EFFICACY AND SAFETY OF BACTERIAL-BASED CANCER THERAPIES: A META-ANALYSIS OF PRECLINICAL AND CLINICAL STUDIES

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Abstract

Cancer remains one of the leading causes of morbidity and mortality worldwide, despite significant advancements in conventional therapies such as chemotherapy, radiotherapy, and immunotherapy. However, these approaches often come with severe side effects, treatment resistance, and limited efficacy in certain tumor types, underscoring the urgent need for alternative therapeutic strategies. This meta-analysis explores the therapeutic potential and safety profile of bacterial-based cancer therapies through a systematic review of both preclinical and clinical studies. By targeting the unique properties of the tumor microenvironment, specific bacterial species have shown an ability to preferentially colonize cancerous tissues, modulate immune responses, and serve as delivery vehicles for therapeutic agents. In preclinical models, bacterial treatments demonstrated significant tumor growth inhibition and improved survival outcomes, with minimal systemic toxicity. Clinical trials evaluated a range of bacterial species including engineered forms of Salmonella, Listeria, Clostridium, and Bifidobacterium. Findings indicated varied levels of efficacy in terms of tumor response rates, progression-free survival, and overall survival across different patient cohorts. While some bacterial therapies were associated with notable therapeutic benefits, particularly in prolonging survival and enhancing immune activation, others showed limited efficacy or were accompanied by high rates of adverse events, especially in treatments involving Listeria-based agents. Conversely, Bifidobacterium-based therapies appeared to offer a more favorable safety profile. The heterogeneity in outcomes highlights the influence of bacterial strain, tumor type, dosage, and treatment combinations. This analysis concludes that bacterial-based therapies represent a promising frontier in oncology, offering a unique mechanism of action and potential synergy with existing treatments. Nevertheless, further large-scale and controlled clinical studies are necessary to optimize bacterial selection, enhance delivery mechanisms, and mitigate toxicity risks. Advancing this therapeutic modality could significantly contribute to the development of more personalized, targeted, and effective cancer treatments in the future.

Keywords: Bacteria-based, carcinoma, tumor, therapeutics, anticancer, clinical, immunotherapy, drug delivery

1 Introduction

Cancer is still a leading cause of illness and death worldwide, which emphasizes the necessity of constant advancements in therapeutic approaches. Despite having higher survival rates, conventional treatments like chemotherapy, radiation, and immunotherapy can have serious side effects and increase the risk of resistance, which can reduce their long-term efficacy. Alternative and complementary therapeutic approaches, especially those incorporating bacterial-based cancer therapies (BBCTs), are therefore becoming more and more popular.[1–4] The inherent characteristics of bacteria and the tumor microenvironment justify their use in cancer treatment.[5] Bacteria can use both passive and aggressive methods to colonize tumors in a specific way. While active targeting entails chemotaxis towards chemicals produced by dying tumor tissue and the hypoxic conditions common in malignancies, passive targeting requires bacteria to enter the tumor through the disordered tumor vasculature. The hypoxic cores of tumors, which are frequently resistant to chemotherapy, are ideal environments for anaerobic bacteria. This makes it possible to target these previously unreachable places specifically. Within the tumor microenvironment, bacteria can trigger antitumor immune responses. It is possible to design bacteria to directly transport medications, genes, or therapeutic substances to cancer cells.[6] Because of their special capacity to target tumor tissues specifically, elicit immune responses, and transport therapeutic chemicals directly to cancer cells, several bacteria have been found to be potent anticancer medicines.[7–10] Numerous bacterial strains have demonstrated promising anticancer benefits in both laboratory and clinical settings, including *Salmonella spp.*[11], *Clostridium spp.*[12–14], *Listeria monocytogenes*[15–17], *Bifidobacterium spp.*[18–20], and *Mycobacterium bovis* (BCG)[21,22], which have exhibited encouraging anticancer effects in both laboratory and clinical studies. It is also possible to design microbes to create and transport anticancer medicines through synthetic bioengineering and genetic manipulation.[23] Attenuation by deleting key virulence genes showed a preference for the tumor. Bacteria can also be genetically modified to produce and release particular substances or change their metabolic pathways, and they can also function as powerful anticancer agents. In order to improve the therapeutic efficacy of treatment, BBCT may use bacteria either by themselves or in conjunction with more traditional techniques.

One of the most efficient ways is genetic engineering, which involves deleting or inactivating critical virulence genes. Researchers have successfully created safer variants of *Salmonella typhimurium* by altering it. One such variant, VNP20009, has undertaken phase I clinical studies to evaluate its safety and possible effectiveness in treating metastatic melanoma.[24] Auxotrophy induction is another popular tactic, in which bacteria are genetically altered to need particular nutrients that are only present in the tumor microenvironment. By limiting bacterial development to malignant tissues and ensuring selective bacterial colonization, this strategy reduces systemic toxicity.[25] Researchers have looked into using naturally non-pathogenic microorganisms as medicinal agents in addition to genetic modifications. For instance, some species of *Clostridium* flourish in hypoxic conditions, which are

typical of solid tumors. Healthy cells are unaffected by these bacteria's selective colonization and destruction of malignant tissue. Scientists have preserved the tumor-targeting capabilities of bacterial-based medicines while making them considerably safer for clinical use by utilizing these diverse attenuation techniques. Although BBCT has demonstrated potential as an independent treatment, when paired with other therapeutic modalities, its efficacy can be greatly increased. Bacteria and traditional cancer treatments can work together to better eradicate tumors, get beyond resistance mechanisms, and lessen the side effects. The combination of BBCT and chemotherapy is one of the most thoroughly studied. Within the tumor microenvironment, bacteria can be genetically modified to create enzymes that specifically transform prodrugs into active chemotherapeutic medicines. This technique lowers systemic toxicity while increasing medication concentration at the tumor location. Bifidobacterium longum, for instance, has been employed as a gene therapy delivery method; it specifically localizes within hypoxic tumors to increase the therapeutic effect.[26] Hypoxic areas form in many solid tumors, which renders them resistant to radiation therapy. Nevertheless, bacterial colonization can aid in reoxygenating these regions, increasing the radiation susceptibility of tumor cells.[27] BBCT can increase tumor destruction and the effectiveness of radiation-based treatments by altering the tumor microenvironment. Additionally, treatments based on microorganisms may boost immunotherapy. The host immune system is stimulated by some bacterial species, which results in an antitumor response. BBCT can enhance the immune system's capacity to identify and combat tumor cells when paired with immune checkpoint inhibitors. Research has demonstrated that bacterial treatments based on Listeria can overcome immunological resistance specific to tumors, enhancing the immune system's overall ability to fight cancer.

Despite the increasing interest in bacterial-based cancer therapies, their overall efficacy and safety profile remain unclear. Whether bacterial treatments considerably increase anticancer efficacy and investigate their safety is still an essential concern. In order to compare these characteristics across different research, we conducted a meta-analysis of preclinical and clinical trials. Preclinical studies often report promising outcomes, but their translation into clinical success has been inconsistent. Additionally, concerns regarding potential toxicity, infection risks, and immunerelated adverse effects necessitate a thorough evaluation of their safety profile. Several individual clinical trials and animal studies have explored the therapeutic potential of bacterial therapies, but a comprehensive meta-analysis comparing their efficacy and safety has not yet been conducted. By synthesizing data from both preclinical and clinical studies, this review aims to provide a quantitative assessment of the effectiveness and risks associated with bacterial-based cancer treatments.

By systematically analyzing the available evidence, this meta-analysis will help clinicians, researchers, and policymakers understand the therapeutic potential and limitations of bacterialbased cancer therapies. The findings may also guide future clinical trials and the development of safer and more effective bacterial-based

treatment strategies. Specifically, this study will assess treatment efficacy, including tumor growth inhibition, progression-free survival (PFS), overall survival (OS), optimal response rate (ORR), and Tumor growth inhibition (TGI). It will also evaluate any safety outcomes, including treatment-related adverse events, toxicity, and infection risks. Compare findings between preclinical and clinical studies to determine the translational potential of bacterial-based therapies.

2 Methods

2.1. Literature Search

We carefully followed the Preferred Reporting Items for Systematic Reviews and Metaanalyses PRISMA guidelines' requirements and protocol for this review. A wide range of observational studies and randomized controlled trials (RCTs) that looked at different bacterialbased treatments for different types of cancer were included in the compilation. Using MeSH terms and phrases associated with cancer, bacterial therapy, and tumors, the literature was thoroughly searched from a range of academic sources, including PubMed and Google Scholar. Only clinical trials were included in the article type filter while searching in PubMed. The terms "bacterial therapy" "tumor," "murine" and "animal" were used in the databases to discover preclinical research using the Boolean search operator. To find any relevant literature, a comprehensive manual search of references from certain scholarly journals was also carried out. Any potentially pertinent publications discovered in reference lists were examined and considered for inclusion, much like in the clinical literature search.

2.2. Study Selection

We set inclusion criteria that allowed for a wide range of investigations to be conducted over the allotted time. Randomized trials with single and multicohort studies that assessed and discussed factors such as PFS, ORR, OS, and adverse effects of the treatment were required to be included in the meta-analysis. Included were studies conducted on every kind of cancer. Excluded were studies that did not provide clear efficacy and safety data. The review was restricted to full-text English-language publications in order to ensure a comprehensive evaluation. Duplicate studies were identified and removed using Zotero to ensure a refined and non-redundant dataset for the analysis.

2.3. Extracting outcome data

Examining study titles and abstracts, determining eligibility, and settling disputes were all part of the screening process. The results of each intervention and comparison were evaluated qualitatively. For clinical studies, authors, year of publication, study design, sample size, age of participants, study variables like adverse effects, ORR, PFS, OS, and 95% confidence intervals [CI] were among the criteria that were noted. In the case of preclinical investigations first author, publication year, and study characteristics such as bacterial species, animal model, tumor type, number of animals, TGI (%), and side effects were noted. The meta-analysis used the corresponding 95% CI for clinical data survival factors like OS and PFS, and the findings were displayed as forest plots.

3 Results

3.1. Literature search and screening

The results of a thorough and methodical literature search across several databases, including PubMed (n = 8,856), Google Scholar (n = 2,530), and Cochrane (n = 118) with an outcome of a total 11,504 entries. An additional 2,473 records were excluded after being deemed ineligible based on predetermined inclusion and exclusion criteria, and 8,258 records were eliminated by automated filtering based on relevancy prior to screening. Only possibly pertinent studies advanced to the screening stage thanks to this first filtering process. After that, 781 papers were screened for titles and abstracts; 697 of them were rejected because they were irrelevant, duplicated, or lacked necessary information. The full-text retrieval of the remaining 84 articles was attempted, but 35 were unavailable for various reasons, including unavailability or limited access. Only the most pertinent studies were kept after 49 publications were evaluated for eligibility and 19 were rejected based on predetermined standards.

Manual searches of reference lists and citations from important articles yielded 116 more records than database searches. Of these, 47 articles were attempted to be retrieved; however, 77 records were inaccessible. Nine of the eleven full-text articles that were evaluated were disqualified for not being in English, twelve because of access restrictions, and seven because they were deemed irrelevant. A final set of 20 studies that satisfied all inclusion criteria were added to the meta-analysis following the stringent screening process. The PRISMA criteria were followed in the systematic approach used to identify studies, guaranteeing a clear and repeatable process.

3.2. Study characteristics

The overall sample size for all the clinical investigations is 409 patients, with individual sample sizes ranging from 30 to 93 participants. The age range of participants ranges from 28 to 92 years, with median ages differing between studies. In order to reflect both short-term and longterm therapy efficacy evaluations, study durations vary from three months to twenty-four months. Both single- and multicohort designs are used in the studies; however, for a more reliable comparison analysis, the majority of them use a multicohort structure.

With a total sample size of 298 mice, 11 preclinical research investigated the safety and effectiveness of bacterial-based cancer treatments in murine models. The studies used a variety of bacterial strains, such as *Salmonella typhimurium* (VNP20009, attenuated, ΔppGpp), *Escherichia coli* (MG1655, Nissle 1917, 25922), *Bifidobacterium, Clostridium butyricum,*
Magnetospirillum magneticum, and S. typhi porins, to target glioblastoma and cancers of the
colon, breast, bladder, liver, and skin. Balb/c and C57BL/6 mice were used in most of the research; in some, the age range of the mice was reported to be 6 weeks. Several research progressed until tumor volumes surpassed predetermined ethical limitations, and study durations ranged from 22 to 90 days.

3.3. Meta-analysis

In clinical studies, *Listeria monocytogenes* is the most researched bacterial strain, accounting for six of the nine investigations, followed by *Bifidobacterium spp.* in two and *Clostridium butyricum* in one. Although reported side effects vary, several studies report significant rates of grade 3 or 4 toxicities, such as immune-related adverse events, tiredness, gastrointestinal problems, and neutropenia. The most common serious adverse effects were seen in *Listeria monocytogenes* trials, with rates ranging from 52% to 100%. On the other hand, research on *Bifidobacterium species* showed somewhat lower rates of serious adverse events (40–52%), whilst *Clostridium butyricum* showed very little documented toxicity.

Regarding efficacy, objective response rates (ORR) ranged from 5% to 74%, indicating varying degrees of tumor response across bacterial therapies. The highest ORR (74%) was observed in *Bifidobacterium spp.* therapy (Ebrahimi et al., 2024), while the lowest (5%) was noted in *Listeria monocytogenes* treatment (Stein et al., 2022). Progression-free survival (PFS) was reported in five studies, with median values ranging from 2.8 to 7.5 months. Similarly, overall survival (OS) was available in six studies, with a median range between 0.27 and 33.7 months, suggesting considerable variability depending on the bacterial strain, cancer type, and patient characteristics. Notably, *Listeria monocytogenes* treatment in Brockstedt et al. (2013) and Hassan et al. (2019) yielded an OS of 14.7 months, whereas Tomita et al. (2020) with *Clostridium butyricum* reported a markedly lower OS of 0.27 months, indicating potential limitations in its efficacy.

The maximum suppression in preclinical studies was seen in *Salmonella typhimurium* (~85%, Yi et al., 2020) and *Clostridium butyricum* (91.7%, Shi et al., 2022). The tumor growth inhibition (TGI) rates varied from 50% to 91.7%. Tumor-specific thrombosis, angiogenesis inhibition, immune system activation, and increased effectiveness of checkpoint inhibitors like anti-PD-1 treatment were among the therapeutic mechanisms. Furthermore, a number of research showed how photothermal therapy (Xu et al., 2022; Sun et al., 2022) and bacterialderived nanomagnets (Howard et al., 2022) might enhance tumor targeting and treatment response. Crucially, every study found only minor adverse effects including localized inflammation and no significant systemic toxicity (Moreo et al., 2022).

Survival outcomes showed significant improvements, with Yi et al. (2020) reporting 80% survival at 90 days, and Howard et al. (2022) demonstrating a 50% increase in survival compared to control groups. Most studies also reported enhanced immune responses, including T-cell infiltration, macrophage polarization, and CD8+ T-cell priming (Sivan et al., 2015; Xu et al., 2022). These findings suggest that bacterial-mediated therapies hold promise as innovative and effective cancer treatments, with potential for clinical translation. However, further dose optimization, safety profiling, and mechanistic studies are essential to ensure reproducibility and therapeutic efficacy in human trials.

The studies that mentioned median PFS and OS values were represented as a forest plot for a clear comparison across different studies. In Figure 2, the PFS plot (A) shows a range of median survival values, with most studies clustering around 6-8 units, except for one study (Stein et al., 2022) reporting a broader CI. The overall

average suggests a relatively consistent PFS improvement across studies. The consistency in the median values suggests that bacterial-based therapies contribute to delayed tumor progression, likely by modulating immune responses or directly suppressing tumor growth.

The OS plot (B) demonstrates a wider variation in survival outcomes, with Stein et al. (2022) reporting a significantly longer survival (above 35 units), indicating a potentially superior effect of the intervention in this study. Other studies report median OS values ranging between 10 and 20 units, suggesting variability in bacterial therapy efficacy, possibly due to differences in bacterial strains, tumor models, or experimental conditions. The average median survival across studies suggests that bacterial-based interventions contribute to an increase in overall survival, although individual study outcomes vary. The wider confidence intervals in some studies indicate greater heterogeneity, necessitating further research to optimize bacterial strains, dosing strategies, and combination therapies for more consistent and reproducible survival benefits.

4 Discussion

The results of this meta-analysis highlight the prospect of bacterial-based cancer treatments as a cutting-edge therapeutic method that can augment or supplement current therapeutic approaches. The effectiveness findings imply that, especially in preclinical models, BBCTs help reduce tumor growth and prolong survival. The majority of clinical studies show a median survival range of 6– 8, indicating that bacterial therapy significantly inhibits tumor growth, according to PFS statistics. This implies that bacterial interventions may be able to delay the course of the disease, most likely by means of direct bacterial oncolysis, immunological activation, and tumor hypoxia targeting. Furthermore, bacteria's ability to colonize tumors and release therapeutic substances emphasizes their potential as anticancer drug delivery vehicles, which would increase the effectiveness of these medications. More variation can be seen in the OS data, though, since some studies indicate noticeably longer survival. This implies that although BBCTs can improve long-term survival, the host immune system, tumor microenvironment features, and bacterial strain selection may all have a significant impact on how effective they are. Numerous studies have demonstrated the synergistic effects of immunotherapy and bacterial-based treatments, especially when combined with anti-PD-1 checkpoint drugs. According to these results, bacterial treatments may operate as immunological modulators, increasing antitumor immunity by improving T-cell infiltration, macrophage polarization, and CD8+ T-cell priming. The necessity for standardized bacterial alterations and combination tactics with current medications to maximize therapeutic efficacy is reflected in the variation in survival results. Furthermore, since many potential bacterial medicines do not produce comparable results in human studies, it is still difficult to translate preclinical success to clinical efficacy.

The studies highlight *Listeria monocytogenes* as the most extensively studied bacterial strain, though it is associated with significant adverse events. This bacterium has been utilized for its immune-stimulating properties, which enhance

the body's ability to recognize and attack tumors. *Listeria*-based therapies primarily function as vaccine vectors, delivering tumor-associated antigens to antigen-presenting cells, thereby boosting the immune response against cancer cells. However, studies reported significant toxicity levels, with up to 100% of patients experiencing grade 3 or 4 adverse effects, including fever, nausea, and fatigue. Despite its toxicity, *Listeria monocytogenes* therapies showed varying objective response rates (ORR), ranging from 5% to 57%, and survival benefits in some trials. *Bifidobacterium spp*., another well-known bacterial strain that was studied, showed less toxicity than *Listeria monocytogenes*. A probiotic bacterium called *Bifidobacterium* can be used for targeted therapy because it preferentially colonizes hypoxic tumor areas. It is a desirable option for bacterial cancer treatment because to its capacity to both boost immune responses and act as a drug delivery mechanism. An ORR of up to 74% was found in clinical trials (Ebrahimi et al., 2024), indicating notable efficacy, especially in combo therapies. The capacity of another anaerobic bacterium, *Clostridium butyricum*, to colonize necrotic tumor regions and release toxins that cause tumor cell death was investigated. Its overall survival (OS) was a pitiful 0.27 months, despite its reported ORR of 49%, suggesting possible limitations in efficacy. Nonetheless, *Clostridium* showed a strong tumor growth inhibition (91.7%) in preclinical studies, which makes it a viable option for additional research. The non-pathogenic nature of the strain also might be the contribution to these effective results.

According to preclinical research, *Salmonella typhimurium* treatment increased animal models' longevity and inhibited tumor growth by up to 85% (Yi et al., 2020). Furthermore, research using Salmonella in photothermal therapy revealed improved tumor suppression outcomes. In addition to these main bacterial strains, *Mycobacterium bovis* (BCG), *Escherichia coli*, and *Magnetospirillum magneticum* were investigated. Through mechanisms including TGF-β blocking, *E. coli Nissle* 1917 has been researched for its ability to enhance immune responses and decrease tumors. The nanomagnetic characteristics of *Magnetospirillum magneticum* were studied because they enable the use of bacteria for targeted tumor therapy by manipulating an external magnetic field. Finally, immunotherapy based on BCG, which is well-known for its use in bladder cancer, demonstrated promise in enhancing immune checkpoint inhibitor responses.

In brief, a variety of tumor-targeting mechanisms, such as direct bacterial infection, immune system activation, and drug transport, were demonstrated by the bacterial-based therapies investigated in the included trials. Our work does not fully address a number of recent trends, such as the fact that bacterial derivatives, like outer membrane vesicles (OMVs), have created new opportunities for cancer immunotherapy. By carrying tumor antigens, OMVs can efficiently activate the host's immune system to identify and combat cancer cells. This tactic makes use of the immunogenic qualities of bacterial components to produce a strong anti-tumor reaction.[48] Apart from these technological advancements, new research has discovered naturally existing microorganisms that have built-in anti-cancer capabilities in the genetic traits. The application of bacterial nanotechnology is

another new strategy. Scientists can accomplish targeted drug delivery by conjugating nanoparticles with bacterial vectors, guaranteeing greater concentrations of chemotherapeutic drugs within the tumor microenvironment. This approach reduces systemic toxicity while simultaneously improving the therapeutic index.[49]

Although all the methods of administration and dosage of treatment vary from study to study the overall data suggests that there is definitely a potential for bacteria as a cancer therapy. Using these in combination with other therapies increases the effectiveness of the treatment. The precise attenuation helps in decreasing pathogenicity and avoid infections due to administration. Future research should focus on optimizing bacterial therapy regimens, mitigating toxicity, and identifying patient subgroups that may derive the greatest benefit. These findings underscore the necessity for larger randomized controlled trials to further validate bacterial immunotherapy as a viable treatment option for cancer patients. They exhibit strong potential as adjunctive treatments, particularly in enhancing tumor suppression and survival outcomes. However, further preclinical and clinical investigations are needed to refine bacterial delivery mechanisms, identify optimal patient populations, and assess long-term safety and efficacy. Future research should also focus on personalized approaches, leveraging microbiome profiling and immune landscape analyses to maximize therapeutic benefits while minimizing variability.

5 Conclusion

The outcomes of this meta-analysis demonstrate the encouraging potential of bacterial-based cancer treatments as a cutting-edge method of cancer care. Bacterial species like *Salmonella typhimurium*, *Clostridium butyricum*, *Bifidobacterium spp.*, and *Listeria monocytogenes* have shown notable advantages in tumor suppression, immune activation, and survival in both clinical and preclinical investigations. Depending on the bacterial strain, kind of cancer, and treatment approach, the objective response rates (ORR) in clinical trials varied from 5% to 74%, while the tumor growth inhibition (TGI) in preclinical models varied from 50% to 91.7%. The therapeutic capacity of bacterial treatments was further supported by evidence that they improved overall survival (OS) and progression-free survival (PFS), with OS ranging from 0.27 to 33.7 months and PFS values ranging from 2.8 to 7.5 months.

Safety is still a major worry despite their effectiveness, especially with treatments based on *Listeria monocytogenes*, which have significant rates of grade 3 or 4 toxicities (52%–100%). *Bifidobacterium*-based therapies, on the other hand, showed a better safety profile (40–52%), indicating that they would be a safer substitute. Preclinical research also showed that there was no systemic toxicity and that the negative effects were mostly limited to localized inflammation. These studies' molecular findings imply that bacterial treatments function by promoting immune infiltration, preventing angiogenesis, and cooperating with immunotherapy strategies like checkpoint inhibitors.

To sum up, BBCTs are a promising but developing area of oncology. There is a compelling case for more research because of their capacity to target tumors specifically, alter immune responses, and act as biological drug carriers. However,

thorough validation through extensive trials, bacterial strain refining for improved tumor selectivity, and methods to reduce side effects are necessary for practical translation. Determining the long-term feasibility of these treatments in the treatment of cancer will require extensive clinical trials and mechanistic research. Bacterial treatments, which provide a targeted, immune-boosting, and maybe safer alternative to conventional medications, have the potential to completely transform the treatment of cancer with further development. In order to optimize patient-specific benefits while minimizing dangers, future research should focus on integrating BBCTs into customized cancer therapy by utilizing genetic engineering and microbiome analysis.

ТАБЛИЦЫ

Table 1. A comprehensive review and meta-analysis of clinical studies denoting the safety and efficacy of therapies.

Author	Sample size (N)	Age	Duration	Design	Species	Adverse Effects	ORR (%)	Median PFS	Median OS
Brockstedt et al. 2013 [28]	38	71 (5182)	25 weeks	Single cohort	*Listeria monocytogenes*	Grade 1, 2, 3, and 4 adverse Events	57	7.5 (7 - 9.9)	14.7 (11.2 -21.9)
Le et al. 2015 [29]	93	63 (4587)	20 weeks	Multicohort	*Listeria monocytogenes*	Grade 3 to 4 adverse events like erythema, 77%; induration, 71%; pain, 62%; pruritis, 71%), nausea (53%), vomiting (43%), chills (67%), fever (62%), and fatigue (53%	51	-	10.3 (3.2 - Not Evaluable)
Basu et al. 2018 [30]	54	48 (2860)	3 months	Multicohort	*Listeria monocytogenes*	-	14.7	6.44 (4.17 - 8.94)	8.78 (7.4 - 13.3)

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Huh et al. 2020 [32]	50	46 (2970)	12 months	Single cohort	*Listeria monocytogenes*	98% grade 3 and 4 adverse evewents like chills (58%), fatigue (54%), fever (36%), headache (36%), and nausea (32%)	14.3	2.8 (2.6 3)	6.1 (4.3 - 12.1)
Tomita et al. 2020 [33]	39	68 (6271)	6 months	Multicohort	*Clostridium butyricum*	-	49	-	0.27 (0.11-0.66)
Stein et al. 2022 [34]	37	68.0 (45-92)	24 months	Multicohort	*Listeria monocytogenes*	100%	5	5.4 (2.3 7.9)	33.7 (15.4 - Not Evaluable)

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Dizman et al. 2022 35	30	66 (45–90)	12 weeks	Multicohort	*Bifidobacterium* spp.	52% showing grade 3 or 4 adverse events such as Neutrophil count decreased, Fatigue, Glucose intolerance, Diarrhea, Adrenal insufficiency, Rash maculopapular, Acute kidney injury, Abdominal pain, Alkaline phosphatase increase, Acidosis, Chest wall pain, Pancreatitis, Transaminitis, Pruritus, Dehydration, Hypothyroidism, Hyperthyroidism, Arthralgia or myalgia, and Weight gain	58	-	-

Ebrahimi et al. 2024 36	30	60 (48–67)	13 weeks	Multicohort	*Bifidobacterium* spp.	40% showing grade 3 or 4 adverse events like Hyponatremia, Transaminitis, Hypertension, Dianbea, Palmar plantar, erythrodysesthesia syndrome, White blood cell count drop, Hypocalcemia, Arthralgia, Bullous dermatitis, Caugh, Pneumonitis, Vomiting, Hypoalbuminemia, Anemia, Hemorrhoids, Hyperkalemia, Hypermagnesemia, Hypokalemis, Hypothyroidism, Lipase elevation,	74	-	-

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		Sore throat, Upper gastrointestinal, hemorrhage, and Weight loss

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Table 2. A comprehensive review and meta-analysis of preclinical studies denoting safety and efficacy of therapies.

Study	Sample Size	Design	Duration (Estimate)	Bacterial Strain Used	Cancer Type Model	Animal Tumor Growth Inhibitio (TGI%)	Safety (Toxicity, Side n Effects, etc.)	Survival
Sivan et al. 2015 [37]	10	Multicohort	28 days	*Bifidobacterium*	Melanoma	C57BL/6 mice	50-70%	No reported safety concerns, and immune modulation observed	Improved survival vs. control
Shi et al. 2019 [38]	4	Multicohort	27 days	*E. coli* Nissle 1917 (EcN)	Hepatocellular carcinoma (H22), Breast Cancer (4T1)	Murine models	70%	No significant toxicity	Mice euthanized at tumor volume ~2000 mm^3
Leteliar et al. 2020 [39]	12	Multicohort	28 days	*S. typhi* Porins	Melanoma	C57BL/6 Murine Model	50%	No severe adverse effects	Not reported
Yi et al. 2020 [40]	105	Multicohort	45-90 days	*Salmonella typhimurium* (attenuated)	Colorectal & breast cancer	Balb/c & Nude mice (subcutaneous &	~85%	Limited systemic toxicity, rapid	~80% survival at 90 days

						orthotopic models)		bacterial clearance	
Liu et al. 2021 [41]	35	Multicohort	22 days	*S. typhimurium* VNP20009	Breast Cancer	Mouse Model	62%	No significant toxicity	Not reported
Xu et al. 2022 [42]	25 (Female)	Multicohort	Not specified	*E. coli* MG1655	Colon Cancer (CT26)	Balb/c Mice	65%	No severe toxicity	Not reported
Sun et al. 2022 [43]	5	Multicohort	30 days	*S. typhimurium* VNP20009, *E. coli* 25922	Glioblastoma (Luc-G422)	GBM-bearing mice	78%	Minimal systemic toxicity	Significant survival improvement
Moreo et al. 2022 [44]	16	Multicohort	70 days	*MTBVAC, BCG Tice*	Bladder Cancer	Orthotopic MB49 model	55%	Some bladder inflammation observed	Not reported
Howard et al. 2022 [45]	32	Multicohort	21 days	*Magnetospirillum magneticum AMB-1*	Breast Cancer	C57BL/6 Mice	68%	No severe side effects	50% increased survival

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Xu et al. 2022 [46]	12	Multicohort	30 days	*Salmonella typhimurium* (ΔppGpp)	Colon cancer	Balb/c mice (6 weeks old)	~60%	No significant toxicity, major organs normal in H&E staining	Extended survival (Kaplan-Meier analysis)
Shi et al. 2022 [47]	42	Multicohort	27 days	*Clostridium butyricum*	Melanoma	C57BL/6 mice	91.7 ± 3%	No serious adverse effects	Not reported

РИСУНКИ

Figure 1. PRISMA Flowchart of Literature Search and Screening

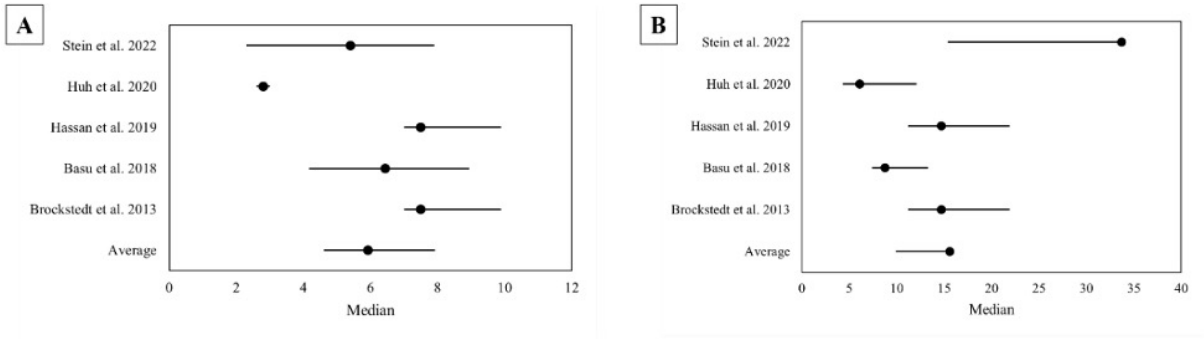
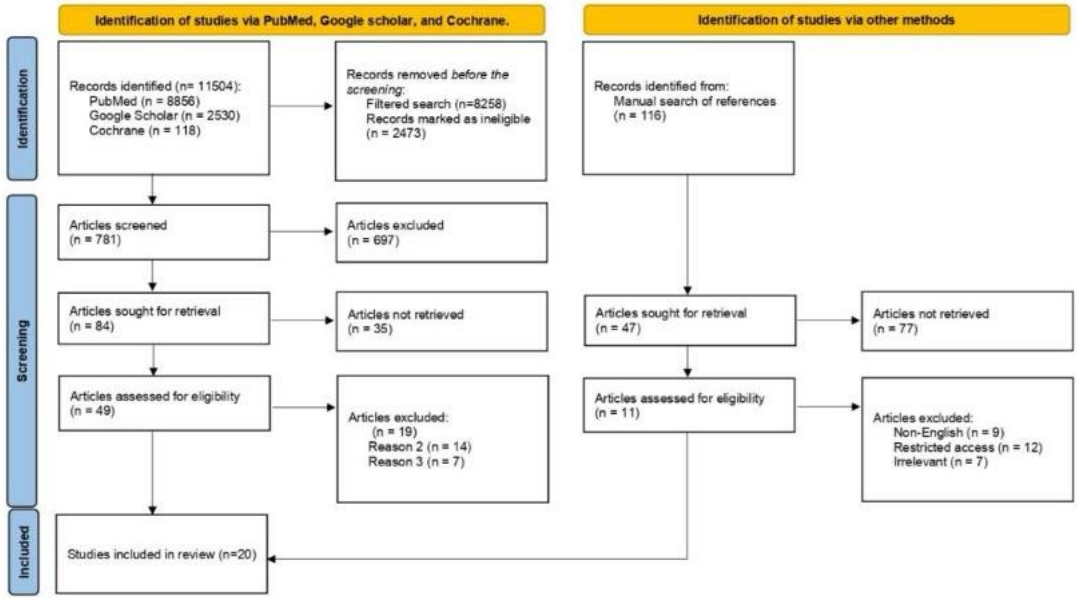


Figure 1. Forest Plots of Progression-Free Survival and Overall Survival



Opisanie: The forest plots illustrate the impact of bacterial-based cancer therapies on progression-free survival (PFS) (Plot A) and overall survival (OS) (Plot B) across five preclinical studies.

ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

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Блок 3. Метаданные статьи

Efficacy and Safety of Bacterial-Based Cancer Therapies: A Meta-Analysis of Preclinical and Clinical Studies

Сокращенное название статьи для верхнего колонтитула: Bacterial Cancer Therapies Meta-Analysis

Keywords: Bacteria-based, carcinoma, tumor, therapeutics, anticancer, clinical, immunotherapy, drug delivery

Обзоры.
Количество страниц текста 9,
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СПИСОК ЛИТЕРАТУРЫ

№	Authors	Title & Source (Original)	Official English Title & Source	DOI / URL
1	Badie, F.; Ghandali, M.; Tabatabaei, S. A.; Safari, M.; Khorshidi, A.; Shayestehpour, M.; Mahjoubin-Tehran, M.; Morshedi, K.; Jalili, A.; Tajiknia, V.; Hamblin, M. R.; Mirzaei, H. Use of Salmonella Bacteria in Cancer Therapy: Direct, Drug Delivery and Combination Approaches. Front. Oncol. 2021, 11, 624759. https://doi.org/10.3389/fonc.2021.624759.		—	https://doi.org/10.3389/fonc.2021.624759
2	Basu, P.; Mehta, A.; Jain, M.; Gupta, S.; Nagarkar, R. V.; John, S.; Petit, R. A Randomized Phase 2 Study of ADXS11-001 Listeria Monocy’togenes-Listeriolysin O		—	https://doi.org/10.1097/IGC.0000000000001235

	Immunotherapy With or Without Cisplatin in Treatment of Advanced Cervical Cancer. International Journal of Gynecological Cancer 2018, 28 (4), 764–772. https://doi.org/10.1097/IGC.0000000000001235.			
3	Biot, C.; Rentsch, C. A.; Gsponer, J. R.; Birkhäuser, F. D.; Jusforgues-Saklani, H.; Lemaître, F.; Auriau, C.; Bachmann, A.; Bousso, P.; Demangel, C.; Peduto, L.; Thalmann, G. N.; Albert, M. L. Preexisting BCG-Specific T Cells Improve Intravesical Immunotherapy for Bladder Cancer. Sci. Transl. Med. 2012, 4 (137). https://doi.org/10.1126/scitranslmed.3003586.		—	https://doi.org/10.1126/scitranslmed.3003586
4	Brockstedt, D	G.; Giedlin, M. A.; Leong, M. L.; Bahjat, K. S.; Gao, Y.; Luckett, W.; Liu, W.; Cook, D. N.; Portnoy, D. A.; Dubensky, T. W. Listeria - Based Cancer Vaccines That Segregate Immunogenicity from Toxicity. Proc. Natl. Acad. Sci. U.S.A. 2004, 101 (38), 13832–13837.	—	https://doi.org/10.1073/pnas.0406035101

		https://doi.org/10.1073/pnas.0406035101.		
5	Brockstedt, D	G.; Le, D. T.; Hassan, R.; Murphy, A.; Grous, J.; Dubensky, T. W.; Jaffee, E. M. Clinical Experience with Live-Attenuated, Double-Deleted (LADD) Listeria Monocytogenes Targeting Mesothelin-Expressing Tumors. j. immunotherapy cancer 2013, 1 (S1), P203, 20511426-1-S1-P203. https://doi.org/survical.	—	https://doi.org/survical
6	Cheong, I.; Huang, X.; Bettegowda, C.; Diaz, L. A.; Kinzler, K. W.; Zhou, S.; Vogelstein, B. A Bacterial Protein Enhances the Release and Efficacy of Liposomal Cancer Drugs. Science 2006, 314 (5803), 1308–1311. https://doi.org/10.1126/science.1130651.		—	https://doi.org/10.1126/science.1130651
7	Dizman, N.; Meza, L.; Bergerot, P.; Alcantara, M.; Dorff, T.; Lyou, Y.; Frankel, P.; Cui, Y.; Mira, V.; Llamas, M.; Hsu, J.; Zengin, Z.; Salgia, N.; Salgia, S.; Malhotra, J.; Chawla, N.; ChehraziRaffle, A.; Muddasani, R.; Gillece, J.; Reining, L.; Trent, J.;		—	https://doi.org/10.1038/s41591-022-01694-6

	Takahashi, M.; Oka, K.; Higashi, S.; Kortylewski, M.; Highlander, S. K.; Pal, S. K. Nivolumab plus Ipilimumab with or without Live Bacterial Supplementation in Metastatic Renal Cell Carcinoma: A Randomized Phase 1 Trial. Nature Medicine 2022, 28 (4), 704–712. https://doi.org/10.1038/s41591-022-01694-6.			
8	Duong, M	T.-Q.; Qin, Y.; You, S.-H.; Min, J.-J. Bacteria-Cancer Interactions: Bacteria-Based Cancer Therapy. Exp Mol Med 2019, 51 (12), 1–15. https://doi.org/10.1038/s12276-019-0297-0.	—	https://doi.org/10.1038/s12276-019-0297-0
9	Ebrahimi, H.; Dizman, N.; Meza, L.; Malhotra, J.; Li, X.; Dorff, T.; Frankel, P.; Llamas-Quitiquit, M.; Hsu, J.; Zengin, Z. B.; Alcantara, M.; Castro, D.; Mercier, B.; Chawla, N.; Chehrazi-Raffle, A.; Barragan-Carrillo, R.; Jaime-Casas, S.; Govindarajan, A.; Gillece, J.; Trent, J.; Lee, P. P.;		—	
10	Felgner, S.; Kocijancic, D.; Frahm, M.; Weiss, S. Bacteria in Cancer		—	https://doi.org/10.1155/2016/8451728

	Therapy: Renaissance of an Old Concept. International Journal of Microbiology 2016, 2016, 1–14. https://doi.org/10.1155/2016/8451728.			
11	Gholami, A.; Mohkam, M.; Soleimanian, S.; Sadraeian, M.; Lauto, A. Bacterial Nanotechnology as a Paradigm in Targeted Cancer Therapeutic Delivery and Immunotherapy. Microsyst Nanoeng 2024, 10 (1), 113. https://doi.org/10.1038/s41378-024-00743-z.		—	https://doi.org/10.1038/s41378-024-00743-z
12	Guo, C	Bifidobacterium Breve as a Delivery Vector of IL-24 Gene Therapy for Head and Neck Squamous Cell Carcinoma in Vivo. Gene Ther 2017, 24 (11), 699–705. https://doi.org/10.1038/gt.2017.74.	—	https://doi.org/10.1038/gt.2017.74
13	Gupta, K	H.; Nowicki, C.; Giurini, E. F.; Marzo, A. L.; Zloza, A. Bacterial-Based Cancer Therapy (BBCT): Recent Advances, Current Challenges, and Future Prospects for Cancer Immunotherapy. Vaccines 2021, 9 (12), 1497.	—	https://doi.org/10.3390/vaccines9121497

		https://doi.org/10.3390/vaccines9121497.		
14	Hassan, R.; Alley, E.; Kindler, H.; Antonia, S.; Jahan, T.; Honarmand, S.; Nair, N.; Whiting, C. C.; Enstrom, A.; Lemmens, E.; Tsujikawa, T.; Kumar, S.; Choe, G.; Thomas, A.; McDougall, K.; Murphy, A. L.; Jaffee, E.; Coussens, L. M.; Brockstedt, D. G. Clinical Response of LiveAttenuated, Listeria Monocytogenes Expressing Mesothelin (CRS-207) with Chemotherapy in Patients with Malignant Pleural Mesothelioma. Clinical Cancer Research 2019, 25 (19), 5787– 5798. https://doi.org/10.1158/1078-0432.CCR-19-0070.		—	https://doi.org/10.1158/1078-0432.CCR-19-0070
15	Howard, F	H. N.; Al-Janabi, H.; Patel, P.; Cox, K.; Smith, E.; Vadakekolathu, J.; Pockley, A. G.; Conner, J.; Nohl, J. F.; Allwood, D. A.; Collado-Rojas, C.; Kennerley, A.; Staniland, S.; Muthana, Nanobugs as Drugs: Bacterial Derived Nanomagnets	—	https://doi.org/10.1002/smll.202104763

		Enhance Tumor Targeting and Oncolytic Activity of HSV-1 Virus. Small 2022, 18 (13), 2104763. https://doi.org/10.1002/smll.202104763.		
16	Huh, W	K.; Brady, W. E.; Fracasso, P. M.; Dizon, D. S.; Powell, M. A.; Monk, B. J.; Leath, C. A.; Landrum, L. M.; Tanner, E. J.; Crane, E. K.; Ueda, S.; McHale, M. T.; Aghajanian, C. Phase II Study of Axalimogene Filolisbac (ADXS-HPV) for Platinum-Refractory Cervical Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study. Gynecologic Oncology 2020, 158 (3), 562–569. https://doi.org/10.1016/j.ygyno.2020.06.493.	—	https://doi.org/10.1016/j.ygyno.2020.06.493
17	Ijaz, M.; Hasan, I.; Chaudhry, T. H.; Huang, R.; Zhang, L.; Hu, Z.; Tan, Q.; Guo, B. Bacterial Derivatives Mediated Drug Delivery in Cancer Therapy: A New Generation Strategy. J Nanobiotechnol 2024, 22 (1), 510.		—	https://doi.org/10.1186/s12951-024-02786-w

	https://doi.org/10.1186/s12951-024-02786-w.			
18	Kwon, S.-Y.; Thi-Thu Ngo, H.; Son, J.; Hong, Y.; Min, J.-J. Exploiting Bacteria for Cancer Immunotherapy. Nat Rev Clin Oncol 2024, 21 (8), 569–589. https://doi.org/10.1038/s41571-02400908-9.		—	https://doi.org/10.1038/s41571-02400908-9
19	Lai, M	G.; Zhang, R.; Wang, L.-S.; Zeng, W. S. Bifidobacteria Expressing Tumstatin Protein for Antitumor Therapy in Tumor-Bearing Mice. Technol Cancer Res Treat 2016, 15 (3), 498–508. https://doi.org/10.1177/1533034615581977.	—	https://doi.org/10.1177/1533034615581977
20	Le, D	T.; Wang-Gillam, A.; Picozzi, V.; Greten, T. F.; Crocenzi, T.; Springett, G.; Morse, M.; Zeh, H.; Cohen, D.; Fine, R. L.; Onners, B.; Uram, J. N.; Laheru, D. A.; Lutz, E. R.; Solt, S.; Murphy, A. L.; Skoble, J.; Lemmens, E.; Grous, J.; Dubensky, T.; Brockstedt, D. G.; Jaffee, E. Safety and Survival With GVAX Pancreas Prime and	—	https://doi.org/10.1200/JCO.2014.57.4244

		Listeria Monocytogenes – Expressing Mesothelin (CRS-207) Boost Vaccines for Metastatic Pancreatic Cancer. Journal of Clinical Oncology 2015, 33 (12), 1325–1333. https://doi.org/10.1200/JCO.2014.57.4244.		
21	Liang, S.; Wang, C.; Shao, Y.; Wang, Y.; Xing, D.; Geng, Z. Recent Advances in BacteriaMediated Cancer Therapy. Front. Bioeng. Biotechnol. 2022, 10, 1026248. https://doi.org/10.3389/fbioe.2022.1026248.		—	https://doi.org/10.3389/fbioe.2022.1026248
22	Liu, X.; Wu, M.; Wang, M.; Duan, Y.; Phan, C.; Qi, G.; Tang, G.; Liu, B. Metabolically Engineered Bacteria as Light-Controlled Living Therapeutics for Anti-Angiogenesis Tumor Therapy. Mater. Horiz. 2021, 8 (5), 1454–1460. https://doi.org/10.1039/D0MH01582B.		—	https://doi.org/10.1039/D0MH01582B
23	Lou, X.; Chen, Z.; He, Z.; Sun, M.; Sun, J. Bacteria-Mediated Synergistic Cancer Therapy: Small Microbiome		—	https://doi.org/10.1007/s40820020-00560-9

	Has a Big Hope. Nano-Micro Lett. 2021, 13 (1), 37. https://doi.org/10.1007/s40820020-00560-9.			
24	Lu, J.; Tong, Q. From Pathogenesis to Treatment: The Impact of Bacteria on Cancer. Front. Microbiol. 2024, 15, 1462749. https://doi.org/10.3389/fmicb.2024.1462749.		—	https://doi.org/10.3389/fmicb.2024.1462749
25	Morales, A.; Eidinger, D.; Bruce, A. W. Intracavitary Bacillus Calmette-Guerin in the Treatment of Superficial Bladder Tumors. Journal of Urology 1976, 116 (2), 180–182. https://doi.org/10.1016/S0022-5347(17)58737-6.		—	https://doi.org/10.1016/S0022-5347(17)58737-6
26	Moreo, E.; Uranga, S.; Picó, A.; Gómez, A. B.; Nardelli-Haefliger, D.; Del Fresno, C.; Murillo, I.; Puentes, E.; Rodríguez, E.; Vales-Gómez, M.; Pardo, J.; Sancho, D.; Martín, C.; Aguilo, N. Novel Intravesical Bacterial Immunotherapy Induces Rejection of BCG-Unresponsive Established Bladder Tumors. J Immunother Cancer 2022, 10 (7),		—	https://doi.org/10.1136/jitc-2021-004325

	e004325. https://doi.org/10.1136/jitc-2021-004325.			
27	Ngo, N.; Choucair, K.; Creeden, J. F.; Qaqish, H.; Bhavsar, K.; Murphy, C.; Lian, K.; Albrethsen, M. T.; Stanbery, L.; Phinney, R. C.; Brunicardi, F. C.; Dworkin, L.; Nemunaitis, J. Bifidobacterium SPP : The Promising Trojan Horse in the Era of Precision Oncology. Future Oncol. 2019, 15 (33), 3861–3876. https://doi.org/10.2217/fon-2019-0374.		—	https://doi.org/10.2217/fon-2019-0374
28	Nguyen, D.-H.; Chong, A.; Hong, Y.; Min, J.-J. Bioengineering of Bacteria for Cancer Immunotherapy. Nat Commun 2023, 14 (1), 3553. https://doi.org/10.1038/s41467-023-39224-8.		—	https://doi.org/10.1038/s41467-023-39224-8
29	Nuyts, S.; Van Mellaert, L.; Theys, J.; Landuyt, W.; Lambin, P.; Anné, J. Clostridium Spores for Tumor-Specific Drug Delivery: Anti-Cancer Drugs 2002, 13 (2), 115–125. https://doi.org/10.1097/00001813-200202000-00002.		—	https://doi.org/10.1097/00001813-200202000-00002

30	Pal, S	K. Cabozantinib and Nivolumab with or without Live Bacterial Supplementation in Metastatic Renal Cell Carcinoma: A Randomized Phase 1 Trial. Nature Medicine 2024, 30 (9), 2576–2585. https://doi.org/10.1038/s41591-024-03086-4.	—	https://doi.org/10.1038/s41591-024-03086-4
31	Parks, T	P.; Takahashi, M.; Hayashi, A.; Kortylewski, M.; Caporaso, J. G.; Lee, K.; Tripathi, A.;	—	
32	Patyar, S.; Joshi, R.; Byrav, D. P.; Prakash, A.; Medhi, B.; Das, B. Bacteria in Cancer Therapy: A Novel Experimental Strategy. J Biomed Sci 2010, 17 (1), 21. https://doi.org/10.1186/1423-012717-21.		—	https://doi.org/10.1186/1423-012717-21
33	Sedighi, M.; Zahedi Bialvaei, A.; Hamblin, M. R.; Ohadi, E.; Asadi, A.; Halajzadeh, M.; Lohrasbi, V.; Mohammadzadeh, N.; Amiriani, T.; Krutova, M.; Amini, A.; Kouhsari, E. Therapeutic Bacteria to Combat Cancer; Current Advances, Challenges, and Opportunities. Cancer		—	https://doi.org/10.1002/cam4.2148

	Medicine 2019, 8 (6), 3167–3181. https://doi.org/10.1002/cam4.2148.			
34	Shi, L.; Sheng, J.; Wang, M.; Luo, H.; Zhu, J.; Zhang, B.; Liu, Z.; Yang, X. Combination Therapy of TGF-β Blockade and Commensal-Derived Probiotics Provides Enhanced Antitumor Immune Response and Tumor Suppression. Theranostics 2019, 9 (14), 4115–4129. https://doi.org/10.7150/thno.35131. León-Letelier, R. A.; Castro-Medina, D. I.; Badillo-Godinez, O.; Tepale-Segura, A.; HuanostaMurillo, E.; Aguilar-Flores, C.; De León-Rodríguez, S. G.; Mantilla, A.; Fuentes-Pananá, E. M.; López-Macías, C.; Bonifaz, L. C. Induction of Progenitor Exhausted Tissue-Resident Memory CD8+ T Cells Upon Salmonella Typhi Porins Adjuvant Immunization Correlates With Melanoma Control and Anti-PD-1 Immunotherapy Cooperation. Front. Immunol. 2020, 11, 583382. https://doi.org/10.3389/fimmu.2020.583382.		—	https://doi.org/10.7150/thno.35131

35	Shi, L.; Liu, X.; Li, Y.; Li, S.; Wu, W.; Gao, X.; Liu, B. Living Bacteria-Based ImmunoPhotodynamic Therapy: Metabolic Labeling of Clostridium Butyricum for Eradicating Malignant Melanoma. Advanced Science 2022, 9 (14), 2105807. https://doi.org/10.1002/advs.202105807.		—	https://doi.org/10.1002/advs.202105807
36	Sieow, B	F.-L.; Wun, K. S.; Yong, W. P.; Hwang, I. Y.; Chang, M. W. Tweak to Treat: Reprograming Bacteria for Cancer Treatment. Trends Cancer 2021, 7 (5), 447–464. https://doi.org/10.1016/j.trecan.2020.11.004.	—	https://doi.org/10.1016/j.trecan.2020.11.004
37	Sivan, A.; Corrales, L.; Hubert, N.; Williams, J. B.; Aquino-Michaels, K.; Earley, Z. M.; Benyamin, F. W.; Man Lei, Y.; Jabri, B.; Alegre, M.-L.; Chang, E. B.; Gajewski, T. F. Commensal Bifidobacterium Promotes Antitumor Immunity and Facilitates Anti–PD-L1 Efficacy. Science 2015, 350 (6264), 1084–		—	https://doi.org/10.1126/science.aac4255

	1089. https://doi.org/10.1126/science.aac4255.			
38	Song, S.; Vuai, M. S.; Zhong, M. The Role of Bacteria in Cancer Therapy – Enemies in the Past, but Allies at Present. Infect Agents Cancer 2018, 13 (1), 9. https://doi.org/10.1186/s13027-0180180-y.		—	https://doi.org/10.1186/s13027-0180180-y
39	Stein, M	N.; Fong, L.; Tutrone, R.; Mega, A.; Lam, E. T.; Parsi, M.; Vangala, S.; Gutierrez, A. A.; Haas, N. B. ADXS31142 Immunotherapy ± Pembrolizumab Treatment for Metastatic Castration-Resistant Prostate Cancer: Open-Label Phase I/II KEYNOTE-046 Study. The Oncologist 2022, 27 (6), 453–461. https://doi.org/10.1093/oncolo/oyac048.	—	https://doi.org/10.1093/oncolo/oyac048
40	Sun, R.; Liu, M.; Lu, J.; Chu, B.; Yang, Y.; Song, B.; Wang, H.; He, Y. Bacteria Loaded with Glucose Polymer and Photosensitive ICG Silicon-Nanoparticles for		—	https://doi.org/10.1038/s41467-022-32837-5

	Glioblastoma Photothermal Immunotherapy. Nat Commun 2022, 13 (1), 5127. https://doi.org/10.1038/s41467-022-32837-5.			
41	Tomita, Y.; Ikeda, T.; Sakata, S.; Saruwatari, K.; Sato, R.; Iyama, S.; Jodai, T.; Akaike, K.; Ishizuka, S.; Saeki, S.; Sakagami, T. Association of Probiotic Clostridium Butyricum Therapy with Survival and Response to Immune Checkpoint Blockade in Patients with Lung Cancer. Cancer Immunology Research 2020, 8 (10), 1236–1242. https://doi.org/10.1158/2326-6066.CIR20-0051.		—	https://doi.org/10.1158/2326-6066.CIR20-0051
42	Toso, J	F.; Gill, V. J.; Hwu, P.; Marincola, F. M.; Restifo, N. P.; Schwartzentruber, D. J.; Sherry, R. M.; Topalian, S. L.; Yang, J. C.; Stock, F.; Freezer, L. J.; Morton, K. E.; Seipp, C.; Haworth, L.; Mavroukakis, S.; White, D.; MacDonald, S.; Mao, J.; Sznol, M.; Rosenberg, S. A. Phase I Study of the Intravenous	—	https://doi.org/10.1200/JCO.2002.20.1.142

		Administration of Attenuated Salmonella Typhimurium to Patients With Metastatic Melanoma. Journal of Clinical Oncology 2002, 20 (1), 142–152. https://doi.org/10.1200/JCO.2002.20.1.142.		
43	Wang, L.; Vuletic, I.; Deng, D.; Crielaard, W.; Xie, Z.; Zhou, K.; Zhang, J.; Sun, H.; Ren, Q.;		—	
44	Wei, C.; Xun, A. Y.; Wei, X. X.; Yao, J.; Wang, J. Y.; Shi, R. Y.; Yang, G. H.; Li, Y. X.; Xu, Z. L.;		—	
45	Wood, L	M.; Paterson, Y. Attenuated Listeria Monocytogenes: A Powerful and Versatile Vector for the Future of Tumor Immunotherapy. Front. Cell. Infect. Microbiol. 2014, 4. https://doi.org/10.3389/fcimb.2014.00051. Van Pijkeren, J. P.; Morrissey, D.; Monk, I. R.; Cronin, M.; Rajendran, S.; O'Sullivan, G. C.; Gahan, C. G. M.; Tangney, M. A Novel Listeria Monocytogenes -Based DNA Delivery System for Cancer Gene	—	https://doi.org/10.3389/fcimb.2014.00051

		Therapy. Human Gene Therapy 2010, 21 (4), 405–416. https://doi.org/10.1089/hum.2009.022.		
46	Xu, W.; Ren, D.; Yu, Z.; Hou, J.; Huang, F.; Gan, T.; Ji, P.; Zhang, C.; Ma, L.; Hu, Y. BacteriaMediated Tumor Immunotherapy via Photothermally-Programmed PD1 Expression. Nanoscale Adv. 2022, 4 (6), 1577–1586. https://doi.org/10.1039/D1NA00857A.		—	https://doi.org/10.1039/D1NA00857A
47	Xu, H.; Piao, L.; Wu, Y.; Liu, X. IFN-γ Enhances the Antitumor Activity of Attenuated Salmonella-Mediated Cancer Immunotherapy by Increasing M1 Macrophage and CD4 and CD8 T Cell Counts and Decreasing Neutrophil Counts. Front. Bioeng. Biotechnol. 2022, 10, 996055. https://doi.org/10.3389/fbioe.2022.996055.		—	https://doi.org/10.3389/fbioe.2022.996055
48	Yan, S.; Gan, Y.; Xu, H.; Piao, H. Bacterial Carrier-Mediated Drug Delivery Systems: A Promising Strategy in Cancer Therapy. Front.		—	https://doi.org/10.3389/fbioe.2024.1526612

	Bioeng. Biotechnol. 2025, 12, 1526612. https://doi.org/10.3389/fbioe.2024.1526612.			
49	Yazawa, K.; Fujimori, M.; Amano, J.; Kano, Y.; Taniguchi, S. Bifidobacterium Longum as a Delivery System for Cancer Gene Therapy: Selective Localization and Growth in Hypoxic Tumors. Cancer Gene Ther 2000, 7 (2), 269–274. https://doi.org/10.1038/sj.cgt.7700122.		—	https://doi.org/10.1038/sj.cgt.7700122
50	Yi, X.; Zhou, H.; Chao, Y.; Xiong, S.; Zhong, J.; Chai, Z.; Yang, K.; Liu, Z. Bacteria-Triggered Tumor-Specific Thrombosis to Enable Potent Photothermal Immunotherapy of Cancer. Sci. Adv. 2020, 6 (33), eaba3546. https://doi.org/10.1126/sciadv.aba3546.		—	https://doi.org/10.1126/sciadv.aba3546
51	Zheng, P.; Fan, M.; Liu, H.; Zhang, Y.; Dai, X.; Li, H.; Zhou, X.; Hu, S.; Yang, X.; Jin, Y.; Yu, N.; Guo, S.; Zhang, J.; Liang, X.-J.; Cheng, K.; Li, Z. Self-Propelled and Near-		—	https://doi.org/10.1021/acsnano.0c08068

	InfraredPhototaxic Photosynthetic Bacteria as Photothermal Agents for Hypoxia-Targeted Cancer Therapy. ACS Nano 2021, 15 (1), 1100–1110. https://doi.org/10.1021/acsnano.0c08068.			