DISSECTING IMMUNE CORRELATES OF RISK OF SIV ACQUISITION IN MACAQUES VACCINATED WITH A PROMISING HIV VACCINE CANDIDATE

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SESSION II. DEVELOPMENT OF HIV VACCINES

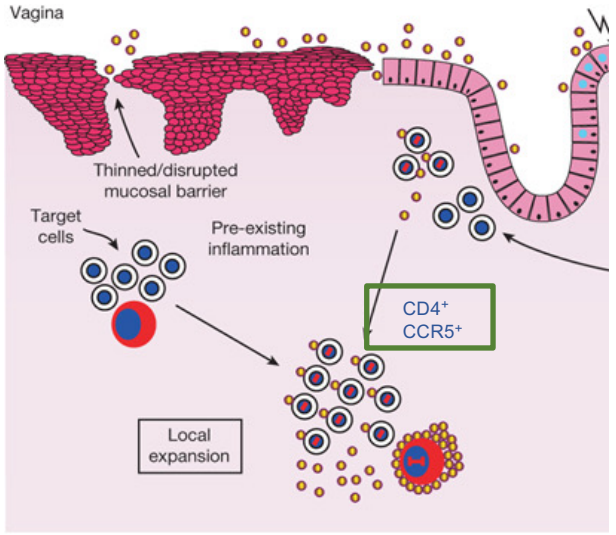
Importance of an HIV vaccine

- 1.5 million new HIV-1 infections per annum
  - –80% of new infections occur via mucosal transmission (STI)
- ART cost billions dollars per year
  - 38 million infected = Billions
- Vaccine with 50% efficacy could meaningfully reduce HIV transmission

UNAIDS 2022.
Tagar et al. 2014.

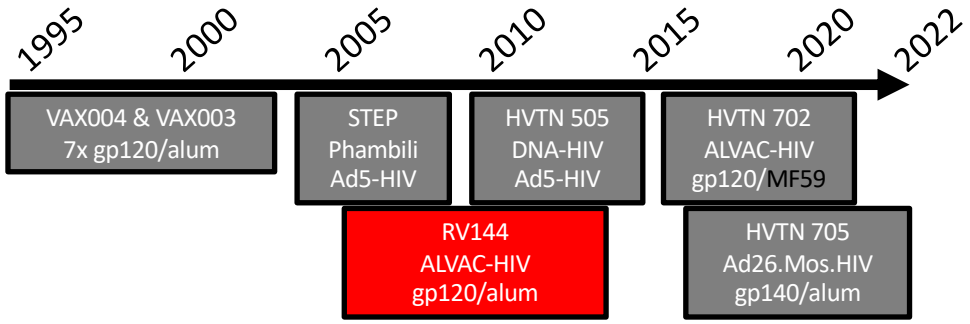
Challenges of developing an HIV vaccine

- ❑ Genetically heterogeneous virus swarms
- ❑ Resistance to neutralization of primary HIV
  - Difficult to elicit cross-clade neutralizing antibodies
- ❑ Vaccines induce antigen-specific responses via inflammation
- ❑ HIV co-opts inflammatory pathways
  - NF-κB binding sites in LTR
  - Swarm induces inflammation to recruit target cells
- ❑ Vaccines may recruit $CD4^+$ $CCR5^+$ target cells



Ashley Haase 2010.
UNAIDS 2022.
Tagar et al. 2014.

HIV vaccine phase IIb/III trials



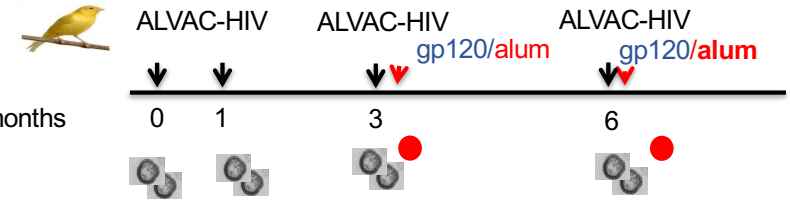
31.2% vaccine efficacy

Rerks-Ngarm et al., NEJM, 2009.

2009: RV144 HIV vaccine efficacy trial in Thailand

RV144

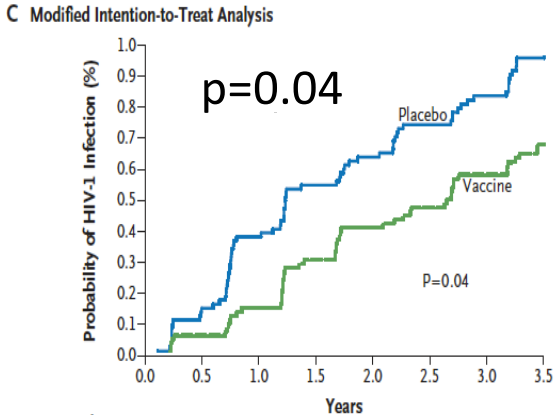
~16,000 volunteers



Virus like particles= VLP

● 120 & alum (bivalent) Clades B,AE

🡻 ALVAC (Avian Poxvirus) Gag /pro / gp120-TM/ Clade AE/B

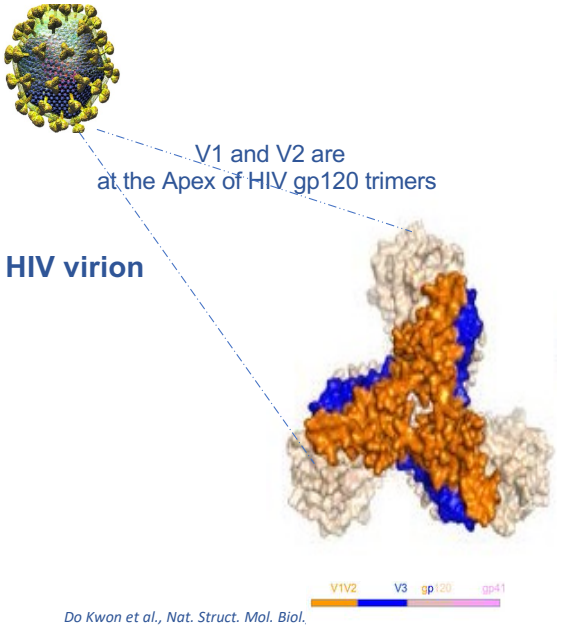


31,2% efficacy

RV144 immune correlates of reduced risk

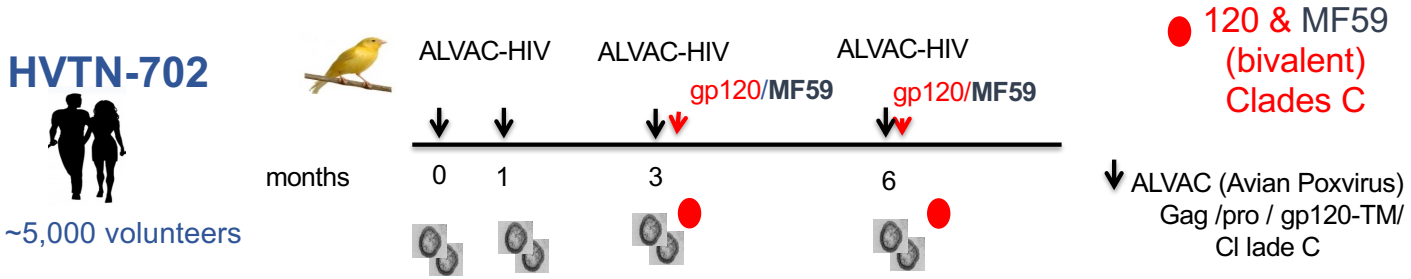
- Binding, non-neutralizing anti-V1/V2 IgG correlated with reduced risk
- $V2^{166\text{-}178}$ is a hotspot for ADCC
- ADCC correlated with reduced risk in vaccinees with low IgA
- IgG1 and IgG3 required for optimal ADCC
- Polyfunctional V2-specific T-cells correlated with reduced risk

V1/V2



- V1 & V2 loops are at the apex of gp120 trimer anchored by disulfide bonds
- V2 contains binding sites for $\alpha_4\beta_7$

2021: HVTN-702 HIV vaccine efficacy trial in South Africa



HVTN-702

- ALVAC Clade C
- Bivalent clade C gp120 boost in MF59
- Incidence of HIV: 4.2% (women)
- No efficacy

RV144

- ALVAC clade A/E
- Bivalent clade A/E and B gp120 boost in Alum
- Incidence of HIV: 0.3% (women)
- 31.2% efficacy

- Conclusion :

The absence of a parallel arm with gp120/alum boost in HVTN-702 precludes conclusions on the efficacy of the ALVAC /gp120/boost platforms

Vaccine Efficacy of ALVAC-HIV and Bivalent Subtype C gp120/MF59 in Adults. GE Gray et al. **New Engl. J. Med. 2021**

Analysis of the HIV Vaccine Trials Network 702 Phase 2b– 3 HIV-1 Vaccine Trial in South Africa Assessing RV144 Antibody and T-Cell Correlates of HIV-1 Acquisition Risk Moodie et al. *J. Infecious Diseases, 2022*

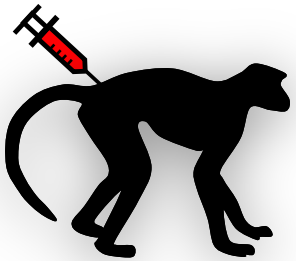
Methods to evaluate relative HIV vaccine candidates efficacy and immunological correlate in macaques

Systemic and mucosal Immune responses

10-14 weekly Vaginal or rectal challenges

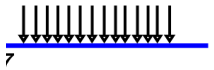
End Point
Time of infection

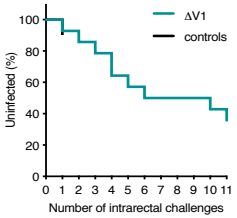
Vaccinated



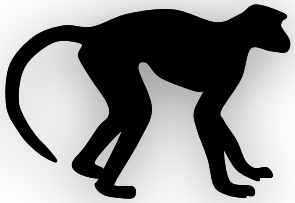
3-6 months

SIV_{mac251}

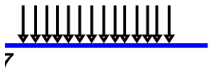




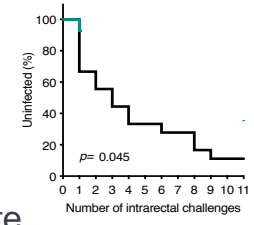
Controls



SIV_{mac251}



20-30% average rate of infection at each challenge



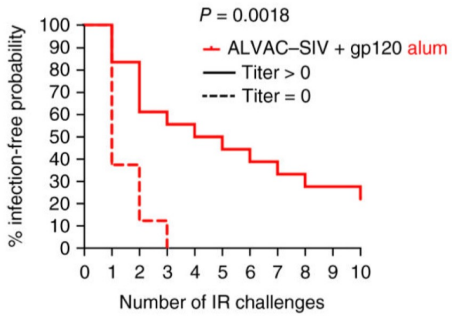
READ-OUT OF VACCINE EFFICACY:

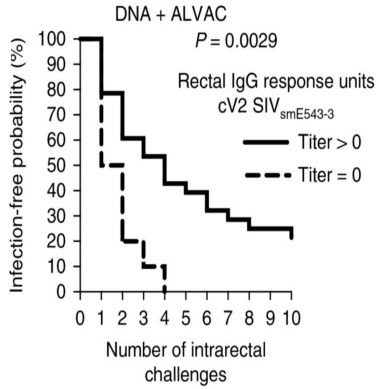
Analyses of per exposure risk of virus acquisition

Relevance of the SIV_{mac251} model to humans

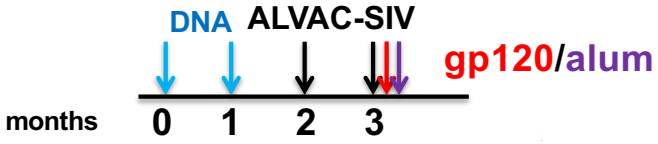
- **Recapitulated the results of RV144**
- **Predicted the failure of HVTN-702**
- **Confirmed the binding Abs to V2 correlate**

- Compared priming (DNA/ALVAC/Ad26)
- Compared viral vectors (NYVAC/ALVAC)
- Compared Adjuvants (alum/MF59)
- Compared genetically modified gp120s

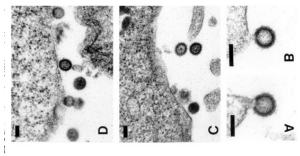




- **Streamlined regimen with DNA/ALVAC/gp120/alum**



DNA= VLP
ALVAC= VLP

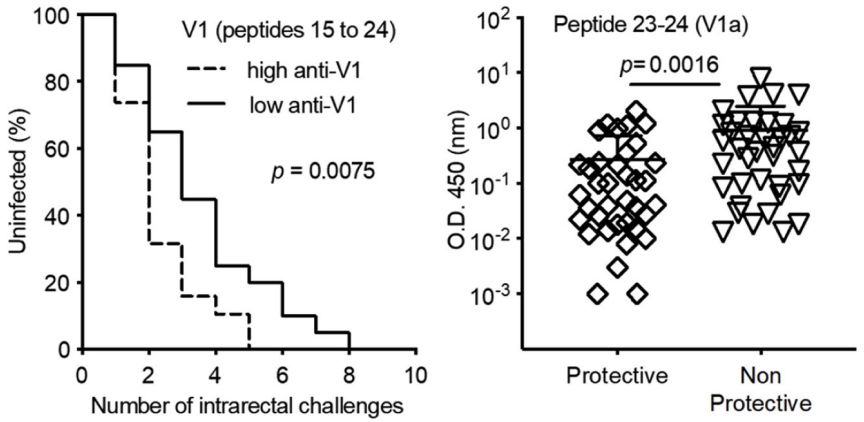


Pegu et al. *J.Virol, 2014*
Fouts et al. *PNAS, 2015*
Gordon et al. *J.Immunol, 2016*
Vaccari et al. *Nature Med., 2016*
Vaccari et al. *Nature Med., 2018*
Vaccari et al. *Frontiers in Immunology 2019*
Schifanella et al. *Plos Pathogens 2019*
Gorini et a .*Plos Pathogens 2021*
Silva de Castro et al. *J.Virol ,2020*

ΔV1 envelope vaccine platform

- V1 antibody responses associated with increased risk

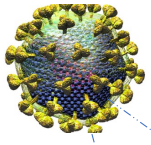
Vaccinated animals with higher Abs to V1
acquire SIV_{mac251} early



Silva de Castro et al. iScience, 2021

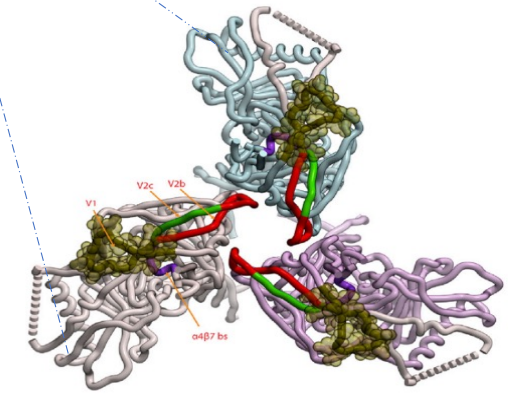
V1: an immunological decoy?

V1 partly masks V2

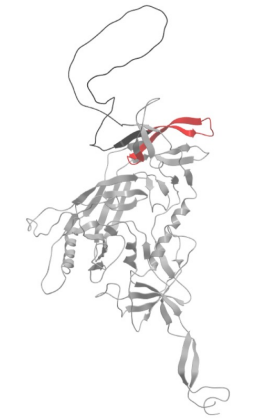


HIV virion

gp120
Top down view



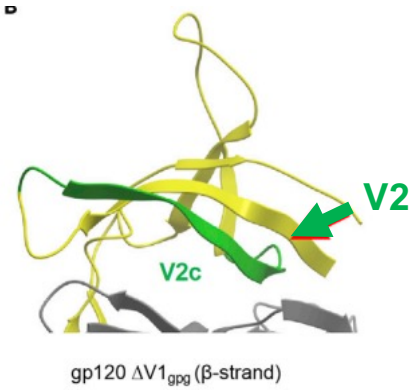
gp120
Side view

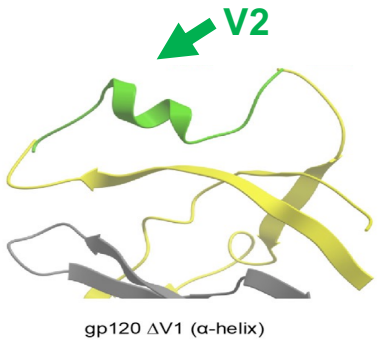


Hypothesis: deletion of V1 may improve vaccine efficacy

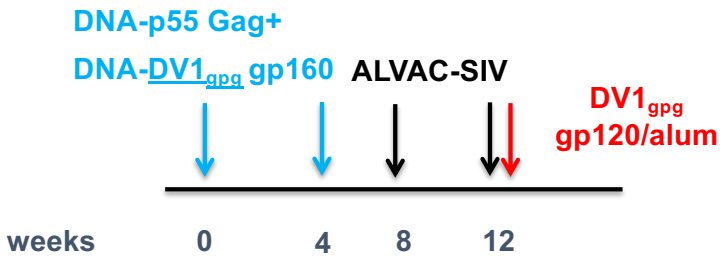
V1 deletion in SIV envelope: protein engineering Tim Cardozo (NYU)

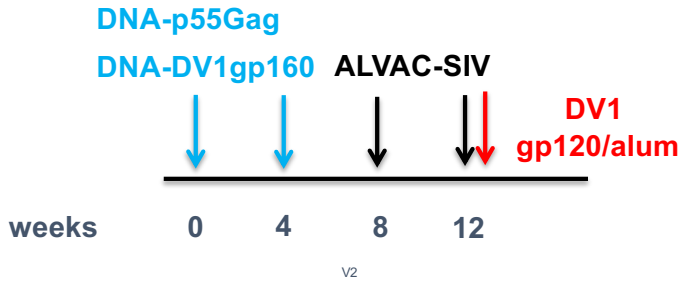
gp120 DV1**gpg**
V2 b-sheet





gp120 DV1
V2 a-helix

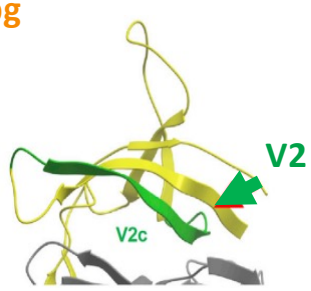




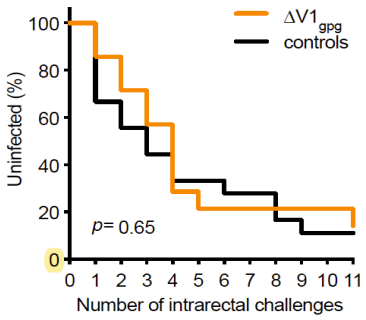
V2

V1 deletion in SIV envelope favoring V2 helical conformation decreases the risk

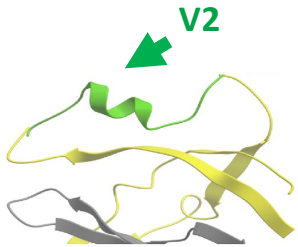
gp120 ΔV1**gpg**
V2β–sheet



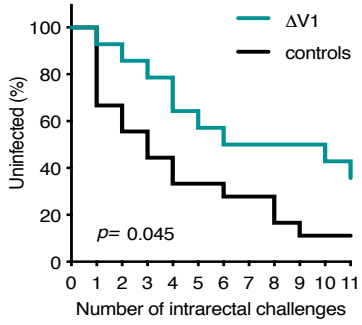
gp120 ΔV1$_{gpg}$ (β-strand)



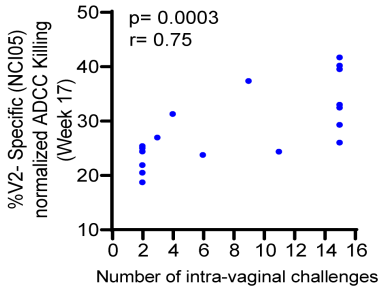
gp120 ΔV1
V2 α-helix



gp120 ΔV1 (α-helix)



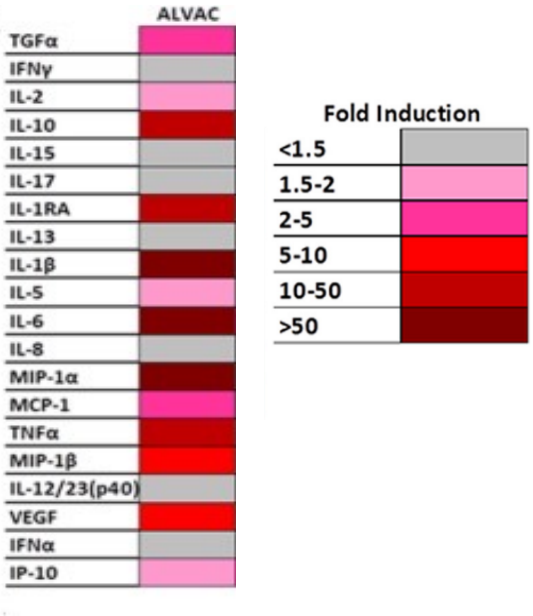
V2-specific ADCC

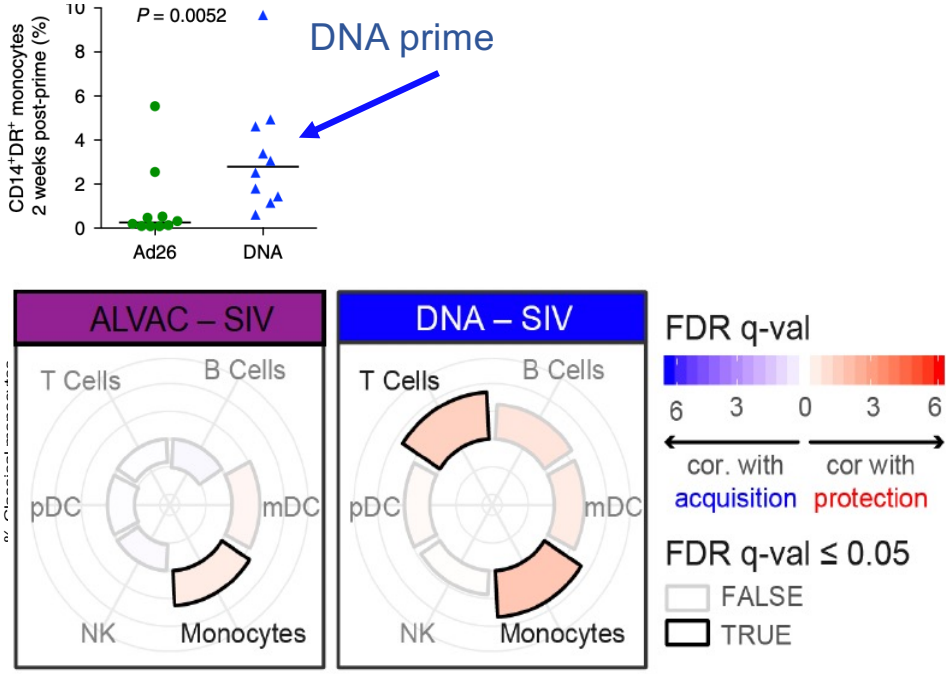


I. Silva de Castro et al., iScience, 2021

- There is more than Abs to V2…
- Intrinsic effect of ALVAC, DNA and alum on immunity

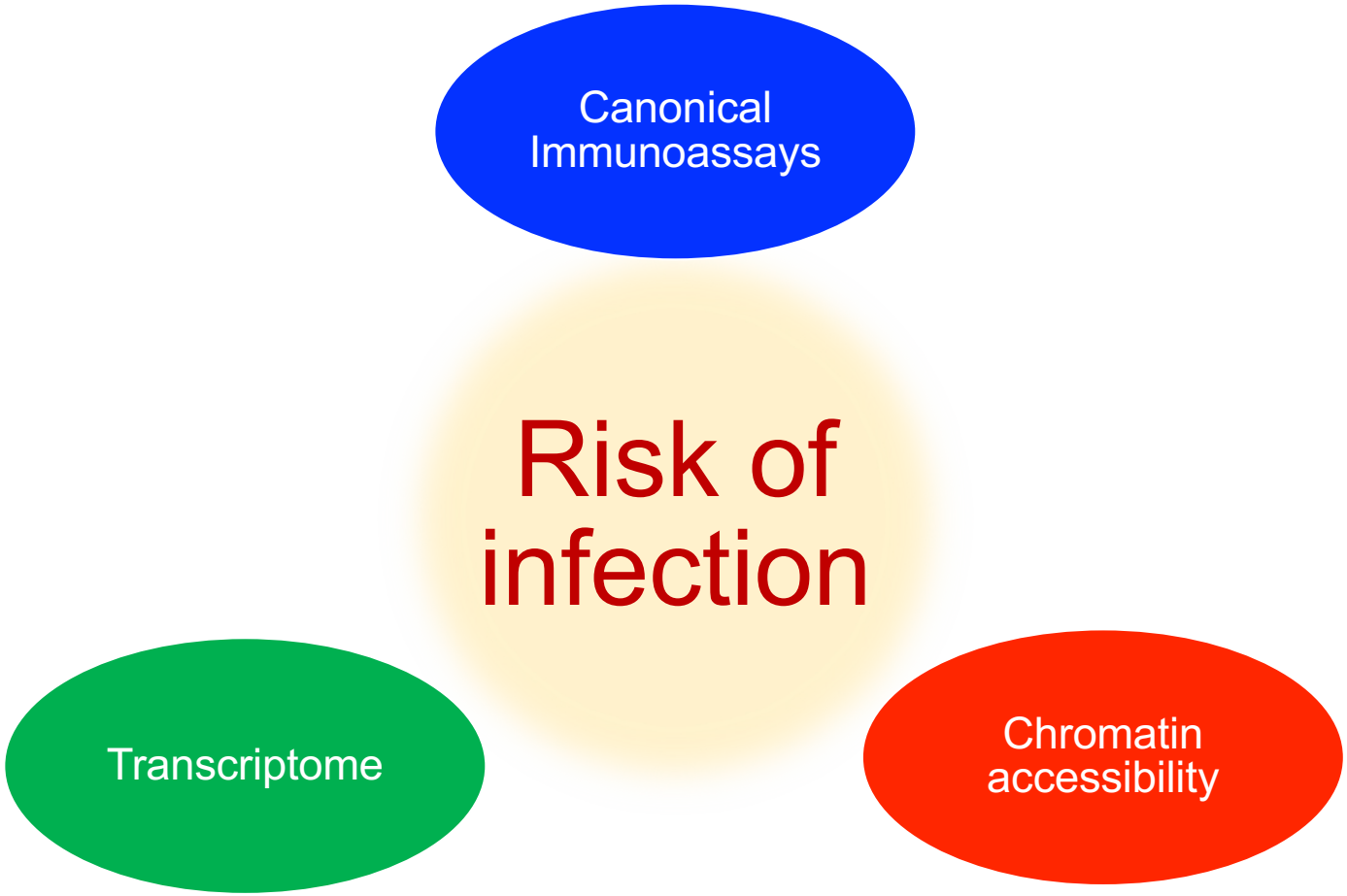
ALVAC preferentially infects CD14+cells





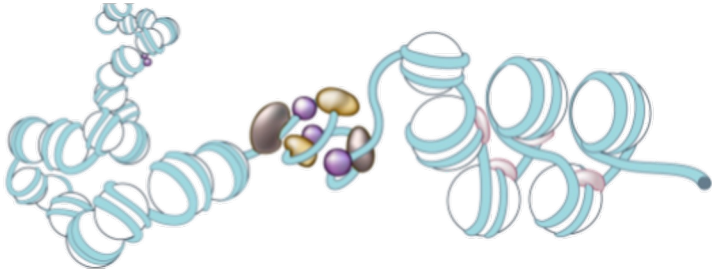
Vaccari et al., *Nature Med., 2018*
Tiegler et al., *J. Virol., 2015*

System vaccinology to identify protective responses

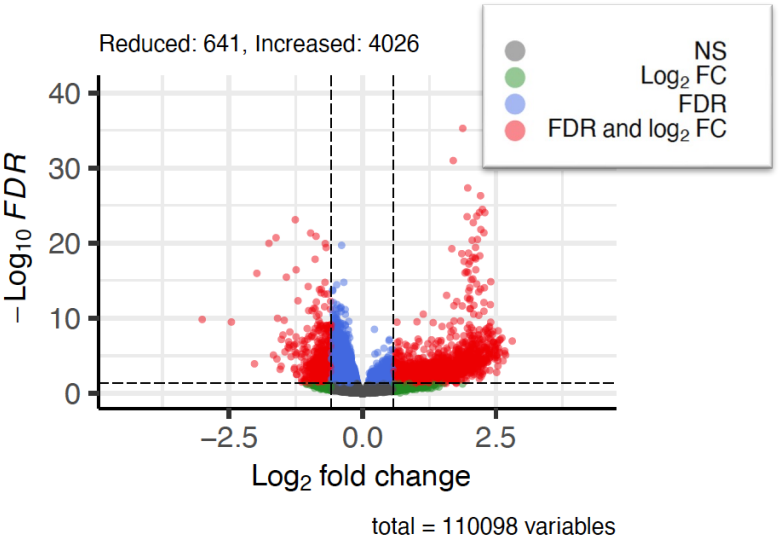


Vaccination changed the chromatin accessibility in CD14^{+} cells

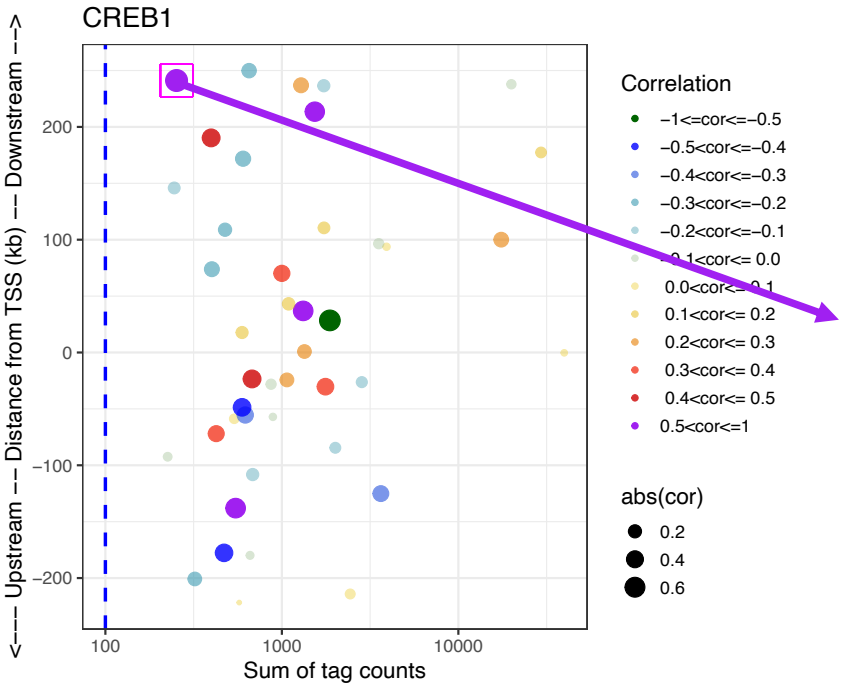
Accessible chromatin

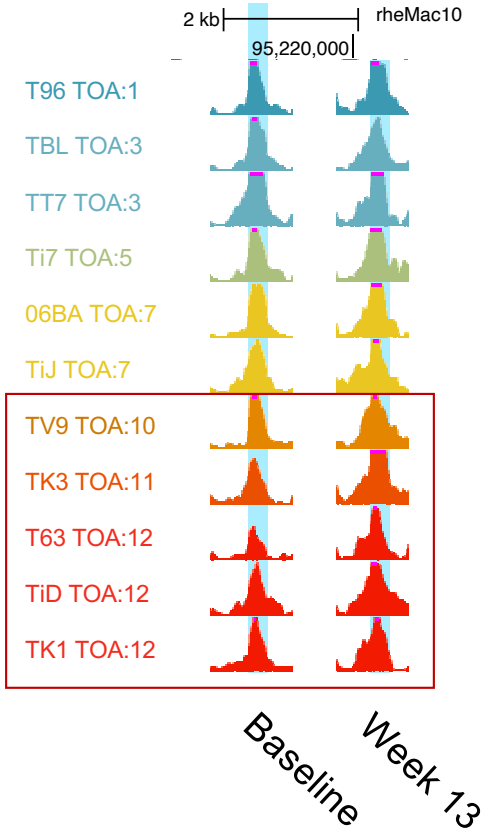


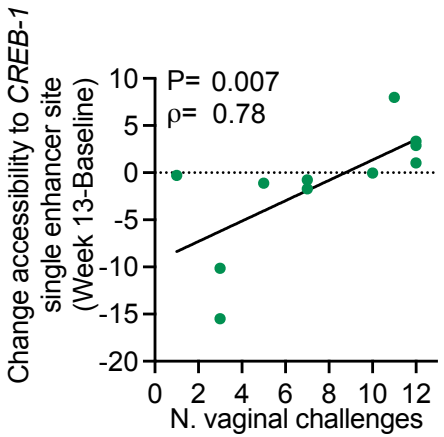
Mapping these regions with ATAC-Seq will identify most regulatory elements



Vaccine-induce accessibility to *CREB-1* enhancer region associated with risk of acquisition



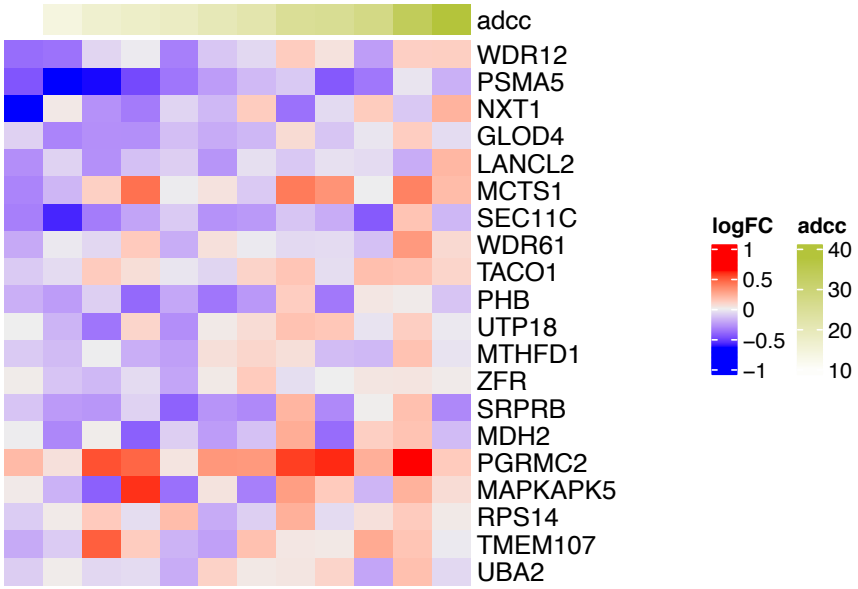




CREB1 pathway activation and *CREB-1* accessibility enhancer region associated with V2 specific ADCC

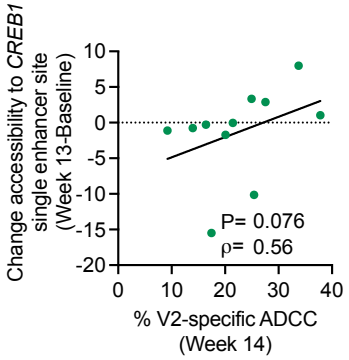
TRANSCRPTOME in CD14⁺ cells

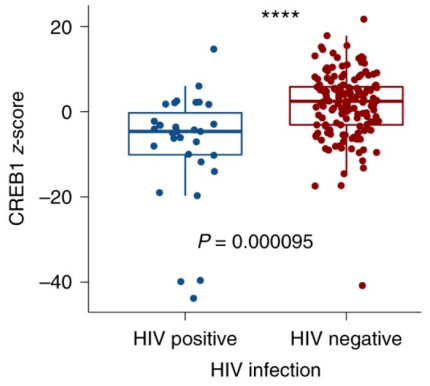
CREB1 pathway activation influences V2-ADCC (p=0.019)



CHROMATIN ACCESSIBILITY in CD14⁺ cells

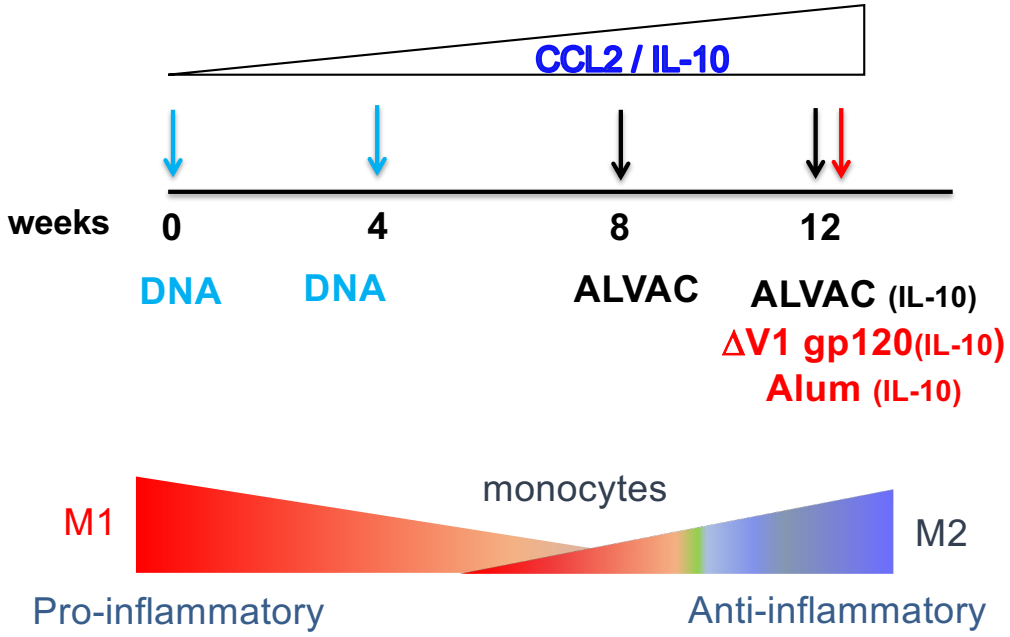
CREB1 enhancer accessibility correlated with V2-ADCC

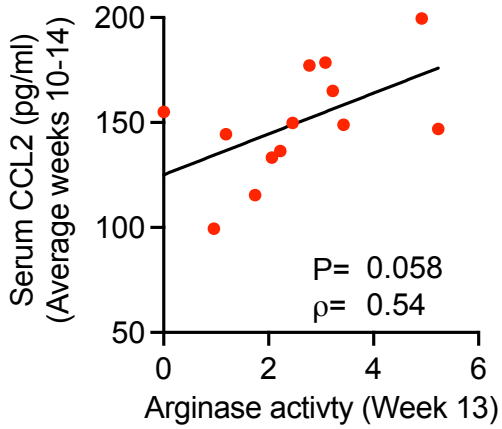




CREB1 expression was associated with protection in the RV144 human trial and NHP study (*Tomalka et al, Nature Immunology, 2021*)

Engagement of the CCL2/CCR2 axis & cAMP/CREB-1 activation and re-programming of pro-inflammatory M1 to anti-inflammatory M2 monocytes





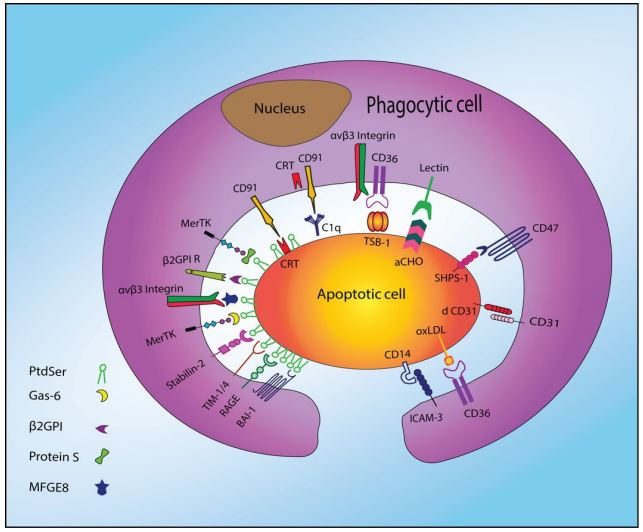
Cyclic AMP Regulates Recruitment, Reprogramming and Efferocytosis.
GL Negreiros-Lima et al. *Cells, 2020*

J.Tomalka et al. *Nature Immunol 2021*

Bissa M. et al. *Nature. Comm, in revision 2022*

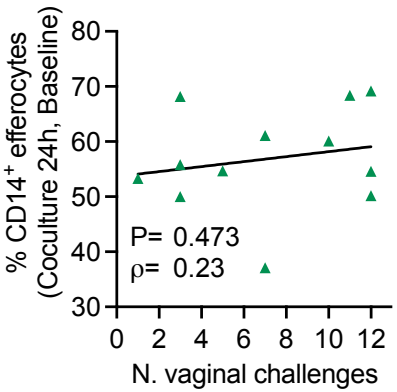
CD14⁺ cells efferocytosis

(latin: bring to the grave): ability of CD14+ cells to engulf and destroy **apoptotic cells**
Efferocytes are induced by IL-10

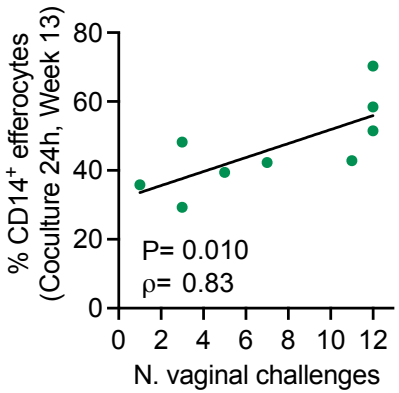


- Efferocytosis is a tightly regulated process involving the coordinated engulfment of dead and dying cells, maturation of the phagosome and then breakdown of phagolysosomal contents
- Every day, approximately 0.4% of the estimated 37.2 trillion cells in an adult human die . However, even in tissues where cell turnover is high, apoptotic cells (ACs) are scarce, indicating very high efficiency of and capacity for AC clearance.
- **Defective efferocytosis= inflammation**

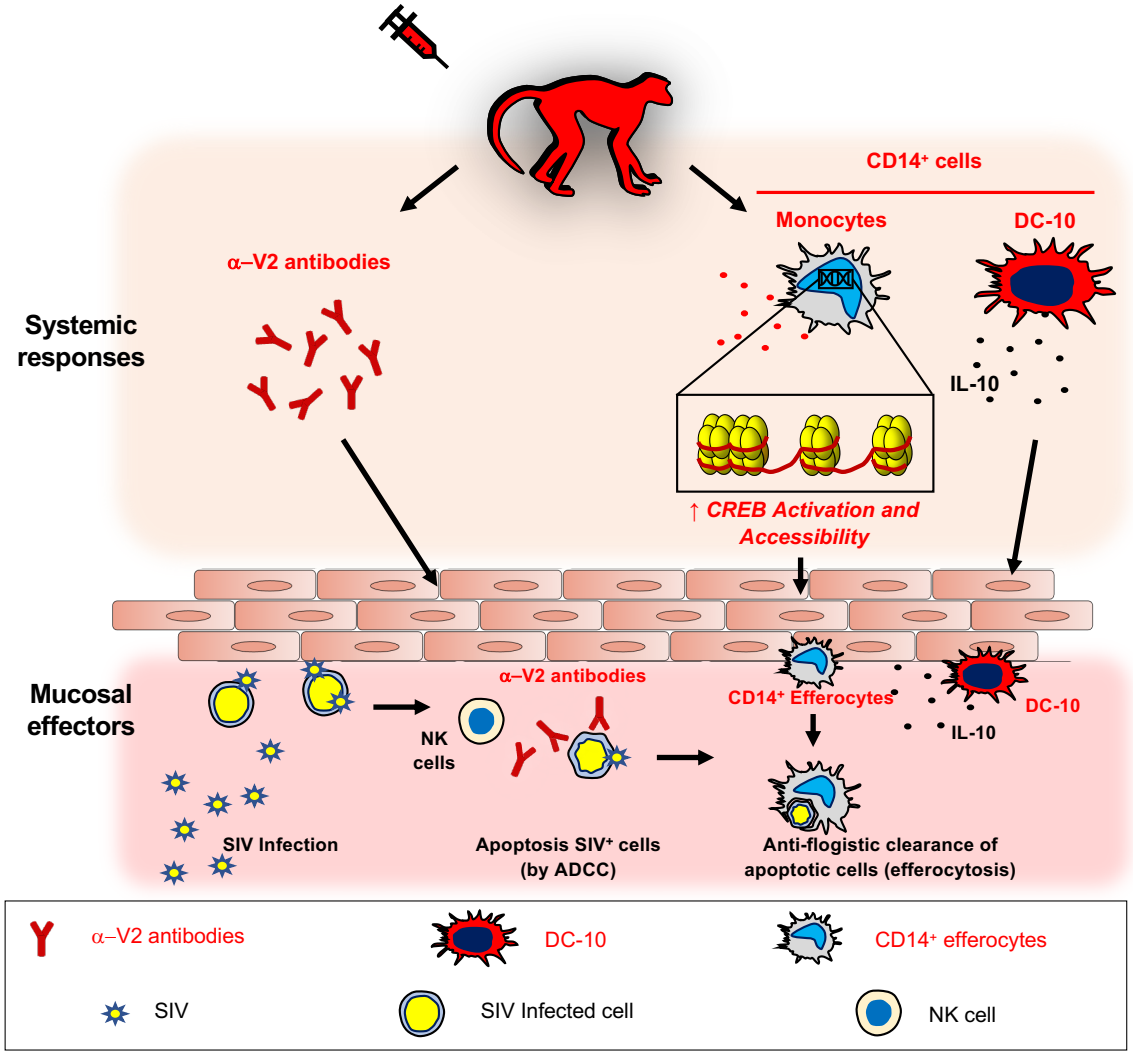
Pre-vaccination



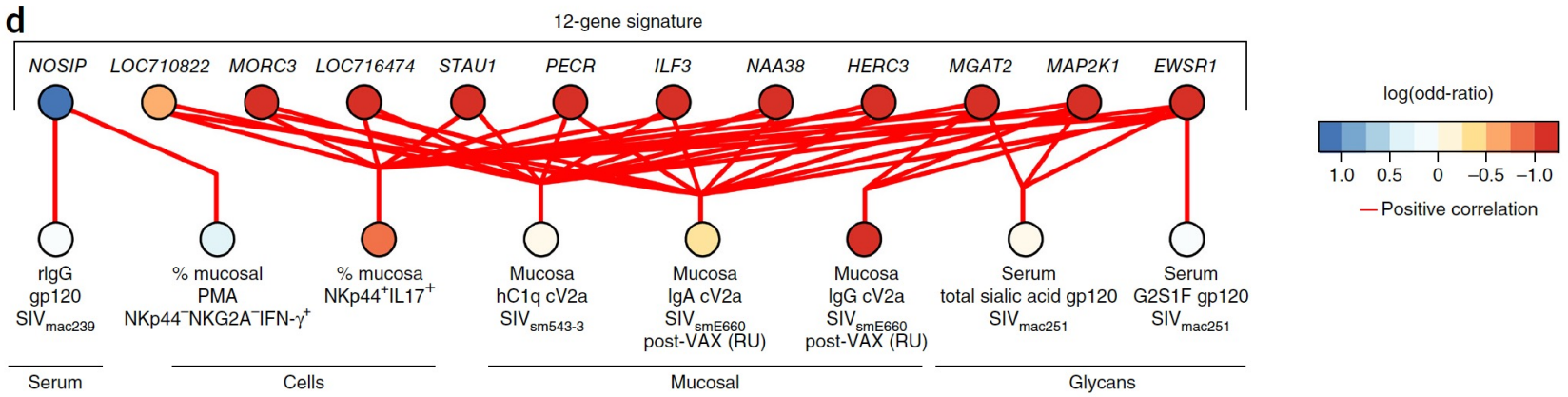
Post-vaccination



SM Gheibi Hayatet al., Immunology & Cell Biology, 2019

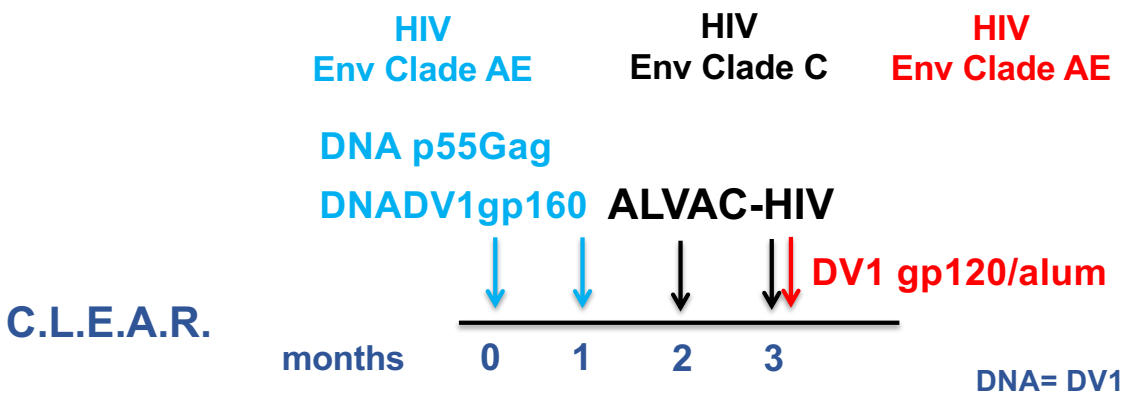

CD14+ cells
Monocytes
DC-10
α–V2 antibodies
Systemic responses
IL-10
↑ CREB Activation and Accessibility
Mucosal effectors
α–V2 antibodies
CD14+ Efferocytes
DC-10
IL-10
NK cells
SIV Infection
Apoptosis SIV+ cells (by ADCC)
Anti-flogistic clearance of apoptotic cells (efferocytosis)
α–V2 antibodies
DC-10
CD14+ efferocytes
SIV
SIV Infected cell
NK cell

In macaques the expression of 12 genes are associated with different immune responses, ten of them are involved in the RAS pathway

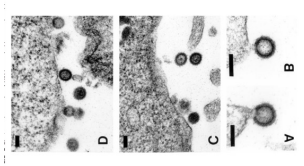


Vaccari et al., at Med, 2016

Future plans: the Phase-I HIV vaccine trial C.L.E.A.R.
(Combined Long-term Efferocytosis and ADCC Responses)

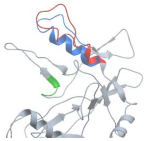


DNA= DV1-VLP
ALVAC= VLP



COLLABORATIVE STUDY
Frank Maldarelli (NCI)
& Julie Ake & Merlin Robb (MHRP)
Starting in 2024/2025

Monovalent
DV1 gp120/alum



Anti-V2 antibodies virus vulnerability revealed by envelope V1 deletion in HIV vaccine candidates
I. Silva de Castro et al., iScience 2021

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