Molecular Imaging Leadership in Academia and Industry

A Conversation with Mark Mintun

Mark Mintun[1] and David Mankoff[2]

[1]*Avid Radiopharmaceuticals and Eli Lilly and Co., Philadelphia, Pennsylvania; and* [2]*Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania*

David Mankoff, MD, PhD, associate editor for *The Journal of Nuclear Medicine*, talked with Mark Mintun, MD, about Mintun's career as a leader in molecular imaging in academia and the pharmaceutical industry, including his current roles as senior vice president, neuroscience R&D, at Eli Lilly and Company and president of its wholly owned subsidiary, Avid Radiopharmaceuticals.

Dr. Mintun has directed research and early-phase development programs for Alzheimer disease (AD), Parkinson disease, and migraine and chronic pain conditions. He joined Avid in 2010 and became its president in 2014, leading development programs for both amyloid and tau imaging in patients with neurodegenerative diseases. Dr. Mintun previously served as professor and vice chair of radiology at the prestigious Mallinckrodt Institute of Radiology at the Washington University School of Medicine in St. Louis. His research portfolio includes publishing the first report showing PET imaging of brain receptors, development of methods for imaging oxygen metabolism, and pioneering techniques for mapping human brain function. His recent work has focused on the use of amyloid PET imaging to identify the earliest pathologic changes in AD. Dr. Mintun holds an undergraduate degree from the Massachusetts Institute of Technology and a medical degree from Washington University School of Medicine. He completed a research fellowship in neurology and residency training in nuclear medicine and has coauthored more than 200 research publications.

Dr. Mankoff*: Mark, thanks very much for meeting with me. It has been a great pleasure to talk with you many times in the past in a number of contexts. Today I'd like to talk to you primarily about your current role as a leader in the radiopharmaceutical and pharmaceutical industry, especially as someone who also has considerable experience as a leader in academic molecular imaging. To start, what do you think are the top industry opportunities for radiopharmaceuticals?*

Dr. Mintun: The interaction of radiopharmaceutical imaging with therapy, including both standard therapeutic drugs and radiopharmaceuticals targeted for radiotherapy, will drive the field, opening up new ways of treating patients. This whole idea of being able to take a known pathological target for pathology (such as amyloid plaques) and develop imaging molecules to detect that target, as well as new advances we have made by combining imaging tracers for cancer with therapeutic isotopes, will combine to yield many new opportunities. But this focus on therapy will require a more complicated proof of efficacy—with the need to show how using imaging guides treatment to achieve better outcomes—so that means that it will be even more important for nuclear medicine physicians to be comfortable going back and forth between diagnosis, treatment evaluations, and treatment itself. I think we, as nuclear medicine practitioners, will need to be more intimately involved in treatment decisions; we need to be more comfortable being a key part of the treatment team. This is tied to the idea of nuclear medicine not just being a diagnostic specialty but part of a team tailoring therapy both for nonradioactive drugs and therapeutic radiopharmaceuticals.

Mark Mintun, MD

Dr. Mankoff: *To follow up on that answer from a scientific standpoint, we talk about paired diagnostic therapy agents for theranostics. Should this be the same molecule, pairs of molecules, or either?*

Dr. Mintun: It absolutely could be either. The importance here with either approach is to conduct the studies and collect the data carefully, with the right measurements, rather than simply making assumptions about what will work best, as we often do. Clearly when you use the same molecule for imaging and therapy, it feels very tempting to assume you have the ideal combination—but there are still pitfalls. As you probably are aware, factors that may change for imaging versus therapy, such as the total mass administered, can make a difference, particularly for large molecules. My sense is that no matter how you approach theranostics—as a single molecule for diagnosis and therapy versus diagnostic/therapeutic pairs—you're going to have to figure out the details. This includes the subtle differences in pharmacokinetics and biodistribution between tracer and pharmacologic doses and between a therapeutic molecule and a diagnostic or treatment-monitoring molecule. Going for the best molecule for each job will, I think, almost always be the best answer.

Dr. Mankoff: *What do think are the top industry threats for radiopharmaceuticals?*

Dr. Mintun: We have to pay attention to the value of what we're doing. We are constantly perceived as being expensive and, almost by definition, therefore not providing enough value. We need to protect ourselves against that perception. Otherwise, we will be constantly under attack. We know that nuclear medicine has a complicated supply chain from the manufacturing to the patient. It also involves highly technical imaging acquisition and a nuanced image interpretation. We do more than just look at a few pictures, often needing to compare across other modalities or incorporate quantification. The complexity of these factors (supply chain, technology, and image/data interpretation) means that there

DOI: 10.2967/jnumed.121.263451

are a lot of things that can get in the way and impact the timeliness and quality of the result if not carefully addressed. From the very beginning, we have to establish how our approach will make patients' lives better, especially how we are altering and improving management. It's been a threat that we have faced for a long time, and it will very likely get bigger as our field expands. I think we can counter this threat by better aligning ourselves with therapeutic options and better targeting therapeutic dilemmas.

For example, the whole issue of guiding immune drug targeting and understanding and advancing immunotherapy into new areas is where nuclear medicine and targeted radiopharmaceuticals can have an impact. Understanding regression of cancer after immunotherapy is a recent example of a problem in need of more tools. In general, we need to think about where imaging can help patients and the physicians managing their care. We need to link those things not only to pretty pictures and cool numbers but to patient outcomes. That's admittedly so hard to do, but it must be the standard. I think we're up for the challenge.

Dr. Mankoff: *What is the future of amyloid and tau PET imaging? What clinical questions will drive their use: diagnosis, therapy guidance?*

Dr. Mintun: The landscape for diagnosing and treating AD and related diseases is rapidly evolving. There are several companies with drugs in Phase 3 trials for AD, and one company with a drug that recently received FDA approval. At the moment, most of these are amyloid-targeted drugs, but there are also antitau drugs in clinical testing for efficacy. So being able to identify the amount of amyloid and/or tau someone has in his or her brain—and where it sits—may be increasingly important for guiding and assessing treatment for AD and related diseases, in addition to diagnosis. I see increased amyloid and tau imaging as an absolutely essential tool to meet this need, and I'm confident that is where the field will be. Of course, being able to show all of the value of using amyloid and tau PET to guide precision medicine by assessing drug targets for AD patients may need more data, but I think we're going to be there eventually. Monitoring drug activity is a logical extension of target assessment and may well be an important component of our future, as well. Nuclear medicine should be involved in all 3 of those levels of managing AD: diagnosis, advice on therapy options, and then treatment monitoring. To do that for both amyloid and tau imaging—well, there's a lot more data needed and a lot more regulatory interactions with the companies involved. But I think it is very logically where the field is going. I am confident that's going to happen and bring nuclear medicine into an essential role in managing AD and related diseases.

Dr. Mankoff: *A related question: As a cancer-focused investigator, I think of PET's roles in broad terms of diagnosis, staging, and guiding therapy. There may be different radiotracers for each task. As we get drugs that are effective in AD and related neurodegenerative diseases, will these concepts also apply?*

Dr. Mintun: That's a very interesting question. Let's take that analogy a little further. In the very beginning (and I was around in those early days) diagnosis was the main topic for PET cancer research; for example, looking at solitary nodules in the lung and trying to decide whether they were cancer. We found, however, many cases where we could see unexpected hot spots in other sites, such as the mediastinum. We quickly realized that staging was equally if not more important. Almost a decade later, people started asking about therapy monitoring, and research began in diseases such as lymphoma to test whether ^{18}F-FDG PET can help to determine whether responses are adequate, whether or not to continue treating, and when to switch treatments. So staging and therapeutic monitoring have grown to be even more important than diagnosis in PET cancer imaging clinical practice. As cancer treatment evolves toward precision medicine, there is a need for PET to grow with it. Oncologic PET imaging until recently has been entirely FDG based. As the range of treatments and targets expanded, that drove the oncologic field to develop more targeted cancer imaging agents beyond FDG, including several recent FDA approvals.

I think the roadmap for AD-related diseases looks similar, not simply because I think there are similarities between FDG and amyloid/tau imaging but because of the way medicine works. The simplest questions are the easiest to answer but not always the most valuable. Diagnosis is an important start, but an estimation of disease severity (analogous to staging in cancer) is quite important, as is the question of therapeutic response. This last question can be the hardest and requires collaborative work between imaging and therapy. I think back on how hard it was to get to the point where PET became a routine part of lymphoma care—all the various specific work that had to be done to even demonstrate lymphoma response, to define at what point PET imaging should be performed, and determine how long to wait after the last therapy to image. All that had to be worked out, and we will be doing the same thing for AD-related diseases. For example, when monitoring with tau imaging after antitau therapy, when should we look? Is it 6 months, a year, 2 years? We don't know yet. We will have to find out, and it will take a lot more data and a lot more time. But I do believe people in nuclear medicine will be thinking about the research that is necessary to make PET provide the same value for AD that it does for cancer.

"From the very beginning, we have to establish how our approach will make patients' lives better, especially how we are altering and improving management."

Your question is really important from one other aspect, which is a simple diagnosis that might also be thought of as the probability of having an AD-related disease. The diagnosis may one day start with a blood test and not just imaging. This is why no one should be assuming that diagnosis will rest on any single approach. (I guess no one should be doing that in medicine in any field, anyway.) Even in diagnosis, we need to be better connected with therapy, because if we are going to continue to thrive as a field we are going to quickly realize that diagnosis needs to evolve into "staging" and into therapy monitoring. I suspect there are blood tests that will be useful in guiding people on their risk of AD, and these may work together with amyloid and tau imaging for both diagnosis and therapeutic guidance, analogous to evolving approaches in cancer.

Dr. Mankoff: *You have worked as a leader in molecular imaging in both academics and industry? How would you compare and contrast the 2?*

Dr. Mintun: From a personal standpoint, it was incredibly rewarding to be in both places. I spent a lot of time and energy in academia at Washington University and other universities and

absolutely enjoyed it. I also have been incredibly lucky in industry. I was at a few different academic places and found all of them different, equally challenging, and incredibly rewarding. For my roles in industry, I would say that Lilly is truly a unique pharmaceutical company that I believe has a true love of finding what's best for patients and then doing it. I couldn't be more pleased at working at a place that has such high ethics and compassion for patients and with colleagues who are working so hard. I can point to one of the more obvious examples: an incredible commitment to AD. We've had multiple setbacks in AD as a field and multiple setbacks at Lilly. The people at Lilly have never had a point where we wanted to throw in the towel, never wanted to just walk away.

An interesting aspect of the difference between industry and academics is that in academics you have this the ability to follow your nose to interesting sets of data in unique patients. You greatly appreciate the freedom to explore new areas when you are leading teams of researchers and scientists. Sometimes people can't articulate exactly what the research will yield, but they know it's going to be interesting. It's important in academics to give scientists the room, resources, space, and encouragement to pursue their ideas. That is the intangible benefit of academics: to be able to use the sense of following your nose into brand new areas of science to see where it goes. As a society, we have to encourage that, nurture it, and give people space to do it. Clearly, we have to have results, but we can have a longer timeline, and the path doesn't have to be straight … and it almost never is. Academia needs people who don't mind having setback after setback without losing their vision. Being able to have a vision is so important in academia and makes it fun to be a part of, because it's invigorating and challenging to see the different ideas that people can come up with when you give them that kind of room.

In industry, goals need to be a bit more weighted towards delivering results to patients, but academia and industry can set goals together to make a more comprehensive environment for delivering those results. A fun aspect of being in industry is the ability to marshal the resources to test a new approach and move quickly toward finding out whether you are right or wrong. If you're right, that's great. If it doesn't work the way you thought it would, that is also helpful for making decisions. That doesn't mean it wasn't a really cool idea, but it does mean that you have to stop that work and go on to the next really cool idea. This is an important component of industry that does not necessarily apply to academics, where there is knowledge to be gained in new methodology that fails to meet expectations. But as long as you work in a place that can make good decisions (and I think industry is getting even better at this than it was before) you can make progress and have an impact on health care and patients' lives. This is the environment that I enjoy at Lilly and at Avid. You can make decisions, get them quickly funded, and move quickly to get to the answer. If it is a positive answer, you celebrate and go to the next step. If not, you move on.

In both academics and industry, it is important to remember that you can't bring a new drug to patients with a single experiment or study. In industry, I've felt really invigorated by the support and the speed of progress to bring new methods to patients. It's much like rowing together in the sport of crew. My son did rowing, and I also took it up in St. Louis, where I was part of the St. Louis Rowing Club. You can be guiding a boat of 8 novice rowers and seeing them getting better and better over a season. Then, all of a sudden, they are rowing in perfect coordination and the boat literally rises up out of the water. You realize that rowing is all about teamwork, and feeling it in action is so cool! In industry, we can take those cool ideas and create a team pulling together to quickly test whether or not the cool idea will work for patients. Perhaps I'm taking the crew analogy way too far.

Dr. Mankoff: *Not at all! As another parent of a rower (I think we saw each other at the 2010 national junior championships in Cincinnati), I love that analogy! A related question: how can nuclear medicine practitioners and researchers best row together with industry to support and advance the specialty?*

Dr. Mintun: I think that researchers in nuclear medicine coming up with new inventions need to stay attentive to the issue of intellectual property (IP). It is one of the horrible facts of life in the industry that someone can have a perfectly good idea and maybe even a perfectly good molecule, but if there's no IP, it can be difficult to commercialize. It's not that the molecule doesn't work, but it's incredibly hard to spend lots of money on a molecule that has no protection. It remains so expensive to develop drugs for therapy and for diagnosis; you have to be thinking about financial implications very early on. Academics should learn to have a good relationship with their IP lawyers at their institutions. My advice if you're in that situation: don't do everything by email and text message. When you're talking about something as complicated as IP, never forget the most important thing is to have an actual conversation. Set up a Zoom call or an in-person meeting and actually talk to the lawyer about what you're worried about. Listen to what they are worried about. Just have a conversation and have a relationship. It's really important.

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

Dr. Mintun: I think there are a few items already out there that might be staring us in the face that could be incredibly important. One is fibroblast-activating protein, and I think we have to keep an eye on this target. There is the rapidly evolving work using pretargeting techniques for imaging and even radiotherapy. We especially need more agents for imaging inflammation: specifically high-dynamic-range inflammation-specific imaging drugs that can monitor the full complexity of the immune system. I often remind people that if you're working in the immune system, you're working in the system that is second in importance, and complexity only to the brain. I am awed by how complex the immune system is. It's scattered in fascinating ways around the whole body, and you can never keep track of it. At least the brain stays in one place! The immune system is a mobile system that is just as complicated as the brain, amazingly old in evolutionary terms, and with an amazing array of parallel pathways. There are multiple feedback mechanisms that are astonishingly complex. Harnessing the immune system for therapeutic benefit has been truly difficult, but science will continue to crack the code, and the field will change. We can use these advances to also crack the code for inflammation/immune imaging.

Dr. Mankoff*: Mark, it is always a pleasure to talk to you. I've admired your work ever since I started in nuclear medicine, and I always learn from you. Thanks so much for doing this interview, and let's get together in person soon.*

Dr. Mintun: You bet, and my pleasure.