# Stony Brook University
# The Graduate School

Doctoral Defense Announcement

## Abstract

The impact of PPARδ on cancer-immune cell competition and immunotherapy efficacy

By

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Colorectal cancer (CRC) is the third most diagnosed cancer worldwide and remains a leading cause of cancer-related mortality. Although immunotherapies have transformed cancer treatment, most CRC cases are microsatellite stable (MSS) and exhibit limited responsiveness to current immunotherapeutic strategies. This is largely due to the immunosuppressive tumor microenvironment (TME). Understanding the mechanisms that regulate immune cell fitness within the TME is therefore essential for improving immunotherapy responses. Metabolic reprogramming is critical for effective T cell responses, yet how cellular metabolism and metabolic competition between cancer and immune cells shape anti-tumor immunity remains incompletely understood. The lipid-sensing transcription factor peroxisome proliferator-activated receptor delta (PPARδ) regulates fatty acid oxidation (FAO), but its role in cancer and immunity remains controversial. Here, we show that PPARδ activity is a critical determinant of cancer-immune cell competition and tumor immunogenicity. Activation of PPARδ in cancer cells promotes tumor growth, whereas immune-specific PPARδ activation suppresses tumor progression. Immune-intrinsic PPARδ activation promotes CD8 T cell infiltration and clonal expansion in immune-evasive MSS metastatic CRC. Mechanistically, PPARδ enhances mitochondrial fitness in CD8 T cells through Cpt1a-mediated FAO, although increased FAO alone is insufficient to enhance anti-tumor immunity. Importantly, activation of PPARδ selectively in CD8 T cells is sufficient to enhance anti-tumor immunity and increase cytotoxic T cells within the TME. PPARδ activated CD8 T cells also improve responses to immune checkpoint blockade in established MSS CRC and engineered human CAR-T cells with active PPARδ suppress tumor growth. Together, these findings identify PPARδ as a key regulator of immune cell fitness and cancer-immune cell competition in the TME and highlight immune-specific PPARδ activation as a promising strategy to improve immunotherapy responses in resistant solid tumors.

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**Program**: Genetics
**Dissertation Advisor**: Dr. Semir Beyaz

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