Engineering bacteria to target antibiotic resistant and cancer-associated pathogenic microbial species

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1. Introduction

- Bacteria have a profound effect inside the human body.
- Several human-colonising **bacteria species are associated with the development of patient disease**.
- As antibiotics become increasingly less effective, **new methods of specifically targeting pathogenic bacteria are needed**.

2. Background: *heroes & villains*

Villains: Antibiotic resistance & Cancer microbiome

- **Antibiotic resistance is becoming increasingly prevelant** worldwide, leading to deaths from previously treatable diseases.
- We are now also aware that **bacteria can colonise human tumours**, and may affect cancer prognosis, progression and treatment.
- Both cancer and antibiotic resistance lead to thousands of deaths.

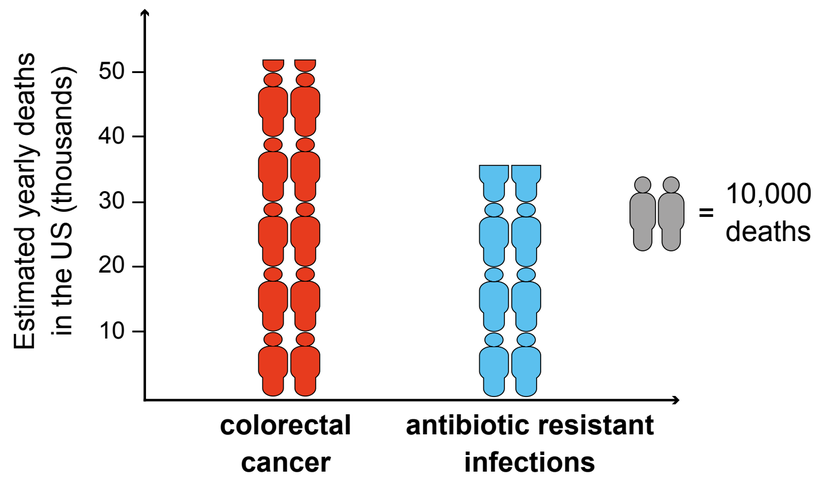

Figure 1: *Annual estimated deaths in the US alone, linked to colorectal cancer and antiobiotic resistant infections.*

Heroes: Bacteriocins

- Bacteriocins are small proteins produced by bacteria.
- They display **targeted anti-microbial activity** against specific bacteria.
- Currently they are used in the food industry to prevent food spoilage.
- With help from our industrial partners (Syngulon, Belgium), we hope to use them to **target pathogenic species in the body**.

3. Our system

- ***Escherichia coli* Nissle is a bacterial probiotic**, widely used in microbiome engineering studies.
- We will engineer *E. coli* Nissle for the **production of bacteriocins**.
- We are developing **two methods for the bacteriocins to be released**, so that they can kill our target bacteria:

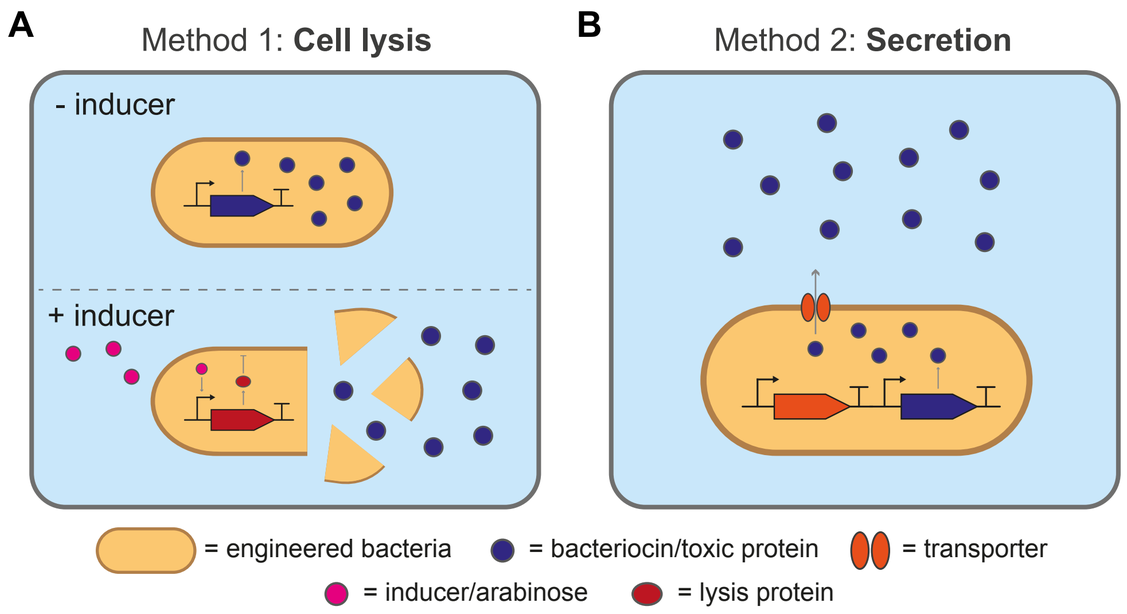

Figure 2: *The two proposed systems for bacteriocin release: (**A**)* Cells produce the bacteriocins internally *and then are lysed to release them into the local environment, (**B**) Bacteriocins are produced in the presence of an accompanying secretion system that is able to transport them out of the cell.*

4. Applications

Problem A: **Antibiotic resistance**

- Antibiotics can be used to treat infections in the body.
- However, their use has led to the **emergence of bacterial species that are resistant** to even the most potent antibiotics.
- In addition, **antibiotics often affect a wide range of bacteria**, killing 'good bacteria' and allowing the **growth of opportunistic pathogens**.
- Bacteriocins offer an alternative to target specific bacteria.

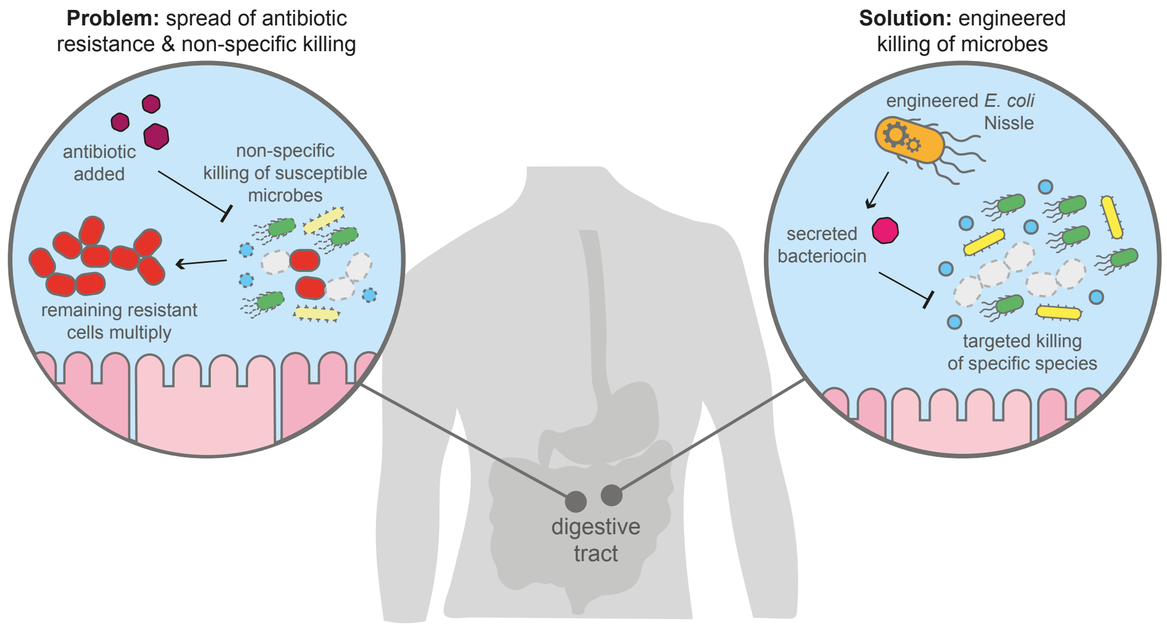

Figure 3: *Antibiotics may inadvertently target 'good bacteria' and allow the spread of antibiotic resistant microbes. Engineered bacteriocin production can be used to specifically target only pathogenic bacteria.*

Problem B: **Cancer-associated microbes**

- Bacterial **species are able to colonise and grow within** the micro-environment of **human tumours**.
- Some species, such as *E. faecalis* (which is often antibiotic resistant), are linked to poor cancer prognosis.
- These species can be **difficult to target via traditional therapies**.
- We hope to use our engineered system as an adjuvant therapy, to help **target and kill these pathogenic species**.

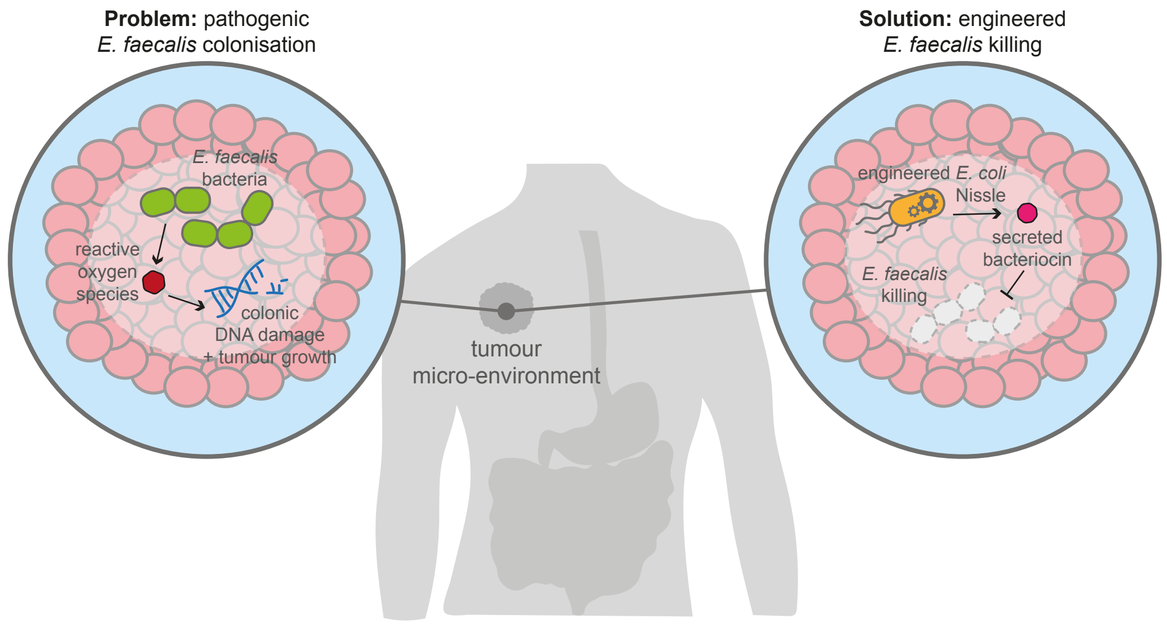

Figure 4: E. faecalis *is suspected of damaging host cell DNA, promoting tumour growth. Engineered bacteria, placed within the tumour micro-environment, can target pathogenic strains via bacteriocin activity.*

5. Outlook: *potential new therapies?*

- **Bacteriocin-secreting probiotic bacteria** are a promising method for **killing specific bacterial species**.
- To realise this potential **systems capable of producing bacteriocins in different environments are needed**.
- This research is still in its early stages and **systems will need to be tested *in vivo*** before their clinical potential can be assessed.

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References:

[1] Yang *et. al* (2014), Frontiers in Microbiology, doi:10.3389/fmicb.2014.00241.
[2] Geldart *et. al* (2018), Bioengineering and Translational Medicine, doi:10.1002/btm2.10107.