2021 SNMMI Highlights Lecture: Oncology and Therapy, Part 2

Heiko Schöder, MD, MBA, Memorial Sloan Kettering Cancer Center, New York, NY

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 2021 Highlights Lectures were delivered on June 15 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the second part of the lecture by Heiko Schöder, MD, MBA, chief of the Molecular Imaging and Therapy Service at Memorial Sloan Kettering Cancer Center (New York, NY) and a professor of radiology at the Weill Medical College of Cornell University (New York, NY), who spoke on oncology and therapy highlights from the meeting. The first part of the lecture appeared in the October issue of Newsline. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine (2021;62[suppl 1]).

In the first part of this lecture, presentations on clinical diagnostics (including fibroblast-activated protein inhibitors [FAPI], innovations in prostate cancer diagnosis and staging, and other applications) and several new therapies were reviewed.

New Targets for Radionuclide Therapy: Other Therapy Approaches

We will highlight just a few of the many abstracts that were submitted on novel targets for radionuclide therapies. The first target is the insulin-like growth factor (IGF) receptor, which is relevant for proliferation, inhibition of apoptosis, protein synthesis, and also regulating metabolism. Juneau et al. from the Centre Hospitalier de l’Université de Montréal (Canada), Princess Margaret Hospital (Toronto, Canada), Roswell Park Comprehensive Cancer Center (Buffalo, NY), CDE Dosimetry Services (Knoxville, TN), Fusion Pharmaceuticals, Inc. (Hamilton, Canada; Boston, MA), and CHU de Québec/Université Laval (Québec City, Canada) reported on “Preliminary dosimetry results from a first-in-human phase 1 study evaluating the efficacy and safety of [225]Ac-FP1-1434 in patients with IGF-1R [IGF type-1 receptor]–expressing solid tumors.” [74]. IGF-1R is a tyrosine kinase receptor implicated in breast, prostate, lung, and other cancers. As is common in these studies, the researchers used an [111]In-labeled analog with identical antibody and bifunctional chelate for biodistribution studies and patient selection based on quantification of IGF-1R–expressing targets and organ-based dosimetry prior to therapy. The aim of the study was to evaluate the safety and tolerability of both [111]In-FPI-1547 and [225]Ac-FPI-1434 in patients with advanced refractory solid tumors and to determine the recommended phase 2 dose of the [225]Ac-labeled compound in patients with IGF-1R–expressing tumors. Results were available for 13 patients from the single-dose portion of the study, and avidity in at least 1 lesion was demonstrated in each patient. Dosimetry determined all 13 to be eligible for therapeutic administration of [225]Ac-FPI-1434, and 12 received at least 1 such administration (range, 0.80–4.2 MBq) with no drug-related serious adverse events and/or dose limiting toxicity. Figure 1 shows high uptake in a 69-year-old man with castrate-resistant prostate cancer and liver metastasis and emphasizes the promise of theranostic pairs that facilitate patient-specific treatment planning. We look forward to future data that will tell us more about how this agent can be integrated into the armamentarium of treatment options for prostate cancer.

The next interesting target addressed by presenters at the SNMMI meeting was transforming growth factor-β (TGF-β) and its role in the tumor immune environment as a source for therapeutic applications. TGF-β has many functions involved in promotion of angiogenesis, activation of cancer-associated fibroblasts, increased fibrosis, and escape from immune surveillance—all of which contribute to a more favorable environment for tumor growth and metastasis. Burvenich et al. from La Trobe University (Melbourne, Australia), Olivia Newton-John Cancer Research Institute (Melbourne, Australia), Austin Health Melbourne (Australia), University of Melbourne (Australia), and EMD Serono Research & Development Institute (Billerica, MA) reported on “Preclinical evaluation of [89]Zr-Df-radiolabeled bispecific anti-PD-L1/TGF-βRII fusion protein bintrafusp alfa” [66]. They used a next-generation programmed death ligand-1 (PD-L1) targeting molecule that allows simultaneous targeting of PD-L1 and “trapping” of TGF-β. The aim of the study was to establish the [89]Zr-radiolabeling of the investigational agent and characterize in vitro and in vivo both the [89]Zr-Df-M7824 and [89]Zr-Df-control radioconjugates. The process involved converting a so-called immune-excluded tumor into an inflamed tumor, thereby reenergizing the tumor immune microenvironment, allowing targeted binding.
to PD-L1 on tumor cells and “trapping” TGF-β, thereby inhibiting 2 mechanisms that would otherwise interfere with antitumor immune response. Figure 2 shows quantitative PET analysis of tumor, liver, lungs, and bone in mice at days 2 and 7 after injection, which allowed direct comparison with the biodistribution data available for these imaged mice. Tissue uptake assessed via PET analysis corresponded with the biodistribution results, and the authors concluded that PET imaging using $^{89}$Zr-Df-bintrafusp-$\alpha$ was suitable for use in clinical trial studies. A bioimaging study was subsequently opened at Austin Health focusing on $^{89}$Zr-M7824 PET in patients with advanced or metastatic non–small cell lung cancer and high PD-L1 expression receiving M7824 alone or in combination with chemotherapy. Sometimes, in scientific discovery and development, not all is always well that ends well. Since this abstract was submitted for presentation at this meeting, Merck, the company sponsoring the first trial, has stopped clinical trials with this drug because accumulating data did not prove promising in terms of meeting endpoints in progression-free survival in lung cancer (1) and, more recently, biliary duct cancer (2). This is perhaps a cautionary tale. If, for example, molecular imaging such as this had been employed earlier for patient selection, documentation of target engagement, and documentation of response (or lack thereof), substantial funds could have been saved as compared to conducting a clinical trial and then concluding that the treatment was not working as expected.

CD46 is a transmembrane complement regulatory protein overexpressed in various cancers and highly expressed in aggressive, advanced-state, de-differentiated prostate cancer and with very high overexpression in multiple myeloma. It inhibits complement activation, promotes immune evasion and growth, and regulates cellular metabolism. Wang et al. from the University of California San Francisco and others reported in April of this year on molecular imaging of prostate cancer, targeting CD46 using immunoPET with $^{89}$Zr-DFO-YS5 in a murine model (3). At this meeting, the same group reported on “Molecular imaging of multiple myeloma targeting CD46 using immunoPET” [62]. $^{18}$F-FDG PET/CT can result in false-negative findings in multiple myeloma, and CD46 targeting holds promise for greater accuracy. They studied the $^{89}$Zr-DFO-YS5 tracer in both NSG mice bearing subcutaneous xenograft tumors and in an orthometastatic model of myeloma. Figure 3 shows immunoPET images acquired at 6 and 4 days after injection in subcutaneous and orthometastatic models, respectively. They found that $^{89}$Zr-DFO-YS5 binds specifically to CD46+ human MM1s subcutaneous xenografts, with significantly higher uptake than in comparative cold antibody–blocking groups. In the orthometastatic model, $^{89}$Zr-DFO-YS5 also demonstrated specific uptake in the bone marrow. Analysis of ex vivo bioluminescence data indicated that heterogeneous osseous tumor involvement correlated with tracer uptake. The authors concluded that this CD46-targeted imaging “shows great potential for clinical translation as an imaging agent, theranostic platform, and companion biomarker in multiple myeloma.”

The last target we will look at in this section is a CUB domain–containing protein 1, CDCP1. CDCP1 is a cell-surface, single-pass transmembrane glycoprotein upregulated in multiple malignancies (including but not limited to triple-negative breast cancer, pancreatic ductal adenocarcinoma,
renal cell carcinoma, hepatocellular carcinoma, acute myeloid leukemia, and ovarian cancer) and with relevance to prostate cancer progression. It has a role in cancer growth, survival, and therapy resistance. CDCP1 is being targeted in research with antibody drug conjugates and with radiolabeled antibodies for theranostics. Evans et al. from the University of California San Francisco and PGIMER (Chandigarh, India) reported that “CDCP1 is a novel target for radioligand therapy in metastatic castration-resistant prostate cancer refractory to treatment with PSMA [prostate-specific membrane antigen]-directed radioligands” [92]. Figure 4 shows microCT and PET/CT of their monoclonal antibody 4A06 agent across a number of tumor models. The highest uptake, both in terms of %ID/g and also tumor-to-background ratio, was seen in the PSMA-negative, androgen receptor-negative tumor model. The antibody was also labeled with $^{177}$Lu, leading to growth inhibition as shown in the right-hand side of the figure. The authors concluded that these data provide evidence that “CDCP1 can be targeted for radioligand therapy in metastatic cancer-resistant prostate cancer” and “position CDCP1-directed radioligand therapy as a potential complement or alternative to the current repertoire of radioligand therapies.”

We will look briefly at increasing interest in photodynamic therapy. Those of you who regularly attend the World Molecular Imaging Congress may be familiar with recent advances. The 3 principal components are the light source, the photosensitizer, and the generation of reactive oxygen species, which lead eventually to targeted and irreversible tissue damage. Of note, it does not matter how the light is created (X-rays, Cerenkov luminescence, or radioluminescence). Most recently, researchers have looked at ways to combine photodynamic therapy with chemoimmunotherapy or targeted radionuclide therapy. Jeon et al. from Seoul National University (Republic of Korea) reported on “Photodynamic therapy induced by a combination of scintillating liposome and radiolabeled antibody” [97]. Europium is a rare earth metal that can be excited and then eliminates the radioluminescence. In this very intriguing presentation, they described using a europium-loaded scintillating liposome and a $^{177}$Lu-labeled human epidermal growth factor receptor 2-targeting antibody (Fig. 5). In in vivo and ex vivo murine studies they showed that the europium liposome/$^{177}$Lu-antibody combination achieved 8-fold higher...
radioluminescence than Cerenkov imaging. When combined with the photosynthesizer Victoria blue for photodynamic therapy, reactive oxygen species production was similar to a much greater amount of 100 μCi of \(^{177}\)Lu-antibody alone but with only 10% of the radioactivity, with no apparent cytotoxicity. In in vitro studies, the combination showed a 2.5-fold higher cell-killing effect compared to \(^{177}\)Lu-antibody alone. The authors concluded that a novel treatment strategy using this photodynamic therapy approach could, with further validation, “lower the systemic adverse effect while enhancing the treatment efficacy of \(^{177}\)Lu conjugated theranostic radiopharmaceuticals.”

New Techniques: Methods for Data Analysis

A number of new techniques and types of instrumentation were presented at this meeting, many dealing with motion correction, including data-driven motion correction,
Artificial intelligence (AI) is becoming increasingly relevant and available for clinical practice and to support multicenter clinical trials. Niman et al. from MIM Software, Inc. (Cleveland, OH) and St. Vincent’s Hospital (Sydney, Australia) reported on the “Improved clinical feasibility of total tumor burden quantification on Ga-PSMA-11 PET/CT through deep learning autosegmentation of organs for automatic physiological uptake removal” [1327]. Their question was whether an AI algorithm can intelligently segment tumor and subtract normal background. They used data from the $^{177}$Lu-PSMA-617 and idronoxil trial in men with end-stage metastatic castrate-resistant prostate cancer (LuPIN) to create CT-based organ volumes of interest and automatically remove the majority of PET physiologic uptake. Figure 6 shows the ground truth, as segmented by 3 investigators, compared with results from the algorithm, very nicely identifying tumor lesions and subtracting normal background across a number of patients. The authors concluded that application of fully automatic organ-based physiologic uptake removal results in very similar volumes to those produced by manual editing of total tumor burden volumes, suggesting also that “minimal additional time would be necessary if used in the clinical workflow.”

Borelli et al. from Sahlgrenska University Hospital (Gothenburg), Chalmers University of Technology (Gothenburg), University of Gothenburg, Skåne University Hospital (Malmö), and Lund University (Malmö; all in Sweden) reported that an “AI tool decreases interobserver variability in the analysis of PSMA PET/CT” [1006]. The aim of this study was to address current challenges in interobserver variability by developing an AI tool for detection and quantification of primary prostate tumors, bone metastases, and lymph node lesions in PSMA PET/CT studies. The tool was based on a previously developed CT-based segmentation approach (4) and was applied to direct segmentation of lymph node lesions in $^{68}$Ga-PSMA imaging in 10 patients referred for initial staging of prostate cancer (5). Total lesion uptake was analyzed with and without AI assistance. The AI tool was found to have significantly lower interobserver variability in prostate tumors, bone metastases, and lymph node metastases. Figure 7 shows differences in human reader and AI identification. The authors concluded that “this AI tool may help in facilitating comparison of studies from different centers, pooling data within multicenter trials, and performing metaanalysis.” (They also added that the AI tool developed in this project is available upon reasonable request for research purposes at www.recomia.org).

We will close out these highlights with images from the Penn PET Explorer developed by Joel Karp, PhD, and colleagues. Pantel et al. from this group at the University of Pennsylvania (Philadelphia) reported on “Human research studies on the PennPET Explorer” [55]. The prototype for this whole-body PET device had a 64-cm axial field of view. The expanded scalable PennPET Explorer has a 1.12-m field of view, and the group showed human studies illustrating the resulting benefits. In addition to clinical studies with $^{18}$F-FDG, the group has conducted research using $^{89}$Zr-Df-IAB22M2C (an anti-CD8 minibody for immune imaging), $^{18}$F-(2)FA (for nicotine receptor imaging), $^{18}$F-FNOS (for inflammation imaging), $^{18}$F-fluoroglutamine (for glutamine metabolism), and $^{11}$C- and $^{18}$F-trimethoprim (for infection imaging). The increased sensitivity afforded by the extended...

![FIGURE 6. Total tumor burden quantification on $^{68}$Ga-PSMA-11 PET/CT through deep learning autosegmentation of organs for automatic physiologic uptake removal. Paired images shown using data from patients in clinical trial treatment for end-stage metastatic castrate-resistant prostate cancer. Left image in each pair shows proposed artificial intelligence total tumor burden segmentation after physiologic uptake removal (red) and volume of uptake correctly removed by the algorithm (blue). Right images show ground truth tumor segmentation (red), as segmented by 3 investigators.]

![FIGURE 7. Artificial intelligence (AI) tool for detection and quantification of primary prostate tumors, bone metastases, and lymph node lesions in PSMA PET/CT. Images show $^{68}$Ga-PSMA PET foci (top row) on the prostate in (left to right) axial, coronal, and sagittal views. Middle row depicts manual annotation without AI assistance. Bottom row depicts manual annotation with AI assistance. Orange pixels were annotated by only 1 reviewer; red by 2; and blue by all 3.]

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axial coverage of whole-body PET imagers can be leveraged for numerous clinical and research applications (Fig. 8). They showed examples of imaging performed in 3 settings: (1) as part of a clinical standard-of-care (SOC) PET/CT scan using a U.S. Food and Drug Administration (FDA)-approved tracer without administration of additional radiotracer; (2) with PET/CT imaging as part of research studies, with specific radiotracers and protocols dictated by the relevant studies; and (3) imaging with an FDA-approved radiotracer without concomitant SOC imaging, with an injected activity that could be lower than that used for SOC imaging. The results across the spectrum of applications showed good whole-body kinetics, very nice uptake, and high sensitivity. The authors are now focusing on optimizing the many potential associated protocols.

**Summary**

Several oncologic themes and questions emerged from presentations and related discussions at this meeting. We need to define how many PSMA-based probes are really needed in the future, and which should be applied when and in what settings. FAPI is the focus of a growing number of promising applications and excitement, but it is important to think now about methods of quantification to better define its role in the clinic and clinical trials. In the rapidly expanding field of radionuclide-based therapy, the VISION and TheraP trials have helped to establish the role of 177Lu-PSMA. My appeal to you is to make sure that the nuclear medicine community maintains ownership of these new treatments.

I would like to conclude with a few tasks that we should collaboratively undertake for the future. We need to better define the role of diagnostic or therapeutic PSMA in various states of disease. We should continue to define the role and place of α emitters in various therapies (a topic which I did not cover in this lecture because of time limitations). We must encourage appropriate and timely clinical translation of the many molecules that are coming forward, as well as ensure that these are suitable for specific applications. We need to establish artificial intelligence solutions for nuclear medicine agents for clinical trials. Finally, I believe we need to establish and proactively pursue models of “co-opetition” with radiation oncology, medical oncology, and surgical oncology for theranostic applications.

**REFERENCES**


