Optimizing Strategies for Immune Checkpoint Imaging with Immuno-PET in Preclinical Study

TO THE EDITOR: Recently, we have read with interest the paper by Mayer et al. published in *The Journal of Nuclear Medicine* (*1*). The authors assessed the effects of 6 immuno-PET radiotracers on human programmed cell death ligand 1 (PD-L1) immune checkpoint imaging and discussed important design considerations that may affect biodistribution of radiotracers. Those radiotracers were specifically against human PD-L1 but did not cross-react with murine PD-L1. As we inferred, clinical immuno-PET tracers can bind not only to PD-L1 expressed by tumors, but also to PD-L1 expressed by normal cells. It is known that PD-L1 is expressed wildly on T cells, B cells, monocytes, and endothelial cells in both humans and mice (*2*). Therefore, radiotracer can be taken up by PD-L1–positive cells in organs, including lymphoid organs, lung, and liver, resulting in unexpected background signal and confounding determination of PD-L1 level in tumors. To optimize the immuno-PET imaging effect, especially in terms of background signal, we suggest using antimurine radiotracers and murine tumor cell lines for syngeneic tumor engraftments, because these will better fit the putative clinical status, rather than performing in vivo study in human tumor xenografts.

We are also concerned about the inherent characteristic of PD-L1 after immuno-PET imaging. It is known that radiotracers can induce cell internalization; thus, the targeted receptor could be involved and relocated from membrane to cytoplasm (*3,4*). During immuno-PET imaging, PD-L1 is internalized but the metabolic mechanism is unclear, partially including degradation and repopulation back to the tumor cell surface. Moreover, whether the affinity between PD-L1 and tracer would change after being detected by immuno-PET for the first evaluation and monitoring assessment during treatment remains unknown. To identify the potential affinity change, we suggest conducting another immuno-PET scan or surface plasmon resonance after the radiotracer is entirely eliminated.

Additionally, it is possible that the expression level of PD-L1 may not be a favorable biomarker for predicting anti–PD-L1 response. By analyzing the outcome of patients with different PD-L1 level, Robert et al. reported no difference in overall survival between the high-expression PD-L1 group and low or negative group after immunotherapy with anti–PD-L1 antibody (*5*). Therefore, high uptake of radiotracer at a tumor site may not predict a good response whereas low uptake may not indicate a poor response. To better predict anti–PD-L1 response, a combination of PD-L1 status and other cancer genetic biomarkers should be further considered (*6*).

Generally, immuno-PET imaging represents a novel imaging procedure and is helpful for selecting optimal patients and monitoring the expression status of specific molecules during anti–PD-L1 treatment. It could become the go-to complement to immunotherapy in the near future.

REFERENCES

1. Mayer AT, Natarajan A, Gordon SR, et al. Practical immuno-PET radiotracer design considerations for human immune checkpoint imaging. *J Nucl Med.* 2017;58:538–546.
2. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol.* 2007;8:239–245.
3. Fani M, Mueller A, Tamma ML, et al. Radiolabeled bicyclic somatostatin-based analogs: a novel class of potential radiotracers for SPECT/PET of neuroendocrine tumors. *J Nucl Med.* 2010;51:1771–1779.
4. Varasteh Z, Velikyan I, Lindeberg G, et al. Synthesis and characterization of a high-affinity NOTA-conjugated bombesin antagonist for GRPR-targeted tumor imaging. *Bioconjug Chem.* 2013;24:1144–1153.
5. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372:320–330.
6. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 2016;387:1909–1920.

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REPLY: In response to the comments made by Chen et al. regarding our paper "Practical Immuno-PET Radiotracer Design Considerations for Human Immune Checkpoint Imaging" published recently in *The Journal of Nuclear Medicine* (*1*), we have taken the opportunity to discuss several important points.

Chen et al. begin by suggesting the development of murine versus human radiotracers for testing in syngeneic models. In fact, this is a valuable suggestion, and our laboratory often develops and validates complementary murine and human radiotracers in parallel. An active area of investigation is the development of cross-reactive binders (with affinity for both human and murine targets), to help further streamline biologic characterization and clinical translation processes. That said, the greater debate here surrounds the question of model selection. Model selection is critical to the development of imaging agents, and the appropriate model should be chosen given the goals and hypotheses of the study at hand. Although the verdict is still out on the value of mouse models in drug development, we often use syngeneic models when our primary question pertains to the biology of the model system. Here, we used a human xenograft tumor model to assess and characterize the ability of our engineered tracer to bind specifically to human programmed cell death ligand 1 (PD-L1). This decision was made because our primary goal was toward clinical translation. Because of the rapid pace of immunotherapeutic drug development, we believe the imaging community must act quickly to