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Review Article

AI-Guided Nanorobots for In Vivo Immune Cell Programming: Bridging Nanomedicine and Cancer Immunotherapy

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Abstract

Recent advancements at the intersection of nanotechnology, artificial intelligence (AI), and immunotherapy are transforming the field of cancer treatment. This review explores the transformative potential of AI-guided nanorobots for in vivo immune cell programming. This strategy overcomes the limitations of conventional ex vivo adoptive cell therapies, including high cost, limited scalability, and reduced efficacy in solid tumors. We examine the principles of immune cell engineering, including CAR-T, CAR-NK, and TCR therapies, as well as the associated clinical challenges. Furthermore, we discuss how AI-guided nanorobots can autonomously navigate biological systems to deliver genetic or immunomodulatory payloads, remodel the tumor microenvironment, and enhance therapeutic precision. By integrating multimodal sensing and real-time decision-making capabilities, these nanorobots represent a novel class of autonomous agents that can detect cancer early, activate the immune system, and potentially intervene preemptively. This convergence of disciplines signals a new frontier in personalized, minimally invasive cancer therapy, offering hope for broader accessibility and improved outcomes. This review outlines a transformative approach to autonomous, minimally invasive, and personalized immune modulation, providing a blueprint for the next generation of cancer immunotherapy.

Keywords: *Cancer Immunotherapy; AI-Guided Nanorobots; In Vivo Immune Cell Programming; Tumor Microenvironment; Personalized Nanomedicine.*

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Introduction

The Evolving Landscape of Cancer Therapy

Cancer remains a significant global health challenge that requires continuous innovation in therapeutic strategies. Traditional treatments, such as chemotherapy, radiotherapy, and surgery, have long been the mainstays of oncological practice. However, these treatments often have significant limitations, such as severe side effects due to a lack of specificity and the development of treatment resistance (D. Sun et al., 2024). For instance, the systemic toxicity of chemotherapy arises from its indiscriminate action on rapidly dividing cancerous and healthy cells. Similarly, while radiotherapy and surgery can be effective for localized disease, they are less effective for metastatic cancers and can cause considerable morbidity.

In response to these limitations, immunotherapy has rapidly emerged as a "cornerstone of cancer treatment" (CAR T Cells: Engineering Immune Cells to Treat Cancer — NCI, n.d.). Immunotherapy aims to harness and amplify the patient's immune system to recognize and eliminate cancer cells. This offers a more targeted and potentially more effective approach (Abodunrin et al., 2025; Booth & Roland, 2024). Despite these advancements, significant challenges persist. Many cancers, particularly solid tumors, are resistant to current immunotherapies. Issues such as treatment resistance, tumor heterogeneity, and the complexities of the tumor microenvironment (TME) continue to hinder therapeutic success (Huhulea et al., 2025). Consequently, there is an urgent need for more personalized, precise, and effective therapeutic strategies that can overcome these obstacles.

The Promise of Immunotherapy and Engineered Immune Cells

Many modern immunotherapies are based on the principle of engineering immune cells to enhance their ability to fight cancer, resulting in the development of "living drugs" (D. Sun et al., 2024). These therapies modify a patient's immune cells, usually T cells or natural killer (NK) cells, to target and destroy malignant cells specifically. Chimeric antigen receptor (CAR) T-cell therapy has been at the forefront of this revolution, demonstrating remarkable success in treating certain hematological malignancies (Sun et al., 2024). Genetically modifying a patient's T-cells to express CARs enables these cells to recognize specific antigens on cancer cells, leading to their potent activation and cytotoxic effects. Similarly, NK cells, which are part of the innate immune system, can be engineered with CARs (CAR-NK cells) to improve their tumor-targeting abilities (Abodunrin et al., 2025).

Despite these successes, including the high remission rates observed in diseases such as B-cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkin lymphoma (NHL), engineered immune cell therapies have significant limitations. They are less effective against solid tumors, largely due to the hostile and immunosuppressive nature of the tumor microenvironment (TME) (D. Sun et al., 2024). Furthermore, these therapies can be associated with severe adverse events, such as cytokine release syndrome (CRS) and neurotoxicity, and the manufacturing process is often complex and costly.

Introducing AI-Guided Nanorobots for In Situ Immune Cell Programming

In order to overcome the limitations of current immunotherapies, a new conceptual shift is emerging: transitioning from the ex vivo manipulation of immune cells to their in vivo autonomous programming directly within the patient's body (Fu et al., 2025). This paradigm shift is driven by the convergence of nanotechnology and artificial intelligence (AI), particularly through the development of AI-guided nanorobots. These nanoscale machines typically range from one to 100 nanometers (nm) to a few micrometers (μm) in size. They are engineered to navigate, sense, decide, and act therapeutically within biological systems under the direction of sophisticated AI algorithms (Irvine et al., 2022; Mitra et al., 2023).

The central hypothesis of this approach is that AI-guided nanorobots can deliver genetic payloads, such as mRNA or CRISPR-Cas9 components, or immunomodulatory agents to specific immune cell populations in situ with unprecedented precision. This targeted delivery can reprogram immune cells directly within the tumor microenvironment (TME) or lymphoid organs, enhancing their anti-tumor efficacy while potentially minimizing systemic side effects and overcoming the logistical and biological challenges associated with ex vivo cell manufacturing.

Integrating AI-guided nanorobots with in situ immune cell programming could transform cancer treatment by shifting from reactive to proactive, and potentially even preventive, interventions. Current immunotherapies, including advanced cell therapies such as CAR T-cells, are usually administered after a cancer diagnosis, often when the disease has already progressed (D. Sun et al., 2024). However, nanorobots are being developed to detect cancer early through highly sensitive biosensing capabilities. These capabilities enable nanorobots to identify cancer biomarkers or precancerous changes at their inception (Morcillo-Martín-Romo et al., 2025). AI algorithms are essential for this, enabling nanorobots to analyze complex biological data in real time and make autonomous decisions (Balkhi et al., 2025; Greenberg, n.d.). If nanorobots can achieve early detection and are equipped with

in situ immune cell programming, they could theoretically initiate a targeted immune response at the earliest signs of malignant transformation. This could involve priming immune cells in high-risk individuals or modulating the immune system to eliminate precancerous lesions before they become clinically significant. This capability would transform nanorobots into autonomous sentinels and modulators that actively maintain immune surveillance and health. This would be a significant leap from merely improving treatments for established tumors. This review will explore the fundamental principles, enabling technologies, synergistic potential, inherent challenges, and future outlook of this convergent field. The goal is to provide a comprehensive understanding of its transformative promise for cancer therapy.

Foundations of Immune Cell Programming for Cancer Therapy

Adoptive Cell Therapies (ACT): An Overview

Adoptive cell therapy (ACT) is a powerful immunotherapy strategy that uses a patient's (autologous) or donor's (allogeneic) immune cells. These cells are often expanded and genetically engineered outside the body (ex vivo) to target and eliminate cancer cells (Abodunrin et al., 2025). Several distinct ACT approaches have been developed, each with unique mechanisms and applications.

CAR T-cell therapy is one such approach. This is arguably the most prominent form of ACT. The process begins with collecting T-cells from the patient's blood. These T cells are then genetically engineered in a laboratory to express chimeric antigen receptors (CARs) on their surface. A CAR consists of an extracellular antigen-binding domain, often derived from an antibody fragment (scFv), that recognizes a specific antigen on tumor cells (e.g., CD19 on B-cell malignancies). It also consists of intracellular signaling and co-stimulatory domains (e.g., CD3ζ, CD28, or 4-1BB), which activate the T cell upon antigen binding. After engineering, these CAR T cells are expanded in large numbers and infused back into the patient (CAR T Cells: Engineering Immune Cells to Treat Cancer — NCI, n.d.). Once in the body, the CARs guide the T cells to cancer cells that express the target antigen. This leads to T cell activation, proliferation, and the potent, targeted killing of cancer cells (D. Sun et al., 2024). This approach has been described as administering a "living drug" due to the cells' ability to persist and expand within the patient (CAR T Cells: Engineering Immune Cells to Treat Cancer - NCI, n.d.).

CAR NK-Cell Therapy: Natural killer (NK) cells are a type of cytotoxic lymphocyte in the innate immune system that can recognize and kill cancer cells without prior sensitization or major histocompatibility complex (MHC) restriction. Similar to CAR T-cells, NK cells can be engineered to express chimeric antigen receptors (CARs), thereby enhancing their tumor-targeting specificity and cytotoxic potential (Morcillo-Martín-Romo et al., 2025). CAR-NK cell therapy has several potential advantages over CAR T-cell therapy. For example, it has a lower risk of inducing severe side effects, such as cytokine release syndrome (CRS) and neurotoxicity. Furthermore, NK cells can be sourced from allogeneic donors, which reduces the risk of graft-versus-host disease (GvHD) and opens the possibility of "off-the-shelf" therapies (Morcillo-Martín-Romo et al., 2025).

Engineered T Cell Receptor (TCR) Therapy: In this approach, T cells are genetically engineered to express specific T cell receptors (TCRs) that recognize tumor-associated antigens (Irvine et al., 2022). Unlike CARs, which typically target cell surface antigens, TCRs can recognize processed intracellular peptides presented on the cancer cell surface by major histocompatibility complex (MHC) molecules (Stephan, 2021). This significantly broadens the range of potential tumor antigens that can be targeted, including those derived from intracellular proteins, which constitute the vast majority of cellular proteins (AI Nanobots: Transforming Pharma’s Precision Medicine Landscape — Eularis, n.d.).

Tumor-Infiltrating Lymphocyte (TIL) Therapy: TIL therapy involves isolating T cells that have naturally infiltrated a patient's tumor because these cells are often reactive against the cancer. These TILs are then activated and multiplied in large numbers outside the body before being reinfused into the patient (Greenberg, n.d.). The goal is to provide the patient with a large army of tumor-specific T cells capable of mediating an anti-tumor response.

Scientific Principles of Immune Cell Reprogramming

The ability to modify or reverse the fate of a cell experimentally is a cornerstone of engineered immune cell therapies (Abu Taha et al., 2025; Suma Sri Potti et al., 2025; Weerarathna et al., 2025). A cell's identity is determined by its specific epigenetic and transcriptional landscape. Reprogramming involves altering these landscapes to generate a desired immune cell type or enhance its function. This can be achieved through several experimental approaches, including the enforced expression of specific transcription factors. For instance, introducing key lineage-specific transcription factors can convert one somatic cell type into another or even induce pluripotency (Team EMB, 2025). This principle is fundamental to genetic engineering processes, such as CAR T-cell or CAR-NK cell generation. In these processes, viral vectors or other gene delivery methods introduce genetic material encoding the CAR into target immune cells.

The immune system's primary role is to detect and eliminate pathogens, foreign particles, and aberrant cells, including tumor cells, in order to maintain homeostasis (T. Sun et al., 2024). Immune engineering seeks to leverage and enhance these natural capabilities. This field focuses on applying fundamental immunological discoveries to engineer innovative strategies for disease prevention, detection, and treatment by precisely modulating immune activity. This modulation can involve bolstering defenses or tempering overactive responses (Greenbaum et al., 2021; Logesh et al., 2024; Pires et al., 2019).

Current Successes and Prevailing Limitations

Adoptive cell therapies, particularly CAR T-cell therapies, have achieved remarkable success in transforming the treatment landscape for several hematological malignancies. As of April 2023, six CAR T-cell products had received regulatory approval, showing unparalleled effectiveness in treating patients with relapsed or refractory B-cell leukemias, lymphomas, and multiple myeloma. For example, CAR T cells targeting the CD19 antigen have induced long-lasting remissions in a significant proportion of patients with B-cell acute lymphoblastic leukemia (B-ALL) and B-cell non-Hodgkin lymphoma (B-NHL) (D. Sun et al., 2024). CAR-NK cells have also shown promise in early clinical trials, demonstrating favorable safety profiles and encouraging efficacy (Morcillo-Martín-Romo et al., 2025).

Despite these triumphs, significant limitations persist. One major challenge is the limited efficacy of current ACTs in treating solid tumors (D. Sun et al., 2024). Solid tumors present a formidable barrier due to factors such as inefficient infiltration of engineered cells into the tumor mass, heterogeneous expression of target antigens, and a profoundly immunosuppressive tumor microenvironment (TME) (Irvine et al., 2022). The TME can actively inhibit the function of infused immune cells through various mechanisms, including the presence of immunosuppressive cells (e.g., regulatory T cells and myeloid-derived suppressor cells), physical barriers such as a dense extracellular matrix, and metabolic challenges.

Toxicity remains a serious concern, especially with CAR T-cell therapies. Cytokine release syndrome (CRS), which is a systemic inflammatory response resulting from the rapid activation and proliferation of CAR T cells, and immune effector cell-associated neurotoxicity syndrome (ICANS) can be life-threatening. Antigen escape, in which tumor cells downregulate or lose the target antigen, can lead to relapse following an initial response. Furthermore, the ex vivo manufacturing process for autologous cell therapies is complex, expensive, and time-consuming. It typically takes several weeks from T-cell collection to product infusion (D. Sun et al., 2024). This "one patient, one batch" approach limits scalability and accessibility (Stephan, 2021). Engineered T-cells can also become dysfunctional or "exhausted" after prolonged antigen exposure within the tumor microenvironment (TME) (Irvine et al., 2022). Finally, on-target, off-tumor toxicity can occur if the target antigen is also expressed in healthy tissues, causing unintended damage (D. Sun et al., 2024). General immunotherapy side effects, such as flu-like symptoms, skin reactions, and gastrointestinal issues, can impact patients' quality of life (Booth & Roland, 2024).

The Rationale for In Vivo Immune Cell Reprogramming

The limitations of conventional ex vivo engineered cell therapies have spurred research into in vivo immune cell reprogramming strategies. The basic concept involves delivering the genetic engineering machinery directly to patients to program immune cells within their natural physiological context (Stephan, 2021). This approach offers several potential advantages that could address many prevailing challenges.

First, in vivo programming could significantly simplify the manufacturing process. Rather than using complex, individualized ex vivo cell culture and genetic modification, in vivo strategies could use "off-the-shelf" reagents, such as nanoparticles carrying genetic payloads. These reagents can be mass-produced, stored, and administered more like conventional pharmaceuticals. This simplification could reduce costs, shorten the time to treatment, and expand patient access beyond specialized treatment centers (Stephan, 2021).

Secondly, programming immune cells within their physiological environment may result in cells that are more functional and persistent. Ex vivo culture conditions often involve supraphysiological levels of cytokines and can alter cell phenotypes or lead to exhaustion before the cells are infused into the patient (Stephan, 2021).

In vivo programming avoids these artificial conditions, enabling immune cells to be engineered in their native environment and potentially resulting in more robust and durable anti-tumor responses. Additionally, in vivo methods usually do not require lymphodepleting preconditioning regimens for recipients, which are often necessary for ex vivo therapies to make space for infused cells (Stephan, 2021).

The potential of in vivo programming to democratize access to advanced cell therapies is particularly compelling. Current ex-vivo adoptive cell therapies (ACTs), such as CAR T-cell therapy, are

logistically demanding and expensive, largely confining their availability to well-resourced academic medical centers (D. Sun et al., 2024). The shift towards

In vivo reprogramming using readily manufacturable nanomedicines could drastically reduce the specialized infrastructure and personnel required. This could make these powerful treatments accessible to a much larger global patient population, similar to how monoclonal antibody therapies became widely available after their initial complex development phases. Table 1 provides a comparative overview of ex vivo versus in vivo immune cell programming strategies, highlighting these key differentiators.

AI-Guided Nanorobots: Engineering Precision at the Nanoscale

The development of nanorobots for medical applications marks a significant advancement in the precision of engineering at the cellular and molecular levels. These sophisticated nanoscale entities are designed to perform complex tasks within the human body, opening new avenues for diagnosis and therapy (Suma Sri Potti, 2025).

Design, Materials, and Construction of Medical Nanorobots

Medical nanorobots are typically defined as autonomous structures at the nanoscale, ranging from approximately 1-100 nm (Immunotherapy Side Effects, 2019; Program for Immune Engineering, n.d.; Naik et al., 2024) to 0.1-10 µm (Weerarathna et al., 2025). These nanorobots are engineered to perform specific medical interventions. This size range enables interaction with biological components at a fundamental level. The design and construction of these nanorobots involve the careful selection of materials to ensure biocompatibility, functionality, and stability within the physiological environment (Fu et al., 2025).

A variety of materials are employed in nanorobot fabrication:

- The presence of biocompatible organic components is indicated by the following: Lipids are frequently utilized in the fabrication of nanocarriers, such as liposomes, while polymers can provide structural frameworks or form nanoparticles for drug encapsulation (Onkar et al., 2024). In the field of nanotechnology, DNA is utilized as a structural material in a process known as "DNA origami," which enables the precise fabrication of nanoscale structures with programmable functionalities (Naik et al., 2024).

- The following categories comprise inorganic materials: Carbon, frequently in the form of nanotubes or diamond-like coatings, is valued for its inertness, strength, and thermal conductivity (Naik et al., 2024). Gold nanoparticles are utilized for their unique optical properties in imaging or photothermal therapy, and some designs even propose mechanical disruption of cells using gold nanostructures (Naik et al., 2024). Silica is another inorganic material that is utilized due to its stability and ease of surface functionalization (Onkar et al., 2024).

- The following components are of a biological nature: An innovative approach involves the incorporation of biological entities into the design of nanorobots, encompassing the utilization of biological components as integral components of the nanorobot or as a constituent part of its operational functionality. This encompasses genetically modified bacteria, including non-pathogenic strains of Salmonella, which can be engineered to target tumors and deliver therapeutic payloads (Naik et al., 2024). Viruses are of particular interest in this regard due to their intrinsic capacity to facilitate the delivery of genetic material. Consequently, they have emerged as a source of inspiration for the design of nanorobots (Aggarwal & Kumar, 2022; Glécia Virgolino da Silva Luz et al., 2016).

The construction techniques for nanorobots include molecular self-assembly, wherein components spontaneously organize into the desired structures, as well as more direct fabrication methods such as electron beam lithography and chemical vapor deposition (Team EMB, 2025). The bottom-up assembly of nanostructures is also facilitated by nanomanipulation using scanning probe microscopes (SPMs) (Naik et al., 2024). Key design principles emphasize the optimization of size for navigation through biological barriers, the selection of appropriate shapes for specific functions, the capacity to bear a payload, and, crucially, biocompatibility to avert adverse immune responses (Fu et al., 2025).

Translational and Technical Challenges of AI-Guided Nanorobots

Notwithstanding the encouraging outlook, several substantial challenges must be addressed before AI-guided nanorobots can be translated into clinical practice. First, the real-time decision-making by AI systems in vivo necessitates ultra-compact, biocompatible processing units. However, these units currently face constraints related to power, miniaturization, and thermal dissipation. Secondly, biosafety concerns encompass nanoparticle-induced toxicity, immunogenicity, and the potential for chronic accumulation in vital organs such as the liver and spleen. Thirdly, the potential for off-target effects, wherein nanorobots may interact with non-cancerous cells or tissues due to non-specific surface markers or biodistribution variability, persists as a substantial impediment. Furthermore, the ethical landscape is intricate; the implementation of autonomous therapeutic systems within the human body gives rise to

inquiries concerning control, consent, and liability. These considerations necessitate meticulous long-term preclinical evaluation, standardized safety metrics, and regulatory frameworks to guide subsequent human trials (Huhulea et al., 2025).

AI-Guided Nanorobots for Modulating the Tumor Microenvironment (TME) to Enhance Immunotherapy

Solid tumors present formidable delivery challenges due to heterogeneous vasculature, elevated interstitial pressure, and physical barriers posed by the dense extracellular matrix (ECM). The efficacy of nanocarriers is often hindered by their suboptimal penetration beyond the tumor periphery. Furthermore, the presence of antigen heterogeneity and immune evasion strategies, such as PD-L1 overexpression or MHC loss, contributes to the complexity of the immune response. The employment of AI-guided nanorobots holds potential in addressing these challenges, as they possess the capacity to adapt their targeting strategies in real-time in response to local environmental cues. These cues may include parameters such as pH level, oxygen levels, or immune cell density. This adaptability enables more precise penetration and delivery, thus facilitating more targeted therapeutic outcomes. However, the efficacy of these strategies in solid tumor contexts remains to be extensively validated in 3D organoid or orthotopic animal models. The TME is a complex ecosystem comprising cancer cells, stromal cells, immune cells, blood vessels, and the extracellular matrix (ECM). It plays a critical role in tumor progression and response to therapy (D. Sun et al., 2024). In many cases, particularly in solid tumors, the TME is highly immunosuppressive, creating a significant barrier to the efficacy of immunotherapies, including engineered cell therapies. The employment of AI-guided nanorobots holds considerable promise in the precise modulation of the TME, thereby rendering it more conducive to anti-tumor immune responses.

The engineering of nanorobots to deliver a variety of agents is a promising avenue for future research.

- The depletion or reprogramming of immunosuppressive cell populations is a critical step in the process. This includes the targeting of M2-like tumor-associated macrophages (TAMs) for depletion or repolarization to an M1-like anti-tumor phenotype, or the neutralization of regulatory T-cells (Tregs) that dampen immune responses (Zhang et al., 2022).

- It is imperative to diminish the dense ECM. The ECM has the capacity to function as a physical barrier, impeding immune cell infiltration. The utilization of nanorobots in this manner could facilitate the delivery of enzymes such as hyaluronidase, which have the capacity to disintegrate components of the extracellular matrix (ECM). This, in turn, has the potential to enhance the accessibility of cytotoxic T-cells and natural killer (NK) cells to tumor cells (Kavousinejad, 2024).

- It has been demonstrated that alleviating hypoxia is a crucial component of effective treatment regimens. Hypoxia within tumors has been shown to promote immunosuppression and treatment resistance, underscoring the need for targeted therapeutic interventions to counteract these effects. The integration of nanorobots within the TME holds potential for oxygen delivery or the delivery of oxygen-generating compounds, such as those derived from microalgae through photosynthesis (Zhang et al., 2022). This approach aims to enhance the reoxygenation of the TME.

- The delivery of immune checkpoint inhibitors in a local capacity is imperative. The delivery of molecules, such as anti-PD-L1 or anti-CTLA-4 antibodies, can be facilitated directly within the TME by nanorobots. This localized delivery strategy aims to reinvigorate exhausted T-cells while minimizing the systemic side effects associated with conventional checkpoint blockade therapy (Zhang et al., 2022). For instance, nanophotosensitizer-engineered CAR T biohybrids have been shown to remodel the TME following laser treatment, thereby enhancing blood flow and immune cell infiltration (Komala et al., 2024).

The employment of artificial intelligence (AI) guidance is imperative for the successful implementation of these TME-modulating strategies. The TME is characterized by significant heterogeneity. The employment of AI algorithms facilitates the processing of sensor data from nanorobots, enabling the mapping of spatial variations within the TME (e.g., regions of high immunosuppressive cell density, hypoxia, or dense ECM). These algorithms direct nanorobots to deliver their payloads with precision, addressing local cues in real-time.

Future Perspectives

The convergence of artificial intelligence (AI), nanorobotics, and immunology is poised to redefine the boundaries of medical intervention, particularly in the challenging field of cancer therapy. Despite the considerable challenges that still lie ahead, the trajectory of research suggests a future in which autonomous nanomedicine will assume a pivotal role in the development of personalized and highly effective treatments.

Advancing Nanorobot Intelligence and Capabilities

Subsequent advancements in this field are likely to prioritize the enhancement of the intelligence and capabilities of medical nanorobots. This includes the development of more sophisticated artificial intelligence (AI) and machine learning models that

allow for improved perception of complex biological environments, more robust and adaptive navigation, more nuanced decision-making, and greater resilience to unforeseen circumstances (Sun et al., 2024). The integration of multi-modal sensing capabilities (e.g., the combination of biochemical, optical, and mechanical sensors) coupled with real-time feedback loops will enable more precise control and responsiveness. Sparse nonlinear modeling and control techniques are being explored to create data-efficient, interpretable, and generalizable models for control. These models have the potential to address some of the "black box" concerns (Bhange & Telange, 2025; Kavousinejad, 2024; Ordóñez, n.d.).

There is also considerable interest in the potential of nanorobot "swarms" or collectives that can work in a coordinated fashion to perform tasks beyond the capacity of individual units. These tasks include creating localized therapeutic gradients, physically remodeling tissue structures, or performing complex surveillance tasks (Ordóñez, n.d.). Reinforcement learning frameworks are currently undergoing active development with the objective of optimizing nanorobot navigation and interaction within biological systems (Kavousinejad, 2024). The clinical readiness of AI-guided nanorobots remains in the nascent stages of development. The majority of contemporary designs are currently in the preclinical development stage, with minimal in vivo validation in animal models. According to the Technology Readiness Level (TRL) framework, the majority of prototypes are situated between TRL 3, which denotes analytical proof of concept, and TRL 5, which signifies validation in relevant environments. Notable examples include DNA-origami-based nanorobots that have been tested for vascular occlusion in mouse tumor models and AI-assisted microrobots for targeted drug delivery in zebrafish and murine systems. Regulatory agencies such as the FDA and EMA currently lack specific guidelines for autonomous nanodevices, posing additional challenges in standardizing manufacturing, bio-distribution, and functional control. Consequently, the process of translating these findings into clinical practice necessitates the collaborative efforts of biomedical engineers, ethicists, and regulatory scientists.

Expanding Applications Beyond Cancer

While cancer therapy is a primary driver for the development of AI-guided nanorobots for immune programming, the underlying technologies have far-reaching implications for treating a wide range of other diseases. The capacity of nanorobots to traverse biological barriers, including the blood-brain barrier (BBB), has emerged as a promising avenue for addressing neurological disorders such as Alzheimer's disease and Parkinson's disease by facilitating direct delivery of therapeutic interventions to the brain (Kavousinejad, 2024). In the context of autoimmune diseases, nanorobots have the potential to function as highly targeted immunomodulators, delivering agents that can suppress aberrant immune responses or reprogram specific immune cell subsets (Program for Immune Engineering, n.d.). In the domain of infectious diseases, nanorobots have the potential to identify and neutralize pathogens or deliver antimicrobial agents with high precision (Irvine et al., 2022). Moreover, the capacity for targeted cell delivery and interaction with tissues renders nanorobots promising tools for regenerative medicine, with the potential to deliver stem cells or growth factors to repair damaged tissues. The development of "respirocytes," theoretical nanorobots capable of carrying oxygen, points to potential applications in treating cardiovascular diseases or in emergency medicine (Aggarwal & Kumar, 2022). The prospect of continuous health monitoring and early disease detection through the utilization of artificial intelligence (AI)-powered nanobiosensors is a plausible future scenario, one that would effectuate a shift in healthcare toward a more preventative and early intervention model (Mi, 2020).

The Trajectory Towards Personalized Autonomous Nanomedicine

The overarching objective is the actualization of personalized autonomous nanomedicine. AI algorithms will play a central role in this process by analyzing vast amounts of patient-specific data, including genomics, proteomics, transcriptomics, medical imaging, and real-time physiological monitoring from nanorobots themselves. This analysis will allow for the tailoring of nanorobot design, payload selection, and therapeutic strategies to the unique biological landscape of each individual (Huhulea et al., 2025). This could entail nanorobots that autonomously adapt their behavior in vivo based on the patient's evolving response to treatment.

While the notion of "nanosubmarines in the bloodstream" remains largely speculative, ongoing advancements in bio-compatible processors, swarm logic, and soft robotics indicate the potential for such multifunctional devices to become a reality in the foreseeable future within the domain of biomedical engineering. These developments remain in the preliminary experimental phases, and their realization in humans will necessitate a period of at least a decade of iterative preclinical and clinical validation, in addition to rigorous ethical and safety oversight.

Conclusion

The integration of AI-guided nanorobots into cancer immunotherapy signifies a paradigm shift from reactive, late-stage intervention to proactive, personalized immune modulation. These nanodevices offer unparalleled precision in targeting immune cells

and remodeling the tumor microenvironment, thereby addressing the critical limitations of current engineered cell therapies, including poor solid tumor penetration, systemic toxicity, and manufacturing bottlenecks. Beyond the field of oncology, the platform technologies underpinning AI-driven nanorobots hold promise for extension into neurology, infectious disease, and regenerative medicine. Despite the persistent technical, regulatory, and ethical challenges, the rapid advancements in the fields of artificial intelligence (AI), biomaterials, and nanoscale engineering are expediting the convergence of theoretical concepts and clinical applications. As research progresses, the prospect of autonomous, intelligent nanomedicine—capable of diagnosing, treating, and preventing cancer at its earliest molecular roots—becomes increasingly feasible.

Declarations

Ethics approval and consent to participate

Not applicable – no participants involved.

Consent for Publication

Not applicable.

Availability of Data and Material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflicts of Interest / Competing Interests

The authors declare that there are no conflicts of interest.

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A.T.M: Conceptualization, Methodology, Visualization, Writing of the original draft.

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Use of Generative AI and AI-Assisted Technologies

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