# Stony Brook University
# The Graduate School

Doctoral Defense Announcement

## Abstract

CXCR4 Crosslinking and T Cell Adhesion as a Mechanism of Immune Evasion in Pancreatic Ductal Adenocarcinoma

By

**Jordan Pearson**

Pancreatic ductal adenocarcinoma (PDA) is an aggressive cancer known for evading immune surveillance, primarily by preventing T cell infiltration. While immune exclusion in PDA has been linked to factors like the tumor's stromal environment and immune checkpoint evasion, the molecular mechanisms preventing T cell entry remain unclear. In this thesis, I identify a novel mechanism where CXCL12 signaling induces T cell adhesion to fibronectin, impeding T cell migration. I demonstrate that polymeric CXCL12 triggers PTK2B phosphorylation in T cells, which arrests their movement by enhancing adhesion to fibronectin. This phosphorylation occurs through CXCR4 receptor crosslinking independently of G protein signaling, while monomeric CXCL12, acting through G proteins, does not induce PTK2B phosphorylation. I also investigate the TNFα-TNFR2 signaling axis, which promotes T cell adhesion via integrin activation, contributing to immune exclusion in PDA. Furthermore, I examine the clinical failure of BMS-936564 (BMS), an anti-CXCR4 monoclonal antibody initially developed for cancer immunotherapy. Despite promising preclinical results, BMS failed in clinical trials due to its unexpected agonistic effects on CXCR4, which inhibited T cell motility. To address this, we explored alternative antibodies that avoid these agonistic effects. These findings provide new insights into the molecular mechanisms of immune exclusion in PDA and suggest that targeting the CXCL12-CXCR4-PTK2B pathway, along with TNFα-TNFR2 signaling, could offer novel therapeutic strategies to improve T cell infiltration and immune responses in PDA.

**Date**: May 9, 2025 **Program**: Genetics
**Time**: 1:00 PM **Dissertation Advisor**: Douglas Fearon
**Place**: Hawkins Auditorium, Wendt Building, Cold Spring Harbor Laboratory

*To attend virtually, contact the Program Director at* martha.furie@stonybrook.edu.