REDC Product Development and Cf Program Group

Nuclear Medicine Program
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Our research is focused on the development of improved reactor production and processing methods to provide medical radioisotopes, the development of new radionuclide generator systems, the design and evaluation of new radiopharmaceuticals for applications in nuclear medicine, oncology and interventional cardiology, and association with Medical Cooperative Programs throughout the world for the further preclinical testing and clinical evaluation of agents developed at ORNL. In the United States, only ORNL has available the combined resources of the stable isotope inventory, a High Flux Isotope Reactor (HFIR), hot cell processing capabilities, and a wide range of support functions required for such research. These collective resources provide unique capabilities in nuclear medicine research and production.

The ORNL Nuclear Medicine Program has dedicated research laboratories available for radiochemistry, synthetic chemistry, animal experiments and target preparation, and we also have available hot cells and glove box facilities for radioisotope processing. The ORNL High Flux Isotope Reactor (HFIR) provides a key resource for radioisotope production for our research program, providing a maximum steady state thermal neutron flux of about 2.3 x 1015neutrons per square centimeter per second, which is the highest of any reactor in the world. The versatile HFIR irradiation positions within the core and reflector regions include an online, hydraulically operated system which provides access to the core of the reactor, for both short and long term irradiations. These capabilities offer unparalleled capability for production of very large quantities of high specific activity radioisotopes. We are currently developing new improved processing and purification procedures and produce a variety of radioisotopes which are of current interest in medicine and biology, especially for cancer therapy. A key example is multi-Curie HFIR production of tungsten-188 (from the enriched stable isotope 186w), which is the parent of the tungsten-188/rhenium-188 generator system which we developed to provide carrier-free rhenium-188. Rhenium-188 from our generator is used for both research and also in over 50 clinical trials throughout the world for various forms of cancer therapy and for coronary restenosis therapy. Other examples of HFIR-produced medical radioisotopes include high specific activity holmium-166 (from natural, high-purity Ho), lutetium-177 (from enriched Lu-176), platinum-195m (from enriched Pt-194) and tin-117m (from enriched Sn-117). Most of the enriched stable isotopes used to produce these medical radioisotopes in HFIR are obtained from the ORNL calutrons. Although DOE has decided not to operate the calutrons any longer, varying amounts of these stable isotopes remain in the ORNL inventory.

Alternate stable isotope enrichment capabilities are being considered, as are alternate sources (primarily Russia). Our research program also includes production of the alpha-emitting radioisotope actinium-225, which is used in radiotherapy of cancer. Actinium-225 is routinely extracted from the thorium-229 stock, and ORNL is currently the largest supplier of this medical radioisotope.

Nuclear Medicine Program

The ORNL Nuclear Medicine Research Program follows a long tradition in developing useful diagnostic and therapeutic applications of radioisotopes. Our research focuses on the development of medical radioisotope processing techniques, radionuclide generator research and the development of new tissue-specific radiopharmaceuticals for diagnostic and therapeutic applications in nuclear medicine, oncology and interventional cardiology. Key strengths are in the areas of radiopharmaceutical chemistry, radiochemistry, radioisotope process research and biomedical applications. The ORNL High Flux Isotope Reactor (HFIR) represents an important resource which provides primarily neutron-rich radioisotopes. We are developing new processing procedures and also making important contributions in the development of new radionuclide generator systems which provide radioisotopes for various therapeutic applications in the areas of tumor therapy and diagnosis. We are actively collaborating with a variety of programs within ORNL and at universities, medical schools and other research institutions throughout the world. These Medical Cooperative Programs provide an important opportunity for further preclinical research and clinical evaluation of new agents developed in our ORNL program. The clinical evaluation and commercialization of new agents developed at ORNL illustrates the important transition of our new technologies from the laboratory to availability for routine clinical use.

Radioisotope Processing Technology and Radionuclide Generator Research

The ORNL HFIR is a key resource for the ORNL program. This powerful research reactor has the highest steady-state neutron flux of any reactor in the world. Our optimization of the reactor production and processing of tungsten-188 and tin-117*m* are key examples of our research which now make these important radioisotopes routinely available. A clinical prototype alumina-based tungsten-188/rhenium-188 generator has been developed, optimized for clinical use and a new efficient process for rhenium-188 concentration developed and patented. This process was initially licensed to Mallinckrodt Medical in 1997 and a Cooperative Research and Development Agreement (CRADA) was established for evaluation of rhenium-188 and rhenium-186 for inhibition of arterial restenosis after balloon angioplasty. A variety of physician-approved clinical protocols are in progress for use of rhenium-188 for restenosis therapy and bone pain palliation and generators are routinely provided through the ORNL Isotope Business Office. Production of tin-117*m* in the HFIR has also been optimized and this radioisotope has been provided for clinical trials for Sn-117m-DTPA for bone pain palliation. Bismuth-213 is available from the actinium-225/bismuth-213 generator and the actinium-225 parent is provided routinely for sale from ORNL.

Development and Testing of New Tissue-Specific Radiopharmaceuticals

The development and testing of new tissue-specific radiopharmaceuticals for in vivo nuclear imaging and therapeutic applications are important research areas. A variety of agents are currently being developed for tumor therapy, which are being evaluated in animal models and have shown good therapeutic effectiveness (See following sections describing rhenium-188 and bismuth-213). A key example of a diagnostic agent is the research and clinical use for evaluation of myocardial viability of the methyl-branched BMIPP fatty acid analogue which was developed in the ORNL Nuclear Medicine Program. Iodine-125-labeled BMIPP is continuing clinical trials at several institutions in the United States and Europe and has been marketed in Japan by Nihon Medi-Physics, Inc., since 1993, as an approved radiopharmaceutical named "Cardiodine®" for evaluation of myocardial viability. This agent has been used in over 350,000 patient studies through 2001. More recently, BMIPP has seen a renaissance as an important agent in cardiology research for the evaluation of fatty acid metabolism and trafficking in conjunction with studies of the physiology of the CD36 transport protein and the involvement of lipoproteins and foam cells in the atherosclerotic process. Using db/db diabetic mice, we have used BMIPP at ORNL and demonstrated for the first time unexpected alterations in lipid metabolism resulting from the nuclear targeting of agonists for the nuclear peroxisomal proliferator activated receptor (PPARgamma) which control gene expression and are used for resensitization of cells to insulin in Type II diabetes.

The Tungsten-188/Rhenium-188 Generator System and Development and Clinical Evaluation of Rhenium-188-Labeled Therapeutic Agents

We optimized the reactor production and processing of tungsten-188 and have developed the alumina-based adsorbant-type tungsten-188/rhenium-188 generator system and developed and patented new improved methods for the concentration of rhenium-188 bolus solutions to very high specific volumes. Because of the long physical half-life of the tungsten-188 parent (69 days) and the long useful generator shelf-life of several months with consistently high rhenium-188 yields (75-80 % at equilibrium), this generator system holds great promise in providing the cost-effective rhenium-188 radioisotope for routine use for a variety of therapeutic applications. An important aspect of using rhenium-188 for many applications in contrast to other therapeutic radioisotopes is the anticipated very low costs for unit-dose, which would contribute to the reduction of health care costs. The tungsten-188/rhenium-188 generator is the major medical radioisotope distributed for routine sale through the ORNL Isotope Business Office.

Several collaborative clinical programs are evaluating our rhenium-188-labeled phosphonates for bone pain treatment, and Phase I studies with the rhenium-188-labeled HEDP and Re(V)-DMSA agents have shown specific targeting of skeletal metastases in patients presenting with metastases from various cancers (See Clinical Trials section). Protocols have also been developed initially with collaborators at Columbia University for clinical evaluation of new rhenium-188 agents for inhibition of restenosis following coronary angioplasty. A CRADA had also been established with to explore various HFIR-produced radioisotopes for introvascular brachytherapy. Protocols have also been developed for use of particles for arthritis therapy and tumor-specific antibodies for radioimmunotherapy.

We are also working closely with the Nuclear Medicine Section at the International Atomic Energy Agency (IAEA) as a Research Agreement Holder for the design and implementation of the use of rhenium-188 for three major multi-center clinical trials involving the use of rhenium-188 for restenosis therapy following PTCA, for a new therapeutic strategy for therapy of refractory liver cancer and for radionuclide synovectomy. The tungsten-188/rhenium-188 generator is expected to have an important role in the developing world in providing rhenium-188 as a cost-effective therapeutic radioisotopes for a variety of applications because of the long useful shelf-life of several months.

Alpha Emitting Radioisotopes for Tumor Therapy

Alpha particles are of considerable interest for radioimmunotherapy applications since their short range in soft tissue is limited to only a few cell diameters. The delivery of such high energy in such a small volume, or high-linear-energy-transfer (LET), makes alpha particles especially well suited for targeting micrometastatic disease and single tumor cells such as leukemia and other blood-borne disease. The bismuth-213 radioisotope is of special interest because of its unique nuclear properties, which include a short 45 minute half-life and high energy (8.4 MeV) alpha-particle emission. Its unique availability from the actinium-225/bismuth-213 generator system makes this radioisotope particularly well suited for medical use. The actinium-225 is formed from radioactive decay of radium-225, the decay product of thorium-229, which is obtained from decay of uranium-233. The National depository of uranium-233 is at ORNL, and we have developed effective methods for obtaining thorium-229 (half-life 7340 years) as our feed material to routinely obtain actinium-225.

The very short 45 minute half-life of bismuth limits its use, however, only when attachment to a carrier molecule can be conducted very quickly and the targeting is rapid following intravenous administration, such as the clinical treatment of acute myeloid leukemia, as described later, where trials are being conducted at the Memorial Sloan Kettering Cancer Center in New York. The actinium-225 used for the generators which provide the bismuth-213 for these studies is provided from ORNL. We are also conducting research with alpha emitting radioisotopes such as bismuth-213. Radioimmunotherapy with alpha particles has the advantages of high energy deposition (~ 100 KeV/mm) in a short path length (< 100 m), which produces significant cellular damage close to the site of radioisotope deposition. Several alpha-particle emitting radioisotopes have been studied for therapy and the antibody-targeted bismuth-213 for treatment of leukemia and intracranial placement of astatine-211 for adjuvant therapy after surgery for brain tumors. Research at ORNL has shown that monoclonal antibodies targeting bismuth-213 to lung vasculature is also successful for the therapy of lung tumors in mice. Bismuth-213 decays with a half-life of 46 minutes and emits very energetic alpha particles. (~ 8 MeV). Carrier-free bimuth-213 is obtained from the actinium-225/bismuth-213 generator system. The actinium-225 parent (half-life = 10 days) is obtained from decay of thorium-229 (half-life 7,340 years). The majority of the available thorium-229 stock has been recovered from the nuclear waste material which has been stored at ORNL for about 30 years. Actinium-225 batches of up to 40 mCi are available for sale through the ORNL Isotope Business Office on a bi-monthly schedule and smaller quantities are available on a weekly schedule.

Medical Collaborative Programs, Technology Transfer Efforts and Clinical Evaluation of ORNL Radiopharmaceuticals

Collaboration with external organizations and technology transfer are important activities that bridge the gap between development and testing of new agents developed at ORNL and use at other institutions. Several patents have recently been issued for new technologies developed at ORNL. Various new agents are evaluated in collaborative programs with Medical Cooperative Programs at clinics, universities, and other research institutions in the United States, Europe, Australia and Asia.

Nuclear Medicine Program Facilities and Resources

The Nuclear Medicine Program has approved procedures and laboratories and facilities available for radiochemistry, pharmaceutical synthesis and analytical studies. Available instrumentation includes two multichannel analyzers, a variety of high performance liquid chromatographs, and other laboratory instrumentation. Approved procedures and facilities are also available for testing of targets for reactor irradiation.

Facilities are available for housing small rodents and for conducting injections and tissue distribution animal experiments, which has been approved by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). All animal experiments are conducted under procedures approved by the ORNL "Animal Care and Use Committee."

The ORNL High Flux Isotope Reactor (HFIR) has the highest thermal neutron flux available in the western world with versatile in core facilities available for high flux irradiation of samples from time periods as short as minutes up to a full operating cycle (22-24 days). The high flux hydraulic tube positions are given priority for the production of medical radioisotopes. Major required maintenance and upgrades of the HFIR were conducted in 2001, which ensure continued operation of this reactor with increased capabilities well into this century. Hot cell facilities are available for radioisotope processing, and Drug Master Files (DMF's) can be developed for radioisotope products as required.

It is also expected that Current Good Manufacturing Practices (cGMP) will be instituted at ORNL in 2002, so that radioisotope products can be provided under cGMP's to our commercial customers. A variety of other resources at ORNL are available in support of this program, including target chemical processing and fabrication facilities and extensive nuclear magnetic resonance spectroscopic and mass spectrometry capabilities.

Summary of Clinical Studies

Although ORNL is not licensed to distribute radioisotopes and radiopharmaceuticals approved for human use, a number of agents and radionuclide generators systems developed in the ORNL Nuclear Medicine Program are distributed through the ORNL Isotopes Business Office as radiochemicals for research and clinical studies being conducted at institutions throughout the world. Clinical studies are conducted under physician- sponsored protocols. The Nuclear Medicine Program offers technical expertise and guidance on the use of medical radioisotopes to the ORNL Isotopes Business Office. Key examples of ORNL products being used in clinical research include the tungsten-188/rhenium-188 generator system developed at ORNL, where rhenium-188 is being used for a variety of therapeutic applications in over 60 clinical projects throughout the world in the areas of nuclear medicine, oncology and interventional cardiology, as described in the attached Tables. In addition, bismuth-213 is being used for cancer therapy at a variety of centers and is available from the actinium-225/bismuth-213 generator system, using actinium-225 provided from ORNL.

New Technology at Oak Ridge National Laboratory

Although ORNL is not licensed to distribute radioactive agents for human use, a variety of agents and new technologies developed at ORNL are used in physician-sponsored clinical protocols and have been commercialized for routine use. Examples include the ORNL-developed BMIPP cardiac imaging agent which has been commercialized by Nihon Medi-Physics in Japan, and has been used in over 350,000 patient studies since 1993. This agent is also used in several research protocols, and an example is shown from the Clinic for Nuclear Medicine in Bonn, Germany.

The ORNL tungsten-188/rhenium-188 generator provides carrier-free rhenium-188 for various therapeutic applications. The use of liquid-filled rhenium-188 balloons for restenosis therapy after angioplasty is being evaluated in over ten clinical sites throughout the world and an example showing pathology results from a swine study.

Rhenium-188-labeled HEDP agent is also used been developed as a cost-effective alternative to other agents for bone pain palliation of metastatic disease, as shown in a study from Bonn, Germany.

Examples of other agents developed in the ORNL Program include an orally administered radioactive fat which is use for evaluation of pancreatic insufficiency by a simple urine test, radioactive agents for cerebral imaging to evaluate activity of the muscarinic-cholinergic receptor, and the use of radioactive agents for evaluation of the effects of new insulin sensitizing drugs on lipid and glucose metabolism in animal models of Type II diabetes.

The Tungsten-188 and Rhenium-188 Generator Information

Although ORNL is not licensed to distribute radioactive agents approved for human use, a variety of new agents developed in the ORNL Nuclear Medicine Program are used in clinical trials throughout the world under physician-sponsored protocols. A key example is the tungsten-188/rhenium-188 generator system, which began development at ORNL in 1986. This generator provides the carrier-free rhenium-188 therapeutic radioisotope. Because of the long 69-day half-life of the tungsten-188 parent, the generator has a very long useful shelf-life and provides rhenium-188 at very low costs, which is especailly important in developing regions. We also developed at ORNL a variety of agents and approaches for using rhenium-188 for therapeutic applications, including rhenium-188-HEDP for bone pain palliation and rhenium-188 agents for the inhibition of restenosis, and proposed and demonstrated for the first time the feasibility of using liquid-filled balloons with rhenium-188. Other applications which are being purusued by our collaborators and customers are the use of rhenium-188-labeled peptides and antibodies for cancer therapy and rhenium-88 particles for hepatocellular carcinoma therapy and treatment of arthritis.

The generators are sold from ORNL as radiochemicals, and over 60 clinical trials are in progress in over 20 countries including two multi center trials initiated by the International Atomic Energy Agency (IAEA) in 2001 for the treatment of hepatocellular carcinoma and for restenosis therapy. The success of the development, promotion and widespread use of this generator system highlights the important role the Nuclear medicine Program continues to have in the development of important new technology.

Please direct any questions concerning nuclear medicine to:

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