NEWSLINE

Aebersold Award Winner Recognized for Development of Novel Radiopharmaceuticals

Kenneth A. Krohn, PhD

When Kenneth A. Krohn, PhD, a radiology professor at the University of Washington in Seattle, was nominated to be this year's winner of the Paul C. Aebersold Award, nuclear physicians, biologists, chemists and engineers stepped up to do the honors. This diverse group of 11 nominators is indicative of Dr. Krohn's ability to integrate concepts from divergent disciplines. His result has been the introduction of novel radiopharmaceuticals for in vivo measurement of receptor systems and new radiolabeled oncologic agents for detection and therapy.

A consistent theme throughout Dr. Krohn's work is the correlation of chemical structure with biological function via rigorous applications of an appropriate scientific paradigm. For example, his development of the receptor-binding radiopharmaceutical ^{99m}Tc-galactosyl-neoglycoalbumin utilized kinetic theory to determine the optimal chemical structure for in vivo measurement of receptor biochemistry. When designing ^{18}F-fluoromisonidazole, he utilized current concepts of tissue radioresistance in search of the optimal hypoxic agent for quantifying tumor hypoxia in vivo. This ability to synthesize and apply concepts from many scientific fields led to innovations which changed the practice of nuclear medicine. "It is this pioneering work which serves as a prototype for evaluating those parameters which will enable the development of other novel radioligand systems," reads the nominating letter of Robert C. Stadalnik, a professor of radiology at the University of California, Davis. Thus, it is fitting that Dr. Krohn should be this year's winner of the Paul C. Aebersold Award for basic research in the field of nuclear medicine.

Dr. Krohn's vision of radiopharmaceutical design as the integration of chemical structure and biologic function via sound scientific methods, has provided his collaborators with exceptional insight and resulting progress. Two examples come from his work with receptor-binding agents and radiolabeled antibodies. As the project's radiochemist, Dr. Krohn insisted that the team from the University of Washington in Seattle use the proven technology of iodination for both diagnostic and therapeutic antibodies.

After moving to Seattle, Dr. Krohn extended this concept to the measurement of myocardial blood flow. In collaboration with James Bassingthwaighte, Jeannie Link and Stephen Little of the University of Washington Center for Bioengineering, he coauthored a series of papers which introduced and validated the first gamma-emmitting molecular microsphere, radioiodinated desmethylimipramine.

Man of Many Disciplines

The development of radiolabeled antibodies for diagnosis and therapy required Dr. Krohn to draw from his vast knowledge of immunology, radiochemistry and radiobiology. He used these disciplines as rational guides on the search for labeled antibodies with optimum tumor deposition and dosimetry. "His contributions to nuclear medicine reflect an extremely wide range of areas of interest and impact covering nearly every aspect of the discipline from the production of the radionuclides we use to the careful selection and verification of the radiotracers to the ultimate modeling of the results from their use," wrote Thomas J. Ruth, PhD, director of the UBC/TRIUMF PET Program, in his nomination letter.

The remote system for high specific-activity iodination developed by Dr. Krohn in 1984 is still in use today. As he envisioned, his technique reliably provides higher per patient dose than any other immunotherapy program.

Dr. Krohn's decision not to develop the various chelator-radiometal combinations paid off handsomely. His articles published in *JAMA* and the *Journal of Clinical Investigation* in 1983 are among the first reports of radioimmunotherapy. The early entry into radiotherapy with a reliable radiolabel enabled the University of Washington group to explore monoclonal antibodies as a chemical vehicle for the delivery of radiation to tumors—in other words—to explore the structure-function relationship of this new class of radiopharmaceutical. As a result the research team produced the first comprehensive set of requirements for the rational design of a successful diagnostic or therapeutic antibody to be used in humans.

Among the requirements outlined in a 1990 paper published in Nuclear Medicine Biology with researcher Janet Eary, MD, was the analytical determination of antibody binding avidity by Scatchard analysis. Dr. Krohn considered this analysis as the quantifiable link between the chemical structure of a radiopharmaceutical and biological function of the target tissue.

Designer of Receptor-Binding Radiopharmaceuticals

Dr. Krohn's insistence on rigorous and reliable methods led his Seattle team to implement a traditional labeling method for radioimmunodiagnosis and therapy. His work at the University of California, Davis with Robert Stadalnik, MD, Paul Scheibe, PhD, and myself led to a distinctly nontraditional approach to the design of receptor-binding radiopharmaceuticals.

After the introduction of receptor-based radionuclides by William C. Eckelman, PhD, and colleagues at George Washington University in Washington, D.C. in 1979, radiochemists thought that an optimally designed receptor-binding radiopharmaceutical would have the highest possible specific activity and receptor affinity. Their rationale for the first criterion was inherited from the classical concept of a radiotracer as a physiologic probe that does not perturb the system under study. Consequently, the reasoning continued, the amount of radioligand injected must be significantly lower than the number of receptors—hence the requirement for high specific activity. The second criterion of receptor affinity was based on traditional in vitro binding experiments where successful evaluation of receptor concentrations within a glass test tube required the highest possible receptor affinity.

Dr. Krohn, however, suspected that these traditional approaches were not consistent with the goal of maximizing the amount of physiologic information from this new class of radiopharmaceuticals. By combining kinetic theory with engineering principles, he presented the essential properties required to simultaneously evaluate target plasma flow, receptor-ligand affinity and receptor concentration at a radiotracer workshop held in 1980. He argued that imaging studies using receptor-binding radiopharmaceuticals of high specific activity and high receptor affinity would measure only target organ plasma flow. Moreover, by kinetic simulation he predicted that accurate measurement of receptor concentration would require the injection of enough radiopharmaceutical to perturb the number of free receptors at the target tissue.

Dr. Krohn's research with ^{99m}Tc-DTPA-galactosyl-neoglycoalbumin enabled it to become the first commercially available receptor-binding radiopharmaceutical when it was introduced in September, 1992 by Nihon Medi-Physics Co., Ltd., in Japan. In the final analysis, the unique contribution that Dr. Krohn brings to the nuclear medicine field is his ability to synthesize divergent facts and concepts.

—Based on the Aebersold Award nomination letter of David R. Vera, PhD, associate professor of radiology at the University of California, Davis.

Telemedicine *(Continued from page 21N)*

Israel, this is vital because primary care physicians, cardiologists and other specialists outside of nuclear medicine have been reading the results of their patients' nuclear scans on their own departmental computers for years—first on a PACS system and now on the Web.

The biggest concern about web pages is the issue of security. Although patient files are protected by passwords, the possibility of hackers breaking into the system has been raised by several nuclear physicians who spoke with *Newsline*. "We have seen some major security issues with Web access. There are an estimated 200 break-ins a day to federal Web sites," said Robert Henkin, MD, professor of radiology and director of nuclear medicine at Loyola University Medical Center in Maywood, IL. "I don't feel safe putting in my credit card number, so I can't say that we would feel safe putting patient data on the Web at this point." Fletcher said the VA network has also been cautious about going on the Web for this reason. "Security is one principle issue that needs to be nailed down. We're dealing with confidential information, which is a real concern," he said.

Larry Barbaras, a senior computer programmer and creator of the Web site at Beth Israel, has taken pains to ensure that patients' records are secure. Since the Web site is not public, he said he has been able to implement unique security measures. These include user name/password combinations that will only work when originating from the unique Internet address of the physician's computer (so stolen passwords pose a small risk). He has also added such things as coded subdirectories and patient identification by number not by name. "Are we continually upgrading our security? Yes. Can we guarantee that an accomplished hacker can't break in? Probably not," said Barbaras.

FYI Questions about setting up a telemedicine system in your hospital? Contact Tony Parker, MD, PhD, past president of the SNM Computer and Instrumentation Council, at Beth Israel Hospital in Boston by e-mail: tony_parker@bih.harvard.edu. You can also contact Trevor D. Cradduck, PhD, general manager of a nuclear medicine usenet group, LARG*net, at the University of Western Ontario by e-mail: cradduck@largnet.uwo.ca.

Most likely, nuclear medicine departments will venture with tepidation onto the Web, with most waiting until another institution tries it out first. "Ironically, it is much easier to access confidential information in a typical hospital by impersonating a physician on the phone or dialing into digital dictation voice lines," said Barbaras. As was the case with the minute computational flaw in the Pentium chip, humans expect computers to meet a much higher standard.

—Deborah Kotz