

Industry Perspective on the Changing Nuclear Medicine Landscape

A Conversation Between Jonathan Allis and David Mankoff

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David Mankoff, MD, PhD, an associate editor for *The Journal of Nuclear Medicine*, talked with Jonathan Allis, DPhil, about his career as a leader in the radiopharmaceutical industry, including his latest efforts as founding chief executive officer of Blue Earth Diagnostics (BED). Dr. Allis, originally from South Africa, received his undergraduate degree in physics from the University of Cape Town and a doctorate in biochemistry from the University of Oxford (U.K.). His doctoral thesis and early career focused on nuclear MR and MR physics. Before his current role, he was the general manager for PET at GE Healthcare Life Sciences, with global responsibility for GE Healthcare's PET agent and PET synthesis platforms business. He has previously held positions in research and development and marketing/product development at Amersham plc, Siemens Medical Solutions, and Oxford Magnet Technology. At BED, Dr. Allis oversaw U.S. Food and Drug Administration approval and clinical rollout of ¹⁸F-fluciclovine (Axumin; BED), one of the earliest PET agents approved for prostate cancer imaging, with more than 120,000 doses administered since 2016. He has been active in the SNNMI, including as cochair of the SNNMI Value Initiative Industry Alliance for 2018 and 2019.

Dr. Mankoff: *Jonathan, it's always a pleasure to talk to you, and thanks for the chance to talk about your role as a leader in the radiopharmaceutical industry and other nuclear medicine—focused commercial efforts. You've worked as a leader in molecular imaging in industry for several companies. How did you get there, and how did your role evolve over time?*

Dr. Allis: I started out doing all sorts of premed courses at the University of Cape Town in South Africa. I thought I would become a physician, but it turned out that physics was really so much more fun. So, I carried on doing physics. I came across nuclear MR in my third year at the university. I thought it was fantastic that you could do these cool physics things that could apply to biology. I got a scholarship to Oxford to do a doctorate in biologic nuclear MR in the 1980s—when it was so new, you could publish almost anything. After my postdoc, I joined Oxford Magnet Technology and designed MRI magnets and gradient systems for scanners. Then Siemens bought us, so I went off to Germany for a few years and then to the United States for 4 years. In the United States I looked after all the academic collaborations in the MR area, much as the Blue Earth Medical Affairs team does for us now. I wanted to move back to the United Kingdom and so joined a British company, Amersham. There I worked on a whole range of imaging agents, covering MR, x-ray, CT, ultrasound, and nuclear

medicine. GE bought Amersham in 2004, and, after a while, I ended up running the PET business unit. I was excited to be part of this field, and we invested a lot to get amyloid PET for Alzheimer disease (AD) to market but had less focus in the oncology area. A group of us said to GE, “Would you consider spinning this oncology PET work into a separate company?” GE liked the idea, and BED was born in early 2014. It's been huge fun, I have to say, so maybe I did make the right decision not to go to medical school.

Dr. Mankoff: *BED was extraordinarily successful in getting approval for Axumin and moving it into clinical practice. What factors supported this success? How will BED pivot Axumin and its radiopharmaceutical portfolio now that prostate-specific membrane antigen (PSMA) agents are taking a larger role in prostate PET imaging?*

Dr. Allis: There was certainly an element of serendipity. We were lucky that GE had done a lot of work on fluciclovine and had shown that it did seem to address a real clinical need: “Has your prostate cancer come back? Where is it? What should be done about it?” The other thing that helped set the stage was having very good clinical data from David Schuster, MD, at Emory University, and Stefano Fanti, MD, from the University of Bologna. We have a lot to thank Emory University for, as of course fluciclovine was invented by Mark Goodman, PhD, at Emory University. That provided a real motivation for moving ahead. There was a group of us inside GE, about 5 people, who were interested in doing something new and were very keen to move fluciclovine forward. Then there was access to money from a new venture fund set up by the Wellcome Trust in London. We were able to license fluciclovine from GE, acquire rights to most of the clinical data, and reanalyze it. This provided a route to Food and Drug Administration approval that obviated a new prospective phase 3 study. The Food and Drug Administration was really supportive and recognized a genuine clinical need. So that's the history of BED and its launch of Axumin.

For the future, we are working on our own PSMA agent, now in phase 3 clinical trials. I think the combination of fluciclovine with a PSMA agent (2 radiopharmaceuticals with different uptake mechanisms) will allow us to come up with a very comprehensive way of looking at prostate cancer. Because fluciclovine is a more general metabolic amino acid tracer, it could be useful in lots of other cancers. We recently started a phase 3 trial in brain metastases. We are thinking about a couple of other areas to look at for fluciclovine



Jonathan Allis, DPhil

as well. We know the prostate cancer space well but also see expanding beyond prostate cancer as an important part of our future.

Dr. Mankoff: *What do think are the top industry opportunities for radiopharmaceuticals? What are the greatest threats? What does the future of cancer PET imaging look like to you? What clinical questions will drive use: diagnosis, treatment biomarkers, theranostics?*

Dr. Allis: On the diagnostic side, in the last 10 years or so we've seen several radiopharmaceuticals get approved in different clinical settings, for example, for AD, neuroendocrine disease, and prostate cancer. It feels like it's all looking pretty good. Amyloid PET has not yet worked out commercially, but it may still work out. NETSPOT for neuroendocrine tumors is doing well. Axumin for biochemically recurrent prostate cancer worked out really well. PSMA agents are coming out soon from us and others. It's wonderful to see those agents come to market and get reimbursed at a level that supports investments. I hope we see lots and lots more.

Nuclear medicine has been a little bit in the doldrums about therapy for many years, but that is also looking very exciting. The fact that you can switch out an isotope in the same or a similar compound and go from imaging to therapy (as is the case for ¹⁷⁷Lu-DOTATATE, metaiodobenzylguanidine, and PSMA compounds in development) shows the promise of paired diagnostics/therapeutics. It's an exciting time for nuclear medicine. Theranostics is really capturing people's attention.

In terms of threats for diagnostics, I think the issues are that diagnostic agents are treated as drugs, and the cost to develop them is prohibitive if they are not reimbursed at an appropriate level. Unless radiopharmaceutical payment in the United States is corrected to reflect the true cost of diagnostic agents, ultimately innovation will suffer and the therapy side will also be impacted. However, I see this as a solvable issue, and I am feeling very optimistic about nuclear medicine and radiopharmaceuticals at the moment.

Dr. Mankoff: *How do you see cancer diagnostics and theranostics from an industry standpoint? Can new diagnostic PET cancer imaging*

these reasons, the drug biomarker space feels a bit harder to me outside of diagnostic/theranostic radiopharmaceutical pairs. However, there are some broad areas linked to specific biologic events or conditions (well-established targets, such as in immunotherapy and estrogen receptors in breast cancer) where predicting response and monitoring drug action will be helpful in the clinic. I think the biomarker space is scientifically very interesting but am not 100% convinced that it is a standalone business yet. But, certainly, from the drug development side it's very attractive.

In answer to the question "Do you think we will ever see clinicians being willing to use a PET scan to direct their therapy other than in theranostics?" I want the answer to be "yes." It probably depends on having alternative therapies from which to choose, based on PET, or drugs that are very expensive, very toxic, or both.

You ask, "Could you use a PET scan to direct therapy?" Yes, that happens now in areas such as radiotherapy, although not yet from a drug side. This would require a lot of data and persuasion with referring physicians. I think if you have limited treatment options, oncologists would be unlikely to use a PET scan to take someone off therapy when they didn't have an alternative. I suspect using a PET agent to select patients for drug therapy might be simpler.

As we just discussed, theranostics is going to be one of the most exciting things in nuclear medicine. It's probably one of the most exciting things in medicine generally: imaging and treating a patient with the same molecule. That's pretty cool, if you ask me.

Dr. Mankoff: *How can nuclear medicine practitioners and researchers best work with industry to support and advance the specialty? How should academics bring new compounds to industry?*

Dr. Allis: The BED model has always been external innovation. We can't "out-invent" the world, especially at the early stages of development. This belongs naturally within a university environment. There is no shortage of PET agents out there in the literature, but there is a shortage of clinical data validating use cases.

"Imaging studies are now looking at changes in management and even changes in outcome associated with information provided by a PET scan."

agents return sufficient revenues on their own, or will they increasingly be driven by paired theranostic agents (e.g., DOTATATE, PSMA)?

Dr. Allis: Obviously, from a diagnosis-and-staging perspective in oncology, ¹⁸F-FDG has been a major success, although it took a while to work out where it was useful. But ¹⁸F-FDG doesn't work well everywhere. So we've focused on those other areas, such as the prostate and the brain, and there are others, too. There is a viable commercial opportunity for standalone PET diagnostics to fill in where ¹⁸F-FDG does not work well.

The treatment biomarker side is harder. Of course, a lot of non-radiopharmaceutical pharma companies now use PET agents to work out where their drug goes, how long it takes to get there, and whether the drug has an impact on the disease. All of those things, of course, make sense. But there are pitfalls for a PET diagnostic. The more specific a diagnostic is to a specific therapy, the greater the risk that, if the therapy fails, you end up with nothing. If the therapy is highly limited by target assessment (where imaging might help the most), then you don't get a commercially viable diagnostic product. For

As soon as you have good clinical data, it just is much simpler for a company to understand the opportunities. That for me is the perfect interface between industry and academia. Early research belongs in universities, and chemical scale-up and phase 3 studies probably fit better with companies.

As for new radiopharmaceuticals, it would be fun to hear about them early. I think the first time industry can truly get excited about new agents is when they hear: "Look, I've done these 5 patients, and this is what it looks like, and it's just so compelling." Clearly, it's interesting at any stage, but the "I've done 5 patients, and it looks good" stage is very exciting.

Dr. Mankoff: *Industry is an important career path for clinicians and researchers in many areas of medicine. Should nuclear medicine training consider this path as part of clinical or research training? How might we academics help train individuals to support careers in industry?*

Dr. Allis: Absolutely, this should be a consideration. Some years back, nuclear medicine did not seem to be in a happy place, but now

with new products, and exciting things such as theranostics about to become mainstream, nuclear medicine is once again exciting.

I think the physicians who work for us are probably enjoying themselves, but that may well be prejudice on my side. For physicians there is obviously a great satisfaction in individual patient interactions and changing your patients' lives, but working within industry there's an opportunity to change thousands of patients' lives. Developing a new imaging or therapy agent is very exciting—working on how to develop it, optimize its use, and seeing it rolled out and then used in huge numbers of patients. We like to see people who are inquisitive about not just the medicine but also the chemistry, all those weird statistical tests we end up using in phase 3 studies, and the business itself. Industry work also provides insight into the interests of investors on the business side that drives the whole process of commercialization.

A nice thing about nuclear medicine and PET specifically is that you probably know whether a new agent is going to work by looking at data in a relatively small population. It's not like you have to worry about the enormous safety issues that you have with traditional drugs. This increases the impact of insightful nuclear medicine clinicians and translational scientists working in industry.

Dr. Mankoff: *What is the next game changer in nuclear medicine/molecular imaging?*

Dr. Allis: Of course, you know I love theranostics. But there is a clear need for PET cancer diagnostics as well; however, they have to answer a very specific actionable question. I really like that imaging studies are now looking at changes in management and even changes in outcome associated with information provided by a PET scan.

Pure diagnostics are always going to have a role, but, of course, treating the patient is really the ultimate goal. This makes theranostics incredibly compelling. In some territories, when you talk to regulators it is clear that they are starting to think of the combination as being really easy to approve. The idea that the diagnostic and the therapeutic go together and, in fact, support each other makes the combination, I think, a game changer.

Dr. Mankoff: *Jonathan, thanks so much for doing this; it is always a pleasure to speak with you. I hope we get to talk in person soon, after all of this COVID craziness passes.*

Dr. Allis: Tell me where and when, and I'll hop on a plane to meet you any time or place.

Dr. Mankoff: *You're on!*