Pseudomonas aeruginosa biofilms and their partners in crime

Maria del Mar Cendra[1,2] , Eduard Torrents[1,3]

[1]Bacterial infections & Antimicrobial Therapies Group, Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute of Science and Technology, Barcelona, Spain
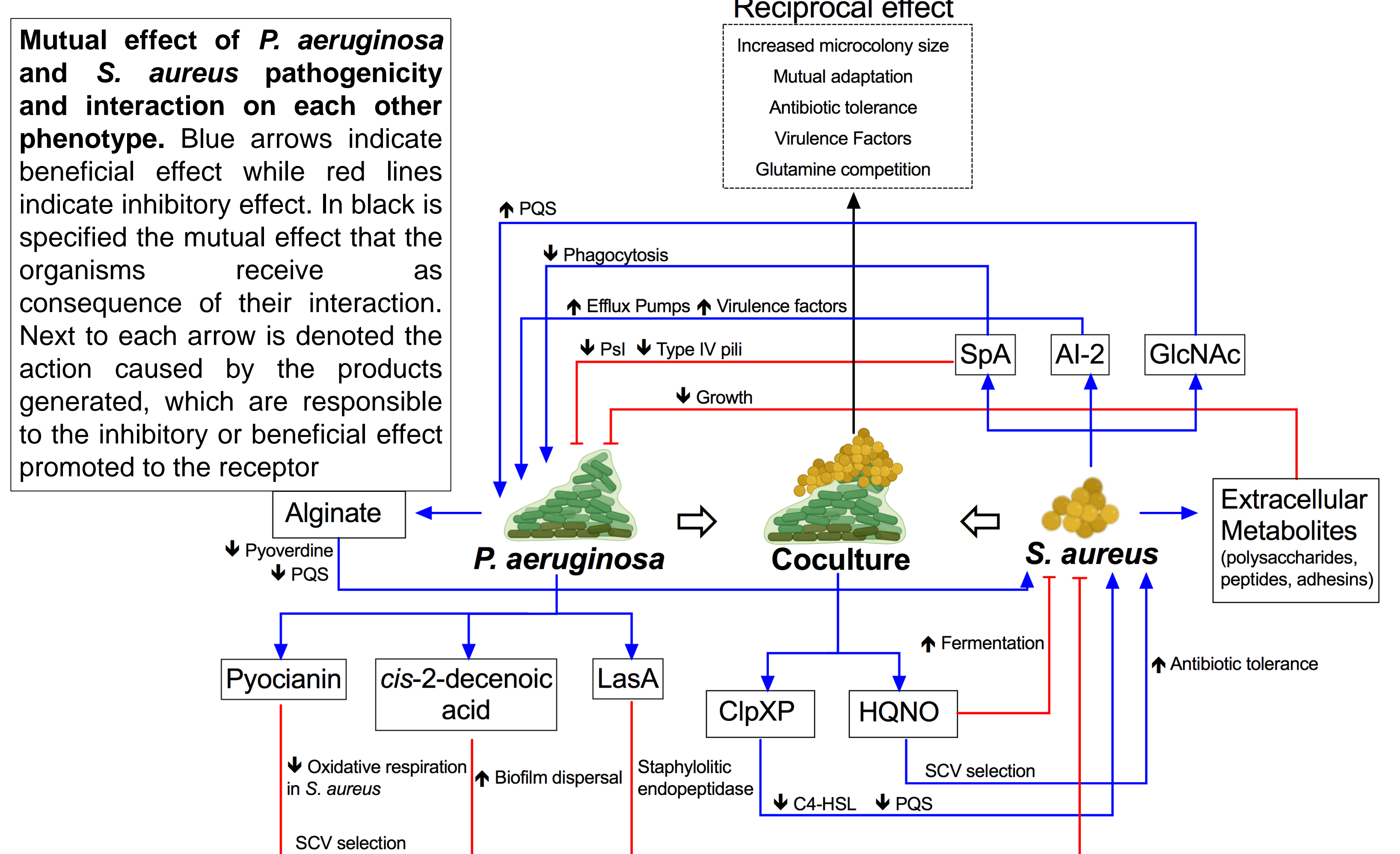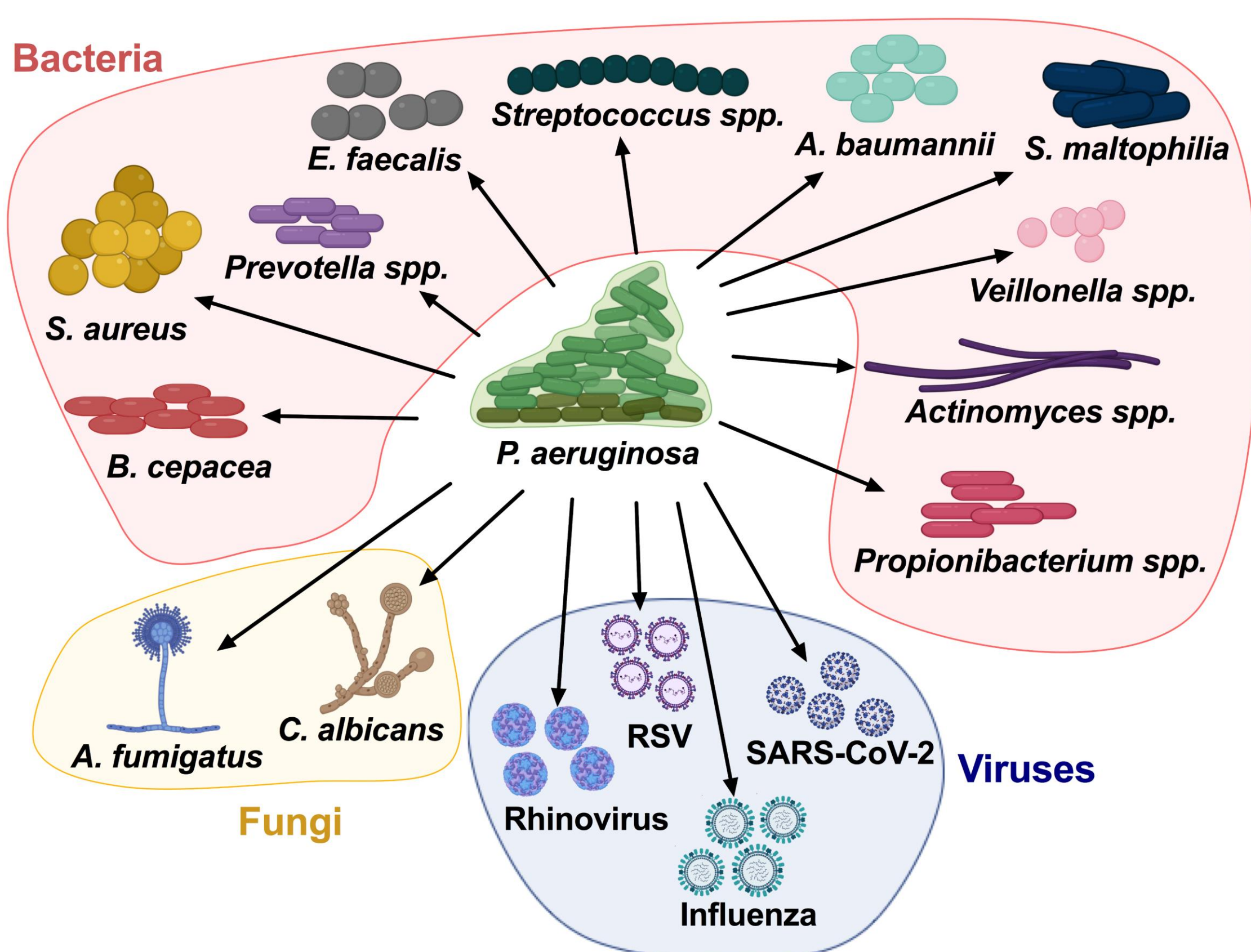[2]Department of Agri-Food Engineering and Biotechnology, Barcelona School of Agri-Food and Biosystems Engineering, Universitat Politècnica de Catalunya-BarcelonaTech, Castelldefels, Spain
[3]Microbiology Section, Department of Genetics, Microbiology and Statistics, Faculty of Biology, University of Barcelona, Barcelona, Spain

The ability of *Pseudomonas aeruginosa* to colonize medical devices and human tissues while growing in resistant communities called biofilms is a worldwide public health concern. *P. aeruginosa* biofilms have increased antibiotic tolerance and are more resistant to host responses than their planktonic counterparts, which makes the clearance of these biofilms difficult and infections chronic. A critical clinical trait of *P. aeruginosa* is its capacity to interact and coexist with other microorganisms in multispecies communities. From a clinical point of view, these interactions are usually detrimental to the patient, as infections caused by multiple species are often associated with worse prognosis. On the other hand, from a biotechnological perspective, there is a challenge to recreate the optimal conditions to grow multiple bacterial species simultaneously. *P. aeruginosa* can interact with other bacteria, fungi and viruses and together infect a wide range of human tissues. This study focuses on the main traits of *P. aeruginosa* biofilms, placing particular emphasis on the clinical challenges they represent in terms of antimicrobial susceptibility and biofilm infection clearance. Furthermore, it also highlights the main microbial interactions of *Pseudomonas* and the current models used to recreate them under laboratory conditions. The antimicrobial and antibiofilm strategies developed against *P. aeruginosa* biofilms are also detailed (1).

P. aeruginosa interacts and coexists with a wide range of microorganisms including fungi, bacteria and viruses.
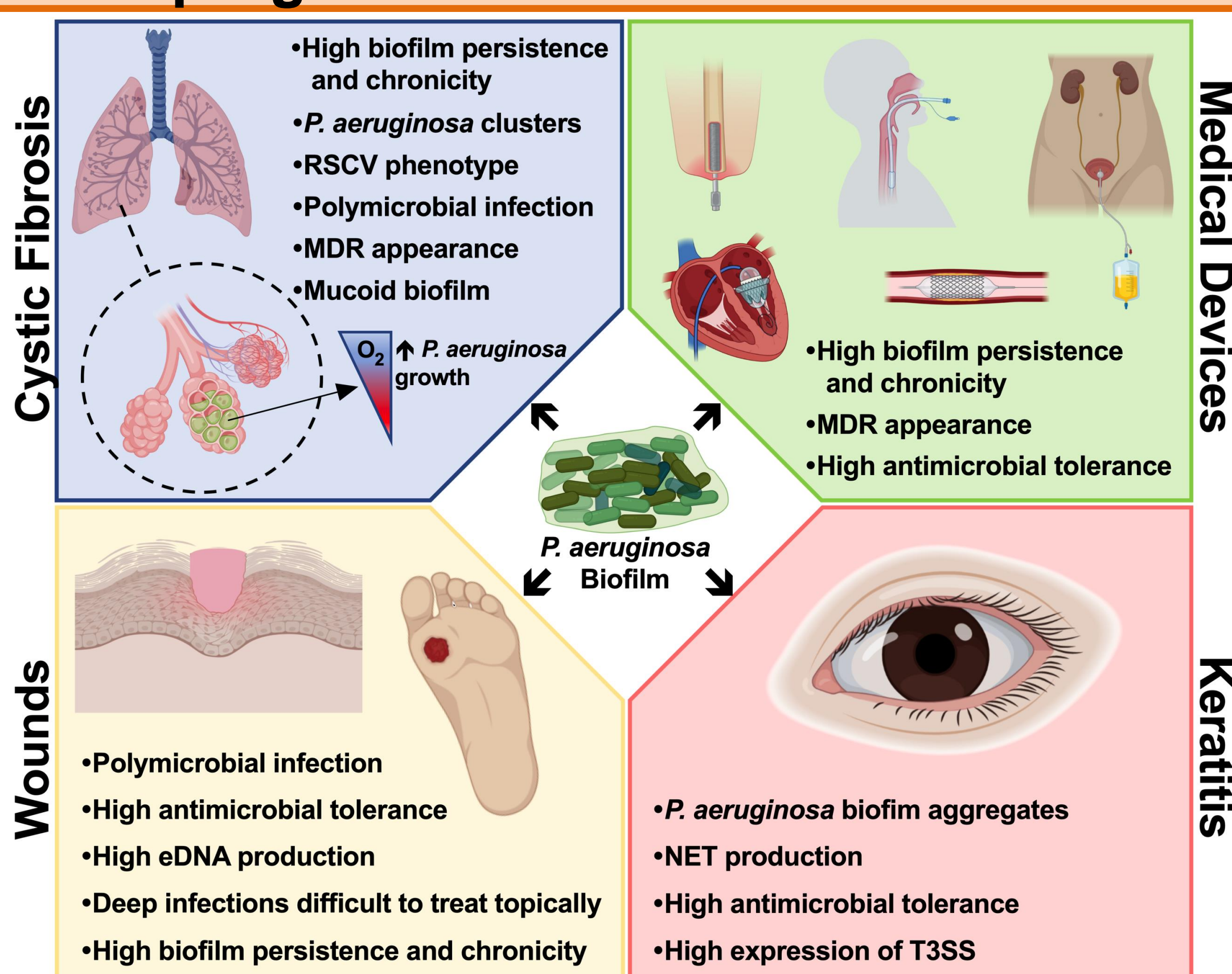

Staphylococcus aureus is a major partner in crime of *P. aeruginosa* and the interaction lead to multiple consequences on their mutual pathogenicity.

Mutual effect of *P. aeruginosa* and *S. aureus* pathogenicity and interaction on each other phenotype. Blue arrows indicate beneficial effect while red lines indicate inhibitory effect. In black is specified the mutual effect that the organisms receive as consequence of their interaction. Next to each arrow is denoted the action caused by the products generated, which are responsible to the inhibitory or beneficial effect promoted to the receptor

Multiple strategies have been designed to combat *P. aeruginosa* biofilms.

Antibiofilm strategy	Mechanism of action
Inhibition of QS	Use of compounds to inhibit QS signaling
Inhibition of adhesion	• Surface coating with antimicrobial NPs/molecules that prevent bacterial adhesion • Modification of the surface material to inhibit biofilm formation
Inhibition of c-di-GMP	Molecules that inhibit, decrease or sequester c-di-GMP promoting biofilm dispersal
Antibiofilm and antimicrobial molecules and peptides	Molecules and peptides with direct antimicrobial or antibiofilm properties
Bacteriophage therapy	Pseudomonas-targeted bacteriophages that infect and kill the bacterium
Bioacoustic effect	Ultrasonication increases antibiotic diffusion across biofilms

Models that fight with the challenge to reproduce *P. aeruginosa* chronic infections.

Model	Exemples
Medium optmization	• Addition of albumin ,L-arginine, adenosine monophosphate or nicotinamide adenine dinucleotide phosphate (NADPH) to compromise *Pseudomonas* while increasing *S. aureus* survival
Modification of the physicochemilar parameters of the coculture system	• Continuous supply of oxygen • pH maintenance ~7 • Different inoculation ratios of microorganisms
3D printed models	• Gelatin-based multiphoton lithography
Cell *in vitro* models	• 2D monolayers • lung organoids
Cystic Fibrosis Models	• Artificial Cystic Fibrosis Sputum Media • Agar and alginate-beads to grow *P. aeruginosa,* alone or with other microbes found in CF infections • Use of supernatant instead of live-bacteria • Mice/rat models • *ex vivo* pig lung models
Wound models	• Lubbock chronic wound biofilm (LCWB) model • Simulated wound fluid over collagen matrices • Tryptic soy broth enriched with NaCl and glucose • Murine wound infection models • Porcine burn models

Main features of *P. aeruginosa* biofilms among infections and the respective consequences on the infection progression.

Cystic Fibrosis:
• High biofilm persistence and chronicity
• *P. aeruginosa* clusters
• RSCV phenotype
• Polymicrobial infection
• MDR appearance
• Mucoid biofilm
• O_2 ↑ *P. aeruginosa* growth

Medical Devices:
• High biofilm persistence and chronicity
• MDR appearance
• High antimicrobial tolerance

Wounds:
• Polymicrobial infection
• High antimicrobial tolerance
• High eDNA production
• Deep infections difficult to treat topically
• High biofilm persistence and chronicity

Keratitis:
• *P. aeruginosa* biofim aggregates
• NET production
• High antimicrobial tolerance
• High expression of T3SS

Reference: 1.Cendra MdM and Torrents E (2021) "*Pseudomonas aeruginosa* biofilms and their partners in crime". Biotechnology Advances 49 (107734).https://doi.org/10.1016/j.biotechadv.2021.107734