Heart Imaging Agents Form Core of ORNL Nuclear Medicine Group Effort

Oak Ridge National Laboratory Incites Active Nuclear Medicine Research Program

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The Oak Ridge National Laboratory (ORNL), established in 1947 when the US Atomic Energy Commission (AEC) took over the Manhattan Engineering District which produced plutonium for the first atomic bomb, has grown into a vast research and development facility that occupies 2,900 acres in East Tennessee. Today, a staff of almost 5,000 handles approximately 600 investigative projects in nuclear technology, engineering, physical sciences, biomedical and environmental sciences, and advanced energy systems at this federal lab, principally funded by the US Department of Energy (DOE) and operated by Martin Marietta Energy Systems, Inc.

The Oak Ridge National Laboratory evolved from a secret project isolated in the Tennessee hills to a world-renowned nuclear research center. **(Courtesy of ORNL)**

Within this complex structure, the ORNL's Nuclear Medicine Group is actively pursuing the development of a variety of new radiopharmaceuticals, in particular, new agents to evaluate heart disease—radioiodinated fatty acids to evaluate aberrations in regional fatty acid uptake and metabolism, and iridium-191m from an improved short-lived radionuclide generator for angiographic applications. Other continuing areas of interest include the design of new radiopharmaceuticals, the development of new radiolabeling methods, and the preparation of various radioiodinated deoxyglucose analogs and organic cations to measure myocardial perfusion.

The mission of the ORNL Nuclear Medicine Group encompasses the production and purification of radionuclides, and the development of new, innovative radiolabeling techniques for the introduction of useful radionuclides into a variety of tissue-specific radiopharmaceuticals. "New radioiodination techniques are being developed to chemically stabilize radioiodine toward in vivo deiodination and for easy onsite radiolabeling," explained F.F. (Russ) Knapp, Jr., PhD, who has directed the group since 1978.

Preclinical testing of new agents in laboratory animals falls within the purview of the ORNL group, which has several Medical Cooperative Programs set up with outside institutions that conduct further preclinical testing and, eventually, clinical trials.

Fatty Acid Agents

In 1979 Dr. Knapp's group began work on designing various radiolabeled fatty acid agents, choosing these biomolecules because the heart depends on long-chain fatty acids as a primary source of energy (unlike other organ systems that oxidize glucose for energy).

"We're shooting for SPECT [single-photon emission computed tomography] applications with these

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Linda Ailey and F.F. (Russ) Knapp, PhD, operate the gamma camera system used to evaluate tissue distribution and biokinetics of ORNL-developed radiopharmaceuticals in experimental animals. (Courtesy of ORNL)

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agents," said Dr. Knapp. The group conducted animal studies of tellurium-123m-labeled fatty acids to develop a compound that would target the heart while not being degraded.

Once the investigators selected the best derivative, they retained nonradioactive tellurium on the molecule to serve as a metabolic blocking agent, and labeled the compound with iodine-123. "These molecules worked well in animal studies and established for the first time that the 'trapping' of fatty acid energy substrate analogs in the heart muscle was feasible," said Dr. Knapp.

More recent studies have focused on the introduction of methyl-branching into radioiodinated fatty acid analogs to interfere with oxidative degradation. The group developed a model agent, iodine-123-labeled 15-(p-iodophenyl)-3-R S-methylpentadecanoic acid (BMIPP), which shows significantly delayed myocardial clearance. "More recently, the 3 3-dimethyl analog (DMIPP) has been developed and shows nearly irreversible myocardial retention in animals for the first 1–2 hours after injection," said Dr. Knapp.

These compounds are methyl-branched analogs of an unbranched fatty acid analog, developed in Essen, Federal Republic of Germany, by H-J. Machulla, which is currently used at several European institutions to evaluate heart disease in patients. The ORNL agents are retained much longer in the myocardium, however, making them more suitable for SPECT imaging, explained Dr. Knapp.

Through collaborative programs, ORNL supplies substrates (ORNL is licensed to distribute radiochemicals, not radiopharmaceuticals) for preparing the iodine-123-labeled agents for clinical trials at several European institutions, including the University of Vienna, Austria (Dr. R. Dudczak), and the Institute for Clinical and Experimental Nuclear Medicine in Bonn, Federal Republic of Germany (Drs. S. Reske and H-J. Biersack), where Dr. Knapp is on sabbatical this year. "Clinical studies with iodine-123-labeled BMIPP and DMIPP are now in progress at these institutions with SPECT, and both agents show the retention properties observed in animals," said Dr. Knapp.

Through another cooperative effort with Brookhaven National Laboratory (Drs. A.B. Brill and P. Som) and the Massachusetts General Hospital (Dr. H.W. Strauss), investigators are studying possible applications for evaluating hypertensive heart disease with the iodine-123-labeled methyl-branched fatty acid compounds. Autoradiography studies indicate an uneven distribution of the fatty acid but an even distribution of thallium-201 in the myocardial tissue of hypertensive rats.

"The thallium results show that regional blood flow is normal in the hypertensive rat hearts, indicating that fatty acid delivery to the heart was not impaired. However, the heterogeneous distribution of fatty acid indicates that hypertensive heart disease may have altered the ability of portions of the heart to metabolize fatty acids," explained Dr. Knapp.

These observations are important, he said, because they suggest that a metabolic change occurs in severe hypertension before any differences in blood flow can be detected. "The combination of iodine-123-labeled fatty acids and SPECT can potentially allow clinicians to evaluate hypertensive disease and assess drug therapy," he added.

Improved Iridium-191m Generator

Since 1981 the ORNL group has been working to develop an improved osmium-191/iridium-191m generator. "Because there is a need for an iridium-191m generator that has a good yield and a low breakthrough of osmium-191 with increased use, and because ORNL is the main source of the osmium parent, our group has been exploring improved designs," said Dr. Knapp.

The key to improving the design was in selecting the best absorbent that would tightly bind the parent radionuclide while allowing the daughter to be easily eluted. "In collaboration with Dr. Claude Brihaye, who was at Oak Ridge on sabbatical from the Cyclotron Center at the Sart Tilman University in Liège, Belgium, we evaluated 40 different absorbents," said Dr. Knapp. The group

found that specially treated activated carbon increases the iridium-191m elution yield to about 20% with a breakthrough of 1×10^{-4}% per bolus, extending the generator's life from several days to two or three weeks, he added.

The ORNL group has submitted a patent disclosure to the DOE for the generator, now in clinical use at the Cyclotron Center in Liège and in Bonn. Collaboration with investigators at the Massachusetts General Hospital (Dr. Strauss) on the use of this new generator for the evaluation of regional coronary perfusion and perfusion of other organs under continuous elution conditions is in progress. "These studies should result in the submission of an application to the Food and Drug Administration (FDA) for approval for human use of this new generator system in the United States," said Dr. Knapp. (The DOE allows ORNL to request patent waivers for newly developed products, whereby the government waives its rights and sells the patent to private industry.)

An earlier iridium-191m generator was developed for clinical use by Salvador Treves, MD, of Children's Hospital in Boston, MA. That institution is now evaluating iridium-191m, which "has been shown to be well suited for radionuclide angiography to detect left-to-right shunts in infants," said Dr. Knapp.

The federal laboratory at Oak Ridge offers unique resources to nuclear medicine research, noted Dr. Knapp. The High Flux Isotope Reactor (HFIR) irradiates highly enriched stable isotopes to produce substantial quantities of a range of radionuclides, including osmium-191, platinum-195m, and tin-117m. ORNL is also equipped with many "hot-cells," enclosed lead-lined rooms and associated equipment for the safe handling of large quantities of radioactive materials.

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Linda E. Ketchum

Nuclear Medicine Milestones at Oak Ridge

Oak Ridge National Laboratory (ORNL) played an important role in the birth of nuclear medicine. The historic Atomic Energy Act of 1946 gave the US Atomic Energy Commission (now the US Department of Energy) and ORNL an opportunity to explore a much wider application of atomic energy for industrial and medical uses.

The first medical radionuclide was produced at ORNL in 1946, when a mCi of carbon-14 (as barium carbonate) was shipped on August 2, 1946, to Barnard Free Skin and Cancer Hospital, St. Louis, MO. The field lay dormant with no significant historical developments in this area until 1955 when J.E. Francis, Persa R. Bell, ScD, and C. Craig Harris published their classic paper on scintillation spectrometry (*1*). Soon afterward, the Isotope Division, directed by Paul C. Aebersold, PhD, was formed in 1956. Potassium-43 was developed in 1968 for the evaluation of heart disease with the subsequent development of gallium-67, first produced at ORNL in 1969 for tumor localization studies. A study of methods for reactor production and purification of a rare earth element, gadolinium-153, at ORNL began almost at the same time when interest arose in its use for dual-photon absorptiometry to evaluate bone mineral content.

The sequence of these milestone events at ORNL, and the wide application of radioactive tracers in medical diagnosis, treatment, and biomedical research testified to the wisdom of the Atomic Energy Act, which stimulated continuous contributions to health care delivery and biomedical research in the United States.

In April 1974, a special Nuclear Medicine Committee was commissioned by ORNL to review the nuclear medicine program and make recommendations to strengthen it. The committee, chaired by Henry N. Wagner, MD, consisted of some outstanding experts (S. James Adelstein, MD, Robert N. Beck, MD, Floro D. Miraldi, MD, ScD, and Manuel Tubis, PhD), representing a diversity of technical interests within the broad field of nuclear medicine. In September of 1974, the committee recommended to Chester R. Richmond, PhD, associate director of ORNL, that the strengths and resources of ORNL be used to develop a center of excellence with particular emphasis in the areas of: radionuclide research and development, synthesis of radiopharmaceuticals, elucidation of biologic mechanisms of pharmaceutical distribution in the body, radiation dosimetry to body organs from radiopharmaceuticals, and development of instrumentation for nuclear medicine applications. As a result, the Nuclear Medicine Group was formed in 1975.

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References

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