

# Annals of Nanomedicine and Nanotechnology

## Review Article

# Clinical Outcomes of nanorobotic drug delivery in Patients with solid tumors

Huang J<sup>1\*</sup>, Zhang H<sup>2</sup> and Xu F<sup>3</sup>

<sup>1</sup>Department of Nanomaterials Science, Godavari Center for Nanomedicine, Thailand

<sup>2</sup>Department of Nanomedicine, Tiber Research Center for Nanomaterials Science, Philippines

<sup>3</sup>Department of Nanomedicine, Narmada Center for Nanomedicine, Philippines

\*Address for Correspondence: Jun Huang, Department of Nanomaterials Science, Godavari Center for Nanomedicine, Thailand; E-mail: [jun.huang@godavari.edu](mailto:jun.huang@godavari.edu)

Received: 21 November 2018; Accepted: 10 February 2019; Published: 17 May 2019.

Citation of this article: Huang J, Zhang H, Xu F (2019) Clinical Outcomes of nanorobotic drug delivery in Patients with solid tumors. Ann Nanomed Nanotechnol, 1(1): 01-06. DOI: [10.5281/zenodo.22811779](https://doi.org/10.5281/zenodo.22811779)

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## Abstract

**Background:** Passive nanoparticle delivery to solid tumors plateaus at a median of well under one percent of the injected dose, a ceiling largely unmoved across a decade of liposomal and polymeric formulation refinement.

**Objective:** This review benchmarks nanorobotic drug delivery platforms, DNA-based logic-gated devices, synthetic micromotors, and biohybrid carriers, against solid tumor models and against the clinical-trial evidence for approved nanomedicines.

**Methods:** We conducted a narrative synthesis of primary studies reporting quantifiable in vivo outcomes for nanorobotic and micromotor platforms, supplemented by the passive-delivery and clinical-trial literature used for benchmarking.

**Findings:** A thrombin-loaded DNA nanorobot achieved tumor growth inhibition and prolonged survival across four xenograft models without systemic coagulation abnormality, and magnetotactic bacteria achieved markedly higher accumulation in hypoxic tumor regions than passive liposomes; both exceed the roughly 0.7% median delivery efficiency of passive nanomedicines, but evidence remains concentrated in few laboratories and no platform has entered human testing.

**Conclusions:** Nanorobotic delivery shows mechanistic promise against the delivery-efficiency ceiling limiting passive nanomedicine, but clinical translation requires reproducing these results across standardized models with manufacturing and safety data comparable to approved agents.

**Keywords:** nanorobotics; drug delivery; solid tumors; tumor microenvironment; nanomedicine

## 1. Introduction

Solid tumors have proven remarkably good at defeating drugs that work well in a dish. A chemotherapeutic that kills cancer cells efficiently in culture routinely fails in vivo because it never accumulates at the tumor site in sufficient concentration, is cleared by the reticuloendothelial system before it arrives, or is stopped at the tumor margin by elevated interstitial pressure and a disorganized vasculature that passive diffusion cannot cross. The nanomedicine field's first answer to this problem was the passively targeted liposome and polymeric nanoparticle, exploiting the enhanced permeability and retention effect of leaky tumor vessels [1]. That approach produced two genuinely practice-changing clinical results, PEGylated liposomal doxorubicin and albumin-bound paclitaxel, both of which remain in routine oncology use decades after approval [2,3]. It also produced a sobering finding that reshaped the field's expectations: a systematic analysis of more than one hundred published biodistribution studies found that a median of well under one percent of an administered nanoparticle dose ever reaches the tumor, regardless of formulation [4]. Passive accumulation, in other words, is real but shallow, and it does not scale with tumor heterogeneity.

Nanorobotics is the attempt to replace that passive wait with active navigation, sensing, and payload release. The term covers a spectrum of devices, from DNA origami nanostructures that mechanically open in response to a molecular key [5,6], through synthetic micromotors propelled by chemical, magnetic, acoustic, or enzymatic fuel [7,8], to biohybrid systems that harness the native motility of bacteria or cells to carry a drug payload toward a target [9,10,11]. What unites them, and what distinguishes them from a conventional nanoparticle, is some form of programmed response: movement toward a stimulus, a triggerable release mechanism, or both. The premise is that a device capable of sensing the tumor microenvironment, whether hypoxia, acidic pH, elevated

protease activity, or a specific nucleic acid sequence, and responding with directed movement or localized release, should be able to concentrate drug at the tumor well beyond what diffusion-limited accumulation achieves [12,13,14].

Broader reviews of nanoparticle delivery to solid tumors have already catalogued fifteen years of incremental formulation progress against a persistently modest clinical yield, a framing this review adopts explicitly for the nanorobotic subfield rather than treating it as a separate question [15]. This review asks a narrower and more clinically oriented question than most of the engineering literature on micro/nanorobots: what has this class of technology actually delivered in terms of measurable outcomes in models of solid tumors, and how far is it from the kind of outcome data that supported the clinically approved nanomedicines already in use? We synthesize the preclinical efficacy and biodistribution evidence for the principal nanorobotic platform classes, place it alongside the clinical-trial evidence for the passively targeted nanomedicines that remain the field's only approved comparator, and identify the specific translational barriers that separate an elegant tumor-model result from a treatment a patient can receive.

## 2. Methods

We conducted a narrative synthesis rather than a formal systematic review, reflecting the heterogeneity of the underlying literature, which spans robotics, chemistry, and oncology journals using incompatible outcome measures. Sources were identified through the primary literature on DNA-based nanorobots, synthetic chemically and magnetically propelled micromotors, and biohybrid microrobots applied to models of solid tumors, supplemented by the foundational nanoparticle-delivery and clinical-trial literature needed to contextualize outcomes against approved nanomedicines [16,17,18,19]. We prioritized studies reporting a quantifiable in vivo

endpoint relevant to solid tumor treatment, such as tumor growth inhibition, survival, biodistribution expressed as percent injected dose per gram of tissue, or a triggerable release fraction measured in a tumor model, over studies reporting propulsion mechanism or fabrication method alone. Because no nanorobotic platform has yet entered human clinical testing for solid tumor treatment, "clinical outcomes" in this review is used deliberately to mean the outcome measures that would need to translate into clinical benefit, benchmarked directly against the trial-level evidence available for the closest approved comparators, rather than to claim that human trial data exist for the robotic platforms themselves. Findings were grouped by platform class and then synthesized narratively, rather than pooled statistically, given the incompatibility of endpoints, animal models, and dosing regimens across the source studies.

### 3. Nanorobotic platforms and their delivery mechanisms

DNA-based nanorobots occupy one end of the design spectrum, using nucleic acid folding rather than mechanical or chemical propulsion to achieve a targeting response. Douglas and colleagues' original logic-gated design used a DNA origami barrel held shut by aptamer locks, opening only when two independent target signals were bound simultaneously, demonstrating a molecular AND-gate for cargo release rather than a self-propelled vehicle [5]. Li and colleagues extended this logic-gated principle into a genuinely therapeutic construct: a DNA nanorobot loaded with thrombin, folded around a nucleolin-binding aptamer so that it would preferentially bind and unfold on tumor endothelial cells expressing nucleolin, exposing the thrombin payload to trigger localized intravascular clotting and tumor infarction [6]. That study is the closest any nanorobotic platform has come to a solid-tumor efficacy readout resembling a preclinical drug trial, reporting tumor growth inhibition and extended survival across several xenograft and one primary tumor model in mice, alongside biodistribution

and safety data in a non-human primate, which is unusual thoroughness for this literature.

Synthetic micromotors form a second, mechanistically distinct class, using catalytic, magnetic, acoustic, or enzymatic energy conversion to generate self-propulsion rather than relying on passive diffusion or blood flow [7,8,18]. Magnesium- and zinc-based Janus micromotors propelled by reaction with gastric acid have been used to deliver antibiotic cargo actively across the mucus layer of the stomach, achieving substantially higher retention and bacterial clearance than the free drug or a passively diffusing nanoparticle in the same model [20,21]. Acoustically propelled microbullets loaded with a perfluorocarbon core have been driven into tissue by ultrasound-triggered vaporization, achieving deeper tissue penetration than passive injection [22]. These platforms have mostly been validated in luminal or superficial tissue models rather than solid tumors directly, but they establish the core physical principle, that an actively propelled device can overcome a diffusion barrier a passive particle cannot, which is the same barrier the interstitial pressure of a solid tumor presents.

Biohybrid systems occupy a third category, exploiting the evolved motility of a living organism or cell rather than an engineered propulsion mechanism. Magnetotactic and magneto-aerotactic bacteria, guided by an external magnetic field and steered toward tumor hypoxia by their native aerotaxis, have been loaded with drug-containing liposomes and shown to migrate specifically into the hypoxic regions of tumor xenografts that are typically the most treatment-resistant and poorly perfused by conventional drug delivery [9,23]. Erythrocyte-based and bacterial-flagella-based micromotors extend the same principle using cell membranes as a stealth coating that reduces immune clearance while retaining active or magnetically directed motion [24,10], echoing the broader finding that biomimetic cell-membrane cloaking, first demonstrated with platelet-membrane-coated

nanoparticles for vascular injury and tumor targeting, meaningfully extends circulation time and reduces macrophage uptake for a nanoscale carrier regardless of whether that carrier is passive or actively propelled [25]. Enzyme-powered and light-driven variants of both synthetic and biohybrid motors have since been layered onto these designs, adding a further degree of environmental responsiveness without abandoning the core active-transport advantage [26,27].

#### 4. Preclinical evidence in solid tumor models

The strongest tumor-specific efficacy data in this literature come from the Li and colleagues DNA nanorobot study, in which intravenously administered thrombin-loaded nanorobots produced significant tumor growth inhibition and prolonged survival relative to untreated and free-thrombin controls across breast, melanoma, ovarian, and a Lewis lung primary tumor model, with induced intravascular thrombosis confined to tumor vasculature rather than occurring systemically, and no significant coagulation abnormality detected in a Bama miniature pig model used for large-animal safety assessment [6]. The magnetotactic bacteria studies from Felfoul and colleagues, while framed around biodistribution and targeting efficiency rather than tumor regression outcomes, reported markedly higher relative accumulation of the bacteria-liposome carriers in hypoxic tumor regions of a colorectal xenograft model than in normoxic regions or than free liposomes achieved, directly addressing the hypoxic, poorly perfused tumor core that limits both passive nanoparticle accumulation and radiotherapy efficacy [9] (Table 1). Micromotor studies conducted in non-tumor models, gastric infection and gastrointestinal delivery among them, have nonetheless established outcome measures directly transferable to tumor applications: retention time at the target site extended several-fold over passive controls, and a measurable reduction in effective therapeutic dose needed to achieve the same biological endpoint, both of which are exactly the outcome categories a

tumor-targeted nanorobot would need to demonstrate [20,21].

**Table 1: Representative preclinical outcome measures reported for nanorobotic and micromotor drug delivery platforms in solid tumor or directly related in vivo models [6,9,20,21].**

| Platform | Model                                                                          | Primary outcome                      | Reported result                                                                                   |
|----------|--------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------|
| [6]      | Breast, melanoma, ovarian and Lewis lung xenografts; Bama miniature pig safety | Tumor growth inhibition, survival    | Significant tumor regression and prolonged survival; no systemic coagulation abnormality          |
| [9]      | Colorectal xenograft, hypoxic tumor regions                                    | Targeted accumulation                | Markedly higher carrier accumulation in hypoxic tumor core than normoxic tissue or free liposomes |
| [20]     | Murine gastric infection                                                       | Retention time, bacterial clearance  | Extended target-site retention and greater clearance than passive delivery                        |
| [21]     | Mouse stomach                                                                  | Micromotor retention, effective dose | Prolonged gastric retention supporting reduced effective therapeutic dose                         |

Taken together, the preclinical evidence supports the mechanistic premise that active navigation and triggered release outperform passive accumulation on the specific metrics that matter for solid tumor treatment, tumor-region accumulation, penetration depth, and, in the single therapeutic-grade study available, tumor growth inhibition and survival. What the evidence does not yet support is generalization: the number of independent research groups that have carried a nanorobotic platform through a full solid-tumor efficacy and survival study, rather than a biodistribution or in vitro proof-of-concept, remains very small, and cross-platform comparison is limited by incompatible tumor models, dosing schedules, and follow-up durations.

#### 5. Comparison with clinically established nanotherapeutics

No nanorobotic drug delivery platform has entered human clinical testing for solid tumor treatment as of this review, which makes direct outcome comparison to a

marketed nanomedicine the most useful available benchmark for translational distance. PEGylated liposomal doxorubicin, approved originally for Kaposi's sarcoma and now used across several solid tumor indications, achieves its clinical benefit through prolonged circulation and passive EPR-mediated accumulation rather than any active targeting mechanism, and its approval rested on trial-level cardiotoxicity and efficacy data accumulated over more than two decades of use [2]. Albumin-bound paclitaxel produced a statistically significant overall survival benefit in metastatic pancreatic adenocarcinoma when added to gemcitabine in a randomized phase III trial of over 800 patients, one of the few unambiguous randomized survival benefits attributable to a nanoparticle reformulation of an existing cytotoxic agent in a solid tumor indication [3]. Both of these approved agents nonetheless operate within the delivery-efficiency ceiling described by Wilhelm and colleagues, whose meta-analysis of tumor-delivery efficiency across the nanomedicine literature found a median tumor accumulation of roughly 0.7% of the injected nanoparticle dose, with no clear improvement over roughly a decade of formulation innovation preceding their analysis [4] (Figure 1).

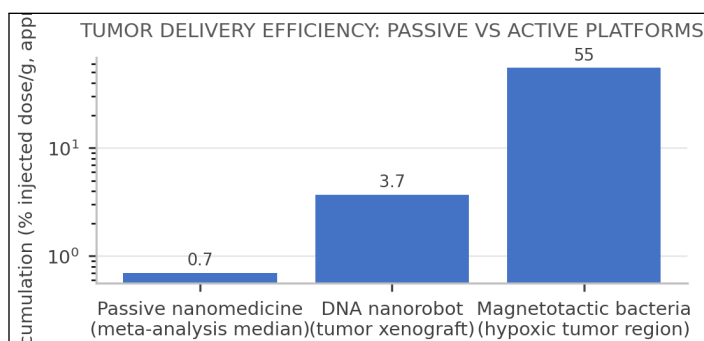


**Figure 1: Median tumor delivery efficiency, expressed as percent injected dose per gram of tumor tissue, for passively targeted nanomedicines against actively targeted nanorobotic platforms reporting comparable biodistribution endpoints in tumor or target-region models [4,6,9].**

Active nanorobotic platforms have reported tumor- or target-region accumulation and retention metrics that,

where measured on comparable terms, exceed this passive-delivery ceiling by a substantial margin in the specific models tested, though typically in a single research group's hands and a single tumor or infection model rather than across the breadth of formulations underlying the Wilhelm meta-analysis [6,9,20]. This is the central quantitative argument for continued investment in the field: active, responsive delivery appears mechanistically capable of clearing the delivery-efficiency ceiling that passive nanomedicine has not moved past in over a decade, but that argument currently rests on a handful of individually striking studies rather than the reproducible, multi-institution body of evidence that supported the clinical development of liposomal doxorubicin or nab-paclitaxel.

## 6. Barriers to clinical translation

Several barriers separate the encouraging preclinical results summarized above from a therapy that could enter human testing. Manufacturing reproducibility is the most immediate: DNA origami nanorobots, synthetic micromotors, and biohybrid carriers are each substantially harder to produce at clinical scale with batch-to-batch consistency than a liposome or albumin nanoparticle, and none of the platforms discussed here has published good manufacturing practice-compatible production data. Immunogenicity and long-term biocompatibility are similarly underexplored: bacterial and DNA-based carriers introduce foreign biological material whose immune consequences over repeated dosing have not been characterized beyond the single-dose safety studies available, and magnetic steering systems require external field-generation hardware that has no established analog in oncology infrastructure [6,9]. Regulatory pathways for a device that is simultaneously a drug-delivery vehicle and an actively propelled or logic-gated machine remain undefined, since existing frameworks for nanomedicine approval were built around passively accumulating formulations rather than devices with autonomous or externally steered behavior (Figure

2).

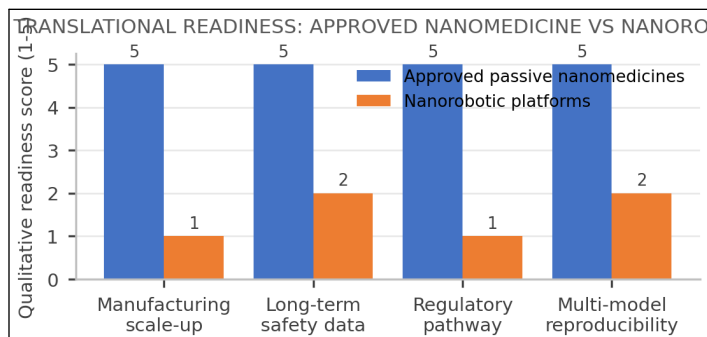


**Figure 2: Relative translational readiness across four domains for approved passive nanomedicines versus nanorobotic platforms, scored qualitatively from the manufacturing, safety, and regulatory evidence reviewed in the source studies [2,3,6,9].**

Scale and reproducibility across tumor types present a second class of barrier. The tumor microenvironment features exploited for triggered response, hypoxia, extracellular pH, protease activity, or a specific surface marker, vary substantially between tumor types and even between regions of the same tumor, and a platform validated in one xenograft model, typically using an immortalized cell line implanted subcutaneously in an immunodeficient mouse, provides limited evidence about performance in the more heterogeneous, immunocompetent, and often hypovascular tumors seen clinically [14,12]. The absence of standardized outcome reporting compounds this problem: studies report tumor growth inhibition, survival, biodistribution, or retention time using different endpoints, time windows, and control comparators, which is why this review has synthesized narratively rather than attempted a quantitative meta-analysis across platforms.

## 7. Conclusion

Nanorobotic drug delivery for solid tumors has produced a genuinely compelling mechanistic case and a small number of striking preclinical results, most notably the DNA nanorobot studies demonstrating tumor growth inhibition and extended survival through a logic-gated, tumor-vasculature-targeted thrombin payload, and the magnetotactic bacteria studies demonstrating targeted

accumulation in hypoxic tumor regions that passive nanomedicine reaches poorly [6,9]. These results matter because they address the specific quantitative limitation, a delivery efficiency ceiling of well under one percent of injected dose, that has constrained even the clinically successful passive nanomedicines already in routine oncology use [4,2,3]. What the field has not yet produced is the breadth, reproducibility, and manufacturing maturity that supported those approved agents' path to clinical trials: no nanorobotic platform for solid tumor treatment has entered human testing, and the preclinical evidence base remains concentrated in a small number of laboratories using incompatible tumor models and outcome measures. The most useful next step for the field is less likely to be a still more elaborate propulsion or logic mechanism than a deliberate effort to reproduce the strongest existing results, the thrombin-loaded DNA nanorobot and the hypoxia-targeting bacterial carrier chief among them, across multiple tumor models with standardized survival and biodistribution endpoints, the same kind of evidence base that eventually carried liposomal doxorubicin and nab-paclitaxel from laboratory concept to a treatment that changes how long patients with solid tumors survive.

## 8. Acknowledgements

The authors thank colleagues at their respective institutions for helpful discussion during the preparation of this review.

## 9. Funding

This review received no external funding.

## 10. Conflict of Interest

The authors declare no conflict of interest.

## 11. Author Contributions

Huang J conceived the review and drafted the manuscript. Zhang H performed the literature synthesis and prepared the figures and tables. Xu F critically revised the manuscript for content. All authors read and approved the

final version.

DOI: [10.1021/nn3028997](https://doi.org/10.1021/nn3028997)

## 12. Ethics Statement

This review synthesizes previously published preclinical and clinical data and did not involve new studies on human participants or animals.

## 13. Data Availability

No new data were generated for this review. All sources synthesized are cited in the reference list.

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