British HIV Association
BHIVA
20th Annual Conference

BASHH
12th Annual Conference

Third Joint Conference

of the
British HIV Association (BHIVA)
with the
British Association for Sexual Health and HIV (BASHH)

1–4 April 2014

Arena and Convention Centre · Liverpool

Professor Jonathan Weber

Imperial College, London

Professor Jonathan Weber

Imperial College, London

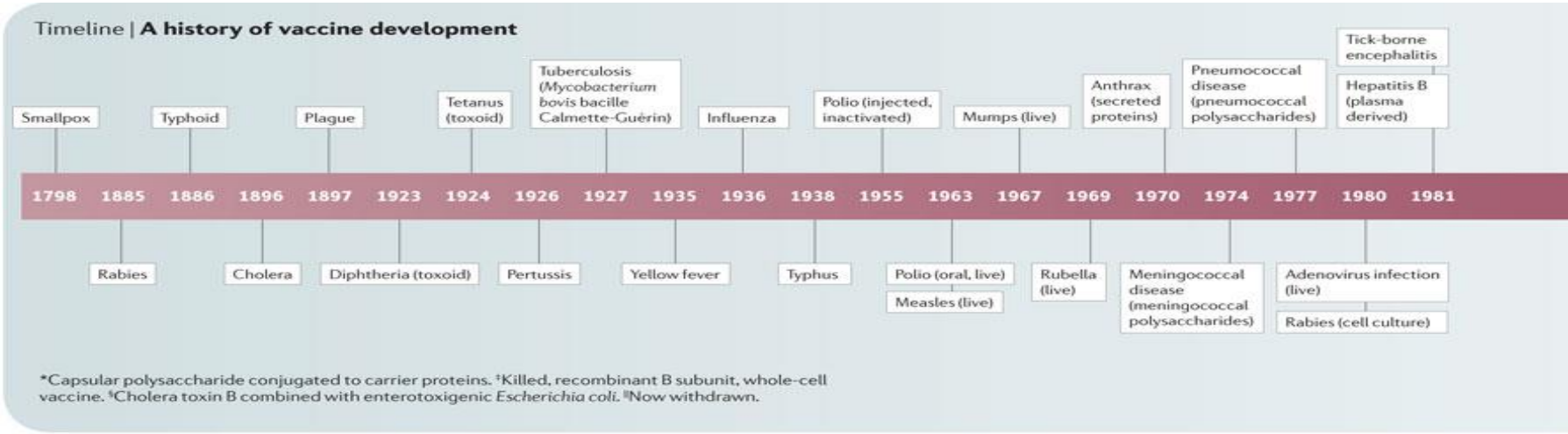
COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Jonathan Weber	
Date	**April 2014**

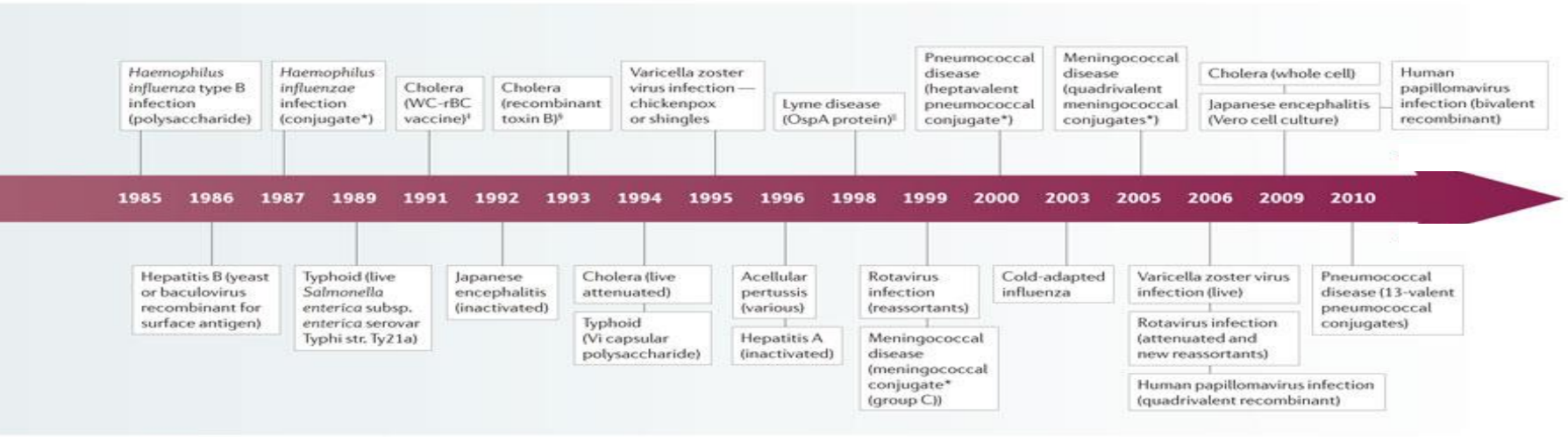
Vaccines for Sexually Transmitted Infections:

c21st prevention

Jonathan Weber
Imperial College London

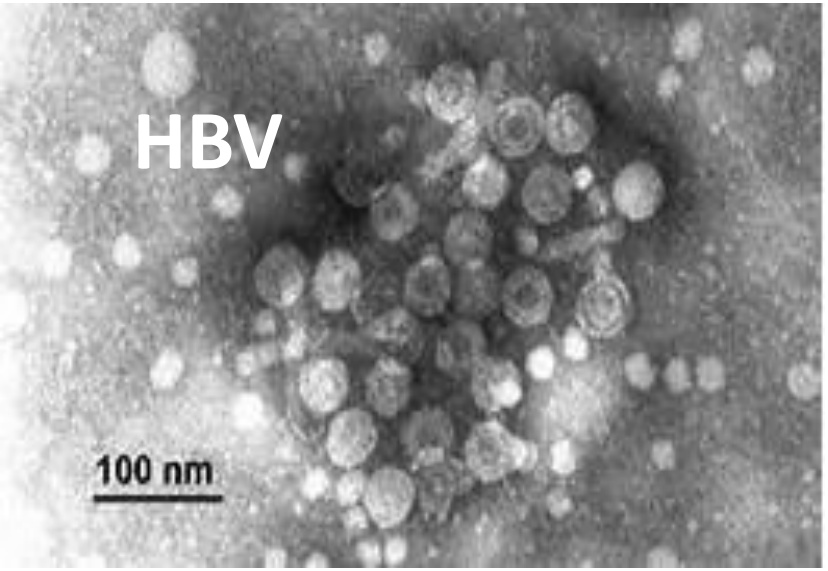
The c20th was the century of vaccination....

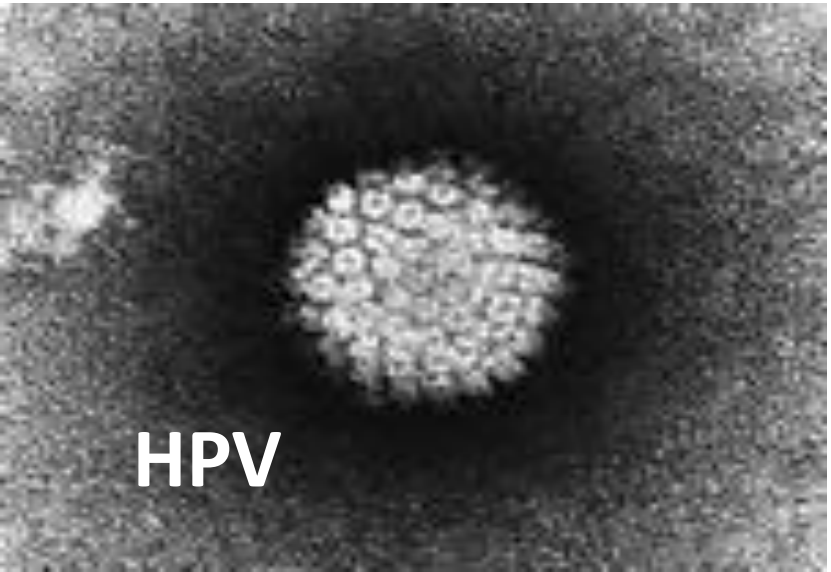




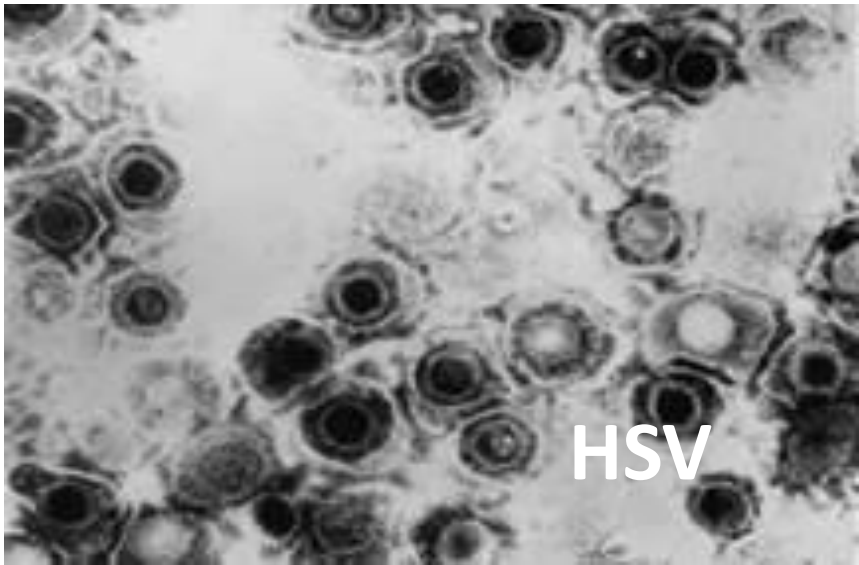
...which continues into the c21st

Successful vaccines

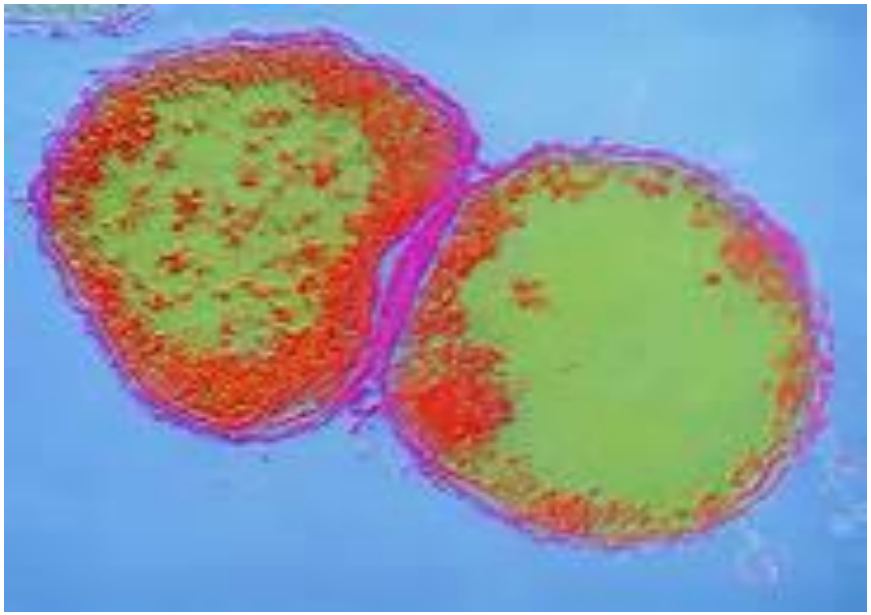




No vaccines



Successful vaccines

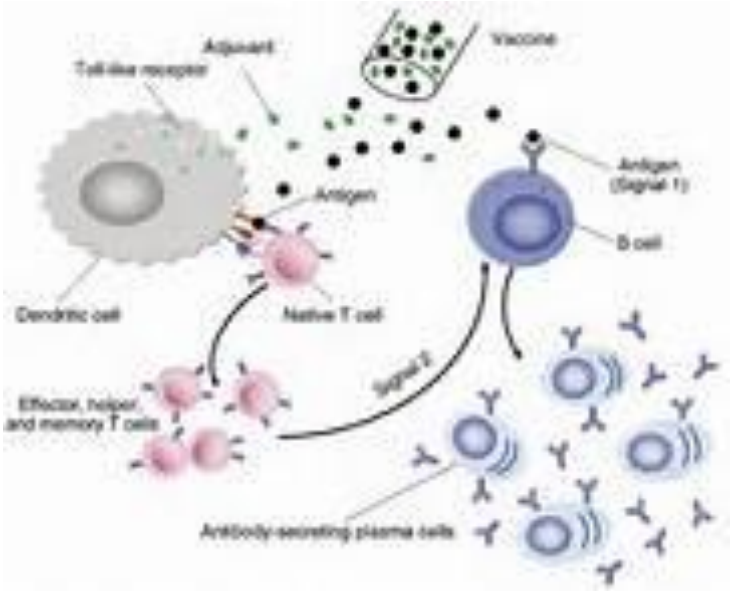


N meningitidis

No vaccine

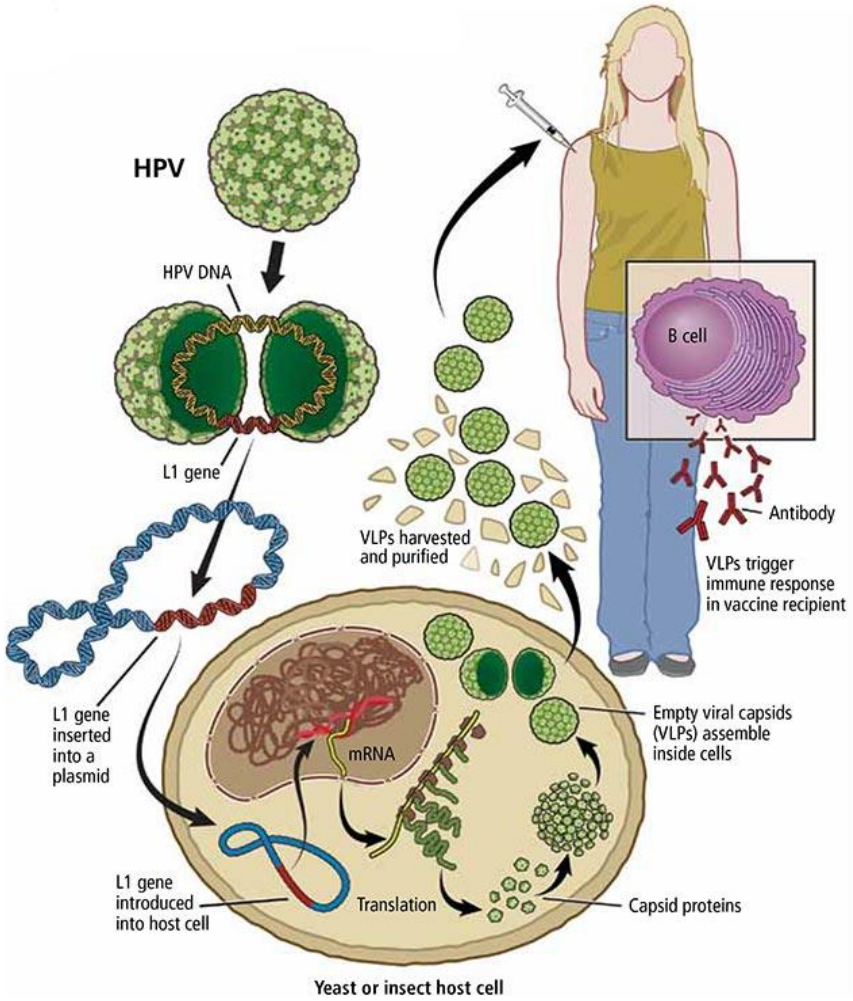
N gonorrhoeae

Hepatitis B vaccine: induction of anti-HB S antigen antibodies



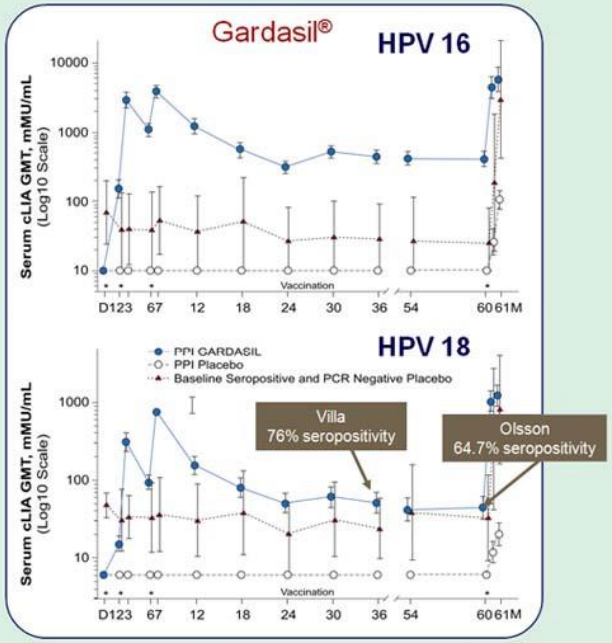
Surrogate marker of vaccine efficacy:
S antigen binding antibody titre

HPV vaccines:
Induction of anti-L1 antibodies

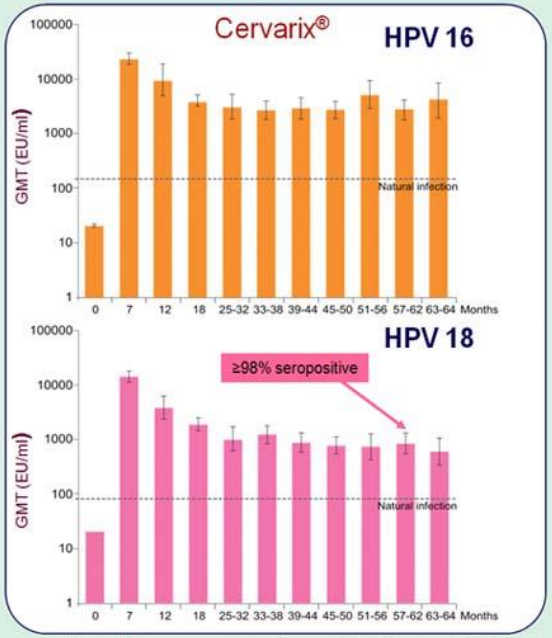


Surrogate of efficacy:
L1 antibody binding titre

Quantitative immune response of Gardasil and Cervarix for HPV 16 &18



Adapted from S. E. Olsson et al., Vaccine 25, 4931 (2007)



Adapted from presentation Dessy IPC Bejing Nov 2007

What have we got?

HPV

HBV

HAV

What do we want?

HIV

HCV

HSV 1/2
KSHV

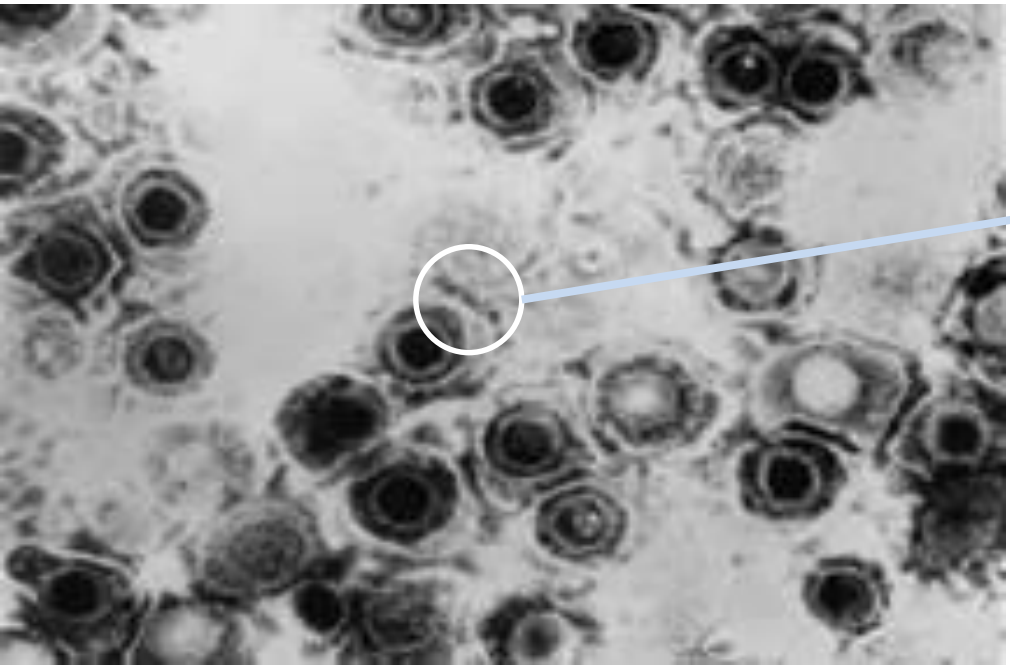
N gonorrhoeae
T pallidum
C trachomatis

Characteristics of licensed vaccines

- **Antigen** is expressed on the surface protein/glycoprotein/carbohydrate
- **Adjuvant** to enhance immunogenicity
- Induce an **antibody** response
- Efficacy measured by binding antibody titre

- **Animal model** for challenge experiments chimpanzee for HBV, rabbit for HPV
- Mechanisms presumed via neutralisation, frequently unknown...

Herpes simplex 2 vaccine:



HSV-2 glycoprotein gD2

Surface antigen
Induces anti-gD abs

Efficacy Results of a Trial of a Herpes Simplex Vaccine
Robert B. Belshe et al.

8323 women 18 to 30 years of age who were negative for antibodies to HSV-1 and HSV-2.

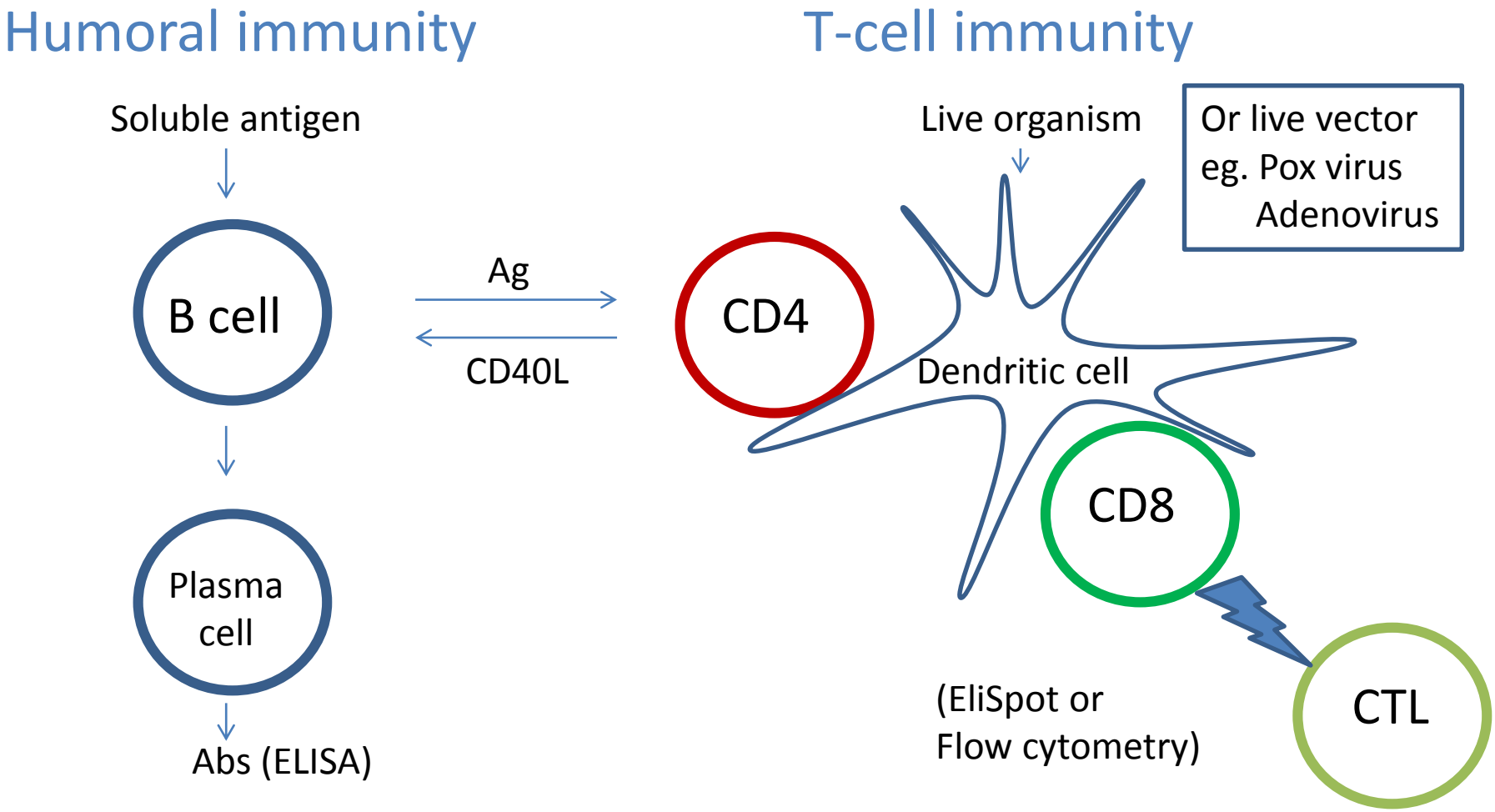
vaccine efficacy was 20% (95% confidence interval [CI], -29 to 50) against genital herpes disease

The vaccine was not effective....

N Engl J Med 2012; 366:34-43

Vaccine efficacy via T-cells?

Nature. 1982 Dec 16;300(5893):655-7.
Influenza A specific cytotoxic T-cell clones that do not recognize viral glycoproteins.
Townsend AR, Skehel JJ.



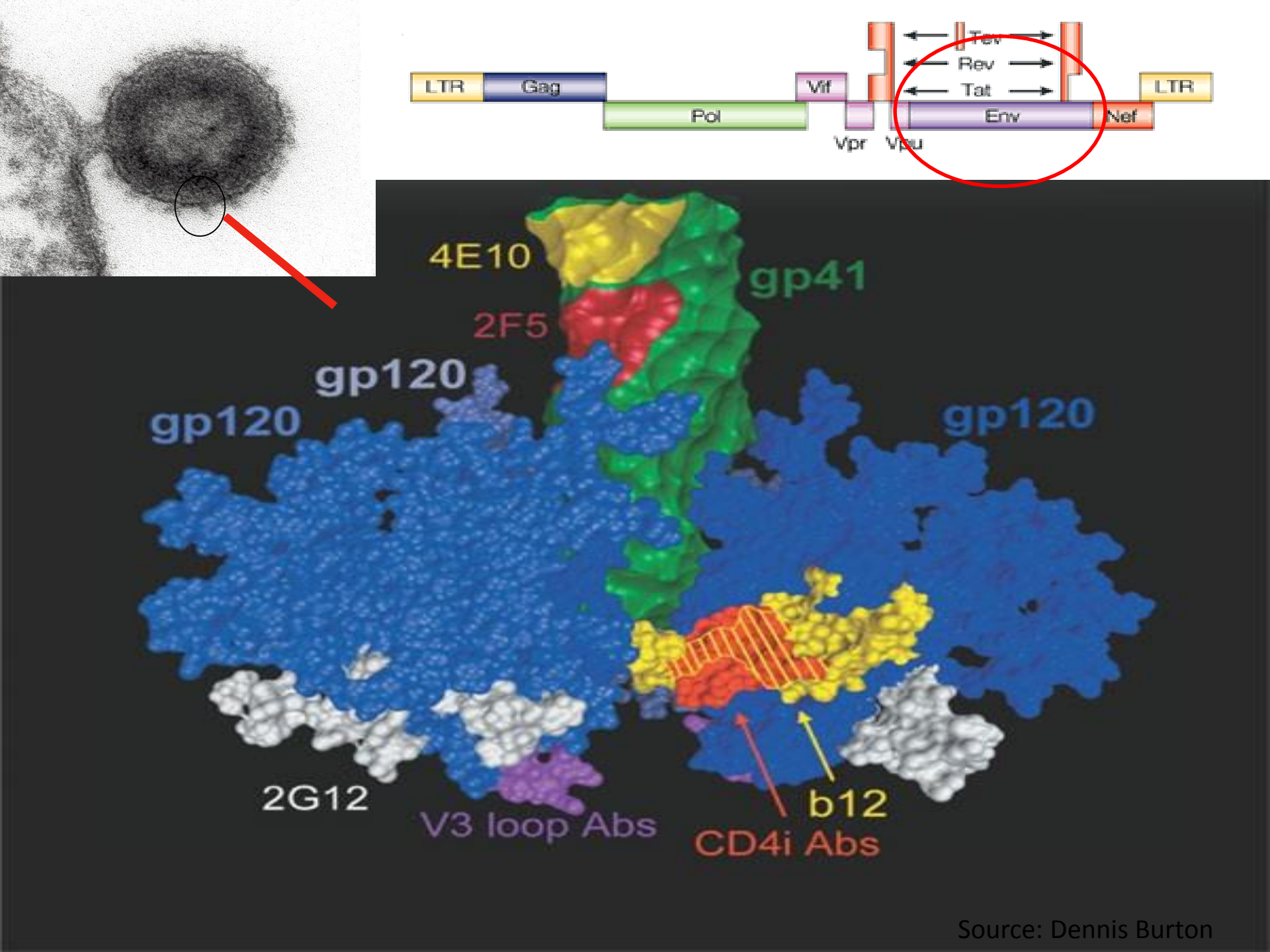
HIV Vaccines – where are we now?

- "B-cell immunity"

  prevent HIV infection through inducing neutralising antibodies

- "T-cell immunity"

  attenuate HIV infection through inducing HIV-specific cellular immunity



Source: Dennis Burton

HIV vaccines - humoral immunity: two phase III trials

- **Env rgp120** (VaxGen)
  - Alum adjuvant
  - **Failed** in two large phase III trials (n=17,000)

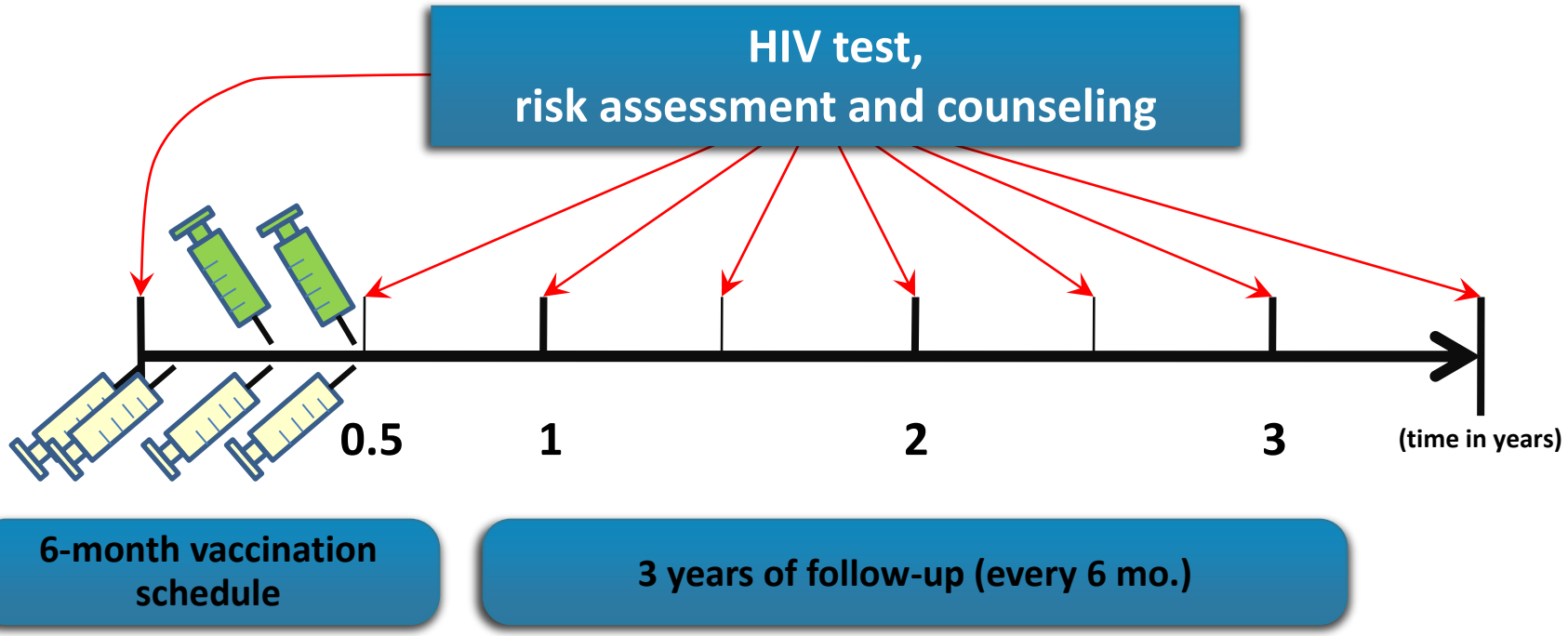
- **Prime-boost - RV 144**

  Sanofi, VaxGen, WR, Thailand
  - AL VAC (canary-pox) prime,
  - rgp120 boost (VaxGen), alum

  - **30% protection against infection (p=<0.05)**

RV 144

RV-144 Vaccination and Follow-up Schedule



ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24

RV 144

Vaccine Efficacy Appeared Highest 6-12 months

3.5 years after first vaccination: Protective Efficacy = 31.2%

P = 0.04 95% CI: 1.1 – 52.1

No effect on viral load

	mITT		PP	
month	***Events***	***Efficacy***	***Events***	***Efficacy***
6	**16**	**54%**	n/a	n/a
12	**42**	**60%**	21	68%
18	**67**	**44%**	41	41%
24	**82**	**36%**	53	27%
30	**95**	**36%**	62	31%

VE @ 12 months = 60% (Cox PH, 95% CI 22, 80)

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

ABSTRACT

- 125 infections from17,115 participants
- 74 out of 8,198 volunteers who received placebo
- 51 out of 8,917 volunteers who received prime boost vaccine
- Protective efficacy a little over 31% p=0.039
- No affect on viral load or CD4 count in subjects infected with HIV
- No measurable T-cell responses
- Binding Abs to rgp120
- Some evidence that anti-V2 Abs protective
- No neutralising Abs detected

Vaccinee sera in human trials: neutralisation does not approach natural infn

Neutralisation of HIV-1 isolates by sera collected at week 30 (after the third vaccination)

	Neutralisation of HIV-1 isolates											
	T-Cell Line Adapted (TCLA)[a]							PBMC derived[b]				
	MN	W61D	SF2	IIIB	M2424	SL7	SL14	W61D	JRCSF	PE065	M2424/4	SL8
Geographical origin & genetic subtype								Holl/B	USA/B	UK/B	UK/B	Thai/E
Biological phenotype								SI/R5X4	NSI/R5	NSI/R5	SI/R5X4	SI/X4
Source of sera:												
Vaccine recipient[c]												
JUX065	320	ND	ND[d]	ND	10	ND	ND	–	–	–	–	–
JUQ006	160	ND	40	–	10	–	–	–	–	–	–	–
JUB063	160	ND	20	–	10	–	–	–	–	–	–	–
JUL008	160	80	40	–	10	–	–	–	–	–	–	–
JUJ009	160	80	40	–	10	–	–	–	–	4	–	–
JUX011	160	80	40	–	10	–	–	–	–	–	–	–
JUF061	160	80	80	–	ND	–	–	ND	–	3	–	–
JUM016	80	40	20	–	ND	–	–	ND	–	–	–	4
HIV-1 infected individual[e]												
PE052	640	640	640	160	160	40	40	203	402	157	979	< 3

McCormack and Weber *Vaccine* 2000

HIV T-cell vaccines: two phase IIb trials

- **Adenovirus 5 (Ad5)** (Step)
  - Merck Adenovirus serotype 5
  - Gag-Pol-Nef antigens
  - **failed** in phase IIb

- **Ad5** (HVTN 503, Phambili)
  - Adenovirus 5 *gag-pol-nef-env* A/B/C
  - VRC/HVTN IIb trial
  - Failed 2013; evidence of enhancement of infection

Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Susan P Buchbinder, Devan V Mehrotra, Ann Duerr, Daniel W Fitzgerald, Robin Mogg, David Li, Peter B Gilbert, Javier R Lama, Michael Marmor, Carlos del Rio, M Juliana McElrath, Danilo R Casimiro, Keith M Gottesdiener, Jeffrey A Chodakewitz, Lawrence Corey, Michael N Robertson, and the Step Study Protocol Team*

Recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up of the phase 2b HVTN 503/Phambili study

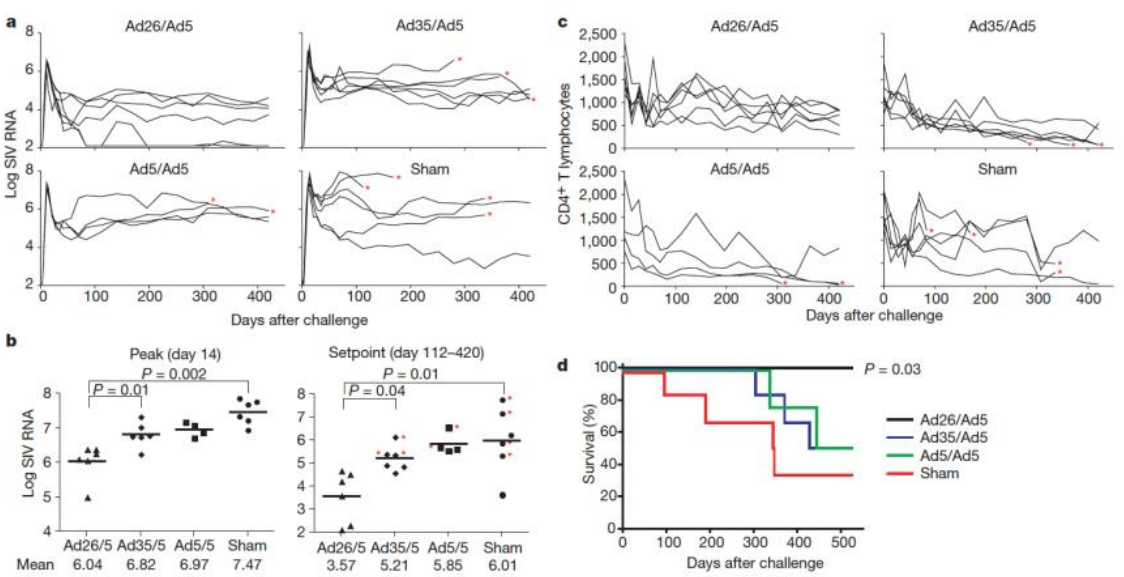
Glenda E Gray, Zoe Moodie, Barbara Metch, Peter B Gilbert, Linda-Gail Bekker, Gavin Churchyard, Maphoshane Nchabeleng, Koleka Mlisana, Fatima Laher, Surita Roux, Kathryn Mngadi, Craig Innes, Matsontso Mathebula, Mary Allen, M Julie McElrath, Michael Robertson, James Kublin, Lawrence Corey, on behalf of the HVTN 503/Phambili study team

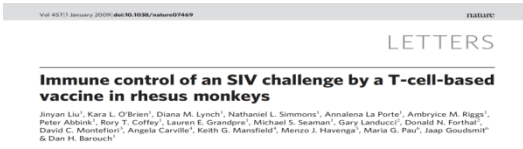
- Adenovirus vector, *gag-pol-nef*, x3 immunisations
- Trial stopped early, for “lack of efficacy”
- No evidence of protection from infection in either study
- Non-significant trends towards harm in STEP
- Significant enhancement in HVTN 503
  - More infections in active arm
  - Viral load (mean) higher in active arm
    - (mean VL: 40,000 vs 26,000, ns)

So what did the models predict?

VaxGen rgp120 did not protect
ALVAC-rgp120 did not protect

Ad-5 Gag attenuated SIV infection
Ad5 gag/pol/nef
attenuated SIV infection





LETTERS

Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys

RV-144 setting the bar: room for improvement >30% protection

- Generate higher titres of anti-Env antibodies
- Induce neutralising antibodies
- Induce a T-cell immune response
- Induce more durable protection > 1yr (re-boost)
- Improve components of the vaccine:

better priming than ALVAC

modified pox, MVA, NYVAC

DNA prime, pox-boost, Ad-pox

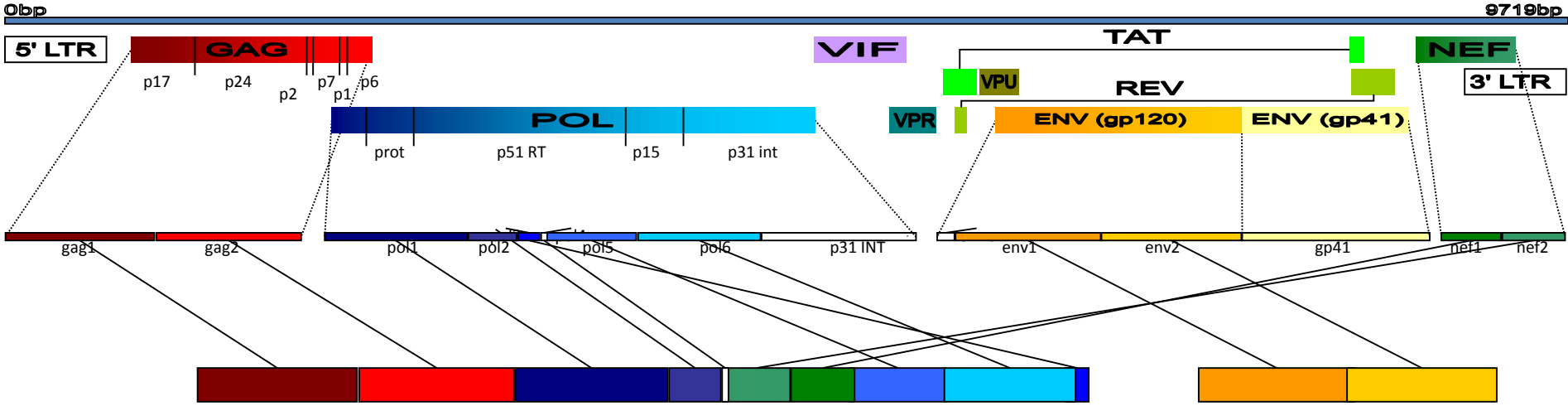
better boosting than monomeric Env gp120

trimeric Env gp140

better adjuvant than alum

GLA, MF59

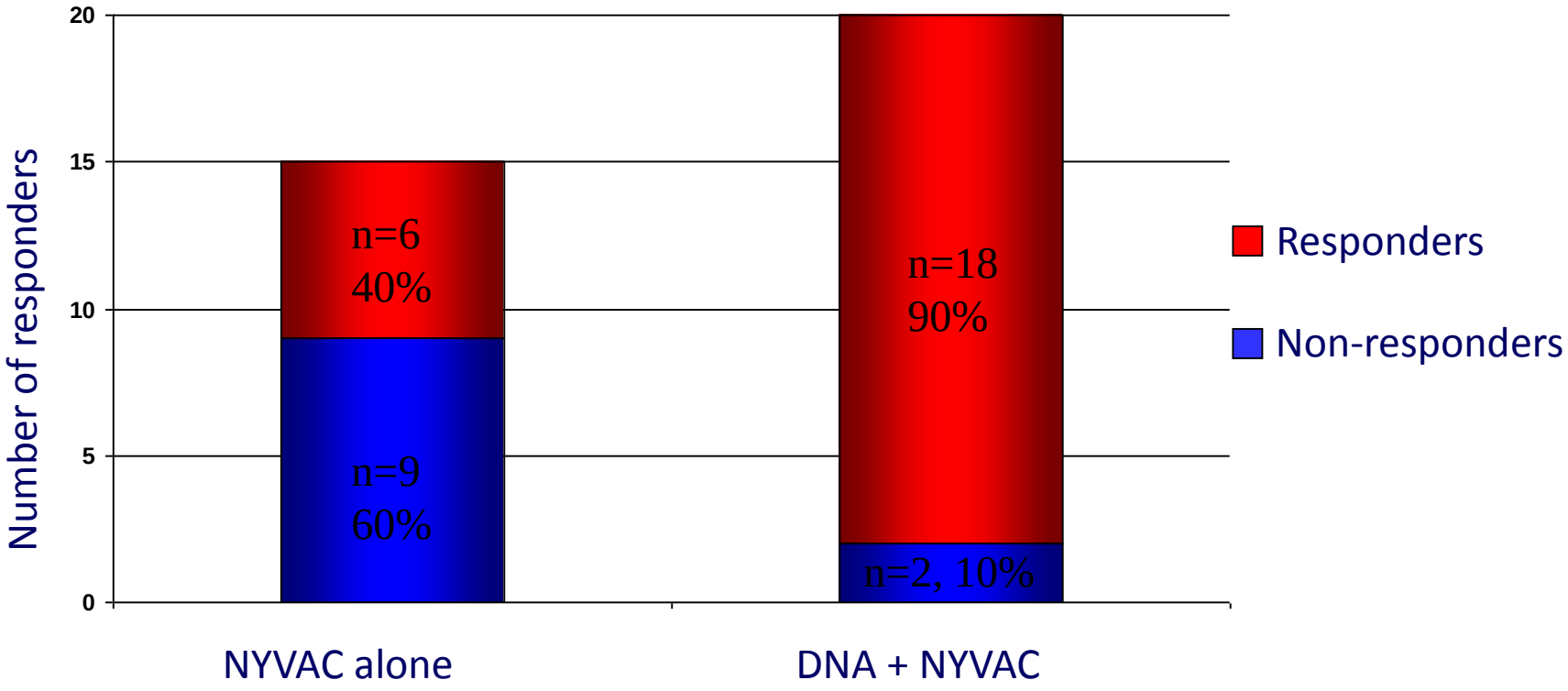
The EuroVacc programme: 2002-12



Regimen		Week 0	Week 4	Week 20	Week 24
1	(n = 20)	DNA C	DNA C	NYVAC C	NYVAC C
2	(n = 20)	Nothing	Nothing	NYVAC C	NYVAC C

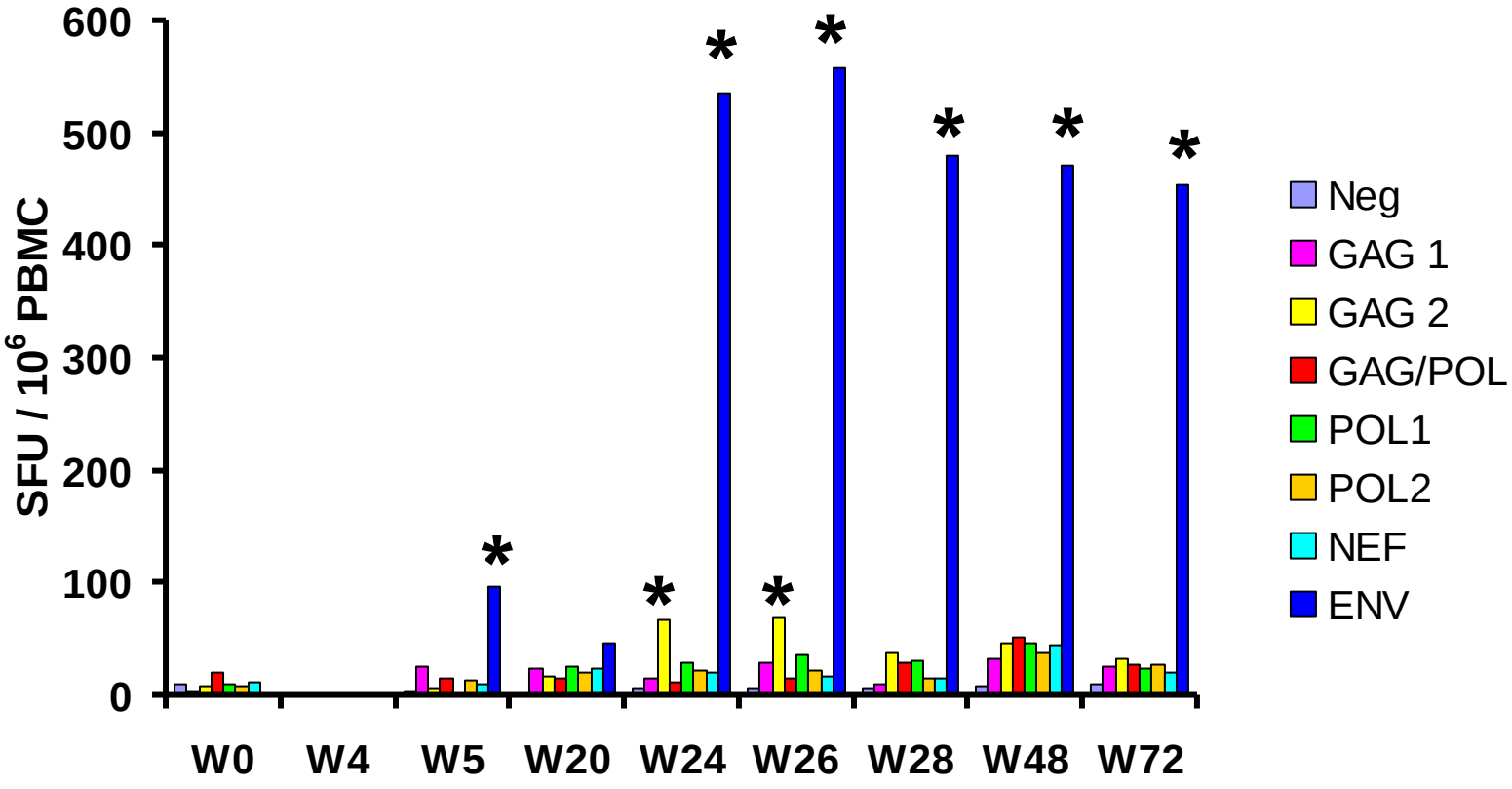
Proportion of Responders at the Primary Endpoint (W26 and W28)

***P* = 0.003**



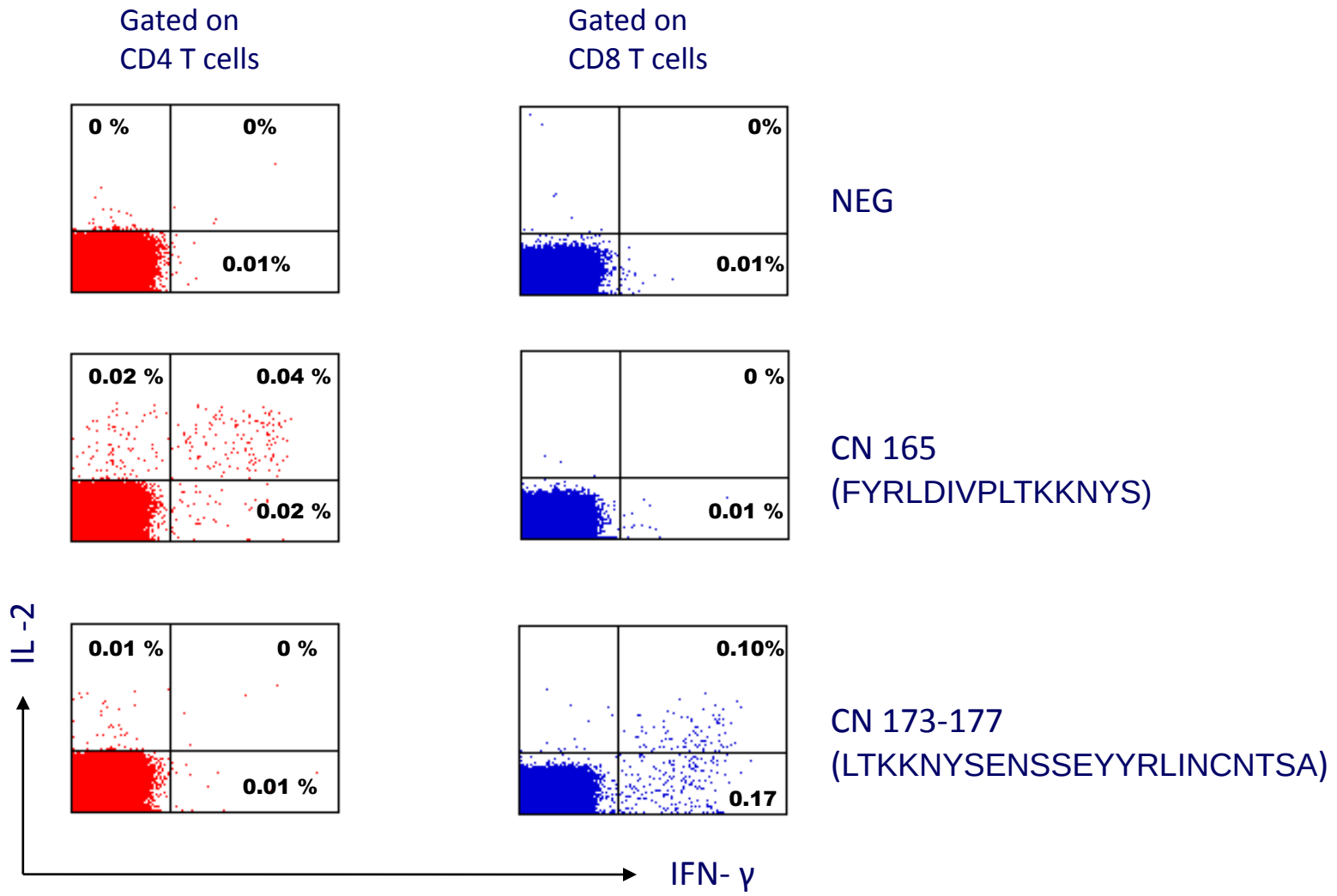
Volunteer # 08

DNA + NYVAC



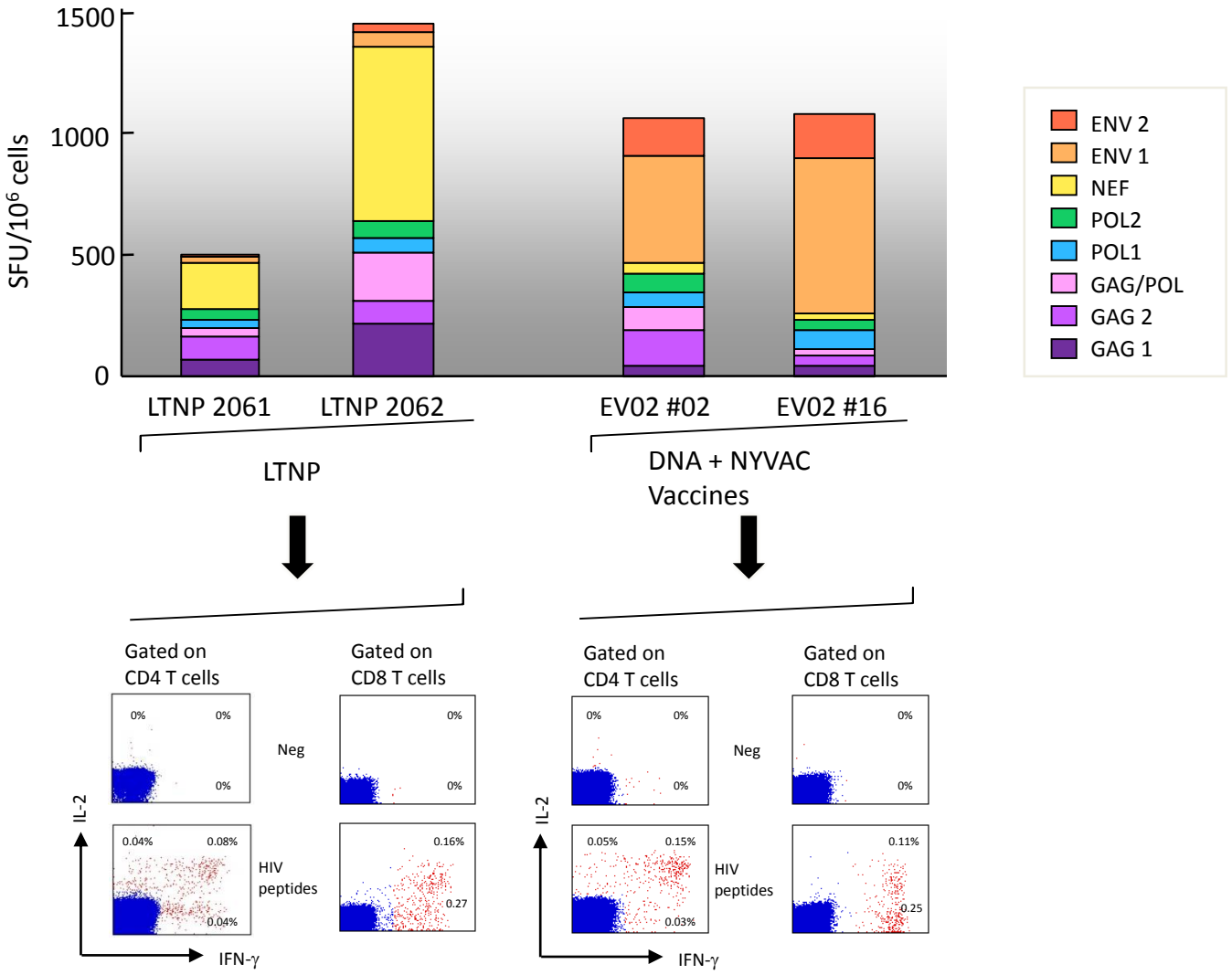
* Positive response according to the criteria

Representative Example of Flow Cytometry (Volunteer # 26 W26)



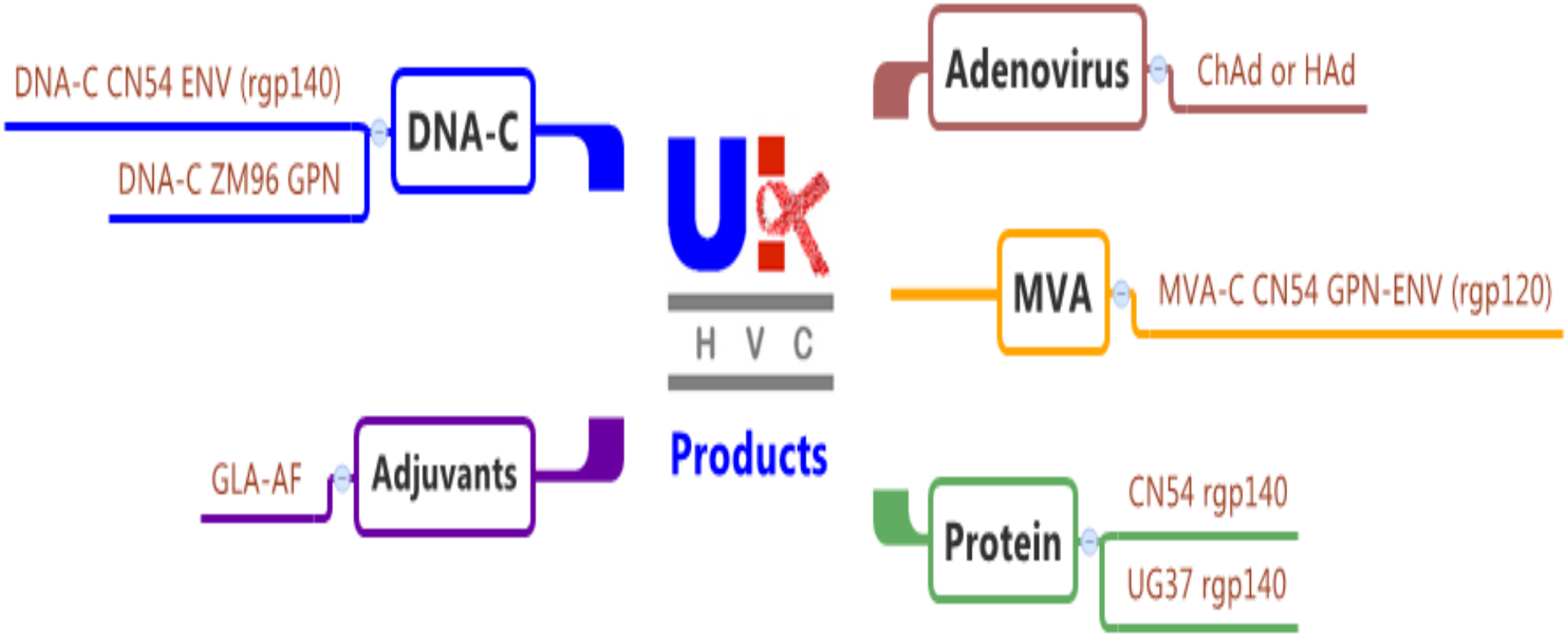
Vaccine-induced HIV-1-specific T-cell Responses are Comparable to Those Observed in LTNP

IFN-γ ELISpot

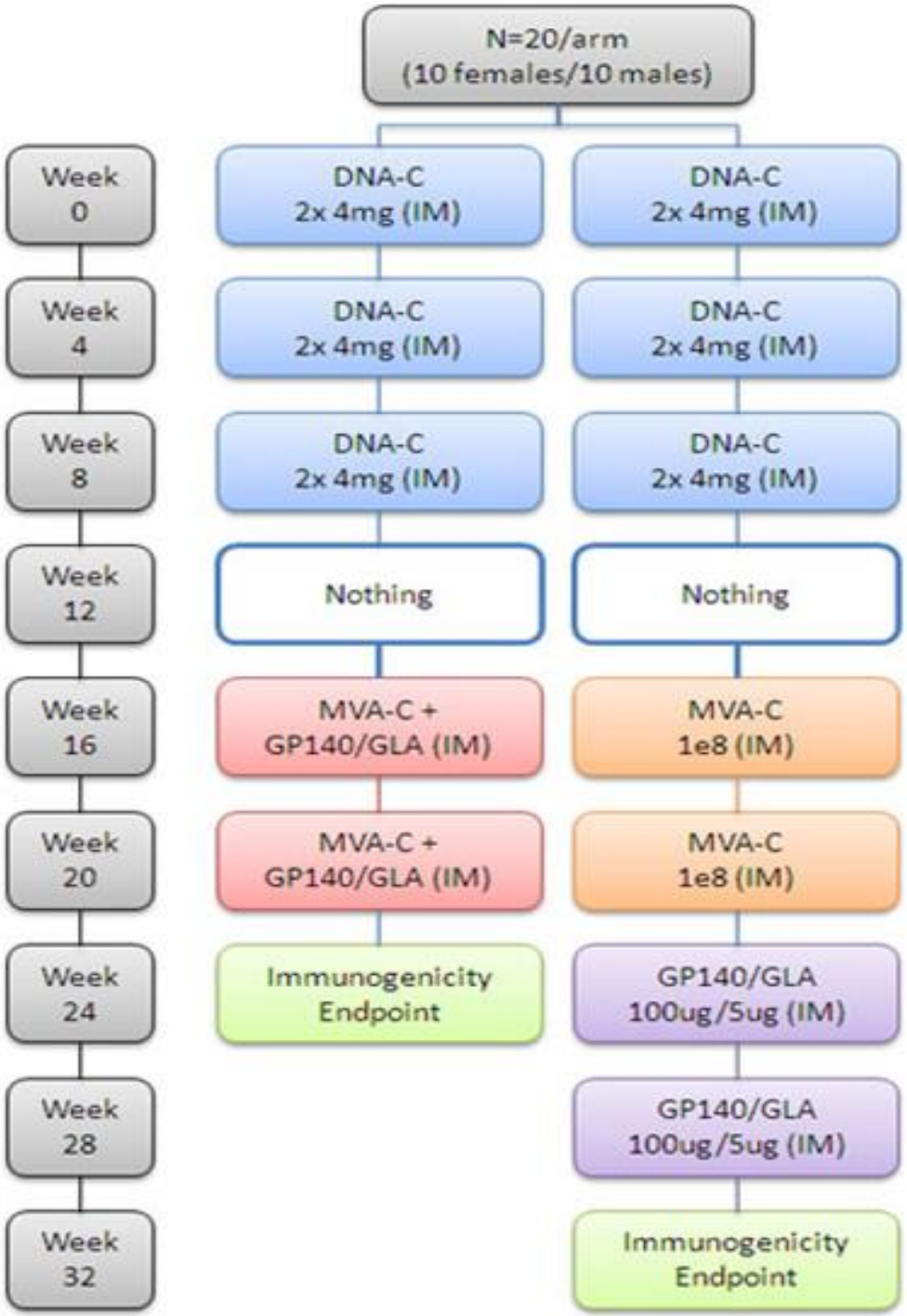


Polychromatic Flow Cytometry

The UKHVC programme, 2008-:



DNA	ZM96GPN and CN54gp140ENV	Althea
MVA	Matched GPNE insert	Bavarian Nordic
rgp140	Trimeric recombinant ENV	Polymun
GLA	Synthetic MPLA (TLR agonist)	IDRI

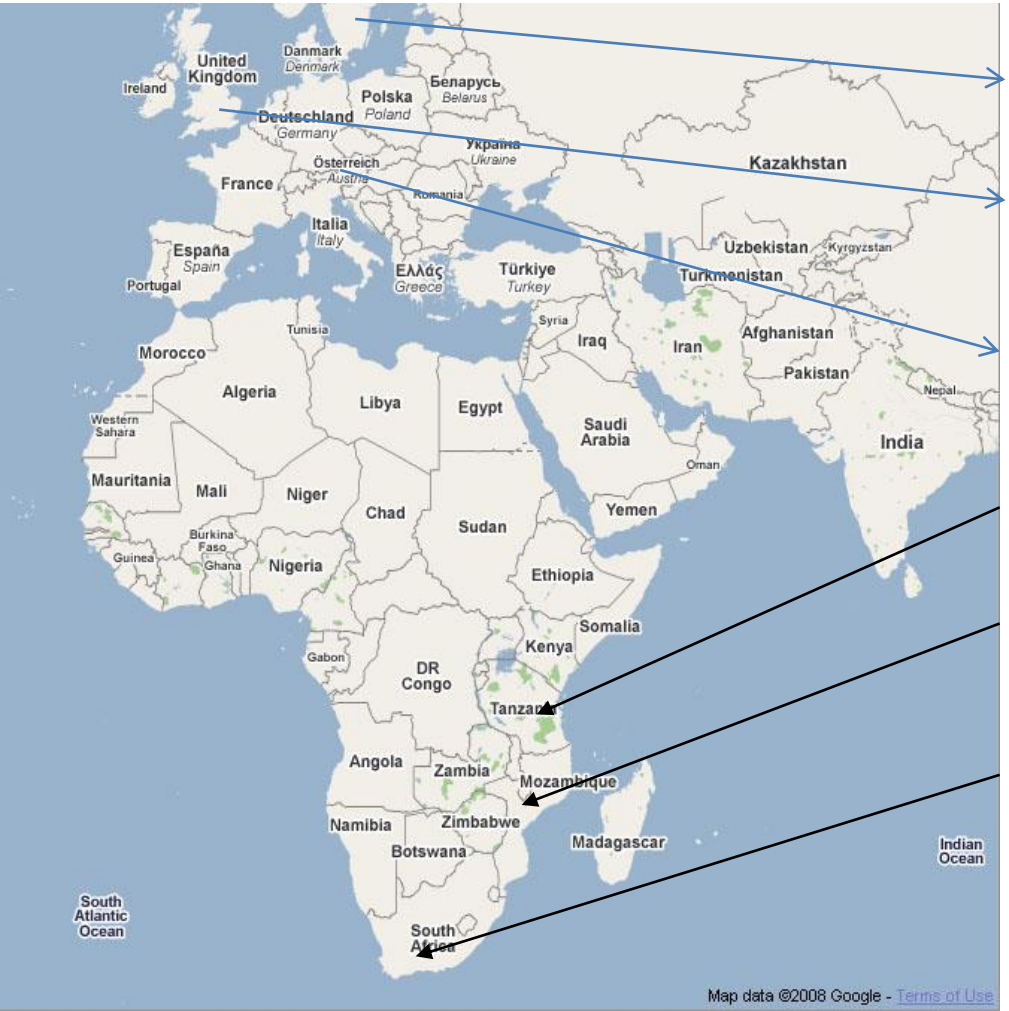


The UKHVC programme:

- 3x DNA more potent than 2x DNA prime
- DNA-MVA drives **Env**, **CD4+** response
- DNA-MVA optimal T-helper prime for
- B-cell response to the rgp140 protein
- Env CN54 Trimeric rgp140 is more potent than monomeric rgp120
- GLA = novel synthetic MPLA adjuvant is more potent than Alum

This should result in a vaccine schedule more potent than RV144

TaMoVac/AfreVacc collaboration: 2008- Multiclade A/B/C DNA – prime, [MVA – rgp140/GLA] boost



SW: Karolinska

UK: Imperial

MRC CTU

DE: Munich

Tanzania

Dar es Salaam

Mbeya

Mozambique

Maputo

Manhica

Beira

South Africa:

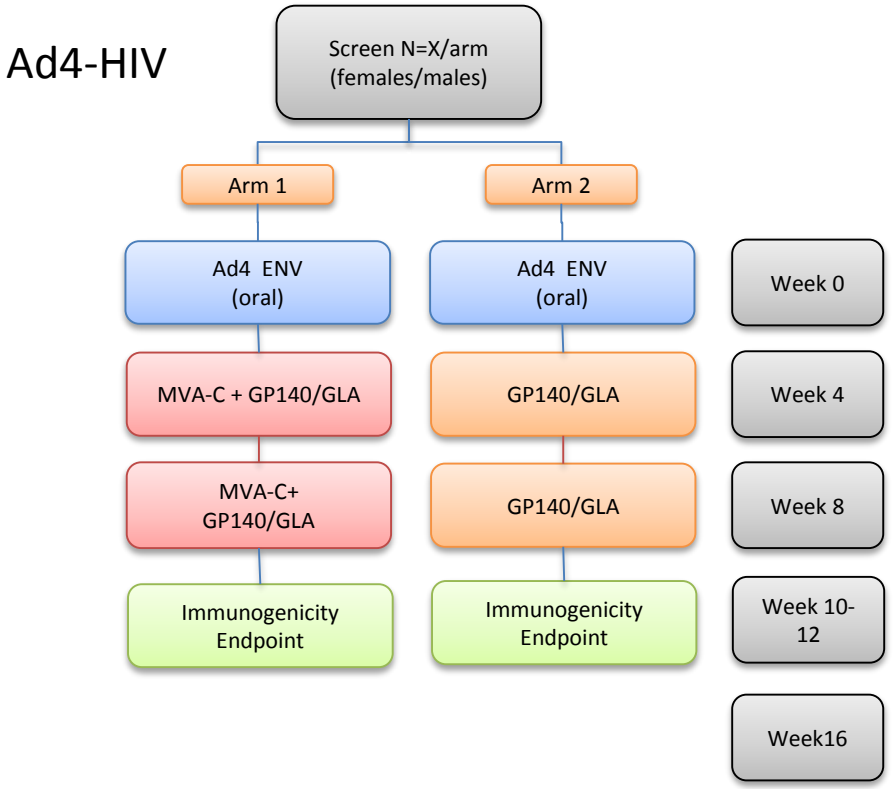
Africa Centre

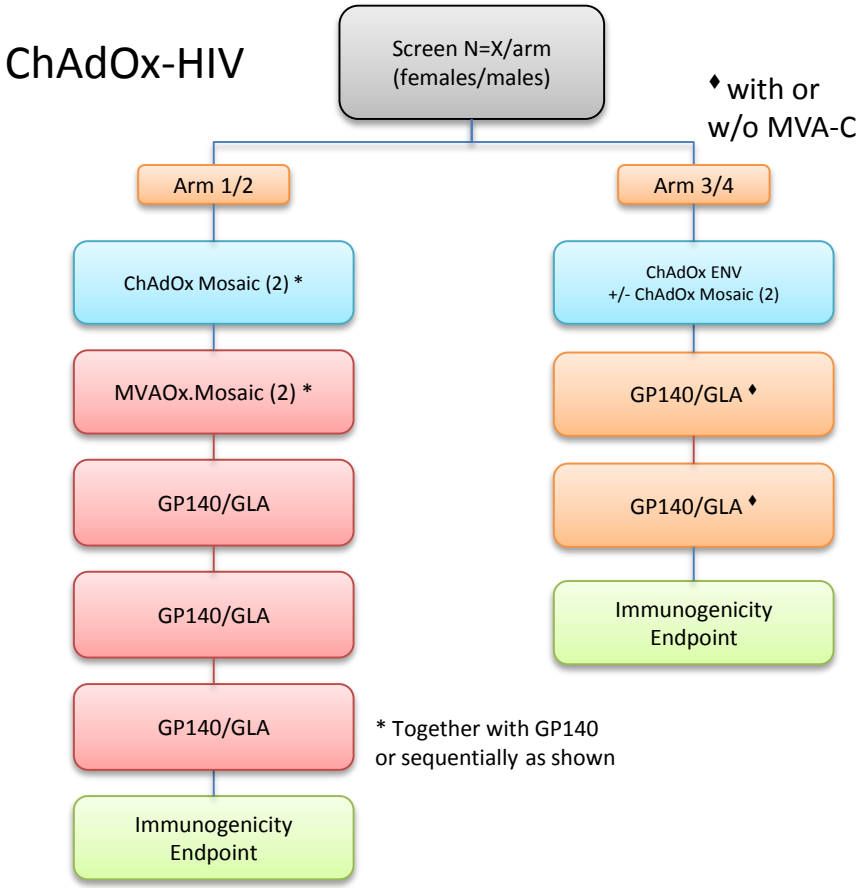
Questions:

- Can we shorten the schedule?
- Focus on clade C or multiclade?
- Maximise antibody response to rgp140
- **Move to proof of concept trial, 2017**

UKHVC Adeno-prime Approaches

1. Compare Adenovirus prime versus DNA prime Ad4HIV versus spoke 003
2. Live Adeno (Ad4HIV) versus attenuted chimp Adeno (ChAdOxHIV)
3. Is MVA needed? (arm 2)





STI vaccines, 2020

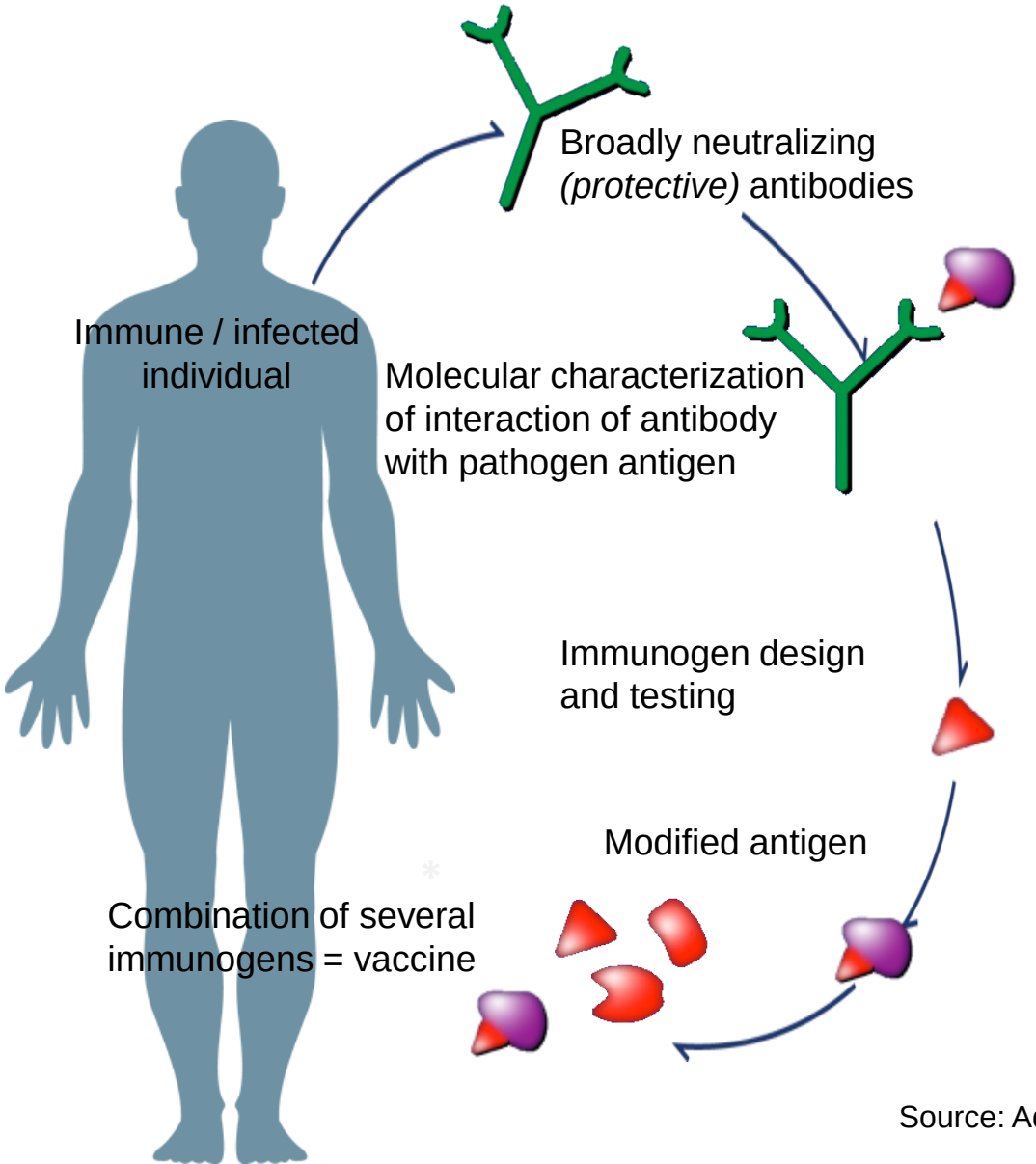
Current HIV vaccine
DNA, pox, rgp140
will have phase IIb proof-of-concept data

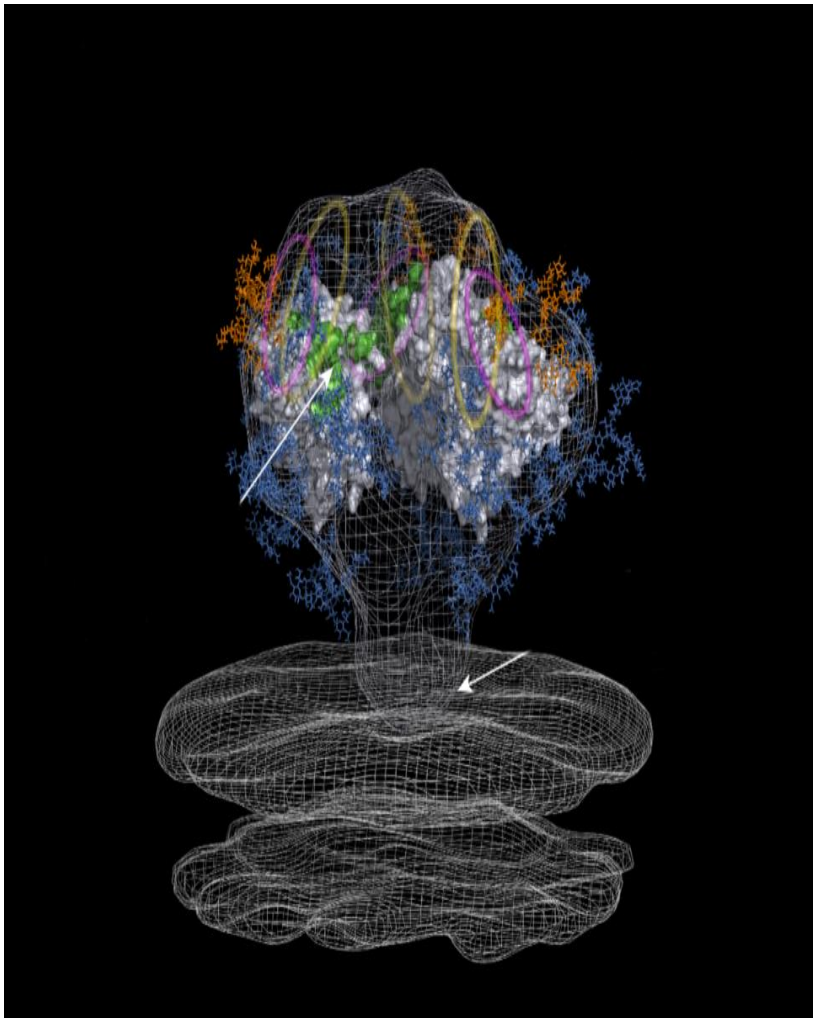
Safety concern of Adeno-5 vaccines leads to diverse primate Adeno studies

HCV (Adeno) and Mtb (MVA) studies will report

We need new science for a better HIV Env protein…

Reverse vaccinology: From antibody to antigen





Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002

I thank:

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Univ of Oxford

Andrew McMichael
Tomas Hanke

MRC CTU

Sheena McCormack
Sarah Joseph
Abdel Babiker

EuroVacc

Gepi Pantaleo
Peter Liljestrom

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