Synthesis of Therapeutic Bacteria

Anderson Lab, UC Berkeley Bioengineering

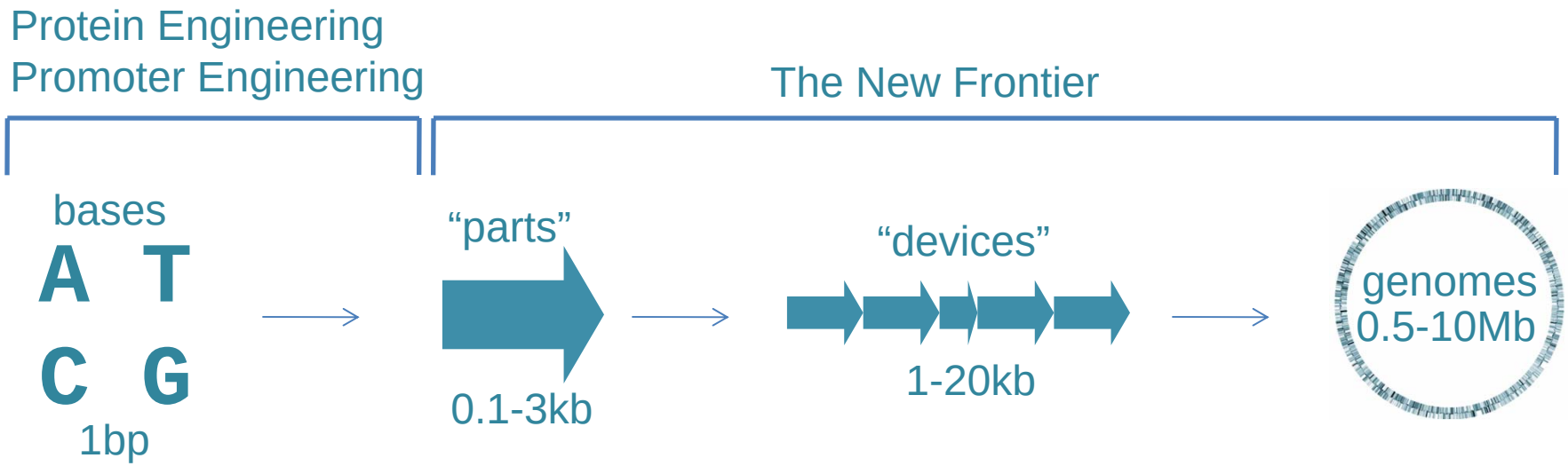
What is Synthetic Biology?

Ground-up Genetic or Cellular Engineering

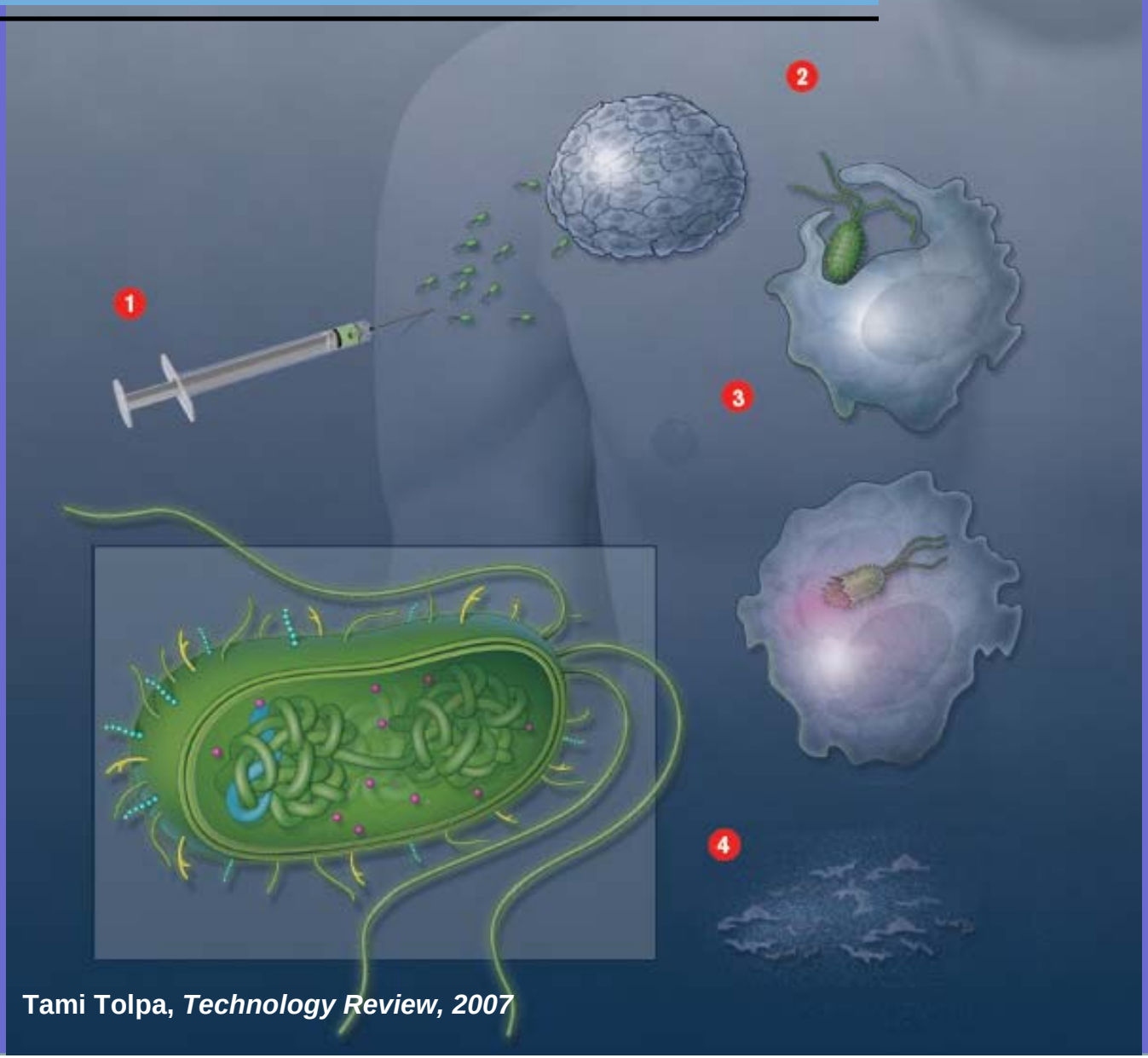
We add DNA sequences into well-characterized model organisms to understand biological behavior and construct useful organisms

Putting the Engineering into Genetic Engineering

Abstraction Hierarchy

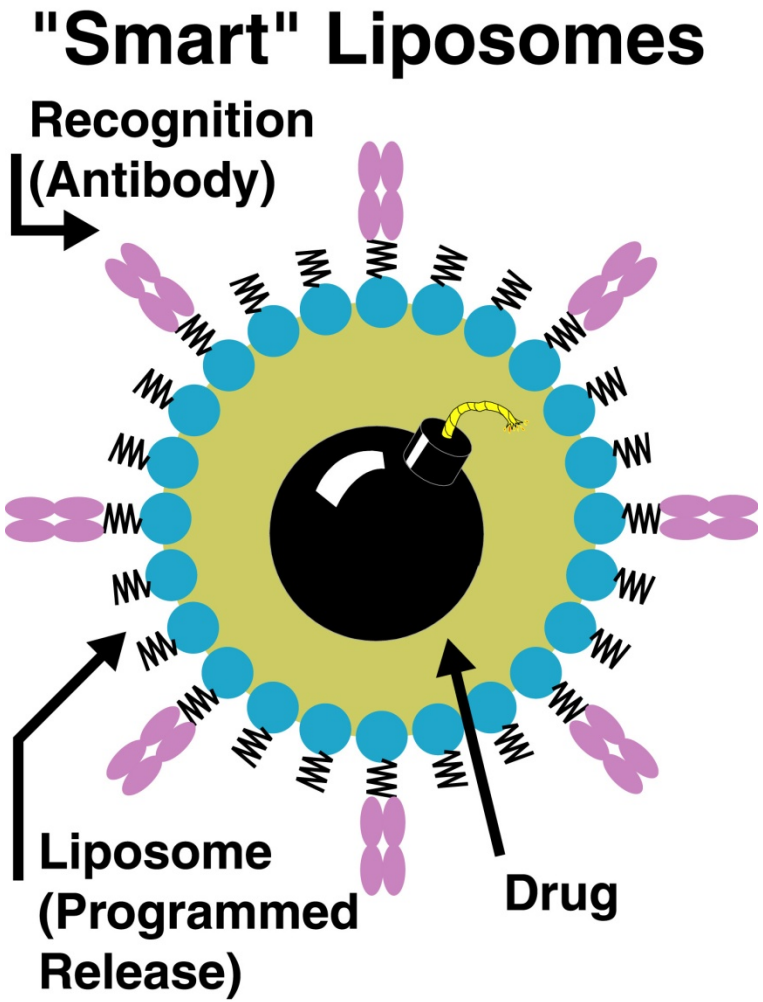


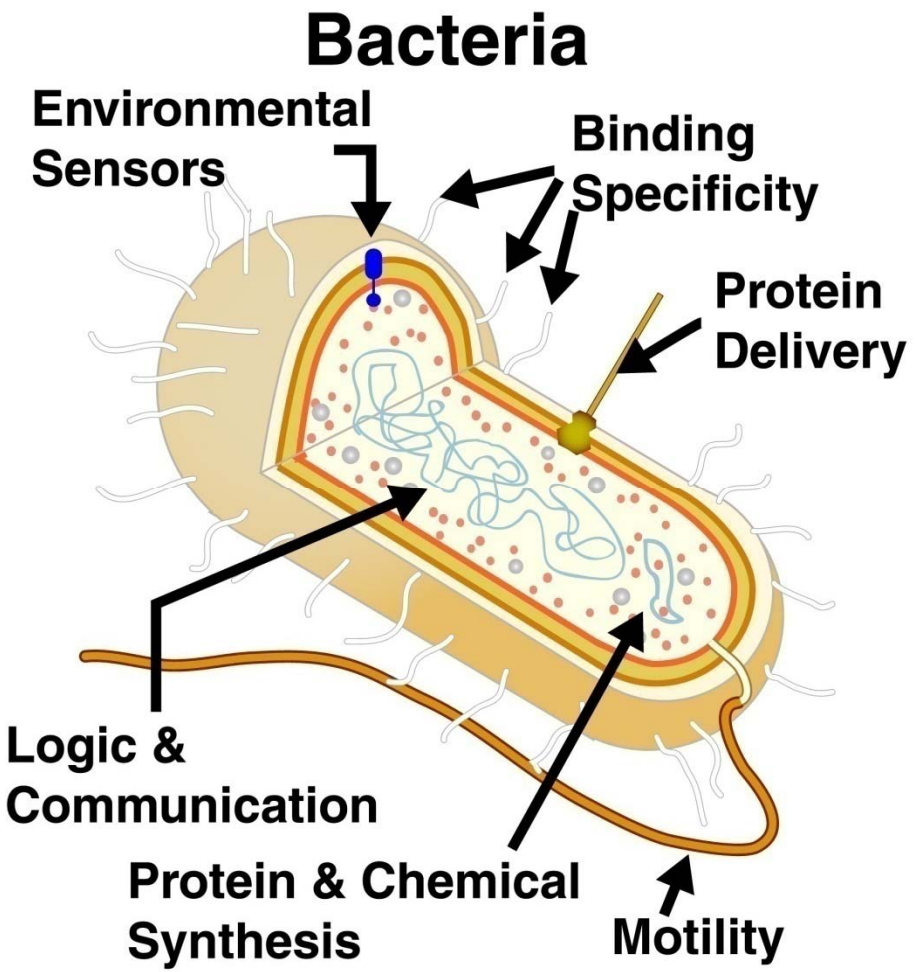
Tumor Killing Bacteria



Tami Tolpa, *Technology Review, 2007*

Very Smart Drugs

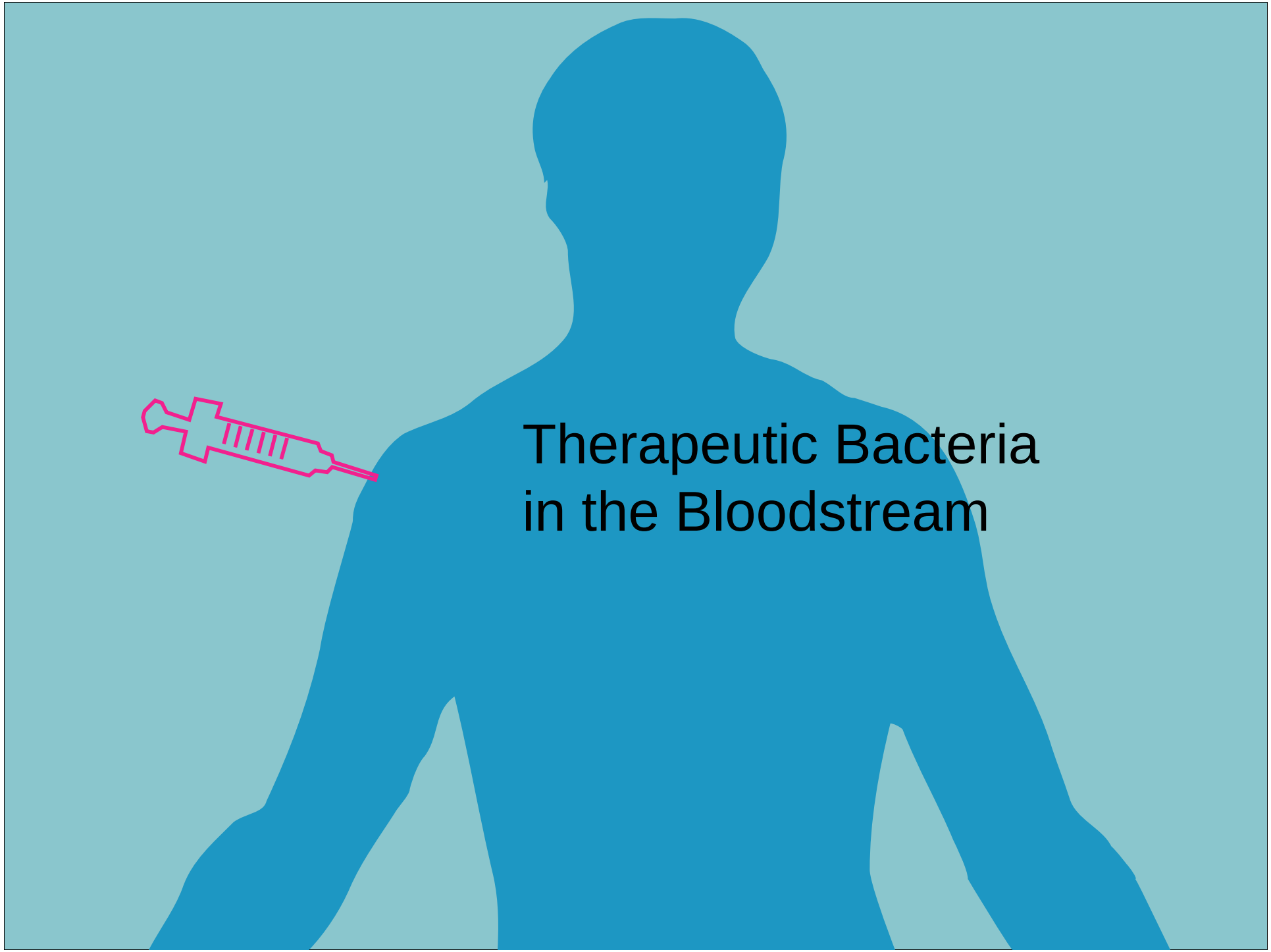


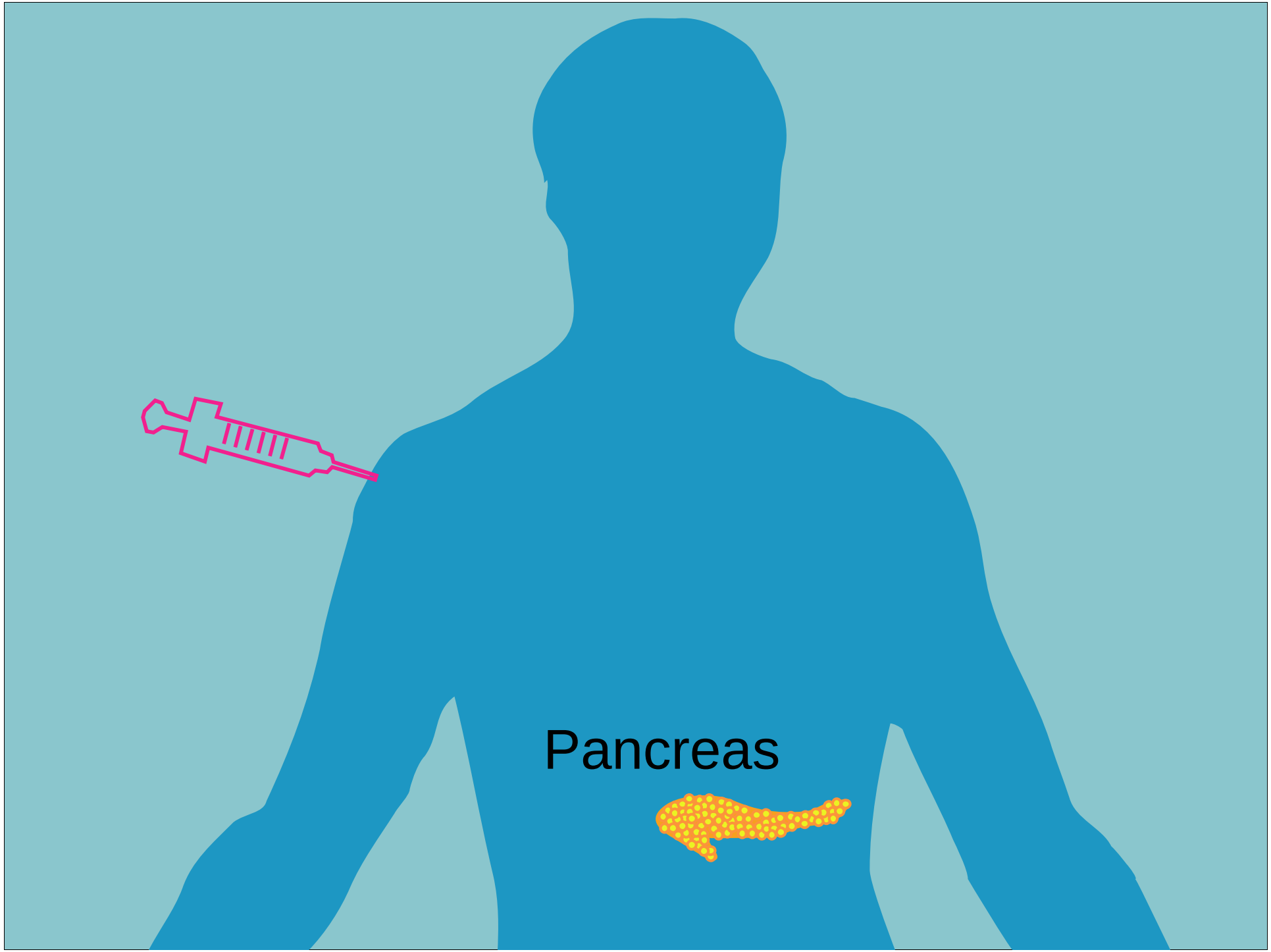


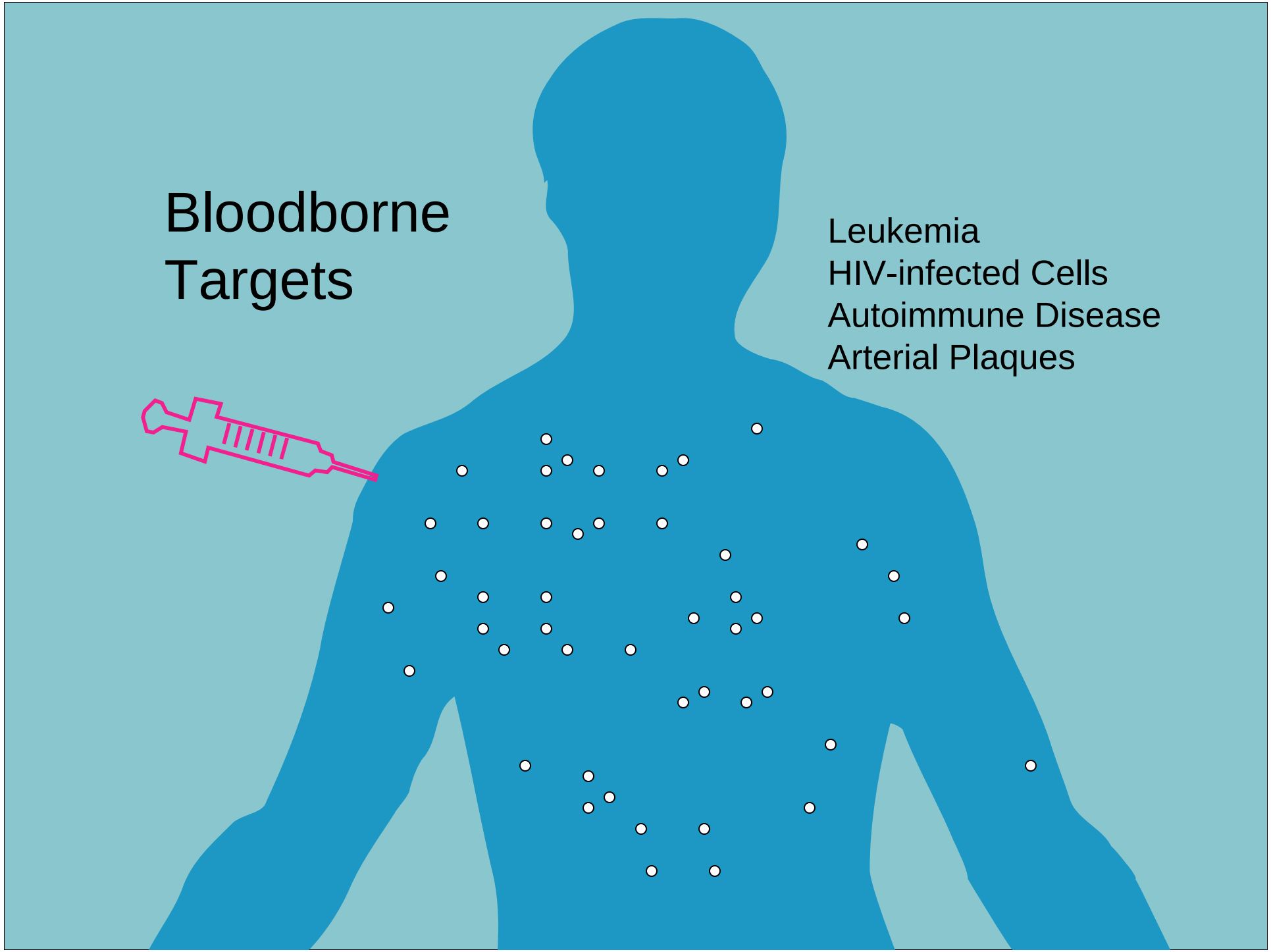
History of Bacterial Therapeutics

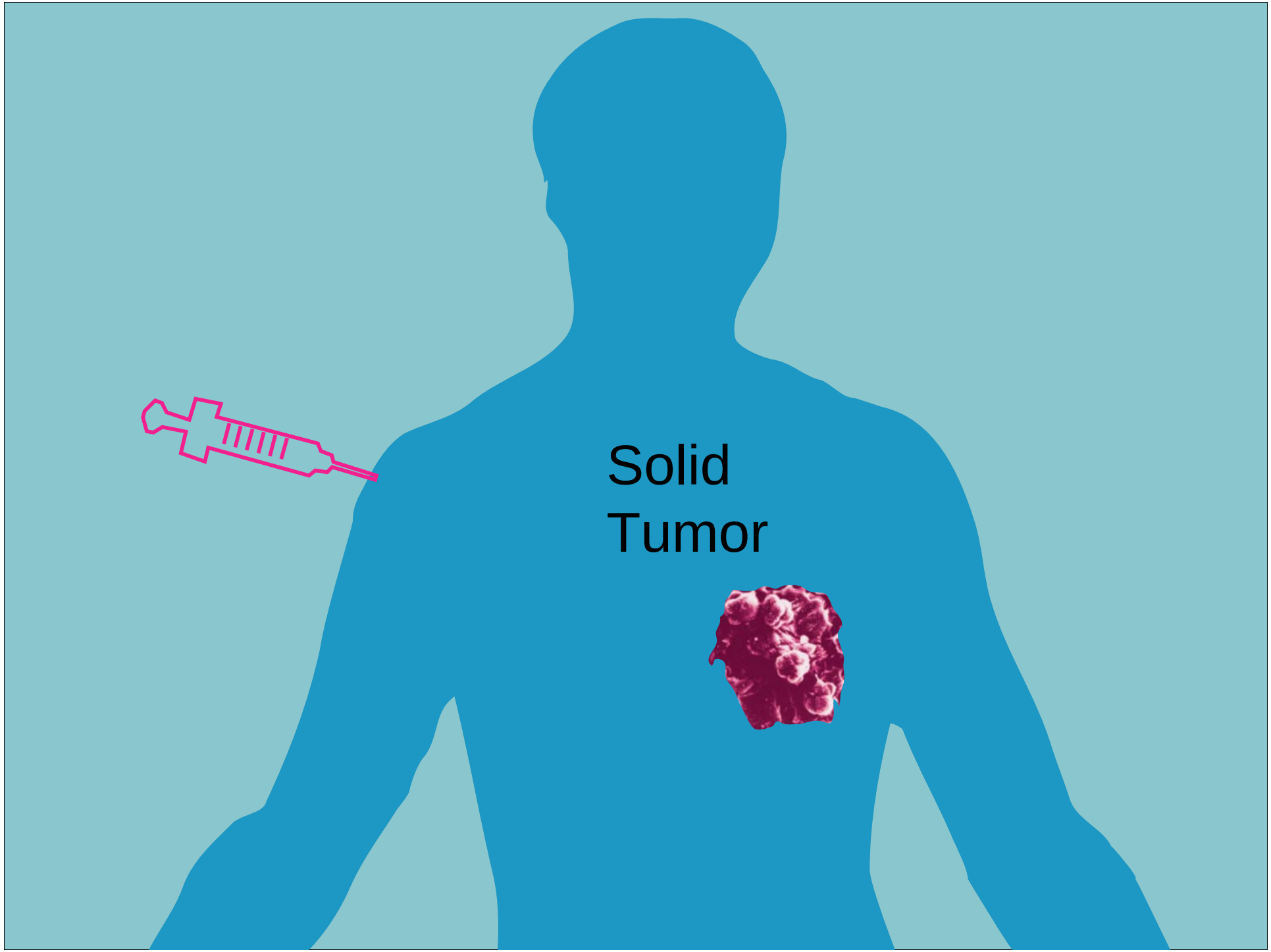
Digestive Disorders

Bladder Cancer


Therapeutic Bacteria
in the Bloodstream


Pancreas


Bloodborne
Targets
Leukemia
HIV-infected Cells
Autoimmune Disease
Arterial Plaques


Solid
Tumor

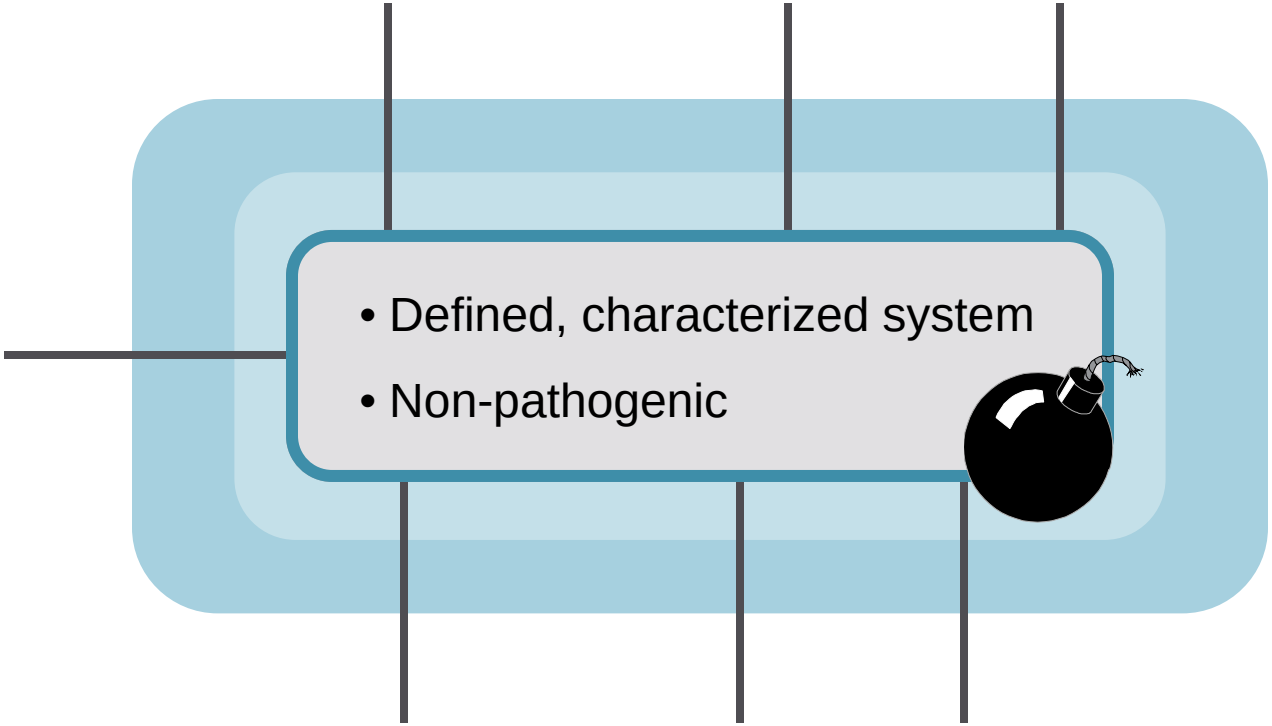
Therapeutic Chassis

1. Highly susceptible to the immune system

   Add protective capsule

2. Lipids evoke strong immune response

   Alter lipopolysaccharide structure



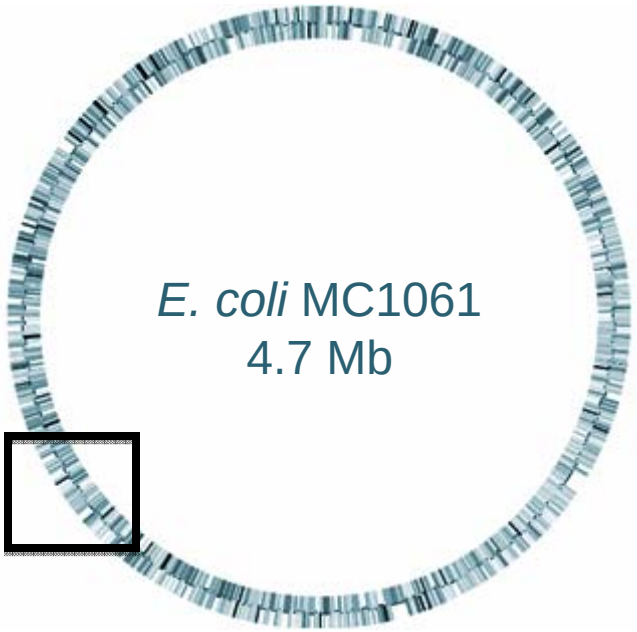
3. Adherent to cell surfaces, such as endothelium and RBCs

   Remove fimbriae

4. Unrestricted growth

   Introduce auxotrophy

Therapeutic Chassis



Insertion: K1 capsule cluster

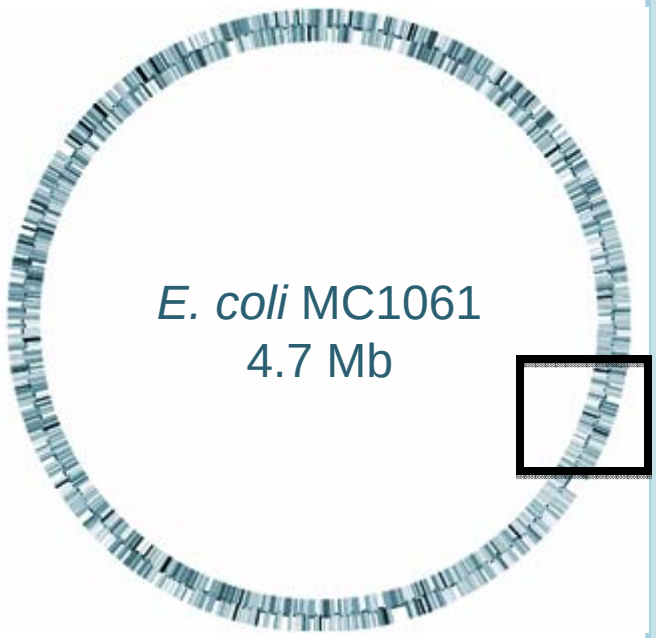
Size	Phenotype	Marker
20 kb	polysialic acid capsule	*CmR*

In vitro characterization

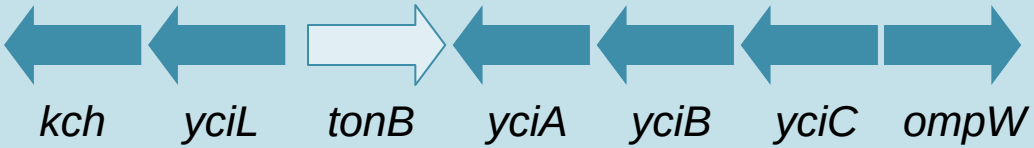
K1E Phage: fully susceptible

T4 Phage: partially susceptible

Therapeutic Chassis



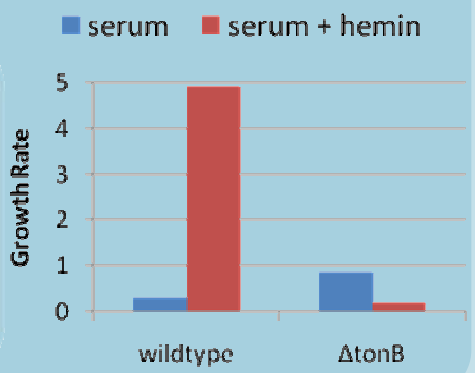
Deletion: *tonB*



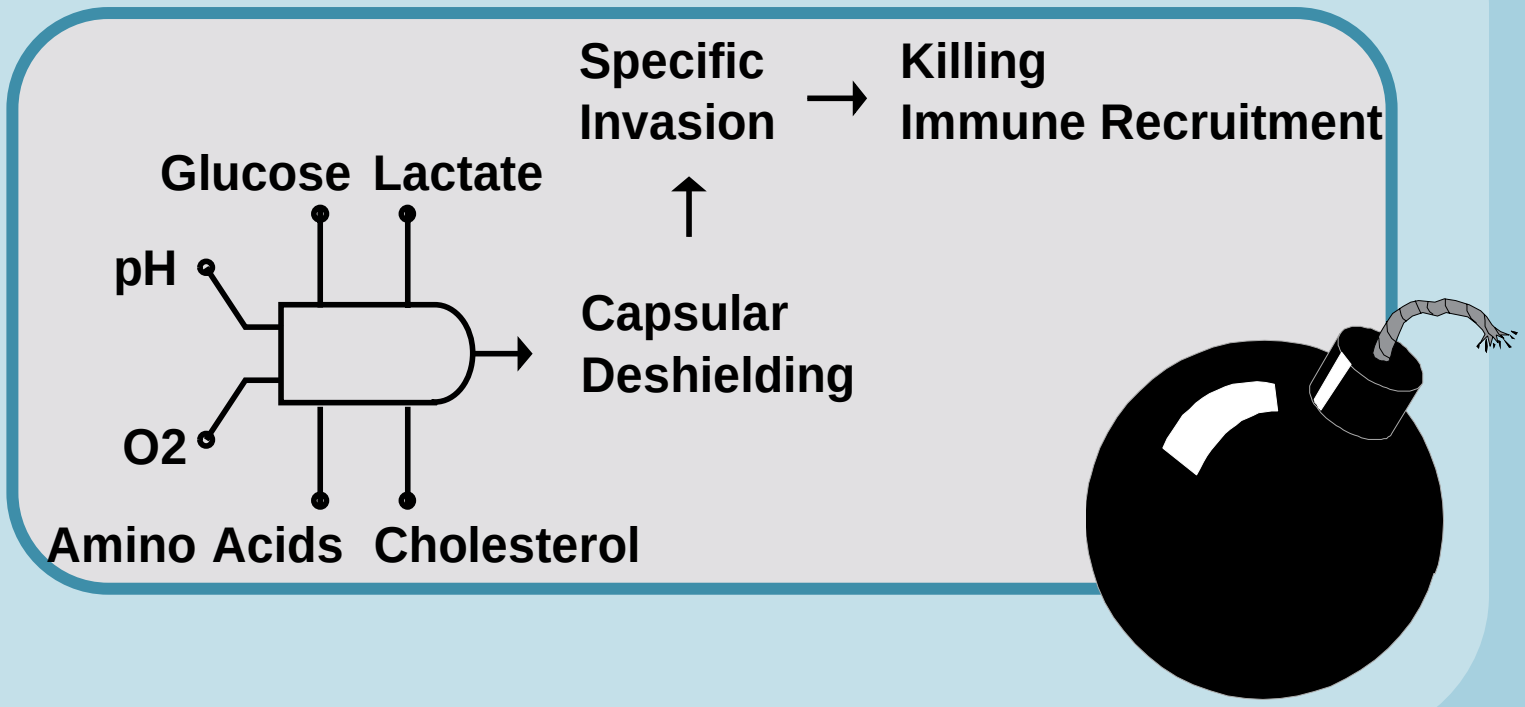
Size	Phenotype	Marker
720 bp	Iron starvation	*CmR*

In vitro characterization

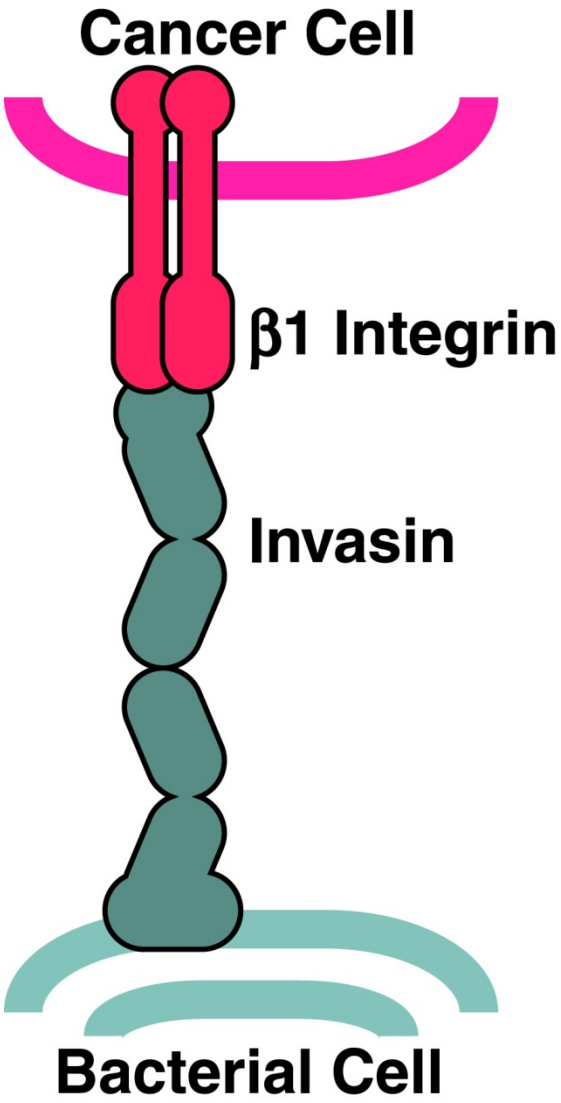
Growth in heat-killed serum supplemented with a high-affinity iron source such as hemin

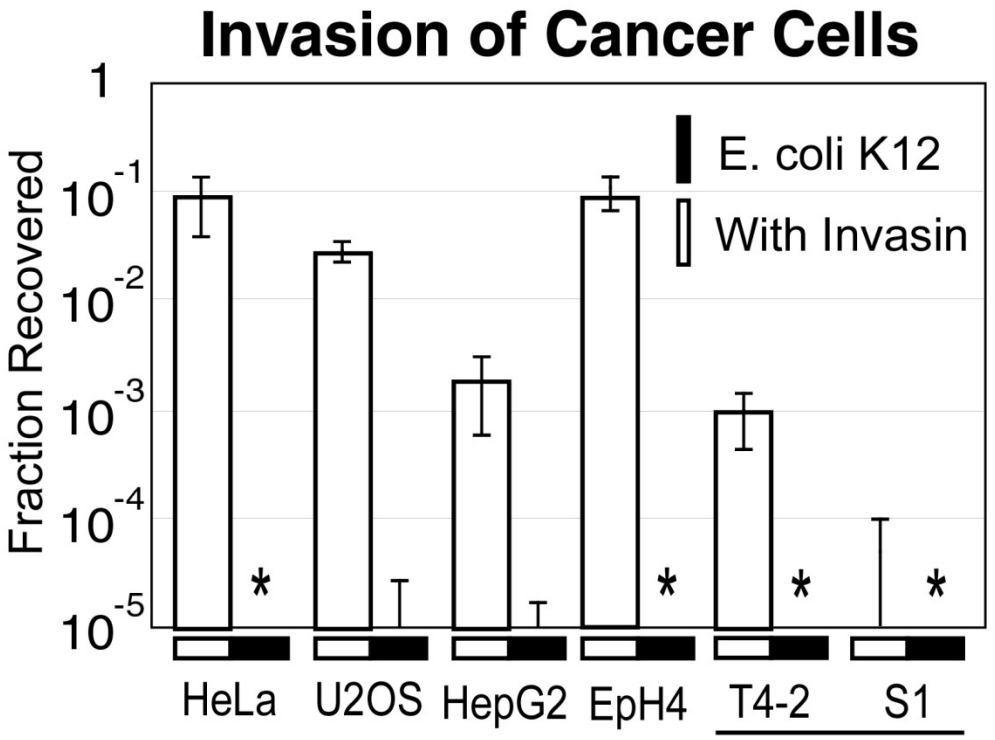


The Target System



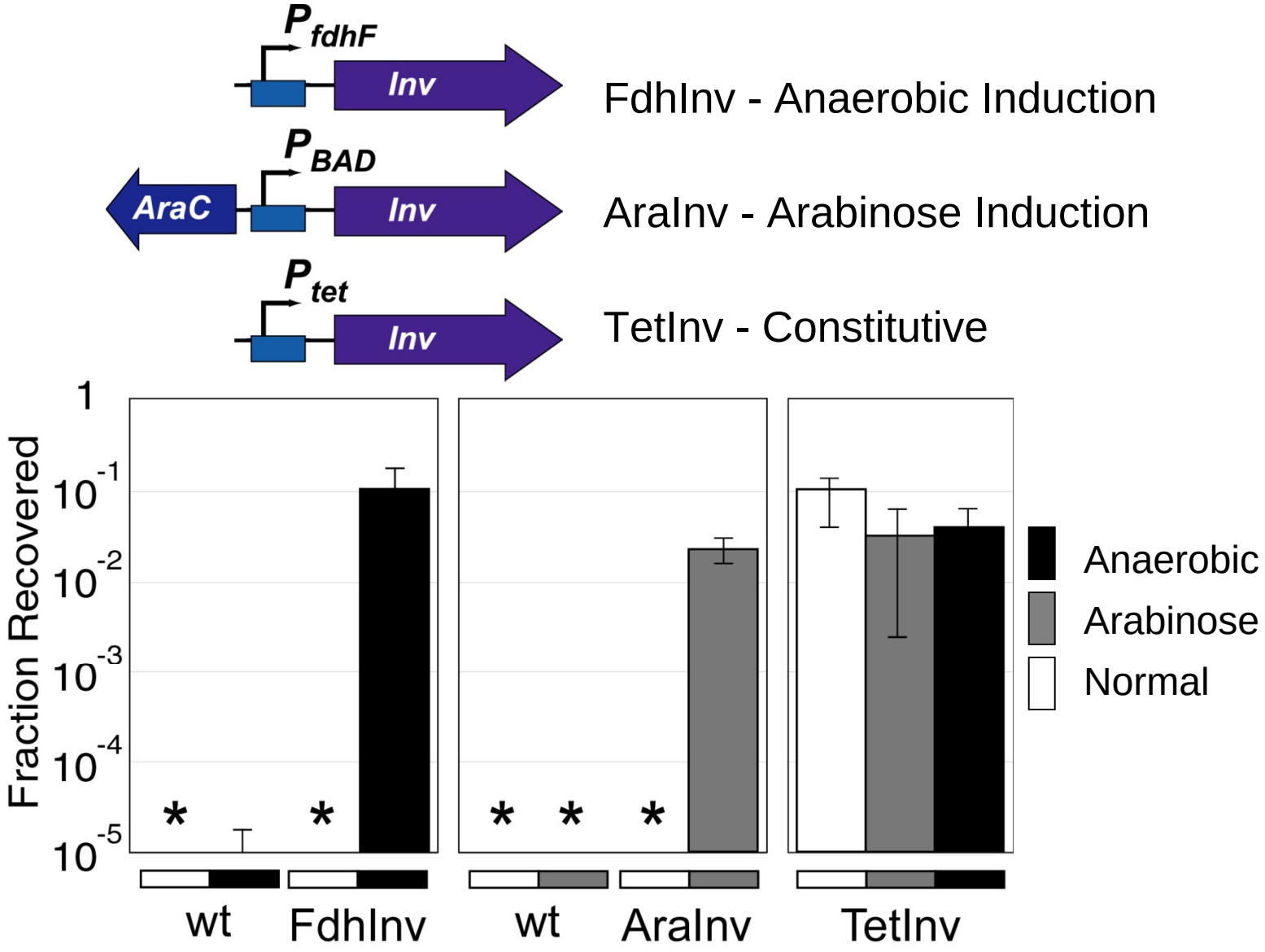
The Invasion Device



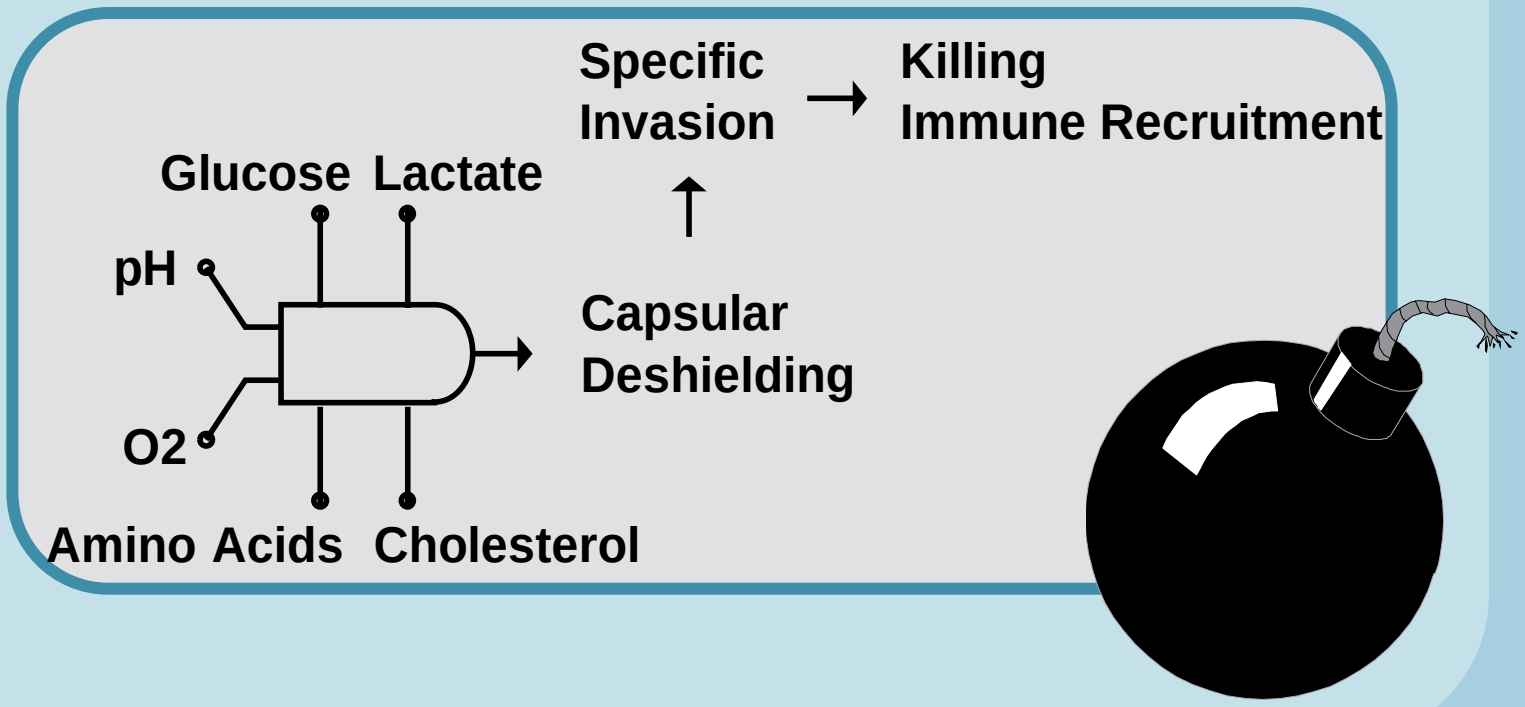


HeLa	Cervical Carcinoma
U2OS	Osteosarcoma
HepG2	Hepatocarcinoma
HMT3522	Breast Epithelial Cells

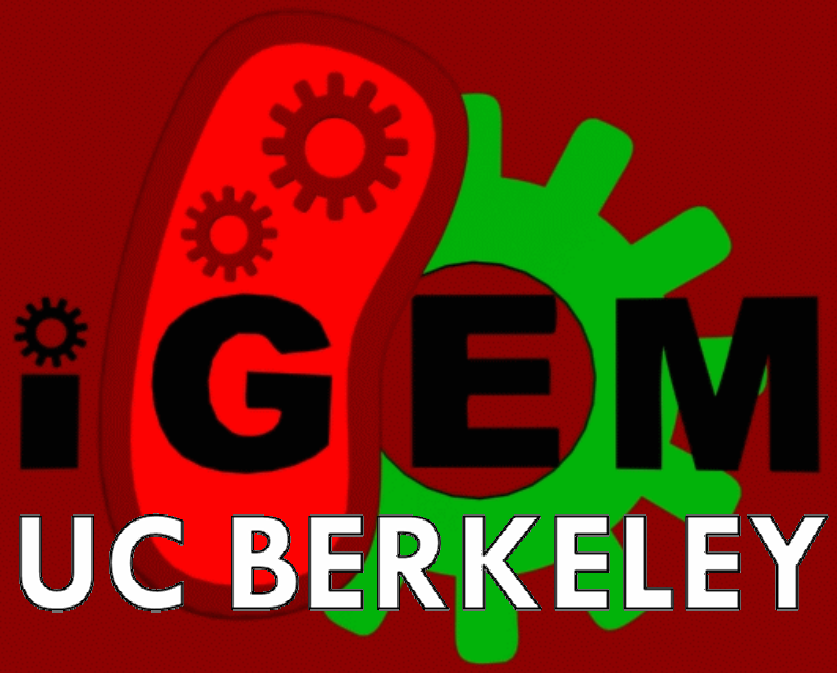
The Invasion Device



The Target System



BACTOBLOOD



Researchers

Arthur Yu • Austin Day • David Tulga • Hannah Cole • Kristin Doan • Kristin Fuller • Nhu Nguyen • Samantha Liang • Vaibhavi Umesh • Vincent Parker

Teaching Assistants

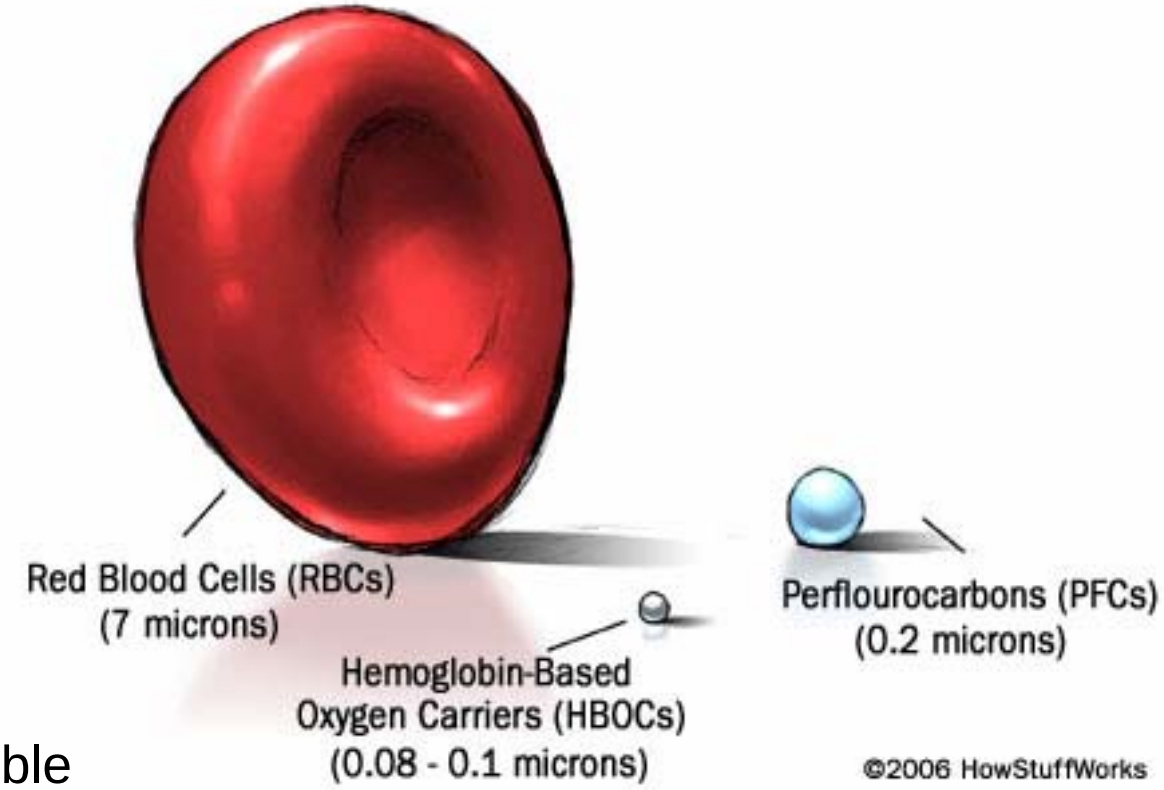
Amin Hajimorad • Farnaz Nowroozi • Rickey Bonds

Advisors

John Dueber • Christopher Anderson • Adam Arkin • Jay Keasling

Creating a Red Blood Cell Substitute

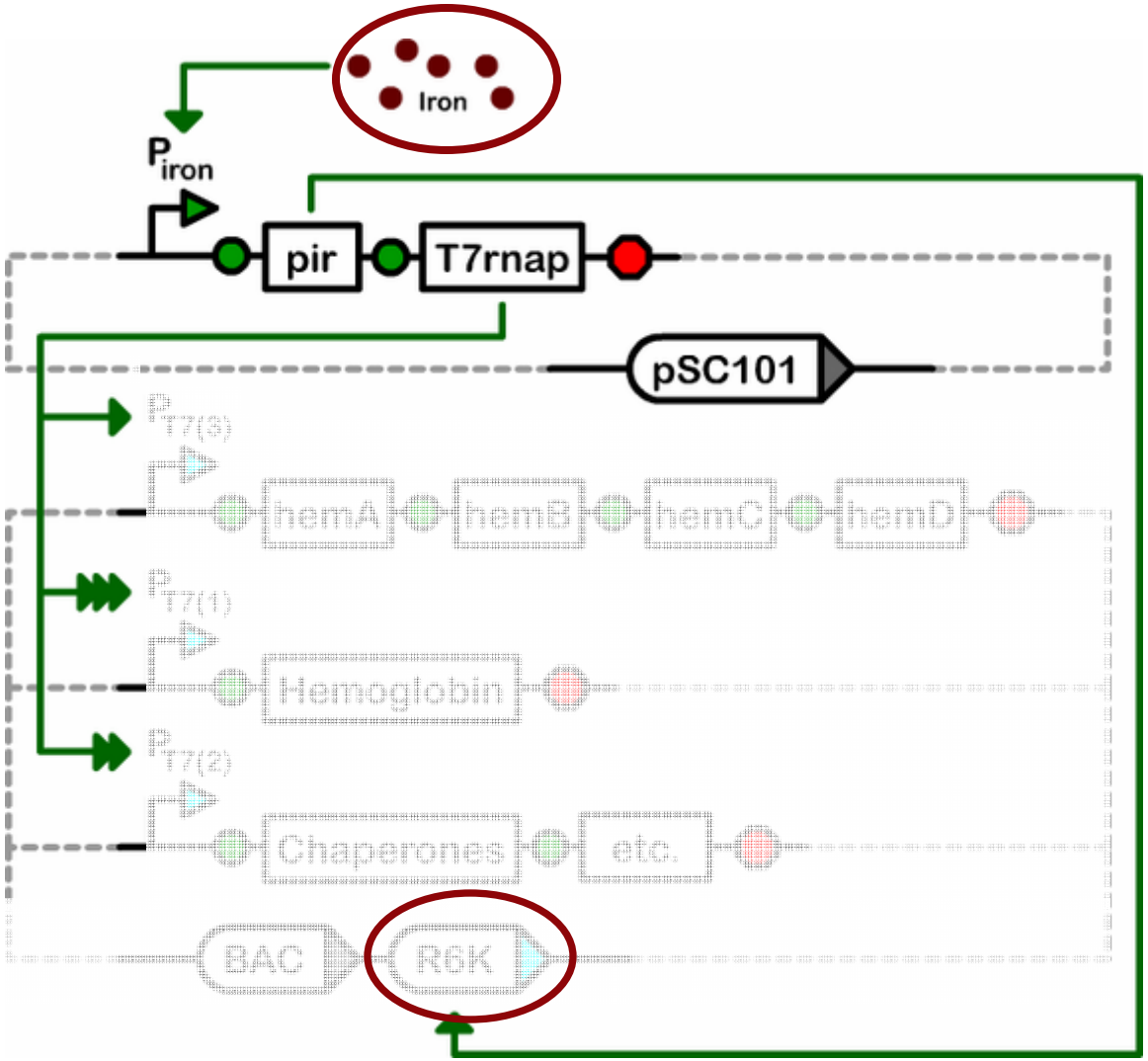
Artificial Blood Substitutes



The Need

- Universally compatible
- Disease-free
- Inexpensive
- Ability to be stored for a prolonged period
- Rapid production in emergency situations

Bactoblood Devices



Bactoblood Culture

Lyophilized Bactoblood

http://parts.mit.edu/igem07/index.php/Berkeley_UC

Why do we do this?

Therapeutic bacteria represent a “grand goal” that challenges the conceptual and experiment toolkit for synthetic biology

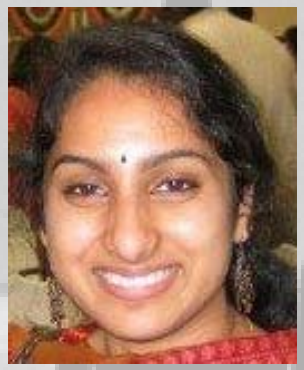
Identify the foundational limitations to making systems on the level of complexity of natural organisms

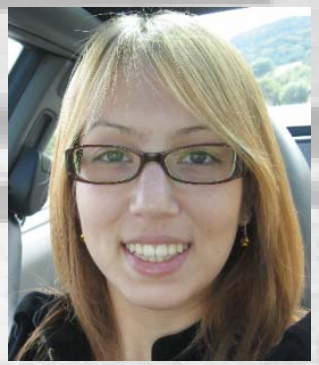
Demonstrates how complex biological activities can be reduced to simpler engineering tasks

Building the foundation for an engineering discipline for biological therapeutics based on modularity, standardization, and engineering for safety

Acknowledgements







Josh Kittleson
Jin Huh
Samantha Liang
Madhvi Venkatesh
Austin Day
Janna Serbo
David Tulga
Berkeley iGEM 2008

Adam Arkin (UCB)
Christopher Voigt (UCSF)
Jay Keasling (UCB)
John Dueber (UCB)

The Camille & Henry Dreyfus Foundation, Inc.

SynBERC
Synthetic Biology Engineering Research Center