"European Contributions to a HIV Vaccine"

Philip Bergin, Ph.D.
International AIDS Vaccine Initiative Human Immunology Laboratory

Unprecedented momentum in the HIV prevention field

MICROBICIDES

- Microbicide gel (CAPRISA 004) reduces HIV infections in women

PRE-EXPOSURE PROPHYLAXIS

- Oral PrEP reduces HIV infections among MSM and transgendered women

TREATMENT AS PREVENTION

- Initiating ART earlier reduces HIV transmission among discordant couples

VACCINES

- AIDS vaccine shows first efficacy in clinical trials
- Replicating viral vector effective in controlling SIV in animal studies
- Multiple new antibodies and targets on HIV discovered

AIDS Vaccine Development

State of the Field: R&D Assessment

- **RV-144 Thai trial (Thai government and US Military)**:
  - First demonstration of “modest” efficacy (31.2%)
  - These findings were not significant enough to engage vaccine industry to putting greater resources to HIV vaccine development – feasibility still needed (Peter Kim-Merck)
- **Major Challenges of HIV**
  - Hypervariability of HIV
  - Short window of opportunity to control HIV infection
    - Suggests the need for BOTH broadly neutralizing Abs to prevent infection, and broad/robust Cell mediated immunity to control infection
- **Clinical Pipeline**
  - No candidates elicit broadly neutralizing antibodies
  - Limited approaches towards broad cell mediated immunity

Key Challenges to a Safe and Effective HIV Vaccine

2. The Short Window of Opportunity to Control HIV

Host Opportunities:

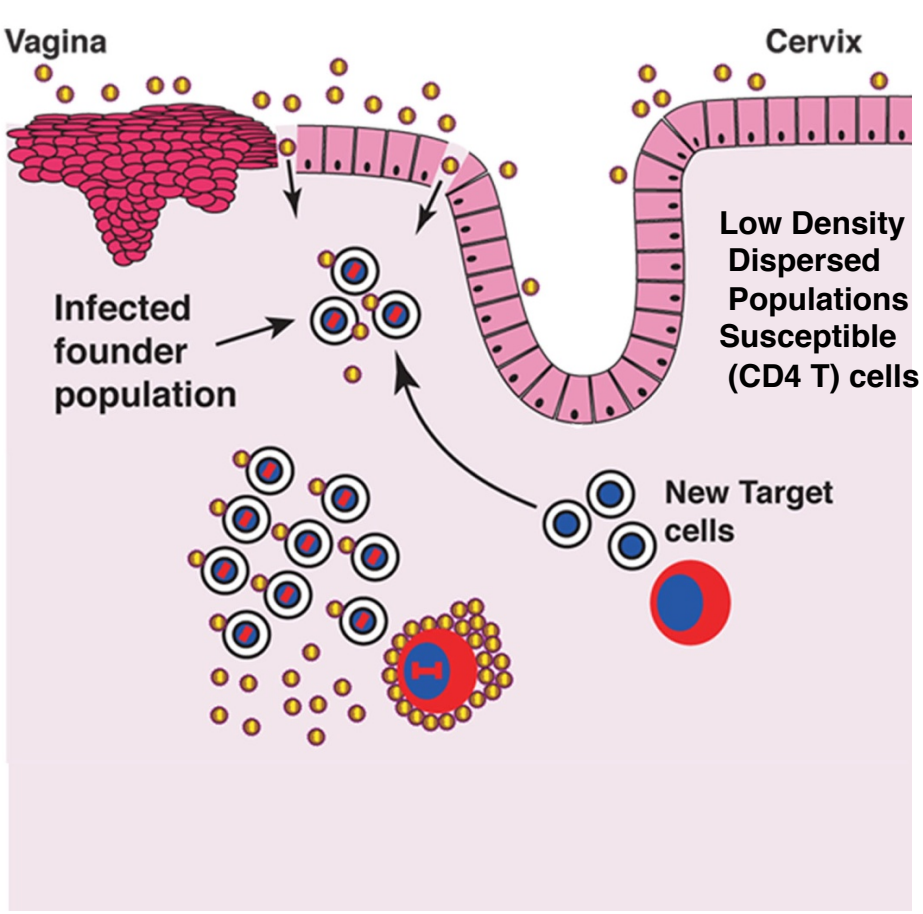
Protective Abs (bnAbs)

Small
Infected Founder Populations
R_0<1

Sufficient local virus production
Infected cells

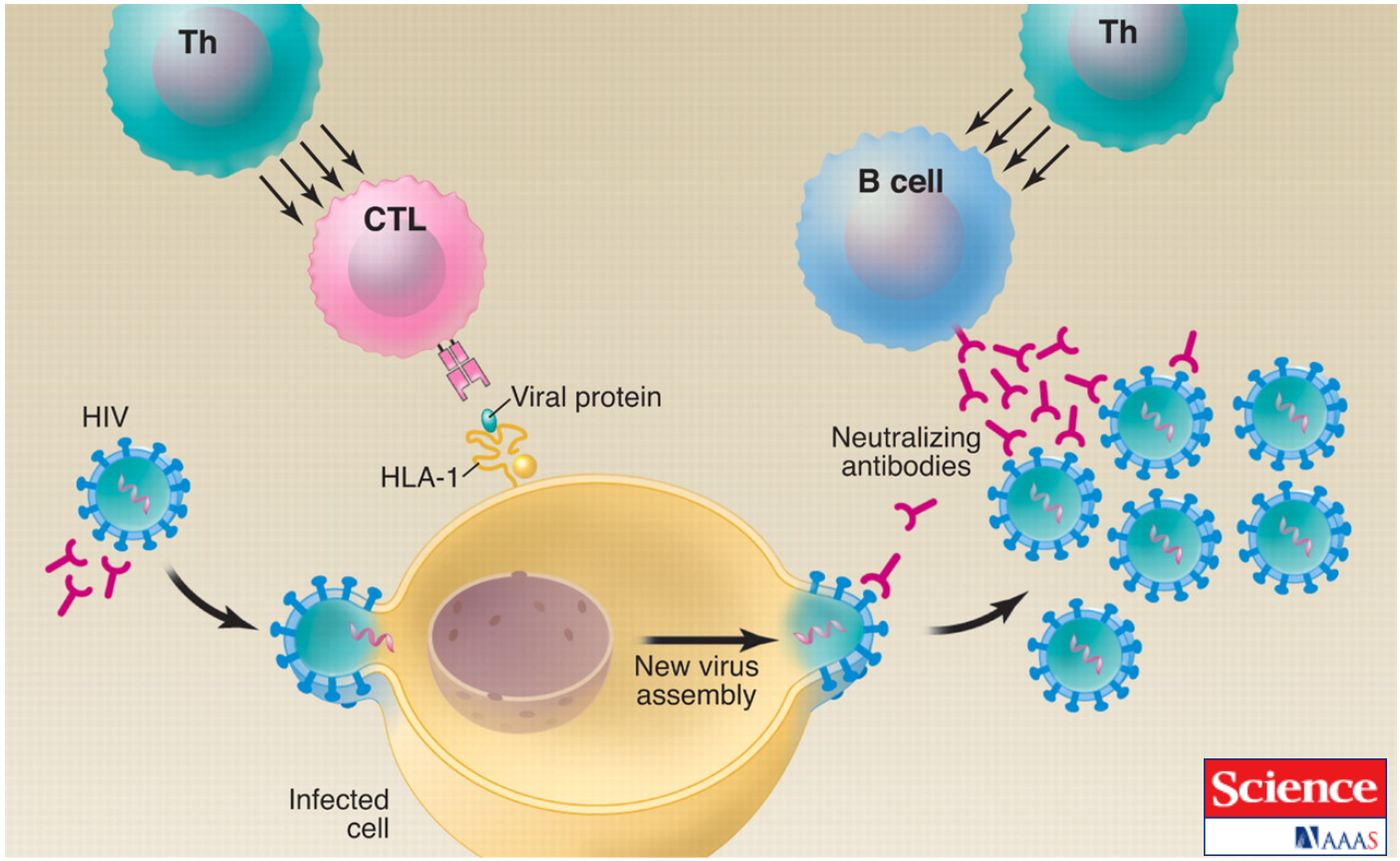
Host Opportunities:

Cell Mediated Immunity to
Select and Kill HIV Infected Cells



AT Haase, Nature 2010; Mar 11;464(7286):217-23

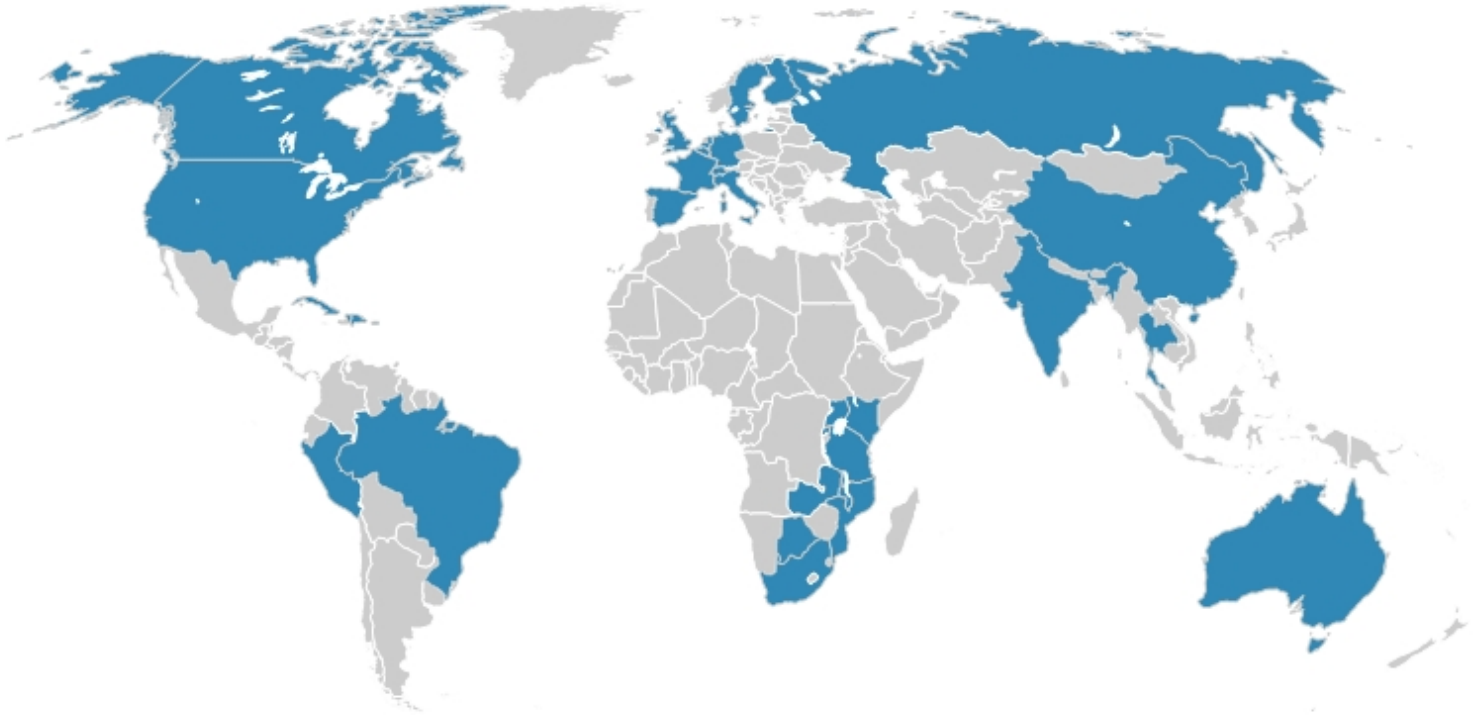
R&D Assessment : An effective HIV vaccine will likely need to engage <u>both</u> arms of the adaptive immune response



B D Walker, D R Burton Science 2008;320:760-764

Broadly neutralizing antibodies to prevent infection and broad cell mediated immune responses to control infection – prevent disease

Vaccine Candidates in Clinical Trials



Source. IAVIReport http://www.iavireport.org/Trials-Database/Pages/default.aspx

-Many European groups work closely with centres in Africa

- Karolinksa work with Uganda, Kenya, Tanzania and others
- Oxford and Imperial College work in Rwanda, Zambia, Kenya, Uganda South Africa and others

European Vaccine candidates in Clinical Trials

All Trials

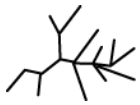
Ongoing - *As 11th Oct 2012*

Source. IAVIReport http://www.iavireport.org/Trials-Database/Pages/default.aspx

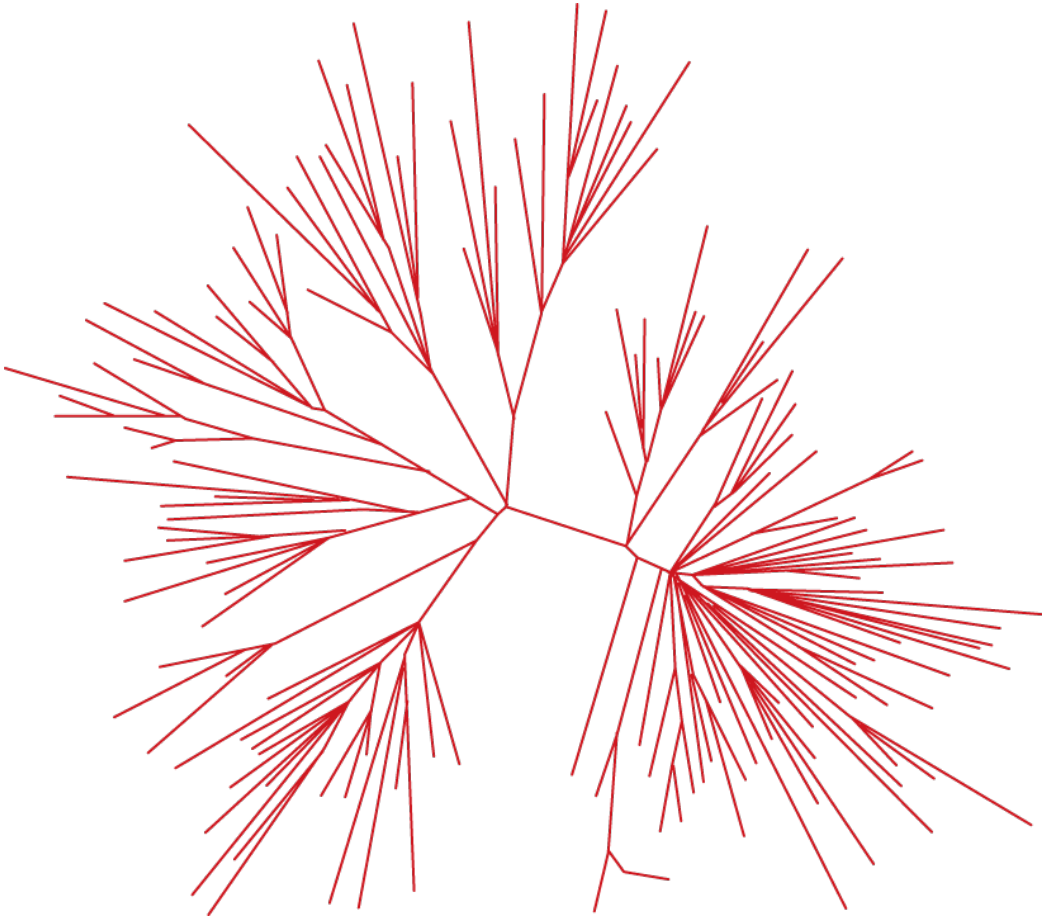
Prevention of HIV:

A vaccine that elicits broadly neutralizing antibodies

HIV Variability: The major scientific challenge for HIV vaccine



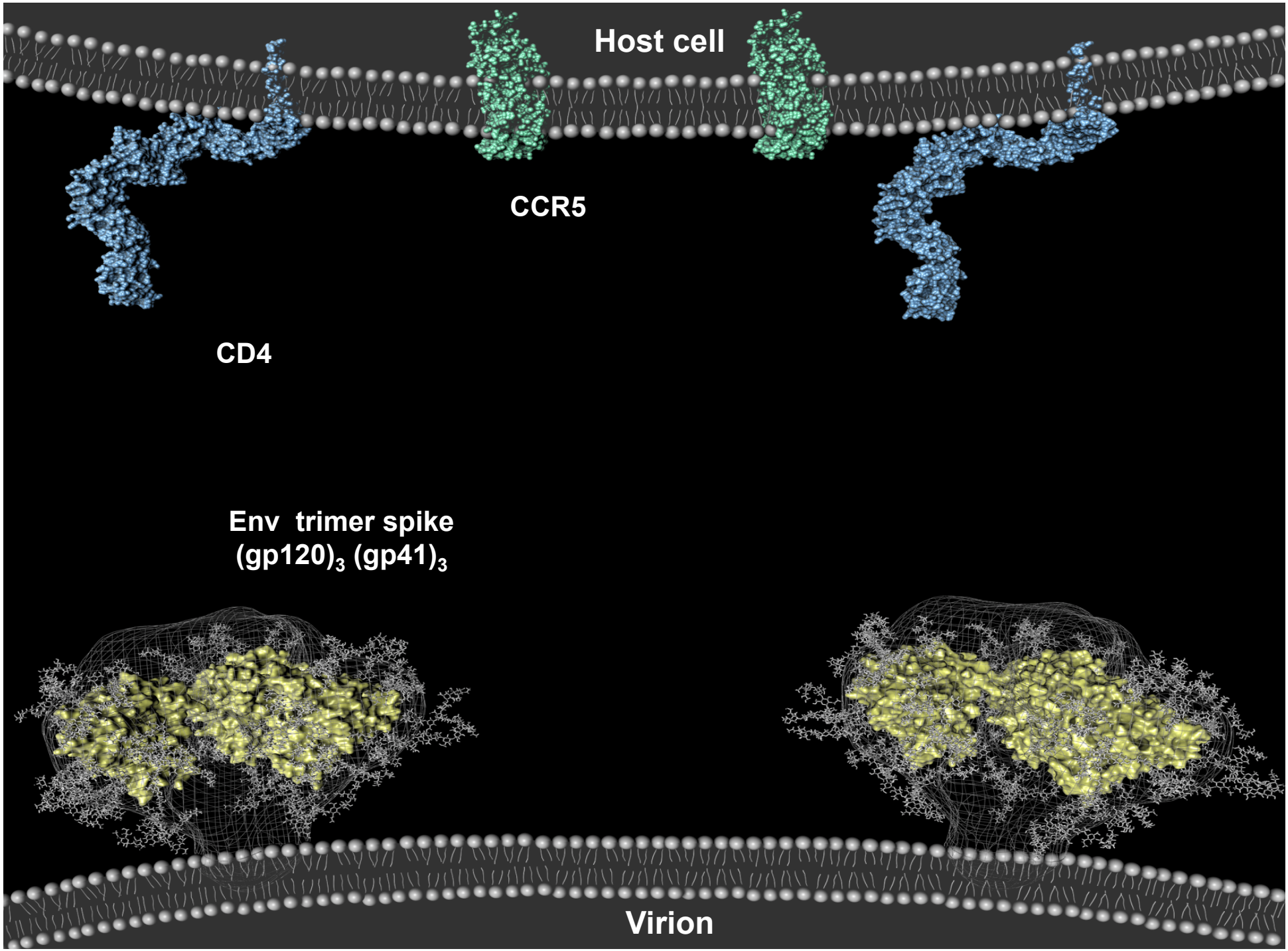
Genetic variability of
global influenza A virus
(1996)

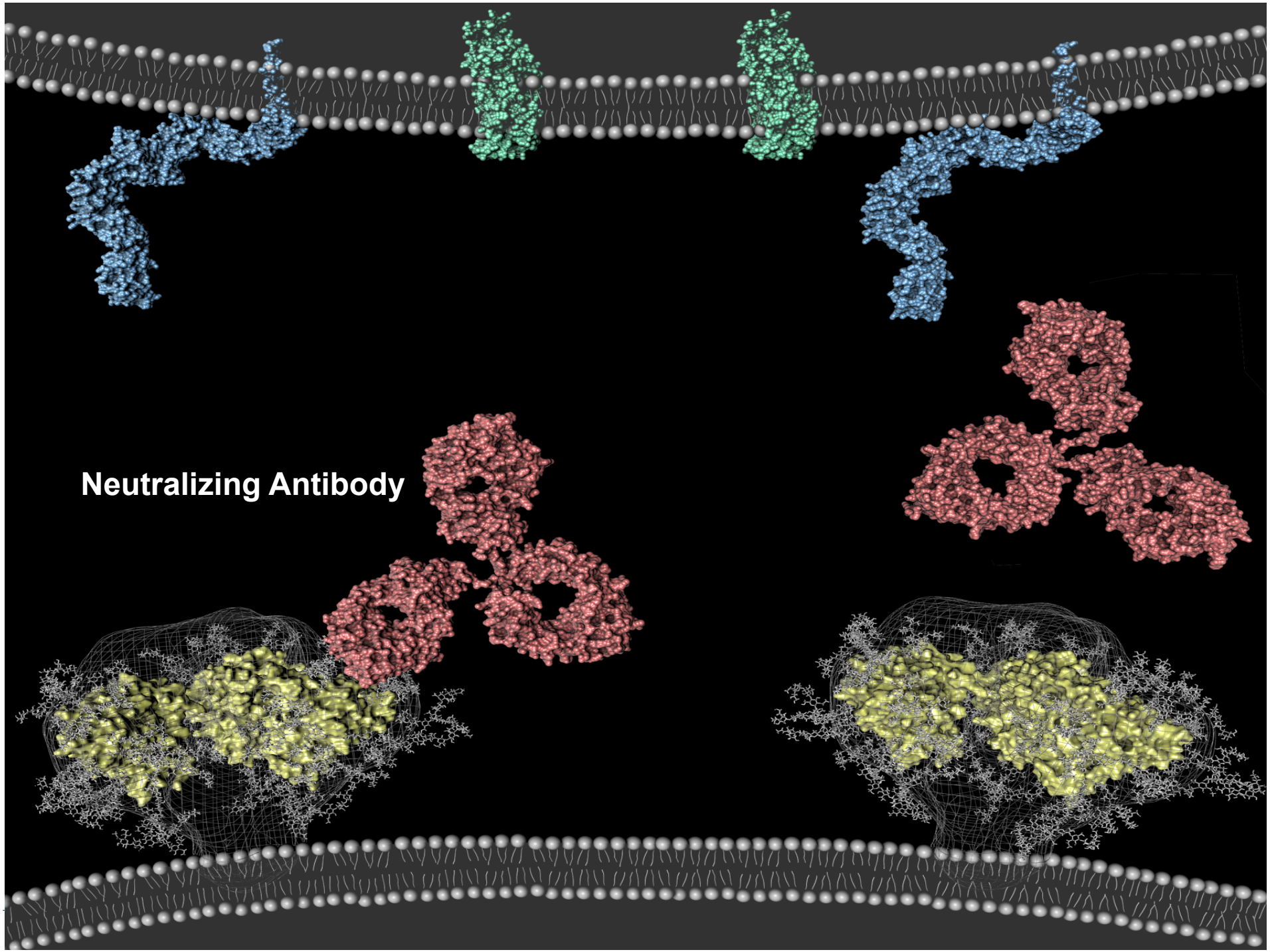


Genetic variability of
HIV-1 V2-C5
(Congo, 1996)

Size = Extent of HIV variability

Source: Weiss, R.A. (2003)


Host cell
CCR5
CD4
Env trimer spike
$(gp120)_3$ $(gp41)_3$
Virion


Neutralizing Antibody

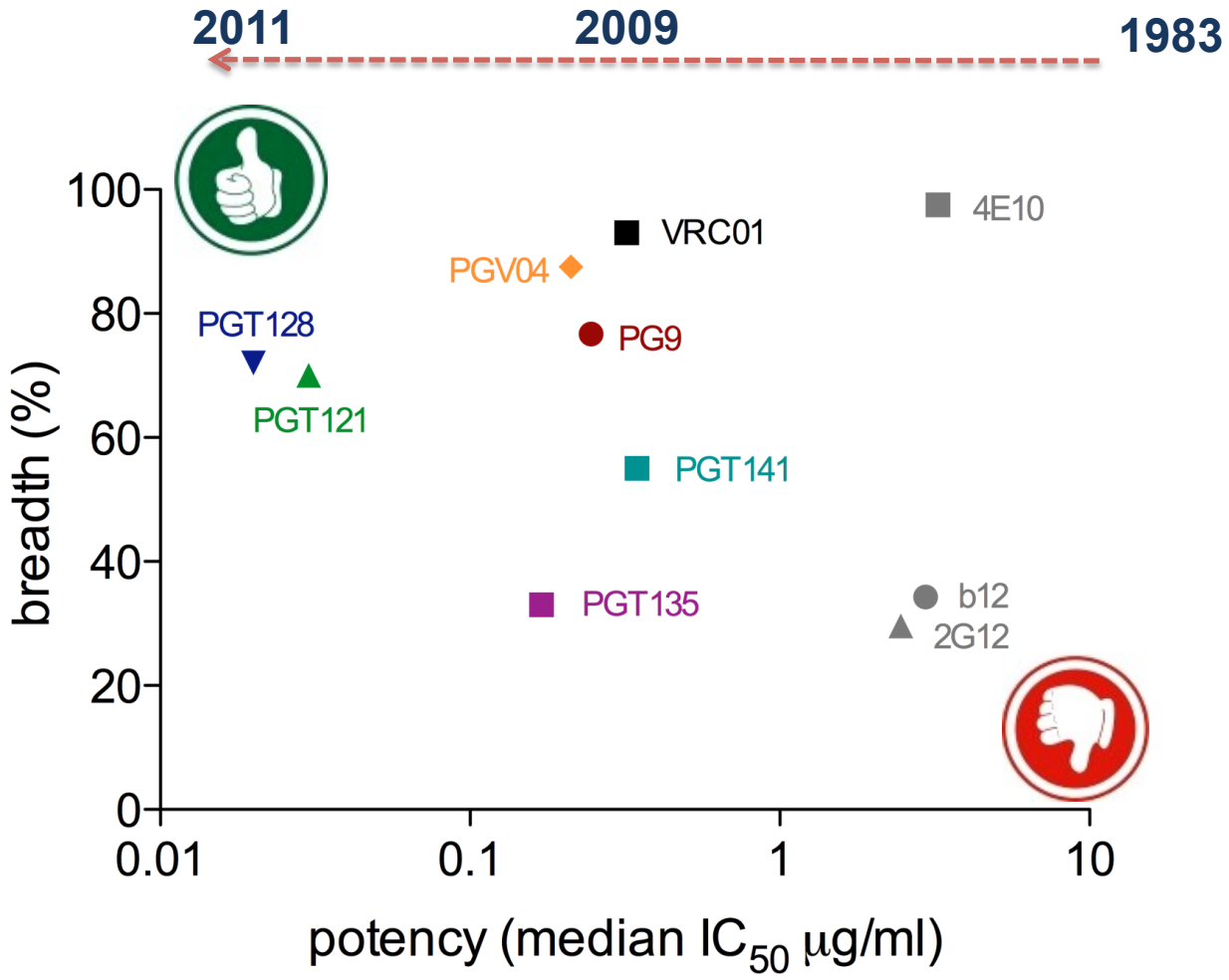
What are broadly neutralizing antibodies?

A broadly neutralizing antibody is defined by:

- **Breadth**: how many type of HIV (or strains) can it block? The more the better.

- **Potency**: how well will it inhibit (the less amount of antibody needed the more potent).

How much better are these bNAbs?

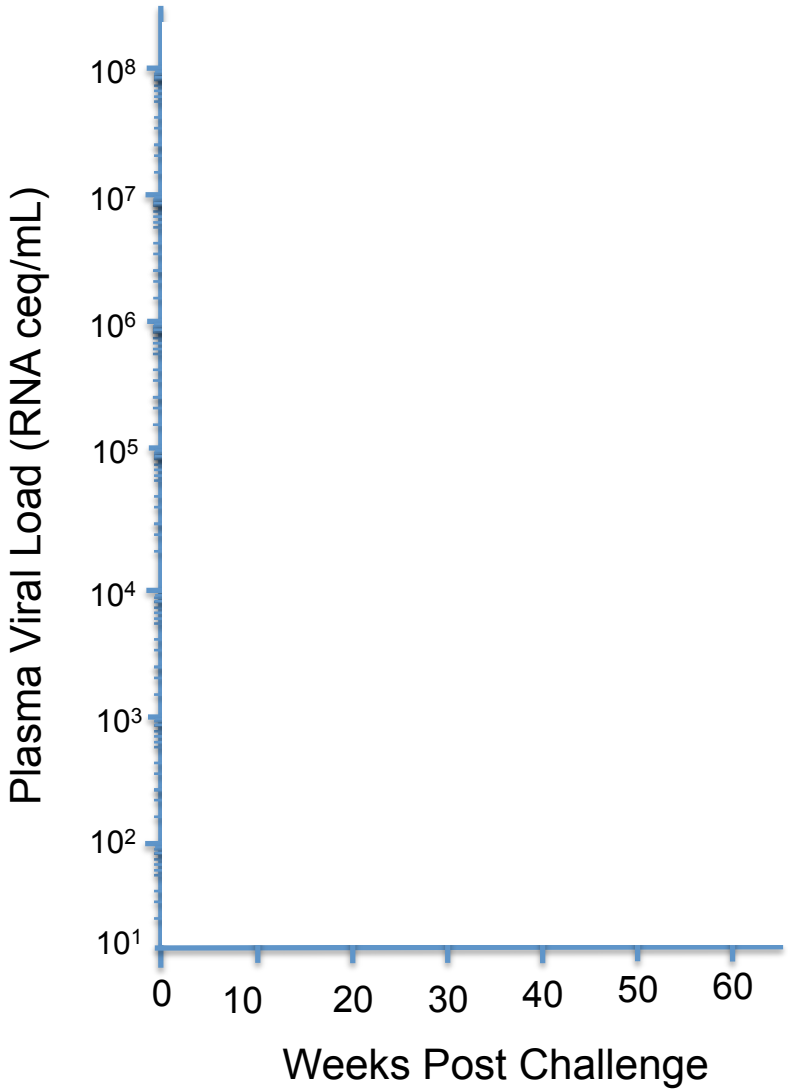


Source: Vaccine Research Center, NIH; IAVI Neutralizing Antibody Consortium

Control of infection:

A vaccine that elicits cellular immune responses
-Has been a major focus of research for the last decade

Live Vaccines control SIV in monkeys infection better than other approaches



- **Live vaccines are among the most effective (measles, polio, mumps)**
- **Live HIV vaccines will not be developed due to safety considerations**
- **How can we mimic the efficacy of live attenuated vaccines while maintaining safety for global use ?**
  - **REPLICATING VECTORS**

Jia PLOS Pathogens 2009

Imagine a world
without AIDS

IAVI International AIDS Vaccine Initiative

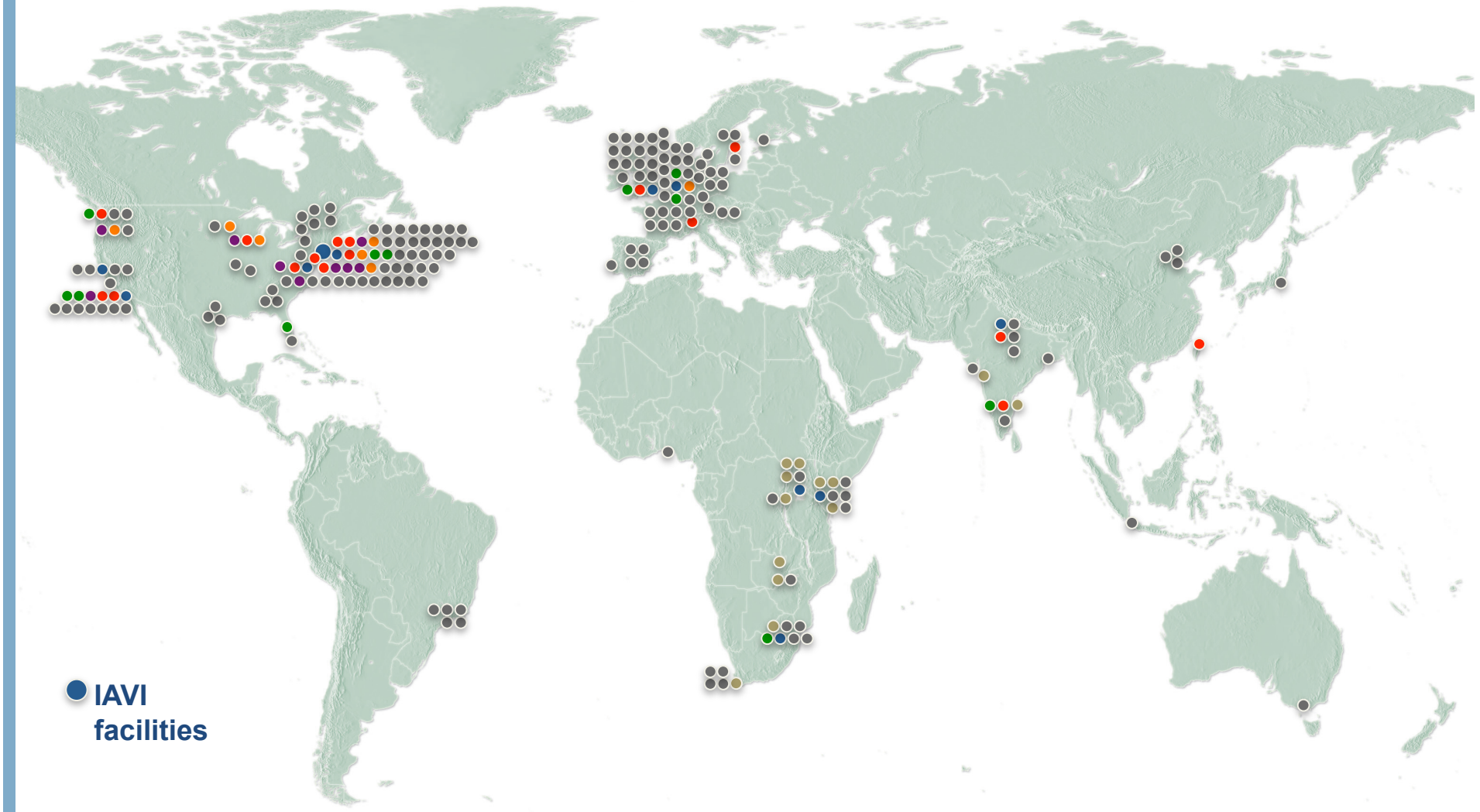
IAVI gratefully acknowledges the generous support provided by the following major donors

Basque Autonomous Government (Spain) ■ Becton, Dickinson and Company (BD) ■ Bill & Melinda Gates Foundation ■ Bristol-Myers Squibb ■ Broadway Cares/Equity Fights AIDS ■ Canadian International Development Agency ■ The City of New York, Economic Development Corporation ■ Foundation for the National Institutes of Health ■ The Gilead Foundation ■ GlaxoSmithKline ■ Google Inc. ■ Government of Japan ■ The Hearst Foundations ■ Institut Mérieux ■ Irish Aid ■ James B. Pendleton Charitable Trust ■ Ministry of Foreign Affairs and Cooperation, Spain ■ Ministry of Foreign Affairs of Denmark ■ Ministry of Foreign Affairs of The Netherlands ■ Ministry of Science & Technology, Government of India ■ National Institute of Allergy and Infectious Diseases ■ Norwegian Royal Ministry of Foreign Affairs ■ The OPEC Fund for International Development ■ Pfizer Inc ■ The Starr Foundation ■ Swedish International Development Cooperation Agency ■ Thermo Fisher Scientific Inc. ■ U.K. Department for International Development ■ The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development ■ United Continental Airlines ■ The World Bank through its Development Grant Facility

And many other generous individuals from around the world

As of July 2012

IAVI partners around the globe



Network of Excellence
European Vaccine and Microbicides Enterprise

EUROPRISE

Coordinator :

Robin Shattock; Imperial College, London

www.europrise.org

EUROPRISE Network Achievements

- **EUROPRISE has established itself as an international driving force in understanding the interface between microbicides and vaccines technologies**
- **Establishment of a Pan-European PhD training program in HIV prevention technology**
- **International visibility for EU researchers working on HIV microbicides and vaccines. Establishment of international collaborations (especially with the US bodies, like NIH)**
- **Integration of research programs on HIV prevention technology across multiple EU institutions, especially on New approaches to the combined use of vaccines and microbicides**
- **More than 300 multi-author papers in high impact**

EUROPRISE Network Achievements

- **Weekly news bulletin and science update providing state-of-the-art coverage (about 200 subscribers)**
- **Major hub for providing reference AIDS reagents (5000/year distribution)**
- **Pan-European PhD training scheme – recognized internationally (60+ students involved)**
- **Involved in 32 separate world-wide clinical trials and 33 NHP studies of Vaccines and Microbicides**
- **Directly supporting 3 clinical trials (MUVAPRED, HIVIS 08, MABGEL projects)**

Vaccine-microbicide NHP study:

- **Vaccinated individuals may benefit from additional approaches for prevention from HIV transmission like PreP, PEP and microbicides**

- **Combining vaccines and microbicides may be more efficient than either strategy alone**

- **Mucosal exposure to HIV in presence of microbicide may modify mucosal and systemic anti-HIV responses previously induced by vaccines**

NHP study using trimeric gp140 (B and C clade) mucosal and systemic administration followed
by Ivag challenge in 1% TDFgel.

EUROPEAN COMMISSION
Community Research

SEVENTH FRAMEWORK PROGRAMME

NGIN

Next Generation HIV-1 Immunogens

inducing broadly reactive Neutralising antibodies

1.feb.2008 - 31.july.2012

Call April 2007: Health 2007-2.3.2-6:
New HIV Vaccines inducing broadly-reactive neutralising antibodies

www.ngin.eu

avi

GIN : The Partners

Next Generation HIV-1 Immunogens inducing broadly reactive Neutralising antibodies

Sweden
ULUND, Lund
Karolinska Institutet, Stockholm
AVARIS, Stockholm

Denmark
SSI, Copenhagen

UK
NIBSC, London
UOXF, Oxford

Belgium
ITG, Antwerp

The Netherlands
AMC, Amsterdam

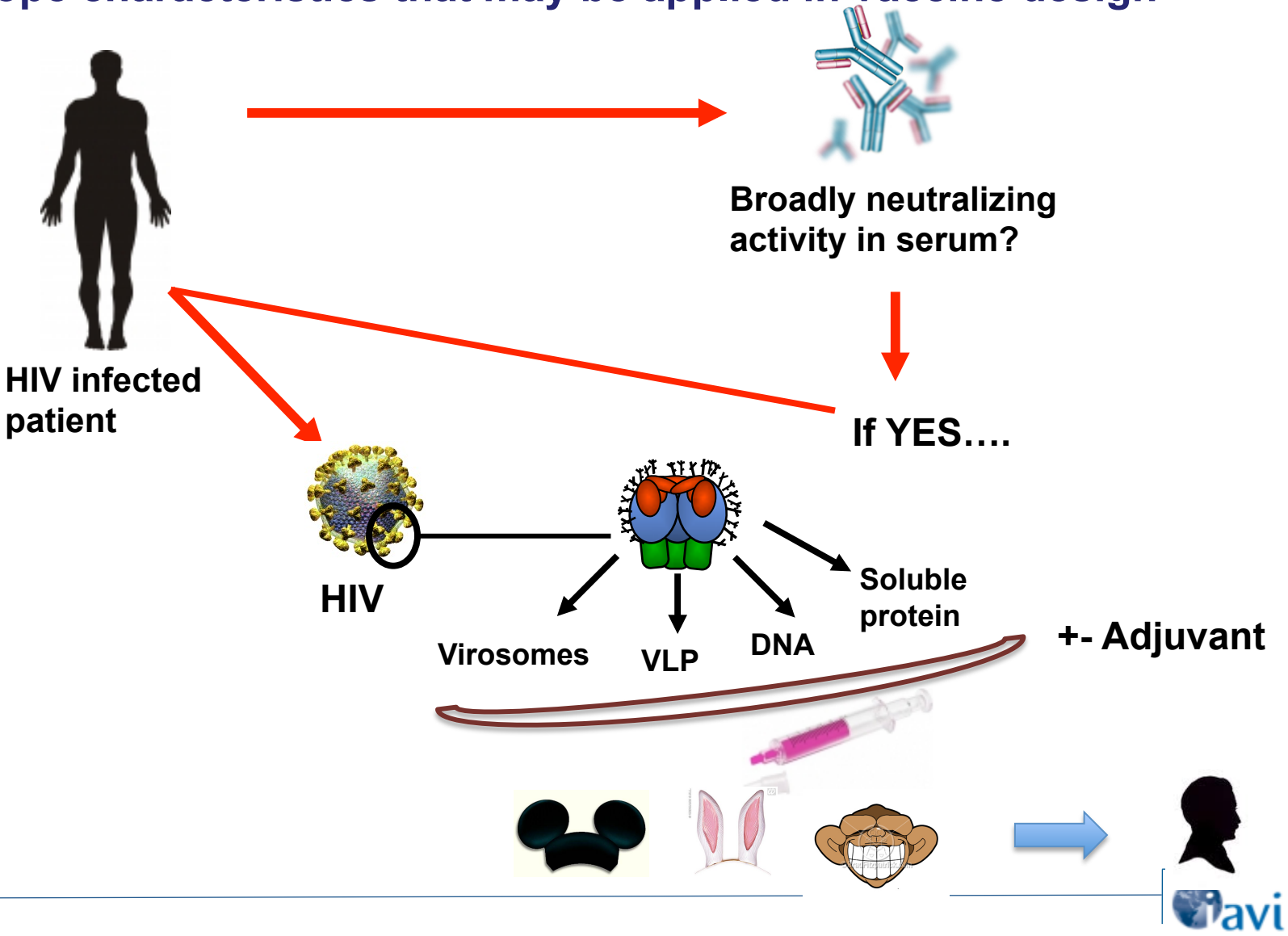
France
CEA, Paris
UPD, Paris

Switzerland
Cytos, Schlieren
Mymetics, Nyon

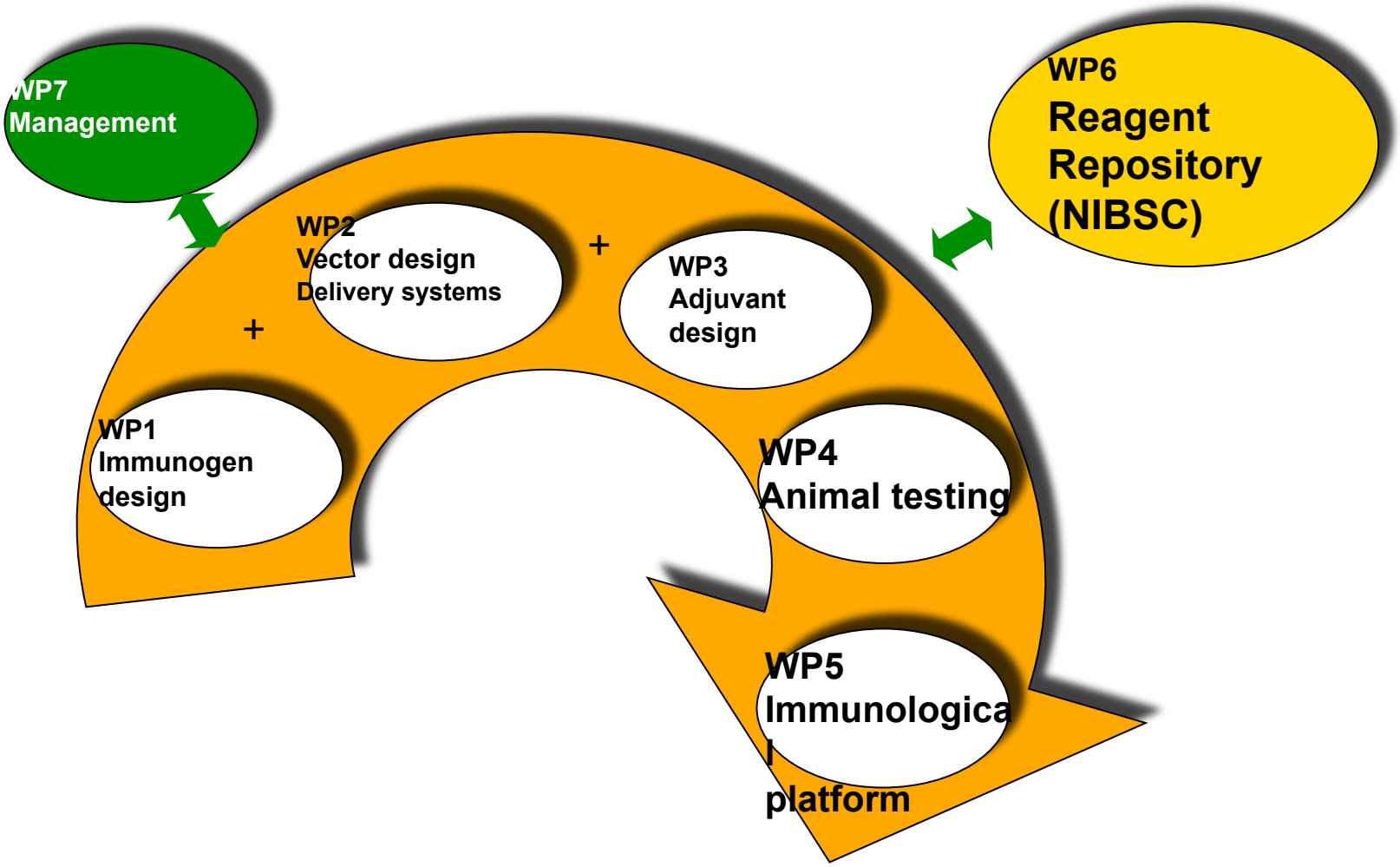
Italy
HSR, Milano
UMIL, Milano
INT-NA, Napoli

SEVENTH FRAMEWORK PROGRAMME

Hypothesis HIV infected individuals who develop cross reactive neutralizing antibodies are infected with an HIV variant with unique envelope characteristics that may be applied in vaccine design

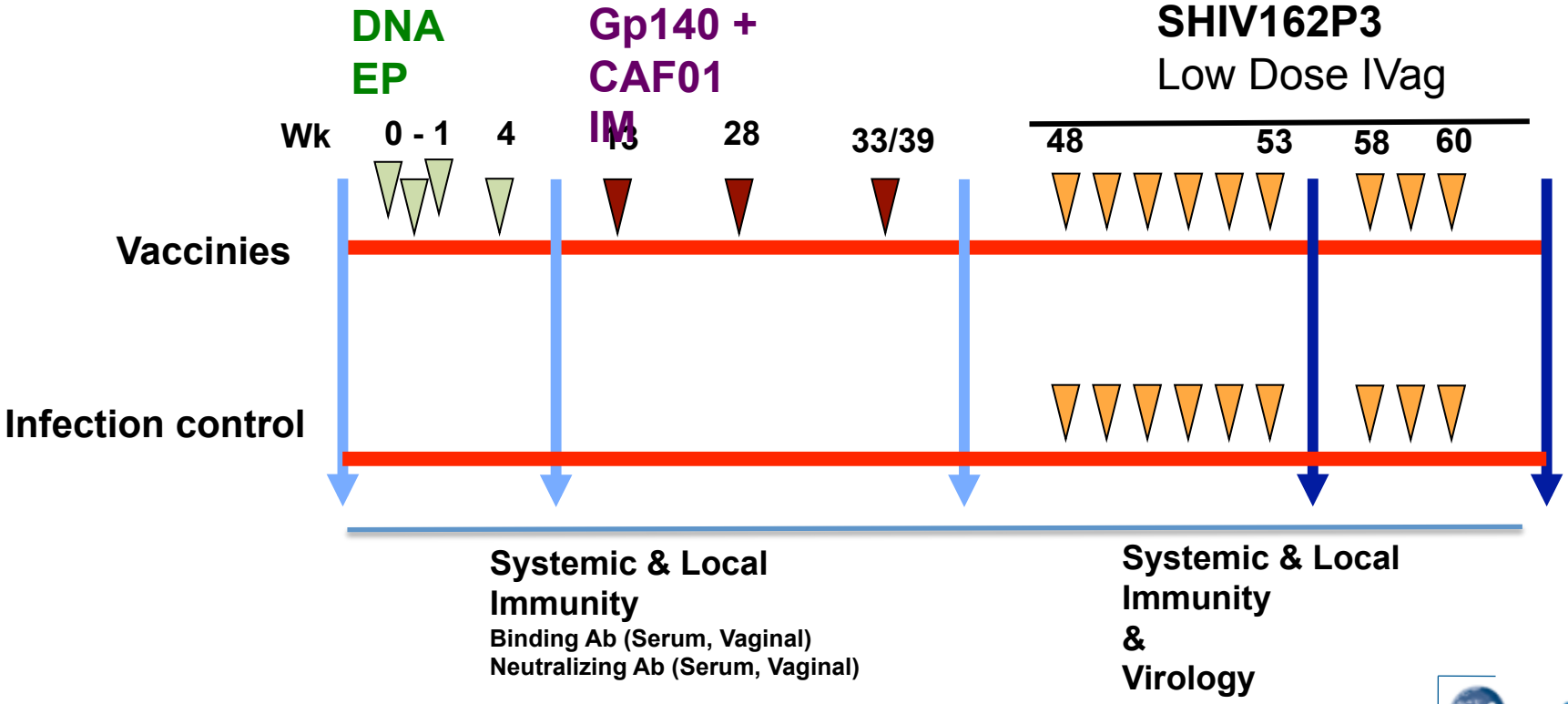


NGIN : The Concept



Prime - Boost strategy

env DNA (B) +
gp140 trimer (HIV-1 A or B)



VACCINE RESEARCH INSTITUTE

The Vaccine Research Institute, VRI

Director : Yves Lévy

T-Cell immunology	DC-based vaccines	B cell immunology and mucosal immunity	Correlates of protection and preclinical models	Clinical Core	HCV Virology and vaccines	Immunology core	Biostatistics and bioinformatics
Division leader O. Schwartz	Division leader G. Zurawski K. Palucka	Division leader G. Scarlatti	Division leader M. Müller-Trutwin R. Le Grand	Division leader J-D. Lelièvre	Division leader J-M. Pawlotsky	Division leader C. Lacabaratz	Division leader R. Thiébaut

anRS Agence nationale de recherches sur le sida et les hépatites virales | Agence autonome de l'Inserm |

Inserm

UPEC Connaissance - Action

UNIVERSITÉ PARIS-EST CRÉTEIL VAL DE MARNE

avi

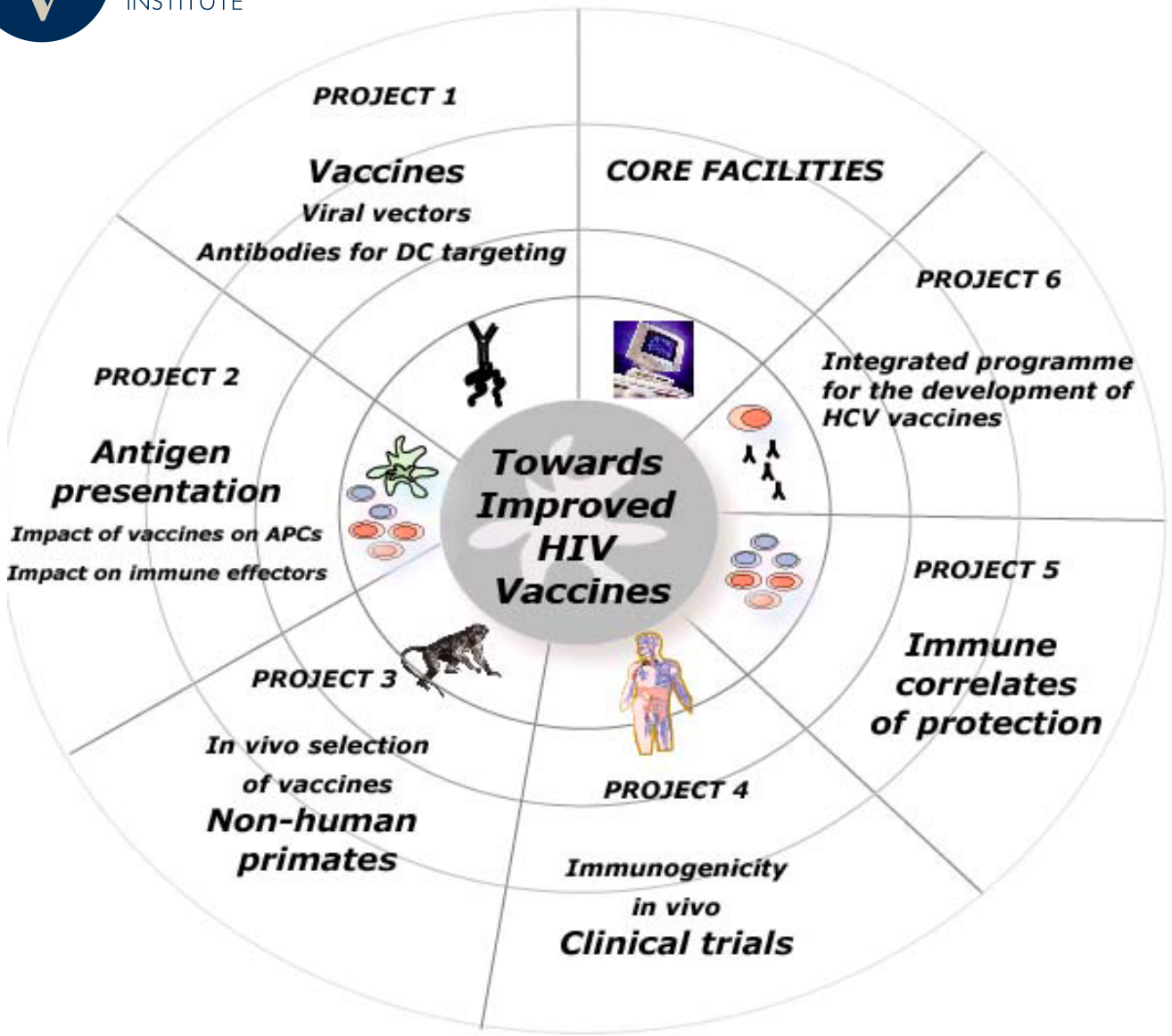
VRI Mission

VACCINE RESEARCH INSTITUTE

The mission of the VRI is to conduct research to accelerate the development of effective vaccines against HIV/AIDS and HCV

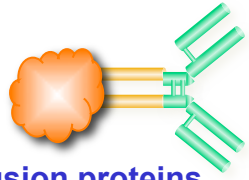
avi

VACCINE RESEARCH INSTITUTE



Candidate vaccine

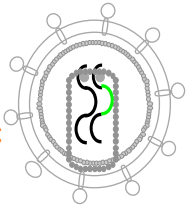
Lipopepties



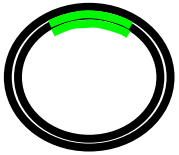
Fusion proteins

MVA

NYVAC



DNA



DC targeting

Ex vivo pulsed DC

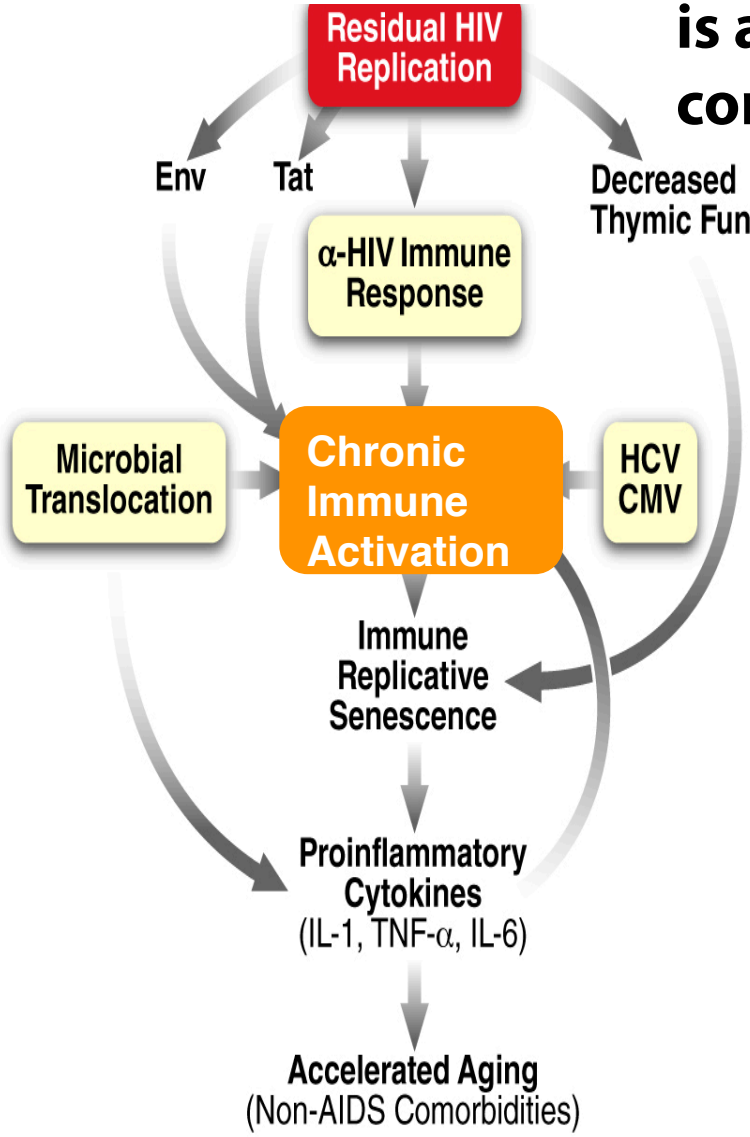
VACCINE RESEARCH INSTITUTE

Public/private partnerships

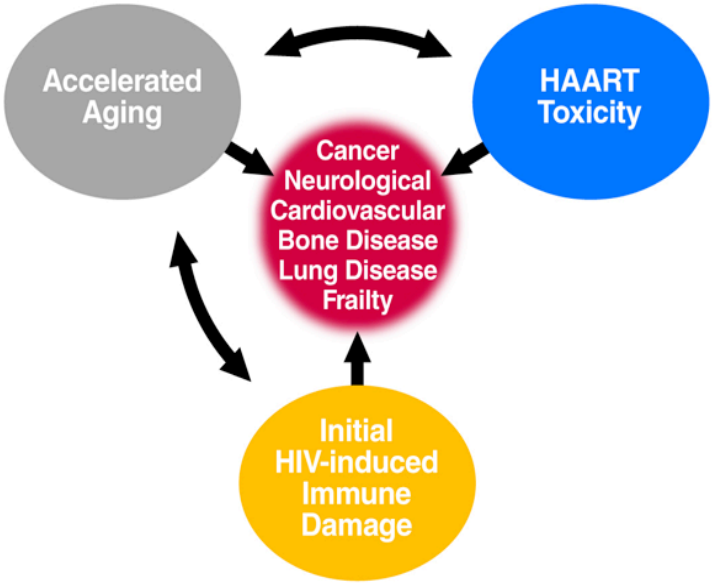
avi

Therapeutic immunization in HIV infection

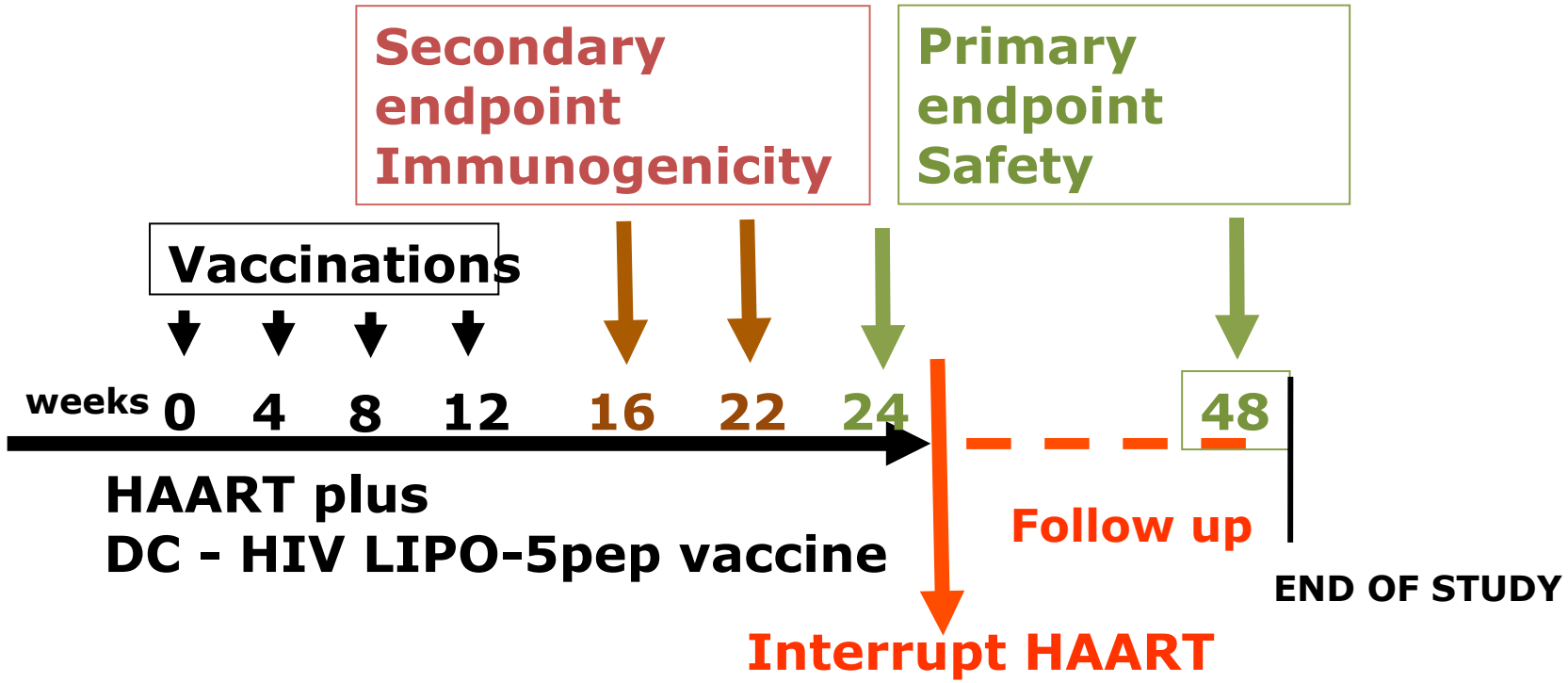
Residual Replication in HAART treated patients



is associated to severe comorbidities



Phase I DALIA
(Dendritic cells And Lipo5 Immunization against Aids)

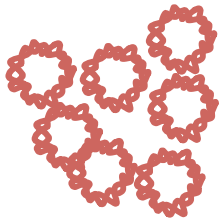


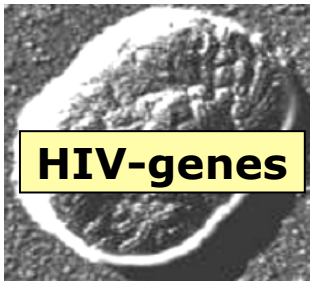
Immunization with HIV-peptide-loaded dendritic cells may improve HIV immune responses and help to contain viral replication in HIV-1-infected patients.

HIVIS/TaMoVac study plan

Months 0 1 3 6-9 10-21-40

Prime Boost





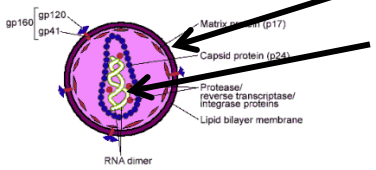
7 DNA Plasmids; KI/SMI

Env A,B,C

Gag A,B

RT B

Rev B



Recombinant MVA;NIH/WRAIR

Env E

Gag A

Pol A

Attenuated vaccina virus with HIV genes

Is priming with low dose DNA intradermally equivalent to 'standard' dose intramuscularly?

Studies and Timelines

Study sites Designation	N Vac. (placebo)	2004	2006	2007	2009	2010	2011	2012	2013
Stockholm HIVIS 01/02/05	40	DNAx3 **i.m vs i.d.**	1st MVA	Published	2ndMVA				Submit MS
Dar es Salaam HIVIS 03/06	40 (+20)			3DNA **i.m. vs i.d.** 1st MVA	2nd MVA		Published	3rd MVA **Late MVA boost**	Analysis ongoing
Dar + Mbeya TaMoVac I(Tz)	108 (+12)					DNAx3 **2 vs 5 inj. i.d.** MVAx2		gp140/GLA **Late protein boost**	Analysis ongoing
Maputo TaMoVac I(Moz)	20 (+4)						DNAx3 **0.1 vs 0.2mL i.d.** MVAx2		Analysis ongoing
Stockholm HIVIS 07	36 (+6) 27						DNAx3 **+/-elpor.*** MVAx2 +/-gp140		Analysis ongoing
Dar+Mbeya+ Maputo TaMoVac II	180 (+18)							DNAx3 **+/- elpor*** MVAx2	Addition of gp140/GLA to MVA boost

Study Objective in red

***elpor = i.d. electroporation**

~~Finished~~; ~~Ongoing~~; ~~Planned~~

Results

- HIVIS 01/02/05

Well tolerated. Good immunogenicity. I.d. ~ i.m. GMCSF adds nothing to DNA prime. Age matters. Previous vaccinia immunizations not critical.

- HIVIS 03

Well tolerated. *Very good immunogenicity. I.d. more efficient prime than i.m.* Balanced CD4 vs CD8 and Gag vs Env responses. Broadly crossreactive and persistent LPA.

- *All serologically reactive after 2nd MVA*. Neutralizing antibodies in up to 83% in PBMC assay, ADCC dependent. (**Bakari M**, et al Vaccine 2011 29:8417-28)

- TaMoVac I

Well tolerated. (Prel.) DNA priming with 2 i.d. injections á 300mg (tot 600mg) almost equivalent to 5 i.d. á 200mg (tot 1000mg).

Injections with Env and Gag plasmids separated gave no advantage.

0.2 mL i.d. well tolerated and feasible with Zetajet.

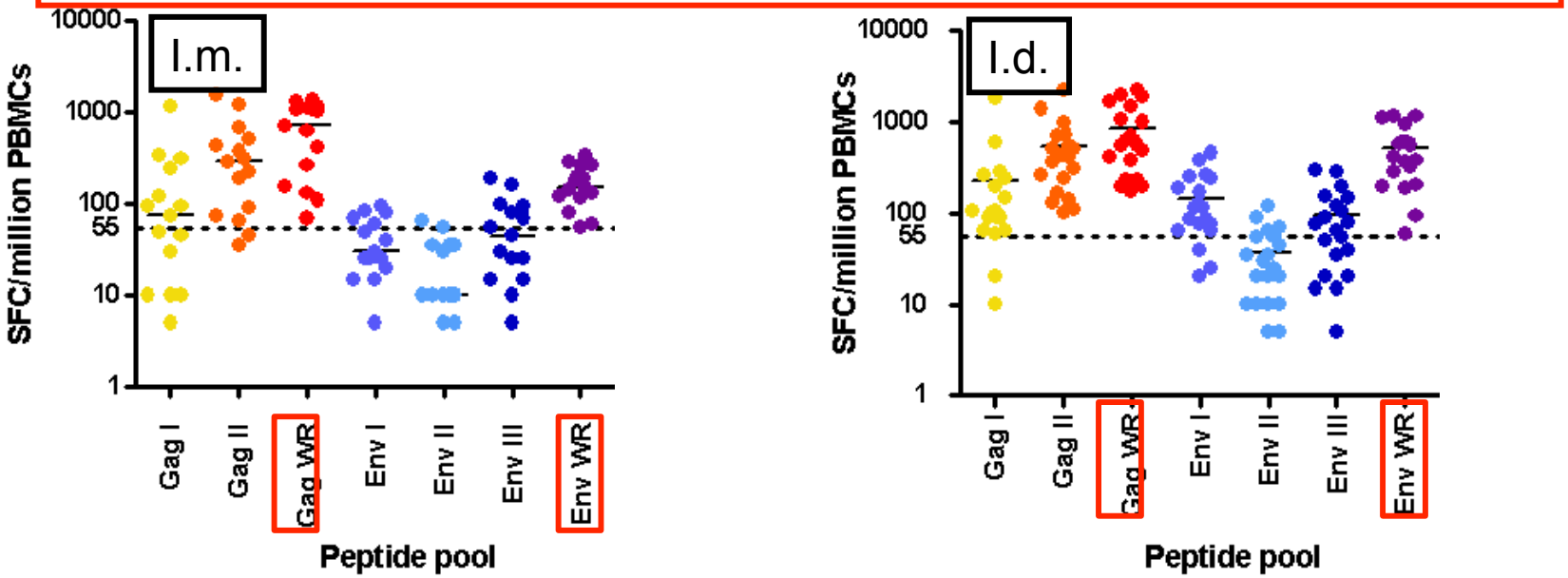
- HIVIS 07

Intradermal electroporation well tolerated.

Strong immune responses to priming and boosting immunogens

Gag I and II; Env I, II and III in DNA prime

Gag WR and Env WR in MVA boost

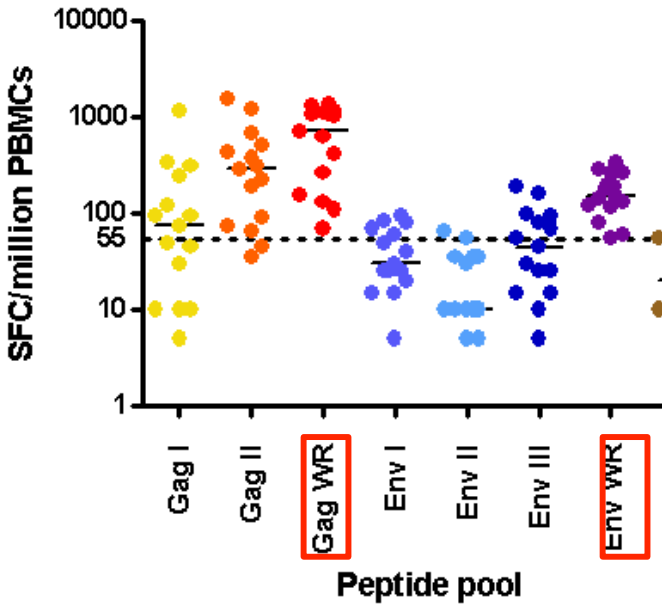


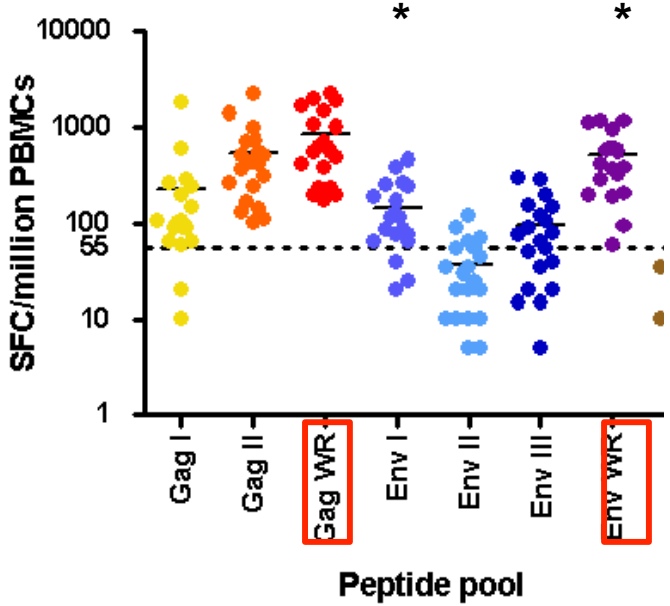
100% responded to gag; 89% responded to env

Strong immune responses to priming and boosting

- 3.8mg i.m. – in the muscl

1 mg i.d. – in the skin

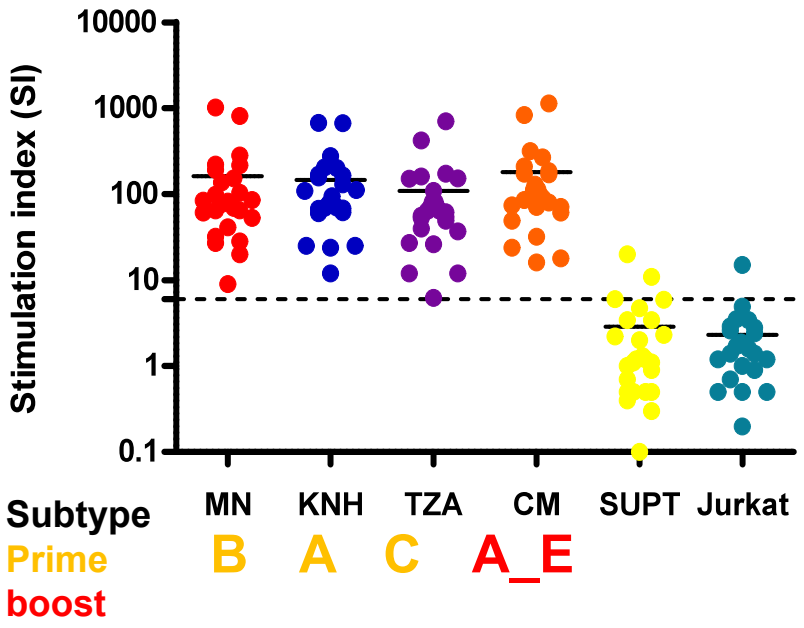




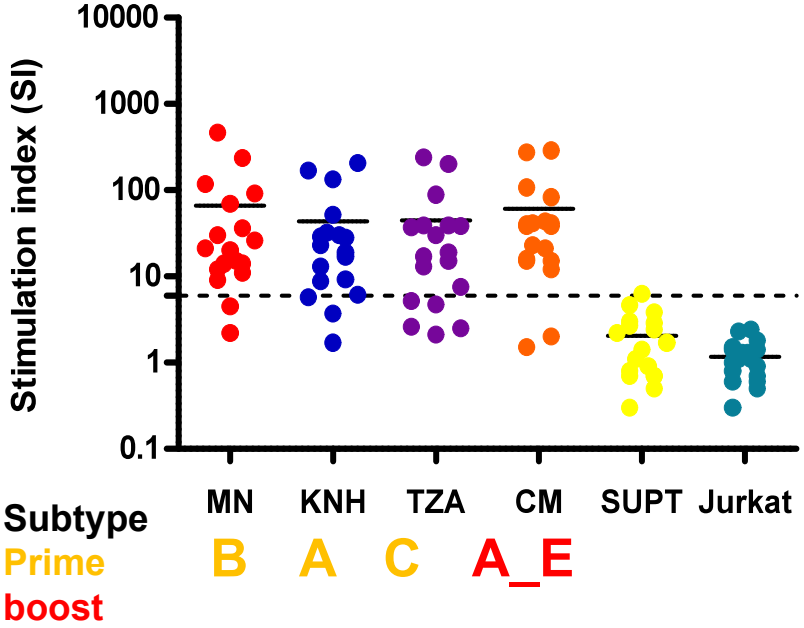
*I.d. DNA primes for significantly higher and broader Env responses than i.m.

Lymphoproliferation in HIVIS 03

2 weeks after the 2nd MVA,
25/25 **(100%)** positive



6 months after the 2nd MVA,
16/18 **(89%)** positive



Broad and sustained LPA responses

HIV serology after second MVA, HIVIS03

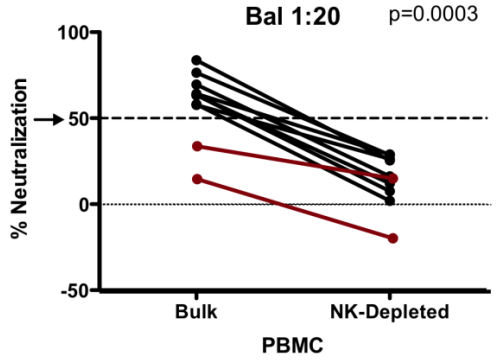
Test	After 1st HIV-MVA N=35	After 2nd HIV-MVA N=30	Long term follow-up 17-22 months after the 2nd HIV-MVA; N=29
1st ELISA	0 (0%)	30 (100%)	28 (97%)
2nd ELISA	0 (0%)	30 (100%)	28 (97%)
Immunoblot	0 (0%)	30 (100%)	20 (69%) positive 9 indeterminate
Gp 160 ELISA	7/33 (21%)	26/29 (90%)	

Every vaccinee positive in rutine serology after **second** MVA boost

The HIVIS 03 sera neutralize in PBMC assays after second MVA

Assay	Virus	Clade	Number of positive/ number tested (%)
Pseudovirus/TZM-bl cells	BaL GS015 CM235	B C CRF01_AE	0/29 (**0%**)
IMC/PBMC	BaL	B	9/29 (**31%**)
	SF162	B	21/29 (**72%**)
	CM235	CRF01_AE	24/29 (**83%**)

Significant decrease of neutralizing activity by NK depletion.



HIVIS and TaMoVac Study groups
Supported by EU, EDCTP and Sida/SAREC

Karolinska Institute, Söder Hospital and Swedish Institute for Infectious Disease Control (SMI)

Eric Sandström
Gunnel Biberfeld
Britta Wahren
Charlotta Nilsson
Bo Hejdeman
Andreas Bråve
Katarina Karlén
Lindvi Gudmundsdotter
Gunnel Engström
Ronnie Ask
Maarit Malinemi

Vecura, Sweden

Pontus Blomberg

Bioject, USA

Richard Stout

Muhimbili University College for Health Sciences, Tanzania

Mohammad Bakari
Eligius Lyamuya
Fred Mhalu
Kisali Pallangyo
Eric Aris
Patricia Munseri
Said Aboud
Muhammed Janabi
Emanuel Salala
Edith Mroso
Suleiman Chum
Deus Buma
Mary Ngatulowa
Judica Mbwana
Theodora Mbunda

University of Cape Town, SA

Carolyn Williamson

CISPOC, Mozambique

Ilesh Jani
Edna Viegas
Nelson Tembo

WRAIR, USA

Nelson Michael
Merlin Robb
Deborah Birx
Mary Marovich

NIH, USA

Bernard Moss
Patricia Earl

University of Munich

Michael Hoelscher
Arne Kroidl
Philipp Mann

MRC, UK

Sheena McCormach
Sarah Banbury
Sue Fleck

IC, UK

Frances Gotch

The volunteers

HIVACAT

Projecte de Recerca de la Vacuna de la Sida

Catalan Program for HIV Vaccine Research

avi

HIVACAT

Projecte de Recerca de la Vacuna de la Sida

Catalan Program for HIV Vaccine Research

IrsiCaixa
Institut de Recerca de la Sida

Generalitat de Catalunya
Departament de Salut

ESTEVE

Obra Social
Fundació "la Caixa"

FUNDACIÓ CLÍNIC
BARCELONA

Generalitat de Catalunya
Departament d'Innovació, Universitats i Empresa

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

CUTHIVAC
Cutaneous HIV Vaccination

SEVENTH FRAMEWORK PROGRAMME

NIDCR National Institutes of Health
National Institute of Dental and Craniofacial Research

avi

The Research Centres

HIVACAT
Projecte de Recerca de la Vacuna de la Sida

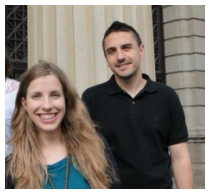
- Two internationally renowned **centres of reference**
- More than **60 investigators**

Program Directors

Scientific Dr

INSTITUT PASTEUR

HIVACAT Strategic Committee



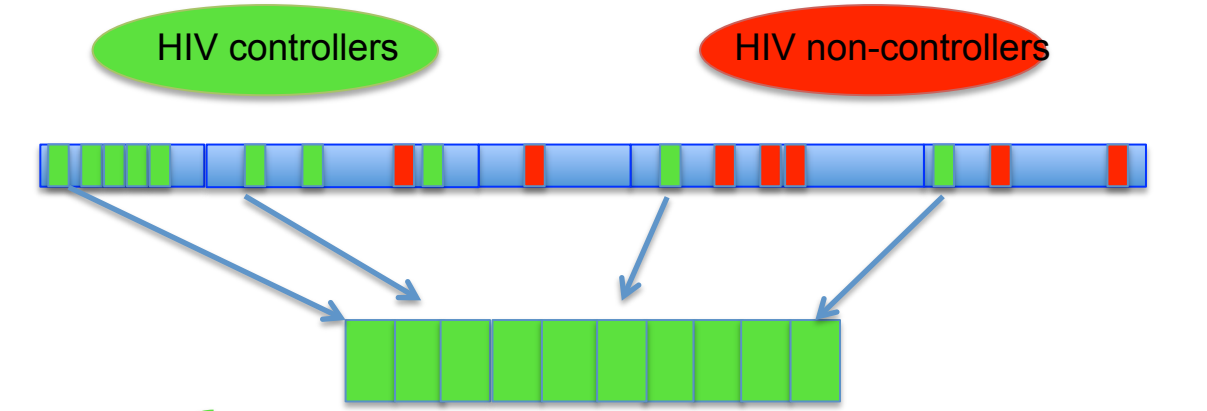
avi

HIVACAT T-cell vaccine development

Ex-vivo analyses of HIV specific T cell responses

Identification and assembly of protective T cell targets

Incorporation into vaccine delivery vehicles



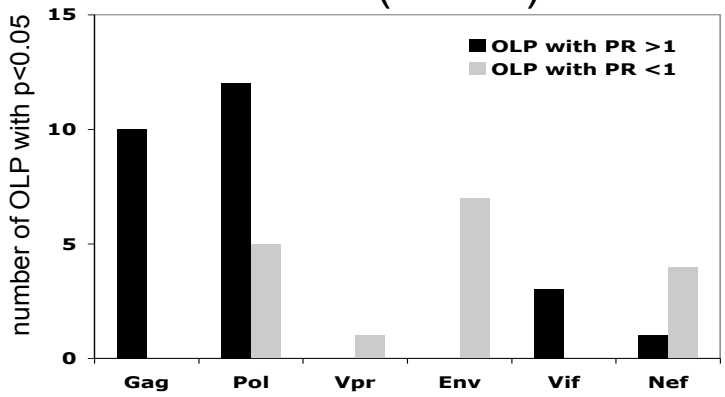
Development of suitable animal model and parallel immunogenicity analyses

Mice (- Pigs)

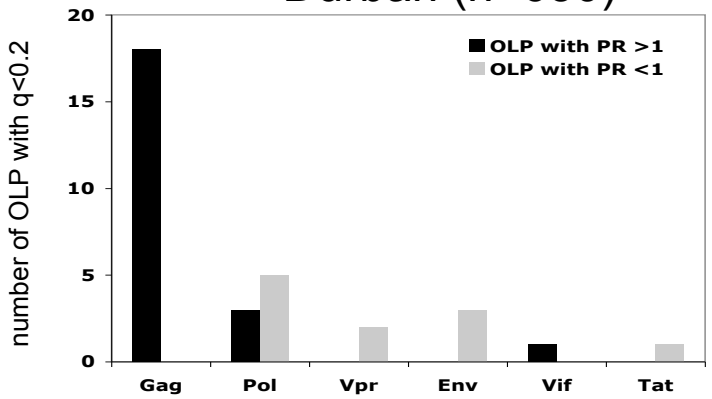
Delivery route and adjuvants
IM, ID (- Nasal, transcutaneous)

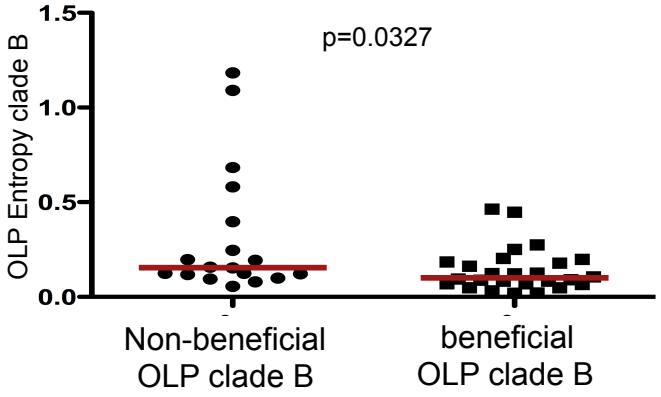
Human clinical trials for preventive and therapeutic application

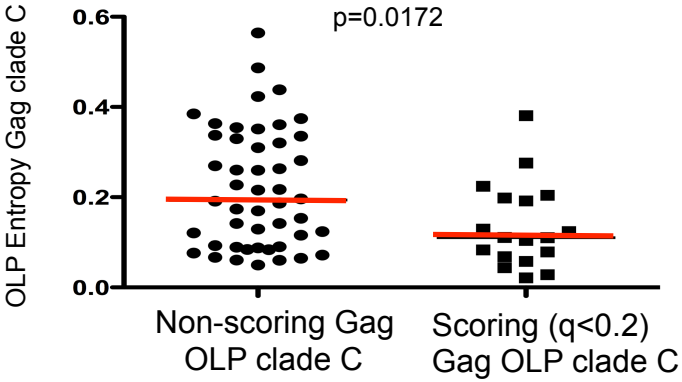
Lima (n=232)

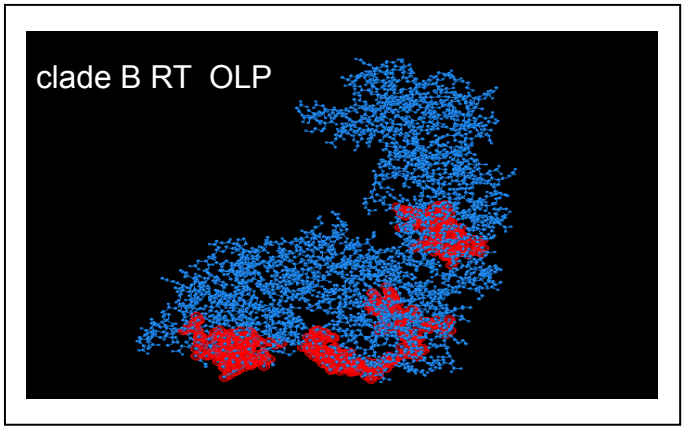


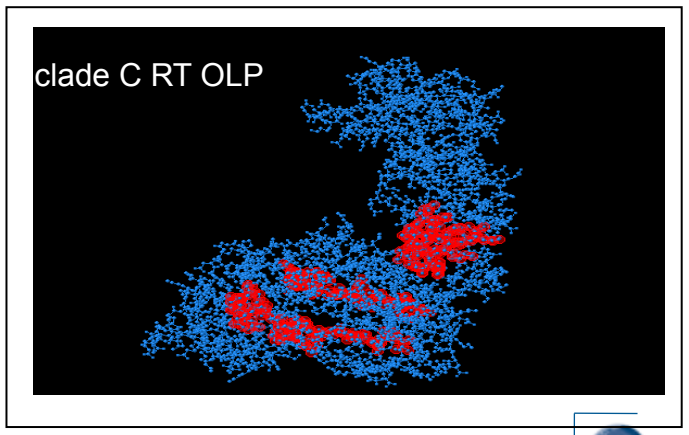
Durban (n=630)





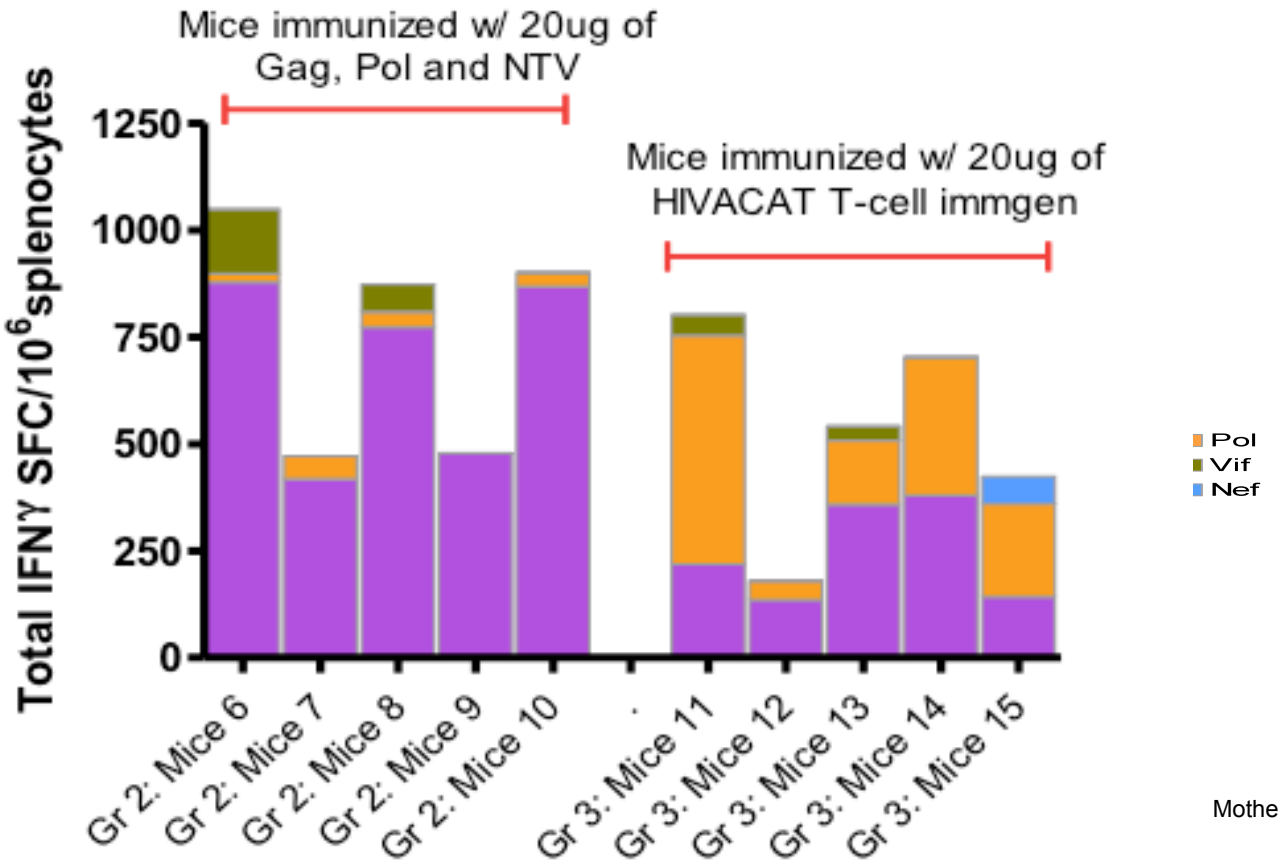






Mothe et al , J Transl. Med. 2011

All protein subunits in HIVACAT-T are targeted and break the common Gag dominance



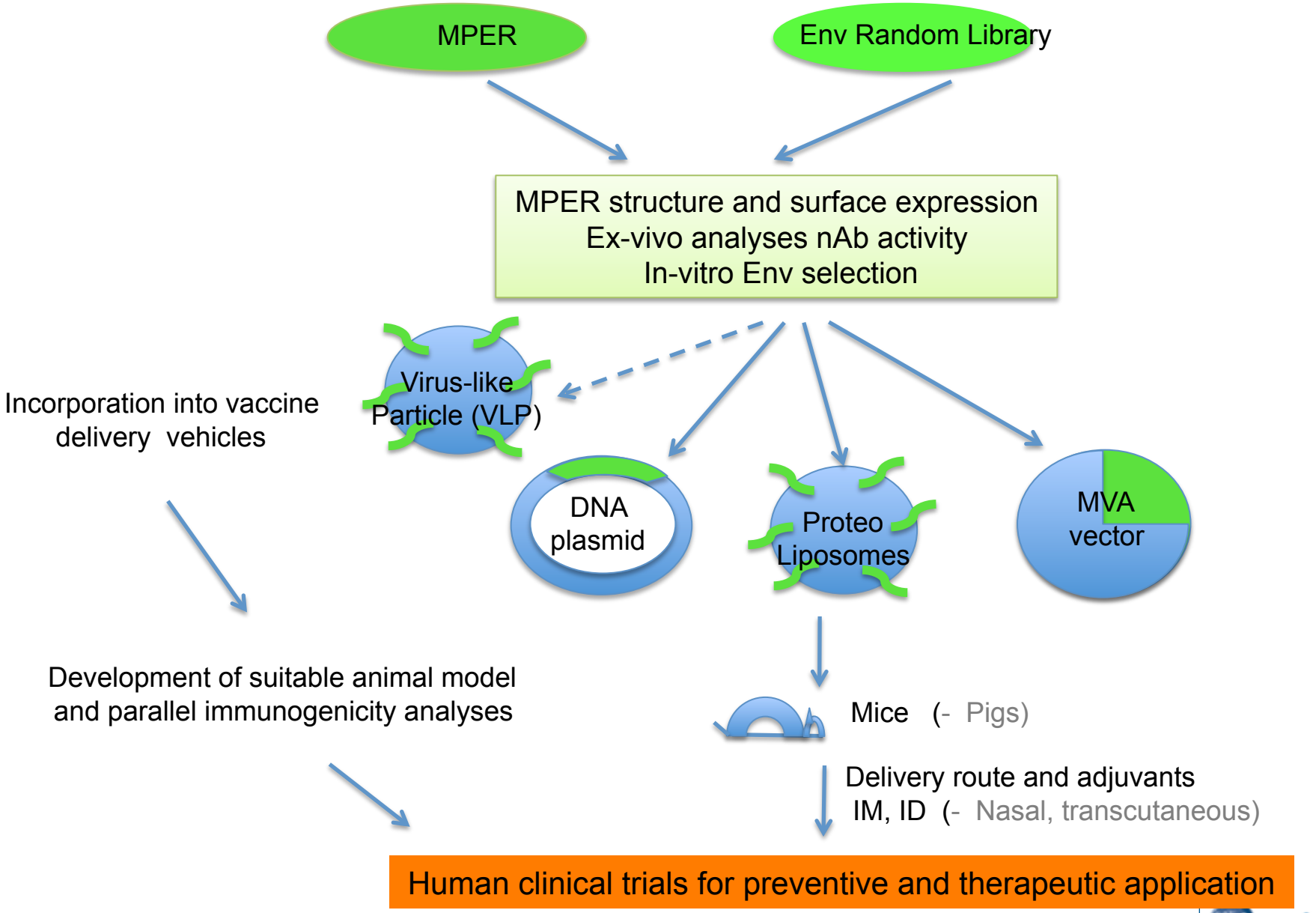
Mothe et al in preparation

→ Immunization of humanized mice with variable HLA background

Mucosal immunity in mice and pigs

Human clinical trial for safety and immunogenicity

HIVACAT B-cell immunogen development



HIVACAT

Projecte de Recerca de la Vacuna de la Sida

Catalan Program for HIV Vaccine Research

IrsiCaixa
Institut de Recerca de la Sida

Generalitat de Catalunya
Departament de Salut

ESTEVE

Obra Social
Fundació "la Caixa"

FUNDACIÓ CLÍNIC
BARCELONA

Generalitat de Catalunya
Departament d'Innovació, Universitats i Empresa

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

CUTHIVAC
Cutaneous HIV Vaccination

SEVENTH FRAMEWORK PROGRAMME

NIDCR National Institutes of Health
National Institute of Dental and Craniofacial Research

avi

Christian Brander graduated from the University of Bern in 1994 with a PhD in Immunology studying exogenous antigen re-presentation on HLA class and T-cell mediated hyper-reactivity to Penicillin. He then spent 13 years at Harvard University focusing on cellular immunity to viral infections and the impact that host genetics have on this immune response. He joined ICREA in 2008 with an appointment at the IrsiCaixa AIDS Research Institute to continue his work on host genetics and the cellular immunity to viral infections, including HIV, HCV and herpesviruses such as KSHV and EBV. He also serves as the scientific director of HIVACAT, the Catalan program for the development of a HIV vaccine, which unites 60 investigators at two premier HIV research centers in Barcelona, Irsicaixa and Hospital Clinic.