

Using big data to study bacterial infections

Bacterial infections

What are the genetic requirements for bacteria to cause infections?

Pseudomonas aeruginosa

P. aeruginosa Infections

51,000 infections



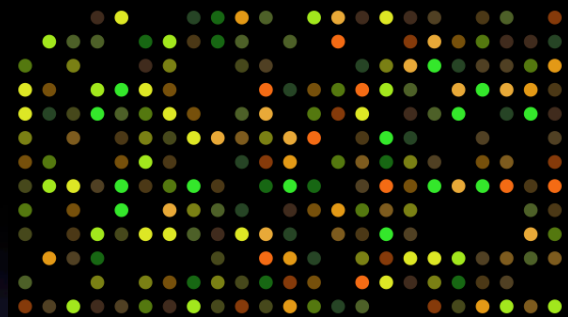
Chronic lung
Chronic wound
Burn wound
Pneumonia
Bloodstream
Urinary tract
Surgical site

6,700 multidrug
resistance
infections (13%)

440 deaths

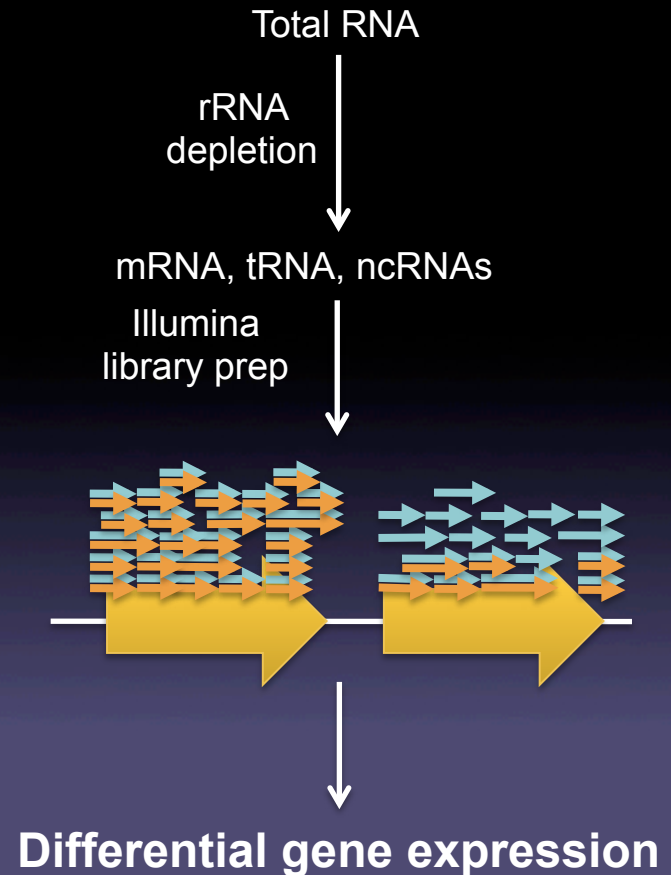
Mulcahy and Lewenza PLoS One 2011

Next-generation sequencing approaches to study bacterial infection

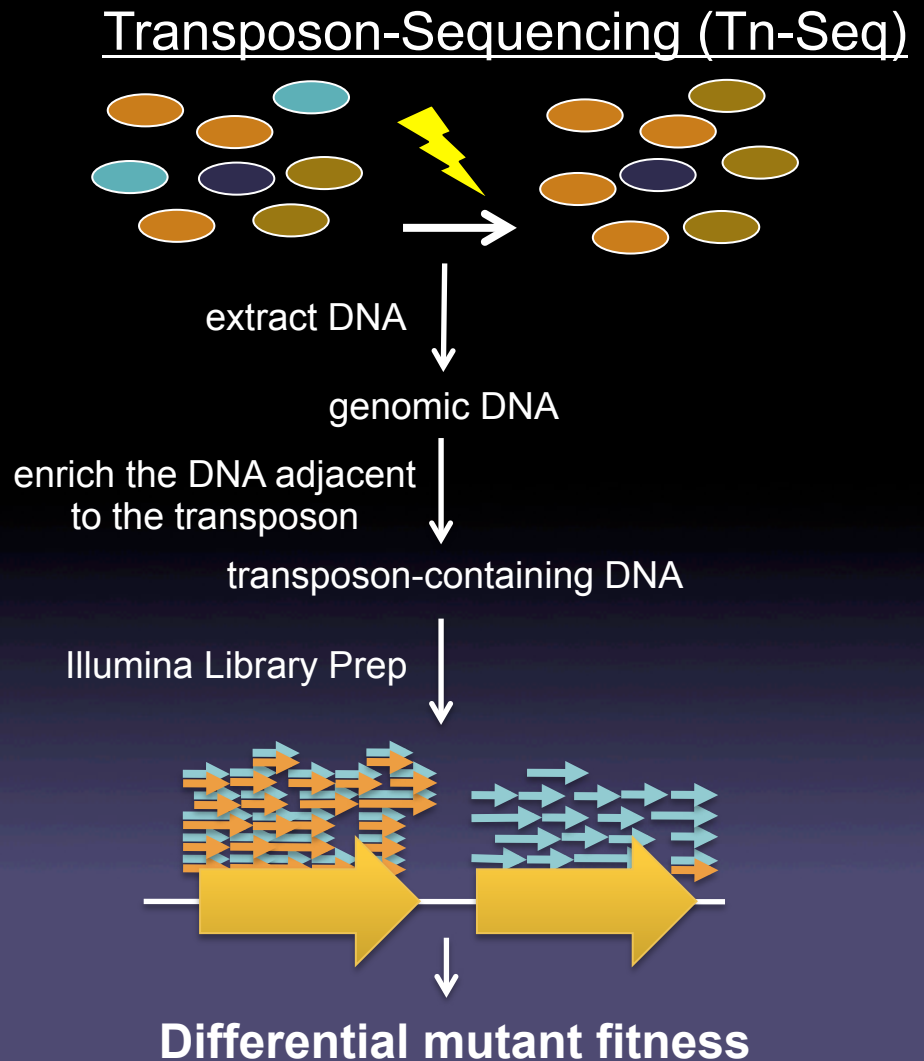
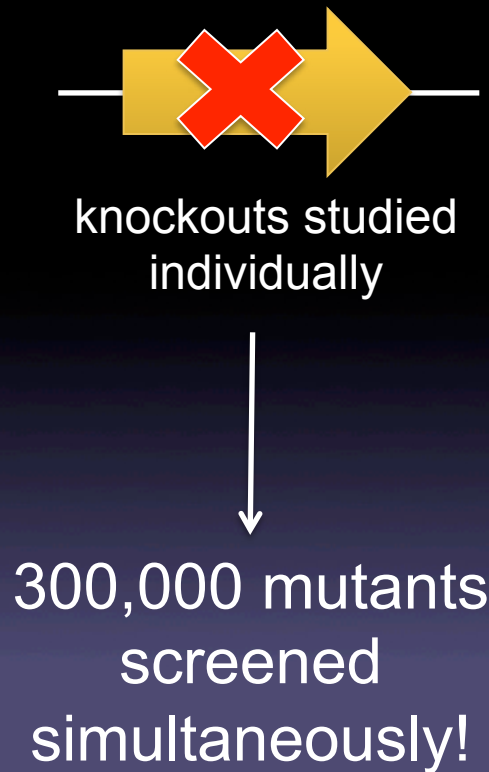


microarrays

RNA-Seq

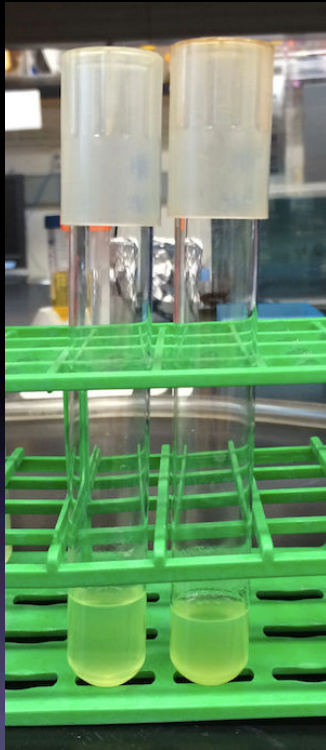


Next-generation sequencing approaches to study bacterial infection



Systems to study bacterial infections

in vitro



Highly-controlled

in vivo



Relevant infection
environment

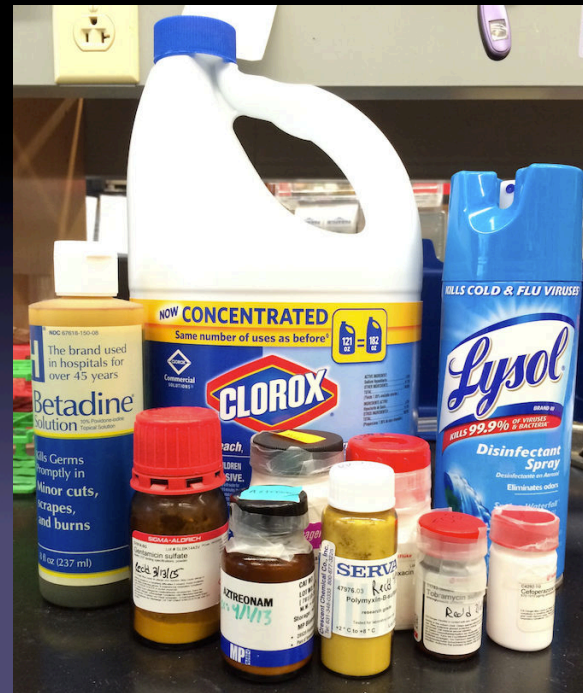
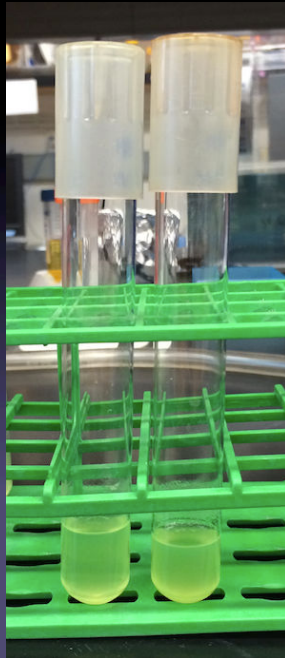
in vitro antimicrobial resistance

How does *P. aeruginosa* respond to antimicrobials?

RNA-seq

Which genes are required for *P. aeruginosa* to grow with antimicrobials?

Tn-seq

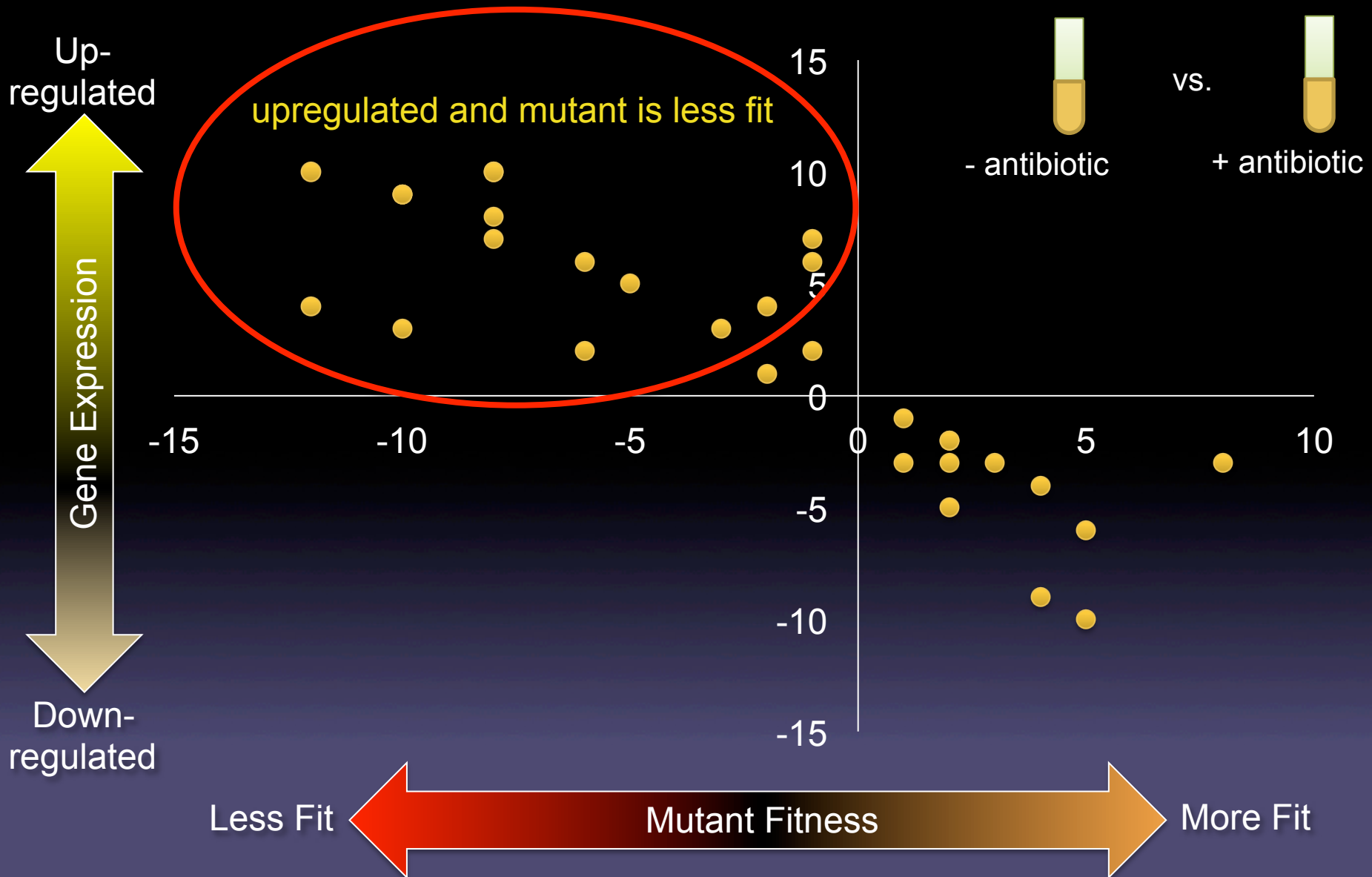


P. aeruginosa drug resistance mechanisms

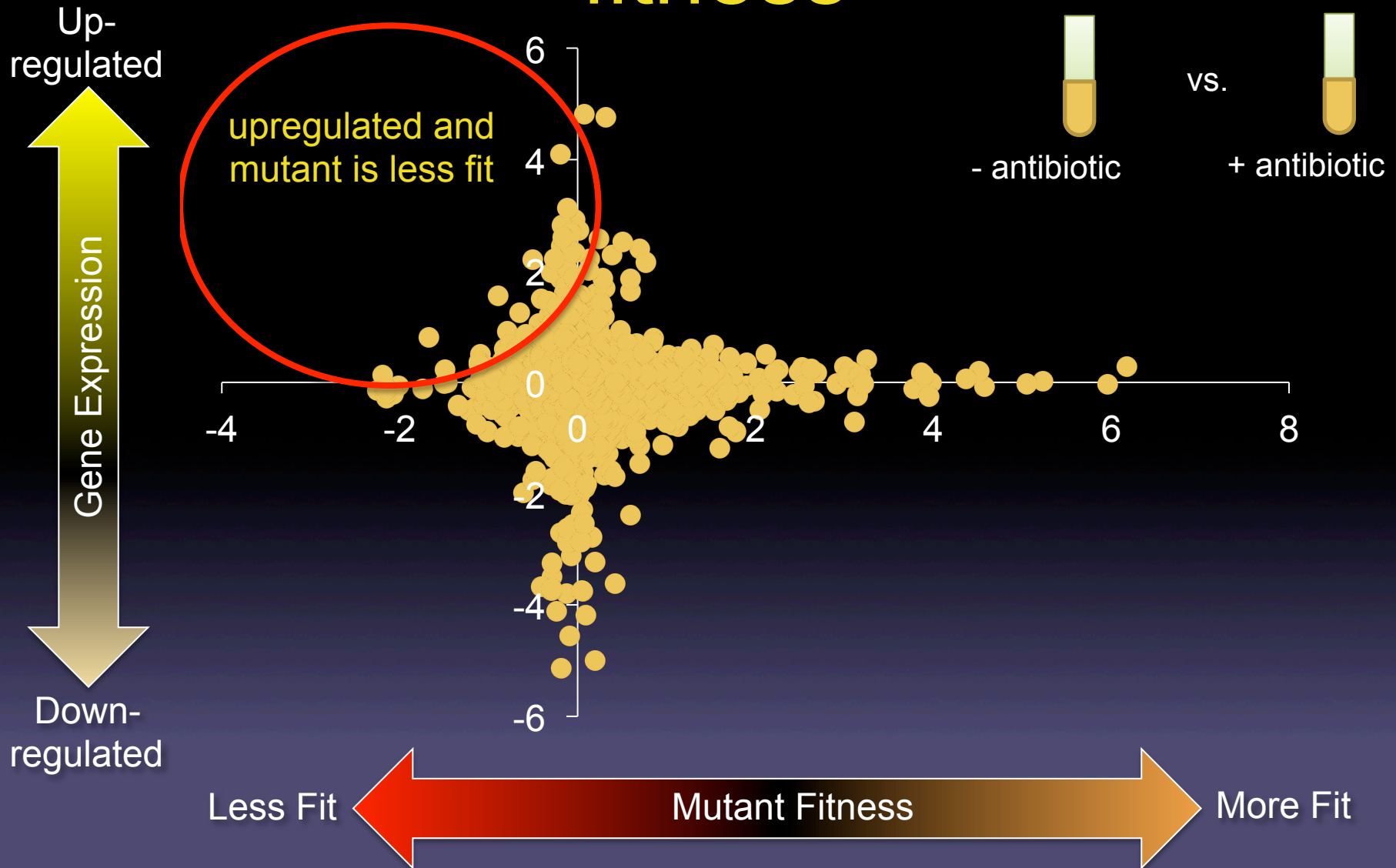
- correlation between expression and fitness
- insights into resistance mechanisms using
Tn-seq

Correlation between expression and fitness

Does expression predict fitness?

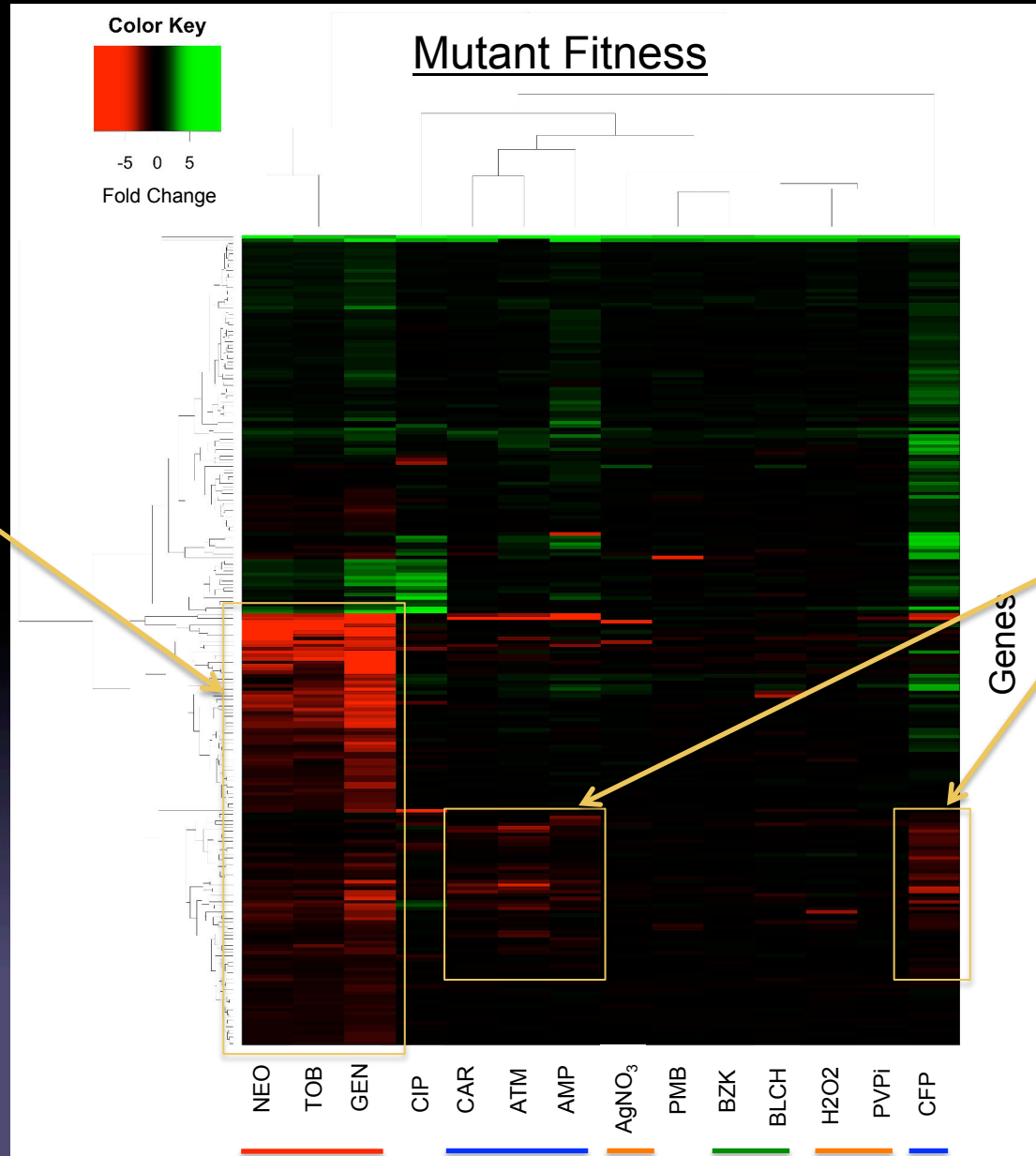


Expression does not predict fitness



Insights into *P. aeruginosa*
resistance mechanisms using
Tn-seq

in vitro antimicrobial resistance



P. aeruginosa in vivo
mechanisms of polymicrobial
synergy

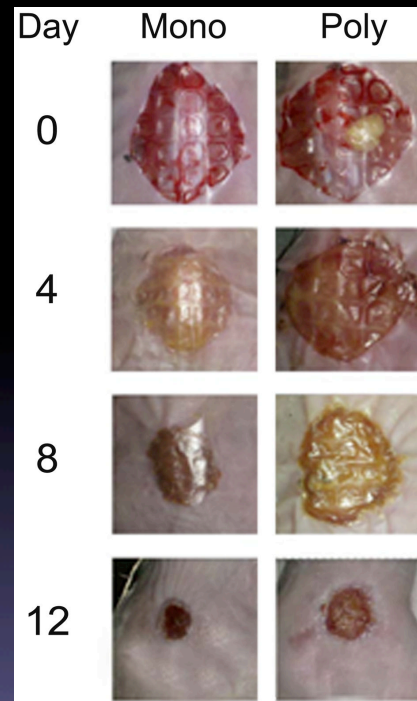
Chronic Wound Infections

- > 5 million Americans
- \$20 billion in health care
- polymicrobial synergy
- *P. aeruginosa* and *Staphylococcus aureus*



Which *P. aeruginosa* genes are required for polymicrobial synergy in chronic wounds?

in vivo murine model for polymicrobial infection



Tn-seq in murine wounds

P. aeruginosa



vs.

P. aeruginosa
+
S. aureus



How does the presence of *S. aureus* impact *P. aeruginosa* genetic requirements in a chronic wound?

Tn-seq in murine wounds

P. aeruginosa



vs.

P. aeruginosa + *S. aureus*



Genes required for *P. aeruginosa* growth with *S. aureus* in coinfection

Gene	Product
<i>pilJ</i>	motility protein
<i>yneJ</i>	transcriptional regulator
<i>str</i>	streptomycin resistance gene
<i>mexT</i>	Multidrug efflux pump
<i>mexE</i>	
<i>mexF</i>	
<i>oprN</i>	
<i>trpF</i>	tryptophan biosynthesis gene
<i>nth</i>	DNA repair gene

Conclusions

- *P. aeruginosa* has specific responses and fitness requirements depending on the classes and types of antimicrobials
- Tn-seq in a polymicrobial infection reveals fitness requirements for coinfection with *S. aureus*
- We can use big data in both *in vitro* and *in vivo* systems to study infection