Discussions with Leaders: A Conversation between Simon Cherry and Johannes Czernin

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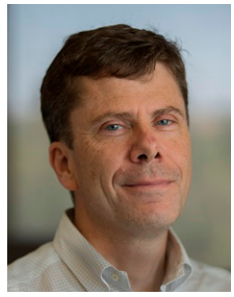
Simon R. Cherry, PhD, is Distinguished Professor of Biomedical Engineering at the University of California, Davis (UC Davis), and has received international recognition for leading teams in developing in vivo molecular imaging systems, applying high-resolution systems for PET and other modalities, and particularly for pioneering microPET technologies. He has contributed to the development of high-performance detectors for PET, the application of Cerenkov luminescence in molecular imaging, and the first proof-of-concept hybrid PET/MR imaging system. Currently, Dr. Cherry, together with Ramsey Badawi, PhD, a professor of radiology at UC Davis, is leading a large NIH-funded program to design and build EXPLORER, the world's first total-body PET/CT scanner.

Dr. Cherry received his BSc (Hons) in physics with astronomy from University College London in 1986 and his PhD in medical physics from the Institute of Cancer Research, University of London, in 1989. After a postdoctoral fellowship at the University of California, Los Angeles (UCLA), he joined the faculty in the UCLA Department of Molecular and Medical Pharmacology. In 2001, he moved to UC Davis as a professor in the Department of Biomedical Engineering and established the Center for Molecular and Genomic Imaging, which he directed from 2004 to 2016. He has authored more than 300 peer-reviewed articles and been honored with a broad range of awards, including the 2018 Paul C. Aebersold Award from SNMMI for outstanding achievement in basic nuclear medicine science.

Dr. Czernin: *I want to start out by asking about the EXPLORER project. When I first heard about the total-body PET concept, I thought (like many others) that PET had already maximized its potential with perhaps some incremental improvements yet to come. When and how did you come up with the idea to pursue the total-body EXPLORER project, and how did you get it going?*

Dr. Cherry: The idea came out of a meeting I had in 2005 with Ramsey Badawi, who has co-led this project with me all along. Ramsey had recently joined us at UC Davis, and we were chatting about projects and ideas on which we could work together. Ramsey had been running computer simulations of what would happen to the performance of a PET scanner if the imaging field of view (FOV) along the body were expanded from 15–20 cm up to 50–60 cm. I was coming from a very different direction. My lab had spent a lot of time working in preclinical PET, developing small animal PET systems, and trying to push resolution and sensitivity—important issues in preclinical imaging. These scanners, that already could provide total-body mouse imaging, were clearly quite useful. The directions of Ramsey's and my work, then, had clear convergences. The fact that we were already doing total-body imaging preclinically and that Ramsey's simulation work suggested that increasing the FOV further would be beneficial for human imaging motivated this project.



Simon R. Cherry, PhD

Then we thought, well, rather than build a scanner with a 40–50-cm FOV, which would still be somewhat incremental, we should do the ultimate and build a total-body human scanner. This is the best we can possibly do in terms of collecting the available signal and would also allow us to see the entire body at once. We knew there would be lots of challenges. But we also knew that we could build the highest-sensitivity scanner ever. That is really what motivated us to move this project forward.

Dr. Czernin: *Sometimes it is obvious that technologies are developed to meet specific clinical needs. But many technologies are developed by industry to create a need that does not exist now or may never exist. Building the total-body system was extremely risky. Was it more the technologic challenge that attracted you to create the best PET scanner ever, with applications as an afterthought? Or was it always a technical idea in parallel with possible clinical and research applications?*

Dr. Cherry: It started off as a sort of challenging idea. But very quickly we identified a range of research areas where we thought this could be hugely impactful, for example, by creating the ability to look kinetically and simultaneously at new drugs and new tracers in all the tissues of the body to enable measurement of whole-body pharmacokinetics of labeled drugs and probes. This was very attractive. As was the idea that we could perhaps extend some of the successes we have had with PET in oncology into other systemic diseases, such as inflammation and infection. So, early on we were positioning this as a very high-end research tool for the molecular imaging community.

Dr. Czernin: *We will get back to the EXPLORER and talk a lot about potential applications later. But for now, take us back to your academic roots. Tell us why you focused on PET from the beginning.*

Dr. Cherry: I received my undergraduate degree in physics and astronomy from University College London and then joined the Royal Marsden Hospital, which is part of the University of London, to do a PhD in medical physics. From the start of my PhD program I was involved with PET technology. Interestingly, in Britain at that time one applied not to a graduate program but for a specific PhD project. I had

a choice between an MR imaging project and a PET project. Fortunately for me I chose PET. We were developing a scanner based on multiwire proportional chamber technology at the Royal Marsden Hospital. The only other PET center in the United Kingdom in the 1980s was at the Hammersmith Hospital and was directed by Terry Jones. I made several visits there and had many good discussions with him, which opened my eyes to the broader opportunities in PET. However, I never directly collaborated with him until we worked together on the EXPLORER project some 35 years later!

Dr. Czernin: *I remember pretty much the day in 1990 when you joined the group led by Edward Hoffman at UCLA. How did you connect with Ed and UCLA?*

Dr. Cherry: I joined on January 6, 1990, and remember it very well. Of course, the UCLA group was famous around the world. The senior people there were Michael Phelps, Hoffman, Sung-Cheng "Henry" Huang, Heinrich Schelbert, John Mazziotta, and Jorge Barrio. These are legendary names in the PET field, and as a PhD student I had read so many of their papers. In my opinion, UCLA was probably the world's leading group at that moment. In 1989 I wrote a letter to Ed Hoffman asking if any positions were available. (This was before email—we actually wrote letters.) I was shocked to get a response back a few weeks later describing a postdoctoral opening at UCLA and saying that I should introduce myself to Ed at the upcoming Society of Nuclear Medicine meeting in St. Louis. MO. I went to that meeting and gave a talk, which Ed attended. Shortly after that he offered me the position, which was a dream come true.

Dr. Czernin: *Ed was working on refining the early prototypes in terms of detector technology as well as on novel image reconstruction methods.*

Dr. Cherry: That is right. He was very much involved in developing next-generation systems with CTI, Inc. He was also working with Magnus Dahlbom on whole-body image acquisition methods.

Dr. Czernin: *When did you become a more or less independent investigator and begin to create your own program?*

Dr. Cherry: That happened quite gradually. I was very lucky, because the environment at UCLA at that time was absolutely superb for a trainee. It was a mix of having these fantastic senior people with an incredible amount of knowledge and experience and then also the next generation that was there at that time. People like yourself, Gerold Porenta, Magnus Dahlbom, Roger Woods, and Denis Buxton, and of course, Sanjiv Sam Gambhir, to name only a few—just a tremendous group of people to bounce ideas off and work together with. I was lucky to be in the right place at the right time. Ed was great at encouraging people to pursue their own ideas. In fact, I remember that when I started I assumed he was going to give me a project on which to work. That was the model I had been used to. But he did not do that. He said, "Take a few days and think about what you want to work on and then come back and tell me what it is." From day 1, he forced me to think about what I thought was important. When I came up with an idea that was silly or wrong, he would gently tell me. He very much forced me to be independent, which was really, really good. He was also incredibly generous. As I started to come up with my own ideas, I had no funding. He had all the money. He would help support those ideas and, if I needed help with equipment, he would buy it. If I needed resources or instrumentation he already had, he would give it to me. Slowly over time I got to the point where I could write my own proposals. The first grant I received was from the Whitaker Foundation to develop high-resolution detectors for small-animal imaging. That idea came out of other projects I worked on. At UCLA we used a CTI-built scanner for dog and monkey imaging. This showed me the potential of PET in large animal research. I thought that if this were useful in monkeys, then why not enable small-animal imaging to study the many mouse models of human disease that were rapidly developing during this time?

Dr. Czernin: *You then created the entire field of microPET imaging. I remember very well one of your presentations in the mid-1990s, where you talked about the concept of microPET imaging. For the first time I understood its potential in terms of drug development, drug screening, treatment assessments, pharmacokinetics, and pharmacodynamics in murine disease models.*

Dr. Cherry: We finished the first prototype in 1996 after a couple of years of development. It was around that time that I became fully independent. Ed secured for me a visiting assistant professor position in 1992 and then was instrumental in creating an assistant professor position at UCLA for which I applied in 1993. He even gave me some of his lab space to use as my own, which was incredibly generous—he did not have to do that.

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Dr. Czernin: *And when and how did you migrate the technology out of UCLA into industry?*

Dr. Cherry: Right around 1997. Of course, I benefited hugely from the existing relationship that UCLA had with industry, particularly with CTI, which had been founded by Phelps, Ron Nutt, and Terry Douglass. Through conversations that involved Ron and Robert Nutt and Phelps, we came up with the idea to commercialize microPET. This was a great time, as my lab worked with a small company, Concorde Microsystems, to translate the technology and turn it into something that could be manufactured and commercialized. This led to a very successful product line that existed for many years.

Dr. Czernin: *When you look at the late 1990s, with the work of David Townsend, for example, it became evident that PET/CT was going to be an important clinical and also preclinical imaging modality. Why did you "skip" preclinical PET/CT in favor of preclinical PET/MR imaging?*

Dr. Cherry: We did a little work in PET/CT, with a graduate student working on a preclinical PET/CT system. But, yes, you are right. We did not put a lot of effort into that area, partly because PET/CT took off incredibly quickly. People flocked to that concept, and I have always believed that if an area is getting hot and crowded and you are only starting to think about it, then you are already too far behind. You have to try to be ahead of the curve and anticipate, which means that sometimes you may work on things that come to nothing because you bet on the wrong horse. Other times it will give you the edge and allow you to be the first. That is where the fun is in research. So, we focused on PET/MR

imaging, which was a concept that was extremely unpopular at the time.

Dr. Czernin: *Are you happy with the outcome of PET/MRI in terms of translational success?*

Dr. Cherry: No, I am bitterly disappointed in many ways. Technologically it has been a marvel and, at the scale of human imaging, is absolutely amazing. But I had really high hopes that we would discover and learn new things about the body and human disease through the combination of what seemed to be the 2 most powerful imaging methodologies, a vast array of radiotracers, and all the different pulse sequences possible with MR, along with spectroscopy, dynamic contrast MR, and now, of course, hyperpolarized MR imaging. I always saw it much more as a research tool than a clinical tool. I hoped that it would teach us innovative ways to use these 2 technologies together. I have to say that to a large extent this has not happened. If you look at the vast majority of PET/MR imaging literature, most studies could have been done on 2 separate scanners. Very few studies show the requirement for acquiring data simultaneously. We do not have PET/MR here at UC Davis, so I cannot really comment on the clinical impact. But my sense from the outside is that there is not a widespread movement from PET/CT to PET/MR imaging.

Dr. Czernin: *Do you think that is because of its operational complexities and high costs? The clinical workflow makes it difficult to take the time to exploit the power of these technologies, which require dynamic imaging. It is somewhat ironic that many attempts were made to shorten acquisition protocols, efforts that are not really helping to exploit MR imaging capabilities.*

Dr. Cherry: I think that is true of both PET and MR imaging. If you want to extract lots of information and be very quantitative, then it takes time to acquire dynamic data. That is completely at odds with the clinical workflow and the cost environments within which we must work.

Dr. Czernin: *You can make the same argument for the EXPLORER system. For many clinical indications, such as routine imaging of cancer patients, very short acquisition times will suffice to get fantastic images because of the extremely high sensitivity of your system. If, however, you want to exploit all the quantitative capabilities, that is no longer true. Do you agree?*

Dr. Cherry: Yes. We face some of those same issues. It will be very interesting to see what happens in the clinical arena. Are people going to use this tool just to push patients through much more quickly (for example, with 30–60 second scan times) at the same diagnostic quality that we currently achieve in 20 minutes? On the other hand, if you now take a 10–15-minute EXPLORER scan the image quality is phenomenal. Are physicians going to demand this as the new quality standard for clinical PET? I do not know the answer until we try it and see. And you are right: some of the research in which we are very interested requires long scan times because the kinetics of the tracer must be followed. We are still left with that paradox that quantitative imaging may be completely at odds with clinical workflow.

Dr. Czernin: *At the time you developed preclinical PET/MR imaging the whole field of molecular imaging was emerging. I remember that you took off from your physics lab at UC Davis for a year or so to work in a biology lab for better insights into biologists' needs from imaging and to understand how biologists are thinking. Do you think that molecular imaging has fulfilled its promise?*

Dr. Cherry: I do not think it has fulfilled its promise yet, but there are encouraging signs. Its success and ultimate impact depend on where medicine and treatment go—especially on the extent to which treatments become more personalized. We currently largely treat patients mostly based on statistical probabilities across large populations. Once we move to a paradigm with much more targeted (and often expensive) therapies that work only in subsets of patients we will need much better stratification tools. The role of imaging for selecting, guiding, and monitoring those treatments will be absolutely essential.

Dr. Czernin: *I completely agree but think you are talking mostly about PET. What about all the other imaging modalities, including optical approaches, smart ultrasound techniques, multiparametric MR, spectroscopy, etc.?*

Dr. Cherry: Optical imaging has had a huge impact in the preclinical arena. It has been hugely helpful for cost-effective screening of new therapies or monitoring gene expression in mouse models. Translation into the clinic, of course, is challenging, but the area in which we are starting to see the promise realized is for intraoperative guidance, where some of the optical agents are finally getting approved for clinical use. I think the impact in that area is going to continue to grow.

Dr. Czernin: *What about other molecular imaging approaches? Are there any other technologies that you think will emerge from 20 years of molecular imaging research?*

Dr. Cherry: It is so hard to predict these things. Every time I try to predict something, I am wrong. Every time I think there are not going to be new imaging modalities, I am wrong. Who would have thought a few years ago that with photoacoustics we would be able to produce these incredibly detailed images of the vasculature? That has emerged as a pretty exciting modality. But, again, clinical translation is not easy.

Dr. Czernin: *Maybe we can talk a little bit more about MR imaging, because it has been around for decades and there is still a lot of discussion about molecular and functional imaging with MR. Where is that going in your view?*

Dr. Cherry: Obviously, as you know, much of the excitement right now is around hyperpolarized MR. This is a very clever approach to dramatically improve sensitivity and image metabolic pathways. The sensitivities start to approach those that we have seen in nuclear medicine. But logistically it is incredibly challenging because of the very short time in which to measure the signal. Will this become a clinical workhorse? It seems unlikely. Is it having an impact in research? Absolutely.

Dr. Czernin: *Getting back to the total-body PET EXPLORER project, you have developed 2 lines of products if I am correct. The first is a preclinical non-human primate system that creates incredibly impressive images. The second is a human system. How far is that in terms of commercial availability? What is the business plan for system rollout?*

Dr. Cherry: Just to give you a little bit of the historical development, the first test system was one on which we collaborated with Siemens. They kindly donated an older scanner to us, and we reformatted that system to create a smaller-bore, longer-axial FOV system. This turned out to be a good size for imaging non-human primates. We then developed the human system, for which we really wanted to use more cutting-edge technology. We collaborated with United Imaging Healthcare to do this. The human system was completed in May 2018. It then underwent about 3 months of extensive physical evaluation and phantom studies. In September 2018 we performed our first human studies in collaboration with Zhongshan Hospital in Shanghai, China. We could have worked with any of the major companies on this project, but

the reason we went with United Imaging was that they were the only company willing to do this and bring it to the market, thus giving us an opportunity to disseminate the EXPLORER technology and impact patients all over the world.

Dr. Czernin: *EXPLORER is a PET/CT system. What is the CT component?*

Dr. Cherry: We have a high-end 80-detector-row CT system on the scanner with very high spatial resolution. It also has very innovative low noise detector technology that will allow us to push radiation doses down for the CT component.

Dr. Czernin: *When you have a system that can acquire a whole-body study in, say, 2 minutes including the CT, the patient could be on and off the table in 7–8 minutes. How do you deal with the patient line-up for tracer injection? Memorial Sloan Kettering performs 120 PET/CT scans per day, and MD Anderson the same or more. Even at smaller institutions like ours we have pretty substantial numbers. The EXPLORER may work really well for high-volume clinical operations. Above all else, image quality is terrific. In addition, operational costs are likely to be much lower because you essentially have 1 scanner instead of 4, 6, or10 scanners, which will reduce personnel requirements. What are the space requirements for the system?*

Dr. Cherry: At least initially, I imagine the system will be adopted only at high-volume sites, where it will make the most sense. These centers may need more uptake rooms; however, there are so many variables that we will not know the requirements until we get some clinical experience. For example, we do not know whether we might modify the uptake time, either to shorten (because we will not need to wait so long because of much improved image quality) or even to lengthen uptake times. You could bring a patient back 3–4 hours after injection and the image contrast would be absolutely amazing. Space requirements are not a major barrier. The estimate is that we need a room that is 3–6 feet longer than that required for a conventional PET/CT system. The width of the room is the same.

Dr. Czernin: *Do you have some idea about the price point?*

Dr. Cherry: The numbers I am hearing, very roughly, are on the order of $10 million, but United Imaging will have to address that question. The system requires roughly 8 times the material of a standard PET system, with about an 8-fold increase in the cost of the PET. The system received FDA clearance in December 2018, so the company now can sell it in the United States for clinical use. It will be very interesting to see how the market responds, who wants it, and what they want to use it for.

Dr. Czernin: *The $10 million sounds quite reasonable, and, as a financial model this may work better than PET/MR imaging. I think it is going to be very successful.*

Dr. Cherry: I hope you are right. But you know this was not the prevailing opinion in the field 10 years ago. The number 1 criticism we received time and time again was that it was going to be too expensive. The nuclear medicine field does itself a disservice sometimes. We really need to push our technology and our applications and do the best we can do for our patients. Sometimes the initial steps may be expensive, but the eventual return may also be great. The MR community has no qualms at all about going after really expensive high-field magnets and exploring where that takes them. A lot of progress and understanding has come from this. In nuclear medicine we worry too much about cost in the first instance and sometimes do ourselves an incredible disservice.

Dr. Czernin: *Simon, you and Ramsey and your team have created an extraordinarily interesting product. You have migrated it out of academia into distribution and use. What are you going to do next?*

Dr. Cherry: I think where we can have the most impact in the next few years, given that we are going to get the first system here at UC Davis, is to really show what it can do both in the clinic and in research. I am gearing myself up to focus on how we use and apply this scanner. Some of my lab members will certainly continue to work on new technology, which has been our bread and butter for many years. But personally, for me, I want to now focus on the applications. It is something I worked on at the early stage of my career, when I was involved in a lot of brain activation studies and we also did interesting animal studies with new tracers. I want to get back to some of that work. I have interacted with the drug industry over the years as well and want to be involved in showing what EXPLORER can do. What I would really like to do is learn something new about the human body or disease process that has never been seen before—not just doing what we already do a bit better but to do something new and fundamentally different, which hopefully can expand the range of applications for PET in the future.

Dr. Czernin: *Thank you, Simon, for taking the time to talk with me.*