Discussions with Leaders: A Conversation Between Steven Larson and Johannes Czernin

Steven M. Larson[1] and Johannes Czernin[2]

[1]Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; and [2]David Geffen School of Medicine at UCLA, Los Angeles, California

Steven M. Larson, MD, is the Donna and Benjamin M. Rosen Chair in Radiology; Attending, Molecular Imaging and Therapy Service, Department of Radiology; Member and Lab Head, Molecular Pharmacology Program, and Director, Radioimmunotherapy and Theranostics, Ludwig Center for Cancer Immunotherapy, Sloan Kettering Institute; and Co-leader, The Imaging and Radiation Sciences Program, Comprehensive Cancer Center Grant, Memorial Sloan Kettering Cancer Center (MSKCC). He is also professor of radiology at Cornell University Medical College (New York, NY). He has had long-term interests in radiopharmaceuticals for oncologic applications in nuclear medicine and is inventor and coinventor on more than 15 patents for radioactive drugs. He developed one of the earliest ^{99m}Tc kit formulations, for ^{99m}Tc S colloid, a product that is still in active use today, more than 50 years after discovery. He has worked in various aspects of PET since 1979, including a major role in the development of 2 large PET programs, at Clinical Center, National Institutes of Health (NIH) 1983–1988; and as Chief of Nuclear Medicine, the MSKCC PET program, between 1988 and 2013. He has served on numerous government advisory committees and chaired the Radioactive Drug Advisory Committee of the U.S. Food and Drug Administration, where he was part of a team that developed the 21CFR361.1 Radioactive Drug Research Committee regulations. He has been principal investigator on several large grants past and present from the U.S. Department of Energy (DOE) and the NIH, including the grant that provided funding for Memorial Sloan Kettering's Center for Multidisciplinary In Vivo Molecular Imaging in Cancer. He has authored or coauthored more than 600 articles in major peer-reviewed journals.

Dr. Czernin: *When I recently visited MSKCC you stated that palliation is insufficient and that we have to cure cancer. Could you elaborate a little bit on that statement, especially in the context of emerging theranostics?*

Dr. Larson: Advanced cancers, especially the common solid tumors, are difficult to cure with targeted therapy of any type, and, when we treat with targeted radiotherapy in humans, we rarely achieve cures. As you know, I have board certification both in internal medicine and in nuclear medicine. I have managed many patients with thyroid cancer and treated many hundreds with ^{131}I—and we *can* achieve cures. The problem is this: over my nearly 50-year career in nuclear medicine, I can count on the fingers of one hand the number of advanced thyroid cancer patients I have actually cured with high-dose ^{131}I therapy. I remember each of these patients by name because it is that unusual. I can think of a number of wonderful examples. One patient had his thyroid tumor discovered incidentally before prostate cancer surgery. It was well-differentiated thyroid cancer that had spread throughout his lungs but that took up radioactivity amazingly well. He already had some bone lesions and, without treatment, would have progressed and died. Over a 5-year treatment period, however, he was cured. Another patient I remember presented with superior vena cava syndrome as a result of a large mediastinal mass; again, she was cured after multiple treatments. I treated and cured a child who presented near death, with extensive metastatic disease from thyroid cancer. There were other patients, too, but the point I want to make is that really good responders are outliers and quite unusual. Today we know that this is explained by "lineage plasticity" or the ability of cancer cells to alter genetic expression, which allows tumor cells to change to a primitive state that is radioiodine resistant.

Steven M. Larson, MD

The same is likely to be true for targeted radiotherapy of other tumor types. Take, for example, radioisotope treatment with radiopeptides, which promises to greatly expand the therapeutic role of nuclear medicine in the very near future. ^{177}Lu-DOTATATE (Lutathera; Advanced Accelerator Applications; Millburn, NJ) for advanced gastroenteropancreatic neuroendocrine tumors (NETs) was recently shown to be far superior to the best standard treatment (long-acting octreotide) in a randomized and adequately powered multicenter trial: the NETTER trial. NETTER showed major benefit in increasing progression-free survival, time to radiographic progression, and fewer deaths. However, at least so far Lutathera use has rarely if ever resulted in cures. Similarly, we are excited to soon learn results from the VISION trial of ^{177}Lu-PSMA-617 (Endocyte, Inc.; West Lafayette, IN), which promises to offer improved therapy for metastatic castrate-resistant prostate cancer, but as yet, no reported cures.

I don't mean to downplay the important role that palliation can play in oncologic therapy—to prolong life with reduced suffering is a wonderful achievement. But what we must do now is set our sights on an even loftier goal, because I believe that we can achieve cures in patients with advanced solid tumors using targeted radiotherapy.

Dr. Czernin: *What would your approach be? Increase the tumor dose and/or develop combination therapies?*

Dr. Larson: Our approach includes *focus* on a design principle for therapy ("hitting the sweet spot") and a *process* that takes deliberate advantage of a multidisciplinary team to implement a fully theranostic research plan. Let me clarify. I have always enjoyed sports but am not a natural athlete. My one athletic triumph came during my senior year in high school, when I led our

baseball team, the Peninsula Seahawks in Gig Harbor, WA, in hitting. I batted .511 for the season and, in fact, led the league that season. I think the reason I succeeded was because I realized that one could really whack the baseball effectively only if you hit it with the bat's sweet spot. That is an area about 1 or 2 inches in diameter and about 3 inches from the end on the thick part of the wooden bat. If you time your swing so that you hit the pitched ball squarely on that part of the bat, you can impart maximum energy from bat to ball and are likely to hit safely in the majority of attempts.

Our plan to achieve successful (curative) targeted radiotherapy without toxicity is like that: we first identify the sweet spot for likely cure of tumors and try to hit it on every treatment attempt. Through trial and error with our own experience in thyroid cancer and listening to the experiences of others, we learned that the sweet spot for successful therapy in solid tumors is at about 10,000 cGy for the tumor, with sufficient targeting so that the therapeutic index (TI; ratio of tumor to sensitive normal tissue) allows for complete recovery of any transient radiation damage. The TI for tumor-to-bone marrow should be >100, for kidney >10, and for the gastrointestinal tract >40. The theranostic approach, with careful attention to radiation dosimetry, guides proper treatment dosing.

In principle, it doesn't matter how these optimized targeted therapy treatment regimens are achieved—with radiopeptides, radiolabeled antibodies or nanoparticles, or other carriers not yet described. But you have to hit the tumor on that sweet spot; otherwise you will either undertreat the tumor or damage radiosensitive normal tissues.

We have been successful. In the clinic, we have achieved cures using the radioantibody ^{131}I-8H9 delivered intrathecally in patients with central nervous system recurrence of neuroblastoma. With intracompartmental therapy like this we take advantage of a natural way to develop optimal TIs at tumoricidal radiation doses. We inject the targeted therapy into the ventricles via an ommaya reservoir. Cerebrospinal fluid (CSF) is produced by the choroid plexus in the third ventricle, and currents sweep the radioantibody throughout the intrathecal space, including down the spinal column and up over the cerebral hemispheres. We bathe tumor deposits with high-affinity antitumor antibody wherever these deposits are—on meninges and even within the brain parenchyma. The high binding strength of the radioantibody means that it is retained for the long term on the tumor. Free or unbound radioantibody is removed from the CSF over 48–72 hours by the Pacchionian granulations in the superior sagittal sinuses and cleared into the blood. In phase II studies, 50 mCi of ^{131}I-8H9 are injected twice at monthly intervals. Careful dosimetry assessments indicate that tumor doses range from 15,000–50,000 cGy and TIs were >100. About 50% of patients have experienced long-term cures without major toxicities. Ninety-three patients have been treated with an average follow-up of 8 years. The FDA has given priority review to a commercial product that is now undergoing phase III testing (Omburtamab; Ymabs Therapeutics Inc.).

We tried also to use the same approach with whole immunoglobulin G–labeled antibodies administered systemically, in a number of solid tumors. Although we saw tumor shrinkage in a variety of tumors, we essentially failed to achieve clinically meaningful responses with systemic injections. So we have gone back to the laboratory. Here we have exploited the fact that advances in antibody production and availability of therapeutic radionuclides make it possible to achieve curative regimens based on 3 distinct antibody–antigen systems in human tumors grown in nude mice. Collaborating with Dane Wittrup of MIT, we use a multistep approach with molecular-engineered reagents, because we have found that we need the boost of TI that can be achieved with these methods. Time will tell whether we can bring these into the clinic, but we won't be satisfied until we have tested these concepts in humans.

I want to emphasize that this work is performed as a multidisciplinary team. The team has been built up over the last 30 years since I came to MSKCC and is still evolving and changing, depending on the disease focus. Yes, we have our superstars at key positions. For neuroblastoma work, that would be Nai-Kong Cheung, who invented and then refined the antibody systems. Gifted pediatric and nuclear medicine clinicians have managed the patient trials, including Kim Kramer, and Shakeel Modak, in pediatrics; and Neeta Pandit-Taskar, Jorge Carrasquillo, and Samuel Yeh, in nuclear medicine. We have also enjoyed indispensable support for the physical sciences from medical physics, especially John Humm, Pat Zanzonico, and Joseph O'Donoghue, and, from radiochemistry, Jason Lewis, and Serge Lyashchenko, Peter Smith-Jones, and Ron Finn. Over the years numerous fellows, postdocs, technicians, nurses, and statisticians have also made key contributions—truly a pan-institutional enterprise. This work would be impossible to do without support from the MSKCC, philanthropy, and multiple internal grants as well as awards from the National Cancer Institute (NCI).

"It is now more than 50 years since I did my early research as a medical student. Today practice and research in nuclear medicine are more exciting and challenging than ever."

Dr. Czernin: *I found your very first publication, from 1965, in the* American Journal of Obstetrics and Gynecology. *There you used ^{99m}Tc-labeled albumin to image the placenta. At that time, there was no CT, no MRI, and no ultrasound. It seems to me that functional imaging was attractive to you.*

Dr. Larson: I was attracted to nuclear medicine in the first place because of a job that I got through my college roommate in a fallout testing laboratory in the School of Fisheries at the University of Washington (Seattle). Biologic specimens from our atmospheric atomic bomb testing program were analyzed for radioactive fission products such as ^{89}Sr and ^{137}Cs. I worked my way through college as a radiochemistry technician, part-time during the year and full-time on summer break. I learned a lot of practical techniques of radiochemistry and became fascinated with radiation and radiation effects. This was during the Cold War, and Hiroshima and Nagasaki were fresh in our minds.

I was at the University of Washington in 1965 when I was awarded an NIH fellowship to take a year between my second and

third year of medical school for dedicated study in nuclear medicine. My mentor was the chief of nuclear medicine at the university, Wil B. Nelp. He was an internist who had a big influence on me. He was the first fellow of Henry Wagner, Jr., at Johns Hopkins and one of the early pioneers in clinical nuclear medicine. He was an extremely good teacher with an excellent fundamental knowledge of radioisotope laboratory methodology, which he passed on to me. In those days, one-on-one preceptor teaching was the way you learned about radiation and radionuclides.

^{99m}Tc had just become available in the mid-1960s. It was a very exciting time to work with others in radiochemistry and clinical applications of this novel radionuclide. Gamma (Anger) cameras also were just being installed when I was in medical school. Commercial radiopharmaceuticals were limited in availability, but patient studies with research radiopharmaceuticals were relatively easy to do. IRB approvals were straightforward. The Atomic Energy Commission was overseeing the use of radioisotopes, and the Nuclear Regulatory Commission was not yet set up. The FDA did not have oversight of radionuclide use in humans, and licensed physicians had great latitude in radionuclide use; Investigational New Drug approvals were not required. For that first paper you mentioned, I made the ^{99m}Tc-labeled albumin myself, made a patient formulation, injected it into the patients, and then did the imaging, which was acquired on rectilinear scanners. So it was, of course, very important to do these kinds of functional imaging studies. Very soon after my article on ^{99m}Tc-labeled albumin for the study of placenta previa was published, it was superseded by better, nonradioactive techniques, like ultrasound. The second publication on my CV is also from that era and is obviously more important because we described the production of ^{99m}Tc-sulfur colloid, a probe that persists virtually in the same kit form invented then. Wil Nelp and I had a lot of fun using ^{99m}Tc-sulfur colloid to look at bone marrow function. It is gratifying to see that ^{99m}Tc-sulfur colloid remains in use throughout the world, although now mostly as a lymphoscintigraphy agent. Its advantage in modern use is that it can be applied anywhere where ^{99m}Tc can be supplied or generated and is cheap and easy to make.

Dr. Czernin: *You became very engaged in molecular imaging before that field existed. You started to explore metabolism in mycobacterium tuberculosis, using labeled substrates, such as [U-^{14}C]acetate or [U-^{14}C]glycerol. You also studied the effects of irradiation on bone marrow function and used ^{51}Cr to study splenic function. You did early ^{67}Ga studies in lymphoma and much more. You imaged transferrin receptor function. These papers set the stage for your very early involvement in PET imaging. Your first papers on PET feasibility were published in 1979 and 1980, only 5 years after the seminal paper by Michael Phelps and Edward Hoffman. Because you did not have PET instrumentation available, you created tumor models and measured, for example, intratumoral tritiated 2-deoxyglucose (2DG) uptake in rodent and canine neoplasms.*

Dr. Larson: I was fascinated by the ability to trace metabolism with radioactivity, and I believed in its potential to image a variety of biochemical processes. I recognized that quantitative imaging, especially with PET, would be hugely important, so I followed PET development closely. Even then, I felt that PET would meet many unmet clinical needs. During the early days, individuals in many disciplines took care of patients while practicing nuclear medicine—internists, cardiologists, endocrinologists, and neurologists—some of whom became intimately involved in PET. It was a very good mix between the disciplines that included a lot of basic scientists as well. I realized early that metabolism and imaging of metabolism were going to be critically important. So I studied tumors and looked at tumor utilization of thymidine and 2DG and other substrates. Because we did not have a PET scanner, I did animal studies for direct metabolic measurements. I felt that this could become very practical in time.

Dr. Czernin: *The first well-studied oncologic application was probably in brain tumors. Even today ^{18}F-FDG PET imaging is dramatically undervalued and underutilized for brain tumor assessments. People talk about sensitivity when we should be talking about tumors with low-versus-high glycolytic activities or phenotypes. You published on FDG in brain tumors with Giovanni Di Chiro. During this time you had already branched out to antibodies and antibody fragments, and you published this in JAMA and in Science in 1984. Here is a quote from your Seminars in Nuclear Medicine review from 1984: "New developments in nuclear oncology based on monoclonal antibodies and positron emission tomography measurements of metabolism promise to broaden the range of applications. . . . Of greatest importance is the prospect of both diagnosing and treating common solid tumors with the same radiolabeled monoclonal antibody pharmaceutical preparation." This is the first or at least extremely early definition and introduction of theranostics.*

Dr. Larson: Yes, that's right. It is gratifying to see how these dreams have now become a daily reality. But it was obvious when you think about it. I was tuned into the effects of radiation on tissues and realized that radiotherapy and accompanying theranostics were where I needed to go. In fact, working with Dr. Carrasquillo in the 1980s we had one of the first therapeutic radioantibody clinical protocols, with 30–40 melanoma patients using ^{131}I-labeled Fab fragments specific for p97, an oncofetal glycoprotein of human melanoma. We published this in the *Journal of Clinical Investigation* in 1983. We had set up a big radiolabeling facility at the University of Washington (UW) with the help of Kenneth Krohn. This was the basis for all subsequent studies in the early and mid 1980s when my colleagues who remained at UW went on to successfully target and actually cured some patients with lymphoma. They could administer ultra-high curative activities because bone marrow transplantation had just become available. After I left UW, Oliver Press, Janet Eary, and Dr. Krohn used these same facilities to investigate the effectiveness of anti-CD20 treatments in advanced lymphoma, treating patients using bone marrow transplant to overcome the relatively low TI for bone marrow with these early antibodies.

I was recruited to NIH in 1983 to head up their nuclear medicine program. At the time, the goal was to develop a large PET program for the purposes of neurologic imaging. I oversaw the development of that program, and we expanded nuclear medicine greatly. I believe that at the time, this became one of the best programs in the world. It was my first experience with a large multidisciplinary team. It was great to work with Louis Sokoloff and Dr. Di Chiro, and, as you mentioned, the first systematic studies of FDG in tumors were done by Dr. Di Chiro and others there. We had a whole-body PET scanner and several dedicated brain units. We did a lot of work in neurodegenerative disease and oncology.

In 1988, after 5 years and building a big program, I moved on and joined Memorial Sloan Kettering. This was a perfect fit because of my oncology interests. Their nuclear medicine was really quite underdeveloped, with most of the work when I arrived being done with rectilinear scanners.

Dr. Czernin: *Was it part of radiology at the time?*

Dr. Larson: No, it was part of medicine; they switched it to radiology when I joined. Medicine was not supportive of development of new imaging equipment. They didn't want to spend the kind of money that was needed to upgrade equipment. I collaborated with outstanding clinician scientists throughout the institution from the day that I walked in. For example, 30 years of collaboration with Dr. Cheung led to the application in pediatric oncology that we discussed previously. Other longstanding collaborations have been in endocrinology, where we developed theranostic ^{124}I to complement ^{131}I reinduction therapies developed by James Fagin and Alan Ho; α radiolabels for antibodies and their first use in humans; and many studies with the prostate group using androgen receptor imaging probes, like ^{18}F-fluorodihydrotestosterone, with Howard Scher and Michael Morris.

Dr. Czernin: *During your time as chief you dramatically grew the PET and later PET/CT programs. You studied close to 100 patients/day?*

Dr. Larson: More like 80–90—when I stepped down in 2013, but now it's up to 110–120 per day. Just incredible. The way we started out was to visit personally all service chiefs in major clinical groups to listen to their unmet needs. Communication is key here. You learn from the doctors caring for patients day in and day out about what they need that can really help them, and you emphasize this in joint clinical conferences and research initiatives.

Dr. Czernin: *Sloan has an interesting business model. If I understand it correctly, most of the funds are centralized so that there's no real incentive for entrepreneurship. I find this kind of system strange, because why wouldn't you let people participate financially in the successes that they create so that they can create new programs. Why wouldn't you allow people to be more independent and support their creativity. Do you agree with me?*

Dr. Larson: Let me explain the situation, because I think it's a little different. Each of the services is, in effect, its own cost center, but all of the revenue goes back to the hospital. So, you have to be operating in the black. When I was chief of service I received a small percentage of the total revenue generated by the faculty into a research fund, as did every service chief. I used these funds to develop our programs. I had a little bit to work with, but most of what we did in terms of research was funded by grants from NIH and DOE. But you are right, MSKCC is highly centralized.

Dr. Czernin: *Wouldn't you think that the incentive could be increased, resulting in much stronger programs? How does one measure the outcome of decentralization?*

Dr. Larson: I guess it's mostly about control. Yes, this administrative pattern was sometimes quite awkward, and we may have had disagreements with leadership. Sometimes I might win the argument, but even under the best conditions it was a compromise. This was not very different from the experience of other service chiefs within the Department of Radiology. Nonetheless, overall the situation was positive because I could get resources from a variety of sources, and I did my best to promote faculty development and multidepartmental programs. This was, in part, because when I came to MSKCC I was given a mandate to develop state-of-the-art nuclear medicine and to use the radiotracer principle to synergize the work of promising young faculty, like Dr. Cheung, David Scheinberg, in immunology, Drs. Scher and Morris in prostate cancer, and then Richard Robbins, Dr. Fagin, and R. Michael Tuttle, in endocrinology. This mandate came from the top levels of the institution, Paul Marks, who at the time was President of MSKCC, and Samuel Hellman, who was the Physician in Chief. The Chairman of Radiology at that time, Robin Watson, concurred in this effort. Thus, to a certain extent, I could always fall back on my research/advanced clinical practice mandate to get support for the nuclear medicine program.

Dr. Czernin: *I guess a centralized model would require an objective way to prioritize. What would be the ideal kind of academic health center model in your view that best promotes research?*

Dr. Larson: Of course, a separate department of nuclear medicine would have been my preference. Radiology became big and dominant. I felt the tension around training: the goals of someone who trained in radiology are usually different than those of someone trained as I was in internal medicine. Up until now, however, having separate departments of nuclear medicine has not been economically feasible. Today nuclear medicine is adding a great deal of revenue to hospitals through PET/CT, so discussions, I am sure, will be ongoing. Clearly others who follow me will have to take up this challenge. I do admit that I look with envy at my friend Andrew Scott, who is in Australia, or to Wolfgang Weber, in Germany, where nuclear medicine as a discipline is respected at the chairperson level.

Dr. Czernin: *Well, you have the same in Europe and Asia, and it comes with great successes.*

Dr. Larson: It is an advantage, because you can go and make your case to the people who really decide the big investment and recruitment decisions, such as the university or hospital president and the dean. Something to consider for the future.

Dr. Czernin: *I think that with the emergence of theranostics the financial situation of nuclear medicine will be further improved. As you and we all have seen, great industry interest is focused on theranostics, which is a good predictor of future success. What do you think about recent conflict-of-interest debates and problems that became a public issue at Sloan? I have a strong bias toward industry/academia collaborations. This is because the decider about the value of a product or idea is the market. This is, of course, gravely simplified, but if a real need is addressed by the product, then the product will be successful. How do you see the industry–academia relationship? How can you make that work really well for both sides?*

Dr. Larson: I stepped down as service chief when I turned 70, for a couple of reasons. One is that I had served as head of nuclear medicine for 25 years. I really wanted to go back to my lab. I could do this because I have a full member appointment in the Sloan Kettering Institute, which entitles me to a lab space. Then, of course, I needed grants to do the development I had targeted. I set as my goal developing intellectual property that would attract sufficient funding so that I can develop an alternative funding stream with sufficient resources. In the last 5 years we've had 12 patents, and those patents have now attracted major funding from academia and industry. In addition, I was able to interact with companies to help them develop their antibodies. So I see a strong relationship between academia and industry as crucial to long-term success. That's what I've done, and I believe we are on the path to succeed with this strategy.

Dr. Czernin: *Let's talk about the future. What will be the role of theranostics? How do you see the field developing, and how do we make sure that we move toward strong and collaborative independence?*

Dr. Larson: I believe that we're going to see continued excitement and growth in academic molecular imaging and therapy because the opportunities are so huge and are growing exponentially. That's largely because of theranostics but also because the ever-expanding variety of imaging probes has begun to broaden PET beyond FDG to other tracers for targets like prostate-specific

membrane antigens and somatostatin receptor expression. At MSK, we are expanding to a variety of satellite sites with centralized reading of PETs and will likely be performing more than 150 PET/CT scans per day in 2–3 years, along with targeted radiotherapy of NETs, thyroid cancer, and prostate cancer. Beyond 5 years, the new antibody-based theranostics will come in and, at least in oncology, will lead to even further expansion in therapy and associated diagnosis. This means expansion of faculty, space, and resources. Whole-body PET/CT with ultrasensitive instruments will replace at least many current-design PET/CT units. PET/MR imaging will find a niche in neurology and pediatrics. Training programs will need to be upgraded to allow for subspecialization within nuclear medicine. We will likely need to collaborate with radiology, radiation oncology, and medicine to achieve our full potential.

Dr. Czernin: *The concept of phenotyping by imaging will become more important. We recently had a patient with a very advanced paraganglioma who was imaged with ^{18}F-FDG, ^{18}F-DOPA, and ^{68}Ga-DOTATATE, so that we assessed glucose metabolism, amino acid transport and decarboxylation, and somatostatin receptor expression. These tools can then be used to optimize the treatment strategy. These applications and concepts require a lot of knowledge. And if you now add antibody approaches for diagnosis and therapy, you need a whole different level of knowledge to do this competently.*

Dr. Larson: I agree. We must expand the diversity of our specialty as well as its person power. We must think toward training at the residency and faculty levels, which introduce people to the excitement of medicine in its broadest sense. So much in molecular imaging and therapy is well suited to track with advances in cancer biology, genetics, and other fields. We all must redouble our efforts to keep up with this—if we don't, we will fail. Initially a few programs in centers of excellence with a balance of diagnostic and therapy capabilities will be best suited to serve as models to other programs for upgrading and expansion. These sites will include translational clinics and laboratories for diagnosis and therapy, first at major centers like the University of California at Los Angeles, NIH, and MSK.

It is now more than 50 years since I did my early research as a medical student. Today practice and research in nuclear medicine are more exciting and challenging than ever. I have trained more than 100 fellows, residents, postdocs, and medical students over the years. The baton has been passed to this new generation represented by these trainees. I believe that the field is in good hands.

Dr. Czernin: *Steve, thank you for providing us with so many insights and for allowing our readers to get a closer look at your life of extraordinary accomplishments.*