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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1995

F. F. Knapp, Jr.

K. R. Ambrose
A. L. Beets
H. Luo
D. W. McPherson
S. Mirzadeh

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DEPARTMENT OF ENERGY

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Health Sciences Research Division

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Environmental Research

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Summary

In this report the conditions for "direct" labeling of the anti-granulocyte (MAb) BW 250/183 monoclonal antibody with rhenium-188 (Re-188) from a generator are described. Re-188-BW 250/183 is of interest for potential use for bone marrow ablation. The labeling time, temperature, pH, and the amount of tin and citric acid were optimized utilizing IgG. Radiolabeling yields of greater than 97% were achieved using 1 mL of a phthalate/tartrate buffer (pH 5.M=?), 250 μ g BW 250/183, 1.0 mg citric acid, 400 μ g tin (II) chloride, and 1 mL of the tungsten-188/rhenium-188 generator eluent (200-800 μ Ci of Re-188). Analysis of the Re-188-labeled IgG and BW 250/183 was performed by Instant Thin Layer Chromatography (ITLC), Sephadex purification and High Performance Liquid Chromatography (HPLC). When the labeling was performed at room temperature or 37 °C, *in vitro* stability studies performed in HSA solution, cysteine solution, 6 M urea solution and a 1% casein solution showed that the Re-188 label demonstrated a similar stability profile in all solutions. Initial studies indicate that Re-188-BW 250/183 retained ~90% of immunoreactivity when compared to the technetium-99m labeled antibody prepared from the same kit.

During this period, several radioisotopes prepared in the ORNL HFIR were also supplied on a cost-recovery basis or provided to collaborators for ongoing collaborative projects. These include tin-117m, processed tungsten-188 and the ORNL alumina-based tungsten-188/rhenium-188 generators.

Labeling of Anti-Granulocyte Antibody BW 250/183 with Rhenium-188 for Potential Bone Marrow Ablation

Rhenium-188 (Re-188) is an attractive isotope for the radiolabeling of monoclonal antibodies (MABs) for radioimmunotheraphy (RAIT) due to its intensive high energy β^- emission (E_{max}= 2.12 MeV) and a gamma photon (155 KeV) which can be imaged by routinely available gamma camera systems. Another attractive feature is the availability of carrier-free rhenium-188 from a tungsten-188/rhenium-188 (W-188/Re-188) generator system,[1] which permits preparation of MABs labeled with high specific activity Re-188. Rhenium chemistry is similar to technetium chemistry so that similar techniques utilizing either direct labeling to reduced disulfide groups or an indirect approach involving the use of a bifunctional chelate, have been developed.[2] Due to higher radiolabeling yields and ease of the labeling of the direct method, this approach was investigated for radiolabeling of the anti-granulocyte MAB, BW 250/183, for the "Non-Specific Cross-Reacting Antigen 95 (NCA 95)" with Re-188. BW 250/183 has been directly labeled with technetium-99m (Tc-99m), is commercially available in kit form and is routinely used for the clinical evaluation of bone marrow anatomy and function,[3] and therefore, Re-188 labeled BW 250/183 is of particular interest as a potential new radiopharmaceutical for use as a method for bone marrow ablation. These methods for Re-188 labeling of BW 250/183 are being developed by Dr. D. W. McPherson who is working through June 1995 as a Visiting Scientist with Professor S. N. Reske, M.D. in the Nuclear Medicine Department at the University of Ulm, Germany.

The labeling of BW 250/183 was investigated with "carrier-free" Re-188 from our alumina-based W-188/Re-188 generator. Due to the high cost of BW 250/183 the optimum radiolabeling parameters were evaluated utilizing human IgG as a model antibody. The use of IgG for the optimization of the labeling parameters initially involved the reduction of the disulfide linkages for the subsequent attachment of Re-188. We chose the pretinning method utilizing tin(II) chloride[4] since we proposed to reduce the rhenium to the +5 oxidation state with tin(II) chloride and therefore no separation of the antibody from the initial reducing agent would be required. Once the initial labeling of IgG was successful, the minimum concentration of tin (Figure 1) and citric

acid (Figure 2) required to achieve a high labeling efficiency were investigated. The effects of temperature (Figure 3), pH of the phthalate/tartrate buffer (Figure 4), and concentrations of the reactants solution (Figure 5) were then investigated.

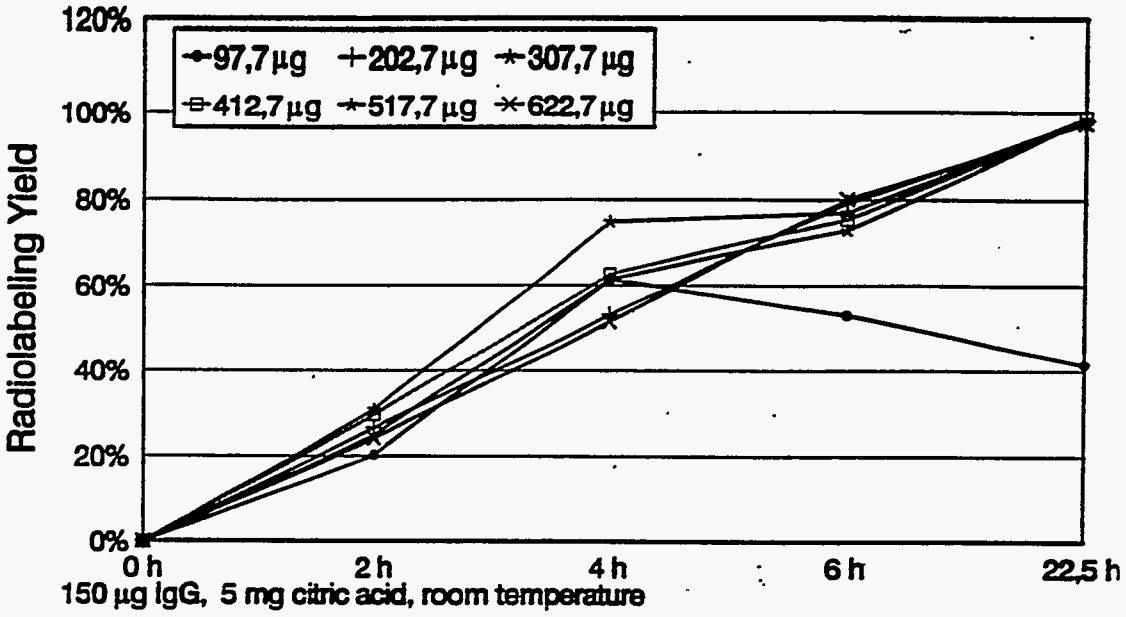

Figure 1 - Effects of stannous concentration on MAB labeling

It was observed from these studies that a labeling efficiency of >97% was obtained with at least 200 μg of tin(II) chloride. The amount of citric acid did not change the radiolabeling yield; therefore, the tin(II) chloride was dissolved in a minimum amount of citric acid (~5 mg/ml). For the reaction (Figure 2) where no citric acid was added, a minimum volume of concentrated HCl (10 μL) was added to dissolve the tin(II) chloride. The pH of the buffer was observed to have an important role in the rate of the labeling. When the pH of the phthalate/tartrate buffer was adjusted to 4.6 (the pH of the labeling solution was measured at 3.3), the reaction proceeded

rapidly with a >97% yield after 4 hours. However, since a low pH may have a detrimental effect on the immunoreactivity of the MAB, the adjustment of the buffer to pH 5.6 (pH 4.2 labeling solution) was chosen for the subsequent labeling of BW 250/183. In addition, when the concentration of reactants was decreased by increasing the total volume of the labeling solution to 4.5 mL, the labeling of the antibody was slower, requiring heating at 37 °C overnight to achieve a high yield. It was also observed that increasing the concentration of IgG did not affect the labeling time. An important observation from these studies demonstrates that care must be taken to exclude air to minimize oxidation of Re back to the +8 oxidation state which does not bind to the MAB (Figure 6).

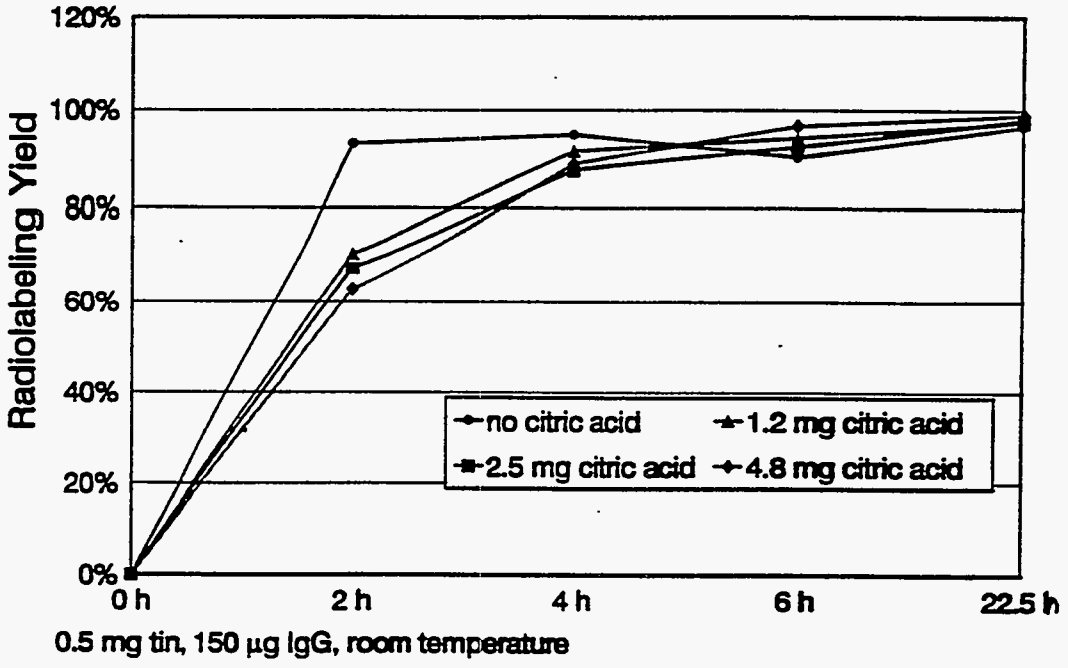

Figure 2 - Effects of citric acid concentration on MAB labeling

In a typical labeling procedure of the MAB with Re-188, the following conditions were utilized. Saline and phthalate/tartrate buffer were purged with nitrogen for at least two hours prior to use, and all labeling reactions were performed under nitrogen. Tin(II) chloride (2 mg) and citric acid (5 mg) were dissolved in 1 mL of a 40 mM K-H phthalate/10 mM K-Na tartrate buffer (pH 5.6). BW 250/183 (1.0 mg, vial 2 from kit, Behring) or IgG (1 mg) was dissolved in 1 mL of the phthalate/tartrate buffer. 250 μL of the antibody solution, 200 μL of the tin/citric acid solution, and 1.0 mL of the eluent from the W-188/Re-188 generator (200-800 μCi), which had been purged with nitrogen for 5 minutes directly prior to use, were added to a nitrogen- purged glass reaction vial. The vial was sealed under nitrogen and set allowed to stand at room temperature or heated in a constant water bath at 37 °C for the desired time. The labeling yield was determined by ITLC analysis using 2M urea as the mobile phase.

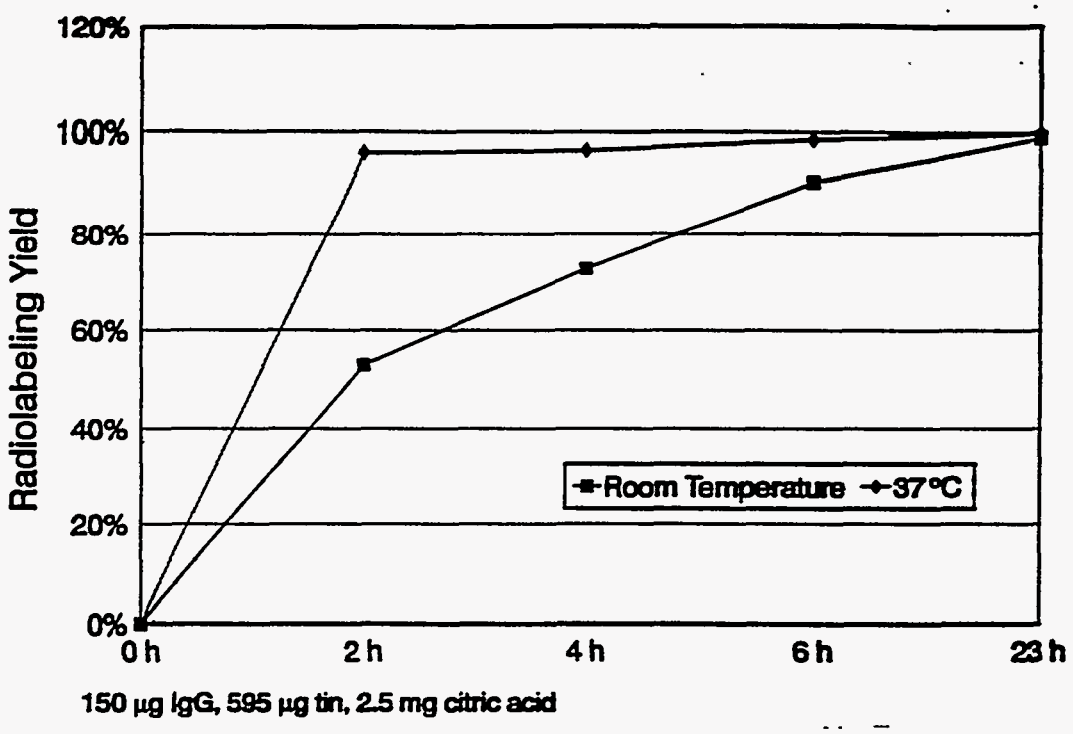

Figure 3 - Effect of temperature on MAB labeling

Control experiments in which Re-188 was reacted with IgG or with tin demonstrate the absence of non-specific binding of Re-188 to IgG and formation of Re-colloids. Analysis of the Re-188-BW 250/183 by "HSA soaked" ITLC sheets also confirms the absence of Re-colloid formation under the labeling conditions utilized. The radiolabeling of IgG was also performed in a 350 fold excess of iodoacetate and the labeling of IgG was 95% blocked after 4 hours. This datum indicates that the attachment of the Re-188 is occurring at the reduced sulfide linkages. An initial attempt to label the antibody directly in the vial from the kit by the addition of tin-buffer solution (400 mg/0.2 mL) and Re-188 from the generator afforded only a modest labeling yield of 60% after 24 hours at room temperature. This low yield may be due to the inability to exclude air from the vial or to the high pH of the labeling solution since the vial from the kit contains 2 mg sodium phosphate.

In vitro stability studies were performed by incubating the Re-188-BW 250/183 or IgG with an excess of various challenge solutions at 37 °C and monitoring the solution by ITLC at designated intervals (Table 1). It was observed that IgG and BW 250/183 demonstrated similar *in vitro* stability when labeling was performed at room temperature and 37 °C. In addition the *in vitro* stability was similar for IgG and BW 250/183. It was also observed that if the labeling solution containing Re-188-MAB was allowed to stand at room temperature for up to 48 hours, Re-188 remained attached to the MAB.

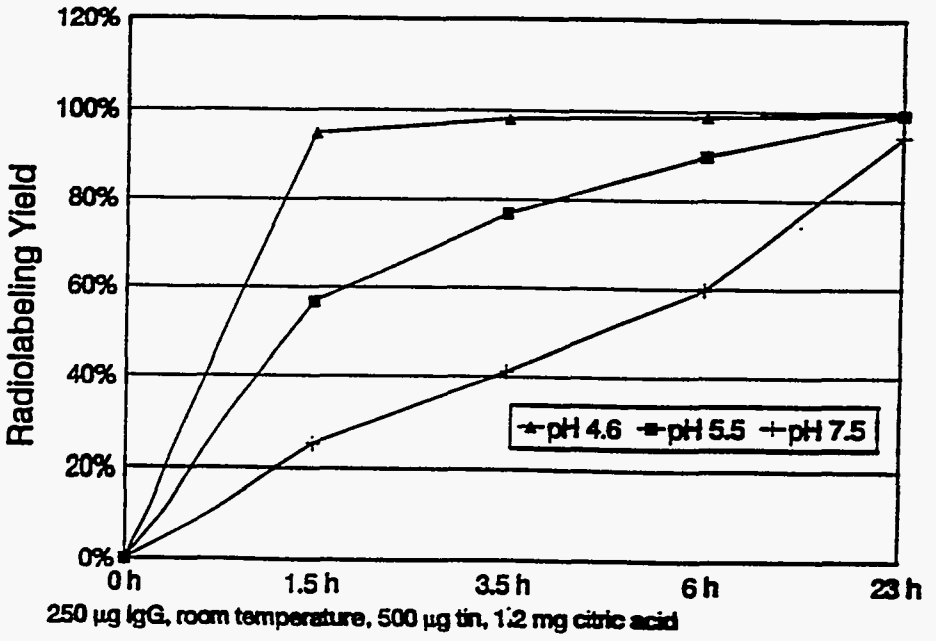

Figure 4 - Effects of pH on MAB labeling

HPLC analysis [Waters Protein Pak 300SW column, 0.1M K_2HPO_4 (pH 7.0)] was performed with Re-188 BW 250/183 and IgG, and no unbound Re-188 was observed, confirming the ITLC results which indicated a labeling efficiency of >97%. However, the Re-188 was readily removed from the antibody by the column, and the activity was released slowly from the column. Control experiments confirmed Re-188 in the +8 oxidation state was not binding to the column. In addition, there was observed to be ~ 7% of high molecular weight components formed during the labeling procedure. Sephadex G-50-150 column purification was also performed on Re-188-IgG. There was no unbound Re-188 detected, and purified Re-188-IgG was obtained. However

as observed in the HPLC analysis, the recovery of radioactivity from the purification procedure was ~60%, indicating that the Re-188 is again removed from the labeled IgG.

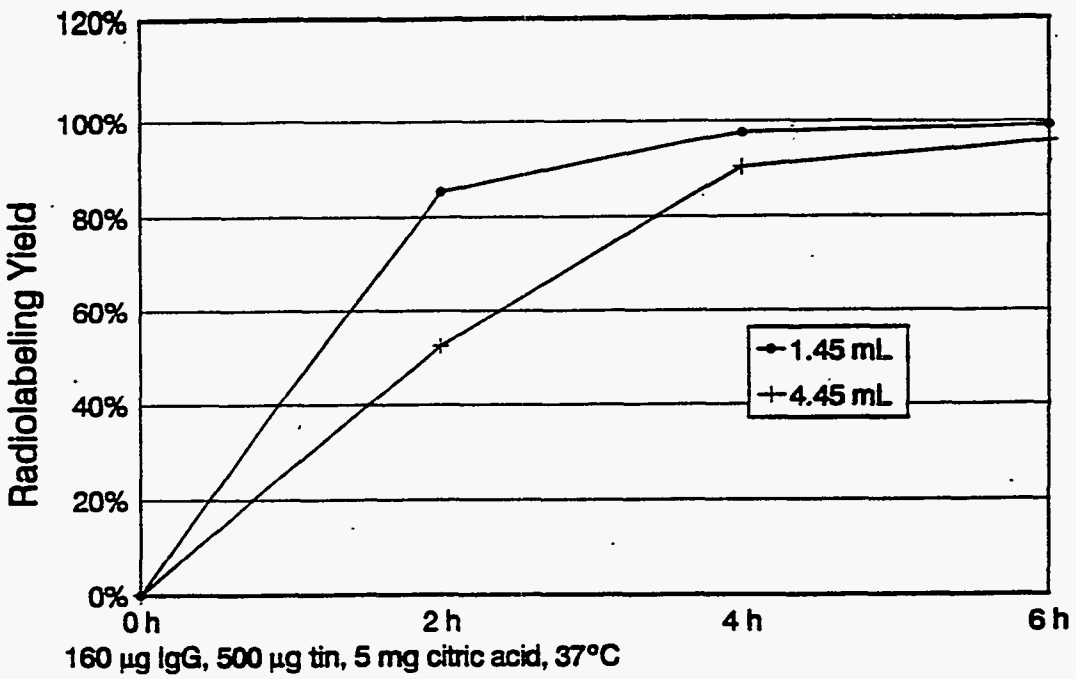

Figure 5 - Effects of reactant concentration on MAB labeling

The immunoreactivity of Re-188-BW 250/183 was determined by incubation of labeled MAB with antigen containing material (ACM) followed by centrifugation, washing, and counting pellet and supernatant to determine ACM-bound to free Re-188. These studies indicate that the immunoreactivity of BW 250/183 when labeled at room temperature is not markedly different from that when the labeling is performed 37 °C. In addition Re-188-BW 250/183 retained ~90% of immunoreactivity as compared to Tc-99m-BW 250/183 prepared by the same kit.

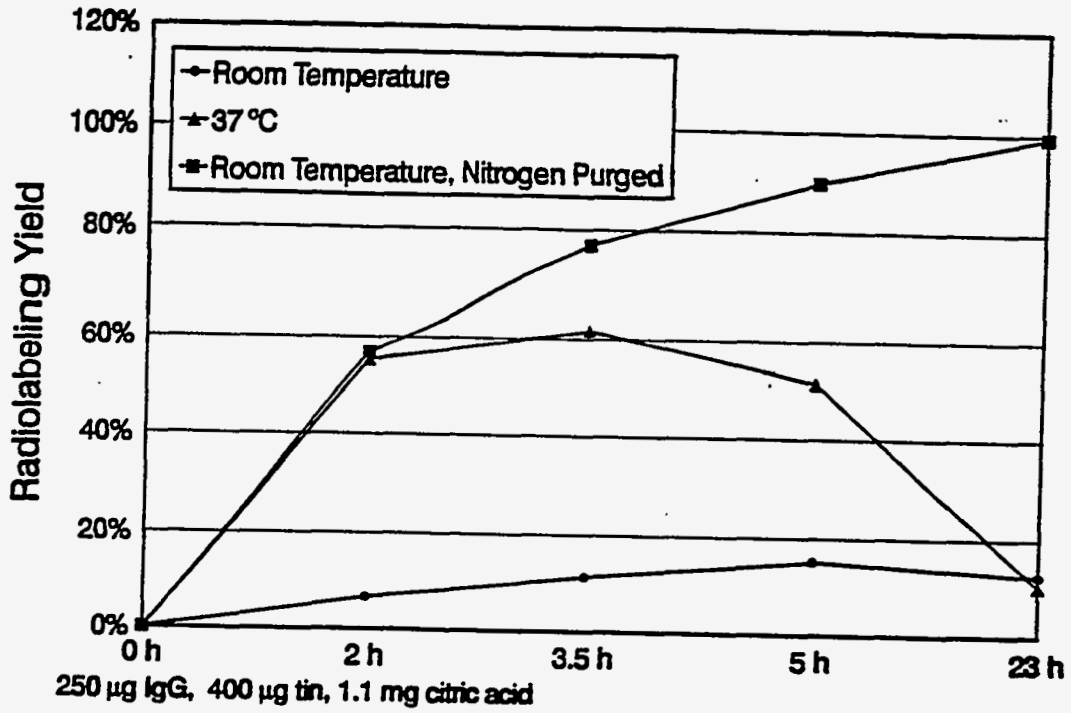

Figure 6 - Effects of temperature and presence of oxygen on MAB labeling

In summary, the anti-granulocyte MAB BW 250/183 has been labeled with generator-produced Re-188. The use of 400 μg of tin(II) chloride, 1 mg citric acid and a phthalate/tartrate buffer (pH 5.6) afforded a labeling efficiency of >97% after 6 hours at 37 °C or 24 hours at room temperature. *In vitro* stability tests indicate no difference in the stability of the antibody between the labeling performed at room temperature or 37 °C. Initial immunoreactivity tests demonstrated that the antibody retains ~ 90% of the Tc-99m-BW 250/183 immunoreactively from the same kit. Therefore this simple radiolabeling method allows for the preparation of Re-188-BW 250/183 with high specific activity for potential use in bone marrow ablation studies.

Table 1. *In Vitro* Stability of Re-188-IgG and BW 250/183

Re-188-IgG

Cysteine/IgG (3500:1)HSA/IgG (1700:1)1% Casien/IgG (1:1, v/v)

Time (h)	RT	37 °C	RT	37 °C	RT	37 °C
1	98.9%	98.4%	99.7%	99.7%	99.7%	99.5%
2.5	98.0%	92.2%	99.7%	99.4%	99.4%	99.3%
6.5	95.0%	81.6%	99.0%	99.2%	99.6%	99.3%
23	79.8%	60.2%	98.0%	94.6%	93.0%	82.1%

Incubation of Re-188-IgG in 6 M Urea

Time (hours)	RT	37 °C
1.5	98.0%	99.6%
4.5	94.2%	96.1%
8.0	82.3%	89.8%
23.5	44.9%	55.2%

Re-188-BW 250/183

Cysteine/MAB (6500:1) HSA/MAB (250:1) HSA/IgG (500:1)

Time (h)	RT	37 °C	RT	37 °C	37 °C
1.5	81.8%	91.2%	95.8%	98.9%	99.6%
4.5	70.9%	72.8%	89.6%	95.7%	99.1%
6.5	62.7%	66.4%	89.1%	93.4%	99.6%
22.5	29.6%	39.8%	79.5%	89.3%	87.0%

Solutions were incubated 37 °C and analyzed by ITLC. Results given as % Re-188 with MAB.

RT= room temperature.

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Other Nuclear Medicine Group Activities

Publications

E. Dadachova, S. Mirzadeh, R. M. Lambrecht, E. L. Hetherington and F. F. (Russ) Knapp, Jr., "Separation of Carrier-Free Holmium-166 from Dysprosium Oxide Targets by Partition Chromatography and Electrophoresis," J. Radioanalyt. Nucl. Chem. Lett., 199, 115-123 (1995).

F. F. (Russ) Knapp, Jr., A. P. Callahan, A. L. Beets, S. Mirzadeh and B.-T. Hsieh, " Processing of Reactor-Produced ^{188}W for Fabrication of Clinical Scale Alumina-Based $^{188}W/^{188}Re$ Generators," Appl. Radiat. Isot., 45, 1123-1128 (1994).

F. C. Visser, J. J. Bax and F. F. Knapp, Jr., "Single-Photon Imaging of Myocardial Metabolism: The Role of ^{123}I-Labelled Fatty Acids and ^{18}F Fluorodeoxyglucose," In, Nuclear Medicine in Clinical Diagnosis and Treatment, Volume 2 of two volumes, Churchill Livingstone, Edinburg-London, 1994, 1239-1248 (1994).

Presentations

On January 19-22, Dr. S. Mirzadeh participated in the Symposium on Nuclear Oncology: Advances in Diagnosis and Therapeutic Applications, held in Key Biscayne, Florida and presented a paper describing the unique production capabilities of the ORNL High Flux Isotope Reactor (HFIR) of Several Radioisotopes of Current Widespread Interest for Therapy:

S. Mirzadeh, A. L. Beets and F. F. Knapp, Jr., " Reactor-Produced Radioisotopes for Cancer Therapy and Bone Pain Palliation."

H. Luo, a Hollaender Distinguished Postdoctoral Fellow working in the Nuclear Medicine Group, participated in the 12th Winter Fluorine Conference sponsored by the American Chemical Society held in St. Petersburg, Florida, on January 22-27, and presented the following paper describing new fluorinated receptor agents:

H. Luo, D. W. McPherson and F. F. Knapp, Jr., "Synthesis of 1-Azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-phenylacetate ("FQNPE")- a New Ligand for Radiolabeling with Fluorine-18 for the Potential Imaging of Muscarinic Receptors by PET."

Medical Cooperative Shipments

During this period several radioisotopes prepared in the ORNL High Flux Isotope Reactor (HFIR) were supplied through collaborative arrangements and on a cost recovery basis. A processed tungsten-188 solution was provided to the Australian National Science and Technology Organization (ANSTO) on a cost-recovery basis. Tin-117m was supplied to the Medical Department at Brookhaven National Laboratory for preparation of tin-117m-DTPA for further clinical trials for bone pain palliation. Through a Cooperative Research and Development Agreement (CRADA), tungsten-188/rhenium-188 generators were provided to RhoMed, Inc. (B.A. Rhodes, Ph.D.) and the Clinic for Nuclear Medicine at the University of Bonn, Germany (Prof. H.-J. Biersack, M.D., and co-workers), for radiolabeling and testing of peptides for cancer therapy. Tungsten-188/rhenium-188 generators were also provided to the Departments of Nuclear Medicine at the University of Ulm, Germany (Prof. S. N. Reske, M.D.) and the University of Nantes, France (Prof. J. F. Chatal, M.D. and M. Hosono, M.D., Ph.D.).

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