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Review

Adaptive smart biomaterials to overcome metastatic tumor microenvironment heterogeneity: Theranostic strategies and clinical translation roadmaps

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Abstract: Over 90% of cancer-related mortality worldwide is due to metastatic disease since the dynamic tumor microenvironment poses huge challenges in preventing the spread of metastatic cancer. Introducing the advent of advanced biomaterials and their swift evolution, this review highlights the great potential of innovative biomaterials to tackle the metastatic tumor environment. Focusing on four distinct categories of biomaterial systems, the action mechanism of biomaterials utilized in anti-tumor therapy is explained in detail: 1. Nanoplatforms sensitive to biochemical cues, including pH, redox, and enzymes, are known as stimuli-responsive nanoplatforms that react according to their environment, 2. Smart nanoplatforms changing their morphology to penetrate impermeable physical barriers at the tumor site, 3. Ingenious biomaterial participating in tumor normalization, and 4. Nanoplatforms with real-time theranostic capabilities due to an innate feedback-loop mechanism. Ingeniously structured biomaterials with extensive evidence in preclinical efficacy encourage their inclusion in metastatic tumor therapy. However, their utilization in medical settings is prevented due to various challenges. Impractical manufacturing costs, regulatory and safety issues, as well as large-scale production, are major challenges restraining their widespread use. A concrete framework is proposed in this review to accelerate the biomaterial structure standardization process, following GMP and other regulatory guidelines, to implement biomaterial-based tumor diagnostics and therapies. Since incorporating advancing technologies in tumor therapy, such as AI-driven, autonomous biomaterial structures or patient-specific tumor models, would enable confronting the proliferating metastatic tumor cases.

Keywords: metastatic microenvironment; stimuli-responsive biomaterials; adaptive drug delivery; tumor heterogeneity; theranostic nanosystems; clinical translation

1. Introduction: The metastatic challenge

The transformation of cancer from a non-metastasizing treatable condition to an advancing malignant disease serves a grave warning in oncology [1]. More than 90% cancer-related mortalities comprise of aggressive cancer cells, metastasizing to remote areas of the body. Although significant progress in the treatment of primary tumor cases has increased the plausibility of the five-year survival rate to surpass 80% [2], the ability to metastasize of certain cancer types drastically decreases the survival rate to 30%. Futile clinical outcomes and proliferating tumor burden are a direct result of shifting cancer cell divergency, detected in many metastatic niches.

Disseminated tumor cells (DTCs) are fractions of the primary tumor that are shed during the continuous multi-step tumor developmental process; DTCs circulate to remote areas of the body during tumor development by the process known as metastasis [3]. Following the typical action mechanism, DTCs circulate throughout

the body, while avoiding immune reaction, and adapt to the local organ's microenvironment before converting it into its own unique TME. This makes the local TME distinguishable from the primary TME [4]. TME is mainly composed of elements like the extracellular matrix (ECM), immune cells, stromal cells and a mesh of blood vessels, but an infected organ has a distinct TME from organs including the primary tumor site [5]. For the tumor to colonize a new organ, DTCs adapting to the organ's local microenvironment is a set condition. Subsequently, such diversity in TME confers uniqueness, preventing conventional therapies from being effective on the tumor.

Many clinically approved nanomedicines, such as Doxil®, that use liposomal or polymer-based formulations have shown significant clinical benefits, mainly by way of better pharmacokinetics, longer circulation time, and reduced systemic toxicities when compared to standard chemotherapy drugs [6]. These benefits have helped to sustain their widespread clinical use, even though they have limitations in delivery specifically to the tumor cells. Moreover, NPs are considered potent cancer therapeutic agents in recent years, despite their inefficiency to counter the dynamic TME, which poses a looming threat [7]. Enhanced permeability and retention (EPR) effect is considered one of the primary action mechanisms for nanocarriers to deliver anti-cancer drugs to tumor sites [8], delivering nanoparticles (NPs) through the disrupted lymphatic drainage or leaky vasculature surrounding the tumor site, but the reinforced physical barriers and hypovascular lesions as a part of the tumor defense system prevent their intervention, halting the EPR effect [9]. Quantitative analyses indicate that only a very small percentage (~0.7%) of the administered dose actually reaches solid tumors on average; however, clinical benefits are most often a result of systemic pharmacokinetic advantages rather than high absolute tumor accumulation [10]. The reliability of the EPR effect is, however, very inconsistent across different tumor types and even patients. This is especially true in metastatic situations where vascular heterogeneity, hypovascular lesions, and high interstitial pressure lead to limited nanoparticle accumulation. The therapeutic dose lowers even more in metastatic lesions, such as in the clinically approved liposomal doxorubicin formulation, Doxil® [11]. Despite Doxil® showing strong clinical results, mainly the lower cardiotoxicity and longer circulation, this drug's effectiveness in metastatic tumors is mainly restricted by heterogeneous accumulation and variable delivery efficiency. Likewise, antibody-drug conjugates (ADCs) that demonstrate aggressive anticancer properties like ado-trastuzumab emtansine (T-DM1) are unable to have a similar potent anticancer effect towards brain metastases due to the fortified blood-brain barrier (BBB) [12]. Despite this, its effectiveness in brain metastases is limited because of physiological barriers like the blood-brain barrier. This points to delivery hurdles at specific sites in the brain rather than the absence of an intrinsic therapeutic effect.

This review reports on proposed smart systems that can detect and respond to various physical and biochemical barriers at metastatic tumor regions in order to improve therapeutic efficacy by targeting each tumor type with utmost precision. The current static therapeutic mechanisms prove inadequate against metastatic cancer, which requires a major upgrade in cancer therapies. It discusses the mainstream metastatic sites while also shifting focus to how next-generation biomaterials are being constructed to counter these unique tumor regions. The following sections take a close

look at different metastatic niches in the major organs, namely bone, brain, liver, and lung. Each of these organs has its own unique microenvironmental and physiological barriers that shape the effectiveness of the therapy. Take a close look at different metastatic niches.

1.1. The bone metastasis microenvironment

Cancers metastasizing towards the skeleton include lung, breast and prostate cancers [13]. TME specific to bone metastases is a unique, marginally alkaline (pH 7.1–7.4) region [14] with mineral deposits and osteoclasts (bone reabsorbing cells) and osteoblasts (bone-forming cells) contributing to the biochemical modulation in the region. Following the tumor colonization, the biochemical balance is disrupted, causing slow yet continual bone damage. Tumor cells trigger excessive production of Receptor Activator of Nuclear Factor-κB Ligand (RANKL) by osteoblasts, moderated by the release of signaling molecules (such as parathyroid hormone-related protein (PTHrP) released by tumor cells themselves [15]. The differentiation of immature osteoclasts and subsequent bone reabsorption is triggered by surged release of RANKL. TGF-β, a growth factor, further reinforces tumor growth.

Bone metastatic sites are extremely challenging for drug delivery systems since penetration by nanocarriers is prevented by the highly mineralized hydroxyapatite matrix, exerting compressive stress over 15 kPa [16]. Moreover, bone metastases lack dense vasculature, which prevents nanocarriers from draining into the tumor site, which statistically reflects less than 5% of the injected dose reaching per gram of tissue at the target site. Therefore, novel biomaterial strategies devised must not only be capable of targeting cancer cells but also inhibit bone destruction caused by it.

1.2. The brain metastasis microenvironment

Cancer cells, metastasized to the brain, are guarded from the body's immune system as well as the anticancer drugs, as they are impeded by the BBB. The BBB is a multilayered barrier composed of highly specialized epithelial cells joined end-to-end by tight junctions with basement membrane, pericytes and astrocytes end-feet [17]. The specialized layers of the BBB portray unique permeability, allowing movement of only small molecules (<400 Da) or those with specific transporters. The paracellular pores in the BBB, sized less than 2 nm, prevent most NPs from diffusing. Furthermore, active efflux pumps with rejection efficiency up to 98%, such as P- glycoprotein (P-gp), reinforce the barrier, halting diffusion of chemotherapeutics into the brain. Advanced imaging techniques and histological research revealed that due to BBB heterogeneity, it may be disrupted non-uniformly during early-stage micrometastasis. Since perivascular niches maintain a neutral pH (7.2–7.4) in brain metastasis, pH-responsive frameworks fail to perform effectively, which works suitably in acidic conditions [18]. Moreover, continual tumor growth creates an intense hypoxic environment (pO_2 < 5 mmHg), strengthening resistance mechanisms towards anticancer therapies. Specialized BBB cells, astrocytes, accommodate chemotherapeutic environment by releasing protective factors glutathione S-transferase π (GSTπ) [19]. Consequently, biomaterials constructed to target brain metastasis are required to display advanced penetrating capabilities to diffuse through

the BBB while circumventing efflux pumps, at the same time, portraying improved abilities to function effectively in dynamic physiological microenvironments.

1.3. The liver metastasis microenvironment

Gastrointestinal cancers commonly populate the liver, while cancers from the breast, pancreas and lungs also tend to metastasize towards the liver. The blood vessels in the liver, with pores sized 100–150 nm, should ideally allow movement of NPs into the liver [20]. Nevertheless, the desmoplastic liver cells, due to metastasis, prevent NP accumulation. During metastasis, hepatic stellate cells start to function as myofibroblast cells, secreting compounds like collagen I and II, turning the ECM extremely dense and impenetrable. The high interstitial fluid pressure encapsulates the tumor while blocking the NPs in the peritumoral space.

Moreover, liver metastasis exhibits unique metabolic activity. Although hepatocytes have a comparatively higher metabolic rate, cancer cells stimulate them to produce an even higher rate of energy by the Warburg effect, which traps acid in the liver tissue (pH 6.8–7.1) [21]. The atypical vasculature promotes hypoxic conditions in the TME, leading to activations of transcriptional regulators such as Hypoxia-Inducible Factor 1-alpha (HIF-1α) [22], which facilitates cancer growth by exhibiting chemoresistance, altering metabolic activity and developing a dense vascular network. For biomaterials to efficiently counter liver metastasis, they initially need to be able to efficiently penetrate the thick desmoplastic extracellular matrix surrounding the tumor and exploit the acidic, hypoxic conditions to therapeutic advantage.

1.4. The lung metastasis microenvironment

Lungs are one of the usual sites of metastasis since lungs are the first capillary bed where cancer cells circulate through after breaking free from the primary tumor. Lung microenvironment maintains approximately neutral pH, ranging from 7.3–7.5, while the lung morphology can be translated as elastic air sacs heavily covered by capillaries for gas exchange and this alveolar-capillary barrier is infeasible for nanomedicines to pass through [23]. Despite the leaky vasculature at the metastatic site, penetrating the extravascular space proves difficult.

Moreover, immune cells recruited in the lung TME display a distinct pattern. Under normal circumstances, alveolar macrophages are responsible for maintaining tissue homeostasis, but their role is suppressed by cancer cells' influence. Surfactant Protein-D (SP-D), one of the abundant surfactant proteins in the alveoli, stimulates the macrophages to halt at the M2-phase, which basically promotes tumor growth [24]. Interestingly, lung TME experiences intermittent hypoxia rather than chronic hypoxia common to other organs' TME due to constant ventilation and cell perfusion, which makes hypoxic-mediated therapies ineffective in lung tumors. Considering the distinct TME, biomaterial targeting lung tumors must be well-equipped to penetrate the alveolar-capillary barrier as well as be able to counter local immunosuppression triggered by metastatic tumors. **Figure 1** demonstrates the tumor metastasis pathway to various organs, brain, lungs, pancreas, liver, and bone in detail, while **Table 1** summarizes the characteristics and compositions of TME of various organs.

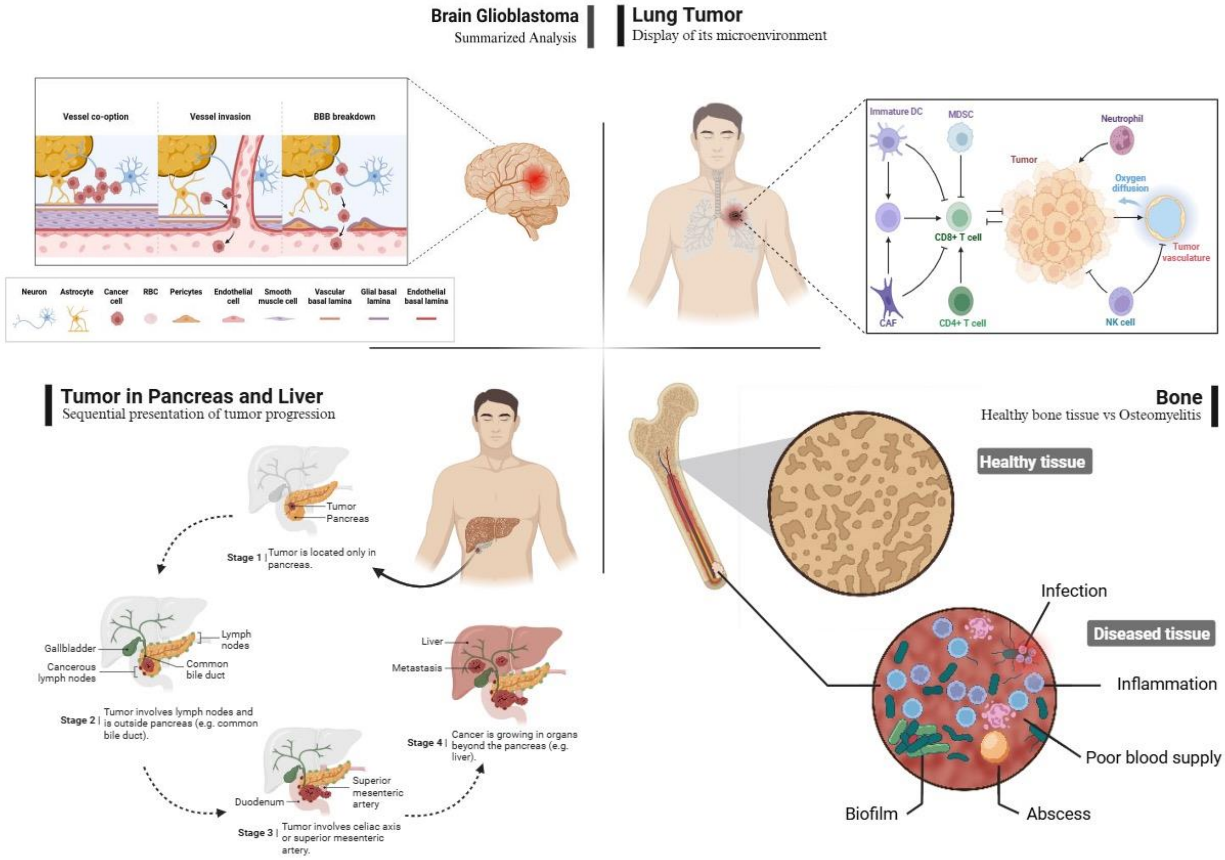


Figure 1. Schematic representation of organ-specific metastatic tumor microenvironments.

Table 1. olecular and Physical Heterogeneity Across Metastatic Niches.

Site	pH	Dominant stromal components	Key therapeutic barriers	Characteristic biomarkers/drivers
Bone	7.1–7.4	Osteoblasts, Osteoclasts, RANKL-rich ECM	Mineralized matrix, high stiffness, hypovascularity	$TRAP^+$ osteoclasts, OPN, SOST, RANKL
Brain	7.2–7.4	Astrocytes, Pericytes, Endothelial Tight Junctions	Blood-Brain Barrier, P-gp efflux, restricted permeability	$GFAP^+$ astrocytes, GLUT1, Claudin-5
Liver	6.8–7.1	Hepatic Stellate Cells, Collagen I/III	Dense desmoplasia, high interstitial pressure, aberrant vasculature	α-SMA^+ CAFs, PDGFRβ, SPARC
Lung	7.3–7.5	Fibroblasts, Alveolar Macrophages, Elastin Networks	Alveolar-capillary barrier, immunosuppression	$SP\text{-}D^+$ macrophages, Elastin, VCAM-1

In short, the generalized approach to cancer therapy is proven to be inadequate for unique metastatic environments. Diverse pathophysiology of every organ metastasis requests therapeutics approaches that are adaptive. The foundation of the review is the exploration of materials science and manufacturing principles employed to construct next-generation biomaterial systems. The range of action mechanisms employed by biomaterials to penetrate fortified tumor barriers and counter ever-transitioning TME is explored in detail in this review. From the array of counteractive strategies utilized by smart biomaterials, TME remodeling is considered a significant

approach that renders the environment hostile for the tumor to grow further, a phenomenon extensively discussed in the article. Furthermore, a synergistic approach of combining biomaterials with innovative diagnostic techniques is mentioned as well. This novel strategy would allow antitumor therapy in real-time and consequently an accelerated pathway of smart biomaterials to clinical translation.

2. Engineering adaptive biomaterials for metastatic niches

The ingenious organization of molecular motifs and structural domains forms specialized adaptive biomaterials that precisely respond to specific biochemical cues in their surrounding TME. Biomaterial systems are highly tunable from particle size to charge and can be conveniently modified in situ to formulate a suitable biomaterial that can overcome biological barriers at the tumor site for successful invasion. The following section focuses on the engineering and functionalization of various logic-gated biomaterial systems that are employed to efficiently respond to biochemical cues present in TME, as well as next-generation biomaterials for TME remodeling.

2.1. Multi-stimuli responsive systems: Logic-gated nanotherapeutics

Prominent physical and biochemical characteristics of a typical metastatic environment include hypoxia, enzymatic overexpression, acidity, and redox dysregulation [25]. Conventional systems that usually respond to single stimuli are incapable of grasping the dynamics of metastatic TME, resulting in early or off-target activation. On the contrary, multi-stimulus responsive systems employ molecular logic gates that are stimulated once multiple required conditions are checked, subsequently reducing systemic toxicity and improving spatial precision.

A well-suited example of a logic-gated approach is discussed in Zhang et al.'s research targeting breast cancer metastasis. For a sustained drug release in a targeted site within the bone niche, researchers structured a layered NP with zoledronic acid (ZA) at its core, a bisphosphonate preventing osteoclast-driven bone reabsorption, and poly(lactic-co-glycolic acid) (PLGA) matrix withholding the core [26]. A pH-sensitive shell coated the inner layers with poly(β-amino ester) (PAE), a polymer that becomes positively charged in slightly acidic environments. NP, with pKa approximately 6.5, sustains a neutral charge at pH 7.4, shifting to a positive charge at pH $\leq$ 6.8. The charge transition from an initial zeta potential -28 mV to +12 mV propels the electrostatic interaction of positively charged NPs with the negatively charged cell membrane, facilitating cell diffusion [27]. Fundamentally, the PAE shell is connected to the core by a cleavable linker peptide (GPLGVRG), which is a substrate for an enzyme usually overexpressed in osteolytic environments, matrix metalloproteinase-2 (MMP-2). The structure is ultimately coated with hyaluronic acid (HA), which attracts CD44 receptors, usually expressed in cancer stem-like cells and breast cancer cells. The meticulous structure initiates a sequence of events starting from docking at the metastatic site by conjugating with CD44 receptors, followed by the drug uptake due to acidic pH, while the drug is released through the shell by MMP-2. Drug accumulation exhibited an 8.7 times increase in one in vivo study based on the MDA-MB-231 breast cancer bone metastatic site, while the tumor burden reduced by 73%

with 89% decrease in osteolytic lesions, validating the therapeutic efficacy of the biomaterial system [28].

To target hepatic lesions in liver metastatic TME by colorectal cancer, Chen et al. formulated a nanoplatform, responsive to three pathological cues [29]. NP design comprised of p-nitrophenyl phosphate (pNPP), an enzymatic substrate, encapsulating calcium phosphate (CaP) core. Initiating a cascade of reactions, the increased activity of alkaline phosphatase (ALP) in TME degrades the NP shell, pNPP. The outermost layer was engineered to respond to a cascade of pathological signals. Initially, elevated alkaline phosphatase (ALP) activity in the liver microenvironment hydrolyzes pNPP, creating a local acidic environment that consequently destabilizes the CaP core, composed of poly(2-(diisopropylamino)ethyl methacrylate) (PDPA). PDPA has the vital chemotherapeutic drug, SN-38, entrapped by redox-labelled disulfide linkages, which are cleaved due to interaction with high concentrations of glutathione (GSH, ~10 mM) upon cellular uptake. The bond cleavage releases SN-38 in cancer cells in a targeted and sequential manner for precise and sustained drug release. The aforementioned triple-responsive nanoplatform exhibited 92% tumor suppression in orthotopic liver metastatic models with minimal hepatotoxicity as compared to a single-stimulus responsive system.

Despite their high performance, the efficacy is hindered due to certain intrinsic limitations. Existing nanosystems commonly target two or three triggers, characteristic of TME, depending upon a few binary inputs. However, it fails to respond to complex gradients and spatial heterogeneity of the metastatic environment in its entirety. For instance, specific nanoplatforms may be rendered ineffective due to a conspicuous difference in pH values and enzyme concentrations within a lesion. Therefore, a multi-stimuli system exhibiting analog-like behavior would prove to be more effective considering its ability to modulate drug release depending upon the presence and intensity of stimulus rather than a complete on/off mode.

Misaligned responses to different stimuli due to time lag may present a structural challenge, considering pH-triggered charge transition in the nanocarrier may occur rapidly in acidic milieu, while protective shell cleavage due to enzymatic exposure may require hours to occur [30]. This misalignment in the reaction cascade can result in early drug release and consequently suboptimal dosing. Matrix metalloproteinases (MMPs), acidic pH, and redox imbalance are among the stimuli that are frequently used in the design of smart biomaterials. These stimuli are not limited to the tumor microenvironment; they are also elevated under systemic inflammation and chronic diseases like diabetes, rheumatoid arthritis, ischemic injury, and inflammatory bowel disease. Inflammation and oxidative stress in such diseases lead to changes in local and systemic physiology that can increase enzyme activity and redox fluctuations. As a result, similar pathological signals may prematurely or off-targetly activate stimulus-responsive nanoplatforms in non-tumor tissues. Such an unintended activation may lead to insufficient drug localization at the target site, diminished therapeutic outcomes, and greater systemic toxicity. Therefore, overcoming this challenge will involve devising more accurate activation methods, such as threshold-dependent responsiveness, multi-input logic-gated systems, or spatially confined activation.

Going beyond the development of biomaterials, it would be a great breakthrough in biomaterial science if we could build nanosystems that can decode Boolean logic

for processing artificial intelligence. Similarly, to design operable biomaterials, activatable moieties with inhibitory molecules can be incorporated into the structure to increase target precision and action regulation. AI-based biomaterials symbolize the accelerating evolution of biomaterial systems in targeted therapy and drug delivery in real-time, justifying their stark impact on metastatic tumor treatment.

2.2. Morphology-shifting systems: Overcoming physical barriers

It is non-negotiable for NPs to penetrate the physical barriers imposed by tumor defense mechanisms to suppress the metastatic TME. Ranging from mineralized bone matrix to fibrotic liver metastatic matrix, metastatic niches vary drastically from each other. With tunable shape and size that activate upon encountering specific TME signals, biomaterials are methodically designed to push through the formidable barriers at the tumor site.

Size-switchable NPs are the usual proposition. By design, these NPs are supposed to be comparatively larger in size (around > 100 nm) to undergo the EPR effect and passively accumulate at the tumor site while avoiding renal clearance [31]. Following the passive accumulation in TME, NPs are minimized to <20 nm to be able to efficiently penetrate the dense ECM into the tumor cells. To solve the problem, Song et al. prepared acidity-responsive size-transformable micelles made of amphiphilic copolymers with pH-sensitive amine groups in the hydrophilic part. At the physiological pH of 7.4, the micelles form large clusters (~120 nm), whereas in the slightly acidic tumor environment (pH ~6.8), the protonation of amine groups results in electrostatic repulsion, and the micelles break down into smaller units. This change in size greatly improves the penetration and accumulation in tumors, which in vivo imaging confirmed, showing better therapeutic efficiency than non-responsive systems [32]. Another proposed solution to physical barriers in metastatic niches is "shape-shifting" NP [33]. Cellular internalization and biodistribution heavily depend upon the nanocarrier's shape, whereas practically filamentous NPs have proven to have longer circulation time than spherical NPs. However, spherical NPs are internalized by cells with greater ease. Speculatively, NPs with the ability to shape-shift between advantageous shapes according to the requirements would highly improve therapeutic efficiency. Conversely, if a filamentous NP is designed for enhanced circulation but transforms into a spherical shape upon encountering the tumor site for easier cellular uptake and be able to detect biochemical cues like MMPs to cleave into smaller spheres.

Critical limitations and future directions for morphological adaptation

The limitations of morphological adaptation include:

Incomplete Transformation: A huge constraint in translating size-switchable NPs in practical settings is the assurance of ubiquitous dispersal of uniformly cleaved particles. Partial disintegration of NPs from larger masses may lead to sub-optimal dosage and therapeutic efficiency greatly decreases.

- Control over Final Size/Shape: Uniform and equally sized nanoparticles are anticipated after the disintegration of larger particles for a reliable and efficacious treatment. Nonuniform NP dispersal may lead to unpredictability or inefficiency in treatment procedures.

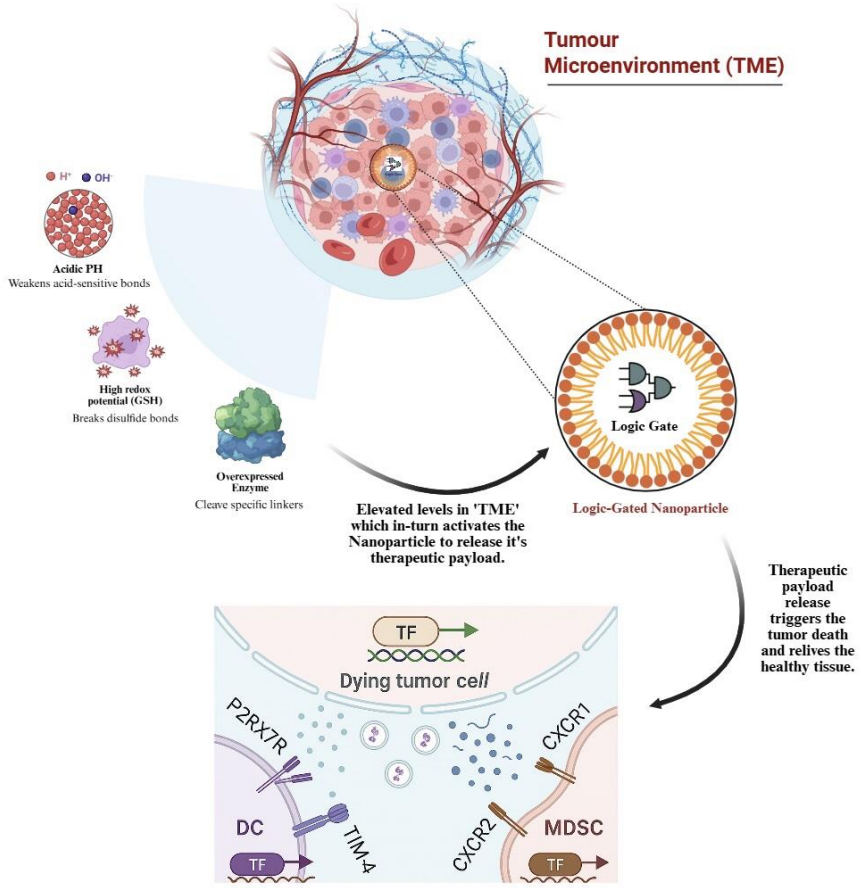
- Potential for Embolism: In rare but possible occurrences, NPs aggregate to make larger molecules following the course of the therapeutic mechanism. However, it may cause embolism in the vasculature, leading to deleterious effects in tumor physiology.

To develop well-structured and reliable transformational nanosystems, intensive research and clinical studies are required. Action mechanisms may involve assessments to ensure the transformations occur under a controlled and specific environment. Incorporating transformational capabilities in concert with specific responsive cues for drug release would formulate an exceptionally fortified nanosystem to tackle the dynamics of various metastatic sites. **Figure 2** illustrates the types of intelligent NPs and their action mechanism.

2.3. Biomaterial-mediated TME normalization: REMODELING the battlefield

Fortified biomaterials actively mitigate the aggressive TME conditions and suppress their progression. However, certain biomaterials are also involved in the dynamic restriction of TME known as TME normalization**.** Biomaterials responsible for TME normalization aim to minimize tumor-favorable conditions and make the niches hospitable for normal functioning, including removing stromal barriers, reactivating immunosuppressive action, and normalizing hypoxic conditions.

A



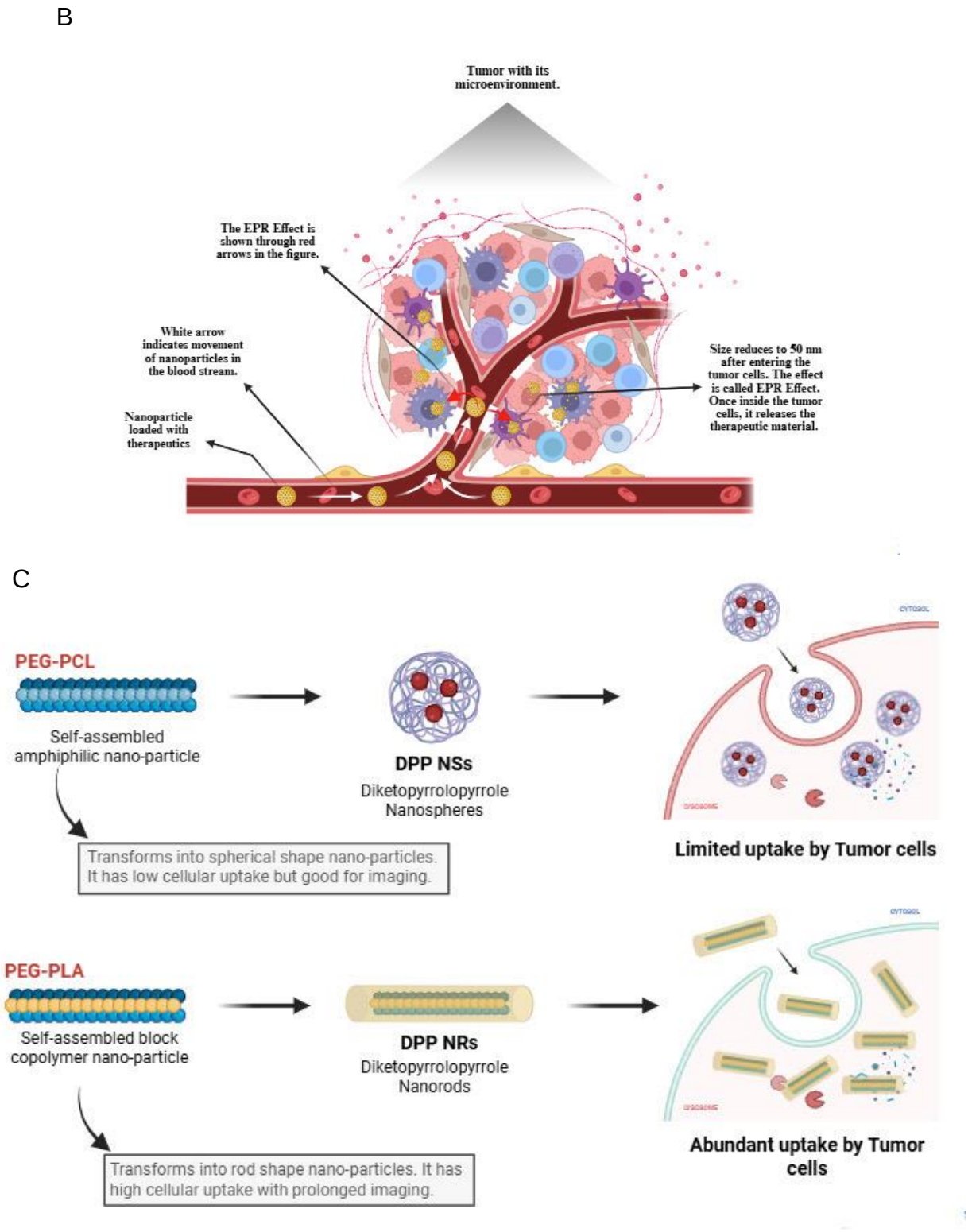


Figure 2. Representative adaptive nanoplatform designs: (A) multi-stimuli logic-gated nanoparticle responsive to pH, enzymatic activity, and redox potential; (B) size-switchable carrier enabling deep stromal penetration; (C) shape-shifting nanoparticle transitioning from filamentous to spherical morphology for optimal biodistribution and cellular uptake.

Hypoxia is one of the most significant characteristics of metastatic niches, enabling tumor progression by suppressing immune cell activity and inhibiting conventional anticancer therapies, including radiotherapy and chemotherapy. However, to overcome hypoxic conditions, emerging oxygen-generating NPs have shown promising results in situ [34]. Oxygen-generating NPs typically entrap oxygen-generating agents like calcium peroxide (CaO) or catalase. As a response to acidic pH in TME, entrapped CaO_2 produces hydrogen peroxide (H_2O_2) upon reaction with water molecules, which further decomposes to produce oxygen and water. Exploiting the already high concentration of H_2O_2 in TME, catalase encapsulated NPs directly convert it to molecular oxygen. Oxygen level restoration in TME aids the production of DNA-damaging free radicals and sensitizes the tumor to radiotherapy while also elevating cytotoxic activity of various chemotherapeutics, which would be ineffective in hypoxic conditions.

Another serious challenge, preventing drug penetration, is the nearly impermeable dense ECM common to most metastatic sites, including the liver and pancreas. Hyaluronic acid, collagen, and fibronectin are the main components of the ECM, imparting interstitial fluid pressure while also restricting NP penetration. Researchers formulated enzyme carriers based on biomaterials to aid ECM penetration. Nanocarriers encapsulating specific enzymes, such as hyaluronidase or collagenase, selectively degrade their respective substrates from the ECM, perforating the tumor barrier for drug delivery. If carried out serially, metastatic treatment increases the plausibility of therapeutic efficacy as backed by a fibrotic tumor preclinical model that comprised an ECM-modifying step followed by immunotherapy and then cancer cell cytotoxicity.

'Cold' immune system is a term used to explain the suppressed immune activity in metastatic TME, which is also a huge constraint in antitumor therapy. The body's defense system is usually dormant in metastatic niches due to immunosuppressive cells, including regulatory T cells (Tregs), tumor-associated macrophages (TAMs, especially M2), and myeloid-derived suppressor cells (MDSCs). Researchers developed smart biomaterials to reorganize the immune microenvironment and formulated NPs to deliver inhibitory molecules such as IL-12 to M2-TAMs to transition to a pro-inflammatory M1 phenotype [35]. Immune microenvironment reorganization also includes reducing Tregs and impeding immunosuppressive cytokines to uplift immunosuppression and enable effector T cells for a rigorous anticancer response. Immune-modulatory biomaterials are also beneficially capable of working in unison with checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies, exposing non-responding patients to immunotherapy for metastatic cancers [36].

Preclinical trials for TME normalization exhibited positive outcomes. The procedure still faces numerous obstacles preventing its translation into the clinical setting. The risk of systemic toxicity from potent enzymes or cytokines is considered the downside of TME normalization. Although the efficacious results in preclinical trials, applying TME normalization in the clinical setting still faces challenges like systemic toxicity while administering potent enzymes or cytokines. Normal tissue structure may be harmed by the interaction of TME normalizing agents, such as IL-12

and collagenase. The specific target of such agents is extremely imperative for safe therapeutic results.

Numerous factors inhibit successful TME remodeling; intrinsic and extrinsic influences on the tumor, patient subjected to other therapies, and the ever-changing TME make its reorganization arduous. Besides, a single dose of remodeling agent proves to be inadequate as the TME is invigorated shortly after. To keep TME under a long-term drug influence, advanced biomaterial systems should be designed for sustainable drug release. TME has an extremely interconnected network of metabolic pathways that impact each other. For instance, ECM degradation, surrounding TME, stimulates the release of TGF-β or VEGF, growth factors that promote tumor growth. The interrelation between metabolic pathways impedes biomaterials' agency to gain efficacious therapeutic outcomes. For the therapeutic agent to successfully mitigate the tumor progression, a thorough understanding of the TME and extensive experimental data is necessary. Adequate data would allow researchers to formulate suitable biomaterials for specific metastatic niches.

In essence, a design upgrade in biomaterial systems is essential to effectively infiltrate biological barriers at tumor sites for the antitumor drug to have its cytotoxic effect and trigger an immune reaction for long-term immunity. Following the aforementioned guidelines, tumor progression and proliferating cancer cases can be restricted.

3. Theranostic integration: Seeing, targeting, and treating in real-time

A dual system entailing therapeutic and diagnostics procedure is known as theranostics, working simultaneously to detect and treat diseases like cancer. Biomaterials provide an array of solutions in metastatic treatments since their characteristics suitably provide treatment strategies such as real-time drug delivery monitoring, targeted drug delivery with continuous drug surveillance to evaluate treatment response. Moreover, it can be utilized as an agent for individually tailored treatments, involving specific nanocarriers designed according to the patient's biology and tumor behavior.

3.1. MRI-guided photothermal platforms

Magnetic Resonance Imaging (MRI) is extensively utilized in cancer therapies because of its refined resolution and definite contrast, for precise targeting in cancer treatments [37]. A prime example of this integration comes from the work of Lee et al., who designed a copper sulfide (CuS) NP with traces of gadolinium to simultaneously serve as a contrast agent for T1-weighted MRI and a transducer agent for photothermal therapy, setting a prime example for an anti-cancer theranostic agent.

CuS-based NP was specialized to absorb near-infrared (NIR) and convert it to thermal energy, destroying cancer cells in the periphery. Gadolinium-DOTA chelates were adsorbed on the NP surface to act as an MRI contrast agent for treatment surveillance. For specific targeting, an anti-EGFR nanobody was also attached to its surface to interact with overexpressed EGFR receptors in cancer cells. The targeted

theranostic approach and reliable treatment assessment are achieved through this experiment.

Administering the formulated NPs intravenously, their circulation is tracked through T1-weighted MRI to assess biodistribution and accumulation at the metastatic tumor site. The NP enables clear visualization, determining the exact tumor site, through stark contrast and photoacoustic imaging. Following the tumor detection, a 980 nm NIR laser is shone to induce localized heat controlled at 42–45 ℃ using MR thermometry to ensure cancer cell destruction without harming normal cells. Simultaneously, heat-sensitive liposomes burst open to release doxorubicin, an anticancer drug, for tumor regression. Gd-CuS NPs displayed promising results in the orthotopic liver metastasis mouse model with 96% complete tumor regression over the course of 90 days and no tumor reoccurrence. The multifunctional NP with detecting, destroying and drug-carrying abilities exhibited synergistic response to liver metastasis.

3.2. PET-traceable CRISPR delivery

Positron Emission Tomography (PET) provides an ultra-sensitive non-invasive imaging option with a detection range in picomolar to monitor drug biodistribution and treatment efficacy. Applying the theory, Liu et al. developed PET-detectable exosomes carrying CRISPR-Cas9 to metastasized tumors. Genetically modified HEK293T cells were employed as exosomes that expressed CD47 and Lamp2b proteins. CD47 proteins, expressed on the exosome surface, were responsible for escaping phagocytic immune reaction and consequently increasing circulation duration.

The exosome-encapsulated CRISPR-Cas9 ribonucleoprotein complex is essential to inhibit the PD-L1 immunosuppressive protein, which is usually overexpressed in a metastatic environment [38]. NOTA chelator was conjugated to the exosome surface that was further bound to copper-64 (^{64}Cu) for rapid detection through PET. ^{64}Cu-exosomes successfully accumulated in 4T1 breast cancer metastasized to lungs as detected by PET/CT scans compared to naked CRISPR molecules. While CRISPR complex efficaciously knocked down PD-L1 proteins by 78% in metastatic lesions, as well as 80% decrease in overall metastatic burden. Moreover, it also exhibited an abscopal effect, referring to tumor regression in untreated metastasized regions. The CRISPR complex encapsulated exosomes not only showed effective antitumor capabilities, combined with real-time treatment assessment, but also stimulated the body's immune response for effective tumor regression in targeted as well as untreated sites. **Figure 3** shows the detailed diagram of smart NPs utilized in concert with imaging technologies for tumor theranostics, whereas **Table 2** lists the smart NPs employed in imaging technologies, while also mentioning their distinct characteristics.

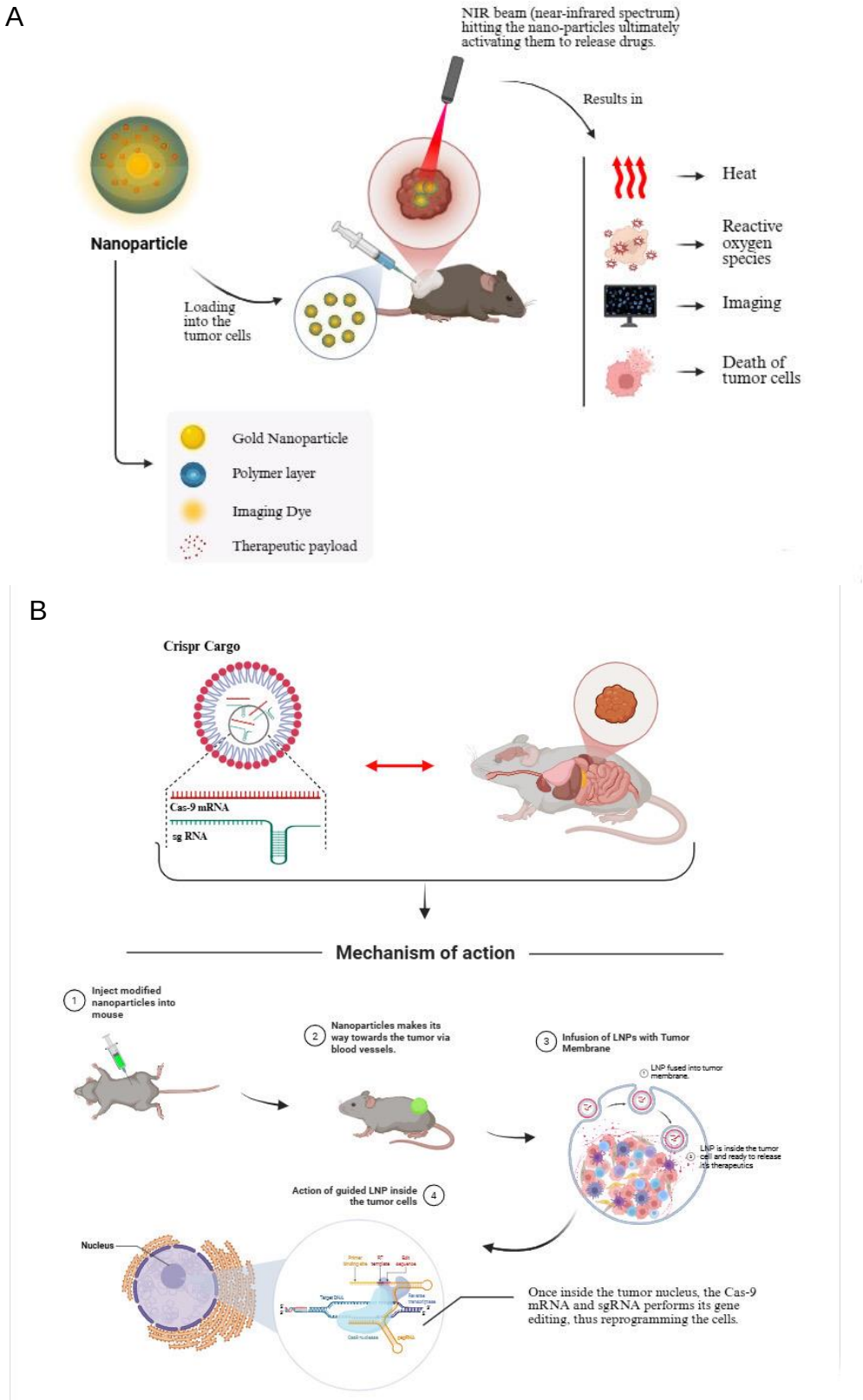


Figure 3. Examples of theranostic adaptive biomaterials: (A) MRI-guided photothermal nanoparticle enabling imaging, targeted heating, and triggered drug release; (B) PET-traceable exosome platform for CRISPR-Cas9 delivery and immune reprogramming in metastatic lesions.

Table 2. Advanced Theranostic Platforms for Metastatic Disease.

Platform	Imaging modality	Therapeutic payload	Activation mechanism	Metastasis model	Key outcomes
Gd-CuS NPs	T1-MRI / Photoacoustic	Doxorubicin (thermosensitive liposomes)	Laser irradiation (980 nm)	Orthotopic liver mets (HCCLM3)	96% regression, no recurrence at 90 days
^{64}Cu-exosomes	PET/CT	CRISPR-Cas9 (PD-L1 KO)	Endosomal escape via GALA peptide	Lung mets (4T1)	80% nodule reduction, abscopal effect
QD-liposomes	NIR-II (1500 nm)	Cisplatin + anti-miR21	MMP-9 cleavage	Bone mets (PC3)	75% osteolysis reduction, significant pain relief
SPION-hydrogels	T2-MRI	TGF-β siRNA + IL-2	Enzymatic degradation (collagenase)	Brain mets (BR16)	5-fold T cell infiltration, survival extension by 21 days

3.3. Clinical translation barriers for theranostics

Although these versatile theranostic nanosystems possess promising dual-functional capabilities, they still encounter various challenges preventing them from being utilized in clinical settings. PET-based therapy showed a favorable outcome, as mentioned earlier, in preclinical trials. However, it poses a high toxicity risk through ionizing radiation exposure. Isotopes employed in PET procedures like ^{64}Cu have longer half-lives; therefore, the therapy requires greater vigilance with rigorous guidelines. To create a safer environment for professionals and patients alike, experiments involving ionizing radiation should be conducted in radiopharmacies. Moreover, theranostic imaging modalities are refrained from being widely used because of operational complexity; expert help is required to conduct procedures like MRI-guided photothermal therapy and sophisticated machines, which pose a huge financial burden. Consequently, such treatment modalities are difficult to be embraced in financially compromised and resource-deficient regions. Compliance issues further added to the list of limitations preventing the utilization of such modalities. On the other hand, interdisciplinary involvement in the manufacturing and biomaterial design creates confusion in the regulatory framework and necessitates the product to comply with regulations in various domains, further complicating the approval process. Inadequate regulatory guidelines for innovative biomaterial designs deprive a fast-track approval process for advance biomaterials systems, demotivating investors and researchers from contributing to the industry. Approval of product design also requires it to be economically feasible at $150,000 per quality-adjusted life year (QALY). Subsequently, researchers also need to be mindful of the financial aspect of biomaterial design during development to fulfil sustainable healthcare budgets.

4. Preclinical models: The critical need for recapitulating human metastasis

Preclinical trials hold immense significance in biomaterial testing for it to be successfully translated into clinical settings. Consequently, preclinical trials are meticulously curated to mimic human tumor environments to evaluate biomaterial's performance in various metastatic niches. Previously, preclinical trials were conducted on subcutaneous tumor tissue lines that lacked specificity to any dynamic metastatic niches, decreasing the plausibility of positive outcomes in clinical trials. However, to

improve the testing process, preclinical models, a major determining factor, are being selected with more careful consideration.

4.1. Advanced murine models

To ensure efficacy in clinical trials, successful outcomes in preclinical testing are extremely critical. Therefore, to evaluate adaptive biomaterial performance, preclinical models are required to exhibit similar conditions to human cancer environments, especially metastatic TME. Selecting a suitable preclinical model not only increases the likelihood of therapeutic efficacy in human testing but also guarantees the efficiency of nanosystems employed for specific cancer cell lines. Subcutaneous tumor xenograft models were utilized earlier, for preclinical trials that did not provide a similar TME to human metastatic niches, resulting in poor clinical outcomes. Consequently, researchers redirected towards more suitable animal models, including murine models for TME like human metastatic cancers.

Organ-specific tumor models helped develop preclinical modeling and metastatic cancer research tremendously by inserting tumor in anatomical locations where it originates in the human body initially. For instance, breast cancer cells are injected into the murine mammary gland instead of simply being injected under the skin. Orthotopic implantation enables the tumor to grow in its familiar environment, surrounded by native tissues, vasculature and connected to the local signaling system. This allows the tumor to rapidly metastasize from the primary site to organs like the lungs, liver, or bone, making multistage metastases research possible in its natural course. Researchers employ a strategy known as intracardiac injection to study tumor metastasis. This procedure involves injecting luciferase-tagged cancer cells, like the MDA-MB-231 breast cancer line, into the heart's ventricle to monitor its circulation throughout the body. The circulation of tagged cancer cells is monitored non-invasively using high-sensitivity bioluminescence imaging, locating tumors sized 1000 times smaller than a cell. However, certain drawbacks were observed in the research method. Older cancer cell cultures may modify genetically, deviating from the original human cancer cell traits. Moreover, due to the use of immunocompromised murine models, research related to immune modulation in a tumor metastatic environment could not be conducted.

To study patient tumors more closely, researchers have developed patient-derived xenograft (PDX) models, which are tumor fragments procured from patients' primary tumors and inserted into immunosuppressed murine models like NOD/SCID or NSG strains [40]. Increasing acceptance of PDXs comes from their ability to preserve patient cancer histopathology, supporting tissues, cancer fibroblasts, ECM and various cancer-related cell types in the microenvironment. Consequently, the tumor behaves closely to the primary tumor in the patient, making preclinical trials reliable and assuring 90% accuracy in clinical tests regarding biomaterial evaluation in human cancers. However, PDX utilization poses several challenges hindering its wide use, including the long culturing duration of about three to six months for a stable PDX model, restraining iteration studies. PDX depositories can also be costly since the murine models need to be kept alive, posing financial stress. Crucially, PDX models do not allow immunomodulatory studies on metastatic cancer, a prime focus in

adaptive nanomedicine research, since the murine models are immunosuppressed to begin with. To include immunomodulatory therapy studies, researchers produced "humanized" PDX models, which basically are murine models with human tumor implantation along with human immune cells. Albeit the ingenuity of the research approach, humanized PDX models increase financial burden, research complexity and uncertainty, requiring troubleshooting and reiteration.

Cancer study models have improved drastically with the enhancement of murine models, providing a more realistic and reliable model for researchers to examine metastatic cancers. Researchers can study and assess metastatic tumors through vigorous experimentation on natural TME, allowing them to evaluate biomaterial performance in metastatic niches. It provides a great research model to assess the capabilities and limitations of numerous biomaterial systems and expedite their implementation in clinical trials.

4.2. Engineered micro physiological systems (metastasis-on-a-chip): Precision micro physiology for nanotherapeutic screening

For innovative theranostic agents, there is a need for advanced research methods and equipment. Animal models have proven to be extremely valuable for research on various disease models. Certain limitations, including financial infeasibility and unreliability, prevent them from being a suitable metastatic tumor research model. Referring to this issue, researchers developed a versatile tool, organs-on-a-chip, that is a replica of human organs comprising human cells in microfluidic channels mimicking physiological conditions and circulation in the human body, which is no larger than a chip. An optimized version of organ-on-chip is metastatic-on-chip, which allows researchers to study tumor metastatic behavior in its natural environment.

Aleman et al. constructed a metastatic-on-chip device to mimic the tumor metastatic environment in normal human physiological conditions [41]. The meticulously designed device is composed of microfluidic channels surrounded by ECM containing collagen I and matrigel for a similar stromal milieu. After extracting the patient's cancer cells, researchers implanted them in the central section of the chip, comprising primary cancer-related fibroblasts and cancer cells for a personalized experimental approach. To replicate the human vasculature and circulation system, a porous polycarbonate membrane lined with human umbilical vein endothelial cells (HUVECs) was utilized for constructing channel linings. Immune cells, macrophages, were also implanted in the chip from the patient's serum to create similar immunological conditions as in the human body to observe interactions between immune cells, tumor, and NP in a real-time setting.

Researchers can appropriately modify the physiological conditions in the chip to reproduce the human TME. Fluid circulation can be adjusted to 0.5–5 μL/min, for instance, imitating the fluid pressure in human capillaries, whereas oxygen concentration can also be simulated around 1–15% according to the TME conditions, depending upon whether it's hypoxic or normoxic. The adjustable physiological condition in the chip allows researchers to determine biomaterial behavior at the tumor site in natural settings, such as the circulation route, while the automated perfusion system enables examination of numerous NPs in the same physiological conditions.

Organs-on-a-chip provides a versatile platform to test out different NPs with efficiency and reliability.

Research methods for tumor metastasis have drastically improved with the advent of metastasis-on-a-chip, providing efficient and reliable results. Validating the instrument's capabilities, NP penetration exhibited a minimal difference of 15% in results for metastatic-on-a-chip and in clinical trials in one study. Research also provided a direct correlation between NP penetration and hyaluronidase concentration in the pancreatic cancer model. Metastatic-on-a-chip provides such detailed and specific observations regarding the TME that animal models are unable to produce, suggesting the powerful impact of microphysiological systems in preclinical testing as an efficient analytical tool.

4.3. 3D-bioprinted metastatic niches: A new frontier in precision modeling

Organ-specific experimental models have radically improved since the advent of 3D bioprinting, enabling scientists to construct highly organized, living tissue models by combining specific human cells, including supporting cells. The 3D bioprinted models are engineered with great precision, methodically layering specific human cells and supporting cells, distinguishing them from conventional cultures such as spheroids and organoids. Imitating the exact physiological and biochemical conditions as in the actual TME, 3D bioprinting streamlined the reconstruction of human organ models [42]. This novel organ design allows tumor behavioral studies in realistic settings and natural TME, while determining the influence of biomaterial systems on the metastatic lesions.

Dai et al., in a research developing 3D bioprinting, structured a living bone metastatic niche model, which is a common site for tumor metastasis. The model was essentially based on a bioink, a gel composed of living cells structured in layers to mimic the bone metastatic niche. The bioink consisted of two fundamental components: a polymer matrix consisting of gelatin methacryloyl (GelMA) and hyaluronic acid methacrylate (HAMA), as well as nano-hydroxyapatite particles. The polymer matrix was responsible for bestowing the 3D model with flexibility and porosity like bone structure, while the nano-hydroxyapatite particles were added to the structure sporadically to replicate the mineralized compartments of the bone sections. Three different types of human cells were utilized in the 3D model: Saos-2 osteoblasts for bone formation, THP-1-derived macrophages to replicate the presence of immune cells at the tumor site and inflammation, and MDA-MB-231 breast cancer cells to represent cancer spread.

Scientists bioprinted living bone models with perfusion reactors to capture the dynamic bone metastatic environment. Osteogenic fluid was circulated continuously throughout the models to keep the bone cells nourished and alive. Researchers simultaneously exerted minimal pressure on the model of about 5% at a 1 Hz rate to recreate the mechanical stress conditions experienced by bone tissues. Following the experimental flow, reasonable bone development was observed with adequate osteogenic cell differentiation and paracrine signaling that is disrupted in metastatic conditions.

Biomaterial interaction and circulation in bone TME was clearly observed by researchers in the 3D bioprinted living bone model, proving itself as an excellent nanomedicine experimental setup. Results revealed 85 μm NP penetration in the tumor, much higher compared to 25 μm penetration observed in static models. The stark difference in penetration values highlights the importance of the application of mechanical pressure for drug distribution. Research also revealed that the use of calcium phosphate NPs rigorously destroyed tumor cells, similar to the results in an animal model depicting tumor repression with over 92% accuracy.

4.4. Redefining efficacy: From tumor volume to functional biometrics

Novel and adequate parameters are required to evaluate rapidly advancing biomaterials for a sustained evolution of metastatic theranostic tools. Since conventional assessment tools, such as animal models, are incapable of providing a reliable estimation of biomaterial systems' capabilities, researchers should devise an all-inclusive and definite evaluation framework to theorize a detailed profile of NPs comprising concrete information on their behavior and influence in various tumor sites and elsewhere in the body. Recording the NP evaluation reports through rigorous experimentation would help researchers determine agent efficacy.

Deducing cancer treatment efficacy can be made possible through circulating tumor DNA (ctDNA) tracking, a prominent biomarker employed in cancer treatment surveillance [43]. Researchers can simply determine the treatment effect with minimal invasion by inspecting variant allele fractions (ΔVAF/week) circulation in the body. Since ctDNA concentration fluctuates depending on the tumor progress, it allows timely estimation of treatment impact; researchers can appropriately optimize the therapeutic method and/or agent if deemed necessary. Furthermore, metastatic stem cell frequency in the blood circulation also informs about the metastatic route and tumor relapses. Limiting dilution assays, involving implantation of serially diluted tumor cells in immunodeficient mice models for metastatic stem cell quantification, allow understanding of therapeutic influence; decreased concentrations of metastatic stem cells imply a positive effect of therapy and long-term defense.

Immune cell interaction and spatial interaction provide valuable insight into the disease state, metastatic tumor, unlike mere immune cell count. Multiplex immunohistochemistry (IHC) and multispectral immunofluorescence are among the advanced imaging modalities, allowing non-invasive observation of multiple immune cells types, including regulatory T cells, $CD8^+$ T cells, and macrophages [44]. Through immune cell surveillance, researchers can categorize tumors according to the immune cell in their milieu, spanning from immune-excluded tumors, inflamed tumors, and immune-desert tumors) which assists in the specific personalized nanotherapy employment. Patient-specific animal models, such as CatWalk are designed to observe the patient's tumor behavior after biomaterial administration. Catwalk, for instance, was designed as a bone metastases research model. It detected subtleties in paw strength, stride length and pattern to make direct correlations with pain intensity and mobility problems. A collection of thorough data enables judgment on individually designed nanotherapies. In summary, treatment surveillance during ongoing treatment

allows the determination of therapeutic efficacy and the need to course-correct and aids the acceptance of novel therapies.

Importantly, it is the clinical success of first-generation nanomedicines that clearly shows that the main therapeutic benefit of nanomedicines is through better drug pharmacokinetics, improved stability, and lowered systemic toxicity, rather than getting high tumor accumulation uniformly. So, the points of limitation that we addressed in this review are more about the uneven delivery in different metastatic tumor environments rather than the lack of overall clinical effectiveness [45].

5. Clinical translation challenges: From bench to bedside

Widespread acceptance of novel biomaterial systems in medical settings confronts numerous challenges, including regulatory issues, inadequate clinical trial framework, and financial and manufacturing constraints- even if it possesses tremendous theranostic capabilities. Overcoming setbacks is as important as the production and optimization of advancing biomaterials.

5.1. Manufacturing scalability and cost of goods (COGs)

Intricate multi-stimulus responsive biomaterials prove their capabilities with positive preclinical outcomes, but their large-scale manufacturing faces complications. Biomaterials' multifunctional design, allowing them to detect and respond to various TME cues, hinders their sustainable and cost-efficient production at a large scale. Advanced biomaterial design entails complex procedures, including surface-receptor conjugation, encapsulating functional NP core, and formulating dual-responsive nanostructures that subsequently make the production workflow arduous to design.

Including NP synthesis and purification, advanced biomaterial production consists of 15 to 20 essential steps, whereas every step undergoes yield losses, summing to 30% accumulative loss on batch yield relative to >85% yield in basic nanosystems such as PEGylated liposomes. Drastic loss of overall yield negatively effects cost of goods (COGs) as nanosystem production requires costly substrates, including lab-graded materials as well as sophisticated purification techniques like fast protein liquid chromatography (FPLC) and ultracentrifugation.

Considering the cost per gram, pricing more than $12,000 as compared to affordable conventional chemotherapeutics, like paclitaxel, estimated at around $350 per gram, large-scale production of stimuli-responsive NPs creates a major financial strain. Moreover, conventional batch-based production techniques further increase the production cost of advanced biomaterials since metastatic cancer patients demand multiple therapeutic sessions.

Researchers devised an improved manufacturing practice, continuous-flow microfluidic manufacturing, to cut down NP production costs. Schmidt et al. assembled a modular microfluidic reactor for stimuli-reactive NP manufacturing. The reactor design is mainly composed of a T-junction mixer, which uniformly combines the substrates, whereas sophisticated serpentine channels ensure adequate reaction time for every step. Every reactor unit is individually temperature-controlled, so multiple stages like amine binding at 20 °C and NP assembly at 37 °C proceed uninterruptedly. Carefully structured modular reactors proposed an effective NP

production method that tremendously increased production yield to 100 g of NPs produced per day, relative to 0.5–1 g of NPs formulated in the laboratory. Besides manufacturing efficiency, it also produced uniformly sized particles while maintaining low polydispersity indices (PDI) of 0.08 compared to batch-based production PDI of 0.25. This can further optimize the production and purification process. The filtration setup can also be attached directly to the reactor to prevent further processing.

Microfluidic manufacturing, in summary, offers an effective route for NP production and also proposes a definitive manufacturing process for sustainable NP production. The manufacturing method also complies with GMP, possibility of scalability, and modular product processing that is essential for extensive production and utilization of biomaterial in cancer therapy, serving as a major milestone in cancer therapeutic evolution.

5.2. Regulatory frameworks: A path to approval

Product regulation institutes worldwide struggle to propose adequate parameters for processing and approval of rapidly advancing biomaterials, such as theranostic and autonomous agents, due to design complexity. Due to multidisciplinary involvement in the proposition and production of smart biomaterials, regulatory bodies find it perplexing to define set standards and parameters to process product approval, which consequently demoralizes biotech companies and investors from entering the industry.

Food and Drug Administration (FDA) in the United States consider such products as “combination products” since their functionality overlaps in various domains while the evaluation process is conducted by several FDA departments including Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER). Although the review process undergoes several FDA branches, it lacks a definite framework, preventing a consistent, closed-loop response. Another layer of burden is added to the challenging evaluation process when the NPs incorporate imaging or AI-driven abilities, since it raises concerns regarding real-time controllability, long-term safety, and software reliability.

Similarly, Europe doesn’t have a clear evaluation and approval framework. Although the European Medicines Agency (EMA) has introduced Advanced Therapy Medicinal Products (ATMP) for cell therapies and genes but does not include adaptive materials containing synthetic or non-biological compounds. Moreover, the National Products Administration (NMPA) in China has developed an evaluation framework for drug-device combination products, but lacks regulatory guidelines for nanosystems with smart responsive drug delivery systems or self-regulating platforms.

The inadequate regulatory guidelines have become a major barrier to the translation of adaptive biomaterials to widespread clinical use. Referring to this issue, we propose a risk-based Adaptive Biomaterial Classification System (ABCS) regulatory framework that assesses biomaterials on their novelty, intricacy, and reactivity, dividing them into three distinct classes as described in **Table 3**.

Class I includes basic systems that are single-stimulus responsive and have a well-defined trigger, such as pH-responsive liposomes or thermosensitive gels. Such systems incorporate well-understood and approved drugs and materials, allowing them

to undergo rapid regulatory processing mechanisms as the 505(b)(2) pathway in the U.S. The partial approval of drugs and materials would reduce the processing time by approximately 3–4 years.

Class II includes relatively advanced biomaterial systems with NPs reacting to multiple stimuli or have imaging and theranostic abilities, such as PET tracers or NPs with enzyme-cleavable linkers. Considering the complexity, evaluation would require a detailed regulatory strategy since it would need to be assessed through various regulatory domains and extensive safety testing procedures, which could approximately take 5–6 years.

Class III includes the most advanced and innovative nanosystems with automated control systems, AI-driven responses, and real-time sensing abilities such as MRI-triggered photothermal systems or autonomous "NanoCyborgs". Due to the unprecedented technology, it would require entirely new regulatory frameworks, plausibly the De Novo classification process, or qualify for Breakthrough Therapy or Priority Review designations. Consequently, due to extensive assessment including safety testing, software validation, and user safety, processing and approval would understandably take a longer time, possibly between 7–8 years.

Executing ABCS would not only assess the safety of novel biomaterials and determine a definite regulatory framework but also expedite the approval process for adaptive nanosystems. Subsequently, it would also enable professionals to accurately inspect the advanced biomaterials without decelerating the assessment process. Without careful consideration of the complexity and functionality of the novel biomaterials, this framework provides a well-suited and practical approach to embrace the advancing innovation in nanoscience.

Table 3. Proposed Adaptive Biomaterial Classification System (ABCS).

Class	responsiveness	Examples	Proposed regulatory pathway	Estimated timeline to approval
I	Single stimulus (well-understood)	pH-sensitive liposomes, Thermosensitive gels	505(b)(2) (leveraging data from approved components)	3–4 years
II	Multiple stimuli, Open-loop theranostics	pH/enzyme dual-responsive NPs, PET-labeled NPs	Combination Product (requiring coordinated review)	5–6 years
III	Closed-loop systems, Autonomous systems	MRI-guided photothermal NPs, AI-controlled systems	De Novo / Breakthrough Therapy Designation	7–8 years

5.3. Clinical trial design for metastatic disease

For reliable biomaterial assessment, researcher need to redesign clinical testing to determine their efficacy in cancer therapy, focusing especially on metastatic cancer [46]. Conventional measures, such as overall survival (OS), require years to confirm treatment efficacy and other treatments that are undergone may influence the recovery. This renders the evaluation process less efficient and time-consuming. To expedite the evaluation process and improve its reliability, future researchers should assess other molecular indicators, including biomarkers revealing if the cancer treatment is effective, mechanism-specific surrogate markers to assess the efficacy of the treatment employed, and patient health status to determine treatment efficiency. The METAdapt trial (NCT05678945) is an ideal example of an enhanced clinical trial framework.

Two experimental study groups were established; one group with HER2-negative breast cancer that dominantly metastasized to the bone, while the other group contained hormone receptor-positive breast cancer. Researchers determined the independent variable by dividing the two experimental groups to record the treatment influence on the disease model. Drug delivery carrier encapsulated nab-paclitaxel and denosumab, which was released on MMP-9 exposure, was carefully designed to counter the bone metastatic environment. The experiment had two distinguishing study groups: one group with hormone receptor-positive breast cancer and the other with HER2-negative breast cancer that mainly metastasized to the bone. Standard care and necessary care were practiced on study groups to ensure test reliability.

Researchers utilized enhanced assessment methods for observing a decrease in ctDNA concentration in the blood circulation after weeks of treatment application [47]. ctDNA is a useful biomarker that provides a detailed tumor profile, including tumor genetic makeup, tumor size, and cancer response to nanotherapy. Individually-focused patient treatment response included skeletal-related events (SREs), including bone fractures indirectly related to cancer, pain intensity that was determined using Brief Pain Inventory (BPI), and bone density quantification using dual-energy X-ray absorptiometry (DEXA) scans.

Biomarkers assuring uninterrupted treatment were also tracked to avoid procedural defectiveness. Mechanistic biomarkers, for example, urinary N-terminal telopeptide (NTX) and serum tartrate-resistant acid phosphatase 5b (TRAP5b), are tracked to monitor osteoclastic activity. Biomarker surveillance assures the NP accumulated in the bone metastatic niche. Utilizing various biomarkers and improving testing methods allows for monitoring adaptive and multi-functional biomaterials resembling a life-like disease model.

5.4. Economic viability and market access

For adaptive biomaterials to be widely utilized in hospital settings, they need to be economically feasible, in addition to being clinically approved. Considering the extensive developmental process (including designing with precision, preclinical and clinical testing, running safety tests, and large-scale production), manufacturing smart nanosystems may cost over $350 million. The high manufacturing cost consequently sharply increases the treatment cost to about $15,000 or more. And encourage the embracement of the innovative treatment, patients need to be assured about the treatment's success and potential of improving their comfort and lives, as well as cutting treatment costs.

In essence, treatment viability can be corroborated through certain factors, to convince patients, including no requirement of subsidiary treatments, including chemotherapeutic administration such as opioids, cancer-related bone fractures within three months, and pain alleviation caused by metastasis (pain reduction of ≥30% on BPI scale). Such definitive factors convince healthcare insurance companies of the importance of pain relief and survival rate, especially when cancer has progressed to a later stage requiring maintenance of quality of life and pain alleviation is prioritized.

Furthermore, strategies proposing novel biomaterial technologies to the market also need to be considered and redesigned. Researchers should partner with companies

(health technology assessment (HTA)) before biomaterials systems development to define medical technology designs and reimbursement plans. Product cost and treatment cost should be determined by professionals. Product budgeting may be bundled -based or value-based, which is subject to the effect of treatment on the patient. To accelerate advanced biomaterial systems approval, defining pricing frameworks and market outreach stands as a critical step.

6. Future perspectives: The next generation of smart biomaterials

Artificial Intelligence (AI), 3D bioprinting, personalized therapy, and material science are major contributors to the advancing field of biomaterial systems [48]. Biomaterial systems are enhanced further with the steady expansion of the field, and novel treatment modalities incorporating biomaterials for metastatic cancer therapeutics emerge. Biomaterial systems, covering all the metastatic cancer-related issues, redefine the treatment approach and allow treatment surveillance in real-time.

6.1. AI-driven material design and autonomous discovery

Human judgment and trial-and-error experiments are the basis of conventional biomaterial-based treatment, which proves inefficient and unreliable. However, AI incorporation in biomaterial system design could improve its performance and efficiency while contributing to its design development. The NanoNet platform is a suitable example of an AI-based biomaterial system designed by Gupta et al., the biomaterial utilized graph neural networks (GNNs) as a form of AI. GNNs aid in NP visualization by providing their molecular structure, including atoms and molecular bonding in their respective spatial location. The diagram illustrating NP's molecular structure included all the details that were overlooked in conventional diagrams.

To procure a reliable structural model, NanoNet was fed with 12,000 experimentally tested NPs designs. NanoNet expertly provides a specific NP structure by inverse design feature. Developers can put in required biological and physicochemical properties, including pH values for stability and disintegration, specific organ targeting, and reduced liver toxicity, while the model would adeptly scrutinize the requirements to present the suitable nanoparticle structure. The AI model has an impressively high accuracy with a reported 94% accuracy in estimating pH reactiveness and 0.91 area under the curve (AUC) for toxicity analysis. Commendably, NanoNet was used to formulate an NP to supply an anti-tumor drug through the blood-brain barrier for treating brain metastasis. It provided a suitable NP structure within 18 h, which was later tested in vivo. Impressively, 12.3% per gram of the injected dose accumulated at the tumor site in the brain targeting MDA-MB-231BR brain metastases. The aforementioned example corroborates the potential of AI to reduce inaccuracy and time consumed in research methods for biomaterial formulations and their clinical studies.

6.2. Patient-specific biomaterials: Toward the "metastasis avatar"

Designing novel biomaterials is constantly evolving since the advent of AI, while individually tailored biomaterials are formulated through patient-specific avatars for targeted therapy [49]. To design patient-specific biomaterials, detailed biological data is procured through omics technology, such as genetic and cellular behavior in TME. A revolutionary discovery is the "Metastatic Avatar" which is basically a replica of a patient's tumor constructed with the help of 3D bioprinting and microfluidic technology and using patient molecular data with tissue sample. The metastatic avatar enables researchers to experiment with various treatments on the tumor to formulate a patient-specific therapy model.

The experimental design begins with extracting a tumor sample from the patient and the cell mass is disintegrated. The individual cells are then analyzed in detail employing omics technology, single-cell RNA sequencing and ECM analysis to decipher TME. With the procured information, researchers meticulously translate the information into a specific bioink comprising the patient's cells and supporting cells from the ECM in proportions similar to those found in the patient's tumor. Utilizing 3D bioprinting, a living sample of the patient's tumor is structured, which is later fixed in a microfluidic device to replicate the dynamic biological conditions in the TME, including nutrient circulation, fluidic pressure, and signaling molecule movement. The replicated living tumor models allow researchers to conveniently test various biomaterials on the tumor to narrow down the suitable match without harming the patient.

Metastatic avatar is an ingenious diagnostic tool in the field of precision medicine. Notably, in a N-of-1 clinical trial, biomaterials exhibited 87% therapeutic efficacy in real patients who were approved by metastatic avatar, implying that these models can drastically increase the therapeutic index in metastatic cancer cases. Employing avatars to test out various biomaterials before picking a suitable choice increases the reliability and therapeutic efficacy of personalized therapy in cancer patients.

6.3. Autonomous therapeutic systems: The rise of the "Nanocyborg"

A novel development, "Nanocyborgs", is a prominent translation of the development in adaptive biomaterials. Nanocyborgs are autonomous feedback-controlled nanosystems that are capable of detecting nuances in the biological milieu while responding accordingly in real time [50]. These smart devices are paired with sensors to confer them with biosensing abilities once administered to a patient without the need for external and extensive aid from machines or professionals.

Graphene oxide-based biosensor is a prototype of a nanocyborg introduced to a metastatic lesion. The structure was designed to specifically detect proliferated inflammatory proteins, which usually increase due to cancer metastasis or elevated stress caused by ongoing treatment, such as IL-6 and TNF-α. Once the proliferated numbers of the inflammatory molecules are sensed by the nanocyborg, it sends an electrical signal to the redox-reactive drug nanocarrier, stimulating drug release by changing the nanoparticle's shape. The inflammatory drug, such as dexamethasone, is released to reduce inflammation in the metastatic TME.

The prototype has already been tested in an early Phase I clinical trial for a certain brain cancer, glioblastoma, where it exhibited a successful reduction in brain inflammation in TME in all five test subjects. Its ability to control and alleviate pain as well as inflammation in patients with bone metastases would make the use of palliative drugs like corticosteroids unnecessary. Moreover, additional research may improve the capabilities and design of the nanocyborg, bestowing it with advanced simultaneous sensing abilities to detect hypoxia, acidosis, and immune cell concentration in TME.

6.4. A translational roadmap for 2030: From bench to global impact

Defining a strategic and detailed plan is essential for introducing smart biomaterials in medical practice. Imperative aspects in the framework include product standardization and manufacturing guidelines, regulatory development, and an efficient market incorporation plan. The following section clarifies the tri-phasic implementation plan to aid integration of smart biomaterial systems in cancer therapies. The three phases expound on the practicality of nanosystem usage in cancer therapy and approval from global regulatory bodies within 10 years.

Phase I (2024–2026) marks the foundational stage, stressing upon incorporating materials and systems while also easing the standardization process. To curate an established regulatory framework, global organizations such as ASTM and ISO need to collaborate to set ground rules for smart biomaterials and define what is acceptable as a stimulus-responsive system. Regulations may include acceptable ranges for the nanoparticle to respond to a certain stimulus (for instance, pH activation range between 6.5 ± 0.2 and enzyme specificity and set concentration for reactivity, like matrix metalloproteinase-2 (MMP-2) concentrations over 10 nanomolar). Moreover, researchers should also construct adjustable "plug-and-play" biomaterials that can conveniently be modified to therapeutic needs. Established tunable biomaterials would allow early acceptance of fundamental materials like liposomes and PLGA NPs, and researchers could easily modify the design by adding necessary groups for enhanced functionality, such as sensing ability and evade the need to undergo the entire regulatory process again. Furthermore, developers should conduct global clinical trial networks like METAdept-II, focusing on biomaterial inclusion in therapies and matching patents with the right therapeutic modality accurately. The trials would run across the globe, incorporating advance thernostic methods and agents, namely ctDNA for tumor tracking, ECM density analysis for tissue morphology examination, and understanding the interaction of stromal biomarkers in TME.

Phase II (2027–2028) focuses on GMP scaling and clinical validation at a real-world scale. Phase II focuses on the employment of advanced manufacturing practices such as continuous flow systems and microfluidic systems to produce biomaterials following the Good Manufacturing Practice (GMP) standards. GMP approval is especially necessary for Class I and II materials, listed as moderately risky in the Adaptive Biomaterial Classification System (ABCS). To keep manufacturing costs to a minimum, treatment costs would be aimed to be kept as low as $500 to make treatment affordable to the masses. Simultaneously, researchers should introduce a group of AI-based NPs in global clinical trials, including studies as large as 3000

patients. Integrating real-time pharmacokinetic (PK) modeling and individuals' computer models would enable researchers to develop personalized medicine for cancer patients while maintaining valuable data regarding safety and efficacy to ease the regulatory process. Finally, approval for widespread use of nanotherapies, compliance of clinical trials with insurance and reimbursement companies is necessary, so developers should work with health technology assessment (HTA) agencies like NICE in the UK, ICER in the USA and IQWiG in Germany to increase framework approval plausibility.

Phase III (2029–2030) aims to transition from clinical trials to regulatory approval and real-world deployment. The goal is to obtain official approval from prominent health authorities, including the FDA and EMA, to classify adaptive biomaterials as Class I and II clinical tools. The innovative devices would target metastatic cancers with conspicuous physical barriers, including breast cancer metastasizing to bone as well as liver cancers otherwise resistant to chemotherapy. Following the approval of adaptive biomaterials, treatment dissemination would be the next aim, which would be put in effect through collaborations between health institutes and insurance companies to set practical and affordable treatment costs according to the therapeutic precision. Moreover, this phase focuses on endorsing the new health regulations supporting faster approvals, such as FDA's Breakthrough Devices Program or EMA Adaptive Pathways, it also encourages the embracement of improved classification frameworks like ABCS for ease in assessment procedures.

To recapitulate, the framework proposes a practical approach to include adaptive biomaterials in the healthcare sector. Combining ingenious structural design, AI technology and innovation manufacturing practices that are aligned with global health standards provides an infallible system for controlling metastatic cancer cases by 2030. **Figure 4** shows the regulatory roadmap for smart biomaterials from material and design standardization to product approval.

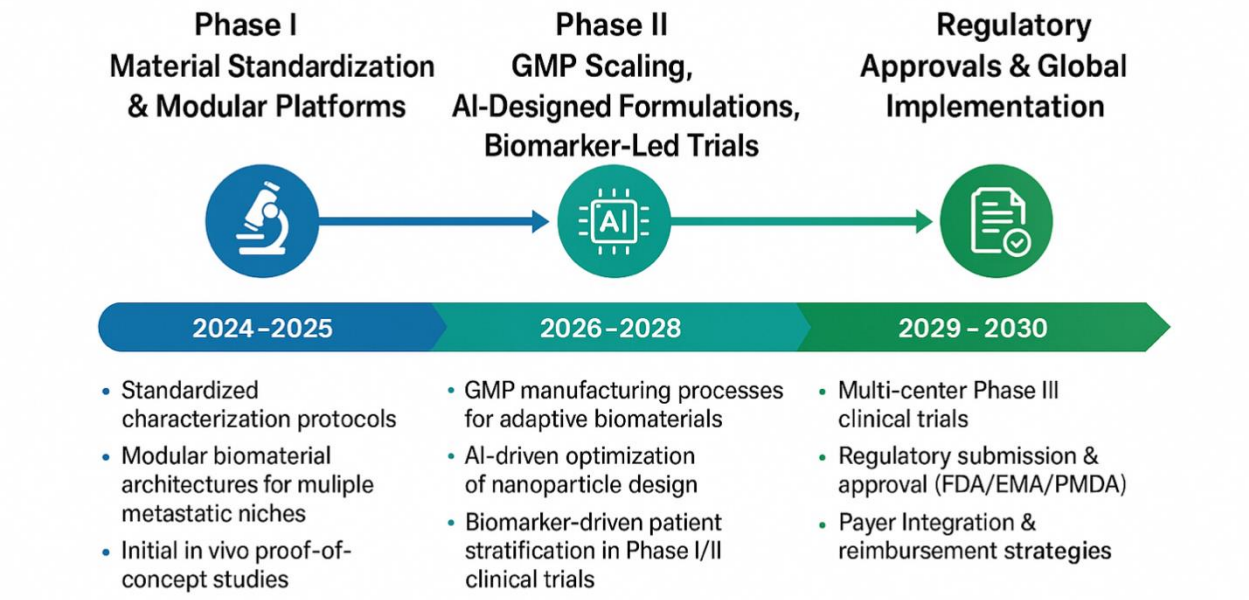


Figure 4. Proposed translational roadmap for adaptive biomaterials in metastatic cancer therapy, outlining key milestones from material standardization to global clinical implementation by 2030.

7. Conclusion

Clinically approved nanomedicines have already demonstrated meaningful therapeutic benefits, particularly by improving drug safety profiles and pharmacokinetics. Cautionary measures against prevalent metastatic cancers demand a deep-seated understanding of the dynamics and intricacies of metastatic TME. Modern therapeutic approaches polish with surfacing novel cancer-related discoveries. The review emphasizes the emerging potential of adaptive biomaterials, which are sensitive to the slightest subtleties in metastatic environmental cues while adeptly responding to such subtleties by changing their biochemical properties to evade the barriers imposed by the tumor defense system. The ingenuity of such smart biomaterial systems allows them to successfully execute their theranostic duties in the TME. With heightened specificity and tumor targeting precision, multi-stimuli responsive biomaterials have exhibited positive pre-clinical outcomes, whereas logic-gated nanoparticles showed drastically higher accumulation (8 times higher) at the tumor site relative to basic nanoparticles. Moreover, smart biomaterials can diminish their size to penetrate physical barriers imposed by tumor defense mechanisms, while closed-loop versions enable real-time imaging for researchers to comprehend the TME.

However, the proposed biomaterial systems encounter translational and clinical acceptance inhibitions. Due to the unexpected and extremely high manufacturing costs of over 35-fold, large-scale biomaterial production faces impediments such as economic infeasibility. Besides the useful multifunctionality, the intricate biomaterial structure, integrating biological and technological instruments, highlights the translation of the next generation of adaptive biomaterials that will always be a challenge, since regulating, manufacturing, and proving their benefits over the current nanomedicine platforms are major points of concern. Additionally, clinical trials have, in some cases, struggled to demonstrate consistent superiority of advanced nano systems over existing therapies, particularly in heterogeneous metastatic settings. The extensive approval challenges suggest the collaboration of global regulatory bodies to introduce a definitive classification and approval framework, such as ABCS, to expedite the approval process. Whereas researchers are required to improve experimental practices to test the adaptive systems targeting metastatic cancer models to find breakthroughs that help cancer patients, such as relief from bone-related complications and preventative measures to inhibit cancer proliferation.

To recapitulate, the advent of potent technologies, AI-based systems, clinical trials utilizing biomarkers, and integrated manufacturing systems has a strong potential to evolve metastatic cancer treatment methodologies and turn a malignant disease into a treatable disease condition. Autonomous therapeutic systems, patient-dependent avatars, and rigorous clinical trial sessions worldwide are reforming the treatment methodologies surrounding metastatic cancer.

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