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Nuclear Medicine Program Progress Report for Quarter Ending September 30, 1992

F. F. Knapp, Jr., Group Leader

K. R. Ambrose
A. L. Beets
A. P. Callahan
D. W. McPherson
S. Mirzadeh
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C. R. Lambert

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Health and Safety Research Division

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OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37831-6285
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CONTENTS

SUMMARY

In this report the radioiodination and *in vivo* evaluation of p-iodocaramiphen are described. p-Iodocaraminphen is a muscarinic antagonist which binds with high affinity to the M_1 receptor subtype *in vitro* and therefore is a promising candidate for radioiodination and *in vivo* evaluation. Biodistribution studies in female Fischer rats demonstrated that [^{125}I]-p-iodocaraminphen had significant cerebral localization, but the uptake did not demonstrate specific uptake in those cerebral regions rich in muscarinic receptors, and radioactivity washed out rapidly from the brain. In addition there was no significant blockage of activity when the rats were preinjected with quinuclidinyl benzilate (QNB) (5 mg/kg). These results suggest that p-iodocaramiphen is not a good candidate for the *in vivo* study of M_1 muscarinic receptor populations by SPECT.

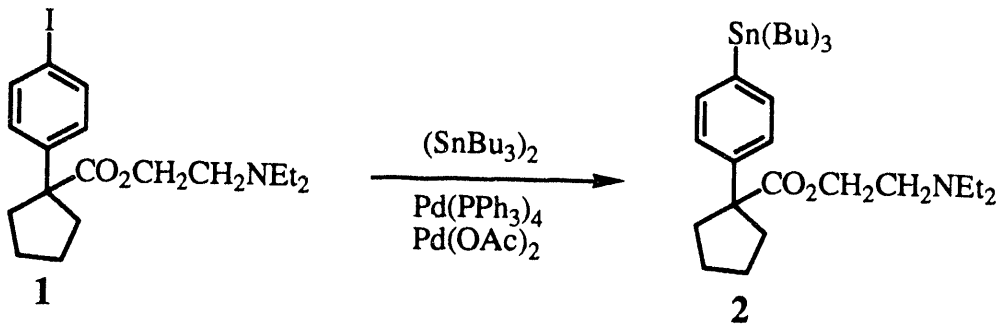
Because of the widespread interest and expected importance of the availability of large amounts of tungsten-188 required for the tungsten-188/rhenium-188 generator systems, we have investigated the large-scale production of tungsten-188 in the ORNL HFIR. We have also compared our production data with the theoretical production values and with experimental data available in the literature from other reactors. Tungsten-188 is produced in a fission nuclear reactor by double neutron capture of tungsten-186. The experimental yield of tungsten-188 is approximately 4 mCi/mg of tungsten-186 at the end of bombardment (EOB) in the HFIR operating at 85 MWt power for a one cycle irradiation ($\sim$21 days) at a thermal neutron flux of 2×10^{15} n.s^{-1}cm^{-2}. We also report the yield of rhenium-187 (the intermediate radionuclide) at EOB from several of our targets.

Also during this period, several ORNL agents were supplied to collaborators for further preclinical and clinical studies. Iodine-125 and iodine-131-labeled samples of the new "IQNP" muscarinic-specific receptor agent were supplied to Brookhaven National Laboratory collaborators for autoradiographic studies. In addition, iodine-125 and iodine-131-labeled supplies of the BMIPP cardiac imaging agent were supplied to study the effects of cocaine on myocardial metabolism. A large clinical-scale tungsten-188/rhenium-188 generator was supplied to the Center for Molecular Medicine and Immunology (CMMI) in Newark, New Jersey, for initiating of patient studies with rhenium-188-labeled antibodies.

EVALUATION OF RADIOIODINATED CARAMIPHEN AS A POTENTIAL MUSCARINIC RECEPTOR-SPECIFIC AGENT

The loss of muscarinic receptor activity in patients with Alzheimer's disease has been observed in post mortem studies and in *in vivo* by Single Photon Emission Computed Tomographic (SPECT) images using the iodine-123-labeled muscarinic antagonist, 3-quinuclidinyl 4-iodobenzilate (4-IQNB). Three distinct muscarinic subtypes, M_1, M_2, and M_3 have been identified using both functional and binding assays. While the M_1 subtype appears to be postsynaptic, the M_2 subtype predominately involve presynaptic muscarinic receptors. Para-iodocaramiphen (**1**), an analogue of caramiphen, has been shown to be a selective M_1 muscarinic agent (M_1, K_i = 2.11 nM; M_2, K_i = 123 nM) as compared to the M_1 prototype agent, pirenzephine (M_1 K_i = 5.21 nM). We report the preparation of iodine-125-labeled p-iodocaraminphen ([^{125}I]-**1**) via a tributylstannyl intermediate (**2**) and the biodistribution studies in rats to evaluate its potential use as a M_1 selective muscarinic ligand for SPECT studies.

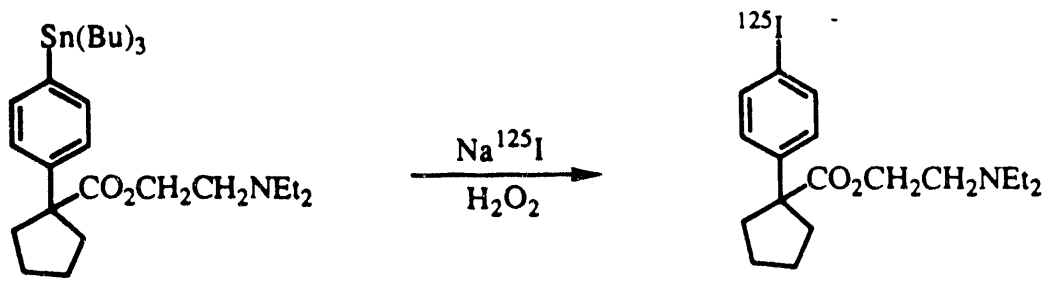
p-Iodocaramiphen (**1**) was initially prepared via the triazine decomposition method. Although this method has been successfully used in the preparation of a variety of radioiodinated compounds, we decided not to pursue this method due to the low radiochemical yields often reported. Iododemetallation reactions involving the tributylstannyl group are well known methods which are easily conducted under mild conditions and result in the high yield incorporation of radioactive iodine into molecules of biological interest. This method was therefore investigated for the preparation of [^{125}I]-p-iodocaramiphen ([^{125}I]-**1**). Initially, p-(tributylstannyl)-caraminphen (**2**) was prepared by reacting **1** with bistributyltin in the presence of palladium (II) acetate and tetrakis(triphenylphosphine)palladium (0) in triethylamine (Scheme I). Flash column chromatography afforded **2**, free of the substrate **1**, as determined by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) analyses. The reaction of **2** with sodium iodide-125 utilizing hydrogen peroxide as the oxidant afforded [^{125}I]-p-iodocaramiphen ([^{125}I]-**1**, Scheme II) in 50% radiochemical yield with a specific activity greater than 1500 mCi/μg as determined by HPLC analysis. The [^{125}I]-**1** had chromatographic properties analogous with **1** when analyzed by TLC and HPLC.



1 2

Scheme I

Biodistribution studies were performed using female Fisher VAF rats (~ 125 g) which were allowed food and water *ad libitum* prior to and during the course of the experiment. The [^{125}I]-1 was dissolved in 100 µl of ethanol followed by the addition of 50 µl of 0.1 N HCl and dilution to 10 ml with a 10% saline:ethanol solution. Following intravenous injection of [^{125}I]-1 into a lateral tail vein, the metophane-anesthetized rats. The animals were anesthetized and killed by cervical fracture at the designated time points. In addition to the removal of the organs, the brains were stored over dry ice prior to dissection. For the QNB blocking experiment, one group of animals was injected with QNB (5 mg/kg) 1 h prior to injection of [^{125}I]-1. Two hours after the injection of [^{125}I]-1, the animals were killed and the various tissues (striatum, cortex, cerebellum, rest of brain, heart and blood) removed and analyzed.



2 [^{125}I]-1

Scheme II

The *in vivo* biodistribution results of [^{125}I]-p-iodocaraminphen ([^{125}I]-**1**) are shown in Table 1. The brain and heart, organs of high muscarinic receptor concentrations, demonstrated high levels of activity 1 h postinjection of [^{125}I]-**1**. The brain to blood and heart to blood ratios after 1 h were observed to be approximately 4:1 and 2:1, respectively. It was also observed that the thyroid activity level was low, demonstrating the *in vivo* stability of the radioiodine label.

Table 1. Biodistribution of [^{125}I]-p-iodocaramiphen ([^{125}I]-**1**) in female Fisher rats (n = 5).

	Percent dose/gram	
	Time (min)	
Organ	15	60
Blood	0.26 ± 0.02	0.22 ± 0.03
Liver	3.44 ± 0.41	3.10 ± 0.30
Kidney	2.73 ± 0.33	1.51 ± 0.03
Heart	0.87 ± 0.08	0.41 ± 0.03
Lung	4.45 ± 0.32	1.97 ± 0.02
Thyroid[a]	0.14 ± 0.03	0.11 ± 0.01
Brain	1.37 ± 0.10	0.87 ± 0.04

[a]% Dose/organ

The cerebral distribution of [^{125}I]-**1** was then evaluated over a 4 h time period, and these results are shown in Table 2. The maximum uptake of activity occurred 1 h post injection but by 4 h the activity had washed out to approximately 85% of its maximum level. In addition, the levels of activity were the same in areas of the brain rich in muscarinic receptors (cortex and striatum) as compared to regions low in receptors (cerebellum) over the time course of the experiment. Blockage of muscarinic receptor sites by the preinjection of 3-quinuclidinyl benzilate (QNB), a potent muscarinic antagonist, resulted in a slight decrease in the uptake of activity as compared to the non-treated animals.

These results demonstrate that the significant activity observed in the brain after 1 h, washes out relatively rapidly, and that [^{125}I]-**1** demonstrated no selectivity toward muscarinic

receptors in both the heart and brain. These results indicate that [^{125}I]-p-iodocaramiphen ([^{125}I]-1) is not a good candidate for the *in vivo* detection and imaging of M_1 subtype muscarinic receptors. The reason for the difference *in vitro* and *in vivo* are not known but may result from the *in vivo* metabolism of 1 or its unfavorable lipid solubility.

Table 2. Cerebral distribution of [^{125}I]-p-iodocaramiphen ([^{125}I]-1) in female Fischer rats (n = 5).

	Percent dose/gram					
	Time (min)					
Organ	15	30	60	120	120[a]	240
Blood	0.88 ± 0.29	0.63 ± 0.20	0.43 ± 0.02	0.36 ± 0.03	0.20 ± 0.03	0.39 ± 0.02
Heart	0.55 ± 0.20	0.36 ± 0.12	0.44 ± 0.03	0.35 ± 0.02	0.25 ± 0.02	0.21 ± 0.01
Cortex	0.47 ± 0.18	0.35 ± 0.13	0.79 ± 0.06	0.43 ± 0.02	0.31 ± 0.02	0.10 ± 0.01
Striatum	0.45 ± 0.15	0.31 ± 0.11	0.70 ± 0.03	0.38 ± 0.03	0.29 ± 0.03	0.08 ± 0.04
Cerebellum	0.40 ± 0.17	0.32 ± 0.13	0.72 ± 0.08	0.40 ± 0.04	0.33 ± 0.03	0.11 ± 0.02
Rest of Brain	0.42 ± 0.17	0.33 ± 0.13	0.77 ± 0.07	0.48 ± 0.04	0.37 ± 0.03	0.14 ± 0.01

[a]Pretreatment with QNB (5 mg/kg).

REACTOR CAPABILITIES FOR PRODUCTION OF TUNGSTEN-188 FOR THE TUNGSTEN-188/RHENIUM-188 GENERATOR SYSTEM

Current widespread interest in the W-188/Re-188 biomedical generator has prompted us to compile and evaluate the data for large-scale production of W-188, which is produced in a fission nuclear reactor by double neutron capture of W-186. The corresponding radiative capture cross-sections for both reactions are summarized in Table 3. As seen, the reported value of the resonance integrals (I_o) for W-187 is very high (2760±550),[1-3] which means that the contribution of epithermal neutrons to the reaction rate of W-188 is significant, especially in the irradiation facilities where the epithermal neutron component of the neutron spectrum is substantial. In addition, the large decay constant of the W-187 intermediate nuclide further limits the number of W-187 atoms present at any time during irradiation for $t_{irr} \geq 6$ d (saturation point of W-187). Furthermore, target depletion and neutron attenuation or self-shielding are two additional factors contributing to the lower yields of W-188. In this work, we report the large-scale production yields of W-188 in the ORNL HFIR Hydraulic Tube Irradiation Facility (HT) and compare our data with experimental data available from other institutions and our theoretical calculations. Theoretical calculations are performed using LAURA[4] which is a generalized program for calculation of the activity of any member of a radioactivity chain undergoing spontaneous decay and/or induced neutron transformation in a nuclear reactor. In addition to the contribution from the resonance integrals (requiring a knowledge of ϕ_{th}/ϕ_{epi}), the effects of target depletion are also included in our theoretical calculation of the reaction rates. Provisions for self-shielding corrections are not, however, yet included in the current version of LAURA.

The experimental yields of W-188 from six reactors (HFIR, Savannah River, HFBR, ORR, MURR, and FFTF) and the corresponding neutron fluxes are given in Table 2. The large-scale production yields of W-188 at EOB from the HFIR (hydraulic tube) at the current power level of 85 MWt for a one-cycle irradiation (~ 21 days) at a thermal neutron flux of 2×10^{15} $n.s^{-1}cm^{-2}$ is 4 mCi/mg of W-186, which is lower than the theoretical value by almost a factor of ten. As shown in Table 3, the ratio of the theoretical to experimental yields ($R_{theo/exp}$) of W-188 for all the data from different reactors range from 1.5 to 14.8 (excluding

the results from FFTF), with an average value of 8.1±4.5. The extent of discrepancy between the theoretical and experimental values cannot be totally attributed to the neutron self-shielding in the target material since the effect was found to be insignificant in the HFBR experiment in which two targets of 5 and 8 mg were irradiated together and the induced activities of W-188 were found to vary within 2% (Table 2).

Recent calculations by Schenter *et al.*,[5] indicated that the self-shielding factor for a 100 mg target of $^{186}WO_3$ could be as large as 30%. In spite of these data, the close agreement between the theoretical and experimental yields of W-187, $R_{theo/exp}=1.5\pm0.3$, lead us to speculate that the actual radiative capture cross-sections of W-187 is somewhat lower than the reported values. The radiative capture cross-section of W-187 thus warrants further evaluation. As indicated in Table 4, the yield of W-187 at EOB is about 850 times higher than W-188 for a 21-d irradiation in the HFIR.

Table 3. Cross-sections for production of W-187 and W-188

Measurements	Cross-section (barn)		I_o/σ_{th}
	Thermal (σ_{th})	Resonance Integrals (I_o)	
Tungsten-187			
Recommended[7]	37.9 ± 0.6	485 ± 15	12.8 ± 0.5
Van Der Linden *et al.*[b]	36 ± 1	410 ± 47	11.4 ± 1.3
Tungsten-188			
Gillette (1966)[6]	64 ± 10	2760 ± 550	43.1

[b] Reference 3, Thetis reactor, Belgium [$(\phi_{th}/\phi_{epi})=23.8\pm0.3$, 18.3 ± 0.2, 144 ± 1; n=20, Au]

Table 4. Large scale production of tungsten-188.

Reactor(MW) Irradiation position	Φ_{th} ($n.s^{-1}cm^{-2}$)	(Φ_{th}/Φ_{epi})	Target mass (mg) as WO_3 (Enrich., %)	T_{irr} (d)	Yield (mCi/mg at EOB) W-187 Exp.	W-187 $R_{theo/exp}$	W-188 Exp.	W-188 $R_{theo/exp}$	References
HFIR-ORNL									
RB (100)	$4x10^{14}$	10	10.0 (97.3)	28	-	-	5.5	1.511	
HT (100) #5	$2.5x10^{15}$	25	10.3 (97.3)	21	-	-	4.49	14.812	
HT (85) #5	$2.0x10^{15}$	25	49.2 (96.07)	19.5	-	-	3.94	11.1	This work
#3	$1.7x10^{15}$	25	50.2 (96.07)	21.1	$3.25x10^{3}$	1.74	3.88	9.1	"
#5	$2.0x10^{15}$	25	50.2 (96.07)	38 [a]	-	-	6.22	9.9	"
#4	$1.9x10^{15}$	25	49.3 (96.07)	79 [b]	$1.75x10^{3}$	1.23	5.28	11.0	"
Savannah River									
	$1.40x10^{15}$	10	24.9 (97.2)	25	-	-	8.13	8.511	
	$1.25x10^{15}$	10	100 (97.3)	60	-	-	14.4	5.311	
HFBR-BNL (60), V-14									
(core-edge)	$8.25x10^{14}$	20	4.97 (97.06)	24.0 h	-	-	$2.62x10^{-2}$ [b]	8.013	
			8.03 (97.06)	24.0 h	-	-	$2.57x10^{-2}$		
ORR-ORNL									
(2-W-B)	$2.8x10^{14}$	15	10.2 (97.2)	19.3	-	-	0.703	2.611	
	$3.2x10^{14}$	15	10.1 (97.2)	67.6	-	-	4.15	1.511	
MURR (10)									
Flux Trap	$4.5x10^{14}$	50	92.1 (96.07)	63.4	-	-	~ 0.3	13.912	
FFTF-Hanford(291)									
	$(2-3)x10^{13}$	0.15-	14.0 (96.07)	10	-	-	$3.89x10^{-2}$	43014	
		0.21	12.7 (96.07)	10	-	-	$3.81x10^{-2}$		

[a] Several short and a 3-d shut down period. [b] Two 3-d shut down period. [c] HFIR = High Flux Isotope Reactor, Oak Ridge National Laboratory (ORNL); ORR = Oak Ridge Reactor, ORNL; HFBR = High Flux Beam Reactor, Brookhaven National Laboratory; MURR = Missouri University Research Reactor; FFTF = Fast Flux Test Facility, Westinghouse Hanford Co.

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1. Gillette *et al.* Report ORNL-4013,5 (1966).
2. Neutron Cross Sections, (Mughabghab, S. F., Divadeenam, M. and Holden, N. E.), Vol. 1, part A&B, Academic Press (1981).
3. R. Van Der Linden, F. De Corte, and J. Hoste, "A Compilation of Infinite Dilution Resonance Integrals, II," *J. Radioanalyt. Chem.*, 20, 695-706 (1974).
4. L. D. McGinn and S. Mirzadeh, "A Generalized Computer Code "LAURA" for Calculation of the Production of Medical Radioisotope" (1991) Unpublished.
5. Report WHC-SP-0632 (1990) (Schenter, R. E. *et al.* Hanford & C.) and Report OSU-NE-MED-9004 (Binney, S. E. *et al.* Oregon State University), *Analysis of $^{188}W/^{188}Re$ from MIP Test* (1990).

AGENTS FOR MEDICAL COOPERATIVES

In a continuation of collaborative studies to evaluate the regional uptake in cerebral structures by high resolution autoradiography (ARG), samples of I-125- and I-131-labeled "IQNP" were supplied to the Brookhaven National Laboratory (P. Som, D.V.M.). In addition, samples of the I-131- and I-125-labeled BMIPP cardiac imaging agent were supplied for continuing ARG studies to determine the effects of cocaine on myocardial metabolism. One shipment of the ORNL tungsten-188/rhenium-188 generator was supplied for clinical studies in a collaborative program with the Center for Molecular Medicine and Immunology (D. M. Goldenberg, M.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Callahan, A. P., Rice, D. E., McPherson, D. W., Mirzadeh, S., and Knapp, F. F., Jr. "The Use of Alumina "SepPaks®" as a Simple Method for the Removal and Determination of Tungsten-188 Breakthrough from Tungsten-188/Rhenium-188 Generators," J. Appl. Radiat. Isot., 43, 801-804 (1992).

Mausner, L. F., Mirzadeh, S., and Srivastava, S. C. "Improved Specific Activity of Reactor Produced ^{117m}Sn with the Szilard-Chalmers Process," Appl. Radiat. Isot., **43**, 1117-1122 (1992).

Proceedings

Members of the ORNL Nuclear Medicine Group authored two papers in a recent book entitled, "Nuclear Data for Science and Technology" (S. M. Quaim, editor), published by Springer Verlag, which were the Proceedings of papers presented at the International Conference on Nuclear Data for Basic and Applied Sciences held at the KFA in Julich, Germany, on May 12-17, 1991.

> Mirzadeh, S. and Chu, Y. Y. "Production of Gallium-66, A Positron Emitting Nuclide for Radioimmunotherapy."
>
> Mirzadeh, S., Knapp, F. F., Jr., and Callahan, A. P. "Production of Tungsten-188 and Osmium-194 in a Nuclear Reactor for New Clinical Generators."

New Patent Granted

A second set of new claims has been allowed by the U.S. Patent Office for the patent describing the ORNL tungsten-188/rhenium-188 radionuclide generator system which provides the carrier-free rhenium-188 as perrhenic acid for therapeutic applications.

Knapp, F. F., Jr., Lisic, E. C., Mirzadeh, S., and Callahan, A. P. "Tungsten-188/Carrier-Free Rhenium-188 Perrhenic Acid Generator System."

Book Chapter

Members of the Nuclear Medicine Group co-authored a chapter in a recent book on current methods of cardiac imaging for the clinical diagnosis of heart disease.

Visser, F. C., Sloof, G. W., and Knapp, F. F., Jr. "Myocardial Metabolic Imaging with Iodine-123-Labeled Fatty Acids," In, *What's New In Cardiac Imaging?*, E. E. van der Wall, H. Sochor, A. Righetti and M. G. Niemeyer, editors, Kluwer Academic Publishers, The Netherlands, pp. 229-247 (1992).

Presentations

Members of the ORNL Nuclear Medicine Program co-authored two papers presented at the European Association of Nuclear Medicine (EANM) Congress in Lisbon, Portugal, on August 23-28, 1992, describing clinical studies with a new agent developed at ORNL. The work on the new pancreatic function test represents the results of recent patient testing of this new ORNL agent and was nominated for the prestigious "Marie Curie Award," which is awarded each year for the most outstanding paper at the EANM Meeting.

Kropp, J., Knapp, F. F., Jr., Weyenberg, A., Bergmann, K. and Biersack, H.-J. "Pancreatic Lipase Activity Tested by Urine Analysis After Oral Administration of a I-131-Triglyceride."

Kropp, J., Koehler, U., Zierz, St., Knapp, F. F., Jr., Briele, B., von Smekal, A. and Biersack, H.-J. "Oxidative Metabolism of the Myocardium in Patients with Systemic Myopathies."

Members of the ORNL Nuclear Medicine Program co-authored a paper describing collaborative studies which was presented at the recent "Fourth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer" held in Princeton, New Jersey, on September 17-19, 1992. The paper described the first successful targeting of rhenium-188-labeled antibodies using rhenium-188 from the ORNL tungsten-188/rhenium-188 generator system to tumors of four patients at the Center for Molecular Medicine and Immunology, in Newark, New Jersey.

Sharkey, R. M., Varga, D., Vagg, R., Siegel, J. A., Goldenberg, D. M., Griffiths, G. L., Jones, A. L., Tejada, G., Ahmad, M., Hansen, H. J., Knapp, F. F., Jr. and Callahan, A. P. "Phase I Radioimmunotherapy Using Directly Labeled Rhenium-188-Labeled Murine Anti-Carcinoembryonic Antigen IgG: Preliminary Results."

ORNL Nuclear Medicine Program Staff Organize International Symposium

Saed Mirzadeh introduced and chaired the opening session of a symposium on "Radionuclide Generator Systems for Nuclear Medicine Applications," at the Annual Meeting of the American Chemical Society (ACS) recently held in Washington, D.C., on August 23-28, 1992. The symposium was organized by ORNL Nuclear Medicine Program members F. F. Knapp, Jr., S. Mirzadeh and A. P. Callahan under the auspices of the ACS "Division of Nuclear Chemistry and Technology." The symposium consisted of four half-day sessions focussing on current research in the development of radionuclide generator systems for diagnostic and therapeutic applications in nuclear medicine. A total of twenty one papers were presented by scientists from the U.S., Belgium, Switzerland, and Taiwan, who represented national laboratories, universities and commercial firms. Proceedings of the symposium will be published in the journal *Radioactivity and Radiochemistry.*

News Release Describes Initiation of Clinical Use of ORNL Generator

Two recent articles in *Science* (September 4, 1992, page 1348) and *Chemical and Engineering News* (September 7, 1992, page 33) have described the initiation of clinical studies

with rhenium-188-labeled antibodies for tumor therapy by Immunomedics, Inc., and CMMI in Newark, New Jersey, in a collaborative project with the ORNL Nuclear Medicine Program using the ORNL tungsten-188/rhenium-188 generator. The news articles resulted from a News Conference held by representatives of Immunomedics, Inc., a Newark, New Jersey company, at the recent "Symposium on Radionuclide Generators for Nuclear Medicine Applications," organized by the ORNL Group at the American Chemical Society held in Washington, D. C., on August 24-28, 1992.

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41. T. F. Budinger, M.D., zmd 55/121, Lawrence Berkeley Laboratory, 1 Cyclotron Road, Berkeley, CA 94720
42. J. G. Davis, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
43. S. J. DeNardo, M.D., Univ. California, Davis Medical Center, Sacramento, CA 95817
44. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205-2179
45. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitatsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
46. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
47. L. Feinendegen, Institut fur Medizin, Forschungszentrum Julich GmbH, Postfach 1913, D-5170, Julich 1, Germany
48. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
49. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103

50. M. M. Goodman, Nuclear Medicine Section, Department of Radiology, University of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920-6999
51. M. Guillaume, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
52. D. R. Hamilton, Director, Division of Technical Development, OTA/CDRH/FDA, 1901 Chapman Avenue, Rockville, MD 20857
53. J. Hiltunen, Technical Research Centre of Finland, Reactor Laboratory, Otakaari 3 A, SF-02150 Espoo, Finland
54. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
55. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
56. G. W. Kabalka, Chemistry Department, University of Tennessee, Knoxville, TN 37996-1600
57. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
58. J. Kropp, M.D., Klinik fuer Nuklear Medizin, Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
59. D. E. Kuhl, M.D., Division of Nuclear Medicine, University of Michigan Hospitals, University Hospital BIG 412/0028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0028
60. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
61. D. J. Maddalena, FRACI, Department of Pharmacology, Sydney University, NSW 2006, Sydney, Australia
62. H. J. Machulla, Eberhard-Karls-Universität Tübingen, Radiologische Universitätsklinik, Pet-Zentrum, Röntgenweg 11, 7400 Tübingen, Germany
63. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
64. R. Patterson, M.D., Nuclear Cardiology, Crawford Long Hospital, 550 Peachtree Street, NE, Atlanta, GA 30365-2225
65. C. L. Partain, M.D., Professor and Vice Chairman, Dept. Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232
66. R. C. Reba, M.D., 5841 S. Maryland Ave., U.C. Hospital Box 429, Chicago, IL 60637
67. S. N. Reske, University Clinic, Dept. of Nuclear Medicine, Steinhoevelstrasse 9, D-7900, Ulm, Germany
68. M. Robbins, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
69. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
70. R. E. Schenter, HO-37, Westington Hanford Co., P.O. Box 1970, Richland, WA 99352
71. S. K. Shukla, Prof., Servizio Di Medicina Nucleare, Ospedale S. Eugenio, Piazzale Umanesimo, 10, Italy
72. F. Snyder, ORAU, Oak Ridge, TN 37831
73. A. Solomon, M.D., UT MRCH, 1924 Alcoa Highway, Knoxville, TN 37920-6999
74. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
75. P. C. Srivastava, DOE-OHER, Washington, DC 20585
76. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
77. H. W. Strauss, M.D., Vice President, Diagnostics, Pharmaceutical Research Institute, Bristol Meyers Squibb, Rt. 202 Provinceline Rd, PO Box 4000, Princeton, NJ 08543-4000

78-88. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831
89. F. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
90. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, 615 N. Wolfe Street, Baltimore, MD 21205-2179
91. A. P. Wolf, BNL, Upton, NY 11973
92. R. Wolfangel, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
93. D. V. Woo, Centocor, 244 Great Valley Parkway, Malvern, PA 19355
94. R. W. Wood, Jr., DOE-OHER, Washington, DC 20585
95. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa
96. T. Yonekura, M.D., Kyoto Univ. Faculty of Medicine, Shogoin, Sakyo-kuy Kyoto 606-01, Japan

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