MEDI PHYSICS AWARD

PET Imaging Radionuclide Copper-64 Tested as Radioimmunotherapy Agent

INVESTIGATORS DEVELOPING monoclonal antibodies and peptides labeled with copper-64 to treat patients with colon cancer received in June the first Society of Nuclear Medicine/Medi-Physics Award for Innovation in Therapy with Unsealed Sources. The lead investigator is Carolyn J. Anderson, PhD, an assistant professor at Washington University's Mallinckrodt Institute of Radiology in St. Louis, Missouri. Her collaborators are Sally Wagner Schwarz, MS, a research instructor in radiology at Washington University's Mallinckrodt Institute of Radiology, and Judith M. Connett, PhD, a research assistant professor at Jewish Hospital, an affiliate of Washington University. With the $30,000 award, they plan to assess the potential of an anti-colorectal carcinoma monoclonal antibody labeled with ^{64}Cu versus ^{67}Cu in cell culture and animal models.

The new annual fellowship is sponsored by Medi-Physics, Inc., an Amersham company, and awardees are chosen by the SNM awards committee for their potential to advance therapeutic applications of nuclear medicine.

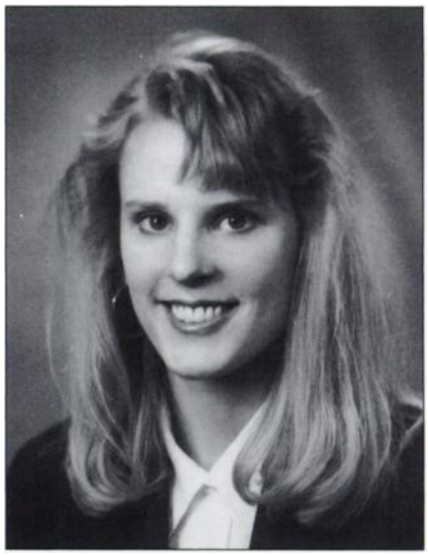
Seeking Alternatives

Cancer researchers for many years have focused on ^{67}Cu as one of the most promising radionuclides for cancer therapy, but efforts to ready the new therapeutic agents for widespread treatment of cancer patients have been hampered by the limited availability of the accelerator-produced radioisotope. Amid continuing uncertainty, researchers such as Dr. Anderson and colleagues are considering the advantages of radioimmunotherapy agents that use isotopes produced in a nuclear reactor.

Despite decaying by different schemes, limited in vitro studies suggest that ^{64}Cu could be as lethal to cancer cells as ^{67}Cu, Dr. Anderson says. Decaying by negatron emission, ^{67}Cu yields an abundance of β^- particles (and low energy gamma emissions suitable for gamma camera and SPECT imaging). In contrast, ^{64}Cu decays by electron capture and beta and gamma emission, releasing auger electrons along with positrons (suitable for PET imaging) and gamma radiation. The auger electrons, Dr. Anderson says, probably are responsible for the isotope's lethal effects, depositing energy over short distances with a high linear energy transfer that limits the ability of cells to repair damage to DNA.

Despite any potential advantages of ^{67}Cu, severe shortages of accelerator-produced isotopes could hamper research on these products for several years. This fall, the Los Alamos Meson Physics Facility is scheduled to close, leaving the U.S. with only one source for many radioisotopes, the Brookhaven Linac Isotope Producer, or BLIP, at Brookhaven National Laboratory in New York. An upgrade at BLIP is expected to be complete by 1996 and a proposed National Biomedical Tracer Facility gained preliminary funding this year, but construction of the NBTF is far from certain and it will take five years or more to complete.

Given these conditions, Dr. Anderson says ^{64}Cu could be a more practical agent for radioimmunotherapy. "I could go on and on about the advantages," she says. "It is reactor produced and therefore more readily available and less expensive than accelerator-produced ^{67}Cu." The University of Missouri Research Reactor produces ^{64}Cu on a regular basis. As a chemist, Dr. Anderson finds ^{64}Cu easier to work with and says the radioisotope is typically very pure and has fewer trace contaminants than ^{67}Cu.



Carolyn J. Anderson, PhD

Perhaps a more significant advantage, Dr. Anderson points out, is that the distribution of a therapeutic agent labeled with ^{64}Cu, a positron emitter, can be mapped more precisely and quantitatively because PET imaging is possible. Quantitative biodistribution could enable clinicians to prepare extremely accurate individualized therapy doses. Imaging with ^{67}Cu-labeled agents is limited to gamma cameras or SPECT instruments.

PET Imaging

The therapy experiments planned by Dr. Anderson are, in fact, an outgrowth of tumor-imaging studies conducted at Washington University with Gordon W. Philpott, MD, of Jewish Hospital and others. In a report of preliminary results given in June at the SNM Annual Meeting, Dr. Philpott concluded that the radiolabeled monoclonal antibody, called

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Cardiology Awards

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technetium-99m sestamibi, cardiologists can predict to some extent whether revascularization surgery will improve ventricular dysfunction. But questions about the mechanisms and the accuracy of such predictions in human patients remain unanswered. Dr. Daley and colleagues, working in the nuclear cardiology laboratory directed by James E. Udelson, MD, at the New England Medical Center, propose to extend previous investigations of these questions by correlating single photon emission computed tomography imaging with regional tissue uptake of ^{99m}Tc-sestamibi, or MIBI, in patients with coronary artery disease.

The investigators will analyze the relation of MIBI uptake to metabolic parameters of viable myocardium and correlate the data with prospective assessments of the timing of improvement of myocardial tissue in patients following revascularization procedures.

Among other hypotheses, they expect that myocardium with mild to moderate reductions in MIBI activity will have relatively greater concentrations of ATP and creatine phosphate and will improve faster following surgery than segments with severe reductions of MIBI activity.

To assess uptake of MIBI and regional metabolism, investigators will take biopsies of scarred, ischemic, and adjacent non-ischemic myocardium prior to aortic cross-clamping. Divided into segments, the samples will be assayed for MIBI activity.

Metabolism will be assessed by assaying for lactate, ATP, creatine phosphate and glycogen. Global cardiac function will be assessed by hemodynamic measurements and measurements of cardiac extraction of lactate and oxygen. Recovery will be assessed by echocardiography.

In his proposal, Dr. Daley says the planned research will characterize, perhaps for the first time in humans, the correlation between quantitative imaging and regional tissue activity of ^{99m}Tc-sestamibi with regional myocardial metabolism and the extent of collateral flow, which previously has been explored only in animal models. He expects the work to corroborate the predictive value of ^{99m}Tc-MIBI SPECT imaging in assessing the recovery of function in dyssynergic myocardial segments following surgery and clarify the time course of recovery of regional ventricular function. ■

Therapy Award

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Cu-64-benzyl-TETA-MAb 1A3, developed against colorectal cancer is safe in humans and can be used with PET to detect very small colorectal tumors. The researchers tested the agent in ten patients with advanced colorectal cancer.

The antibody binds selectively to an antigen distributed abundantly on the surface of primary colon cancer cells that is rare or entirely absent in normal colon tissue. Previous studies have established that the antibody is internalized by colon cancer target cells, a mechanism which, Dr. Anderson points out, seems likely to increase the antibody's ability to kill cancer cells by bringing the radionuclide closer to the genetic material.

With the SNM/Medi-Physics fellowship, the researchers hope to establish whether ^{64}Cu-labeled monoclonal antibodies should be further developed for radioimmunotherapy in humans. "Getting this fellowship is really wonderful because it enables us to complete our cell studies and move on to the in vivo [animal] studies," says Dr. Anderson. "If the data looks good we hope to get a major NIH grant so we can move on to human clinical trials." ■

RIA

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surface and exciting a fluor.

For demonstration purposes, Dr. Jay used iodine-125 in his membrane-based assay, but he says the system should allow the use of higher energy beta emitters such as tritium, carbon-14, or sulfur-35. In the past, researchers assaying beta emitting radioisotopes like tritium had to add a "scintillation cocktail" containing dissolved fluors. Used cocktail contains both organic solvents and radioactive waste, which can be a disposal problem. With systems in which fluors are imbedded in beads, or now membranes, no mixed wastes are generated.

But with beads, Dr. Jay says, labeling with higher energy beta emitters is impractical. "You only want the stuff bound to beads to be detected," he says. "If the beta particles have a long enough range, particles from unbound radioligands might strike beads" and cause fluors to emit light. Dr. Jay is experimenting with membranes coated with films that are porous enough to allow molecules to penetrate into the membrane pores, but thick enough to shield fluors from beta particles emitted from unbound radioligands.

Another advantage of membranes is that they can be cast into many useful shapes and sizes, Dr. Jay says. His team is beginning to work on membranes attached to fiber-optic filaments, which could be used for remote assays of minute quantities of a radiochemical in body cavities, or outside of medicine in other industrial applications.

For now, he is in the process of patenting the membrane-based RIA technique. Experiments to optimize the membrane RIA system should be complete in about six months, but Dr. Jay says he hasn't begun efforts to commercialize the idea. "I tend to be an academic type," he says, adding that he's preoccupied with research and teaching graduate students.

The Berson-Yalow Award is named for the late Solomon A. Berson, MD and Rosalyn S. Yalow, who developed the RIA technique. The Society established the award in 1977, the year the Dr. Yalow received the Nobel Prize for Physiology or Medicine. ■