UCI School of Physical Sciences

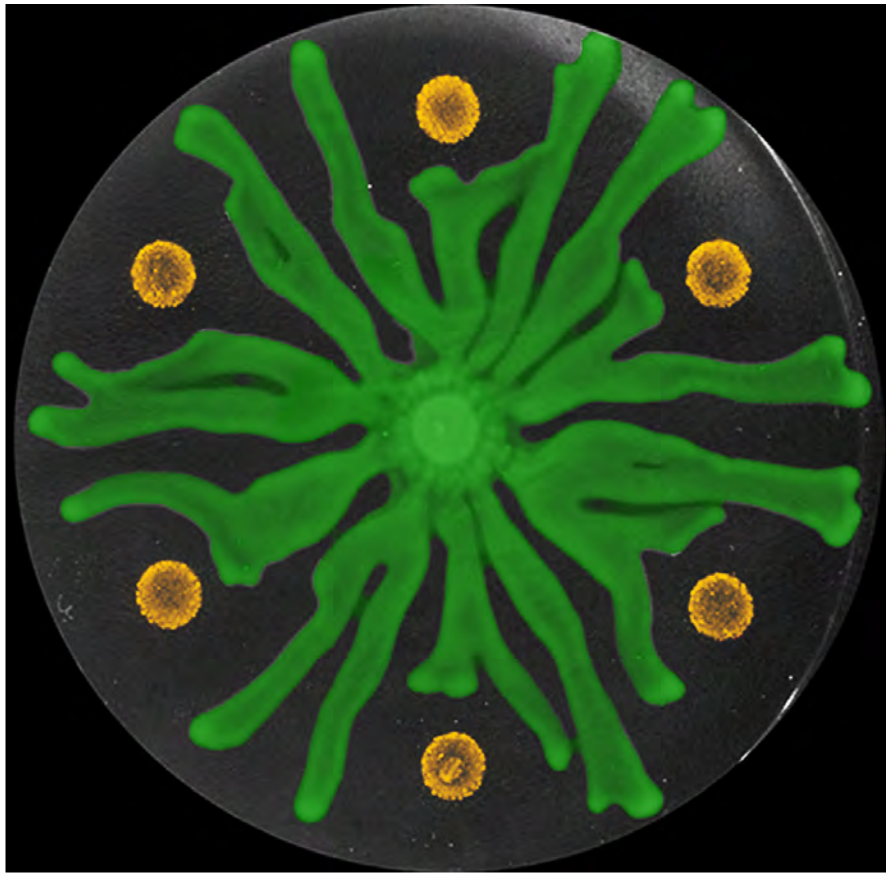
Lessons Learned From Bacteria as we Fight COVID-19 with Professor Albert Siryaporn

Welcome, we will begin shortly

For questions, please utilize the Q&A feature at the bottom of your screen

Text PSBLS to 41444 to give!

Lessons learned from bacteria: How to stop the spread of a virus



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What is Biological Physics?

- Inert matter with collective properties

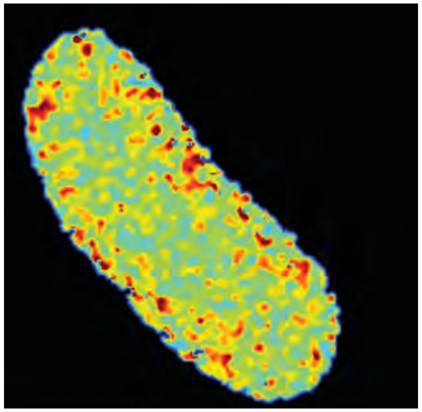
- Complex physical system
  - Systems operate by exception
  - Physics of biological systems is complex
    - (Fluid mechanics, statistical mechanics, quantum mechanics, E&M) all rolled into one

- Identifying unifying principles / general principles

- Solutions at the interface between biology and physics

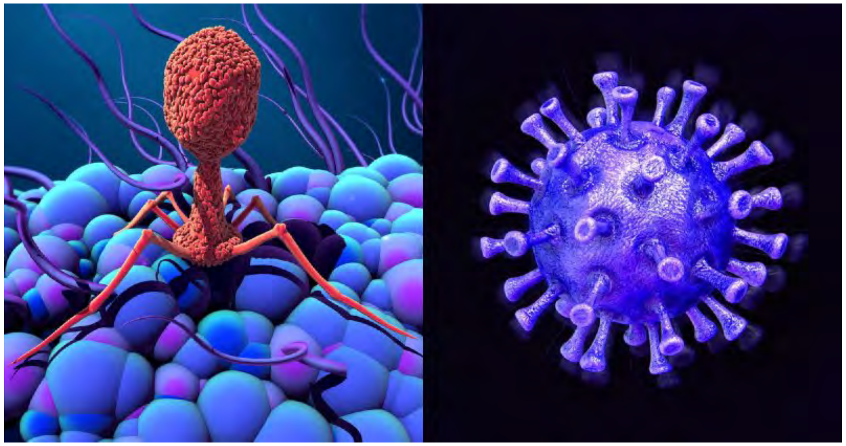
Microbes: complex physical systems

Bacteria



Size = 1 micron

Viruses



Size = 0.1 micron

Low Reynolds number (no inertia)
What are general principles that predict dynamics of these systems?

We start with a philosophical question

- Thomas Malthus (1798): *An Essay on the Principle of Population*

- Human population: balance between growth and availability of resources

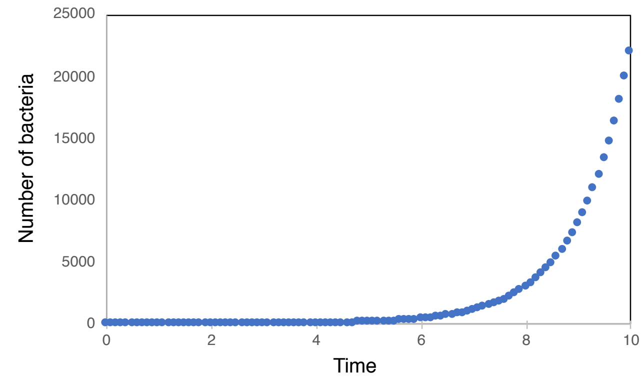
- Population needs cannot surpass available resources

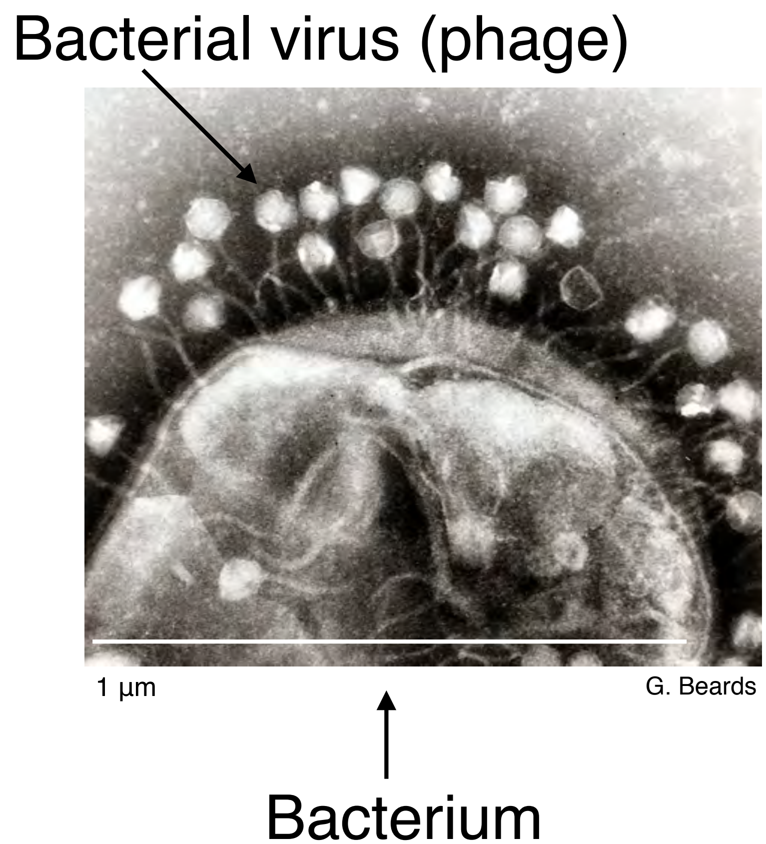
- Malthusian catastrophe: outbreaks, plagues, epidemics keep population numbers in check

How is a growing population affected by an outbreak? (What are the dynamics of an outbreak?)

Bacterial: fast growing and infected by viruses

- Bacteria grow exponentially
- If left unchecked, would be most abundant organism on earth
- But bacteria not most abundant: bacterial viruses (bacteriophage or phage) are
- 10^{31} virus particles on earth!
- Bacteria bombarded by viruses





How do bacteria deal with viral outbreaks?

Assumption: bacteria must have evolved mechanisms to protect against decimation of the population

How do bacteria prevent viruses from propagating through a population?

Outline

Foundation for a new antiviral strategy

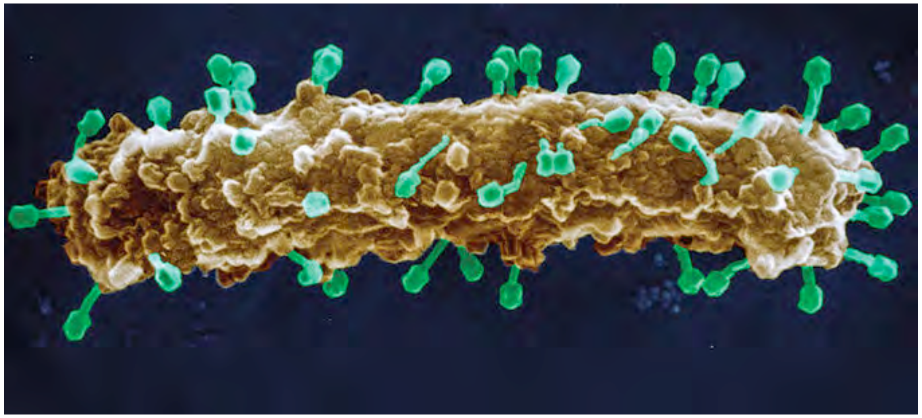
1. How **bacteria** protect against **threats** from **viruses**

2. Using lessons from bacteria to develop **SARS-CoV-2** anti-viral treatment

Bacteriophage: one of the biggest threats for bacteria

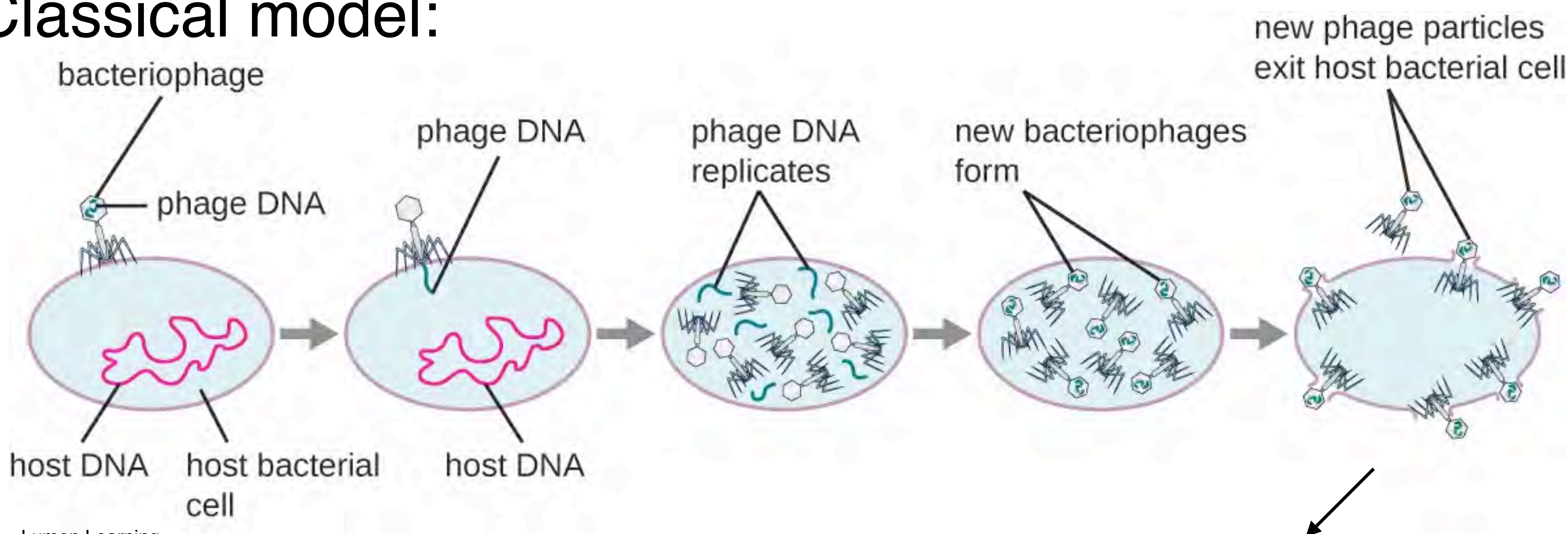
Phage & bacteria:
inseparable partners

On earth: 10^{30} bacteria
10^{31} phage



Science Mag.

Classical model:

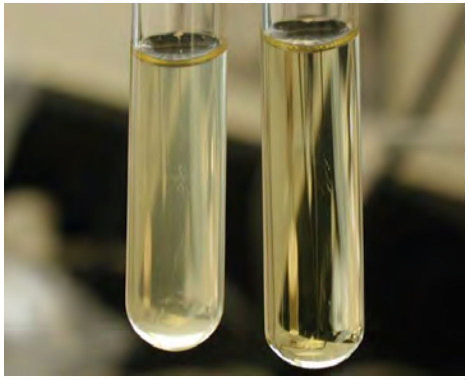


Lumen Learning

What is the role of spatial component?

Role of spatial component in phage infection

Growing phage in lab



Test tubes well-mixed

Medical News Today

TransCanada Organic Certification

Natural and human environments
not well-mixed

Role of the spatial component in virus propagation

How does infection spread spatially?

↕

How do viruses spread through a population?

- 1 billion bacteria in an overnight culture

- 7.8 billion people on earth

Goal: track viral dynamics in large number of individual organisms

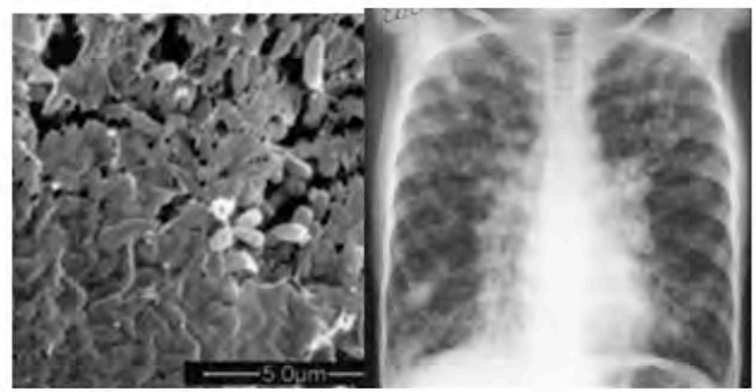
Pseudomonas aeruginosa: a bacterial opportunistic pathogen

Habitats

Soil, water, surfaces of plants and animals

Human infection

Cystic fibrosis, burn wounds, immunocompromised, lung infections, sepsis



Antibiotic resistant

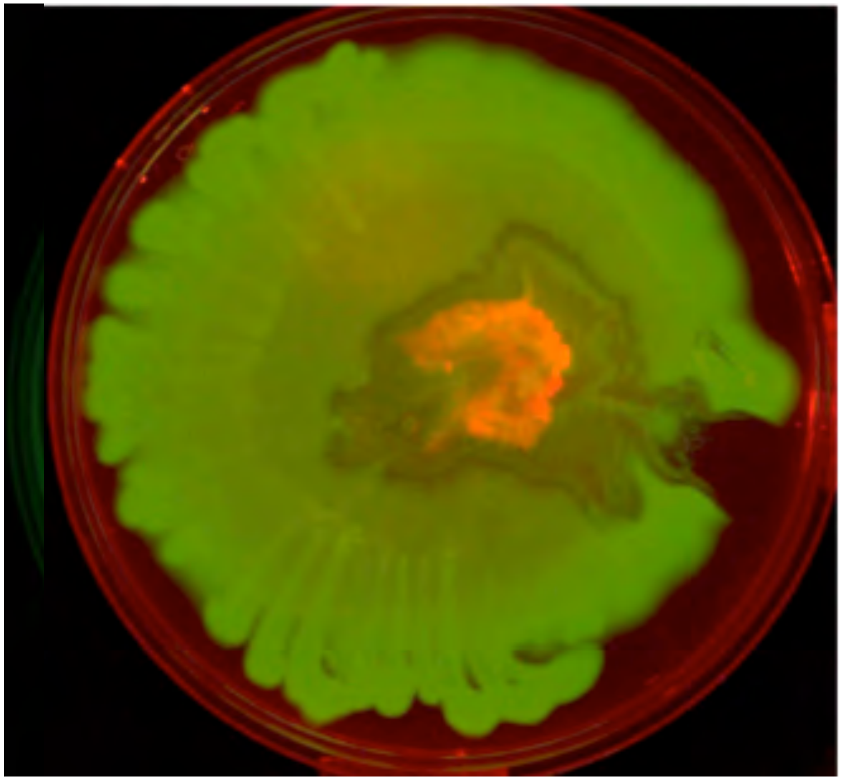
World Health Organization: 1 of 3 highest priority bacteria

Biofilms

Exist as large dense fast-growing populations: biofilms
Consider as a collective

How does phage infection spread spatially?

Brandon Rawson,
Undergrad in Physics



Media composition, phage strains, bacterial strains, moisture

Does the virus beat diffusion?

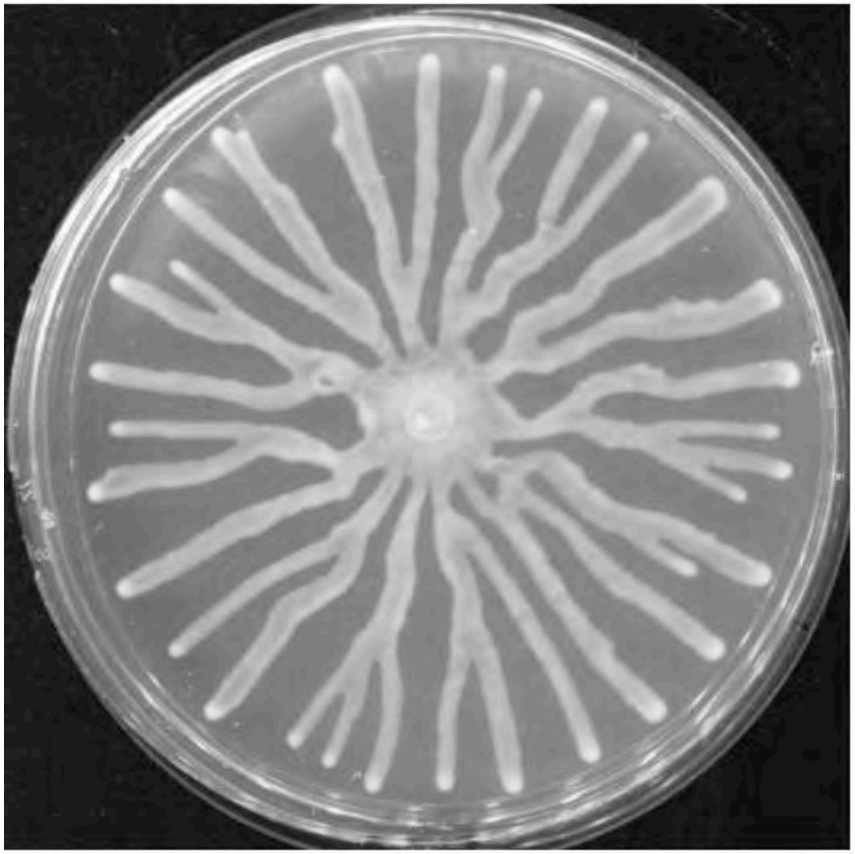
Green - bacteria

Yellow - beads (diffusion)

Dim green - lysis by phage

6-9 months later…Some infection when bacteria are in active state

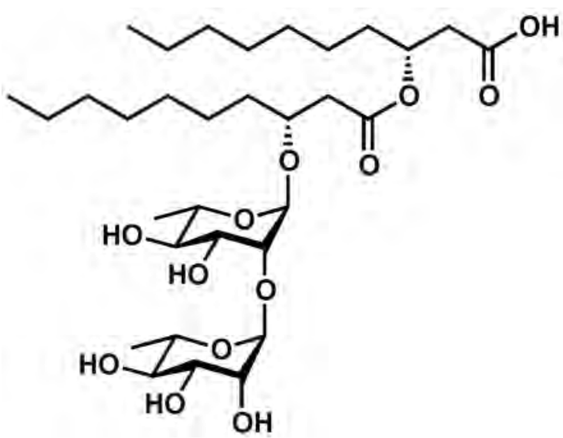
Infection spread in active populations



- Space search for nutrients, resources
- Tendril pattern: maximize efficiency
- Dense, motile populations

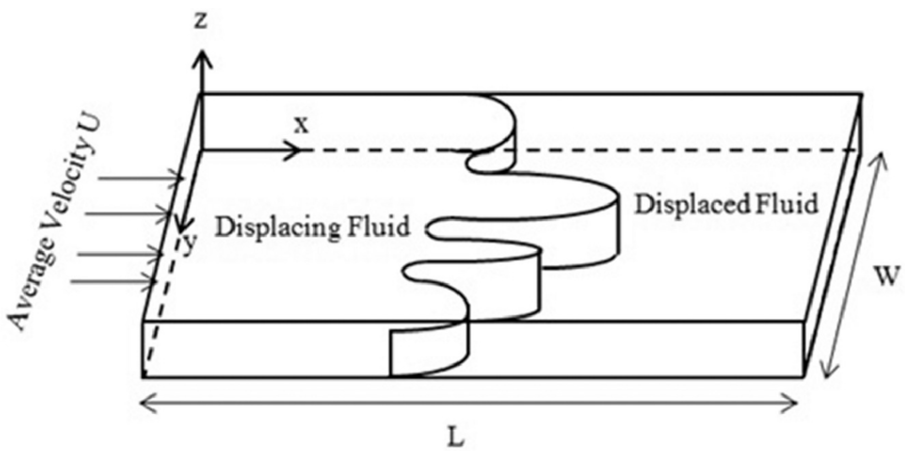
Bacterial swarming

- Bacteria adapted for growth / usage of resources
- Bacteria produce own surfactant to move along surface



(Rhamnolipid)

How patterns are formed: liquid instability



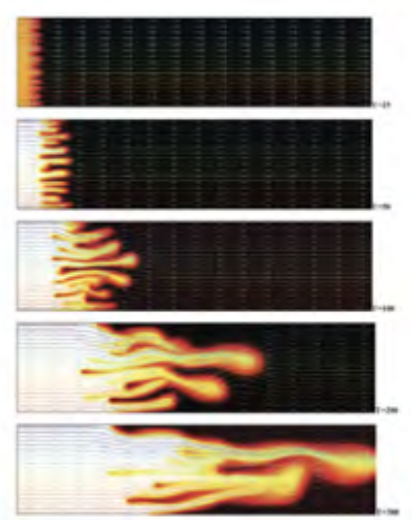
Shokri et al, Int. J. of Mech Sci. 2018

Saffman-Taylor instability

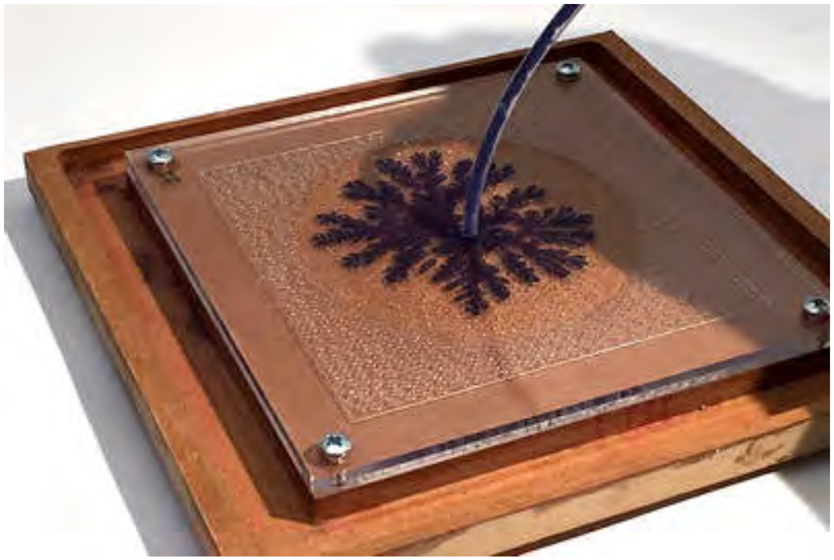
Displacement of viscous liquid by lower viscosity liquid

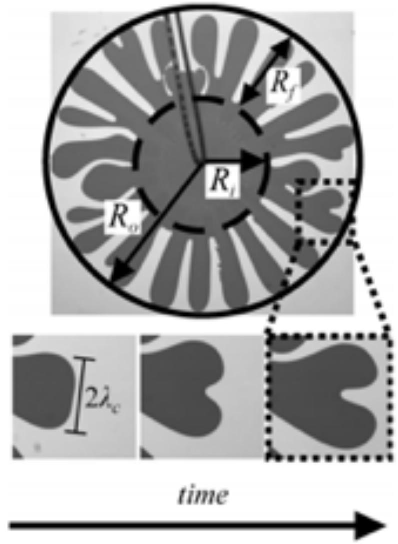
Pressure-driven flow

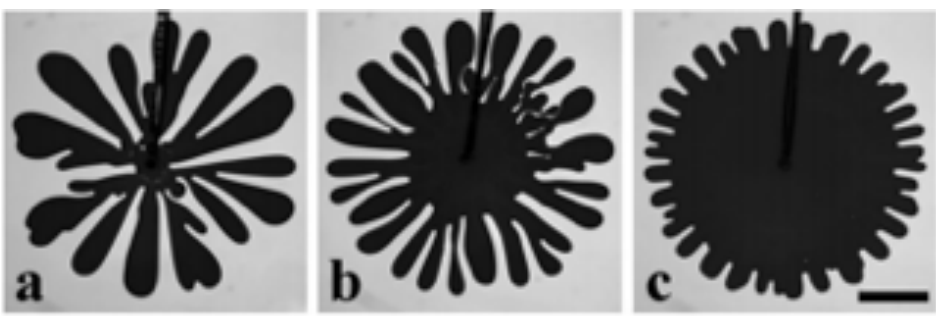
$$\vec{q} = -\frac{\kappa}{\mu}(\vec{\nabla} P)$$



Viscous fingering in Hele-Shaw cell







Bischofberger et al, Soft Matter, 2015

Viscous fingering in Hele-Shaw cell

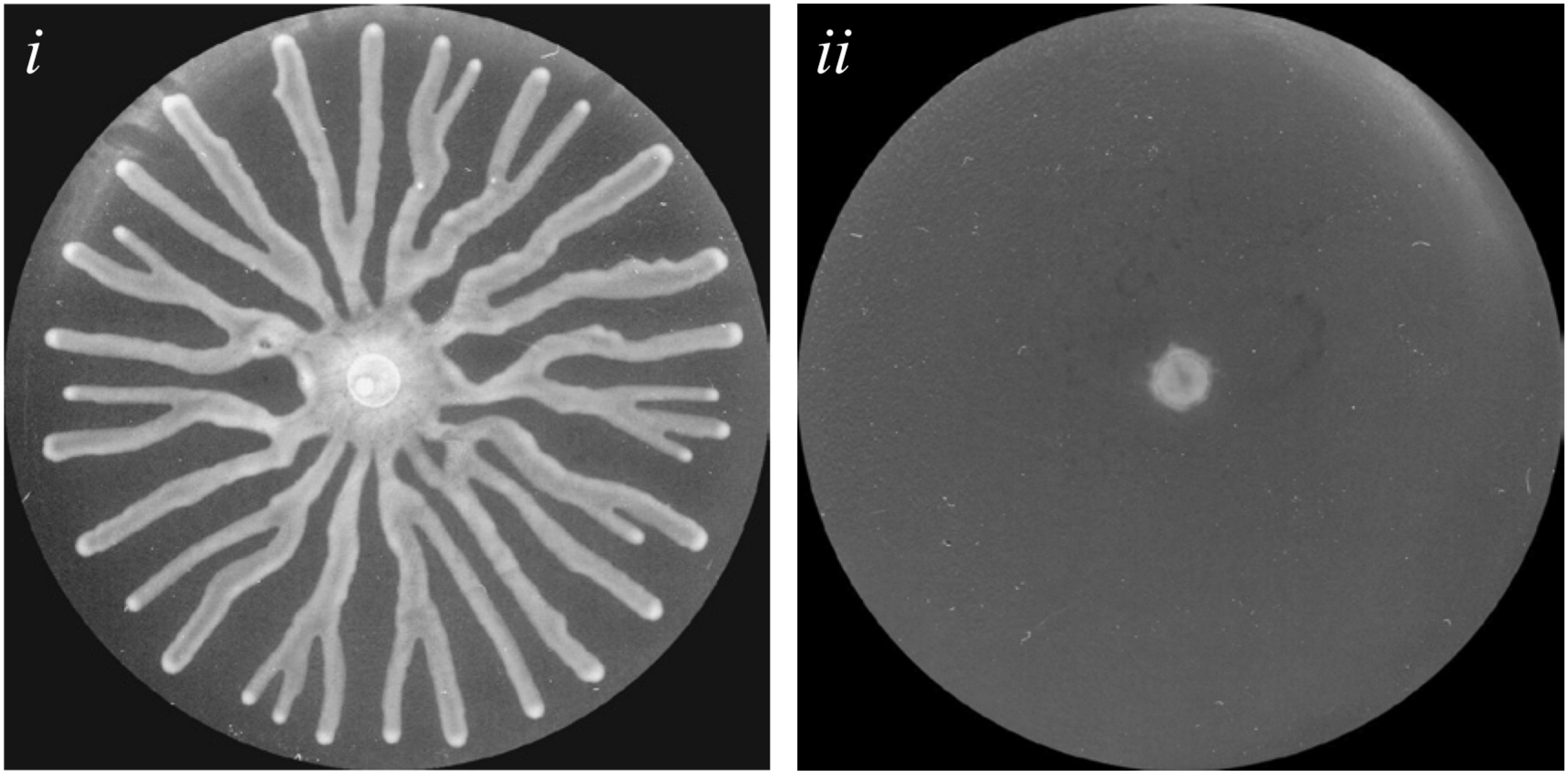
Bacterial tendril pattern is part biology, part physics

Simplifying the complexity of phage infection

Separate infected from non-infected populations

Uninfected

Phage-infected



Phage infection suppresses swarming

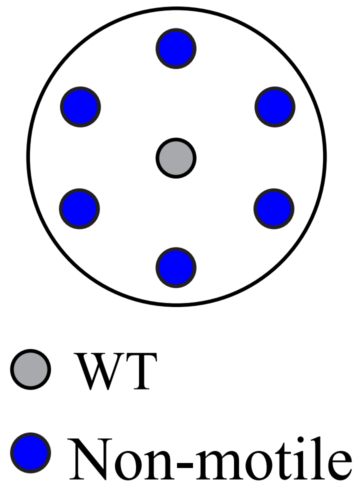
How do infected and uninfected populations interact?

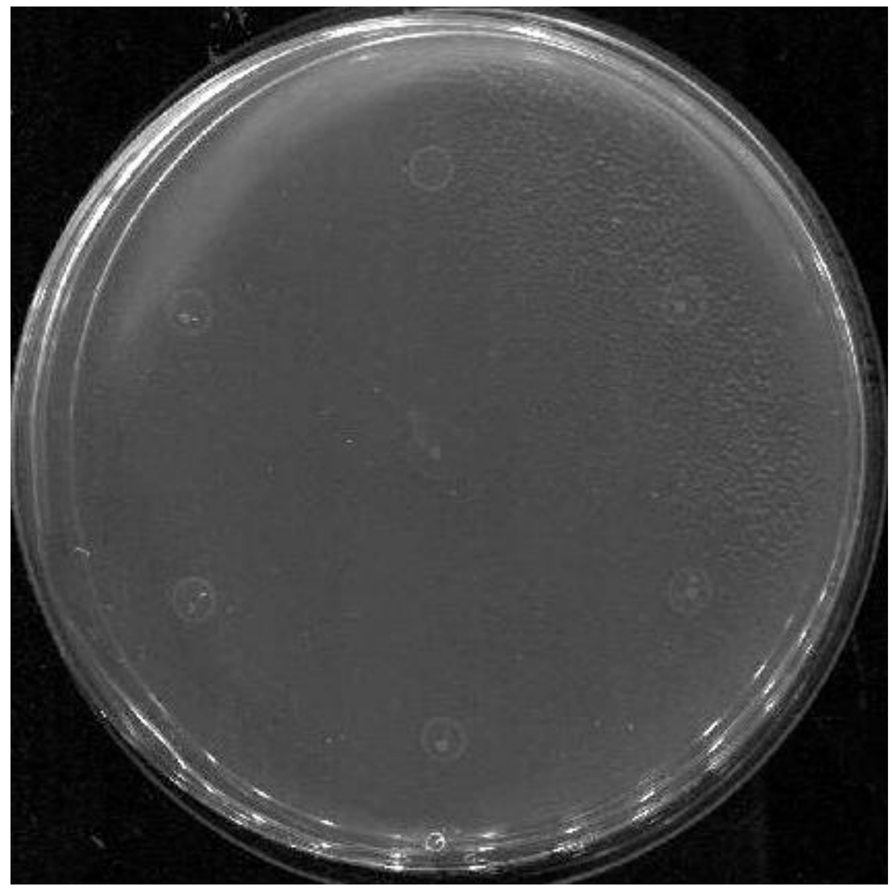
And then Brandon graduated and went to graduate school…

Quantifying interactions between different populations

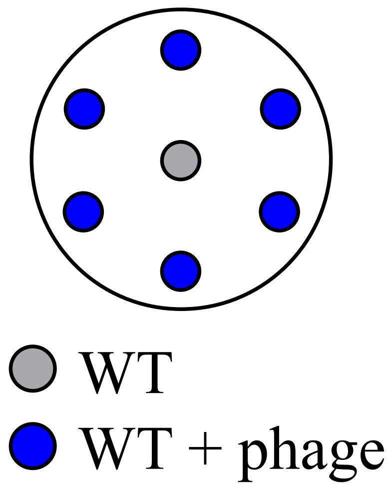
Louis Bru

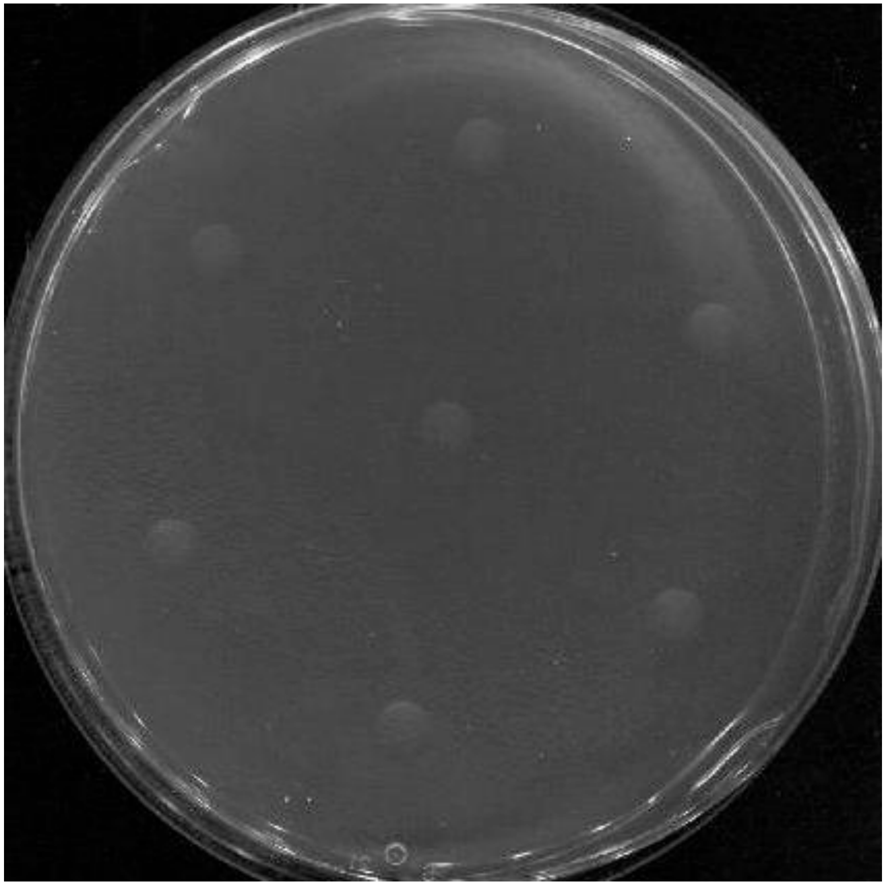
- Developed time-lapse imaging
- Time resolution, statistical power





Infected bacteria self-quarantine

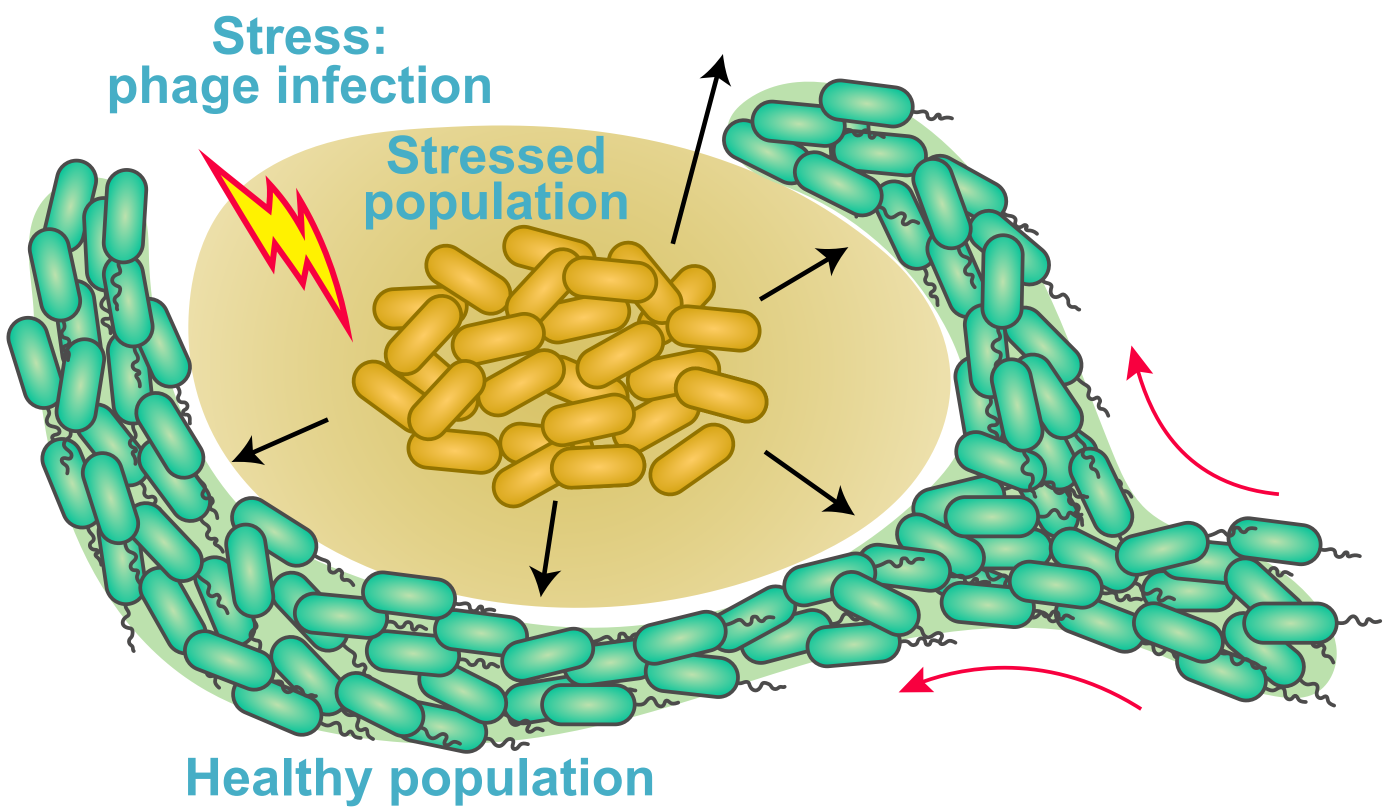




Bru et al., *J. Bact.*, 2019

- Viral-infected bacteria repel healthy population
- Viral infection does not spread to healthy population

Bacterial self-quarantine hypothesis

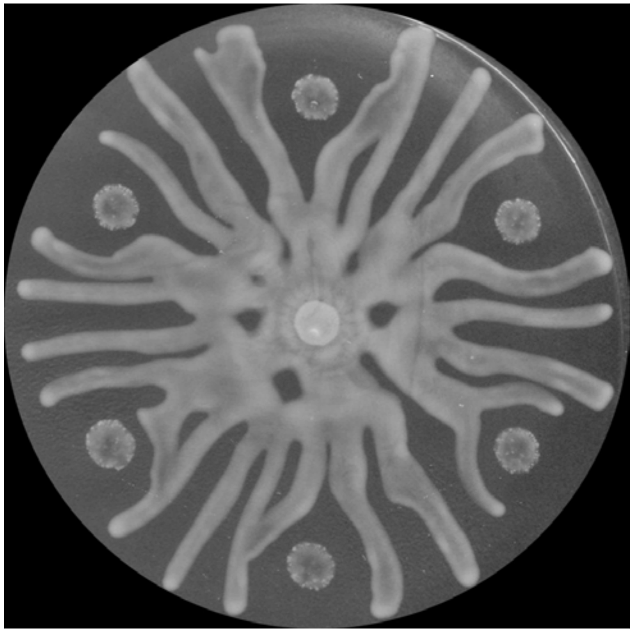


Signal transmitted by the stressed population
Infected population self-quarantines

What is the signal? When & how does it help?

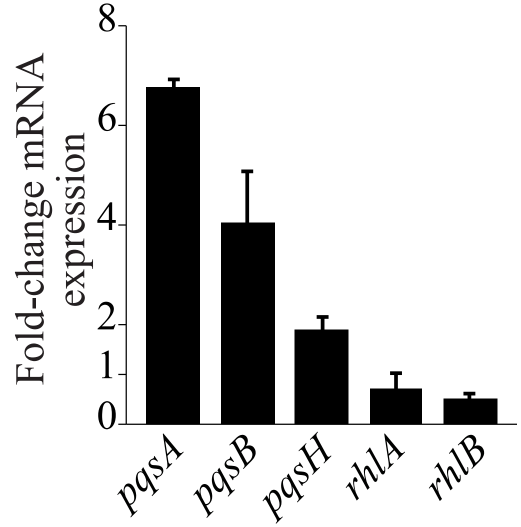
Phage infection activates *pqs*

9 months later



Center: WT
Satellites: WT + phage

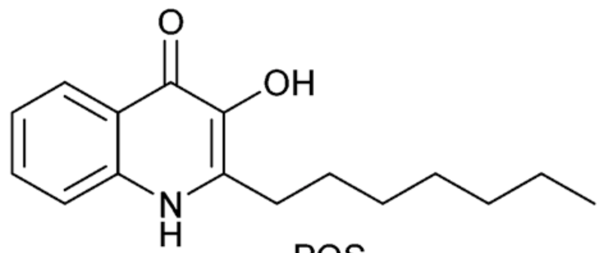
Phage-infected vs. uninfected transcription



Mass spectrometry: PQS detected in repulsion zone

Bru et al., *J. Bact.*, 2019

Pseudomonas quinolone signal (PQS)

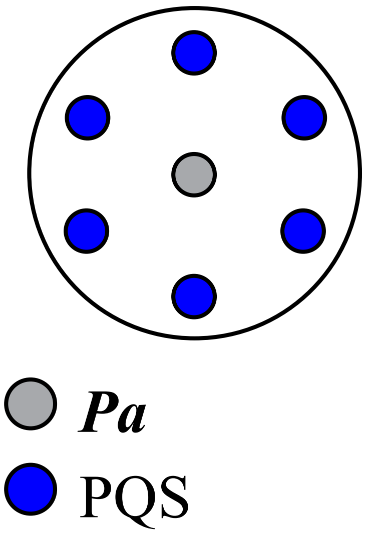


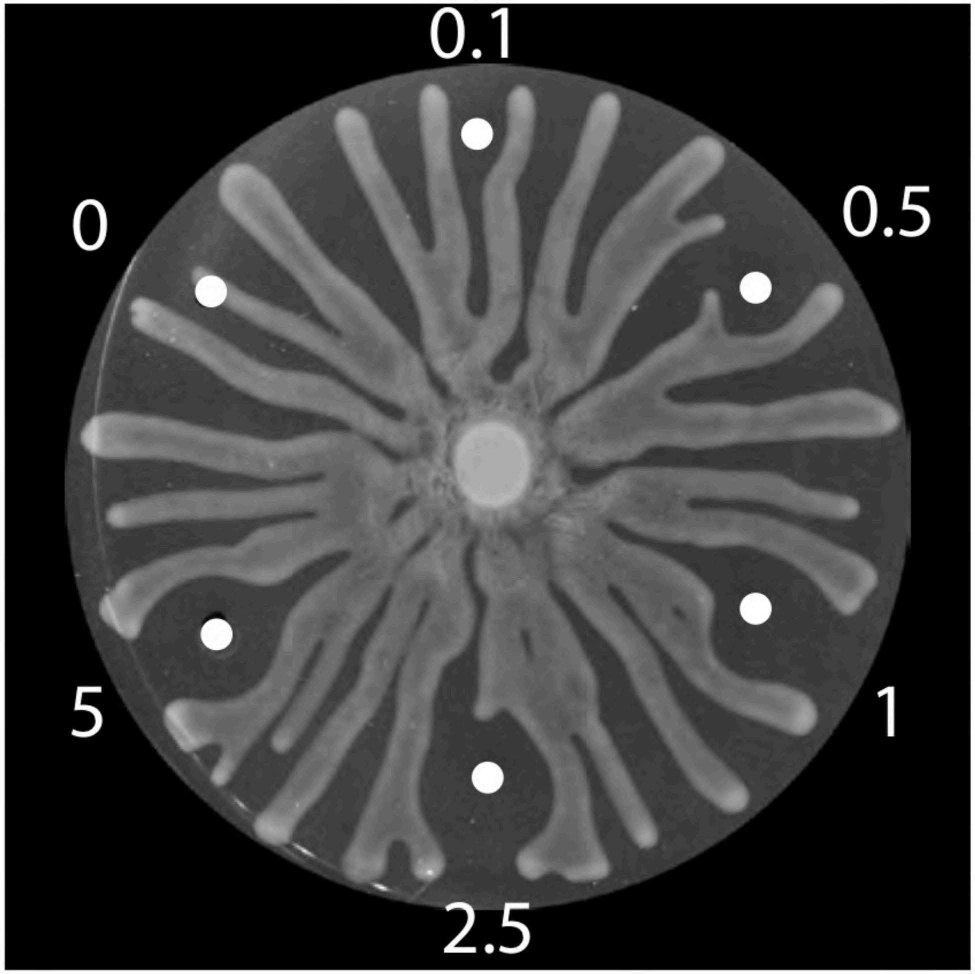
PQS

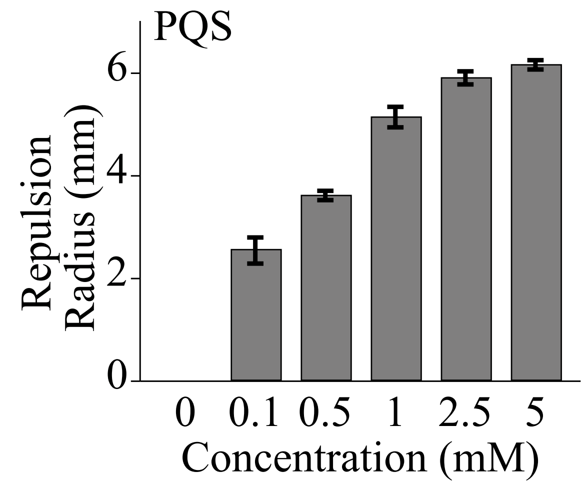
<u>Multi-functional molecule:</u>

- Quorum-sensing signal (cell-to-cell communication)
- Induces membrane stress & cell death
- Antibacterial properties
    - Many antibiotics based on quinolones (naladixic acid, ciprofloxacin)

PQS repels swarms

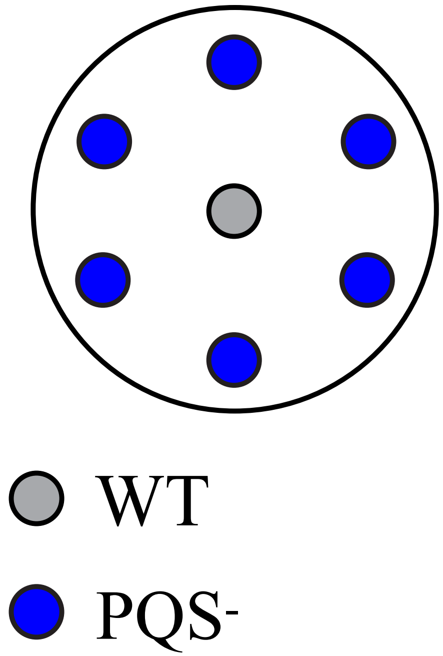


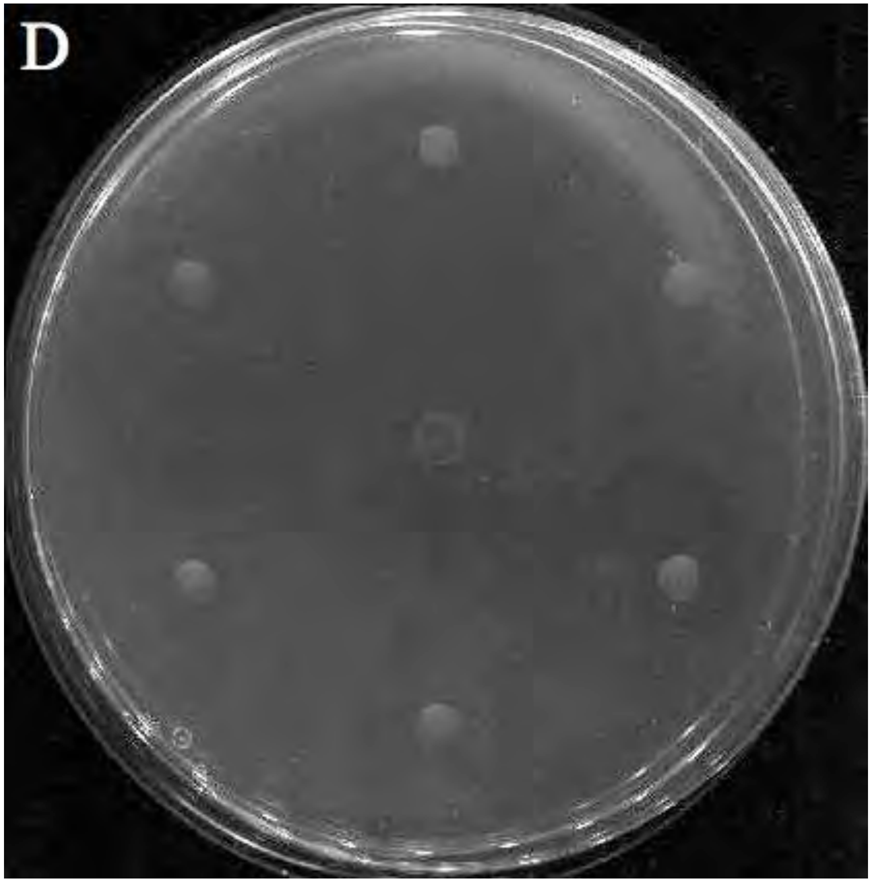




Disabling PQS production

Is PQS required for self-quarantine?





PQS is major repulsion molecule

Generality of stress response

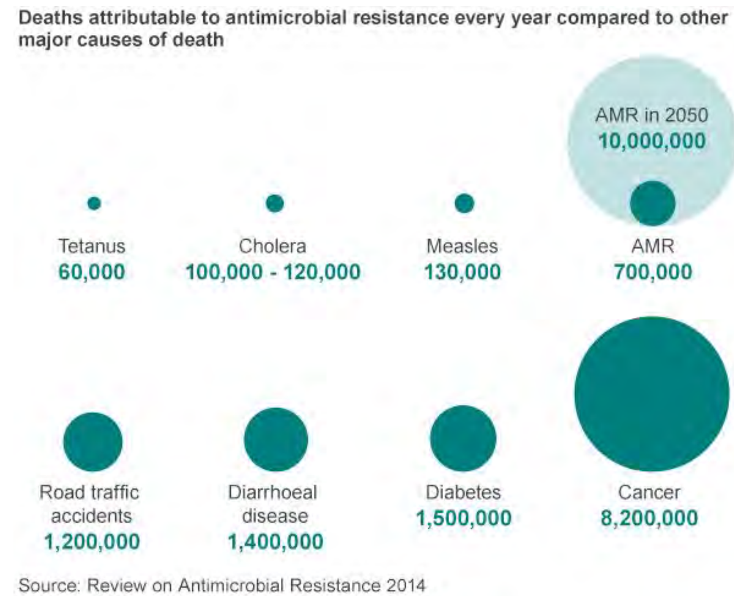
Is self-quarantine general response to stress?

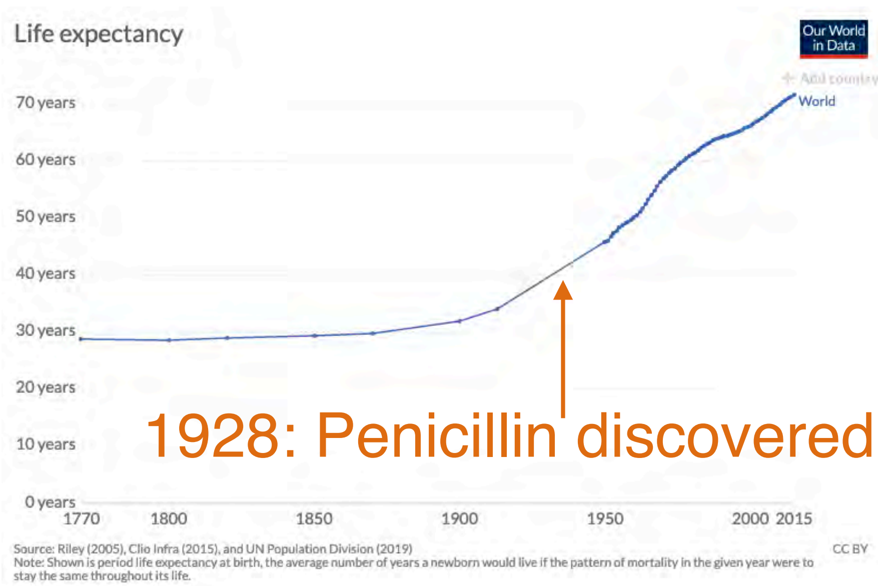
Antibiotics apply stress to bacteria

- *Pa* is one of most antibiotic resistant bacterial pathogens
- Gentamicin: common clinical treatment *Pa* infections

The new era of antibiotic resistance

- Bacteria becoming more resistant to current antibiotics
- Current: 700,000 deaths/yr
- **By 2050: 10 M deaths/yr**
- Current life expectancy: 72 yrs.

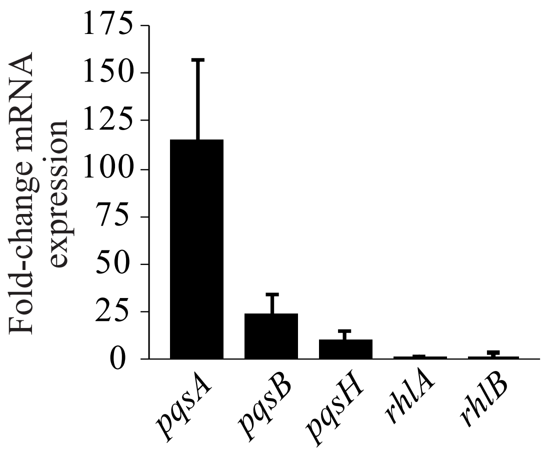


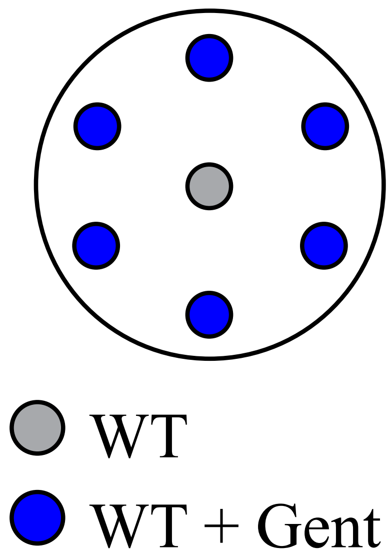


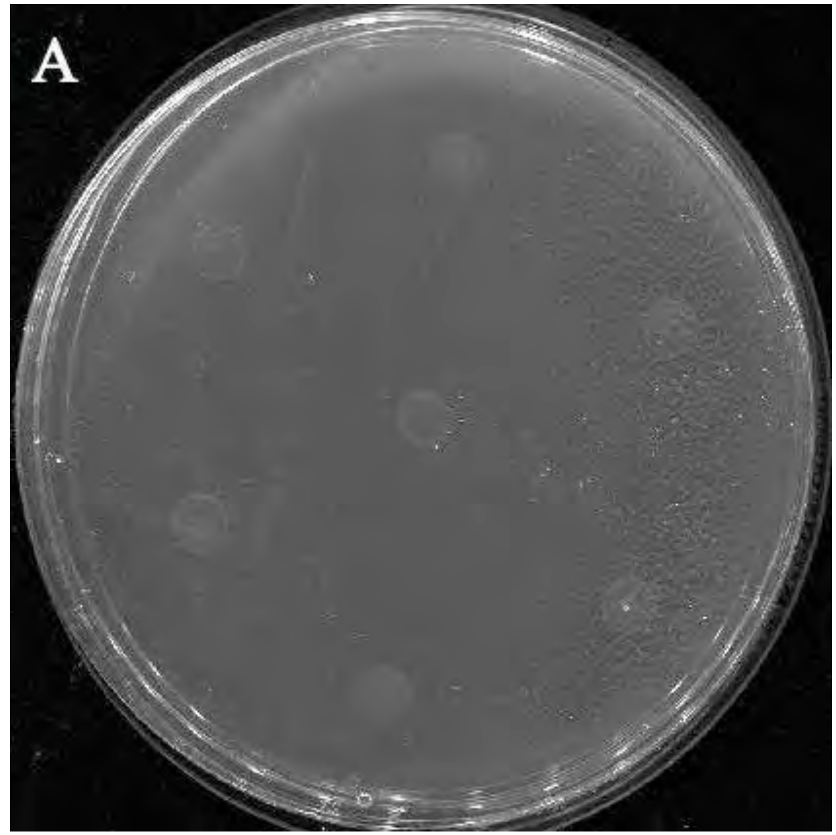
- Life expectancy in pre-antibioic era: **34 yrs**.

The antibiotic gentamycin induces self-quarantine

Gent.-treated vs. untreated transcription





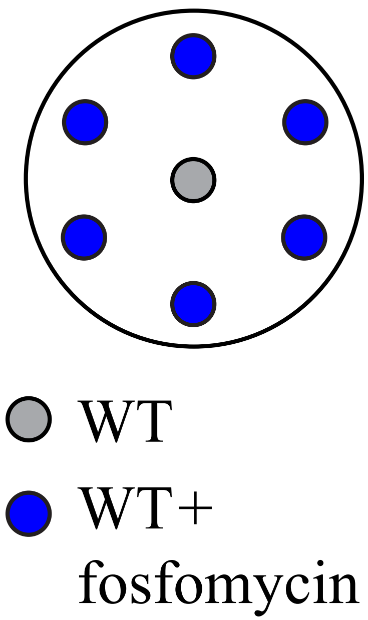


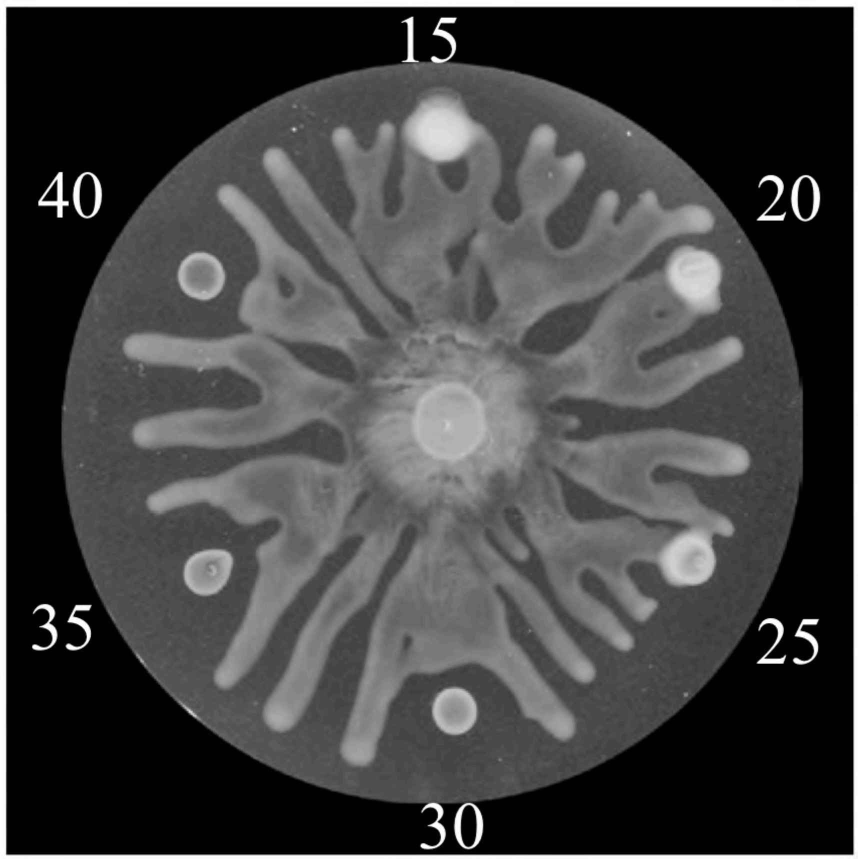
Bru et al., *J. Bact.*, 2019

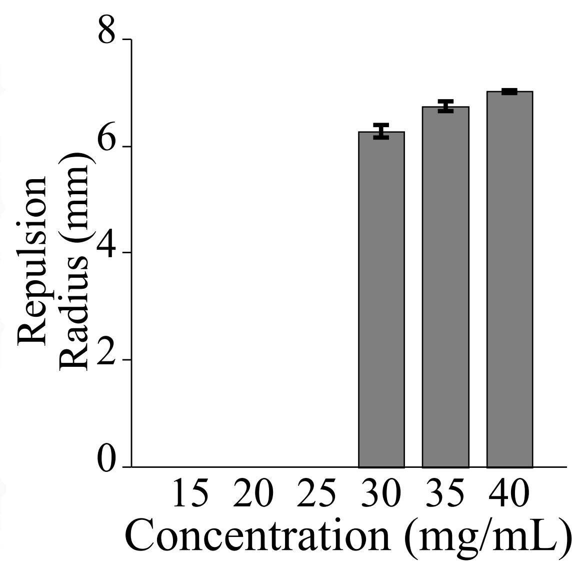
Stress response enables general antibiotic evasion

Also observed using:

- Other antibiotics:
  - Kanamycin, fosfomycin (cell wall inhibitor)







Healthy populations never exposed to the antibiotics!

Bru et al., *J. Bact.*, 2019

Novel stress response mechanism in bacteria

Summary:

- Viral infection or antibiotics induce **self-quarantine**:
  1. repels healthy populations from approaching
  2. induces secretion of PQS molecule

- Limits the spread of viral infection to the healthy population

- We call this: **collective stress response**

- Current work: understanding physics of repulsion, tendril deflection

- Current: how bacteria detect the presence of antibiotics and viruses

Can stress response be used to block other types of viral infections?

Outline

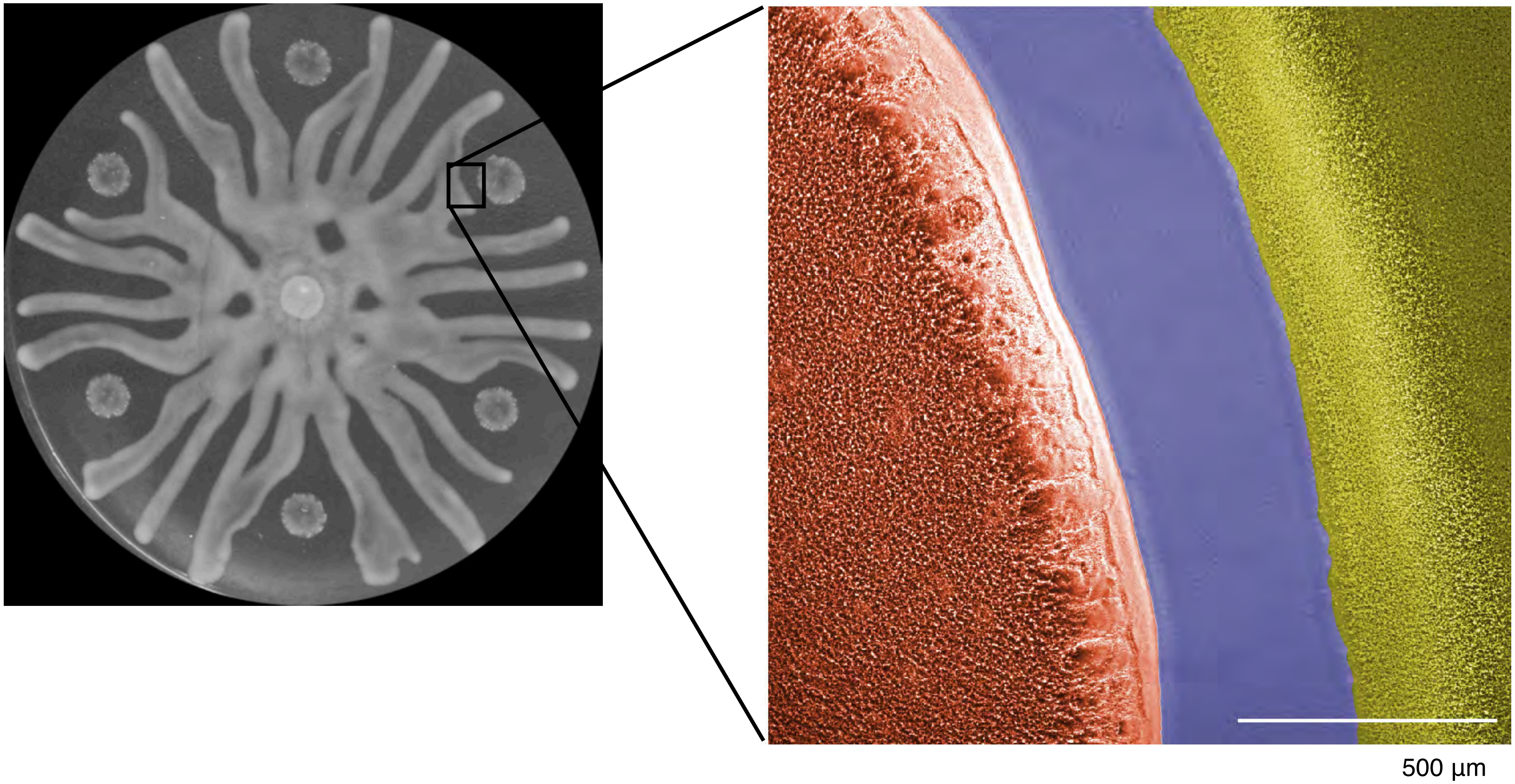
Foundation for a new antiviral strategy

1. How **bacteria** protect against **threats** from **viruses**

2. Using lessons from bacteria to develop **SARS-CoV-2** anti-viral treatment

How does stress response inhibit viral infection?

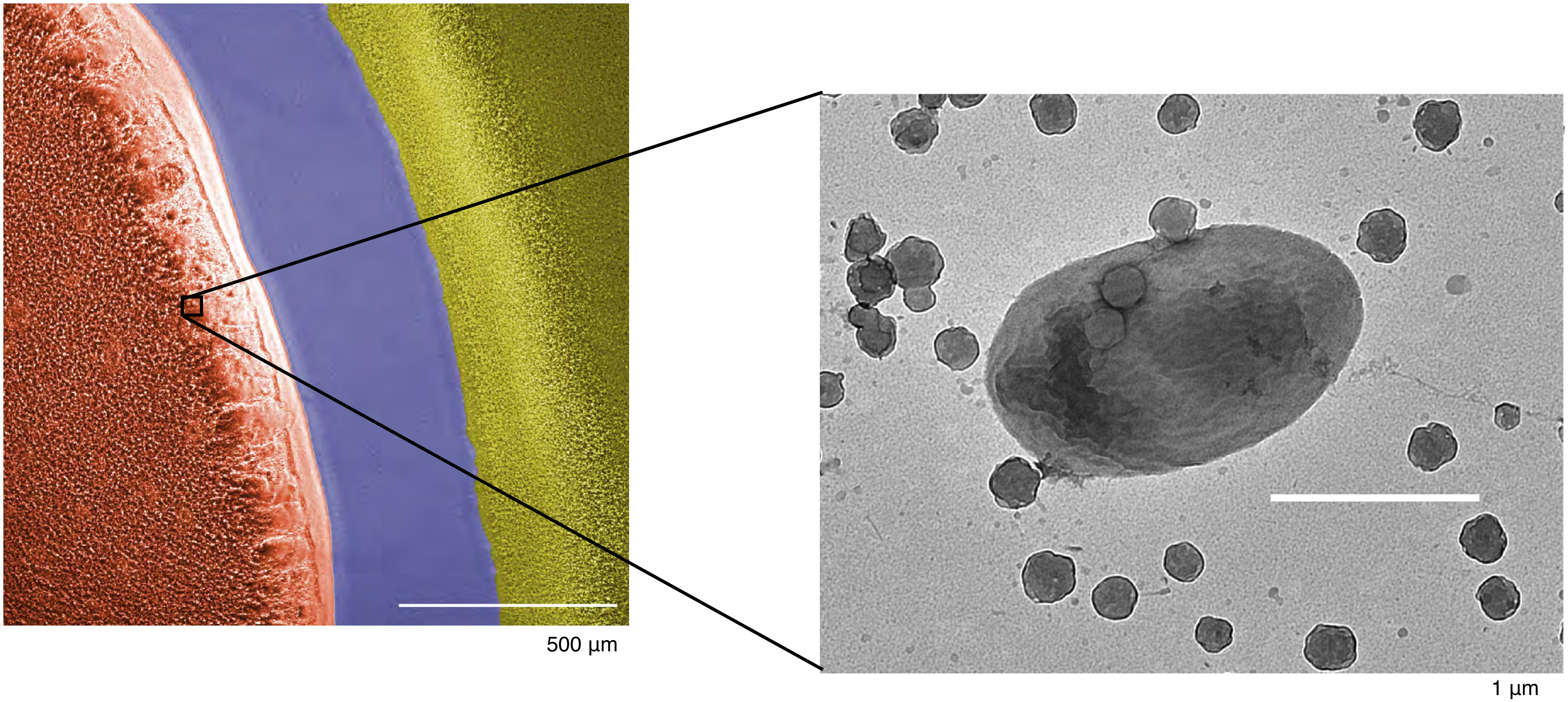
Zooming in…



1. Physical repulsion / distancing

Red = viral infected bacteria
Blue = PQS
Green = Uninfected bacteria

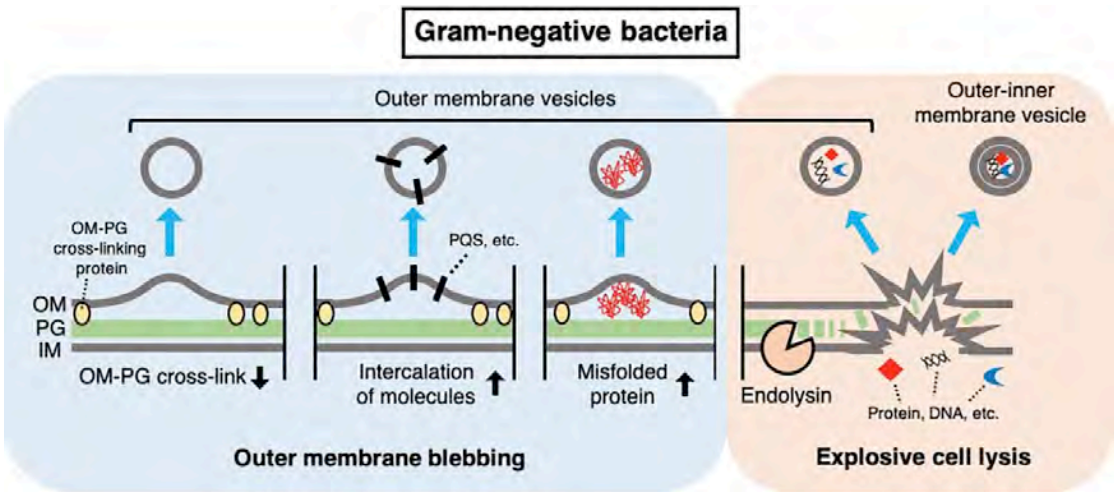
How does stress response inhibit viral infection?



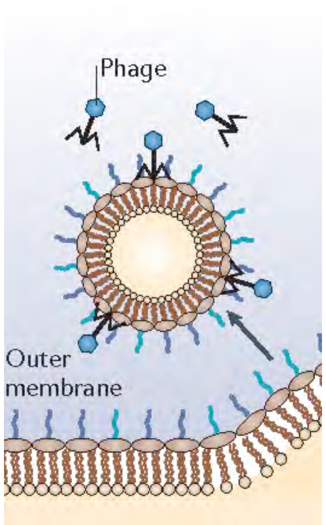
Closer inspection: production of membrane vesicles
Cells blow up (die) and release many small particles in the process

Stress response creates outer membrane vesicles

PQS induces membrane curvature



Nagakubo et al., *Frontiers in Micro.*, 2020



Schwechheimer and Kuehn, *Nat. Rev. Micro*, 2015

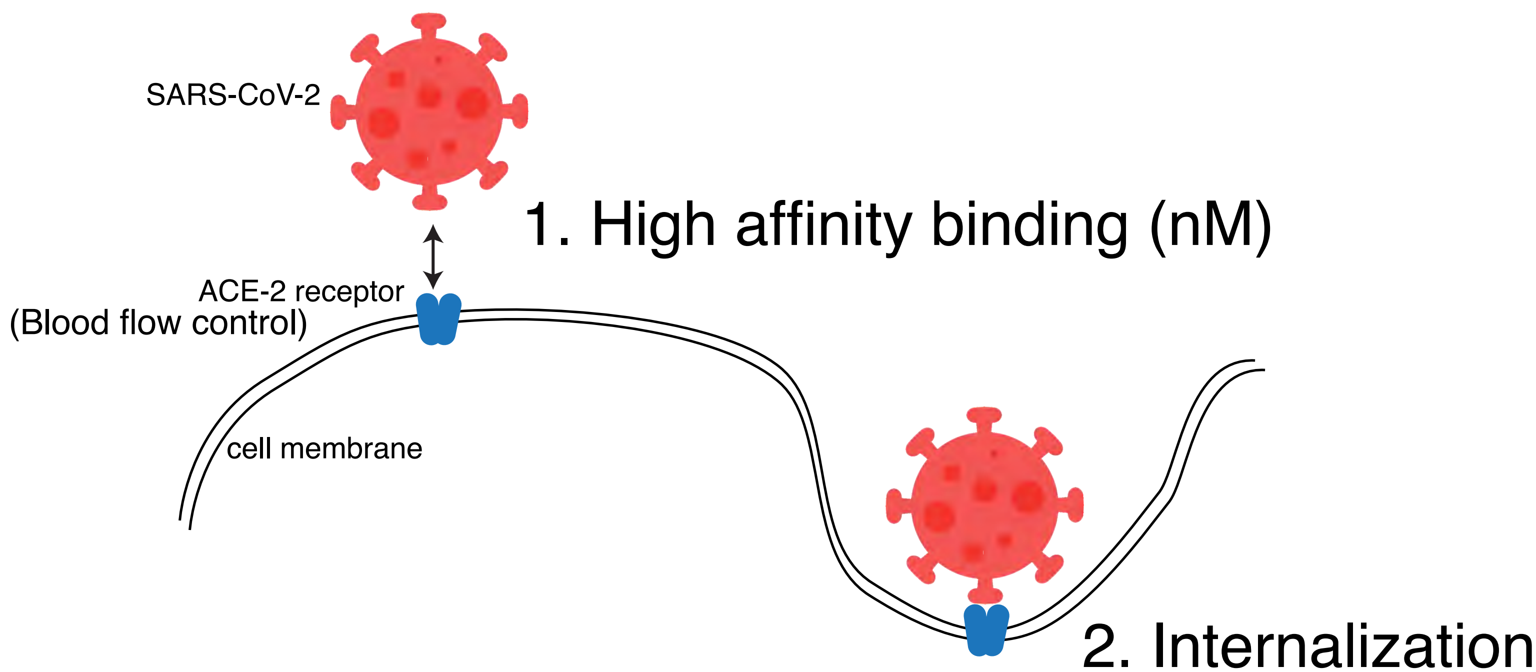
- Membrane vesicles function as viral decoys
- Small fraction of cells blowing up: protects population

<u>Why this strategy can be effective</u>

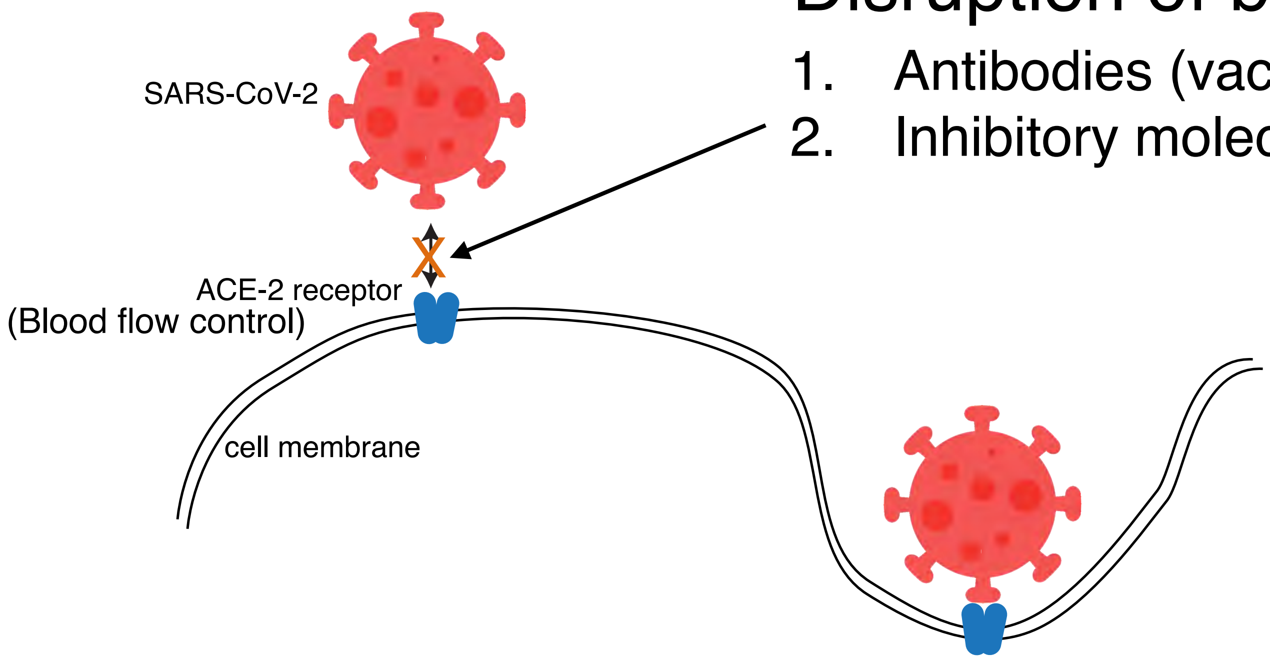
- Single cell produces large number of vesicles
- Virus binds vesicles instead of live bacterial cell
- Virus cannot replicate inside vesicle because it lacks necessary machinery
- Virus typically outnumber bacterial cells
- Vesicles alter stoichiometry: large # of unproductive virus binding sites

Applying anti-viral strategy to SARS-CoV-2

Background



Current strategies



Disruption of binding

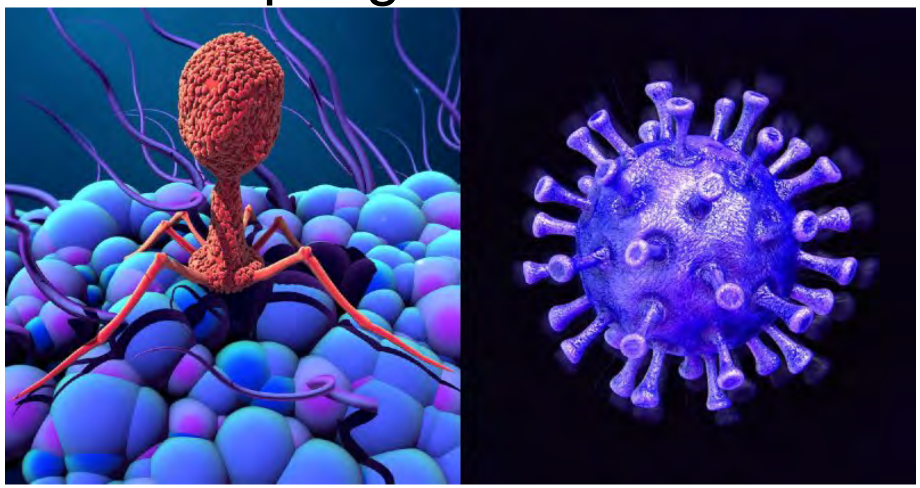
1. Antibodies (vaccine)
2. Inhibitory molecules / drugs

Challenges

1. Inherently difficult problem: disruption of high affinity binding
2. Mutation of virus

How bacterial and human viruses compare

Bacteriophage SARS-CoV-2



Bacteriophage.news

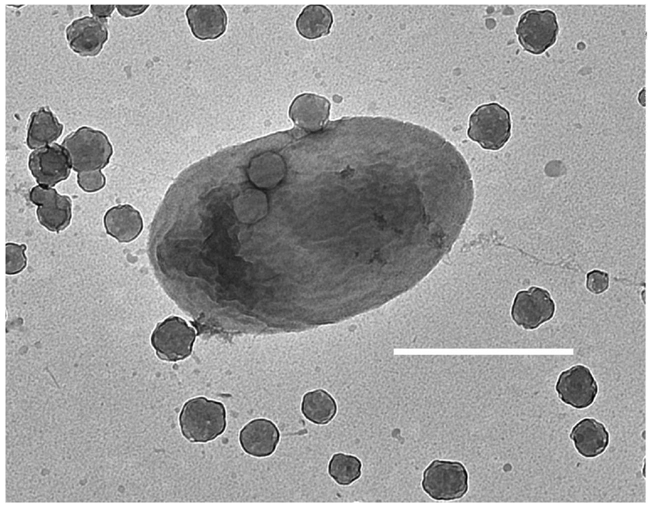
<u>Similarities:</u>

- ~100 nm wide
- Binding affinities ~nM range
- Bind to receptors on the surface of target cell

<u>Notable Differences:</u>

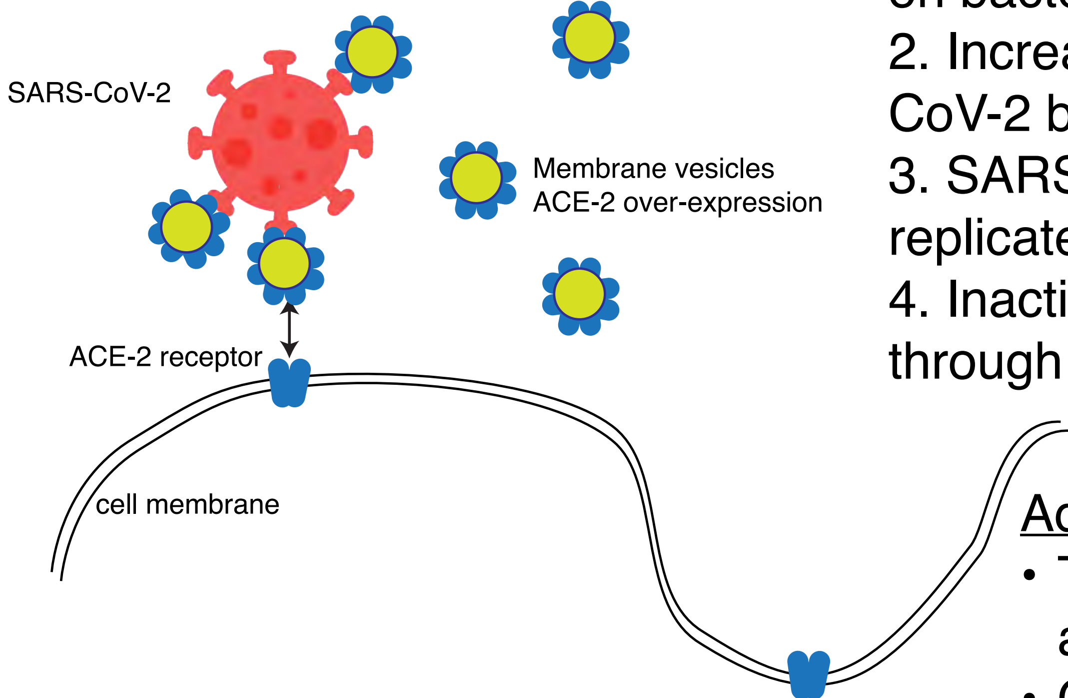
- Replication machinery / mechanism
- Lifespan: bacteria (days) vs. lung cell (years)

Why cell lifespan matters



- Bacteria can replicate quickly to replace dead bacteria
- Lung cells (life span of years) cannot use this strategy every time virus infects
- How can bacterial strategy be used for human cells?

Proposed anti-viral strategy against SARS-CoV-2



Inactivation

1. Expression of ACE-2 receptor fragment on bacterial membrane vesicles
2. Increases # of unproductive SARS-CoV-2 binding sites
3. SARS-CoV-2 is inactivated and does not replicate in membrane vesicles
4. Inactivated SARS-CoV-2 removed through routine digestion

Advantages

- Takes advantage of existing high affinity binding
- Can be modified for virus variants using synthetic targeted approach:
  - Synthetic mutation of ACE-2 receptor fragment to increase binding to SARS-CoV-2
- General approach may work against other viruses

Proposed anti-viral strategy against SARS-CoV-2

Objectives

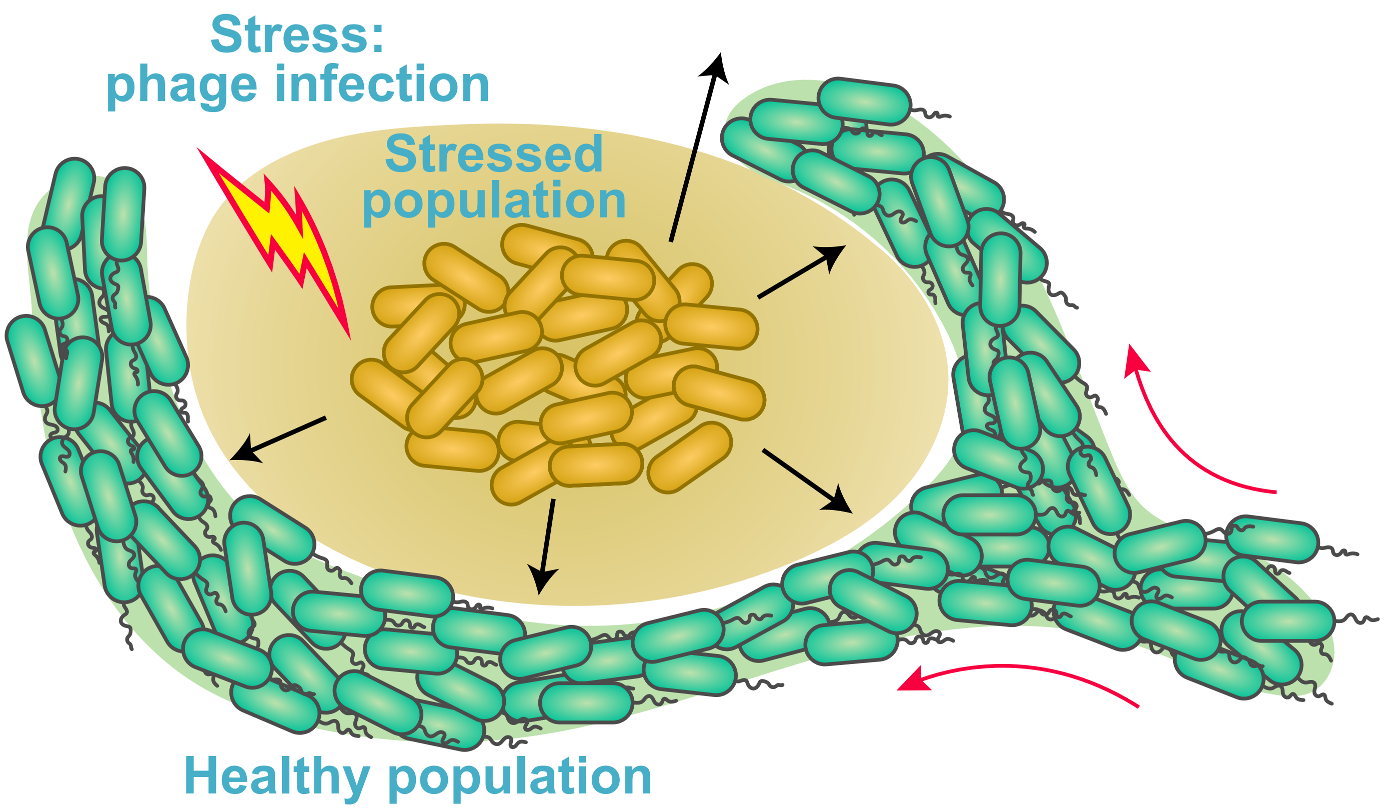
Obj 1. Expression of the ACE2 peptidase domain on bacterial outer membrane proteins in MVs

Obj 2. Demonstration of ACE2 expression on MVs and binding of the S1 protein to ACE2-expressing MVs.

Obj 3. Assessment of the impact of ACE2-expressing MVs on SARS-CoV-2 infection using lung epithelial cells.

Summary

- Bacteria (i) avoid antibiotics & (ii) halt viral propagation
- Alter spatial organization of population



Summary

Lessons learned from bacteria: **How bacteria save their populations from viral outbreaks**

1. Self-quarantine / distancing infected populations from healthy ones
2. Inactivate viruses using membrane vesicle decoys

How we use this strategy to defeat SARS-CoV-2

1. Inactivate SARS-CoV-2 by using synthetic membrane vesicle decoys

Acknowledgements

Henry Amir
Louis Bru
Tory Doolin
Ilona Foik
Jacqueline Nguygen
Kumar Perinbam
Jennifer Poo
Brandon Rawson (UCSD)
Annie Trinh
Calvin Trinh
Lauren Urban

Katrine Whiteson (UCI)
Nina Høyland-Kroghsbo (U Copenhagen)

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NIH NIAID

UCI School of Physical Sciences

Lessons Learned From Bacteria as we Fight COVID-19 with Professor Albert Siryaporn

For questions, please utilize the Q&A feature at the bottom of your screen

Text PSBLS to 41444 to give!