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**Nuclear Medicine Program
Progress Report for Quarter
Ending December 31, 1996**

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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT
FOR QUARTER ENDING December 31, 1996

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SUMMARY

In this report we describe the use of an effective method for concentration of the rhenium-188 bolus and the results of the first Phase I clinical studies for bone pain palliation with rhenium-188 obtained from our tungsten-188/rhenium-188 generator. Initial studies with therapeutic levels of Re-188-HEDP at the Clinic for Nuclear Medicine at the University of Bonn, Germany, have demonstrated the expected good metastatic uptake of Re-188-HEDP in four patients who presented with skeletal metastases from disseminated prostatic cancer with good pain palliation and minimal marrow suppression. In addition, skeletal metastatic targeting of tracer doses of Re-188(V)-DMSA has been evaluated in several patients with metastases from prostatic cancer at the Department of Nuclear Medicine at the Canterbury and Kent Hospital in Canterbury, England. Since the generator has a useful shelf-life of several months, cost-effective ready availability of Re-188 from the ORNL alumina-based tungsten-188/rhenium-188 generator system is an important advantage in favor of the possible broad clinical use of Re-188-HEDP, in comparison with Re-186-HEDP.

In this report we also describe further studies with the E-(R,R)-IQNP ligand developed in the ORNL Nuclear Medicine Program as a potential imaging agent for detection of changes which may occur in the cerebral muscarinic-cholinergic receptors (mAChR) in Alzheimer's and other diseases. The results of the first *ex vivo* autoradiographic studies (ARG) using human brain tissue binding studies obtained in conjunction with the Karolinska Institute in Stockholm, Sweden, with the iodine-125-labeled E-(R,R)-IQNP ligand have demonstrated high binding to M₁ subtype receptor-rich brain regions and receptor uptake was completely blocked by co-administration of radioiodinated E-(R,R)-IQNP with biperiden, a selective M₁ muscarinic antagonist. The first primate imaging studies with iodine-123-labeled E-(R,R)-IQNP in a Cynomolgus monkey with both planar and SPECT imaging have also demonstrated high uptake in the neocortex and other receptor-rich regions. In an analogous study in collaboration with the Service Hospital Frederic Joliot, Orsay France, a brominated analogue of IQNP ("BrQNP) was evaluated using rats and Papio Papio baboons. It was demonstrated that the receptor uptake and localization in rats of the various

stereoisomers of bromine-76-labeled BrQNP was similar to that observed for the iodinated analogues. In PET studies, E- And Z-(R,R)-BrQNP demonstrated important specific binding to mAChR *in vivo*. In addition, Z-(R,R)-BrQNP showed higher specific binding in M₂ rich structures as compared to E-(R,R)-BrQNP. These combined studies will serve as a prelude for initial Phase 1 clinical human trials expected to begin in 1997.

Also 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. Weinberger, M.D.), Columbia University, New York, and the Department of Nuclear Medicine (J. Kropp, M.D.) at the University Hospital, Dresden, Germany. 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 a tungsten-188/rhenium-188 generator was sold to CIS/Bio International for Re-188-labeled antibody research which is being conducted at the University of Nantes, France (Prof. Chatal, M.D.).

Initial Clinical Studies with Rhenium-188-Labeled Agents Using the ORNL Tungsten-188/Rhenium-188 Generator

The treatment of painful skeletal metastases is a common clinical problem and the use of therapeutic radioisotopes which localize at metastatic sites has been found to be an effective method for treatment of pain, especially for multiple sites for which the use of external beam irradiation is impractical. The palliative treatment of bone pain associated with metastases to the skeleton is thus an important application which has many advantages over traditional use of analgesics and external radiation. There are currently several metastatic-targeted agents radiolabeled with various therapeutic radioisotopes which are in various stages of clinical investigation (Table 1). Since neutron-rich radioisotopes are produced in research reactors and often decay by emission of β -particles, most radioisotopes used for bone pain palliation are reactor-produced. Key examples produced by single neutron capture of enriched targets include rhenium-186 and samarium-153. In addition, generator systems which provide therapeutic daughter radioisotopes from the decay of reactor-produced parent radioisotopes are also of interest. Tin-117m is an example of a reactor-produced radioisotope which decays with the emission of low energy conversion electrons rather than by β -decay.

One important example is rhenium-188, available from generators via decay of reactor-produced tungsten-188. Since rhenium-188 is readily available from the tungsten-188/rhenium-188 generator, interest has recently developed for use of these therapeutic radioisotopes as an alternative to rhenium-186 for bone pain treatment. Although the 16.9 hour half-life is shorter than the 90 hour half-life of rhenium-186, the shorter half-life may offer several important advantages which include the opportunity to "titrate" the dose required for maximal palliative action by fractional administration with monitoring of marrow suppression. In this manner the dose can be optimized. In addition, the short half-life of rhenium-188 may provide an important opportunity for marrow ablation using agents such as rhenium-188-HEDP, prior to stem cell rescue, which is impractical with long-lived beta-emitting radionuclides.

Table 1. Examples of Radioactive Agents Used for Treatment of Bone Pain from Skeletal Metastasis.

Agent/Radionuclide	Availability	Comment
Phosphorus-32 Phosphate	Available in most countries	In use for over 20 years; no gamma photons for imaging
Strontium-89 "Metastron [®] "	Commercially available in the U.S. and Europe (Amersham International)	In use for over 20 years; Expensive; no gamma photons for imaging
Rhenium-186 "HEDP"	Phase III Studies in U.S. and Europe; Available in Europe by physician prescription (Mallinckrodt Medical)	Use of reactor-produced Re-186; Expected to be expensive; 136 keV for imaging
Samarium-153 "EDTMP"	Phase II-III Studies Cytogen/Dow Chemical	Under development using reactor-produced samarium- 153; 103 keV photon for imaging
Rhenium-188 "HEDP"	Phase I Studies, Germany and Uruguay (Under physician-sponsored approval in association with ORNL)	Rhenium-188 available from tungsten-188/rhenium-188 generator; long shelf-life; 155 keV photon for imaging; Expected to be cost effective
Rhenium-188 "DMSA"	Phase I Studies, England (Under physician-sponsored approval in association with ORNL)	Uses commercially available approved Tc-99m(III)-DMSA "kit"
Tin-117m-DTPA	Phase III Studies (Diatide, Inc. and Golden Pharmaceuticals)	Emission of low energy conversion electrons; no β^- ; Low reactor production yield

HEDP = Hydroxyethylidenediphosphonate

EDTMP = Ethylenediaminetrimethylenephosphonate

DMSA = Dimercaptosuccinic Acid

DTPA = Diaminetriethylenepentaacetic Acid

Since there is now broad interest in the use of rhenium-188-labeled therapeutic agents for treatment of bone pain we have optimized use of our generator system and established collaborative clinical programs for the evaluation of new agents. The generator which we have developed and optimized at ORNL is a chromatographic system which uses alumina as the adsorbent (Callahan, et al., 1992; Knapp, et al., 1992, 1994a, 1995, 1996; Kamioki, et al., 1994). Since one of the major issues facing the health care industry is the reduction of costs, an evaluation of the most cost-effective agents for treatment of bone pain is an important goal. A major important advantage for use of rhenium-188 is the inexpensive, ready availability from the generator which has a very long useful shelf-life. Although in-house use for providing rhenium-188 on a daily basis is a major advantage, the regulatory issues associated with in-house preparation of the Re-188-labeled agents add another dimension compared to the commercial availability of therapeutic agents such as Re-186-HEDP (Verdera, et al., 1996; Gohlke, et al., 1996a). Another advantage is the emission of the 155 keV gamma photon for imaging. There are several rhenium-188-labeled agents for bone palliation which are currently under investigation (Table 3). Although the β^- from decay of rhenium-188 has a high energy (2.1 MeV) similar to yttrium-90, the short 16.9 hour half-life may compensate for this high energy. The short half-life of rhenium-188 may be a distinct advantage, since the effectiveness in reducing bone pain may be possible by "titration" with a fractionated dose regimen.

Table 2. Characteristics of the ORNL Clinical-Scale Alumina-Based Tungsten-188/
Rhenium-188 Generator System.*

Parameter	Typical Values
Clinical-Scale - mCi Tungsten-188 Loaded	500 mCi
Generator Column Adsorbant	5-6 gm Aluminum Oxide
Generator Column Dimensions (length x i.d.)	3 cm x 1.6 cm
Rhenium-188 Elution Yields (% of available)	75-85 %/bolus
Equilibrium Rhenium-188 Elution Yields (mCi) - Initial Values Before Tungsten-188 Decay	375-425 mCi/bolus
Daily Rhenium-188 Elution Yields (mCi) - 24 Hours Between Elutions (65% available)	245-275 mCi/bolus
Tungsten-188 Parent Breakthrough	$< 10^{-6}$ /bolus
Other Radionuclide Impurities **	Iridium-192 $< 5 \mu\text{Ci/bolus}$ Osmium-191 $< 1 \mu\text{Ci/bolus}$
Initial Bolus Volume	12-15 mL
Concentrated Bolus Volume - After Tandem Cation/Anion Column Elution	< 1 mL 0.9% NaCl
Shelf-life	Unlimited - at least 6-8 months

* Data are based on experience with > twenty 500 mCi generators.

** Iridium-192 and osmium-191 are formed by nuclear reactions during the irradiation of enriched tungsten-186 and are not formed by activation of impurities present in the target material. Impurities are essentially only detected in the initial eluant and are removed by subsequent passage through the cation-exchange /anion-exchange column system.

We have demonstrated that large, clinical-scale generators loaded with levels of tungsten-188 as high as one Curie (Knapp, *et al.*, unpublished data), which still provide reproducibly high rhenium-188 yields of 75-85 %/bolus and low tungsten-188 parent breakthrough ($< 10^{-6}$) for periods of several months. These studies have demonstrated that the costs of rhenium-188 will be very low on a bolus or unit dose basis. The bolus volume from a typical 500 mCi alumina-type tungsten-188/rhenium-188 generator is about 10-12 ml. Although the void volume can be discarded and the principal bolus peak collected, the initially high specific volume (30-40 mCi/ml) of eluant of course decreases with time as the tungsten-188 (69 day half-life) decays. Since the long useful shelf-life is an important aspect for use of this generator system, the availability of simple, efficient methods for concentration of the generator eluant is very important. The technical problem involves development of methods required for separation of very low microscopic levels of perrhenate anions in the generator eluant from large macroscopic levels of chloride anions. One approach "traps" the perrhenate anion on an anion exchange resin in nitrate form, but perrhenate is difficult to remove from this column, and nitric acid is the only eluate which we have found to be effective (Knapp, *et al.*, 1994, 1995).

A more recent approach developed by Blower and associates (Blower, *et al.*, 1993; Singh, *et al.*, 1993) is based on the unique use of initial cation columns containing silver ions. In this manner, the high levels of chloride ion in the generator eluant solution are selectively trapped as insoluble silver chloride. The solution eluted from the silver-cation column contains only perrhenate as the anion which is then trapped by passage through the quaternary ammonium anion column (Figures 1 and 2). This system represents a simple disposable concentration unit. Commercially available columns can be used and we are currently using the "AG Plus" cartridges available from Alltech as the cation column, and the Waters "AccellV™ Light QMA SepPak®" cartridge for the anion trapping column. The concentration capacity is essentially unlimited, since the silver cation columns have a capacity for about 5 ml of 0.9% saline solution (about 2 milliequivalents), and can be "stacked" based upon volume requirements. The QMA Light columns have a total void volume, including Luer connectors, of about 0.8 mL, so that the total bolus volume of perrhenate solutions can be readily concentrated to less than 1 mL by elution with saline.

Phase I clinical studies with Re-188-HEDP are in progress in collaboration at several institutions (Table 3). The first patient studies with Re-188-HEDP have recently been initiated at the Clinic for Nuclear Medicine at the University of Bonn, Germany (Palmedo, et al., unpublished data), and initial studies exhibit the expected high skeletal metastatic localization with successful pain palliation, suggesting that broader multicenter evaluation of this agent should be pursued.

Table 3. Examples of Rhenium-188-Labeled Agents Under Evaluation for Bone Pain Palliation.

Rhenium-188 Agent	Clinical Status	Collaborating Institution (s)	Comment
HEDP	Phase I	Universities of Bonn and Dresden, Germany ; Italia Hospital, Montevideo, Uruguay	Analogue of Re-186 HEDP
Re(V)-DMSA	Phase I	Canterbury and Kent Hospital, England	Use of Tc(III)-DMSA "Kit", No Additives Required
MDP	Pre-clinical	Catholic University Hospital, Rome, Italy, In Conjunction with Sorin Biomedica S.P.	Protocol in Preparation

Because of the importance of developing new cost-effective alternatives for the treatment of bone pain, we have optimized the use of the tungsten-188/rhenium-188 generator and developed the preparation of Re-188 agents for treatment of bone pain. The availability of the ORNL tungsten-188/rhenium-188 generator provides a readily available supply of an inexpensive and important therapeutic radioisotope for a variety of therapeutic applications, including cancer therapy, arthritis therapy, intraarterial brachytherapy for inhibition of restenosis following coronary angioplasty, and bone pain palliation. Since clinical-scale (> 500 mCi W-188) generators have a useful shelf-life of at least several months, the use of Re-188 as an attractive and cost-effective alternative to the use of Re-186-HEDP and other therapeutic β^- -emitting radioisotopes. A key requirement for the routine preparation of rhenium-188-labeled radiopharmaceuticals for clinical

use is the availability of simple and efficient methods for concentration of the Re-188 bolus from the W-188/Re-188 generator. Since the volume of the Re-188 bolus obtained from the typical clinical-scale (500-1000 mCi) ORNL alumina-based clinical-scale generator (5-6 gm alumina) is 10-12 mL, the specific volume (mCi/mL) is often too low for the "kit" labeling of tissue-specific radiopharmaceuticals, especially after 2-4 months (1-2 half-lives) of generator use. For this reason, the development of simple and efficient methods for bolus concentration have been pursued. The most effective strategy for concentration involves "trapping" of the Re-188 perrhenate anion on an anion-trapping (i.e. cation) column from which it then be retrieved by elution with saline. Since physiological saline (0.9 % NaCl) is the traditional generator eluant, the concentration of chloride anions far exceeds the concentration of the carrier-free perrhenate anions. Use of ion-exchange columns for eluant concentration thus requires specific removal of the chloride anions prior to the specific trapping of perrhenate.

One recently developed method (Singh, et al., 1993; Blower, et al., 1995) for perrhenate concentration involves the use of a "tandem" cation-anion column system. The generator eluant is initially passed through a cation-exchange column containing silver cations (Figure 1) in which the chloride anions are effectively trapped by precipitation as insoluble silver chloride. Readily available disposable columns for this purpose are available as the Ag Plus (Analtech, Inc.). The resulting eluant which passes through the Ag-cation column has the same volume, but contains only the perrhenate anions, which are then subsequently "trapped" on an anion trapping column such as the Millipore "QMA" SepPak (Figure 2). Elution of the SepPak with physiological saline then provides a concentrated (< 1 mL) solution of sodium perrhenate. The advantages of this system are its low expense and disposability. It also rapidly provides highly concentrated solutions of Re-188 Na perrhenate in a very simple "in-line" manner.

Figure 1. Schematic diagram of the elution and concentration system for the alumina-based tungsten-188/rhenium-188 generator system.

Figure 2. Detailed schematic of the cation/anion tandem concentration system to provide concentrated solutions (> 500 mCi/mL) of rhenium-188.

In conjunction with collaborators at the Clinic for Nuclear Medicine (Drs. Palmedo, Guhlke, and Biersack, *et al.*) at the University of Bonn, Germany, and at the Department of Nuclear Medicine (Drs. P. J. Blower and M. O'Doherty, *et al.*) two agents which have been evaluated are Re-188-HEDP and Re-188(V)-DMSA (Figure 3). Preparation of Re-188-HEDP using well established methods provides an alternative to Re-186-HEDP. Concentration of the Re-188 bolus followed by reductive coupling with HEDP provides the Re-188-HEDP in 60-70% yield. Initial studies (35 mCi Re-188-HEDP) in four patients presenting with skeletal metastases resulting from prostatic cancer conducted at the Clinic for Nuclear Medicine at the University of Bonn have demonstrated the expected high metastatic uptake of Re-188-HEDP (Figure 4) with good palliation and only minimal marrow suppression.

Figure 3. Chemical structures of Re-HEDP and Re(V)-DMSA isomers.

Figure 4. Example of the metastatic targeting of rhenium-188-HEDP in a 65 year old patient with primary prostatic cancer (Courtesy of H. Palmedo, M.D. and H.-J. Biersack, M.D., Clinic for Nuclear Medicine, University of Bonn, Germany).

As an alternative to the use Re-188-HEDP for bone pain palliation, the use of Re-188(V)-DMSA has also been recently explored in a collaborative program using rhenium-188 from the ORNL alumina-based tungsten-188/rhenium-188 generator (Blower, et al., 1996). Although a comparison of the relative metastatic uptake and palliative properties of Re-188-HEDP and Re-188(V)DMSA have not yet been pursued, initial targeting tracer studies with the Re-188 DMSA agent in patients with disseminated prostatic cancer at the Kent and Canterbury Hospital in England have demonstrated targeting of this agent to skeletal metastases (Figure 5). One advantage of the possible therapeutic use of this agent is that the commercially available "kit" used for preparation of the renal Tc-99m(III)-DMSA renal imaging is used (Blower, et al., 1996).

Figure 5. Example of the metastatic targeting of an 84 year patient with disseminated prostatic cancer (Courtesy of M. O'Doherty, M.D. and P. J. Blower, Ph.D., Kent and Canterbury Hospital, Canterbury, England).

Our studies have thus demonstrated that large, > 1 Curie clinical-scale tungsten-188/rhenium-188 generators perform well and have an extended useful shelf-life and that high specific volume solutions of rhenium-188 can be readily obtained by simple ion-exchange column concentration methods. The initial clinical trials described here in association with collaborators are demonstrating that the various rhenium-188-labeled therapeutic agents can be easily prepared in-house and may represent inexpensive alternatives to many other therapeutic radioisotopes that are currently under clinical evaluation.

***In Vivo* Metabolic and Animal Imaging Studies With [I-123]-E-(R,R)-IQNP
and [Br-76]-E- and Z-(R,R)-BrQNP**

The various stereoisomers of 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -(1-iodo-1-propen-3-yl)- α -phenylacetate (IQNP, **1**) have been developed as ligands for the imaging of the muscarinic acetylcholinergic (mAChR) complex by Single Photon Emission Computed Tomography (SPECT). *In vitro* studies utilizing cloned muscarinic subtypes (m1, m2) have shown that the stereoisomers of IQNP display different binding affinity for the various subtypes. The E-(R,R)-IQNP isomer demonstrates a high binding affinity and selectivity for the m1 subtype while Z-(R,R)-IQNP displays high binding affinity for m1 and m2 mAChR subtypes. *In vivo* studies in female rats confirmed the *in vitro* binding assays with E-(R,R)-IQNP displaying high uptake and long retention in regions of the brain which contain high concentrations of the m1 subtype and Z-(R,R)-IQNP binding to regions containing both the m1 and m2 subtypes of the mAChR (Rayeq, *et al.*, 1996). *In vivo* metabolic studies with E-(R,R)-IQNP demonstrated that the unmetabolized ligand was the only radioactive species observed binding to the receptor complex in the brain.

The next stage of our development of these agents has involved a collaborative effort between our ORNL Nuclear Medicine Group and the Department of Clinical Neuroscience at the Karolinska Hospital in Stockholm, Sweden. Initial *in vivo* SPECT imaging and metabolic studies were performed with iodine-123-E-(R,R)-IQNP using a Cynomolgus Monkey. In addition, *ex vivo* postmortem autoradiographic studies with iodine-125-E-(R,R)-IQNP were performed utilizing human brains obtained from clinical autopsy and whole hemisphere horizontal (cantomeatal) sections of 100 μ m were taken from different levels from vertex. The binding of E-(R,R)-IQNP to the m1 mAChR subtype was studied by simultaneous incubation with the m1 selective antagonist biperiden. The sections were incubated for 60 min, exposed to film for 2-5 days, developed, analyzed and color coded. In these studies E-(R,R)-IQNP showed high binding in the neocortex and striatum, regions containing a high density of the m1 subtype (Figure 6). Addition of biperiden decreased the binding significantly in the neocortex. These results are in agreement with the previous *in vivo* studies performed in rats and demonstrate that E-(R,R)-IQNP has potential to be utilized for *in vivo* tomographic studies for imaging the m1 mAChR subtype.

Control

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Figure 6. Autoradiographic studies of human brain slices showing the binding (dark areas) of iodine-125-E-(R,R)-IQNP in the absence and presence of biperiden (Courtesy of K. Bergstorm and C. Halldin).

For the SPECT imaging study, a three-headed SPECT camera system with a low energy collimator affording a spatial resolution of about 7 mm at 10 cm was utilized. SPECT scan was performed between 70-90 min after injection. Planar dynamic imaging were performed using one detector head of the gamma camera up to 60 min after injection and 170-210 min after injection. A male Cynomolgus monkey (3-4 kg) was injected with 41 Mbq of E-(R,R)-IQNP as a bolus into the sural vein. The specific activity of iodine-123-labeled E-(R,R)-IQNP was greater than 70 Gbq/mmol. A head fixation system was used to maintain the position of the head parallel to the plane of the cantomeatal line. The baseline and displacement studies with biperiden (0.5 mg/kg) were performed on the same monkey. The displacement study was performed at 180 min after injection of E-(R,R)-IQNP. Blood samples (2 mL) were obtained from the Cynomolgus monkey at 4.5, 16, 30, 45, 59, 120, 173, 182 and 240 min after injection of E-(R,R)-IQNP. Plasma was separated from the whole blood by centrifuging for 1 min. After centrifugation, the plasma was removed and mixed with acetonitrile. The resultant solution was centrifuged and the supernatant was removed and analyzed by gradient HPLC (Waters μ Bondapak C18 column eluted with a mixture of acetonitrile in phosphoric acid (10 mM) from 25% acetonitrile to 60% in 5.5 min, back to 25% in one min and stop at 7.5 min with a flow of 6 mL/min). The SPECT study in the

Cynomolgus monkey demonstrated a high brain uptake of E-(R,R)-IQNP (Figure 7). The whole brain activity curve reached a plateau at 40-50 min post-injection. E-(R,R)-IQNP showed high binding in the frontal cortex and the temporal cortex 80 min post-injection. However, there was no marked displacement of the radioactivity after the injection of biperiden. One possibility for this result may be it is difficult to detect a weak displacement in the m1 subtype mAChR regions with planar imaging in which whole brain activity is visualized.

Figure 7. Cross-sectional SPECT images obtained in a Cynomolgus Monkey following intravenous administration of iodine-123-E-(R,R)-IQNP (Courtesy of K. Bergstorm and C. Halldin).

In gradient HPLC analysis of the monkey plasma after injection of E-(R,R)-IQNP, the amount of unchanged E-(R,R)-IQNP was less than 2% in the plasma 10 min post-injection. However, a major metabolite in the plasma was observed and was more lipophilic than the parent compound based on gradient HPLC analysis. This lipophilic metabolite was observed to have the same HPLC retention time as α -hydroxy- α -(1-iodo-1-propen-3-yl)- α -phenylacetic acid (IQNP acid), which we prepared by hydrolysis of the corresponding quinuclidinyl ester. A biodistribution study with iodine-125-IQNP acid in rats demonstrated that this metabolite did not cross the blood-brain-barrier. In

with iodine-125-IQNP acid in rats demonstrated that this metabolite did not cross the blood-brain-barrier. In our detailed studies with rats, this metabolite was not detected in the plasma indicating this metabolic pathway for E-(R,R)-IQNP may be species specific and therefore may not be a major metabolic pathway in humans.

We also collaborated with the Service Hospital Frederic Joliot, Orsay, France, to evaluate IQNP analogues for use in PET studies of mAChR, the brominated analogue of IQNP ("BrQNP", 2). Since bromine behaves in a similar manner as iodine, analogous labeling methods can be utilized. The long half-life ($t_{1/2} = 16.2$ h) of the positron emitter bromine-76 permits extensive non-specific tracer clearance and prolonged data acquisition which is of value in the quantification of mAChR density using biomathematical models. In addition, the use of a positron emitting isotope allows a higher resolution and more accurate quantification as compared to a SPECT radioisotope. E-(R,S)-, E-(R,R)-, and Z-(R,R)-BrQNP were evaluated as potential candidates for the imaging of mAChR by PET in both rats and primates. The labeling of BrQNP were successfully accomplished by radiobromination *via* electrophilic destannylation of the respective 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -phenyl- α -(1-tributylstannyl-1-propen-3-yl)acetate isomers with no carrier added [Br-76]-BrNH₄ as described previously (Strickman, et al., 1996). Specific activities were approximately 250 mCi/ μ mol (9.25 Gbq/ μ mol) for each isomer of BrQNP. The results of a typical tissue distribution study of the three isomers of BrQNP in Wistar male rats (180 g) is shown in Table 4. For each isomer, preferential brain accumulation was observed in the cortex, striatum and hippocampus. Lower accumulation of radioactivity was observed in the colliculi, pons, and cerebellum.

Table 4. Biodistribution of Bromine-76-Z-(R,R)-BrQNP in Male Wistar Rats (n=3).

Organ	Percent Injected Dose/Gram (+S.D.)					
	0.5 h	1 h	2 h	3 h	4 h	6 h
Medulla /Pons	0.85±0.09	0.98±0.08	0.82±0.09	0.83±0.09	0.95±0.09	1.02±0.07
Cerebellum	0.73±0.09	0.74±0.04	0.52±0.09	0.48±0.07	0.50±0.05	0.46±0.04
Colliculi	0.91±0.09	1.02±0.09	1.0±0.1	1.0±0.2	1.1±0.2	1.3±0.2
Diencephalon	0.87±0.09	1.0±0.1	0.9±0.3	1.0±0.2	1.2±0.2	1.1±0.3
Hippocampus	0.8±0.1	0.96±0.07	0.9±0.3	1.0±0.2	1.2±0.2	1.5±0.2
Striatum	0.84±0.08	1.01±0.05	1.0±0.4	1.0±0.2	1.2±0.2	1.5±0.3
Frontal Cortex	1.1±0.2	1.2±0.1	1.1±0.4	1.2±0.3	1.5±0.2	1.8±0.3
Post Cortex	1.2±0.2	1.3±0.1	1.2±0.4	1.3±0.3	1.6±0.2	2.0±0.3

Table 5. Biodistribution of Bromine-76-E-(R,R)-BrQNP in Male Wistar Rats (n=3).

Organ	Percent Injected Dose/Gram (+S.D.)					
	0.5 h	1 h	2 h	3 h	4 h	6 h
Medulla /Pons	0.39±0.04	0.41±0.02	0.38±0.04	0.35±0.05	0.31±0.02	0.24±0.01
Cerebellum	0.27±0.03	0.24±0.01	0.18±0.02	0.16±0.02	0.13±0.01	0.11±0.01
Colliculi	0.43±0.03	0.50±0.04	0.48±0.06	0.49±0.7	0.43±0.04	0.35±0.02
Diencephalon	0.48±0.05	0.55±0.04	0.56±0.07	0.61±0.08	0.54±0.03	0.47±0.04
Hippocampus	0.47±0.06	0.60±0.07	0.63±0.08	0.70±0.08	0.65±0.05	0.63±0.06
Striatum	0.49±0.03	0.59±0.03	0.63±0.05	0.70±0.09	0.62±0.04	0.62±0.02
Frontal Cortex	0.56±0.05	0.67±0.07	0.72±0.09	0.78±0.7	0.73±0.06	0.70±0.07
Post Cortex	0.57±0.06	0.66±0.09	0.77±0.09	0.83±0.09	0.78±0.05	0.75±0.08

Table 6. Biodistribution of Bromine-76-Z-(R,S)-BrQNP in Male Wistar Rats (n=3).

Organ	Percent Injected Dose/Gram (+S.D.)					
	0.5 h	1 h	2 h	3 h	4 h	6 h
Medulla /Pons	0.35±0.04	0.24±0.03	0.20±0.02	0.17±0.01	0.17±0.05	0.17±0.02
Cerebellum	0.25±0.03	0.18±0.02	0.15±0.01	0.14±0.01	0.14±0.03	0.15±0.03
Colliculi	0.35±0.03	0.24±0.03	0.18±0.01	0.18±0.02	0.16±0.04	0.16±0.03
Diencephalon	0.43±0.04	0.30±0.04	0.21±0.01	0.19±0.01	0.17±0.05	0.18±0.03
Hippocampus	0.60±0.09	0.49±0.05	0.41±0.03	0.35±0.02	0.28±0.08	0.24±0.04
Striatum	0.56±0.09	0.47±0.06	0.38±0.05	0.31±0.03	0.24±0.07	0.20±0.03
Frontal Cortex	0.61±0.05	0.51±0.05	0.41±0.04	0.32±0.02	0.25±0.07	0.21±0.03
Post Cortex	0.62±0.03	0.54±0.04	0.42±0.04	0.33±0.03	0.25±0.07	0.22±0.04

In peripheral organs, the various isomers of BrQNP demonstrated preferential uptake in the lung, heart and kidneys. Z-(R,R)-BrQNP demonstrated the highest uptake in the heart (time, % injected dose/gram; 0.5 h, 2.69; 6 h, 0.61) as compared to E-(R,R)-BrQNP (0.5 h, 0.96; 6 h, 0.20) and E-(R,S)-BrQNP (0.5 h, 0.56; 6 h, 0.21) which was analogous to that observed for IQNP. Radioactivity in the blood was observed to be 0.7 %ID/G, 0.3 %ID/G and 0.6 %ID/G for Z-(R,R), E-(R,R)- and E-(R,S)-BrQNP, respectively, at 6 h.

Blocking experiments were performed to determine the selectivity of the binding of the radioactivity to the mAChR complex. Coinjection of ketanserin (5HT₂/5HT_{1C} antagonist), haloperidol (dopamine antagonist) and (+)-butaclamol (dopamine antagonist) did not interfere in the binding of the various radiolabeled BrQNP isomers. Two hours post-injection of dextetimide (nonselective mAChR antagonist), radioactivity in areas containing a high concentration of the M₁ subtype was reduced by 70-75 % for E-(R,S)-, 50-55% for E-(R,R)- and 15-25 % for Z-(R,R)-BrQNP. In regions containing a high concentration of the M₂ subtype (pons/medulla, cerebellum, heart), the uptake of radioactivity was blocked by 60 to 80% for E-(R,R)- and Z-(R,R)-BrQNP. In a metabolic study performed in these male rats, we observed that for E-(R,R)- and Z-(R,R)-BrQNP that 80 to 100% of the extracted radioactivity corresponded to the unmetabolized ligand at 3 h. In

contrast, E-(R,S)-BrQNP underwent significant metabolism during this same time period. It was also observed for all three radiotracers, only a slight amount of unmetabolized ligand was observed in the plasma at 3 h.

Ex vivo autoradiographic images of the distribution of radioactivity in horizontal slices passing through the frontal cortex, striatum, thalamus, hippocampus and cerebellum demonstrate that the uptake of E-(R,R)- and Z-(R,R)-BrQNP parallels that observed in the rat biodistribution studies. Preferential localization was observed in cortical areas, striatum, hippocampus, dentate gyrus, superior colliculi and inferior colliculi. Studies performed with E-(R,S)-BrQNP confirmed lower uptake of activity in these regions and higher non-specific uptake as compared to E- and Z-(R,R)-BrQNP. Extending these investigations further, PET studies were performed utilizing Papio Papio baboons weighing about 22 kg. The PET images were obtained using a brain scanner that allowed simultaneous acquisition of 31 slices every 3.37 mm with spatial and axial resolution of 5.7 and 5.0 mm, respectively. The images of the cerebral distribution of the radioactivity were accumulated for 2 h post-injection of the radiotracers with imaging times of 2-10 min. After 3 weeks, the cerebral distribution of Z-(R,R)- and E-(R,R)-BrQNP were studied in the same baboon treated with 1 mg/kg dexetimide 0.5 h post-injection of the radiotracers. The metabolism of the various radiotracers was performed on the plasma at 10, 20, 30, 45 and 60 min post-injection of the radiotracers.

In the PET studies, the three isomers of BrQNP rapidly entered the brain. At 5 min post-injection, radioactivity per unit volume measured as a function of time showed rapid accumulation in the various brain structures with the greatest accumulation in the cortex and thalamus. Z-(R,R)-BrQNP reached a maximal cortex uptake of 27 %ID/L at 2 h and the pons reached a maximum at 20 min post-injection followed by a plateau at 23 % ID/L. The accumulation of radioactivity for E-(R,R)-BrQNP reached a plateau at 10 min post-injection in the cortex, thalamus and pons (27, 24 and 19 % ID/L, respectively) that remained constant during the time course of the experiment. The radioactivity observed in the cortex for E-(R,S)-BrQNP reached a plateau within 10 min (13.4 % ID/L) while the radioactivity observed in the thalamus and pons decreased slowly to 7 % ID/L with a half-life of 100 min. For the three isomers of BrQNP, the radioactivity in the cerebellum peaked 10 min post-injection and decreased slowly during the duration of the experiment with a half life of 60 to 100 min for the two E-isomers and 200 min for the Z-isomer. Clearance of radioactivity from

the plasma was rapid for each isomer and by 2 h post-injection the radioactivity decreased to 4 % ID/L.

In the study in which the baboons were pretreated with dexetimide 0.5 h post-injection of E-(R,R)-BrQNP, the uptake of radioactivity in the cortex and thalamus was reduced by 80 % and in the pons by 60 %. For Z-(R,R)-BrQNP, the total uptake in the thalamus, cortex, pons and cerebellum was reduced by 85, 75, 77 and 70 %, respectively. Thus, by subtracting the data obtained in the control brain structures from that obtained in the saturated dexetimide brain of the same baboon, bromine-76-labeled E- and Z-(R,R)-BrQNP demonstrated important specific binding to mAChR. In addition, Z-(R,R)-BrQNP demonstrated higher specific binding in M₂ rich structures as compared to E-(R,R)-BrQNP. Evaluation of the metabolites in the plasma obtained from the *In vivo* studies demonstrated that the time-course of unmetabolized BrQNP isomers were different. At 1 h post-injection of the various isomers values of 81%, 53% and 3% of the radioactivity detected by HPLC analysis represented unmetabolized E-(R,R)-, E-(R,S)-, and Z-(R,R)-BrQNP, respectively. For E-(R,R)- and E-(R,S)-BrQNP, various polar metabolites were observed in contrast to Z-(R,R)-BrQNP in which a lipophilic metabolite representing 80 % of the total activity was detected.

In conclusion, these various *in vivo* imaging studies in nonhuman primates of the different stereoisomers of IQNP and BrQNP demonstrate that E-(R,R)- and Z-(R,R)-IQNP and BrQNP are attractive candidates for the imaging of the various subtypes of mAChR in humans and serve as a prelude for initial Phase 1 human clinical trials which are expected to be initiated in 1997.

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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, for a project evaluating the effectiveness for post balloon angioplasty irradiation of coronary arteries with rhenium-188 to inhibit restenosis. Generators were also provided for collaborative studies for clinical research projects to evaluate the effectiveness of Re-188-HEDP for bone pain palliation at the Department of Nuclear Medicine, at the Italia Hospital in Montevideo, Uruguay (J. Gaudiano, M.D.), and the Clinic for Nuclear Medicine, University of Bonn, Germany (H.-J. Biersack, M.D., *et al.*).

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 a tungsten-188/rhenium-188 generator was sold to through CIS/Bio International for Re-188-labeled antibody research which is being conducted at the University of Nantes, France (Prof. Chatal, M.D.).

Recent Publications

Knapp, Jr., F. F., Goodman, M. M., Kirsch, G., Reske, S. N., Kropp, J., Biersack, H.-J., Ambrose, K. R., Lambert, C. R., and Goudennet, A. "Both Total Chain Length and Position of Dimethyl-Substitution Effect the Myocardial Uptake and Retention of Radioiodinated Analogues of 15-(p-iodenphenyl) Pentadecanoic Acid," *Annals of Nucl. Med.*, **10** (1), 19-32 (1996).

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Meetings

F. F. (Russ) Knapp, Jr., Group Leader of the ORNL Nuclear Medicine Program, participated in the 6th Asia and Oceania Congress of Nuclear Medicine and Biology, held in Kyoto, Japan, September 30 - October 4, 1996, and presented a paper entitled, "Comparative Tissue Distribution, Metabolism and Excretion of 3(R)-BMIPP and PHIPA 3-10 in Rats." Following the Kyoto Symposium, he was the guest of the Institute of Nuclear Energy Research (INER), in Lung-Tan, Taiwan, and presented a series of lectures at INER and at the Veterans Hospitals in Taipei and Taichung, Taiwan.

Technical Highlights

Licenses Signed for New ORNL Technology for Concentration of Technetium-99m Solutions

On December 23, 1996, DeRoyal Industries, Inc., a Knoxville-based health care products manufacturer, licensed two new ORNL technologies which involve methods of concentration of solutions of the technetium-99m radioisotope, the most widely used diagnostic radioisotope in nuclear medicine. Over 35,000 diagnostic tests are conducted in the U.S. daily (10-12 million tests annually) with technetium-99m agents. DeRoyal Industries was formed in 1973 and currently has about 2,000 employees globally with facilities in 38 countries. DeRoyal has international sales in excess of \$ 250 million, primarily involving soft goods, which include operating room procedure trays, surgical accessories, and critical care and wound care products.

The new ORNL technologies are simple and efficient concentration methods which are required when technetium-99m solutions are obtained from generators which are prepared from the molybdenum-99 parent radioisotope produced by direct reactor production. An important advantage is that highly enriched uranium is not required as the target material. Other advantages of the new technologies include the simplicity of processing which is completed in a much shorter time period, and the absence of highly radioactive waste from the molybdenum-99 processing. In contrast, the currently used production and processing technology requires use of highly

enriched uranium targets and produces very high levels of radioactive waste which require special storage and disposal. In addition, all of the molybdenum-99 used in the U.S. for generator production is currently foreign produced.

The new technology, which will require approval from the U.S. Food and Drug Administration (FDA) prior to clinical use, allows use of several reactors in the U.S. and overcomes reliance on molybdenum-99 imported from foreign sources. Inventors for one patent for technology developed between the ORNL Chemical Technology and Health Science Research (HSRD) Divisions for which exclusive rights were granted to DeRoyal Industries are Saed Mirzadeh, F. F. (Russ) Knapp, Jr. and Emory Collins. The inventors on a second patent for which non-exclusive rights were given for technetium-99m concentration technology are HSRD Nuclear Medicine Group members F. F. (Russ) Knapp, Jr., Arnold L. Beets, Saed Mirzadeh, and Stefan Gohlke, from the Clinic for Nuclear Medicine in Bonn, Germany, who worked with Knapp and his colleagues at ORNL as a postdoctoral fellow for six months through July 1996.

Pete DeBusk, DeRoyal Industries president and chief executive officer, expects to develop a global market for this technology and estimates that 30-50 people will be employed in the Oak Ridge area for production of the concentrator units. Production is expected to begin in 12-15 months with annual sales of \$ 75-100 million. DeRoyal also announced plans to invest \$ 5-10 million in the construction of a new processing facility at ORNL near the High Flux Isotope Reactor (HFIR).

Clinical Studies Initiated with New Agent Developed in ORNL Nuclear Medicine For Bone Pain Treatment In Cancer Patients

Phase I clinical studies have been initiated at the Clinic for Nuclear Medicine, University of Bonn, Germany, for the first time with the rhenium-188-labeled HEDP agent for treatment of bone pain (palliation) in cancer patients associated with the spread of the disease to the skeleton (metastases). The HEDP agent is prepared using the rhenium-188 radioisotope obtained from the tungsten-188/rhenium-188 generator system developed at ORNL, which uses tungsten-188 produced in the ORNL HFIR. The preparation, purification and quality control procedures for the

rhenium-188 HEDP agent were developed in a collaborative program in conjunction between the ORNL Nuclear Medicine Program and colleagues in Bonn.

Treatment of bone pain with radioisotopes is a new, cost effective procedure which can greatly improve the quality of life of cancer patients. Use of radioisotopes is an alternative to the more traditional use of external beam irradiation and analgesics and other drugs, which can have major side effects. Although treatment of bone pain with radioisotopes is widely practiced in Europe, these radioactive agents have only recently become available in the U.S. The new use of rhenium-188 for this application is expected to be substantially less expensive in comparison with other therapeutic radioisotopes in current use. Since many thousands of cancer patients present with bone pain in the U.S. annually, the potential widespread use of rhenium-188 HEDP and other rhenium-188 agents for palliative treatment is expected to be an important step in the reduction of health care costs for this important application.

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