



**SESSION IV**  
**INFECTION, TRAFFICKING & BUDDING**  
**Eric Freed & Carol Carter**

Jim Hurley  
Juan Bonifacino  
Hidde Ploegh  
Susan Baker  
Scott Emr  
Wes Sundquist

Roger Herr /Pradeep Uchil /Nadia Giannakopoulos

# SESSION IV: Trafficking & Budding

## HIGHLIGHTS

- HIV-1 Nef degrades CD4 by linking CD4 to AP-2 and inducing CD4 internalization into endosomes.
- Nef may link CD4 to MVB pathway via Alix.
- Herpesviruses encode tegument proteins with DUB activity.
- DUB enzymatic activity linked to viral pathogenesis (e.g., Marek disease virus)
- P1pro (SARS CoV) has DUB activity and is an IFN agonist; these functions are genetically separable.
- Ub can be attached to non-Lys residues.
- TRIMs play varied roles (+ and -) in regulating retroviral replication.
- Viruses encode ovarian tumor (OTU) domains that target Ub and ISG15 conjugates.

# SESSION IV: Trafficking & Budding

## HIGHLIGHTS

- The endosomal sorting machinery is organized into a series of multi-protein complexes (ESCRTs) that recruit cargo proteins into MVBs in a coordinated fashion.
- A vast amount of structural information is now available about the ESCRT complexes and associated machinery (e.g., Alix, Vps4, etc.).
- The ESCRT machinery is required for retrovirus release via interaction with “late” domains.
- For HIV-1, ESCRT-I (Tsg101) plays the major role (via binding to PTAP motif in Gag); Alix plays a secondary role.
- Ubiquitin modification often plays a central role in recruitment of cargo proteins by ESCRT machinery.
- Retroviral Gag proteins are ubiquitinated.
- Nedd4L also assists in HIV-1 budding via activation (ubiquitination) of Tsg101.

# SESSION IV: Trafficking & Budding

## Research Opportunities & New Directions

- Use of Ub-vinyl methyl esters as discovery tools for Ub-specific proteases
- Develop viral DUBs as antiviral targets.
- Define the role of DUB enzymes in viral replication; what are the target(s).
- Elucidate the mechanism by which protease activity of SARS-CoV PLpro is regulated during replication.
- Characterize how SARS-CoV escapes from DUB inhibitors.

# SESSION IV: Trafficking & Budding

## Discussion Topics

- What is the role of Mvb12 in ESCRT-I function?
- What is the role of ESCRT-II in cargo sorting and virus release?
- What role does Gag ubiquitination play in virus release?
- How is membrane fission during budding accomplished?
- What is the function of “secondary” late domains?
- How do Nedd4 Ub ligases recruit Gag into ESCRT pathway?
- What is the role of the numerous isoforms of ESCRT complexes in cargo sorting and virus budding?