2018 SNMMI Highlights Lecture: Oncology and Therapy

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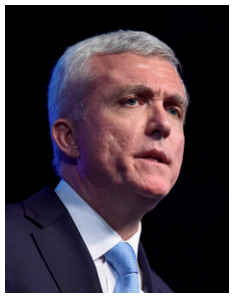
From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2018 Highlights Lectures were delivered on June 26 at the SNMMI Annual Meeting in Philadelphia, PA. In this issue we feature part 1 of the lecture by Andrew Scott, MD, Director of the Department of Molecular Imaging and Therapy, Austin Health, and Head, Tumor Targeting Laboratory, Olivia Newton-John Cancer Research Institute (Melbourne, Australia), who spoke on oncology highlights from the meeting. The second part of the lecture will appear in the January issue of Newsline. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2018;59[suppl 1]).*

I am delighted to be here and honored to have the opportunity to provide an overview of the oncology program at the 2018 SNMMI Annual Meeting. I would like to echo the comments of the chair of the SNMMI Scientific Committee, Umar Mahmood, MD, PhD, in saying that these Highlights sessions are my favorite part of the conference.

Much is happening in oncology, as evidenced at this meeting. Earlier this month, at the American Society of Clinical Oncology (ASCO) meeting in Chicago (IL), attendees were amazed at the progress being made in oncology diagnosis and treatment. We in nuclear medicine are pivotally involved in the ways in which the biology of cancer, diagnosis and management in cancer, and development of new therapies in cancer are progressing. We continue to see dramatic changes in understanding the mechanisms by which cancers develop, spread, and are suited to tailored treatment options. This is true in a number of areas. Actionable mutations are being targeted for effective cancer control, including ways in which new therapies can be targeted to specific somatic mutations. The heterogeneity and variability that occur within cancers cannot be determined with standard biopsies or blood tests alone and require new and advanced techniques. Immunotherapy continues to expand in indications, changing the ways in which oncologists and the public look at cancer—however, these treatments are quite complex. We play a very important role in being able to explore and identify through accurate staging and restaging those patients who are responding, how they respond, and what new treatments should be provided. Complex treatments (like immunotherapies) have complex toxicities, and these must be addressed. The treatment nominated at ASCO as the most important clinical advance for 2018 was adoptive cell immunotherapy, specifically chimeric antigen receptor (CAR) T cell therapies, which now have 2 approvals in hematologic malignancies and are being evaluated in solid tumors. One area of focus in my presentation will be on the ways in which all of these new imaging and treatment methods, now entering the clinic and becoming more commonplace, are profoundly affecting the ways in which we see patients and implement personalized nuclear medicine techniques.



Andrew Scott, MD

At the SNMMI meeting, a total of 1,781 abstracts were accepted for core poster or podium presentations, with 844 (47%) related to aspects of oncology. Many of the presentations at this conference represent important contributions to the field. Abstracts selected for this meeting came from 44 countries, with the United States (>700 abstracts) and China (>500 abstracts; more than half in the Oncology Track) representing a large proportion of the total. It was a daunting task to look at the depth and breadth of this activity to select highlights and illustrative examples. I apologize if I am unable to highlight all of the important and wonderful presentations. I will, instead, offer perspective on where nuclear medicine is going and how our discipline is engaging with oncology.

The topics addressed in this overview will include molecular probes for drivers of oncogenesis, immuno-oncology, novel imaging targets in cancer, multimodality imaging probes, molecular imaging in treatment response assessment (including outcomes analyses to justify imaging approaches), imaging and theranostics in prostate cancer, and novel therapeutics and trials.

Molecular Probes for Drivers of Oncogenesis

Consistent with the involvement of actionable mutations as well as metabolic profiles within tumors, we know that certain types of metabolic changes can be altered in certain types of tumors. Zhang et al. from the Nemours/Alfred I. duPont Hospital for Children (Wilmington, DE) and the Mayo Clinic (Jacksonville, FL) reported on "Brain tumor PET imaging in a transgenic medulloblastoma mouse model using a novel ^{18}F-labeled tryptophan tracer" [63]. Abnormal tryptophan metabolism via the kynurenine pathway has been noted in a range of neurologic diseases, including brain tumors, epilepsy, and autism. In this study, an inducible

medulloblastoma expression within a transgenic mouse aided the evaluation of a novel ^{18}F-labeled tracer (1-2-^{18}F-fluoroethyl-L-tryptophan [L-1-^{18}F-FETrp]) and was able to demonstrate the presence of tryptophan metabolism within a specific tumor (Fig. 1). This has clear implications for certain types of mutant changes within specific types of tumors, as well as for understanding upregulation of indoleamine 2,3-dioxygenase and tryptophan-2,3-dioxygenase 2 (TDO2), rate-limiting enzymes for tryptophan metabolism. The authors concluded that these "preclinical studies suggest that TDO2 may be a therapeutic target for medulloblastoma, and L-1-^{18}F-FETrp has potential for PET imaging of medulloblastoma." I commend these researchers for adapting the transgenic mouse approach for this novel tracer.

Heat shock protein 90 (Hsp90) is a protective chaperone that plays an important role in the phenotype of a number of cancers. Several inhibitors of Hsp90 have been reported in the clinic. Wang et al. from the Keck School of Medicine of the University of Southern California (Los Angeles) and Lanzhou University Second Hospital (China) reported on "PET imaging of Hsp90 expression in pancreatic cancer using a new ^{64}Cu-labeled dimeric Sansalvamide A derivative" [460]. The authors described a new ^{64}Cu-labeled molecule (^{64}Cu-Di-San A1) that can image Hsp90 expression in tumors in a mouse model of pancreatic cancer (Fig. 2). Blocking studies with 17AAG, an HSP90 inhibitor, confirmed that the tracer was specific. These researchers are now looking at ways to optimize the tracer's in vivo kinetics, with a goal of providing a noninvasive method to quantitatively characterize Hsp90 expression in pancreatic cancer. I look forward to seeing the results and whether this technique can be successfully translated into clinical studies.

Poly-[adenosine diphosphate ribose]-polymerase 1 (PARP-1) is a nuclear protein known to interact with histones

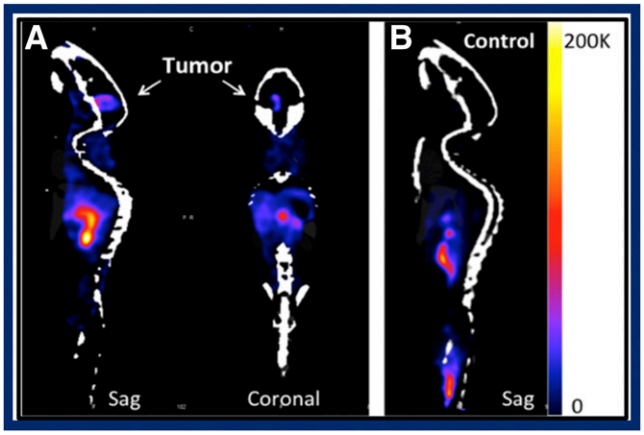


FIGURE 1. (A) PET imaging in a transgenic medulloblastoma mouse model using a novel ^{18}F-labeled tryptophan tracer, L-1-[^{18}F]FETrp, showed an increased accumulation in tumor (arrows; SUV = 2.2–4.0) compared to cerebellum (SUV = 0.3–1.0). (B) Comparative imaging in a control mouse.

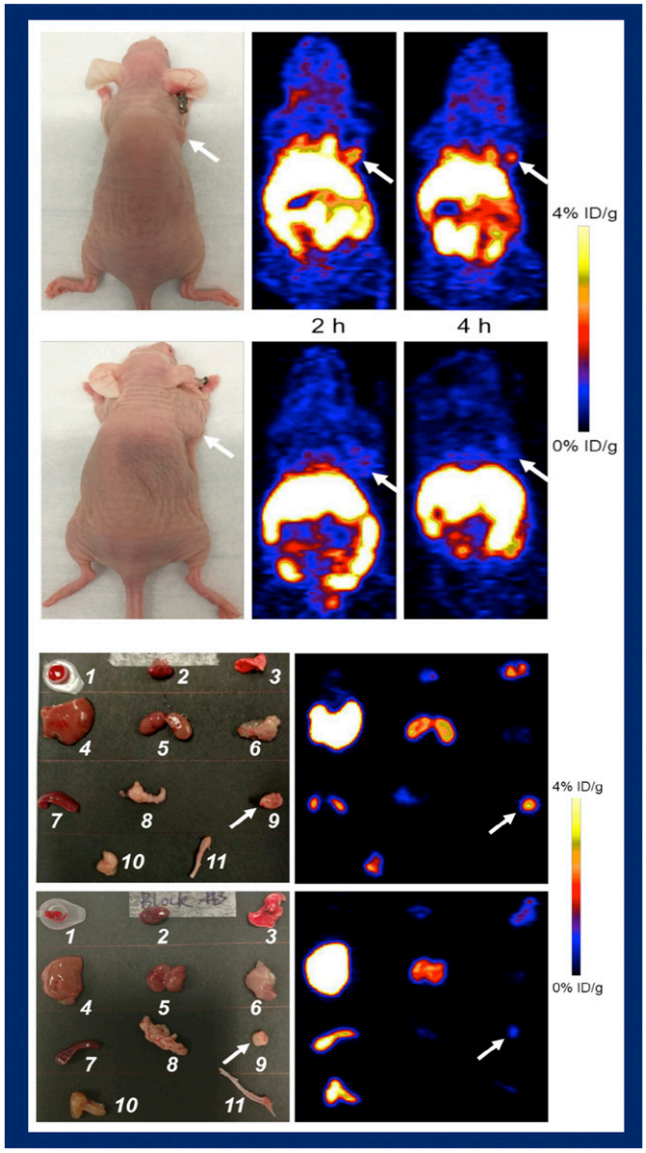


FIGURE 2. Preclinical PET imaging of Hsp90 expression in pancreatic cancer using a new ^{64}Cu-labeled dimeric Sansalvamide A derivative. Top block: In vivo microPET imaging at 2 and 4 hours without a blocking agent (top row) and with a blocking agent (bottom row). Bottom block: Ex vivo histology and microPET at 4 hours after injection without (top row) and with (bottom row) a blocking agent.

and to be responsible for single-strand DNA break repair. Inhibitors of PARP have been shown to have efficacy, particularly in ovarian cancer, so being able to identify this nuclear target as both a focus for therapy and as an indication of DNA activity is quite relevant and important. MaKvandi et al. from the University of Pennsylvania (Philadelphia) reported on "PARP-1 as a molecular target for the delivery of theranostic Auger emitters to cancer chromatin" [59]. In this study, a small-molecule PARP inhibitor, KX1, was labeled with both ^{125}I and ^{131}I to explore the possibility of directly targeting delivery of Auger emitters to DNA and allowing SPECT imaging (Fig. 3). Their results showed that ^{123}I/^{125}I-KX1 induces DNA damage through Auger electrons

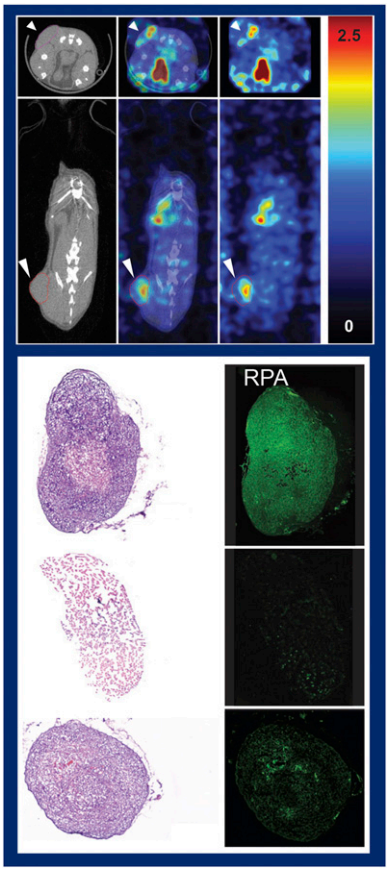


FIGURE 3. PARP-1 as a molecular target for delivery of theranostic Auger emitters to cancer chromatin. Top block: Imaging with (left to right) CT, fused SPECT/CT, and SPECT in transverse (top) and coronal views (bottom). Bottom block: Ex vivo imaging of (top to bottom) tumor, muscle, and tumor with autoradiography (left) and immunofluorescent cell microscopy (right). SPECT imaging visualized the tumor and confirmed DNA damage.

without altering physiologic processes. Other studies are now underway to assess effects in preclinical models of ovarian cancer.

By using transgenic models we are able to interrogate not only the presence of mutations but also the signaling cascades involved in those mutations, one of which is KRAS. Mutant KRAS is well known in colorectal cancer, because tumors with the KRAS mutation will not respond to classic epidermal growth factor receptor–inhibiting therapeutics. MYC has a linkage to KRAS expression. Henry et al. from the Memorial Sloan Kettering Cancer Center (New York, NY) and the University of California at San Francisco reported on "Interrogating KRAS, ERK, and MYC signaling in pancreatic cancer with endogenous PET imaging" [72]. These researchers looked at a novel transferrin receptor–targeted PET agent, ^{89}Zr-Tf, to see whether it was possible to measure changes in MYC, depending on the KRAS status of pancreatic cancer tumors. They were able to demonstrate tumor uptake in 2 cell lines of pancreatic cancer (Suit-2 and Capan-2) in mice with pancreatic ductal adenocarcinoma (PDAC) xenografts (Fig. 4). Moreover, using an agent that knocked down MYC function, reduced uptake was seen in these mice but not in wild-type KRAS-expressing tumors (BxPC-3). The authors concluded that this radiotracer shows promise "as a tool for interrogating proteins downstream of oncogenic KRAS such as ERK and MYC via transferrin receptor in PDAC," with potential future applications in assessing oncogene status and predicting early therapy response to targeted inhibitors in pancreatic cancer. This was an elegant way to demonstrate that it is possible to use a PET imaging probe to look at the signaling cascades related to tumor-expressed mutations.

Immunooncology

All of us—scientists, physicians, and the public—are hearing news about immunooncology advances (for example,

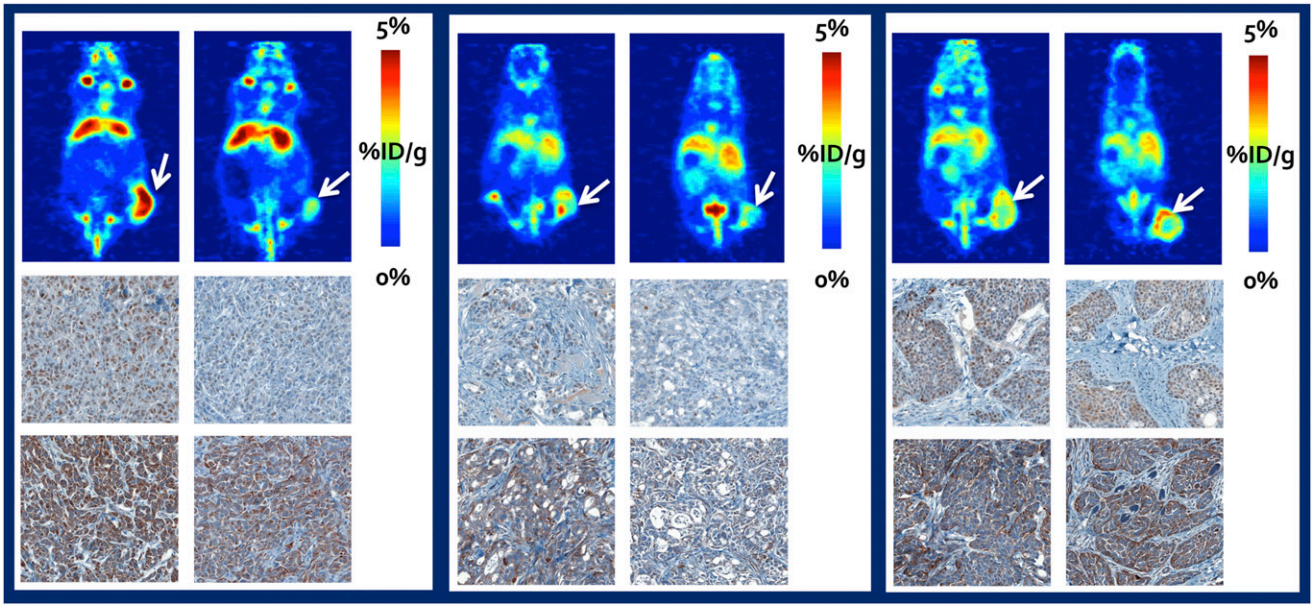


FIGURE 4. Interrogating signaling in pancreatic cancer with endogenous ^{89}Zr-Tf transferrin-targeted PET imaging. The study measured changes in MYC, depending on the KRAS status of pancreatic cancer tumors in mice. Top images demonstrate tumor uptake in 3 cell lines of pancreatic cancer (left to right: Suit-2, Capan-2, and BxPC-3) in mice with pancreatic ductal adenocarcinoma xenografts after treatment with vehicle only (left in paired images) and the BRD4 inhibitor JQ1 (right in paired images). Bottom images show associated histology for MYC (middle row) and the transferrin receptor (bottom row).

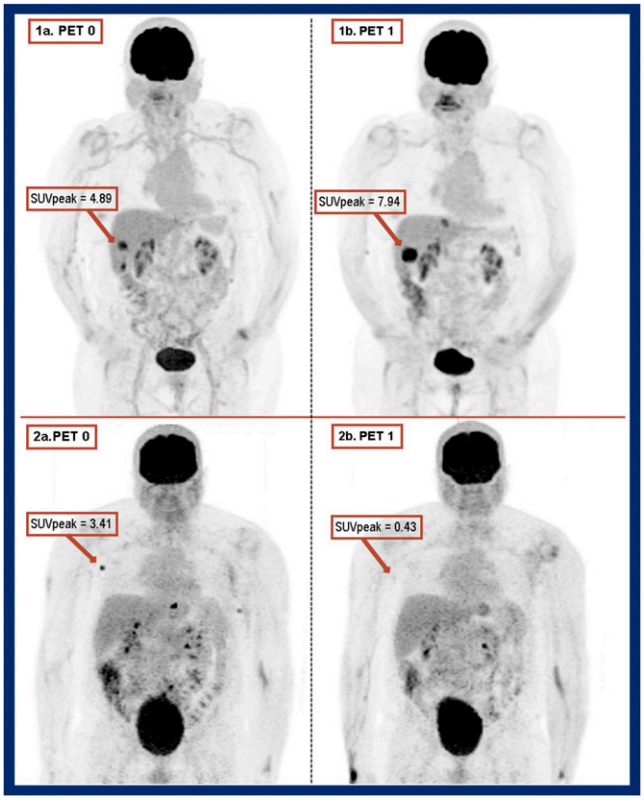


FIGURE 5. Evaluation of ^{18}F-FDG PET/CT for response assessment in patients with advanced melanoma treated with pembrolizumab checkpoint inhibitor monotherapy. Maximum-intensity projection images show progression and response in patients before initiation of therapy (left) and after 3 cycles of treatment (right). Top: 88-year-old patient with melanoma metastatic to the liver. Progressive disease was seen after 3 cycles. Disease ultimately progressed during therapy. Bottom: 58-year-old patient with metastatic disease to an axillary lymph node. After 3 cycles of therapy the patient showed a complete response on imaging. The patient later was classified as having no evidence of disease.

immune-checkpoint inhibitors and CAR T cells) on almost a daily basis. A recent timeline published in *Science* (2018; 359[6382]:1350–1355) outlined the introduction and growing implementation of 7 immune-checkpoint treatments approved since 2000. At meetings this year, reports have described additional indications, even in first-line lung cancer, for some of these molecules. Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)/programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) are targets for which therapeutics are already approved in a broad range of indications. A range of other immune-checkpoint targets are under investigation in clinical trials. Second- and third-generation immunooncology drugs are now being developed. But immunotherapy with these agents is complex: response to treatment may be difficult to predict with pretreatment screening, the side effects can be quite severe, and "pseudoprogression" is not uncommon. This means that we must be aware of the specific targets and the associated new therapies, because as these come into trials and clinical practice, patients will be coming to us for staging and restaging scans. We must be familiar with the toxicities and response profiles. We can also play a pivotal role in development of new immunotherapies and techniques for response evaluation and prognosis, whether these approaches are antibody-, protein-, or even CAR T cell–based.

Fuser et al. from the Mallinckrodt Institute of Radiology and the Alvin J. Siteman Cancer Center at Washington University in St. Louis (MO) reported on "Evaluation of ^{18}F-FDG PET/CT for response assessment in patients with advanced melanoma treated with pembrolizumab checkpoint inhibitor monotherapy" [133]. These researchers focused on the ways in which standard PET/CT imaging could be used for response assessment of a PD-1 inhibitor treatment. Figure 5 shows examples from a patient (top) with melanoma metastatic to the liver who showed progressive disease with no reduction in ^{18}F-FDG uptake after 3 cycles of immune-checkpoint immunotherapy (nonresponder), and a patient (bottom) with metastatic disease

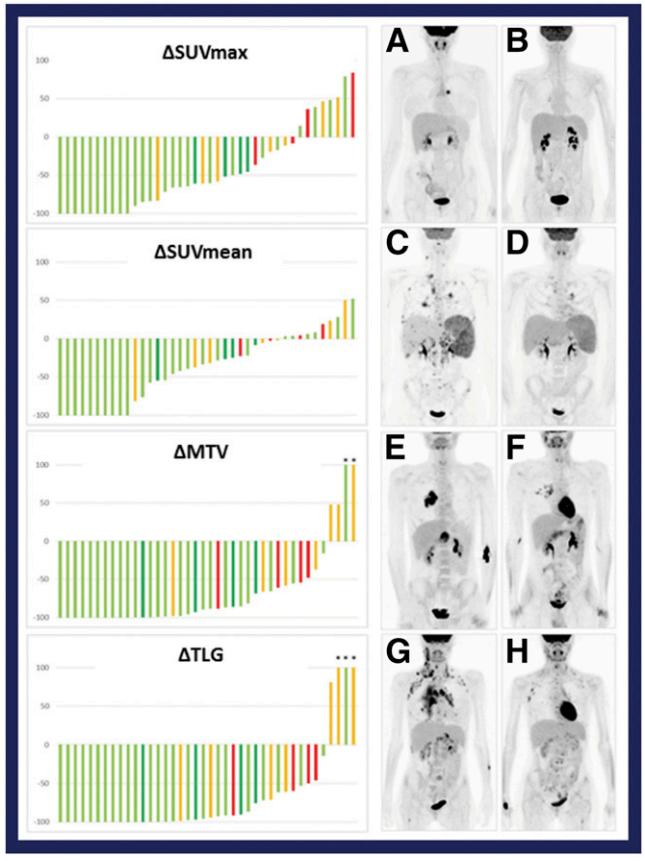


FIGURE 6. ^{18}F-FDG PET/CT for response assessment in Hodgkin lymphoma undergoing immunotherapy with checkpoint inhibitors. Left: average changes in (top to bottom) SUV_{max}, SUV_{mean}, metabolic tumor volume, and total lesion glycolysis in 43 patients with relapsed or refractory Hodgkin lymphoma over a median follow-up of 19 months. Right: Images before treatment initiation (left) and at 17 weeks (right) in patients who showed (top to bottom) complete response, partial response, partial response with an associated immunorelated lung adverse event; and progressive disease with multiple new lesions but partial response on some initial sites.

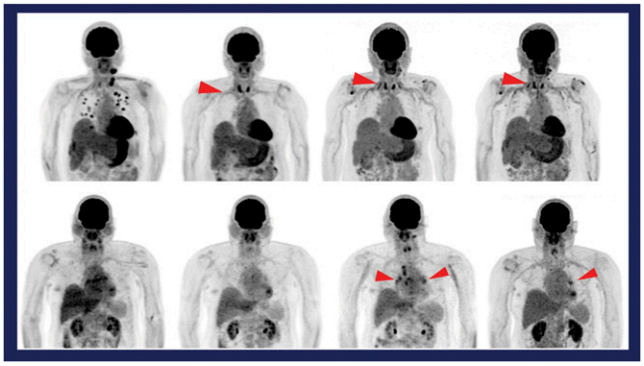


FIGURE 7. Potential role of ^{18}F-FDG PET/CT for early response assessment of immune-checkpoint inhibitors. Top: Patient with immune-related thyroiditis (arrowheads) imaged at (left to right) baseline and 3, 10, and 14 months after treatment initiation. Bottom: Patient with immune-related lymphadenopathy (arrowheads) at baseline and 2, 6, and 9 months after treatment initiation. The average peak of SUV_{max} was seen earlier in thyroiditis than in lymphadenopathy. Elevated ^{18}F-FDG uptake in thyroid may be a candidate sign for monitoring immunotherapy effectiveness.

to an axillary lymph node who showed a complete response on imaging after 3 cycles of immunotherapy. The authors found that SUV_{max} and SUV_{peak} were higher at baseline in nonresponders and also increased after treatment in these patients. They concluded that "markedly increased ^{18}F-FDG uptake on interim response PET/CT scans in patients treated with pembrolizumab appears to identify nonresponding patients." This indicates that the pattern of uptake of ^{18}F-FDG within target lesions can be used as a potential guide.

Castello and Lopci from the Humanitas Clinical and Research Hospital Rozzano (Italy) reported on "Hodgkin's lymphoma response to checkpoint inhibitors determined with ^{18}F-FDG PET/CT" [25]. They looked at response assessment using 2 PD-1 inhibitors, nivolumab and pembrolizumab, in scans from 43 patients with relapsed or refractory Hodgkin lymphoma at baseline, at 8 weeks, and after 17 weeks of treatment, which is the timepoint at which we are often asked to do these types of scans (Fig. 6). They found that the reduction of ^{18}F-FDG uptake as assessed by Deauville scores was highly correlated with eventual responses of patients at follow-ups. They noted that tumor burden changes in responders were seen appreciably later in the course of immunotherapy, perhaps as a result of prior reactivation of the immune system and increased glucose consumption in lymphocytes. It is clear that SUV_{max}, as well as timing of imaging, are particularlyy important parameters in assessing response to immunotherapy.

Another very interesting presentation came from Nobashi et al. from Stanford University/Stanford Hospital (CA) and the Oregon Health and Science University (Portland), who reported on "The potential role of ^{18}F-FDG PET/CT for early response assessment of immune checkpoint inhibitors" [595]. These authors looked retrospectively at patterns of change in scans in patients with malignant melanoma, malignant lymphoma, or renal cell carcinoma who were being treated with various types of immune-checkpoint inhibitors. Patients underwent imaging at baseline and at up to 5 restaging points. What they observed, as many of us have seen, was increased uptake in most organs after the first restaging scan, as well as in the thyroid (thyroiditis) in some patients (Fig. 7). Four patients presented with reactive and often symmetric lymphadenopathy during therapy. These patterns seemed to be very strongly and positively linked to response, which makes sense: if an immune response is engendered, then off-target inflammatory changes may occur. The average times from initial treatment until emergence of therapy-related thyroid uptake and lymphadenopathy uptake were 123 and 183 days, respectively. The authors concluded that their results indicated that early favorable signs on PET vary among diseases and checkpoint inhibitors, and that elevated FDG accumulation in the thyroid might be "a candidate sign of monitoring effectiveness of immunotherapy observed earlier than immune-related lymphadenopathy."

One of the problems with looking at ^{18}F-FDG uptake alone or solely at patterns of uptake within target lesions is that it is common to see pseudoprogression following immune-checkpoint inhibitor therapy. It is for this reason that very early on in the development of immunotherapy a different type of Response Evaluation Criteria in Solid Tumors (iRECIST) was first proposed. Figure 8 shows a melanoma

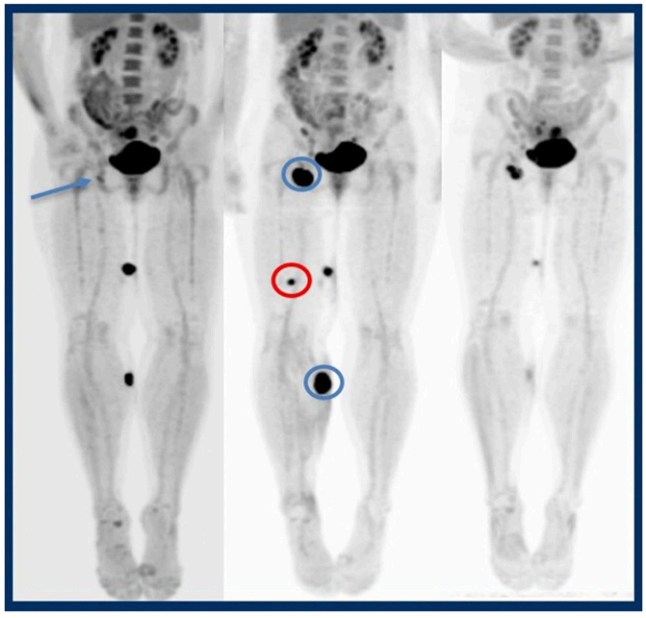


FIGURE 8. Pseudoprogression and new false-positive lesions in a patient with melanoma treated with ipilimumab. Images acquired (left to right) before treatment and at first and second follow-ups. Patient originally had disease in the right groin (arrow) as well in-transit disease subcutaneously in the medial aspect in the left leg. At first follow-up, uptake was seen in a new false-positive lesion (red circle) and was markedly increased in 2 previously identified lesions (blue circles). At second follow-up the new lesion had disappeared and uptake in the other 2 lesions was greatly diminished.

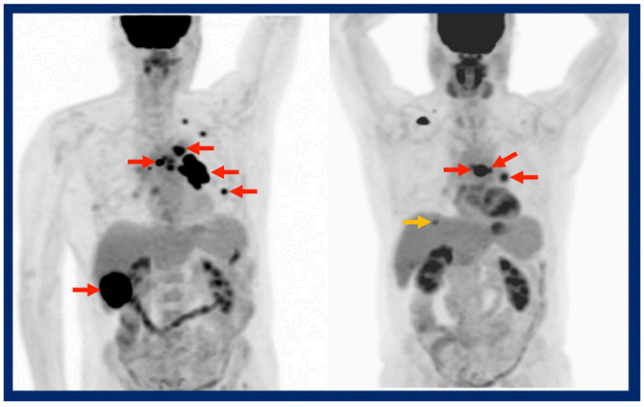


FIGURE 9. ^{18}F-FDG PET/CT for monitoring immunotherapy with PD-1 blockade in patients with advanced non–small cell lung cancer (NSCLC). Example PET/CT images in a patient with advanced NSCLC at baseline (left) and on follow-up PET (right) show target lesions (red arrows) and new false-positive lesion (yellow arrow at follow-up). Using PERCIST, the patient would have been classified as having progressive metabolic disease. Using imPERCIST, the patient was classified as having a partial metabolic response. The use of PERCIST for assessment in this 50-patient study indicated progressive metabolic disease in 39, whereas the use of imPERCIST indicated progressive disease in only 21. Overall survival, however, was not correlated with differences in tumor response prediction in the 2 criteria. Visualizing a new lesion after immune-checkpoint treatment initiation does not necessarily imply worse outcomes.

patient treated with ipilimumab who originally had disease in the right groin as well as in-transit disease subcutaneously in the medial aspect in the left leg. At first follow-up, imaging showed markedly increased uptake in 2 previously identified lesions and in a new lesion. Yet at the second follow-up the lesions had all but disappeared, along with the increases in uptake noted at first follow-up. In other words, false-positive sites can occur. It is for this reason that an immune PET Response Criteria in Solid Tumors (imPERCIST) has been proposed. I would encourage you to contemplate this carefully, because it uses the standard PERCIST criteria, for example, of looking at SUL_{peak} in up to 5 target lesions, but does not use the appearance of new lesions as a criterion for progressive disease.

Why is this distinction important? Ito et al. from the Memorial Sloan Kettering Cancer Center (New York, NY) reported on "F-18 FDG PET/CT for monitoring immunotherapy with PD-1 blockade in patients with advanced non–small cell lung cancer (NSCLC)" [279]. In addition to assessing increased or decreased tracer uptake on follow-up imaging, they assessed the presence or absence of new lesions. In the 50 patients in this study, the use of PERCIST indicated progressive metabolic disease in 39, whereas the use of imPERCIST indicated progressive disease in only 21 (Fig. 9). Using PERCIST, the patient in this example would have been classified as having progressive metabolic disease. Using imPERCIST, the patient was classified as having a partial metabolic response. In addition, the authors looked at survival and found no difference between survival curves based on conventional PERCIST and imPERCIST. Tumor response with each set of criteria was significantly correlated with overall survival. In other words, visualizing a new lesion after treatment initiation does not necessarily imply worse outcomes. Additional work is needed to define the impact of imPERCIST in other tumor types and in multicenter trials. The results of these and other reports suggest that we should be thinking carefully about interpretation of new lesions in patients undergoing immune-checkpoint therapy.

Immunooncology: novel imaging probes

The exploration of new imaging probes is going well beyond ^{18}F-FDG as we learn more about the ways in which these immune therapies work. The immunoenvironment—the microenvironment within the tumor—is inextricably linked to the therapeutic response. Within that microenvironment are not only stromal cells but lymphocytes, macrophages (either local or bone-marrow derived), and a whole host of different phenotypes of cells. This microenvironment is increasingly recognized as playing a pivotal role in patient response to treatment. Modulation of this microenvironment and immune suppressive cells can enhance immune-checkpoint therapy. The new generation of immunooncology drugs may go beyond blocking PD-1 or

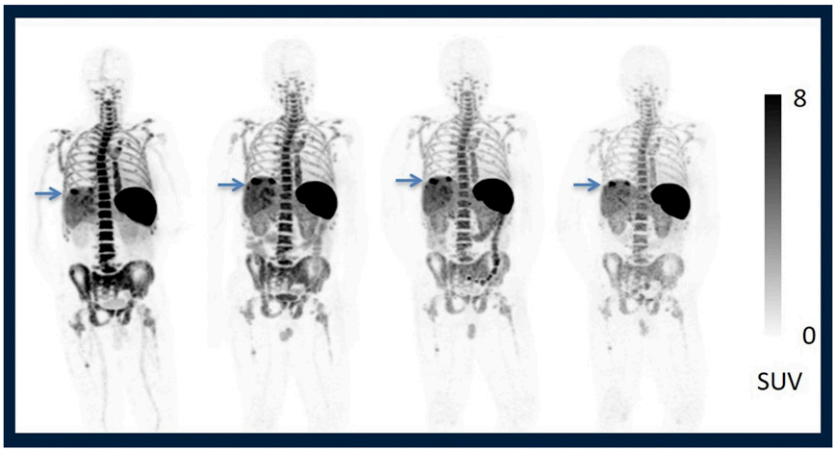


FIGURE 10. First-in-human phase I imaging study with ^{89}Zr-IAB22M2C anti-CD8+ minibody in patients with solid tumors. Patient with metastatic hepatocellular carcinoma (left to right) before initiation of treatment with an immunotherapeutic agent and on days 2, 3, and 7. ^{89}Zr-IAB22M2C imaging shows uptake in normal nodes, marrow, spleen, and liver. Lesions (blue arrows) could be visualized as early as 2 hours after tracer injection and during the entire 7-day period. This technique allows serial imaging of activated T cells and their distribution throughout the body.

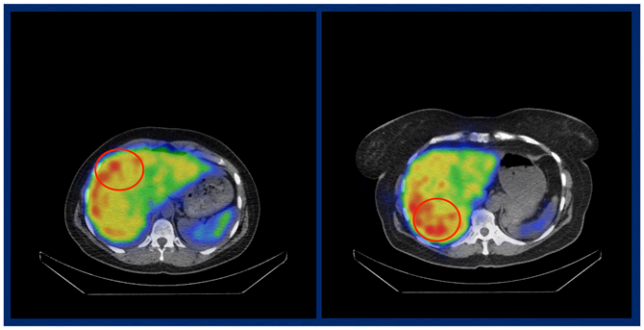


FIGURE 11. ^{99m}Tc-tilmanocept in SPECT/CT imaging of activated macrophage infiltration in metastatic liver colorectal adenocarcinoma. Fused SPECT/CT images acquired 4–6 hours after ^{99m}Tc-tilmanocept injection in 2 patients shows the presence of tumor-associated macrophage populations (CD206+ macrophages) around metastases (red circles).

PDL1 to inducing stimulatory effects through a bispecific or a fusion protein. Researchers developing these agents need to know precisely how the microenvironment of each tumor is constituted and what effects the novel agent is likely to have there. New approaches to immune microenvironment imaging will provide important information on prognosis, prediction of response, and resistance to therapy.

Pandit-Tasker et al. from the Memorial Sloan Kettering Cancer Center (New York, NY), the David Geffen School of Medicine/University of California at Los Angeles, Imaginab Inc. (Inglewood, CA), and Imaging Endpoints (Scottsdale, AZ) reported on a "First in human phase I imaging study with ^{89}Zr-IAB22M2C anti CD8+ minibody in patients with solid tumors" [596]. The researchers wanted to determine the safety and feasibility of PET/CT imaging of CD8+ T cells with this agent in patients undergoing immunotherapy. Two patients (1 with melanoma, 1 with hepatocellular carcinoma) were included. Figure 10 is an example in the patient with metastatic hepatocellular carcinoma, in which we can actually visualize activated T cells and their distribution in the body over 7 days. Only 2 hours after initial infusion, this technique visualized the infiltration of T cells into the tumor. The results highlight the fact that the lesions with uptake are, in fact, quite immune enhanced. This is an extremely important advance that could accelerate immunooncology drug development and contribute to new imaging techniques to assess whether a patient might be responsive to established or more complex immunotherapy treatments.

We see SPECT-based imaging in oncology less and less frequently, but SPECT/CT is proving to have applications in immunotherapy. Cope et al. from Navidea Biopharmaceuticals (Dublin, OH) and the University of Alabama at Birmingham reported on "Intravenous ^{99m}Tc-tilmanocept in planar and fused SPECT/CT imaging of activated macrophage infiltration in subjects with metastatic liver colorectal adenocarcinoma (ML-CRC)" [56] These authors are conducting a larger study to determine the effectiveness of a single dose of ^{99m}Tc-tilmanocept, a radiopharmaceutical that binds with high affinity to the mannose receptor (CD206), in patients with ML-CRC. Their report at this meeting focused on imaging the tumor-associated macrophages activated in immunotherapy. Figure 11 shows SPECT/CT imaging results in 2 patients with MLC-CRC in which the tumor-associated macrophage populations are visualized. As we learn more about the different targets and cell populations in tumor microenvironments, it appears likely that we will develop a range of target-specific PET probes to address these.

Tumor immune microenvironment: optimizing immune-based therapies

Identifying new PET probes is important because the multiple, complex, and variable components in the microenvironment combine to form what have been categorized as 3 distinct types of cancer microenvironments. (1) In the infiltrated-excluded microenvironment, immune-excluded cells surround the tumor, so that large numbers of infiltrating T cells are not present in the tumor, nor do tumors exhibit high PD-L1 expression. This type of tumor does not respond as well to immune-checkpoint therapy. (2) Infiltrated-inflamed microenvironments ("hot" tumors) have an abundance of lymphocyte infiltration, as well as high PD-L1 expression on the tumor cells themselves. The T cells have high interferon gamma production/granzyme B secretion. These tumors are more likely to respond. (3) Some tumors, termed infiltrated–tertiary lymphoid structure (TLS) microenvironment types, have characteristics almost like those of lymph nodes, including lymphocyte infiltration phenotypes such as B cells, dendritic cells, and T cells.

One reason that understanding these different types of tumor microenvironments is important is that it may be possible to "convert" a tumor from being cold to hot and thereby increase the therapeutic efficacy of immune-checkpoint treatments. We already have in our armamentarium agents and techniques that might do this, but this remains a

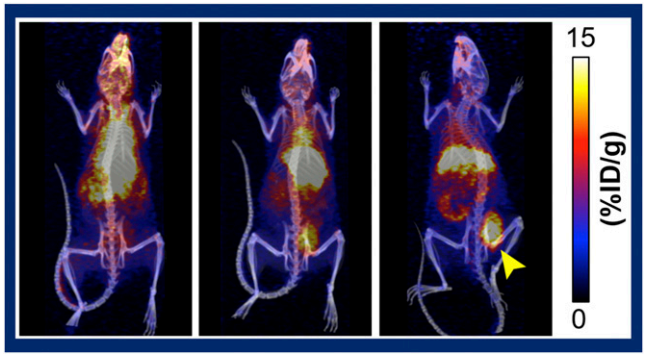


FIGURE 12. Combination of targeted radionuclide therapy and checkpoint blockade in a syngeneic murine model of melanoma with an antimouse CTL4 antibody at 3, 24, and 48 hours after injection of a radiolabeled alkylphosphocholine analog (^{90}Y-NM600), intended to enhance therapeutic response. PET/CT showed selective uptake of the agent, prolonged retention in tumor, and elicited a dose-dependent tumor response. No systemic toxicities were noted in injected activities <50 μCi.

relatively unexplored area. Hernandez et al. from the University of Wisconsin (Madison) reported that a "Combination of targeted radionuclide therapy and checkpoint blockade augments therapeutic response in a syngeneic murine model of melanoma" [119]. These researchers evaluated whether response to immune checkpoint blockade could be enhanced with a radiolabeled alkylphosphocholine analog (^{90}Y-NM600) capable of delivering tumor-selective targeted therapy to all tumors in the setting of metastatic disease. They combined a syngeneic mouse melanoma model with an antimouse CTL4 antibody and used PET/CT to identify uptake of ^{90}Y-NM600 at 3, 24, and 48 hours after injection (Fig. 12). ^{90}Y-NM600 showed selective uptake, prolonged retention, and elicited a dose-dependent tumor response. We know that combined radiotherapy and administration of an immune-checkpoint inhibitor results in enhanced response. It is logical, then, to believe that neoantigen release with any of our radionuclide therapies could enhance some immune therapies. I encourage the nuclear medicine community to explore these possibilities in the context of their research and even clinical trials.

(This lecture will be continued in the January 2019 issue of Newsline)