Radioimmunotherapy of Human Colorectal Carcinoma Xenografts Using 90Y-labeled Monoclonal Antibody CO17-1A Prepared by Two Bifunctional Chelate Techniques

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ABSTRACT

Monoclonal antibody CO17-1A, which has specificity for colorectal and pancreatic carcinomas, was radiolabeled with the pure 90Y emitters, 90Y, by either the cyclic diethylenetriaminepentaacetic acid (DTPA) anhydride technique or by site-specific bifunctional chelate technique using 1-(p-aminobenzyl)DTPA (p-NH2-Bz-DTPA). Male nude mice bearing SW 948 human colorectal carcinoma xenografts were given injections i.v. of 90Y-labeled monoclonal antibody CO17-1A at dosages of 100, 150, and 200 μCi/25 g body weight. Unlabeled CO17-1A (100 μg/25 g body weight) was coinjected.

In animals receiving 90Y-CO17-1A prepared by the cyclic DTPA anhydride technique, tumor volume was unchanged from base line at a dose of 200 μCi/25 g. As the dosage of 90Y-CO17-1A increased, the rate of tumor growth decreased, but all experimental animals in this group died between 14 and 21 days. In contrast, CO17-1A radiolabeled with 90Y by the site-specific p-NH2-Bz-DTPA bifunctional chelate technique produced a maximum tumor volume reduction of 87% in the 200 μCi/25 g group by day 15, and no deaths were noted in any of the 90Y-CO17-1A-treated groups for 71 days. Dose-response curves again showed increased tumoricidal effects with increased dosages of 90Y-CO17-1A.

INTRODUCTION

Radiolabeled monoclonal antibodies have shown significant potential for the diagnosis and therapy of various malignant diseases (1, 2). Most of the studies to date have used 131I as a radiolabel (3–5); however, many unfavorable characteristics (6–8) have limited the clinical application of radiiodinated MoAbs. 90Y is one of the optimal radionuclides for use in radioimmunotherapy (9) for the following reasons: (a) suitable half-life (64 h); (b) pure β emitter; (c) ready availability from a long-lived parent; (d) stable daughter; and (e) good chelation properties. As first described by Hnatchow et al. (10), successful radiolabeling of MoAbs with 90Y, using the cyclic DTPA anhydride bifunctional chelate technique, has been used for the preparation of 90Y-labeled MoAbs for animal experiments. Radioimmunotherapy using 90Y-labeled MoAbs was studied in mice infected with Rauscher leukemia virus (11) and in nude mice bearing human colon cancer xenografts (12). Both studies demonstrated that tumor-specific radioimmunotherapy is feasible using 90Y-labeled MoAbs. Preliminary clinical studies that have been carried out with 90Y-labeled antiferritin antibodies have indicated safety and evidence of tumor remission in hepatocellular cancer patients (13).

In the reported series of experiments, monoclonal antibody CO17-1A, which has specificity for colorectal and pancreatic carcinomas, was radiolabeled with 90Y by the cyclic DTPA anhydride method and by a site-specific bifunctional chelate technique using p-NH2-Bz-DTPA. The therapeutic effects of 90Y-CO17-1A radiolabeled by these two techniques were compared in nude mice bearing SW 948 human colorectal carcinoma xenografts.

MATERIALS AND METHODS

Radioactivity

90Y (in 0.1 N HCl) was obtained from Oak Ridge National Laboratory, Oak Ridge, TN, and converted to the acetate form by combination with 2 volumes of 2.5 M sodium acetate, pH 5.5 (made from ultrapure sodium acetate, Alfa Products, Danvers, MA). All glassware used was soaked in concentrated HNO3 and rinsed with triple-distilled water. The radioactivity was measured with an Accucal 2002 dose calibrator (Synroc International Corp., Sylmar, CA). The dose calibrator was adjusted to the setting recommended by the manufacturer for measuring 90Y, and assays obtained with this instrument were periodically compared with the assays for 90Y obtained from Oak Ridge National Laboratory. The decay-corrected values have always agreed to within ±5%.

Antibody Coupling with Chelators

MoAb CO17-1A was obtained from Dr. Zenon Stepinski of The Wistar Institute, Philadelphia, PA. This MoAb is of the IgG2a isotype, has specificity for colorectal and pancreatic carcinomas (14), and has also been found to be effective in inhibiting tumor growth in vivo (15). DTPA was coupled to CO17-1A by the following two methods.

Cyclic DTPA Anhydride Method. This method was developed by Hnatchow et al. (16). The detailed procedures for antibody coupling with the cyclic DTPA anhydride method were as previously described (17). A ratio of 2 mol of cyclic DTPA anhydride per mol of monoclonal antibody was used. These reaction conditions gave 1.0–1.4 DTPA groups per antibody molecule, determined by 11C labeling of the coupling mixture (16). The radiochemical purity of the cyclic anhydride-coupled CO17-1A was monitored by silica gel instant thin-layer chromatography (Gelman Instrument Co., Ann Arbor, MI) developed with 0.1 M sodium acetate, pH 5.5. In this system antibody-bound 90Y remains at the origin, while unbound 90Y migrates to the top. Usually, the purity of the 90Y-CO17-1A coupled by cyclic DTPA method was...
greater than 95%. The specific activity of the CO17-1A labeled with cyclic DTPA anhydride is 23 $\mu$Ci $^{90}$Y/$\mu$g of CO17-1A before dilution with cold CO17-1A. About 45% incorporation of initially added $^{90}$Y versus the yield of the final product was obtained.

Site-specific Bifunctional Chelate Technique. p-NH$_2$-Bz-DTPA was obtained from Drs. O. A. Gansow and M. W. Brebhill of the National Cancer Institute, who have reported the synthesis of the compound (18). The site-specific conjugation procedures used are modifications of the method of Rodwell et al. (19). Coupling p-NH$_2$-Bz-DTPA to CO17-1A was accomplished by the following three steps. (a) Oxidation of oligosaccharide moieties of MoAb CO17-1A to aldehydes. Sodium periodate (4.75 mg) was added to 1 ml of CO17-1A solution (10 mg/ml in 0.05 M sodium acetate buffer) and the reaction mixture was shaken to dissolve the solid NaIO$_4$. This reaction mixture was incubated on ice for 1.5 h and then purified on a Sephadex G-50 column (1 x 10 cm) equilibrated with acetate-buffered saline, pH 6.0. (b) Coupling of chelators to oxidized MoAb CO17-1A. Oxidized CO17-1A was incubated with a 30-fold molar excess of p-NH$_2$-Bz-DTPA for 1 h at room temperature. (c) Reduction. Sodium cyanoborohydride (final concentration, 10 mm) was added to the DTPA-conjugated CO17-1A solution. The reaction mixture was incubated at room temperature for 5 h and then dialyzed at 4°C with one change of 0.1 M acetate-buffered saline, pH 6, and three changes of 0.1 M acetate-buffered saline, pH 6. After dialysis, the chelated MoAb (50 $\mu$g in 10 $\mu$l) and the $^{90}$Y-labeled acetate solution (1 $\mu$Ci in 10 $\mu$l) were incubated at room temperature for 30 min, and the purity of the $^{90}$Y-CO17-1A was checked by instant thin-layer chromatography before the isolated CO17-1A was stored. Usually greater than 90% purity was obtained. These reaction conditions gave approximately one DTPA group per MoAb molecule, determined by $^{11}$In or $^{90}$Y labeling of the crude coupling mixture (16). This method for determination of the number of chelating groups was validated for this type of 3-step, site-specific conjugation procedure with oxidation and reduction sequences via use of $^{14}$C-labeled p-aminobenzyl-1,4,7,10-tetraazacyclododecanetriacetic acid. The chelate-conjugated CO17-1A (1 mg/0.2 ml) was aliquoted and stored at -70°C.

Radioimmunoassay

Indirect RIA using live cells in suspension was routinely carried out on both nonconjugated and chelate-conjugated CO17-1A to determine the retention of immunoreactivity (20). SW 948 cells were trypsinized, resuspended in L-15 medium, centrifuged at 1200 rpm for 10 min, and adjusted with RIA buffer (phosphate-buffered saline containing 5% y-globulin-free horse serum) to a final concentration of 5 x 10$^6$ cells/ml. To each well of a microtiter plate were added 50 $\mu$l of cell suspension and 50 $\mu$l of antibody solution (containing varying amounts of CO17-1A coupled by different methods and the unconjugated CO17-1A). The sealed plates were shaken for 1 h at room temperature, the cells were washed 3 times with 200 $\mu$l RIA buffer, and 50 $\mu$l of 125I-labeled rabbit anti-mouse IgG (New England Nuclear, Boston, MA) in RIA buffer were added. The sealed plate and its contents were again shaken for 1 h at room temperature, the cells were washed 3 times with 200 $\mu$l of RIA buffer, and 25 $\mu$l of RIA buffer were added to each well. The wells were swabbed, and the swabs were counted in a gamma counter.

Animal Model

Female nude mice (11-14 weeks old, Harlan Sprague Dawley, Inc., Indianapolis, IN) bearing SW 948 human colorectal carcinoma xenografts were used for the experiments. Five animals/group were used throughout the experiments. Culture conditions for the SW 948 human colorectal carcinoma cell line and the method for implantation of SW 948 cells into nude mice have been described (20). Xenografts were used when approximately 5-10 mm in diameter (~22 days after inoculation).

Radioimmunotherapy

In therapy experiments, groups of 5 nude mice bearing SW 948 colorectal carcinoma xenografts were given injections via the tail vein of $^{90}$Y-CO17-1A (radio labeled by either the cyclic DTPA anhydride technique or the site-specific p-NH$_2$-Bz-DTPA technique) at dosages of 100, 150, and 200 $\mu$Ci/25-g body weight. The weight of MoAb CO17-1A (labeled plus cold) administered to each set of animals was 100 $\mu$g. Since the specific activity was very high in both labeling methods (23 $\mu$Ci $^{90}$Y/$\mu$g MoAb CO17-1A by using cyclic DTPA anhydride method and 18 $\mu$Ci $^{90}$Y/$\mu$g MoAb CO17-1A by using p-NH$_2$-Bz-DTPA method), a group that received only 100 $\mu$g of unlabeled CO17-1A/25 g was used as a control.

Test of WR-2721 as a Radioprotective Agent

WR-2721 was studied as an adjunct to treatment with $^{90}$Y-CO17-1A (radio labeled either by the cyclic DTPA anhydride technique or the site-specific p-NH$_2$-Bz-DTPA technique) at dosages of 100, 150, and 200 $\mu$Ci/25 g body weight. Unlabeled CO17-1A (100 $\mu$g/25 g) was coadministered. S-2-(3-Aminopropylamino)ethylphosphorothioic acid, WR-2721, was freshly prepared in saline and injected i.p. (200 mg/kg body weight) daily for 5 days. A group of mice receiving only WR-2721 was used as a control.

Determination of Tumor Growth Rate

Tumor volumes were determined by measuring the length, width, and thickness of each tumor by using a caliper and were expressed in mm$^3$. Measurements taken prior to injection of $^{90}$Y-CO17-1A were designated as $T_0$. The initial tumor volumes ranged from 250 to 640 mm$^3$ for the experiment using the cyclic DTPA anhydride technique, while that in the experiment using the site-specific method ranged from 180 to 490 mm$^3$. The tumor size was measured on a once or twice weekly schedule. The tumor volume as a function of time was calculated as follows:

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\text{% of tumor volume change from } T_0 = \frac{\text{Tumor volume at time } T - \text{tumor volume at } T_0}{\text{Tumor volume at } T_0} \times 100
\]

Hematological Studies

Twenty $\mu$l of blood were obtained for determination of WBC and hemoglobin levels by nicking the tails of the nude mice. WBC (x 10$^7$ mm$^{-3}$) and hemoglobin (g/dl) determinations were performed by the Methodist Medical Center of Oak Ridge, Oak Ridge, TN, using a Sysmex Microcell Counter CC-180 (TOA Medical Electronics, USA distributor, Carson, CA). Differential cell counts (percentage of segmented cells and percentage of lymphocytes) were measured on slides stained by Hema-TEK Stain Pak (modified Wright stain) of HEMA-TEK 1000 (Miles Laboratories, Elkhart, IN).

RESULTS AND DISCUSSION

Hnatowich et al. (10) reported that $^{90}$Y-labeled MoAbs prepared by the cyclic DTPA anhydride technique are quite stable in serum at 37°C, showing a dissociation rate of 8–9%/day, which is comparable to that of $^{111}$In-labeled MoAbs. Therefore, they suggested that $^{90}$Y-labeled MoAbs may be suitable for radioimmunotherapy. In our experiments, the immunoreactivity of the cyclic DTPA anhydride-conjugated CO17-1A is greater than 90% as compared to the unconjugated CO17-1A (Fig. 2A). In animals receiving $^{90}$Y-CO17-1A radio labeled by
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Hnatowich's cyclic DTPA anhydride technique (Fig. 1), the tumor volume was unchanged from base line at a dose of 200 μCi/25 g, and all experimental animals in this group died between day 14 and day 18 postinjection. At the conclusion of the experiment (29 days), tumor sizes were increased 123 and 275% from the base line for the 150 μCi 90Y-CO17-1A and 100 μCi/25 g groups, respectively. The percentage of tumor volume increase was very high (approximately 500%) for the three control groups (CO17-1A alone, CO17-1A plus WR-2721, and WR-2721 only). Tumor growth curves for groups receiving 90Y-CO17-1A with and without WR-2721 were similar, indicating that WR-2721 did not affect the rate of tumor growth in nude mice. The toxic effect of WR-2721 was observed when all the animals died in the 150 μCi 90Y-CO17-1A plus WR-2721 group, while none died in the 150 μCi 90Y-CO17-1A group at day 19.

Sharkey et al. (12) reported that the toxicity of a 90Y-labeled MoAb may be reduced by improving the linkage of DTPA to the MoAb. In search of an optimum bifunctional chelate method, Washburn et al. (21) of our laboratory have published an abstract comparing five bifunctional chelate techniques for radiolabeling MoAb CO17-1A with 90Y: cyclic DTPA anhydride, SCN-Bz-DTPA and its methyl derivative, SCN-Bz-Mx-DTPA, and p-NH2-Bz-DTPA and its methyl derivative, p-NH2-Bz-Mx-DTPA. Radiation dosimetry calculations have been made based on timed tissue distribution studies (6, 24, 48, 72, 120, and 168 h postinjection) in nude mice bearing SW 948 human colorectal carcinoma xenografts. The ratio of the tumor dose to the bone marrow dose for the latter four reagents were all much higher than that for the cyclic DTPA anhydride. The values for the site-specific p-NH2-Bz-DTPA and the SCN-Bz-DTPA technique were similar (21).4

We have also studied radioimmunotherapy using 90Y-CO17-1A prepared by a site-specific p-NH2-Bz-DTPA bifunctional chelate technique. The advantage of using a site-specific method is that the covalent modification of antibodies was based upon attachment of chelating groups to the oligosaccharide moieties of the Fc portion of the antibody molecule, which are located distal to the antigen binding site (19). Although the site-specific labeling method involved oxidation and reduction of the antibody, the retention of the immunoreactivity is still greater than 90% (Fig. 2B). As shown in Fig. 3, the percentage of tumor volume change from base line showed a dose-related correlation with the dosage of 90Y-CO17-1A administered, with greater tumoricidal effects observed at higher dosages. In the 200 μCi/25 g 90Y-CO17-1A and 150 μCi/25 g groups, the percentage of tumor volume change from base line reached ~87% and ~50% at day 15 and day 14, respectively. The percentage of tumor volume change from base line for the 100 μCi/25 g group and the unlabeled CO17-1A only group exhibited nearly the same slopes, indicating that such a low dose of 90Y-CO17-1A had little therapeutic effect. However, the three groups which showed the greatest increases in percentage of tumor volume change from base line were the WR-2721 only group, the 100 μCi 90Y-CO17-1A/25 g plus WR-2721 group, and the unlabeled CO17-1A plus WR-2721 group.

The effect of coadministration of unlabeled antibody was discussed in the papers of Washburn et al. (17) and Larson et al. (22). High liver uptake is a major problem in the use of radiolabeled MoAb in animal studies. This may be due to the fact that high-specific-activity radiolabeled MoAb can complex most of the radioactivity to circulating antigen with subsequent

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4 A paper to discuss these bifunctional chelate methods is in preparation.
CO17-1A/25 g plus WR-2721, and WR-2721 only.

Three control groups were given 100 μg CO17-1A/25 g only, 100 μg unlabeled CO17-1A/25 g body weight, with or without adjunctive i.p. injections of WR-2721 (200 mg/kg body weight daily for 5 days). All ΔY-CO17-1A and ΔY-CO17-1A plus WR-2721 groups received 100 μg of unlabeled CO17-1A/25 g body weight as a coinjection. Three control groups were given 100 μg CO17-1A/25 g only, 100 μg CO17-1A/25 g plus WR-2721, and WR-2721 only.

Table 1: Survival of animals administered ΔY-CO17-1A conjugated with the cyclic DTPA anhydride or site-specific p-NH2-Bz-DTPA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cyclic DTPA anhydride</th>
<th>NH2-Bz-DTPA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 μCi CO17-1A/25 g + WR-2721</td>
<td>0/5</td>
<td>5/5</td>
</tr>
<tr>
<td>150 μCi CO17-1A/25 g + WR-2721</td>
<td>2/5</td>
<td>5/5</td>
</tr>
<tr>
<td>100 μCi CO17-1A/25 g + WR-2721</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>100 μCi unlabeled CO17-1A/25 g + WR-2721</td>
<td>4/5</td>
<td>5/5</td>
</tr>
<tr>
<td>100 μCi unlabeled CO17-1A/25 g + WR-2721</td>
<td>5/5</td>
<td>5/5</td>
</tr>
</tbody>
</table>

*Groups of mice were given i.v. injections of ΔY-CO17-1A (radiolabeled either by the cyclic DTPA anhydride technique or the site-specific p-NH2-Bz-DTPA technique), either alone or in conjunction with i.p. injections of WR-2721 (200 mg/kg body weight daily for 5 days). Unlabeled CO17-1A/100 μg/25 g body weight was coinjected. Three control groups were given 100 μg unlabeled CO17-1A/25 g only, 100 μg unlabeled CO17-1A/25 g plus WR-2721, and WR-2721 only.

This experiment ended on day 29. Data are expressed as total number of surviving animals/total animals in the group.

This experiment ended on day 71. Data are expressed as total number of surviving animals/total animals in the group.

Animals died at 14 to 21 days after injection of ΔY-CO17-1A.

Animals died on day 28 after injection of ΔY-CO17-1A.

clearance into the liver (22). We have used coadministration of unlabeled antibody in our previous studies and obtained higher and more uniform 48-h tumor uptake of ΔY-CO17-1A and lower reticuloendothelial (liver, spleen, and bone marrow) uptake. Blood concentrations were also higher in animals receiving coinjections of the unlabeled antibody (17, 23).

WR-2721 has been shown to have a selective ability to protect cells in culture against radiation damage (24, 25) and to protect tissues against lethal effects of chemotherapeutic agents (26–28). Also, WR-2721 has reached Phase II clinical trials (29) and has been shown to protect against bone marrow depression in irradiated humans (30). As shown in Table 1, all five mice in the 200 μCi/25 g group and 3 of 5 mice in the 150 μCi/25 g group in which ΔY-CO17-1A was prepared by using the cyclic DTPA anhydride technique died between day 14 and day 21 as a result of radiation-induced bone marrow toxicity. However, in the corresponding WR-2721 plus 200 μCi/25 g and WR-2721 plus 150 μCi/25 g groups, all animals died between day 14 and day 21. Therefore, WR-2721 did not show any radioprotective effect in the ΔY-CO17-1A-treated groups in this experiment. On the other hand, when ΔY-CO17-1A prepared by the site-specific p-NH2-Bz-DTPA technique was used, all animals except two in the 200 μCi/25 g CO17-1A plus WR-2721 group survived through the entire 71-day experimental period (Table 1). This may indicate that WR-2721 has some toxic effect and shows no protection from radiation-induced bone marrow suppression. The lack of radioprotection observed in these studies can likely be attributed to the short duration of the effectiveness of WR-2721 following treatment. Yuhas and Storer (31) reported that, for the greatest radioprotective effect, WR-2721 must be administered about 15 to 30 min prior to radiation exposure. At later times the radioprotection is greatly decreased. In the case of ΔY-labeled monoclonal antibodies, the tissues would be continuously irradiated over a period of several days. Therefore, although WR-2721 is an effective agent for protection against the radiation-induced free radicals resulting from short-duration radiation exposures, our studies indicate that it is not likely to be useful for reducing radiation toxicity from ΔY-labeled monoclonal antibodies. From our therapeutic studies using two bifunctional chelate techniques, it is obvious that ΔY-CO17-1A prepared via a site-specific bifunctional chelate technique using p-NH2-Bz-DTPA is superior to that prepared by the cyclic DTPA anhydride method.

Hematological studies were performed in a similar set of experiments using the site-specific p-NH2-Bz-DTPA bifunctional chelate technique. As shown in Fig. 4A, severe leukopenia (WBC < 1000/mm³) was observed in all ΔY-CO17-1A-treated groups. Leukopenia in the ΔY-CO17-1A-treated groups showed a dose-response relationship with the nadir occurring at approximately 2 weeks after administration, which is in agreement with the observations of Anderson-Berg et al. (11) and Sharkey et al. (12). The WBC returned to 60% of control values at the end of the experiment on day 56. The hemoglobin was reduced to 3.7 and 9.6 g/dl for the 200 μCi/25 g and 150 μCi/25 g groups, respectively, at day 21, and returned to 90% of control values at day 56 (Fig. 4B). For all ΔY-CO17-1A-treated groups, the percentage of segmented cells showed a decrease of 13–33% at day 21 when compared to the control group (Fig. 4C). On the contrary, the percentage of lymphocyte counts for the ΔY-CO17-1A-treated groups showed an increase of 7–32% at day 21 when compared to the control group (Fig. 4D). These hematological observations correspond well with dose-limiting bone marrow toxicity which is generally seen at 2 to 3 weeks after injection. Such hematological data are valuable in choosing the proper time for reinjecting ΔY-labeled MoAb if multiple injections are considered.

Anderson-Berg et al. (11) reported that in their erythroleukemic nude mouse model 50 μCi of ΔY-labeled MoAb 103A/25 g was the highest dose that could be administered without killing animals due to excessive toxicity. Sharkey et al. (12) also observed the same highest dose (50 μCi of ΔY-labeled MoAb NP-2/25 g) that was tolerated by their human colon cancer xenograft nude mouse model. In our experiments, we observed a 2-fold (Table 1; no deaths at 100 μCi/25 g) increase in the tolerated dosage of ΔY-labeled MoAb radiolabeled with the cyclic DTPA anhydride bifunctional chelate technique, as had been used in the previous studies. When the site-specific p-NH2-Bz-DTPA technique was used for radiolabeling, a 4-fold increase in the tolerated dose was observed (Table 1; no deaths at 200 μCi/25 g). This clearly shows that the toxicity can be reduced by improvements in the bifunctional chelate technique.
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Fig. 4. Hematological study of athymic nude mice bearing SW 948 human colorectal carcinoma xenografts, which had been injected i.v. with $^{90}$Y-CO17-1A prepared with the site-specific technique, using p-NH$_2$-Bz-DTPA. All groups received 100 µg of unlabeled CO17-1A/25 g as a coinjection. A, circulating total WBC ($x10^3$/mm$^3$) in nude mice receiving 150, 200, and 250 µCi $^{90}$Y-CO17-1A/25 g body weight. The control group received only 100 µg of unlabeled CO17-1A/25 g. B, hemoglobin levels (g/dl) in nude mice given 150, 200, and 250 µCi $^{90}$Y-CO17-1A/25 g body weight. The control group received only 100 µg of unlabeled CO17-1A/25 g. C, percentage of segmented cells in nude mice receiving 150, 200, and 250 µCi $^{90}$Y-CO17-1A/25 g body weight. The control group received only 100 µg of unlabeled CO17-1A/25 g. D, percentage of lymphocytes in nude mice receiving 150, 200, and 250 µCi $^{90}$Y-CO17-1A/25 g body weight. The control group received only 100 µg of unlabeled CO17-1A/25 g.

In conclusion, i.v. injection of $^{90}$Y-CO17-1A conjugated via the site-specific p-NH$_2$-Bz-DTPA technique has been found to significantly reduce the tumor volume of SW 948 human colorectal carcinoma xenografts in nude mice (up to 87% reduction from base line at a dosage of 200 µCi/25 g of body weight). However, bone marrow toxicity is still a dose-limiting factor.

REFERENCES


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