Review

Combining Sonodynamic Therapy with Nanocarriers: Enhancing Treatment Targeting and Efficacy

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Posted Date: 3 February 2026

doi: 10.20944/preprints202602.0054.v1

Keywords: sonodynamic therapy; nanocarriers; targeting; efficacy; ultrasound; immune

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Combining Sonodynamic Therapy with Nanocarriers: Enhancing Treatment Targeting and Efficacy

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Abstract

Sonodynamic therapy (SDT) is a non-invasive treatment modality that leverages the deep tissue penetration and spatiotemporal controllability of ultrasound to activate sonosensitizers and induce cytotoxic bioeffects, predominantly through reactive oxygen species (ROS)-mediated oxidative stress and cavitation-associated mechanical injury. Despite encouraging progress, early SDT development has been limited by poor aqueous solubility and nonspecific biodistribution of many sonosensitizers, inadequate intratumoral accumulation, and challenges in standardizing and monitoring ultrasound dosimetry. Nanocarrier technologies have substantially expanded the therapeutic design space of SDT by improving pharmacokinetics, reducing off-target exposure, preserving sensitizer activity (e.g., mitigating aggregation-related quenching), and enabling tumor- and organelle-directed delivery. This review summarizes the historical evolution of SDT and nanocarriers and synthesizes current mechanistic understanding, including cavitation-centered biophysics, multi-route ROS generation (sonochemistry, conditional sonoluminescence pathways, and mechano-electronic charge-redox processes), and downstream regulated cell death and immunogenic cell death. We further organize SDT-nanocarrier synergy into key modules: pharmacokinetic/spatial control, ultrasound-enhanced transport (sonoporation and barrier modulation), hypoxia relief and redox reprogramming to amplify ROS, engineered cavitation/energy transduction, and immune reprogramming enabling sono-immunotherapy. Finally, we discuss emerging application strategies-targeted delivery, tumor microenvironment modulation, and multimodal combination regimens-alongside translational progress and remaining barriers such as delivery heterogeneity, real-time exposure verification, long-term biosafety, manufacturability, and clinical trial design. Future advances are expected to prioritize simplified GMP-compatible platforms, delivery diagnostics for patient stratification, and closed-loop ultrasound control for consistent, safe, and precision SDT.

Keywords: sonodynamic therapy; nanocarriers; targeting; efficacy; ultrasound; immune

1. Historical Evolution of Sonodynamic Therapy

1.1. Early Research and Discoveries

Sonodynamic therapy (SDT) has emerged as a promising non-invasive therapeutic modality [1–3], leveraging the synergistic interaction between ultrasound and sonosensitizers to induce cytotoxic effects in tumor cells [4–6]. This approach has been particularly effective due to its ability to penetrate deeply into tissues, offering a significant advantage over photodynamic therapy (PDT), which is limited by the shallow penetration of light [7,8].

The earliest experimental evidence for sonodynamic effects was reported by Yumita and colleagues in 1989, showing that hematoporphyrin could sensitize cells to ultrasound-induced damage in the absence of light [9]. Subsequent work by Umemura et al. (1990) further elucidated the mechanism of this cytotoxicity, laying the foundation for what would become sonodynamic therapy

 doi:10.20944/preprints202602.0054.v1

[10]. The early research and discoveries in SDT have laid the groundwork for its application in various medical fields, including tumor therapy and antimicrobial therapy [4,11,12].

1.2. Progression and Challenges

During the early 1990s, the term "sonodynamic therapy" was gradually introduced to describe this ultrasound-activated, sensitizer-mediated therapeutic approach, explicitly drawing an analogy to photodynamic therapy while emphasizing its independence from optical energy sources. Initial mechanistic investigations suggested that acoustic cavitation played a central role in SDT-induced cytotoxicity [13]. The oscillation and collapse of cavitation bubbles generated localized extreme conditions, including transient high temperatures and pressures, which were believed to activate sonosensitizers and initiate biological damage [14,15]. Concurrently, early evidence indicated the involvement of ROS, such as singlet oxygen and free radicals, linking SDT mechanistically to oxidative stress pathways similar to those observed in PDT, albeit triggered through fundamentally different physical processes [16–19].

In parallel with mechanistic exploration, early SDT research focused on identifying suitable sonosensitizers. Porphyrin-based compounds, including hematoporphyrin derivatives and protoporphyrin IX, were among the agents evaluated due to their established use in PDT and favorable redox properties [20,21]. These studies demonstrated that certain sensitizers could be selectively activated by ultrasound to enhance cytotoxicity, providing proof-of-concept for sensitizer-dependent SDT [22,23]. Beyond porphyrins, early investigations also explored the synergistic effects of ultrasound with chemotherapeutic agents, suggesting the potential for combination strategies that could amplify therapeutic outcomes [5].

Despite these encouraging advances, early-generation SDT faced several critical limitations, including poor water solubility, non-specific biodistribution, and systemic toxicity of sonosensitizers, as well as a lack of precise control over ultrasound parameters. These challenges significantly constrained therapeutic efficacy and hindered clinical translation [24–26].

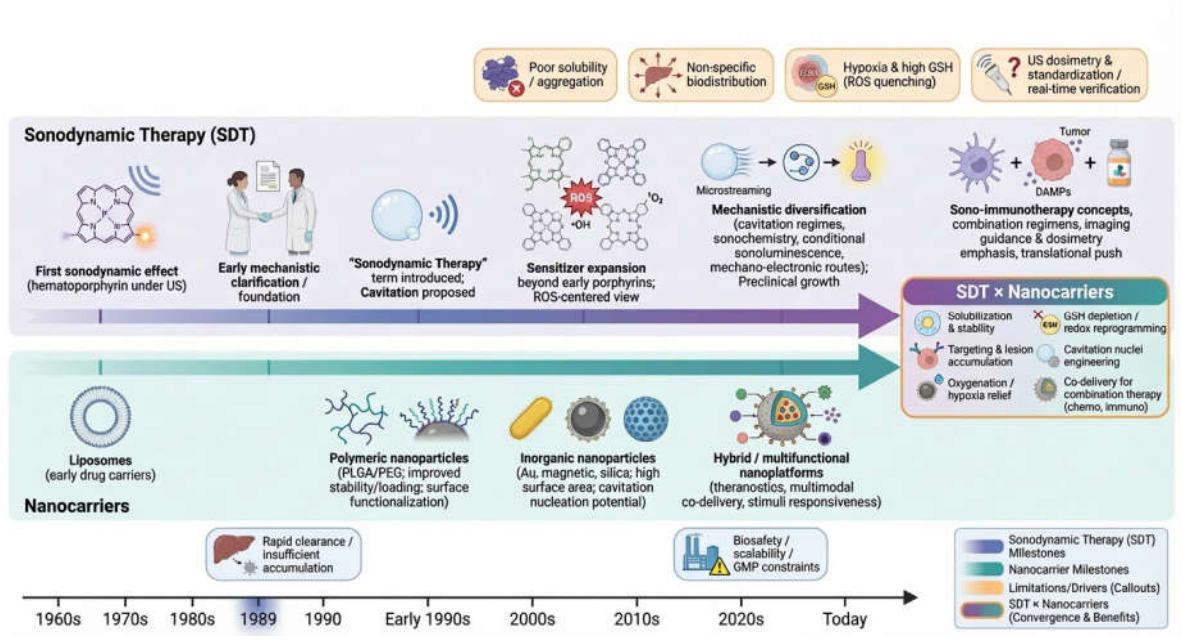

Figure 1. Historical Milestones of SDT and Nanocarriers: Why SDT x Nanocarriers? Created in BioRender.

2. Historical Evolution of Nanocarriers

Nanocarrier technology has undergone significant advancements over the past few decades, dramatically improving the delivery and efficacy of therapeutic agents, including sonosensitizers used in SDT [27,28]. These innovations have addressed several limitations associated with early

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sonosensitizers, such as poor solubility, limited tissue penetration, non-specific biodistribution, and systemic toxicity. By encapsulating or conjugating sonosensitizers with nanocarriers, researchers have enhanced their stability, controlled their release, and facilitated targeted delivery to tumor sites, which is critical for increasing the therapeutic efficacy of SDT [4,29]. The evolution of nanocarriers can be divided into four key phases: liposomes, polymeric nanoparticles, inorganic nanoparticles, and multifunctional nanoplatforms [30–33]. Each phase represents a leap in nanocarrier design, contributing to the refinement of SDT and expanding its therapeutic potential.

2.2.1. Liposomes and Early Nanocarriers

Liposomes, introduced in the 1960s [34], were among the first nanocarrier systems to be investigated for drug delivery and subsequently for SDT [35]. These spherical vesicles composed of phospholipid bilayers can encapsulate both hydrophilic and lipophilic substances, making them highly versatile carriers for sonosensitizers [35–38]. Early research into liposomes for SDT primarily focused on overcoming the solubility challenges of hydrophobic sonosensitizers, such as hematoporphyrin derivatives, and improving their bioavailability. For instance, hematoporphyrin monomethyl ether (HMME)-loaded liposomes were developed to facilitate targeted delivery and ultrasound-responsive release for improved SDT outcomes [39]. Encapsulation strategies have also been reported to improve tumor accumulation of hematoporphyrin while reducing side effects in vivo [40]. Moreover, fundamental studies on hematoporphyrin–liposome interactions demonstrated that liposomal lipid matrices can solubilize hematoporphyrin through partitioning behavior, providing a physicochemical basis for using liposomes to address solubility limitations of porphyrin sensitizers [41].

Liposomes offered several advantages, such as the ability to encapsulate drugs with varying solubility profiles, extend the circulation time of drugs, and provide a controlled release mechanism [42–45]. These properties were particularly useful in SDT, as they allowed for higher concentrations of sonosensitizers to be delivered to tumor tissues [39,46,47], while minimizing off-target effects [48]. However, despite these advantages, liposomes were not without limitations. They suffered from issues such as poor tumor targeting [49–51], rapid clearance by the mononuclear phagocytic system (MPS) [52–55], and limited tissue penetration [56,57], which hindered their widespread clinical application. Nevertheless, liposomes played a crucial role in the initial development of nanocarrier-based strategies for SDT, highlighting the importance of improving drug delivery systems for enhanced treatment efficacy.

2.2.2. Polymeric Nanoparticles: Enhancing Stability and Loading Capacity

As research into nanocarriers progressed, polymeric nanoparticles (PNPs) emerged as a promising alternative to liposomes [58]. These solid nanoparticles, typically composed of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) [59–61], offered several advantages, including higher drug loading capacities [62,63], better stability [64,65], and more flexible design options [64,66]. Polymeric nanoparticles could be easily modified in terms of size, surface charge, surface charge and drug loading capacity, allowing for more precise control over drug release profiles [63,67–69].

In the context of SDT, polymeric nanoparticles can encapsulate sonosensitizers with improved loading efficiency and formulation stability, and enable controlled (often stimuli/ultrasound-responsive) release, thereby helping maintain an effective local concentration of sonosensitizers in tumor tissue over time [12,70–72].

Moreover, the surface of polymeric nanoparticles can be functionalized with targeting ligands such as antibodies, aptamers, or small molecules that specifically bind to tumor cells, significantly improving the selectivity and specificity of SDT [12,72–74]. This modification reduced the non-specific accumulation of sonosensitizers in healthy tissues, thus minimizing side effects and increasing the therapeutic efficacy of SDT [72,75,76].

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However, polymeric nanoparticles face technical challenges in fabrication, including complex multi-step synthesis and difficulties in achieving controlled, uniform particle sizes due to the diversity of preparation techniques and the sensitivity of parameters such as solvent systems and polymerization conditions [77,78]. Despite their generally favorable biocompatibility, polymeric nanoparticles may interact with the immune system, leading to opsonization, immune clearance, or inflammatory responses depending on their physicochemical properties, thereby raising potential immunogenicity concerns that require careful evaluation [79–82]. Besides these challenges, polymeric nanoparticles have become a cornerstone in nanocarrier-based drug delivery systems for SDT.

2.2.3. Inorganic Nanoparticles: Overcoming Biological Barriers

The development of inorganic nanoparticles (INPs) represented a significant shift in nanocarrier technology [83,84]. Gold nanoparticles (AuNPs), magnetic nanoparticles (MNPs), and silica nanoparticles have attracted considerable attention due to their unique physical properties, such as high surface area, ease of functionalization, and the ability to enhance sonodynamic effects [85].

AuNPs exhibit strong localized plasmonic behavior, high biocompatibility and surface modification flexibility, while MNPs can be tailored in magnetic response and surface chemistry for targeted delivery, and silica-based nanoparticles provide large surface area and controllable pore architectures for loading and release [86–88]. These nanoparticles show promise in enhancing SDT efficacy through optimized ultrasound activation and improved deep-tumor targeting [89].

AuNPs exhibit localized surface plasmon resonance (LSPR), a collective oscillation of conduction electrons at specific resonant frequencies that gives rise to enhanced electromagnetic fields and distinctive optical and thermal responses [90,91]. In the presence of ultrasound, AuNPs have been shown to act as cavitation nuclei that reduce the cavitation threshold and enhance acoustic cavitation activity, leading to increased localized heat generation when exposed to focused ultrasound fields [92,93]. This synergistic effect enhances the activation of sonosensitizers, resulting in more efficient tumor cell destruction, as the ultrasound-triggered generation of reactive oxygen species (ROS) by sonosensitizers has been shown to increase cytotoxicity against cancer cells [89,94,95]. Furthermore, AuNPs can be easily functionalized with targeting moieties such as folate, human epidermal growth factor receptor 2 (HER2), or tumor-specific antibodies, improving the selectivity of SDT [72,96–98]. Other inorganic nanoparticles, such as magnetic nanoparticles, offer the additional advantage of magnetic targeting, where an external magnetic field can guide the nanoparticles to the tumor site, further improving the precision of SDT [99–101].

Despite their advantages, the use of inorganic nanoparticles in SDT is not without challenges [102]. For example, the cytotoxicity of certain materials, nanoparticle aggregation, and the difficulty in achieving precise control over drug release and targeting specificity remain significant barriers [103,104]. Nonetheless, the ability of inorganic nanoparticles to combine therapeutic and diagnostic functions, including imaging, hyperthermia, and drug delivery, makes them highly promising for enhancing SDT's therapeutic efficacy [89,94,105].

2.2.4. Multifunctional Nanoplatforms: Towards Precision Sonodynamic Therapy

The most recent and perhaps most exciting development in nanocarrier technology is the advent of multifunctional nanoplatforms [106]. These advanced nanocarriers combine multiple therapeutic and diagnostic capabilities into a single nanoparticle system, offering the potential to optimize SDT and other therapeutic modalities simultaneously [72,107–110]. Multifunctional nanoplatforms can integrate features such as chemotherapy, immunotherapy, radiotherapy, gene therapy, and thermal therapy, creating a multimodal treatment approach that improves overall treatment efficacy [111–116].

In SDT, multifunctional nanoplatforms allow for combination therapies, where sonosensitizers are delivered alongside other therapeutic agents [27]. This enables synergistic effects that can tackle tumor heterogeneity [111] and overcome resistance to single-modal therapies [117–119]. Additionally, the integration of diagnostic functionalities such as magnetic resonance imaging (MRI), positron

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emission tomography (PET), and fluorescence imaging into multifunctional nanoplatforms enables real-time monitoring of sonosensitizer delivery and activation, while stimuli-responsive features (e.g., pH, temperature, or ultrasound triggers) ensure controlled release and tumor microenvironment–specific activation of the therapeutic agents [120–122].

The integration of multiple functions into a single nanoplatform represents the cutting edge of nanomedicine, allowing for more precise targeting, controlled drug release, and enhanced therapeutic efficacy. However, the design and fabrication of multifunctional nanoplatforms remain complex and face challenges related to scalability, biocompatibility, and regulatory approval [123–125]. Nevertheless, these platforms are likely to play a critical role in the future of SDT and other cancer therapies.

3. Mechanisms of Sonodynamic Therapy and Nanocarrier Synergy

3.1. Mechanisms of Sonodynamic Therapy in Disease Treatment

Sonodynamic therapy is generally understood as a spatiotemporally controlled oxidative (and partly mechanical) insult produced when focused ultrasound (US) interacts with a sonosensitizer in biological media [6,23,126–130]. The therapeutic outcome is therefore not dictated by a single pathway, but by the coupling among (i) ultrasound physics, (ii) sensitizer photophysics/sonochemistry (or mechano-chemistry), and (iii) cellular stress-response programs and immunity. Reviews increasingly converge on four major contributors: acoustic cavitation, reactive oxygen species (ROS) generation, mild thermal effects, and (in some models) sonoluminescence [126–130]. Reviews increasingly converge on four major contributors: acoustic cavitation, ROS generation, mild thermal effects, and (in some models) sonoluminescence [6,12,28,94,112].

3.1.1. Ultrasound-Tissue Interactions: Cavitation-Centered Biophysics

In SDT-relevant regimes, typically “low-intensity” compared with ablative high intensity focused ultrasound (HIFU), US propagates through tissue as a mechanical wave, generating pressure oscillations that can (a) deform membranes and cytoskeleton [131–133], (b) induce microstreaming and shear forces in fluids [134,135], and (c) trigger cavitation when pre-existing gas nuclei or introduced gas bodies (e.g., microbubbles) undergo oscillation [136–138]. Cavitation is usually categorized as stable cavitation and inertial (transient) cavitation [136].

Stable cavitation refers to sustained oscillation of bubbles that produces microstreaming and localized shear, enhancing membrane permeability and mass transport, while inertial (transient) cavitation means violent collapse of bubbles that can produce shock waves, microjets, localized high temperature/pressure, and radical chemistry at the bubble interface [139–141]. Stable cavitation can induce microstreaming and shear forces, leading to enhanced permeability of biological membranes, while inertial cavitation generates microjets, shock waves, and high local temperature and pressure, which can drive radical chemistry at the bubble interface [142–144]. These effects can directly damage cellular membranes and organelles [72,139,145], and also create conditions that amplify sonochemical ROS formation and/or sensitizer activation [130,146,147].

3.1.2. ROS Generation: Multiple Co-Existing Routes

Most SDT frameworks place ROS as the central cytotoxic intermediate (e.g., singlet oxygen $^1O_2$, hydroxyl radicals •OH, superoxide O_2•−), but the origin of ROS under ultrasound can vary across sensitizer classes and acoustic conditions [6,89,94,120,148–150].

For cavitation-driven sonochemistry (water/oxygen activation), inertial cavitation can yield highly reactive species through extreme microenvironments at bubble collapse, including water sonolysis and oxygen activation near the bubble interface [147,151,152]. These radicals can diffuse short distances to attack lipids, proteins, and nucleic acids [153,154], and they may also initiate

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secondary oxidative cascades such aslipid peroxidation and mitochondrial ROS amplification [155,156].

For sonoluminescence-mediated excitation, there exists debated contribution. A long-standing hypothesis proposes that light emitted during cavitation (sonoluminescence, SL) can excite sensitizers in a photodynamic-therapy-like manner, leading to ROS generation [28,157–159]. Recent literature shows active debate: some analyses argue SL may be a major mechanistic focus in certain contexts, while other experimental work suggests the emitted light/ROS levels under typical regimens may be insufficient to explain therapeutic effects, implying sonoluminescence may be minor or conditional [160,161].

Taken together, these mechanistic uncertainties translate into actionable nanocarrier design rules: even if SL is not universally dominant, formulations that introduce or co-localize sensitizers with cavitation nuclei (e.g., micro-/nanobubbles, gas-stabilizing interfaces) can bias SDT toward more inertial-cavitation–like, ROS-producing events. In fact, microbubble cavitation under *therapeutic* ultrasound has been shown to generate detectable SL, and the SL intensity correlates with broadband cavitation emissions—supporting the idea that "more cavitation activity" can shift the mechanistic balance [160]. Because SL exhibits threshold-like behavior and depends on exposure parameters (e.g., duty cycle, temperature), its contribution is plausibly conditional rather than constant across regimens [161]. Consistent with this view, recent SDT reviews still present ROS generation as a multi-route outcome of cavitation/SL/pyrolysis-type processes, rather than a single pathway [89].

Beyond SL-mediated excitation, many inorganics or hybrid nanosonosensitizer systems support "mechano-electronic" ROS routes: ultrasound-driven mechanical deformation can generate internal electric fields and charge separation, enabling surface redox reactions that yield ROS without requiring optical excitation [130,162,163]. Finally, even when primary ROS output is modest, it can trigger secondary biological amplification, most notably mitochondrial ROS-induced ROS release (RIRR)—a positive-feedback process that escalates oxidative stress and broadens downstream damage [156].

3.1.3. Downstream Cell Death and Immunological Consequences

Once oxidative and mechanical stress surpasses cellular repair capacity, SDT can engage multiple regulated cell death programs [72,129]. Apoptosis is frequently observed, but resistance to apoptosis in aggressive tumors has motivated strategies that bias SDT toward ferroptosis (iron-dependent lipid peroxidation) or mixed death phenotypes to improve efficacy [163].

A particularly important modern view is that SDT can induce immunogenic cell death (ICD)—characterized by danger-associated molecular patterns (DAMPs) such as calreticulin exposure, ATP release, and HMGB1 release—thereby promoting dendritic cell maturation and T-cell priming [164–166]. This provides a mechanistic bridge from "local ROS killing" to systemic antitumor effects, but it also highlights why spatial control matters for safety and for immune programming [167–169].

3.1.4. Key Determinants of SDT Efficacy and Mechanistic Levers

Mechanistically, SDT outcome can be viewed as a function of three coupled "dials": acoustic parameters, sensitizer properties and oxygen/redox microenvironment [170]. Acoustic parameters include frequency, pressure amplitude, duty cycle, exposure time, focusing geometry (which set cavitation probability, microstreaming, and heating) [149,171,172]. Sensitizer properties include ROS quantum yield, subcellular localization, aggregation state, and stability [94,173–176]. Reviews on sonosensitizer development emphasize that sensitizer chemistry and microenvironment strongly influence ROS pathways [148,170]. Oxygen/redox microenvironment include hypoxia and high glutathione (GSH) in tumors can quench ROS and limit SDT; therefore, oxygen supply and redox modulation are recurring design targets [177–180].

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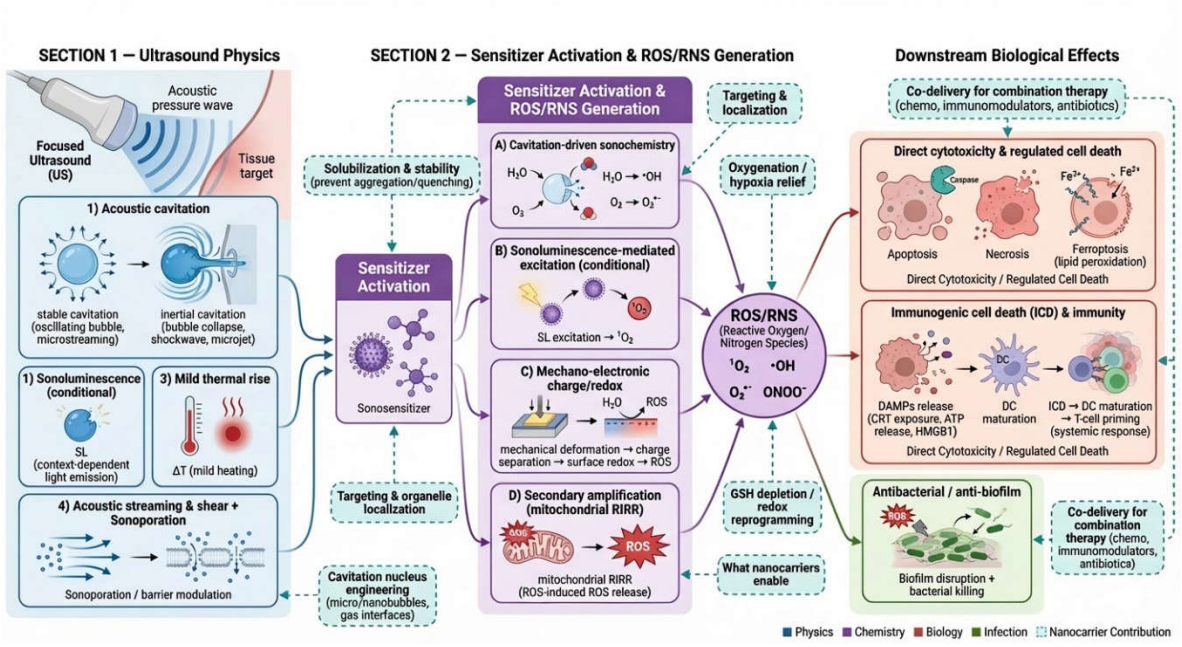

Figure 2. Mechanisms of Sonodynamic Therapy (US Physics → Chemical Activation → Biological Effects). Created in BioRender.

3.2. Mechanisms of Nanocarrier-Mediated Drug Delivery

Nanocarriers improve SDT not only by "delivering more sensitizer," but by reshaping where the sensitizer resides, how long it persists, and what microenvironmental constraints it experiences (oxygen, pH, enzymes, redox) [104,173,181–183]. Mechanistically, nanocarrier delivery is a multi-stage process with distinct bottlenecks [184–186].

3.2.1. Systemic Fate: Protein Corona, Clearance, and "Stealth"

Upon entering biological fluids, nanoparticles rapidly adsorb proteins to form a protein corona [187–189], which can alter colloidal stability [190,191], cellular recognition [192], targeting ligand availability [193,194], and cellular uptake pathways [195]. Reviews on corona biology emphasize that corona composition and dynamics strongly influence in vivo fate and pharmacokinetics [187,196,197]. Therefore, design implications for SDT nanocarriers include: (i) surface chemistry to control corona formation [198–200]; (ii) "stealth" layers (e.g., PEGylation or zwitterionic coatings) to reduce opsonization [183,201–203]; and (iii) biomimetic cloaks (cell membranes) to modulate biocompatibility, tumor enrichment, and immunological effects [48,204–206].

3.2.2. Tumor Accumulation: EPR, Transcytosis, and Heterogeneity

The classical explanation for tumor nanomedicine accumulation is the enhanced permeability and retention (EPR) effect, wherein leaky vasculature and impaired lymphatic drainage favor macromolecule retention [207,208]. However, modern perspectives stress that tumor delivery is heterogeneous and may involve additional mechanisms such as active trans-endothelial transport (transcytosis) and microenvironment-dependent vascular behavior [49,209–212]; a 2024 Nature-hosted review discusses delivery mechanisms and strategies beyond a simplistic EPR-only model [208]. For SDT, this heterogeneity is critical: insufficient accumulation lowers efficacy [94,149,170,183]. Besides, SDT efficacy is strongly dependent on local sonosensitizer availability and ROS generation, so insufficient intratumoral accumulation can markedly reduce therapeutic response. In such settings, the relative contribution of ultrasound-only bioeffects, thermal/mechanical effects such as cavitation and sonoporation may become more pronounced [127,145,213,214].

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3.2.3. Cellular Internalization and Subcellular Trafficking

After reaching the tumor interstitium, nanoparticles must cross cellular membranes via endocytosis or, less commonly, direct fusion or penetration depending on material type [215–218]. Intracellular trafficking often leads to endosomal or lysosomal compartments; for sensitizers, this localization can be beneficial, as lysosomal rupture can amplify stress, or limiting, like quenching or enzymatic degradation [216,218–220]. Thus, organelle-targeting motifs and endosomal escape strategies can reshape which death pathways dominate, like apoptosis, ferroptosis or ICD [163,164,220,221].

3.2.4. Release Mechanisms: Diffusion, Degradation, and Stimuli Responsiveness

Nanocarriers can be engineered for controlled drug release through both passive and triggerable mechanisms. In passive modes, payloads are liberated by diffusion/desorption (including surface-bound drug), by gradual matrix erosion/degradation of the carrier material, or—especially for lipid-based systems—via lipid exchange with surrounding membranes/lipoproteins that perturbs bilayer composition and promotes cargo leakage/transfer [222–224].

Endogenous, disease-associated cues then enable "smart" on-site release, leveraging hallmarks of the tumor microenvironment and intracellular trafficking routes such as acidic pH (tumor interstitium/lysosomes), elevated GSH and ROS, overexpressed enzymes (notably matrix metalloproteinases, MMPs), and hypoxia, typically via cleavable linkers or stimulus-labile materials [225,226]. Exogenous ultrasound—highly compatible with sonodynamic-therapy workflows—can further provide spatiotemporally controlled activation, where acoustic fields promote release by mechanical disruption of carrier shells, cavitation-mediated permeabilization/rupture, acoustic radiation forces that enhance carrier–tissue interactions, and phase transitions of perfluorocarbon (PFC) cores (acoustic droplet vaporization) that rapidly destabilize the nanocarrier and "burst" payloads on demand [35,227–229]. Recent reviews emphasize that ultrasound-responsive designs deliberately couple these physicochemical triggers to tune release thresholds and improve on-target activation while limiting off-target leakage [227,230].

Table 1. Comparison of Sonosensitizer Families and Key Properties Favorable for Nanodelivery.

Category (Representative Examples)	Key ROS Types and Mechanistic Features	Advantages / Limitations	Standard Delivery Methods	Representative References
Porphyrins / PpIX-precursors	*Mainly $^1O_2$ plus radicals depending on microenvironment*	Advantages: Clinically familiar; strong redox activity; benefits from encapsulation to improve PK Limitations: Hydrophobicity/aggregation; potential dark toxicity; oxygen dependence	Liposomes; polymeric NPs; albumin-based carriers	[348,349]
Chlorin derivatives (e.g., Ce6, Photochlor)	Predominantly $^1O_2$; can be boosted by	Advantages: Strong ROS yield; easy co-loading with O_2 modulators	Microbubbles/nanobubbles; lipid NPs; membrane camouflage	[205,300]

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	oxygenation modules	Limitations: Aggregation quenching; hypoxia sensitivity		
Cyanine / heptamethine dyes (e.g., IR780, iodinated cyanine)	Mixed with radical and $^1O_2$; often coupled to hypoxia relief or catalytic ROS loops	Advantages: NIR imaging/theranostics-ready; mitochondrial affinity Limitations: Photothermal/sonothermal crosstalk; instability; higher off-target risk without "stealth"	Hollow MnO_2 shells; mesoporous silica; antibody conjugates	[75,98,307]
AIEgens / AIE-active sonosensitizers	Often designed toward radical under hypoxia; aggregation-tolerant	Advantages: "Anti-ACQ" by design; good for high-loading nanoformulations Limitations: Chemistry varies; activation threshold needs tuning	Polymeric micelles; amphiphilic assemblies; targeted ligands	[74,237]
Inorganic semiconductors / sonocatalysts / piezoelectric	•OH / O2•− via mechano-electronic charge separation / catalytic surfaces	Advantages: High stability; oxygen-independent (partly); can lower cavitation threshold Limitations: Potential long-term biosafety; clearance; surface defects variability	Inorganic core–shell; metal-doped catalysts; membrane camouflage	[150,162,231]
MOF / COF framework-based	Frequently radical + catalytic cascades (Fenton-like, GSH-responsive)	Advantages: High payload capacity; modular catalytic nodes; can integrate imaging + TME triggers Limitations: Stability/ion release; reproducibility; biodegradation products	MOF/COF nanoparticles; bacteria/OMV modification; HA coating	[109,114,116,297]

3.3. Synergy Between Sonodynamic Therapy and Nanocarriers

The "SDT + nanocarrier" synergy can be mechanistically organized into five cooperating modules: pharmacokinetic control, ultrasound-enhanced transport, ROS amplification, cavitation/energy transduction engineering, and immune reprogramming.

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3.3.1. Pharmacokinetic and Spatial Control: Concentrating the Sensitizer Where Ultrasound Will Act

Nanocarriers extend circulation time and reduce premature clearance/metabolism of sensitizers, increasing the probability that sensitizer and focused ultrasound overlap in space and time [12,231–233]. This is a uniquely important safety lever in SDT: ultrasound exposure is localized, but off-target sensitizer distribution can still raise risks if broad-field ultrasound is used or if sensitizer persists in sensitive tissues [12,48,72,232]. Encapsulation also mitigates aggregation-induced quenching for hydrophobic sensitizers, preserving ROS competence [234–237].

3.3.2. Ultrasound-Enhanced Delivery: Sonoporation and Barrier Modulation

Ultrasound can transiently increase membrane and vascular permeability, often termed sonoporation, particularly when cavitation nuclei (microbubbles) are present [238–241]. This can improve extravasation, interstitial penetration, and intracellular uptake of nanocarriers [101,242–246], creating a positive feedback loop: more nanocarrier uptake → more sensitizer in cells → more SDT effect [101,247]. Foundational work on sonoporation mechanisms emphasizes transient pore formation and enhanced endocytosis driven by microbubble oscillation and associated stresses [136,246,248,249]. From a design standpoint, pairing SDT nanocarriers with (i) microbubbles, (ii) gas-generating components, or (iii) phase-change droplets can convert ultrasound from a "trigger" into a "delivery accelerator" would make sense [101,245,250–253].

3.3.3. ROS Amplification and Hypoxia Mitigation: Oxygen-Carrying and Oxygen-Generating Nanoplatforms

Because ROS production often requires molecular oxygen, tumor hypoxia is a frequent SDT bottleneck [89,178,254]. A major nanocarrier synergy strategy is oxygen supply: Perfluorocarbon (PFC)-based oxygen carriers can dissolve and transport oxygen, alleviating hypoxia and improving ROS yield in oxygen-dependent therapies [180,254–256].

Oxygen-sufficient or oxygen-loaded core-shell platforms have been demonstrated in chemo-sonodynamic settings, explicitly using oxygen-carrying cores to boost singlet oxygen generation and reduce hypoxia-associated resistance [118,182,257]. Complementary approaches include catalase- or MnO_2-like components that convert endogenous H_2O_2 into O_2, simultaneously lowering oxidative buffering and increasing available oxygen [258–261]. These "self-oxygenating" concepts are also attractive for strengthening ICD, since robust oxidative stress can enhance DAMP release [164,221,254,259].

3.3.4. Engineering Cavitation and Energy Transduction: Making Ultrasound "Work Harder" at the Tumor

Nanocarriers can be engineered to increase the probability of acoustic cavitation and to concentrate ultrasound energy deposition within tumors, thereby amplifying both direct mechanical injury (e.g., microjets/shock effects) and sonochemistry-driven ROS production [14,72]. Because cavitation is widely regarded as a key prerequisite underpinning SDT efficacy, "cavitation-first" nanodesigns offer a practical route to intensify local bioeffects without relying solely on higher external power [167,262].

Mechanistically, representative strategies include: (i) cavitation-nuclei incorporation, such as micro-/nanobubbles, solid gas-trapping or porous/concave architectures, and in situ gas-generating chemistries (e.g., oxygen- or CO_2-forming reactions) that seed bubble nucleation [250,262–267]; (ii) phase-change droplets, typically PFC nanodroplets that undergo acoustic droplet vaporization to form local bubbles, enhancing cavitation while enabling ultrasound-triggered "burst" release [228,253,254,268]; and (iii) mechano-catalytic sensitizers, including piezoelectric or semiconductor nanomaterials that convert ultrasound-induced stress into charge separation and subsequent ROS formation [269,270]. These designs are especially relevant for deep tissues, where acoustic intensity must remain within safety constraints; improving nanoscale "energy conversion efficiency"

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(lowering cavitation thresholds and strengthening stress-to-chemistry transduction) can help preserve efficacy without escalating macroscopic exposure [89,159].

3.3.5. Immunological Synergy: From Local SDT to Systemic Control

When nanocarriers concentrate SDT damage in tumors and boost oxidative stress, they can increase the likelihood of ICD and subsequent adaptive immune activation (CRT/ATP/HMGB1 signaling, dendritic cell maturation, T-cell priming) [129,254,271,272]. This creates a mechanistic rationale for combining SDT nanomedicines with checkpoint blockade or other immunomodulators (often co-loaded in the same nanocarrier): SDT provides antigen release and inflammatory cues, while immunotherapy prevents T-cell exhaustion and immunosuppressive rebound [48,254,272,273].

4. Nanocarrier-Based Strategies for Enhancing SDT Targeting and Efficacy

Nanocarriers have become central to modern SDT research because they directly address the key biological and engineering bottlenecks that limit standalone SDT [72,89,274]: (i) insufficient tumor accumulation and heterogeneous intratumoral penetration of sonosensitizers [146,275,276], (ii) premature clearance and off-target distribution [48,146,275], (iii) tumor-microenvironment (TME) suppression of reactive oxygen species (ROS) through hypoxia and antioxidant systems (e.g., glutathione, GSH) [89,146,181], and (iv) the need for spatiotemporal control of sensitizer activation and co-therapeutic release [28,38,275]. Recent reviews emphasize that "nanotechnology-enabled SDT" is evolving from simply "loading a sonosensitizer" into designing multi-stage, responsive delivery systems that coordinate pharmacokinetics, TME modulation, and ultrasound-triggered actuation [72,89,104,275].

4.1. Targeted Drug Delivery Systems in SDT

4.1.1. Passive Targeting: Circulation Engineering and Transport Optimization

Although the EPR effect can facilitate nanoparticle accumulation in some tumors, its variability across tumor types, stages, and patients makes passive targeting alone unreliable [73,277,278]. Consequently, contemporary SDT nanocarriers increasingly optimize system-level transport: prolonging circulation (e.g., PEGylation or alternative "stealth" coatings), controlling size (typically balancing extravasation vs. renal clearance), and tuning surface charge to reduce opsonization while preserving tumor uptake [72,278,279]. The design logic is to maximize the area-under-the-curve for tumor exposure, then leverage ultrasound to achieve local activation and/or release [72,227,280]. These principles are discussed prominently in recent SDT nanotechnology reviews and in the broader ultrasound-responsive nanocarrier literature [183,278].

4.1.2. Active Targeting: Ligand/Receptor Recognition and Multi-Receptor Strategies

Active targeting adds a molecular recognition layer on top of passive accumulation. In SDT, active targeting is not only about increasing uptake; it also improves selectivity of ultrasound-triggered ROS damage by enriching sensitizers at the tumor site and reducing sensitizer exposure in normal tissues [281–283]. Common ligand-receptor axes include: (i) Hyaluronic acid (HA)-CD44 targeting (frequent in breast, ovarian, and other CD44-high tumors) [75]; (ii) RGD/iRGD peptides-integrins (tumor endothelium and invasive tumor cells, can also support deeper tissue penetration) [284]; (iii) Folate receptor, transferrin receptor, EGFR/HER2 antibodies, and aptamers, depending on tumor biology and intended clinical indication [281]. A representative 2025 example is an HA-modified hollow MnO_2 platform loaded with IR780 (IR780@H-MnO_2@HA), which uses CD44 targeting to enhance tumor delivery and couples TME-triggered MnO_2 decomposition with imaging/therapy functions for SDT [75].

Active targeting is also being integrated with immunomodulatory payloads to convert SDT from a purely cytotoxic modality to a "tumor vaccination"-like process. An Acta Biomaterialia 2025 study

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reported a targeted nanosensitizer-augmented sono-immunotherapy platform co-delivering a STING agonist (MSA-2) with an RGD-targeting element to enhance immune activation alongside SDT [285]. MSA-2 is a recognized small-molecule STING agonist with the potential to be combined with SDT to enhance immune responses [286]. Additional studies exploring strategies for the local release of STING agonists co-encapsulated with photosensitizers, among other agents, may serve as supplementary background information [287].

4.1.3. Biomimetic Targeting: Cell-Membrane Coating and Endogenous Trafficking

Biomimetic strategies, such as cancer-cell membrane, platelet, red-blood-cell (RBC), or immune-cell membrane camouflage, are increasingly used to (i) reduce immune clearance, (ii) exploit homologous targeting, and (iii) improve vascular margination or immune-cell-mediated trafficking into tumors [48,288–292]. A 2025 review highlights how "sonodynamic biomimetic nanomedicine" can tackle off-target toxicity and TME barriers by integrating biological interfaces with ultrasound-activated therapeutics [48].

4.1.4. Subcellular Targeting: Mitochondria/Lysosome/Nucleus-Directed SDT

Because SDT efficacy depends on the proximity of ROS generation to vulnerable subcellular structures, recent nanocarriers increasingly incorporate organelle-targeting motifs (e.g., mitochondrial targeting groups such as triphenylphosphonium, nuclear localization sequences, or lysosome-affinity designs) [220,293–296]. The rationale is: ROS are short-lived and diffusion-limited, so organelle-localized sensitizers can produce disproportionately higher damage per ROS unit [175,297].

In summary, the most efficacious approach to targeting within the context of sonodynamic therapy (SDT) is frequently characterized by a multi-layered strategy. This involves a combination of systemic transport, tumor selectivity, and, in certain instances, organelle localization. This multi-faceted targeting is further enhanced by the application of ultrasound-triggered activation, which serves to refine spatial precision [104,117,220,293].

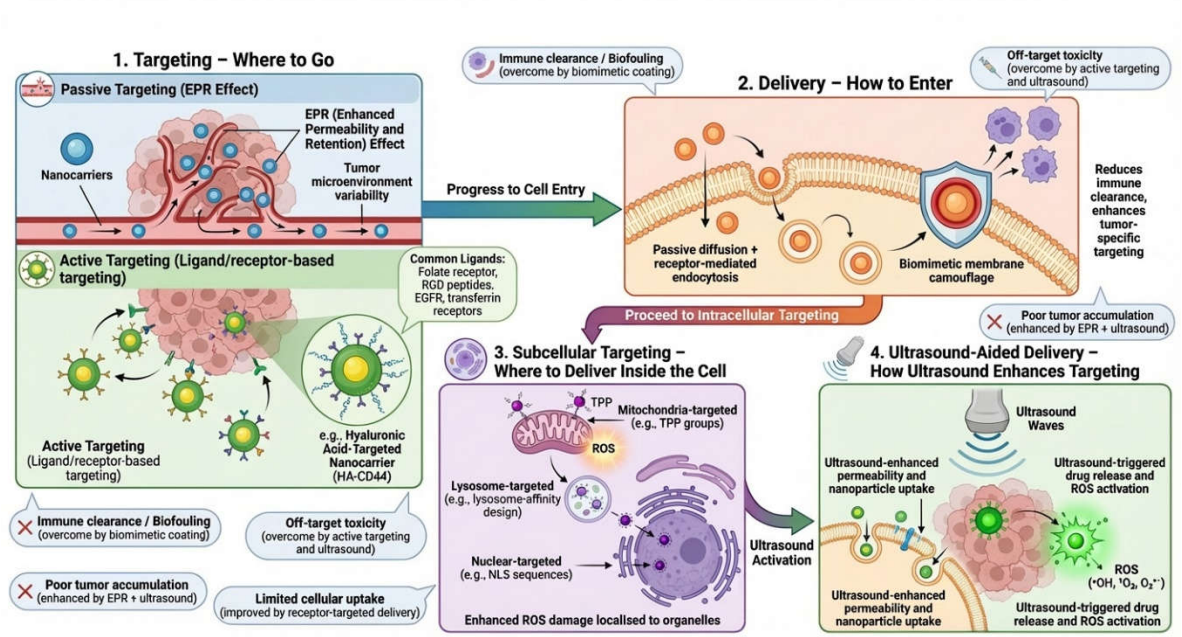

Figure 3. Scientific mechanism map: Targeted Delivery Strategies in SDT: From 'Where to Go' to 'Where to Enter'. Created in BioRender.

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4.2. Tumor Microenvironment Targeting

The TME is frequently hostile to SDT because ROS-based killing is attenuated by hypoxia, high GSH, and immunosuppressive cell populations [177,178,181,298]. Thus, many state-of-the-art SDT nanocarriers are explicitly designed to reprogram the TME rather than merely deliver sensitizers [180,181,255,258,299].

4.2.1. Hypoxia Alleviation: Oxygen Delivery and Oxygen Generation

Hypoxia reduces oxygen-dependent ROS pathways and can also promote therapy resistance [113,300,301]. Nanocarriers address this via oxygen carriers (e.g., perfluorocarbon-based droplets) that physically transport O_2 into tumors [113,121,254,301]. Some systems combine oxygen delivery with ultrasound-triggered phase transitions or cavitation to improve local release and perfusion [253,300,302]. In situ oxygen generation, often using catalytic components that convert endogenous H_2O_2 into O_2 (e.g., MnO_2-based shells) or oxygen-releasing compounds (e.g., CaO_2) [121,181,258,303]. A 2025 Journal of Materials Chemistry B report describes a cascade strategy (including CaO_2-based oxygenation and antioxidant disruption) to counter hypoxia and improve SDT outcomes [181]. A compelling "integrated oxygenation + immunomodulation" approach is the Chemical Engineering Journal 2025 ImmunoSonogen platform, which combines sonodynamic oxygenation with immune activation to overcome hypoxia-linked immunosuppression and promote stronger antitumor responses [113].

4.2.2. Redox Targeting: GSH Depletion and ROS Amplification Loops

Elevated GSH in tumor cells and the tumor microenvironment can rapidly quench SDT-generated ROS, thereby weaken oxidative damage and ultimately reduce SDT efficacy [304,305]. Accordingly, redox-targeting nanocarriers are often designed to undergo GSH-responsive disassembly/decomposition—for example, MnO_2 is reduced by GSH (Mn(IV)→Mn(II)), which can both trigger on-site release or activation of the sonosensitizer and simultaneously consume GSH to diminish antioxidant buffering capacity [259,304]. To further boost killing, many platforms construct cascade ROS-amplification loops, where SDT-initiated ROS and/or endogenous H_2O_2 is funneled into secondary radical-generating reactions (e.g., Mn^{2+}- or Fe-based Fenton/Fenton-like processes) to continuously produce highly cytotoxic •OH and related oxidants [259,306]. In parallel, coupling SDT with ferroptosis can reinforce lipid-peroxidation "positive feedback" by depleting GSH and/or disabling GPX4/FSP1 defenses, enabling lipid peroxides to accumulate and sustain ROS-driven membrane damage [304–307].

Consistent with this logic, recent reviews of stimuli-/microenvironment-responsive nanosonosensitizers increasingly frame tumor redox homeostasis (the antioxidant network) as a central therapeutic target for improving SDT selectivity and overall efficacy [89,104].

4.2.3. ECM/Stromal Targeting: Penetration Enhancement and Immune Infiltration

Dense ECM can limit both nanoparticle penetration and immune-cell trafficking [308–310]. Beyond enzyme-based ECM degradation, recent work demonstrates physical/thermal modulation to soften barriers and enhance delivery [311–313]. The SnSNP "denaturation-and-penetration" strategy is notable because it directly addresses stromal restriction and links improved penetration to improved cytotoxic T lymphocyte infiltration and antitumor immunity [183].

4.2.4. Immune Microenvironment Targeting: ICD, STING, and Macrophage Reprogramming

A major advance in SDT nanocarrier research is the shift from viewing SDT as purely localized cytotoxicity to treating it as an immunogenic therapy that can induce ICD and remodel the tumor immune microenvironment [129,164]. A 2025 review in Frontiers in Immunology summarizes how SDT-oriented nanoparticle delivery systems can be engineered to enhance ICD hallmarks and

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improve immune-contexture outcomes (e.g., dendritic cell activation and T-cell infiltration) by optimizing sensitizer delivery and stimulus responsiveness [164].

Two representative immuno-TME-targeting nanocarrier routes have emerged. First, STING-pathway activation plus SDT uses co-delivery of STING agonists (e.g., MSA-2-based designs) with nanosensitizers so that ultrasound-triggered SDT can synergize with innate immune activation, amplifying dendritic cell priming and downstream T-cell responses [285,314]. Second, tumor-associated macrophage (TAM) reprogramming employs ultrasound-responsive nanocarriers to deliver immunomodulators (such as siRNA or pathway inhibitors), shifting macrophages from an immunosuppressive M2-like state toward a pro-inflammatory M1-like phenotype to enhance antitumor immunity; a 2024 open-access study in Journal of Nanobiotechnology exemplifies this approach using ultrasound-responsive carriers integrating siRNA and Fe_3O_4 to modulate macrophage polarization and strengthen immune control of tumors [315].

Overall, modern SDT nanocarriers increasingly target tumor-microenvironment vulnerabilities (oxygen/redox imbalance, ECM barriers, and immune suppression) as deliberately as they target tumor cells, thereby improving targeting specificity and therapeutic efficacy [48,316].

Table 2. A Checklist of Tumor Microenvironment (TME) Modulation Strategies for Enhanced SDT.

TME bottleneck	Nanoengineering Techniques	How it Boosts SDT	Key Risk Points	Representative References
Hypoxia	O_2 carriers (e.g., PFC-based)	Restores O_2-dependent ROS; improves response consistency	Gas embolism concerns; formulation complexity	[180,301]
Hypoxia	Catalytic O_2 generation (MnO_2, CAT-like)	Converts H_2O_2 to O_2; supports sustained ROS production	Metal ion release; H_2O_2 dependency	[258,300]
Hypoxia	O_2-releasing compounds (CaO_2)	Local O_2 supply under hypoxia; "always-on" oxygenation	Local alkalinization; Ca^{2+} overload/toxicity	[181,303]
High GSH / strong antioxidant buffering	GSH-consuming shells (MnO_2, pMOF)	Depletes GSH leading to less ROS quenching; can unlock cascade catalysis	Oxidative stress to normal tissues; Mn-related safety	[179,235]
Redox resilience	Self-amplifying ROS loops (CDT/SDT cascades)	SDT initiates ROS leading to feeds secondary radical generation	Off-target inflammation; metal-catalyst byproducts	[177,306]

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Dense ECM / high interstitial resistance	ECM degradation (e.g., collagenase)	Improves penetration + intratumoral distribution	Vascular leakage; inflammation; metastasis concern if uncontrolled	[311,313]
Mechanical barriers	Mechanical microenvironment modulation	Lowers transport resistance; improves perfusion/uptake	Edema; unpredictable perfusion changes	[308]
Immunosuppression	STING agonist co-delivery / sono-STING	SDT→ICD + innate activation → stronger T cell priming	Systemic cytokine risk; autoimmunity-like toxicity	[314,343]
Immune resistance (checkpoint dominance)	SDT + ICB / nanovaccine	SDT-induced ICD supplies antigens; ICB prevents T cell exhaustion	Immune-related adverse events	[344,345]
TAM polarization / poor phagocytosis	siRNA / magneto-acoustic immunomodulation	Reprograms macrophages; increases antigen presentation & clearance	Off-target gene silencing; RES accumulation	[315]

4.3. Combining SDT with Other Modalities Using Nanocarriers

Nanocarriers are uniquely suited to SDT combination therapy because they can co-load multiple agents, control their ratios, and coordinate sequential or conditional release under TME cues and/or ultrasound [12,104,298,317,318]. This has led to a surge of "SDT+X" platforms where SDT serves as the deep-penetrating trigger and ROS generator, while co-therapies address complementary resistance mechanisms [48,72,89,104,119,250,298,317,319].

4.3.1. SDT + Chemotherapy/Molecular Inhibitors

Nanocarriers can synchronize chemotherapy exposure with ultrasound activation, improving tumor-local drug concentration and potentially reducing systemic toxicity [118,320,321]. Ultrasound-triggered permeabilization can also improve drug penetration into poorly perfused regions [320,322–324].

4.3.2. SDT + Gene/RNA Therapy (RNAi/CRISPR-Adjacent Strategies)

Gene silencing can remove intrinsic SDT resistance pathways such as antioxidant defenses [325–327], survival signaling [328,329], autophagy/mitophagy [325,330]. A 2025 Theranostics paper reported a reduction-responsive RNAi nanoplatform co-delivering Nrf2 siRNA, a mitophagy inhibitor (3-MA), and a sonosensitizer (purpurin-18), aiming to enhance cancer sonoimmunotherapy by dual inhibition of mitophagy and Nrf2 pathways [325].

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4.3.3. SDT + Immunotherapy (Checkpoint Blockade, STING Agonists, Nanovaccines)

SDT can trigger ICD and the release of tumor antigens/DAMPs, while nanocarriers enable co-delivery of immune adjuvants or pathway agonists to convert local tumor ablation into systemic antitumor immunity [112,129]. Targeted STING-agonist co-delivery nanosystems, such as liposomes co-loading a sonosensitizer with the non-nucleotide STING agonist MSA-2—combine SDT-triggered antigen liberation with STING activation to enhance dendritic cell maturation and cytotoxic T-cell priming [285,331]. Oxygenation–immunomodulation designs (e.g., the ImmunoSonogen platform) integrate ultrasound-driven oxygen generation with immunomodulatory components to relieve hypoxia and overcome hypoxia-associated immune suppression, thereby strengthening downstream immune activation [113,332]. Consistently, recent reviews summarize ICD-oriented SDT nanomedicines as both ICD inducers and tumor immune microenvironment remodelers, and emphasize their compatibility with immune checkpoint blockade and other immunotherapeutic regimens [72,112,129].

4.3.4. SDT + Ferroptosis / Chemodynamic Therapy (CDT) / Catalytic Therapies

Because lipid peroxidation is central to ferroptosis, SDT-generated ROS can synergize strongly with ferroptosis induction and iron-catalyzed reactions [119,173,260,304,333]. A 2025 Journal of Nanobiotechnology study described an SDT-boosted biomimetic nanoplatform targeting ferroptosis and immune microenvironment remodeling, reporting macrophage polarization effects and durable immune memory in preclinical models [304].

4.3.5. SDT + Phototherapy (PDT/PTT) and Multi-Trigger Platforms

Hybrid sonosensitizer/photosensitizer systems can exploit complementary activation windows (light for superficial or intraoperative contexts; ultrasound for deep lesions) [72,89,334–337]. The SnSNP work is an instructive example of combining mild photothermal effects with SDT to improve penetration and immune activation [183].

Table 3. The Combination Works in SDT-Based Regimens.

Combination direction	Core logic of synergy	Carrier Design Notes	Representative References
Chemo / metabolic inhibitors	SDT increases permeability + ROS stress → sensitizes to chemo; chemo can weaken repair pathways	Co-loading vs. sequential release; ultrasound-triggered burst to align timing	[108,171,182,293]
Gene / RNA therapeutics	Knock down antioxidant/escape pathways → SDT ROS becomes “unbuffered”; can rewire immune context	Protect nucleic acids; endosomal escape; redox- or US-triggered unpacking	[296,315,325]

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Immunotherapy (STING, ICB, vaccines)	SDT → ICD/DAMPs + antigen release; immune adjuvants/ICB sustain systemic response	Keep immunostimulant shielded systemically; tumor-local activation; avoid cytokine burst	[183,295,314,343–345]
Ferroptosis / CDT	SDT ROS seeds lipid peroxidation; CDT supplies •OH; ferroptosis disables GSH/GPX4/FSP1 defenses → positive feedback	Metal/catalyst nodes + GSH depletion; membrane/mitochondria targeting improves efficiency	[177,304–307,352]
PDT/PTT	PTT improves perfusion/oxygenation and accelerates kinetics; PDT adds orthogonal ROS modality; multimodal imaging-ready	Avoid overheating; choose trigger hierarchy (US-first vs. light-first); spatial co-localization	[116,300,301]

5. Clinical Applications and Translational Research

5.1. Preclinical Studies

Over the past decade, nanocarrier-assisted SDT has progressed from proof-of-concept ROS generation to disease-oriented therapeutic engineering, especially for deep-seated tumors where light-based photodynamic therapy is limited by penetration [12,89]. Contemporary SDT typically employs low-intensity focused ultrasound (LIFU/FUS) to activate sonosensitizers and induce oxidative stress–dominated cytotoxicity; recent summaries place commonly used ultrasound settings broadly within MHz frequencies and low W/cm² intensities depending on the application and device configuration [158,338].

5.1.1. Cancer Models (Solid Tumors, Orthotopic Tumors)

Preclinical efficacy has been repeatedly demonstrated in murine xenograft and orthotopic systems by packaging sonosensitizers (e.g., porphyrin/chlorin derivatives, ALA/PpIX precursors, inorganic sonosensitizers, or hybrid catalysts) into liposomes, polymeric nanoparticles, MOFs, exosome-like vesicles, and inorganic-organic composites to improve pharmacokinetics and tumor accumulation, mitigate premature clearance, and enable stimulus-responsive release [72,89,94,109,231,339–341]. It is emphasized that nanomaterials can (i) increase intratumoral sensitizer concentration, (ii) relieve hypoxia or amplify ROS chemistry, and (iii) provide theranostic functions (MRI/PA/US imaging) that are particularly valuable for orthotopic disease where dose delivery is otherwise uncertain [72,89,94,109,231,339–342].

5.1.2. Immunological “Second Wave” of SDT Efficacy

A major translational trend is to treat SDT not only as a local ablation-like approach but also as a method to induce ICD and reshape the tumor immune microenvironment [112,164,167]. Multiple preclinical reports indicate that SDT-mediated oxidative injury can promote antigen release and

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immune activation; recent work continues to refine this concept via nanocarriers that co-deliver immune adjuvants, ferroptosis amplifiers, or checkpoint blockade partners [183,255,298,304,343–345].

Notably, a 2025 study combining 5-ALA-mediated SDT with a novel high-intensity focused ultrasound (HIFU) approach reported effective tumor suppression at reduced acoustic intensities while enhancing anti-tumor immune responses, supporting the idea that ultrasound engineering and sensitizer biology can be co-optimized to expand the therapeutic window [346].

5.1.3. Brain Tumor Relevant Preclinical Evidence

Because the brain is an early clinical focus for SDT, preclinical glioma work, especially with 5-ALA → PpIX, has been influential [339,347,348]. Experimental evidence suggests 5-ALA-SDT can reduce glioma viability and may affect invasive margins, motivating clinical exploration [339,349,350].

5.1.4. Anti-Bacterial / Anti-Biofilm Applications

Beyond oncology, SDT has been explored as a non-antibiotic antimicrobial strategy, leveraging ultrasound penetration and ROS-mediated multi-target damage to reduce resistance pressure [351–353]. Recent syntheses specifically highlight nanoplatform-based antibacterial SDT (nanocarriers delivering organic sonosensitizers or nanosonosensitizers themselves) for deep infections and biofilm-associated disease [351–354].

5.2. Clinical Trials and Progress

Despite extensive preclinical activity, SDT's clinical footprint remains small, consistent with earlier translational analyses noting that only limited clinical reporting existed historically and that standardization and dosimetry were major barriers [170,172,347,355,356]. The situation is now changing, driven largely by drug repurposing (5-ALA) and the availability of clinically deployed ultrasound platforms [348]. A key recent milestone is the first-in-human early clinical study of 5-ALA (SONALA-001) + MRgFUS SDT in recurrent high-grade glioma (NCT04559685). The report describes assessment of safety and biological efficacy across ascending MRgFUS energy doses in nine patients, supporting feasibility of this drug–device approach in humans [348]. Besides, there are still some ongoing or registered clinical trials. Conference updates also indicate ongoing maturation of these programs. For example, CTNI-76 is a phased "trial update" for the SDT-202 (SONALA-001 + Exablate) project of rGBM [357].

Clinically, SDT is currently evolving as a combination product paradigm with glioma trials leveraging tumor-selective PpIX accumulation [348,358]. This makes targeting and dosimetry the central clinical development themes.

5.3. Limitations and Challenges in Clinical Translation

5.3.1. Biological Delivery Variability

Nanocarrier-enhanced SDT often assumes passive tumor accumulation via the EPR effect, yet multiple clinical-focused reviews emphasize that EPR is heterogeneous and dynamic across tumor types, stages, and even regions within one tumor, driving inconsistent nanoparticle deposition and variable efficacy [277,359–361]. For SDT, this is especially problematic because therapeutic effect depends on co-localization of (a) sonosensitizer/nanocarrier and (b) a sufficiently dosed ultrasound field [89,172]. Translation will likely require patient stratification (imaging or biomarkers of nanoparticle delivery) and/or "EPR-enhancing" strategies (vascular normalization, ECM modulation, ultrasound-assisted transport), rather than relying on passive targeting alone [89,172].

5.3.2. Ultrasound Dosimetry, Standardization, and Real-Time Monitoring

Unlike pharmacologic dosing, ultrasound dose depends on parameters (frequency, duty cycle, intensity, pulse structure), tissue acoustics, and cavitation dynamics [172,363]. Lack of standardized

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reporting and real-time verification can impede reproducibility across sites [172]. Emerging approaches that combine real-time cavitation monitoring with imaging (e.g., passive cavitation imaging/mapping integrated with B-mode guidance) illustrate how SDT could move toward closed-loop control and safer, more consistent exposures [363,364].

5.3.3. Safety of Complex Nanocarriers: Immunogenicity, Long-Term Fate, and "Silent" Accumulation

Many advanced SDT nanoplatforms incorporate heavy atoms, inorganic lattices, catalytic metals, or persistent polymers [89,338]. Even when acute toxicity appears low, clinical translation requires addressing: complement activation / infusion reactions, RES accumulation (liver/spleen), degradation pathways and metabolite safety, potential interactions between ultrasound and nanoparticle surfaces (heating, fragmentation, altered biodistribution) [280,365,366]. These concerns push the field toward biodegradable or clinically precedent materials (lipids, PLGA, albumin-like systems) and to simplified designs compatible with scalable GMP [365,367].

5.3.4. Clinical trial design challenges

Key practical issues include: selecting endpoints that capture SDT's local + systemic effects (imaging response, immune correlates, survival) [129], controlling for standard-of-care heterogeneity (especially in GBM) [368], ensuring device operator consistency across centers [369], etc.

6. Future Perspectives and Research Directions

6.1. Nanocarrier Design for Personalized SDT

Personalized SDT will likely develop along two coupled axes: The first is personalizing nanocarrier exposure. Given EPR variability, future trials may incorporate delivery diagnostics. For example, contrast-enhanced imaging, radiolabel tracing, or ultrasound/PA reporters embedded in the carrier, to confirm tumor deposition before therapeutic ultrasound is applied [105,277,370–372]. The second is personalizing ultrasound dose. Integrating real-time cavitation mapping, thermometry (where relevant), and patient-specific acoustic modeling could enable patient-tailored sonication plans and reduce under- or over-treatment [373–376].

6.2. SDT + Blood Brain Barrier (BBB) Modulation / Enhanced Brain Delivery

For central nervous system (CNS) disease, one compelling direction is pairing SDT with ultrasound-mediated BBB permeabilization (often with microbubbles), either to increase nanocarrier entry or to combine SDT with systemically delivered drugs [371,376,377]. Current clinical and translational reviews of BBB opening by focused ultrasound provide a roadmap for safety monitoring, workflow integration, and agent selection [317,347,378].

6.3. Closed-Loop Ultrasound Control

A central limitation of SDT is that the delivered ultrasound settings (e.g., nominal acoustic power, duty cycle, duration) are not equivalent to the biologically effective dose at the tumor [170,172,379]. Variations in acoustic coupling, tissue attenuation, patient anatomy (especially transcranial pathways), and microbubble/nanocarrier interactions can shift the therapy from sub-therapeutic activation to excessive cavitation or unintended bioeffects [72,378–382]. Consequently, next-generation SDT, particularly nanocarrier-enabled SDT will likely require closed-loop ultrasound control to ensure consistent activation while maintaining safety margins across patients and centers [72,378,380,382]. This direction parallels focused-ultrasound fields where monitoring modalities such as passive cavitation detection/mapping and MR thermometry are used to improve treatment controllability and reproducibility [374,378,383–386].

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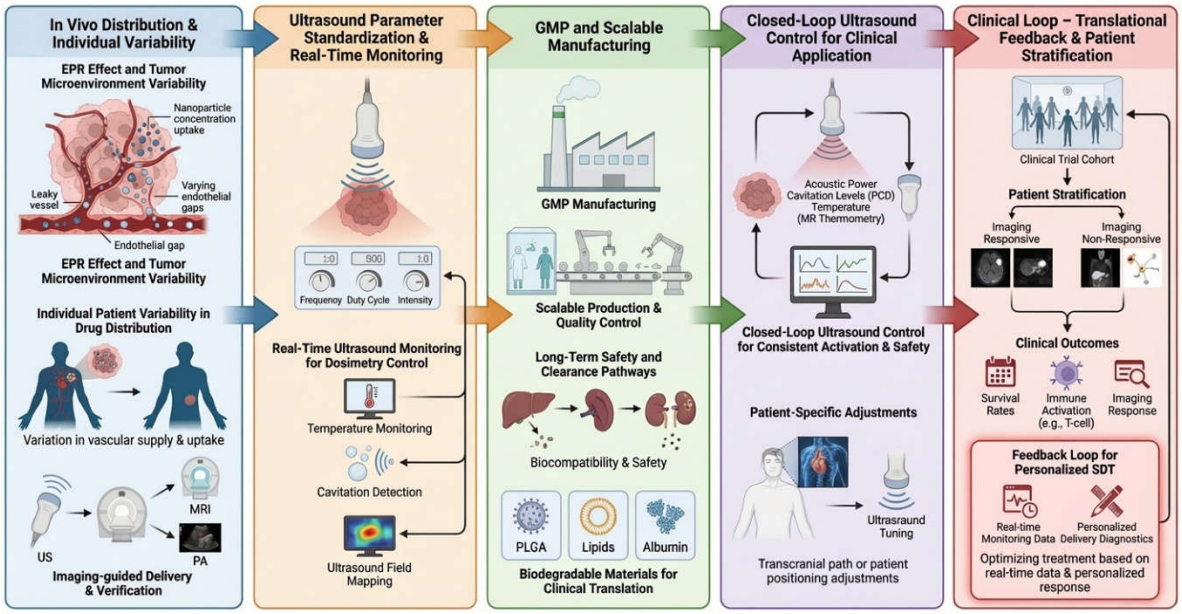

Figure 4. From Materials to Clinical Loop: Translational and Engineering Roadmap for SDT. Created in BioRender.

7. Conclusion

SDT has emerged as a promising non-invasive therapeutic strategy that leverages the deep tissue penetrability and spatiotemporal controllability of ultrasound to activate sonosensitizers and generate ROS for disease treatment. However, early SDT development was constrained by key translational barriers, including the poor solubility and non-specific biodistribution of many sensitizers, systemic toxicity concerns, and limited standardization and control of ultrasound exposure.

The integration of nanocarriers has substantially expanded the therapeutic design space of SDT. By encapsulating or conjugating sonosensitizers, nanocarriers can improve aqueous dispersibility, pharmacokinetics, and local retention while reducing off-target exposure. Importantly, modern SDT nanoplatforms go beyond "delivering more sensitizer": they enable microenvironment-aware engineering (e.g., hypoxia relief, redox modulation, and ROS amplification), multimodal imaging/theranostic guidance, and rational co-delivery of synergistic agents. These capabilities support combination regimens (e.g., chemo-SDT, catalytic/ferroptotic amplification, and sono-immunotherapy) and offer a path toward more precise and reproducible SDT activation in vivo.

Despite rapid progress, several challenges remain before nanocarrier-assisted SDT can be widely translated, including inter- and intra-tumoral variability in nanoparticle delivery, the need for quantitative ultrasound dosimetry and real-time monitoring, and rigorous evaluation of long-term biosafety and manufacturability for complex formulations. Future advances will likely center on simplified yet functional and GMP-compatible designs, delivery diagnostics for patient stratification, and closed-loop ultrasound control to ensure consistent activation and safety across patients and clinical sites. With continued interdisciplinary collaboration across nanomedicine, ultrasound engineering, and clinical research, nanocarrier-enabled SDT is poised to evolve from a promising concept into a clinically feasible, precision-targeted therapeutic platform.

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