# Stony Brook University
# The Graduate School

Doctoral Defense Announcement

## Abstract

Unraveling Tumor-Immune Interactions in Endometrial and Colorectal Cancers:

Roles of Major Histocompatibility Complex in Immune Response

By

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High-grade endometrial cancers (HGECs), which disproportionately affect women of African ancestry, exhibit limited responses to immunotherapy. The mechanisms underlying this poor response remain incompletely understood, partly due to the lack of preclinical models that capture the complexity of the tumor immune microenvironment and ancestral diversity. To address these gaps, we established an autologous patient-derived organoid (PDO)–immune cell co-culture platform, incorporating cancer cells and immune components from the same patients across diverse ancestries. We characterized the immunological landscape of endometrial cancers and performed proof-of-principle assays to validate the critical roles of major histocompatibility complex (MHC) expression and mismatch repair (MMR) status in cancer–immune interactions. Furthermore, we assessed the safety and efficacy of immunotherapeutic modalities such as bispecific T-cell engagers and chimeric antigen receptor T cells within our system. This sustainable and scalable platform offers a personalized approach for developing novel immunologic treatments for endometrial cancers.

Cancer MHC-II plays dual roles in modulating anti-tumor immunity. We found that *Helicobacter* colonization inhibits tumor progression and metastasis, thereby extending survival in four CRC models across mouse strains in an MHC-II dependent manner. Microbiome-mediated cancer MHC-II augmentation resulted in enhanced immune cell functionalities. We demonstrated that cancer MHC-II is necessary and sufficient for meditating anti-tumor effects, and enhanced MHC-II expression improves the efficacy of immunotherapy. Notably, contrary to pro-tumor roles in literature, we found that c-AMP Response Element-Binding protein (CREB) is required for cancer MHC-II expression and the microbial anti-tumor effects. Furthermore, elevating MHC-II expression on human CRC PDOs resulted in more effective cancer clearance in autologous PDO-immune cell co-cultures, indicating anti-tumor roles of MHC-II in human context. These findings suggest that modulation of cancer MHC-II expression, such as via microbes, can boost anti-tumor immunity and potentially improve the efficacy of immunotherapies.

**Date**: April 23, 2025 **Program**: Genetics
**Time**: 1:00 PM **Dissertation Advisor**: Semir Beyaz
**Place**: Samet Conference Room, Koch Building, Cold Spring Harbor Laboratory
*To attend virtually, contact the Program Director* at martha.furie@stonybrook.edu.