Advances in Brief

Positron Emission Tomography-based Boron Neutron Capture Therapy Using Boronophenylalanine for High-Grade Gliomas: Part I

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Abstract

Determination of tumor boron-10 (10B) levels is required for accurate neutron dosimetry during boron neutron capture therapy. We assessed a new method for quantitative measurement of boronated drug uptake in high-grade gliomas. This method uses positron emission tomography (PET) with fluorine-18-labeled L-fluoroborophenylalanine (18F-10B-FBPA), which was synthesized as an analogue of L-boronophenylalanine. We studied the accumulation of 18F-10B-FBPA by PET in patients with high-grade gliomas. Dynamic PET studies of brain tumors revealed that 18F-10B-FBPA accumulated gradually after bolus injection, and the value of PET activity divided by the integrated plasma activity reached a constant level 42 min after injection, which was defined as the incorporation constant (IC*). This constant reflected the appropriate 18F-10B-FBPA accumulation in tumor tissue. Based on the IC* constant, the methods for estimating tumor 10B concentration were devised. With this method, the estimated values of 10B concentration in gliomas were very close to the 10B levels in surgical specimens. This method was based solely on PET and can potentially provide data that would assist in the selection of patients for future treatment with boron neutron capture therapy after surgical resection of their brain tumors.

Introduction

Thermal neutrons, which have weaker radiobiological effects than neutrons per se, are used in BNCT. BNCT involves administering a compound containing boron atoms (10B) to cancer patients and irradiating the tissue that has incorporated the boron with thermal neutrons (mean, 0.025 eV). Short-range α particles are produced by the nuclear reaction between boron atoms and the low-energy neutron beam in the cell. This permits high linear energy transfer radiation (mean, 2.33 MeV) to be applied exclusively to tumor cells without damaging the surrounding normal tissues, making this an ideal method of selectively destroying infiltrating cells (1-5). Primary malignant glioma infiltrates and destroys the surrounding brain tissue (6). Therefore, neurosurgeons must consider treatment of the region of infiltration as well as resection of the main part of the tumor. However, damage to normally functioning brain tissue must be avoided. The track length of one cell diameter produced by neutron capture is very effective for selective killing of individual infiltrating cells.

Important issues in this therapy include improving the boron compound that selectively accumulates in the tumor, because accumulation results in more intense irradiation with relatively little effect on normal tissues. Also, to ensure sufficient therapeutic effects, the boron compound must enter the cells. We selected L-10B-BPA as a candidate for a boron compound meeting these conditions (7, 8). The pharmacological characteristics of L-10B-BPA must be examined in vivo. For this purpose, we used a positron-labeled boronophenylalanine analogue, 18F-10B-FBPA, and examined the tumor accumulation and pharmacokinetics of 18F-10B-BPA noninvasively by PET (9). In BNCT, the 10B concentration in tumor cells must be determined for each patient, because 10B accumulation varies with the nature of the tumor. Collection of accurate data for individual patients is extremely important in properly performing neutron dosimetry. In this study, we therefore evaluated the tumor accumulation of 18F-10B-FBPA and designed a method for measuring tumor 10B concentration using 18F-10B-FBPA.

Patients and Methods

Synthesis of 18F-10B-FBPA. The basic labeling method of 18F-10B-FBPA was reported by Ishiwata et al. (10), and the procedures for clinical use were detailed in our previous report (9). L-3-(p-boronophenyl)alanine (95% 10B; MW

Received 12/18/97; revised 5/22/98; accepted 7/1/98.

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3 The abbreviations used are: BNCT, boron neutron capture therapy; PET, positron emission tomography; 18F-10B-FBPA, fluorine-18-labeled L-fluoroborophenylalanine; 10B-BPA, L-boronophenylalanine; GBM, glioblastoma multiforme; ROI, region of interest; BBB, blood-brain barrier; BSH, mercaptopendecahydrodecaborate, Na3B12H12,SH.
1826 PET-based BNCT Using L-\(^{10}\)B-BPA: Part I

Thereafter, the solution was added slowly to 0.8 ml of 1 diluted condition present in the plasma (12). The solution of equilibrium between free molecules and the complex in the guidelines established by the PET Committee of Nishijin Hos
d-\(^{14}\)-fructose (2.22 g), H\(_2\)O (30 ml), and 1N NaOH

\[
\text{HO} + \text{BHP} \rightarrow \text{[BHP]H} - \text{CH} - \text{COOH}
\]

\[
\text{HO} + \text{BHP} \rightarrow \text{[BHP]H} - \text{COOH}
\]


\[\text{2-[^{18}F]fluoro-4-[^{10}B]boronophenylalanine (^{18}F-^{10}B-FBPA)}\]

\[\text{Fig. 1 Chemical structures of} \text{ } ^{10}\text{-B-BPA and} \text{ } ^{18}\text{-F-}^{10}\text{-B-FBPA.} \]

208.21) was purchased from Boron Biologicals, Inc. (Raleigh, NC). The specific activity was 3.6 mCi/\(\mu\)mol. The radiochemical purity was above 98%. The chemical structures are shown in Fig. 1. The performance of \(L-^{18}\text{F}-^{10}\text{B-FBPA}\) PET studies on humans and the quality control of \(L-^{18}\text{F}-^{10}\text{B-FBPA}\) followed guidelines established by the PET Committee of Nishijin Hospital (Kyoto, Japan) in January 1991.

Preparation of \(L-^{10}\text{B-BPA-}^{14}\text{Fructose Complex.} \text{ } L-^{10}\text{B-BPA}\) is relatively insoluble in water. For i.v. administration, we prepared a \(L-^{10}\text{B-BPA-}^{14}\text{Fructose complex solution as reported by Yoshino et al. (11). This complex dissociates and reaches an equilibrium between free molecules and the complex in the diluted condition present in the plasma (12). The solution of} \text{ } L-^{10}\text{B-BPA-fructose complex consisted of} \text{ } L-^{10}\text{B-BPA (1 g),} \text{ } D-(\text{-})-\text{fructose (2.22 g),} \text{ } H_2O (30 ml), \text{ } \text{and} \text{ } 1N \text{NaOH (5.55 ml). Thereafter, the solution was added slowly to 0.8 ml of 1 n HCl, and the pH value was adjusted to 7.5. To buffer the solution, 7\% NaHCO}_3 \text{was added. The molar concentration of the final solution was 115 mm, and the} \text{ } ^{10}\text{B concentration was 5.52 mm. The molar ratio of} \text{ } L-^{10}\text{B-BPA:fructose was 1.2:57. Finally, the fructose complex was prepared by filtration using a Millipore filter (MILLEX-GS 0.22 \mu m; Waters).} \text{ } L-^{10}\text{B-BPA solution was then tested for a pH of 8.5. The i.v. infusion rate was 10 ml/min.}

Patients. The subjects were 20 patients with high-grade gliomas (Table 1), all of whom had been diagnosed with glioma in our hospital between 1992 and 1997. Surgery was performed for all patients, and in each case, the diagnosis was confirmed histologically. The degree of malignancy was classified histologically using the WHO grading criteria (All, astrocytoma WHO grade II; AllI, anaplastic astrocytoma WHO grade III; and GBM). Conventional computed tomography (X-ray computed tomography) images were obtained for comparison in each case before PET studies. PET using \(L-^{18}\text{F}-^{10}\text{B-FBPA}\) was performed for all 20 patients. For all patients, the incorporation constant \((k^*)\) and the utilization ratio \((U_r^*)\) were determined. Seven of these patients underwent resection of the tumor after PET studies using \(L-^{18}\text{F}-^{10}\text{B-FBPA}, \text{ and the} ^{10}\text{B concentration estimated using PET data was compared with that in the tissue obtained at surgery (Table 2).}

Choice of ROIs. All regions of macroscopically necrotic tumor were excluded when ROIs were designated. The variation in radioactivity associated with each pixel was less than 18% of the mean value. Using this as a criterion, we limited macroscopic heterogeneity to a minimum when designating ROIs. ROI images consisted of 49-171 pixels on the tumor center and a non-tumor control area and hence had a minimum voxel volume of 2.94 cm\(^3\). Patients with a hot area (active area) smaller than the above-mentioned area were excluded from the evaluation. The tumor areas of all 20 cases presented in this study satisfied this voxel volume requirement. No partial volume corrections were performed for any patient. We designated several ROIs from tumor-affected areas and used the region with the highest values as a representative ROI.

Correction of Blood Concentration Data. Generally, plasma:whole blood ratios of \(^{18}\text{F} radioactivity and \(^{10}\text{B} level are 1.3 for both} \text{ } L-^{18}\text{F}-^{10}\text{B-FBPA and} \text{ } L-^{10}\text{B-BPA. We determined the time course changes in both ratios. The plasma:whole blood ratios of} \text{ } ^{18}\text{F radioactivity and} \text{ } ^{10}\text{B levels changed little over time. Based on these results, we judged it reasonable to treat the ratio as a constant. When} ^{10}\text{B levels of whole blood are measured by the prompt \gamma method, they should be corrected by multiplication using a factor of 1.3, because the input function is based only on plasma concentrations. Ishiwata et al. (13) reported that the amounts of labeled metabolites of} \text{ } L-^{18}\text{F}-^{10}\text{B-FBPA in arterial plasma were small during the 1-h animal experiments. In our human PET studies, the metabolic fractions were negligible during the 42 min after injection, because we observed that more than 95% of the total radioactivity in plasma was due to the free} \text{ } ^{18}\text{F}^{10}\text{F-FBP fraction during the 42-min arterial sampling. These findings suggest that plasma metabolite correction is not necessary, and that the metabolism of} \text{ } L-^{10}\text{B-BPA can be treated like that of} \text{ } L-^{18}\text{F}-^{10}\text{B-FBP.}

\text{Table I Incorporation constants of} \text{ } L-^{18}\text{F}-^{10}\text{B-FBPA in patients with high-grade gliomas}

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>(k^* \times 10^4) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade gliomas</td>
<td>20</td>
<td>3.17 ± 1.01</td>
</tr>
<tr>
<td>GBM</td>
<td>12</td>
<td>3.12 ± 0.91*</td>
</tr>
<tr>
<td>AllI</td>
<td>8</td>
<td>3.38 ± 1.20*</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>1.11 ± 0.21</td>
</tr>
</tbody>
</table>

\* Significant difference between GBM and control \((P > 0.001)\).
\* AllI, anaplastic astrocytoma, WHO grade III.
\* Significant difference between AllI and control \((P < 0.001)\).
during the experiment. This incorporation rate, $I_c(t)$, of $\text{L-}^{10}\text{B}-\text{FBPA}$ is expressed as $Ur(t)$, the ratio of $\text{L-}^{10}\text{B}-\text{FBPA}$ incorporation rate as a function of time. The mathematical model used for data analysis can be represented as a function of time, but it may become constant after a sufficient amount of time.

Mathematical Model of L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA Incorporation Constant ($I_c(t)$). For quantification of incorporation, we calculated the L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA incorporation rate $I_c(t)$ (in s$^{-1}$). The mathematical model used for data analysis can be represented by equation A in the “Appendix”. Radioactivity of $C_c(t)$ indicates the amount of incorporated L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA in the tumor tissue. $C_c(t)$ was divided by plasma nonmetabolized L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA radioactivity $[C_c(t)]$ integrated over time (t) during the experiment. This incorporation rate, $I_c(t)$, is a function of time, but it may become constant after a sufficient amount of time.

Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Grade, total injection dose of L-\textsuperscript{10}B-FBPA (g)</th>
<th>Body weight (kg), body surface (m$^2$)</th>
<th>Dose of L-\textsuperscript{10}B-FBPA (mg/kg body weight)</th>
<th>$Ur(t)$ (s/m$^2$)</th>
<th>$I_c(t) \times 10^4$ (s$^{-1}$)</th>
<th>Estimated \textsuperscript{10}B (µg/ml)</th>
<th>Tumor \textsuperscript{10}B (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIII, 5$^a$</td>
<td>98, 2.10</td>
<td>51.0</td>
<td>0.089</td>
<td>2.58</td>
<td>5.52</td>
<td>2.1 (71 min)</td>
</tr>
<tr>
<td>2</td>
<td>GBM, 2.3</td>
<td>68, 1.81</td>
<td>33.8</td>
<td>0.133</td>
<td>3.89</td>
<td>5.72</td>
<td>2.3 (50 min)</td>
</tr>
<tr>
<td>3</td>
<td>AIII, 5</td>
<td>44, 1.35</td>
<td>113.6</td>
<td>0.158</td>
<td>2.07</td>
<td>7.86</td>
<td>5.4 (60 min)</td>
</tr>
<tr>
<td>4</td>
<td>GBM, 5</td>
<td>70, 1.83</td>
<td>71.4</td>
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<td>8.41</td>
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<td>0.143</td>
<td>3.20</td>
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$^a$ AIII, anaplastic astrocytoma, WHO grade III.

time-activity curves for the tumor obtained by L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA revealed an accumulation of \textsuperscript{18}F activity. Dynamic PET studies using L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA in patients with brain tumors revealed a selective accumulation of L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA in malignant brain tumors. Notably, accumulation of L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA was accomplished within 42 min after the end of the i.v. injection.

Table 2: Estimation of tumor \textsuperscript{10}B level using $Ur(t)$ and $I_c(t)$ values

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<th>Grade, total injection dose of L-\textsuperscript{10}B-FBPA (g)</th>
<th>Body weight (kg), body surface (m$^2$)</th>
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<th>$Ur(t)$ (s/m$^2$)</th>
<th>$I_c(t) \times 10^4$ (s$^{-1}$)</th>
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Results

Tumor Imaging and L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA Pharmacokinetics. Fig. 2 shows dynamic PET studies obtained using L-\textsuperscript{18}F-\textsuperscript{10}B-FBPA in patients with GBM. As shown in Fig. 3A, the
Fig. 2  Typical dynamic PET images of L-\(^{18}\)F-\(^{10}\)B-FBPA in patients with high-grade gliomas. A sequential scanning was performed nine times (1–9) at 2-min intervals and six times (10–15) at 4-min intervals. The total examination took 42 min. A, GBM; these images show a typical pattern of the expansive growth to the bilateral frontal lobes. B, GBM; tumor location is the left prefrontal surface.
be the representative value. On the other hand, in the case of a surgical sample, the selection of only a high area of $^{10}$B is impossible. For this simple reason, a discrepancy develops between them. Therefore, surgical samples may be underestimated. However, in patients from whom a homogenous tumor sample was obtained, the surgical sample is close to the estimated value, and the data are considered as validating the adequacy of the present method.

**Discussion**

**PET-based BNCT for Cancer.** The methodology of BNCT is complicated, because the irradiation conditions of both the neutrons and the boron compound capturing the neutrons must be considered (4, 5). Moreover, the boron compound must accumulate densely around or in the cancer cells. The selection of a compound with such properties is an important problem (15). Nakagawa and Hatanaka (16) used $^{10}$B-BSH (mercaptoundecahydrododecaborate, Na$_3$B$_{12}$H$_{12}$SH), a cage-type boron compound, for the treatment of brain tumors. Marked antitumor effects were observed in some patients using the methods of Nakagawa and Hatanaka (16). However, this method has not been properly recognized for a number of important reasons, as discussed in Refs. 4 and 5. Probably the most important reasons for the suboptimal results of Nakagawa and Hatanaka were that an insufficient amount of $^{10}$B was localized in residual tumor cells, and an insufficient number of neutrons reached the tumor. Early studies showed that $^{10}$B-BSH only minimally enters normal cells, and that it accumulates in the intercellular spaces of tumor tissues with disrupted BBB, as well as in brain tumors, and is passively retained in general equilibrium with the blood concentration. Therefore, the injury of vascular endothelial cells is a potential problem in planning irradiation. The ratio of the concentrations in tumor tissue and blood (tumor:blood ratio) may vary, because the degree of BBB disruption may not be determined by the tumor alone. On the other hand, in normal brain tissue, the BBB prevents the entry of $^{10}$B-BSH. This increases the apparent ratio of the concentrations in tumor cells:normal tissue (tumor:normal ratio), but it also limits the uptake of the boron compound in many part of the tumor cells, as well as that of the brain tissue around the tumor. We have observed brain swelling immediately after irradiation with $^{10}$B-BSH in BNCT. $^{10}$B-BSH may produce edema, because admixture of the infiltrating glioblastoma cells is usually observed among normal brain cells, and the microvasculature is already formed in the tumor, influencing adjacent normal brain cells. Also, Hatanaka observed marked swelling in the surrounding brain tissues after BNCT in patients who developed recurrence after conventional radiotherapy and noted that BNCT was dangerous in such cases. In recent studies, an uptake of $^{10}$B-BSH by cells has sometimes been confirmed, but details regarding the microdistribution of $^{10}$B-BSH remain controversial (17–19).

We measured $^{10}$B levels in tumor tissue by PET in vivo, which is based on tracer technology and plays a role in pathological studies as a biochemical imaging modality. The envi-

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**Fig. 3** Dynamic PET studies using $^{18}$F-$^{10}$B-FBPA in a patient with glioblastoma. **A,** the time-activity curves $[C_i^*(t)]$ obtained by a dynamic PET study. **B,** the input function $[C_p^*(t)]$ obtained by arterial blood sampling in bolus injection. **C,** the time course of $Ic^*(t)$, demonstrating that values of $Ic^*(t)$ gradually became constant 42 min after bolus injection.
environment examined by PET differs greatly from the isolated in vitro conditions used in conventional biochemical studies. Therefore, in PET, special analytical techniques and modeling such as the use of the three-compartment model with \( K_1 \) (in \( \text{mllg/min} \)), \( k_2 \) (in \( \text{min}^{-1} \)), \( k_3 \) (in \( \text{min}^{-1} \)), and \( k_4 \) (in \( \text{min}^{-1} \)) are required to examine the dynamics of pharmacokinetics (9). Solutions to these problems will enable noninvasive quantitative evaluation of tissue pharmacokinetics. Mishima et al. (20) advocated the use of \(^{10}\text{B}\)-BPA based on the characteristics of biochemical processes in cancer and was the first to treat melanoma with BNCT. This method had marked antitumor effects in the treatment of melanoma. Coderre et al. (21) confirmed \(^{10}\text{B}\)-BPA uptake in gliosarcoma, and its applicability to glioma was suggested (22-24). Recently, Coderre et al. (25) have used BNCT clinically for high-grade gliomas with epithermal neutrons.

**Conditions for Estimation of Tissue \(^{10}\text{B}\) Levels by PET.** \( Ic^* \) differs significantly between benign and malignant tumors and is therefore a proper constant for tumors (Table 1). On the other hand, \( Ur^* \) is a factor representing the metabolism and excretion of \(^{10}\text{B}\)-FBPA (13, 26). \( Ur^* \) is markedly affected by metabolism in the liver and excretion by the kidneys. Therefore, it is not a proper constant for gliomas. As shown in Fig. 4, \( Ic^* \) is highly \( K_1 \)-dependent. Therefore, \(^{10}\text{B}\)-FBPA is rapidly transported to the tissue through amino acid transport after the bolus injection (9), and its concentration reaches equilibrium after 42 min. On the other hand, \( Ur^* \) increases time dependently. Therefore, after 42 min, when a certain level of \(^{18}\text{F}\) radioactivity is reached in PET, \( Ur^* \) is constant as the ratio of the circulating amount that can be supplied to the tissue during the 42-min period:the administered dose. Table 2 shows that \(^{10}\text{B}\) in tumor tissue can be estimated using only values of \( Ic^* \) and \( Ur^* \) obtained by PET measurement, even without the use of \(^{10}\text{B}\)-BPA, and the PET-based \(^{10}\text{B}\) value was compared with that in resected tumor tissue. Thus, using \( Ic^* \) and \( Ur^* \), the amount of \(^{10}\text{B}\)-BPA required can be determined before future BNCT. In addition, it is pointed out that there is no consistent relationship between the administered dose and tumor concentration (Table 2). There are biochemical properties of the tumors themselves, in that levels of \(^{10}\text{B}\)-BPA-uptake vary greatly depending on the amino acid uptake by tumors, even when respective tumors were of the same grade. Therefore, simple linearity cannot be always expected between the administered dose and tumor concentration. Furthermore, in contrast to the experimental brain tumor transplantation model, a certain linearity between dose and tumor concentration cannot be obtained in cases of human glioma due to its heterogeneity. \(^{10}\text{B}\) concentrations vary due to the admixture of necrotic regions and the cerebral parenchyma during surgery. Based on these observations, the values shown in Table 2 included many factors of variation.

We considered the macroscopic properties observed in the main part of the tumor to be representative features that could be applied to residual tumors and infiltrating cells. The following issues must be considered: (a) whether plasma \(^{10}\text{B}\) levels maintain linearity with the amount of \(^{10}\text{B}\)-BPA administered. This question was answered by Honda et al. (27) using a rodent model, with administration of \(^{10}\text{B}\)-BPA up to a limitation dose of 500 mg/kg. Tumor \(^{10}\text{B}\) level was directly proportional to the
amount of $^{10}$B-BPA administered, up to the dose used for clinical BNCT. We have used $^{10}$B-BPA up to 280 mg/kg in human subjects (28) and have observed a tendency toward linearity in the $^{10}$B concentration in plasma within this range. The $^{10}$B level in plasma was proportional to the administered dose and sequentially increased the $^{10}$B level in the tumor (23, 24); and (b) kinetic differences between $^{10}$B-BPA and $^{18}$F-$^{10}$FBPA. Ishiwata et al. (26) noted the similarity between the two compounds, which exhibited an almost one-to-one correspondence between $^{10}$B level and $^{18}$F radioactivity. It was demonstrated that the concentration of $^{10}$B-BPA measured by inductively coupled plasma atomic emission spectroscopy corresponded almost one-to-one in hamsters receiving $^{18}$F-$^{10}$FBPA. In the present study, when we compared the $^{10}$B values estimated by PET with those of the surgical specimens, the estimated values were found to be very close to the $^{10}$B levels in the surgical specimens, as shown in Table 2.

In conclusion, PET studies using $^{18}$F-$^{10}$FBPA not only provide images of treatable brain tumors but also permit the determination of local $^{10}$B levels. This method was based solely on PET and can be used for real time pharmacokinetic and biodistribution studies, providing data that would assist in the selection of patients for future BNCT after surgical resection of their brain tumors.

Appendix

$$C^*(t) = \frac{C^*(t)}{\int C^*(t) \, dt}$$

Tissue $^{10}$B level ($\mu g/ml) = \text{total injection dose (}$\mu g$) \times U_r(s/ml) \times I_e(s^{-1}) \times 10/208$.

where utilization ratio = $U_r(s/ml)$, incorporation constant = $I_e(s^{-1})$, and 10/208 is the $^{10}$B molecular ratio to $^{18}$F-$^{10}$BPA.

Acknowledgments

We acknowledge the technical support and effort of Kazuo Wakita and Hitoshi Horii (Cyclotron Unit, Nishijin Hospital, Kyoto, Japan). We gratefully thank Dr. Kiichi Ishiwata (PET Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan) for helpful advice regarding $^{18}$F-$^{10}$B-FBPA synthesis and its biological properties.

References


Clinical Cancer Research

Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I.

Y Imahori, S Ueda, Y Ohmori, et al.


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