Perspectives on Theranostics and Nuclear Medicine

A Conversation Between Andrew Scott and Johannes Czernin

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Johannes Czernin, editor in chief of *The Journal of Nuclear Medicine,* talked with Andrew M. Scott, director of the Department of Molecular Imaging and Therapy at Austin Health, head of the Tumor Targeting Laboratory at Olivia Newton-John Cancer Research Institute, a professor at the School of Cancer Medicine at La Trobe University, and a professor at the University of Melbourne (all in Australia), about his role and perspective on the extraordinary growth and promise of theranostic applications in nuclear medicine.

Dr. Scott is an internationally recognized physician/scientist whose research has focused on defining and characterizing antigen and receptor targets for cancer therapy, signaling and metabolic pathways in cancer cells, antibody-based therapy and immune regulation of tumors, and molecular imaging of cancer. His research has led to translation of multiple novel antibodies and proteins from basic development to phase 1 and 2 cancer trials. In addition to his clinical and research activities, he is engaged in strategic planning for training, health-care policy, and molecular imaging/nuclear medicine therapy advocacy in countries around the world, as well as with the International Atomic Energy Agency and the World Health Organization. He is a former president of the World Federation of Nuclear Medicine and Biology and has published more than 390 peer-reviewed articles and 27 book chapters.

Dr. Czernin: *Andrew, I want to first talk to you about theranostics, which is now becoming mainstream in oncology and is considered one of the major accomplishments in the history of nuclear medicine. How do you see the presence and future of theranostics?*

Dr. Scott: The future is extremely bright. It is quite gratifying to see improved progression-free and overall survival in prostate-specific membrane antigen (PSMA)–targeted radionuclide multicenter trials, which build on a history of innovation in our field. I started my theranostics research with radiolabeled antibodies back with Steven Larson, at Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY). Today our understanding of suitable targets in tumors and therapeutic strategies, including delivery systems, is more sophisticated. We are also much more expert in conducting multicenter trials, either investigator-led cooperative group or industry-led studies. If we had relied only on industry-led studies, I don't think we would have achieved the progress that has been made. And I do think that we need to maintain our roots in biology and in physiology to ensure that innovation and progress continue. Nuclear medicine isn't just about looking at images; if that's all we did, we would not be where we are with theranostics. We have to maintain that rich pipeline—that deep understanding of the fundamentals of biology, the connection to imaging, and how that leads to radiopharmaceutical approaches—to achieve therapeutic outcomes for patients.

Andrew M. Scott, MD

Dr. Czernin: *Much of the impetus for designing the prospective PSMA trials came from compassionate-use studies done in Germany. Of course, these wouldn't have been sufficient to move the field forward, because prospective data are needed. At the same time, in Australia even before the VISION trial you provided important data from prospective studies of PSMA therapeutics (e.g., the TheraP trial) and for somatostatin-targeted therapies. Could you treat patients outside of trials?*

Dr. Scott: There is a regulatory mechanism in Australia to treat people with compassionate therapeutics under certain circumstances, and this has been done. But we have also introduced a discipline and rigor in Australia to perform prospective clinical trials for novel imaging and therapeutic radiopharmaceuticals. That dates back to our early studies in PET, where, in order to achieve Medicare rebates for PET, our federal government provided support for a nationwide program in which we performed prospective studies over 2 years in more than 30,000 patients to generate evidence of PET's impact. We also explored detailed management outcome data in prospective studies in more than 900 additional cancer patients. These data allowed us to get approval for PET in Australia for a range of cancers and to develop a clinical trial network that we have then been able to reapply to theranostic programs.

Dr. Czernin: *Given the enormous interest in PSMA-targeted theranostics, do you have any volume predictions in Australia? How many patients will you treat per year?*

Dr. Scott: We don't have precise numbers, and we are actually working on that at the moment. But it's many, many thousands of patients.

Dr. Czernin: *We came up with an estimated 40,000 patients in the United States initially, including all patients with advanced disease—that's 160,000–240,000 cycles, which is an enormous number when you know that we may have a hundred sites where these treatments can be done. The volume will be staggering.*

Dr. Scott: It will be! We have been thinking a lot about the provision of PSMA therapies in Australia and how this can be done in an effective and equitable manner. From a supply chain perspective, I think the supply of lutetium is going to be a major issue globally.

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Dr. Czernin: *Yes, we hope that the market will take care of it, because someone will make a lot of money if the supply problem is solved.*

Dr. Scott: Another key issue we have been doing a lot of work on is workforce training and standards. This involves creating standards both for professional training for our clinical and scientific professionals and for site credentialing.

Dr. Czernin: *Theranostics has created a whole new image for nuclear medicine. It has led to the recognition that nuclear medicine has something unique to offer in the therapeutic realm.*

Dr. Scott: There is no doubt that theranostics is going to take nuclear medicine into a bold new direction, so that it is not just seen as an imaging specialty. This will be a worldwide trend and one that we need to pursue collectively. Over the last 5 years in particular, the profile and reputation of nuclear medicine in Australia among our oncology, cardiology, and neurology colleagues have been progressively increasing due to the success of our clinical and basic research. Many clinical trial groups are now asking us to participate in the design of large studies. We now have a group of highly talented young nuclear medicine physicians such as Michael Hofman, Louise Emmett, Roslyn Francis, Sze Ting Lee, and others who are really taking charge and leading impactful clinical trials. It's wonderful to see. But there are even more opportunities moving forward.

Dr. Czernin: *Let's talk about the next targets. I found your earlier* Journal of Clinical Oncology *(1994;12:1193–1203) article where you worked with Steve Larson to target fibroblast activation protein (FAP). It's actually a wonderful paper because it focuses on this very interesting target but also applies SPECT/CT, a technology that was new at that time.* JNM *has recently published two articles, one from Baum et al. and one from Ferdinandus et al. with two different compounds targeting FAP for therapy. And Clovis has recently recruited the first site for their therapeutic FAP inhibitor trial. What do you think about targets such as this?*

Dr. Scott: I have long thought that FAP is an excellent target. Lloyd Old, who was among the founders of modern tumor immunology, developed the first anti-FAP molecule (antibody F19). I was involved in the first-in-humans imaging trial that validated FAP as a target in tumors. This was followed by a trial that I led with the humanized anti-FAP antibody sibrotuzumab, which combined imaging with therapy using this antibody. We also undertook a small radioimmunotherapy trial in cancer patients with ^{131}I-sibrotuzumab. We confirmed that FAP is expressed across a range of different tumor types and have continued to explore the biologic role of FAP in the tumor microenvironment. It is exciting to see that FAP is now emerging as an important target for PET imaging and potentially therapy with radionuclides.

"Innovation and success will always bring challenges, but we are very well positioned to bring these new imaging and theranostic approaches to our nuclear medicine profession and to patients."

Dr. Czernin: *Talk a little bit about your career. How did you get to MSKCC, and how did the work there shape your work as a translational scientist?*

Dr. Scott: I did my medical training in Sydney (Australia) and after residency undertook internal medicine training and completed my Fellow of the Royal Australasian College of Physicians exams. In Australia one typically undergoes additional specialty training after internal medicine. I was impressed by the nuclear medicine department at the large hospital at which I was working and decided to pursue this as a career. Nuclear medicine training took an additional 3 years. I felt that PET in oncology had great potential, although at the time it was mainly focused clinically only on cardiology, neurology, and brain cancer. No PET sites had been established in Australia. I was also interested in monoclonal antibodies from my reading of the scientific literature. Steve Larson happened to travel to Australia toward the end of my nuclear medicine training, and I asked if he had any fellowship positions available. He did, and soon afterward I found myself in New York, working at MSKCC. While there, I spent a lot of time in the lab and clinic working on monoclonal antibody research and trials. This led me to work closely with Lloyd Old, who had an extraordinary program at MSKCC of discovery and clinical translation of monoclonal antibodies. I was very fortunate to spend time in his lab developing cutting-edge technologies and also to work closely with Steve Larson in his world-class PET and SPECT program, including targeted antibody therapeutics. Toward the end of almost 3 years at MSKCC I was offered a position back in Melbourne in the Ludwig Institute for Cancer Research (LICR) to develop a laboratory and clinical program in targeted antibodies and in oncologic PET. I was quite fortunate to be in the right place at the right time, because Lloyd Old was the scientific director of the LICR and my new position coincided with an expansion of the LICR global clinical program. Since returning to Australia, I have led a laboratory program focused on antibody and small-molecule therapeutics and cancer biology, on PET in oncology, and on radionuclide therapy at the Austin Hospital.

Dr. Czernin: *What would you consider your most important contribution to improve patient outcomes through your work in imaging and theranostics?*

Dr. Scott: From a patient impact perspective, probably designing and conducting large multicenter trials in PET that led to Medicare approvals. In Australia almost 90,000 cancer patients now undergo Medicare-funded PET studies each year. Also, contributing to the development of theranostics, which I have been doing for almost 25 years. Seeing theranostics achieving such successes is very gratifying.

Dr. Czernin: *You know the American, the Australian, and the European health-care systems. What should the ideal health-care system look like?*

Dr. Scott: I think the Australian system works very well, because we have a universal health-care coverage safety net that provides basic essential health care and access to major teaching hospitals for complex treatment. But we also have a private insurance system, which is very important if you want to be able to select your own specialist for obstetric care, for orthopedics, or for elective surgery.

Dr. Czernin: *What percentage of Australians have private insurance?*

Dr. Scott: I believe it is just over 40%.

Dr. Czernin *So it's a pretty high percentage.*

Dr. Scott: That is correct. There is a tax advantage for having private health insurance. One of the reasons that our health system

works well is that if you have an acute illness, the major teaching hospitals that are university-affiliated are as good as any in the United States and Europe. Anyone who is an Australian citizen can go to these hospitals and have treatment for free during acute admissions. In the context of the global health-care environment, the government through Medicare actually sets the reimbursement for consultations and procedures. You can see any primary care provider you want for free, although some do charge a small copayment. We have an advantage of being able to have access to virtually all of the modern technologies and pharmaceuticals. Of course, there can be delays in some new and expensive therapies being provided, and for nuclear medicine we are still putting in health technology applications for some PET indications. If you want to see a specialist of your choice or have elective surgery without being on a long waiting list, private insurance can be beneficial and therefore is common. The approval and reimbursement for new radiopharmaceutical therapies (e.g., ^{177}Lu-PSMA) will be an interesting journey!

Dr. Czernin: *Back to the clinical trials network: how do you motivate sites to participate?*

Dr. Scott: Our major teaching hospitals have well-established systems for approval and conduct of clinical trials. The regulatory environment is also supportive, because within public hospitals there is no requirement for current-good-manufacturing-practice certification for early-phase investigator-initiated radiopharmaceutical trials. Of note, we have a large network of enthusiastic nuclear medicine clinicians, scientists, and technologists who work well together. Through our Australasian Radiopharmaceutical Trials Network *(J Nucl Med.* 2021;62:755–756) we have also developed site credentialing and central data review processes that make participation much easier for smaller sites. An important advantage in the last 5 years has been the availability of major grant funding initiatives for clinical trials that we have been able to tap into. This has been a federal government initiative and has been quite transformative. There has also been support from major philanthropic and charity organizations, such as the Prostate Cancer Foundation and Movember, as well as the Australian Nuclear Science and Technology Organization, for many of the trials performed.

Dr. Czernin *So that brings me to what I think is the most important topic that needs to be addressed worldwide, and that is inequalities in health care. How can we address disparities in health care?*

Dr. Scott: This is a key issue in improving access to nuclear medicine globally and was the topic of the recent Lancet Oncology Commission on Medical Imaging and Nuclear Medicine (*Lancet Oncol.* 2021;22:e136–e172), for which I was a lead commissioner. The key initial part of this project was that we had no clear understanding of the imaging infrastructure and workforce around the world. We had some information for nuclear medicine, mainly through the International Atomic Energy Agency database, but there was minimal information for radiology. One of the principal achievements of this project was to bring together accurate information on imaging equipment and workforces in 200 countries. From the nuclear medicine standpoint, there was impressive cooperation and support from many societies and individuals around the world. We then performed a very detailed Delphi analysis of the role of imaging in diagnosis and treatment of 11 common cancers. We subsequently performed sophisticated modeling to determine the impact of improvement in access to imaging on survival across all 200 countries. There were several important outcomes from this analysis. The first was that improvement in basic imaging access to technologies such as ultrasound and x-rays would have the greatest impact in low-income countries. In middle-income countries, improved access to MRI, PET, and CT would have the greatest impact on survival. Interestingly, in high-income countries, improved access to PET, CT and SPECT would have the greatest impact on survival. The other very important outcome of this Lancet Oncology Commission was that increasing imaging access for cancer patients was projected to cost just over $6 billion for a 10-year period but would result in lifetime productivity gains of $1.23 trillion—a net return of $179.19 per $1 invested. We are now working to have these pivotal findings translated into health-care policy and also to identify mechanisms to support initial funding, particularly in low- and middle-income countries.

Dr. Czernin: *You also write in this article about changes in education and training that would include health-care economists and public health experts, as well as imaging experts and oncologists, to educate medical students and then postdocs and young experts. You also address the need for establishing centers of excellence.*

Dr. Scott: If you create centers of excellence where nuclear medicine professionals can train and learn, you can achieve the workforce you need for cancer imaging and theranostics. This can be at a country level or at a regional level. Also, we need to work with governments to influence health-care policy for nuclear medicine and medical imaging that is justified by economic evidence. We need to ensure that our nuclear medicine community is much more aware of this sort of information and is able to engage with regulatory and reimbursement bodies in their countries to improve funding and access. Many other medical specialties, such as cardiology, neurology, oncology, and mental health, are very proficient at obtaining such approvals. Our nuclear medicine profession now has evidence in cancer to justify country-based investment, and we should work together to achieve improved access to PET- and SPECT-based imaging in cancer patients.

Dr. Czernin: *What is your advice for young colleagues entering the field, and what is your final message to our readers?*

Dr. Scott: I would say to young colleagues that nuclear medicine has never been a better specialty to work in than it is now. I was enthusiastic when I started more than 25 years ago, but the future is even brighter now! Be flexible, open-minded, and read the literature—not only in nuclear medicine but in the areas where medicine and science are heading. It is a time of significant change, so keep up to date with the latest advances and opportunities. Be strategic and forward thinking. If we provide leadership, our other medical colleagues will come along with us. Innovation and success will always bring challenges, but we are very well positioned to bring these new imaging and theranostic approaches to our nuclear medicine profession and to patients.

Dr. Czernin: *Thank you for taking the time to talk to our readers and me.*