Reimagining Bacteriophages to Treat Lung Infections

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2019 NTM & Bronchiectasis Physician/Patient Conference

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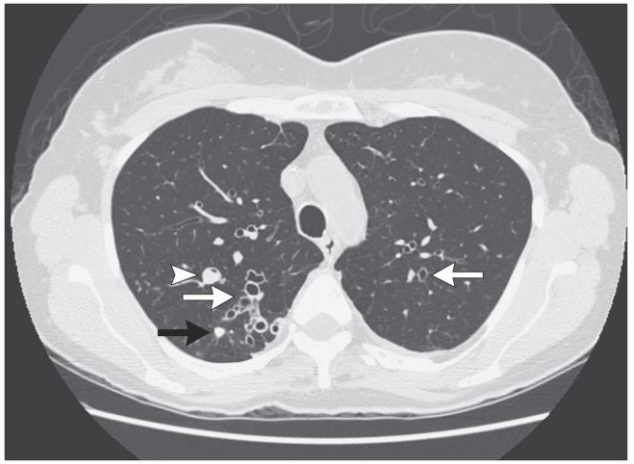
Yale SCHOOL OF MEDICINE

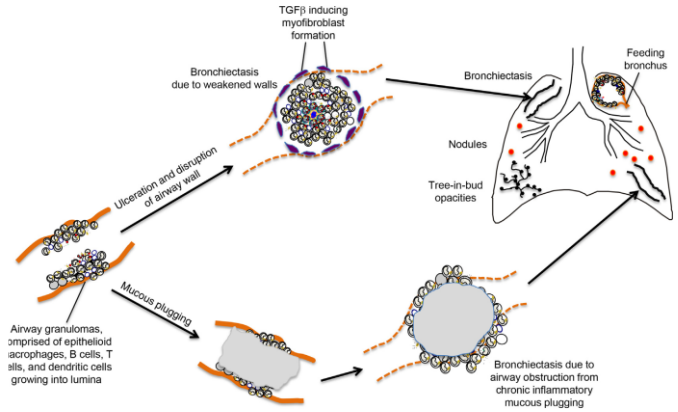
Outline

- Discuss Bacteriophage(s)
  - Brief History
  - Potential Clinical Applications
  - NTM
  - *Pseudomonas*
- Clinical Experience at Yale
- Future Directions



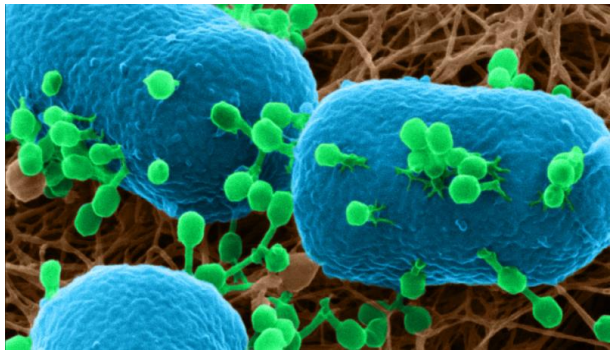
Bronchiectasis

Image: JE Mojica et al. NEJM 2018



NTM

Image: Clinics in Chest Medicine 2015



Phage and Bacteria

Image: University of Jyväskylä

Bacteriophages (Phages)

Naturally occurring replicating antibacterial

- Bacterial viruses (e.g., bacterial parasites)
- Only infect bacteria- therefore incapable of infecting humans
- Discovered in 1914 (Twort) & 1917 (D'Herelle)
- ***~ 10^{31} phages in the environment (10:1 bacteria)***
- ***Lytic*** vs. Lysogenic phage(s)
- Specific phage for each bacteria
  - Potential for personalized medicine approach
- Previously phage treatment from Tbilisi, Georgia
  - Concerns about standardization, efficacy,
  - treatment algorithm (single phage vs "cocktail"), etc….

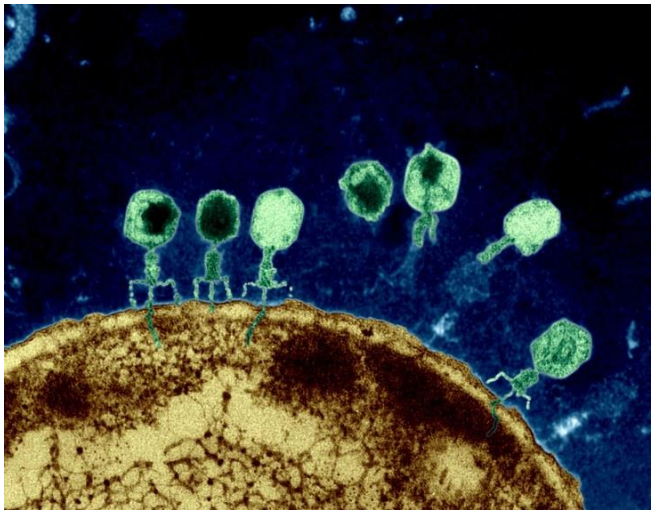
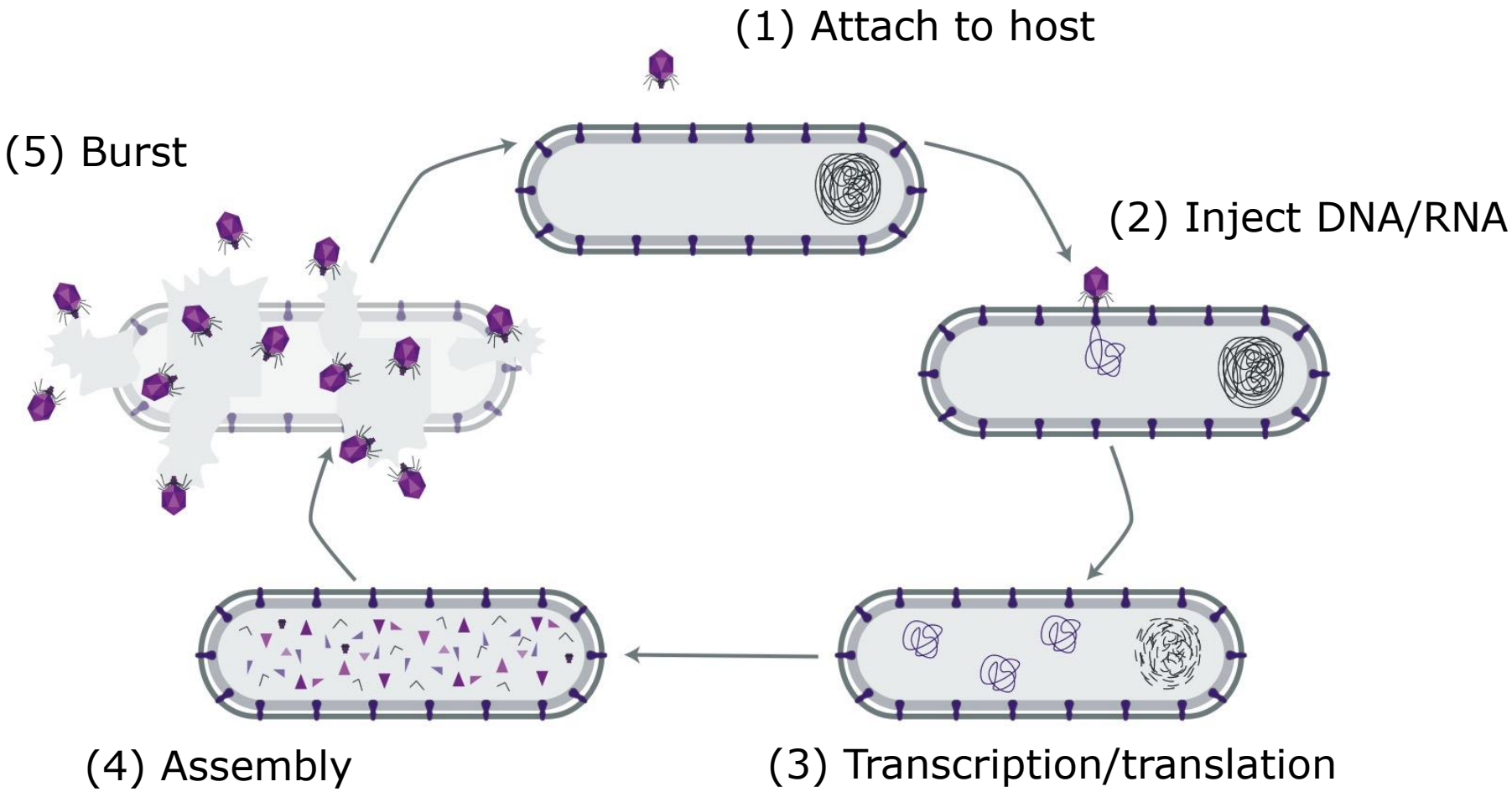


Image from Eye of Science

Phages are abundant and only infect bacteria

Lytic Phage Lifecycle

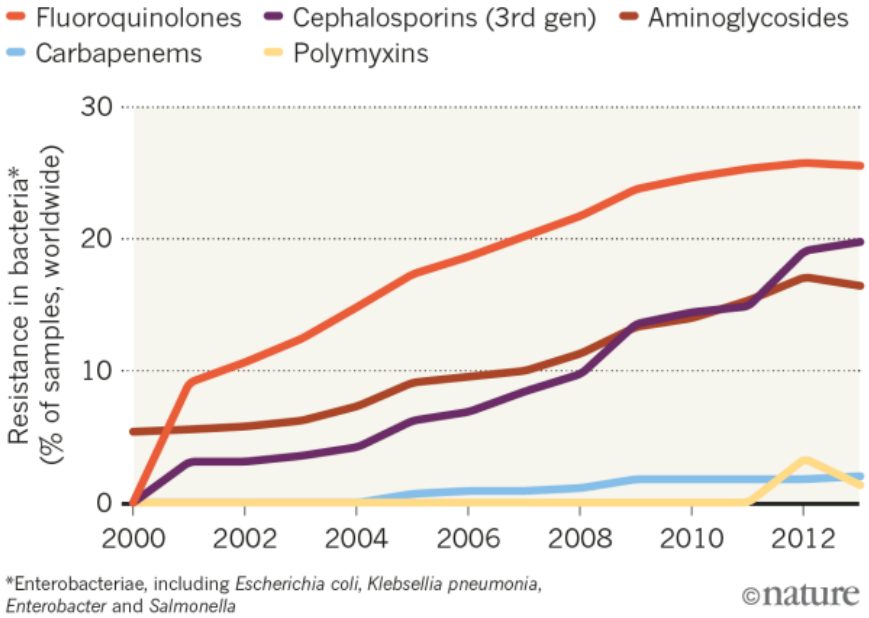


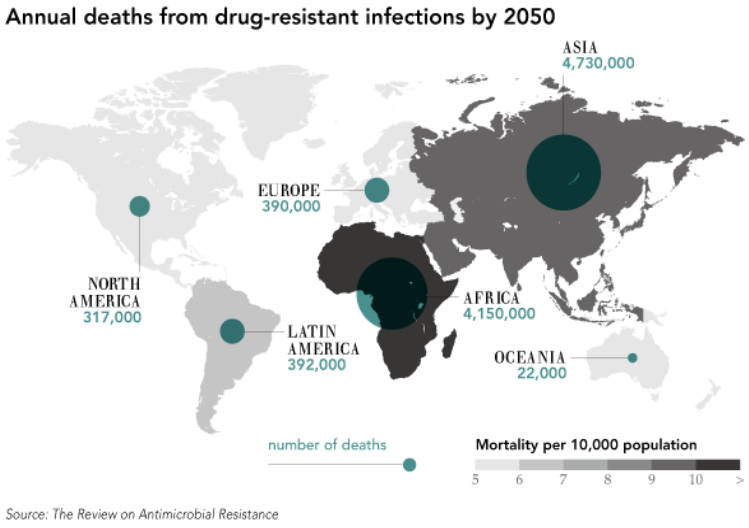
Kortright, KE Cell Host Microbe 2019

Phages infect and replicate in bacteria

Antibiotic Resistance Crisis

1) Global problem:
   Increasing proportion of bacteria show resistance to antibiotics.
2) Antibiotic Discovery:
   Has not kept up with evolution of bacterial resistance.

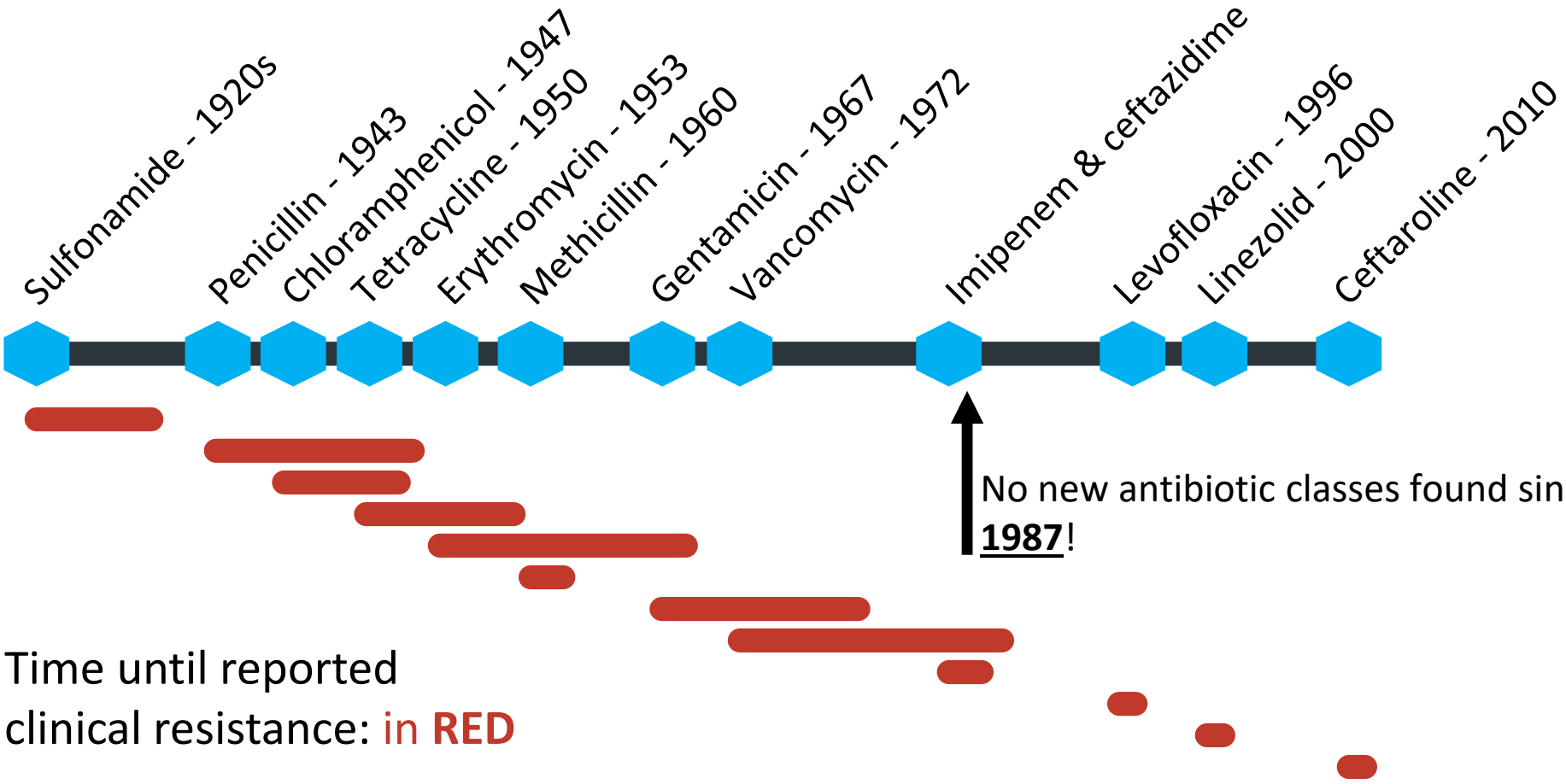




Bacteria are becoming more resistant to available antibiotics

Antibiotic Resistance

Discovery of antibiotics over the previous 100 years



Bacteria quickly become resistant to new antibiotics

Treatment of NTM

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-019-0437-z
nature medicine

Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick[1,4], Carlos A. Guerrero-Bustamante[1,4], Rebecca A. Garlena[1], Daniel A. Russell[1], Katrina Ford[2], Kathryn Harris[2], Kimberly C. Gilmour[2], James Soothill[2], Deborah Jacobs-Sera[1], Robert T. Schooley[3], Graham F. Hatfull[1*] and Helen Spencer[2*]

- 15 year-old with cystic fibrosis post-lung transplant
- Disseminated *M. abscessus* (lung, sternal wound, and skin infections)
- Three phage cocktail topical and intravenous (IV) for 32 weeks with resolution of infection

Phage cocktail treated NTM in a patient with extensive infection

Treatment of NTM

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1) First use of phage to treat mycobacterial infection in human
2) First us of an engineered phage in human

Phage cocktail treated NTM in a patient with extensive infection

Yale University Phage Program

Basic Science & Clinical Collaboration

Yale Phage research team

Paul Turner: Professor

Ben Chan: Research Scientist

1) Locally, environmentally sourced phages
2) Target and kill *Pseudomonas*
3) Novel strategy to decrease MDR
4) FDA eIND to deliver to patients

Yale University Phage Program

Locally-sourced phages

1) Obtain phages from local environment
2) Isolated, propagated, purified, and sequenced
3) Tested for ability to target and kill bacteria

We find and purify phage

Phages target *Pseudomonas aeruginosa (PsA)*

100 CF sputum PsA isolates (CFF: Seattle Children's Repository)

- *Using 5 selected phages*

90% were sensitive to at least 1 phage

13% sensitive to all 4 phages

76% sensitive to >1 but <4

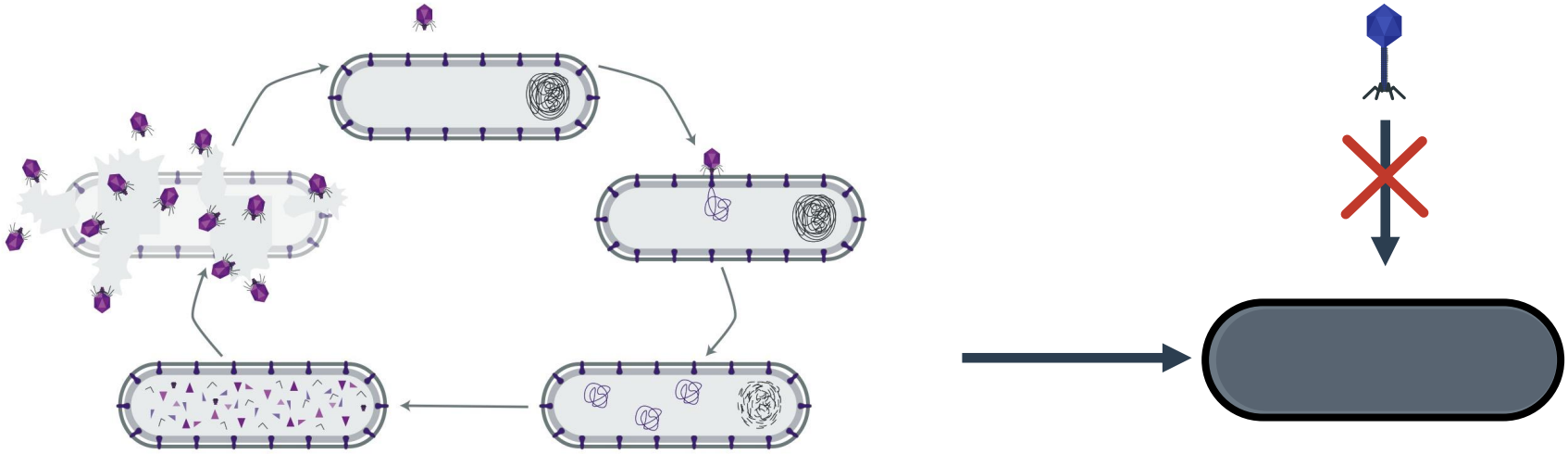
- *Using larger library, no PsA were resistant.*

Phage	Fraction Resistant
#1	0.33
#2	0.50
#3	0.60
#4	0.25
#5	0.63

Phages kill *Pseudomonas* from CF patient sputum

Using Phages to manipulate community dynamics

Chan, BK Sci Rep 2016; Kortright, KE Cell Host Microbe 2019



Evolutionary response could, therefore, be directed (with phage) to:

1. Reduce/reverse antibiotic resistance
2. Attenuate virulence
3. Control production of extracellular virulence factors

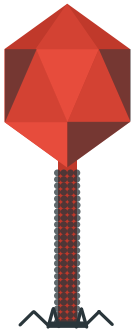
When *Pseudomonas* is resistant to our phages, *Pseudomonas* is weaker

Using Phages to manipulate community dynamics

Chan, BK Sci Rep 2016

	Antibiotic	Class	Isolate MIC (mg/L)	Phage Resistant Isolate MIC (mg/L)	Fold-increased Drug Sensitivity
Efflux provides resistance	Tetracycline	Tetracycline	92.1	7.15	12.88
	Erythromycin	Macrolide	265.5	21.75	12.21
Efflux may provide resistance	Gentamicin*	Aminoglycoside	2.41	1.13	2.13
	Tobramycin*	Aminoglycoside	3.63	1.12	3.24
	Ciprofloxacin*	Fluoroquinolone	3.1	0.77	4.03
	Ceftazidime	Cephalosporin	1.12	0.45	2.49
Efflux does not provide resistance	Ampicillin	Penicillin	>256	>256	0

* > 1 isolate showed reversal from clinical resistance to susceptibility (EUCAST 2015 breakpoints)

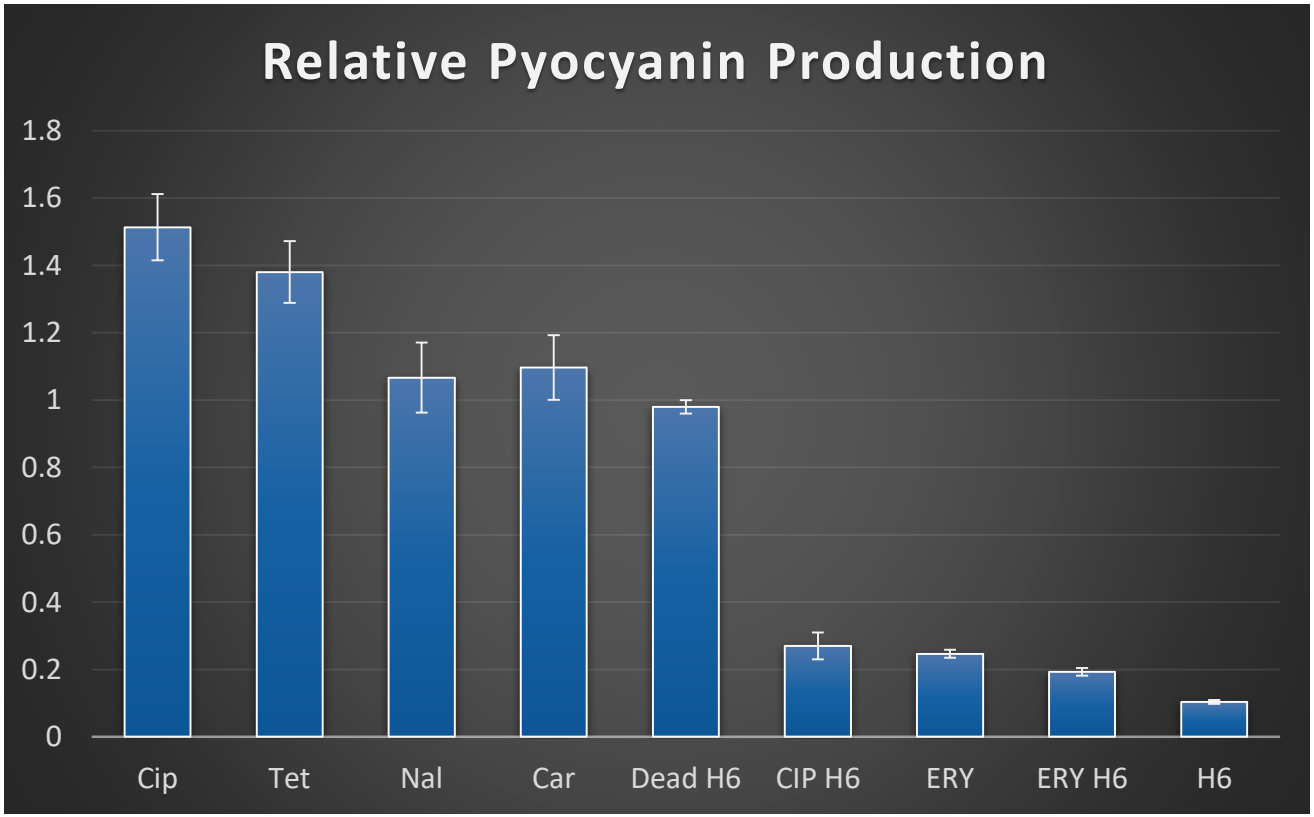


Phage OMKO1
Phikzlike-virus
242kb genome

Pseudomonas resistant to our phage is more susceptible to antibiotics

Using Phages to manipulate community dynamics

Targeting Type 4 pilus that produces pyocyanin



Cip = Ciprofloxacin
Tet = Tetracycline
Nal = Naladixic acid
Car = Carbapenem
Dead H6 = heat-inactivated
Ery = Erythromycin
H6 = type 4 pilus targeting

Unpublished

Pseudomonas resistant to our phage is less inflammatory

Yale University Phage Program

Paul Turner (PI)

Ben Chan: Assoc. Research Scientist

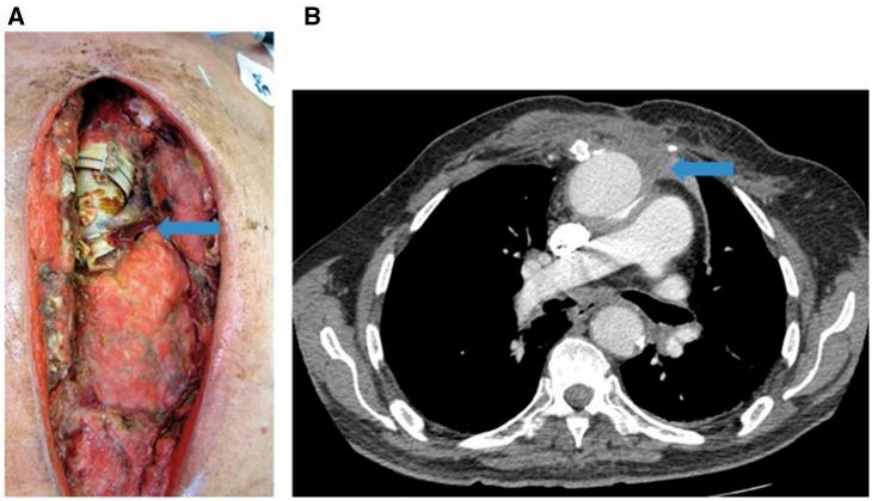
1) Locally, environmentally sourced phages
2) Target and kill PsA
3) Novel strategy to decrease MDR
4) FDA eIND to deliver to patients

- FDA IND to use phage to treat patients
- Emergent indication
  - Pan-drug resistant (PDR)
  - MDR
  - No other options for clinical care (e.g., other treatments have failed)

1) Approval from FDA
2) Identify phage & treat
3) Notify IRB

Yale University Phage Program

Chan BK et. al. 2018 (Patient #1)



- Pseudomonas infection of Dacron graft.
- Phage injected into graft.
- Resolution of infection.

IV Phage treated *Pseudomonas* infection

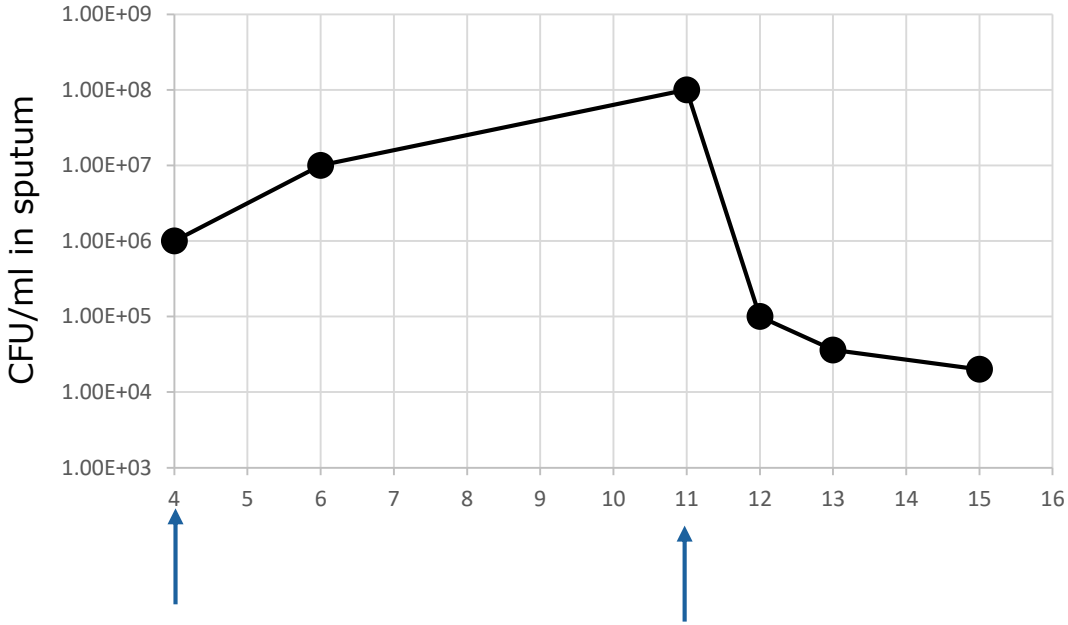
Case Presentation

Case #3 eIND #18483 (Chan, Kazmierczak, & Koff)

- 72-year old male with COPD and bronchiectasis
- Chronic/recurrent infections with MDR PsA (since 2016)
- Since May 2018, six admissions despite outpatient piperacillin-tazobactam and doripenem.
- Admitted in September with shortness of breath, worsening cough, and hypoxia.
- Chest CT significant abscess in left lung
- MICU on HFNC & treated with nebulized phage TID (LPS & Type IV Pilus)

Case Presentation

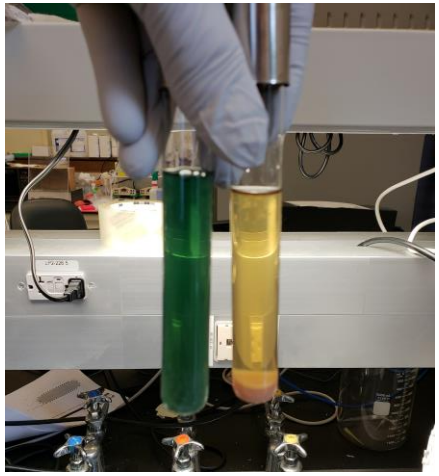
Case #3 eIND #18483 (Chan , Kazmierczak, & Koff)



Admission
IV ceftolozane + tazobactam
IV gentamicin

Phage therapy
Initiated

IR to ceftolozane + tazobactam



Left: (Pre-phage)
Pyocyanin (green)

Right: (Post-phage)
Decreased pyocyanin
(yellow)

Nebulized phages decreased MDR *Pseudomonas* and inflammation

Case Presentation

Case #4 eIND#18544 (Chan & Koff)

- 71-year old man with non-CF bronchiectasis
- Recurrent MDR PsA (sensitive to Tobra only)
- Admitted to Yale New Haven Hospital (YNHH) with pulmonary exacerbation
- Treated with nebulized phage BID (LPS & Type IV Pilus)

PsA	Treatment day	CFU/mL
MDR	0	2.5×10^7
	5	4×10^3
Retreated 2 months later as outpatient (QD nebulized phage)		
MDR	0	2×10^3
	20	0*

* Confirmed at local laboratory x 2

Research Summary

1. Phages can kill NTM and *Pseudomonas* in humans without evidence for significant side effects.
2. Phage targeting PsA allows for additional “trade offs” (e.g., increased antibiotic sensitivity and decreased inflammation).
3. FDA eIND allows for phage treatment to patients after FDA approval.
4. Established an effective dosing regimen for the ICU, hospital floor, and outpatient clinic setting.
5. Potential for ”personalized” medicine approach to design phage for each clinical isolate.
6. Re-treat with same or new phage appears to be safe, and may be more effective.

Future Directions

1. Clinical trial with CF patients to treat PsA.

2. Continue FDA eIND to treat additional patients.
   This can be done at other institutions:
   Sputum sent to Yale
   Phage selected & shipped
   Patient(s) treated locally

3. Phages available target *Pseudomonas, E. coli, Klebsiella, Achromobacter*.

Future Directions continued

1. Phage(s) for additional targets
   - Resistant Gram-negative bacteria
     - *Burkholderia*
     - *Pandoraea*
     - *Ralstonia*
     - *Stenotrophomonas*
   - MRSA
   - Nontuberculous mycobacteria (NTM)

2. Increase size of phage libraries

3. Phage strategies
   - Combination phages
   - Targeting multiple virulence factors
   - Development of resistance

Acknowledgements

All of our patients

Ben Chan & Paul Turner

Koff lab

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Cystic Fibrosis Foundation

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Yale Liver Center Pilot Award

Adult CF Program Support

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2) Laura Norton Fund
3) OutRun 38
4) Yale New Haven Hospital Auxillary
5) CF Foundation Care Center Grant
6) Department of Medicine and Section of Pulmonary, Critical Care, & Sleep Medicine
7) Yale New Haven Hospital

Yale CF Center