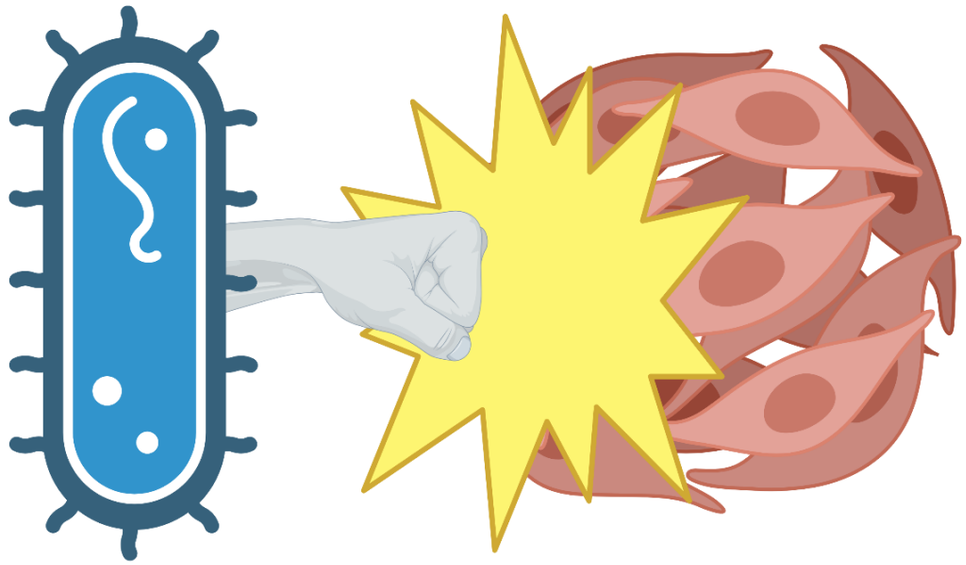
Bacterial Anticancer Therapy



Sean Huth

MacMillan Group

Lit. Talk

November 29th, 2022

Outline

- Introduction/History
  - St. Peregrine
  - Coley's Toxins
- How and why?
  - How does bacterial therapy work
  - Why would we use bacteria as therapy?
- Current/future therapeutic opportunities
  - Current FDA approved therapy
  - Current clinical trials/outlook

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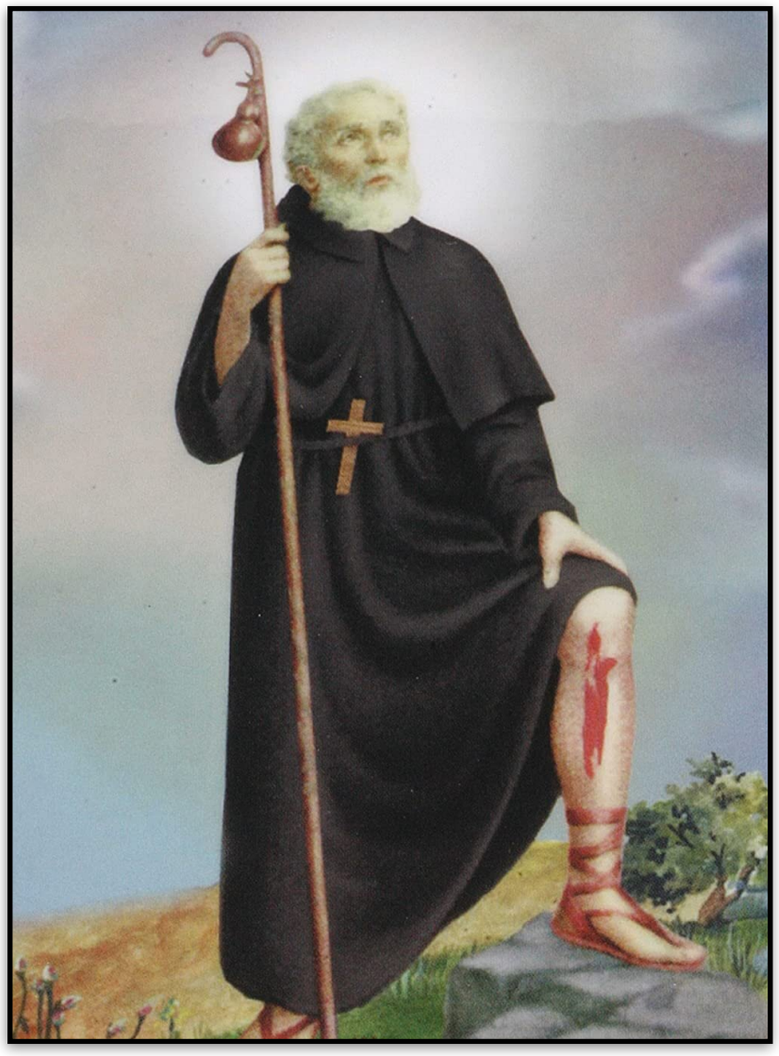
Introduction

St. Peregrine's Tumor



St. Peregrine

- Born 1265 in Italy. Initially rebellious against religion.
- Later became a priest and founded a monastery.
- At the age of 60, developed malignant tumor in his foot

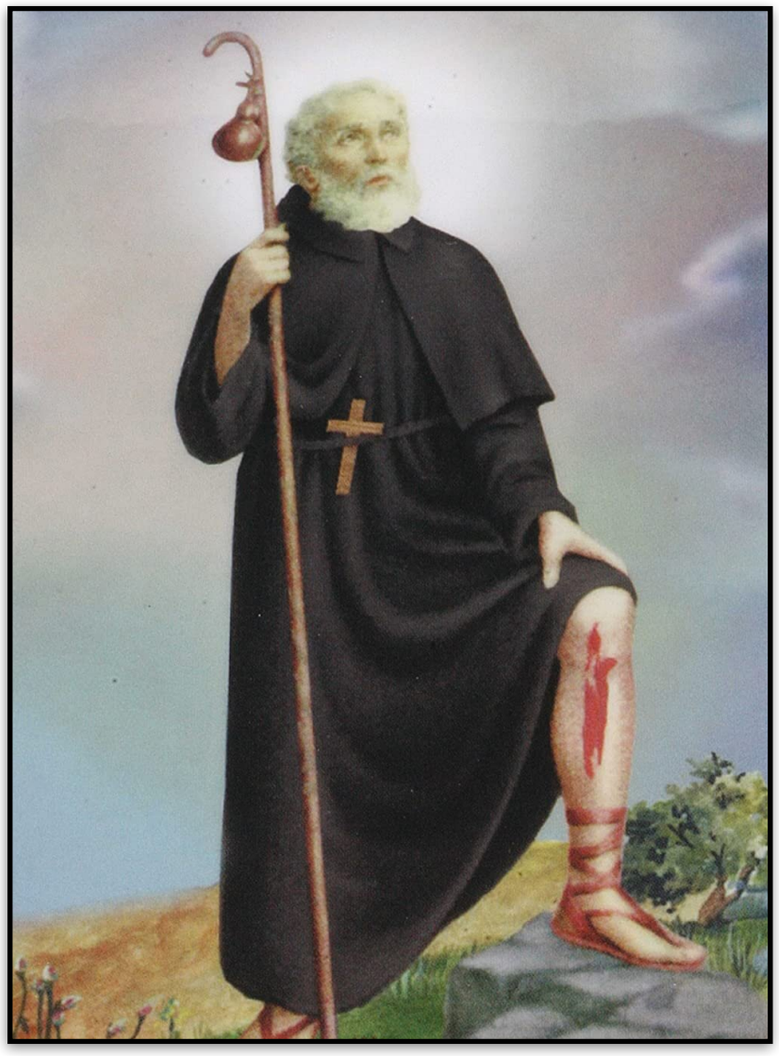
Tumor grew until it burst out of his foot as a lesion and became badly infected.

amputation recommended

Grange, John M.; Koelmel, Klaus F; Krone, Bernd. *BMC Cancer*. **2014.** 14, 595.

Introduction

St. Peregrine's Tumor



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Day of the surgery: The tumor appeared to be recovering

St. Peregrine lived to be 80 years old

Divine Intervention?

Grange, John M.; Koelmel, Klaus F; Krone, Bernd. *BMC Cancer*. **2014.** 14, 595.

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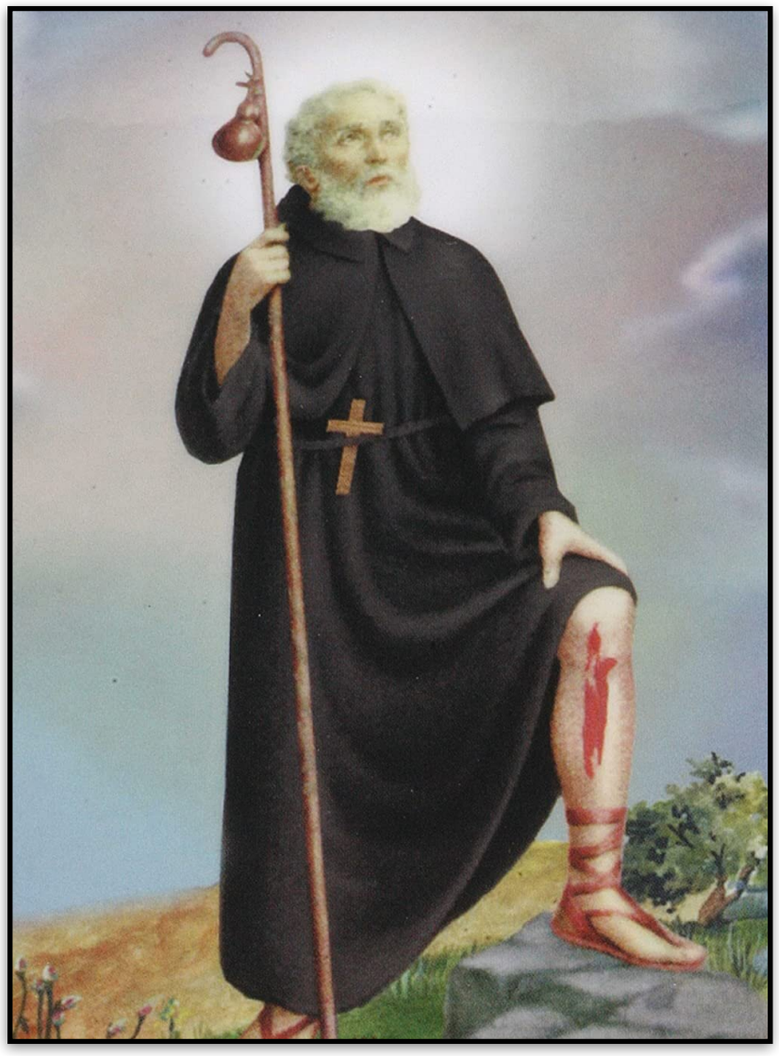
St. Peregrine's Tumor



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"Spontaneous Regression"

likely the infection that had a curative effect

Grange, John M.; Koelmel, Klaus F; Krone, Bernd. *BMC Cancer*. **2014.** 14, 595.

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Introduction

Dr. William Coley

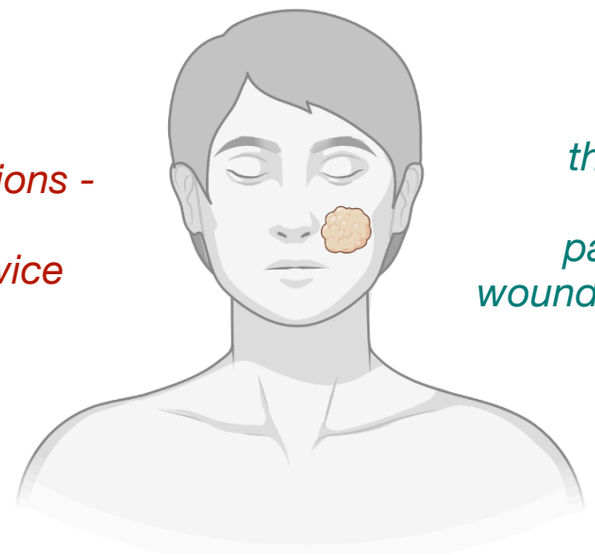
Dr. William Coley

- Worked at New York Memorial Hospital late 1800s
- Loss of first patient in 1891 severely affected him
- Prompted search for alternatives to traditional treatment

Case: patient with sarcoma on left cheek

repeated excisions -

recurrence twice



third attempt -

partial excision
wound left partially open

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Introduction

Dr. William Coley

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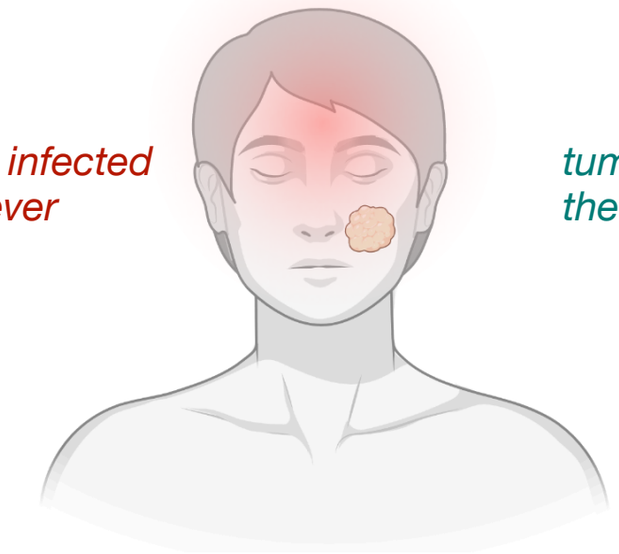
- Loss of first patient in 1891 severely affected him
- Prompted search for alternatives to traditional treatment

Case: patient with sarcoma on left cheek

wound gets infected
high fever



tumor clears over
the next 4 months

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Introduction

Dr. William Coley

Dr. William Coley

- Worked at New York Memorial Hospital late 1800s
- Loss of first patient in 1891 severely affected him
- Prompted search for alternatives to traditional treatment

patient still alive 7 years later

infected by:

Streptococcus pyogenes

Did the infection have a curative effect?

inspired, Coley infected next 10 patients

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Introduction

Dr. William Coley

Dr. William Coley

Difficulties quickly arose:

Inconsistent infection success rate

Dangerous/lethal infections

led to development of **Coley's toxin**

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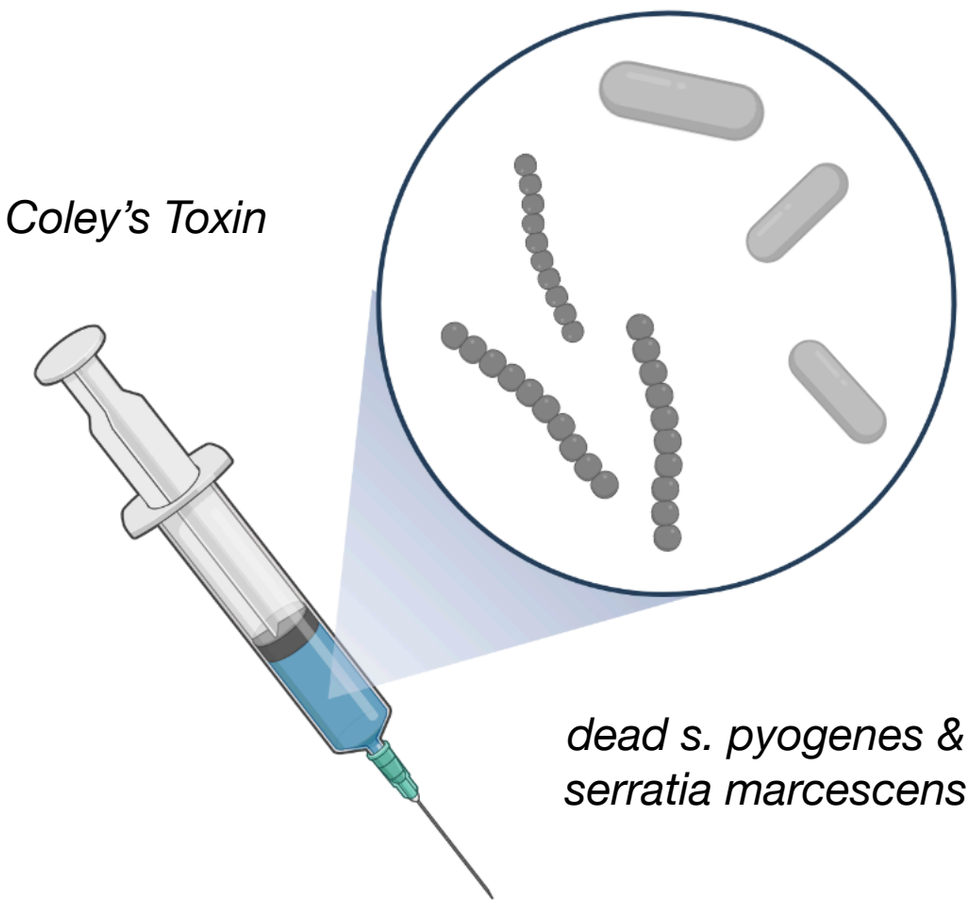
Introduction

Dr. William Coley

Coley's Toxin



dead s. pyogenes &
serratia marcescens

Difficulties quickly arose:

Inconsistent infection success rate

Dangerous/lethal infections

led to development of **Coley's toxin**

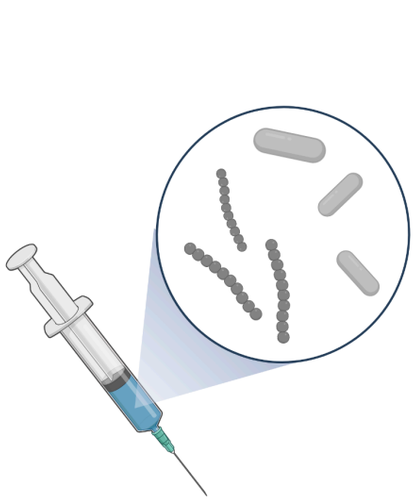
Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Introduction

Coley's Toxins throughout the years

1893

Coley's toxins developed



1903

improvement via filtration

1923

Parke-Davis sells commercially

1963

Kefauver Harris Amendment

"drug-efficacy amendment"

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Introduction

Coley's Toxins throughout the years

1963

Kefauver Harris Amendment

passed in wake of thalidomide tragedy

previous drugs are reclassified

Coley's Toxin assigned "new drug" status

unusable outside clinical trials

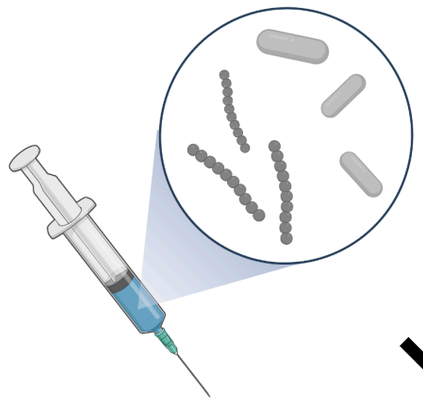
"drug-efficacy amendment"

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

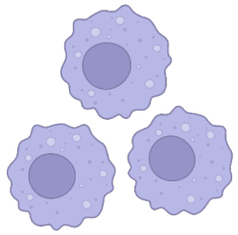
Mechanisms of Action

Local effects of bacteria

LPS



M0 Macrophages

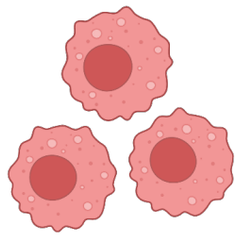


innate immune response present at all times

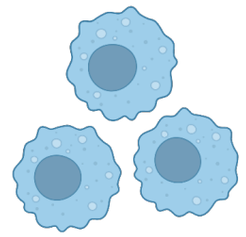
IFNγ, TNF-α, GM-CSF, LPS

IL-4, IL-10, IL-13, IL-33, PGE2, TGF-β

"attack"



M1 Macrophages



M2 Macrophages

"repair"

boost in M1 macrophages aids in anti-tumor response

Van Netten, C.; Van Netten, J.P.; Hoption Cann, S.A. *Postgrad Med J* **2003**, 79, 672-680.

Mechanisms of Action

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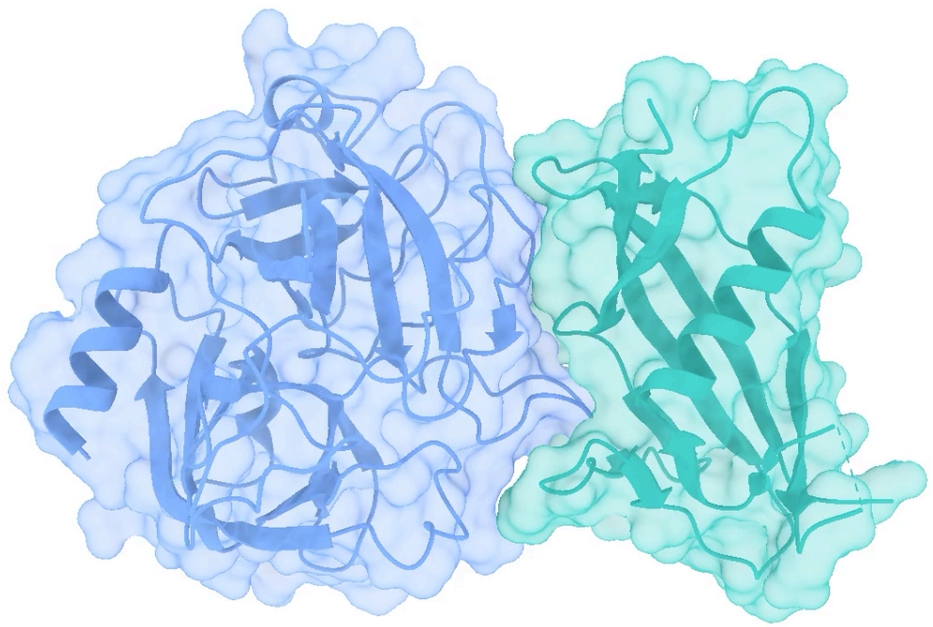

Streptokinase

- bacterial enzyme from streptococcus
- forms dimer with human plasminogen
- degrades fibrin and other plasma proteins

natively: helps bacteria avoid blot clots to aid infection

Microplasminogen Streptokinase

thrombolytic medication

in tumor conditions: may aid immune infiltration

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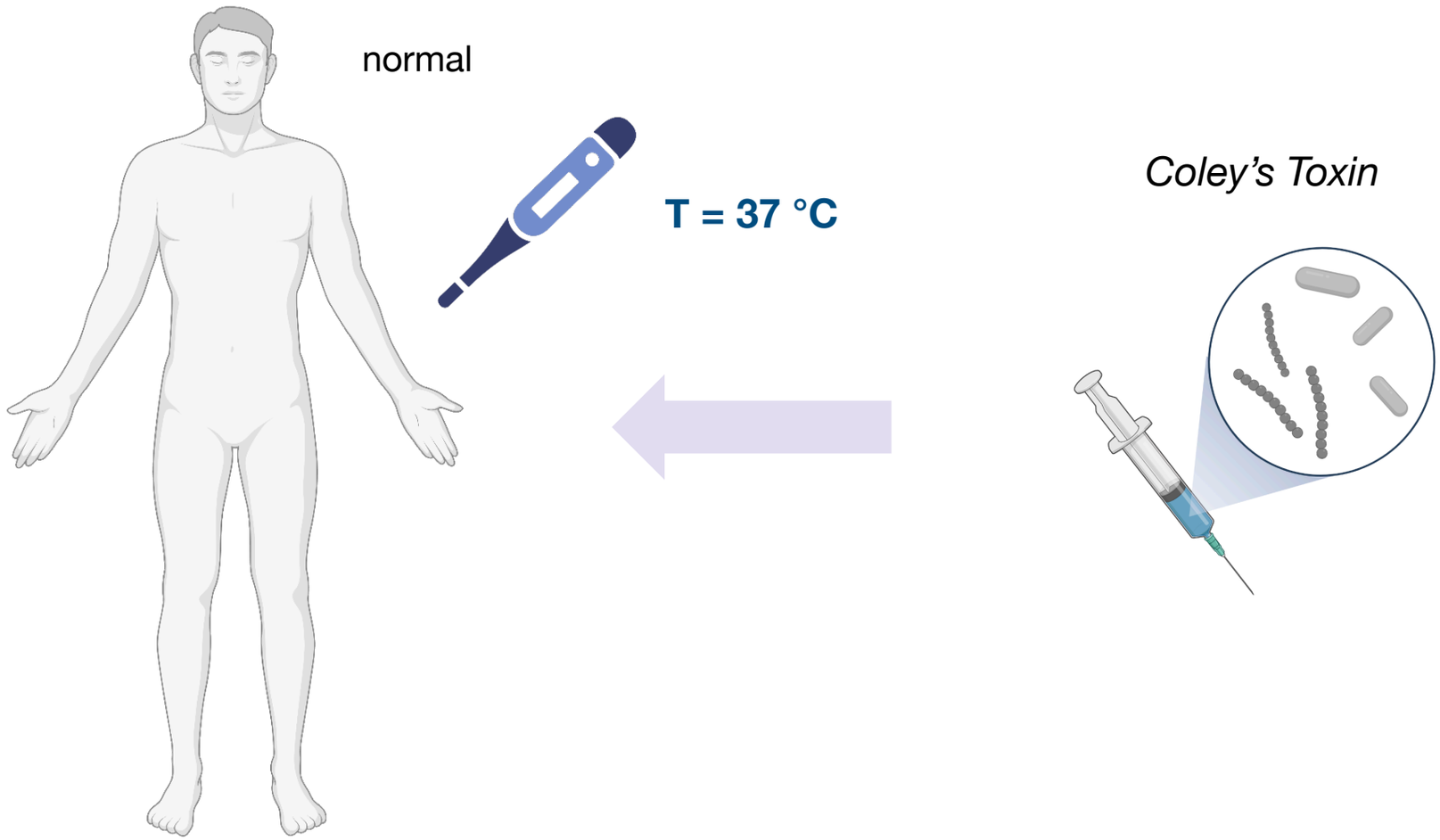
Mechanisms of Action

Coley's Toxin - systemic effects



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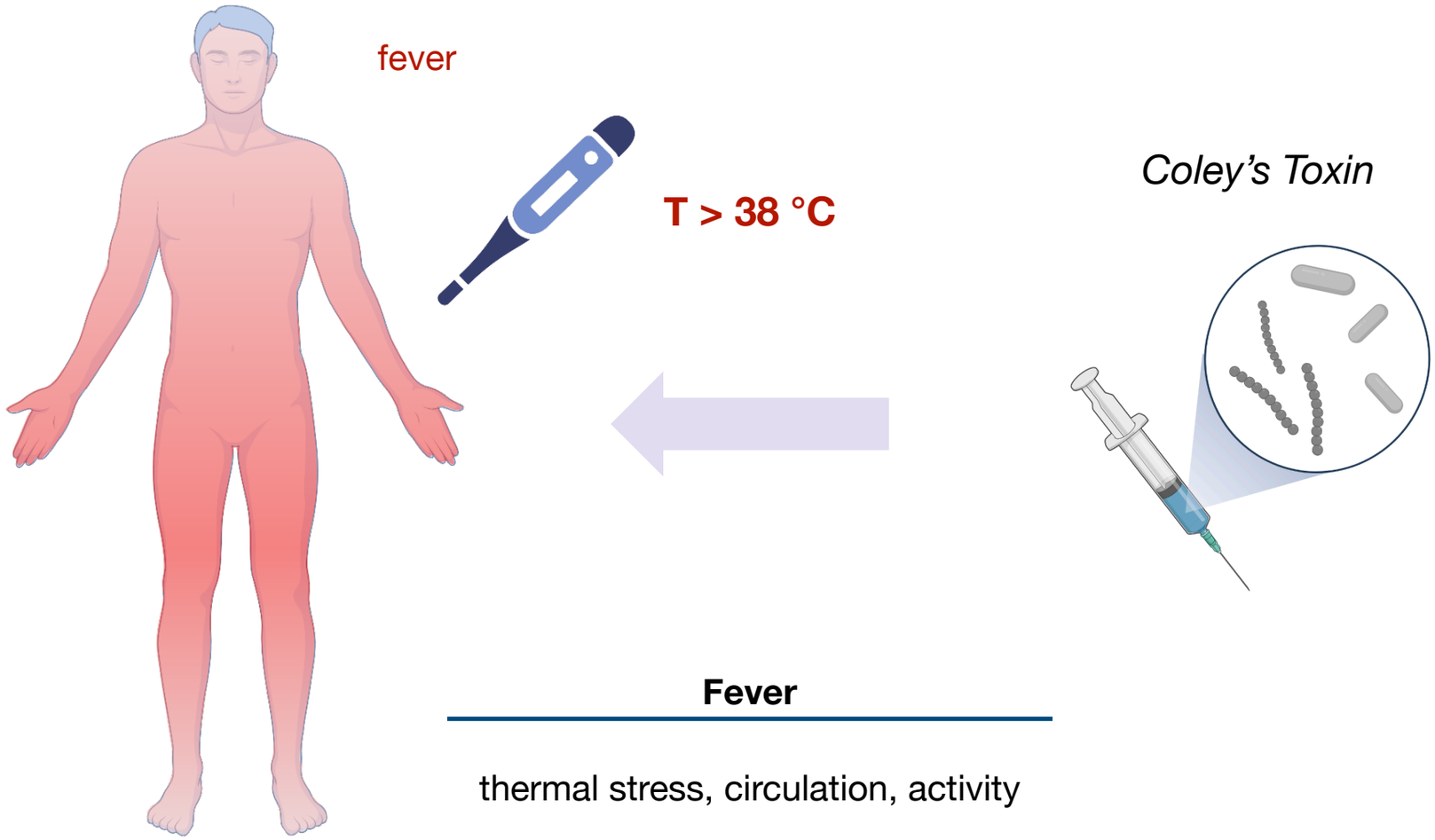


Fever

thermal stress, circulation, activity

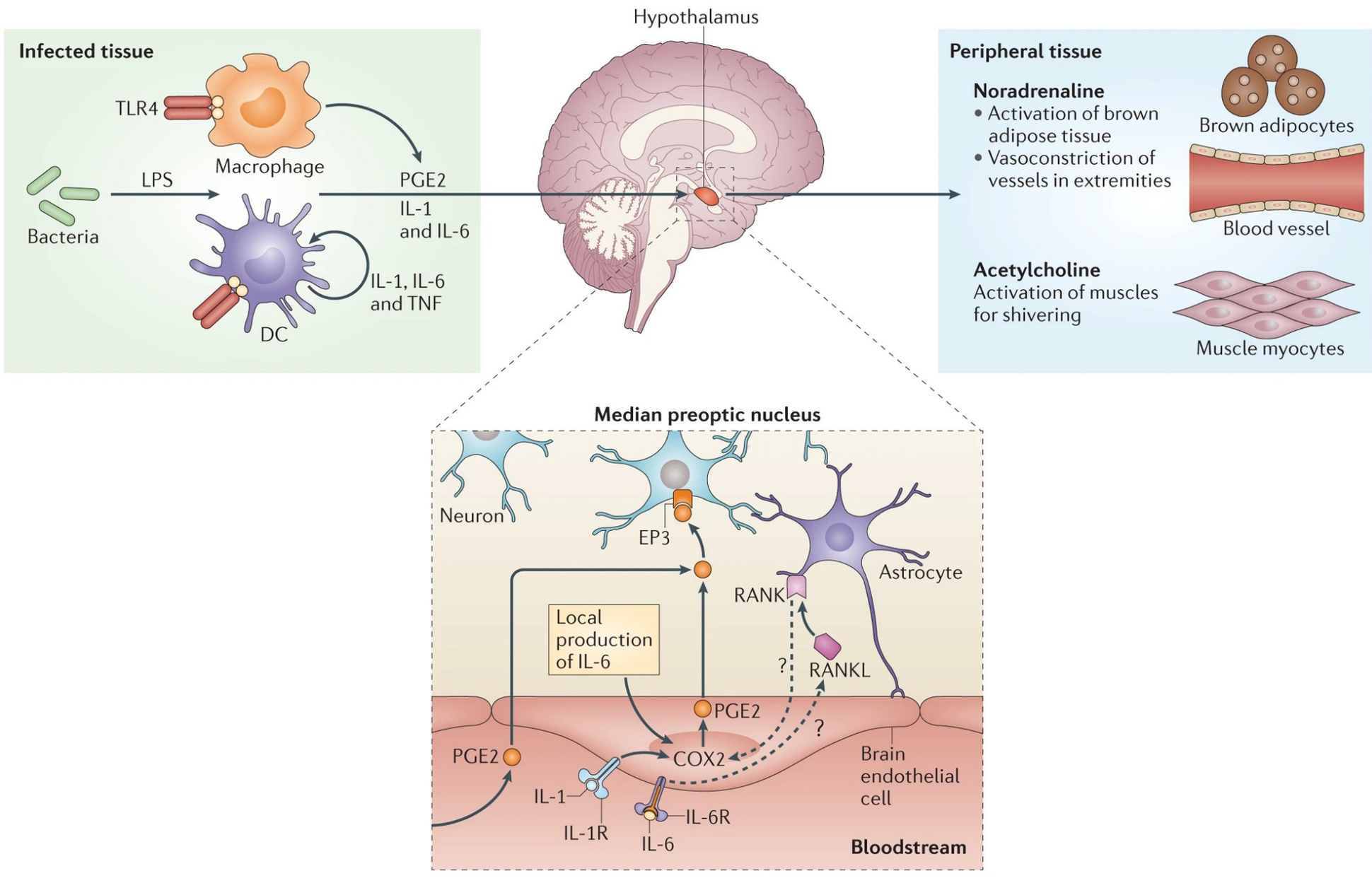
immune stimulation, trafficking, expression

Fisher, Daniel T.; Repasky, Elizabeth A.; Evans, Sharon S. Nature Reviews Immunology **2015**, 15, 335–349.

Mechanisms of Action

Coley's Toxin - systemic effects

Fever response in hypothalamus



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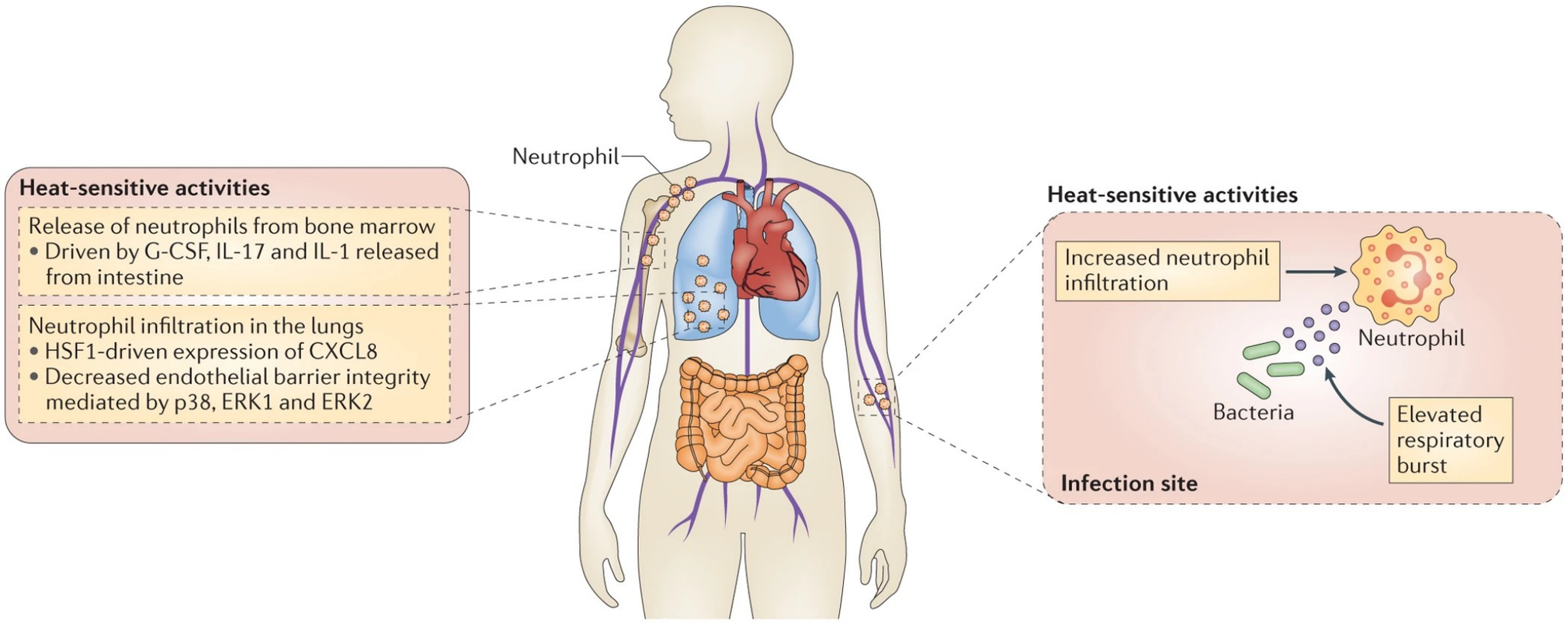

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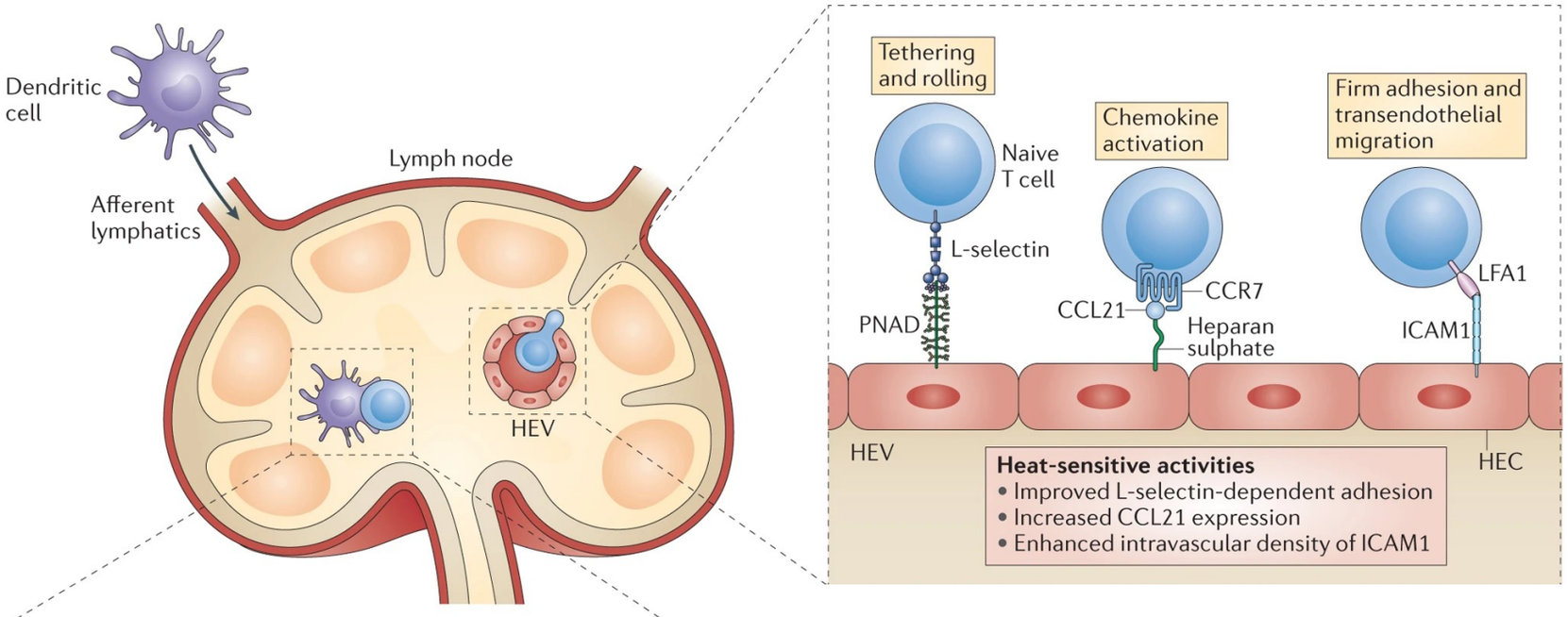

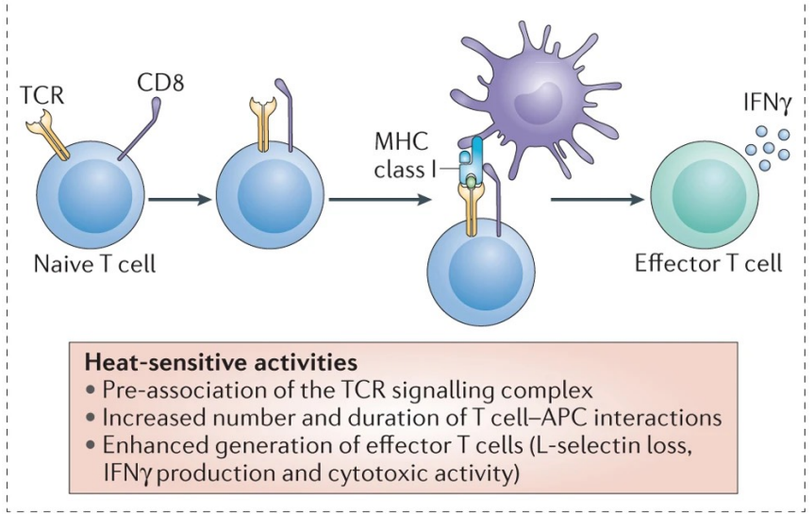

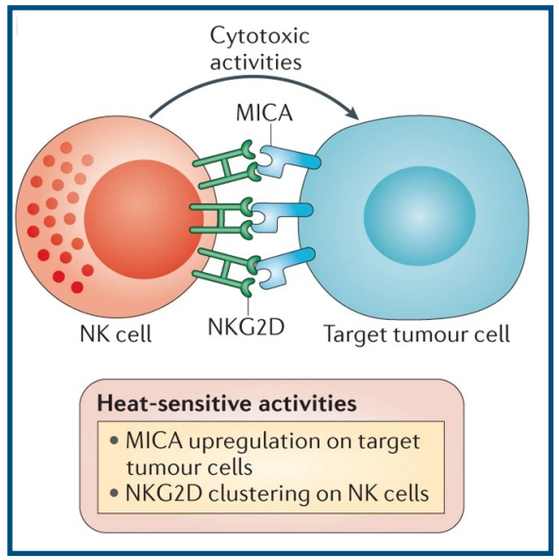

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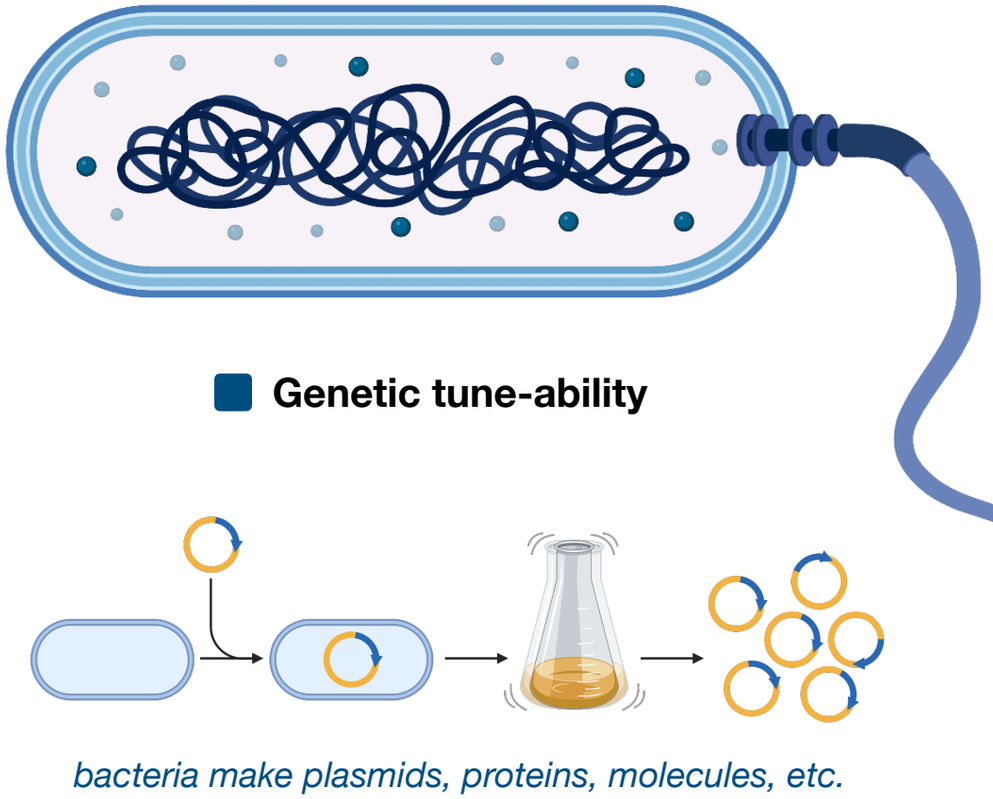
Bacteria as Therapy

Why would we use bacteria therapeutically?



Genetic tune-ability

bacteria make plasmids, proteins, molecules, etc.

Bacteria as Therapy

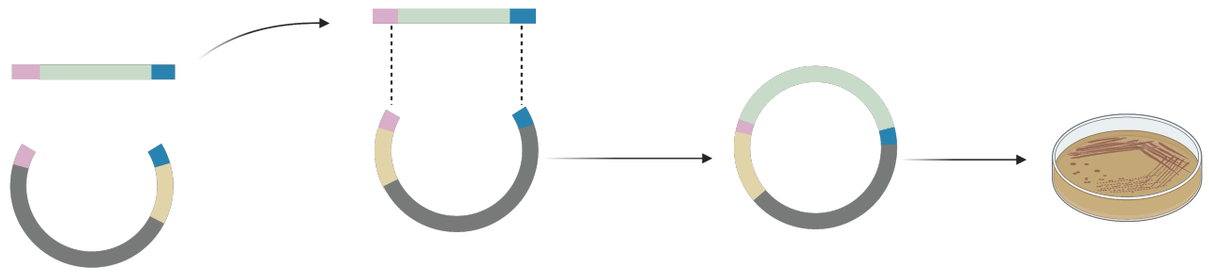
Bacteria that manufacture proinsulin

Walter Gilbert

- Harvard - initially physics, transitioned into biochemistry
- Pioneer in genomic sequencing - 1980 Nobel Prize in Chemistry
- Set out to engineer bacteria to manufacture proinsulin

genetic recombination

piecing together existing DNA fragments in new ways



e.g. restriction cloning

Gilbert, Walter et al. *Proc. Nati. Acad. Sci.* **1978**, 75, 8, 3727-3731.

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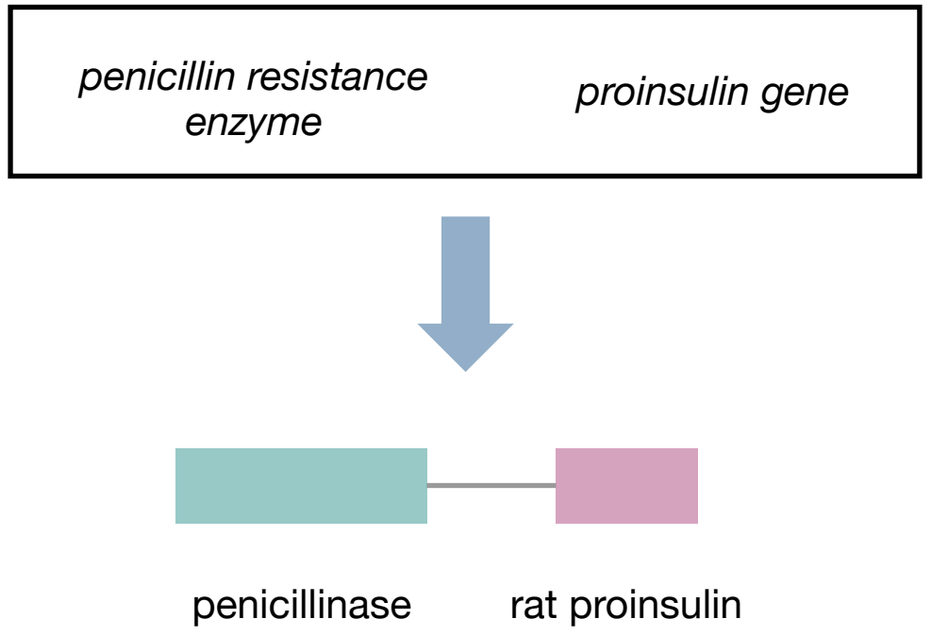

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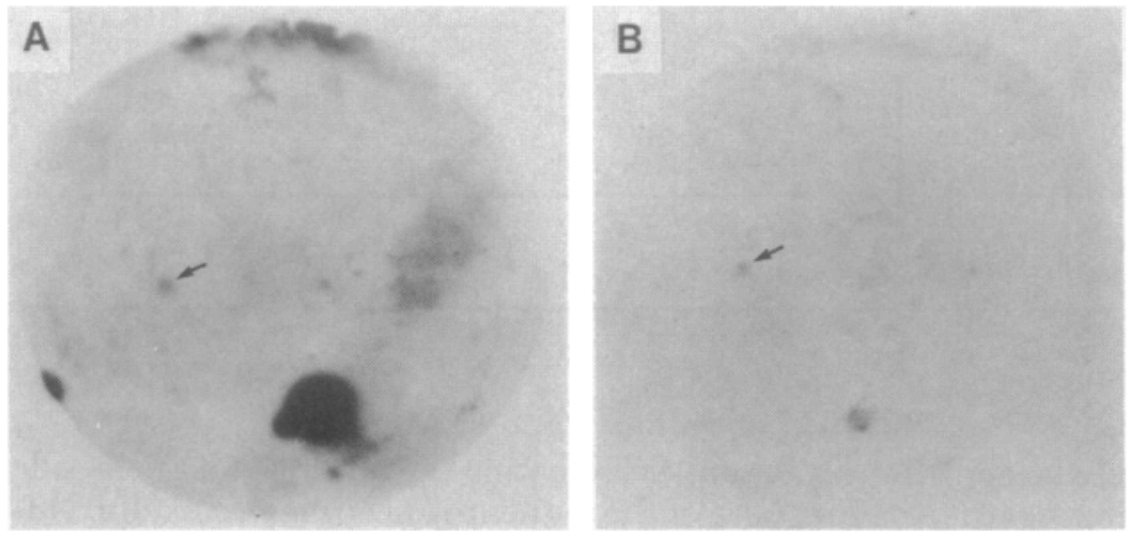


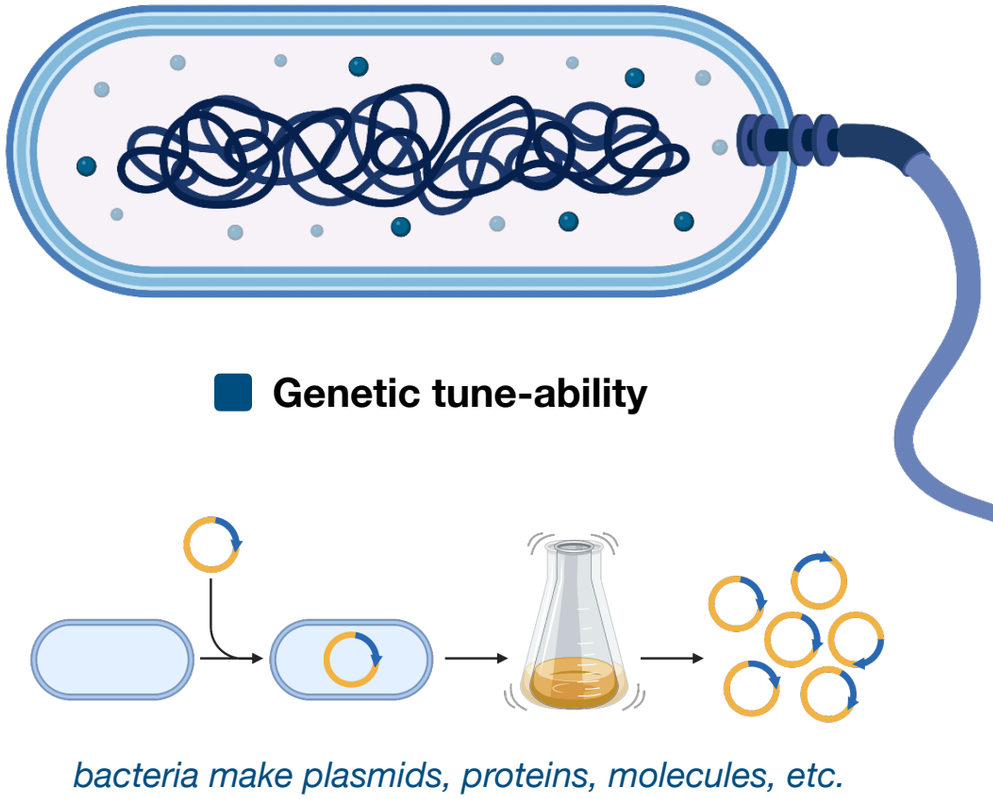
Insulin staining on culture plate, arrow indicates clone

Gilbert was narrowly beaten to this feat by Genentech who built the gene artificially

Gilbert, Walter et al. *Proc. Nati. Acad. Sci.* **1978**, 75, 8, 3727-3731.

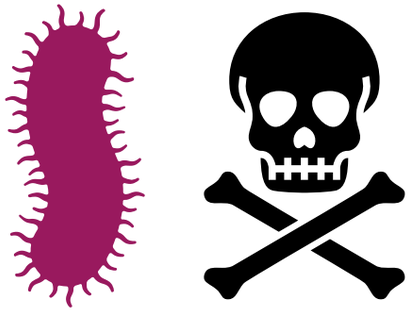
Bacteria as Therapy

Why would we use bacteria therapeutically?



Genetic tune-ability

bacteria make plasmids, proteins, molecules, etc.



we can genetically ablate toxicity

Bacteria as Therapy

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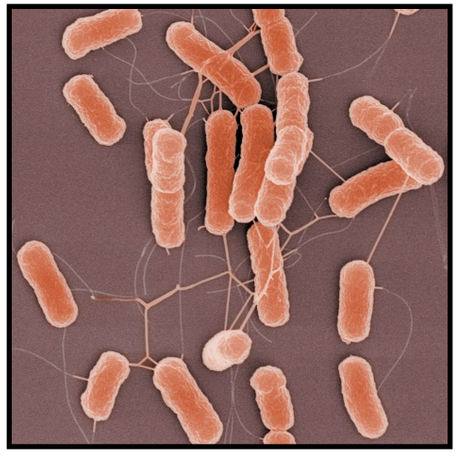

E. coli Nissle Strain (_Ec_N)

- nonpathogenic bacterial strain - discovered 1917
- used for probiotic delivery of therapeutics

probiotic Mutaflor® consists of EcN

- no toxin production
- no pathogenic adhesion factors
- no antibiotic resistance genes
- no sepsis risk

Rodrigues, J.; Rodrigues, L. *Trends in Biotechnology*. **2018**, 36, 2.

Bacteria as Therapy

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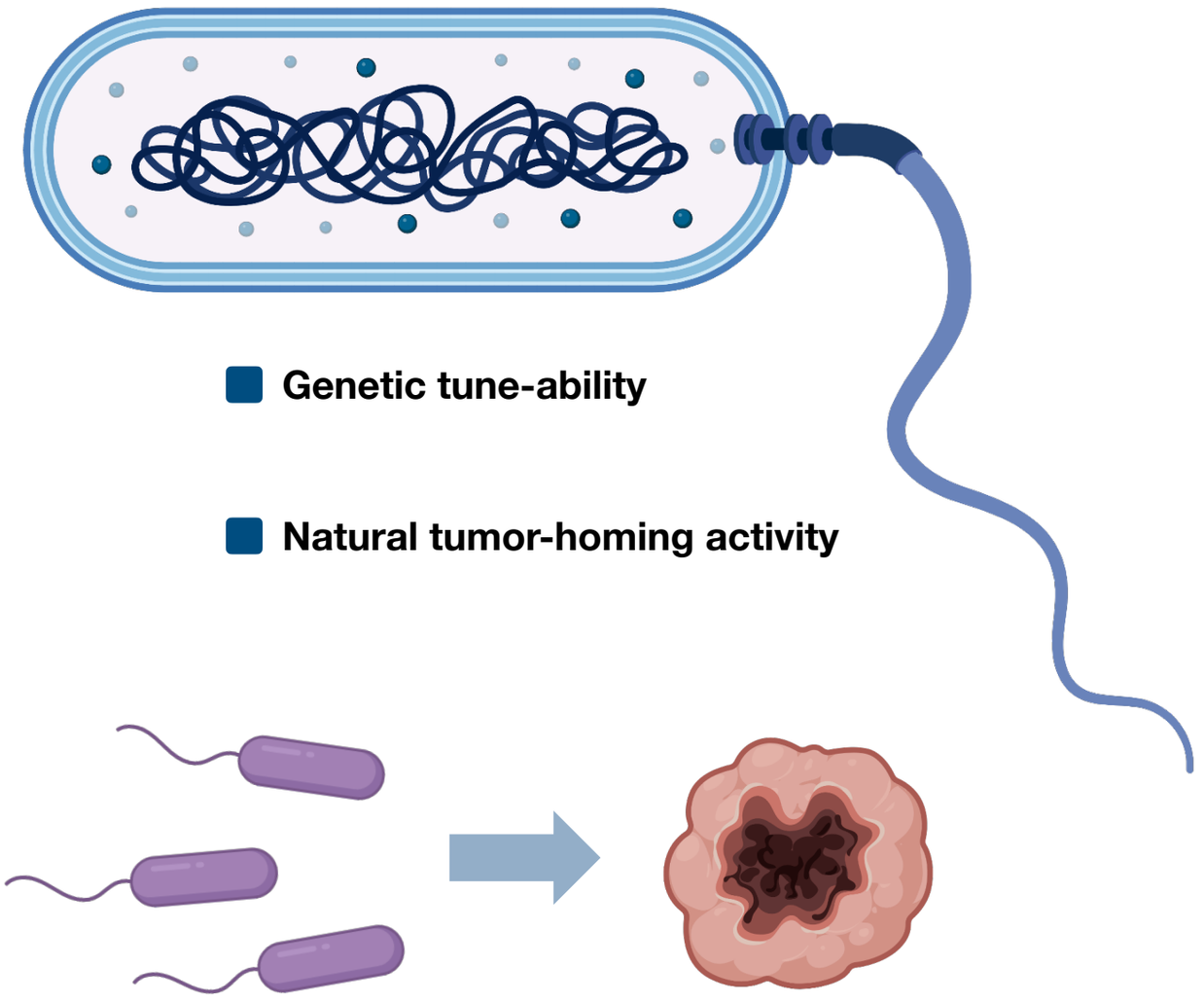
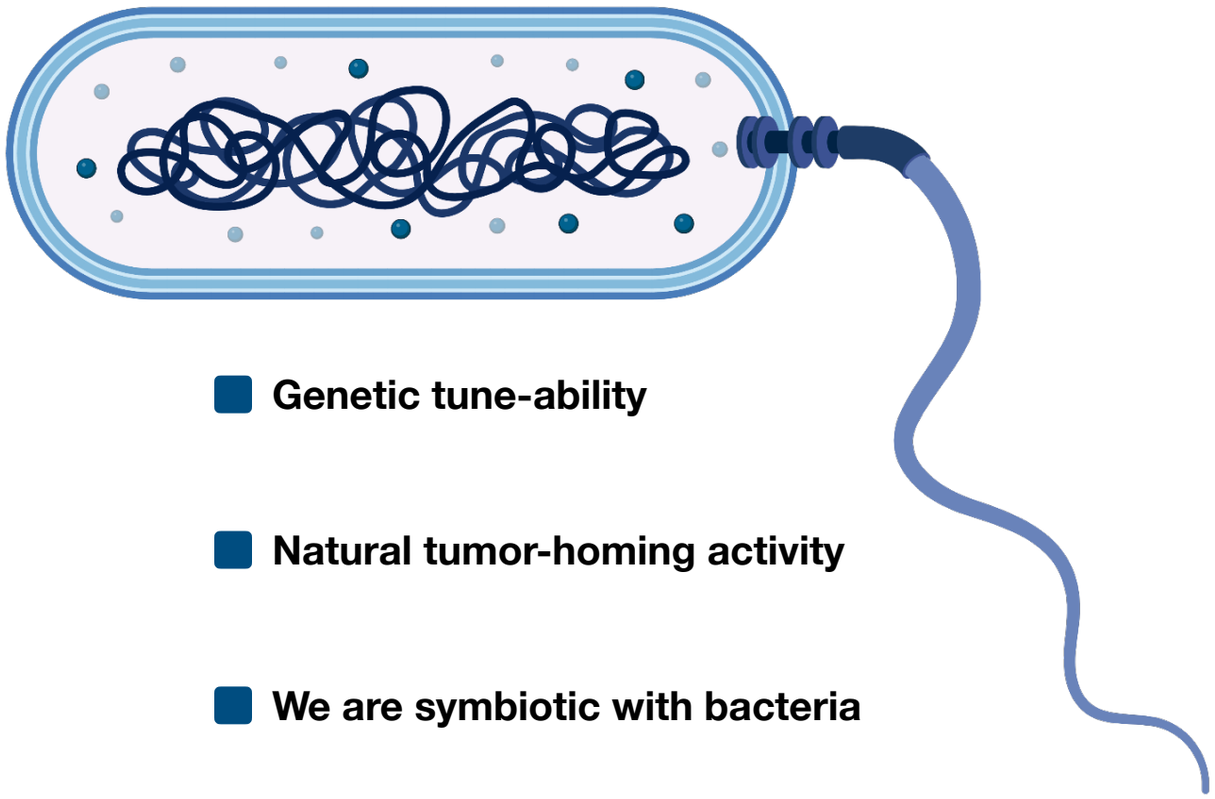


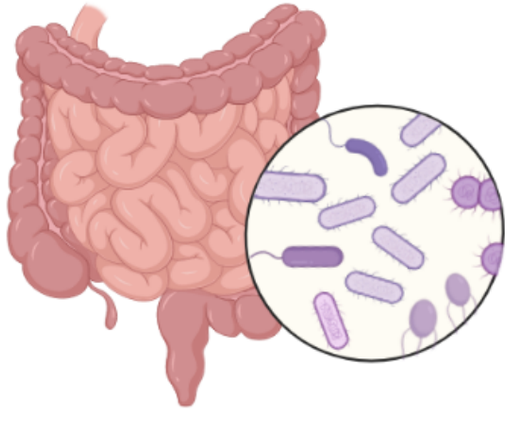
bacteria will naturally migrate to necrotic tumors

Bacteria as Therapy

Why would we use bacteria therapeutically?



- **Genetic tune-ability**
- **Natural tumor-homing activity**
- **We are symbiotic with bacteria**



est. ratio of human to bacterial cells is 1:1

Sender, Ron; Fuchs, Shai; Milo, Ron. *PLoS Biol.* **2016**, 14, 8.

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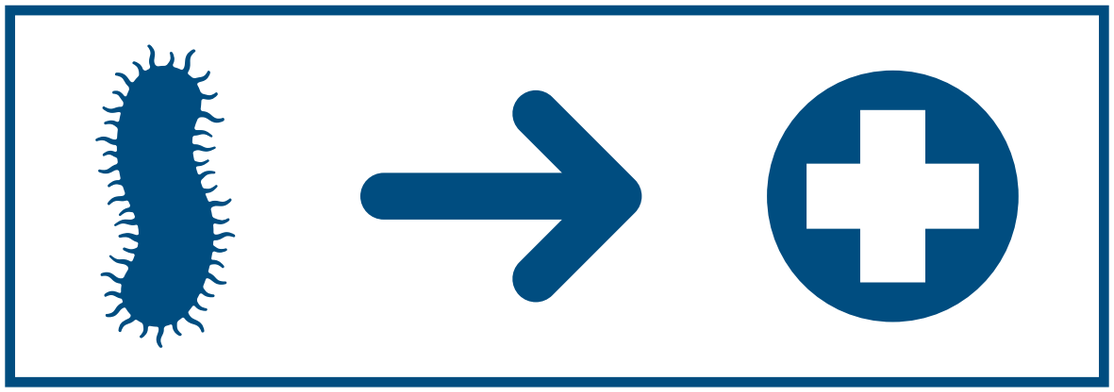
What about bacteria in the clinic?



1. current FDA approved

Bacteria as Therapy

A current FDA-approved bacterial therapy

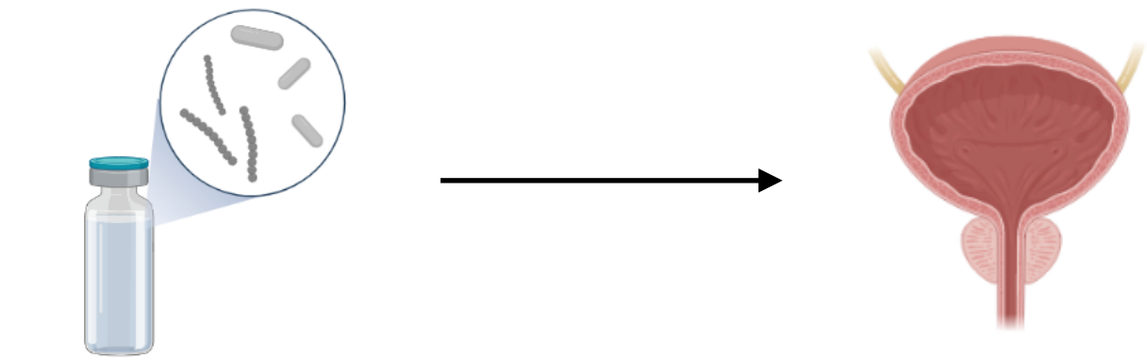
BCG Vaccine

Bacillus Calmette–Guérin

Developed against tuberculosis in early 1900s

Found widespread use after WWII

Adopted as standard care for bladder cancer in 1977

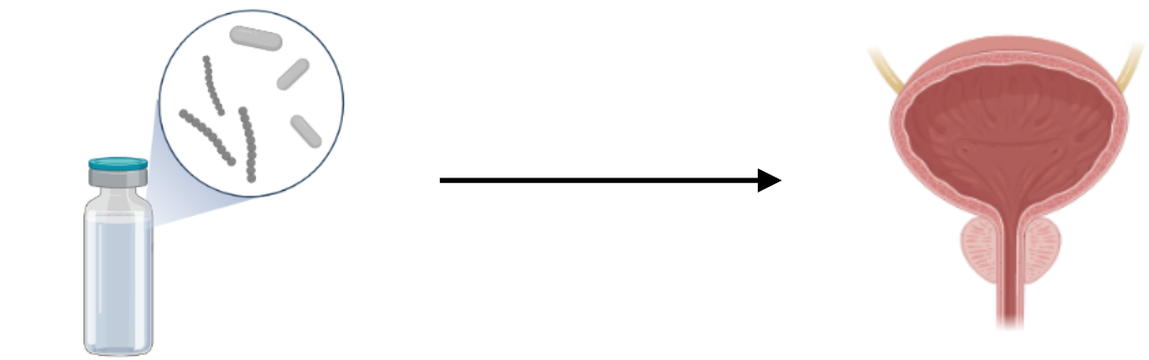


Sylvester, Richard J. *International Journal of Urology*. **2011**. 18, 113-120.

Bacteria as Therapy

A current FDA-approved bacterial therapy

Adopted as standard care for bladder cancer in 1977



BCG Vaccine

Bladder

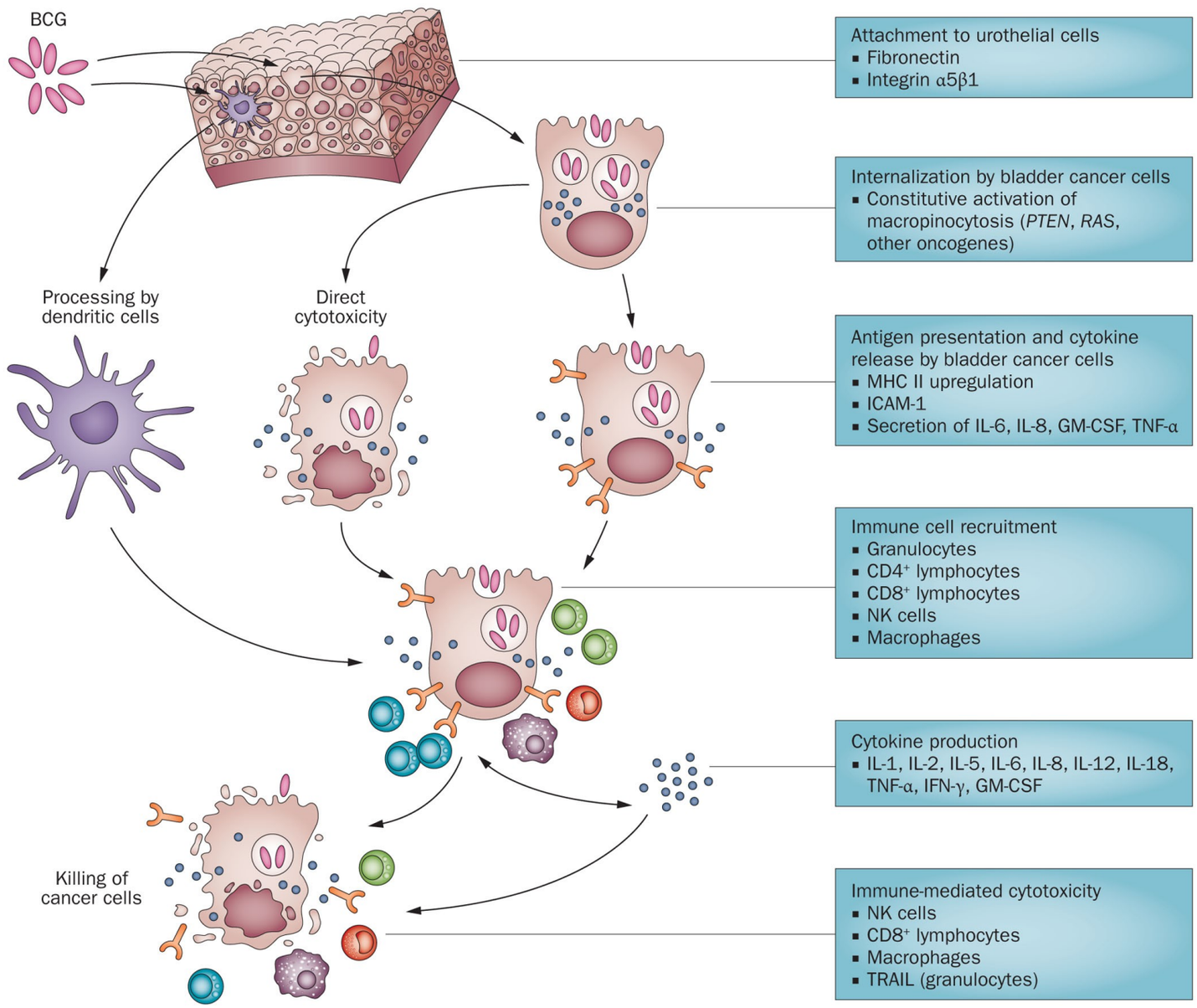
→ Function is analogous to coley's toxins - immune stimulation

Sylvester, Richard J. *International Journal of Urology*. **2011**. 18, 113-120.

Bacteria as Therapy

A current FDA-approved bacterial therapy

Mechanism of action similar to Coley's Toxin



Bochner, Bernard M.; Glickman, Michael S.; Redelman-Sidi, Gil. *Nature Reviews Urology*. **2014**, 11, 153–162.

Bacteria as Therapy

A current FDA-approved bacterial therapy

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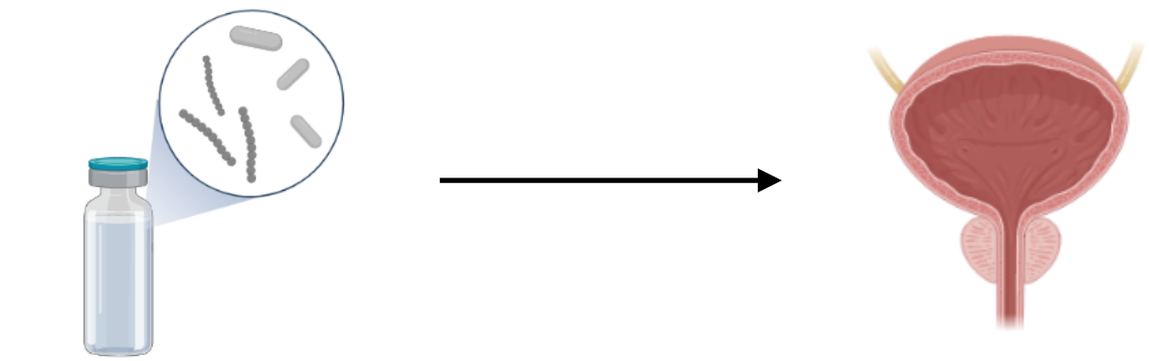


→ Function is analogous to coley's toxins - immune stimulation

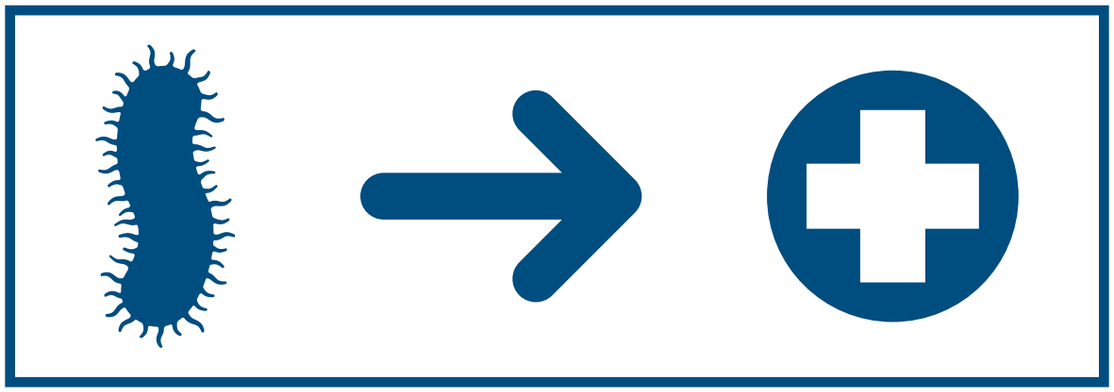
→ Prevents recurrence in 67% of cases of suitable candidates

→ In general: more effective than chemotherapy, but also *more dangerous*

further investigations into colon cancer treatment are ongoing (Vaccinogen)

Sylvester, Richard J. *International Journal of Urology*. **2011**. 18, 113-120.

What about bacteria in the clinic?

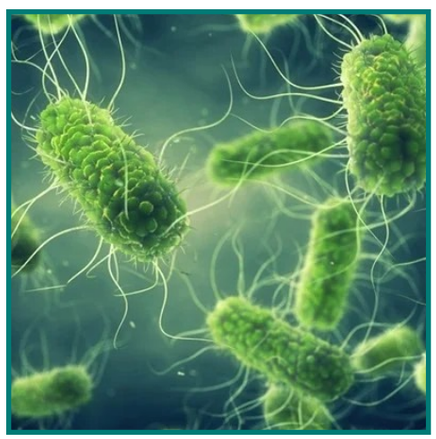


1. current FDA approved

2. Salmonella

Bacteria as Therapy

Salmonella for Bacterial therapy



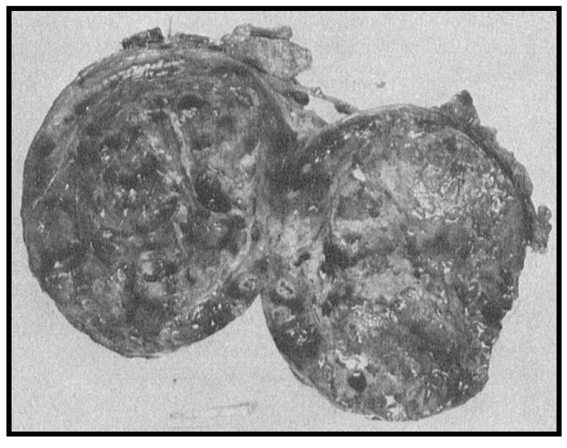
Salmonella

Salmonella typhimurium

- Common cause of food borne illness, typhoid fever
- Intracellular pathogen/parasitic infection
- Uses secretion system to enter host cells

1954

adrenal gland tumor
colonized by salmonella



Genetic modification to reduce virulence

Giel, Charles P. *N Engl J Med*. **1954**, 251, 980-982.

Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

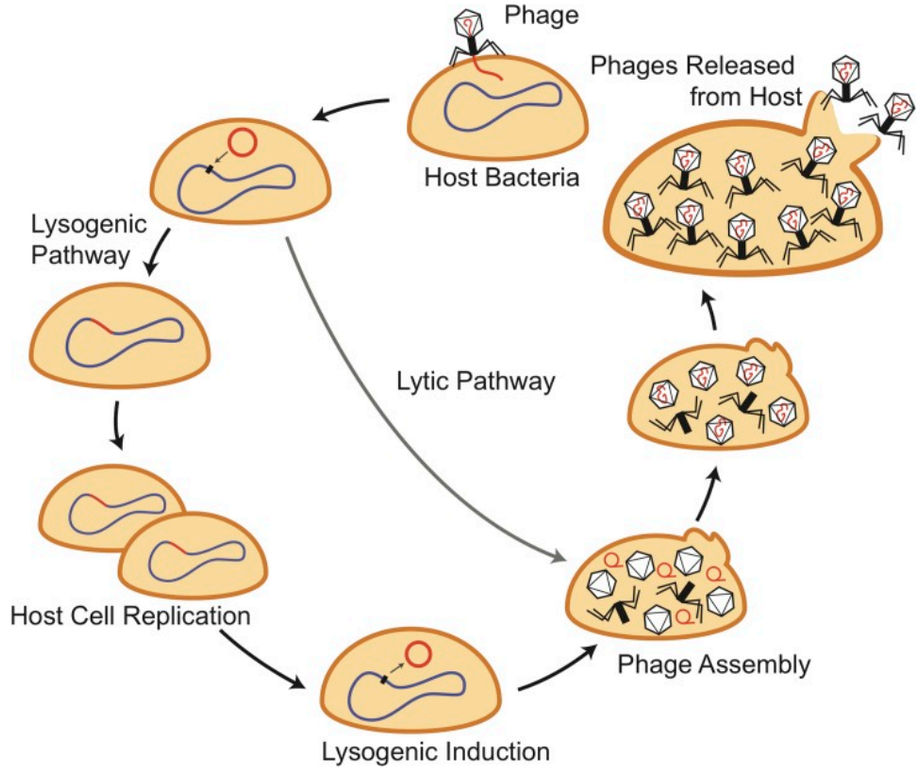
Salmonella for Bacterial therapy

VNP20009

genetically modified salmonella

- Deletions in *msbB* and *purI* loci - both virulence factors
- msbB - myristic acid moiety of lipid A
- purI - phosphoribosylaminoimidazole synthetase

phage usage to insert DNA into Salmonella



Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Salmonella for Bacterial therapy

VNP20009

genetically modified salmonella

series of insertion and selection processes to arrive at VNP20009

Properties	Strain/plasmid	Process
Wild type	*Salmonella typhimurium*, ATCC 14028	
		Mutagenize with UV and nitrosoguanidine
pur⁻, *xyl*⁻ *hyperinvasive	strain YS72	
		Transduction of *tet* marker using P22 phage with strain TT11 (*purI1757*::Tn *10*) as donor
purI⁻ and Tet^R (*xyl*⁻, *pur*⁻)	strain YS1641	
		Bochner selection (19)
Tet^S, Δ*purI*⁻ (*pur*⁻, *xyl*⁻)	strain YS1642	
		Transduction of Δ*msbB1*::*tet* using P22 phage with strain YS8211 (2) as donor
Δ*msbB1*::*tet* (*pur*⁻, Δ*purI*⁻, *xyl*⁻)	strain YS1643	
		EGTA^R selection
EGTA^R (Δ*msbB1*::*tet*, *pur*⁻, Δ*purI*⁻, *xyl*⁻)	strain YS1644	
		Transduction of pCVD442-15.2 Δ *msbB2* using P22 phage (see Figure 2)
Suc^S, Amp^R, (Δ)*msbB2* (EGTA^R, Δ*msbB1*::*tet pur*⁻, Δ*purI*⁻, *xyl*⁻)	strain YS1645	
		Plate on LB-sucrose to select Suc^R, Amp^S, Tet^S, Δ*msbB2*
Suc^R, Amp^S, Tet^S, Δ*msbB2* EGTA^R *pur*⁻, Δ*purI*⁻, *xyl*⁻	VNP20009 (strain YS1646)	

*Not studied in subsequent strains

Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Salmonella for Bacterial therapy

VNP20009

genetically modified salmonella

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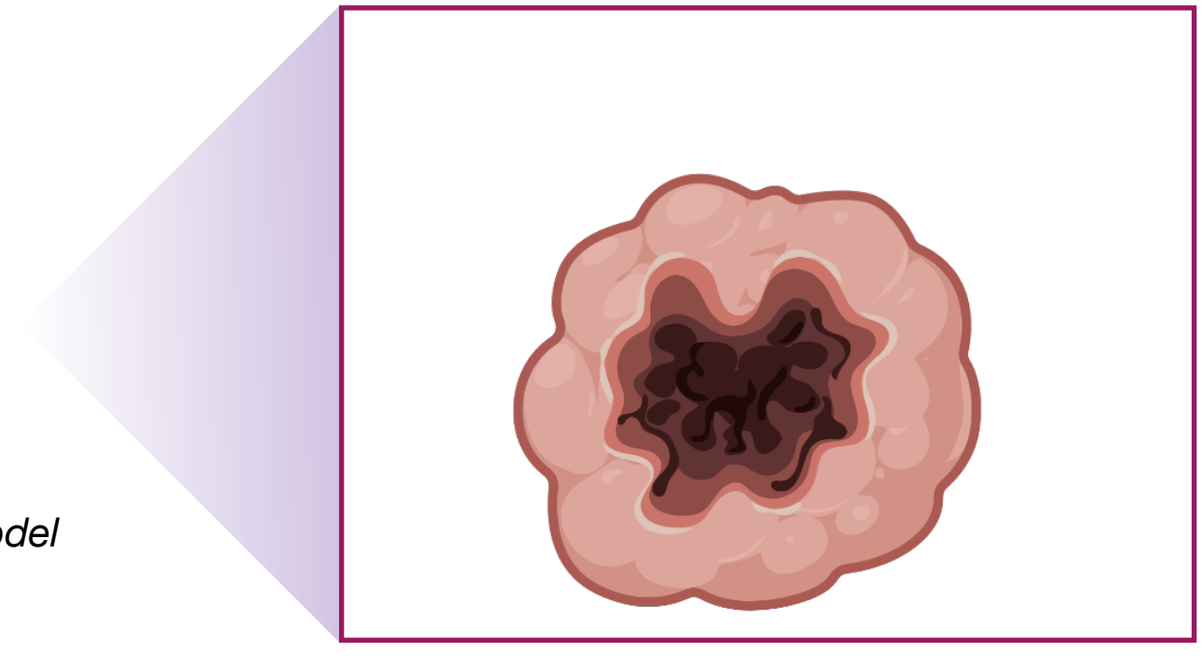
Utilization in mouse xenograft model



Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Salmonella for Bacterial therapy

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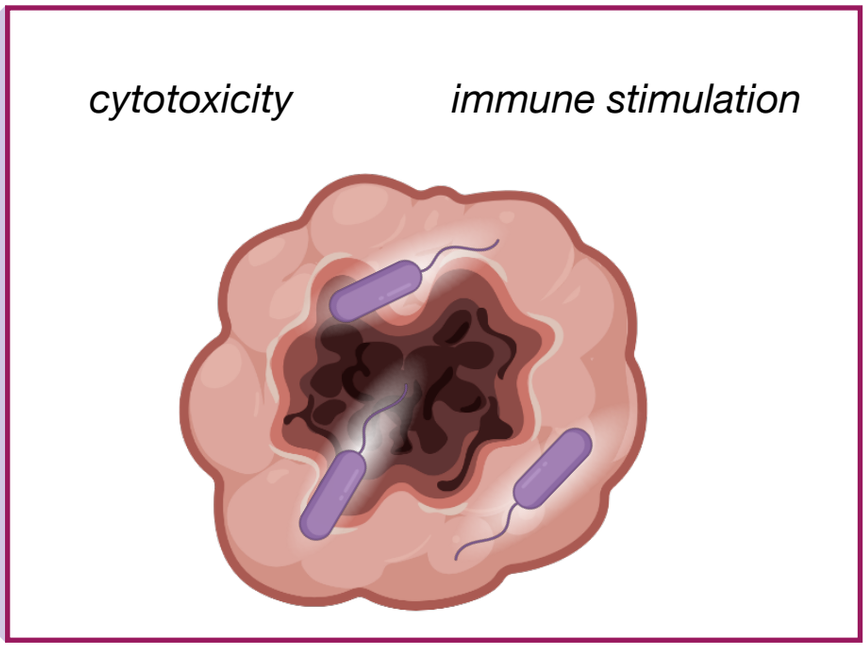

Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Salmonella for Bacterial therapy

VNP20009

genetically modified salmonella

Utilization in mouse xenograft model

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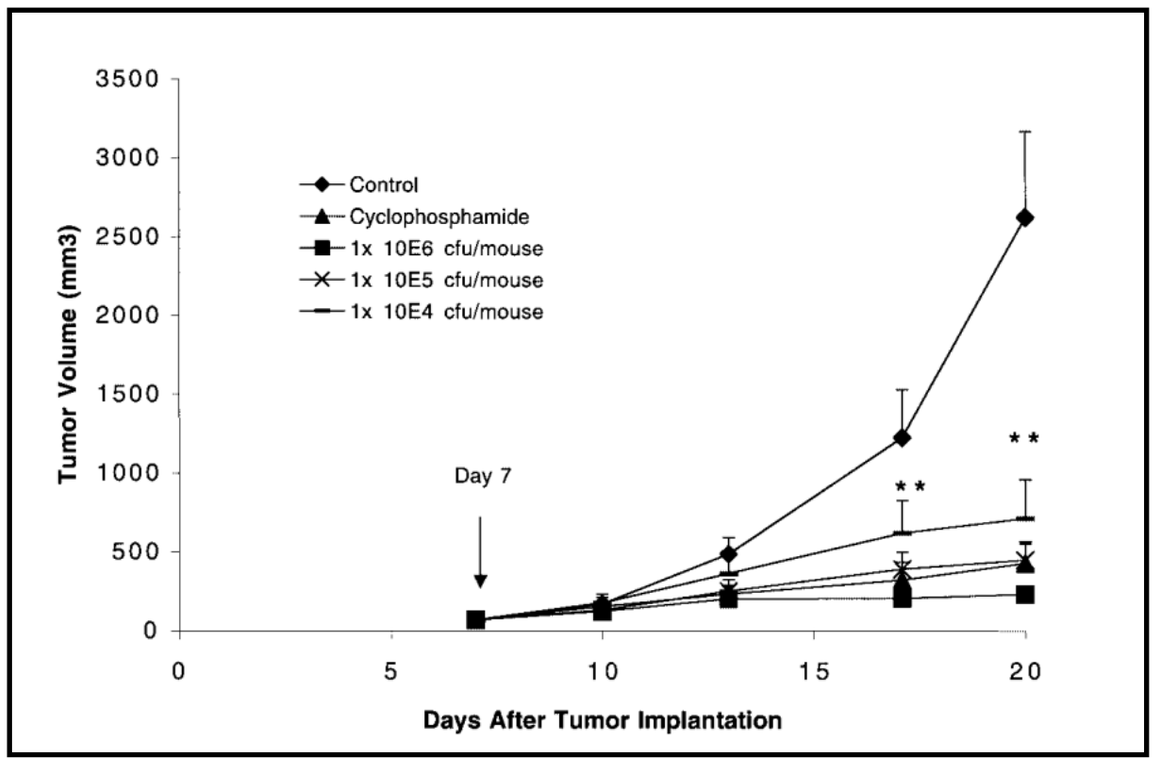

Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Salmonella for Bacterial therapy

VNP20009

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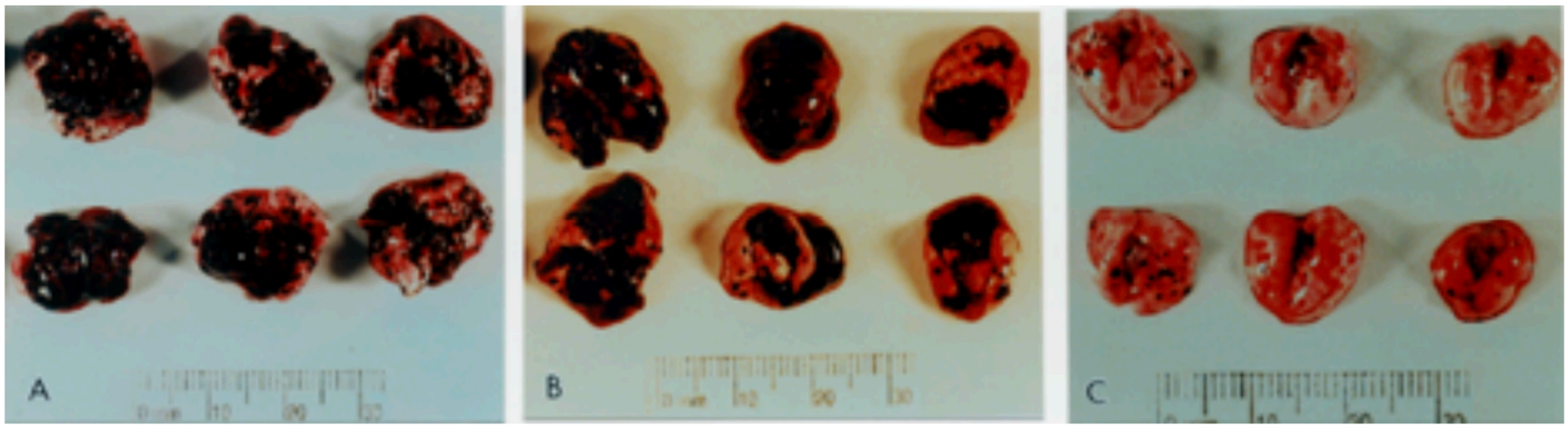


PBS | Dead VNP20009 | Live VNP20009

Zheng, Li-Mu et al. *Oncology Research.* **2002**, 12, 501–508.

Bacteria as Therapy

Clinical Trials: Salmonella

Treatment of Patients With Cancer With Genetically Modified Salmonella Typhimurium Bacteria

VNP20009

genetically modified salmonella

→ toxicity genetically attenuated

→ hypothesis - tumor homing ability in humans

→ strain showed tumor growth shrinkage in mice

Results:

\+ No adverse effects from salmonella inoculation

\- Very limited tumor colonization (3/20 patients)

\- No benefit in tumor reduction observed

terminated after phase 1 trials

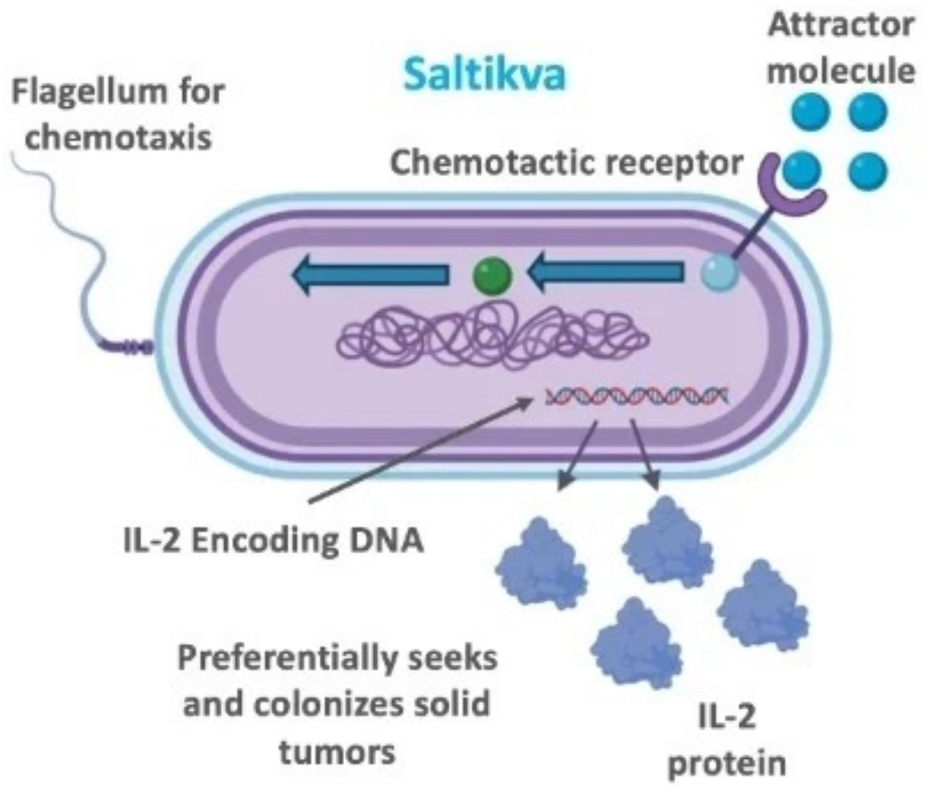
ClinicalTrials.gov. Trial NCT00004988. Web. Accessed Nov. 2022.

Bacteria as Therapy

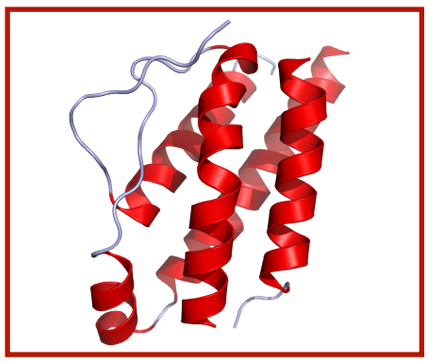
Clinical Trials: Salmonella with Immunomodulators

salspera

MICROBIAL IMMUNOTHERAPY



Payload: IL-2 cytokine



increases killing activity by T-cells and NK cells

narrow therapeutic window, systemic administration difficult

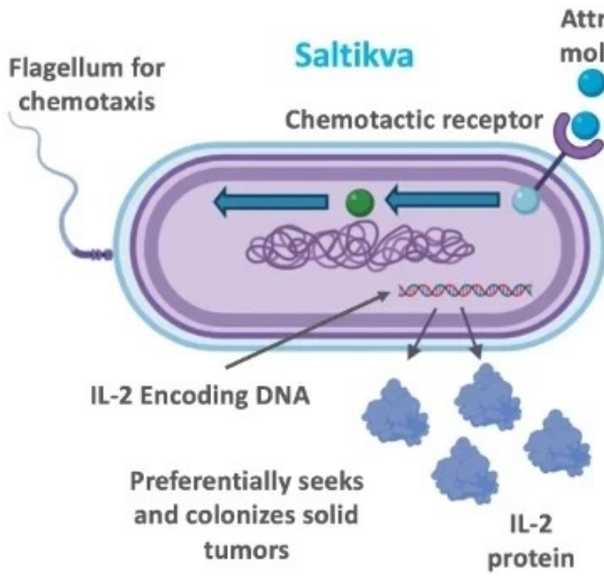
Koten, JW et al. *Cancer Immunology, Immunotherapy*. **2008**, 57 (7): 931–50.

Saltzman, Daniel. *Cancer Res*. **2021**, 81, LB161.

Bacteria as Therapy

Clinical Trials: Salmonella with Immunomodulators

Saltikva for Metastatic Pancreatic Cancer



→ localized IL-2 delivery

→ improved colonization/reduced toxicity

→ successful canine trials

n = 1 patient study

Saltzman, Daniel. *Cancer Res.* **2021**, 81, LB161.

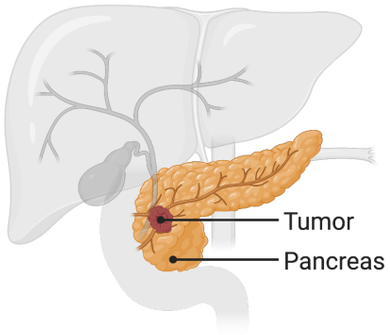
Bacteria as Therapy

Clinical Trials: Salmonella with Immunomodulators

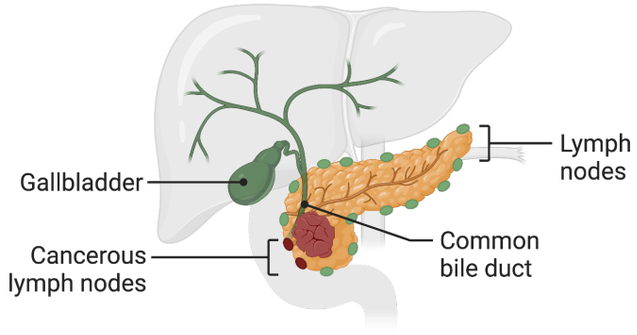
Saltikva for Metastatic Pancreatic Cancer

n = 1 patient study

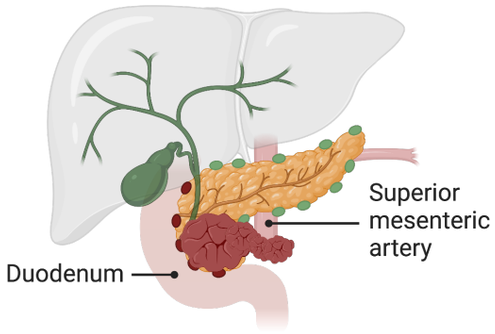
Stage 1 | Tumor is located only in pancreas.



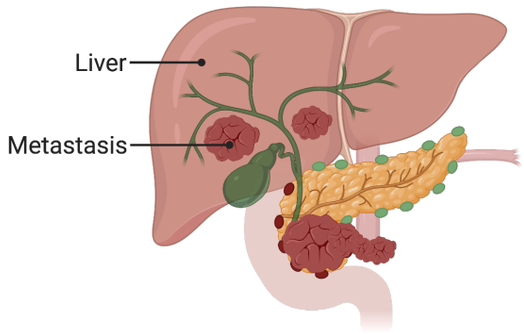
Stage 2 | Tumor involves lymph nodes and is outside pancreas (e.g. common bile duct).



Stage 3 | Tumor involves celiac axis or superior mesenteric artery.



Stage 4 | Cancer is growing in organs beyond the pancreas (e.g. liver).



Saltzman, Daniel. *Cancer Res.* **2021**, 81, LB161.

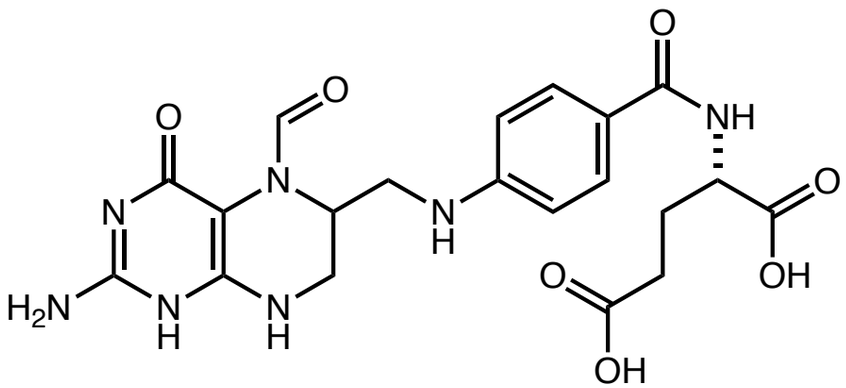
Bacteria as Therapy

Clinical Trials: Salmonella with Immunomodulators

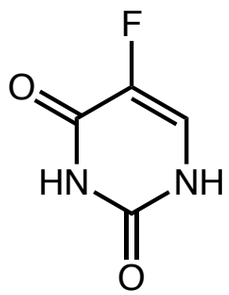
Saltikva for Metastatic Pancreatic Cancer

n = 1 patient study

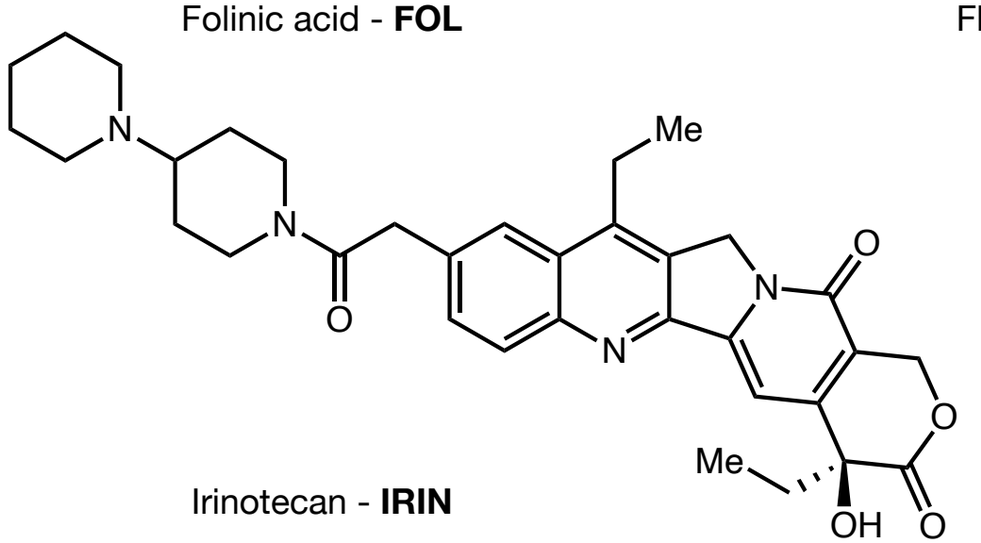
Saltikva + **FOLFIRINOX** administered



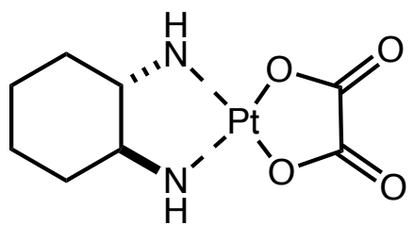
Folinic acid - **FOL**



Fluorouracil - **F**

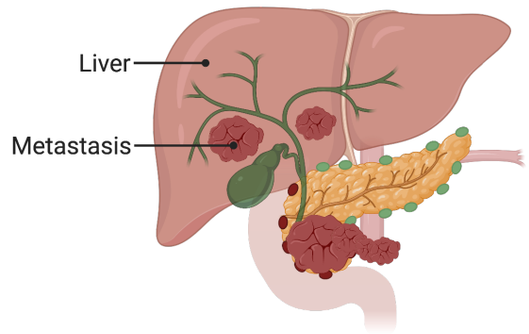


Irinotecan - **IRIN**



Oxaliplatin - **OX**

Stage 4 | Cancer is growing in organs beyond the pancreas (e.g. liver).



Saltzman, Daniel. *Cancer Res.* **2021**, 81, LB161.

Bacteria as Therapy

Clinical Trials: Salmonella with Immunomodulators

Saltikva for Metastatic Pancreatic Cancer

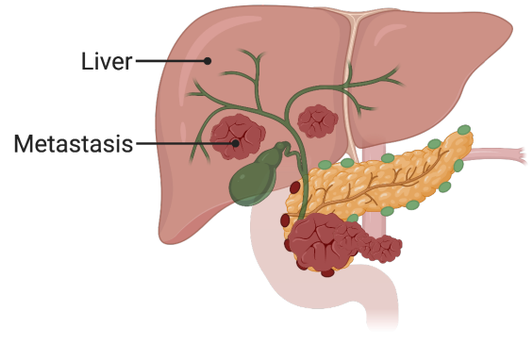
n = 1 patient study

Saltikva + **FOLFIRINOX** administered

significant increase in NK cell levels observed

indicative of immunomodulatory effect

Stage 4 | Cancer is growing in organs beyond the pancreas (e.g. liver).



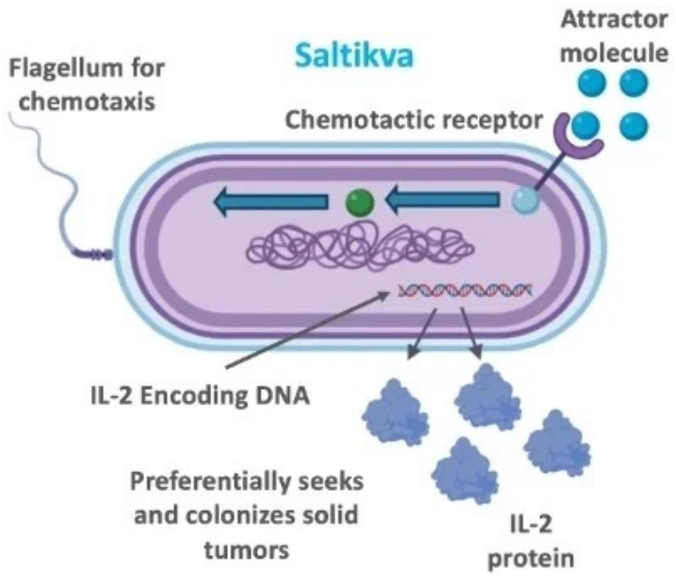
eventually, patient makes full recovery, healthy 24 months later

Saltzman, Daniel. *Cancer Res.* **2021**, 81, LB161.

Bacteria as Therapy

Clinical Trials: Salmonella with Immunomodulators

Saltikva for Metastatic Pancreatic Cancer



→ localized IL-2 delivery

→ improved colonization/reduced toxicity

→ successful canine trials

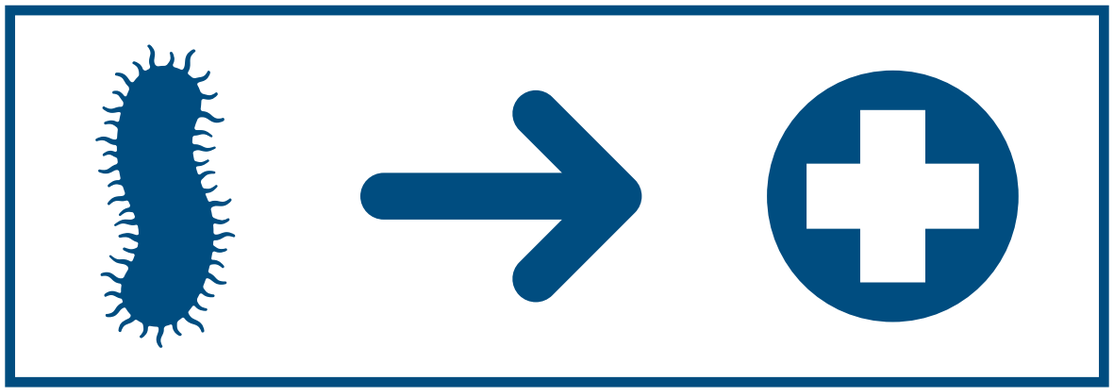
Results:

+ No adverse effects from salmonella inoculation
+ Successful tumor colonization
+ Full patient recovery - healthy 24 months later

currently in phase 2 trials

Saltzman, Daniel. *Cancer Res.* **2021**, 81, LB161.

What about bacteria in the clinic?



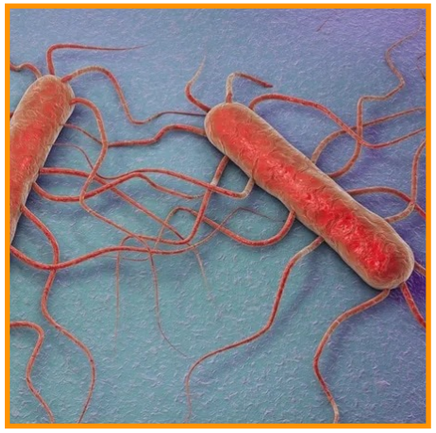
1. current FDA approved

2. Salmonella

3. Listeria monocytogenes

Bacteria as Therapy

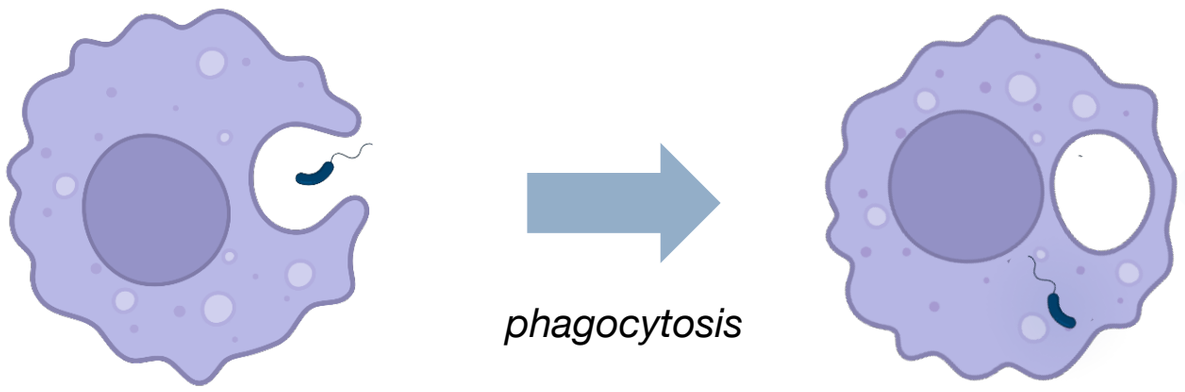
Listeria monocytogenes for bacterial therapy



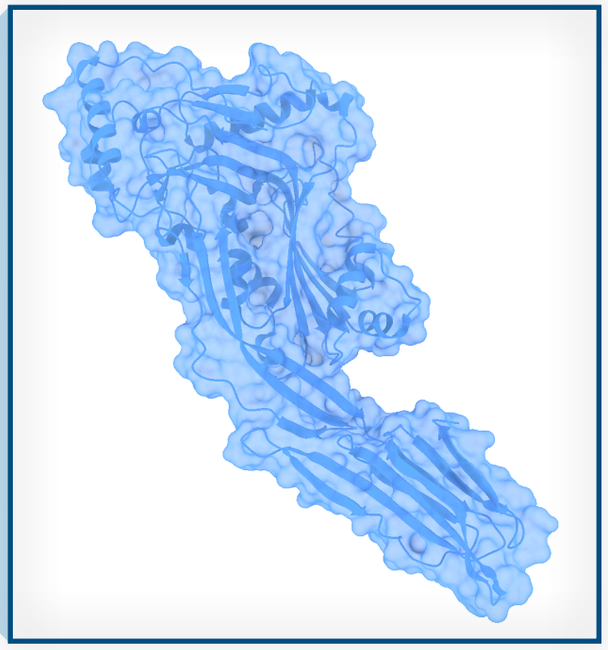
Listeria

Listeria monocytogenes

- Gram positive parasitic bacteria
- Cause of listeriosis - serious food poisoning condition
- Unique infection mechanism of listeria into cells



Listeriolysin O



Listeriolysin O allows for lysosomal escape

Cossart, P. *Infection*. **1988**, 16, 157-159.

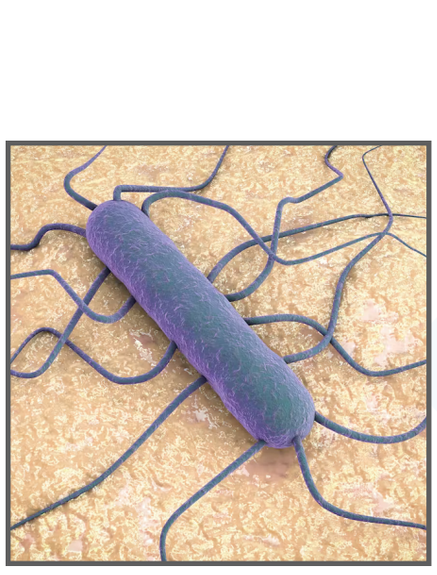
Bacteria as Therapy

Clinical Trials: Listeria

Modified listeria as an HPV induced cervical cancer treatment

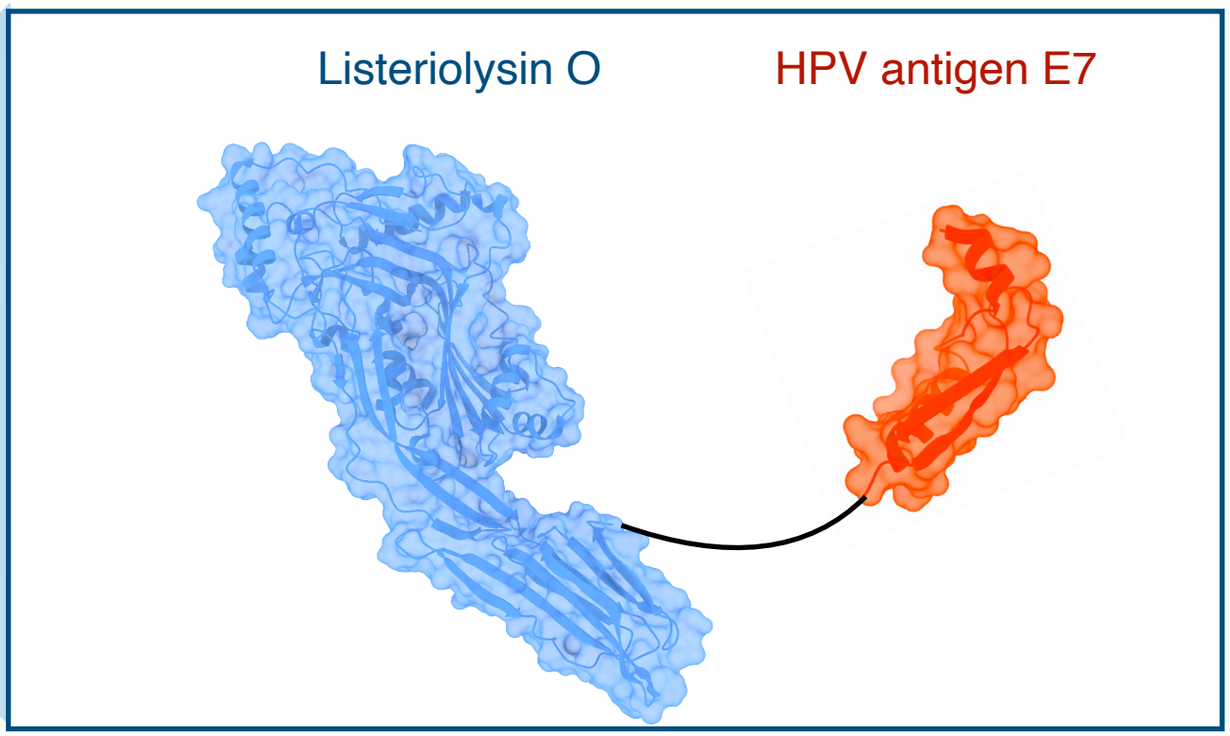
ADVAXIS IMMUNOTHERAPIES™

- Despite vaccines, HPV treatments inefficient
- Modified listeria that produce HPV antigen fusion protein



ADXS11-001

genetically modified
Listeria monocytogenes



Cetina-Perez, Lucely et al. *Human Vaccines and Immunotherapeutics*. **2021.** 17, 8, 2617–2625

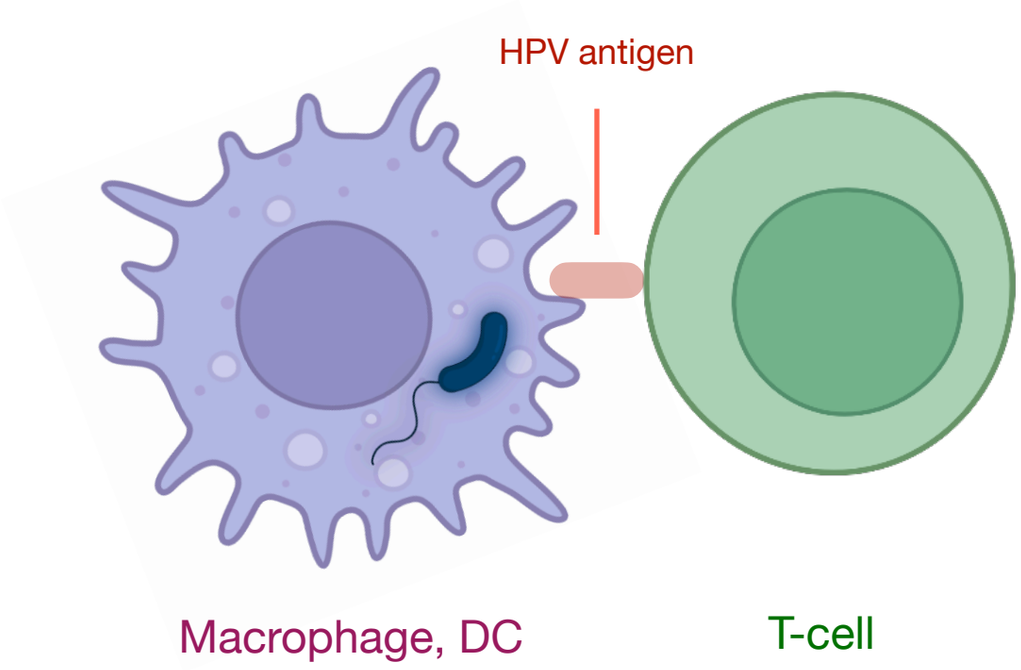
Bacteria as Therapy

Clinical Trials: Listeria

Modified listeria as an HPV induced cervical cancer treatment

ADVAXIS IMMUNOTHERAPIES™

- Despite vaccines, HPV treatments inefficient
- Modified listeria that produce HPV antigen fusion protein
- T cells recognize antigen and attack HPV infected cells



MHC interaction allows T-cell to recognize HPV antigen

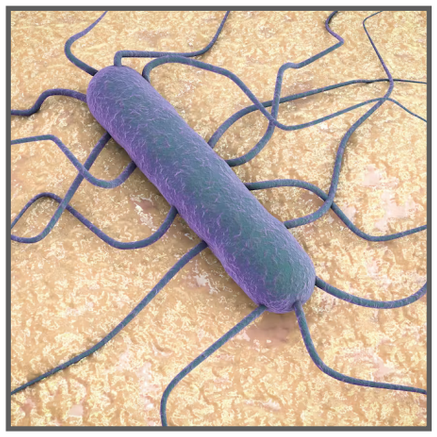
T-cells can now kill HPV-infected cells

Cetina-Perez, Lucely et al. *Human Vaccines and Immunotherapeutics*. **2021.** 17, 8, 2617–2625

Bacteria as Therapy

Clinical Trials: Listeria

Study of ADXS11-001 in Subjects With High Risk Locally Advanced Cervical Cancer



ADXS11-001

genetically modified
Listeria monocytogenes

→ genetically ablated toxicity/pathogenicity

→ produces HPV fusion protein which present antigen

→ allows for T-cell mediated killing of HPV-infected cells

Results:

\+ No serious adverse side effects

\+ 31% of patients saw tumor size reductions

\- Only 1 complete response

currently in phase 3 trials

Cetina-Perez, Lucely et al. *Human Vaccines and Immunotherapeutics*. **2021.** 17, 8, 2617–2625

Bacteria as Therapy

Why hasn't it been more widely adopted?

1. Toxicity

Lübeck disaster (1930s)

BCG vaccine accidentally contaminated with live tuberculosis strain

they were stored in the same incubator

73 infants ending up dying as a result

Bacteria as Therapy

Why hasn't it been more widely adopted?

1. Toxicity

2. Efficacy

In all live cell bacterial therapies we have discussed:

response rates peak at around 30%

attenuated toxicity, but lack of true efficacy

solutions:

- **combination therapy**
- **better patient-matching**
- **addition of therapeutic payloads**

nature

Article

Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer

https://doi.org/10.1038/s41586-022-05435-0

Received: 9 March 2022

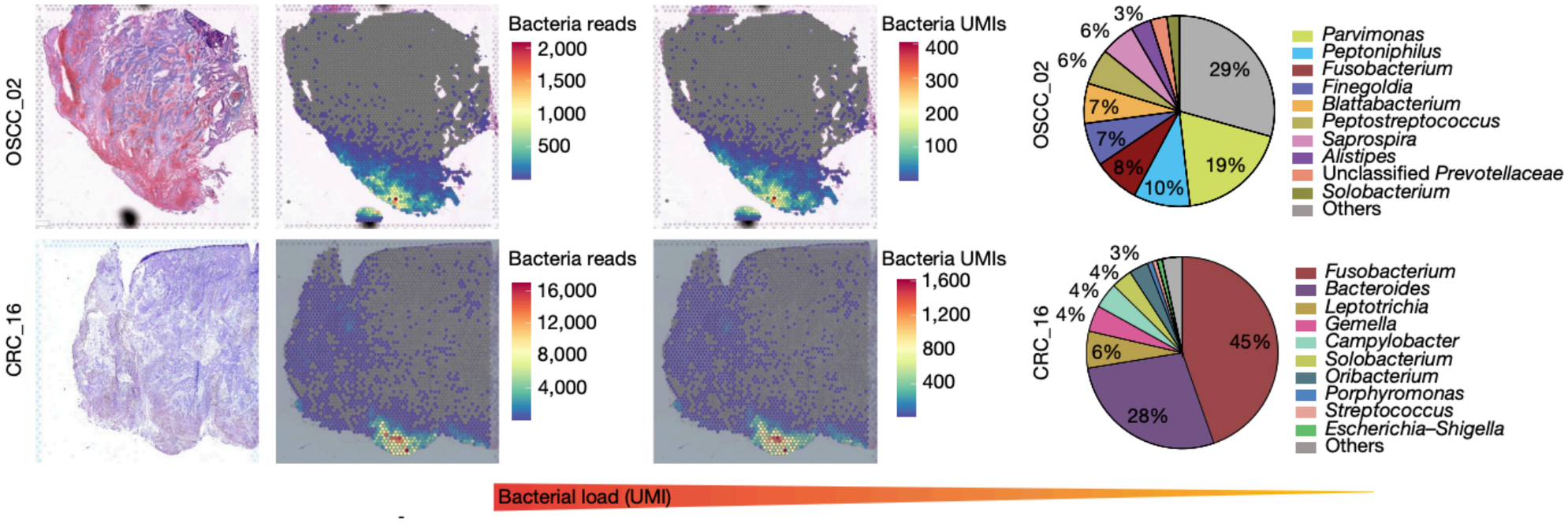
Accepted: 10 October 2022

Published online: 16 November 2022

Jorge Luis Galeano Niño[1], Hanrui Wu[1,9], Kaitlyn D. LaCourse[1,9], Andrew G. Kempchinsky[1], Alexander Baryiames[1], Brittany Barber[2], Neal Futran[2], Jeffrey Houlton[2,8], Cassie Sather[3], Ewa Sicinska[4], Alison Taylor[5], Samuel S. Minot[6], Christopher D. Johnston[7]✉ & Susan Bullman[1]✉

Bacteria as Therapy

Bacteria in the intratumoral environment



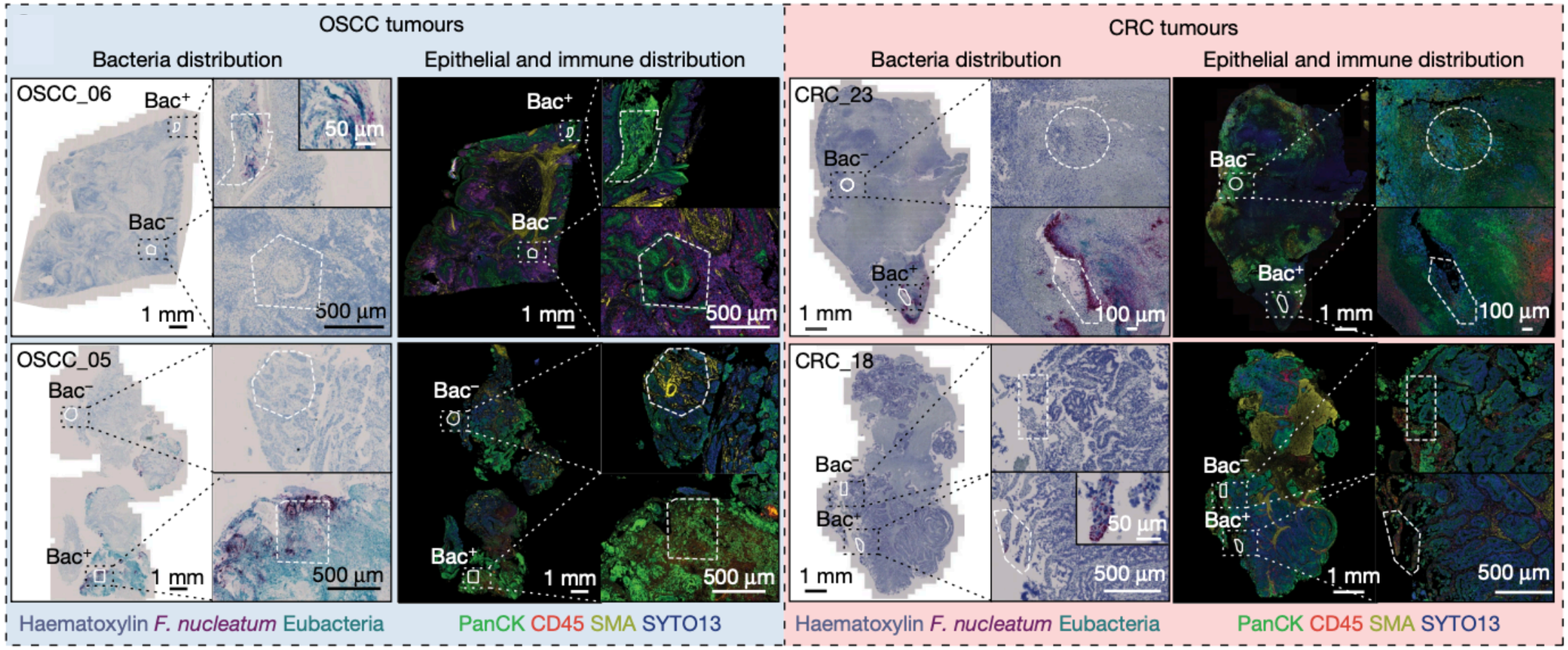
bacterial distribution is not even

bacterial species vary by cancer type

Bullman, S.; Johnston, C.; Minot, S. et al. *Nature* **2022**, 611, 810–817.

Bacteria as Therapy

Bacteria in the intratumoral environment

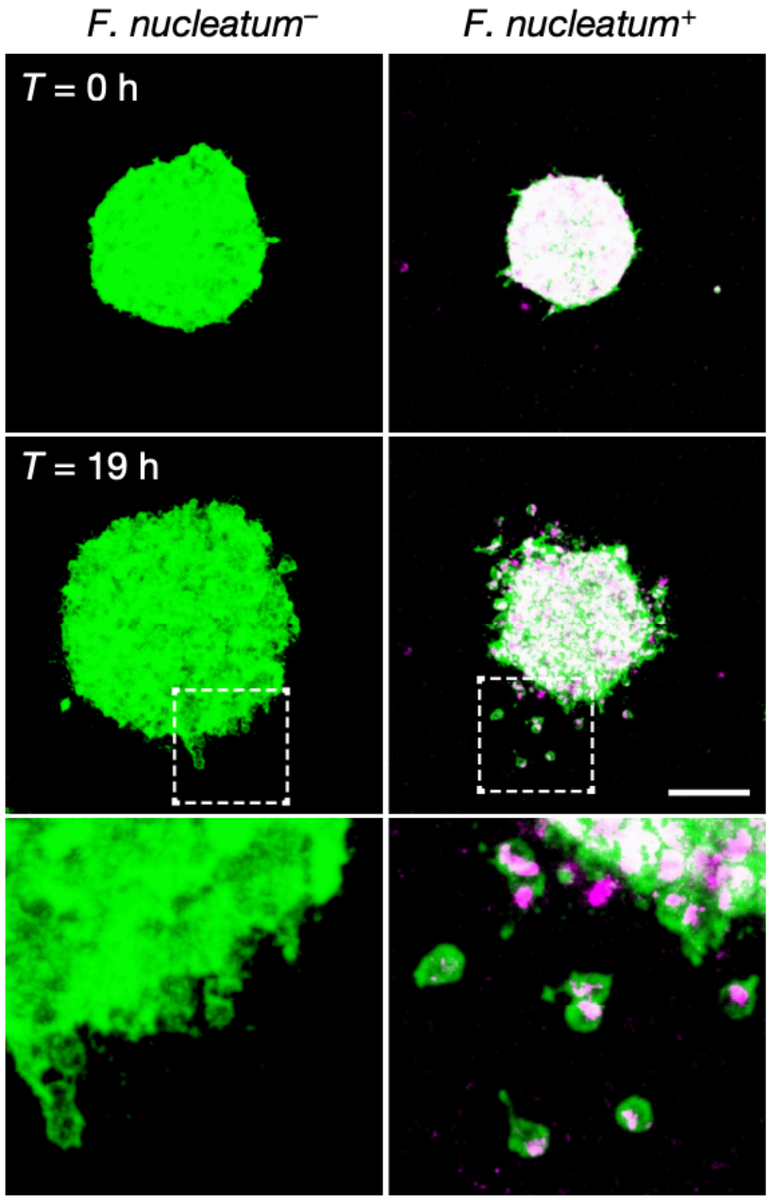


→ **bacteria change local mammalian gene expression**

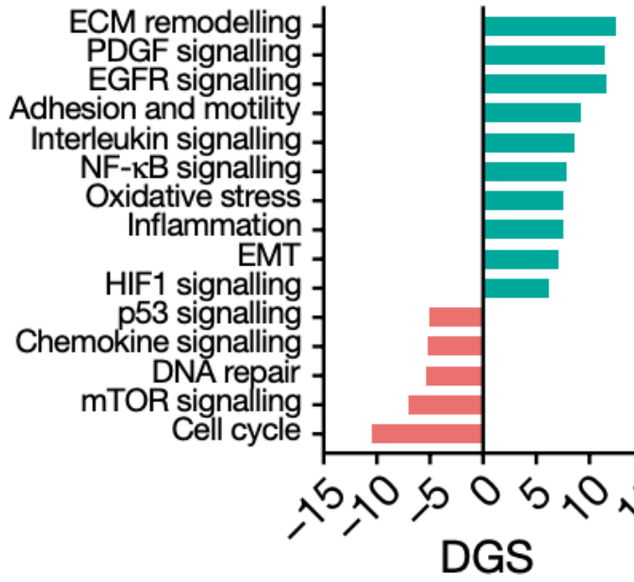
Bullman, S.; Johnston, C.; Minot, S. et al. *Nature* **2022**, 611, 810–817.

Bacteria as Therapy

Bacteria in the intratumoral environment



Epithelial cancer cells *F. nucleatum*



→ **bacteria aid in cancer cell migration**

→ **bacteria induce pro-cancer expression**

Bullman, S.; Johnston, C.; Minot, S. et al. *Nature* **2022**, 611, 810–817.

Bacteria as Therapy

Why should we care today?

nature

Article

Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer

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in the future, we will want to consider each patient's tumoral microbiota

Questions?