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Biofilm targets for the development of novel therapeutics



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Living in suspension vs living on a surface









Are antibiotics losing their efficacy?



New strategies to control bacterial infections are highly desirable!

One possible definition: Biofilms are functional consortia of microorganisms adhered to a surface and to each other and/or embedded within extracellular polymeric substances (EPS), concentrated products of their own metabolism, ions and nutrients from the environment.

What is the problem?

Biofilm cells can be 10 to up 1000 times more resistant to

antimicrobial agents than planktonic cells

Hypochlorous acid used for killing Klebsiella pneumoniae

	Planktonic	Adhered to glass
Concentration (µg/ml) necessary to kill 99% of bacteria	0.065	9.5 (150× higher!!)



Over 80% of bacterial infections in humans involve the formation of biofilms





- Cystic fibrosis
- Osteomyelitis
- Otitis
- Dental caries
- Oral infections
 - Surface of cathether lines
 - Pacemakers
 - Heart valve encocarditis









The biofilm formation process Medium flow we O₂ and Nutrients Simões and Simões (2013) 2. 7. co ANT O 1. 8. **Adhesion Surface** (1) Preconditioning the adhesion surface by macromolecules (2) Transport of planktonic cells from the bulk liquid to surface (3) Adsorption of cells at the surface

- (4) Desorption of reversibly adsorbed cells
- (5) Irreversible adsorption of cells
- (6) Production of cell-cell signalling (quorum sensing) molecules
- (7) Transport of substrates to and within the biofilm

(8) Substrate metabolism by the biofilm-bound cells and transport of products out of the biofilm, accompanied by cell growth, replication, and production of extracellular polymeric substances (EPS)

(9) Biofilm removal by detachment or sloughing

The biofilm matrix



Quorum sensing



Biofilm resistance mechanisms

There are five interesting hypothesized mechanisms:

- 1) direct interactions between the biofilm matrix constituents and antimicrobials
- 2) an altered chemical microenvironment within the biofilm leading to areas of reduced or no growth
- 3) the development of biofilm/attachmentspecific phenotypes
- 4) possibility of damaged bacterial cells undergoing apoptosis
- 5) persister cells





Prevent adhesion



• Surface chemistry (nanocoatings,

antimicrobial and superhydrophobic) and

topography



• Biomimetic surfaces



Anti-quorum sensing

• Brominated Furanones



Delisea pulchra



• N-acyl homoserine lactonase

and other enzymes

Motility

Pilicides

Derivatives of ring-fused 2-pyridones





Aberg and Almqvist (2007)

Biofilm control

- Antibiotics
- **Biocides** (alcohols, aldehydes, halogens, isothiazolones, peroxides, etc)
- *cis*-2-decenoic acid
- Enzymes
- Phages
- Surfactants

Novel antibiofilm agents

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Phytochemical	Mode of action	OH O ON	
Apigenin; Farnesol	Biofilm inactivation		
Cinnamaldehyde	Autoinducer-2 and QS inhibition	o o	
Dihydroxybergamottin;	Autoinducer-1 and 2 inhibition	Н	
Bergamottin		0,0,0,0	
Epigallocatechin gallate;	Inhibition of biofilm formation	ОН	
Ellagic acid; Tannic acid		0	
Hamamelitannin	QS inhibition		
Salvipisone;	Prevention of antibiotic resistant, of adhesion and		
Aethiopinone	biofilm inactivation	но стор	
Resveratrol	QS inhibition	он он он	

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Novel antibiofilm agents



- ✓ There are no biofilm control strategies able to effectively remove the biopellicle and inactivate the biofilm embedded microorganisms
- ✓ Biofilm removal and inactivation are distinct phenomena – one can inactivate a biofilm without causing its removal



Thanks!