ICTP-SAIFR
Summer Workshop
Mathematical Models of Evolution
Sao Paulo
Jan 21-26, 2019

Support:
Army Research Office
Georgia Tech

SYNERGISTIC ELIMINATION OF BACTERIAL PATHOGENS BY PHAGE AND THE INNATE IMMUNE SYSTEM

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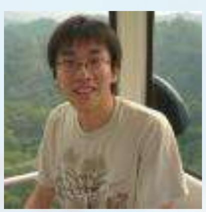

Dr. Joey Leung
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Ms. Devika Singh
GT, Bioinformatics '16

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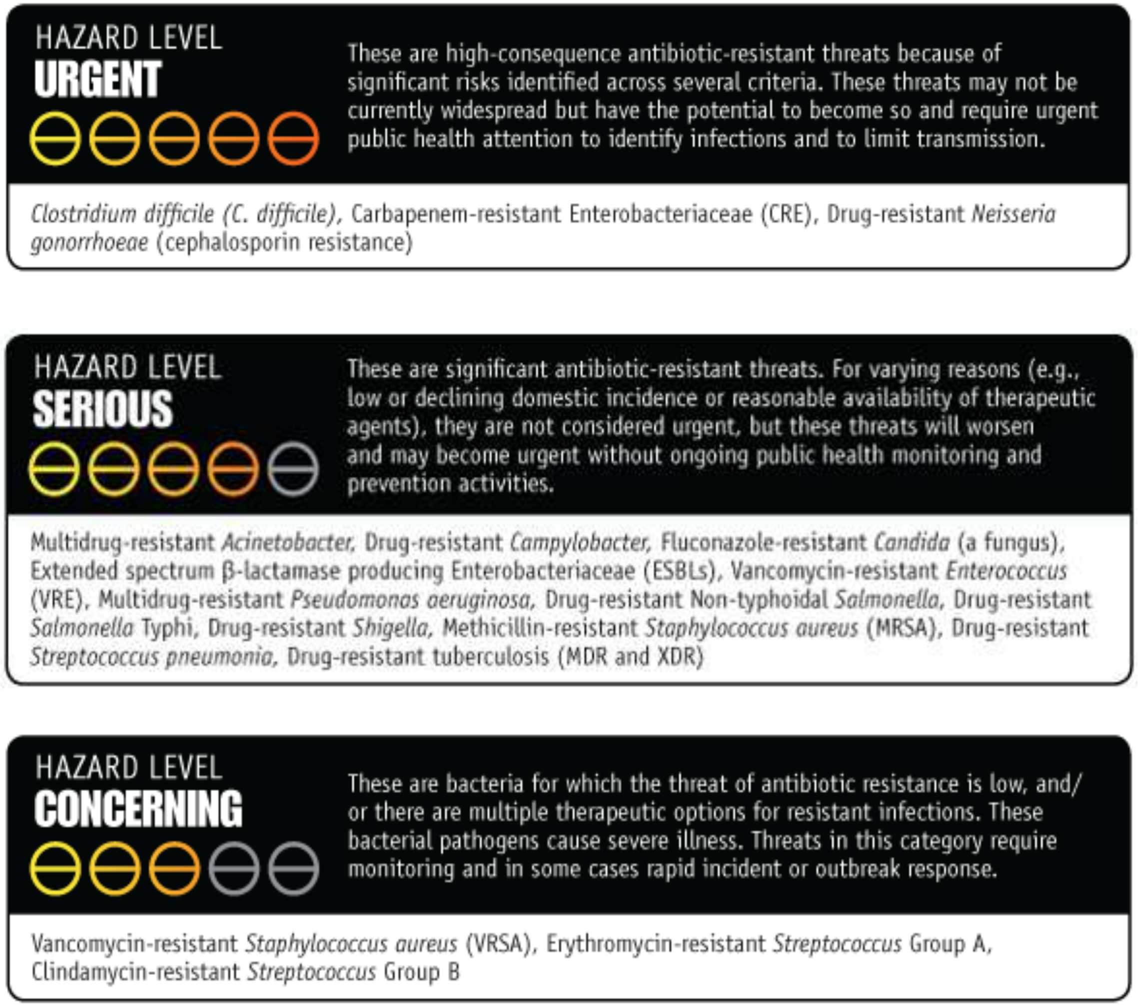


HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL
SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia*, Drug-resistant tuberculosis (MDR and XDR)

HAZARD LEVEL
CONCERNING

These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

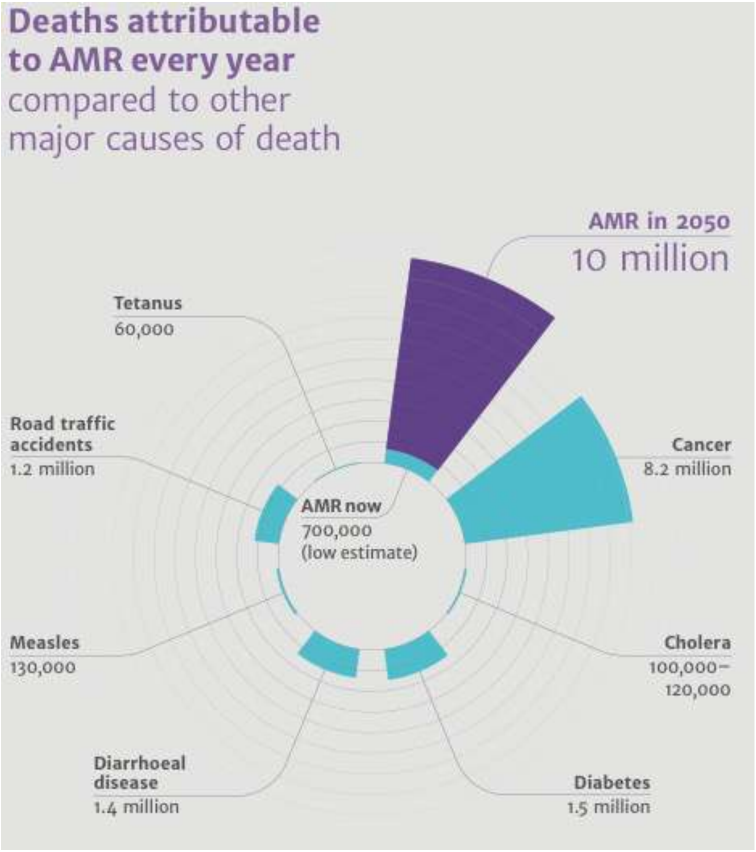
Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

C. diff
N. gonorrhoeae
…

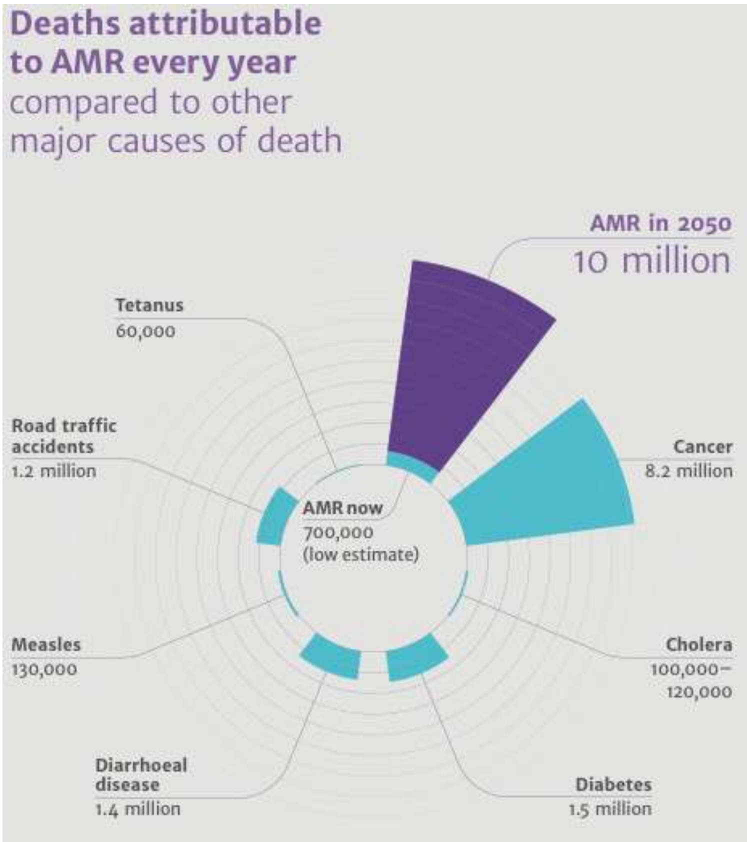
P. aeruginosa
MR *Staph. aureus*
Candida
Campylobacter
…

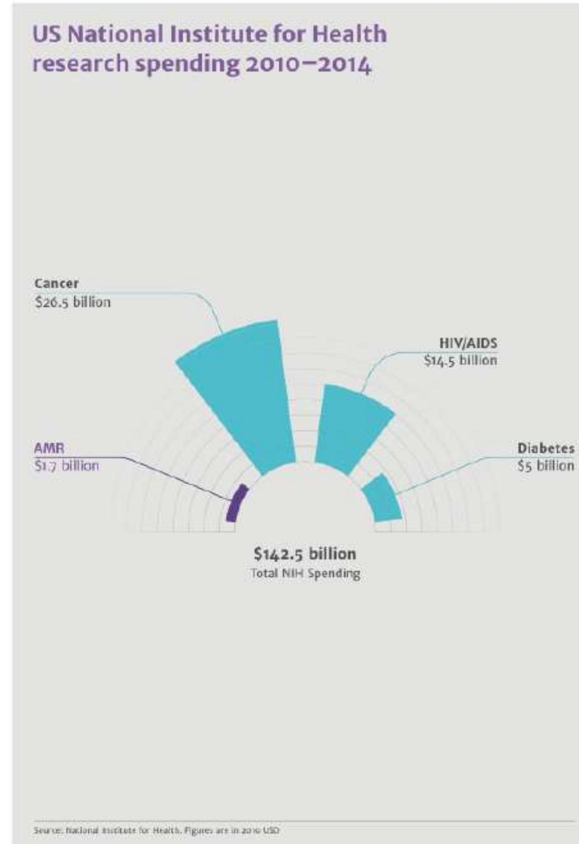
Strep Group A
Strep Group B
...

Source: CDC biggest drug-resistant threats,
https://www.cdc.gov/drugresistance/biggest_threats.html

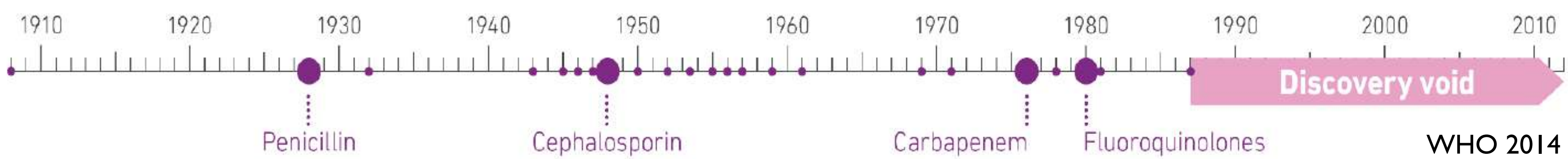


Source: The Review on Antimicrobial Resistance, 2014 (J. O'Neil), UK
http://amr-review.org



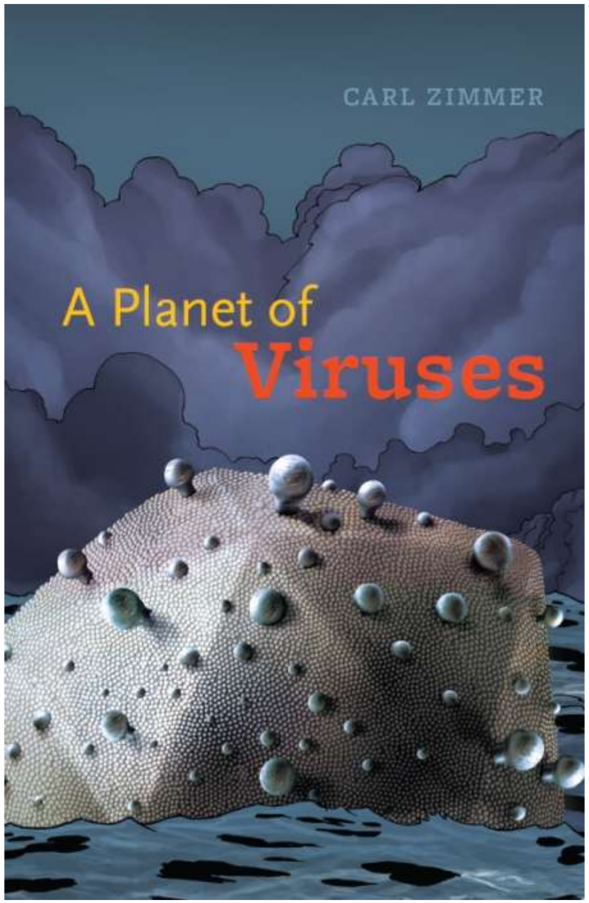


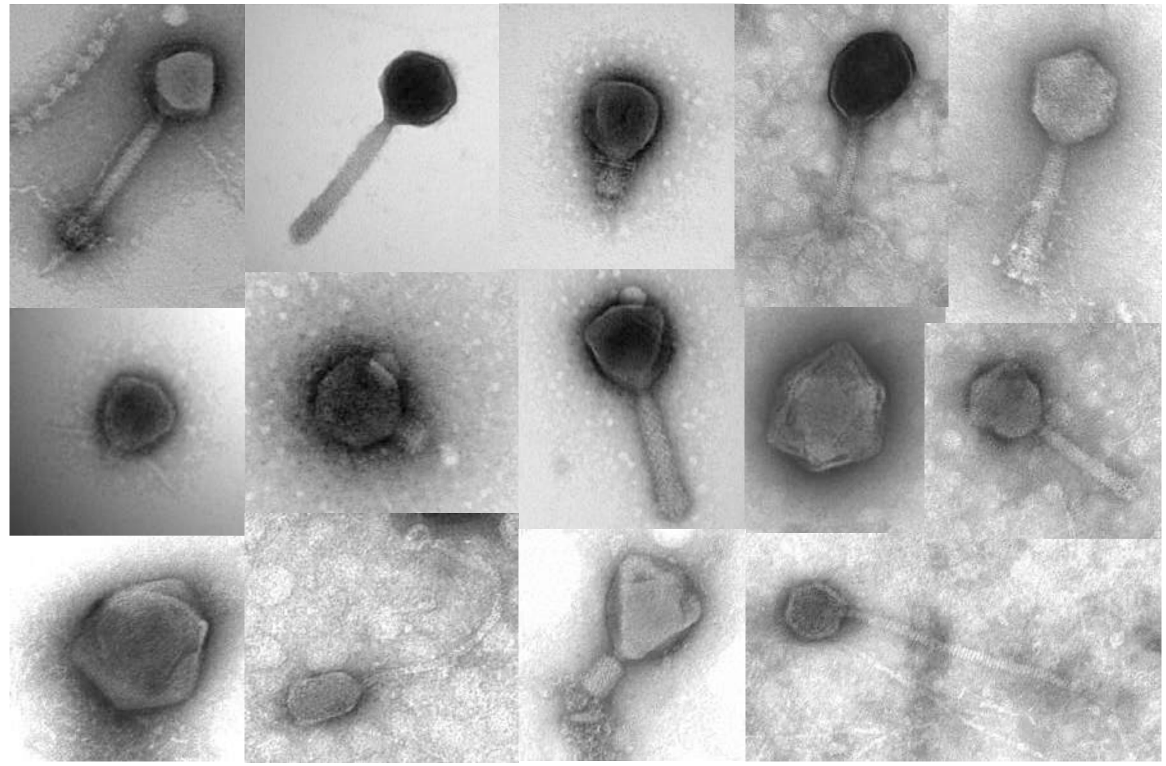
Over the last 30 years, no major new types of antibiotics have been developed



WHO 2014

(…Teixobactin, 2015)





Brum et al. 2013. *The ISME Journal.* doi:10.1038/ismej.2013.67.

Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection

April 25, 2017 | Scott LaFee and Heather Buschman, PhD

Phage Therapy

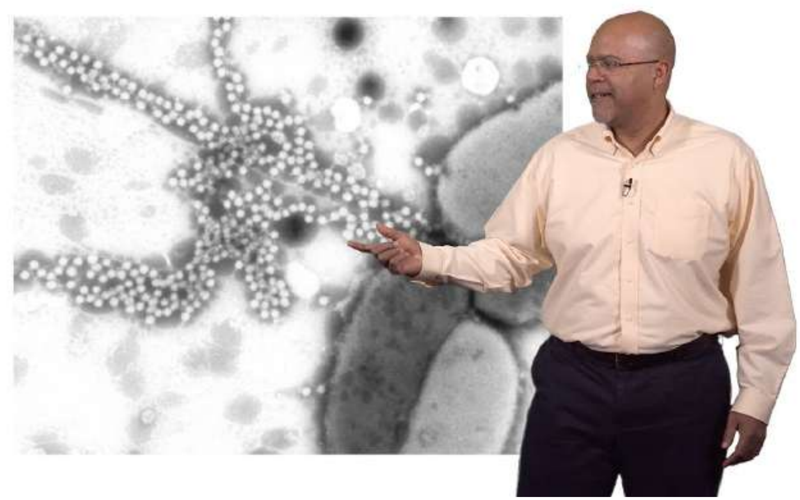
Phage Therapy Infected with a multidrug-resistant bacterium, Tom Patterson was comatose and near-death. Physicians and scientists at UC San Diego Health, with many collaborators, used an experimental bacteriophage therapy — viruses that target and consume bacteria — to save his life. The success may be a catalyst to developing new remedies to the growing global threat of antimicrobial resistance.

A. baumannii

IN THE LAB

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

By CARL ZIMMER @carlzimmer / DECEMBER 7, 2016

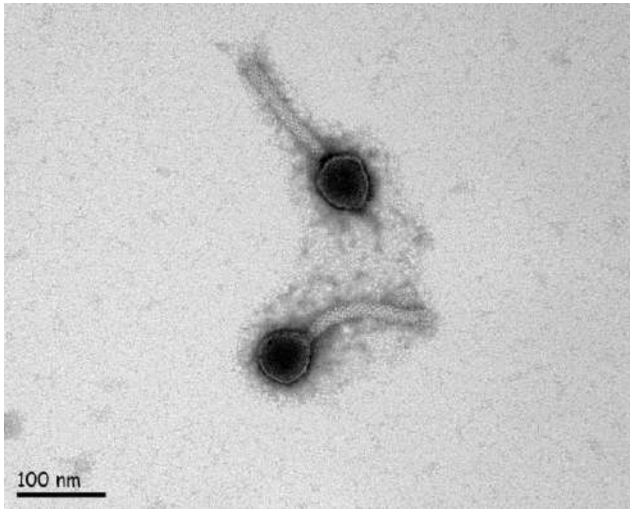


P. aeruginosa

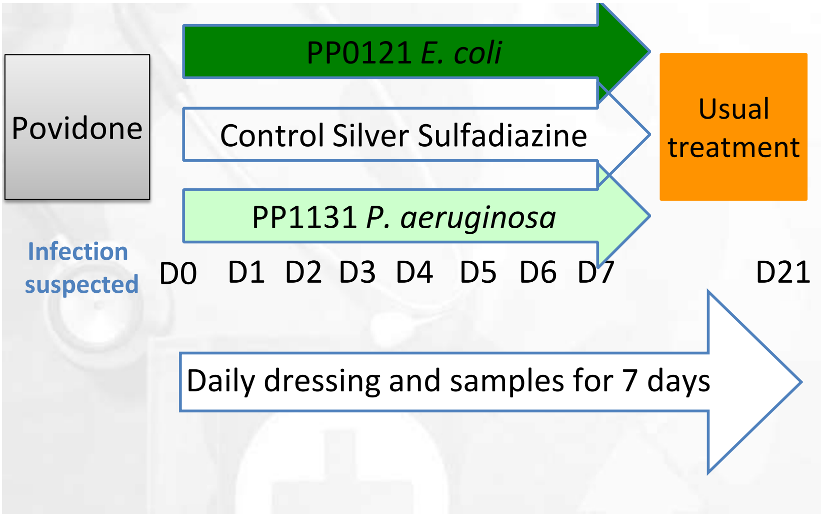
September 9, 2015

A world first: Pherecydes Pharma launches multicenter clinical study of phage therapy in serious burn victims

For the first time, an industry-standard clinical trial is evaluating the tolerance and effectiveness of phages in fighting sensitive antibiotic-resistant infections



Pherecydes



Dr. Patrick Jault, Critical Care, HIA Percy Clamart, France

One year later…

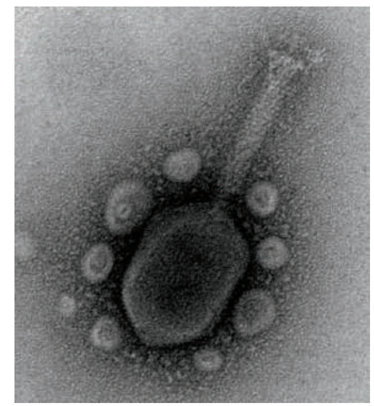
DRUG DEVELOPMENT

Beleaguered phage therapy trial presses on

Setbacks suggest difficult road for much-needed antibiotic alternatives

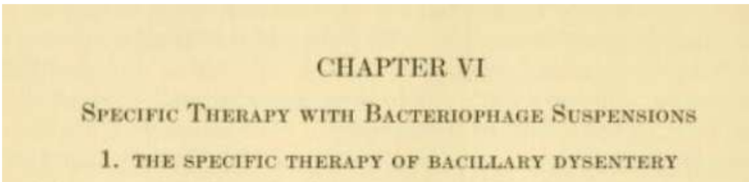
Kelly Servick (June 23, 2016)
Science **352** (6293), 1506. [doi: 10.1126/science.352.6293.1506]

"The trial has faced a series of delays and shrunk in size and scope, hinting at some of the many barriers phages will confront in getting to market…"



In practice, only recruited 15 of the 220 intended patients.

... 90 years before


CHAPTER VI

SPECIFIC THERAPY WITH BACTERIOPHAGE SUSPENSIONS

1. THE SPECIFIC THERAPY OF BACILLARY DYSENTERY

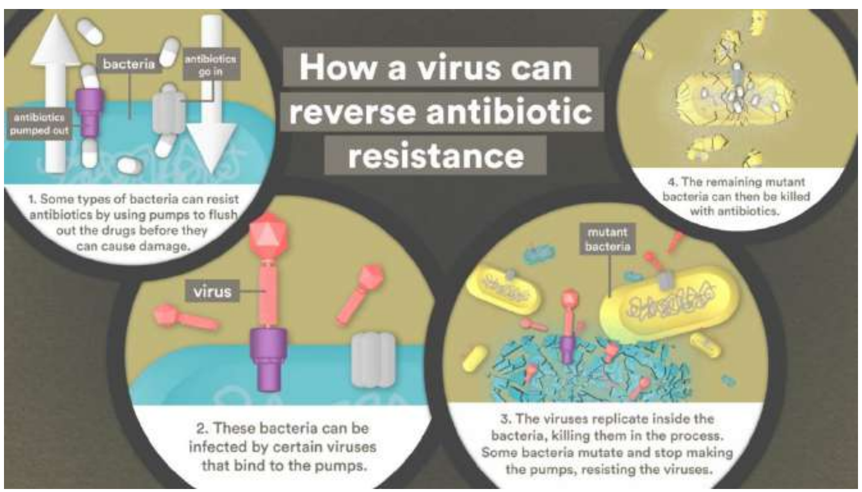
"After being assured that no harmful effects attended the ingestion of the Shiga-bacteriophage, this treatment was applied for therapeutic purposes to patients afflicted with [culture-confirmed] bacillary dysentery."

- Dr. Felix d'Herelle, <u>Bacteriophage and its Behavior</u>, 1926


Felix d'Herelle
wikipedia

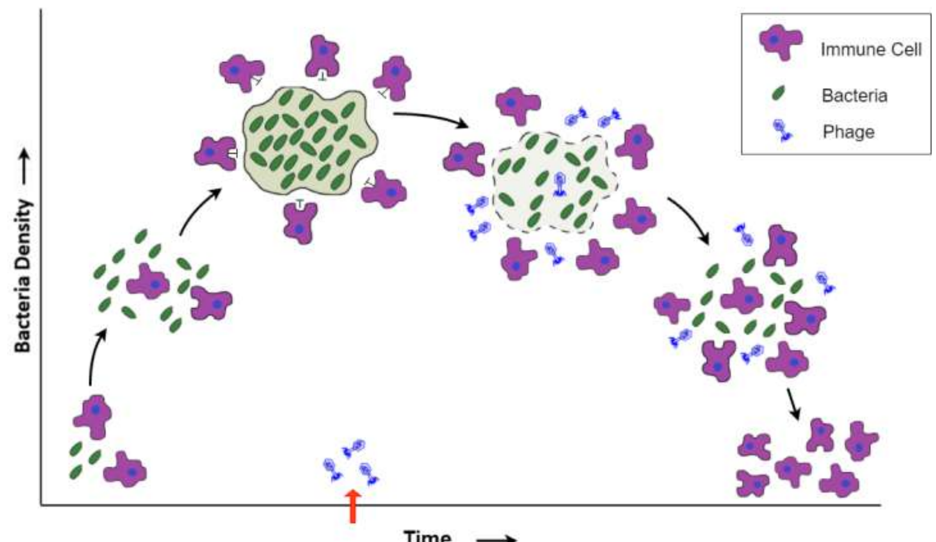
"It's not like there's been some transformative development or technology that means that it's open season on phage therapy."
- Dr. Paul Bollyky, Stanford (in Servick, Science, 2016)

Transformative Development 1



Paul Turner, Yale
Phage-Antibiotics Synergy
Chan et al., Sci. Rep, 2016, 10.1038/srep26717

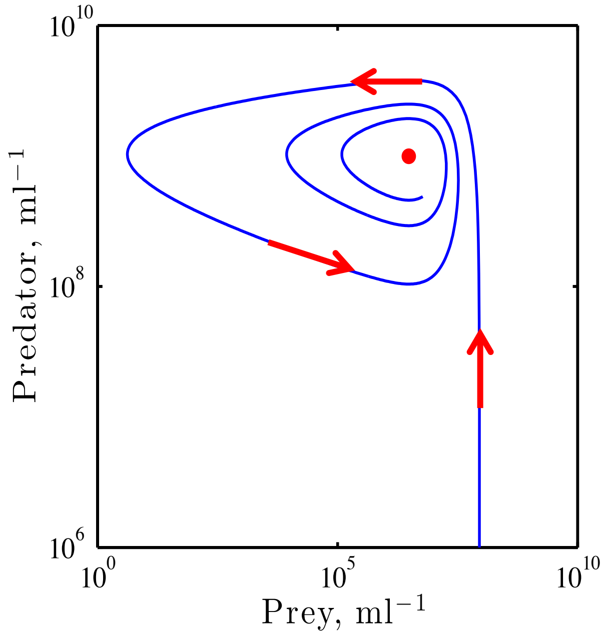
(Transformative) Development 2



Today's talk
Phage-Immune Synergy
Leung & Weitz, J. Theor. Biol. (2017)
Roach, Leung…Weitz & Debarbieux, Cell Host Microbe (2017)
Leung & Weitz, Trends in Microbiology (2019)

From Models to Mice: En Route to a Modern Immunophage Therapy

- The limits of virus-microbe ecology in dynamic elimination of hosts
- Theoretical principles underlying "immunophage synergy"
- Curative treatment of otherwise fatal respiratory diseases using phage in immunomodulated mice



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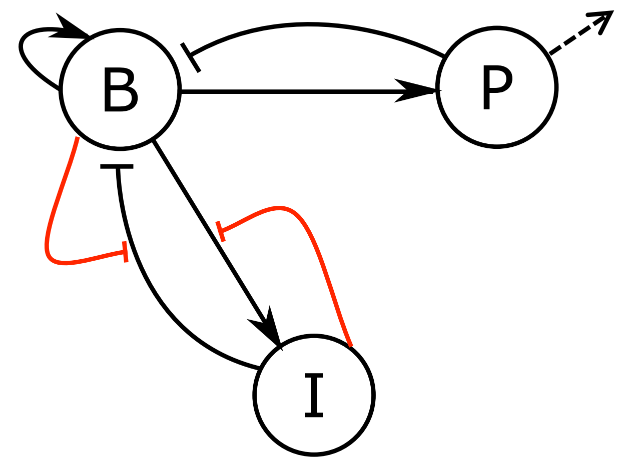

From Models to Mice:
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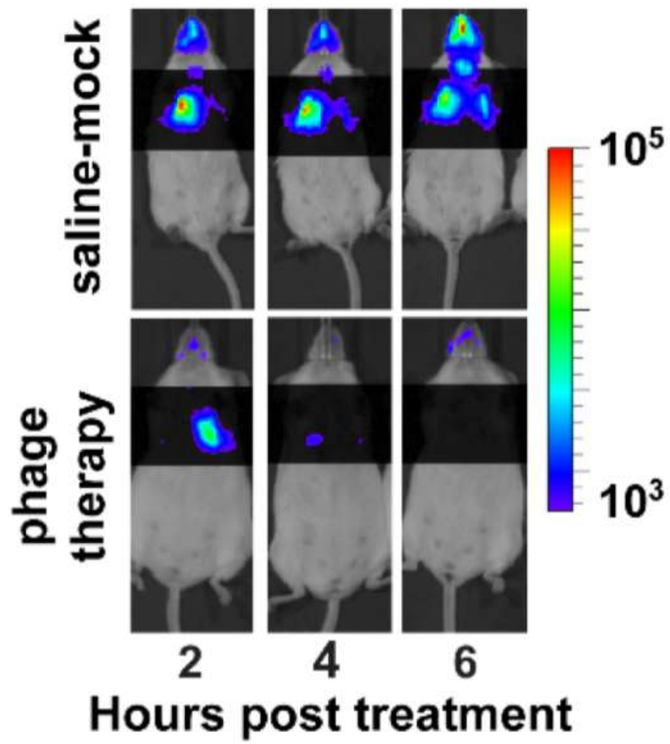
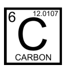


Part 1:

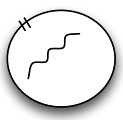
The limits of virus-microbe ecology in dynamic elimination of hosts

Nonlinear model of phage-bacteria population dynamics

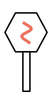
Dynamic model



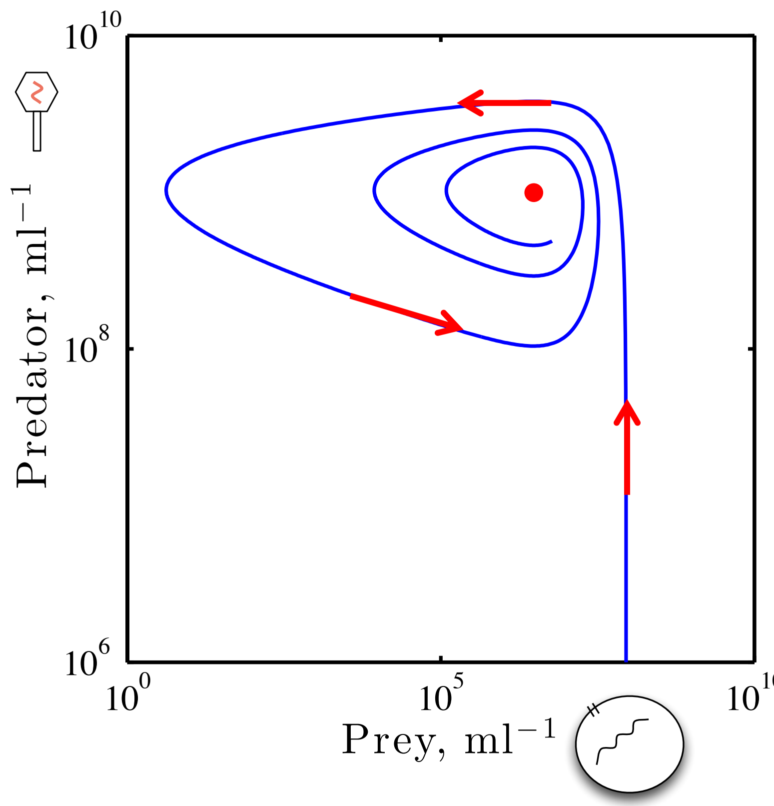
$$\frac{dR}{dt} = \overbrace{\omega R_0}^{\text{media inflow}} - \overbrace{f(R)N}^{\text{nutrient consumption}} - \overbrace{\omega R}^{\text{outflow}}$$



$$\frac{dN}{dt} = \overbrace{\epsilon f(R)N}^{\text{cell division}} - \overbrace{\phi NV}^{\text{infection and lysis}} - \overbrace{\omega N}^{\text{outflow}}$$



$$\frac{dV}{dt} = \overbrace{\beta\phi NV}^{\text{lysis}} - \overbrace{\phi NV}^{\text{infection}} - \overbrace{\omega V}^{\text{outflow}}$$



Counter-clockwise cycles

Interactions:

Resource inflow/outflow

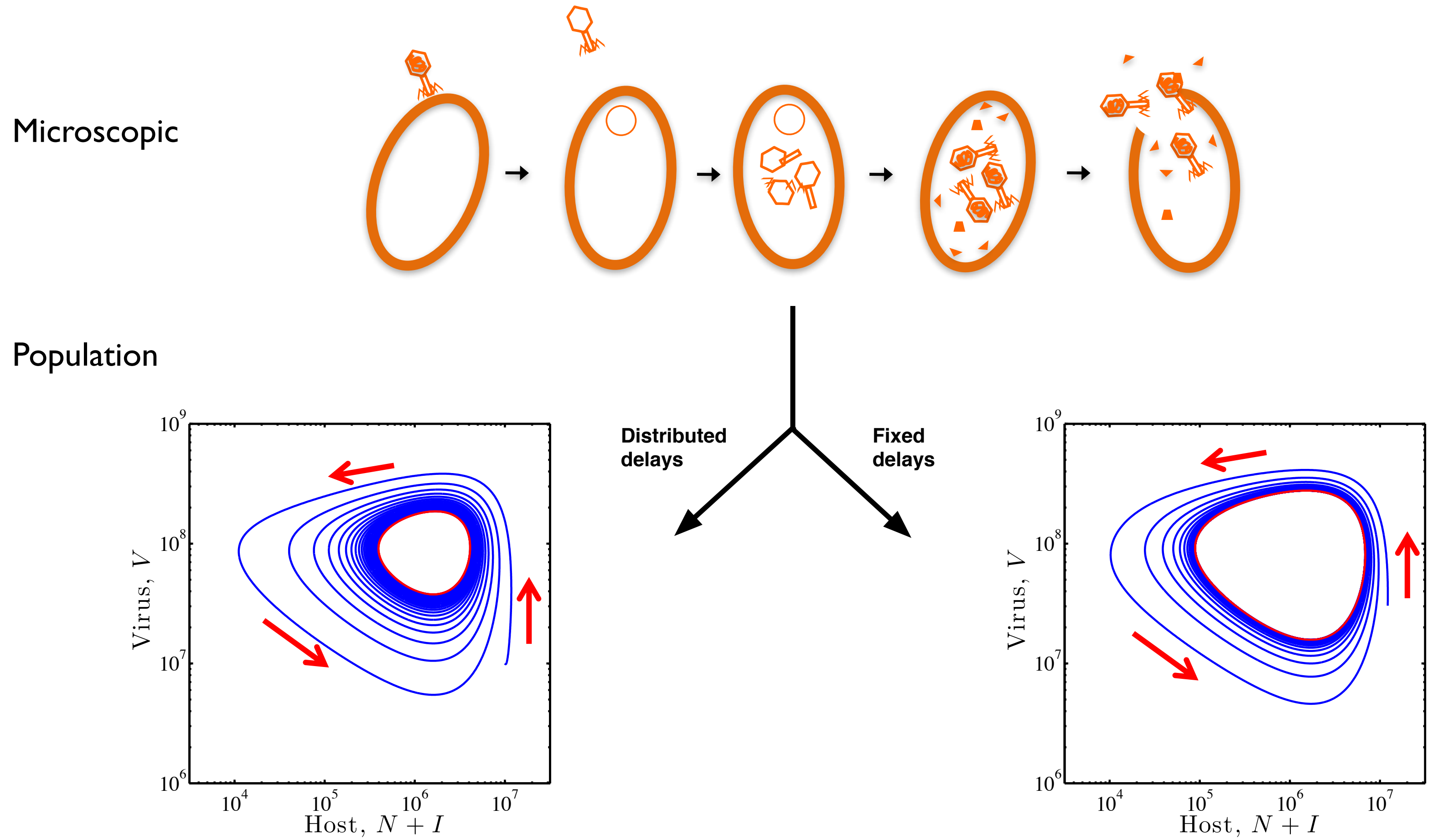
Host growth and outflow

Viral lysis and outflow

(note: original model included time delays)

Similar model proposed by Campbell (1961) Evolution 15: 153
& adapted to phage-bacteria chemostats by Levin et al. (1977) Am. Nat. 111:3

Lotka-Volterra like "counter-clockwise" cycles are robust to many viral interaction mechanisms



Models with an infected class

Models with a single delay between infection and lysis

The same types of cycles can be observed in virus-host population dynamics (in the lab)

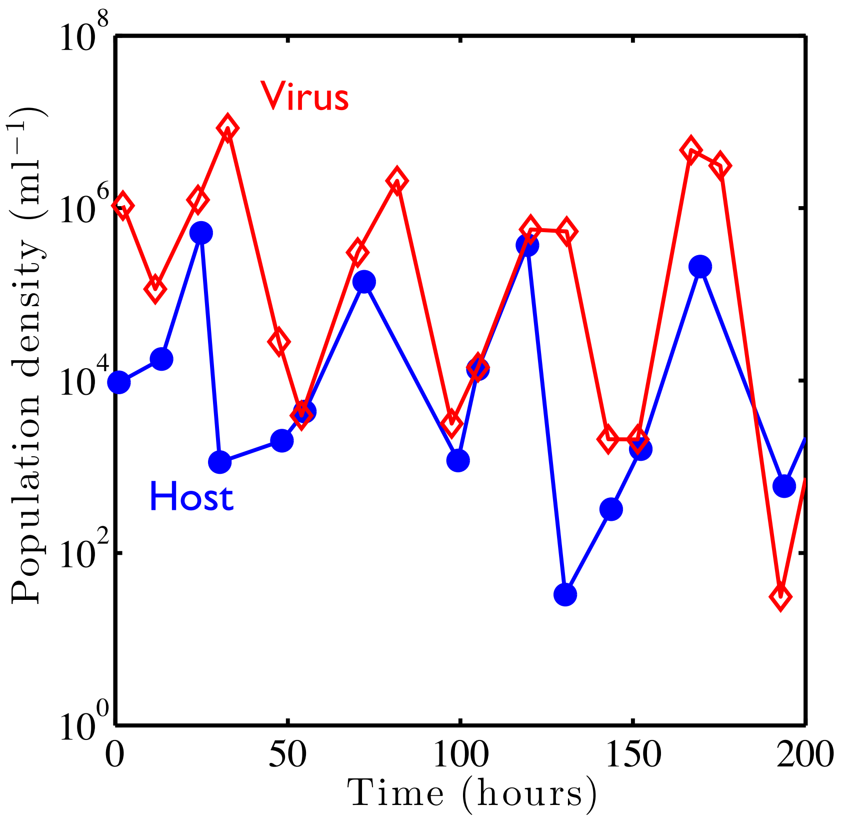
"Lotka-Volterra" like cycles between T4 and *E. coli* B

Data: Bohannan & Lenski, Ecology (1997)

Take-home message:

Original models of viral-host dynamics presuppose a "simple" one virus, one host relationship.

Further analysis of this and other cases in:
Weitz, Quantitative Viral Ecology: Dynamics of Viruses and Their Microbial Hosts, Princeton University Press, 2015.

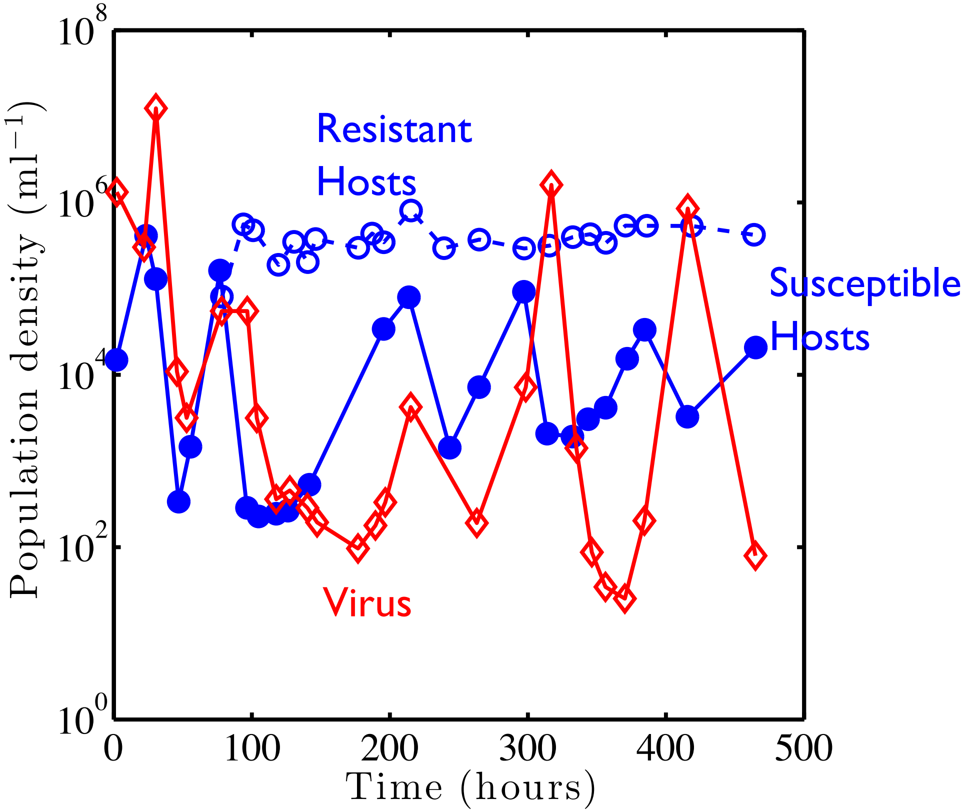


Yet, virus-host dynamics also exhibit "cryptic" dynamics, when hosts evolve…

"Lotka-Volterra" like cycles between T4 and *E. coli* B…

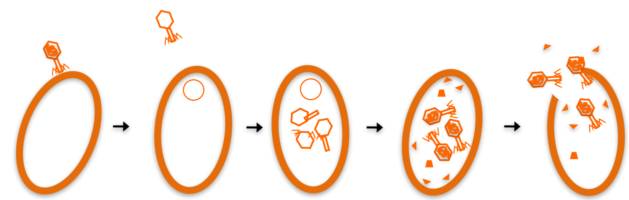
Until something happens at about 200 hrs.

Data: Bohannan & Lenski, Am. Nat. (1999)

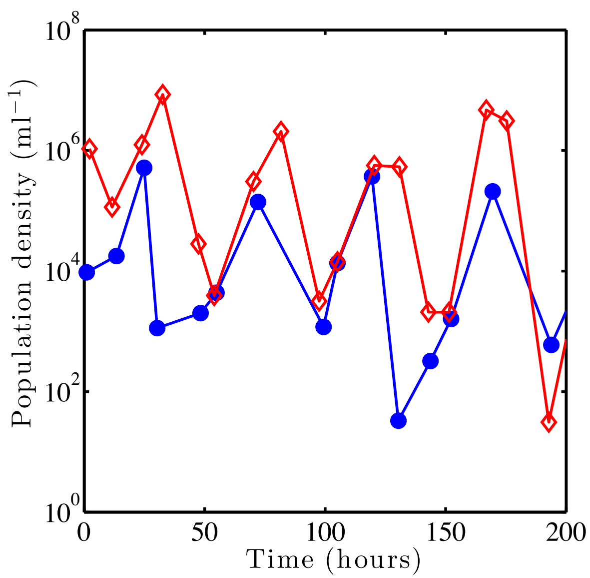


Eco-evolutionary theory and experiments provide a counterpoint to standard phage therapy

1. Viruses can kill individual cells.



2. But, viral populations often *coexist* with host populations.



ance amongst bacteria can lead to the

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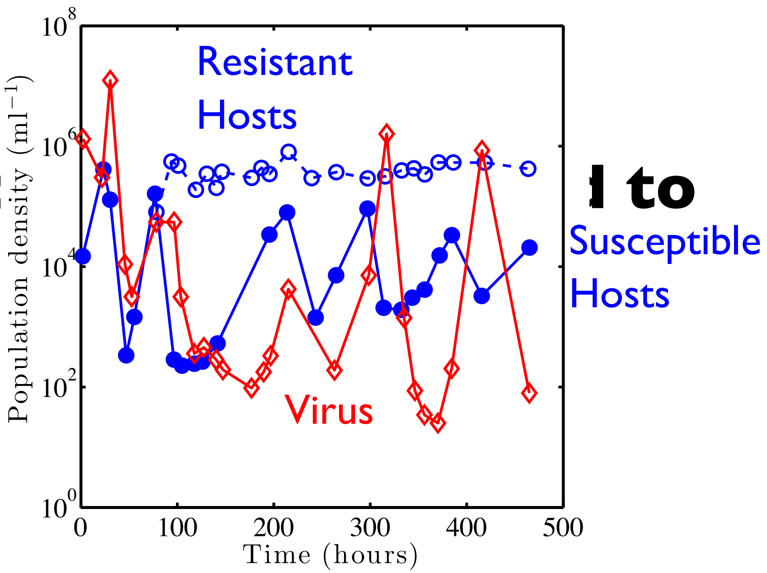
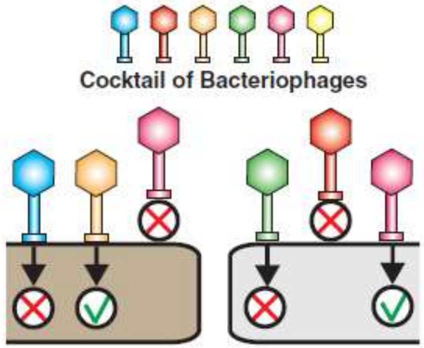
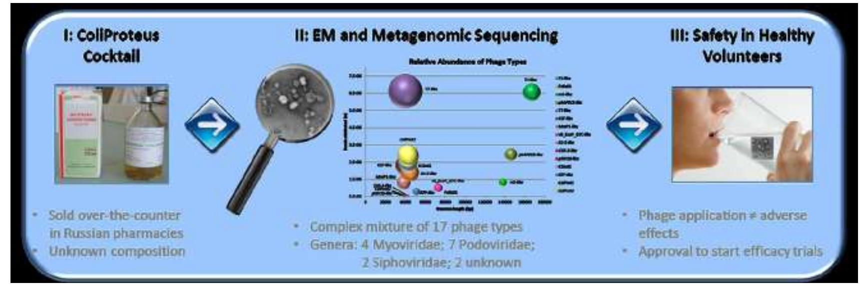




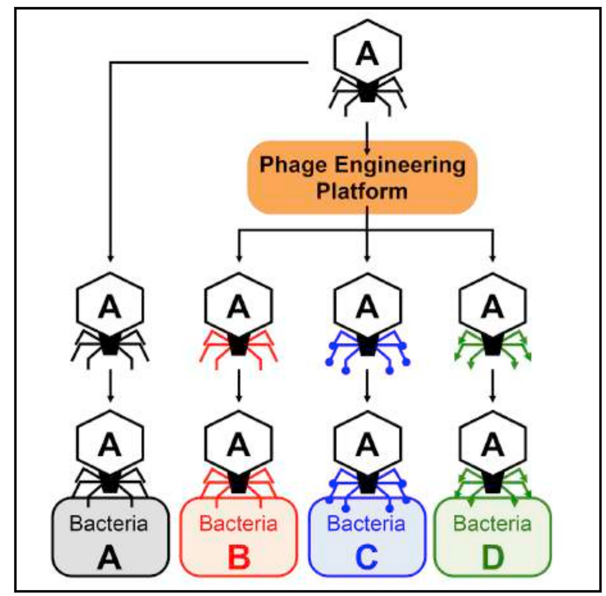
Steven Liu, Cal Poly



Shawna McCallin et al., Virology, 2013

Cocktails

Alex Betts, alexbetts.info, OTC phage cocktails from the Eliava institute

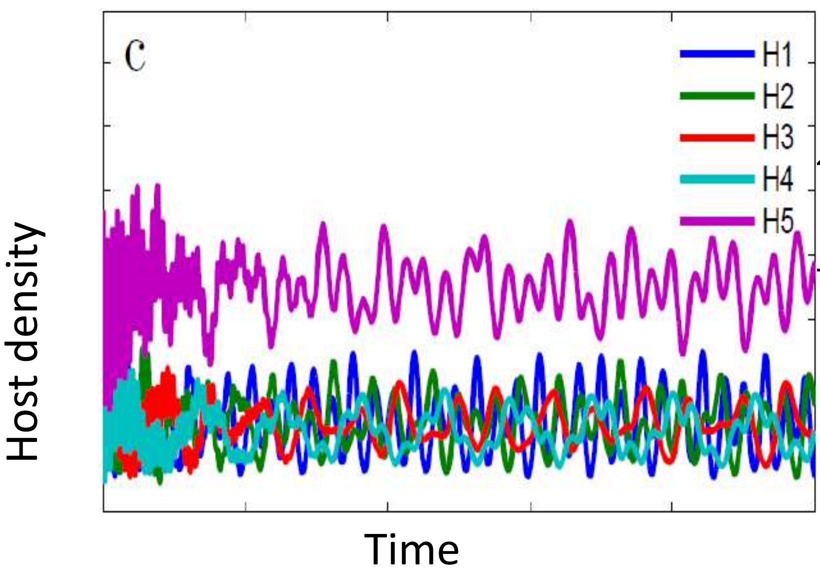


Ando et al., Cell Systems, 2015

Dynamic counterpoint to standard phage therapy still remain *with cocktails*

1. Viruses can kill individual cells. *Cocktails may kill more, but not all, and there are trade-offs with coverage*.

2. But, viral populations *coexist* with host populations, *even when there are multiple populations in a community*.



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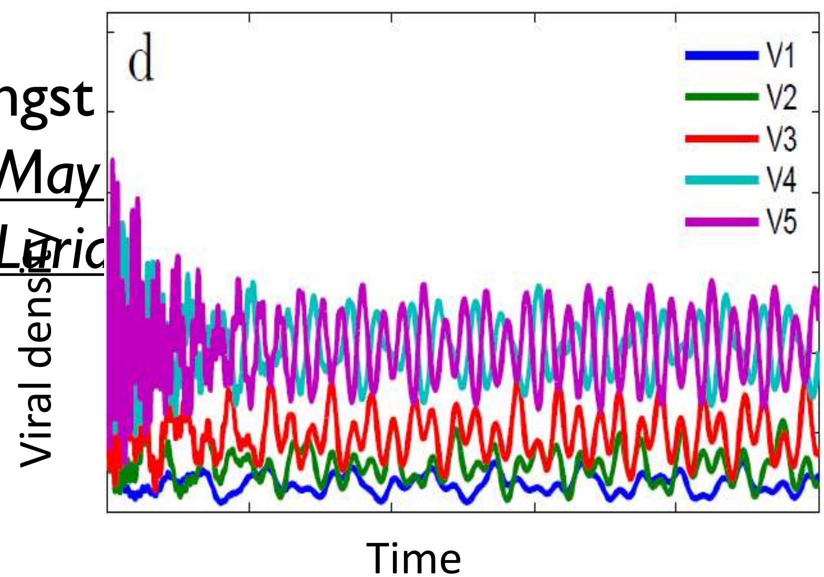
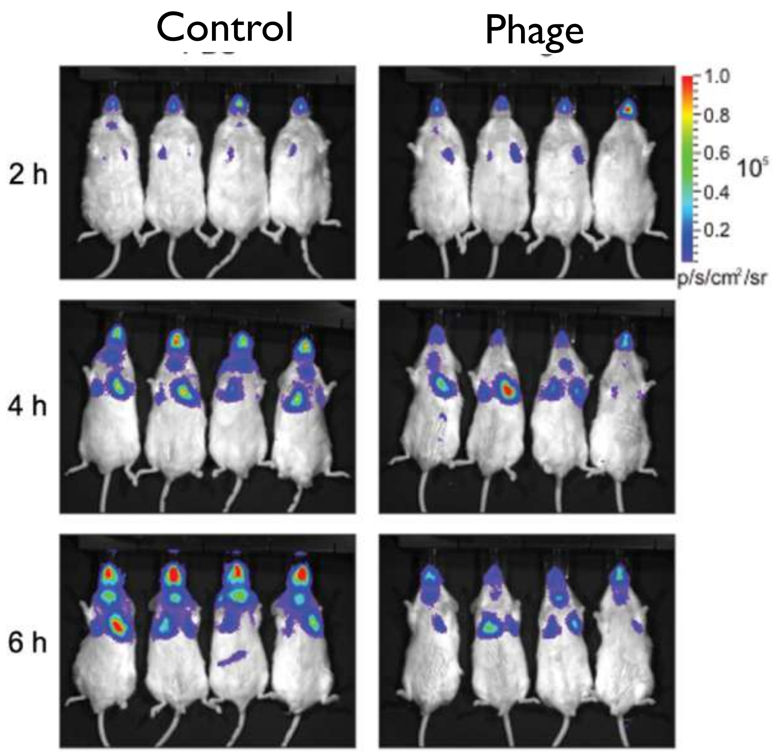
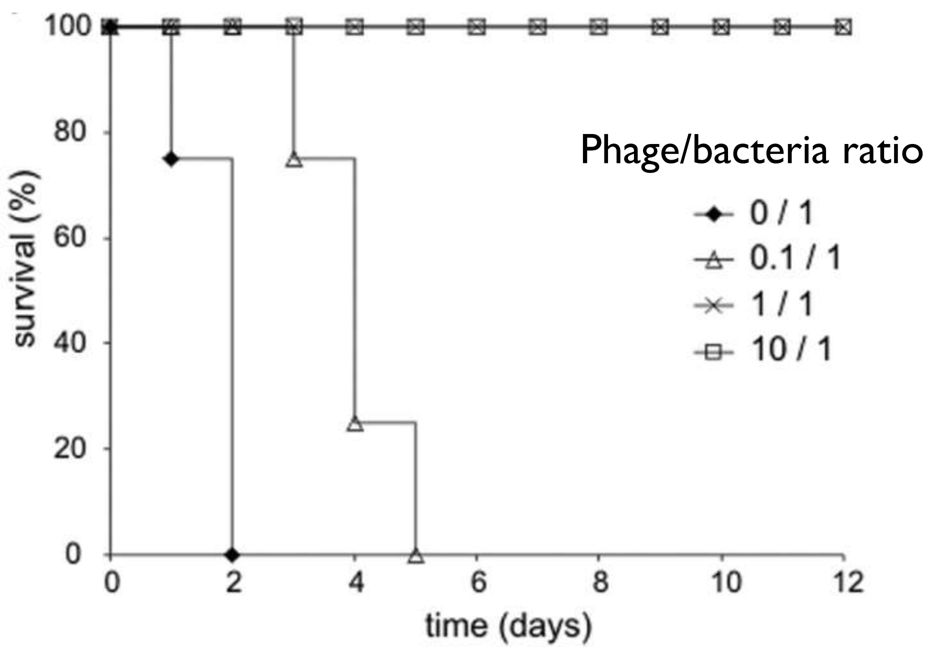


Part 2:

Theoretical principles underlying "immunophage synergy"

A starting point: *In vivo* examples of phage therapy efficacy in mice





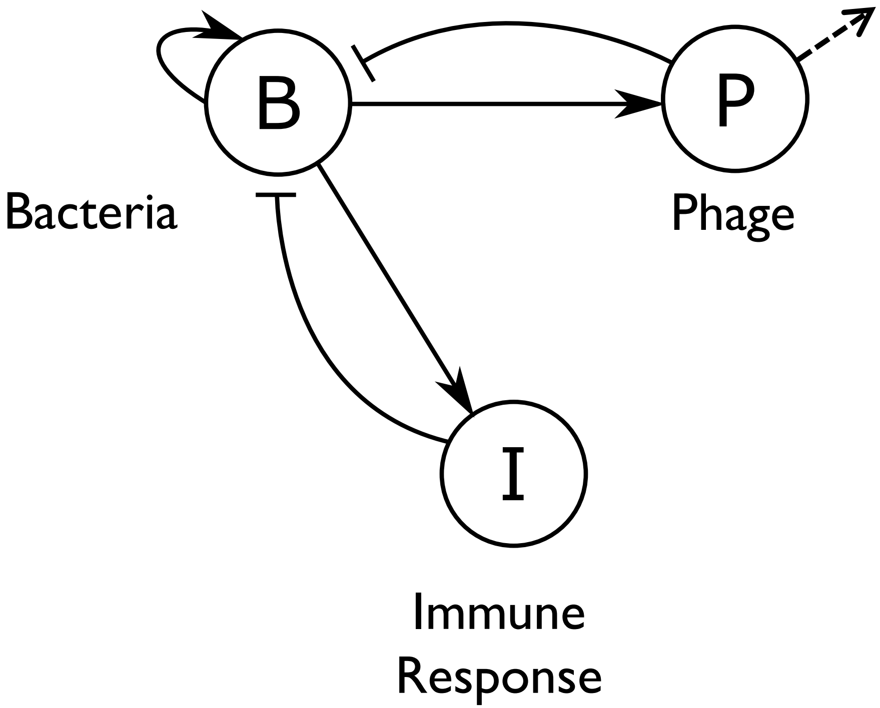
Time-course bacterial load in the infected mice as measured by bioluminescence

Survival curves of mice infected with *P. aeruginosa* treated with diluent or phage at different dosages

L Debarbieux et al., J. Infect. Dis. **201**, 1096 (2010).

Tripartite model of virus-microbe-immune interactions

First proposed by Levin & Bull, Nat. Micro, 2004

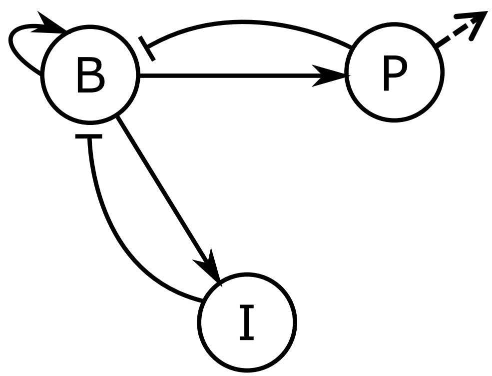


$$\frac{dN}{dt} = \overbrace{\epsilon f(R) N}^{\text{cell division}} - \overbrace{\phi N V}^{\text{infection}} - \overbrace{\chi I N}^{\text{immune killing}}$$

$$\frac{dV}{dt} = \overbrace{\beta \phi N_\tau V_\tau}^{\text{lysis}} - \overbrace{\phi N V}^{\text{infection}} - \overbrace{\omega V}^{\text{viral decay}}$$

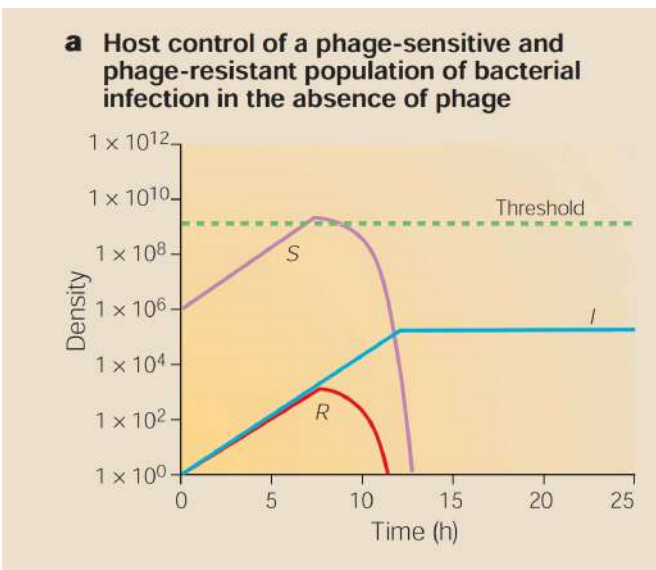
$$\frac{dI}{dt} = \overbrace{\alpha I \left(\frac{N}{N + K_N} \right)}^{\text{immune stimulation}}$$

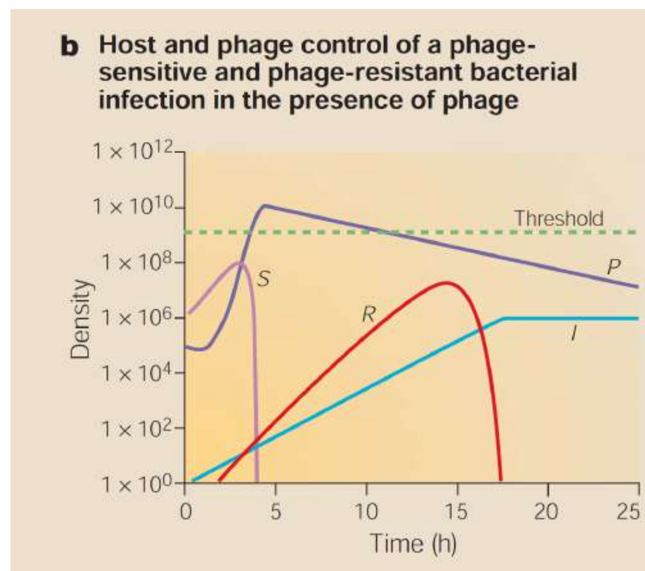
Tripartite model of virus-microbe-immune interactions
First proposed by Levin & Bull, Nat. Micro, 2004



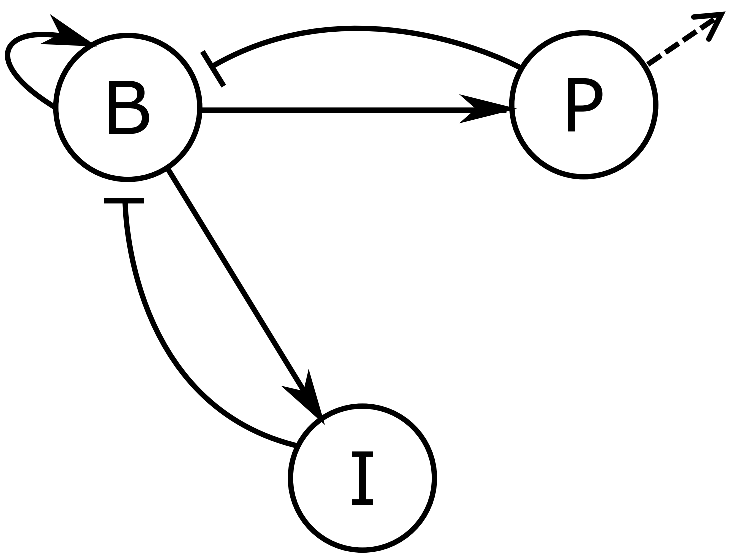
Some challenges:

- Disease state is tied to crossing transient population threshold – rather than elimination.
- Immune system response can grow w/out bound.
- Crucially, phage are not needed to eliminate bacteria in the long-term.





Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)



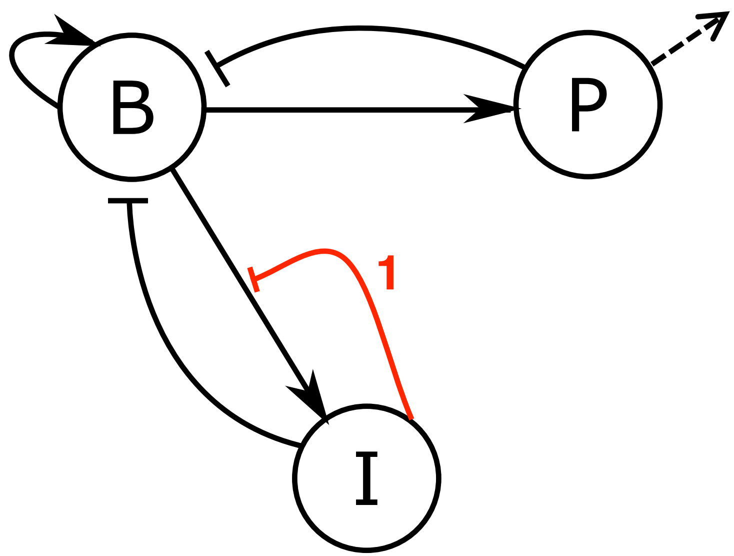
$$\frac{dB}{dt} = \overbrace{rB\left(1 - \frac{B}{K_C}\right)}^{\text{Growth}} - \overbrace{\phi BP}^{\text{Lysis}} - \overbrace{\epsilon IB}^{\text{Immune killing}}$$

$$\frac{dP}{dt} = \overbrace{\beta\phi BP}^{\text{Viral release}} - \overbrace{\omega P}^{\text{Decay}}$$

$$\frac{dI}{dt} = \overbrace{\alpha I\left(\frac{B}{B + K_N}\right)}^{\text{Immune stimulation}}.$$

We begin with a modified Levin-Bull model and extend it in two key ways:

Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)



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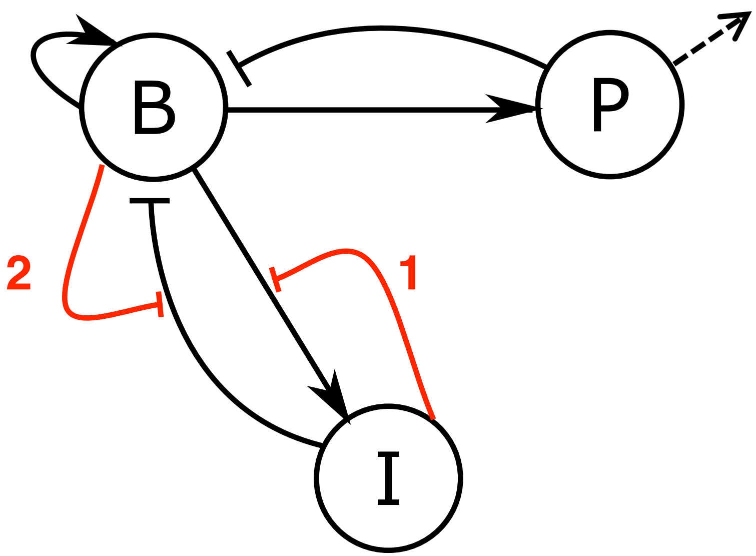
We begin with a modified Levin-Bull model and extend it in two key ways:

1. **Immune stimulation has a biological "carrying capacity"**

Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)



$$\frac{dB}{dt} = \overbrace{rB\left(1 - \frac{B}{K_C}\right)}^{\text{Growth}} - \overbrace{\phi BP}^{\text{Lysis}} - \overbrace{\frac{\epsilon IB}{1 + B/K_D}}^{\text{Immune killing}}$$

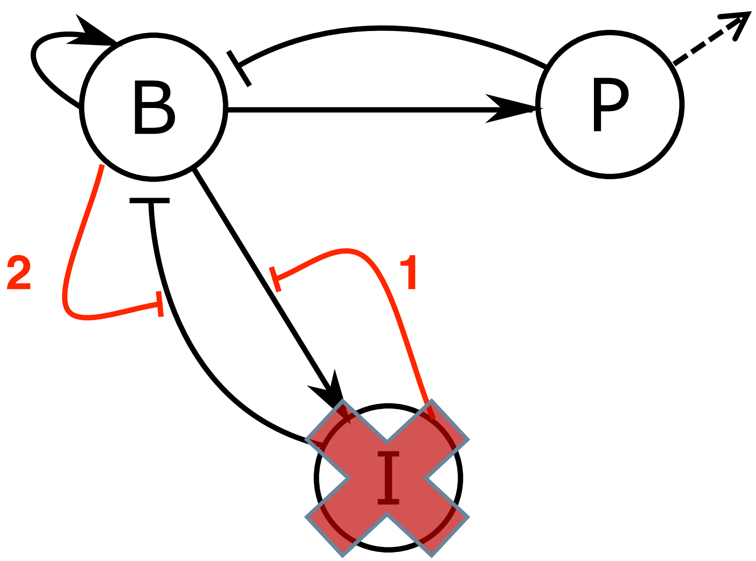
$$\frac{dP}{dt} = \overbrace{\beta\phi BP}^{\text{Viral release}} - \overbrace{\omega P}^{\text{Decay}}$$

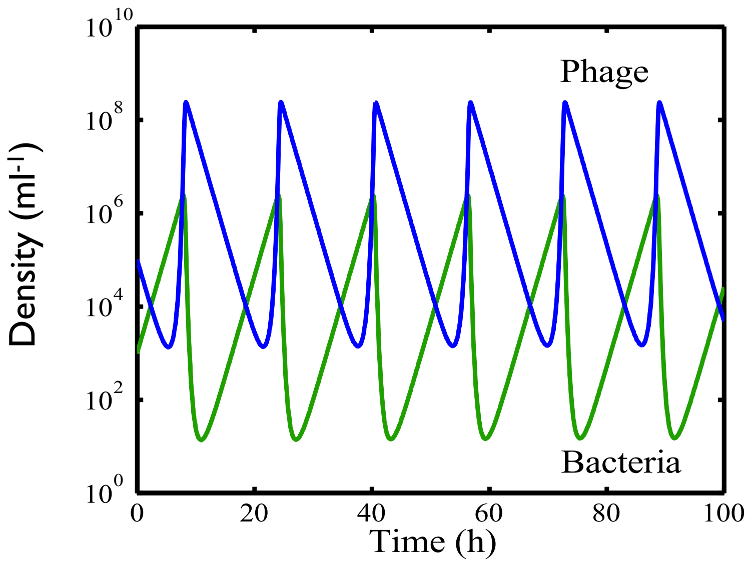
$$\frac{dI}{dt} = \overbrace{\alpha I\left(1 - \frac{I}{K_I}\right)\left(\frac{B}{B + K_N}\right)}^{\text{Immune stimulation}}.$$

We begin with a modified Levin-Bull model and extend it in two key ways:

1. **Immune stimulation has a biological "carrying capacity"**
2. **Bacteria can initiate density-dependent defenses (e.g., biofilms) to evade the immune response**

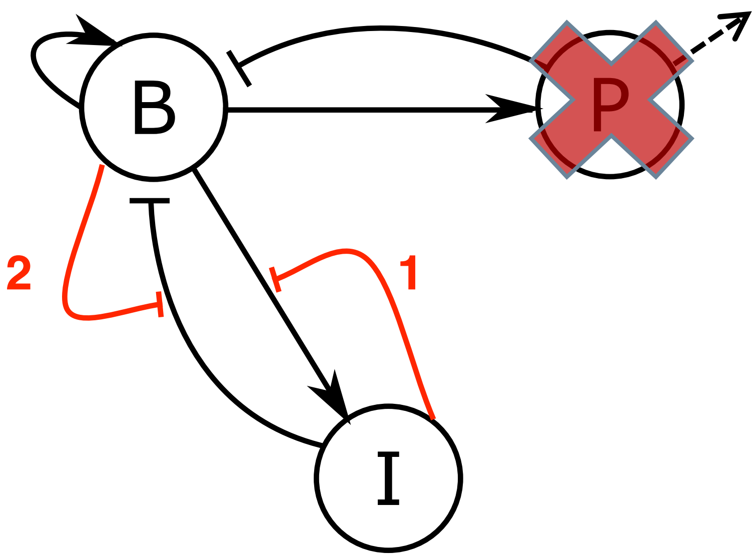
Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)

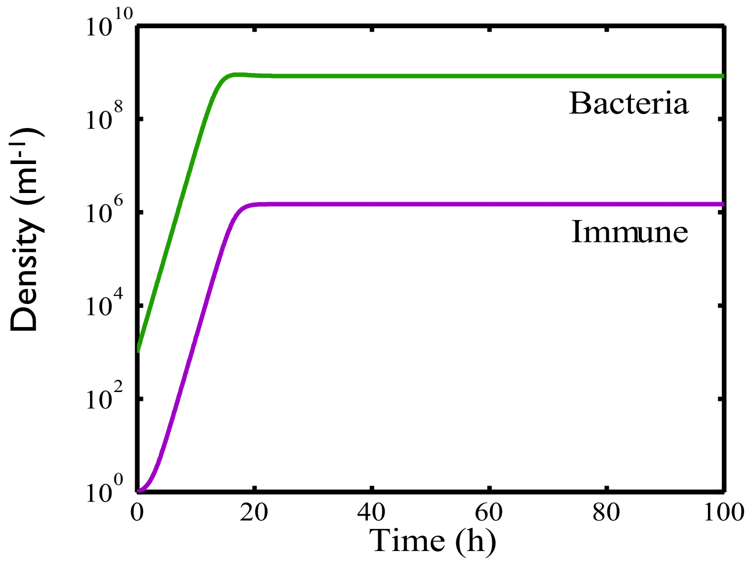




Immunophage synergy model – dynamics w/out immune response

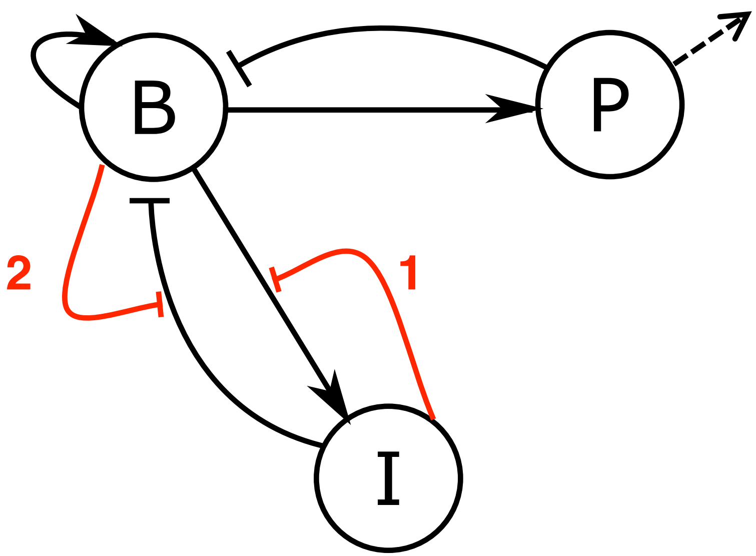
Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)

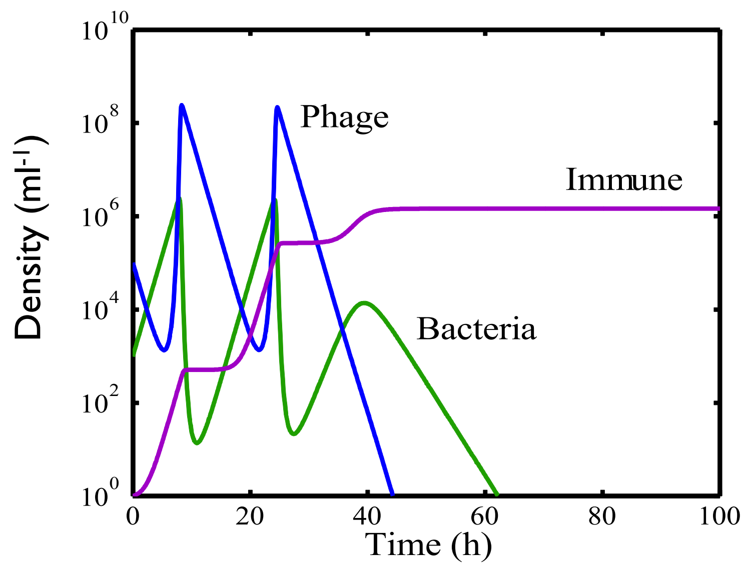




Immunophage synergy model – dynamics w/out phage

Proposed immunophage synergy model
Leung & Weitz, J. Theor. Biol (2017)

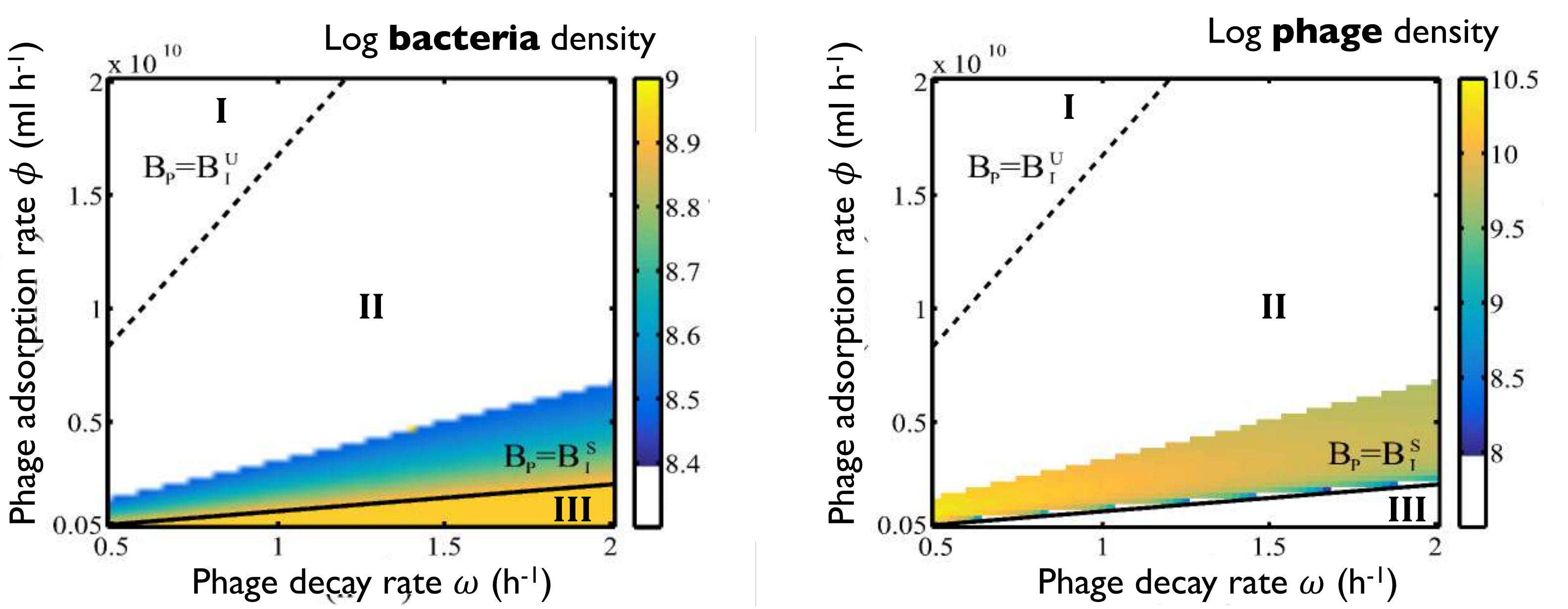




Immunophage synergy model – tripartite dynamics

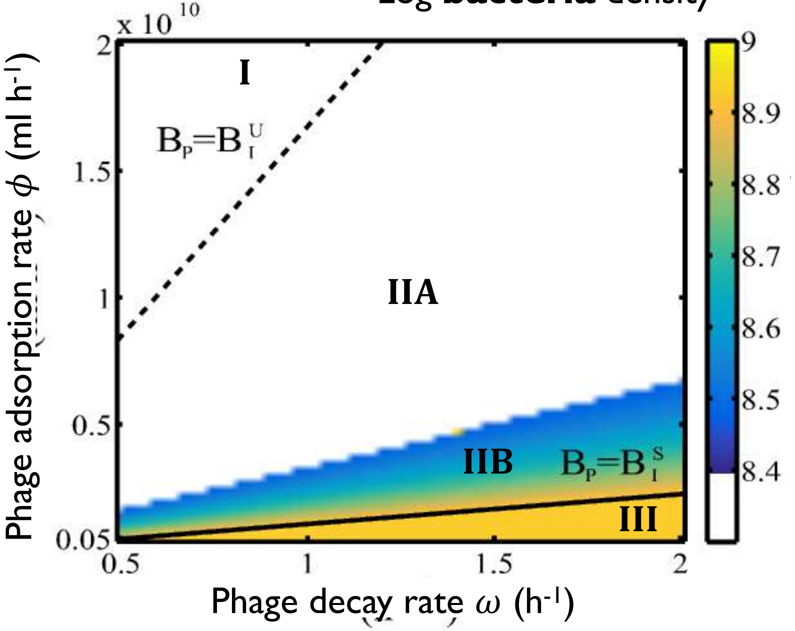
Hypothesis: phage drive *equilibrium* microbial densities to levels *controllable* by the immune response

I	$B_P < B_I^U$	Bacteria extinction (synergy)
II	$B_I^U < B_P < B_I^S$	Coexistence
III	$B_P > B_I^S$	Phage extinction

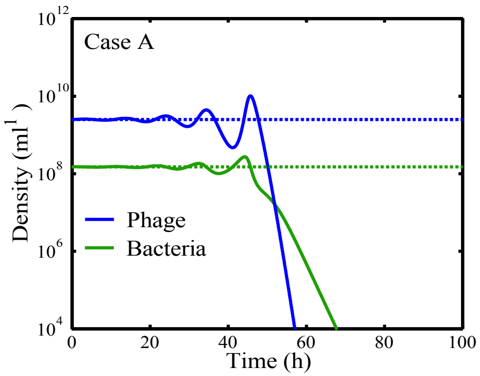


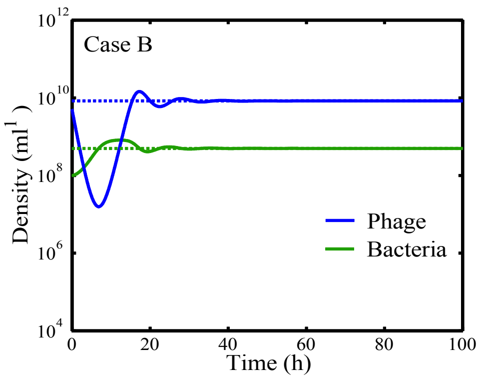
Discrepancy: the model seems to work more robustly than fixed point comparison predicts (see Region II).

Stability of fixed points extends the predicted region of immunophage synergy



IIA. Dynamic instability enables synergy

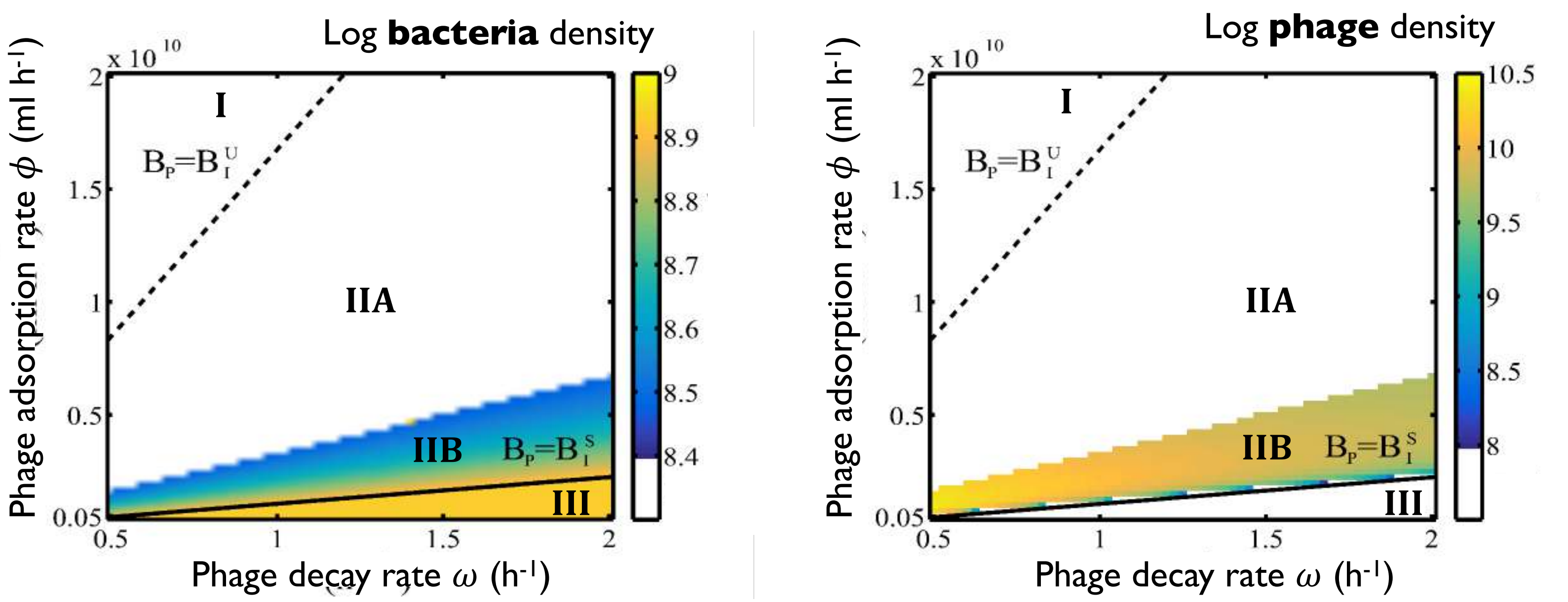




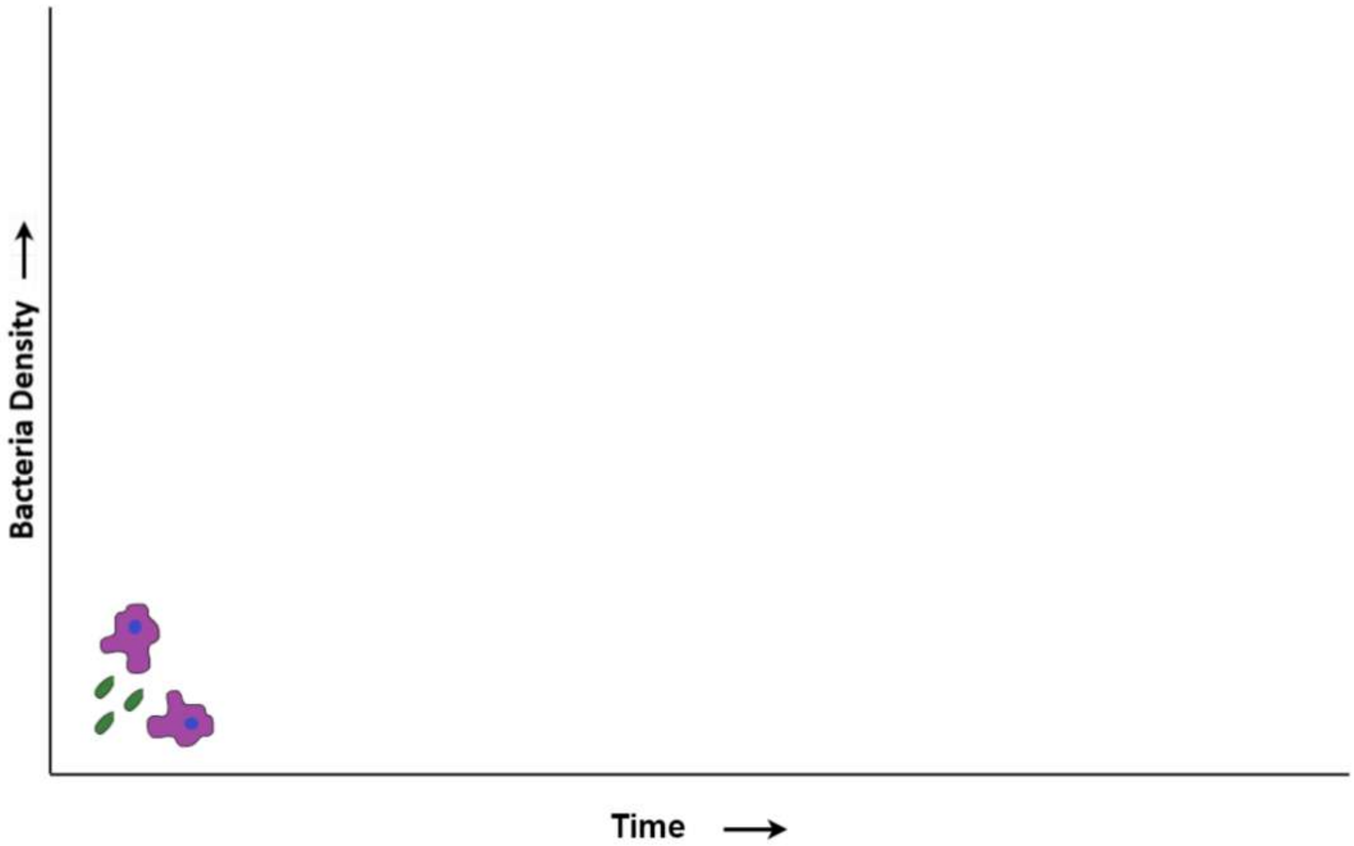
IIB. Dynamic stability enables coexistence

Sufficient conditions for robust immunophage synergy leading to bacterial elimination

I	$B_P < B_I^U$	Bacteria elimination (fixed synergy)
IIa	$B_I^U < B_P < B_I^M$	Bacteria elimination (dynamic synergy)
IIb	$B_I^M < B_P < B_I^S$	Stable coexistence
III	$B_P > B_I^S$	Phage extinction



Synopsis of the Proposed Mechanism of Phage-Immune Synergy



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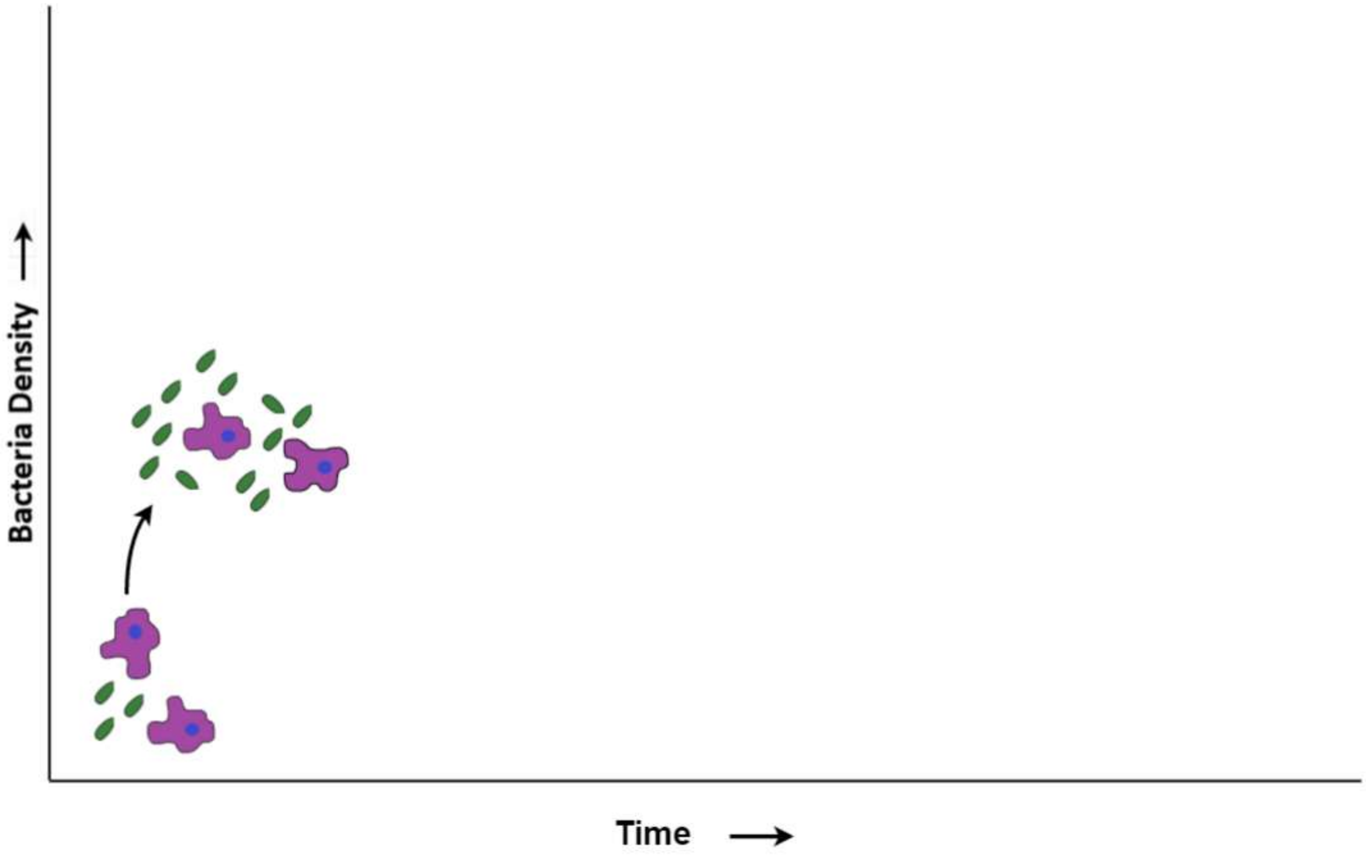

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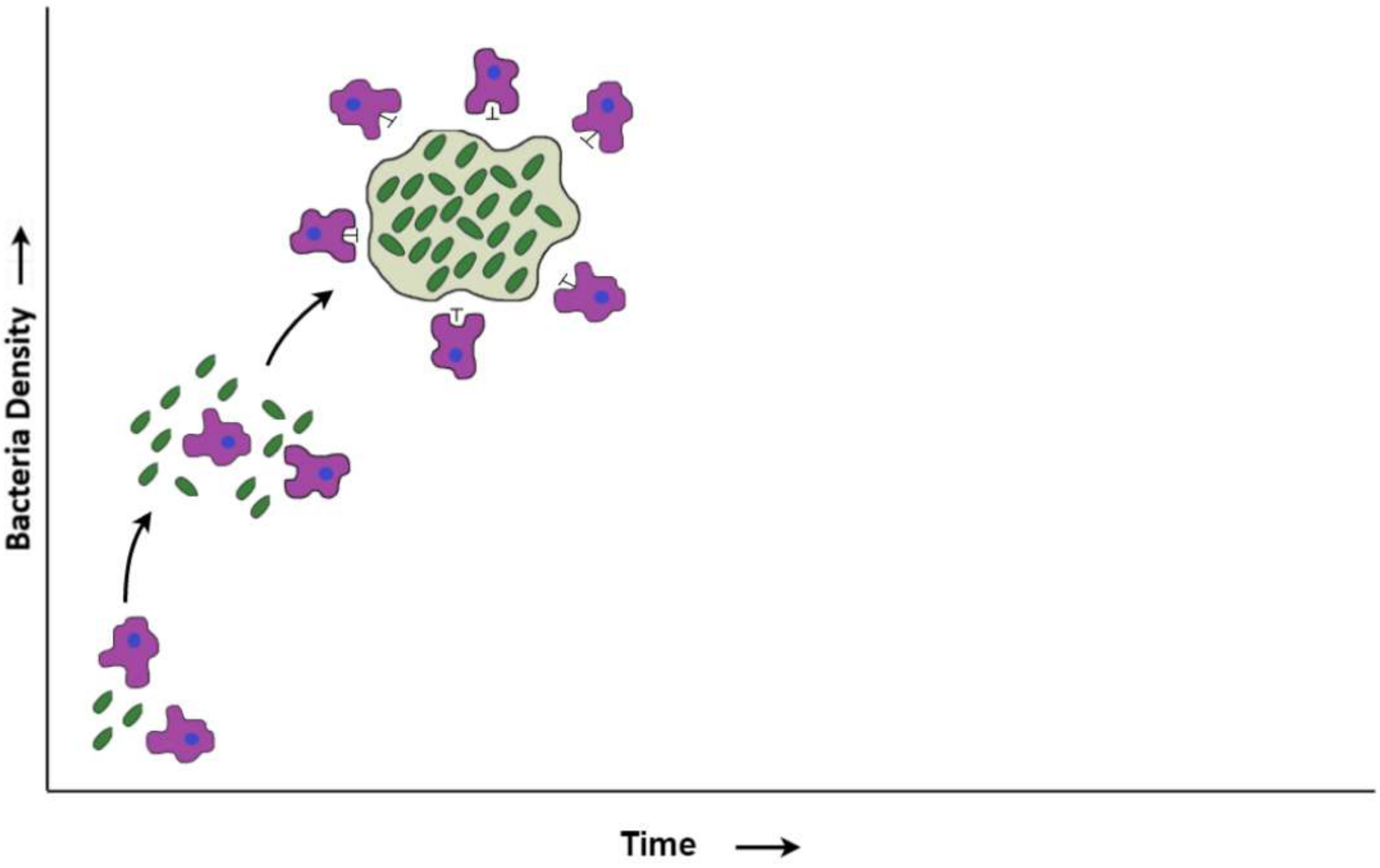

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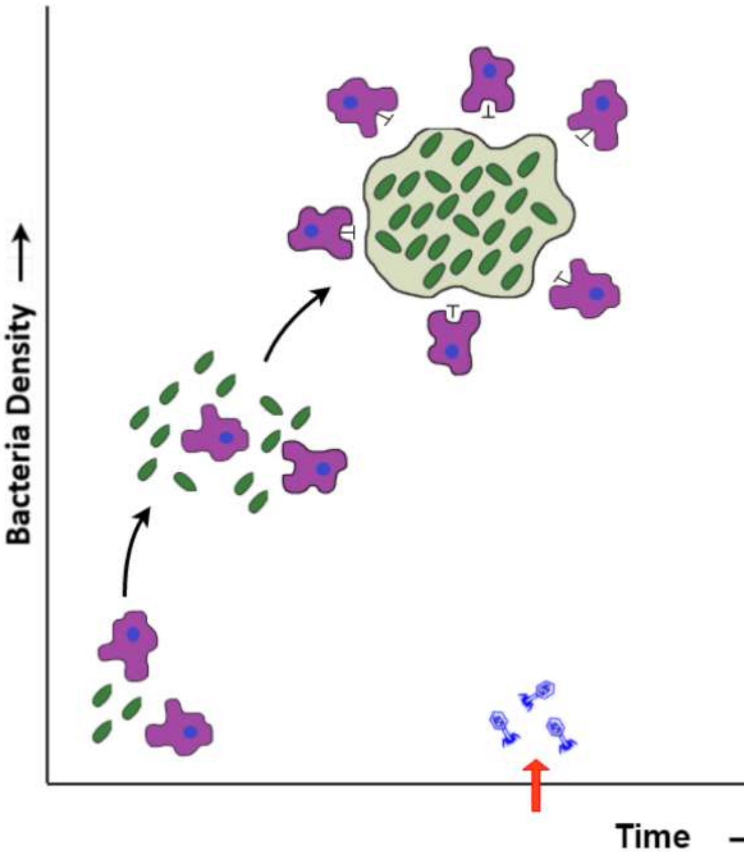
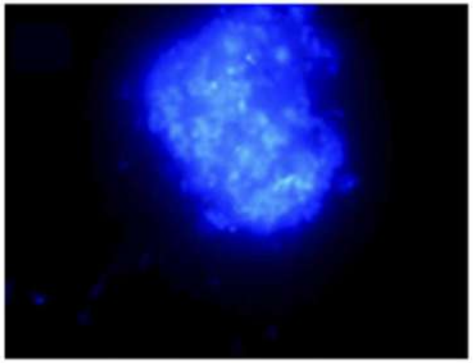
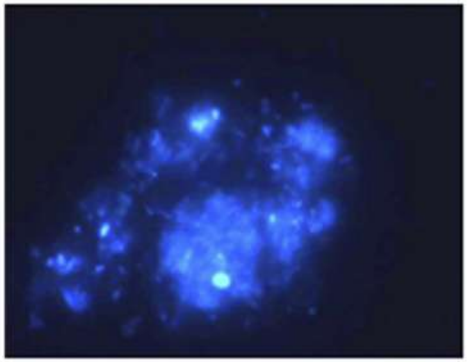


Biofilm before phage treatment



D Alemayehu et al., mBio **3**, e00029-12 (2012)

Biofilm after phage treatment



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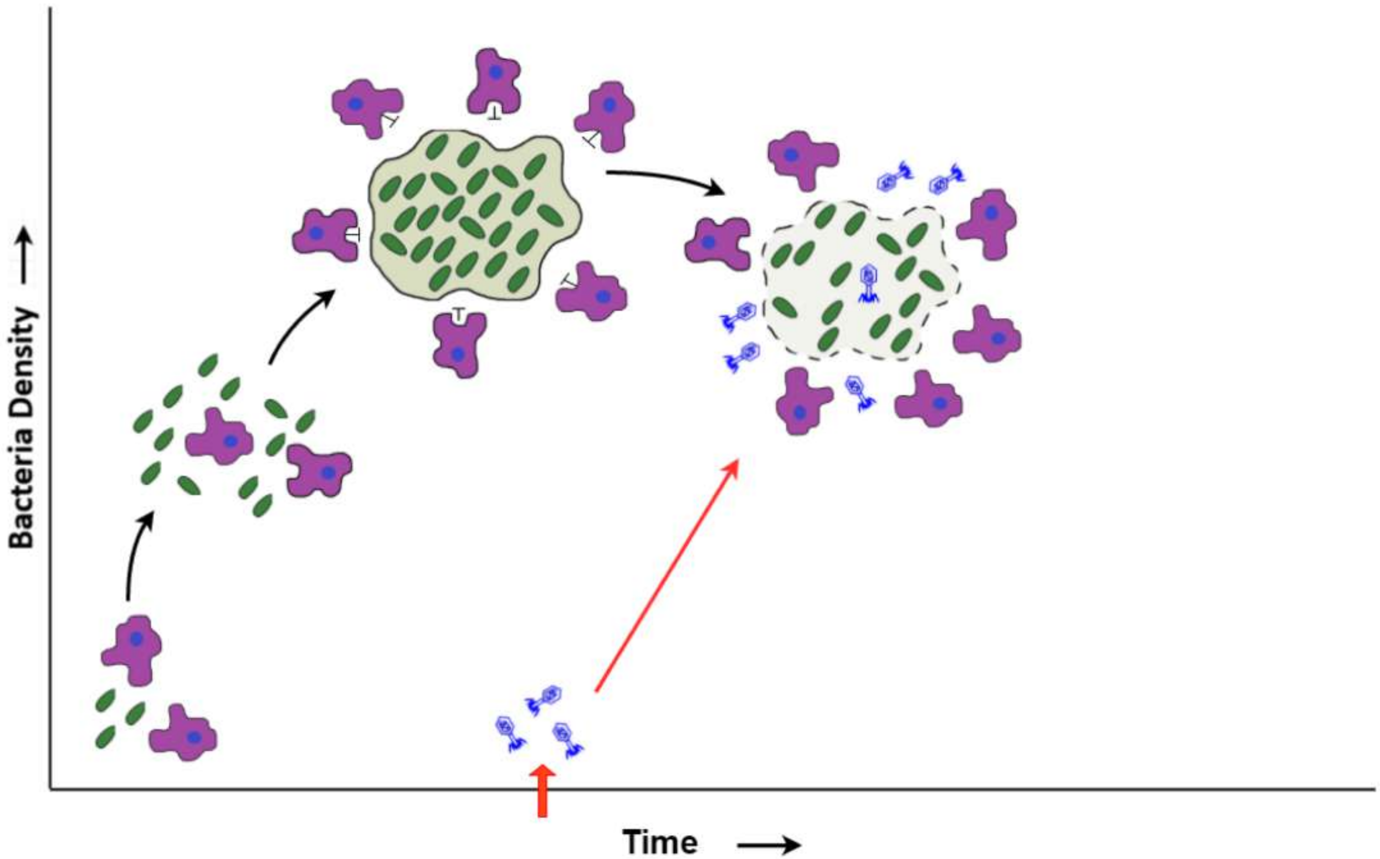

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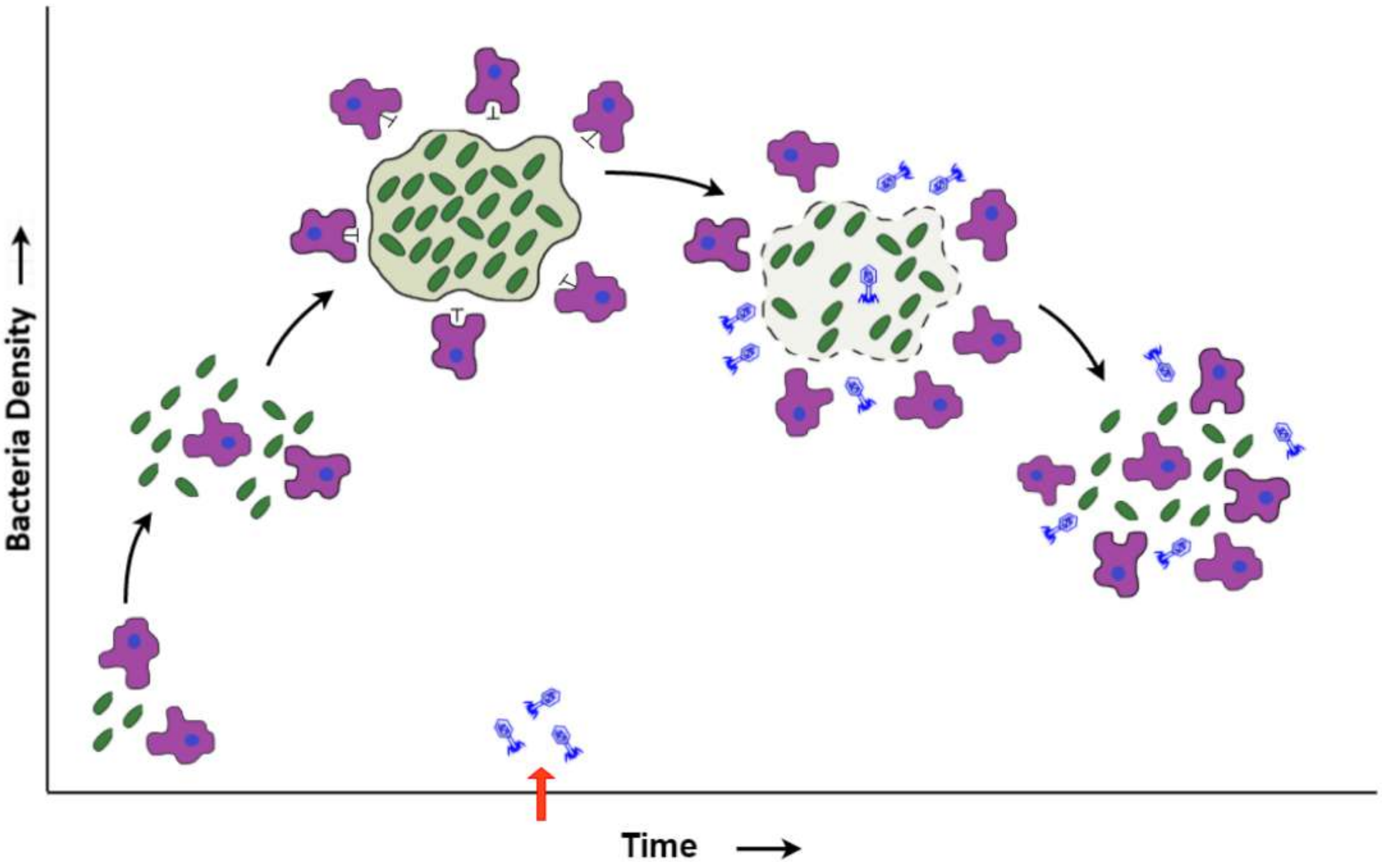
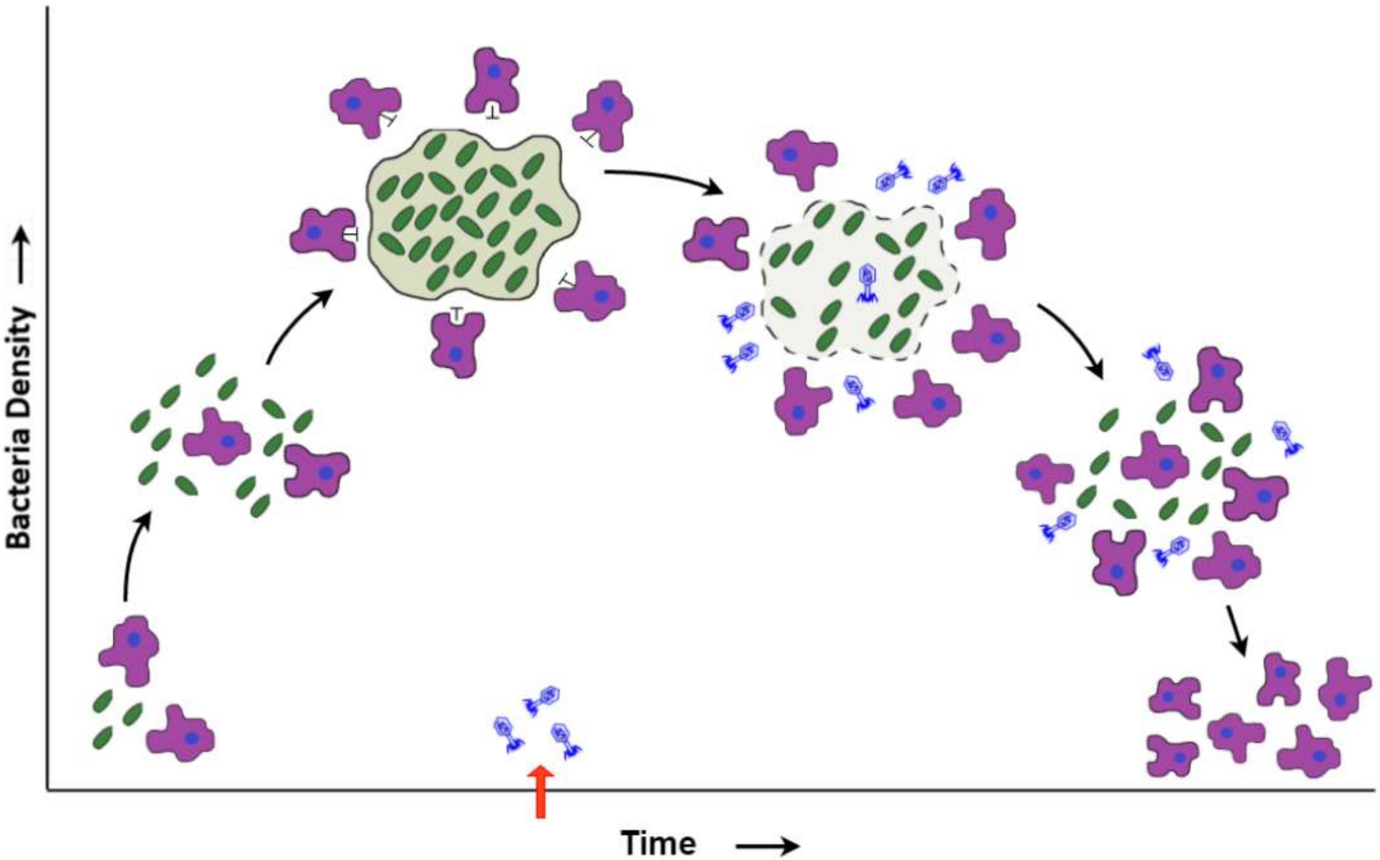


Synopsis of the Proposed Mechanism of Phage-Immune Synergy



Part 3:

Curative treatment of otherwise fatal respiratory diseases using phage in immunomodulated mice

Viruses of Microbes 2016

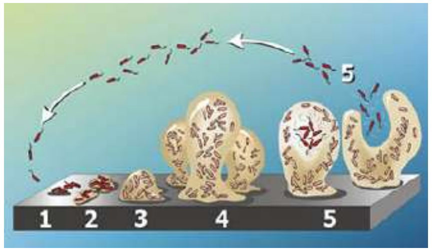
18-22 July 2016

One of the first presenters on "phage therapy" focus session… Dwayne Roach

Dr. Dwayne Roach
Pasteur Institute

Prof. Laurent Debarbieux
Pasteur Institute

Prof. James Di Santo
Pasteur Institute



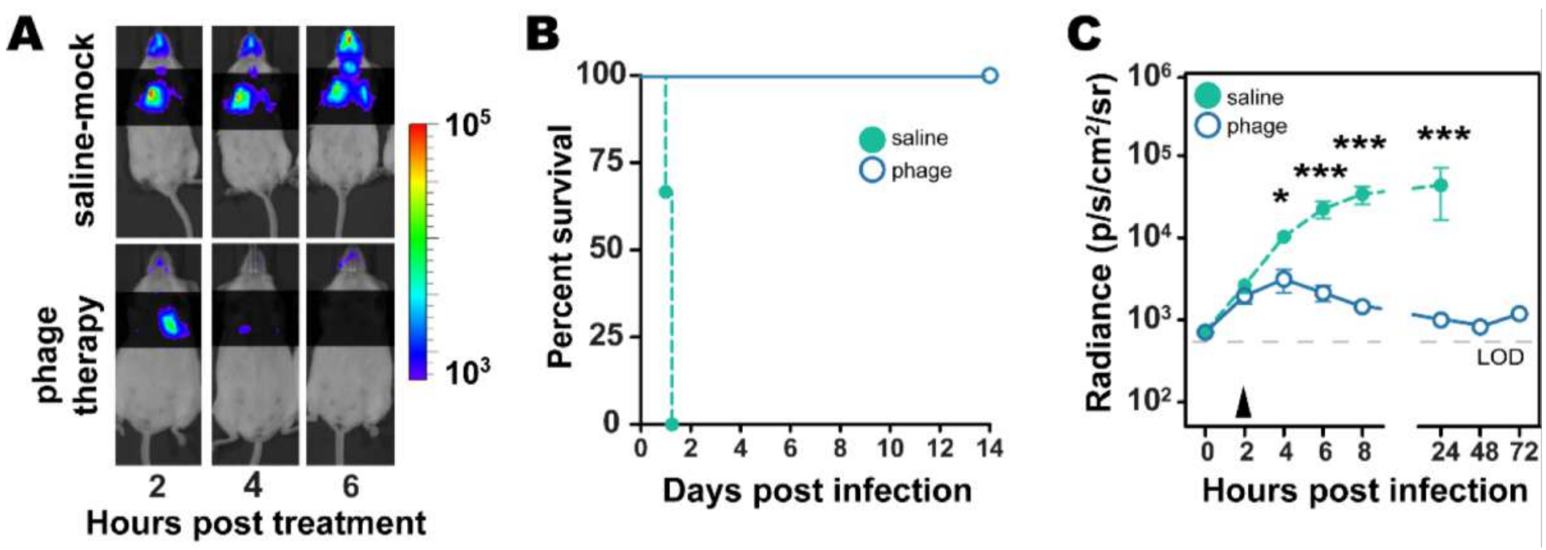
MicrobeWiki

Bacteria:
<u>Multi-drug resistant</u> *Pseudomonas aeruginosa,* fatal acute pneumonia model

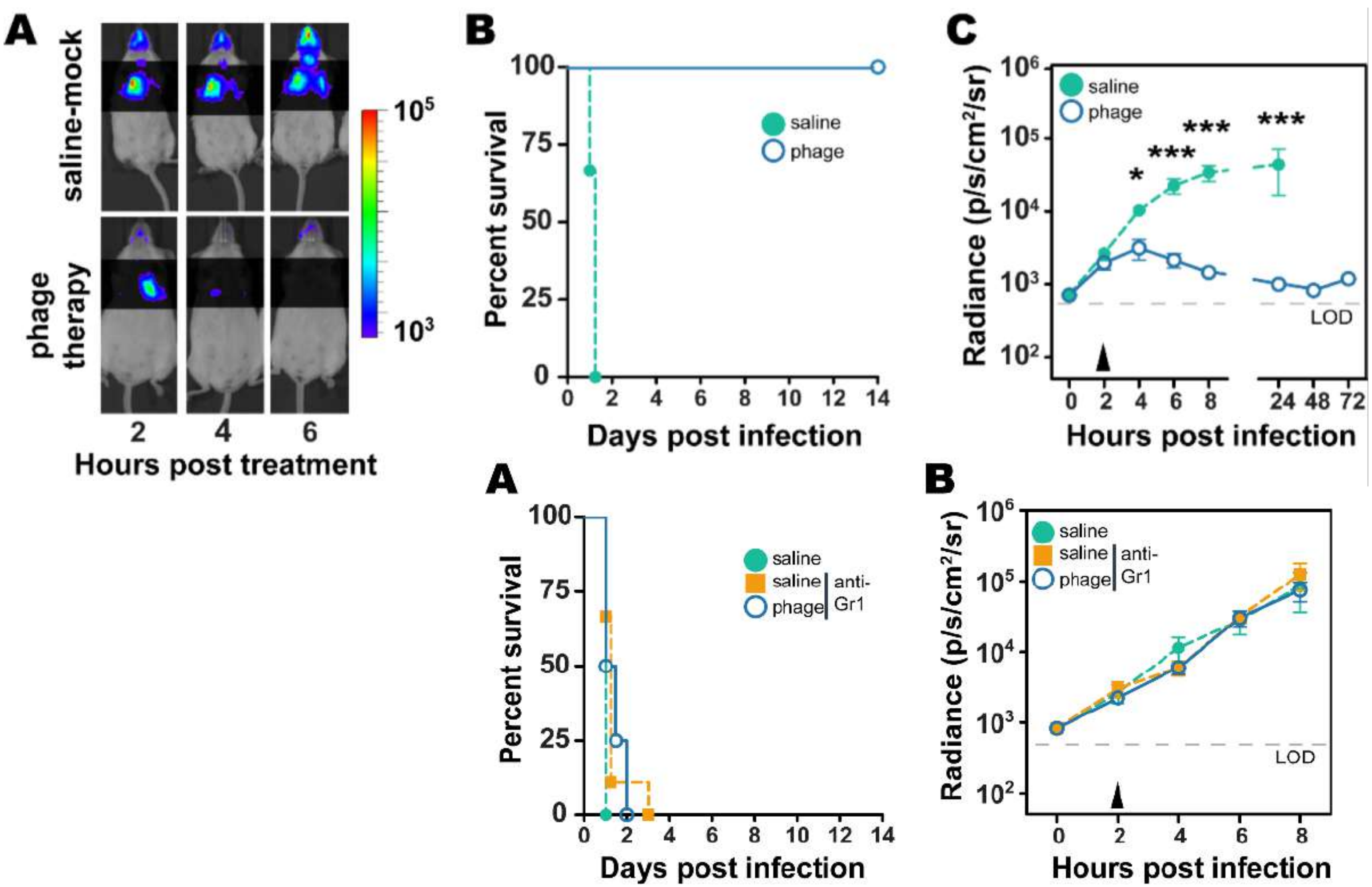
Phage:
PAK_P1, shown to prevent fatal acute pneumonia *in vivo*

Focus:
Phage therapy efficacy in **immunomodulated** mice.

That moment when…

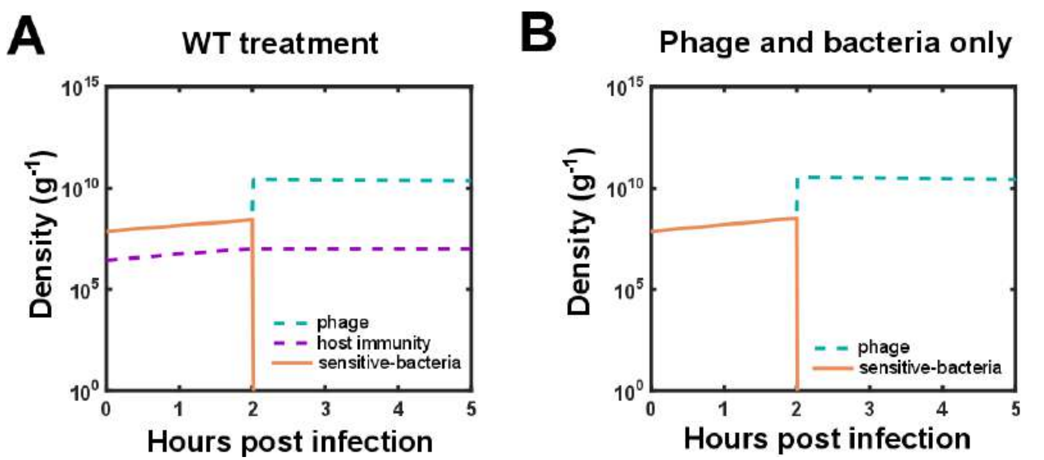


That moment when…
one thinks **this just might work.**

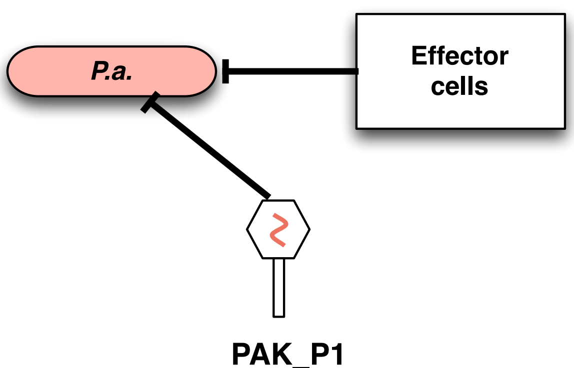


The challenge, bridging *in vitro* models to *in vivo* outcomes

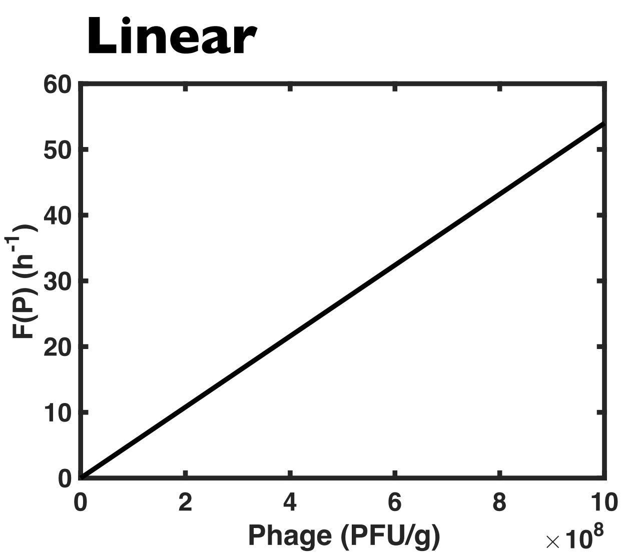
Challenge 1 – Theory
Direct scaling of *in vitro* model to lungs leads to nearly immediate mixing and bacterial elimination.



Challenge 2 - Immunology
Can we diagnose the basis for the failure of phage therapy given immunomodulated mice?



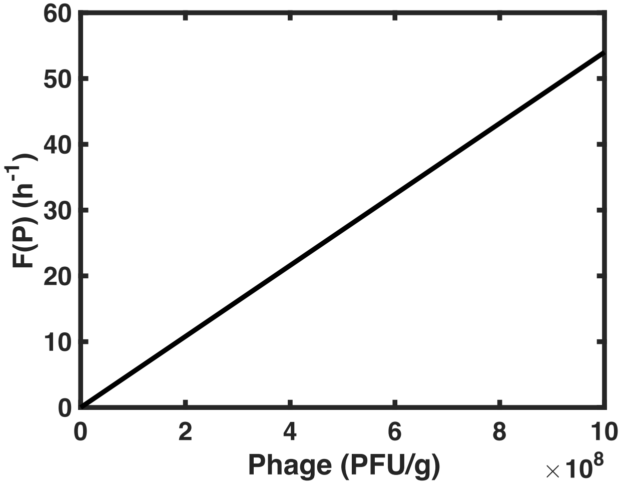
Alternative forms for the "attack" rates of phage *in vivo*



Levin & Bull, Nature Reviews Micro, 2004
Leung & Weitz, JTB (2017)

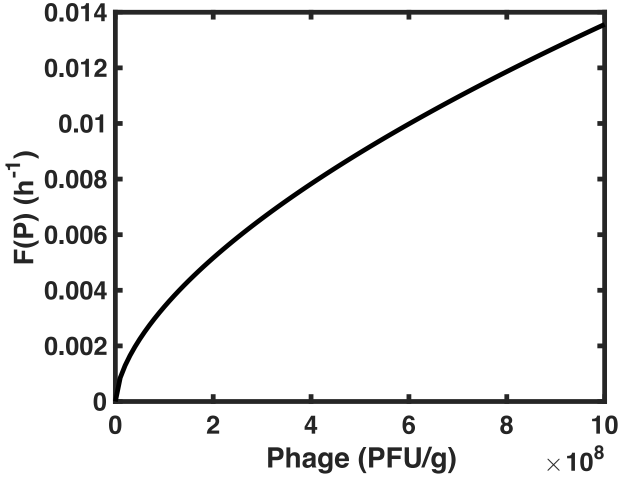
Alternative forms for the "attack" rates of phage *in vivo*

Linear

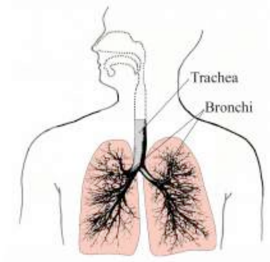


Levin & Bull, Nature Reviews Micro, 2004
Leung & Weitz, JTB (2017)

Heterogeneous mixing (HM)



Roach, Leung, …, Weitz & Debarbieux, *CHM (2017)*



Alternative forms for the "attack" rates of phage *in vivo*

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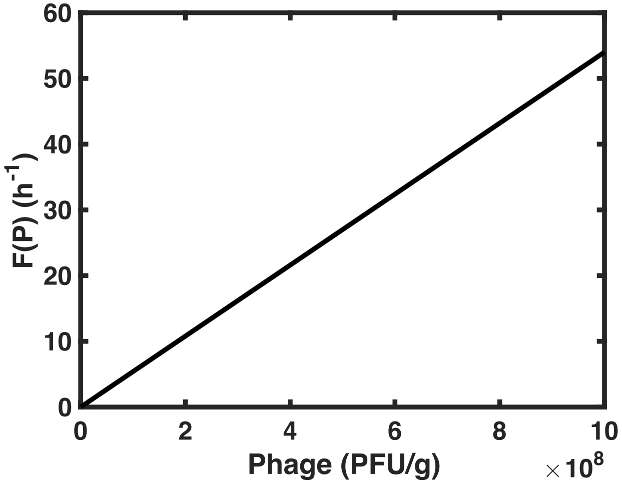

Levin & Bull, Nature Reviews Micro, 2004
Leung & Weitz, JTB (2017)

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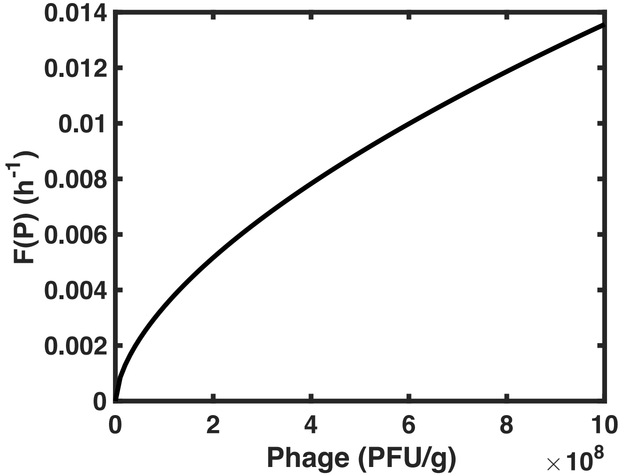
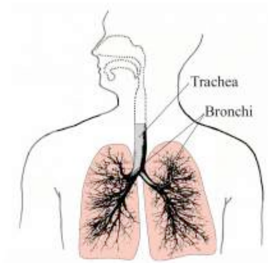
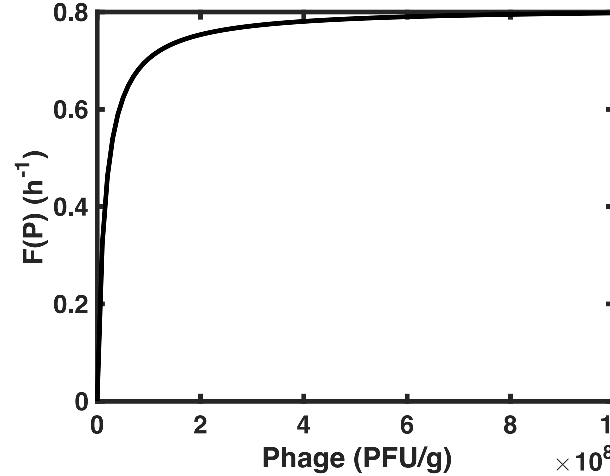
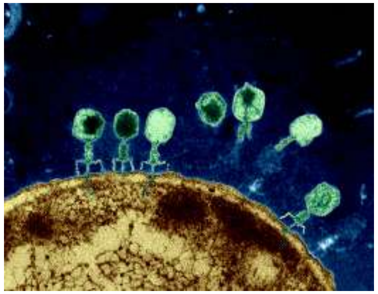


Roach, Leung, …, Weitz & Debarbieux, *CHM (2017)*

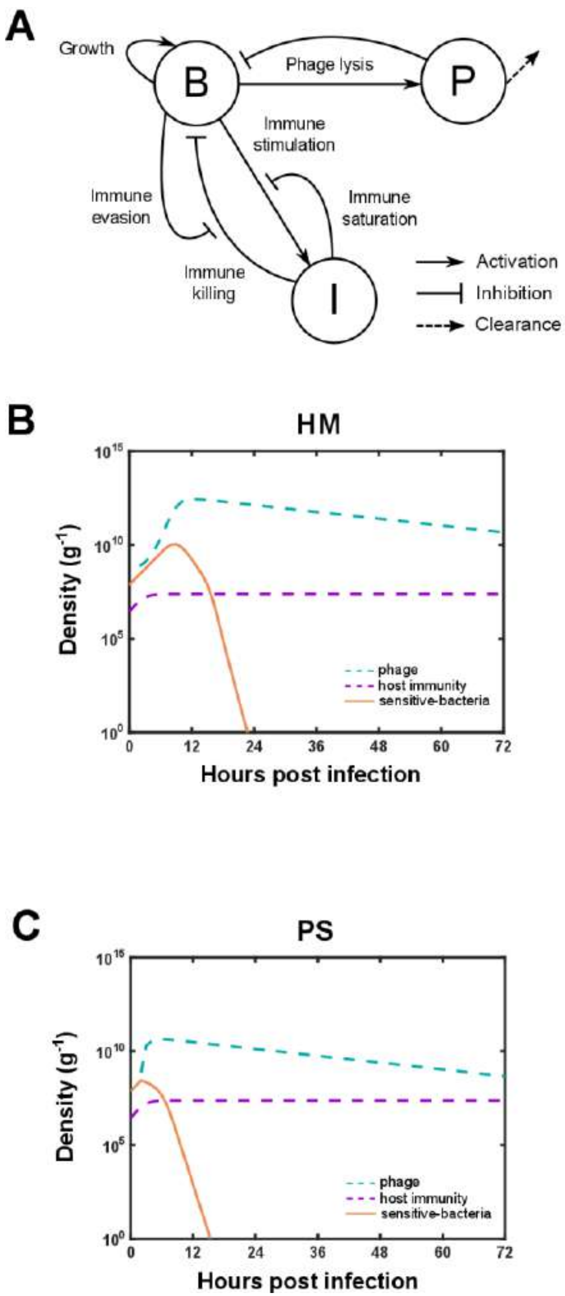


Phage saturation (PS)



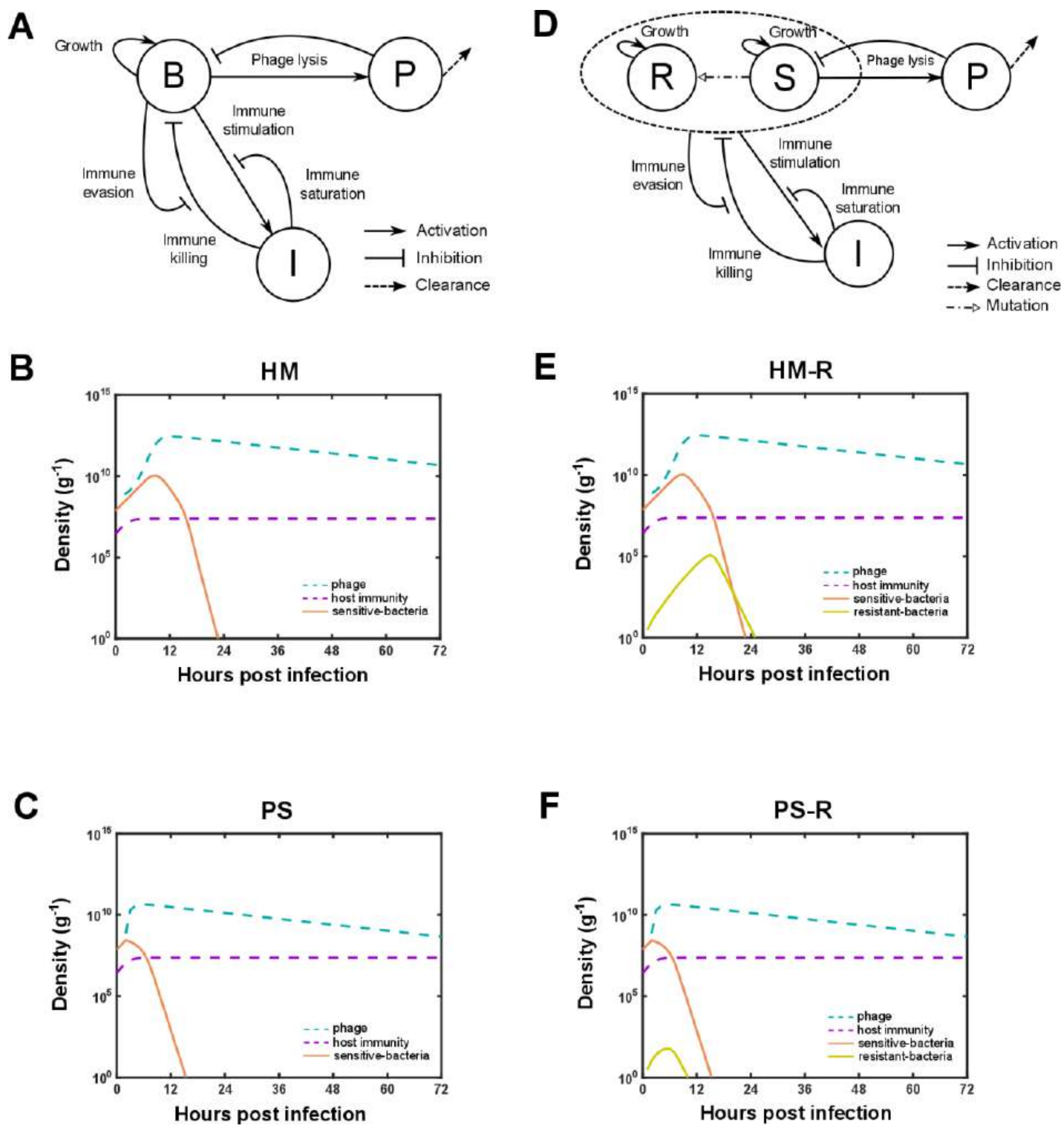


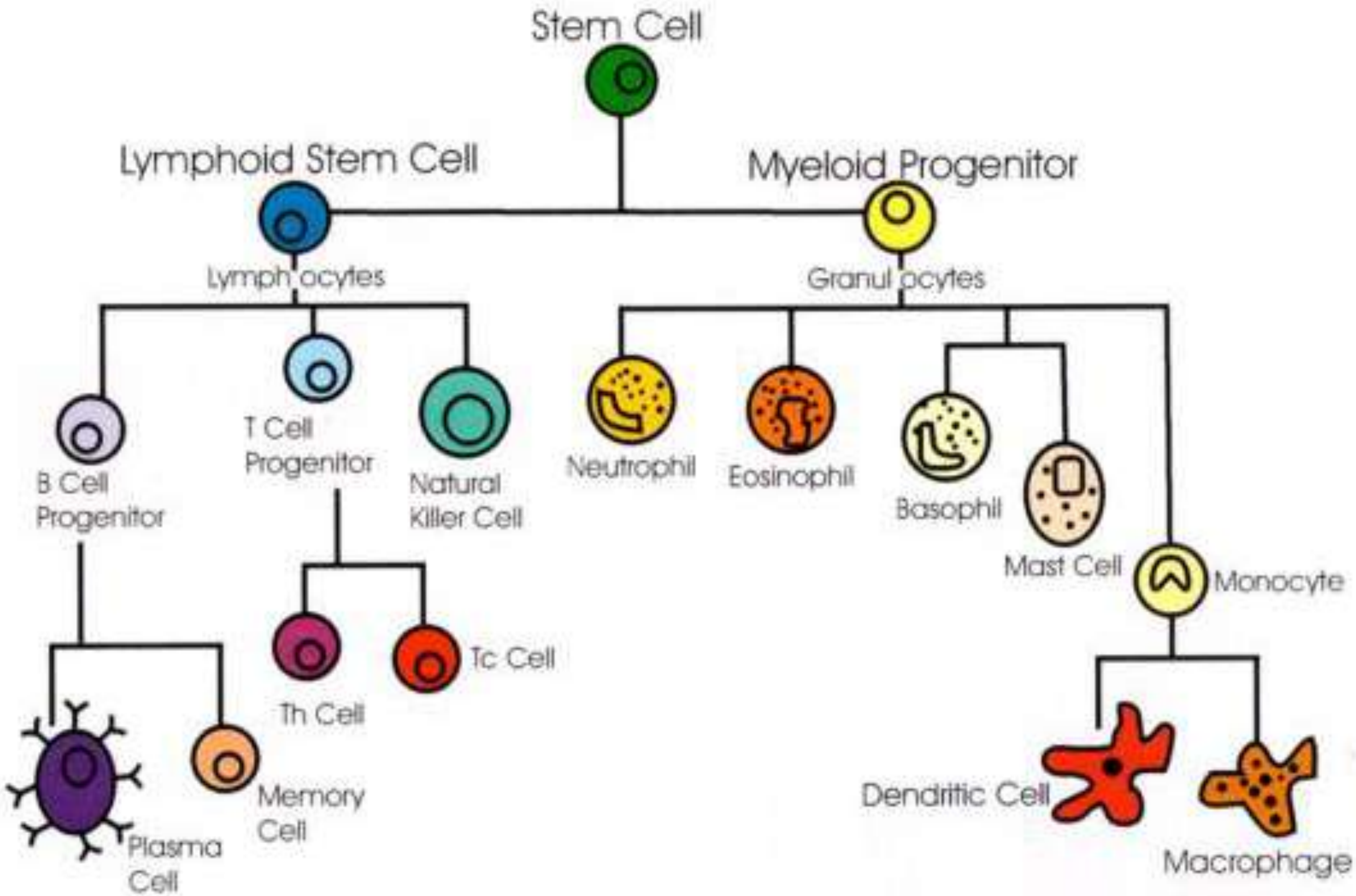
without resistance



without resistance

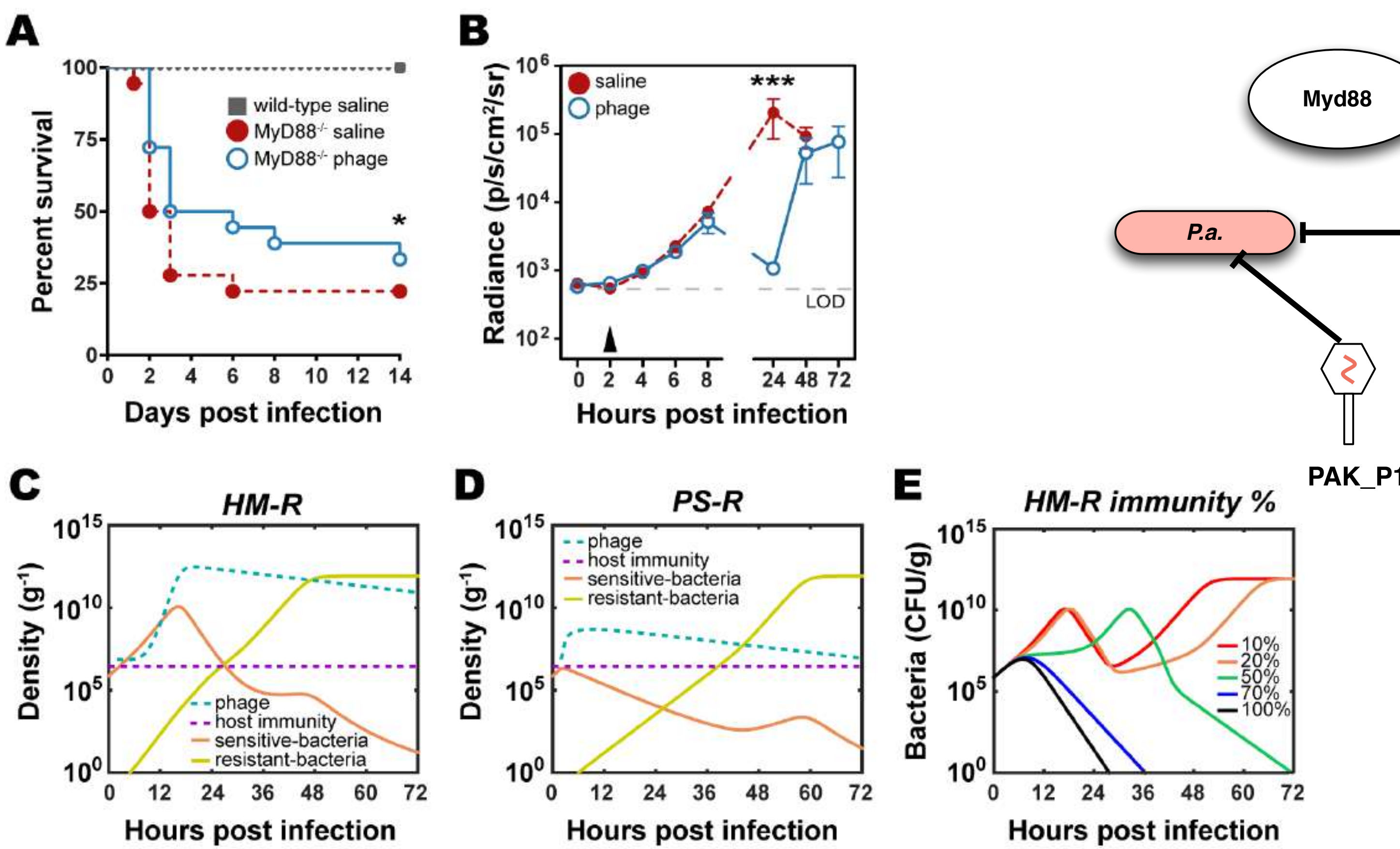
with resistance





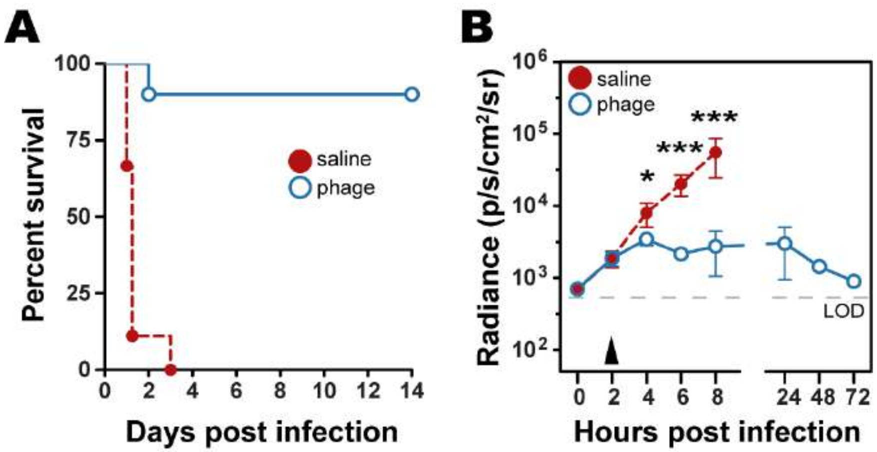
Dwayne Roach

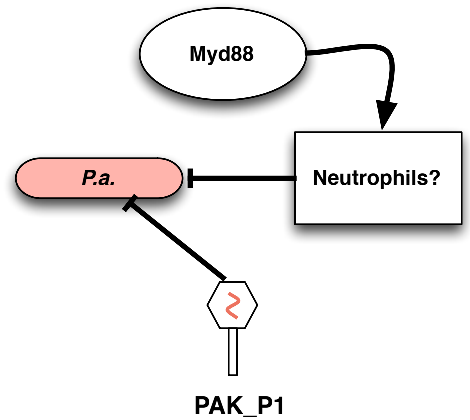
Phage therapy is inefficient in the innate immunity activation deficient host (*Myd88⁻*)



Roach, Leung, …, Weitz & Debarbieux, *CHM*

Phage therapy is efficient in the innate and adaptive lymphocyte deficient host.



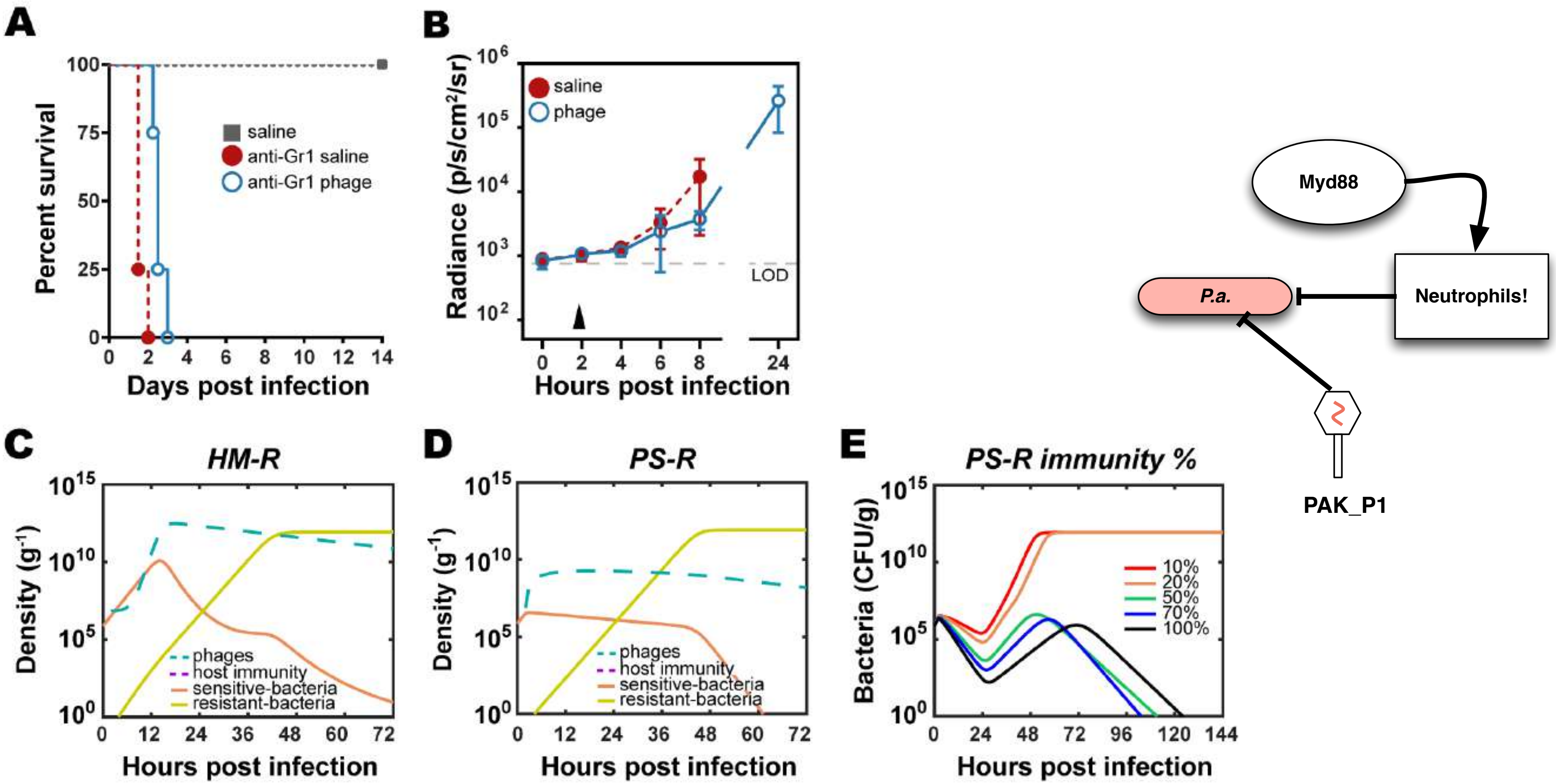


Inhaled monophage therapy (MOI of 10) after a 2h delay provided *Rag2-/-Il2rg-/-* mice void of all innate lymphoid cells, B-cells and T-cells, exhibits a 90% survival probability from acute respiratory infection by *P. aeruginosa* (10^7 CFU) (n=6 per group).

Conclusion: synergy is not with innate lymphoid, B-cells and T-cells

Roach, Leung, …, Weitz & Debarbieux, *CHM.*

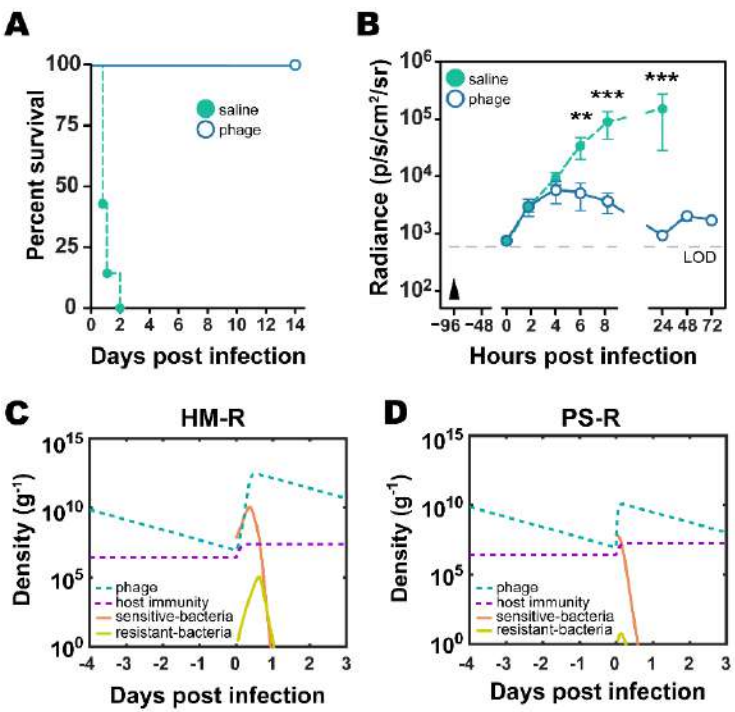
Phage-neutrophil alliance is required for effective therapy



Anti-granulocyte receptor-1 (Gr1) monoclonal antibody was used to deplete neutrophils in wild-type mice 24h before an intranasal inoculum of *P. aeruginosa* (n=4 per group).

Roach, Leung, …, Weitz & Debarbieux, CHM.

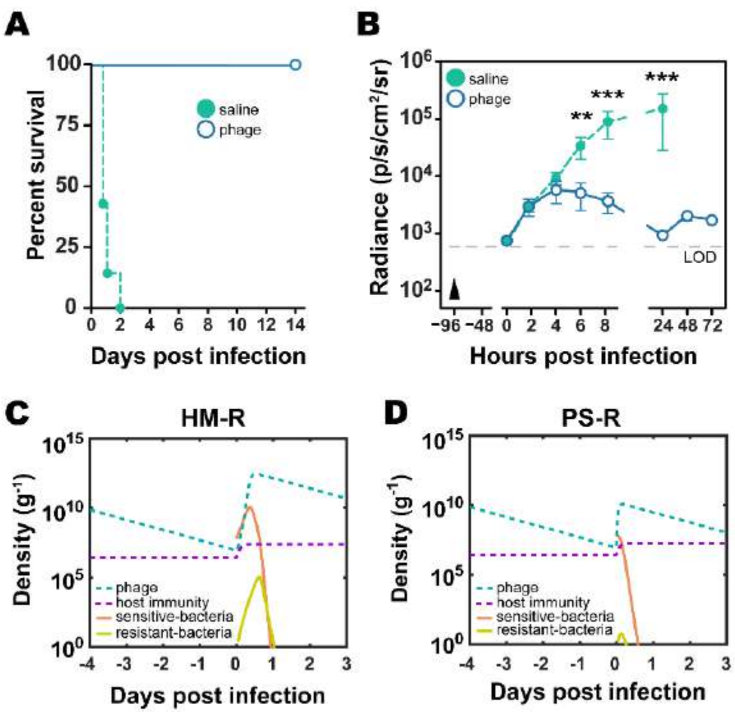
Efficient non-immune priming phage prophylaxis in the immunocompetent host



Wild-type mice received a single inhaled monophage dose (10^9 PFU) which gave prophylaxis for 4d against P. aeruginosa (10^7 CFU) pneumonia (n=6 per group).

Roach, Leung, …, Weitz & Debarbieux, *CHM*.

Efficient non-immune priming phage prophylaxis in the immunocompetent host



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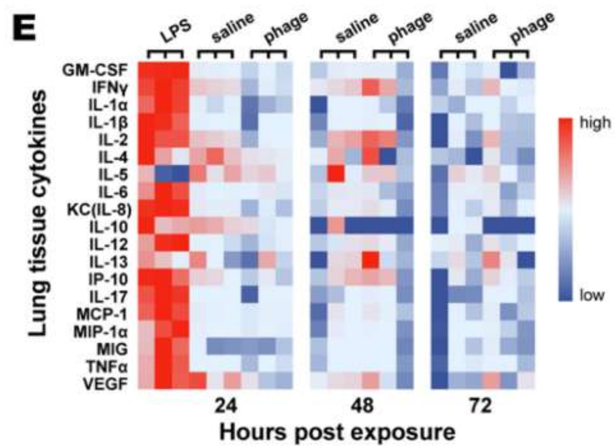


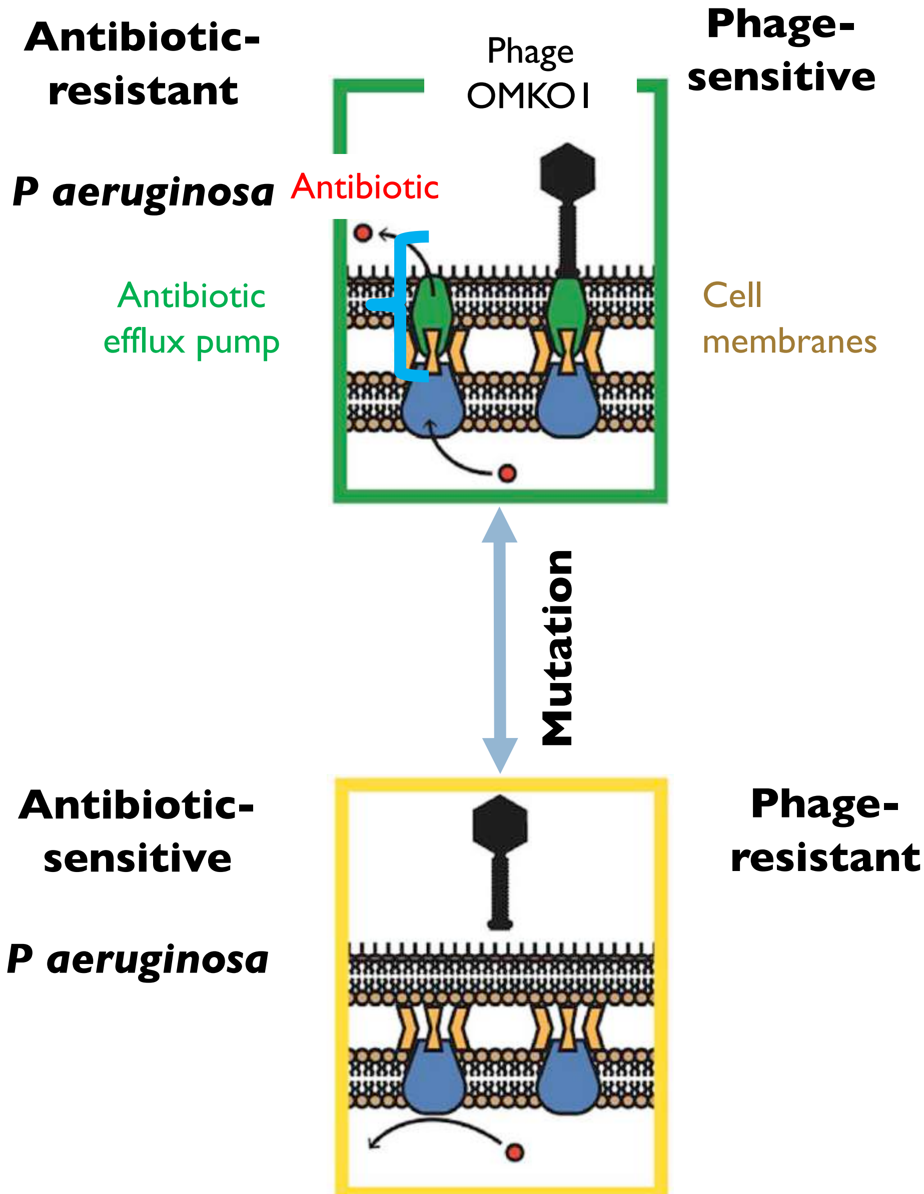
Differential production of cytokines in mouse lung tissues after exposure to 10 μg LPS, saline, or phages (10^9 PFU).

Tentative conclusion:
Significant priming of host immunity does not occur.

Roach, Leung, …, Weitz & Debarbieux, *CHM*.

Part 4:

New directions in combining phage and antibiotics for curative treatment of multi-drug resistant infections

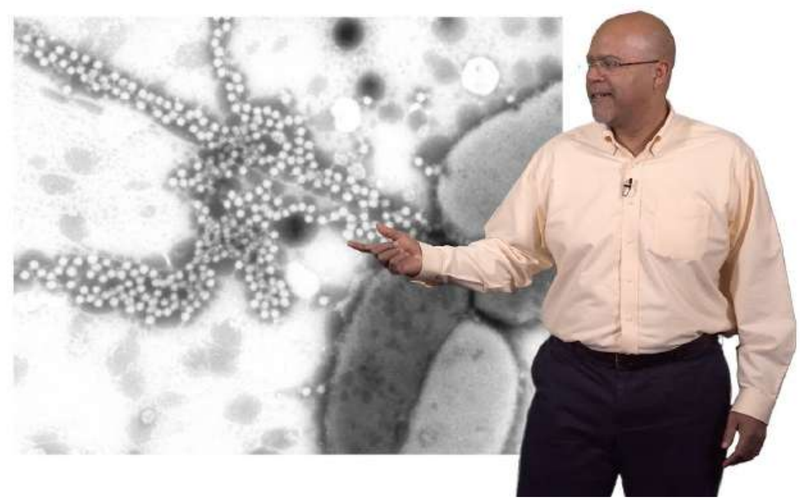


Chan et al., Sci. Rep. 6, 26717 (2016).

IN THE LAB

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

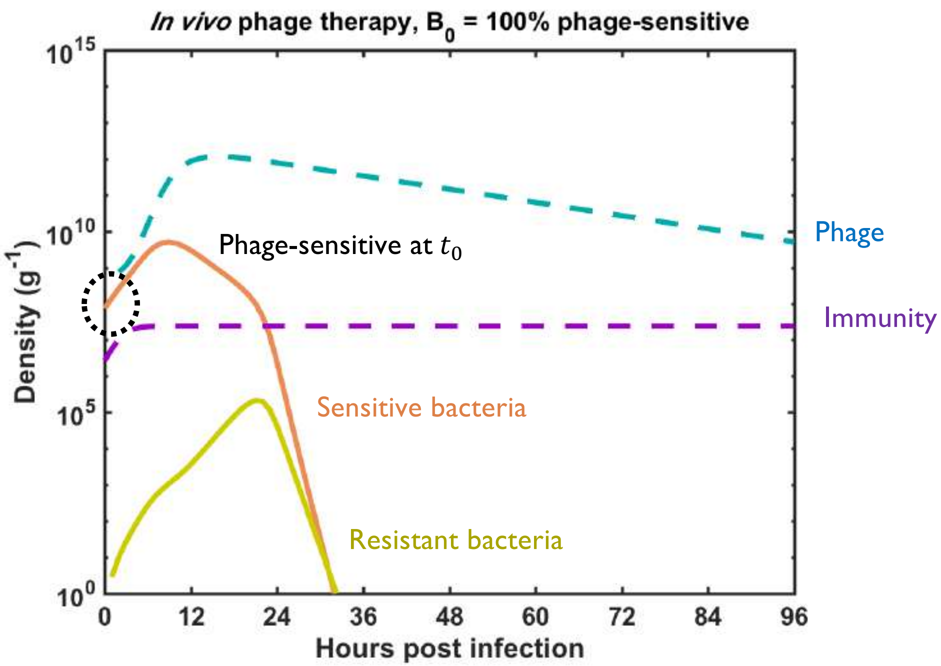
By CARL ZIMMER @carlzimmer / DECEMBER 7, 2016



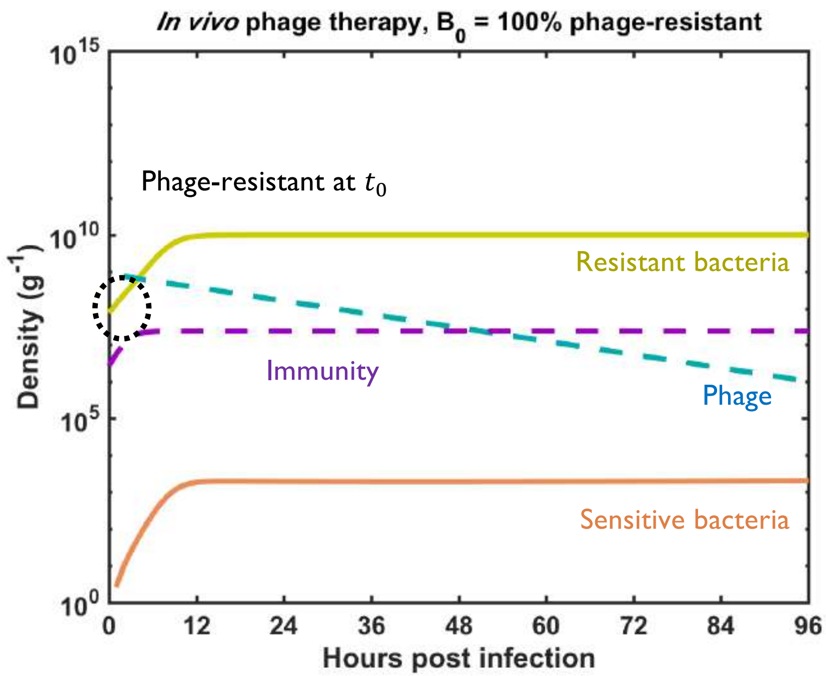
P. aeruginosa

Caveat: phage treatment can fail if targets the wrong strain or if high levels of phage-resistance is present in the host

Phage-sensitive inoculum

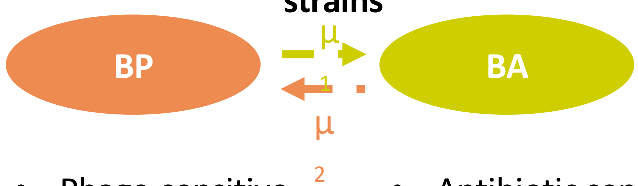


Phage-resistant Inoculum



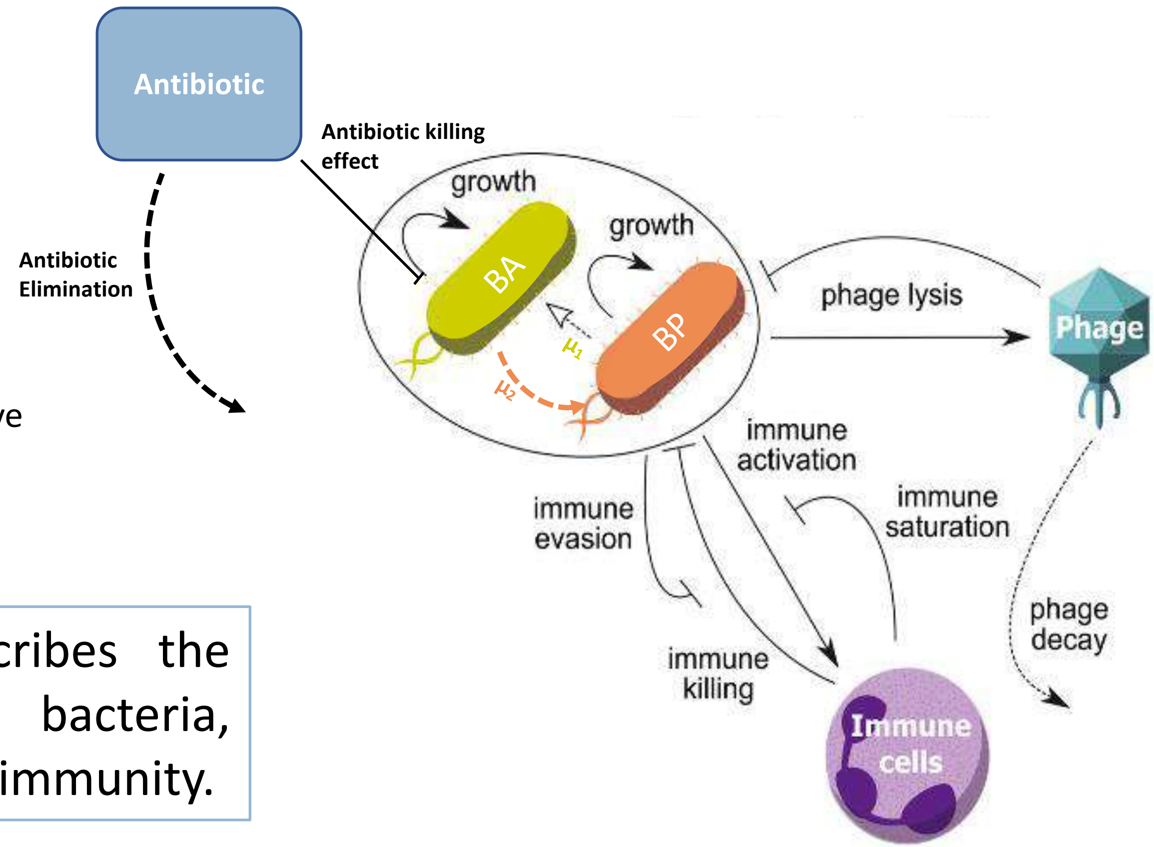
A model of phage-antibiotic combination therapy

We model **two bacterial strains**



- Phage-sensitive
- Antibiotic-resistant

- Antibiotic sensitive
- Phage-resistant



The generalized model describes the interactions between phage, bacteria, **antibiotic**, and the host innate immunity.

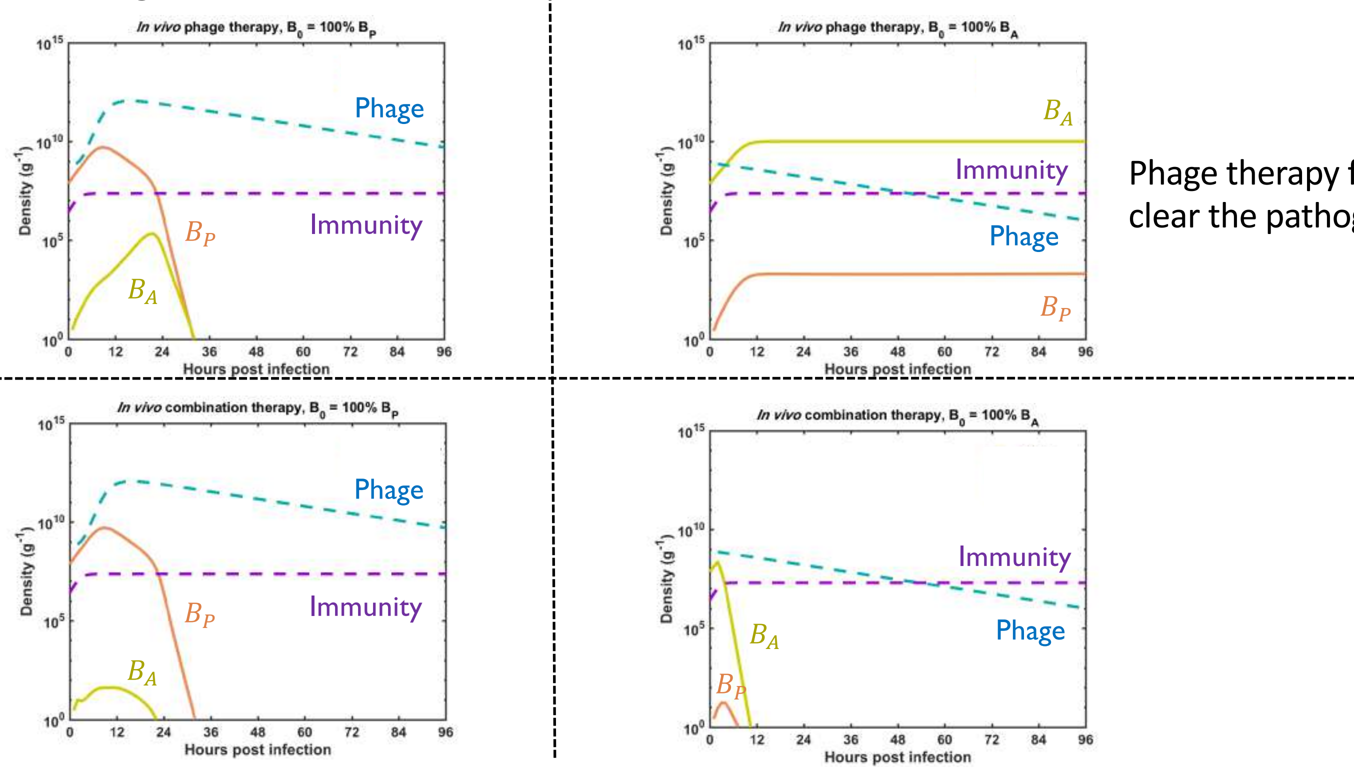
Rodriguez, Leung, … , Turner, Weitz (in prep)

Phage-antibiotic combination restores efficacy to mis-targeted phage therapy

Phage-sensitive Inoculum | **Antibiotic-sensitive Inoculum**

Phage Therapy

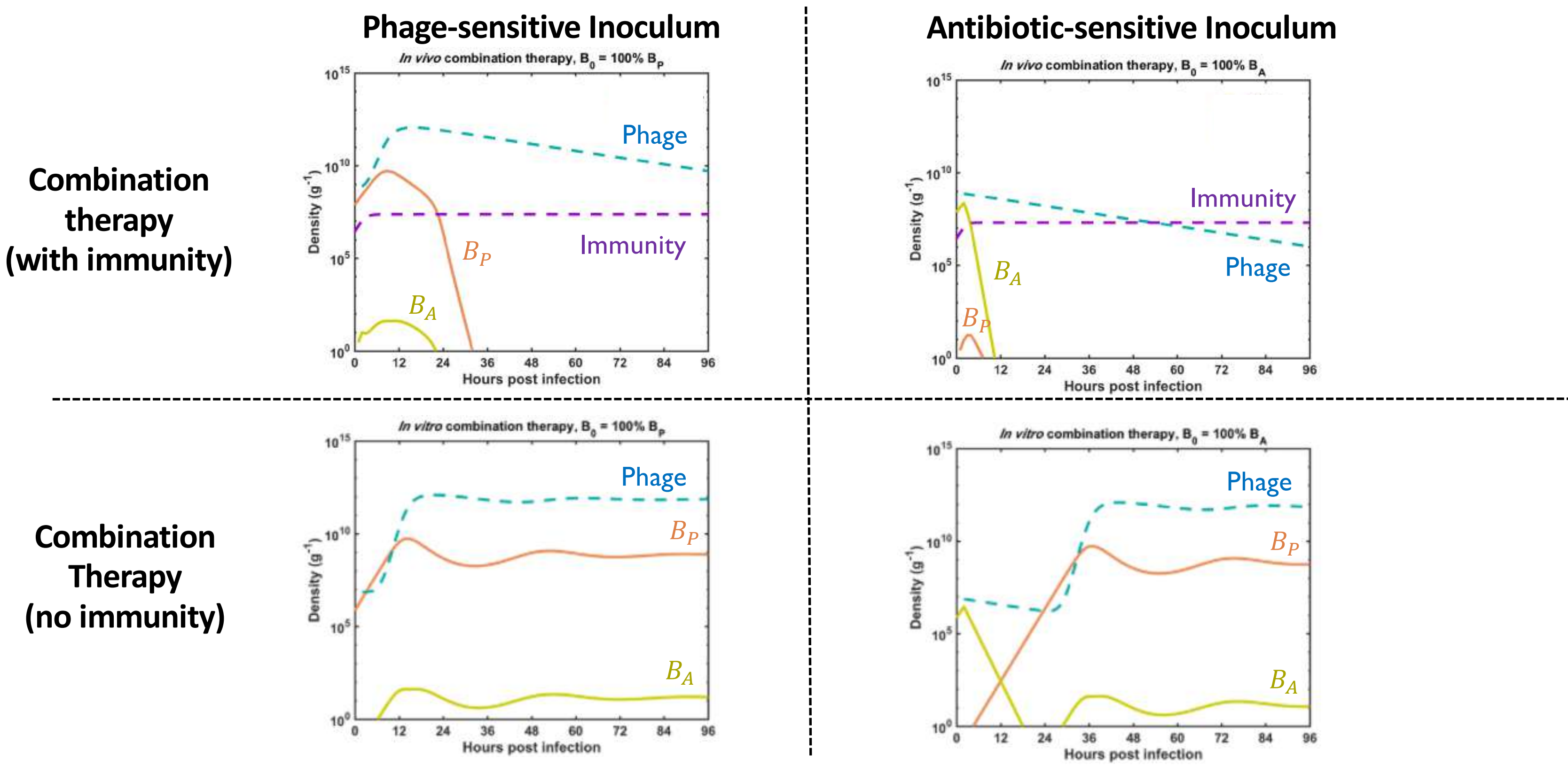
Combination Therapy



Phage therapy fails to clear the pathogen

Rodriguez, Leung, … , Turner, Weitz (in prep)

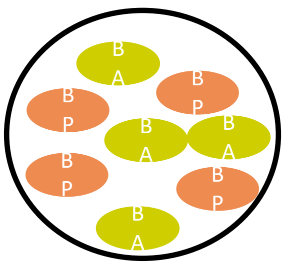
Phage-antibiotic-immune synergy provides robust curative efficacy



Rodriguez, Leung, … , Turner, Weitz (in prep)

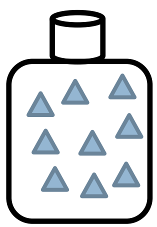
The limitations of antibiotic therapy

Bacterial composition of the inoculum

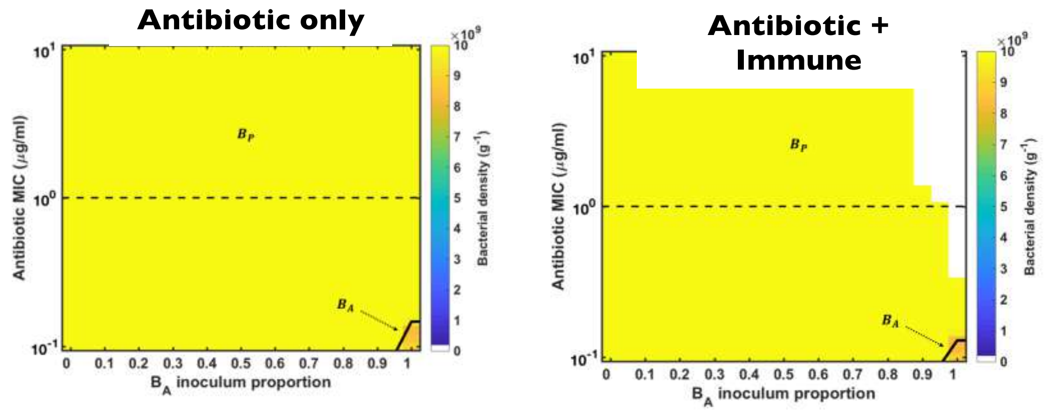


x-axis

Antibiotic conc. (multiples of MIC)



y-axis



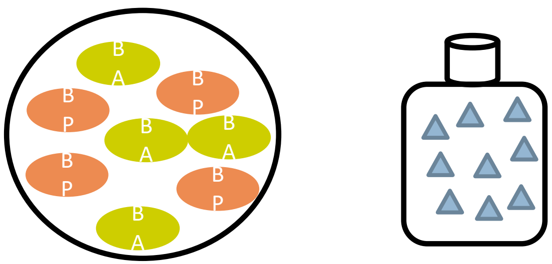
We vary the above initial conditions and run the model for 96 hours and compute the **bacterial density**.

Rodriguez, Leung, … , Turner, Weitz (in prep)

Phage-antibiotic combination therapy significantly increases therapeutic robustness

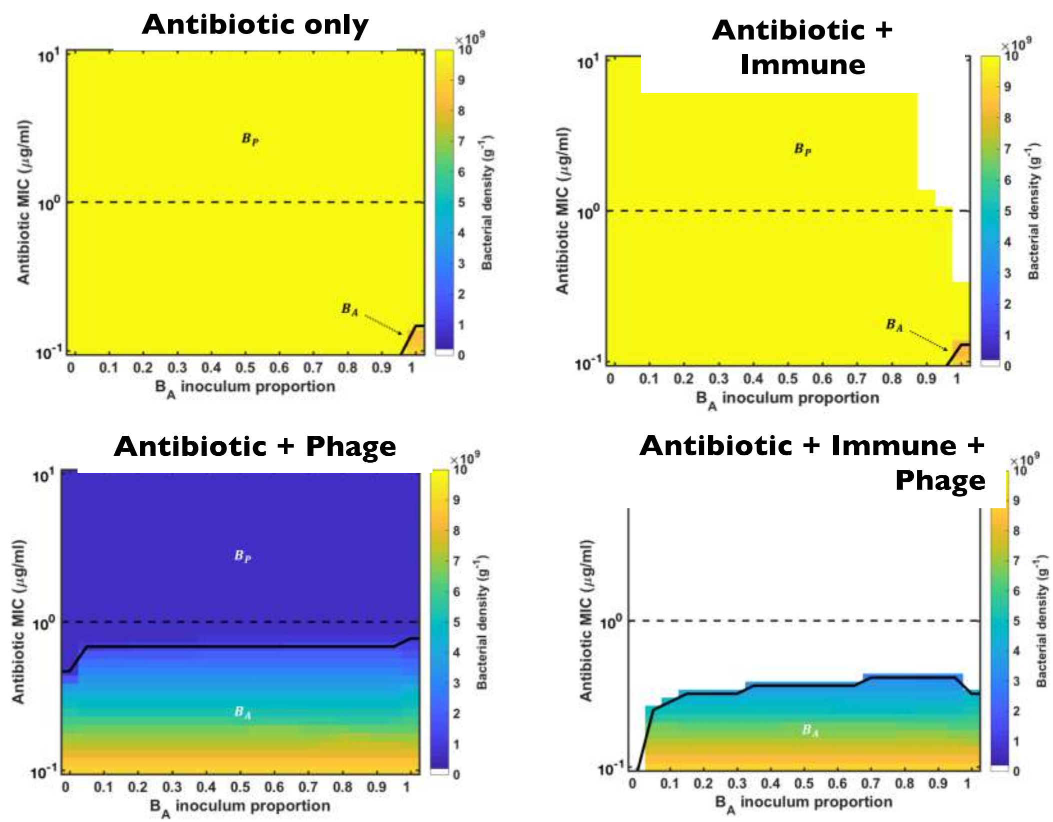
Bacterial composition of the inoculum

Antibiotic conc. (multiples of MIC)



x-axis

y-axis



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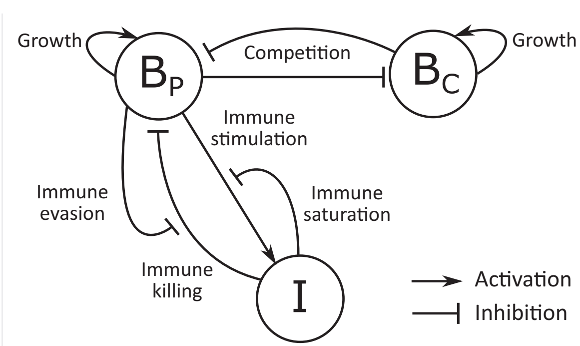
Rodriguez, Leung, … , Turner, Weitz (in prep)

Trends in Microbiology
Cell Press REVIEWS

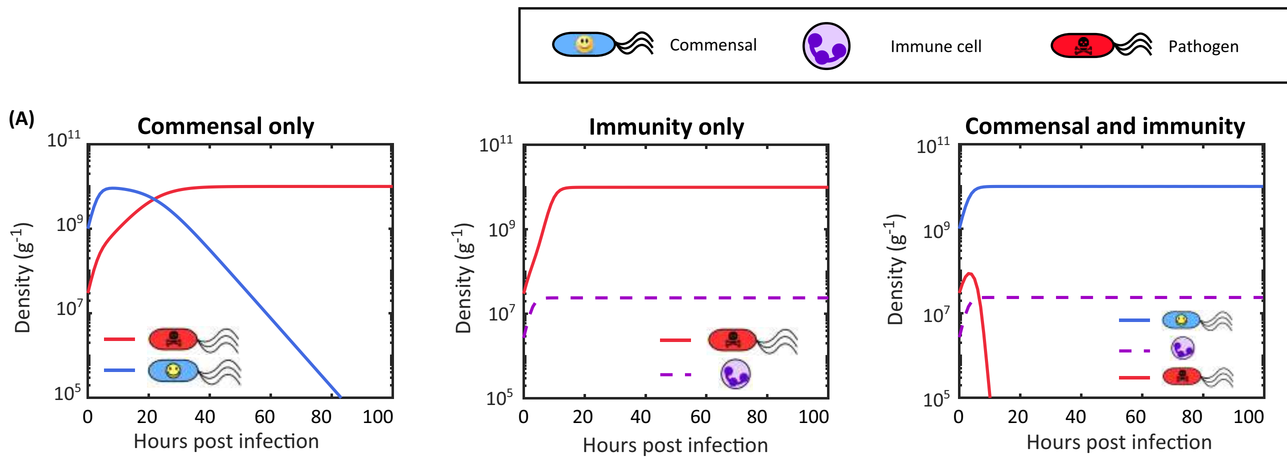
Opinion

Not by (Good) Microbes Alone: Towards Immunocommensal Therapies

Chung-Yin Leung[1,2,*] and Joshua S. Weitz[1,2,*]

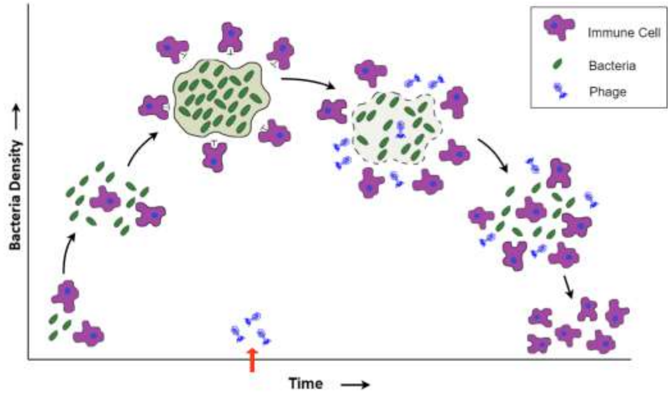


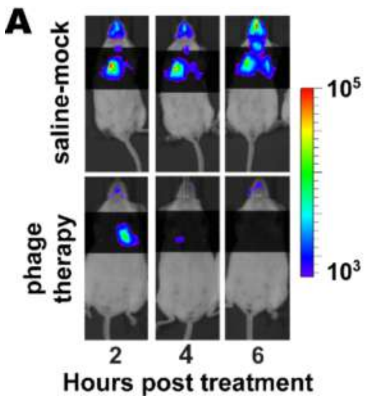
Trends in Microbiology

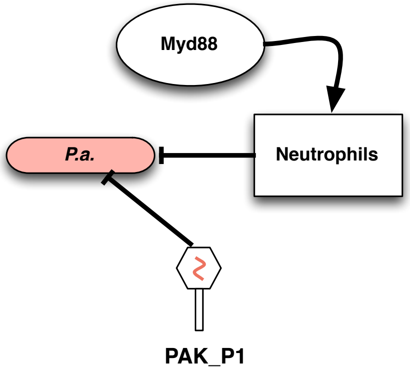


Conclusions

- Tripartite model of phage-immune-bacteria dynamics identifies mechanism for **immunophage synergy** to explain successful therapeutic clearance of pathogens.
- *In vivo* analysis shows curative success depends on **phage and immune response.**
- Immunomodulation points to a **phage-neutrophil alliance** necessary for therapy.
- **Synergy resolves the resistance problem** – the immune response eliminates susceptible and resistant pathogens.
- Generalized synergy ongoing to include **commensals** and **antibiotics**.

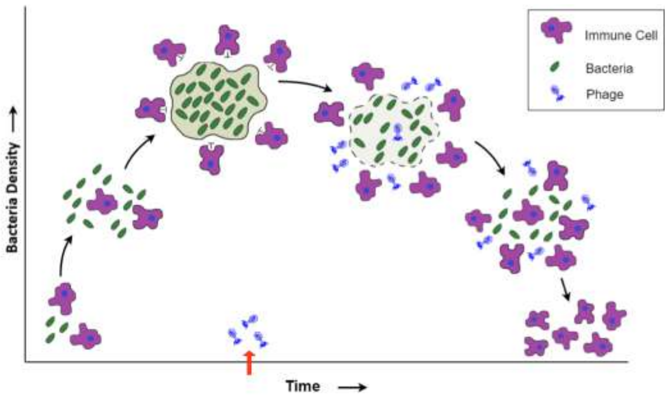


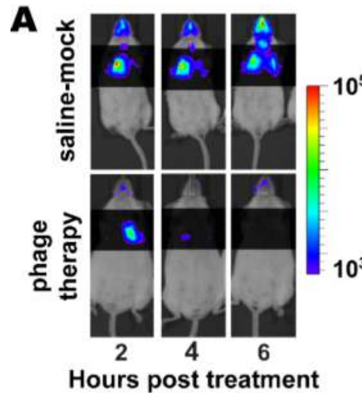


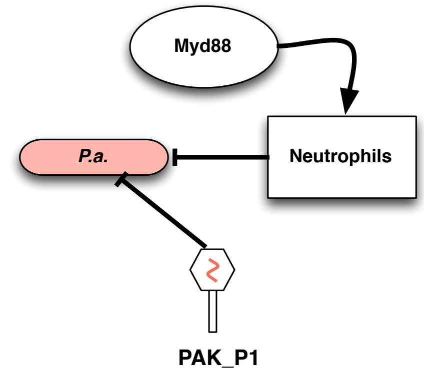


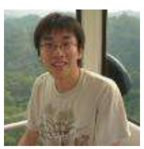
Theoretical Ecology & Quantitative Biology @ Georgia Tech

Weitz Group
http://ecotheory.biology.gatech.edu
http://qbios.gatech.edu









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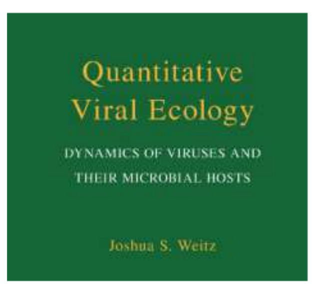

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Army Research Office

References

Leung & Weitz, J. Theor. Biol (2017)
Roach, Leung et al., Cell Host Microbe (2017)
Leung & Weitz, Trends in Microbiology (2019)
Rodriguez, Leung, ..., & Weitz (in prep)

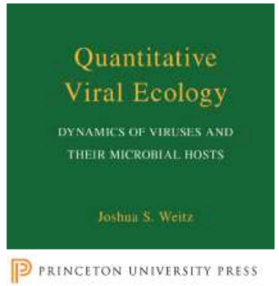
Viral Ecology and Evolution: Lectures at the Interface

ICTP-SAIFR
Summer Workshop
Mathematical Models of Evolution
Sao Paulo
Jan 21-26, 2019

From Ecology to Evolution (Lectures 1-2)

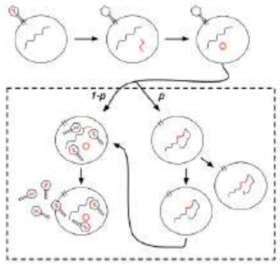
Principles of eco-evolutionary dynamics: Monday Jan 20

Dynamics in complex communities: Wednesday Jan 22



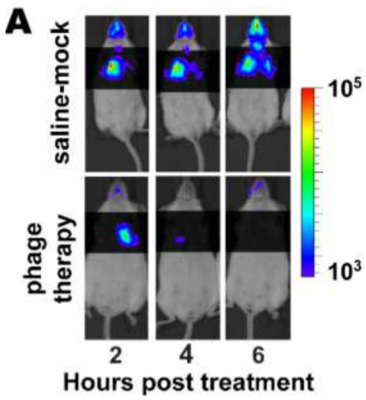
From Lysis to Latency (Lecture 3)

Friday Jan 25



From Theory to Therapy (Lecture 4)

Saturday Jan 26



Thank you for listening!!!