Engineering Bacteria as Living Therapeutics in Cancer Therapy

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Outline

1. Introduction
2. Rationale for Bacterial Therapy
3. Tumor-Targeting Mechanisms
4. Engineered Systems and Examples
5. Safety and Challenges
6. Clinical Trials and Future Prospects

Why do we need new cancer therapies?



Non-selective action

Drugs hit cancerous and healthy cells alike, causing systemic toxicity and severe side effects



Organ damage

Long-term or even irreversible damage to organs is possible



Drug resistance

Resistance lowers efficacy, causing treatment failure and shorter survival

≈ 9 million

cancer deaths worldwide every year

The goal :

high precision, fewer side effects, and the ability to overcome drug resistance

Why bacteria?

They stimulate immunity

Bacteria can trigger and amplify antitumor immune responses

They favor tumors

They prefer the hypoxic, immunosuppressive tumor microenvironment and colonize resistant regions

They make metabolites

Bacterial metabolites act directly on tumor cells and remodel the microenvironment

up to 10,000×

higher bacterial concentration in tumors than in normal tissue



Focus of this review

Earlier reviews

Bacterial derivatives and non-living systems

- Outer membrane vesicles (OMVs)
- Biohybrid platforms
- Nanoparticles
- Delivery strategies
- Focus on material-based carriers

This review

Living bacterial therapeutics

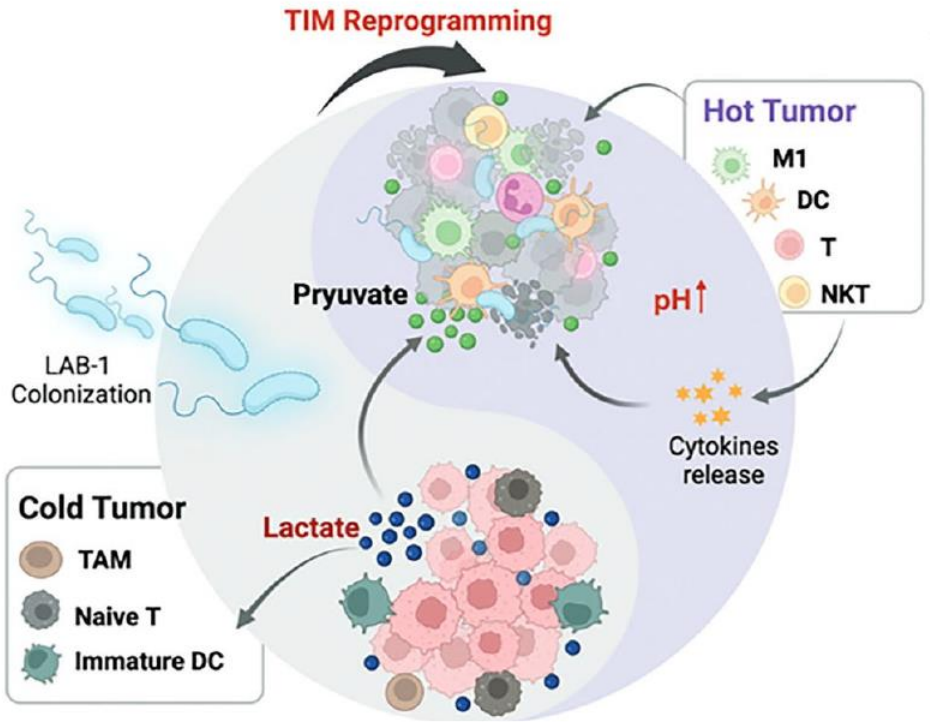
- Dynamic, stimulus-responsive design
- Integrative immune engineering
- Programmable, tumor-adaptive therapies
- Complements the existing literature with new perspectives

Tumor targeting: natural strains

The tumor microenvironment is hypoxic, acidic and immunosuppressive; some bacteria naturally accumulate in it.

R. palustris LAB-1

- Grows in hypoxic, lactate-rich tumor regions
- Consumes lactate as a carbon source
- Eases immunosuppression and slows tumor growth

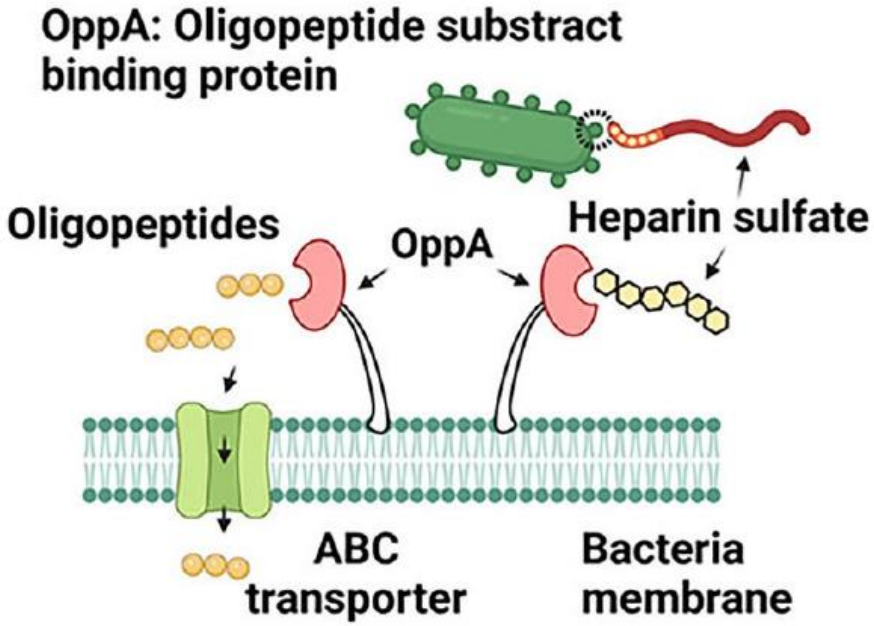


Selective accumulation without engineering: chemotaxis, hypoxia and low-pH tolerance

Tumor targeting: natural strains

L. plantarum WCFS1

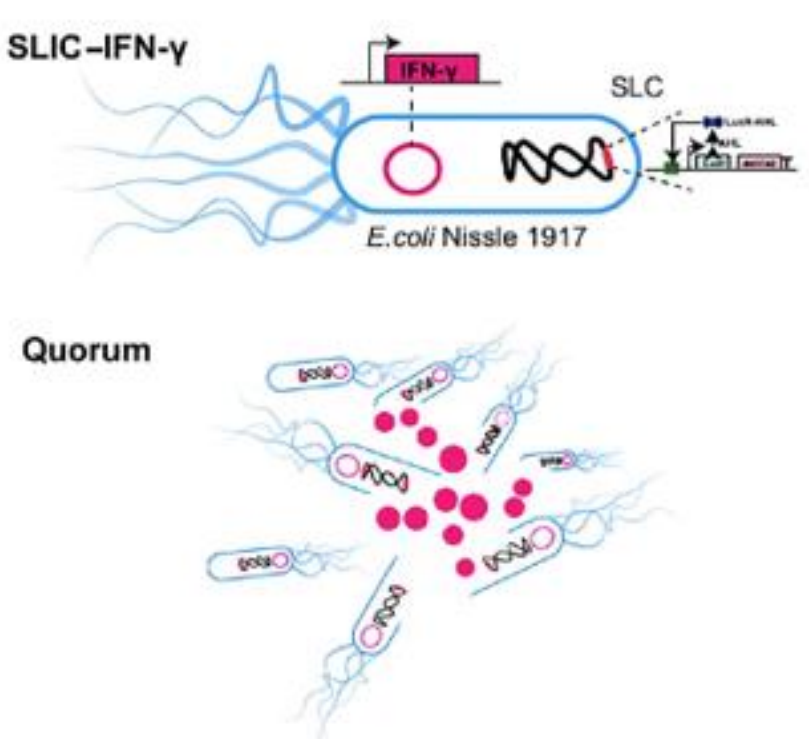
- OppA binds heparan sulfate on NPC cells
- ROS in the TME activates the prodrug TL-SN
- Up to 67% tumor inhibition



Tumor targeting: natural strains

E. coli Nissle 1917

- Quorum-sensing synchronized lysis circuit (SLIC)
- Releases IFN-γ and PAMPs in MC38 and CT26 models
- Avoids systemic IFN-γ inflammation

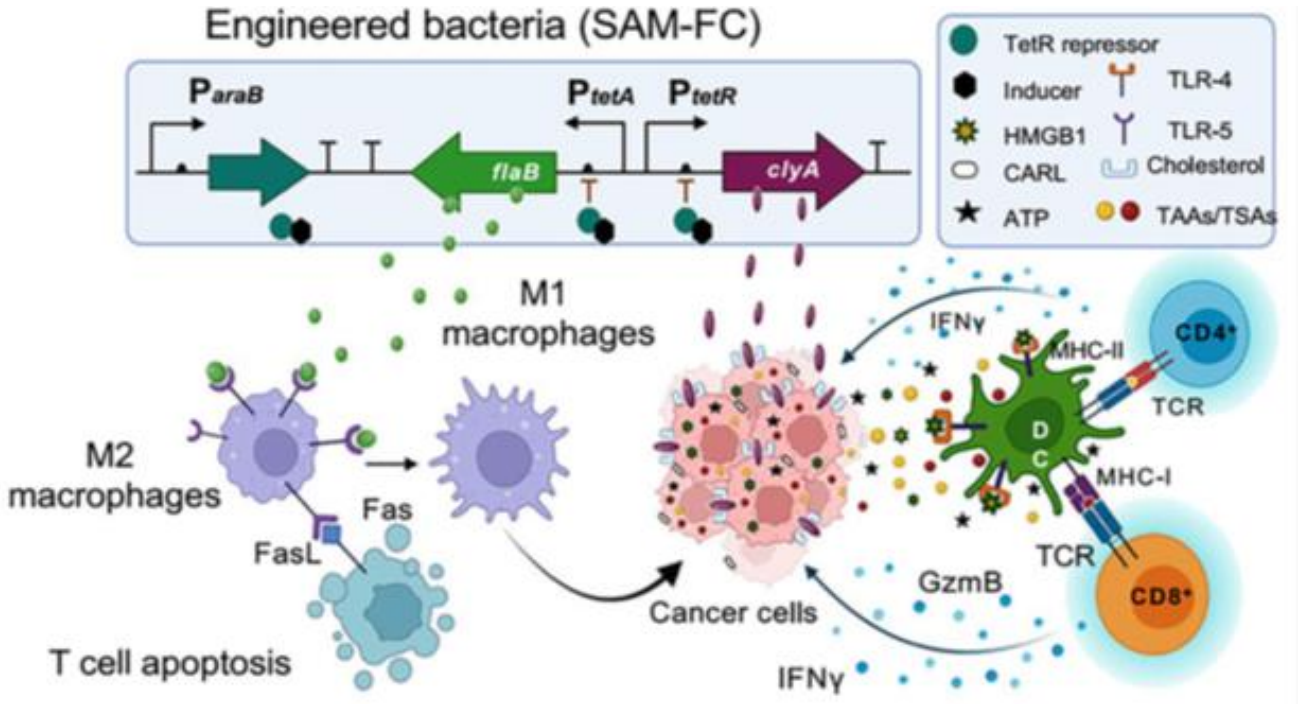


Engineering strategies for precision and safety

Virulence attenuation

S. typhimurium SAM-FC with a tetracycline-inducible system for ClyA and FlaB

Complete tumor regression in 75–80% of cases

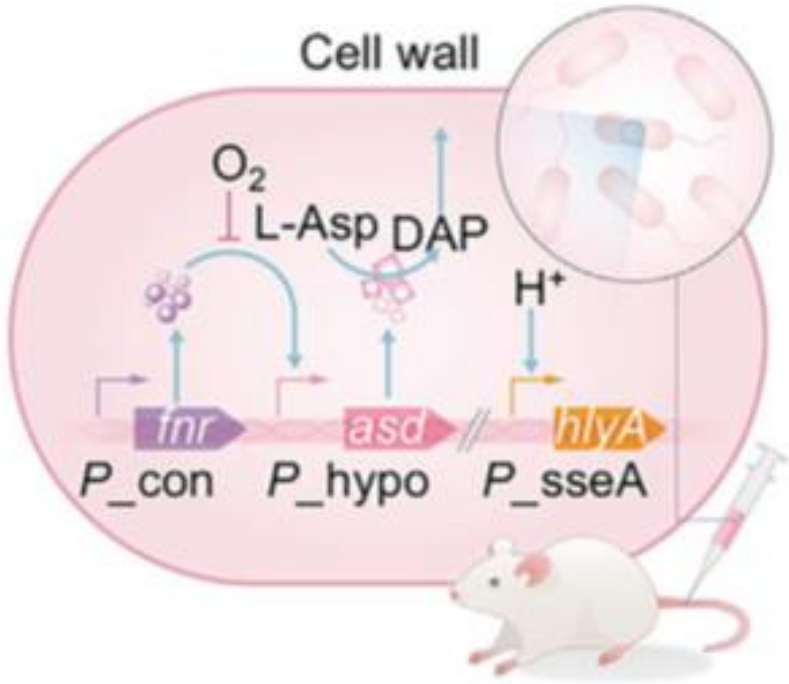


Engineering strategies for precision and safety

Hypoxia-responsive circuits

S. typhimurium DB1 with asd under the Phypo promoter; rapidly cleared from normoxic tissue

Tumor inhibition in bladder, melanoma and colorectal models

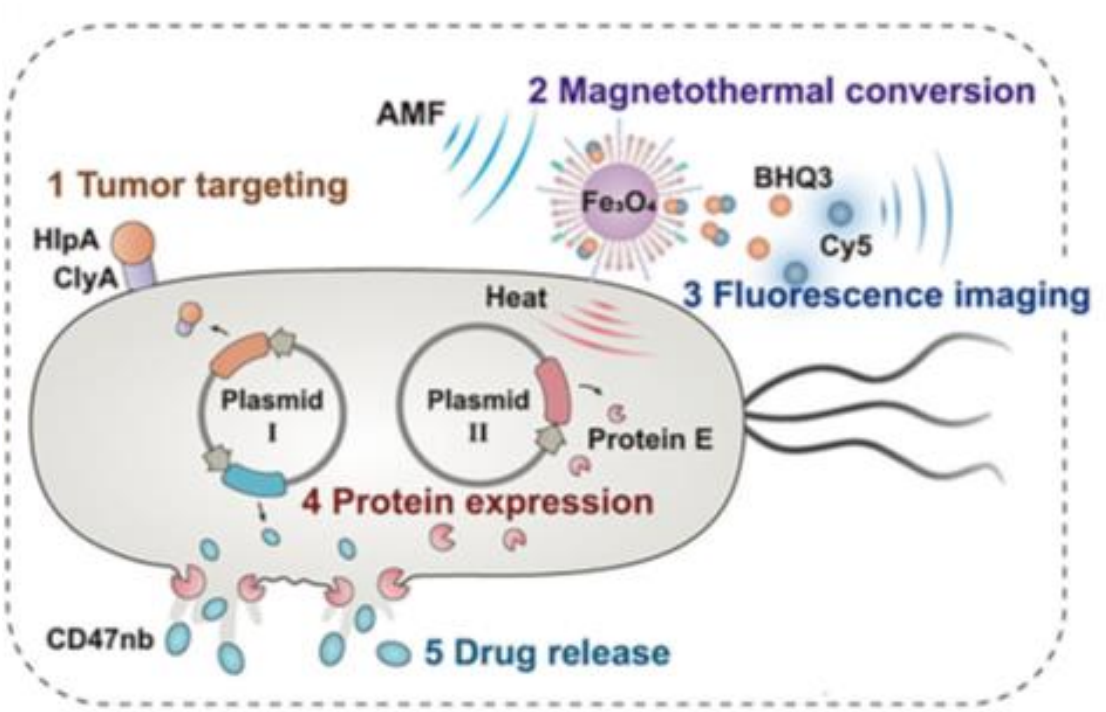


Engineering strategies for precision and safety

Synthetic targeting ligands

E. coli MG1655 displays HlpA to bind HSPG and carries a CD47 nanobody

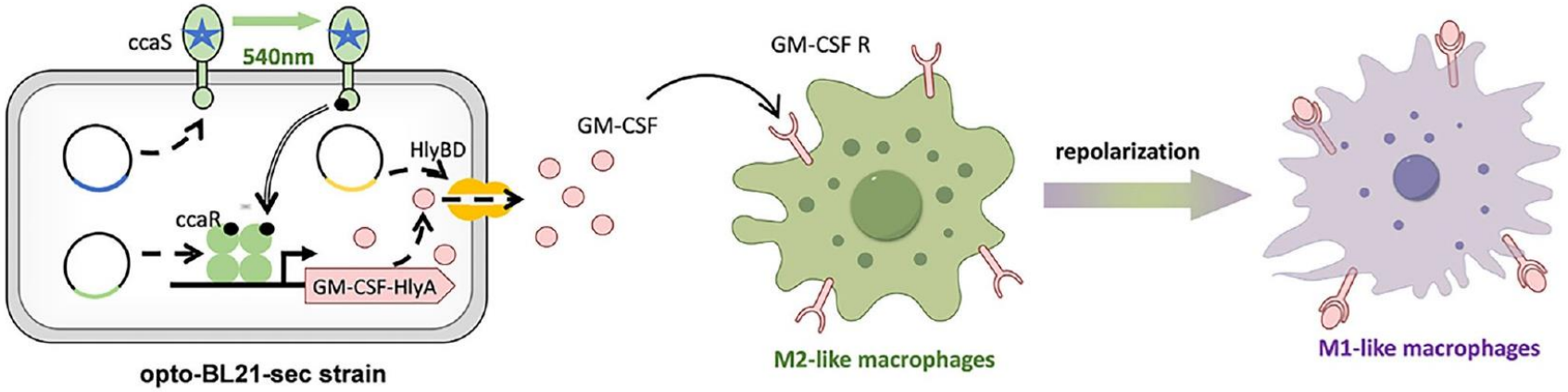
Up to 94.7% tumor inhibition in a colorectal model



Remodeling the tumor microenvironment

Light-controlled macrophage repolarization

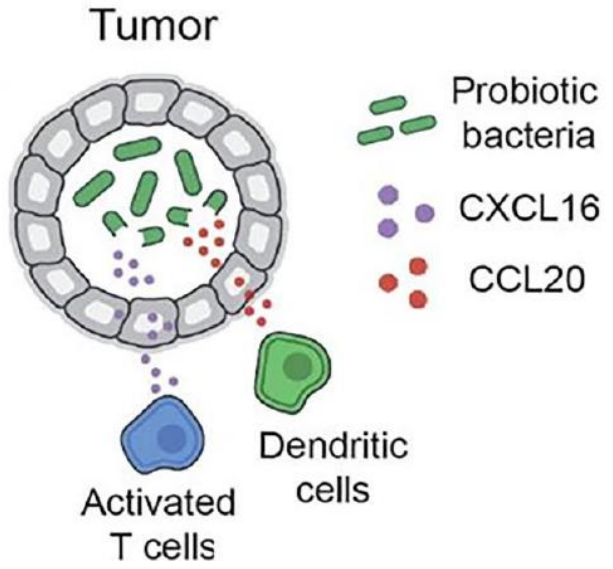
- E. coli BL21-sec with the ccaS/ccaR optogenetic system
- Green light at 540 nm induces GM-CSF secretion
- TAMs switch from immunosuppressive M2 to inflammatory M1
- Tumor growth inhibited in the 4T1 model



Remodeling the tumor microenvironment

Recruiting cells into cold tumors

- Cold tumors have few infiltrating T cells and respond poorly to PD-1/PD-L1 blockade
- EcN with SLC releases the chemokines CXCL16 and CCL20
- Recruits CD8+ T cells and precursor DCs; IFN-γ and granzyme B rise

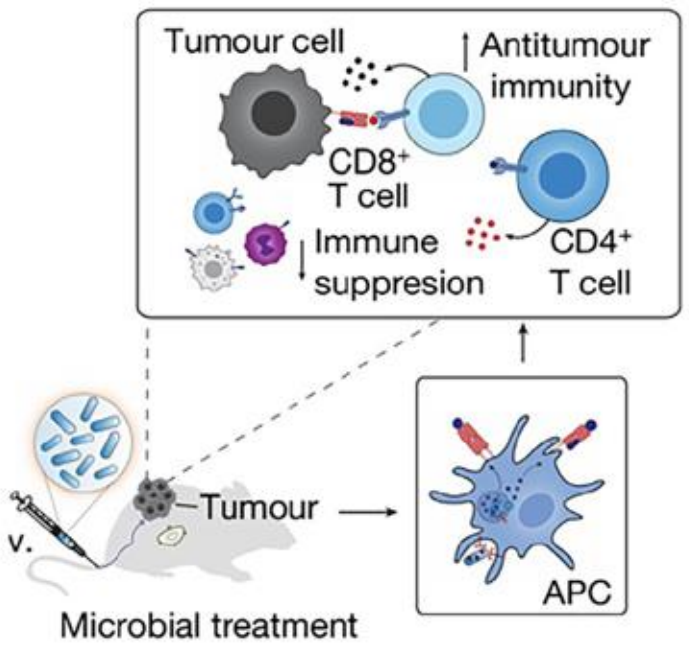


Activating antigen-specific immunity

Bacteria express neoantigens → **Antigen-presenting cells** → **Tumor-specific CD8+ and CD4+ T cells** → **Durable immune memory**

Live vaccine based on EcN

- Expresses neoantigen peptides from tumor-specific mutations (Redenti et al.)
- Given intravenously in CT26 and B16F10 models
- Activates T cells via MHC-I and MHC-II, with a Th1 response



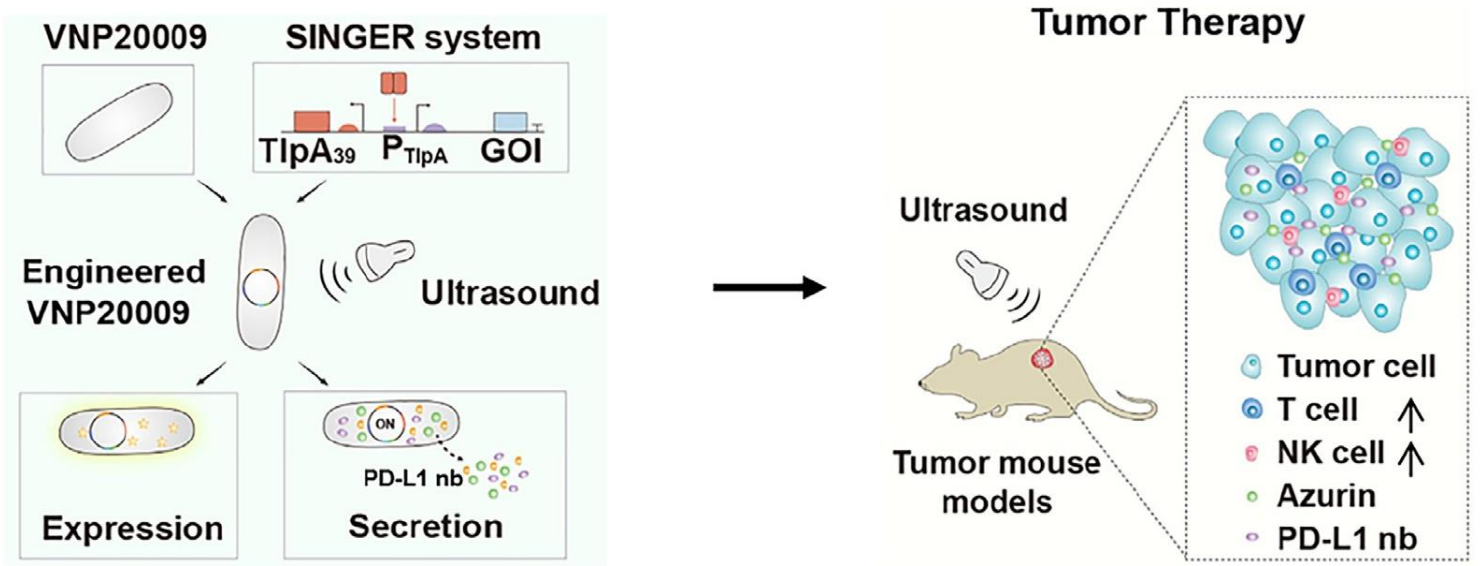
Blocking immune evasion: the PD-L1/PD-1 axis

Tumors raise PD-L1 to exhaust T cells; bacteria can release the blocking agent right at the tumor.

Gao et al.

Sonogenetic S. typhimurium VNP20009

Low-intensity pulsed ultrasound induces anti-PD-L1 nanobody expression in the tumor



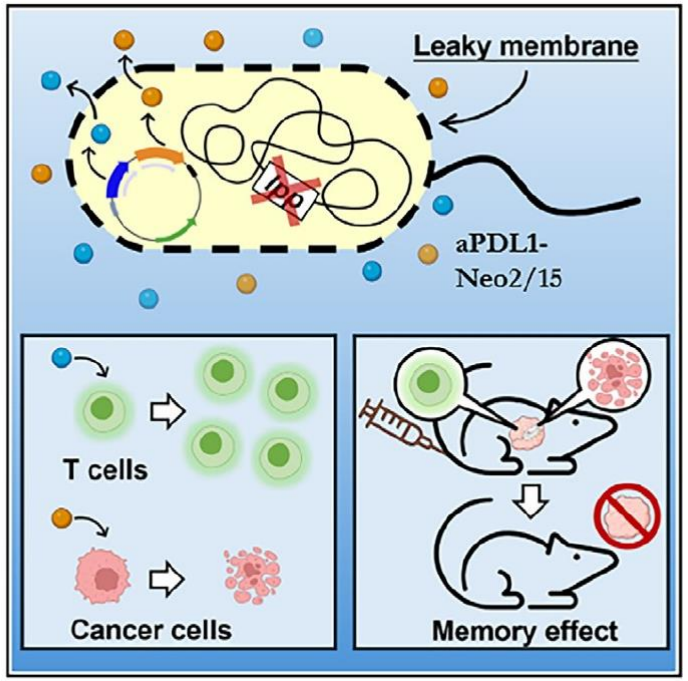
Blocking immune evasion: the PD-L1/PD-1 axis

Tumors raise PD-L1 to exhaust T cells; bacteria can release the blocking agent right at the tumor.

Liu et al.

EcNΔlpp-CIOP with a leaky outer membrane

Releases aPDL1-Neo2/15, improving CD8+ T cell function and inhibiting tumors



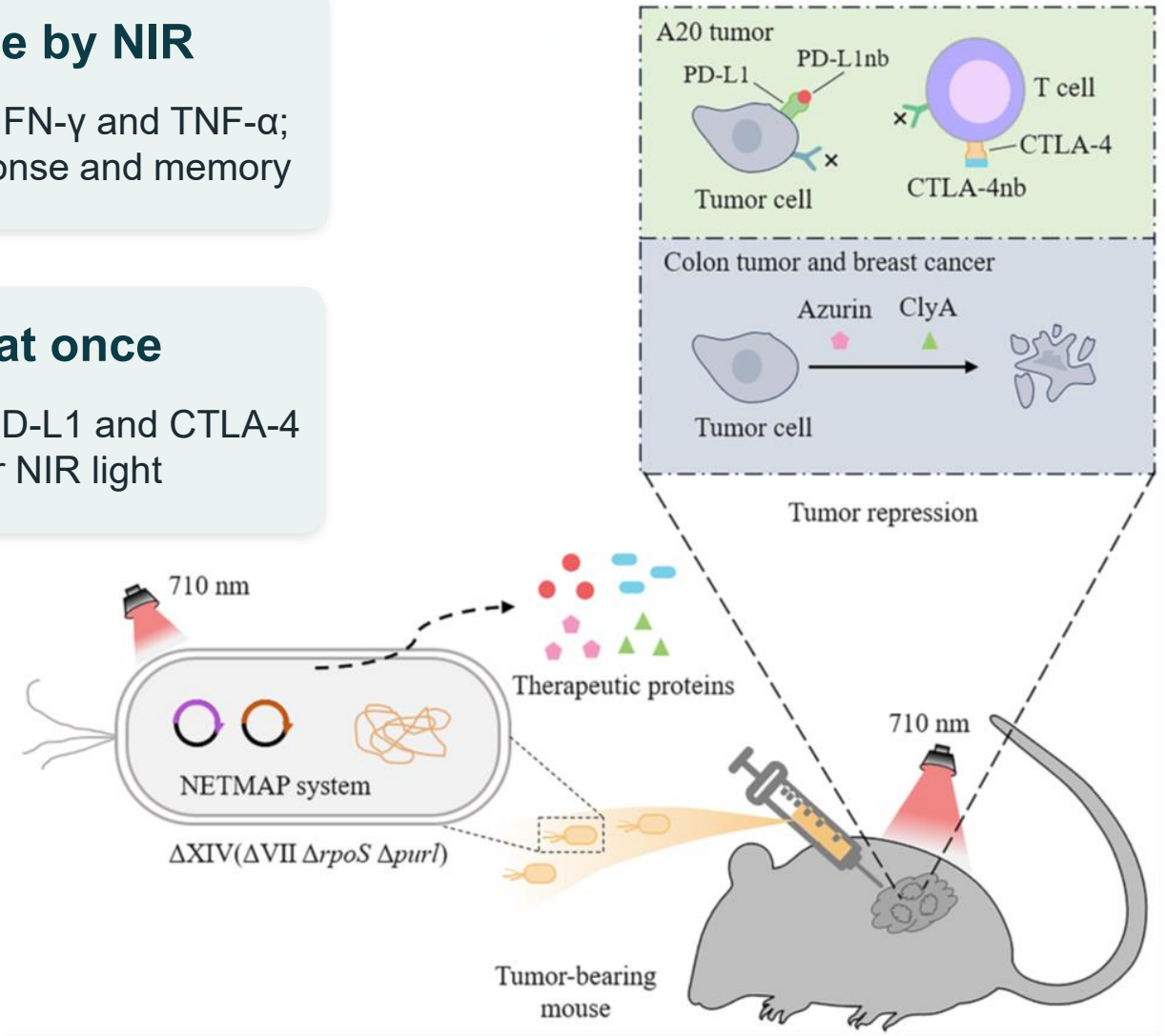
Combination therapy: multi-agent blockade

Dual checkpoint blockade by NIR

S. enteritidis : more CD8+ T, NK, IFN-γ and TNF-α; fewer Tregs and M2; distant response and memory

NETMAP: several agents at once

S. enteritidis 3934 ΔXIV secretes PD-L1 and CTLA-4 nanobodies, azurin and ClyA under NIR light



Challenges for clinical translation

Safety vs. immunogenicity

LPS activates TLR4; rising IL-10 can impair DC maturation and T cell activation

Dose control

Live, replicating bacteria make precise dosing difficult

Variable outcomes

Competition with native microbiota and differences in host immune memory

Long-term risks

Systemic infection, chronic inflammation and excessive immune activation

Safety strategies and manufacturing



Safety strategies

- Attenuate virulence by deleting pathogenicity genes
- Biocontainment with inducible “suicide” circuits that clear bacteria after delivery
- Engineered polysaccharide capsules temporarily mask antigens and reduce unwanted immune responses



GMP manufacturing

- Live bacteria cannot be terminally sterilized by heat or filtration
- Production must be aseptic with strict contamination control
- Genetic stability, uniform bioactivity and correct dose must hold across every batch

Early clinical evidence

SYNB1891

Engineered E. coli Nissle 1917 that produces a STING agonist under hypoxia

- Phase I (NCT04167137)
- Intratumoral injection, alone or with atezolizumab
- Well tolerated; activated STING signaling and T cell responses in patients with advanced malignancies

VNP20009

Attenuated S. typhimurium in patients with metastatic melanoma

- Intravenous administration
- Tumor colonization
- Systemic cytokine response

Reference

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Thank you

Questions?