Yale *Systems Biology Institute*

Research in Progress talk:

# "Discovery of Novel Cancer Immunotherapy Targets with Advanced CRISPR Screens"


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Abstract: Immunotherapy has led to remarkable clinical benefits in a variety of different cancers; however, a large fraction of patients encounter resistance. Identifying which genes are involved in mediating this resistance or allow the immune system to overcome this resistance is thus of great interest. We developed new tools for screening and discovering such genes using CRISPR gene editing technology. We performed a screen in in vivo glioblastoma (GBM) models with a CRISPR system integrating adeno-associated viruses for gene template delivery and Sleeping Beauty transposons for integration. We found that mutating Pdia3, Mgat5, Emp1 or Lag3 genes in CD8+ T cells and transferring them back into GBM-bearing mice enhances their survival. RNA-sequencing, cytokine assays, T cell signaling analyses, and chimeric antigen T cell co-culture experiments revealed that Pdia3 mutation enhances T cell killing capacity. In order to identify genetic interactions that mediate cancer cell resistance to T cell killing, we performed a screen in cancer cells mutating matched combinations between significantly mutated cancer genes and immune resistance genes. We identified genetic interactions including between Jak1-Trp53, Jak1-Kmt2d, and Ifngr1-Kmt2d, where joint loss-of-function renders altered cellular response to T cell cytotoxicity. In these studies, we demonstrate the development of novel CRISPR-based screening platforms for target discovery in the context of immune-oncology.


1:00 p.m.
Wednesday, October 13, 2021
Via Zoom Conference
*Please contact benita.palmer@yale.edu for the Zoom Link*