Paleovirology

Plate 5.1. The mummified head of Ramses V of Egypt (died 1157 BC) showing the pustular eruption that may have been due to smallpox. (From Smith, 1912.)

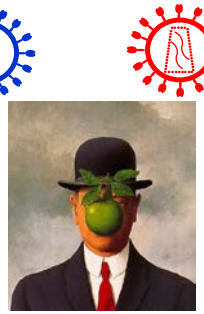
Modern consequences of ancient viruses

Why are humans infected with some lentiviruses and not others?

Chimpanzee

HIV-1

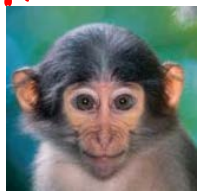
4X



Human

HIV-2

>7X

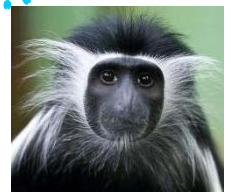


Sooty Mangabey

RCM

AGM

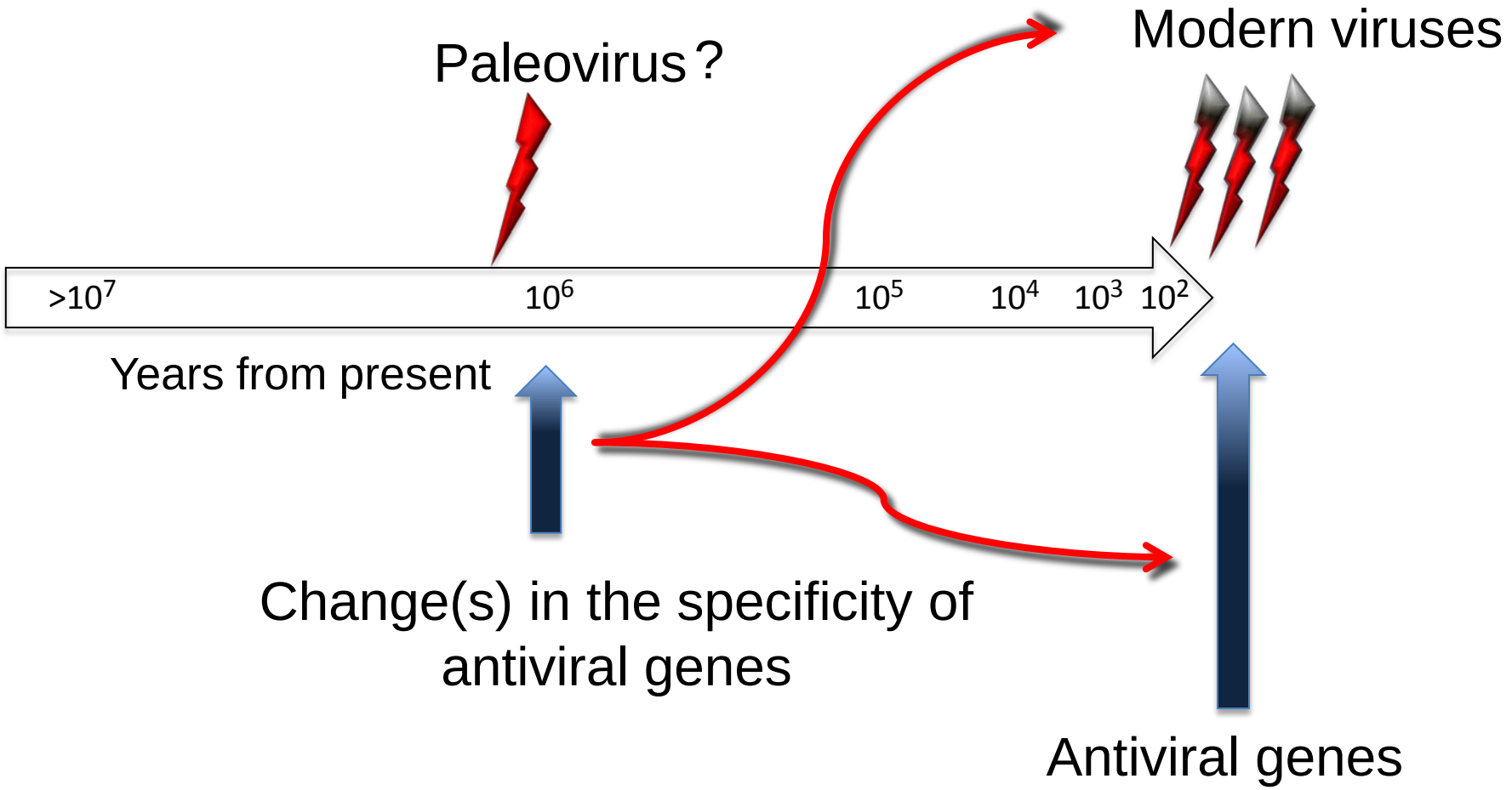
Mandrill



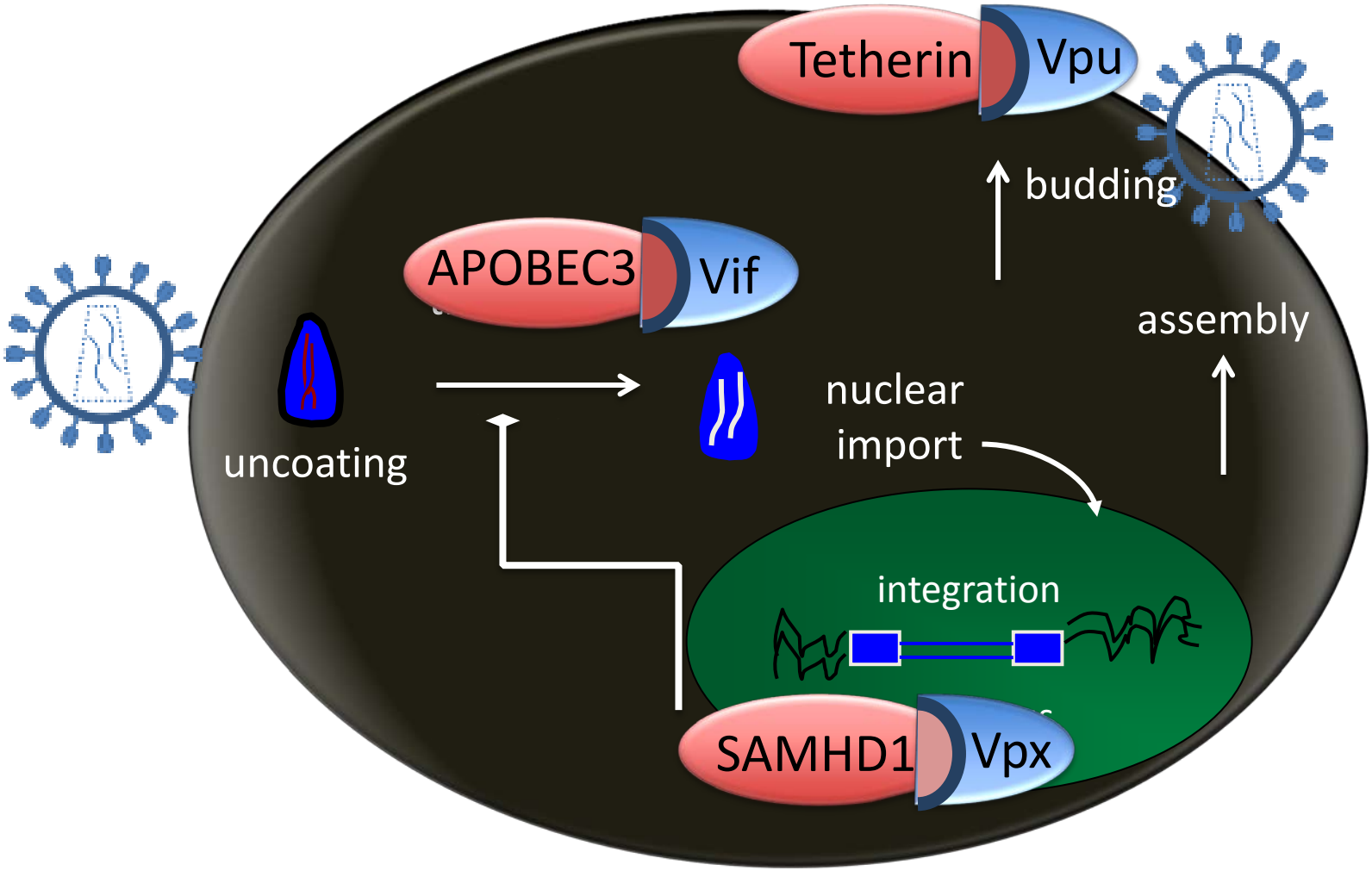
Colobus

How did HIV-1 and HIV-2 adapt to humans?

Ancient viral pathogens of humans and human ancestors have shaped our immunity to modern viruses

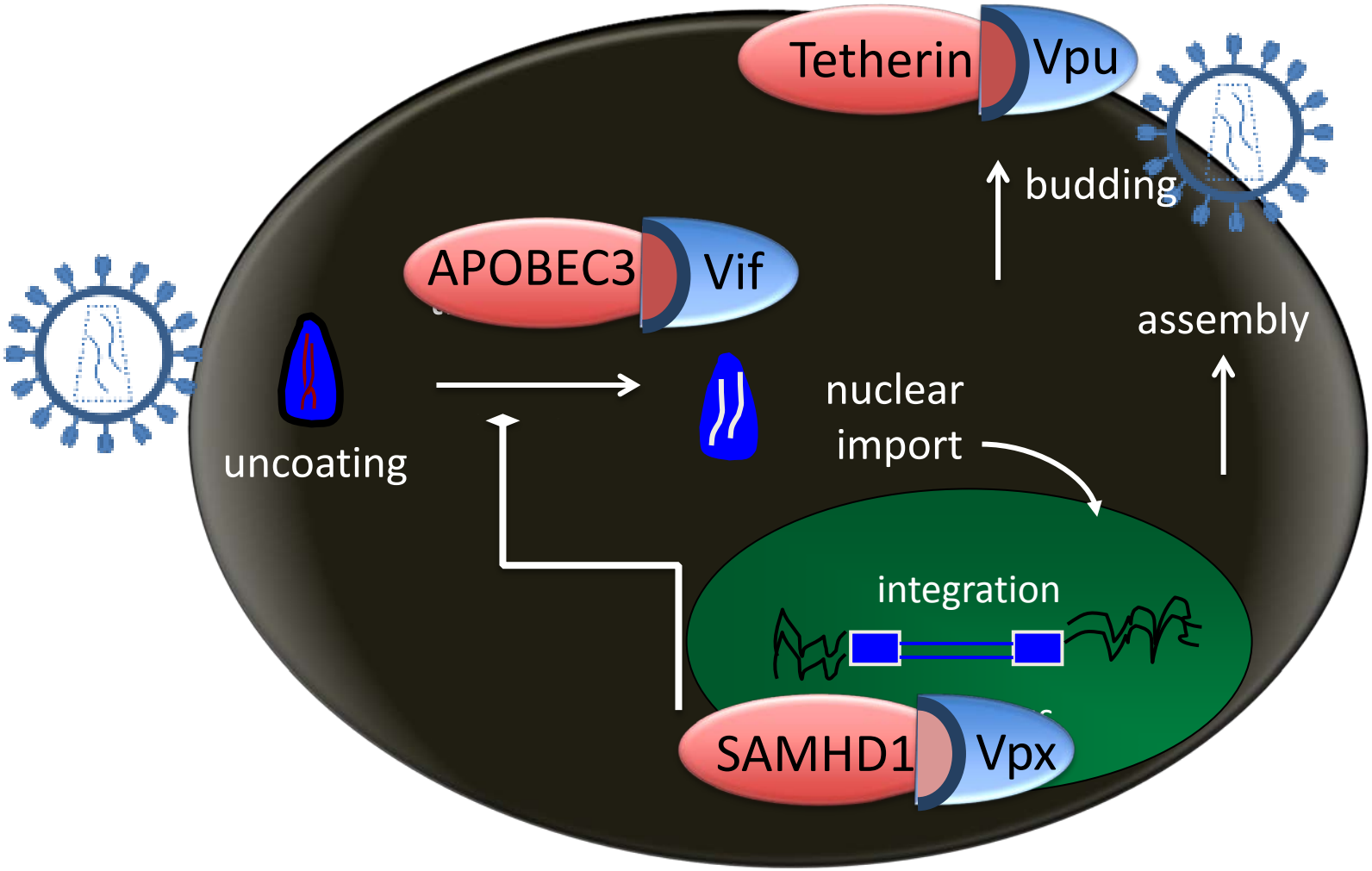


Primates encode antiviral factors that limit virus replication



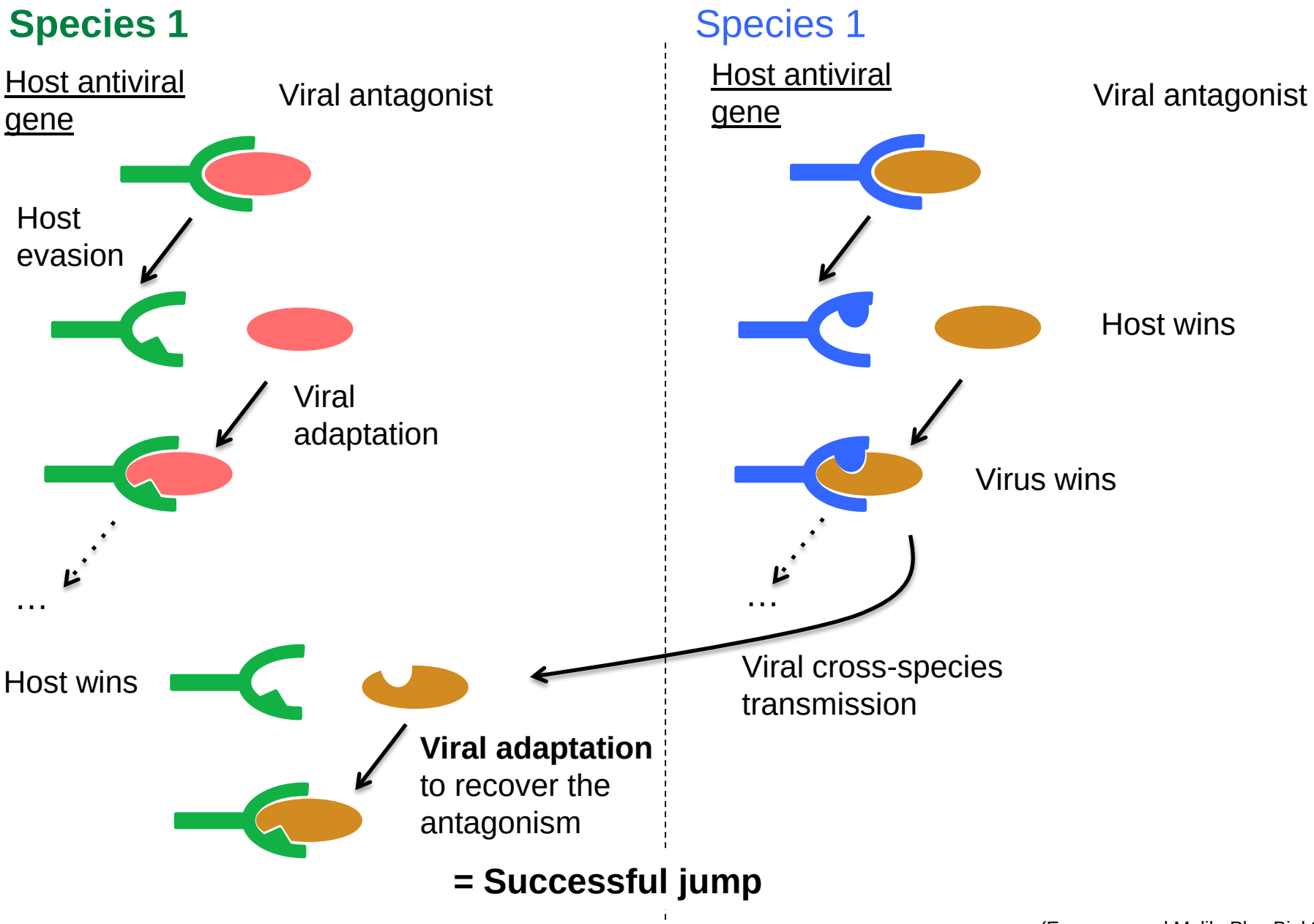
Viruses encode proteins to evade the antiviral factors

Host susceptibility = sum of the interactions between host antiviral factors and viral antagonists



Leading to an evolutionary “arms race” between host genomes and viruses

Viral-host ‘arms race’ and Species barriers



(Emerman and Malik, Plos Biol 2010)

Virus-host interactions drive positive selection

REPLACEMENT (dN) **SYNONYMOUS (dS)**

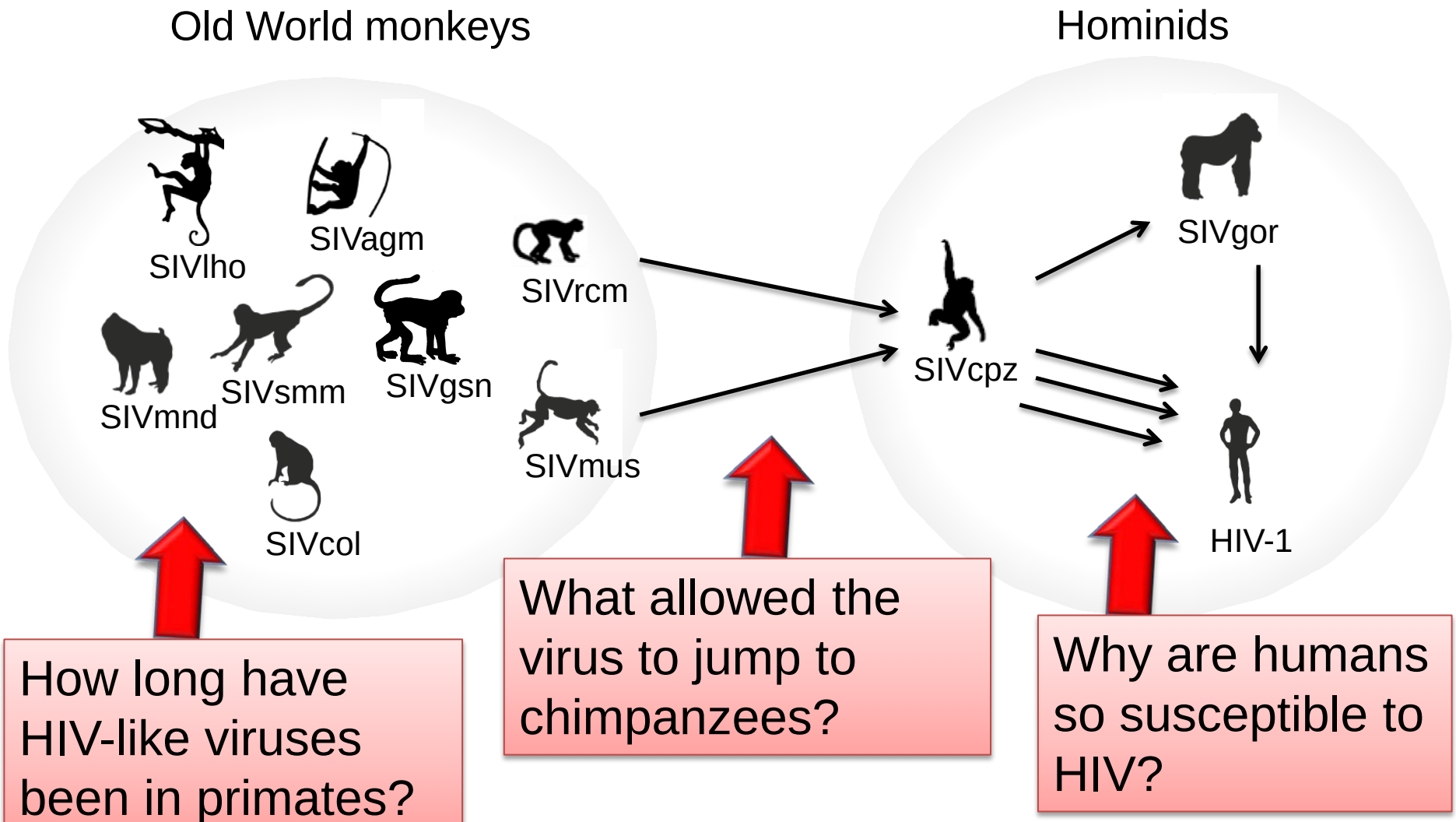
```
S   E   A   T   T   L   E
TCA GAA GCA ACG ACC TTA GAA
TCA GAG GCA ACA ACC CTA GTA
S   E   A   T   T   L   V
```

$\frac{dN}{dS} < 1$ PURIFYING SELECTION

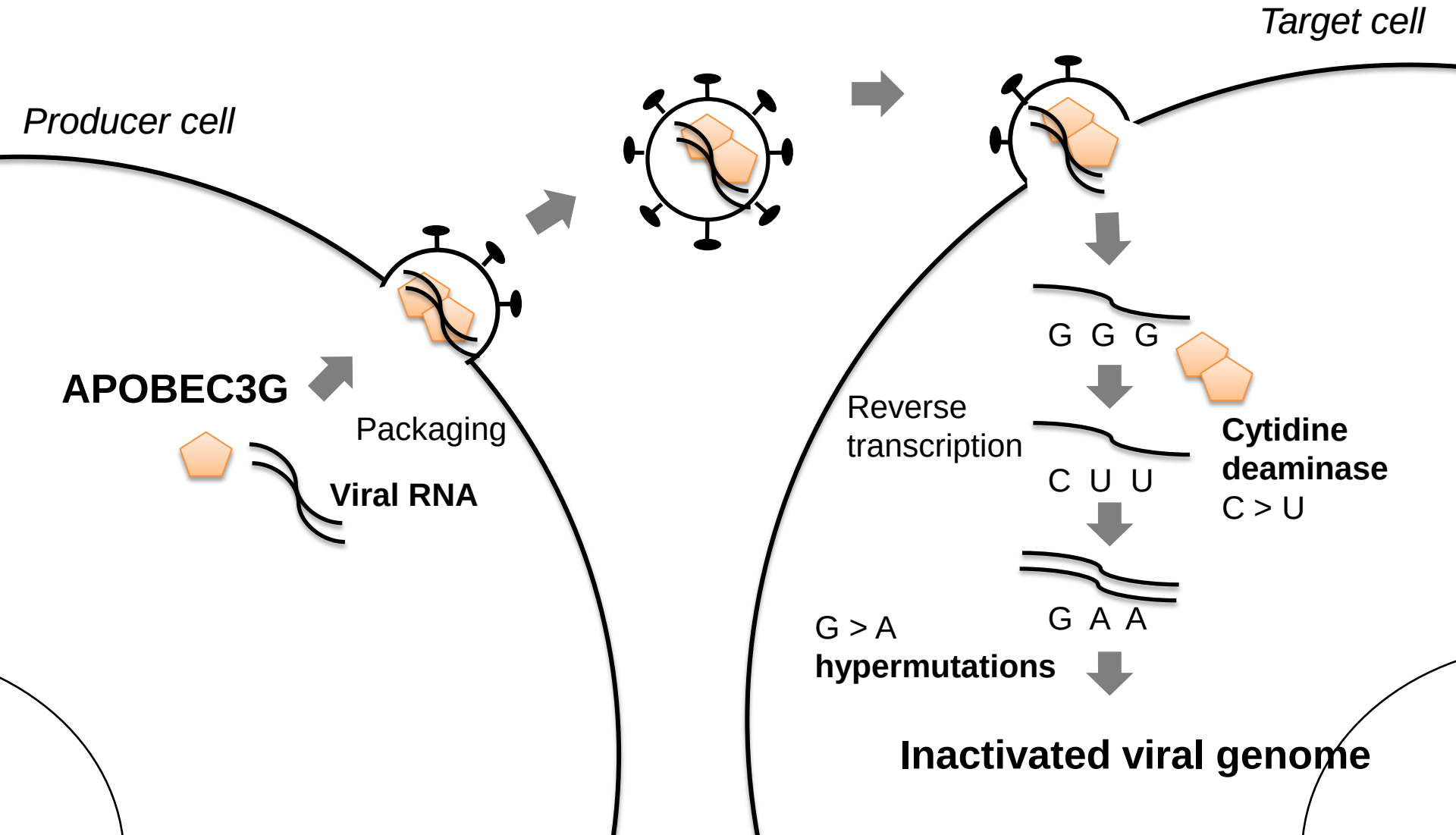
```
S   E   A   T   T   L   E
TCA GAA GCA ACG ACC TTG GAA
ACA GAA GCC ACG ATC ATG GAA
T   E   A   T   I   M   E
```

$\frac{dN}{dS} > 1$ POSITIVE SELECTION

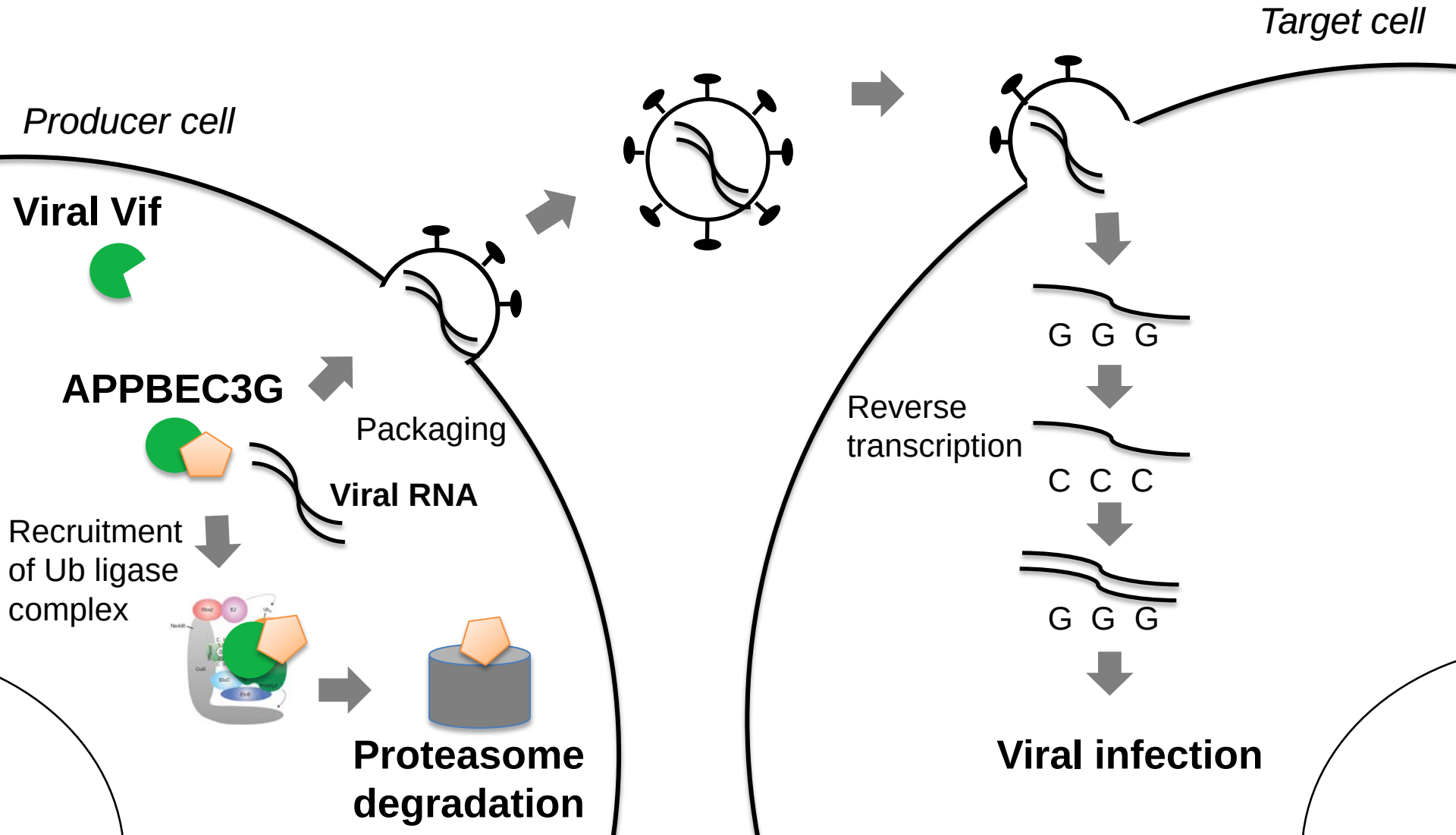
The ancient origins of HIV-1



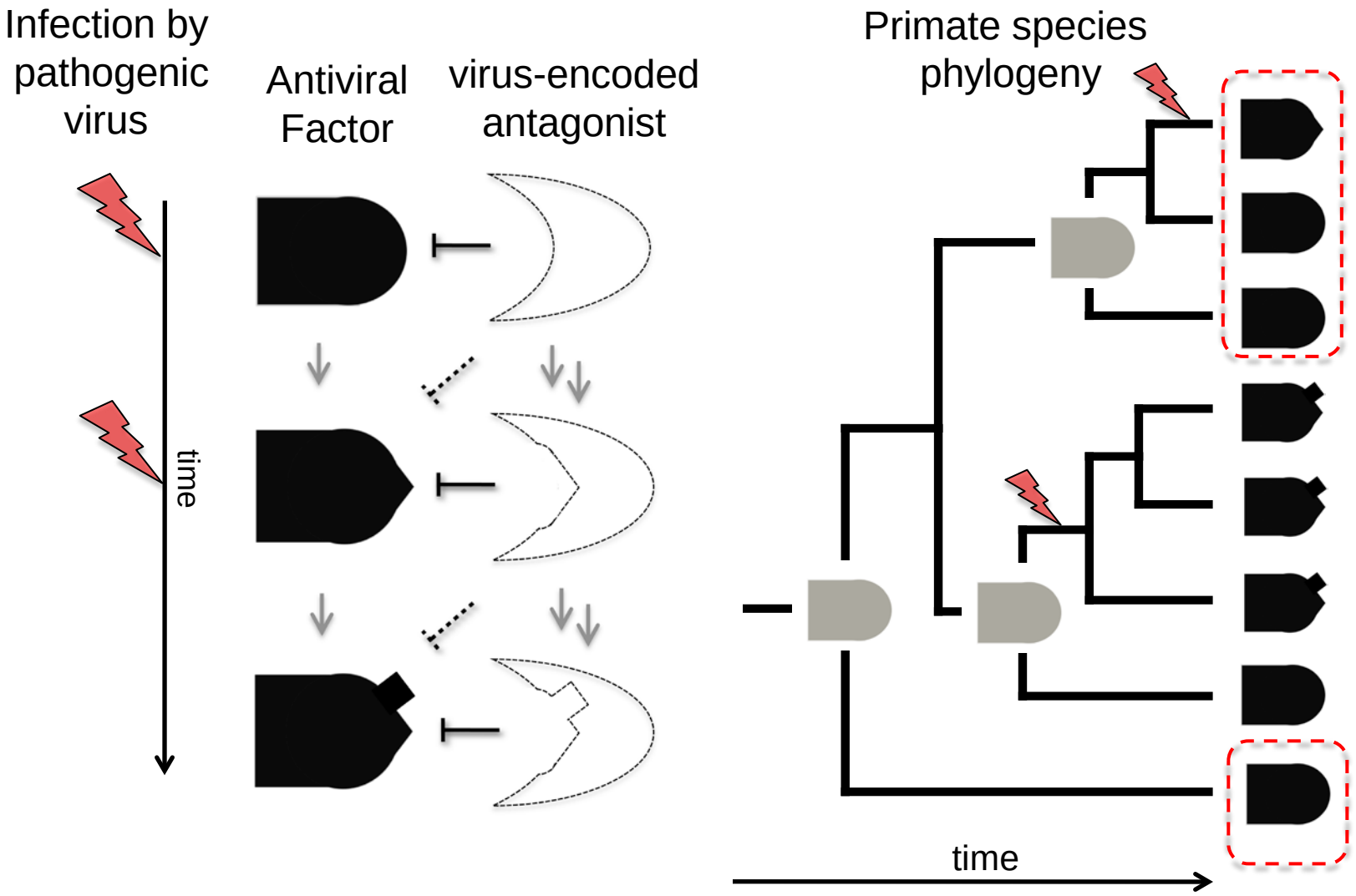
APOBEC3G inhibits HIV/SIV during reverse transcription



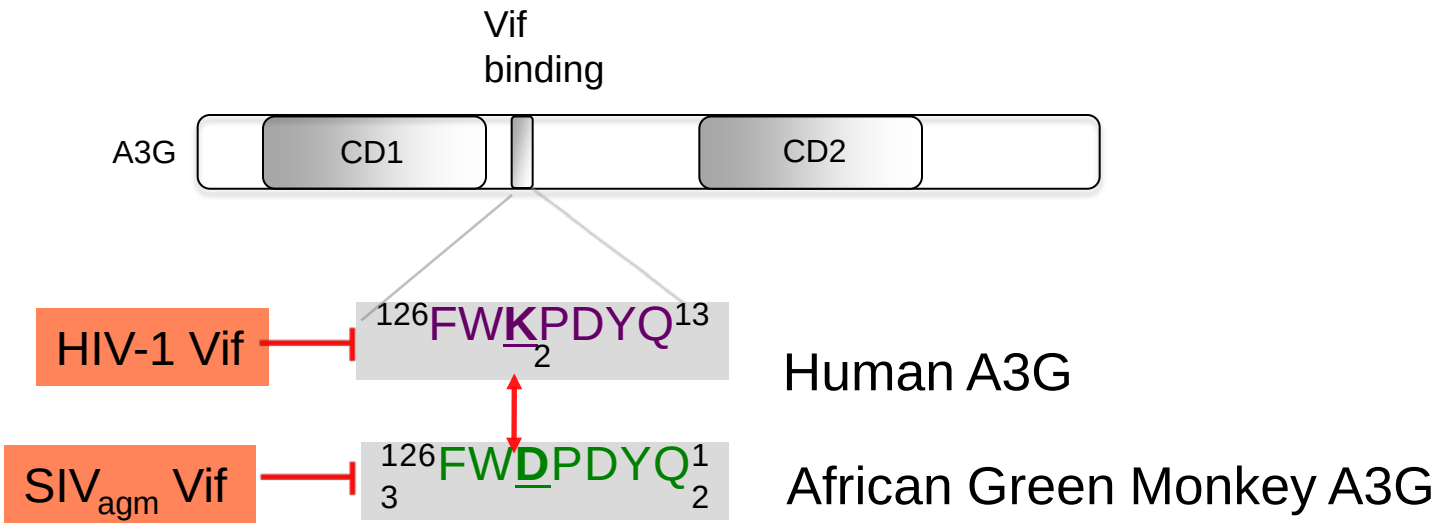
Lentiviral Vif antagonizes APOBEC3G (A3G)



Using the virus-host interaction sites to identify ancient pathogens

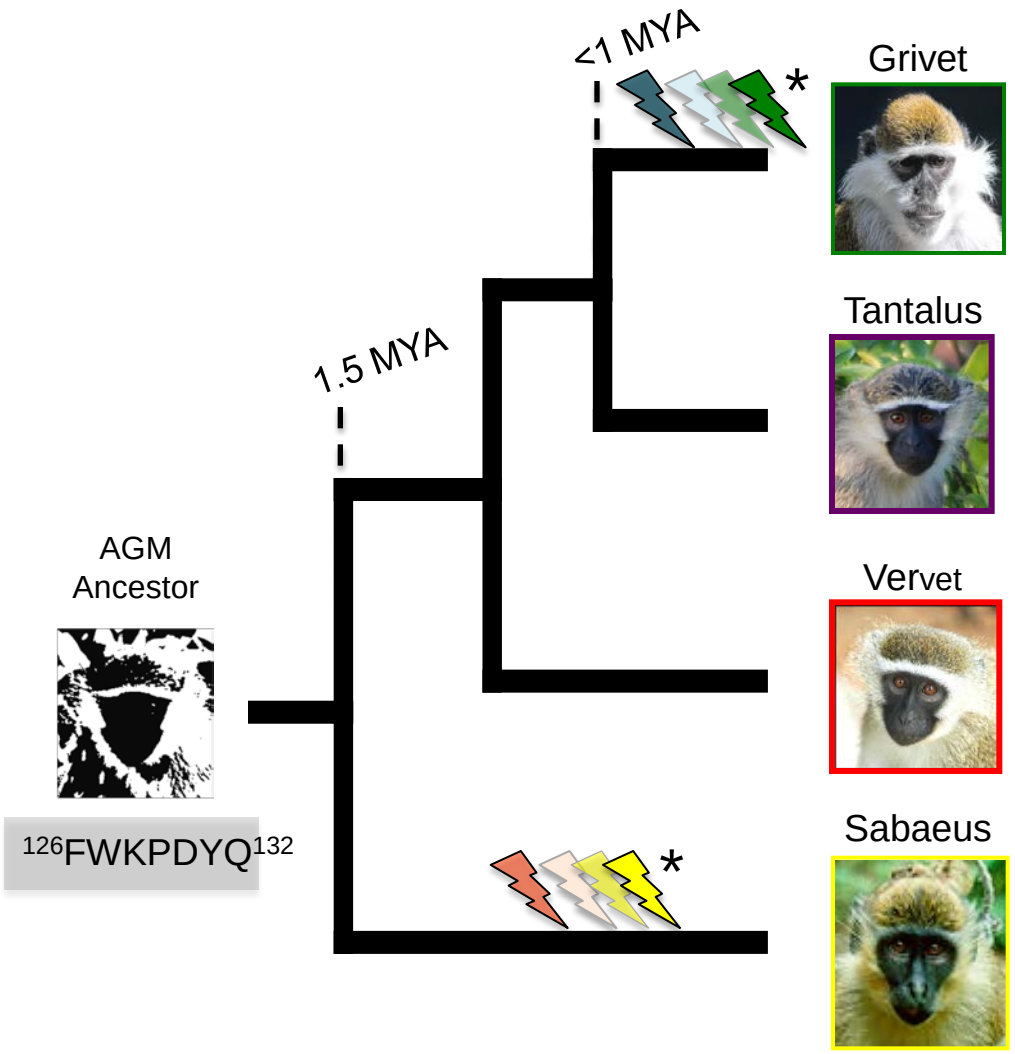


Species-specific mutations in A3G govern sensitivity to Vif

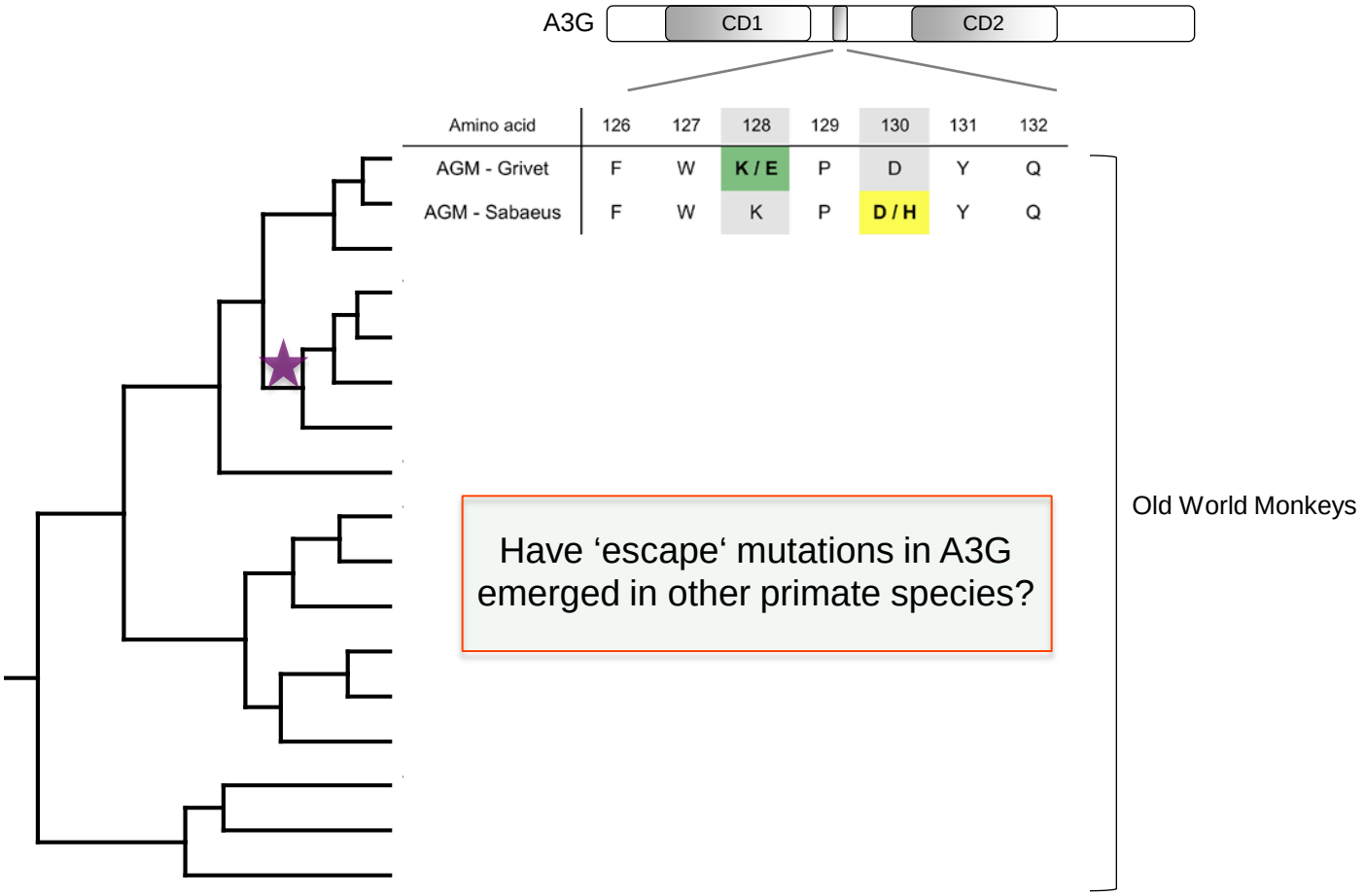


- Residue 128 of A3G is a critical determinant of Vif sensitivity
- Positive selection in this region of A3G driven by viral interactions

Ancient and ongoing co-evolution of AGMs and their lentiviruses

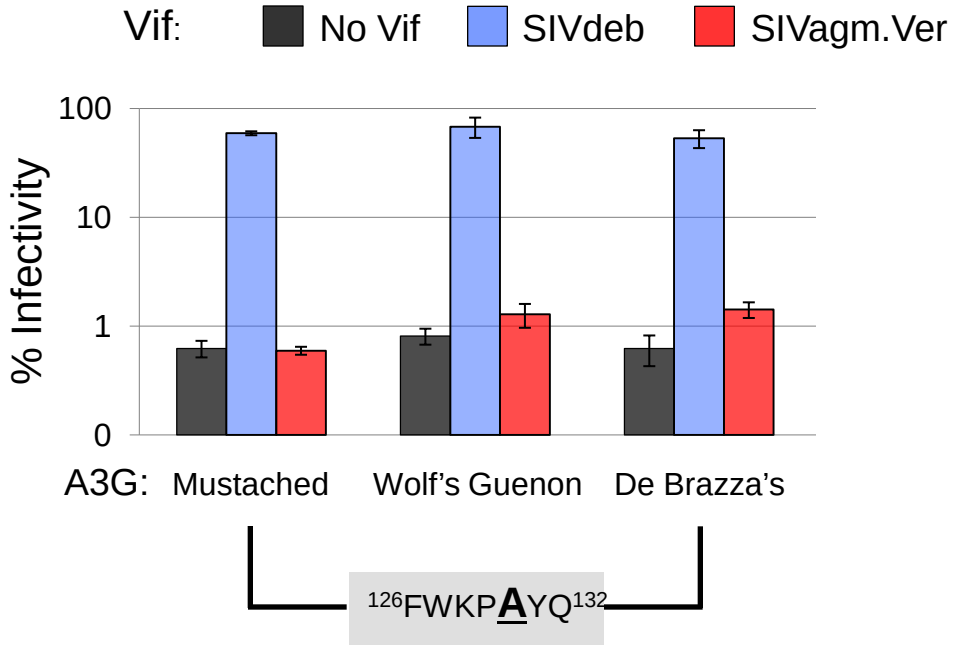


Adaptive evolution of *A3G* in *deep* time: inferring ancient viruses



Compton and Emerman, PLOS Pathogens, 2013

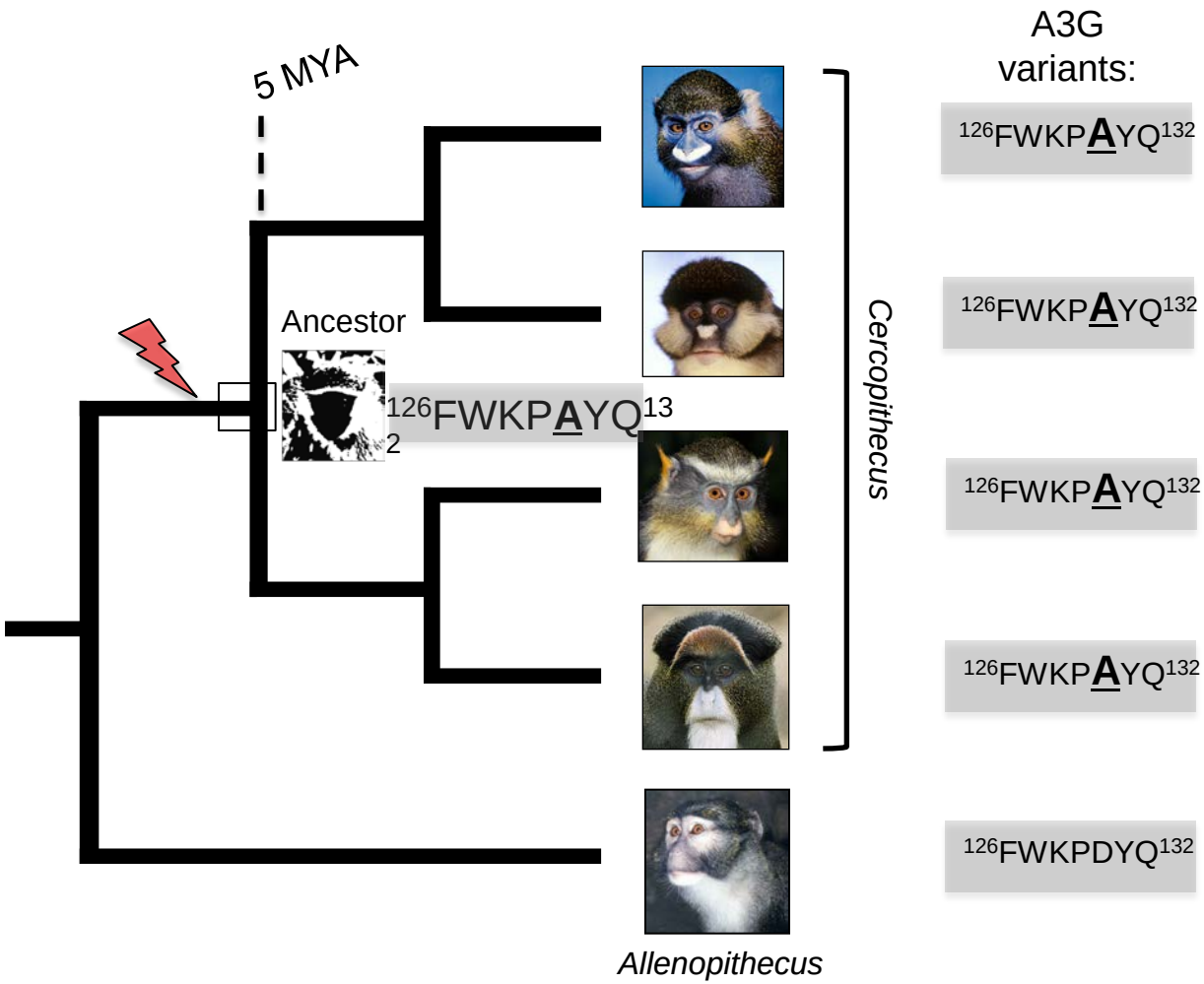
A mutation common to *Cercopithecus* genus allows evasion of Vif



- D130A allows escape from Vif
- SIV Vif infecting *Cercopithecus* genus has counter-evolved

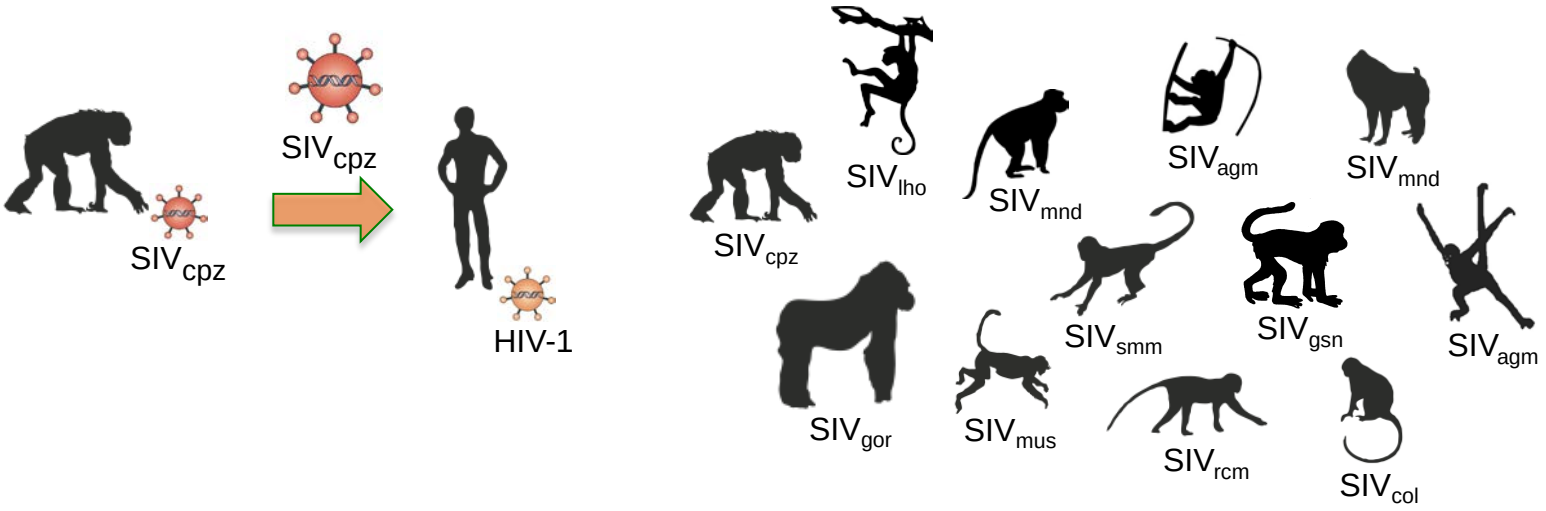
Compton and Emerman, PLOS Pathogens, 2013

A pathogenic lentivirus infected the *Cercopithecus* ancestor at least 5 MYA



Compton and Emerman *PLOS Pathogens, 2013*

How old are the primate lentiviruses?

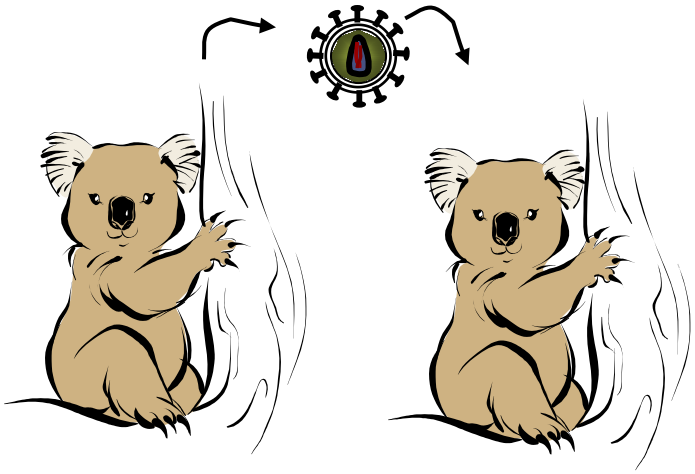


A pathogenic lentivirus was present in some simian primates at least 5 million years ago. Probably longer.

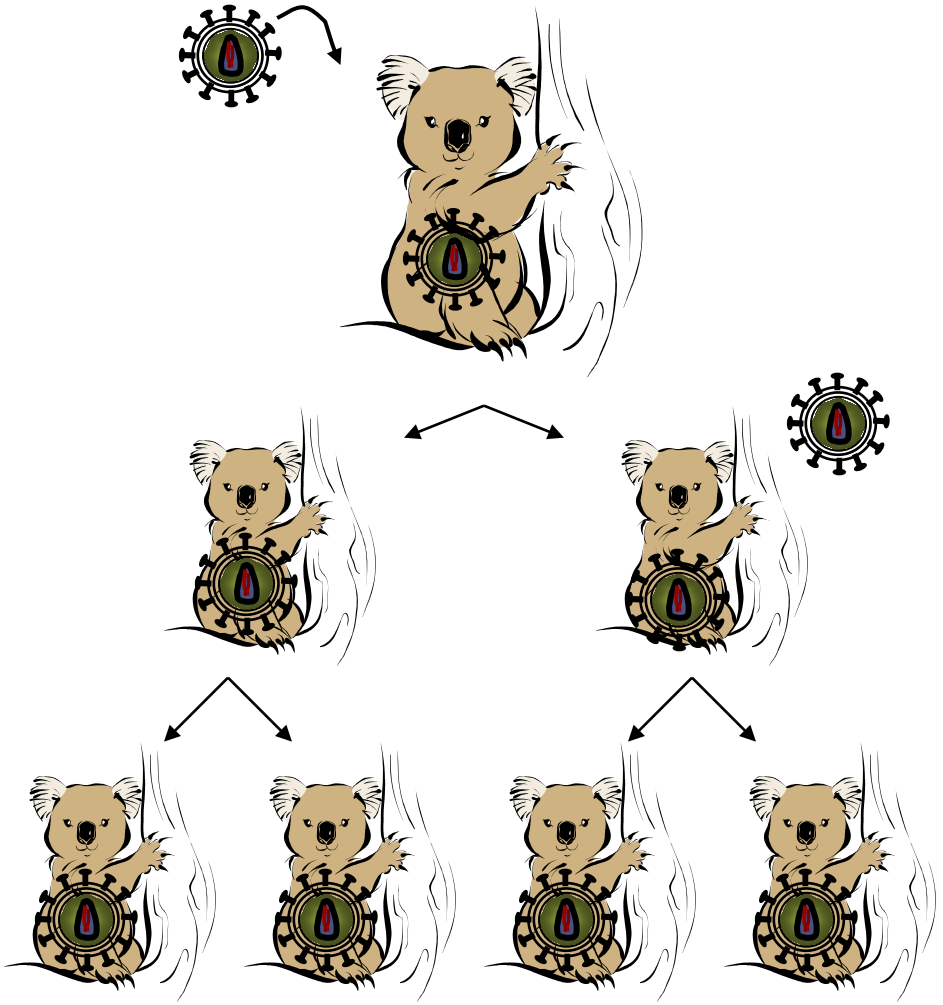
Viral fossils also point to ancient pathogenic viruses

Sometimes exogenous retroviruses enter the germline

exogenous virus



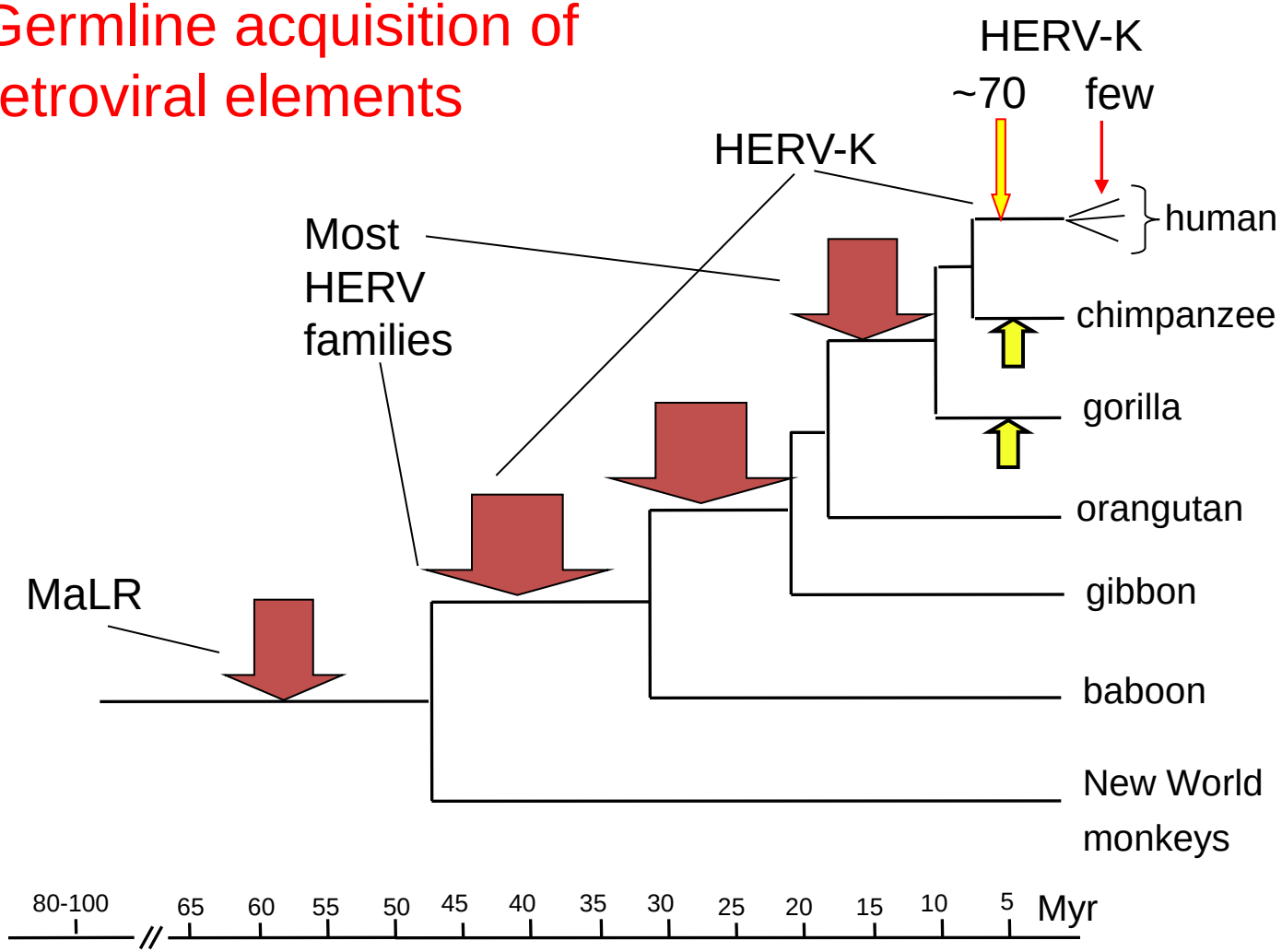
endogenous virus



where they become inherited and fixed within the species

Large numbers of Retroviral fossils in the human genome

Germline acquisition of retroviral elements



100,000 integrants of 31 families of retroviruses

8% of human genome

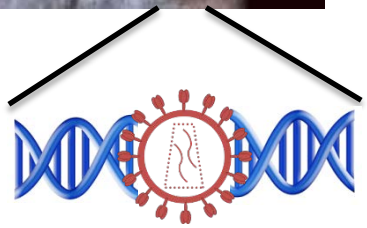
Human endogenous retroviruses are all defective.

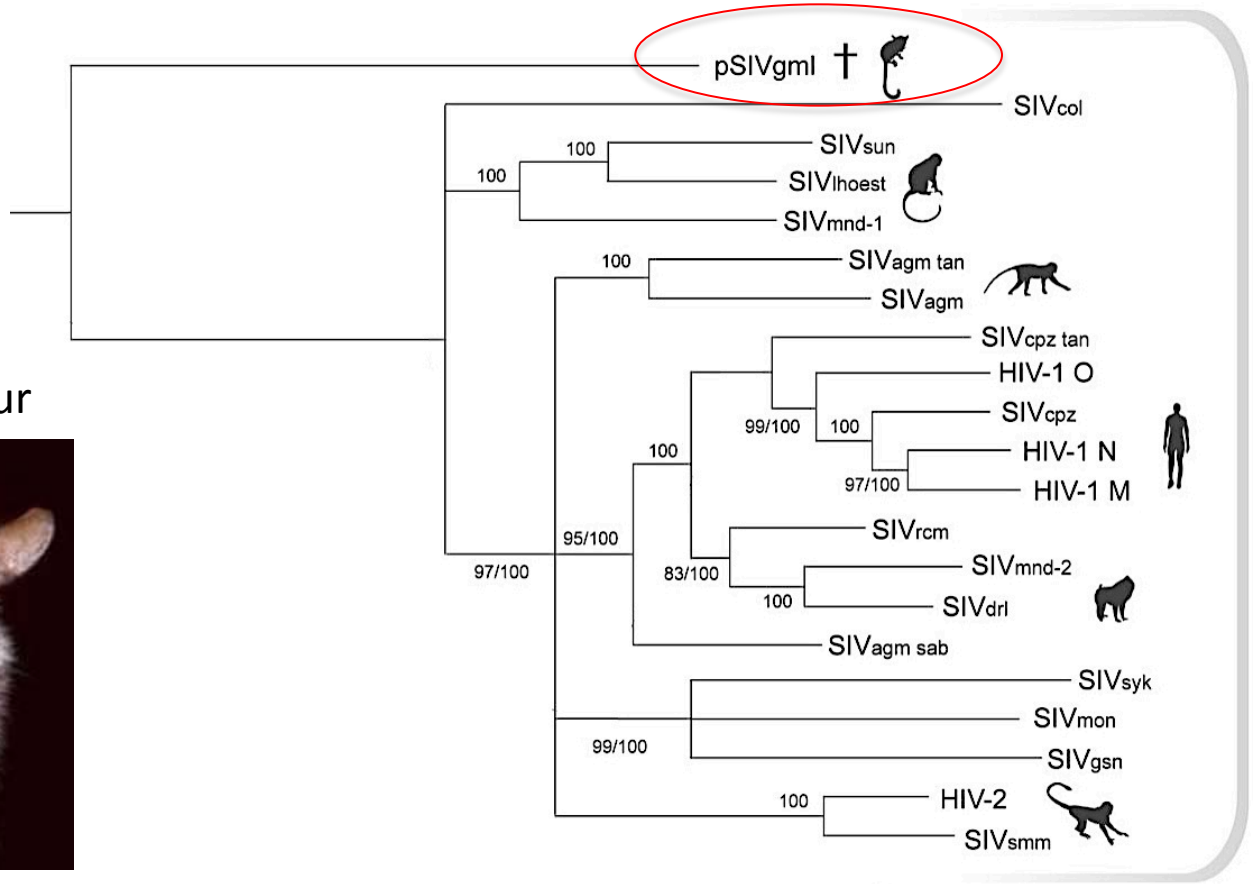
Implications of endogenous retroviruses in the human genome

- There have been many retroviral infections of human ancestors
- Retroviral lineages go extinct in their host
- Host wins!

An endogenous lentivirus in the genome of a prosimian

Grey mouse lemur

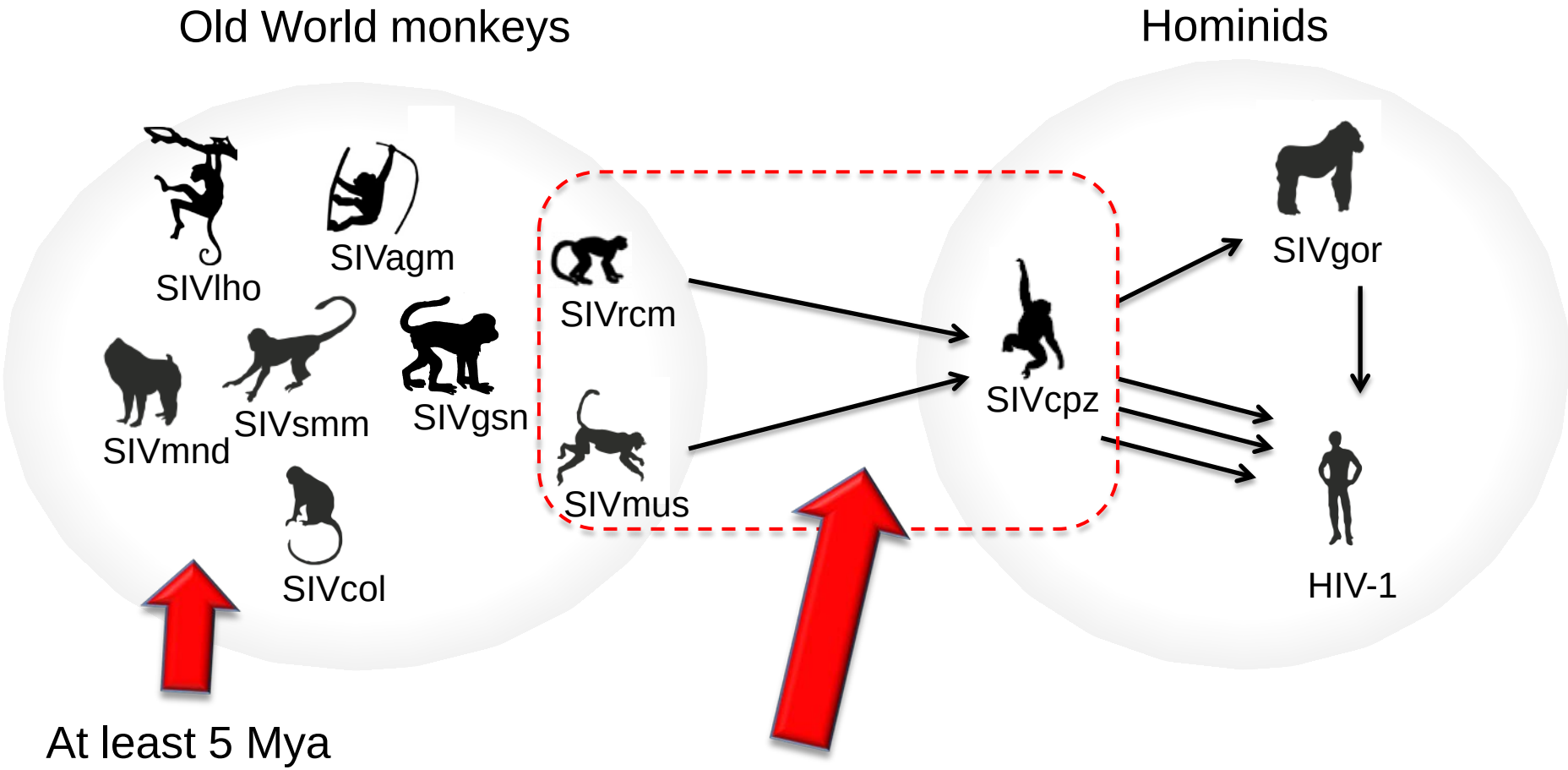




There was a distantly related lentivirus in a prosimian at least 4 million years ago

Gifford, Katzourakis et al. PNAS, 2008

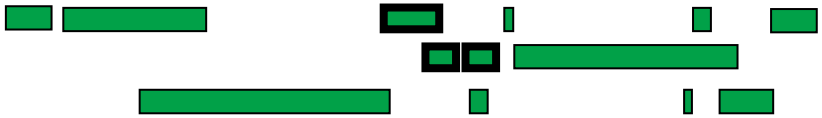
The ancient origins of HIV-1



SIVcpz is a recombinant between two viruses from old world monkeys

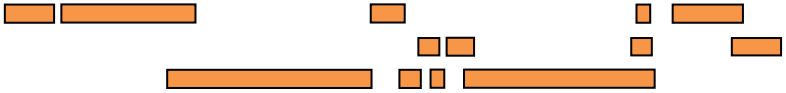
Red-capped mangabeys

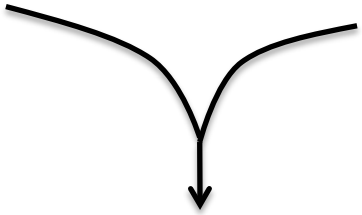
SIVrcm



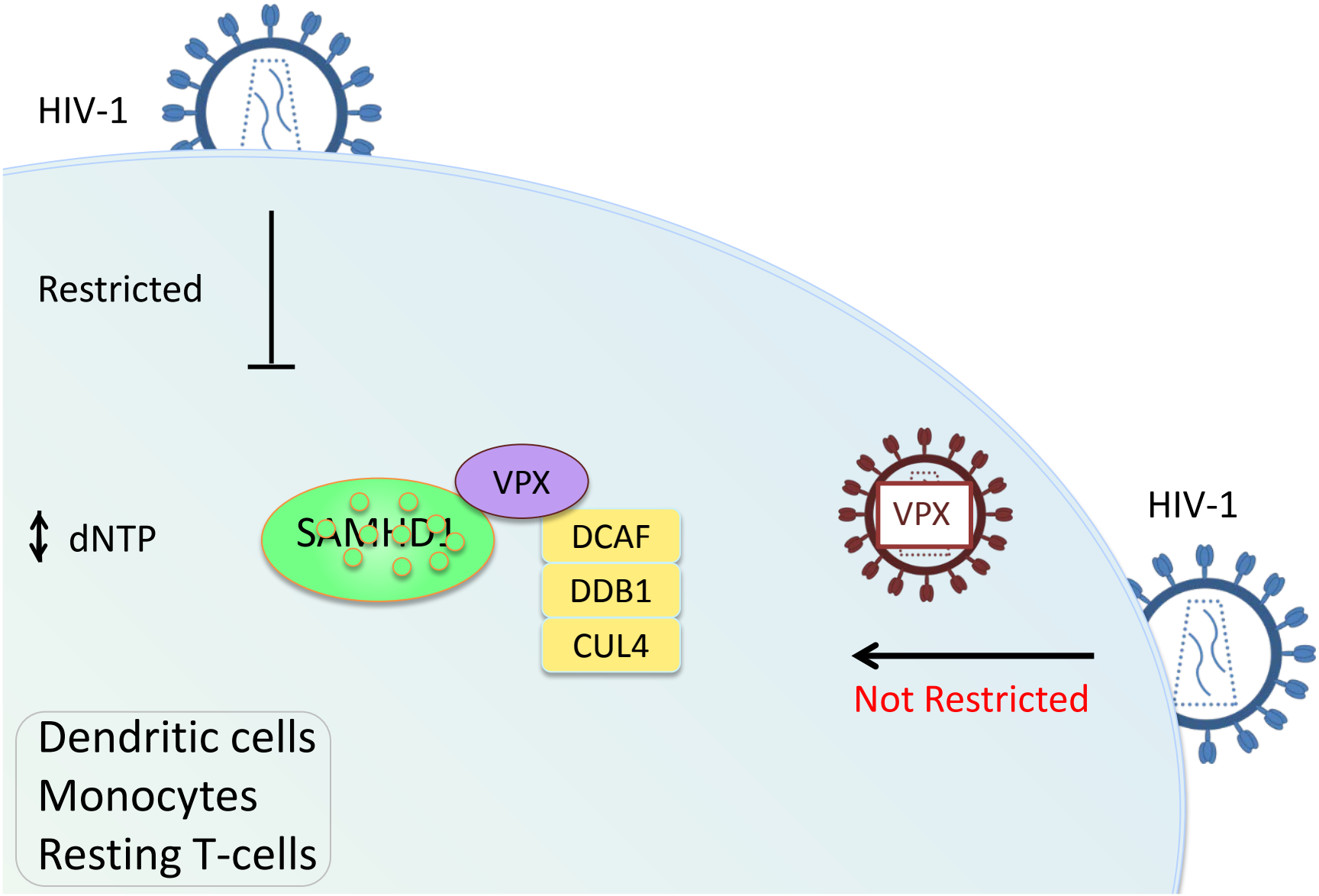
Guenons

SIVmus/mon/gsn

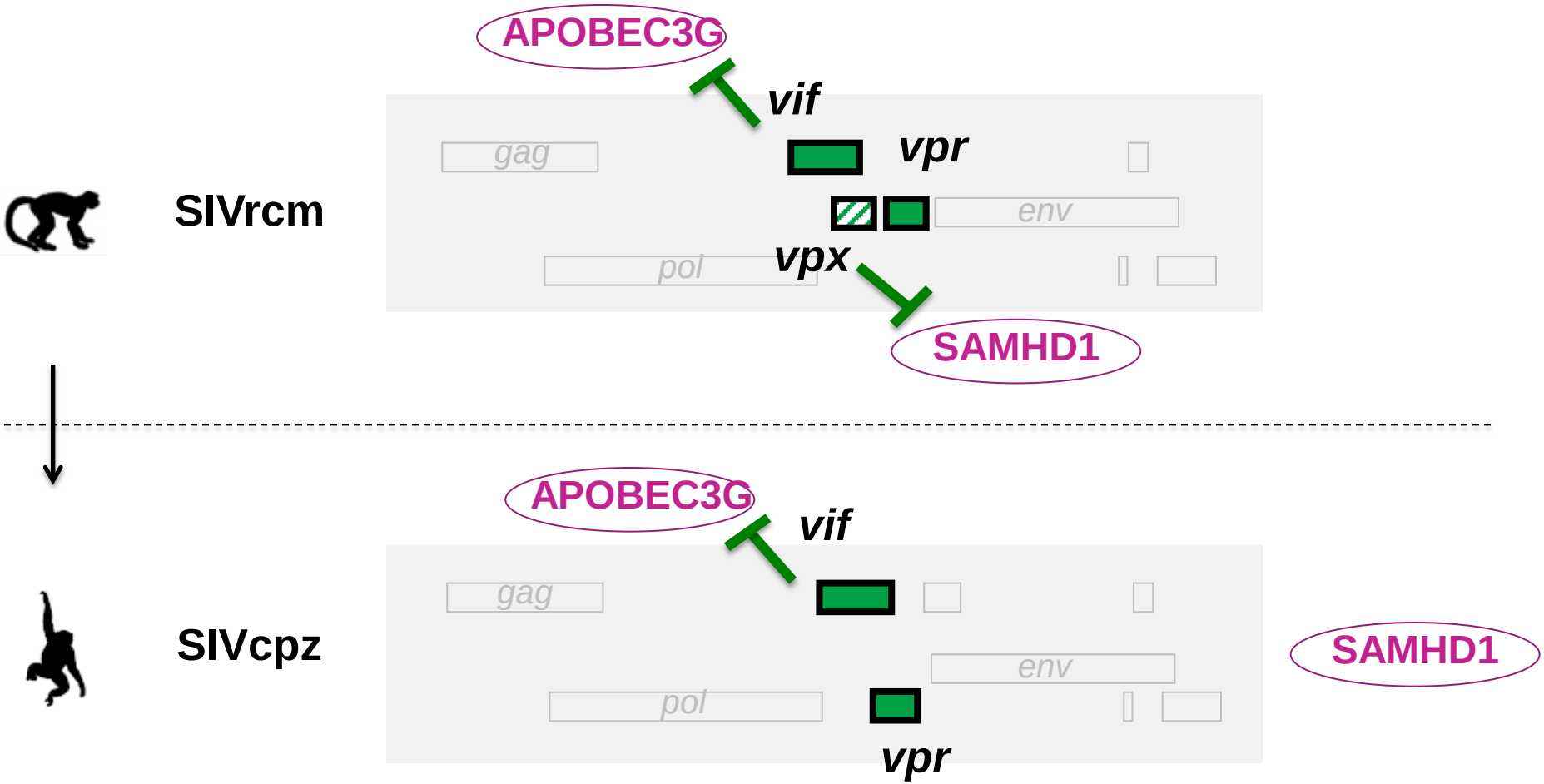




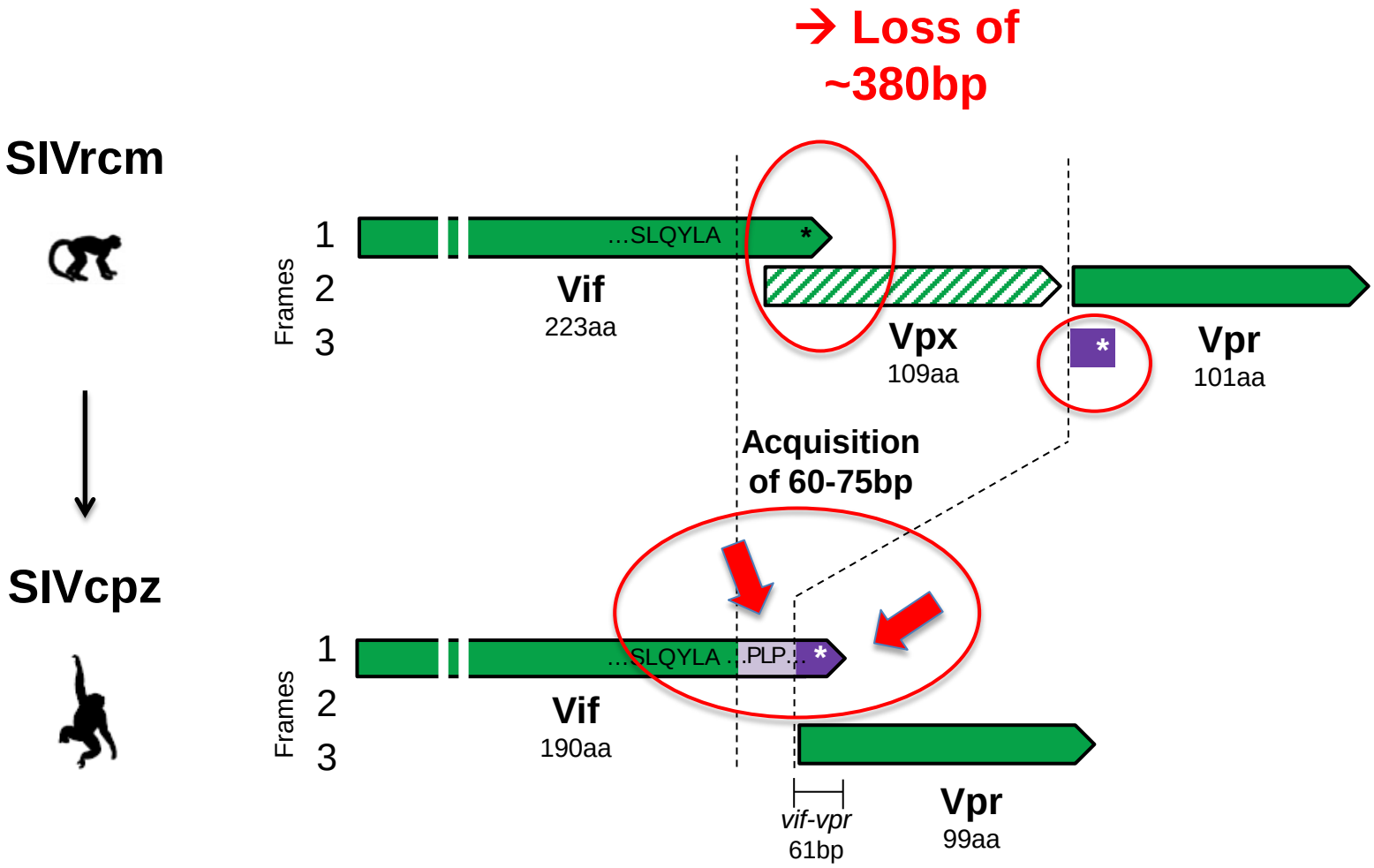
Vpx antagonizes the host SAMHD1 protein



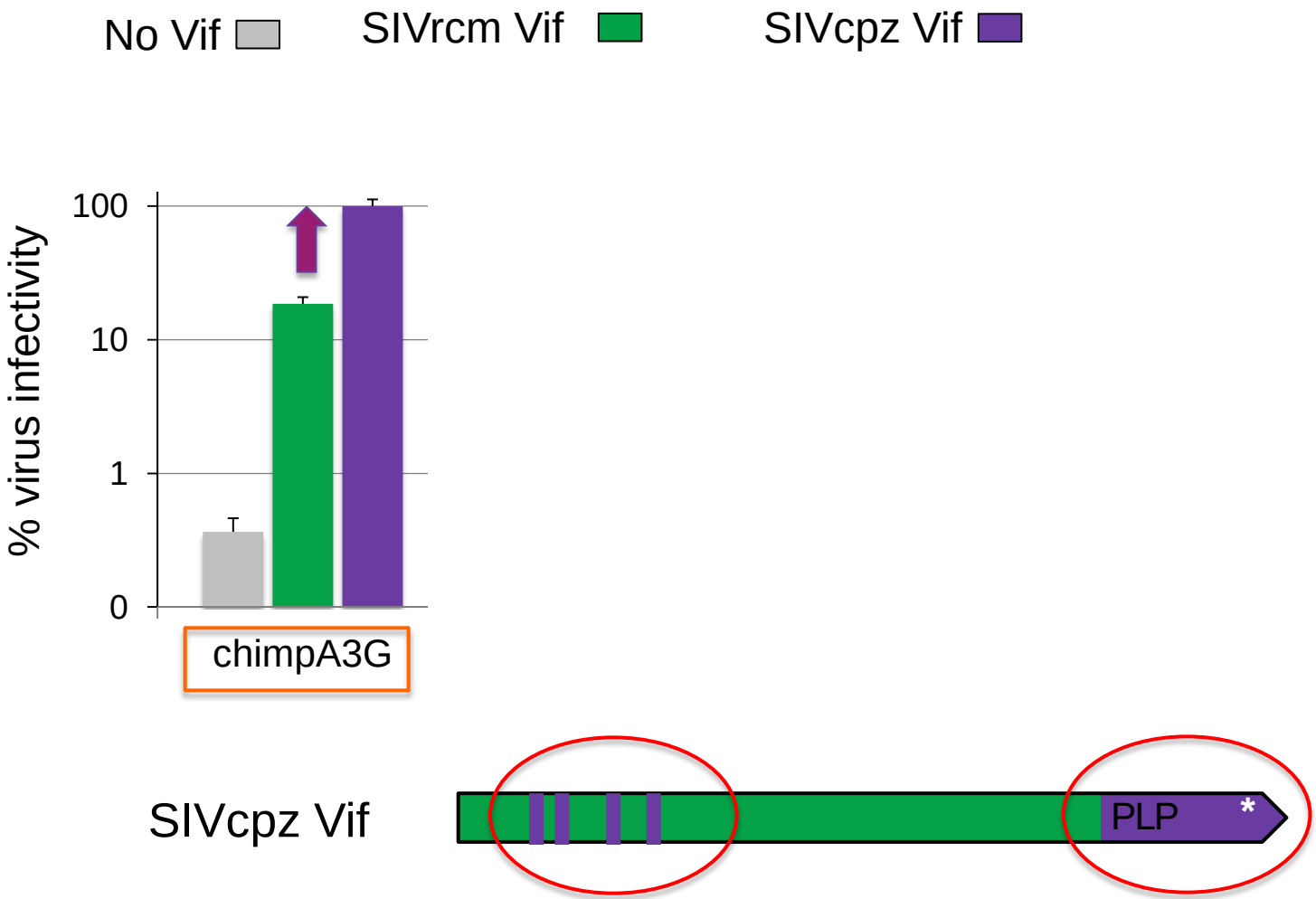
The capacity to antagonize SAMHD1 was lost during the genesis of SIVcpz



The deletion of Vpx from SIVcpz also altered Vif



Loss of *vpx* was driven by selection for changes in *vif* to gain APOBEC3 antagonism



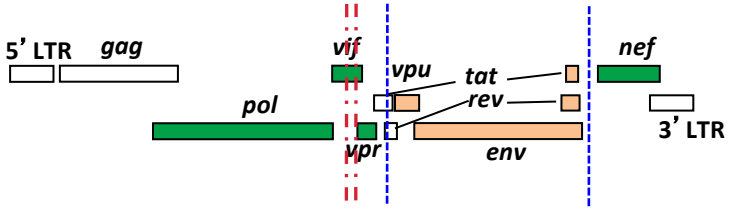
Red-capped mangabeys

Guenons

SIVrcm

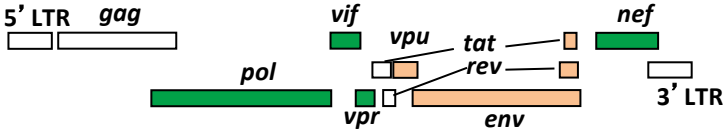
SIVmus

Recombination between distant SIVs



Loss of Vpx
Reconstruction of Vif

SIVcpz



Adaptation of Vif to chimpA3G and A3D

SIVcpz epidemic in chimpanzees

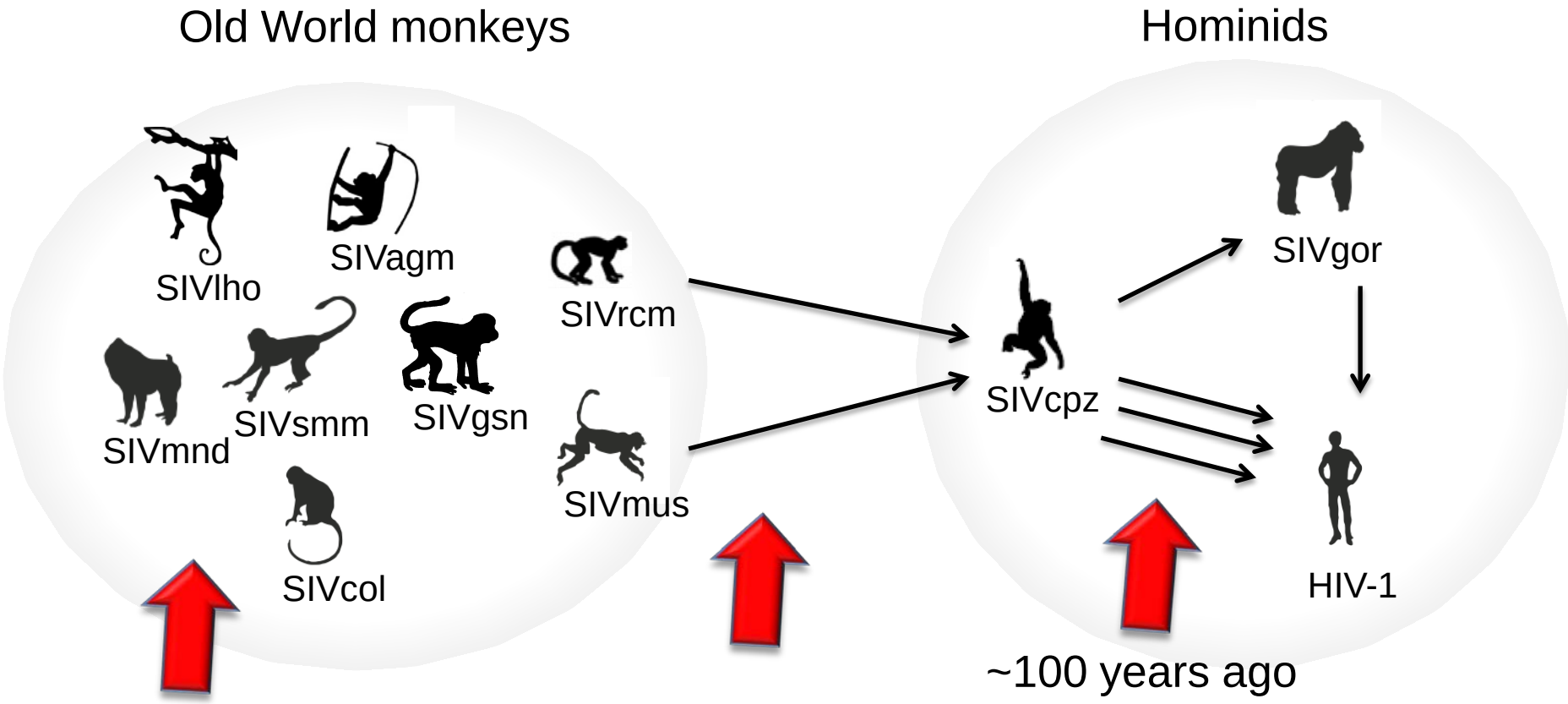
SIVcpz Vif was pre-equipped to degrade humA3G

Hominoids

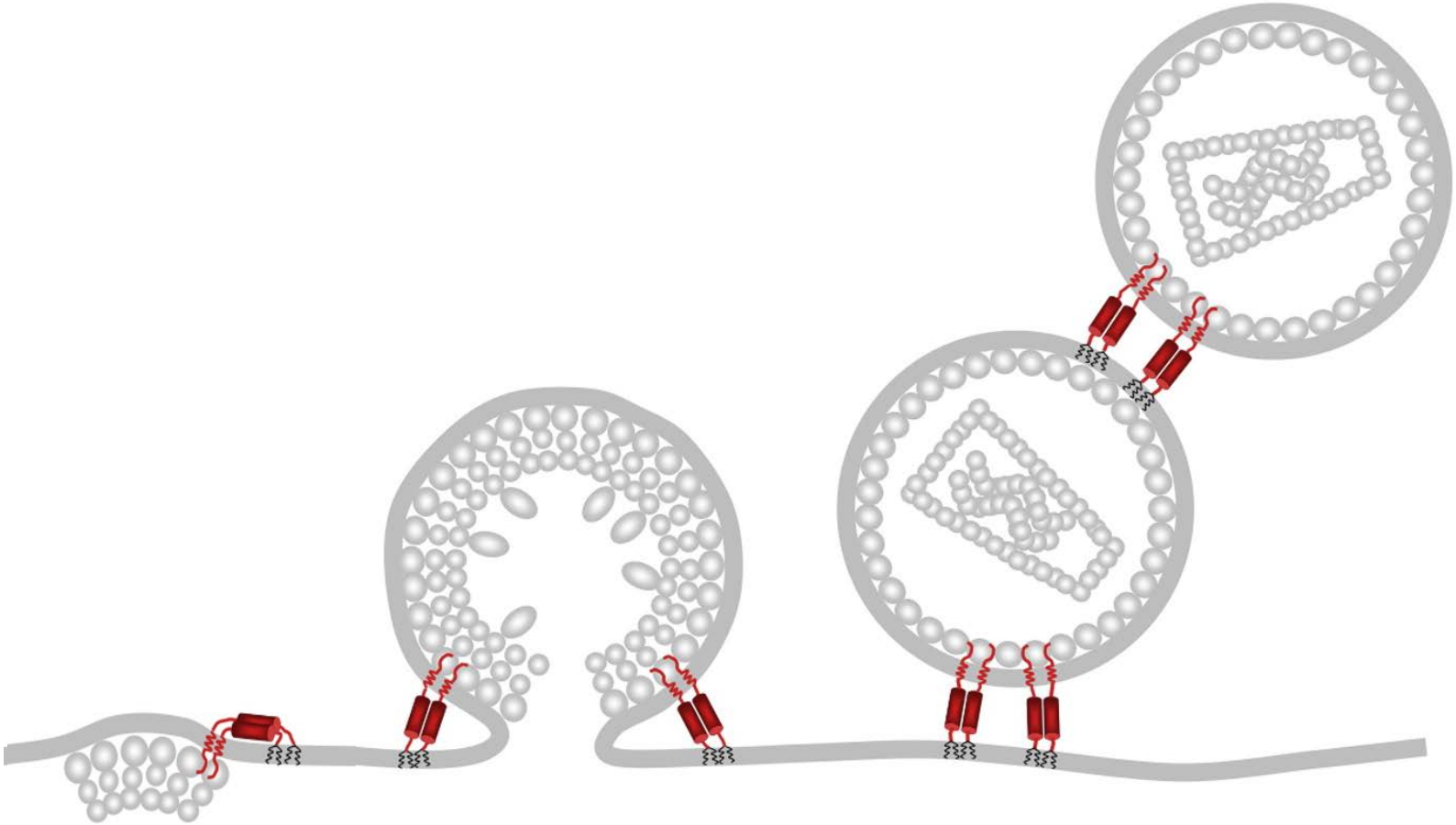
SIVgor in gorillas 

HIV-1 in humans 

The ancient origins of HIV-1



Tetherin directly tethers virions to cells



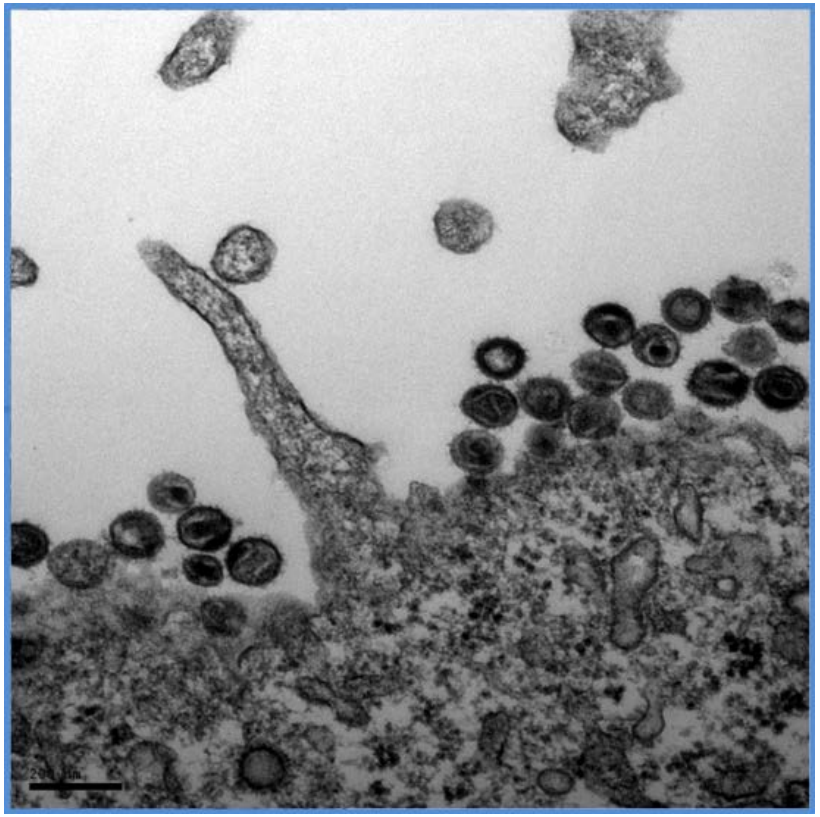
Counter-acted by HIV-1 Vpu which removes Tetherin from the cell surface

Perez-Caballero *et al. Cell, 30 October 2009*

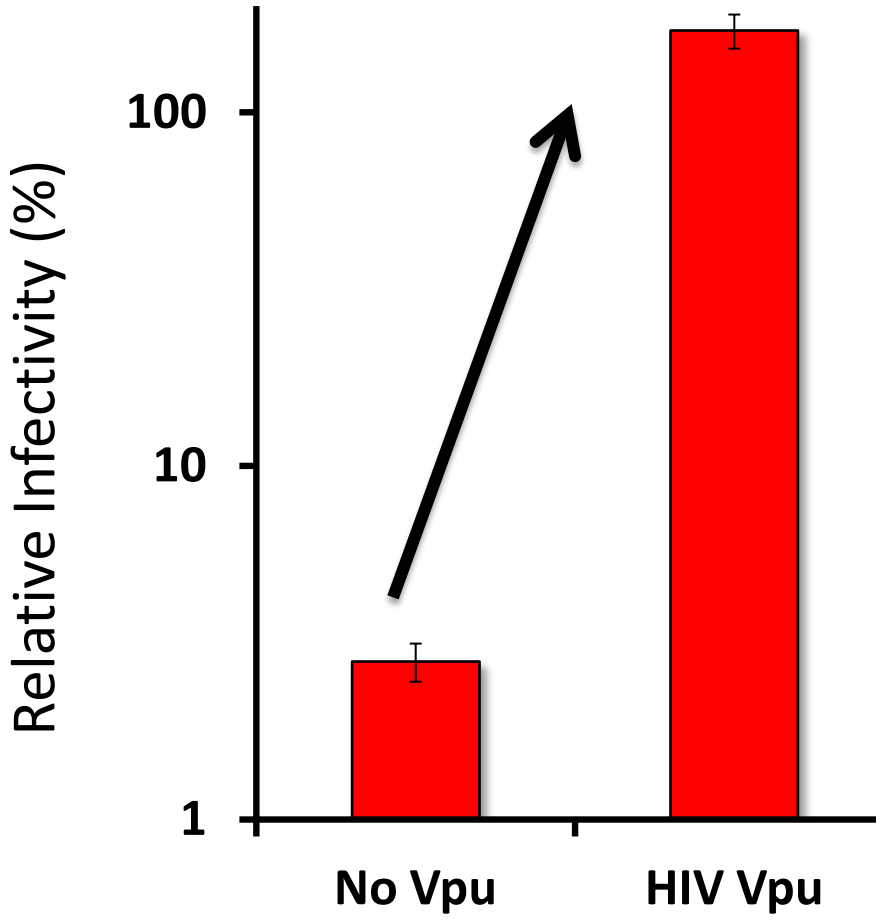
Virus release is inhibited by Tetherin

No Tetherin

+ Tetherin



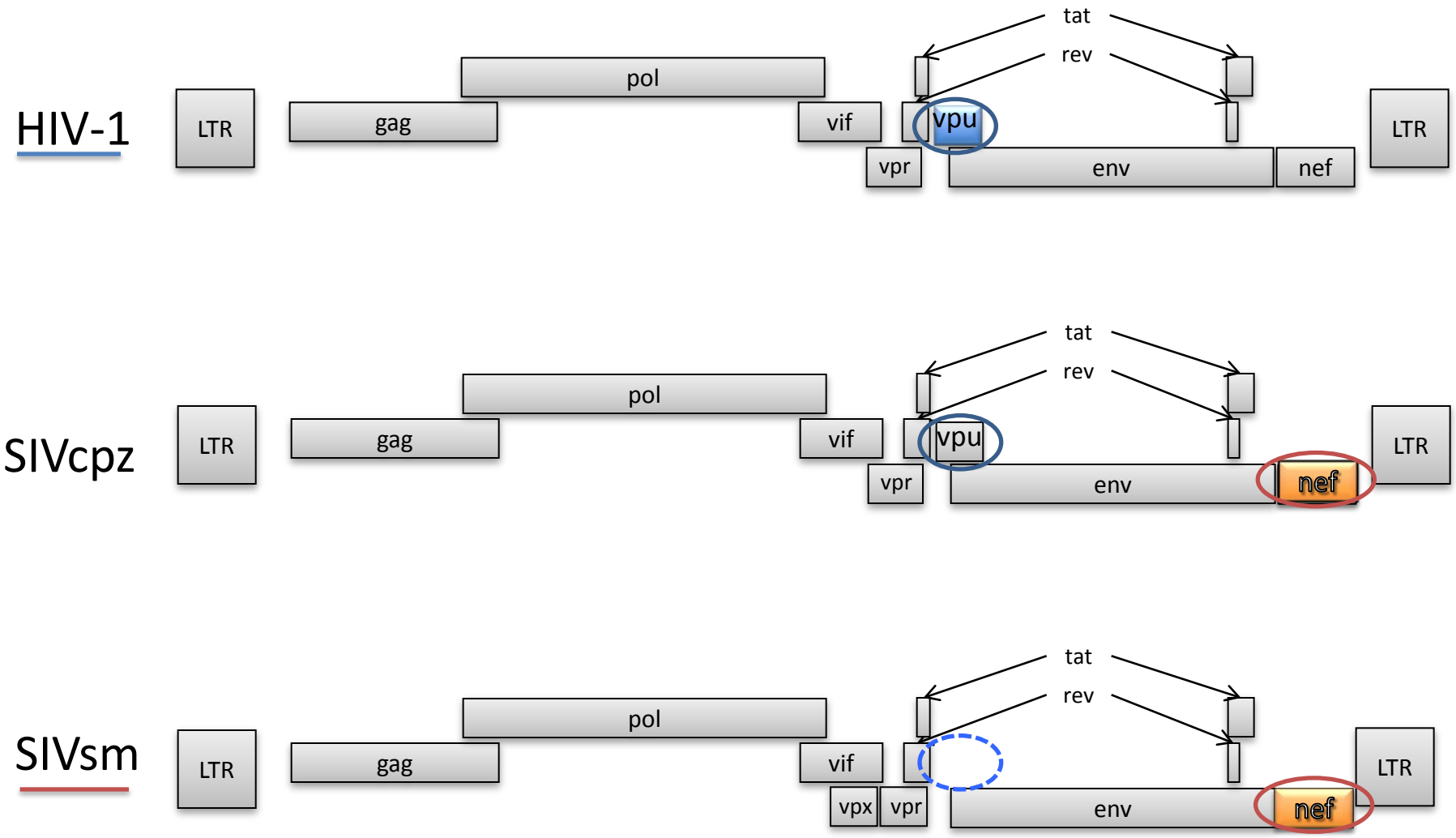
SIVcpz Vpu cannnot antagonize Tetherin



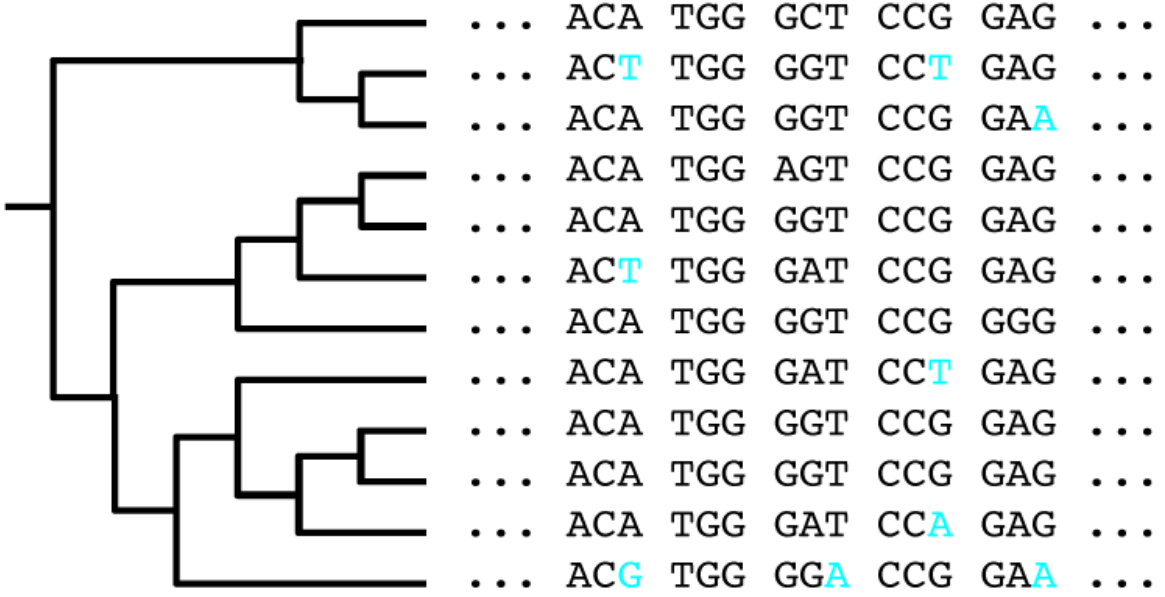
Virus production in the presence of Tetherin

Lim ES, Malik HS and Emerman M. *JV, 2010*

Most SIVs use Nef, not Vpu, to counteract Tetherin



Evolution-guided identification of host-virus interaction sites

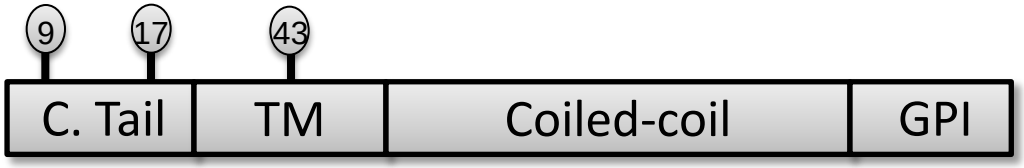


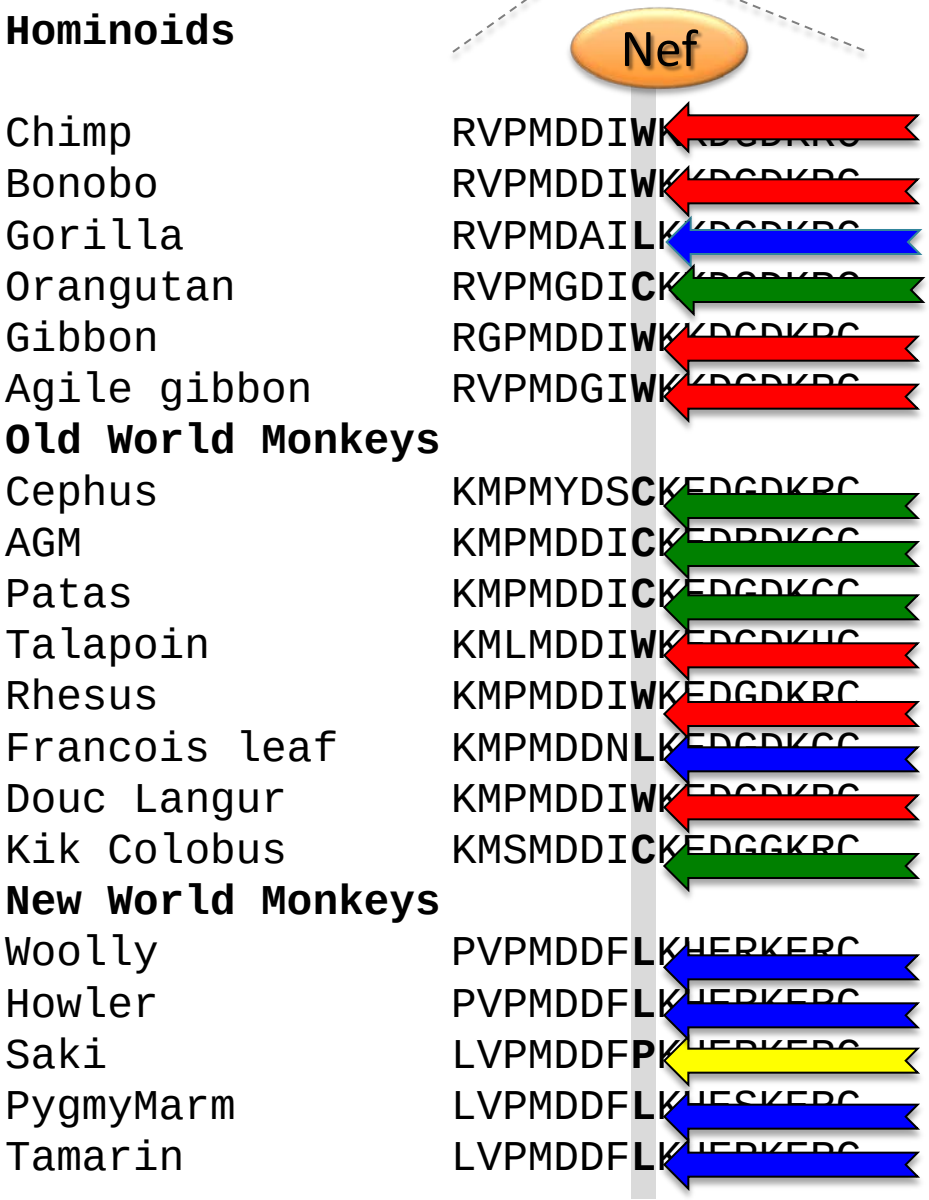
Target binding surface

Purifying selection (dN/dS < 1)

Positive selection (dN/dS > 1)

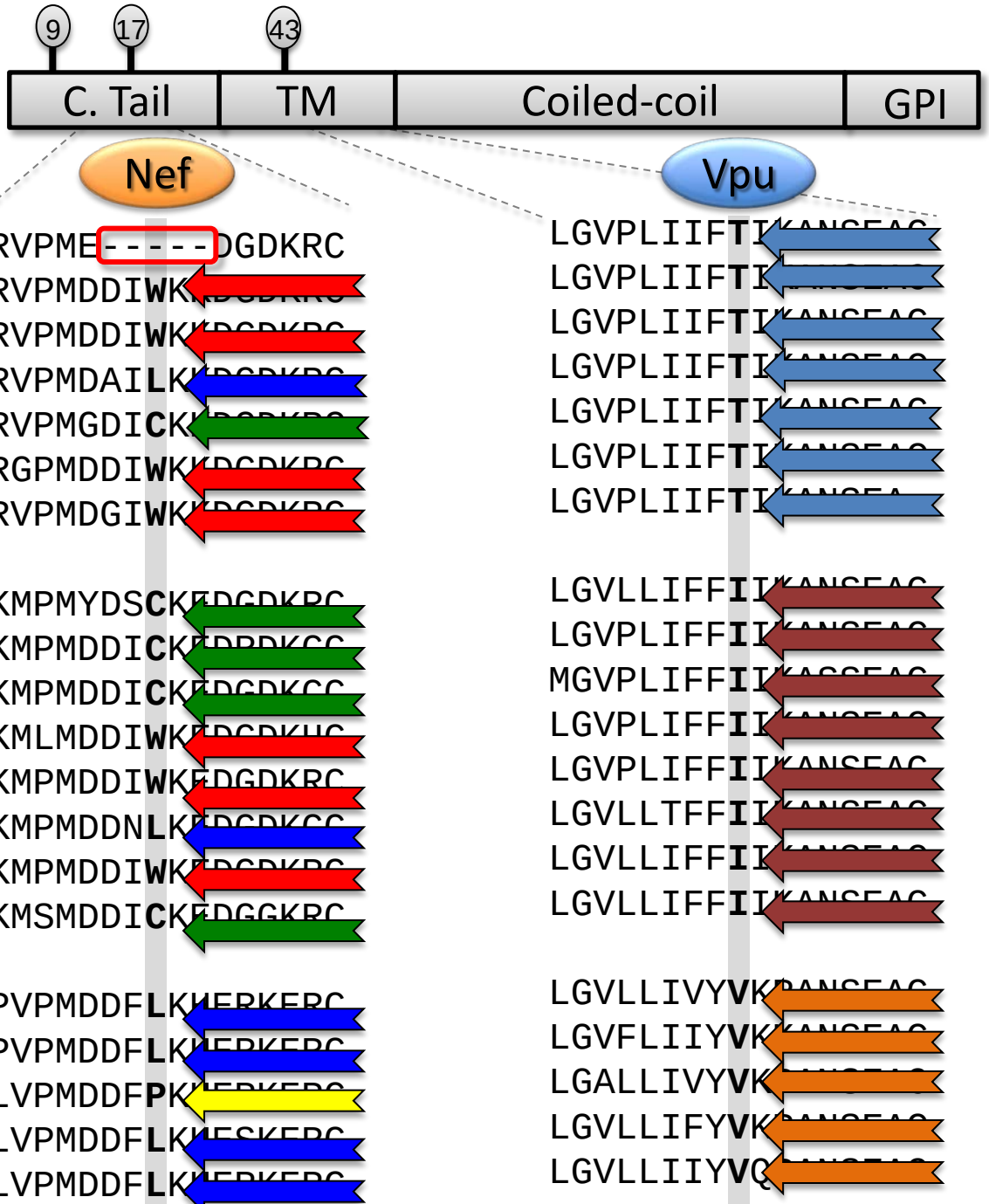
Tetherin





Strong signal of positive selection

Tetherin


9
17
43
C. Tail
TM
Coiled-coil
GPI
Nef
Vpu
Hominoids
Human
Chimp
Bonobo
Gorilla
Orangutan
Gibbon
Agile gibbon
Old World Monkeys
Cephus
AGM
Patas
Talapoin
Rhesus
Francois leaf
Douc Langur
Kik Colobus
New World Monkeys
Woolly
Howler
Saki
PygmyMarm
Tamarin
RVPME-----DGDKRC
RVPMDDIWK
RVPMDDIWK
RVPMDAILK
RVPMGDICK
RGPMDDIWK
RVPMDGIWK
KMPMYDSCK
KMPMDDICK
KMPMDDICK
KMLMDDIWK
KMPMDDIWK
KMPMDDNLK
KMPMDDIWK
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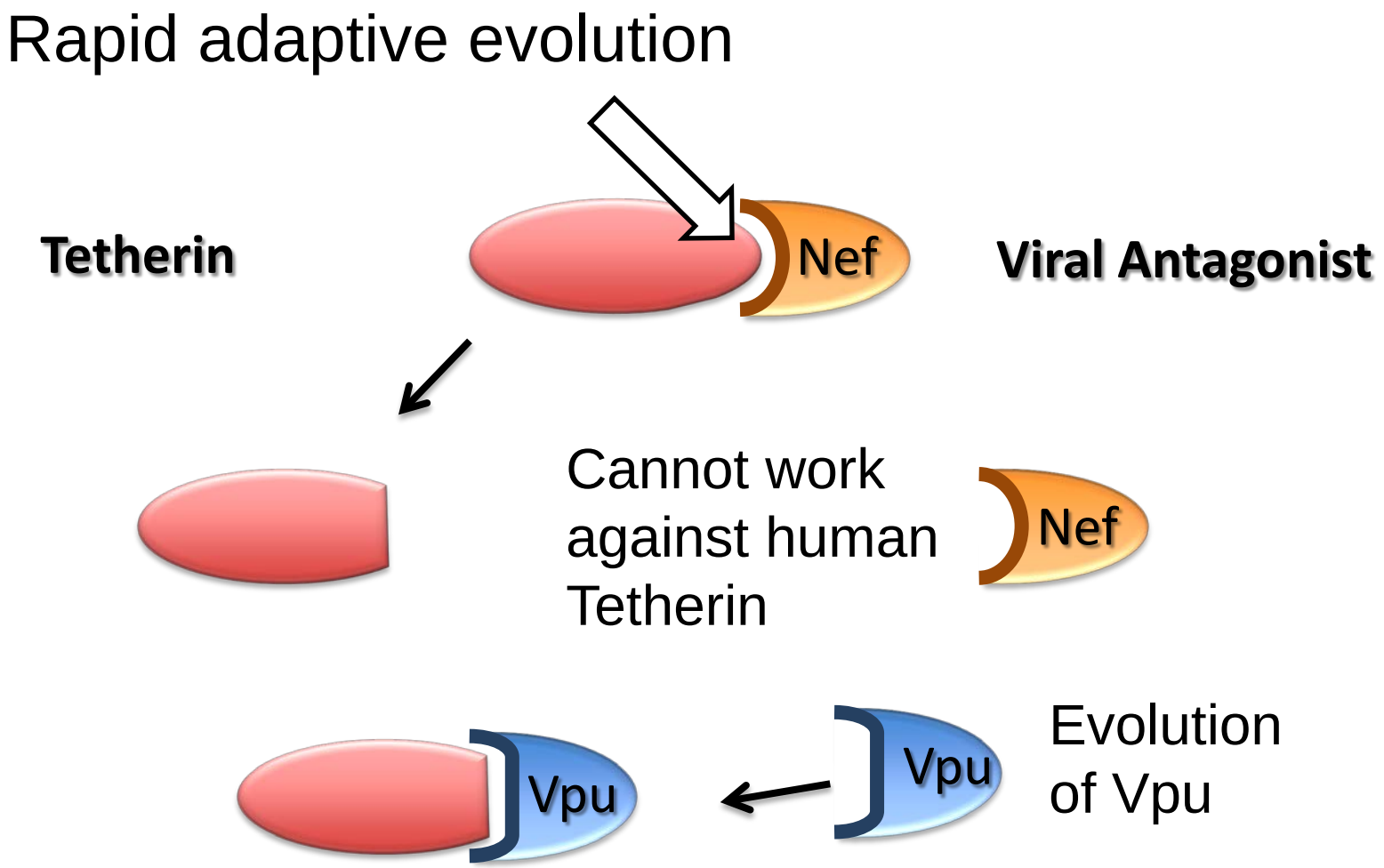
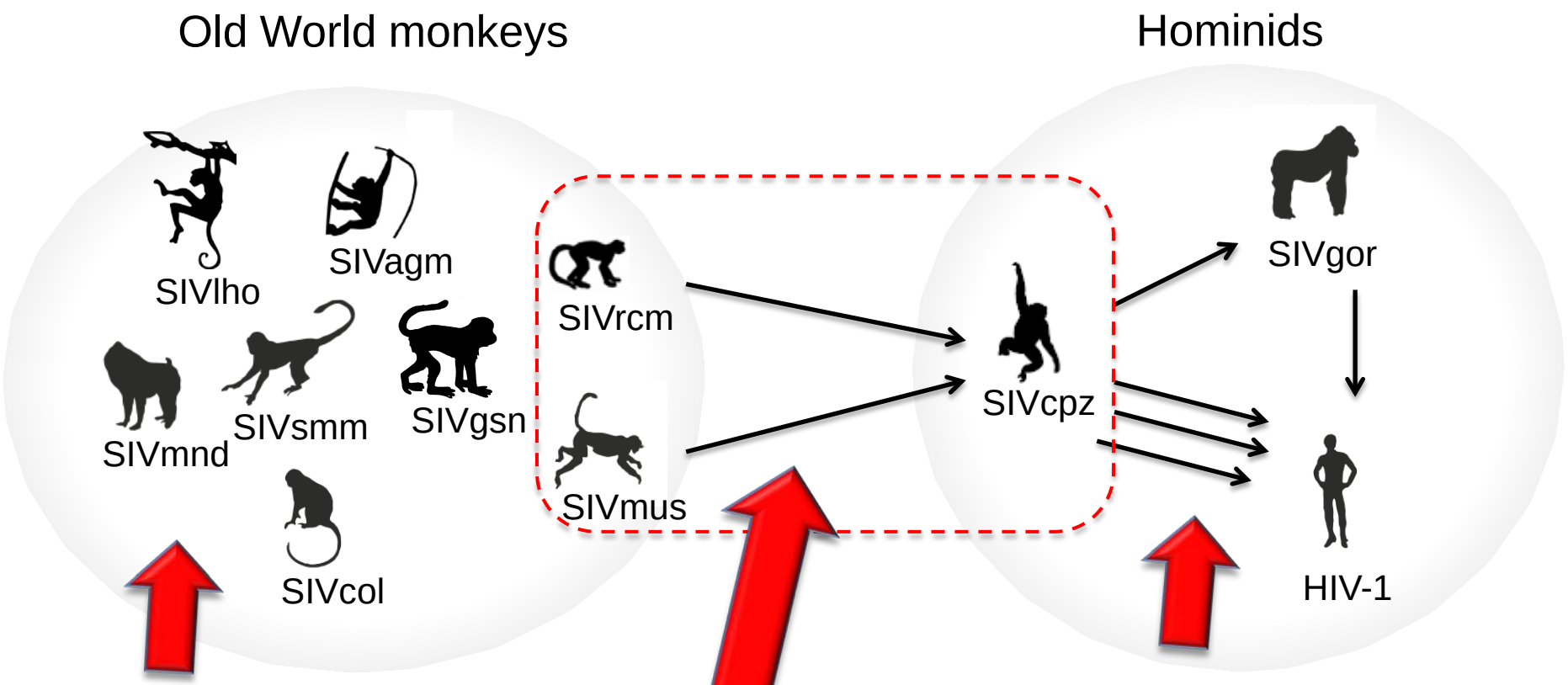
LVPMDDFLK
LGVPLIIFTI
LGVPLIIFTI
LGVPLIIFTI
LGVPLIIFTI
LGVPLIIFTI
LGVPLIIFTI
LGVPLIIFTI
LGVLLIFFII
LGVPLIFFII
MGVPLIFFII
LGVPLIFFII
LGVPLIFFII
LGVLLTFFII
LGVLLIFFII
LGVLLIFFII
LGVLLIVYVK
LGVFLIIYVK
LGALLIVYVK
LGVLLIFYVK
LGVLLIIYVQ

HIV-1 adapted to humans by evolution of Vpu towards the unique form of human Tetherin



Only occurred in the pandemic HIV-1 (group M)

The ancient origins of HIV-1

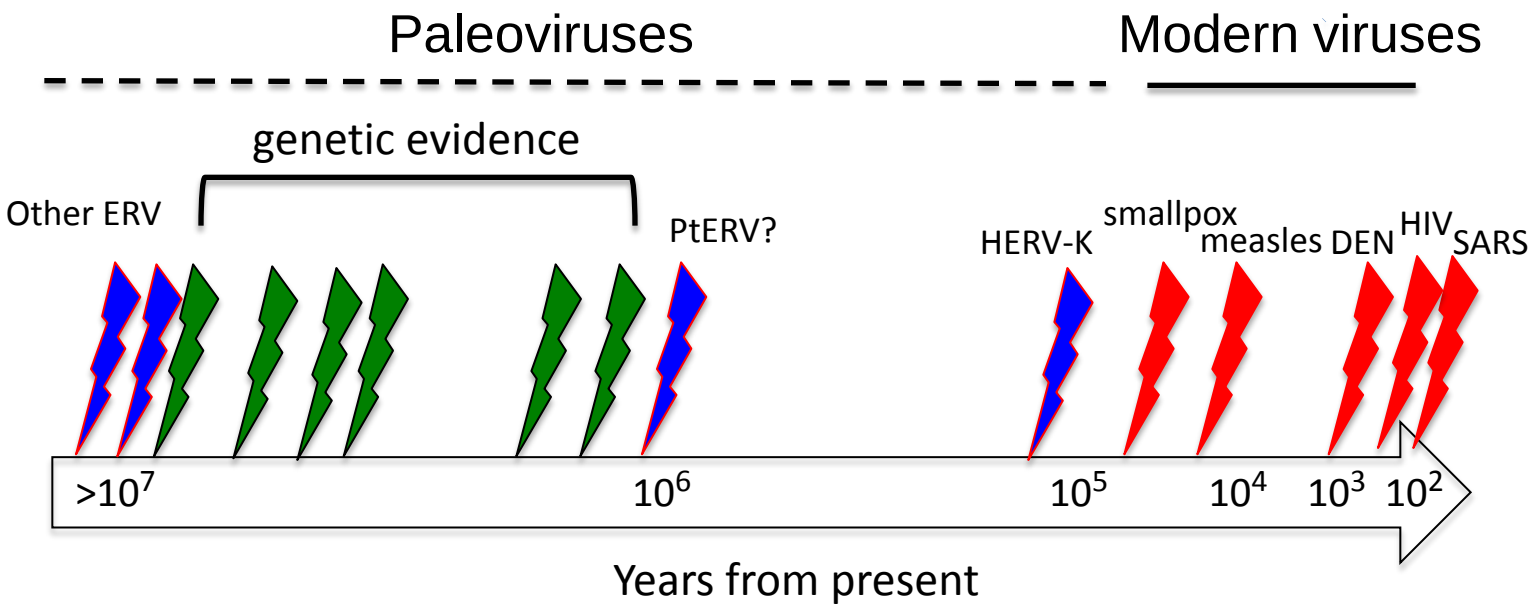


Viruses similar to HIV are ancient pathogens of primates

Adaptation of an HIV-like virus to hominids by gene deletion and

The pandemic form of HIV- 1 acquired a final adaptation to humans

Modern and ancient viral pathogens of humans and human ancestors



Episodic selections by ancient pathogenic viruses has driven the evolution of current innate immunity genes

Ancient infections influence modern virus susceptibility

Fred Hutchinson Cancer Research Center