Advances in Nanoparticle-Based Boron Delivery Agents for BNCT

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Abstract

Boron neutron capture therapy (BNCT) is an effective cancer treatment modality; however, its clinical application has been restricted by the poor targeting efficacy, limited boron loading capacity, and high toxicity of first- and second-generation boron delivery agents. Nanoparticles, capable of loading various boron compounds and conjugating diverse tumor-targeting molecules, can efficiently deliver boron to tumor tissues in a targeted manner to achieve therapeutic concentrations. As such, they represent a class of boron carriers that has garnered considerable attention in preclinical BNCT research. This article reviews, analyzes, and summarizes the research advances in nanoparticle-based boron delivery agents for BNCT, with the aim of providing a reference for the development of novel nanoparticle-based boron carriers and promoting the progress and clinical translation of BNCT technology.

Full Text

Progress in Nanomaterial-Based Boron Agents for BNCT

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Abstract

Boron neutron capture therapy (BNCT) is an effective modality for tumor treatment, but its clinical application has been constrained by the limitations of first- and second-generation boron agents, including poor targeting capability, limited boron loading capacity, and high toxicity. Nanoparticles can load various 10B compounds and be conjugated with diverse tumor-targeting molecules to efficiently deliver 10B to tumor tissues, achieving the therapeutic concentrations required for effective treatment. These nanoparticle-based boron carriers have

attracted considerable attention in preclinical BNCT research. This review systematically analyzes and summarizes recent research progress in nanoparticle-based boron carriers for BNCT, aiming to provide valuable references for developing novel nanomaterial-based boron agents and advancing BNCT technology.

Keywords: BNCT; nanoparticle; nanomaterial-based boron agents

Boron neutron capture therapy (BNCT) is a binary targeted therapy for tumor treatment that involves delivering 10B compounds (boron carriers) to tumor tissues through specific means. Upon local irradiation with a neutron beam, 10B undergoes a nuclear reaction with low-energy neutrons, generating high linear energy transfer (LET) α-particles that effectively kill tumor cells. For BNCT to be effective, boron carriers must meet stringent criteria: high tumor uptake (10B concentration greater than 30 μg/g tumor tissue or 10^9 10B atoms/cell), low toxicity, excellent tumor targeting capability (tumor-to-blood and tumor-to-normal tissue 10B concentration ratios, i.e., T/B and T/N values greater than 3), and prolonged intratumoral retention. The development of boron carriers has progressed through three generations. The first two generations (boric acid, sodium mercaptoundecahydrododecaborate, boronophenylalanine, etc.) suffered from poor targeting, high toxicity, low boron loading, short tumor retention, or significant individual variability, severely hindering BNCT development and application. The third generation primarily comprises nanoparticle-based boron carriers modified with various targeting molecules, which promise to overcome the limitations of low boron loading and short retention, delivering substantial amounts of 10B compounds to tumor tissues for optimal BNCT efficacy.

Nanoparticle-based boron carriers are mainly categorized into liposomes, polymeric nanoparticles, dendrimers, boron carbide nanoparticles, boron nitride nanomaterials, metal nanoparticles, and carbon-based nanomaterials. Nanoparticles with appropriate sizes can penetrate the gaps in tumor capillaries and accumulate in tumor tissues due to the incomplete lymphatic drainage system, a phenomenon known as the enhanced permeability and retention (EPR) effect. Functionalization of nanoparticles enables more selective and targeted delivery of 10B compounds to tumor tissues. Consequently, related research has attracted significant attention in recent years, demonstrating rapid development and promising potential in tumor therapy.

1 Liposome-Based Boron Carriers

Liposomes are bilayer spherical carriers composed of cholesterol and natural phospholipids, offering excellent biocompatibility and simple preparation with minimal requirements for the water or lipid solubility of encapsulated drugs. Liposomes can deliver various 10B compounds, including boronophenylalanine (BPA), sodium mercaptoundecahydrododecaborate (BSH), and carboranes.

Based on their structure and functionalization, liposome-based boron carriers can be classified into passive targeting liposomes, long-circulating liposomes,

and active targeting liposomes.

1.1 Passive Targeting Liposomes

Passive targeting liposomes are prepared by modifying only the membrane materials without external surface modifications, relying on the EPR effect for tumor accumulation. Kueffer et al.[1] developed liposomes loaded with borane derivatives in both the hydrophobic bilayer and aqueous phase. In breast tumor-bearing mice, multiple injections maintained tumor boron concentrations at 67.8 μg/g after 54 hours, effectively improving spatial utilization and boron loading capacity. Altieri et al.[2] encapsulated carboranes in cationic liposomes and observed approximately 30-fold higher boron uptake in colon and melanoma cells compared to BPA controls. Unlike conventional passive targeting liposomes that enter cells via membrane fusion or endocytosis, the interaction between negatively charged tumor cell surfaces and cationic liposomes significantly enhanced 10B uptake. Li et al.[3] inserted carborane derivatives into phospholipid bilayers and radiolabeled liposome surfaces with 64Cu. In breast tumor-bearing mice, boron content measurements in various tissues showed high concordance with boron distribution assessed by positron emission tomography (PET) imaging.

1.2 Long-Circulating Liposomes

Liposomes with larger particle sizes are readily phagocytosed by the reticuloendothelial system (RES). Surface modification with polyethylene glycol (PEG), phosphatidylinositol, chitosan, or sodium alginate can prolong systemic circulation and tumor retention while avoiding RES uptake, forming long-circulating liposomes. Pavanetto et al.[4] used PEGylated liposomes to encapsulate BPA-fructose complexes, achieving tumor boron concentrations approximately 50 times higher than non-PEGylated controls in hepatoma-bearing rats three hours post-administration. Yanagie et al.[5] employed PEGylated liposomes loaded with BSH, demonstrating tumor boron concentrations about twice those of non-PEGylated controls in pancreatic tumor-bearing mice 24 hours after injection. These studies collectively demonstrate that PEG modification effectively enhances liposomal tumor retention.

1.3 Active Targeting Liposomes

Active targeting liposomes (immunoliposomes) conjugate drug-loaded liposomes with tumor-targeting molecules to achieve targeted delivery. Various tumor-targeting molecules, including monoclonal antibodies (mAb), transferrin (TF), folic acid (FA), and epidermal growth factor (EGF), have been successfully utilized for targeted delivery of liposomal boron carriers. Yanagie et al.[6] conjugated carcinoembryonic antigen (CEA) monoclonal antibodies to BSH-loaded liposomes, enabling specific targeting of CEA-overexpressing tumor cells. Incubation with human pancreatic cancer cells followed by neutron irradiation significantly inhibited cell growth. Transferrin liposomes can enter tumor cells via transferrin receptor-mediated endocytosis, which is overexpressed on tumor cell

surfaces. Maruyama et al.[7] conjugated TF to the distal ends of PEG chains on BSH-loaded liposomes, achieving high tumor retention. In colon tumor-bearing mice, tumor boron concentrations remained above 30 μg/g 72 hours post-injection, with a T/B ratio of 6.0 (compared to 2.5 for non-TF-conjugated controls).

Yanagie et al.[8] developed TF-conjugated PEGylated liposomes loaded with BSH [Figure 1a: see original paper]. In pancreatic tumor-bearing mice, tumor boron concentrations reached approximately 12 ppm at 60 hours, compared to 6.5 ppm in non-TF-conjugated controls and only 2.8 ppm in BSH controls. Pan et al.[9] conjugated FA to PEGylated liposomes loaded with boronated polyamines, demonstrating approximately 10-fold higher cellular boron uptake in squamous carcinoma cells compared to non-targeted controls. Singh et al.[10] coupled FA to PEGylated liposomes loaded with boron nanoparticles, achieving significantly higher boron uptake (3.7 pg/cell) in C6 brain tumor cells than non-FA-conjugated controls (1.5 pg/cell). In vitro studies suggested that FA-PEG liposomes (100-120 nm) could potentially cross the blood-brain barrier (BBB). Pan et al.[11] inserted cetuximab into PEGylated liposomes loaded with soluble boron salts via membrane cholesterol, achieving boron concentrations of 509.75$±$148 μg/g in EGFR(+) glioma cells, approximately eight times higher than non-targeted controls. Feng et al.[12] conjugated anti-EGFR antibodies to BSH-loaded nickel-containing liposomes via a protein A (ZZ) antibody affinity scaffold [Figure 1c: see original paper], enabling effective BSH delivery to EGFR-overexpressing glioma cells. Koning et al.[13] conjugated RGD peptides to liposomes loaded with disodium dodecahydrododecaborate (DHDB). After 24-hour incubation with human umbilical vein endothelial cells followed by neutron irradiation, cell viability was significantly inhibited. Multiple tumor-targeting molecules have been employed for targeted delivery of boron-containing liposomes, enhancing both tumor retention time and cellular boron uptake while avoiding toxic side effects caused by boron compounds.

Various liposome-based boron carriers with different compositions and functionalization strategies can improve boron loading efficiency, prolong intratumoral retention, and confer tumor specificity. Passive targeting liposomes offer simple preparation but relatively weak tumor-targeting ability and cannot avoid RES phagocytosis when particle sizes are large. Long-circulating liposomes effectively prevent RES uptake through PEGylation, extending blood circulation and tumor retention while increasing intratumoral boron concentration. However, multiple injections can cause liposome aggregation and accelerated blood clearance (ABC). Active targeting liposomes significantly enhance tumor specificity and boron content through targeting molecule conjugation, but the coupling process may alter liposomal properties such as particle size, requiring specific evaluation.

2 Polymer-Based Boron Carriers

Polymeric nanoparticles self-assemble from block copolymers composed of two or more polymer chains with different hydrophobicities. Advances in polymer chemistry have enabled the creation of functionalized polymeric nanoparticles with controllable shape, size, internal morphology, and surface charge, making them excellent candidates for BNCT drug delivery[14,15]. Various polymer nanoparticles loaded or coated with boron compounds have demonstrated superior boron delivery efficiency. Mi et al.[16] conjugated BSH with poly(ethylene glycol)-b-poly(glutamic acid) copolymer [PEG-b-P(Glu)] to form [PEG-b-P(Glu-SS-BSH)]. In colon tumor-bearing mice, tumor boron concentrations reached 69 ppm 24 hours post-administration, compared to 13 ppm and 10 ppm for P(Glu-SS-BSH) and BSH controls, respectively. Twenty days after neutron irradiation, tumor volumes in the experimental group were only 1/20th of those in the BSH neutron control group.

Xiong et al.[17] used amphiphilic copolymers conjugated with carborane to encapsulate the chemotherapeutic drug doxorubicin (DOX), forming DOX@PLMB. After neutron irradiation, tumor volumes in the DOX@PLMB neutron group were only one-third of those in the non-irradiated DOX@PLMB group 27 days later. Among seven mice, three showed complete disappearance of leg tumors, with a tumor inhibition rate of $92.9\$\pm 18.9\pm 15.8g/ginmelanoma-bearingmiceeighthourspost-administration, withintratumoral10Bconcentrations3.5-4.2timeshigherthancarborane-albumincomplexesandT/Bratiosexceeding5between8-12hours.Daietal.[19]coatedBPAwithpolydopamine(PPDAnanoparticles.Inmelanoma-bearingmice, tumorboronconcentrationsreached31.485\pm\$2.369$ ppm 24 hours after administration of 200 μg/mL B-PDA, with T/B and T/N ratios of approximately 4.922 and 6.32, respectively. Following neutron irradiation, the median survival time for mice receiving 200 μg/mL B-PDA or 100 μg/mL B-PDA combined with photodynamic therapy was 23.5 days, compared to less than three weeks for control groups. This study suggests that BNCT-photodynamic combination therapy may reduce the minimum tumor boron concentration required for BNCT, providing insights for combining BNCT with multiple treatment modalities.

Investigating the in vivo distribution and pharmacokinetics of boron carriers is crucial for BNCT development. Fluorescence imaging and positron emission tomography (PET) have been employed to study polymer-based boron carriers. Ruan et al.[20] synthesized an amphiphilic triblock polymer micelle with polycaprolactone and polycarborane as hydrophobic segments and poly(ethylene glycol) methyl ether methacrylate as the hydrophilic segment, conjugated with a fluorescent dye for imaging [Figure 2a: see original paper]. Boronated porphyrins accumulate in tumors with long retention times, but their development for BNCT has been hindered by low tumor-to-blood ratios and direct platelet toxicity observed in Phase I clinical studies. Shi et al.[21] encapsulated tetraboronated porphyrin in methoxy-polyethylene glycol-poly(lactide-co-glycolide) micelles to form boronated porphyrin nanocomplex (BPN) [Figure 2b: see orig-

inal paper]. Porphyrins possess intrinsic optical imaging properties, and the team additionally used 64Cu radiolabeling for PET imaging to visualize BPN cellular uptake and pharmacokinetics through dual imaging modalities.

Tumor cell-specific uptake of boron-containing polymer micelles can be enhanced by preparing charged micelles or conjugating targeting molecules. Azab et al.[22] synthesized cationic acrylamide copolymers with varying ratios of aminophenylboronic acid (APB) for targeting rat intestinal polyps, achieving T/N ratios of 6.5 and polyp boron concentrations of 88.5$±$15.1 μg/g 60 minutes post-administration. The asialoglycoprotein receptor (ASGP-R) is considered an ideal target for hepatocellular carcinoma-specific drug delivery, with galactose residues showing high receptor affinity. Zhang et al.[23] synthesized PEGylated galactose polymer micelles loaded with carborane. Incubation with human hepatoma cells for 24 hours yielded significantly higher intracellular boron concentrations than BSH controls. Following neutron irradiation, the acute cell death rate in the micelle group was 36.95%, approximately double that of the BSH neutron control group.

Reactive oxygen species (ROS) are known intracellular signaling cascade mediators. However, γ-rays produced during BNCT generate substantial ROS, potentially causing oxidative stress, loss of cellular function, and inflammation. To scavenge ROS generated by BNCT, boron cluster-containing redox nanoparticles (BNPs) have been extensively studied for their ROS scavenging ability, high colloidal stability, and specific accumulation in tumor cells. Gao et al.[24] synthesized two polymers [Figure 2c: see original paper] containing BSH and ROS scavenger monomers, respectively, which were coupled via polyion complexation to obtain BNPs. Incubation with rectal cancer cells for 18 hours showed significantly higher BNP uptake compared to BSH controls, while normal human aortic endothelial cells showed no significant uptake. In rectal tumor-bearing mice, neutron irradiation produced no adverse reactions (low white blood cell levels).

Polymer-based boron carriers offer simple preparation and stable properties, making them widely used in BNCT research. Charged and targeting molecule-conjugated boron-containing polymer micelles can effectively target tumor tissues. However, studies have shown that positively charged polymer micelles can cause toxic side effects in vivo, necessitating careful evaluation of their systemic toxicity. Additionally, polymer micelles containing ROS scavengers can mitigate BNCT-induced adverse reactions, potentially improving post-treatment outcomes.

3 Dendrimer-Based Boron Carriers

Dendrimers (DEs) possess well-defined chemical structures and molecular weights with uniform molecular sizes, and their surface and internal structures are readily modifiable. Drug loading using dendrimers can increase loading capacity while preventing drug leakage or degradation caused by external en-

vironments. Dendrimer-based boron carriers offer high boron loading capacity and are easily modified to conjugate various tumor-targeting molecules.

Filling dendrimer interiors or loading carboranes onto dendrimer exteriors are common methods for preparing boron-containing dendrimers[25]. Parrott et al.[26] conjugated carborane derivatives to dendrimers, creating water-soluble, boron-containing dendrimers with adjustable overall solubility that could encapsulate up to 16 carboranes internally [Figure 3a: see original paper]. Dash et al.[27] synthesized phenylene-cored carborane dendrimers via "click" chemistry, capable of loading 3-9 carboranes [Figure 3b: see original paper]. Cabrera-González et al.[28] prepared optically active tetraphenylporphyrin-cored carborane dendrimers with a maximum loading capacity of 32 carboranes [Figure 3c: see original paper]. Compared to small boron-containing molecules, these dendrimers showed improvements only in boron content or in vivo distribution, with limited tumor-targeting capability.

Functionalized boron-containing dendrimers can significantly enhance tumor specificity and retention. The vascular endothelial growth factor receptor (VEGFR) gene is overexpressed in tumor neovasculature. Backer et al.[29] conjugated VEGF to boronated dendrimers (BD) containing 1,050-1,100 boron atoms and labeled them with fluorescent dye Cy5 for distribution studies (VEGF-BD/Cy5). In breast tumor-bearing mice, VEGF-BD/Cy5 selectively accumulated in the peripheral regions of tumor growth, where neovascularization is most active. EGFR represents a potential target for brain glioma drug delivery, and many EGFR-targeting drugs and monoclonal antibodies have been developed for BNCT. Capala et al.[30] conjugated EGF to boronated starburst dendrimers (BSD) and labeled them with 125I to evaluate boron uptake levels in glioma cells. Wu et al.[31] conjugated cetuximab (IMC-C225) to fifth-generation boron-containing dendrimers to obtain C225-G5-B1100 [Figure 3d: see original paper]. In F98EGFR glioma-bearing rats, tumor boron concentrations reached 23.3 μg/g 24 hours post-administration, compared to only 3.6 μg/g in non-targeted G5-B1100 controls. The folate receptor is overexpressed on various tumor cell surfaces. Shukla et al.[32] used PEG to coat folate-modified boron-containing polyamidoamine (PAMAM) dendrimers to reduce RES uptake, creating boronated G3-DE [Figure 3e: see original paper]. However, in 24JK-FBP sarcoma-bearing mice, high uptake was observed in tumors, liver, and kidneys.

Dendrimer-based boron carriers offer high boron content and facile surface modification, and conjugating different targeting molecules can enhance tumor specificity. However, the complex synthesis steps, difficulty in precisely controlling boron drug release, and unclear in vivo stability and metabolism have limited their further development in BNCT.

4 Boron Carbide Nanoparticle-Based Boron Carriers

Boron carbide particles are synthesized through simple, convenient methods with low toxicity, high boron content, and excellent biochemical and thermal stability. Their large specific surface area and unique nanostructure provide abundant adsorption sites and space for drugs, enabling functionalization and efficient drug loading, making them suitable for BNCT research.

Tsuji et al.[33] conjugated transferrin to boron carbide particles coated with poly-L-lysine and poly-γ-glutamic acid, forming spherical transferrin boron carbide nanoparticles (Tf-SBCPs) labeled with fluorescent dyes. Incubation with cervical cancer cells for two hours showed extensive internalization of Tf-SBCPs, while albumin-conjugated SBCPs accumulated only on cell surfaces. Competitive inhibition experiments with free TF confirmed receptor-mediated uptake. Kaur et al.[34] incubated nanostructured boron carbide (B4C) with cervical cancer and glioblastoma cells for three hours. Following neutron irradiation, B4C induced 61% acute cell death in cervical cancer cells, comparable to BPA controls, while glioblastoma cells showed 78% acute death, significantly higher than BPA controls (33%). These results demonstrate B4C' s superior therapeutic potential over BPA in vitro for BNCT.

Boron carbide nanoparticle-based carriers exhibit high boron loading capacity and promising cancer cell uptake rates in vitro. However, preclinical studies remain limited, and further investigation is needed regarding their in vivo biodistribution, pharmacokinetics, and therapeutic efficacy following neutron irradiation in animal models.

5 Boron Nitride Nanomaterial-Based Boron Carriers

Boron nitride nanoparticles exhibit stable properties, low toxicity, good biocompatibility, and high boron content. They are primarily classified into boron nitride nanoparticles (BNNPs) and boron nitride nanotubes (BNNTs), representing a promising class of boron carriers.

BNNPs can significantly improve 10B delivery efficiency. Li et al.[35] coated BNNPs with phase-transitioned lysozyme (PTL) to form PTL@BNNPs, effectively preventing hydrolysis during delivery. Post-neutron irradiation, on-demand degradation of BNNPs could be achieved by administering vitamin C, avoiding toxic side effects from long-term accumulation. Zhang et al.[36] grafted poly(glycerol) onto hexagonal boron nitride particles to form h-10BN-PG [Figure 4a: see original paper]. In colon tumor-bearing mice, intratumoral 10B concentrations remained as high as 80 μg/g 24 hours post-administration, with significant tumor volume reduction following neutron irradiation. This represents a rare case where boron-containing drug administration alone achieved tumor shrinkage in BNCT.

Compared to BNNPs, BNNTs can avoid self-decomposition during in vivo drug delivery. Ciofani et al.[37] coated BNNTs with biocompatible poly-L-lysine

(PLL) and surface-functionalized them with fluorescent dyes and folic acid to form F-PLL-BNNT [Figure 4b: see original paper]. After 90-minute incubation with glioblastoma cells, F-PLL-BNNT uptake was significantly higher than PLL-BNNT controls. Nakamura et al.[38] coated BNNTs with DSPE-PEG2000 to form BNNT-DSPE-PEG2000. One-hour incubation with melanoma cells yielded intracellular boron accumulation approximately three times higher than BSH controls.

Boron nitride nanoparticles inherently possess high boron content, but challenges including poor water solubility, in vivo decomposition, and potential toxic side effects from accumulation remain to be addressed. Surface functionalization may offer solutions to these problems.

6 Metal Nanoparticle-Based Boron Carriers

Metal nanoparticles offer advantages of facile surface modification and precise size control for drug delivery. Using metal nanoparticles such as silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) for boron loading and targeted delivery has become a hot topic in BNCT research.

6.1 Silver Nanoparticles

AgNPs, typically smaller than 100 nm, are easily surface-modified and can improve drug pharmacokinetics and biodistribution, facilitate biomembrane penetration, and enable controlled release. Kennedy et al.[39] surface-functionalized AgNPs with mercaptocarborane and conjugated anti-EGFR antibodies, achieving approximately 4.8$×$10^8 10B atoms per hepatoma cell. The team also demonstrated that AgNPs could absorb energy to generate local hyperthermia, potentially enabling combined BNCT-thermal ablation therapy. While AgNPs represent a promising boron carrier, their potential toxicity observed in cell viability tests warrants careful attention.

6.2 Gold Nanoparticles

Gold nanoparticles (AuNPs) exhibit good biocompatibility, low toxicity, small size, and optical imaging capability. For BNCT, AuNPs conjugated with targeting molecules can selectively deliver 10B compounds to tumor tissues while capturing neutrons to release β-rays during irradiation, producing synergistic therapeutic effects[40].

Ligand-protected metal nanoclusters are termed monolayer protected clusters (MPCs), where different ligands determine water solubility and functionality. Gold nanoparticle-based boron carriers are typically functionalized with mercapto-o-carborane for ligand protection. Cioran et al.[41] directly surface-functionalized AuNPs with o-carborane to obtain water-soluble AuNPs with an average diameter of approximately 3.2 nm and the ability to cross biomembranes (i.e., traverse membrane boundaries to exist freely in cytoplasm,

nucleus, and even mitochondria). The team further investigated 10 nm AuNPs prepared via ligand exchange between o-carborane and citrate-coated AuNPs [Figure 5a: see original paper], finding that the ability to adjust particle ionic and electronic charges for phase transfer likely correlates with biomembrane penetration capability[42].

"Click"chemistry enables simple conjugation of o-carborane with macromolecules such as dendrimers and polymers and has been applied to synthesize functionalized AuNPs. Li et al.[43] synthesized a series of water-soluble o-carborane and PEGylated dendritic AuNPs via "click" chemistry. Liang et al.[44] conjugated o-carborane with polystyrene through "click" chemistry to coat AuNPs (average diameter ~2.6 nm) and palladium nanoparticles (average diameter ~1.7 nm). Ciani et al.[45] coupled o-carborane AuNPs with poly(ethylene oxide)-b-poly(caprolactone) diblock copolymer (PEO-b-PCL) via "click" chemistry, significantly improving AuNP water solubility and preventing non-specific interactions with proteins in vivo.

Non-invasive imaging facilitates evaluation of AuNP biodistribution and pharmacokinetics. Pulagam et al.[46] PEG-coated AuNPs functionalized with boron-rich anion [3,3 -Co(1,2-C2B9H11)2]− and radiolabeled them with 124I for PET imaging. However, PET imaging in human fibrosarcoma mice showed low tumor accumulation and poor tumor targeting. Mandal et al.[47] coated AuNPs with multilayered boronated polyelectrolytes of fluorescein isothiocyanate (FITC)-BPA-FA, creating multifunctional AuNPs for both boron targeting and in vivo imaging. Human epidermal growth factor receptor 2 (Her2) is overexpressed on various cancer cell surfaces. Wu et al.[48] functionalized AuNPs with PEG, carborane, and azide compounds, conjugated them with anti-Her2 antibody (61 lgG), and radiolabeled them with 123I via "click" chemistry to obtain 123I-61-B-AuNPs [Figure 5b: see original paper]. In gastric tumor-bearing mice, single-photon emission computed tomography (SPECT) imaging 12 hours post-administration revealed a tumor-to-muscle radioactivity ratio of approximately 12.02.

Metal nanoparticle-based drug delivery remains a hot research topic. Although silver nanoparticles possess intrinsic tumor cell-killing ability, carborane-functionalized AgNPs have shown potential toxicity. Gold nanoparticles offer low toxicity, high boron loading efficiency, and controlled drug release, while surface coating with fluorescent materials or radiolabeling enables non-invasive imaging for in vivo biodistribution assessment. Despite these advantages, synthesizing and purifying AuNPs with uniform size, good dispersity, and resistance to aggregation remains extremely cumbersome.

7 Carbon Nanomaterial-Based Boron Carriers

Carbon nanomaterials are primarily categorized into carbon nanoparticles, carbon nanotubes, and nanodiamonds. Their facile surface modification enables functionalized carbon nanomaterials to significantly prolong systemic circula-

tion time, providing possibilities for long-term drug retention at lesion sites, making them suitable for 10B compound delivery.

7.1 Carbon Nanoparticles

Carbon nanoparticles (CNPs) can improve biocompatibility and targeting through surface modification. Environment-sensitive chemical bonds can control drug release rate and timing in vivo, achieving on-demand release. CNPs also possess intrinsic fluorescence and magnetic resonance imaging capabilities and can be used for photodynamic and photothermal therapy to achieve synergistic treatment effects. Hwang et al.[49] prepared boron-containing carbon nanoparticles (BCo@CNPs) modified with FA. Incubation with cervical cancer cells followed by neutron irradiation resulted in 52% acute cell death and significantly inhibited cell proliferation. Dai et al.[50] incubated FA-modified BCo@CNPs with invasive nonfunctional pituitary adenoma (NFPA) cells, demonstrating that FR(+) NFPA cells could selectively uptake BCo@CNPs via FR-mediated endocytosis.

7.2 Carbon Nanotubes

Carbon nanotubes exhibit water solubility and biocompatibility, and surface modification enables efficient drug loading, targeted delivery, and improved drug stability. Zhu et al.[51] functionalized single-walled carbon nanotubes (SWCNTs) with carborane on sidewalls to create water-soluble boron-containing carbon nanotubes. In breast tumor-bearing mice, intratumoral boron concentrations peaked at 22.8 μg/g 30 hours post-administration and remained at 21.5 μg/g after 48 hours, demonstrating long intratumoral retention though slightly below BNCT requirements. SWCNTs possess fluorescence imaging capability, facilitating in vivo distribution assessment. Yamagami et al.[52] non-covalently functionalized SWCNTs with BSH-conjugated PAMAM dendrimers, providing an effective imaging method that avoids fluorescence quenching effects from covalent BSH-SWCNT functionalization.

7.3 Nanodiamonds

Nanodiamonds (NDs) are easily surface-modified and serve as effective drug delivery carriers, though their in vivo biodistribution is difficult to assess. Lin et al.[53] embedded red-fluorescent 10B ions into nanodiamonds using physical particle injection technology to obtain boron-rich, non-toxic B-NDs. This approach provides a novel boron carrier while solving the challenge of observing ND distribution at cellular and animal levels.

Carbon nanoparticles are readily surface-modified, and functionalized CNPs can target deliver 10B compounds to tumor tissues. Their potential for photodynamic and photothermal therapy enables synergistic tumor treatment with BNCT. Single-walled carbon nanotubes offer fluorescence imaging capability,

facilitating visualization of 10B compound delivery and biodistribution assessment. Nanodiamonds' biodistribution challenges can be addressed by embedding fluorescent 10B ions. Overall, carbon nanomaterial-based boron carriers enable efficient drug loading, targeted delivery, and in vivo distribution assessment, but complex preparation processes and potential immune system reactions require urgent solutions.

8 Other Nanomaterial-Based Boron Carriers

Beyond the aforementioned categories, numerous other nanomaterial-based boron carriers have attracted widespread attention from BNCT researchers due to their unique physicochemical properties, functional characteristics, and potential applications in biomedicine and materials science.

8.1 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) can load drugs through physical adsorption or chemical conjugation, enabling efficient drug transport under external magnetic field guidance and targeted release triggered by environmental stimuli or external stimulation. Kuznetsov et al.[54] prepared ultra-dispersed ferro-carbon (Fe-C) and iron-boron (Fe-B) composite particles capable of adsorbing borax. Zhu et al.[55] conjugated o-carborane to propargyl-rich starch Fe3O4 nanoparticles via "click" chemistry [Figure 5a: see original paper], achieving efficient tumor targeting under continuous external magnetic guidance with maximum intratumoral boron concentrations of approximately 51.4 μg/g, T/N ratios up to 10, and intratumoral retention of about 48 hours. Iron oxide nanoparticles face challenges including easy aggregation, low stability, and poor biocompatibility. Tulebayeva et al.[56] used 3-aminopropyltrimethoxysilane-coated Fe3O4 nanoparticles with high stability, good biocompatibility, low toxicity, and low cost as carborane delivery vehicles. Oleshkevich et al.[57] coated Fe3O4 nanoparticles with m-carboranyl phosphinate [Figure 5b: see original paper]. In glioma-bearing mice, no obvious toxic side effects were observed, and neutron irradiation of glioblastoma cells incubated with these nanoparticles significantly reduced cell proliferation compared to controls.

8.2 Inactivated Hemagglutinating Virus of Japan Envelope

Inactivated Hemagglutinating Virus of Japan envelope (HVJ-E) possesses antitumor activity, can activate anti-tumor immunity, and induce tumor cell death. Fujii et al.[58] combined HVJ-E with cationized gelatin (CG) to significantly reduce hemagglutination activity and cytotoxicity while loading BSH to form CG-HVJ-E-BSH for BNCT. Incubation with osteosarcoma cells for 30 minutes yielded intracellular boron concentrations far exceeding BSH controls. In mice with multiple liver tumors, T/N ratios remained higher than BSH controls for 48 hours. Neutron irradiation 24 hours after CG-HVJ-E-BSH administration (versus 1 hour for BSH) resulted in longer survival times and minimal histolog-

ical damage to normal liver tissue surrounding tumors. Functionalizing HVJ-E with boron-containing polymers can also achieve high 10B loading and hemolysis inhibition. Yoneoka et al.[59] coated HVJ-E with 2-methacryloyloxyethyl phosphorylcholine (MPC) and methacrylamide benzoxaborole (MAAmBO) to form HVJ-E/p[MPC-co-MAAmBO]. Fluorescence imaging after 45 and 90 minutes of incubation with liver cancer cells revealed uniform cytoplasmic distribution.

8.3 Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) utilize their internal mesoporous structure for drug loading. Yu et al.[60] first covalently linked carborane to mesoporous silica surfaces, creating boron-rich nanoparticles with stable structures and controllable hydrophilicity/hydrophobicity. Zhang et al.[61] prepared liver cancer-targeted mesoporous silica loaded with carborane, achieving 92.8% acute cell death in human liver cancer cells after incubation and neutron irradiation. Tang et al.[62] used SP94 peptide-modified lipid bilayer (LB)-coated MSNs loaded with 10B-boric acid (10BA) to obtain SP94-LB@BA-MSN. Cellular boron concentrations remained higher than 10BA and BPA controls throughout incubation with human liver cancer cells, and neutron irradiation produced more pronounced viability inhibition compared to control groups.

8.4 Metal-Organic Frameworks

Metal-organic frameworks (MOFs) are emerging materials developed over recent decades, featuring high tunability, large drug loading capacity, good biocompatibility, and easy chemical modification, making them ideal drug carriers that have attracted attention from materials scientists, bionic researchers, and particularly biomedical researchers. Wang et al.[63] prepared nano-co-crystals (MNCs) using zirconium-meso-tetra(4-carboxyphenyl)porphyrin MOFs and 10BA, demonstrating good stability, colloidal dispersity, and biocompatibility. In orthotopic glioma-bearing mice, intratumoral 10B concentrations reached 67.5$±$4.2 μg/g two hours post-administration, with T/N and T/B ratios of approximately 6.20 and 3.80, respectively. Fluorescence imaging and 89Zr-mediated PET imaging both confirmed that MNCs could cross the blood-brain barrier and effectively accumulate in tumors. After neutron irradiation, 75% of tumor-bearing mice survived at five weeks, while all BPA control mice died within three weeks. Wang et al.[64] evaluated the relative biological effectiveness (RBE) of BNCT, finding that MNCs exhibited 4.1-fold higher RBE than 10BA.

8.5 Nanofiber Mats

As a novel drug-loading material, nanofiber mats enable precise regulation of in vivo drug release rates by controlling structural parameters and drug loading. Huang et al.[65] prepared 10BA-loaded polylactide-polyethylene glycol (PLA-PEO) nanofiber mats for in situ administration and controlled 10BA release. In liver tumor-bearing mice, using PLA80-PEO20 with appropriate drug release rate (too fast accelerates 10BA metabolism, too slow prevents sufficient 10B

accumulation) achieved T/B ratios up to 80.6. Neutron irradiation resulted in slow tumor growth, with volumes increasing only three-fold after 25 days compared to 25-fold increase in 10BA-alone controls.

8.5 Covalent Organic Frameworks

Covalent organic frameworks (COFs) are crystalline porous materials formed by covalent bonding of organic molecules. Shao et al.[66] synthesized multifunctional boron-rich COFs that can be surface-modified with various peptide targeting molecules and efficiently load immune adjuvants, photosensitizers, sonosensitizers, and chemotherapeutic drugs for combined BNCT and immunotherapy.

8.5 Ferritin Nanoparticles

Ferritin nanoparticles (FNP) represent an attractive protein nanoplatform for in vivo antigen delivery, presentation, and immune stimulation. Ferritin can directly target tumor cells and tissues overexpressing transferrin receptor 1 (TfR1), enriching in tumors while showing minimal distribution in other organs. Ferritin nanoparticles possess numerous modification sites and offer advantages including physicochemical stability, simple boron compound loading methods, good biocompatibility, dispersity, and uniform particle size. Zhang et al.[67] loaded BPA into ferritin nanoparticles, and near-infrared imaging in glioma-bearing mice revealed predominant 10B accumulation at tumor sites.

8.5 Multifunctional Vesicles

Multifunctional vesicles self-assemble from membrane materials under specific conditions, structurally similar to liposomes, and can encapsulate anti-tumor drugs internally. Dai et al.[68] prepared boron-containing vesicles from lipoic acid-boronophenylalanine derivatives (LA-BPA) under specific pH conditions, encapsulating doxorubicin internally. Unlike L-BPA entering tumor cells via LAT1 transporters, these vesicles rapidly react with overexpressed sialic acid on tumor cell surfaces through phenylboronic acid groups, significantly enhancing cell-vesicle interactions and promoting vesicle internalization. Additionally, increased ROS levels after vesicle entry facilitate mitochondrial dysfunction and apoptosis induction. In pancreatic tumor-bearing mice, 350 mg/kg administration achieved T/B ratios up to 5, and neutron irradiation after six hours completely suppressed tumors within 15 days through BNCT-chemotherapy synergy and mitochondrial apoptosis.

Magnetic nanoparticle-based boron carriers can target deliver boron to tumor tissues under continuous external magnetic guidance with prolonged intratumoral retention. However, MNPs face complex preparation processes, potential premature 10B compound release when loaded via adsorption, and stability, biocompatibility, and aggregation issues when conjugated via “click” chemistry, though silane-functionalized MNPs partially address these challenges. HVJ-E

nanocarriers enable tumor cell internalization through membrane fusion capability, and their intrinsic anti-tumor activity synergizes with BNCT, though the relationship between dosage and cytotoxicity/hemolysis requires continued attention. MOFs, nanofiber mats, COFs, and MSNs can load 10B compounds and achieve intracellular boron concentrations meeting BNCT requirements with prolonged retention through porphyrin-mediated active targeting, in situ passive targeting, or targeting molecule-guided active delivery. However, challenges including drug leakage during administration, precise control of drug release, and potential toxicity from in vivo accumulation remain. BPA-loaded ferritin nanoparticles targeting TfR1-overexpressing tumors and sialic acid-targeting boron-containing vesicles represent relatively novel nanocarriers warranting further investigation due to limited current research.

Summary and Outlook

In summary, nanoparticle-based boron carriers have ushered boron carrier research into a new era characterized by excellent tumor targeting capability and high boron loading capacity. Despite numerous research achievements, therapeutic outcomes in animal models following neutron irradiation remain suboptimal, with few studies demonstrating tumor volume reduction. This may be related to carrier stability, drug release profiles, and accelerator neutron beam characteristics. Combined therapeutic approaches integrating BNCT with chemotherapy, immunotherapy, photodynamic therapy, or photothermal therapy are highly promising, with multiple studies demonstrating tumor volume reduction rather than mere growth inhibition.

Among various nanoparticle-based boron carriers, liposome-based systems demonstrate particular advantages. They offer high boron loading capacity through both hydrophilic cavities and hydrophobic domains; prolonged intratumoral retention via the EPR effect and PEGylation; simple preparation and facile surface modification; relatively good biocompatibility without severe adverse reactions; and easy clearance from the body, avoiding potential toxicity from long-term accumulation. Additionally, multiple anti-tumor liposomal formulations have been approved and demonstrate promising clinical prospects.

In conclusion, liposome-based boron carriers possess significant potential and may emerge as the next approved drug in BNCT research, bringing new breakthroughs and hope for BNCT technology development. Furthermore, theranostic integration has long been desired, holding even greater significance for BNCT technology. Determining maximum intratumoral 10B concentrations for neutron irradiation optimization is crucial for achieving the best therapeutic outcomes. Radionuclide-mediated PET/SPECT imaging has been applied to evaluate in vivo biodistribution and maximum tumor boron content of nanoparticle-based boron carriers, demonstrating certain advantages and potentially representing a future research hotspot.

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