Advancing Nuclear Medicine at the Multiomics Intersection

Johannes Czernin Discusses Innovation and Translation with Kalevi Kairemo

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Johannes Czernin, MD, editor-in-chief of *The Journal of Nuclear Medicine* and a professor at the David Geffen School of Medicine at UCLA, talked with Kalevi Kairemo, MD, PhD, MSc (Eng), about his career in pioneering novel radiolabeled therapeutics. Dr. Kairemo is now retired as chief physician/professor, molecular radiotherapy and nuclear medicine, at the Docrates Cancer Center (Helsinki, Finland) and, since 2015, has served as a visiting professor in nuclear medicine at the University of Texas M.D. Anderson Cancer Center (Houston). His research is based on multiomics, making discoveries at the nexus of genomics, transcriptomics, proteomics, metabolomics, microbiomics, epigenomics, imaging, and precision medicine.

Dr. Kairemo graduated with an MSc (Eng) degree from the Helsinki University of Technology (Finland) in 1980 before completing his medical (1986) and doctorate (1993) degrees at the University of Helsinki. From 1989 to 1993 he held a postdoctoral research fellowship at the Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY). He undertook specialist training in clinical chemistry (1994), nuclear medicine (1996), health care administration (2002), and pharmaceutical medicine (2006) at the Helsinki University Central Hospital. He has held faculty leadership positions at the Norwegian University of Science and Technology (Trondheim), Uppsala University Hospital (Sweden), and the Docrates Cancer Center. He has been active in transitioning new agents and techniques through the developmental pipeline and is the author of more than 250 peer-reviewed publications. Dr. Kairemo is the president-elect of the World Association of Radiopharmaceutical and Molecular Therapy (WARMTH).

Dr. Czernin: *You had a very diverse training and professional career. You were trained in chemical engineering but then switched to medicine, became chief physician of a big clinic, and are still a visiting professor at M.D. Anderson. You also were trained in health care administration. You ended up in nuclear medicine and were elected to serve as president of WARMTH. Can you briefly describe this unusual career trajectory?*

Dr. Kairemo: At the Helsinki University of Technology in the 1970s, I was majoring in physical chemistry and technical biochemistry. My thesis was about electrochemistry, and suddenly I realized that I did not know anything about human physiology or cellular electrolyte balance. Therefore, in the 1980s I started to study medicine. From the beginning I was interested in research. After various attempts, nuclear medicine became my research choice. While I was doing a summer job, I learned "the tracer principle" from, strangely enough, a pediatric patient. In 1986 a preschool boy asked me very precise questions, and I was obliged to answer at a level that a child could understand—from the most basic perspective. The following summer I worked in the same place and embarked on a dissertation on radiolabeled monoclonal antibodies. I pursued a multidisciplinary career with a clear focus that required administrative skills and flexibility.

Kalevi Kairemo, MD, PhD, MSc (Eng)

Dr. Czernin: *What attracted your interest in joining the lab of Steven Larson, MD, at MSKCC?*

Dr. Kairemo: I had heard his Georg de Hevesy Lecture about radiolabeled monoclonal antibodies at the European Association of Nuclear Medicine conference in Budapest, Hungary, in 1987. Then I met him personally at the 1988 SNMMI conference in San Francisco (CA), where I had 2 clinical posters about immunoscintigraphy. After discussions, he offered a fellowship at MSKCC.

Dr. Czernin: *You stayed at MSKCC for 4 years. What prompted you to return to Europe, and what did you learn from your time in New York? What did you take home to Finland?*

Dr. Kairemo: Those 4 years were spent in 2 phases. At that time there were 4 isotopes of radioiodine (^{123}I, ^{124}I, ^{125}I, and ^{131}I) that could be given to patients. I first did nonclinical experiments and brought new methods back to Finland, such as radioimmunohistochemistry and digital autoradiography. I also learned the theranostic concept, that one can use the same radioactive compound in vitro and in vivo in diagnostics and therapy and then confirm the results with ex vivo tissue sampling. The MSKCC period gave me courage to start new therapies, including radioimmunotherapy and Auger–chemotherapy in Helsinki in the early 1990s. At MSKCC I also learned how to build a team and that a critical mass is needed for team success.

Dr. Czernin: *Early in your career you developed a strong interest in industry–academia relationships. How did this interest develop?*

Dr. Kairemo: In 2000 I was introduced to Erkki Koivunen, PhD, from the lab of Erkki Ruoslahti, MD, PhD, who discovered the phage display technique and the RGD peptides. I briefly showed Dr. Koivunen some of the animal imaging and radiolabeling we were performing in Helsinki. We decided to join forces and introduced the idea of targeted nanoparticles. My role was in translational research, developing in silico/in vitro/ex vivo data to create new multidisciplinary compounds for in vivo research and to optimize their pharmacokinetic and -dynamic behavior. This idea was selected as "best business idea" in Finland in 2001, and

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we established the biotech CTT Cancer Targeting Technologies in Finland. Initially, I thought that it was impossible to develop nanoparticles that could contain cytotoxic molecules, gas bubbles, RNA strains, and other targeted loads at the good-manufacturing-practice level—but I was wrong.

Dr. Czernin: *With which companies were you involved, and what was the focus of your industry work?*

Dr. Kairemo: In industry, I worked as medical director of CTT Cancer Targeting Technologies, medical director of Imanext (2006–2008), and clinical director at Advanced Accelerator Applications (AAA; 2009) (now Novartis Co.). The CTT biotech company that we started in 2001 was a good example of success, going from laboratory bench to a phase I clinical trial in 5 years, with many contracts between multinational conglomerates and small spinoff biotech companies. We also grew quickly from 0 to 30 employees. In 2006, we founded Imanext as a contract research organization. Within 1 year, we had a large U.S. pharma customer that wanted us to conduct global clinical trials in radionuclide therapy in approximately 25 centers in 15 countries. The trials could not be finished because of the U.S. financial crisis in 2008.

When AAA started to develop its first theranostic compound in 2009, I created the regulatory environment and was involved in designing the phase 1/2 trial of Lutathera (^{177}Lu-DOTATATE), which received marketing authorization in 2017. The company was sold for €3.9 billion to Novartis.

Dr. Czernin: *How did your university view your industry relationships? Were they supportive?*

Dr. Kairemo: When I first asked in the mid-1990s, the university hospital had no capabilities for supporting industry collaboration, so I could not patent anything. Later, in the early 2000s, my university had its own company to support this kind of development. We held 12 patents in our biotech portfolio.

Dr. Czernin: *You also started your own company? What was its focus?*

Dr. Kairemo: We founded Imanext in 2006 as a contract research organization, with a focus on providing imaging services for the pharmaceutical industry. Among the products were phase 0 trials (exploratory investigational new drugs), also using SPECT/CT. We designed a major clinical trial for big pharma globally, including Africa, Australia, and South America.

Dr. Czernin: *You were quite heavily involved in designing clinical trials. How did you learn about the regulatory landscape?*

Dr. Kairemo: I had collaborated with multiple radiopharmaceutical companies since the late 1980s, so I had to know the regulatory rules. In the CTT biotech we were aiming for clinical tracers, so I was forced to learn the regulatory environment. We collaborated with many contract research organizations. As clinical director of the AAA in France/Italy in 2009 I set up the regulatory environment. I was involved with initiating and designing the NETTER-1 study. I learned how regulatory requirements had grown to make large-scale physician-initiated trials almost impossible without massive institutional support.

Dr. Czernin: *After your academic career you became involved in a private center that provided diagnostic and therapeutic services. Can you describe this clinic? How large was it?*

Dr. Kairemo: In 2009, the full-service private oncology Docrates Center was built in Helsinki. In the same building there was a radiopharmaceutical company that owned a cyclotron. The Docrates Cancer Center had PET/CT, SPECT/CT, 3-T MRI, and 2 linear accelerators, with about 50 employees. I started ^{177}Lu-octreotate therapies in 2010 and soon treated Finnish residents and patients from other countries. We introduced voxel-based dosimetry to improve therapy planning. Our clinic also had many cancer patients, and we introduced imaging probes, including ^{68}Ga-prostate-specific membrane antigen [PSMA]–11 and ^{18}F-PSMA compounds, ^{18}F-fluorestradiol, and ^{18}F-Na for evaluating ^{223}Ra therapy response. In the mid-2010s we started using ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T. I introduced these radioligand therapies in neighboring countries such as Sweden, Norway, and Estonia. Later I helped many institutions to set up their own treatment protocols.

Dr. Czernin: *You set up mobile PET services. How did this work, and why was this necessary?*

Dr. Kairemo: Finland has 5 university hospitals for 5.5 million inhabitants. It is a large country with long distances outside the capital region. PET cameras initially were only in Turku and Helsinki (southern Finland). Mobile PET/CT trucks visited hospitals in different locations every day and also went to Sweden and Estonia. Today there is not much need for this, because all university hospitals and multiple regional hospitals have their own PET scanners.

Because of their sensitivity, specificity, time factors, and depth resolution in imaging, radionuclide methods cannot be replaced. Relevant therapy products can be designed for targeting and optimal kinetic constants. I have believed in this method for more than 30 years, and now we have products such as Pluvicto that have changed the treatment paradigm. Theranostics are here to stay.

Dr. Czernin: *How is nuclear medicine set up in Finland and other Scandinavian countries? Is it an independent specialty or part of radiology? You are aware that even in Europe some institutions merge radiology with nuclear medicine. What do you think about this?*

Dr. Kairemo: Briefly, nuclear medicine in Finland used to be a subspecialty (when I studied) within radiology, clinical physiology, or clinical chemistry. Later it became an independent specialty combined with clinical physiology (which used to be a main specialty in Finland, Sweden, and Denmark). In Norway, nuclear medicine could be combined with clinical chemistry as well. Therefore, in Scandinavia, the pressure to merge radiology with nuclear medicine has not been as high as in many other European countries (e.g., The Netherlands). It is fine that radiologists are fond of nuclear medicine and want to read scans. However, most radiologists are not interested in treating patients. Nuclear medicine is more than interpretation of images; it is also radiochemistry, pharmacology, nuclear physics, immunology, and more.

Dr. Czernin: *Can you describe briefly the Finnish health care system? Is it public only or public and private? What percentage of patients have private insurance?*

Dr. Kairemo: Public health care covers more than 90% of medical treatment, with no large regional differences in availability or quality. Private health care is often used in situations where there are long treatment waits or medical debt. Only a fourth of the

population (<1.3 million individuals) has private insurance, and almost half of these are children.

Dr. Czernin: *When you compare the health care systems in Europe with the ones in the United States in terms of quality of care for patients, accessibility, and availability, which system do you personally prefer? The question that I often ask Europeans in this series is: Do you prefer a system for everyone or a system for many that may leave out many?*

Dr. Kairemo: I absolutely prefer a system for everyone. We are almost there in many countries in Europe. However, the resources, including quality, accessibility, and availability, vary and will remain different despite national and international harmonization efforts.

Dr. Czernin: *Let's talk about theranostics. How did you get into theranostics? What is your view of the current state and future in Scandinavia and beyond?*

Dr. Kairemo: I started radioimmunotherapy in Finland in the mid-1990s and had to select patients by either in vivo or ex vivo imaging. In the next phase I became interested in peptide-receptor radionuclide therapy with somatostatin receptor ligands, first in Helsinki with an ^{111}In-labeled compound, then in Uppsala with a ^{90}Y-labeled compound. Then I worked with AAA and gained experience in France with ^{177}Lu-labeled compounds. At Docrates my own department was known as the "molecular radiotherapy" or "theranostics" department.

Because of their sensitivity, specificity, time factors, and depth resolution in imaging, radionuclide methods cannot be replaced. Relevant therapy products can be designed for targeting and optimal kinetic constants. I have believed in this method for more than 30 years, and now we have products such as Pluvicto that have changed the treatment paradigm. Theranostics are here to stay.

Dr. Czernin: *What are your treatment protocols like in Finland? In Germany, all patients must be inpatients. It's the same in Austria. In the United States, every patient is an outpatient.*

Dr. Kairemo: In our case, they can be either in- or outpatients. If they live nearby and the measured activity is less than 15 μSv/h at a 1-m distance, they can leave the institution; others are inpatients in lead-shielded hotel rooms or in the hospital.

Dr. Czernin: *One important development is the emergence of dosimetry as a routine component of theranostics. How did you implement this and use it in your practice?*

Dr. Kairemo: I knew that patient dosimetry is very individual. I also knew that nephrotoxicity may exist and that individual values vary in this respect. Luckily, my physicist was specialized in nuclear physics and had mathematic skills. Together we created a voxel-based dosimetry program in 2010 that could routinely be applied in patients.

Dr. Czernin: *Your work has reached beyond Scandinavia. Can you tell us a little about your work for WARMTH and your outreach to African countries?*

Dr. Kairemo: I knew the key people in WARMTH even before it was established in 2009. I was present at the founding meeting of WARMTH's predecessor, the World Radiopharmaceutical Therapy Council, at the SNMMI meeting in 1999. My second contact with this group was at an International Atomic Energy Agency congress in 2002 in Beijing, China, where there were 150 participants from 72 countries.

WARMTH has arranged 2 world conferences in Africa: in Capetown, South Africa, in 2010 and Accra, Ghana, in 2023. During our last meeting in Ghana, the first therapy dose of ^{177}Lu-PSMA was given in Accra. In addition, we visited another hospital in Ghana that has been established by a European initiative. I am currently working with a research collaboration in Ghana.

Dr. Czernin: *Dr. Kairemo, yours has been an astonishingly diverse career encompassing research, industry–academia relationships, private health care experiences, leadership in international organizations, and much more. This may serve as an example of the near limitless opportunities in the fields of nuclear medicine, molecular imaging, and theranostics. I thank you very much for your time.*