Comparative Metabolism and Retention of Iodine-125, Yttrium-90, and Indium-111 Radioimmunoconjugates by Cancer Cells

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ABSTRACT

Radioiodinated antibodies have produced encouraging remissions in patients with chemotherapy-resistant hematological malignancies; however, the selection of therapeutic radionuclides for clinical trials remains controversial. In this study, we compared the internalization, lysosomal targeting, metabolism, and cellular retention of radioiodinated murine and humanized monoclonal antibodies targeting the CD33 antigen (monoclonal antibodies hP67 and hP67, respectively) on myeloid leukemia cell lines (HEL and HL-60) and of anti-carcinoma antibodies (monoclonal antibodies hCTM01 and hA33) targeting breast cancer and colorectal carcinoma cell lines (MCF7 and Colo 205, respectively). Each antibody was labeled with 125I (by the IodoGen method) and with 111In and 90Y using macrocyclc elution technology. Targeted tumor cells were analyzed for retention and metabolism of radioimmunoconjugates using cellular radioimmunonucluss, Percoll gradient fractionation of cell organelles, SDS-PAGE, and TLC of cell lysates and culture supernatants. Our results suggest that antibodies are routed to lysosomes after endocytosis, where they are proteolytically degraded. [125I]monodiotyrosine is rapidly excreted from cells after lysosomal catabolism of antibodies radioiodinated by conventional methods, whereas small molecular weight 111In and 90Y catabolites remain trapped in lysosomes. As a consequence of the differential disposition of small molecular weight catabolites, 111In and 90Y conjugates displayed superior retention of radioactivity compared with 125I conjugates when tumor cells were targeted using rapidly internalizing antibody-antigen systems (e.g., hP67 with HEL cells and hCTM01 with MCF7 cells). When tumor cells were targeted using antibody-antigen systems exhibiting slow rates of endocytosis (e.g., hP67 on HL-60 cells and hA33 on Colo 205 cells), little difference in cellular retention of radioactivity was observed, regardless of whether 125I, 111In, or 90Y was used.

INTRODUCTION

Systemic chemotherapy has achieved limited success in eradicating disseminated malignancies, emphasizing the need for innovative new approaches to cancer therapy. Recent clinical trials with radioiodinated MoAbs6 directed against tumor-associated antigens have demonstrated considerable promise (1-6); however, many uncertainties remain concerning the optimal implementation of this new modality. One of the most contentious issues remains the selection of the optimal radionuclide for clinical trials. Iodine-131 has been the radioiodidel used in the majority of studies to date because of its ready availability, low cost, simple radiochemistry, and long track record of success in curing thyroid carcinoma. In addition, the highest reported response rates, complete response rates, and longest response durations reported with radioimmunoconjugates have been observed in clinical trials using 131I as the therapeutic nuclide (1, 2, 4).

On the other hand, several limitations of 131I have been defined. Its energetic y emissions pose a risk to health care personnel and contribute to myelosuppression. Furthermore, 131I-labeled antibodies prepared by conventional chloramine T or IodoGen methods are rapidly degraded after endocytosis by target cells, with rapid release of 131I-labeled tyrosine from cells after lysosomal proteolysis (7-13). Several investigators have suggested that alternative radionuclides may prove superior to 131I for radioimmunotherapeutic applications, including alternative B emitters (e.g., yttrium-90, rhenium-186, and copper-67) and α-emitters (e.g., astatine-211 or bismuth-212). Although little consensus has emerged regarding the optimal radioisotope, 90Y has been proposed most often as a replacement for 131I (14, 15). Favorable characteristics of 90Y include its lack of y emissions, high energy B emissions, and superior tumor retention (14-17). It is widely assumed that the favorable retention of 90Y in tumor cells is due to prolonged retention of 90Y inside target cell lysosomes, in a manner analogous to that reported for 111In (11, 13, 18, 19). However, few studies supporting this contention have been published (13). This point merits direct experimental confirmation, since differences in the behavior of indium and yttrium in vivo have been reported (20-22), and because it has been demonstrated that some radiometals, such as rhenium-188, are rapidly excreted from tumor cells after lysosomal targeting (18).

In this report, we compare and contrast the internalization, metabolism, and retention of 125I, 111In, and 90Y-labeled antibodies targeting malignant human tumor cell lines. Our experiments initially focused on the behavior of radioimmunoconjugates prepared with the anti-CD33 MoAb P67 because of its potential usefulness in treating patients with myeloid leukemias (23). Previous studies demonstrated rapid internalization and metabolism of 131I-labeled murine P67 by the HEL cell line in vitro, by HEL xenografts in nude mice, and by myeloid leukemia cells in patients in vivo (23, 24). Rapid expulsion of radioiodine from leukemic cells after endocytosis of 131I-labeled P67 resulted in poor retention of radioactivity and the consequent discontinuation of clinical trials using 131I-labeled P67 prepared by the chloramine T method (23). Novel 131I-labeled P67 constructs prepared using the nonmetabolizable tyramine cellulbiose carbohydrate adduct improved cellular retention of 131I, but the limited specificity achievable with this approach has hindered therapeutic applications (23, 24).

In the present report, cellular radioimmunonucluss and Percoll gradient fractionation of cell organelles were used to test whether the retention of radioactivity targeted to tumor cells using MoAbs could be improved by using radionuclides such as 111In and 90Y in place of 131I, and to determine whether the improved retention of radioactivity was due to lysosomal trapping of the radiometals. SDS-PAGE and TLC were used to test whether retained cell-associated radioactivity was present on intact radioimmunoconjugates or on catabolized fragments. Our experiments showed that retention of radioactivity by tumor cells was better for 111In and 90Y than 131I if rapidly internal-
izing antibodies were used but that little difference was observed if antibodies undergoing minimal endocytosis were used. Cell fractionation studies confirmed trapping of small molecular weight catabolites in lysosomes and suggested that the cellular processing of $^{111}$In and $^{90}$Y were similar.

**MATERIALS AND METHODS**

**Cell Suspensions.** The human myeloid leukemia cell lines, HEL (from Dr. Paul Martin, Fred Hutchinson Cancer Research Center, Seattle, WA) and HL-60 (from the ATCC), and the Colo 205 colon carcinoma cell line (from ATCC) were maintained in log-phase growth in RPMI 1640 (Life Technologies, Inc., Grand Island, NY) supplemented with 12% FCS, 2 mm glutamine, and 1 mm pyruvate at 37°C in 5% carbon dioxide. The MCF7 breast carcinoma cell line (from ATCC) was grown in DMEM (BioWhittaker, Walkersville, MD) with 10% FCS, 100 units/ml penicillin, 100 μg/ml streptomycin, 2 mm glutamine, and 5 μg/liter insulin. The viability of cells ranged from 90–98% by trypan blue exclusion in the experiments described. A series of control experiments demonstrated that trypsinization of the adherent Colo 205 and MCF7 cell lines prior to plating in microtiter plates did not diminish the binding of radiolabeled hA33 or hCTMO1 antibodies, respectively.

**Antibodies.** Antibodies used in these experiments included humanized anti-CD33 MoAb hP67 (IgG4), humanized anti-mucin antibody hCTMOI (IgG4), and humanized anti-carcinoma MoAb hA33 (IgG1), which were prepared and purified by Celltech, Ltd. (Berkeley, United Kingdom) by methods published previously (25–29). Protein concentrations were determined using the BCA assay following the recommendations of the manufacturer (Pierce Chemical Co., Rockford, IL).

**Radiolabelling.** MoAbs were iodinated by incubating 100 μg MoAb with 0.5 mCi of Na$^{125}$I (Amersham) in glass tubes coated with 10 μg of IodoGen (Pierce Chemical Co.) for 10 min at room temperature. Free $^{125}$I was removed by chromatography on a Pharmacia PD-10 column (Pharmacia, Piscataway, NJ).

**Radiotoxication.** MoAbs were iodinated by incubating 100 μg MoAb with 0.5 mCi of Na$^{125}$I (Amersham) in glass tubes coated with 10 μg of IodoGen (Pierce Chemical Co.) for 10 min at room temperature. Free $^{125}$I was removed by chromatography on a Pharmacia PD-10 column (Pharmacia, Piscataway, NJ).

**Radiometal Conjugation.** Antibodies were conjugated to the proprietary homobifunctional macrocyclic cross-linking reagent, 9N3-maleimide (for $^{125}$I) and 12N4-maleimide (tetra-azocyclododecane tetra-acetic acid, for $^{90}$Y) via thiotether bonds under metal-free conditions as described previously (28, 29). $^{90}$Y labeling was carried out on preparations dialysed with 0.1 m potassium acetate buffer (pH 6) at antibody concentrations ≥ 1 mg/ml (29). $^{90}$Y (0.42 mCi; Amersham) was added to 0.14 mg antibody in 200 μl 0.1 m potassium acetate buffer (pH 6), and the preparation was incubated at room temperature for 15 min. The labeling efficiency was assessed by TLC and TCA precipitation, and generally approximated 90%. Free $^{90}$Y was removed by desalting on a PD-10 column (Phar
ter (Pierce Chemical Co., Rockford, IL).

**Radioiodination.** MoAbs were iodinated by incubating 100 μg MoAb with 0.5 mCi of Na$^{125}$I (Amersham) in glass tubes coated with 10 μg of IodoGen (Pierce Chemical Co.) for 10 min at room temperature. Free $^{125}$I was removed by chromatography on a Pharmacia PD-10 column (Pharmacia, Piscataway, NJ).

**TLC.** The radioactive molecular species present in the acetone-soluble portion of cell culture supernatants were characterized by TLC by the method of Geissler et al. (7, 8).

**Statistics.** Cellular radiimunoassays were performed with triplicate replicates, and the means and SEs were calculated. Differences were compared using the two-tailed, unpaired t test.

**RESULTS**

**Metabolism of $^{125}$I-, $^{111}$In-, and $^{90}$Y-labeled hP67 (anti-CD33) Antibodies by HEL Cells.** The degradation and retention of the anti-CD33 MoAb hP67 was studied after conjugation to $^{125}$I, $^{111}$In, and $^{90}$Y using the human erythroleukemia cell line, HEL. $^{125}$I-labeled hP67 was rapidly internalized by HEL cells and degraded with the release of small molecular weight, TCA-soluble catabolites to the culture supernatant (Fig. 1a). By 24 h of incubation at 37°C, 53 ± 5% of the initially bound radioactivity had been processed by cells and released to the culture medium in TCA-soluble form. TLC demonstrated that >75% of TCA-soluble radioactivity derived from $^{125}$I-labeled MoAbs in such cultures was present in the form of monoiotyrosine (data not shown). A small fraction (11 ± 3%) of initially bound radioactivity was released from cells in intact, TCA-precipitable form. SDS-PAGE electrophoresis demonstrated that the TCA-precipitable supernatant radioactivity was almost entirely composed of intact hP67 immunoglobulin (data not shown). As might be expected, total cell-bound radioactivity declined progressively during culture, with only 35 ± 1% of initially bound radioactivity remaining cell associated after 24 h of culture. Ten concordant experiments demonstrated the reproducibility of these observations.
Fig. 1. Internalization and degradation of 125I-labeled (a), 111In-labeled (b), and 90Y-labeled (c) anti-CD33 MoAb hP67 by the HEL leukemia cell line. HEL cells (10^6) were incubated with 150 ng of trace-radiolabeled hP67 at 4°C, washed, placed in fresh culture medium, and incubated at 37°C for 0, 1, 4, 18, and 24 h before quantifying the amounts of cell-associated (•) and supernatant (O) radioactivity by gamma counting. Supernatant radioactivity was fractionated into small molecular weight, TCA-soluble (A) and larger, TCA-precipitable (A) components. SE bars are plotted for triplicate replicates but are too small to be visualized for most time points.

a result of diminished exocytosis of small molecular weight, TCA-soluble catabolites from cells binding 111In- and 90Y-labeled hP67 (9 ± 1% and 5 ± 1% of culture radioactivity, respectively, after 24 h of culture versus 53 ± 5% with 125I-labeled hP67; P ≤ 0.0002 for 125I versus either 111In or 90Y; Fig. 2). Interestingly, hP67 labeled with 111In or 90Y was more prone to passive dissociation or "shedding" from HEL cells than 125I-labeled hP67, with TCA-precipitable supernatant radioactivity accounting for 25 ± 2% of total culture radioactivity with the radiometals, compared with 11 ± 3% for 125I-labeled hP67 (P ≤ 0.015 for 125I versus either 111In or 90Y). Enhanced shedding of the metal-chelated antibodies compared with the radiiodinated antibody was consistently observed in six consecutive experiments and has been reported by other investigators (18). As noted by Shih et al. (18), the shedding of intact radiolabeled MoAb occurred early during the culture period, reaching maximal levels by 4 h of incubation and then plateauing (Fig. 1).

Comparative Metabolism of 125I-, 111In-, and 90Y-labeled hP67 Conjugates by a Cell Line with a Slower Rate of Endocytosis (HL-60). Our experimental results with the rapidly internalizing hP67-HEL system suggested that radiometal conjugates might provide superior retention of targeted radiotherapy than that observed with 125I-labeled hP67. To assess whether this observation pertained to cell lines with slower rates of endocytosis, we compared the internalization and degradation of the three radioimmunoconjugates by the HL-60 leukemia cell line, which was known to internalize anti-CD33 antibodies more slowly than HEL cells. Although the diminished release of small molecular weight, TCA-soluble catabolites was again observed with 111In- and 90Y-labeled hP67 compared with 125I-labeled hP67, the magnitude of the differences was small and only reached statistical significance after 18–24 h of culture (Fig. 3). Because of greater shedding of intact TCA-precipitable 111In- and 90Y-labeled hP67 compared with 125I-labeled hP67 (data not shown), retention of cell-associated radioactivity after 4 h was actually superior for cells labeled with 125I-labeled hP67 (84 ± 1%) than with...
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Fig. 4. Transit of $^{111}$In-labeled and $^{125}$I-labeled anti-CD33 MoAb hP67 from the cell surface (fraction 2) to lysosomes (fractions 17–19) in HEL cells (a and c) and HL-60 cells (b and d) as demonstrated using Percoll gradient fractionation of cell organelles. Cells were surface labeled with $^{125}$I- or $^{111}$In-labeled hP67, washed and incubated for 0 h (●), 8 h (○), or 24 h (□) before disrupting cells in a Dounce homogenizer and separating cell organelles by buoyant density using continuous Percoll gradients. The location of lysosomes was confirmed using the enzyme marker, β-galactosidase (not shown).

$^{111}$In-labeled hP67 (78 ± 1%) or $^{99}$Y-labeled hP67 (71 ± 2%) after 4 h of incubation ($P < 0.001$ for $^{125}$I versus $^{111}$In or $^{99}$Y; Fig. 3). However, because shedding of intact hP67 conjugates occurred mainly in the first 4 h of culture, whereas metabolism and exocytosis of small molecular weight TCA-soluble $^{125}$I-labeled catabolites began at 4 h and progressively increased, the cell retention patterns were similar for all three radioimmunoconjugates by 24 h of culture (Fig. 3). The overall areas under the cell-retention curves were not significantly different for any of the three conjugates using HL-60 cells as the target cell line (Fig. 3). Seven experiments with HL-60 cells demonstrated similar findings.

Intracellular Location of Radioimmunoconjugates. To determine the intracellular location of internalized radioimmunoconjugates, HEL or HL-60 cells were surface-labeled with $^{125}$I-, $^{111}$In-, or $^{99}$Y-labeled hP67 antibodies at 4°C, washed, incubated for various time periods at 37°C, and disrupted with a Dounce homogenizer; then cell organelles were separated by Percoll gradient centrifugation. These experiments documented the progressive transfer of radioimmunoconjugates from low density surface membrane fractions to high density lysosomal fractions (Fig. 4), as confirmed by colocalization of β-galactosidase activity (data not shown; Refs. 7, 8, and 48). Because low molecular weight $^{125}$I-labeled catabolites were rapidly released from lysosomes to the culture medium whereas low molecular weight $^{111}$In- and $^{99}$Y-labeled catabolites were retained inside lysosomes (Refs. 11, 13, and 18; Fig. 1), the lysosomal accumulation of radio metals was consistently more striking than the cumulative accretion of $^{125}$I in this organelle (Fig. 4, compare a and b with c and d).

Comparative Degradation and Retention of $^{111}$In- and $^{125}$I-labeled MoAbs by Carcinoma Cells. To assess the relevance of our observations for the radioimmunotherapy of solid tumors, we analyzed the comparative retention of $^{111}$In- and $^{125}$I-labeled antibodies targeting the MCF-7 breast cancer cell line (MoAb hCTMO1) and the Colo 205 colorectal carcinoma cell line (MoAb hA33). The hCTMO1 antibody was readily internalized and degraded by MCF7 cells, resulting in the release of more radioactivity to the supernatant of cultures of $^{125}$I-labeled hCTMO1 cells (58 ± 4% after 24 h) than in cultures of $^{111}$In-labeled hCTMO1 cells (34 ± 3%; $P < 0.02$). As a consequence, cellular retention of $^{111}$In-labeled hCTMO1 was significantly better than retention of the $^{125}$I-labeled conjugate (66 ± 1% versus 42 ± 2% after 24 h; $P < 0.001$ Fig. 5a).

In contrast, the hA33 conjugates were slowly internalized by the Colo 205 cell line, resulting in minimal release of radioactivity to the supernatant with either $^{111}$In- or $^{125}$I-labeled conjugates. Accordingly, cellular retention of both reagents was excellent (82 ± 1% for $^{111}$In-labeled hA33 and 89 ± 2% for $^{125}$I-labeled hA33 after 24 h; Fig. 5b). Analysis of intracellular trafficking by the Percoll gradient method confirmed lysosomal targeting of hCTMO1 with progressive accumulation of $^{111}$In in lysosomes (Fig. 6). As in the myeloid leukemia model, lysosomal accretion of $^{125}$I was less impressive than that of...
Six conclusions can be derived from the experiments reported in this study: (a) cellular retention of 111In and 90Y was superior to retention of radioiodine when radioiodinates were targeted to tumor cells with antibodies undergoing rapid endocytosis (>20% of antibody internalized within 4 h); (b) retention of 111In, 90Y, and radioiodide were similar when targeted to tumor cells using MoAbs, which were slowly internalized; (c) 125I-labeled MoAbs were rapidly degraded in lysosomes to monooiodotyrosine (7, 8) and other low molecular weight catabolites, which were rapidly expelled from cells; (d) radiometals were retained intracellularly, even after trafficking to lysosomes. Consequently, little TCA-soluble radioactivity accumulated in the supernatants of tumor cells targeted with radiometal conjugates; (e) radiometal conjugates were “shed” in intact form to a greater degree than comparable 125I-labeled conjugates; and (f) 111In- and 90Y-labeled antibodies appeared to be internalized, shed, metabolized, and excreted identically by tumor cells, using the methods of analysis used in this study.

These findings confirm and extend reports from other investigators describing superior intracellular retention of 111In-labeled antibodies compared with 125I-labeled MoAbs (13, 18, 36, 37). More importantly, this report is one of the first to directly demonstrate the cellular processing and disposition of 90Y-labeled MoAbs by tumor cells (13). This demonstration is important, because 90Y has been promulgated as the best radionuclide for therapeutic clinical trials (14, 15) and because previous work has demonstrated variable intracellular processing of different radiometal nuclides, with protracted lysosomal retention reported for 111In (11, 13, 18) and 67Cu (38) but rapid exocytosis for 188Re (18). Our findings suggest that the cellular processing of 111In and 90Y by tumor cells is similar, validating extrapolations of 90Y behavior based on prior observations with 111In conjugates (11, 13, 18). Our experiments also confirm the enhanced rate of “shedding” of radiometal conjugates compared with radioiodinated conjugates reported by Shih et al., (18), possibly due to a 2-fold difference in measured antibody avidity between 125I-labeled hP67 and 90Y-labeled hP67 (5.7 × 10^9 liters/s/μM and 2.7 × 10^9 liters/μM, respectively). Shih et al. (18) have hypothesized that antibodies possessing critical lysine residues in the antigen-combining site may have diminished antibody avidity after radiometal chelation using lysine-directed methods as opposed to tyrosine iodination, leading to a higher shedding rate. In spite of the higher shedding rate, overall cellular retention of rapidly internalized antibodies was superior after labeling with 111In or 90Y compared with 125I due to markedly greater intracellular retention of the former.

Although we believe that our conclusions are well supported by our data and by the literature, caution must be exercised to avoid overinterpretation. These experiments have addressed only the retention of radionuclides by tumor cells in vitro and do not test their comparative retention by normal tissues (e.g., liver, kidney, and bone) in vivo. Animal studies indicate that the retention of 111In and 90Y is prolonged in normal organs such as liver, bone and kidney as well as in tumor sites (24, 39–41), partially mitigating the salutary effects of enhanced tumor retention of radiometal conjugates. Nevertheless, several model systems have suggested enhanced tumor:normal organ ratios of retained radioactivity using 111In and 90Y, especially when internalizing antibodies are studied (14, 24, 42, 43).

Our studies do not assess the impact of the different β particle energies and path lengths of 90Y and 131I on radioimmunotherapeutic efficacy. It is theoretically conceivable that the higher maximal β particle energy (2.2 versus 0.6 MeV) and longer maximal path length of 90Y (5.3 versus 0.8 mm) may yield superior radioimmunotherapeutic effects, even if the retention of 90Y and 131I-labeled MoAbs are identical. Conversely, the enhanced bone and liver retention of 90Y-labeled conjugates may result in increased myelosuppression and hepatotoxicity compared with 131I-labeled conjugates.

It is important to recognize that several strategies besides the use of radiometal nuclides may be used to augment cellular retention of radioimmunoconjugates. Deliberate selection of noninternalizing antibodies targeting surface-stable antigens has been shown to successfully circumvent lysosomal degradation of MoAbs and to produce superior cellular retention of 131I-labeled conjugates (24, 44). This approach has been employed using 131I-labeled anti-CD20 antibodies for B-cell lymphomas and 131I-labeled anti-CD45 antibodies for myeloid leukemias with excellent clinical results (1–4). A second alternative is to employ novel radioiodination techniques using nonmetabolizable carbohydrate adducts [i.e., “residualizing” moieties such as pyruvic acid (45, 46), N-succinimidyl 3-(tri-n-butylstannyl)benzoate (47), or dilactitol-125I-labeled pyruvic acid (12, 18)]. These 131I-labeled conjugation methods produce 131I-labeled carbohydrate intermediates, which are retained in lysosomes after internalization in a manner similar to the radiometals because the radioiodinated carbohydrate moieties cannot be fully degraded and excreted (42, 45–47). Clinical adoption of this approach for therapeutic applications has, unfortunately, been retarded by limitations in the specific
activity that can be obtained with these novel residualizing 131I-labeled carbohydrate conjugates using current methodologies. A third alternative involves the systemic administration of lysosomotropic amines (e.g., chloroquine and amantadine), carboxylic ionophores (monensin and nigericin), or calcium channel blockers (verapamil), which have been shown to inhibit lysosomal degradation and exocytosis of 125I-labeled MoAbs (48). In vitro these methods permit a doubling of the retention half-time of 125I-labeled MoAbs by tumor cells (48); however, currently available drugs have proven to be too toxic at the requisite concentrations for safe clinical application.6

Rigorous evaluation of the relative clinical merits of conventional 131I-labeled MoAb conjugates, novel residualizing 131I-labeled conjugates, radiometal conjugates, and comparisons of internalizing and noninternalizing antibodies will require comparative biodistribution studies in cancer patients. Only a single study has been reported addressing these issues in a controlled scientific fashion. In this report, patients with cutaneous T-cell lymphomas received infusions of a rapidly internalizing 131I- or 111In-labeled anti-CD5 MoAb T101, followed by serial quantitative gamma camera imaging (43). Only four patients were studied with 131I-labeled T101, and only two received infusions of 111In-labeled T101, but both achieved better biodistributions with 111In-labeled T101 than with 131I-labeled T101. In our opinion, more studies with larger patient numbers will be required to assess the relative merits of the various radiolabeling strategies and the relative attractiveness of internalizing and noninternalizing antibodies. Because large inter-patient variations in tumor burden, tumor MoAb uptake and retention, serum half-lives, and MoAb catabolic rates have been repeatedly observed (49), we believe that the best strategy for such studies in lymphoma patients will be the sequential administration of trace-labeled MoAb conjugates prepared by various methods on successive days, followed by serial quantitative gamma camera imaging, tumor and normal tissue biopsies, and estimation of absorbed radiation doses to tumor sites and normal organs. We have demonstrated previously the feasibility of administering up to five sequential trace-labeled infusions in patients with lymphomas (1) and believe that such studies will be crucial in settling current controversies concerning the optimal radionuclide-antibody combinations for clinical cancer therapy. Sequential antibody administration studies will be more difficult to perform in patients with solid tumors, due to the rapid formation of human antimouse antibodies that will complicate studies and administration studies will be more difficult to perform in patients with solid tumors, due to the rapid formation of human antimouse antibodies that alter antibody pharmacokinetics and biodistributions.

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