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### Nuclear Medicine Program Progress Report for Quarter Ending September 30, 1990

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT  
FOR QUARTER ENDING SEPTEMBER 30, 1990

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## SUMMARY

An evaluation of the Oak Ridge National Laboratory (ORNL) alumina-based tungsten-188/rhenium-188 (W-188/Re-188) generator system has continued. Our goal is to develop a prototype system which will provide sufficient levels of Re-188 for radiolabeling of tumor-specific antibodies for radioimmunotherapy. Since the W-188 parent emits gamma photons of very low intensity at 227 keV (0.22%) and 290 keV (0.40%), W-188 breakthrough cannot be detected in the presence of high levels of Re-188 (155 keV, 15% intensity) by gamma spectroscopy. In order to remove and quantitate levels of W-188 in "real time" without having to wait several days for decay of the Re-188 daughter, we have developed a simple and highly effective technique which utilizes acidic alumina "SepPaks®" in tandem with the alumina generator as a scavenger to trap the W-188 breakthrough. The efficiency of this technique was demonstrated by doping 2 mCi of Re-188 with 2  $\mu$ Ci of W-188. This doped sample provided a control which would correspond to a very high value of 0.1% breakthrough, which is  $10^3$  times greater than the usual breakthrough of the alumina system, which is less than  $10^{-4}$ %. Even these very high levels of W-188 could not be detected in the presence of the Re-188. When the eluant was subsequently passed through an acid-washed alumina SepPak® followed by thorough washing (20 mL) with 0.9% NaCl, the 227 and 290 keV gamma lines were clearly detected and readily allowed quantification of the W-188 breakthrough levels. Breakthrough levels 1000 times lower could still be detected by this method, making it a valuable quality control tool in assessing generator performance.

During this review period several samples were supplied for collaborative studies. Samples of rhenium-188 from the ORNL W-188/Re-188 generators were supplied to the National Institutes of Standards and Technology (NIST) as a calibration standard. Iodine-125-labeled IMP protein labeling agent was supplied to the University of Michigan for antibody radiolabeling studies (D. Buchsbaum, Ph.D.). The iodine-123-labeled BMIPP fatty acid analogue developed at ORNL was also supplied to collaborators at BNL for SPECT imaging studies of the effects of cocaine intoxication on myocardial fatty acid uptake in a canine model. Iodine-125-BMIPP was also supplied to the University of Bonn, Germany for continuing metabolic studies in an isolated heart model. In this report the resumption of radioisotope production in the HFIR following the restart of this important facility in July 1990 and the preparation and review and evaluation of issues for the DOE Tiger Team visit to ORNL on November 1 – December 7 are also discussed.

USE OF ALUMINA SEPPAKS® AS A CONVENIENT AND SIMPLE  
METHOD TO DETERMINE PARENT BREAKTHROUGH LEVELS FROM  
TUNGSTEN-188/RHENIUM-188 GENERATORS

The alumina-based tungsten-188/rhenium-188 (W-188/Re-188) generator system described earlier (ORNL/TM-10531 and -11550) provides a convenient source of Re-188 as sodium perrhenate for antibody radiolabeling by simple elution with physiological saline (0.9% NaCl). Because only low levels of low specific activity W-188 have been available for fabrication of small generators (< 5 mCi) since November 1986, the restart of the ORNL HFIR in July 1990 was an important milestone for the preparation of the high levels (> 100 mCi) of W-188 required for fabrication and testing of a clinical "prototype" generator system. As has been discussed earlier (ORNL/TM-10531), Re-188 is readily available from the ORNL generator system and has excellent properties for therapy ( $\beta^-$  average energy of 805 keV). In addition, the gamma photon emitted at 155 keV (15%) is suitable for imaging with Anger cameras, and the chemical properties of perrhenate are "similar" to pertechnetate. These attractive characteristics make the Re-188 radioisotope a key candidate for the next generation of radiolabeled antibodies for radioimmunotherapy (RAIT).

Although tungsten introduced into the Re-188 ( $T_{1/2} = 17$  h) eluant from the W-188 ( $T_{1/2} = 69$  d) parent breakthrough may not be expected to follow the same chemical fate as Re-188 during the subsequent chemical manipulations required for attachment of the rhenium to antibodies or other therapeutic agents, it is important to have an understanding and good record of the breakthrough history to evaluate generator performance. In the laboratory setting, the Re-188 bolus is usually allowed to decay over a several day period to permit evaluation of the W-188 levels by analysis of the 227 (0.4%) and 290 (0.5%) keV W-188 emissions. In the radiopharmacy it will be important to have a "real time" method for evaluation of both generator performance and levels of W-188 in the Re-188 daughter before use of the Re-188 for radiolabeling and use of therapeutic agents.

We have evaluated the use of commercially available alumina "SepPaks®" as a convenient "scavenger" column system attached in tandem with the generator (Figure 1). Such a system could easily be automated for micro-processor control, which would be necessary for any large-scale routine production. The SepPaks® can be conveniently attached

to the luer fittings of the extension tubes from the generator and to the recipient vessel. The eluant is passed directly through the SepPak®. Use of three-way valves on either side of the SepPak® easily allows the scavenger to be washed thoroughly with the 0.9% NaCl eluent and then detached and counted directly in gamma spectrometer or dose calibrator.

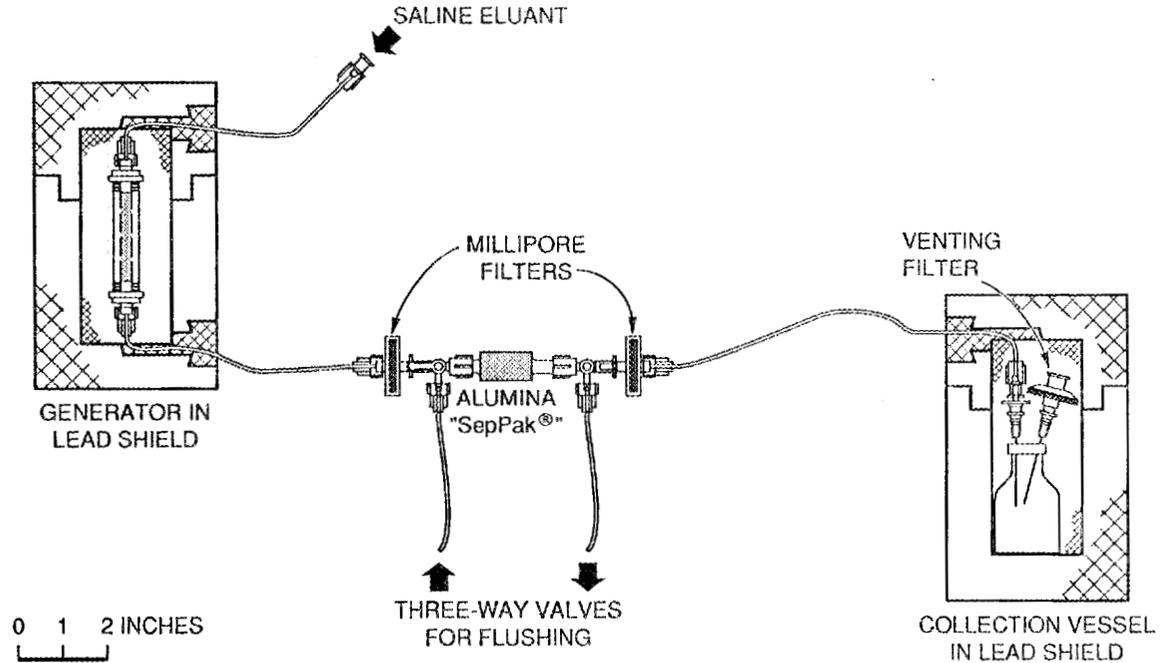


Figure 1. Example of attachment of alumina SepPak® in tandem with elution of alumina-based W-188/Re-188 generator system.

Since the long-lived W-188 (69 d) decays with the emission of only weak gamma photons at 227 (0.22%) and 290 (0.40%) keV, low levels of W-188 (0.1-1  $\mu\text{Ci}$ ) cannot be detected (Figure 2) by gamma spectroscopy in the presence of high levels (10-100 mCi) of the Re-188 daughter (155 keV, 15%). For "real time" measurement of W-188 levels, passage of the eluant through an acidic alumina SepPak® is an efficient method to trap W-188 for breakthrough determination. After the Re-188 is washed off, the SepPak® is then analyzed directly in a gamma spectrometer, since the weak photons are readily detected following removal of the Re-188. In a typical study, elution of a prototype generator loaded with 2 mCi of W-188 provided Re-188 to which was added 2  $\mu\text{Ci}$  of W-188. As shown in Figure 2, the 227 and 290 keV emissions could not be detected even in this W-188 "doped" sample. After subsequent elution through an alumina SepPak®, and washing with 75 mL of saline, the

W-188 emissions are readily seen. In this manner the low levels of W-188 can be removed from the Re-188 daughter and the levels quantitated to evaluate the performance of the generator.

Using a constant geometry and a Ge(Li) detector attached to a Nuclear Data 660 analyzer system, we have found the maximal error from attenuation to be  $< 10\%$ , which is within acceptable limits. A series of standards could also be prepared and counted in a dose calibrator to prepare a calibration curve from which the  $\mu\text{Ci}$  levels of W-188 could be readily interpolated. In this case the SepPak® would be counted at the same pre-determined time period after detachment that the standards were counted so as to have the same percentage ingrowth of the Re-188 daughter.

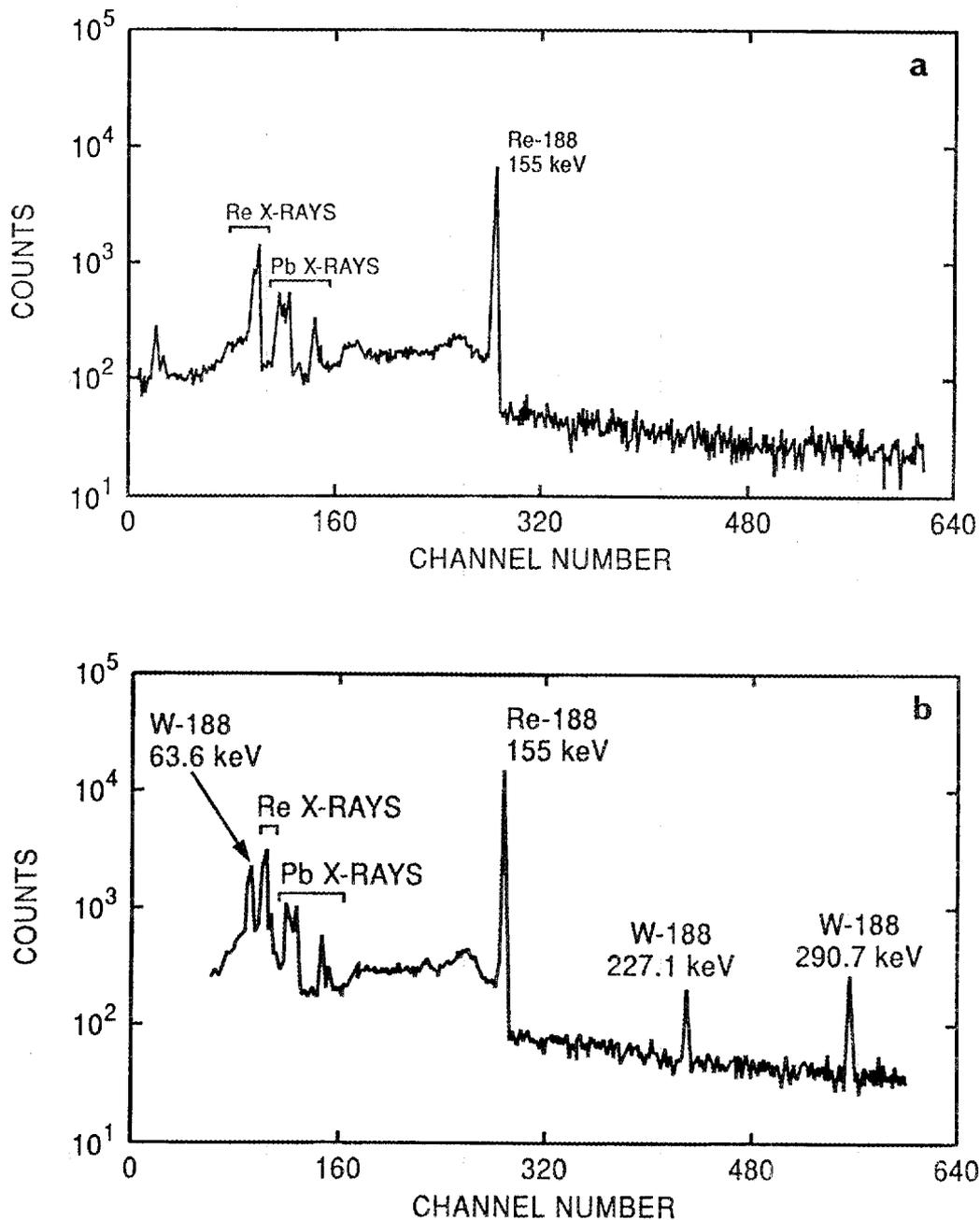


Figure 2. A gamma-ray spectrum of a) 0.9% NaCl eluant from the prototype alumina-based W-188/Re-188 generator which was "doped" with 0.1  $\mu\text{Ci}$  of W-188. Note that the W-188 gamma-rays at 227.1 and 290.7 keV are not visible, and b) the alumina "SepPak®" scavenger after passage of the eluant and thorough washing with 0.9% NaCl.

## RESTART OF THE HIGH FLUX ISOTOPE REACTOR (HFIR)

In July 1990, the HFIR began routine operation following a shutdown of over three years required for a facility and management structure upgrade. The restart of the HFIR was a major milestone which made this important resource available again for neutron diffraction studies for materials science and other applications, for production of the transuranium isotopes such as californium-252, and for the production of radioisotopes for our Nuclear Medicine Program. During the nearly three-and-one-half year shutdown, the Operations Division was dissolved (1987) and the Radioisotope Department and Isotopes Distribution Office programs were transferred at that time to the ORNL Chemical Technology Division. Since the HFIR was not operating, no services were offered during the shutdown period for the production and distribution of HFIR-produced radioisotopes. With the restart of the HFIR, the procedures and infrastructure required to coordinate fabrication of the HFIR target cans and testing required for certification of the targets had to be re-established, since these procedures were originally managed and coordinated by the Isotopes Distribution Office (IDO) in the Operations Division. The transfer of the DOE Isotopes Program from the Energy Research (ER) Division of DOE to the Nuclear Energy (NE) Division resulted in a change in budget guidance which necessitated reassignment of the trained staff in the IDO required to coordinate service irradiations to other ORNL programs. For these reasons, following restart of the HFIR, the infrastructure required to fabricate and certify targets was no longer available. This necessitated a concerted effort that required our Nuclear Medicine Program to formulate new procedures and calibration guidelines consistent with the current quality assurance requirements. The following new Nuclear Medicine Group Procedures were developed:

Procedure 49, "Fabrication, Certification, and Irradiation of HFIR Hydraulic Tube Targets,"

Procedure 51, "HFIR Irradiation Unit Loading, Welding, and Testing Procedure,"

Procedure 52, "HFIR Irradiation Unit -- Helium Leak Test."

These new procedures had to be developed and approved before irradiations in the HFIR for the Nuclear Medicine Program could be resumed. A variety of targets are now being irradiated in the HFIR for our Nuclear Medicine Program. These are summarized in Table 1.

Table 1. Radioisotopes Being Produced in the HFIR for the ORNL Nuclear Medicine Program

Radioisotope	Production Route	Application
Copper-67	Zn-67(n,p)-Cu-67	Development of New Processing Techniques
Gold-199	Pt-198(n, $\gamma$ )-Pt-199( $\beta$ )-Au-199	Radiolabeling of Antibodies through "Gold-Cluster" Chemistry
Osmium-194	Os-192(n, $\gamma$ )-Os-193(n, $\gamma$ )-Os-194	Os-194/Ir-194 Generator - Ir-194 for Antibody Labeling
Rhenium-186	Re-185(n, $\gamma$ )-Re-186	Antibody Labeling
Scandium-47	Ti-46(n, $\gamma$ )-Ti-47( $\beta$ )-Sc-47	Antibody Labeling
Tin-117m	Sn-117(n,n' $\gamma$ )-Sn-117m	As Sn-DTPA Complex for Palliative Treatment for Bone Pain Associated with Tumor Metastasis
Tungsten-188	W-186(n, $\gamma$ )-W-187(n, $\gamma$ )-W-188	W-188/Re-188 Generator - Re-188 for Antibody Labeling

The reduced power (*vide infra*) of the ORNL High Flux Isotope Reactor (HFIR) is expected to translate to an approximate reduction of the maximal thermal neutron flux in the central hydraulic tube positions (4 and 5) from about  $2.5 \times 10^{15}$  to  $2 \times 10^{15}$  neutrons/cm<sup>2</sup>/sec. Mapping of the neutron spectra of the reactor will involve a subsequent detailed evaluation of flux monitors in various positions.

## ENVIRONMENT, SAFETY, AND HEALTH ISSUES

Anticipation of the ORNL "Tiger Team" visit scheduled during the October-November period necessitated an intensive self-assessment of our facilities, updating of all procedures and training of staff as required by federal guidelines. One of the major efforts has involved a complete inventory of all chemicals and discarding of unnecessary chemicals. Although the detailed "Nuclear Medicine Group Procedure Manual" describing our procedures was instituted in 1979, a detailed self-assessment was required to both bring these procedures up to date and to formulate new procedures that were required. As part of these efforts, a computer-based inventory for all chemicals in the Nuclear Medicine Program was prepared. For each chemical, the inventory includes the quantity, location, Chemical Abstracts Service (CAS) number, and Health (H), Fire (F), and Reactivity (R) indices, as well as data on carcinogenicity and information on the availability of the Material Safety Data Sheet (MSDS). In addition, a procedure was written, and all staff were trained to access the official ORNL MSDS on-line data base system. These activities required major efforts by the Nuclear Medicine Program staff. We are now, however, in a much better position to document our long-term commitment and success in environment, safety, and health areas.

## AGENTS FOR MEDICAL COOPERATIVES

Two shipments of iodine-123-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) were made to Brookhaven National Laboratory, Upton, New York (P. Som. D.V.M.), for SPECT studies of the effects of cocaine intoxication on fatty acid metabolism in a canine model. Two samples of iodine-125-BMIPP were made to the University of Bonn, Bonn, West Germany (J. Kropp, M.D.), for the evaluation of physiological factors affecting metabolism in an isolated working rat heart model. The University of Michigan (D. Buchsbaum, Ph.D.) received one shipment of iodine-125-labeled iodophenylmaleimide (IPM) for continuing studies of antibody radiolabeling. One shipment of rhenium-188 was supplied to determine the decay characteristics and for standardization of dose calibrators by collaborators at The National Institute for Standards and Technology (NIST), Gaithersburg, Maryland (B. Coursey, Ph.D.).

## OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

**Presentations**

Members of the Nuclear Medicine Group co-authored a presentation at the World Federation of Nuclear Medicine and Biology Meeting held in Montreal, Canada, on August 27-31, 1990:

Kairemo, K. J. A., Kestila, M. S., Korhola, O. A., Hiltunen, J. V., Svahn, R. I., Knapp, F. F., Jr., and Brihaye, C. "Determination of Kidney Perfusion Using Ultra-Short Lived Iridium-191m," *Eur. J. Nucl. Med.*, 16:5-42 (1990).

Members of the Nuclear Medicine Group co-authored two presentations at the XIIth Congress of the European Society of Cardiology held in Stockholm, Sweden, on September 16-20, 1990:

Visser, F. C., Sloof, G. W., Comans, E., van Eenige, M., and Knapp, F. F., Jr. "Radioiodinated Heptadecanoic Acid, Phenylpentadecanoic Acid and Dimethylpentadecanoic Acid in the Normal Canine Heart. Comparison of Uptake, Oxidation, and Lipid Distribution."

Visser, F. C., Sloof, G. W., Comans, E., van Eenige, M., and Knapp, F. F., Jr. "Metabolism of Radioiodinated 17-Iodoheptadecanoic Acid in Normal and Ischemic Dog Heart."

**Publications**

Goodman, M. M., Waterhouse, R. N., Kabalka, G. W., and Knapp, F. F., Jr. "Synthesis and Biological Evaluation of 3-C(E)-2-(I-125)Iodoethylenyl)-D-Allose: A New Strategy for the Preparation of *In Vivo* Stable Radioiodinated Carbohydrates," *NucCompact-European/American Communications in Nuclear Medicine*, 21(2), 64-69 (1990).

McPherson, D. W., Lee, T. W., and Knapp, F. F., Jr. "A Simple Colorimetric Method for Determination of the Specific-Activity of Spallation-Produced Copper-67 Using Phenylglyoxal (PG) bis-(<sup>4</sup>N-methyl)thiosemicarbazone (TSC) Derivatives," *Appl. Radiat. Isotopes*, 41(7):689-692 (1990).

McPherson, D. W., Umbricht, G., and Knapp, F. F., Jr. "Radiolabeling of Proteins with Radioisotopes of Copper Using p-Carboxyalkylphenylglyoxal bis-(<sup>4</sup>N-Methylsemicarbazone) (TSC) Bifunctional Chelates," *J. Label. Cmpds. Radiopharm.*, 28(6): 877-900 (1990).

Reugg, C. L., Anderson-Berg, W. T., Brechbiel, M. W., Mirzadeh, S., Gansow, O. A., and Strand, M. "Improved *In Vivo* Stability and Tumor Targeting of Bismuth-Labeled Antibody," *Cancer Res.*, 50:4221-4226 (1990).

#### **Awards**

P.C. Srivastava, Ph.D., received the prestigious 1989 R&D-100 Award for "Iodophenyl-maleimide Radioimmunoconjugator" for the p-(iodophenyl) maleimide antibody radiolabeling technology developed in the Nuclear Medicine Group. The award honors 100 most significant technological achievements of the year and was the first received by the Nuclear Medicine Program. He has also received an "United Nations Distinguished Scientist Award" to visit India to encourage Indo-U.S. collaboration and technology transfer through participating in projects requiring special skills and holding workshops and seminars. The recipient is nominated for the award by a selection panel and receives international exposure under the auspices of the United Nations.

#### **Meetings**

P. C. Srivastava participated in the "9th International Round Table Conference on Nucleosides and Nucleotides and Their Biological Applications," held in Uppsala, Sweden, on July 28-August 5, 1990, and presented a talk entitled "Design, Synthesis and Tumor Specificity of Azomyzin Ribo- and Acyclonucleosides."

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