L-Amino Acid Transporter-1 and Boronophenylalanine-Based Boron Neutron Capture Therapy of Human Brain Tumors

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Abstract

The system L-amino acid transporter-1 (LAT-1) imports p-boronophenylalanine (BPA) into cells and may play a major role in the effectiveness of BPA-based boron neutron capture therapy. The functional status of LAT-1 and its relationship to cell proliferation were simultaneously examined in the same section of human tumor material using a dual-labeling technique. The uptake of BPA (boron inductively coupled plasma mass spectrometry) was profiled in the presence of agonists and antagonists in fresh tumor explants. The number of LAT-1–expressing cells (mean ± SD) was three times higher than that of proliferating cell nuclear antigen (PCNA)–expressing cells (71.5 ± 17.02% versus 23.8 ± 16.5%; P < 0.0001; n = 38 glioblastoma and metastatic tumors). There was no correlation between PCNA cells and the number of LAT-1/PCNA double-stained cells, and not all PCNA-expressing cells coexpressed LAT-1. Boron uptake reached 30 ± 15 μg/g of wet weight of tissue by 4 hours both in tumor and brain around tumor tissue containing tumor cells compared with time 0 (P < 0.005; n = 4 glioblastoma tumors). This uptake was inhibited by both phenylalanine and 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid. These LAT-1 data indicate that BPA-based boron neutron capture therapy might affect up to 70% of tumor cells, representing a three times higher proportion of tumor cells than their cell cycle status might suggest. Cells expressing PCNA, but not LAT-1, will require a different therapeutic strategy. [Cancer Res 2009;69(5):2126–32]

Introduction

There is increasing interest in the use of boron neutron capture therapy (BNCT) as a tumor-selective treatment for malignant intracerebral tumors where these tumors currently remain incurable despite aggressive treatment with surgery, chemotherapy, and conventional radiotherapy (reviewed in ref. 1). The therapeutic potential of BNCT rests in the selective accumulation of a sufficient amount of 10B within the cancer cell. Partitioning of 10B within and outside the cell is also critical because the short spatial range (4–7 μm, roughly one cell diameter) of the α particles and lithium ions, resulting from the capture reaction, limits the ionizing effect to those cells that have taken up the boron (1). The success of BNCT depends on the preferential uptake of boron by the malignant cell. In the case of boronophenylalanine (BPA), a rational carrier for 10B and used in BNCT trials for the treatment of brain tumors (2–4), as well as currently under further pharmacokinetic investigation for clinical use (ref. 5, and our own clinical study),1 selective accumulation is thought to be enabled by specific uptake mechanisms involving the system L family of heterodimeric, sodium-independent, amino acid transporters located at the plasma membrane, in particular LAT-1 (ref. 6; for a review of LAT transporters, see refs. 7, 8). LAT-1 has been associated with growth, proliferation, and tissue development and is highly expressed in malignant tumors and tumor cell lines, where it is thought to contribute to growth autonomy by increasing amino acid transport (9, 10). LAT-1 expression has not been studied to any great extent, in the context of BNCT, in human malignant brain tumors where it is likely to play a central role in trafficking BPA selectively to tumor cells. Moreover, expression profiles of LAT-1 in such tumors will provide essential information about the distribution of BPA in the tumor because the effectiveness of BNCT largely depends on the uniformity of distribution of the boron compound within the tumor mass.

The issue of cell cycle–specific uptake of BPA is particularly important. Several studies point to a direct relationship between the uptake of BPA and cell replication. In a preclinical study using a mouse melanoma model and comparing boron and [3H]thymidine (TdR incorporated into cells at the S phase) uptake in double-labeled whole body–sectioned autoradiographs, it was concluded that the i-isomer of BPA accumulated selectively in the actively dividing (TdR-accumulating) cells of the tumor, although at this low resolution it was not possible to discern individual cells (11). Following up on this report, Ono and colleagues (12) also studied the microdistribution of boron compounds in peripheral (thigh) tumors using a squamous cell carcinoma mouse model, with attention particularly given to the quiescent cells, and concluded that the distribution of BPA was heterogeneous and that quiescent cells may not accumulate BPA. Yoshida and colleagues (13), in an in vitro study where G0-G1 and G2-M phase tumor cells were sorted by flow cytometry after exposure to BPA and BSH, found higher levels of BPA in the G2-M phase, concluding that BPA uptake was dependent on the cell cycle. Langen and colleagues (14), studying the single photon emission computed tomography (SPECT) tracer 112I-α-methyl-l-tyrosine (IMT) in vitro, suggested that the Na+-insensitive, L system–mediated uptake of this compound was dependent on the proliferation rate of the human glioma (86HG-39) cells, whereas in a study of 27 glioma patients, Kuwert and colleagues (15) found a positive correlation between the in vivo IMT transport rate, as measured by SPECT, and the histologically determined Ki-67 proliferation index.

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1 A Cancer Research UK pharmacokinetic study of BPA in patients with high-grade glioma to optimize uptake parameters for clinical trials of BNCT.
If the implication of these reports is correct, that BPA uptake by tumor cells is coupled to their proliferation status, then BPA-based BNCT in malignant tumors will have a very low efficacy because the only cells targetable will be the ones temporally in cycle in the tumor—approximately 10% (16, 17). Therefore, it is important to verify this relationship in the tumor in situ, in the original specimen. To do this, it is hypothesized that all proliferating cells express functional LAT-1. Therefore, proliferating and LAT-1–expressing cells were simultaneously identified in the same section with a dual-stain immunohistologic technique, and LAT-1 function was probed by measuring the importation of BPA in the presence of LAT-1–specific substrates in biopsied brain tumor tissue slices.

Materials and Methods

The rabbit polyclonal LAT-1 antibody was provided by Serotec, whereas the biotinylated donkey anti-rabbit immunoglobulin was from Amersham Biosciences UK Limited. The mouse monoclonal proliferating cell nuclear antigen (PCNA; clone PC10), monoclonal and polyclonal gial fibrillary acidic protein (GFAP), goat anti-mouse immunoglobulins, mouse alkaline phosphatase anti–alkaline phosphatase, and StreptABCComplex/alkaline phosphatase were supplied by DakoCytomation. The enzymes substrates naphthol AS-MX phosphate, levamisole, Fast Blue BB salt, and aminoethylcarbazole; the solvent, dimethylformamide; and the aqueous mountant, glycerol gelatin, were from Sigma-Aldrich.

Clinical grade BPA was a generous gift from Cancer Research UK and was formulated at 100 mg/mL in 110 mg/mL mannitol. All other chemicals, including 2-aminoxyethylene (2,2,1)-heptane-2-carboxylic acid (BCH), phenylalanine, tyrosine, and the vital stain dyes (ethidium bromide and acridine orange), were from Sigma-Aldrich.

Immunohistochemistry. Routine histologic sections of tumor tissue and nontumorous brain tissue from epileptic patients, as well as freshly excised tumor and brain around tumor tissue, were collected from the operating theatre in accordance with current hospital ethical guidelines. Approval with written consent was obtained from patients undergoing craniotomies. All tumor specimens were nonrecurrent from patients that were unirradiated and chemotherapeutically naive. Sections were stained with a Babington nebulizer, quartz spray chamber, and nickel cones. Calibration used matrix-matched aqueous standards prepared from boron-10–enriched boric acid. Standards and specimens to be assayed were diluted with an aqueous solution containing 2% butanol, 0.05% EDTA, 1% NH₄OH, and 0.05% Triton X-100. Beryllium was used as the internal standard (20). Perished tissue (0% viability; see below) served as control for nonspecific uptake/entrapment of BPA. Boron values were corrected for nonspecific uptake and are expressed as micrograms of boron per gram of wet weight of tissue.

Tissue slice viability was monitored over the course of the experiment using a vital stain method described elsewhere (21). Briefly, imprints of the slices were exposed to the vital stain (containing 3.4 mg/mL each of ethidium bromide and acridine orange dyes), and the live (green) and dead (orange/red) cells counted immediately under a fluorescence microscope.

Statistical analysis. Relative differences in the stained cell populations were analyzed by Student-Newman-Keuls test using the GraphPad Instat program, whereas differences in BPA uptake were analyzed by unpaired t test. Significance was set at P < 0.05.

Results

LAT-1 expression and profiles. Immunohistochemical LAT-1 and PCNA profiles of human brain tumors in situ were examined to verify the relationship between LAT-1 expression and cell proliferation. For this, archival brain tumor tissue was screened using immunohistology with a LAT-1 antibody. The specificity of the LAT-1 antibody was confirmed using human placental and cerebral cortical tissues. In the placenta, staining with this antibody was confined mostly to the apical surface of the syncytiotrophoblasts, consistent with previous reporting (22), whereas the cerebral cortical specimen showed no staining. Histologic sections were then subjected to the LAT-1/PCNA dual-staining procedure described above to concurrently visualize individual and dual-expressing LAT-1 and PCNA cells. The PCNA protein, which is present in the nucleoplasm of continually cycling cells throughout the cell cycle (23), was used as a marker of proliferating cells.
Because the normal cortex specimen showed no staining for PCNA, it was screened for LAT-1 and GFAP immunoreactivity instead to verify the double-labeling technique.

The LAT-1/PCNA staining profiles of placenta and cortex are shown in Fig. 1A and B. In the placenta, the apical surface syncytiotrophoblasts were highly positive for LAT-1 expression (red stain) but were negative for PCNA immunoreactivity (blue stain), which was confined to the luminal trophoblasts; there was no staining of fibrous areas (Fig. 1A, bottom right). In contrast, the specimen of normal cortex was negative for LAT-1 immunoreactivity, except for the occasional lymphocyte (Fig. 1B, middle left), but positive for GFAP (blue cells). These observations of LAT-1 immunoreactivity in placental syncytiotrophoblasts and of the inability to detect PCNA in the cortex were taken as confirmation of the specificity of the antibodies and also of the validity of the dual-staining technique.

In the tumors, at low magnification, LAT-1 and PCNA staining was seen to follow the distribution of viable areas of the specimen (Fig. 2A and B), analogous to the pattern of PCNA immunoreactivity described previously (18). Fibrous, necrotic, and hematogenous areas were negative for both LAT-1 and PCNA immunostaining except for lymphocytes, which were highly reactive for LAT-1,

![Figure 1. Higher-power photomicrograph of LAT-1 and PCNA staining in placenta (A). Staining for LAT-1 was confined almost entirely to the apical syncytiotrophoblasts (arrowheads) whereas that of PCNA was confined predominantly to luminal cells (asterisk; bottom middle). Normal cortex (B) was negative for both LAT-1 [except for the odd lymphocyte (asterisk) visible in the middle left of the photomicrograph] and PCNA but was positive for GFAP immunoreactivity (arrowheads). Bar, 50 μm.](image)

![Figure 2. Low-power photomicrographs of LAT-1 and PCNA showing staining profiles of glioblastoma (A) and metastasis (melanoma; B). LAT-1 and PCNA immunoreactivity followed viable areas of the tumor; there was no staining of necrotic, fibrous, or hematogenous areas except for LAT-1–immunoreactive lymphocytes in the latter (B, middle left). Higher-power photomicrographs (C and D) of the same specimens showing stained cell types. Dual-stained LAT-1/PCNA+ cells appear as purple or blue-red (arrowheads) and are readily distinguishable from the single-stained LAT-1 (red) and PCNA (blue) cells. All three stained cell types were seen colocated and interspersed among the viable tumor matrix. A small number of unstained cells are visible in C. Bar, 100 μm in A and B; 50 μm in C and D.](image)

particularly in the metastatic tumors (Fig. 2B). The glioblastomas and the metastases were highly positive for both LAT-1 and PCNA expression, whereas the meningiomas were mostly positive for LAT-1 only, but all tumors showed LAT-1 expression.
At a higher magnification, three distinct types of cells could be distinguished: red cells (LAT-1+), blue cells (PCNA+), and purple/black or red and blue (LAT-1+PCNA+ dual-stained) cells, the latter showing clearly a blue nucleus surrounded by a red cytoplasm (Fig. 2C and D). All three types of cells were found interspersed and were readily distinguishable. The numbers of these stained cells were recorded in each specimen and their relative proportions are shown in Fig. 3A to C and summarized in Table 1. Lymphocytes, which stained positive for LAT-1 (Fig. 2B), were excluded from analysis. No double-stained cells were found in the placenta or cortex. There was no significant difference in the proportion of LAT-1+ cells between glioblastoma and the metastatic tumors (72.6% versus 71.2%), but there was a relatively higher proportion of LAT-1+ cells between glioblastoma and the metastatic tumors cortex. There was no significant difference in the proportion of analysis. No double-stained cells were found in the placenta or which stained positive for LAT-1 (Fig. 2C).

PCNA+ cells in the malignant tumor groups (72.6% versus 22.8% (Table 1). Overall, there were three times as many LAT-1+ cells as and 4.8% and 5.1% in the glioblastoma and metastases, respectively abundant, numbering only 1% of detected cells in the meningiomas expression, a higher proportion of LAT-1+PCNA+ (proliferating-only, single-labeled) cells. To verify such a relationship, data related to the malignant tumor categories (glioblastoma and metastases) were pooled and PCNA+ values were plotted as a function of those with dual-staining LAT-1+ and PCNA+ cells falling above the lower 95% confidence interval (n = 30). The graph showed no significant correlation between the two (i.e., LAT-1 expression was not related to proliferation; Fig. 4). There was also no relationship between patient’s age and LAT-1 or PCNA expression (data not shown).

**BPA uptake (LAT-1 function).** The functional integrity of the LAT-1 transporter was examined in malignant brain tumor specimens by measuring the importation of BPA in the presence of LAT-1-specific substrates in biopsied brain tumor tissue slices to preserve and maintain the original tissue integrity and viability. Uptake of BPA was measured in the presence and absence of the system L–specific agonist, phenylalanine; the antagonist, BCH (24); and the augmentor, tyrosine (25). Tissue slices were incubated with BPA 1 hour after exposure and removal of tyrosine (25), 10 minutes after BCH (without removal; refs. 24, 26), and simultaneously with phenylalanine for the time periods shown in Fig. 5, after which they were washed and analyzed for boron content. Tissue viability was monitored at the start and end of the experiment. The boron data did not require correction for any differences in viability because such changes were not significant (Fig. 5A and B, topmost line). Viability scores [expressed as the ratio of live (green) to dead (red) cells x100] ranged from 90.7 ± 4.2% to 87.3 ± 4.0% and from 89.3 ± 5.6% to 85.5 ± 7.5% for the tumor and brain around tumor groups at the start and end of the experiment, respectively.

The uptake profiles of boron (BPA) in tumor and brain around tumor tissue slices are shown in Fig. 5A and B. The accumulation...
of boron was curvilinear over the time course, reaching significantly elevated levels by 2 hours in both tumor and brain around tumor tissue \((P = 0.0191 \text{ and } P = 0.008, \text{ respectively})\), compared with time 0) and approximating a plateau level of around tumor tissue \((P \geq 0.013, 4 \text{ hours } \text{BPA} \text{ versus } 2 \text{ hours } \text{phenylalanine or } \text{BCH})\). The uptake was markedly and effectively inhibited by both phenylalanine and the antagonist, BCH, over the initial 2 hours of the time course in both tumor and brain around tumor tissue, after which levels tended to decrease. Values were corrected for nonspecific uptake/entrapment. The profile of BPA accumulation and inhibition was similar in both tissue groups and there was no significant difference between the peak accumulated BPA levels \((P = 0.597)\). Substrate selectivity of BPA uptake was assessed by measuring its accumulation in the presence of 10 mmol/L phenylalanine. The uptake was markedly and effectively inhibited by both phenylalanine and the antagonist, BCH, over the initial 2 hours of the time course in both tumor and brain around tumor tissue \((P = 0.013, 4 \text{ hours } \text{BPA} \text{ versus } 2 \text{ hours } \text{phenylalanine or } \text{BCH})\) and tended to increase thereafter, whereas it was not affected by pretreatment with tyrosine.

**Discussion**

The relationship between LAT-1 and PCNA expression and the functionality of the transporter, crucial to our understanding of BPA-based BNCT, was explored in human malignant brain tumors \(\text{in situ}.\) Our results indicate that the situation \(\text{in vivo}\) is complicated by the considerable heterogeneity of human brain tumors with microscopic areas of viable and nonviable cells \((18)\), making direct comparisons with clonal animal tumor models difficult. Contiguous positive LAT-1 and PCNA staining was naturally restricted to viable tumor areas. In this study focusing on viable tumor areas, there was no correlation between the cellular expression of LAT-1 and PCNA. Additionally, examination of the significance of LAT-1 in primary explants of these tumors, which represent a closer \(\text{in vivo}\) model of the functionality of the transporter, crucial to our understanding of BPA uptake with proliferative indices is explained by the occurrence of contiguous LAT-1 and PCNA-stained cells found in this study. Indeed, other lines of evidence suggest that the linkage between overall uptake of BPA by BCH indicates the apparently critical role of LAT-1 in determining the uptake of BPA. The system L transporter (LAT-1) mediates the transport of L-amino acids into cells and likely plays a major role in the uptake of BPA in BPA-based BNCT for malignant brain tumors.

**LAT-1 expression.** LAT-1 expression has been detected in several tissue types including the blood-brain barrier and glial cells \((10, 27)\). The expression of LAT-1 has been shown to be markedly elevated in various tumor cells \((10)\) and notably in glioma cells \((28, 29)\). Up-regulation of LAT-1 thus seems to be a common feature of tumor cells and of interest in targeting treatments dependent on LAT-1 function, such as transported cytotoxic drugs \((e.g., \text{melphalan}; \text{ref. 26})\) or enhancement of BNCT by increased uptake of boron using BPA. Clinical evidence of the role of LAT-1 has been implied by Langen and colleagues and Kuwert and colleagues in studies \((14, 15)\) that showed increased tracer (IMT) concentration in progressively more active tumors, suggesting a link between tracer uptake (L-amino acid handling) and proliferative activity and, at the same time, calling into question the use of the LAT-1/BPA system for BNCT treatment of malignant tumors where the proliferation rate \(\text{in vivo}\) has been shown to be low \((16, 17)\). Whereas a relationship between L amino acid uptake and proliferation might be expected, the apparent correlation of IMT uptake with proliferative indices is explained by the occurrence of contiguous LAT-1 and PCNA-stained cells found in this study. Published OnlineFirst February 24, 2009; DOI: 10.1158/0008-5472.CAN-08-2345

### Table 1. Summary of immunohistologically identified cell types in human brain tumors

<table>
<thead>
<tr>
<th>GROUP</th>
<th>(n)</th>
<th>Mean (SD), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM-LAT+ (PCNA—)</td>
<td>29</td>
<td>72.6 (16.9)</td>
</tr>
<tr>
<td>GBM-PCNA+ (LAT—)</td>
<td>29</td>
<td>22.8 (16.9)</td>
</tr>
<tr>
<td>GBM-LAT+PCNA—</td>
<td>29</td>
<td>4.8 (2.2)</td>
</tr>
<tr>
<td>MET-LAT+ (PCNA—)</td>
<td>9</td>
<td>71.2 (11.4)</td>
</tr>
<tr>
<td>MET-PCNA+ (LAT—)</td>
<td>9</td>
<td>23.6 (9.4)</td>
</tr>
<tr>
<td>MET-LAT+PCNA—</td>
<td>9</td>
<td>5.1 (2.5)</td>
</tr>
<tr>
<td>MEN-LAT+ (PCNA—)</td>
<td>4</td>
<td>97.1 (1.6)</td>
</tr>
<tr>
<td>MEN-PCNA+ (LAT—)</td>
<td>4</td>
<td>19.1 (1.4)</td>
</tr>
<tr>
<td>MEN-LAT+PCNA—</td>
<td>4</td>
<td>1.0 (0.2)</td>
</tr>
</tbody>
</table>

**NOTE:** Summary of the statistical analysis of the relative proportions of stained cells identified (and enumerated) with the dual-stain immunohistologic technique. The tumor categories are shown against their mean staining ratios with SD. Abbreviations: GBM, glioblastoma; MET, metastatic tumor; MEN, meningioma; LAT+ (PCNA—), LAT—positive only; PCNA+ (LAT—), PCNA-positive only; LAT+PCNA—, double-labeled LAT-1 and PCNA cells.

![Correlation of proliferation and LAT-1 expression](image)

**Figure 4.** Ratio of PCNA-stained cells as a function of proliferating LAT-1 \((\text{LAT}^+\text{PCNA}^+)\) in the malignant tumors \((\text{glioblastoma and metastases})\). Linear regression fit shows lack of a relationship between proliferation and LAT-1 expression \((n = 30; \text{see text for details})\).
proliferation and LAT-1 activity is less clear. For example, De Wolde and colleagues (30), in an attempt to correlate the protein synthesis rate of human brain tumors with histologic parameters of proliferation (Ki-67 and AGNOR counts), found no correlation between L-tyrosine positron emission tomography and Ki-67 in human brain tumors. Similarly, Sasajima and colleagues (31), in exploring the relationship between proliferative activity, amino acid transport, and glucose metabolism in glioma cell lines, found an inverse relationship between the influx of a nonmetabolizable transport, and glucose metabolism in glioma cell lines, found an inverse relationship between the influx of a nonmetabolizable

*Figure 5. Time course of BPA accumulation (µg boron/g wet wt tissue) in tumor (A) and brain around tumor tissue (B). Tissue slices were incubated at 37°C for 0, 1, 2, 4, and 8 h in the presence of BPA alone or with other agonists and antagonists (see text for details). Values have been corrected for nonspecific uptake/entrapment. Points, mean (n = 4 glioblastoma tumors); bars, SD. Tissue viability is shown by the topmost line. *, P < 0.05, compared with time 0.

BPA uptake in these cells, whether they are localized within the tumor mass or dispersed in the brain around tumor. Accordingly, functional imaging biomarkers such as IMT or [methyl-11C]methionine (amino acids) may be superior in delineating the radiation therapy target volume than proliferation-based markers, such as bromodeoxyuridine, or nonspecific metabolic markers such as [18F]fluorodeoxyglucose. It is also important to note that a number of PCNA-positive (proliferating) tumor cells (up to 25%) do not express detectable LAT-1 and, hence, are unlikely to accumulate BPA and will require a different therapeutic approach than BNCT with this agent.

**LAT-1 and BPA uptake.** Based on BPA import and efflux measurements in the presence of system L– and system A–specific substrates in the rat 9L gliosarcoma in vitro model, Wittig and colleagues (6) concluded that BPA was transported by the L system, a mechanism that is likely to play a major role in BPA-based BNCT. The capacity of our explant system to take up BPA has not been evaluated in this study, but the peak levels of boron achieved, 30 µg/g, are in the range estimated to enable the therapeutic advantage of BNCT (33, 34) despite the heterogeneity of the explants used. This still clinically relevant level of boron is not unexpectedly lower than that achieved in the more homogeneous rat 9L gliosarcoma in vitro model (6). Interestingly, in the clinical samples used here, the similarity in BPA uptake profiles of tumor and brain around tumor may be a reflection of higher LAT-1 expression by the infiltrating neoplastic cells in the brain around tumor (35), although the number of neoplastic cells in this region, by definition, will be lower than their core mass counterparts. To confirm this requires quantitative assessment of LAT cell numbers and their corresponding expression levels correlated with BPA uptake, which is beyond the scope of this study. Importantly, the uptake profiles of tumor and brain around tumor indicate the presence of LAT-1 tumor cells dispersed in brain around tumor tissue and that they are accessible to available BPA through LAT-1 activity.

**Implications for BNCT.** This study does not consider the issue of bioavailability of BPA for access to LAT-1 for its uptake into tumor cells. The uptake profiles were, however, measured in the presence of excess BPA and showed a delayed time course to peak ∼4 hours, which may be relevant to in vivo studies of BPA uptake and sampling. It remains to be seen whether prolonged infusions, elevated BPA concentrations, or blood-brain barrier manipulation will enhance bioavailability in vivo to the extent of increasing tumor boron concentrations through LAT-1 transporter activity. These data suggest that a much larger proportion of the tumor, regardless of cell cycle status, will be available for BNCT, with BPA uptake being mediated by LAT-1, and that consideration of the expression of LAT-1 and its distribution may be needed to interpret the variability in clinical response to BNCT using BPA. Furthermore, our study has identified a proportion of tumor cells that are cycle dependent but will escape the neutron reaction by failing to accumulate available BPA due to the absence of the transporter LAT-1. These cells will require a different treatment strategy, such as cycle-sensitive conventional radiation or chemotherapy.

In summary, LAT-1 seems to be more widely expressed in malignant brain tumors than expected and is unrelated to the lower number of PCNA-expressing cells. BPA-based BNCT might be expected to affect an average 70% of detected tumor cells, which is three times the proportion suggested by their cell cycle status. In addition, not all PCNA-expressing cells coexpressed LAT-1.
The overall uptake of BPA could be specifically inhibited by LAT-1, demonstrating the value of LAT-1 determination in planning BPA-based BNCT studies. Our data also underline the issues of heterogeneity in these tumors and the value of LAT-1 determination in planning BPA-based BNCT studies.

 Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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