Structural insights into the molecular arms race between HIV-1 Vif and APOBEC3G

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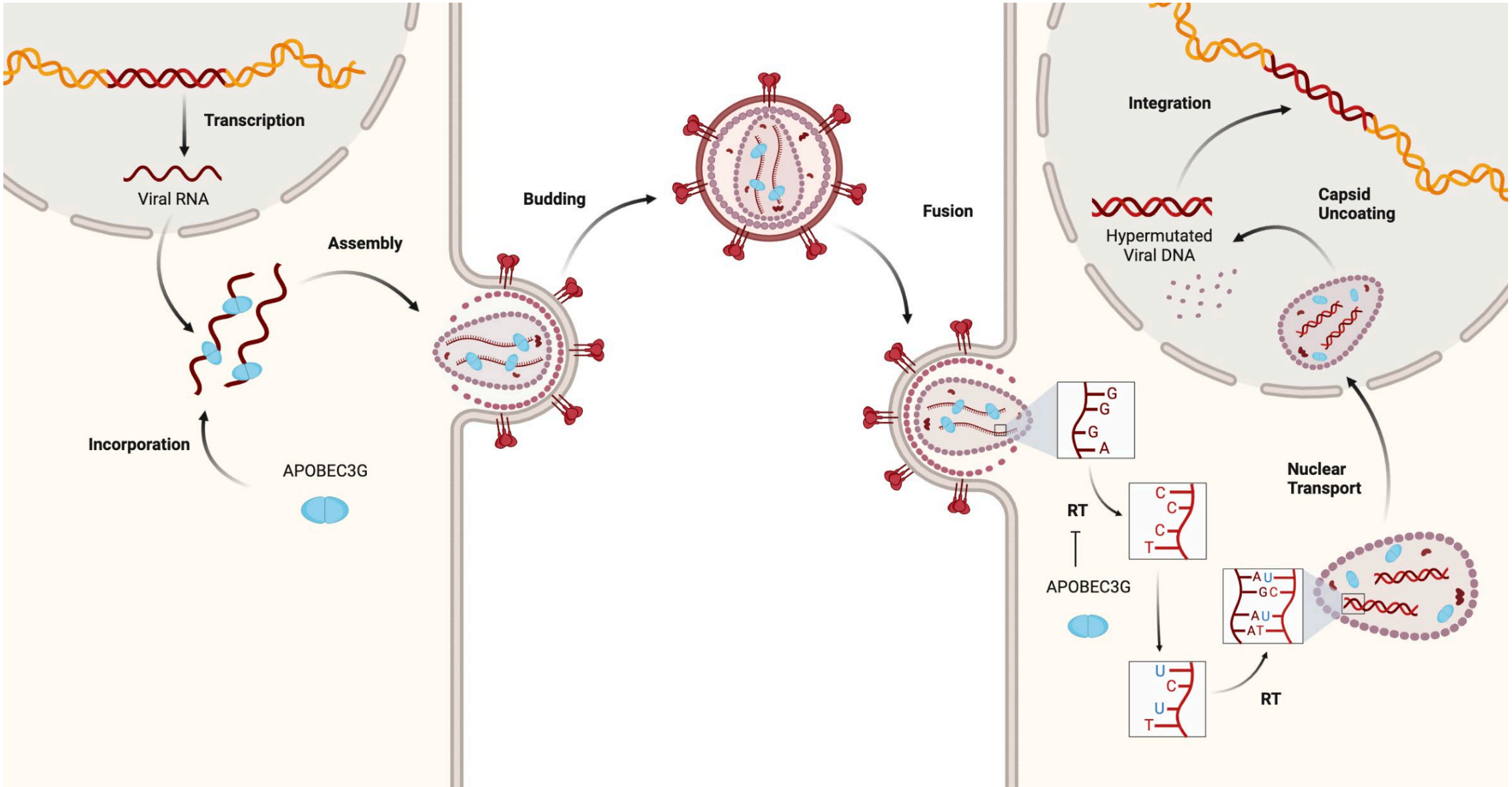
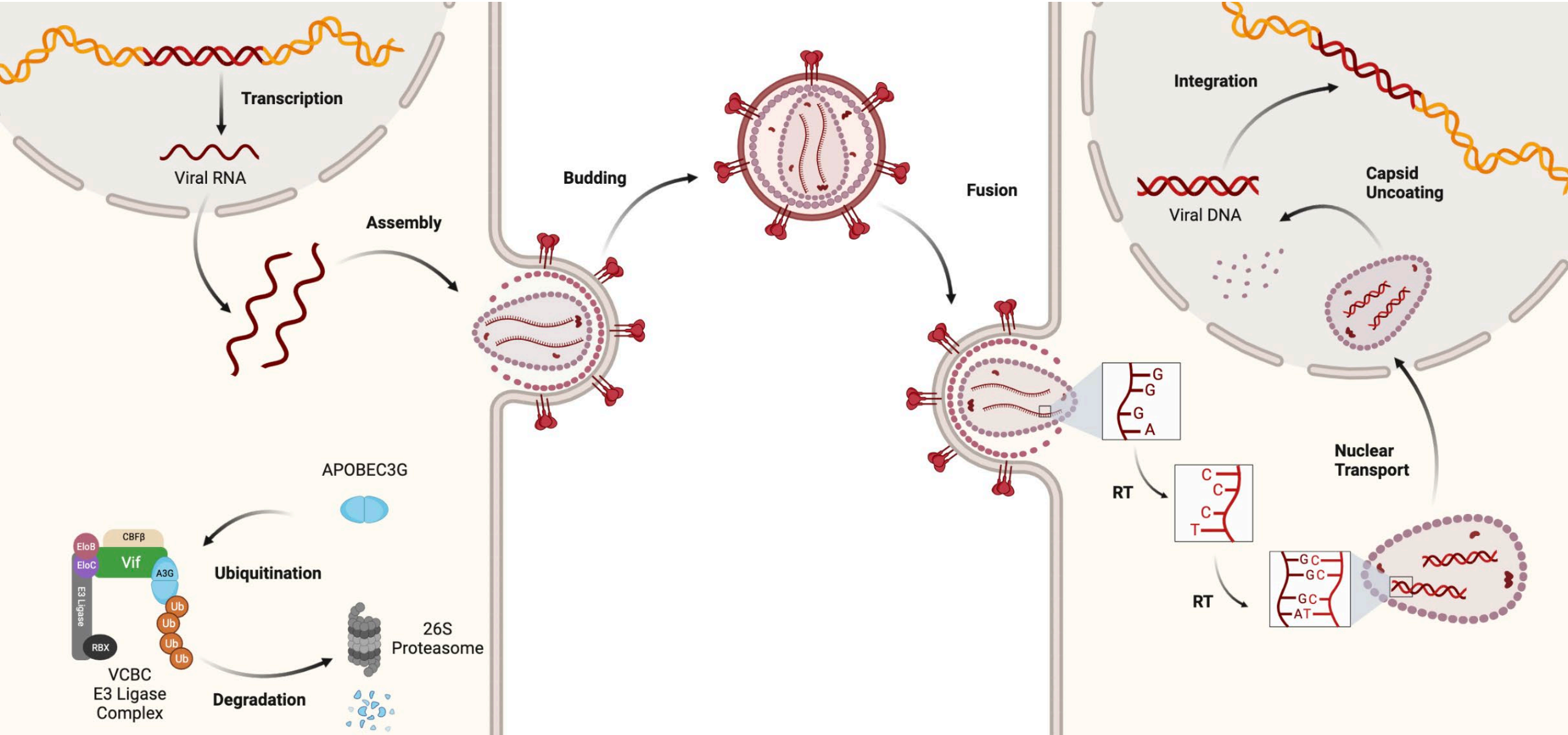
HARC
HIV Accessory &
Regulatory Complexes

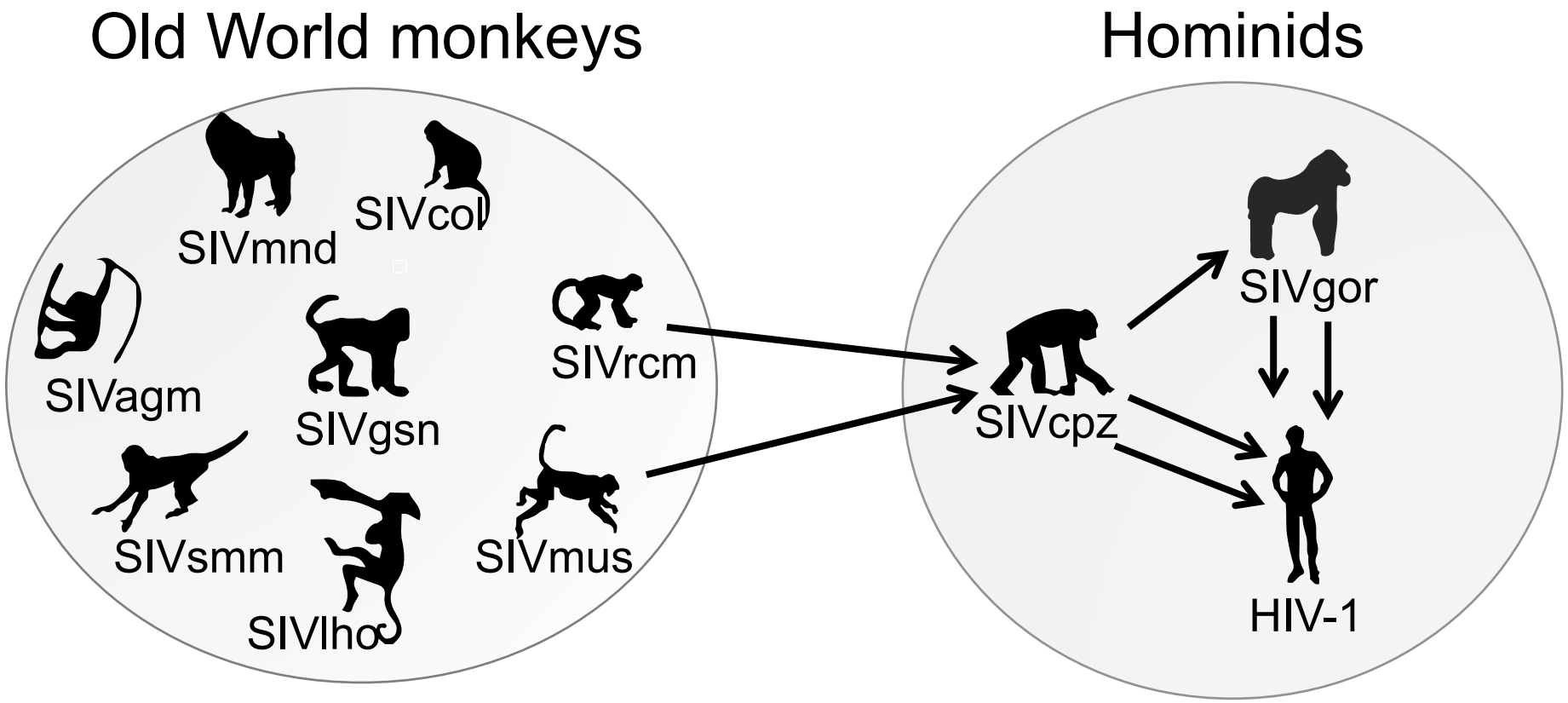
APOBEC3G (A3G) blocks retroviral replication



Vif antagonizes A3G by targeting it for degradation

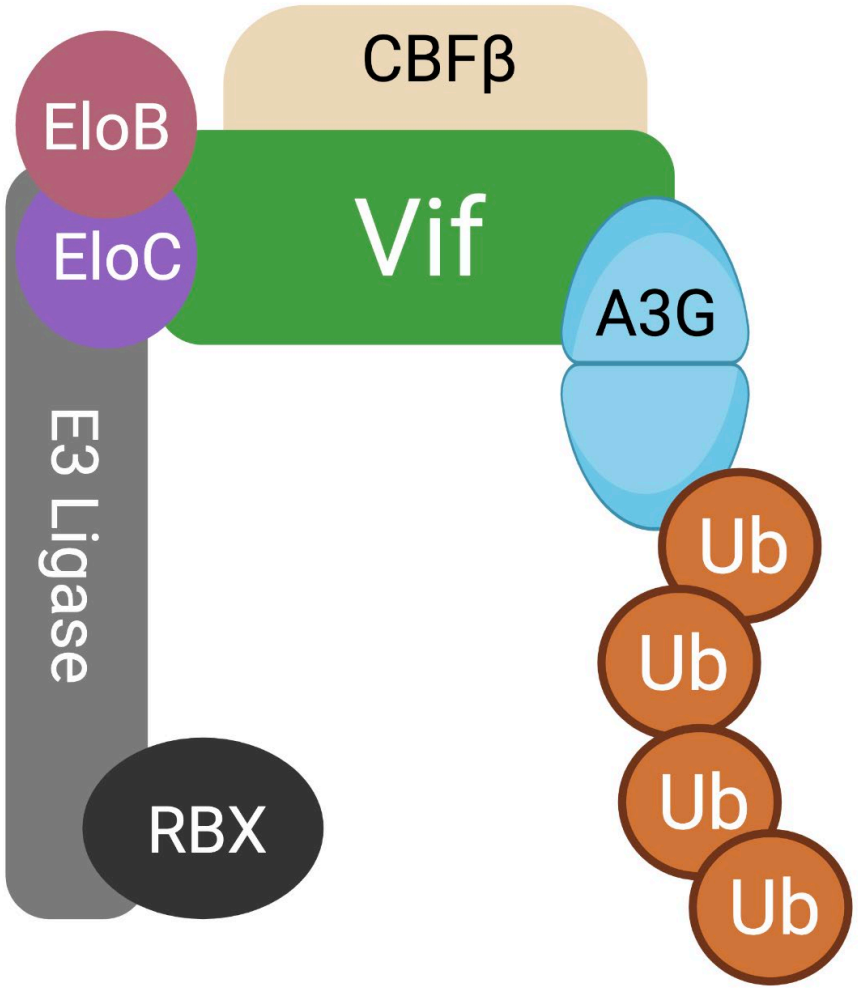


The Vif-A3 arms race defines cross species events



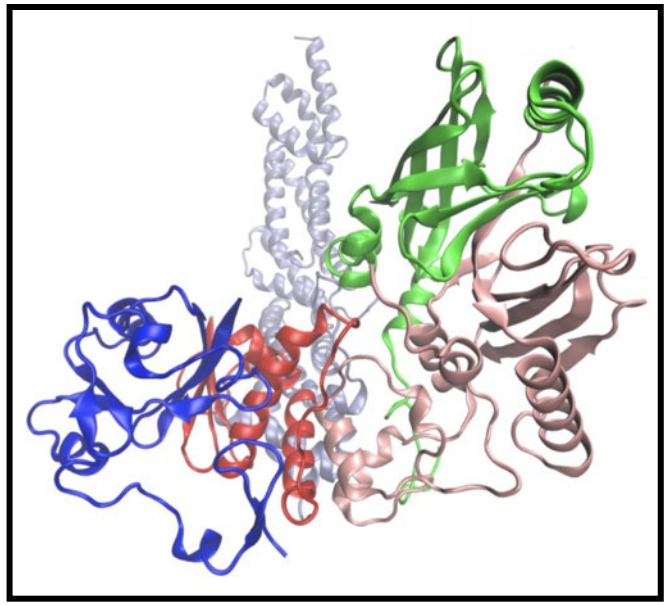
How can we better understand the constraints human A3 genes have on HIV-1 vif evolution?

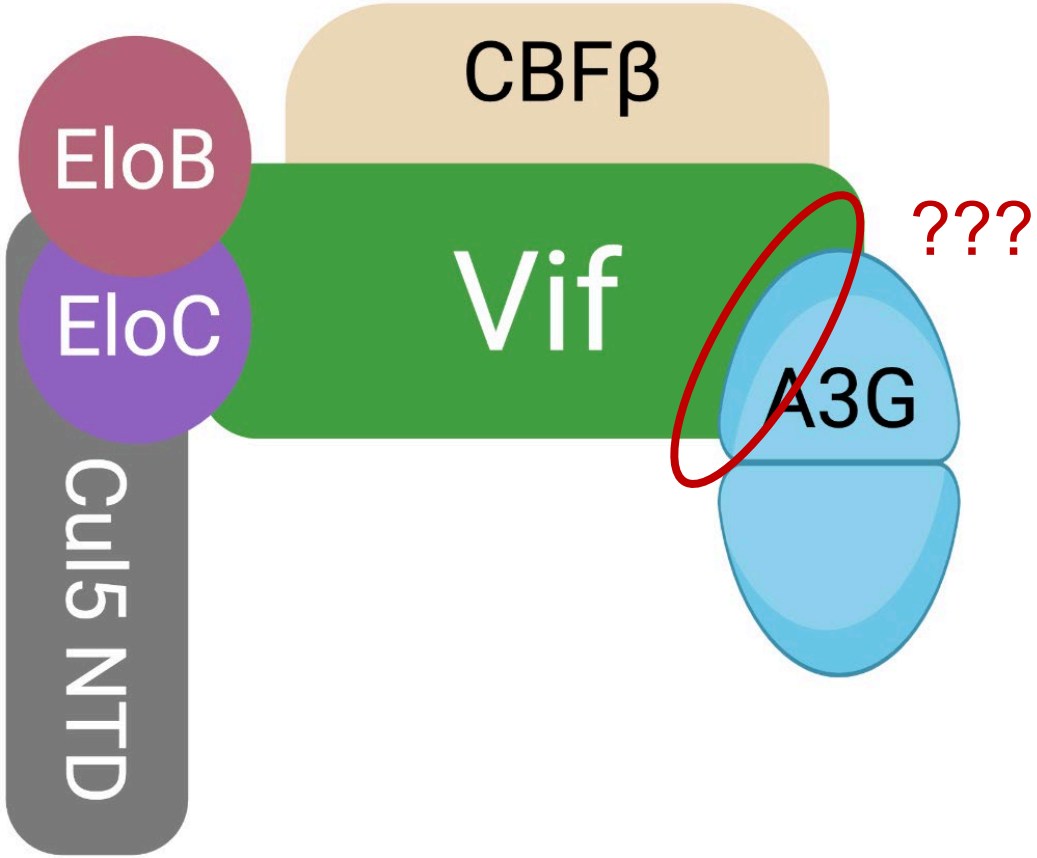
Vif Ub-dependent degradation of A3 requires formation of E3 Ligase



Yu et al, Science, 2003
Jaeger et al, Nature 2011
Zhang et al, Nature 2011

Vif Ub-dependent degradation of A3 requires formation of E3 ligase

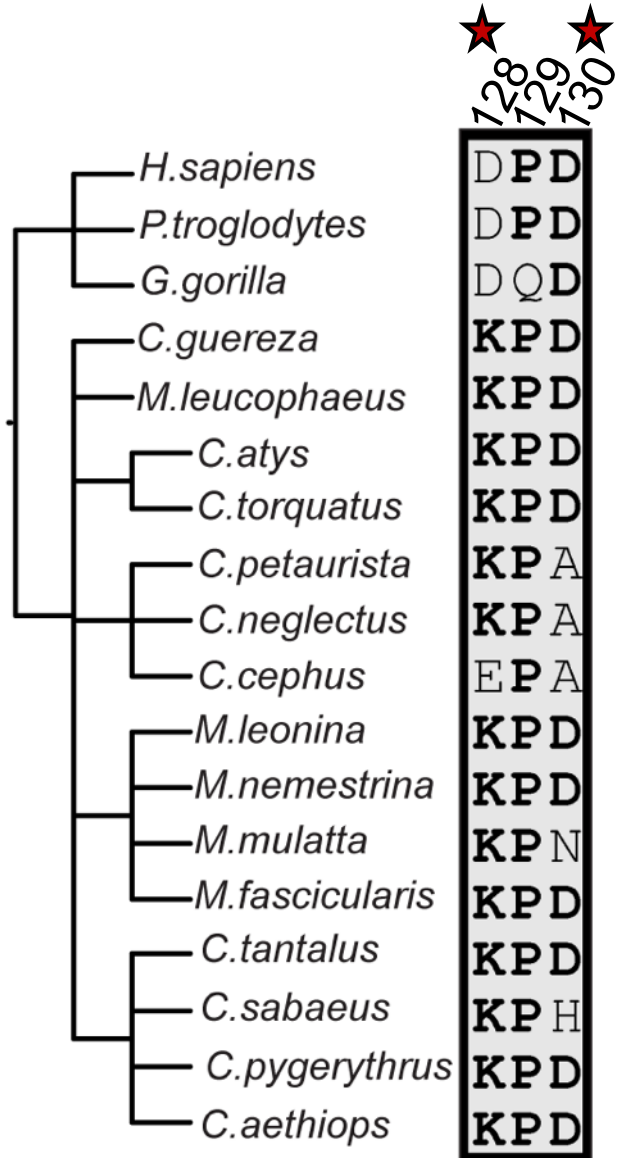




Guo, Nature 2014

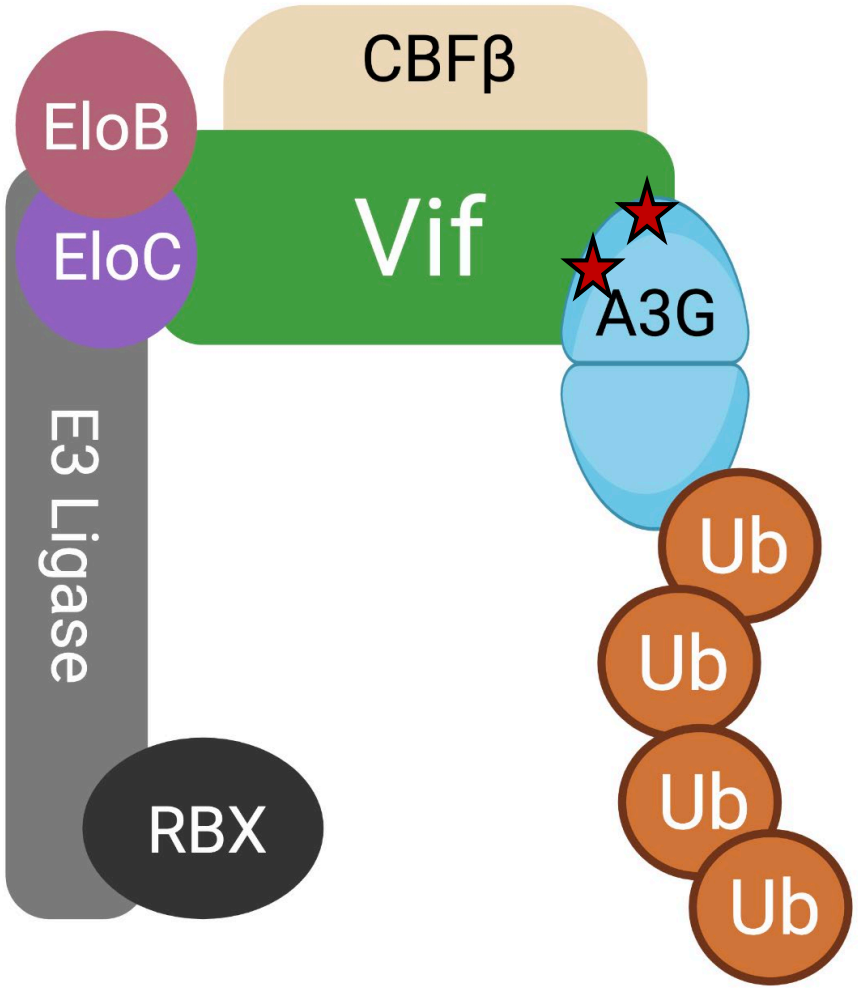
Vif ub-dependent degradation of A3 requires formation of E3 complex

A3G sequence diversity



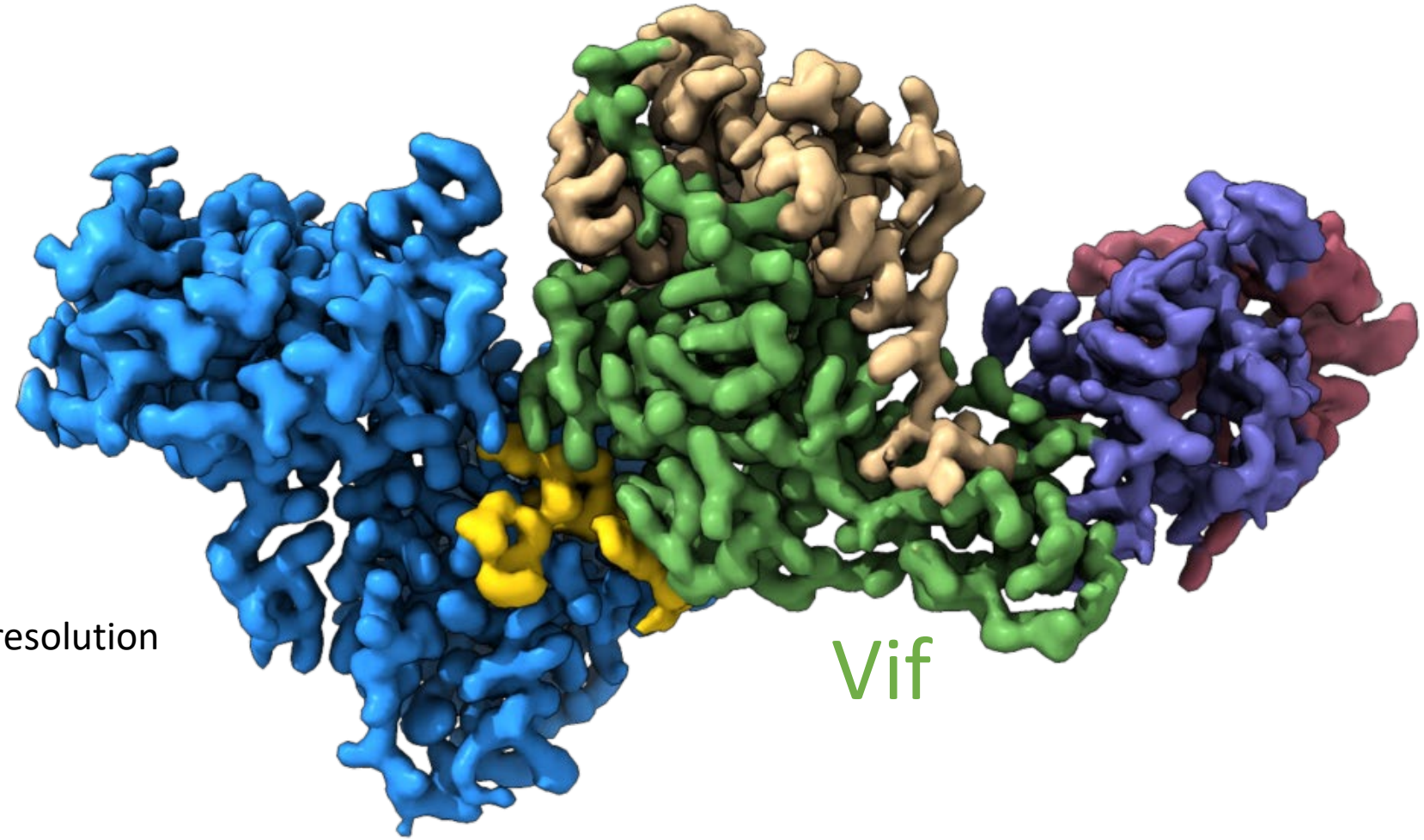
Convergence and Divergence in the Evolution of the APOBEC3G-Vif Interaction Reveal Ancient Origins of Simian Immunodeficiency Viruses

Alex A. Compton[1,2], Michael Emerman[2*]



2 A3G residues in evolutionary conflict with Vif

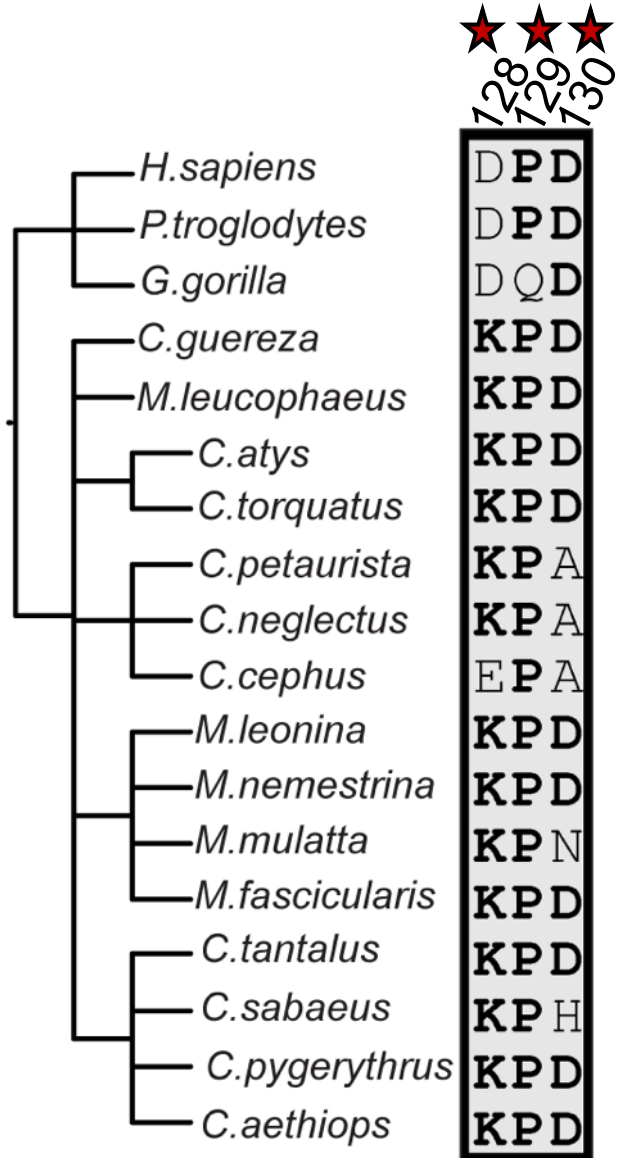
CryoEM Structure of human A3G bound to HIV-1 Vif



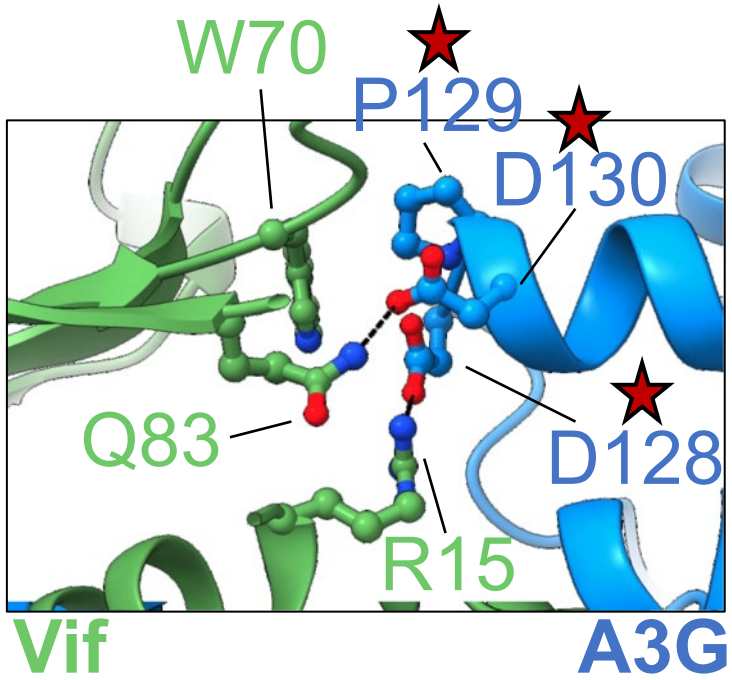
2.7 Å resolution

A3G 128-130 determines Vif species specificity

A3G sequence diversity

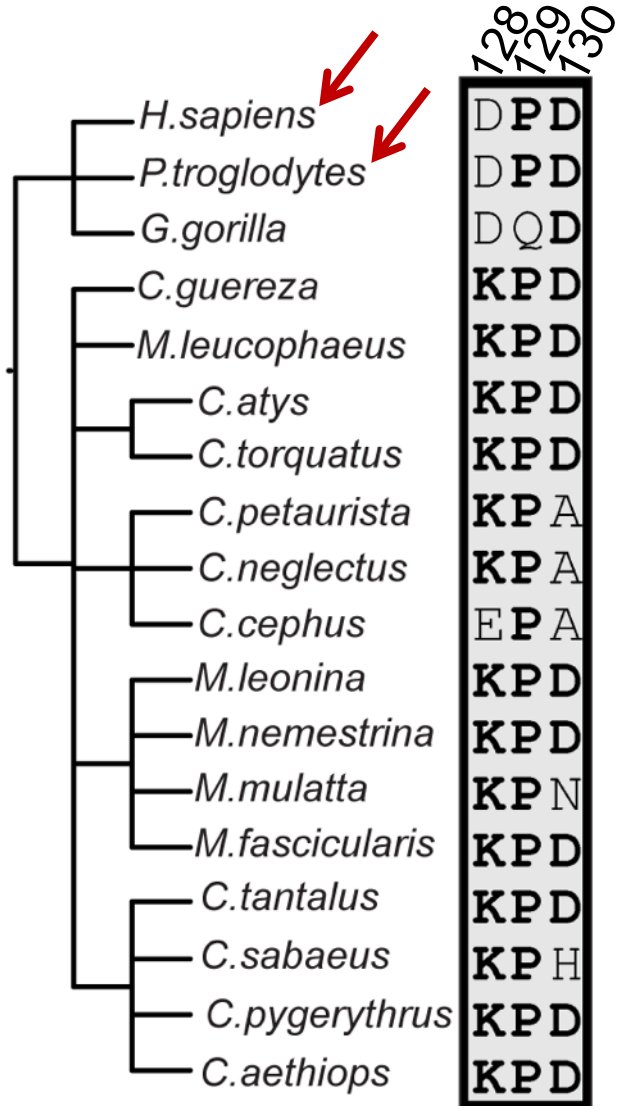


arms race interface



SIVrcm Vif was poised for cross species spillover

A3G residues in the arms race



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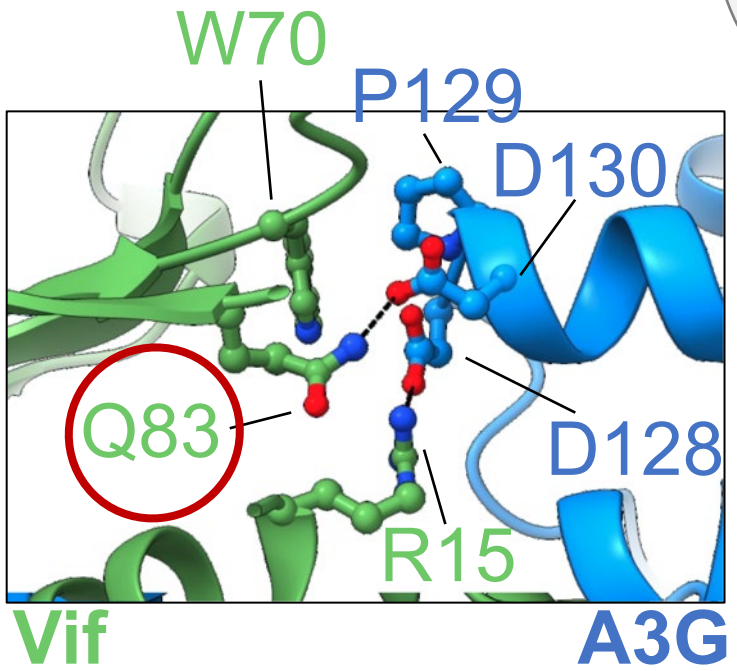

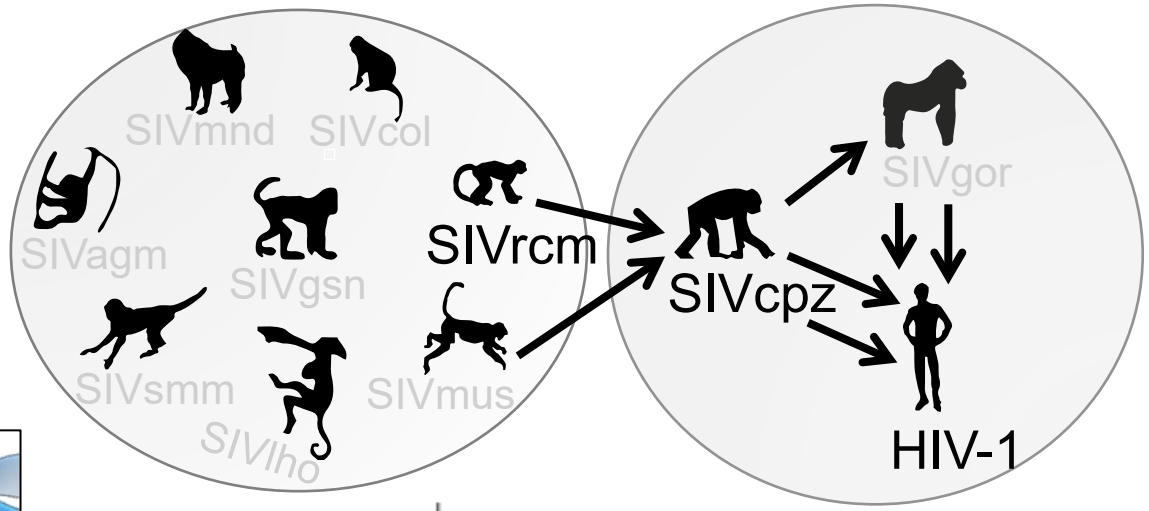

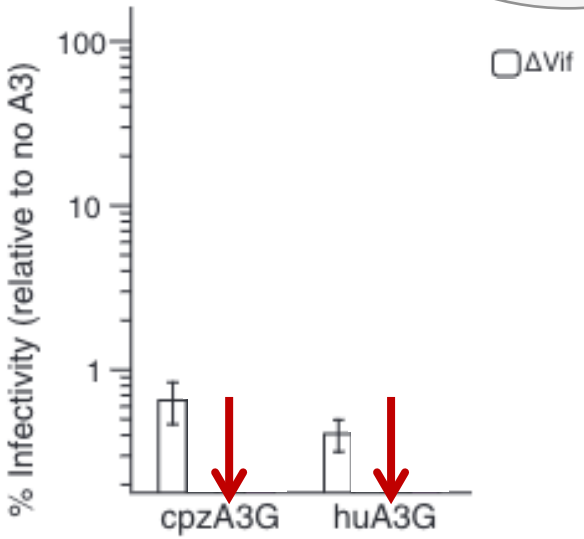

Structural Basis for a Species-Specific Determinant of an SIV Vif Protein toward Hominid APOBEC3G Antagonism

Jennifer M. Binning,[1] Nicholas M. Chesarino,[2] Michael Emerman,[2,*] and John D. Gross[1,3,*]

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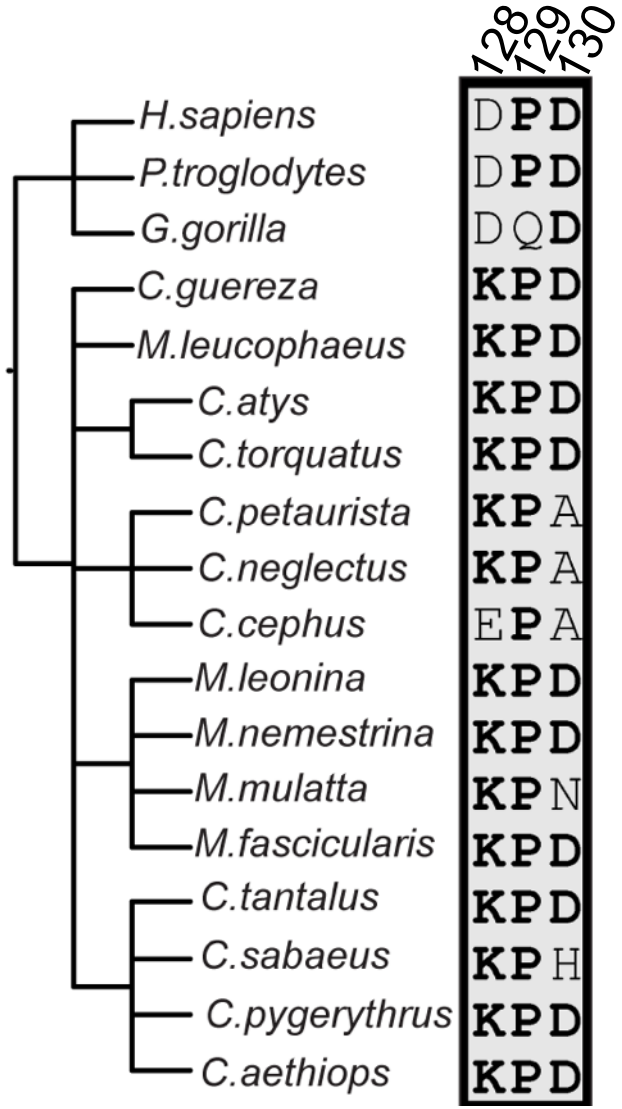
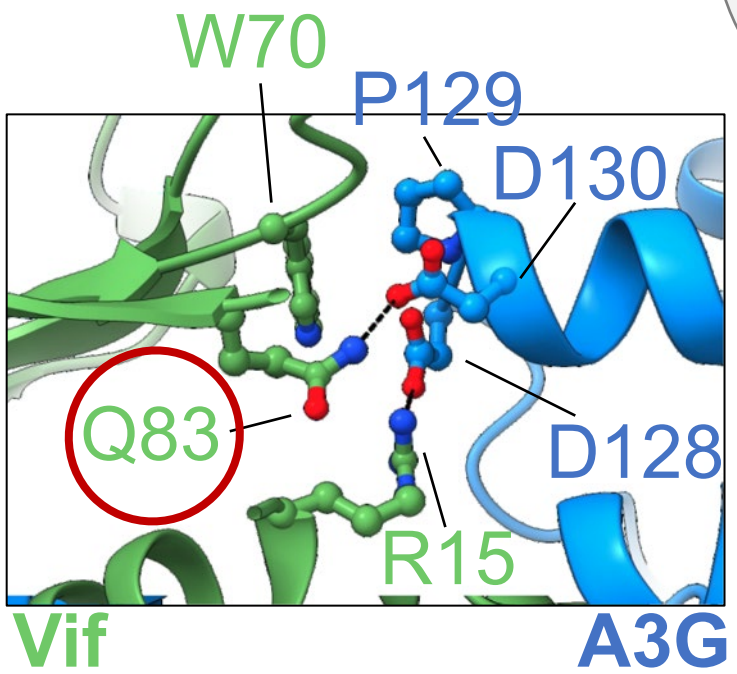
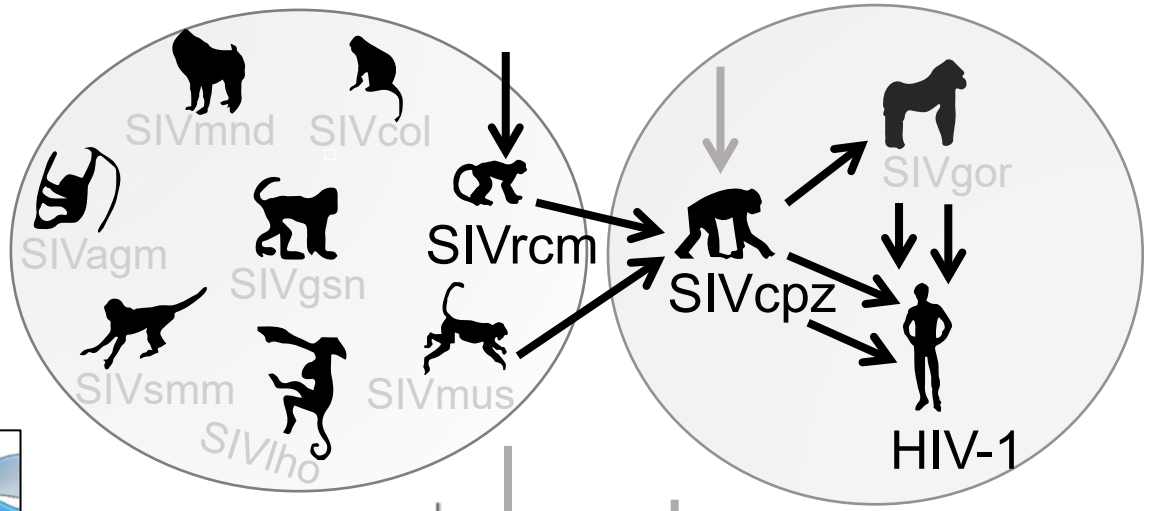
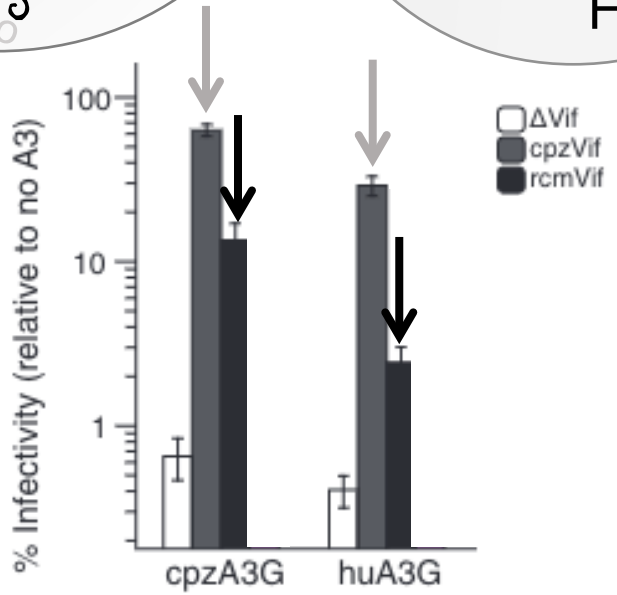
A3G residues in the arms race



arms race interface







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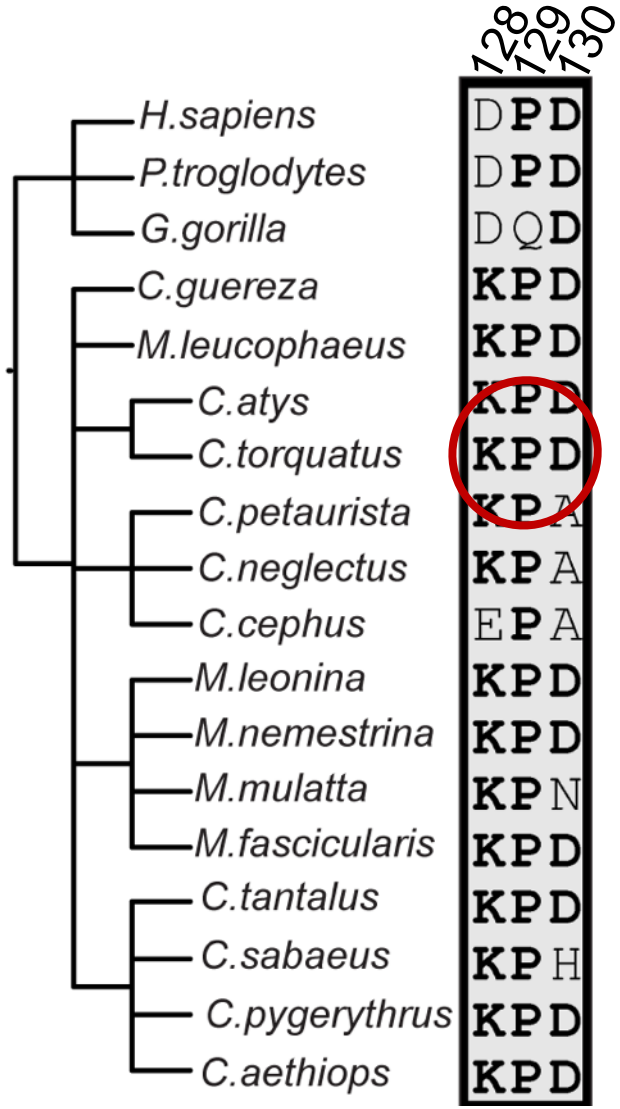
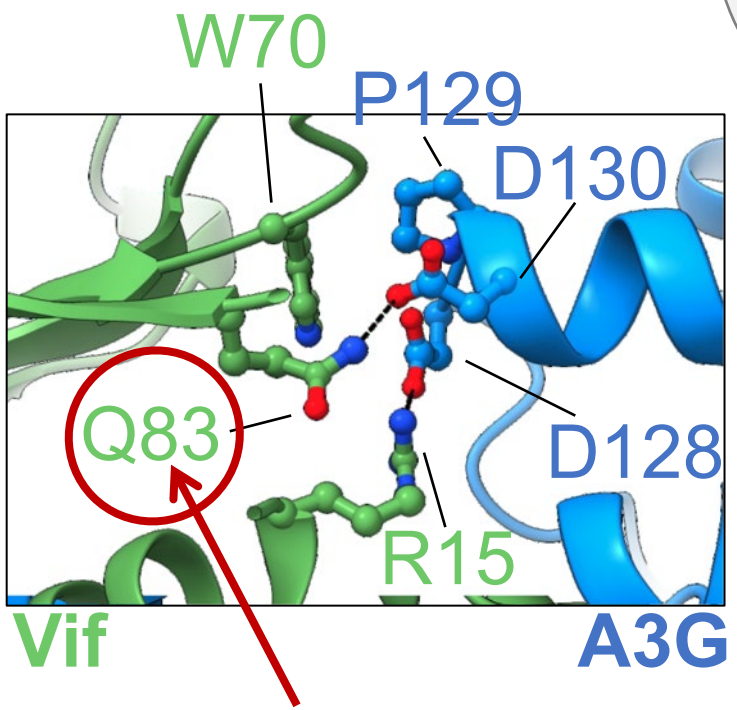
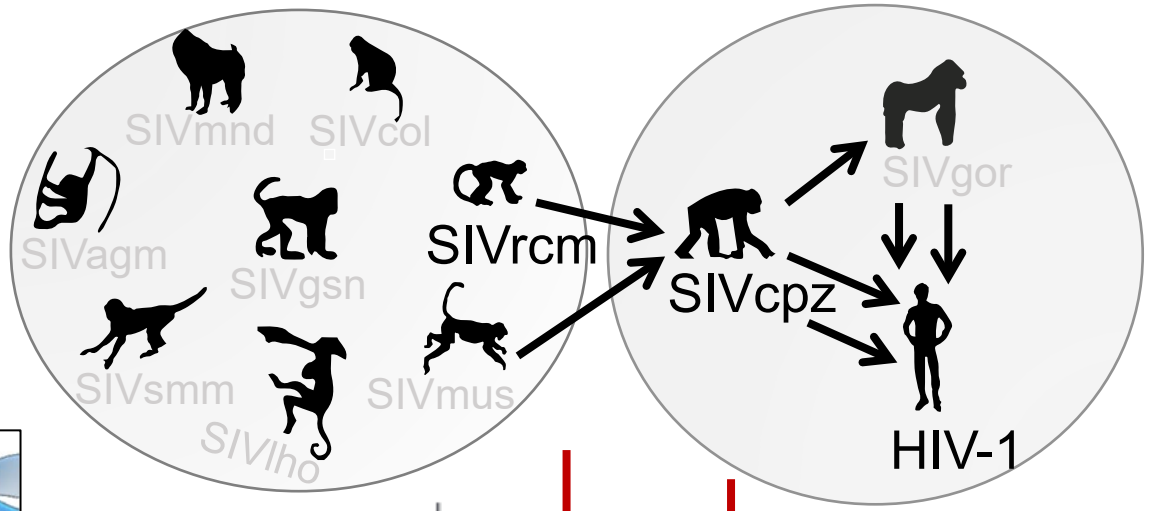
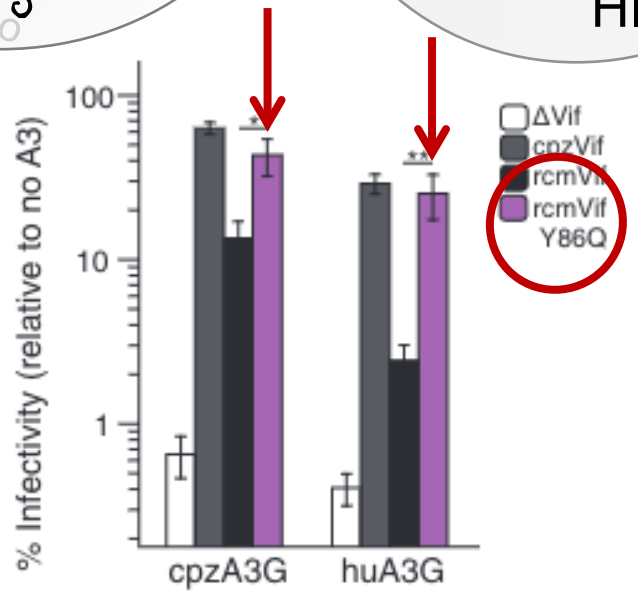


arms race interface





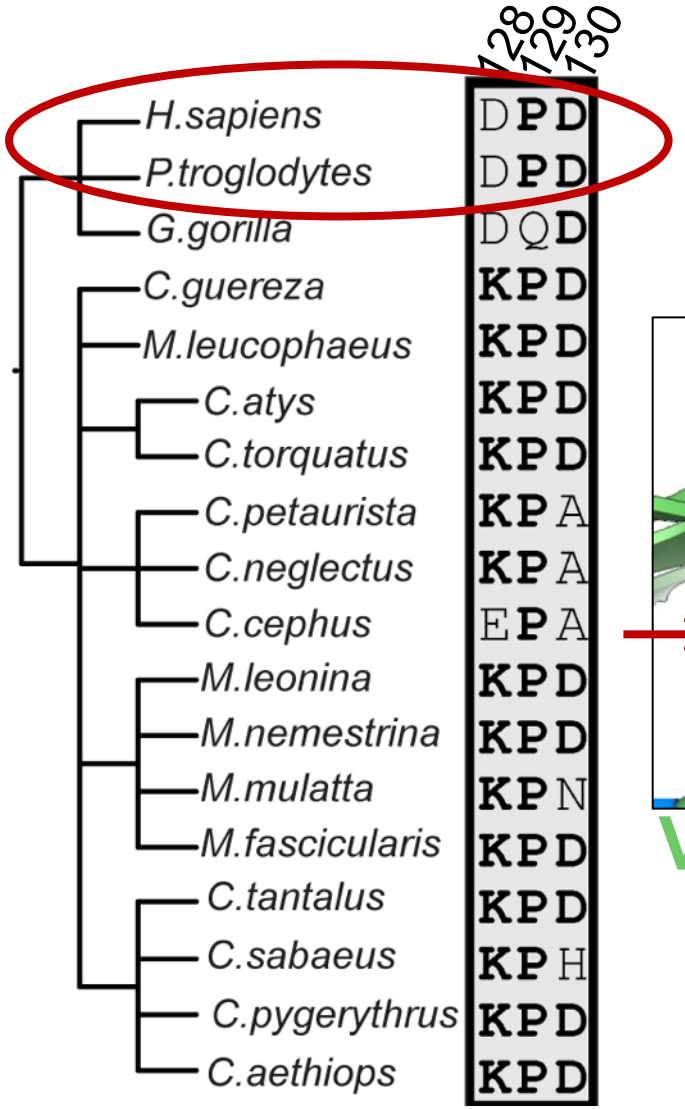


evolutionary analysis 🤝 structural biology

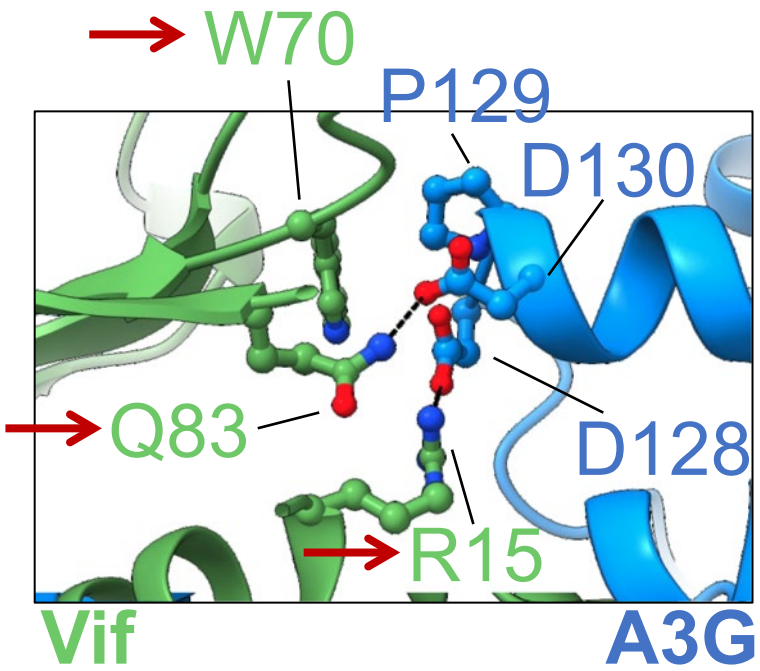
Jennifer M. Binning,[1] Nicholas M. Chesarino,[2] Michael Emerman,[2,*] and John D. Gross[1,3,*]

Arms race interface sequence identity is species specific

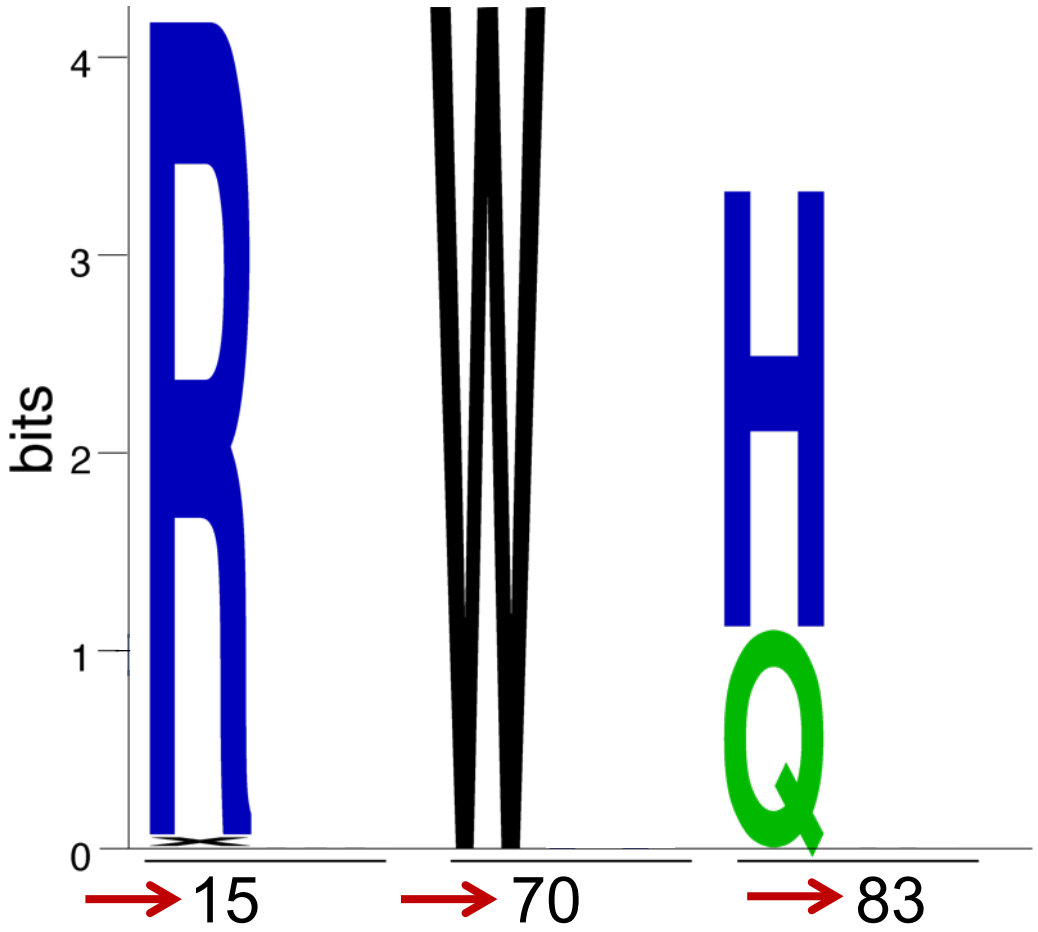
A3G residues in the arms race



arms race interface



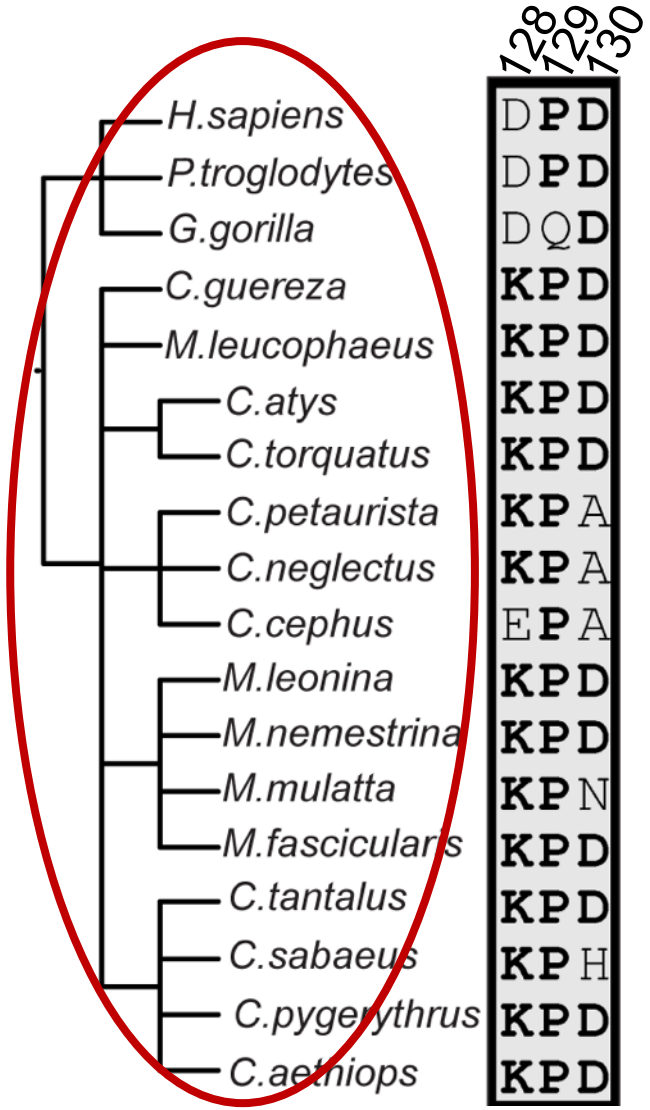
Vif residues in the arms race



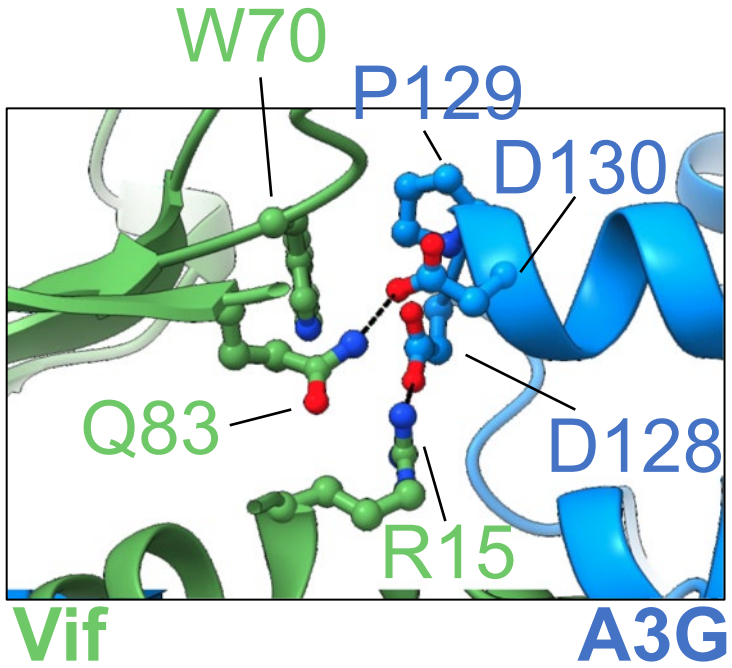
Using HIV-1 subtype and SIVcpz consensus sequences

Arms race interface sequence identity is species specific

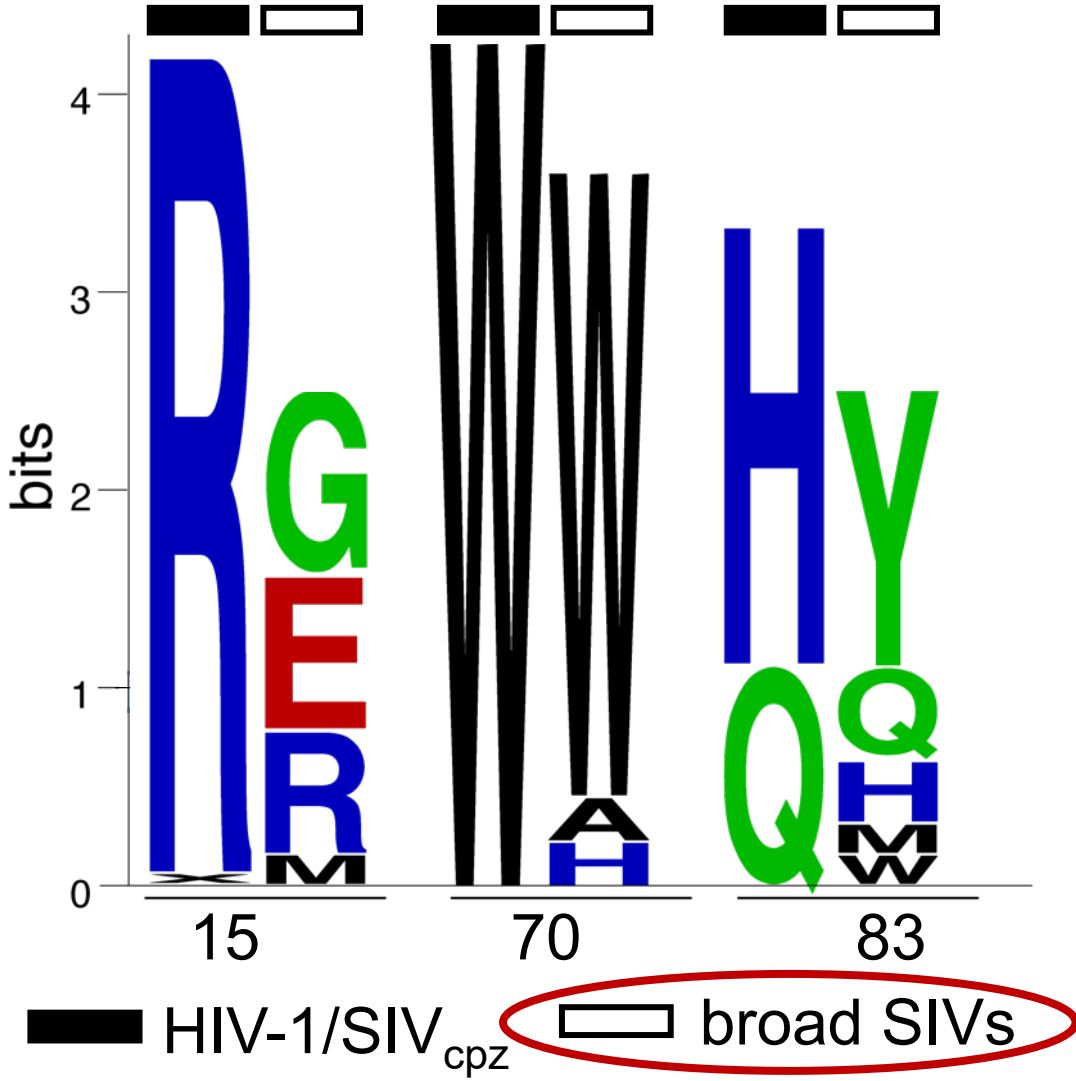
A3G residues in the arms race



arms race interface

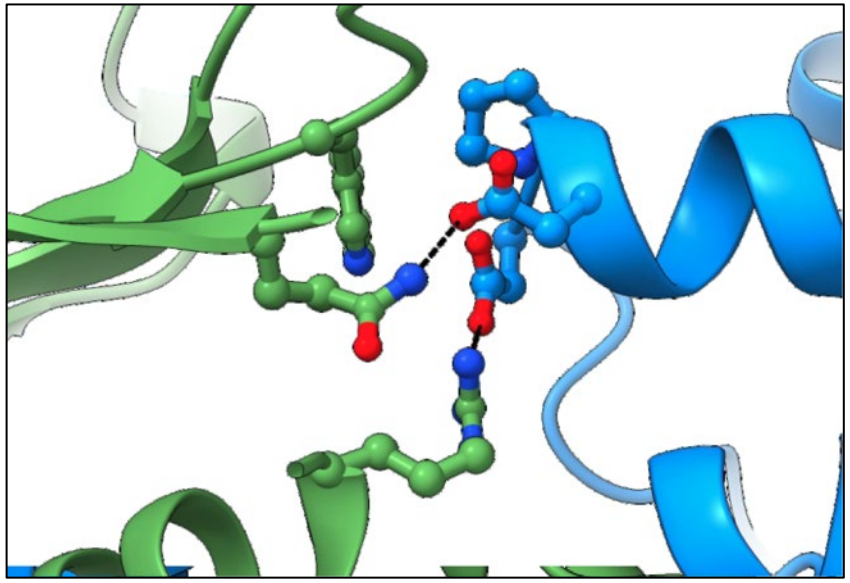


Vif residues in the arms race

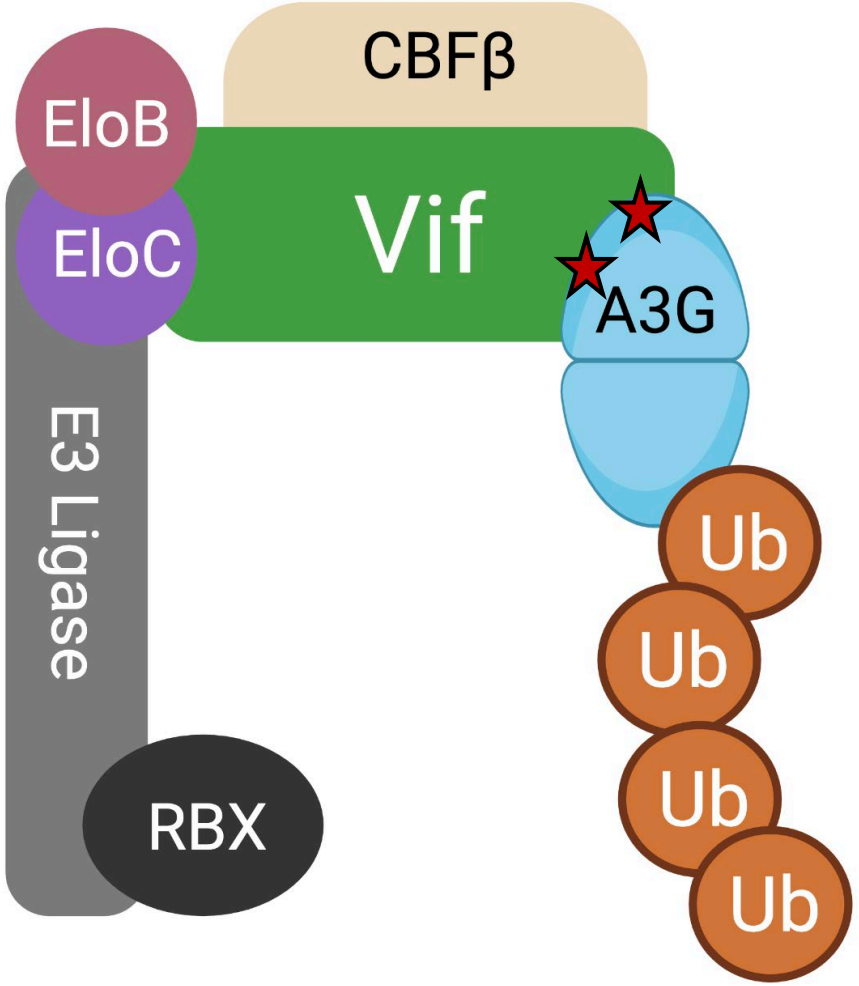


Is the arms race interface sufficient for Vif function?

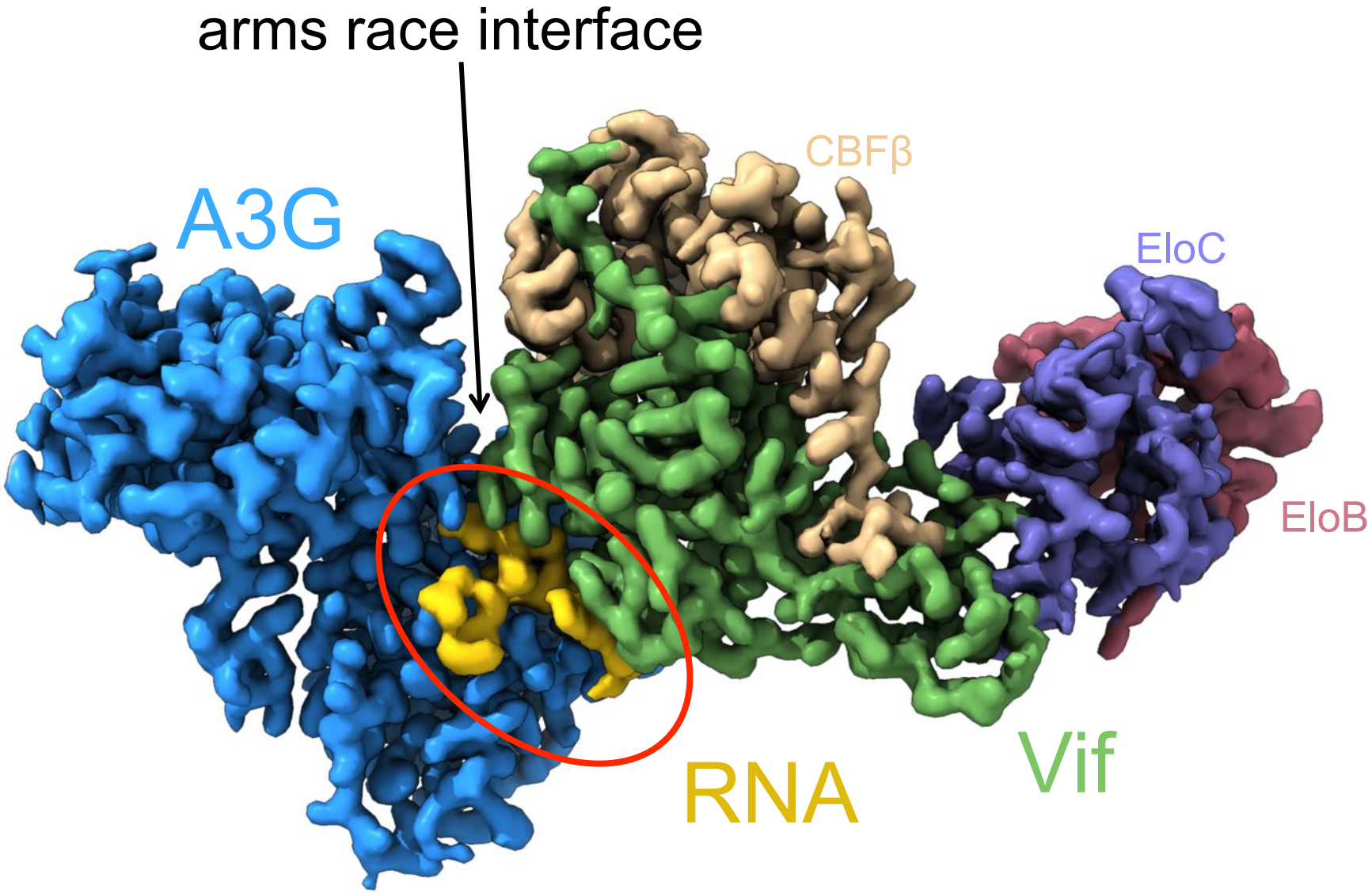
arms race interface



Vif A3G

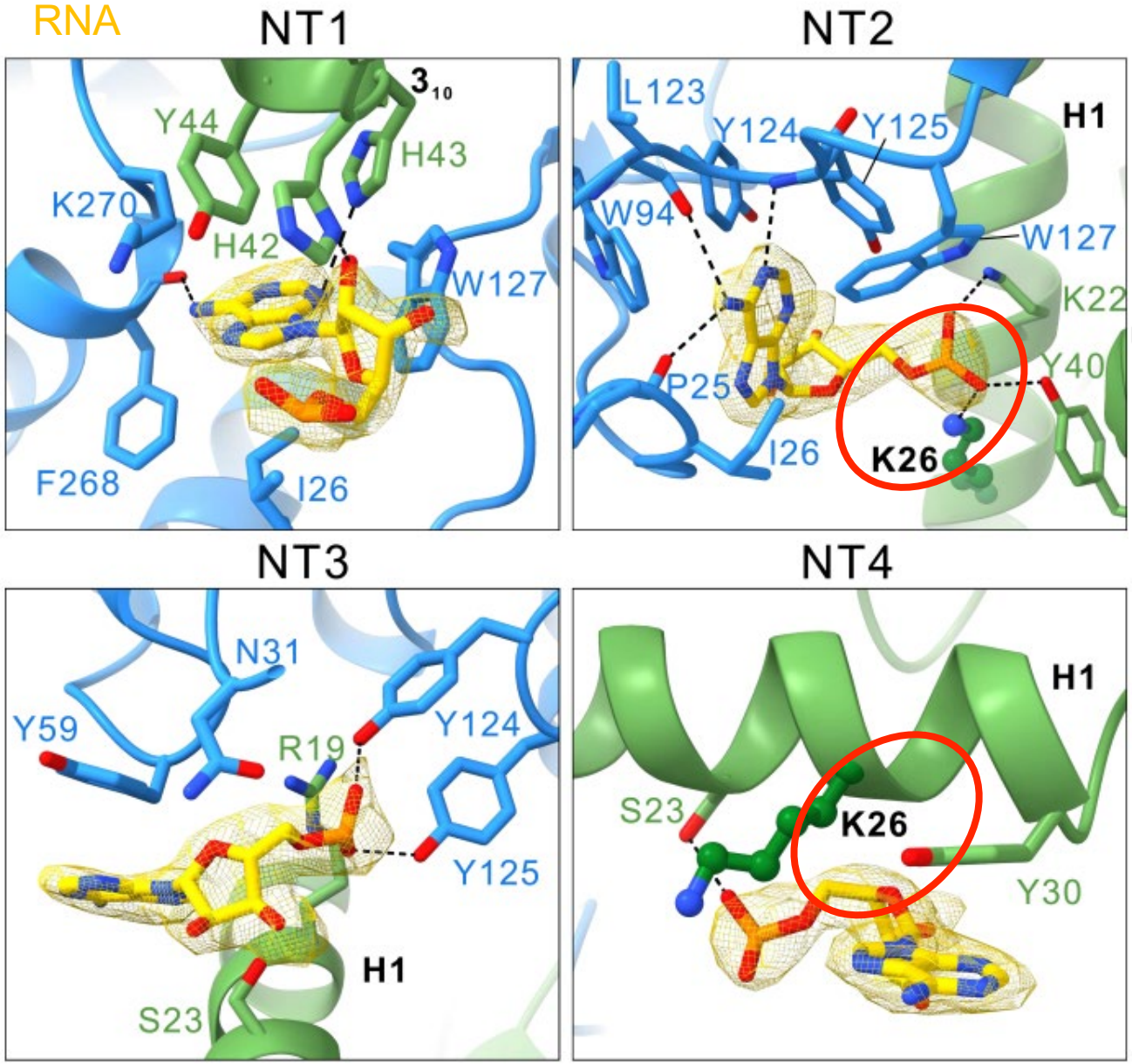


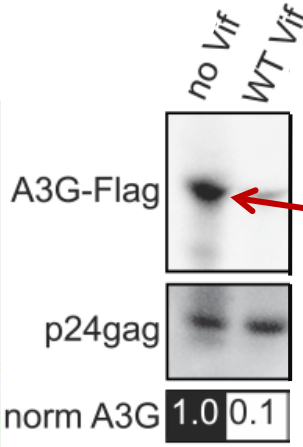
RNA copurified with Vif-A3G

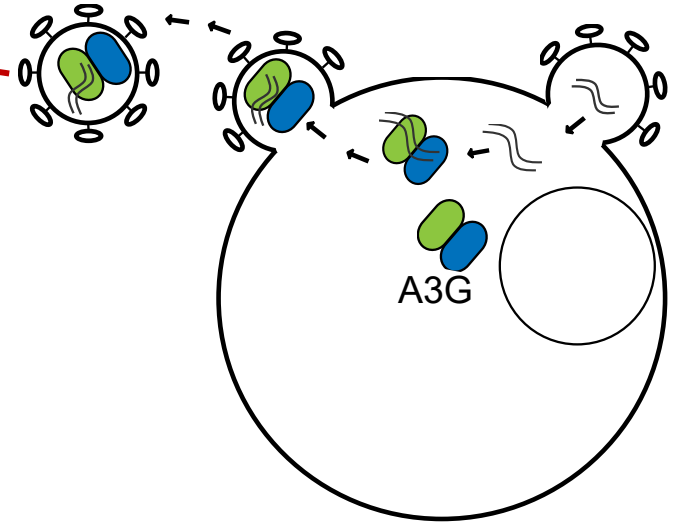


Testing the role of RNA

Vif
A3G
RNA

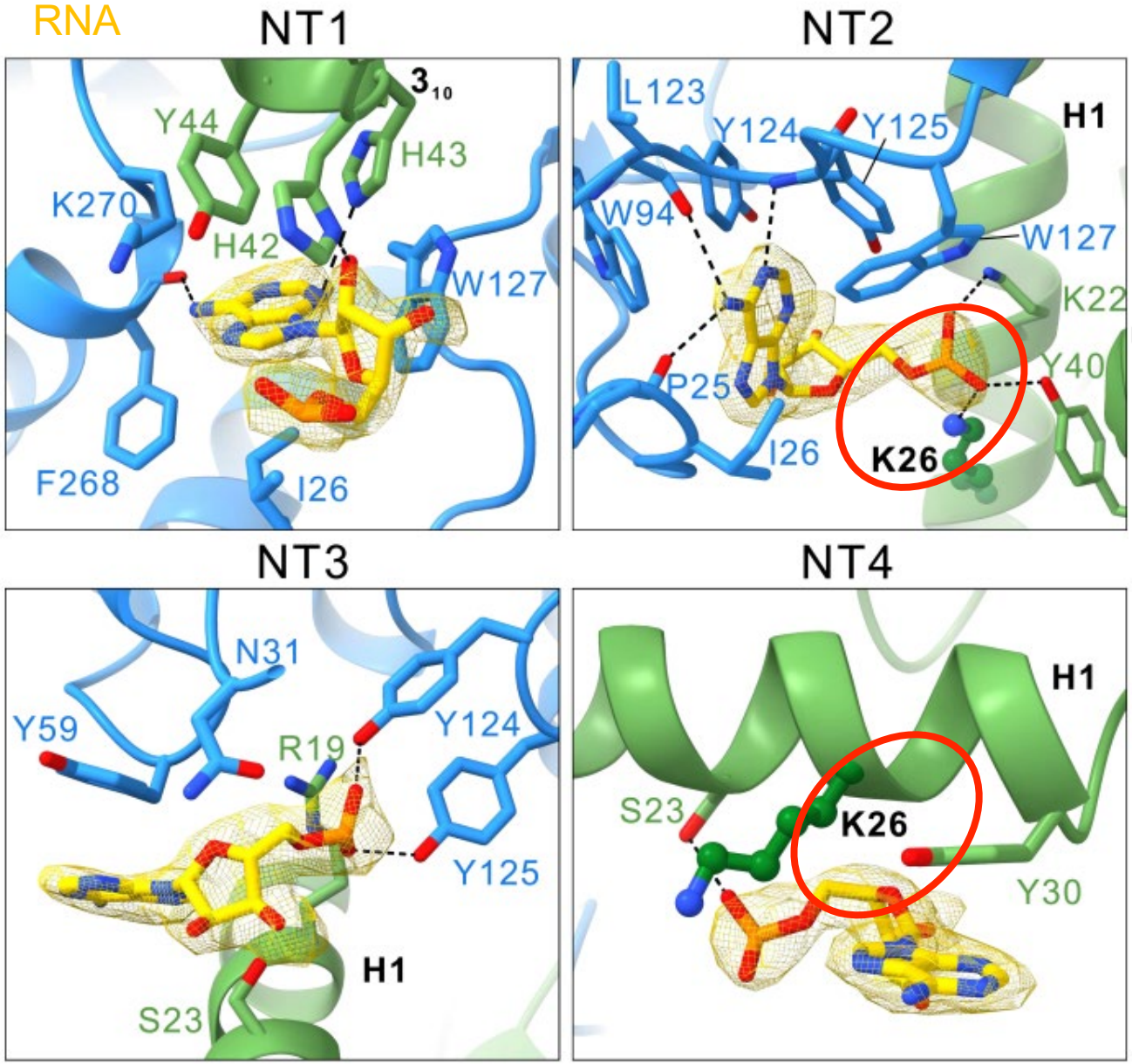


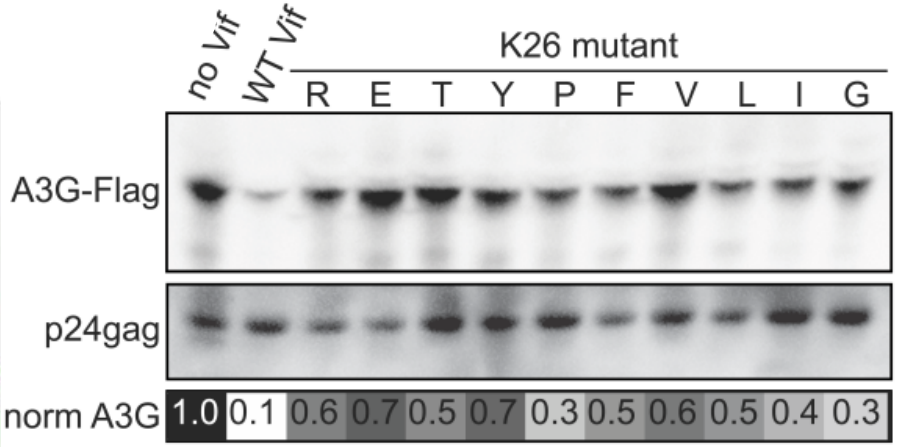




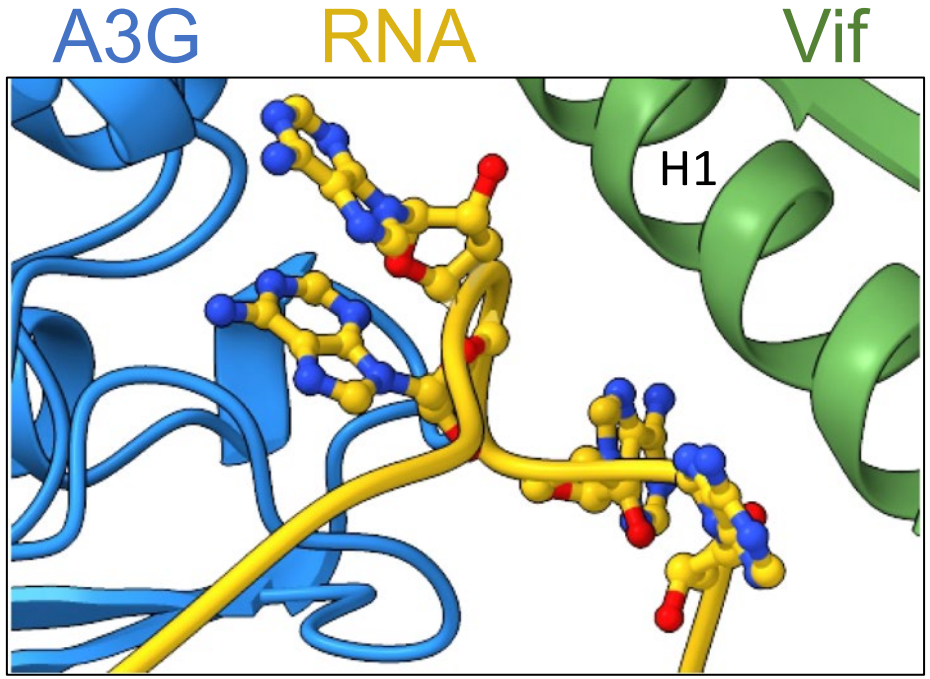
RNA acts as a molecular glue for Vif-A3G

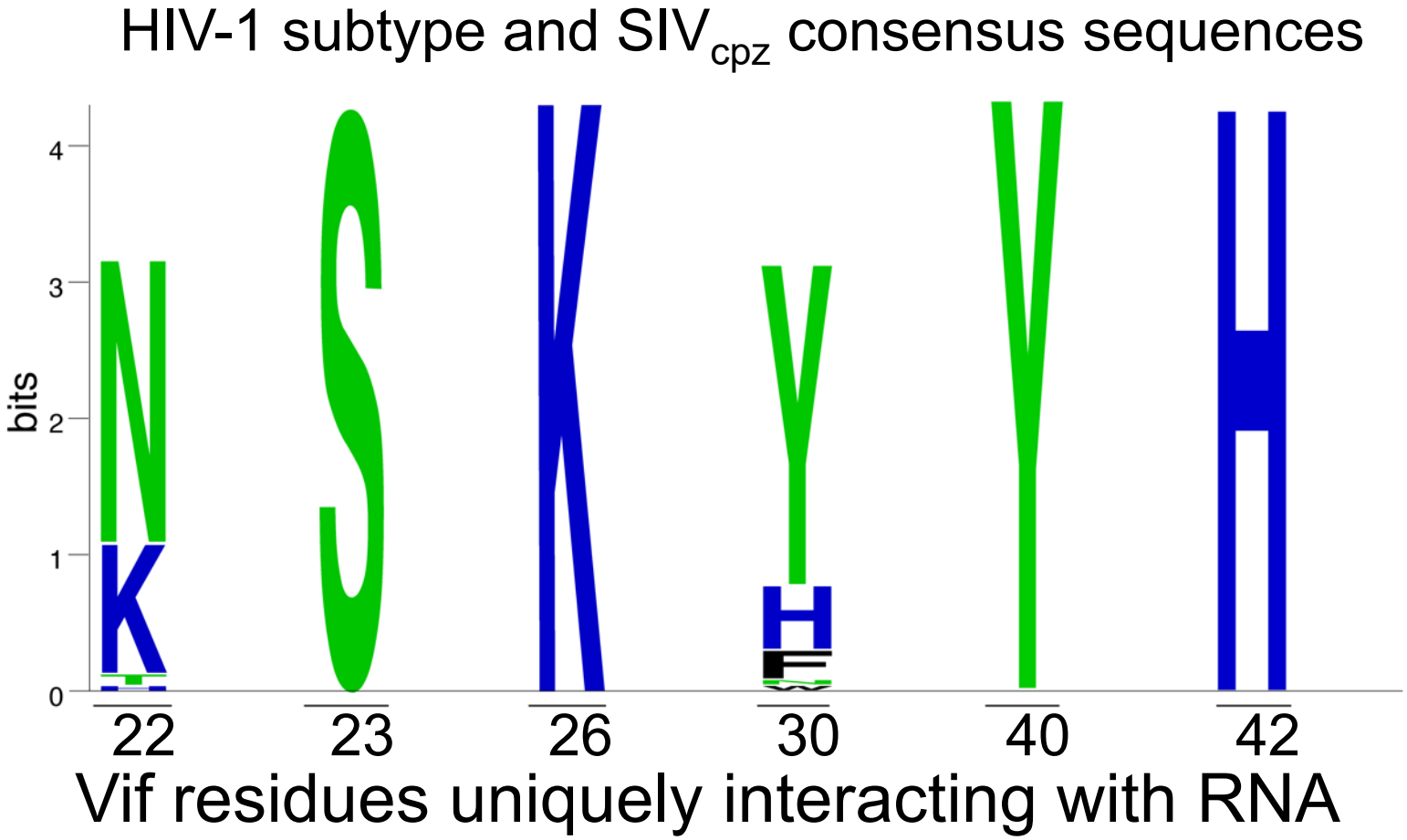
Vif
A3G
RNA





RNA interacting residues are conserved across HIV and SIV





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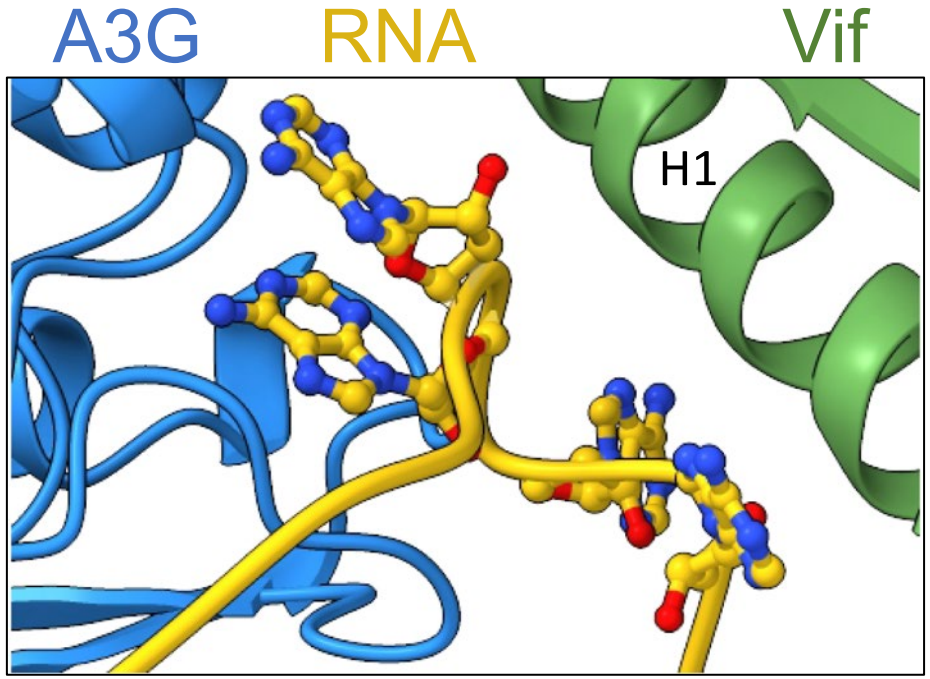
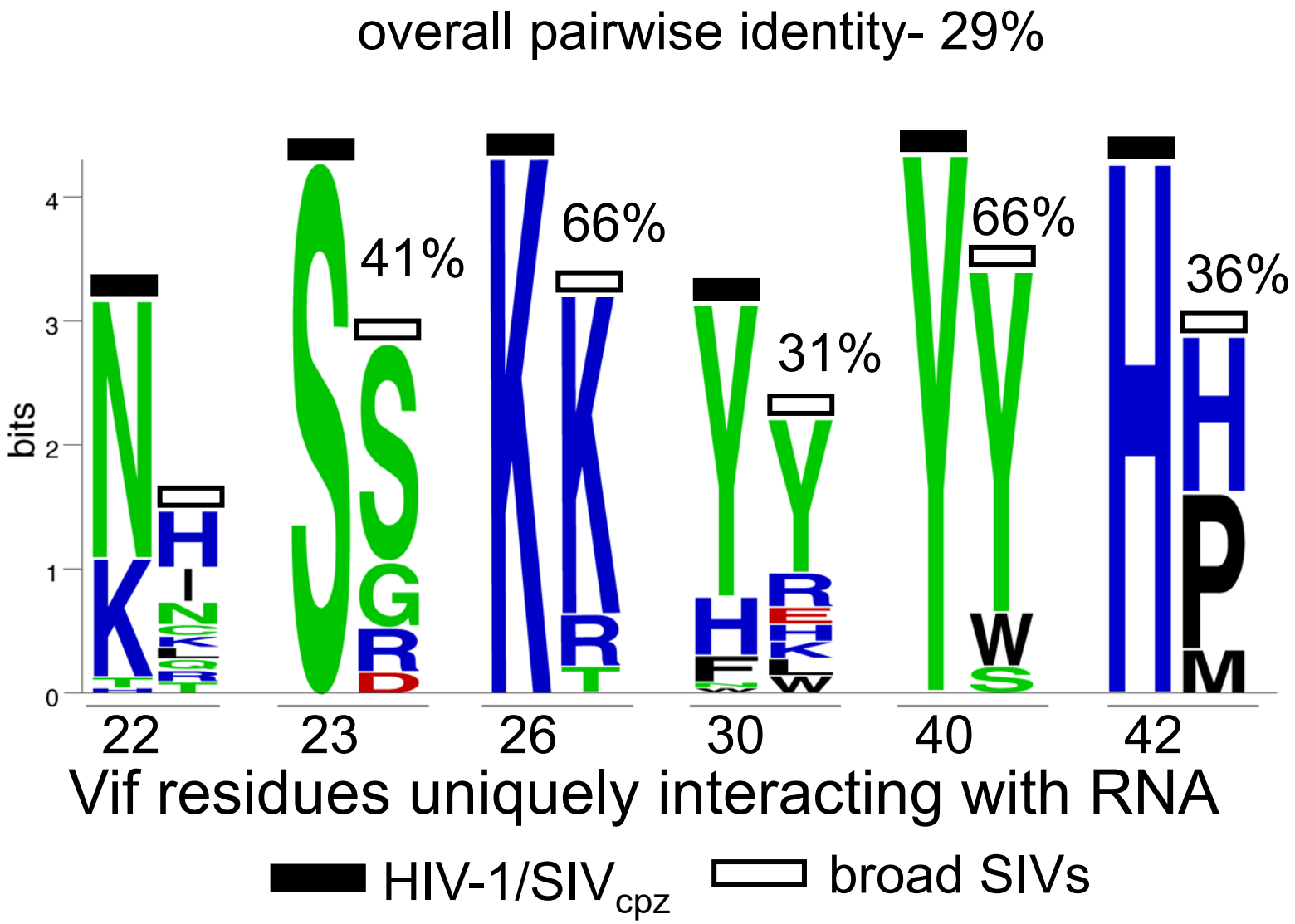
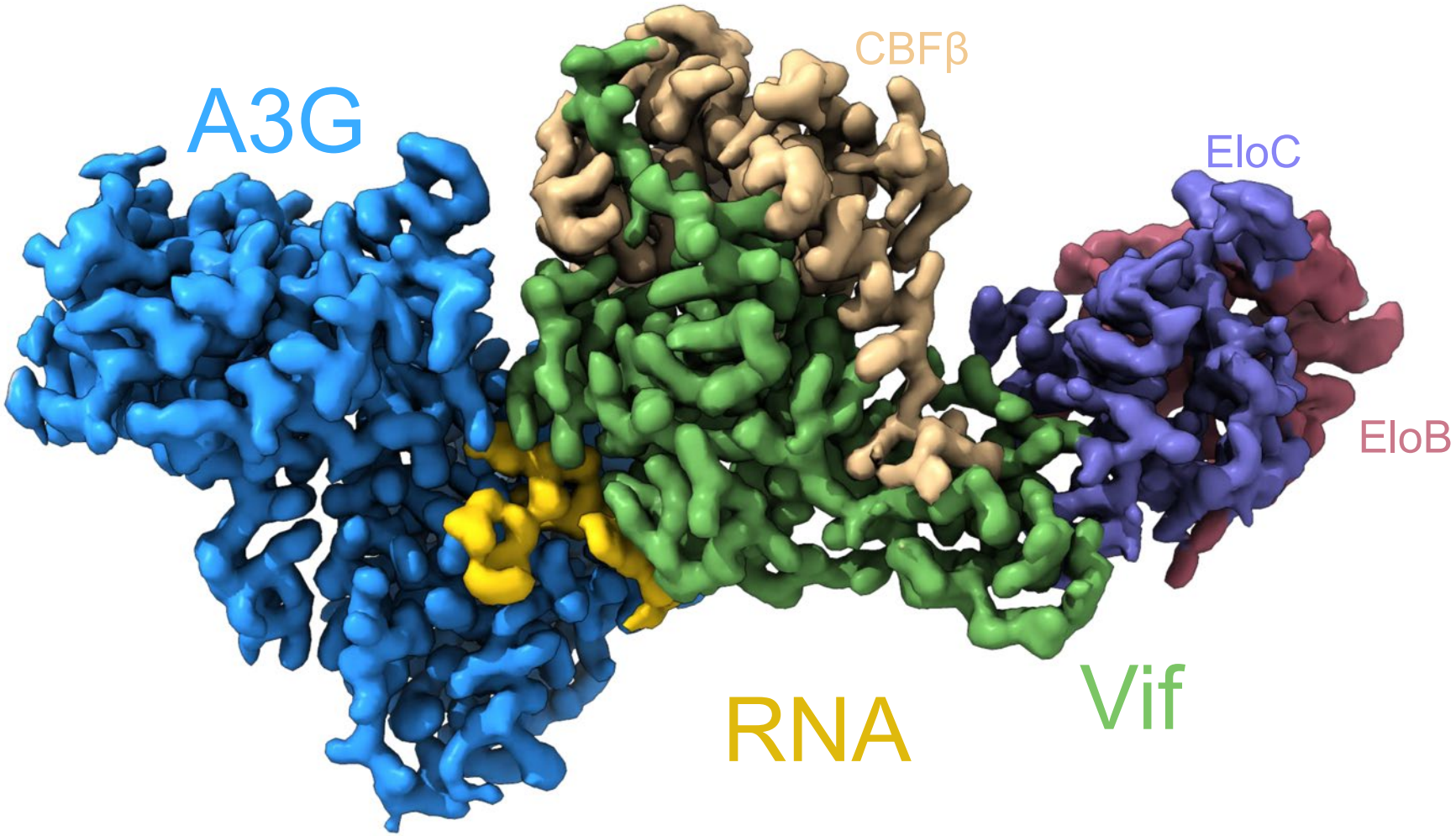
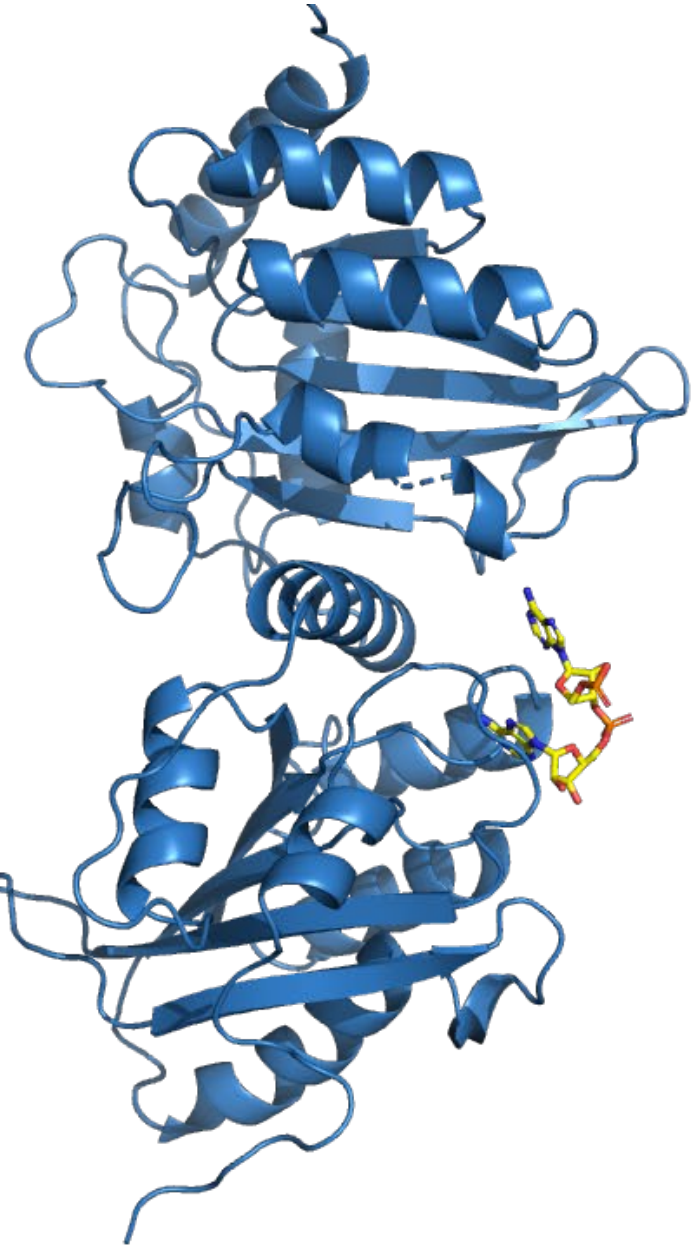




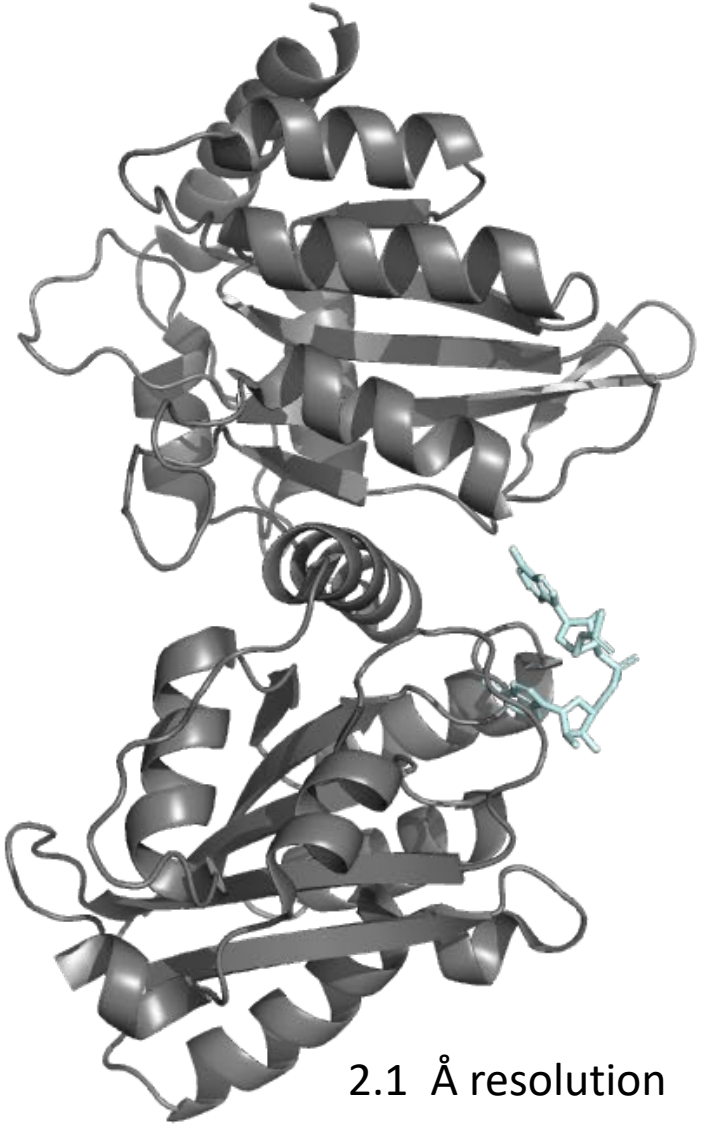
What is the origin of the RNA ‘glue’?



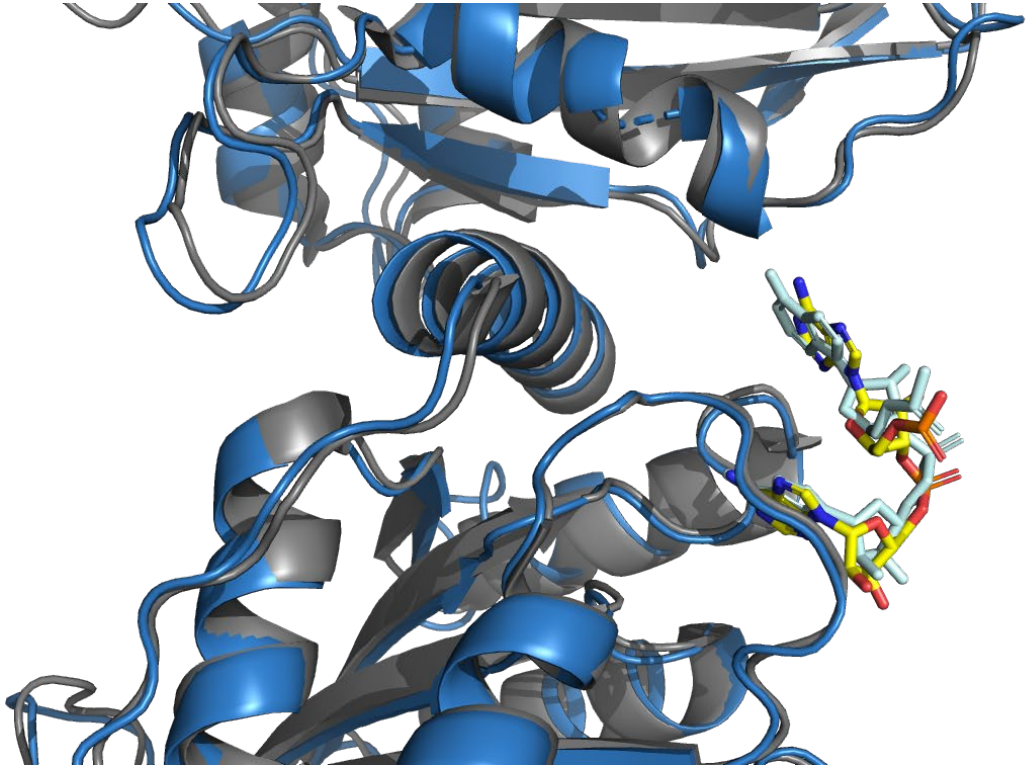
cryoEM: hA3G NT1 and NT2



Crystal Structure rhA3G with di-adenine ssRNA



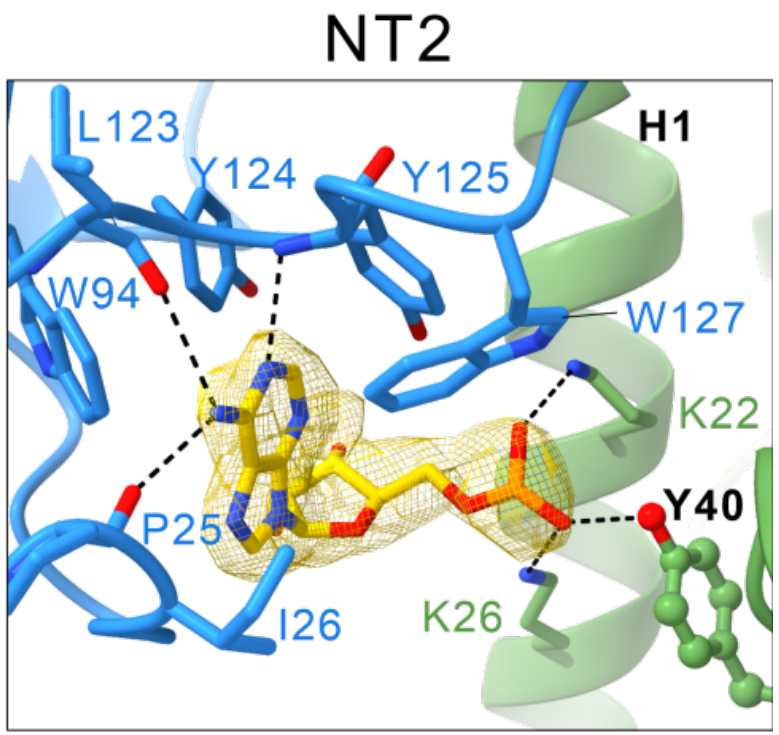
2.1 Å resolution

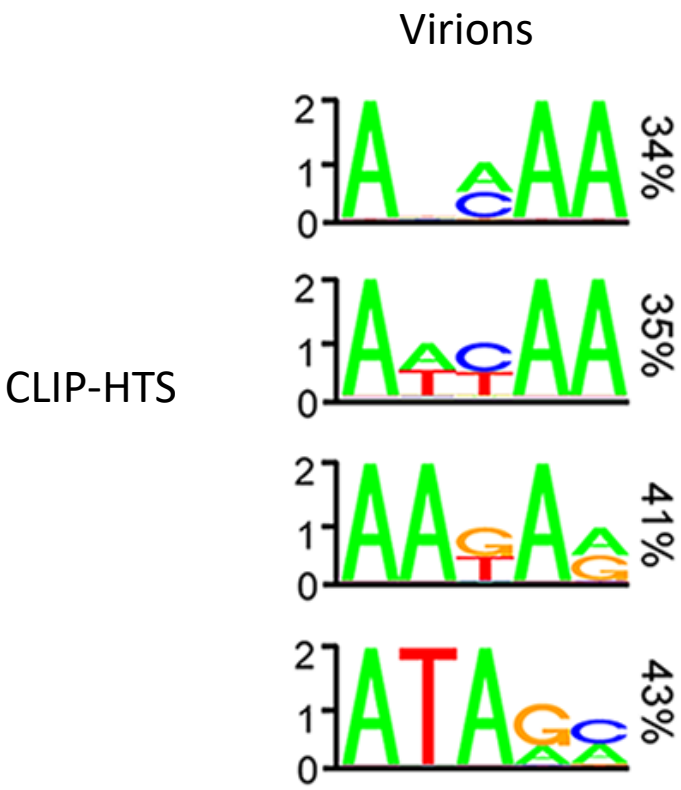


RMSD 0.8 Å

Yang et al (Xiaojiang Chen), 2022

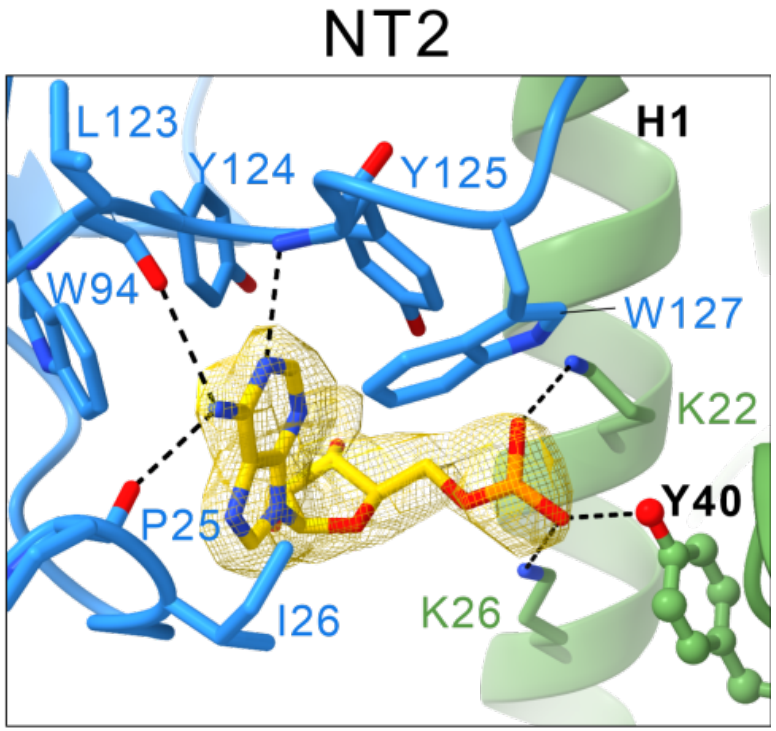
A3G adenine pocket consistent with CLIP-HTS

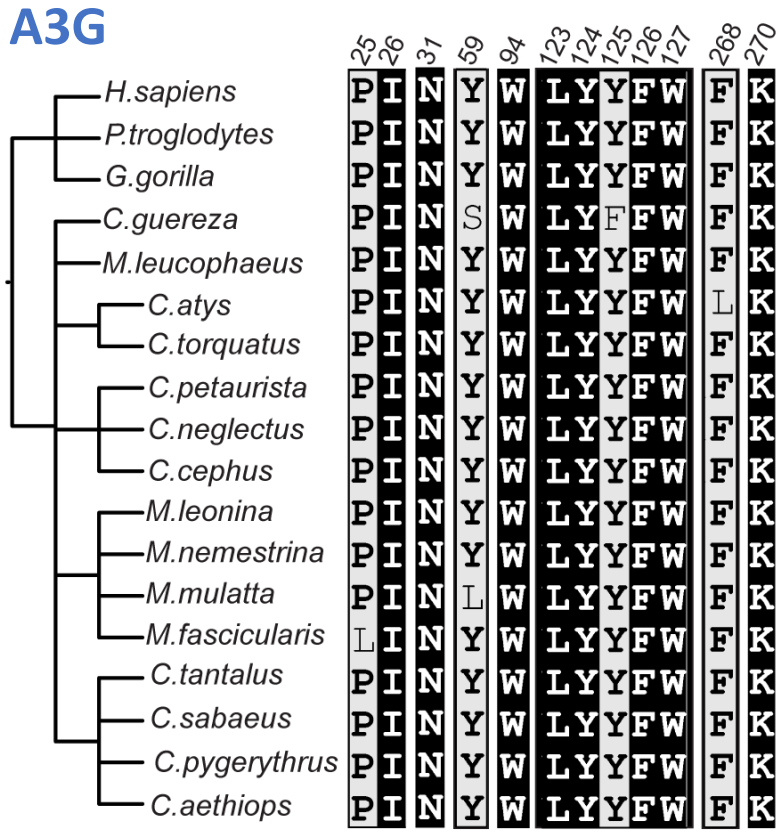




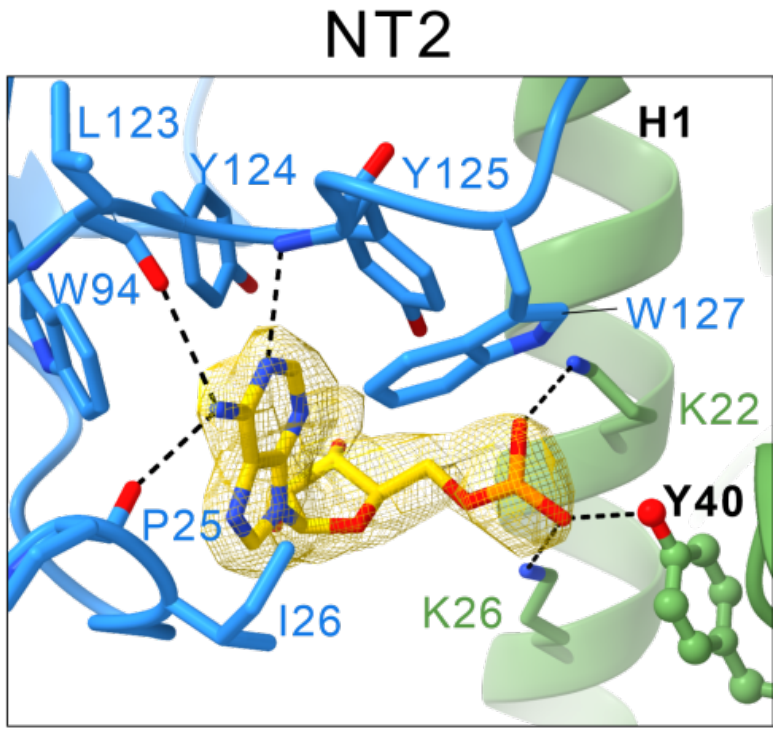
York et al, PLoS Pathogens, 2016

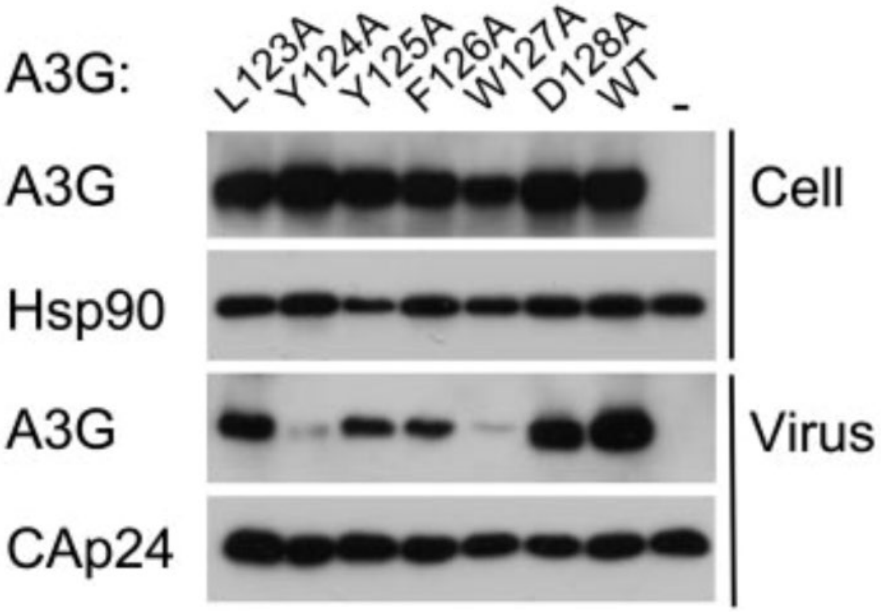
Adenine binding pocket residues are conserved across A3Gs





RNA binding residues of A3G required for packaging
In the absence of Vif





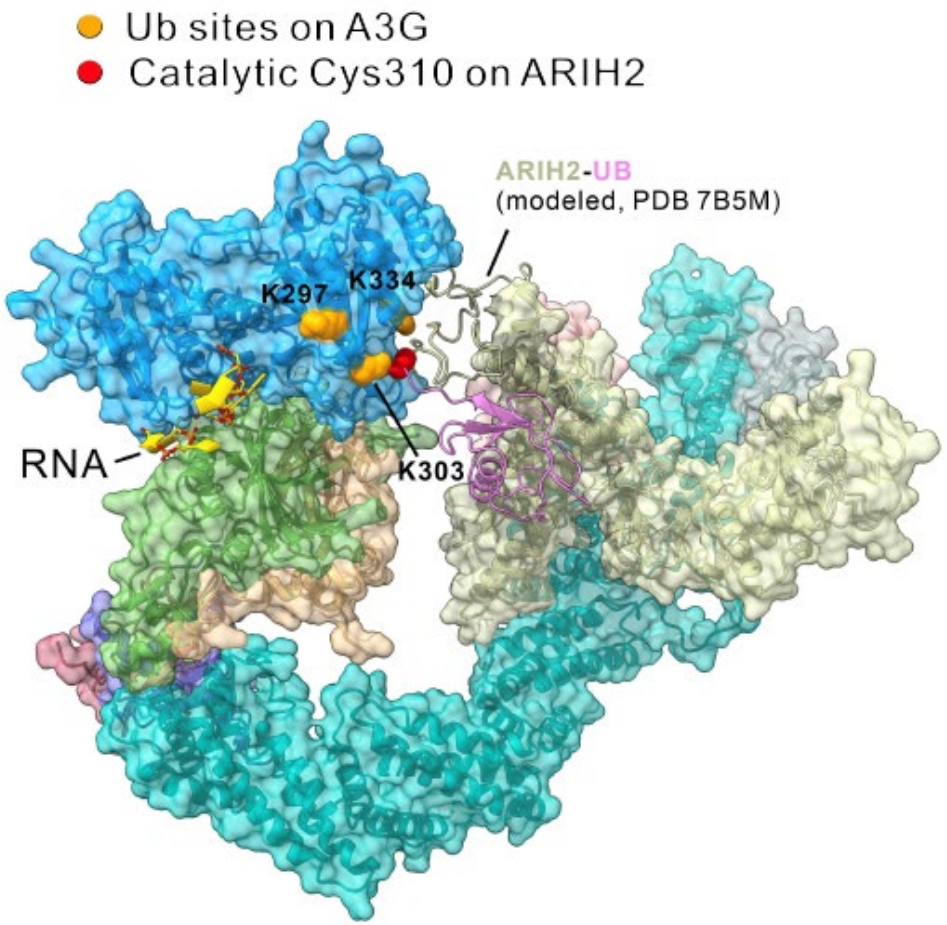
Hendrik Huthoff & Michael H. Malim, JVI 2007

- The substrate for Vif E3 ligase is not A3G but instead A3G bound to an RNA containing diadenosine

- The residues of A3G that bind RNA are essential for its function

- Vif binding to an A3G/RNA complex is a viral strategy that limits host escape

cryoEM structure of Vif.A3G/RNA is compatible with ubiquitination

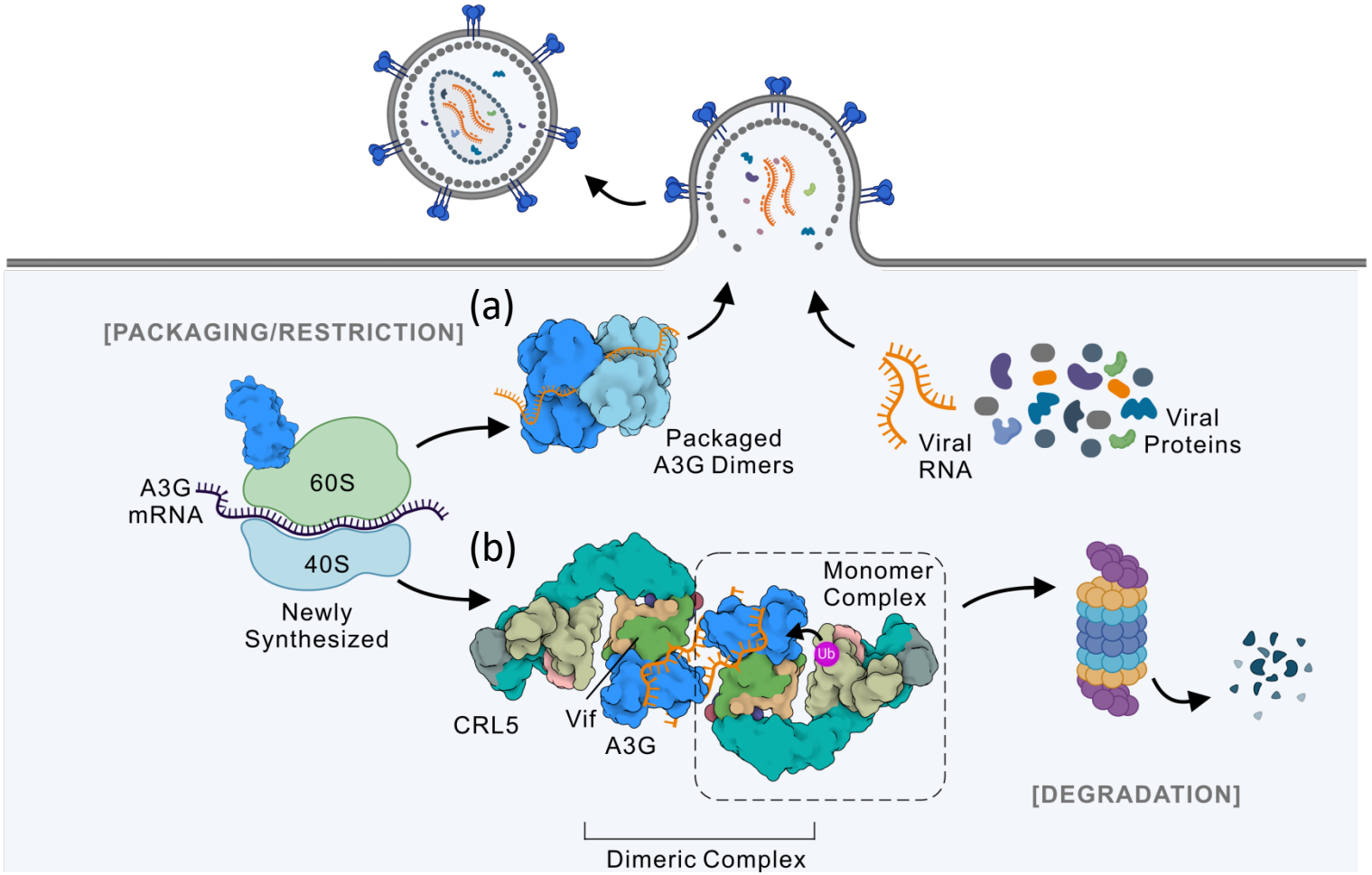


A3G-Vif-CBFβ-ELOC-ELOB-
CUL5-RBX2-NEDD8-ARIH2-UB

Iwatani et al. PNAS 2009
Albin et al. JMB 2013
Guo et al. Nature 2014
Hüttenhain et al. Cell Host Microbe 2019
Kostrhon et al. Nat. Chem. bio, 2021

Model by Ignacia Echeverria Riesco

Model: Vif intercepts RNA-bound A3G en route to packaging for degradation by the 26S proteasome



(a) In absence of Vif, A3G gets packaged
(b) Vif prevents A3G dimerization and packaging, targeting to proteasome