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OAK RIDGE NATIONAL LABORATORY

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Nuclear Medicine Program Progress Report for Quarter Ending September 30, 1996

F. F. Knapp, Jr.
K. R. Ambrose
A. L. Beets
R. Boll
H. Luo
D. W. McPherson
S. Mirzadeh

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SUMMARY

The reactor production yields of tungsten-188 produced by neutron capture by enriched tungsten-186 in the HFIR and other reactors are nearly an order of magnitude lower than expected by calculation using established cross section values. Since neutron capture of tungsten-188 may be the major factor which significantly reduces the observed yields of tungsten-188, we have evaluated the possible "burn-up" cross section of the tungsten-188 product. Tungsten-189 was produced by irradiating a radioactive target containing a known amount of ^{188}W. In order to reduce the radiation level to an acceptable level (<20% detector dead time), we chemically removed >90% of ^{188}Re, which is the decay product of ^{188}W, prior to irradiation. We were able to confirm the two predominant γ-rays in the decay of ^{189}W, 260.1 ± 1.4 and 421.5 ± 1.6 keV. By following the decay of these γ-rays in two sets of experiments, a half-life of 10.8±0.3 m was obtained for ^{189}W. Based on a knowledge of the ^{188}W content of target (52.6 mBq), neutron flux of $5x10^{13}$ $n.s^{-1}.cm^{-2}$, irradiation time of 10 min and with the assumption of 100% intensity for 260.1 and 421.5 keV γ-rays, a cross-section of 12.0 ± 2.5 b was calculated for burn-up cross-section of ^{188}W, which helps explain the greatly reduced production yields of ^{188}W.

During this period, several radioisotopes, generators and other medical radioisotopes were provided to collaborators for joint research, including tungsten-188/rhenium-188 generators which were provided to the Department of Interventional Cardiology (J. Wienberger, M.D.), Columbia University, New York, and the Department of Nuclear Medicine (J. Kropp, M.D.) at the University Hospital, Dresden, Germany. Platinium-193m was provided to the Clinic for Nuclear Medicine (S. N. Reske, M.D.), The University of Ulm, Germany, for a collaborative project focused on evaluating the kinetics of uptake into ovarian cancer cells refractive to *cis*-DDP therapy. Medical radioisotopes provided for full cost recovery through the ORNL Isotope Production and Distribution Program included a sample of tungsten-188 provided to Nordion, Inc., and high, specific activity rhenium-186 which was sold to Mallinckrodt Medical, Petten, Holland. A tungsten-188/rhenium-188 generator was provided to Altarex, Inc., Alberta, Canada.

Evaluation of the Neutron Burn-Up cross Section of Tungsten-188

There is currently widespread interest in the clinical use of rhenium-188 (^{188}Re) for various medical applications [1-2]. The convenient 16.9 hour half-life and 100% ß$^-$ emission with high-end point energy ($E_ß^{av}$=*764 keV*) make ^{188}Re an attractive candidate for therapeutic applications. One major advantage is the availability of carrier-free ^{188}Re from the decay of ^{188}W, ($t_{1/2}$=*69.4 d*) via our alumina-based generator system [2]. The ^{188}W parent radionuclide is produced in a nuclear reactor by double neutron capture on highly-enriched ^{186}W. As we have found using the ORNL High Flux Isotope Reactor (HFIR), and others have reported [3], large-scale production yields of ^{188}W are much lower than theoretical yields by almost one order of magnitude. The cross-sections for the production of the ^{187}W intermediate radionuclide are well-known. We have found reasonable agreement between the theoretical and experimental yields of ^{187}W (Y_{theo} / Y_{exp} = 1.5 ± 0.3) [3]. The thin-target production yield of ^{188}W as a function of irradiation time at a neutron flux of 2x10^{15} n.s^{-1}.cm^{-2} (HFIR) is shown in Figure 1 [4] and the cross-section for ^{187}W[n,γ]^{188}W reaction is currently under evaluation.

The very high neutron capture cross-section ("burn-up" cross-section) of ^{188}W is another factor which could be partly responsible for the discrepancy between the experimental and theoretical yields of ^{188}W. Unfortunately, the ^{189}W radionuclide (formed by neutron capture product of ^{188}W) is only poorly known. Since the absolute intensity of the γ-ray from ^{189}W is not known, in the current studies we report a value for the lower limit of the burn-up cross-section of ^{188}W. In addition, we also describe the results of preliminary data on the decay of ^{189}W produced via the ^{188}W(69 h, ß$^-$)[n,γ] reaction. Our attempts to measure the absolute intensity of observed γ-rays were not successful mainly due to the high background from the ß$^-$ radiation of ^{187}W, which is produced by neutron capture of stable ^{186}W in the target. In addition, high background from the decay of the ^{188}Re decay product of ^{188}W also interferes with these measurements.

Prior to irradiation, the assay of radioactivity of the target precipitate and the combined supernates indicated that >95% of ^{188}Re was removed from W in the process, and the $WO_3 \cdot nH_2O$ precipitate typically contained >80% of the initial ^{188}W. After irradiation, when W targets were purified by precipitation, the chemical recovery of W was ~50%. The elapsed time between irradiation and start of counting was about 22 minutes. In two experiments, the targets were counted with no additional chemical separation, and the time period between irradiation and start of counting was about 10 minutes.

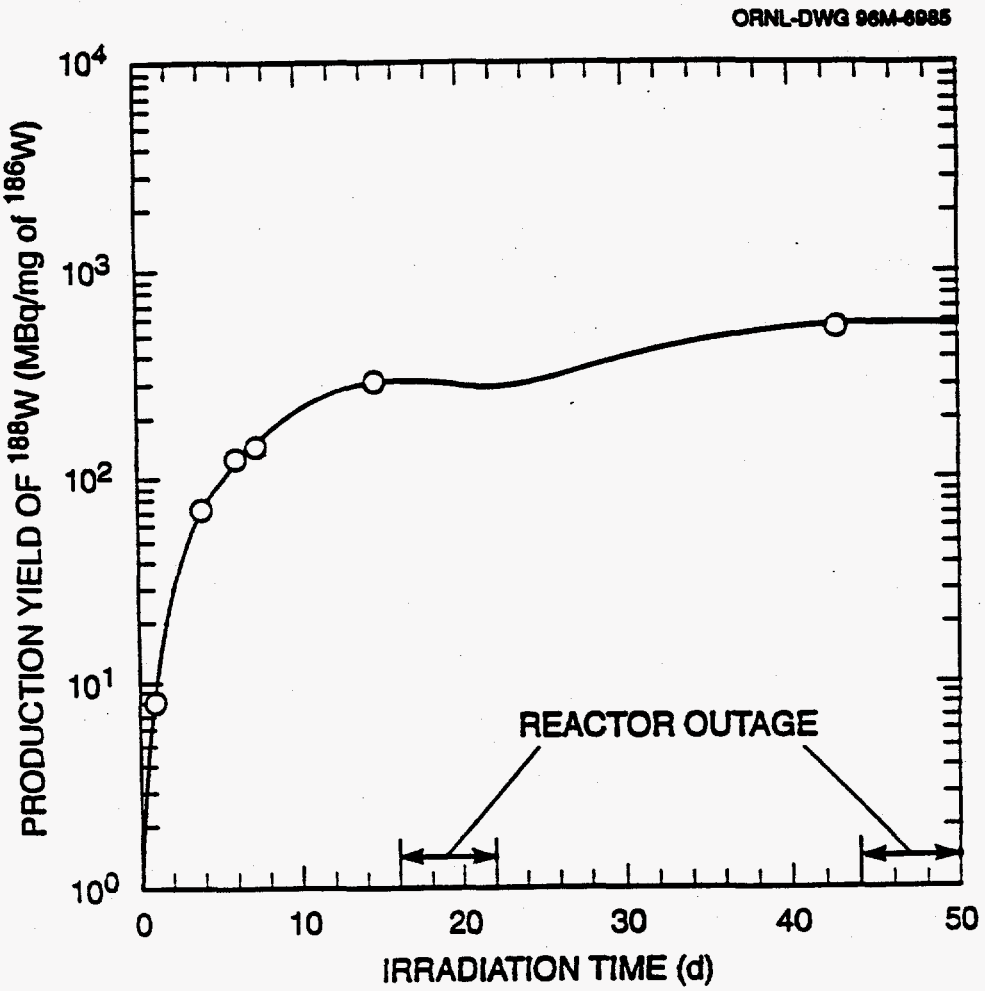

Figure 1. Thin target production yields of tungsten-188 as a function of irradiation time at a thermal neutron flux of 2 x 10^{15} neutrons per second per cm^2 in the ORNL HFIR (Data from Ref. [4]). Target mass = 10 µg of W (natural isotopic abundance). The solid curve represents an empirical calculation which accounts for reactor shutdown.

Table. 1. Gamma-rays Observed During Decay of ^{189}W			
From Reference [8]		This Work	
Eγ (keV)	Iγ (%)	Eγ (keV)	Iγ (%)
94 ± 5	3	-[a]	-
130 ± 2	12	130 ± 2[b]	-
178 ± 2	13	-[a]	-
222 ± 8	3	-[a]	-
258 ± 3	100	260.2 ± 1.4	97
360 ± 8	10	-[a]	-
417 ± 4	96	421.5 ± 1.6	100
550 ± 10	28	545 ± 3[b]	-
855 ± 15	20	-[a]	-
955 ± 20	17	975 ± 3	8

[a]Not observed.
[b]Uncertain about assignment to ^{189}W.

The γ-spectrum of purified ^{189}W is shown in Figure 2. Only three γ-rays at 260.1±1.4, 421.5±1.6 and 975±3 keV can be attributed to ^{189}W. The decay of these γ-rays are shown in Figure 3. The 260.1 and 421.5 keV γ-rays have equal intensity, whereas the relative intensity of the 975 keV γ-ray is about 8% (Table 1). Two γ-rays at 130 and 545 keV were also observed only in the first two 5-min counts (Figure 2). As shown in Table 2, the weighted average of ^{189}W half-life obtained from two sets of experiments is 10.8±0.3 m. The errors associated with the measured $t_{1/2}$ in each γ-ray were used as the weighing factors to obtain the weighted average. Two and half hours post irradiation, the γ-spectrum of the Re fraction showed a weak signal from 24.3-h ^{189}Re at 216.5 keV (5.5%). Due to the high background from the ß$^-$ radiation of ^{187}W and ^{188}Re, no short-lived component could be deduced from the ß$^-$ assay of the sample.

Table 2. Half-life of ^{189}W			
Exp. No.	Eγ (keV)	No. Of Points	$t_{½}$ (%)
A	260.2	7	9.3 ± 0.2
	421.5	3	7.2 ± 0.8
B	260.2	5	11.9 ± 0.2
	421.5	5	12.6 ± 0.3
	975	4	8.0 ± 0.9
	Weighted Average:		10.8 ± 0.2[a]

[a]Error associated with each value is taken as the weighing factor.

A: After irradiation, the γ-spectrum taken without chemical manipulations.

B: After irradiation, the γ-spectrum taken of purified target.

Tungsten-189 was initially identified by Flegenheimer, *et al.* [7] and produced through the $^{192}Os[n,\alpha]^{189}W$ reaction with fast neutrons (~ 14 MeV) and a half-life of 11 min was assigned to ^{189}W by following the β^- decay of a purified source of ^{189}W. Later, Kauranen and Ihochi [8], using the same reaction, produced a stronger source and assigned two predominant γ-rays at 258 and 417 keV with almost equal intensities (100 and 96%, respectively) to ^{189}W. Based on spectra taken using a NaI detector, a number of lower intensity γ-rays, ranging from 94 to 955 keV, were also assigned to ^{189}W (Table 1). These investigators reported a half-life of 11.5±0.3 min for ^{189}W deduced from the decay of the observed γ-rays.

In our approach, we produced ^{189}W by irradiating a radioactive target containing a known amount of ^{188}W. In order to reduce the radiation level to an acceptable level (<20% detector dead time), we chemically removed >90% of ^{188}Re (the decay product of ^{188}W) prior to irradiation. Nevertheless, due to the formation of substantial levels of ^{187}W which is produced by neutron capture of stable ^{186}W in the target and in growth of ^{188}Re, this results in a continuous increase in the background. We could only confirm the two predominant γ-rays in the decay of ^{189}W at 260.1 ± 1.4 and 421.5 ± 1.6 keV. By following the decay of these γ-rays in two sets of experiments, a half-life of 10.8 ± 0.3 m was obtained for ^{189}W.

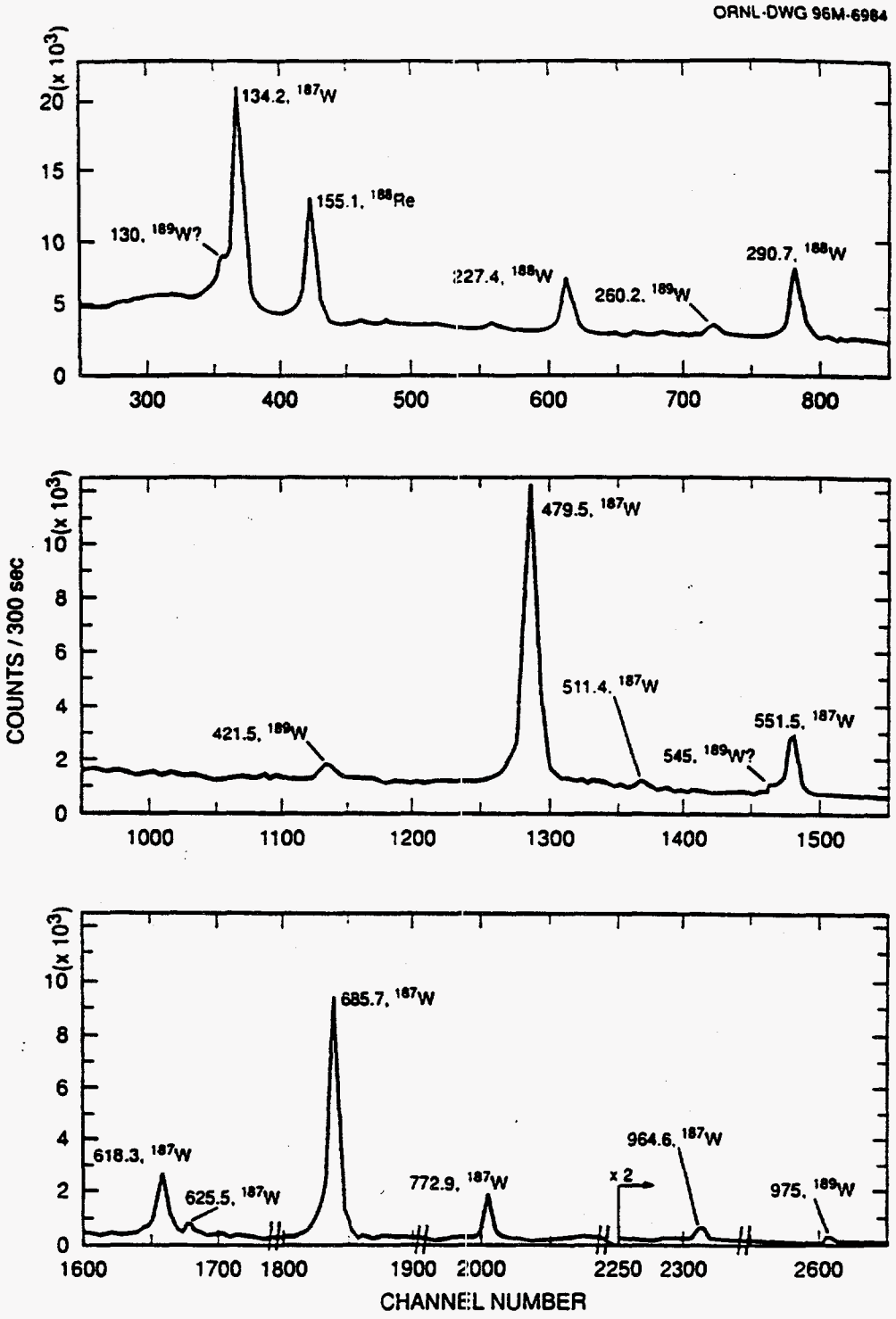

Figure 2. Gamma-ray spectrum of ^{189}W produced by neutron irradiation of ^{188}W target.

From the list of weaker γ-rays (Table 1), we observed a line at 975 ± 3 keV which decayed with a 8.0 ± 0.9 m half-life. This line is most likely the 955 ± 20 line reported earlier [8]. We are uncertain about the assignments of 130 and 545 keV γ-rays to ^{189}W, as these lines are weak and are positioned at the lower edge of two strong signals at 134.2 (15%) and 551.6 keV (23%), both from ^{187}W, respectively. Based on a knowledge of the ^{188}W content of target (52.6 mBq), neutron flux of 5 x 10^{13} $n.s^{-1}.cm^{-2}$, irradiation time of 10 min and with the assumption of 100% intensity for 260.1 and 420.5 keV γ-rays, a cross-section of 12.0 ± 2.5 b was calculated for the burn-up cross-section of ^{188}W.

These results are important since they help explain the discrepancy reported earlier [9,10] between the calculated and observed production yields for tungsten-188 by irradiation of tungsten-186. Even though we had developed processing methods for the complete dissolution of either enriched tungsten-186 metal or oxide targets, the production values have consistently been nearly an order of magnitude lower than those calculated. Our demonstration of the significant burn-up cross section for tungsten-188 will now provide an opportunity to further develop our computer code to iterate the expected production yields of tungsten-188 in the HFIR.

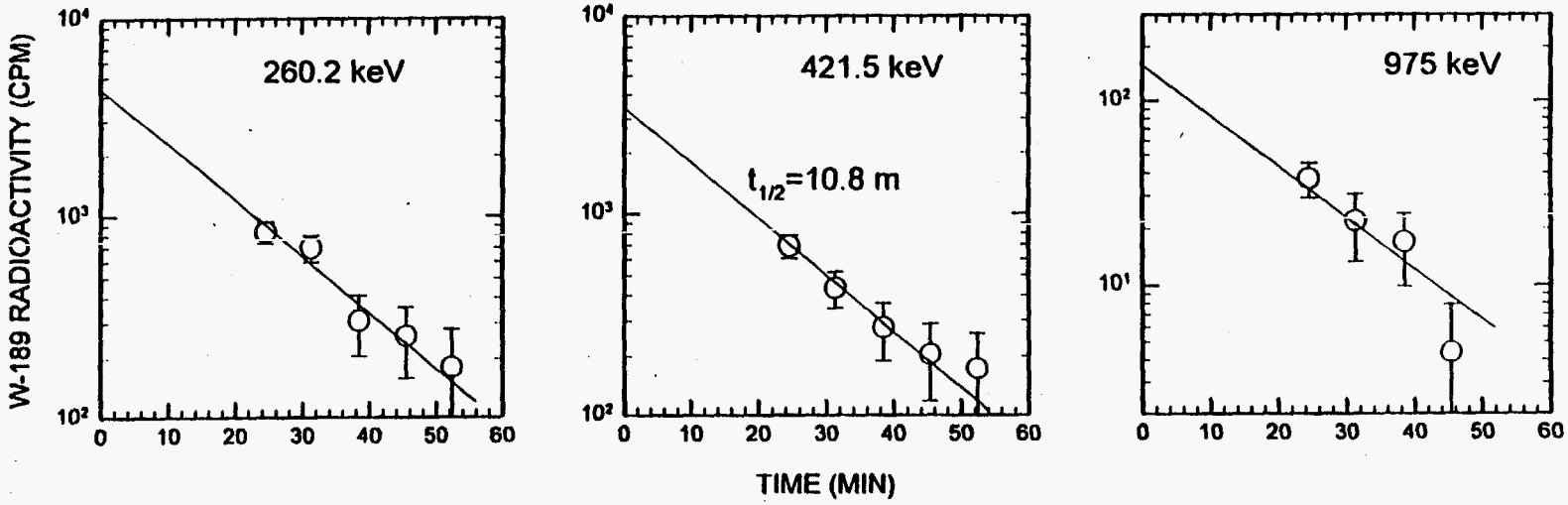

Figure 3.The decay of 260.2, 421.5, and 975 keV.γ-rays following the β- decay of 10.8-m ^{189}W.

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10. Knapp, Jr., F. F., Mirzadeh, S., and Beets, A. L. "Reactor Production and Processing of Therapeutic Radioisotopes for Applications in Nuclear Medicine," J. Radioanalytical and Nucl. Chem., Articles, **205** (1), pp. 93-100 (1996).

Other Nuclear Medicine Group Activities

Medical Cooperative Programs

During this period, several radioisotopes, generators, and other medical radioisotopes were provided to collaborators for joint research, including tungsten-188/rhenium-188 generators which were provided to the Department of Interventional Cardiology (J. Wienberger, M.D.), Columbia University, New York, and the Department of Nuclear Medicine (J. Kropp, M.D.), The University Hospital, Dresden, Germany. Platinium-193m was provided to the Clinic for Nuclear Medicine (S. N. Reske, M.D.), The University of Ulm, Germany, for a collaborative project focused on evaluating the kinetics of uptake into ovarian cancer cells refractive to *cis*-DDP therapy.

Distribution of Radioisotopes By Cost Recovery Through the ORNL Isotopes Distribution Office (IDO)

Medical radioisotopes which were provided for full cost recovery through the ORNL Isotope Production and Distribution Program included a sample of tungsten-188 provided to Nordion, Inc., and high specific activity rhenium-186 which was sold to Mallinckrodt Medical, Petten, Holland. A tungsten-188/rhenium-188 generator was provided to Altarex, Inc., Alberta, Canada.

Recent Publications

1. Lin, H., Luo, H. Mokler, F., Knapp, Jr., F. F., Beets, A. L., Ambrose, K. R., McPherson, D. W., and Kroff, J. "Effects of Configuration on the Myocardial Uptake of Radioiodinated 3(R)-BMIPP and 3(S)-BMIPP," *J. of Nucl. Med., submitted.*
2. Knapp, Jr., F. F., McPherson, D. W., Luo, H., and Zeeburg, B. "Radiolabeled Ligands for Imaging the Muscarinic-Cholinergic Receptors of the Heart and Brain," *AntiCancer Research, submitted.*

Meetings

American Chemical Society

A Symposium entitled, "*Radiochemistry and Radioimmunotherapy*" was recently organized by S. Mirzadeh, F. F. (Russ) Knapp, Jr., and S. J. Kennel in association with the *Biannual Meeting of the American Chemical Society*, Orlando, Florida, August 25-28, 1996. Twenty-four technical papers were organized in three scientific sessions. The "*Proceedings*" of this Symposium will be published in a special issue of *Radiochimica Acta*.

1. Alberto, R., Schibli, R., Egli, A., Schubiger, P. A., and Knapp, Jr., F. F. "Potential of the Organometallic "$[M(CO)_3]^{+n}$" (M = Re, Tc) Fragment for the Labeling of Proteins and Small Molecules."
2. Kennel, S. J. and Mirzadeh, S. "Vascular Targeting for Radioimmunotherapy with Bismuth-213."
3. Mirzadeh, S. and Kennel, S. J. "Optimizations of Radiolabeling of Immunoproteins with Bismuth-213."
4. Verdera, E. S., Gaudiano, J., Leon, A., Martinez, G., Robles, A., Savio, E., Leon, E., McPherson, D. W., and Knapp, Jr., F. F. "Rhenium-188 HEDP - Kit Formulation /Quality Control."
5. Zamora, P. O., Guhlke, S., Rhodes, B. A., Marek, M. J., Bender, H., Biersack, H.-J., and Knapp, Jr., F. F. "Radiotherapy Using Re-188-Labeled RC-160 peptide."

Participation in Bone Pain Palliation Symposium

Members of the ORNL Nuclear Medicine Program were invited to present two talks at the recent *"Symposium for Radionuclides Used in Bone Pain Palliation Therapy,"* held under the auspices of the Council on Ionizing Radiation Measurements and Standards (CIRMS), at the National Institute for Standards and Technology (NIST), Gaithersburg, Maryland, September 27, 1996. The *"Proceedings"* of this Symposium will also be published in a special publication.

1. Mirzadeh, S. "Generator-Produced Alpha-Emitting Radioisotopes."
2. Knapp, Jr., F. F. "Reactor-Produced Radionuclides from the ORNL-HFIR for Treatment of Bone Pain."

Participation in International Congress

D. W. McPherson and F. F. (Russ) Knapp, Jr., participated in the *European Association of Nuclear Medicine (EANM) Congress,* held in Copenhagen, Denmark, September 14-18, 1996. Following the Congress, they also participated in the *"Post Congress" Symposium* on "Radiolabeled Peptides," Oslo, Norway, September 19-20. Following the EANM Congress, F. F. Knapp also visited the Nuclear Medicine Department at the University of Bonn, Germany, to coordinate ongoing collaborative studies and to participate in a Breast Cancer Symposium. He also visited Mallinckrodt Medical, Petten, Holland, and presented a seminar on the development and clinical applications of the ORNL tungsten-188/rhenium-188 generator, and to discuss the commercial availability of medical radioisotopes from ORNL.

1. Bergstrom, K. A., Halldin, C., Hall, H., Hiltunen, J., Ito, H., Ginovart, N., Swahn, C.-G., McPherson, D. W., Knapp, F. F., Jr., Larsson, S., Schnell, P. O. and Farde, L.," *In Vitro* Characterization and *In Vivo* Metabolic Studies with I-125 and I-131 Labeled E-(-,-)-IQNP: A New Radioligand for Visualization of M_1 Muscarinic Acetylcholine Receptor in Brain."

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