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Nuclear Medicine Progress Report for Quarter Ending June 30, 1987

F. F. Knapp, Jr.
J. F. Allred
K. R. Ambrose
A. P. Callahan
D. E. Rice
P. C. Srivastava

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SUMMARY

In this report the performance of two tungsten-188/rhenium-188 (W-188/Re-188) radionuclide generator systems utilizing either alumina (Al_2O_3) eluted with physiological saline or hydrated zirconium oxide (HZO) eluted with methyl ethyl ketone are described. Because of its emission of high-energy β^- and availability from a reactor-produced parent (W-188) with a long ($T_{1/2}$ 69 days) half-life, Re-188 is an excellent candidate for various therapeutic applications. Both systems gave reproducible daily yields (>85%) over several weeks with very low W-188 parent breakthrough ($<10^{-6}$%). The production of W-188 in the High Flux Isotope Reactor (HFIR) was evaluated, and a one cycle irradiation (21 d) of enriched W-186 gave W-188 with a specific activity of 3.5 mCi/mg W-186. The results demonstrate that W-188/Re-188 generators with reproducible performance, long shelf-life and high yields of Re-188 can be prepared from both HZO and Al_2O_3.

Also in this report, the isolation of a polar catabolite from isolated Langendorff-perfused rat hearts administered the radioiodinated 3-methyl-branched fatty acid, 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP), is described. This is the first demonstration of the identification of the release of an apparent metabolite associated with the myocardial clearance of BMIPP and suggests that the formation of such a catabolite may occur in vivo. Studies are now in progress in an attempt to identify this component which may be a hydroxy acid.

During this period several radioiodinated agents were supplied to investigators at the University of Michigan, and the University of Bonn, West Germany, for collaborative studies, and collaborative studies with the osmium-191/iridium-191m radionuclide generator system have continued.

DEVELOPMENT OF TUNGSTEN-188/RHENIUM-188 (W-188/Re-188) GENERATOR SYSTEMS

The current increased interest in the availability of radionuclides for therapy has resulted from the recent success and potential widespread importance of radiolabeled antibodies for both diagnosis and therapy. By attaching various radionuclides, the radiolabeled tumor-specific antibodies or antibody fragments can potentially be targeted to tumor tissue for diagnostic or therapeutic applications. There are a limited number of radionuclides, however, that have the optimal combination of availability, chemistry and radionuclidic properties. In Table 1 the properties of several radionuclides of current interest are summarized.

Table 1. Some useful radionuclides of current interest for therapy

Radionuclide	Physical $T_{1/2}$	Energy Deposition* Δ(g-rad/μCi-h)
Iodine-131	8.0 d	0.387
Copper-67	61.9 d	0.301
Yttrium-90	64.1 d	1.990
Rhenium-188	16.9 h	1.630
Rhenium-186	90.6 d	0.692

*Non-penetrating

The most useful radionuclides would be those available from radionuclide generator systems that could be obtained from the radiopharmacy for daily elution. Because the radiolabeling of antibodies and fragments is often performed with very small amounts of substrate, the availability of very high specific-activity radionuclides is important and is a unique characteristic of generator-derived radionuclides. Yttrium-90 has very attractive properties for therapeutic applications and is now being widely explored for radiolabeling of a variety of antibodies.[1] The possibility of generator breakthrough of the Sr-90 parent and the in vivo

instability of Y-90-labeled antibodies and potential release of Y-90 with subsequent bone marrow uptake and depression can occur. These are important problems which must be evaluated and overcome.

The use of rhenium-188 (Re-188) from a tungsten-188/rhenium-188 radionuclide generator system (W-188/Re-188) represents an attractive alternative radionuclide. Rhenium-188 ($T_{1/2}$ 16.9 h) is produced from β-decay of the tungsten-188 parent ($T_{1/2}$ 69 d). In addition to the emission of high energy electrons with an average energy of 769 keV, Re-188 also decays with emission of a gamma photon with an energy of 155 keV in 15% abundance. Besides the therapeutic usefulness of Re-188, the emission of the 155 keV gamma photon is an added advantage since the biodistribution of Re-188-labeled agents can be evaluated in vivo with a gamma camera. In this manner the distribution in vivo can be used to determine target tissue specificity, and the absorbed radiation dose values can be estimated. An evaluation of dosimetry is very important and often not possible with Y-90 and many other therapeutic radionuclides, although the bremmstrahlung radiation can be measured.

The production and decay scheme for the W-188/Re-188 pair is shown in Figure 1. The W-188 is produced by initial neutron capture by enriched W-186 to form the intermediary W-187 which is then available for a second neutron capture to form the W-188 parent. Because W-188 is formed by this double neutron capture process, the thermal neutron flux is a very important parameter for high yields of the W-188 product. It is interesting to note that studies with the W-188/Re-188 generator system, which now appears so attractive for therapeutic applications, were pursued more than 20 years ago when rhenium-188 was suggested as an alternative to technetium-99m for diagnostic applications.[2] The biodistribution of a saline solution of Re-188 obtained from evaporation of the eluant from a zirconium oxide system eluted with methyl ethyl ketone (MEK) was evaluated in human volunteers and showed a biodistribution pattern and excretion properties through the urinary bladder very similar to that of technetium-99m.[3]

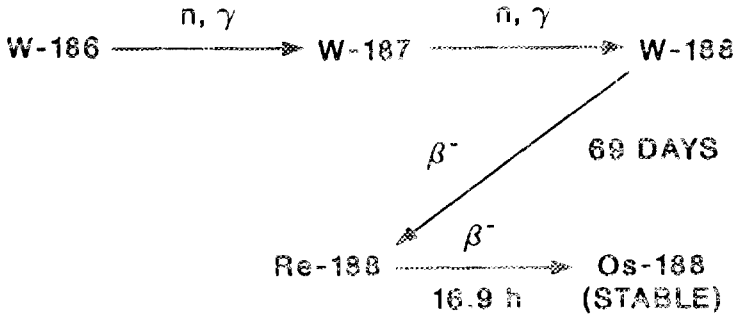

Figure 1. Production and decay scheme for rhenium-188 from neutron irradiation of enriched tungsten-186.

The initial goals of the current work were to determine the production yields of W-188 in the ORNL High Flux Isotope Reactor (HFIR), to evaluate the performance of W-188/Re-188 generator systems using either alumina (Al_2O_3) or hydrated zirconium oxide (HZO) as the absorbents, and to determine yield, breakthrough and shelf-life. Optimization of these parameters is important to determine the feasibility of developing a generator system that could be available in the radiopharmacy for daily elution. Because of the relative physical half-lives of the W-188 parent and Re-188 daughter, elution of the generator every 24 h would be expected to provide about 63% of the expected ingrowth of Re-188 (Figure 2).

For the current studies, enriched W-186 WO_3 was irradiated in the HFIR for 21 days prior to the temporary shutdown in November 1986. The production yield of 3.6 mCi/mg of enriched W-186 is very similar to that reported earlier.[2] Processing of the target involves dissolution of the WO_3 in potassium hydroxide to form a potassium tungstate solution.

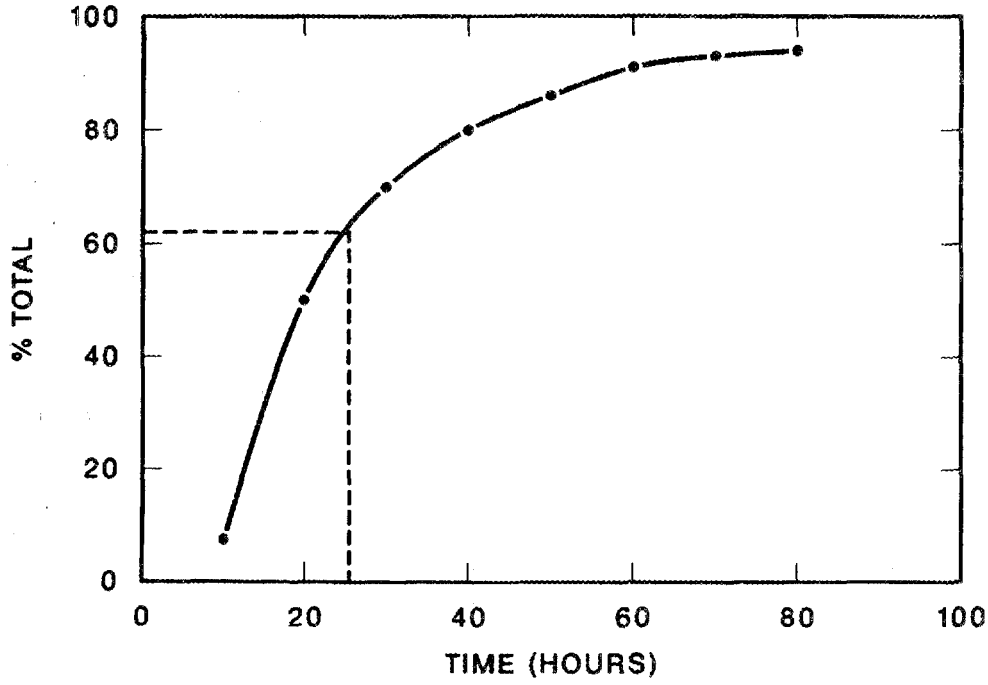

Figure 2. Expected daily ingrowth of rhenium-188.

For the initial studies described here, generators were prepared from either HZO or alumina. Elution of the HZO column with physiological saline gave yields of ~ 60% but elution with MEK gave consistently high yields of greater than 90% (Figure 3). Breakthrough of the parent was very low, and could only be estimated to be less than 10^{-6}%/elution. Subsequent radiolabeling with Re-188 via reduction of perrhenate eliminates any tungsten present and breakthrough of the parent is not crucial. An important observation was the consistent performance of the HZO generator over 50 days. As described earlier, dissolution of the residue obtained by simple evaporation of the MEK solution gives a physiological solution of Na tungstate[1] that can be used for subsequent radiolabeling (reductive coupling, etc.). As an alternative, basic alumina was also evaluated as an adsorbent and excellent yields of W-188 were obtained by elution with physiological saline solution (Figure 4). This system also gave very low breakthrough and consistent performance over a long time period.

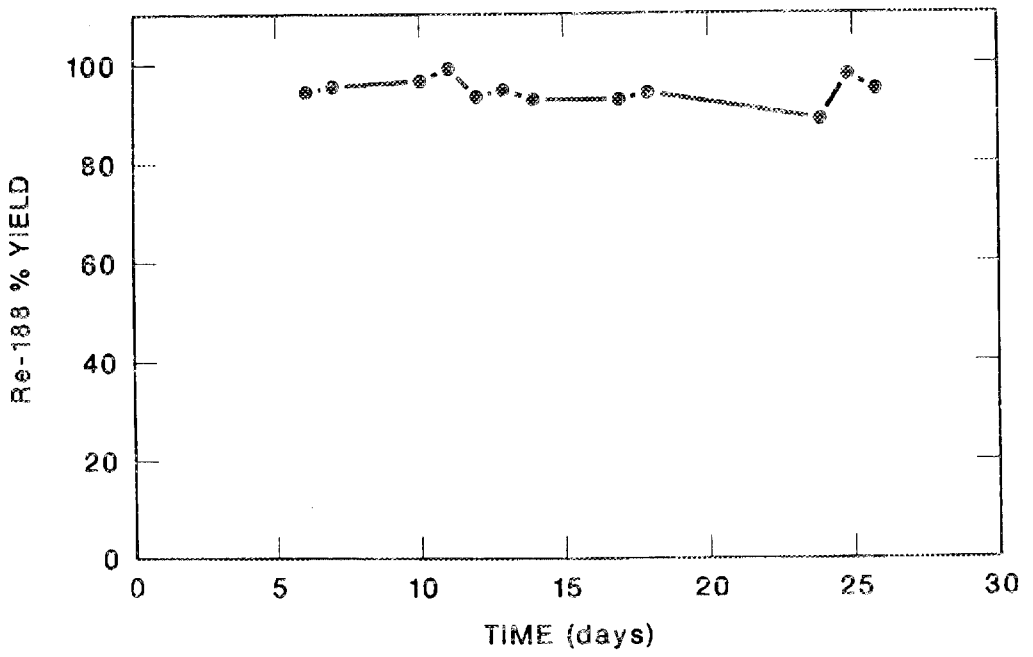

Figure 3. Performance of HZO W-188/Re-188 generator system eluted with methyl ethyl ketone as a function of shelf-life.

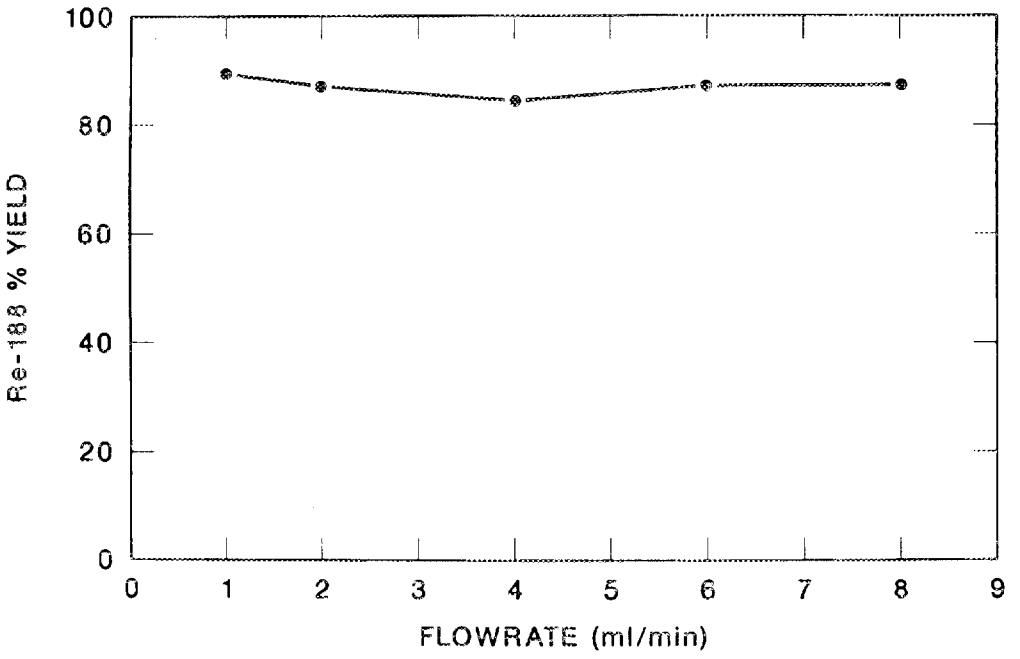

Figure 4. Performance of Al_2O_3 W-188/Re-188 generator system eluted with physiological saline as a function of flowrate.

Studies now in progress include an evaluation of the effects of specific activity on the elution performance of the alumina system since it is important to demonstrate that generators prepared from tungsten-188 produced in reactors with a much lower specific activity than that produced in the HFIR can be used. In addition, methods are now being developed for the radiolabeling of tumor-specific antibodies and other therapeutic agents with Re-188.

EVALUATION OF METABOLITES FROM THE RADIOIODINATED β-METHYL-BRANCHED FATTY ACID, 15-(p-IODOPHENYL)-3-R,S-METHYLPENTADECANOIC ACID (BMIPP), USING AN ISOLATED PERFUSED RAT HEART SYSTEM

In the last report in this series (ORNL/TM-10441), the use of an isolated Langendorff-perfused rat heart system for the evaluation of the release kinetics and metabolism of the 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid (BMIPP) and the 3,3-dimethyl (DMIPP) analogue was described. These studies represent the first report of the release of an apparent metabolite from BMIPP. The isolation of the polar metabolite released from isolated hearts following administration of radioiodinated BMIPP to the inflow tract has now been pursued.

In order to analyze the chemical nature of the unknown component, it was demonstrated that the purified metabolite could be extracted from $CHCl_3$ solution with 1 N NaOH. Radioactivity could not be extracted from a basic solution with ethyl ether, indicating that the unknown catabolite is acidic. Upon acidification, however, all of the radioactivity was extracted into ethyl ether, indicating the material was a weak acid, probably a carboxylic acid. In addition, the material was methylated with diazomethane, after which it could not be extracted into base. These combined studies demonstrate the unknown component released from isolated hearts administered BMIPP contains a carboxylic acid group. Analysis of the methylated product by TLC illustrated the presence of material more polar than methyl BMIPP. The product migrates in the region of the methyl esters of 3-hydroxymyristic and 9- and 12-hydroxy-myristic acids. These data indirectly suggest that the unidentified product may be a hydroxy acid. Such products would be expected to formed by α-hydroxylation or partial metabolism through the β-oxidative chain as

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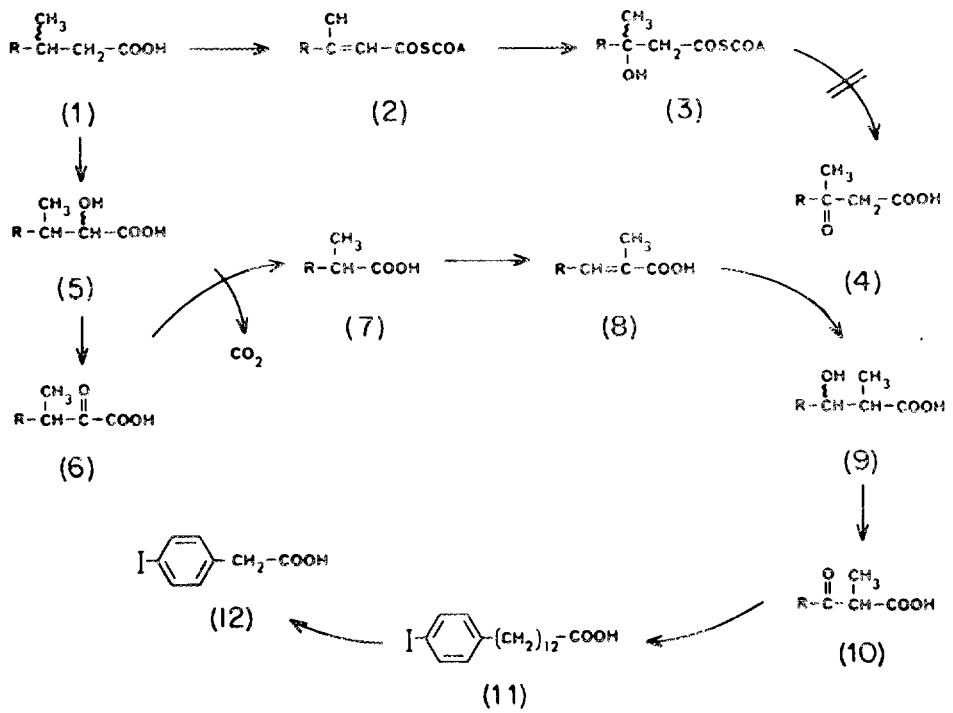

Figure 5. Possible degradation of BMIPP by partial β-oxidation through the stage of the β-hydroxy-β-methyl product or via α-hydroxylation.

shown in Figure 5. Studies now in progress are directed at isolating additional quantities of the unknown metabolite from isolated rat hearts for high pressure liquid chromatographic (HPLC) analysis and gas-liquid chromatographic (GLC) analysis. An additional goal will be to isolate sufficient amounts of the unknown component from either multiple rat hearts or from a larger isolated heart such as a swine heart for analysis by mass spectrometry (MS). Synthetic efforts are also now in progress to prepare α-hydroxy and β-hydroxy BMIPP since these compounds are currently not commercially available for comparison with the chromatographic properties of this unknown component, shown for the first time to be formed from radioiodinated BMIPP.

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AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Osmium-191

Several shipments of osmium-191 were made during this period. One of the new activated carbon osmium-191/iridium-191m radionuclide generators was supplied to collaborators at the UCLA Medical Center, Torrance, California (Dr. I. Mena). One shipment of osmium-191 as potassium perosmate was supplied for geochemical research to the Massachusetts Institute of Technology, Cambridge, Massachusetts (Prof. S. Hart). Two shipments were supplied to Loma Linda University Medical Center, Loma Linda, California (Dr. R. Adams) and one shipment to George Washington University, Washington, D.C. (Dr. B. Wessels).

Radioiodinated Agents

Three shipments of iodine-125 labeled agents were made to collaborators. Two shipments of the new [I-125] N-(p-iodophenyl)malemide protein labeling agent were supplied to University of Michigan, Ann Arbor, Michigan (Dr. D. J. Buchsbaum) for antibody labeling studies. A sample of [I-131]DMIPP was supplied to the University of Bonn, West Germany (Drs. A. Kropp and H. J. Biersack) for metabolic studies with a working isolated rat heart system.

Platinum-195m

One shipment each of platinum-195m-labeled cis-dichlorodiammine-platinum(II) (cis-DDP) was made on a cost-recovery basis to Shields Warren Radiation Laboratory, Boston, Massachusetts (Dr. A. I. Kassis), the University of California, San Diego, in La Jolla, California, and New York University Medical Center, New York, New York (Dr. T. Reich).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Meetings

F. F. Knapp, Jr., and P. C. Srivastava attended the 34th Annual Meeting of the Society of Nuclear Medicine in Toronto, Canada, on June 1-5, 1987. Staff members of the ORNL Nuclear Medicine Program authored and co-authored the following nine papers at this meeting, and F. F. Knapp, Jr. co-chaired a seminar on radiopharmaceutical chemistry.

Ambrose, K. R., Rice, D. E., Goodman, M. M., and Knapp, F. F., Jr. "Effects of 3-Methyl-Branching on Myocardial Lipid Metabolism of Terminally Iodovinyl Substituted Long Chain Fatty Acids,"

Callahan, A. P., Rice, D. E., and Knapp, F. F., Jr. "Availability of Rhenium-188 (Re-188, $T_{1/2}$ 16.9 h) from a Tungsten-188/Re-188 Generator System for Therapeutic Applications,"

Goodman, M. M., Goudonnet, A., and Knapp, F. F., Jr. "The Position of Geminal Dimethyl-Substitution Affects Myocardial Uptake and Clearance Kinetics of DMIPP Analogues in Fasted Rats,"

Goodman, M. M., Neff, K. H., Ambrose, K. R., and Knapp, F. F., Jr. "(E)-19-[^{125}I]Iodo-3,3-Dimethyl-18-Nonadecenoic Acid: A New Imaging Agent to Evaluate Regional Myocardial Fatty Acid Uptake,"

Knapp, F. F., Jr., Kohlen, S., Kolkmeier, J., Reske, S. N., Goodman, M. M., Ambrose, K. R., Cunningham, E. B., and Rice, D. E. "Polar Products are Formed from Methyl-Branched Fatty Acids by Isolated Langendorff Rat Hearts,"

Srivastava, P. C., Knapp, F. F., Jr., Dickson, D. R., and Allred, J. F. "Design and Synthesis of a New N-(p-[^{125}I]Iodophenyl)maleimide ([^{125}I]IPM) "Kit" for Labeling Antibodies with ^{131}I and ^{123}I,"

Srivastava, P. C., Knapp, F. F., Jr., Kabalka, G. W., and Varma, M. "Effects of Internal Trans Iodoalkene and Tellurium Position on the Heart Uptake and Retention of [^{125}I]Iodotelluraoctadecenoic Acid Analogues,"

Srivastava, P. C., and Knapp, F. F., Jr. "Synthesis of Radiobrominated Phosphonium Cations of High Myocardial Specificity for Potential PET Imaging,"

Reske, S. N., Knapp, F. F., Jr., Lange, L., Nitsch, J., Biersack, H.-J., Kropp, J., and Reichman, K. "Aberrations of Cardiac Free Fatty Acid Metabolism after Submaximal Exercise in CAD."

Visitors

Professor Hans J. Biersack, M.D., Chief of the Institute for Clinical and Experimental Nuclear Medicine in Bonn, West Germany, visited the Nuclear Medicine Group on April 16 and presented a seminar on clinical applications of radiolabeled antibodies for diagnosis and therapy. He also visited the nuclear medicine facilities at the Medical and Health Sciences Division of the Oak Ridge Associated Universities. In addition, a seminar was arranged at the Radiology Department at the University of Tennessee Hospital where Prof. Biersack discussed the development and applications of new agents for the evaluation of brain disorders by single photon tomography (SPECT).

Dr. Claude Brihaye, from the Cyclotron Research Center at the University of Liege, Belgium, joined the Nuclear Medicine Group for a 3 month summer sabbatical to continue collaborative studies with the Os-191/Ir-191m and W-188/Re-188 radionuclide generator systems. Dr. Gilbert Kirsch, from the Chemistry Department at the University of Metz, France, has also joined the Nuclear Medicine Group for a 6 month sabbatical to investigate the synthesis and metabolism of new fatty acid analogues under development by the Nuclear Medicine Program.

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