

Molecular Imaging for Personalized Cancer Immunotherapy

By

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Abstract

The development of checkpoint immunotherapy treatments has greatly improved outcomes for many cancer patients relative to the previous standard-of-care. However, only a subpopulation of patients responds to these groundbreaking therapies, and the mechanisms of response are still largely unknown. Molecular imaging techniques, especially direct imaging of the checkpoint molecules themselves, hold potential for stratifying patients, predicting outcomes, and monitoring response. Therefore, positron emission tomography (PET) imaging of three major checkpoint molecules (PD-1, PD-L1, and CTLA-4) in murine models using clinically-available antibodies will be presented in this dissertation, representing many of the first studies in this area.

We developed radiolabeled tracers for the three aforementioned targets: ^{64}Cu -NOTA(DOTA)-ipilimumab and ^{64}Cu -NOTA-ipilimumab-F(ab')₂ targeting CTLA-4; ^{89}Zr -Df-pembrolizumab and ^{89}Zr -Df-nivolumab for imaging of PD-1; and ^{89}Zr -Df-atezolizumab and ^{64}Cu -NOTA- α PD-L1 Fab, binding to PD-L1.

The CTLA-4 tracers were first validated through imaging of CTLA-4+ tumor tissues, wherein significantly higher tracer accumulation was noted in positive tumor xenografts. The tracers were then applied in humanized mouse models (immunodeficient mice engrafted with human PBMCs) to track human T-cells, providing noninvasive insight into their accumulation sites following graft-versus-host disease onset. Similarly, PD-1 imaging was first conducted in naïve humanized mice in the graft-versus-host disease setting to prove the tracers' specificity.

Humanized mice bearing tumor xenografts were then imaged with the PD-1 tracer, in order to visualize tumor-infiltrating T-cells. Finally, the α PD-L1 Fab tracer was used to map the normal tissue biodistribution of PD-L1, and ^{89}Zr -Df-atezolizumab proved useful for imaging radiotherapy-induced changes in tumor PD-L1 expression.

Continued work in the immune-imaging space will inevitably lead to great strides in the understanding of these novel treatments, and may have immense impact on patient care in the future. Particularly for immunotherapy treatments, the dynamic information that can be obtained from molecular imaging of immune targets will be of utmost importance as we strive to better elucidate these revolutionary therapies.