Characterization of ACE Inhibiter

SNM Selects Dah-Ren Hwang, PhD, as 1990 Berson-Yalow Award Winner

The Society of Nuclear Medicine (SNM) has selected Dah-Ren Hwang, PhD, a research instructor at the Mallinckrodt Institute of Radiology, Washington University School of Medicine, in St. Louis, Missouri, as this year's recipient of the Berson-Yalow Award for excellence in radioimmunoassay (RIA) research. SNM's Scientific Program Committee selected Dr. Hwang for his preparation of radiopharmaceuticals in a study entitled, "Synthesis and Biodistribution of [F-18]-labeled Angiotensin Converting Enzyme Inhibitor: [F-18]-Fluorocaptopril." Co-authors of the winning research project included Michael J. Welch, PhD, and Carla J. Mathias, of the Mallinckrodt Institute, and Edward W. Petrillo, PhD, John Lloyd, PhD, and William C. Eckelman, PhD, of the Bristol Myers-Squibb Institute for Medical Research, New Brunswick and Princeton, New Jersey. Chairman of the Scientific Program Committee, Peter T. Kirchner, MD, director of nuclear medicine, professor of radiology at the University of Iowa Hospitals and Clinics, in Iowa City, will present the Award to Dr. Hwang during SNM's Annual Meeting in Washington, DC.

Using PET to Study ACE

The winning scientific investigation demonstrated the feasibility of using fluorine-18-labeled captopril in vivo with positron emission tomography (PET) in examinations of cardiac patients suffering from hypertension. Captopril, a potent inhibitor of angiotensin converting enzyme (ACE), has become an important therapeutic agent for the treatment of both hypertension and congestive heart failure. During periods of high blood pressure, the kidneys secrete renin, an enzyme that interacts with the plasma protein angiotensinogen to form angiotensin I. Angiotensin I is subsequently converted by ACE to angiotensin II, a substance that severely constricts the blood vessels. Captopril retards this conversion process and, thereby, lowers blood pressure, without adverse side effects.

The research group synthesized fluorocaptopril labeled with fluorine-18, an isotope that has a 110-minute half-life. After administering the drug to rats, the researchers used PET and found high uptake in areas known to have elevated concentrations of ACE — the lungs, kidneys, and aortae — 30 minutes postinjection. Dr. Hwang says that the findings indicate that PET, in conjunction with captopril, provides a noninvasive method of monitoring the therapeutic drug treatment of hypertension.

"Since we have demonstrated that PET images produced with fluorine-labeled captopril can effectively probe ACE in rats, we hope that this procedure can ultimately be applied to humans with diseases where ACE is implicated," says Dr. Hwang. "PET gives us an excellent picture of enzyme activity in the blood."

Uncovering the Pathophysiology of Hypertension

Commenting on the project selected for the award, Dr. Kirchner told *Newsline*, "This project was chosen for its significance, innovation, and its large potential clinical impact." Joanna S. Fowler, PhD, senior chemist at Brookhaven National Laboratory, in Upton, New York, praises the research group's study and adds that "this is an important use of PET, for it can show us the regional distribution and time course of the therapeutic drug localizing in the body." Scientific Program Committee member, Kenneth A. Krohn, PhD, professor of radiology and radiation oncology, and adjunct professor of chemistry at the University of Washington, in Seattle, says, "Dr. Hwang's study demonstrated that an invivo technique, like radioimaging with PET, can obtain the same results as an invitro test-tube study. The fact that this abstract successfully showed an alternative to invasive methods of studying ACE really caught the attention of the Committee."

Dah-Ren Hwang, PhD

Co-author of the study, Edward W. Petrillo, PhD, comments that "hypertension is a disease that can only be

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controlled by normalizing blood pressure through the chronic use of drugs like captopril. It cannot yet be cured. However, this PET technique can show us exactly how the drug works in the blood and could eventually lead to a greater understanding of the biochemical causes and pathophysiology of hypertension. This, in turn, can lead to more effective therapy for the disease." Dr. Petrillo adds that "Previously, enzyme activity was studied ex vivo by the classical technique of carbon-14 labeling, which required the physical removal of organs, like the kidneys, and the killing of animals under experimentation. We hope that the mechanism of more drugs can be studied in detail using the PET procedure." Dr. Petrillo, associate director of chemistry-cardiovascular agents at Squibb Institute, adds that the causes of hypertension are still largely unknown, but are probably due to a complex biochemical mechanism.

The pharmaceutical industry forecasts that the market for cardiovascular drugs will rise 16% each year, as new medications are being developed to reduce the risk factors — notably hypertension — associated with heart disease. The market for ACE inhibitors, such as captopril, enalapril, and lisinopril, is expected to grow annually by 33%. Although the detection and treatment of hypertension has increased in recent years, the incidence of atherosclerotic heart disease in diagnosed hypertensive patients remains high. The survival rate of patients with heart disease has not improved despite the availability of drugs effective against symptoms of the disease. "This is why it is imperative to understand in greater detail how the drugs we have available function inside the body," asserts Dr. Hwang. "PET offers us that capability."

Born in Taiwan, Dr. Hwang, 35, obtained his bachelor's degree in chemistry at National Taiwan Normal University, Taipei, Taiwan, in 1977, and his doctorate in organic chemistry from the State University of New York at Stony Brook in 1982. Subsequently, he started his postdoctoral research in the department of chemistry at Brookhaven National Laboratory, with Alfred P. Wolf, PhD, director of the cyclotron PET program, and Dr. Fowler. Dr. Hwang's work at Brookhaven concentrated on the synthesis of carbon-11- and fluorine-18-labeled opiate agonists and antagonists for the in vivo mapping of opiate receptors with PET.

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Dr. Hwang credits Dr. Fowler with drawing him to the field of radiopharmaceutical compounds development, while he was working as a research assistant at Stony Brook. "I was fascinated by a lecture she gave on the application of [fluorodeoxyglucose] FDG PET in the brain," Dr. Hwang recalls. "At that time I did not even know there were means by which one could observe the functions of the brain in such astonishing detail. Of course, being a chemist, I was interested from the perspective of the radiopharmaceutical compounds that were prepared for these imaging studies."

Dr. Hwang has been associated with the Mallinckrodt Institute since 1985, initially as a post-doctoral research associate with Dr. Welch, who is professor of radiation chemistry and radiology at the Mallinckrodt Institute. In July 1989, Dr. Hwang was appointed research instructor. His research activities at Mallinckrodt have primarily focused on the development of new labeling techniques for the synthesis of positron-labeled radiopharmaceuticals designed for PET studies. In collaboration with Dr. Welch, Dr. Hwang has been instrumental in the preparation of a variety of labeled compounds used in conjunction with PET to study dopamine receptors and muscarinic acetylcholine receptors in the brain, to image prostate tumors, and to detect hypoxic but viable tissues.

The Berson-Yalow Award commemorates Rosalyn S. Yalow, PhD, and the late Solomon A. Berson, MD, who together developed the RIA technique in the 1950s. The Award was established by the Society in 1977, the same year that Dr. Yalow received the prestigious Nobel Prize for Physiology/Medicine in acknowledgment of the RIA breakthrough. The objective behind the Berson-Yalow Award is to honor investigators who submit "the most original scientific abstracts and make the most significant contributions to basic or clinical radioassay." In 1987, the Scientific Program Committee expanded its criteria for the Award to include all research that made use of the indicator-dilution method. Categories such as neurology, oncology, and radiopharmaceuticals, in addition to radioassay, fall under the new criteria.

Palash R. Ghosh