Reply: PSMA-Targeted Therapeutics: A Tale About Law and Economics

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Published online May 20, 2021.
DOI: 10.2967/jnumed.121.262566

REPLY: I thank Dr. Notni for his recent letter in which he provides his perspective on one part of the success story of PSMA-targeted theranostics. Success stories often come with conflicts and intellectual ownership discussions.

Dr. Notni makes important points. He acknowledges the pivotal role of the inventors of ^{177}Lu-PSMA I&T in shaping the field (1). He also emphasizes our obvious responsibility to honor patent protection. I would like to highlight that both patented and unpatented compounds can be successful and become market drivers. It is important to allow free market forces to compete for business. For instance, one company is currently initiating a phase 3 clinical trial with the nonpatented compound ^{177}Lu-PSMA I&T in patients with castration-resistant prostate cancer (2). As another example, the U.S. Food and Drug Administration recently granted a new-drug application for the non–patent-protected ^{68}Ga-PSMA-11 for a wide range of indications in patients with prostate cancer (3). This development further establishes the high clinical relevance and impact of PSMA-targeted PET imaging in the care of prostate cancer patients (4). Reimbursement will set the stage and prepare the market for several soon-to-be-approved compounds with comparable diagnostic performance. Then the market will decide which ones are most conveniently used clinically. It is thus important to recognize that both patented and nonpatented compounds can address unmet clinical needs, improve patient outcomes, and create significant revenues while following very different business models. I would, however, urge caution regarding exploiting the lack of patent protection for rebranding long-established compounds. Such measures would simply create market and customer confusion.

Theranostics are rapidly growing and have generated substantial interest from industry. Both protected and unprotected compounds will have their place in the clinic and in research. Non–patent-protected compounds could greatly facilitate translational research, addressing (independent of Big Pharma) resistance to PSMA-targeted therapeutics, for instance.

Protected and nonprotected compounds will give rise to larger and smaller companies, all aiming to become fiscally solid despite very different business models.

They all are part of the new nuclear medicine ecosystem, make important contributions to patient care, and will shape the further development of our discipline. We should therefore appropriately appreciate the outstanding contributions that have given nuclear medicine an immense boost over the past 15 years.

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^{18}F-FDG–Avid Axillary Lymph Nodes After COVID-19 Vaccination

TO THE EDITOR: In a recent patient with a left-side parotid malignancy (biopsy-proven mammary analog secretory carcinoma), ^{18}F-FDG PET/CT was obtained during the workup (Fig. 1). The findings showed ^{18}F-FDG avidity in the left axillary lymph nodes with an overall SUV_{max} of 4.5 and an ^{18}F-FDG–avid left supraclavicular lymph node. This result prompted an ultrasound-guided biopsy of the lymph nodes before surgery. Pathologic examination of both subsites revealed lymphocytes consistent with a benign lymph node. Around the time of the biopsy, the patient recalled that she had received the first dose of the Moderna Therapeutics messenger RNA-1273 vaccine 10 d beforehand in her left deltoid. After vaccination, she had injection site soreness and some mild fatigue and general malaise for about 4 h. She then underwent successful superficial parotidectomy, with margin-negative and node-negative resection of the left parotid mammary analog secretory carcinoma.

Shortly after the aforementioned patient was seen, 3 mo post-treatment PET imaging was obtained as part of oncologic surveillance for a patient with a history of oral cavity/oropharyngeal squamous cell carcinoma. On physical examination 3 d before her PET study, laryngoscopy revealed findings concerning for recurrence in the previous surgical bed. Both sides of the neck were palpated, and no lymphadenopathy was appreciated. On PET, the left axillary and left supraclavicular nodes had ^{18}F-FDG avidity, with an SUV_{max} of 5.1. Because of our previous experience with the other patient, this second patient was questioned specifically regarding coronavirus disease 2019 (COVID-19) vaccination. She was able to recall that she had received the first dose of the COVID-19 vaccine 14 d beforehand, though she could not recall the manufacturer. The patient reported minimal symptoms after vaccination and was asymptomatic at the time of the PET scan. She was taken to the operating room for direct laryngoscopy, and biopsy of the concerning area revealed mild dysplasia with no evidence of carcinoma.

^{18}F-FDG uptake is not tumor-specific and can be seen in infection, inflammation, and granulomatous disease (1). Axillary lymph node ^{18}F-FDG avidity has been reported in patients receiving several types of vaccines, including vaccinations to influenza, H1N1, and the human papillomavirus vaccine, but has not been reported in association with the COVID-19 vaccine (2–4). Ultrasound-guided fine-needle aspiration is generally a low-morbidity procedure, though no procedure is without risk. Biopsy of her axillary node could likely have been avoided if the correlation between her recent history of vaccination and her left axillary ^{18}F-FDG–avid lymph nodes had been determined. Limited data on mammary analog secretory carcinoma shows a 5.5% rate of cervical nodal metastasis, but biopsy of a

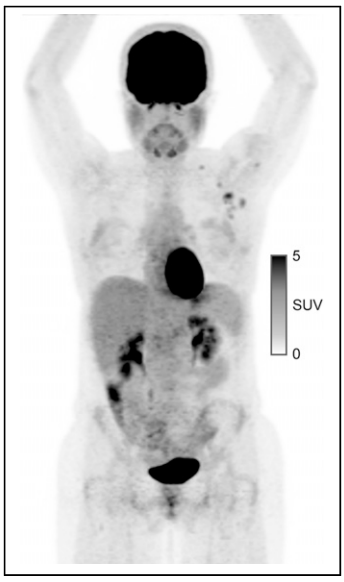

FIGURE 1. ^{18}F-FDG PET/CT showing left axillary and left supraclavicular avidity. Maximum-intensity-projection image with SUV scale at right.

supraclavicular node with ^{18}F-FDG uptake is prudent in the setting of an ipsilateral parotid malignancy (5).

As vaccination against the 2019 novel coronavirus becomes more widespread, it will be important to consider vaccination history, especially in patients who undergo ^{18}F-FDG PET/CT for cancer staging or surveillance. Reporting the vaccine history and injection location before obtaining PET imaging may help with interpretation of these studies. Further study could reveal what percentage of patients have ^{18}F-FDG–avid lymph nodes after vaccination and elucidate the time required after vaccination to allow for resolution of uptake in regional lymph nodes. This information may be able to guide recommendations on the timing of PET imaging and COVID-19 vaccination.

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Published online March 19, 2021.

DOI: 10.2967/jnumed.121.262108

Specific and Nonspecific Uptake in Quantitative ^{89}Zr-Immuno-PET

TO THE EDITOR: In a recent review, van Dongen et al. illustrated why ^{89}Zr-immuno-PET has become an important tool for the in vivo characterization of novel biologic drugs and their targets (*1*). A technical "State of the Art" article summarized PET quantification of ^{89}Zr-tracer uptake, stressing that total tissue uptake results from a target-specific and a nonspecific contribution. The latter involves a first, so-called reversible, part related to free tracer in blood and interstitium, quantified by the Patlak *y*-intercept (V_t). The second, irreversible, part is related to ^{89}Zr residualization after monoclonal antibody (mAb) uptake and degradation by antigen-negative cells, quantified by the Patlak uptake-rate constant (K_i). This description is fully in line with a previous study coauthored by van Dongen, using Patlak analysis in normal tissues (kidney, liver, lung, and spleen) without known target expression for 4 ^{89}Zr-labeled mAbs, respectively (*2*). van Dongen et al. thus suggested that future quantitative ^{89}Zr-immuno-PET studies should consider multiple-time-point acquisitions to assess nonspecific uptake versus time, with at least 3 late time points, and that sophisticated modeling strategies should be developed (*1*,*2*).

We believe that this suggestion warrants further comments that might be helpful for anticipating quantitative ^{89}Zr-immuno-PET studies in tumors, designed for assessing in vivo target engagement. First, the nonspecific-irreversible uptake should be quantitatively compared with the total-tumor uptake, in order to actually determine whether it might be significant or negligible (*1*,*2*). To justify this proposal, let us consider recent results about ^{89}Zr-anti-PD-L1, designed for monitoring in vivo chemotherapy-mediated modulation of tumor-PD-L1 expression (*3*). After extracting tracer input function and tumor data showing irreversible uptake (using the Web-Plot-Digitizer software in Jung et al.'s Figures 2B and 3B, respectively (*3*)), Patlak analysis provides a total-tumor K_i of 0.0289 $mL \cdot g^{-1} \cdot h^{-1}$ ($R^2 = 0.9993$). For comparison, combining 4 ^{89}Zr-labeled mAbs, the baseline value of the nonspecific K_i in the kidney, liver, lung, and spleen was previously found to be 0.0007, 0.0011, 0.0002, and 0.0005 $mL \cdot g^{-1} \cdot h^{-1}$, respectively (*2*). The total tumor K_i value of the ^{89}Zr-anti-PD-L1 random example thus appears to be between 26- and 145-fold higher than the nonspecific K_i values of normal tissues. Even assuming that the nonspecific contribution might vary depending on tumors and patients, unlike for normal tissues across patients, we do suggest this first issue deserves consideration.

Second, we suggest that the principle of a 3-time-point method, previously described for quantitative ^{64}Cu-immuno-PET, might be adapted to ^{89}Zr-immuno-PET (*4*). Rather than the 3 late time points suggested by van Dongen et al., 3 time points are needed at early (after reaching equilibrium), mid, and late imaging, for assessing K_i, V_t, and a release-rate constant (k_R). Indeed, we believe the Patlak assumption of irreversible uptake cannot be justified in an arbitrary tissue, including tumors, as evidenced by ^{64}Cu-NOTA-RamAb in VEGFR-2–positive HCC4006 tumors: $K_i = 0.0314$ $mL \cdot g^{-1} \cdot h^{-1}$, $k_R = 0.0387$ h^{-1}, and $V_t = 0.2075$ $mL \cdot cm^{-3}$ (without a RamAb blocking dose) (*4*). Noteworthy, this method cannot differentiate between specific and nonspecific uptake, and the actual meaning of the 3 kinetic parameters should be specified under each situation. However, it should be emphasized that a kinetic modeling analysis able to differentiate between specific and nonspecific uptake may probably increase the number of parameters involved in fitting 3-time-point PET data, which is contrary to the Akaike criteria (*5*).