Co-evolution of host and pathogen: HIV as a model

Can Keşmir

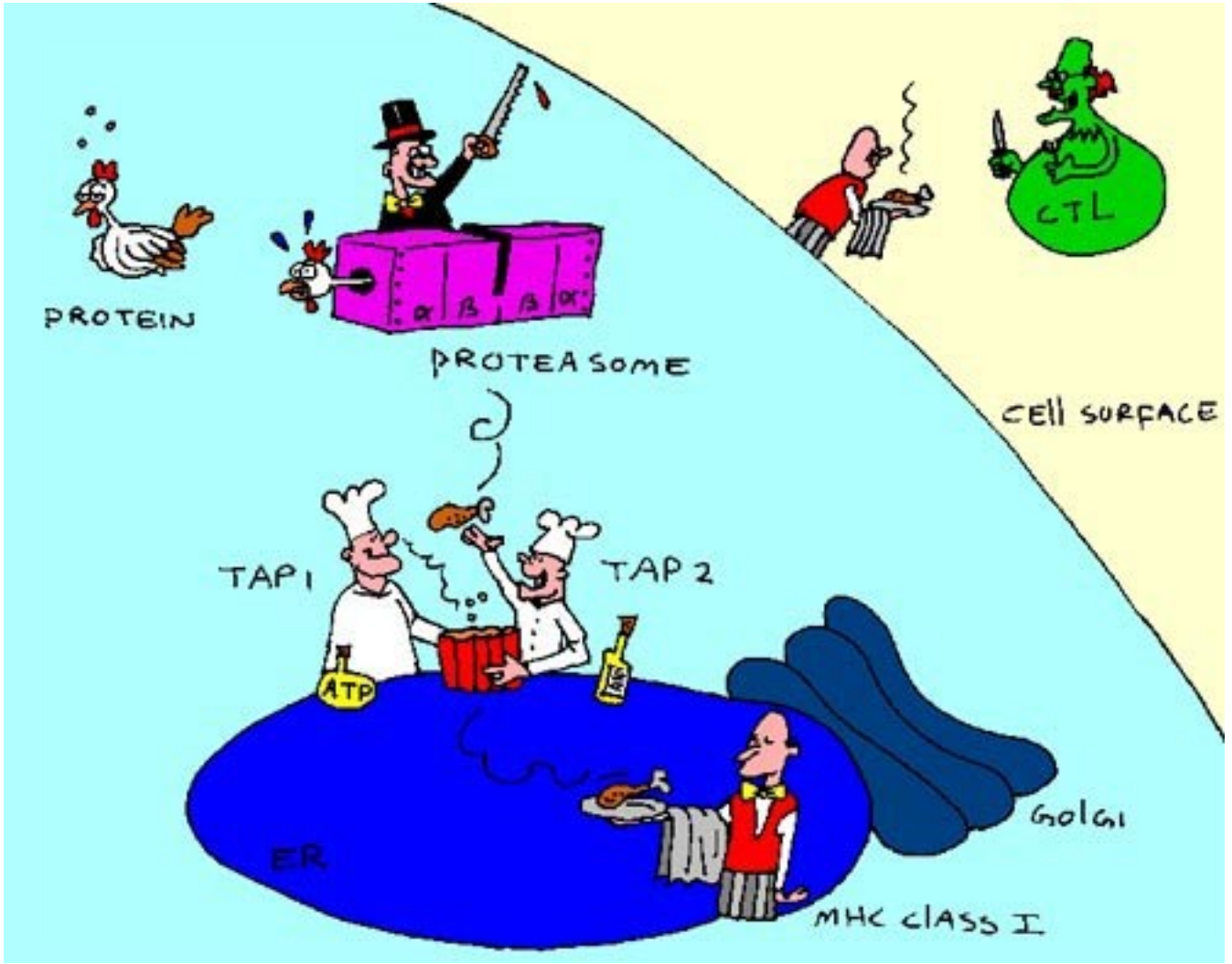
Universiteit Utrecht

Theoretical Biology/Bioinformatics
Utrecht University, NL
c.kesmir@bio.uu.nl

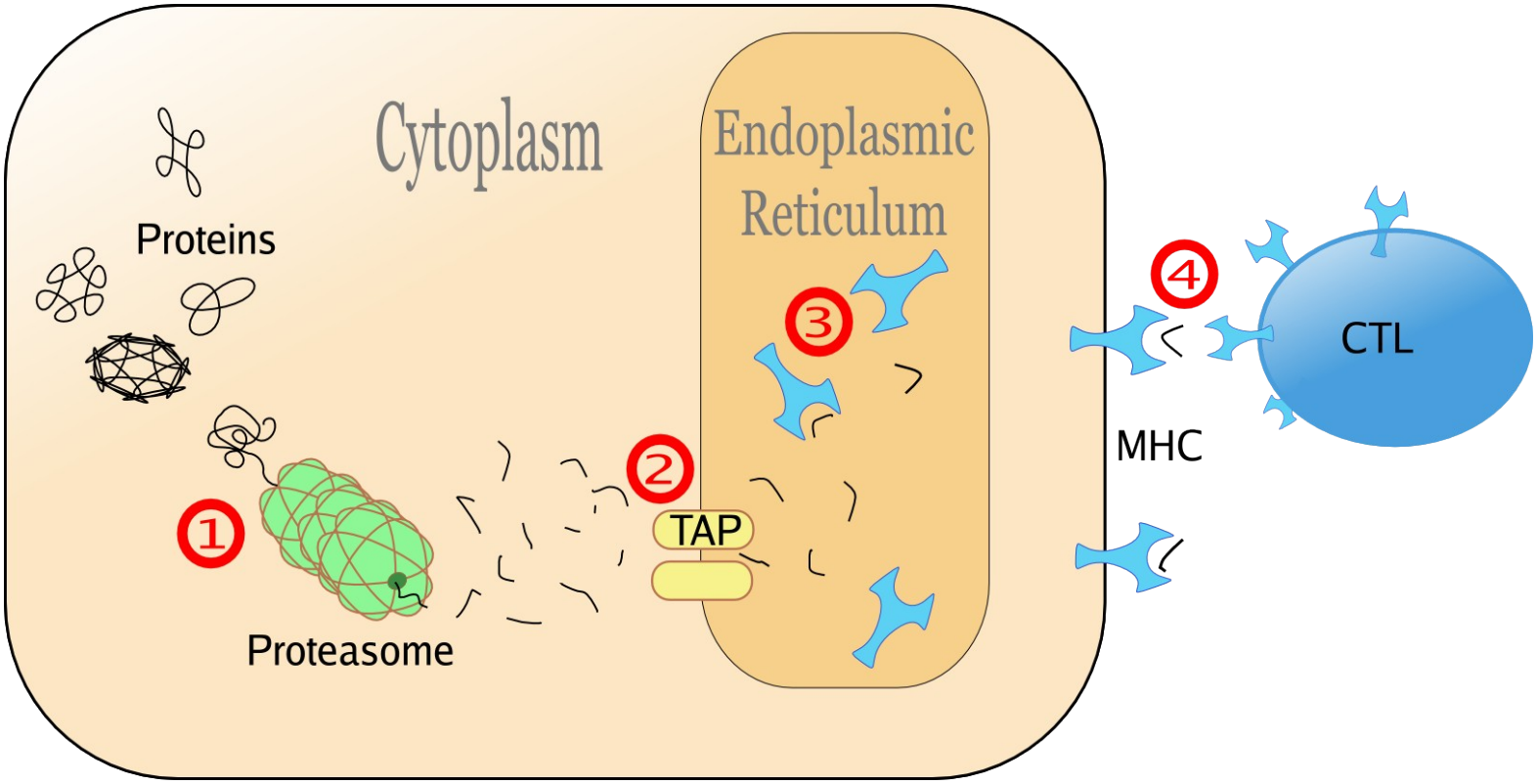
Outline

- Does HIV adapt to monomorphic human molecules?
- Polymorphic molecules: What is the mechanism behind different disease outcomes?
- Can we learn more about which molecules/mechanisms are important in disease induction by studying evolution of SIV in African monkeys?

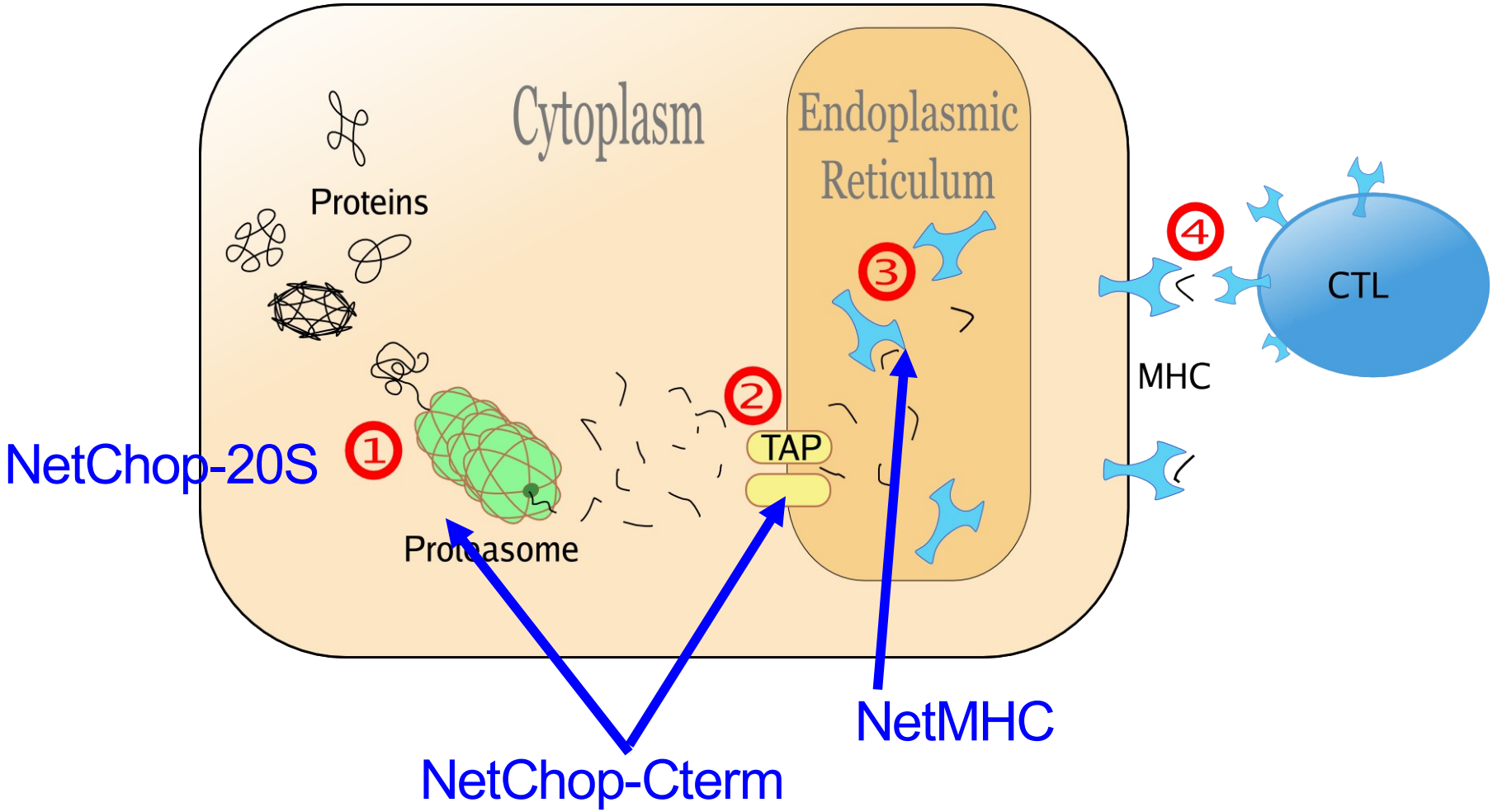
Antigen processing and presentation (Class I MHC)



How can a pathogen “hide” from CTL response?



Specificity of molecules

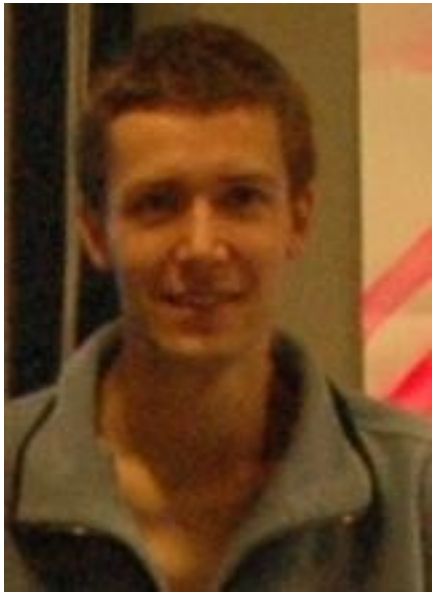


Specificity of the molecules

• Proteasome	30%	monomorphic
• TAP	70%	monomorphic
• MHC	1-5%	polymorphic
• TCR	0.001%	highly diverse

Are monomorphic molecules easy targets of escape during HIV infection?

Boris Schmid (UU)



Adaptation on single host level

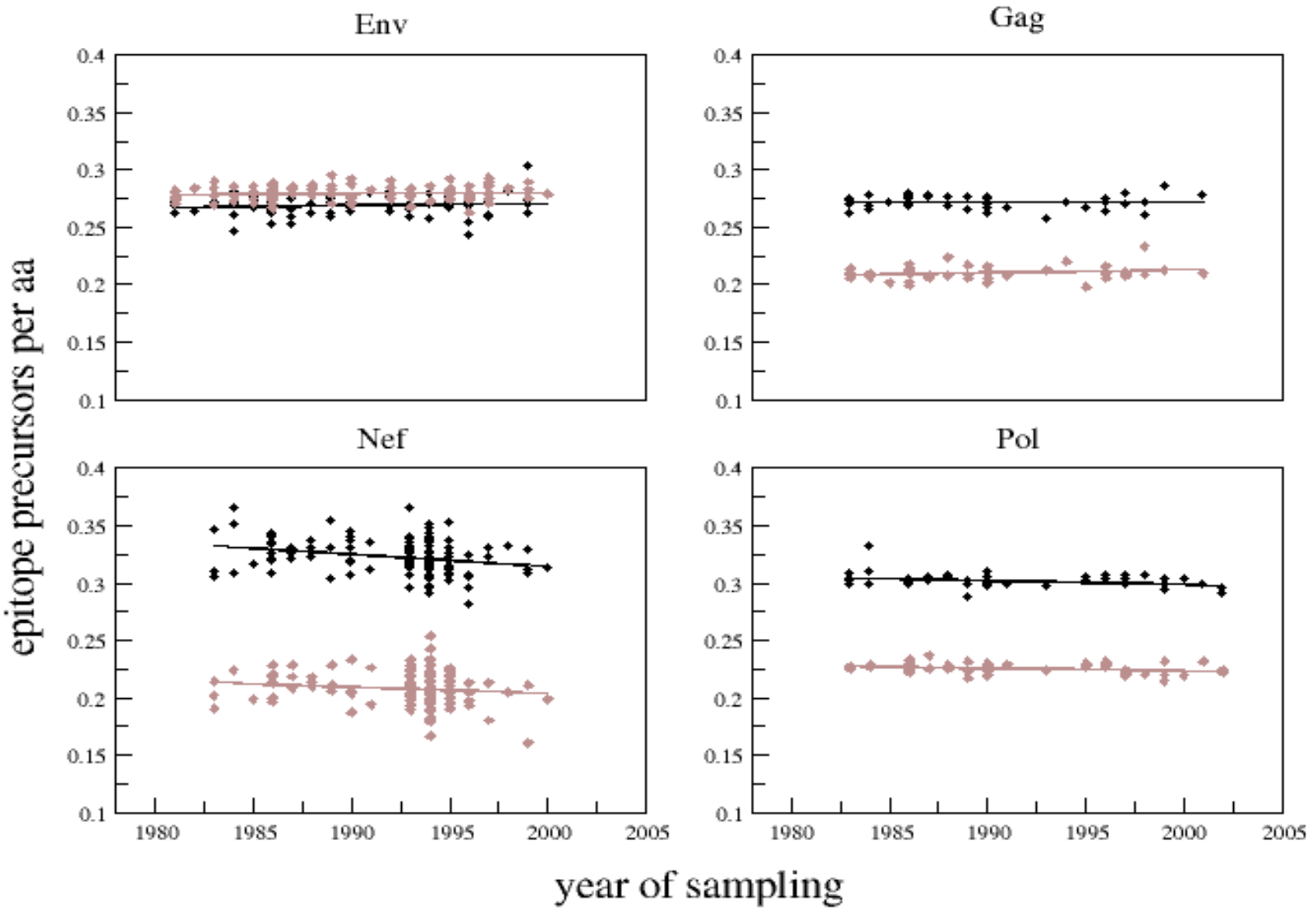
- Two full HIV genome sequencies (1986 and 1997) of a long term survivor
- Total of 66 non-silent mutations
- 62 mutations can be associated with CTL responses given the patient MHCs

Escape from strong epitopes: 13

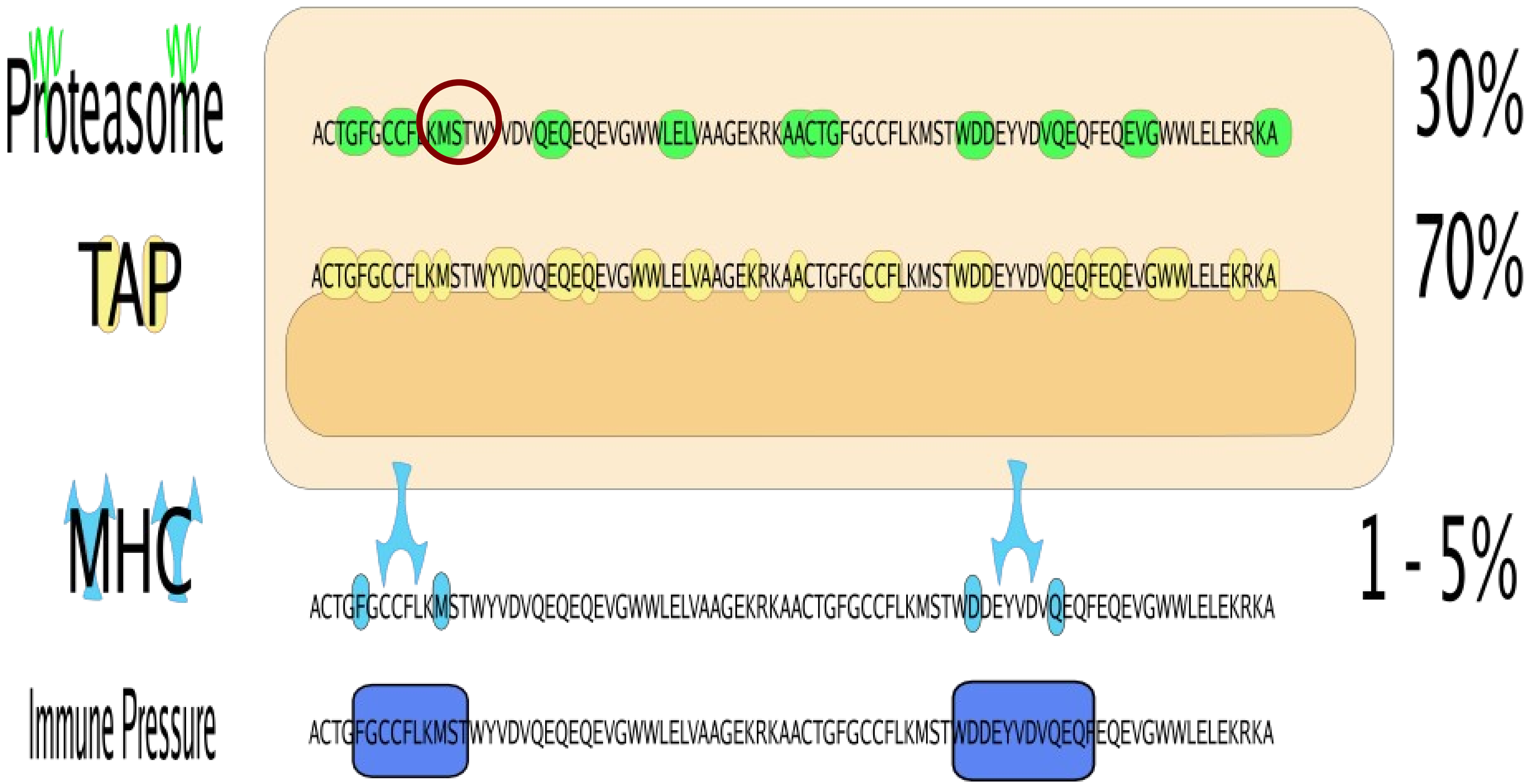
MHC escapes: 10

Processing escapes: 7

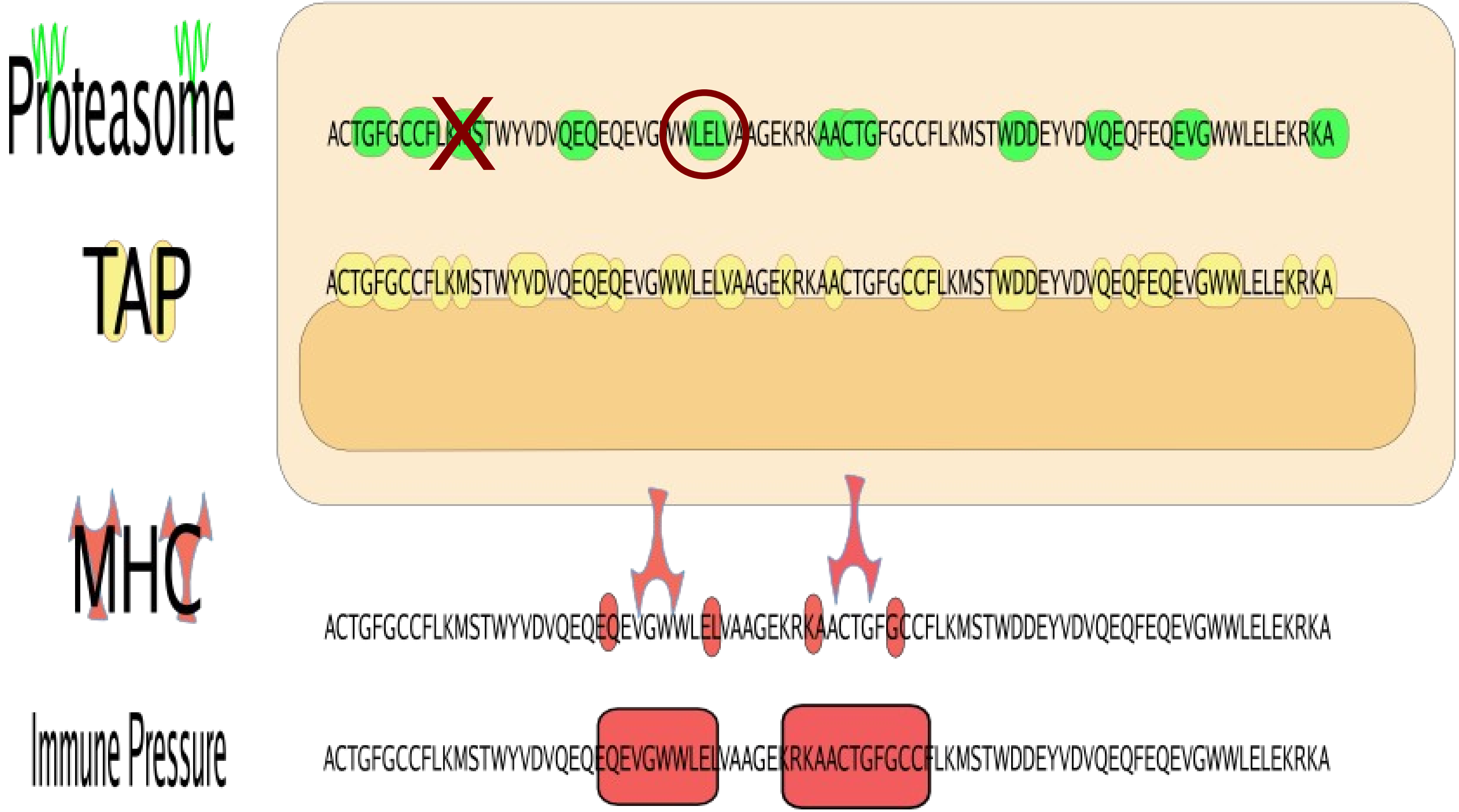
Adaptation on population level



Why HIV is not evading processing?



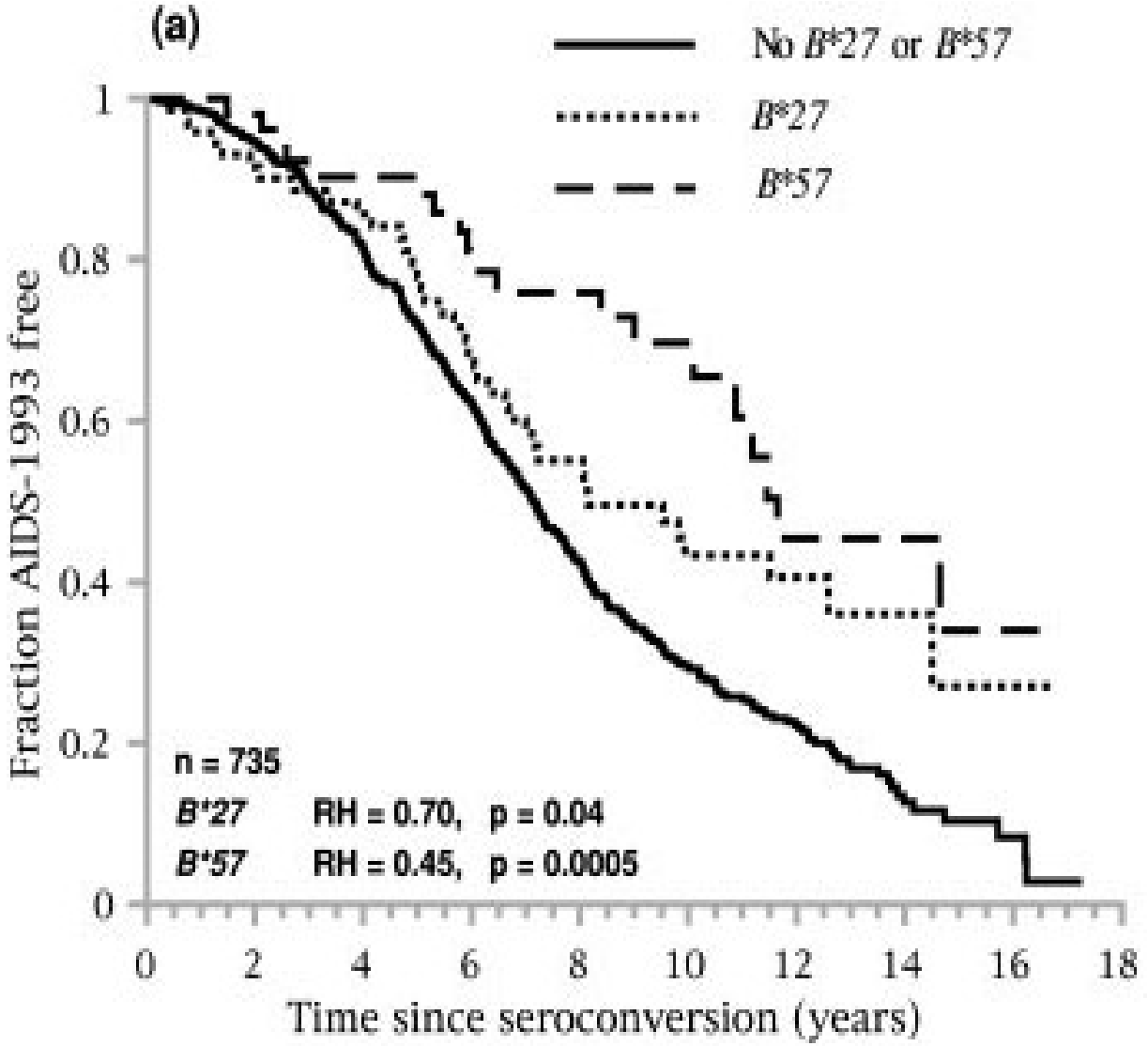
Shadowing due to MHC polymorphism



Conclusions: adaptation to monomorphic molecules?

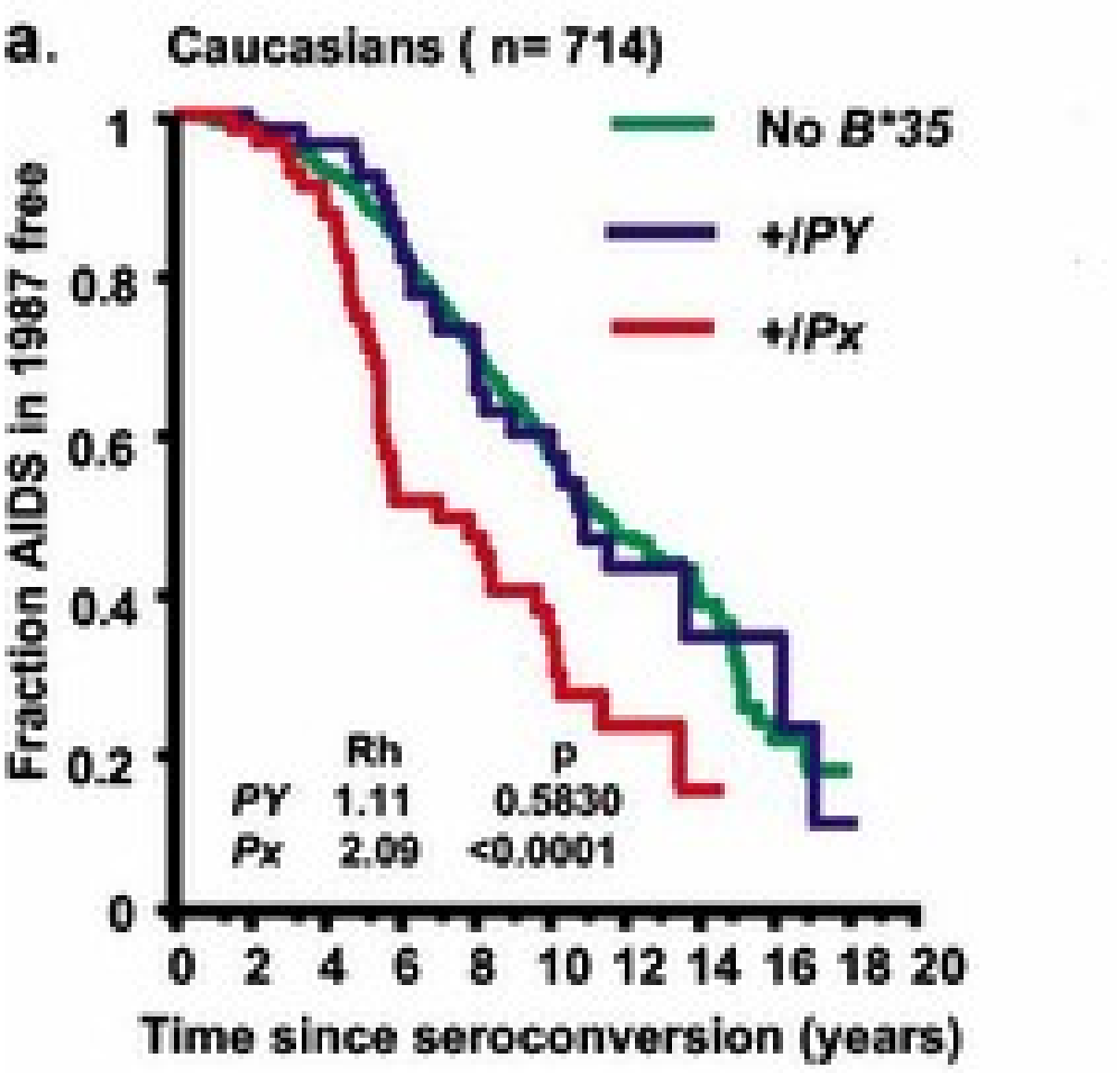
- At the population level processing escape mutants do not get fixed because of the shadowing by MHC polymorphism
- The degeneracy of proteasome and TAP might make make it difficult for HIV to evade antigen processing (we need to analyse more data to be able to say this).

MHC effect on AIDS: Low Risc



Carrigton, et al. 2003

MHC effect on AIDS: High Risc



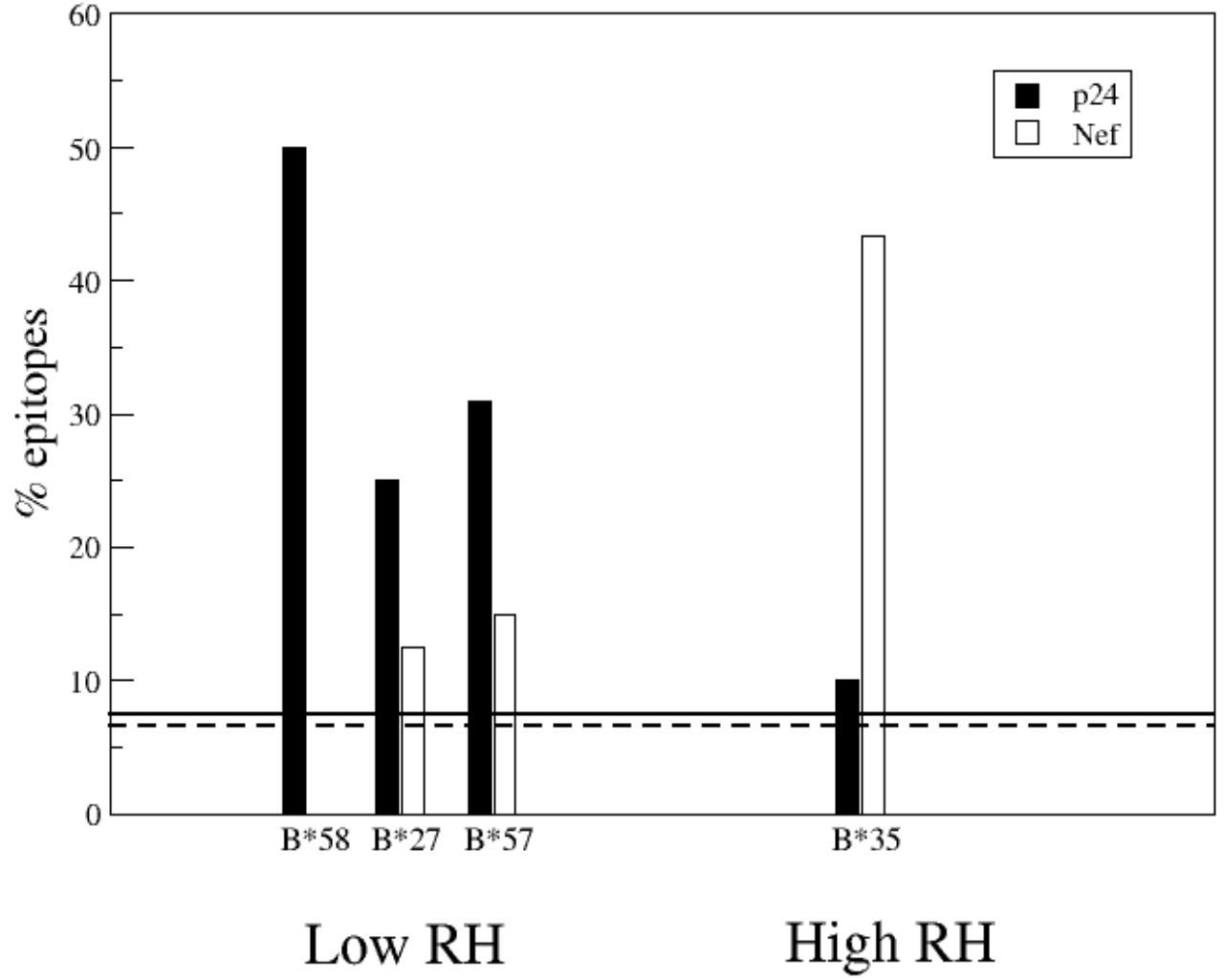
Gao, et al. 2001

What is special about Low risc MHC molecules?

- Rare allele advantage????
- Are they differing in their presentation profile? (Targetting different proteins?)

Jose' Borghans &
Rob de Boer (UU)

HIV epitopes in LANL database

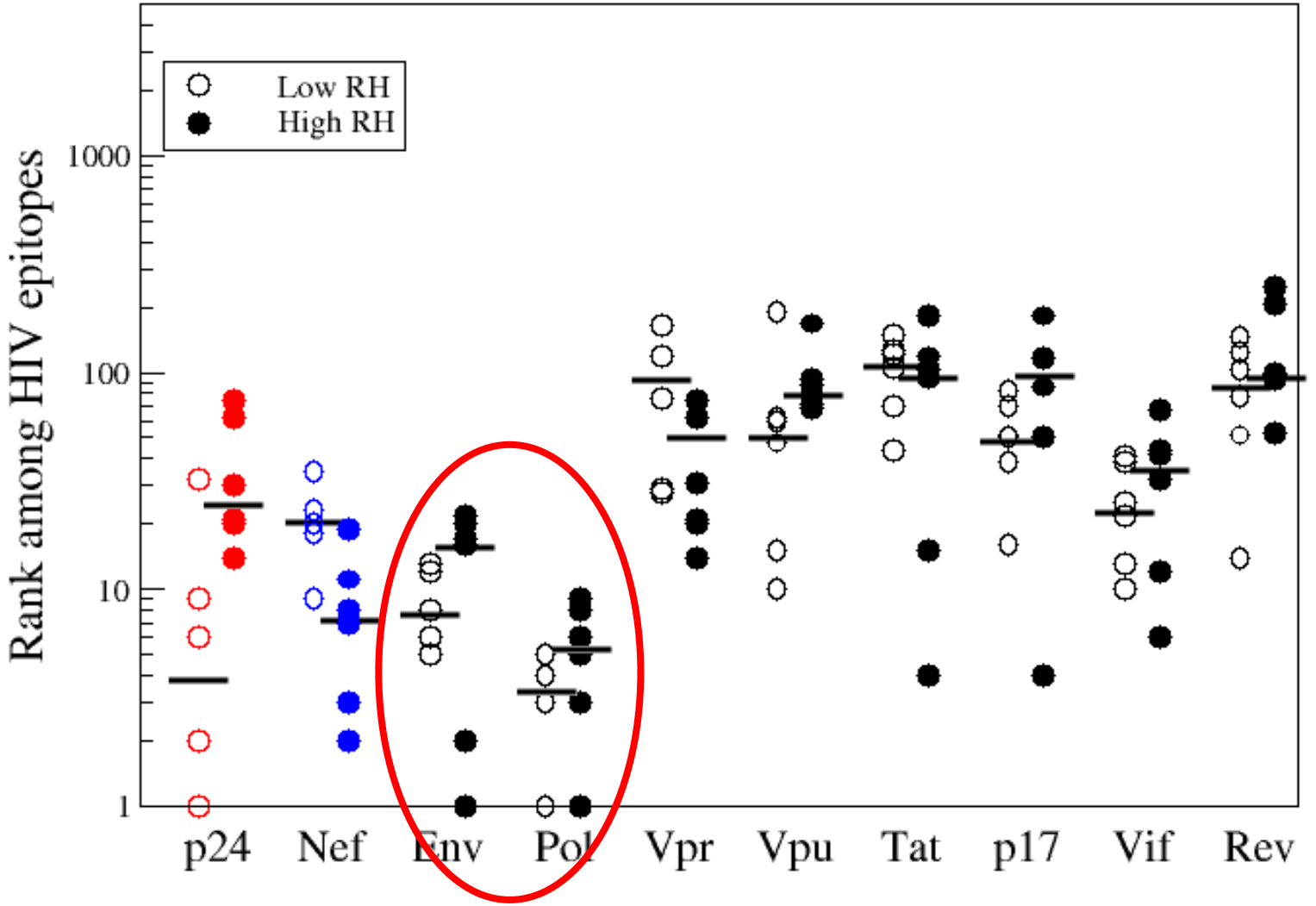


B53 is also a high risc allele, but there are not yet enough epitopes known!

Genome-wide predictions

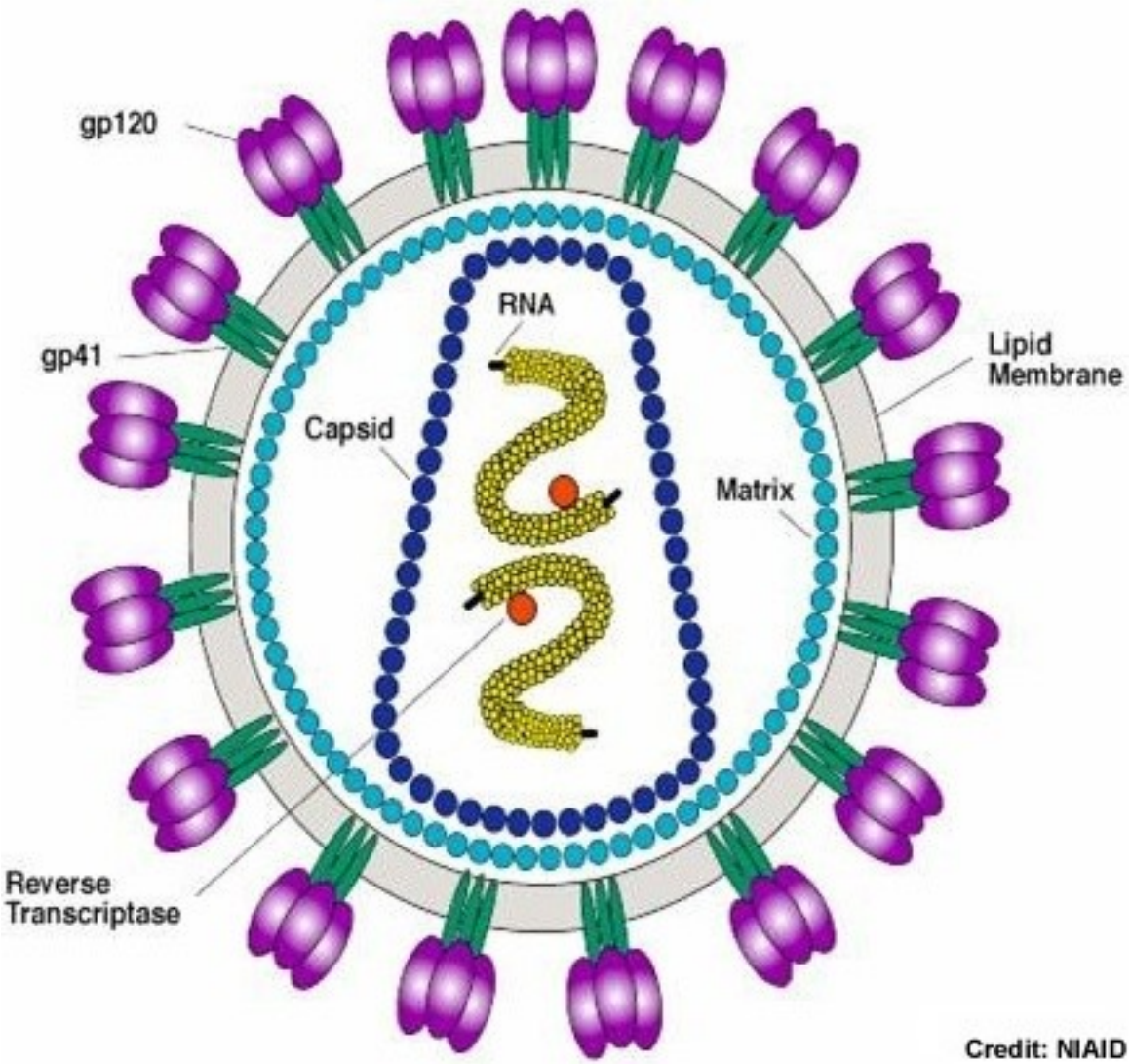
- Predict MHC binding for Low RH and High RH alleles for all 9mers/10mers
- Rank for each allele all 9mers/10mers of HIV according to their MHC binding
- For each HIV protein look at the rank of the best 3 “epitopes”
- Is there a significant difference in the rank of 3 best epitopes between low and high RH alleles?
- Remember: larger proteins have more chance of having high ranking 9mers!

Genome wide predictions



Why targetting p24 is protective?

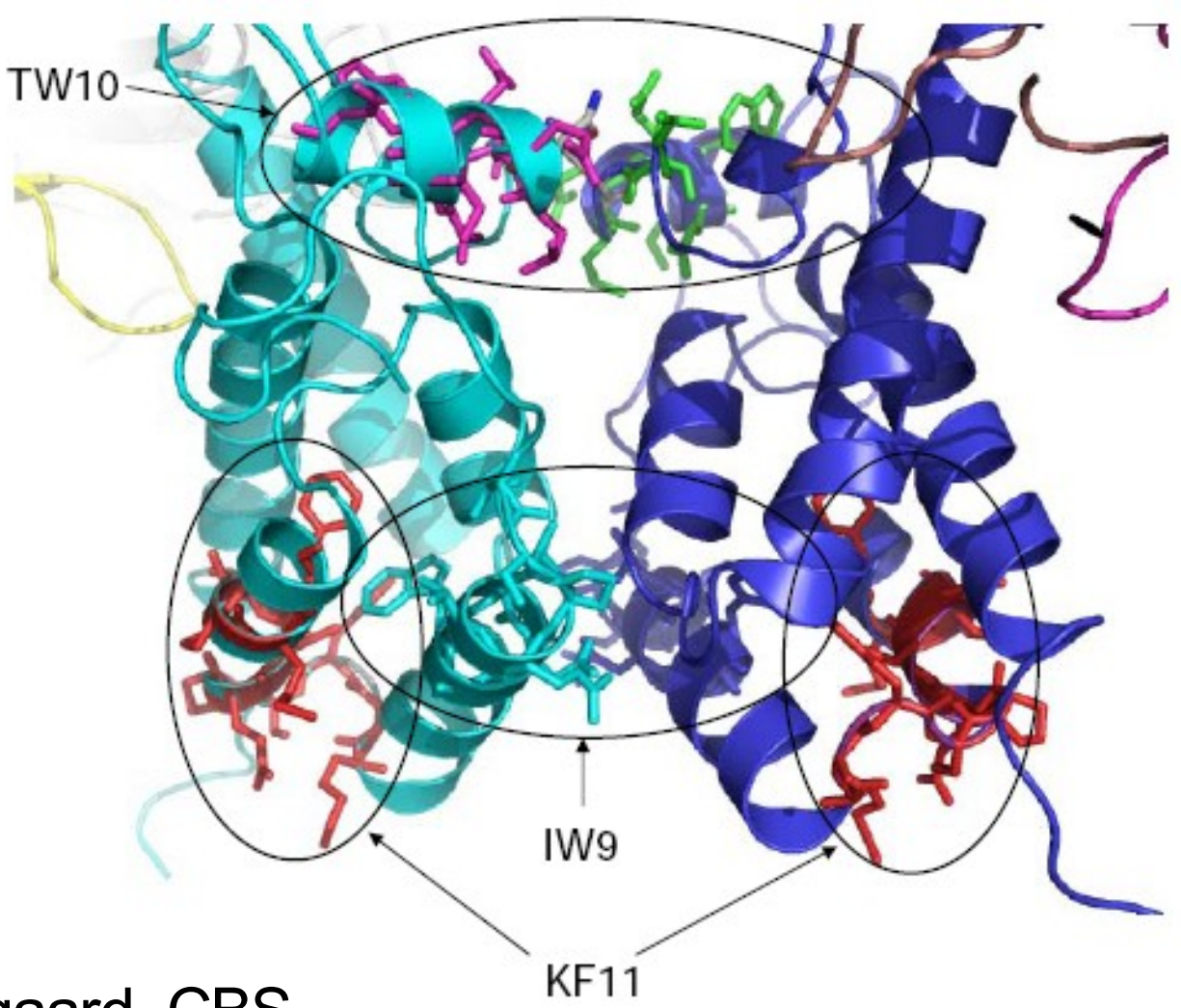
- p24 is the capsid protein
- Expressed in large numbers (>1000 copies per virion)
- Expressed very early during infection
- Crucial for the production of new virions --> highly conserved



However.....

- Even elite suppressors of HIV can have mutations in p24 (Barley et al J. Exp. Med. 2006)
- These mutations come with a high fitness cost: replication capacity is 10-fold lower
  - ➢ HIV escapes the host immune response, but heavily crippled
- The viral load remains very low --> no progression to AIDS

Low Risc MHC target constrained regions of p24

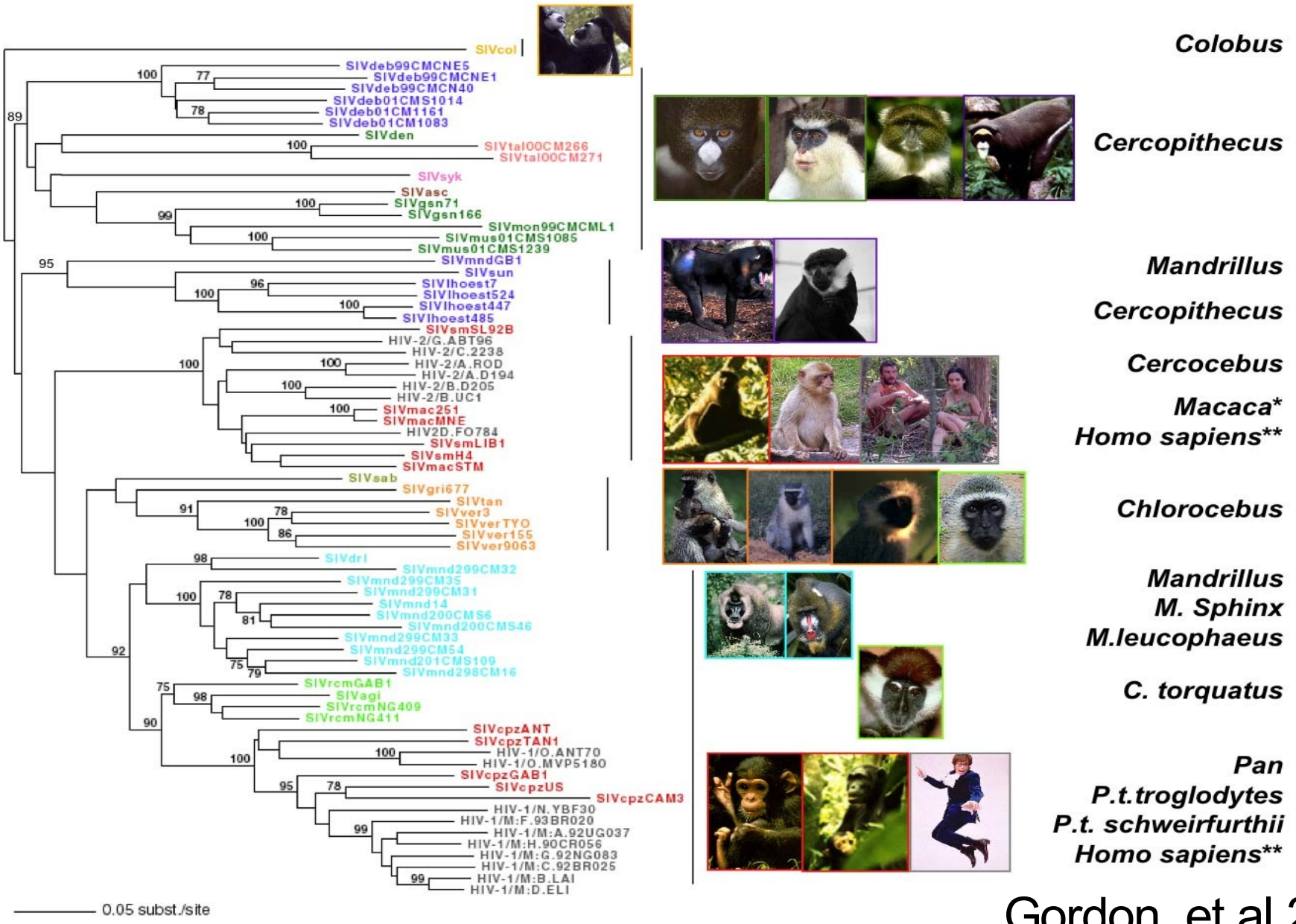


Anne Mølgaard, CBS

Conclusions: MHC effect on adaptation of HIV

- Immune selection pressure can cause escape mutants with high fitness cost.
- “Protective” MHC molecules are those that target constrained regions of HIV

Primates and SIV/HIV



Gordon, et al 2005

Natural host response to SIVsm by S. mangabeys

- Prevelance upto 60% or more, increasing with age
- Normal CD4 T cell counts, no signs of hyper-activation
- High viral loads, however hardly any AIDS
- SIVsm is not ignored by the host, but a mild T cell response is generated

Rhesus macagues infected with modified SIVsm develop AIDS

Chimpanzee and SIV

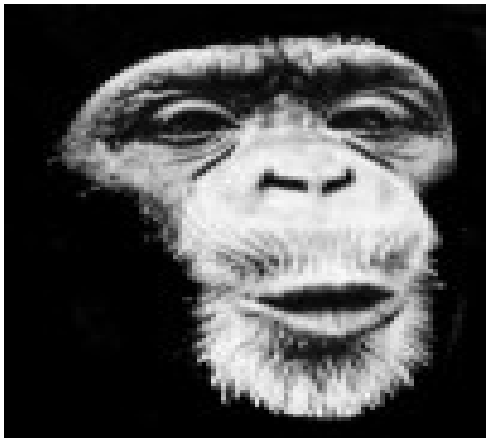
- Up to 60% infected with SIVcpz ---> no AIDS
- 200 chimpanzees so far infected experimentally with HIV-1 --> only 1 case of possible AIDS.
- Low viral loads --> Efficient T cell response???
- MHC diversity is much lower compared to human. Especially protective MHC-B has lower diversity.
  - ➢Has been through a severe selection (bottleneck)
- Common MHC molecules in the chimpanzee population target the same epitopes as human long-term non-progressors

Can we find more signs of adaptation/selection?

Comparative genomics

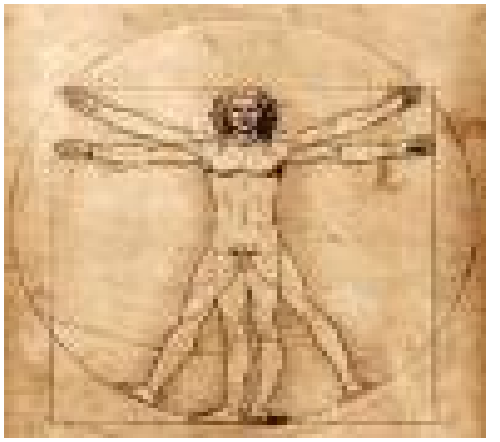
AIDS

SIVmac



~~**AIDS**~~

SIVcpz



AIDS

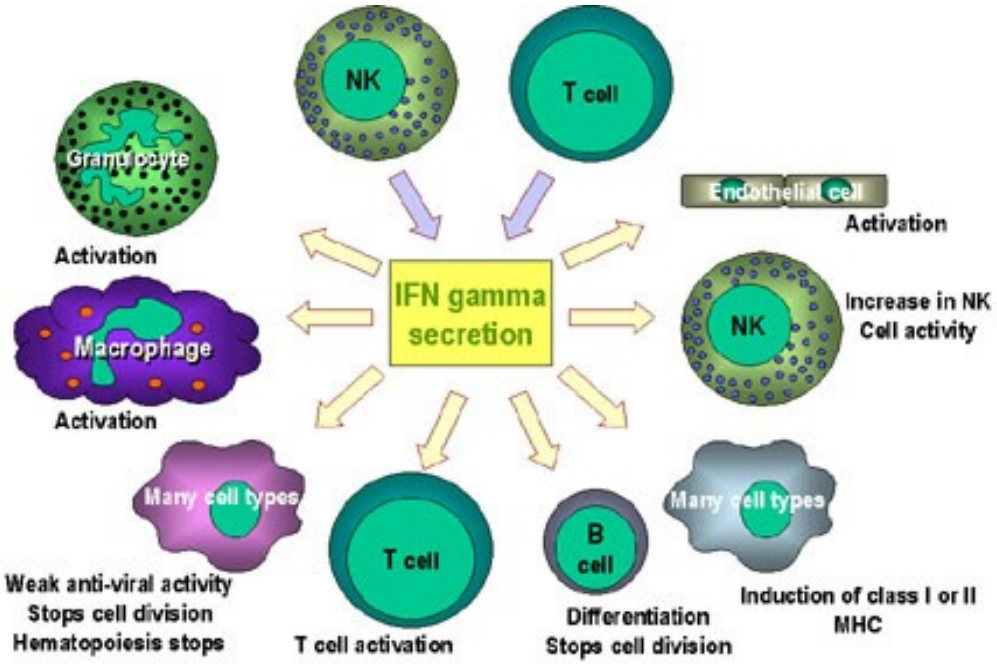
HIV-1/2

Comparative analysis

- Lineage specific genes (~500) → difficult to predict the function
- Look for orthologs in macaques and human that are not existing chimpanzee
- PanTro2.1 (March 2006) & Ensemble automatic orthology detection (manual check afterwards)
- There are 312 ortholog groups that are deleted in chimpanzee
- 153 of these have GO annotations
- 12 genes are related to immune response and thus our candidates for possible host adaptation

Almost for sure missing in chimpanzee

- ICEBERG: inhibitor of caspase-1.
- IL1F7 & ILF18: members of IL1 super family



Some genes are very diverged!

Table 4 | Rapidly diverging gene clusters in human and chimpanzee

Location (human)	Cluster	Median K_A/K_S*
1q21	Epidermal differentiation complex	1.46
6p22	Olfactory receptors and HLA-A	0.96
20p11	Cystatins	0.94
19q13	Pregnancy-specific glycoproteins	0.94
17q21	Hair keratins and keratin-associated proteins	0.93
19q13	CD33-related Siglecs	0.90
20q13	WAP domain protease inhibitors	0.90
22q11	Immunoglobulin-λ/breakpoint critical region	0.85
12p13	Taste receptors, type 2	0.81
17q12	Chemokine (C-C motif) ligands	0.81
19q13	Leukocyte-associated immunoglobulin-like receptors	0.80
5q31	Protocadherin-β	0.77
1q32	Complement component 4-binding proteins	0.76
21q22	Keratin-associated proteins and uncharacterized ORFs	0.76
1q23	CD1 antigens	0.72
4q13	Chemokine (C-X-C motif) ligands	0.70

*Maximum median K_A/K_S if the cluster stretched over more than one window of ten genes.

Chimp Consortium, Nature, 2005

CCR5

```
Human       MNYQTSTPYYDIDYGTSEPCQKVNVRQIAARLLPPLYSLVFIFGFVGNVLVVLILIDCKK
Chimp       MDYQVSSPIYDIDYYTSEPCQKINVKQIAARLLPPLYSLVFIFGFVGNMLVILILINCKR
            *:**.*:* ***** *******:**:**********************:**:****:**:

Human       LKSMTDIYLLNLAISDLLFLLTIPFWAHYAADQWTFGNKMCQLLTGLYYIGFFTGNFFII
Chimp       LKSMTDIYLLNLAISDLFFLLTVPFWAHYAAAQWDFGNTMCQLLTGLYFIGFFSGIFFII
            ******************:****:******** ** ***.*********:****:* ****

Human       LLTMDRYLAIVHAVSASKARTVTFGVVTSGIAWVVAVLASFPRIIFTRSQKEGSRFTCSP
Chimp       LLTIDRYLAIVHAVFALKARTVTFGVVTSVITWVVAVFASLPGIIFTRSQKEGLHYTCSS
            ***:********** * ************ *:*****:**:* ********** ::***.

Human       HFPPSQHHFWKNFQALKMSVLGLILPLLVMIIGYSAILKTLLRCRNEKKRHKAERLIFVI
Chimp       HFPYSQYQFWKNFQTLKIVILGLVLPLLVMVICYSGILKTLLRCRNEKKRHRAVRLIFTI
            *** **::******:**: :***:******:* **.***************:* ****.*

Human       MIVYFLFWAPYNIVLLLSTFQEFFGLNNCNSSNRLDQAMQITETLGMTHCCINPIIYAFV
Chimp       MIVYFLFWAPYNIVLLLNTFQEFFGLNNCSSSNRLDQAMQVTETLGMTHCCINPIIYAFV
            ******************.**********.**********:********************

Human       GEKFRRYLSLFFRKHIARRFCKCCPIFQGELPDRVSSVYTRSTGEQEISVAL
Chimp       GEKFRNYLLVFFQKHIAKRFCKCCSIFQQEAPERASSVYTRSTGEQEISVGL
            *****.** :**:****:******.*** * *:*.***************.*
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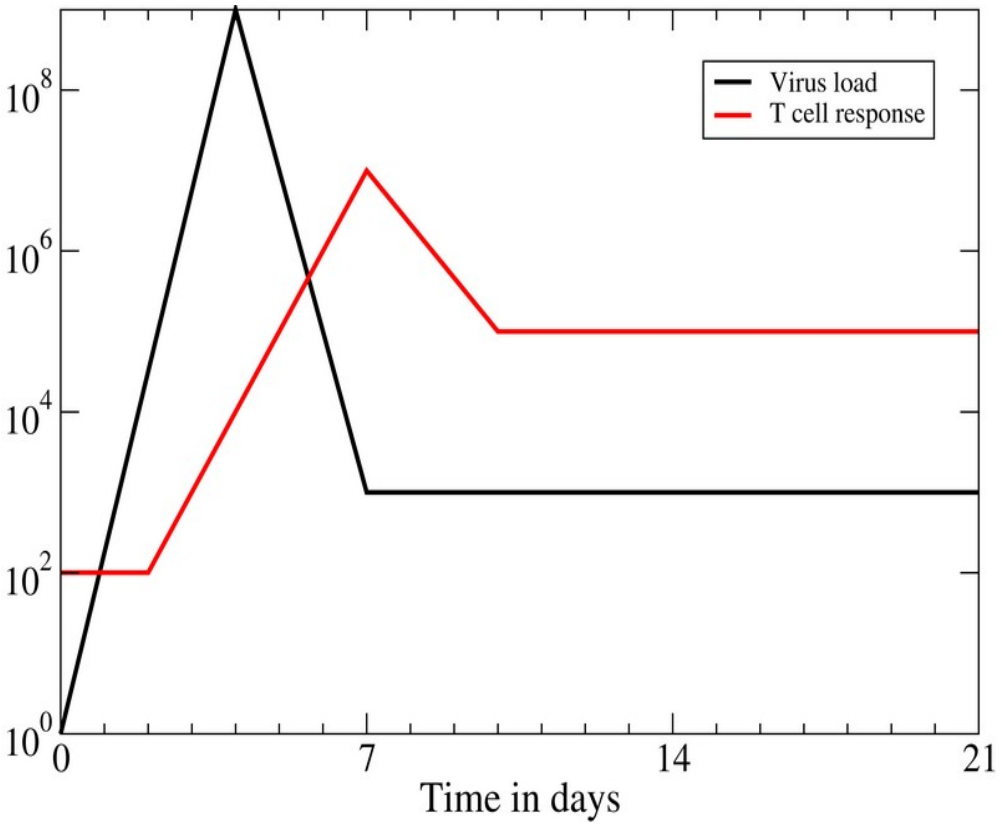
Conclusions

- Processing do not shape HIV evolution, because:
  1. MHC polymorphism shadow the immune selection pressure on processing
  2. The processing is degenerate and thus difficult to escape from
- MHC alleles targeting constrained regions of HIV are protective.
- Chimpanzee do not develop AIDS, because they lack some immuno-regulatory genes or HIV/SIV receptors?

Immuno-epidemiology

What immune response is controlling HIV?

- CD8 T cells: MHC polymorphism
- APOBEC3G: 8 SNPs in 384 AA
- Toll like receptors: Many SNPs in each gene!



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