



Nuovi approcci terapeutici contro le infezioni da batteri Gram-negativi

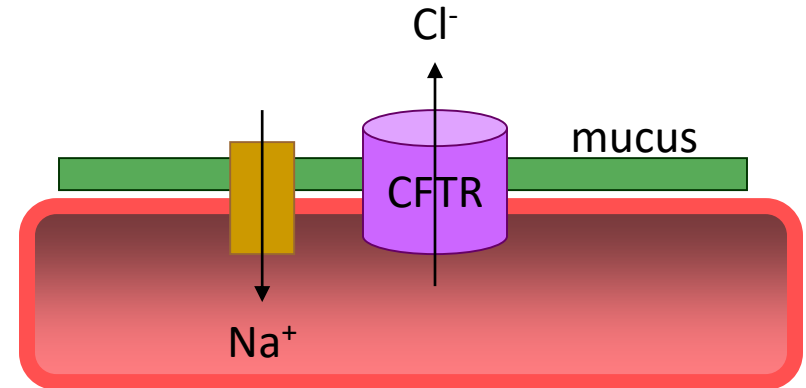
Silvia Buroni

silvia.buroni@unipv.it

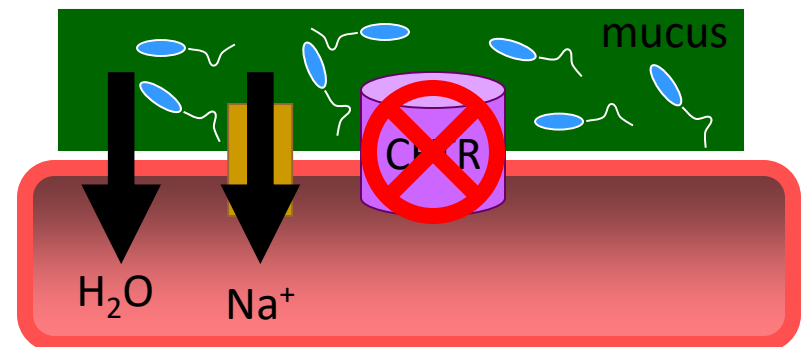
4 Aprile 2024

Cystic Fibrosis

- Autosomal, recessive disease
- 1 every 2,500 live births
- Caused by a defective Cystic Fibrosis Transmembrane Regulator
- Pulmonary disease
 - **Chronic microbial colonization**
 - Spectrum of pathogens
 - *Pseudomonas aeruginosa*
 - *Burkholderia cenocepacia*

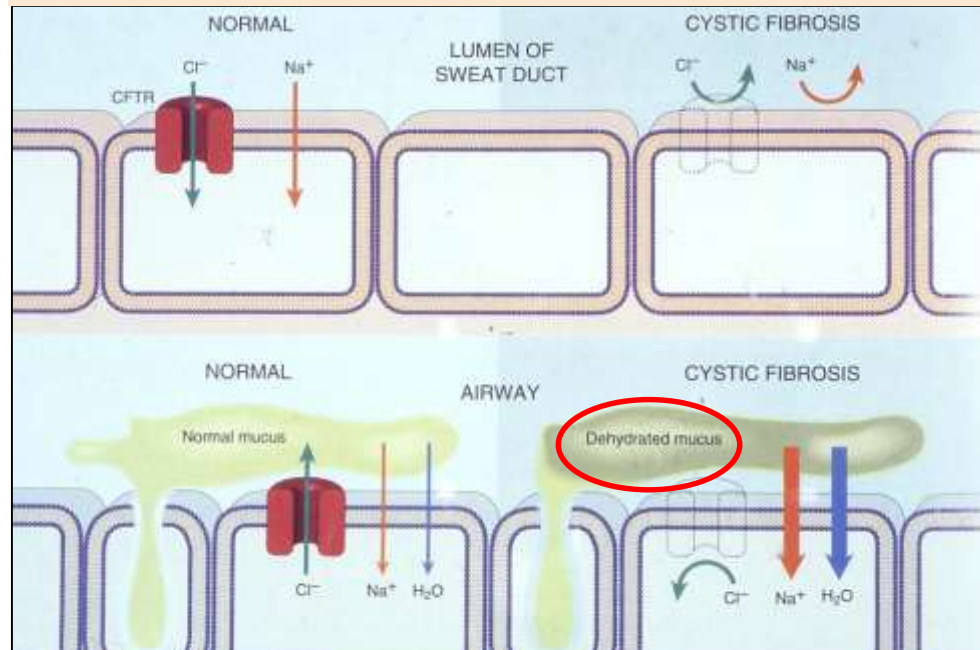
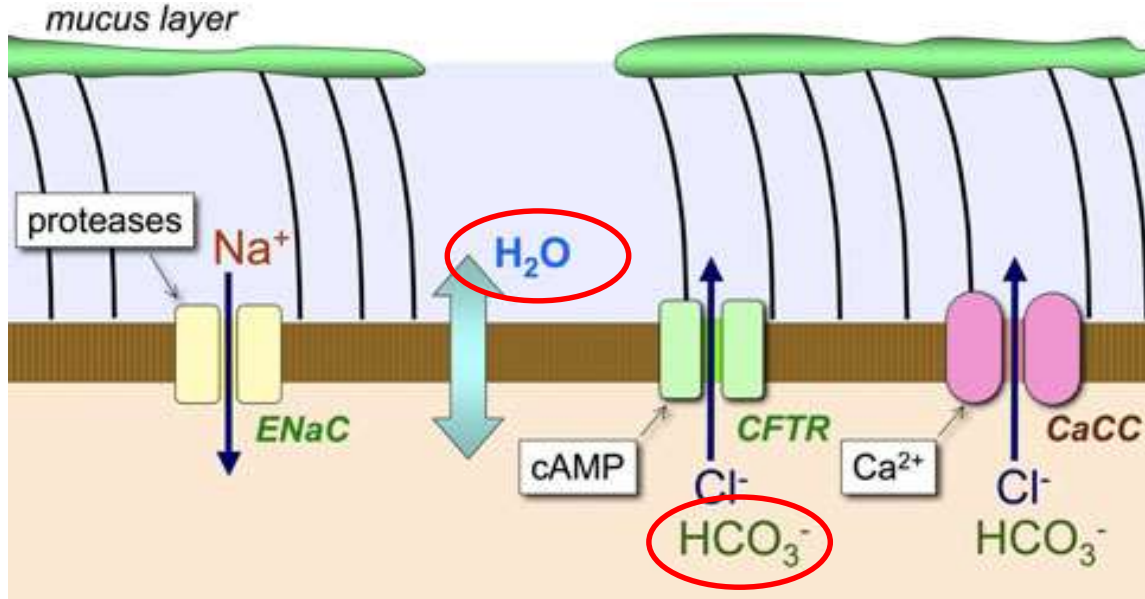


Fully Functioning CFTR



Defective CFTR

Protein Function



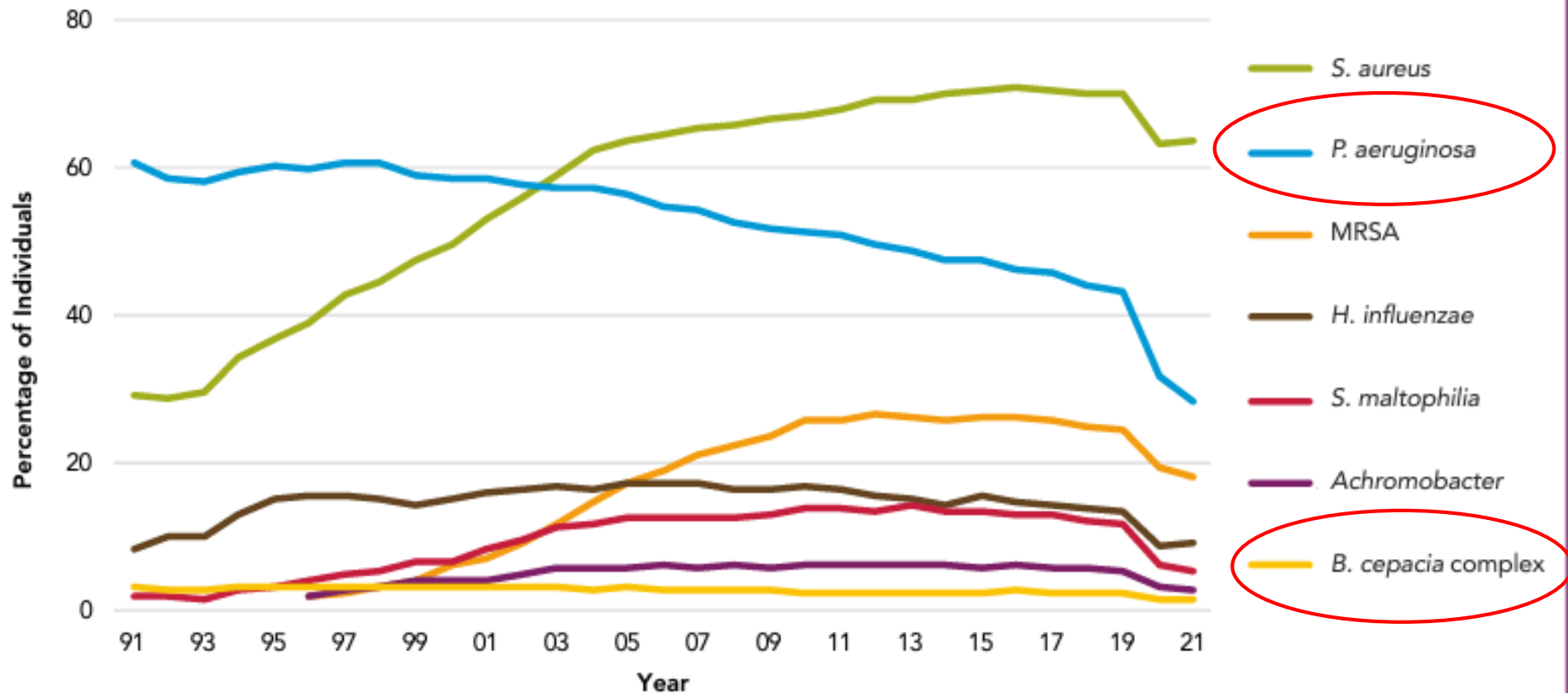
abnormally high chloride concentration in the sweat

most important diagnostic test for CF

airway colonization by bacteria

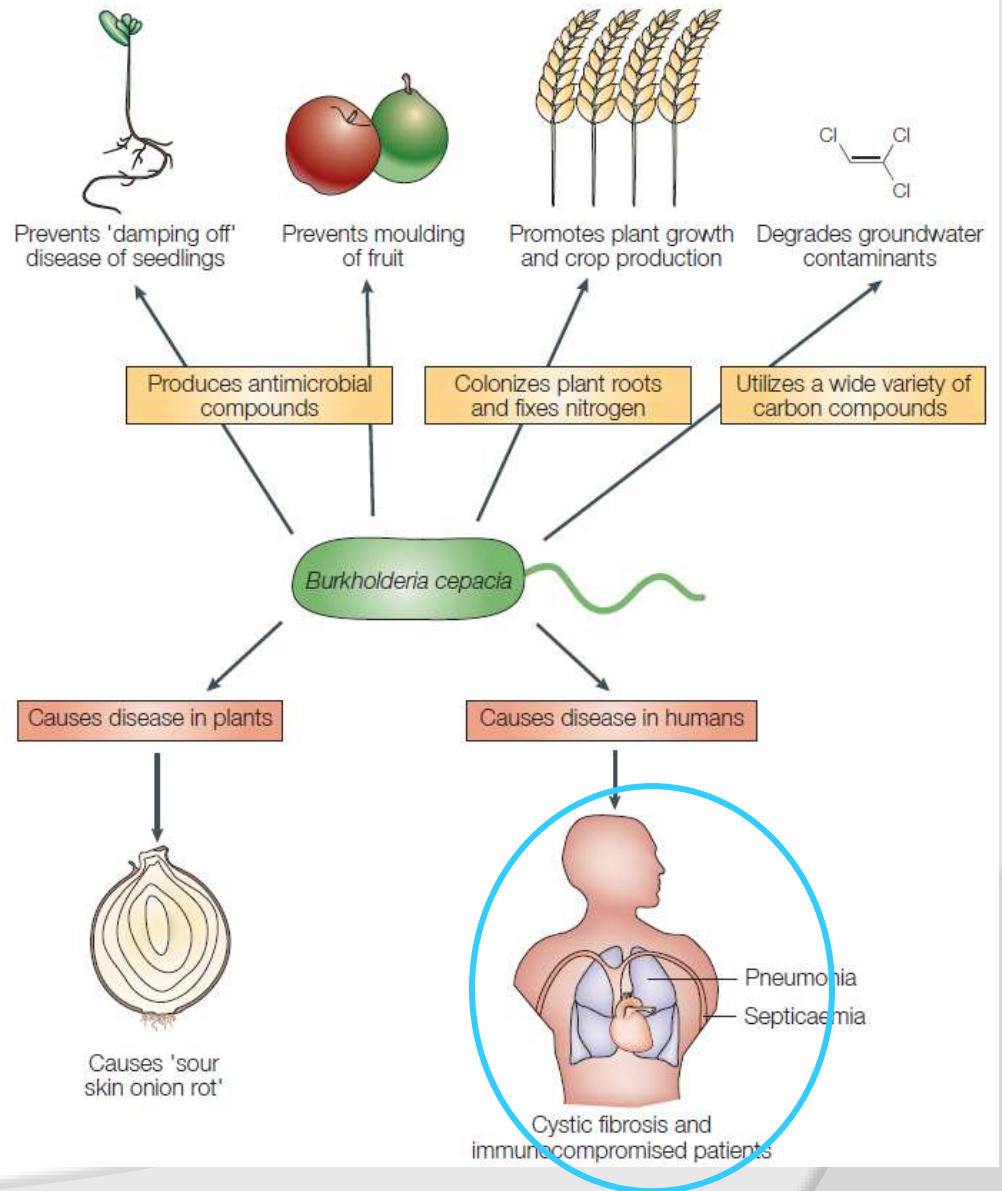
Infections among cystic fibrosis patients

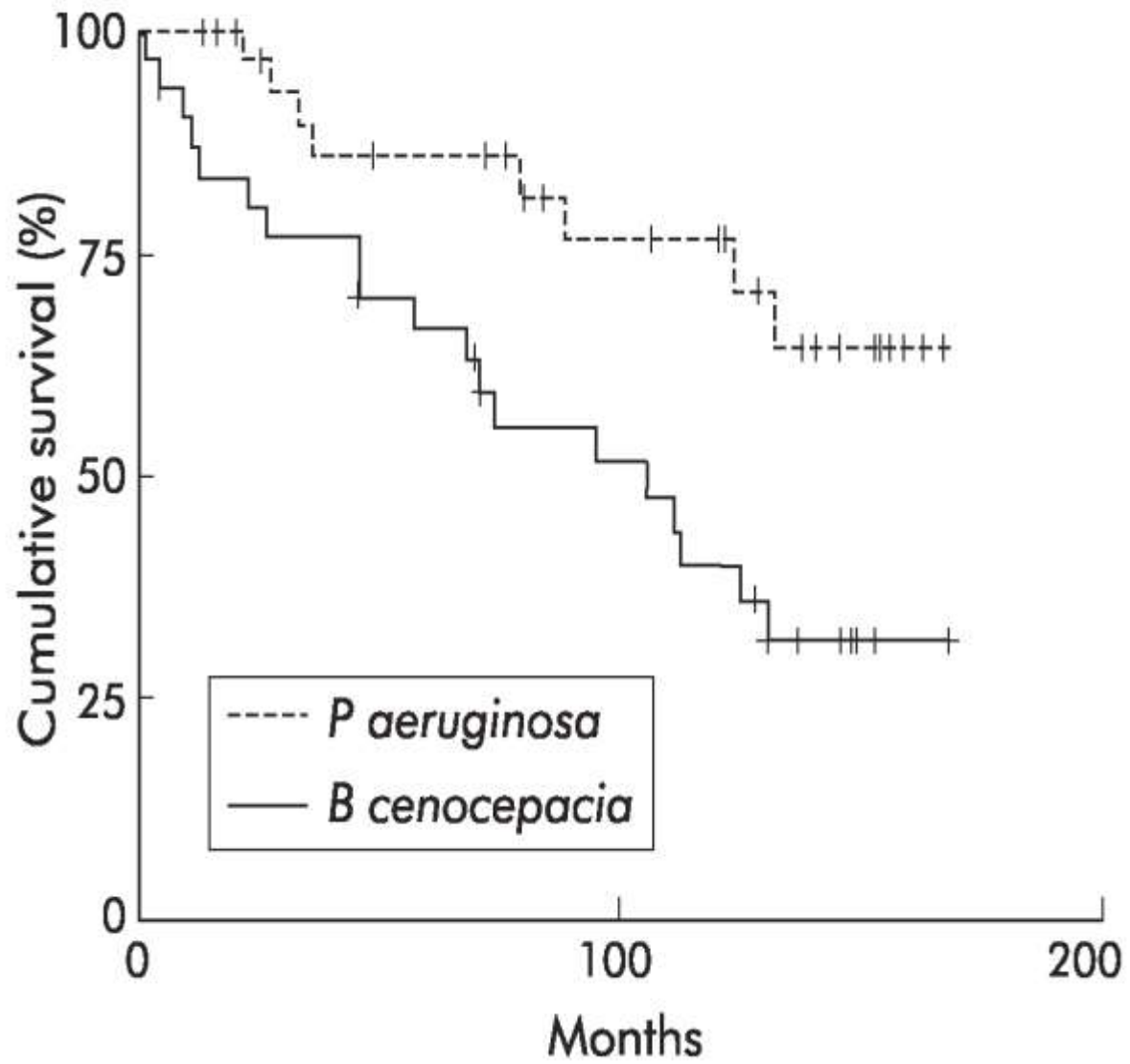
Prevalence of Respiratory Microorganisms, 1991–2021



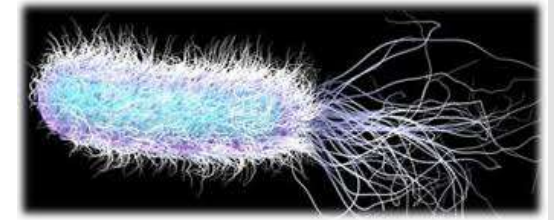
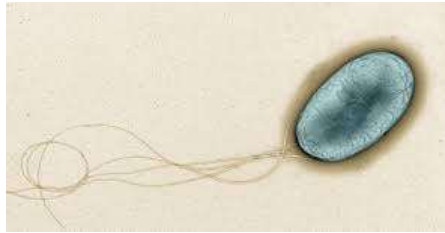
B. cenocepacia: 1-3% patients

Burkholderia cenocepacia



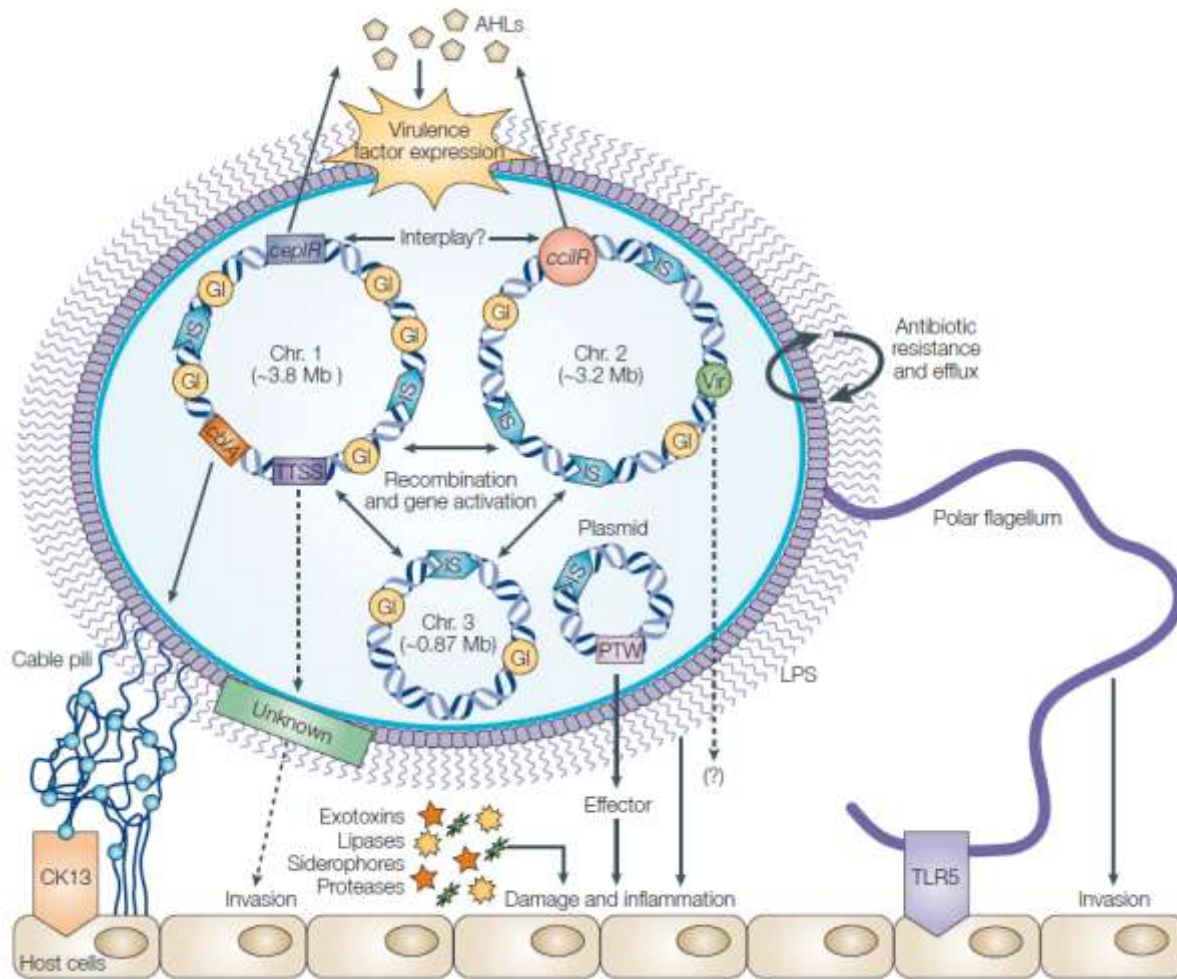


Burkholderia vs Pseudomonas



- **Opportunistic** pathogens
- **Ubiquitously distributed** in nature (soil, water, plants and industrial settings)
 - (i) extraordinary **metabolic versatilities**
 - (ii) abilities to **interact with other bacteria** as well as with their eukaryotic hosts via signal molecules
 - (iii) to adapt their genetic repertoire to the needs of a particular niche by **acquiring genetic material** from other bacteria
- Frequent exchange of genetic material between *P. aeruginosa* and *B. cepacia* → bacteria colonize the same habitats
- *B. cepacia* is capable of perceiving the **QS signals** produced by *P. aeruginosa* but not *vice versa*

B. cenocepacia Genome Structure and principal Virulence Factors

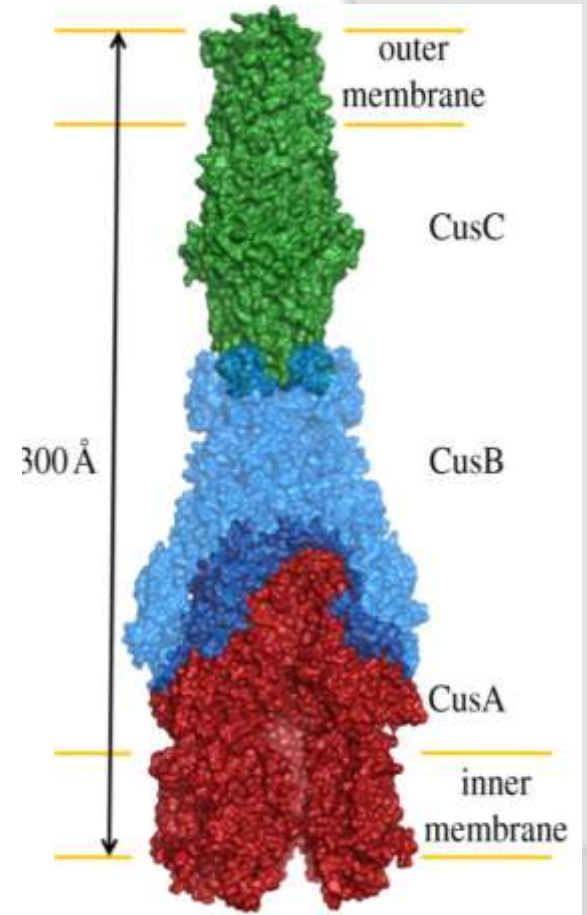
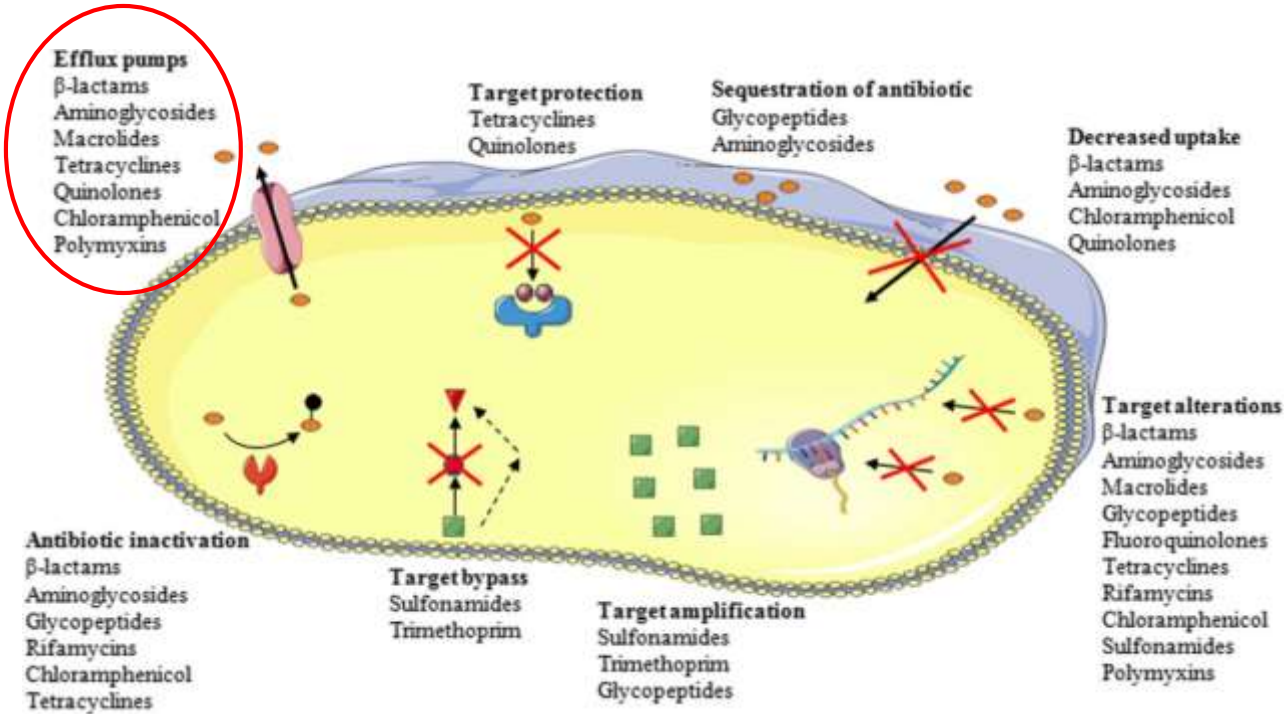


1. Drug resistance;
2. Biofilm formation;
3. EPS synthesis;
4. Cable pili (adherence to mucin and epithelial cells);
5. Flagella (invasion);
6. Production of catalase and SOD (intracellular survival);
6. Secretion of lipases, proteases, hemolysins and siderophores;
7. Quorum sensing signals;
8. Secretion systems.

-GI= Genomic Islands

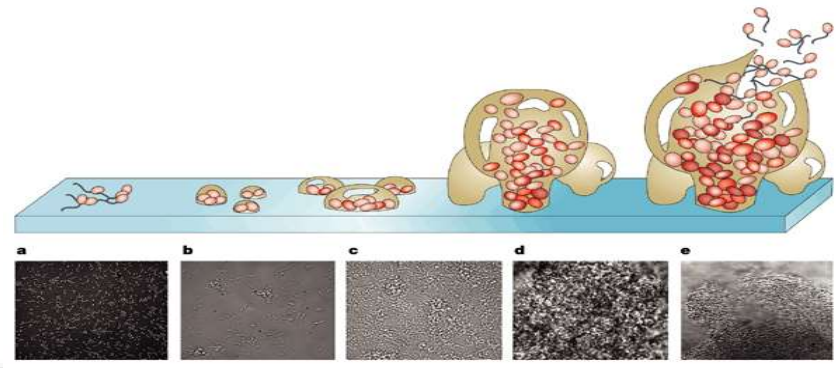
-IS= Insertion Sequence

Drug Resistance Mechanisms RND Efflux Pumps



Long et al., 2012

Biofilm



Nature Reviews | Drug Discovery

Resistance mechanisms in *Burkholderia*

Modification of drug target site

- penicillin binding proteins for β -lactams (Δ PBP3 in *B. pseudomallei*);
- ribosomes for aminoglycosides, macrolides, tetracyclines, and chloramphenicol;
- DNA gyrase for fluoroquinolones (*gyrA* in *B. cepacia*);
- folic acid biosynthesis for trimethoprim and sulphonamides (*dhfr* in *B. cepacia*).

Enzymatic drug inactivation

- Overexpression of β -lactamases;
- Aminoglycoside-inactivating enzymes through N-acetylation
O-nucleotidylation
O-phosphorylation.

Reduced membrane permeability

- LPS structure \rightarrow aminoglycosides, polymyxins and cationic peptides;
- Porines \rightarrow chloramphenicol, trimethoprim, ciprofloxacin or β -lactams;
- bacterial capsule.

No standard eradication protocol

	Medication	Dosing	Frequency	Route
2 weeks	Tobramycin	10 mg/kg	daily	IV
	Ceftazidime	50 mg/kg	3 times daily	IV
	Temocillin	2 g	Twice daily	IV
3 months	Tobramycin	100-300 mg	Twice daily	Nebulised

Kitt *et al.* (2016) BMC Pharmacology and Toxicology 17:14

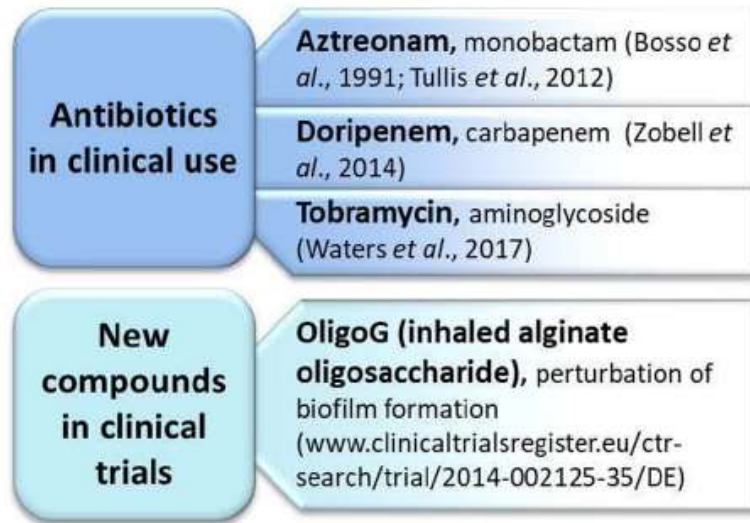
Table 1 *Burkholderia* Eradication Protocol

	Medication	Dosing	Frequency	Route	Bacteria Targeted
Induction Period (21 Days):	Tobramycin	6 mg/kg (per kinetics)	Daily	IV	<i>PsA, Bcc</i>
	Ceftazidime	2 g	Every 8 h	IV	<i>PsA, Bcc</i>
	Trimethoprim/Sulfamethoxazole	800/160 mg	Twice Daily	Oral	<i>Bcc</i>
	Tobramycin inhaled ^a	300 mg	Twice Daily	Nebulized	<i>PsA, Bcc</i>
	Azithromycin	250 mg	Daily	Oral	Anti-inflammatory
Consolidation Period (2 months):	Trimethoprim/Sulfamethoxazole	800/160 mg	Twice daily	Oral	<i>Bcc</i>
	Tobramycin inhaled ^a	300 mg	Twice daily	Nebulized	<i>PsA, Bcc</i>
	Azithromycin	250 mg	Daily	Oral	Anti-inflammatory

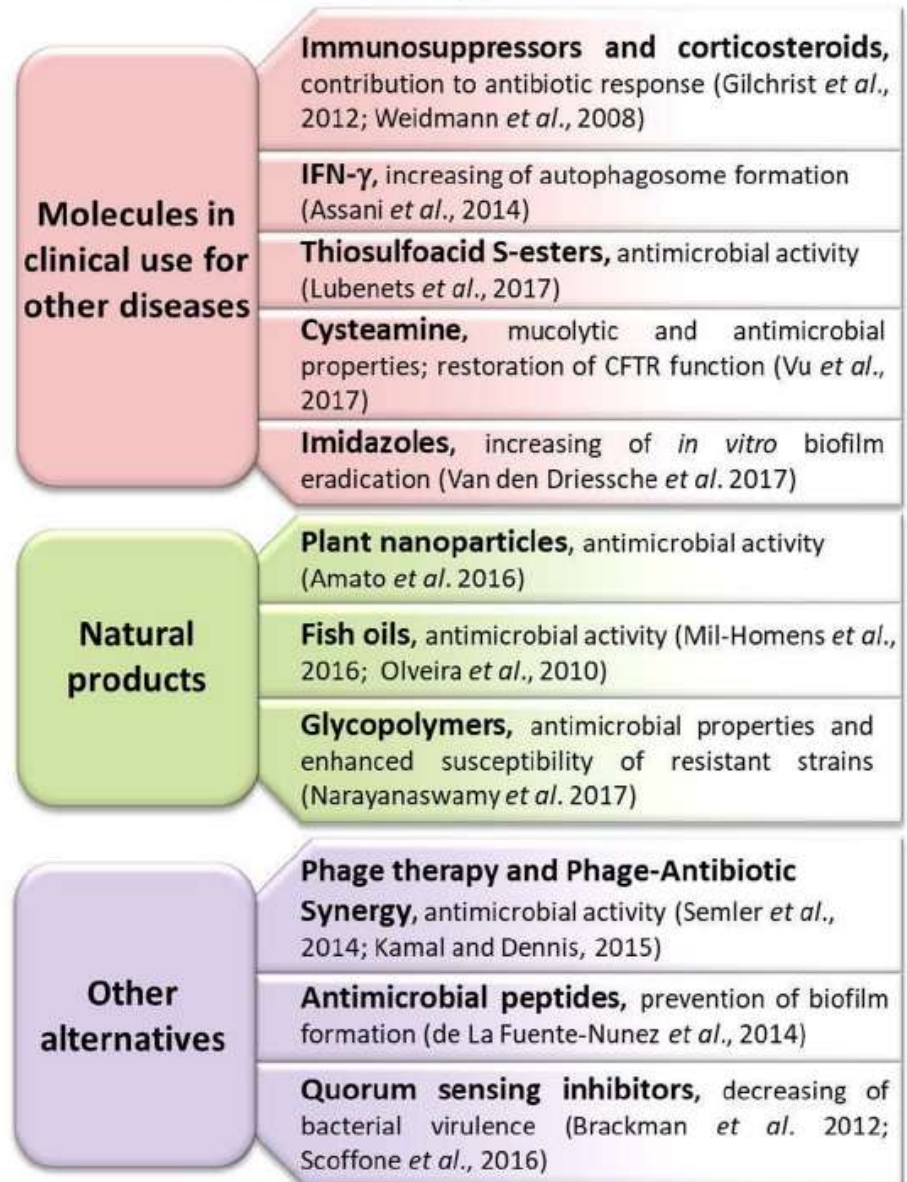
^aAlternative- TIP (tobramycin dry powder for inhalation, 4 caps (28 mg/cap)) every 12 h

Only few antibiotics are effective against *B. cenocepacia*

A Current approaches



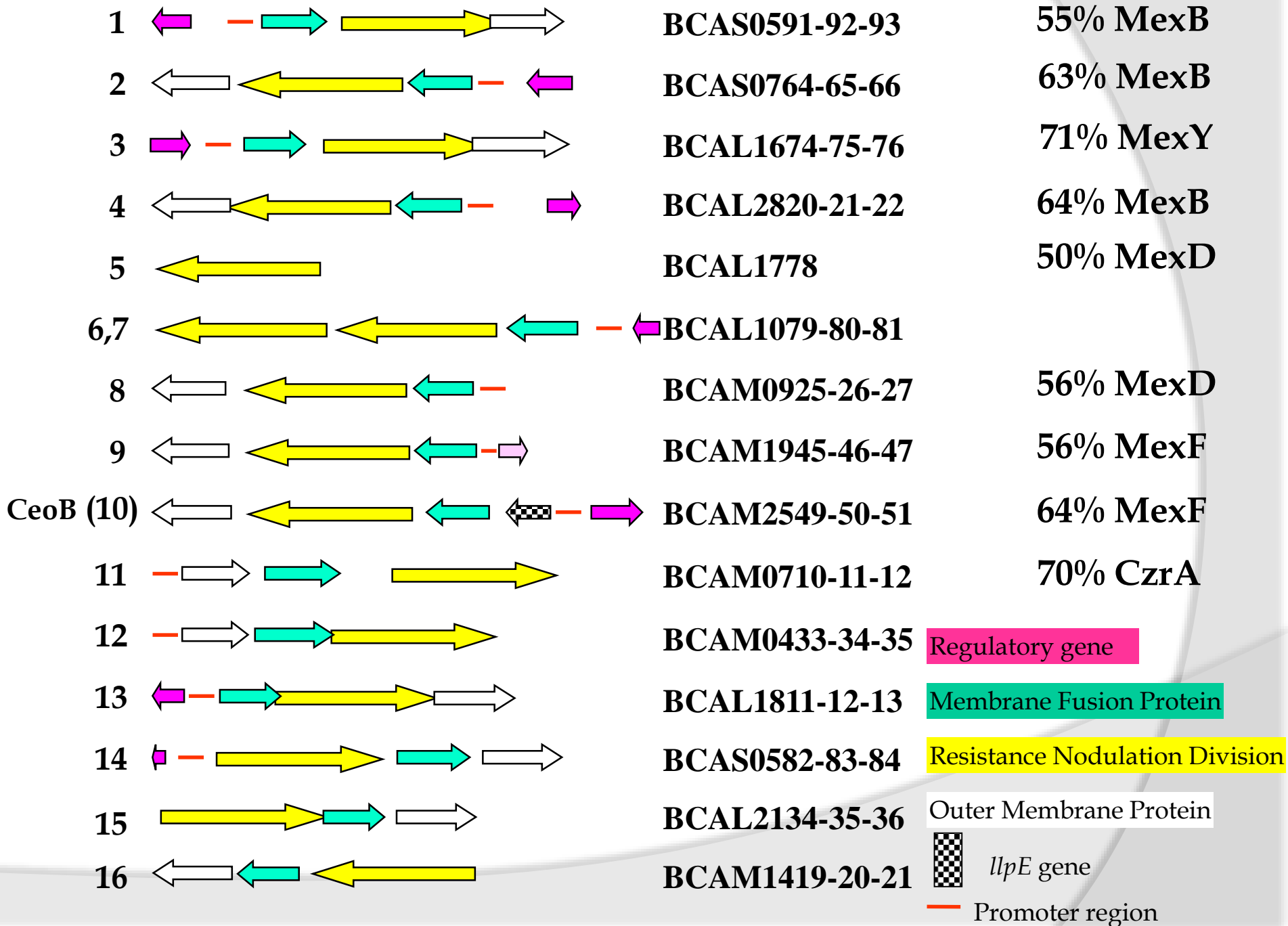
B Alternative approaches



Burkholderia cenocepacia Infections in Cystic Fibrosis Patients: Drug Resistance and Therapeutic Approaches

Viola C. Scoffone¹, Laurent R. Chiarelli¹, Gabriele Trespidi¹, Massimo Mentasti^{2,3}, Giovanna Riccardi¹ and Silvia Buroni^{1*}

RND efflux pumps in *B. cenocepacia*



RND Efflux Pumps in *B. cenocepacia*

BMC Microbiology



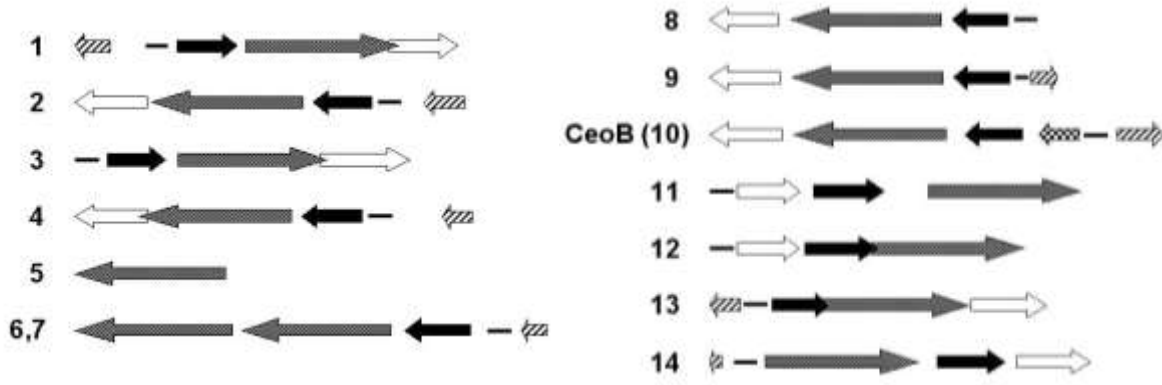
Research article

Open Access

Efflux pump genes of the resistance-nodulation-division family in *Burkholderia cenocepacia* genome

Paola Gugliera^{1†}, Maria Rosalia Pasca^{1†}, Edda De Rossi¹, Silvia Buro¹, Patrizio Arrigo², Giulia Manina¹ and Giovanna Riccardi^{*1}

→ RND operons identified in J2315



BMC Microbiology



Research article

Open Access

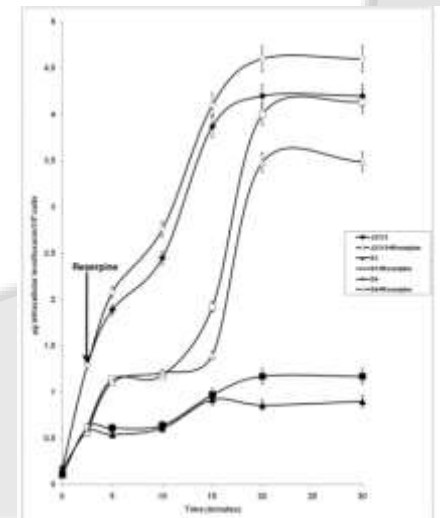
Assessment of three Resistance-Nodulation-Cell Division drug efflux transporters of *Burkholderia cenocepacia* in intrinsic antibiotic resistance

Silvia Buro^{*1}, Maria R Pasca¹, Ronald S Flannagan², Silvia Bazzini¹, Anna Milano¹, Iris Bertani³, Vittorio Venturi³, Miguel A Valvano² and Giovanna Riccardi¹

→ RND-4 plays a crucial role in the intrinsic resistance of *B. cenocepacia*

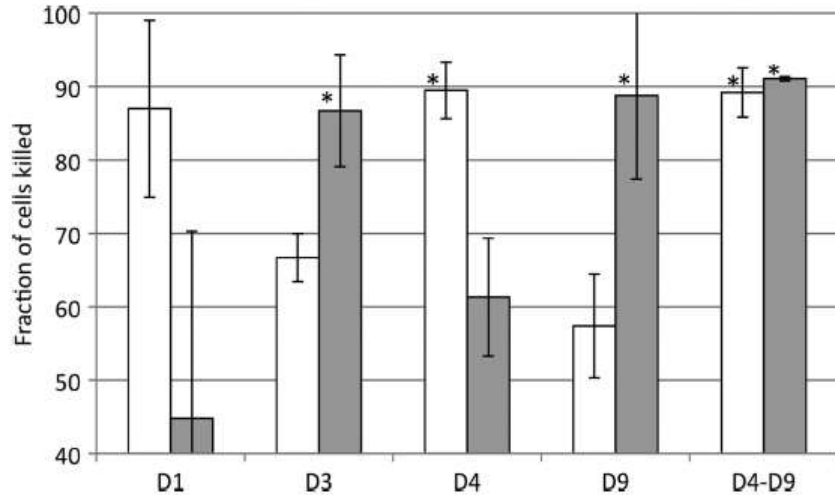
to **Azt, Caf, EtBr, Genta, Tobra, Nal Ac, Cip, Levo, Norflo and Sparflo**

→ Transport of **QS** signal molecules



Molecular Mechanisms of Chlorhexidine Tolerance in *Burkholderia cenocepacia* Biofilms^{▽†}

Tom Coenye,^{1*} Heleen Van Acker,¹ Elke Peeters,¹ Andrea Sass,² Silvia Buroni,³ Giovanna Riccardi,³ and Eshwar Mahenthalingam²



RND-3 and RND-9 → **chlorhexidine** tolerance for biofilm cells
 RND-4 → chlorhexidine tolerance for planktonic cells

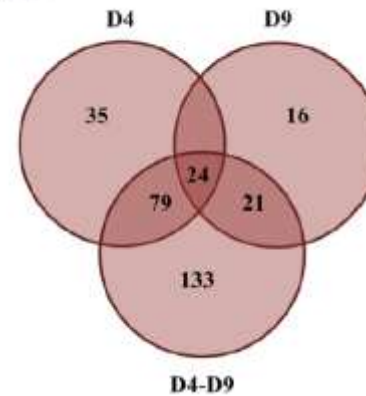
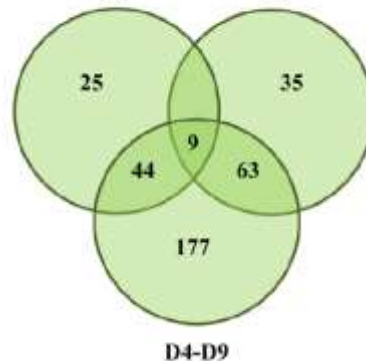
OPEN ACCESS Freely available online

PLoS one

Deciphering the Role of RND Efflux Transporters in *Burkholderia cenocepacia*

Silvia Bazzini^{1*}, Claudia Udine^{1*}, Andrea Sass^{2*}, Maria Rosalia Pasca¹, Francesca Longo³, Giovanni Emiliani⁴, Marco Fondi⁵, Elena Perrin⁵, Francesca Decorosi⁶, Carlo Viti⁶, Luciana Giovannetti⁶, Livia Leoni³, Renato Fani⁵, Giovanna Riccardi¹, Eshwar Mahenthalingam², Silvia Buroni^{1*}

transcriptome analysis of Δ RND-4 and Δ RND-9 → **wider role than drug resistance**



Motility
 Chemotaxis
 Biofilm production

Differential Roles of RND Efflux Pumps in Antimicrobial Drug Resistance of Sessile and Planktonic *Burkholderia cenocepacia* Cells

Silvia Buroni,^a Nele Matthijs,^b Francesca Spadaro,^a Heleen Van Acker,^b Viola C. Scoffone,^a Maria Rosalia Pasca,^a Giovanna Riccardi,^a Tom Coenye^b

16 RND knock-out mutants

RND-3 and **RND-4** involved in resistance of planktonic cells

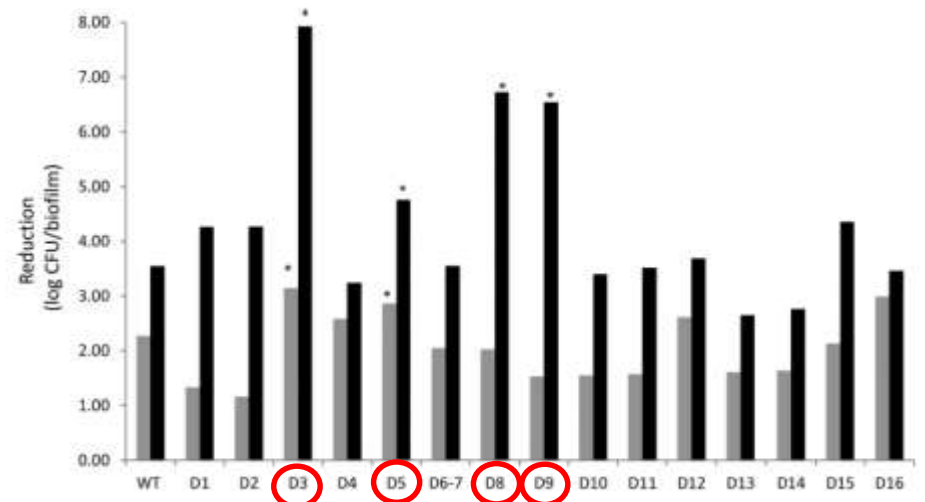
RND-3, RND-5, RND-8 and RND-9 involved in resistance of sessile cells

TABLE 2 MICs of the various antibiotics for some of the *B. cenocepacia* strains tested

Strain	MIC ($\mu\text{g/ml}$) for ^a :				
	CIP	TOB	MIN	MER	CHL
J2315 (WT)	8	256	16	64	32
D3	2	2	— ^b	32	16
D4	2	128	4	64	8
D16	8	256	4	32	16

^a CIP, ciprofloxacin; TOB, tobramycin; MIN, minocycline; MER, meropenem; CHL, chloramphenicol.

^b —, no clear minocycline breakpoint was observed for this mutant.



Strategies to fight antibiotic resistance

Essential Proteins

- **Antibacterial compounds for *B. cenocepacia*:**
C109

Virulence Factors

- **4 antivirulence compounds**
Diketopiperazines

Vaccines

From drug to target: screening of new compounds to find new drugs effective against *Burkholderia*

➔ **8000** compounds from AstraZeneca company with unknown chemical structure and mechanism of action. **Resistant**

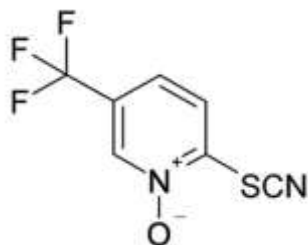
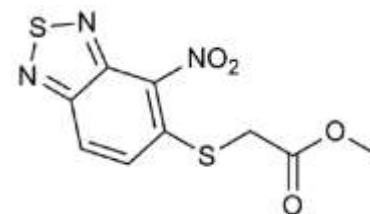
➔ **150** antitubercular compounds from Prof. M. Baltas (CNRs, Toulouse). **Resistant**



100 new compounds from Dr. Vadim Makarov

One new compound for *B. cenocepacia*
MIC = 8 $\mu\text{g/ml}$

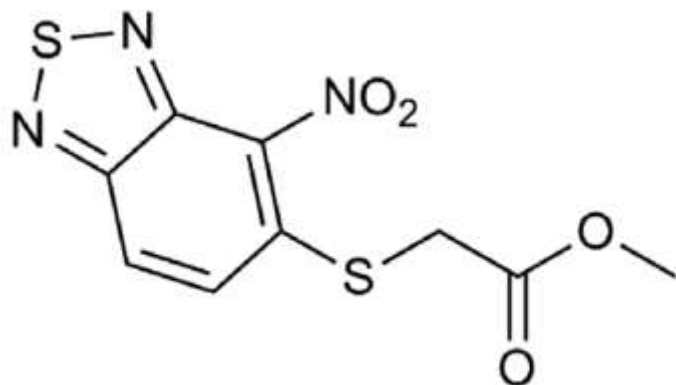
10126109



One new compound for *B. cenocepacia*
MIC = 16 $\mu\text{g/ml}$

11026103

C109: a benzothiadiazol derivative active against *B. cenocepacia*



It is a **bactericidal** compound

MIC = 8 $\mu\text{g/ml}$

TC₅₀ on human CF cells = 75 μM

C109 is effective against the *Burkholderia cepacia* complex strains, more than 50 clinical isolates ...

...other Gram negatives and *S. aureus* (including MRSA strains)

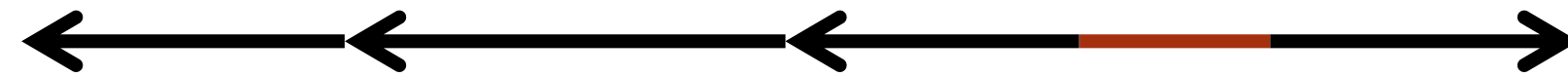
Strain	MIC 10126109 ($\mu\text{g/ml}$)
<i>E. coli</i> ATCC 25922	8
<i>A. baumannii</i> ATCC 19606	16
<i>K. pneumoniae</i> ATCC 13883	64
<i>P. aeruginosa</i> PAO1	256
<i>S. aureus</i> ATCC 25923	4

BCAM1945

BCAM1946

BCAM1947

BCAM1948



8X MIC

SB5: R20C

SB6

16X MIC

SB34: L127P

SB36: R20H



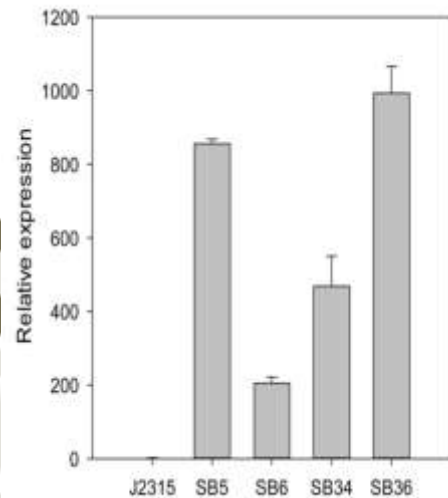
* ΔA_{49}

* C₅₈T

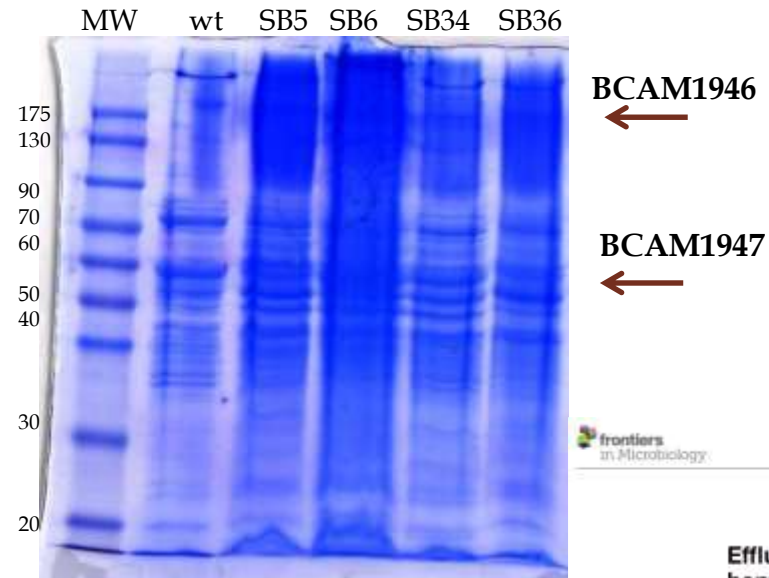
* T₃₈₀C

* C₅₈A

qRT-PCR



Membrane Fraction Extraction



frontiers
in Microbiology

ORIGINAL RESEARCH
published: 20 March 2014
doi: 10.3389/fmicb.2014.00515

Efflux-mediated resistance to a benzothiadiazol derivative effective against *Burkholderia cenocepacia*

Viola C. Scorrone¹, Olga Ryabikova¹, Vladimir Makarov¹, Paolo Iadonola¹, Marco Farnagalli¹, Marco Foresti¹, Renato Fani¹, Edda De Rossi¹, Giovanni Riccardi¹ and Silvia Danzè^{1*}



Competitive Fitness of Essential Gene Knockdowns Reveals a Broad-Spectrum Antibacterial Inhibitor of the Cell Division Protein FtsZ

Andrew M. Hogan,^a Viola C. Scoffone,^b Vadim Makarov,^c April S. Gislason,^a Haben Tesfu,^a Maria S. Stietz,^a Ann Karen C. Brassinga,^a Michael Domaratzki,^d Xuan Li,^e Alberto Azzalin,^{b,f} Marco Biggogera,^b Olga Riabova,^c Natalia Monakhova,^c Laurent R. Chiarelli,^b Giovanna Riccardi,^b Silvia Buroni,^b Silvia T. Cardona^{a,g}

High-density **transposon mutant library** in *B. cenocepacia* K56-2 by delivering a **transposon element** containing an outward tightly regulated rhamnose-inducible promoter (*PrhaB*)



Essential genes identified by transposon-based delivery of *PrhaB* throughout the bacterial chromosome followed by screening for **absence or growth without rhamnose**

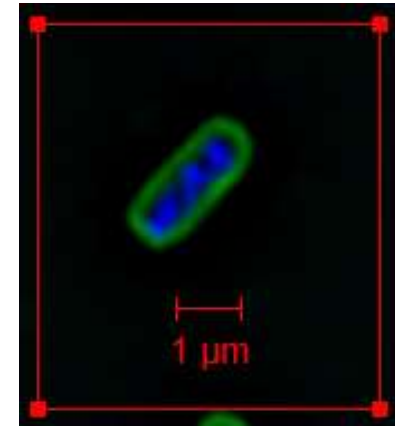
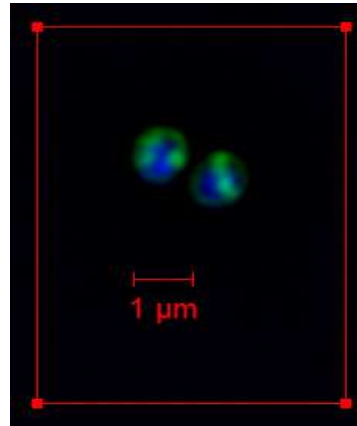
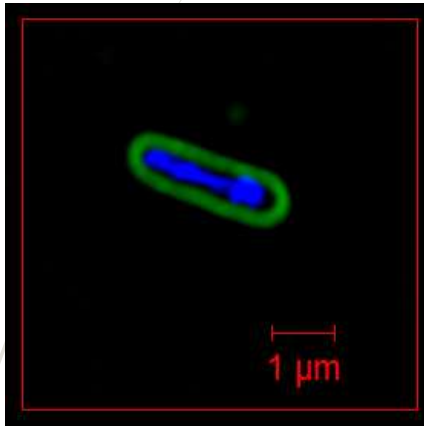
Phenotypic effect of C109 treatment: 3D super resolution microscopy

B. cenocepacia

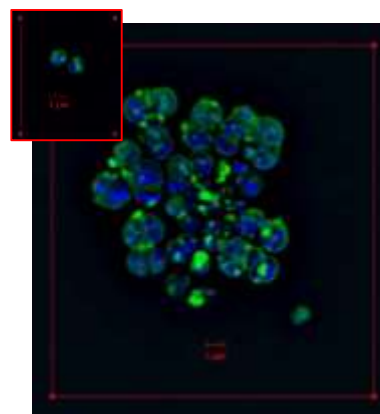
S. aureus

E. coli

Control



(+) C109 [6 μg/mL]

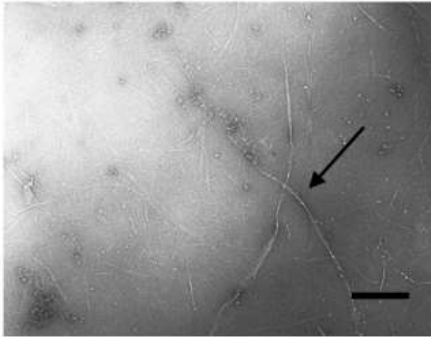


Identification of the cellular target

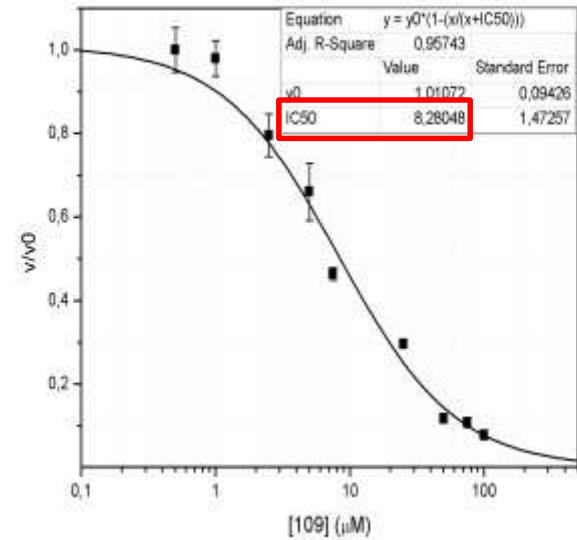
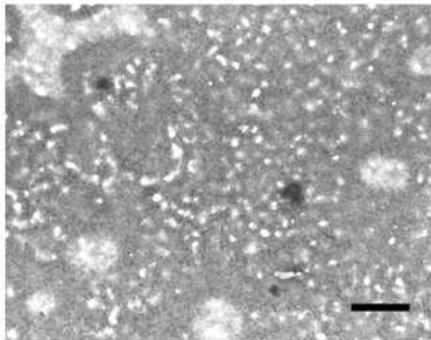
FtsZ GTPase spectrophotometric assay

FtsZ polymers visualized by TEM

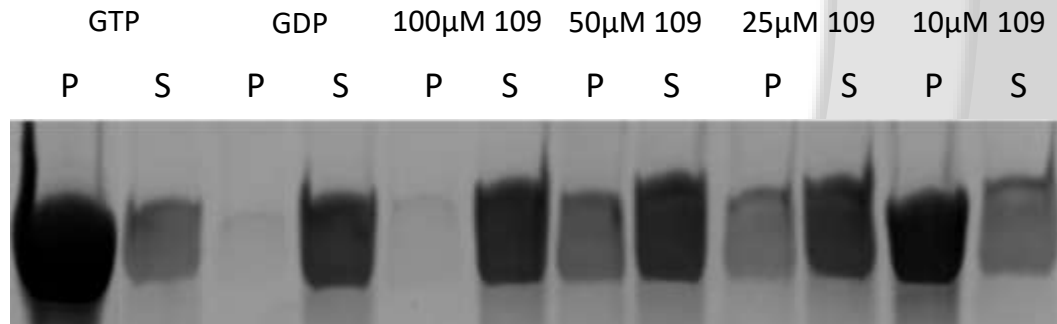
C109 -
GTP +
GDP -



C109 100 μM
GTP +
GDP -



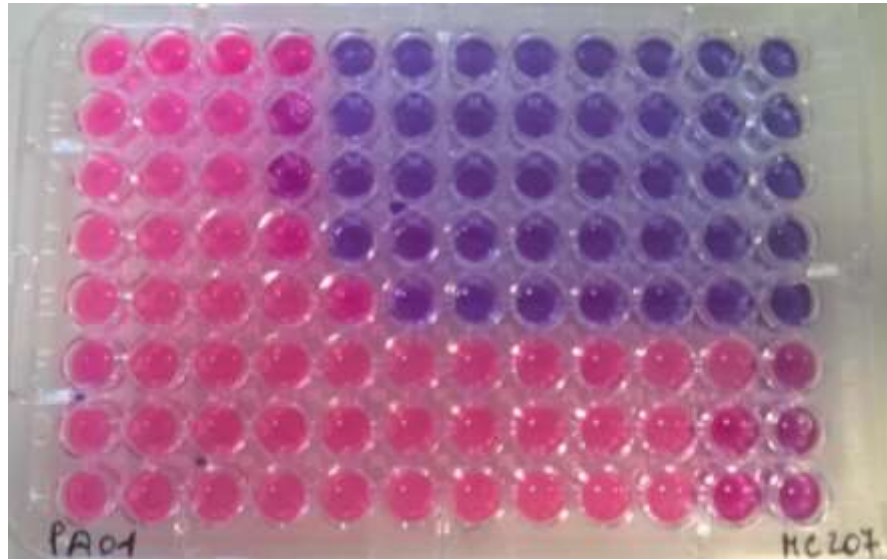
FtsZ polymerization assay



FtsZ is C109 cellular target

A. MICC109+MC207,110

P. aeruginosa



MC207,110 µg/ml

$$\frac{\text{MIC207comb}}{\text{MIC207alone}} + \frac{\text{MICC109comb}}{\text{MICC109alone}} =$$

$$\frac{32}{256} + \frac{1}{256} = 0.125 + 0.004 = 0.129 < 0.5$$

SYNERGY

109 µg/ml
0 0.125 0.25 0.5 1 2 4 8 16 32 64 128

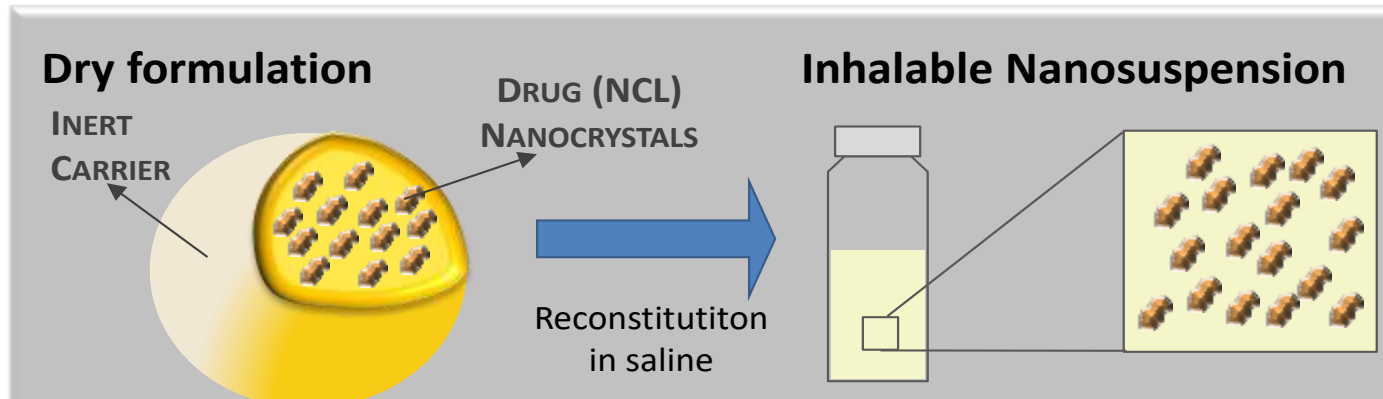
The efflux pump inhibitor MC207,110 enhances C109 activity against *P. aeruginosa*

B. FtsZ purification and enzymatic assay

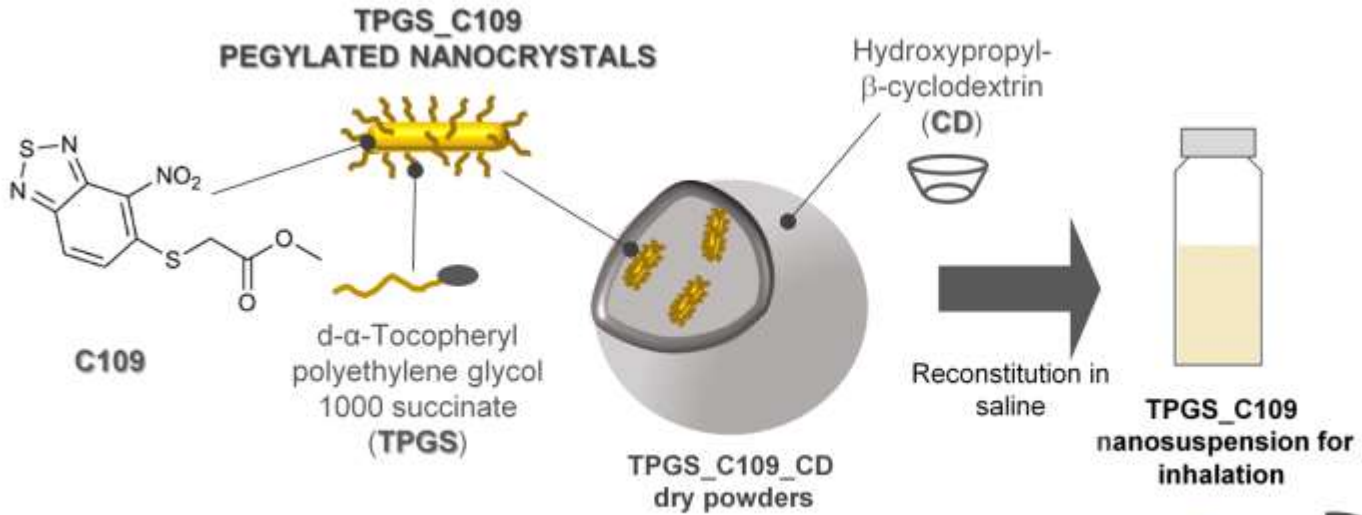
FtsZ_{PAO} has a 53% aa identity with FtsZ_{J2315} → C109 is effective against the FtsZ_{PAO} purified protein
IC50 = 5 µM

FtsZ is C109 cellular target
In *P. aeruginosa* C109 is extruded by efflux pumps

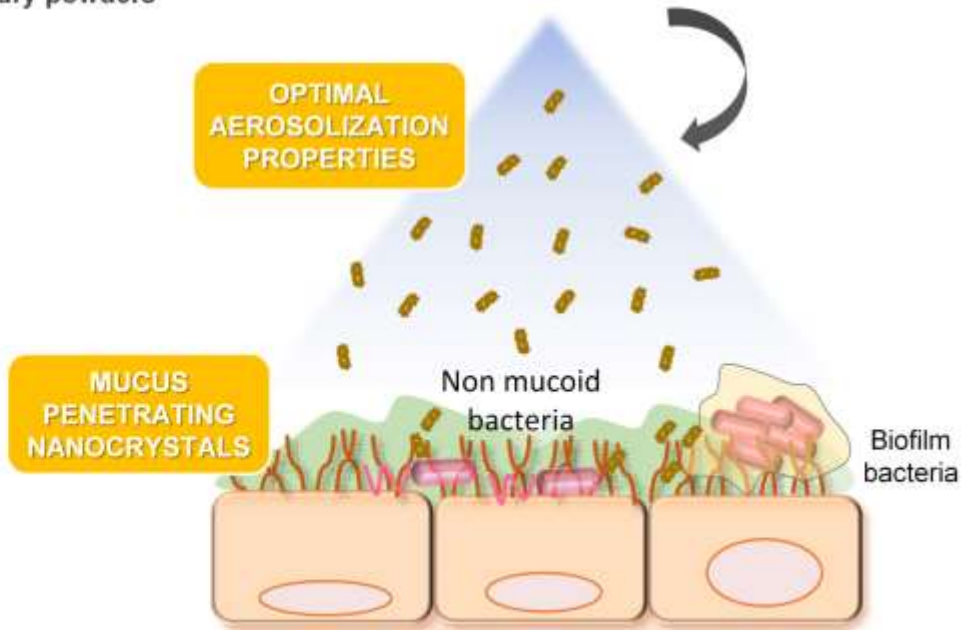
Inhalable formulations of new molecules effective against *Burkholderia cenocepacia*: from *in vitro* to *in vivo* applications



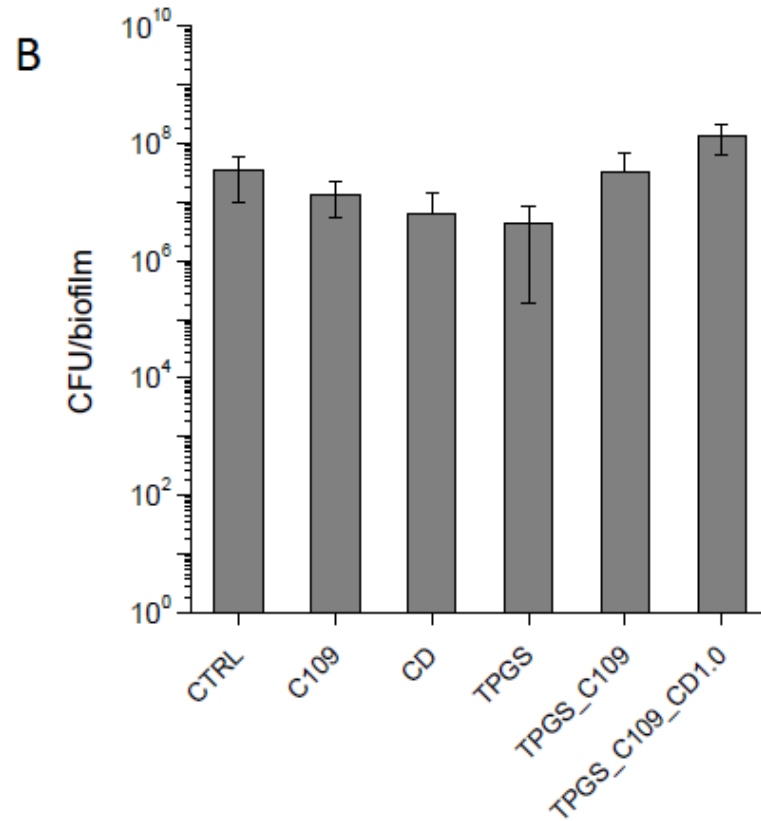
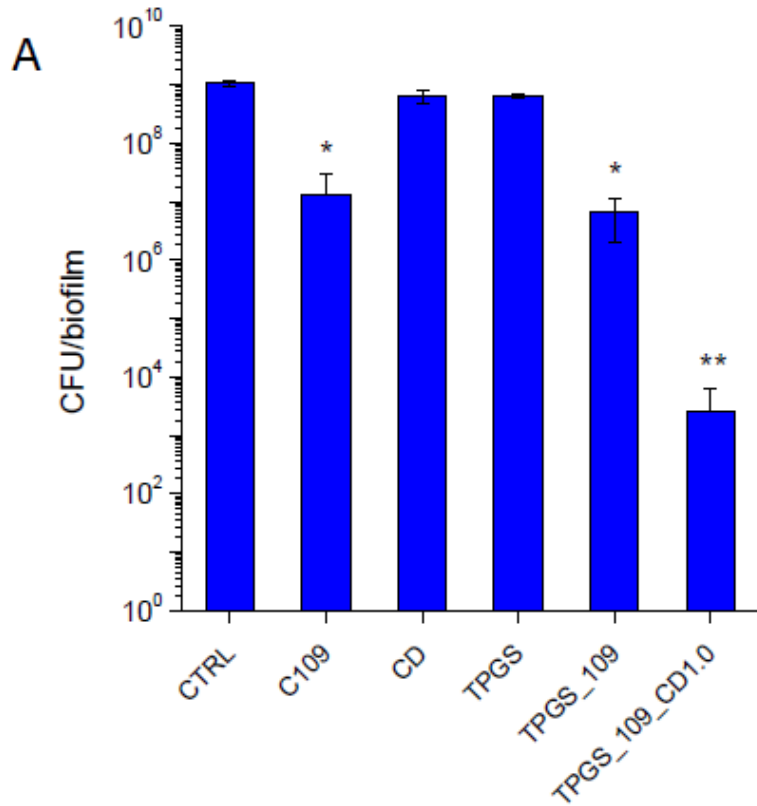
- Biodistribution
- Efficacy in mouse model of *B. cenocepacia* infection



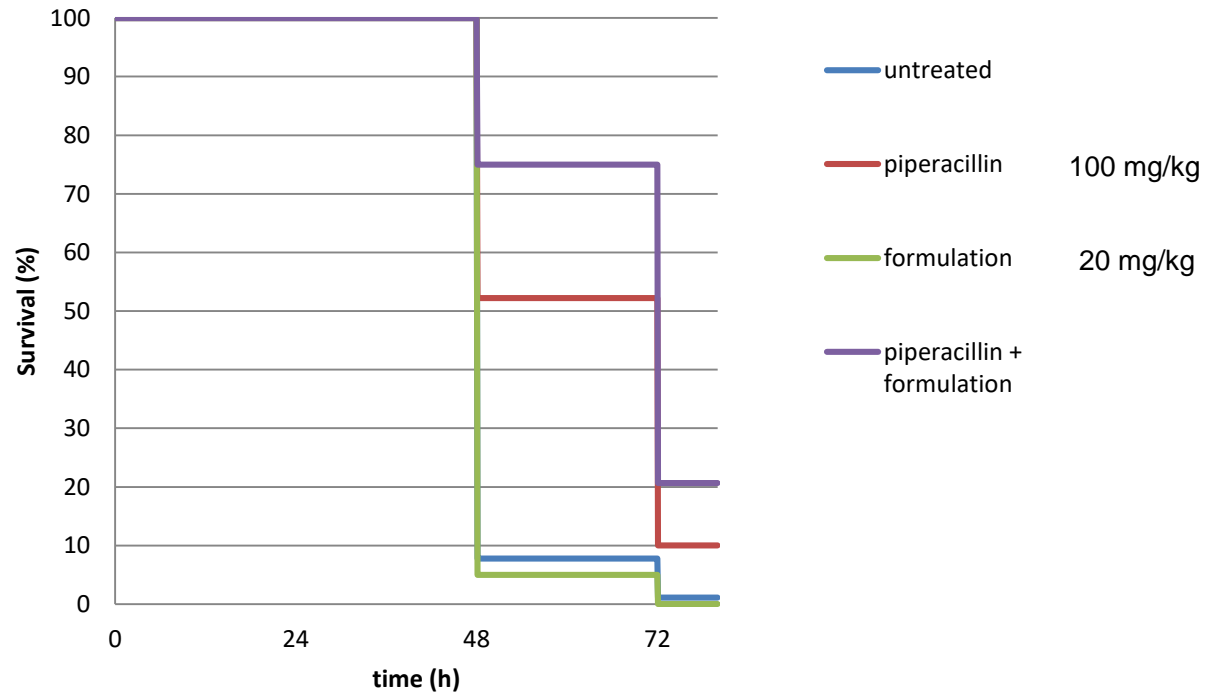
- BROAD-SPECTRUM *IN VITRO* ANTIMICROBIAL ACTIVITY**
- IMPROVED INHIBITION ABILITY AGAINST *B. CENOCEPACIA* BIOFILM**
- IN VIVO* SYNERGISTIC ACTIVITY WITH PIPERACILLIN**



Inhibition and eradication ability of C109 and of formulations against *B. cenocepacia* J2315 biofilm



Galleria mellonella infection model



Strategies to fight antibiotic resistance

Essential Proteins

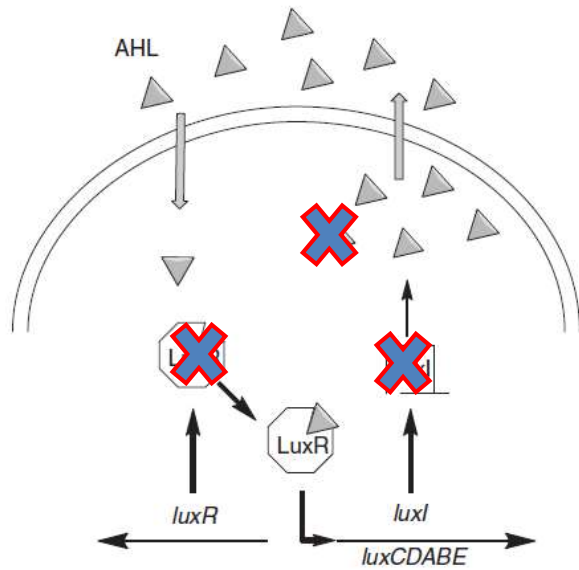
- **Antibacterial compounds for *B. cenocepacia*:**
C109

Virulence Factors

- **4 antivirulence compounds**
Diketopiperazines

Vaccines

Antimicrobial Compounds targeting Virulence Factors



Jiang and Li, 2013

Quorum Sensing Synthases

CepI (BCAM1870)

CciI (BCAM0239a)

DfsA (BCAM0581)

Ham cluster

1. Bacteria unable to produce virulence factors
2. No direct bacteria killing = development of resistance less probable
3. Anti-virulence drugs could potentially be used in combination with established or novel antimicrobials to improve the current therapy

Targeting *B. cenocepacia* CepI synthase

SCIENTIFIC REPORTS

OPEN

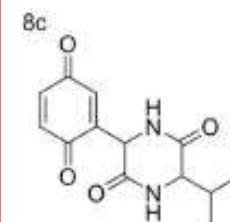
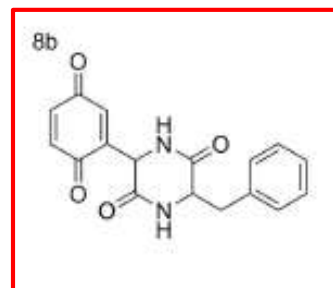
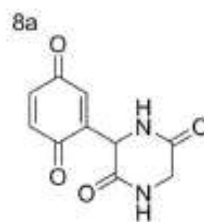
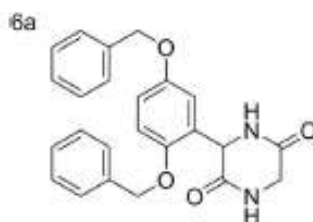
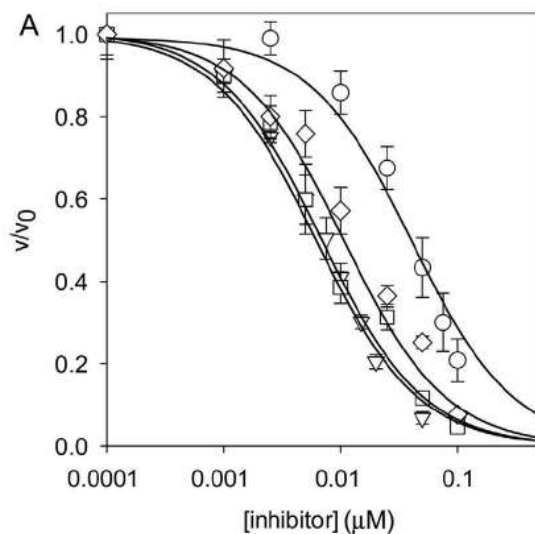
Discovery of new diketopiperazines inhibiting *Burkholderia cenocepacia* quorum sensing *in vitro* and *in vivo*

Received: 01 June 2016

Accepted: 08 August 2016

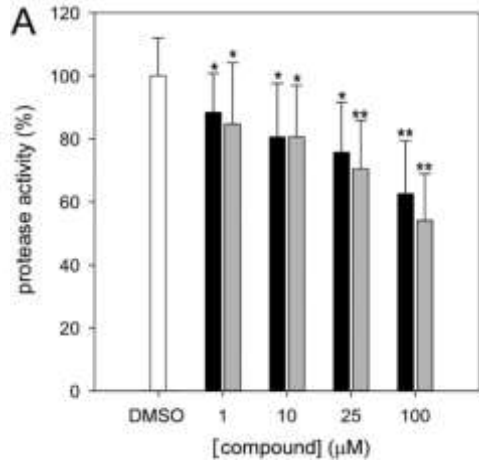
Published: 01 September 2016

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Aygun Israyilova^{1,4}, Alberto Azzalin^{5,6}, Federico Forneris¹, Olga Riabova², Svetlana Savina²,
Tom Coenye³, Giovanna Riccardi¹ & Silvia Buroni¹

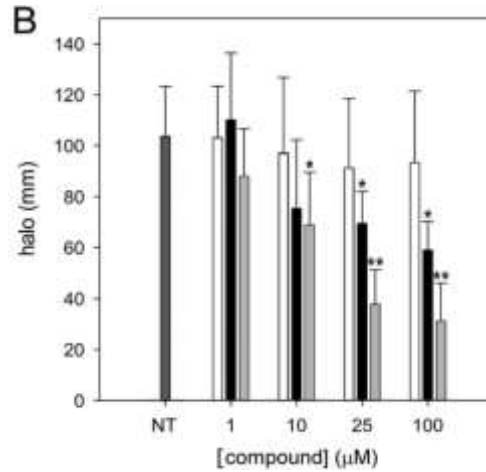


	IC ₅₀
6a ○	30 μM
8a ◇	10 μM
8b ▽	5 μM
8c □	6 μM

Protease production



Siderophore production



C. elegans survival

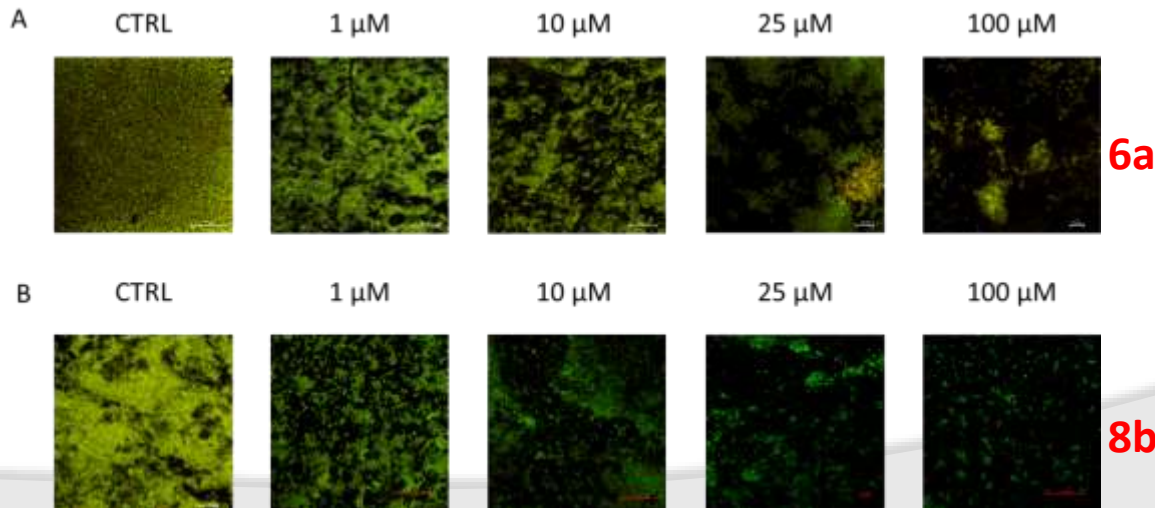
Significant increase of survival (30-40%) after 24h and 48h even at low concentrations

No toxicity on HeLa cells

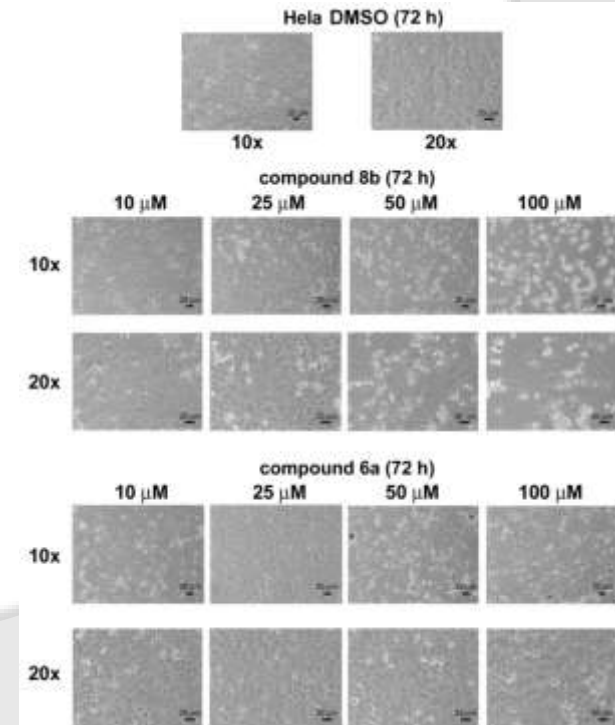
6a (- 16-46%)
 8b (- 12-38%)
 DMSO

6a (- 13-69%)
 8b (- 25-42%)
 DMSO

Biofilm formation



Biofilm less structured, with fewer cells and unable to colonize the entire surface



Strategies to fight antibiotic resistance

Essential Proteins

- **Antibacterial compounds for *B. cenocepacia*:**
C109

Virulence Factors

- **4 antivirulence compounds**
Diketopiperazines

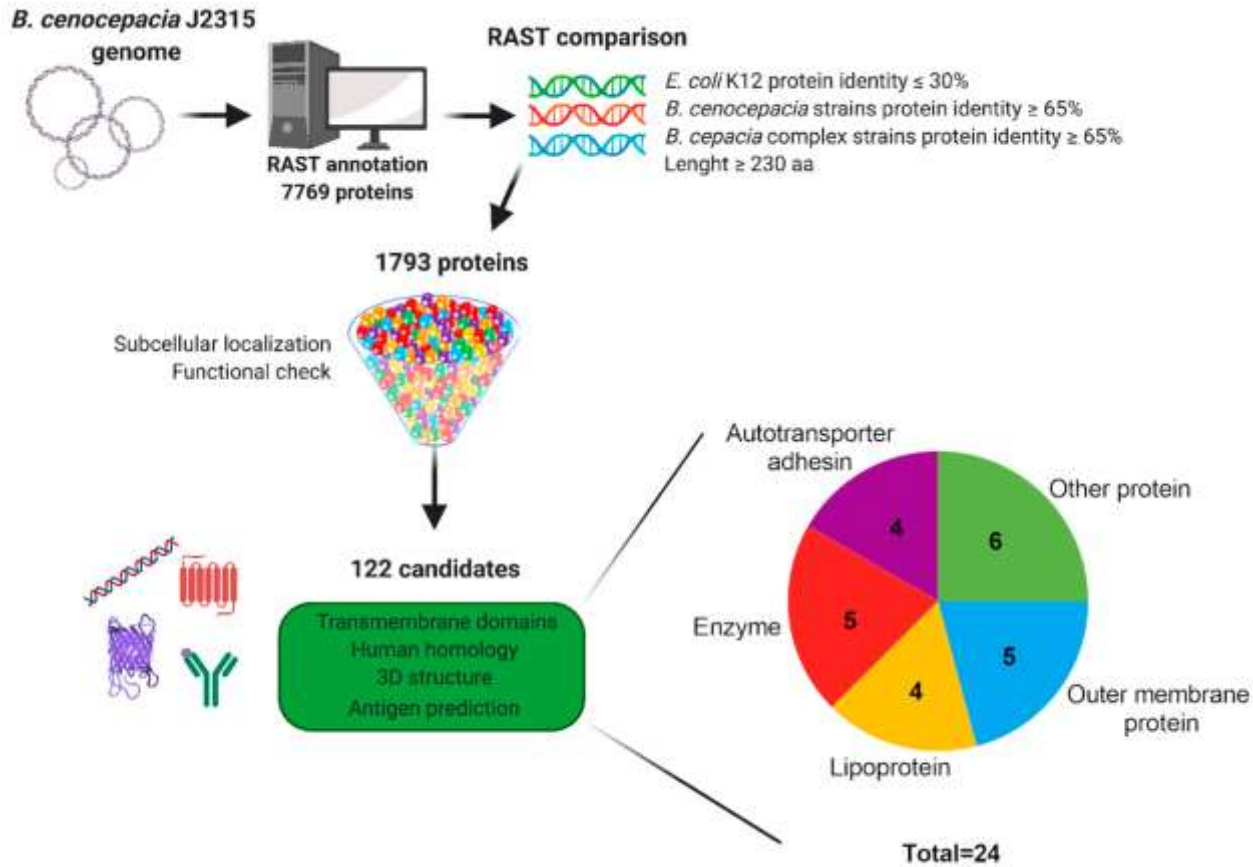
Vaccines

Vaccines for *B. cenocepacia*

Article

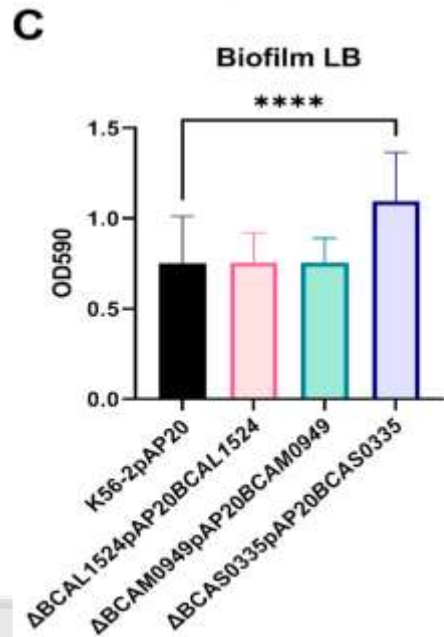
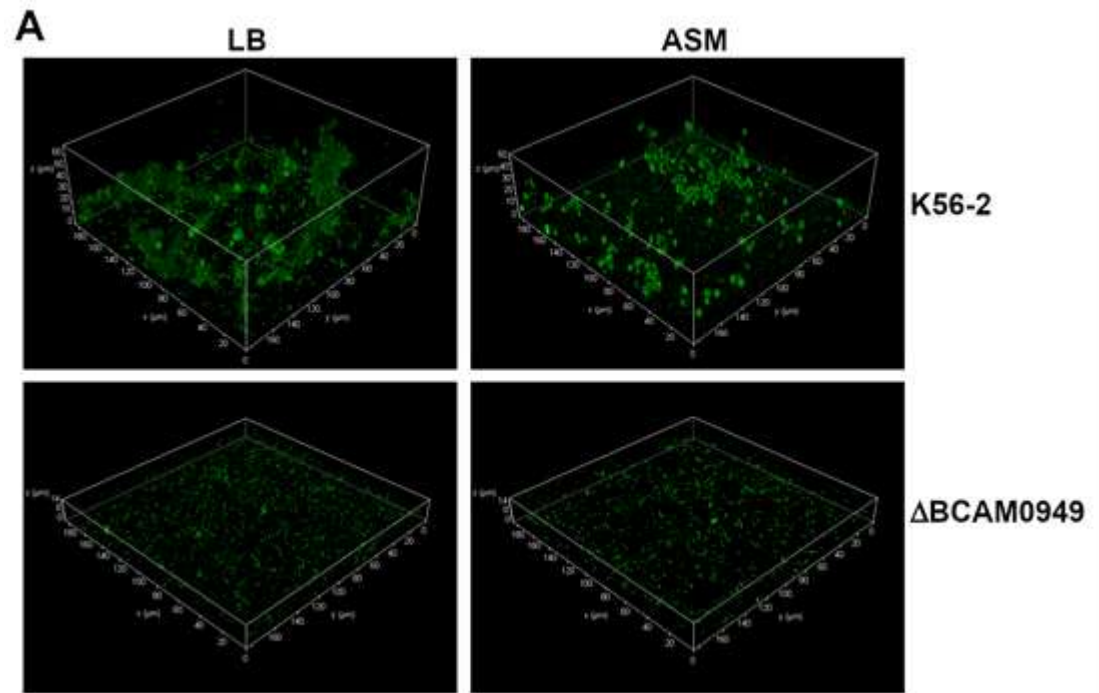
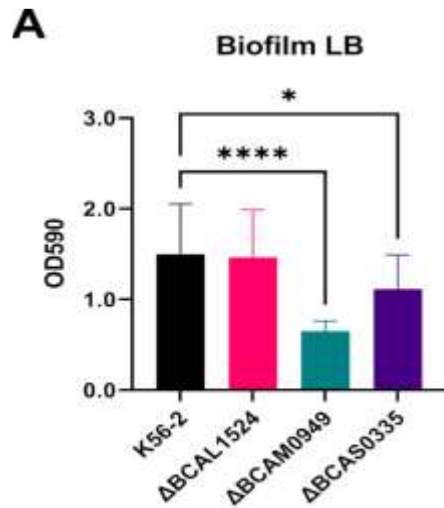
Identification by Reverse Vaccinology of Three Virulence Factors in *Burkholderia cenocepacia* That May Represent Ideal Vaccine Antigens

Samuele Irudal ¹, Viola Camilla Scoffone ¹, Gabriele Trespidi ¹, Giulia Barbieri ¹, Maura D'Amato ², Simona Viglio ², Mariagrazia Pizza ³, Maria Scarselli ⁴, Giovanna Riccardi ¹ and Silvia Buroni ^{1,4}



Collage-like protein **BCAL1524**
Lipase LipA **BCAM0949**
Autotransporter adhesin **BCAS0335**
selected for further analysis

Biofilm formation

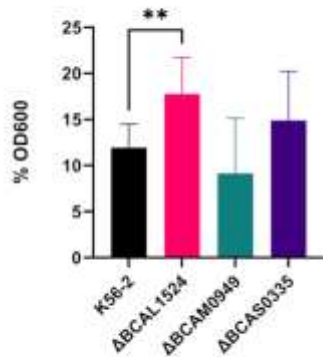


the lipase BCAM0949
and the autotransporter adhesin protein BCAS0335
contribute to biofilm formation

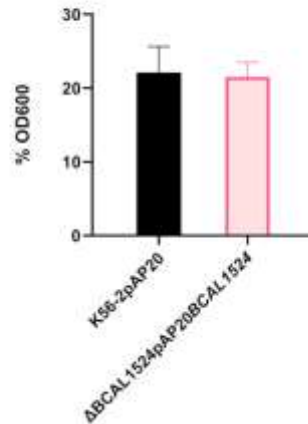
Autoaggregation

Involved in bacterial colonization and persistence in the host

A



B

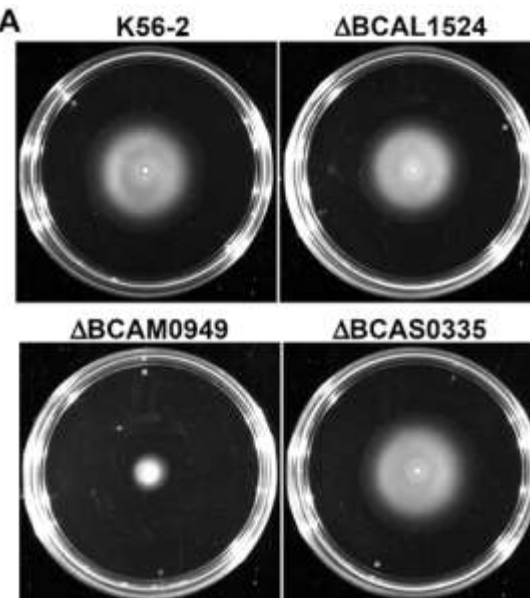


The Collage-like protein BCAL1524 is involved in autoaggregation

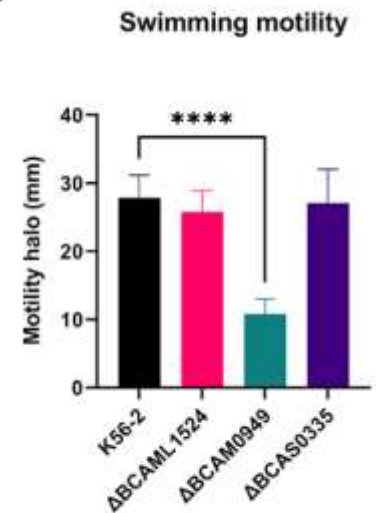
Swimming Motility

The Lipase LipA BCAM0949 is involved in swimming motility

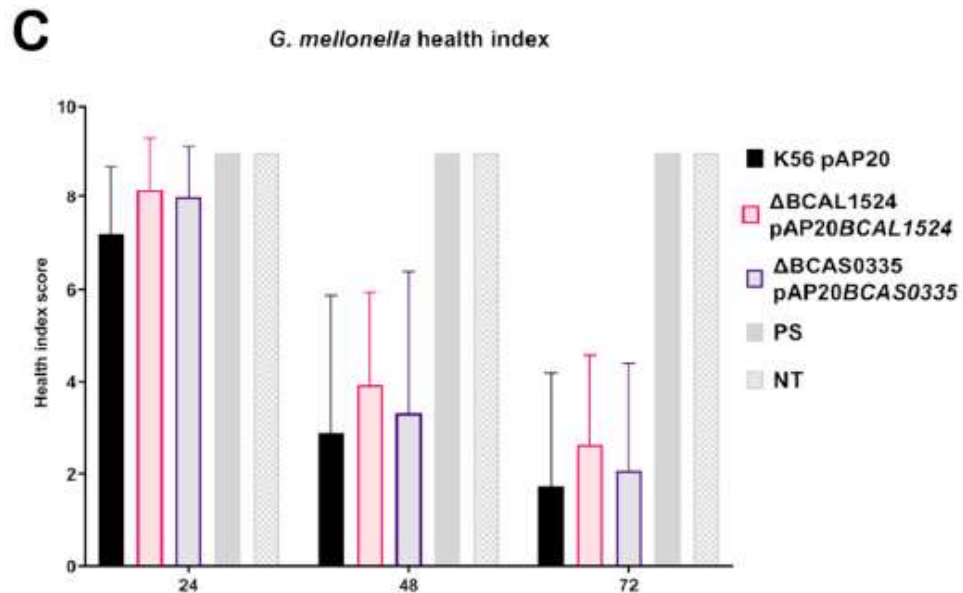
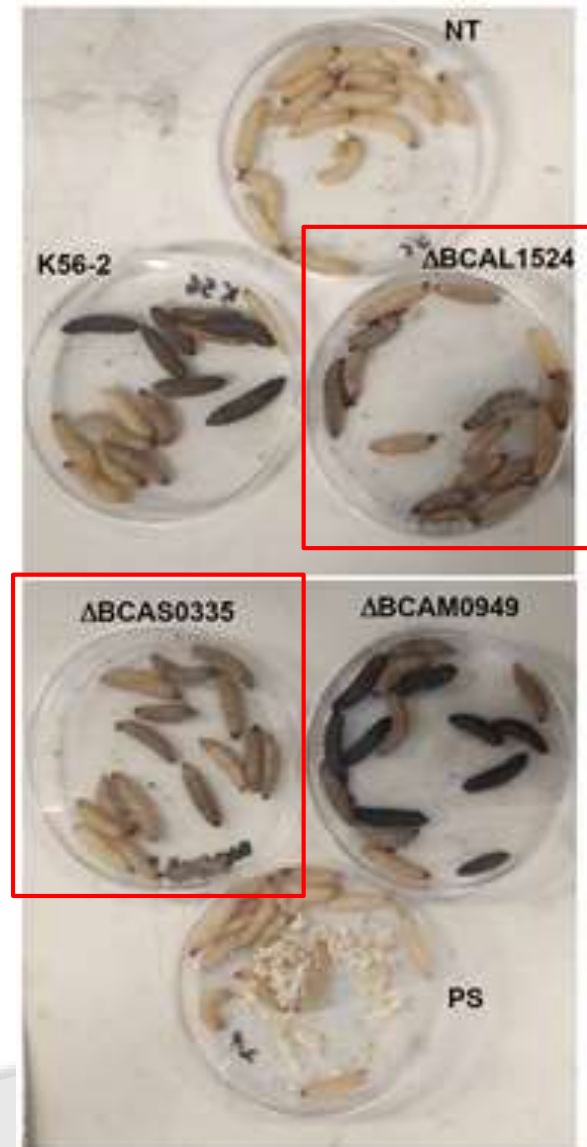
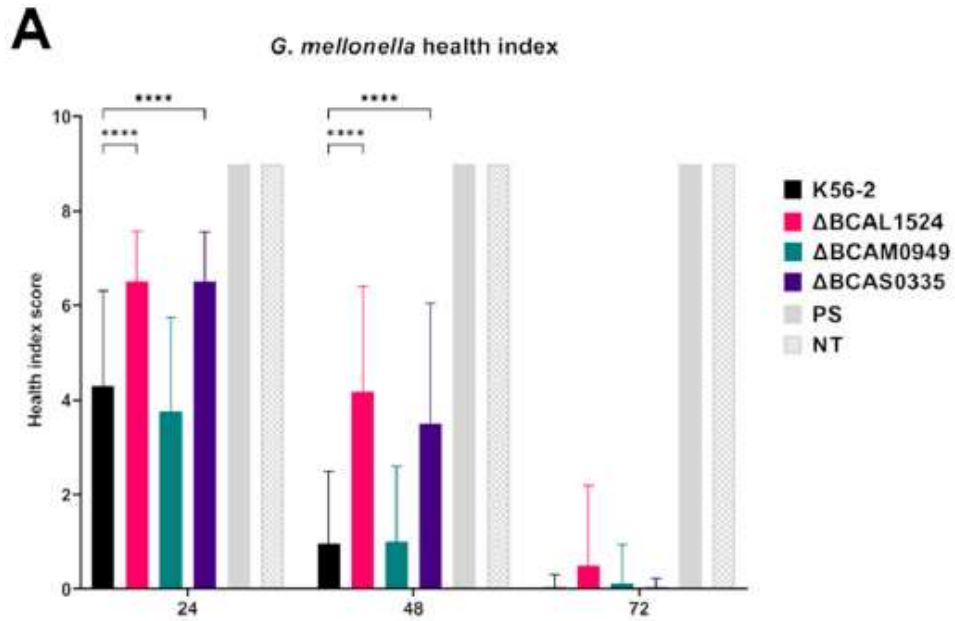
A



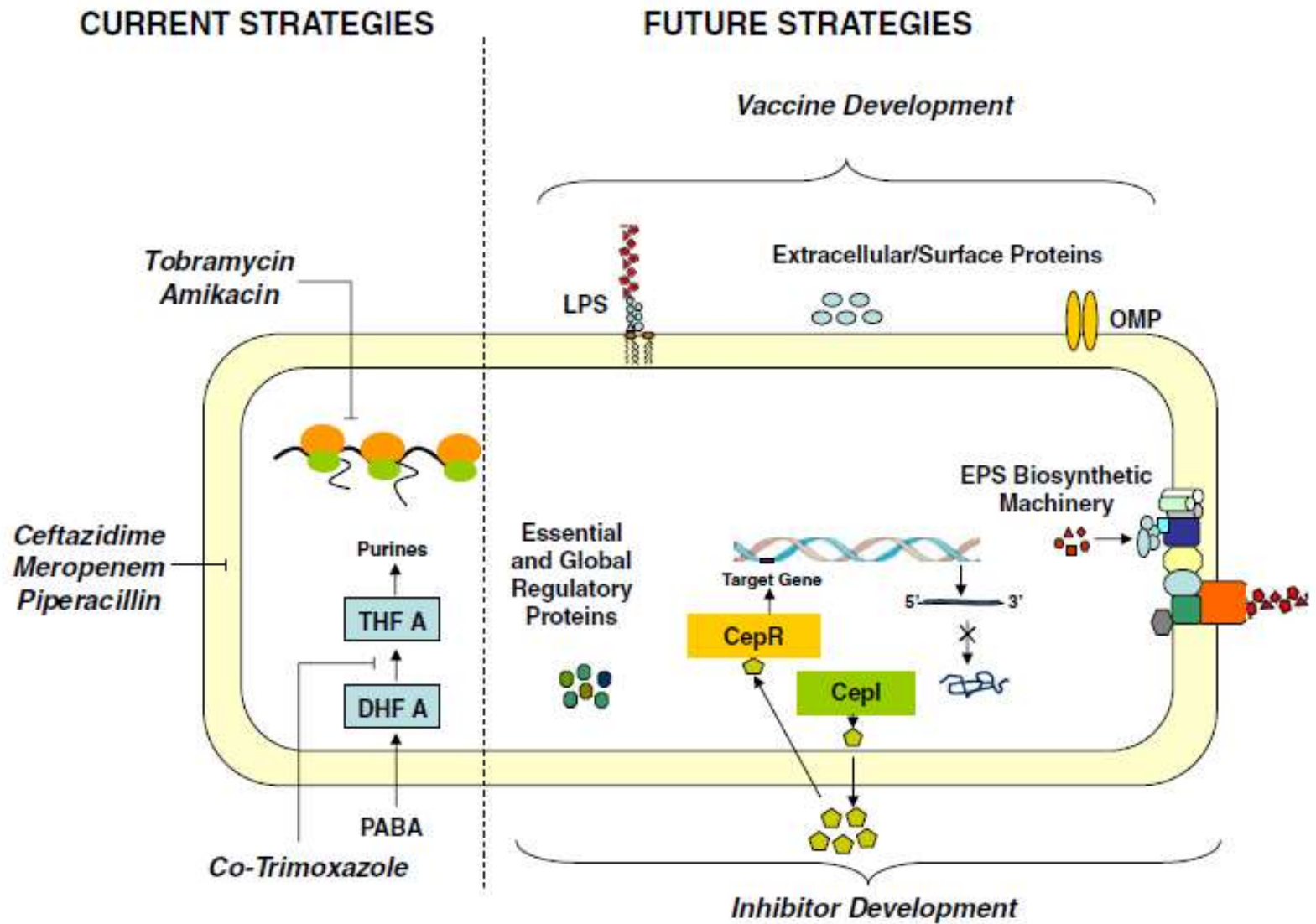
B



Virulence in *Galleria mellonella*



Strategies to fight *B. cenocepacia*



Using a Virtual Screening approach to find
new drugs against
Pseudomonas aeruginosa and *Staphylococcus aureus*



UNIVERSITÀ DI PAVIA
Department of Biology
and Biotechnology
"Lazzaro Spallanzani"

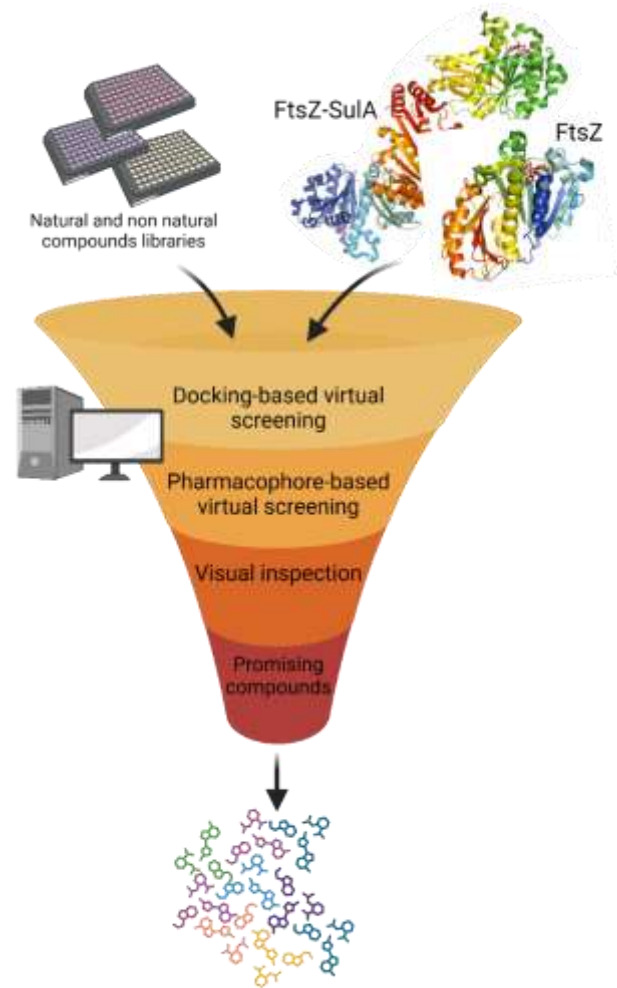
Silvia Buroni and Antonio Coluccia



SAPIENZA
UNIVERSITÀ DI ROMA
DIPARTIMENTO DI CHIMICA
E TECNOLOGIE DEL FARMACO

Background and rationale

- **Virtual Screening (VS)**: fast and cheap method for the selection of **small molecules** effective in the inhibition of the **selected enzymes**.
- **Filter rules** with descriptors to evaluate **drug-like** and **toxicological properties** of the compounds → **quick** identification of new hits to be tested in clinical trials



Hypothesis and objectives

VS targeting **cell division** proteins:

- *S. aureus* and *P. aeruginosa* **FtsZ**

First protein involved in cell division

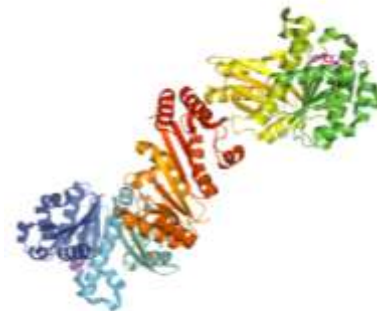
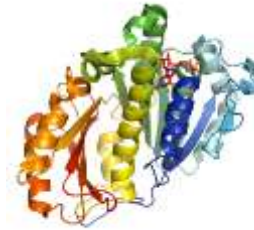
Assembly of “divisome”

- The complex **FtsZ-SulA**

- Small protein induced as part of the SOS response to DNA damage

- It binds to FtsZ and blocks cell division until the DNA is repaired

- It regulates FtsZ activity



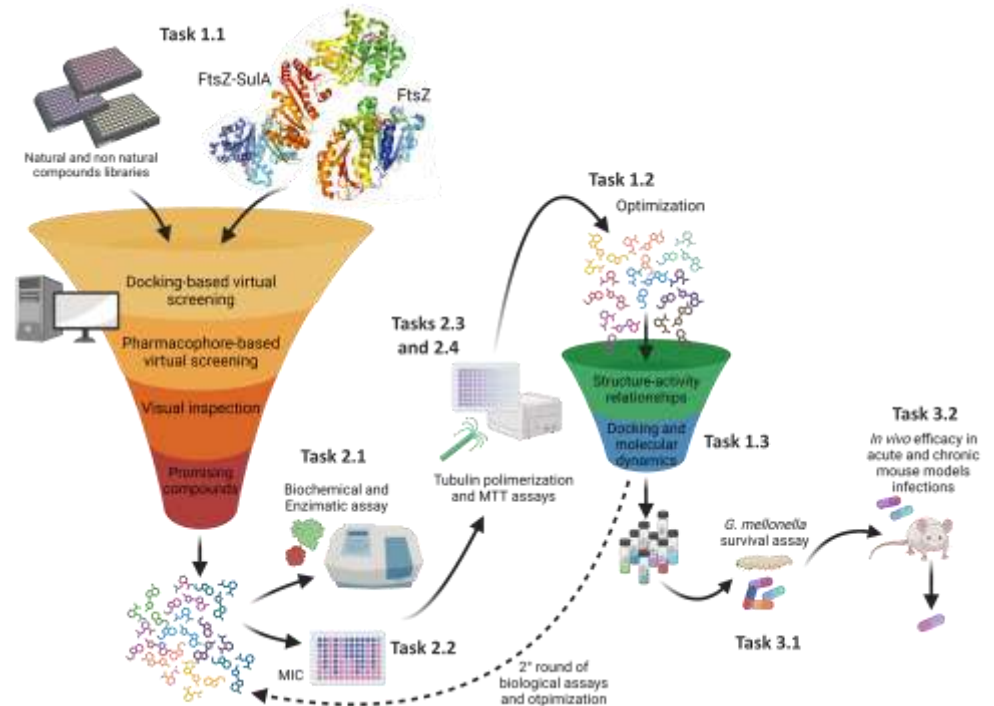
Essential for bacterial survival

Widely **conserved**

No antibiotic in clinical use has these two proteins as targets

Essential methods

- WP1: **chemistry**
- Task 1.1 Identification of compounds targeting *P. aeruginosa* FtsZ or FtsZ-SulA by **VS**.
- Task 1.2 Compound **optimization**.
- Task 1.3 Hit to lead optimization.
- WP2: **compound characterization**
- Task 2.1 Enzymatic **assays**.
- Task 2.2 **MIC** evaluation.
- Task 2.3 Evaluation of the activity of the compounds against **human tubulin**.
- Task 2.4 Evaluation of the **toxicity** of the compounds by MTT.
- WP3: **in vivo assays**
- Task 3.1 *In vivo* assays in ***Galleria mellonella***.
- Task 3.2 *In vivo* assays in **mouse models** of infection.

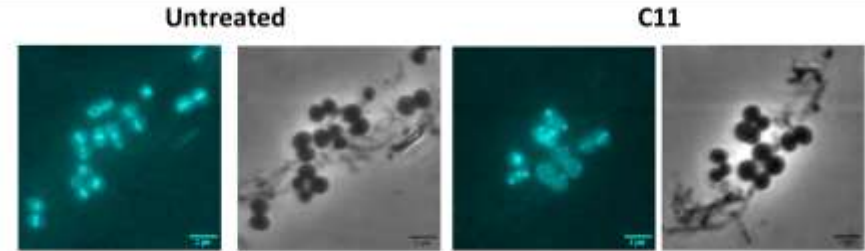


Dr. Alessandra Bragonzi



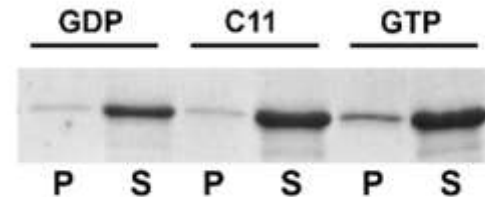
Preliminary results

Compound	% of GTPase residual activity	IC ₅₀	MIC
C109	23 %	1.5 μM	2-4 μg/ml
C1	78 %		> 256 μg/ml
C2	35 %		> 256 μg/ml
C3	16 %	14.6 μM	> 256 μg/ml
C4	71 %		> 256 μg/ml
C5	95 %		> 256 μg/ml
C6	92 %		> 256 μg/ml
C7	100 %		> 256 μg/ml
C8	12 %	8.4 μM	> 256 μg/ml
C9	34 %		> 256 μg/ml
C10	87 %		> 256 μg/ml
C11	82 %		2 μg/ml
C12	17 %	60 μM	> 256 μg/ml



In untreated cells FtsZ localizes in the middle of the cell and forms the Z-ring.

In the treated sample, cells are larger and FtsZ is mislocalized.



C11 (100 μM) blocks FtsZ polymerization

Toxicity evaluation

At 25 μM C11: - 20% human tubulin polymerization.
90% of HeLa cells survived the treatment.

Conclusions

- Our final goal is to identify new therapeutic solutions against the two MDR pathogens that mostly affect CF patients, with a **new mechanism of action** with respect to currently used drugs.
- In the future the same approach could be applied to **other proteins and bacteria** to find new therapeutic solutions for airway pathogens, thus promoting the introduction of innovative treatments for CF patients.

Characterization of the dispirotripiperazine derivative PDSTP as antibiotic adjuvant and antivirulence compound against *Pseudomonas aeruginosa*

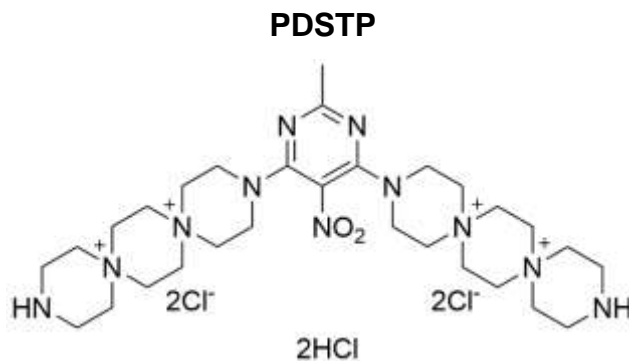
Front. Microbiol. 15:1357708.
doi: 10.3389/fmicb.2024.1357708

Andrea Bonacorsi^{1†}, Gabriele Trespidi^{1†}, Viola C. Scoffone¹,
Samuele Irudal¹, Giulia Barbieri¹, Olga Riabova²,
Natalia Monakhova², Vadim Makarov² and Silvia Buroni^{1*}

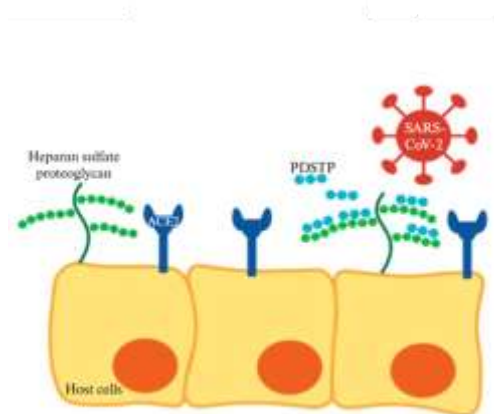
Dispirotripiperazines: broad spectrum antiviral compounds

PDSTP is active against:

- ✓ Herpes simplex virus type-1 and 2
- ✓ Human cytomegalovirus
- ✓ Human immunodeficiency virus
- ✓ Human papilloma virus
- ✓ SARS-CoV-2



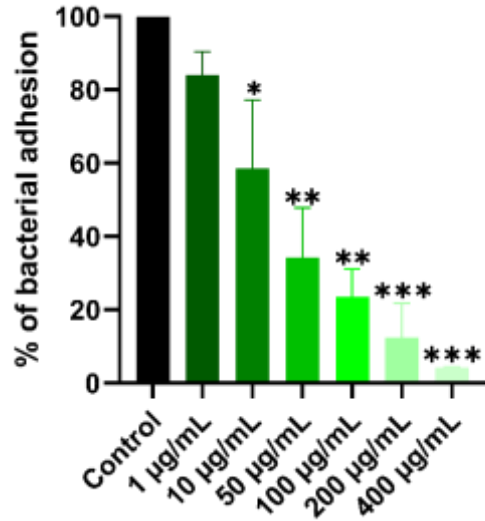
Dr. Vadim Makarov



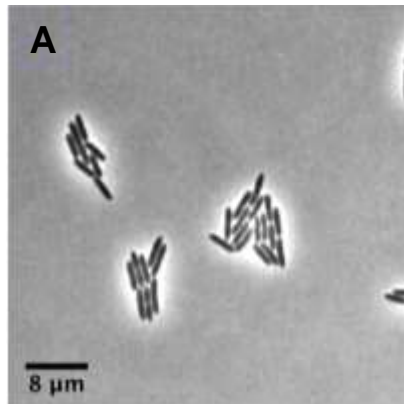
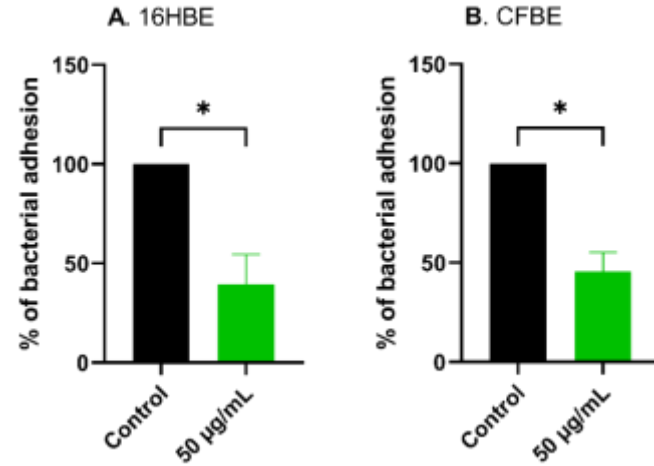
Makarov and Popov, 2022

PDSTP impairs *P. aeruginosa* adhesion

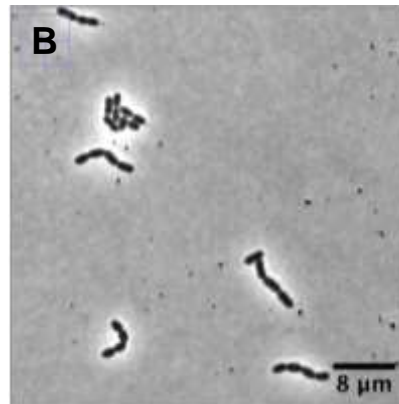
PA01 adhesion on A549 monolayers



PA01 adhesion on 16HBE and CFBE monolayers



No treatment



PDSTP 50 µg/mL

PDSTP enhances efficacy of antibiotics used in clinics

PDSTP-antibiotic combinations tested on PA01 and 9 drug resistant CF clinical isolates

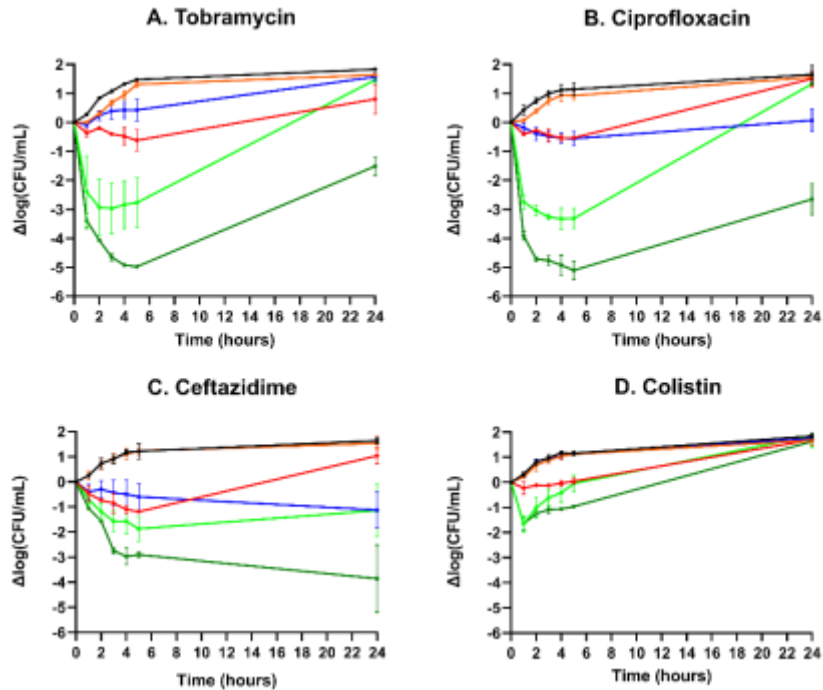
Antibiotic	MIC reduction
Tobramycin	0x to 2x
Ciprofloxacin	2x to 16x
Ceftazidime	4x to 128x
Meropenem	8x to 32x
Colistin	16x to 32x

6/7 resistant strains below the CLSI susceptibility breakpoint

4/4 resistant strains below the CLSI susceptibility breakpoint

MIC of 2 resistant strains **decreased from 64-128 µg/mL to 4 µg/mL**

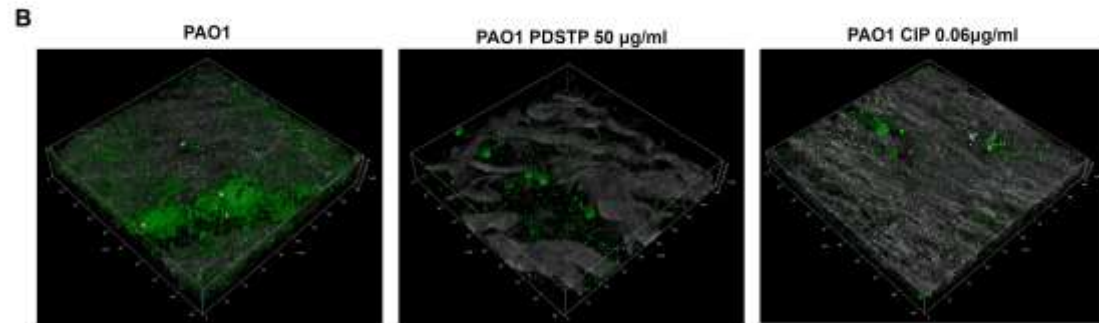
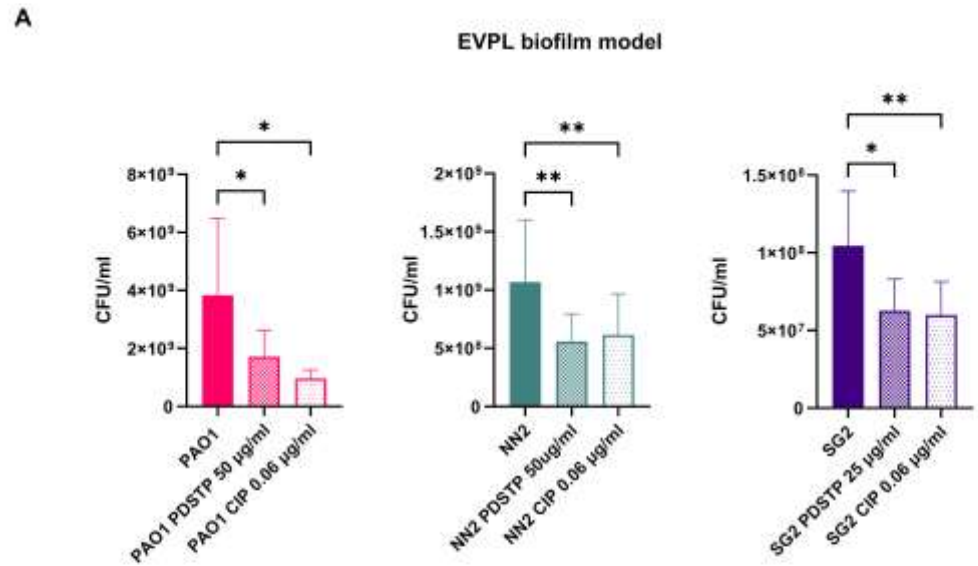
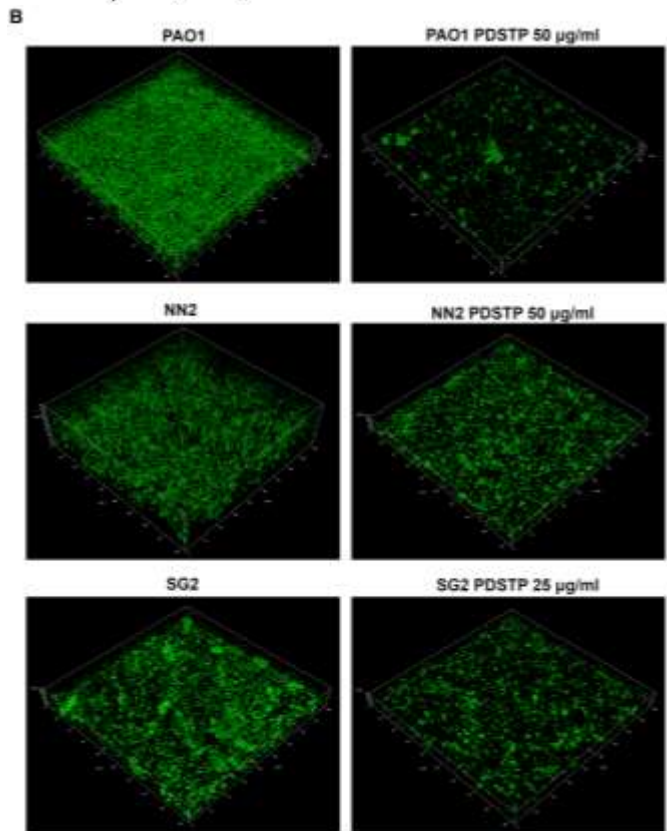
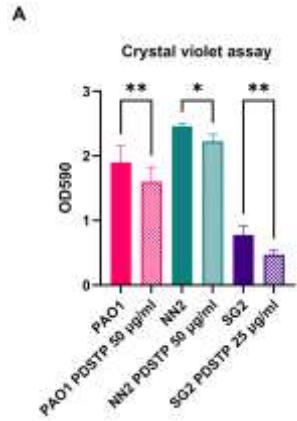
PDSTP-antibiotic combinations tested on PA01 and 9 drug resistant CF clinical isolates



- Control
- PDSTP (50 $\mu\text{g/mL}$)
- PDSTP (200 $\mu\text{g/mL}$)
- Antibiotic (1/2 MIC)
- PDSTP (50 $\mu\text{g/mL}$) + Antibiotic
- PDSTP (200 $\mu\text{g/mL}$) + Antibiotic

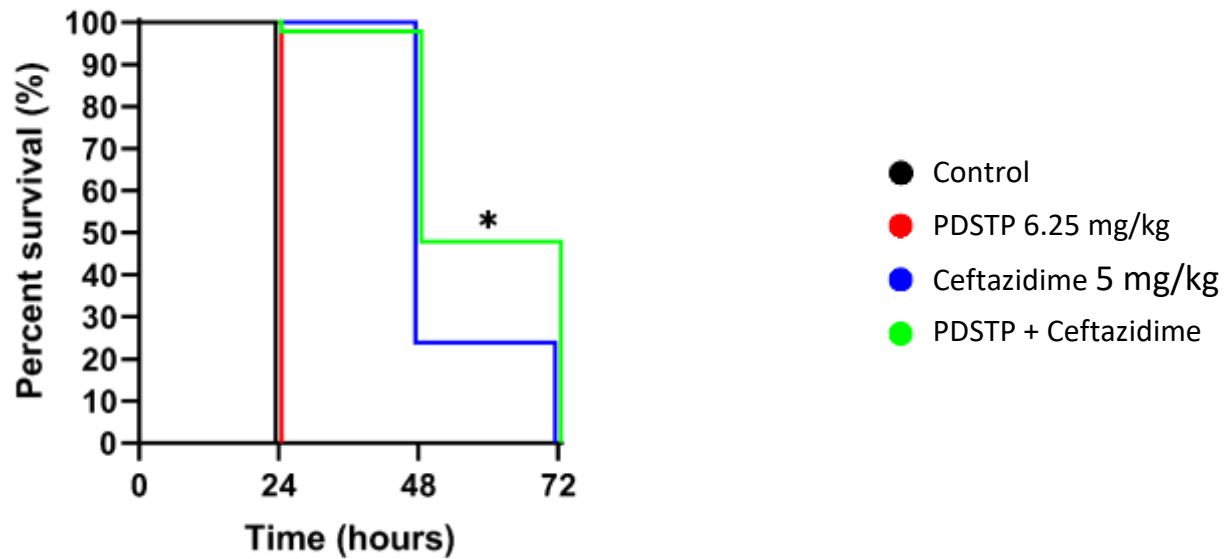
Comparable efficacy of the combinations was observed by time-killing assays on 7/9 clinical isolates

PDSTP inhibits biofilm formation *in vitro* and in an *ex vivo* pig lung model



PDSTP - Ceftazidime combination is effective *in vivo*

Galleria mellonella infection model



Conclusions

Vaccines

Adjuvants



Strategies to fight antibiotic resistance



Essential proteins

Virulence factors

FtsZ

Quorum Sensing



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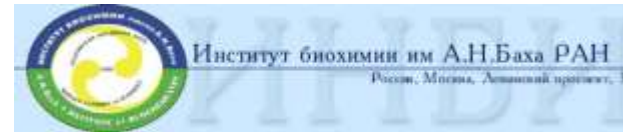


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Progetti di Rilevante
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