Indium-111 T101 Monoclonal Antibody is Superior to Iodine-131 T101 in Imaging of Cutaneous T-Cell Lymphoma

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We have reported that [^{111}In]T101 is highly effective in the detection of cutaneous T-cell lymphoma (CTCL) in nodal and cutaneous (erythroderma and tumor) sites. This study compares the biodistribution of [^{131}I]T101 (1 to 7.1 mg, 2 mCi) in four patients with CTCL; two of these patients also received [^{111}In]T101 (1 mg, 5 mCi). There was rapid clearance of [^{131}I]T101 from whole-body, spleen, liver, and bone marrow, with evidence of loss of ^{131}I tracer from the T101. Lymph node uptake was minimal in three of four patients, and there was no localization in skin lesions. This contrasted with [^{111}In]T101 where there was prolonged retention of activity in these organs and excellent uptake in skin tumors, erythroderma, and lymph nodes. The study showed that [^{131}I]T101 was suboptimal for imaging CTCL patients and demonstrates that the isotope or labeling method can dramatically alter the apparent biodistribution and tumor targeting of a given monoclonal antibody.

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The T101 monoclonal antibody (MoAb) has been shown to localize in sites of cutaneous T-cell lymphoma CTCL involvement in vivo when administered unlabeled during serotherapy trials (*1,2*) or when administered after indium-111 (^{111}In) labeling for imaging studies (*3*). The [^{111}In]T101 is concentrated in areas of erythroderma, skin tumors, and lymph nodes. Absolute concentration of the radiolabeled [^{111}In]T101 was considerably greater than previously reported for patients with solid tumors (*4–6*).

T101 has been labeled successfully with iodine-125 at high specific activities and has been shown to retain excellent immunoreactivity with several orders of magnitude of cell kill in vitro (*7*). Experience in a phase I therapy trial with iodine-131- (^{131}I) labeled antimelanoma (*8*) and antiferritin antibodies (*9*) suggests that ^{131}I radiolabeled antibodies could be used not only for imaging but also to deliver therapeutic amounts of radiation. The purpose of the current study is to evaluate the differences in biodistribution and tumor localization between ^{131}I- and ^{111}In-labeled T101. To accomplish this, four patients with CTCL were studied with [^{131}I]T101. Two of these patients were also studied with [^{111}In]T101 allowing direct comparison of the biodistribution of the two nuclides. Further comparisons were made to a group of five different patients previously studied with [^{111}In]T101 (*10*).

MATERIALS AND METHODS

T101 is a murine IgG2a MoAb (*11*) that recognizes a 65,000 dalton glycoprotein (T65) on circulating mature normal T-cells but not on most normal B-cells, granulocytes, monocytes or platelets; it is also expressed in nearly all T-cell malignancies, including CTCL, and B-cell chronic lymphocytic leukemia (CLL). The T101 was purified from hybridoma

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ascites of BALB/c mice by precipitation with 18% Na sulfate and DEAE-Sephacel column.†

Approximately 1 mg of T101 was labeled with ^{131}I,‡ with a labeling efficiency of 81%, through the chloramine-T method (23 μg) at specific activities of ~2 mCi/mg (*12*). The [^{131}I] MoAb was separated from the free iodine by Sephadex G-10 gel filtration chromatography.§

The T101 was labeled with ^{111}In by a modification of the bifunctional chelating method of Krejcarek (*13*). Approximately two diethylenetriaminepentaacetic acid (DPTA) moieties were attached to each molecule of antibody. The antibody was obtained in a kit¶ which contained 1 mg DTPA-conjugated T101 MoAb in 1% human serum albumin. Labeling was performed by incubating ~5 mCi ^{111}In with 1 mg of DTPA conjugated T101. Excess DTPA was then added to scavenge free ^{111}In as the final step prior to injection.

To determine the percent incorporation of isotope into T101 conjugate, instant thin layer chromatography in silica gel was performed: methanol:water (1:1) with 5% ammonium acetate for ^{111}In and 85% methanol for ^{131}I (*14*). The strips were counted in a strip counter and the counts per minute (CPM) at the origin were expressed as a percentage of the total counts. Trichloroacetic acid precipitation (TCA) of serum samples from patients receiving [^{131}I]T101 was performed. The precipitate was pelleted by centrifugation and the percent counts in the pellet versus the total counts added was determined as the percent antibody bound ^{131}I. The [^{131}I]T101 was found to be apyrogenic and sterile.

Immunoreactivity

The immunoreactivity of the [^{111}In]T101 was determined by a cell binding assay. Serial dilutions (0.5×10^6 to 10×10^6) of T65-antigen-bearing cell line HUT102 (*15*), or T65 antigen-bearing-CLL were incubated with 5 ng/ml of radiolabeled T101 at 4°C for 1 hr. The cells were then separated by centrifugation in PBS 1% bovine serum albumin. The cell pellet was counted in a gamma counter and the binding data were expressed as the percentage of radioactivity on cells compared with the total added.

Human Anti-Mouse Antibodies (HAMA)

One microliter of patient baseline serum was incubated with 0.5–1 ng (10,000 cpm) of ^{125}I-labeled B72.3 anticarcinoma MoAb, a murine IgG1, for 20 h at 4°C. Twenty milligrams of formalin fixed staphylococcus A cells** were added and, following a 15-min incubation (4°C), the bound counts were separated by centrifugation (3,000 rpm × 5 min). Percent binding for each patient's serum was calculated as bound counts/total counts ×100 and compared to the mean for a group of normal controls. A serum was considered positive for HAMA if the percent binding was at least 3 s.d.s greater than the mean of the normal group.

Patients

Four patients with histologically confirmed advanced stage of CTCL were studied (Table 1). Staging evaluation included biopsies of lymph node, bone marrow, and skin as well as peripheral blood evaluation. Studies were performed under a National Cancer Institute approved protocol, and all patients gave their informed consent.

Three patients received 2.0 mCi of [^{131}I]T101 (1 to 1.5 mg). A fourth patient received 2 mCi (0.7 mg) of [^{131}I]T101 co-infused with 6.4 mg of unlabeled T101. Two patients received 5 mCi [^{111}In]T101 (1 or 1.5 mg) within 1 wk of receiving the [^{131}I]T101. The thyroid of patients undergoing [^{131}I]T101 scanning was blocked with ten drops of saturated solution of potassium iodide (SSKI) twice a day starting 24 hr prior to the injection and for 10 days after. The T101 was infused intravenously over 2 hr. Vital signs were monitored and serial blood plasma samples were obtained at 5 min, 30 min, 1 hr, 2 hr, 24 hr, 48 hr, and 72 hr postinfusion. Plasma and blood volume estimates were obtained from a nomogram (*17*) utilizing the patients' body surface area. Utilizing these volumes, the percent of the total injected dose in the circulation was then calculated. Serial 24-hr urine collections were obtained. Whole-body radioactivity was assessed daily using a 5x5 cm sodium iodide detector placed at 7.1 m from the patient. Radioisotope retention was determined using the immediate postantibody administration cpm value as 100%.

TABLE 1
Patient Data

					Staging data						Scanning data		
Patient no.	Age/sex	Stage*	Prior† treatment	Skin status	Palpable lymph node	Lymph node* histology	PB involvement‡	Liver biopsy	Bone marrow biopsy	Total§ dose T101	Skin status	Nodal status	Liver and spleen
1	66 M	IVA	INT, Chemo	Erythroderma	+	LN4	+	NA	–	1 mg ^{131}I	–	±	+
2	48 F	IVA	INT, Chemo	Generalized plaques	+	LN3	–	–	–	1 mg ^{131}I	–	±	+
3	69 M	IVA	none	Erythroderma and tumor	+	LN3	–	NA	+	1.5 mg ^{131}In	–	–	+
3	As above	IVA	none	Erythroderma and tumor	+	LN3	–	NA	–	1.5 mg ^{111}In	+	+	+
4	63 M	IVA	none	Skin tumor	+	LN4	–	–	–	7.1 mg ^{131}I	–	±	+
4	As above	IVA	none	Skin tumor	+	LN4	–	–	–	1 mg ^{111}In	+	+	+

* Committee on staging CTCL (*16*).
† Chemo = systemic chemotherapy; INT = interferon.
‡ PB = peripheral blood lymphocytes; + = CTCL cells; – = no circulating CTCL cells; NA = not available.
§ Nodal status; + = all known sites detected; ± = faintly positive but not all sites detected; – = negative.

Imaging

Scintillation camera images were recorded with a large field-of-view gamma camera within 2 hr postinfusion, and after 24 hr, 48 hr, and 72 hr. The [^{131}I]T101 was imaged with a high-energy collimator using a 20% window centered over the 364-keV photopeak. The [^{111}In]T101 was imaged with a medium-energy collimator utilizing separate 20% windows centered over the 173-keV and 247-keV gamma-ray peaks of ^{111}In. Anterior and posterior whole-body images as well as spot views (5 to 10 min) were recorded on film or acquired as digital data on a data analyzer.†† Typical spot views for [^{111}In]T101 had 300,000 to 1 million counts while ^{131}I images had 100,000 to 500,000 counts. No blood-pool or organ subtraction was performed. Serial images were analyzed with manually drawn regions of interest (ROIs) of the anterior and posterior liver, spleen, positive lymph nodes, and bone marrow. Values were expressed as cpm per pixel corrected for isotope decay and background.

RESULTS

No scanning evidence of localization in skin plaques, in erythroderma, or subcutaneous tumor was seen in any of the patients receiving [^{131}I]T101. With the exception of minimal nodal uptake in the inguinal femoral lymph nodes of Patients 1 and 2 and a left cervical node of Patient 4, no localization in clinically involved nodal regions was seen with [^{131}I]T101 (Fig. 1). The [^{111}In]T101 scans showed uptake in areas of erythroderma, focal skin tumors, and in multiple nodal regions that included several sites not seen in the [^{131}I]T101 scans (Fig. 2).

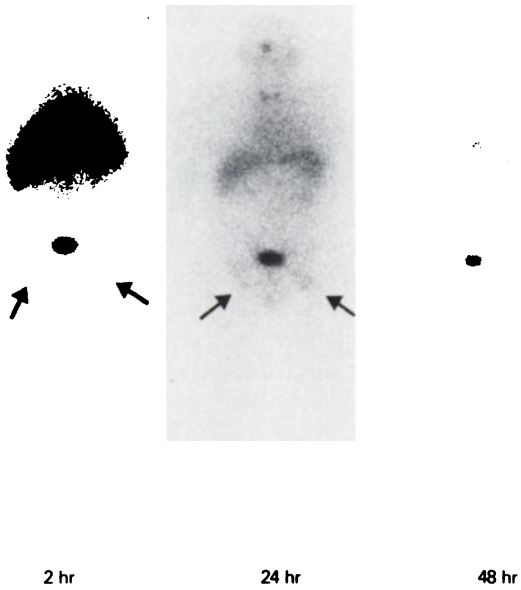

FIGURE 1
Serial anterior whole-body images of Patient 1 indicating early accumulation in spleen, liver, faint bone marrow and lung uptake with rapid clearance at 24 and 48 hr. Faint inguinal femoral lymph node uptake (arrow) is seen at 2 hr and 24 hr. Other clinically involved lymph node regions are not visualized. Iodine-131 is seen in the bladder at all time points and thyroid uptake is seen at 24 and 48 hr.

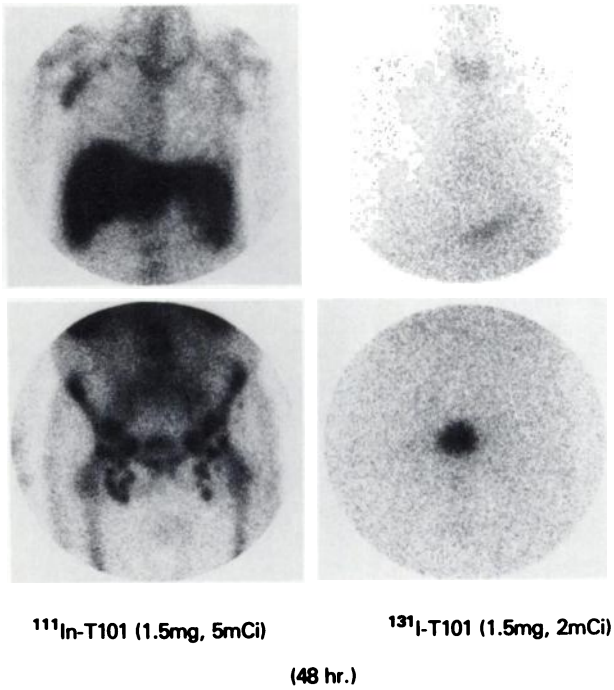

FIGURE 2
Left upper and lower panels show spot images 48 hr after [^{111}In]T101 (5 mCi, 1.5 mg); localization in multiple involved sites: axillary and inguinal lymph nodes as well as erythroderma are seen. The upper and lower right panels show spot images 48 hr after [^{131}I]T101 (2 mCi, 1.5 mg). Rapid clearance from liver, spleen, and whole body is seen with no accumulation in clinically involved skin and lymph nodes.

At 2 hr postinfusion of [^{131}I]T101, the liver, and spleen were the predominant sites of radiotracer uptake. The bone marrow was faintly visible also (Fig. 1). ROI analysis from serial images showed a rapid clearance of radioactivity from the whole-body, liver, spleen, and bone marrow. Whole-body clearance measurement of [^{131}I]T101 performed using the probe counts showed a biologic $T_{1/2}$ of 27 hr (Fig. 3) compared with that of [^{111}In]T101 ($T_{1/2} > 7$ days). Based on the urinary excretion measurements, the clearance was through the kidneys and was significantly greater than seen with [^{111}In]T101 (<5% per day) (*10*); TCA precipitation of the urine showed predominately nonprecipitable ^{131}I suggesting free ^{131}I (Table 2).

After [^{131}I]T101 infusion, the plasma clearance for the 1 mg to 1.5 mg doses was rapid with a mean retention of 27% in the plasma at the end of the 2-hr infusion and a mean of 6% at 24 hr postinfusion. These values are similar to those seen in the two patients receiving [^{111}In]T101 (Fig. 4). The plasma retention for

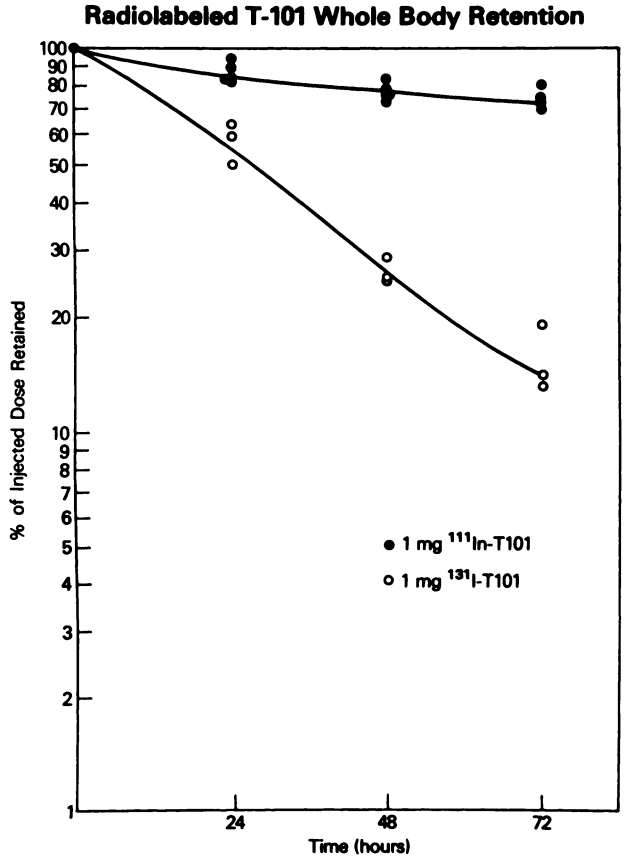

FIGURE 3
The mean and the individual measurements of the whole-body retention for the three patients receiving [^{131}I]T101 is plotted and compared to that of five previously studied patients receiving [^{111}In]T101.

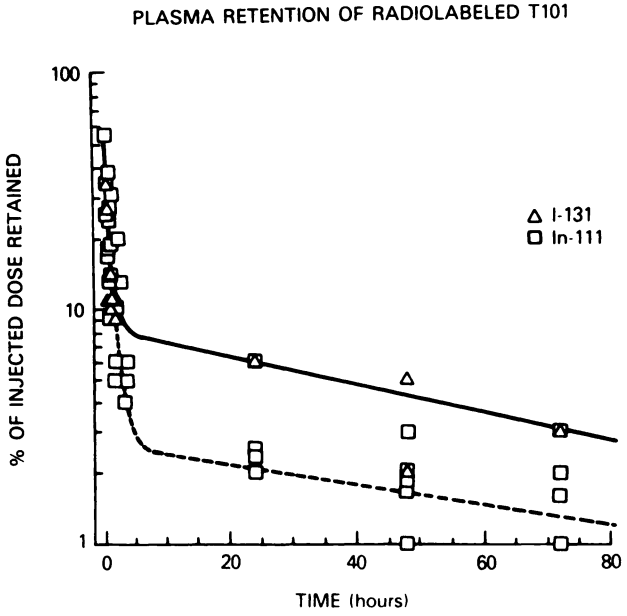

FIGURE 4
Iodine-131 T101 plasma retention measurements (corrected for TCA precipitable ^{131}I) from individual patients (△) were fit (least square) and compared with individual measurements of five previously studied patients (□) with [^{111}In] T101 at similar protein mass. Time 0 is the percent of the injected dose retained at the end of the 2-hr infusion. Although there is a trend toward slightly higher retention of [^{131}I]T101 versus [^{111}In]T101 after 2 hr postinfusion, the curves were not statistically different (T-test $p > 0.5$).

Patient 4, who received 0.7 mg of [^{131}I]T101 co-infused with 6.4 mg of cold antibody, showed a more prolonged plasma retention with 91% present at the end of infusion and 35% at 24 hr. These values were similar to those observed in the plasma of patients receiving 10 mg doses of [^{111}In]T101 (*10*). Although the plasma retention of ^{131}I was prolonged using 7.10 mg versus 1 mg of T101, no improvement in tumor localization was observed. The ^{131}I activity circulating in the blood pool was predominantly in the plasma (>94%), with the exception of Patient 1 where 65% of the blood radioactivity was still on circulating cells at the end of infusion. This patient had Sezary syndrome and a lymphocyte count of 33,197 cells per cubic milliliter. Serial differential cell counts on peripheral blood showed a drop in lymphocyte counts of 26% to 60% from baseline values with gradual return toward normal levels by 24 hr. The patients receiving 1 mg of [^{131}I]T101 had predominantly protein bound ^{131}I circulating in plasma after the end of infusion (Table 3) but at 2, 24, and 48 hr, a large percentage of the ^{131}I circulating activity was nonprotein bound; whereas it was 92% and 80% protein bound at 2 and 24 hr in the patient receiving 7.1 mg who had prolonged plasma retention.

In vitro testing of the radiolabeled MoAb (Table 4) showed that both preparations were similar in terms of the quality control parameters, with good incorporation of the isotope onto the T101 and good immunoreactivity with at least 74% of the injected radioactivity capable of binding to antigen.

TABLE 2
Urinary Excretion Data of Radiolabeled T101

Time (hr)	^{131}I urine excretion	TCA precipitable	^{111}In urine excretion
0–2	9%* (range 3–14%)	5%* (range 3–8%)	(2 and 3%)
2–24	39% (range 32–45%)	5% (range 4–6%)	(5%)
24–48	23% (range 20–26%)	3% (range 3–4%)	(6 and 7%)

*Mean.

TABLE 3
Protein Bound* ^{131}I

	Patient no.†			
	1	2	3	4
[^{131}I]T101 Plasma	93%	93%	93%	93%
Time 0	81%	91%	89%	98%
0.5 hr	73%	76%	82%	98%
2 hr	66%	62%	76%	97%
24 hr	63%	65%	NA‡	93%
48 hr	34%	77%	32%	80%

* Protein bound determination by TCA.
† Patient 1 to 3 received < 1.5 mg T101, Patient 4 received 7.1 mg.
‡ NA = not available.

Human antimouse antibodies were not present in any of the patients' plasma prior to scanning. The patient receiving 7.1 mg of [^{131}I]T101 developed urticaria and pruritus which was treated symptomatically with benadryl and resolved without sequelae. One week later he received a second injection of 0.96 mg T101 with no side effects. Similar reactions have been observed by others using large doses or rapid injection of T101 (*2*).

DISCUSSION

The majority of studies of antitumor antibody targeting have been with ^{131}I-labeled antibodies (*6,18,19–24*). The advantages of ^{131}I are its availability in large amounts at a low price, the ease of use, and long experience with the labeling methodologies; and its potential use for radioimmunotherapy (*8,9*). The disadvantages of ^{131}I are its high-energy gamma rays (not optimal for imaging), the high radiation dose to patients from beta radiation, and the de-iodination that occurs in vivo. Recent work utilizing bifunctional chelates and metallic radionuclides has demonstrated differences in biodistribution when compared with radioiodinated antibodies, with higher concentration in tumors both in animal studies and in human studies (*26*).

TABLE 4
[^{131}I] and [^{111}In]T101 Quality Control

	[^{131}I]T101	[^{111}In]T101
Radioactivity	Dose 2 mCi	4.6 and 5 mCi
Antibody mass	Range 0.7–1.5 mg*	0.96 and 1.5 mg
T101 bound isotope†	Range 92–96%	91 and 97%
Immunoreactivity‡	Range 74–77%	76 and 90%

* One patient received co-infusion 0.7 mg ^{131}I-labeled T101 and 6.4 mg of unlabeled T101.
† ITLC (*14*).
‡ Cell binding assay.

Experience in imaging human tumors with [^{111}In] MoAb has been predominantly limited to solid tumors with stationary cell populations that do not modulate the antigen. Imaging studies of [^{111}In]T101 in patients with advanced cutaneous T-cell lymphoma have shown excellent targeting of skin tumors, diffuse erythroderma, and nodal sites of tumor involvement. The excellent targeting is probably related to the biologic behavior of the target cells in which antigenic modulation results in internalization of the radiolabeled antibody from the cell membrane into the cell (*27–29*) and intracellular retention of the isotope. In addition, these targeted cells maintain their ability to traffic to involved areas (*30,31*).

The initial handling of the [^{131}I]T101 had marked similarities with that of the [^{111}In]T101. When administered at low doses (≤1.5 mg), there was very rapid clearance of the radiolabeled antibody from blood in the first 2 hr. This was probably a result of the binding of labeled T101 antibody to circulating cells with clearance into the liver and spleen as well as direct binding to antigen-bearing cells in the spleen. The patient who received the larger doses of MoAb had prolonged blood-pool retention, equal to that observed for similar doses of [^{111}In]T101 (*10*), suggesting saturation of antigenic sites.

In the present study we observed markedly different biodistribution in two patients studied with both [^{131}I] T101 and [^{111}In]T101. The initial gamma camera images showed that both for ^{111}In- and ^{131}I-labeled T101 there was very rapid clearance into the spleen and liver. Although marrow was seen with the [^{131}I]T101, it was significantly less prominent than with [^{111}In]T101. The delayed [^{131}I]T101 images showed rapid clearance from the liver, spleen, and bone marrow with little or no localization in involved lymph nodes; this contrasted with the prolonged retention of [^{111}In]T101 and the excellent lymph node uptake which persisted for up to 7 days (limits of the investigation). The whole-body and urine measurements were consistent with loss of ^{131}I from the T101. Although it is well known that iodine labeled antibody and other proteins undergo de-iodination (*32,33*), the rapid clearance from the whole body and from the major organs is faster than that observed for other ^{131}I-labeled polyclonal or monoclonal antibodies targeted to solid tumors (*34,35*). The prolonged blood-pool retention and the larger amount of protein bound iodine in the blood pool at the larger MoAb dose indicates that the loss of ^{131}I tracer is not occurring in the plasma but at the level of major organs or T65 antigen bearing cells. Analysis of the images suggested that a great deal of separation of ^{131}I from the T101 is occurring in the liver and spleen where there was initial concentration and subsequent rapid clearance.

Several mechanisms could be responsible for the differences in biodistribution. It is unlikely that this is

secondary to loosely bound iodine since the quality control studies showed good radiopharmaceutical purity and good immunoreactivity of the [^{131}I]T101. In vitro incubations in serum showed good stability with no release of the ^{131}I from the T101 over 72 hr. We have had experience with other MoAb labeled with comparable methods that were more resistant to deiodination when injected in vivo. Pre-existing HAMA, which could cause rapid clearance of MoAb, were not present in these patients.

Previous in vitro and in vivo work has shown that the T65 antigen modulates in the presence of T101 and becomes internalized (*27–29*). In vitro work has shown that the antigen will modulate when incubated with [^{125}I]T101 and that free ^{125}I will be liberated from the cells (*27*). This is the most likely explanation for the rapid loss of ^{131}I in vivo, since other ^{131}I-labeled antibodies, including some that concentrate in liver or spleen but do not modulate, have a more delayed clearance (*35*). In contrast, our studies suggest that the ^{111}In internalized with the T101 is retained for prolonged periods within the cell.

The current study indicates that, although the radiolabeled antibodies may behave the same in vitro, the in vivo handling of the antibody and/or the isotope may be drastically different, this in turn can cause dramatic differences in biodistribution. Consequently, [^{111}In]T101 is much superior to [^{131}I]T101 for immunodetection of tumor deposits of cutaneous T-cell lymphoma. Furthermore, [^{131}I]T101 labeled with chloramine T is a suboptimal radiopharmaceutical for radioimmunotherapy of CTCL, because of rapid in vivo catabolism with subsequent release of ^{131}I.

NOTES

† Pharmacia Fine Chemicals, Piscataway, NY.
‡ New England Nuclear, North Billerica, MA.
§ Pharmacia, Uppsala, Sweden.
¶ Hybritech Inc., La Jolla, CA.
** BRL, Bethesda, MD.
†† (Hewlett Packard Scintigraphic Data Analyzer) Hewlett Packard

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