Dissertation Defense - Leanna Sealey, PhD Biosciences

December 5th, 2022 10:00 AM - 12:00 PM

All are invited to attend the defense. For more information please contact Graduate Coordinator at

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Candidate: Leanna Sealey

Program: PhD, Biosciences

Date: Monday December 5th 2022

Time: 10:00 AM

Meeting Location: https://gmu.zoom.us/j/99614423196?pwd=dWxVK0p6dlZlbUNYN1FFcG14RG9iUT09

Title: Molecular Characterization of PSGL-1 Decameric Repeats For Inactivating HIV-1 Infectivity

Committee Chair: Dr. Yuntao Wu

Committee Members: Dr. Lance Liotta, Dr. Ramin M Hakami, Dr. Tshaka Cunningham

ABSTRACT:

P-selectin glycoprotein ligand-1 (PSGL-1/CD162) is a dimeric glycoprotein that has been identified as a restriction enzyme factor of HIV-1. PSGL-1 is expressed on the surface of CD4+ T cells, primarily on lymphoid and myeloid cells. This mucin-like surface protein binds to P, E, and L selectin, is upregulated during inflammation, and mediates leukocyte tethering and rolling. Previous studies showed PSGL-1 blocks the infectivity of virions released through steric hindrance, preventing particles from attaching to target cells. Mapping studies showed PSGL-1's extracellular N-terminus is needed for the antiviral activity. Polymorphisms of PSGL-1 contain an extracellular domain containing 14-16 tandem repeats of 10 amino acids, with the consensus sequence, (-A-T/M-E-A-Q-T-T-X-P/L-A/T-). The extracellular region contains highly O-glycosylated Threonines (30%) and Prolines (10%), which in addition to the tandem repeats form a sturdy elongated backbone for the protein. To determine if the presence of the decameric repeats (DRs) in PSGL-1 is required for its anti-HIV activity, we performed DR deletion mutagenesis studies of PSGL-1, deleting single DR to all DRs. We found that deleting all DRs eliminated PSGL-1's antiviral activity, but the presence of a single DR, dependent on location, was sufficient to maintain its antiviral activity. The PSGL-1 mutant containing 1 DR has lower antiviral activity than full-length PSGL-1. Mutagenesis of N-linked and O-linked glycosylation sites inside and outside the DRs demonstrated that these sites contribute to PSGL-1's restriction of HIV-1 activity. However, residues involved in selectin-binding did not appear to be critical for PSGL-1's antiviral activity. Furthermore, we show that the availability of glucose also affected the antiviral activity of PSGL-1. The results demonstrate that PSGL-1 maintains significant antiviral activity in the absence of certain decameric repeats and the presence of glycosylation sites also influences its anti-HIV activity.