

Formulation Innovations Targeting ACTB Pathways in Breast Cancer: From Cytoskeletal Dysregulation to Precision Drug Delivery

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Abstract: Breast cancer remains the most prevalent malignancy among women worldwide, contributing significantly to cancer-related morbidity and mortality. The actin cytoskeleton protein ACTB (β -actin) has emerged as a pivotal player in breast cancer progression, orchestrating cytoskeletal remodeling that fuels tumor invasion, metastasis, and resistance to conventional therapies through its regulation of critical pathways such as NF- κ B and Wnt/ β -catenin.

This review aims to synthesize recent advances in formulation strategies designed to selectively target ACTB-mediated signaling in breast cancer. Key focus areas include the mechanistic role of ACTB within cytoskeletal and metastatic cascades, and the translation of molecular insights into innovative drug delivery approaches. Highlighted are nanoparticle-based formulations—such as liposome-encapsulated ACTB-siRNA, targeted polymeric nanoparticles, gold nanoconjugates, dendrimers, and exosome-mimicking carriers—that demonstrate enhanced specificity, efficacy, and tumor penetration in preclinical models. The review further discusses ongoing clinical studies and the hurdles of translating ACTB-targeted formulations into effective therapies, including challenges of tumor heterogeneity, bioavailability, and regulatory milestones.

Looking forward, the integration of AI-driven formulation design, biomarker-guided personalization, and combination therapeutic strategies are underscored as essential for realizing next-generation, ACTB-targeted precision nanomedicines in breast cancer management.

Keywords: ACTB, β -actin, breast cancer, metastasis, drug delivery systems, nanoparticle formulations, targeted therapy, nanomedicine.

Introduction:

Breast cancer remains the most prevalent malignancy among women globally, constituting a major burden on public health systems and representing the leading cause of cancer-related mortality for women in both developed and developing regions.¹ Recent projections estimate that over 316,000 women will be diagnosed with invasive breast cancer in the United States in 2025 alone, with global cases predicted to surpass 6 million annually by 2050 a steep rise predominantly burdening Asian and African populations, reflecting wide disparities in access to early detection, treatment, and supportive care.² The five-year survival rates for breast cancer have improved with advances in therapeutic regimens and diagnostics; however, subsets such as triple-negative breast cancer (TNBC) continue to face high recurrence rates, early metastasis, and limited options for targeted interventions. Approximately 40% of patients with early-stage TNBC experience disease recurrence, with survival dropping dramatically in the metastatic setting.³

The persistent clinical challenge of breast cancer lies not only in late detection and subtype heterogeneity but also in biological mechanisms that enable tumor cells to evade existing therapies. Among the cellular machineries hijacked by malignant cells, ACTB (β -actin) has garnered considerable attention for its role in cytoskeletal dynamics.⁴ Traditionally considered a ubiquitous "housekeeping" protein, β -actin underpins cell migration, polarity, and division through its dynamic assembly within the actin cytoskeleton. In breast tumors, particularly in aggressive phenotypes such as TNBC and HER2-positive subtypes, ACTB is frequently overexpressed, enhancing cellular motility and invasive behavior—vital contributors to the establishment of metastatic lesions.⁵ Transcriptomic and proteomic profiling of breast cancer specimens has revealed that high abundance or activity of ACTB and its associated

actin-binding proteins (ABPs) correlates with increased risk of metastasis and poor patient survival. For example, imbalances among β -actin and other cytoskeletal isoforms (e.g., γ -actin) shift the migratory capacity of taxane-resistant TNBC cell populations and drive chemoresistance.⁶

Beyond direct influences on cell movement, ACTB is now appreciated as a critical regulator of several oncogenic signaling cascades, most notably the NF- κ B and Wnt/ β -catenin pathways.⁷ These interconnected routes govern not only cytoskeletal remodeling but also tumor cell proliferation, inflammatory microenvironment modulation, immune evasion, and the induction of epithelial–mesenchymal transition (EMT)—processes intimately linked to tumor progression and therapy resistance.⁸ Growing evidence from pan-cancer analyses suggests that ACTB is not just a bystander in cellular homeostasis but an active contributor to pro-tumorigenic signaling, with its overexpression predicting both poor prognosis and higher degrees of immune infiltration, further complicating therapeutic responses.⁹

The rationale for targeting ACTB-mediated pathways in breast cancer thus stems from its dual role as a central orchestrator of invasion/metastasis and as an immune microenvironment modulator. Functional knockout or pharmacological suppression of ACTB disrupts actin remodeling, reduces migratory potential, and attenuates downstream metastatic signaling—results that have been repeatedly observed across preclinical breast cancer models.¹⁰ Simultaneously, elevated ACTB expression profiles may serve as valuable biomarkers for patient stratification, risk assessment, and prediction of therapeutic efficacy, especially in high-risk and treatment-refractory populations. Such insights lay the groundwork for precision oncology strategies and open the door for targeting cytoskeletal components alongside canonical oncogenic drivers.¹¹

Despite these mechanistic advances, clinical translation of ACTB-targeted therapies has been stymied by significant challenges. Traditional small-molecule inhibitors and cytotoxic regimens often lack specificity for tumor-associated actin dynamics, leading to unacceptable toxicities in normal cells and rapid onset of drug resistance.¹² The necessity to move beyond such broad-spectrum agents has fueled interest in formulation innovations that offer programmable, tumor-selective, and multi-modal delivery of ACTB-targeted payloads. In this context, nanomedicine has emerged as a transformative arena, enabling not just solubility enhancement and controlled release but also tumor microenvironment-responsive delivery, immune engagement, and the potential to bypass multidrug resistance mechanisms.¹³

The present review aims to critically synthesize the progress and promise of advanced drug delivery strategies designed to disrupt ACTB-driven signaling in breast cancer. It will document the evolution from conventional cytotoxics toward precision-engineered nanoparticles, including liposomes, polymeric micelles, gold nanostructures, dendrimer complexes, and exosome-mimicking carriers.¹⁴ Special attention will be paid to formulation platforms that have demonstrated the capacity to encapsulate and deliver ACTB-targeted small molecules, siRNAs, or peptides with minimal off-target effects and heightened tumor specificity. The clinical landscape will be surveyed, highlighting emerging results from *in vivo* models, proof-of-concept studies in patient-derived xenografts (PDX), and ongoing or recently completed clinical trials.¹⁵

Notably, this review restricts its scope to breast cancer, leveraging comparative data from other cancers only to inform the translational journey or to contextualize mechanistic similarities and differences. The ultimate emphasis is on the intersection of cytoskeletal biology and biomedical engineering—the nexus where the next generation of anti-metastatic, ACTB-modulating strategies will likely arise.¹⁶

The convergence of molecular oncology, nanotechnology, and translational pharmacology is reframing the approach to targeting ACTB in breast cancer. As subpopulation stratification and patient-specific therapy become clinical imperatives, the development and optimization of novel formulations that precisely disrupt ACTB-mediated pathways hold considerable potential for reducing recurrence, overcoming resistance, and extending survival in individuals most at risk.¹⁷

ACTB Pathways in Breast Cancer: Molecular Biology, Dysregulation, and Key Signaling Cascades

Molecular Biology of ACTB: Structure, Expression Regulation, and Cytoskeletal Functions

Beta-actin (ACTB) is a highly conserved cytoskeletal protein encoded by the ACTB gene, expressed ubiquitously in eukaryotic cells as a fundamental component of the microfilament network that underpins cell shape, motility, and intracellular transport. Structurally, ACTB monomers (G-actin) polymerize into filamentous actin (F-actin), which dynamically remodels in response to cellular signals and mechanical cues.¹⁸ This polymerization is tightly regulated by actin-binding proteins (ABPs) modulating nucleation, elongation, severing, and capping activities in processes such as lamellipodia and invadopodia formation essential for cell migration. ACTB regulates membrane protrusions

and focal adhesions crucial to migratory behavior, establishing its role beyond structural support to integrating mechanical and signaling systems.¹⁹ At a transcriptional level, ACTB expression is modulated via feedback mechanisms involving the serum response factor (SRF) pathway and coactivator MAL, linking actin dynamics with gene regulation. Monomeric β -actin pools influence expression of cytoskeletal regulators, with disruption impacting cell cycle, migration, and motility patterns.²⁰

Dysregulation of ACTB in Breast Cancer: Overexpression Patterns and Prognostic Implications

In breast cancer, ACTB is frequently overexpressed, with higher levels particularly noted in aggressive subtypes such as triple-negative breast cancer (TNBC) and HER2-positive tumors. Elevated ACTB expression supports enhanced cytoskeletal remodeling, promoting tumor cell invasiveness and metastatic potential.²¹ Studies demonstrate that ACTB overexpression correlates with increased migration capabilities, aggressive tumor phenotypes, and poorer overall prognosis in breast cancer patients. Analysis of transcriptomic data reveals subtype-specific dysregulation where TNBC shows pronounced ACTB upregulation, likely contributing to its characteristic high metastatic propensity and chemoresistance.²² These expression patterns have prompted investigations into ACTB as a prognostic biomarker, as its abundance relates to tumor stage, metastatic burden, and survival outcomes across breast cancer cohorts, with implications for stratifying high-risk patients to more aggressive or targeted therapies. Additionally, altered ratios of β -actin relative to other actin isoforms influence cytoskeleton organization, cellular polarity, and signaling, further modulating tumor cell behavior and emphasizing the importance of isoform-specific targeting.²³

Key ACTB-Related Pathways in Breast Cancer

1. Cytoskeletal Remodeling and Metastasis

ACTB's role in forming and regulating filamentous actin structures directly supports cellular processes critical to cancer metastasis, particularly the formation of invadopodia and lamellipodia that facilitate extracellular matrix degradation and invasion.²⁴ The dynamic polymerization and depolymerization cycles promote protrusive activity at the leading edge of migrating cells, enhancing directional motility and transmigration through tissue barriers. Proteins like cofilin and TM9SF4 modulate actin filament turnover, influencing cancer cell adhesion and spreading, with their dysregulation linked to elevated metastatic capacity in breast tumors.²⁵ The actin cytoskeletal remodeling also affects cell-cell junctions and epithelial-to-mesenchymal transition (EMT), processes by which epithelial cancer cells acquire mesenchymal traits essential for invasion and dissemination.²⁶

2. NF- κ B Signaling Pathway

The NF- κ B pathway is a central regulator of inflammation, cell survival, and proliferation in breast cancer. ACTB interfaces with this pathway by influencing signaling intermediates involved in cytoskeletal rearrangements required for cell migration and invasion.²⁷ Activation of NF- κ B in breast cancer cells leads to transcriptional upregulation of genes that promote EMT, angiogenesis, and resistance to apoptosis, contributing to invasive progression and therapy resistance. NF- κ B activation correlates with chemoresistance, particularly to endocrine therapies in hormone receptor-positive breast cancers and other standard treatments.²⁸ Additionally, NF- κ B modulates the tumor immune microenvironment by regulating pro-inflammatory cytokine production and immune cell recruitment, underscoring its role in tumor-immune interactions.²⁹

3. Wnt/ β -catenin Signaling Pathway

The Wnt/ β -catenin pathway critically contributes to breast cancer stemness, proliferation, and metastasis, with evidence particularly strong in triple-negative breast cancer where it regulates tumor-initiating cell populations.³⁰ ACTB is implicated in this pathway mainly through its role in cell adhesion complexes, where cytoskeletal integrity influences β -catenin localization and activity. Upon Wnt ligand binding, stabilized β -catenin translocates to the nucleus to activate transcriptional programs that sustain cancer stem cell features, resistance mechanisms, and metastatic competence. Dysregulation of this pathway enhances tumor cell motility and chemoresistance, making it a critical target for intervention in refractory breast cancers.³¹

4. Immune Modulation and Checkpoint Interactions

Emerging studies reveal that ACTB-related remodeling can influence the tumor immune milieu, impacting the expression of immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4, which govern immune surveillance and escape.³² The crosstalk between cytoskeletal dynamics and immune signaling affects tumor-associated macrophage activation, T-cell exhaustion, and secretion of immunomodulatory cytokines, shaping the balance between tumor progression and immune control.³³ ACTB-driven structural changes can

modulate checkpoint ligand presentation, influencing the efficacy of immune checkpoint inhibitors and fostering localized immune suppression that facilitates metastasis. Thus, ACTB pathways serve not only structural and migratory functions but also significant immunological roles within the breast cancer microenvironment.³⁴

Current Therapeutic Landscape Targeting ACTB in Breast Cancer: Conventional Approaches, Emerging Molecular Targets, and Challenges

Conventional Approaches: Limitations of Chemotherapeutics

Historically, breast cancer treatment has relied on cytotoxic chemotherapeutics such as taxanes (paclitaxel, docetaxel), anthracyclines, and platinum-based agents. These drugs often exert their anti-tumor effects partly by disrupting microtubule dynamics and other cytoskeletal components, indirectly impacting actin filaments including those formed by ACTB (β -actin).³⁵ While effective in reducing tumor burden, conventional chemotherapy suffers from poor specificity for malignant cells, and off-target toxicities remain a significant clinical obstacle. One major limitation is the lack of selective targeting of ACTB or its polymerization processes, which are fundamental not only for tumor cells but also for normal cell migration, wound healing, and immune cell function. This nonspecificity results in adverse effects such as peripheral neuropathy, myelosuppression, and impaired tissue repair. Moreover, therapeutic doses needed to disrupt actin dynamics may also excessively damage normal healthy tissue, limiting dose escalation.³⁶

Another intrinsic challenge of conventional cytotoxics is their ineffectiveness against metastatic and cancer stem cell (CSC) populations, which are often highly motile and reliant on actin cytoskeletal remodeling for dissemination.³⁷ These populations frequently escape chemotherapy-induced cell death via mechanisms involving epithelial-to-mesenchymal transition (EMT), promoted in part by ACTB-mediated structural alterations and associated signaling. Chemoresistant phenotypes are enriched in breast cancer subtypes such as triple-negative breast cancer (TNBC), where relapse rates and aggressive progression remain high despite systemic therapy. These clinical realities highlight the urgent need for therapies that can selectively inhibit ACTB functions underlying metastasis while sparing normal cells.³⁸

Emerging Molecular Targets: Small Molecules, siRNAs, and Antibodies Disrupting ACTB Polymerization

Recognizing the limitations of conventional agents, recent research has focused on developing targeted molecular therapeutics aiming directly at ACTB or its regulatory network. Among these, several classes show promise in preclinical breast cancer models:

1. **Small-Molecule Inhibitors of ACTB Polymerization**

Research into small molecules that can bind ACTB or associated actin-binding proteins (ABPs) to inhibit filament formation and stabilize cytoskeletal architecture has accelerated. These compounds interfere with monomer polymerization, filament elongation, or severing.³⁹ Though relatively few small molecules specifically targeting ACTB have advanced to clinical testing, preclinical studies have demonstrated the ability of certain molecules to inhibit breast cancer cell migration, invasion, and viability by disrupting actin dynamics. For example, compounds targeting cofilin-actin interactions or inhibiting the Arp2/3 complex reduce invadopodia formation and metastasis in TNBC xenografts. Such agents may offer more selective inhibition of metastatic phenotypes with reduced systemic toxicity compared to classic chemotherapies.⁴⁰

2. **RNA Interference (siRNA) and Gene Editing Approaches**

RNA interference technology utilizing siRNAs designed against ACTB mRNA has emerged as a powerful tool to downregulate β -actin expression in breast cancer cells. Delivery of ACTB-siRNAs via lipid nanoparticles or polymeric carriers reduces cytoskeletal remodeling and invasive capabilities in vitro and in vivo models.⁴¹ These approaches allow precision targeting of gene expression rather than direct protein inhibition, potentially enabling greater tumor specificity. Moreover, CRISPR/Cas9-based gene editing is under investigation for knocking out ACTB or modulating ABPs, though clinical translation remains in early stages.⁴²

3. **Monoclonal Antibodies and Peptides**

While ACTB resides primarily intracellularly, antibody-based strategies targeting aberrant extracellular or membrane-associated actin structures or actin-like protein conformations have been explored. Monoclonal antibodies designed to disrupt actin filament nucleation or binding domains indirectly dampen actin-driven migratory signaling. These biologics may be engineered for targeted internalization and delivery via nanocarriers to improve tumor penetration and efficacy, and to minimize off-target effects.⁴³

Preclinical Evidence in Breast Models

Various *in vitro* and *in vivo* breast cancer models validate these emerging candidates' ability to reduce tumor cell motility, invasion, EMT characteristics, and metastatic burden. Notably, xenograft and patient-derived tumor models demonstrate that ACTB-targeted siRNAs encapsulated in liposomal or gold nanocarriers achieve significant knockdown of ACTB expression, leading to decreased tumor growth and fewer metastatic nodules in the lungs and liver. Combination regimens pairing ACTB inhibitors with chemotherapeutics or immune checkpoint blockers show synergistic effects in preclinical TNBC models, offering hope for integrated therapeutic strategies.⁴⁴

Challenges in Therapeutic Development Targeting ACTB

Despite encouraging preclinical evidence, several challenges must be overcome for successful clinical translation:

1. **Bioavailability and Delivery**
ACTB-targeted therapeutics, especially siRNAs and biologics, face significant hurdles in achieving sufficient tumor bioavailability due to rapid degradation by nucleases, renal clearance, and limited tumor penetration. Effective delivery systems are critical to overcome these barriers.⁴⁵ Nanoparticle formulations, including liposomes, dendrimers, and polymeric micelles, improve stability and enable tumor-selective accumulation via the enhanced permeability and retention (EPR) effect. Stimuli-responsive carriers that release payloads in the acidic and redox-rich tumor microenvironment further enhance specificity. However, controlling biodistribution, avoiding immunogenicity, and ensuring endosomal escape remain major formulation challenges.⁴⁶
2. **Tumor Heterogeneity and Resistance**
Heterogeneous expression of ACTB and its regulators across breast cancer subtypes complicates uniform therapeutic responses. TNBCs, HER2+, and ER+ tumors differ in ACTB-related pathway activation and reliance on cytoskeletal remodeling for metastasis, necessitating subtype-specific or combinatorial approaches.⁴⁷ Moreover, cancer cells may activate alternative cytoskeletal or signaling pathways to bypass ACTB inhibition, leading to acquired resistance. EMT-mediated plasticity driven by ACTB also fosters resistance to therapies by maintaining stemness and mesenchymal phenotypes, requiring multi-targeted regimens.⁴⁸
3. **Off-Target Effects and Toxicity**
Given ACTB's essential role in normal cellular physiology, therapies directly perturbing actin dynamics risk unintended consequences on non-malignant cells, including immune cells, endothelial cells, and fibroblasts. Minimizing systemic toxicity demands highly selective targeting, achieved through sophisticated delivery platforms or tumor-specific ligands. Modulating ACTB expression rather than complete inhibition may balance efficacy and safety.⁴⁹
4. **Clinical Evaluation and Biomarkers**
Translating ACTB-targeted agents into clinical practice necessitates robust biomarkers for patient selection, early response monitoring, and resistance detection. Integration of genomics, proteomics, and liquid biopsy analyses targeting ACTB and related pathways can stratify patients likely to benefit. Designing clinical trials that incorporate these biomarkers is key for accelerating regulatory approval and adoption.⁵⁰

Formulation Innovations Targeting ACTB Pathways in Breast Cancer:

Targeting ACTB (β -actin) pathways in breast cancer demands highly specialized drug delivery systems due to the protein's ubiquitous presence in normal cells and its fundamental role in cytoskeletal functions.⁵¹ Innovative formulations aim to selectively disrupt ACTB-mediated signaling in cancer cells while minimizing off-target effects and enhancing tumor penetration. These next-generation delivery platforms capitalize on the tumor microenvironment's unique physicochemical features and aim to enhance payload stability, specificity, and efficacy.⁵² This section explores key formulation modalities including nanoparticle-based systems, advanced nanomaterials, stimuli-responsive carriers, biomimetic vesicles, and current progress toward clinical translation.⁵³

Nanoparticle-Based Systems: Liposomes and PLGA Nanoparticles for ACTB-siRNA Delivery

Liposomes and polymeric nanoparticles such as poly(lactic-co-glycolic acid) (PLGA) have emerged as versatile carriers for delivering nucleic acids like ACTB-targeted siRNAs in breast cancer therapy. These nanoparticles can encapsulate siRNA molecules, protecting them from enzymatic degradation in circulation and facilitating cellular uptake via endocytosis.⁵⁴

Liposomes are phospholipid bilayer vesicles capable of carrying hydrophilic siRNAs within their aqueous core. They can be functionalized with polyethylene glycol (PEG) to enhance circulation half-life and decorated with tumor-targeting ligands such as folate or antibodies that recognize breast cancer-specific markers.⁵⁵ This selective binding improves tumor uptake and intracellular delivery of ACTB-siRNA, effectively silencing β -actin expression as demonstrated in TNBC xenograft models, leading to reduced invasion and metastatic nodules.⁵⁶ Liposomal ACTB-siRNA therapies also leverage the enhanced permeability and retention (EPR) effect characteristic of tumors, allowing passive accumulation of nanoparticles in leaky vasculature regions. This feature, combined with active targeting, improves specificity and reduces systemic exposure.⁵⁷

PLGA nanoparticles offer an alternative biodegradable polymeric matrix for sustained and controlled siRNA release. Their physicochemical properties can be tailored (e.g., size, surface charge) to optimize tumor penetration and cellular internalization.⁵⁸ Dual encapsulation strategies delivering ACTB-siRNA alongside chemotherapeutics such as doxorubicin have shown synergistic efficacy in preclinical breast cancer models, suppressing tumor growth and invasion more effectively than monotherapies. Moreover, PLGA's FDA-approved clinical status supports translational potential.⁵⁹

However, challenges remain in overcoming endosomal entrapment and achieving robust cytosolic siRNA release, leading to development of pH-sensitive or proton sponge polymers incorporated within nanoparticles to promote endosomal escape and improve gene silencing efficiency.⁶⁰

Advanced Nanomaterials: Gold Nanoparticles and Dendrimers Conjugated with ACTB Inhibitors

Gold nanoparticles (AuNPs) and dendrimers represent cutting-edge nanomaterials demonstrating superior payload loading capacity, tunable surface chemistry, and multimodal functionality for ACTB-targeted therapeutics.⁶¹

AuNPs possess unique optical and physicochemical properties, allowing for stimulus-responsive drug release and imaging-guided delivery. Their surfaces can be functionalized via thiol-gold chemistry to conjugate ACTB polymerization inhibitors or siRNAs with high density.⁶² In breast cancer xenograft models, gold nanoconjugates delivering ACTB inhibitors exhibit enhanced tumor retention, improved bioavailability, and potent anti-metastatic efficacy by disrupting actin filament formation and invasion pathways. AuNPs also enable photothermal therapy adjuncts, wherein near-infrared irradiation triggers localized heat production to enhance cytoskeletal disruption synergistically.⁶³

Dendrimers are highly branched, monodisperse polymers with interior cavities for drug encapsulation and multivalent peripheral functional groups enabling precise targeting and stimulus responsiveness.⁶⁴ Dendrimer-based formulations carrying ACTB-siRNA or small molecules have demonstrated efficient cellular uptake and gene knockdown in breast cancer cells, exploiting receptor-mediated endocytosis or charge interactions. Their size and surface can be tailored to optimize penetration and reduce immunogenicity.⁶⁵

Furthermore, combination strategies employing dendrimers and gold nanomaterials enhance multifunctionality, allowing simultaneous delivery of ACTB inhibitors, imaging agents, and immune modulators, providing theranostic capabilities.⁶⁶

Stimuli-Responsive Formulations: pH- and Redox-Sensitive Micelles Targeting the Tumor Microenvironment

To increase selectivity and efficacy, stimuli-responsive drug delivery systems are engineered to exploit the acidic and redox-altered environment of breast tumors, especially important for targeting invasive ACTB-driven cells residing in hypoxic niches.⁶⁷

pH-sensitive micelles comprise amphiphilic block copolymers with acid-labile linkages that remain stable at physiological pH (~7.4) but undergo rapid disassembly in mildly acidic conditions (pH ~6.5–5.5), typical of tumor interstitial spaces and endosomes.⁶⁸ These carriers encapsulate ACTB-targeted siRNA or drugs, releasing their payload preferentially within the tumor microenvironment or intracellular compartments, thereby reducing systemic toxicity and enhancing intracellular bioavailability. For instance, pH-responsive micelles delivering ACTB-siRNA suppressed breast tumor growth and metastatic spread more effectively than pH-insensitive systems in murine models.⁶⁹

Redox-sensitive formulations incorporate disulfide bonds cleavable by elevated glutathione concentrations found in tumor cytosol. These systems maintain payload stability extracellularly but rapidly release cargo upon cellular entry, facilitating efficient ACTB pathway inhibition. Combining pH and redox responsiveness in dual stimuli-responsive micelles provides an added layer of control to overcome heterogeneous tumor conditions.⁷⁰

Further advancements include enzyme-triggered release and ligand-mediated targeting to further enhance selectivity toward ACTB-overexpressing breast cancer cells.

Biomimetic Approaches: Exosome-Mimicking Vesicles for Immune-Modulating ACTB Therapeutics

Biomimetic vesicles that replicate natural exosomes hold promise for delivering ACTB-targeted therapeutics with minimal immunogenicity and enhanced cellular communication capabilities. Exosomes, nanoscale extracellular vesicles secreted by cells, inherently possess surface proteins enabling targeted uptake by specific recipient cells, including immune and tumor cells.⁷¹

Engineered exosome-mimicking vesicles encapsulating ACTB-siRNA or inhibitors exploit these properties for precision delivery, modulating both tumor cell actin dynamics and the immune microenvironment.⁷² Preclinical studies in breast cancer models reveal these vesicles facilitate robust ACTB knockdown and simultaneously alter immune checkpoint expression, augmenting anti-tumor immune responses. Their natural origin enables evasion from reticuloendothelial clearance, enhancing circulation time.⁷³

Moreover, loading ACTB therapeutics into patient-derived exosomes allows personalized approaches with potentially reduced adverse reactions. Challenges persist in scalable manufacturing, cargo loading efficiency, and standardized characterization, but ongoing work is addressing these barriers.⁷⁴

Clinical Translation: Ongoing Trials and Efficacy in Patient-Derived Xenograft Models

Despite robust preclinical data supporting ACTB-targeted formulation innovations, clinical translation is nascent but accelerating. Phase I/II clinical trials are underway or in planning stages involving actin-targeted nanodrugs designed to suppress cytoskeletal remodeling in advanced breast cancers, especially triple-negative and metastatic cases.⁷⁵

Patient-derived xenograft (PDX) models have been instrumental in this translational bridge. Nanoparticle formulations delivering ACTB-siRNA or polymerization inhibitors show significant tumor growth inhibition and metastasis reduction in PDX mice that recapitulate human tumor heterogeneity and microenvironmental complexity better than cell-line-derived xenografts. These efforts guide dose-finding, biomarker identification, and safety evaluations critical for human studies.⁷⁶

Challenges, Limitations, and Future Directions in Targeting ACTB Pathways in Breast Cancer

Technical Hurdles: Stability In Vivo and Off-Target Effects

Therapeutically targeting ACTB (β -actin) pathways in breast cancer faces substantial technical barriers principally rooted in ACTB's ubiquitous expression and critical roles in normal cytoskeletal functions.⁷⁷ The intrinsic instability of many ACTB-targeted agents such as siRNAs and peptide inhibitors in physiological environments necessitates sophisticated delivery formulations to protect payloads from enzymatic degradation, renal clearance, and opsonization. Nanoparticle carriers, liposomes, and polymeric micelles have been developed to address these challenges, yet maintaining stability during circulation while enabling efficient payload release in tumor cells remains a complex balance.⁷⁸

A major limitation arises from the high physiological abundance of ACTB in normal tissues, including immune, endothelial, and stromal cells, raising concerns of off-target effects that could disrupt vital processes like cell motility, wound healing, and immune function. Non-specific inhibition of actin dynamics could lead to cytotoxicity manifested by tissue damage or impaired immunity.⁷⁹ This necessitates the design of highly tumor-selective delivery systems that minimize systemic exposure via active targeting (e.g., ligand-receptor mediated uptake), stimulus-responsive release (e.g., pH/redox triggers), or physiological barrier traversal strategies. Off-target toxicity assessment and mitigation remain a critical translational barrier, mandating rigorous preclinical evaluation.⁸⁰

Clinical Barriers: Biomarker Validation and Regulatory Considerations

Clinical translation of ACTB-targeted therapies requires robust and validated biomarkers for patient stratification, therapeutic monitoring, and predicting resistance. While ACTB overexpression and activity have been correlated with poor prognosis in breast cancer, standardized assays quantifying ACTB levels or functional pathway activity are lacking in clinical practice. Development and validation of companion diagnostics incorporating tumor biopsy profiling, circulating tumor DNA (ctDNA), and liquid biopsy technologies are essential to empower precision medicine approaches tailored to ACTB-dependent tumors.⁸¹

From a regulatory perspective, nanotherapeutics and RNAi-based drugs face complex approval pathways due to their multifaceted formulations, heterogeneous pharmacokinetics, and manufacturing complexities. Ensuring batch-to-batch consistency, large-scale GMP production, and long-term safety monitoring is resource-intensive and time-consuming.

Regulatory agencies require comprehensive toxicology and immunogenicity assessments, particularly given potential off-target effects on normal actin functions.⁸² Furthermore, integration of biomarkers into clinical trial design is critical to demonstrate patient benefit and support regulatory endorsements. Multidisciplinary collaboration between scientists, clinicians, and regulatory bodies is therefore vital to expedite clinical translation.⁸³

Future Opportunities: AI-Driven Design, Combination Therapies, and Personalized Medicine

Emerging technologies offer transformative opportunities to overcome current challenges and expedite the development of effective ACTB-targeted formulations.⁸⁴

1. AI-Driven Formulation Design

Artificial intelligence (AI) and machine learning (ML) platforms can rapidly optimize nanoparticle formulations by predicting physicochemical properties, stability, biodistribution, and target cell uptake based on large datasets.⁸⁵ AI algorithms facilitate rational design of ligand-receptor pairs for tumor targeting, stimuli-responsive release mechanisms, and payload combinations to maximize efficacy and minimize toxicity. These tools accelerate preclinical screening and reduce costly trial-and-error experimentation, enhancing translational success prospects.⁸⁶

2. Combination Therapies

Given tumor heterogeneity and compensatory signaling pathways, combining ACTB-targeted therapies with other modalities presents a promising direction. Synergistic combinations with immunotherapies such as immune checkpoint inhibitors may enhance antitumor immune responses by perturbing ACTB-dependent immune evasion mechanisms.⁸⁷ Concurrent inhibition of parallel signaling cascades (e.g., NF- κ B, Wnt/ β -catenin) or integration with conventional chemotherapies can mitigate resistance and improve durable control of metastatic disease. Designing rational combinations guided by tumor molecular profiling will be critical.⁸⁸

3. Personalized Approaches via Liquid Biopsies

Innovative liquid biopsy platforms assessing circulating tumor cells, RNA, or DNA enable real-time monitoring of ACTB expression and pathway activity across treatment courses.⁸⁹ Personalized medicine approaches leveraging these data can tailor ACTB-targeted therapy dosing and timing to individual tumor biology, improving therapeutic windows and limiting systemic toxicity. Multi-omics integration expands the potential to predict responders versus non-responders and identify emergent resistance early, informing adaptive clinical strategies.⁹⁰

Conclusion:

ACTB (β -actin), long regarded as a fundamental housekeeping protein, has now emerged as a central orchestrator of breast cancer progression, metastasis, and therapy resistance. Its critical involvement in cytoskeletal remodeling, cellular motility, and signaling pathways, notably NF- κ B and Wnt/ β -catenin cascades, underpins the aggressive phenotypes and poor prognosis observed in subtypes such as triple-negative and HER2-positive breast cancers. The dysregulated ACTB axis contributes not only to structural processes fundamental to tumor invasion but also to modulation of the tumor immune microenvironment, highlighting its multifaceted role as a promising biomarker and therapeutic target.

Traditional chemotherapeutics, while foundational, lack specificity for ACTB-mediated pathways and often cause collateral damage to normal tissues due to ubiquitous expression and indispensable physiological functions of β -actin. This has driven the urgent need for innovative formulation strategies that enable selective delivery of ACTB-targeted therapeutics with enhanced tumor specificity and minimized systemic toxicity. Nanoparticle-based systems, including liposomes and PLGA nanoparticles, have demonstrated effective encapsulation and delivery of ACTB-siRNA, exploiting the enhanced permeability and retention effect for tumor accumulation. Advanced nanomaterials such as gold nanoparticles and dendrimers extend these capabilities, offering multifunctional platforms for sophisticated drug conjugation, imaging, and stimulus-responsive release.

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