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REVIEW

Targeting Glucose Transporter 1 (GLUT1) in Cancer: Molecular Mechanisms and Nanomedicine Applications

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Abstract: Glucose transporter 1 (GLUT1), a central orchestrator of tumor metabolic reprogramming, sustains malignant progression by enforcing glycolytic dependency and conferring therapeutic resistance. While conventional GLUT1-targeted small-molecule inhibitors demonstrate preclinical efficacy through glucose transport blockade and chemo-radiosensitization, their clinical translation is impeded by intrinsic limitations. Emerging nanomedicine paradigms have redefined GLUT1-targeted interventions through multi-functional platforms that synergistically unify precision therapeutics, imaging guidance, and immunometabolic modulation. Meanwhile, advanced formulations further exploit GLUT1-mediated endocytosis to achieve blood-brain barrier penetration, thus potentially addressing key challenges in the treatment of CNS malignancies. Notably, combinatorial nanoarchitectures simultaneously disrupt metabolic pathways and reprogram immunosuppressive niches via dual-targeting strategies, thereby counteracting tumor adaptation mechanisms. These innovations transcend conventional therapeutic boundaries by establishing metabolic-immune interplay regulation and barrier-defying delivery systems. This review systematically analyses the evolving landscape of GLUT1-targeted nanomedicine, evaluating both traditional molecular inhibitors and next-generation nanoplatforms that harness GLUT1 through diverse modalities. By dissecting molecular mechanisms and translational applications, we elucidate the diagnostic and therapeutic value of GLUT1-targeted nano-strategies in precision oncology while outlining future directions for clinical implementation.

Keywords: GLUT1, nanomedicine, precision oncology, metabolic reprogramming

Introduction

Glucose transporter (GLUT) is a key protein facilitating glucose transport across cell membranes, playing a crucial role in maintaining cellular metabolic homeostasis and energy balance. Glucose transporter 1 (GLUT1), a member of the glucose transporter family, features a 12-transmembrane domain structure characteristic of transmembrane proteins.[1] Humans have identified 14 members in the GLUT family, which show different substrate specificity and tissue expression.[2] However, GLUTs show a high degree of homology, have common sequence features, and can be divided into three categories, which differ in the position of the predicted long extracellular loop.[3] Under normal physiological conditions, GLUT1 is expressed in almost all tissues, including brain, erythrocytes, and placenta, ensuring their energy supply.[1,4] In addition, the highly conserved GLUT1 has a high affinity for glucose (K_m=3mM) and can also transport galactose, mannose, glucosamine, and DHA.[2] While GLUT1 expression is significantly upregulated in tumor cells, supporting their enhanced glycolytic activity and rapid proliferation.[5] In tumor cells, glucose metabolism undergoes reprogramming, a phenomenon known as the "Warburg effect", where cells preferentially perform aerobic glycolysis even in oxygen-rich conditions, consuming more glucose to meet the energy demands of rapid proliferation.[6] GLUT1 plays a pivotal role in this process as a critical node of cellular energy metabolism, enabling rapid glucose transport to support the high metabolic demands of tumor cells. With the

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continuous deepening of research, GLUT1 has been confirmed to be highly expressed in various cancer types including lung cancer, prostate cancer and gastric cancer,[7] and its upregulation is closely related to tumor proliferation, invasion and drug resistance,[8–10] involving multiple classic cancer pathways or transcription factors such as phosphatidylinositol 3-kinase (PI3K)-Akt pathway,[11] hypoxia-inducible factor-1 (HIF-1) complex,[12] Ras GTPases,[13] MYC family[14] and P53 gene.[15] These alterations position GLUT1 as a key regulator of tumor metabolic adaptation and an emerging target for cancer therapy.

Tumor cells upregulate GLUT1 expression to enhance glucose uptake, a function that becomes particularly critical under hypoxic conditions.[16] Studies have shown that high expression of GLUT1 is associated with poor prognosis in a variety of malignant tumors, including hepatocellular carcinoma,[17] pancreatic tumors,[18] prostate cancer,[19] cervical squamous cell carcinoma[20] and inhibiting its function has become a potential anti-cancer strategy. For example, GLUT1 inhibitors have been shown to reduce tumor cell proliferation and enhance the efficacy of radiotherapy and chemotherapy.[21] In recent years, research has increasingly focused on targeting GLUT1 for cancer therapy. Clinically, GLUT1 inhibitors or antibodies targeting specific regions of the protein are believed to disrupt tumor cell glucose dependency and significantly reduce tumor growth. Meanwhile, as our understanding of GLUT1's role in the tumor microenvironment deepens, precise interventions targeting its structural and functional characteristics are advancing into preclinical studies, presenting new prospects for cancer therapy. This review aims to synthesize current research on GLUT1 in cancer therapy, and GLUT1-related nanomaterials and tumor treatment (Figure 1), exploring its potential and associated challenges.

GLUT1 Inhibitors in Tumor Therapy

GLUT1 facilitates glucose transport into cells by alternating the substrate cavity's exposure to each side of the membrane. GLUT inhibitors interfere with this transport by disrupting the conformational cycling between the outward-facing (substrate cavity exposed to extracellular space) and inward-facing states (substrate cavity exposed to the cytosol)

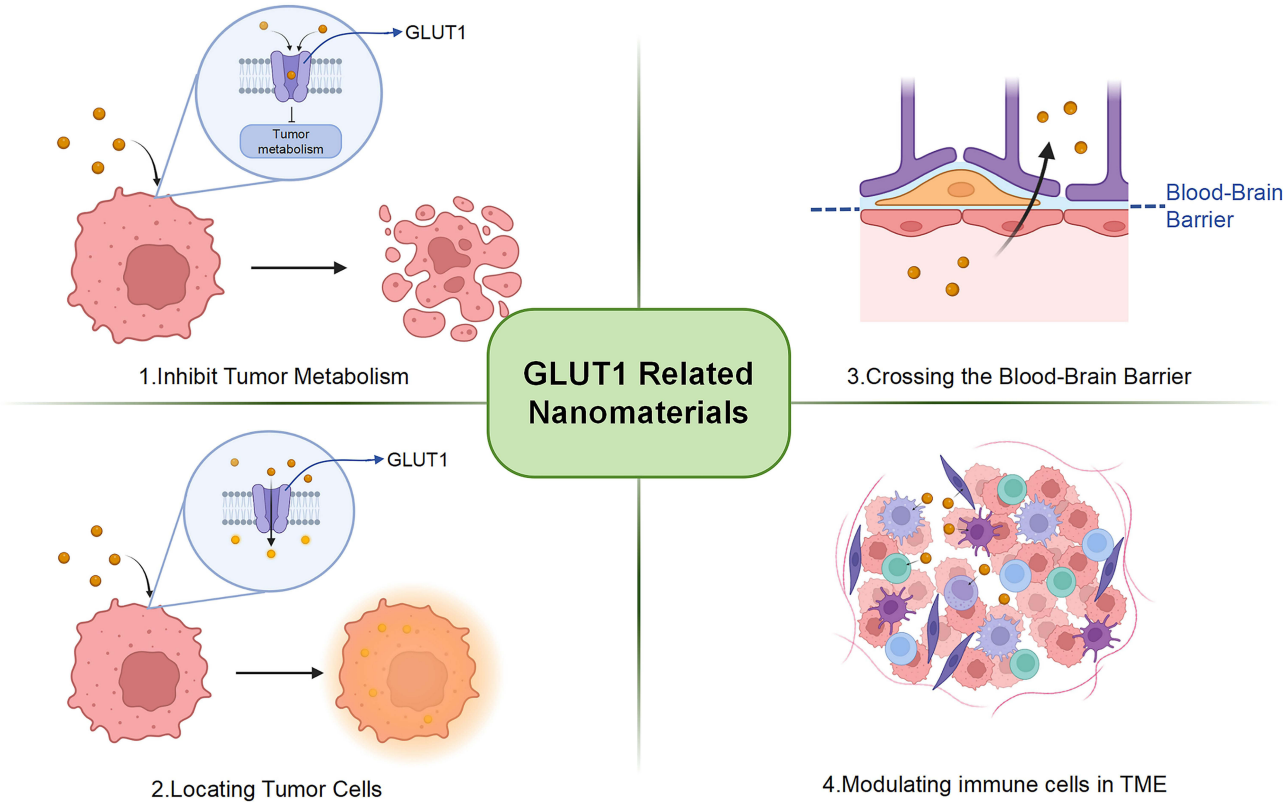


Figure 1 The main Mechanism of Action of GLUT1 Related Nanomaterials. Created in BioRender. Y, N . (2025) https://BioRender.com/bkhkfpn.

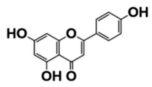
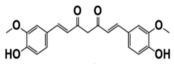
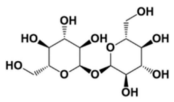
or by blocking glucose passage in one or both conformational states.[22] Currently, research on GLUT inhibitors focuses on screening natural and synthetic compounds and elucidating their mechanisms of action. These natural compounds include cytochalasin B, phloretin, apigenin, curcumin, trehalose, silibinin and genistein, etc. These compounds have shown significant anti-cancer potential in various tumor models and can enhance the efficacy of radiotherapy and chemotherapy through various mechanisms[23] (Table 1).

Apigenin was found to increase the radiosensitivity of laryngeal cancer xenografts by reducing GLUT1 expression via the PI3K/Akt signaling pathway. In a nude mouse model, combining apigenin with X-ray radiation significantly suppressed tumor growth, with the combined treatment group displaying reduced tumor volume.[24] Additionally, apigenin synergistically increased cisplatin sensitivity in Hep-2 laryngeal cancer cells by dose-dependently inhibiting GLUT1 and p-Akt expression.[25] Curcumin, combined with GLUT1 antisense oligodeoxynucleotide (AS-ODN), further enhanced radiotherapy sensitivity in laryngeal cancer models by modulating autophagy and inducing apoptosis.[26] Trehalose, a natural glucose disaccharide, exerts antiproliferative effects by blocking GLUTs.[27] Trehalose enters cells via GLUT8 and induces autophagy by regulating the Akt pathway. In melanoma models, trehalose combined with temozolomide (TMZ) significantly reduced colony-forming ability and improved autophagic activity. When further combined with radiotherapy, this combination exhibited superior antitumor effects at lower doses compared to TMZ or trehalose with radiotherapy alone.[28] New GLUT1 inhibitors continue to be derived from natural compounds. For example, during the isolation and purification of cytotoxic extracts from *Gekko japonicus*, the most potent peptide, Gekko peptide LH-20-15, was identified and analyzed via de novo sequencing. LH-20-15 significantly inhibited the proliferation of human esophageal squamous carcinoma EC9706 cells in a dose-dependent manner and induced apoptosis via the mitochondrial pathway. Further studies revealed that LH-20-15 suppressed the PI3K/Akt/GLUT1 signaling pathway.[29]

Synthetic GLUT inhibitors encompass compounds such as indinavir, ritonavir, 6-benzylthioinosine (6-BT), WZB117, WZB27, WZB115,[18] FDG, STF31, BAY-876, palbociclib, CG-5, 2-deoxyglucose (2-DG), and Compound 20.[23] These inhibitors exhibit diverse antitumor mechanisms, particularly in overcoming resistance and enhancing existing treatments (Table 2).

GLUT1 overexpression is closely associated with chemoresistance. For example, WZB117 overcomes doxorubicin resistance in MCF7 breast cancer cells by activating BAX translocation, AMPK activation, and mTOR pathway suppression.[30] When combined with the Akt inhibitor MK-2206, WZB117 synergistically induces apoptosis by enhancing Akt phosphorylation inhibition, impairing DNA repair mechanisms, and inducing DNA damage.[31] Additionally, WZB117 enhances radiotherapy efficacy in MCF7 and MD-MBA-231 breast cancer cells, likely by resensitizing radioresistant cells to

Table 1 Effects of Natural Compound GLUT Inhibitors Against Various Cancers

Compound	Molecular Structure	Cancer Type	Effect	Ref.
Apigenin		Laryngeal	↓PI3K/AKT ↑Cisplatin Sensitivity	[24,25]
Curcumin		Laryngeal	↑Autophagy ↑Apoptosis ↑Radiotherapy Sensitivity	[26]
Trehalose		Melanoma	↑Autophagic ↑Radiotherapy sensitivity	[27,28]
LH-20-15	–	Esophageal	↓PI3K/Akt ↓Proliferation ↑Apoptosis	[29]

Abbreviations: P.S.:↑, increase; ↓, decrease; GLUT, Glucose transporter; PI3K/AKT, The phosphatidylinositol 3-kinase/AKT pathway.

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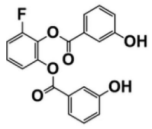
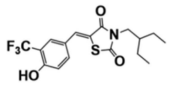
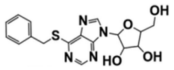
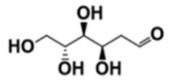
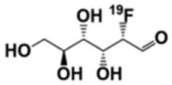
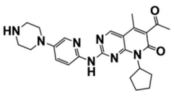
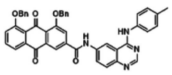
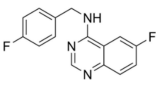
Table 2 Effects of Combination Treatments of Synthetic Small Molecule GLUT Inhibitors Against Various Cancers

Compound	Molecular Structure	Cancer Type	Effect	Ref.
WZB117		Breast	↑AMPK ↓mTOR ↓DNA repair ↑DNA damage ↑Radiotherapy Sensitivity	[30–32]
CG-5		Pancreatic	↓Chemotherapy Resistance	[33]
6-BT		Leukemia	↓Glycolytic Flux	[34]
2-DG		Breast Pancreatic Liver	↓HIF-1α ↓Growth	[35–39]
^{19}FDG		Cervical Breast	↑Apoptosis ↑Necrosis	[40]
Palbociclib		Breast	↓Glucose Uptake ↓Proliferation	[41]
Compound H		Nasopharyngeal Breast	↓ATP ↓MMP ↓Intra-cellular Lactic Acid ↓EGFR Nuclear Transfer	[42]
Spautin-1		Prostate	↑Apoptosis	[43]

Abbreviations: P.S.:↑, increase; ↓, decrease; GLUT, Glucose transporter; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of rapamycin; HIF-1α, Hypoxia-inducible factor-1alpha; MMP, Matrix metalloproteinase; EGFR, Epidermal growth factor receptor.

treatment through reduced glucose metabolism.[32] CG-5, a GLUT1 inhibitor and thiazolidinedione (TZD) derivative, overcomes chemoresistance in pancreatic cancer Panc-1 cells when combined with gemcitabine. The mechanism likely involves upregulation of ribonucleotide reductase M2 subunit expression induced by gemcitabine, restoring its anticancer activity.[33]

6-BT, combined with metformin, shows strong synergy in FLT3-ITD acute myeloid leukemia (AML) cells by significantly reducing glycolytic flux and GLUT1 mRNA expression, leading to energy crises and ATP depletion.[34] 2-DG, a competitive hexokinase inhibitor, mimics glucose structurally and can be metabolized by hexokinase but cannot proceed further through glycolysis, leading to accumulation in the cytoplasm.[35] As a competitive inhibitor of GLUT1 and GLUT4, 2-DG demonstrates anticancer potential in various cancers. For instance, when combined with cell cycle regulator mibefradil, 2-DG significantly enhances antitumor effects in MDA-MB-231 breast cancer cells, likely through cell cycle synchronization at the G1/S phase. Furthermore, combining 2-DG with Ras inhibitor FTS enhances anticancer effects in pancreatic cancer cells by suppressing HIF-1α expression.[36,37] However, the efficacy of 2-DG under hypoxic conditions is limited, and ^{19}FDG is considered a more effective alternative. Studies show that ^{19}FDG, when combined with doxorubicin, induces apoptosis and necrosis more significantly than 2-DG under both normoxic and hypoxic conditions.[40] ^{18}F-FLT PET is a biological specimen that suppresses and inhibits the production of ^{18}F-FLT PET, and ^{18}F-FDG PET is a unique and robust specimen.[44] Recently, 2-DG has been used as an adjuvant in hepatocellular carcinoma and breast cancer cell lines, showing synergistic growth inhibition in vitro when combined with sorafenib and metformin, respectively.[38,39] Palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, reduces GLUT1 expression, inhibits glucose uptake, and enhances the efficacy of paclitaxel in triple-negative breast cancer cells. Furthermore, its combination with the PI3K/Akt/mTOR inhibitor BYL719 exhibits synergistic antiproliferative effects, further downregulating GLUT1 expression and suppressing glucose metabolism.[41] Compound H simultaneously targets the ATP-binding site of EGFR tyrosine kinase and inhibits GLUT1-mediated energy metabolism, reducing ATP, MMP, intracellular lactate, and EGFR nuclear translocation. Compound H demonstrates superior antitumor activity compared to the combination of GLUT1 inhibitor BAY876 and EGFR inhibitor gefitinib.[42] Spautin-1 reduces GLUT1 expression and significantly induces cell death under glucose deprivation conditions. In prostate cancer models, Spautin-1 causes cell cycle arrest and apoptosis in a USP10/USP13-independent manner. In vivo, Spautin-1 alone or combined with enzalutamide exhibits strong antitumor effects.[43]

With further advancements in screening methods for GLUT1 inhibitors, clinical applications continue to face significant challenges, including limited specificity and potential toxicity. Due to the ubiquitous expression of GLUT1 in normal tissues, nonspecific inhibition may induce severe side effects or poor therapeutic efficacy. For example, silibinin—a flavonoid derived from milk thistle—demonstrates preclinical antitumor activity by targeting GLUT and suppressing glucose uptake.[45] However, phase I trials revealed inadequate tissue penetration in prostate cancer patients after two weeks of treatment,[46] and a separate study in advanced hepatocellular carcinoma was terminated following enrollment of only three participants.[47] Tumor cells further compromise drug efficacy by adapting to GLUT1 inhibition through upregulation of alternative glucose transporters (eg, GLUT3[48]) or metabolic pathway alterations. Although glycolysis inhibitors exhibit limited efficacy as monotherapies, their potential in combinatorial regimens warrants exploration. Consequently, optimizing the safety and efficacy of GLUT1-targeted therapies via advanced nanodelivery strategies remains imperative.

GLUT1-Related Nanomaterials and Tumor Treatment

Directly using GLUT1 inhibitors to intervene in tumor metabolic reprogramming presents several challenges, including poor drug selectivity, significant side effects, and inconsistent therapeutic efficacy. These limitations have driven the exploration of alternative therapeutic strategies. The emergence of targeted nanomaterials offers a promising solution to these challenges. Precisely engineered nanoparticles enable scientists to efficiently target specific sites in tumor cells, thereby regulating GLUT1 expression and function to inhibit tumor growth. Nanomaterials possess unique physicochemical properties, such as small size, large surface area, excellent biocompatibility, and tunable surface functionalities, making them highly promising for targeted drug delivery and therapy. These nanomaterials enable researchers to not only precisely regulate glucose metabolism in tumor cells through receptor-mediated precise targeting, but also serve as a medium for blood-brain barrier penetration, as well as indirectly modulate tumor immunity by regulating immune cells in the tumor microenvironment, thereby paving the way for novel cancer treatment approaches.

Nanomedicine Related to Inhibiting GLUT1 to Block Energy Metabolism for Anti-Tumor Effects

Rapidly proliferating cancer cells rely on excessive glucose uptake to meet their high energy demands, driven primarily by GLUT1 overexpression. GLUT1 facilitates glucose uptake and plays a central role in the altered energy metabolism of many malignant tumors. Some researchers have explored direct strategies to inhibit GLUT1 (Figure 2). For example, a combination strategy involving WZB117 (a GLUT1 inhibitor), OCMC (O-carboxymethyl chitosan), and MET has been proposed to target both GLUT1 and mTOR, altering breast cancer metabolism.[49] Glucose-modified PLGA and chitosan nanoparticles (GPNPs and GCNPs) have been developed in CT26 colorectal cancer cells to investigate the potential of

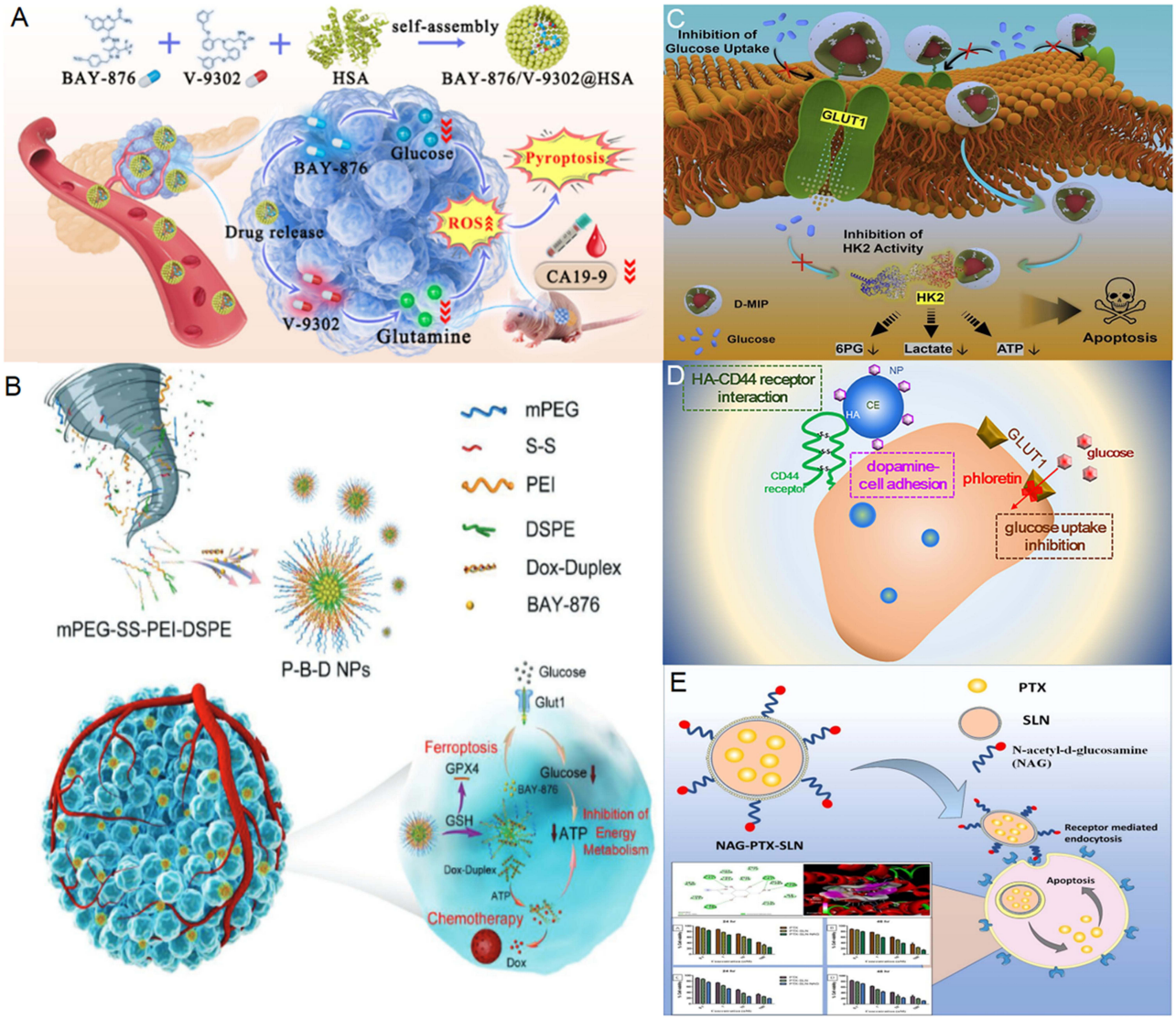


Figure 2 Nanomaterials that directly inhibit GLUT1. (**A**) Human serum albumin nanoparticles (HSA NPs) loaded with GLUT1 and ASCT2 inhibitors (BAY-876/V-9302). Reprinted with permission from Wang X, Ding B, Liu W, et al. Dual starvations induce pyroptosis for orthotopic pancreatic cancer therapy through simultaneous deprivation of glucose and glutamine. J Am Chem Soc. 2024;146(26):17854–17865. Copyright © 2024 American Chemical Society.[51] (**B**) Smart nanoparticles (P-B-D NPs). Reprinted from Jiang W, Luo X, Wei L, et al. The sustainability of energy conversion inhibition for tumor ferroptosis therapy and chemotherapy. Small. 2021;17(38):e2102695. Copyright © 2021 Wiley-VCH GmbH.[52] (**C**) A novel dual-template that specifically recognizes GLUT1 and hexokinase-2 (HK2) molecularly imprinted polymer (D-MIP). Reprinted from J Colloid Interface Sci. Volume 683. Wang D-W, Ren X-H, Ma Y-J, et al. Dual-template epitope imprinted nanoparticles for anti-glycolytic tumor-targeted treatment. 890–905. Copyright © 2024 Elsevier Inc.[54] (**D**) A nanomaterial incorporating phloretin (a GLUT1 inhibitor). Reprinted with permission from Lee SY, Park J-H, Ko S-H, Shim J-S, Kim -D-D, Cho H-J. Mussel-inspired hyaluronic acid derivative nanostructures for improved tumor targeting and penetration. ACS Appl Mater Interfaces. 2017;9(27):22308–22320. Copyright © 2017 American Chemical Society.[58] (**E**) functionalizing SLNs (PTX-SLNs) loaded with paclitaxel using N-acetyl-d-glucosamine (GLcNAc). Reprinted from Int J Pharm. Volume 637. Jagdale S, Narwade M, Sheikh A, et al. GLUT1 transporter-facilitated solid lipid nanoparticles loaded with anti-cancer therapeutics for ovarian cancer targeting. 122894. Copyright© 2023 Elsevier B.V.[59]

blocking overexpressed glucose transporters (GLUTs) and preventing glucose uptake.[50] Human serum albumin nanoparticles (HSA NPs) loaded with GLUT1 and ASCT2 inhibitors (BAY-876/V-9302) were prepared using a self-assembly process. In pancreatic cancer, these nanoparticles release BAY-876 and V-9302 to inhibit glucose and glutamine uptake by cancer cells, inducing nutrient deprivation and oxidative stress. The inhibition of glutamine further suppresses glutathione synthesis, exacerbating oxidative stress. These processes result in significant reactive oxygen species (ROS) accumulation, activating caspase-1 and GSDMD, ultimately inducing pyroptosis (Figure 2A).[51] Smart nanoparticles (P-B-D NPs) have been reported, in which BAY-876, a GLUT1 inhibitor, and Doxorubicin (Dox)-Duplex were loaded into disulfide-linked polymer-based nanoparticles. These nanoparticles effectively combat malignant tumors by targeting tumor cell energy metabolism and growth, thereby inhibiting cancer cell proliferation (Figure 2B).[52] In bladder cancer studies, si-m/hVDAC1-B, encapsulated in PLGA-PEI nanoparticles, was directly injected into the bladder, reducing tumor size, morphological damage, and muscle invasion, demonstrating its potential as an effective bladder cancer treatment.[53] In breast cancer, a novel dual-template molecularly imprinted polymer (D-MIP) was developed to specifically recognize GLUT1 and hexokinase-2 (HK2) for anti-glycolytic tumor therapy, exhibiting significant inhibitory effects on cell lines and excellent biocompatibility (Figure 2C).[54] A novel FOXM1-PROTAC molecule inhibits GLUT1 expression by degrading FOXM1 protein, thereby slowing glycolytic metabolism in tumor cells and suppressing their proliferation and migration. This study demonstrates that protein degradation technology can precisely regulate tumor metabolism by targeting GLUT1 expression.[55] A nanoliposomal formulation containing the COX-2 inhibitor celecoxib and the GLUT1 inhibitor luteolin was designed for prostate cancer cells. This inhibitor mixture selectively exerts synergistic effects by inducing ROS production, downregulating GSH, and inhibiting COX-2 and GLUT1, leading to apoptosis in PC-3 cells.[56] Additionally, another team developed nanoliposomes (~100 nm) encapsulating plumbagin and genistein, which suppressed the PI3K/AKT3 signaling pathway and reduced GLUT1 transporter levels in tumor cells, thereby slowing tumor growth while maintaining favorable biosafety.[57] The amphiphilic hyaluronic acid-ceramide-dopamine (HACE-d) conjugate, incorporating phloretin (a GLUT1 inhibitor), enhances tumor targeting through both passive (enhanced permeability and retention effect) and active (HA-CD44 receptor interaction) mechanisms, representing a promising tumor-targeting and penetrable nanosystem (Figure 2D).[58] Paclitaxel was developed by functionalizing SLNs (PTX-SLNs) loaded with paclitaxel using N-acetyl-d-glucosamine (GLcNAc) to reduce the proliferation, growth, and metastasis rates of ovarian cancer cells overexpressing GLUT1. These particles exhibited relatively large size and distribution while maintaining hemocompatibility (Figure 2E).[59]

Metal-ion-based nanomaterials, owing to their unique physicochemical properties and broad biological activities, have become a critical area of research in nanomedicine, demonstrating significant potential in cancer therapy. Metal ions, such as zinc (Zn^{2+}), copper (Cu^{2+}), and iron (Fe^{2+}/Fe^{3+}), are key components in the design of novel nanomaterials due to their biocompatibility, tunability, and ability to interact with biomolecules. These metal ions can inhibit tumor cell growth through direct biochemical interactions and synergize with other nanomaterials to enhance therapeutic efficacy (Figure 3). For example, a "nano-energy disruptor" capable of specifically disrupting Zn(II) homeostasis in melanoma cells can induce Zn(II) overload, suppress glycolysis, and trigger GLUT1 consumption for energy depletion-based tumor therapy, while having negligible effects on Zn(II) homeostasis and energy metabolism in normal cells (Figure 3A).[60] Constructed CS/NPs leverage coordinated Zn^{2+} to disrupt glycolysis and downregulate GLUT1 expression, depleting energy in cancer cells. Additionally, Zn^{2+} activates the AMPK pathway, leading to PD-L1 protein degradation and sensitizing CRC cells to immunotherapy, with tumor-specific targeting and reduced systemic toxicity (Figure 3B).[61] Engineered AuNPs@anti-miR-21/siGlut1 complexes utilize nucleic acid-modified gold nanoparticles (AuNPs) to deliver small interfering RNA (siRNA) targeting Glut1 via microRNA 21 (miR-21)-mediated strand displacement for starvation therapy in lung cancer. Overexpression of miR-21 triggers toehold-mediated strand displacement, releasing siRNA to knock down Glut1 in cancer cells, accelerating intracellular glucose depletion and promoting cancer cell starvation (Figure 3C).[62] Additionally, researchers synthesized polymers conjugated with folate-modified AuNPs, exhibiting excellent biocompatibility and tumor-targeting activity. These act on key glycolytic enzymes, including GLUT1, disrupting mitochondrial structure and function in tumor cells, leading to excessive oxidative stress, mitochondrial apoptosis, and metabolic inhibition (Figure 3D).[63] For cancer stem cells (CSCs), researchers developed a 50 nm

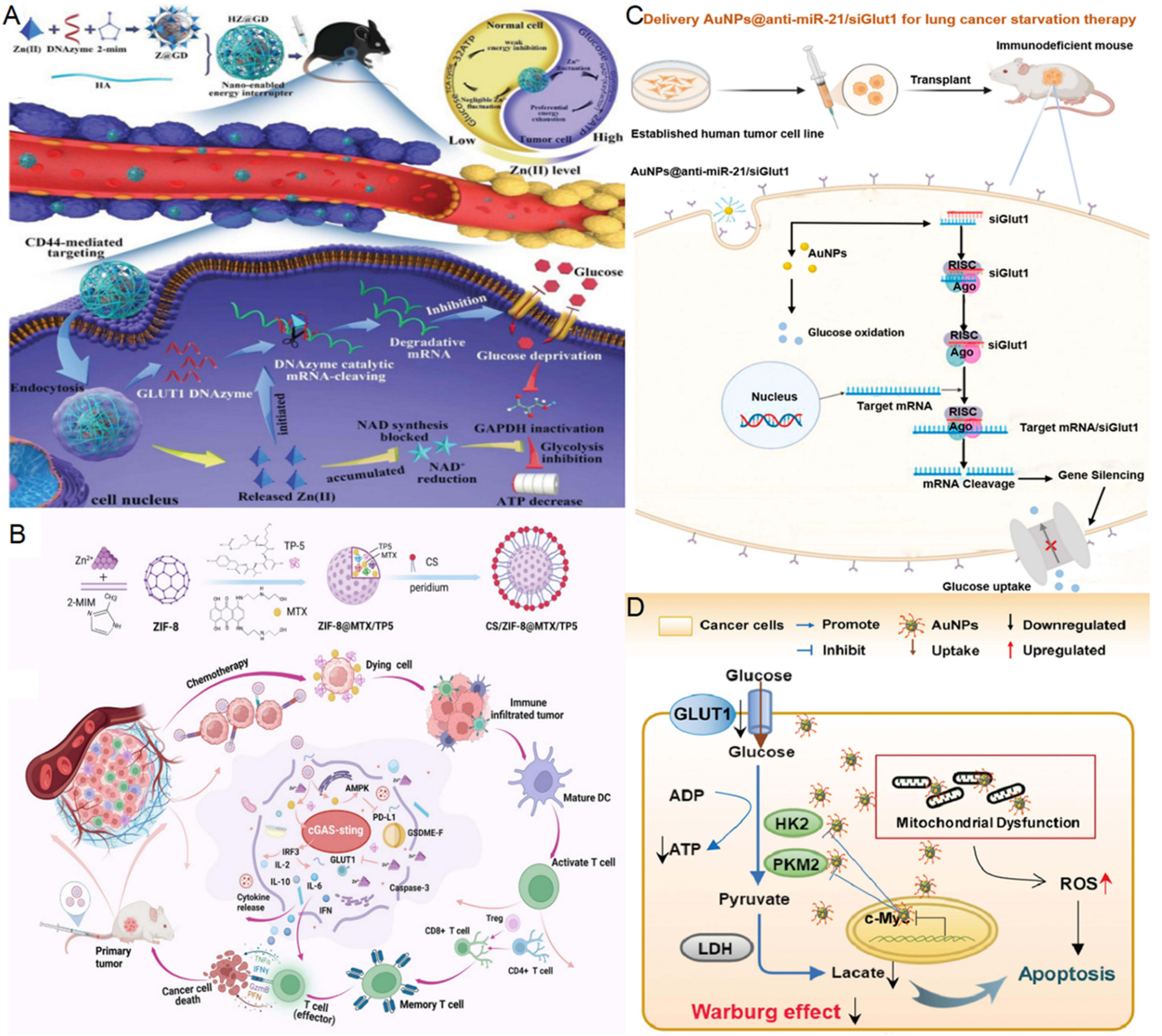


Figure 3 Metal ion-based Nanomaterials Related to GLUT1. (**A**) A "nano-energy disruptor" capable of specifically disrupting Zn(II) homeostasis. Reprinted from Wu S, Zhang K, Liang Y, et al. Nano-enabled tumor systematic energy exhaustion via zinc (II) interference mediated glycolysis inhibition and specific GLUT1 depletion. Adv Sci. 2022;9(7):e2103534. © 2021 The Authors. Advanced Science published by Wiley-VCH GmbH.[60] (**B**) CS/NPs leverage coordinated Zn2+ to disrupt glycolysis and downregulate GLUT1 expression. Reprinted from Zhang X, Tian H, Chen Y, et al. A metal-organic nanoframework for efficient colorectal cancer immunotherapy by the cGAS-STING pathway activation and immune checkpoint blockade. J Nanobiotechnol. 2024;22(1):592. Creative Commons.[61] (**C**) Engineered AuNPs@anti-miR-21/siGlut1 complexes. Reprinted from Li J, Yu J, Fang Q, Du Y, Zhang X. Gold nanoparticle delivery of Glut1 SiRNA facilitates glucose starvation therapy in lung cancer. Chembiochem. 2024;25(12):e202400239. Copyright © 2024 Wiley-VCH GmbH.[62] (**D**) Polymers conjugated with folate-modified AuNPs. Reprinted from Acta Biomater. Volume 158. Sun L, Liu Y, Yang N, et al. Gold nanoparticles inhibit tumor growth via targeting the Warburg effect in a c-Myc-dependent way. 583–598. Copyright © 2023. Published by Elsevier Ltd.[63]

nanocarrier comprising AuNPs and siRNA, targeting GLUT1 overexpressed on the CSC surface via selective glucose ligand recognition. This system achieved effective tumor suppression both in vitro and in vivo.[64]

Additionally, inhibitors targeting the respiratory or metabolic chain can alter GLUT1 expression or suppress its function due to pathway interference.[65] Hypoxia-inducible factor-1 (HIF-1) is frequently upregulated in the hypoxic microenvironment of solid tumors. Suppression of HIF-1α can reduce lactate production at its source, subsequently downregulating glycolysis-related enzymes, including GLUT1 and lactate dehydrogenase A (LDHA). Therefore, some researchers have focused on inhibiting lactate metabolism via HIF-1 while simultaneously suppressing GLUT1 expression (Figure 4). For instance, a light-responsive aptamer-modified nanoparticle, labeled Mn-D@BPFe-A, was designed for lactate oxidation and cancer phototherapy. Mn-D@BPFe-A was constructed by assembling functional complexes with

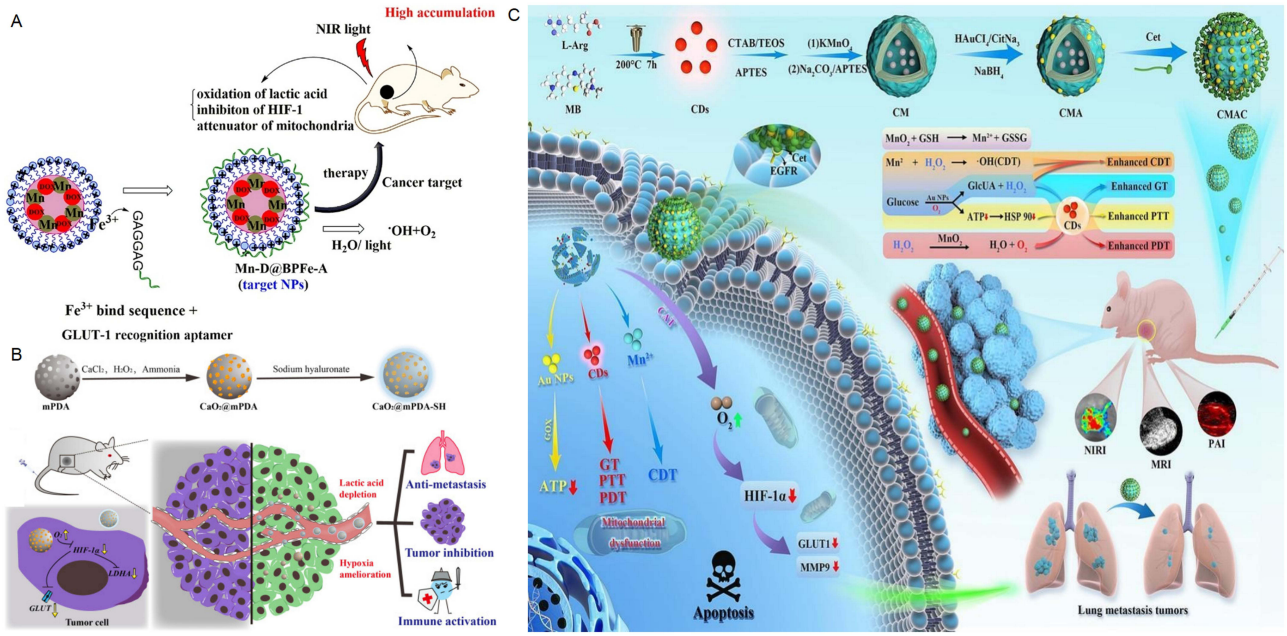


Figure 4 GLUT1-related Nanomaterials Targeting the Respiratory chain or Metabolic chain. (**A**) Silver nanoparticles (AgNPs), widely used as antibacterial agents, are also effective inhibitors of HIF-1. Repritned from Yang T, Yao Q, Cao F, Liu Q, Liu B, Wang XH. Silver nanoparticles inhibit the function of hypoxia-inducible factor-1 and target genes: insight into the cytotoxicity and antiangiogenesis. *Int J Nanomed*. 2016;11:6679–6692. Creative Commons. [67] (**B**) Hyaluronic acid-modified mesoporous polydopamine nanoparticles loaded with CaO2 (designated as CaO_2@mPDA-SH). Reprinted from Ruan S, Yin W, Chang J, et al. Acidic and hypoxic tumor microenvironment regulation by CaO(2)-loaded polydopamine nanoparticles. J Nanobiotechnol. 2022;20(1):544. Creative Commons.[68] (**C**) A tumor microenvironment (TME)-responsive carbon dot-based (CDs) nanoplatform, CDs-MnO_2-Au-Cet (CMAC). Reprinted from *J Control Release*. Volume 376. Ren G, Wang X, Yang Z, et al. TME-responsive nanoplatform for multimodal imaging-guided synergistic precision therapy of esophageal cancer via inhibiting HIF-1α signal pathway. 518–529. Copyright © 2024 Elsevier B.V.[69]

BSA, followed by surface metal coordination and Fe^{3+} recognition involving GAG sequences. Upon phototherapy, Mn-D@BPFe-A nanoparticles undergo oxidation, converting lactate into pyruvate both in vitro and in vivo. The photodriven oxidation of lactate and mitochondrial dysfunction caused by these nanoparticles inhibit tumor cells, reduce lactate levels in tumor tissues, and suppress HIF-1α and GLUT1 expression in HepG-2 cells.[66] Silver nanoparticles (AgNPs), widely used as antibacterial agents, are also effective inhibitors of HIF-1. Under hypoxic conditions or cobalt chloride treatment (a hypoxia mimic), AgNPs suppress the activation of HIF-dependent reporter gene constructs, inhibit HIF-1α protein accumulation, and downregulate endogenous target genes VEGF-A and GLUT1 (Figure 4A).[67] Hyaluronic acid-modified mesoporous polydopamine nanoparticles loaded with CaO_2 (designated as CaO_2@mPDA-SH) gradually accumulate at tumor sites. When exposed to acidic microenvironments, CaO_2 effectively consumes lactate while generating oxygen. This process downregulates HIF-1α, reducing lactate production at its source, thereby suppressing glycolysis-related enzymes such as GLUT1 and LDHA. Consequently, it remodels the acidic and hypoxic tumor microenvironment, inhibiting tumor progression, promoting immune activation, and preventing metastasis and angiogenesis (Figure 4B).[68] In prostate cancer, a tumor microenvironment (TME)-responsive carbon dot-based (CDs) nanoplatform, CDs-MnO_2-Au-Cet (CMAC), was developed. It significantly downregulates HIF-1α and its downstream targets GLUT1 and MMP9. Designed for multimodal imaging-guided precision therapy, it demonstrates excellent antitumor growth and metastasis capabilities with good biocompatibility (Figure 4C).[69] Multi-responsive silk fibroin nanoparticles (SFN) were co-loaded with the chemotherapeutic drug doxorubicin (DOX) and PX478 (a hypoxia-inducible factor inhibitor), with PX478 functionalized using folic acid (FA). This combination actively targets tumor cells and triggers PX478 release, suppressing hypoxia-inducible factor (HIF) genes and associated downstream resistance-related targets, including GLUT1, to achieve an effective synergistic chemotherapy strategy.[70] Paclitaxel and BAY-876 combined with human serum albumin nanoparticles (HPB) were integrated with Escherichia coli Nissle 1917 (EcN) to construct engineered biohybrid biomaterials named EcN@HPB. Leveraging the inherent tumor tropism of EcN, EcN@HPB actively targets tumor sites and competitively depletes glucose through bacterial respiration. Simultaneously, BAY-876 is internalized with HPB nanoparticles, further inhibiting glucose uptake by suppressing GLUT1. The reduced glucose bioavailability in tumor

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cells activates macropinocytosis in an AMPK-dependent manner, enhancing nanoparticle uptake and boosting the therapeutic efficacy of paclitaxel.[71] Therefore, with the development of research, it can be observed that most therapeutic drugs have shifted from targeting a single target to simultaneously targeting multiple targets on a certain pathway or multiple related pathways to enhance the therapeutic effect.

Targeting GLUT1 to Enhance the Tissue Selectivity and Transmembrane Efficacy of Nanodrugs

GLUT1, a critical membrane receptor, is highly expressed in tumor cells due to their metabolism closely linked to the Warburg effect, particularly during active tumor growth, with expression levels significantly exceeding those in normal cells. This selective expression characteristic provides a crucial target for precise tumor localization, leading to extensive research employing GLUT1 for targeted tumor diagnosis and therapy. Furthermore, GLUT1 functions not only as a molecular marker but also as a glucose transporter with well-defined transmembrane transport capabilities. Leveraging this feature, certain nanomaterials have been designed to enter tumor cells via GLUT1-mediated transport mechanisms (Figure 5). During this process, nanomaterials exploit GLUT1's efficient transport capability to cross the cell membrane, significantly improving targeted drug delivery efficiency and enhancing intracellular activity. This strategy fully capitalizes on GLUT1's dual functionality: serving as a specific targeting marker for tumor cells and enabling efficient transmembrane drug delivery,

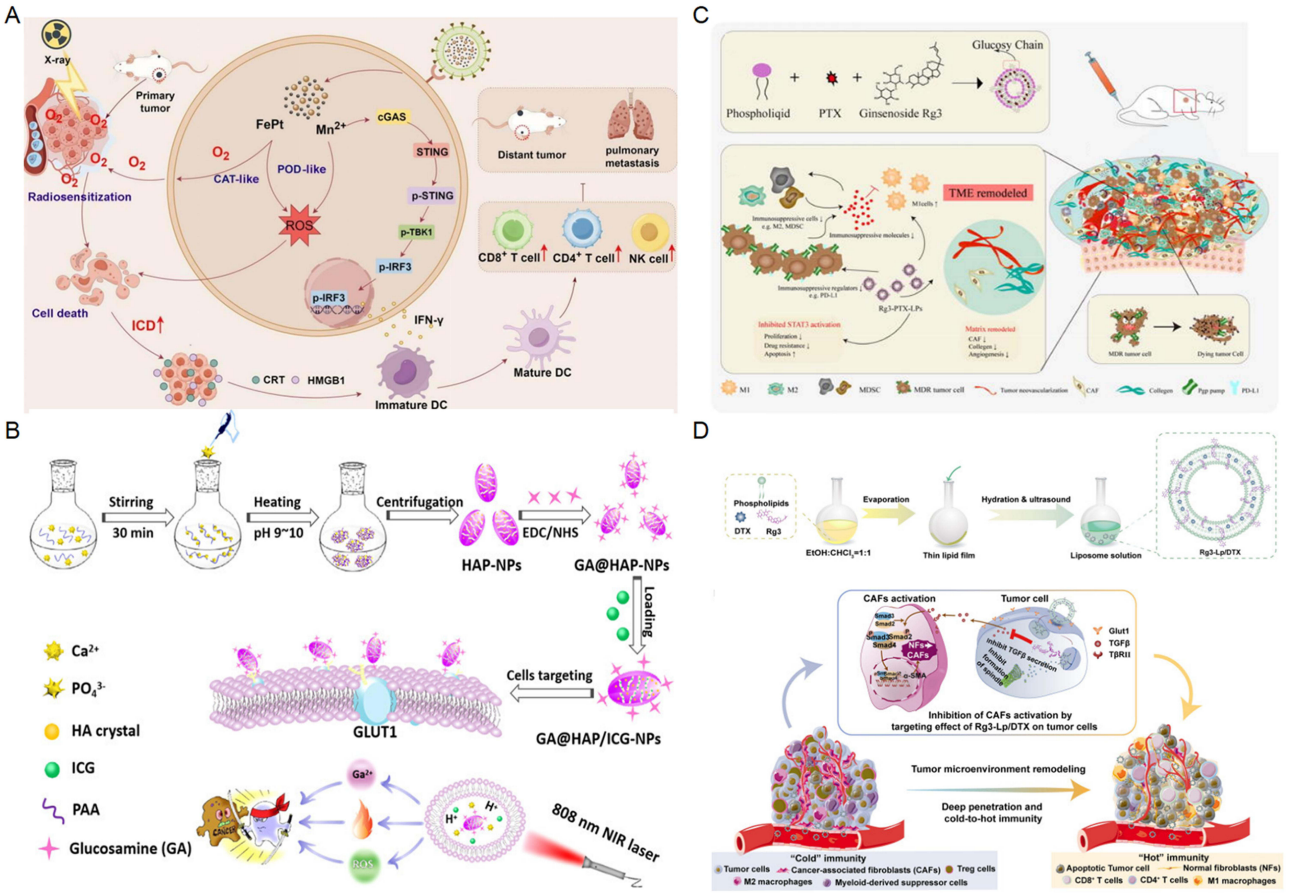

Figure 5 Related Nanomaterials for GLUT1-mediated Transport Mechanisms. (**A**) A self-assembled glutathione (GSH)-responsive system with tumor accumulation ability.[74] Reprinted from Guo Q, Li C, Zhou W, et al. GLUT1-mediated effective anti-miRNA21 pompon for cancer therapy. *Acta pharmaceutica Sinica B*. 2019;9(4):832–842. Creative Commons. (**B**) Amphiphilic nanoparticles based on hydrolyzed galactomannan (hGM). Reprinted with permission from Cheng X, Xu Y, Zhang Y, et al. Glucose-targeted hydroxyapatite/indocyanine green hybrid nanoparticles for collaborative tumor therapy. ACS Appl Mater Interfaces. 2021;13(31):37665–37679. Copyright © 2021 American Chemical Society.[76] (**C**)Multifunctional docetaxel (DTX)-loaded Rg3 liposome (Rg3-Lp/DTX). Reprinted from Xia J, Zhang S, Zhang R, et al. Targeting therapy and tumor microenvironment remodeling of triple-negative breast cancer by ginsenoside Rg3 based liposomes. *J Nanobiotechnol*. 2022;20(1):414. Creative Commons.[80] (**D**) Novel alkyl glycoside-modified dihydroartemisinin liposome. Reprinted from Shen S, Du M, Liu Q, et al. Development of GLUT1-targeting alkyl glucoside-modified dihydroartemisinin liposomes for cancer therapy. *Nanoscale*. 2020;12(42):21901–21912. © Royal Society of Chemistry.[81]

thereby opening new avenues for precision medicine in cancer treatment. For instance, a novel method called Metal Vapor Synthesis (MVS) was used to prepare glucose-coated superparamagnetic iron oxide nanoparticles (SPIONs). Cell uptake experiments using specific GLUT1 inhibitors pretreated on cancer cells demonstrated that all inhibitors reduced the cellular uptake of Glc-SPIONs, confirming GLUT1's role in tumor internalization of this nanomaterial.[72] An oxygen self-supplying nanoradiosensitizer targeting immunogenic cell death (ICD) and the cGAS-STING signaling pathway effectively targets GLUT1 receptors in TNBC via ALFM, enabling efficient tumor cell entry. It modulates cellular ROS levels and activates related pathways to achieve anti-tumor effects and enhance radiotherapy and immunotherapy efficacy.[73] A self-assembled glutathione (GSH)-responsive system with tumor accumulation ability was developed using rolling circle transcription (RCT) to create novel nanospheres carrying millions of anti-miR21 sequences. GSH-responsive cationic polymer polyethylenimine (pOEI) was synthesized to protect the nanospheres from degradation by Dicer or other RNases in normal cells. This nanomaterial utilized dehydroascorbic acid (DHA) molecules to target glucose transporter 1 (GLUT1) as the localization marker (Figure 5A).[74] The active component of ginseng, 20(S)-Protopanaxadiol (PPD), and cannabidiol (CBD) derived from cannabis were co-loaded into liposomes, with glucose residues anchored on the surface as GLUT1 ligands. These liposomes exploit GLUT1's high expression on tumor surfaces for localization and deliver cytotoxic effects on tumor cells.[75] Nanoscale hydroxyapatite, a promising drug carrier, faces limitations in vivo due to a lack of active functional groups. Researchers combined it with polyacrylic acid (PAA) and indocyanine green (ICG) to develop a photodynamic organic-inorganic hybrid nanosystem. This nanosystem was further modified with glucose to create a targeted nanosystem (GA@HAP/ICG-NPs). Experiments confirmed that glucose-coated particles significantly enhanced GLUT1-mediated endocytosis, resulting in a marked increase in intracellular ICG concentration.[76] A glycosylated poly (amidoamine)/celastrol (PAMAM/Cel) complex was developed, which demonstrated specific uptake in GLUT1-overexpressing tumor cells and mitochondrial accumulation under hypoxic conditions. When combined with near-infrared (NIR) laser irradiation, it utilized a synergistic chemo-thermal effect, leading to enhanced cytotoxicity, apoptosis induction, and metastasis inhibition, making it suitable for hypoxia-activated, mitochondria-specific drug delivery and chemotherapy to suppress tumor growth and metastasis.[77] In pediatric patient-derived sarcomas, amphiphilic nanoparticles based on hydrolyzed galactomannan (hGM) were designed. The study demonstrated their potential to target GLUT1-expressing tumors and selectively deliver anticancer drugs (Figure 5B).[76] Glucose-conjugated camptothecin-loaded glutenin nanoparticles (Glu-CPT-glutenin NPs) were developed for breast cancer treatment. These nanoparticles delivered camptothecin to MCF-7 cells via GLUT1 transporters.[78] Ginsenoside Rg3 was formulated into a unique Rg3-based liposome loaded with paclitaxel (Rg3-PTX-LPs) using a thin-film hydration method. Rg3-PTX-LPs selectively accumulated in MCF7/T cancer cells and the tumor microenvironment (TME) by targeting GLUT1.[79] Another study on ginsenoside Rg3 developed multifunctional docetaxel (DTX)-loaded Rg3 liposomes (Rg3-Lp /DTX). By leveraging the interaction between the exposed glycosyl portion of Rg3 on the liposome surface and GLUT1 overexpressed in tumor cells, Rg3-Lp/DTX demonstrated preferential uptake by 4T1 cells and enhanced accumulation at tumor sites, leading to effective cytotoxicity (Figure 5C).[80] In addition to ginsenoside Rg3, artemisinin, another potent active ingredient, has been optimized. Using GLUT1 as a target, researchers developed novel alkyl glycoside-modified dihydroartemisinin liposomes, with the glucose moiety of the alkyl glycoside serving as the targeting head. Both in vitro and in vivo studies demonstrated enhanced targeting efficacy to human hepatocellular carcinoma cells (HepG2) and tumors due to the glucose moiety on the liposomes (Figure 5D).[81] In gastric cancer, researchers developed a "Sweet Tooth"-oriented SN38 prodrug delivery nanoplatform (Glu-SNP) by conjugating 7-ethyl-10-hydroxycamptothecin (SN38) to biocompatible polylactic acid (PLA) with an optimal polymerization degree (n = 44), synthesizing the SN38-derived prodrug (PLA-SN38). The PLA-SN38 conjugate was further assembled with glycosylated amphiphilic lipids to form glucosamine-modified nanoparticles (Glu-SNP). Glu-SNP exhibited potent antitumor efficacy both in vitro and in vivo by enhancing cancer cell-specific targeting associated with GLUT1 overexpression, offering a promising approach for gastric cancer treatment.[82]

Additionally, the high expression of GLUT1 in tumors is considered a promising biological target in tumor imaging and imaging enhancement technologies. Several researchers have designed GLUT1-targeted nanomaterials to enhance tumor imaging quality and detection sensitivity. These nanomaterials can precisely label tumor tissues by recognizing the high expression of GLUT1 on the surface of tumor cells, thereby improving lesion resolution and localization accuracy during imaging (Figure 6). Firstly, some photosensitizers utilize GLUT1 to successfully target and enhance both localization efficiency and imaging performance via photothermal effects. For example, the evaluation of PcGal16, a new, efficient third-generation

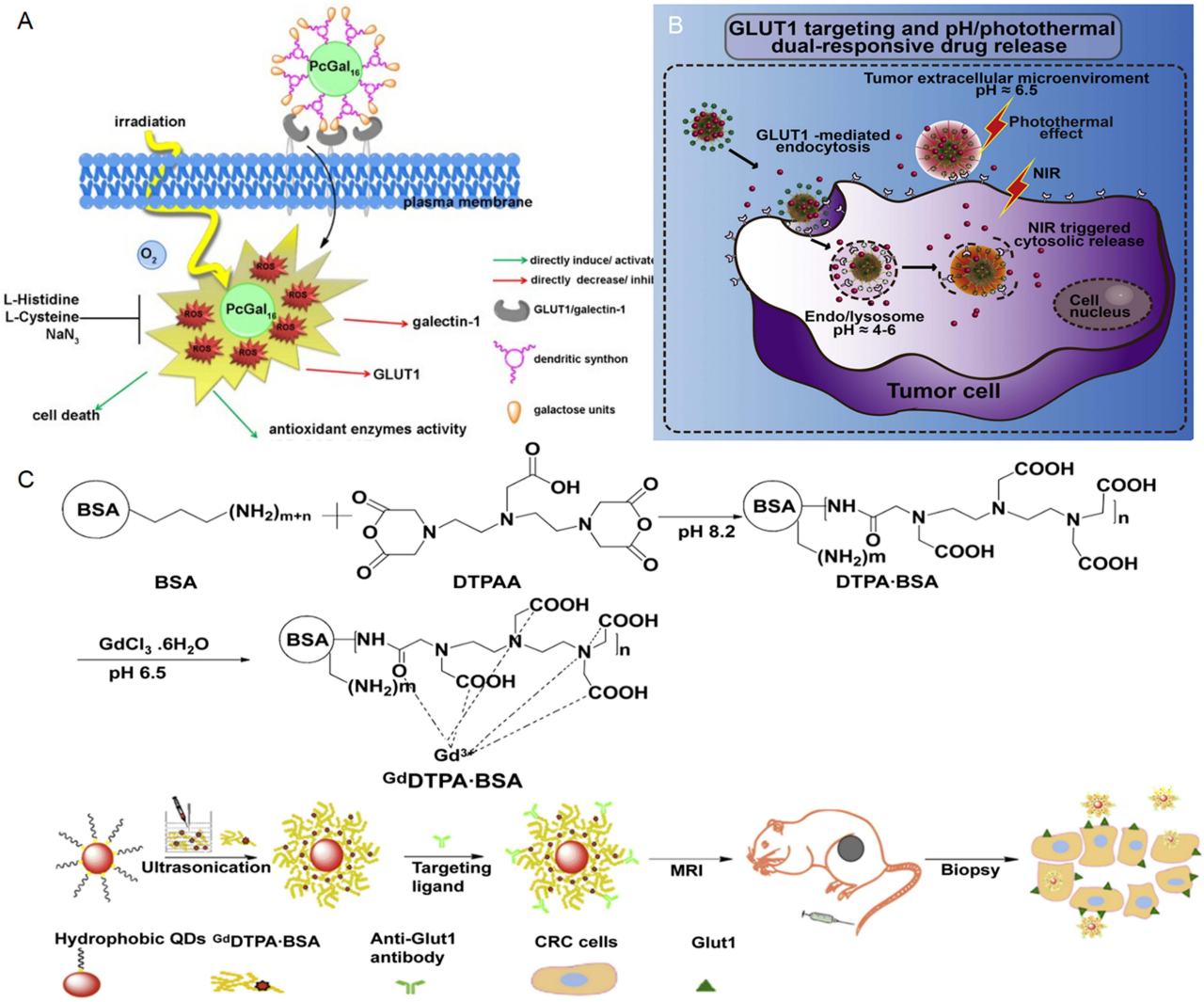

Figure 6 GLUT1-related Nanomaterials for tumor Imaging and Imaging Enhancement Technologies. (**A**) A new, efficient third-generation photosensitizer, PcGal16. Reprinted from Pereira PM, Silva S, Cavaleiro JA, Ribeiro CA, Tomé JP, Fernandes R. Galactodendritic phthalocyanine targets carbohydrate-binding proteins enhancing photodynamic therapy. *PLoS One*. 2014;9(4):e95529. Creative Commons.[83] (**B**) Nitrogen-doped CDs (G-CDs). Reprinted from *J Control Release*. Volume 317. Li Y, Hong W, Zhang H, et al. Photothermally triggered cytosolic drug delivery of glucose functionalized polydopamine nanoparticles in response to tumor microenvironment for the GLUT1-targeting chemo-phototherapy. 232–245. Copyright © 2020. Published by Elsevier B.V.[84] (**C**) A unique cell-targeted paramagnetic-fluorescent dual-signal molecular nanoprobe was constructed by coupling DTPA-Gd with BSA (GdDTPA·BSA). Reprinted from *Biomaterials*. Volume 48. Xing X, Zhang B, Wang X, Liu F, Shi D, Cheng Y. An "imaging-biopsy" strategy for colorectal tumor reconfirmation by multipurpose paramagnetic quantum dots. 16–25. Copyright © 2015 Elsevier Ltd.[86]

photosensitizer with a carbohydrate shell composed of 16 galactose units, induces oxidative stress upon photoactivation, leading to changes in the levels of galectin-1 and GLUT1 proteins. Moreover, siRNA-mediated knockdown of galectin-1 and GLUT1 reduces the cellular uptake and phototoxicity of PcGal16, indicating that GLUT1 is a critical binding receptor for this nanomaterial (Figure 6A).[83] Carbon dots (CDs) are multifunctional nanomaterials that, due to their excellent photoluminescence, biocompatibility, and chemical stability, are considered ideal candidates for applications in biological imaging, drug delivery, sensing, and optoelectronics. The incorporation of nitrogen enhances the fluorescence of CDs, alters their electronic properties, and improves their multifunctionality. Therefore, researchers developed a method for synthesizing nitrogen-doped CDs (G-CDs) using glucose and ethanolamine as precursors in a Maillard reaction. After pre-incubation with GLUT1 inhibitors, cellular uptake of G-CDs was reduced by up to 25%. These characteristics make G-CDs suitable for in vitro biological imaging and photothermal therapy in prostate cancer cells.[69] A nanomaterial using polydopamine (PDA) nanoparticles (NPs) as photothermal agents and drug carriers, with a glucose-functionalized ligand as a GLUT1 targeting moiety and the anticancer drug bortezomib (BTZ) conjugated to PDA NPs via pH-dependent catechol bonds, was developed for treating breast cancer in mice. This material

efficiently accumulates in tumor sites and localizes in tumor cell lysosomes. It responds to the tumor microenvironment, lysosomal pH, and near-infrared (NIR) irradiation, facilitating BTZ release to achieve NIR-triggered photothermal and chemotherapy integration, synergistically ablating tumors (Figure 6B).[84] Furthermore, traditional magnetic resonance imaging (MRI) is enhanced by the incorporation of metal particles in nanomaterials and their GLUT1 targeting, which improves targeting ability and imaging effectiveness. For example, γ-Fe_2O_3 nanoparticles coated with DMSA and modified with 2-DG were prepared to create γ-Fe_2O_3@DMSA-DG NPs. Experiments showed that treatment with γ-Fe_2O_3@DMSA-DG NPs significantly decreased MRI T2 signal intensity in MDA-MB-231 cells, and their effects were inhibited by competition with GLUT1 antibodies. This indicates that γ-Fe_2O_3@DMSA-DG NPs target tumors via GLUT1 and can be used as MRI-targeted tumor agents to enhance tumor imaging.[85] A unique cell-targeted paramagnetic-fluorescent dual-signal molecular nanoprobe was constructed by coupling DTPA-Gd with BSA (GdDTPA·BSA) and targeting GLUT1 using polyclonal antibodies, for in vivo magnetic resonance imaging (MRI) diagnosis and subsequent biopsy in CRC (Figure 6C).[86] This nanoprobe effectively binds to GLUT1 on the tumor cell surface, enhancing tumor detection sensitivity through magnetic resonance imaging (MRI). Overall, GLUT1-targeted nanomaterials have demonstrated great potential in tumor imaging, drug delivery, and integrated diagnosis and therapy. These nanomaterials, through their specific recognition of GLUT1, enhance the accuracy of tumor imaging while facilitating effective drug penetration into tumor cell membranes, thereby improving therapeutic outcomes.

Targeting GLUT1 Enhances the Ability of Nanomaterials to Cross the Blood-Brain Barrier

The blood-brain barrier (BBB), as a highly selective barrier, protects brain tissue from harmful substances while significantly limiting the effective delivery of drugs to the brain.[87] The BBB strictly regulates the transport of substances between the blood and brain parenchyma, preventing most conventional drugs from reaching the therapeutic concentrations needed in the brain, thereby limiting the effectiveness of treatments for brain diseases. On the surface of the BBB, highly expressed transporters and receptors, such as GLUT1, not only supply the brain with essential energy and nutrients but also show great potential in brain-targeted drug delivery. Receptor-mediated transcytosis (RMT) and carrier-mediated transport (CMT) are key mechanisms for drug penetration across the BBB.[4] By combining nanomaterials with RMT and CMT, the BBB penetration efficiency of drugs can be effectively improved, enabling systemic brain-targeted delivery (Figure 7). This strategy shows significant advantages in treating invasive brain tumors, such as glioblastoma. The high invasiveness and resistance of glioblastoma to conventional therapies make it a major challenge in brain tumor treatment. Although surgery can remove the primary tumor, infiltrating tumor cells in normal brain tissue are protected by the BBB, making them difficult to eliminate completely and leading to tumor recurrence (Figure 7A).[88] During the development of brain tumors, significant changes occur in the structure and function of the BBB, forming the blood-brain tumor barrier (BTB).[89] The BTB has higher permeability than the normal BBB but exhibits greater heterogeneity, which still poses a challenge for drug delivery.[90] Studies have found that changes in the permeability of the BTB are closely related to various molecular mechanisms, including changes in the expression of transmembrane transporters like GLUT1. This change not only provides ample energy support for tumor growth but also offers a unique opportunity for GLUT1-targeted nanomaterials to cross the BBB or BTB.[91] For example, glucose uronate-functionalized iron oxide nanoparticles (IONPs), due to their extremely small size, can successfully cross the BBB and significantly enhance GLUT1-mediated transcytosis to reach tumors, thereby achieving more efficient targeted delivery. Studies have shown that this effect is more pronounced under mild hypoglycemia induction, and with this metabolically driven active targeting strategy, the functionalized IONPs not only demonstrate unprecedented efficacy in targeting glioblastoma but are also designed as mediators for magnetic hyperthermia (MH). Its dual-functional characteristics have been validated in preclinical studies, where intravenous injection enabled MRI tracking and subsequent MH treatment.[92] Shao et al, developed dehydroascorbic acid-modified intracellular microenvironment-responsive release nanodevices for high integrity in blood, specific binding with tumor cells, and drug release triggered by intracellular glutathione in tumor cells.[93] Micelles based on dehydroascorbic acid derivatives have been developed for the treatment of highly invasive malignant gliomas and have shown excellent efficacy (Figure 7B).[93] These micelles can achieve "unidirectional" continuous accumulation within tumor cells, highlighting the potential for efficient drug delivery to central nervous system cancer

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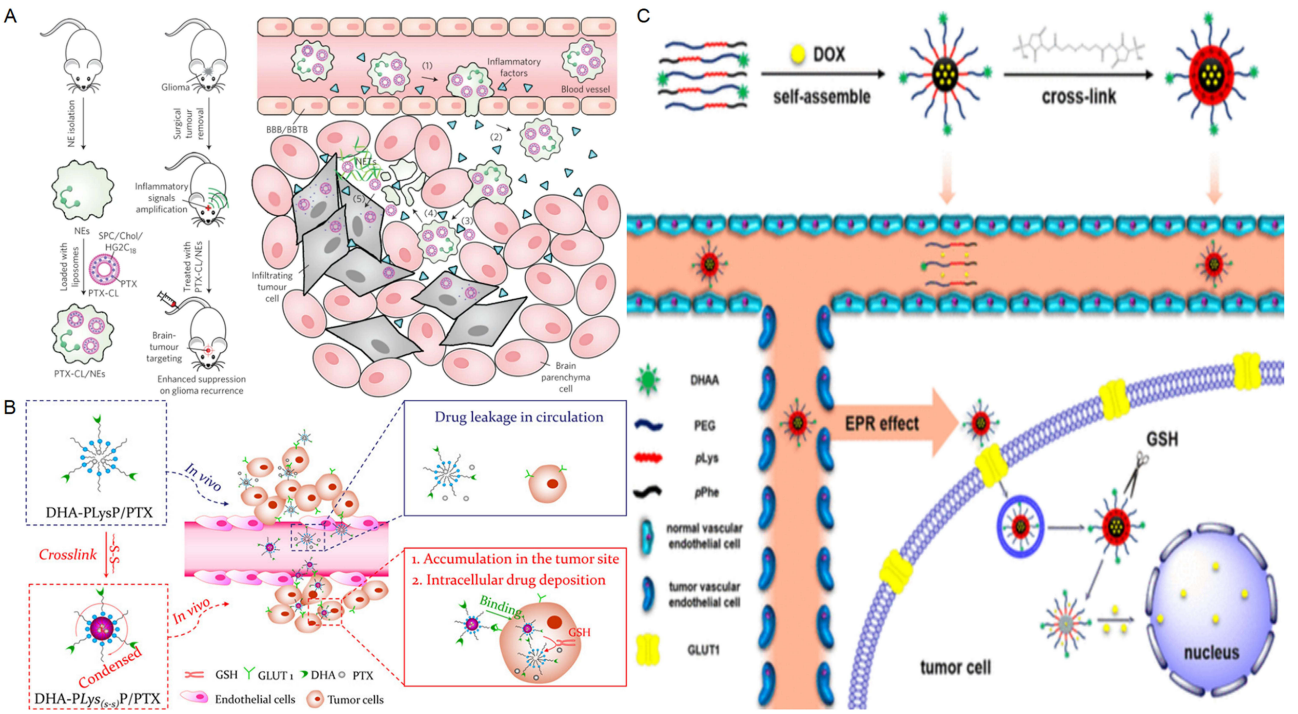

Figure 7 GLUT1-related Nanomaterials for the BBB Penetration. (**A**) Combining nanomaterials with RMT and CMT. Reprinted from Xue J, Zhao Z, Zhang L, et al. Neutrophil-mediated anticancer drug delivery for suppression of postoperative malignant glioma recurrence. *Nature Nanotechnol*. 2017;12(7):692–700. Copyright © 2017 Springer Nature.[88] (**B**) Dehydroascorbic acid-modified intracellular microenvironment-responsive release nanodevices. Reprinted with permission from Shao K, Ding N, Huang S, et al. Smart nanodevice combined tumor-specific vector with cellular microenvironment-triggered property for highly effective antiglioma therapy. *ACS Nano*. 2014;8 (2):1191–1203. Copyright © 2014 American Chemical Society.[93] (**C**) Pluronic P105 polymeric micelles. Reprinted with permission from Guo Y, Zhang Y, Li J, et al. Cell microenvironment-controlled antitumor drug releasing-nanomicelles for GLUT1-targeting hepatocellular carcinoma therapy. *ACS Appl Mater Interfaces*. 2015;7(9):5444–5453. Copyright © 2015 American Chemical Society.[94]

sites via GLUT1-mediated transport. Similarly, researchers designed Pluronic P105 polymeric micelles, which are derivatized to target both GLUT1 and folate receptors while encapsulating the chemotherapy drug doxorubicin. These micelles perform excellently in enhancing BBB penetration and accumulation of drugs in glioma cells. In animal experiments, intravenous injection of these micelles significantly inhibited tumor growth, demonstrating their promising potential for brain tumor treatment (Figure 7C).[94] Due to the complex environment of the blood-brain barrier, in recent years, another group of researchers have used a dual-targeting strategy, which has become a more preferred approach. The 2-deoxy-d-glucose-functionalized poly (ethylene glycol)-co-poly(trimethylene carbonate) nanoparticles further optimize the dual-targeting strategy for GLUT1. The core of this nanoparticle design is to utilize GLUT-mediated transcytosis to enhance BBB penetration efficiency, while also using GLUT-mediated endocytosis to increase drug accumulation in gliomas. This dual-targeting mechanism effectively overcomes the barriers to drug delivery to the brain, significantly improving drug delivery efficiency and enhancing therapeutic outcomes.[95] Researchers have successfully designed and developed an innovative cascade reaction nanoparticle capsule delivery system, based on the tumor microenvironment and the abundant reactive oxygen species (ROS) and glutathione (GSH) in the cytoplasm. This novel nanoparticle capsule system is surface-loaded with the glycolysis inhibitor 2-deoxy-D-glucose (2-DG), and also contains conjugates of anti-VEGFR2 monoclonal antibody (aV) and CPT1C siRNA (siCPT1C), which are stably linked via disulfide bond crosslinkers (aV-siCPT1C). This novel nanoparticle capsule system is surface-loaded with the glycolysis inhibitor 2-deoxy-D-glucose (2-DG), and contains conjugates of anti-VEGFR2 monoclonal antibody (aV) and CPT1C siRNA (siCPT1C), which are stably linked through disulfide crosslinkers (aV-siCPT1C). The nanoparticle capsules take advantage of the high expression of GLUT1 on the blood-brain barrier (BBB) and GBM cells, efficiently penetrating the BBB and precisely targeting GBM cells. Through combination delivery, the nanoparticle capsules not only inhibit two major metabolic pathways—glycolysis and fatty acid oxidation (FAO)—in GBM cells, but also significantly reduce angiogenesis, providing a dual strike to the tumor's "internal and external energy supply"[96] These

studies demonstrate the immense potential of GLUT1-based nanoparticle strategies in brain tumor treatment, providing valuable scientific foundation and technical support for the development of new generations of targeted therapies.

GLUT1-Related Nanomedicines and Tumor Immunotherapy

In recent years, tumor immunotherapy has become a revolutionary breakthrough in cancer treatment, owing to its unique mechanism of stimulating the body's immune system to fight tumors. However, the high complexity and immunosuppressive nature of the tumor microenvironment (TME) pose significant challenges to the effectiveness of traditional immunotherapy. Overexpression of GLUT1 not only plays a key role in the energy metabolism of tumor cells but also influences the metabolic activity and functional status of immune cells,[97–99] as well as antibody production.[100] Therefore, nanomedicines targeting GLUT1 have shown great potential in tumor immunotherapy (Figure 8). For instance, GLUT1 expression can promote the prevention of lactate efflux in tumor glycolysis, thereby significantly alleviating lactate-driven immunosuppressive tumor microenvironment (ITM) by reducing tumor-associated macrophages (TAMs) and regulatory T cells (Tregs). Simultaneously, studies have shown that the inflammatory cytokine IFN-γ, produced during immune activation, upregulates the immune checkpoint programmed death ligand 1 (PD-L1) in tumor cells and TAMs, exacerbating immune escape. Consequently, an injectable thermogel loaded with GLUT1 inhibitor BAY-876 and PD-1/PD-L1 blockade agent BMS-1 (Gel@B-B) has been developed for dual modulation of GBM metabolism and immunity (Figure 8A).[101] Bio-synthesized extracellular vesicles (EVs) engineered with ICAM-1 ligands and loaded with miR-146a and Glut1 impede tumor progression and promote a phenotypic shift in immune cells toward a more pro-inflammatory state. This seems to facilitate the infiltration of tumor-targeting T cells, correlating with reduced tumor size and metastatic burden.[102] Regarding dendritic cells (DC), we show that GLUT1 on DCs is a reliable target for antigen delivery, thus, a multifunctional antigen delivery strategy using glucosylated nanovaccines has been developed for DC-targeted antigen delivery and tumor immunotherapy. This novel nanovaccine efficiently binds GLUT1 through glucosylation, significantly enhancing its accumulation in lymph nodes and accelerating antigen delivery and processing within DCs. This novel nanovaccine efficiently binds to GLUT1 through glucose modification, significantly enhancing its accumulation in lymph nodes and accelerating antigen delivery and processing within DCs. Further studies revealed that glucose-modified ovalbumin-loaded nanovaccines effectively promote DC maturation and

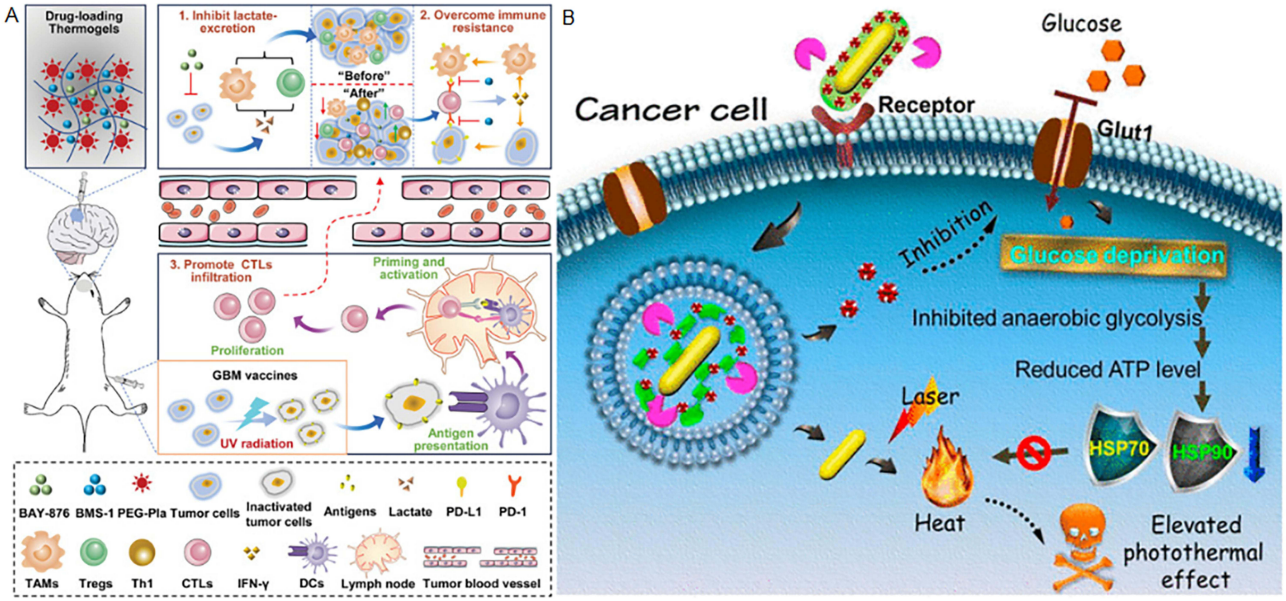

Figure 8 GLUT1-related Nanomaterials for tumor Immunotherapy. (**A**) An injectable thermogel loaded with GLUT1 inhibitor BAY-876 and PD-1/PD-L1 blockade agent BMS-1 (Gel@B-B). Reprinted from Li T, Xu D, Ruan Z, et al. Metabolism/immunity dual-regulation thermogels potentiating immunotherapy of glioblastoma through lactate-excretion inhibition and PD-1/PD-L1 blockade. Adv Sci. 2024;11(18):e2310163. © 2024 The Authors. Advanced Science published by Wiley-VCH GmbH.[101] (**B**) Plasma gold nanorods (GNR/HA-DC) targeting CD44, incorporating hyaluronic acid (HA), diclofenac (DC), and a small-molecule GLUT1 inhibitor. Reprinted with permission from Chen W-H, Luo G-F, Lei Q, et al. Overcoming the heat endurance of tumor cells by interfering with the anaerobic glycolysis metabolism for improved photothermal therapy. ACS Nano. 2017;11(2):1419–1431. Copyright © 2017 American Chemical Society.[104]

antigen presentation, thereby eliciting robust anti-tumor immune responses and demonstrating significant preventive and therapeutic effects against ovalbumin-expressing melanoma. Immunological experiments in animal models depleted of DCs and macrophages further confirmed that the efficacy of glucose-modified nanovaccines is primarily dependent on DC functionality.[103] Regarding immune cell modulators, researchers developed plasma gold nanorods (GNR/HA-DC) targeting CD44, incorporating hyaluronic acid (HA), diclofenac (DC), and a small-molecule GLUT1 inhibitor. Upon specific targeting of CD44, sequential time-dependent DC release is achieved by triggering hyaluronidase (HAase), which is abundantly present in tumor tissues. The released DCs deplete GLUT1 levels in tumor cells by inhibiting glucose uptake, blocking glycolysis, reducing ATP levels, and suppressing heat shock protein (HSP) expression, ultimately rendering malignant cells vulnerable to stress (eg, heat) and leading to cell death (Figure 8B).[104] GLUT1-targeted nanoparticles modulate the function of specific cells within the tumor immune microenvironment through targeted antigen binding. Concurrently, they inhibit tumor cell glycolysis, impairing tumor growth advantages and reprogramming the energy metabolism of the tumor microenvironment, thereby restoring anti-tumor activity in immune cells, particularly effector T cells. Additionally, these nanoparticles enhance immune responses by co-delivering immune checkpoint inhibitors or immunostimulants, addressing the challenge of "cold tumors" in conventional immunotherapy. Furthermore, they serve as a foundation for combination therapies beyond immunotherapy, enabling multi-layered therapeutic strategies that improve overall efficacy.[105] With the integration of nanotechnology, immunology, and other disciplines, GLUT1-targeted nanoparticles provide novel perspectives and directions for optimizing cancer immunotherapy strategies.

Future Perspectives

As a key glucose transporter protein, GLUT1 has emerged as a prominent focus in current anticancer therapeutic research owing to its central role in tumor energy metabolism. In the realm of clinical translation, several GLUT1-targeted clinical trials for malignant tumors have achieved preliminary breakthrough outcomes. For example, the novel bioreductive prodrug AQ4N significantly modulates GLUT1 expression by regulating the hypoxic tumor microenvironment;[106] In patients with advanced solid tumors overexpressing HIF-1α, oral topotecan has demonstrated clear downregulation of GLUT1 expression levels in tumor tissues,[107] providing robust evidence for targeted interventions. Furthermore, drug studies targeting GLUT1 under various metabolic conditions are also underway. In vivo studies have shown that GLUT1-related targeted inhibitors combined with metformin can increase the sensitivity of endometrial cancer cells to metformin under high glucose conditions by modulating cancer metabolism.[108] Nanomaterials engineered around GLUT1 demonstrate exceptional antitumor efficacy and drive advancements in precision medicine through multifunctional designs, encompassing direct inhibition of tumor cell energy metabolism, promotion of chemotherapeutic drug-targeted delivery, penetration of the blood-brain barrier for brain tumor treatment, and enhancement of immunotherapy outcomes. Additionally, with the deepening investigation into the GLUT family, significant scientific interest has emerged in GLUT3, which exhibits similarly robust glucose transport capabilities and is highly expressed in multiple cancers;[109–111] Meanwhile, GLUT4 is present in 20% of human astrocyte tumors,[112] lung cancer subgroups[113] and all gastric cancers, while it is only expressed in 40% of normal gastric mucosa samples.[15] Therefore, pan-GLUT drugs and molecules (such as KL-11743[114] and Glutor[115]), as well as short hairpin RNA (shRNA) and small interfering RNA (siRNA) targeting GLUT molecules,[116] show great promise as active ingredients for targeted therapy. Collectively, these materials offer multi-dimensional application potential, with their diverse designs and integrated functionalities effectively addressing limitations of conventional tumor therapeutics—including low bioavailability and poor targeting specificity—by enabling precise drug delivery through specific binding to glucose transporters, thereby substantially improving therapeutic efficacy and safety.

However, despite numerous breakthroughs, GLUT1-related nanomaterials continue to confront significant challenges and limitations in cancer therapy. Firstly, the broad expression of GLUT1 is not confined to tumor cells but extends to normal tissues, potentially leading to off-target effects that induce side effects and toxicity concerns. Secondly, the heterogeneity in GLUT1 expression levels and functionality across diverse tumor types may result in substantial variability in therapeutic efficacy among patients. Furthermore, many GLUT1-based nanomaterials remain at the laboratory research stage, with clinical translation hindered by complexities in drug delivery systems, stability issues, and long-term biosafety uncertainties. Specifically, formulation complexity arises from the need for precise control over particle size, surface charge, targeting ligand density, and drug loading efficiency—factors critical for targeting accuracy and release kinetics but escalating synthesis

difficulty and costs. Scalability challenges are evident in difficulties maintaining batch consistency, purity, and stability during scale-up from laboratory to industrial production, potentially yielding unpredictable therapeutic outcomes and restricting clinical applicability. Immune response risks involve potential activation of the complement system or induction of inflammatory factor release, triggering non-specific immune responses that exacerbate adverse events such as fever or allergies, thereby narrowing the therapeutic window. Long-term biosafety concerns stem from nanoparticle accumulation, slow biodegradation rates, metabolite toxicity, and chronic organ impacts, necessitating further assessment through extended in vivo models and epidemiological studies. Therefore, in the short term, single-cell sequencing and multi-omics analyses can be combined to elucidate the dynamic expression and functional changes of GLUT1 in the tumor microenvironment, screen for more specific targets and targeting strategies, and improve the specificity and biosafety of nanomaterials. Combining the synergistic effects of immunotherapy and gene editing technology can realize the in vivo verification of dual-targeted nanocarriers or the conduct of metabolic-immunotherapy combined therapy trials.

Conclusion

GLUT1 represents a promising target in tumor metabolic reprogramming, yet its therapeutic strategies must overcome critical challenges such as specificity and heterogeneity. Although nanomedicine offers versatile platforms to address these issues, translational hurdles—including bioavailability and safety concerns—persist. GLUT1-targeted nanomaterials demonstrate unique advantages in cancer therapy, opening new avenues for treatment; however, achieving broad clinical application still requires overcoming numerous technical and scientific barriers. With continuous advances in nanotechnology, tumor biology, and precision medicine, GLUT1-directed nanomaterials are poised to become a cornerstone in oncology therapeutics, providing patients with more efficient and safer treatment options.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Zhen Ren and Jingyuan Zhao are co-first authors for this study. The authors declare no competing interests in this work.

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