Available online www.ijpras.com

International Journal of Pharmaceutical Research & Allied Sciences, 2026, 15(1):10-21
https://doi.org/10.51847/P4qgtoTKhm

Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Living, Biohybrid, and Self-Propelled Drug Carriers: A Horizon Review of Programmable Targeting, Biological Navigation, and Translational Risk

Laura Keller[1]*, Thomas Lehmann[1], Simon Brunner[2], Christoph Meier[3], David Thompson[4]

[1]Department of Living and Biohybrid Drug Carriers, Faculty of Pharmacy, ETH Zurich, Zurich, Switzerland.
[2]Department of Programmable Targeting and Biological Navigation, Faculty of Pharmacy, EPFL Lausanne, Lausanne, Switzerland.
[3]Department of Translational Risk and Horizon Review, Faculty of Pharmacy, University of Bern, Bern, Switzerland.
[4]Department of Self-Propelled Carriers and Safety, Faculty of Pharmacy, University of Basel, Basel, Switzerland.

***Email:** laura.keller@pharma.ethz.ch*

ABSTRACT

Living, biohybrid, and self-propelled drug carriers seek to overcome limitations of conventional nanomedicine by incorporating active movement, biological sensing, endogenous homing, externally directed navigation, or locally triggered release. Their defining opportunities arise from coupling pharmaceutical payloads to microorganisms, mammalian cells, cell-derived membranes, biological vesicles, chemically reactive micromotors, or externally guided microdevices. However, technological novelty frequently exceeds the maturity of the supporting pharmaceutical evidence. This horizon review applies structured literature surveillance, technology classification, weak-signal identification, and opportunity–risk–readiness analysis to distinguish established mechanisms from emerging indications and speculative possibilities. The reviewed modalities include bacteria-driven microswimmers, neutrophil and macrophage carriers, erythrocyte- and sperm-based biohybrids, membrane-coated and exosome-derived particles, reactive gastric micromotors, enzyme-powered bladder nanomotors, magnetically guided systems, and intracellular release platforms. Evidence signals suggest that localized administration, route-constrained propulsion, biological-interface engineering, improved observability, and measurable containment may offer nearer-term development opportunities than unrestricted systemic autonomy. Conversely, uncertain biodistribution, dynamic protein-corona formation, immunogenicity, viable-organism persistence, incomplete shutdown or retrieval, source-material heterogeneity, manufacturing reproducibility, and combination-product ambiguity remain major translational risks. The central conclusion is that active motion or biological navigation cannot alone establish pharmaceutical value. Readiness instead depends on demonstrating that the added biological or mechanical complexity produces a reproducible advantage over simpler carriers while preserving product definition, controllability, safety, manufacturability, and clinically relevant performance. The proposed horizon categories organize emerging evidence but do not constitute validated forecasts, regulatory classifications, or predictions of clinical adoption.

Key words: *Nanomedicine, Targeted drug delivery, Biological barriers, Intracellular release, Biodistribution, Protein corona*

Received: 06 October 2025; **Revised:** 12 January 2026; **Accepted:** 15 January 2026

INTRODUCTION

Nanomedicine has enabled systematic control of carrier composition, size, surface properties, payload association, release behaviour, and biological interactions. Yet precision delivery is not produced by a single material attribute. It depends on the combined behaviour of the formulation, biological interface, administration route, tissue environment, payload, and manufacturing process [1]. Living and self-propelled carriers extend this design space by adding motility, taxis, cellular homing, biological recognition, environmental responsiveness, or externally applied guidance. These functions may address transport barriers that remain difficult for passively distributed particles, but they also introduce new variables that conventional formulation frameworks were not designed to control.

The prevailing language of "smart," "autonomous," or "programmable" delivery can obscure important differences between technical capability and pharmaceutical consequence. Stimulus responsiveness, targeting ligands, environmental sensing, and local release have become central features of smart cancer nanomedicine, but their presence does not establish that the complete system improves exposure, selectivity, safety, or treatment outcome [2]. For a living or biohybrid carrier, programmability may reside in a genetic circuit, cellular phenotype, external field, chemical reaction, surface receptor, mechanical coupling, or release gate. These mechanisms are not interchangeable, and each creates different evidentiary, manufacturing, and safety requirements.

Biological navigation must also be distinguished from observed localization. Nanoparticle entry into solid tumours is heterogeneous and cannot be assumed to result uniformly from passive vascular leakage [3]. The same caution applies to actively moving systems: motion in fluid, chemotactic response, inflammatory homing, tissue adhesion, or image-guided steering does not necessarily demonstrate therapeutically meaningful biodistribution. Carrier accumulation may alternatively reflect administration route, vascular trapping, immune-cell recruitment, local anatomy, clearance, or measurement timing. Claims of targeting therefore require evidence connecting the proposed navigation mechanism to exposure at the intended site and, separately, to an appropriate pharmaceutical or biological consequence.

This Horizon Review Article evaluates living, biohybrid, and self-propelled carriers through structured literature surveillance, modality classification, weak-signal identification, and opportunity–risk–readiness analysis. Clinical experience with nanoparticles remains selective and product-specific despite extensive preclinical innovation [4]. Accordingly, the review does not treat technical novelty as evidence of clinical maturity. Its contribution is an evidence-bounded synthesis of emerging modalities, enabling mechanisms, validation signals, translational risks, and priority milestones. It does not provide an exhaustive effectiveness review, comparative treatment ranking, validated readiness score, clinical recommendation, or regulatory determination.

Horizon-scanning methods and inclusion boundaries

The horizon scan examined recent peer-reviewed literature addressing living carriers, microorganism-driven systems, mammalian-cell carriers, membrane-derived particles, self-propelled micro- and nanomotors, navigation technologies, triggered release, safety, containment, manufacturing, and translation. Article-title variants were combined with mechanism-specific terms covering biological barriers, biodistribution, protein corona, intracellular delivery, tumour microenvironment, imaging, external control, stimuli-responsive release, quality control, and regulatory readiness. Citation chaining and targeted journal surveillance were used to identify emerging platforms and development frameworks that might not be retrieved consistently through one terminology set.

Eligible evidence had to contribute extractable information to a defined review question, modality class, mechanism, validation signal, safety concern, manufacturing constraint, regulatory challenge, or translational milestone. Primary studies were prioritized for claims concerning propulsion, targeting, payload transport, release, biodistribution, imaging, therapeutic activity, containment, or biological interaction. Reviews and perspectives were used principally for taxonomy, field-level interpretation, and translation frameworks. Conference papers, preprints without journal publication, non-peer-reviewed material, promotional accounts, and adjacent studies lacking a direct carrier or translational contribution were excluded.

Evidence was charted according to biological composition, propulsion or transport mechanism, navigation input, cargo architecture, administration context, validation level, observability, controllability, safety liabilities, manufacturing requirements, and regulatory uncertainty. Three qualitative horizons were used as an original synthesis: translationally proximal evidence for systems with reproducible localized or route-constrained validation and a plausible pharmaceutical development path; intermediate evidence for systems with persuasive mechanistic or small-animal findings but unresolved control or product-definition questions; and exploratory evidence for platforms whose autonomy, systemic use, containment, or manufacturing requirements remain

substantially uncertain. These horizons organize interpretation and do not represent validated scores, adoption timelines, or regulatory categories.

Taxonomy of living, biohybrid, and self-propelled carriers

For horizon scanning, the field is best treated as a continuum spanning engineered micro- and nanorobots, microorganism-driven biohybrids, and soft cellular cargo systems [5-7]. A living carrier retains viable biological machinery that contributes directly to transport, sensing, homing, payload handling, or therapeutic activity. A biohybrid carrier combines biological and engineered components, but the biological component may be viable, nonviable, membrane-derived, vesicular, or mechanically coupled. A self-propelled carrier generates motion through a chemical, enzymatic, magnetic, acoustic, optical, or biological mechanism; it need not contain living material. These categories overlap but should not be treated as synonyms.

Sperm-hybrid micromotors illustrate the importance of separating propulsion source from control architecture. Intrinsic cellular motility can provide transport, while an engineered coupling structure carries drug cargo and permits external guidance or release [8]. The resulting platform is biologically propelled and technically guided, but it is not fully autonomous in the pharmaceutical sense. Its performance depends on cellular variability, mechanical attachment, tissue compatibility, cargo retention, guidance conditions, and the ability to release the payload at an appropriate location.

Figure 1 presents the original conceptual synthesis for horizon map of living and self-propelled drug carriers, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

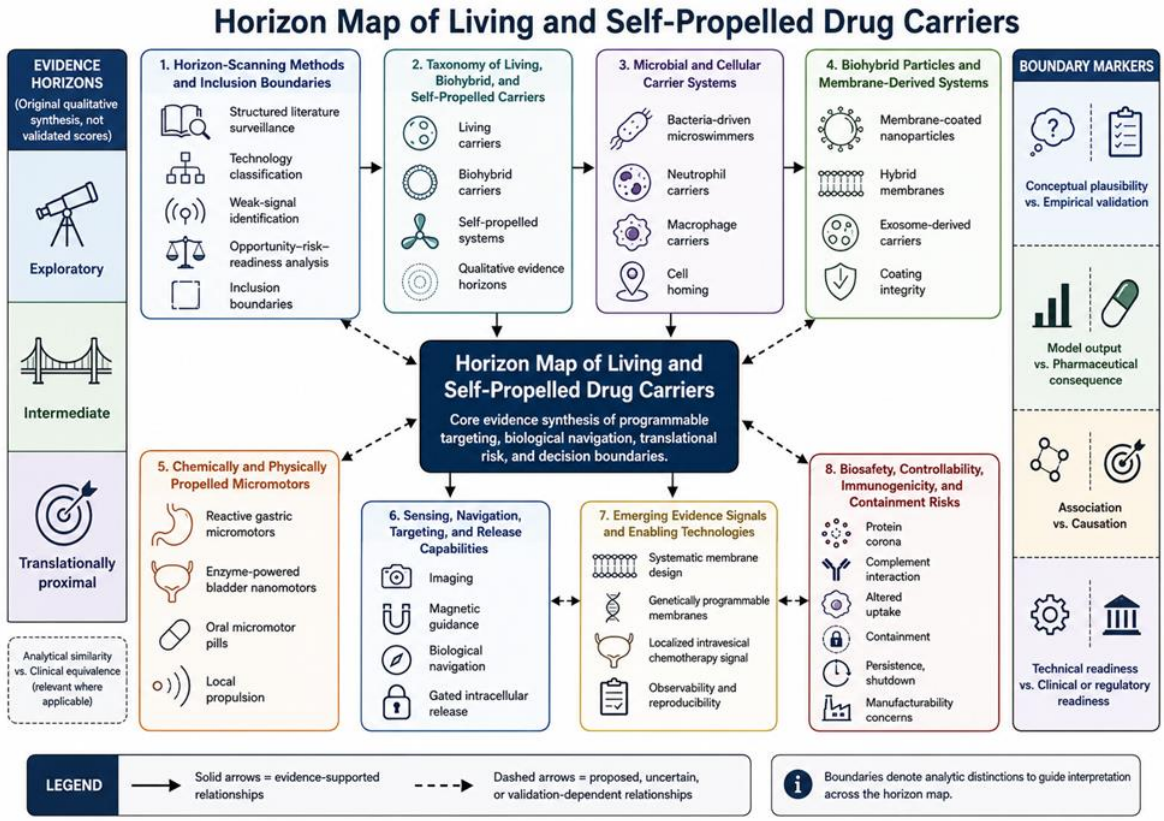

Figure 1. Horizon Map of Living and Self-Propelled Drug Carriers

A useful taxonomy must therefore separate at least five dimensions: the presence and viability of biological material; the origin of propulsion or transport; the source of sensing or guidance; the form of cargo integration; and the maturity of the supporting evidence. Engineered micro- and nanorobots may rely predominantly on synthetic structures and externally applied control [5]. Microorganism-based biohybrids derive movement or environmental responsiveness from living cells while adding engineered cargo, coatings, or steering components [6]. Mammalian-cell carriers may instead use endogenous trafficking, inflammatory recruitment, deformability, or receptor-mediated interactions without generating continuous self-propulsion.

Evidence maturity constitutes a separate axis from architectural sophistication. A complex system displaying coordinated movement under laboratory conditions may remain exploratory if its biodistribution, biological fate, failure modes, or manufacture are poorly defined. Conversely, a less autonomous system used through a localized administration route may be nearer to pharmaceutical development because exposure, retrieval, imaging, and containment are more tractable. Clinical experience with nanocarriers shows that translation proceeds at the level of a defined product rather than an abstract platform class [4]. The proposed taxonomy therefore describes design and evidence characteristics but does not rank efficacy or imply universal superiority of any modality.

Microbial and cellular carrier systems

Bacteria-driven microswimmers combine biological motility with engineered cargo association, creating platforms capable of responding to local chemical or physical conditions. Multifunctional bacterial systems have integrated propulsion, particle attachment, environmental sensing, and targeting-related functions within a single experimental construct [9]. Their potential advantage lies in using biological machinery that already operates in complex fluids. However, bacterial motility is variable, context-dependent, and not equivalent to controlled navigation. Cargo attachment may also alter swimming behaviour, viability, surface recognition, or immune interaction.

Route-specific use may reduce some of these uncertainties. Bioadhesive bacterial swimmers have been investigated for targeted delivery in urinary and gastrointestinal environments, where adhesion and biological motility may support local retention [10]. Such systems may be more tractable than unrestricted systemic carriers because administration confines the initial exposure and permits clearer evaluation of residence and local tissue interaction. Nevertheless, improved retention cannot alone establish appropriate release, tissue penetration, eradication, clearance, or repeated-dose safety.

Mammalian immune cells provide a different form of biological navigation. Neutrophils can migrate toward inflammatory signals and have been used to transport anticancer cargo to postoperative glioma sites in animal models [11]. This behaviour is better described as endogenous inflammatory homing than autonomous destination selection. The same recruitment mechanism could potentially direct carriers toward non-target inflammation, and cargo loading may change cellular deformability, activation, circulation, tissue entry, or survival. Mechanistic evaluation must therefore distinguish native cell trafficking from effects introduced by the pharmaceutical payload and loading procedure.

Macrophage-based systems can combine transport with immunological activity. Living macrophage carriers have been used to deliver a locally released immune-stimulatory cargo while contributing to antitumour responses in preclinical models [12]. This integration is scientifically attractive because the cell is both carrier and biological participant, but it complicates product definition. Cell phenotype, viability, activation state, cargo loading, release kinetics, donor or source variability, and interactions with the host immune environment become interdependent quality attributes. Current evidence supports mechanistic and preclinical feasibility; it does not establish reproducible human biodistribution, controllable shutdown, safe persistence, or superiority over nonliving delivery systems.

Biohybrid particles and membrane-derived systems

Cell-membrane coating transfers selected biological-interface properties to synthetic cores without preserving the complete functions of a living cell. Depending on the source membrane, the resulting particles may display proteins associated with circulation, immune interaction, adhesion, or tissue recognition [13]. They are therefore biohybrid but generally nonliving systems. Their apparent biological identity depends not only on membrane origin but also on isolation, orientation, coverage, storage, and interactions acquired after administration.

Hybrid membranes seek to combine attributes from more than one cellular source. Erythrocyte–cancer membrane particles have been investigated to join prolonged circulation with homotypic tumour interaction in preclinical melanoma models [14]. Such findings support a design hypothesis rather than universal targeting. Apparent accumulation may also arise from circulation time, tumour vascular properties, particle composition, or model-specific receptor expression.

Exosome-derived systems use naturally produced vesicles as carrier interfaces or payload vehicles. Tumour-derived exosome nanoparticles have delivered chemotherapy in animal models, supporting the feasibility of biologically sourced transport systems [15]. However, vesicle populations may vary in molecular composition, size, endogenous cargo, source-cell state, and isolation history. These variables complicate attribution of therapeutic effects and raise concerns about comparability between preparations.

Membrane integrity is consequently a functional quality attribute rather than a cosmetic formulation feature. Incomplete coating can alter nanoparticle internalization mechanisms and undermine assumptions about biological camouflage or receptor presentation [16]. Demonstrating nominal membrane association is insufficient; coverage, orientation, retained function, particle stability, and in vivo biological identity require separate evaluation. **Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for emerging modality taxonomy and horizon-scanning criteria for living, biohybrid, and self-propelled drug carriers.

Table 1. Emerging modality taxonomy and horizon-scanning criteria for Living, Biohybrid, and Self-Propelled Drug Carriers.

Evidence domain or review construct	Review question	Eligible evidence type	Key extraction fields	Appraisal or relevance criterion	Synthesis role	Main limitation	Interpretation boundary
Carrier identity	Does the system contain viable cells, isolated membranes, vesicles, microorganisms, or synthetic components?	Structural characterization and platform studies	Source, viability, composition, assembly	Identity must be experimentally defined	Separates living, biohybrid, and synthetic modalities	Labels may obscure mixed architectures	Classification does not imply efficacy
Biological-interface transfer	Which cellular properties remain functional after membrane isolation or coating?	Membrane-protein, uptake, circulation, and targeting studies [13]	Coverage, orientation, retained proteins, uptake	Functional evidence must exceed nominal coating	Defines membrane-derived biohybrids	In vitro function may not predict in vivo identity	Biomimicry is not equivalent to whole-cell behaviour
Hybrid membrane design	Can two membrane sources provide complementary functions?	Comparative preclinical studies [14]	Source ratio, circulation, tissue interaction, stability	Each claimed function requires direct evidence	Identifies multifunctional combinations	Source-specific variability and tumour-model dependence	Homotypic interaction is not clinical targeting
Vesicle-mediated carriage	Do biological vesicles transport and release pharmaceutical cargo?	Vesicle characterization and animal delivery studies [15]	Source, endogenous contents, loading, release, biodistribution	Cargo effect must be separated from vesicle activity	Positions exosomes within the taxonomy	Isolation and compositional heterogeneity	Delivery feasibility is not product comparability
Coating integrity	Does membrane completeness alter uptake or biological behaviour?	Quantitative coating and internalization studies [16]	Coverage fraction, exposed core, uptake route, stability	Integrity must be linked to function	Defines a candidate critical quality attribute	One assay may not predict all biological outcomes	Proposed quality attribute, not an approved specification
Active movement	Is movement generated biologically, chemically, enzymatically, or externally?	Motility, trajectory, imaging, and propulsion studies [5]	Energy source, speed context, guidance, persistence	Motion must be distinguished from useful localization	Separates active transport from passive carriage	Laboratory movement may not transfer to tissue	Propulsion alone does not establish targeting
Evidence horizon	What evidence would materially change readiness?	Replicated mechanistic, in vivo, manufacturing, and safety evidence	Model relevance, controls, observability, reproducibility	Evidence must address a translational uncertainty	**Proposed horizon-review synthesis**	Categories remain interpretive	Horizons are not scores or adoption forecasts

Chemically and physically propelled micromotors

Reaction-driven micromotors can integrate propulsion with a local pharmaceutical function. Magnesium-based gastric micromotors have used acid consumption to generate movement while increasing local pH and promoting responsive payload release [17]. This coupling is mechanistically attractive because the surrounding environment provides both the propulsion condition and release trigger. The therapeutic contribution of motion must nevertheless be separated from acid neutralization, material degradation, and formulation-dependent release.

In vivo studies of gastric infection have shown that micromotor-enabled administration can produce a treatment signal in a localized organ environment [18]. The evidence supports route-constrained feasibility rather than general systemic navigation. Gastric anatomy, luminal chemistry, administration conditions, and short transport distances reduce several barriers encountered after vascular administration.

Micromotor pills extend the concept toward a recognizable oral dosage form by packaging reactive motors for administration and subsequent activation [19]. This architecture may protect the active components before reaching the intended environment and simplify handling. It also creates additional requirements involving dose uniformity, storage stability, motor activation, excipient compatibility, degradation products, and reproducible integration of the motor with the finished dosage form.

Enzyme-powered nanomotors provide an alternative in which endogenous substrates support local propulsion. Urease-powered systems have demonstrated swarming and imageable distribution after intravesical administration [20]. The bladder offers a comparatively confined space and direct administration route, making exposure and monitoring more tractable than systemic circulation. Even so, enzyme activity, substrate availability, local reaction products, repeated dosing, clearance, and tissue tolerability remain important development questions.

Sensing, navigation, targeting, and release capabilities

A clinically relevant carrier must be observable before it can be considered controllable. Imaging methods for microrobots must distinguish the carrier from surrounding tissue, detect it at sufficient depth, and provide information at a timescale compatible with intervention [21]. Optical visualization in transparent laboratory systems cannot be assumed to translate to deep organs. Imaging agents may also alter carrier mass, surface properties, propulsion, toxicity, or clearance.

Magnetite-containing biohybrid microrobots illustrate how propulsion, imaging contrast, and external guidance may be integrated [22]. Magnetic control can direct movement without requiring an onboard energy store, while magnetic material may support localization. However, steering in a simplified environment differs from controlling trajectories through branching vessels, mucus, tissue pores, or moving organs. External guidance therefore represents a control input rather than proof of precise targeting.

Release programmability is another independent capability. Enzyme-powered mesoporous nanomotors have coupled movement with gated intracellular payload delivery [23]. Such systems demonstrate that propulsion and release logic can coexist within one construct. They do not establish that both functions are necessary for the observed biological effect, nor that activation remains spatially restricted in vivo.

Navigation claims should therefore be decomposed into sensing or guidance input, movement, localization, retention, release, exposure, and biological consequence. Imaging evidence supports observability [21], whereas gated release demonstrates a separate functional transition [23]. A carrier may succeed at one stage while failing at another. Programmability should be evaluated as a traceable chain rather than inferred from motion, accumulation, or payload release alone.

Emerging evidence signals and enabling technologies

Systematic selection of membrane source and coating conditions represents an enabling shift from descriptive biomimicry toward testable design. Comparative membrane engineering has shown that source-cell characteristics and coating architecture can influence tumour targeting and biological performance [24]. The important signal is not that one membrane is universally optimal, but that biological-interface variables can be experimentally compared and linked to function.

Genetic programming further expands this design space. Source cells can be modified before membrane isolation so that selected proteins or therapeutic functions are displayed on the resulting particles [25]. This approach may increase targeting specificity or combine recognition with treatment. It simultaneously introduces genetic stability, expression variability, source-cell qualification, membrane-processing, and comparability requirements.

Recent intravesical nanomotor-assisted chemotherapy has provided an emerging animal-model signal involving tumour reduction and suppression of early regrowth [26]. The localized route, accessible organ, and capacity for

direct administration make this modality important for horizon surveillance. The finding remains preclinical and cannot establish repeated-dose safety, durable benefit, manufacturability, or clinical superiority.

Across modalities, the most readiness-relevant enabling technologies are those that improve observability, functional measurement, containment, reproducibility, or product definition. Added complexity is not itself progress. Imaging must function in clinically relevant settings [21], while membrane programming must remain analytically and biologically controllable [25]. **Table 2** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for enabling mechanisms, evidence signals, and developmental stages of emerging technologies.

Table 2. Enabling mechanisms, evidence signals, and developmental stages of emerging technologies.

Method, platform, or evidence category	Representative application	Reported strength	Validation context	Generalization concern	Contradictory evidence	Evidence gap	Review interpretation
Systematic membrane selection	Source-dependent tumour interaction [24]	Links membrane choice to measurable function	Cellular and animal studies	Results may depend on tumour and source-cell context	No universal best membrane established	Cross-model and process comparability	Emerging design-enabling evidence
Genetically programmed membranes	Targeted combination therapy [25]	Adds defined surface functionality	Preclinical colorectal cancer model	Expression and function may vary after manufacture	Simpler non-programmed comparators may retain activity	Stability, immunogenicity, scale-up	Promising but more complex biohybrid product
Imaging-guided magnetic control	Magnetite biohybrid microrobots [22]	Integrates steering and localization	Experimental and preclinical systems	Field geometry and tissue depth limit transferability	Guidance does not guarantee tissue penetration	Clinically relevant tracking and control	Intermediate evidence
Enzyme-powered gated release	Intracellular payload activation [23]	Couples biochemical propulsion with release control	Cellular proof of concept	Intracellular conditions vary among tissues	Payload effect may not require propulsion	In vivo specificity and off-target activation	Mechanistic enabling signal
Localized enzyme propulsion	Bladder swarming [20] and chemotherapy [26]	Direct administration and organ-confined movement	Animal bladder models	Findings may not transfer to systemic delivery	Local retention may partly explain benefit	Repeated-dose safety and reproducibility	Translationally nearer, but still preclinical
Membrane-integrity measurement	Uptake changes after incomplete coating [16]	Connects a material attribute to mechanism	Quantitative cellular analysis	One uptake model cannot define whole-body behaviour	Different assays may classify integrity differently	Standardized functional release testing	Candidate quality-control enabler
Programmable bacterial encapsulation	Controlled therapeutic-bacteria delivery [27]	Adds a physical containment interface	Mouse models	Shell behaviour may vary by tissue and bacterial strain	Encapsulation does not ensure biological shutdown	Escape, release, scale-up and shelf-life testing	Important containment signal
Horizon classification	Cross-platform maturity interpretation	Integrates opportunity, risk and missing evidence	Review-level synthesis	Categories change as evidence develops	No validated universal readiness scale exists	Prospective testing of milestone relevance	**Proposed qualitative synthesis**

Biosafety, controllability, immunogenicity, and containment risks

The biological identity of a carrier changes after administration. Complement proteins can bind to nanoparticle coronas and exchange dynamically in vivo [28]. This process may affect recognition, circulation, inflammation, uptake, and clearance. The presence of complement does not automatically establish toxicity, but it demonstrates that the administered formulation and the biologically encountered entity are not identical.

Corona composition can also alter the mechanisms by which cells internalize nanoparticles [29]. Consequently, uptake measured in simplified media may not predict behaviour in plasma, tissue fluid, or diseased microenvironments. Differences attributed to targeting ligands, membrane coatings, or propulsion may partly arise from acquired proteins and context-dependent cellular pathways.

Living bacterial carriers introduce additional hazards involving persistence, escape, shedding, immune activation, and uncontrolled replication. Programmable encapsulation has improved therapeutic-bacteria delivery in mice while providing a physical interface between the microorganism and host [27]. Encapsulation may support containment and release control, but it does not establish irreversible shutdown or eliminate strain-dependent biological effects.

Safety evaluation must therefore include both expected function and failure modes. Relevant questions include whether a carrier can be stopped, cleared, retrieved, degraded, or contained; whether biological components retain their intended phenotype; and whether repeated exposure changes immune responses. Corona formation [28], altered uptake [29], and living-organism containment [27] define testing needs rather than validated incidence rates or universal safety thresholds.

Manufacturing and regulatory-readiness horizons

Translation requires fit-for-purpose characterization, scalable quality control, and early alignment among pharmaceutical, clinical, manufacturing, and regulatory requirements [30-32]. Living and biohybrid systems challenge conventional product definitions because biological activity, device-like control, and drug release may jointly determine performance.

Critical attributes will vary by modality. Membrane-coated particles may require assays for coating integrity and exposed core [16]. Enzyme-powered systems may require control of enzyme activity, loading, propulsion conditions, and reaction products [20]. Programmed membrane systems add source-cell expression and comparability requirements [24]. Encapsulated bacteria require linked assessment of viability, shell integrity, release, escape, and biological function [27].

Regulatory classification may become ambiguous when a system combines a drug payload, externally controlled structure, diagnostic component, and viable organism. Existing nanomedicine regulation emphasizes that product characterization and safety evidence must be linked to the specific formulation rather than inferred from a platform label [30]. A single pathway cannot therefore be presumed for all carriers described as microrobots or biohybrids.

Manufacturing constraints are especially important where biological source material contributes directly to function. Scale-up must preserve identity, potency, sterility, stability, and batch reproducibility while controlling source variability [31]. Motility distributions, cell phenotype, membrane coverage, genetic stability, cargo loading, and release may all change during processing or storage.

Readiness is consequently better represented as completion of evidence milestones than as technological sophistication. Development should begin with a plausible clinical use case and a product definition that can be measured throughout manufacture and use [32]. **Table 3** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for opportunity, risk, readiness, and milestone assessment for living, biohybrid, and self-propelled drug carriers.

Table 3. Opportunity, risk, readiness, and milestone assessment for Living, Biohybrid, and Self-Propelled Drug Carriers.

Cross-study pattern or configuration	Context or boundary condition	Mechanism or explanatory factor	Observed or reported outcome	Rival explanation	Certainty or rigour concern	Implication	Research priority
Bacteria-driven transport	Local or route-constrained environments	Biological motility and adhesion [9, 10]	Cargo transport and local retention	Passive trapping or administration geometry	Limited systemic and repeated-dose evidence	Potential for localized delivery	Matched motile/nonmotile controls and containment testing
Immune-cell carriage	Inflamed or postoperative tissue	Endogenous recruitment [11, 12]	Increased delivery and biological activity in animals	Disease-driven cell accumulation independent of payload	Cell phenotype and loading variability	May exploit existing trafficking pathways	Separate native homing, cargo, and cell-activation effects

Membrane-coated particles	Source-dependent biological interfaces	Transferred membrane proteins [13, 16]	Altered circulation, recognition, or uptake	Core properties and acquired corona	Incomplete coating and model dependence	Product function may depend on coating quality	Standardized integrity, orientation, and comparability assays
Exosome-derived carriers	Vesicle-producing source cells	Natural vesicular transport [15]	Preclinical chemotherapy delivery	Endogenous vesicle contents	Isolation and source heterogeneity	Biologically derived carrier opportunity	Define source, cargo, potency, purity, and stability
Reactive gastric micromotors	Acidic, confined gastric environment	Material reaction and pH change [17, 18]	Local propulsion, release, and treatment signal	Acid neutralization without meaningful propulsion	Limited cross-model replication	Route-constrained use may be tractable	Propulsion-matched controls and degradation studies
Enzyme-powered bladder nanomotors	Intravesical administration	Urease activity and local substrate [20, 26]	Swarming, monitoring, and tumour-control signals	Prolonged local exposure or formulation effects	Preclinical and organ-specific evidence	Important localized horizon signal	Repeated-dose safety, imaging, clearance, and scale-up
Magnetic biohybrids	Accessible external-field geometry	Magnetic steering and contrast [22]	Guided movement and imaging in experimental systems	Field-driven bulk displacement	Limited deep-tissue control evidence	Observability and steering may be combined	Clinically relevant field and tracking validation
Living-carrier containment	Viable therapeutic bacteria	Programmable encapsulation [27]	Improved delivery in mice	Altered pharmacokinetics rather than containment alone	Escape and long-term persistence incompletely defined	Physical barriers may reduce risk	Failure-mode, release, shedding, and shutdown studies
Manufacturing-readiness construct	Defined intended use and product architecture	Measurable critical attributes	No universal outcome; **proposed synthesis**	Apparent maturity may reflect publication emphasis	No validated cross-platform readiness score	Progress should be milestone-gated	Link every milestone to a specific translational uncertainty

Priority experiments and translational milestones

Readiness should advance through milestone-gated evidence packages that integrate pharmaceutical developability, product-relevant safety evaluation, and micro/nanorobot-specific technology requirements [33-35]. A milestone should resolve an uncertainty capable of changing a development decision, rather than merely demonstrate another movement pattern or short-term efficacy signal.

Priority studies should isolate the contributions of propulsion, biological targeting, cargo, and release. Reactive micromotors require matched controls that reproduce material composition and payload exposure without active movement [17]. Gated intracellular systems similarly require comparison with non-propelled and non-gated constructs [23]. Untreated controls alone cannot determine which subsystem produced the observed outcome.

Readiness-changing evidence should include clinically relevant tracking, repeated-dose safety, biodistribution and clearance, containment-failure testing, manufacturing reproducibility, and stability. Imaging must demonstrate localization under realistic tissue conditions [21]. Living systems require deliberate escape and persistence testing [27]. Safety packages should be product-relevant [34], while roadmap priorities should remain connected to fabrication, control, powering, imaging, and regulatory feasibility [35].

The strongest translational case will arise when an active or biological function addresses a defined barrier that simpler carriers cannot adequately overcome. Clinical nanoparticle experience shows that successful translation remains product-specific [4]. Development strategy must therefore connect intended use, manufacturability, benefit–risk reasoning, and stakeholder requirements [32]. A structured framework can support these decisions without converting milestone completion into a claim of approval or clinical efficacy [33].

Review limitations

The evidence base is heterogeneous in carrier dimensions, payloads, propulsion mechanisms, administration routes, disease models, controls, and outcome definitions. The broad micro/nanorobot category includes systems that differ fundamentally in composition and intended use [5]. Direct comparative ranking would therefore be misleading.

Observability also varies substantially. Some studies use microscopy or localized imaging that may be appropriate for experimental validation but insufficient for deep-tissue tracking or clinical control [21]. Apparent differences in navigation may partly reflect measurement sensitivity rather than carrier performance.

Most modality-specific evidence remains preclinical, and technically successful prototypes may be more likely to be published than failed or irreproducible systems. Manufacturing and translational analyses indicate persistent barriers involving scale-up, stability, quality control, and development coordination [31]. The magnitude of publication bias or attrition cannot be estimated from this horizon scan.

The qualitative horizons are interpretive and will change as replicated safety, biodistribution, manufacturing, or clinical evidence appears. The review identifies convergent mechanisms, weak signals, and unresolved risks but does not estimate comparative effects, forecast adoption, or establish a universal development sequence.

CONCLUSION

Living, biohybrid, and self-propelled carriers expand drug-delivery design by combining pharmaceutical cargo with biological motility, endogenous homing, membrane-derived recognition, external guidance, environmental sensing, or triggered release. The reviewed evidence supports several promising mechanisms and localized preclinical signals, particularly where administration confines exposure and permits direct imaging or control. However, propulsion, accumulation, biological recognition, or technical programmability cannot alone establish pharmaceutical value. Translation depends on demonstrating a reproducible advantage over simpler carriers while defining biodistribution, failure modes, containment, immune interaction, product identity, manufacturing controls, and clinically relevant observability. The principal horizon opportunity is therefore not unrestricted autonomy, but progressively testable integration of movement, biological function, payload delivery, safety, and product definition. These conclusions remain evidence-bounded and do not constitute clinical recommendations, validated readiness predictions, or regulatory determinations.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101-24. doi:10.1038/s41573-020-0090-8
2. van der Meel R, Sulheim E, Shi Y, Kiessling F, Mulder WJM, Lammers T. Smart cancer nanomedicine. Nat Nanotechnol. 2019;14(11):1007-17. doi:10.1038/s41565-019-0567-y
3. Sindhwani S, Syed AM, Ngai J, Kingston BR, Maiorino L, Rothschild J, et al. The entry of nanoparticles into solid tumours. Nat Mater. 2020;19(5):566-75. doi:10.1038/s41563-019-0566-2
4. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. Bioeng Transl Med. 2019;4(3). doi:10.1002/btm2.10143
5. Li J, Esteban-Fernández de Ávila B, Gao W, Zhang L, Wang J. Micro/nanorobots for biomedicine: Delivery, surgery, sensing, and detoxification. Sci Robot. 2017;2(4). doi:10.1126/scirobotics.aam6431
6. Alapan Y, Yasa O, Yigit B, Yasa IC, Erkoc P, Sitti M. Microrobotics and microorganisms: Biohybrid autonomous cellular robots. Annu Rev Control Robot Auton Syst. 2019;2:205-30. doi:10.1146/annurev-control-053018-023803
7. Alapan Y, Yasa O, Schauer O, Giltinan J, Tabak AF, Sourjik V, et al. Soft erythrocyte-based bacterial microswimmers for cargo delivery. Sci Robot. 2018;3(17). doi:10.1126/scirobotics.aar4423

8. Xu H, Medina-Sánchez M, Magdanz V, Schwarz L, Hebenstreit F, Schmidt OG. Sperm-hybrid micromotor for targeted drug delivery. ACS Nano. 2018;12(1):327-37. doi:10.1021/acsnano.7b06398
9. Park BW, Zhuang J, Yasa O, Sitti M. Multifunctional bacteria-driven microswimmers for targeted active drug delivery. ACS Nano. 2017;11(9):8910-23. doi:10.1021/acsnano.7b03207
10. Mostaghaci B, Yasa O, Zhuang J, Sitti M. Bioadhesive bacterial microswimmers for targeted drug delivery in the urinary and gastrointestinal tracts. Adv Sci (Weinh). 2017;4(6):1700058. doi:10.1002/advs.201700058
11. Xue J, Zhao Z, Zhang L, Xue L, Shen S, Wen Y, et al. Neutrophil-mediated anticancer drug delivery for suppression of postoperative malignant glioma recurrence. Nat Nanotechnol. 2017;12(7):692-700. doi:10.1038/nnano.2017.54
12. Zhou H, He H, Liang R, Pan H, Chen Z, Deng G, et al. In situ poly I released from living cell drug nanocarriers for macrophage-mediated antitumor immunotherapy. Biomaterials. 2021;269:120670. doi:10.1016/j.biomaterials.2021.120670
13. Fang RH, Kroll AV, Gao W, Zhang L. Cell membrane coating nanotechnology. Adv Mater. 2018;30(23). doi:10.1002/adma.201706759
14. Wang D, Dong H, Li M, Cao Y, Yang F, Zhang K, et al. Erythrocyte-cancer hybrid membrane camouflaged hollow copper sulfide nanoparticles for prolonged circulation life and homotypic-targeting photothermal/chemotherapy of melanoma. ACS Nano. 2018;12(6):5241-52. doi:10.1021/acsnano.7b08355
15. Yong T, Zhang X, Bie N, Zhang H, Zhang X, Li F, et al. Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy. Nat Commun. 2019;10(1):3838. doi:10.1038/s41467-019-11718-4
16. Liu L, Bai X, Martikainen MV, Kårlund A, Roponen M, Xu W, et al. Cell membrane coating integrity affects the internalization mechanism of biomimetic nanoparticles. Nat Commun. 2021;12(1):5726. doi:10.1038/s41467-021-26052-x
17. Li J, Angsantikul P, Liu W, Esteban-Fernández de Ávila B, Thamphiwatana S, Xu M, et al. Micromotors spontaneously neutralize gastric acid for pH-responsive payload release. Angew Chem Int Ed Engl. 2017;56(8):2156-61. doi:10.1002/anie.201611774
18. Esteban-Fernández de Ávila B, Angsantikul P, Li J, Lopez-Ramirez MA, Ramírez-Herrera DE, Thamphiwatana S, et al. Micromotor-enabled active drug delivery for in vivo treatment of stomach infection. Nat Commun. 2017;8(1):272. doi:10.1038/s41467-017-00309-w
19. Karshalev E, Esteban-Fernández de Ávila B, Beltrán-Gastélum M, Angsantikul P, Tang S, Mundaca-Uribe R, et al. Micromotor pills as a dynamic oral delivery platform. ACS Nano. 2018;12(8):8397-405. doi:10.1021/acsnano.8b03760
20. Hortelão AC, Simó C, Guix M, Guallar-Garrido S, Julián E, Vilela D, et al. Swarming behavior and in vivo monitoring of enzymatic nanomotors within the bladder. Sci Robot. 2021;6(52). doi:10.1126/scirobotics.abd2823
21. Aziz A, Pane S, Iacovacci V, Koukourakis N, Czarske J, Menciassi A, et al. Medical imaging of microrobots: Toward in vivo applications. ACS Nano. 2020;14(9):10865-93. doi:10.1021/acsnano.0c05530
22. Yan X, Zhou Q, Vincent M, Deng Y, Yu J, Xu J, et al. Multifunctional biohybrid magnetite microrobots for imaging-guided therapy. Sci Robot. 2017;2(12). doi:10.1126/scirobotics.aaq1155
23. Llopis-Lorente A, García-Fernández A, Murillo-Cremaes N, Hortelão AC, Patiño T, Villalonga R, et al. Enzyme-powered gated mesoporous silica nanomotors for on-command intracellular payload delivery. ACS Nano. 2019;13(10):12171-83. doi:10.1021/acsnano.9b06706
24. Liu L, Pan D, Chen S, Martikainen MV, Kårlund A, Ke J, et al. Systematic design of cell membrane coating to improve tumor targeting of nanoparticles. Nat Commun. 2022;13(1):6181. doi:10.1038/s41467-022-33889-3
25. Yang Y, Liu Q, Wang M, Li L, Yu Y, Pan M, et al. Genetically programmable cell membrane-camouflaged nanoparticles for targeted combination therapy of colorectal cancer. Signal Transduct Target Ther. 2024;9(1):158. doi:10.1038/s41392-024-01859-4
26. Fichna K, Crespo-Cuadrado M, Konuparamban A, Di Carlo V, Esporrín-Ubieto D, Macías-Tarrío I, et al. Nanomotor-assisted intravesical chemotherapy for bladder tumor reduction and suppression of early tumor regrowth. Nano Lett. 2026;26(17):5618-27. doi:10.1021/acs.nanolett.5c05411
27. Harimoto T, Hahn J, Chen YY, Im J, Zhang J, Hou N, et al. A programmable encapsulation system improves delivery of therapeutic bacteria in mice. Nat Biotechnol. 2022;40(8):1259-69. doi:10.1038/s41587-022-01244-y

28. Chen F, Wang G, Griffin JI, Brenneman B, Banda NK, Holers VM, et al. Complement proteins bind to nanoparticle protein corona and undergo dynamic exchange in vivo. Nat Nanotechnol. 2017;12(4):387-93. doi:10.1038/nnano.2016.269
29. Francia V, Yang K, Deville S, Reker-Smit C, Nelissen I, Salvati A. Corona composition can affect the mechanisms cells use to internalize nanoparticles. ACS Nano. 2019;13(10):11107-21. doi:10.1021/acsnano.9b03824
30. Foulkes R, Man E, Thind J, Yeung S, Joy A, Hoskins C. The regulation of nanomaterials and nanomedicines for clinical application: Current and future perspectives. Biomater Sci. 2020;8(17):4653-64. doi:10.1039/D0BM00558D
31. Younis MA, Tawfeek HM, Abdellatif AAH, Abdel-Aleem JA, Harashima H. Clinical translation of nanomedicines: Challenges, opportunities, and keys. Adv Drug Deliv Rev. 2022;181:114083. doi:10.1016/j.addr.2021.114083
32. Germain M, Caputo F, Metcalfe S, Tosi G, Spring K, Åslund AKO, et al. Delivering the power of nanomedicine to patients today. J Control Release. 2020;326:164-71. doi:10.1016/j.jconrel.2020.07.007
33. Joyce P, Allen CJ, Alonso MJ, Ashford M, Bradbury MS, Germain M, et al. A translational framework to DELIVER nanomedicines to the clinic. Nat Nanotechnol. 2024;19(11):1597-611. doi:10.1038/s41565-024-01754-7
34. de Jong WH, Geertsma RE, Borchard G. Regulatory safety evaluation of nanomedical products: Key issues to refine. Drug Deliv Transl Res. 2022;12(9):2042-7. doi:10.1007/s13346-022-01208-4
35. Ju X, Chen C, Oral CM, Sevim S, Golestanian R, Sun M, et al. Technology roadmap of micro/nanorobots. ACS Nano. 2025;19(27):24174-334. doi:10.1021/acsnano.5c03911