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MICROBIAL ALLIES: HARNESSING BACTERIA IN THE FIGHT AGAINST CANCER

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Article Info

Abstract

Cancer remains a leading cause of global mortality, and despite advances in chemotherapy, radiotherapy, and immunotherapy. The therapeutic resistance and tumor recurrence continue to limit treatment success. Recent innovations in microbiology and synthetic biology have reinvigorated interest in bacteria as potential allies in oncology. In this study, three bacterial strain were evaluated as engineered Escherichia coli, attenuated Salmonella typhimurium, and spore-forming Clostridium novyi-NT—as experimental therapeutic agents against murine models of breast (4T1) and colorectal (CT26) cancers. The strains were engineered or attenuated to enhance tumor specificity and minimize systemic toxicity. Tumor-bearing mice were randomized into treatment groups receiving bacterial monotherapy, combination with checkpoint inhibitors, or controls. The results showed that all bacterial strains preferentially colonized hypoxic tumor regions and reduced tumor volumes, thereby prolonged survival compared to controls, with E. coli were achieved the most pronounced synergistic effect when combined with anti-PD-1 therapy. Immune profiling revealed significant infiltration of CD8+ T cells, NK cells, and activated macrophages in treated tumors, indicating strong immunostimulatory effects. While Clostridium showed rapid tumor necrosis, in which the toxicity management remained a challenge. In overall, this study demonstrates the therapeutic potential of harnessing bacteria in cancer treatment and highlights the need for strain-specific optimization to maximize efficacy and minimize risks.

Keywords:
Cancer, Clostridium, Bacteria, Immunotherapy, Salmonella.

INTRODUCTION

Cancer is one of the most pressing health challenges of the 21st century, accounting for nearly 10 million deaths worldwide in 2020 alone (WHO, 2021). Despite the development of improved diagnostic tools and therapeutic interventions, many cancers remain incurable at advanced stages, particularly when tumors become resistant to conventional therapies. Standard treatments such as chemotherapy and radiotherapy often lack selectivity, damaging healthy tissues and leading to severe side effects. Immunotherapies such as immune checkpoint inhibitors and CAR-T cell therapy have revolutionized cancer treatment but are not universally effective, with many patients experiencing relapse or failing to respond altogether (Sharma et al., 2022).

These limitations underscore the urgent need for novel therapeutic strategies that can target tumors more specifically, overcome drug resistance, and stimulate durable antitumor immunity. One emerging and unconventional approach is the use of bacteria as therapeutic agents against cancer. The concept of using bacteria in cancer treatment is not new. In the late 19th century, William Coley observed that cancer patients who developed bacterial infections occasionally experienced spontaneous tumor regression. He subsequently developed "Coley's toxins," a mixture of heat-killed Streptococcus pyogenes and Serratia marcescens, which showed some therapeutic benefit but fell out of favor due to inconsistent results and safety concerns (McCarthy, 2006). With the advent of antibiotics and more refined cancer therapies, bacterial approaches were largely abandoned until the resurgence of interest driven by advances in molecular biology, immunology, and genetic engineering. Today, the ability to attenuate pathogens, engineer genetic circuits, and control bacterial behavior in vivo has made bacteria viable candidates for cancer therapy once again (Forbes, 2010; Din et al., 2016)

Bacteria possess several inherent properties that make them attractive for cancer therapy:

Tumor Targeting: Certain anaerobic or facultative anaerobic bacteria preferentially colonize hypoxic and necrotic tumor regions that are poorly accessible to chemotherapeutic drugs (Dang et al., 2020)..

Direct Tumoricidal Activity: Bacteria can induce tumor cell death by releasing toxins, enzymes, or metabolic byproducts.

Immunostimulatory Capacity: Bacterial components such as lipopolysaccharides (LPS), flagellin, and unmethylated CpG DNA act as pathogen-associated molecular patterns (PAMPs), triggering innate and adaptive immune responses (Chowdhury et al., 2019).

Therapeutic Payload Delivery: Advances in synthetic biology enable bacteria to be engineered as "living vectors" for the localized delivery of cytokines, prodrug-converting enzymes, or nanobodies directly within the tumor microenvironment (Din et al., 2016).

Synergy with Existing Therapies: Bacterial therapies can enhance the efficacy of immune checkpoint inhibitors, radiotherapy, and chemotherapy by reshaping the tumor microenvironment (Shi et al., 2022). A wide range of bacterial species have been investigated for anticancer potential, including:

Escherichia coli: Non-pathogenic strains can be engineered with lysis circuits and therapeutic genes for controlled drug release. Salmonella typhimurium: Attenuated strains such as VNP20009 preferentially localize to tumors, though clinical translation remains challenging (Zheng et al., 2017). Clostridium novyi-NT: Obligate anaerobes that germinate in necrotic tumor cores, causing extensive oncolysis but sometimes excessive toxicity (Roberts et al., 2014). Listeria monocytogenes: Used as vectors for cancer vaccines due to their strong antigen presentation capabilities. Bifidobacterium spp.: Considered safer probiotics that can modulate host immunity and synergize with checkpoint blockade. In this study focused on three representative species—engineered E. coli, attenuated Salmonella, and Clostridium novyi-NT—as models for evaluating efficacy, immune response, and toxicity in murine cancer models.

Study Rationale and Objectives

Although preclinical and early clinical studies have demonstrated the potential of bacteria as anticancer agents, comparative studies assessing multiple strains under standardized conditions remain limited. Furthermore, little is known about how different bacterial platforms compare in terms of tumor regression, immune activation, and systemic safety.

The present study was designed with the following objectives:

1. To evaluate and compare the anticancer efficacy of engineered E. coli, attenuated Salmonella, and Clostridium novyi-NT in murine breast and colorectal cancer models.
2. To assess the immune responses triggered by bacterial therapies, with particular focus on T cell infiltration and activation.
3. To examine the safety and toxicity profiles of the bacterial strains
4. To determine the potential synergy with immune checkpoint blockade (anti-PD-1 therapy).

Materials and Methods

Study Design

This study was conducted as a controlled laboratory experiment comparing the therapeutic efficacy of three bacterial strains—engineered Escherichia coli, attenuated Salmonella typhimurium VNP20009, and Clostridium novyi-NT spores—in murine cancer models. Two tumor models were selected: 4T1 murine breast carcinoma and CT26 murine colorectal carcinoma. The study included bacterial monotherapies, combination with immune checkpoint blockade (anti-PD-1 antibody), and untreated controls. All experiments were performed in triplicate cohorts to ensure reproducibility.

Bacterial Strains and Engineering

A non-pathogenic E. coli Nissle 1917 strain was used as the backbone. The strain was engineered with a synchronized lysis circuit (SLC) under quorum-sensing control. A gene encoding a pro-apoptotic peptide (PAP-1) was inserted downstream of the lysis promoter, enabling local release upon bacterial lysis. Plasmids were constructed using Gibson assembly, and stability was verified by PCR and sequencing.**.** Attenuated Salmonella typhimurium VNP20009 strain was selected due to its established tumor-targeting ability. It carries deletions in purI (purine auxotrophy) and msbB (lipid A modification) to reduce systemic

toxicity. Strain identity was confirmed by PCR for purI deletion and LPS profiling.. Clostridium novyi-NT Spore-forming obligate anaerobe lacking the lethal toxin gene (plc). Spores were prepared by anaerobic culturing in reinforced clostridial medium (RCM) and purified by density-gradient centrifugation. Spore viability was assessed by germination assays. All bacterial preparations were tested for endotoxin levels and sterility prior to injection.

Cell Lines and Tumor Models

4T1 breast carcinoma cells and CT26 colorectal carcinoma cells were obtained from the American Type Culture Collection (ATCC) it was collected from udus hospital. Cells were cultured in DMEM supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin, and maintained at 37°C, 5% CO_2. Female BALB/c mice (6–8 weeks old, n = 120 total) were used. Mice were subcutaneously injected in the flank with 1×10^6 tumor cells suspended in 100 µL PBS. Tumors were allowed to grow to ~100 mm^3 before initiating treatment.

Experimental Groups

Mice were randomized into the following groups (n = 10 per group for each tumor model): 1. Control (PBS only) 2. E. coli therap 3. Salmonella therapy 4. Clostridium therapy 5. E. coli + anti-PD-1 antibody 6. Salmonella + anti-PD-1 antibody 7. Clostridium + anti-PD-1 antibody Total: 7 groups × 2 tumor models × 10 mice = 140 mice (20 excluded for health issues).

Treatment Administration

Bacterial Dosing: E. coli: 1×10^6 CFU intratumoral injection once every 3 days for 3 weeks.Salmonella: 1×10^5 CFU intravenous injection weekly for 3 weeks. Clostridium spores: 1×10^7 spores intratumorally injected once at day 0.

Checkpoint Inhibitor: Anti-PD-1 antibody (clone RMP1-14, BioXCell) administered intraperitoneally at 200 µg per mouse every 3 days for 3 weeks.

Tumor Monitoring and Measurement: Tumor volumes were measured every 3 days using calipers and calculated using the formula: V = \frac{L \times W^2}{2} Mice were euthanized when tumor volume exceeded 2000 mm^3 or upon reaching humane endpoints (e.g., >20% body weight loss, ulceration).

Histology and IImmunohistochemistry: Tumor tissues were harvested, formalin-fixed, and paraffin-embedded. Sections were stained with hematoxylin and eosin (H&E) for necrosis assessment. Immunohistochemistry was performed using antibodies against: CD8 (T cells), NKp46 (NK cells), F4/80 (macrophages) Positive cell density was quantified in five random high-power fields (HPFs) per tumor.

Flow Cytometry: Single-cell suspensions were prepared from tumors and spleens. Cells were stained with fluorescent antibodies: CD3, CD8, CD4, FoxP3 (regulatory T cells), CD11b, Gr-1. Flow cytometry was performed using a BD LSRFortessa. Data analyzed with FlowJo v10.

Toxicity and Safety Assessment: Body weight measured twice weekly. Serum samples collected at day 14 and 28 for ALT, AST (liver), BUN, and creatinine (kidney). Cytokine storm risk assessed by ELISA

for IL-6, TNF-α, and IFN-γ. Organs (liver, spleen, lung, kidney) examined histologically for bacterial colonization and inflammation.

Statistical Analysis

Data expressed as mean ± standard deviation (SD). Tumor volumes compared using two-way ANOVA with Bonferroni correction. Survival curves plotted using Kaplan-Meier method, analyzed with log-rank test. Immune cell counts compared using unpaired Student's t-test or one-way ANOVA. $P < 0.05$ considered statistically significant.

Results

1. **Bacteria Preferentially Colonize Tumors:** all three bacterial strains successfully colonized tumor tissues after administration. E. coli localized primarily in hypoxic tumor cores, with minimal presence in healthy organs. Salmonella demonstrated both intratumoral accumulation and low-level persistence in the liver and spleen. Clostridium novyi-NT spores germinated selectively in necrotic tumor regions, producing visible areas of tumor liquefaction. Colony-forming unit (CFU) assays confirmed higher bacterial loads in tumors compared to peripheral organs ($p < 0.01$)
2. **Tumor Regression and Growth Inhibition:** Treatment with bacteria significantly reduced tumor growth compared to controls.
3. **Survival Outcomes:** Kaplan–Meier survival analysis revealed significant improvements in median surviva
4. **Immune Activation and Tumor Infiltration:** Immunohistochemistry and flow cytometry demonstrated enhanced infiltration of immune effector cells in tumors treated with bacteria. 1. Tumor Volume Reduction at Day 21 (Mean ± SD, % vs. baseline) Group 4T1 Breast Cancer CT26 Colorectal Cancer
5. **Toxicity and Safety Assessment:** Weight loss: Mild weight loss (<10%) observed in Salmonella and Clostridium groups, reversible after day 14. Serum biochemistry: Elevated ALT and AST observed in Salmonella group, suggesting mild hepatotoxicity. E. coli group remained within normal range.
6. **Cytokine profiles:** All bacterial therapies triggered transient increases in IL-6 and TNF-α, but levels normalized by day 14.
7. **Histology:** Salmonella showed low-level colonization of liver and spleen; Clostridium caused localized necrosis but no systemic spread; E. coli exhibited tumor-specific localization.

Table 1. Tumor Volume Reduction at Day 21 (Mean ± SD, % vs. baseline)

Group 4T1 Breast Cancer CT26 Colorectal Cancer

Control (PBS)	**+180% +- 15%**	**+170%+- 12%**
E coli	-45% +- 7%	-40%. +- 6%
Salmonella	-35% +- 66%	-30% +- 5%
Clostridium	-50%. +- 8%	-42%. +- 7%
E. Coli + Anti-PD-1	- 70%. +- 5%	-65% +- 6%
Salmonella+Anti-PD-1	-55% +- 6%	-50% +- 7%
Clostridium+Anti-PD-1	-68% +- 7%	-60% +- 5%

Table 2. Median Survival (Days) Group 4T1 Model CT26 Model

Control (PBS)	**18**	**20**
E coli	28	30
Salmonella	26	27
Clostridium	30	32
E coli+Anti-PD-1	40	42
Salmonella+Anti-PD-1	135	34
Clostridium+Anti-PD-1	138	40

Table 3. Immune Cell Density per High-Power Field (HPF) in Tumor Sections (Mean ± SD)

Marker	Control	E coli	Salmonella	Clostridium	E coli+Anti-PD-1
CD8+ T cells	12 ± 3	45 ± 5	40 ± 6	50 ± 7	75 ± 8
NKp46+ NK cells	8 ± 2	30 ± 4	28 ± 5	32 ± 4	55 ± 6
F4/80+ macrophages	15 ± 4	42 ± 6	38 ± 5	45 ± 6	60 ± 7

Table 4. Toxicity Profiles at Day 21

Parameter	Control	E. coli	Salmonella.	Clostridium
Weight loss >10% (mice affected)	0/10	0/10	2/10	1/10
Elevated ALT/AST	0/10	0/10	3/10	1/10
Cytokine storm (IL-6 > 200 pg/mL)	/10	1/10	2/10	1/10
Systemic bacterial spread	0/10	0/10	2/10	0/10

Discussion

The present study evaluated the antitumor potential of three bacterial strains—engineered E. coli, attenuated Salmonella, and spore-forming Clostridium novyi-NT—in murine tumor models. Our results demonstrate that these microbes can suppress tumor growth, prolong survival, and stimulate immune activation, particularly when combined with PD-1 checkpoint inhibition. These findings align with, but also diverge from, several previous studies, offering important insights into the translational prospects of microbial cancer therapies.

It has been observed that E. coli and Clostridium showed strong tumor specificity, while Salmonella exhibited partial systemic spread. This is consistent with Forbes (2010), who noted that facultative anaerobes like Salmonella tend to accumulate in both tumors and reticuloendothelial organs, raising safety concerns. In contrast, Roberts et al. (2014) demonstrated that Clostridium novyi-NT spores selectively germinated in necrotic tumor regions without colonizing healthy tissues, in agreement with our findings of tumor-restricted localization. Similarly, Chowdhury et al. (2019) engineered E. coli with a synchronized lysis circuit and reported exclusive tumor colonization, which mirrors our observation of E. coli's tumor-specific persistence. Thus, while all bacterial strains can colonize tumors, their systemic distribution differs, with Clostridium and E. coli offering more favorable safety profiles than Salmonella.

In these models, Clostridium produced rapid tumor necrosis, while E. coli in combination with PD-1 blockade achieved the most sustained tumor control. These results parallel those of Dang et al. (2021), who reported extensive tumor destruction following intratumoral injection of Clostridium novyi-NT. Similarly, Chowdhury et al. (2019) found that engineered E. coli induced durable tumor regression and systemic antitumor immunity, particularly in combination with checkpoint inhibitors. Our findings of enhanced efficacy with E. coli + PD-1 blockade align with these results, reinforcing the concept of synergy between bacterial therapy and immunotherapy.

By contrast, Salmonella demonstrated moderate tumor suppression in our study, consistent with Zhao et al. (2019), who showed that attenuated Salmonella inhibited tumor growth but required combination with other modalities for durable responses. Collectively, these comparisons suggest that while all bacterial strains possess intrinsic antitumor activity, E. coli and Clostridium exhibit greater translational promise due to stronger efficacy and safe

Kaplan–Meier survival analysis revealed significant survival improvements, with E. coli + PD-1 blockade extending survival by over 100% compared to controls. Similar improvements have been reported in prior work. For instance, Mi et al. (2020) showed that bacterial therapies enhanced tumor infiltration of CD8+ T cells and macrophages, leading to prolonged survival in mouse models. Our immune profiling data, which revealed robust infiltration of CD8+ T cells, NK cells, and macrophages, corroborate these findings. Notably, our results also agree with Zhou et al. (2018), who reviewed evidence that bacteria stimulate both innate and adaptive immunity through the release of PAMPs, thereby converting immunologically “cold” tumors into “hot” ones. The marked increase in immune infiltration we observed in bacterial therapy groups—particularly in E. coli + PD-1 treated tumors—supports the notion that bacterial products can prime the tumor microenvironment for enhanced immunotherapy responsiveness. However, our survival benefits were more modest than those reported in some studies. For example, Zhao et al. (2019) observed complete tumor regression in a subset of mice treated with engineered Salmonella. Differences in tumor models, bacterial strains, and dosing strategies likely account for this discrepancy.

Safety and Toxicity in Comparison with Literature

Safety remains a central concern in bacterial cancer therapy. We found that Salmonella caused mild hepatotoxicity and systemic dissemination, echoing earlier reports by Patyar et al. (2010), who documented liver toxicity in preclinical models. Conversely, E. coli showed minimal off-target colonization, similar to the findings of Chowdhury et al. (2019), who demonstrated tumor-specific bacterial persistence with little systemic burden.

Ther observation of transient cytokine elevation (IL-6, TNF-α) aligns with Guo et al. (2017), who reported acute inflammatory responses following bacterial administration that later subsided as the host immune system adapted. Clostridium caused localized necrosis without systemic spread, consistent with Roberts et al. (2014), who reported manageable adverse events in early-phase clinical trials. Taken together, these comparisons suggest that E. coli and Clostridium offer more favorable safety margins, whereas Salmonella requires further attenuation to minimize systemic toxicity.

Mechanistic Insights Across Studies

The findings highlight three mechanistic pathways: direct oncolysis (Clostridium), immune stimulation (E. coli), and vascular disruption (Salmonella). These mechanisms align with prior studies. Dang et al. (2021) emphasized direct oncolysis as the hallmark of Clostridium novyi-NT. Din et al. (2016) demonstrated that E. coli engineered with lysis circuits released immunostimulatory molecules, priming systemic antitumor immunity. Forbes (2010) and Zhou et al. (2018) noted that Salmonella reduces tumor vascularity and competes metabolically with cancer cells. Our comparative findings therefore validate previously described mechanisms while providing side-by-side evidence of their relative strengths.

Clinical Translation: Comparison with Human Trials

The results provide insights relevant to ongoing clinical efforts. A Phase I trial by Toso et al. (2002) showed that attenuated Salmonella typhimurium could be administered safely to cancer patients, but efficacy was limited. This corresponds with our findings of moderate efficacy and systemic spread. In contrast, intratumoral injection of Clostridium novyi-NT spores induced significant tumor regression in a patient with leiomyosarcoma (Roberts et al., 2014), aligning with the potent necrotic effects observed in our models. While our study did not directly evaluate human efficacy, the synergy between E. coli and PD-1 blockade suggests strong translational potential, especially given the expanding role of checkpoint inhibitors in oncology. Future clinical trials should consider bacteria–immunotherapy combinations, as supported by both our findings and those of Chowdhury et al. (2019).

Conclusion

In comparison with prior research, this findings reinforce that bacterial therapies hold considerable promise as adjuncts to cancer immunotherapy. While Clostridium is most effective for direct tumor lysis, E. coli emerges as the strongest candidate for clinical translation due to its tumor specificity, immune activation, and compatibility with checkpoint blockade. Salmonella, although effective, requires further engineering to reduce systemic toxicity. Collectively, these results highlight the converging evidence that bacteria can function as potent allies against cancer, provided safety and regulatory hurdles are addressed.

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