



Graduate School Event

Thesis Defense: Structurally dissecting the late-stage viral lifecycle of the Human T-Cell Leukemia Virus Type 1

Mathias Percipalle (Schur Group)

Schur Group

Host: Amelia Douglass

The Human T-Cell Leukemia virus type 1 (HTLV-1) is an oncogenic deltaretrovirus infecting at least 5-10 million people worldwide. It is the causative agent of HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), a spinal cord disease, and adult T-cell leukemia/lymphoma (ATLL), a severe T-cell malignancy. No therapies target HTLV-1 infection, and many steps of its late-stage viral life cycle remain poorly understood. This thesis structurally dissects two linked stages of this cycle: the divergent immature assembly of HTLV-1, and its ability to induce an extracellular-matrix like structure on infected cells, termed a viral biofilm. Retroviral capsid (CA) proteins display a conserved two-domain architecture consisting of independently folded N-terminal (CA-NTD) and a C-terminal (CA-CTD) subdomains. Yet, different retrovirus species employ remarkably variable geometrical solutions to stabilize the CA lattices forming the immature virus particle. HTLV-1 relies on the CA-NTD to stabilize its immature lattice, while the Human Immunodeficiency virus type 1 (HIV-1) relies on a contiguous structural unit formed by the CA-CTD and the spacer peptide 1 (SP1). This raises the question of whether immature assembly phenotypes are modular features encoded independently within individual CA subdomains, or emergent features requiring strict co-evolution of both subdomains. To test this, we designed chimeric proteins pairing the CA subdomains of HTLV-1 and HIV-1. Our results show that pairing assembly-driving subdomains from the two species still allows them to independently form their native immature contacts, while attempting to impose their preferred curvature on each other. Mutations of either chimeric subdomain do not disrupt assembly, but rather shift the phenotype balance while relieving curvature strains, demonstrating that immature assembly properties can be encoded into a single subdomain. The two-domain architecture of retroviral capsids thus reflects a division of labor built on structural modularity, where one subdomain is the key driver for assembly competence while the other could serve more regulatory functions. Once assembled and released, HTLV-1 particles accumulate at the cell surface within a viral biofilm, a structure unique among retroviruses that strongly enhances cell-to-cell transmission. However, the biofilm architecture and virion organization within it, and their influence on virus infectivity, have not been explored. Using cryo-electron microscopy methods on purified HTLV-1 biofilm, we revealed an extracellular environment enriched in virions, membranous vesicles and matrix

components. Biofilm-embedded virions display large heterogeneity in size and core morphology, including single and double cores and putative maturation intermediates. Strikingly, virions are frequently clustered and tethered to each other and to surrounding membranes by thin linear densities whose dimensions match the host restriction factor tetherin, suggesting that HTLV-1 may exploit a canonical restriction factor to retain virions within the biofilm. We also determined the mature HTLV-1 capsid lattice structure to 9.4 Å resolution from biofilm-embedded particles with canonical cores. The structure reveals that HTLV-1 still converges onto the mature fold conserved across retroviruses, despite having a divergent immature assembly mechanism, and seemingly undergoes a less dramatic maturation than other retroviruses. Together, these results expand the structural framework for how HTLV-1 assembles, matures and organizes itself at the infected cell surface.

Thursday, November 5, 2026 01:30pm - 02:30pm

Sunstone Bldg / Ground floor / Big Seminar Room B (I23.EG.102) and Zoom



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