

# Lecture 2

The structural biology of HIV-1 assembly

Adelajda Zorba

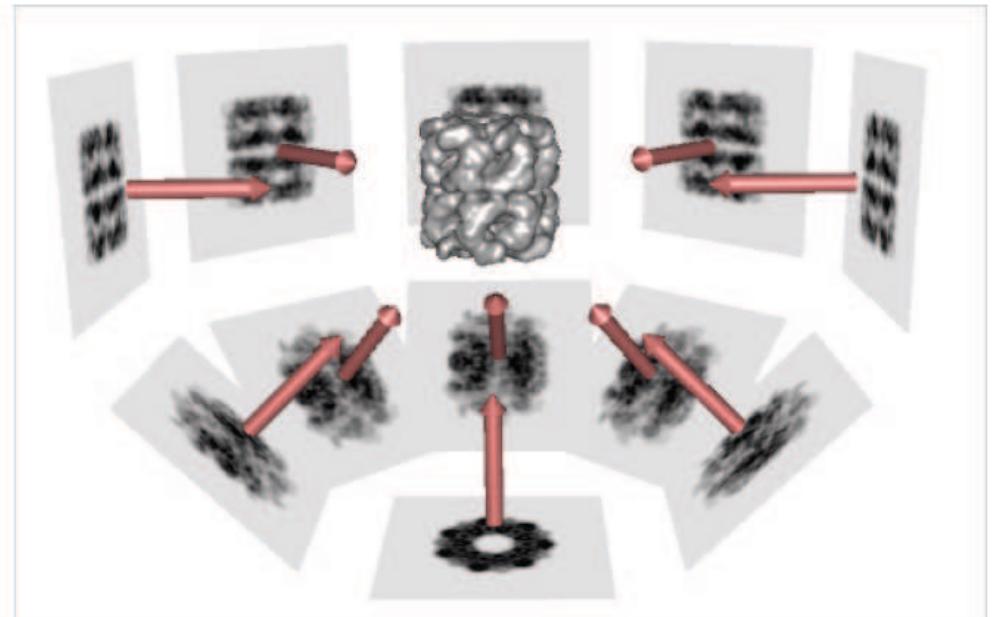
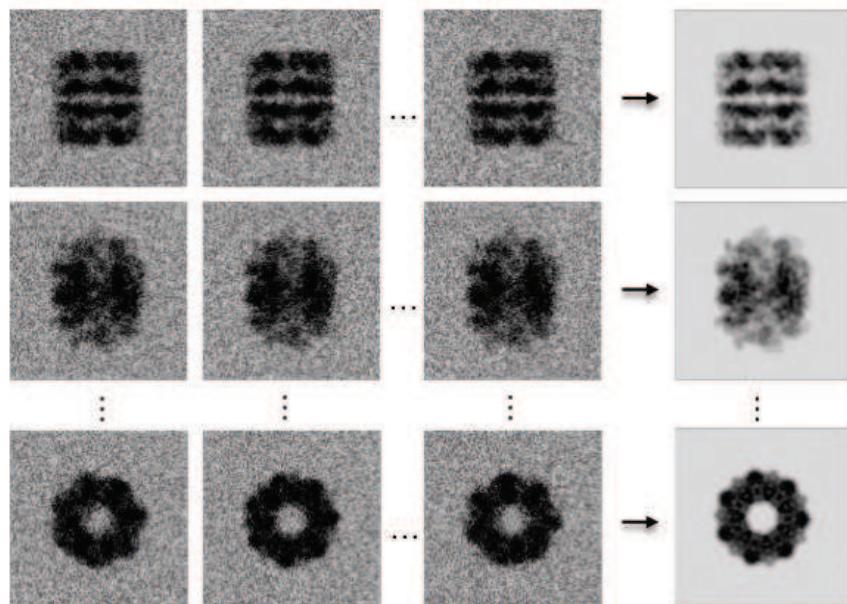
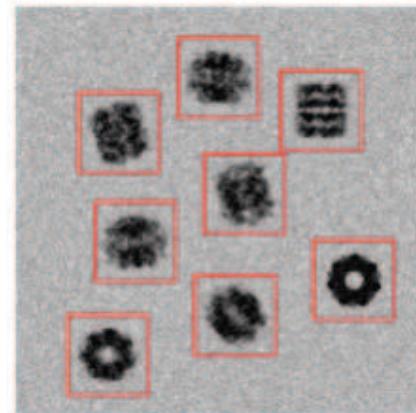
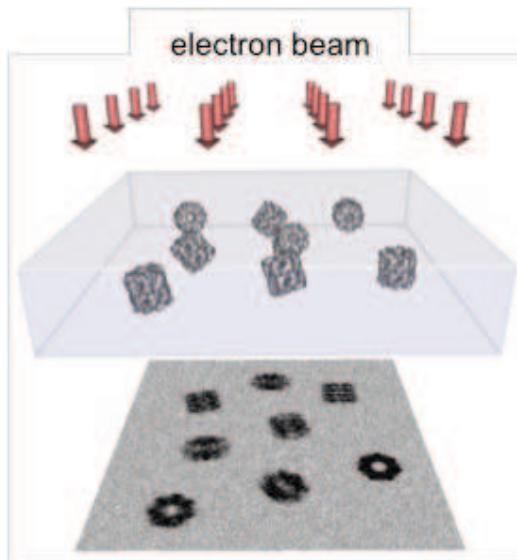
Removal of Arginine 332 Allows Human TRIM5 $\alpha$  To Bind Human  
Immunodeficiency Virus Capsids and To Restrict Infection

Yuan Li,<sup>1</sup> Xing Li,<sup>1</sup> Matthew Stremmelau,<sup>1</sup> Mark Lee,<sup>1</sup> and Joseph Sodroski<sup>1,2\*</sup>

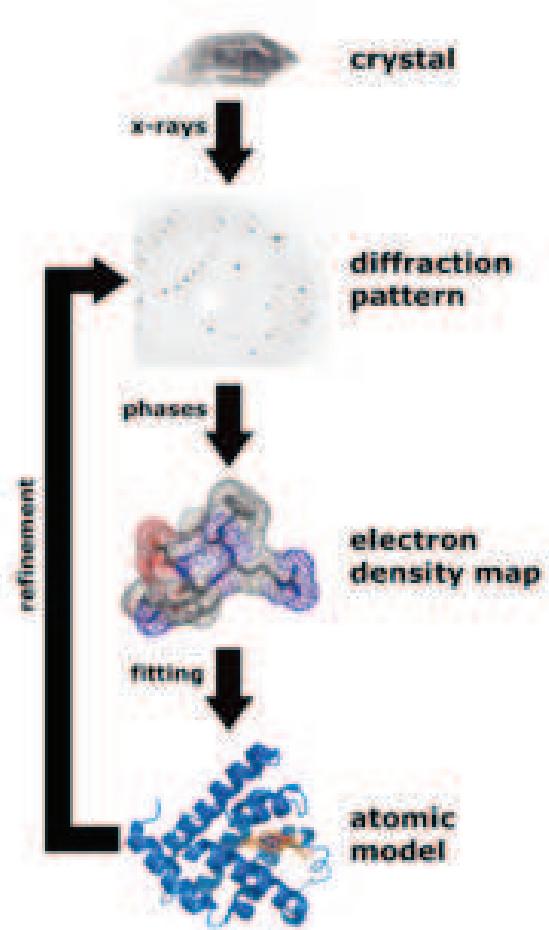
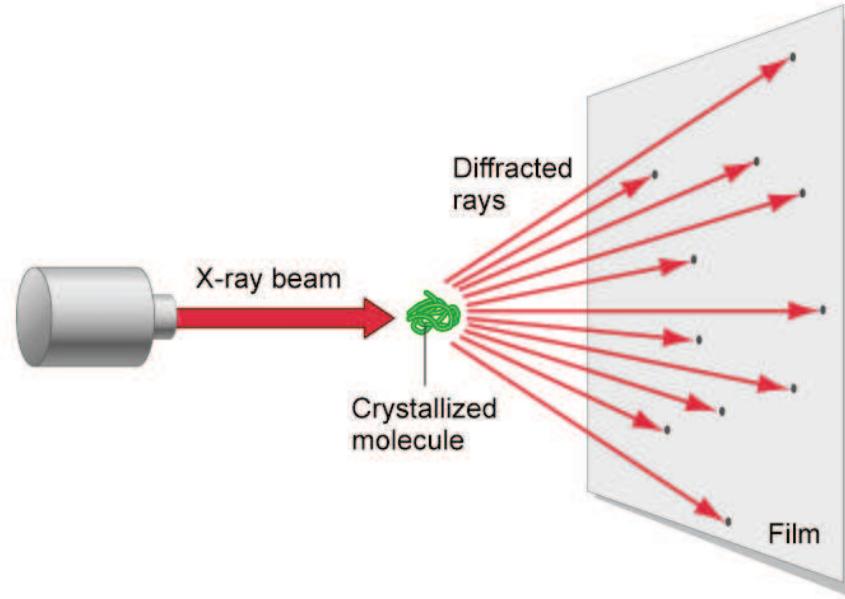


What are those ?

# Cryo-Electron Microscopy



# X-Ray Crystallography

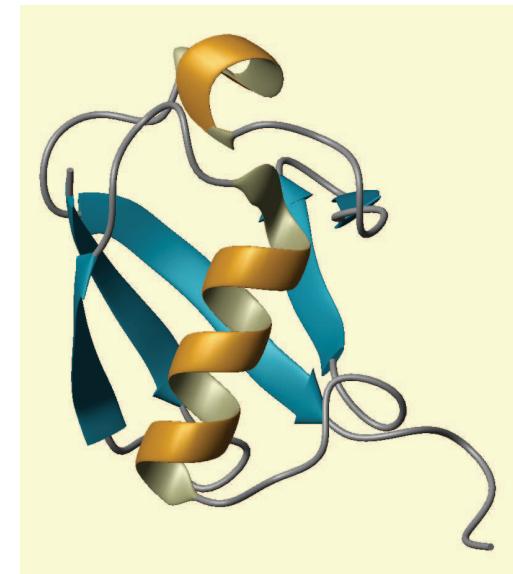
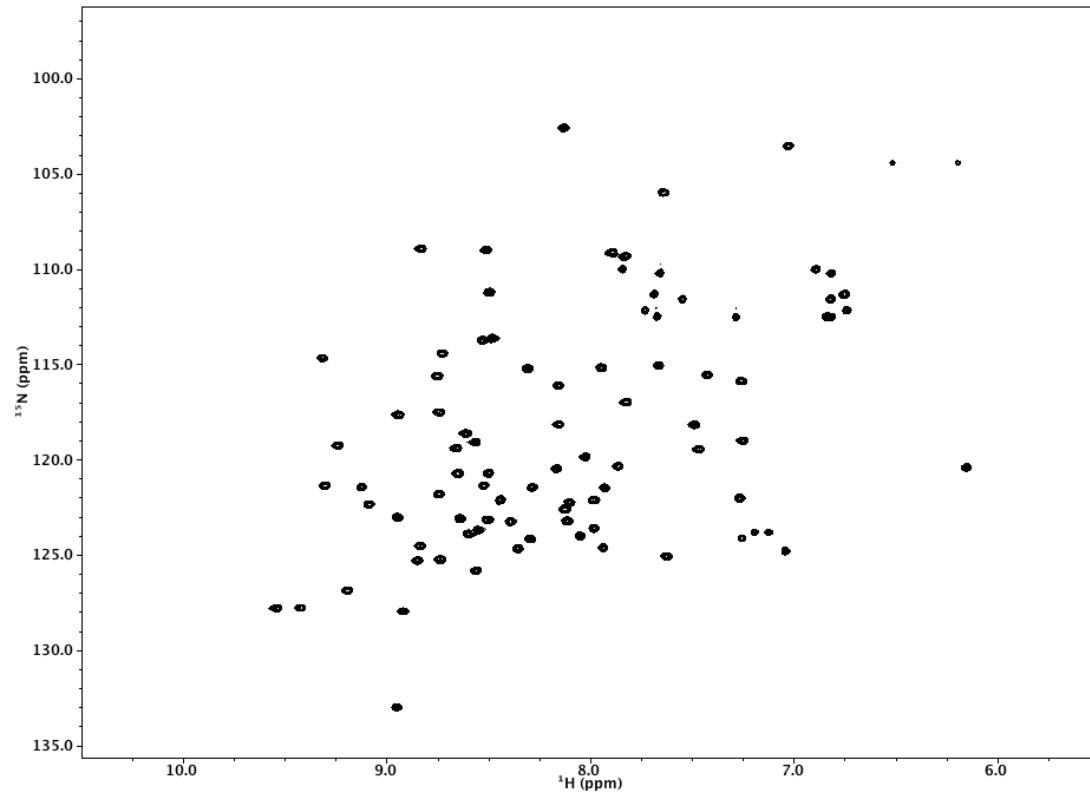


<http://www.biochem.arizona.edu/classes/bioc462/462bh2008/462bhonorsprojects/462bhonors2006/cooperj/protein%20structure%20analysis.htm>

<http://www.websters-dictionary-online.com/definitions/X-ray+crystallography?cx=partner-pub-0939450753529744%3Av0qd01-tdlq&cof=FORID%3A9&ie=UTF-8&q=X-ray+crystallography&sa=Search#920>

# Nuclear Magnetic Resonance (NMR)

Preview of up-coming attractions: HSQC of ubiquitin

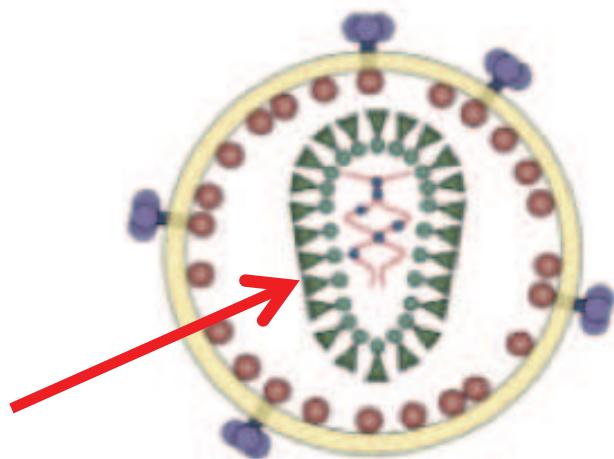


BMRB entry 5387

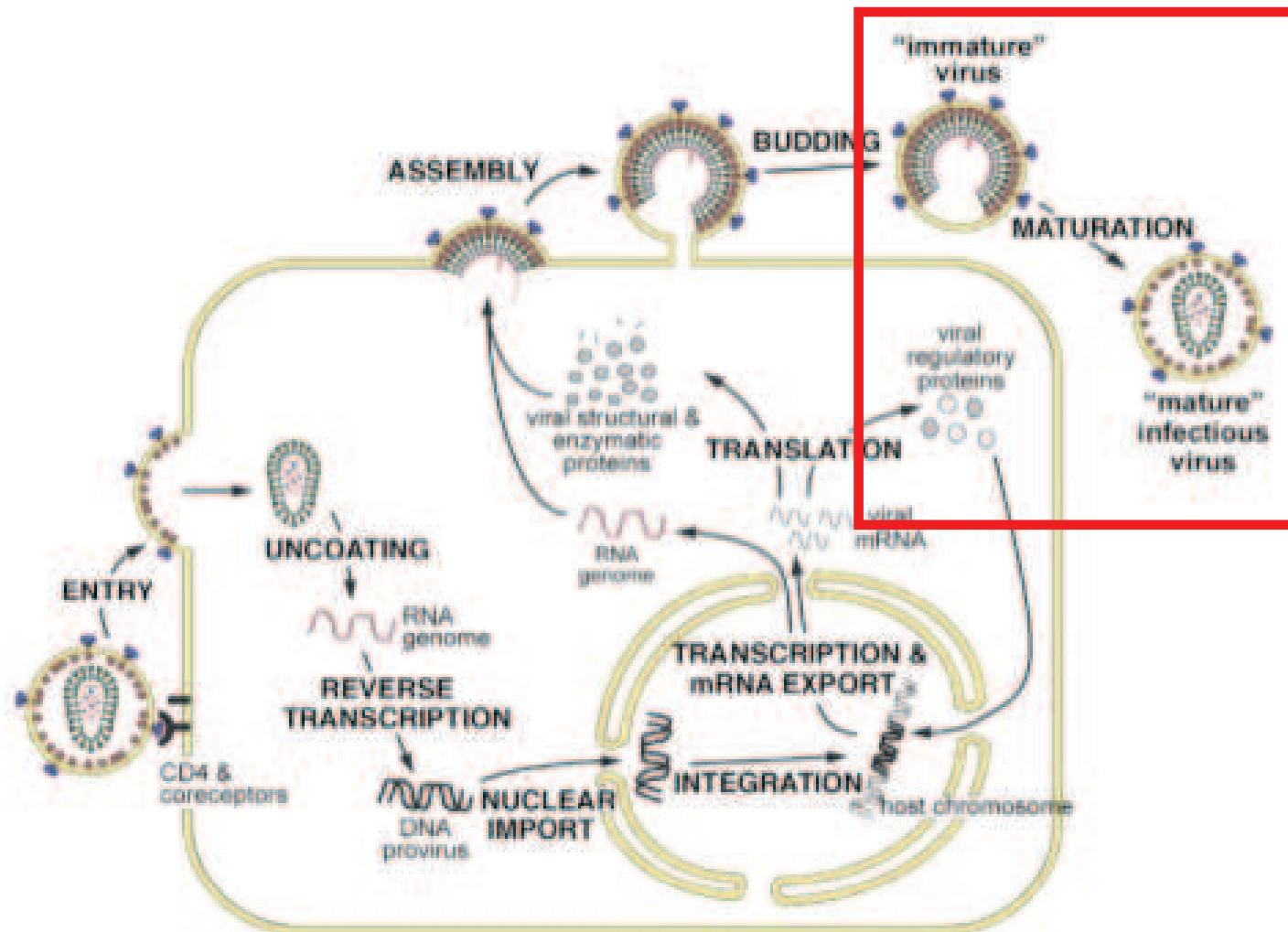
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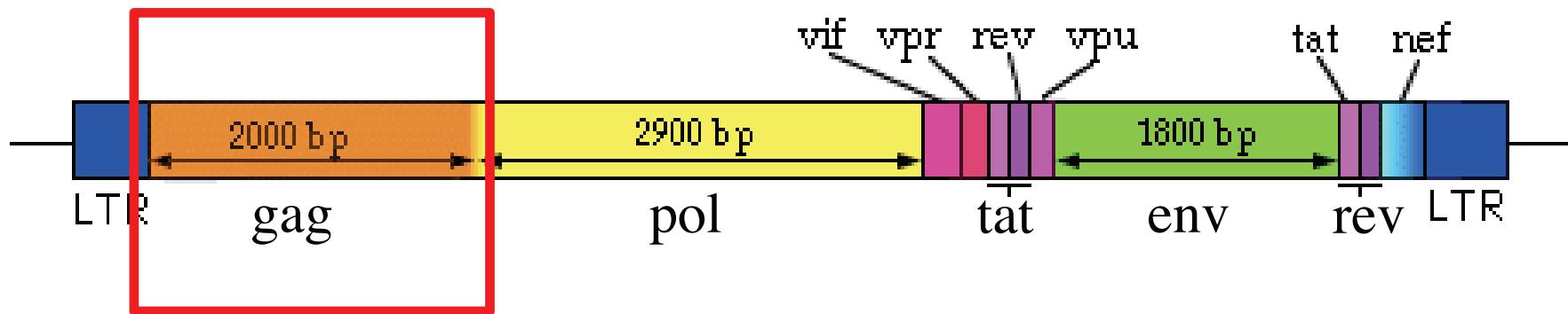
What are those ?



# HIV-1 life cycle

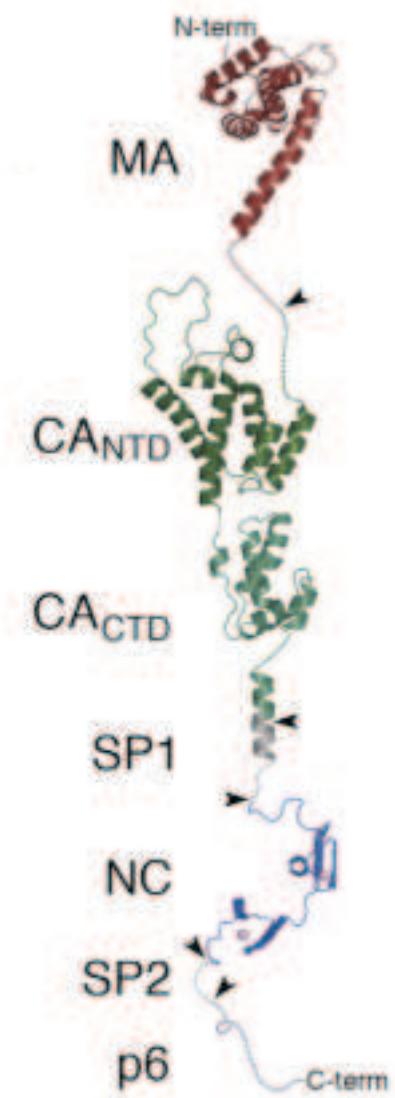
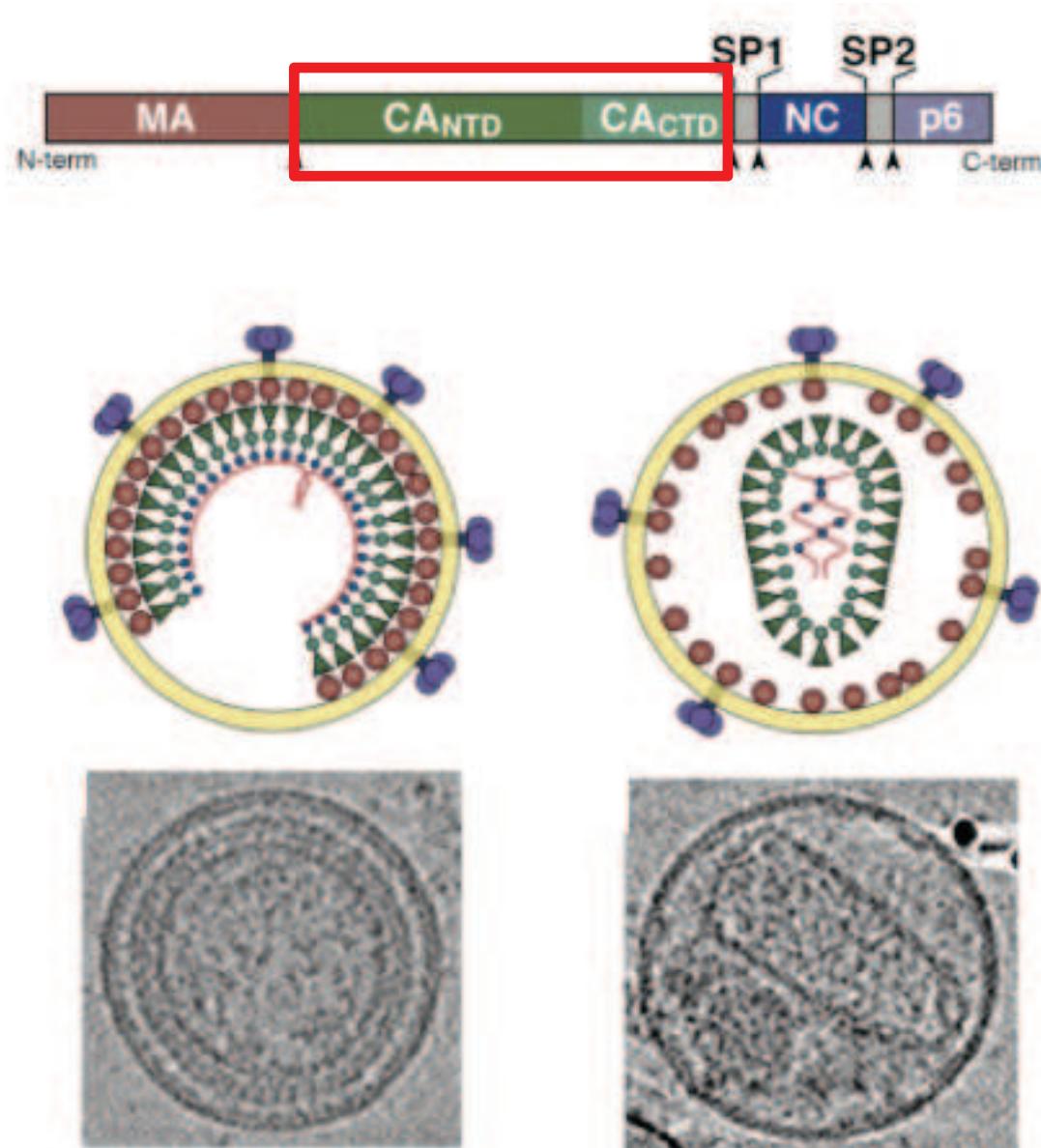


# HIV-1 Genome

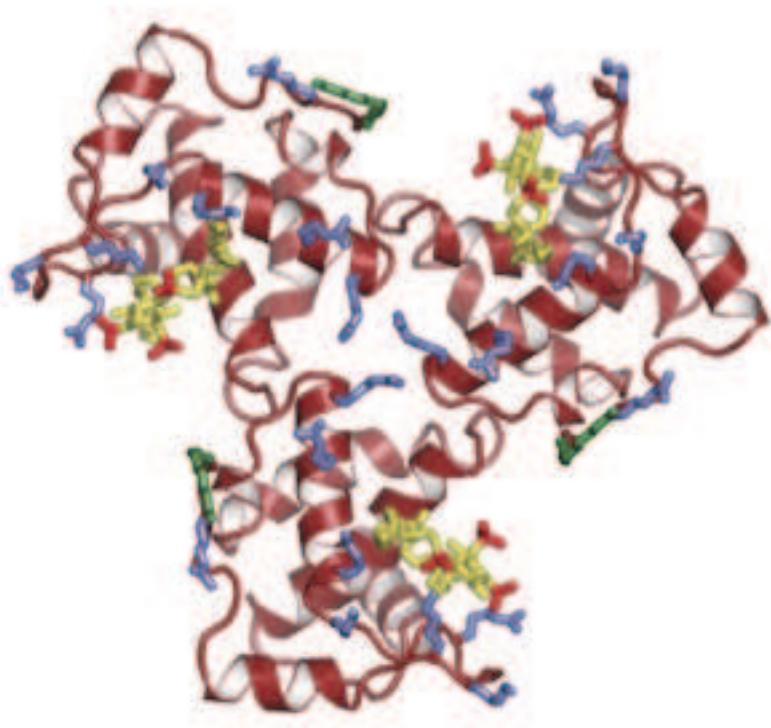
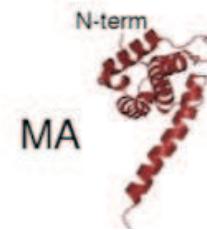
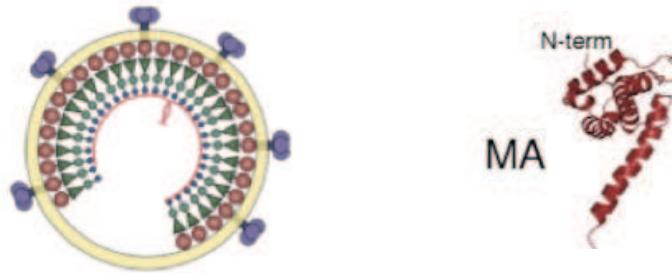


What does Gag do?

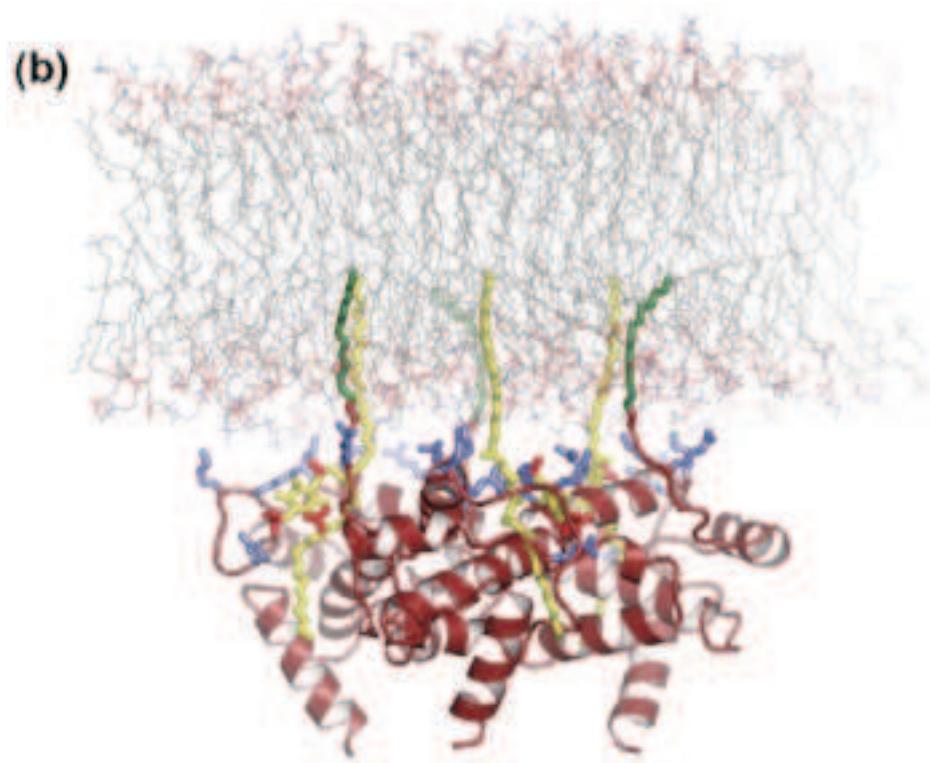
# Structural components of Gag



# Immature Virion: MA domain



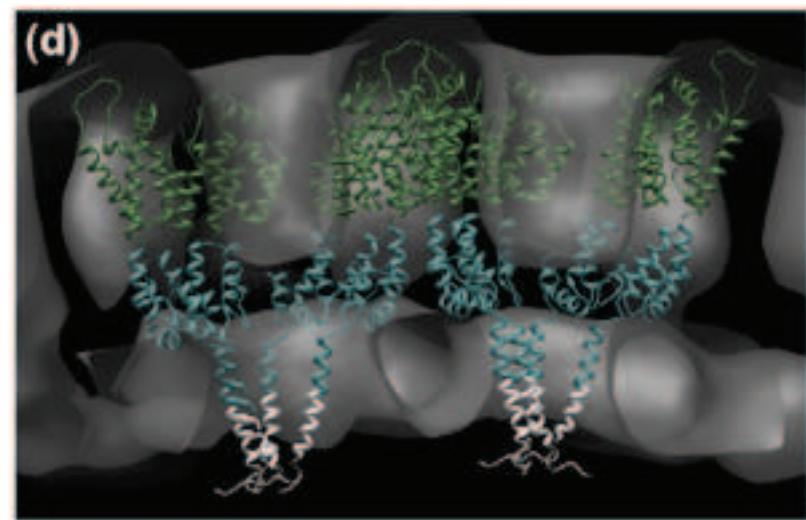
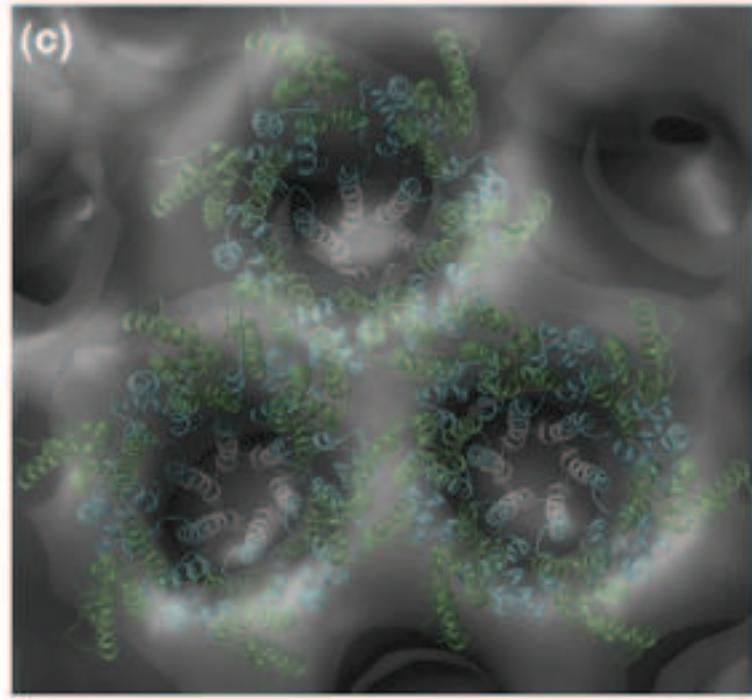
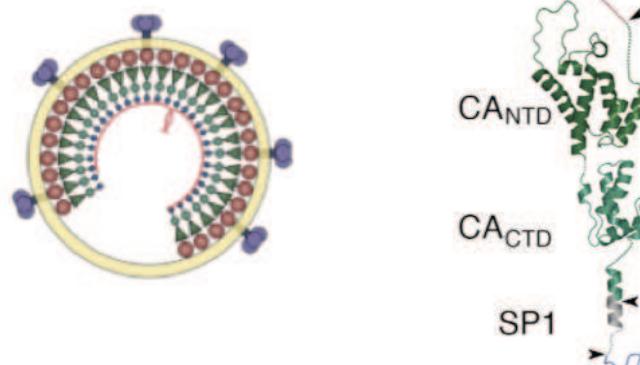
(b)



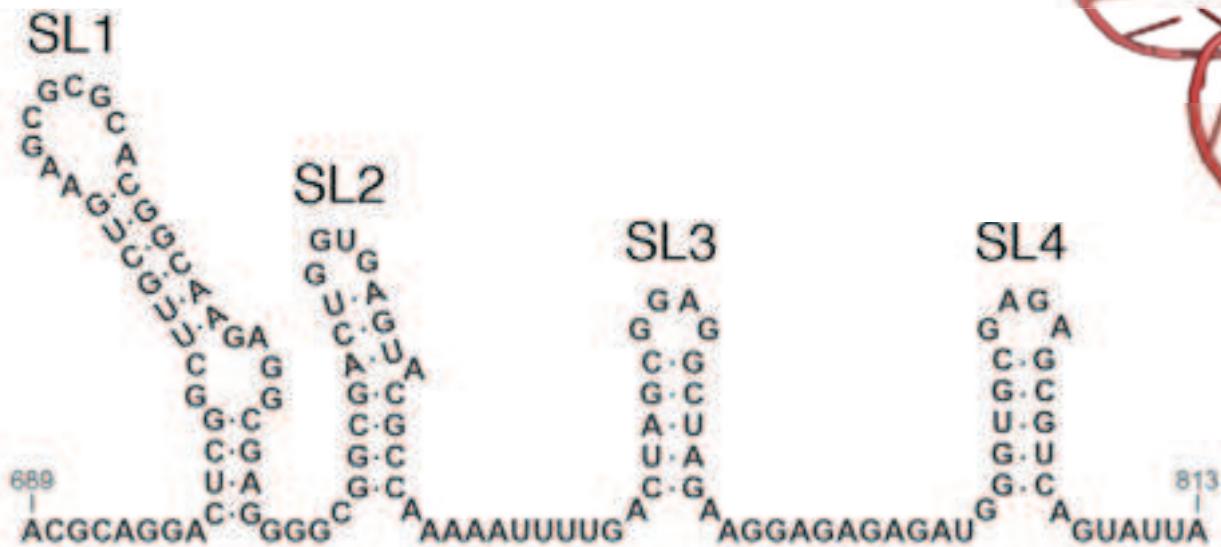
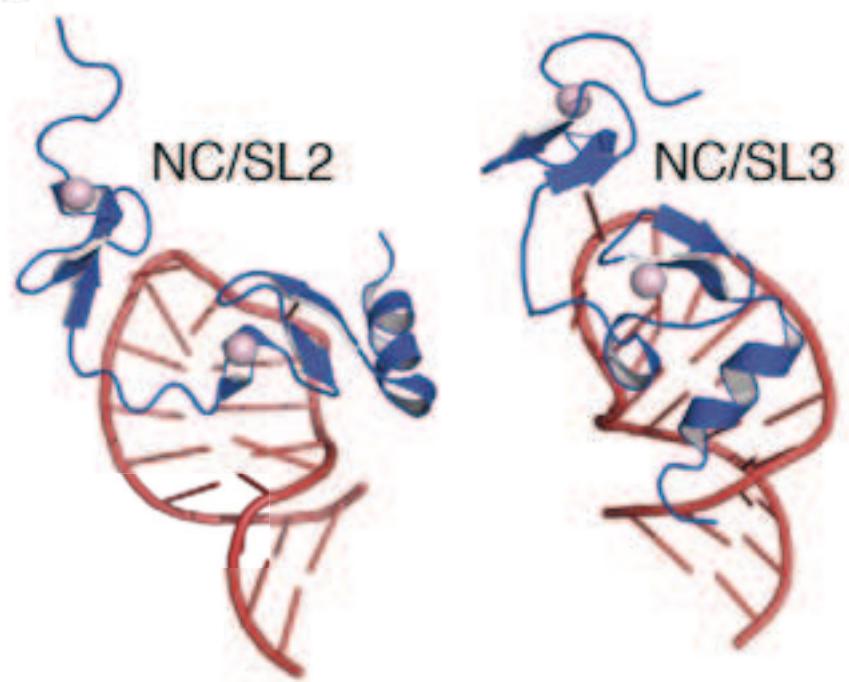
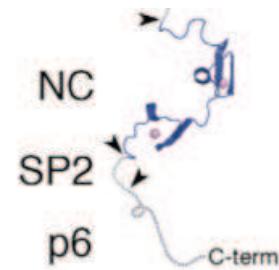
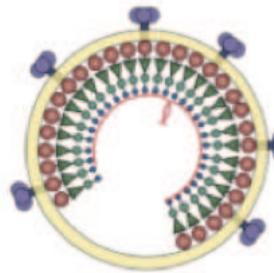
Myristoyl chain = green; basic residues = blue; PI(4,5)  
P2=yellow

Ganser-Pornillos et al., Struc. Biol., 18, 203, (2008)

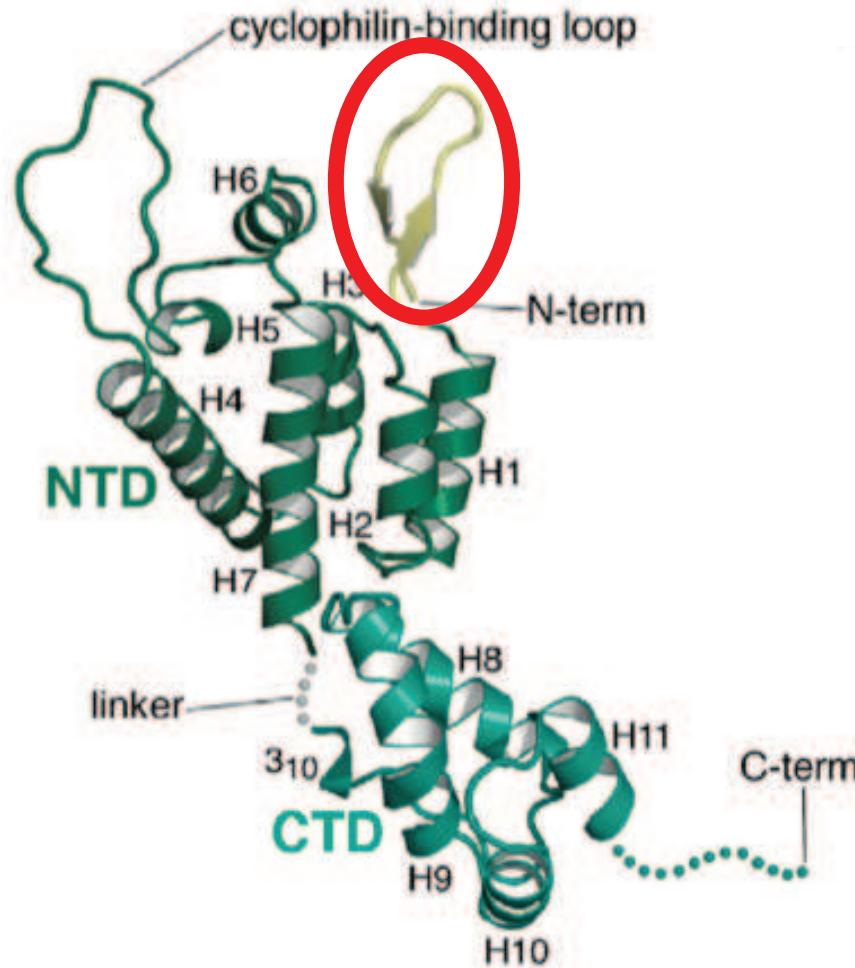
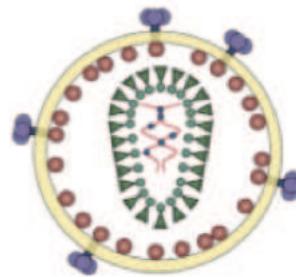
# Immature Virion: Capsid proteins (CA) and SP1



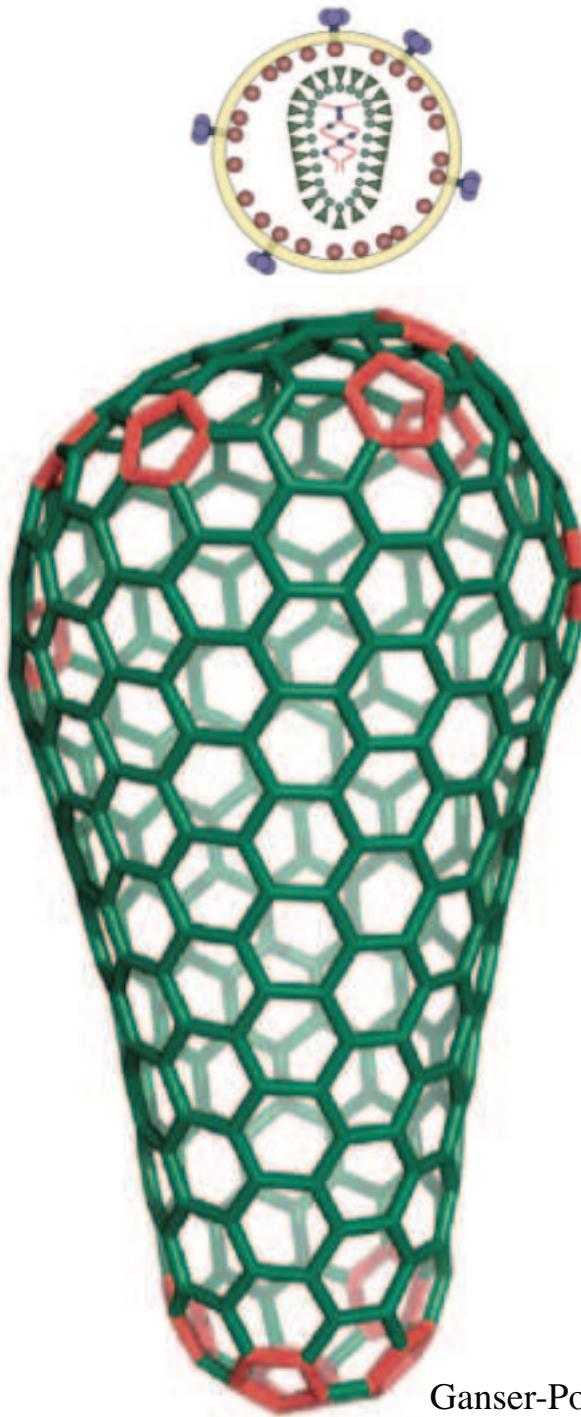
# Immature Virion: Nucleocapsid proteins



# Mature Virion: Capsid proteins

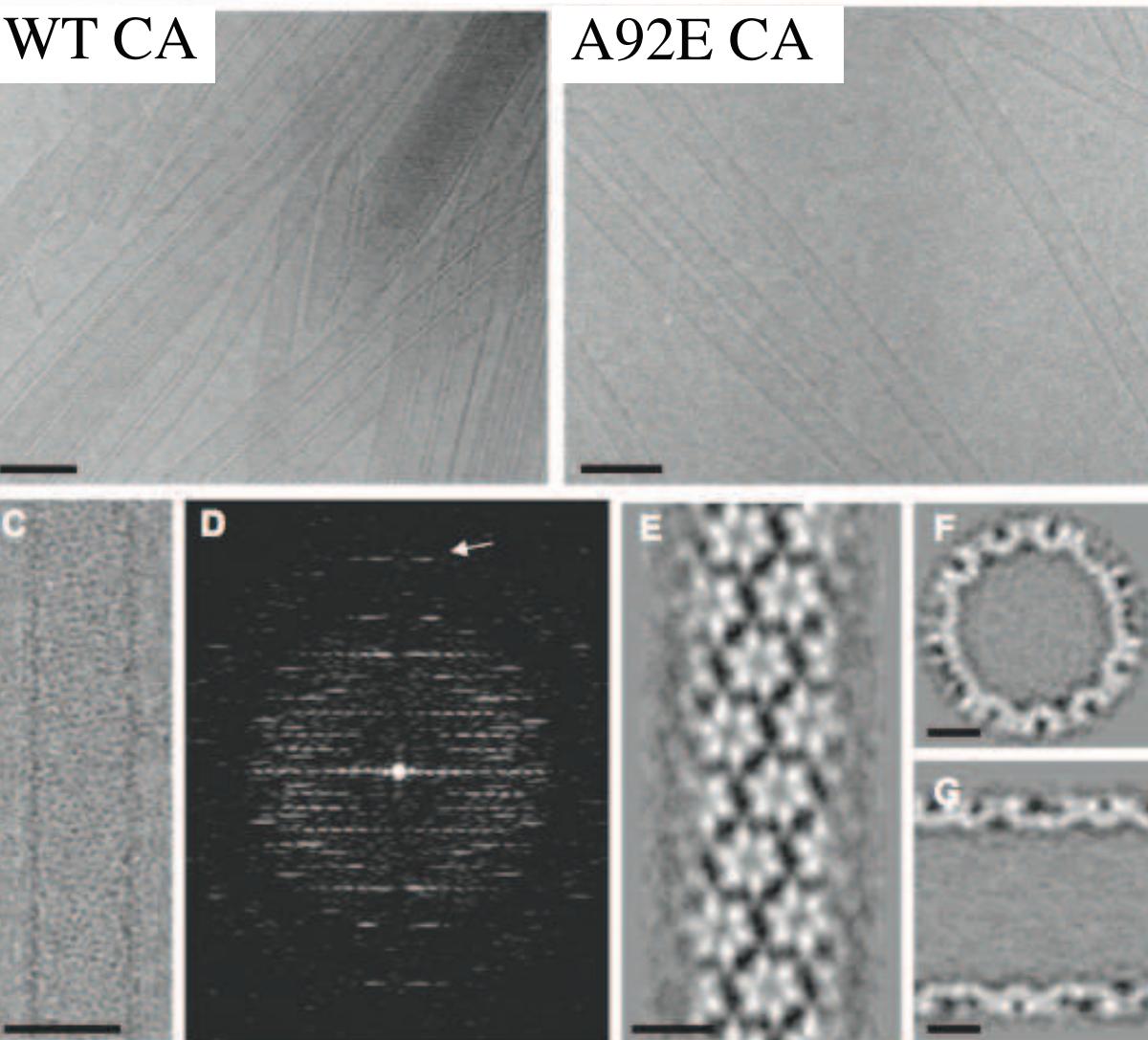


# Mature Virion: Mature Capsid

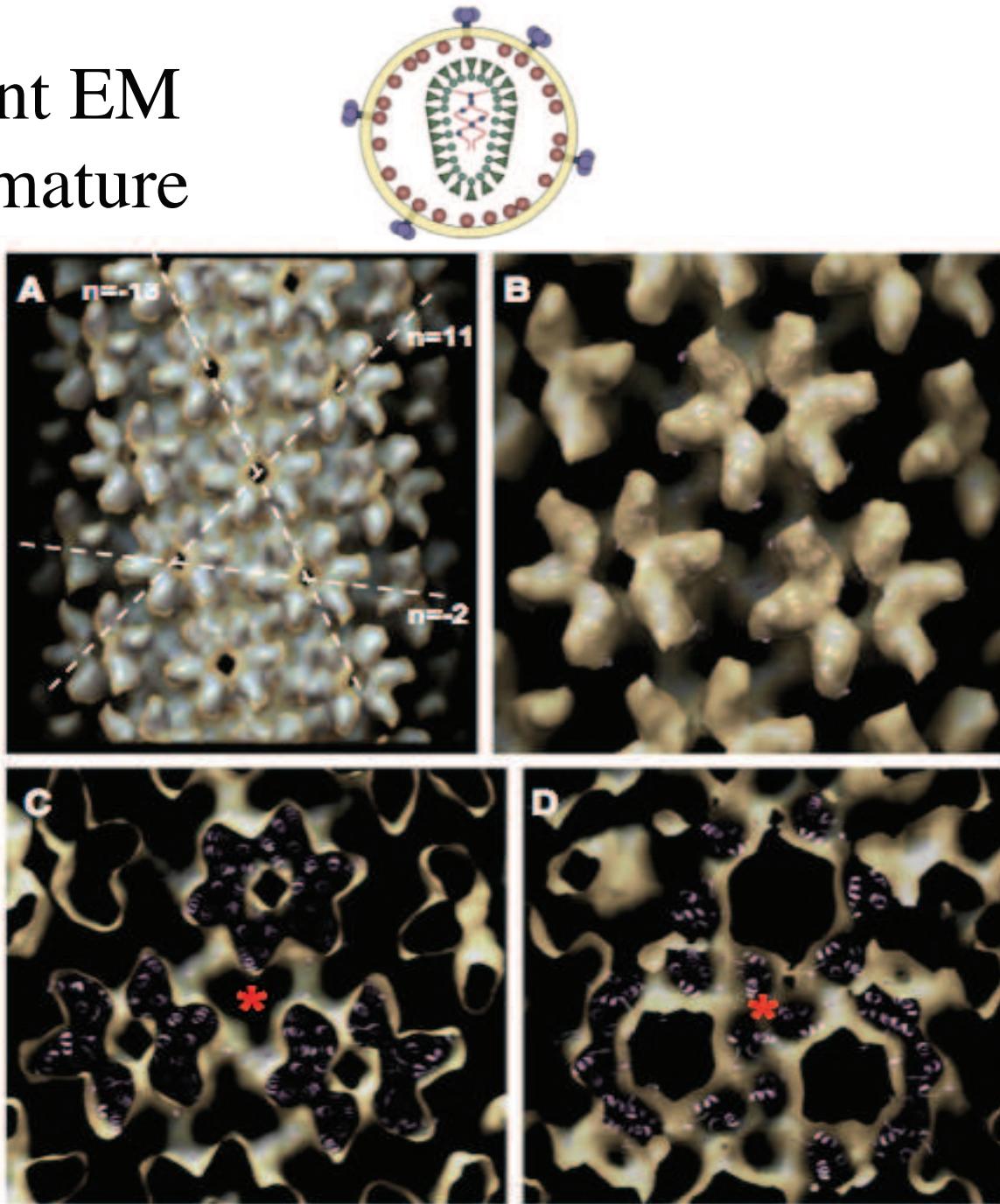


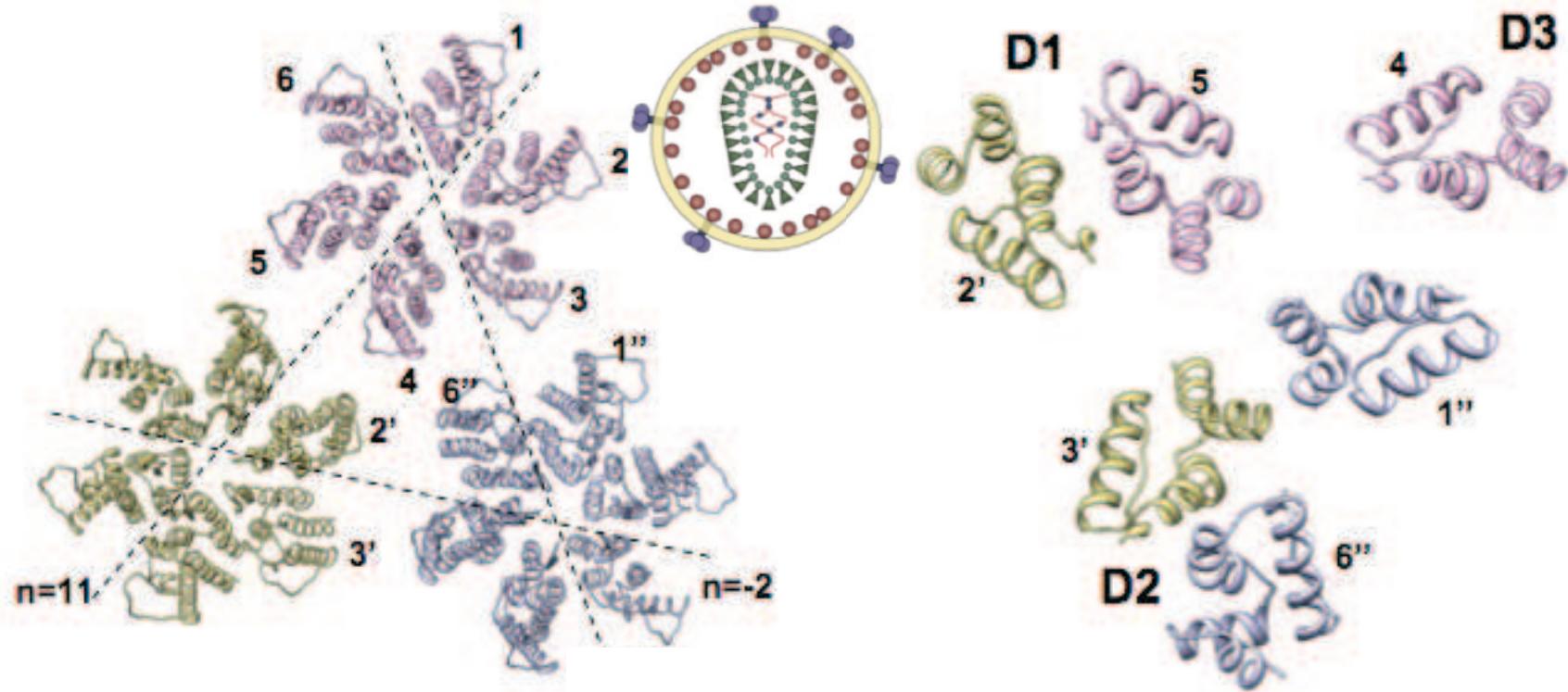
Ganser-Pornillos et al., Struc. Biol., 18, 203, (2008)

# Most recent EM model of mature capsid

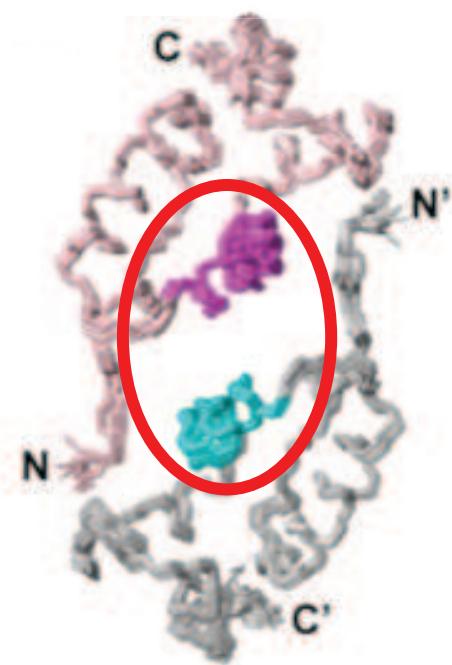


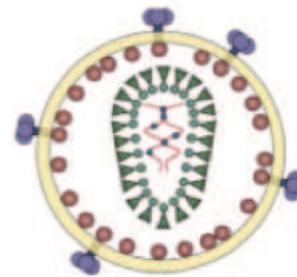
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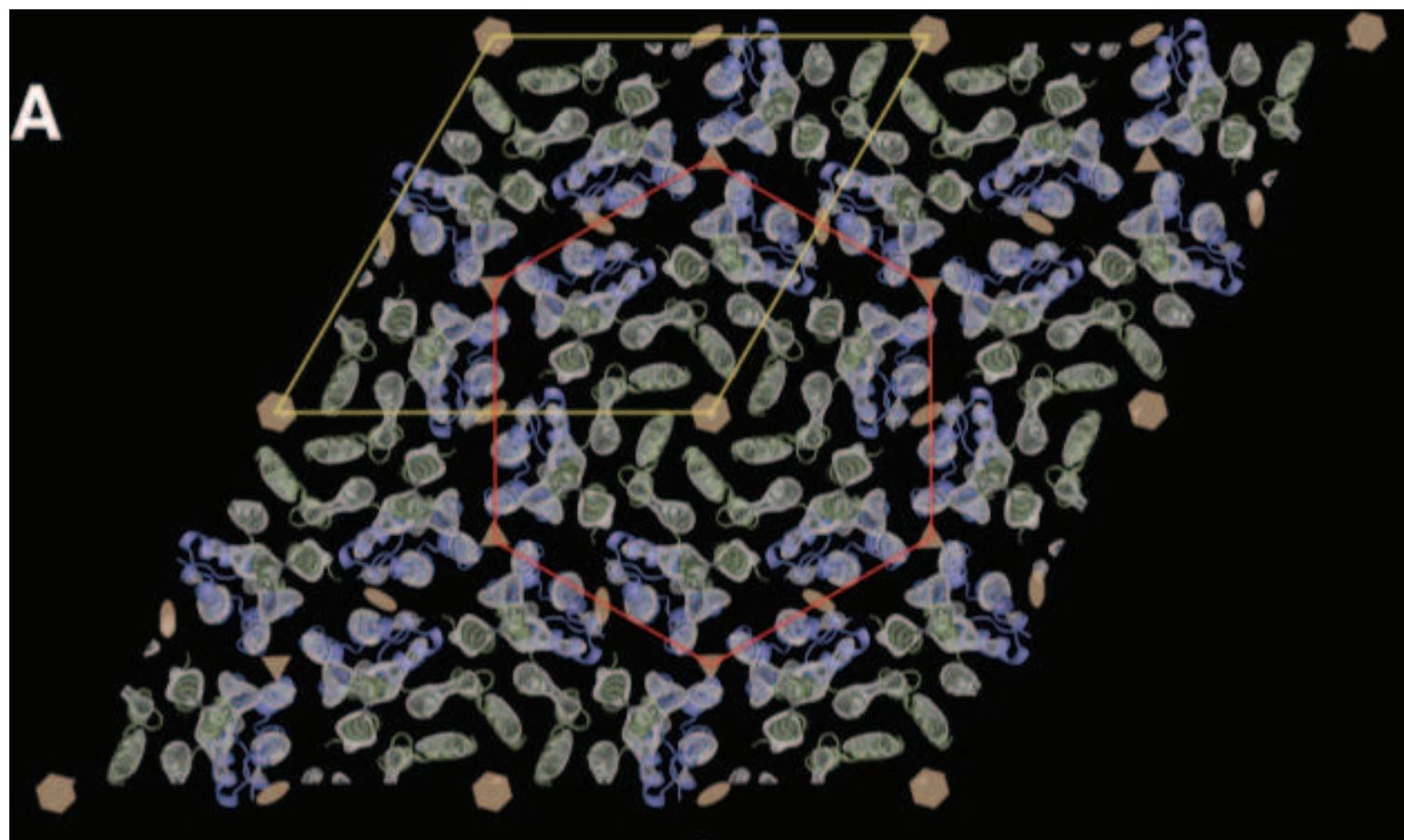


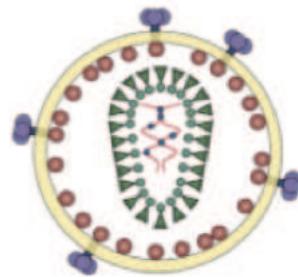
NMR solution  
structure model of  
the building block  
of the mature  
capsid



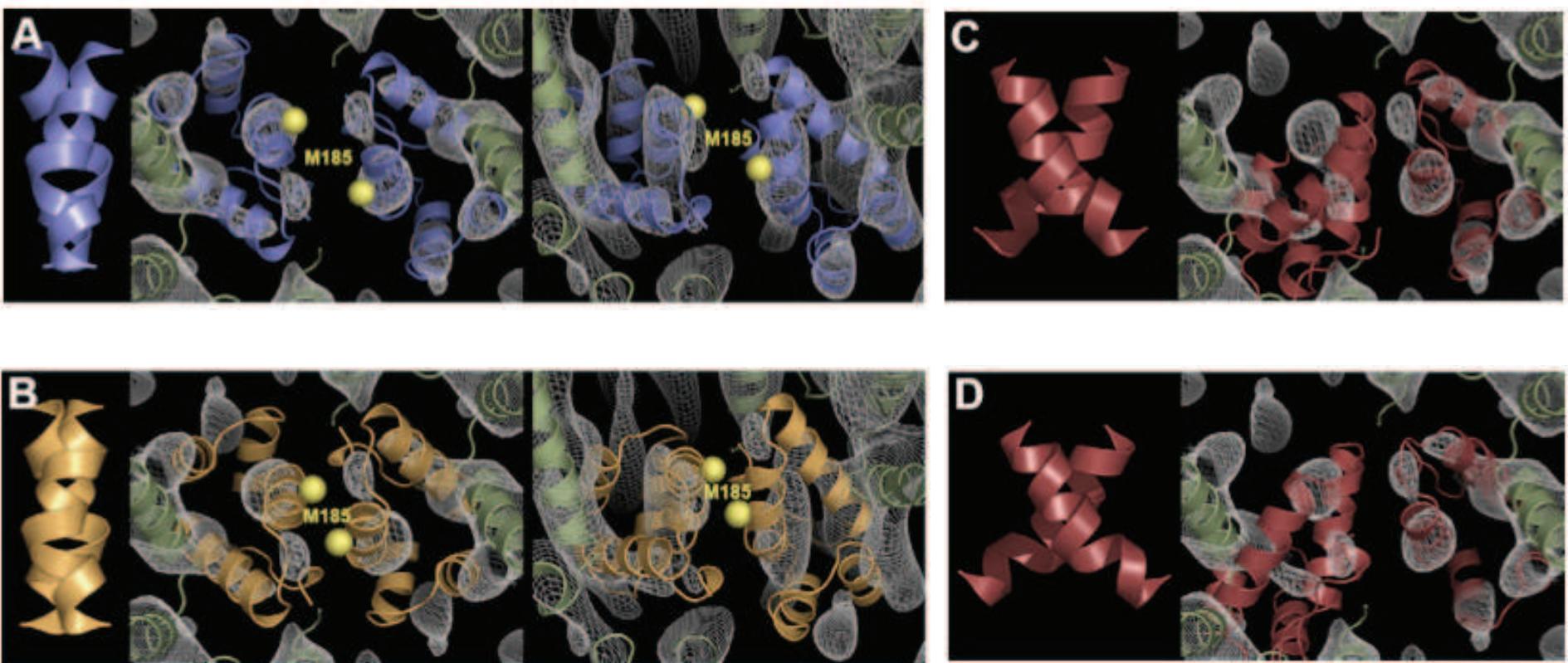


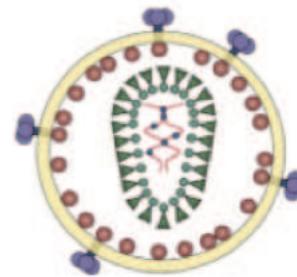
Previous data: hexameric arrays of CA at 9Å resolution



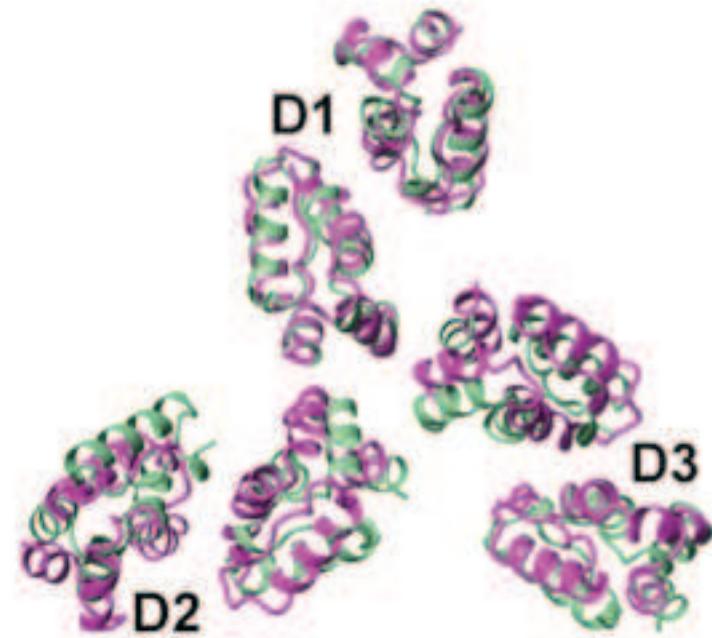
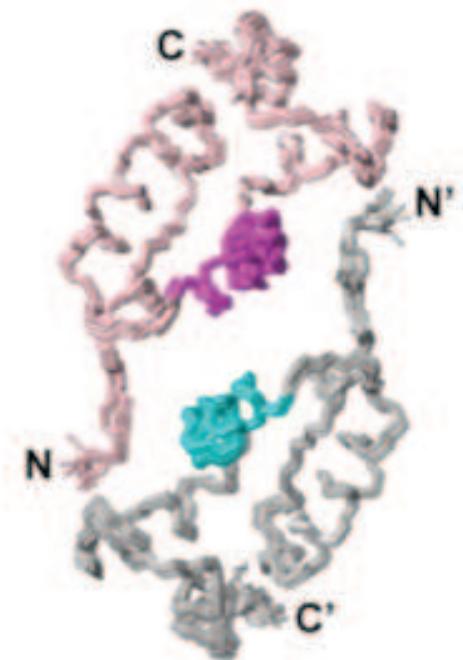


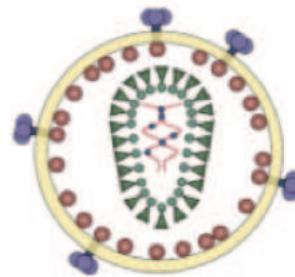
Previous X-ray and NMR models could not fit well into the 9 $\text{\AA}$  EM density map



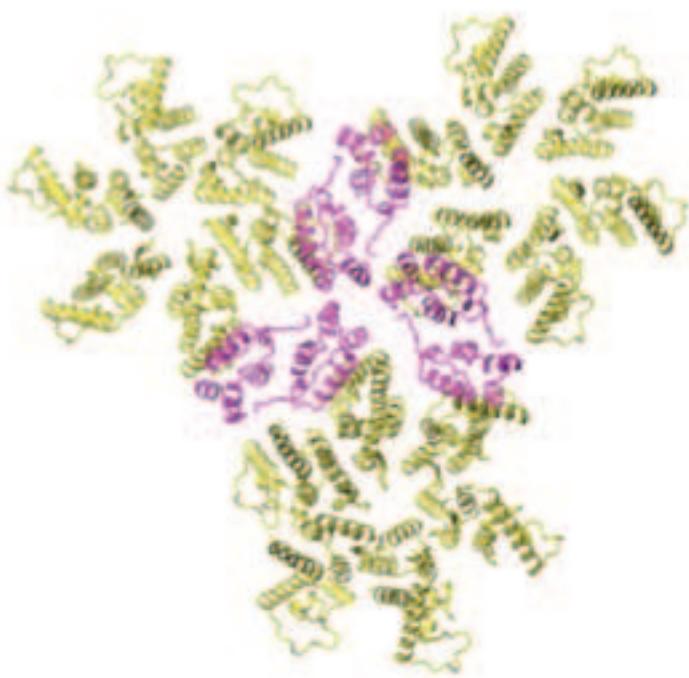


Current model (left) fits well into the 9Å EM reconstruction data (right, magenta)



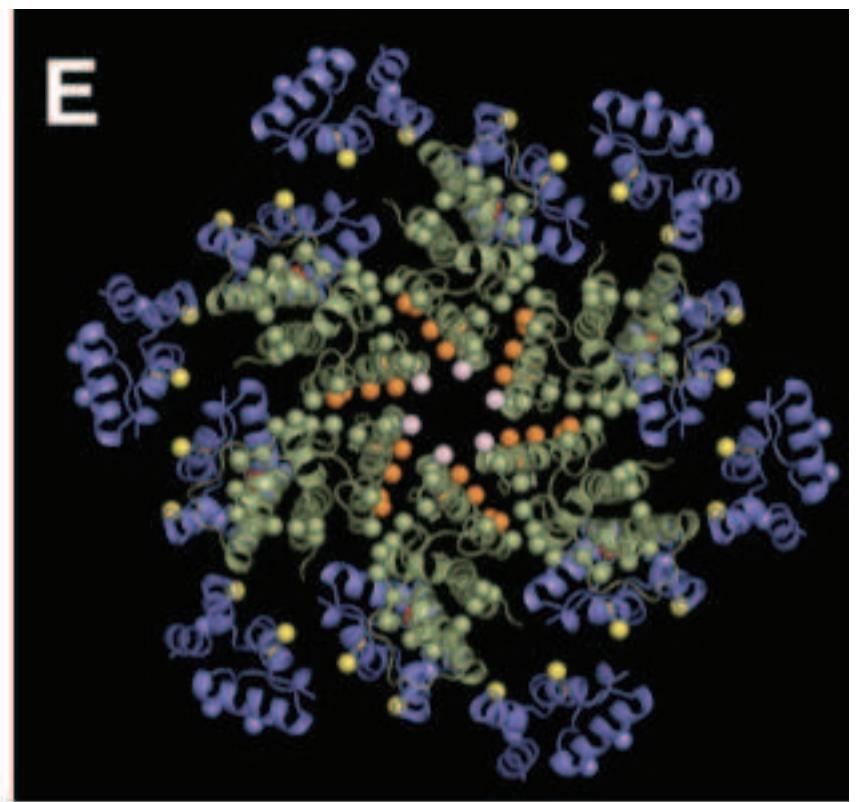


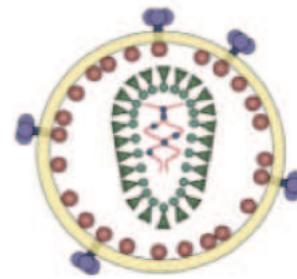
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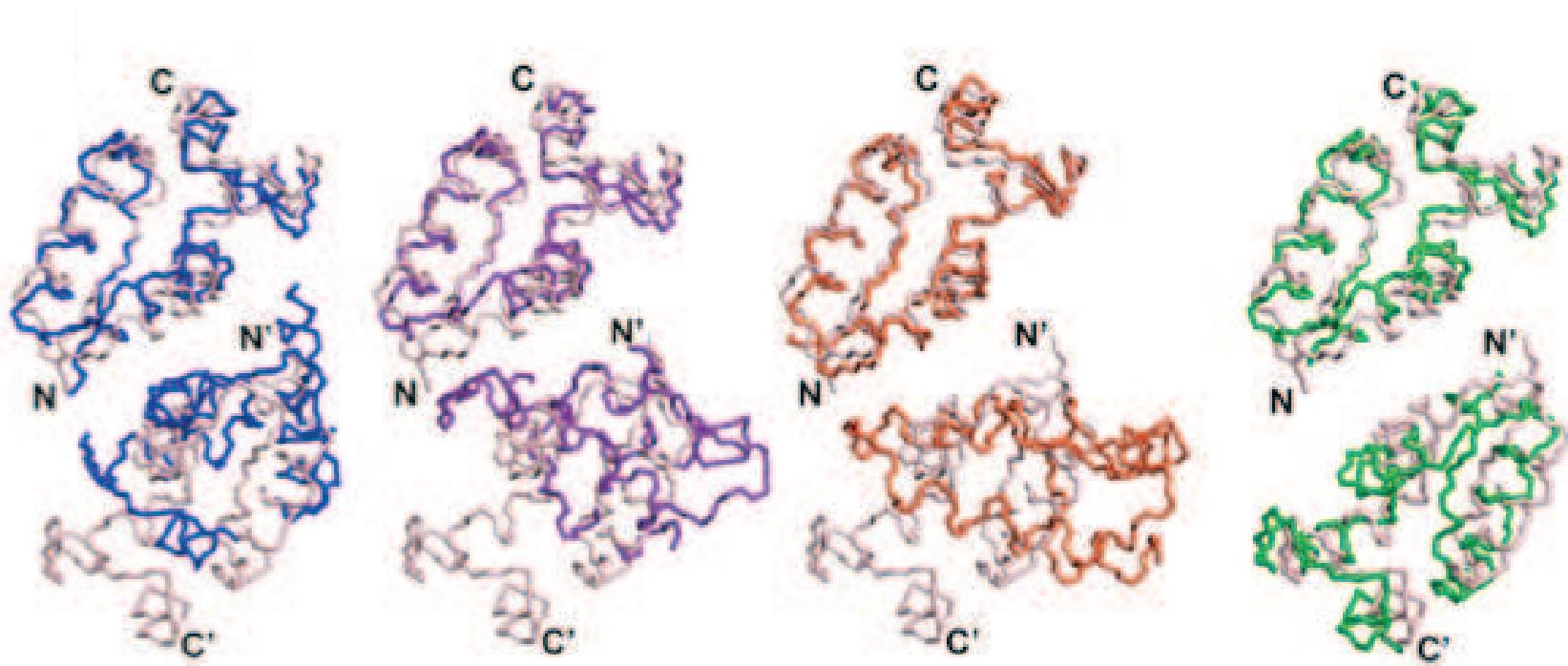
Byeon et al., Cell, 139, 780, (2009)

Ganser-Pornillos et al., Cell, 131, 70, (2007)



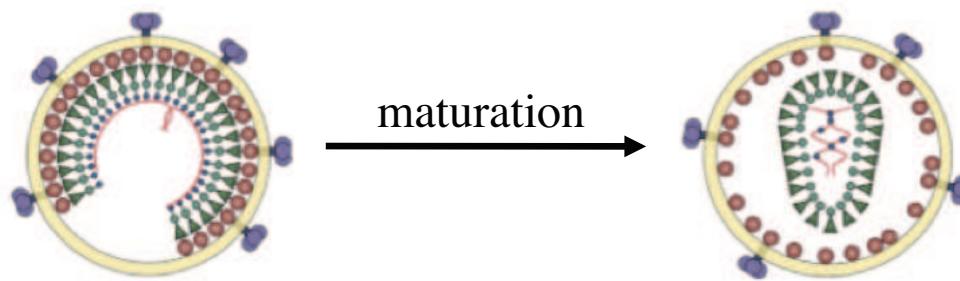


Comparison between current NMR data (pink)  
and previous data



How do you go from a “flat” organization to a spherical assembly?

Why does the virus take the trouble of building the core particle?



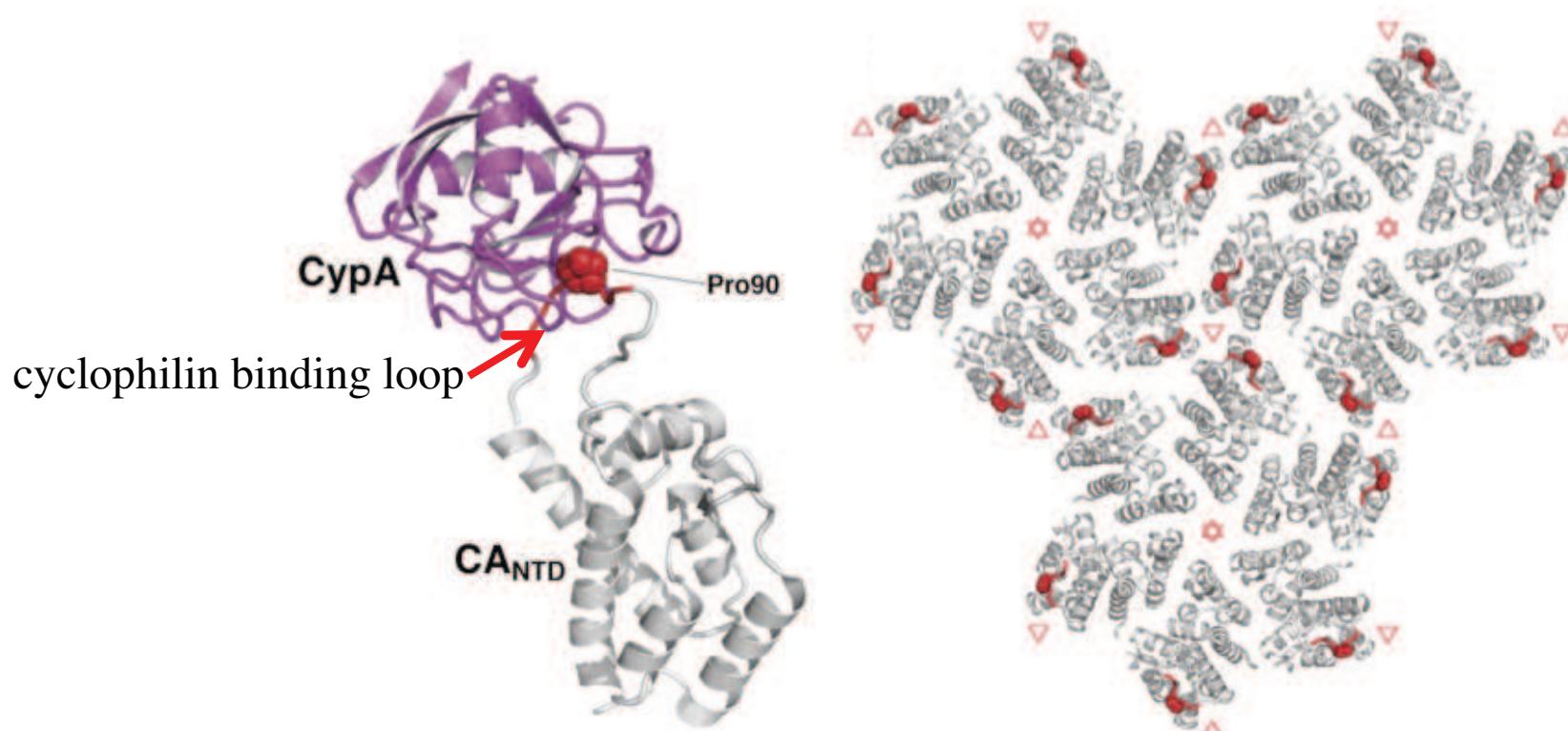
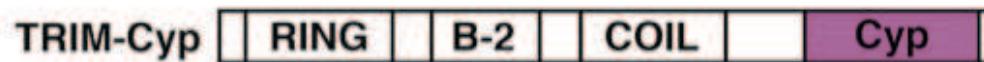
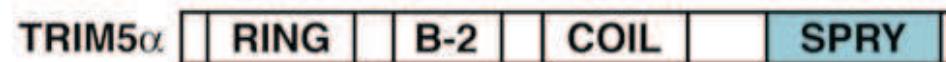
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How does it look like ?

# TRIM-Cyp is a close homologue of TRIM5 $\alpha$

Cyp is a peptidyl prolyl isomerase

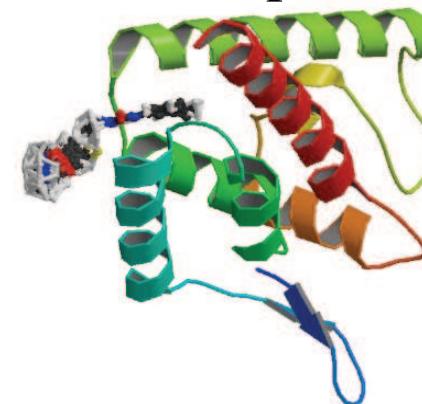


# Novel HIV-1 inhibitors

-viral protease (PR) inhibitors stop Gag processing by PR



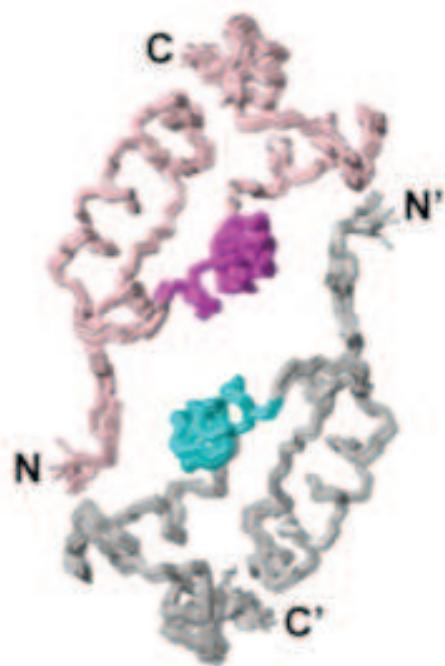
- methylphenylurea compounds (CAP-1) bind to processed CA and inhibit capsid assembly



Kelly et al., JMB, 373, 355, (2007)

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How was CACTD dimer structure determined by NMR?

...to be continued in Lecture 3