Targeting and Therapy of Human Glioma Xenografts in Vivo Utilizing Radiolabeled Antibodies

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Abstract

Radiolabeled antibodies provide a potential basis for selective radiotherapy of human gliomas. We have measured tumor targeting by radiolabeled monoclonal antibodies directed against neuroectodermal and tumor-associated antigens in nude mice bearing human glioma xenografts. Monoclonal P96.5, a mouse IgG2a immunoglobulin, defines an epitope of a human melanoma cell surface protein and specifically binds the U-251 human glioma as measured by immunoperoxidase histochemistry. Radiolabeled P96.5 specifically targets the U-251 human glioma xenograft and yields 87.0 μCi of tumor activity/g injected activity compared to 4.5 μCi following administration of 100 μCi radiolabeled irrelevant monoclonal antibody. Calculations of targeting ratios demonstrate the deposited dose to be 11.6 times greater with radiolabeled P96.5 administration compared to irrelevant monoclonal antibody. The dose found in normal organs is less than 20% of that in the tumor, further supporting specific targeting of the human glioma xenograft by this antibody. Monoclonal antibody ZME018, which defines a second melanoma-associated antigen, demonstrates positive immunoperoxidase staining of the tumor, but comparatively decreased targeting. To test the therapeutic potential of ³¹¹I-radiolabeled P96.5 and ZME018, tumors and normal sites were implanted with miniature thermoluminescent dosimeters. Average absorbed doses of 3770 ± 445 cGy in tumor, 353 ± 41 and 222 ± 13 cGy in a contralateral control i.m. site, 980 ± 127 and 651 ± 63 cGy in liver, and 275 ± 14 and 256 ± 18 cGy in total body were observed 7 days following administration of 100 μCi ³¹¹I-radiolabeled P96.5 and ZME018, respectively. Calculations of absorbed dose by the medical internal radiation dose method confirmed thermoluminescent dosimeter absorbed dose measurements. To test the therapeutic potential, tumor-bearing nude mice were given intracardiac injections of either buffer or ³¹¹I-radiolabeled P96.5 or ZME018. Tumor regression was measured in 1 of 12, 9 of 10, and 12 of 12 compared to 0 of 10, 1 of 10, and 2 of 10 animals following administration of 50, 100, or 200 μCi ³¹¹I-radiolabeled P96.5 and ZME018, respectively. Average maximal decreases in tumor volume were 42.7 ± 11.9 and 94.2 ± 3.3% 28 and 58 days following 100 and 200 μCi ³¹¹I-radiolabeled P96.5 administration, respectively. In contrast, no average decrease in tumor volume was noted following 50, 100, or 200 μCi ³¹¹I-radiolabeled ZME018. The time required to achieve 4 times the initial tumor volume was 6.1 ± 0.9 days for buffer; 43 ± 12 and 63 ± 10 days for 50 and 100 μCi ³¹¹I-radiolabeled P96.5; and 9 ± 1, 13 ± 1, and 29 ± 3 days for 50, 100, and 200 μCi ³¹¹I-radiolabeled ZME018, respectively. Average tumor regrowth failed to occur 120 days following administration of 200 μCi ³¹¹I-radiolabeled P96.5. Shared cell surface antigens among neuroectodermally derived neoplasms provide a basis for exploration of human glioma radioimmunotherapy.

Introduction

Human malignant gliomas are rarely cured and conventional postoperative external beam radiotherapy only extends median survival (1). With higher radiation doses, median survival, but not long-term survival, is improved (2). The tolerance of adjacent normal brain limits the total radiation dose which can be safely administered (3). Radiolabeled antibodies offer potential selectivity in the delivery of radiation to human neoplasms (4-11). The role of radioimmunotherapy in the treatment of human gliomas, however, remains largely unexplored (12-17). The results of many studies utilizing both monoclonal and polyclonal antibodies indicate shared antigenicity among neuroectodermally derived tissues including glioma, melanoma, neuroblastoma, and fetal brain (18-28). Radiolabeled antibodies directed against neuroectodermal antigens may provide differential delivery of radiation to gliomas and sparing of surrounding normal brain.

P96.5, a murine monoclonal antibody of the IgG2a subclass, targets p97, a cell surface glycoprotein with a molecular weight of 97,000. Initially described in high concentrations in human melanomas (29, 30), p97 has subsequently been found in a variety of cultured cells of neuroectodermal origin including glioblastoma, neuroblastoma, and retinoblastoma (19, 31, 32). Similarly, monoclonal antibody ZME018 targets gp240, a second melanoma cell surface glycoprotein with a molecular weight of 240,000 (33, 34). To the present, gp240 has not been assessed in human glial neoplasms.

Radiolabeled P96.5 (7) and ZME018 (34) have successfully targeted disparate human neoplasms in vivo. Despite the possible cross-reactivity with neuroectodermally derived neoplasms, the systematic analysis of these antibodies for possible human glioma immunotherapy has not been performed. We therefore tested histochemical binding, in vivo targeting, and therapeutic potential of these antibodies in a human glioma xenograft—nude mouse model.

Materials and Methods

Tumor Cell Line

Human Grade IV glioma cell line, U-251, was obtained from the Division of Cancer Treatment Tumor Repository, National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD. Cells were cultured in Dulbecco's modified minimal essential medium/Fam's F-12 nutrient mixture containing 10% fetal bovine serum (GIBCO, Grand Island, NY) and antibiotics (penicillin and streptomycin) in 12-x 80-cm plastic culture dishes (Falcon Plastics). Cells were grown in a humidified incubator at 37°C and gassed with a mixture of 5% carbon dioxide and 95% air. Medium was changed twice weekly and cells were passaged at confluence with 0.5% trypsin (GIBCO).

Nude Mice

Six-week-old male athymic nude mice were given s.c. injections in the left posterior thigh of 5 x 10⁶ glioma cells. Tumors were visible 1 week after injection. All assays of radiolabeled antibody distribution utilized animals bearing 0.1-g tumors, while the human glioma xenograft...
Immunoperoxidase Staining

Immunoperoxidase staining of U-251 human glioma xenografts was performed utilizing monoclonal antibodies P96.5, ZME018, and control PAY276. U-251 tumors grown s.c. were excised, fixed sequentially in Bouin-Holland's solution and 70% ethanol, and subsequently cut into 8-μm sections with a microtome and mounted on glass slides.

Following deparaffinization, sections were rinsed sequentially in xylene and absolute alcohol for 2 min each. Sections were then incubated in methanol:3% H₂O₂ (9:1) for 20 min. Following rinsing in several changes of deionized water, sections were washed in TBS for 5 min and then incubated in a moist chamber for 20 min in normal goat serum diluted 1:20 with TBS. Sections were then washed in TBS for 5 min and incubated in a moist chamber with primary antiserum overnight at 4°C. Sections were then washed in three rinses of TBS for 5 min each and then incubated in biotinylated mouse immunoglobulin diluted 1:100 with TBS for 20 min. Following rinsing in three changes of TBS for 5 min each, sections were incubated for 30 min in horse-ridish peroxidase-avidin D diluted 1:150 with TBS. Following rinsing with TBS, sections were incubated for 10 min in amnioethylnbacarbole solution. Following rinsing in running water for 5 min, sections were counterstained with Mayer's hematoxylin and mounted.

Antibody Radiolabeling

Monoclonal antibodies were labeled with ¹¹¹In (P96.5, ZME018, PAY276) or ⁹⁰Y (P96.5 and ZME018) by chelation using a proprietary procedure developed by Hybritech, Inc., at a labeling ratio of 5 mCi/mg of protein. The percentage of binding of isotope to antibody was determined by thin layer chromatography and exceeded 95% in each experiment.

Assay of Radiolabeled Antibody Distribution

Tumor-bearing nude mice were given injections of 100 μCi of radiolabeled antibody in a final volume of 0.2 ml by i.c. injection and sacrificed 1, 2, 5, and 7 days following injection in groups of at least two animals/time point.

Calibration of Wall Counter. A known quantity of ⁹⁰Y or ¹¹¹In was placed in a radiospectroscopist bone (sensitivity to 1 μCi), cpm were plotted from the well counter as a function of μCi allowing direct conversion to activity.

Expression of Accumulated Activity in Organs and Ratio Calculation. The tumor and all organs were individually weighed (Mettler Balance Model H51AR with 0.01 mg sensitivity). cpm were obtained from the wall counter and then converted to μCi by a conversion factor as determined above. The cpm/g of each organ and tumor were recorded. The resulting activity in the tumor and organs was then expressed as μCi/g of tissue as a function of time. A single exponential fit to the curve of activity/g versus time was calculated and a best fit was determined by the method of least squares for each organ and tumor experiment. The effective half-life in days (T½) and initial concentration (A₀) of antibody in tumor or organ were calculated.

The total dose deposited in tissue is equal to the sum of the penetrating and nonpenetrating radiations. The majority of dose (D) is deposited by the nonpenetrating component. Assuming a uniform isotropic model for the distribution of radiolabeled antibody, the total deposited dose for any organ resulting from the sum of nonpenetrating radiations (NP) accumulated over time is given by

\[ D = 1.44 \times A_0 \times T_{en} \times NP \quad (cGy) \]

Although the NP component is difficult to assess in small organs, expressing the results as a dose ratio of specific/nonspecific antibody cancels this term in the equation. Thus, the targeting ratio equals

\[ \frac{A_0 \times T_{en}}{A_0 \times T_{en} + A_0 \times T_{en}} \]

in the tumor or normal organ in question (35).

The percentage of the tumor dose found in normal organs was determined by normalizing the product of initial activity and effective half-life of accumulated radioactivity (A₀ × Tₚ) in each normal organ to that in the tumor.

Absorbed Dose Calculations

Thermoluminescent Dosimetry. Paired miniature Teflon-embedded CsSO₂-Dy TLDs were implanted directly into the human glioma xenografts and dorsal interscapular s.c. sites, while individual TLD were implanted in liver and a contralateral s.c. site via a 20-gauge needle as described previously (11, 36). Each TLD was first cross-calibrated with known activities of ⁹⁰Y as described previously (37). Mice bearing 0.3–0.4-g tumors and dosimeters were given injections of 100 μCi ⁹⁰Y-labeled P96.5 or ZME018 as described above and sacrificed 7 days following injection. TLDs were removed, rinsed in Radiac, and measured for absorbed radiation dose as follows. The TLD glow curve peak was integrated over 50 s with T₁ = 115°C and T₂ = 275°C. Temperature ramping was 3.5°C/s with preradout annealing cycle of 5 s. The major integration peak occurs at 220–240°C with a minor peak (5%) at 120°C for this TLD.

MIRD Method. Calculations of absorbed dose (cGy) in tumor and liver were also made utilizing the MIRD method (38). The method utilizes maximal initial activity [A₀ × μCi/g] and effective radiolabeled antibody half-life [Tₚ] days calculated as described above, an equilibrium dose rate constant of 1.98 (g-cGy)/(μCi/h) for ⁹⁰Y (38), and an infinite volume boundary correction factor of 0.4 (36, 39). Thus

\[ D (cGy) = A_0 (μCi/g) \times 1.44 \times 24 \times T_{en} (g-cGy)/(μCi-h) \times 0.4 \]

Human Glioma Xenograft Therapy

Groups of at least 10 tumor-bearing animals received either 2% bovine serum albumin in phosphate-buffered saline, unlabeled P96.5, or 50, 100, or 200 μCi ⁹⁰Y-radiolabeled P96.5 (therapy experiment 1) or 50, 100, or 200 μCi ⁹⁰Y-radiolabeled ZME018 (therapy experiment 2) in a final volume of 0.2 ml i.c. injection. Tumor volume was calculated as

\[ \text{Tumor volume} = \frac{4/3 \times \pi \times (L \times W \times H)}{2} \]

where L, W, and H are tumor length, width and height, respectively.

The change in tumor volume with time was calculated as the ratio of tumor volume (V) to its initial volume (V₀). The logarithm of the ratio of average tumor volume to average initial tumor volume was plotted versus time. Initially, this ratio is unity and the logarithm of this ratio is zero. Increases or decreases above or below this baseline value indicate tumor growth or regression over time.

Tumor Regression. Tumor regression is defined as any decrease in an individual tumor volume below its initial value (V/V₀ < 1).

Tumor Maximal Volume Reduction. The maximal reduction (percentage) in tumor volume is the average V/V₀ × 100 at the nadir of the log V/V₀ versus time plot.

Tumor Growth Delay. Tumor growth delay is the time (days) required for a 4-fold increase in average tumor volume (V/V₀ > 4) following a given treatment.

Results

Immunoperoxidase Staining. Positive immunoperoxidase staining of fixed U-251 tumors was demonstrated with monoclonal antibodies P96.5 and ZME018 (Table 1). No staining was seen with irrelevant monoclonal antibody PAY276. These results demonstrated the presence of the antigens p97 and gp240 in the U-251 human glioma xenograft and provided a basis for radiolabeled antibody targeting studies.

U-251 Human Glioma Initial Accumulated Activity (A₀). The initial accumulated activities (A₀) of radiolabeled antibodies in tumor and normal organs are shown in Fig. 1 and summarized

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U-251 Human Glioma Percentage Dose (Tumor). Dose to normal organs, when calculated as a percentage of the dose to the tumor, defines the therapeutic ratio. Radiolabeled P96.5 results in a greater therapeutic ratio when compared to monoclonal antibody ZME018 (Fig. 3). With p96.5 administration, the doses to normal organs are 20% or less of that in tumor. In contrast, doses to spleen and all remaining normal organs are a higher percentage of tumor dose following radiolabeled ZME018 administration.

The superior maximal initial activity in tumor (A0) and tumor-targeting ratio of 111In-radiolabeled P96.5, and the low percentages of absorbed dose in normal organs suggested comparison of the therapeutic potentials of 90Y-radiolabeled P96.5 and ZME018.

Thermoluminescent Dosimetry. Direct measurement of absorbed radiation dose by microthermoluminescent dosimetry revealed average absorbed doses (cGy) of 3770 ± 445 and 645 ± 48 in tumor, 980 ± 127 and 651 ± 63 in liver, 353 ± 41 and 222 ± 13 in contralateral i.m. control sites, and 275 ± 14 and 256 ± 18 cGy in total body sites, following administration of 100 μCi 90Y-radiolabeled P96.5 and ZME018, respectively (Table 2; Fig. 4).

MIRD Dosimetry. By the medical internal radiation dose formalism, calculated absorbed radiation doses (cGy) of 3725 and 548 in tumor and 844 and 745 in liver were observed following administration of 100 μCi 90Y-radiolabeled P96.5 and ZME018, respectively (Table 3).

Human Glioma Xenograft Therapy. Following i.e. administration of buffer or unlabeled P96.5 no tumors regressed, and the average growth delays (days) to 4 times initial tumor volume were 6.1 ± 0.9 and 6.9 ± 0.6, respectively (Table 4). Following administration of 50 or 100 μCi 90Y-radiolabeled P96.5, the in Table 1. The initial accumulated activity (A0) in the glioma xenograft is 87.0 μCi/g following 111In-radiolabeled monoclonal antibody P96.5 administration (Table 1). This value exceeds initial accumulated activities of both control radiolabeled monoclonal antibody PAY276 (4.5 μCi/g) and radiolabeled monoclonal antibody ZME018 (22.0 μCi/g).

U-251 Human Glioma Targeting Ratios. The targeting ratios of specific antibody to control nonspecific antibody in the tumor and normal organs are shown in Fig. 2. The targeting ratio is the quotient of absorbed dose (cGy) in tumor or normal organs following specific antibody administration, and the absorbed dose (cGy) in tumor or normal organs following nonspecific antibody administration. The doses deposited in tumor by 111In-radiolabeled P96.5 and ZME018 are 11.6 and 2.6 times greater, respectively, than control PAY276 (Fig. 2).

Table 1 Antibody activity in U-251 human glioma xenografts

<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Immunoperoxidase staining</th>
<th>Initial deposited activity (A0)* (μCi/g)</th>
<th>tₘ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P96.5</td>
<td>+</td>
<td>86.7</td>
<td>2.2</td>
</tr>
<tr>
<td>ZME018</td>
<td>-</td>
<td>22.0</td>
<td>1.7</td>
</tr>
<tr>
<td>PAY276</td>
<td>-</td>
<td>4.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*μCi 111In-monoclonal antibody/g/100 μCi injected.

Table 2 Thermoluminescent dosimetry absorbed dose (cGy) following 100 μCi 90Y-labeled P96.5 or ZME018 administration

<table>
<thead>
<tr>
<th>Site</th>
<th>P96.5</th>
<th>ZME018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>3770 ± 445</td>
<td>645 ± 48</td>
</tr>
<tr>
<td>Liver</td>
<td>980 ± 127</td>
<td>651 ± 63</td>
</tr>
<tr>
<td>Contralateral control</td>
<td>353 ± 41</td>
<td>222 ± 13</td>
</tr>
<tr>
<td>Total body</td>
<td>275 ± 14</td>
<td>256 ± 18</td>
</tr>
</tbody>
</table>

Absorbed dose (cGy) mean ± SEM.
proportion of tumors regressing was 1 of 12 and 9 of 10, the average percentage decrease in tumor volume was 43 ± 12, and the average growth delay to 4 times initial tumor volume was 42.7 ± 11.9 and 62.6 ± 9.7 days, respectively (Table 4; Fig. 5). Following administration of 200 μCi of 90Y-radiolabeled P96.5, 12 of 12 tumors regressed an average of 94 ± 3% in volume, and regrowth to initial average volume was not achieved 120 days after injection (Table 4; Fig. 5). Following administration of 50, 100, or 200 μCi 90Y-radiolabeled ZME018, 0 of 10, 1 of 10, and 2 of 10 tumors regressed; no average decrease in tumor volume was measured; and the time to 4 times initial tumor volume was 9 ± 1, 13 ± 1, and 29 ± 3 days, respectively (Table 4; Fig. 6).

Discussion

Shared Tumor Antigenicity. Antigenic specificity is the fundamental characteristic of antibodies allowing targeting of tumors. Common antigenic expression among phenotypically disparate but embryologically related tissues following neoplastic dedifferentiation has been observed in a wide variety of tumors. Colorectal, gastric, and pancreatic carcinomas express both antigens 17-1A (40) and carcinoembryonic antigen (CEA) (41) small cell lung carcinomas express disparate neuroendocrine antigens (42) and transitional cell carcinomas of the bladder express the myelomonocytic antigen Leu-M1 (43).

The cross-reactivity of anti-melanoma antibodies with cultured glioma cells has been noted as well. Herlyn et al. (31) noted specific immunoreactivity of monoclonal anti-melanoma antibodies to cultured glioma cell lines. One hybridoma antibody bound to 13 of 17 melanoma cell lines and 6 of 7 astrocytoma lines by cell surface radioimmunoassay. Liao et al. (32) studied 2 monoclonal antibodies from a mouse immunized with a melanoma cell line and found cross-reactivity with different melanoma cell lines. Additional testing revealed a broad cross-reactivity among melanomas, neuroblastomas, retinoblastomas, and glioblastomas. DeMurtal et al. (44) studied the reactivity spectrum of 3 monoclonal antibodies reactive with a human glioma and 5 monoclonal antibodies reactive with a melanoma by cell surface radioimmunoassay. One of 3 antiglioma monoclonal antibodies reacted with melanomas, while the 5 anti-melanoma monoclonal antibodies reacted with gliomas, neuroblastomas, and medulloblastomas.

Carrel et al. (19) studied the reactivity spectrum of five different monoclonal anti-melanoma antibodies which cross-

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reacted with gliomas and neuroblastomas and one monoclonal anti-glioma antibody which cross-reacted with a melanoma cell line. Comparison of binding activity of these monoclonal antibodies for 11 melanoma, 7 glioma, and 3 neuroblastoma cell lines showed that each of these clones had a different pattern of cross-reactivity. The results indicated that the antigenic determinants detected by these antibodies were not associated with the same antigen and thus suggested the existence of at least six different antigens common to melanomas, gliomas, and neuroblastomas.

Our results confirm the observed sharing of antigens in melanoma and glioma and now extend the observation to significant blood-borne targeting of a human glioma by a radiolabeled antibody in vivo. The results show a clear distinction between accumulated activity in tumor compared to normal organs and blood. The dose (expressed as a targeting ratio compared to irrelevant monoclonal antibody) to the human glioma xenograft from P96.5 exceeds 11.6. Antibodies P96.5 and ZME018 are both synthesized utilizing human melanoma cell surface antigens (p97 and gp240, respectively), but only P96.5 targets the human glioma xenograft significantly. Hence, although antigens are likely shared between this glioma and human melanomas determined by peroxidase-immunoperoxidase studies, the in vivo concentration of p97 available for binding by antibody exceeds that of gp240 in the U-251 human glioma xenograft in vivo.

Dosimetric Comparison of Radiolabeled Antibody Deposition. Absorbed tumor radiation dose (cGy) deposition over time determines the utility of radiolabeled antibodies in cancer treatment. Thermoluminescent dosimetry measures cumulative dose deposition in vivo, while the MIRD methodology utilizes serial ex vivo determinations of tumor and normal organ activities in the calculation of absorbed dose. Direct thermoluminescent dosimetry of absorbed radiation dose in tumor following 90Y-labeled P96.5 or ZME018 administration indicates disparate absorbed radiation dose in the tumor compared to the contralateral control site (Table 2; Fig. 4) and corroborates in vivo biodistribution calculations discussed above. Absorbed dose in normal liver is moderate, a finding supported both by the current mouse biodistribution data and by human biodistribution studies of radiolabeled P96.5.4 Thermoluminescent dosimetry demonstrates delivery of 3770 cGy to the tumor in 7 days following administration of 100 µCi 90Y-P96.5 (3770 cGy/100 µCi). These values for tumor-absorbed dose, duration of study, and administered activity compare favorably to that seen in other studies (45–49).

The measurement of absorbed dose by thermoluminescent dosimetry is corroborated by the MIRD method (Table 3). The similar results by these two dosimetric techniques support their mutual validity in the measurement of absorbed dose in this experimental model.

Dose Response. If radiolabeled antibodies are to be considered single agents causing remission of tumors, a dose-response relationship should exist. Administration of increasing activities of 90Y-radiolabeled P96.5 results in a dose-dependent and proportionate number of tumor regressions, reduction in tumor volumes, and delay in tumor growth. The reductions in tumor volume and resultant tumor growth delay compare favorably to results reported by others. Lee et al. (48) reported 0 of 6, 1 of 16, 7 of 38, and 15 of 28 regressions following administration of 50, 250, 500, and 1000 µCi 90Y-radiolabeled 81C6 monoclonal antibody in nude mice bearing s.c. D-54 human glioma xenografts. The percentage decrease in human glioma xenograft tumor volume was not quantified in that study. Sharkey et al. (50) utilized 90Y-labeled NP-2 anti-carcinoembryonic antigen monoclonal antibody to demonstrate 77% growth inhibition (defined as difference in control versus experimental tumor volume after 28 days) of human colon carcinoma xenografts following administration of 50 µCi of radiolabeled antibody. No decrease in tumor volume, however, was shown. Badger et al. (51) reported complete regression of 0.5–1.0-cm-diameter s.c. T-cell lymphoma in nude mice in 70% of animals receiving 1500 µCi of 131I-anti-Thy-1.1 antibody, whereas 750 µCi of control antibody resulted in complete regression in 27% of animals. However, an equivalent activity (1500 µCi) of control antibody resulted in the same percentage of complete tumor regression, and all animals receiving this high dose eventually died of marrow aplasia. Cheung et al. (52) reported dose-dependent regression of 0.5 to 2.0 g human neuroblastoma xenografts following administration of 125, 500, and 1000 µCi 131I-radiolabeled monoclonal antibody 3F8 with greater than 95% tumor volume reduction following 1000 µCi radiolabeled antibody administration.

90Y-labeled P96.5 effectively targets human glioma xenografts in vivo and yields substantial tumor absorbed radiation doses as measured directly by thermoluminescent dosimetry and confirmed by MIRD calculations. Low to modest uptake in various normal organs implies a very favorable therapeutic ratio. Finally, targeting by 90Y-radiolabeled P96.5 results in dose-dependent tumor regression and growth delay. On the basis of these preclinical studies, we are now prepared to evaluate glioma dose deposition in humans utilizing 111In-radiolabeled P96.5.

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References

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