ReformúlaTe

EN BUSCA DEL TESORO

"Nuevas estrategias terapéuticas"

Jordi Vila Estapé

Hospital Clinic de Barcelona / Jefe del Servicio de Microbiología

Burden of multidrug-resistant bacteria in the European Union

Human burden

Infection (6 most frequent MDR bacteria, 4 main types of infection).	approx.	400,000 / year *671.689 / year 2015
Attributable deaths	approx.	25,000 / year *33.110 / year 2015
Extra hospital days	approx.	2.5 million / year

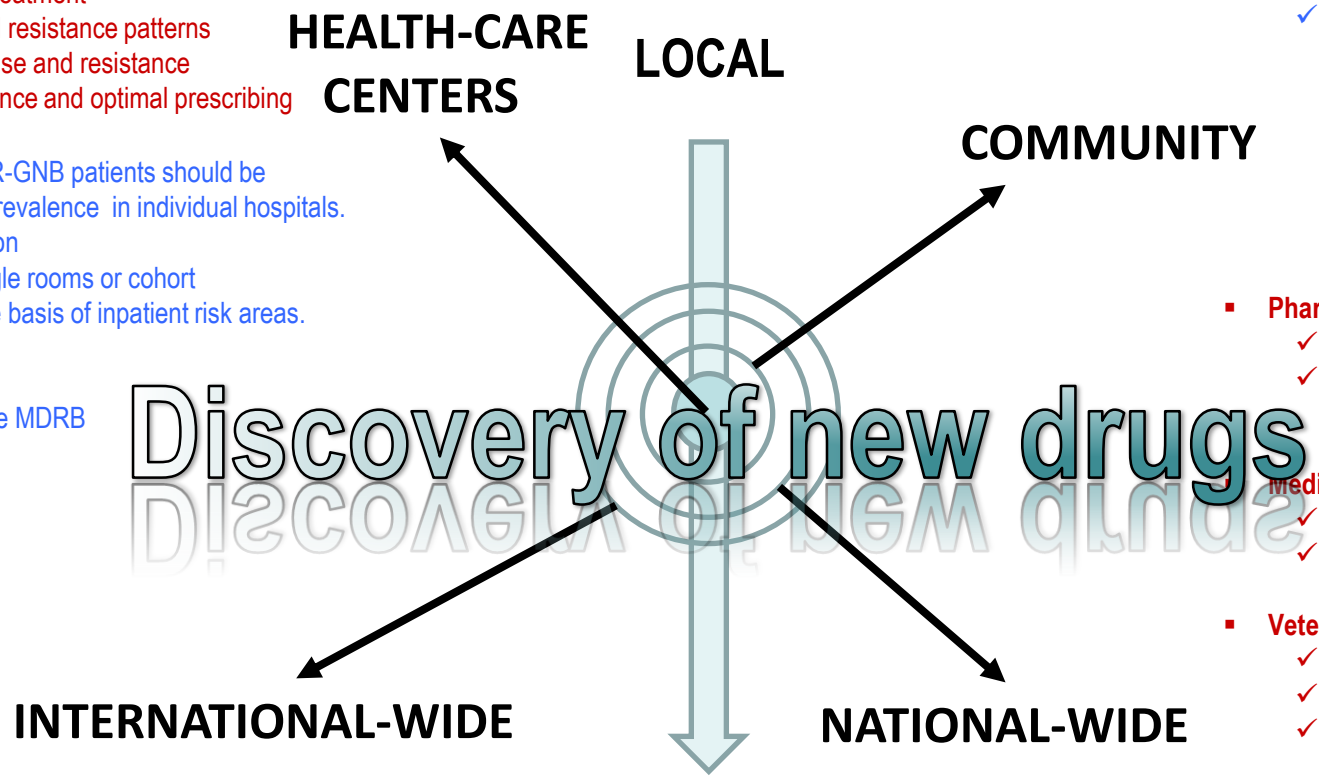
Economic burden

Extra in-hospital costs	approx.	€ 1 billion / year
Productivity losses	approx.	€ 600 million / year

Source: ECDC, 2009; * Cassini et al. (2018) Lancet ID

How to diminish the emergence and spread of antimicrobial resistance bacteria?

- **Antimicrobial stewardship**
  - ✓ Leadership commitment and appointing AS team
  - ✓ Rapid and affordable diagnostic (Diagnostic stewardship)
  - ✓ Systematic evaluation of on-going treatment
  - ✓ Monitoring antibiotic prescribing and resistance patterns
  - ✓ Reporting information on antibiotic use and resistance
  - ✓ Education of clinicians about resistance and optimal prescribing
- **Control**
  - ✓ Active screening of contacts of MDR-GNB patients should be decided on the background of prevalence in individual hospitals.
  - ✓ Screening of patients upon admission
  - ✓ Barrier isolation and isolation in single rooms or cohort isolation are implemented on the basis of inpatient risk areas.
  - ✓ Hand hygiene
  - ✓ Environmental cleaning
  - ✓ Decolonization or sensitization of the MDRB



- **General Population**
  - ✓ Adhere strictly to therapeutic schemes
  - ✓ Respect proper treatment duration
  - ✓ Avoid self-medication with antibiotics
  - ✓ Proper cooking and handling of food
  - ✓ Hand-washing, when:
    - ✓ Before eating
    - ✓ Before and after touching a sick person
    - ✓ After using the bathroom
    - ✓ After touching an animal or handle animal waste
    - ✓ After handling rubbish
    - ✓ After being in places frequented by many people (example: public transportation)
- **Pharmacists**
  - ✓ Reject to sale without prescription
  - ✓ Inform patients about when are antibiotics needed, how to take them correctly and the consequences of a misuse.
- **Medical doctors**
  - ✓ Practice safe prescription of antibiotics
  - ✓ Use of point-of-care tools to ensure when are antibiotics needed
- **Veterinarians**
  - ✓ Reduce the use of antibiotics in livestock
  - ✓ Avoid using antibiotics as prophylaxis
  - ✓ Provide veterinarians with latest information regarding antimicrobial resistance

- Antimicrobial resistance surveillance at an international level
- Antibiotic consumption at an international level
- Defining integrated plans at a global level

- Antimicrobial resistance surveillance at a national level
- Antibiotic consumption at a national level
- Implementation of action plan in each country in terms of Education strategies among General Population as well as among Health specialists and Veterinarians

Vila J (2018) CMI 24: 684

WHO PRIORITY PATHOGENS FOR R&D OF NEW ANTIBIOTICS

March 2017

World Health Organization

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

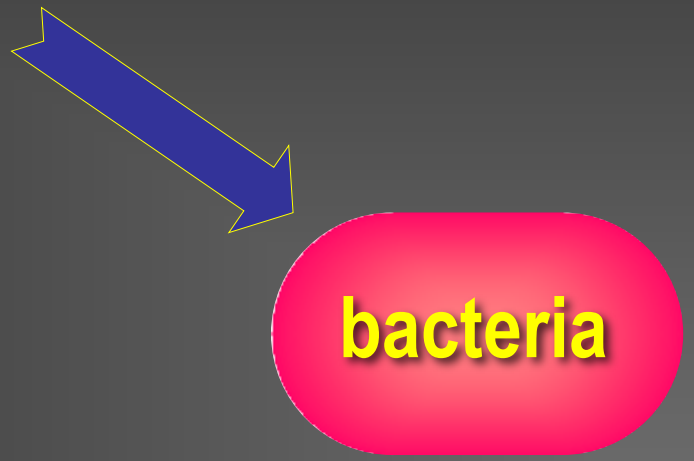
Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

45 traditional and 31 non traditional in the pipeline

(Average success rate of about 14%)

1. Derivative of known antibacterial agents

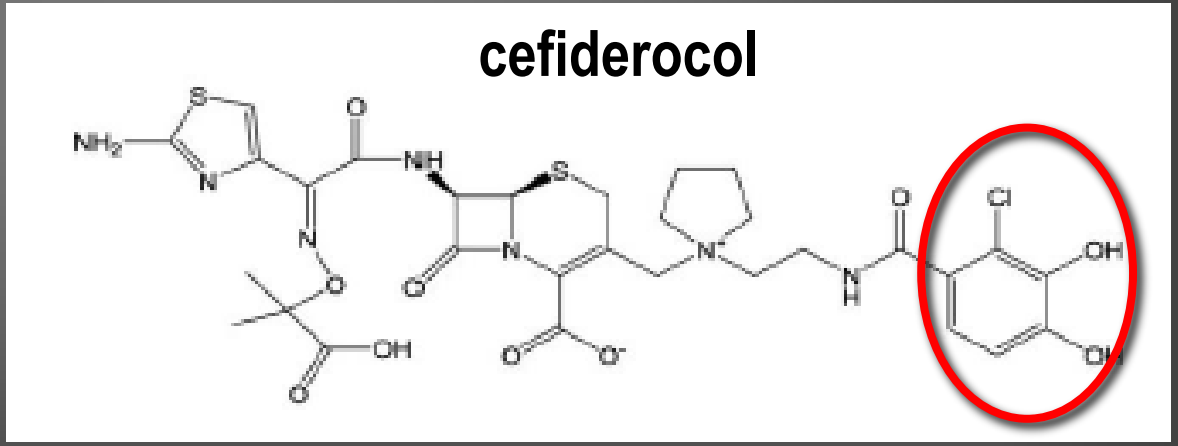


Vila et al. (2019) CMI 26: 596

Derivative of known antimicrobial agents

- Modification of the basic structure of the antimicrobial agent which circumvents antibacterial resistant mechanisms

Cefiderocol



- It has enhanced stability to β-lactamases

Derivative of known antimicrobial agents

- Modification of the basic structure of the antimicrobial agent which circumvents antibacterial resistant mechanisms

- Development of a compound inhibiting the mechanisms of resistance for an antibacterial agent

Derivative of known antimicrobial agents

Blocking antibacterial resistance mechanisms

- Inhibition of beta-lactamases
- Inhibition of efflux pumps
- Inhibition of aminoglycoside-modifying enzymes

Derivative of known antimicrobial agents

Blocking antibacterial resistance mechanisms

- Inhibition of beta-lactamases

A	Clavulanic acid, tazobactam, sulbactam	
B	carbapenemases	new inhibitors
C	AmpC	
D	carbapenemasas	

New beta-lactamase inhibitors:

- Avibactam: inhibits class A and C and some class D enzymes (Ceftazidime)
- Relebactam: inhibits class A and C (Imipenem)
- Vaborbactam: inhibits class A and C (Meropenem)

Combinations of BL / BLI in clinical trials

Antibacterial agent	"Target"	Phase	Pharma. Indust.
Durlobactam + sulbactam	DBO-BLI / PBP-2 binder – BLI / PBP 1, 3*	3	Entasis
Taniborbactam + cefepime	Boronate BLI	3	VenatoRx Phar.
Enmetazobactam + cefepime	BLI	3	Allecra
Zidebactam + cefepime	DBO-BLI / PBP-2 binder*	1	Wockhardt
Nacubactam + meropenem	DBO-BLI / PBP-2 binder*	1	Meiji Seika
ETX0282 + cefpodoxime	DBO-BLI / PBP-2 binder*	1	Entasis
VNRX-7145 + ceftibuten	Boronate BLI	1	VenatoRx Phar.

** 6 more combinations

*** DBO - diazabicyclooactane

Derivative of known antimicrobial agents

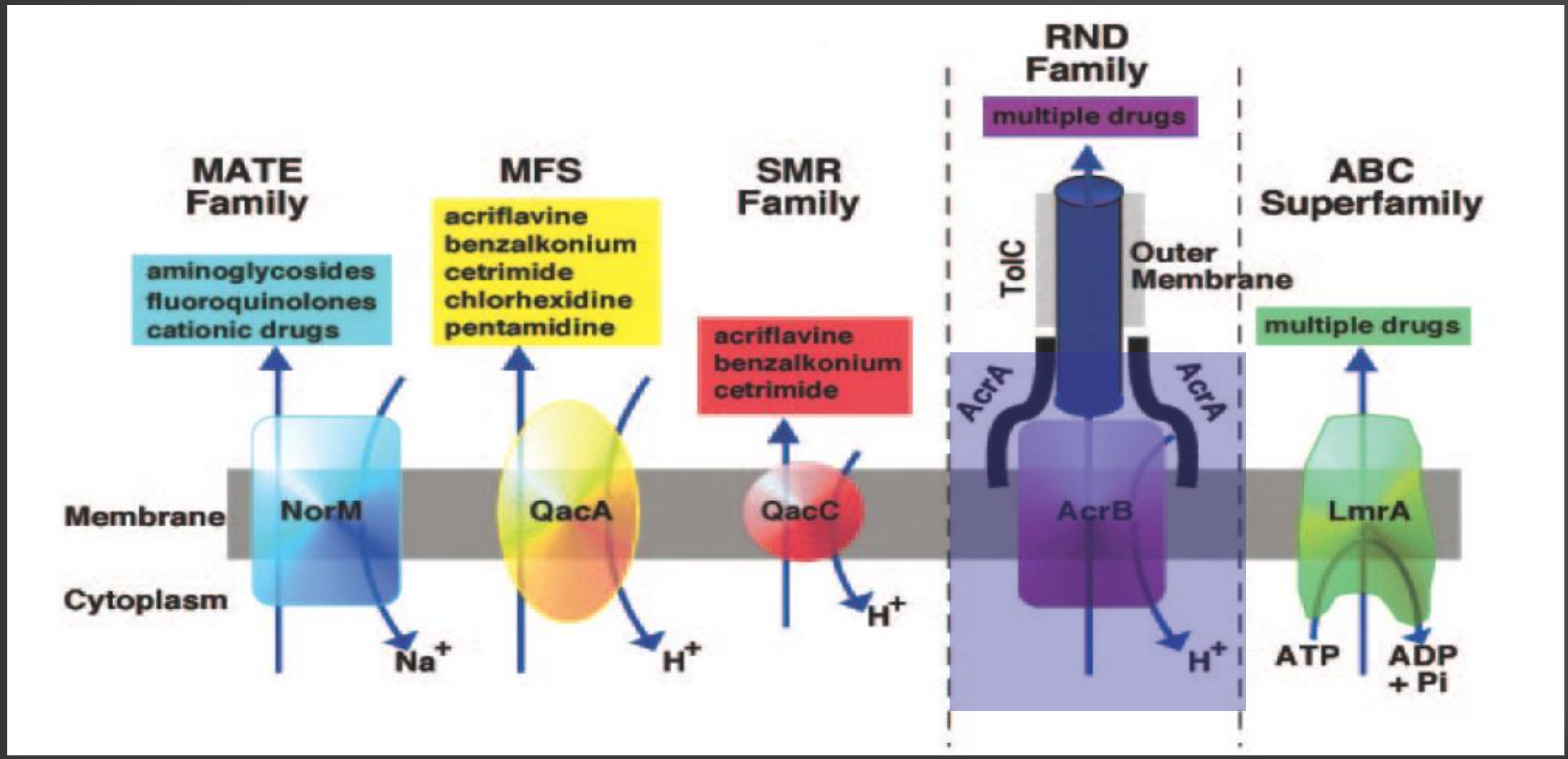
Blocking antibacterial resistance mechanisms

- Inhibition of beta-lactamases
- Inhibition of efflux pumps
- Inhibition of aminoglycoside-modifying enzymes

Vila J, Fàbrega A, Roca I, Hernández A, Martínez JL

Efflux pumps as an important mechanism for quinolone resistance

Adv Enzymol Relat Areas Mol Biol 2011: 77; 167-235

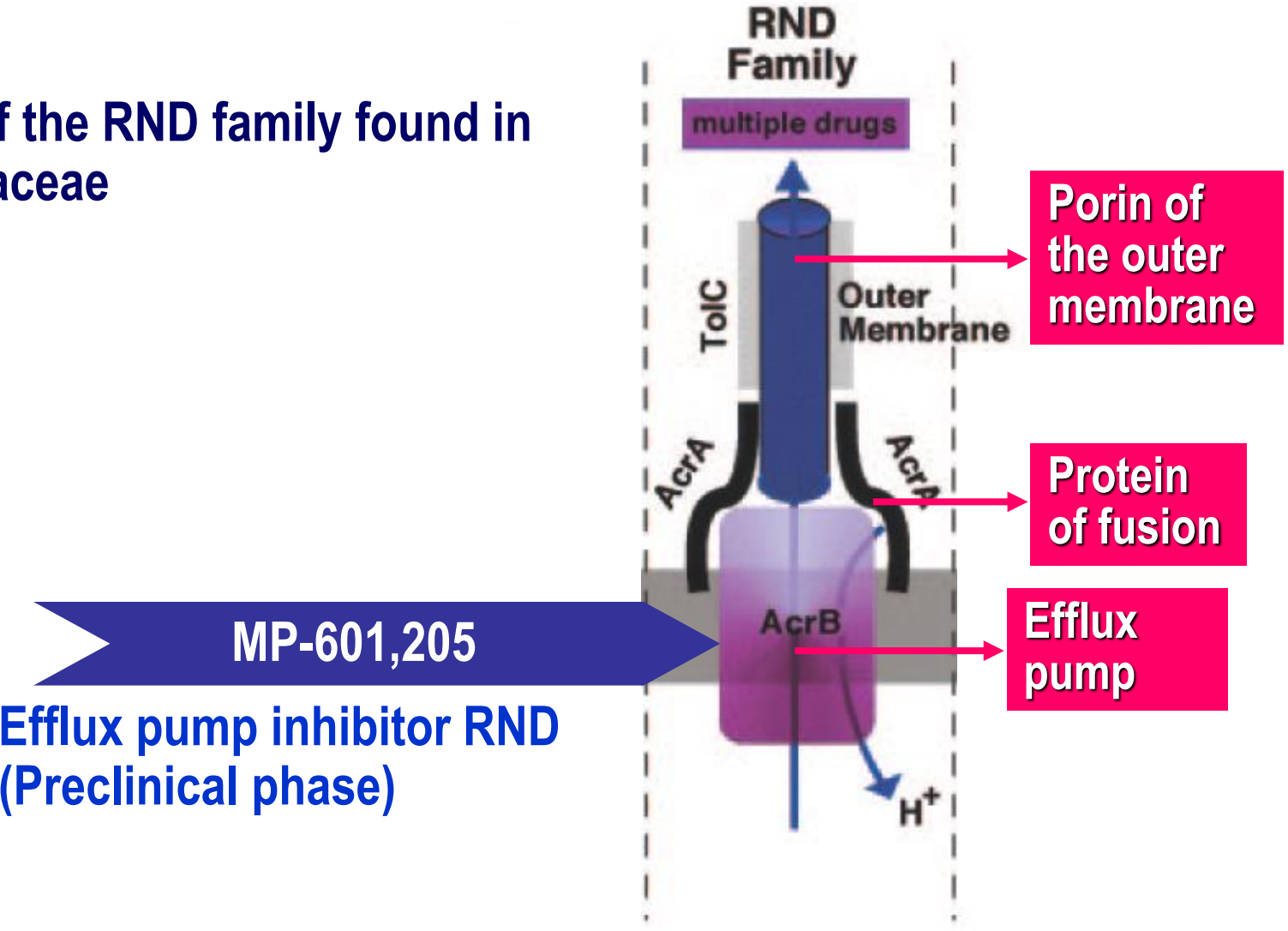


Vila J, Fàbrega A, Roca I, Hernández A, Martínez JL

Efflux pumps as an important mechanism for quinolone resistance

Adv Enzymol Relat Areas Mol Biol 2011: 77; 167-235

Efflux pump of the RND family found in Enterobacteriaceae

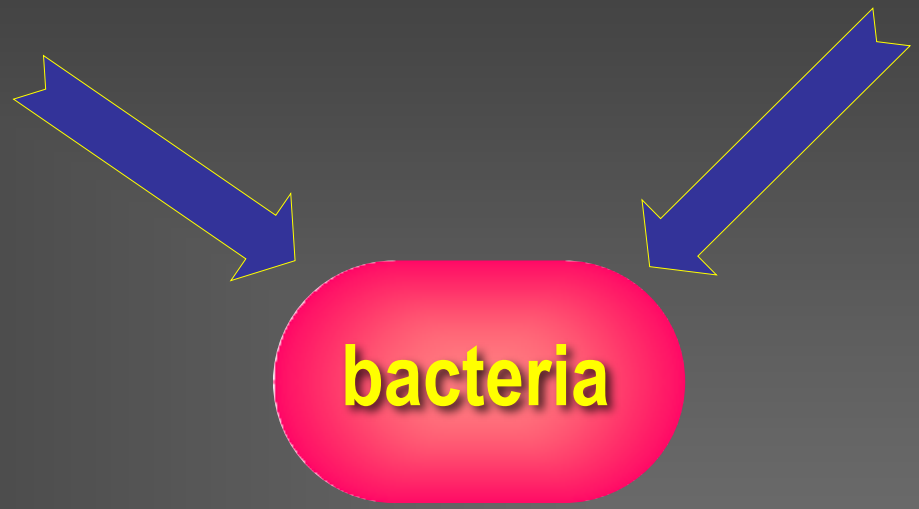


MP-601,205

Efflux pump inhibitor RND (Preclinical phase)

1. Derivative of known antibacterial agents

2. New antibacterial agents



Vila et al. (2019) CMI 26: 596

DISCOVERY OF NEW ANTIBACTERIAL AGENT

- Classical
  - Secondary metabolites of bacteria and fungi with antimicrobial activity
  - Plant extracts
  - Marine macro and microorganisms
  - Human microbiota

DISCOVERY OF NEW ANTIBACTERIAL AGENT

- Genomic
  - New tools on chemistry and molecular biology
    - Genomics and recombinant DNA.
    - Molecular modeling
    - Combinatorial chemistry and chemical structure.

Inhibitors of new protein targets

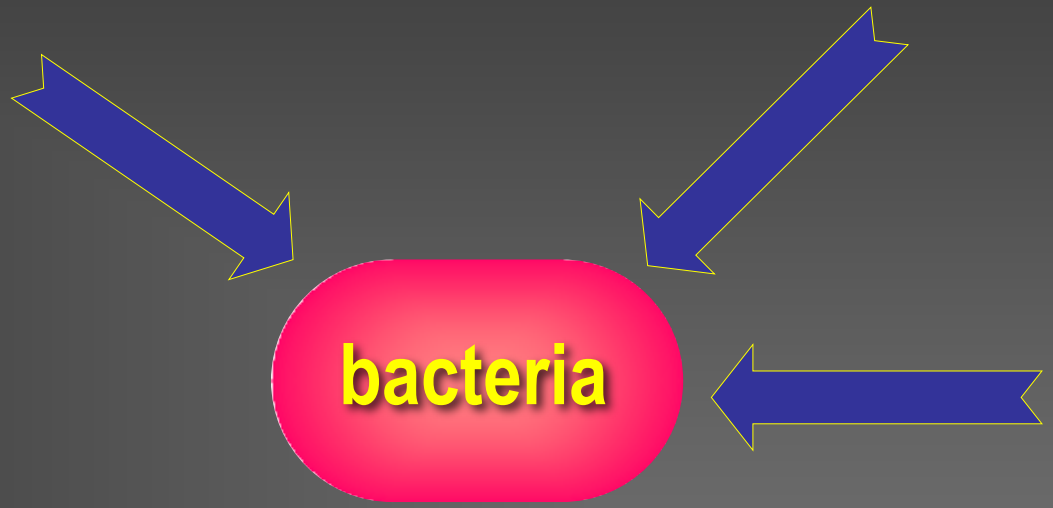
45 antibiotics in clinical development

Antibacterial agent	Target	Phase	Pharma. Indust.
TXA-709 Difluobezamide	**FtsZ innhibitor** Protein involved in cell division	1	Taxis Pharmaceutical
Afabicin Pyrido-enamide	**FabI inhibitor** Fatty acid biosynthesis	2	Debiopharma
Zoliflodacin* Spiropyrimidenetrione	**Topoisomerase inhibitor** DNA gyrase (gyrB – B subunit)	3	Entasis / GARDP
Gepotidacin* Triazaacenaphthylene	**Topoisomerase inhibitor** DNA gyrase (gyrA – A subunit)	3	GSK

"New antibacterial agents against *M. tuberculosis* and *C. difficile* are not included"

1. Derivative of known antibacterial agents

2. New antibacterial agents



3. Blockers of virulence factors

Vila et al. (2019) CMI 26: 596

Antivirulence drugs: A therapeutic alternative?

- In the presence of these compounds, bacterial pathogens will have difficulties to generate an infection and will therefore be more easily eliminated by immune systems
- Proposed targets for antivirulence drugs:
  - Fimbria (GNB), Surface proteins (GPB)
  - Toxins
  - Type III secretion systems
  - Quorum sensing
  - Regulation of virulence factors:
    - Two component systems; e.i: *Enterococcus,* the *vanA* gene is regulated by *vanR-vanS*
- Monoclonal antibodies

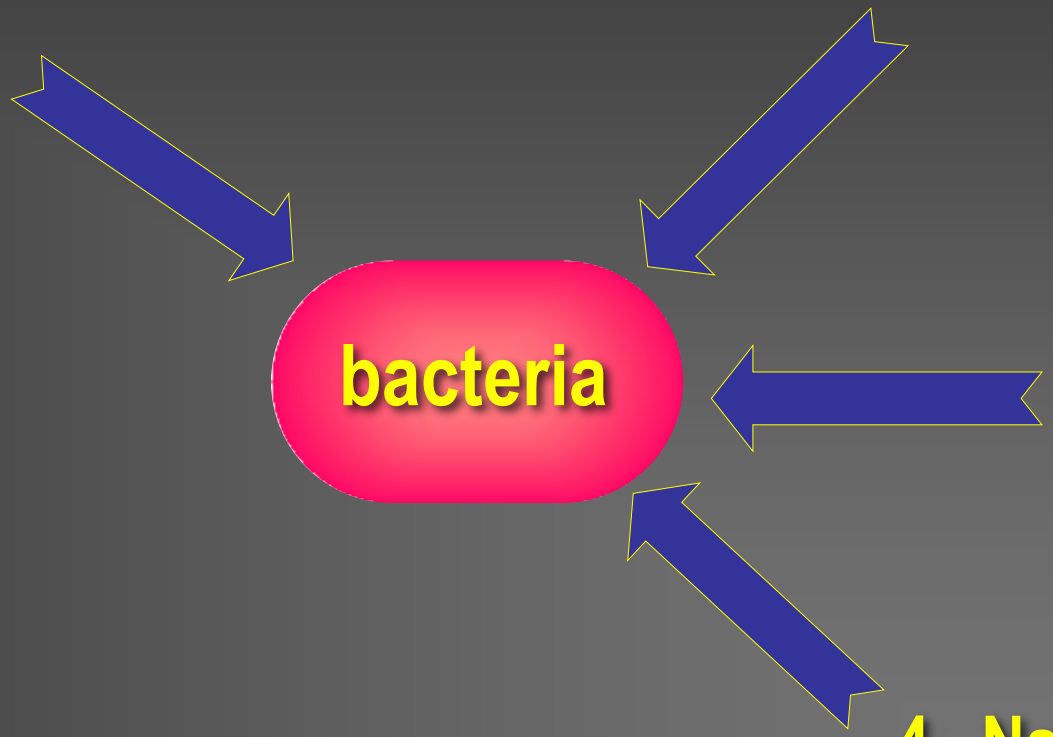
Monoclonal antibodies and virulence factor inhibitors

Antibacterial agent	"Target"	Phase	Pharma. Indust.
Tosatoxumab	alpha-toxin *S. aureus*	3	Aridis Pharm.
Suvratoxumab	alpha-toxin *S. aureus*	3	Aridis Pharm.
TRL1068 (MAb)	Targets the DNABII protein family Biofilm	1	Trellis Biosci.
DSTA4637S (MAb)	Conjugation of Ab against WTA w/ rifamycin against *S. aureus*	1	Genentech / Roche
LMN-101	Variable heavy chain designed to inhibit flagellin in *C. jejuni*	2	Lumen Biosci.
Ftortiazinon + cefepime	Thyazinone inhibits TTSS in *P. aeruginosa*	2	Gamaleya

* Three other compounds in phase 1

1. Derivative of known antibacterial agents

2. New antibacterial agents



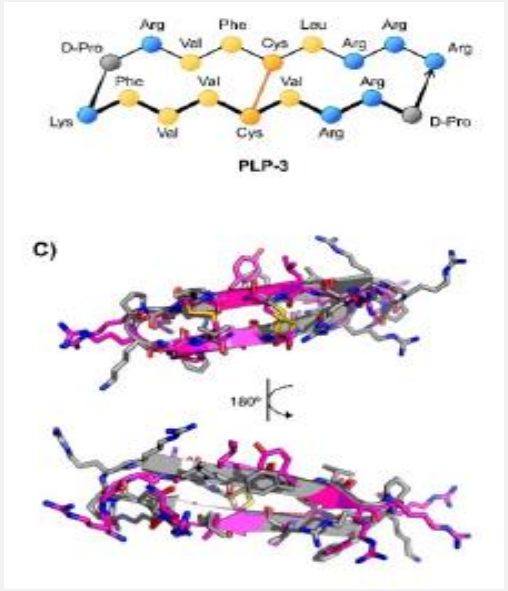
3. Blockers of virulence factors

4. Nanoparticles and Antibacterial peptides / peptidomimetics

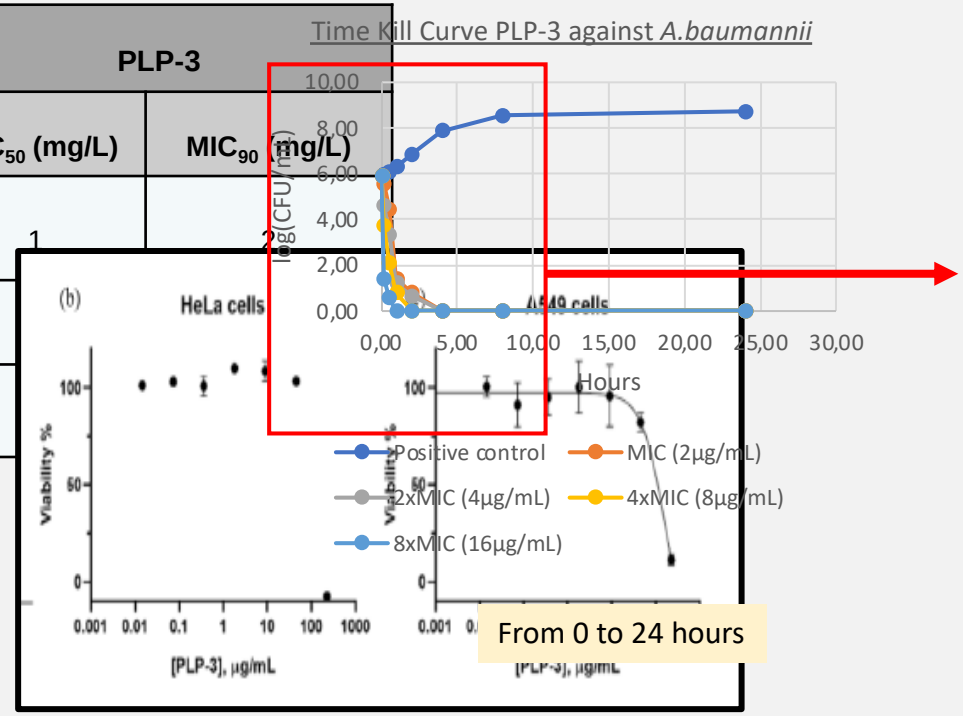
Vila et al. (2019) CMI 26: 596

Peptids and peptidomimetics

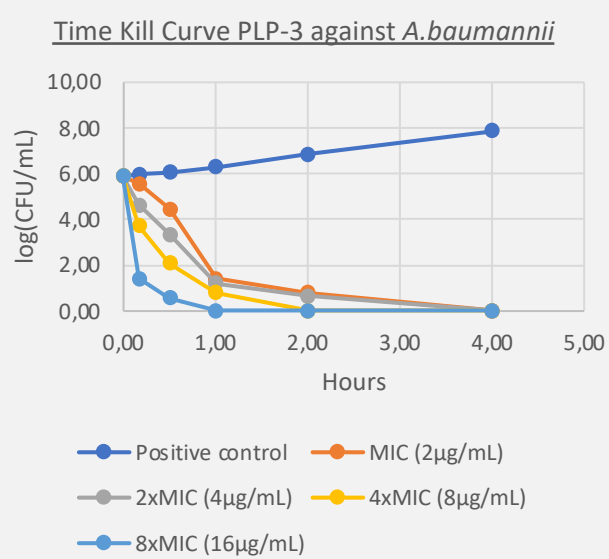
Antibacterial agent	"Target"	Phase	Pharma. Indust.
PLG-0206	Cationic peptide (Eliminates biofilm / PJI)	1	Peptilogics



	PLP-3	
Species	MIC_{50} (mg/L)	MIC_{90} (mg/L)
A. baumannii	1	2
K. pneumoniae		
P. aeruginosa		

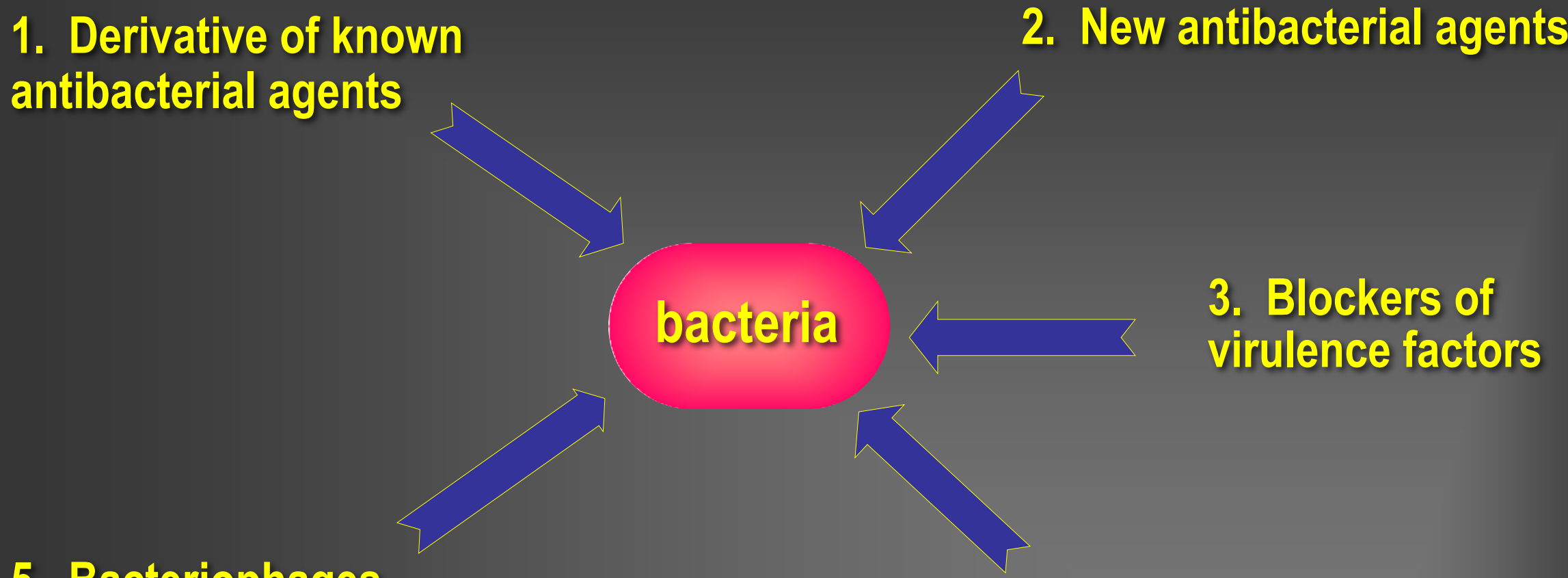


From 0 to 24 hours



From 0 to 4 hours

Moreno-Morales J (2022) JAC, in press

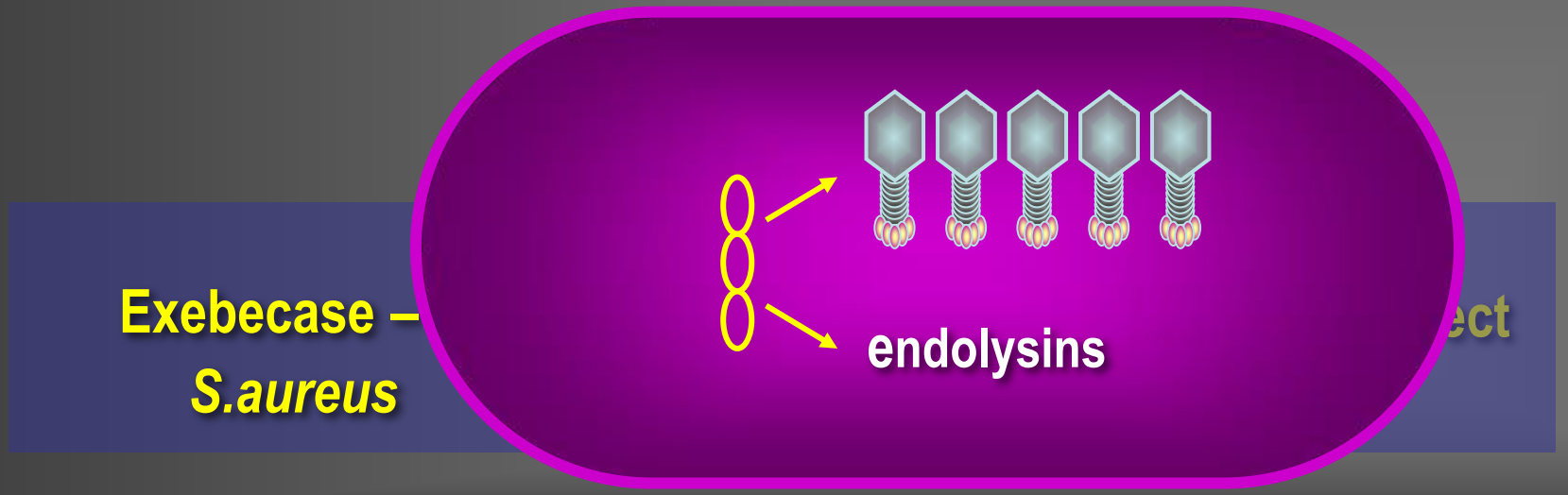


Vila et al. (2019) CMI 26: 596

BACTERIOPHAGES and ENDOLYSINS

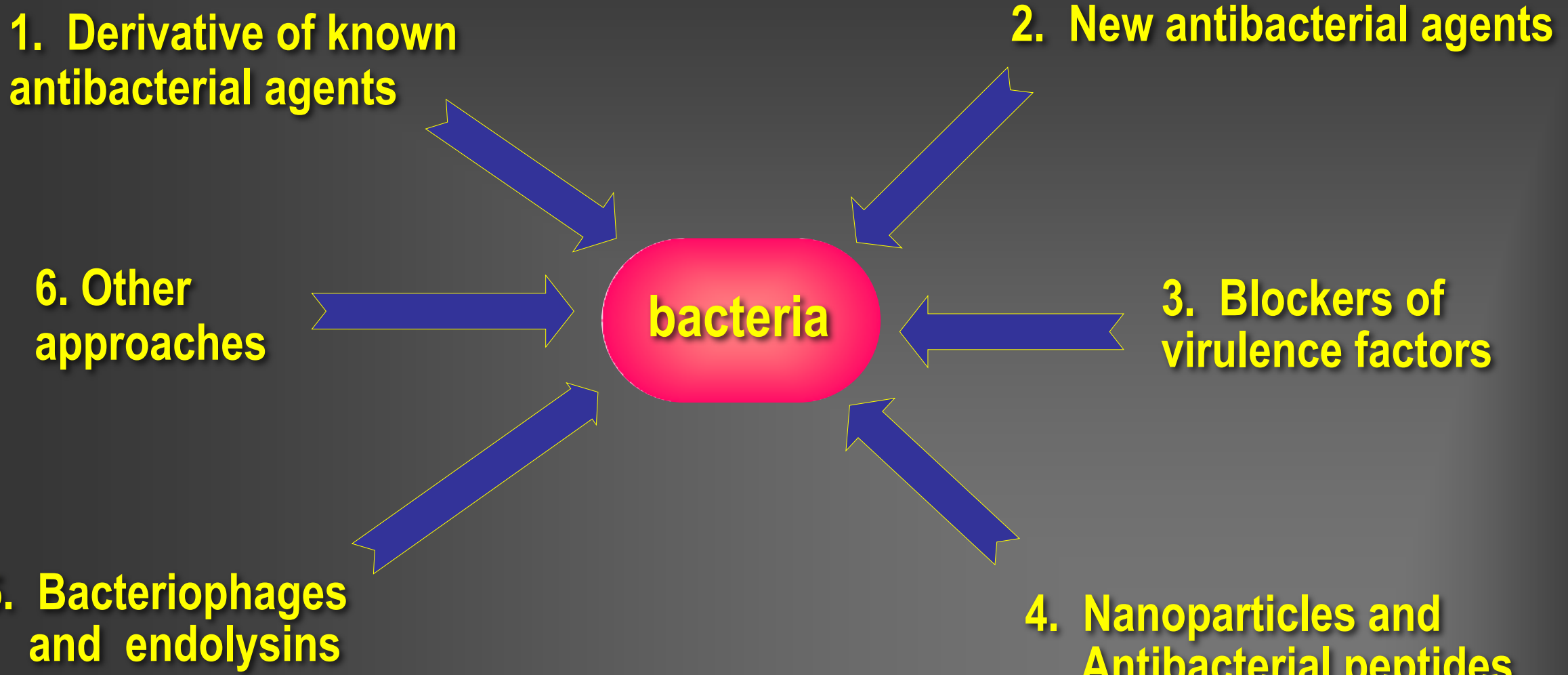
Bacteriophage (virus which "infects" a bacteria, a extreme biodiversity in nature)

endolysins (hydrolyse peptidoglycan – murein hydrolases)



Endolysins and bacteriophages

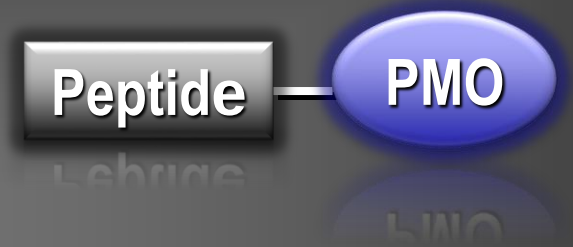
Name	"Antibacterial class"	Phase	Pharma. Indust.
LSVT-1701 (Tonabacase)	Endolysin *S. aureus* (i.v.)	1	Roivant Sciences
???	Phage *E. coli* (i.v.)	1	Adaptative Phage
AP-PA02	Phage *P. aeruginosa* (inhalation)	1	Armata
YPT-01	Phage *P. aeruginosa* (inhalation)	1	Felix Biotech.
BX004-A	Phage *P. aeruginosa* (inhalation)	1	BiomX
LBP-EC01	CRISPR-Cas3 enhanced phage - *E. coli* (i.v.)	1	Locus Bioscience



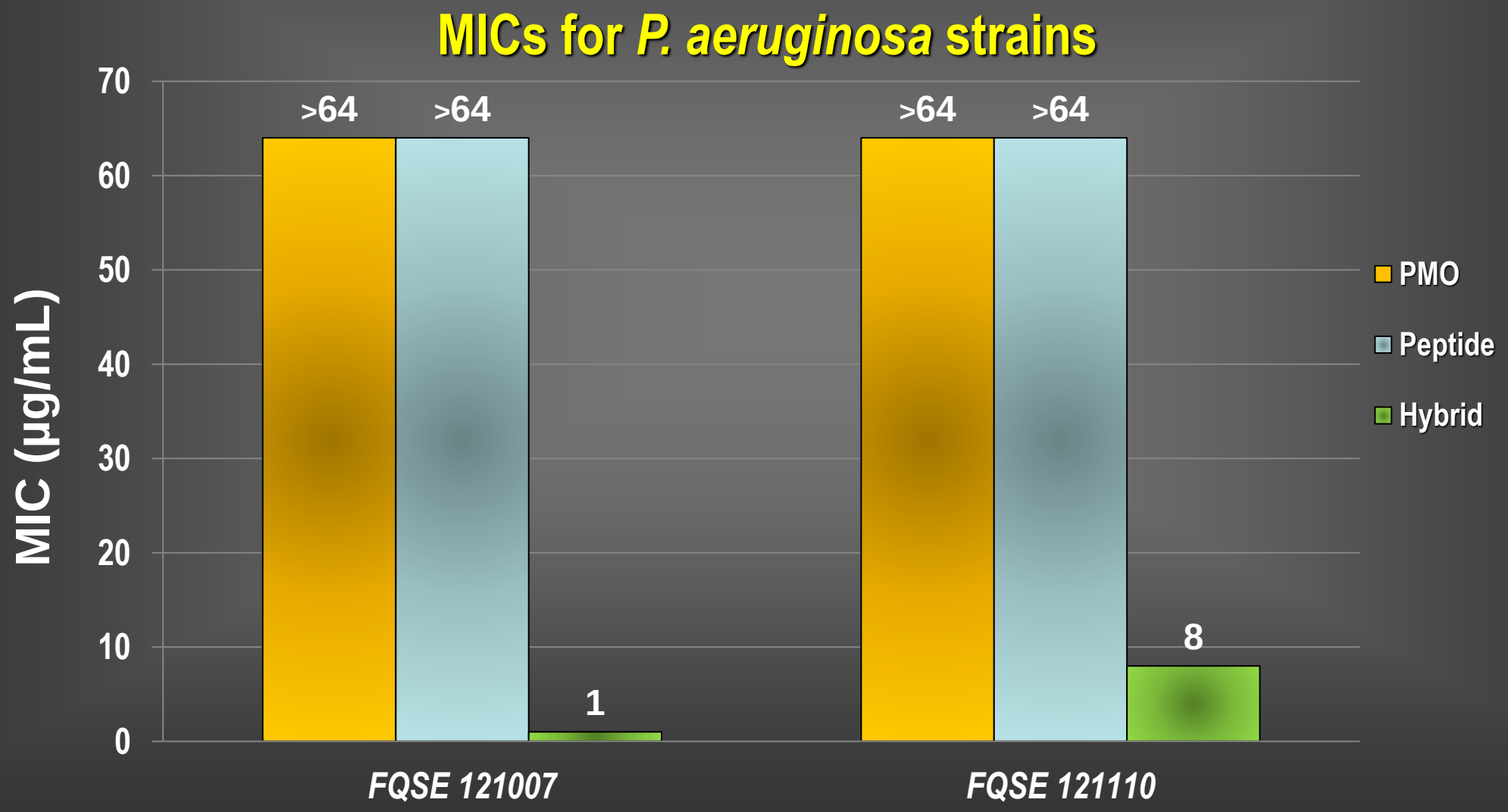
Vila et al. (2019) CMI 26: 596

Other approches

- Gene-silencing antisense oligomers

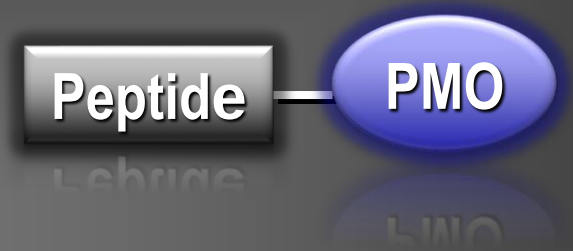


Gene-silencing antisense oligomers



Other approches

- Gene-silencing antisense oligomers



- Microbiota modulating (Treatment of *C. difficile* infections – Phase 3)

Antibacterial agent	"Route of administration"	Pharma. Indust.
BB128	Colonoscopy	BiomeBank
SER-109	Oral	Seres Therapeutics
RBX2660	Enema	Ferring

CONCLUSIONES

- La principal barrera para el desarrollo de nuevos agentes antibacterianos es una combinación de desafíos científicos y económicos
- Existe una necesidad médica no satisfecha de nuevos antibióticos para tratar infecciones por *A. baumannii* (p. ej., CRAB) y *P. aeruginosa* (p. ej., CRPA) MDR, XDR o PDR.
- Se pueden utilizar diferentes enfoques para desarrollar nuevas estrategias para tratar las infecciones causadas por bacterias resistentes, ya sean tradicionales o no tradicionales.
- La cartera de proyectos es insuficiente para contrarrestar la creciente resistencia en estas bacterias prioritarias (Durante 2011-2020 los proyectos contra el cáncer se financiaron 17 veces más que los antibacterianos. Actualmente, hay 160 proyectos de medicamentos clínicos solo para el cáncer de mama frente a los 45 proyectos antibacterianos tradicionales)
- Implementación de modelos de negocios que mejoren la dinámica actual del mercado con un enfoque en desarrollar y asegurar la aprobación de tratamientos antibacterianos verdaderamente innovadores y clínicamente diferenciados.

Gracias por su atención

Gràcies per la seva atenció

Eskerrik asko zure arretagatik

Grazas pola súa atención