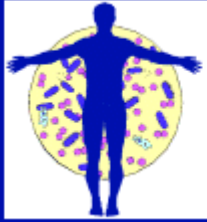




SBIMC  
BVIKM



Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

## **Catheter-related infections: practical aspects in 2003**

A joint meeting of the *Société Belge d'Infectiologie et de Microbiologie Clinique / Belgische Vereniging voor Infectiologie en Klinische Microbiologie* (21st meeting) and the *Groupement pour le Dépistage, l'Etude et la Prévention des Infections Hospitalières / Group ter Opsporing, Studie en Preventie van Infecties in de Ziekenhuizen*

**Thursday 20th November 2003**

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# Origin and pathogenesis of catheter-related infections

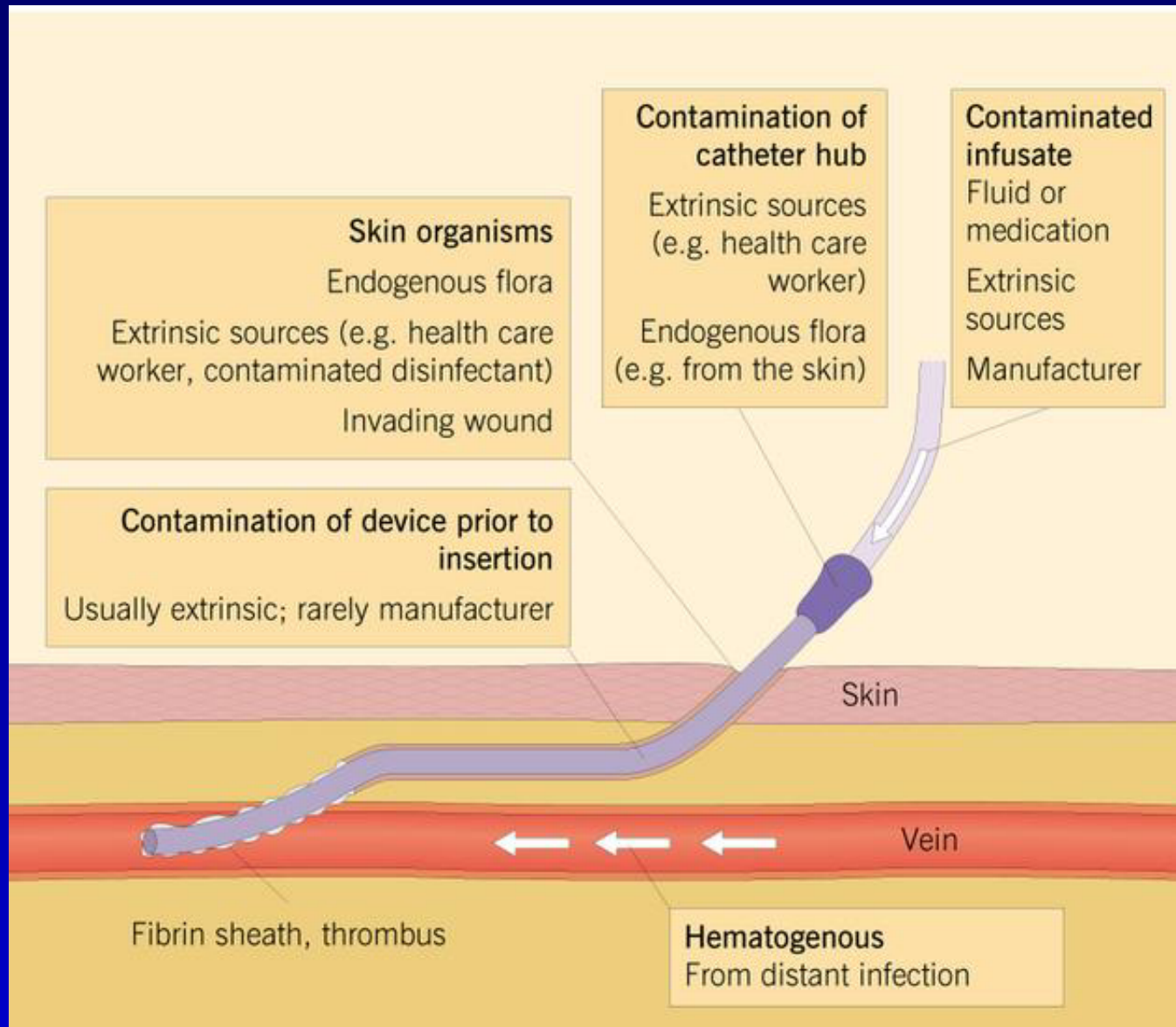
J. Van Eldere

Rega Institute and UZ  
Gasthuisberg - KULeuven

# contents

- Origin of catheter-related infections
- Molecular events in CRI's
  - CRI's, foreign-body infections and the pathogenesis of biofilm formation in CRI's
- Conclusions

# Origin of CRI's



# Origin of CRI's

- Colonisation of catheters
  - Short term (<8 days)
    - Micro-organisms from the skin (70-90%)
    - Bacteria from the hub/lumen (10-50%)
    - Bacteria from bloodstream (3-10%)
    - Bacteria from infusate (<3%)
  - Long term (>8 days)
    - Most frequent : hub
    - Also frequent : skin

# Origin of CRI's

- Common micro-organisms
  - *Staphylococcus aureus*
  - Coagulase-negative staphylococci
  - Enterococci
  - *Candida* spp.
- Uncommon micro-organisms
  - *Enterobacter* spp.
  - *Acinetobacter* spp.
  - *Serratia marcescens*
  - *Pseudomonas* spp.
  - *Malassezia furfur*

# Molecular events in CRI's

- Three stages:
  - Attachment:
    - Uncoated plastic material
    - Material coated with host-derived proteins
  - Biofilm formation
    - Intercellular adhesion and accumulation of multi-layered cell clusters
    - Generation of slime glyocalix
  - Biofilm persistence and detachment of cell-clusters

# Molecular events in CRI's : attachment

- Initial attachment to uncoated plastic material
  - primary adhesion: within seconds, aspecific, dependent on physicochemical interactions (vd Waals, electrostatic) and surface properties of foreign body surface
  - Main bacterial parameter: hydrophobicity of bacterial surface
    - Role of AtlE (autolysin) in surface hydrophobicity, of lipoteichoic-like acids?, of fimbria-like polymers
- Significance for biofilm formation considering rapid (seconds) coating of foreign body?

» Ferreiros, FEMS Microbiol Lett, 89, Vacheethasanee, J Biomed Mat, 98, Vacheethasanee, J Biomed Mat, 00, Heilmann, Infect Immun, 96, Gross, Infect Immun, 01, Lambert, FEMS Immun Med Micro, 00



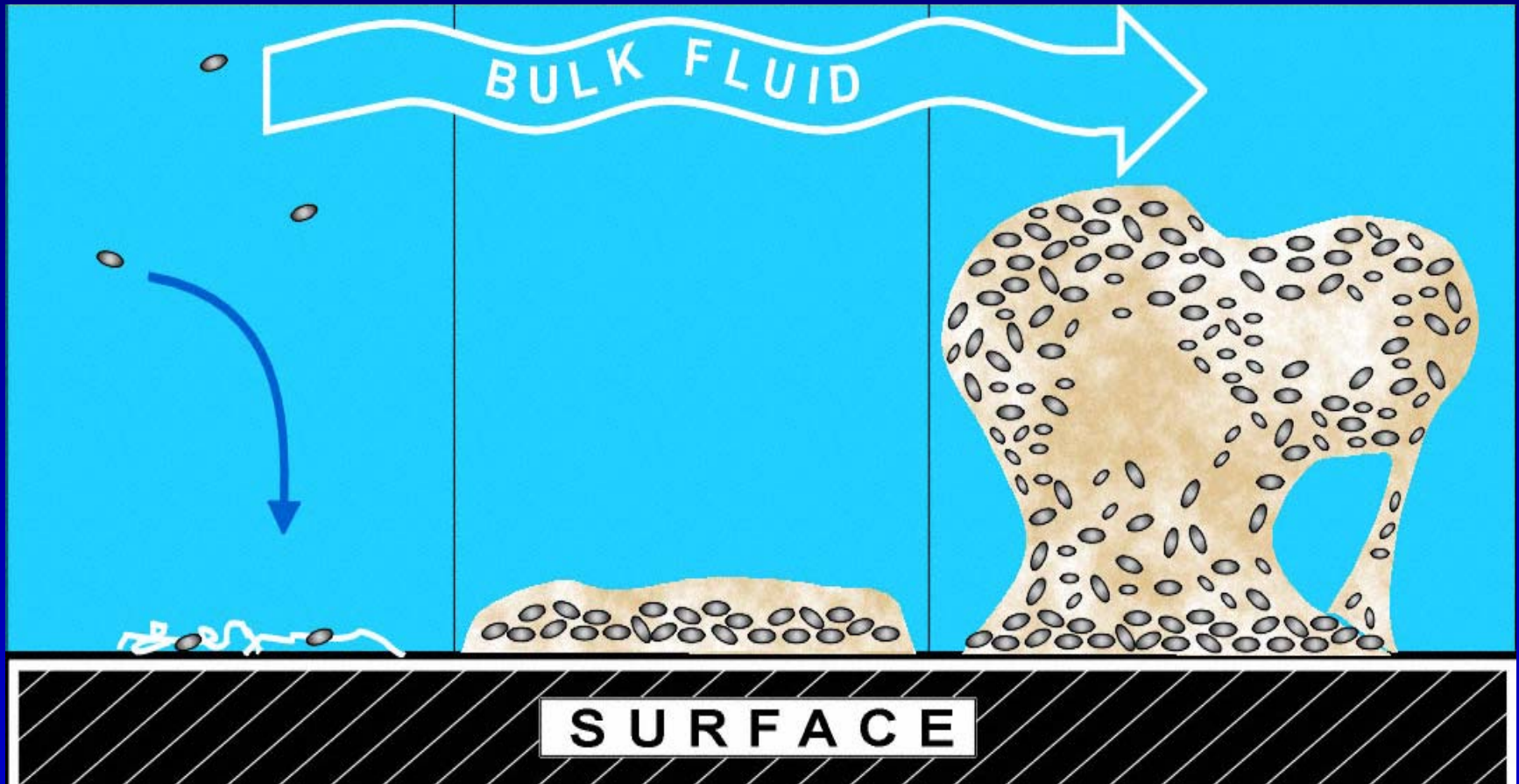
# Molecular events in CRI's : attachment

- (Secondary) attachment to material coated with host-derived proteins
  - Promoted by surface irregularities, host-derived substances (fibronectin, collagen, laminin, vitronectin, fibrinogen, fibrin thrombi, activated platelets)
  - MSCRAMM's:
    - fibrinogen-binding protein (Fbe)
    - Few peptidoglycan-bound surface proteins
    - Role of non-covalently linked surface proteins (AtIE)
  - Capsular polysaccharide adhesin (PS/A)
    - Encoded by *icaABCD*
      - » Gross, Infect Immun, 01, Franson, JCM, 84, Heilman, Mol Microbiol, 97, Timmerman, Infect Immun, 91, Tojo, JID, 88, Mc Kenney, Infect Immun, 98, Dunne, CMR, 02, Nilsson, Infect Immun, 98

# Molecular events in CRI's

Attachment

Biofilm formation



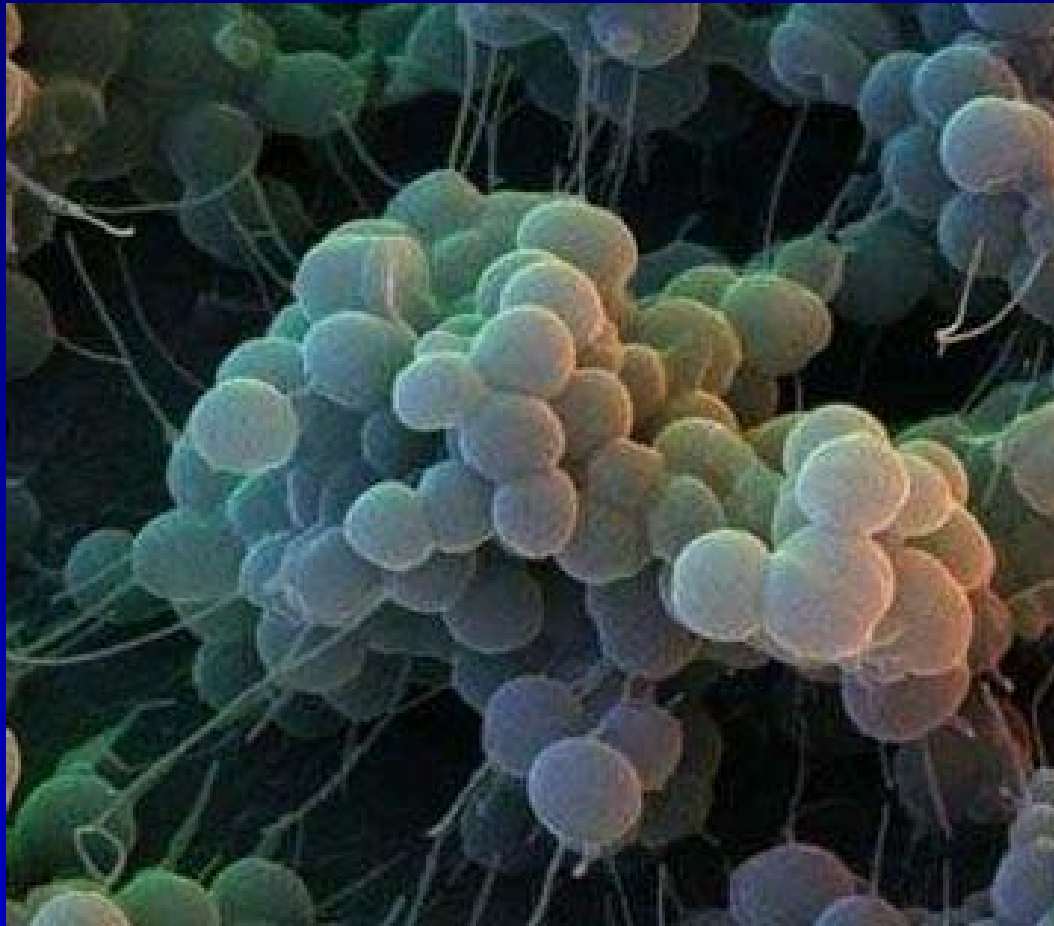
# Molecular events in CRI's: biofilm formation

- Intercellular adhesion and accumulation
  - 40 to 60 min after adhesion
  - multi-layered clusters of interconnected cells
  - Several polymeric carbohydrates and proteins involved
    - Accumulation Associated Protein (AAP)
    - Polysaccharide Intercellular Adhesin (PIA) or PS/A?
      - encoded by *icaABCD*
        - » Mack, J Bac, '96, Heilmann, Mol Microbiol, '97, Husain, Infect Immun, '97, Stewart, Lancet, '01, Zimmerli, JID, '82

# Molecular events in CRI's: biofilm formation

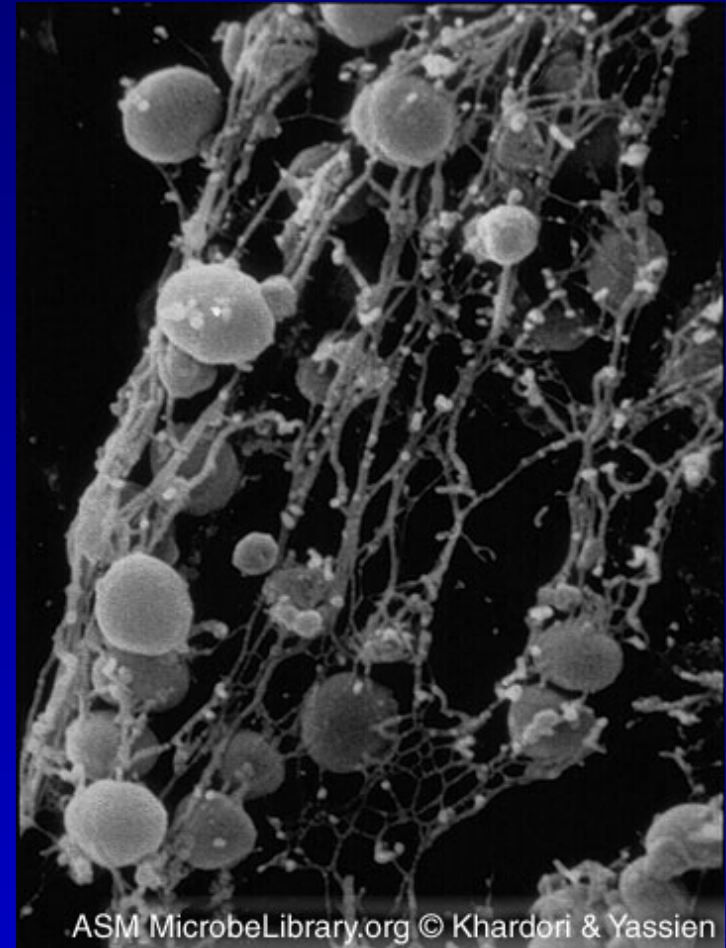
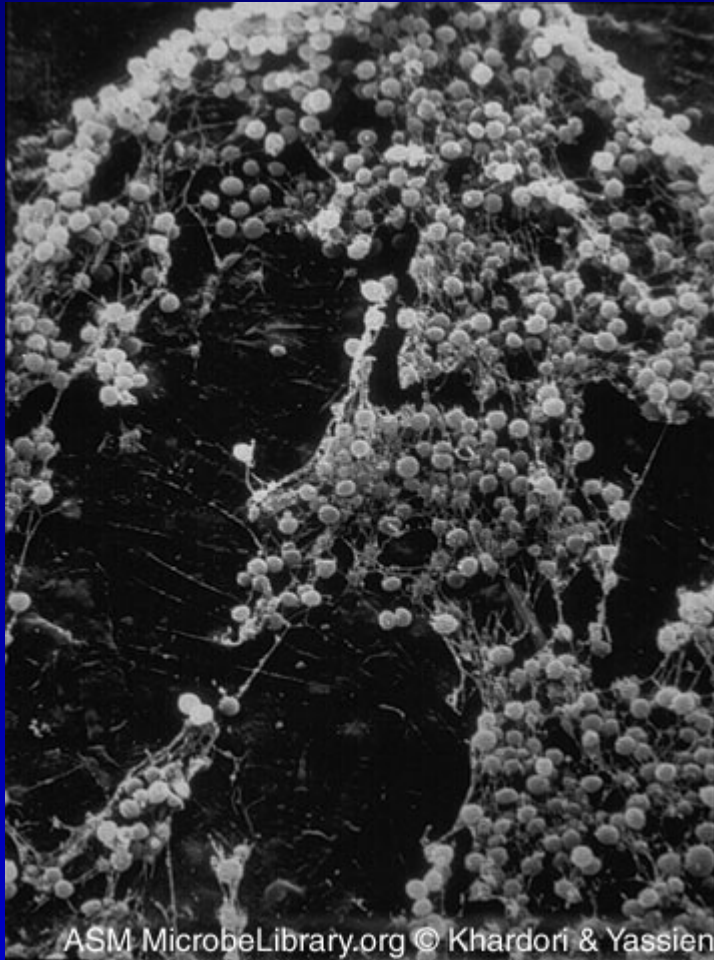
- Generation of extracellular slime
  - Composition extracellular slime
    - Teichoic acid
    - Bacterial and host proteins
    - Polysaccharide Intercellular Adhesin (PIA)
      - ≈  $\beta$ -1,6-linked *N*-acetylglucosamine (20% non-acetylated)
    - Capsular polysaccharide adhesin (PS/A)
      - $\beta$ -1,6-linked *N*-succinylglucosamine
        - » Hussain, FEMS Microbiol Rev, '93, Kojima, JID, '90, Mack, J Bac, '96, McKenney, Infect Immun, '98, Gerke, J Biol Chem, '98,

# Staphylococcal biofilm formation: intercellular adhesion

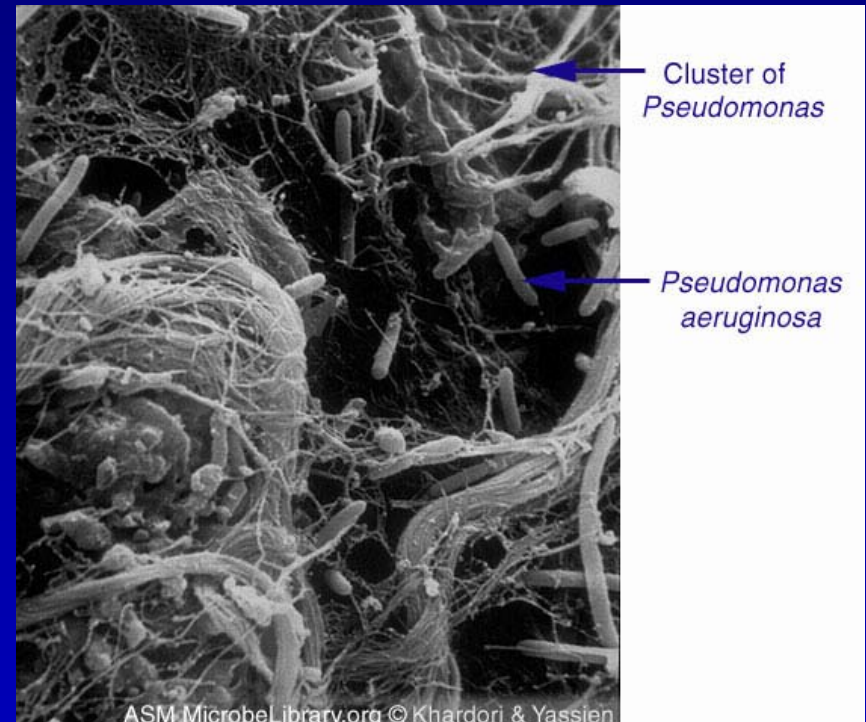
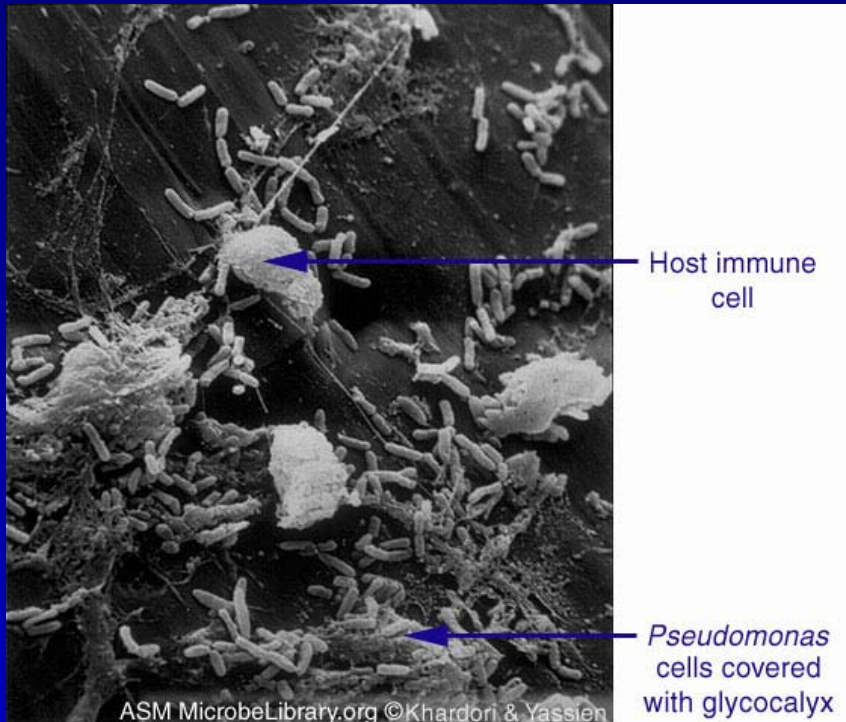


Intercellular adhesion

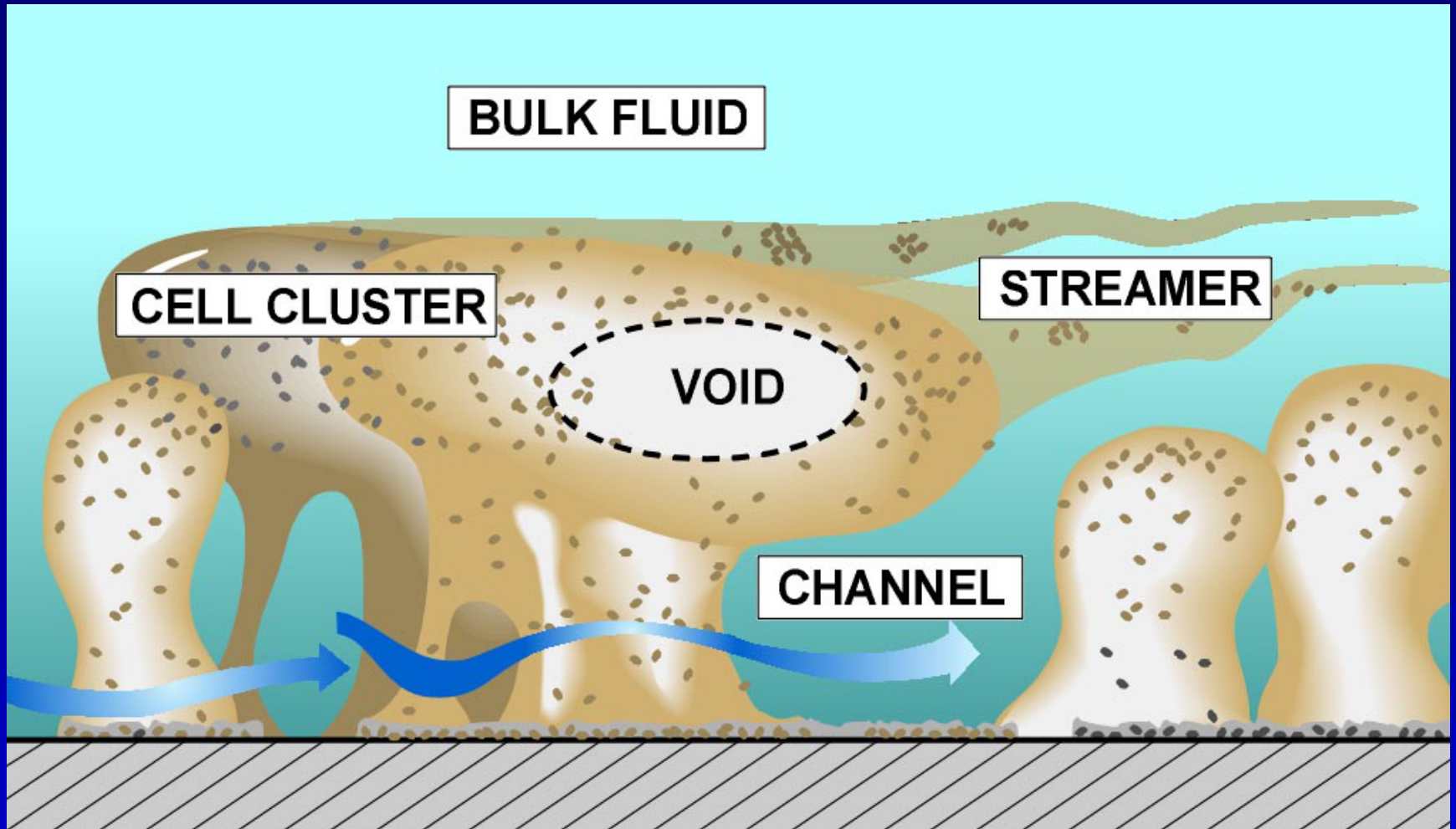
# Staphylococcal biofilm formation



# *Pseudomonas* biofilm formation

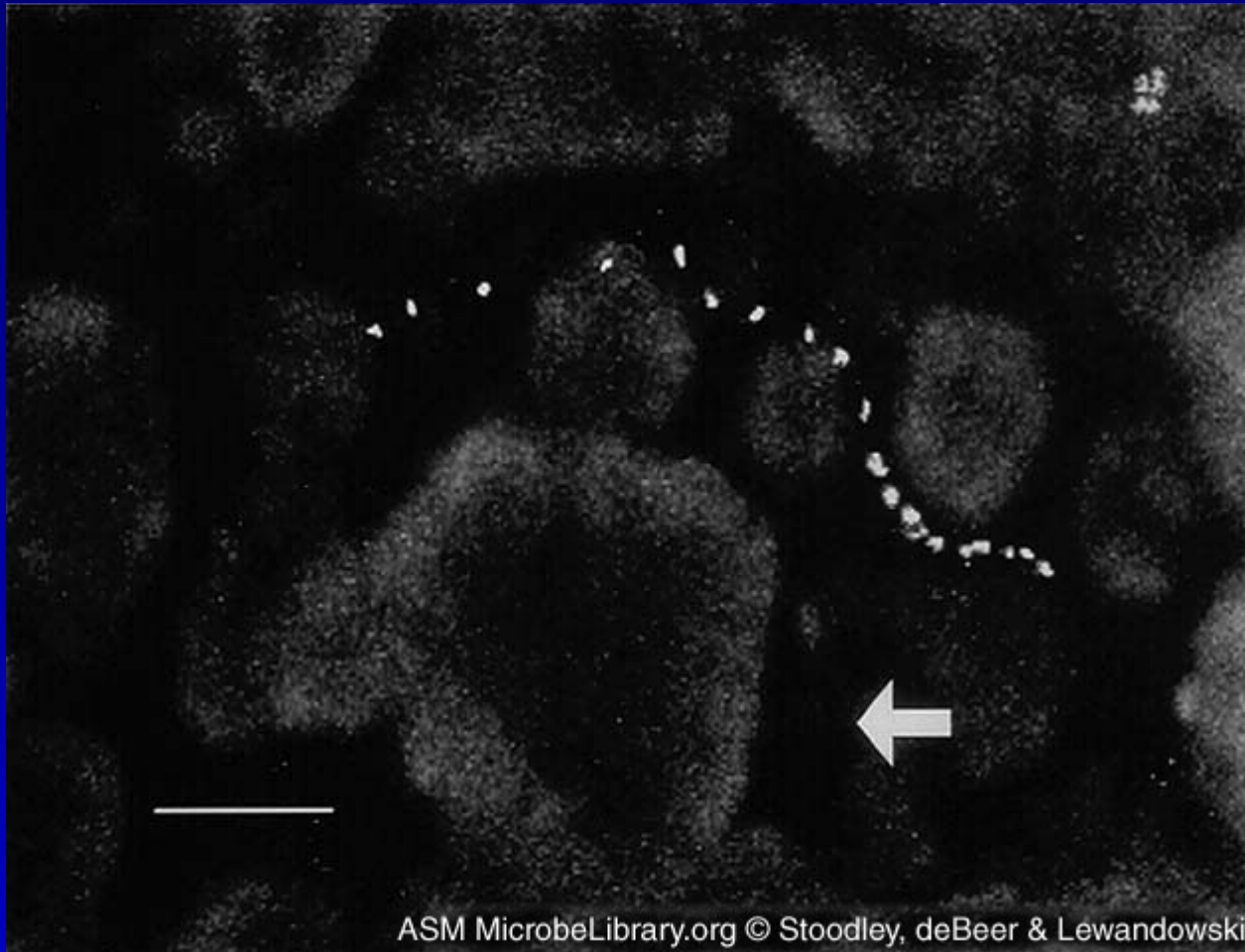


# Biofilm ultrastructure

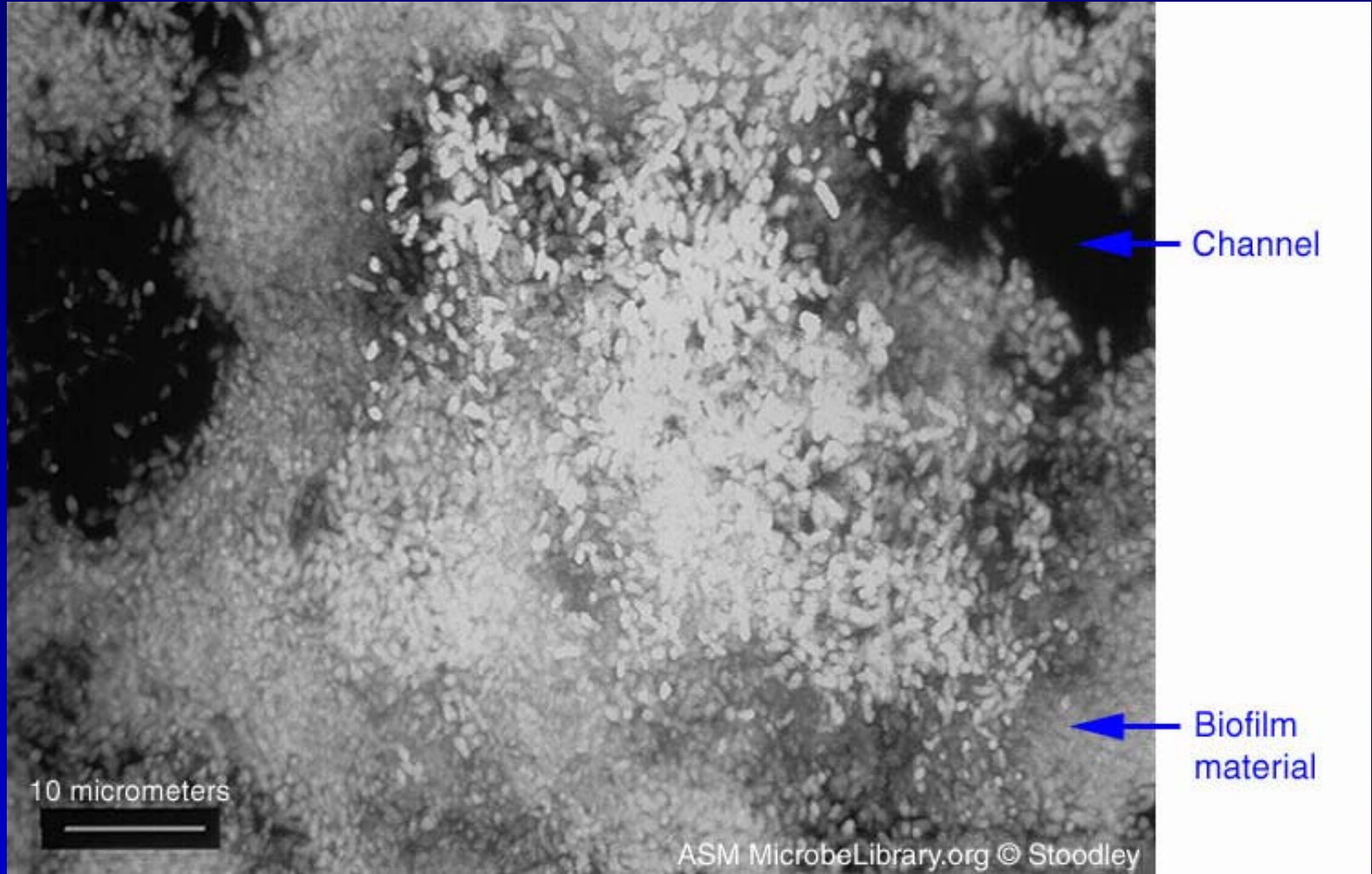




# Biofilm ultrastructure



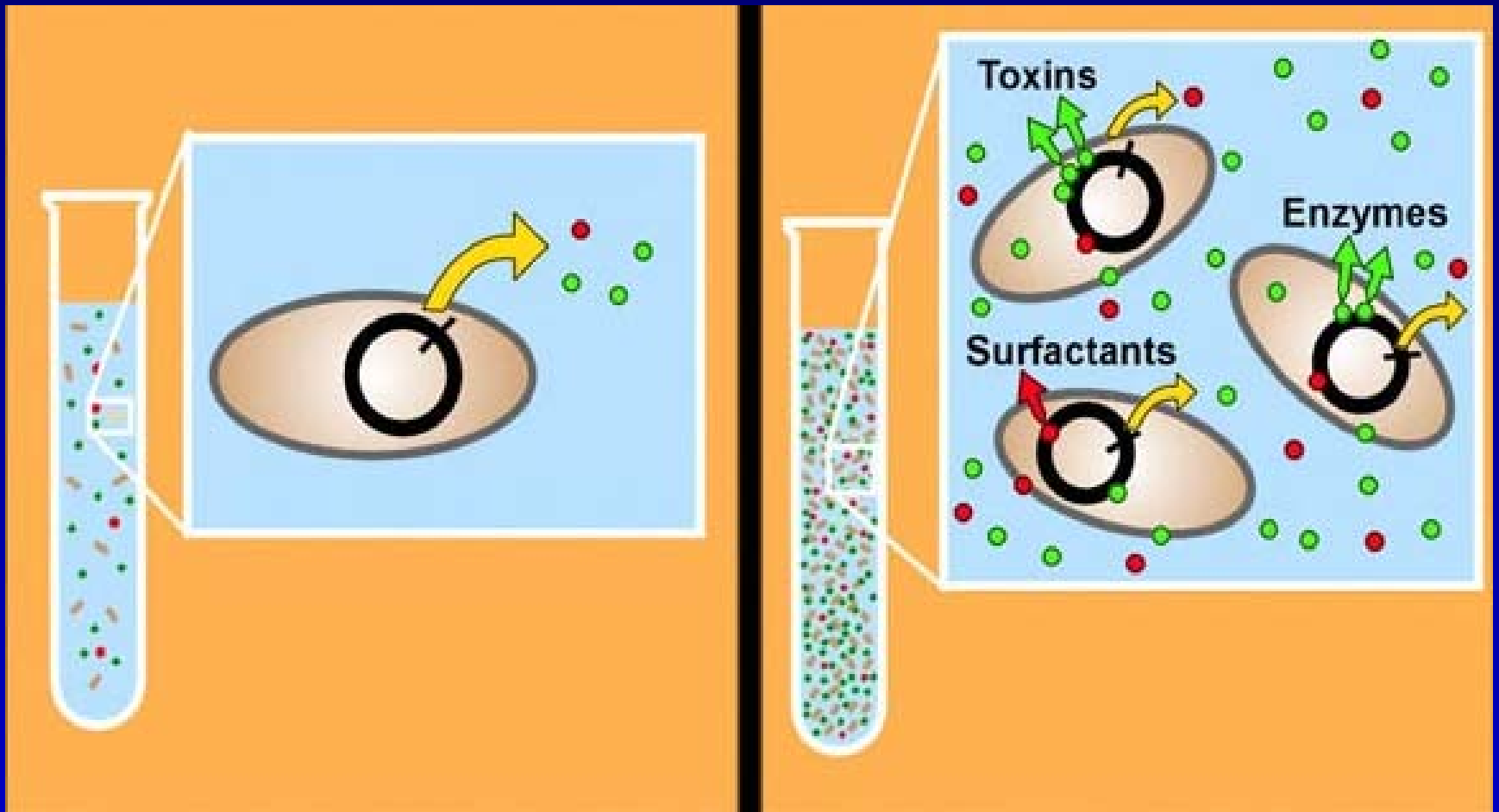
# Biofilm ultrastructure



# Molecular events in CRI's: biofilm formation

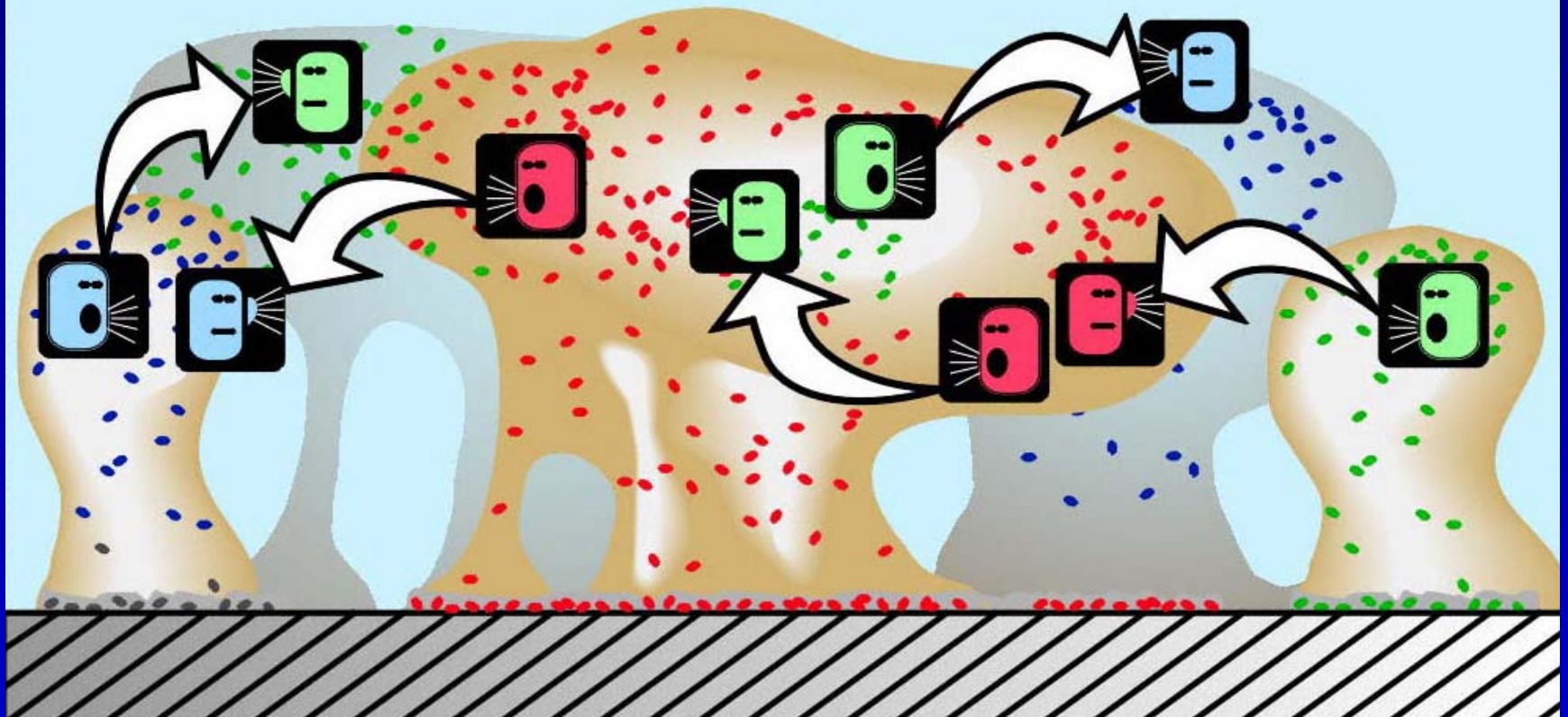
- Cellular control of biofilm formation
  - Role of *agr* quorum-sensing system:
    - Stimulates expression virulence factors
    - Down regulates expression of surface–proteins (including AtIE)
  - Role of additional regulatory loci:
    - *sar*: SarA co-stimulates with AgrA~P transcription RNAIII
    - SigB: stimulates PIA and biofilm production
      - » Otto, FEBS Lett, '98, Rachid, AAC, '00, Fluckiger, Infect Immun, '98, Vuong, Infect Immun, '00, Otto, Pept, '01

# Quorum-sensing in biofilms



# Quorum-sensing in biofilms

## Cell-Cell Communication



# Molecular events in CRI's

Attachment

biofilm formation

persistence & detachment

Planktonic cells

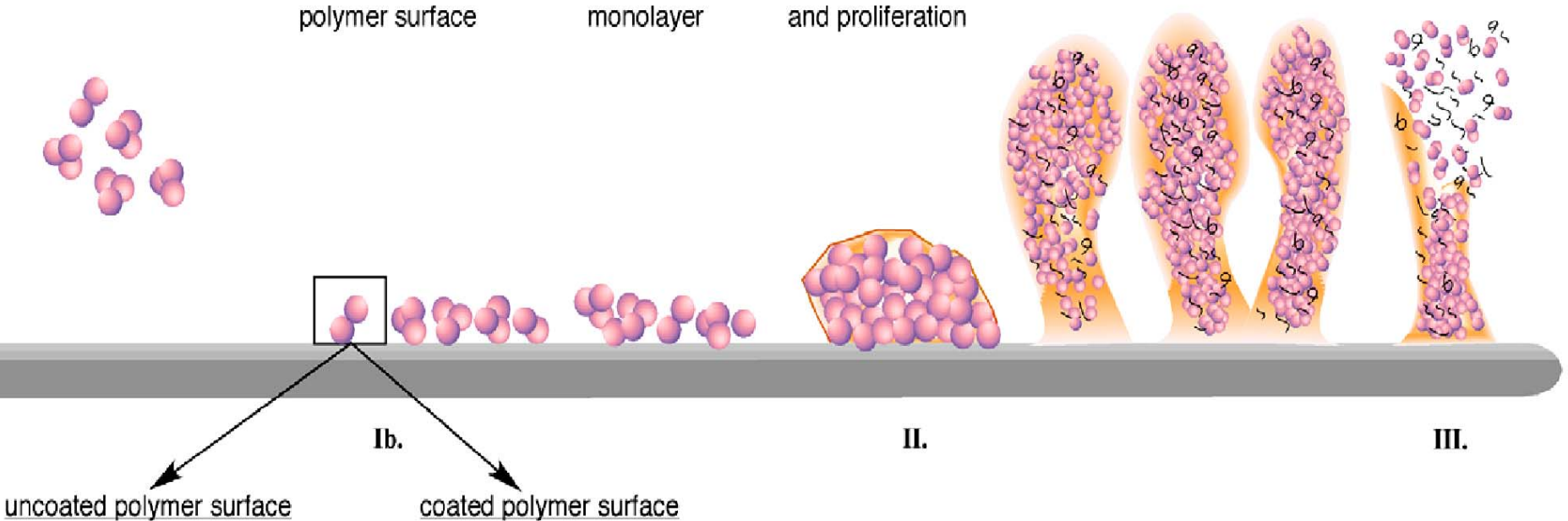
Attachment to polymer surface

Attached cell monolayer

Cell-cell adhesion and proliferation

Mature biofilm

Detachment



# Molecular events in CRI's: persistence

– Deficiencies/modulation of local host immune response

- Due to bacterial products
- Due to the foreign body

» Zaat, NTG, '02, Chuard, JID, '91, Chuard, AAC, '93, Baddour JID, '88, Zimmerli, JID, '82,

– Intrinsic resistance to antimicrobial compounds:

- increased MBC values

# Molecular events in CRI's: persistence

persistence of CoNS biofilms:

- resistance against host immune defences

	blood	foreign body
Numbers log <sub>10</sub> CFU	6.3 / 1.7	6.2 / 2.1
Chemotactic index	2.4 / 0.2	2.0 / 0.5
phagocytosis	410 / 74	60 / 8.9
respiratory burst activity	12.2 / 0.5	4.4 / 2.8
expression of ICAM-1	3.7 / 2.4	43 / 9.8

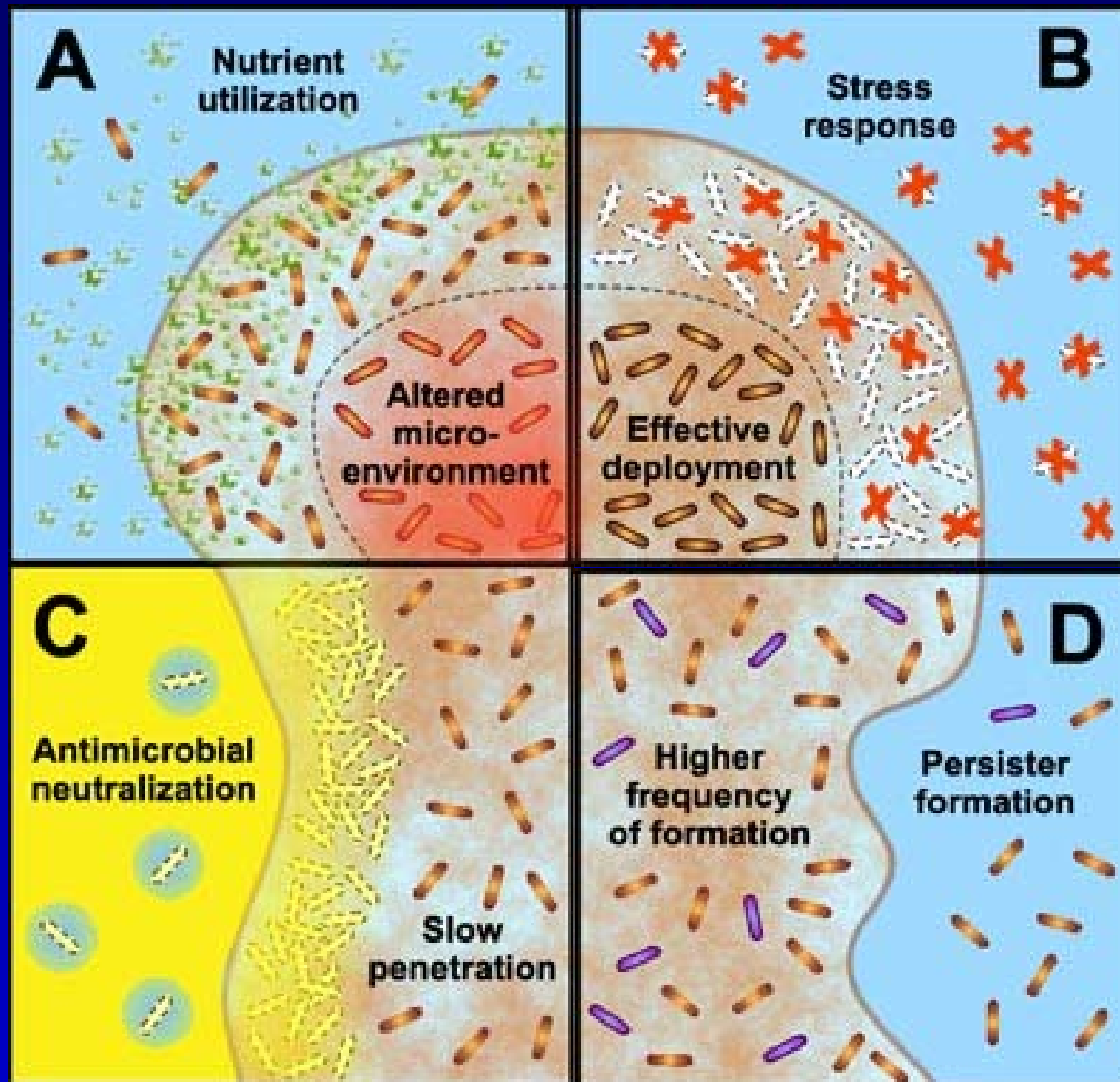


# Molecular events in CRI's: persistence

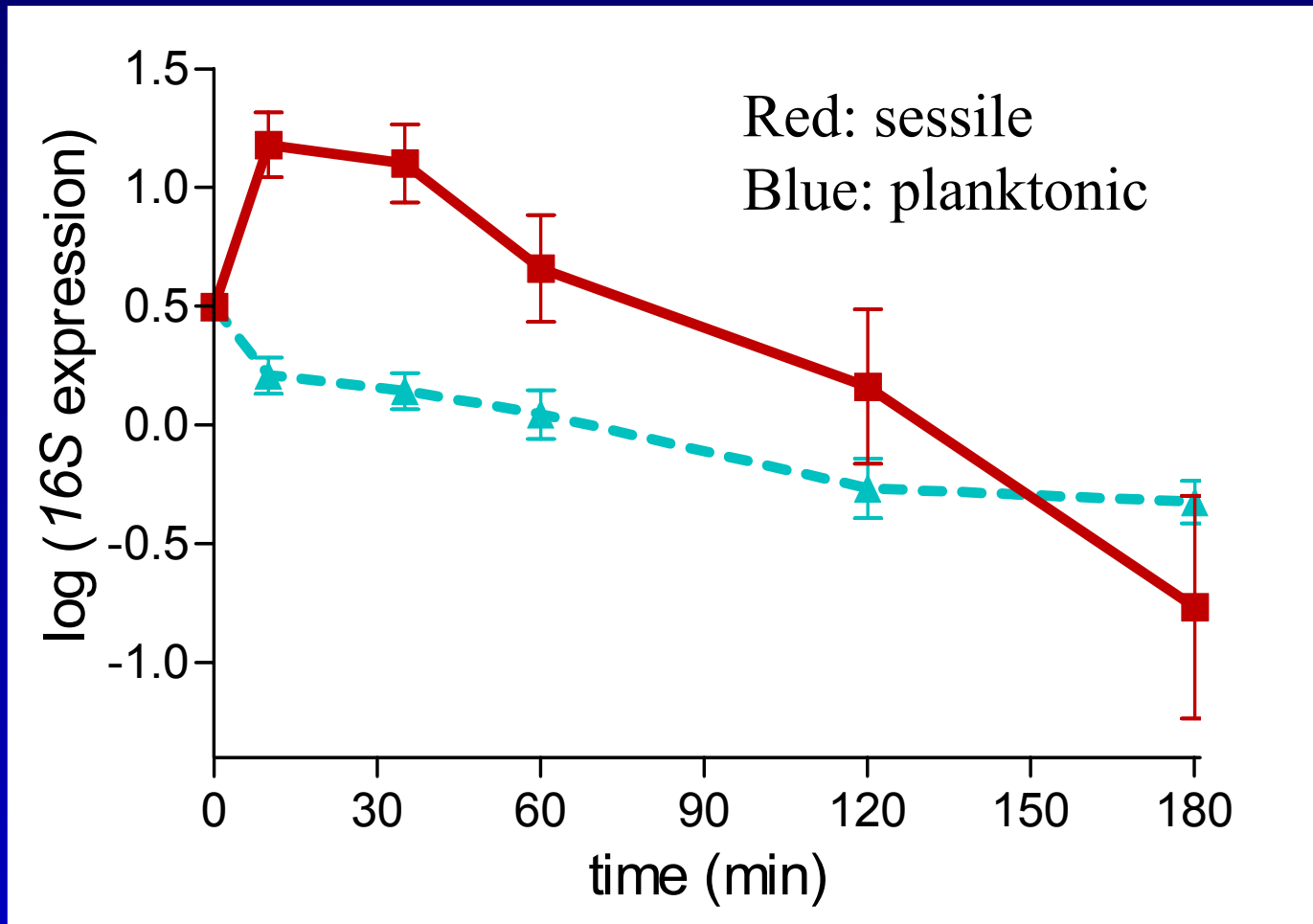


Leid, J.G., Shirtliff, M.E., Costerton, W.J., Stoodley, P. 2002.

# Molecular events in CRI's: persistence

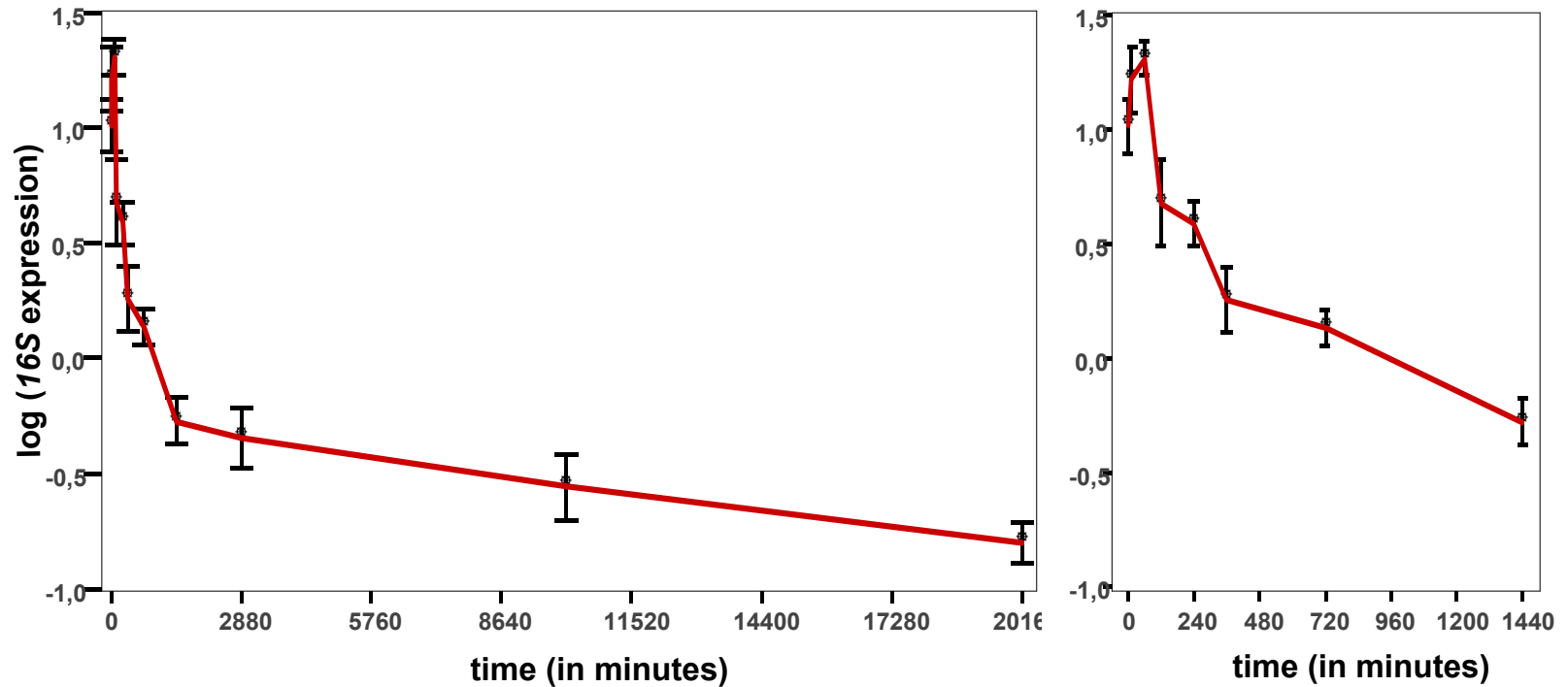


# Molecular events in CRI's: persistence



16S gene expression in FBI-associated *S. epidermidis* *in vitro*

# Molecular events in CRI's: persistence



16S gene expression in FBI-associated *S. epidermidis* *in vivo*

# Summary

- CRI's are the result of colonisation of the catheters by bacteria that establish biofilms
- Biofilms are complex, structured bacterial communities with special characteristics
- Persistence of biofilms is due to altered characteristics of bacteria in the biofilm and a local immune deficiency

# acknowledgements

- S. Vandecasteele
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