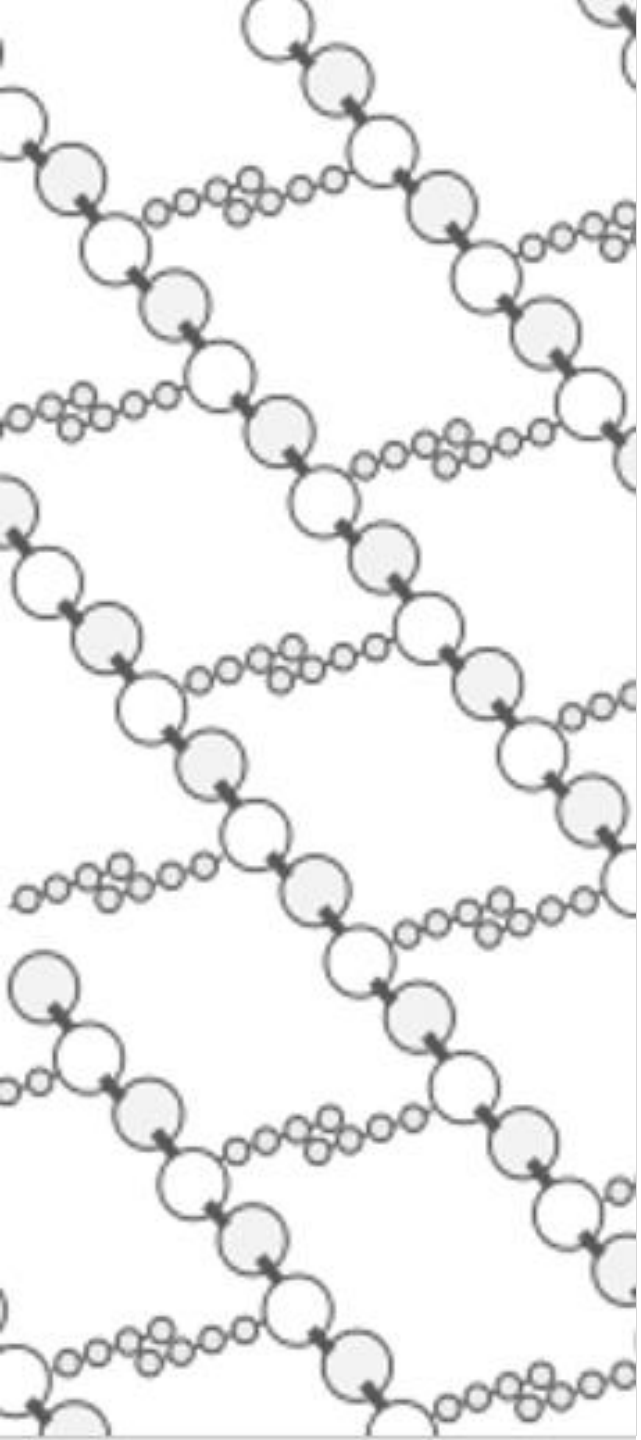
Peptidoglicano

(*The Murein Sacculus*)

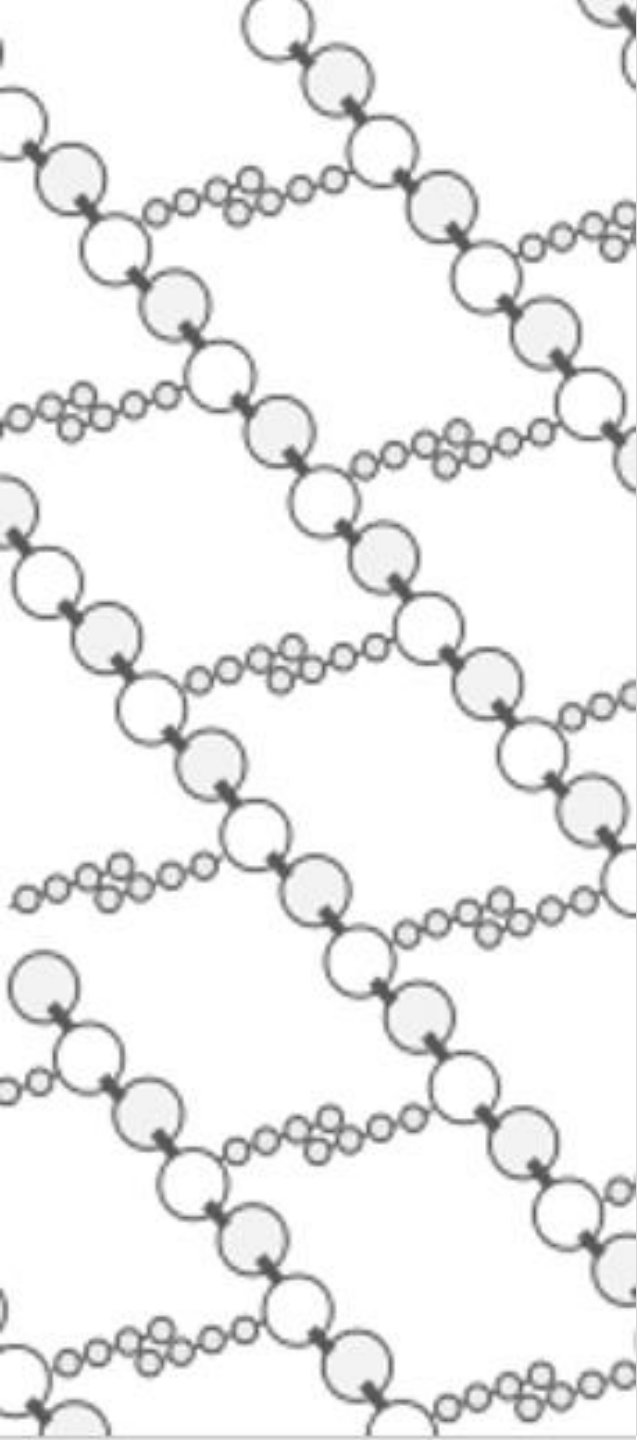
Alunas:
Aline Valério Lima
Giovanna de Brito Carneiro
Lais Gomes da Silva
Marília Bixilia Sanchez

BMM5829-4 Estudo do Envoltório de Bactérias Gram-Positivas e Gram-Negativas



Peptidoglicano

- **Estrutura e Função**
- **Biossíntese**
- **Antimicrobianos**
  - Inibidores de fase citoplasmática
  - Inibidores transporte de precursores
  - Inibidores da organização estrutural



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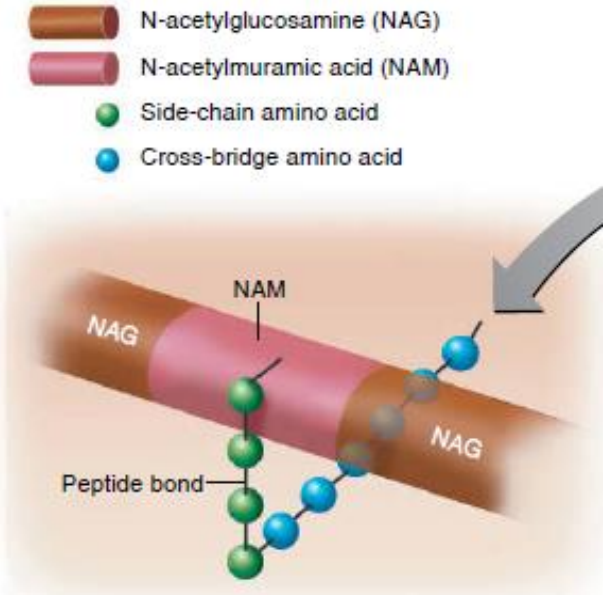
Marília

Estrutura e Função

- Mureína = parede
- Macromolécula
- Gram-positiva e Gram-negativa
- Excluindo micoplasma e planctomicetos
- Fios de Glicano + peptídeos curtos
- Mudo de peptídeos = unidades de repetição
- Sáculo de mureína
- Semelhante ao exoesqueleto

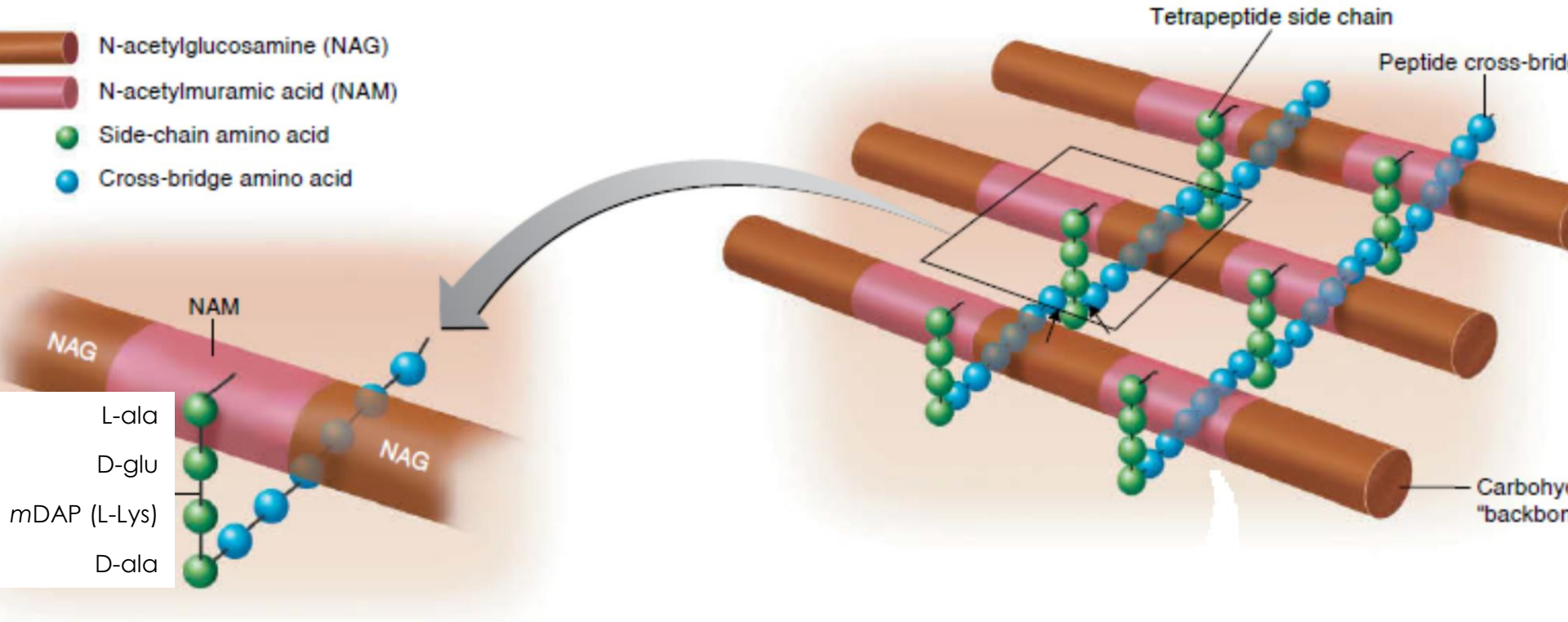
- Estabiliza a MC e o citosol
- Proteção do meio ambiente
- Determina a forma
- Suporte da pressão osmótica
- Ancoragem de proteínas e outros compostos



TORTORA, G.; FUNKE, B.; CASE, C. 13ª Ed. 2019, Microbiology
MADIGAN, et. Al, 14ª Ed. 2016, Microbiologia de Brock

Estrutura

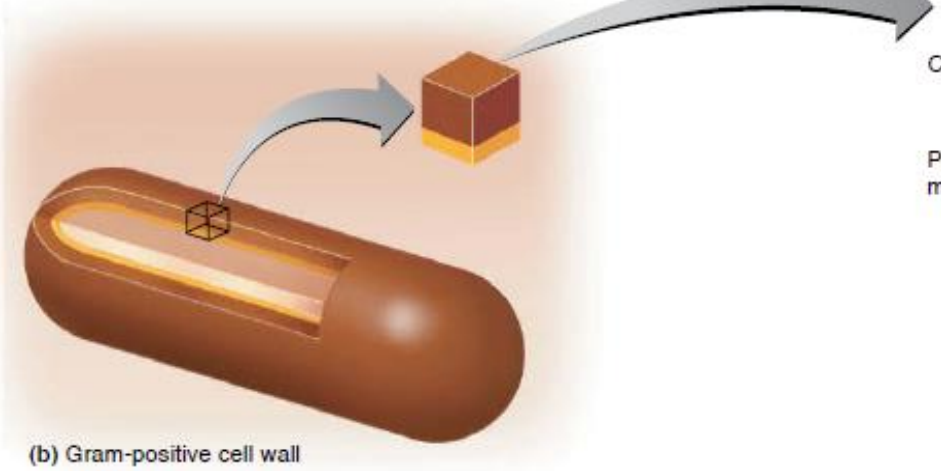
- A molécula

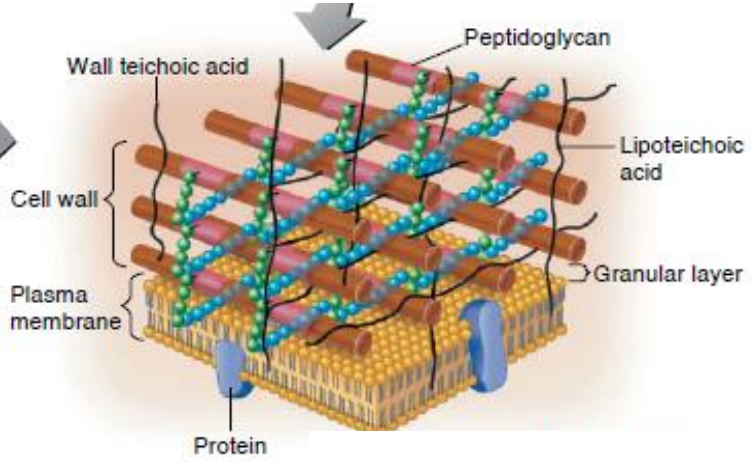


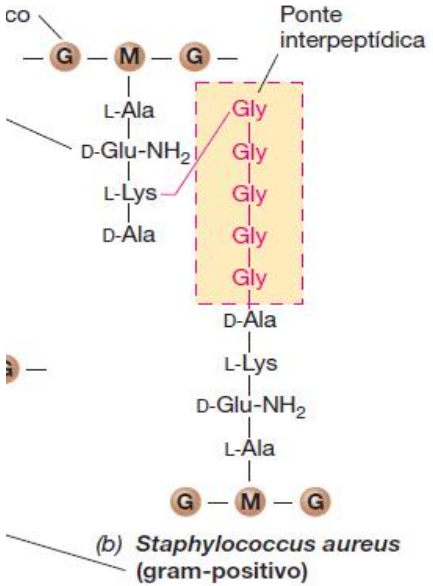
TORTORA, G.; FUNKE, B.; CASE, C. 13ª Ed. 2019, Microbiology
MADIGAN, et. Al, 14ª Ed. 2016, Microbiologia de Brock

Estrutura

- Em Gram-positiva



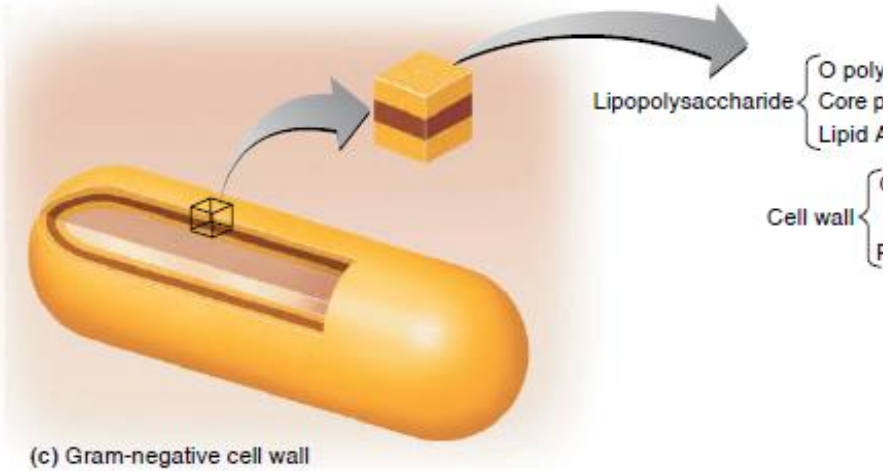


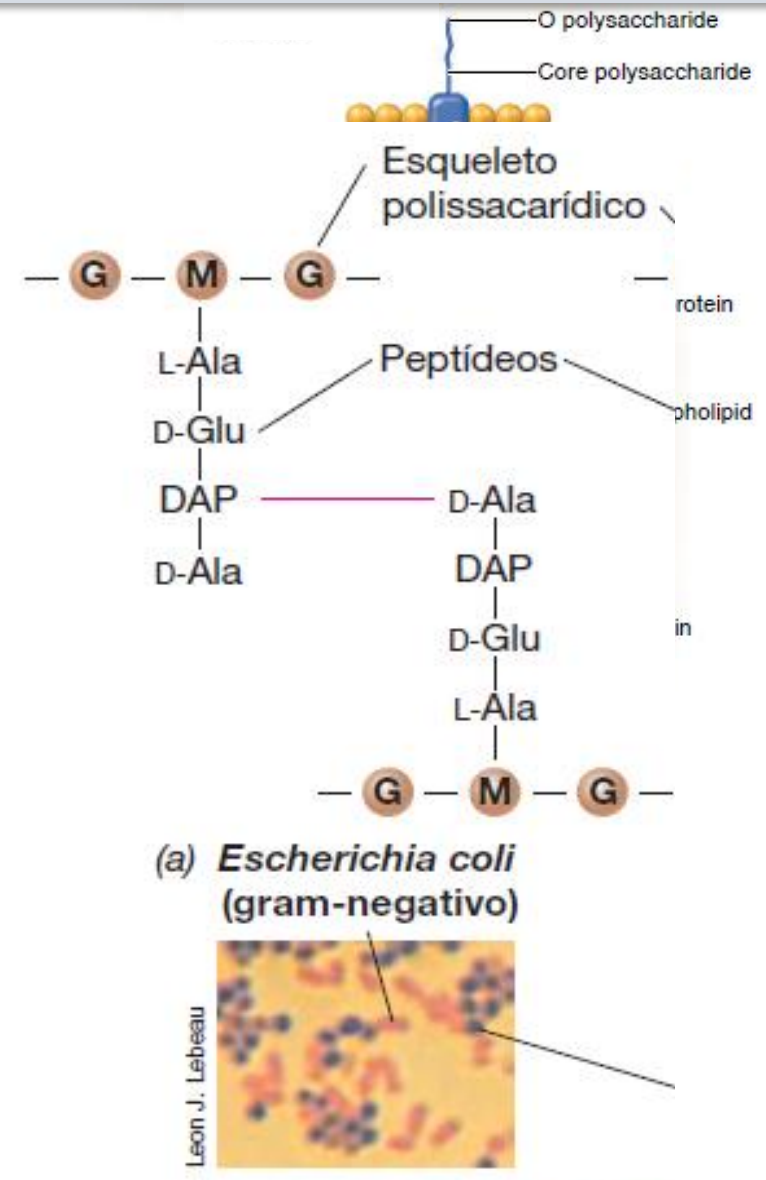


TORTORA, G.; FUNKE, B.; CASE, C. 13ª Ed. 2019, Microbiology
MADIGAN, et. Al, 14ª Ed. 2016, Microbiologia de Brock

Estrutura

- Em Gram-negativa

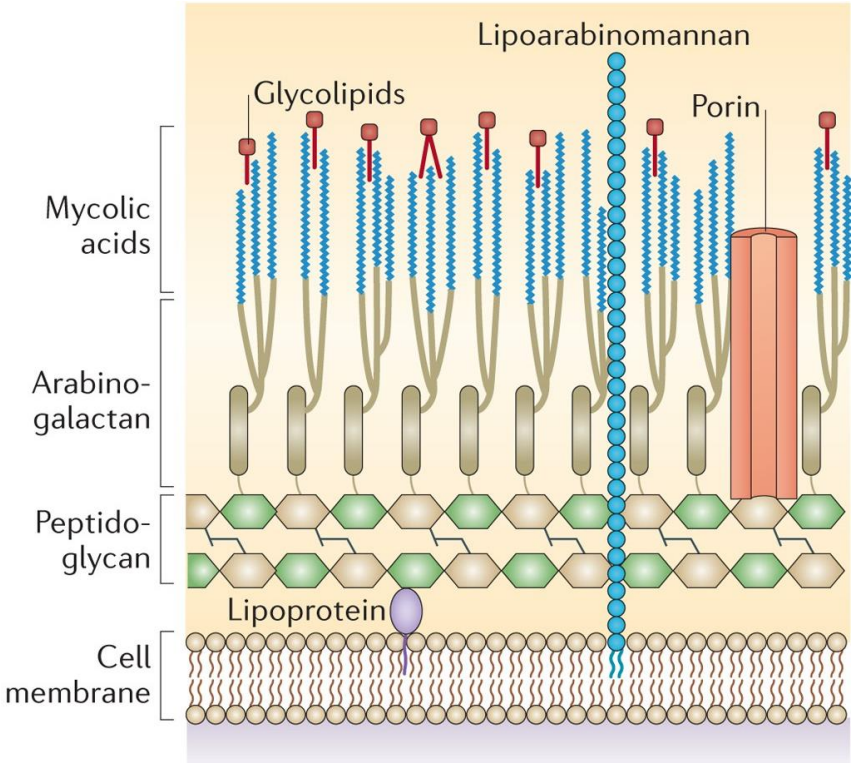




TORTORA, G.; FUNKE, B.; CASE, C. 13ª Ed. 2019, Microbiology
MADIGAN, et. Al, 14ª Ed. 2016, Microbiologia de Brock

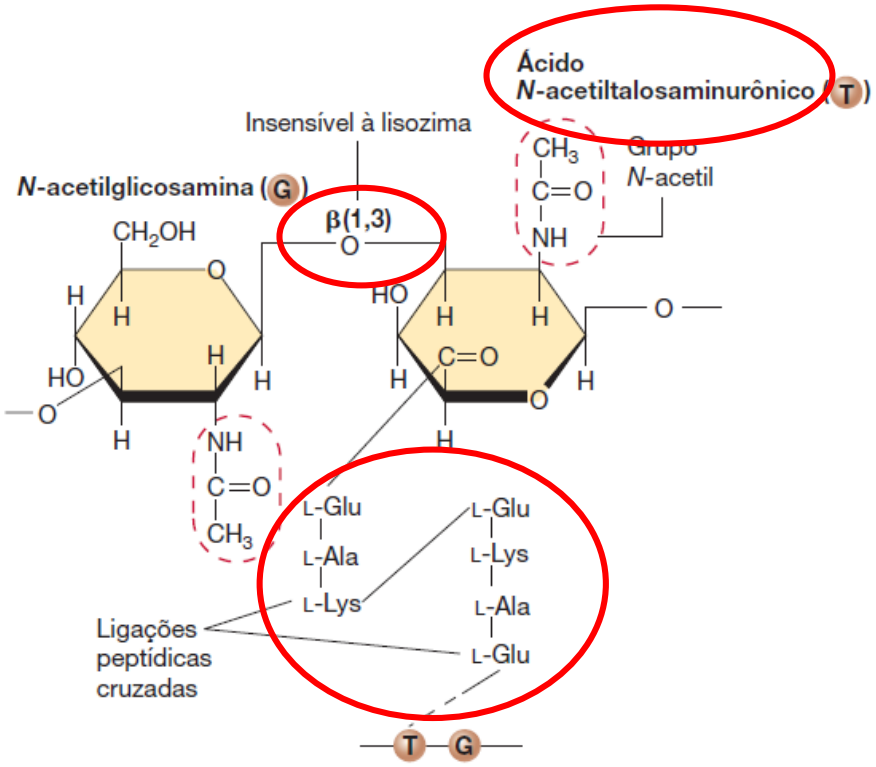
Estrutura

Em Mycobacteria



Archaea

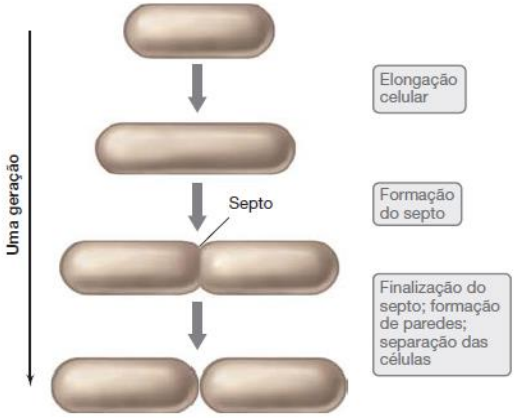
Pseudomureina

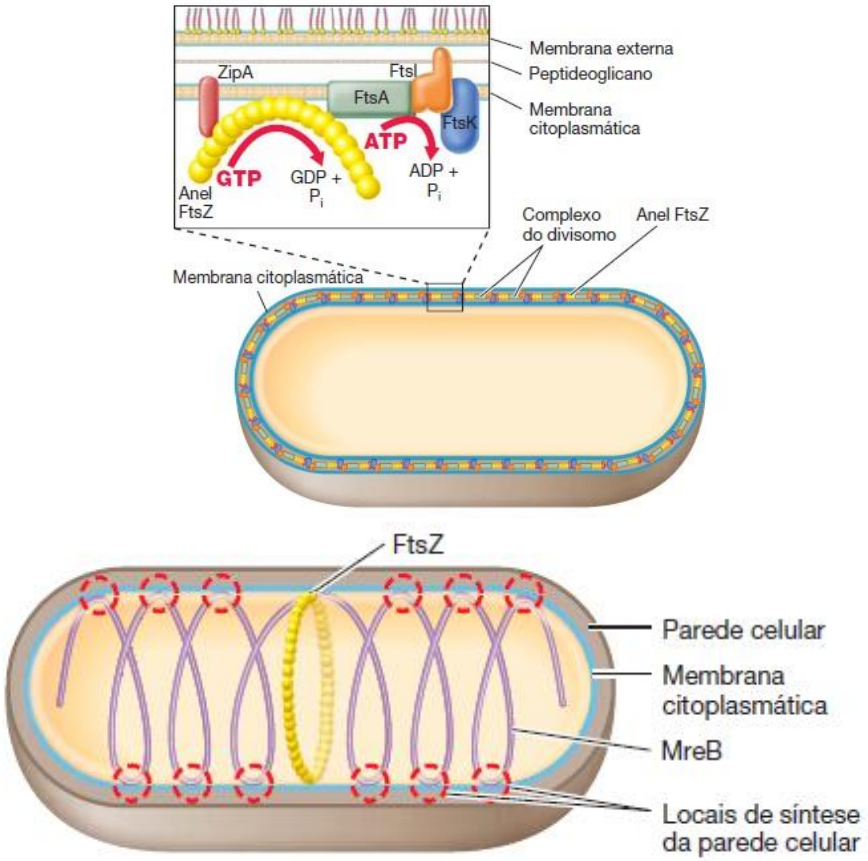


BROWN, et al. 2015; doi:10.1038/nrmicro3480
TORTORA, G.; FUNKE, B.; CASE, C. 13ª Ed. 2019 Microbiology

Estrutura e Função

- Divisão Celular

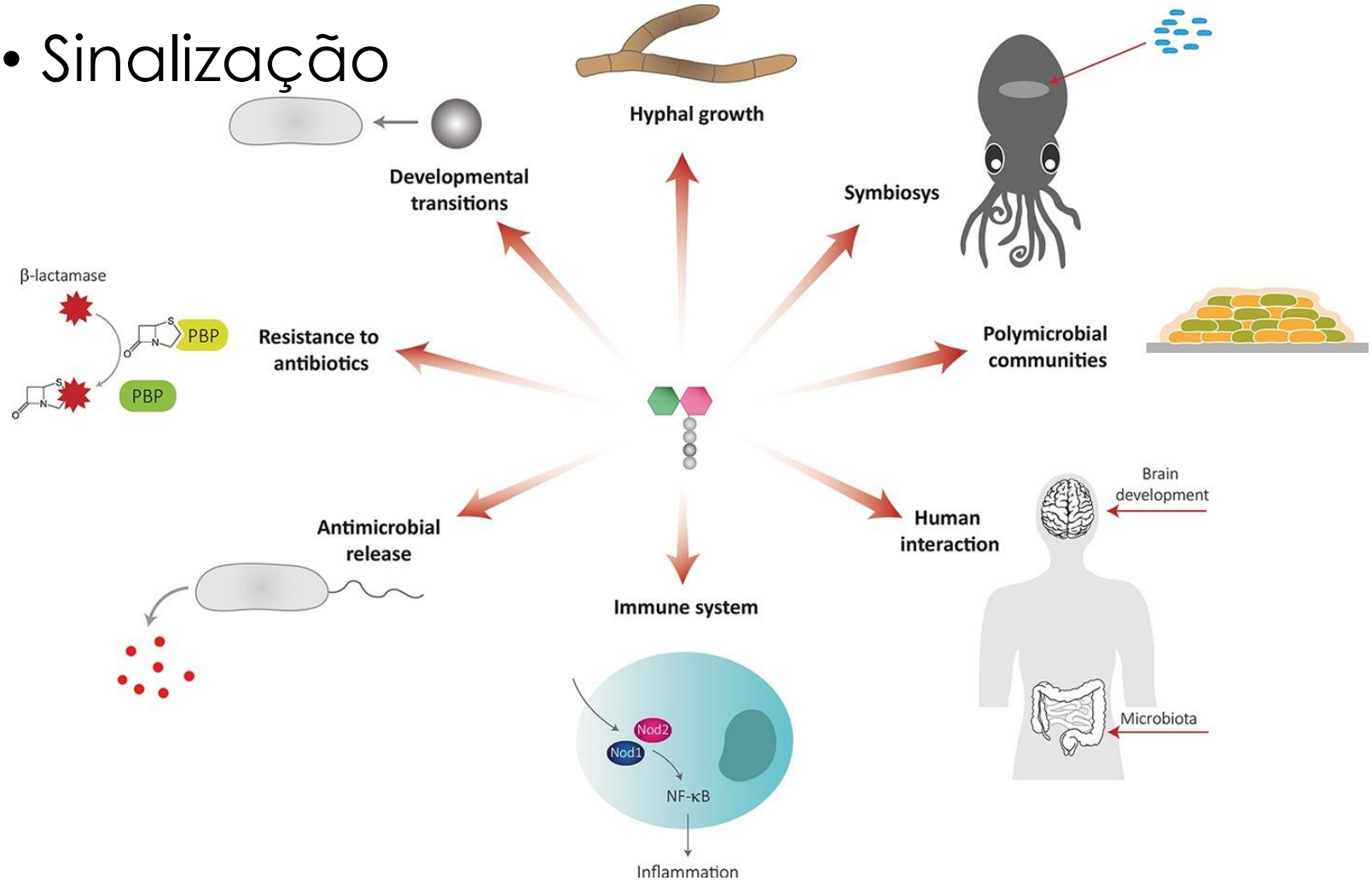




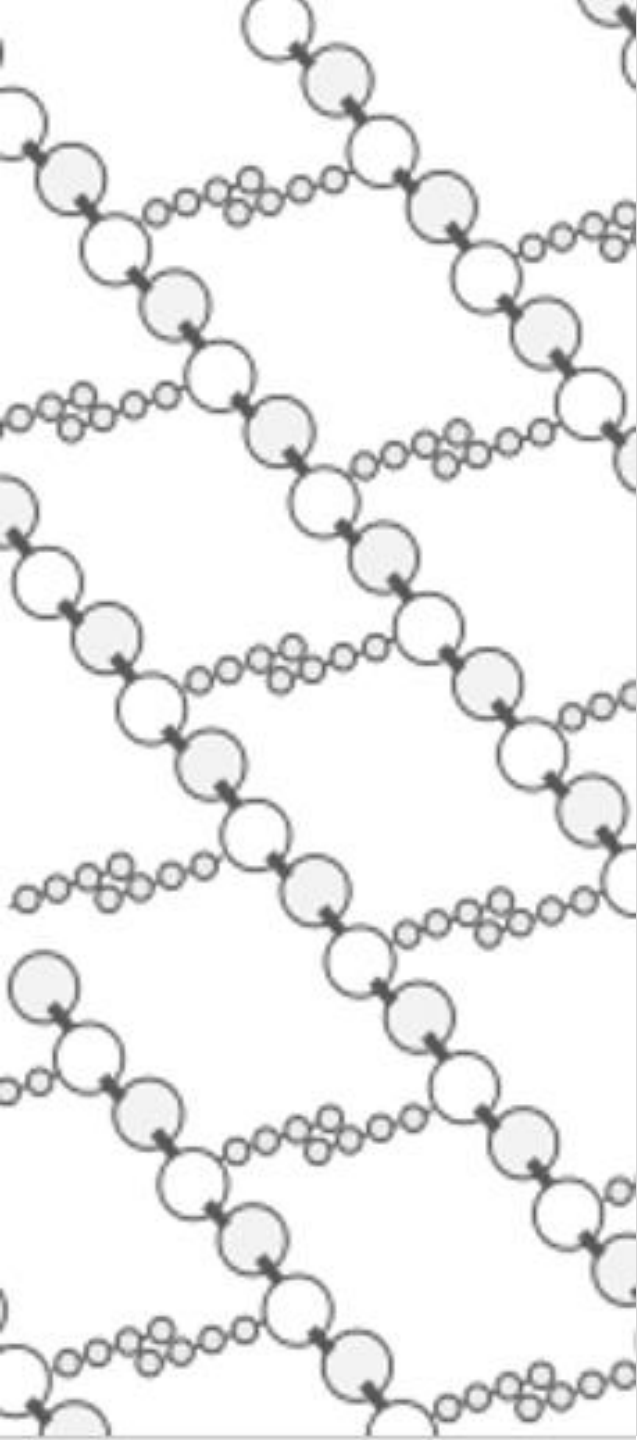
TORTORA, G.; FUNKE, B.; CASE, C. 13º Ed. 2019 Microbiology

Estrutura e Função

- Sinalização



IRAZOKI, O.; HERNANDEZ, S. B.; CAVA, F.; 2019, https://doi.org/10.3389/fmicb.2019.00500



Peptidoglicano

- **Estrutura e função**
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  - Inibidores de fase citoplasmática
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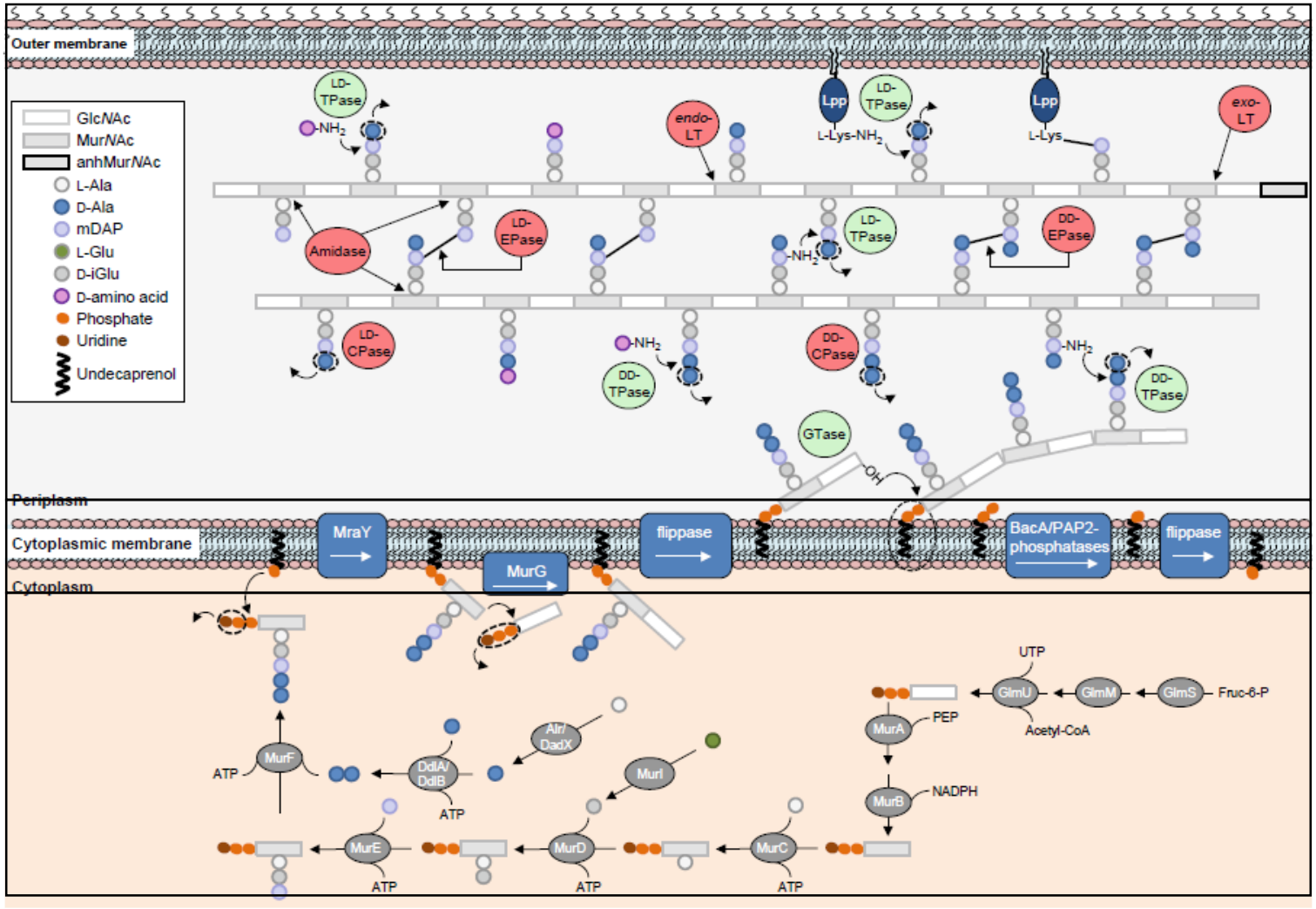
  - Inibidores da organização estrutural

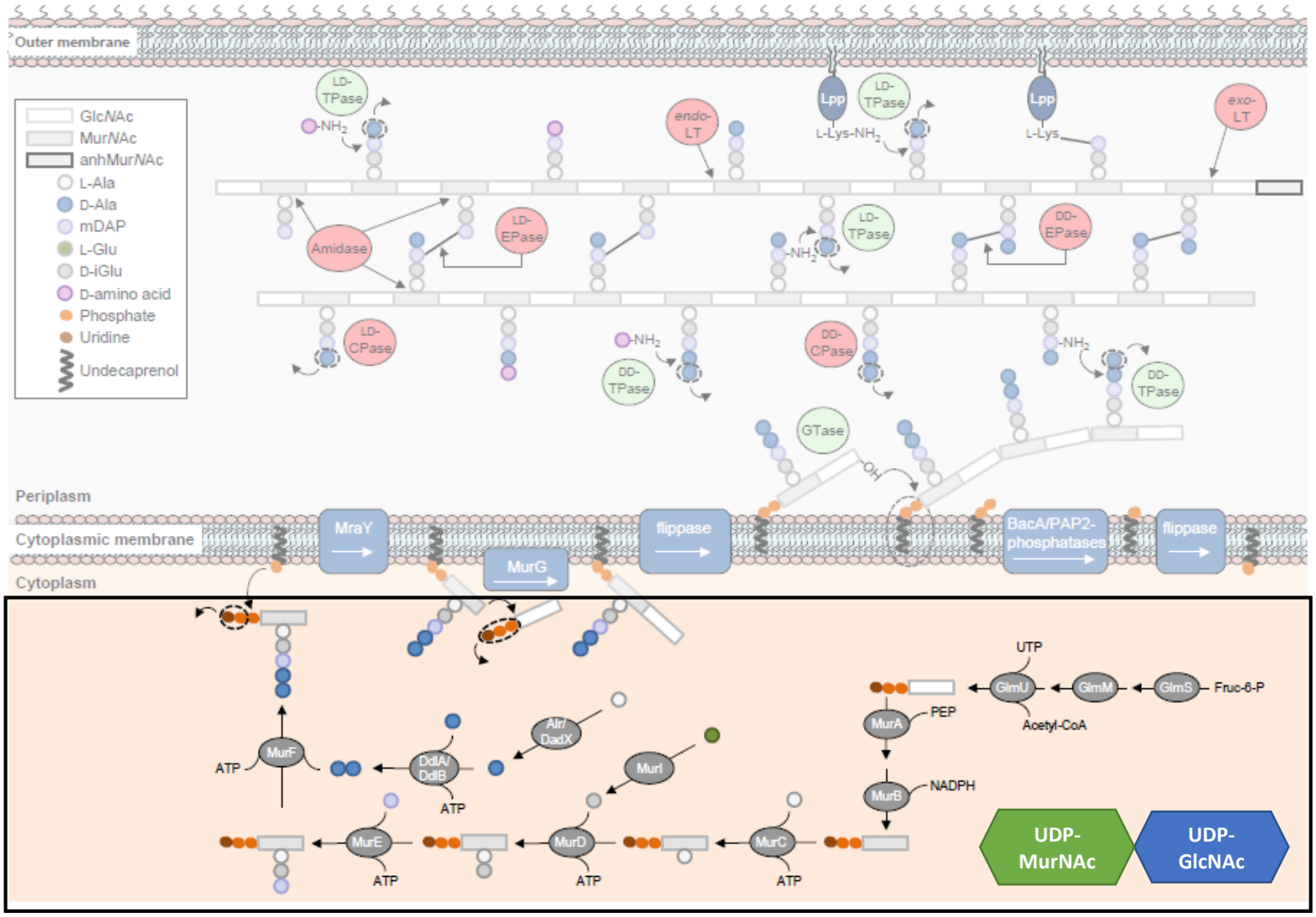
Lais

Biossíntese



PAZOS, Manuel; PETERS, Katharina. 2019. https://doi.org/10.1007/978-3-030-18768-2_5

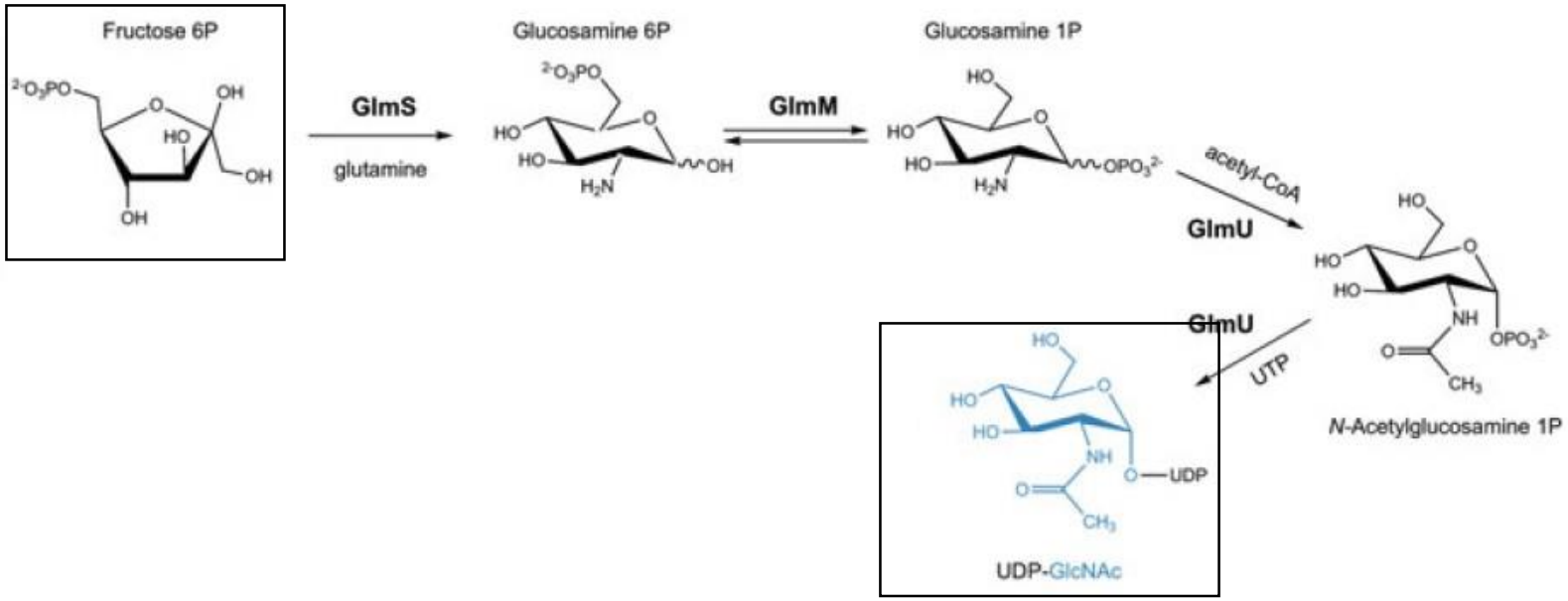
Citoplasma



PAZOS, Manuel; PETERS, Katharina. 2019. https://doi.org/10.1007/978-3-030-18768-2_5

Citoplasma

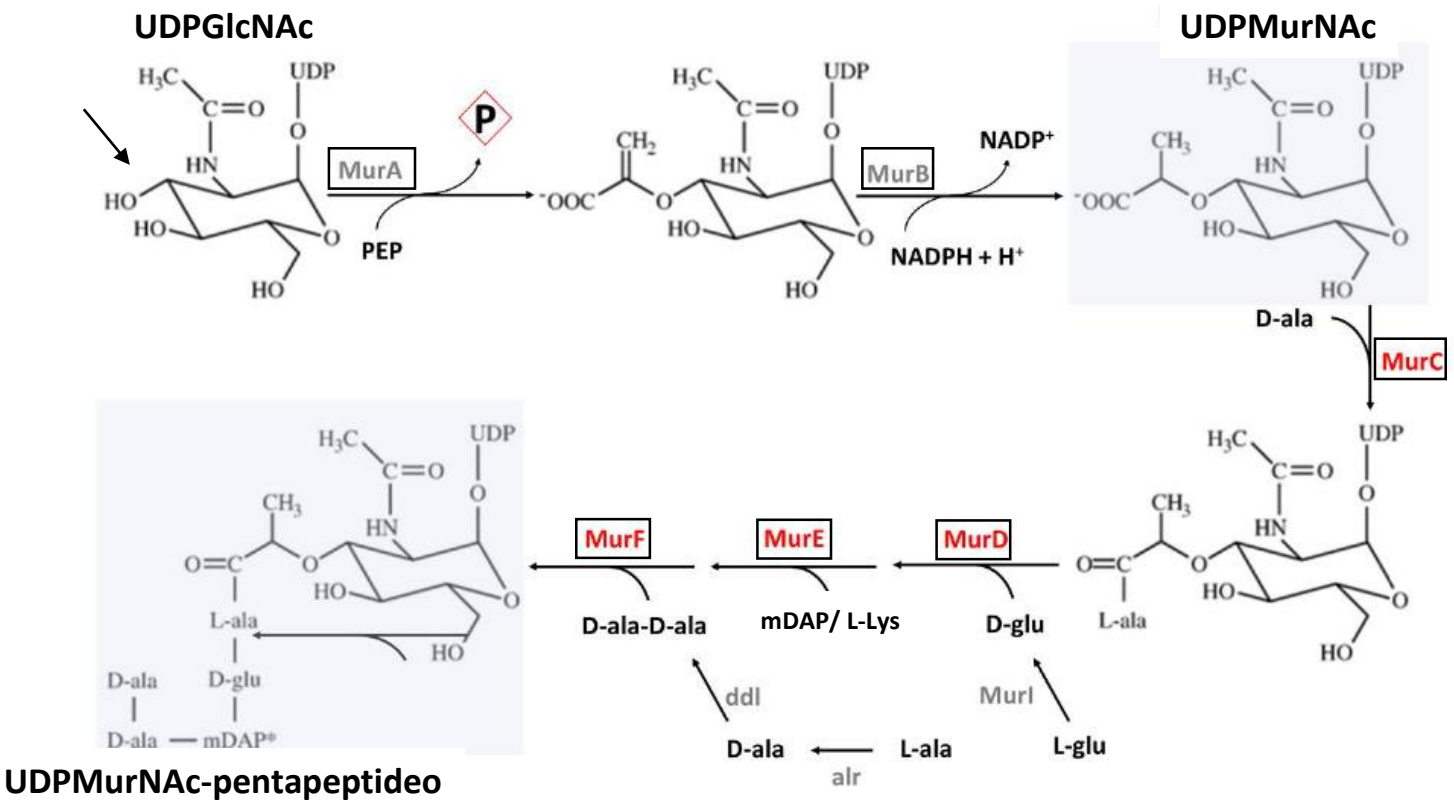
- UDP-GlcNAc



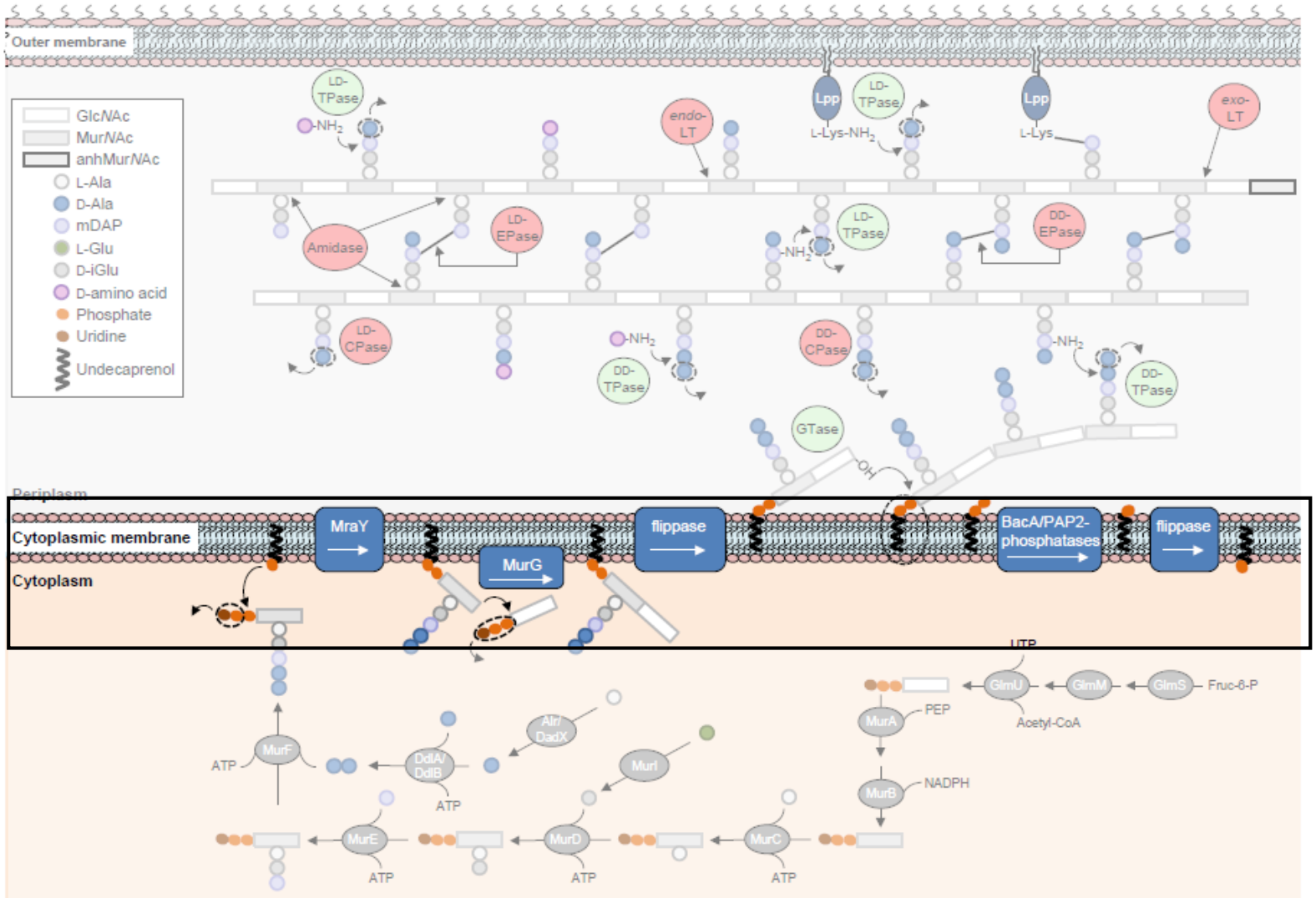
Adaptado de COHEN; MERZENDORFER, 2019.

Citoplasma

- UDP-MurNAc-pentapeptídeo



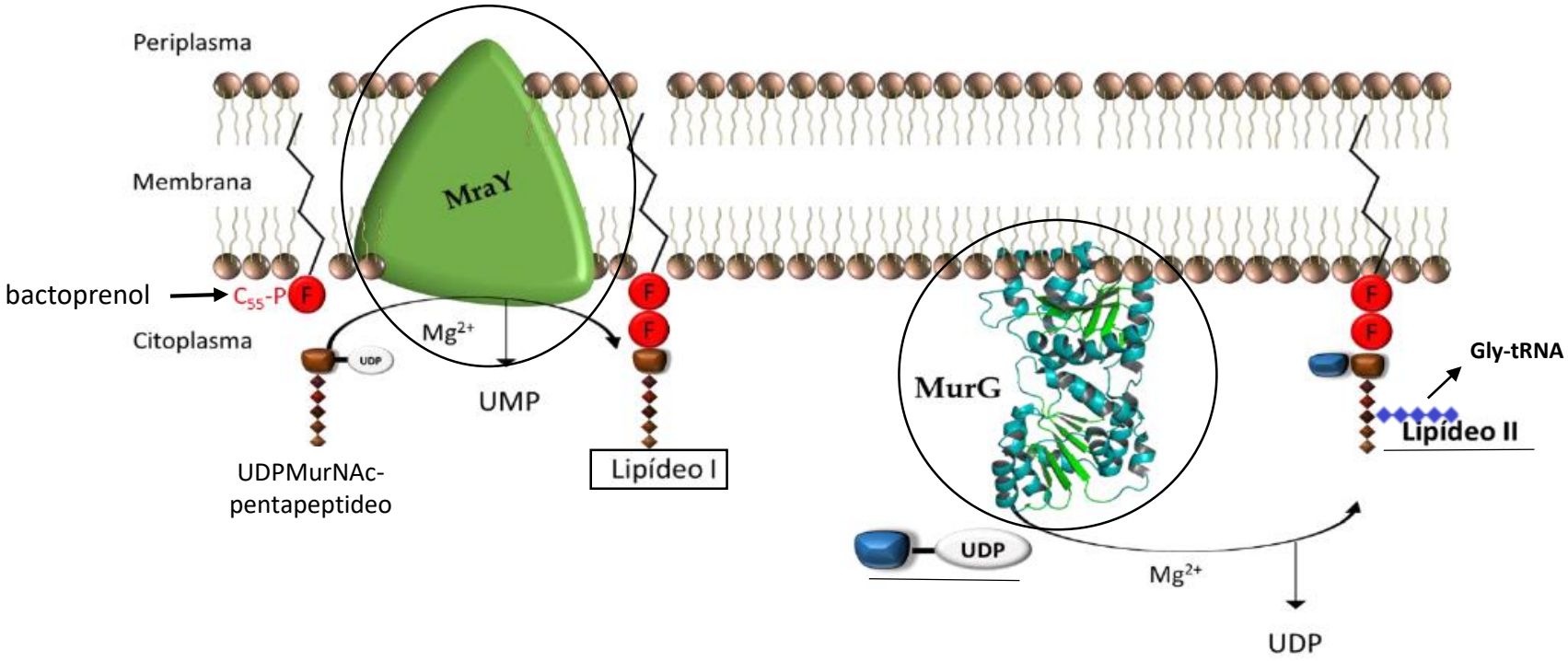
Membrana plasmática



PAZOS, Manuel; PETERS, Katharina. 2019. https://doi.org/10.1007/978-3-030-18768-2_5

Membrana plasmática

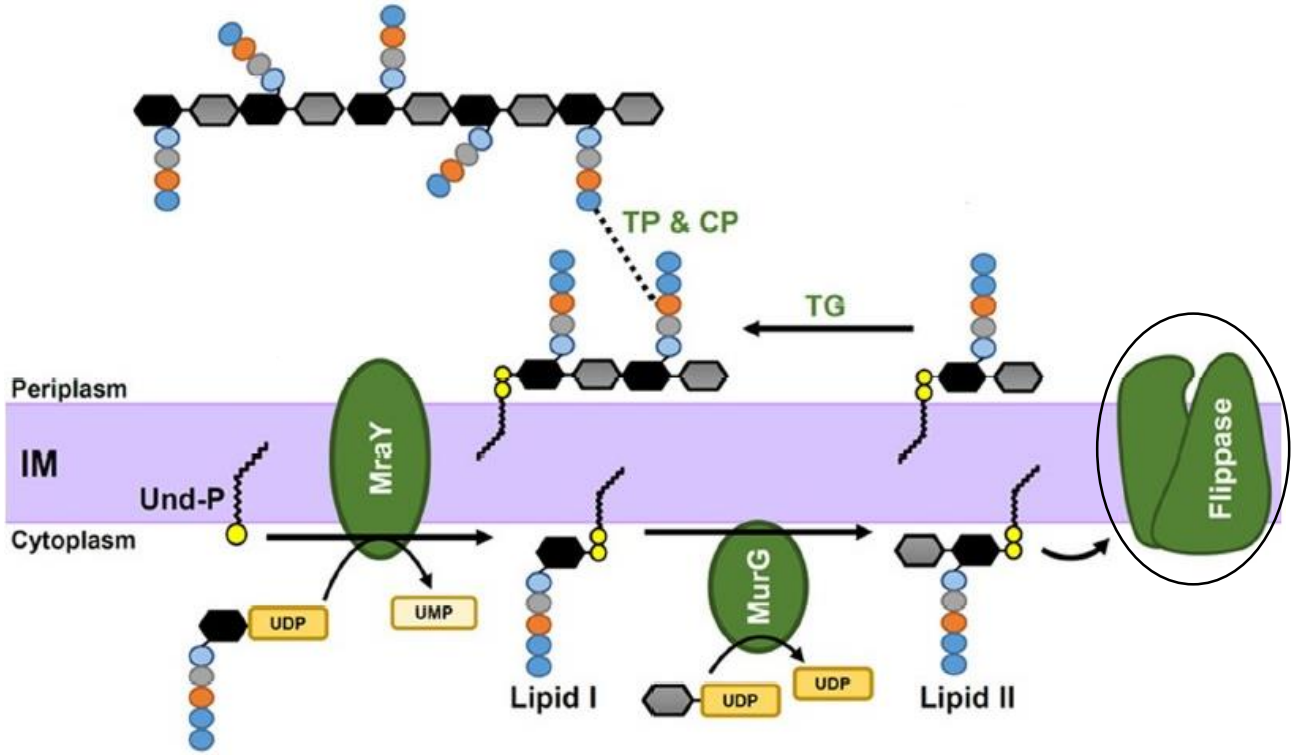
- Produção do Lipídeo II



Adaptado de MIACHIRO, Mayara Mayele. 2018

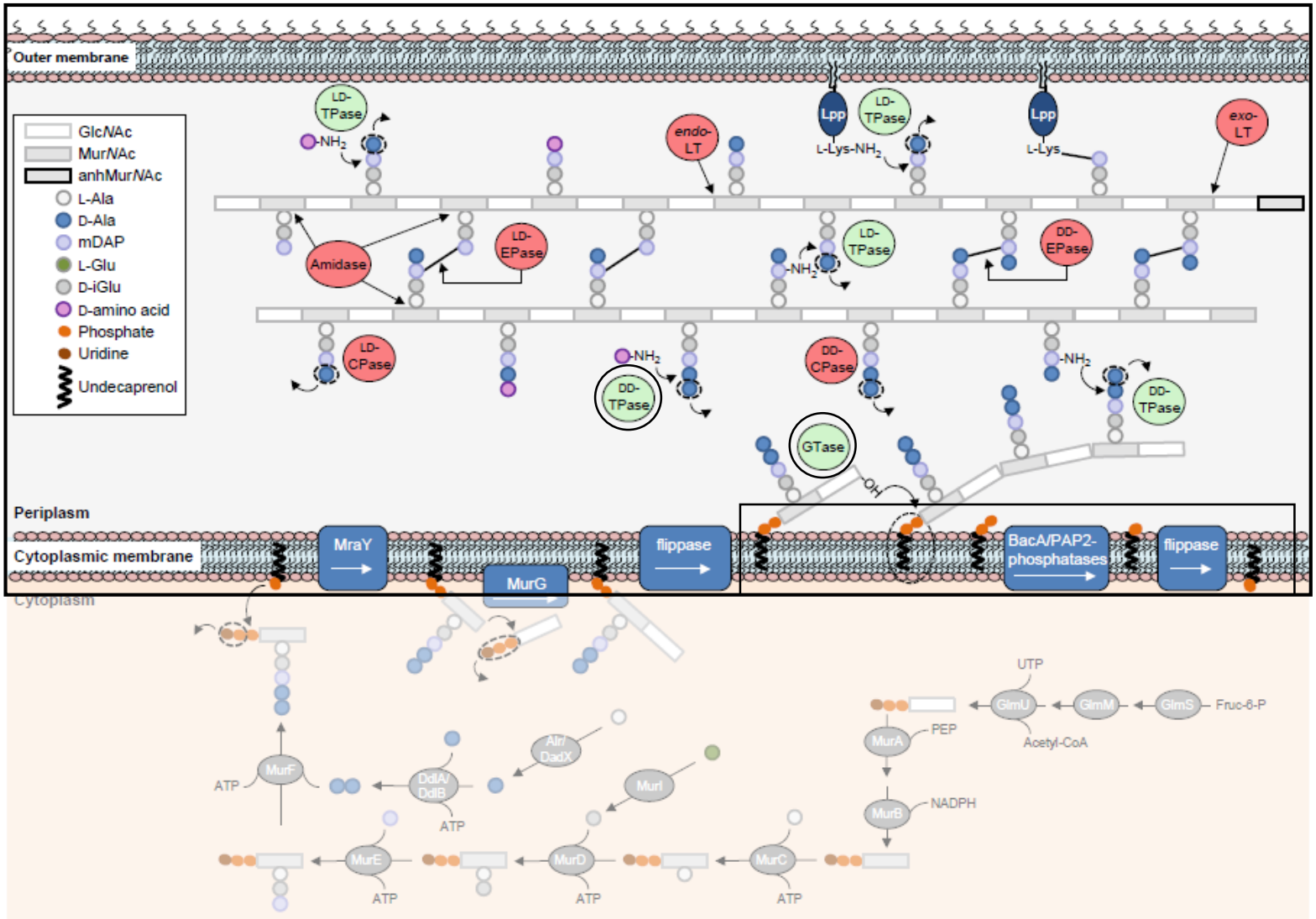
Membrana plasmática

- Transporte para a superfície celular / periplasma



NATIVIDAD, RUIZ. 2016. https://doi.org/10.4137/LPI.S31783

Superfície celular/Periplasma



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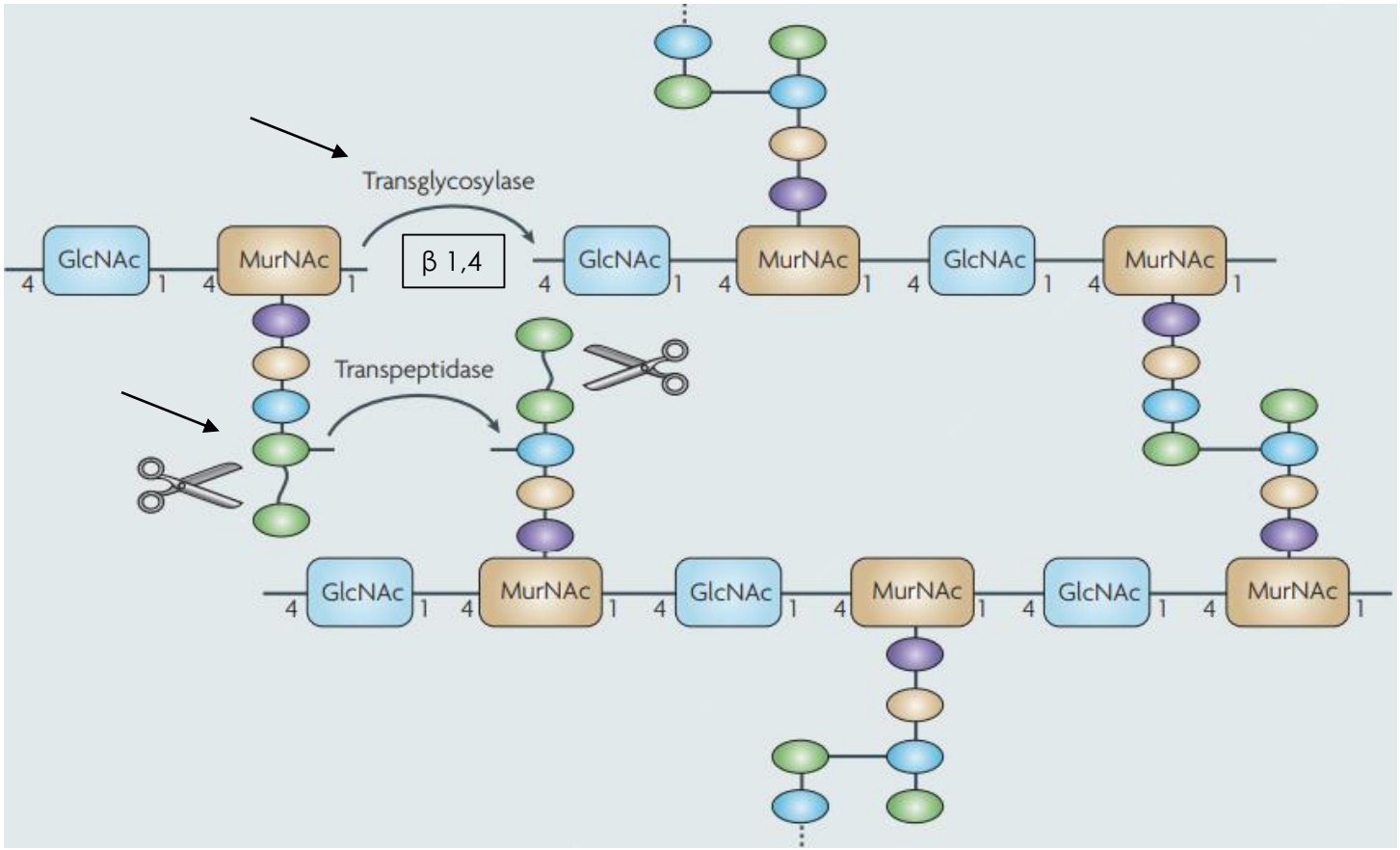
Extracelular/Periplasma

- Polimerização do peptideoglicano



THANBICHLER; SHAPIRO. 2008. doi:10.1038/nrmicro1795

Extracelular/Periplasma

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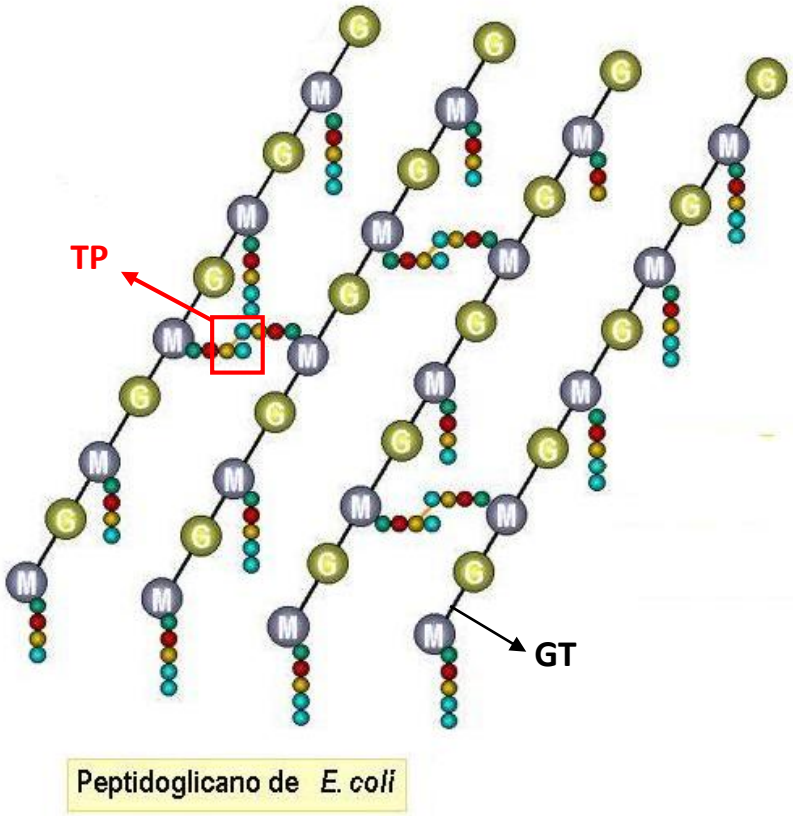
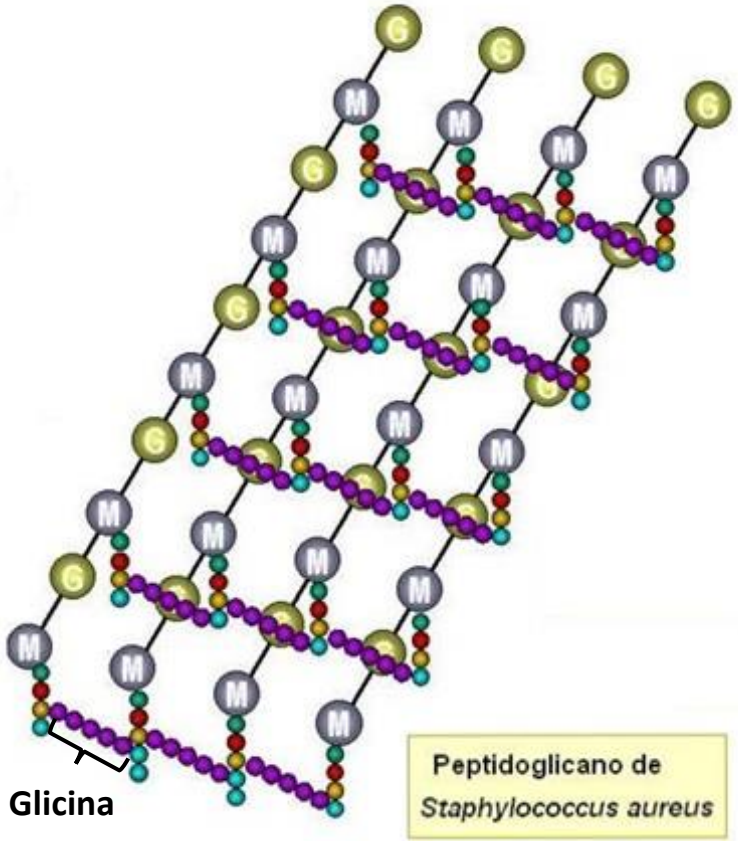
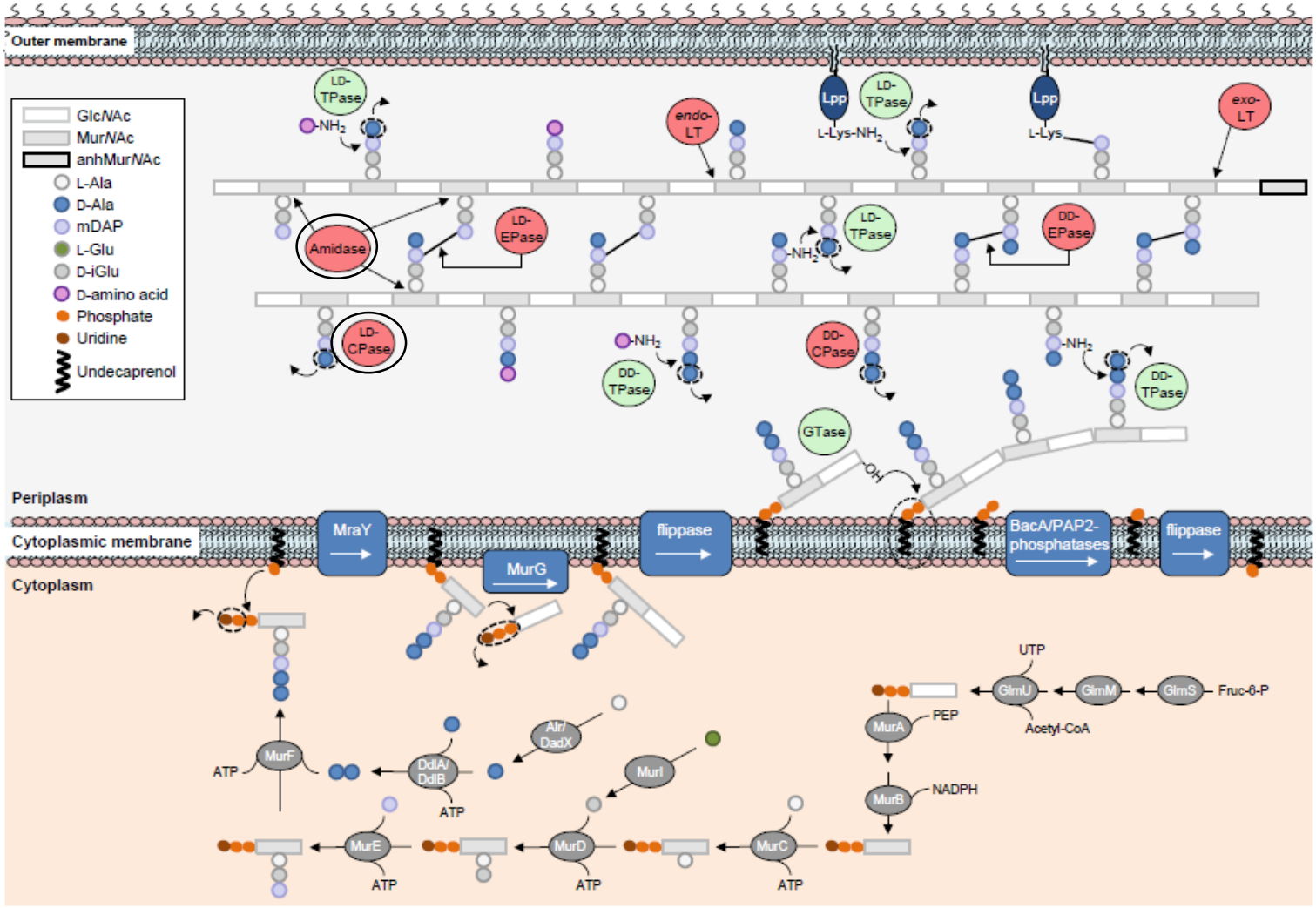




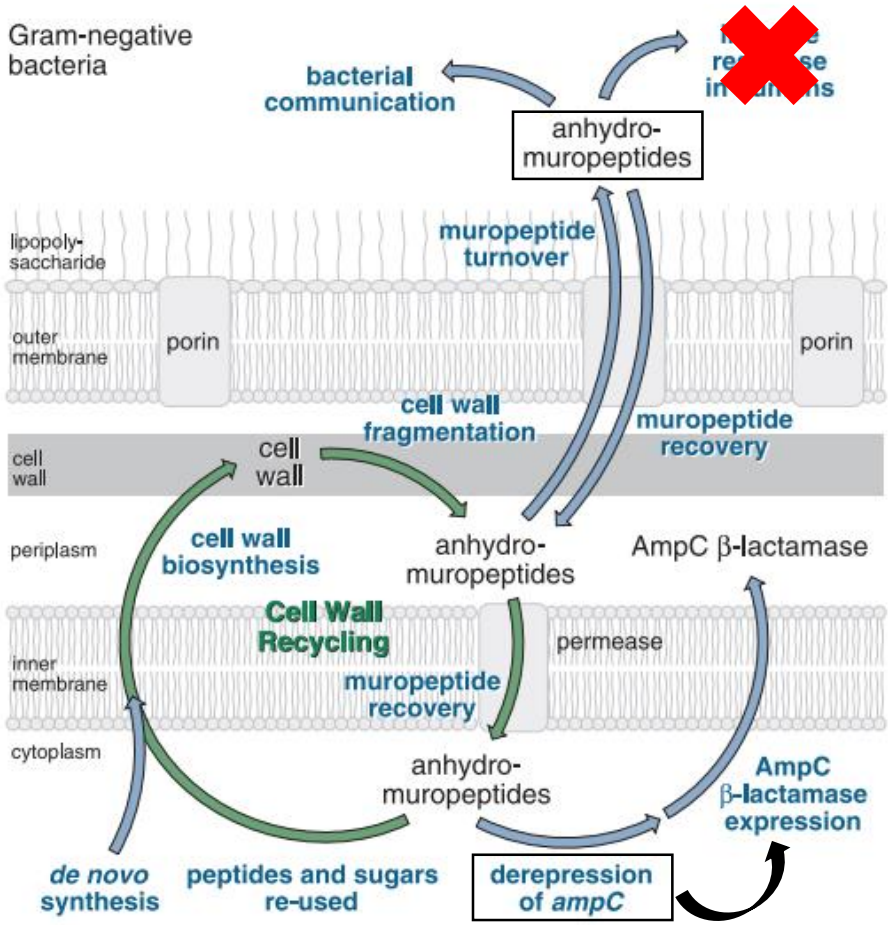
https://www.microbiologybook.org/Portuguese/chapter_4_bp.htm

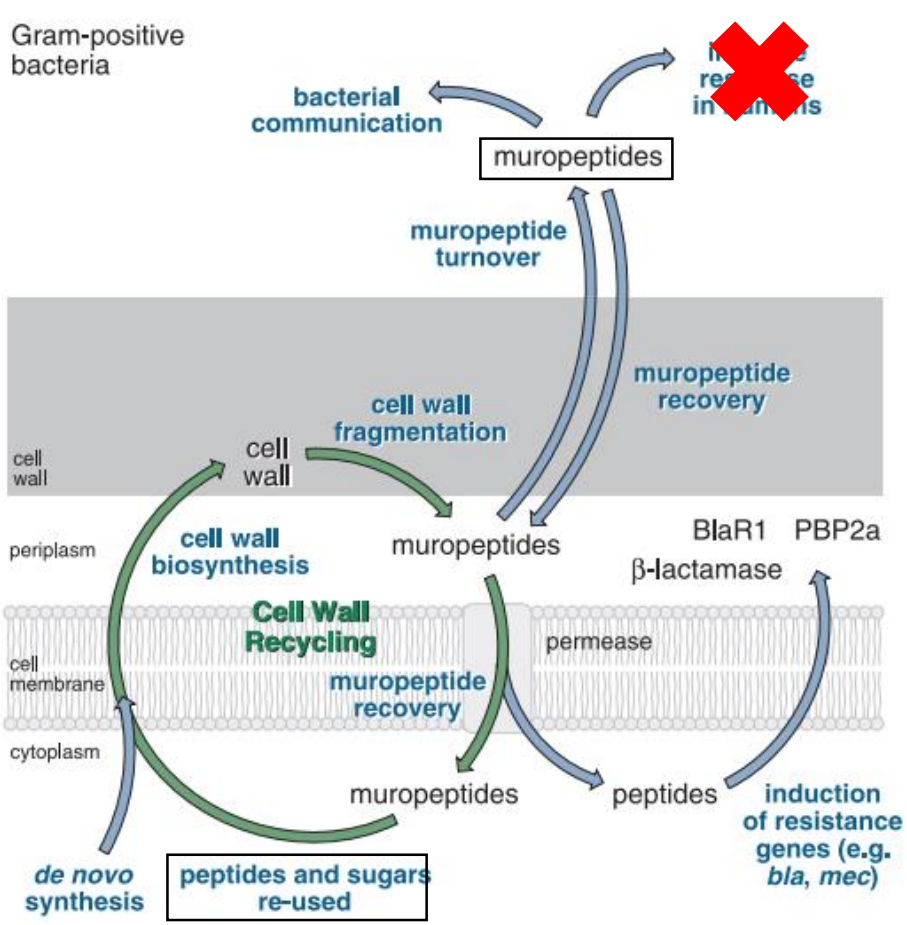
Autolisinas



PAZOS, Manuel; PETERS, Katharina. 2019. https://doi.org/10.1007/978-3-030-18768-2_5

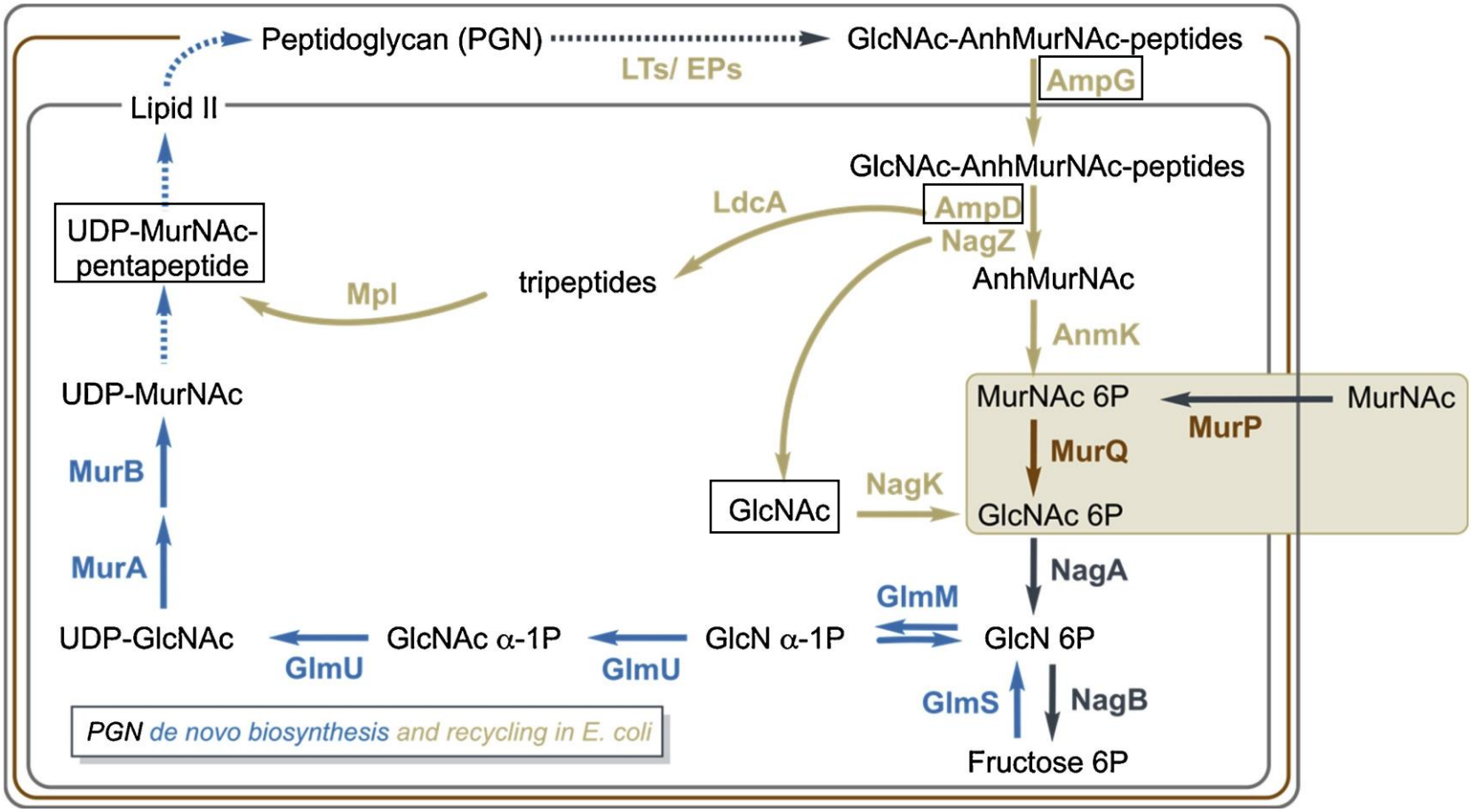
Reciclagem



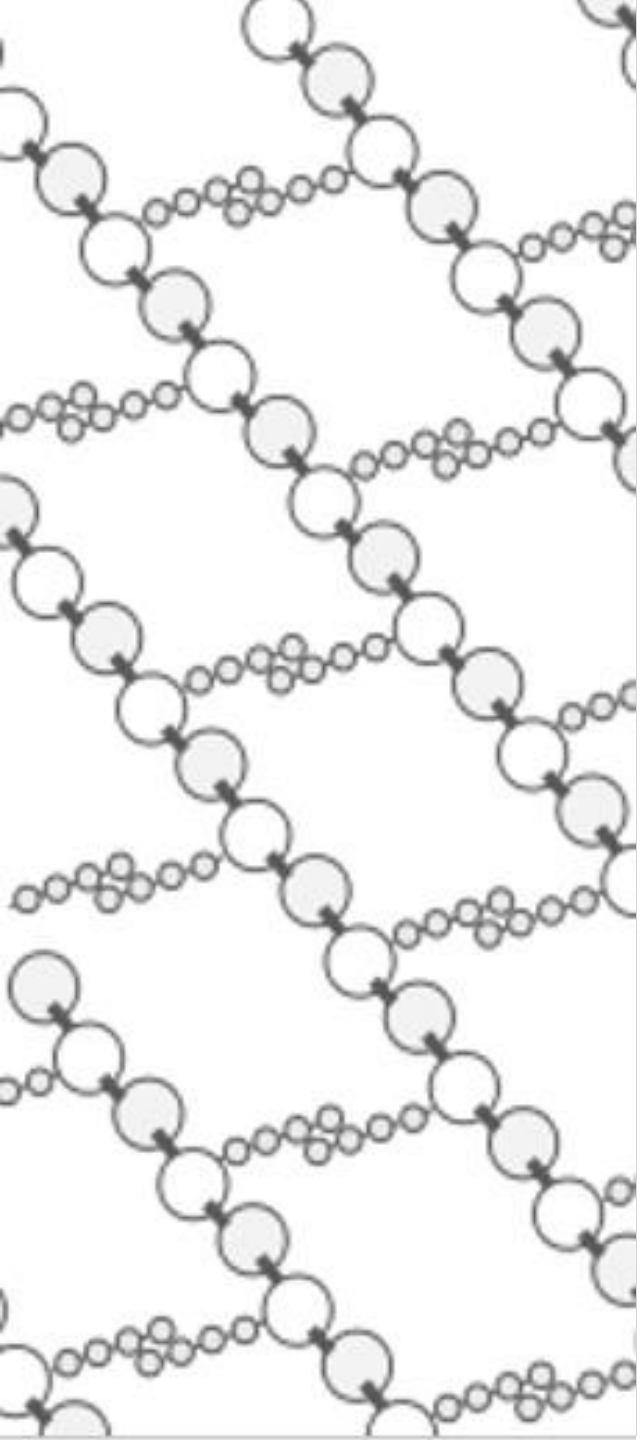


JOHNSON; FISHER; MOBASHERY, 2013. 10.1111 / j.1749-6632.2012.06813.x

Reciclagem



MAYER, Christoph et al, 2019. https://doi.org/10.1016/j.ijmm.2019.06.006



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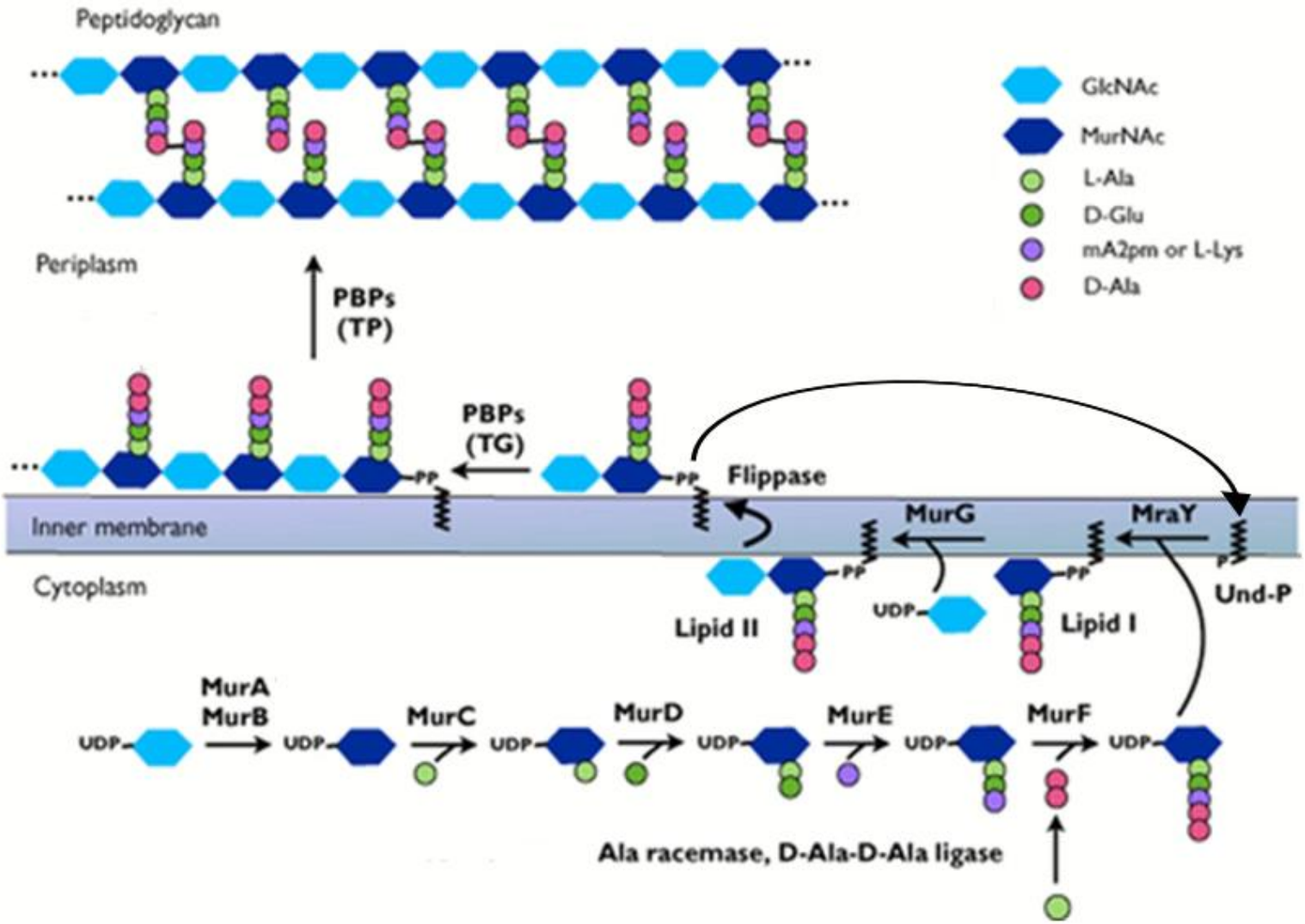
Giovanna

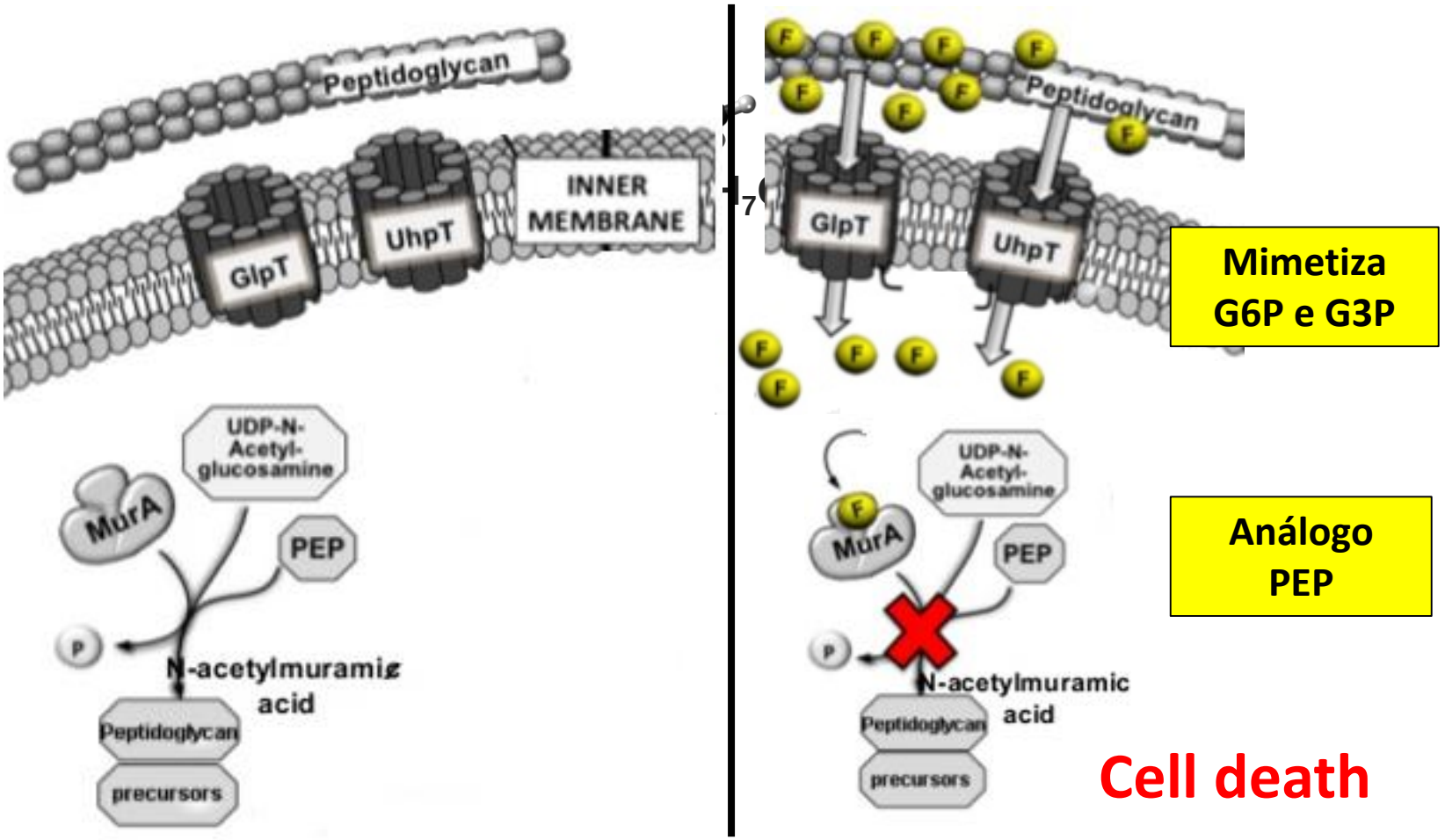
Inibidores da síntese de peptideoglicano



Adaptado de Kouidmi *et al*., 2014 – DOI: 10.1111/mmi.12758

Fosfomicina

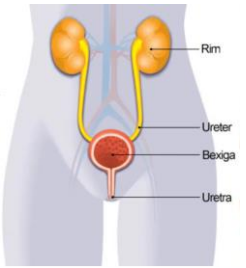
Mecanismo de ação



Adaptado de Castañeda-García *et al.*, 2013 – DOI: 10.3390/antibiotics2020217

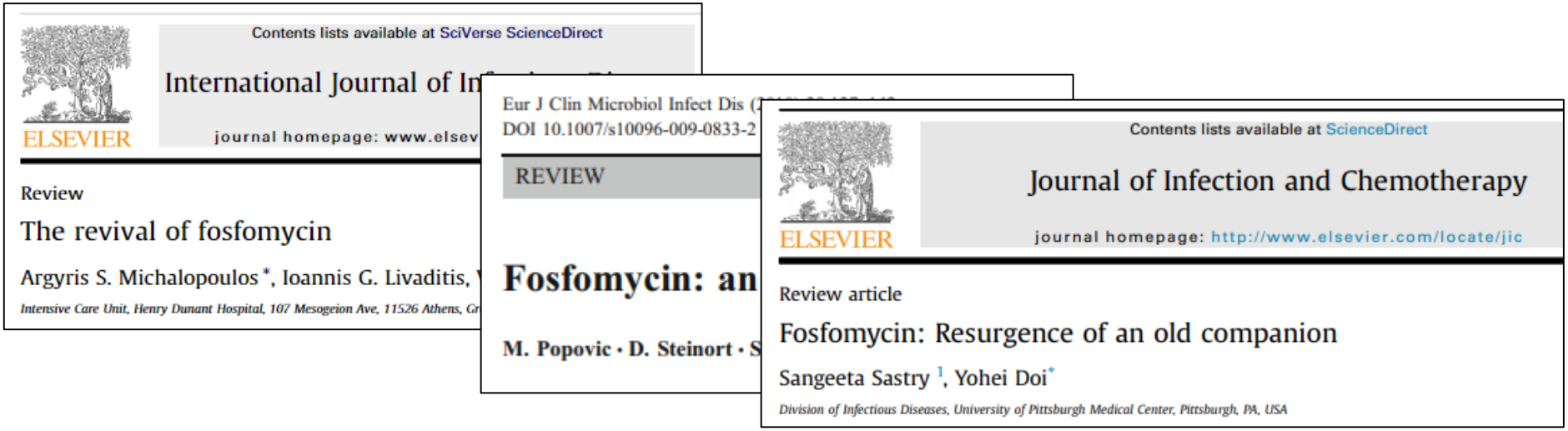
Fosfomicina

Aplicação



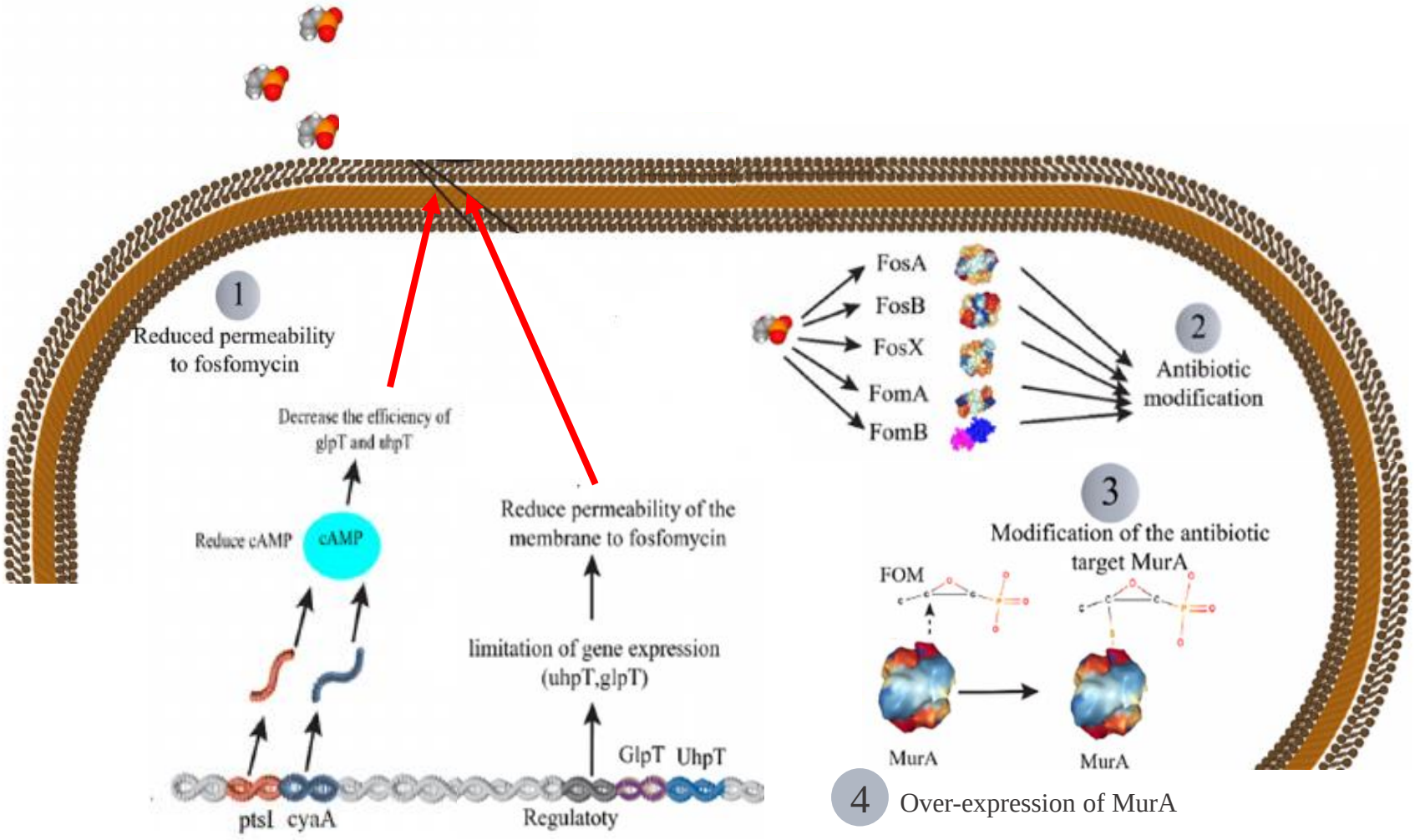
Antibiótico de amplo espectro:
Gram-positivas e Gram-negativas

- *Enterococcus* spp.
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Salmonella* spp.
- *Shigella* spp.
- *Escherichia coli*
- *Klebsiella* spp.
- *Enterobacter* spp.
- *Serratia* spp.
- *Citrobacter* spp.
- *Proteus mirabilis*
- *Listeria monocytogenes*
- *Neisseria gonorrhoeae*
- *Aerococcus urinae*



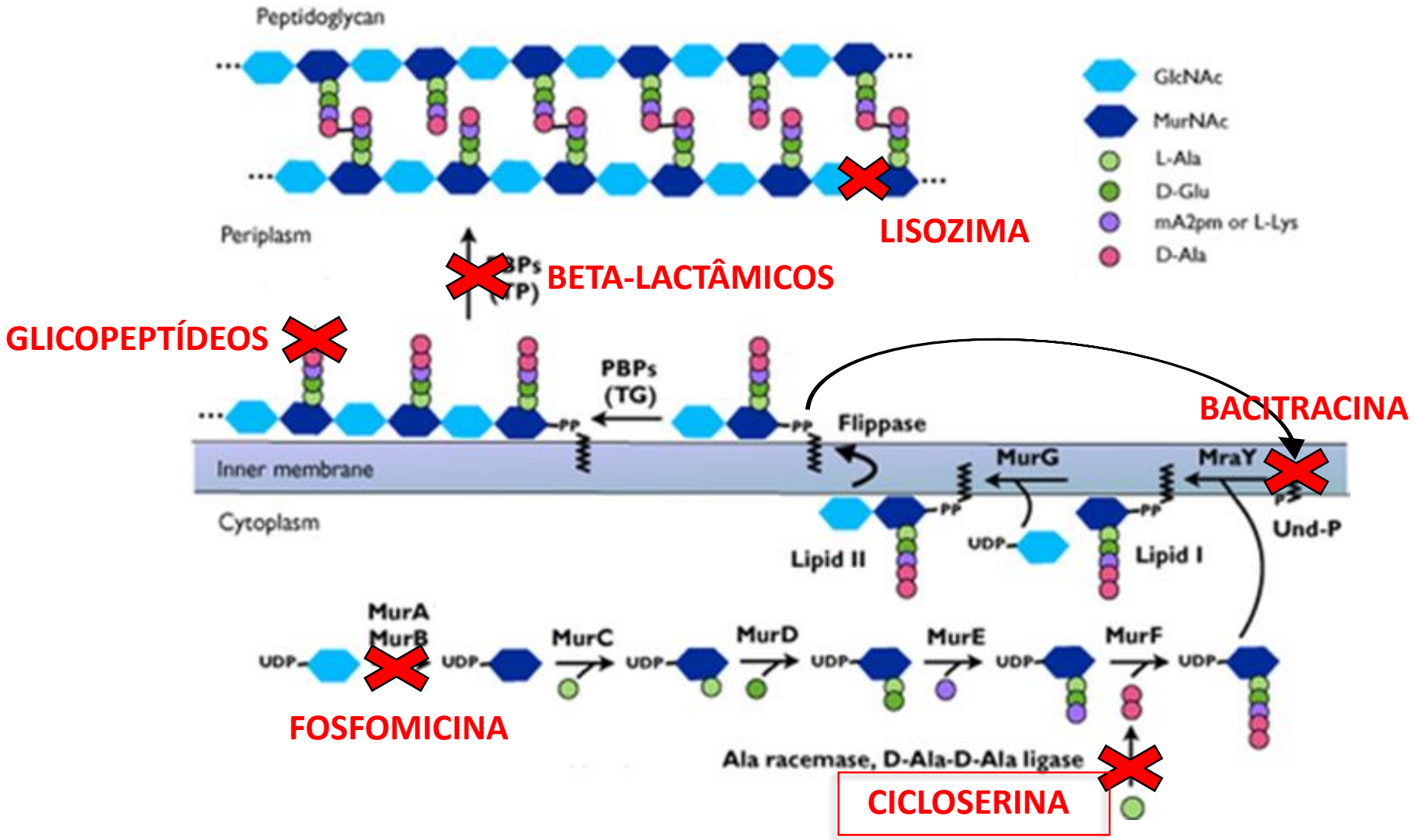
Fosfomicina

Mecanismos de resistência



Adaptado de Tajik *et al.*, 2020 - DOI: 10.1016/j.genrep.2020.100640

Inibidores da síntese de peptideoglicano



Adaptado de Kouidmi *et al.*, 2014 – DOI: 10.1111/mmi.12758

Cicloserina

D-Cycloserine D-Alanine

Mecanismo de ação:

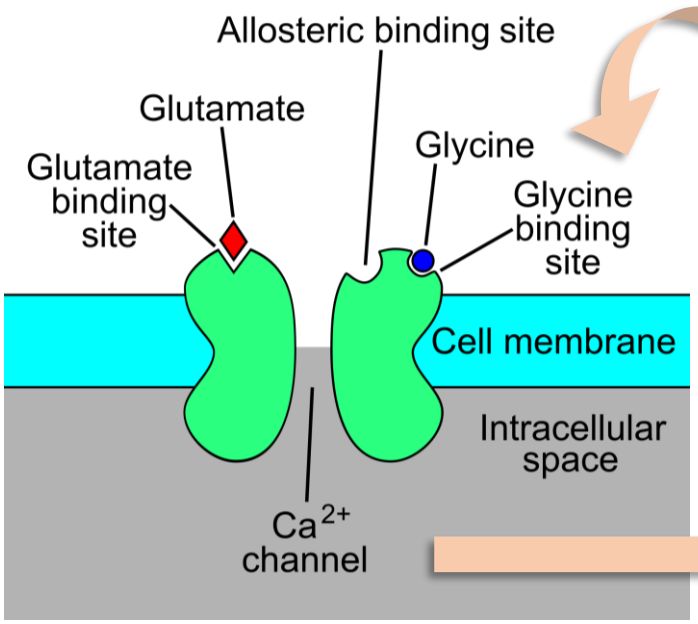
Adaptado da fonte: immunopaedia.org.za/treatment-diagnostics/tb-drugs/

Cicloserina

Aplicação

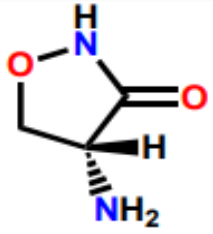
Medicamento de segunda linha contra cepas MDR *Mycobacterium tuberculosis*

Alta toxicidade



NMDAR

(receptor de ácido N-metil-D-aspártico)



D-Cycloserine

Co-agonista

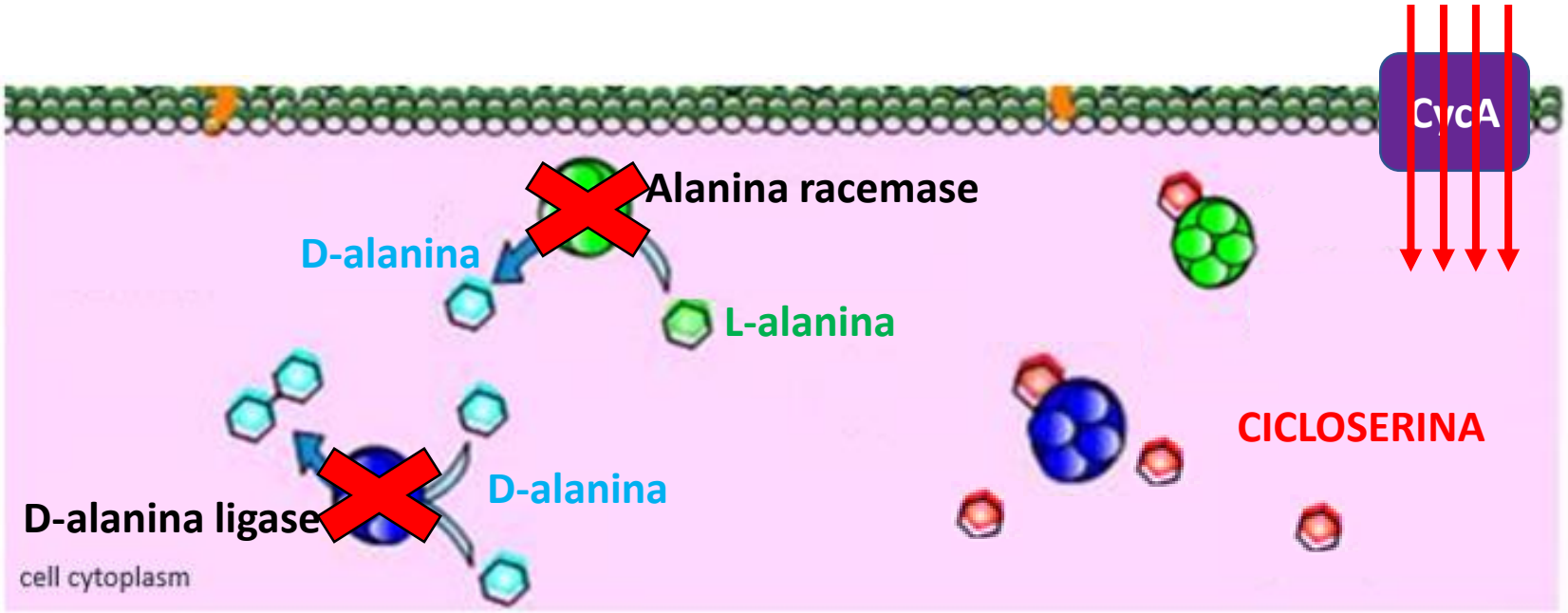
Possíveis **efeitos adversos graves**, incluindo convulsões e neuropatia periférica

Laube at al., 1997 – DOI: 10.1016/S0896-6273(00)81249-0

Cicloserina

Mecanismos de resistência

- **Mutações em CycA**

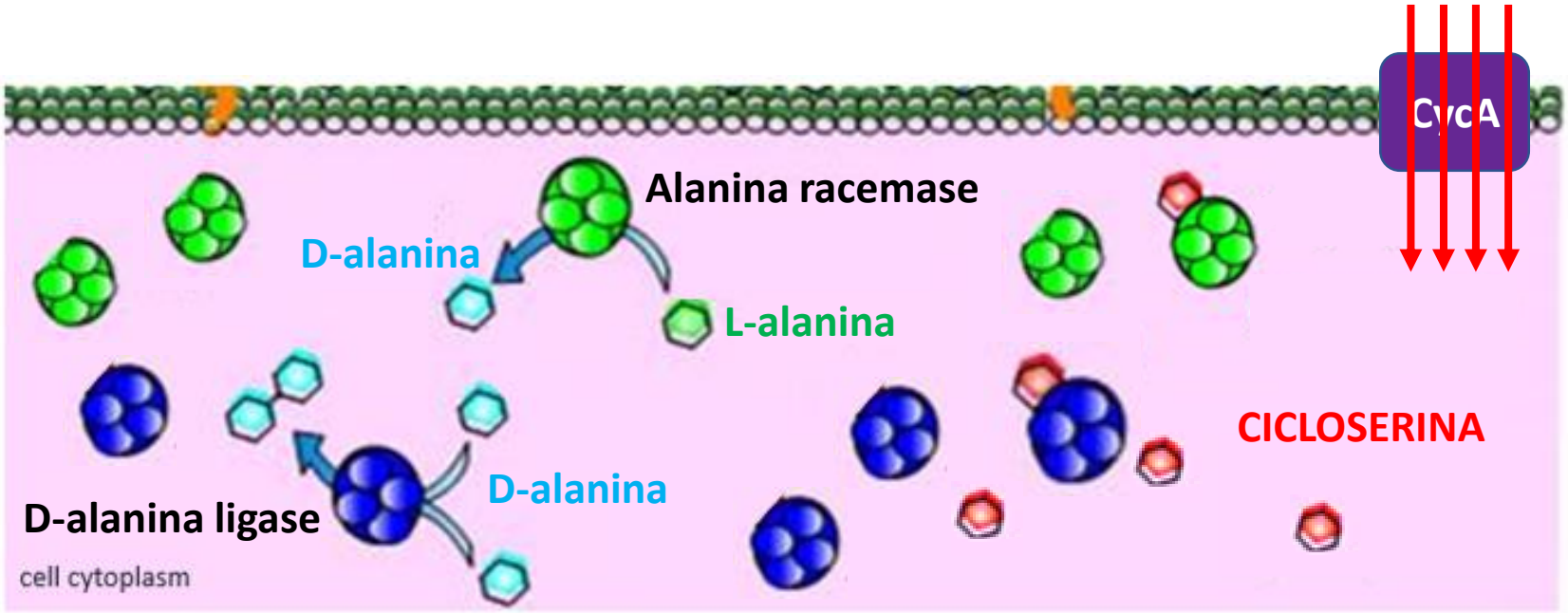


Adaptado da fonte: immunopaedia.org.za/treatment-diagnostics/tb-drugs/

Cicloserina

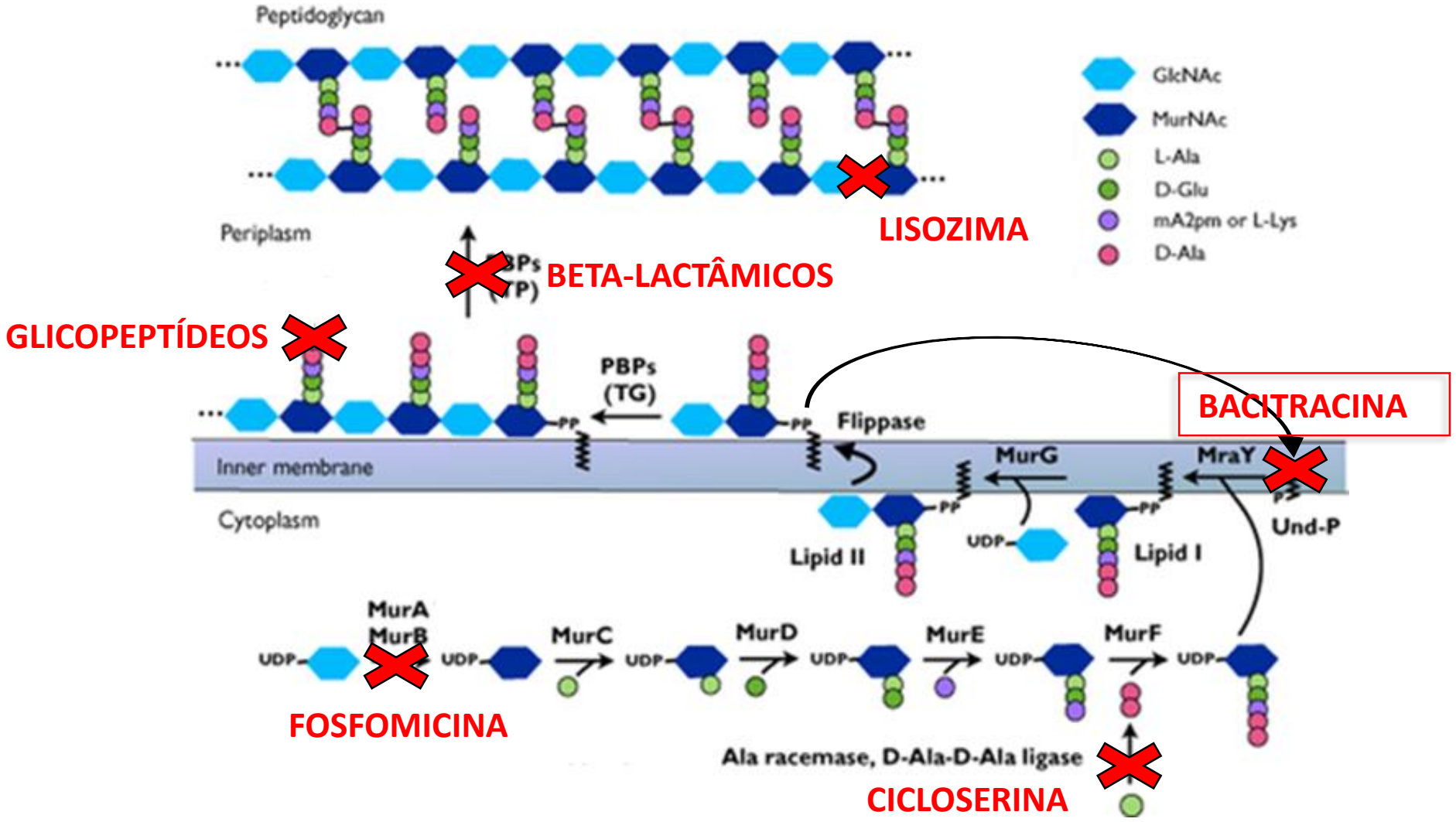
Mecanismos de resistência

- Mutações em CycA
- **Over-expression racemase e D-ala ligase**



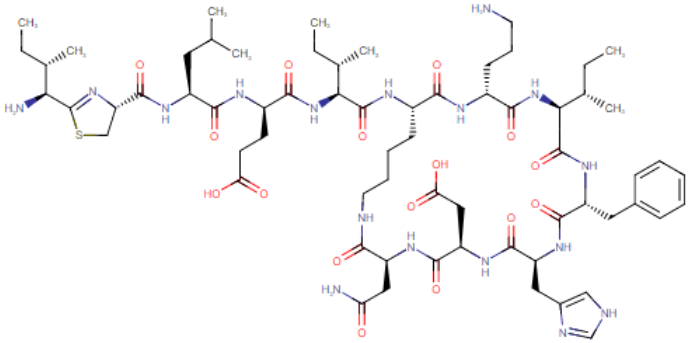
Adaptado da fonte: immunopaedia.org.za/treatment-diagnostics/tb-drugs/

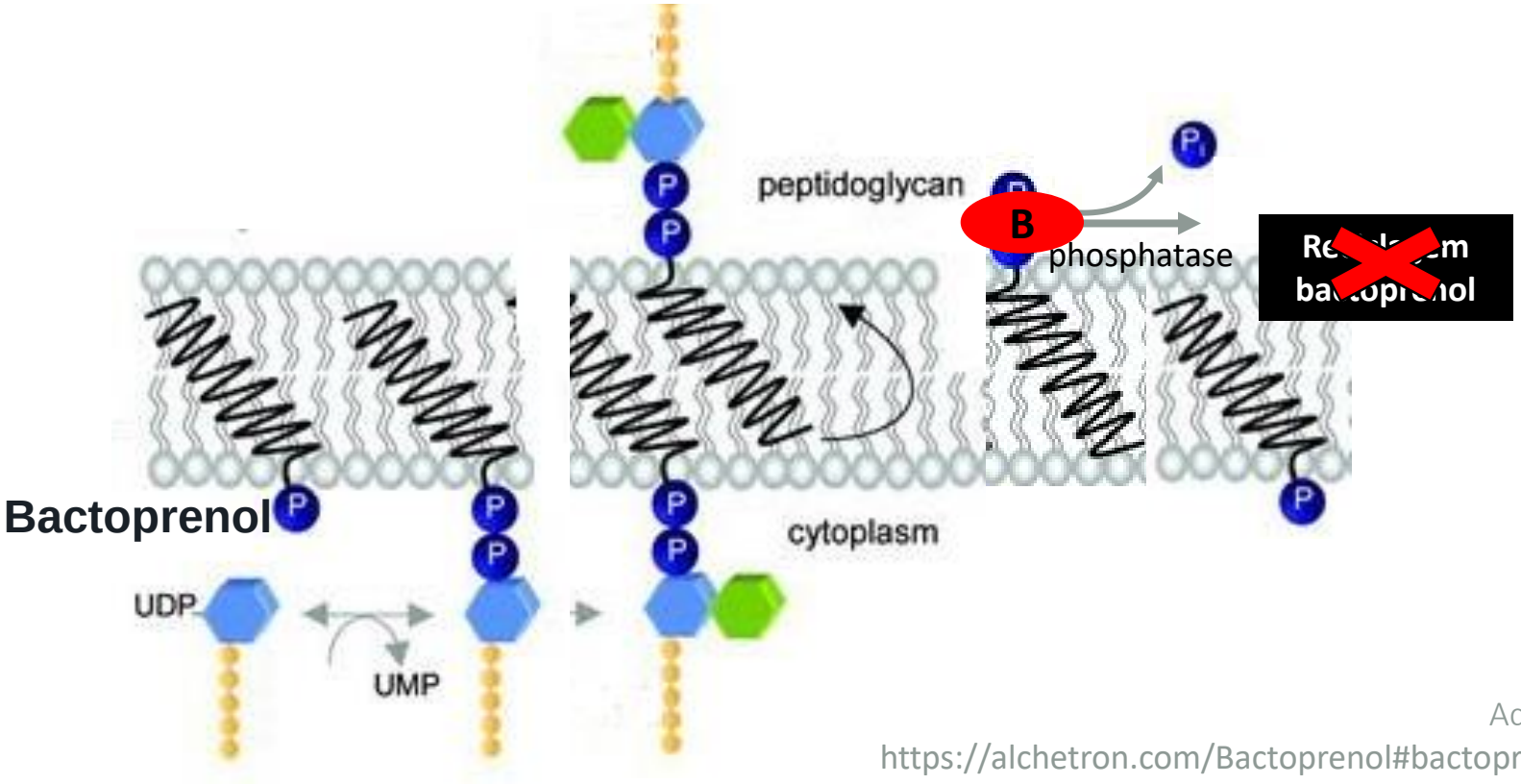
Inibidores da síntese de peptideoglicano



Adaptado de Kouidmi *et al.*, 2014 – DOI: 10.1111/mmi.12758

Bacitracina





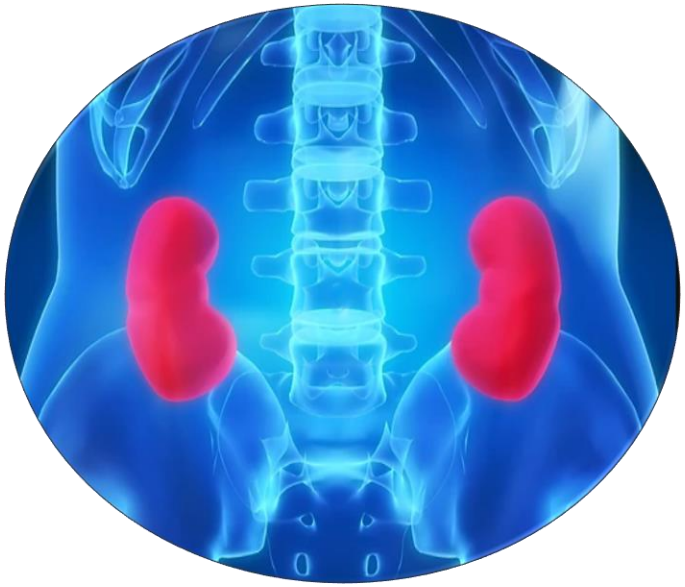
Adaptado da fonte:
https://alchetron.com/Bactoprenol#bactoprenol-f34897d1-7

Bacitracina

Aplicação

Gram-positivas

- *Staphylococcus* spp.
- *Streptococcus* spp.
- *Corynebacterium* spp.
- *Clostridium* spp.
- *Actinomyces* spp.

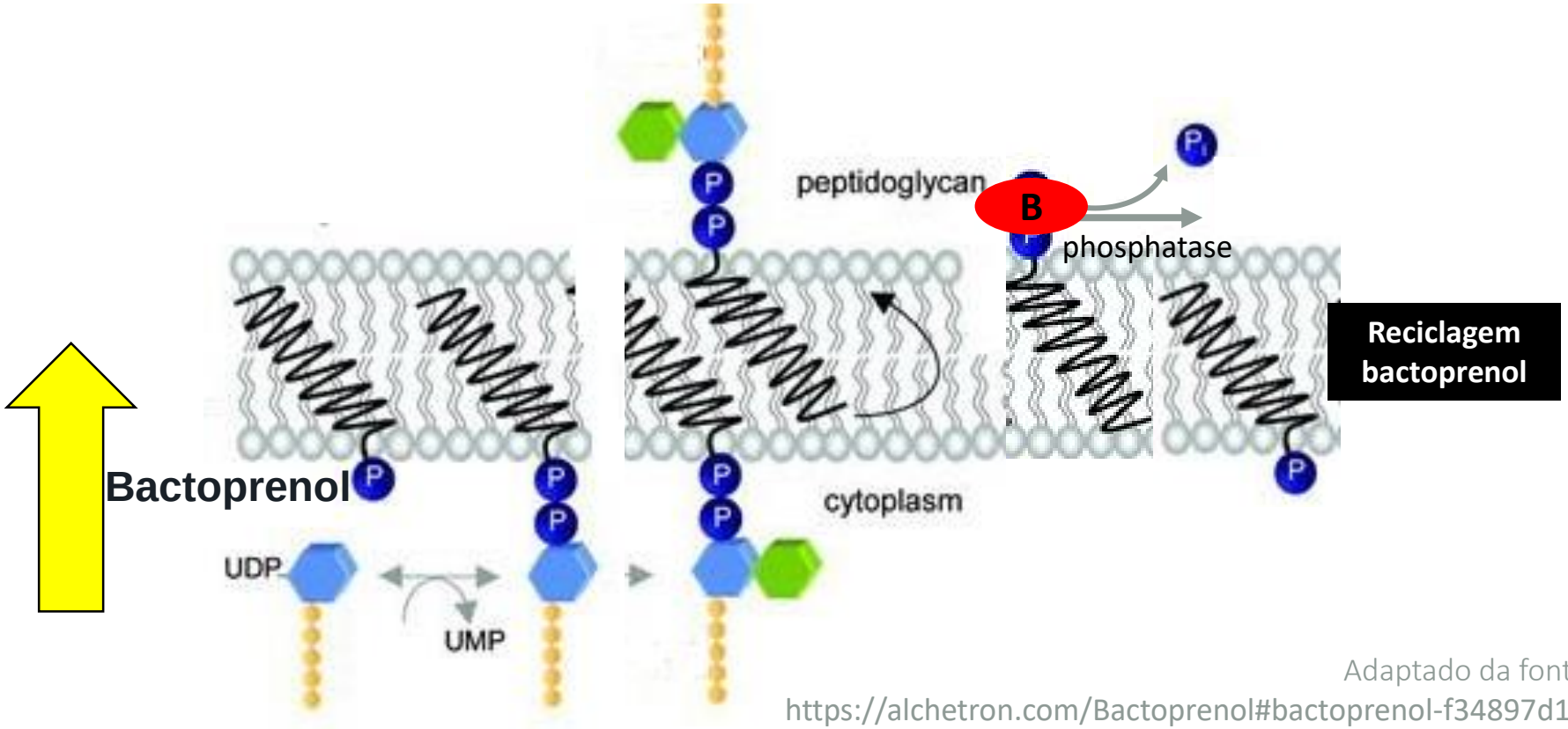


Infecções cutâneas

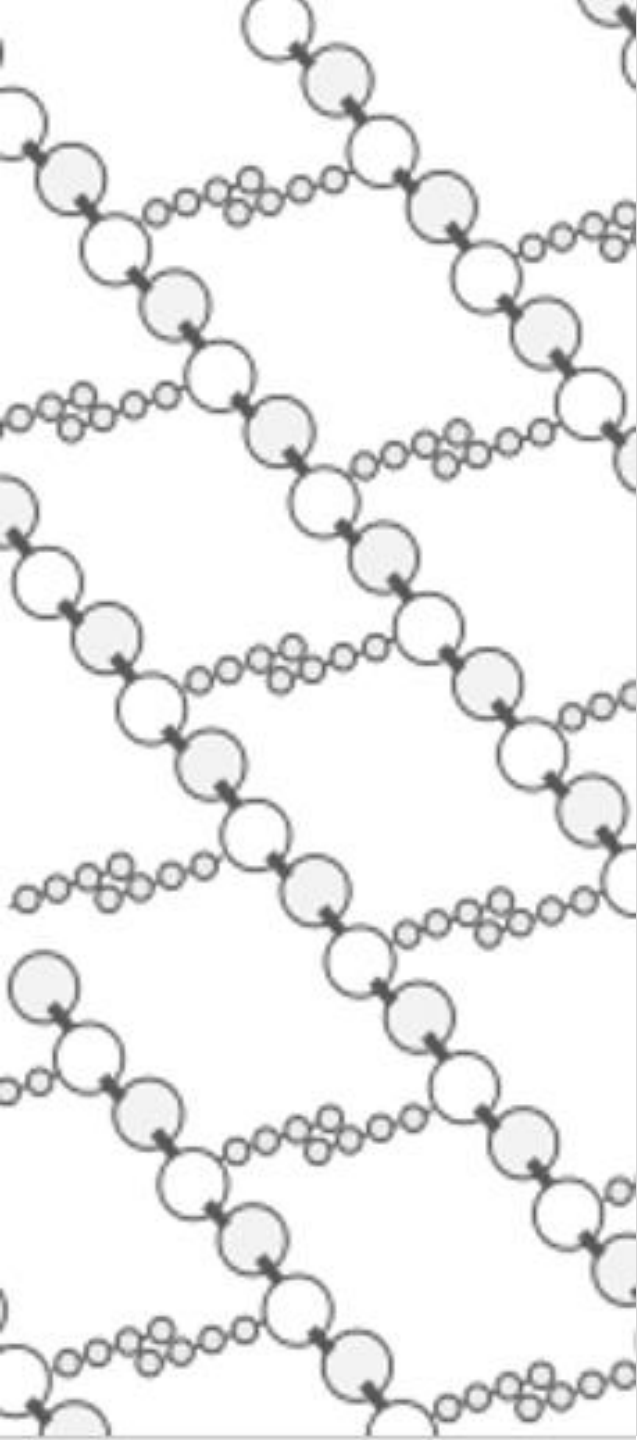
Bacitracina

Mecanismos de resistência

- **Super produção undecaprenol quinase**



Adaptado da fonte:
https://alchetron.com/Bactoprenol#bactoprenol-f34897d1-7

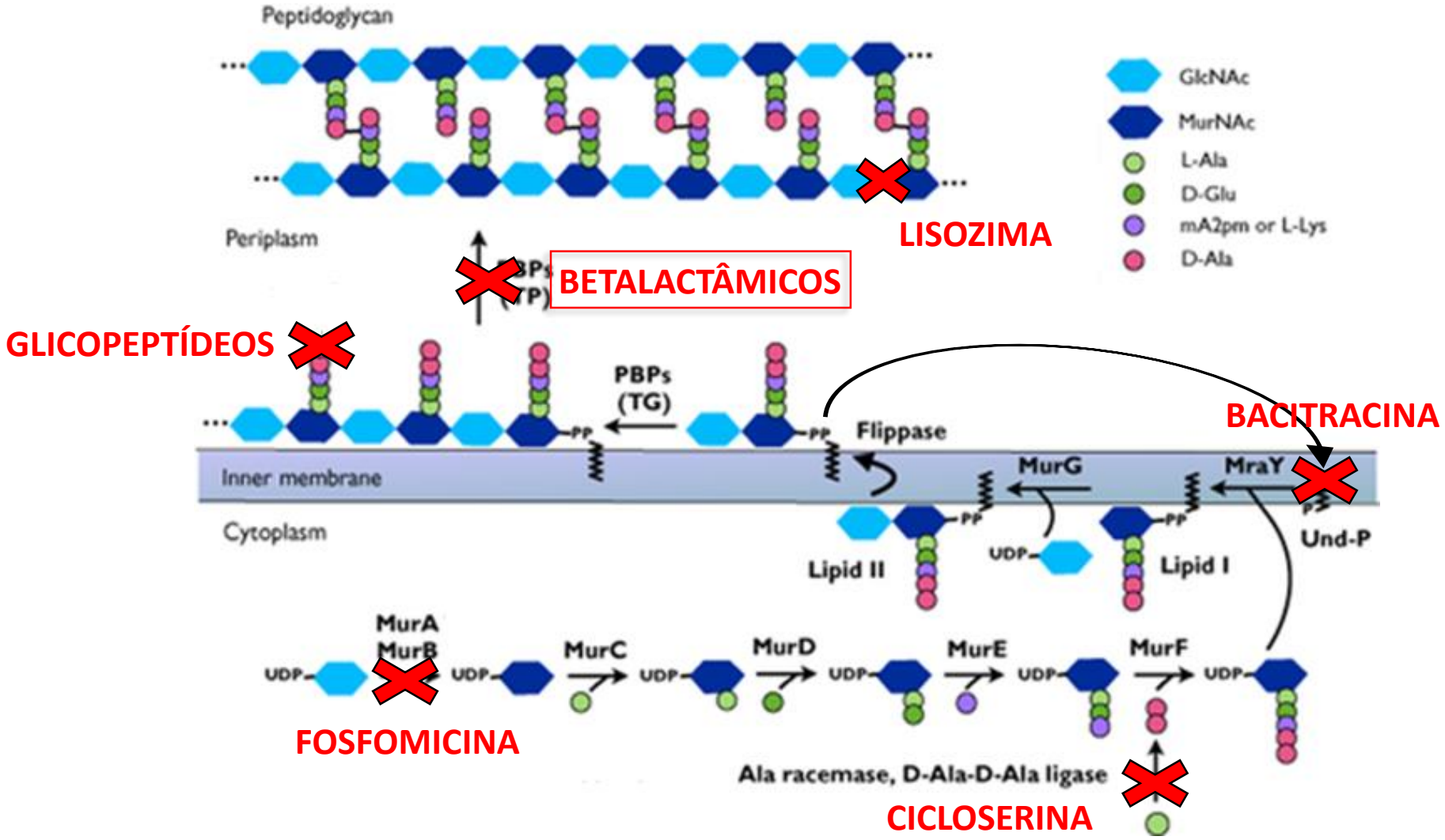


Peptidoglicano

- **Estrutura e função**
- **Biossíntese**
- **Antimicrobianos**
  - Inibidores de fase citoplasmática
  - Inibidores transporte de precursores
  - Inibidores da organização estrutural

Aline

Inibidores da síntese de peptideoglicano



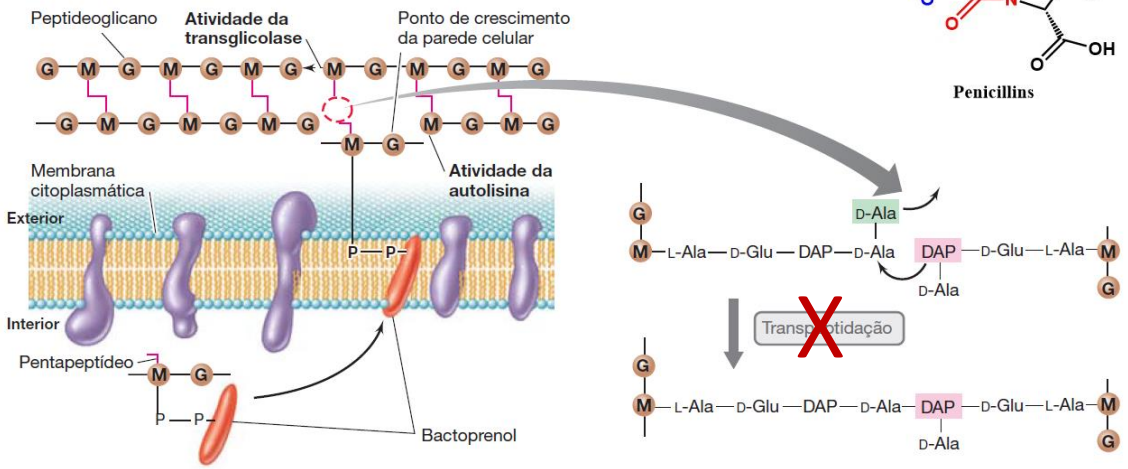
Adaptado de Kouidmi *et al.*, 2014 – DOI: 10.1111/mmi.12758

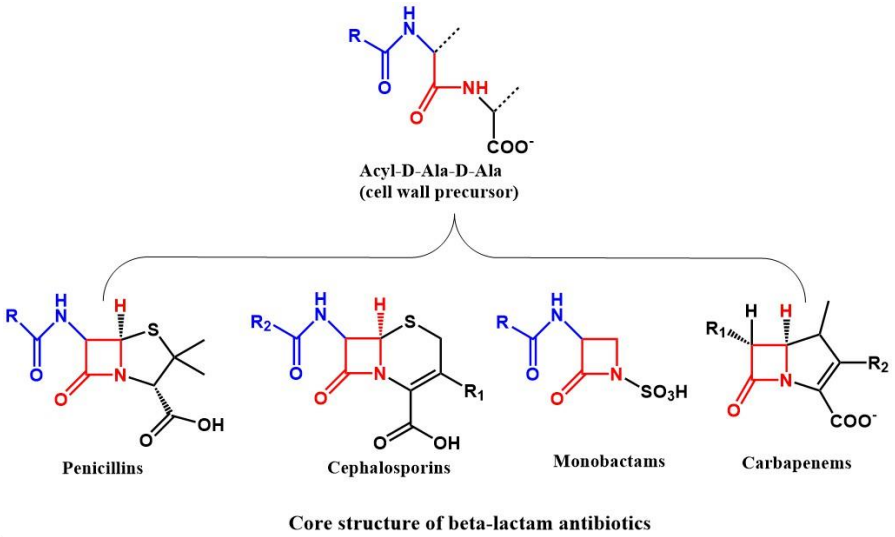
Betalactâmicos

Alvo: Transpeptidase (PBP)

Ação: Inibição da síntese da parede celular (Bactericida)

Espectro: Gram-positivos e/ou Gram-negativos





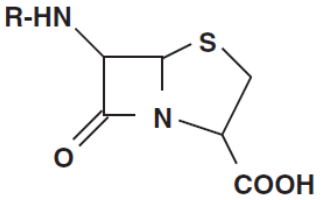
Fonte: https://ringbio.com

MARDIGAN et al., 2016. De Brock, 14 ed.

Betalactâmicos

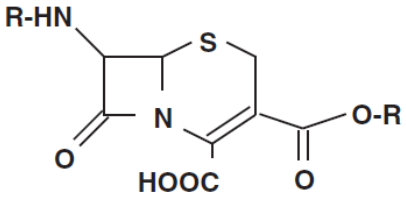
Grupo de Betalactâmicos

β-lactams



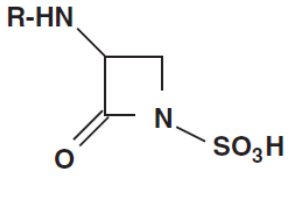
Penicillins

Penicillin G (e.g. benzypenicillin)
Penicillin V(e.g. Phenoxymethylpenicillin)
Penicillin M (e.g. Oxacillin, Cloxacilline)
Aminopenicillins (e.g. Amoxicillin)
Caboxypenicillins (e.g. Ticarcillin)
Ureidopenicillins (e.g. Piperacillin)
Aminidopenicillins (e.g. Pivmecillinam)



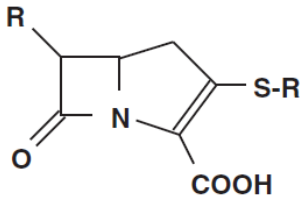
Cephalosporins

1st generation (e.g. Cefalotin)
2nd generation (e.g. Cefoxitin, Cefuroxime)
3rd generation (e.g. Cefotaxime, Ceftazidime)
4th generation (e.g. Cefepime, Cefpirome)



Monobactam

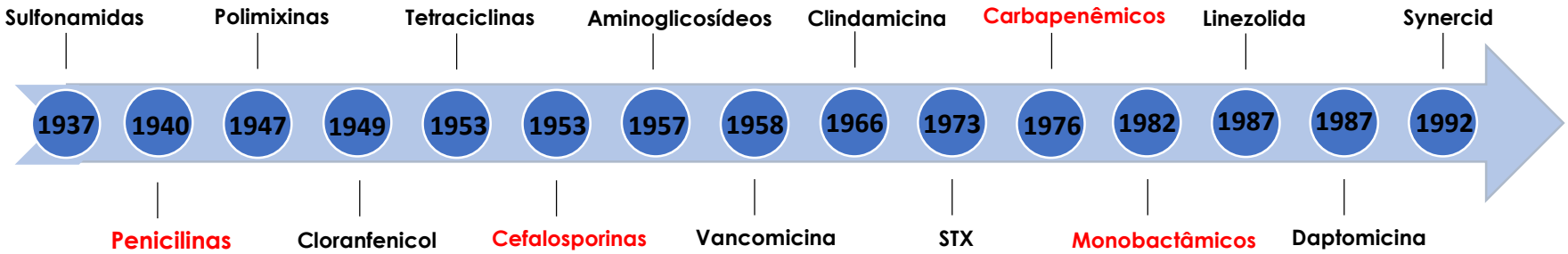
Aztreonam



Carbapenems

Imipenem
Meropenem
Ertapenem
Doripenem

NORDMANN; POIREL, 2012. DOI:10.1016/j.molmed.2012.03.003

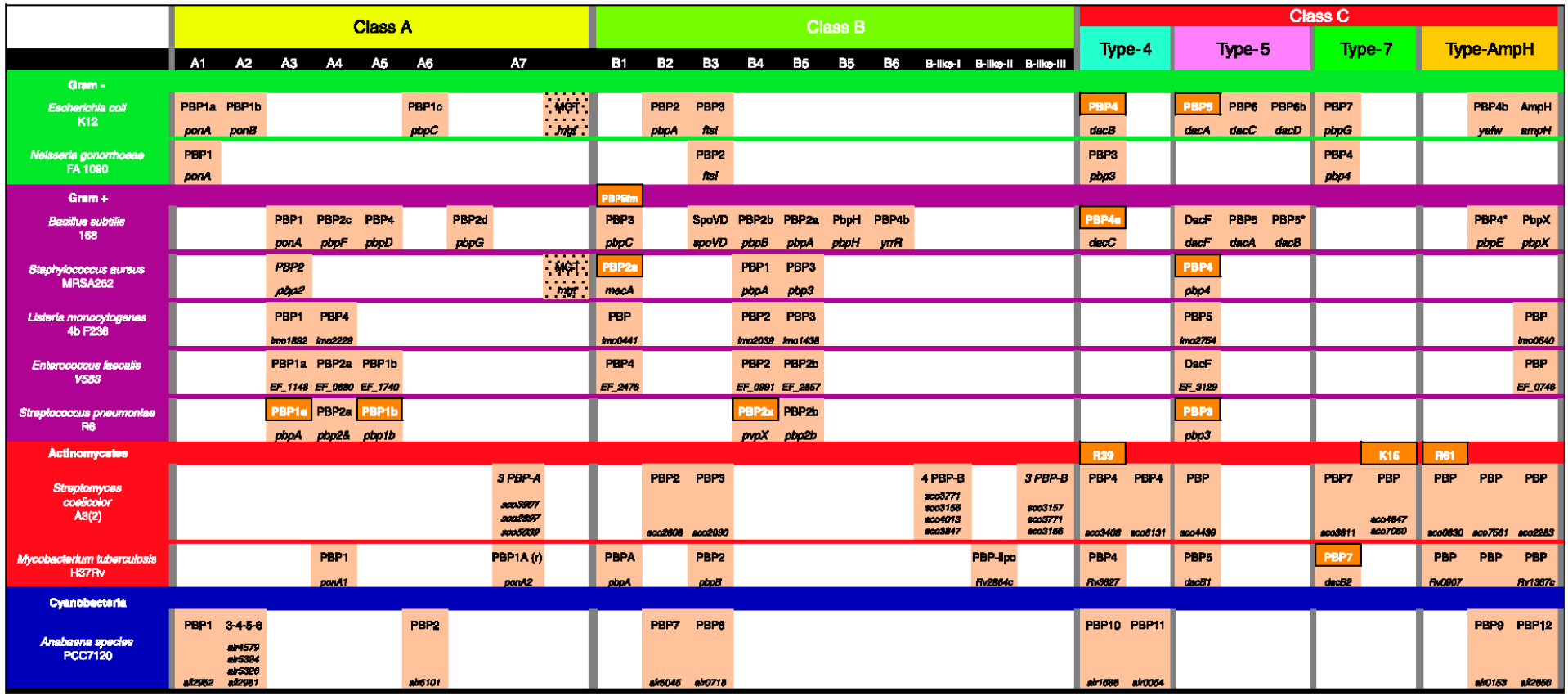


Betalactâmicos

The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis

Eric Sauvage[1], Frédéric Kerff[1], Mohammed Terrak[1], Juan A. Ayala[2] & Paulette Charlier[1]

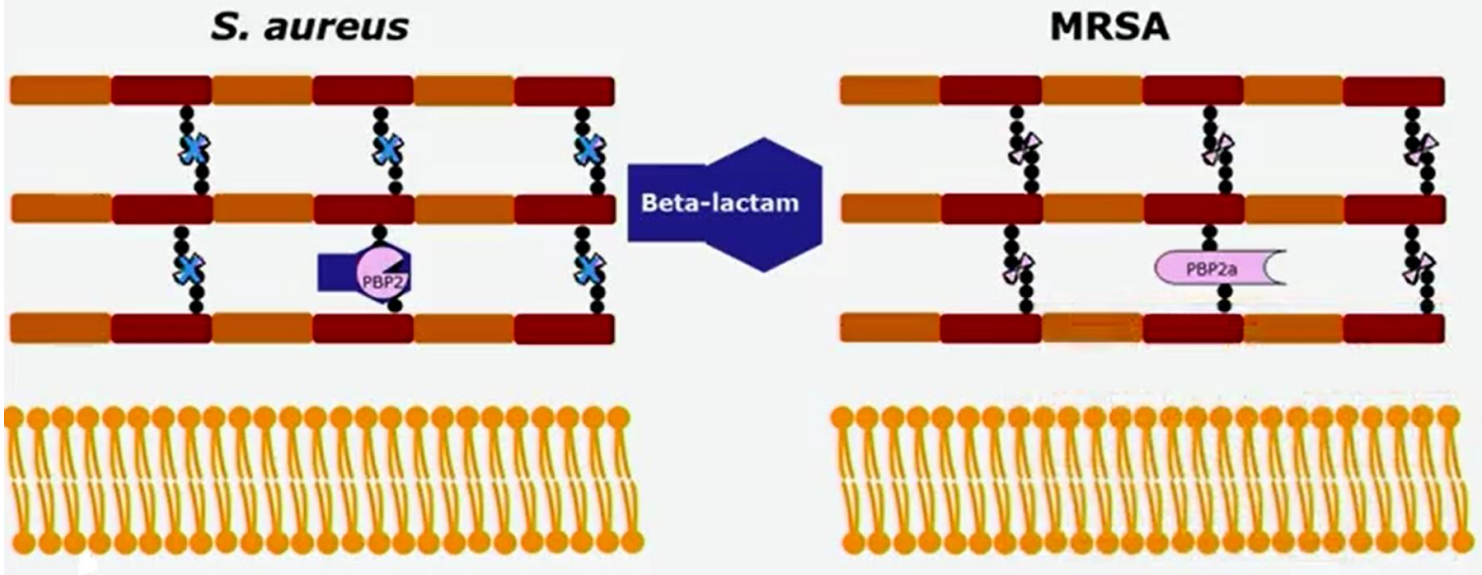
[1]Centre d'Ingénierie des Protéines, Institut de Physique B5a et Institut de Chimie B6a, University of Liège, Sart Tilman, Belgium; and [2]Centro de Biologia Molecular ' Severo Ochoa ' CSIC-UAM, Campus de Cantoblanco, Madrid, Spain



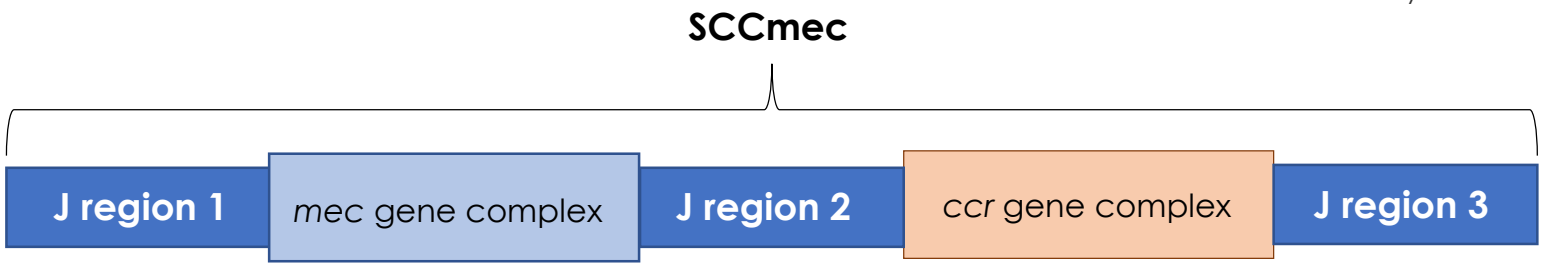
Betalactâmicos

Mecanismo de resistência em Gram-positivos

Principal mecanismo: modificação das PBPs



Course: Antimicrobial resistance - theory and methods – Technical University of Denmark. 2020.



Betalactâmicos

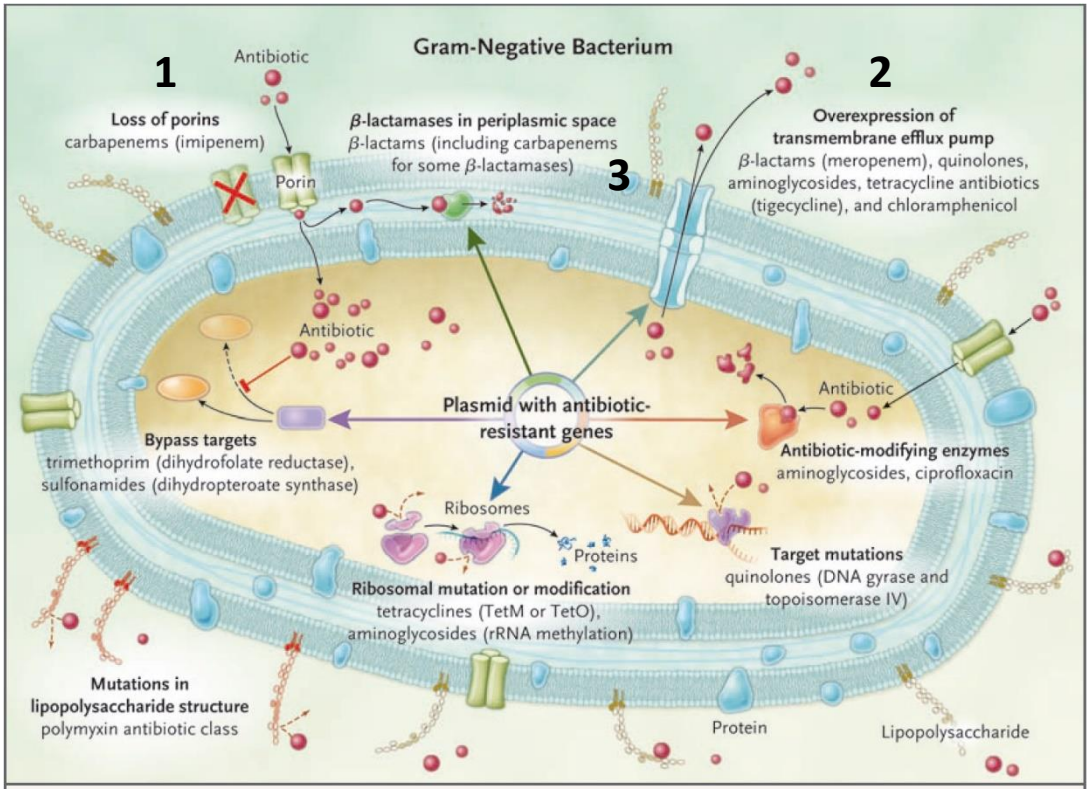
Mecanismo de resistência em Gram-negativos

1. Diminuição da permeabilidade

2. Bombas de efluxo

3. Produção de betalactamases

- **Mais eficiente**
- **Mais frequente**

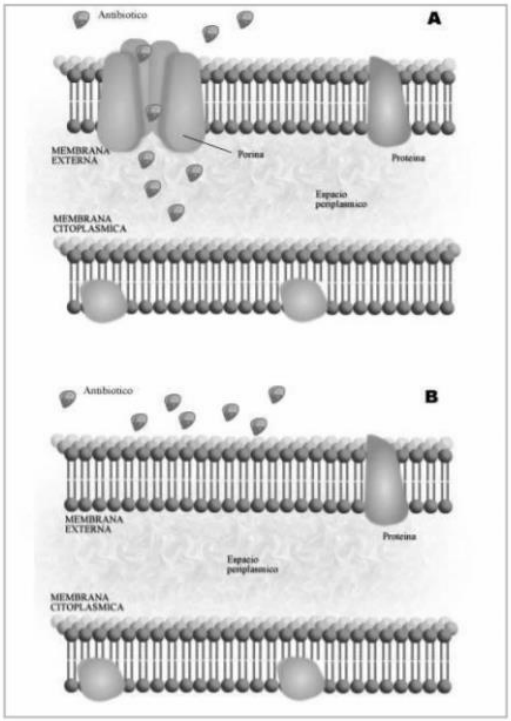


PELEG; HOOPER, 2010. DOI: 10.1056/NEJMra0904124

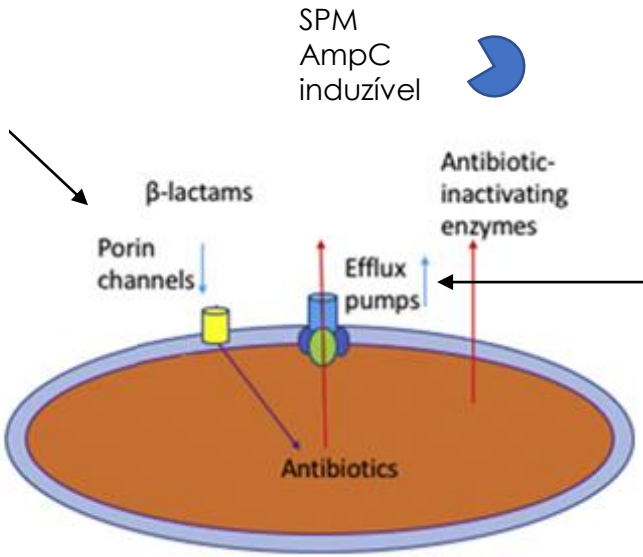
Betalactâmicos

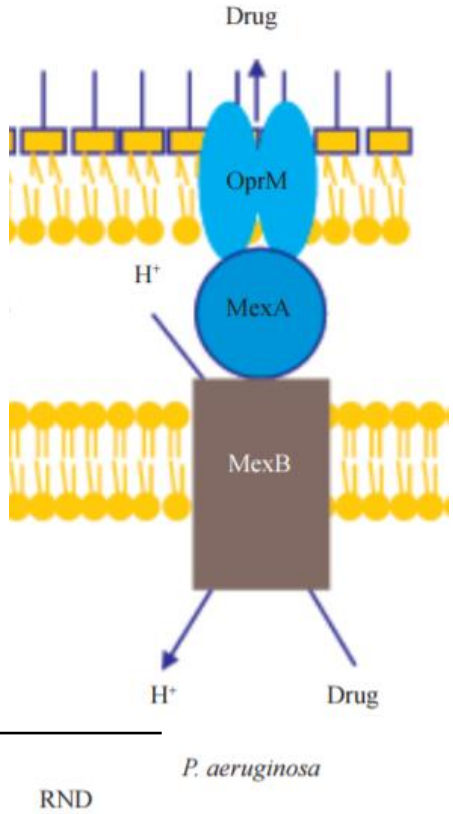
Mecanismo de resistência em *Pseudomonas aeruginosa*

Perda de OprD



ALVAREZ et al., 2005. Rev Fac Med Univ Nac





Hiperexpressão de MexAB-OprM

Adaptado de Schweizer (2002). PMID: 12917802

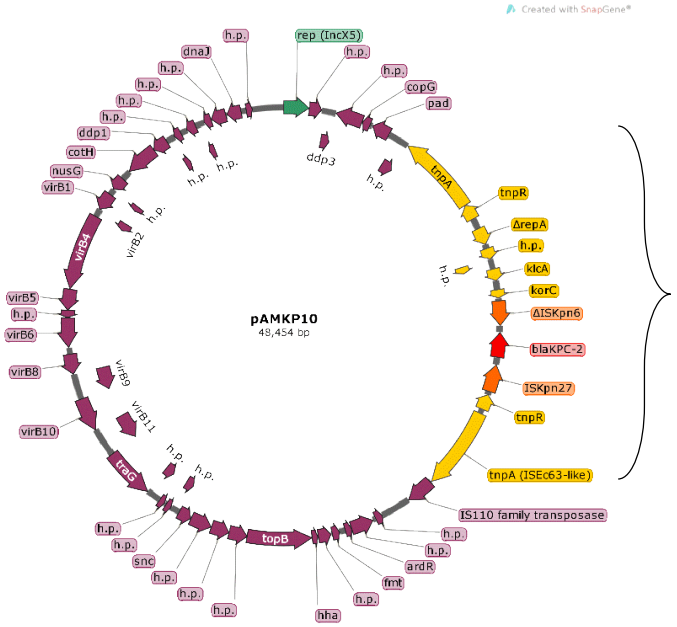
Adaptado de Pang et al. (2019). DOI: 10.1016/j.biotechadv.2018.11.013

Betalactâmicos

Carbapenemases em *Enterobacterales*

Grupo de enzimas mais frequentes:
KPC (*Klebsiella pneumoniae* carbapenemase)
57 variantes identificadas

Problemática:



Fonte: https://www2.ifsc.usp.br

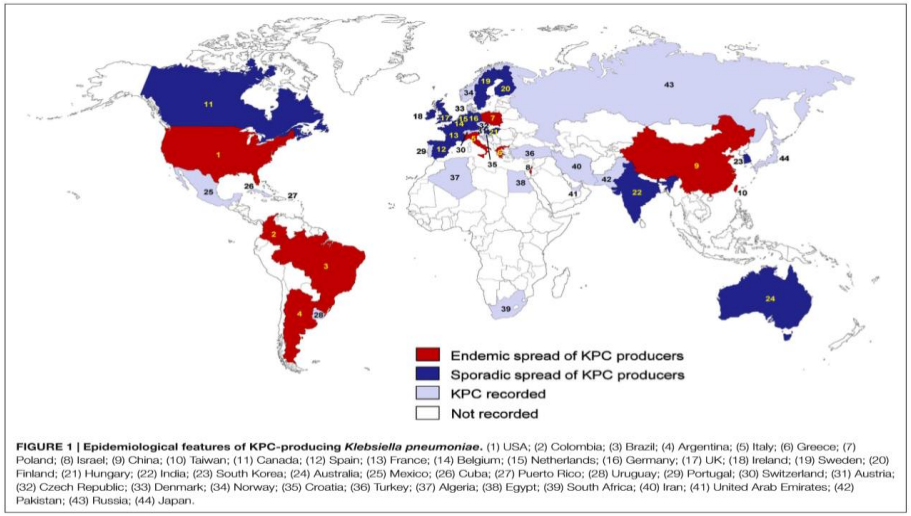
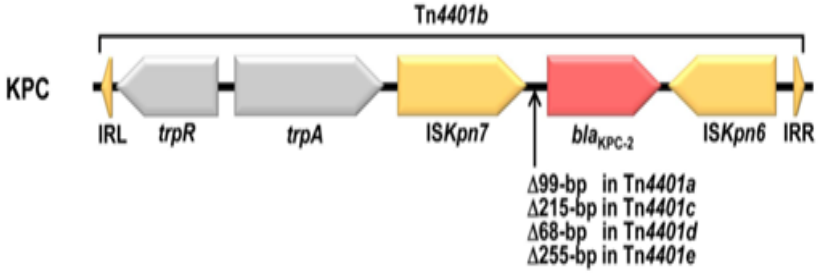


FIGURE 1 | Epidemiological features of KPC-producing *Klebsiella pneumoniae*. (1) USA; (2) Colombia; (3) Brazil; (4) Argentina; (5) Italy; (6) Greece; (7) Poland; (8) Israel; (9) China; (10) Taiwan; (11) Canada; (12) Spain; (13) France; (14) Belgium; (15) Netherlands; (16) Germany; (17) UK; (18) Ireland; (19) Sweden; (20) Finland; (21) Hungary; (22) India; (23) South Korea; (24) Australia; (25) Mexico; (26) Cuba; (27) Puerto Rico; (28) Uruguay; (29) Portugal; (30) Switzerland; (31) Austria; (32) Czech Republic; (33) Denmark; (34) Norway; (35) Croatia; (36) Turkey; (37) Algeria; (38) Egypt; (39) South Africa; (40) Iran; (41) United Arab Emirates; (42) Pakistan; (43) Russia; (44) Japan.

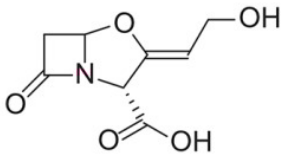
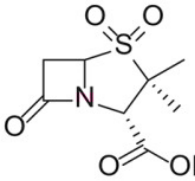
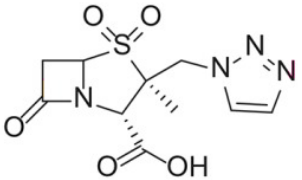
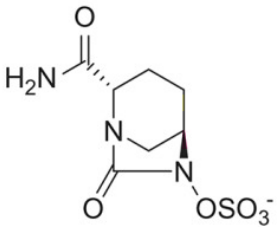


LEE et al., 2016. DOI: 10.3389/fmicb.2016.00895

Betalactâmicos

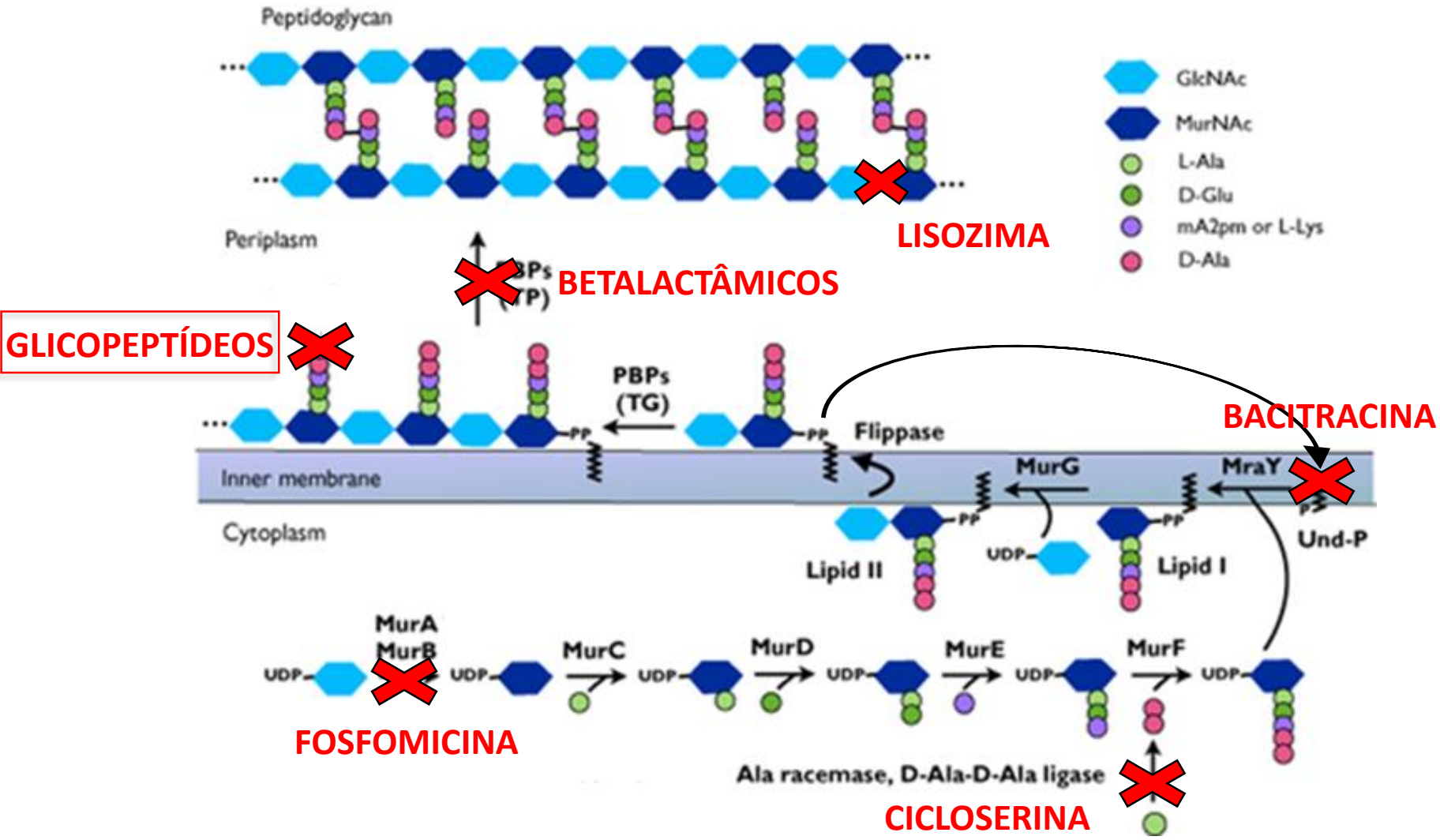
Inibidores de Betalactamase

Table 6. β-lactamase inhibitors of current interest

Name	Structure	Subclass	Partner β-lactam	Approval date[a]	Status
Clavulanic acid[b]		Clavam	Amoxicillin	1984	Widely available
Sulbactam[c]		Penicillanic acid sulfone	Ampicillin	1986	Widely available
Tazobactam		Penicillanic acid sulfone	Piperacillin Ceftolozane	1993 2014	Widely available Available in the United States and Europe
Avibactam[d]		DBO[e]	Ceftazidime[d]	2015	Widely available

BUSH; BRADFORD, 2016. DOI: 10.1101/cshperspect.a025247

Inibidores da síntese de peptideoglicano



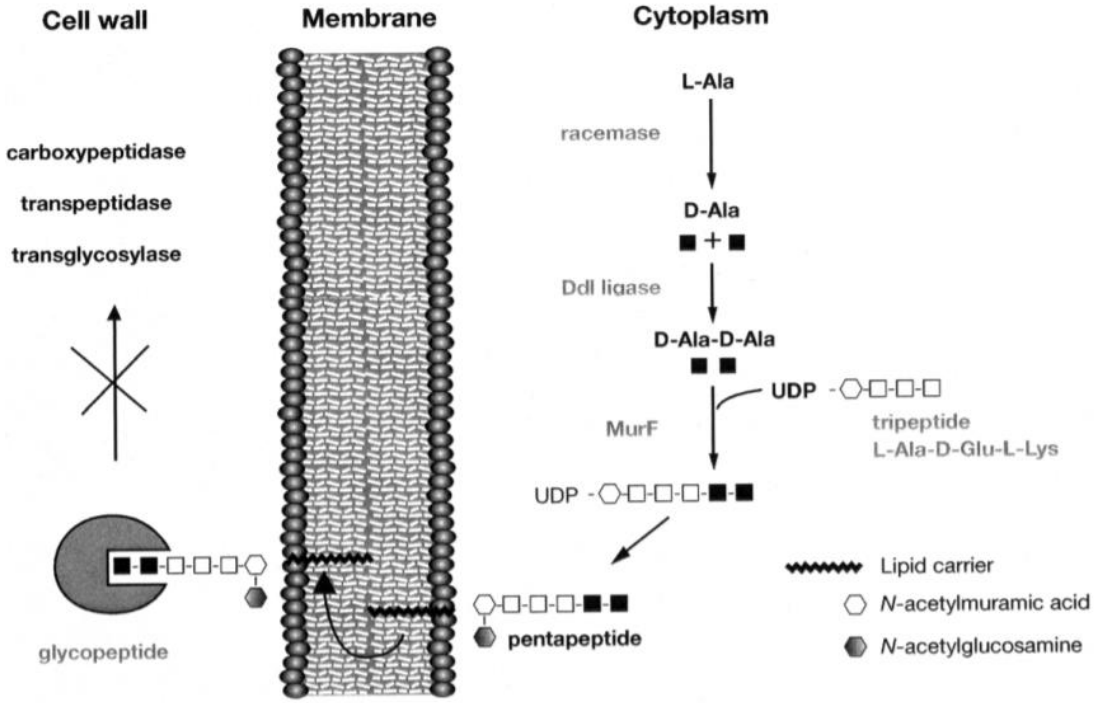
Adaptado de Kouidmi *et al.*, 2014 – DOI: 10.1111/mmi.12758

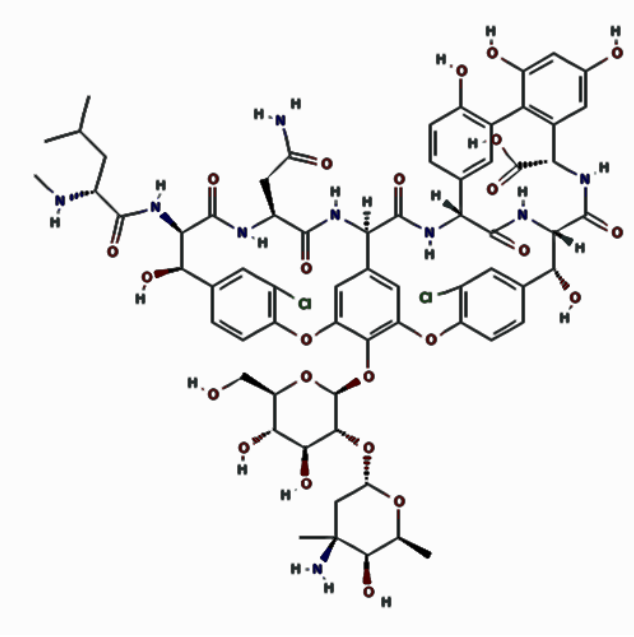
Glicopeptídeos

Alvo: Extremidade D-Ala-D-Ala do pentapeptídeo

Ação: Inibição da síntese da parede celular (Bactericida)

Espectro: Gram-positivos



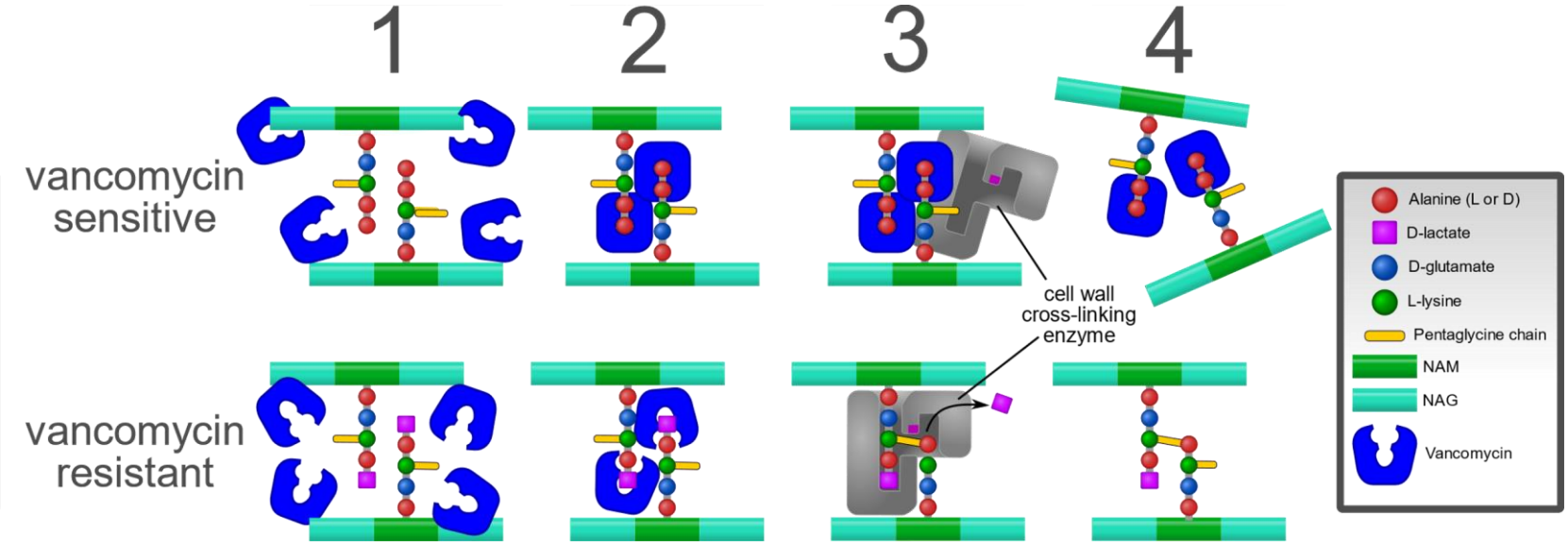


Fonte: pubchem.ncbi.nlm.nih.gov

COURVALIN, 2006. DOI: 10.1086/491711

Glicopeptídeos

Mecanismo de resistência



Fonte: commons.wikimedia.org

Glicopeptídeos

Resistência em *Enterococcus* sp. (VRE)

Table 1. Level and type of resistance to vancomycin in enterococci.

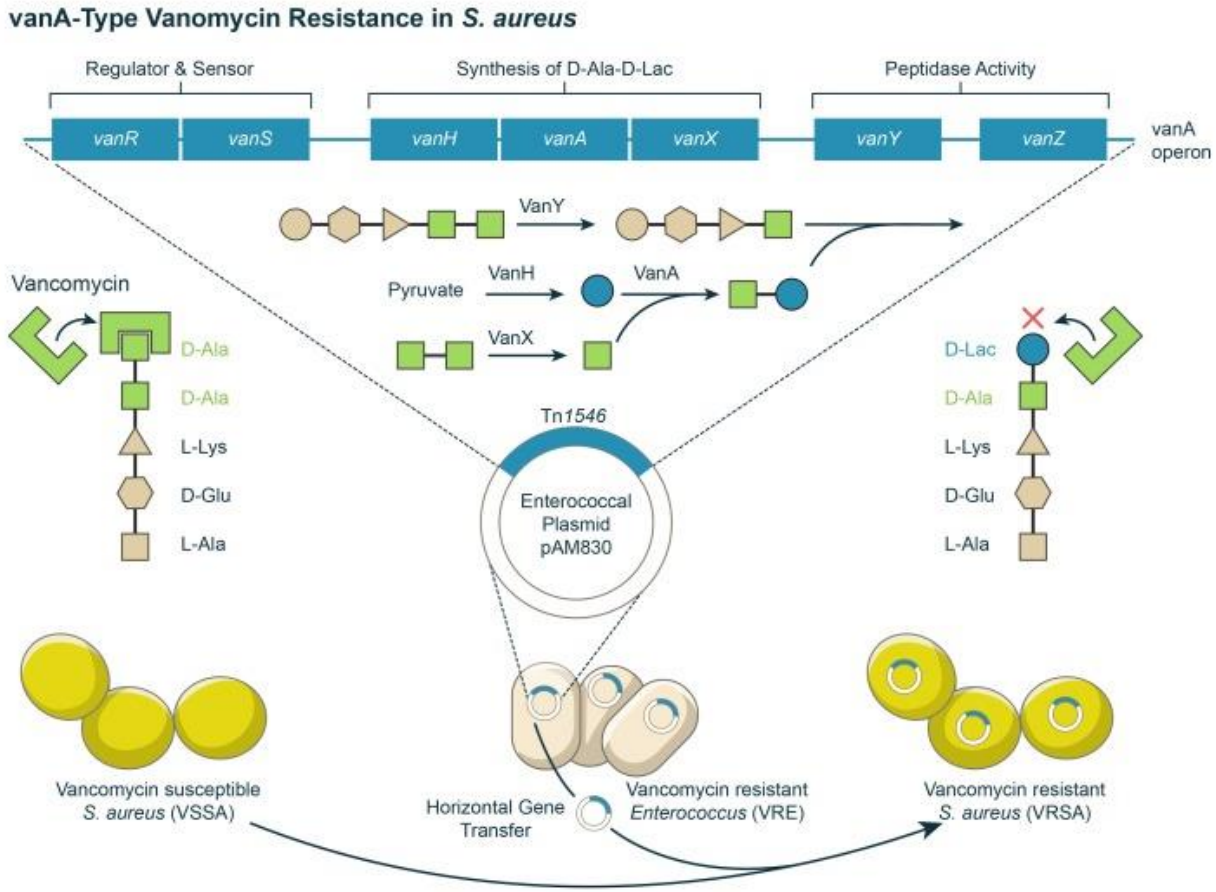
Strain characteristic	Acquired resistance level, type					Intrinsic resistance, low level, type VanC1/C2/C3
	High, VanA	Variable, VanB	Moderate, VanD	Low		
				VanG	VanE	
MIC, mg/L						
Vancomycin	64–100	4–1000	64–128	16	8–32	2–32
Teicoplanin	16–512	0.5–1	4–64	0.5	0.5	0.5–1
Conjugation	Positive	Positive	Negative	Positive	Negative	Negative
Mobile element	Tn*1546*	Tn*1547* or Tn*1549*	…	…	…	…
Expression	Inducible	Inducible	Constitutive	Inducible	Inducible	Constitutive Inducible
Location	Plasmid chromosome	Plasmid chromosome	Chromosome	Chromosome	Chromosome	Chromosome
Modified target	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser

NOTE. D-Ala-D-Lac, D-alanine-D-lactate; D-Ala-D-Ser, D-alanine-D-serine.

COURVALIN, 2006. DOI: 10.1086/491711

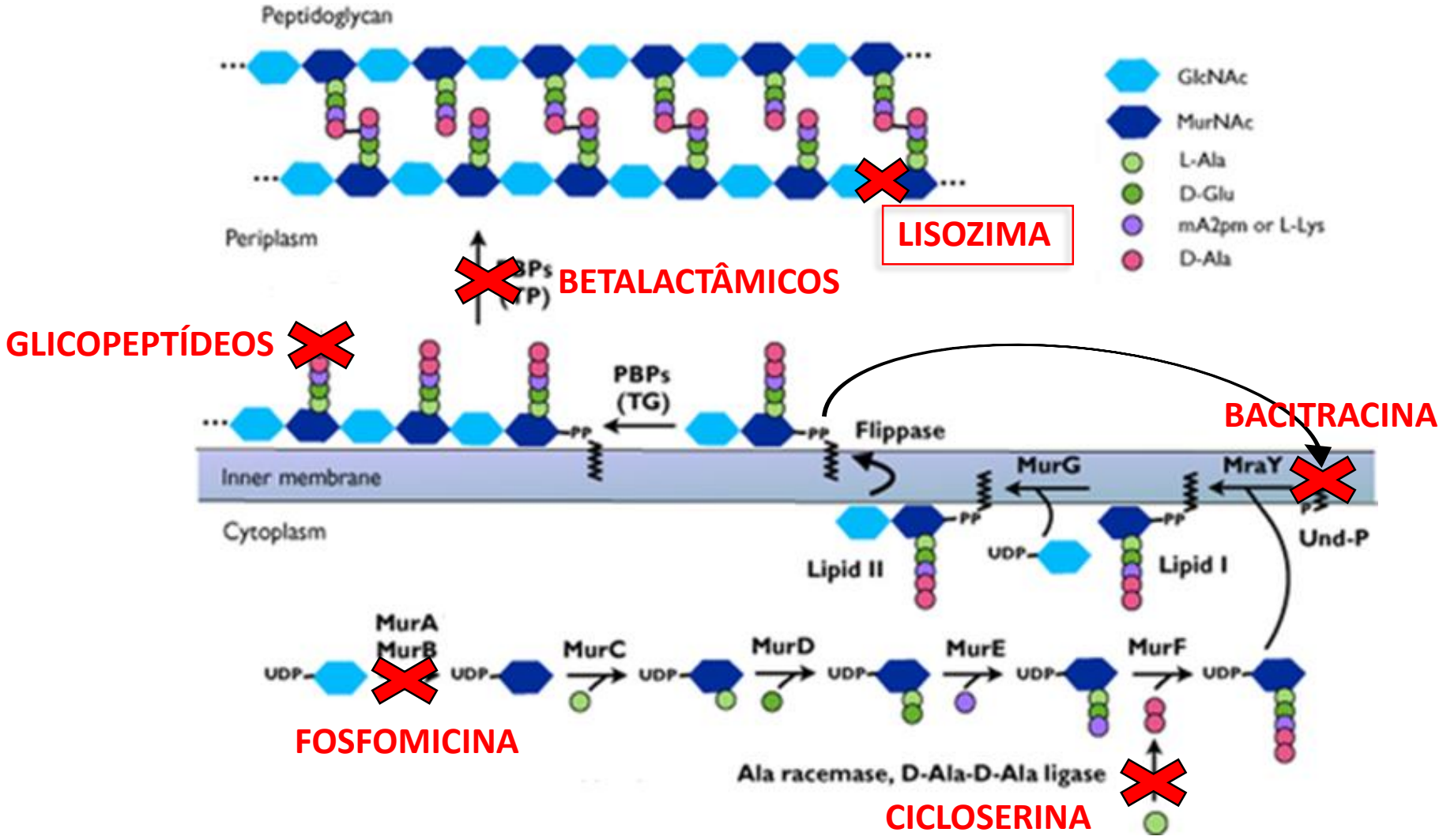
Glicopeptídeos

Resistência em *Staphylococcus aureus* (VRSA)



MCGUINNESS, et al., 2017. PMCID: PMC5482303

Inibidores da síntese de peptideoglicano



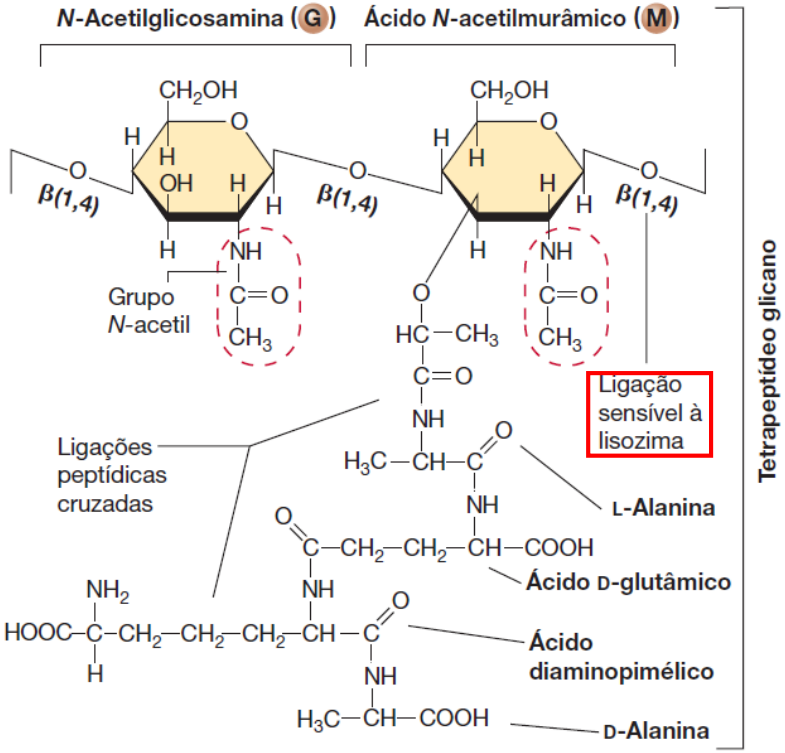
Adaptado de Kouidmi *et al.*, 2014 – DOI: 10.1111/mmi.12758

Lisozima

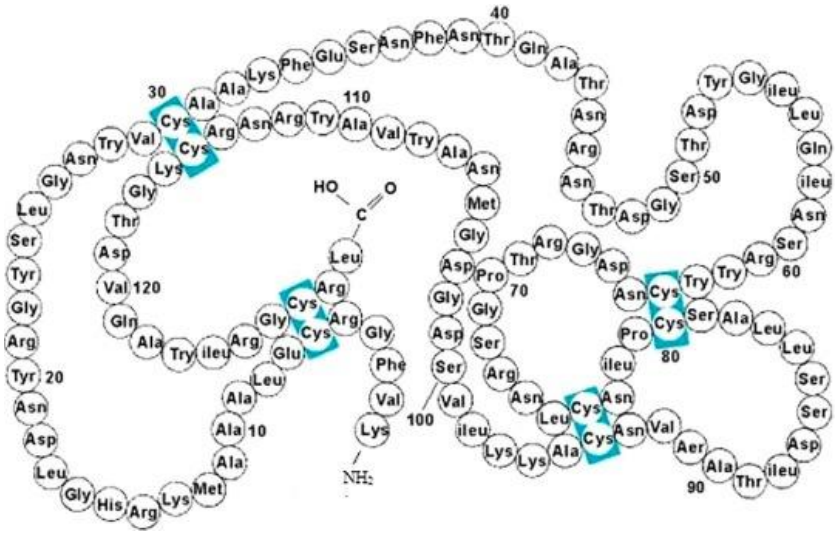
Alvo: Ligação β- 1,4 glicosídica ente NAG e NAM

Ação: Inibição da síntese da parede celular (Bactericida)

Espectro: Gram-positivos



MARDIGAN et al., 2016.



JIANG, 2019. DOI: 10.1016/j.foodchem.2018.09.017

Lisozima

Microrganismos fortemente lisados ou inibidos pela lisozima

a. Organismos fortemente lisados ou inibidos por lisozima

Bacillus coagulans

Bacillus stearothermophilus

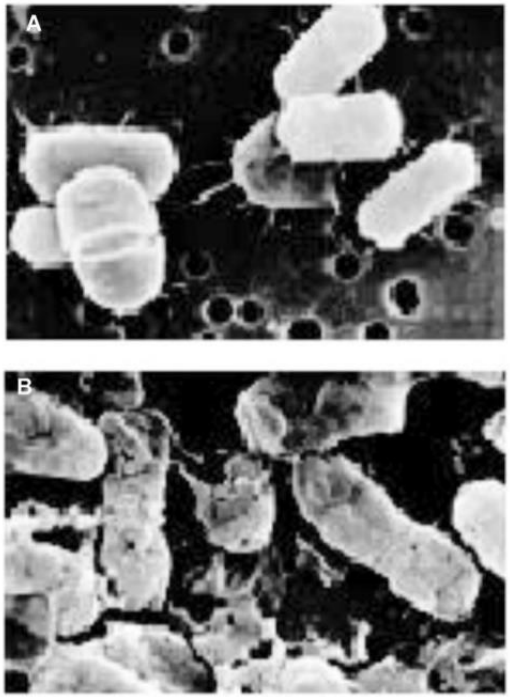
Clostridium thermosaccharolyticum

Clostridium tyrobutyricum

Micrococcus spp.

Sarcina spp.

Adaptado de Silva, S. G. S. 2019. Tese.

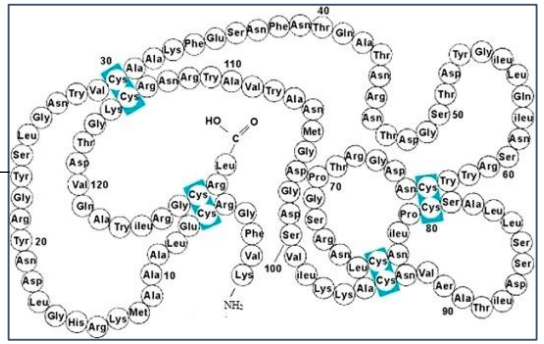


AMINLARI et al., 2014. DOI: 10.1111/1750-3841.12460

Lisozima

Aplicações

- Indústria alimentícia
- Adjunto em suplemento alimentar animal
- Indústria de cosméticos
- Indústria farmacêutica



Obrigada!

Marília

Laís

Giovanna

Aline