Persister cell—dormancy and tolerance to antibiotics

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Dec. 5 2013
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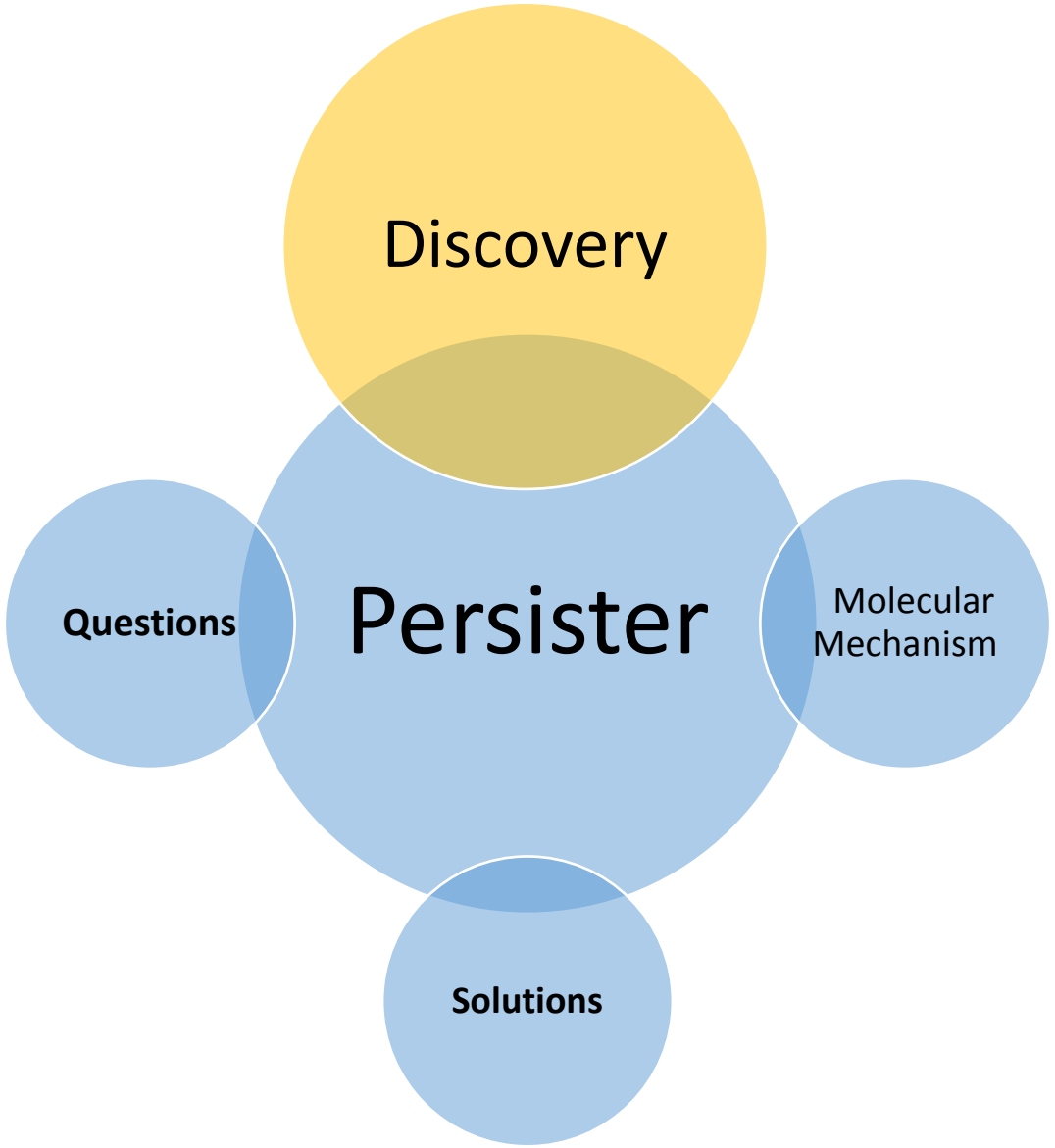
Once upon a time:

“The time has come to close the book on infectious diseases”

William Stewart, the Surgeon General of USA, said in 1967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The Discovery of Persister

- Persisters were described by Joseph Bigger in 1944 in one of the first studies on the mechanism of penicillin action using *Staphylococcus*.

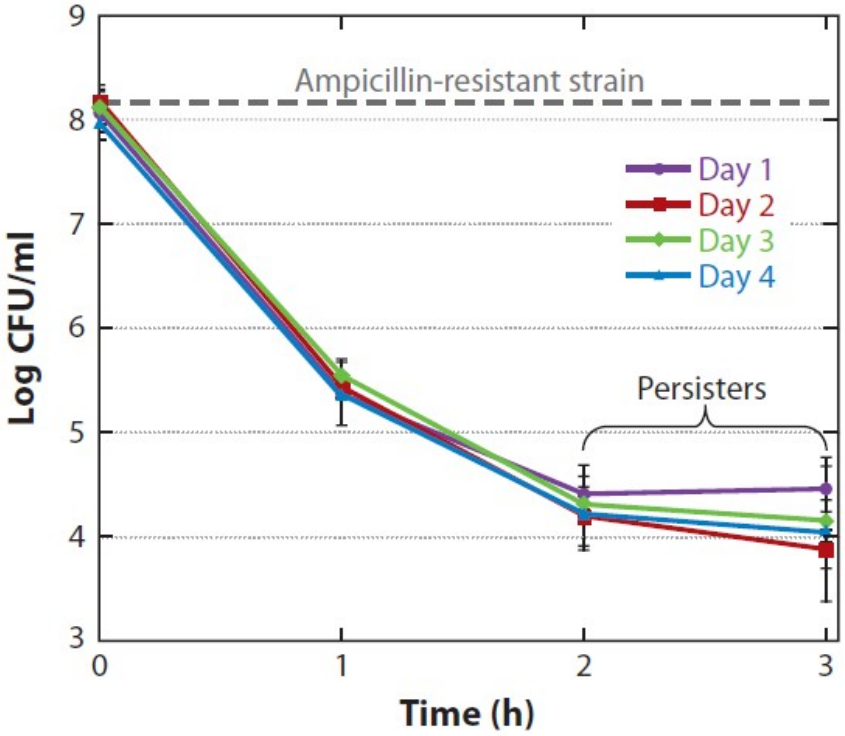


Figure 1, The repeat of Bigger's experiment

Kim Lewis, Annu. Rev. Microbiol. 2010. 64:357–72

What's persister cells

- "a small new subpopulation"
- "surviving colonies"
- "regrown"
- "not simply antibiotic-resistant mutants"

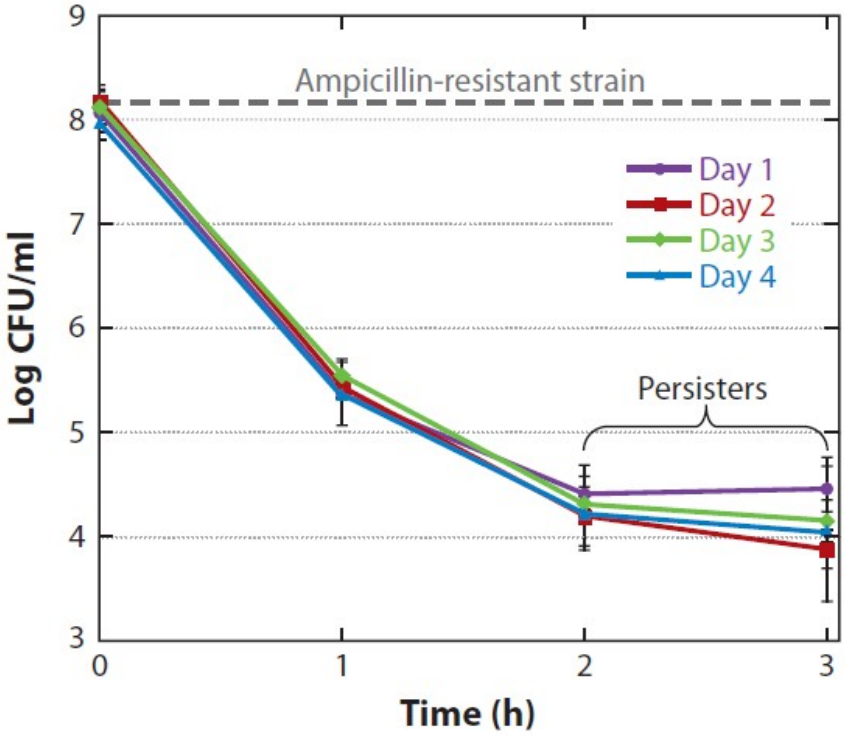


Figure 1, The repeat of Bigger's experiment

Kim Lewis, Annu. Rev. Microbiol. 2010. 64:357–72

Re-discovery

- A half century gap
- An abnormal high antibiotic resistance from biofilm
- The high resistance depends on presence of a small “super-resistant” cell fraction
- The “super-resistant” was confirmed to be the tolerance from persisters.
- Different phenotype in tolerance to different antibiotics

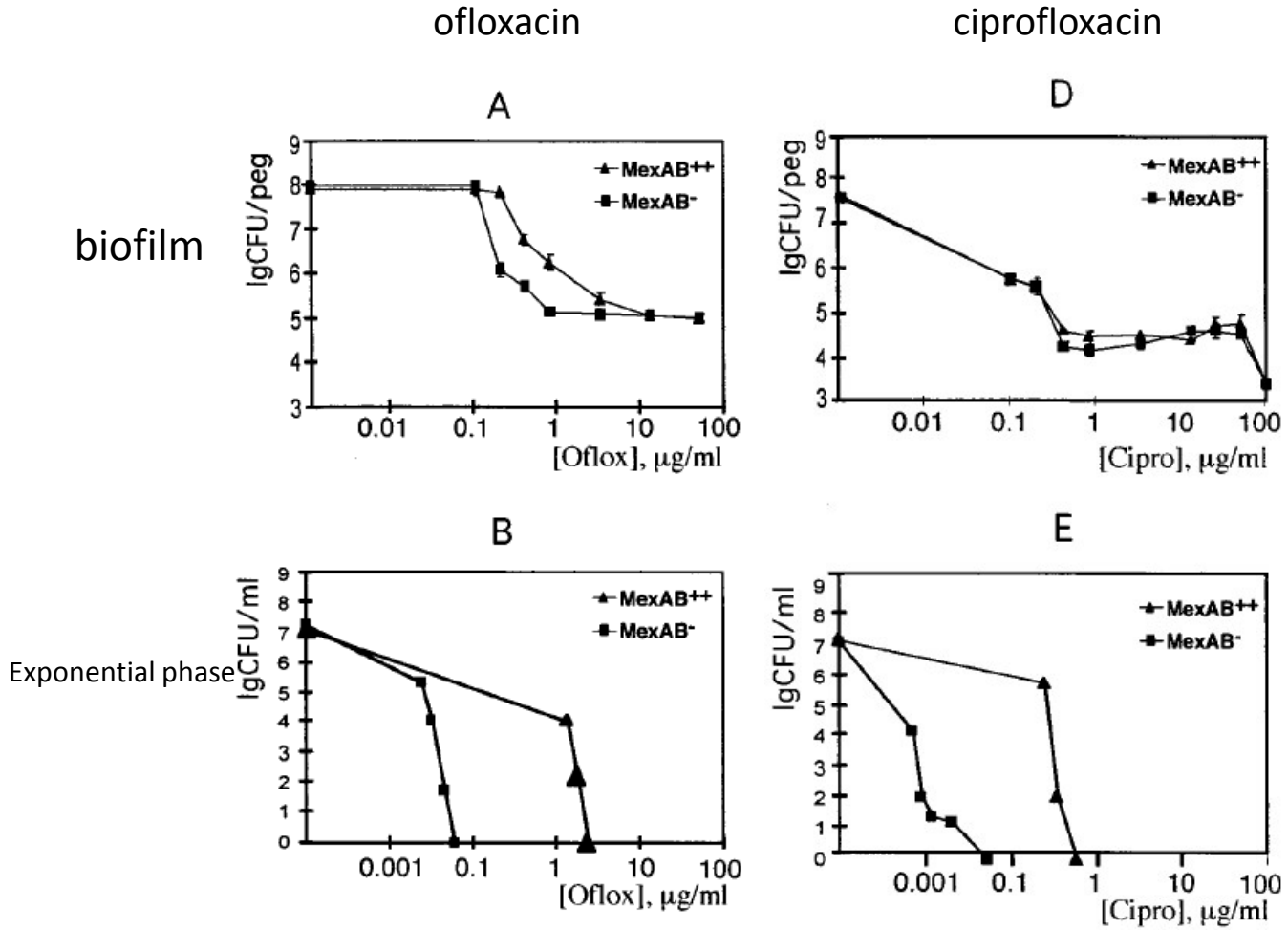


Figure 2: The abnormal high antibiotic resistance from biofilm

ALEXEI B, A Dose-Response Study of Antibiotic Resistance in *Pseudomonas aeruginosa* Biofilms (2000), DOI: 10.1128

Tolerance VS Resistance

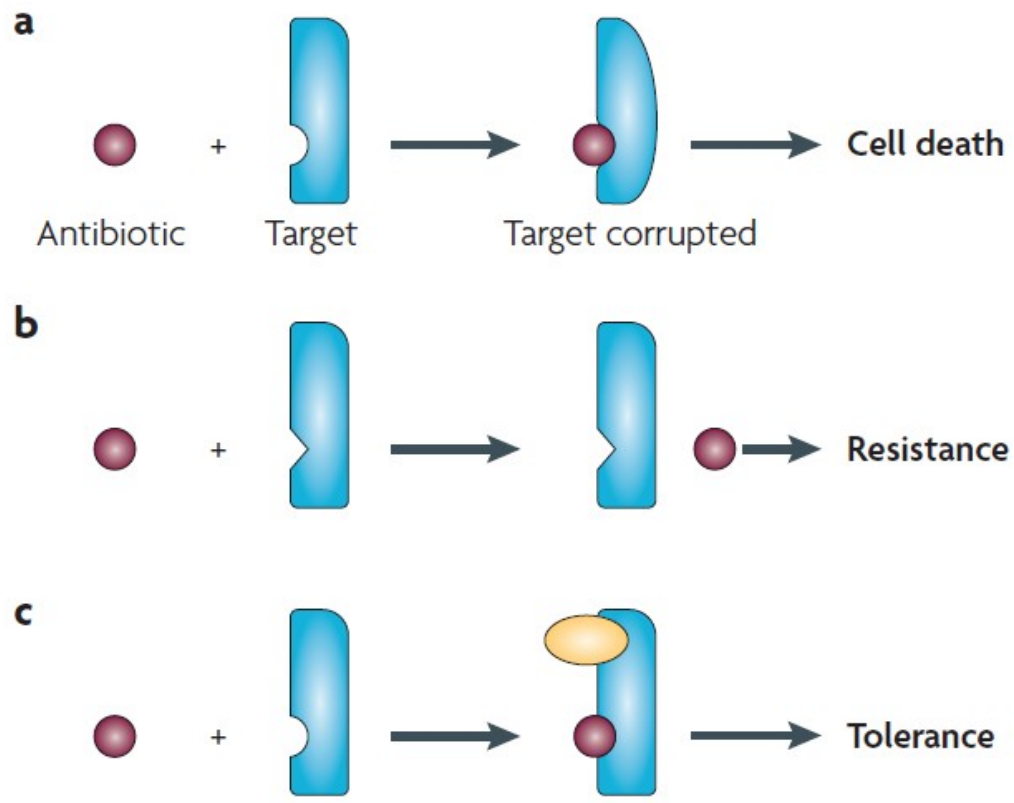


Figure 3. Tolerance VS Resistance

Kim Lewis, nature 2007, doi:10.1038

Resistance is to prevent the antibiotic from binding to its target

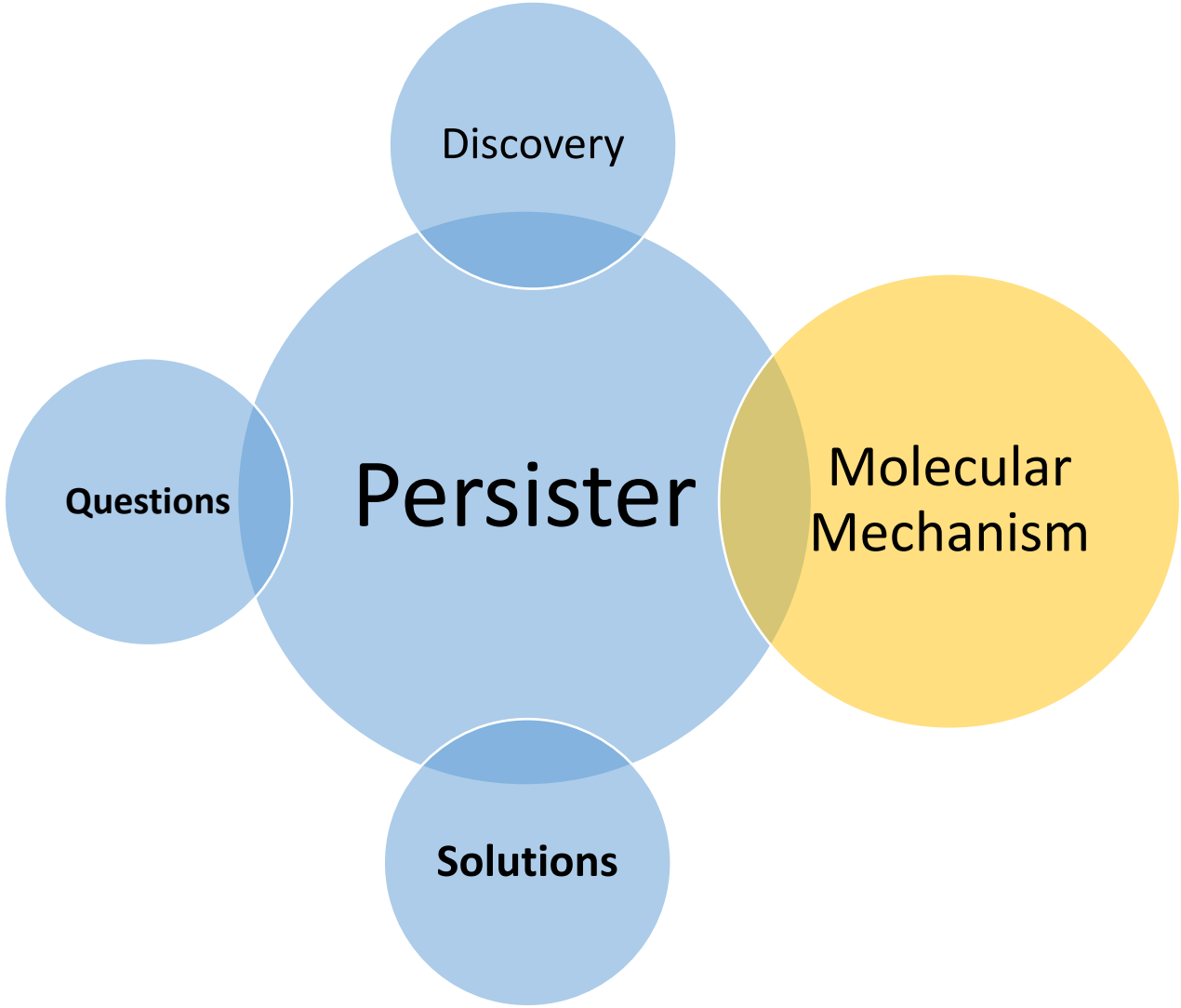
Genetic mutations

Tolerance is preventing target corruption by a bactericidal agent through the blocking of the antibiotic target

Physiology changes

Link to diseases

- cystic fibrosis (CF) : high persister levels in isolation from patients (2003)
- Tuberculosis: 1 in every 3 people carry latent; persisters are equivalent to the latent form of the pathogen (2002)
- Speculated existing in most chronic infections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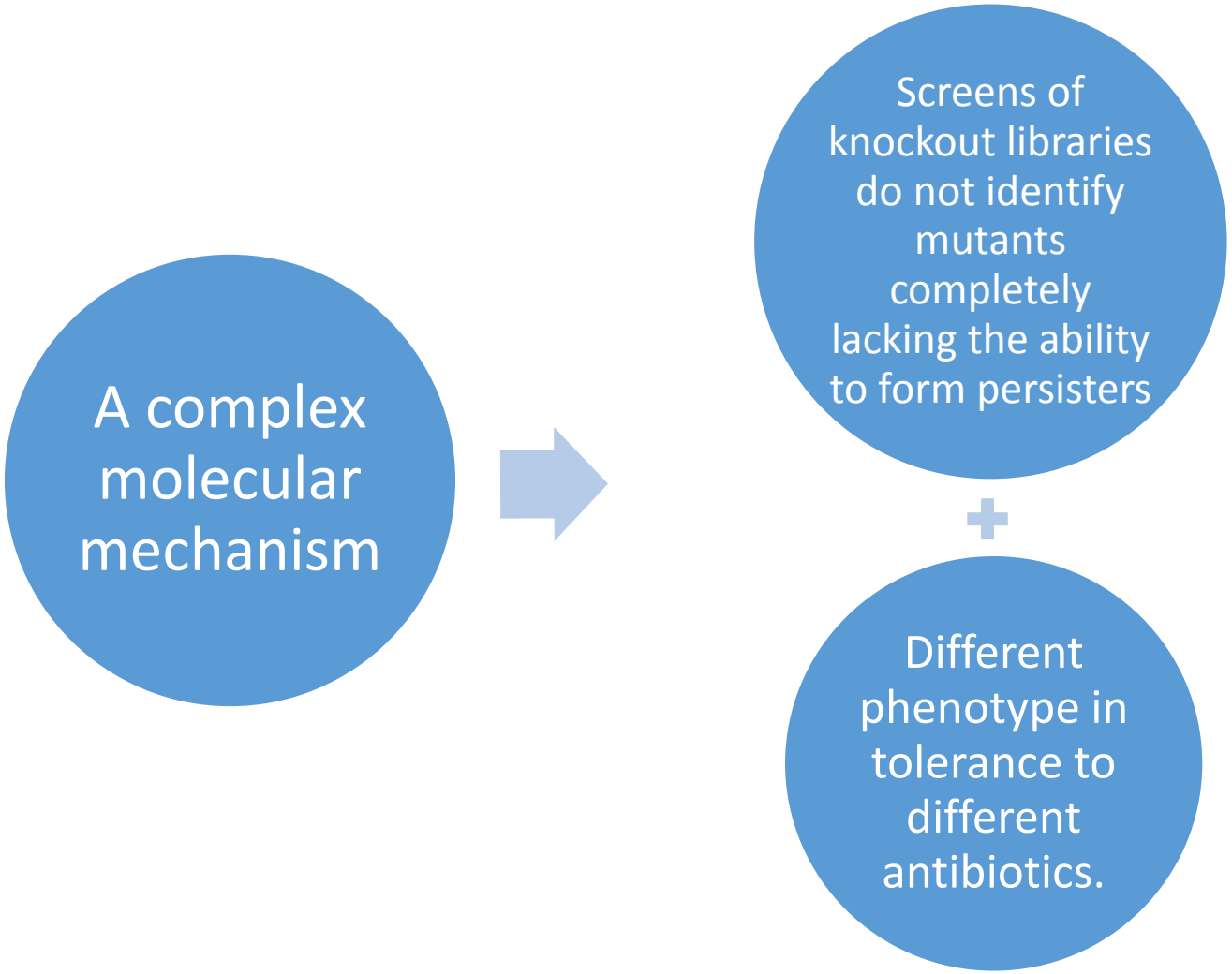
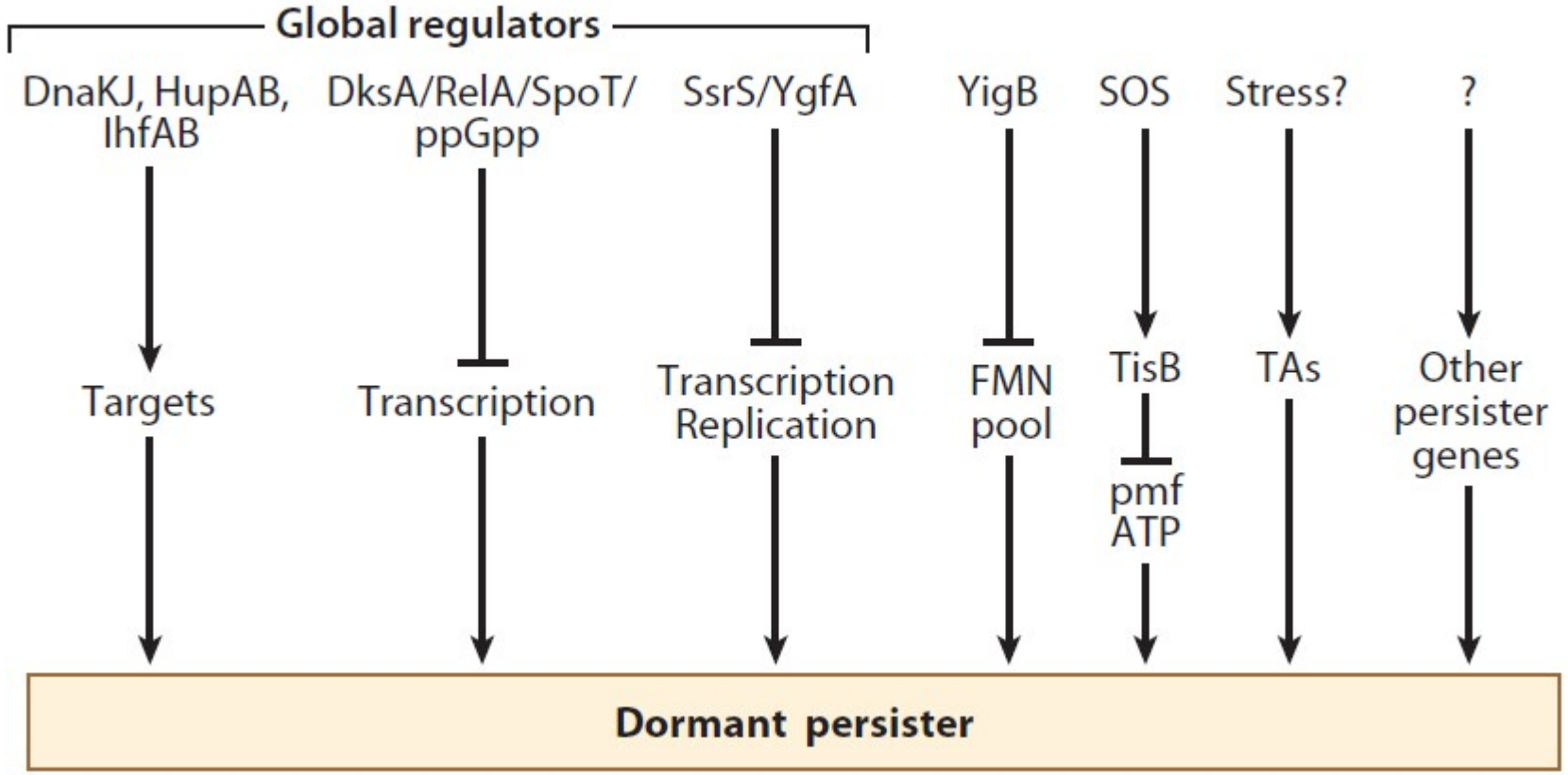


Summary of related genes



TA modules

- toxin–antitoxin (TA) modules
- The toxin always be a stable protein, the antitoxin usually be a unstable molecular, has a toxin-inhibiting domain, introduce the proteolysis of toxin.
- Important in bacterial stress physiology and might form the basis of multidrug resistance.
- eg. *MazEF*

TA modules in persister formation

- HipAB: The first identified TA module in persister formate Mechanism (1987), which encodes a toxin (HipA) increased the frequency of persister by 10,00-fold
- HipA is a kinase, inactive, which leads to a block in translation and dormancy
- Other confirmed Toxin–antitoxin: RelBE, MazEF, DinJH, YafQ, YgiU
- In *E. coli*, there are at least 15 TA modules,and more than 80 in *M. tuberculosis*

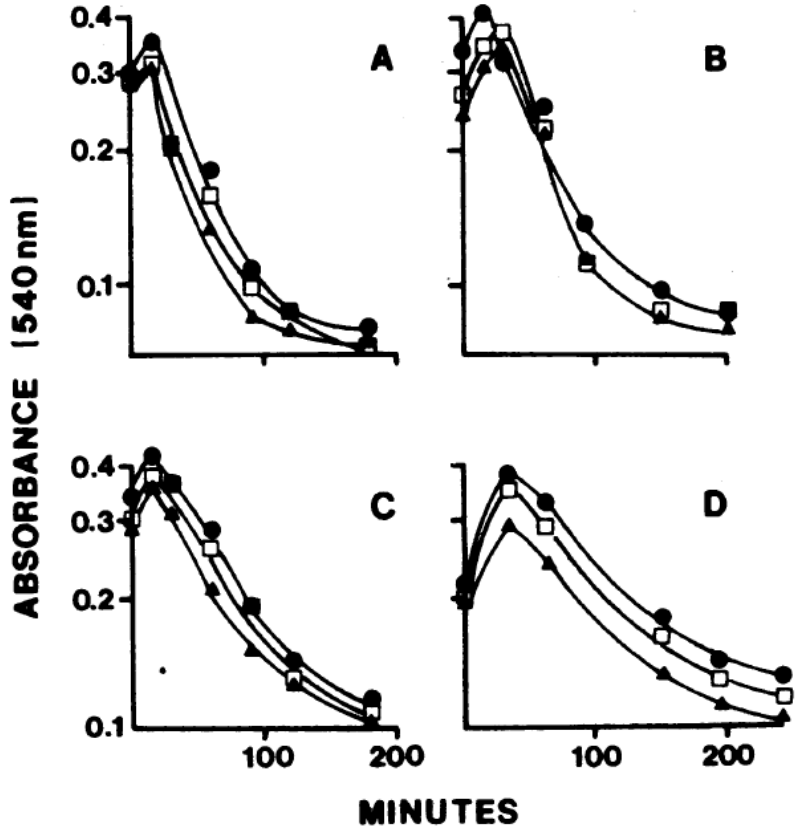


Figure4: the antibiotic tolerance related gene hipA ●hipA+ Δ hipA7- □hipA9-. A to D: ampicillin, Phosphomycin, cycloserine, DAP.

HARRIS S. MOYED, JBC, 1987, p. 768-775

Stochasticity mechanism
—more than deterministic event

- Random stochastic events, multy-genes, Threshold and Distribution

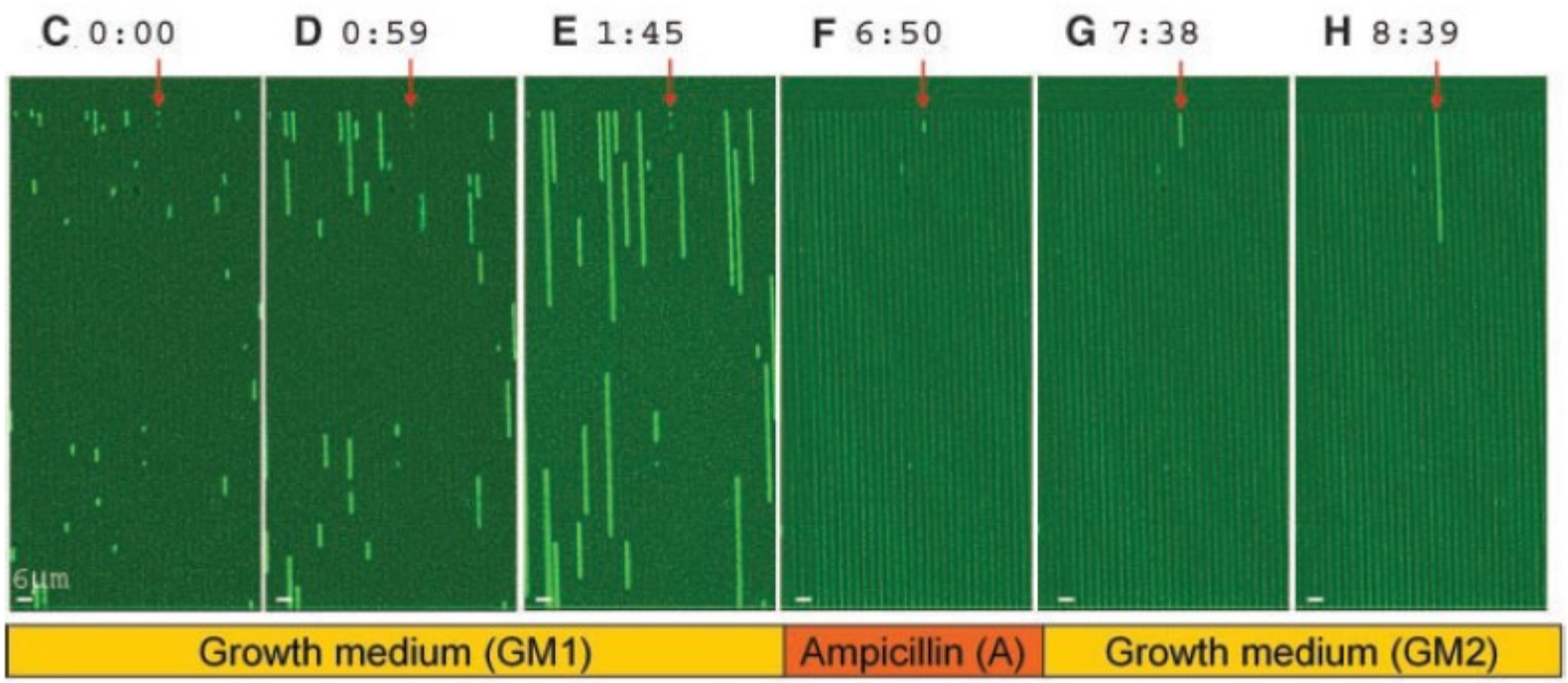
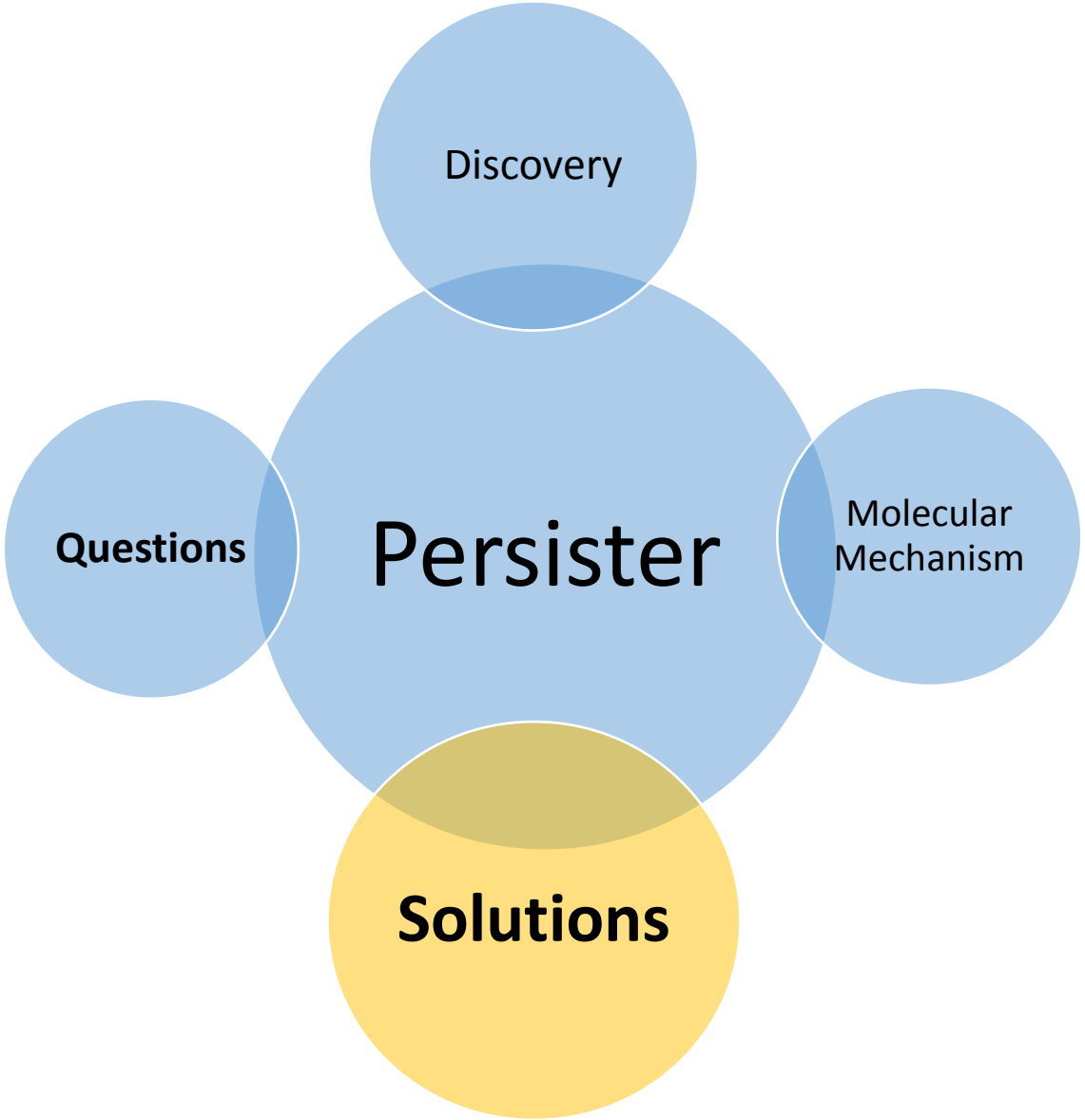


Figure 5. **Stochasticity mechanism** Q. Balaban, *Science* **305**, 1622 (2004); DOI: 10.1126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Solution: traditional methods

- Control the Concentration of antibiotic, enable persisters to resuscitate and start to grow, and a high dose of an antibiotic.
- An anti-persister drug based on combining a conventional antibiotic and an inhibitor of an essential persister protein
- Antiseptics: producing a relatively non-toxic antiseptic

Solution: acyldepsipeptide antibiotic (ADEP4)

- Activate ClpP
- ADEP4-activated ClpP becomes a nonspecific protease and kills persisters by degrading over 400 proteins
- This would help kill persisters with low energy levels
- Eradicated a chronic biofilm (staphylococcus aureus) infection

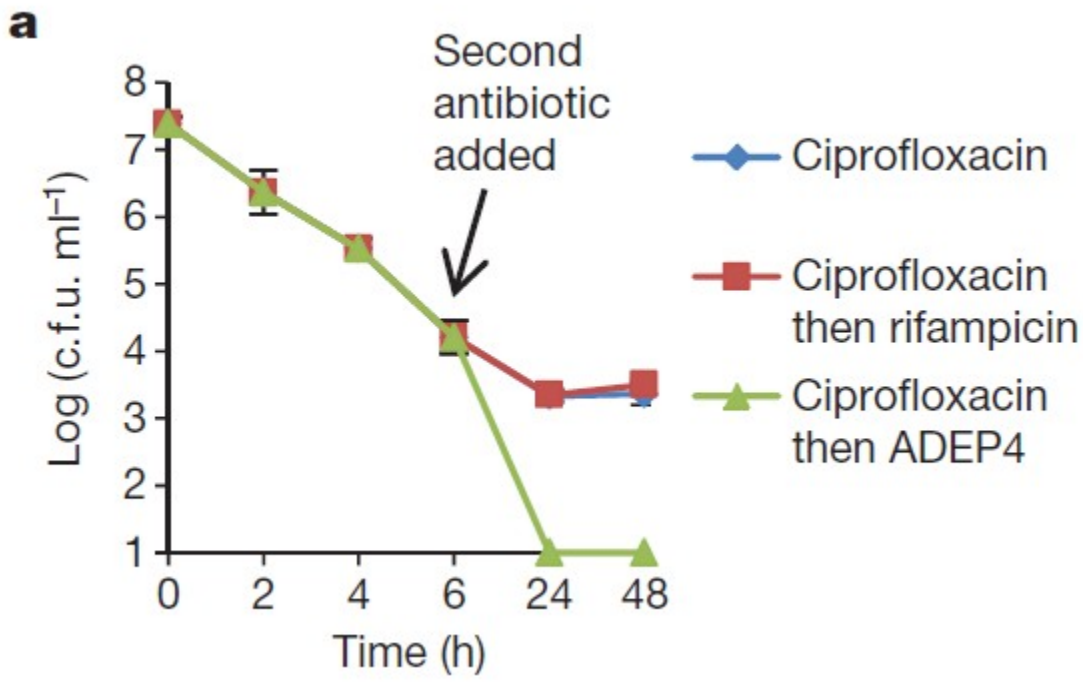
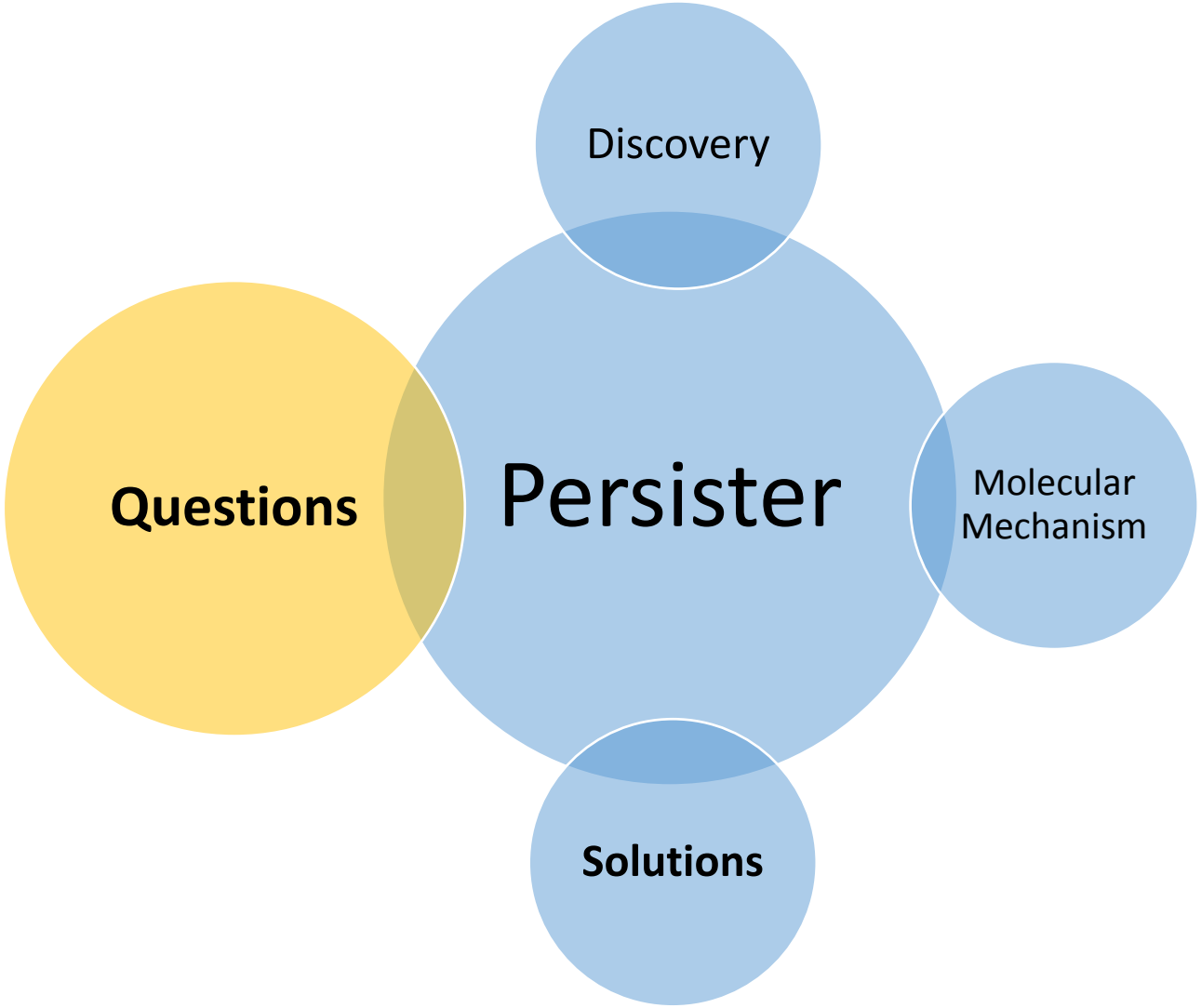


Figure 6: ADEP4-activated ClpP kill persisters

B. P. Conlon, nature (2013), doi:10.1038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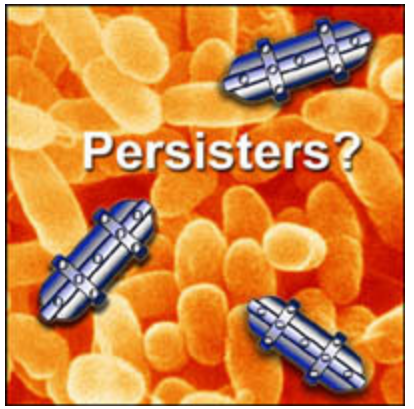
Remaining **QUESTIONS**

- The relatively complete list of Persister genes
- The role of persisters in survival in the external environment
- Resuscitation (basically nothing about its mechanism)
- Persister eradication (effectively methods in clinical)



Thank you