Reprogramming biological functionalities for autonomous therapeutic cells

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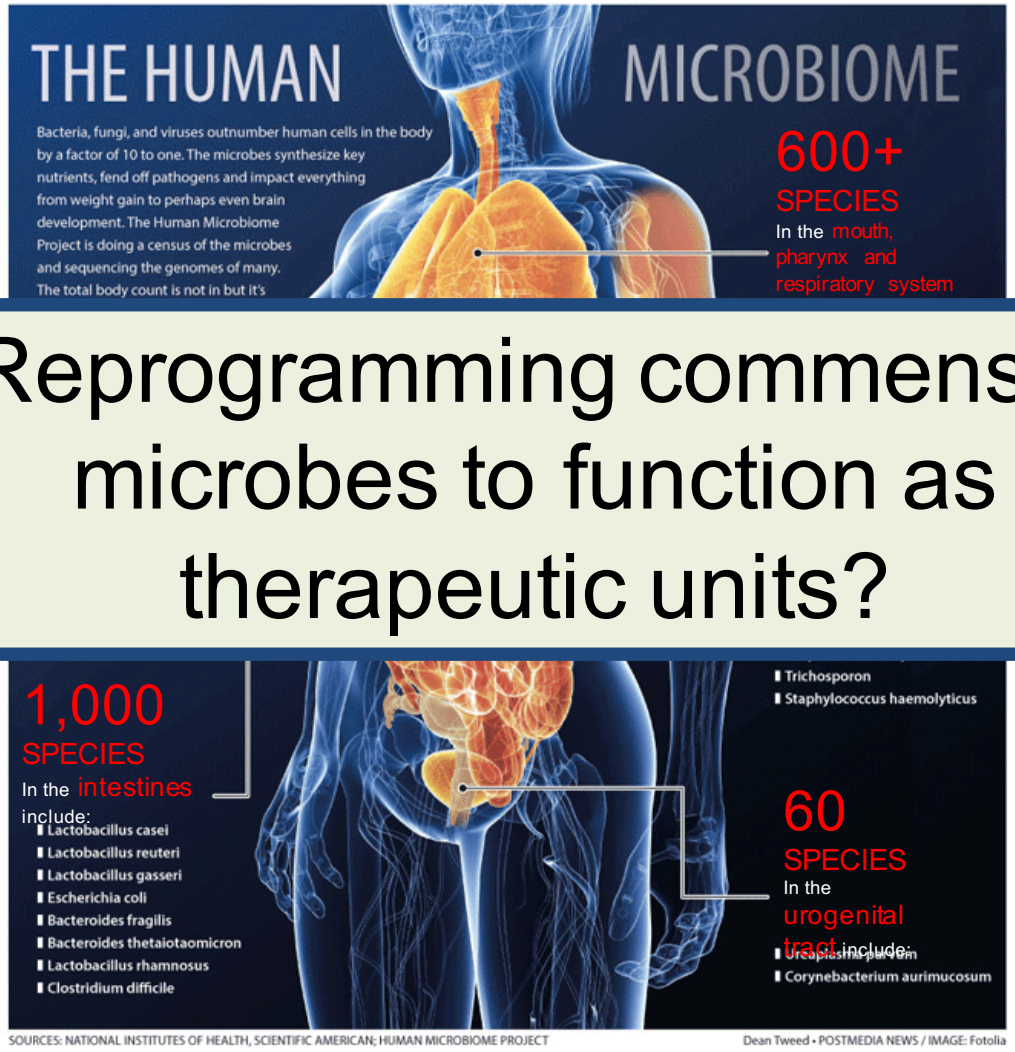
MICROBIOME

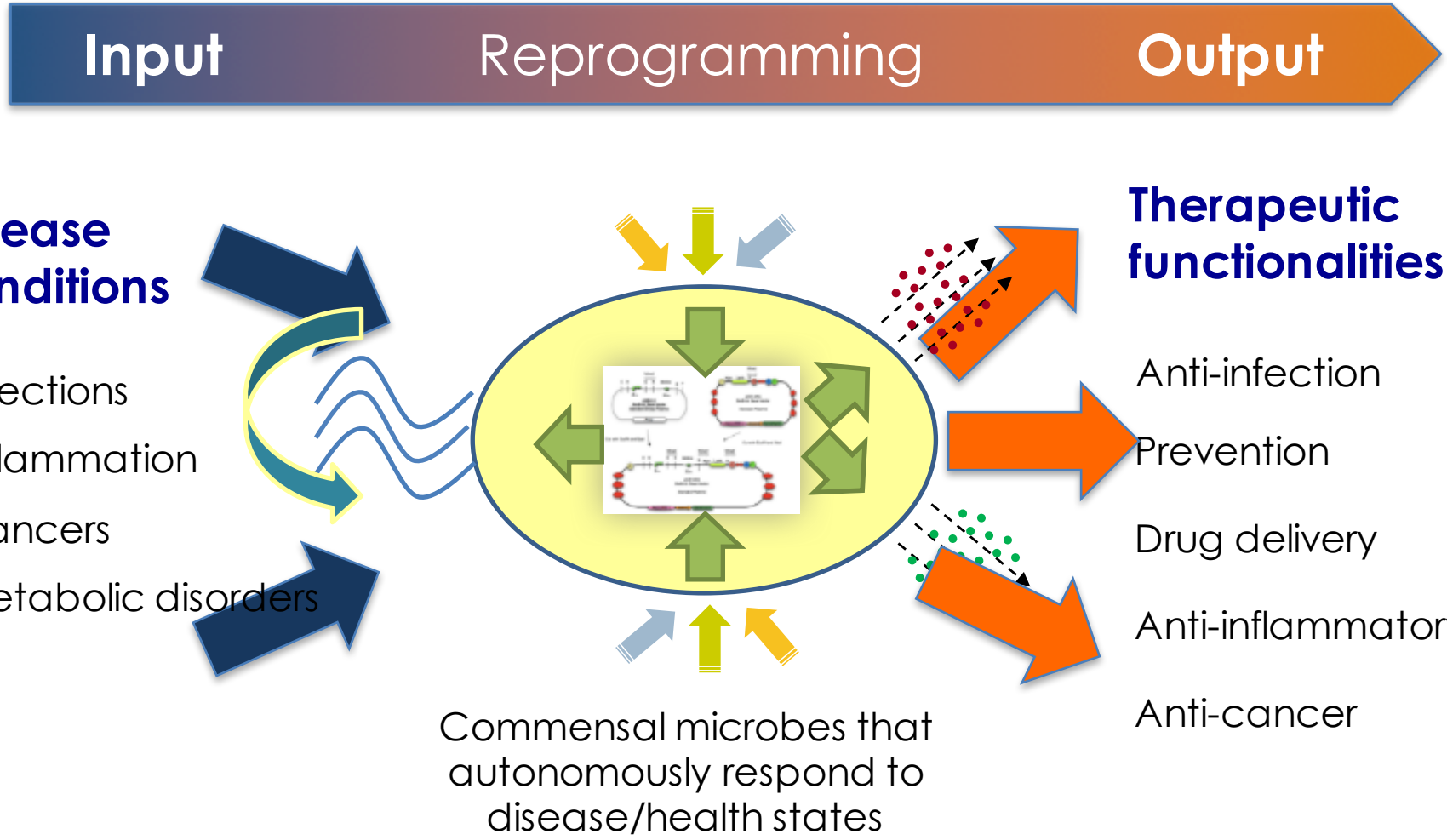
DENIZENS OF THE HUMAN BODY AND AFFECTS OUR HEALTH



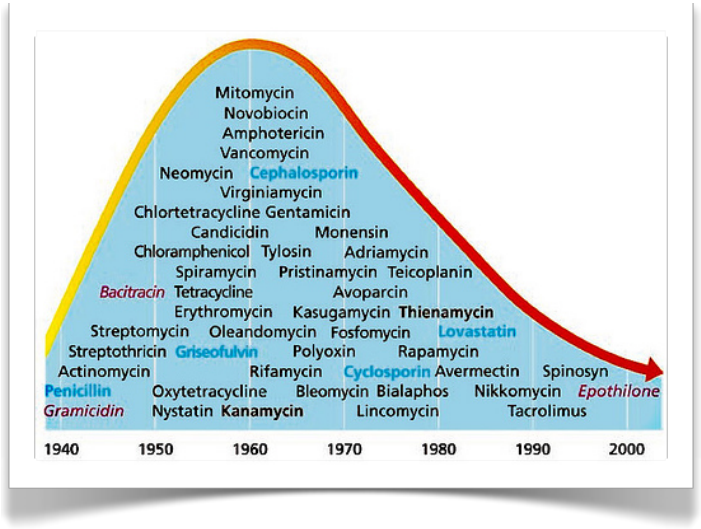
Reprogramming commensal microbes to function as therapeutic units?

Functional commensal microbes

Responding to disease conditions in an autonomous manner



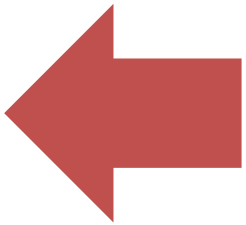
ANTIBIOTIC RESISTANCE: PROBLEM?



- Most major classes of antibiotics developed in 1940's to 1960's
- Since 1980's, the pharmaceutical industry focusing on chronic diseases that require life-long daily treatment
- Fewer new classes of antibiotics available

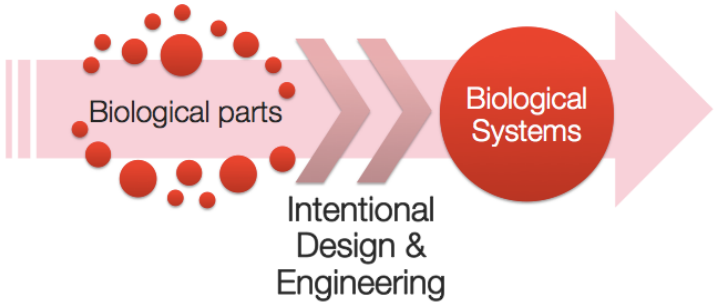
POTENTIAL SOLUTIONS?

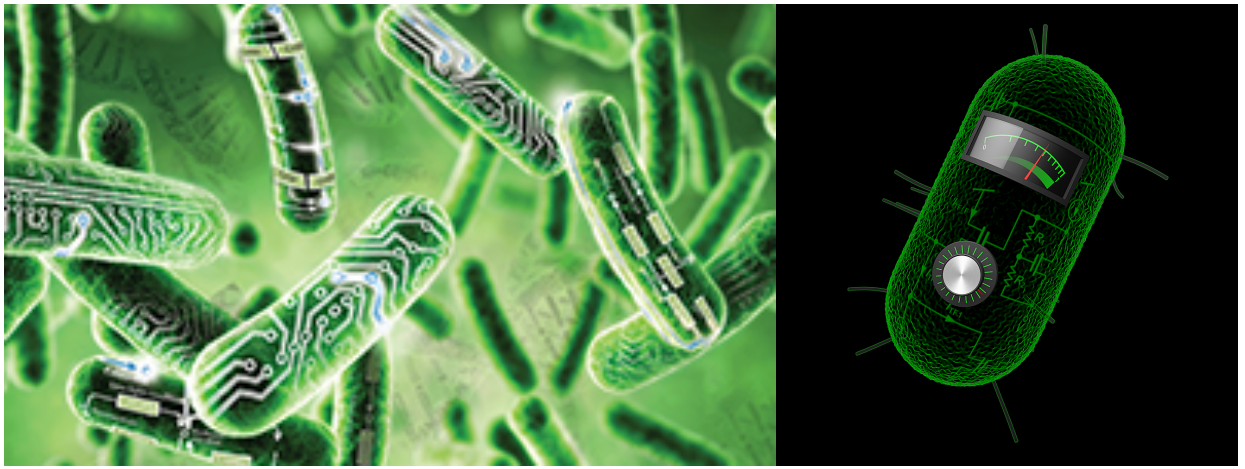
- Develop new classes of antibiotics
- Diversify our antimicrobial strategies
  - Exploiting synthetic biology approaches?



RESEARCH OBJECTIVE

- **Intentional design**
  - Programmable behaviors
    - Sensing, seeking and killing a target pathogen



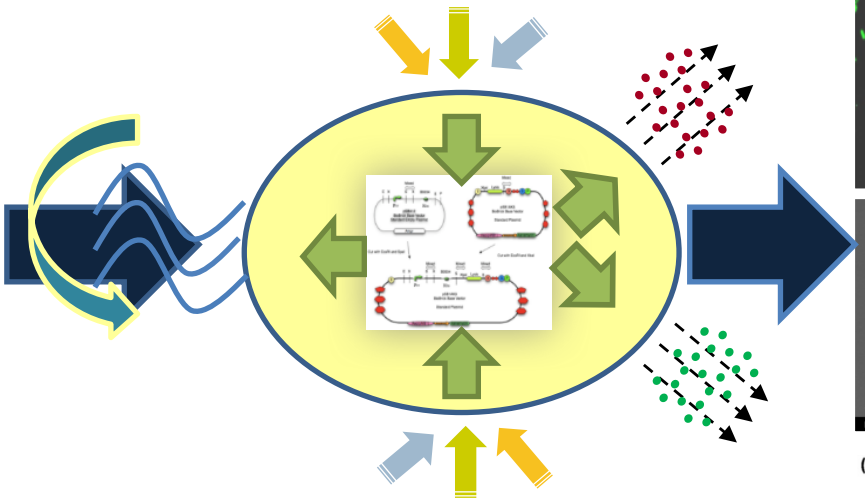


DESIGN: INPUT & OUTPUT

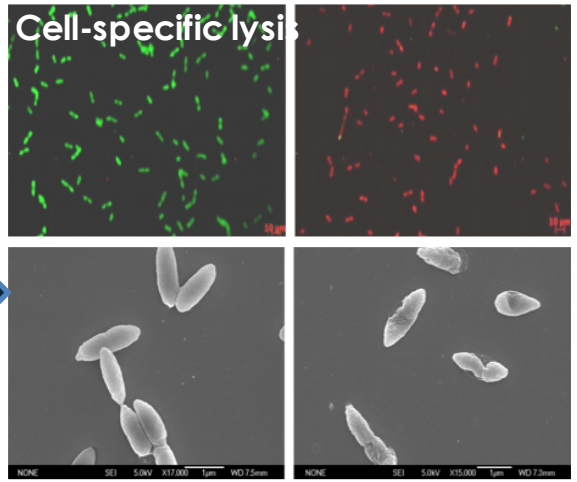
QUORUM SENSING (QS) & BACTERIOCINS

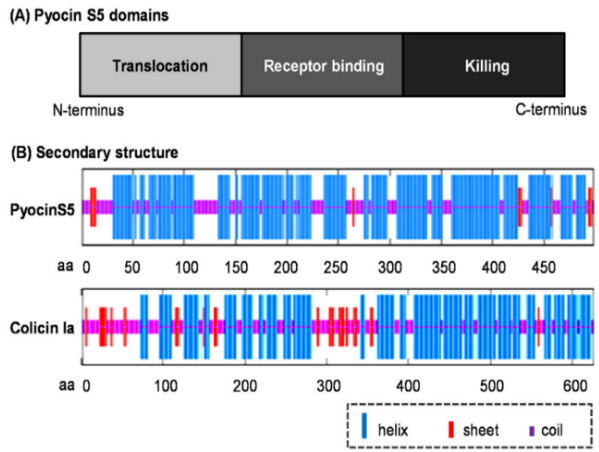
QS molecules

- Intercellular communication
- Transition between cellular lifestyle



Bacteriocins

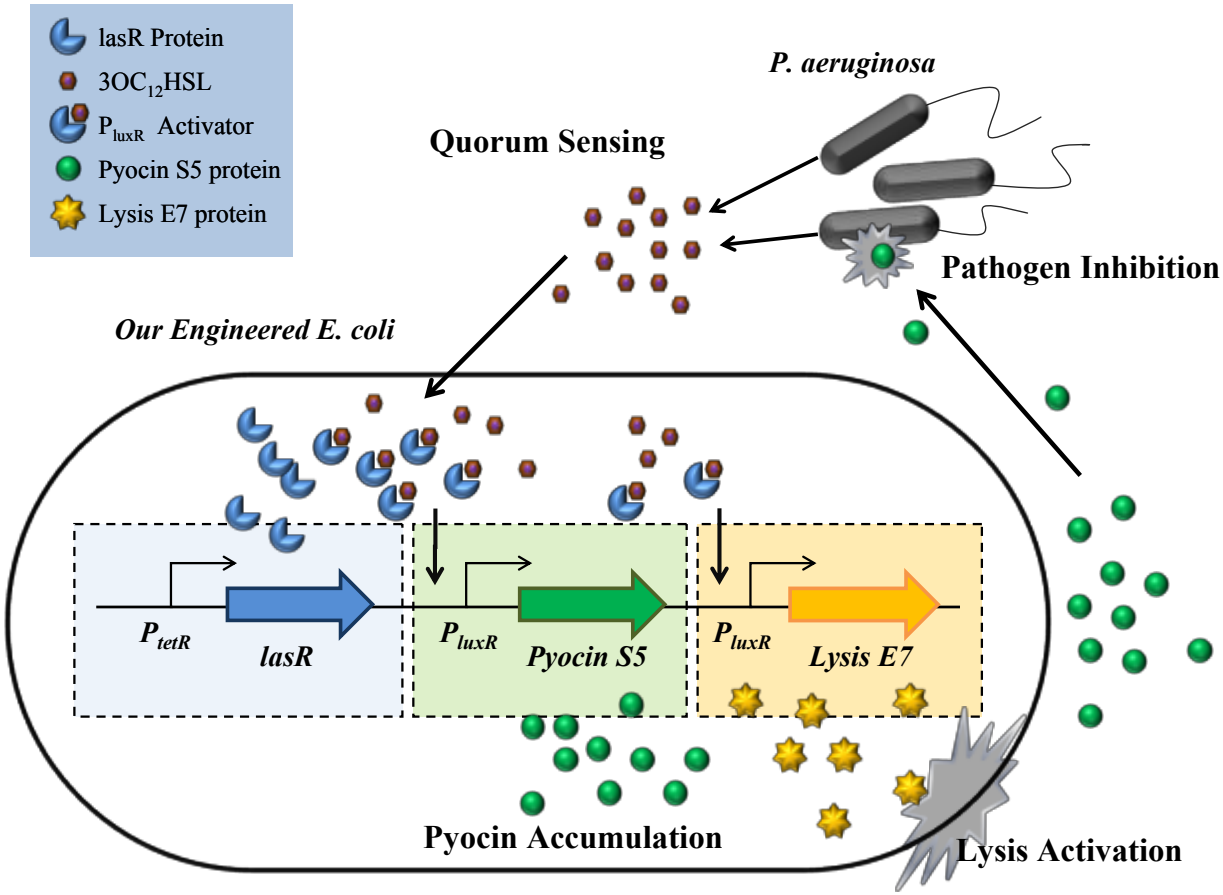




FEBS Lett (2010); BBRC (2010); Chem Eng Sci (2013); ChemBioChem (2013)

Pathogen-killing microbes

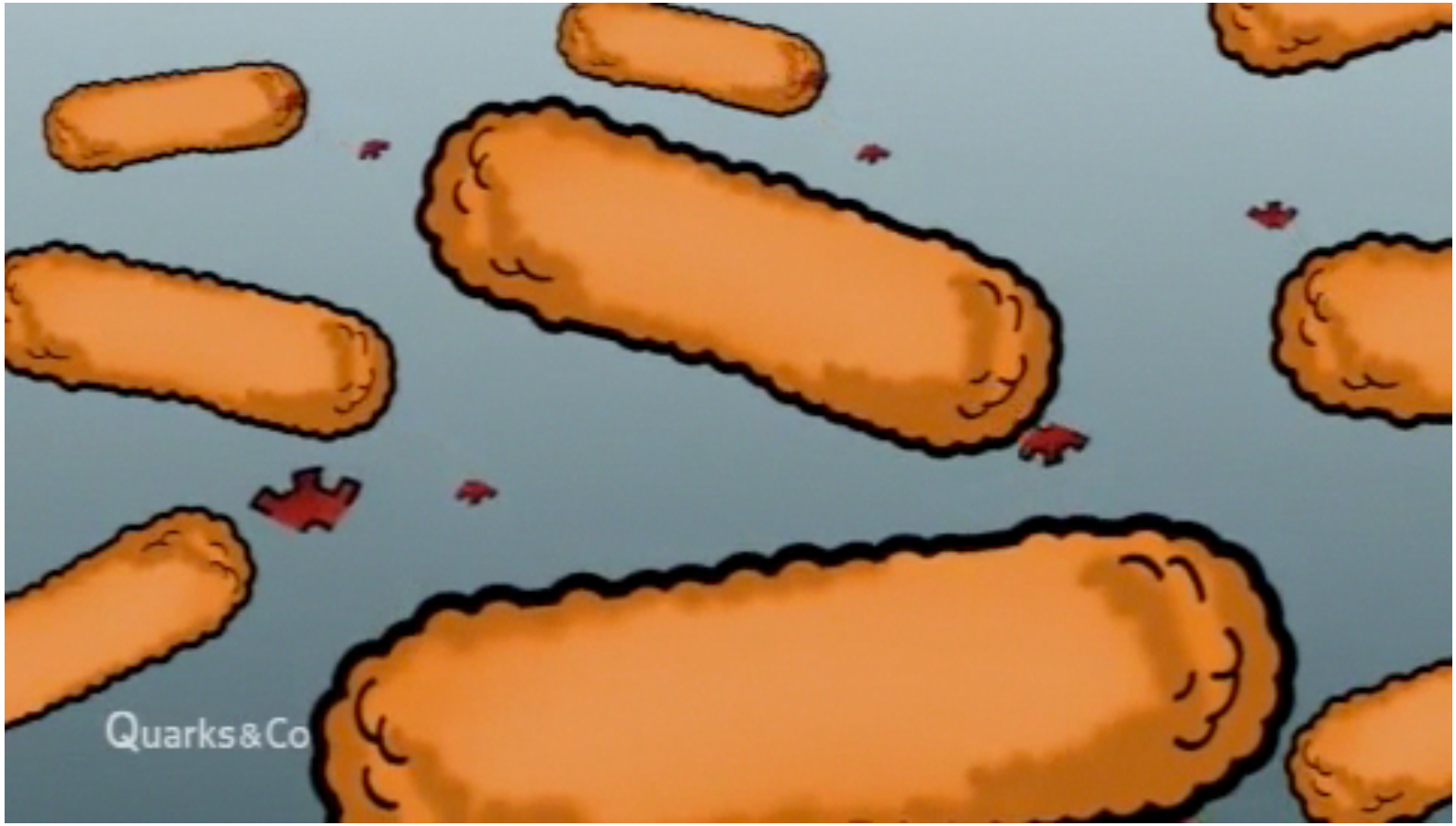
Prototype



Hwang et al. ACS Syn Biol, 2014
Rasouliha et. ChemBioChem, 2013
Saeidi et al. Mol Sys Biol, 2011
Ling et al. FEBS Lett, 2010

How our synthetic microbes work..

Courtesy of West German Broadcasting (WDR)



http://www.wdr.de/tv/quarks/sendungsbeitraege/2011/1213/008_bakterien_2.jsp

Hwang et al. ACS Syn Biol, 2014
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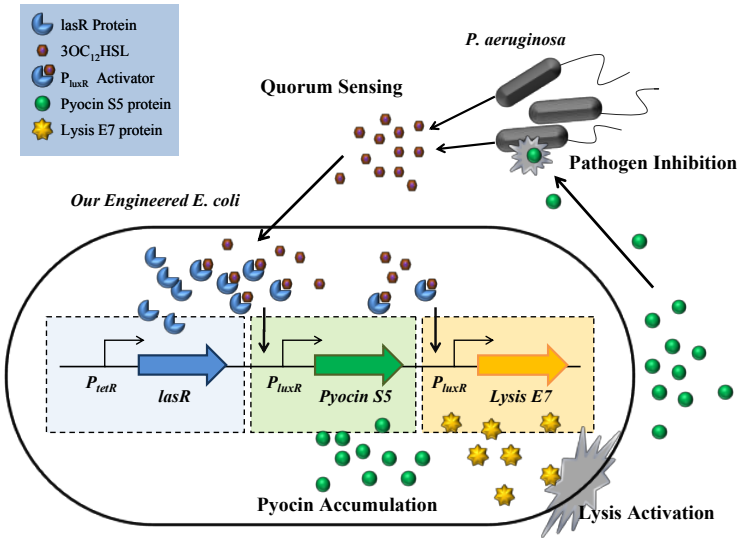
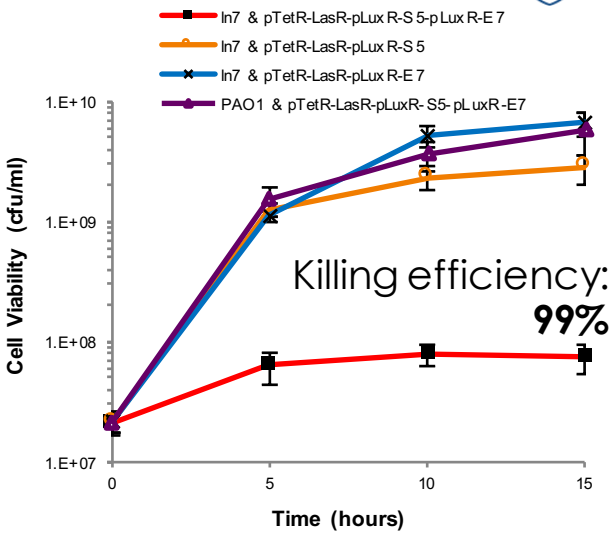
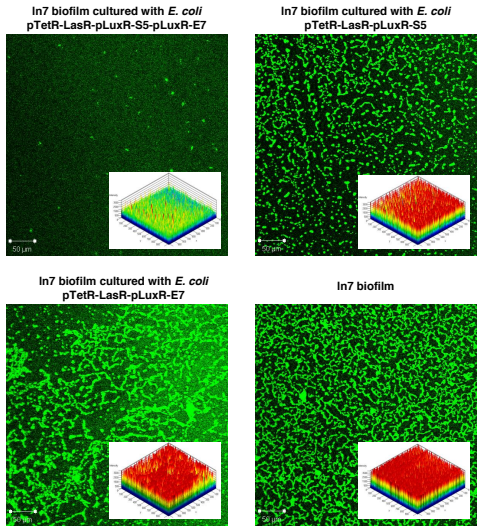
PATHOGEN-KILLING MICROBES

PROTOTYPES - STILL EVOLVING







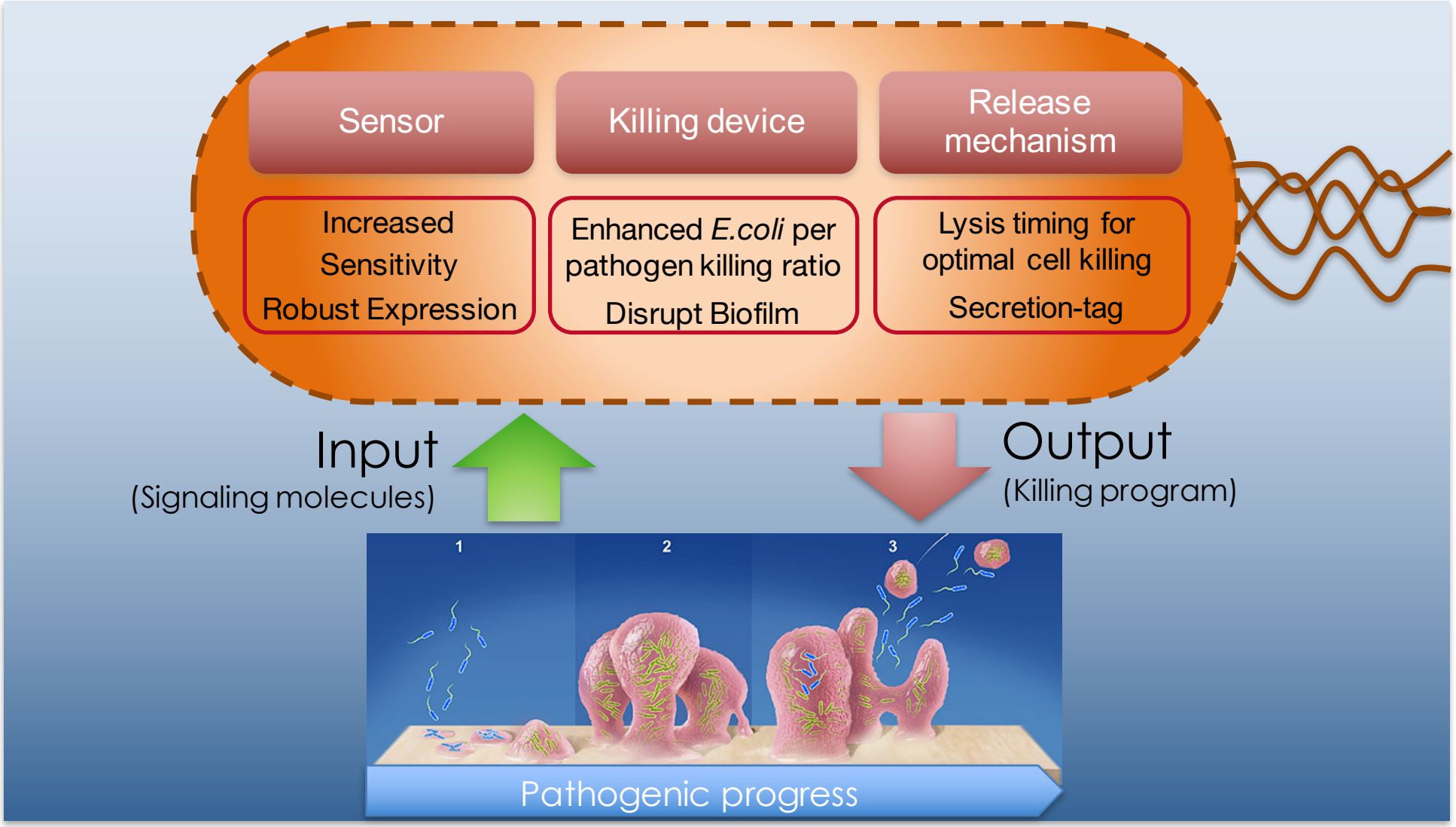
- Targeted killing, minimizing negative effects on the microbiome
- Preventive effects

Biofilm inhibition: **90%**

- Molecular Systems Biology (2011), Featured in Reuters, Nature, Science, etc.

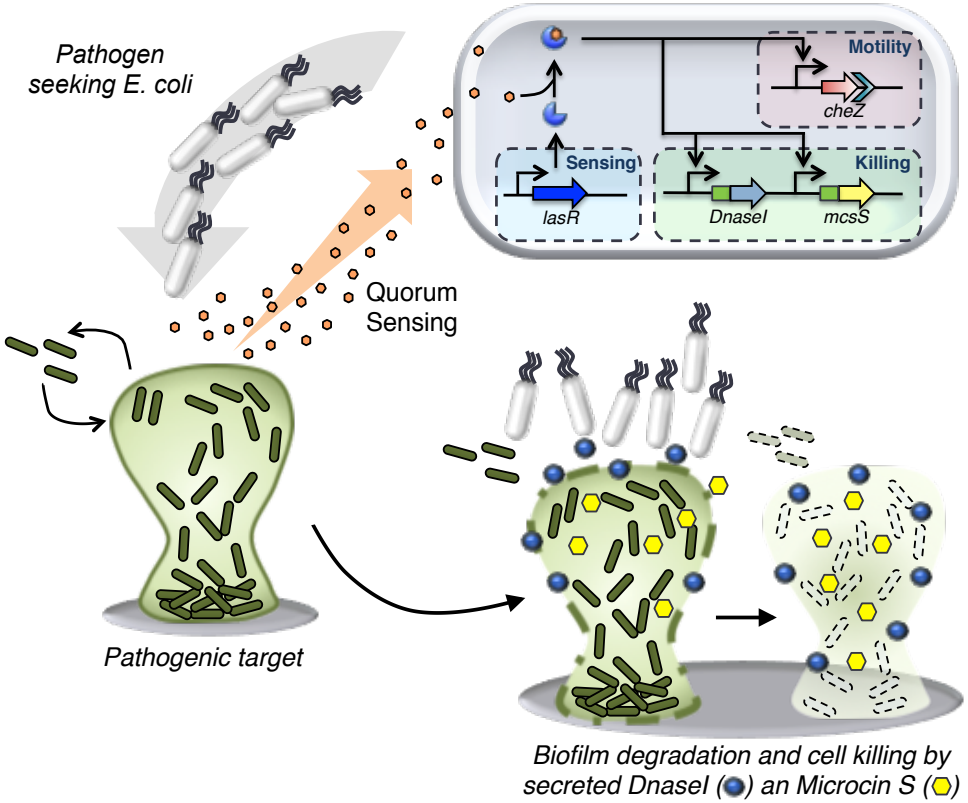
System optimization

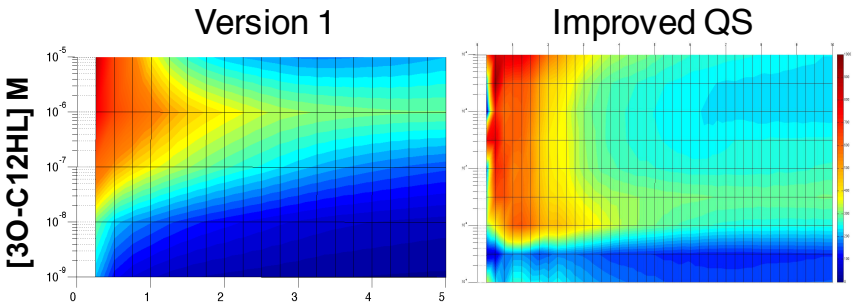
Advancing the system towards more effective killing

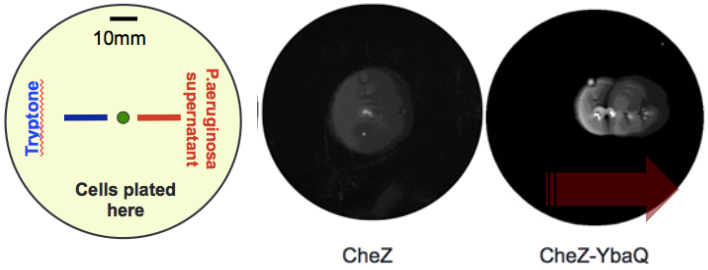


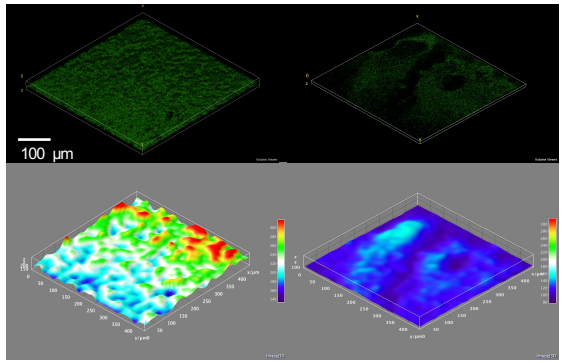
PATHOGEN-KILLING MICROBES

PROTOTYPES - STILL EVOLVING







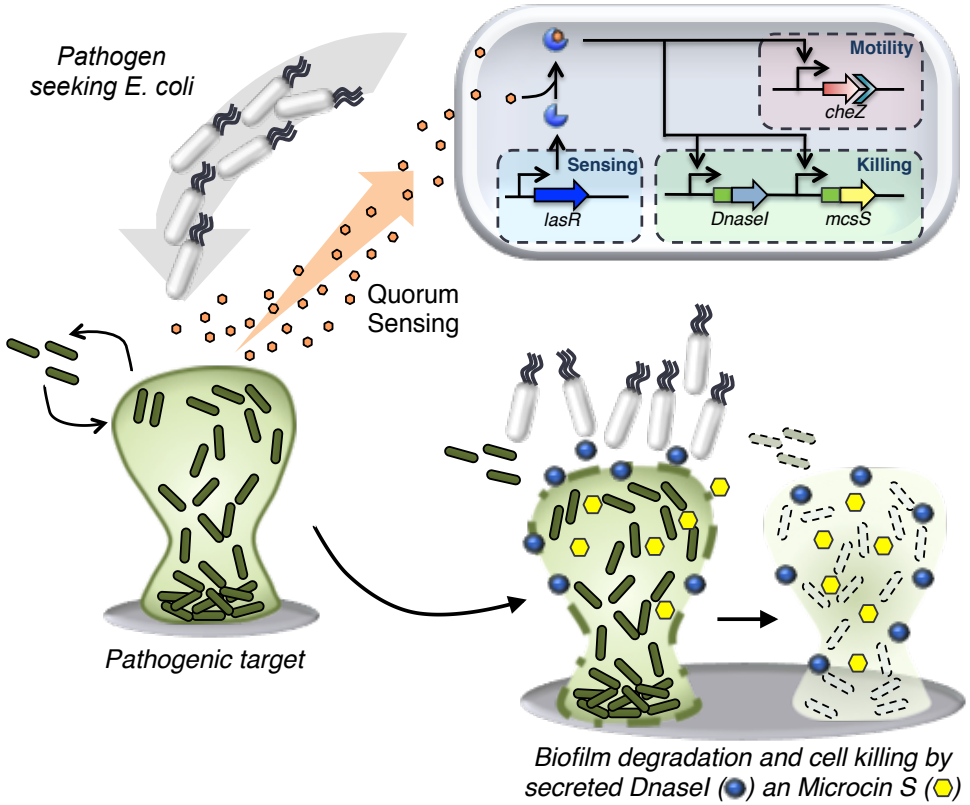


1. Sensitivity and robust expression
2. Target localization (motility)
3. Improved killing efficiency

- ACS Synthetic Biology (2014), Featured in The Economist, Nature News, etc.

Advanced therapeutic functionalities

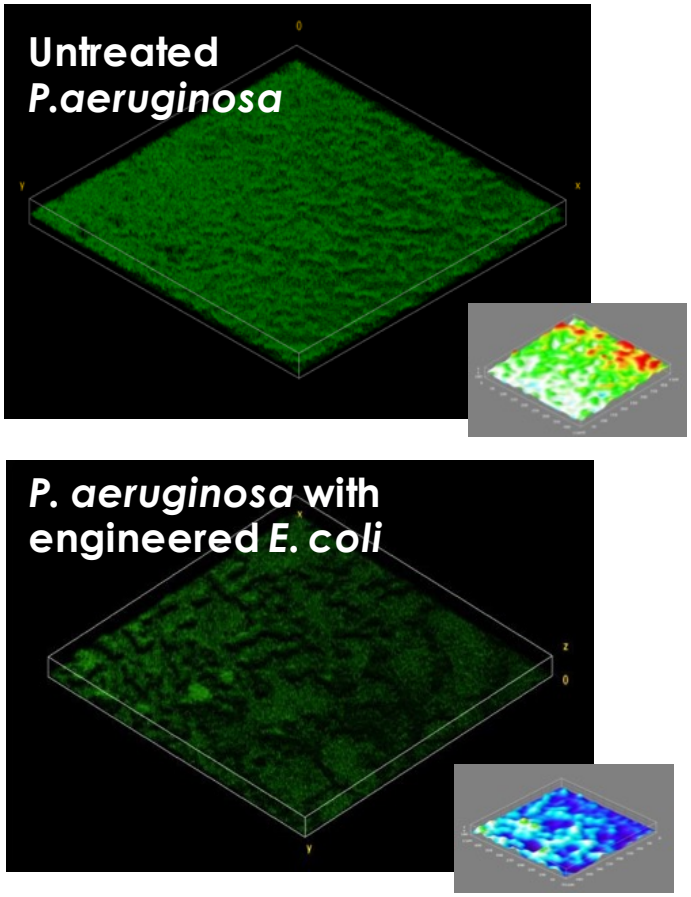
Programmed motility towards a target pathogen

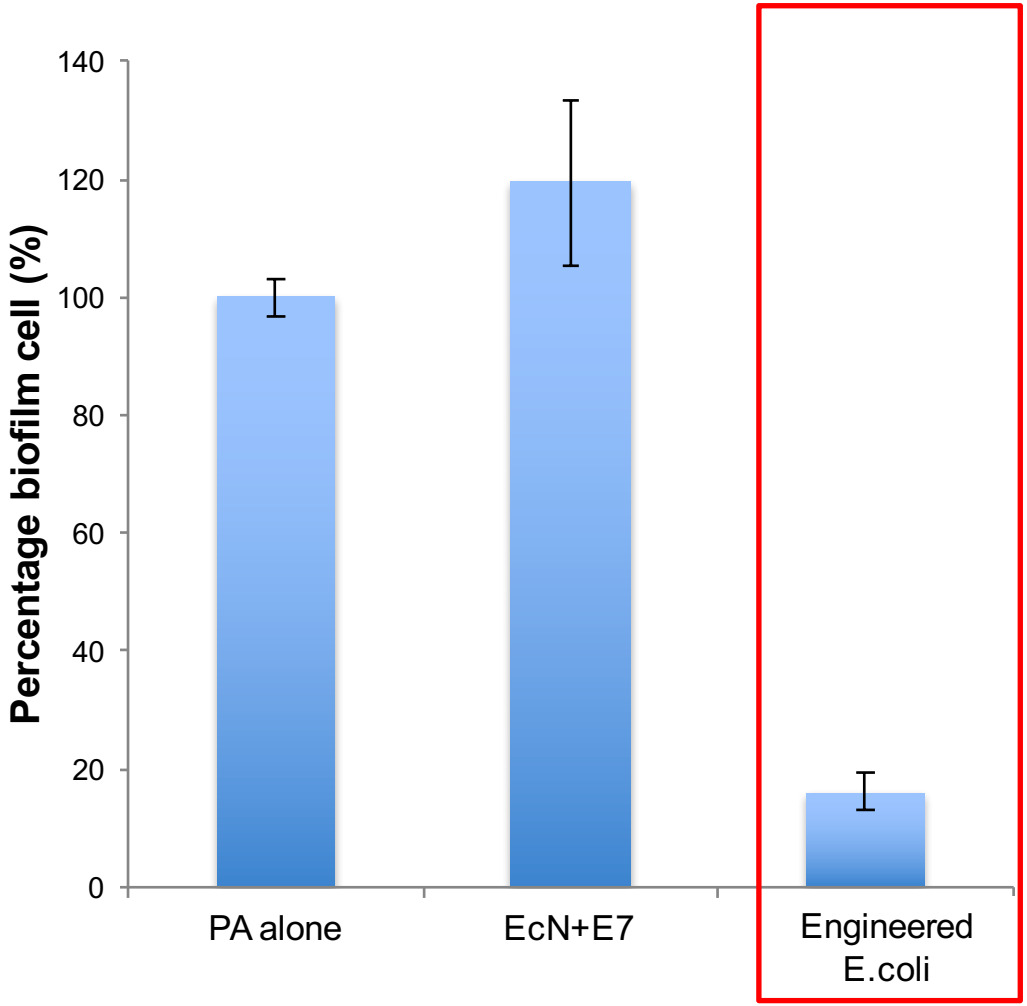


ACS Synthetic Biology (2014), Featured in The Economist, Nature News, etc.

PREVENTION OF INFECTION STRATEGIES

Enzymatic dispersal of mature biofilm

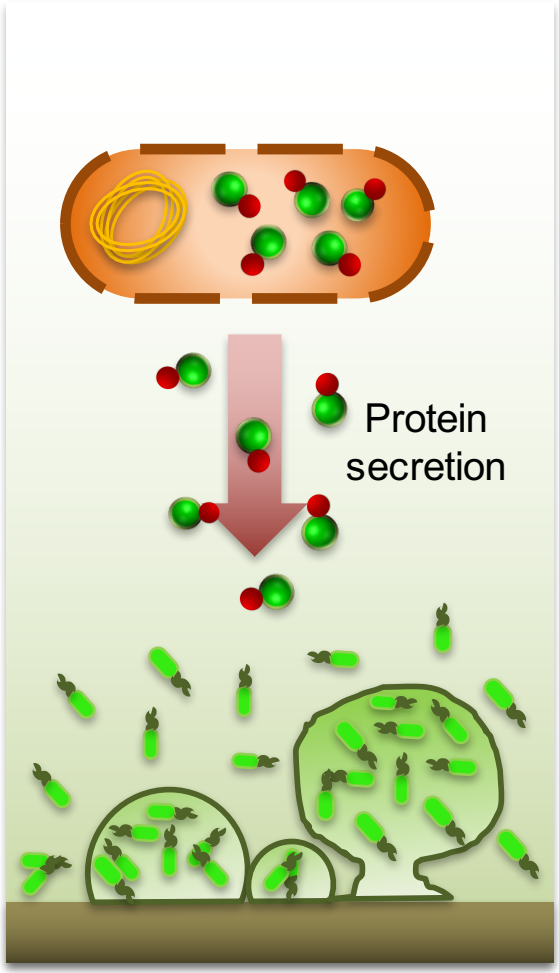


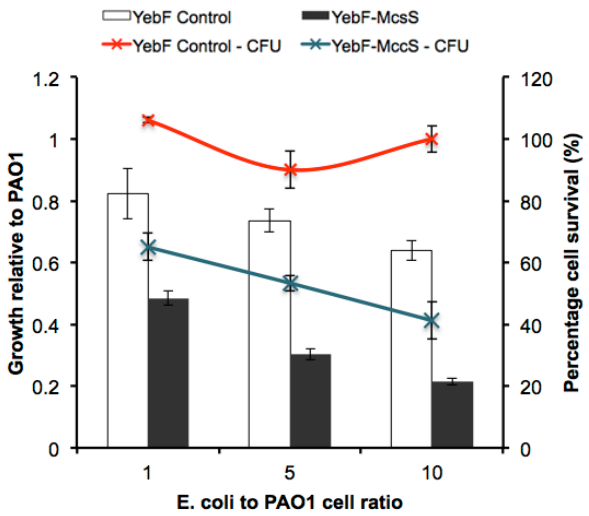


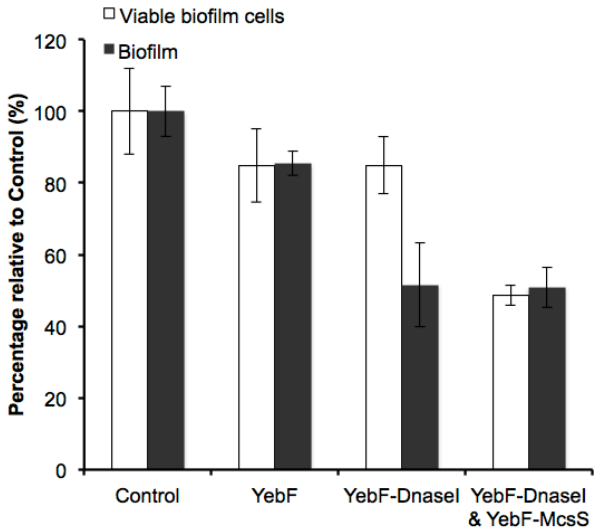
ACS Syn Biol (2014)

DELIVERY STRATEGIES

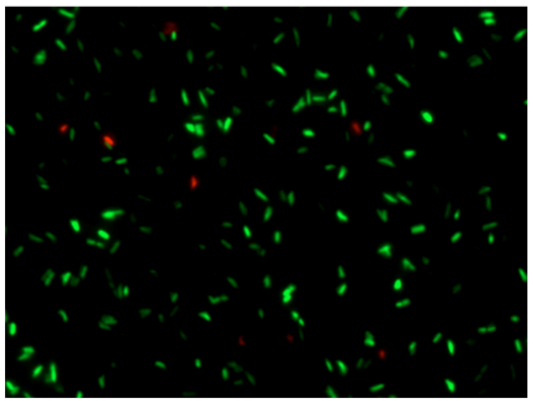
Targeted killing by protein secretion



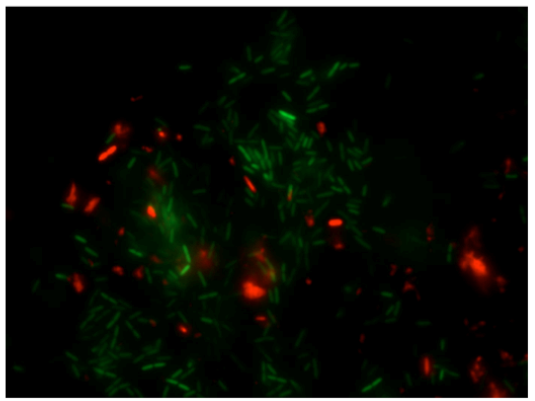




PAO1 treated with E.coli supernatant



PAO1 treated with YebF-MccS supernatant

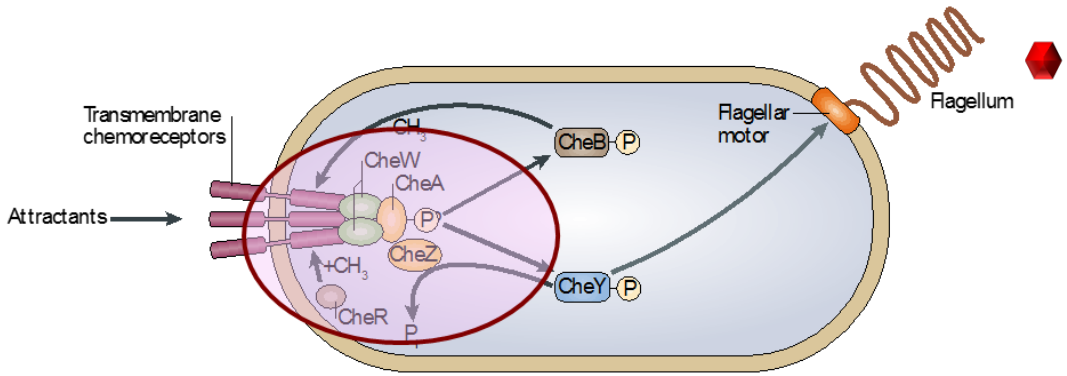


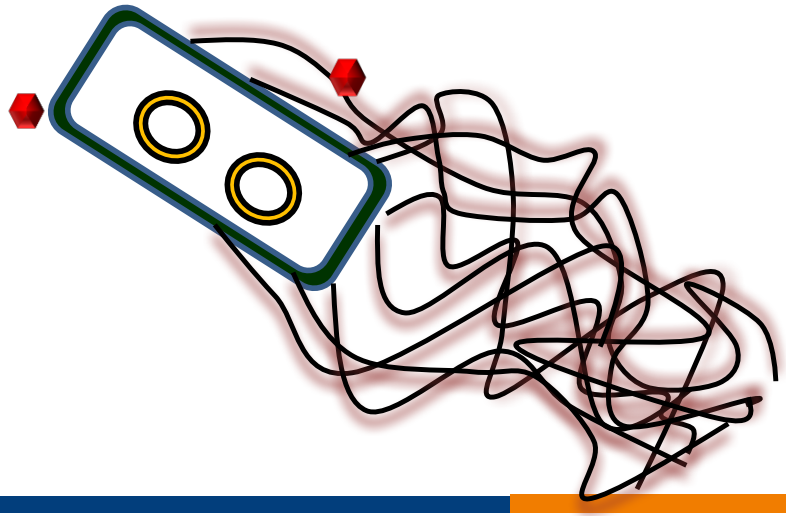
ACS Syn Biol (2014)

CELLULAR DRUG DELIVERY STRATEGIES

Motility via chemotaxis pathway

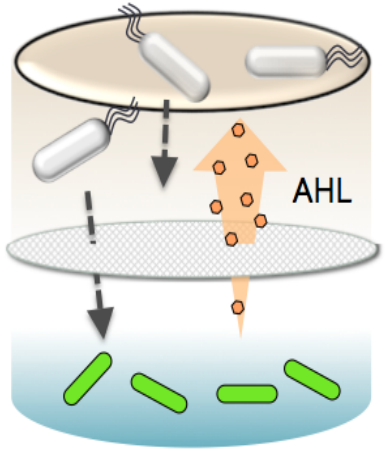
Pseudomonas aeruginosa



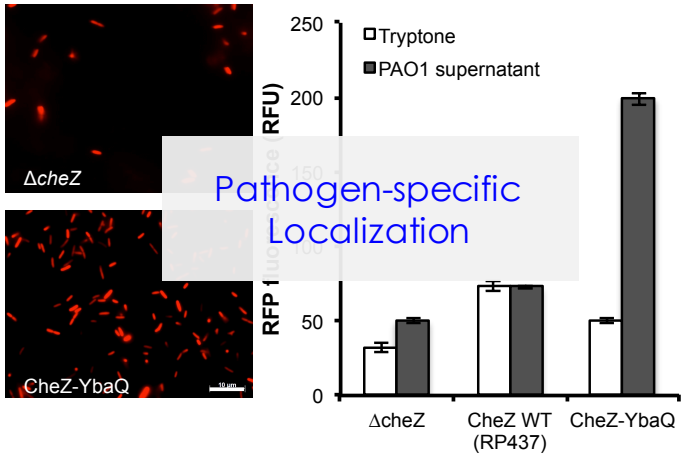


FULLY FUNCTIONAL MODEL

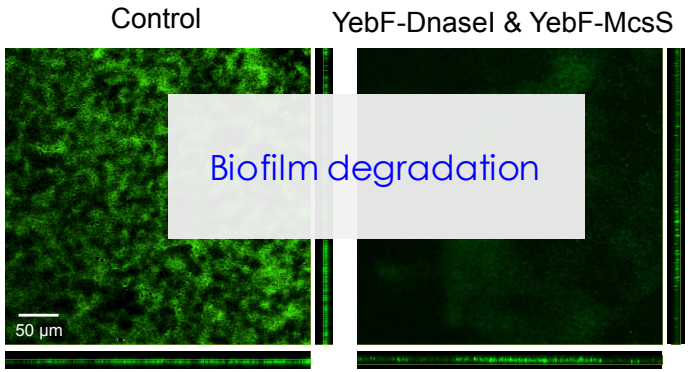
PROGRAMMED MOTILITY-DRIVEN KILLING



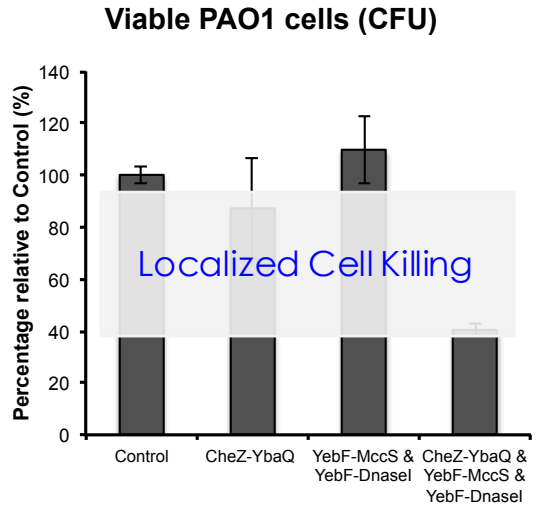
Reprogramed E. coli
(+ killer enzymes)
swims towards target
cells



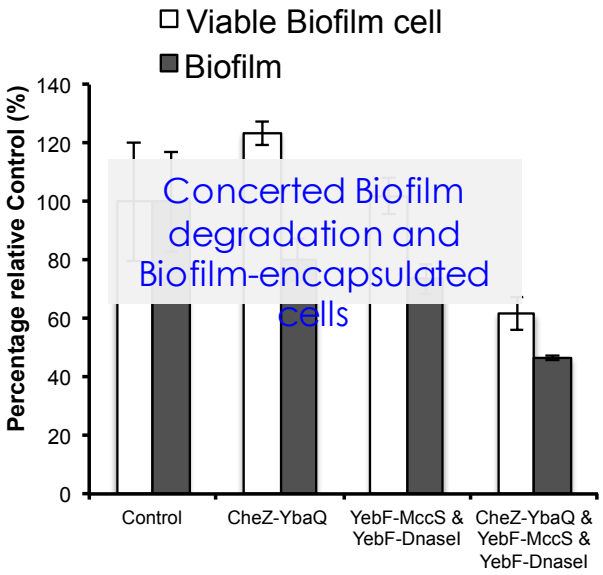
Pathogen-specific Localization



Biofilm degradation



Localized Cell Killing



Concerted Biofilm degradation and Biofilm-encapsulated cells

ACS Syn Biol (2014)

TEST MODELS

Killing effects in eukaryotic models (*Mus musculus)*

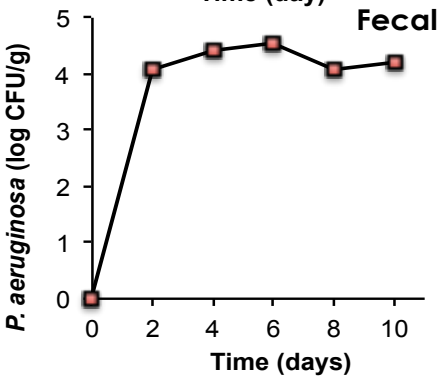
P.aeruginosa infection

Treatment

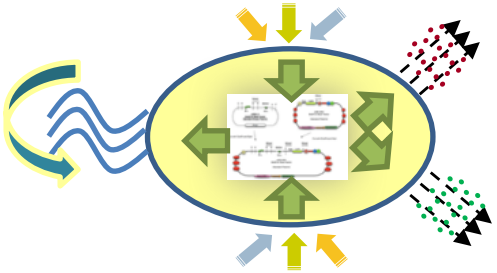
Antibiotic treatment

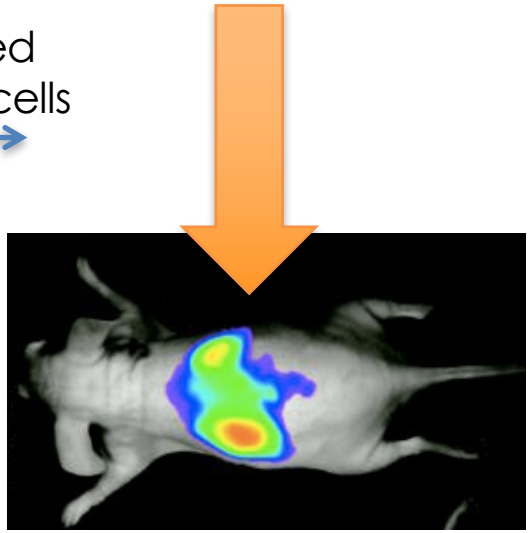
infection

gut colonization



Programmed therapeutic cells





ALL-IN-A-PAGE

What we have learned so far and what will come