A selective sweep in chimpanzees: Is SIV the culprit?

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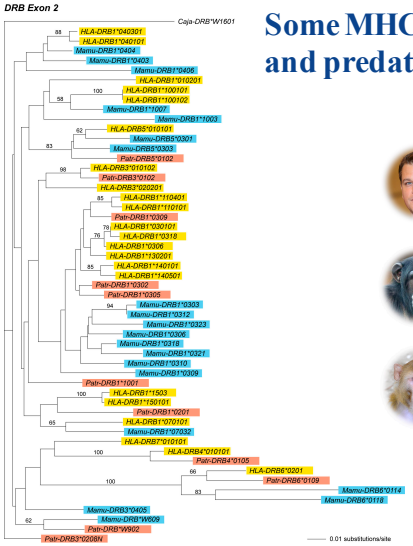
Biomedical Primate Research Centre

RIJSWIJK, THE NETHERLANDS

The ABC of MHC

Polymorphism : Some MHC loci display variation at the population level



Some MHC lineages are old and predate speciation

Human

Chimpanzee

Rhesus macaque

MHC class I and II allotypes are peptide receptors

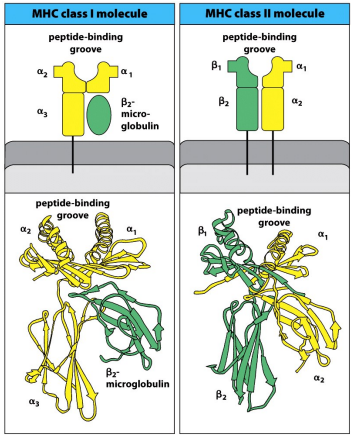
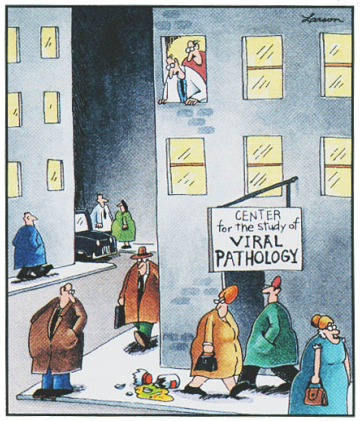


Figure 5.13 The Immune System, 3ed. (© Garland Science 2009)

most polymorphic amino acid residues map to the peptide binding groove

MHC & Disease



"Uh-oh."

Mhc polymorphisms are associated with susceptibility and resistance to diseases

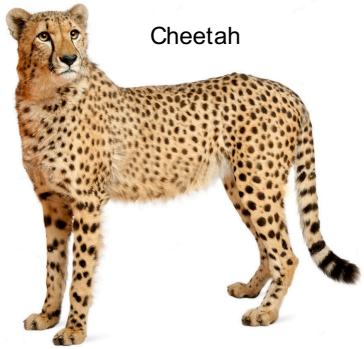
Any evidence for selection on the MHC

Selection
Operates on a individual

Evolution
Operates on a population and may result in differences in gene frequencies

MHC and selection: The monomorphic MHC argument

Syrian hamster

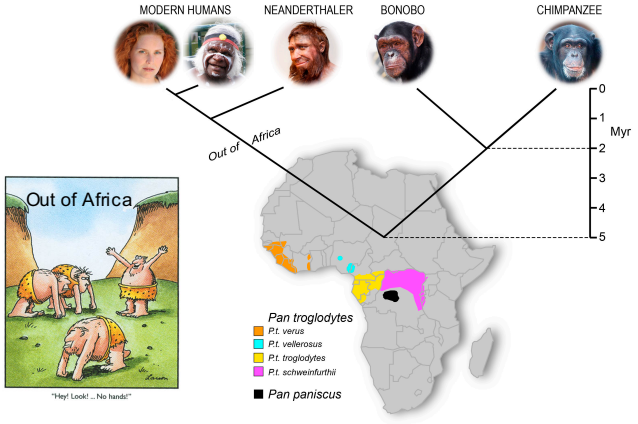


Cheetah

Time for monkey business

"Shh. Listen! There's more: 'I've named the male with the big ears Bozo, and he is surely the nerd of the social group—a primate bimbo, if you will.'"

Introducing the players (part I)



Humans & Chimpanzees

About similarities & differences

Humans & Chimpanzees

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- Nucleotide sequence similarity : 98.7%

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Humans & Chimpanzees
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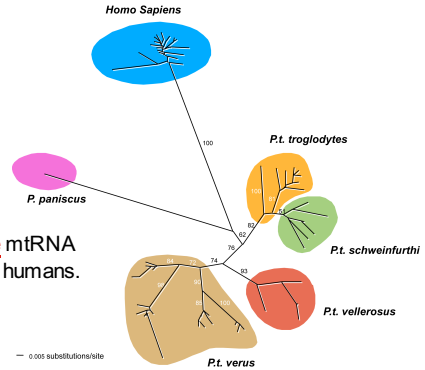

- Chimpanzees display more mtRNA and genomic variation than humans.

Humans & Chimpanzees
About similarities & differences

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- Chimpanzees display more mtRNA and genomic variation than humans.

Differential disease susceptibility

Chimpanzees and AIDS: Some Facts

- Worldwide more than 150 animals (Ptv) have been infected with various HIV-1 isolates…No **evidence** for AIDS-like disease
- Only one report of an **experimentally** infected animal with AIDS-like disease (Novembre et al. J. Virol. 1997, 4086)
- Evidence for **natural** infections (SIVcpz) and AIDS? (Keele et al. Nature 2009, 460)

Introducing the players (part II)

Structure of HIV-1

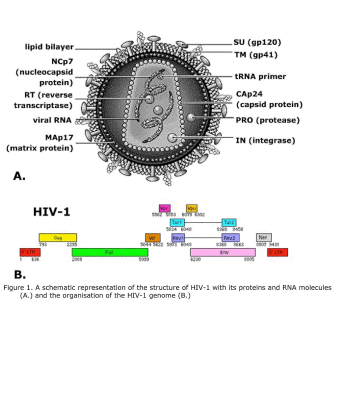
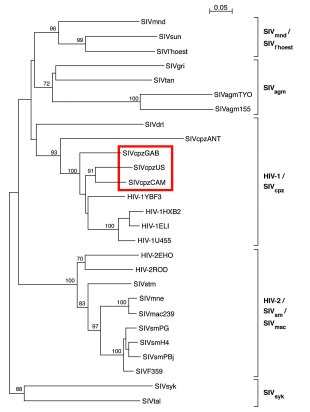
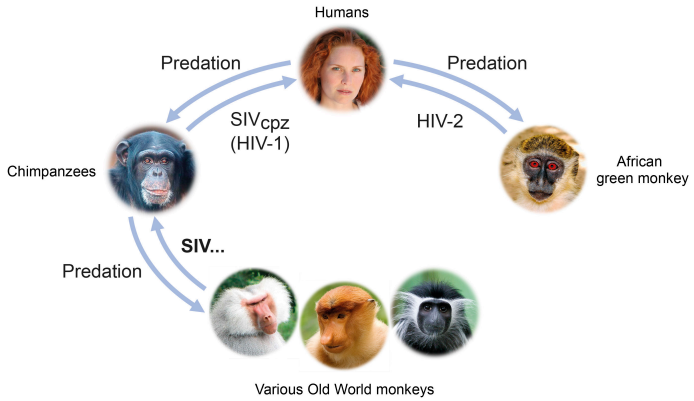


Figure 1. A schematic representation of the structure of HIV-1 with its proteins and RNA molecules (A.) and the organisation of the HIV-1 genome (B.)

Origin of HIV-1 in *Pan troglodytes* ?



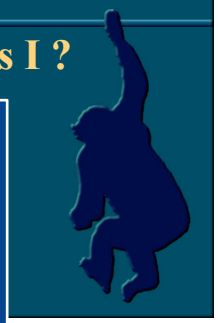
Predation and the route of SIV/HIV infections



Why are chimpanzees relatively resistant to AIDS?

Candidate resistance genes

MHC class I ?



Specialization of functions

- MHC class I molecules (HLA-A, -B, and -C) bind and present antigenic peptides from intracellular origin to the receptors on CD8-positive cells resulting in the lysis of infected cells
- MHC class II molecules (HLA-DR, -DQ and -DP) play a similar role in the presentation of peptides from extracellular origin to CD4-positive cells resulting, for instance, in the production of antibodies

Similarities and dissimilarities at the locus level

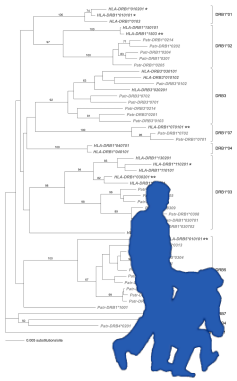
HLA-	Patr-
A B C	A B C
E F G absent	E F G AL
DR DQ DP	DR DQ DP

The devil is in the details?

Bontrop & Watkins.TII 2005

Initial observations part I:

Signatures of selection....the first hints



Chimpanzees versus Humans

- Chimpanzees **only** possess orthologues of the HLA-A1/A3/A11 family
- Seem to have a **severely** reduced B/C locus repertoire (lineages)
- Evidence for **loss** of particular class II lineages

Initial observations part II:
Further evidence for selection

Chimpanzees experienced a **selective sweep** affecting the MHC class I gene repertoire, approximately 2-3 myr ago, as was illustrated by intron 2 analyses.
(de Groot et al., PNAS, 11748-53, 2002)

Chimpanzees have only one hybrid MIC gene, displaying limited polymorphism.
(de Groot et al., Mol Biol Evol, 1375-85, 2005)

Small Tandem Repeat analysis maps strongest effect of the sweep to the Patr-B region.
(de Groot et al., Mol Ecol, 2074-2078, 2008)

Hypothesis:

The MHC class I repertoire reduction in chimpanzees may have been caused by an HIV-1/SIV like retrovirus.

Preliminary studies identified conserved and shared HIV-1 epitopes

gag epitope	restriction elements	
HQAISPRTL KRWIILGLN	*HLA-B*5701* *HLA-B*2705*	*Patr-B*02* *Patr-B*03*

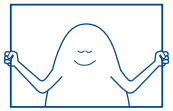
Balla-Jhagjhoorsingh *et al.* J Immunol 1999, 2308

Aim of the subsequent functional studies

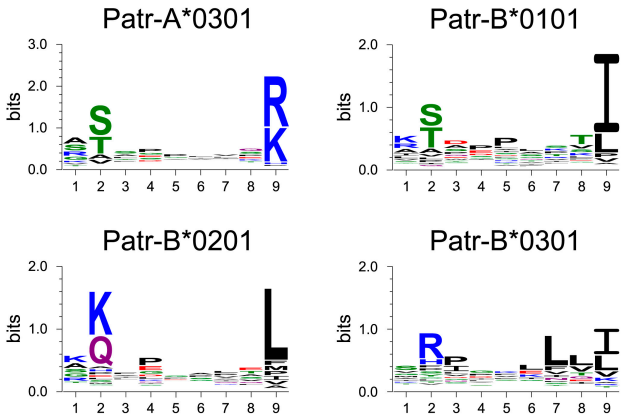
To investigate whether the selective sweep was possibly caused by HIV-1/SIV_{cpz} (or a closely related ancestor) and has resulted in the preferential selection of Patr molecules that are similar to AIDS-resistant molecules in human individuals, such as HLA-B*27/B*57.

Outline of the study

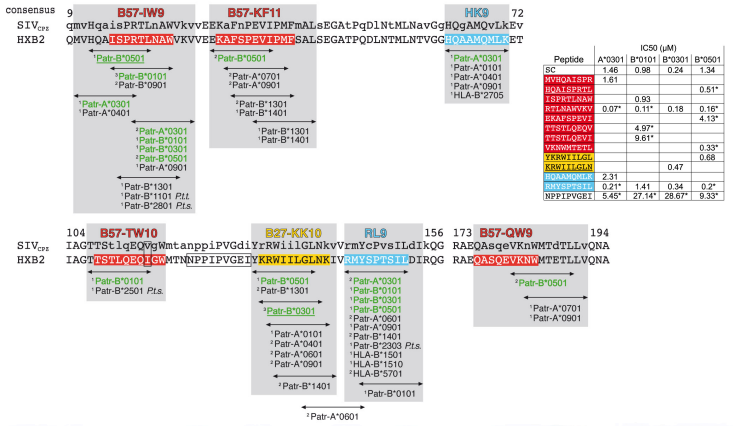
- Determine peptide binding motifs. (Patr-A*0301, -B*0101, -B*0301, -B*0501).
- Scan of the HIV-1/SIV$_{cpz}$ proteomes. Attention was focussed on the Gag protein.
- Selected peptides/potential epitopes were tested for actual binding to their corresponding MHC class I molecules.
- Re-evaluation of cellular immune response data of three chimpanzees of an HIV-1 infected cohort.



Chimpanzee MHC class I peptide binding motifs



Patr class I molecules target similar conserved areas of HIV-1 Gag as HLA-B*27/B*57



Peptide	IC50 (μM) A*0301	B*0101	B*0301	B*0501
SC	1.46	0.98	0.24	1.34
MVHQAISPR	1.61			
HQAISPRTL				0.51*
ISPRTLNAW		0.93		
RTLNAWVKV	0.07*	0.11*	0.18	0.16*
EKAFSPEVI				4.13*
TTSTLQEQV		4.97*		
TTSTLQEVI		9.61*		
VKNWMTETL				0.33*
YKRWIILGL				0.68
KRWIILGLN			0.47	
HQAAMQMLK	2.31			
RMYSPTSIL	0.21*	1.41	0.34	0.2*
NPPIPVGEI	5.45*	27.14*	28.67*	9.33*

Evaluation of CTL data in the context of peptide binding studies

Laurens

Gag Peptide pool	1-3	4-6	7-10	11-14	15-18	19-22
CTL response	+ (52%)			+ (8%)	+ (5%)	+ (8%)
Patr-A*0301	MVHQAISPR RTLNAWVKV			RMYSPTSIL	RMYSPTSIL	
Patr-B*0101	ISPRTLNAW RTLNAWVKV			TTSTLQEQI RMYSPTSIL	RMYSPTSIL	
Patr-B*0501	HQAISPRTL RTLNAWVKV EKAFSPEVI			YKRWIILGL RMYSPTSIL	VKNWMTETL RMYSPTSIL	
Patr-A*0901	RTLNAWVKV AFSPEVIPM			RWIILGLNK RMYSPTSIL	RMYSPTSIL	

Zeef

Gag Peptide pool	1-3	4-6	7-10	11-14	15-18	19-22
CTL response				+ (55%)		
Patr-B*0101				TTSTLQEQI RMYSPTSIL		
Patr-B*0301				KRWIILGLN RMYSPTSIL		
Patr-A*0101				RWIILGLNK		
Patr-A*0601				RWIILGLNK GLNKIVRMY RMYSPTSIL		

Thijs

Gag Peptide pool	1-4	5-8	9-12	13-16	17-19	20-22
CTL response	+ (18%)	+ (12%)		+ (35%)		
Patr-B*0101	ISPRTLNAW RTLNAWVKV			RMYSPTSIL		
Patr-A*0401[a]	MVHQAISPR	HQAAMQMLK		RWIILGLNK		
Patr-B*1401	FSPEVIPMF EVIPMFSAL			WIILGLNKI RMYSPTSIL		

Grey background indicates data obtained using only the NetMHCpan 2.0 algorithm; [a]Animal is homozygous for this allotype.

Chimpanzee founder haplotypes

Chimpanzee	A*	B*
Carolina	0401 NT	0101 NT
Debbie	0901 0101	0101 1401
Diana	0501 0302	0101 1301
Frits	0601 0401	0301 1401
Gerrit	0501 0301	1301 2901
Gina	0901 NT	0101 1401
Igor	0701 NT	2402 NT
Indira	0101 0701	1401 0501
Isaac	0101 1401	0401 0101
Jacob	0301 0501	0501 1301
Jolanda	0901 0301	0101 2901

Chimpanzee	A*	B*
Karin	0701 1101	0501 1301
Lady	NT 0301	NT 2402
Liesbeth	0701 0301	0101 2402
Louise	0602 0101	0901 0101
Marco	0901 NT	0101 0501
Marga	NT 0101	0501 16011
Mario	0701 NT	0301 1401
Nina	0901 0601	0101 0501
Pearl	1101 0601	1301 0101
Regina	0401 0201	0101 1401
Renee	0901 1401	0101 0101

Chimpanzee	A*	B*
Renza	NT 0701	1301 NT
Sherry	0701 1401	0501 0101
Sonja	0401 0901	0101 0101
Susie	0301 NT	2402 NT
Tasja	0301 0501	1301 2402
Tineke	0401 NT	0101 NT
Toetie	0901 0301	0101 2402
Wodka	NT 0101	0501 1401
Yoko	0301 1401	0501 16011
Yvonne	0301 NT	2402 NT

B*57-like B*27-like + B*57-like

NT: not typed, because data are no longer accessible.

A quantitative aspect of Ir genes

Chimpanzee	A*	B*
Carolina	0401 NT	0101 NT
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Frits	0601 0401	0301 1401
Gerrit	0501 0301	1301 2901
Gina	0901 NT	0101 1401
Igor	0701 NT	2402 NT
Indira	0101 0701	1401 0501
Isaac	0101 1401	0401 0101
Jacob	0301 0501	0501 1301
Jolanda	0901 0301	0101 2901

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Nina	0901 0601	0101 0501
Pearl	1101 0601	1301 0101
Regina	0401 0201	0101 1401
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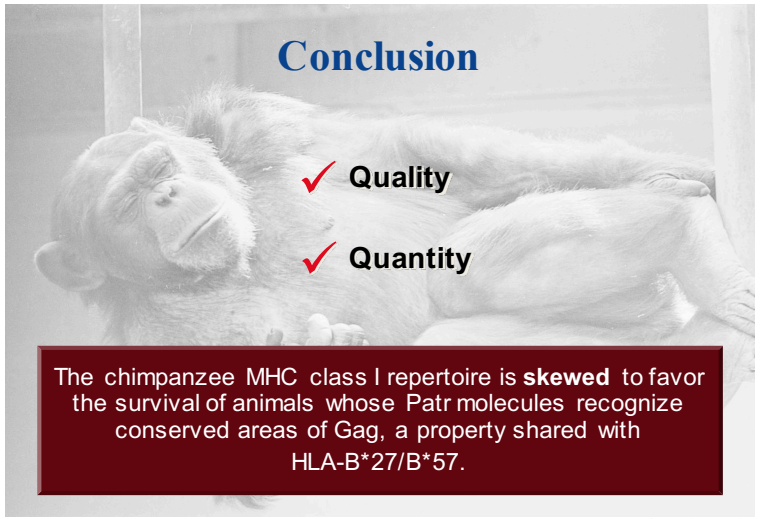
Conclusion

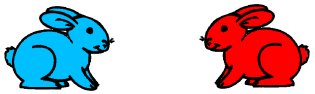


- ✓ Quality
- ✓ Quantity

The chimpanzee MHC class I repertoire is **skewed** to favor the survival of animals whose Patr molecules recognize conserved areas of Gag, a property shared with HLA-B*27/B*57.

The evolutionary rat race between hunters (pathogens) and prey (host)

Bottle neck/founder effect



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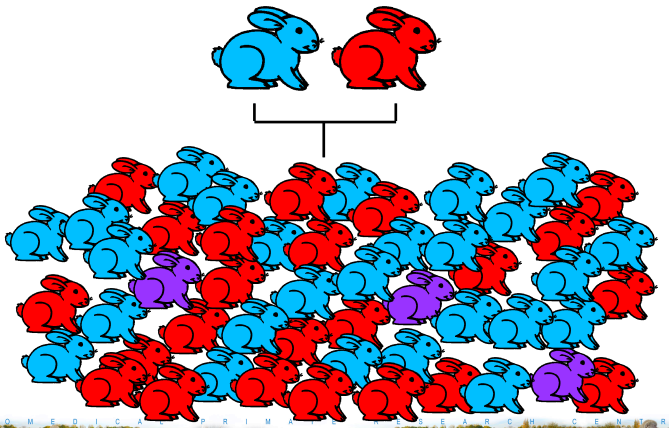
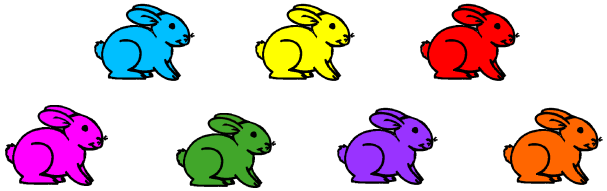


Selective sweep



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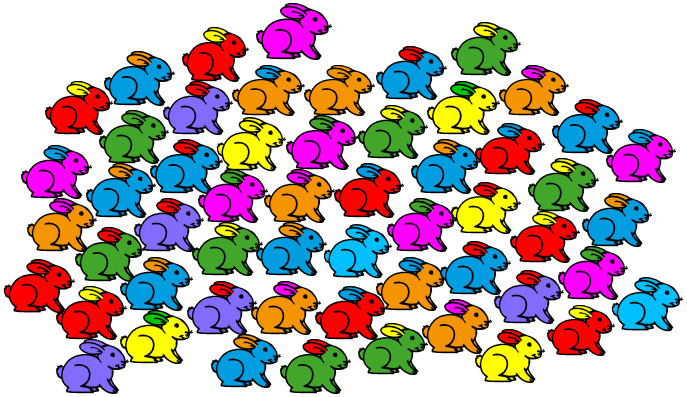

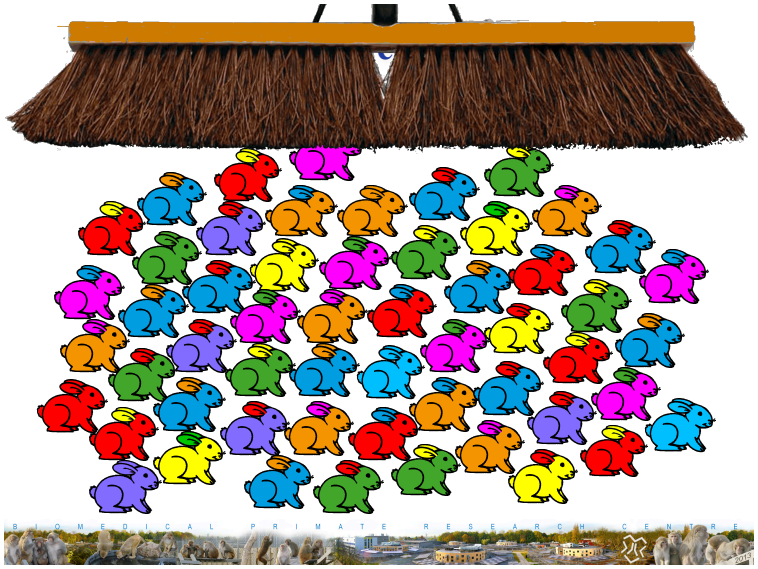

What is the biological function of MHC polymorphism?

The CG&R team

Thanks to all other collaborators/team members at the BPRC, LUMC and UU.

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