

HARVARD-MIT RESEARCH PROGRAM IN
SHORT-LIVED RADIOPHARMACEUTICALS

PROGRESS REPORT

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Project 1D: The Development and Radiotherapeutic Application of ^{211}At -Labeled Radiopharmaceuticals

ABSTRACT

This project is concerned with developing the potential of alpha-emitting radionuclides as agents for radiotherapy. Alpha-emitters seem ideally suited for this application because their high linear energy transfer and short range permit the deposition of considerable energy in a very small volume of tissue. Unlike the beta particles of ^{131}I which have a range of about 1-2 mm in tissue, 5-7 MeV alpha particles would traverse only a few cell diameters. Among the available alpha-emitters, ^{211}At appears most promising for therapeutic applications because, 1) it has some chemical similarities to iodine, an element that can readily be incorporated into numerous proteins and peptides, 2) it has a half-life that is long enough to permit chemical manipulation yet short enough to minimize destruction of healthy cells due to degradation of the label over time, 3) it can be produced conveniently using a cyclotron, and 4) alpha emission is associated with 100% of its decays with no accompanying beta emission.

In the past year the evaluation of an astatine-tellurium colloid as an agent for the destruction of malignant ascites has been completed. The therapeutic efficacy of ^{211}At -tellurium colloid has been compared with that of several beta-emitting radiocolloids. Studies on the application of monoclonal antibodies as carriers for selective delineation and destruction of malignant cell populations have also been initiated.

PROGRESS REPORT

1. Objectives

The overall objective of this proposal is the development of ^{211}At -labeled radiotherapeutic agents for the selective destruction of specific cell populations. Our goals are to develop techniques for labeling physical and biological carriers with ^{211}At and to assess the radiotoxicity of these ^{211}At -labeled substances in appropriate in vitro and in vivo models.

2. Work in Progress

a) Astatine-211-Tellurium Radiocolloid Cures Experimental Malignant Ascites

Although the potential of directed but unsealed sources of radiation for cancer therapy was recognized early, the therapeutic potential of such sources remains largely unrealized. The shortcomings have been both physical and biological; not only must the radionuclide deposit its energy within a short range of action, but it must also be localized preferentially within or in close proximity to tumor cells. If appropriate carriers can be devised and labeled with alpha-emitting radionuclides,

these requirements should be satisfied.

The alpha-particles emitted in the process of radioactive decay (i) are directly ionizing, (ii) have energies (E_{α}) of 5 to 8 MeV, (iii) have a range of several cell diameters, and (iv) have a high linear energy transfer which results in high specific ionization; their radiobiological effects are largely independent of cellular oxygenation. Among the available alpha-emitters, ^{211}At appears the most promising. The average E_{α} is 6.8 MeV, and the range in water is 60 μm ; the average linear energy transfer is 113 keV/ μm . The chemical properties of astatine are quite different from those of iodine, its nearest halogen neighbor; nonetheless, astatine is concentrated by thyroid tissue, albeit less avidly than iodine.

We have prepared ^{211}At -tellurium colloid and investigated its therapeutic efficacy in a malignant ascites tumor model. The therapeutic ratio should be highly favorable in this system because the radionuclide is administered directly into the peritoneal cavity and is brought directly into contact with tumor cells. The decay characteristics of ^{211}At emissions are such that the critical normal tissue, intestinal mucosa, is largely spared the cytotoxic effects of the emitted alpha-radiations because of the thickness of the serosa and muscularis relative to the alpha-particle range. The model provides a quantitative experimental system in which to assess risk-benefit considerations that may be directly applicable for evaluating human radiocolloid therapy.

The ^{211}At was produced on the 60-inch cyclotron of the Brookhaven National Laboratory. Targets were prepared by melting bismuth-209 onto circular aluminum disks. These targets were water-cooled and irradiated with alpha-particles (21 to 28 MeV) to produce ^{211}At via the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ reaction. The beam current was 10 to 15 μA , and the irradiation time was 2 to 6 hours. We isolated the ^{211}At from the target by distillation at 700°C and collected it in a trap containing 0.1N sodium hydroxide and 0.01N sodium bisulfite. Preparations were determined to be chemically pure by elemental analysis and by gamma- and alpha- spectrometry. Finely ground elemental tellurium was chosen as the colloidal material because of its strong affinity for astatine at neutral and acidic pH. We prepared the tellurium particles just before use by grinding elemental tellurium to a fine powder. Particles between 2 and 25 μm were obtained by a series of sedimentations, centrifugations, and filtrations. Then we acidified the ^{211}At solution with 2N nitric acid, added it to the tellurium colloid, and shook the mixture for 1 minute at room temperature. The radiocolloid was washed in distilled water; supernatants from these washes contained <0.5 percent unbound ^{211}At .

The tumor used in these experiments arose spontaneously in the ovary of a C3H mouse and has been maintained in its ascitic form by serial intraperitoneal transplantation in female C3HeB/FeJ mice. A regular relationship has been observed between the size of the tumor cell inoculum and the median time to death. Consequently, therapeutic efficacy can be expressed not only as the percentage increase in median survival but also as a cellular surviving fraction. Such a calculation implies little or no

repair of radiation damage, an assumption that is substantiated by in vitro studies.

Single graded doses of the ^{211}At -tellurium colloid were administered into the peritoneal cavity 24 hours after intraperitoneal injection of 10^6 tumor cells. Mice treated with $<50 \mu\text{Ci}$ of radiocolloid demonstrated a dose-related increase in median survival; furthermore, doses of 25 to $50 \mu\text{Ci}$ were curative in all animals so treated (Fig. 1). Although some mild morbidity was manifested by weight loss and change in fur nap with doses of 25 to $50 \mu\text{Ci}$, there were no acute deaths. Doses of radiocolloid $<75 \mu\text{Ci}$ were uniformly fatal in 5 to 7 days, presumably the result of gastrointestinal injury. When the cellular surviving fraction after treatment with ^{211}At colloid was expressed as a semilogarithmic function of dose (Fig. 2), a linear relationship with no shoulder in the low-dose region was observed at doses $<20 \mu\text{Ci}$.

Cured animals observed for at least 200 days were sleek, agile, and alert. Histological sections of major organs showed no evidence of tumor and were unremarkable as compared to those of untreated mice except for the thyroid. Thyroid tissue, which was identified with much less frequency in treated mice, contained considerable fibrosis as well as granular and refractile material. These findings probably reflect some *in vivo* release of ^{211}At from the tellurium colloid. No second tumors were identified; however, the number of cured animals was small and the duration of follow-up relatively short. Although intravenous injection of ionic ^{211}At in comparable doses has been reported to induce mammary tumors, endometrial polyps, and endocrine adenomas in immature rats, these adverse effects may be minimized under conditions of directed colloidal administration. Moreover, thyroid uptake and other potentially adverse effects of ^{211}At may be minimized by preliminary treatment with iodide.

The ^{211}At -tellurium colloid is highly effective in the treatment of experimental malignant ascites. Not only is the prolongation of median survival dose-related, but this alpha-emitting radiocolloid can also be curative without serious morbidity. The most compelling reason for this increased efficacy is the direct and densely ionizing character of the emitted alpha-radiations.

These experiments form the basis for further investigations and development of alpha-emitting radiocolloids. The most obvious applications of such radiocolloids are in the therapy of ascites and surface-spreading abdominal and pelvic malignancies. Another use may be in the treatment of rheumatoid arthritis, particularly in selected joints where the synovial thickness does not exceed the alpha-particle range.

b) Comparison of Therapeutic Efficacy of Alpha- and Beta-Emitting Radiocolloids

The therapeutic efficacy of ^{211}At -tellurium colloid was compared with that of several beta-emitting radiocolloids: ^{32}P -chromic phosphate, ^{90}Y -citrate and ^{165}Dy -ferric hydroxide macroaggregates (Fig. 3).

Although ^{32}P -chromic phosphate is used clinically as adjuvant therapy to surgery in early stages of human ovarian cancer, it has no antineoplastic

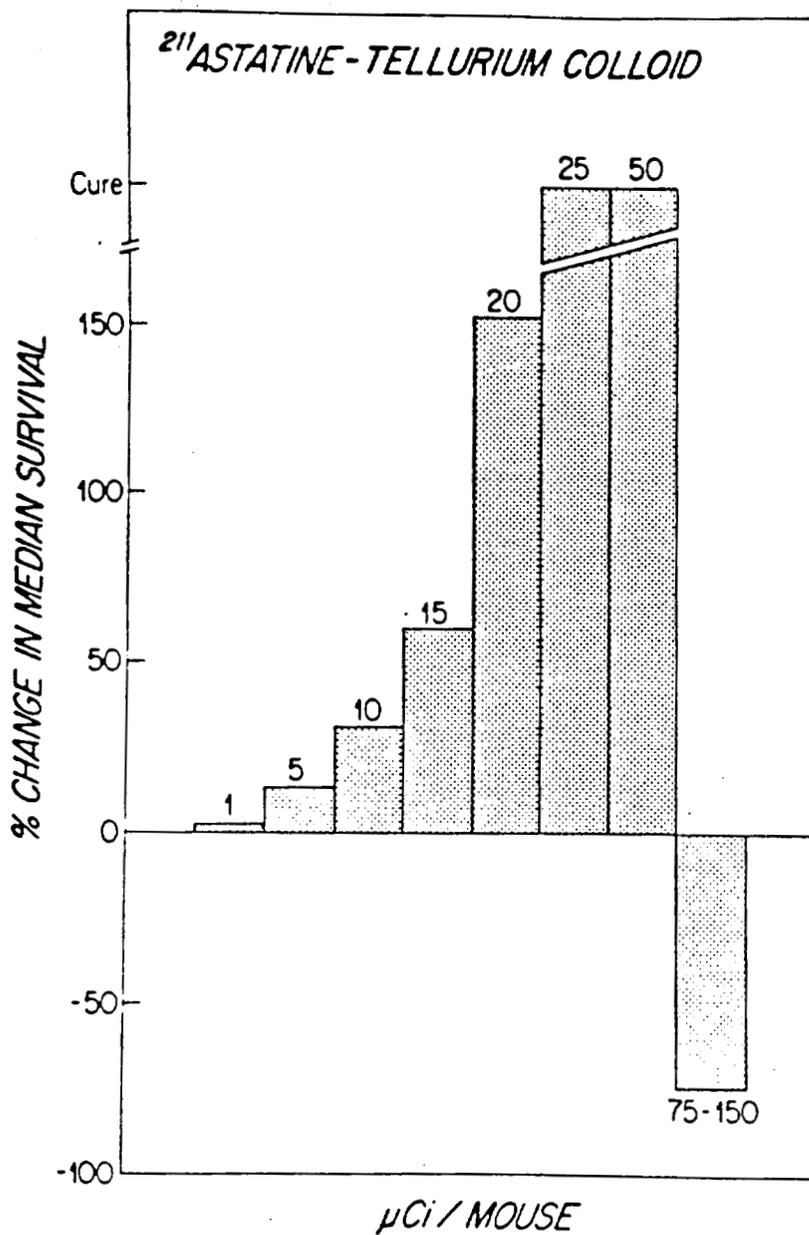


Figure 1. Results of radiocolloid therapy on experimental malignant ascites in mice, expressed as the percentage of change in median survival. Each experimental group contained 10 to 12 mice; experiments were performed three times. Nonradioactive tellurium colloid $<2 \mu\text{m}$ in size is uniformly lethal in 3 days, presumably the result of pulmonary insufficiency.

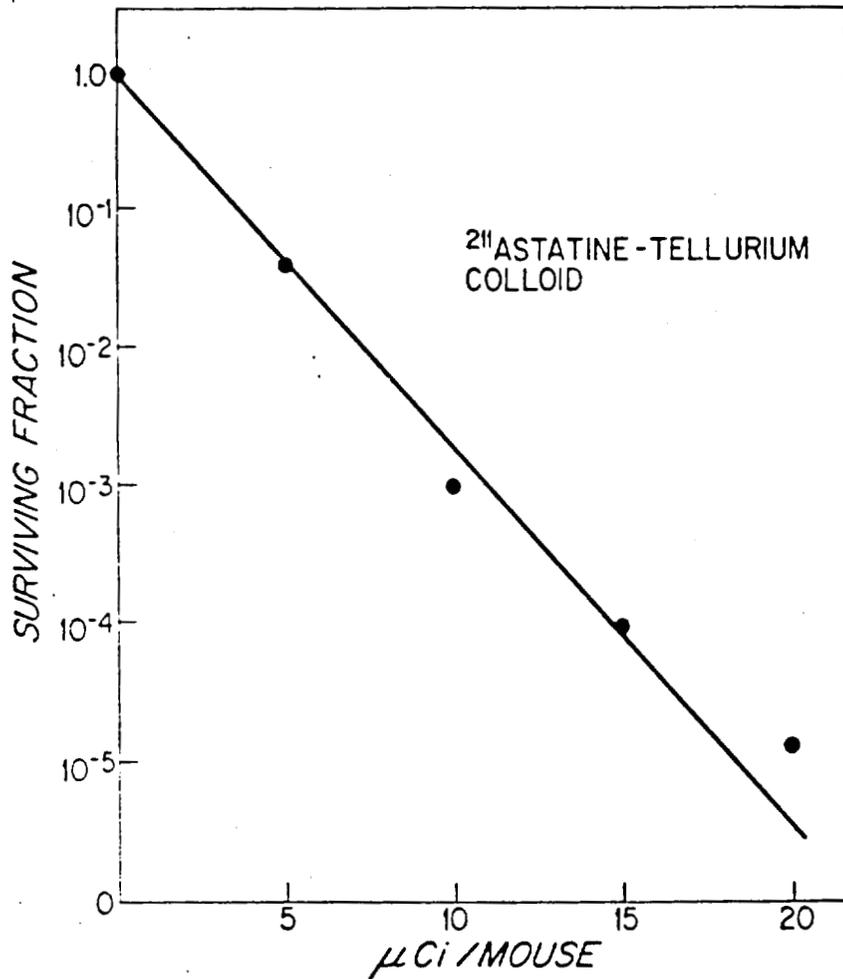


Figure 2. Results of ^{211}At colloid therapy expressed as cellular survival fraction. The slope of the line was determined by semilogarithmic linear regression analysis. The correlation coefficient is $>.99$. The dose to reduce survival to 0.37 is 1.6 μCi .

activity in this experimental tumor model. At high doses (>100 μCi), it exhibited marked gastrointestinal toxicity.

In comparison with ^{32}P , ^{211}At radiations have 1/100 of the range of action but ten times the energy deposition per unit path length. Thus, the indirect and sparse ionizations of ^{32}P appear to be insufficient to kill tumor cells in this system despite their close physical proximity to tumor cells. Because 1-day-old ascitic tumor cells are considered to be well oxygenated, the increased radiobiological effectiveness of ^{211}At relative to ^{32}P probably reflects differences in linear energy transfer rather than hypoxic cell sensitization by the emitted alpha-radiations.

^{90}Y -citrate is not used for intraperitoneal therapy, but it has gained widespread use in Europe for radiation synovectomies. In this ascites tumor model the maximum prolongation of median survival (80%) was achieved with doses of 200 μCi .

^{165}Dy -FHMA has been developed by this laboratory in conjunction with Dr. Clement B. Sledge as a potential therapeutic colloid for radiation synovectomy. Maximum therapeutic efficacy (100% prolongation of median survival) was achieved with dose of 8000 μCi .

The striking differences in therapeutic efficacy observed with the three beta-emitting radiocolloids in Fig. 3 cannot be adequately explained by the relatively minor differences in E_{max} energies. On the other hand, there are marked differences in physical half-life for the three radionuclides. The therapeutic index (defined as the dose where change in median survival changes from positive to negative in Fig. 3) is plotted as function of physical half-life for the three radiocolloids in Fig. 4. The interesting linear relationship between therapeutic index and physical half-life merits further investigation with other β -emitting radiocolloids.

c) Monoclonal Antibodies as Tumor-Specific Carriers

We are currently investigating two monoclonal antibodies as potential tumor-specific carriers of radioactivity for both diagnostic and therapeutic applications. Since the constraints imposed on a potential therapeutic carrier of radioisotope are related to but more stringent than a similar application in the diagnostic realm, our initial studies were directed towards determining whether radiolabeled monoclonal antibodies could be utilized to selectively delineate tumors. We are investigating the feasibility of imaging tumors with radiolabeled monoclonal antibodies in collaboration with Drs. J. Schlom and D. Colcher of the NIH using a monoclonal antibody against human breast carcinoma (6.23) and with Dr. B. Benacerraf at Harvard using an anti-prostate carcinoma monoclonal antibody (F77-129). Both antibodies were developed from hybridomas resulting from the fusion of murine mouse myelomas with splenic lymphocytes of mice immunized with either human breast or prostate carcinoma cell extracts.

Monoclonal antibodies were labeled with ^{125}I using the stationary phase chloramide 1,3,4,6-tetrachloro-3 α -6 α -diphenylglycouril (Iodogen). The advantage of this chloramide is that it is only sparingly soluble in water and can be used as a solid phase reagent. In this technique, an organic solution of Iodogen is first evaporated in a test tube and then an aqueous

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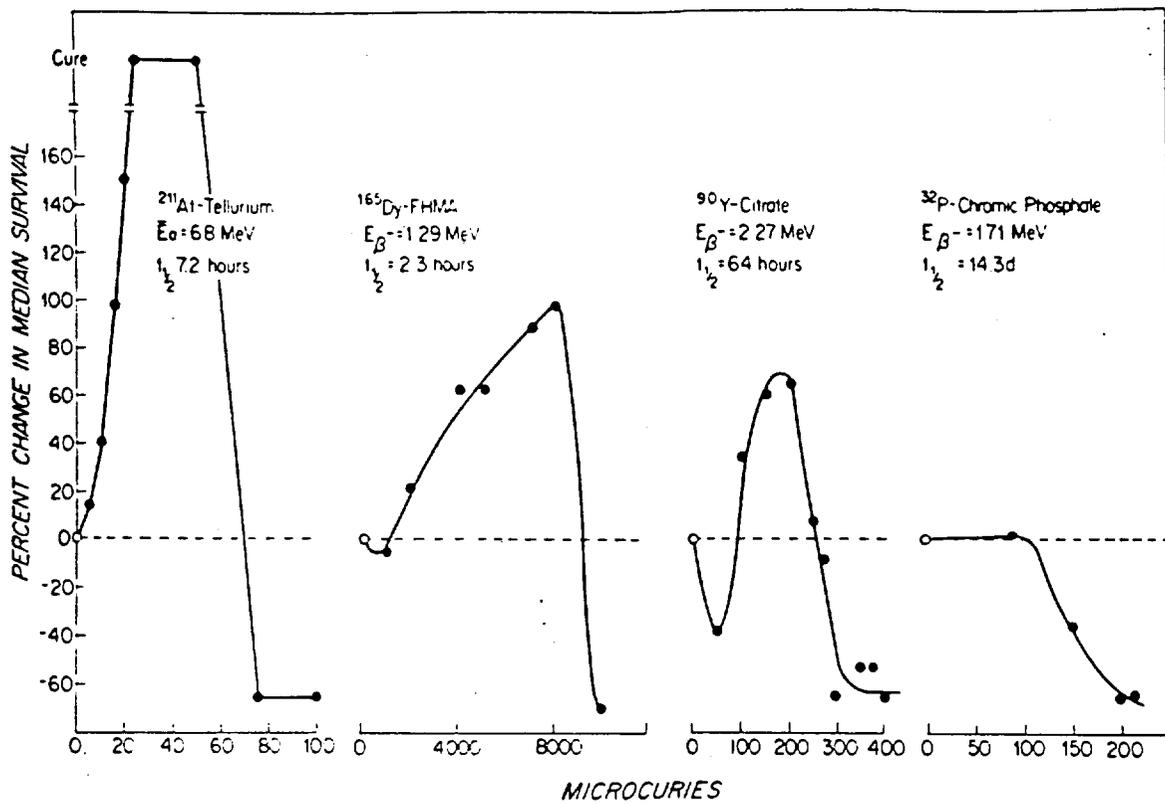
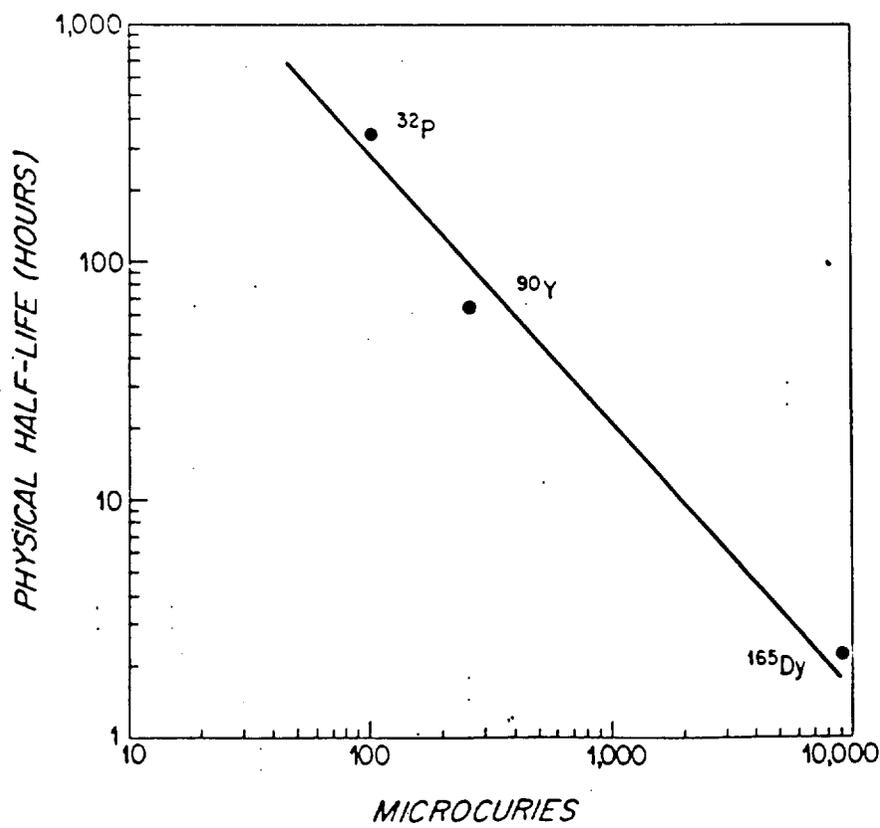


Figure 3

Figure 4



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solution containing both the monoclonal antibody and the ^{125}I activity is added to the film deposited on the tube. When the iodination is completed, the monoclonal antibody is separated from the water insoluble chloramide by simply transferring the reaction mixture to a second tube. Thus, the Iodogen technique should be well suited for labeling sensitive biological carriers such as monoclonal antibodies because this method both minimizes exposure of the protein to oxidants and obviates the need for the addition of reducing agents such as bisulfite to terminate the reaction.

We have investigated the effect of several variables on the optimization of the iodination yield and the retention of immunospecificity by the ^{125}I -labeled monoclonal antibody. Parameters investigated included reaction time (0.5-30 min), protein concentration (10-200 μg), and Iodogen concentration (0.5-200 μg).

Iodination yield was determined by TCA precipitation. About 1 mg of BSA and 1 ml of 10% TCA were added to an aliquot of the reaction mixture and the solution was allowed to stand at room temperature for 20 min. After centrifugation, the precipitate was washed with 10% TCA, resuspended and centrifuged again. The precipitate containing the ^{125}I -labeled monoclonal antibody was then counted in order to determine the radiolabeling efficiency.

The effect of each radiolabeling procedure on the immunospecificity of the monoclonal antibody was assayed using a fluorescence-activated cell sorter. For the anti-breast carcinoma antibody, immunospecificity was also tested using a solid phase cell binding assay. In this procedure, aliquots of radiolabeled antibody were incubated with cell extracts of both a human breast metastasis to the liver and normal liver tissue. The fraction of antibody bound to the metastasis extract as well as the ratio of tumor to normal tissue binding were then measured. A similar cell binding assay is being developed for the F77-129 anti-prostate monoclonal antibody.

The following procedure was adopted for labeling monoclonal antibodies with ^{125}I : Prior to radiolabeling a methylene chloride solution containing 5 μg of Iodogen is evaporated with a stream of nitrogen in a 10 x 75 mm glass tube. The iodination is initiated by adding to the chloramide-coated tube 100 μl of pH 7.2 phosphate buffer containing both 100 μg of antibody and the ^{125}I activity and reacting at room temperature for 10 min. The reaction mixture is removed, and the reaction tube is washed twice with 150 μl of phosphate buffer. The reaction mixture and washings are combined and added to a Sephadex G-25 column to separate the radiolabeled antibody from unreacted iodide.

Using this method, both monoclonal antibodies could be iodinated in yields of about 50-70% with trace amounts of ^{125}I (less than 1 μCi). The labeling efficiencies observed at higher levels of ^{125}I activity were somewhat lower and less predictable, ranging from 25-60%. In future experiments, the effect of stable iodine on the efficiency of antibody iodination with Iodogen will be investigated. The maximum specific activity obtained using 100 μg of protein was about 2 iodine atoms per antibody molecule. The *in vitro* stability of the radiolabeled antibody was determined using serial dialysis. The rate of deiodination for both ^{125}I -labeled monoclonal antibodies was observed to be less than 1%/day.

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The tissue distribution of the ^{125}I -labeled antibodies was studied in nude mice implanted with human tumor cells. All mice received 0.05% KI in order to block thyroid uptake of ^{125}I activity resultant from in vivo deiodination of the ^{125}I -labeled antibody. Mice were imaged using a low energy mobile camera equipped with a 6mm-aperture pinhole collimator. Groups of mice were imaged and then sacrificed at 24,48,72, and 96 hr post injection.

i. Anti-prostate carcinoma antibody (F77-129)

Nude mice were injected with 5×10^6 PC-3 human prostate carcinoma cells and imaged about 2 weeks later when tumors were about 100-200 mg in weight. Each mouse was injected with approximately 10 μg of F77-129 antibody labeled with 115 μCi of ^{125}I . Tumors could easily be delineated at all imaging times in both lateral and posterior views. Figure 5 is a lateral view obtained 72 hrs post injection of a nude mouse bearing a 90 mg PC-3 tumor in its back. The tissue distribution and tumor to nontarget ratios of ^{125}I (F77-129) monoclonal antibody are given in Tables 1 and 2. The best tumor to nontarget ratios were observed at 72 hr post injection when the tumor to blood ratio was 8 to 1 and the tumor to tissue ratio was greater than 10 to 1 for all other tissues studied. Tumor uptake was about 24% per gram at 24 hrs and decreased to about half that level at 72 hr post injection. Thyroid blocking was effective; in all mice the thyroid uptake was less than 0.1% of injected dose. The results from both the imaging and tissue distribution experiments clearly indicate that in the nude mouse model, ^{125}I (F77-129) monoclonal antibody selectively localizes in human prostate carcinomas.

ii. Anti-breast carcinoma antibody (6.23)

The biodistribution of ^{125}I (6.23) anti-breast carcinoma antibody was studied in three groups of nude mice. Two groups of mice had tumors derived from human mammary carcinoma cell lines (Clouser and MCF-7) and the third group of mice served as negative controls, bearing the nonbreast carcinoma A375 cell line. The size of the tumors ranged from 0.3-2.3 gm for the Clousers, 10-300 mg for the MCF-7 mice, and 100-500 mg for the A375 line. All mice were injected with 3 μg of 6.23 antibody labeled with about 60 μCi of ^{125}I . The results for the ^{125}I (6.23) antibody in the Clouser mice were qualitatively similar to those obtained with the ^{125}I (F77-129) antibody. Tumors could be easily detected at all imaging times with optimal contrast between tumor and surrounding tissue observed at 72 hrs post injection (Figure 6). However, for the Clouser mice, the percent injected dose per gram tumor and tumor to nontarget tissue ratios were about half those observed with the ^{125}I (F77-129) antibody-(PC-3) tumor system (Tables 3 and 4). With the Clouser mice, the smaller tumors had greater percent uptake per gram of ^{125}I (6.23) at all time points. When a 0.8 gm tumor was sectioned it was found that the percent uptake per gram in the core of the tumor was about 20% less than on its surface.

TABLE 1
 TISSUE DISTRIBUTION OF ^{125}I (F77-129) MONOCLONAL ANTIBODY
 AGAINST PROSTATE CARCINOMA IN NUDE MICE BEARING PC-3 PROSTATE TUMORS

% Injected Dose / Gram Tissue

Tissue	<u>24 hr</u>	<u>48 hr</u>	<u>72 hr</u>	<u>96 hr</u>
Tumor	23.97	12.82	11.78	6.32
Liver	2.03	1.05	0.54	0.53
Spleen	3.89	1.41	0.71	0.62
Lung	5.49	2.59	1.05	0.91
Heart	3.19	1.32	0.62	0.61
Kidney	3.51	1.64	0.80	0.48
Skin	4.55	2.69	1.13	1.02
Muscle	2.12	0.96	0.47	0.40
Bone	2.68	0.93	0.49	0.33
Blood	4.86	3.24	1.48	1.46

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TABLE 2
TUMOR TO NONTARGET TISSUE RATIOS FOR ^{125}I (F77-129) MONOCLONAL
ANTIBODY AGAINST PROSTATE CARCINOMA IN NUDE MICE
BEARING PC-3 PROSTATE TUMORS

Tumor to:	Ratio			
	<u>24 hr</u>	<u>48 hr</u>	<u>72 hr</u>	<u>96 hr</u>
Blood	4.9	3.9	8.0	4.4
Liver	11.9	12.1	22.2	12.1
Lungs	4.4	4.9	11.0	6.9
Spleen	6.2	9.1	17.4	10.7
Heart	7.5	9.6	19.0	10.4
Kidneys	6.8	7.8	14.5	13.3
Skin	5.3	4.7	10.5	6.3
Muscle	11.4	13.3	24.7	15.8
Bone	9.4	13.8	24.4	19.4
Stomach	5.6	10.3	17.8	32.5
Small Intestine	14.1	15.4	33.6	23.9
Large Intestine	14.6	13.9	36.4	30.0

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TABLE 3

TISSUE DISTRIBUTION OF ^{125}I (6.23) MONOCLONAL ANTIBODY AGAINST BREAST
 CARCINOMA IN NUDE MICE BEARING CLOUSER AND MCF-7 TUMORS

Tissue	% Injected Dose/Gram Tissue							
	24 hr		48 hr		72 hr		96 hr	
	Clouser	MCF-7	Clouser	MCF-7	Clouser	MCF-7	Clouser	MCF-7
tumor	13.08	6.59	5.72	4.45	13.04	12.05	8.39	19.90
liver	3.06	2.56	1.63	1.65	1.63	2.57	2.08	1.66
spleen	2.02	1.41	1.64	0.88	0.72	2.50	1.14	1.47
lung	7.30	8.73	4.31	2.23	2.18	5.79	5.18	4.97
heart	2.59	2.42	1.70	1.34	1.61	3.45	2.21	1.75
kidney	3.56	3.40	1.73	1.85	2.06	2.63	2.11	1.71
skin	5.78	3.00	4.89	2.37	1.86	4.05	4.03	3.40
muscle	2.20	1.27	1.79	1.04	0.87	1.53	1.23	1.05
bone	1.64	0.94	1.04	0.61	0.35	1.69	0.87	0.90
blood	11.74	6.47	13.48	4.78	5.39	15.71	7.70	8.33

TABLE 4

TUMOR TO NONTARGET TISSUE RATIOS FOR $^{125}\text{I}(6.23)$ MONOCLONAL ANTIBODY AGAINST

BREAST CARCINOMA IN NUDE MICE BEARING CLOUSER AND MCF-7 TUMORS

Tumor to:	Ratio							
	24 hr		48 hr		72 hr		96 hr	
	Clouser	MCF-7	Clouser	MCF-7	Clouser	MCF-7	Clouser	MCF-7
blood	1.2	1.0	0.5	0.9	2.6	0.8	1.1	2.4
liver	4.4	2.6	3.4	3.0	8.1	4.7	4.1	12.0
lungs	1.8	0.8	1.3	2.0	6.1	6.5	1.6	4.0
spleen	6.9	4.7	3.4	5.4	18.2	4.9	7.1	13.5
heart	5.0	2.7	3.2	3.4	8.5	3.5	3.6	11.4
kidney	3.7	1.9	3.3	2.6	6.4	4.7	4.4	11.6
skin	2.3	2.2	1.1	1.8	7.3	3.1	2.1	5.9
muscle	6.0	5.2	3.1	4.6	15.0	8.0	6.6	19.0
bone	8.2	7.0	5.4	6.5	41.0	7.3	9.3	22.1
stomach	4.9	2.9	3.0	4.5	21.6	6.5	9.9	7.9
small intestine	10.4	6.2	6.4	5.2	24.5	10.6	10.1	25.2
large intestine	10.6	3.3	5.6	5.0	31.1	5.0	12.5	33.7

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Figure 5. Lateral view of nude mouse bearing PC-3 prostate tumor 72 hr after injection of ^{125}I (F77-129) anti-prostate carcinoma monoclonal antibody

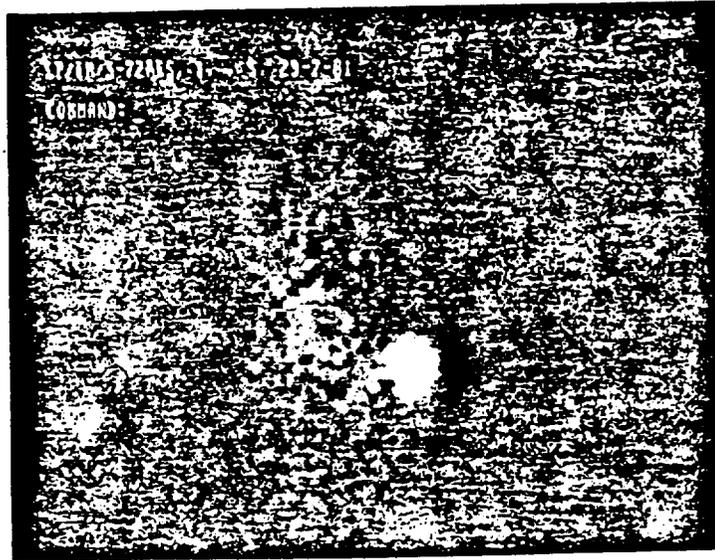
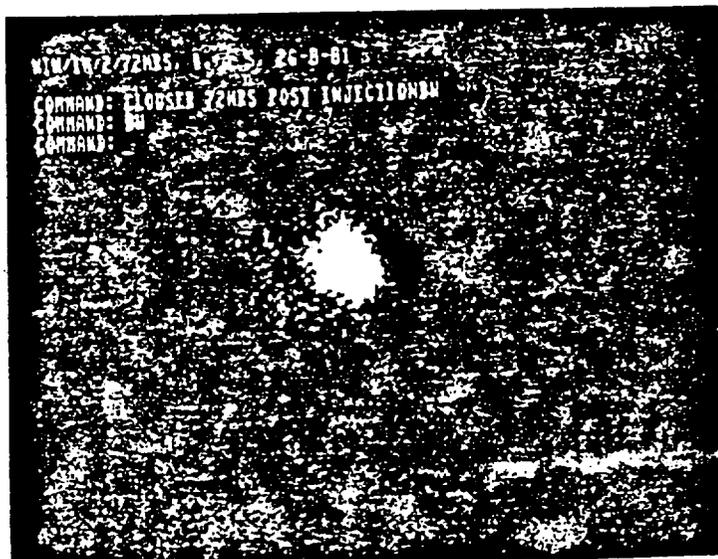


Figure 6. Lateral view of nude mouse bearing Clouser mammary carcinoma 72 hr after injection of ^{125}I (6.23) anti-breast carcinoma monoclonal antibody.



With the MCF-7 and A375 tumor mice the tumors could not be detected on any of the images. In the tissue distribution measurements with MCF-7 mice, optimal localization of ^{125}I (6.23) antibody occurred at 96 hr post injection (Tables 3 and 4). The distribution of ^{125}I (6.23) antibody to breast carcinoma was as expected in the negative control A375 mice; the tumor to tissue ratios were less than unity at all time points.

iii. Conclusions

These preliminary results suggest that radiolabeled monoclonal antibodies can be used to selectively delineate tumors in vivo. The ability of ^{125}I (F77-129) antiprostata carcinoma antibody to localize in human prostate tumors grown in nude mice is most encouraging. The differences observed in the distribution of the two monoclonal antibodies in the various cell lines may be a reflection of a multiplicity of factors which affect the fate of radiolabeled monoclonal antibodies in vivo. These include tumor size and vascularity and the specific activity of the radiolabeled antibody. In addition, tumor specificity could be masked if the tumor sheds appreciable levels of antigen into the bloodstream. In conclusion, monoclonal antibodies appear to have potential as radioactive carriers for the detection of tumor cell populations. If the aforementioned variables could be optimized to further increase tumor specificity it also may be possible to use monoclonal antibodies labeled with alpha emitters such as ^{211}At to selectively destroy malignant cells in vivo.

3. Goals for the Coming Year

- A. To develop methods for producing liposomes which (i) are of appropriate size to minimize leakage from the target site; (ii) are stable and impermeable in vivo; and (iii) have high efficiencies of encapsulation of ^{211}At .
- B. To synthesize ^{211}At -labeled melanocyte stimulating hormone (MSH) and to determine if it can be used to selectively destroy melanocytes in tissue culture and in mouse melanoma lines.

4. Staffing

<u>Name</u>	<u>Role</u>	<u>% Effort for Reporting Period</u>	<u>% Effort for Remainder</u>
Adelstein, S.J.	Principal Investigator	5	5
Zalutsky, M.R.	Co-principal Investigator	100	100
Bloomer, W.D.	Co-investigator	5	5

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5. Publications

Bloomer WD, McLaughlin WH, Neirinckx RD, Adelstein SJ, Gordon PR,
Ruth TJ, Wolf AP. Astatine-211-Tellurium Radiocolloid Cures
Experimental Malignant Ascites. Science 212:340-341, 1981.