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Nuclear Medicine Program Progress Report for Quarter Ending September 30, 1994

F. F. Knapp, Jr.

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

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Health Sciences Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING SEPTEMBER 30, 1994

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Work sponsored by
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Summary

In this report we describe the synthesis of the Z *(cis)* isomers of R-1-azabicyclo[2.2.2]oct-3-yl R- and S-α-hydroxy-α-(1-iodo-1-propen-3-yl)-α-phenylacetate. We also report the results of the *in vitro* binding assays of the E and Z isomers of the (R,R)-and (R,S)-isomers of IQNP. The Z isomers of IQNP were prepared by the reaction of (R,R)- or (R.S)-1-azabicyclo[2.2.2]oct-3-yl-α-hydroxy-α-phenyl-α-1-propyn-3-yl)acetate with tributyltin hydride in HMPA followed by subsequent reaction of the *cis* tributylstannyl substrate with iodine. In an attempt to increase the yield of the Z isomers, the preparation of the Z isomers of the R-or S-ethyl α-hydroxy-α-phenyl-α-(1-propyn-3-yl)acetate was also investigated under a variety of reaction conditions. Results of the *in vitro* binding assays demonstrated that although all the isomers showed high affinity for the muscarinic receptor, the E-(R,R)-IQNP isomer had a 100 times greater higher affinity for m_1 and m_3 receptor subtypes as compared to m_2 subtype.

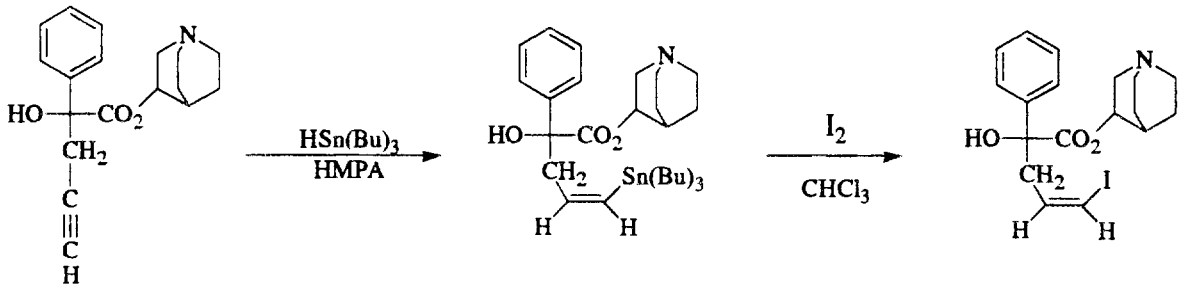
In this report the evaluation of methods for the separation of carrier-free holmium-166 for reactor-irradiated dysprosium-165 targets is also discussed. Holmium-166 decays with emission of high energy β particles (1855 and 1776 KeV) and a gamma photon suitable for imaging (80.5 KeV). Since the most common oxidation state of holmium is as a trivalent cation, the chelation chemistry of holmium is similar to yttrium and holmium-166 is of interest for various therapeutic applications. Reverse phase ion-exchange chromatography using α-hydroxyisobutyric acid as the eluent and either Dowex AG50Wx12 or Aminex-A5 cation exchangers have been developed for separation of carrier-free holmium-166 from milligram quantities of $^{164}Dy_2O_3$.

During this period a Cooperative Research and Development Agreement (CRADA) was established between the ORNL Nuclear Medicine Program and RhoMed, Inc., in Albuquerque, New Mexico, for the evaluation of rhenium-186 and rhenium-188-labeled peptides and antibodies for cancer therapy, and a tungsten-188/rhenium-188 generator was provided for this labeling studies. Large-scale (> 500 mCi) levels of tin-117m were produced in the ORNL High Flux Isotope reactor (HFIR) and provided to the BNL Medical Department for ongoing studies of the effectiveness of tin-117m-DTPA for the clinical treatment of cancer bone pain.

Synthesis of Z-R-1-azabicyclo[2.2.2]oct-3-yl R- andS-α-hydroxy-α-1-iodo-1-propen-3-yl)-α-phenylacetate.

We have previously reported on the synthesis and initial in vivo study in female rats of E-and Z-R-1-azabicyclo[2.2.2]oct-3-yl R-and S-α-hydroxy-α-1-iodo-1-propen-3-yl)-α-phenylacetate (1)(ORNL/TM-0000). The E isomers of 1 (*trans* configuration of the iodide on the double bond) were readily synthesized by the treatment of the R-1-azabicyclelo[2.2.2]oct-3-yl R- and S-α-hydroxy-α-phenyl-α-(1-propy-3-yl)acetate (**2**) with tributyltin in the presence of AIBN in toluene. Subsequent treatment of **2** with iodine in chloroform afforded E-(R,R)- or (R,S)-1 (Scheme 1). The Z isomers that were utilized for the initial in vivo study utilizing female rats were isolated as minor products from the stannylation reaction of the corresponding E isomers of **1**. The synthesis and characterization of Z-(R,R)- and Z-(R,S)-IQNP have now been completed, along with the *in vitro* binding assays of the E and Z isomers of (R,R) and R,S)-IQNP in collaboration with) the George Washington University Medical Center (B. Zeeberg, Ph.D. and V. Sood, Ph.D. et al.) and the University of Chicago (R. C. Reba, M.D.).

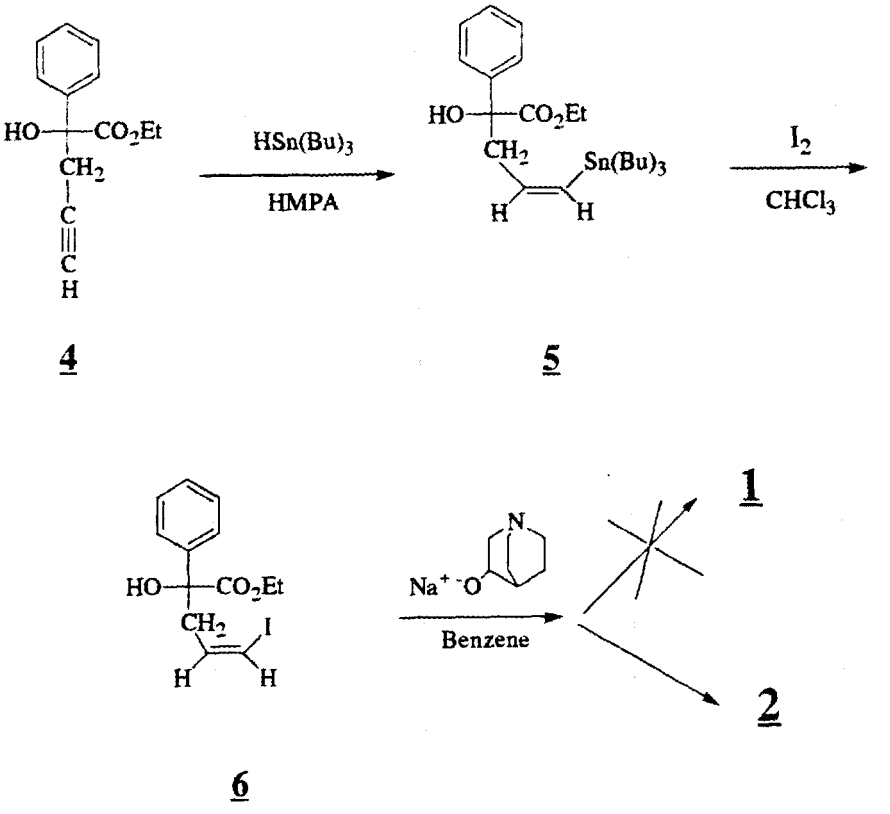
Since iododestannylation reactions normally proceed with retention of stereochemistry, the orientation of the tributylstannyl group on a double bond can be influenced by the choice of solvent used for the preparation of vinyl tributylstannyl intermediate. The use of a slight excess of tributyltin hydride in toluene with a radical initiator affords primarily the E isomer while the use of an aprotic solvent such as hexamethylphosphoric triamide (HMPA), affords mainly the Z isomer.



2 **3** **1**

Scheme 1

When the reaction of **2** with tributyltin hydride was performed using HMPA as the solvent under a variety of reaction conditions (Table 1), only minor amounts of the Z-(R,R)- or Z-(R,S)-**3** isomers along with the E isomers were isolated from the reaction mixture. It therefore appears that the E to Z ratio is not only dependent on the reaction conditions, but may also be influenced by steric hinderance around the acetate center, which favors formation of the less hindered E configuration. In addition, the levels of the Z isomer isolated from the reaction mixture varied even under identical reaction conditions (see entries 2 and 6, Table 1). At temperatures greater than 30°C, it was also observed that compound **2** decomposed and could not be recovered during the purification of the stannylated product. Surprisingly, when Z-(R,R)- or Z-(R,S)-**3** was treated with iodine in chloroform both the E- and Z-(R,R)- or (R,S)-**1**, respectively, were isolated in an approximate 20:80 ratio as determined by HPLC and NMR analyses. As observed with the racemic mixture, the E and Z isomers of IQNP could not be effectively separated by flash column chromatography. Due to the low yield of Z-(R,S)- and Z-(R,R)-**3** and **1**, the specific rotation of these compounds could not be measured.



Scheme 2

An alternate route was thus pursued for preparation of the Z isomers in an attempt to improve the yield and avoid racemization of the vinyl iodide (Scheme 2). This route was chosen to simplify the chemistry by addition of the quinuclidinyl moiety during the final step of the synthetic pathway. To insure that this route would not cause racemization to occur at any of the chiral centers, E-(R,S)-IQNP (E-(R,S)-**1** was synthesized by this route and compared to the product isolated from previous preparations of E-(R,S)-**1**. For this approach, (S)-ethyl α-hydroxy-α-phenyl-α-1-propyn-3-yl)acetate ((S)-**4**) was treated with tributyltin hydride in the presence of AIBN and the resulting tributyltin intermediate was treated with iodine to afford E-(S)-**6**, as confirmed by NMR and TLC analysis. Transesterification with R-3-quinuclidinol afforded E-(R,S)-**1**. The optical rotation of E-(R,S)-**1** prepared by both routes was in agreement, demonstrating that this reaction sequence does not cause racemization at the chiral centers.

However, as observed before, reaction of either (S)- or (R)-**4**, with tributyltin hydride in HMPA under a variety of conditions still formed both the E and Z isomers (Table 1). Repeated purification by flash column chromatography afforded the desired Z-(S)- or Z-(R)- isomer of **5** free of the E isomer, as determined by NMR analysis. In contrast to the approach described above, treatment of the Z isomers of **5** with iodide, afforded the desired Z-(S)- OR Z-(R)-**6** as determined by NMR analysis. It was observed that the specific rotations of the respective E- and Z- **5** along with the respective E-and Z-**6** were similar. However, transesterification of either Z-(S)- or Z-(R)-**6** with (R)-**3**-quinuclidinol under the usual conditions afforded only a minor amount of IQNP in which the configuration of the vinylic iodide had racemized and the major product isolated being the loss of the vinyl iodide to afford wither (R,S)- or (R,R)-**2**. The conversion of Z-(S)-**6** to the free acid followed by the activation of the acid with carbodiimidazole and subsequent reaction with R-3-quinuclidinol was also investigated. However, treatment of E-(S)-**6** with ethanolic sodium hydroxide caused both rapid loss of the vinylic iodide to afford the propargyl-substituted acid as well as the saponification of the ethyl ester.

The results of *in vitro* binding assays of E and Z-(R,R)- and (R,S)-**1** are shown in Table 2. All the isomers demonstrated high binding affinity for the muscarinic receptor, although some differences were also observed. While E-(R,S)-IQNP demonstrated the lowest affinity for the muscarinic receptor, it demonstrated a moderate 6-fold selectively for the M_1 (m_1, m_3) over the M_2 (m_2) receptor subtype. E-(R,R)-IQNP demonstrated a high affinity for the muscarinic receptor, comparable to QNB, but *in vitro*, exhibits a 100-fold selectively for the M_1 subtype over the M_2 subtype. E-(R,R)-IQNP therefore is one of the most selective M_1 muscarinic ligands containing iodine which has been developed which readily

passes the blood brain barrier. This ligand also has potential use in the development of M_2-selective muscarinic ligands because of its ability *in vitro* to selectively block the M_1 receptor subtype. Z-(R,R)- and Z-(R,S)-IQNP both demonstrate high binding affinity for the muscarinic receptor but demonstrate no selectively for the different receptor subtypes. We are currently evaluating the *in vivo* biodistribution properties and pharmocokinetic and autoradiographic analyses of these promising new ligands in detail for potential use of the iodine-123-labeled agents to study muscarinic receptors by Single Photon Emission Computed Tomography (SPECT).

Table 1. Stannylation Products From the Preparation of the Z Isomers.

Substate	TBTH/SUB (mmol/mmol)	HMPA/SUB (mL/mmol)	Temp (°C)	Time (hours)	Yield %E	%Z	E/Z
R-3	2.6	3.1	70	36	21.8	18.1	1.2
	2.9	1.5	50	72	3.1	11.8	0.3
	2.9	1.6	50	96	35.6	3.9	9.1
S-3	2.5	1.6	80	65	36.2	18.0	2.0
	2.5	1.8	80	44	53.5	10.5	5.1
	2.9	1.5	50	72	13.7	19.7	0.7
	2.9	1.5	50	24	61.4	4.5	13.6
R,S-6	4.2	1.5	40	22	18.7	31.0	0.6
	3.0	1.5	40	27	11.1	11.1	1.0
	3.5	1.9	50	45	ND	17.8	ND
R,R-6	2.8	1.3	55	45	18.8	23.2	0.8
	1.5	1.2	55	45	10.7	10.7	1.0
	2.9	1.6	55	45	20.0	8.2	2.4
	2.7	4.8	70	50	7.8	3.4	2.3

ND= not determined
HMPA= hexamethylphorphorous
SUB= substrate
TBTH= tributyltin hydride

Table 2. Binding Affinity of the Various Isomers of IQNP (1).

K_D, nM (mean + standard error)

Subtype	QNB	E-(R,R)-	E-(R,S)-	Z-(R,R)-	Z-(R,S)-
m_1	0.32	0.383	6.83	0.13	0.23
	(±0.05)	(±0.102)	(±1.48)	(±0.04)	(±0.12)
m_2	0.20	29.6	41.2	0.43	0.62
	(±0.03)	(±9.70)	(±10.3)	(±0.06)	(±0.16)
m_3	ND	0.356	2.39	ND	ND
		(±0.020)	(±0.263)		

ND= not determined

Separation of Carrier-free Holmium-166 from Neutron-irradiated Dysprosium Targets

Holmium-166 (^{166}Ho) is utilized in medical radiotherapeutic applications (1-7) due to its physical properties which include high-energy beta radiation [$E_{\beta 1}$=1855 KeV (51%), $E_{\beta 2}$=1776 KeV (48%), and E_{β}^{av}=666 KeV], a 26.4-h half-life and decay to a stable daughter. In addition, ^{166}Ho has chemical characteristics suitable for protein labelling with bifunctional chelates. Holmium-166 also emits low intensity and low energy γ-rays (80.5 KeV, 6%) which are suitable for imaging. Due to the absence of high energy γ-rays in its decay, ^{166}Ho may be used for outpatient therapy without significant external radiation to other individuals. Although ^{166}Ho with moderate specific activity can be produced by the $^{165}Ho[n,\gamma]^{166}Ho$ reaction, its radionuclidic parent, ^{166}Dy ($t_{1/2}$=81.5 h), can serve as a source of high specific activity ^{166}Ho. Dysprosium-166 is produced by double neutron capture reaction on ^{164}Dy [8]. In certain applications, such as protein labelling, the use of a high specific activity radioisotope is essential. In addition, generator-produced ^{166}Ho is free from 1200-y ^{166m}Ho which is unavoidably coproduced with ^{166}Ho by the $^{165}Ho[n,\gamma]$ reaction.

The applicability of reverse phase ion-exchange chromatographic methods were demonstrated for the separation of carrier-free ^{166}Ho from milligram quantities of $^{164}Dy_2O_3$ irradiated targets. An efficient and quantitative separation was achieved utilizing a metal-free HPLC system with Dowex AG50Wx12 (Figure 1) or Aminex-A5 (Figure 2) cation exchangers and α-hydroxy-isobutyric acid (α-HIBA) as the eluent (0.085 M, pH=4.3 adjusted with NH_4OH). The Aminex-A5 column gave a separation factor of ~10^3 between Ho and Dy. Subsequent to the acidic destruction of the Ho-HIBA complex, Ho^{3+} was further purified on a small cation exchange column from acidic chloride solutions (Figure 3). The separation was achieved within 2 hours, with a 95% overall radiochemical yield for carrier-free ^{166}Ho with a Dy breakthrough of <0.1 %.

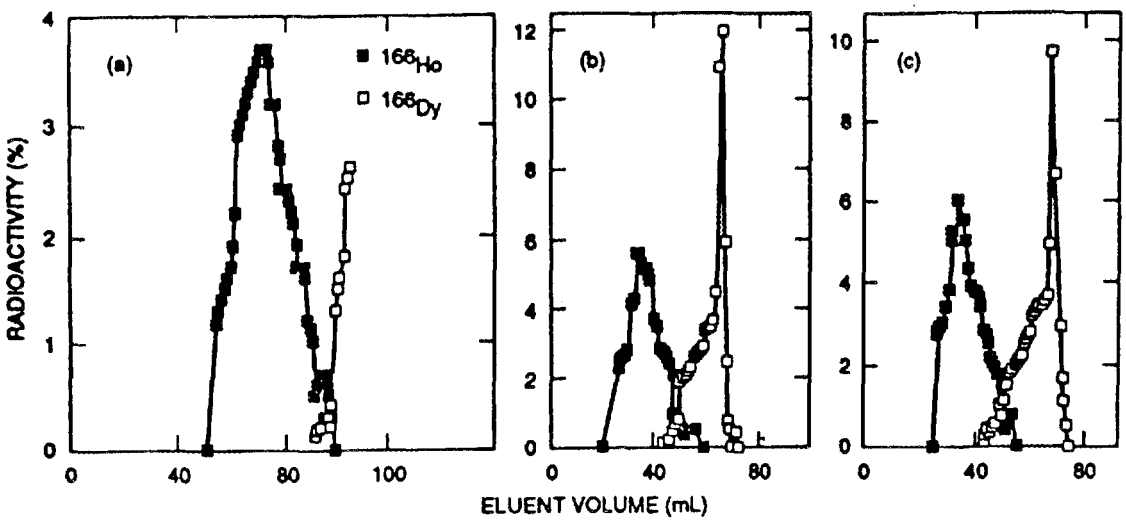


Figure 1. Separation of ^{166}Ho from 1.5-2.5 mg of Dy on a metal-free HPLC using an AG 50WX12 column (200-400 mesh, 0.4x15 cm) via elution with 0.085 M α-HIBA at pH=4.27 and p=200 psi. Dy load (mg) = (a) 1.5, (b) 2.0, (c) 2.5; Dy was stripped off the column with 0.132 M α-HIBA from (a) not used, (b) 59 mL, (c) 63 mL

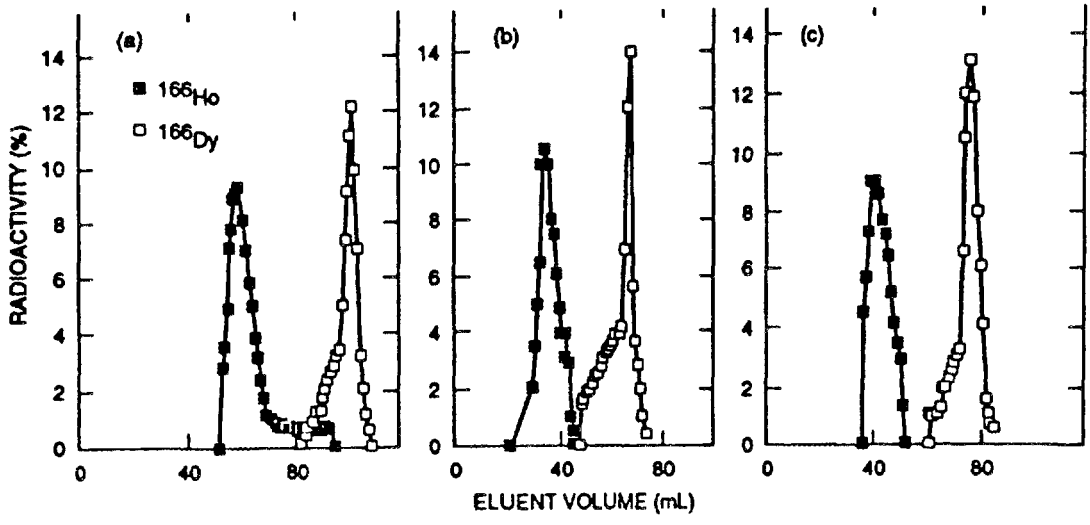


Figure 2. Separation of ^{166}Ho from 1.5-2.5 mg of Dy on a metal-free HPLC using an Aminex-A5 column (0.4x25 cm) via elution with 0.085 M α-HIBA at pH=4.27. Dy load (mg) = (a) 1.5, (b) 2.0, (c) 2.5; System pressure (psi) = (a) 750, (b) 1000, (c) 1400; Dy was stripped off the column with 0.132 M α-HIBA from (a) 92 mL, (b) 62 mL, (c) 70 mL

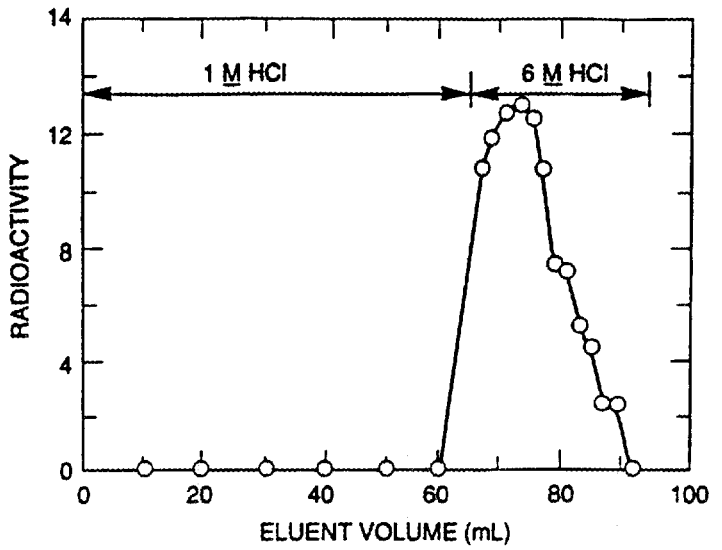


Figure 3. Elution profile of carrier-free ^{166}Ho from an AG 50WX12 column (200-400 mesh,1.3x2.1 cm) with HCl solutions

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OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Recent Publications

Kamioki, H., Mirzadeh, S., Lambrecht, R. M., Knapp, Jr., F. F., and Dadachova, E. "Tungsten-188/Rhenium-188 Generator for Biomedical Applications," Radiochim. Acta, 65, 39-46 (1994).

Recent Meetings

Dr. Saed Mirzadeh, a staff member of the Nuclear Medicine Group, and Dr. Huimin Luo, a Alexander Hollaender Postdoctoral Fellow, participated in the Biannual Meeting of the American Chemical Society, held in Washington, D.C., on August 22-25, 1994.

F. F. (Russ) Knapp, Jr., Group Leader of the Nuclear Medicine Program, presented a lecture entitled, "Curie-Scale Tungsten-188/Rhenium-188 Generators Can Cost Effectively Provide Carrier-Free Rhenium-188 for Routine Clinical Applications", at the Fourth International Symposium on Technetium and Rhenium, held in Bressenaro, Italy, on September 11-14, 1994. He also co-authored two other papers in conjunction with collaborators describing the labeling of peptides and antibodies with rhenium-188 for cancer therapy. Prior to the symposium, he participated in the European Nuclear Medicine Congress in Dusseldorf on August 21-24, and met with collaborators and presented lectures at several Nuclear Medicine Departments in Germany, including Dresden, Rossendorf, Bonn, Mainz and Frankfurt, describing the development of new radiopharmaceuticals at ORNL.

ORNL License Established with Isotope Products Laboratories, Inc. for Tungsten-188/Rhenium-188 Generator

An exclusive license for marketing and sale of the tungsten-188/rhenium-188 generator system developed in the ORNL Nuclear Medicine Group has been established with Isotope Product Laboratories, Inc. (IPL), a company located in Burbank, California. The IPL parent company has established "IPL Imaging and Therapeutics", as a new medical products company. The ORNL generator provides highly-concentrated solutions of the rhenium-188 radioisotope. High radioisotope concentrations are required for radiolabeling radiopharmaceuticals used for nuclear medicine.

Rhenium-188 is of widespread interest as a cost-effective agent for various therapeutic applications, including treatment of tumors with various rhenium-188-labeled agents, including tumor-specific monoclonal antibodies. Additional major areas of use are expected to include the palliative treatment of bone pain from cancer using rhenium-188-labeled phosphonate agents and treatment of inflammatory arthritis of the fluid-filled synovial joints using rhenium-188-labeled particles. The tungsten-188 parent radioisotope in produced in the ORNL High Flux Isotope Reactor.

ORNL Nuclear Medicine Program Moves to New Renovated Laboratories

The ORNL Nuclear Medicine Program has initiated relocation of radiochemical laboratories from ORNL Buildings 3047 and 3026C to Building 4501. Renovation of a suite of labortaories in Building 4501 was initiated in 1993. These facilities include an animal experimentation laboratory and an animal housing and handling room equipped with air handling and monitoring systems required to meet all federal guidlines. Two other laboratories are dedicated to radiochemistry and radiopharmaceutical synthesis.

Visitors

August 11-12, 1994	Dr. Van Zyl DeVilliers, Reactor Research Center, Pretoria, South Africa
August 17, 1994	Mr. Len Hendrickson, Isotope Products Laboratories, Burbank, California
September 8, 1994	Herbert Moore, Diatech and Radioisotope Services Inc., Londonderry, NH

Medical Cooperative Program Shipments

During this period a tungsten-188/rhenium-188 generator was provided to RhoMed (B.A. Rhodes, Ph.D.), Inc., in Albuquerque, New Mexico, as part of a DOE-funded CRADA arrangement to explore the radiolabeling of tumor-specific antibodies and peptides for therapy. HFIR-prepared tungsten-188 was provided through the ORNL Isotopes Distribution Office (IDO) on a cost-recovery basis to the Australian Nuclear and Science Technology Organization (ANSTO). A large sample of tin-117m (>600mCi) was provided through a inter-laboratory collaborative program to the Medical Department at the Brookhaven National Laboratory (S. C. Srivastava, Ph.D. and L. Mausner, Ph.D.) where tin-117m-DTPA is being prepared as a new agent for palliative treatment of bone pain from cancer. High specific activity rhenium-186 from HFIR irradiation of rhenium-185 was provided to the Center for Molecular Medicine and Immunology for therapeutic studies in tumor-bearing animals.

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36. A. Bockisch, Ph.D., M.D., Klinik und Poliklinik fuer Nuklearmedizin, Postfach 39 60, Langenbeckstrasse 1, 55101 Mainz, Germany
37. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
38. A. B. Brill, M.D., Ph.D., Dept. of Nuclear Medicine, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655
39. T. F. Budinger, M.D., MS 55/121, Lawrence Berkeley Laboratory, 1 Cyclotron Road, Berkeley, CA 94720
40. A. P. Callahan, Route 1, Box 305, Harriman, TN 37748
41. D. Cole, Medical Applications and Biophysical Research Division, ER-73, Department of Energy, GTN, Washington, D.C. 20585
42. B. Coursey, National Institute for Standards and Technology, Building 245, RM C214 Gaithersburg, MD 20899
43. J. G. Davis, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
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. G. Ehrhardt, Missouri University Research Reactor, University of Missouri, Research Park, Columbia, MO 65211
47. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
48. L. Feinendegen, Medical Department, Brookhaven National Laboratory, Upton, NY 11973

49. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
50. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103
51. G. Goldstein, DOE-OHER, Washington, DC 20585
52. G. Griffiths, Immunomedics, Inc., 300 American Rd, Morris Plains, NJ 07950
53. J. Hiltunen, Managing Director, MAP Medical Technologies, Inc., Elementtitie 27, SF-41160 Tikkakoski, Finland
54. Bor-Tsung Hsieh, Ph.D., Institute of Nuclear Energy Research, (INER) Lung-Tan, Taiwan, Republic of China
55. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
56. B. Johannsen, Ph.D., Forschungszentrum Rossendorf e.V.Postfach 51 01 19, D-01314 Dresden, Federal Republic of Germany.
57. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
58. G. W. Kabalka, Chemistry Department, University of Tennessee, Knoxville, TN 37996-1600
59. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
60. J. Kropp, M.D., Klinik fur Nuklearmedizin, der Medizinischen Akademie, Fetscher - Str. 74, 01307 Dresden, Germany
61. 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
62. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
63. J. Lister-James, Ph.D., Director, Research Administration, Diatech, Inc., 9 Delta Drive, Londonderry, New Hampshire 03053.
64. O. Lowe, Isotope Production and Distribution Program, U.S. Department of Energy, NE-46, GTN, Room B-419, Washington, D. C. 20585.
65. G. Limouris, Nuclear Medicine Department, Areteion University Hospital, Athens Medical School, Athens, Greece
66. D. J. Maddalena, FRACI, Department of Pharmacology, Sydney University, NSW 2006, Sydney, Australia
67. John Maddox, 4608 Flower Valley Drive, Rockville, MD 20853-1733.
68. H.-J.Machulla,Eberhard-Karls-Universität Tübingen,RadiologischeUniversitätsklinik,Pet-Zentrum, Röntgenweg 11, 7400 Tübingen, Germany
69. Frederick J. Manning, National Academy of Sciences, Institute of Medicine, 2101 Constitution Ave., M.W., Washington, D.C. 20418
70. M. Meyer, M.D., Biomedical Research Foundation, P.O. Box 38050, Shreveport, LA 71133-8050
71. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
72. G. Notohamiprodjo, M.D., Ph.D., Institute of Nuclear Medicine, Heart Center North Rhine-Westphalia, Bad Oeynhansen, D-4970, Germany
73. C. L. Partain, M.D., Professor and Vice Chairman, Dept. Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN 37232
74. R. C. Reba, M.D., Department of Radiology, 5841 S. Maryland Ave., MC 2026, Chicago, IL 60637
75. S. N. Reske, M.D., Klinik für Nuklearmedizin, Arztlicher Direktor der Nuklearmedizin, Klinikum der Universität Ulm Oberer Eselsberg, D-7900, Ulm, Germany
76. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
77. R. E. Schenter, HO-37, Westington Hanford Co., P.O. Box 1970, Richland, WA 99352

78. A. Serafini, Nuclear Medicine Division (D-57), University of Miami School of Medicine, P. O. Box 016960, Miami, FL 33101
79. S. K. Shukla, Prof., Servizio Di Medicina Nucleare, Ospedale S. Eugenio, Pizzale Umanesimo, 10, Rome, Italy
80. A. Solomon, M.D., UT MRCH, 1924 Alcoa Highway, Knoxville, TN 37920-6999
81. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
82. J. Smith, Ph.D., Senior Director, Research & Development, DuPont Merck Pharmaceutical Company, 331 Treble Cove Rd., North Billerica, MA 01862
83. S. Smith, Biomedicine & Health Program, Australian Nuclear Sci. & Tech. Org., Lucas Heights Research Laboratories, Private Mail Bag 1, Menai NSW 2234, Australia

84. P. C. Srivastava, DOE-OHER, Washington, DC 20585
85. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
86. G. Strathearn, Isotope Products Laboratories, Inc., 3017 N. San Fernando Blvd., Burbank, CA, 91504.
87. H. W. Strauss, M.D., Division of Nuclear Medicine, Stanford University Medical Center, Room H0101, Stanford, California 94305-5281

88-89. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831

90. E. A. van Royen, M.D., Ph.D., Head, Department of Nuclear Medicine, Academic Medical Center,University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam ZO, The Netherlands.
91. F. C. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
92. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, 615 N. Wolfe Street, Baltimore, MD 21205-2179
93. A. P. Wolf, Chemistry Department, Brookhaven National Laboratory, Upton, NY 11973
94. R. Wolfangel, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
95. J.-I. Wu, Ph.D., Senior Research Representative, Nihon Medi-Physics Co., Ltd., 2200 Powell Street, Suite 765, Emeryville, CA 94608.96.
96. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa
97. Y. Yonekura, M.D., Kyoto University Faculty of Medicine, Shogoin, Sakyo-kuy, Kyoto, 606-01, Japan