Lecture 1

Origin and progression of HIV-1

Adelajda Zorba

HIV is the causative agent of AIDS

- 60 million infected people
- 25 million deaths
- 14 million orphaned children in South Africa alone

UNAIDS 2009 report

AIDS does not develop in monkeys where HIV originated from.

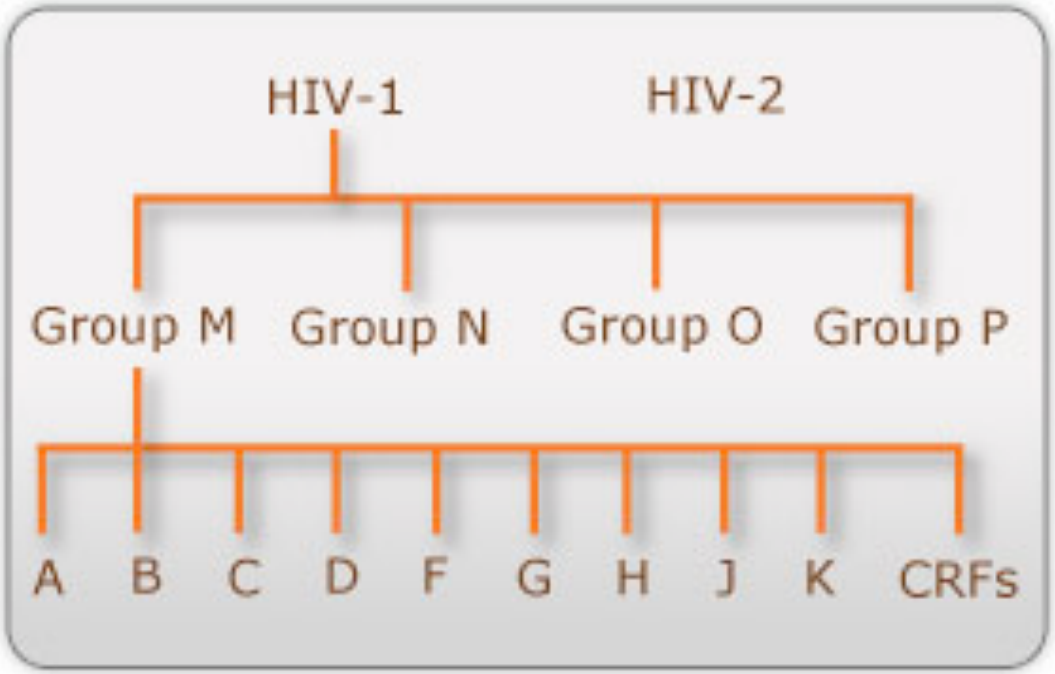
How come?

Did it really?

HIV is a

zoonotic (can be transmitted from non-human animals to humans)

lentivirus (lt. lenti=slow, virus=poison)



Found in chimpanzees today is SIVcpz (<-misnomer)

http://www.avert.org/hiv-types.htm

HIV-1 origin: chimpanzee

HIV-2 origin : Sooty mangabey

http://www.prn.org/index.php/progression/article/origin_of_the_aids_pandemic_58
http://monkeysphotos.blogspot.com/2008/10/white-collared-mangabey.html

Humans acquired HIV-1 from chimpanzees:

LETTERS TO NATURE

Genetic organization of a chimpanzee lentivirus related to HIV-1

1990

Thierry Huet, Rémi Cheynier, Andreas Meyerhans, Georges Roelants* & Simon Wain-Hobson

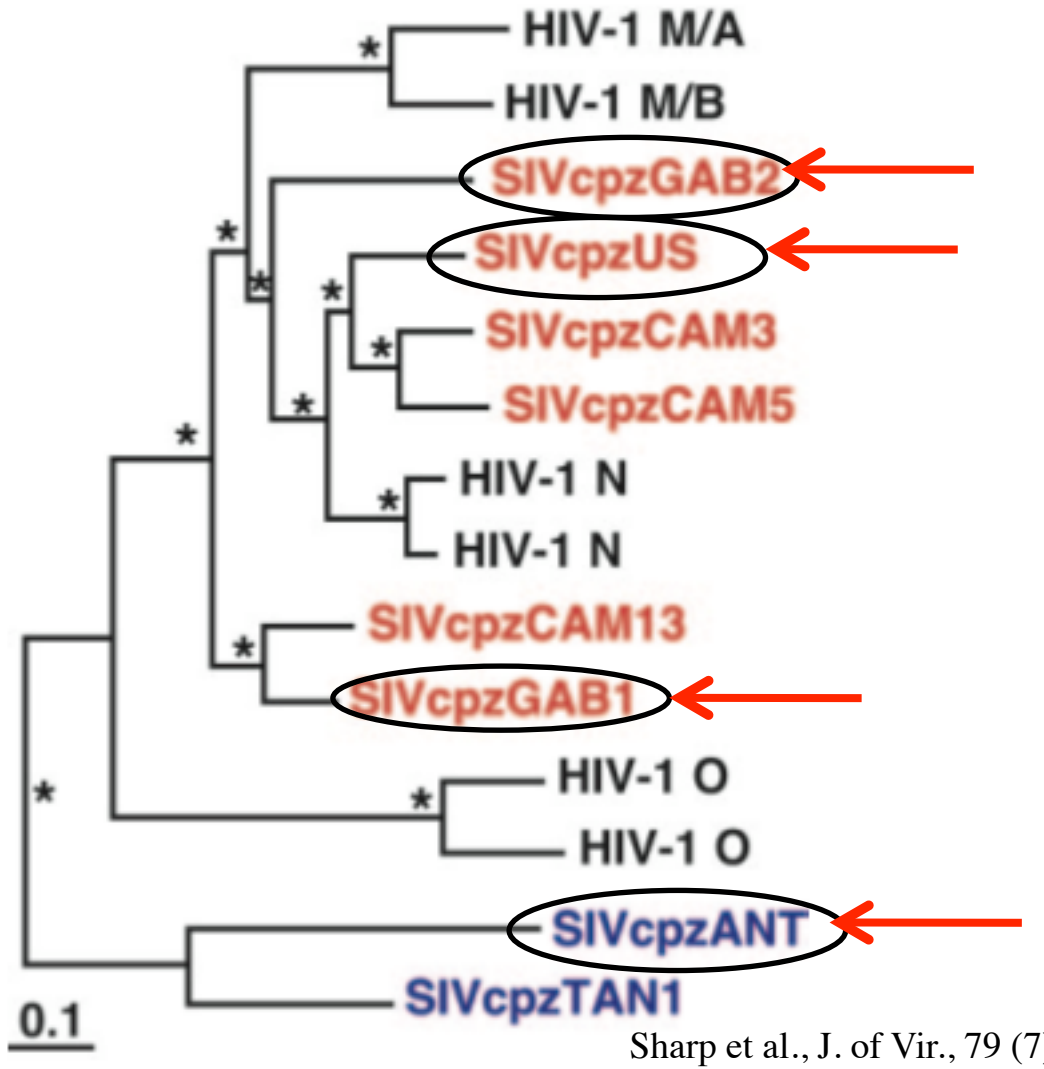
Laboratoire de Biologie et Immunologie Moléculaires des Rétrovirus, Institut Pasteur, 28 Rue de Dr Roux, 75724 Paris cedex 15, France
* Centre International de Recherches Médicales de Franceville, BP 769, Franceville, Gabon

TABLE 1 Amino acid homology between HIV/SIV isolates (%)

								ENV			
SIV_{CPZ} compared with:	*gag*	*pol*	*vif*	*vpr*	*tat*	*rev*	*vpu*	*env*	SU	TM	*nef*
$HIV\text{-}1_{BRU}$	74.8	84.0	67.2	79.2	63.9	54.3	35.8	62.7	59.5	66.9	70.2
$HIV\text{-}1_{OYI}$	74.7	83.7	67.7	80.2	65.6	55.2	38.5	63.5	61.5	65.9	74.1
$HIV\text{-}1_{MAL}$	73.4	84.1	67.7	79.2	65.5	55.2	37.3	65.8	63.4	69.0	72.9
$HIV\text{-}1_{ELI}$	74.3	83.5	67.2	83.3	61.6	56.4	37.5	65.1	65.0	65.2	69.7
$HIV\text{-}2_{ROD}$	56.2	57.2	35.1	47.3	36.1	32.0	—	37.0	34.2	40.6	36.5
SIV_{MAC}	54.9	57.4	35.8	49.0	39.8	32.0	—	35.3	31.3	40.5	36.1
SIV_{AGM}	55.9	60.4	33.7	—	34.1	39.8	—	38.6	33.2	45.9	45.0
SIV_{MND}	52.1	58.1	30.6	34.4	32.2	28.0	—	32.7	28.1	38.3	41.8

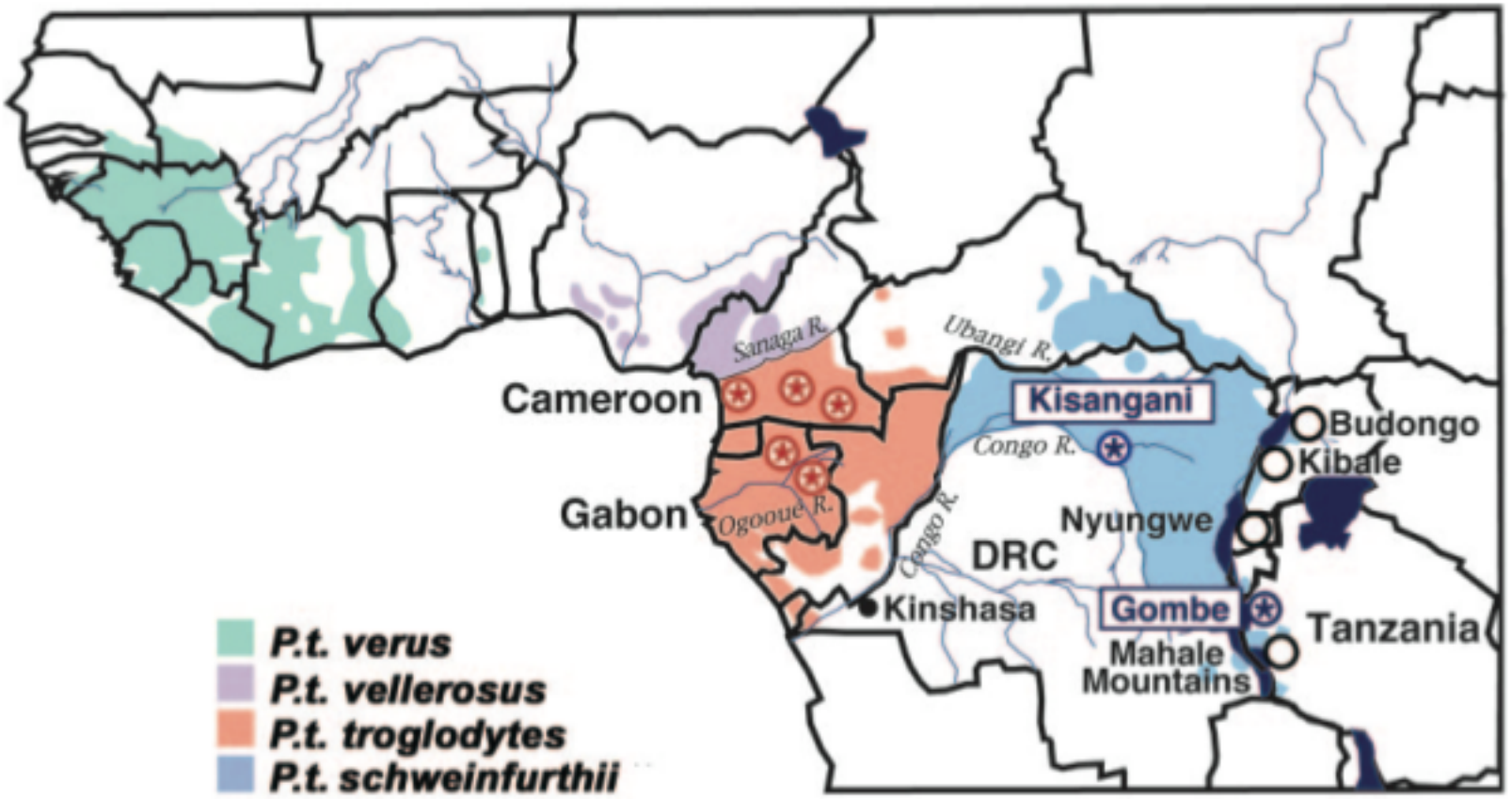
Similarity between pairs of protein sequences using SIV_{CPZ} as reference. Sequences were aligned using the program of Wilbur and Lipman[21] (k-tuple size 1, window 20, gap penalty 2). The sequences (and geographical origin) are $HIV\text{-}1_{BRU}$ (France)[11], $HIV\text{-}1_{OYI}$ (Gabon)[22], $HIV\text{-}1_{MAL}$ and $HIV\text{-}1_{ELI}$ (Zaire)[1,2], $HIV\text{-}2_{ROD}$ (Cape Verde)[1,3], SIV_{MAC} 142 (Boston)[7], SIV_{AGM} TYO (Kenya)[23] and SIV_{MND} GB-1 (Gabon)[24].

Evolutionary relationship of SIVcpz and HIV-1 based on envelope protein sequence analysis



Sharp et al., J. of Vir., 79 (7), 3891, (2005)

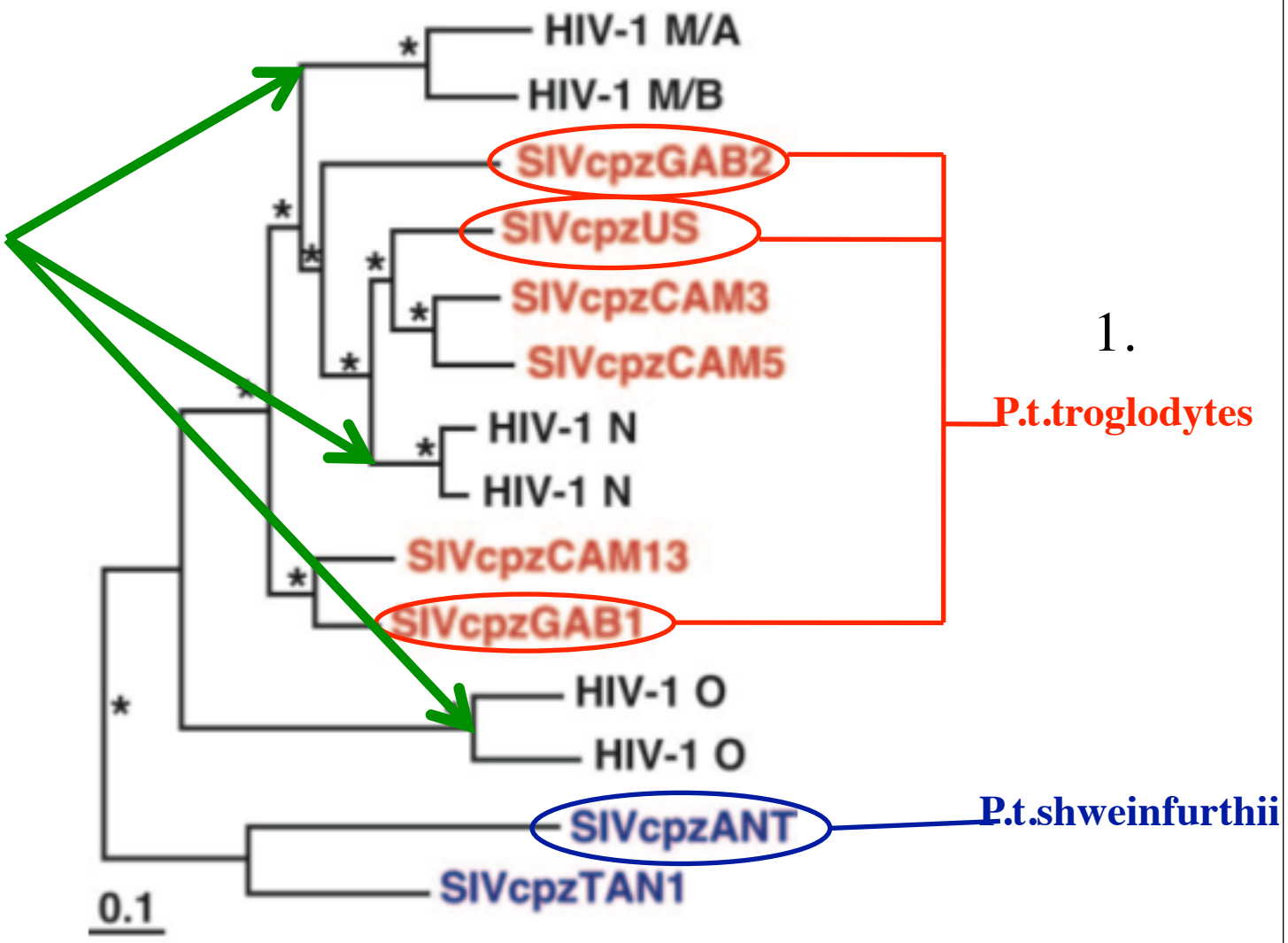
Four chimpanzee subspecies based on mtDNA sequence differences



Sharp et al., J. of Vir., 79 (7), 3891, (2005)

Two important observations

2. Three separate introductions of SIVcpz in the human population



Sharp et al., J. of Vir., 79 (7), 3891, (2005)

Humans acquired HIV-1 from cross-species transmission of SIVcpz from chimpanzees

Chimpanzees acquired SIVcpz from:

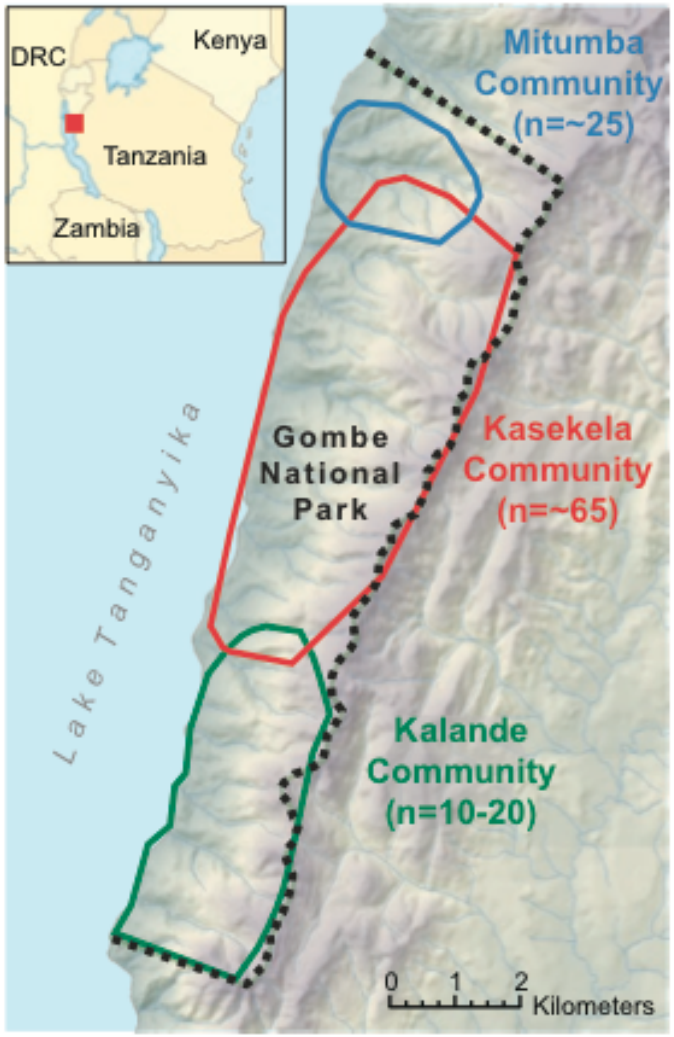
Red-capped mangabeys

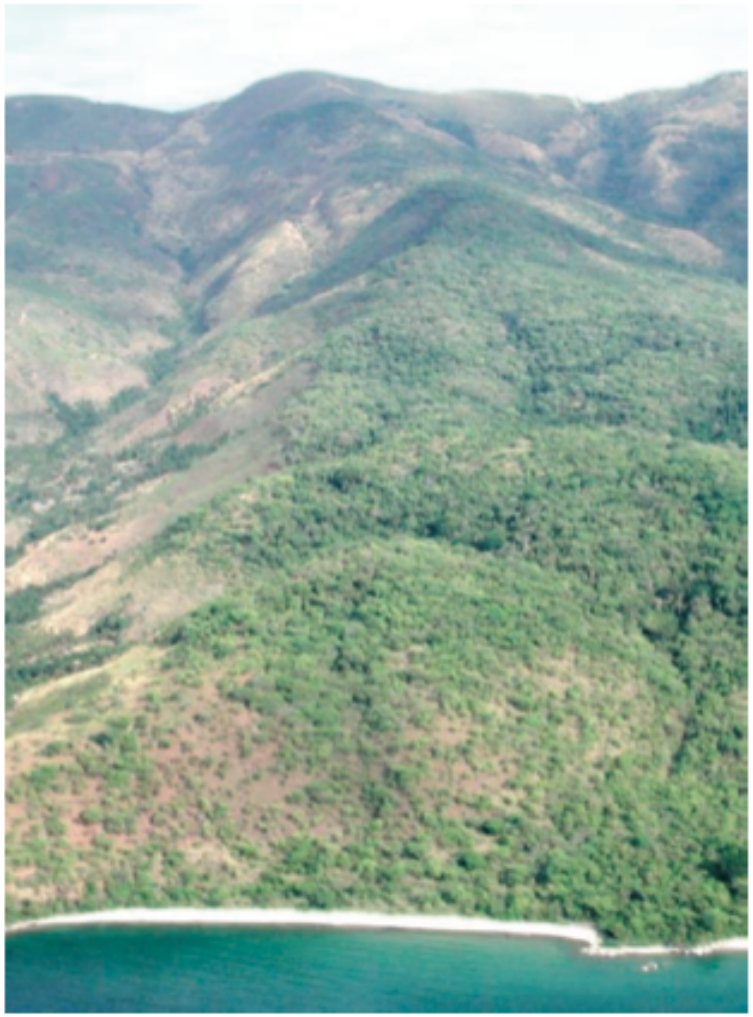
Spot-nosed monkeys

http://cercopan.wildlifedirect.org/tag/red-capped-mangabey/
https://chrisdixonstudios.com/wildprints/top-wildlife-prints/apex0002934_Lesser%20Spot%20Nosed%20Monkey-Close-up.jpg

How to go about studying chimpanzees?

Gombe National Park (Tanzania)





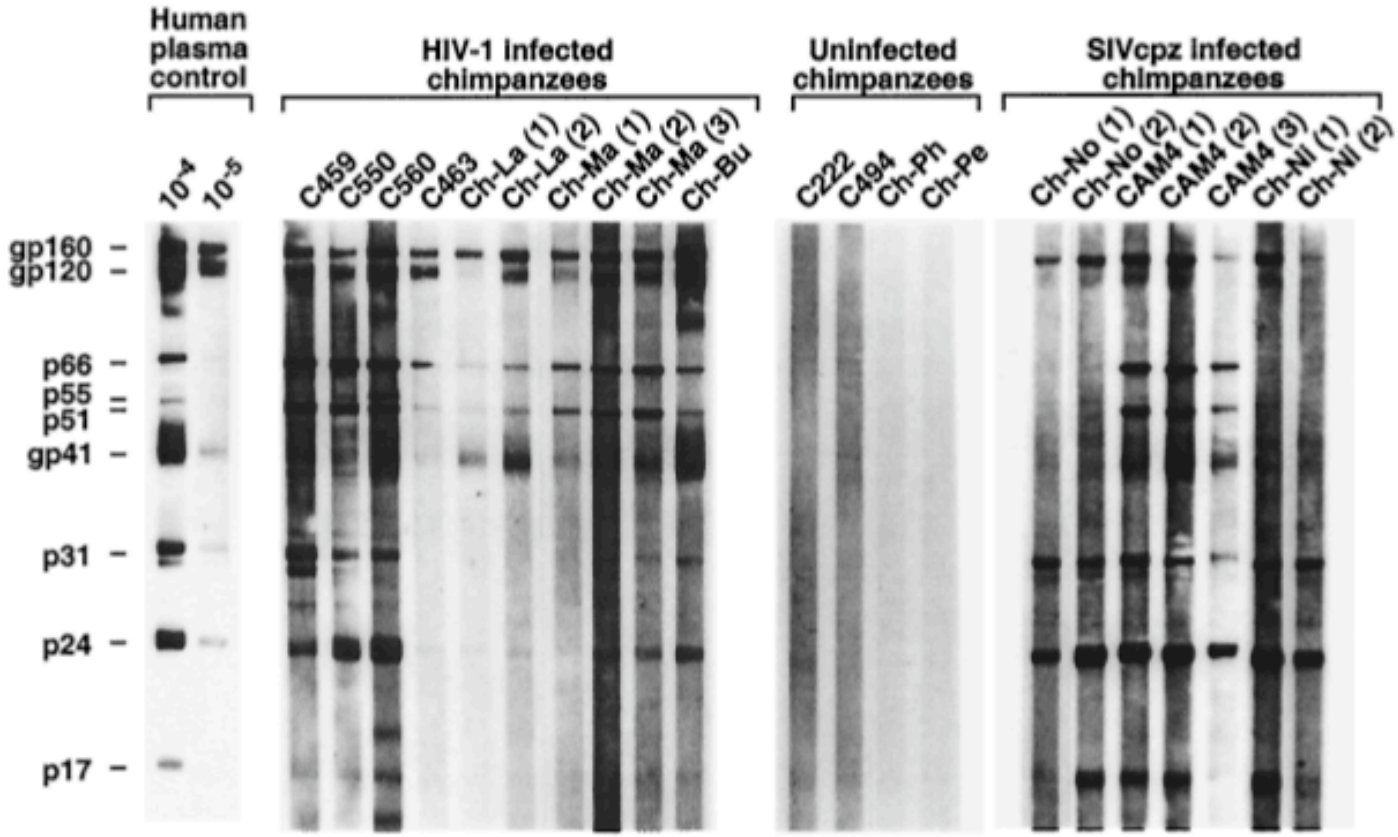
Keele et al., Nature, 460, 515, (2009)

How to go about studying chimpanzees?

Gombe National Park (Tanzania)

- non-invasive (urine and fecal-based Western blots assays)

- RT PCR



Sharp et al., J. of Vir., 79 (7), 3891, (2005)

AIDS does not develop in monkeys where HIV originated from.

How come?

Did it really?

Yes!

Not only SIVcpz but also HIV-1 infected chimpanzees do not develop AIDS

Which model system should be used to research AIDS?

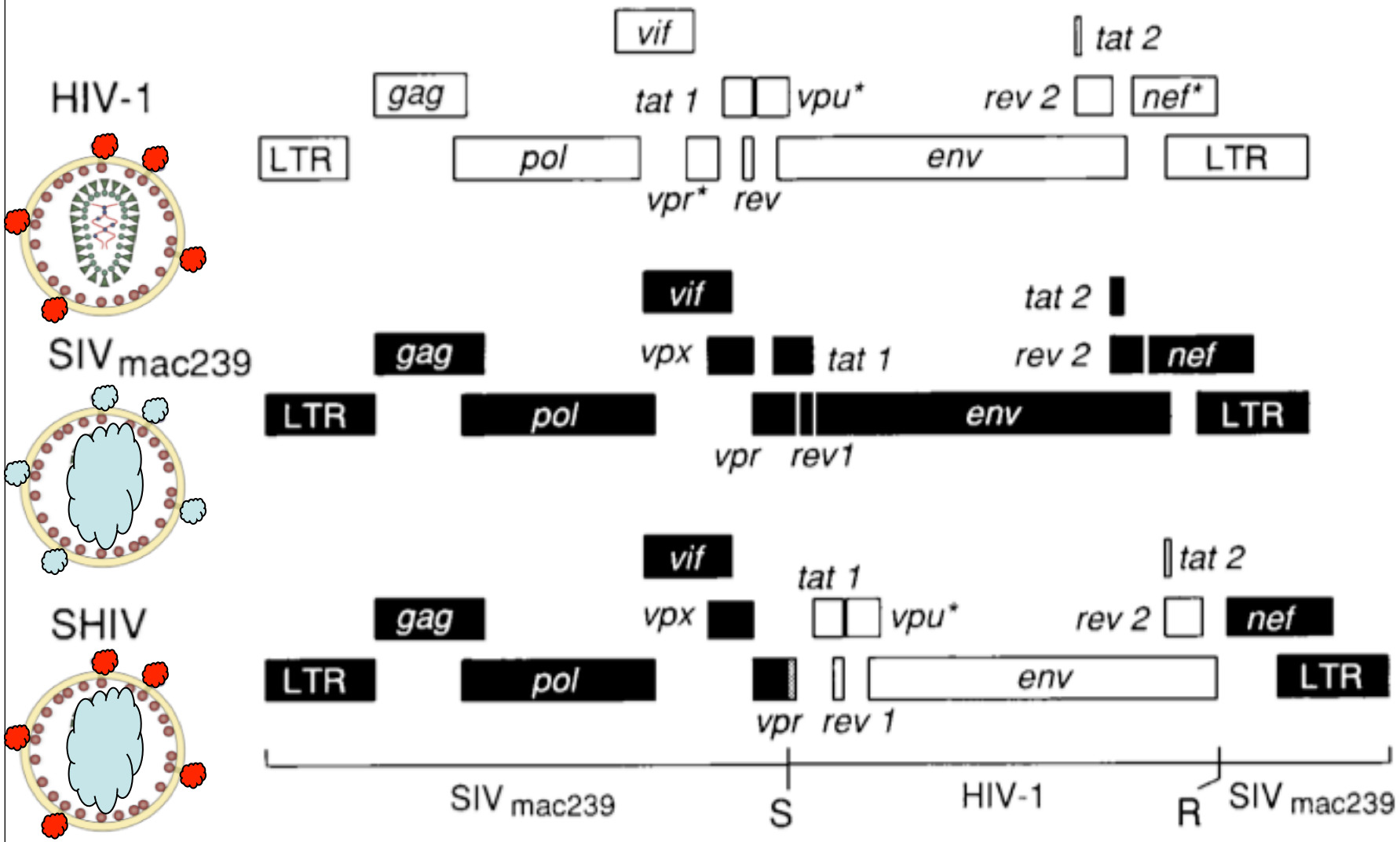
A new model system: Rhesus Macaques

(develop AIDS-like symptoms when infected with SIVcpz not HIV-1)

http://barelyimaginedbeings.blogspot.com/2008_09_01_archive.html

An infectious, even-closer mimic of HIV-1: SHIV

(contains HIV-1 envelope glycoproteins)



Li et al., J. of Acq. Imm. Def. Syn., 5, 639, (1992)

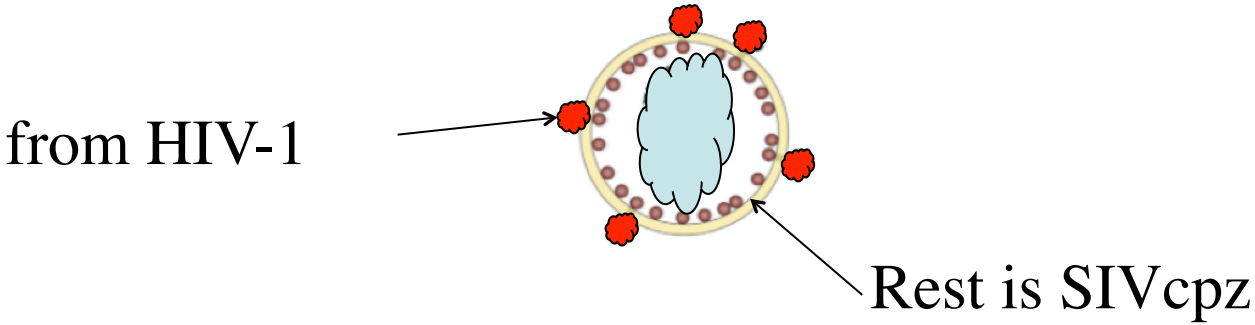
Chimpanzees	Rhesus Macaques	Humans
		
SIVcpz = harmless	SIVcpz = harmful	SIVcpz = ?
HIV-1 = harmless	HIV-1 = harmless	HIV-1 = harmful
	SHIV = harmful	

Why?

http://www.prn.org/index.php/progression/article/origin_of_the_aids_pandemic_58
http://barelyimaginedbeings.blogspot.com/2008_09_01_archive.html
http://thelaughingstork.com/2009/03/funny-baby-pictures-bah-humbug-edition/

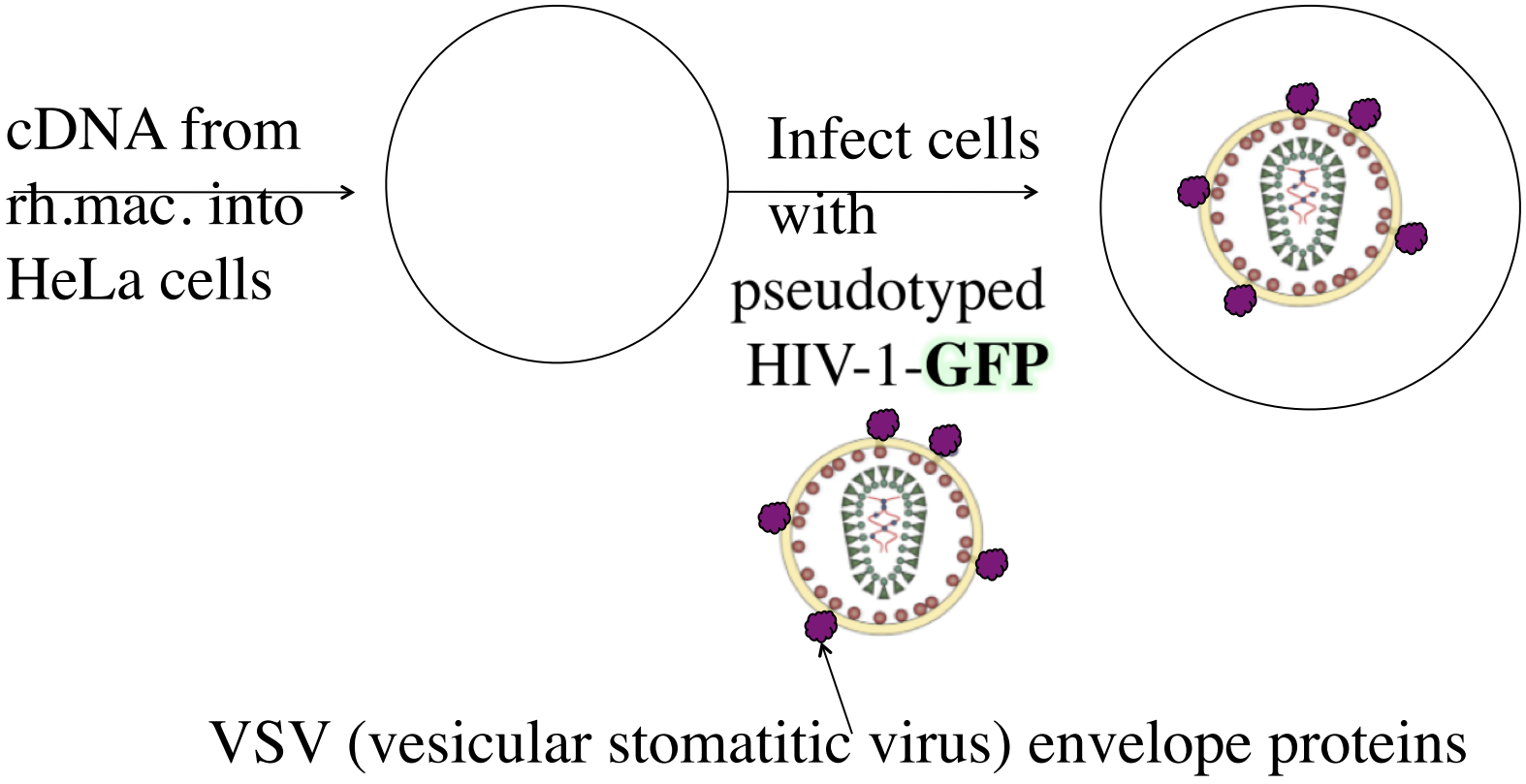
1. Viral Entry Level: An incompatible receptor in the Old World Monkey cells?

SHIV



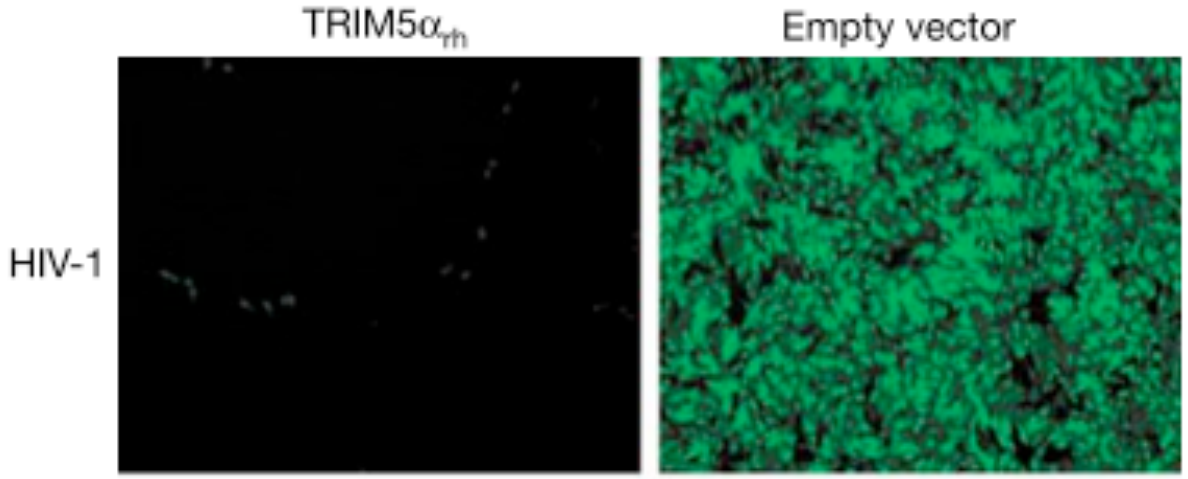
No, because SHIV can replicate at a high titer in rhesus macaques

2. Post-Entry Events: A block that targeted the viral capsid prevented permanent infection?



-look for GFP-negative colonies
-check for infection with SIVcpz

TRIM5α_{rh} inhibits HIV-1 infection but not SIVcpz or SHIV-based infection **2004**



(it must not work on the particle-recognition level,
but at an even more atomistic level)

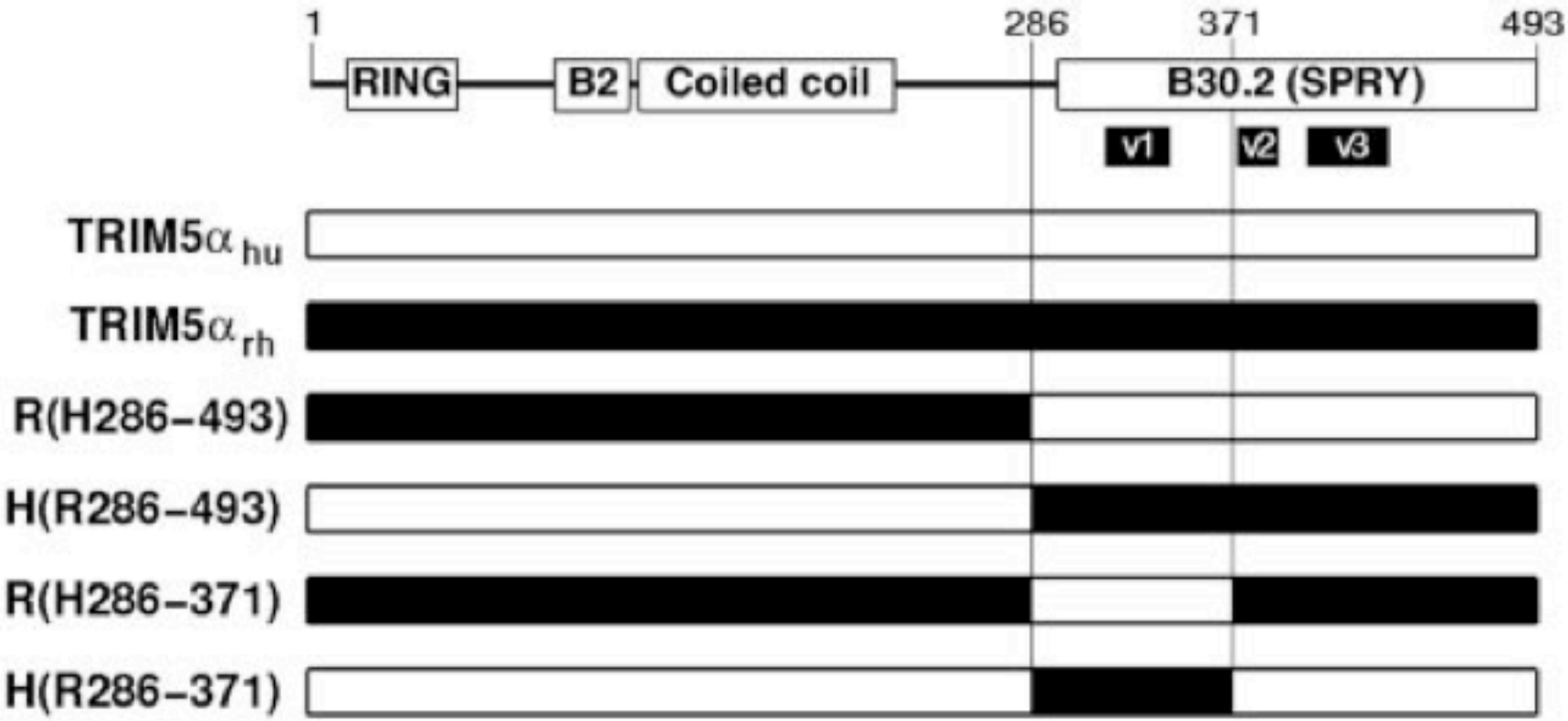
Stremlau et al., Nature, 427, 848, (2004)

Although rhesus macaque TRIM5α_{rh} inhibits HIV-1, human TRIM5α_{hu} does not inhibit HIV-1

Why not?

Stremlau et al., Nature, 427, 848, (2004)

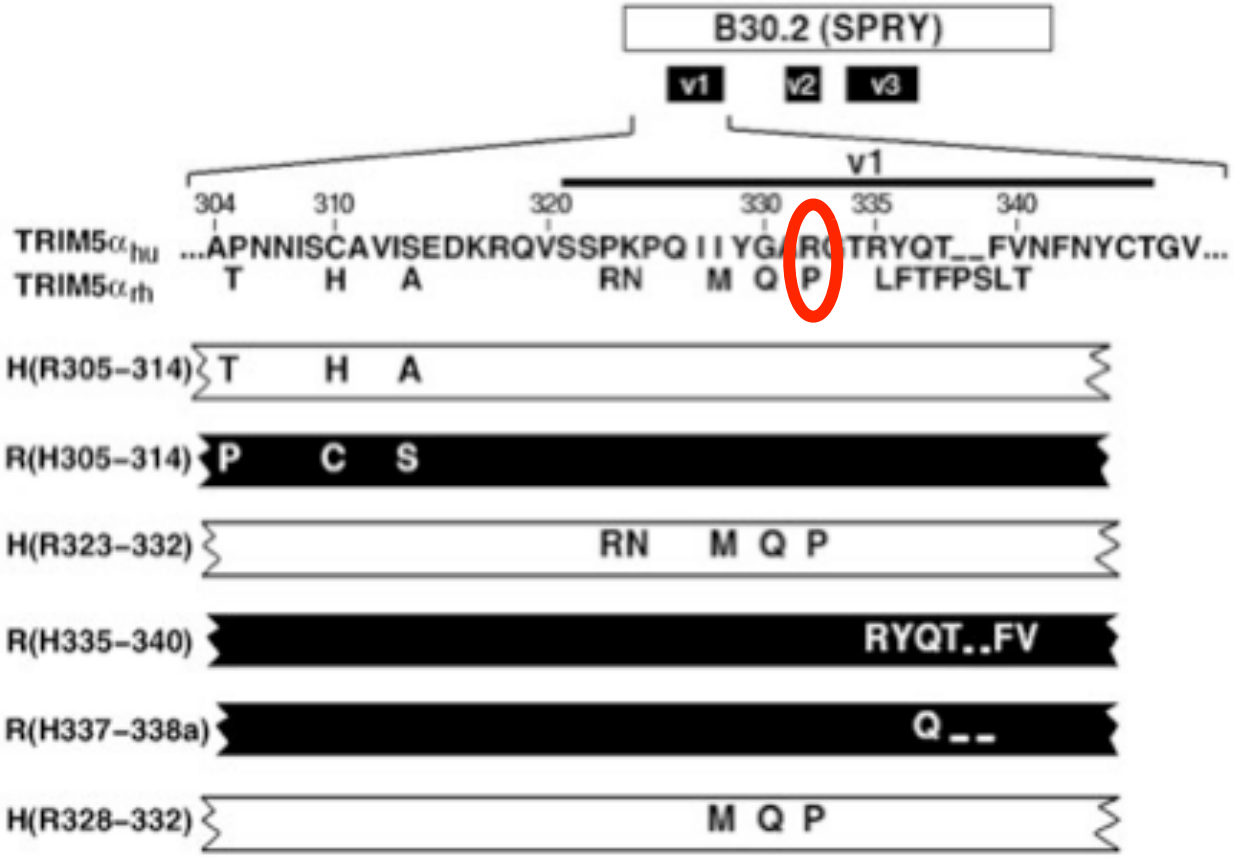
Study the infectivity of chimeric TRIM5α proteins



Stremlau et al., J. of Vir., 79 (5), 3139, (2005)

Removal of Arginine 332 Allows Human TRIM5α To Bind Human Immunodeficiency Virus Capsids and To Restrict Infection

Yuan Li,[1] Xing Li,[1] Matthew Stremlau,[1] Mark Lee,[1] and Joseph Sodroski[1,2]*



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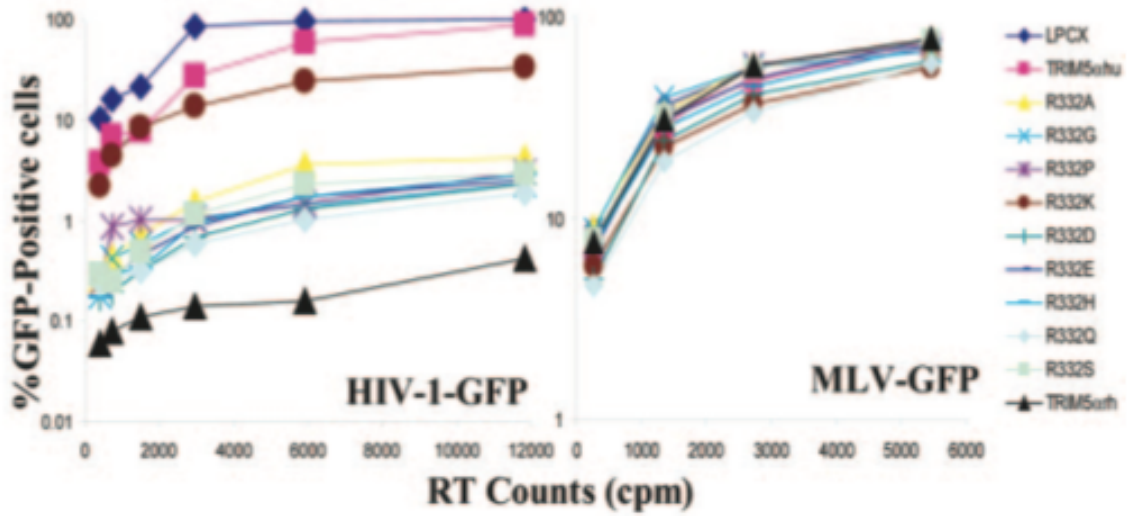

What we know so far..

1. Humans contracted HIV-1, the virus responsible for AIDS, from chimpanzees and sooty mangabeys.

2. Both SIVcpz and HIV-1 are harmless to chimpanzees.

3. SIVcpz is harmful to rhesus macaques, but HIV-1 is harmless.

4. TRIM5α could explain why this is the case.

5. We need to understand what capsids are…

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What are those ?

…to be continued in Lecture 2