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Nuclear Medicine Program Progress Report for Quarter Ending March 31, 1991

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ORNL/TM--11830

DE91 015942

Contract No. DE-AC05-84OR21400

Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1991

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DATE PUBLISHED: AUGUST 1991

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CONTENTS

SUMMARY

In this report the first fabrication and evaluation of an activated carbon-based osmium-194/iridium-194 generator system is described. Iridium-194 ($t_{1/2}$ = 19.2 h) decays by β^- emission (E_{max} = 2.24 MeV) and is a potential candidate for radioimmunotherapy. An important characteristic is availability of ^{194}Ir from decay of reactor-produced ^{194}Os ($t_{1/2}$ = 6 y). We report the fabrication of the first ^{194}Os/^{194}Ir generator system using activated carbon. In addition, a novel gas thermochromatographic method was developed for the one step conversion of metallic Os to OsO_4 and subsequent separation and purification of OsO_4. In this manner, the reactor irradiated enriched ^{192}Os target was converted to $^{194}OsO_4$ which was then converted to the K_2OsCl_6 for generator loading. The yield and the elution profile of carrier-free ^{194}Ir, and ^{194}Os breakthrough were determined for a prototype generator which was evaluated over a 10 month-period.

During this period several agents were also supplied to Medical Cooperative investigators, including iodine-123-labeled and iodine-125-labeled fatty acid analogues for studies at the Brookhaven National Laboratory. In addition, gold-198 and tungsten-188/-rhenium-188 generators were shipped to various investigators for therapeutic studies involving tumor-specfic antibodies.

PREPARATION AND EVALUATION OF THE FIRST CARBON-BASED OSMIUM-194/IRIDIUM-194 RADIONUCLIDE GENERATOR SYSTEM

There is widespread interest in the availability of radionuclides from generator systems for therapeutic applications, but there have been evaluated only a limited number of systems. Yttrium-90 ($t_{1/2}$=62 h, a pure β^- emitter with no imagable gamma-ray) which is currently used for antitumor therapy in patients.[1] is also generator based and is produced from decay of 27-y ^{90}Sr. A major concern of the use of ^{90}Y is the possibility of loss of free (ionic) ^{90}Y or the contamination of ^{90}Y radiopharmaceuticals for human use with ^{90}Sr. This is due to the *in vivo* toxicity (accumulation in bone) of free ^{90}Y and ^{90}Sr.[2,3] The ^{194}Os/^{194}Ir generator does not have this draw-back since neither osmium or iridium concentrate in bone, and both are excreted primarily through the urinary bladder.[4] In addition, the decay of ^{194}Ir follows with emission of a predominant 328 KeV γ-ray (13.0%)[5] which is within the detection range of most gamma cameras for *in vivo* biodistribution and kinetic studies. The absence of high energy and high intensity γ-rays in the decay of ^{194}Ir with the exception to the 328.5 KeV, enhances the attractiveness of ^{194}Ir for radioimmunotherapy.

Iridium-194 is conveniently available from the ^{194}Ir/^{194}Os generator system and is a potential candidate for therapy with monoclonal antibodies directed against tumor-associated antigens.[6] In addition to the emission of an abundant high-energy particle, an appropriate physical half-life and stable daughter, ^{194}Ir has suitable characteristics for protein labeling through bifunctional chelates. Iridium-194 also emits a moderate-intensity γ-ray which would provide an evaluation of organ distribution by gamma camera imaging. Furthermore, if long term performance were maintained, the ^{194}Ir/^{194}Os generator would be expected to have a shelf-life of many years. Iridium-194 is a β^--emitter and decays to the ground state of stable ^{194}Pt 86% of the time ($E_{\beta 1}{}^{max}$=2.236 MeV) and to the first excited state 9.2% ($E_{\beta 2}{}^{max}$=1.92 MeV) of the time.[5] The convenient 19.15 h half-life and 100% β^- emission with high end-point energies resulting in an average β^- energy of 804 KeV make ^{194}Ir an attractive candidate for therapeutic applications. The mean equilibrium dose constant of ^{194}Ir (1.72 g-rad/µCi-h) is comparable with that of ^{90}Y (1.99 g-rad/µCi-h[7]).

Iridium-194 is obtained in carrier-free state from β^- decay of ^{194}Os ($t_{1/2}$=6 y, E_β^{max}=100 KeV) in a generator system.[6,8] The ^{194}Os parent nuclei is produced in a fission nuclear reactor with double neutron capture on ^{192}Os (41.0% natural abundance). A cross-section value of 250 mb for ^{193}Os(n,γ)^{194}Os reaction was recently measured.[9]

$$\begin{tikzcd}
{}^{192}\mathrm{Os}[n,\gamma] \arrow[r, "\sigma=2.0\pm0.1\ \mathrm{b}"] & {}^{193}\mathrm{Os}[n,\gamma] \arrow[r, "\sigma=250\ \mathrm{b}"] \arrow[dr, "\beta^-,\ 30.0\ \mathrm{h}"'] & {}^{194}\mathrm{Os} \arrow[dr, "\beta^-,\ 6.0\ \mathrm{y}"'] & \\
 & & {}^{193}\mathrm{Ir} & {}^{194}\mathrm{Ir}\ (\beta^-,\ 19.15\ \mathrm{h})
\end{tikzcd}$$

Osmium belongs to the nobel metals family, and most of the common methods of dissolution of nobel metals such as treatments with *aqua regia*, chlorination in the presence of sodium chloride and alkaline oxidations (e.g. hypochlorites) are equally applicable to Os[10-14]. On fusion with caustic oxidizing mixture such as KOH or NaOH in the presence of air or $NaNO_3$, Os is converted to soluble perosmates, OsO_5^{2-}. Formation of the volatile tetroxide of Os (m.p. = 41, b.p. = 130°C) similar to ruthenium in aqueous media containing oxidizing agents has been extensively employed for separation of Os from other elements and for further purification of this element. Due to the substantial vapor pressure of OsO_4 ($1.1x1^{-8}$ mmHg[15]) at room temperature and the biological toxicity of OsO_4, not only the distillation but the fusion and dissolution of Os must be performed in a semi-closed system.

In addition to the methods outlined above, one can take advantage of the reactivity of molecular oxygen toward metallic Os at elevated temperatures[10] with subsequent isolation and purification of OsO_4 in a gas-thermochromatograph (GTC). The applicability of the GTC technique for separation and purification of elements has been demonstrated for At,[16,17] Re,[18] and others.[19]

The goal of this project was to fabricate and evaluate the performance of the first prototype activated carbon based ^{194}Os/^{194}Ir generator system and to develop an efficient GTC technique for separation and purification of neutron-irradiated Os metal. For development and testing purposes, we used 15.4-d ^{191}Os and 74.2-d ^{192}Ir which are produced simultaneously in the ^{190}Os target by the [n,γ] and [n,γ]^{191}Os(β^-) ^{191}Ir[n,γ] reactions, respectively.[13] The target material was either dry-distilled according to the method described later or dissolved according to the previously described procedure.[13]

According to our previously reported procedure,[13] perosmic ions ($HOsO_5^-$, orange-yellow) in alkaline solution containing ^{194}Os were sequentially reduced and converted to osmate ions (OsO_4^{-2}, lavender-pink) and hexachloroosmate(IV) ($OsCl_6^{-2}$, yellow) by treatment with absolute ethanol and concentrated HCl, respectively. Upon evaporation of the solution to dryness in a inert atmosphere, K_2OsCl_6 is formed and the reddish-brown colored solid is then dissolved in a minimum volume of 1 M NaCl and loaded on to pre-eqilibrated 200 mesh KI-impregnated activated carbon (0.25% w/w) and was pre-equilibrated with NaCl reagent (the column design and preparation details can be found elsewhere).[12] The ^{194m}Ir daughter is eluted with 20 ml of NaCl reagent at a flow rate of 0.25 ml/min. The thermo-chromatography apparatus for distallation of OsO_4 from the metallic osmium (Figure 1). The irradiated ^{192}Os (50 mg or less) target was transferred to the quartz boat which was then placed in the chromatography tube assembly. While maintaining an air flow rate of 10-20 mL/min the furnace was turned on. As OsO_4 formed it was carried by the air and trapped in 2 mL of 0.1 M KOH placed down stream (Figure 1). The first evidence of conversion of metallic Os to OsO_4 occurs at ~300°C within the first 30 minutes of start of distillation, as indicated by the slight yellowish color in the first trap. Distillation was continued for the next

2 hours where the furnace temperature increased to ~500°C. At this point, conversion was considered complete, and the furnace was turned off. The air flow was continued for an additional 3 hours to insure quantitative transport and recovery of the OsO_4. The quantitative conversion of 50 mg of Os to OsO_4 within 2.5 hours and under the above conditions was demonstrated by analysis of the mass of the boat before and after distillation in several cold runs employing natural Os metal. Consistently, a light-weight black residue (~1% of the Os mass) remained in the boat after distillation. By spectrographic analysis, the residue was found to be primarily graphite.

Our first prototype $^{194}Os/^{194}Ir$ generator system employs activated carbon as the absorbent, which we initially developed for separation of ultra-short-lived ^{191m}Ir in the $^{191}Os/^{191m}Ir$ generator system.[11-13] The prototype generator contained 250 μCi of ^{194}Os and its performance (i.e. yield and breakthrough) was monitored over a period of 10 months with a bimonthly elution schedule. During this period and under our experimental conditions the yield of ^{194}Ir remained constant at 73±4%. Typically, ~60% of the ^{194}Ir is recovered in the first 10-mL of eluent and the 2nd 10-mL of eluent contained the next ~10%. A typical elution profile of ^{194}Ir from a carbon-based generator is shown in Figure 2. Analysis of the generator eluents after one month of decay showed no traces of ^{194}Os yielding an estimated value of $\leq 3.7 \times 10^{-4}\%$ for the ^{194}Os breakthrough.

Consistent with the previous observation, the reaction between Os and O_2 occurs rapidly at ~300°C.[10] Below this critical temperature, however, reaction rate is quite slow with no measurable reaction at room temperature within 24 hours. The Teflon tubing which was used as the delivery tube, connecting the chromatograph column to the KOH trap, showed no affinity for adsorption of OsO_4 at room temperature. The mean transfer time for 100 mg of OsO_4 in a 50-cm long 0.6-mm I.D. Teflon tubing was found to be ~2 h when volume flow rate of the carrier gas (air) was 15 mL/min. The recovery of Os was found to be essentially quantitative. Greater than 99% of the activity was recovered in the first trap, with less than 1% of the activity in the 2nd trap and no activity on the activated carbon filter. The radioisotopic purity of distilled ^{194}Os in the described thermochromatograph was 100% with a separation factor of $\geq 10^6$ from ^{192}Ir which is the predominant radioisotope impurity.

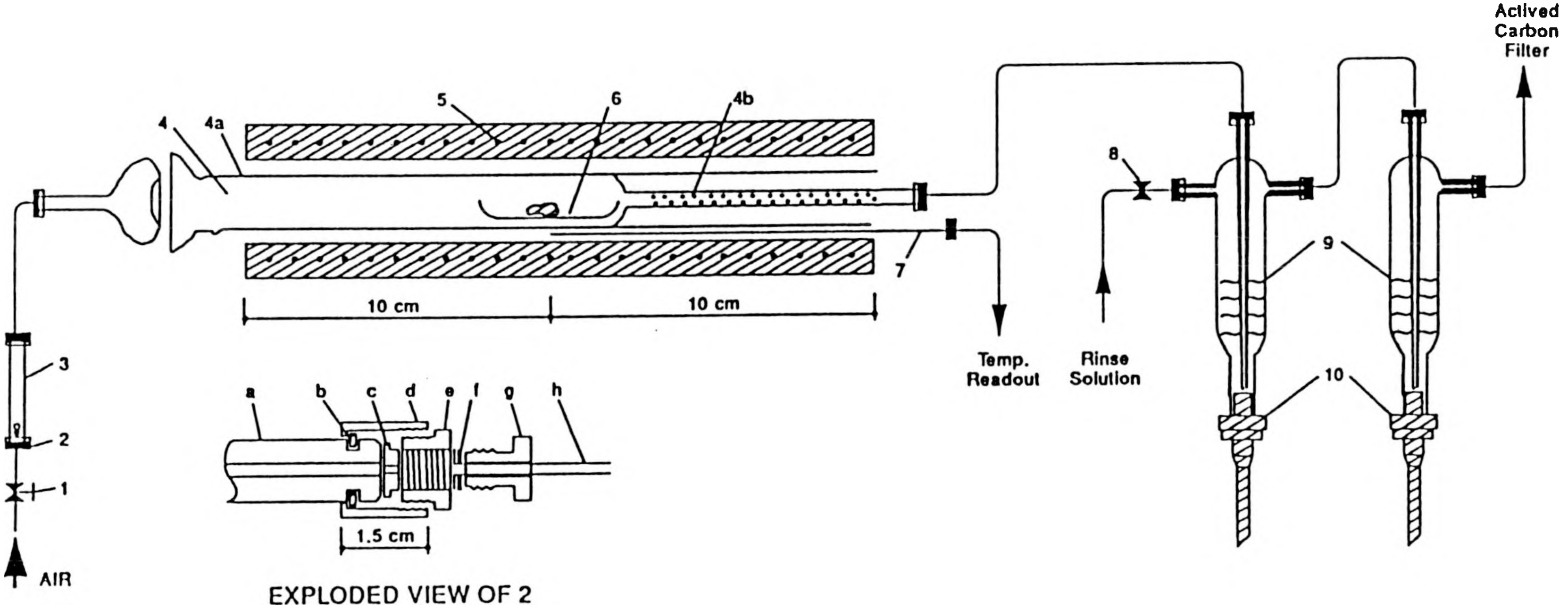

Figure 1. Schematic of the Thermochromatograph for Separation of Neutron Irradiated Enriched Osmium-192.

1. metering valve, **2.** CHEMINERT® glass/Teflon connector (see the exploded view), **3.** air volume flow meter, **4.** chromatographic tube assembly; **4a.** quartz tube (2.8 cm O.D., 2.4 cm I.D. and 20 cm long), **4b.** chromatographic tube (quartz, 6 mm O.D., 12 cm long, containing 60-mesh quartz powder held in the tube by quartz wool, **5.** split furnace, **6.** quartz boat containing Os target, **7.** thermocouple, **8.** sliding Teflon valve, **9.** 15-ml extraction funnel containing 2 ml of 0.1 M KOH, **10.** Teflon stopcock.

Exploded view of 2. **a.** Glass connector (2 mm I.D., 6 mm O.D.), **b.** split ring (PVC), **c.** bed support (Teflon), **d.** nut (PVC), bushing (PVC), **f.** washer (SS), **g.** tube end fitting (PVC), **h.** Teflon tubing (0.6 mm I.D.) with flanged end.

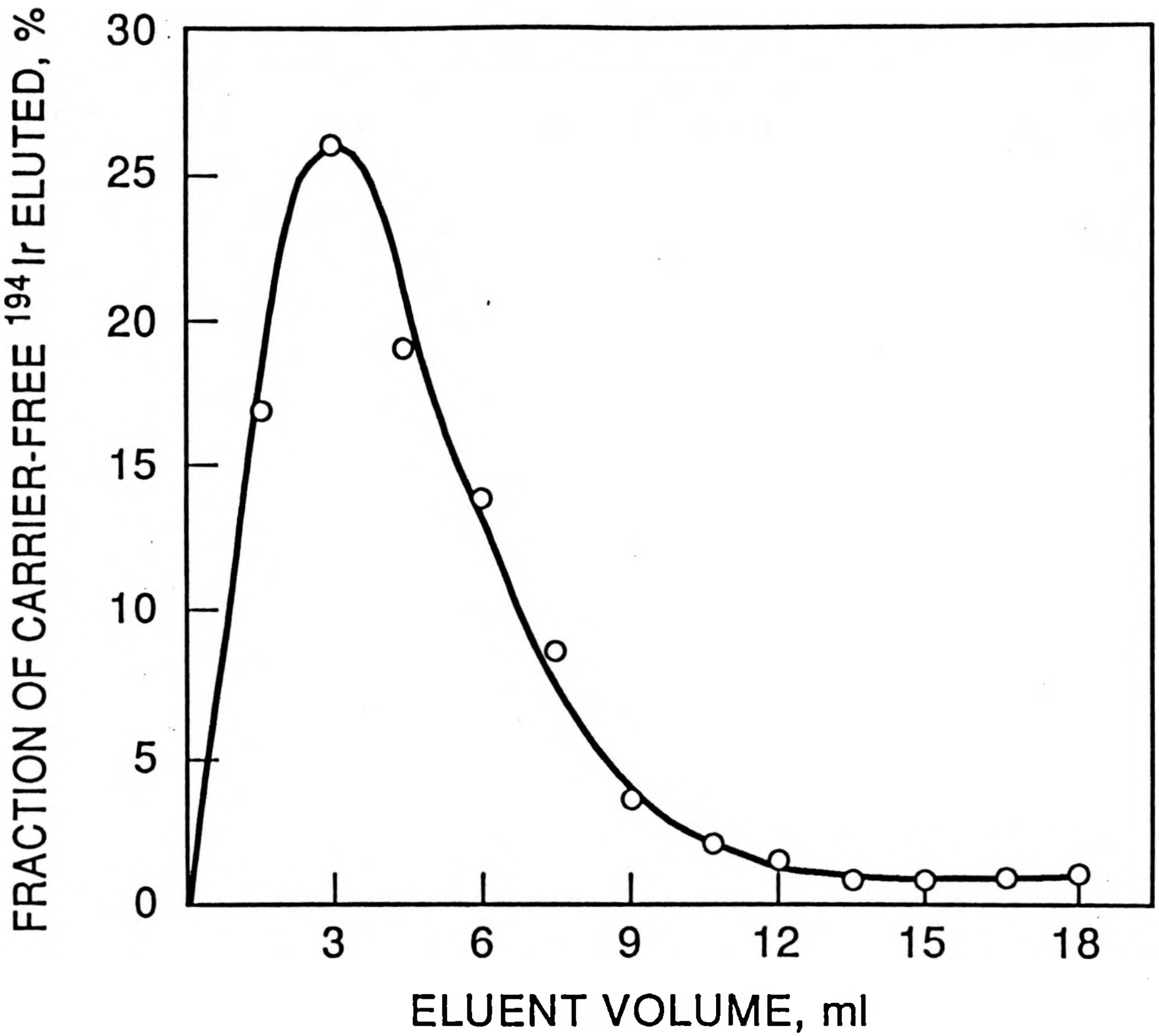

Figure 2. Elution Profile of Carrier-free ^{194}Ir from Activated Carbon-Based ^{194}Os/^{194}Ir Generator with NaCl reagent.

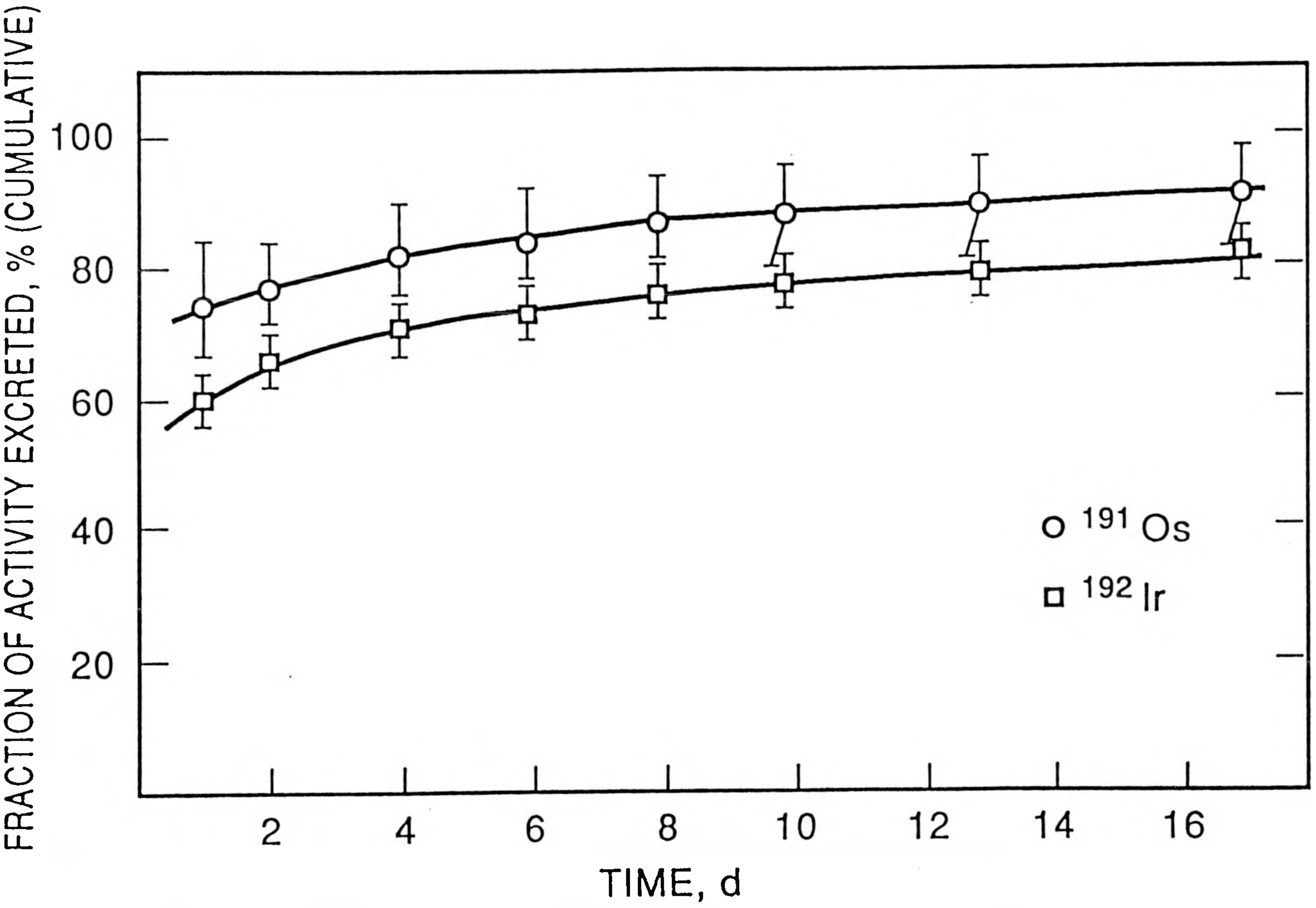

Figure 3. Metabolism of ^{191}Os and ^{192}Ir in the Rat – Cumulative Excretion (urine plus feces).

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AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Two shipments of iodine-123, and one shipment of iodine-125 were supplied for a collaborative program with Brookhaven National Laboratory (BNL) to study the effects of cocaine on myocardial uptake and metabolism of fatty acid energy substrates in a rat model (P. Som, D.V.M.). Gold-198 produced by the Pt-197(n,γ)Pt-198→Au-198 reaction, and tin-117m produced by the Sn-117(n,n'γ)Sn-117m reactions were prepared and also shipped to BNL for a collaborative program focussed on the labeling of the tumor-specific antibodies with carrier-free Au-198 and for bone cancer therapy with Sn-117m-DTPA (L. Mausner, Ph.D.). Two tungsten-188/rhenium-188 generators were shipped to Immunomedics, Inc., Newark, NJ (G. Griffiths, Ph.D.). One shipment each of tungsten-188 and osmium-191 were made to the VTT Reactor Laboratory in Espoo, Finland, for collaborative studies involving the radiolabeling of therapeutic base agents with carrier-free rhenium-188 and the clinical first-pass evaluation of patients with ultrashort-lived iridium-191m (J. Hultunen). Theragenics, Inc., Atlanta, GA, (J. Carden, Ph.D.) received one shipment of palladium-103.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Kropp, J., Knapp, F. F., Jr., Nissen, H. P., Assman, T., Ambrose, K. R., and Biersack, H.-J., "Metabolites of IPPA, BMIPP and DMIPP Fatty Acids in Rat Hearts. A Quantitative Study", in, Nuclear Medicine - The State of the Art of Nuclear Medicine in Europe," Proceedings of the European Nuclear Medicine Congress 1990, held in Amsterdam, the Netherlands, May-24, 1990, pp. 109-111 (1991).

Srivastava, P. C., and Hasan, A. "The Synthesis of 2-Nitro-1-[2-hydroxyethyoxy)-methyl]imidazole (Azomycin Acyclonucleoside)," Nucleosides and Nucleotides, 9(7), 899-905 (1990).

Miscellaneous

The first large-scale clinical prototypes of the ORNL tungsten-188/rhenium-188 radionuclide generator (e.g., 85-174 mCi tungsten-188) have been prepared and evaluated. Elution of the new prototype, which has been especially designed to allow use of lower specific activity tungsten-188 produced in low flux reactors, provides high yields of rhenium-188 in perrhenic acid which can be readily concentrated for small volume antibody radiolabeling studies. There is widespread interest in the use of rhenium-188 for therapeutic applications, primarily for the radiolabeling of antibodies for radioimmunotherapy (RAIT). The U.S. patent has been filed for this new prototype system. The first public disclosure for the new prototype was made in May 1991, at the Fourth European Symposium on Radiopharmacy and Radiopharmaceuticals in Zurich, Switzerland.

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