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

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Recently, we have read with interest the paper by Mayer et al published on The Journal of Nuclear Medicine(*1*). They assessed the effects of six 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 tumor-expressed PD-L1, but also to PD-L1 expressed by normal cells. It is known that PD-L1 expressed wildly on T cells, B cells, monocytes and endothelial cells in both human and mouse(*2*). Therefore, radiotracer could be uptaken by PD-L1 positive cells in organs, including lymphoid organs, lung and liver, result in unexpected background signal and confounding judgement of PD-L1 level of tumor. To optimize immuno-PET imaging effect, especially in terms of background signal, we suggest yield anti-murine radiotracers and use murine tumor cell lines for syngeneic tumor engraftments because it fits the putative clinical status, rather than performing in vivo study in human tumor xenografts.

We also concern about the inherent characteristic of PD-L1 after immuno-PET imaging. It is known that radiotracers could induce cell internalization, the targeted receptor could be involved and relocated from membrane to cytoplasm (*3,4*). During immuno-PET imaging, PD-L1

was internalized but the metabolic mechanism was unclear, partially including degradation and repopulation back to the tumor cells 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 conduct another immuno-PET or surface plasmon resonance after radiotracer was entirely eliminated.

Additionally, the expression level of PD-L1 could 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, had reported no difference in overall survival between high expression PD-L1 group and low or negative group after immunotherapy with anti-PD-L1 antibody(*5*). Therefore, high uptake of radiotracer in tumor site may not predict a good response while low uptake may not indicate a poor one. To better predict anti-PD-L1 response, 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, monitoring expression status of specific molecule during anti-PD-L1 treatment. It would be the “right-hand man” of immunotherapy in the near future.

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