To Be or Not To Be Fitness Costs of Antibiotic Resistance

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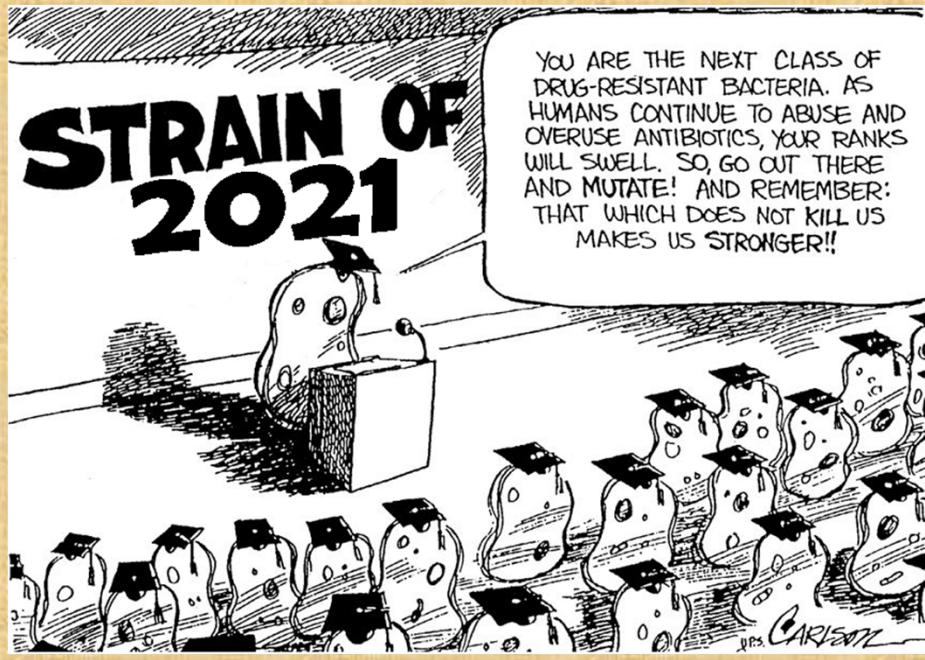
Outline

- Fitness costs and methods for analysis
- Antibiotic resistance incurs fitness costs
- Factors influencing fitness costs
- Strategies to compensate for fitness costs
- Applications of fitness costs studies
- Summary



FITNESS COSTS AND METHODS FOR ANALYSIS

Methods for Analysis

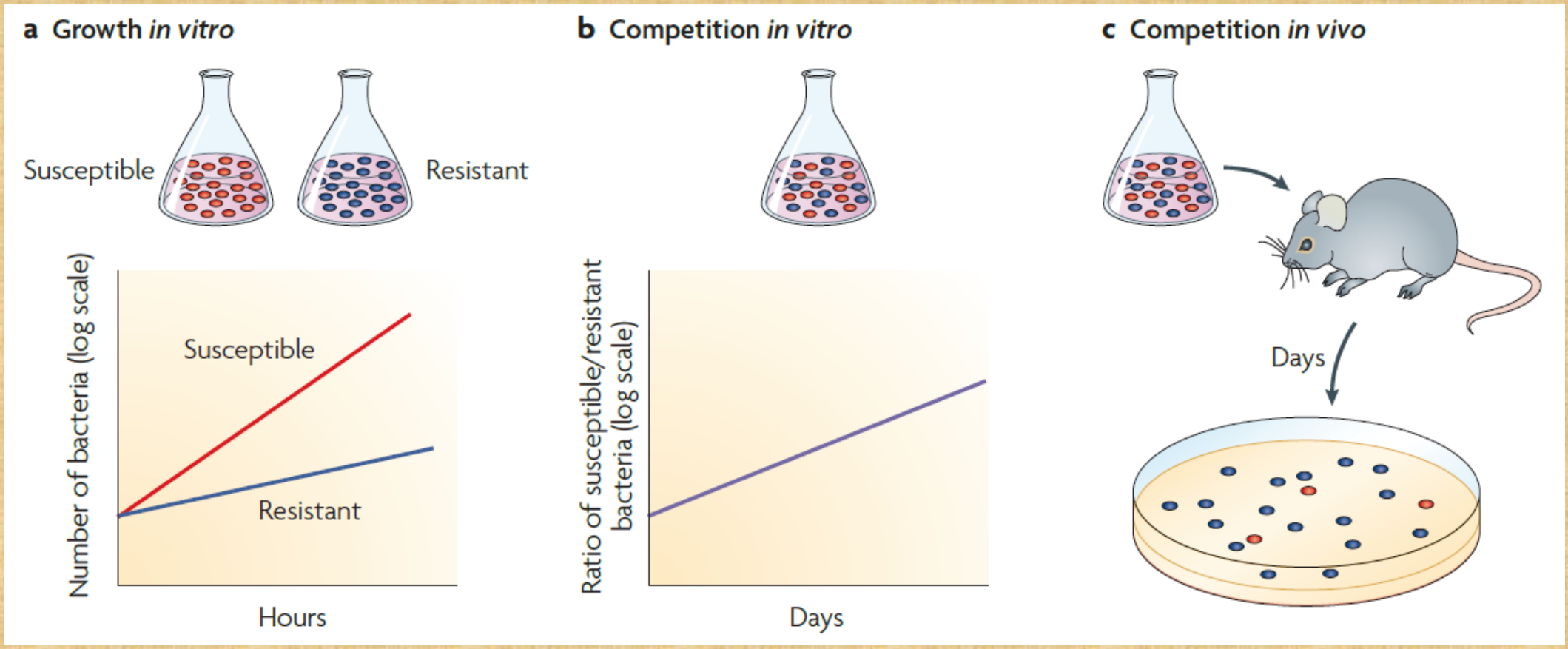
Ideal: should be measured in defined group of infected patients

In real life: controlled laboratory experiments

- Isogenic strains
- Amenable to genetic manipulation
- The model system could be evaluated with different fitness assays

(Hughes & Brandis, 2013)

Parameters

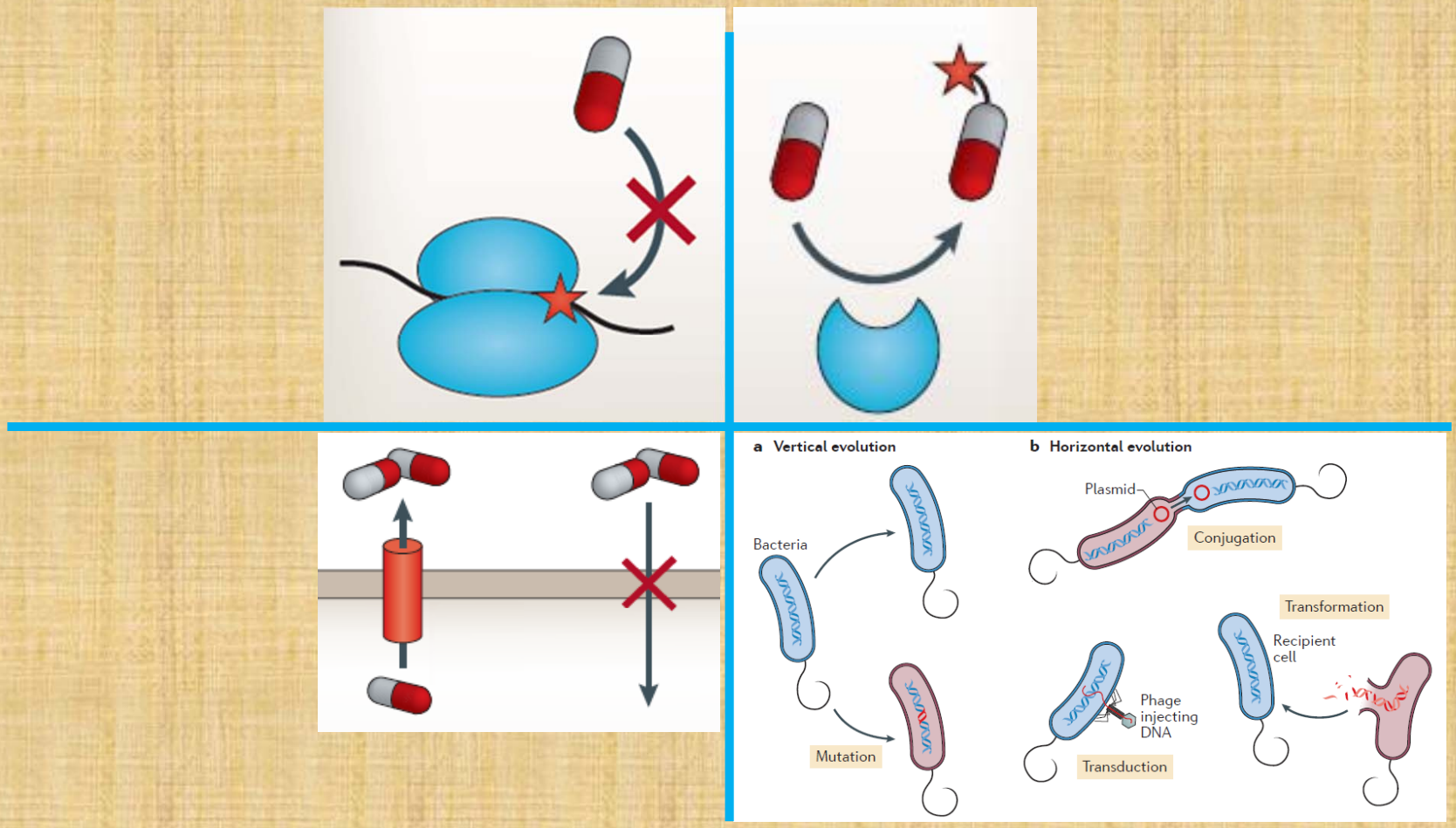


(Andersson & Hughes, 2010)

- Parameters depending on the organism and characteristics: growth rate, biofilm formation, virulence…

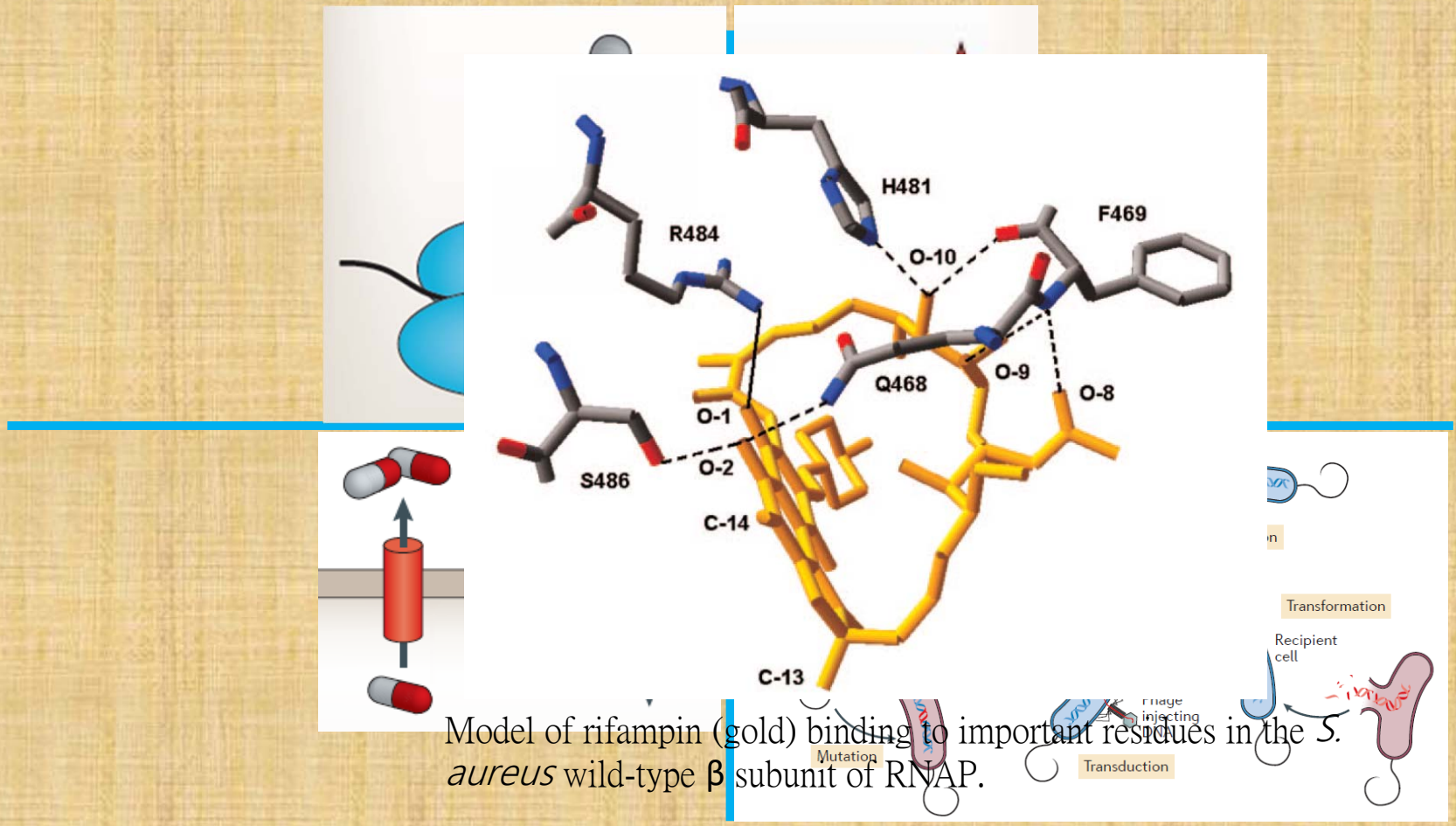
ANTIBIOTIC RESISTANCE INCURS FITNESS COSTS

Antibiotic Resistance Incurs Fitness Costs



(Hughes & Andersson, 2015; Sommer *et al*., 2017)

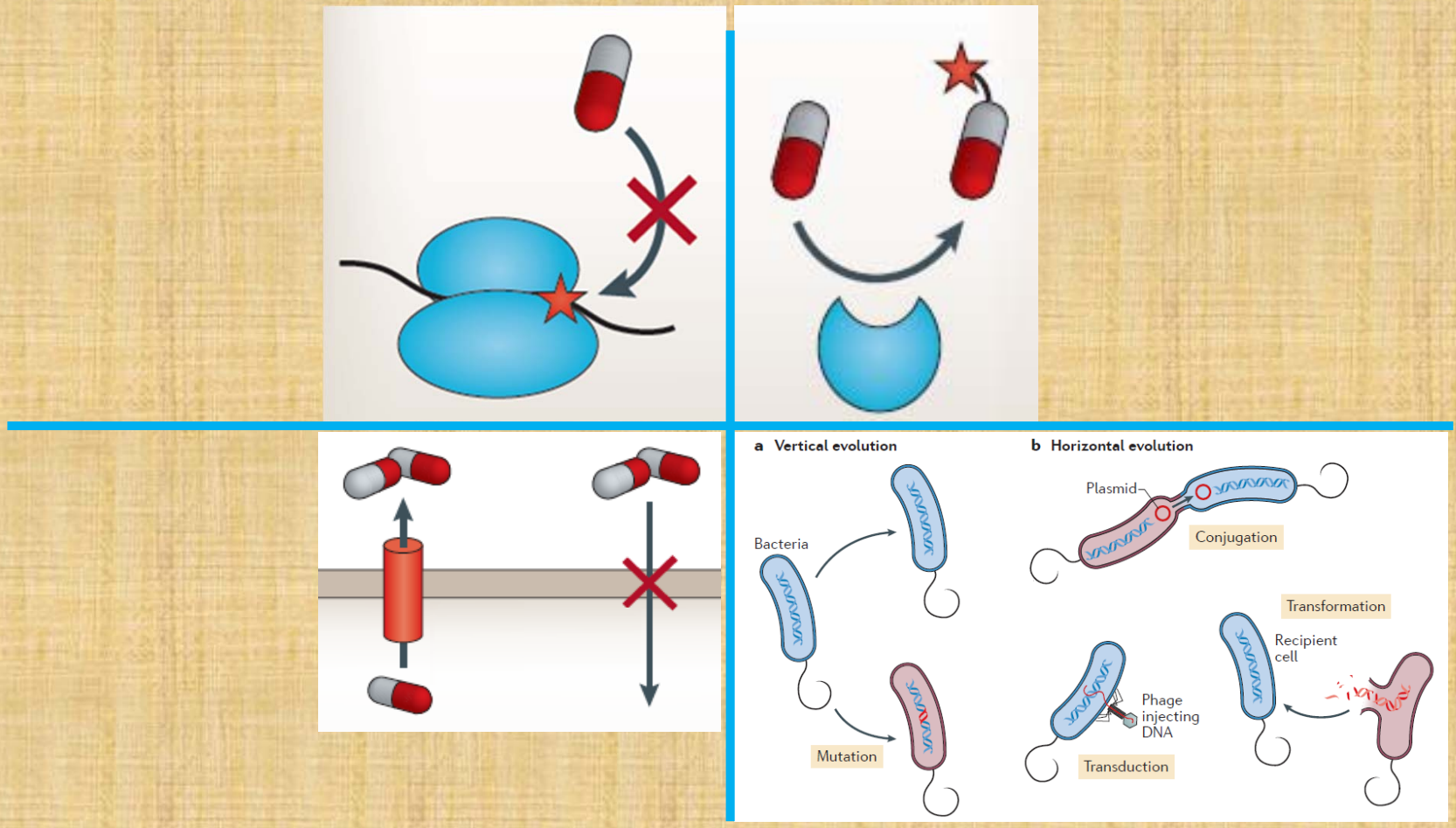
Antibiotic Resistance Incurs Fitness Costs



Model of rifampin (gold) binding to important residues in the *S. aureus* wild-type β subunit of RNAP.

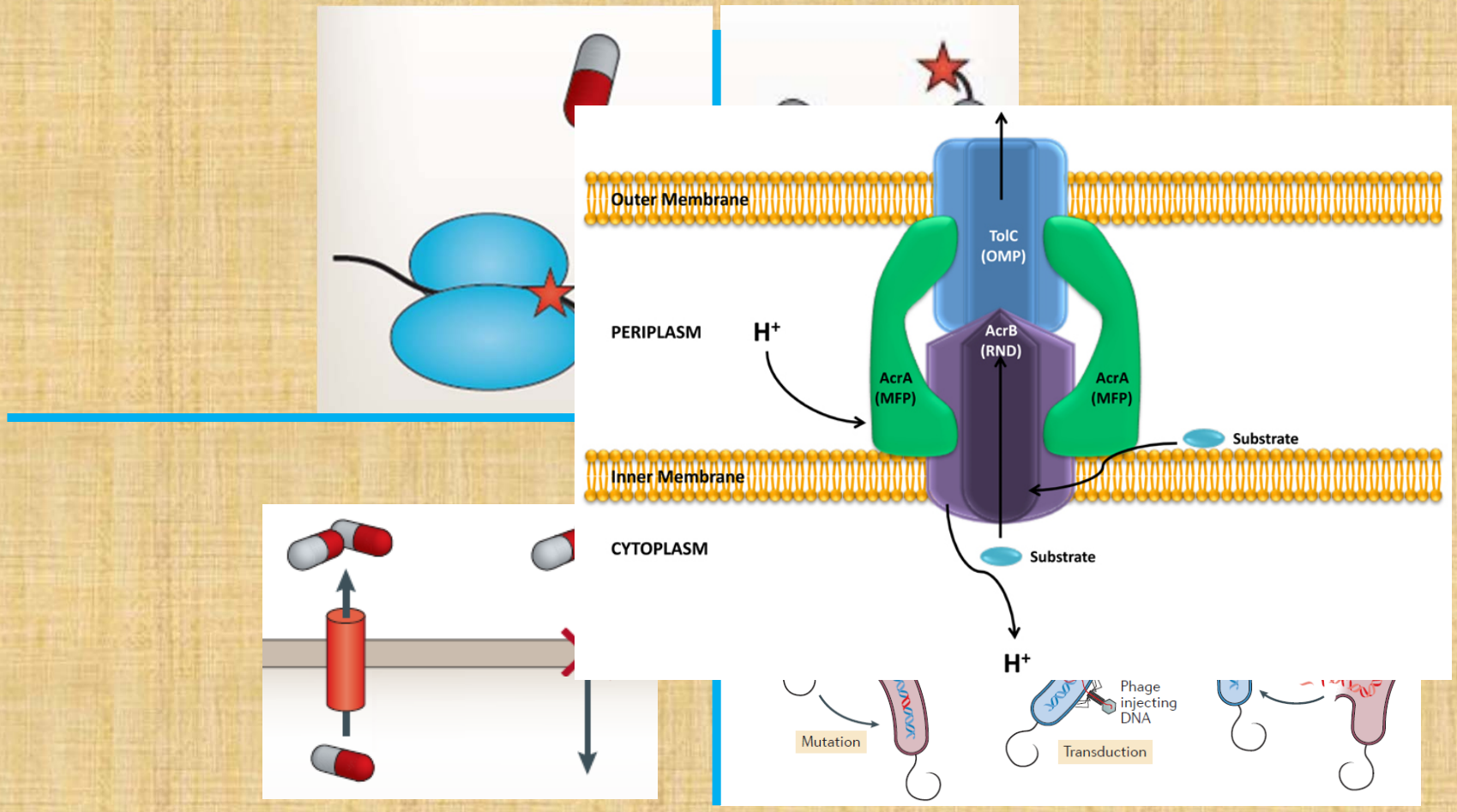
(Hughes & Andersson, 2015; Sommer *et al.*, 2017; O'Neill *et al.*, 2006)

Antibiotic Resistance Incurs Fitness Costs



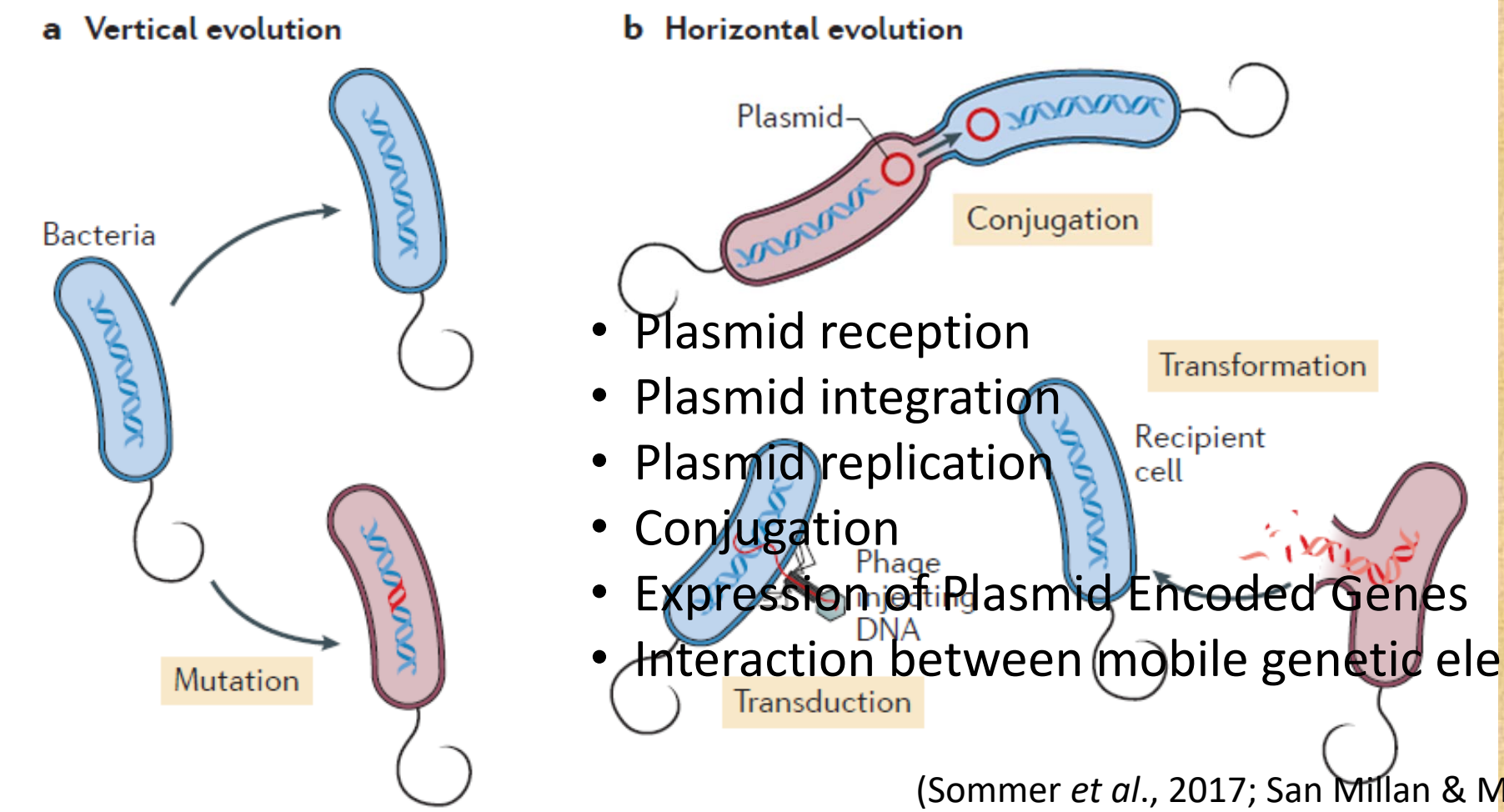
(Hughes & Andersson, 2015; Sommer *et al*., 2017)

Antibiotic Resistance Incurs Fitness Costs



(Alvarez-Ortega *et al*., 2013; Hughes & Andersson, 2015; Sommer *et al*., 2017)

Antibiotic Resistance Incurs Fitness Costs



- Plasmid reception
- Plasmid integration
- Plasmid replication
- Conjugation
- Expression of Plasmid Encoded Genes
- Interaction between mobile genetic elements

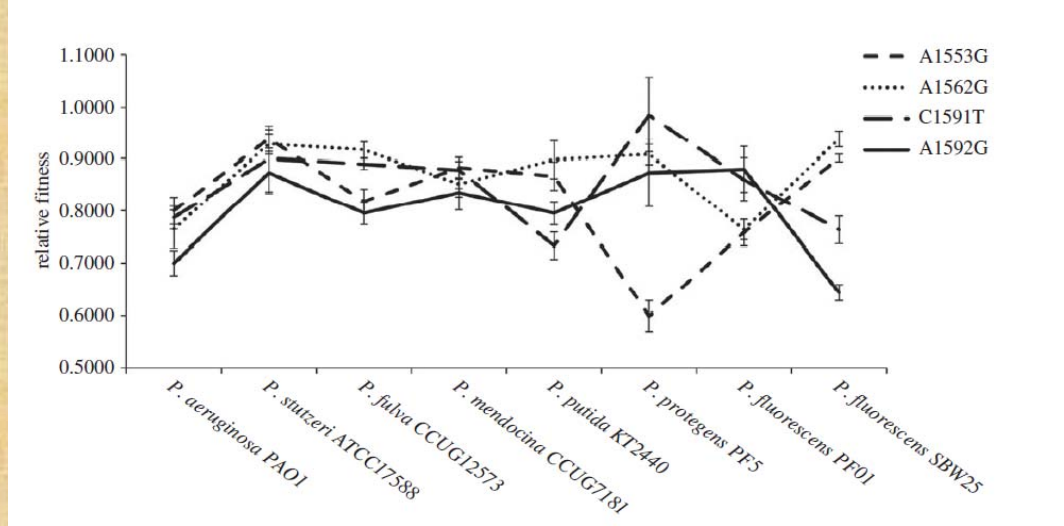
(Sommer *et al*., 2017; San Millan & Maclean, 2017)

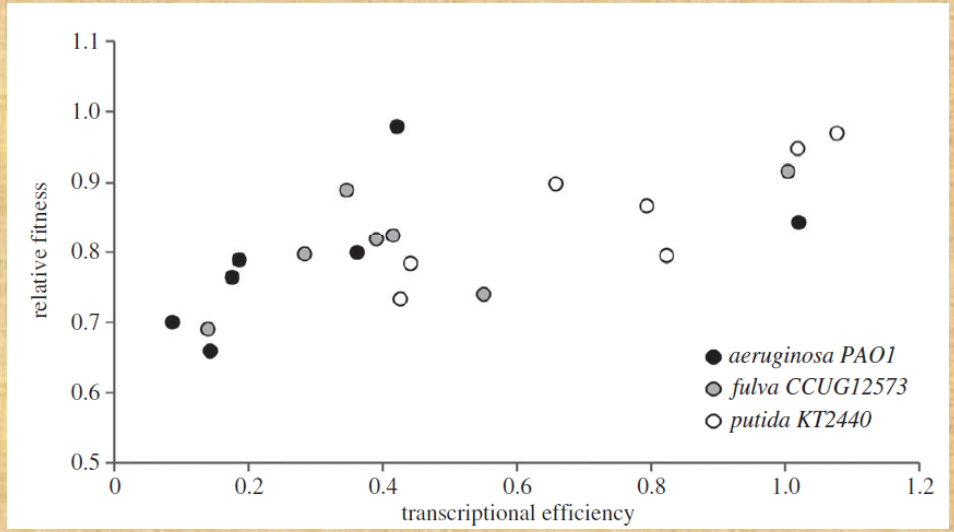
FACTORS INFLUENCING FITNESS COSTS

Factors Influencing Fitness Costs

***In vitro* and *in vivo* studies**

- Epistasis





(Andersson & Hughes, 2010; Vogwills *et al*., 2016)

Mutants that have low fitness cost and high level of antibiotic resistance are more likely to be fixed in the populations.

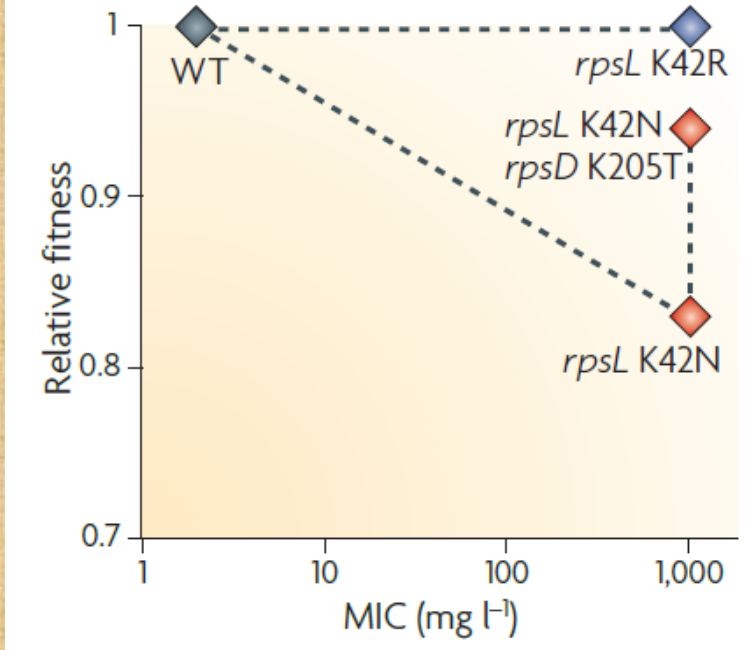
(Andersson & Hughes, 2010)

STRATEGIES TO COMPENSATE FOR FITNESS COSTS

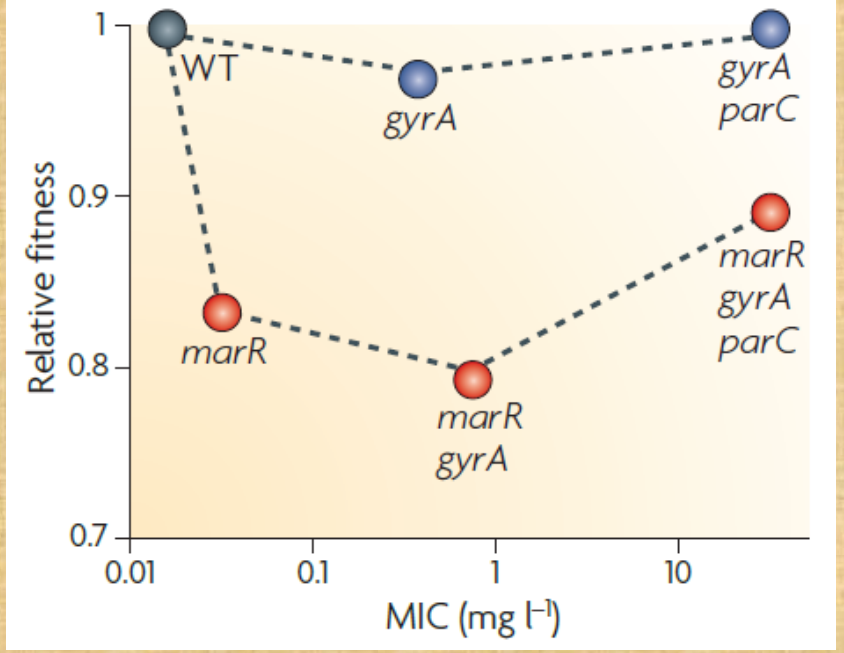
Strategies to Compensate for Fitness Costs

- Secondary mutation
- Gene overexpression
- Metabolic compensation

Secondary Mutation



Resistance to streptomycin in *Salmonella enterica*



Resistance to fluoroquinolones in *Escherichia coli*

(Andersson & Hughes, 2010)

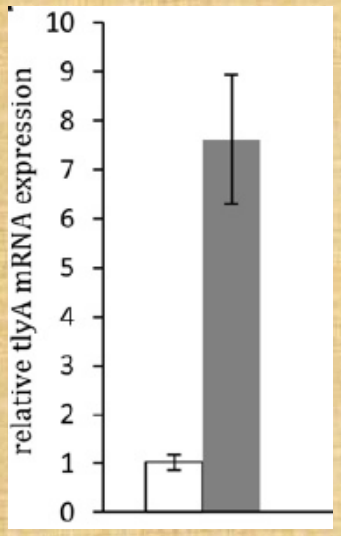
Gene Overexpression

- Capreomycin-resistant *Mycobacterium* spp.

  Loss-of-function mutation of rRNA methylase TlyA or point mutations in 16S rRNA

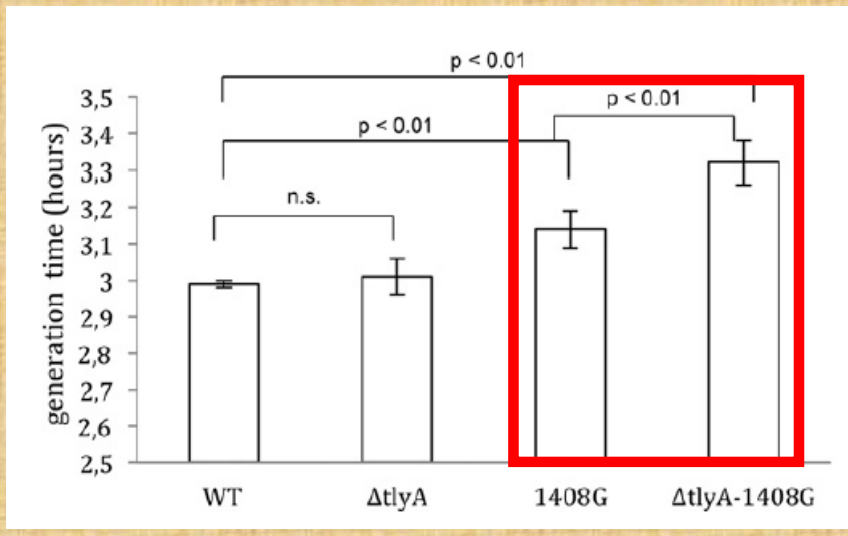
- One of the common mutations: A1408G in 16S rRNA

  Overexpression of *tylA*



WT A1408G

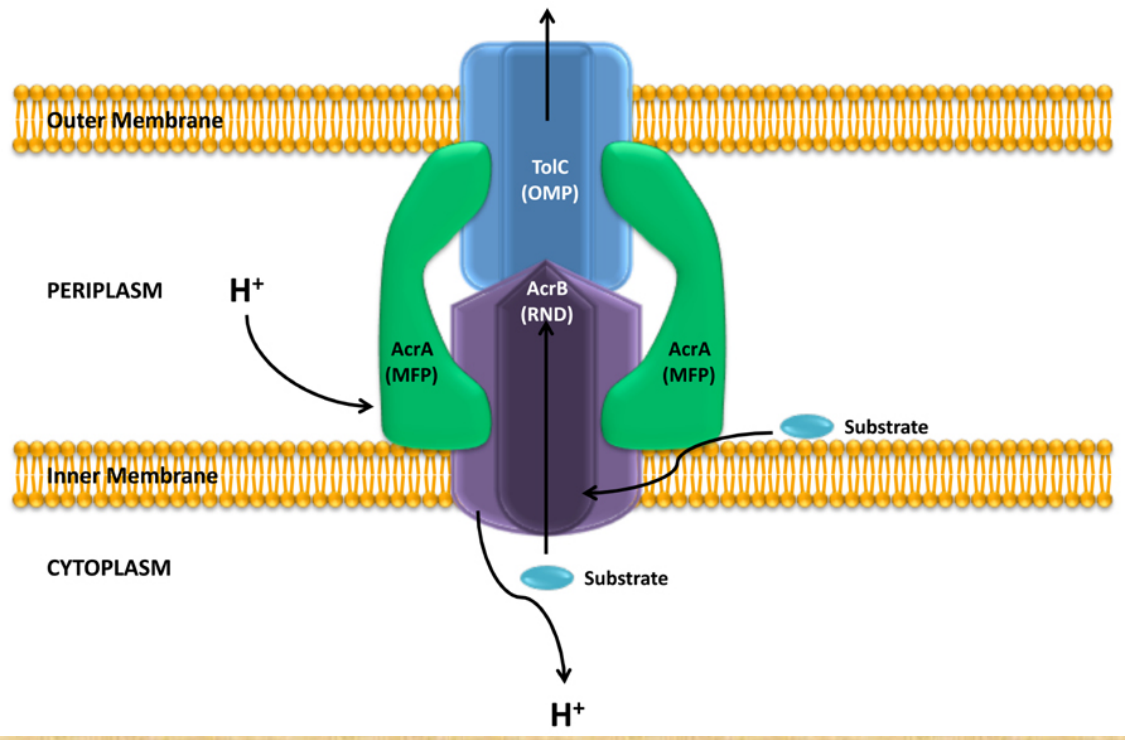
Mycobacterium smegmatis

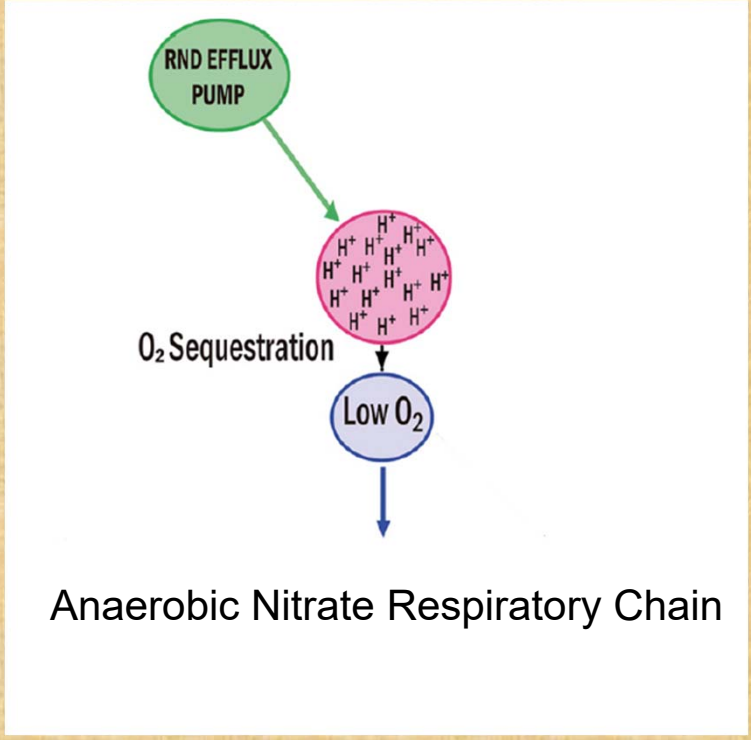


(Freihofer *et al.*, 2016)

Metabolic Compensation

Antibiotic resistant *Pseudomonas aeruginosa*





(Alvarez-Ortega *et al*., 2013; Olivares *et al*., 2014; Olivares *et al*., 2017)

POTENTIAL APPLICATIONS OF FITNESS COSTS STUDIES

Potential Applications of Fitness Costs Studies

- Predict antibiotic resistance
- Develop combination antibiotic therapies and novel antibiotics

nature microbiology

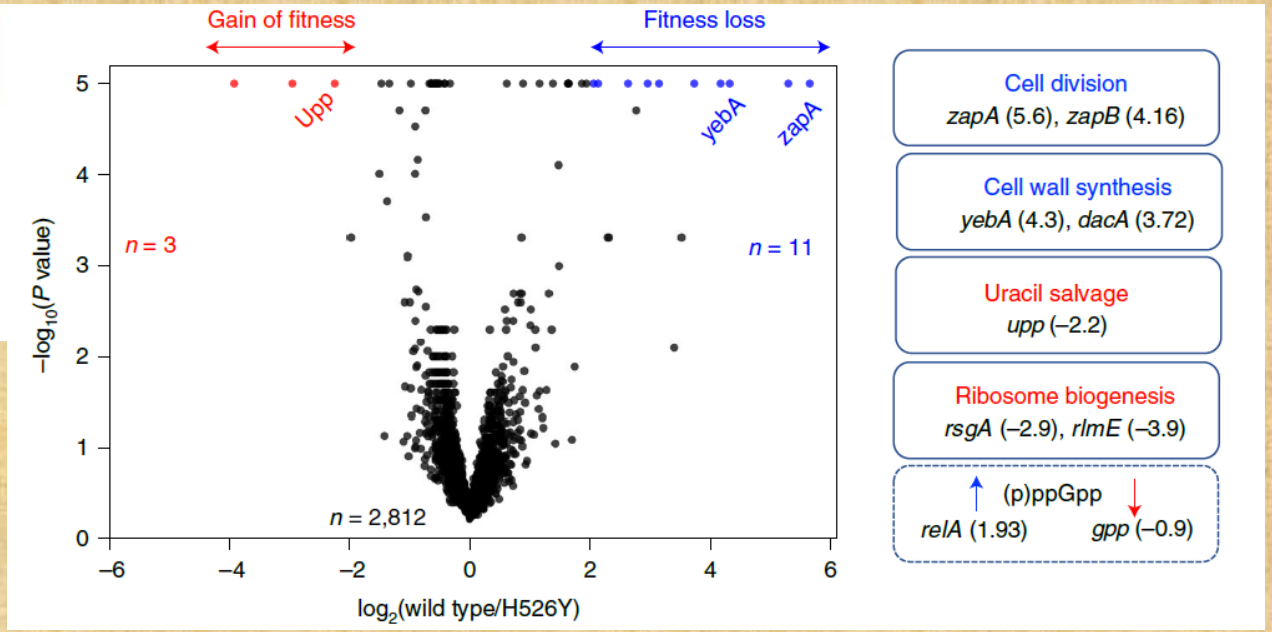
ARTICLES

https://doi.org/10.1038/s41564-021-00973-1

Check for updates

Analysing the fitness cost of antibiotic resistance to identify targets for combination antimicrobials

Aviram Rasouly[1,2,5], Yosef Shamovsky[1,5], Vitaly Epshtein[1], Kayan Tam[3], Nikita Vasilyev[1], Zhitai Hao[1], Giulio Quarta[4], Bibhusita Pani[1], Lingting Li[1], Carmen Vallin[1], Ilya Shamovsky[1], Shankarling Krishnamurthy[1], Aaron Shtilerman[1], Samantha Vantine[1], Victor J. Torres[3] and Evgeny Nudler[1,2]



(Rasouly *et al.*, 2021)

Summary

- Antibiotic resistance usually entailed with fitness cost.
- Fitness cost could be affected by different factors.
- Compensation of fitness cost leads to emergence of low-cost or no-cost antibiotic resistant strains which have higher risk of spread and further resistance evolution.
- Fitness cost study helps to predict antibiotic resistance and development of antibiotics.

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THANK YOU!