L-type amino acid transporter 1 in enhancing boron neutron capture therapy: Mechanisms, challenges and future directions (Review)

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Received April 25, 2025; Accepted August 7, 2025

DOI: 10.3892/ijmm.2025.5611

Abstract. L-type amino acid transporter 1 (LAT1) has emerged as a critical molecular target for advancing boron neutron capture therapy (BNCT), a promising treatment that leverages selective boron accumulation and neutron irradiation to eradicate cancer cells. The frequent upregulation of LAT1 in aggressive tumors (such as gliomas and specific subtypes of lung and breast cancer) underpins its essential role as the principal mediator of tumor-selective boron compound uptake in BNCT. The present review comprehensively examines the structure and function of LAT1, the mechanistic principles of boron transport (including LAT1 mediation) and the key regulatory pathways governing BNCT efficacy. Building on this and given the role of LAT1 in reprogramming tumor metabolism through amino acid transport, advanced metabolomics tools, particularly liquid chromatography-mass spectrometry and nuclear magnetic resonance, offer a novel approach for clarifying the contribution of LAT1 to BNCT. These techniques hold significant potential to map metabolic profiles altered by LAT1-mediated boron compound uptake, thereby elucidating downstream biochemical consequences relevant to the therapeutic efficacy and resistance mechanisms. Synthesizing the dual role of LAT1 as both a vulnerability and therapeutic target in BNCT, the present review systematizes key challenges, including the need for selective boron compounds, resistance mechanisms and off-target effects, while mapping actionable pathways to unlock its potential via refined regulation strategies, next-generation delivery agents and personalized approaches. By addressing these knowledge gaps, this synthesis provides a foundational framework to harness LAT1-targeted BNCT, offering potential to advance precision oncology paradigms and improve clinical outcomes for patients with LAT1-enriched tumors.

Contents

1. Introduction

Cancer remains a global health burden, with aggressive tumors such as glioblastoma (GBM) presenting some of the most challenging scenarios in oncology. Despite the long-standing use of conventional therapies (such as surgery, radiotherapy and chemotherapy), treatment outcomes remain suboptimal due to therapeutic resistance and tumor recurrence. For patients with GBM, even aggressive multimodal approaches yield a median survival time of <15 months and a 5-year survival rate <5% (1), underscoring the urgent need for novel strategies that selectively eradicate malignant cells while sparing healthy tissues.

Boron neutron capture therapy (BNCT) has emerged as a promising targeted modality to address this clinical impasse. In a cohort of 79 patients with locally recurrent head and neck cancer treated with BNCT in a single-arm study, an overall

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Key words: L-type amino acid transporter 1, boron neutron capture therapy, aggressive tumors, boron transport, tumor metabolism

response rate of 68.1% (36.2% complete response, 31.9% partial response), with a median overall survival (mOS) time of 10 months and a 2-year survival rate of 21% was achieved (2). Similarly, among 44 patients with recurrent/refractory high-grade meningioma, BNCT provided durable local control and an mOS time of 29.6 months (3). These data demonstrate the efficacy of BNCT against conventionally treatment-resistant tumors. The therapeutic foundation of BNCT lies in the unique nuclear properties of boron-10 (^{10}B). When irradiated by thermal neutrons, ^{10}B undergoes a fission reaction that releases high linear energy transfer (LET) radiation at the cellular level (4). This mechanism enables precise tumor targeting, a critical advancement for managing aggressive malignancies.

The efficacy of BNCT critically depends on selective tumor delivery of boron compounds primarily mediated by L-type amino acid transporter 1 (LAT1) (5). This transporter is upregulated in diverse aggressive malignancies (such as GBM, melanoma and hepatocellular carcinoma), rendering it an ideal target for tumor-specific ^{10}B accumulation (6-10). Clinically, LAT1-targeted boron carriers, have demonstrated success by exploiting this upregulation to achieve selective boron delivery while sparing normal tissues (4). These favorable safety and efficacy profiles underscore the potential of LAT1-targeted therapies as a cornerstone for BNCT.

Building on this foundation, innovative boron carriers have been engineered to enhance tumor specificity and improve boron delivery (11,12). Despite these advances, clinical translation remains hindered by critical hurdles and necessitates predictive biomarkers to stratify patients (13,14). These critical hurdles include: i) Endogenous competition: Amino acid substrates (such as tyrosine, a L system substrate) compete with boron carriers for LAT1 binding, reducing uptake efficiency (15). ii) Off-target risks: Non-specific boron accumulation in LAT1-expressing non-malignant tissues (such as brain endothelium) poses safety concerns (16-18).

To address these challenges, a multidisciplinary strategy integrating advanced analytical and molecular techniques is essential. Emerging metabolomics studies employing advanced platforms such as liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) spectroscopy could uncover the complex dynamics of LAT1-mediated boron metabolism, shedding light on carrier optimization strategies. Concurrently, protein interaction screening techniques may identify critical binding partners that modulate LAT1 function, informing the design of carriers with reduced off-target toxicity. A deeper understanding of the biological functions of LAT1, particularly its role in amino acid transport and metabolic reprogramming, is imperative for the development of next-generation boron delivery vectors. Crucially, this requires concurrent exploration of the regulatory mechanisms of LAT1 at the molecular and cellular levels. Genetic mutations, epigenetic alterations and environmental factors that influence LAT1 expression could serve as biomarkers for personalized therapeutic strategies (19). By mapping these regulatory networks, researchers can synchronize boron delivery systems with individual tumor biology to advance personalized BNCT.

Critical unanswered questions include defining long-term BNCT efficacy, elucidating resistance mechanisms and identifying synergistic combination therapies (20). For instance, integrating BNCT with immune checkpoint inhibitors could harness radiation-induced immunogenic cell death to potentiate antitumor immunity (21). Additionally, nanocarrier engineering and prodrug strategies may further enhance boron delivery specificity (22-24). By bridging mechanistic understanding with technological innovation, BNCT has the potential to redefine cancer treatment paradigms, offering a beacon of hope for patients with aggressive malignancies.

The present review provides a comprehensive analysis of the role of LAT1 in BNCT and points the way forward to address current limitations and realize the full transformative potential of this precision medicine approach.

2. Therapeutic principle of BNCT

As aforementioned, BNCT is a binary targeted radiotherapy predicated on the nuclear capture reaction between ^{10}B isotopes and thermal neutrons. This process triggers a nuclear reaction that produces high-energy α particles and lithium ions, selectively killing tumor cells. BNCT achieves tumor selectivity through a binary process, including: i) Tumor-targeted accumulation of ^{10}B carriers: It is essential to transport sufficient ^{10}B to tumor cells, with ~10^9 ^{10}B atoms per cell or ~15 μg of ^{10}B per gram of tumor tissue (25), while minimizing boron in healthy tissues to avoid toxicity (26,27); and ii) controlled irradiation with thermal neutrons: Based on the selective uptake of boron-containing compounds by tumor cells, BNCT is followed by irradiation with low-energy thermal neutrons (28,29). The neutron capture reaction produces high LET particles, resulting in extensive DNA damage and cancer cell death (Fig. 1). This approach spares healthy tissues due to the limited penetration range of high LET particles (4-9 μm), making it a precision-based treatment (29-31).

Historical evolution and technical advances. The concept of BNCT originated in the 1950s, with early efforts focusing on inorganic boron compounds (32). Critical milestones in its development include the synthesis of sulfhydryl-containing boron hydrides by Soloway *et al* (33) at Massachusetts General Hospital in the 1960s, which led to the identification of sodium borocaptate (BSH) as the first clinically viable boron carrier through thiol-mediated tumor targeting (34). Subsequently, in the 1980s, Hatanaka and Nakagawa (35) conducted pioneering clinical trials in Japan that established the application of BSH for treating brain tumors. Additionally, boronophenylalanine (BPA) emerged later, initially for cutaneous melanomas, expanding the applicability of BNCT (36).

Parallel to these advances in pharmacology, a significant evolution in technology occurred. Historically, BNCT relied exclusively on nuclear reactors for neutron generation, imposing significant limitations on clinical accessibility due to facility complexity and regulatory constraints. The paradigm shifted post-2015 with the maturation of accelerator-based neutron sources (37), which enabled hospital-based deployment, exemplified by Japan's 2020 regulatory approval of BNCT for recurrent head and neck cancer. This technological evolution underscores the emergence of BNCT as a precision radiotherapy modality, providing the foundation for its expanded clinical investigation.

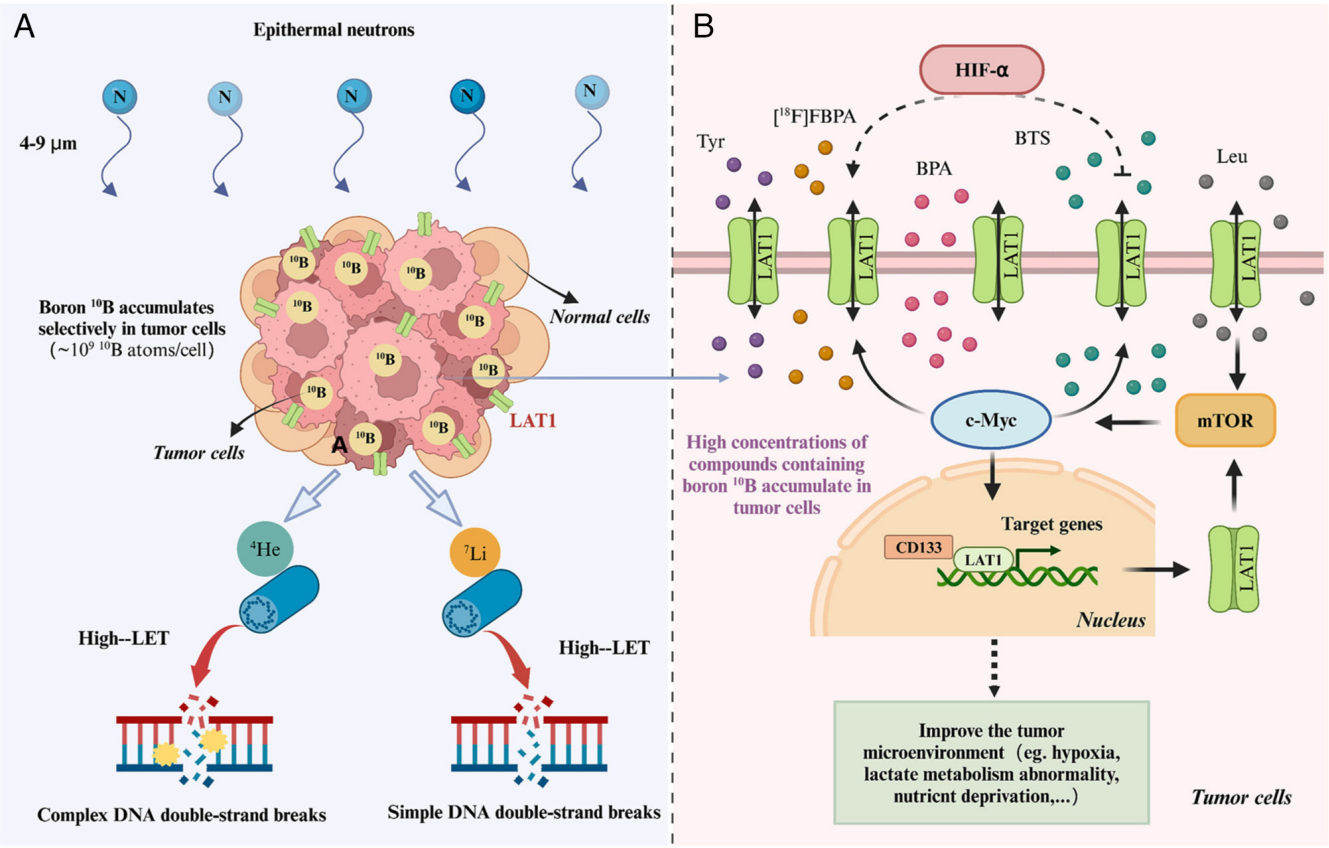

Figure 1. Schematic representation of the therapeutic principle of BNCT and the specific uptake of boron-containing compounds by LAT1 in the TME. (A) During epithermal neutron irradiation, ^{10}B selectively accumulated in tumor cells undergo the neutron capture reaction, producing high-LET α-particles (^{4}He) and lithium ions (^{7}Li) that induce complex DNA double-strand breaks. LAT1-targeted strategies enhance the selective accumulation of ^{10}B-containing compounds in tumor cells, highlighting its role in BNCT efficacy. (B) Novel boron-containing compounds with structural similarity to Tyr, such as BPA, are transported into the cell through LAT1 on the cell membrane, leading to an increase in the concentration of ^{10}B-containing compounds in cancer cells. The oncogene c-Myc binds to the LAT1 promoter, which promotes LAT1 transcription and expression in the nucleus. In addition, the CD133 promoter can also promote LAT1 upregulation. Together they improve the TME. LAT1, L-type amino acid transporter 1; BNCT, boron neutron capture therapy; TME, tumor microenvironment; LET, linear energy transfer; BPA, boronophenylalanine; BTS, 3-borono-L-tyrosine; [^{18}F]FBPA, ^{18}F-fluoro-borono-phenylalanine; HIF-α, hypoxia-inducible factor-α.

Therapeutic potential and clinical applications. Capitalizing on these technical and pharmacological advancements, BNCT demonstrates significant potential for invasive and recurrent malignancies (such as GBM and head and neck squamous cell carcinoma) by exploiting molecular disparities between tumor and normal tissues (Table I) (38-40). To date, >14 registered clinical trials (ClinicalTrials.gov and ChiCTR.org.cn) across multiple cancer types have been validating the broadening therapeutic scope of BNCT. A key element in modern BNCT is the use of BPA, an amino acid analog internalized by cancer cells via specific transport pathways, most notably LAT1 (36). To visualize and quantify its uptake, ^{18}F-labeled BPA (^{18}F-FBPA) has been developed as a potent positron emission tomography (PET) tracer. The high tumor-to-normal tissue uptake ratio of ^{18}F-FBPA allows for non-invasive assessment of boron biodistribution, which is crucial for patient selection, treatment planning and verifying the efficacy of boron delivery (34,41). Despite these advances, clinical data reveal a persistent challenge: Achieving sufficiently high and tumor-selective boron concentrations to maximize the therapeutic effect.

To address this limitation, LAT1 has become a central molecular target for enhancing BNCT. As shown in Fig. 1, LAT1 is upregulated in metabolically active tumors (such as GBM and squamous cell carcinoma) and facilitates BPA uptake by mimicking essential amino acid transport (17). The expression of LAT1 positively correlates with intracellular ^{10}B accumulation, which is critical for BNCT efficacy (42). Although LAT1 upregulation often indicates a poor prognosis (43), it enhances BNCT sensitivity by enabling higher boron delivery and increased cytotoxicity after neutron irradiation (31). Once boron compounds have selectively accumulated in tumor cells, patients undergo thermal neutron irradiation, which triggers the neutron capture reaction. This reaction produces ^{4}He and ^{7}Li that cause localized and substantial damage to cancer cells (44).

Current and future research is intensely focused on refining this targeted approach. Key strategies include elucidating the molecular biology of LAT1 and developing novel boron compounds with improved tumor specificity and delivery efficiency (11,36,45,46). These efforts, combined with ongoing improvements in neutron source technology and computational treatment planning, aim to optimize the therapeutic index of BNCT. By systematically addressing its current challenges, these advancements are poised to establish BNCT as a more effective and widely applicable treatment modality for a broad spectrum of intractable cancer types.

Table I. Clinical trials of boron neutron capture therapy registered on ClinicalTrials.gov and ChiCTR.org.cn[a].

Start date	NCT number	Study status	Sponsor	Phase	Enrollment, n	Agents	Combination therapy	Disease
April 1, 1996	NCT00002781	Unknown	Beth Israel Deaconess Medical Center	Phase 1	15	BPA-F	Single agent	Melanoma (skin)
May 1, 1999	NCT00115453	Terminated	Boneca Corporation	Phase 1 and 2	50	BPA	Single agent	GBM
March 1, 2001	NCT00115440	Completed	Boneca Corporation	Phase 1 and 2	22	BPA-F	Single agent	Supratentorial GBM or anaplastic astrocytoma
May 1, 2002	NCT00059800	Completed	Beth Israel Deaconess Medical Center	Phase 2	36	Not mentioned	Not mentioned	Melanoma (skin)
May 1, 2002	NCT00039572	Completed	Beth Israel Deaconess Medical Center	Phase 1 and 2	16	BPA-F	Single agent	GBM and intracranial melanoma
June 1, 2002	NCT00004015	Completed	EORTC	Phase 1	36	BSH	Single agent	GBM removed during surgery
April 1, 2003	NCT00062348	Completed	EORTC	Phase 1	27	BPA-F and/or BSH	Not mentioned	Thyroid cancer, head and neck cancer or liver metastases
December 1, 2003	NCT00114790	Completed	Boneca Corporation	Phase 1 and 2	30	BPA	Single agent	Head and neck cancer
April 1, 2004	NCT00085059	Terminated	EORTC	Phase 2	4	BPA-F	Single agent	Melanoma (skin)
October 1, 2007	NCT01233492	Terminated	Cancer Research UK	Phase 1	36	BPA	Mannitol	GBM
June 1, 2009	NCT00927147	Terminated	Boneca Corporation	Phase 1 and 2	17	BPA	Cetuximab	Locally recurring head and neck cancer
September 1, 2009	NCT00974987	Completed	Translational Research Center for Medical Innovation, Kobe, Hyogo, Japan	Phase 2	32	BSH and BPA	Temozolomide	Newly diagnosed GBM
July 1, 2010	NCT01173172	Completed	Taipei Veterans General Hospital, Taiwan	Phase 1 and 2	17	BPA	Single agent	Head and neck cancer
July 1, 2013	NCT02759536	Unknown	The Third Xiangya Hospital of Central South University	Phase 1 and 2	30	BPA-F	Single agent	Malignant melanoma
November 1, 2013	NCT02004795	Unknown	Taipei Veterans General Hospital, Taiwan	Phase 1 and 2	28	BPA	Image-guided intensity modulation radiotherapy	Recurrent head and neck cancer
November 19, 2019	NCT04293289	Completed	Cancer Intelligence Care Systems, Inc.	Phase 1	10	Borofalan (^{10}B)	Single agent	Malignant melanoma and angiosarcoma

Table I. Continued.

Start date	NCT number	Study status	Sponsor	Phase	Enrollment, n	Agents	Combination therapy	Disease
June 1, 2020	NCT05883007	Active, not recruiting	Southern Tohoku BNCT Research Center	Phase 1	30	Borofalan (^{10}B)	Single agent	Head and neck squamous cell carcinoma
September 19, 2022	[b]ChiCTR2200066473	Unknown	Xiamen Honghai Hospital	Not applicable	6	BPA, L-^{18}F-BPA	Not mentioned	Advanced refractory malignant tumors
November, 1 2022	NCT05601232	Active, not recruiting	Stella Pharma Corporation	Phase 2	10	Borofalan (^{10}B)	Single agent	Unresectable angiosarcoma
December 5, 2022	NCT05737212	Recruiting	Dawonmedax Co., Ltd.	Phase 1 and 2	39	BPA	Single agent	Recurrent high-grade glioma
December 26, 2022	NCT05538676	Recruiting	Xiaohua Zhu	Not applicable	10	F-BPA (diagnosis agent)	Single agent	Solid tumors
October 17, 2023	[b]ChiCTR2300078618	Unknown	Xiamen Hongai Hospital	Not applicable	16	BPA, L-^{18}F-BPA	Not mentioned	Advanced refractory malignancies
March 15, 2024	[b]ChiCTR2400082903	Unknown	Ethics Committee of Xiamen Hongai Hospital	Phase 1	48	BPA, L-^{18}F-BPA	Not mentioned	Recurrent head and neck malignancies
June 13, 2024	[b]ChiCTR2400088140	Unknown	Xiamen Humanity Hospital	Not applicable	6	BPA, L-^{18}F-BPA	Not mentioned	Advanced recurrent solid tumors
October 14, 2024	NCT06668987	Recruiting	Heron Neutron Medical Corp.	Phase 1 and 2	10	B^{10} L-BPA	Single agent	Recurrent meningioma
March 1, 2025	NCT06603987	Not yet recruiting	Stella Pharma Corporation	Phase 1 and 2	30	Borofalan (^{10}B), [^{18}F]FBPA (diagnosis agent)	Not mentioned	Unresectable and recurrent thoracic solid tumors

[a]Results obtained using the keywords 'BNCT' and 'cancer.' [b]Results from ChiCTR were obtained using the keywords 'BNCT' (accessed on January 23, 2024). BPA, boronophenylalanine; BPA-F, BPA-fructose complex; GBM, glioblastoma; EORTC, European Organisation for Research and Treatment of Cancer; BSH, sodium borocaptate; F-BPA, fluoride-labeled BPA.

3. Structure and functional mechanisms of LAT1

Acting as a member of the solute carrier family, LAT1 plays a critical role in cellular amino acid transport, particularly in rapidly proliferating tumor cells (47). The high expression of LAT1 in various cancer types underscores its importance in supporting the metabolic demands of malignancies (16). LAT1 forms a heterodimeric complex with 4F2hc, crucial for its transport activity and plasma membrane localization (Fig. 2) (48). The structural and functional characteristics of LAT1 allow for the selective uptake of large neutral amino acids, which are essential for protein synthesis, cell growth and signaling pathways (49). This section explores the structural features and functional mechanisms of LAT1, laying a

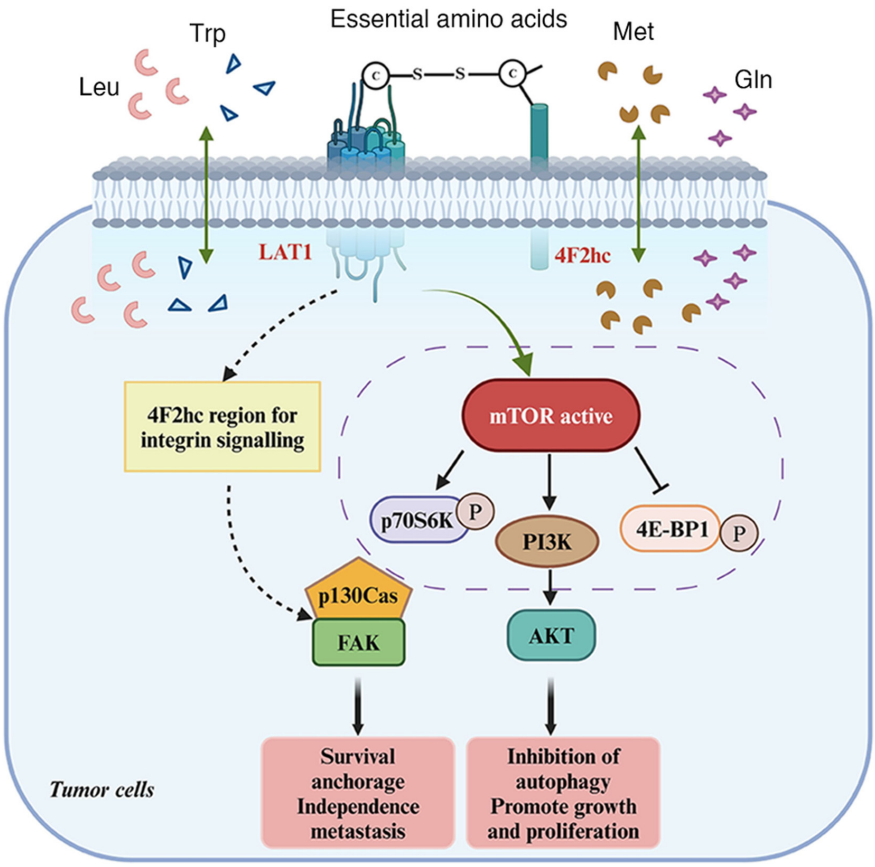

Figure 2. Schematic representation of the structure and functional mechanisms of LAT1. LAT1 forms a functional heterodimer with 4F2hc at the plasma membrane, covalently linked by disulfide bonds. This complex facilitates the transport of essential amino acids such as Leu, Trp, Met and Gln into the cell. The accumulated amino acids activate the mTOR pathway, leading to the phosphorylation of the translation regulators p70S6K and 4E-BP1. This activation also inhibits autophagy and promotes tumor cell proliferation via the PI3K pathway. In addition, upregulating the expression of LAT1 could activate integrin signaling pathways, including p130CAS/FAK. This signaling promotes tumor cell survival, anchorage independence and metastasis, highlighting the central role of LAT1 in cancer progression. LAT1, L-type amino acid transporter 1; p70S6K, p70 S6 kinase; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; PI3K, phosphatidylinositol 3-kinase; p130CAS, p130 Crk-associated substrate; FAK, focal adhesion kinase.

foundation for grasping its potential as a therapeutic target in BNCT.

Structural characteristic of LAT1. LAT1, also known as SLC7A5, is a member of the heterodimeric amino acid transporter family. Structurally, it forms a complex with two distinct subunits: A light chain (LAT1) and a heavy chain (4F2hc). The LAT1 subunit is directly responsible for translocating amino acids across the cell membrane. However, it requires a functional partnership with the 4F2hc heavy chain, which is essential for stabilizing the LAT1 subunit and ensuring its correct localization to the plasma membrane (50). This partnership is maintained through extensive interactions at the extracellular, intramembrane and intracellular interfaces. A crucial covalent disulfide bond between Cys164 on LAT1 and Cys210 on 4F2hc links the two subunits (Fig. 2). The stability of this complex is further enhanced by non-covalent polar interactions at the extracellular interface, such as those between Thr163 and Glu303 of LAT1 and Lys533 and Arg535 of 4F2hc. Additionally, the transmembrane helix of 4F2hc stabilizes the complex via hydrophobic interactions with transmembrane helix (TM) 4 of LAT1 and contributes to membrane localization through an intracellular lipid-binding pocket involving residues such as Arg183 (48,51). The functional significance of this intricate structural arrangement is underscored by experimental evidence. Purified LAT1 alone exhibits no transport activity, whereas the recombinant LAT1-4F2hc complex is fully functional. Consistent with this, deletion of the extracellular domain of 4F2hc abrogates >90% of transport activity (48). Therefore, the precise and multi-faceted interaction between LAT1 and 4F2hc is indispensable for the structural integrity, stability and overall transport function of the complex (52,53).

The transport process is dictated by the specific structure of the LAT1 subunit, which is composed of 12 transmembrane helices arranged in a characteristic LeuT fold (49). These helices and specific amino acids play a critical role in substrate recognition and binding, enabling efficient substrate translocation across the membrane through dynamic conformational changes (48,52,54). The substrate binding pocket of LAT1, formed by the Gly255 side chain, accommodates amino acids with larger side chains, thereby conferring the substrate selectivity of LAT1 (49,55). This selectivity allows it to preferentially bind amino acids with specific side chain sizes and shapes. Critical residues, such as Trp405 and Tyr259, stabilize substrates within the transporter through hydrogen bonding and electrostatic interactions (48,56). Mutations in these residues significantly impair the transport efficiency of LAT1 (48,52,57).

LAT1 undergoes dynamic conformational changes during substrate translocation, alternating between outward-facing and inward-facing states (48,52,54). In its outward-facing conformation, LAT1 binds substrates such as histidine at the binding site, triggering a transition to the inward-facing state. This conformational change facilitates the extracellular transport of substrates such as glutamine. LAT1 exhibits different affinities for different amino acid substrates, including isoleucine, during this bidirectional transport process (58).

The unique structural features of LAT1 allow it to recognize neutral amino acids with branched or aromatic side chains. The α-amino and α-carboxyl functional groups are key determinants for substrate recognition (59). LAT1 has a strong binding affinity for its substrates, with a K_m value between 15 and 50 μM (56). In addition, the charge of the carbonyl oxygen near the amino group (ranging from -0.55 to -0.56) influences substrate recognition. The introduction of lipophilic and aromatic groups enhances LAT1-mediated drug transport. Factors such as pK_a, log P, polar surface area and hydrogen bond donor groups further influence LAT1-mediated transport (58).

Biological functions of LAT1. As aforementioned, LAT1, a sodium-independent transmembrane protein, plays multiple significant roles in organisms. The specialized structural configuration and transport mechanism of LAT1 allows for selective and efficient amino acid transport across cell membranes (60,61). LAT1 mainly facilitates the uptake of large neutral amino acids such as leucine, phenylalanine, tyrosine and methionine, which are fundamental for protein synthesis, cell growth and energy metabolism (11,62,63). Notably, the critical role of LAT1 in regulating essential cellular processes extends to pathological contexts, particularly in the development and progression of cancer.

In oncogenesis, LAT1 extends beyond nutrient transport, serving as a critical modulator of pro-tumorigenic signaling pathways. As depicted in Fig. 2, LAT1 positively regulates mTORC1 and β1-integrin pathways, directly accelerating tumor proliferation and metastatic dissemination (16). The upregulation of LAT1 in tumor cells ensures a continuous supply of nutrients, facilitating faster growth. Meanwhile, LAT1 forms a functional heterodimer with 4F2hc (CD98hc), activating focal adhesion kinase (FAK)/SRC cascades essential for cancer survival (58). In the tumor microenvironment, LAT1 displays notable adaptability, operating efficiently under fluctuating ionic conditions and independent of sodium gradients. This adaptability allows LAT1 to maintain amino acid transport and metabolic support for tumor cells even in stressful environments (16,64). Moreover, in malignant cells, LAT1 upregulation creates a feed-forward loop. Beyond its role in oncogenesis, LAT1 is also indispensable for central nervous system homeostasis. LAT1 transports essential amino acids across the blood-brain barrier, supporting neurotransmitter synthesis and overall neuronal health. Disruptions in LAT1 activity have been associated with several neurological disorders, making it a promising therapeutic target for diseases of the nervous system (61).

In summary, LAT1, a vital amino acid transporter, is highly expressed in numerous types of cancer cells, supporting rapid proliferation and survival under challenging conditions. The unique functional properties of LAT1 make it a compelling target for novel therapeutic strategies, including its application in targeted cancer therapies such as BNCT.

4. Mechanistic analysis of LAT1 in BNCT

In the context of BNCT, the amino acid transport mechanisms of LAT1 (as shown in Fig. 1) play a key role in the selective uptake of boron-containing compounds such as BPA. Through its interaction with 4F2hc, LAT1 not only facilitates the transport of amino acids, but also enables the targeted delivery of boron to tumor cells, ensuring preferential accumulation in malignant tissues (5). This mechanistic advantage positions LAT1 as a key player in optimizing the efficacy and specificity of BNCT, making it a promising avenue for targeted cancer treatment.

LAT1-mediated boron compound uptake. BPA, a key boron carrier in BNCT, is predominantly transported into tumor cells via the L-type amino acid transport system, particularly LAT1. The recognition of substrates by LAT1 occurs within a sterically defined binding pocket. For canonical substrates such as L-phenylalanine and L-tyrosine, the α-carboxyl and α-amino groups interact with the backbones of TM1 and TM6, respectively. Concurrently, the aromatic side chain is oriented toward Gly255 and stabilized by van der Waals forces (55,65). This specific binding mechanism also accounts for the transporter's recognition of structural analogs, such as BPA. In melanoma cells, BPA uptake occurs through mechanisms similar to L-tyrosine transport (66), involving both amino acid carrier-mediated uptake and passive intracellular accumulation due to its lipophilicity. L-tyrosine is primarily transported by the L system but also via the ASC (alanine, serine and cysteine) transport system (66). Preloading with L-tyrosine increases BPA uptake by altering intracellular amino acid gradients; however, co-incubation leads to competitive inhibition, reducing BPA uptake by ~50% (66). In gliosarcoma cells, BPA uptake is specifically mediated by the L system rather than the A system and is modulated by amino acid concentrations across the cell membrane. Pre-accumulation of L-tyrosine or BCH induces a trans-stimulation effect, enhancing BPA influx through exchange mechanisms, whereas simultaneous incubation results in competitive inhibition (15). BPA efflux is also an exchange-based process, with its rate influenced by the presence of amino acids and L/A system substrates in the extracellular medium. For instance, in C6 glioma cells, preloading with L-DOPA significantly enhances BPA uptake (up to five-fold), likely through activation of membrane-bound LAT transporters. This effect is selectively observed in tumor tissues *in vivo*, suggesting the potential clinical benefit of amino acid preloading strategies in BNCT (67).

Moreover, ^{18}F-FBPA, a radiolabeled BPA derivative, has been identified as a selective substrate for LAT1 and LAT4, confirming the predominant role of the L system in its tumor-specific accumulation (68). In other tumor cell lines, including human hepatocellular carcinoma (HuH-7), human colorectal adenocarcinoma (CaCo-2) and mouse melanoma (B16-F1) cell lines, preloading with L-BPA, L-tyrosine or L-DOPA has been shown to significantly enhance ^{18}F-FBPA uptake (69). These findings reinforce the therapeutic potential

of modulating extracellular amino acid levels and administration timing to optimize LAT1-mediated drug delivery in cancer treatment.

The specificity of LAT1 for boron compounds, such as BPA, boronotyrosine and fluoroboronotyrosine (12,14), is driven by their structural similarity to natural substrates such as tyrosine, allowing competitive binding and selective uptake in LAT1-upregulated tumor cells (49,70). This uptake is further optimized by designing boron compounds that mimic amino acid substrates or modifying side chains to enhance LAT1 affinity (12,71). For example, compounds such as 4(benzo[d] thiazol-2-yl)phenylboronic acid, which exhibit high brain permeability, or ^{18}F-FBPA, which predicts ^{10}B concentrations in tumors, demonstrate the potential for enhancing tumor targeting and boron delivery. These innovations aim to maximize LAT1-mediated delivery and improve therapeutic outcomes (72).

The development of boron carriers, such as BPA, has been pivotal in BNCT but faces challenges, such as its low boron content and suboptimal pharmacokinetics (68). The core objective of the next-generation boron drugs is to address the shortcomings of existing boron drugs (including BPA and BSH), such as insufficient targeting, low boron content and toxic side effects, through precise targeting, efficient delivery and multi-functional integration, thereby promoting the clinical application of BNCT in more tumor types (36,71). Additionally, nanotechnology-based delivery systems, such as polyboronate ester micelles, are being explored to enhance pharmacokinetics and tumor selectivity while minimizing systemic toxicity (21,73).

Heterogeneity of LAT1 expression in tumors and BNCT efficacy. LAT1 is a critical protein in oncology, serving as both a marker of aggressive disease and a key mediator for therapeutic intervention. LAT1 is upregulated in a wide variety of malignancies, including brain, head and neck, lung, breast and pancreatic cancer (18,47,74), where its presence is strongly correlated with increased tumor proliferation, angiogenesis and poor prognosis (42,49,75). Crucially for BNCT, LAT1 is the primary transporter for boron-containing agents such as BPA. Since LAT1 is expressed in ~70% of viable tumor cells, its expression level is a key determinant of how much boron can be delivered to the cancer, directly influencing the potential efficacy of the therapy (17). While high LAT1 expression is necessary for BNCT, its inconsistent and heterogeneous expression within and across tumors presents a major therapeutic obstacle (Table II) (76,77). This variation leads to the uneven microdistribution of BPA, where regions with high LAT1 levels respond favorably, while regions with low LAT1 levels are undertreated, creating pockets of resistant cells (17,78). This heterogeneity is a direct cause of treatment failure and recurrence. For example, in a study of patients with recurrent head and neck cancer, non-homogeneous BPA uptake contributed to frequent local recurrence despite a high initial response rate (12/17 patients) (79). Similarly, in high-grade glioma, uneven BPA delivery resulted in inconsistent tumor regression and, in some cases, led to cerebrospinal fluid dissemination post-BNCT, particularly in highly heterogeneous small-cell GBM (80). The correlation between LAT1 expression and tumor grade can also be inconsistent; while it rises with malignancy in glioma (77), prostate (81) and neuroendocrine (82) tumors, no clear link has been established for biliary tract, ovarian or lung cancer (47).

This clinically significant heterogeneity is not random but is driven by complex molecular signals within the tumor microenvironment (TME). Key regulatory factors include: i) Hypoxia: The hypoxic TME regulates LAT1 via hypoxia-inducible factors (HIFs) (62). While HIFs can upregulate LAT1 to facilitate nutrient uptake in deprived conditions (47,76), some factors such as HIF-1α can also reduce its expression, limiting the effectiveness of BNCT in certain tumor zones (83). ii) Oncogenic pathways: Several major cancer-driving pathways directly control LAT1 expression. Signaling through c-Myc (84,85) and mTOR (64), as well as pathways associated with cancer stem cell markers such as CD133 (86), can significantly alter LAT1 levels, contributing to the mixed expression patterns observed in tumors.

Overcoming LAT1 heterogeneity is paramount for improving BNCT outcomes. A multi-pronged approach is required, focusing on assessment, modulation and further research. Advanced imaging techniques capable of mapping LAT1 expression across the entire tumor are urgently needed to optimize treatment planning. Furthermore, future clinical trials must incorporate larger patient samples and stratification by LAT1 expression to definitively correlate expression with survival and tumor control rates (17). Additionally, strategies aimed at upregulating LAT1 expression could sensitize resistant tumor regions to BNCT. This includes pharmacological interventions or gene therapies, such as using the CD133 promoter to drive LAT1 upregulation specifically in cancer stem cells, thereby enhancing boron uptake in this critical population (86). Targeting the regulatory pathways (such as mTOR and c-Myc) may also offer a route to normalize LAT1 expression. Continued research should also focus on developing next-generation, LAT1-targeted boron compounds with improved uptake and retention, alongside exploring novel gene regulation mechanisms to ensure more uniform and effective boron delivery across diverse tumor types.

5. Metabolomic insights into LAT1-mediated metabolism in BNCT

Amino acids are essential cellular components that serve as the primary nitrogen source for synthesizing nucleotides, glutathione, amino sugars and proteins (87). Amino acids also act as fuel sources, producing ATP, and play a key role in the biosynthesis of sterols and lipids. In cancer cells, amino acids are reprogrammed to support rapid growth, with altered pathways enhancing tumor survival, often alongside the aerobic glycolysis characteristic of cancer (88). Consequently, LAT1, an amino acid transporter, is upregulated in tumors and plays a pivotal role in maintaining the tumor metabolome by supplying essential nutrients. Metabolomics, using advanced tools such as LC-MS and NMR spectroscopy, provides crucial insights into the role of LAT1 in boron compound metabolism (Fig. 3). These technologies help clarify how LAT1 mediates the uptake, distribution and metabolism of boron compounds, which is vital for optimizing the efficacy and safety of BNCT.

Application of LC-MS in BNCT. LC-MS provides distinct analytical advantages for characterizing metabolites in

Table II. Overview of LAT1 expression in different cancer types and its relevance to BNCT.

Cancer type	mRNA/protein expression of LAT1 in cells or tissues	Preclinical/clinical evidence of BNCT efficacy	Prognostic significance
GBM	LAT1 is upregulated in tumor cells from human GBM, orthotopic murine GBM (Gl261) or patient-derived xenografts compared with normal cells (77). LAT1 protein abundance is increased in isolated microvessels of glioblastoma compared with human normal brain microvessels (135).	In a study of the glioblastoma T98G cell line, overexpression of LAT1 enhanced the therapeutic efficacy of BNCT (31,86). In a phase 2 clinical trial involving 27 patients with recurrent malignant glioma treated with BNCT, the median overall survival time was 18.9 months (105).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (136).
Head and neck cancer	LAT1 was shown to be upregulated in 121 (69.9%) out of 173 untreated head and neck squamous cell carcinoma biopsy samples (137). LAT1 is expressed in KB human oral epidermoid carcinoma cells and is weakly detected in human normal oral keratinocytes (138).	In a study of 28 head and neck cancer patients, LAT1 expression correlates with ^{18}F-FBPA uptake and evaluation of LAT1 expression may help predict the therapeutic effect of BNCT (13). In a phase 1/2 study involving 30 patients with recurred head and neck cancer treated with BNCT, the median overall survival time was 13.0 months (39).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (137,139).
Melanoma	LAT1 mRNA expression levels in MM tissues (0.45±0.43) were significantly higher than in normal tissues (<0.01). LAT1 protein expression detected in 5 MM cell lines (CMeC-1, CMeC-2, LMeC, PuMeC and KMeC) (140).	In a Japanese group (1987-2002), non-nodular melanomas showed excellent responses, with an 81.2% CR rate (13/16) and 100% response rate (16/16). For patients with primary melanoma, the 5-year cause-specific survival rate was 74%. In another Japanese group (2003-2014) 8 patients with early-stage ($T_{1-2}N_0M_0$) cutaneous melanoma achieved a 75% CR rate (6/8). In an Argentine group (2003-2007) with multiple metastases cases, the lesion-based response rate (CR + PR) was 69.3%. (8,141).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (142,143).
Lung cancer	LAT1 expression among 27 patients with lung cancer and lung metastasis: 3 cases (11.1%) showed no significant expression, while mild, moderate and high expression levels were observed in 8 (29.6%), 8 29.6%) and 7 (25.9%) (cases, respectively (41). The positive rate of LAT1 expression inadenocarcinoma and non-adenocarcinoma was 79.6 and 15.1%, respectively (74).	In a study exploring BNCT for NSCLC, the tumor control probability value was ~0.8 for localized early stage NSCLC. The mean number of expected controlled lesions in oligometastatic disease was ~60.4% (3.02/5). Additionally, the cumulative probability distribution indicated that in 93% of the cases, the expected number of controlled lesions was 50% (2.5 nodules) or more (144).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (74).
Breast cancer	LAT1 protein levels showed a clear gradient among different cancer cell types: Lowest in FLC-4 cells (hepatocarcinoma); medium in MCF-7 (breast cancer cell line) and MIA PaCa-2 cells (pancreatic cancer); highest in HeLa S3 (cervical cancer) and T3M4 cells (pancreatic cancer cell line) (5). Positive LAT1 expression was found in different subtypes of breast cancer: 27 (84.4%) with the luminal A subtype, 27 (64.3%) with the luminal B/triple positive subtype, 29 (82.9%) with the triple negative subtype and 24 (66.7%) with the HER2-only positive subtype (145).	In a study of the breast cancer MCF-7 cell line, the LAT1 protein levels were proportional to the BPA uptake rate. BNCT efficacy relied on ^{10}B uptake (5).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (146).

Table II. Continued.

Cancer type	mRNA/protein expression of LAT1 in cells or tissues	Preclinical/clinical evidence of BNCT efficacy	Prognostic significance
Renal cancer	The expression rate of LAT1 in the cancerous areas of renal cell carcinoma was 97.8% (147).	Not available	High LAT1 expression is an independent prognostic factor predicting a poor outcome (147).
PCa	Stronger LAT1 immunoreactivity was detected in PCa cancerous lesions compared with non-cancerous lesions (148)	BPA-mediated BNCT reduced PCa progression without affecting apoptosis in a PCa xenograft model (149).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (150).
Pancreatic cancer	LAT1 expression is low in pancreatic cancer and even lower in high CA19-9 pancreatic cancer (127). The high expression rate of LAT1 in pancreatic cancer was shown to be 52.6% (151).	BNCT using glucose-BSH demonstrated showed strong cytotoxic activity against CA19-9 producing pancreatic cancer cells and significant tumor volume reduction in pancreatic cancer mouse models (127).	High LAT1 expression is an independent prognostic factor predicting a poor outcome (151).

LAT1, L-type amino acid transporter 1; BNCT, boron neutron capture therapy; BPA, boronophenylalanine; ^{18}F-FBPA, ^{18}F-fluoro-borono-phenylalanine; BSH, sodium borocaptate; GBM, glioblastoma; MM, malignant melanoma; NSCLC, non-small cell lung cancer; PCa, prostate cancer; CR, complete response; PR, partial response.

LAT1-expressing tumors. Unlike elemental detection techniques (such as inductively coupled plasma atomic emission spectroscopy), LC-MS enables the simultaneous quantification of parent compounds and their biotransformation products in biological matrices, offering critical insights into metabolic stability (89,90). Critically, LC-MS uniquely resolves species-specific biodistribution patterns. In a preclinical study, LC-MS was used to assess the metabolic stability of agents such as ^{18}F-FIMP and its biodistribution in tumor-bearing models (91), demonstrating the utility of LC-MS in LAT1-mediated tumor targeting. This molecular specificity makes LC-MS indispensable for mapping the metabolic fates of boron carriers and identifying LAT1-dependent biomarkers predictive of BNCT response.

Application of NMR spectroscopy in BNCT. NMR spectroscopy is crucial for studying the structure and behavior of boron compounds used in BNCT, such as L-p-B and its complexes (92,93). NMR helps researchers understand the structural configurations of these compounds in solution, aiding in the optimization of therapeutic efficacy. Beyond structural analysis, NMR methods, such as non-destructive ^{10}B NMR, allow the quantification of boron species such as ^{10}B-BPA, facilitating the monitoring of BPA concentrations in the blood (94). This real-time tracking is essential for evaluating selective tumor uptake and minimizing off-target effects. NMR also provides reliable methods for monitoring the chemical stability of boron complexes, ensuring their efficacy and safety. Understanding how LAT1 influences the intracellular distribution of boron compounds could lead to more targeted BNCT strategies, improving outcomes in LAT1-expressing tumors.

Integration of LC-MS and NMR in LAT1 mechanistic studies. The integration of LC-MS and NMR in metabolomic studies offers a powerful approach for advancing the understanding of LAT1 in BNCT (95). Specifically, LC-MS enables precise quantification of metabolites and metabolic pathway tracing, whereas NMR provides structural and dynamic insights into boron compound behavior. The combination of these techniques, along with metabolic flux analysis and stable isotope tracing, could unveil how LAT1 affects boron compound metabolism and tumor-specific metabolic signatures (96).

Building on this technical synergy, multi-omics integration further expands mechanistic insights through a three-tiered causal inference framework (97): i) Genomic input: Transcriptomic profiling (such as RNA-sequencing) and somatic mutation data may identify cohorts with aberrant LAT1 regulation; ii) metabolomic correlations: LC-MS/NMR-derived metabolic profiles (such as amino acid pool imbalances) can be mapped to genomic subgroups using multivariate regression; and iii) functional validation: Machine learning can help prioritize candidate metabolic vulnerabilities for experimental validation via CRISPR-interference or pharmacologic inhibition (98). Collectively, this pipeline can

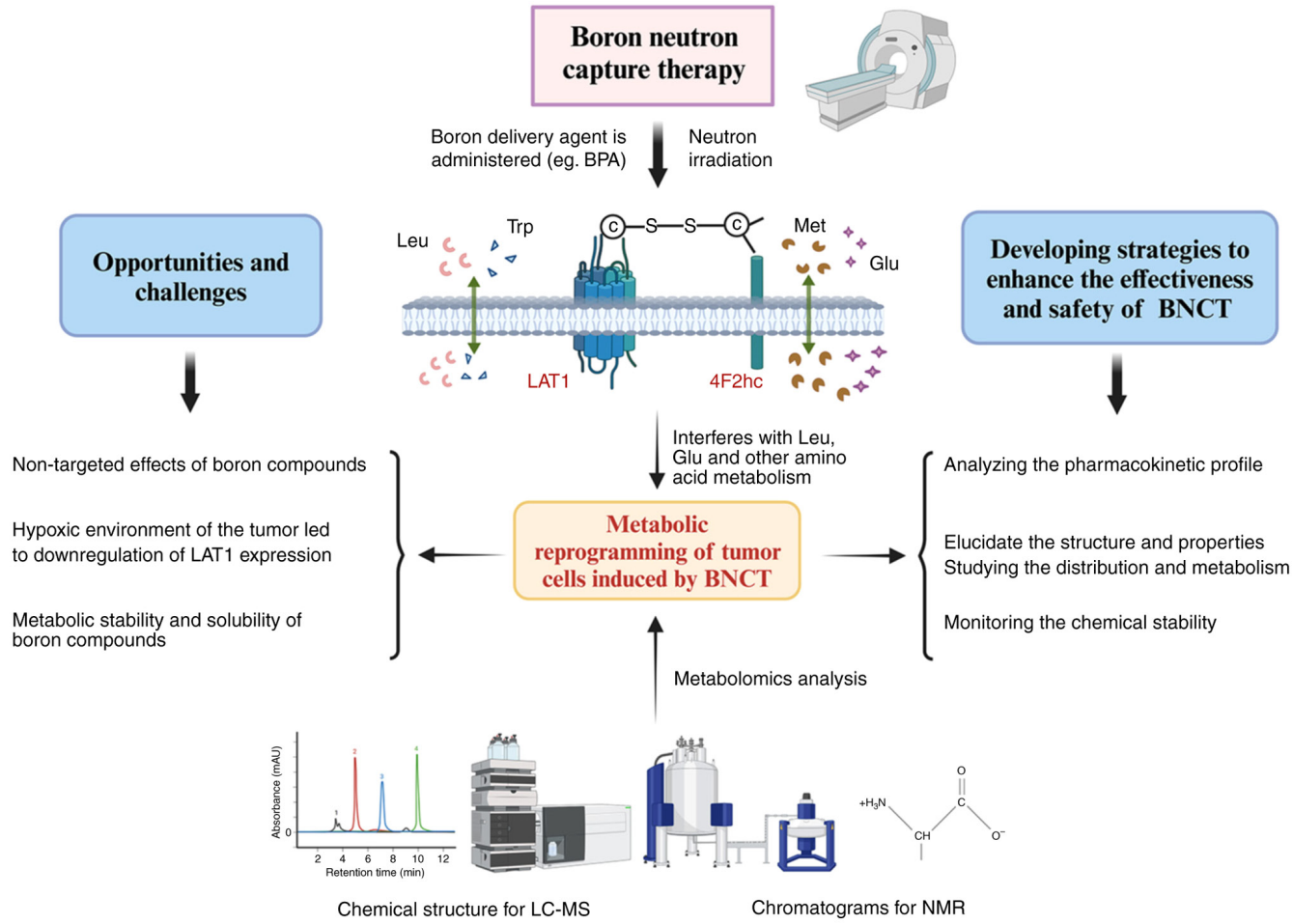

Figure 3. Application of metabolomics in BNCT. LAT1 facilitates amino acid transport and contributes to the formation of a distinct tumor metabolic microenvironment. BNCT uses LAT1 to promote the selective accumulation of boron-containing compounds in tumor cells, thereby inducing metabolic changes within the tumor microenvironment. Metabolomics techniques such as NMR and LC-MS enable comprehensive profiling of metabolic pathways in tumors, providing critical insights that can guide physicians in developing more effective and safer BNCT treatment strategies. LAT1, L-type amino acid transporter 1; BNCT, boron neutron capture therapy; LC-MS, liquid chromatography-mass spectrometry; NMR, nuclear magnetic resonance.

establish mechanistic links between the LAT1 genomic status and metabolic rewiring.

By leveraging these multi-omics approaches, researchers can develop comprehensive systems biology models of LAT1-targeted BNCT and uncover regulatory mechanisms governing boron uptake. Ultimately, these advances will enable more effective BNCT strategies, overcoming resistance and improving patient outcomes.

6. Challenges and potential of LAT1 as a therapeutic target in BNCT

LAT1 has emerged as a promising target for improving the precision and efficacy of BNCT. The upregulation of LAT1 in a number of tumor types and its role in transporting essential amino acids and boron compounds to tumor cells make it an ideal candidate for selective cancer treatment. However, there are challenges that need to be addressed, such as the heterogeneity of LAT1 expression across tumor types, the need for optimized boron compounds and the influence of the TME on LAT1 activity. Despite these obstacles, the potential of LAT1-targeted BNCT can be maximized by combining molecular insights, advanced drug design and personalized therapeutic approaches. This section explores the challenges and opportunities in targeting LAT1, focusing on boron compound optimization, tumor heterogeneity and improving treatment efficacy.

Selection and optimization of LAT1-targeted boron compounds. An ideal boron carrier for targeted cancer therapy should exhibit sustained high tumor accumulation, minimal normal tissue accumulation, rapid metabolism, excellent biocompatibility, non-toxicity, thermal and chemical stability and uniform tumor distribution (71). The ability of LAT1 to selectively transport boron compounds such as BPA into tumor cells positions it as a critical target for BNCT (12,46,99).

Structural research has expanded the scope of LAT1-targeted therapeutic strategies by providing insights into its binding affinity and interactions with boron compounds. Modifications of the amino acids within the binding pocket of LAT1 can increase its affinity for boron compounds, thereby optimizing therapeutic efficacy (100,101). In addition, identifying regions where LAT1 interacts with regulatory proteins, as well as its mechanism of action, provides new avenues for modulating LAT1 activity and improving the selectivity of cancer therapy (56,57). Advances in computational modeling

have deepened the understanding of LAT1 dynamics and ligand interactions, revealing how ligands influence drug and nutrient delivery via LAT1. These insights are enabling the characterization and optimization of ligands through advanced techniques such as structure-based drug design and high-throughput screening, expanding the potential of LAT1 as a transporter for a wide range of therapeutic agents (56,102).

The ability of BPA to carry only a single boron atom also limits its overall efficiency in BNCT (11). To overcome this limitation, researchers are developing novel boron compounds with higher boron atom content to increase boron delivery to tumor cells. For example, polyboronate compounds and boron-rich nanomaterials are being explored as next-generation agents to maximize therapeutic efficacy (71). These advancements aim to improve the boron loading capacity while maintaining high selectivity and stability *in vivo*. Continued innovation in boron compound design, supported by computational modeling and experimental validation, is essential to overcome these challenges and unlock the full potential of LAT1-targeted BNCT.

Challenges and optimization strategies for off-target effects. The widespread expression of LAT1 in both cancerous and non-cancerous tissues raises concerns about potential off-target effects, including the inadvertent uptake of boron compounds in healthy tissues, which may result in collateral damage during neutron irradiation (16,17,103).

Clinical data have clearly documented specific adverse events associated with BNCT across different tumor types. In head and neck cancer trials, the most common acute toxicities are low-grade oral mucositis, radiation dermatitis and alopecia, with rare severe events such as grade 4 laryngeal edema and carotid hemorrhage (79,104). For high-grade gliomas and meningiomas, adverse events are primarily characterized by brain edema (48.1% of cases) (105), radiation necrosis (13.6% of cases) (3) and transient hyperamylasemia (81.5% of cases) (105). Additionally, 18% of patients with glioma treated in Finland experienced grade 3 seizures (78), and 2 out of 17 patients with head and neck cancer developed cranial neuropathy (79). The causes of these adverse events are supported by clinical observations. Radiation-induced tissue damage is a key factor; for instance, transient hyperamylasemia is attributed to salivary gland irradiation (105), while brain edema and radiation necrosis result from normal brain tissue exposure to neutrons, exacerbated by prior radiotherapy (3,10). Cumulative treatment effects also play a role, as patients with multiple prior radiotherapy courses or short intervals (such as 5 months) between prior radiation and BNCT face higher risks of severe toxicities such as carotid hemorrhage (104). Furthermore, tumor and treatment characteristics, such as larger target volumes and proximity to critical structures (including the carotid artery and cranial nerves), increase the likelihood of adverse events (3,79). Minimizing these off-target effects is crucial for optimizing BNCT efficacy.

The strategies to enhance the selectivity of LAT1 span several key areas. Gene therapy can selectively increase LAT1 expression in tumors. Oncogenic drivers such as c-Myc and HIF-2α can upregulate LAT1, helping tumors meet their metabolic demands (84,85). Studies have shown that increasing LAT1 expression in GBM cells enhances BNCT efficacy by promoting boron uptake (31,86). Epigenetic changes in tumor cells can also upregulate LAT1, facilitating greater boron uptake. Targeting these epigenetic regulators with agents such as DNA methyltransferase inhibitors or histone deacetylase inhibitors can selectively increase LAT1 expression, improving BNCT outcomes (101,106). Combining epigenetic therapies with BNCT may address LAT1 expression variability and resistance challenges. The TME also plays an important role in regulating LAT1 expression. Tumor-specific conditions such as hypoxia and nutrient deprivation upregulate LAT1 through HIF-2α, enabling cancer cells to maintain metabolic activity. Therapeutic strategies that induce local hypoxia or mimic nutrient-deprived environments can selectively increase LAT1 expression in cancer cells, enhancing boron uptake while minimizing off-target effects (86,102,107).

LAT1 inhibitors offer another avenue for reducing off-target effects and improving therapeutic specificity in BNCT. For example, the LAT1-specific inhibitor JPH203 has been shown to block the mTORC1 pathway and reduce the survival and proliferation of medulloblastoma cell lines (108). An *in vitro* study has shown that 30 μM JPH203 inhibits LAT1-mediated uptake of BPA derivatives by 40-95% in cell models, with stronger effects on LAT1-specific carriers such as D-4-BPA (109). In the context of BNCT, JPH203 could be strategically used to block LAT1 activity in normal cells, thereby reducing unnecessary boron uptake and sparing healthy tissues from collateral damage during neutron irradiation. In summary, these strategies aim to optimize LAT1 expression and function, enhancing BNCT efficacy while reducing off-target effects and improving patient outcomes.

Challenges and optimization strategies for drug resistance mechanisms. A major challenge with LAT1-targeted therapies is the potential for resistance mechanisms that could limit their efficacy (110). For instance, in estrogen receptor-positive breast cancer cells, LAT1-mediated leucine uptake enhances mTORC1 signaling, contributing to the resistance to endocrine therapies and chemotherapy (111,112). Tumor cells can also adapt to targeted therapies by altering LAT1 expression or function through genetic mutations, epigenetic modifications (107,110,113) or by activating alternative amino acid transporters to compensate (114,115). These adaptations complicate the use of LAT1 as a sole target for BNCT and require innovative approaches to overcome resistance.

To address these challenges, combination therapies targeting multiple pathways hold great potential. For example, combining LAT1-targeted BNCT with immunotherapy, radiation therapy or other targeted therapies could have synergistic effects and improve treatment efficacy. Specifically, integrating BNCT with immunotherapy may enhance the ability of the immune system to eliminate residual tumor cells after neutron irradiation. A recent study has shown that boron-rich polymer microspheres used in BNCT can block the programmed death-ligand 1 immune checkpoint, activating the host immune system (21). Additionally, BNCT-induced tumor cell death can release tumor antigens into the microenvironment, potentially enhancing the effects of immune checkpoint inhibitors (116,117). This dual mechanism may be particularly effective in overcoming tumor resistance to LAT1-targeted therapies.

Furthermore, combining LAT1-targeted BNCT with traditional chemotherapeutic agents or molecularly targeted therapies offers promising opportunities. For example, BPA has been combined with the monoclonal antibody cetuximab, which blocks epidermal growth factor receptor signaling, to enhance the efficacy of BNCT. This approach disrupts key signaling pathways and improves tumor cell sensitivity to BNCT (118). Targeted inhibitors of key pathways, such as mTOR inhibitors, could further sensitize tumor cells to BNCT by increasing their dependence on LAT1 for nutrient uptake (82,119). By targeting the mTOR pathway, these inhibitors reduce tumor cell proliferation and metabolic flexibility, thereby increasing the efficacy of LAT1-mediated boron compound delivery. Notably, certain chemotherapeutic agents that induce cellular stress may upregulate LAT1 expression as a compensatory mechanism (111,112,120). This could potentially increase boron uptake in tumor cells, thereby enhancing the efficacy of BNCT. Future research should explore this avenue to identify chemotherapeutic agents that synergize with LAT1-targeted BNCT by exploiting this adaptive response.

7. Future directions

LAT1 holds great promise as a therapeutic target to enhance the precision and efficacy of BNCT. The ability of LAT1 to selectively transport boron-containing compounds into tumor cells improves therapeutic outcomes while sparing healthy tissues. However, challenges such as understanding LAT1 regulation, optimizing boron compounds and integrating advanced technologies such as multi-omics need to be addressed to fully harness the potential of LAT1 in BNCT. Future efforts should focus on developing LAT1 modulators that either enhance its expression in tumors to increase boron uptake or inhibit it to minimize off-target effects. A deeper understanding of LAT1-mediated resistance, particularly in the context of tumor heterogeneity, will be key to overcoming current limitations and optimizing LAT1-targeted BNCT for clinical use.

In-depth study of LAT1 regulatory mechanisms. LAT1 is aberrantly upregulated in a wide range of tumors, but the underlying regulatory mechanisms remain incompletely understood. Future research should focus on elucidating the molecular pathways that control LAT1 expression, including the role of transcription factors such as c-Myc and HIF-2α (107), and epigenetic modifications such as DNA methylation and histone acetylation (101,106). These studies will identify critical factors that influence LAT1 regulation and provide a theoretical basis for the development of targeted intervention strategies to either upregulate LAT1 for improved boron compound delivery or downregulate it to minimize off-target effects.

Furthermore, the function of LAT1 does not operate in isolation, but can be influenced by its interactions with other transporter proteins (11,121), which can significantly affect the intracellular uptake and distribution of boron compounds. Future investigations into the interaction networks of LAT1, including its relationships with other transporters, will provide insight into how these networks affect the efficiency of boron-containing compound transport. Protein interaction screening techniques such as yeast two-hybridization (122), co-immunoprecipitation (123) and high-throughput mass spectrometry (124) could be used to identify LAT1-interacting proteins and elucidate the molecular mechanisms underlying amino acid and nutrient uptake in tumor cells. These findings may shed light on new therapeutic strategies to enhance LAT1-mediated delivery in BNCT.

For example, advances in the design of boron compounds, such as fluorinated and α-methylated 3-borono-L-phenylalanine derivatives, have shown promise. These derivatives show improved water solubility, higher LAT1 selectivity and reduced boron accumulation in non-target tissues (125). Understanding the molecular interactions between LAT1 and boron-containing compounds may guide the design of next-generation boron carriers that optimize LAT1 activity and selectivity. This integration of regulatory and transport dynamics could lead to more efficient and targeted BNCT therapies.

Development of new boron-containing compounds based on LAT1. The advancement of BNCT is critically dependent on the development of boron-containing compounds that possess low toxicity, high stability and the ability to accumulate selectively within tumor cells. Consequently, future research prioritizes the rational design of agents that can exploit tumor-specific biological features. A primary strategy involves targeting membrane proteins that are upregulated in cancer cells. LAT1, which is upregulated on the surface of tumor cells, is a promising therapeutic target. For example, drug design based on the structure-function properties of LAT1 has led to the identification and screening of selective, high-affinity boron-containing compounds (20,126). This targeting principle extends to other transporters, such as the glucose transporter, for which glucose-BSH compounds have been developed as a potential strategy against pancreatic cancer (127). More sophisticated approaches leverage multiple features of the tumor simultaneously. For instance, taking advantage of the unique features of the tumor microenvironment such as hypoxia and acidity, researchers developed the dual-target drug B139, which targets LAT1 and nitroreductase (128). *In vitro*, B139 shows high uptake in hypoxic tumor regions, with a boron content 70-fold that of BPA. *In vivo*, it remains in tumor cells for a long time, maintaining an effective therapeutic concentration, with a tumor-to-blood boron ratio of >3 and low cytotoxicity. Moreover, it may assist in developing prodrug systems for selective boron release in such environments (74,129,130).

Another powerful strategy for improving boron delivery is the application of nanotechnology. Nanoparticles, including polymer-based, liposomal or inorganic materials, have demonstrated the ability to improve the pharmacokinetic properties of boron compounds and achieve synergistic effects with BNCT. These nanocarriers protect boron compounds from rapid clearance *in vivo*, increase their stability and improve permeability in tumor tissues (117,131,132). The selective accumulation of these nanomedicines is largely driven by the enhanced permeability and retention effect, a phenomenon unique to the abnormal vasculature and poor lymphatic drainage of tumors. This passive targeting mechanism allows for prolonged drug retention at the tumor site, which maximizes therapeutic efficacy while minimizing off-target toxicity to healthy tissues (133).

An example of this approach is the development of surface-modified nanoparticles, such as a carboranylphosphatidylcholine based liposome for combinational BNCT and chemotherapy (24). These nanoparticles prolong the blood circulation time and tumor accumulation, allowing the selective delivery of high concentrations of ^{10}B to the tumor microenvironment. Another innovative strategy involves metal nanoparticles that possess photothermal properties that can be activated by external stimuli. These nanoparticles are often used in tumor photothermal therapy (PTT) due to their high photothermal conversion efficiency, adding a complementary mechanism for tumor cell destruction. Recent breakthroughs include the development of boronophenylalanine-containing polydopamine nanoparticles, which combine BNCT with PTT to synergistically enhance tumor cell killing. These nanoparticles target upregulated LAT1 in melanoma using BPA, while their photothermal properties induce localized heating upon external stimulation, resulting in tumor cell death (73). Similarly, compounds with a higher boron content, such as $^{10}B_4C$-PG, have demonstrated significant therapeutic potential in BNCT through pharmacokinetic studies (134).

Future research should also address the challenges of metabolic stability and the biodistribution of boron compounds. Chemical modifications and structural optimization could improve *in vivo* stability while reducing accumulation in normal tissues, thereby minimizing toxicity. In addition, understanding the metabolic pathways of boron compounds and developing strategies to control their metabolism through molecular design will be critical to improving therapeutic outcomes. Through these approaches, the development of next-generation boron compounds tailored to LAT1-targeted BNCT may transform this therapeutic modality into a more effective and precise cancer treatment.

Heterogeneity of LAT1 and exploration of personalized medicine in BNCT. LAT1 expression is heterogeneous across different tumor types, and even within the same type of cancer. This variability is crucial to understanding its role in tumor biology and optimizing BNCT. A key challenge for BNCT is overcoming LAT1 heterogeneity, as it affects boron uptake and the overall effectiveness of the therapy. One approach is to develop dual-targeted therapies, which combine LAT1-targeted BNCT with other treatments to address multiple pathways involved in tumor progression. For instance, the glucose-binding boron compound G-BSH targets pancreatic cancer types with low LAT1 expression and enhances therapeutic efficacy when combined with BPA (127). Combining LAT1-targeted BNCT with immunotherapy may offer synergistic effects, improving treatment efficacy and reducing resistance. For example, engineered polyboronate ester micelles synthesized for BNCT can be paired with immune checkpoint inhibitors to activate the immune system and enhance tumor cell killing (21).

Non-invasive imaging and biomarkers are essential for personalizing BNCT treatments. LAT1-specific PET tracers, such as ^{18}F-FBPA, can help assess LAT1 levels in tumors before treatment, ensuring improved patient stratification (41,68). Integrating high-throughput sequencing, proteomics and metabolomics will help identify factors that influence LAT1 function and improve treatment planning. These technologies can also reveal biomarkers associated with LAT1 activity, helping to predict patient responses and further tailor BNCT strategies.

8. Conclusion

LAT1 holds great promise as a therapeutic target to enhance BNCT due to its upregulation in a variety of tumor types and its ability to facilitate the selective delivery of boron-containing compounds. Despite this potential, several challenges need to be addressed to unlock the full therapeutic benefits of LAT1-targeted BNCT. Key issues include the development of boron-containing compounds with improved stability, solubility and specificity, the need to address hypoxia-induced variations in LAT1 expression and the mitigation of off-target effects to ensure patient safety.

To this end, future research should prioritize a deeper understanding of the regulatory mechanisms governing LAT1 expression, which could inform the development of combination therapies tailored to individual patient profiles. Concurrently, the design of novel boron-containing compounds with enhanced LAT1 affinity and optimized pharmacokinetics, coupled with advanced imaging and biomarker tools, will be essential to refine patient selection and treatment protocols. Ultimately, the integration of LAT1-targeted BNCT into personalized medicine holds transformative potential for improving cancer treatment outcomes while minimizing collateral damage to healthy tissue.

Acknowledgements

Not applicable.

Funding

This review was funded by the National Natural Science Foundation of China (NSFC), grant no. 12261131621.

Availability of data and materials

Not applicable.

Authors' contributions

XZ and WS were responsible for preparing the original draft of the manuscript. XZ, WS, JP and DL participated in reviewing and editing the manuscript. JP and DL provided supervision for the work. JP was in charge of funding acquisition. WS and DL were involved in the conceptualization of the study. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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