Toward Integrated Independence
Johannes Czernin Discusses the Future of Thera
tosics with Ebrahim Delpassand, Eric Rohren,
and Wolfgang Weber

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John Czernin, MD, editor-in-chief of The Journal of Nuclear Medicine, spoke with 3 international leaders in nuclear medicine about the future of theranostics and the challenges in training practitioners with a new set of skills that cross disciplines to deliver integrated and innovative care. The discussion included Ebrahim S. Delpassand, MD, who, after a distinguished academic career at M.D. Anderson Cancer Center (Houston, TX), founded Excel Diagnostics and Nuclear Oncology Center and RadioMedix (both in Houston); Eric M. Rohren, MD, PhD, Chair of the Department of Radiology at Baylor College of Medicine (Houston, TX); and Wolfgang A. Weber, MD, Professor and Chair of the Department of Nuclear Medicine at the Technical University of Munich (Germany).

Dr. Czernin: Today we are looking at the status and future of theranostics and at what will be needed to meet the high demands of clinical theranostic services. First, Abe, tell us a little about your background in theranostics.

Dr. Delpassand: After 12 years at M.D. Anderson, I moved to private practice, with the idea of continuing to conduct clinical research. I thought that we could probably do certain things faster without big-organization red tape. Over the years, I filed several Investigational New Drug (IND) applications to treat patients with metastatic somatostatin receptor-expressing neuroendocrine tumors (NECs). We filed the first physician-sponsored IND for 177Lu-DOTATATE in the United States, at a time when patients had to go to Europe or other parts of the world to receive peptide-receptor radionuclide therapy. We also filed the first physician-sponsored 177Lu-prostate-specific membrane antigen–617 (177Lu-PSMA-617) treatment study for castration-resistant prostate cancer in the United States. Our IND paved the way for approval of the drug after completion of the VISION trial, and the drug is now commercially available. We now have an IND for a first targeted α-emitter therapy for somatostatin receptor–expressing neuroendocrine cancers, using 212Pb-DOTAMTATE. We just completed enrollment for this phase 2 clinical trial. The results are extremely promising, and we hope to have this available to our patients as soon as possible.

Dr. Czernin: Eric, you are Chair of Radiology at Baylor and are dual certified in nuclear medicine and radiology. What is the status of theranostics in your institution, and where is it going?

Dr. Rohren: We clearly see the importance of theranostics. We are treating NET patients with Lutathera and are launching PSMA-targeted theranostics. We have patients who are very much in need and would benefit from these very expensive therapies. Something we are struggling with is figuring out ways to deliver care to patients who are underserved and medically disadvantaged.

Dr. Czernin: Wolfgang, as chair of a major European academic institution with many years of experience in clinical theranostics in the United States and Europe, can you tell us about the current demand for theranostics and how you see the growth of the field?

Dr. Weber: We predict about 2,500 PSMA scans and 600 therapy cycles this year, so there is quite a large demand. It’s even more remarkable because we are doing about the same number of 18F-FDG PET scans. This is very different from the United States. For some reason, Germany has decided that FDG PET scans are required only in rare circumstances. I think that Germany has been so well prepared for therapies because, as a result of limited insurance coverage, FDG PET has never become a big thing. In the United States, FDG PET has been quite dominant since 2000 from a volume and revenue perspective, which has both deepened and narrowed the training of U.S. nuclear medicine physicians. In contrast, conventional nuclear medicine, radionuclide therapies, and providing thyroid cancer care have remained integral parts of nuclear medicine training in Germany.

Dr. Czernin: If FDG PET had not been marginalized in Germany, it would have become the major force of nuclear medicine there, too. But I think there is another element at work here. In the 1990s and 2000s, nuclear medicine politics in the United States were tightly focused on FDG PET reimbursement. As a result, large sections of clinical nuclear
medicine (but not preclinical programs) went into hibernation in regard to all the theranostic developments in Europe. Abe, where do you see the field going now?

Dr. Delpassand: I am a firm believer in developing new radiopharmaceuticals to push the envelope to respond to unmet needs in oncology. α-emitters, such as 225Ac, 212Pb, or 211At, are the wave of the future, and the future is here. With regard to ligands, fibroblast-activation protein inhibitors are a hot topic, but their therapeutic relevance needs to be investigated. We also are putting significant resources behind targets such as the low-density lipoprotein receptor that is expressed in glioblastoma and pancreatic ductal adenocarcinoma. Both conditions are huge unmet needs in oncology. Initial human images in new targeted agents in these areas look quite promising.

Dr. Czernin: Eric, what do you see as the potential of theranostics?

Dr. Rohren: We are only scratching the surface of what can be accomplished with theranostics. We will refine and individualize administered activity, dose schedules, and treatment sequencing. The future will be driven by dosimetry and the introduction of combination therapies. Our use of radiopharmaceuticals as monotherapies is out of step with most other current systemic treatments that attempt to attack cancer with synergistic approaches.

Dr. Czernin: Wolfgang, what is your prediction in terms of the overall future of this discipline?

Dr. Weber: PSMA therapy is used today in advanced prostate cancer, and we know that it is effective. We now need to systematically study PSMA radioligand therapy in earlier stages and look at both effectiveness and safety. Much depends on ongoing clinical trials focusing on these questions—positive results could have implications for a tremendous wave of new patients. I agree with Eric that, in general, combination therapies will be increasingly important, as will different therapies used earlier in the course of disease. We must also focus on long-term toxic effects, relevant to patients who will be treated earlier and live much longer. We need to know more about predictors of specific organ toxicity derived from radiation dose calculations. Dosimetry, then, will be increasingly important as we move to earlier stages of disease. If it becomes clear that toxicity is not an issue in earlier-stage treatment with PSMA, there is great future potential. Numerous theranostic agents for other diseases and targets are already being researched, and these are likely to follow much the same course of rapid development that we see with PSMA.

Dr. Czernin: We all agree, then, that there is huge growth potential, which leads to the more practical part of this discussion. That is, how are we going to do this? How many centers will we need? What patient volumes do we expect? Perhaps most important, what is the optimal training for becoming a consultant who gives the best advice about these treatments so that they are deployed most appropriately? Who is going to deliver this care?

Dr. Delpassand: The number of these diagnostic and therapeutic agents will only increase. I have no doubt that we will have additional treatments and specific diagnostic probes for conditions such as brain tumors, pancreatic and ovarian cancer, and other major unmet needs in oncology in the next 5–7 years. During the last 2 decades, many U.S. academic institutions closed their residency programs, and we are now seeing the results of this poor choice. We need to revamp nuclear medicine residency training programs in the United States and also revise their curricula to meet the demand.

Dr. Czernin: How and where would the training happen? Would it be in fellowships or part of the regular residency curriculum? Where would people train?

Dr. Delpassand: We need to significantly adjust the curricula of residency programs and train a new generation of nuclear medicine physicians and scientists who are capable in theranostics, in assessment and treatment of side effects, in research and development, and in regulatory requirements for developing future radiopharmaceuticals. The centers with expertise in these areas should be our training sites. This is essential for the field. If we don’t capitalize on the tremendous opportunity that we have right now to train a future generation according to the needs of our specialty, we are doing a great disservice to our patients and to our specialty.

Dr. Rohren: The skills that were historically needed to practice nuclear medicine in the United States were very much focused on diagnosis and hybrid imaging. Although nuclear medicine certainly included therapies, physicians interested in molecular or functional diagnostics often came to the specialty via the radiology pathway. The world has changed. Now we need theranosticians at the center of our activities. Skill sets from diagnostic radiology, nuclear medicine, radiation oncology, medical oncology, and other fields are needed. As Abe said, the portfolio of skills that we need to put together so that a future physician can practice at the highest level requires innovative thinking around training pathways. We need to be able to manage the patient’s entire experience and assume more clinical responsibility. If we develop dedicated fellowship training, where will the trainees come from—only from nuclear medicine or also from diagnostic radiology? The average physician starting a radiology residency today has little to no interest in the level of involvement that we’re talking about for theranostics. How about radiation oncology? They have a mindset and clinical training that overlap well with theranostics. What about medical oncology? In my view, the ideal skill set for the theranostician mixes bits and pieces of all these specialties. My preference would be that we fully develop this pathway beginning with nuclear medicine, recognizing that the field is rapidly expanding with a strong demand for dedicated future practitioners.

Dr. Czernin: Our first duty is to protect patients, whatever specialty ultimately supports this new demand. We best protect patients if we ensure that the people who deliver care are the best trained to do this and are real experts at what they are doing. They could come from any and all the specialties that you listed.

Dr. Weber: I would emphasize that one needs to take care of and needs to be able to manage patients—not only the side effects of therapy but all the usual problems that these patients have at various stages of disease and treatment. How will we train physicians in theranostics? They will need to learn the necessary...
anatomy for reading the images but also will need to be familiar with all the relevant literature about alternative therapies and the appropriate contexts in which to use radionuclide therapy. And they will have to be able to talk to the patient and explain the process. It makes a lot of sense to think about giving medical oncologists a shortcut to become nuclear medicine board-certified and the same for other disciplines such as radiation oncology. Radiation oncology can in some ways be a role model. Radiation oncologists operate expensive radiation treatment equipment and need to know anatomy to perform radiation treatment planning, but they also provide direct patient care. They have inpatients and manage patients in collaboration with medical oncology, surgery, and other disciplines. We need to develop the same mindset for nuclear medicine.

**Dr. Czernin:** As you know from your experience in the United States, to be certified in nuclear medicine currently, radiologists essentially need 4 months of training to be able to treat patients. This is insufficient, inadequate, and, for providing therapeutic services, irresponsible.

**Dr. Delpassand:** The time is now right to raise the bar to have an independent specialty. We need to tell members of other specialties that if you want to practice nuclear medicine and theranostics you need to go through deep training and understanding about nuclear medicine. As you said, 4 months of training does not give them the knowledge needed to push the field forward.

**Dr. Czernin:** Wolfgang, can you tell us a little bit about the 5-year training that you have in Germany?

**Dr. Weber:** First, I agree 100% with what Abe just said: this training must be a program that leads to certification and to a specific knowledge set. In Germany, the training program has been 5 years for quite some time. Within that period, the trainee must be on a ward for 1 year, which can be a nuclear medicine ward or, for example, an internal medicine ward. So there is already experience in dealing with inpatients. One year of training can be in radiology and then 3 years must be spent in nuclear medicine. A lot of nuclear medicine training in Germany involves taking care of thyroid patients. That’s a special situation in Germany, because iodine deficiency has been common until fairly recently, as well as a high prevalence of benign thyroid nodules. This is very different from the U.S. situation, where there is no iodine deficiency and benign nodules are much less common. In Germany, the result has been that our trainees see many outpatients, not only to read their scans but to adjust their medications. In many places nuclear medicine takes care of the entire management of patients with benign nodules, thyroid cancer, or other thyroid problems. That, of course, is now valuable in running a theranostic center.

**Dr. Czernin:** How much of the future of theranostics is now becoming political? In Europe, some academic centers are also merging nuclear medicine with radiology. And there is some concern in nuclear medicine that radiation oncology wants to compete for theranostics. My question is: how much of this should be a political issue, or should we really be focused on best patient care by very well-trained experts, regardless of their origin in terms of training?

**Dr. Weber:** I very much like the previous statement that it’s not about protecting nuclear medicine but about protecting patients; this should be our guiding principle. Having said that, politics are involved, because in order for theranostics to move forward we must ensure that there are centers capable of performing translational research in this field. The big success story of theranostic agents has its origins in academic drug development in nuclear medicine. If we say, for example, let radiation oncology do the therapy and radiology do the imaging, then I don’t see who would develop new theranostic agents. We should protect the patient, but we should also protect the academic development of theranostic agents. This requires centers that are focused on doing this. I am not sure whether radiation oncology or radiology departments would see it as their main focus to move theranostic agents from bench to bedside.

**Dr. Czernin:** I call this “integrated independence,” because a sense of ownership is needed to continue to develop the field. I once asked Wolfgang what would happen if nuclear medicine becomes a division of radiology worldwide. He responded that the first thing to die will be basic nuclear medicine research. Although there are exceptions, in general a field can’t be developed based on being a small division of radiology; it is simply not possible. That doesn’t mean that you cannot have excellent collaborations with radiologists and radiation oncologists, as all of us have, but it should be an independent field that is self-driven, self-motivated, has a sense of ownership, creates the business and scientific model, and thereby becomes highly successful, as Wolfgang just said.

**Dr. Delpassand:** In order to protect the patients, we need an independent specialty with training that encompasses diagnostic and therapeutic nuclear medicine procedures, patient management, appropriate use of diagnostic and therapeutic procedures and interventions, and also research and the regulatory principles of drug development. If we don’t do this, we are losing a huge opportunity for the field and for our patients. I like the term integrated independence. Yes, we will work with all other disciplines, but nuclear medicine specialists, with their background knowledge, will be best suited to lead and address the unmet needs in oncology and to develop new targeted radioligand therapy approaches. If we create the right curriculum for this specialty, then the right applicants will be attracted and, because the field is protected, they will feel secure on the financial side and comfortable investing in this field to become an expert in nuclear medicine.

**Dr. Rohren:** Politics are always present. Focusing on quality of care and patient outcomes is paramount. Regardless of background, I think that someone who is devoted to the field of theranostics and goes through a rigorous training program would be welcomed into a big tent. My fear (and the major threat) is that poorly trained or untrained individuals will want to take on the role of theranosticans. We can and need to create a new, vibrant specialty for people coming from diverse backgrounds focused around the area of theranostics. We will create this pathway toward optimal patient care and then encourage people to follow that training pathway and join us in the future of the specialty.

**Dr. Czernin:** Thank you all for participating in this discussion. I am hopeful that it will contribute to positive changes in the training and expertise of nuclear medicine specialists as theranosticans.