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## **Nuclear Medicine Program Progress Report for Quarter Ending December 31, 1989**

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT  
FOR QUARTER ENDING DECEMBER 31, 1989

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Environmental Research

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## SUMMARY

In this report the use of a simple colorimetric assay employing the bis-thiosemicarbazone (TSC) derivative of phenylglyoxal to evaluate the specific activity of spallation-produced copper-67 (Cu-67) samples is described. Four samples from the Los Alamos National Laboratory (LANL) and one sample from the Brookhaven National Laboratory (BNL) were analyzed and the results compared in a "blind study" with specific activity values obtained by isotope coupling plasma (ICP) analysis at the production sites. A good comparison was found, and these results indicate that the TSC approach is a simple, inexpensive, and rapid technique to determine the specific activity of spallation-produced Cu-67.

The synthesis, radioiodination, and evaluation of deiodination in rats in vivo of two new maleimide agents for antibody labeling is also described. Radioiodinated N-(4-[I-125]-iodophenyl)maleimide (IPM) has been shown in our earlier studies to be a useful new agent for radiolabeling of antibodies through linkage with protein thiol groups. Two new agents, N-[2-(4-hydroxyphenyl)ethyl]maleimide (hydroxy-PM) and N-[2-(aminophenyl)ethyl]maleimide (amino-PM) have now been prepared by treatment of the maleic anhydride with the appropriate ethylamine substrate followed by ring closure in the usual manner. Following radioiodination, the hydroxy-PM was evaluated in Fischer rats and showed minimal deiodination indicating the stability of this new agent to facile loss of radioiodide. The amino-PM will be used in future studies as a substrate for preparation of the corresponding triazine derivative which will be evaluated as a substrate for radioiodination.

Also during this period, Saed Mirzadeh, Ph.D., joined the Nuclear Medicine program from the NIH and will provide additional expertise on radionuclide production and radiochemistry. Several agents and radioisotopes were supplied to collaborators including copper-64, which was processed following production at the Missouri reactor and supplied to the Oak Ridge Associated Universities for PET studies. In addition, osmium-191 was supplied to collaborators in Finland where clinical studies have been initiated with the osmium-191/iridium-191m generator at three institutions. Radioiodinated fatty acid analogues were supplied to BNL and the Free University Hospital in Amsterdam for

collaborative studies involving an evaluation of the effects of cocaine intoxication on regional ischemia and fatty acid metabolism in an open-chest canine model (Amsterdam).

### COLORIMETRIC ASSAY OF SPALLATION-PRODUCED COPPER-67 USING BIS-THIOSEMICARBAZONE REAGENT

In the last report (ORNL/TM-11304), we described the development of a new method using the bis-(<sup>4</sup>N-methyl)thiosemicarbazone derivative (TSC) of phenylglyoxal (PG-TSC) as a convenient method to determine the concentration of copper(II) in spallation solutions. This method is based on the strong absorption at the 480-nm visible region of the Cu(II) PG-TSC complex. The absorption is linear up to about 40 ppm with a sensitivity of about 0.4 ppm, using a Carey 219 spectrophotometer. We have now used this method to analyze Cu-67 produced via spallation of zinc targets at the BNL (one sample) and LANL (four samples).

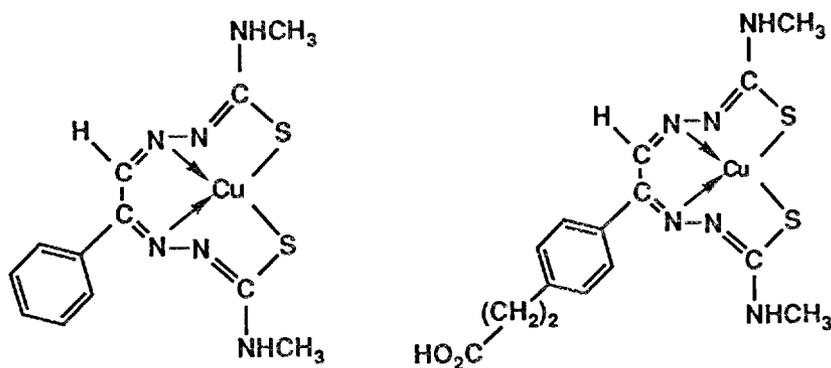


Figure 1. Structure of Cu(II) complex of PG=TSC.

The assay solution consists of an ethanol-HCl-acetate buffer mixture (1:1:1) in a total volume of 2.5 ml. The ethanol is required to solubilize the PG-TSC ligand and the

Cu(II) complex. As described earlier (ORNL/TM-11304), the use of HCl and sodium acetate buffer was found to eliminate any absorbance at 480 nm from the PG-TSC ligand as any Zn(II) PG-TSC complex, since small amounts of zinc are usually present in the processed Cu-67. This mixture also facilitates the direct use of an aliquot of the processed Cu-67, which is supplied in HCl solution. Thus, aliquots of the Cu-67 solution are pipetted directly into the ethanol-HCl-acetate buffer mixture containing the excess PG-TSC ligand, and the absorbance at 480 nm then determined after 15 min. The concentration (ppm) values are then interpolated from a standard curve.

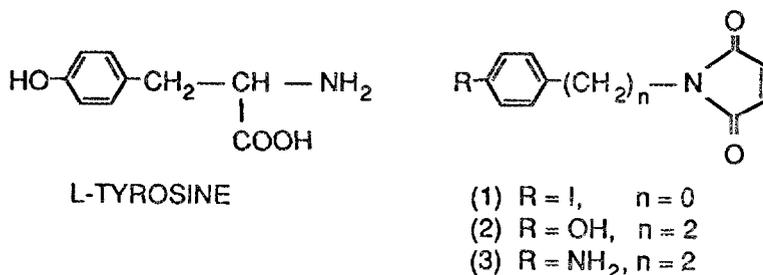
The results of the analysis of Cu-67 samples from both BNL and LANL are summarized in Table 1. The values obtained by the simple PG-TSC technique correspond very well with values obtained by isotope coupling plasma (ICP) analyses determined independently at the production sites. These results illustrate that the use of thiosemicarbazones is an inexpensive and simple approach to determine the specific activity of spallation-produced Cu-67.

Table 1. Analysis of spallation produced copper-67 solutions

Source	Copper-67 Solution		Specific Activity (mCi/ $\mu$ gm)	
	Date Processed at Production Site	Date Analyzed at ORNL	PG-TSC Colorimetric Analysis	ICP Analysis
Brookhaven National Laboratory (BNL), in 0.1 <u>N</u> HCl	5-30-89	7-26-89	7.7	6.0
Los Alamos National Laboratory (LANL), in 2 <u>N</u> HCl				
Sample 1	6-13-89	6-20-89	4.8	4.5
Sample 2	7-13-89	8-18-89	8.8	4.4
Sample 3	8-3-89	8-31-89	6.1	6.9
Sample 4	8-29-89	9-25-89	11.7	9.3

SYNTHESIS AND EVALUATION OF NEW MALEIMIDE ANALOGUES  
FOR EFFECTIVE RADIOIODINATION AND PROTEIN  
LABELING STUDIES

We have reported earlier the conceptual design, synthesis, and evaluation of N-(4-[I-125]iodophenyl)maleimide (1, IPM) as a new antibody-sulphydryl (SH) labeling agent. We have now synthesized two new maleimide analogues, N-[2-(4-hydroxyphenyl)ethyl]maleimide (2, hydroxy-PM) and N-[2-(aminophenyl)ethyl]maleimide (3, amino-IPM), as substrates for high specific activity radioiodination for evaluation as potential radioimmunoconjugates. It is anticipated that such agents may provide radioiodination sites (ortho-to-hydroxy group) similar to tyrosine but may not be the substrates for deiodinases of thyroid hormones.

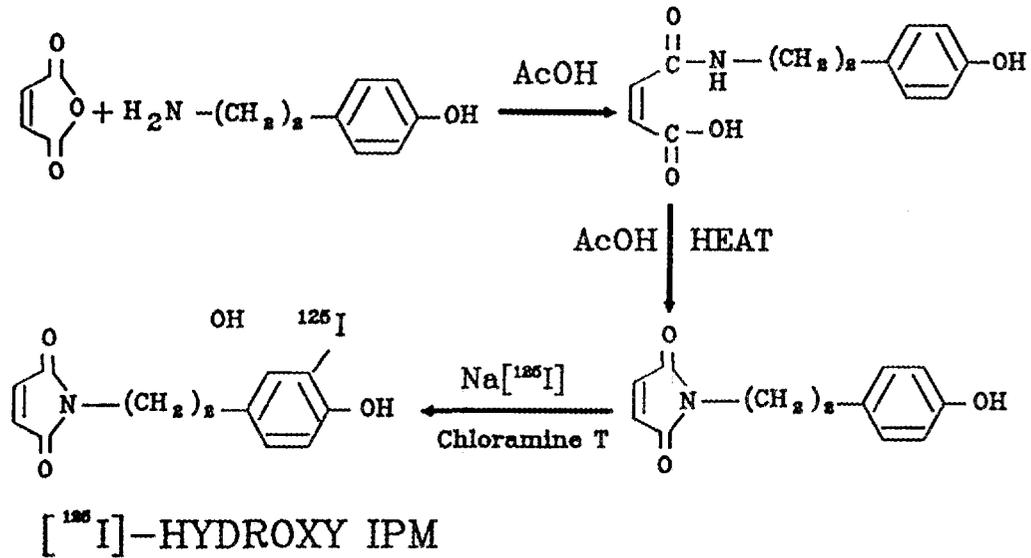


Scheme 1

Radioactive iodine can be incorporated into antigen-specific antibodies either by direct iodination or by immunoconjugation. Direct radioiodination requires exposure of the antibody to electrophilic conditions and allows ready incorporation of iodine into the phenyl moiety of the tyrosine residues. The antibodies, thus radiolabeled, undergo *in vivo* deiodination probably due by deiodinases of thyroid hormones structurally similar to radioiodinated tyrosine residues. Our approach for radioiodination of antibodies is designed to synthesize *in vivo* stable radiolabeled reagents which then can be readily attached to an antibody with retention of its immunoreactivity.

The precursor, hydroxy-PM (2), was prepared following steps shown in Scheme 1. Treatment of (2) with Na<sup>[125]I</sup> and chloramine T in aqueous tetrahydrofuran gave 60% incorporation of radioactive iodine at an ortho position to the hydroxy group in the phenyl

ring of (2). The [ $^{125}\text{I}$ ]-hydroxy IMP was isolated after purification by silica gel column chromatography.



Scheme 2.

[ $^{125}\text{I}$ ]-hydroxy-IPM was formulated in normal saline and injected intravenously into female Fischer rats (body weight, 142-152 grams). The uptake of iodine-125 in the thyroid and other tissues after 5 min, 1 h, 4 h, and 24 h intervals was determined. The data are expressed as percent injected dose/thyroid (Figure 2) and percent injected dose per gram of tissue (Figure 3) (mean of 5 animals/time point). The data show that the thyroid uptake of radioactivity reaches a plateau after 4 h indicating *in vivo* stability of [ $^{125}\text{I}$ ]-hydroxy-IPM.

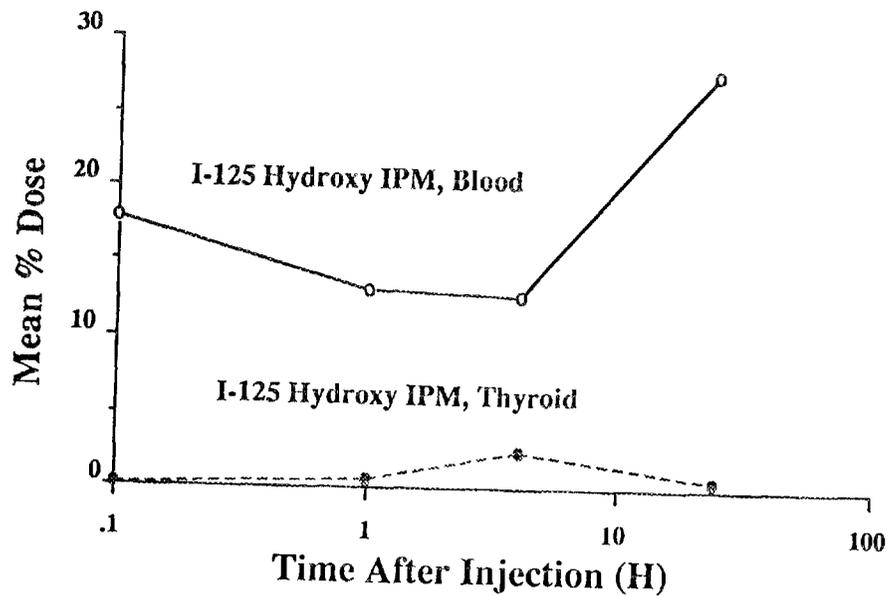


Figure 2. Thyroid and blood concentration of I-125 hydroxy-IPM in rats.

These preliminary studies demonstrate that the new radiolabeled agent, [ $^{125}\text{I}$ ]-hydroxy-IPM, can be readily prepared in high specific activity from the corresponding hydroxyphenyl analogue. The agent shows *in vivo* stability and potential for evaluation as a radioimmunoconjugate for radiolabeling antibodies.

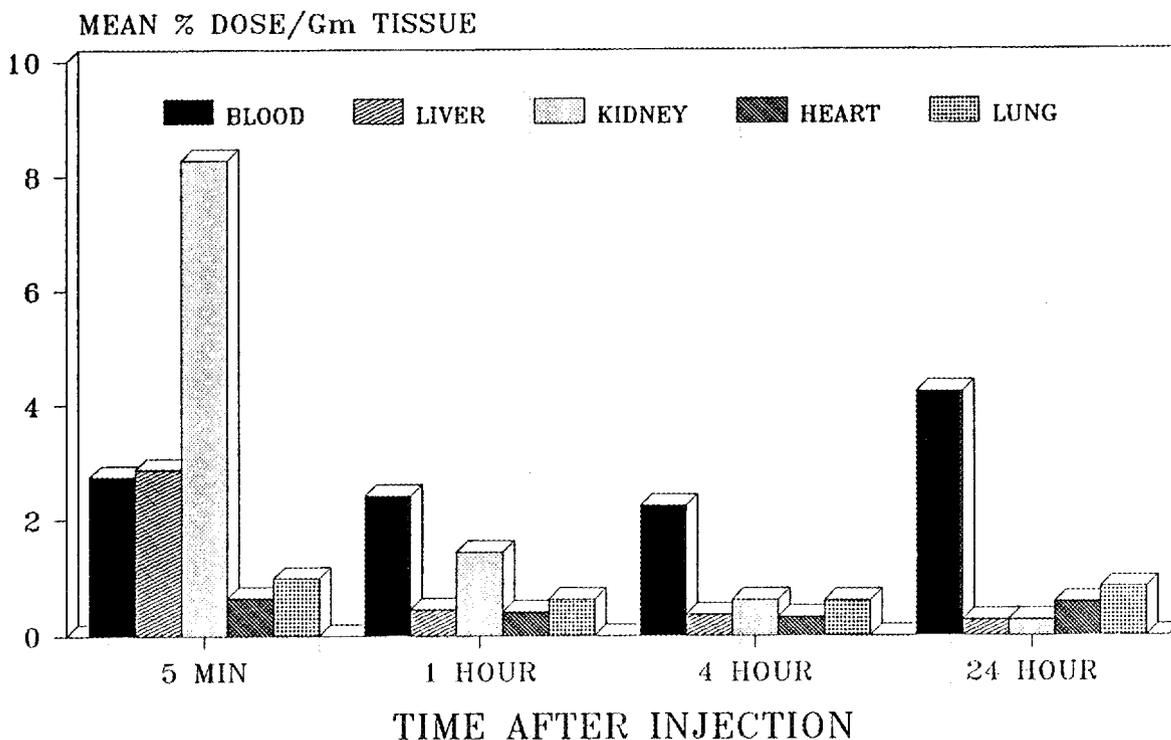


Figure 3. Tissue distribution of I-125 hydroxy-IPM in rats.

#### AGENTS FOR MEDICAL COOPERATIVES

Two shipments of [I-131]IPPA were made to the Free University, Amsterdam, the Netherlands (Dr. F. Visser). This collaborative program involves evaluation of the cardiac metabolism of radioiodinated fatty acid analogues in canine models. In addition, the Free University also received one shipment of [I-125]IPPA, as did BNL, Upton, New York (Dr. P. Som).

One shipment of [Os-191] potassium perosmate was made to Espoo, Finland (Dr. J. Hiltunen), for fabrication of osmium-191/iridium-191m generators for clinical use at two hospitals in Helsinki. Two shipments of Cu-64 were produced by the (n,p) reaction at

the Missouri University Research Reactor (MURR) and sent to the Oak Ridge Associated Universities, Oak Ridge, TN (Dr. J. Crook).

#### AGENTS PREPARED FOR COST-RECOVERY THROUGH THE ORNL ISOTOPES DISTRIBUTION OFFICE

On a cost recovery basis, one shipment each of [Pt-195m]-*cis*-DDP was made to University of New York, NY (Dr. T. Reich); University of Toronto, Toronto, Canada; and, University of California, San Diego, CA.

#### OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

##### New Staff

Saed Mirzadch, Ph.D., joined the Nuclear Medicine Program as a staff member on November 1, 1989, and will provide additional expertise on radionuclide production and radiochemistry. He was previously a member of the Radiation Oncology Branch of the National Institutes of Health (NIH) where he worked for two years on the development of methods for preparation of radiolabeled antibodies. He obtained his doctoral degree in physical chemistry (radiochemistry) from the University of New Mexico in 1978. Prior to his work at NIH he was a scientist in the Medical Department at Brookhaven National Laboratory where he developed radioisotope production methods and played a key role in the design and construction of the Brookhaven Linac Isotope Producer (BLIP II).

##### Publications

Biersack, H.-J., Knapp, F. F., Jr., and Winkler, C. "Perspectives in Nuclear Medicine History — Three Decades of Scientific Liaison Between Oak Ridge and Bonn," in, Newsline, Journal of Nuclear Medicine, 30(11): 1765-1767 (1989).

Srivastava, P. C., Allred, J. F., and Buchsbaum, D. J. "Radioiodinated Iodophenyl Maleimide: A Potential Radioimmunoconjugate with Low In Vivo Deiodination," *NucCompact — European/American Communications in Nuclear Medicine*, 5:145-149 (1989).

Visser, F. C., Duwel, C. M. B., Roos, J. P., Knapp, F. F., Jr., and van der Vusse, G. J. "Biochemistry of Radioiodinated Free Fatty Acids," Invited paper, *Molecular and Cellular Biochemistry*, 88:185-190 (1989).

A postdoctoral fellow in the Nuclear Medicine Group, A. Hasan, has recently published a paper describing work performed during his doctoral work at the Central Drug Research Institute in Lucknow, India.

Hasan, A., Tripathi, R. P., Pratap, R., Bhakum, D. S., Pal, P., Mishra, A., Guru, P. Y., and Katiyar, J. C. "Studies on Nucleosides: Part XX — Synthesis and Antileishmanial Activity of 4,6-Substituted Pyrazolo[3,4-d]pyridine Nucleosides," *Ind. J. Chem.*, 28B: 403-409 (1989).

#### Meetings and Presentations

Members of the Nuclear Medicine Group co-authored an abstract presented at the European Association of Nuclear Medicine Congress held in Strasbourg, France, on August 28 - September 1, 1989, describing the discordance between regional myocardial blood flow and modified fatty acid uptake in an isolated swine heart model. These studies were conducted through a Medical Cooperative Program in conjunction with the Universities of Bonn and Aachen, West Germany.

Reske, S. N., Knapp, F. F., Jr., Nitsch, J., Kohlen, S., and Kolkmeier, S. "3,3-Dimethyl (p-I-123-phenyl)pentadecanoic Acid (DMIPP) Uptake in Excess to rMBF in Reperfused Myocardium," *European Nuclear Medicine Congress, Strasbourg, France, August 28 - September 1, 1989; Eur. J. Nucl. Med.*, 15:398 (1989).

Members of the Nuclear Medicine Program co-authored a poster presentation at the recent 62 Scientific Sessions of the American Heart Association (AHA) held on November 13-16, 1989, in New Orleans, Louisiana.

Martin, S. E., Aaron, A., Knapp, F. F., Jr., Gors, B., Dunn, D., Eisner, R. L., and Patterson, R. E. "Does the Clearance Rate of an Iodine-123 Fatty Acid Distinguish Normal Versus 'Stunned' Myocardium in Dogs?"

While at the AHA Meeting, F. F. Knapp, Jr., met with Gary Murray, M.D., and colleagues at the Houma Heart Clinic in Houma, Louisiana, and staff of Syncor, Inc., a radiopharmaceutical distribution firm, to discuss and coordinate the expected initiation of clinical trials with the ORNL osmium-191/iridium-191m generator system. It is hoped that the iridium-191m studies will be initiated in January 1990, pending "tacit" approval of the Investigational New Drug Application (IND) by the Food and Drug Administration (FDA). He also provided guidance on the preparation of iodine-123-labeled fatty acids for multi-crystal camera clinical studies of myocardial metabolism in patients, since Dr. Murray has FDA approval for these patient investigations.

D. W. McPherson presented an invited lecture on December 7, 1989, entitled "Specialized Aspects of Radiolabeling – Copper-64 Labeled Antibodies" at the recent training course on Radiolabeling Monoclonal Antibodies at the Medical Division of the Oak Ridge Associated Universities.

Two papers were presented by Saed Mirzadeh at the recent "Pacifichem Conference" held in Honolulu, Hawaii, on December 17-22, 1989. The conference was a joint meeting between the chemical societies of America (ACS), Japan, and Canada.

Knapp, F. F., Jr. and Mirzadeh, S. "Reactor-Produced Radioisotopes for Nuclear Medicine Applications."

Mirzadeh, S., McMurry, T., Gansow, O. A., and Chu, Y. Y. "Production of Gallium-66, A Positron-Emitting Nuclide for Radioimmunotherapy."

#### Investigational New Drug (IND) Application

An IND application for the osmium-191/iridium-191m generator system developed and patented at ORNL has been submitted to the FDA by Gary Murray, M.D., from the Houma Heart Institute in Houma, Louisiana. F. F. Knapp, Jr., is co-investigator on the IND with Professor N. Schad, M.D., a nuclear medicine specialist from Passau, West Germany. Professor Schad has developed special rapid-processing computer programs for analysis of the camera data. The goal of these studies is to use sequential iridium-191m first-pass studies to evaluate ventricular performance in conjunction with simultaneous iodine-123-labeled fatty acids for evaluation of metabolism with a multi-crystal camera system. Such unique studies will provide an evaluation in the same setting of temporal changes (changes in time) rather than spatial resolution (resolution in space). For the initial stages of this collaborative project, generators will be fabricated at ORNL and supplied as a radiochemical to Syncor, Inc., in New Orleans for testing and approval for human use at Houma. When approval is received from the FDA, these patient studies will represent the first use of iridium-191m from this generator system for human studies in the United States.

Clinical studies with iridium-191m from the ORNL osmium-191/iridium-191m have now been initiated at two institutions in Finland. These collaborative projects are being coordinated in conjunction with Jukka Hiltunen at the Reactor Laboratory in Espoo, Finland. Groups at the Department of Diagnostic Radiology at the Helsinki University Central Hospital and at Kupio University Central Hospital have completed volunteer studies and will now initiate patient testing with the generator system. This collaborative program is supported through a grant from the National Cancer Institute of the National Institutes of Health. Since shut-down of the Oak Ridge and Brookhaven reactors, the osmium-191 is now produced at the Missouri University Research Reactor, processed at ORNL, and then shipped to Espoo for further processing and generator fabrication.



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