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Jenkins Laboratory

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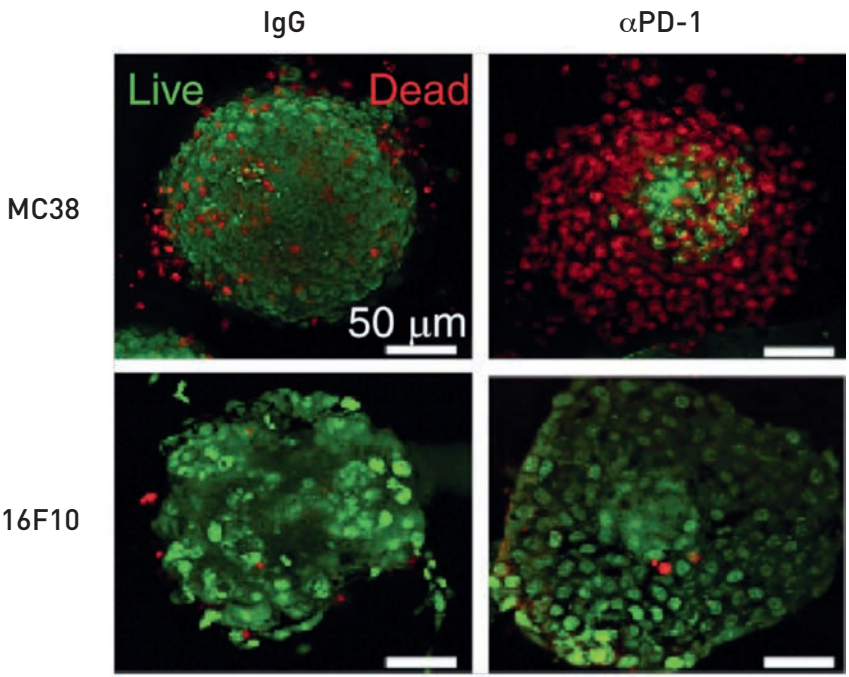
Immunotherapy has transformed the treatment of metastatic melanoma and other cancers, allowing a new avenue of therapeutic options and prolonging lives of many patients. Unfortunately, while immunotherapy is highly effective in some patients, it does not work for every patient and there are no available tests to determine whether or not a patient will respond to immunotherapy before treatment begins. To understand why immunotherapy works for some patients and not others, **the Jenkins laboratory** uses sophisticated tools and techniques to study and investigate the complex and dynamic interactions between cancer cells and the immune system. Our solution to this problem involves a specialized 3-dimensional culture of a patient's own tumor enabling researchers to examine interactions between tumor cells and immune cells. The integration of this novel approach with other emerging technologies is helping us navigate the complex landscape of the tumor immune microenvironment and learn which patients will respond to immunotherapy as well as how to effectively treat cancer patients that do not respond immunotherapy alone.

Precision cancer medicine currently focuses on knowledge of the cancer mutation repertoire and the tailored application of drugs that target altered genes or pathways in individual patients, such as use of BRAF inhibitors in patients with BRAF mutant melanoma. Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown dramatic and durable clinical responses in melanoma and others cancers, but robust predictive biomarkers are lacking and innate resistance is common. Thus, a critical need exists for more sophisticated ex vivo functional testing modalities that recapitulate human tumor biology to predict response to targeted and immune-based therapies and to develop personalized treatment plans in real-time.

Major focus areas of the Jenkins lab include (1) identifying and characterizing mechanisms of response and resistance to PD-1 blockade, (2) discovering novel therapeutic strategies to overcome

resistance to PD-1 blockade, and (3) using the MDOTS/PDOTS as a functional precision medicine platform for the development of novel combinations, and ultimately, personalized immunotherapy to tailor immunotherapy treatment to individual patients. Improved understanding of the response to immune checkpoint inhibitors within the tumor microenvironment will facilitate efforts to identify predictive biomarkers/models for immune checkpoint blockade in real-time, as well as future efforts to screen for therapeutic combinations that enhance the response to immune checkpoint blockade, and may ultimately provide a platform for the 'personalization' of immunotherapy.

Our novel approach for evaluating ex vivo response to PD-1 blockade utilizes murine- and patient-derived organotypic tumor spheroids (MDOTS/PDOTS) cultured in a 3-dimensional microfluidic system. Our study which was recently published



Live/Dead analysis (Acridine Orange – Green-Live; Propidium Iodide – Red-Dead) of murine-derived organotypic tumor spheroids (MDOTS) from PD-1 sensitive (MC38) and resistant (B16F10) syngeneic mouse models treated *ex vivo* with IgG or anti-PD-1 (10 μg/mL) for 6 days in 3D microfluidic culture [ref: Jenkins et al. *Cancer Discovery* 2018].

in *Cancer Discovery* [Jenkins et al., *Cancer Discovery* 2018; PMID: 29101162], has shown that organotypic tumor spheroids isolated from fresh mouse and human tumor samples retain autologous lymphoid and myeloid cell populations, including antigen-experienced tumor infiltrating CD4 and CD8 T lymphocytes, and respond to PD-1 blockade in short-term *ex vivo* culture. Furthermore, we have demonstrated that tumor killing was recapitulated *ex vivo* using MDOTS derived from the anti-PD-1 sensitive MC38 syngeneic mouse cancer model, whereas relative resistance to anti-PD-1 therapy was preserved in the CT26 and B16F10 syngeneic models. Our focused evaluation of rational therapeutic combinations to enhance response to PD-1 blockade using *ex vivo* profiling of MDOTS revealed TBK1 inhibition as a novel strategy to enhance sensitivity to PD-1 blockade, which effectively predicted tumor response *in vivo*. Our findings demonstrated the feasibility of

ex vivo profiling of PD-1 blockade and offer a novel functional approach for the selection of immunotherapeutic combinations. The ultimate goals of these efforts are to identify and characterize novel features of response/resistance to PD-1 blockade and to identify novel therapeutic strategies to overcome resistance to anti-PD-1 therapy, ultimately to bring forward into human clinical trials.

Selected Publications:

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Cañadas I, Thummalapalli R, Kim JW, Kitajima S, Jenkins RW, et al. Tumor innate immunity primed by specific interferon-stimulated endogenous retroviruses. *Nat Med*. 2018 Aug;24(8):1143-1150.

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Deng J, Wang ES, Jenkins RW, et al. CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-cell Activation. *Cancer Discov*. 2018;8(2):216-33.

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