# Translational Cancer Research Priorities and the Role of Molecular Imaging

## A Conversation Between Chi Van Dang, Elizabeth Jaffee, and David Mankoff

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David Mankoff, associate editor for *The Journal of Nuclear Medicine,* talked with Chi Van Dang and Elizabeth Jaffee about their leadership in guiding national priorities for translational cancer research and their perspectives on the role of molecular imaging and theranostics.

Dr. Dang is the scientific director of the Ludwig Institute for Cancer Research (New York, NY), where he oversees the execution of Ludwig's scientific strategy to advance the prevention, diagnosis, and treatment of cancer. He is also a professor of Molecular and Cellular Oncogenesis at the Wistar Institute Molecular and Cellular Oncogenesis Program (Philadelphia, PA). His work focuses on cancer cell metabolism, and his laboratory established the first mechanistic link between the MYC cancer gene and cellular energy metabolism. Dr. Dang is a national leader in cancer research, including roles as former director of the University of Pennsylvania's Abramson Cancer Center, former National Cancer Institute (NCI) Board of Scientific Advisors chair, and member of the Blue Ribbon Panel for the Biden Cancer Moonshot Initiative. He is the current editor-in-chief of *Cancer Research* and cochair of the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) Translational Research Strategy Subcommittee.

Dr. Jaffee runs a National Institutes of Health–funded laboratory dedicated to developing novel therapies for pancreatic cancer and has more than 200 peer-reviewed publications. She serves as the deputy director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD), where she is a professor of oncology. She is also the inaugural director of the new Johns Hopkins Cancer Convergence Institute, which aims to marry emerging technologies with computational biology and to cross-train scientists in biology and data science. She has served on numerous national committees, including as chair of the National Cancer Advisory Board, cochair of the Blue Ribbon Panel of the Cancer Moonshot Initiative, and as president of the American Association for Cancer Research (AACR). She was elected to the National Academy of Medicine and is a fellow of the American College of Physicians, the AACR, and the Society for Immunotherapy of Cancer Academy of Immuno-Oncology.

***Dr. Mankoff:*** *What are the major accomplishments of the Cancer Moonshot Program thus far? What areas still have work to be done?*

Chi Van Dang, MD, PhD

Elizabeth Jaffee, MD

**Dr. Jaffee:** There were 10 original recommendations for prioritizing research funds. These spanned basic discovery to implementation science and included new technology and data science platforms, with emphasis on health disparities throughout all priorities. In the relatively short time since this program was funded (5 y), there has been implementation of NCI-supported and -guided multicenter consortiums and programs in most areas, including discovery science in previously underfunded cancers such as glioblastoma, pancreatic cancer, and pediatric cancers; investment in translational and clinical studies; new and enhanced implementation studies (colorectal cancer as one example); and increased funding opportunities in health disparities through R01s, Specialized Programs of Research Excellence, etc. We are already seeing measurable outcomes, such as Human Tumor Atlas data uncovering new pathways in different tumor types, new multicenter clinical trials, etc.

**Dr. Dang:** There are already some clearly tangible results from the Moonshot Program. I think one important result that the NCI has been able to accomplish is to create networks of investigators who can come together to work on specific issues. For example, the Moonshot has created immunology and immune oncology networks. These networks have worked to standardize immunooncology reagents and assays for translational and clinical research and will play a large role in translational research and advancements in immune oncology research and clinical practice. Another area that has advanced well is the Human Tumor Atlas via the network that was created. This network is now generating several very nice papers on mapping human tumors at the single-cell level, including single-cell imaging and sequencing. That's another tangible accomplishment of the Moonshot Program.

***Dr. Mankoff:*** *I noted your February 2021 Cancer Moonshot 2.0 commentary in* Lancet Oncology *(2021;22:164–165), which called for a new Cancer Moonshot Commission to follow up the prior Commission report published in 2017. What are the priorities for that new commission? Are there specific areas of cancer science and technology you anticipate prioritizing?*

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DOI: 10.2967/jnumed.122.264086

**Dr. Jaffee:** Data science—all aspects—require critical investments. Multiomic, single-cell, and imaging technologies are rapidly expanding and generating unprecedented quantities of data that will require new approaches for safe storage that can handle large quantities of data, processing, and analyzing. In addition, we emphasized development and implementation of new forms of health-care technologies to improve health-care access and real-time assessment in changes in disease states.

**Dr. Dang:** I agree. We have a ton of clinical data, and researchers and research organizations such as NCI should help support work to leverage these data. People are really starting to use machine learning and artificial intelligence to discern features in clinical data that will inform both cancer research and oncologic clinical practice. Imaging should be a priority here. Whether it's digital pathology or radiology, imaging is obviously a natural fit for data science methods.

***Dr. Mankoff:*** *I was delighted that the 2017 Lancet Oncology Commission report included a section on nuclear medicine and molecular imaging. In that section, there are several priorities put forth on using imaging to guide therapy, combining in vitro and in vivo diagnostics, using big data and image analytics to inform cancer decision making, advancing theranostic treatments, creating clinical decision models to guide the use-effective and cost-effective imaging in cancer care, and streamlining regulatory, payment, and clinical integration for molecular imaging and theranostics. Which of these areas have seen progress, and which need more work?*

**Dr. Jaffee:** Imaging should continue to be a high priority. We need to do better with molecular imaging to help guide molecular-based diagnosis and treatment response and resistance. I am very excited to be working with my nuclear medicine colleagues on developing immune-targeted imaging approaches. Imaging can also help us understand cancer development and progression. Invasive biopsies are not easy to obtain, and serial analysis is difficult. Nuclear medicine can provide new ways to do "noninvasive" molecular analyses over time to study cancer development and evolution. Finally, moving to interception, we need new ways to uncover early premalignant changes to intervene early with surgery, immunotherapy, targeted therapies, etc.

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**Dr. Dang:** We need to prioritize funding for people to do more research on image analysis and new imaging technology. For example, we have come to understand—more and more every day—the importance of the tumor microenvironment: how the immune system impacts tumor behavior and response to treatment. Can we image and quantify regional tumor microenvironmental properties? For example, tumor-associated macrophages are increasingly recognized as a factor in tumor initiation and progression, and it would be helpful to be able to not only identify them, as has been done in early studies, but to characterize their phenotypes and behavior in response to treatment. It would be lovely to develop more tools for imaging these phenomena in vivo and for guiding immune oncology practice. Another area of need is in the issue of tumor plasticity and the role of metabolism and epigenetics in mediating changes in tumor behavior, including things such as dormancy. These are still areas we don't completely understand. As we learn more, I can see imaging playing a role in helping us identify and measure factors mediating tumor plasticity and related therapeutic resistance.

***Dr. Mankoff:*** *Theranostics, a term used to describe radionuclide therapy and paired companion imaging diagnostics, has gotten considerable notice recently, with notable advances in neuroendocrine tumors and prostate cancer, for example. From your viewpoints, how does theranostics fit into the future of cancer research and cancer care?*

**Dr. Dang:** I would say that this is a great field. There are still a relatively small number of agents in the clinic, but it would be good to bring theranostics to greater public attention and say: "Look, these agents make a difference in the clinic." I think you may be doing this already through the SNNMI, but more public awareness of the success of radioisotope therapy across a range of venues will help. I would love to see more Food and Drug Administration–approved agents, but at the same time you need to increase the pipeline. This means you need more funding to work on this area for new targets and to provide proof of concept for these targets. There is some new cancer science that may help this process. For example, can you probe proteomics to identify targets with sufficient differences in surface proteomes between tumors and normal tissue, so that you can hit the target and deliver a therapeutic radioisotope payload? This is a process that can be informed by advances in proteomic methods along with advances in science and technology in pairing diagnostic and therapeutic radiopharmaceuticals. This type of approach could yield new targets and agents. I'd love to see more theranostics approved.

***Dr. Mankoff:*** *Liz, another area of emphasis in molecular imaging has been in immune-specific imaging. As a cancer immunotherapy leader, what are the priorities for diagnostics in the field, and how can molecular imaging help?*

**Dr. Jaffee:** As per my answer on imaging priorities, I think the ability to identify immunotherapy targets and assess immune activation will be important components of the ongoing development and refinement of immune-directed cancer therapies and could play an important role in guiding cancer immunotherapy in the clinic.

***Dr. Mankoff:*** *Chi, in addition to your role in the Cancer Moonshot, you've helped lead efforts on translational research on major NCI advisory panels, including serving as coleader on the CTAC Translational Research Strategy Subcommittee. From this viewpoint, what are some areas of translational research priority where nuclear medicine can play an important role?*

**Dr. Dang:** One priority to address is imaging across the scale from microscopic images to images that encompass the whole body. In the future, could we see coregistration of histologic section/tissue assay data with the type of macroscopic imaging data that come from medical imaging? Can advances in imaging technology, at all scales and together with machine learning and data science, help us here? For example, in the immune microenvironment, can we relate measures of immune cells, such as M1 and M2 macrophages and different classes of T cells, to features on a PET or CT scan at the site of tissue sampling and use that approach to enrich what can be learned from both microscopic and macroscopic imaging to help guide immune-targeted therapy?

Related to this question, is it possible to get more than one parameter at a time out of molecular and functional imaging?

Cancer tissue samples undergo increasing numbers of assays for a range of molecular processes relevant to diagnosis and treatment. Advancing technologies for tissue analysis are making multiplexed assays easier and more efficient. Can imaging do the same thing? I know, Dave, that you are working on multiple tracer injections to measure cancer metabolism as part of your Cancer Moonshot–funded effort, as are others in the field. I don't know what factors limit your ability to image multiple processes, but can you push molecular imaging to yield information on a greater number of molecular features at the same time?

***Dr. Mankoff:*** *You have both emphasized integration and collaboration in cancer research. How can nuclear medicine play a role in this effort? Through technology integration efforts? Through specific areas of collaboration with cancer biology, oncology, or radiation oncology research efforts?*

**Dr. Jaffee:** Nuclear medicine is central to multiinvestigator translational science. A major limitation in understanding disease development, progression, and response to new therapies is the lack of noninvasive techniques that can be used safely and repeatedly to get data. Molecular targets for nuclear medicine need to be identified, as well as new ways to assess functional changes in tumors that are specific to pathway changes. These need to be prioritized.

**Dr. Dang:** I have also been impressed that nuclear medicine can be foundational in translational research. This is an area in which more formal inclusion of nuclear medicine in guiding cancer translational research would be helpful. You've done some of this, Dave, as a member of the NCI CTAC Translational Research Subcommittee that I colead, and I know others in nuclear medicine have had similar roles in other NCI research groups. I think nuclear medicine and cancer leaders should look for even more opportunities to bring nuclear medicine expertise to the organization that guide translational cancer research.

***Dr. Mankoff:*** *The Cancer Moonshot Blue Ribbon Panel and Lancet Oncology Commission reports both emphasized a need for improved training in cancer research. For highly specialized and technical fields such as ours, how might this be best accomplished? Any advice on how we can best train the next generation of imaging/nuclear cancer research leaders?*

**Dr. Jaffee:** We need to cross-train the next generation on technologies, biology systems, and data science. Organizations such as AACR can be helpful in providing national education platforms. Collaborations between different national and international societies would be a great first step.

**Dr. Dang:** Imaging will be one area in which we want to train both basic and clinical scientists who really are interested in making a difference in the clinic. This should continue to be emphasized in both clinical and research training in nuclear medicine, across all relevant areas of expertise in the field.

***Dr. Mankoff:*** *What are the next game changers in cancer research? How can we best support advances in these areas?*

**Dr. Jaffee:** Single-cell and spatial technologies and their associated analytic platforms including artificial intelligence are game changers. We are able to quickly uncover and assess changing cancer signals with the tumor microenvironment to understand cancer development and progression, cancer heterogeneity, and cancer sensitivity and resistance to different therapies. This is already allowing us to improve patient-specific treatments, develop more effective and less toxic drugs, and consider interventions at earlier cancer stages and even at the precursor stage.

**Dr. Dang:** I have a related answer. I suspect I'm going to be wrong about this, but I think that over the last several decades, the major hubs of cancer biology have been identified. We know what the hubs are; now we need to better understand how they connect. We know that epigenetic modifiers play a big role. But now what we are confronting is a complex network with major hubs that have modifiers tugging on them. What matters in the clinic is whether a system of cancer biology hubs is going to collapse under the weight of a specific therapeutic approach or is robust enough to resist treatment. We are starting to confront this complexity, in that we realize that we need to really understand the complexity of the tumor, its microenvironment, and the related systems biology of the host. But we need more tools for this task. I think this is the most important remaining challenge in cancer research: to be able to understand in vivo cancer biology across the scale from fundamental molecular processes to integration of biologic systems across the whole body. I think nuclear medicine can help here.

***Dr. Mankoff:*** *Do you have any other advice or suggestions for nuclear medicine scientists and physicians working in cancer research?*

**Dr. Dang:** My big push right now is team science, especially in my role as scientific director of the Ludwig Institute. I realize that individual investigators have their own labs and are a force for innovative, completely new ideas. We want to continue to encourage this innovation. However, I think translating lab discoveries to the clinic for the benefit of patients requires team science. We need to create more incentive for people to collaborate. As an interesting example of a novel approach, one idea that I posed jokingly in a talk I gave was the idea of a "circular" author list for scientific papers—no beginning and no end to the author list. Kind of a crazy idea, but library science might be able to handle this.

As another example, I mentioned artificial intelligence and data science earlier, an area that most cancer biologists know very well. How can we bring together these 2 distinct areas of biology and technology? Nuclear medicine has always lived at the intersection of technology and clinical biology and can perhaps help lead this charge.

***Dr. Mankoff:*** *Liz and Chi, thanks so much for taking the time to have this conversation. I know that, as leaders in cancer research and major cancer research organizations, you are both extraordinarily busy. I and the readers of* The Journal of Nuclear Medicine *greatly appreciate your thoughts about priorities for translational cancer research and the role of nuclear medicine and molecular imaging. Thank you both!*

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