November 17, 2021 1:00 - 3:00 PM

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

**Candidate:** Sarah Saad AlSharif  
**Program:** PhD, Biosciences  
**Date:** Wednesday, November 17, 2021  
**Time:** 1:00 PM  
**Zoom Link:** https://gmu.zoom.us/j/94415563959?pwd=cEZIeTdyTWRSMcRcUhUbTVVOGsvdz09

**Title:** Effect of Extracellular Vesicles (EVs) from HTLV-1 on Cell Proliferation via Autocrine Feedback Loop  
**Committee Chair:** Dr. Fatah Kashanchi  
**Committee Members:** r. Lance Liotta, Dr. Alessandra Luchini, Dr. Mikell Paige

**ABSTRACT:** The Human T-cell Lymphotropic Virus Type-1 (HTLV-1) is a retroviral infection that affects the T cells (1). HTLV-1 infects up to 10 million individuals globally especially in Japan, Africa, the Caribbean, and South America (1-2). HTLV-1 infection transmits via mother-to-child via breastfeeding, sexual intercourse, and blood transfusion. Most of the HTLV-1 infected individuals remain asymptomatic carriers throughout their lives, while almost 5% of affected patients develop associated diseases including Adult T-cell leukemia/lymphoma (ATLL) or HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) (1). There are no vaccines against HTLV neither effective antiviral drugs to eliminate HTLV-1 infection and treat HTLV-1 associated diseases. The two viral regulatory proteins, Tax and HTLV-1 basic zipper protein (HBZ) are responsible for the leukemogenesis of ATLL (3). The oncoprotein Tax is the main source of the abnormal proliferation of HTLV-1 infected cells as cells become IL-2 independent over time (3). Tax targets pathways involved in transcriptional regulation cell cycle control, apoptosis, DNA repair, and transformation. Moreover, HBZ stimulates cell survival and proliferation of ATL cells (3). There is a gap of knowledge for the mechanisms of HTLV-1 spread into uninfected cells and disease progression such as ATLL. Our recent work has shown that HTLV-1 cells release Extracellular Vesicles (EVs) containing viral RNA and proteins (gp61/Tax/HBZ) and promote cell-cell contact (4). Here, we showed that different EV subpopulations (2K, 10K, and 100K EVs) could mediate cell-cell contact between donor-infected cells and recipient-uninfected cells causing an increase in HTLV-1 transmission (5). Moreover, distinct EV subpopulations are responsible for cytokine release and tissue damage. EV profiles of several HTLV-1 EV subpopulations have shown different levels of viral/host proteins (5). The role of EVs in HTLV-1 infection and proliferation that may lead to transformation is still unclear. EV uptake by the same cells has been shown in the process of cell proliferation for many tumors, including chronic myeloid leukemia, colon, and gastric cancer (6-8). In this study, we show the separation of EVs into subpopulations using differential ultracentrifugation (DUC) speeds to obtain 2K, 10K, 100K, 167K (4 hrs), and 167K (16 hrs) from infected cell supernatants. We examined EV uptake by the same cells (Autocrine) and promotion of the host cell growth using either receptor- or non-receptor-mediated uptake. EVs including 2K and 167K (16 hrs) were taken up by the parental HTLV-1 infected cells within one hour. All EV types were taken up by HTLV-1 cells by 24 hrs. Mode of entry for 2K, 10K, and 100K HTLV-1 EVs is mostly dependent on the use of ICAM-1 into the cells, however, 2k uptake may also be dependent on other modes of entry not including macropinocytosis and phagocytosis. For future study, the EV subpopulations and their content that regulate proliferation and survival of the infected cells in drug-treated cells will be determined. Collectively, our data indicate that HTLV-1 infected cells are “addicted” to the EVs secreted by the same cells.