

# High Resolution Particle Structure of Immature HIV-2

Nathaniel Talledge[1], Huixin Yang[1], Luiza Mendonça[1], Ke Shi[1], Hedeki Aihara[1], Wei Zhang[1], and Louis M. Mansky[1]

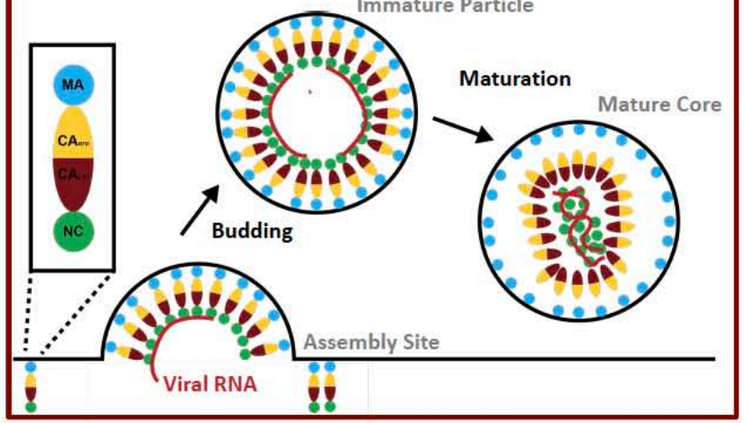
[1]Institute for Molecular Virology, University of Minnesota – Twin Cities, Minneapolis, MN 55455 USA

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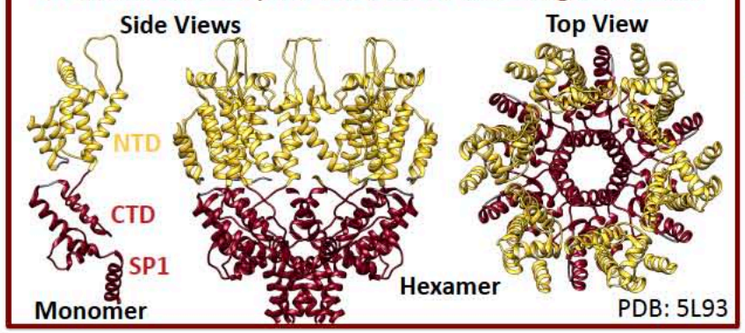
## 1. Overview

- Immature retrovirus particle morphologies are quite distinct among the genera of the *Retroviridae*.
- Here, we sought to investigate morphological differences among retroviruses in the same genera.
- Low resolution cryo-electron microscopy analysis of immature human immunodeficiency virus type 2 (HIV-2) particles has implicated several morphological features distinct from that of HIV-1 – *i.e.*, immature particles that possess a nearly complete immature Gag lattice, a larger average particle diameter, and a higher copy number of incorporated Gag.

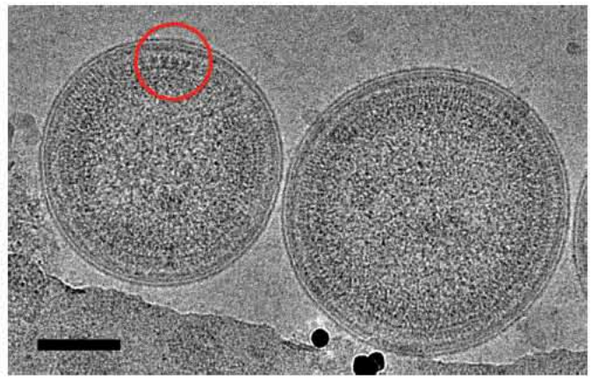
## 2. Retroviral Particle Assembly and Maturation




## 3. Immature Capsid Structure and Organization

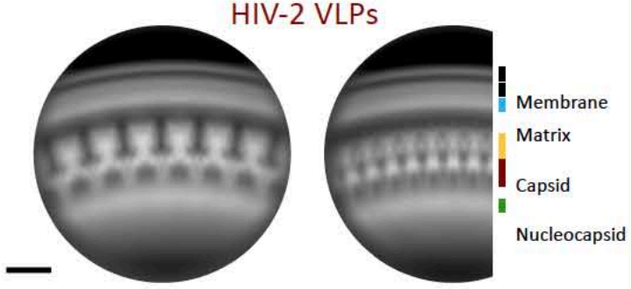



## 4. Single Particle Analysis of HIV-2



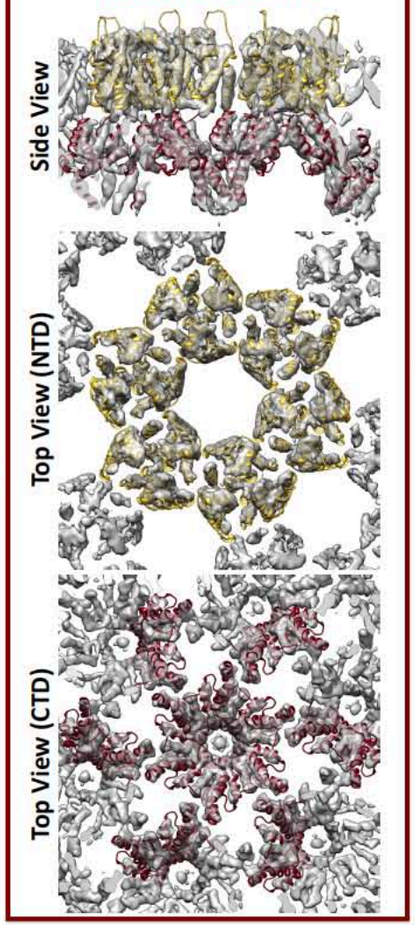
Cryo-TEM of HIV-2 virus like particles produced by transient expression of Gag in 293T cells. Overlapping particles were isolated at the membrane tangent, representative particle (Red circle). **Scale bar, 50 nm**

## 5. Membrane Tangent 2D Class Averages of HIV-2 VLPs

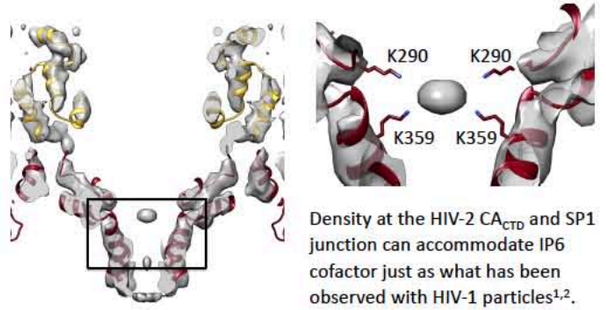



Two reference free 2D Class Averages of HIV-2 VLPs from particles isolated at the particle membrane tangent. **Scale bar, 10 nm**

## 6. HIV-2 Cryo-EM Reconstruction



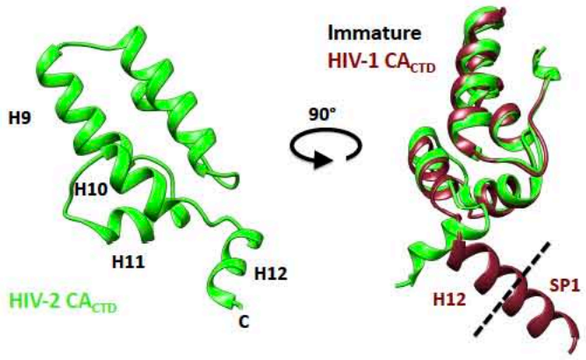

## 7. IP6 Binding Pocket Conserved in HIV-2 Immature Particles




Density at the HIV-2 $CA_{CTD}$ and SP1 junction can accommodate IP6 cofactor just as what has been observed with HIV-1 particles[1,2].

Dick et al. (2018) Nature. Mallery et al. (2018) Elife

## 8. HIV-2 $CA_{CTD}$ Crystal Structure




Crystal structure of the HIV-2 $CA_{CTD}$ from residues Thr282-Met365. Overlay of the immature HIV-1 $CA_{CTD}$ (PDB: 5L93) shows a high degree of similarity except for the angle of the C-terminal helices.

## Conclusions & Future Directions

- We used cryo-electron microscopy (cryo-EM) to obtain a 5.5 Å resolution structure of HIV-2 capsid (CA) domain.
- We solved a 1.98 Å crystal structure of the HIV-2 $CA_{CTD}$ and found a novel $3_{10}$ helix (H12) at the C-terminal region, which is not observed in the domain structures of other retroviral CA proteins.
- Fitting of the HIV-2 $CA_{CTD}$ into the reconstruction map confirmed critical contact interfaces, as well as the inositol hexakisphosphate (IP6) contacts at the six-fold symmetry interface.
- We propose that H12 in CA contributes to the stability of the hexametric interactions in the HIV-2 immature Gag lattice, helping to explain the morphological differences between HIV-2 and HIV-1.
- Taken together, our observations help to support a model in which key molecular interactions can dictate the nature of immature Gag particle morphologies, as well as particle diameter and Gag copy number. Such differences likely impact relative particle infectivity as well as replication fitness and dynamics.

Funding:

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