The background features a textured, light brown surface with a repeating pattern of small, stylized floral or geometric motifs. Overlaid on this is a large, semi-transparent version of the University of Delaware seal, which includes a central shield with a book and a quill, surrounded by a circular border with blue floral elements. To the right, there are vertical panels containing various symbols, including a hexagon, a square with a shield, and a circular emblem. At the bottom, there are stylized figures of people in traditional attire.

# Seven years of HIV research on Blue Waters

Juan R. Perilla

Department of Chemistry & Biochemistry

University of Delaware

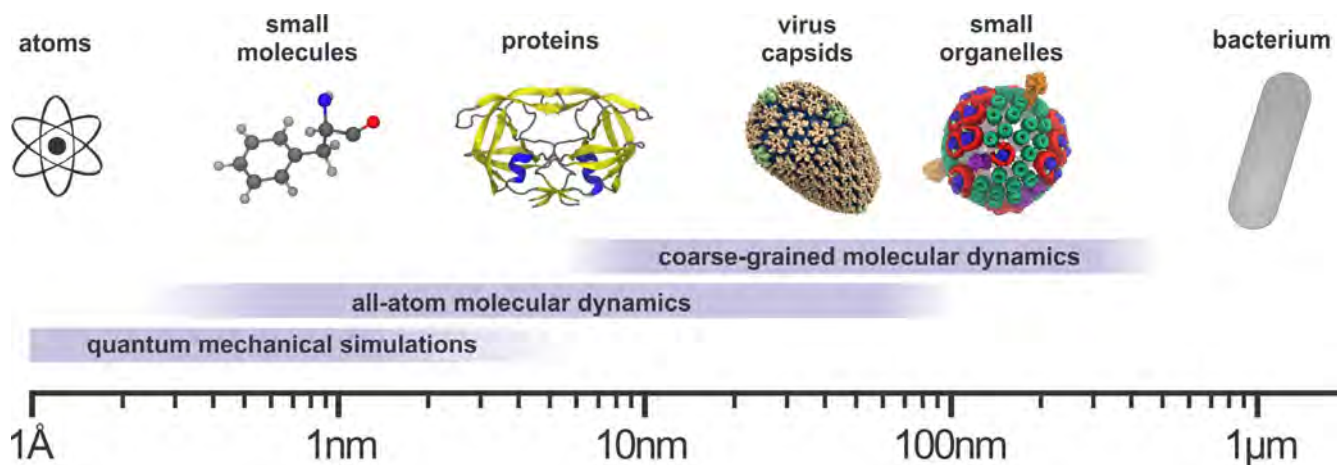


# The dawn of computational microscopy



Perilla et al. Current Opinion in Structural Biology (2015)

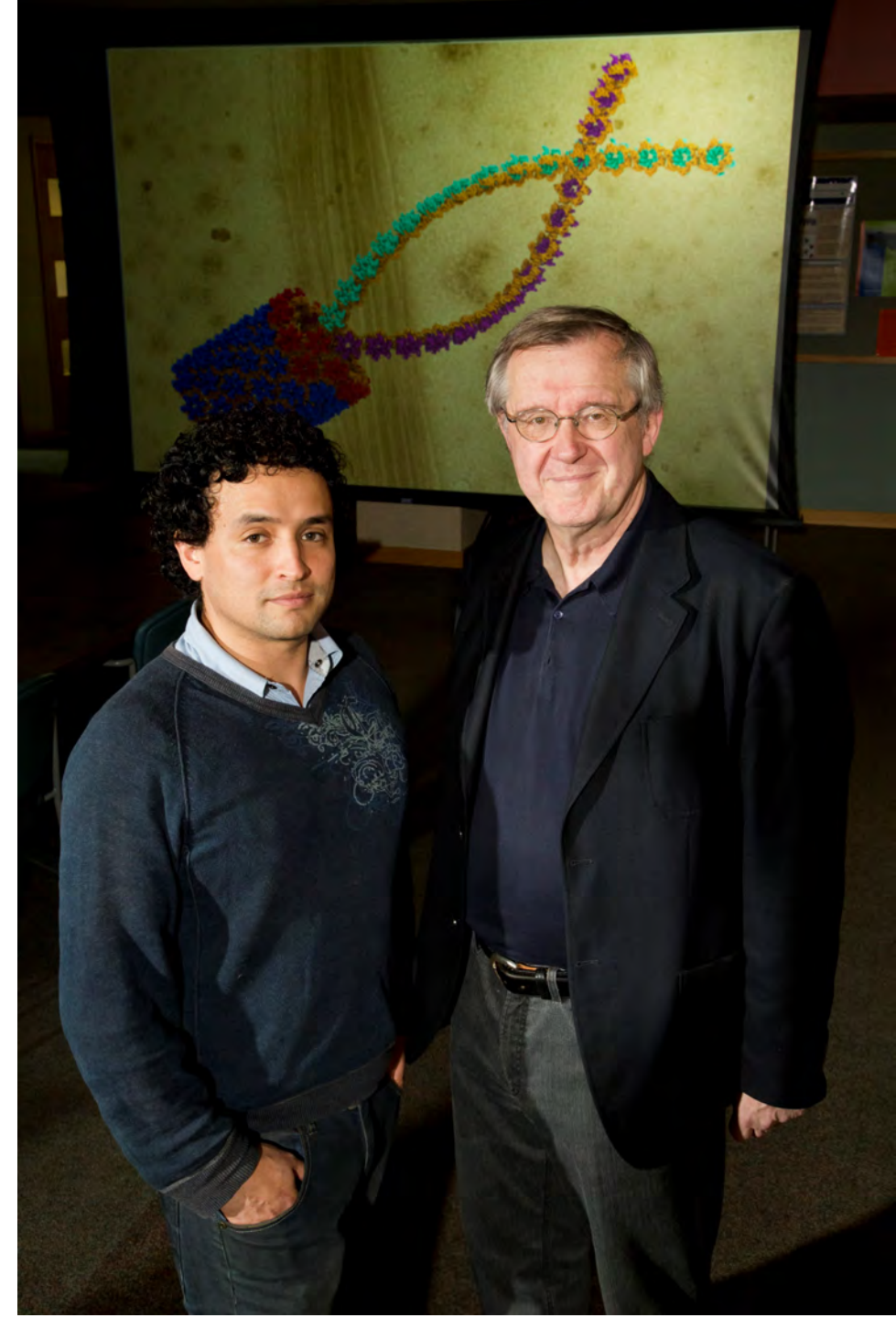
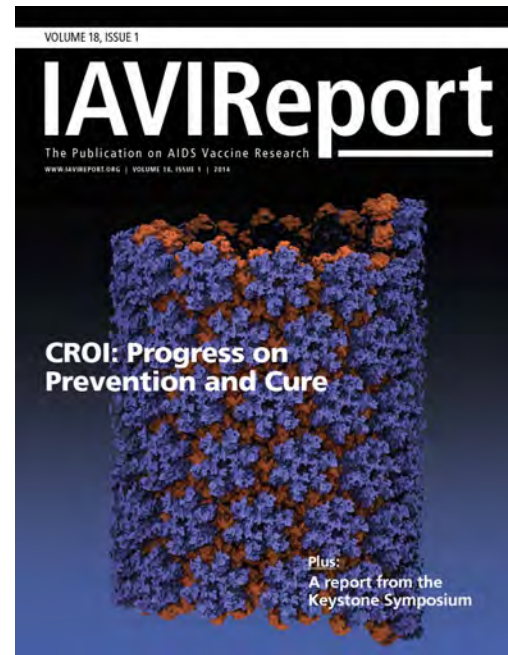
Anton Leeuwenhoek  
Observed microorganisms  
using simple microscopes.  
Discovered Bacteria and  
Sperm. Circa. 1677

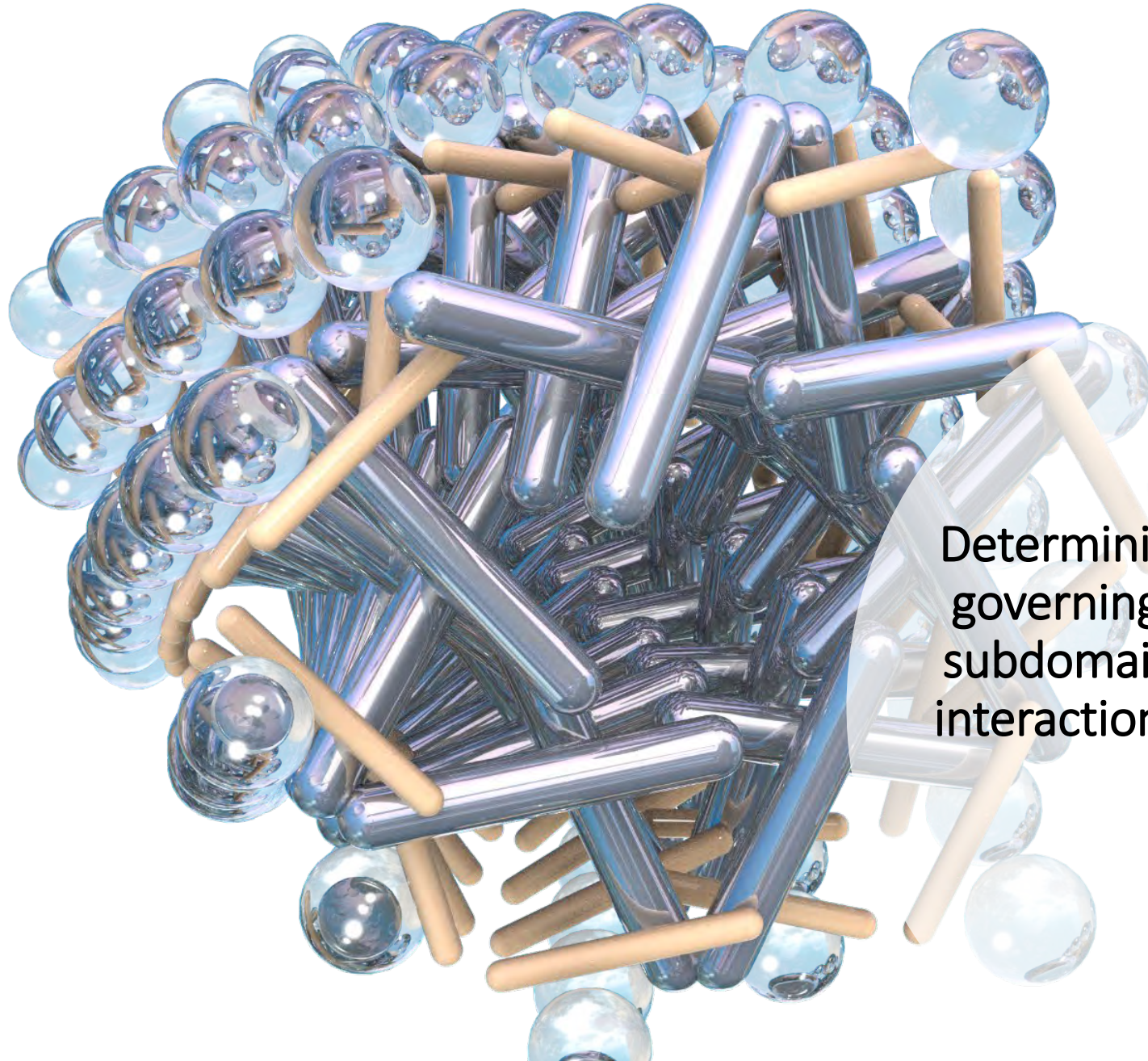


# Products 2012-2016

1. Physical properties of the HIV-1 capsid from all-atom molecular dynamics simulations **Nature Communications**, 2017, 8, Pages: 15959
2. All-Atom Molecular Dynamics of Virus Capsids as Drug Targets **Journal of Physical Chemistry Letters**, 2016
3. Contributions of charged residues in structurally dynamic capsid surface loops to Rous sarcoma virus assembly **Journal of Virology**, 2016
4. Molecular Architecture of the Retroviral Capsid. **Trends in Biochemical Sciences**, 2016
5. Cyclophilin A stabilizes the HIV-1 capsid through a novel non-canonical binding site. **Nature Communications**, 2016, 7:10714
6. CryoEM and computer simulations reveal a novel kinase conformational switch in bacterial chemotaxis signaling. **eLife**, 2015;10.7554/eLife.08419
7. Dynamic Allostery Governs Cyclophilin A – HIV Capsid interplay **Proceedings of the National Academy of Sciences USA**, 2015, 112, 14617-14622.
8. Chemical Visualization of Human Pathogens : Retroviral Capsids **Proceedings of the International Conference on High Performance Computing, Networking, Storage and Analysis**, SuperComputing'15. IEEE Press, 2015
9. Atomic modeling of an immature retroviral lattice using molecular dynamics and mutagenesis. **Structure**, 2015, 23,1-12
10. Molecular dynamics simulations of large macromolecular complexes. **Current Opinion in Structural Biology**, 2015, 31, 64-74
11. Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. **Nature**, 2013, 497, 643-646

PRAC2012

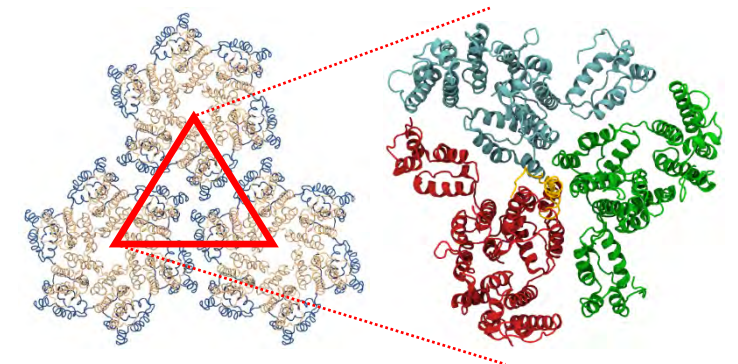
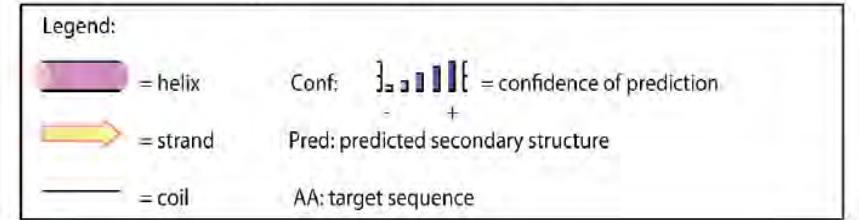
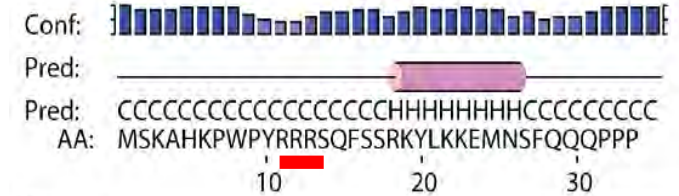
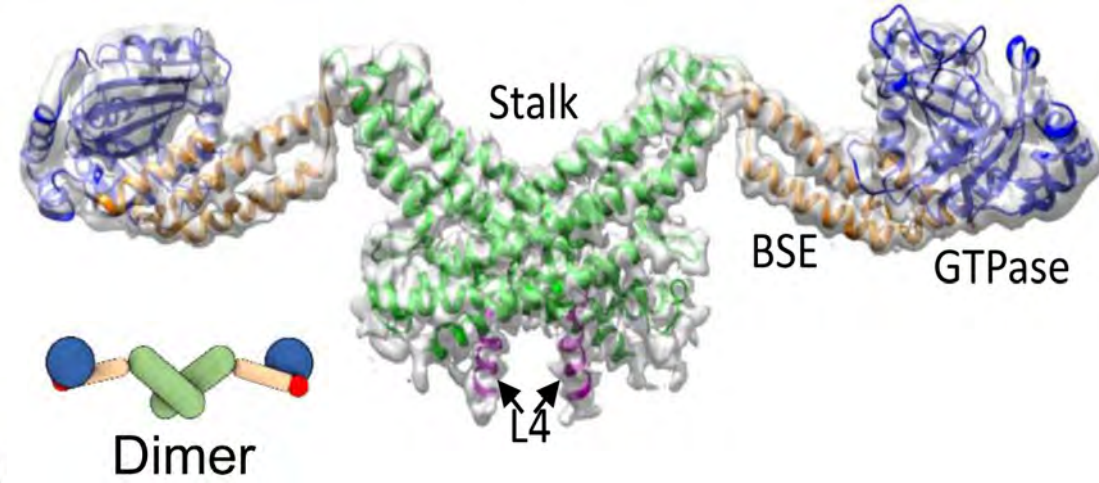
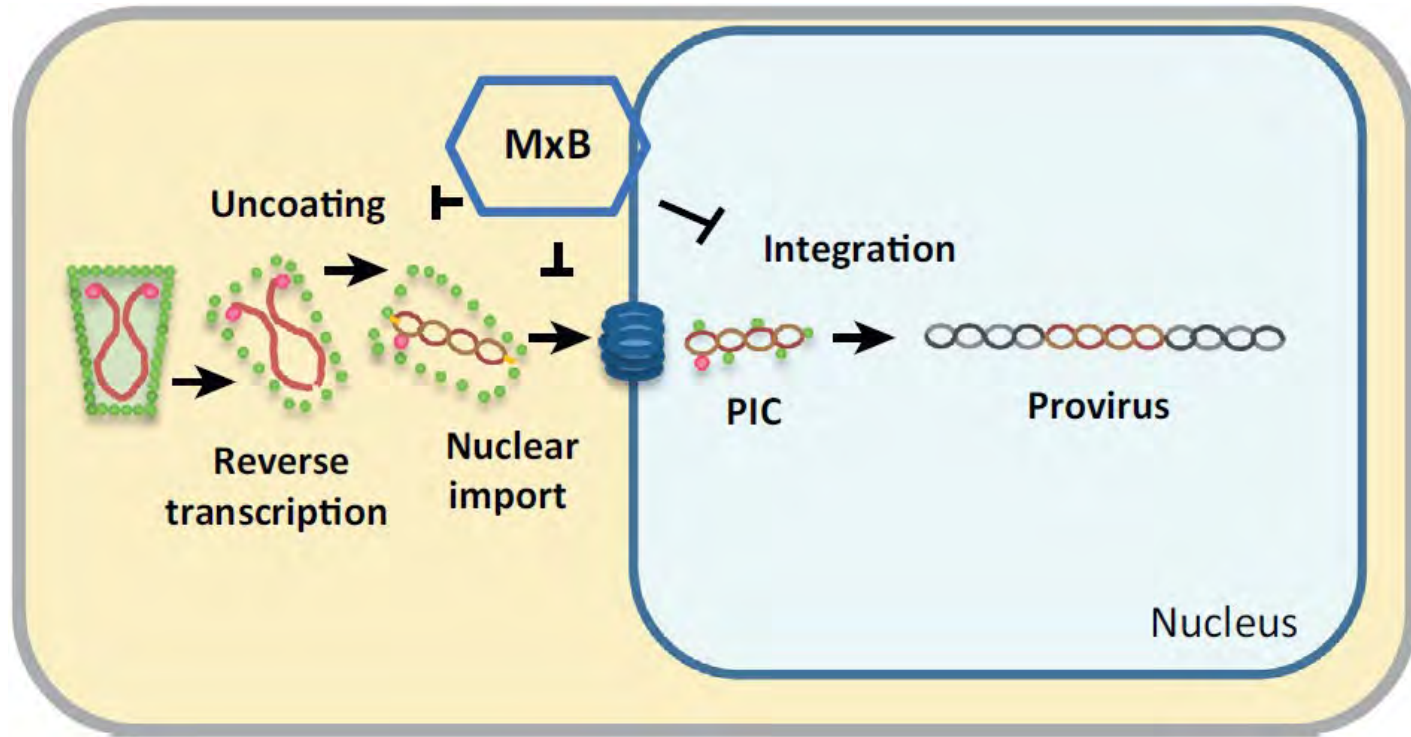




Determining the dynamics governing the N-terminal subdomain of MxB and its interactions with HIV-1 CA.

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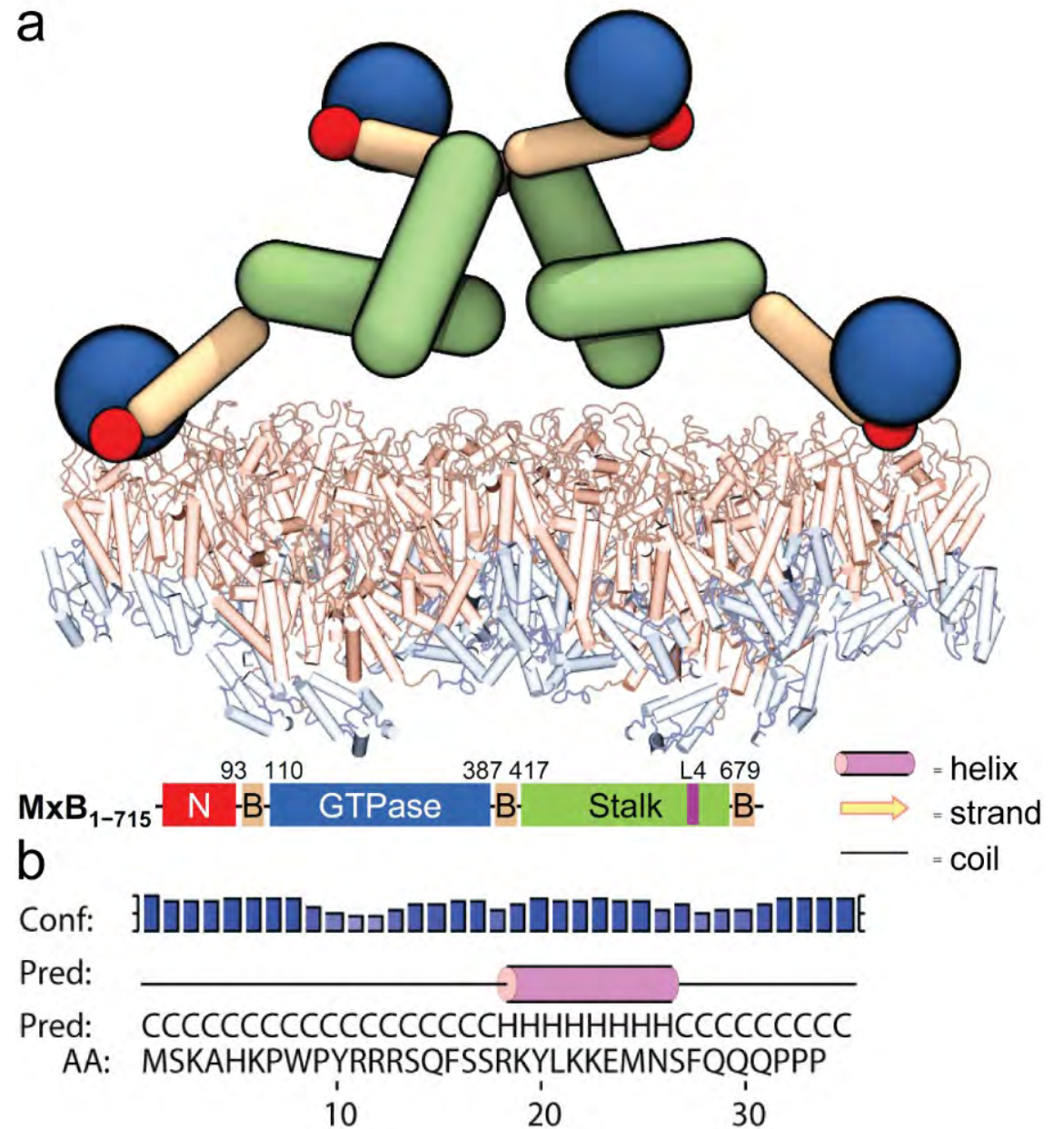
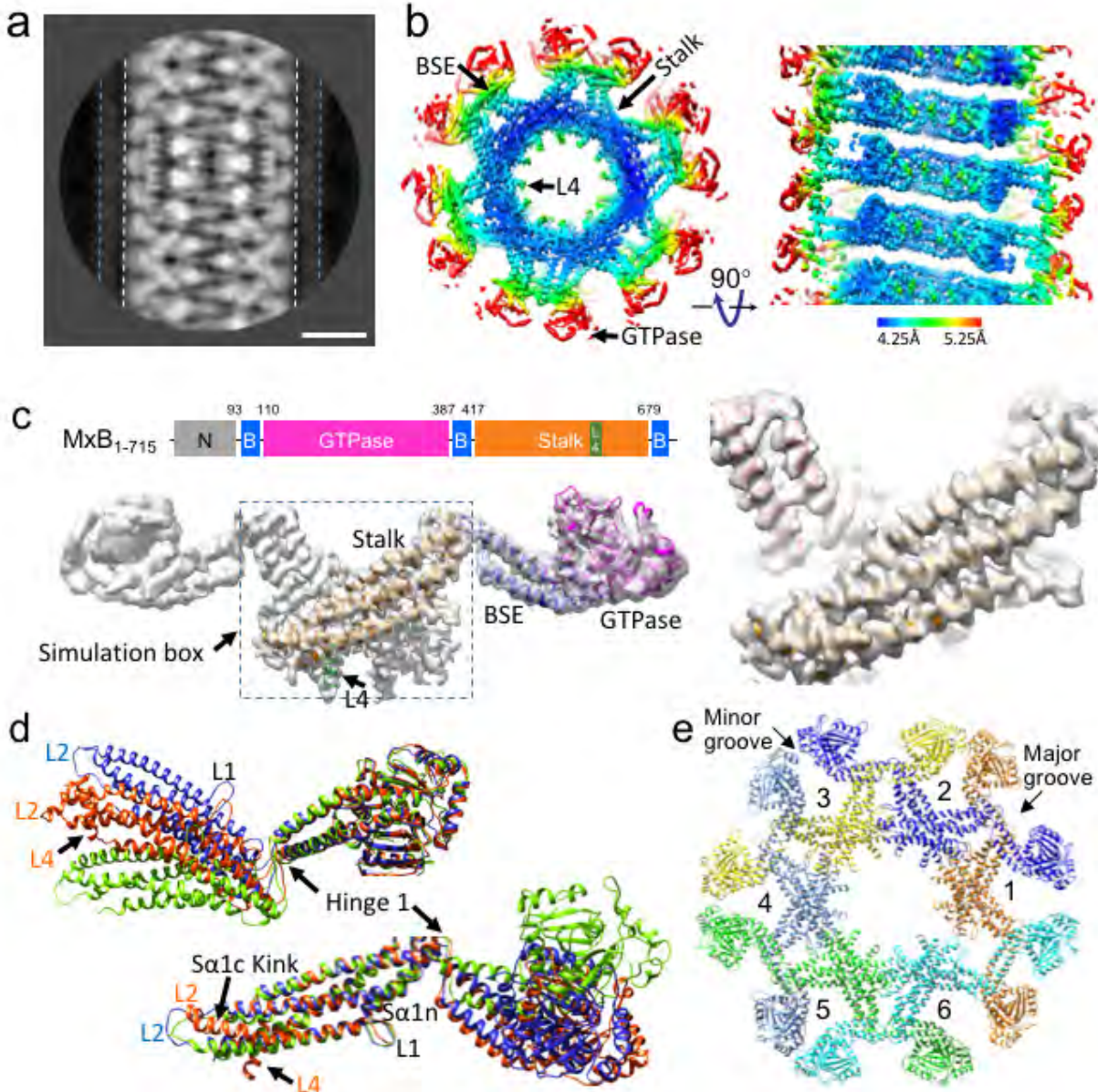
# MxB is a capsid restriction factor



Goujon, C., et al. (2013). Nature **502**(7472): 559-562.  
 Fricke, T., et al. (2014). Retrovirology **11**(1): 68.  
 Haller, O., et al. (2015). Trends in Microbiology **23**(3): 154-163.  
 Schulte, B., et al. (2015). Journal of Virology **89**(16): 8599-8610.  
 Alvarez, F. J. D., et al. (2017). Science Advances **3**(9).

<sup>11</sup>RRR<sup>13</sup> motif in MxB N-terminal domain (NTD) and tri-hexamer region in CA is important for the MxB-capsid binding.

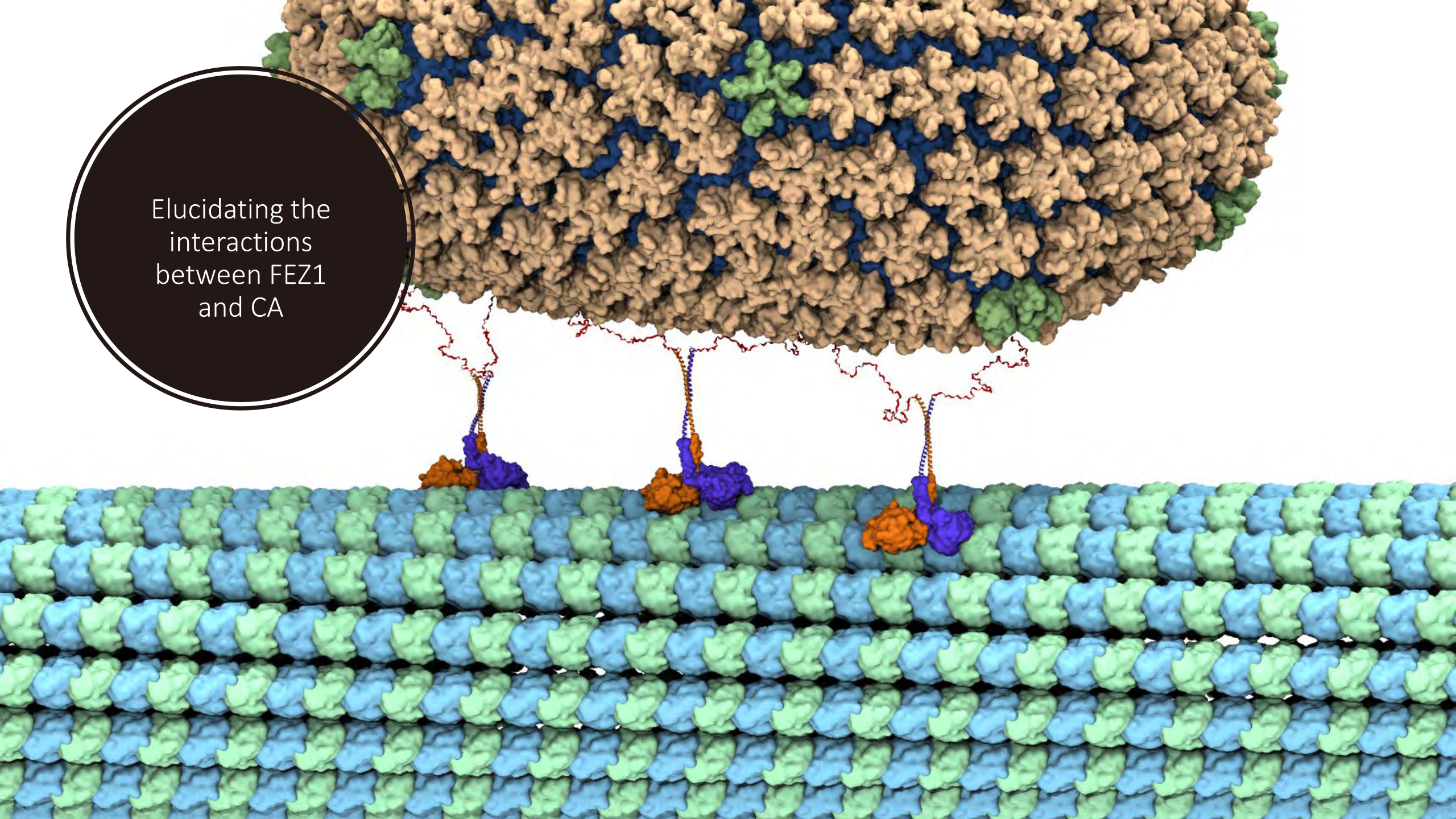
# MxB binds to CA via its N-terminus.



Alvarez et al. Science Advances (2017), Smaga et al. Structure (2019)

The N-terminus is intrinsically disordered.

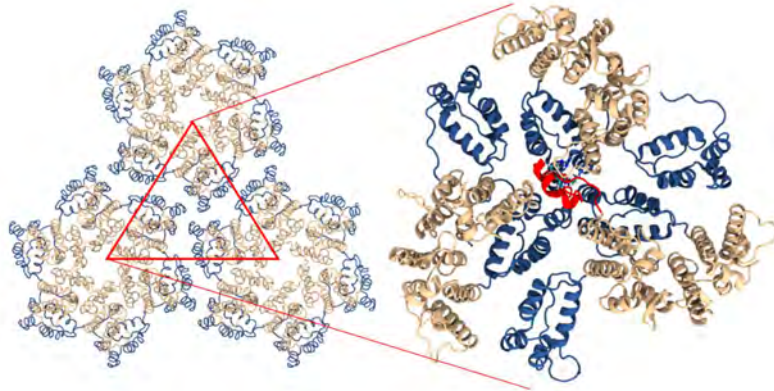
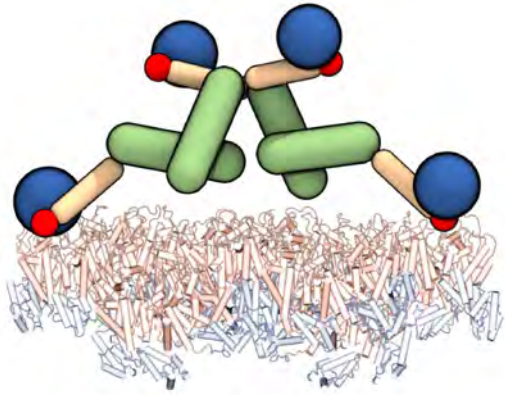
Elucidating the interactions between FEZ1 and CA





# Summary

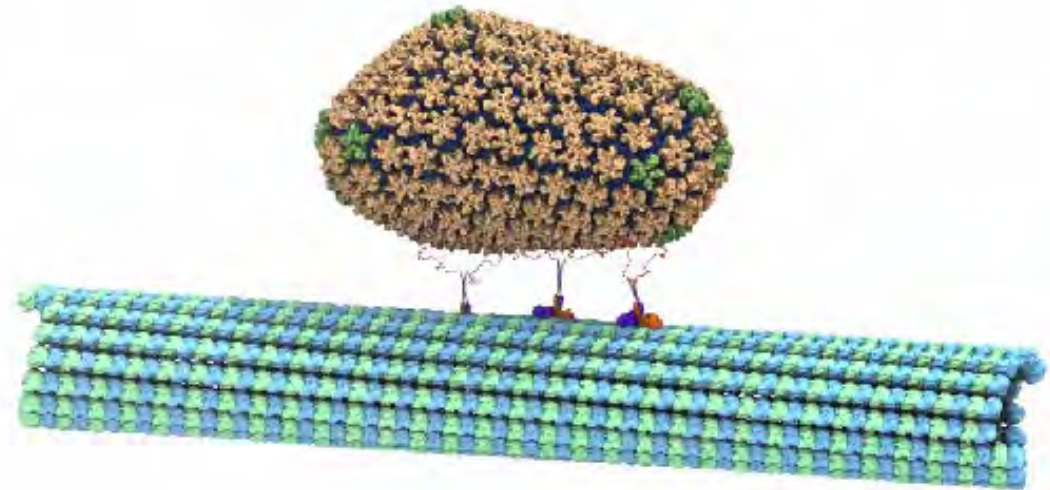
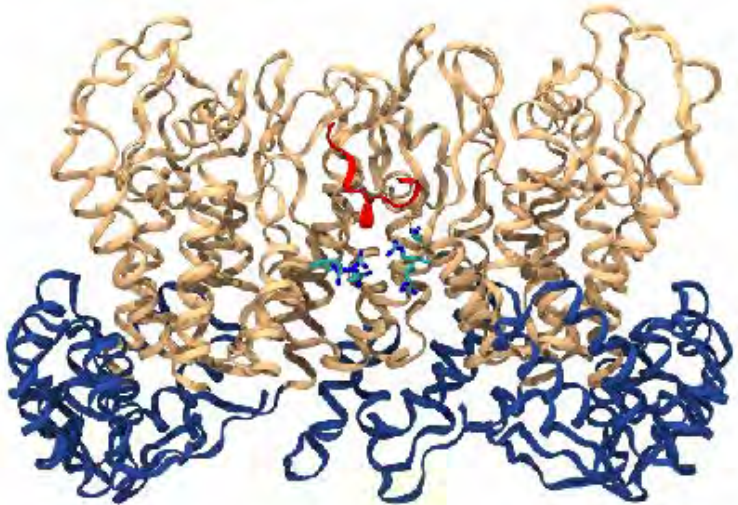
**Aim 1: Determine the dynamics governing the N-terminal subdomain of MxB and its interactions with HIV-1 CA.**



MxB<sub>1-715</sub> 55-102 307-417 679  
GTPase Stak B

Smaga et al. Structure (2019)  
Huang et al. Cell Reports (2019)

**Aim 2: Elucidate the interactions between FEZ1 and HIV-1 CA.**





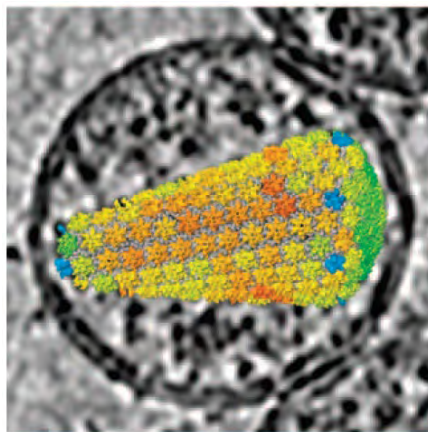
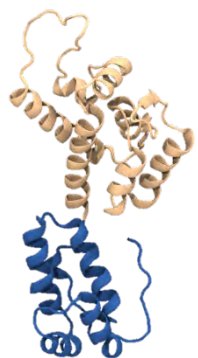
# dNTP import by HIV-1 CA hexamers

Capsid protein  
(the building block)

Capsid (CA) core in HIV-1 virus

NTD

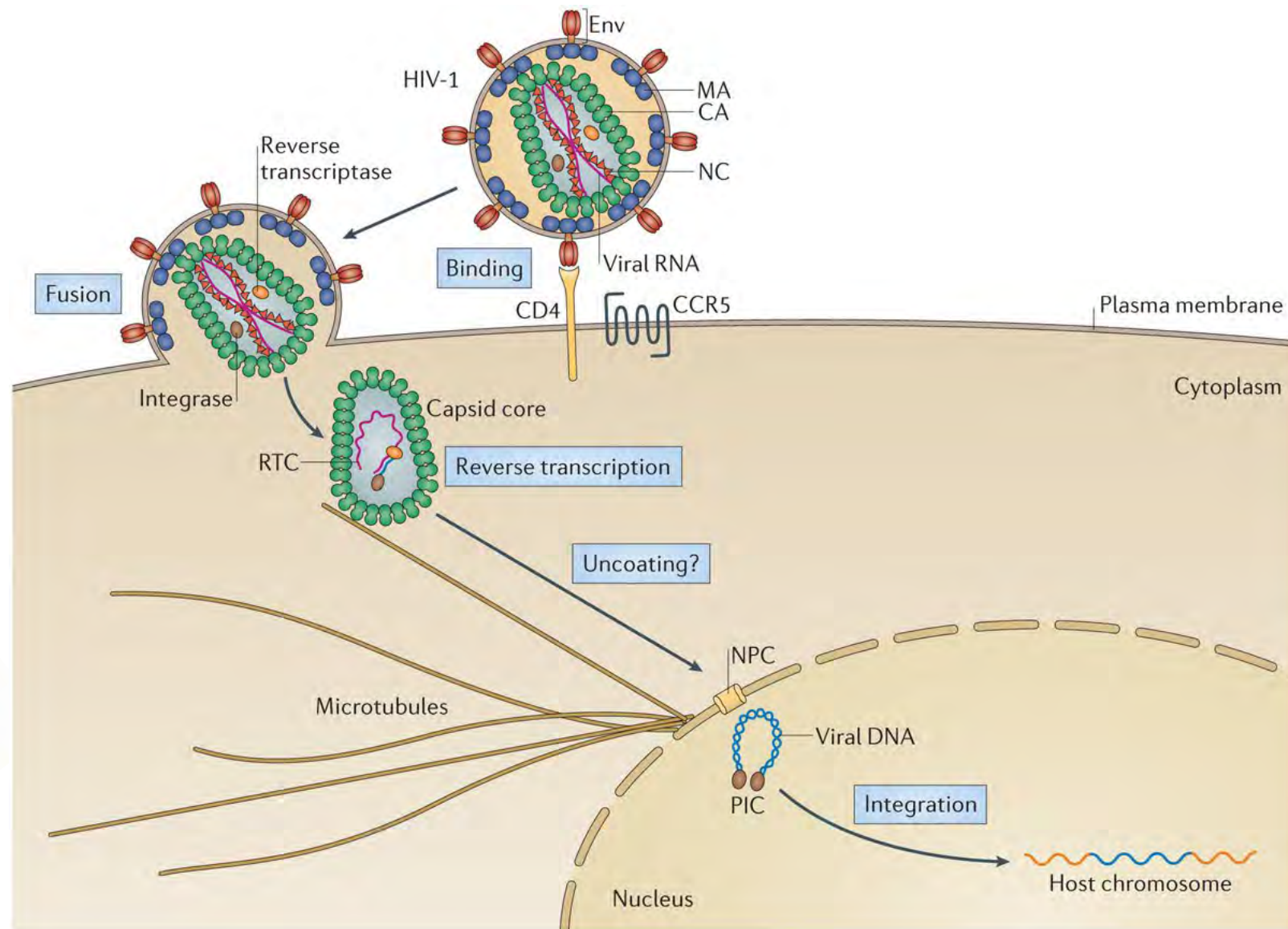
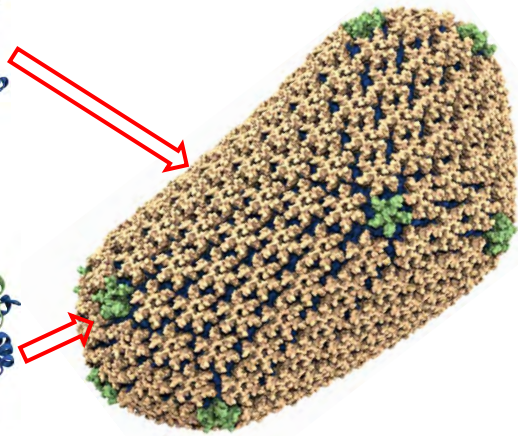
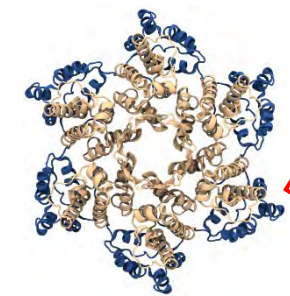
CTD



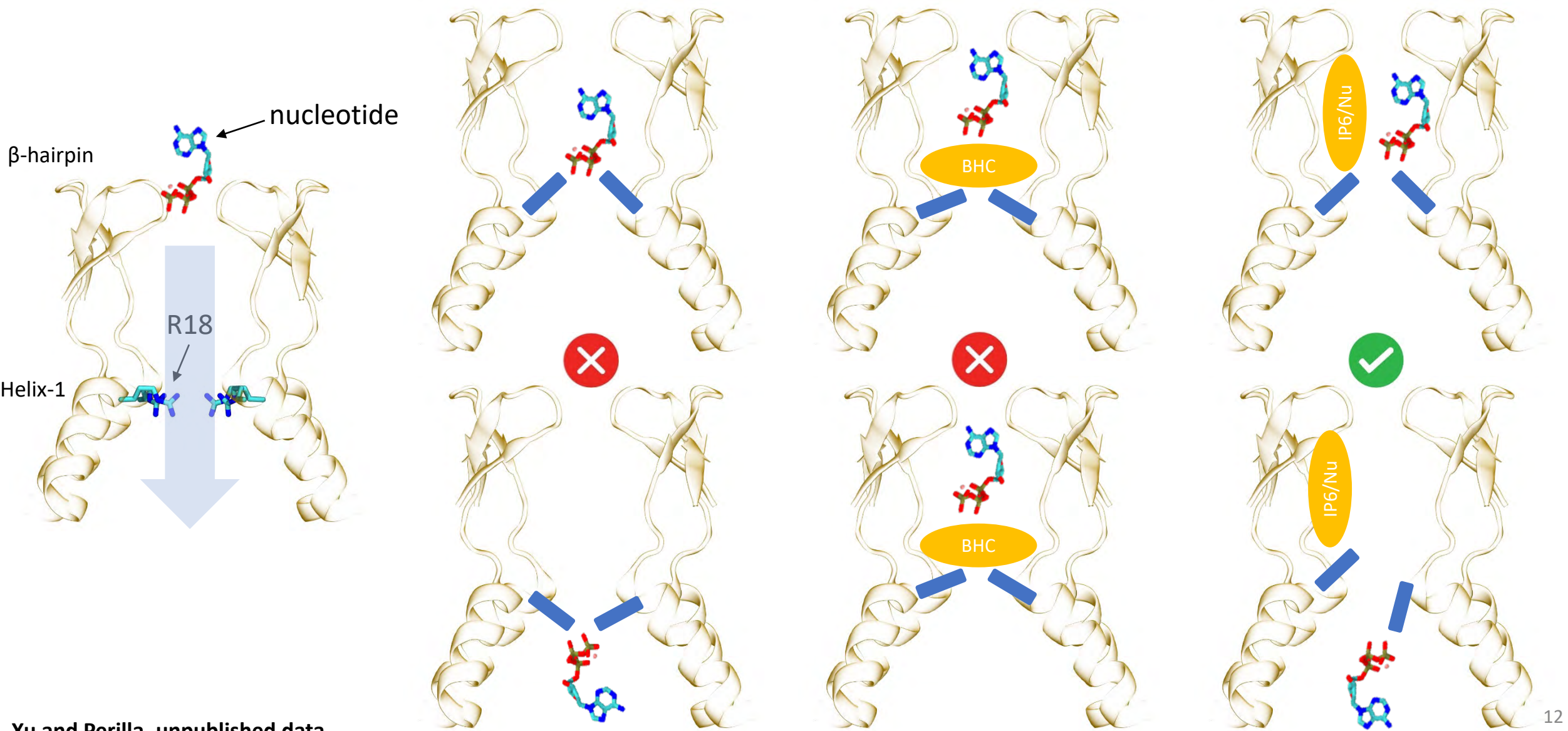
HIV-1 capsid

CA hexamer

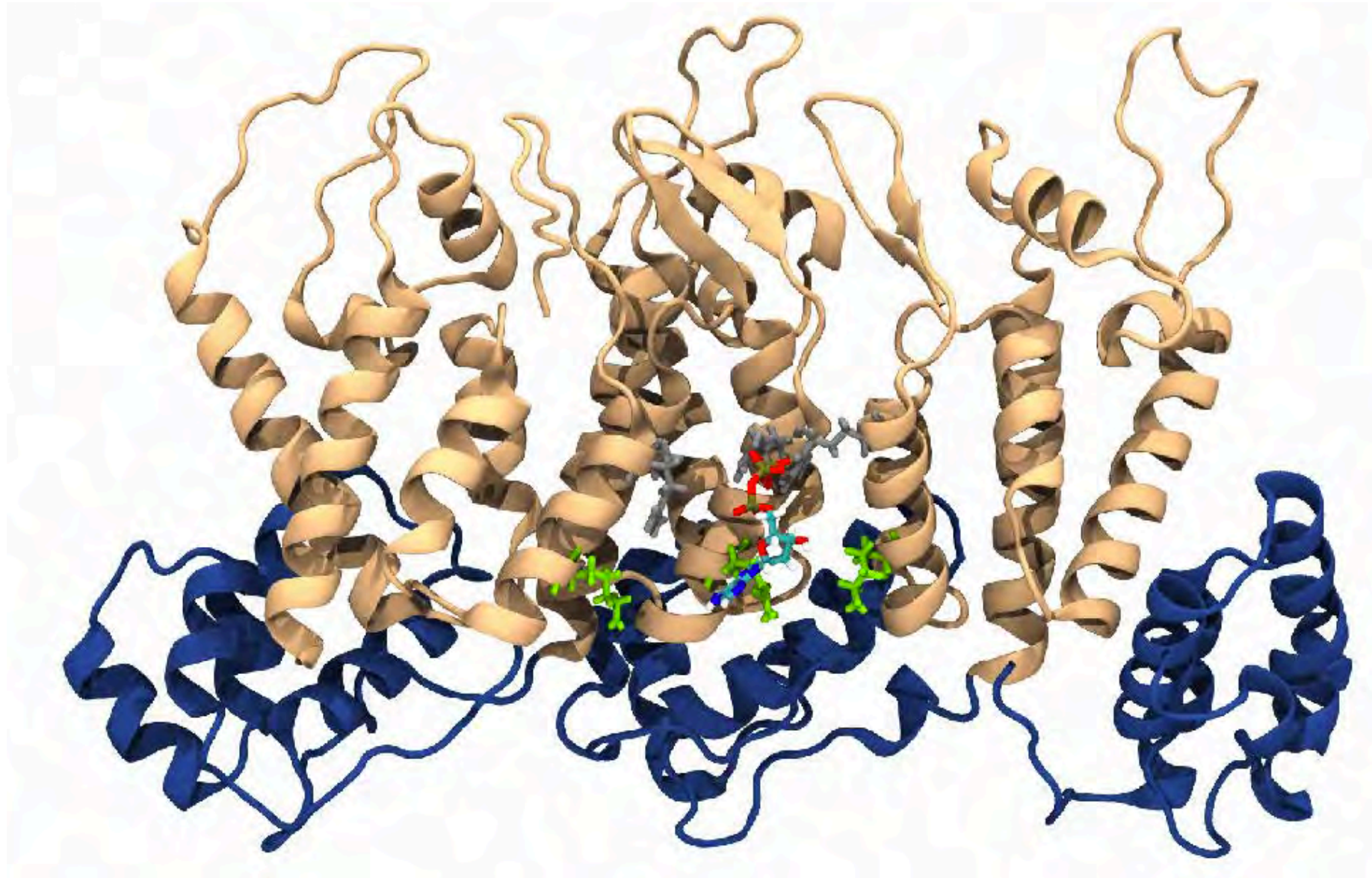
CA pentamer



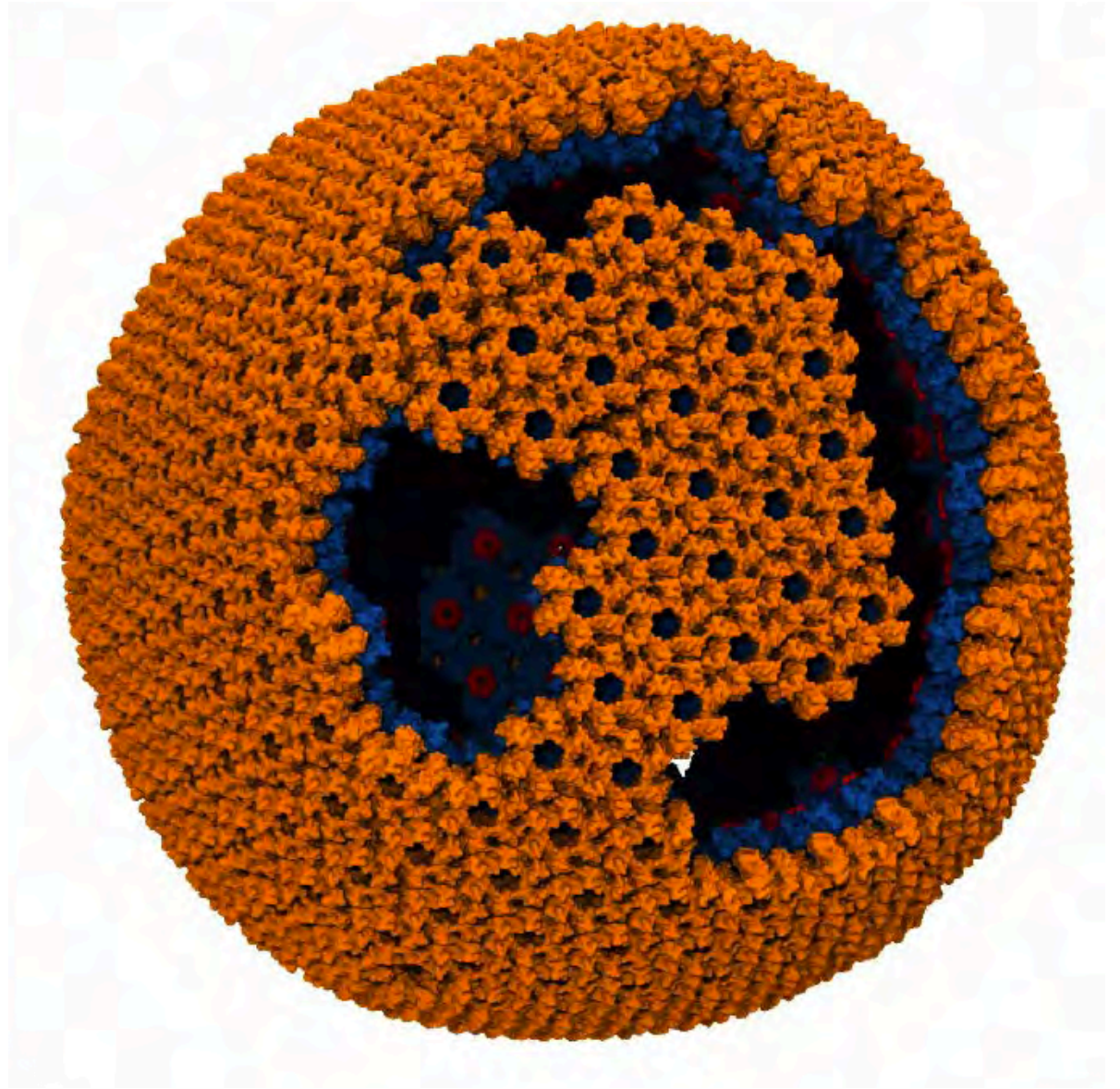
# Molecular mechanisms for dNTPs translocation



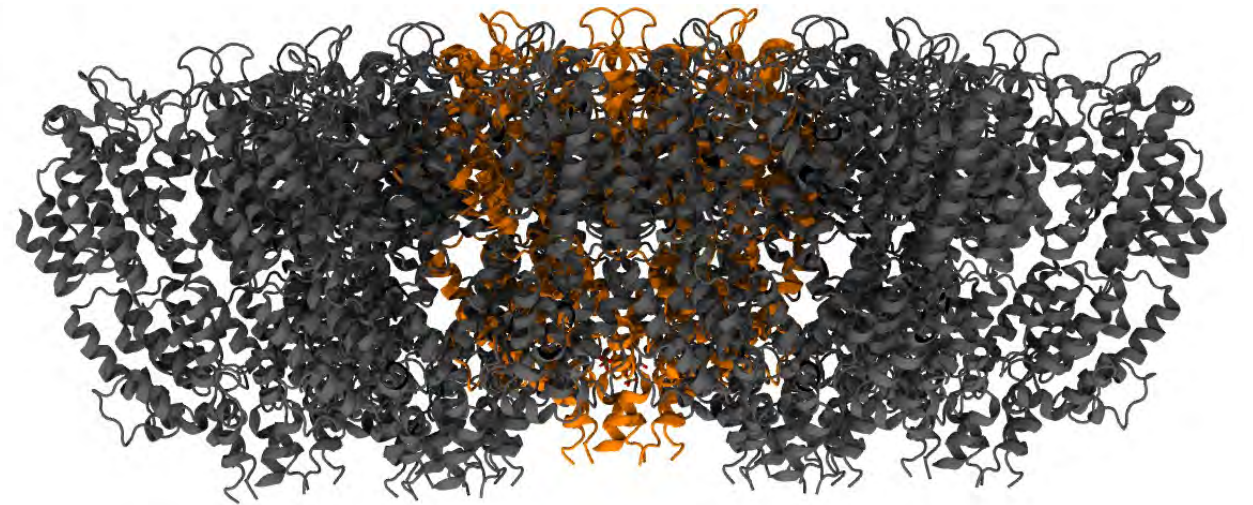
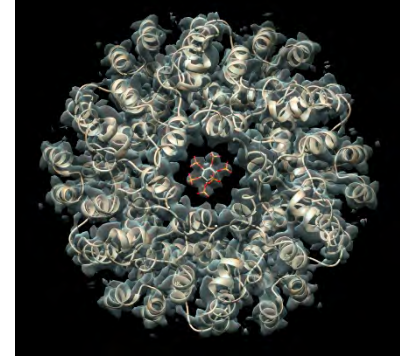
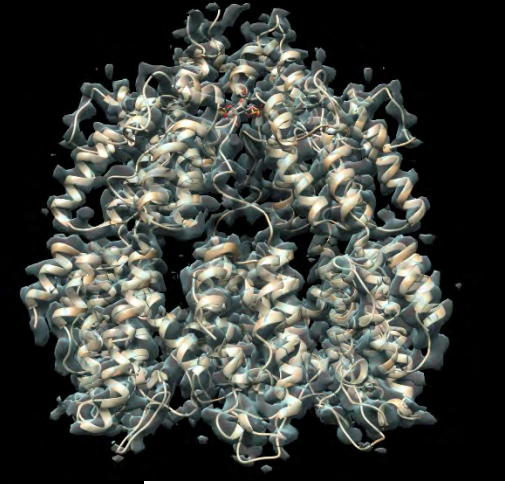
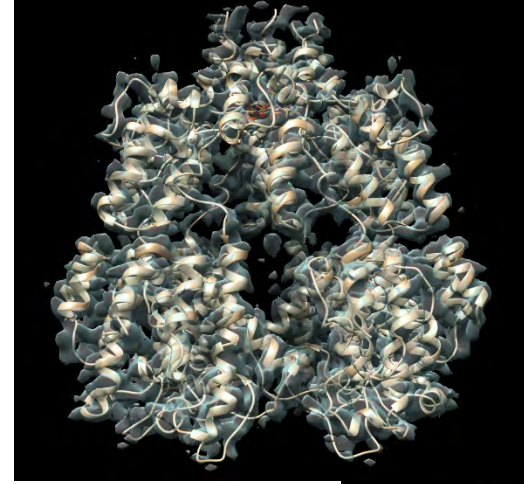
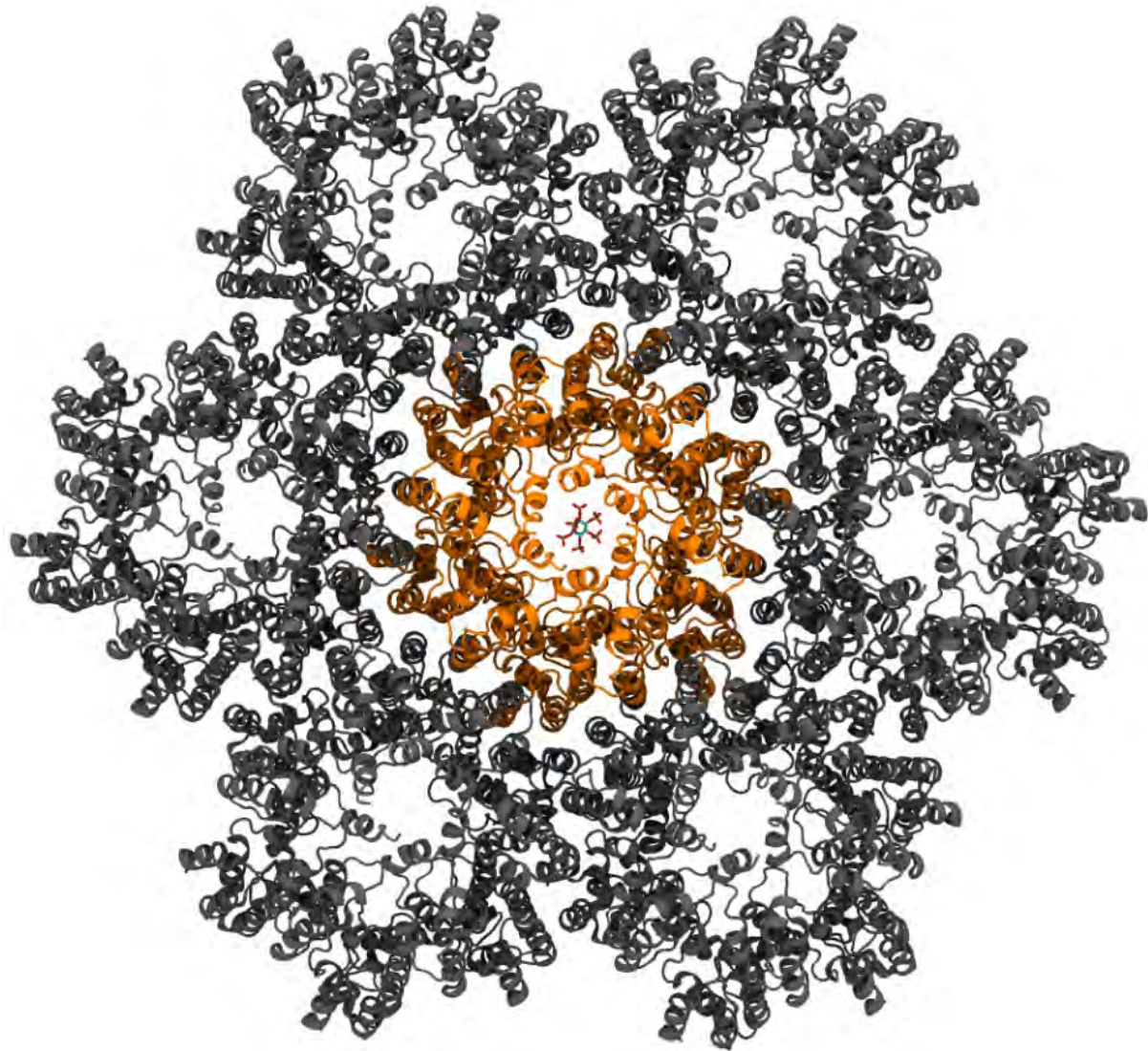
# Nucleotide translocation through the central cavity of CA hexamers



Structure of the  
immature capsid  
lattice



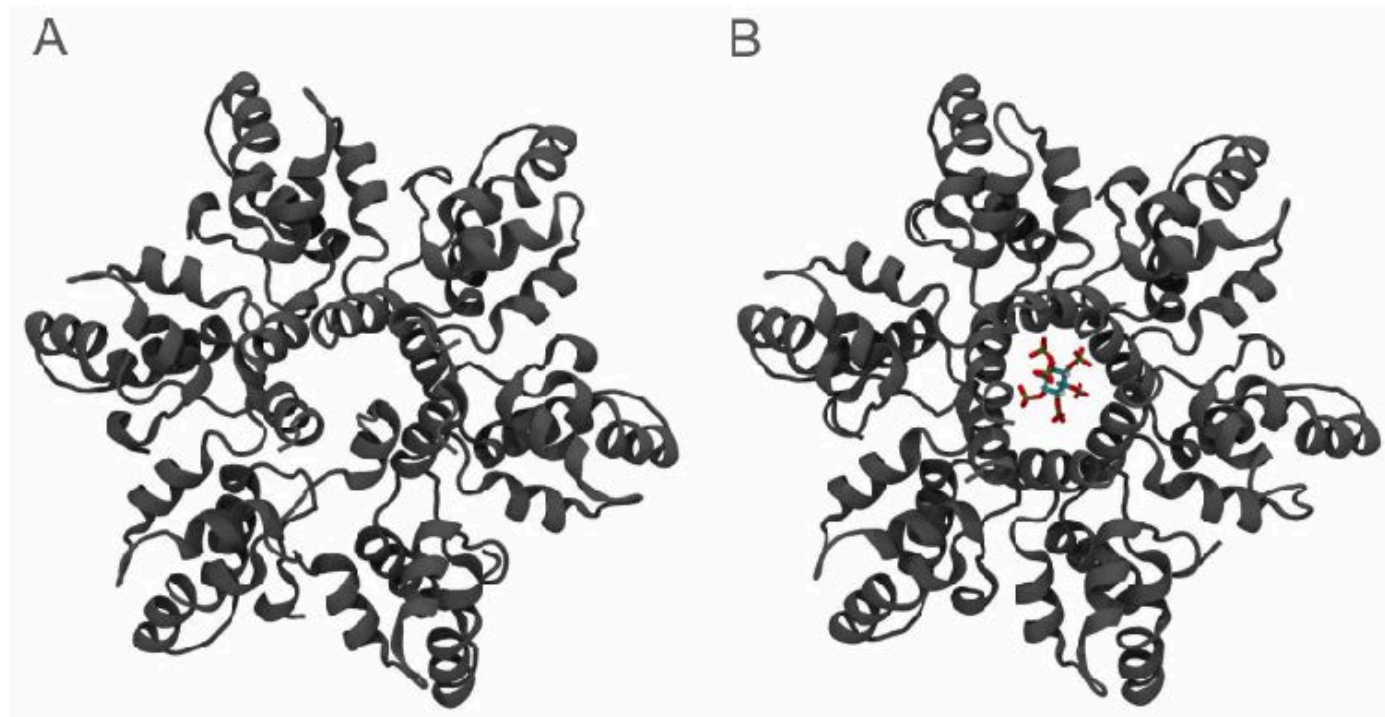
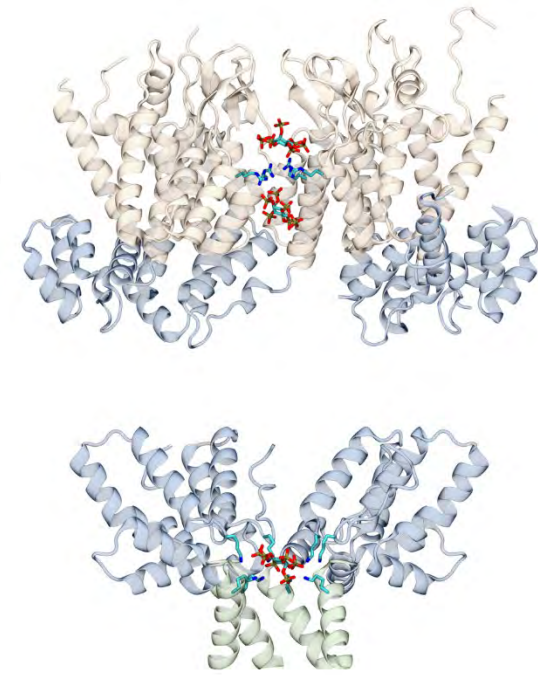
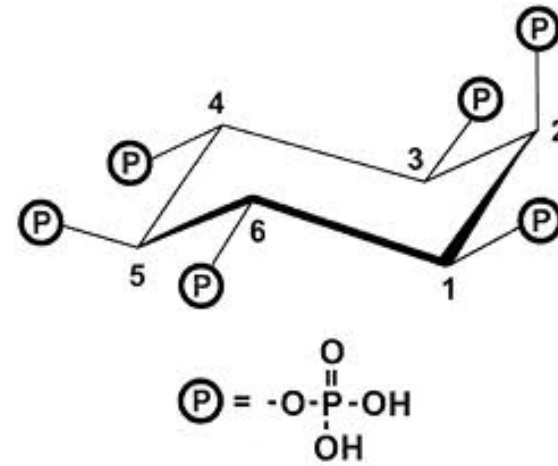
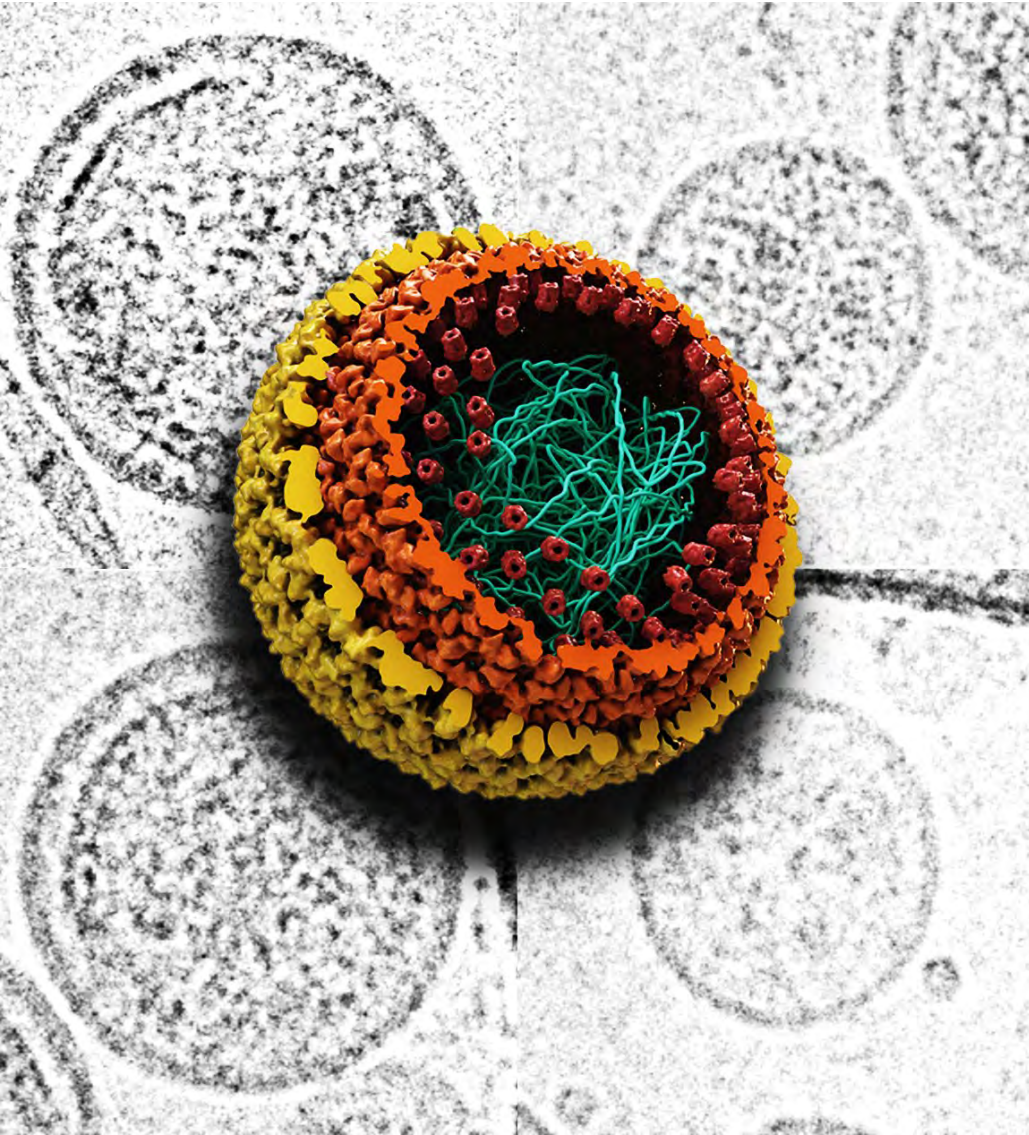
# EIAV Gag lattice





# IP6 stabilizes HIV-1 immature lattice

Collaboration with Volker Vogt & Rob Dick (Cornell University), Owen & Barbie (U. Virginia)



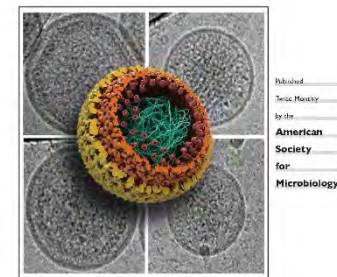


# Products 2017-2019

1. FEZ1 is recruited to a conserved cofactor site on capsid to promote HIV-1 trafficking.  
**Cell Reports**, 2019
2. Structural basis for the homotypic fusion of chlamydial inclusions by the SNARE-like protein Inca  
**Nature Communications**, 2019
3. MxB Restricts HIV-1 by Targeting the Tri-hexamer Interface of the Viral Capsid.  
**Structure**, 2019, 37
4. Dynamic regulation of HIV-1 capsid interaction with the restriction factor TRIM5 $\alpha$  identified by magic-angle spinning NMR and molecular dynamics simulations.  
**Proceedings of the National Academy of Sciences USA**, 2018,
5. All-Atom Simulations of Viruses.  
**Current Opinion in Virology**, 2018
6. Inositol phosphates are assembly co-factors for HIV-1.  
**Nature**, 2018
7. All-atom molecular dynamics of the HBV capsid reveals insights into biological function and cryo-EM resolution limits.  
**eLife**, 2018
8. Critical Role of the HTLV-1 Capsid N-Terminal Domain for Gag-Gag Interactions and Virus Particle Assembly.  
**Journal of Virology**, 2018
9. Molecular Dynamics Simulations of Protein-Drug Complexes: A Computational Protocol for Investigating the Interactions of Small-Molecule Therapeutics with Biological Targets and Biosensors. In: **Computational Drug Discovery and Design**, 2018, Pages: 245-270
10. Quenching protein dynamics interferes with HIV capsid maturation.  
**Nature Communications**, 2017, 8
11. CryoEM structure of MxB reveals a novel oligomerization interface critical for HIV restriction.  
**Science Advances**, 2017, 9, Pages: e1701264
12. CryoEM Structure Refinement by Integrating NMR Chemical Shifts with Molecular Dynamics Simulations  
**Journal of Physical Chemistry B**, 2017, Pages: 10.1021/acs.jpcc.6b13105
13. Physical properties of the HIV-1 capsid from all-atom molecular dynamics simulations  
**Nature Communications**, 2017, 8, Pages: 15959
14. Length of encapsidated cargo impacts stability and structure of in vitro assembled Alphavirus core-like particles.  
**Journal of Physics: Condensed Matter**, 2017

## Software

1. Volln: an unsupervised tool to detect regions of interests in molecular containers of arbitrary shape.

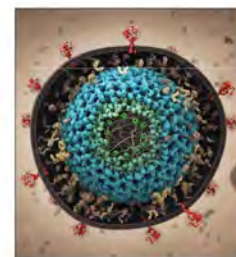


Journal of  
Virology



JVI

JULY 2014, VOLUME 88, NUMBER 14

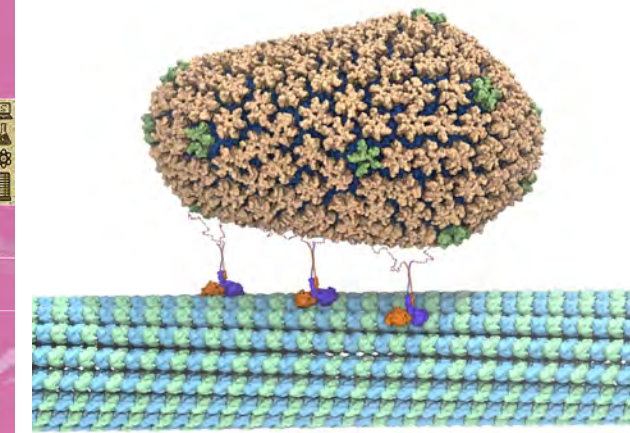
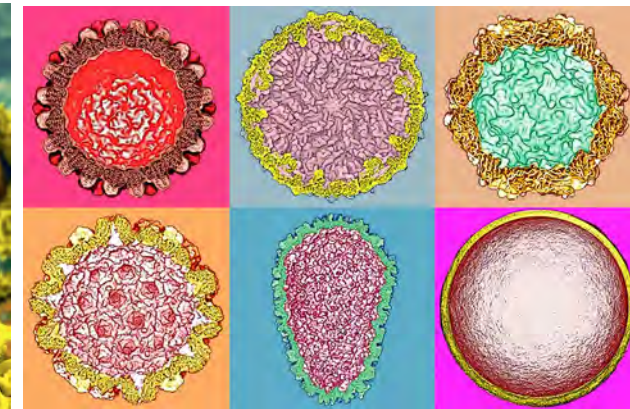


Journal of  
Virology



JVI

JULY 2014, VOLUME 88, NUMBER 14



## Shared data

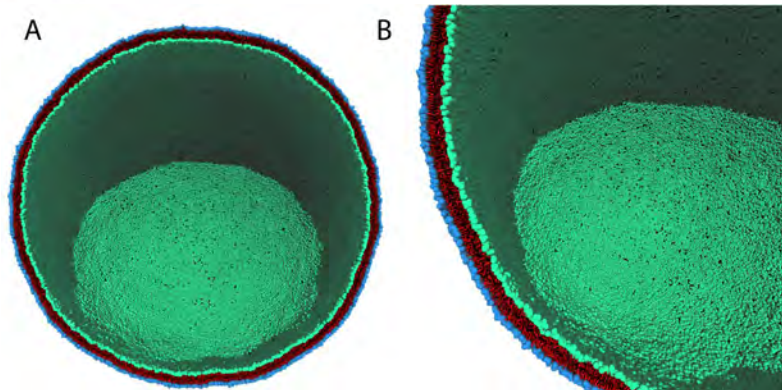
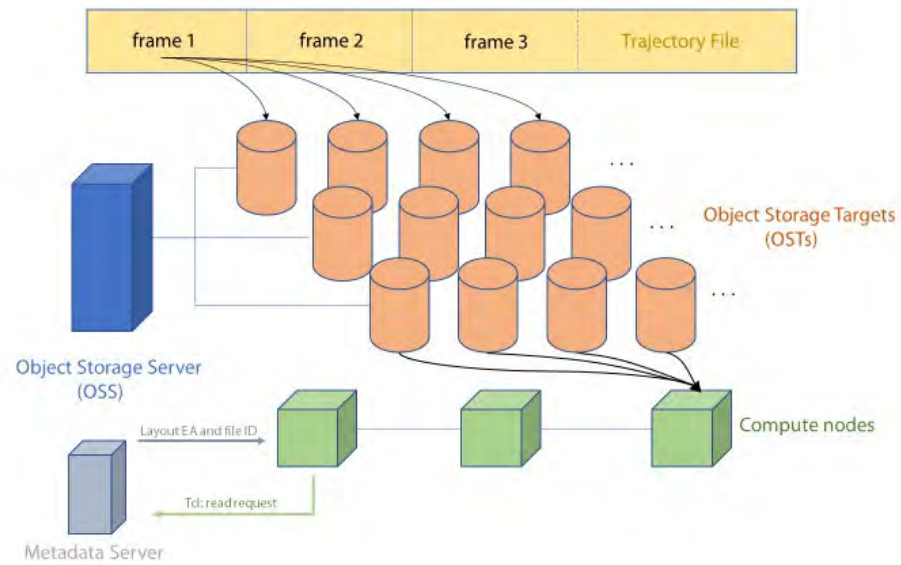
1. Model of the Human T-Leukemia virus immature assembly.
2. Model of human MxB interacting with HIV-1 capsid.
3. Model of human FEZ1 interacting with HIV-1 capsid.
4. Models of IP6 interacting with HIV-1 capsid.

BWillinois 2017

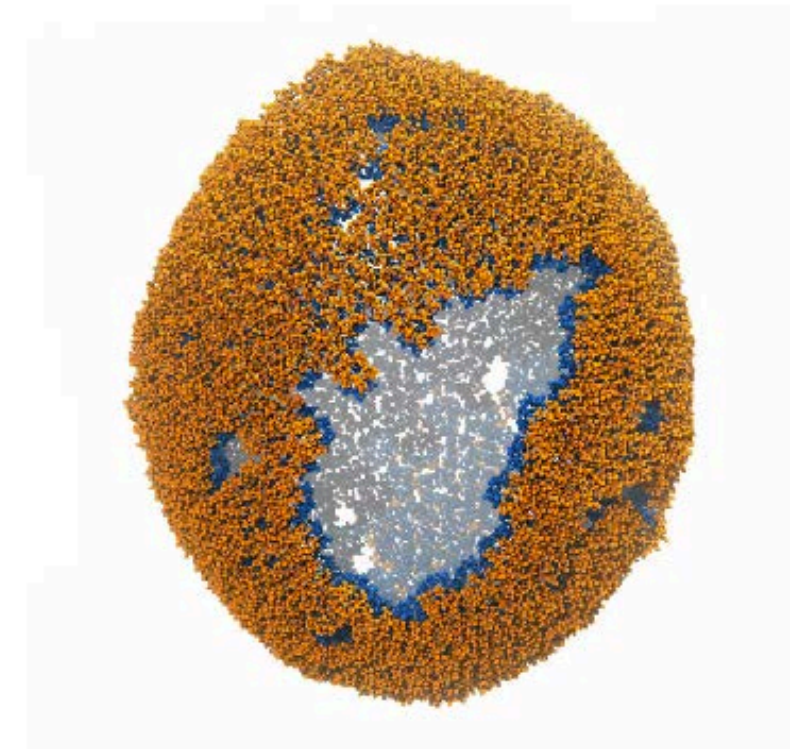
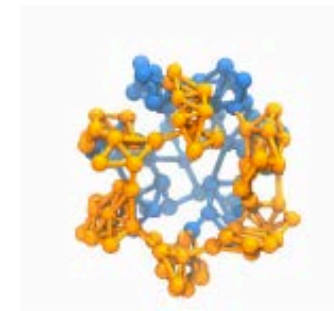
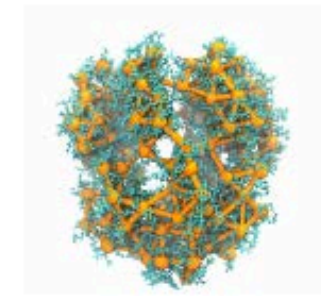
BW GLC2018

# Contributions from Blue Waters Staff

Enabling optimal use of the Lustre filesystem for large-scale analysis



Staff has supported our data-storage needs including staging, transfer and archival.  
Staff worked with us on Augmented Reality project for NCSA's access magazine.  
Staff wrote and edited dissemination articles about our work.  
Staff has provided guidance to new users, **domain graduate students**, in the development of new methods.



# Acknowledgments

**Angela Gronenborn** – University of Pittsburgh  
Solution NMR

**Tatyana Polenova** – University of Delaware  
Solid state NMR

**Sunita Chandrasekaran** – University of Delaware  
Code acceleration and software engineering

**Yong Xiong** – Yale University  
MxB and FEZ1

**John Stone** – University of Illinois at Urbana-Champaign  
Technology development

**Peijun Zhang** – Oxford University  
Cryo-EM, MxB

**Tyler Reddy** – Los Alamos National Laboratory  
HIV-1 virion dynamics

**Barbie Ganser-Pornillos** – University of Virginia  
Structure of mature HIV-1 capsid

**Louis Mzansky** – University of Minnesota  
Molecular architecture of the HTLV Gag lattice

**Owen Pornillos** – University of Virginia  
Small molecule and HIV-1 Gag interactions

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