement inhibitor)
- Protein A
- Staphyloxantins
- Staphylokinase
- Capsule with PNAG

Protein A


Staphylococcus aureus
IgG antibody
Protein A
Fc portion
Fc portion of IgG is not available for receptor
S. aureus is free to begin infecting cells
Fc receptors
Phagocyte

Immune suppression



http://schaechter.asmblog.org/schaechter/2009/03/a-pathogens-swiss-army-knife.html

Toxins

Exfoliative toxins:
Serine proteases

Cytotoxins:
pores in the membranes of target cells

Enterotoxins:
Conventional antigens or superantigens

Superantigene TSST:
Imunity-activation

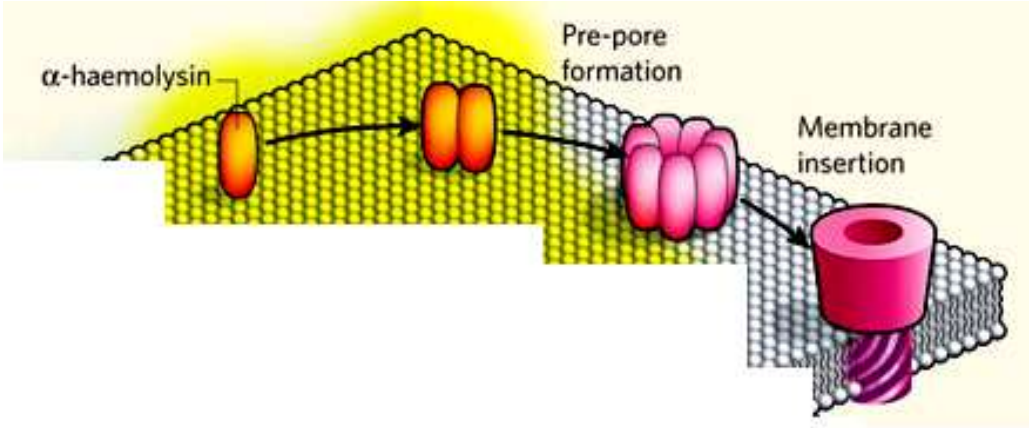
Cytotoxins (cytolysins, hemolysins):

Alpha toxin

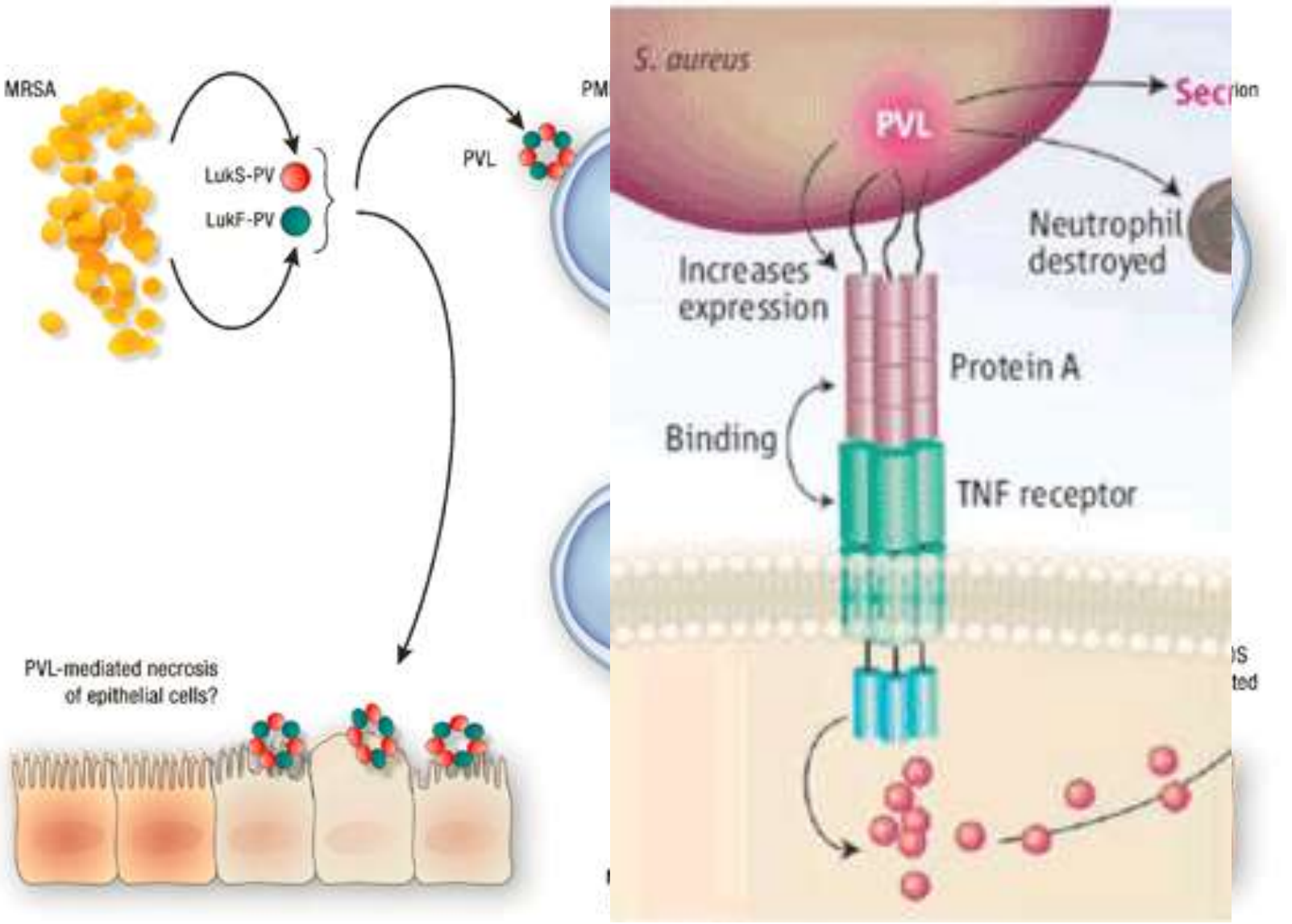
Beta toxin

Gamma toxin

Delta toxin



Panton-Valentine Leucocidin



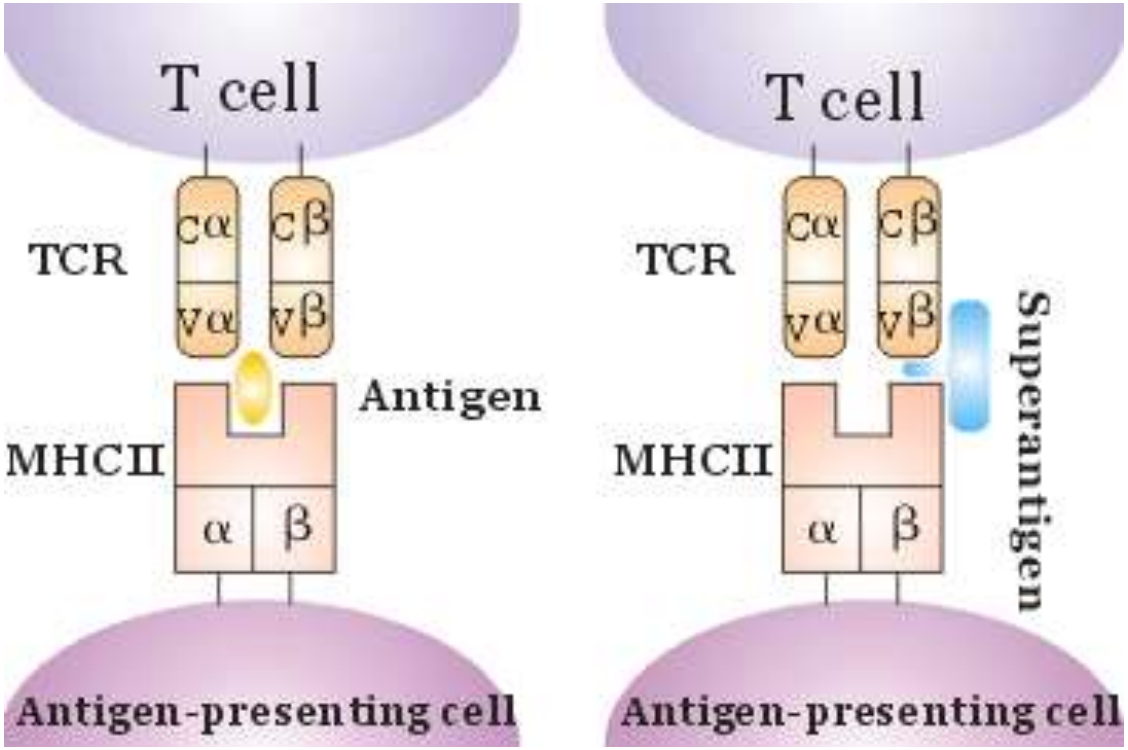
Exfoliative toxins:

serin proteases **ETA, ETB**
→cleavage of Dsg-1
→ intraepidermal peeling

ETC

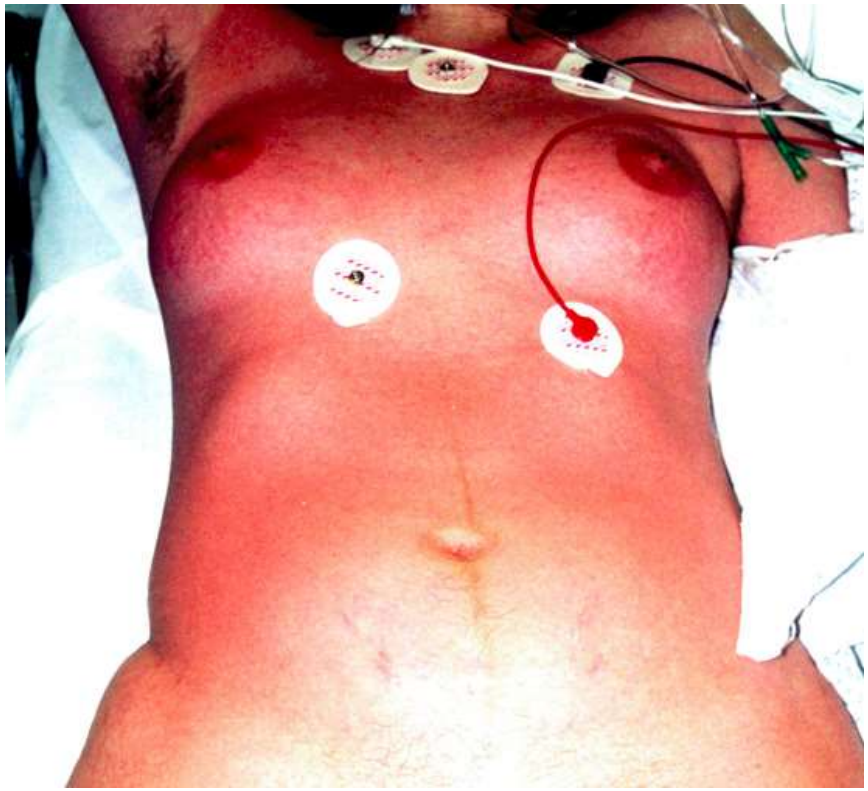
ETD

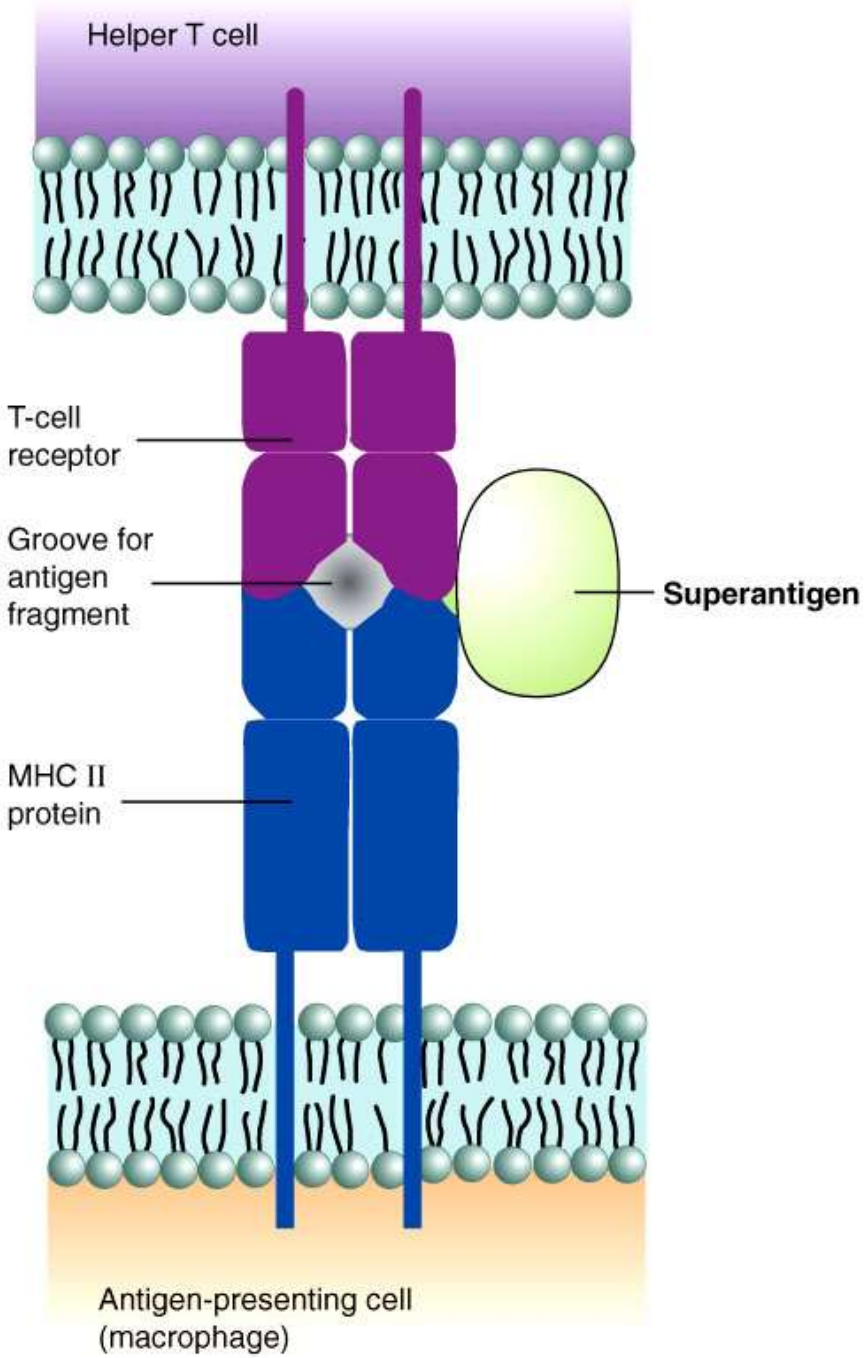
Enterotoxins (A, B, C, D, E, G, H):



Increase of peristaltic, stimulation of emetic centre in brain by derivates of arachidonic acid

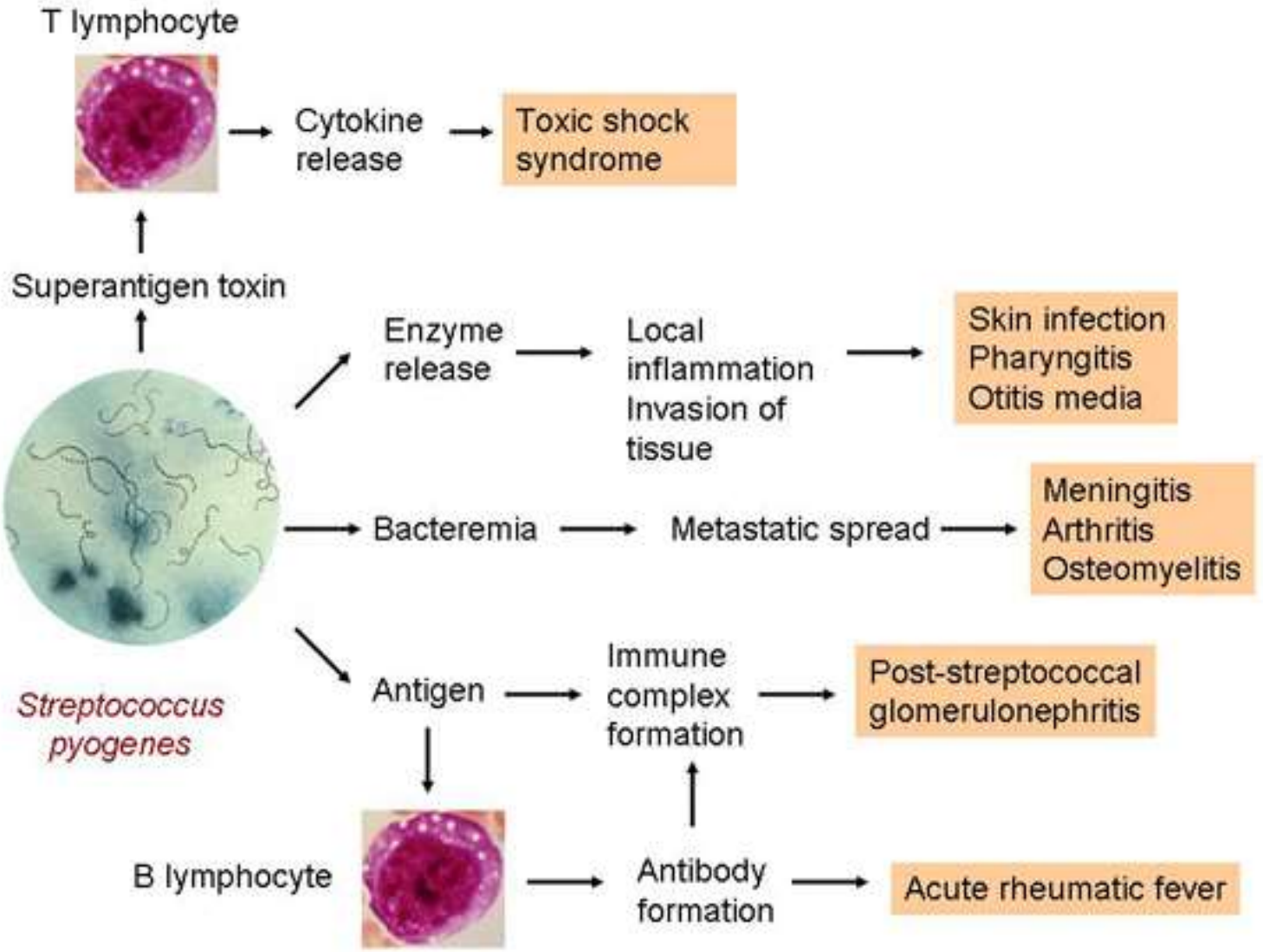
TSST:

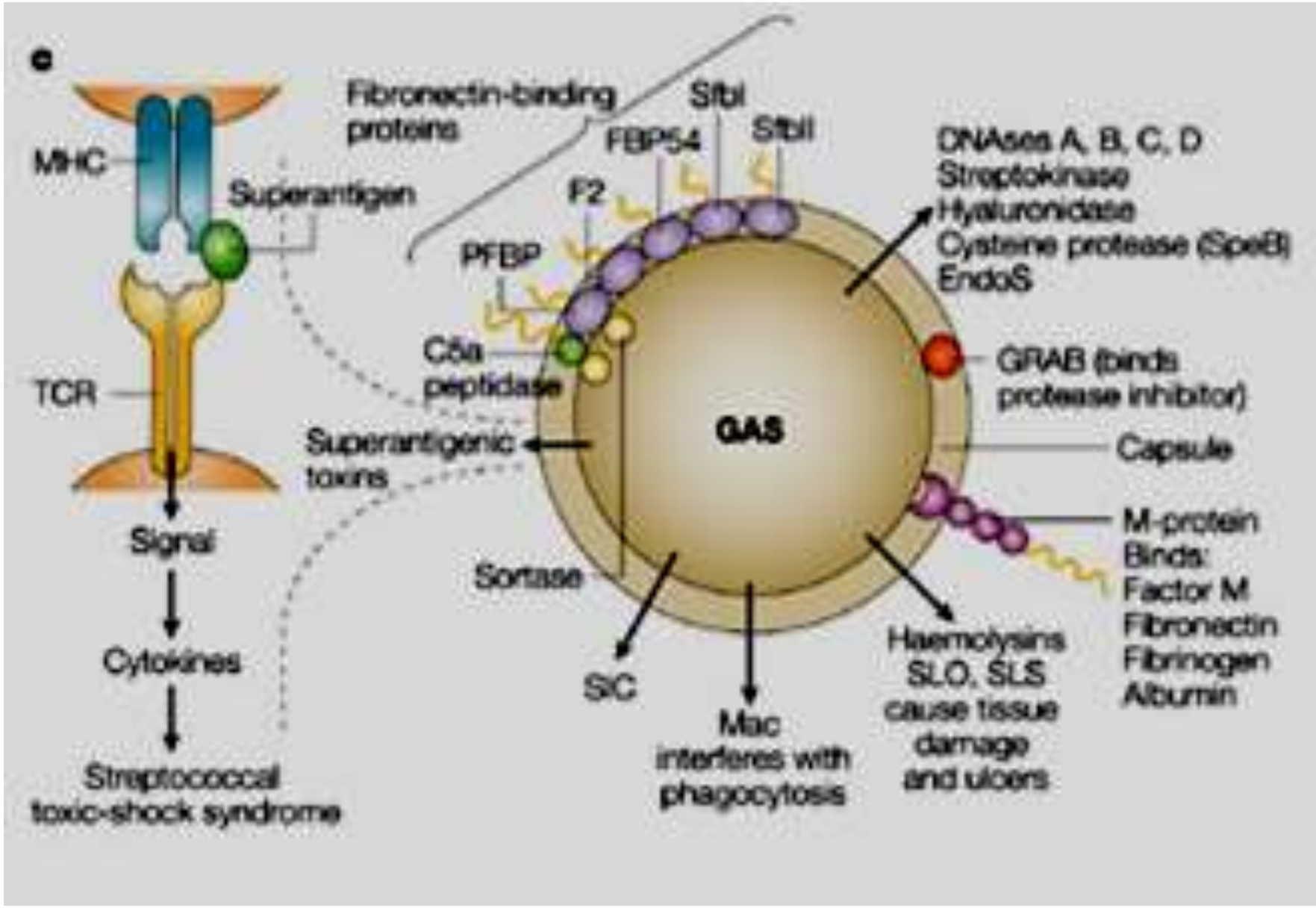




STREPTOCOCCUS PYOGENES

STREPTOCOCCUS PYOGENES




e
MHC
Superantigen
TCR
Signal
Cytokines
Streptococcal toxic-shock syndrome
Fibronectin-binding proteins
Sfbl
FBP54
SfbII
F2
PFBP
C5a peptidase
Superantigenic toxins
Sortase
SIC
Mac interferes with phagocytosis
GAS
DNAses A, B, C, D
Streptokinase
Hyaluronidase
Cysteine protease (SpeB)
EndoS
GRAB (binds protease inhibitor)
Capsule
M-protein
Binds:
Factor H
Fibronectin
Fibrinogen
Albumin
Haemolysins SLO, SLS cause tissue damage and ulcers

Adherence
– fibronectin binding proteins

SfbI (streptococcal fibronectin binding proteinI)

SfbII/SOF (serum opacity factor)

FabA, FabB

FBP54 (fibronectin-binding protein 54)

protein F2

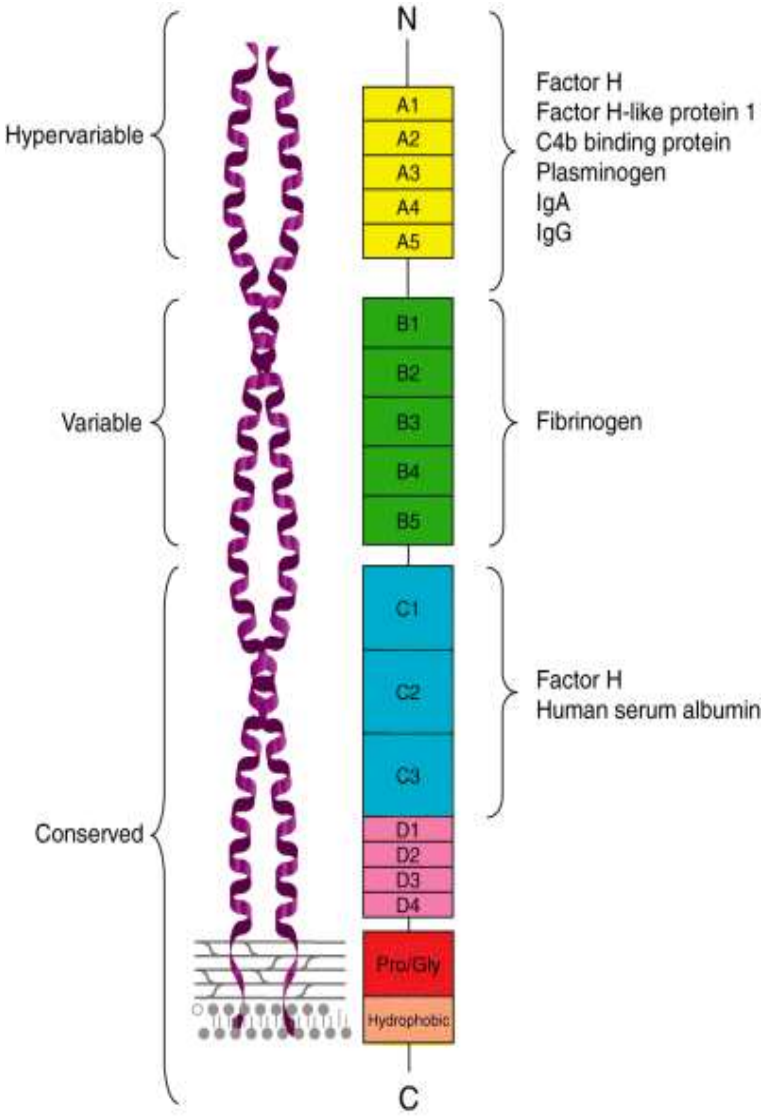
PFBP (*pyogene* fibronectin-binding protein)

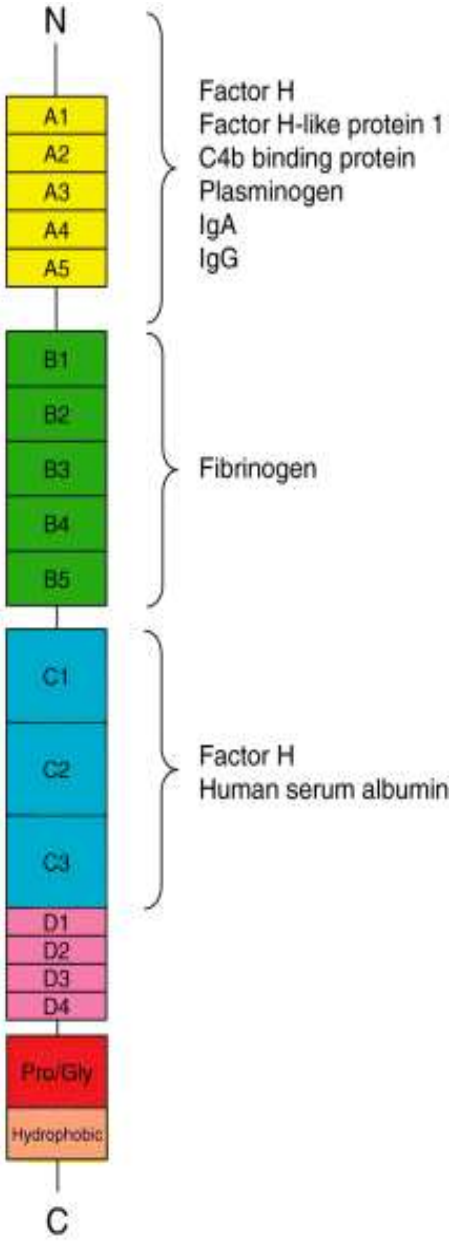
GRAB

- **G-related $\alpha_2$macroglobulin-binding protein**
- **Antiproteolytic molecule**
- protect the M proteins and other surface structures from proteolytic degradation)

M protein (and M-like proteins)

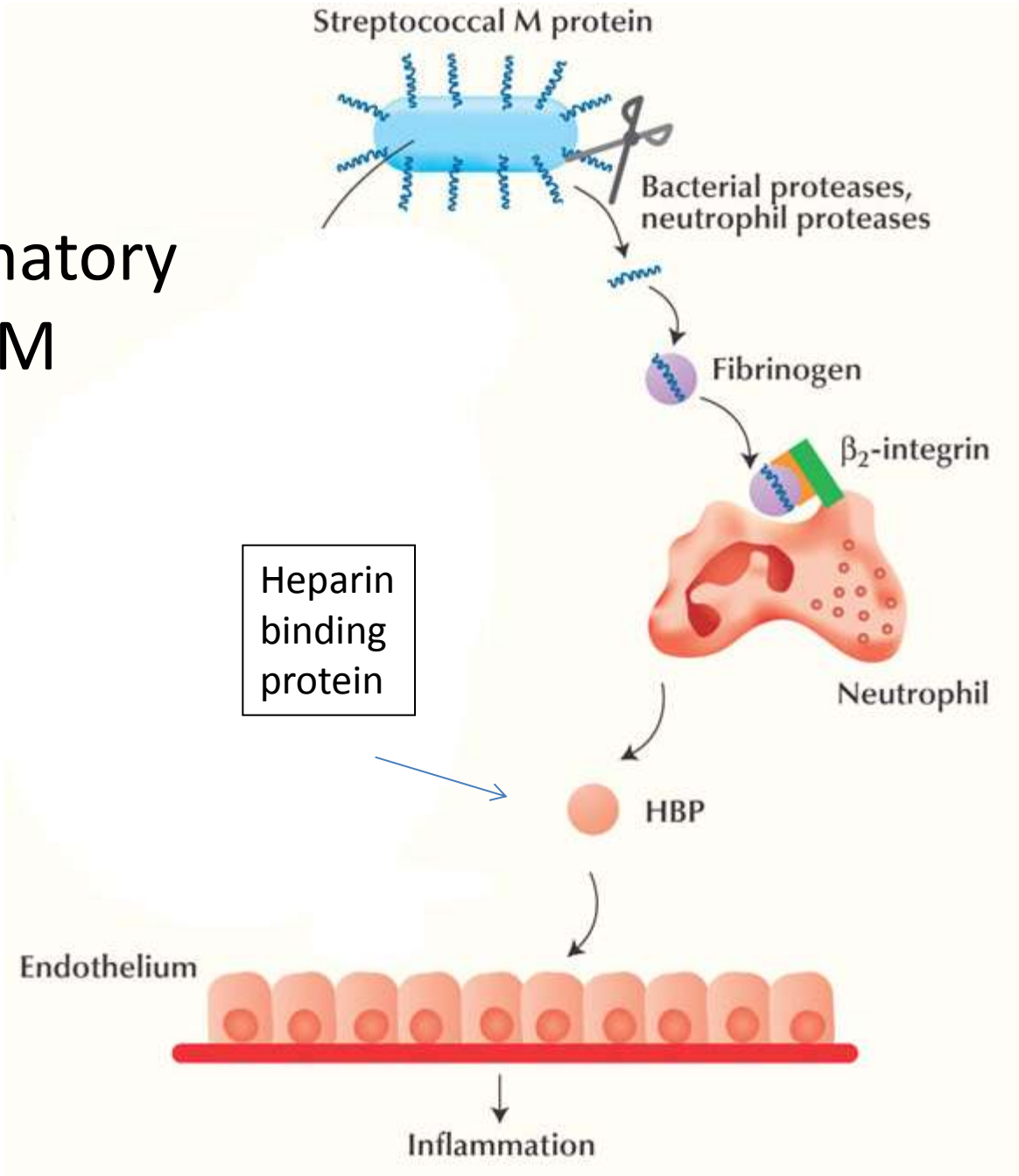
- anchored x cleaved
- coiled coil structure
- A-, B-, C- and D-repeats
- Different M proteins (150) → serotypisation





- Binds to complement control factors → inactivation
- Binds to surface molecule (CD46) on keratinocytes
- binds to fibrinogen, kininogen, or plasminogen → generation of inflammatory response

Proinflamatory effect of M protein



Bacteria invasion

- **Streptokinase & other „Plg binding proteins“**
  plasminogen → plasmin
- **Hyaluronidase**
- **DNAses** (four different DNAses (A,B,C,D))
  reduces the viscosity of pus

Interaction with immunity (1)

C5a peptidase

Serine protease ScpC - degrades IL-8

IdeS (IgG-degrading enzyme of *S. pyogenes*)

SpeB (streptococcal pyrogenic exotoxin B)
cleavage of many proteins including M protein

Interaction with immunity (2)

EndoS (secreted endoglycosidase)

hydrolysis of oligosacharides on IgG

SIC

(streptococcal inhibitor of complement-mediated lysis)

Binds to complement C5b67

Inhibits innate response

Streptolysins (S, O)

Streptolysin S:

- β-hemolysis
- not immunogenic

Streptolysin O:

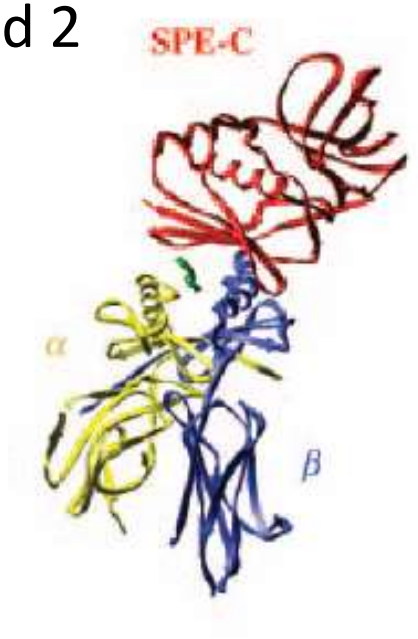
- ASLO
- SLO pores → translocation of NAD glycohydrolase into host cell

Superantigens

12 SAgs identified in GAS
→ **massive systemic release of pro-inflammatory cytokines**,

- streptococcal pyrogenic exotoxins (SPEs) A, C, G-M
- streptococcal superantigen (SSA)
- streptococcal mitogenic exotoxin (SMEZ) 1 and 2

→ ***Acute rheumatic fever*** *(later, heart tissue)*
→ ***Streptococcal toxic shock syndrome*** *(STSS)*



Summary:

Staphylococcus aureus:

MSCRAMMS → attachment

Invasines (enzymes)

Protein A (immunosuppres.)

Clumping f. + plasmacoagulase (abscess formation)

Exotoxins, hemolysins

Streptococcus pyogenes:

Fibronectin binding proteins

Invasines

Protein M (immunomodulation)

GRAB (protease inhibition)
Immune destructing proteins

Superantigenes, streptolysins

Thank you for your attention!