Peptide-based PET to quantify the pharmacologic activity of *PD(L)-1 therapeutics* in the tumor bed

Sridhar Nimmagadda, Ph.D.

Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA-21287
snimmag1@jh.edu

Solid tumors present passive and active barriers to drug penetration that lead to drug resistance, and poor response rates and overall survival. In particular, little is known about pharmacokinetics (PK) and pharmacodynamics (PD) of monoclonal antibodies (mAbs) in the tumor bed, which have emerged as a highly successful class of anti-cancer therapeutics. Studying these parameters in situ and in real-time is essential for optimizing dosing, and designing and developing more effective mAb therapeutics (1). Unfortunately, tissue- and cell-based methods used for quantifying mAb concentrations do not accurately reflect tumor concentrations (2-4).

Positron Emission Tomography (PET) is a powerful noninvasive tool that can be used to quantify target levels anywhere in the body using molecularly targeted imaging agents administered at tracer doses (5). Although PET is routinely used to quantify PD effects of many therapeutics (6), its quantitative power has not been similarly applied to define the activity of mAb therapeutics. Recently, we developed the concept that accessible target levels in the tumors, measured using PET, could elucidate the pharmacologic activity of an mAb treatment, and can function as a common denominator to compare the activity of different mAbs. In developing this approach, we used custom designed peptide (or small- molecule or protein) -derived PET radiotracers, which bind a target of interest with a weaker affinity than the parent mAb, and designed to be rapidly eliminated from the body, to quantify the accessible target levels at the disease site. During this talk, I will discuss our experience in developing novel peptide-based imaging agents for immune checkpoint protein programmed death-ligand 1 (PD-L1) and their evaluation in vivo. I will also discuss how quantitative PD-L1 measures could be used as a common denominator for the evaluation of pharmacological activity of different mAbs targeting PD-L1 and its receptor PD-1. This approach provides a repetitive, non-invasive, real-time, personalized measure of mAb exposure and activity in situ and within a time frame that fits the standard clinical workflow. With a growing number of immuno-oncology clinical trials and a shrinking number of patients per clinical trial, such non-invasive PD measures could form a bridge between preclinical experiments and clinical studies, and assist in drug development, dose finding, and therapy optimization.

1. A. Ribas, J. D. Wolchok, Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350-1355 (2018).
2. M. A. Miller, R. Weissleder, Imaging of anticancer drug action in single cells. *Nat Rev Cancer* **17**, 399-414 (2017).
3. G. M. Simon, M. J. Niphakis, B. F. Cravatt, Determining target engagement in living systems. *Nat Chem Biol* **9**, 200-205 (2013).
4. D. Martinez Molina *et al.*, Monitoring drug target engagement in cells and tissues using the cellular thermal shift assay. *Science* **341**, 84-87 (2013).
5. R. Weissleder, M. C. Schwaiger, S. S. Gambhir, H. Hricak, Imaging approaches to optimize molecular therapies. *Sci Transl Med* **8**, 355ps316 (2016).
6. R. J. Hargreaves, E. A. Rabiner, Translational PET imaging research. *Neurobiol Dis* **61**, 32-38 (2014).