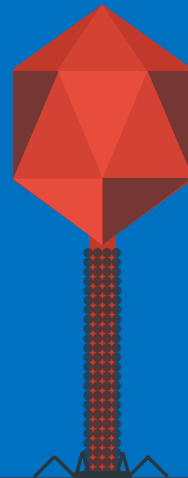


Paci-PHI

Evolution-proof therapy against MDR bacterial pathogens



Paul TURNER, PhD; Benjamin CHAN, PhD; Deepak NARAYAN, MD

EXPERT TEAM



Paul TURNER, PhD
*Dean of Science, Professor of
Microbiology and Ecology &
Evolutionary Biology*
Yale University
Yale School of Medicine

World renowned expert in
bacteriophage biology and
microbial evolution



Benjamin CHAN, PhD
Associate Research Scientist
Yale University

10 years of industry and
academic experience
developing and using
therapeutic phage.

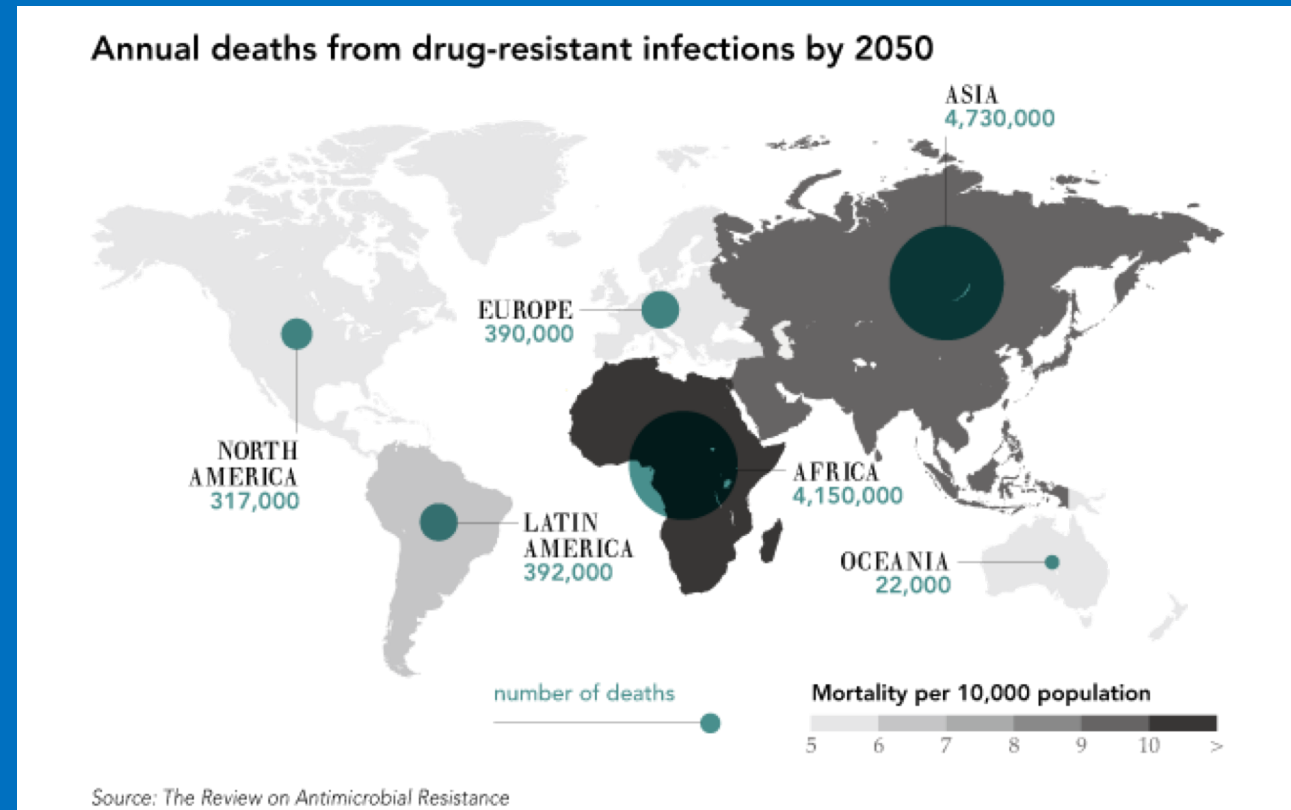
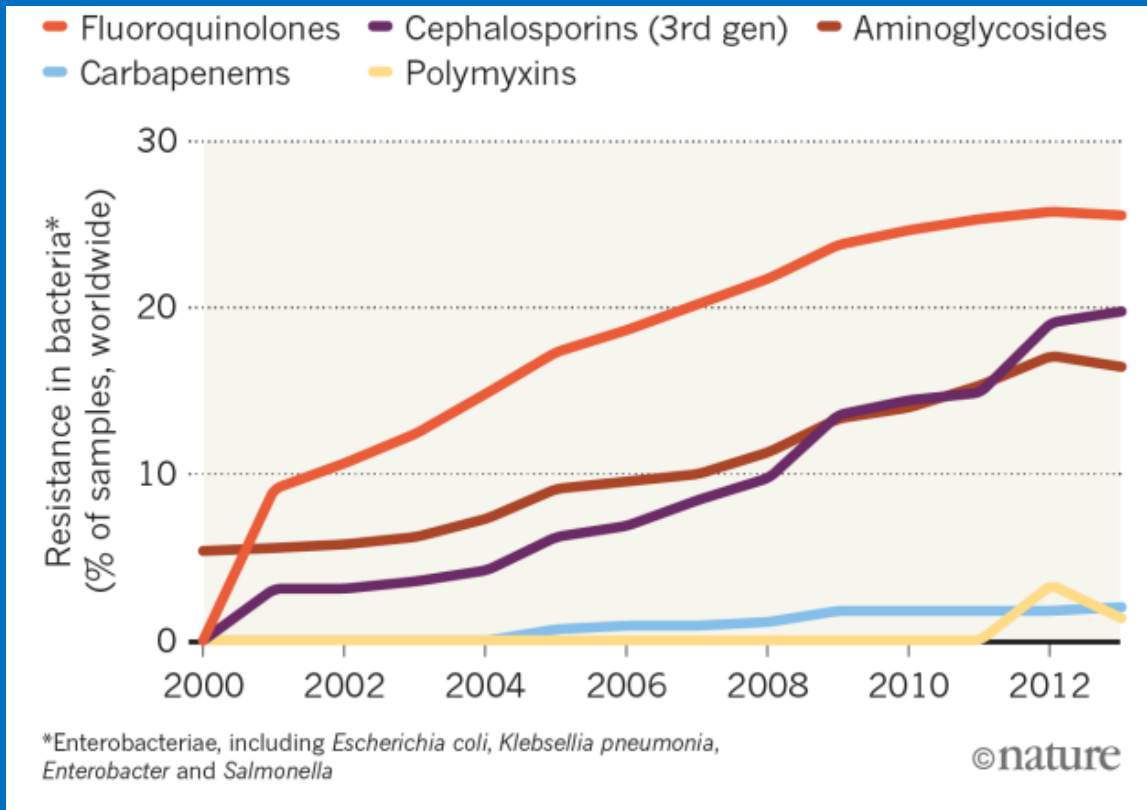


Deepak NARAYAN, MD
Professor, Chief of Surgery
Yale-New Haven Hospital
West Haven VA Hospital

Highly accomplished and
respected physician.

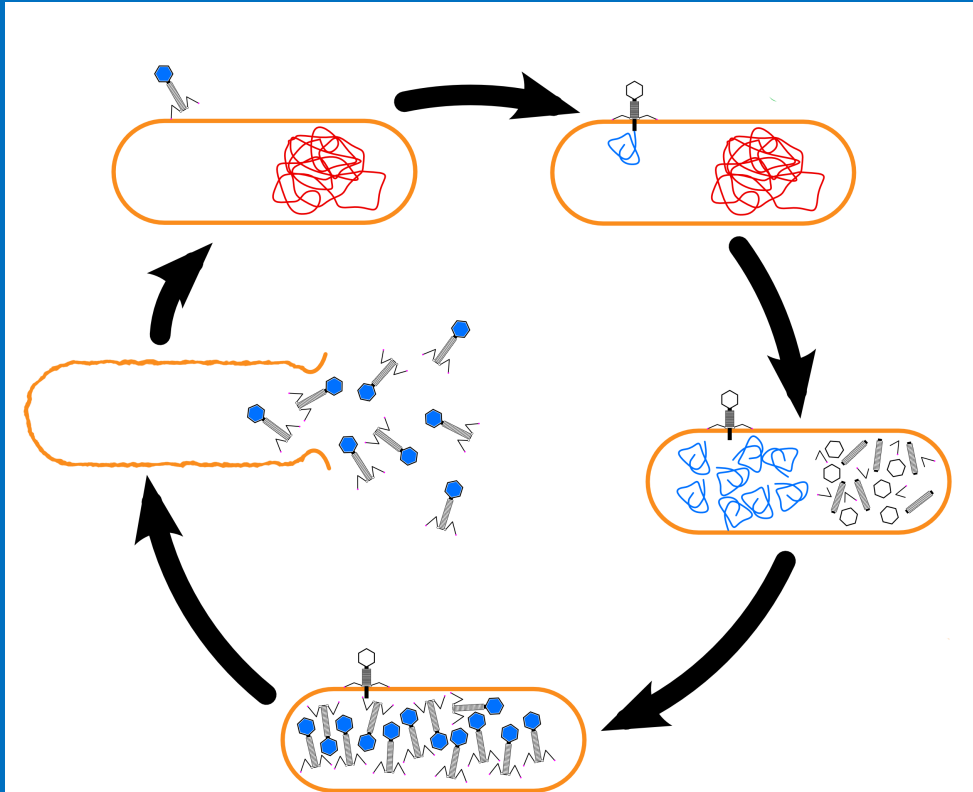
PROBLEM: Antibiotic resistance crisis

- Global problem: Increasing proportion of bacteria show resistance to antibiotics.
- Pace of antibiotic discovery has not kept up with evolution of bacterial resistance.



ALTERNATIVE: Phage therapy

- Phages are viruses that specifically kill only certain bacteria.
- Phages are self-amplifying 'drugs', designated *GRAS* (generally regarded as safe) by FDA.



Lytic phage reproduction

ALTERNATIVE: Phage therapy is SAFE

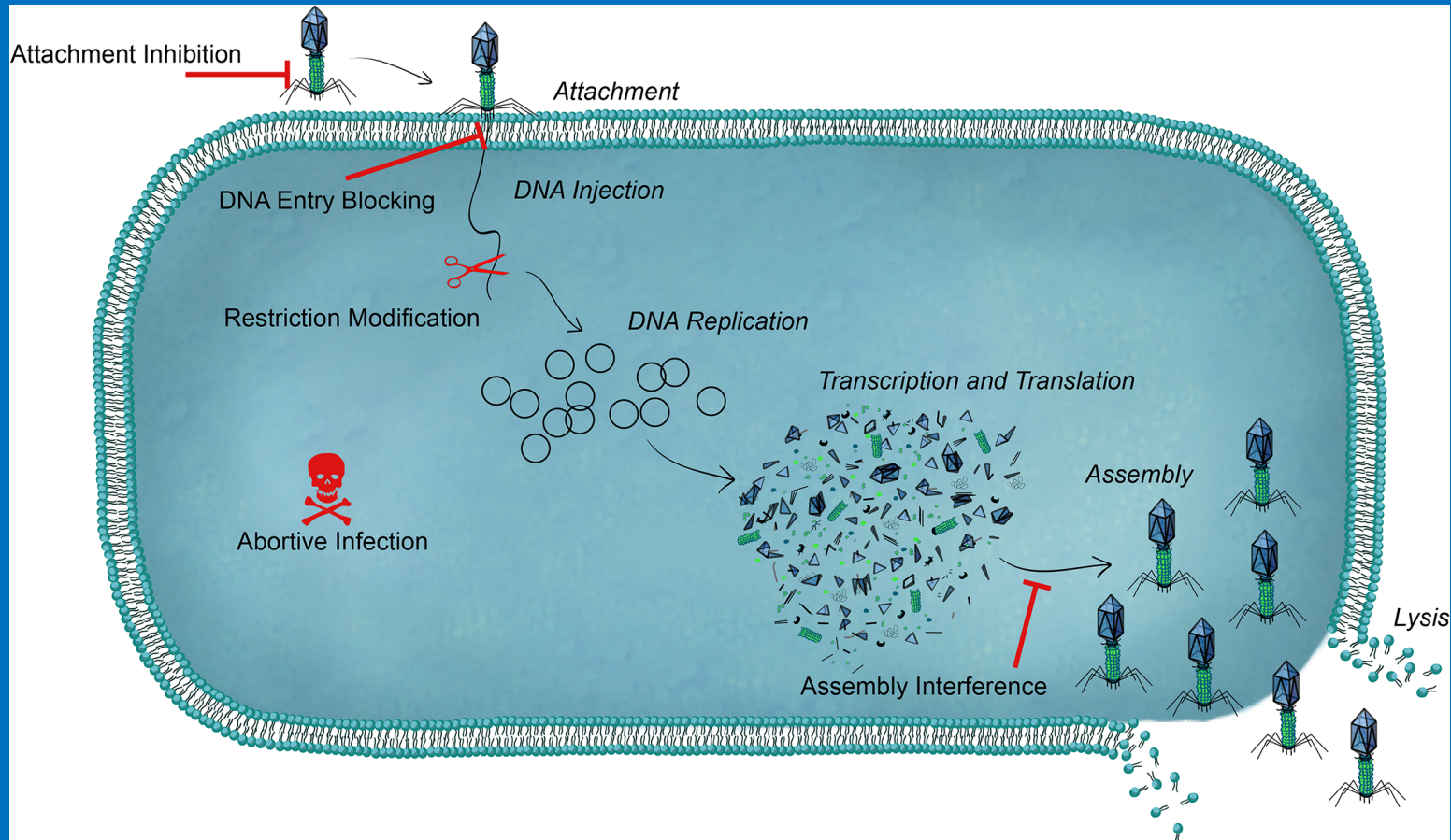
- SAFE: Example phage products designated as *GRAS*:
Listshield (2006), Intralytix, USA
PhageGuard Listex (2008), Microcos, Netherlands
PhageGuard Salmonelex (2010), Microcos, Netherlands
- NON-IMMUNOGENIC: Immune response to phages is minimal (if at all).
- INEXPENSIVE: Phages can be cheaply produced in large volumes.

Accelerated approval for Phase II trials is possibility.



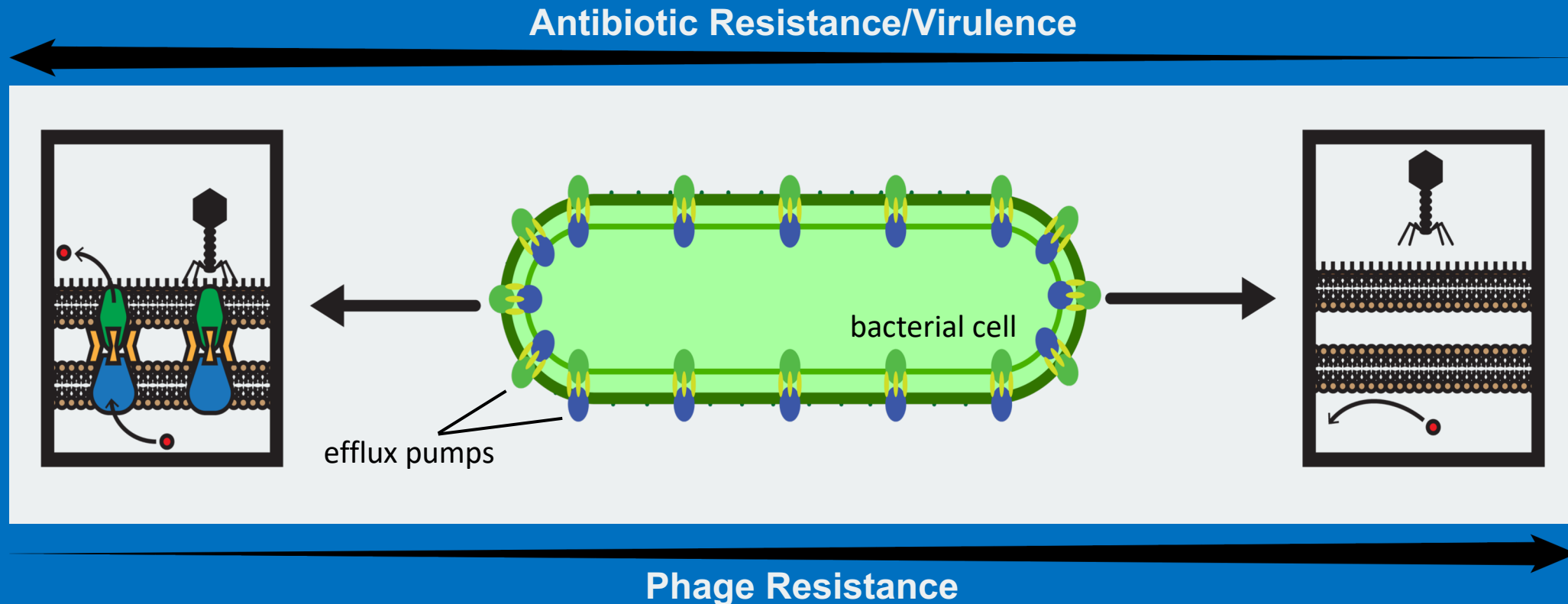
PROBLEM: Evolution of phage resistance

- HOWEVER, bacteria can evolve phage resistance, similar to antibiotic problem:



SOLUTION: Force evolutionary trade-offs in target bacteria

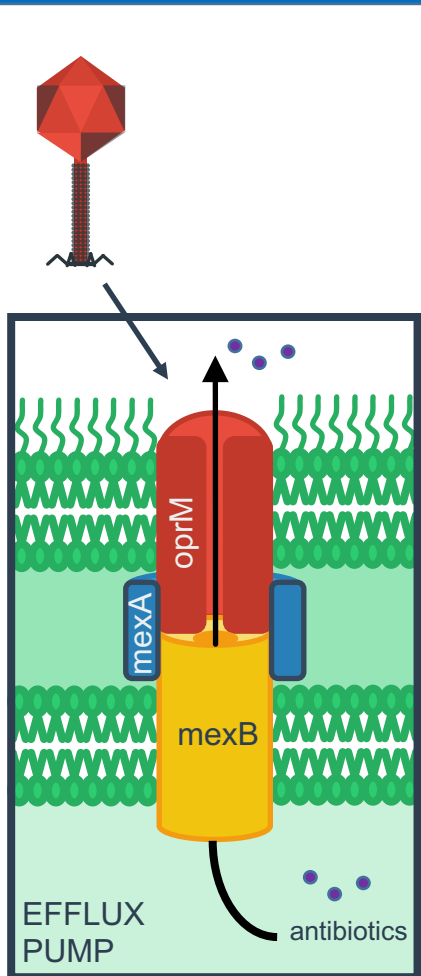
- INNOVATION: Use phages to select for antibiotic re-sensitivity and reduced virulence in pathogenic bacteria



Re-sensitizing bacteria to antibiotics therefore extends the lifetime and improves the effectiveness of current antibiotics.

PROOF: *In vitro* and *in vivo* data targeting MDR *P. aeruginosa*

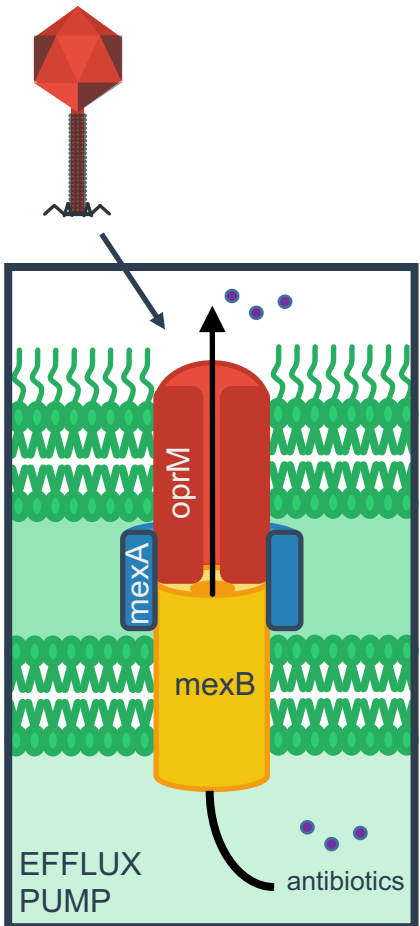
- *Pseudomonas aeruginosa* is priority pathogen (World Health Organization, 2017).
- Hospital infections on rise; high mortality in cystic fibrosis, severe burn, immunocompromised patients.



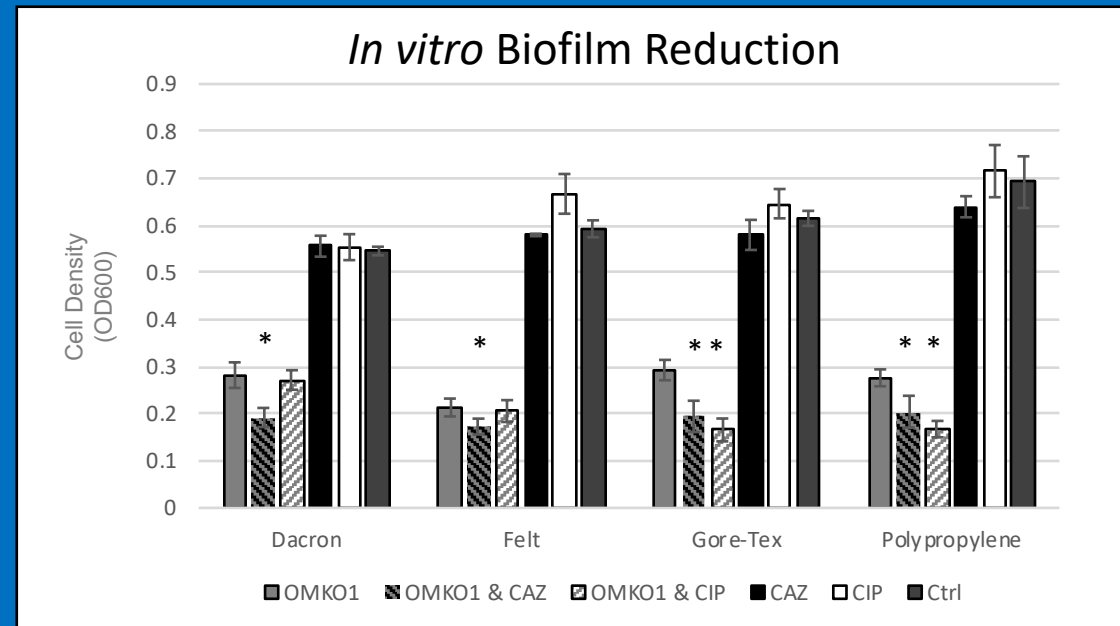
Phage OMKO1 broadly selects for antibiotic re-sensitivity in clinical, environmental, and model strains, because **OprM** binding target highly genetically conserved.

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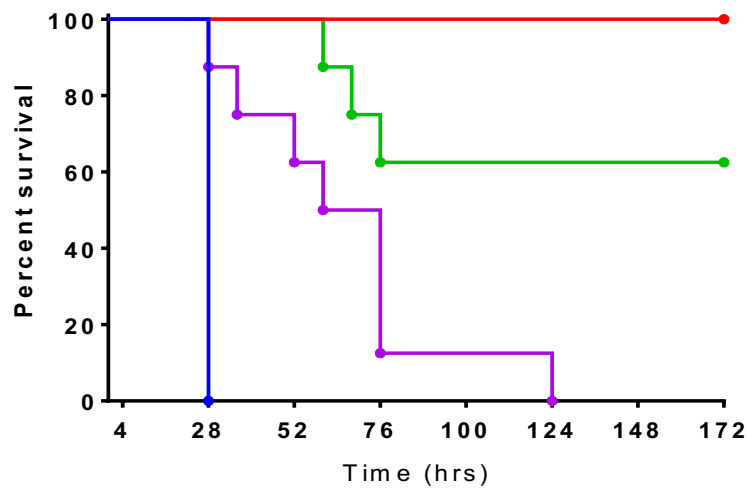
PROOF: *In vitro* and *in vivo* data targeting MDR *P. aeruginosa*

- In vivo* data show phage-antibiotic synergy that rescues mice from lethal pneumonia



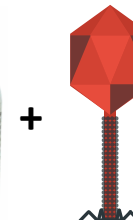
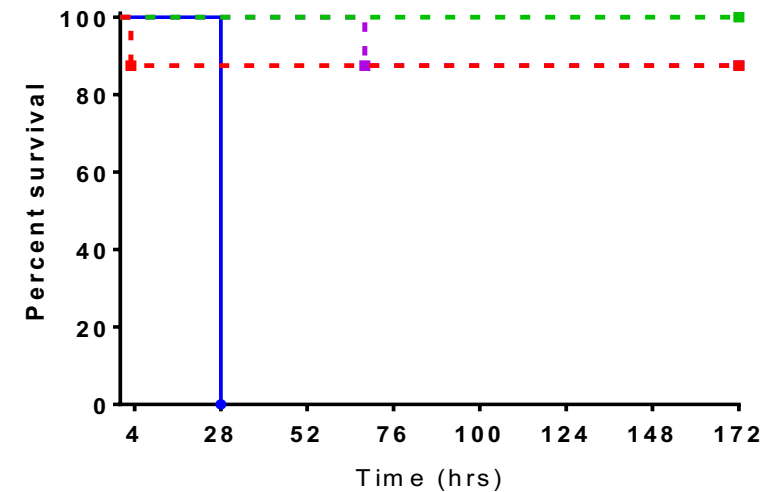
Mouse pneumonia model

Controls:



- No treatment
- High dose Meropenem
- Med dose Meropenem
- Low dose Meropenem

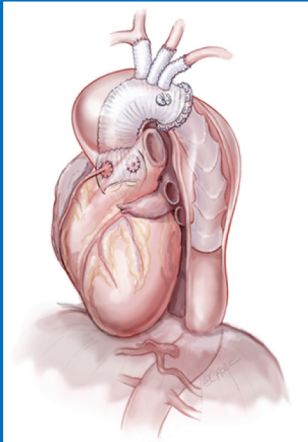
Phage rescue mice at all drug doses:



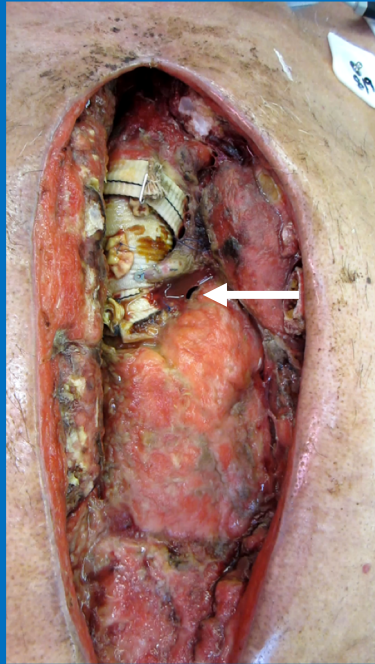
- No treatment
- High dose + phage
- Med dose + phage
- Low dose + phage

PROOF: Emergency phage treatment in 2 patients

- Jan 2016 – complete resolution of MDR *P. aeruginosa* biofilm infection of indwelling prosthesis (aortic arch graft) in elderly man;



aortic arch replacement



intraoperative photo



CT image showing infected collection and site of targeted aspiration during therapy



Treated patient in 2017 with Drs. Turner and Chan

[STAT Online News: In the Lab](#)

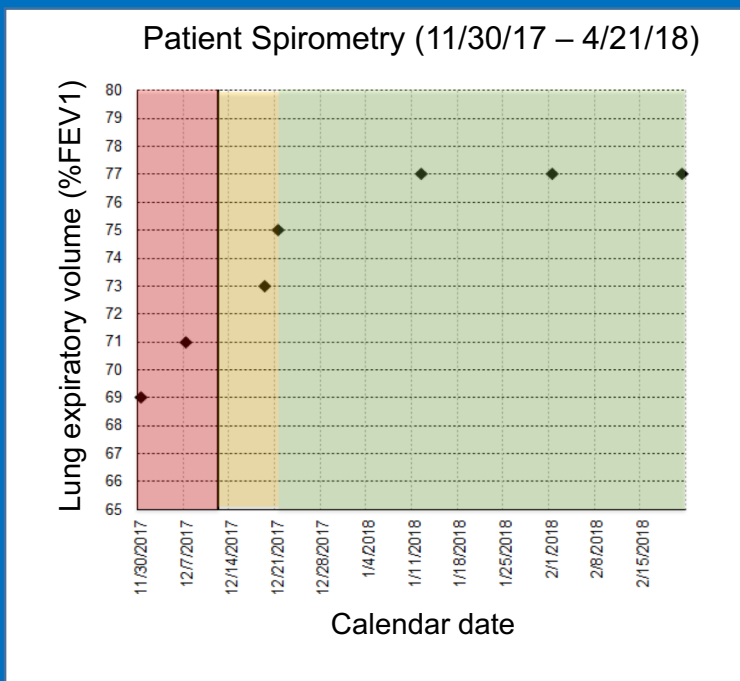
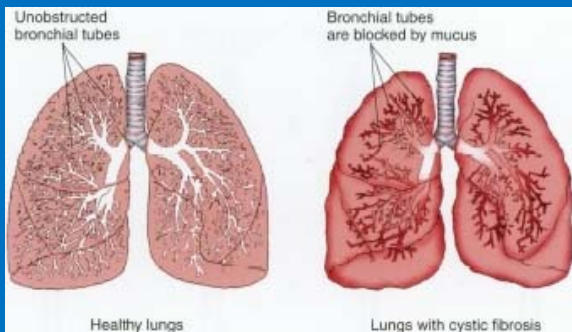
A virus, fished out of a lake, may have saved a man's life — and advanced science

By Carl Zimmer

December 7, 2016

PROOF: Emergency phage treatment in 2 patients

- Dec 2017 – complete re-sensitization to antibiotics in Pan-Drug Resistant *P. aeruginosa*-infected lungs of 22-year-old woman with cystic fibrosis.



Change in <i>P. aeruginosa</i> pre vs. post treatment			
Aminoglycoside	Amikacin	R	S
	Gentamycin	R	S
	Tobramycin	R	IR
Fluoroquinolone	Ciprofloxacin	R	S
	Levofloxacin	R	S
Cephalosporin	Ceftazadime	R	S
	Cefepime	R	S
Beta lactam	Piperacillin	R	S
	Imipenem	R	S
	Meropenem	R	S
	Aztreonam	R	S
Polymyxin	Colistin	R	R



Treated patient in 2018 with Dr. Chan

Intellectual property / Future plans

- ‘Phage composition forcing trade-off between phage resistance and antibiotic sensitivity’ – international patent filed by Yale (2016)
- Seeking U.S. FDA approval (and funding) for phase I/II clinical trials:
 - ❖ Acute (including hospital acquired) pneumonia
 - ❖ Cystic fibrosis associated pulmonary infections
 - ❖ Urinary tract infections (including catheter-associated)
 - ❖ Burn/wound infections



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 - ❖ Urinary tract infections (including catheter-associated)
 - ❖ Burn/wound infections
- Held FDA type B meeting in 2017
 - ❖ No call for toxicology or pharmacokinetic/pharmacodynamics studies
 - ❖ With secured funding, will apply for IND to perform phase I/II trials
 - ❖ Hospital in NC with prepared IRB and identified patients; active discussions with YNHH and TX hospital



Intellectual property / Future plans

- Our library contains 100s of phages, with abundant candidates that force similar trade-offs in clinically relevant bacteria, aside from *Pseudomonas aeruginosa**:
 - ❖ *Salmonella**
 - ❖ *Shigella spp.**
 - ❖ *Klebsiella pneumoniae*
 - ❖ *Vibrio cholerae*
 - ❖ Pathogenic *E. coli*

* World Health Organization Priority MDR Pathogen List (2017)

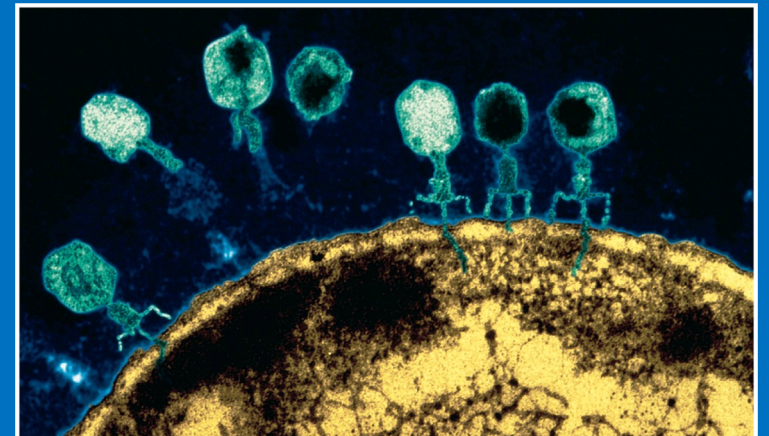
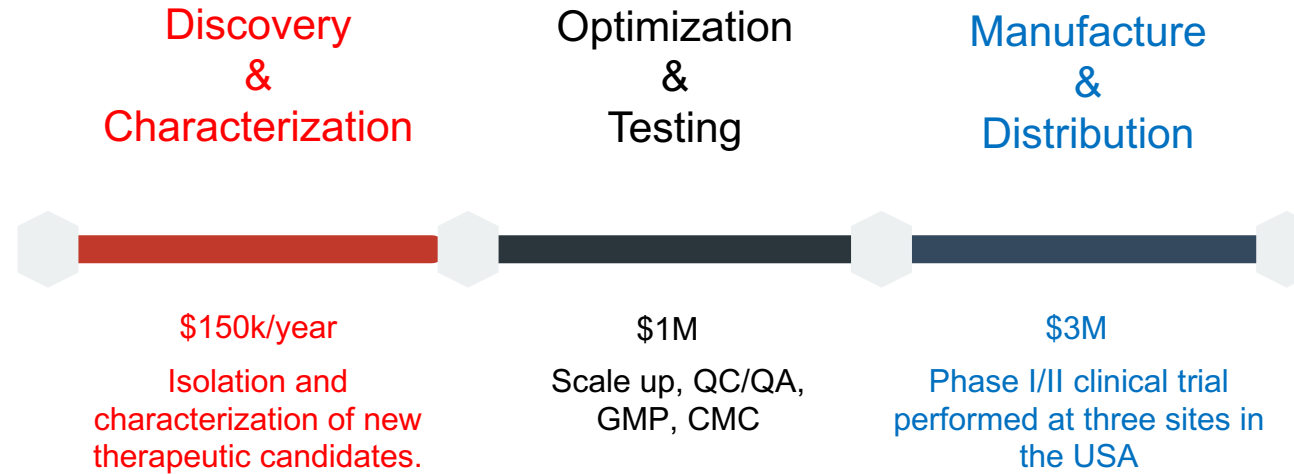


Figure 5-24
Introduction to Genetic Analysis, Tenth Edition
© 2012 W. H. Freeman and Company

Business MODEL / Funding REQUEST



BLAVATNIK FUNDING REQUEST

We request \$300K for scale-up and production, in developing our most promising phage-therapy candidate against MDR *P. aeruginosa*.

FUNDING details

COST BREAKDOWN

Funding used to:

- Establish master bank
- Scale-up production
- Conduct sterility/stability testing of materials for clinical trial (50 patients, phase I/II)

All in approved GMP facility: Adaptive Phage Therapeutics; Gaithersburg, MD

Total cost: \$560K

We negotiated one-time reduced cost as research outcome would be mutually beneficial.

Actual cost: \$300K