MICHIGAN SYNTHETIC BIOLOGY TEAM

MAGNOLYSE

Magnetism Meets Medicine:

Ethical Reflections on a Bacteria-Based Cancer Treatment

TABLE OF CONTENTS

INTRODUCTION

Over two million Americans will be diagnosed with cancer in 2025 [1]. As the second-leading cause of death in the United States, cancer is a well-characterized but poorly addressed illness [2]. While current treatments such as surgery, chemotherapy, and radiation can be lifesaving, they often come with serious side effects. The treatments usually weaken the immune system, damage healthy tissue, and leave patients exhausted. Researchers have long looked for ways to decrease these known risks by making cancer therapy more precise, attacking tumors directly without harming the rest of the body.

Over a century ago, Dr. William Coley experimented with injecting cancer patients with *Streptococcus* bacteria [3]. While some tumors reduced in size, many patients ultimately died of infection [3]. In 1976, building on Dr. Coley's experiments, scientists attempted to treat cancer by injecting patients with other strains, observing that the *Mycobacterium bovis*-based BCG vaccine could safely inhibit bladder tumor recurrence [4].

In the years since Coley's efforts, biologists have developed a far more comprehensive understanding of bacterial immunotherapies. Between modifying *E. coli* to prevent tumor metastasis [5], engineering *P. putida* to aid in drug intake [6], and searching other genomes for useful parts, they've continued to build safer, less invasive routes to treatment. The pressing matter in their research is not drug discovery but rather drug *delivery* – enabling faster progress to improving patient outcomes via a narrower scope of focus.

The novelty of such treatments, however, prompts a few questions. Beyond the need for studies on long-term efficacy, one must also consider the practicality of the treatments. Concerns about cost, scope, and accessibility are vital to address in order to serve our community best. For instance, issues in procurement and distribution tend to arise predictably. While bacterial therapeutics can be synthesized at a price roughly 30,000 times less than traditional oncolytic therapies [7], problems may occur during transport. Keeping bacteria viable is no simple feat; if a strain is to be transported hundreds of miles at a time, distributors must invest in processes to either prolong the cells' lifespan or implement robust storage systems. This effort is especially relevant for patients who lack access to specialized treatment centers. The importance of designing a pragmatic therapy cannot be understated.

More crucially, though, we must understand how any given solution fits the needs of relevant populations (without causing undue harm). Our research is focused on modifying

Magnetospirillum magneticum strain AMB-1 to target and lyse serous ovarian tumors. In catering to a vulnerable community – primarily post-menopausal, immunocompromised women [8] – our treatment must mitigate risk, remain productive, and be accessed equitably.

In turn, we propose a bioethical framework to evaluate our project's responsiveness to such matters. We evaluate our work under four pillars – beneficence, non-maleficence, autonomy, and justice – with the goal of forging well-rounded perspectives on its use. Beneficence and non-maleficence respectively describe doing good and avoiding harm. Justice, in this case, is a matter of our treatment's social impact and accessibility. Autonomy sets standards for informed consent between patients, providers, and families.

Bioethics enables researchers to understand the sensibility of their treatment, offering insights beyond benchwork. It encourages a deeper look into how, where, and when a treatment may be implemented. Evaluating the ethical consequences of our project is essential for providing the community with necessary information, both positive and negative, about our project and the current state of knowledge in the field of bacterial therapy. Ethical perspectives remain vital to any research process (including our own), as in the midst of interpreting prior findings, they provide valuable input into designing new ones.

BACKGROUND

Our project revolves around AMB-1, a strain of *Magnetospirillum magneticum* sensitive to relatively weak magnetic fields [9]. AMB-1 is naturally magnetotactic, meaning that these fields can guide its movement. AMB-1 contains a set of "magnetosomes," phospholipid-coated deposits of iron(II,III) oxide, that are responsible for this phenomenon. Moreover, AMB-1 is microaerophilic and supports this need by following oxygen gradients to reach more hypoxic regions.

As part of our work, we've designed a protocol to convert AMB-1 into a vehicle for treating high-grade serous ovarian cancer (HGSOC). Such cancer is characterized by hypoxic and immunosuppressive tumor growth, along with overexpression of folate receptor alpha (FRα). HGSOC typically begins in the epithelium of the distal fallopian tubes, rapidly spreading throughout the peritoneal cavity. AMB-1's ability to navigate against oxygen gradients would allow it to migrate towards such tumor sites independently, and the use of an external magnetic field would take advantage of its magnetotactic qualities to ensure accurate localization. The

protocol uses a dual-plasmid system, administered via conjugation, to turn AMB-1 cells into delivery capsules for a tumor-suppressing therapeutic.

Our first plasmid (a "localization" plasmid) expresses a folate ligand capable of binding to FRα. This ligand is expressed upstream of the fluorescent protein miniSOG, which can be used for visualization of the bacteria's activity. The second plasmid (our "therapeutic" plasmid) expresses the toxin Cytolysin A (ClyA) dependent on the activation of a heat shock promoter. ClyA is a cytotoxin derived primarily from *Escherichia coli*, although AMB-1 also possesses the machinery to synthesize it [10]. The promoter is activated only upon temperature increases, which we plan to trigger using an alternating magnetic field (AMF).

With the localization plasmid's promoter induced to express the FRα ligand, a modified population of AMB-1 is first injected near a given tumor site. As needed, an external magnetic field may be used to facilitate the population's movement towards the tumor site. An AMF is then used to activate the remaining therapeutic plasmid. By constantly flipping its polarity, an AMF can cause the bacteria to rapidly alternate their direction of movement. This action results in the bacteria "vibrating," which eventually causes an increase in internal temperature and activates the therapeutic plasmid's heat shock promoter. After the heat shock promoter is activated, Cytolysin A is expressed and migrates out of AMB-1 towards a given tumorous region. Cytolysin A, once released, works by creating pores in a targeted tumor cell, forcing the cell to lyse upon stress [11].

Since AMB-1 is non-pathogenic, it does not elicit an immune response from the body at any point during treatment [12]. After the ovarian tumor cells are lysed, the bacteria de-localize as their folate ligands are no longer associated with FRα receptors. The plasma membranes of the tumor cells are disrupted, causing conformational changes to the FRα receptors that lead to ligand dissociation. AMB-1 is subsequently flushed out of the body by the digestive system, finding its way into the small intestine and being excreted in stool [13]. The lysed cancer cells are no longer able to divide or sustain themselves, meeting a similar fate to AMB-1.

BENEFICENCE

For a treatment to be beneficent, it must be effective and serve its intended purpose well. In our case, we can establish a few benchmarks for success: localization to tumorous regions in the ovaries, expression of Cytolysin A, and tumor cell death.

Overexpression of FRα is a common symptom of ovarian cancer, particularly in recurrent tumors [14]. By using folate to mediate the delivery of ClyA, AMB-1 is provided with appropriate and high-affinity machinery for binding to the surface of HGSOC cells [12]. Folate ligands expressed by AMB-1 can form clumps of receptor-ligand complexes along the plasma membrane of tumor cells, enabling secure localization along multiple axes [15].

Moreover, AMB-1 preferentially migrates to hypoxic regions due to its microaerophilic nature [16]. HGSOC is characterized by hypoxic tumor growth, suggesting compatibility with this trait. AMB-1 has also been shown to migrate independently to solid tumors, ensuring broader localization towards the ovarian epithelium. AMB-1's native migration mechanisms guarantee more coarse-grained control over its localization, whereas the design of our localization plasmid offers more fine-tuned controls.

Once bound to tumor cells via FRα, our modified AMB-1 awaits an increase in temperature to trigger expression of ClyA. Heat shock is initiated by activation of an alternating magnetic field (AMF) with a strength of 2.5 T – a level capable of heating AMB-1 to the requisite 42°C for promoter activation [17]. Upon translation, ClyA is released from AMB-1 into the HGSOC cells. ClyA forms pores in the plasma membranes of such cells, resulting in an osmotic imbalance that ends in lysis – cell death, in other words [18].

Through its native and modified design, AMB-1 can effectively migrate towards cancer cells in hypoxic tumor regions. The bacteria's innate response to AMF enables them to reach an adequate temperature for activation of the therapeutic plasmid, leading to precise ClyA expression. ClyA's lysing ability contributes to cell death in HGSOC, marking our therapy's intended effect. Through targeted cell death, tumor volume can be meaningfully reduced, and chances of remission can follow a similar trend [19].

NON-MALEFICENCE

Avoiding harm is crucial to the success of any treatment. Non-maleficence goes hand in hand with beneficence, allowing a treatment not only to show effectiveness but also to minimize risk. The approach of Magnolyse centers on exclusive target-binding machinery, visualization, and multi-step administration to achieve success in this regard.

Exclusivity comes from the fact that FRα expression is limited in non-tumorous tissue, preventing AMB-1 from localizing to healthy cells [15]. The overexpression of FRα in HGSOC

cells is a rather unique trait, as nearby cells in the ovaries (and throughout the reproductive tract) tend not to exhibit the same phenomenon. A lack of alternative ligands on AMB-1 prevents it from attaching to any other cell type but those overexpressing FRα, again promoting specificity in its localization. Off-target effects are thus minimized as ClyA, once expressed, will only travel into cells to which AMB-1 is adhered.

The adherence and detection plasmid also contains miniSOG, a fluorescent protein, downstream of the sequence encoding AMB-1's folate receptor ligand. MiniSOG's fluorescence can be used to track the exact location of AMB-1 within ovarian tissue. The protein is capable of fluorescing in hypoxic regions, such as the regions surrounding serous ovarian tumors. Moreover, the fact that miniSOG is expressed downstream of the folate receptor ligand adds a layer of accuracy to its use. Imaging will not reveal fluorescence until the folate has been expressed, meaning that every bit of fluorescence revealed in an image shows the precise location of AMB-1 cells binding to HGSOC cells. Therefore, clinicians administering this treatment will have a reference for its progress. They will be able to keep tabs on the location of AMB-1 cells not only at the time of localization, but also up until the point of excretion. As such, providers can verify that the therapeutic is being distributed in the correct areas and correct the bacteria's course if necessary via an external magnetic field.

Moreover, it is intentional that the treatment is not continuous from start to finish. After intravenous injection of the AMB-1 and guidance with an external magnetic field, the next step in administration is to validate the bacteria's localization via miniSOG. Once the provider has confirmed that the bacteria have accurately populated the tumor site, a checkpoint arises: AMF activation. Turning on an alternating magnetic field is a manual process, in that the provider must make a conscious decision to proceed with the treatment at this point. Once the treatment has been approved to continue by the provider, the AMF (not sustained for enough time to significantly disrupt the metabolic activities of nearby cells) initiates expression of Cytolysin A.

As Cytolysin A cannot be expressed without AMF-triggered heat shock, it can be concluded that its translation is conditional. It is a highly regulated process, and its initiation requires further attention from the provider (activating the AMF appropriately). Adding such pauses not only encourages providers to offer more attention to the treatment but also offers points for intervention if necessary. If a patient or physician objects to some part of the therapy,

whether out of emotion or physiological need, the AMF checkpoint offers an "out" to minimize risks in continuing the treatment.

If the treatment is halted before AMF activation, the therapeutic plasmid will remain inactive (leaving ClyA unexpressed). AMB-1 is non-pathogenic [20], digestible, and even if internalized by HGSOC cells, is highly likely to be degraded lysosomally. This aspect of AMB-1 also contributes to post-treatment safety, with its magnetosomes easily excreted via the fecal route [13].

The use of AMB-1, along with its two modified plasmids, presents a novel yet minimally risky approach to targeting ovarian tumors. Between localization, heat shock, and digestion, the treatment is designed around highly controllable steps with rigorous attention to safety.

JUSTICE

A useful treatment can be accessed easily and equitably. We've designed our protocols with simplicity in mind, to keep both production costs and treatment prices as low as possible. Strains of *Magnetospirillum* are commonly found in freshwater sediment throughout Europe [21, 22] and Asia [23, 24]. The ease of finding magnetotactic bacteria (not limited to AMB-1) is matched by its ease of isolation.

Growing a colony of AMB-1 is relatively inexpensive. MsGM culture medium, an industry standard in liquid bacterial culture, can be used to plate AMB-1 [13]. The caveat of maintaining a microaerophilic environment for the bacteria can also be overcome by ensuring that the colony is grown in a sealed container. Moreover, the process of conjugating AMB-1 to insert additional plasmids is not inherently difficult. While low-copy numbers have presented some challenges in our own lab work, facilities with larger manufacturing capabilities may be able to use techniques such as library construction and fluorescence-activated cell sorting (FACS) to address these issues [25].

When these limitations are overcome, conjugating AMB-1 can be a scalable process. The conjugation step can be condensed into a single protocol, which can be completed in under five hours. This speed can likely be improved upon by pharmaceutical companies with larger manufacturing capabilities, and the simplicity of the protocol can also encourage mass production efforts to lower costs.

Once transformed, the bacteria face an imposing hurdle: distribution. It is inherently challenging to keep bacteria alive as they are transported across cities, states, and countries. AMB-1 is no exception to this rule, but it should be noted that the strain does not require a tremendous amount of resources to remain stable. Cryopreservation and lyophilization would each work to maintain cell integrity in transportation, and infrastructure for biomaterial transportation (such as cells) is already robust throughout the world. Nothing more than a cooled truck is required to transport such cells from one location to another, facilitating access across markets.

Solutions to generating AMF currents, though, arrive a bit less intuitively. Between coils, sensors, and shields, a current-generating system (suitable for clinical use) could be costly to build from scratch. We therefore found it essential to explore alternatives before settling on a research-and-development route.

Fortunately, we realized that magnetic fluid hyperthermia (MFH) devices – existing treatment systems also reliant on AMFs – are conducive to our approach. MFH systems utilize solenoid-type coils to generate alternating magnetic fields, which are then used to heat magnetic nanoparticles injected into bodily tissue [26]. Among these nanoparticles are the same iron(II,III) oxide chains found in AMB-1 magnetosomes. Field strength is adjustable within a given system, enabling a precisely tuned heat shock.

Certain MFH devices have already been approved for clinical use, allowing us to obtain relatively accurate estimates of their costs. Most recently, NanoTherm® (from MagForce AG) was greenlit throughout Europe. Based on early assumptions, a single course of NanoTherm® treatment is expected to cost approximately €23,000 (roughly $27,000 as of October 2025). This figure is high, but it pales in comparison to the cost of treatment via “traditional” routes – chemotherapy, primarily [27]. As of 2023, the latter is priced at over €70,000 (approximately $84,000 as of October 2025) per patient [28]. MFH systems complement our approach in a way that passes savings on to patients, furthering access across socioeconomic bounds.

Beyond the question of cost, however, it is important to consider whether this treatment will have different impacts on patients from varying backgrounds. The therapy’s primary target, as mentioned earlier, is the folate receptor alpha. The effectiveness of Cytolysin A depends on AMB-1 being able to localize to HGSOC cells, which is again a result of the overexpression of folate receptors on tumor cell surfaces. FRα overexpression is a generalizable symptom for

patients, occurring at similar rates between women of varying ethnicities and ages [29]. It is therefore clear that this treatment's success is independent of patient demographics, maintaining effectiveness across cases.

AUTONOMY

Autonomy is centered around the patient's right to make informed decisions about their own treatment. Patients must be able to understand what the therapy is, how it works, and any potential risks before taking action. Autonomy does not remain solely in the hands of patients, and providers must take action to ensure that patients and their families fully understand the risks and benefits of the treatment plan.

To explore how these ethical considerations are perceived, we designed a survey to gather more insight. We recruited participants who reported direct or indirect experience with cancer care to provide insight into how individuals who are familiar with cancer treatment might view bacterial therapy. Our survey began with a series of questions designed to gauge respondents' prior understanding of cancer treatment, allowing us to assess their familiarity with bacteria-based cancer treatments and existing therapies (Table 1). This was followed by questions regarding perceived risks and benefits (Table 2).

Table 1. Average responses (on a scale from 1-10) to broader prompts related to existing cancer treatment and bacterial therapies.

Prompt	*Knowledge of the cancer treatment process*	*Familiarity with bacterial therapies*	*Favorability of bacteria being used in medicine*
Avg. Rating (out of 10)	5.125	3.375	2.75

Prompt	*Open-mindedness on bacterial therapies*
Avg. Rating (out of 10)	7.5

Table 2. Selected (recurring) responses to prompts on perceived risks and benefits of bacterial cancer treatment – prior to project introduction.

Perceived risks	**Perceived benefits**
"Off-target impacts such as decreased immune function"	"Higher precision and sensitivity"
"Compromised immune system"	"Prolong survival in advanced settings"
"Damage to healthy cells"	"Possibility for a breakthrough in treatment with

	reduced side effects”
“Overall illness, exhaustion, nausea”	“More effective, less side effects, less trauma”

While participants showed limited familiarity with the idea of bacterial cancer treatment, they appeared moderately informed of the broader oncological process (Table 1). Lower support for the use of bacteria in the medical field was evident in participants’ responses to the *risk*-related questions. Contrarily, a higher open-mindedness score translated into promising responses to the *benefits* prompt. It should also be noted that “off-target effects” were brought up on both sides of the risk-benefit analysis, highlighting the issue as a high priority for respondents (Tables 1, 2).

After gauging some of our respondents’ broader opinions, we introduced them to our project. We designed an infographic to provide a brief overview of our proposal (Fig. 1).

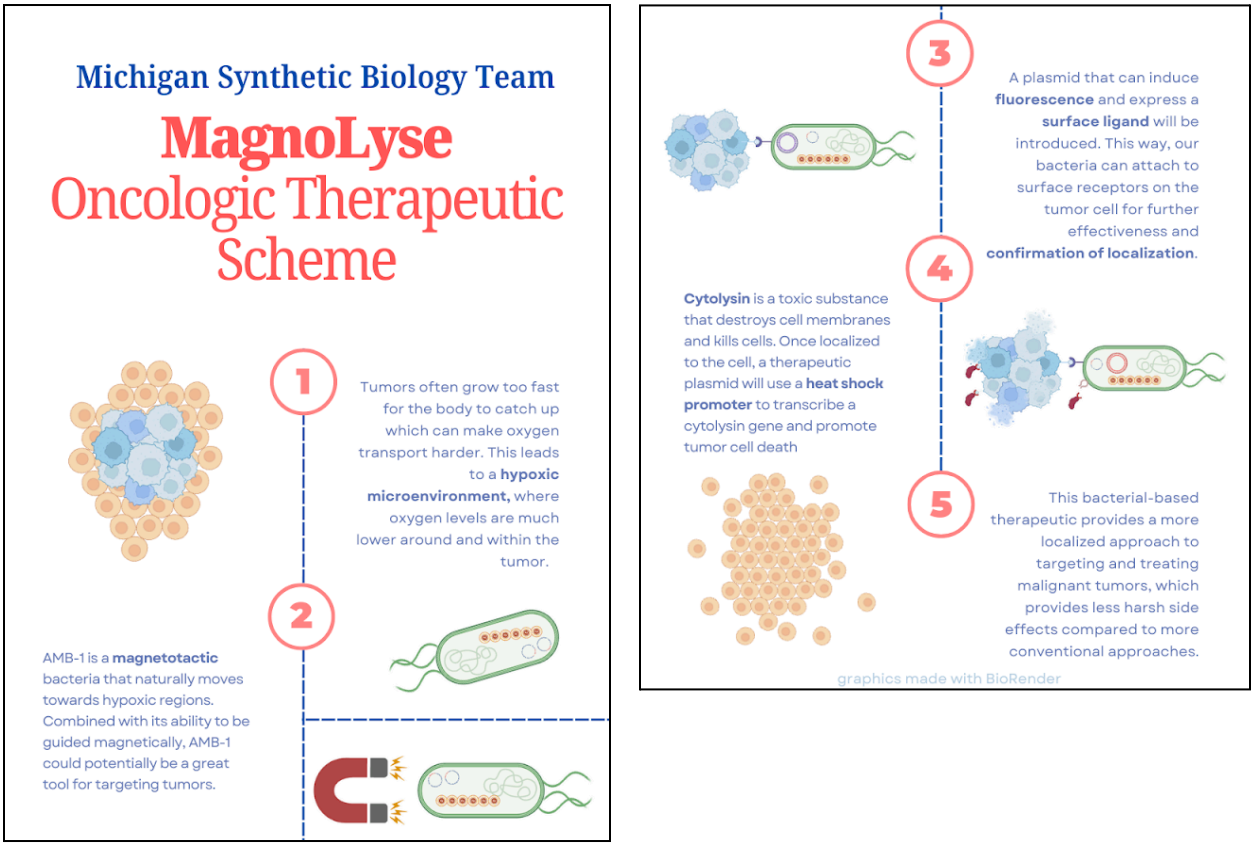

Figure 1. Descriptive infographic included in survey.

After presenting the infographic, we asked participants to share their opinions on several topics related to our project: understanding, favorability, points of hesitation, and, once again, risks and benefits.

Table 3. Average response (on a scale from 1-10) to a question asking how well participants understood the project.

Prompt	*Understanding of project*
Avg. Rating (out of 10)	7.5

Table 4. Selected (recurring) responses to prompts on favorable and unfavorable components of the proposal.

Favorable components	**Points of hesitation**
"Highly tuned and sensitive system"	"Unproven track record. Very experimental."
"More specific to the tumor"	"Are there no other hypoxic regions that the bacteria could be drawn to?"
"The apparent accuracy of the bacteria, and the eventual death of cancer cells"	"Literally burning the tissue seems like it could easily end up damaging healthy tissue"
"The ability to localize treatment"	"I don't know the other impacts of the bacteria and the other things injected on the rest of a human body."

Table 5. Selected (recurring) responses to prompts on perceived risks and benefits of bacterial cancer treatment – after project introduction.

Perceived risks	**Perceived benefits**
"Immune system activation against bacteria."	"Could have fewer side effects than typical treatment, might be more direct"
"Potential mistargeting"	"Creative in approach with potential high efficacy."
"Bacteria evolving, treatment failing"	"Localized attack with reduced side effects"
"Bacteria accidentally targeting the wrong environment"	"Potential synergy…it could be combined with immunotherapy"

With a mean *understanding* score of 7.5, it is clear that respondents showed a meaningful comprehension of our approach (Table 3). As with earlier prompts on risks and benefits, specificity was commonly seen as an advantage by respondents (Tables 4 and 5). Points of hesitation were also similar to the risks outlined in pre-infographic questions (Table 2), centering on a lack of known side effects (Tables 4 and 5).

Although there appeared to be no significant differences in perceptions of risk and benefit after the introduction of the infographic, it is worth noting that participants provided precise

descriptions of their opinions (Tables 4 and 5). All participants submitted explicit descriptions of the risks and benefits associated with the treatment, avoiding vague language (Table 5). This lack of ambiguity in responses may be reflective of a lack of ambiguity in understanding. In other words, it is promising to see participants offering clear and explicit opinions on our treatment. Their opinions appear well-informed and specific to bacterial cancer therapy, offering a testament to their understanding of our project (and the usefulness of ideas shown in the infographic).

Broadly speaking, the survey served three purposes: to estimate patients' understanding of the treatment, to gauge perceptions of risk and benefit, and to gather broader opinions from respondents. Each of these topics constitutes a key part of informed consent, which enables clinicians and patients to achieve a mutual understanding and acceptance of a treatment. Our respondents were able to form meaningful opinions on our treatment with a high degree of understanding.

Our infographic showcases the simplicity with which our treatment can be effectively explained, allowing physicians to use similar terminology and phrasing to describe the treatment to their patients. Autonomy involves a patient's right to know, understand, and have a say in their treatment. Even if this involves refusal midway through treatment, our multi-step administration (as outlined under "Non-Maleficence") allows patients to opt out of treatment safely.

DISCUSSION

The effectiveness of a treatment cannot be defined exclusively by in vitro successes. In addition to fulfilling its intended purpose, it should also protect, be accessible to, and be well understood by a patient. Beneficence, non-maleficence, justice, and autonomy are crucial to the design process, as each should be actively considered by the researchers creating the treatment.

We worked to achieve precisely this. Our plasmid design, choice of bacteria, and magnetic field setups ensure efficacy in tumor cell death and AMB-1 localization. The specificity of FRα, fluorescent properties of miniSOG, and manual activation of our AMF work together to minimize risk wherever possible. Low material costs, scalability, and universal application ensure our treatment is accessible. Survey respondents' understanding of our project's premise, risks, and benefits marks a crucial stride towards furthering autonomy.

While further research is needed for a comprehensive understanding of our proposal, baselines for each of the four pillars of bioethics have been met. Future studies may focus more on the practical aspects of developing this treatment, such as cost analysis and demand forecasting. It may be challenging to estimate the distribution costs of a novel treatment, but it is worthwhile to examine the issue to get closer to an answer.

Bioethics is a unique lens that allows researchers to conduct meaningful studies outside the laboratory. It focuses on the less quantifiable aspects of research – the where, why, and how of implementing a treatment. Ovarian cancer maintains a persistent need to be addressed with low-cost, minimally invasive procedures, and we anticipate that our work treads a few steps closer to meeting this need.

REFERENCES

[1] National Cancer Institute, "Common Cancer Sites (SEER Cancer Stat Facts)," SEER, accessed Sep. 2025. [Online]. Available: https://seer.cancer.gov/statfacts/html/common.html

[2] Centers for Disease Control and Prevention, "Leading Causes of Death," NCHS FastStats, accessed Sep. 2025. [Online]. Available: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

[3] S. Felgner, D. Kocijancic, M. Frahm, and S. Weiss, "Bacteria in cancer therapy: renaissance of an old concept," *International Journal of Microbiology*, vol. 2016, Article ID 8451728, 2016. [Online]. Available: https://doi.org/10.1155/2016/8451728

[4] A. Morales, D. Eidinger, and A.W. Bruce, "Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder cancer," *Journal of Urology*, vol. 116, no. 2, pp. 180–183, 1976. [Online]. Available: https://doi.org/10.1016/S0022-5347(17)58737-6

[5] S.-N. Jiang, T.-X. Phan, T.-K. Nam, V.-H. Nguyen, H.-S. Kim, H.-S. Bom et al, "Inhibition of tumor growth and metastasis by a combination of Escherichia coli–mediated cytolytic therapy and radiotherapy," *Molecular Therapy*, vol. 18, no. 3, pp. 635–642, Mar. 2010. [Online]. Available: https://doi.org/10.1038/mt.2009.295

[6] Z. Asadi, E. Arkan, G. Nowroozi, and F. Aghaz, "Novel Pseudomonas putida-derived nanoliposomes enhance the inhibition of MCF-7 breast cancer cells by superb intracellular uptake of doxorubicin," *Heliyon*, vol. 10, no. 19, p. e38337, Oct. 2024. [Online]. Available: https://doi.org/10.1016/j.heliyon.2024.e38337

[7] K. Prifti, C. Y. Chabu, K. S. Kobayashi, J. Song, A. Han, and P. de Figueiredo, "Bacterial therapeutics: addressing the affordability gap in cancer therapy," *Cancer Research*, vol. 85, no. 14, pp. 2558–2560, Jul. 2025. [Online]. Available: https://doi.org/10.1158/0008-5472.CAN-25-0870

[8] M.-A. Lisio, L. Fu, A. Goyeneche, Z.-h. Gao, and C. Telleria, "High-grade serous

ovarian cancer: basic sciences, clinical and therapeutic standpoints," *International Journal of Molecular Sciences*, vol. 20, no. 4, p. 952, Feb. 2019. [Online]. Available: https://doi.org/10.3390/ijms20040952

[9] X. Zhu, X. Ge, N. Li, L.-F. Wu, C. Luo, Q. Ouyang et al, "Angle sensing in magnetotaxis of *Magnetospirillum magneticum* AMB-1," *Integrative Biology*, vol. 6, no. 7, pp. 706–713, Jul. 2014. [Online]. Available: https://doi.org/10.1039/c3ib40259b

[10] L. Liu, J. Wu, J. Gao, and X. Lu, "Bacteria-derived nanoparticles: multifunctional containers for drug delivery and cancer therapy," *Advanced Healthcare Materials*, vol. 9, no. 20, p. 2000893, Oct. 2020. [Online]. Available: https://doi.org/10.1002/adhm.202000893

[11] A. Ludwig, C. von Rhein, S. Bauer, C. Hüttinger, and W. Goebel, "Molecular analysis of cytolysin A (ClyA) in pathogenic *Escherichia coli* strains," *Journal of Bacteriology*, vol. 186, no. 16, pp. 5311–5320, Aug. 2004. [Online]. Available: https://doi.org/10.1128/jb.186.16.5311-5320.2004

[12] L. M. McGinley, A. M. McGarry, M. R. McGarry, and J. C. McGarry, "Magnetic resonance imaging of human neural stem cells in vivo," *Stem Cells Translational Medicine*, vol. 10, no. 2, pp. 135–144, Feb. 2021. [Online]. Available: https://doi.org/10.1002/sctm.20-0126

[13] E. Alphandéry, S. Faure, O. Seksek, F. Guyot, and I. Chebbi, "Chains of magnetosomes extracted from *Magnetospirillum magneticum* AMB-1: A new class of magnetic nanoparticles for cancer therapy," *ACS Nano*, vol. 5, no. 11, pp. 8752–8761, Nov. 2011. [Online]. Available: https://doi.org/10.1021/nn201290k

[14] K. R. Kalli, A. L. Oberg, G. L. Keeney, T. J. H. Christianson, P. S. Low, K. L. Knutson et al, "Folate receptor alpha as a tumor target in epithelial ovarian cancer," *Gynecologic Oncology*, vol. 108, no. 3, pp. 619–626, Mar. 2008. [Online]. Available: https://doi.org/10.1016/j.ygyno.2007.11.020

[15] M. Scaranti, E. Cojocaru, S. Banerjee, and U. Banerji, “Exploiting the folate receptor α in oncology,” *Nature Reviews Clinical Oncology*, vol. 17, no. 6, pp. 349–359, Jun. 2020. [Online]. Available: https://doi.org/10.1038/s41571-020-0339-5

[16] X. Chen, L. Lai, X. Li, X. Cheng, X. Shan, X. Liu et al, “Magnetotactic bacteria AMB-1 with active deep tumor penetrability for magnetic hyperthermia of hypoxic tumors,” *Biomaterials Science*, vol. 10, no. 22, pp. 6510–6516, Oct. 2022. [Online]. Available: https://doi.org/10.1039/D2BM01029A

[17] Y. N. Zhou, N. Kusukawa, J. W. Erickson, C. A. Gross, and T. Yura, “Isolation and characterization of *Escherichia coli* mutants that lack the heat shock sigma factor σ32,” *Journal of Bacteriology*, vol. 170, no. 8, pp. 3640–3649, Aug. 1988. [Online]. Available: https://doi.org/10.1128/jb.170.8.3640-3649.1988

[18] J. Oscarsson, Y. Mizunoe, L. Li, X. H. Lai, A. Wieslander, and B. E. Uhlin, “Molecular analysis of the cytolytic protein ClyA (SheA) from *Escherichia coli*,” *Molecular Microbiology*, vol. 32, no. 6, pp. 1226–1238, Jun. 1999. [Online]. Available: https://doi.org/10.1046/j.1365-2958.1999.01435.x

[19] R. K. Jain, J. J. Lee, C. Ng, D. Hong, J. Gong, A. Naing, et al, “Change in tumor size by RECIST correlates linearly with overall survival in phase I oncology studies,” *Journal of Clinical Oncology*, vol. 30, no. 21, pp. 2684–2690, Jul. 2012. [Online]. Available: https://doi.org/10.1200/JCO.2011.36.4752

[20] S. Menghini, P. S. Ho, T. Gwisai, and S. Schuerle, “Magnetospirillum magneticum as a living iron chelator induces TfR1 upregulation and decreases cell viability in cancer cells,” *International Journal of Molecular Sciences*, vol. 22, no. 2, p. 498, Jan. 2021. [Online]. Available: https://doi.org/10.3390/ijms22020498

[21] M. Dziuba, V. Koziaeva, D. Grouzdev, E. Burganskaya, R. Baslerov, T. Kolganova et al, “Magnetospirillum caucaseum sp. nov., Magnetospirillum marisnigri sp. nov. and Magnetospirillum moscoviense sp. nov., freshwater magnetotactic bacteria isolated from three distinct geographical locations in European Russia,” *International Journal*

of Systematic and Evolutionary Microbiology, vol. 66, no. 5, pp. 2069–2077, May 2016. [Online]. Available: https://doi.org/10.1099/ijsem.0.000994

[22] K. H. Schleifer, D. Schüler, S. Spring, M. Weizenegger, R. Amann, W. Ludwig et al, "The genus *Magnetospirillum* gen. nov. Description of *Magnetospirillum gryphiswaldense* sp. nov. and transfer of *Aquaspirillum magnetotacticum* to *Magnetospirillum magnetotacticum* comb. nov.," *Systematic and Applied Microbiology*, vol. 14, no. 4, pp. 379–385, 1991. [Online]. Available: https://doi.org/10.1016/S0723-2020(11)80313-9

[23] H. Shimoshige, K. Yanagisawa, M. Miyazaki, Y. Takaki, S. Shimamura, H. Nomaki et al, "Isolation and cultivation of a novel freshwater magnetotactic coccus FCR-1 containing unchained magnetosomes," *Communications Biology*, vol. 8, p. 505, Mar. 2025. [Online]. Available: https://doi.org/10.1038/s42003-025-07981-5

[24] G. Zhang, T. Liu, D. Zhao, X. Sun, W. Xing, S. Zhang et al, "External magnetic field have significant effects on diversity of magnetotactic bacteria in sediments from Yangtze River, Chagan Lake and Zhalong Wetland in China," *Ecotoxicology and Environmental Safety*, vol. 266, p. 115604, Nov. 2023. [Online]. Available: https://doi.org/10.1016/j.ecoenv.2023.115604

[25] M. Getino and F. de la Cruz, "Natural and artificial strategies to control the conjugative transmission of plasmids," *Microbiology Spectrum*, vol. 6, no. 1, p. MTB-0015-2016, Jan. 2018. [Online]. Available: https://doi.org/10.1128/microbiolspec.mtbp-0015-2016

[26] S. Elbeltagi, A. M. Saeedi, M. A. Ali, and S. I. El-Dek, "Magnetic fluid hyperthermia controlled by frequency counter and colorimetric program systems based on magnetic nanoparticles," *Applied Physics A*, vol. 129, p. 566, Jul. 2023. [Online]. Available: https://doi.org/10.1007/s00339-023-06825-5

[27] A. Chauhan, A. Saini, and D. Sharma, "The evolution of integrated magnetic hyperthermia and chemodynamic therapy for combating cancer: a comprehensive viewpoint," *Nanoscale Advances*, vol. 7, pp. 4820–4836, Jul. 2025. [Online]. Available:

https://doi.org/10.1039/d4na01004c

[28] A. Manzano, C. Svedman, T. Hofmarcher, and N. Wilking, “Comparator Report on Cancer in Europe 2025: Disease Burden, Costs and Access to Medicines and Molecular Diagnostics,” *IHE Report 2025:2*, IHE – The Swedish Institute for Health Economics, Lund, Sweden, Mar. 2025. [Online]. Available: https://www.efpia.eu/media/nbbbsbhp/ihe-comparator-report-on-cancer-in-europe-2025.pdf

[29] H. J. Bax, J. Chauhan, C. Stavraka, A. Santaolalla, G. Osborn, A. Khiabany et al., “Folate receptor alpha in ovarian cancer tissue and patient serum is associated with disease burden and treatment outcomes,” *British Journal of Cancer*, vol. 128, no. 2, pp. 342–353, Jan. 2023. [Online]. Available: https://doi.org/10.1038/s41416-022-02031-x