

Development of a Universal T Cell Vaccine

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Development of HIV-1 vaccines

Induction of cell-mediated responses

Immunogens * HIVA, RENTA, HIVconsv

Vaccine vectors * DNA, MVA, Adeno, BCG, SFV, proteins/peptides

Regimen * Heterologous prime-boost

Mice -> Monkeys -> Clinical Trials in Humans

Heterologous vaccine regimens are getting better at inducing high frequencies of HIV-1 specific T cells

However, these vaccine-induced T cells have to recognize multiple HIV-1 strains and escape mutants

Ways to Tackle HIV-1 Diversity

Mixed/heterologous immunogens (immune interference?)

Natural sequences with the shortest distance to other isolates in the clade or group

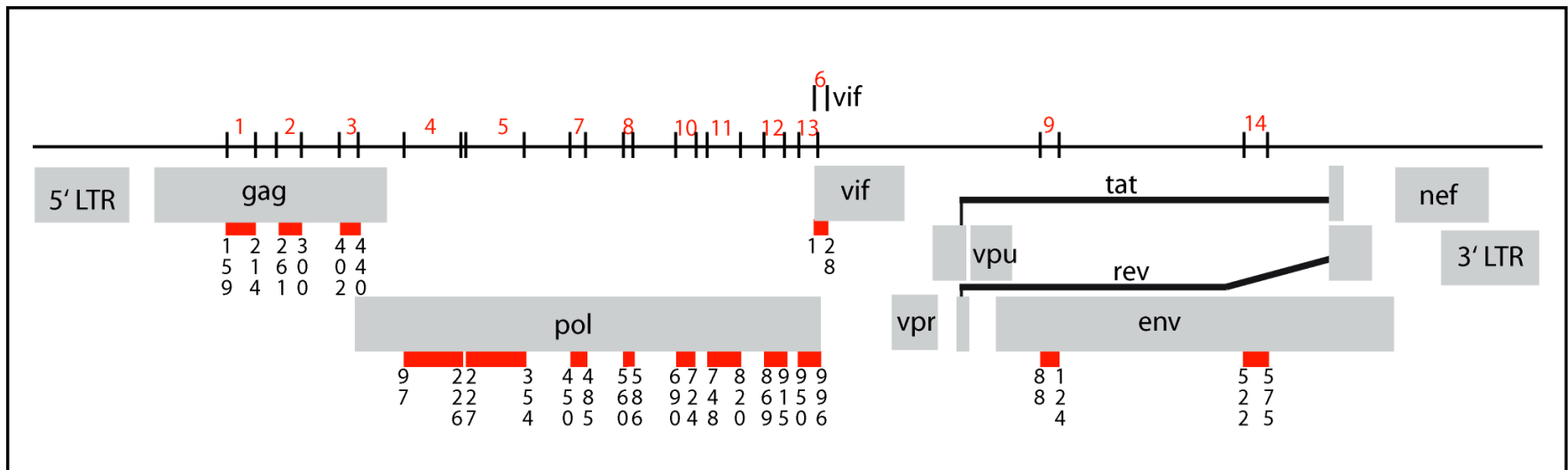
Artificial central sequences
(ancestral, consensus or COT)

Mix of 'mosaic' proteins
(maximize coverage of potential T cell epitopes)

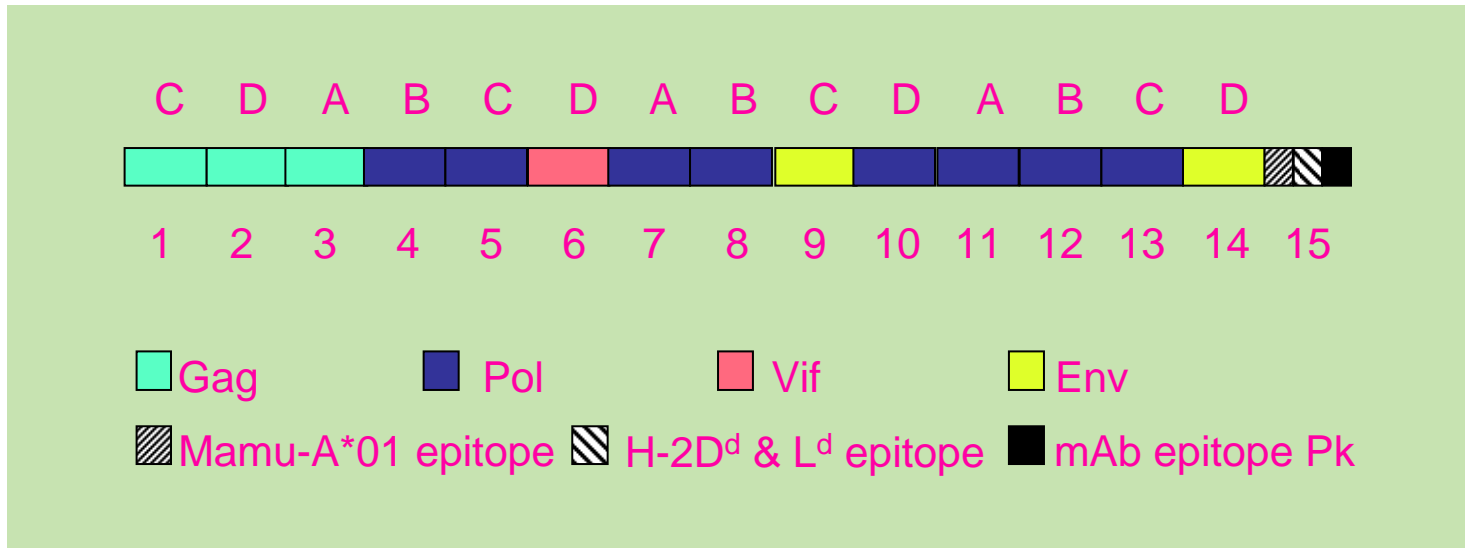
Focus on the small founder population of transmitted viruses

HIVconsv - Immunogen based on conserved regions of the HIV-1 proteome

- Gene of 2.5 kbp, which can be easily inserted into most current vaccine vectors and is likely to support high protein expression HIVconsv
- 2.5 kbp translated into the 14 most highly conserved regions of the HIV-1 proteins



The HIV_{CONSV} Immunogen



Alternating 4 major clades to ensure equal clade representation

Clade Consensus to reflect variation within clades

Each fragment just once to avoid possible immune interference

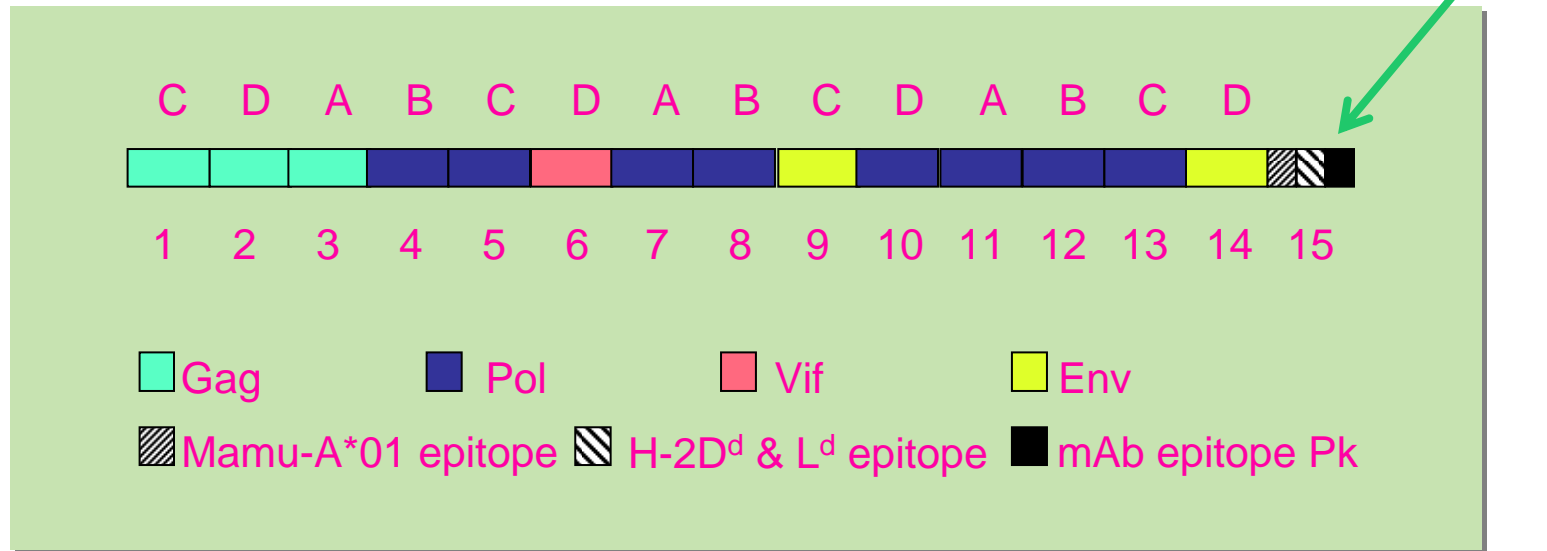
Difficult for HIV to mutate these regions without a fitness cost

Altering natural (unprotective) hierarchy of epitope responses

Theoretical drawbacks of the HIV_{CONSV} design

- Junctional regions can generate novel, irrelevant and immunodominant responses for some HLAs
- Suboptimal processing of some epitopes (processing of some may improve)

Synthetic HIV_{CONSV} gene



Humanized codons



Plasmid DNA

'naked' DNA

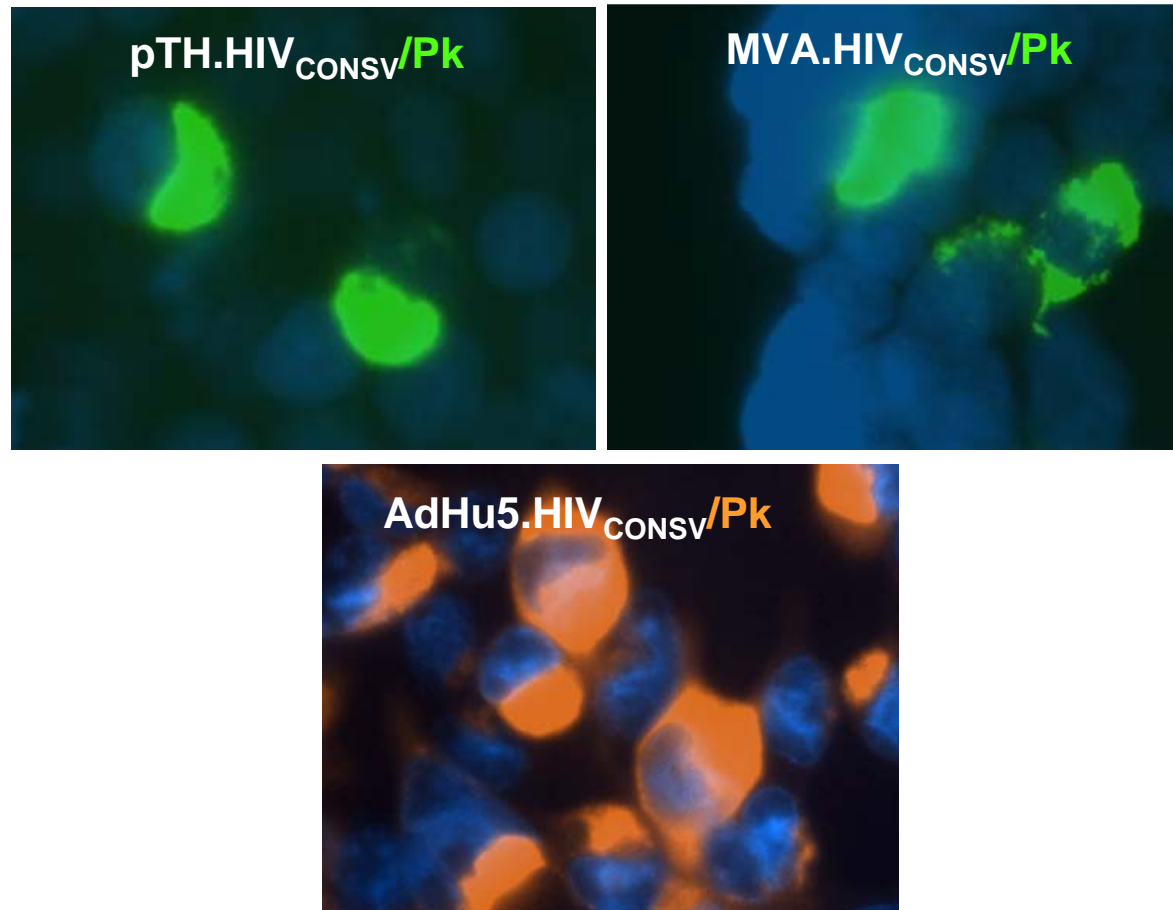
MVA

attenuated
poxvirus

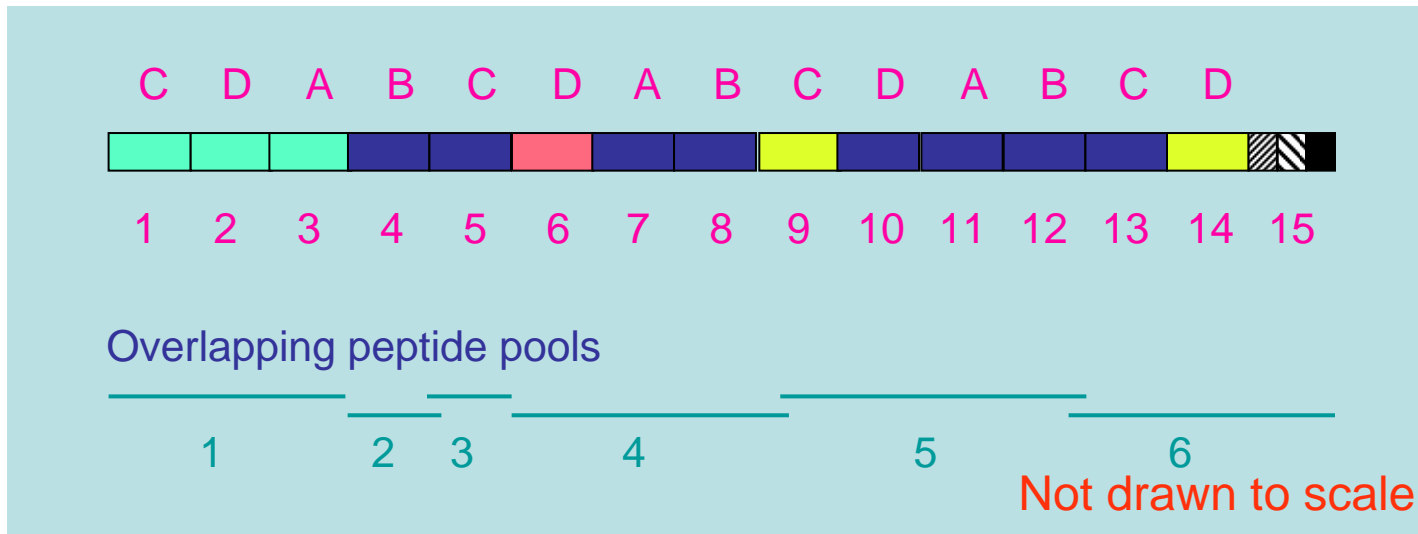
AdHu5

(AdHu6, AdC63, AdC3)
attenuated adenoviruses

High HIV_{CONSV} protein expression in 293T cells



The HIV_{CONSV} peptide pools (15/11)

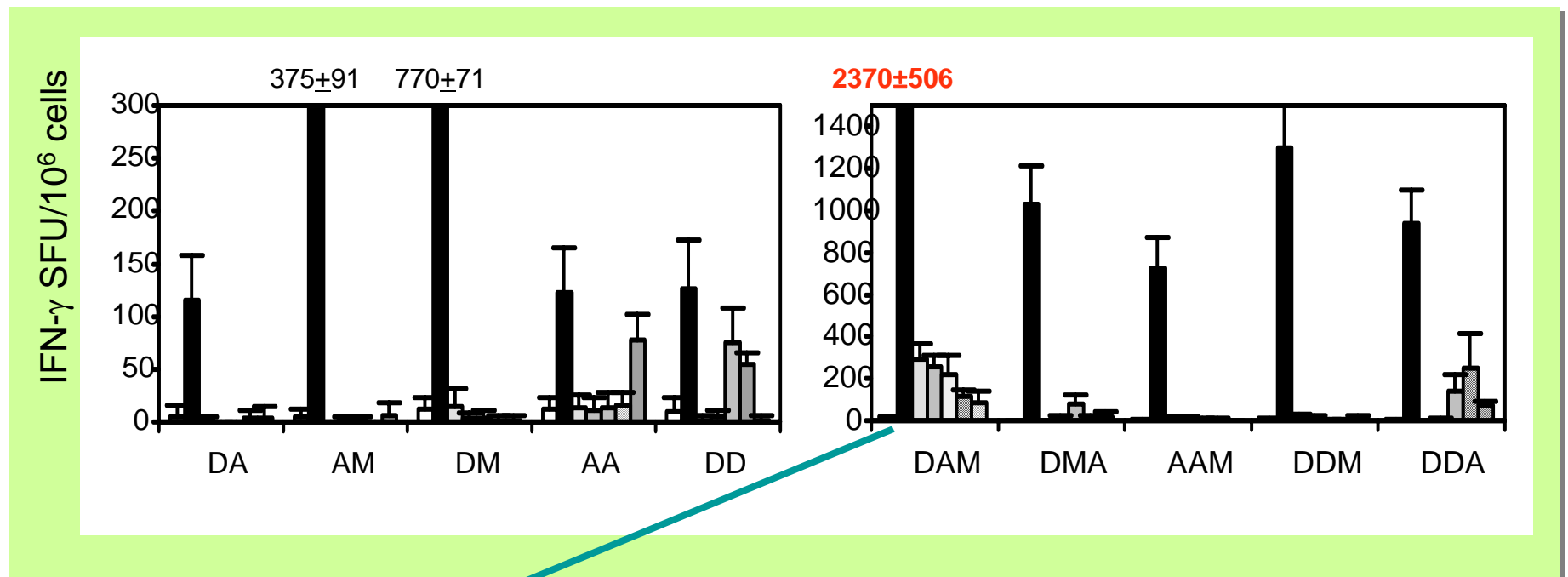


- Gag
- Pol
- Vif
- Env
- Mamu-A*01 epitope
- H-2D^d & L^d epitope
- mAb epitope Pk

Vaccine immunogenicity in BALB/c mice

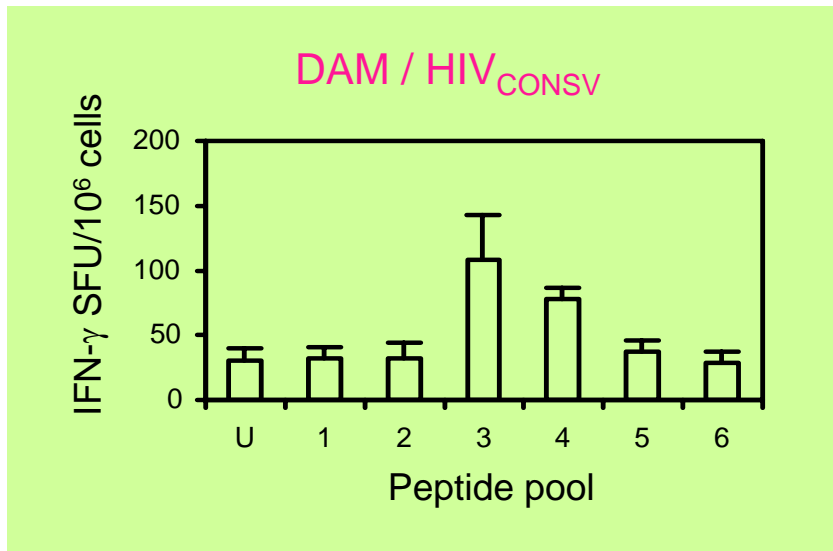
to individual peptide pools 1-6

Heterologous DNA-AdHu5-MVA
(DAM) regimen is superior



Pool 6 contains H-2^d immunodominant RGPGRAFVTI (H) epitope

Immunogenicity in HLA-A*0201-transgenic mice



Peptide Pool No.	Peptide No.	HIV-1 Gene	Epitope
3	94	Pol	VIIYQYMDDL
4	125	Env	QMHEDIISL

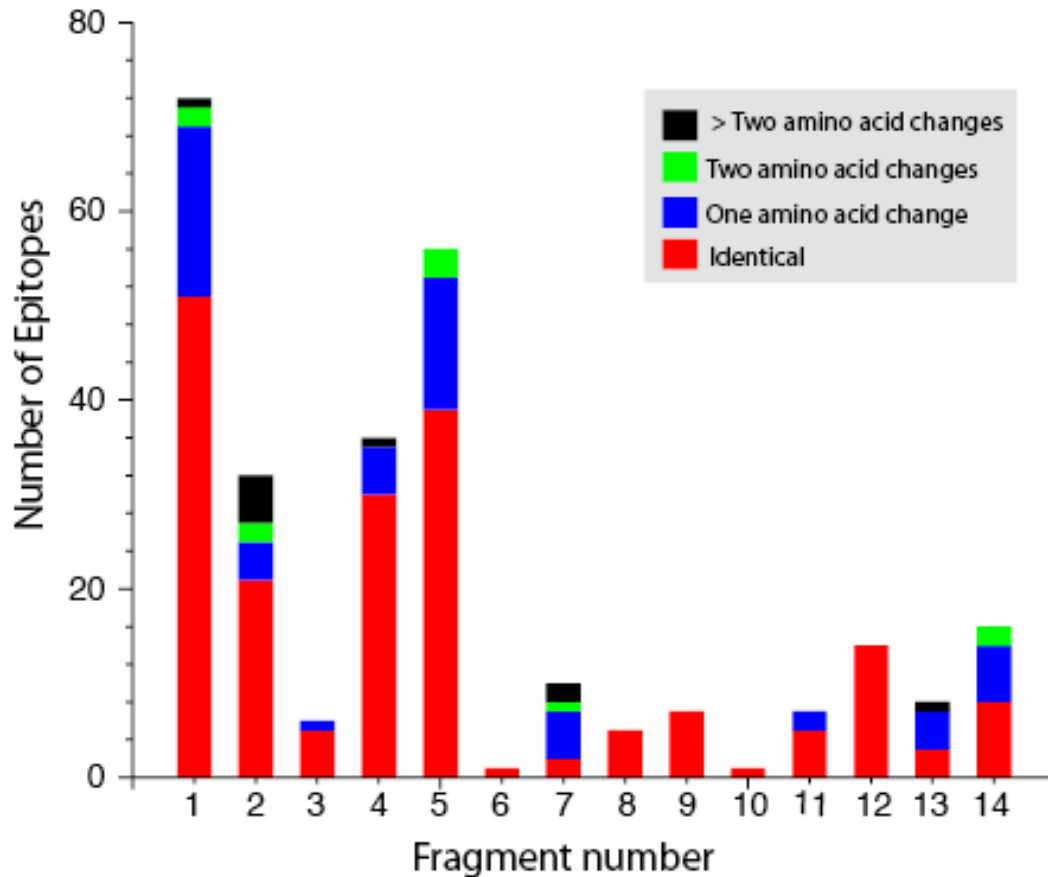
Pol active site



- 37 defined HLA-A*0201 epitopes in HIVconsv
- However, most A2 patients respond to two dominant epitopes absent from HIVconsv
- Therefore, response to 2 subdominant epitopes is encouraging

Conserved fragments are not immunologically inert

Numbers of known CD8 T cell epitopes in HIV_{CONSV}



Total of 1112 CD8 T cell epitopes smaller than 12 AA in the LA database

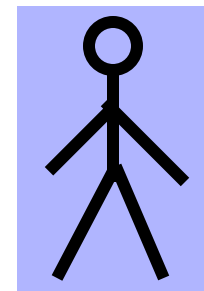
Each fragment contains at least one known epitope

HIV_{CONSV} contains 270 (24%)

Of these 270:

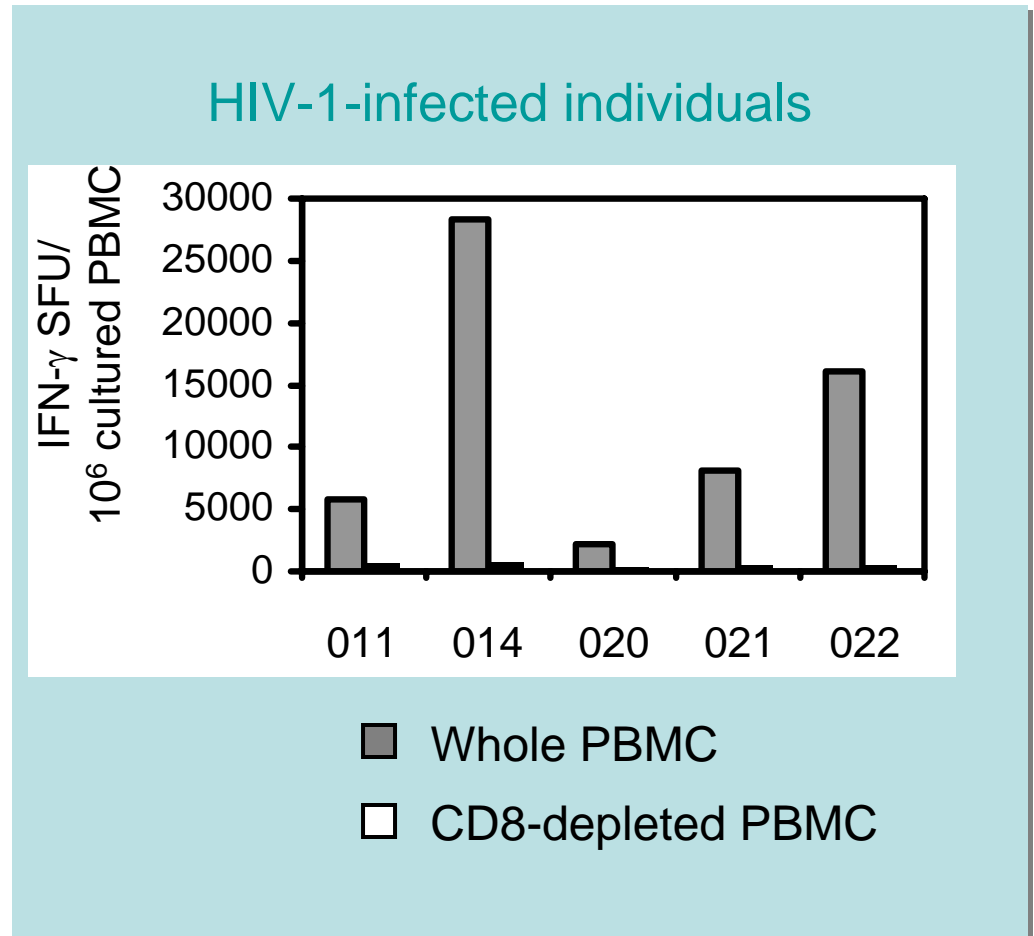
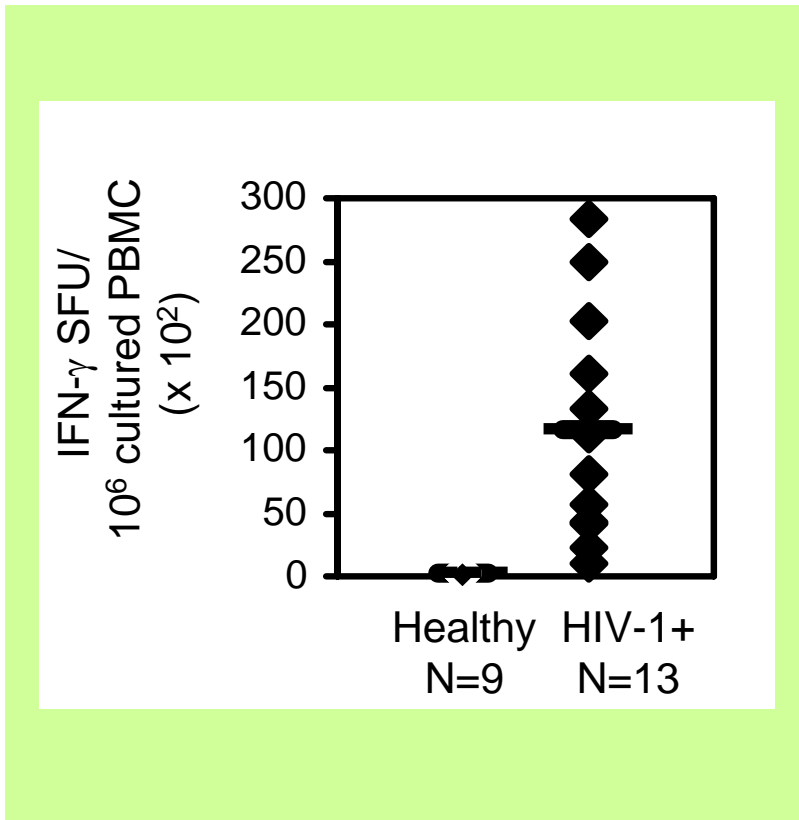
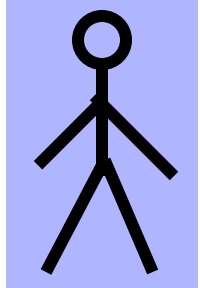
192 (71%) perfect match

59 (22%) differ by one AA



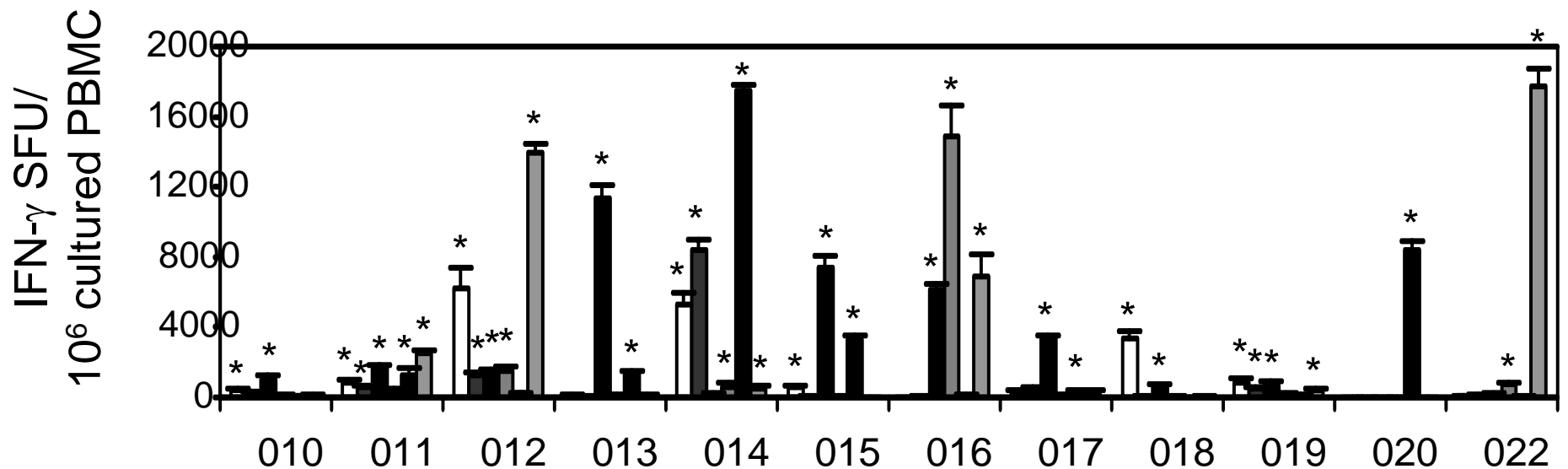
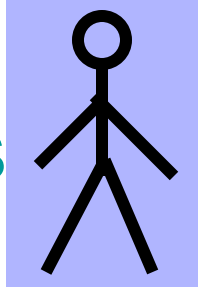
HIV_{CONSV}-derived peptides are recognized by PBMC from HIV-1-infected humans

Cultured IFN- γ ELISPOT assay



Responses to individual HIV_{CONSV} peptide pools by PBMC from HIV-1-infected humans

Cultured IFN- γ ELISPOT assay



All patients have responses to at least one peptide pool
11/12 patients have responses to at least 2 pools

Conserved regions of HIV-1
proteome are immunogenic in
humans

HIVconsv immunogenicity in non-human primates

DAM

3x 4 mg pTH.HIVconsv DNA i.m.

1x 10¹⁰ pfu AdHu5.HIVconsv i.m.

1x 10⁸ pfu MVA.HIVconsv i.m.

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- Immunogenicity of HIVconsv - Specificity and cross-clade reactivity
- Heterologous DAM - Frequency
- Multifunctionality - Quality

On going

Summary

We believe HIVconsv is an interesting novel approach which

- Has the potential to induce cross-clade T cell responses
- Focuses responses on parts of HIV-1 that HIV-1 cannot easily mutate without significant fitness costs
- Redirects responses relative to natural infection
- Is simple in design and delivery

DAM regimen and more complex heterologous regimes are more immunogenic

Might not be practical, but may prove the concept

CONCLUSIONS

We continue to develop and evaluate in mice and non-human primates novel vaccine strategies

We put emphasis on safe, but rapid translation of our laboratory results into humans

We maintain a positive attitude towards the HIV-1/AIDS vaccine development



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