HIV vaccines: challenges and innovations opportunities

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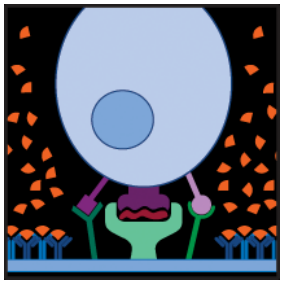
Centro de Pesquisas
AGGEU MAGALHÃES

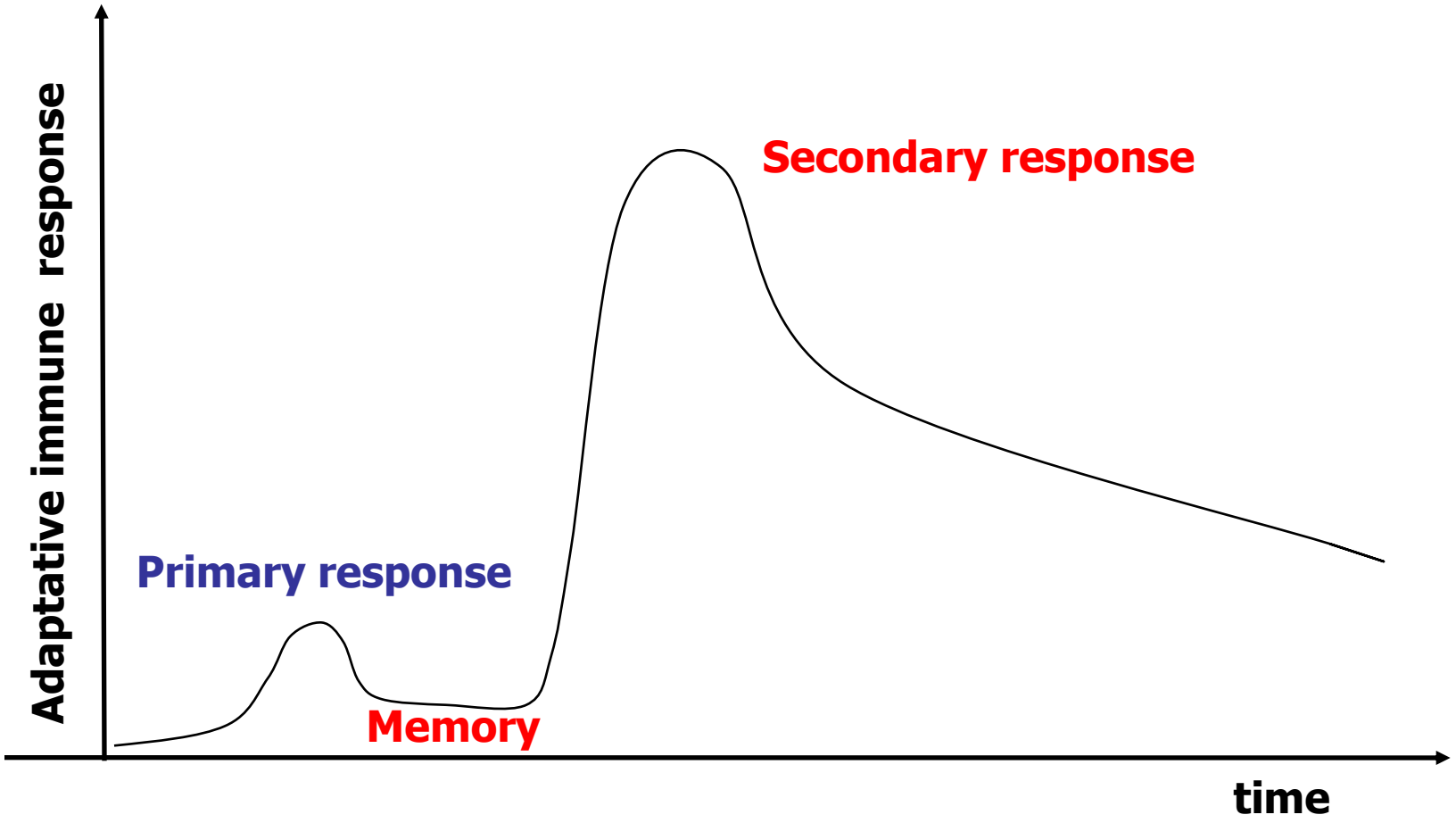


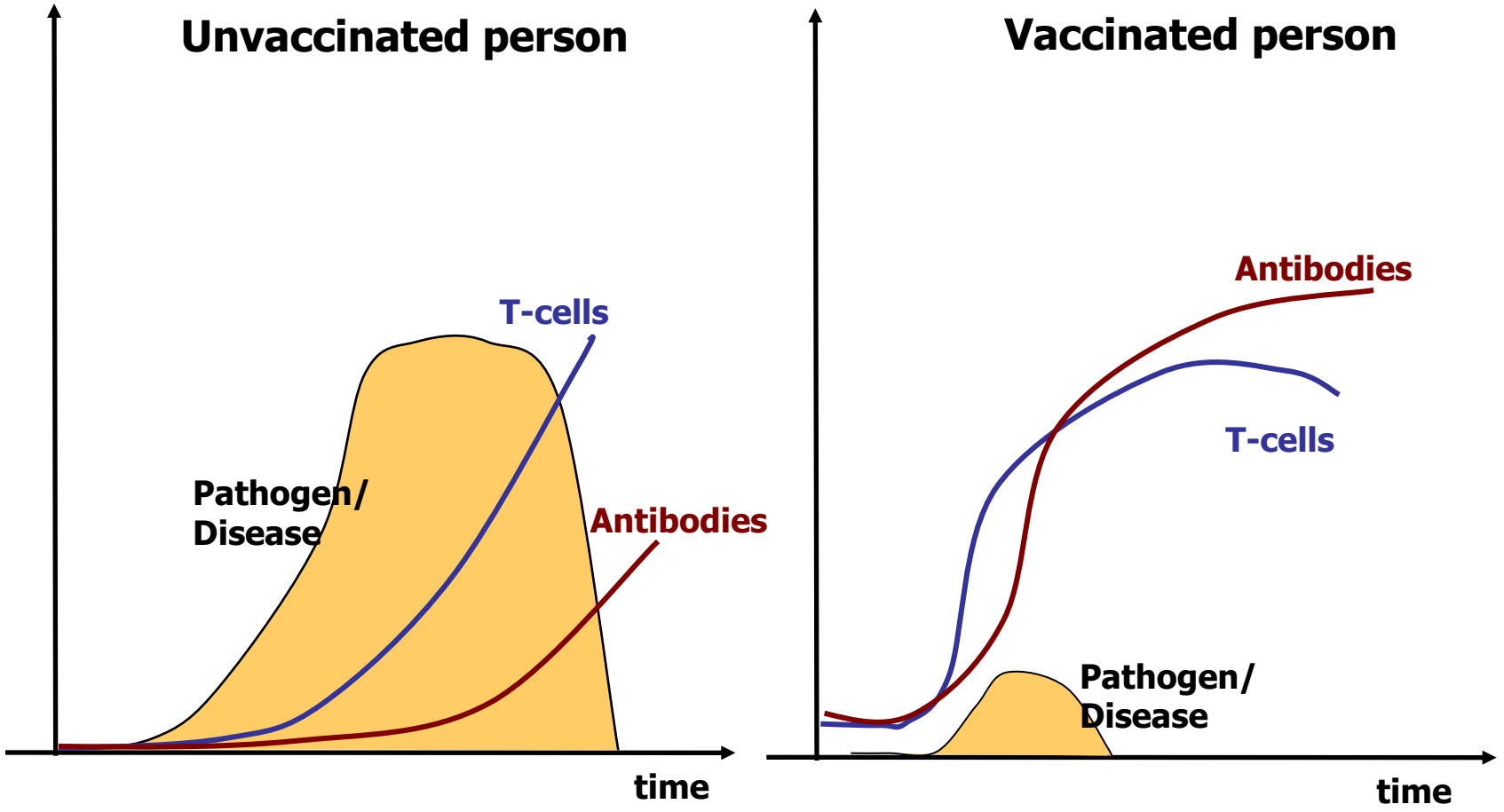
CVR - Functional Immunomics Lab

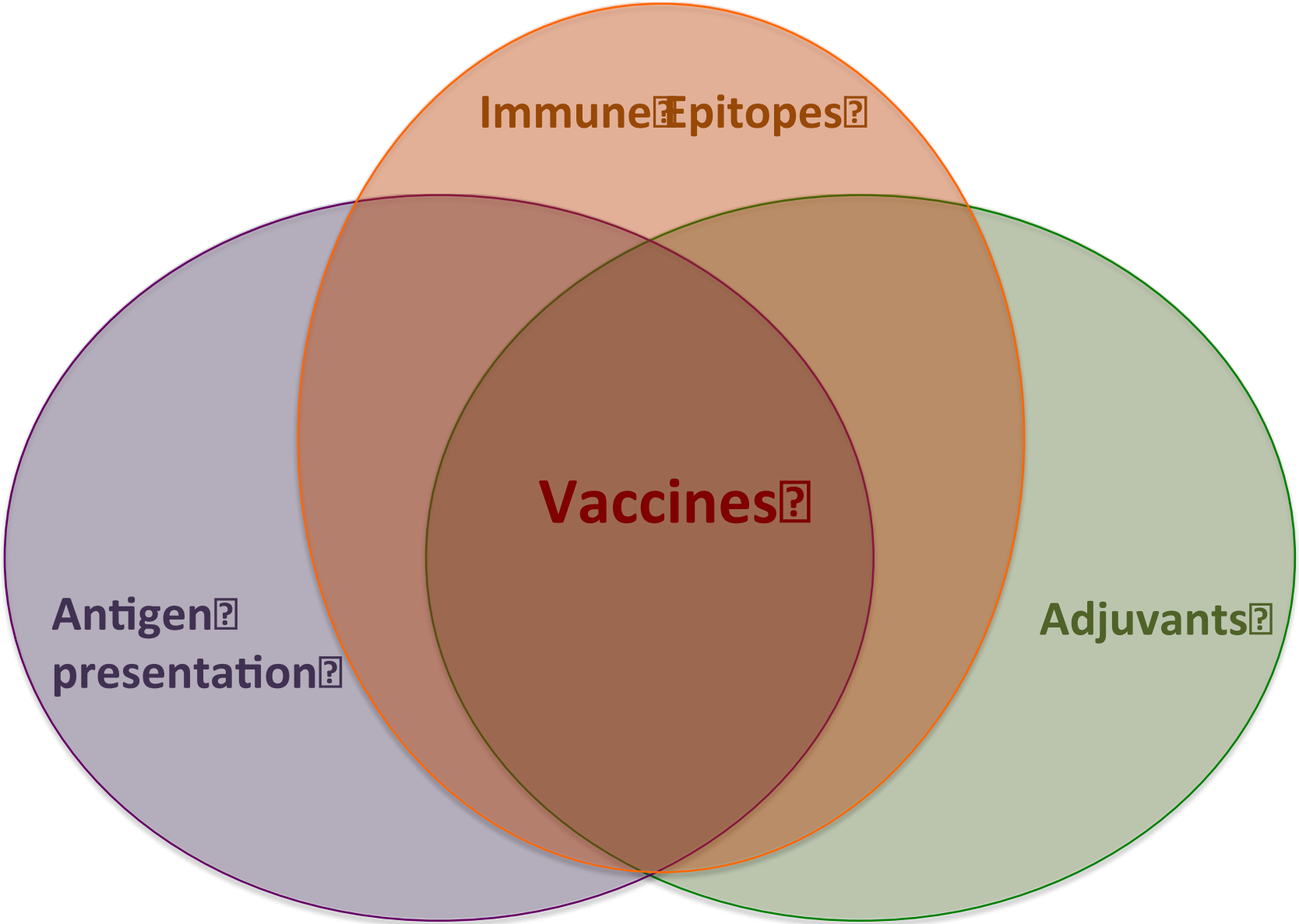
What is a Vaccine?

Any formulation able to elicit antigen specific immunological memory capable of reducing the pathogenicity or the transmission of an agent.

Immunological memory




Unvaccinated person
T-cells
Pathogen/
Disease
Antibodies
time
Vaccinated person
Antibodies
T-cells
Pathogen/
Disease
time


Immune Epitopes
Vaccines
Antigen presentation
Adjuvants

Components of a vaccine formulation

- **Delivery vehicle –** defines the presentation of the antigen to the immune system
- **Adjuvant –** provides immune stimulatory signals to start innate immune responses and shape the adaptative effector mechanisms
- **Active principle** - immunogenic epitopes correlated with protection: B-cell, linear and conformational: T-cell CD4 and CD8.

Modern Vaccine Design principle

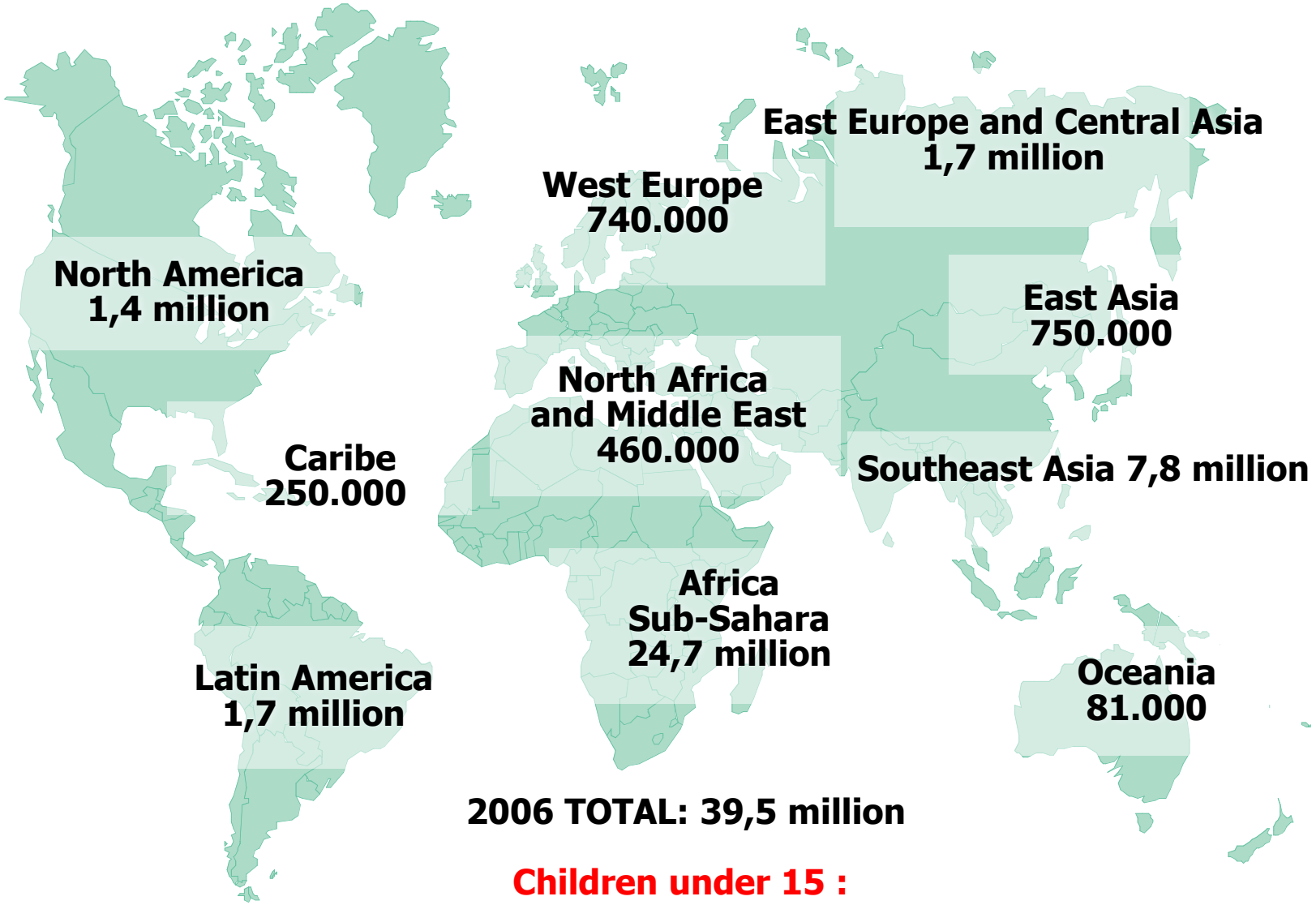
- **CLASSIC - Vaccine mediated protection is based on the exposure of an immunogenic agent to a host followed by the natural development of immunity. (Many classic antigen formulations failed to produce immunity against HIV, Malaria, Cancer and etc)**

- **MODERN - The antigen formulation include bio-active strategies to induce the modulation of immunological mechanisms to target specific cognitive and effector responses and in order to achieve immunity and reduce immune-related toxicity. In addition new technologies can provide easier preparation, and greater stability.**

HIV/AIDS: The Problem

- **HIV/AIDS has become the worst epidemic in human history**
- **At current rates, 45 million more people were infected with HIV between now and 2010**
- **At least 29 million infections could be prevented with greater access to proven HIV prevention tools and information**
- **Today, fewer than one in five people at risk worldwide has access to prevention interventions, such as condoms, behavior-change programs or STD treatment**

HIV/AIDS in the world

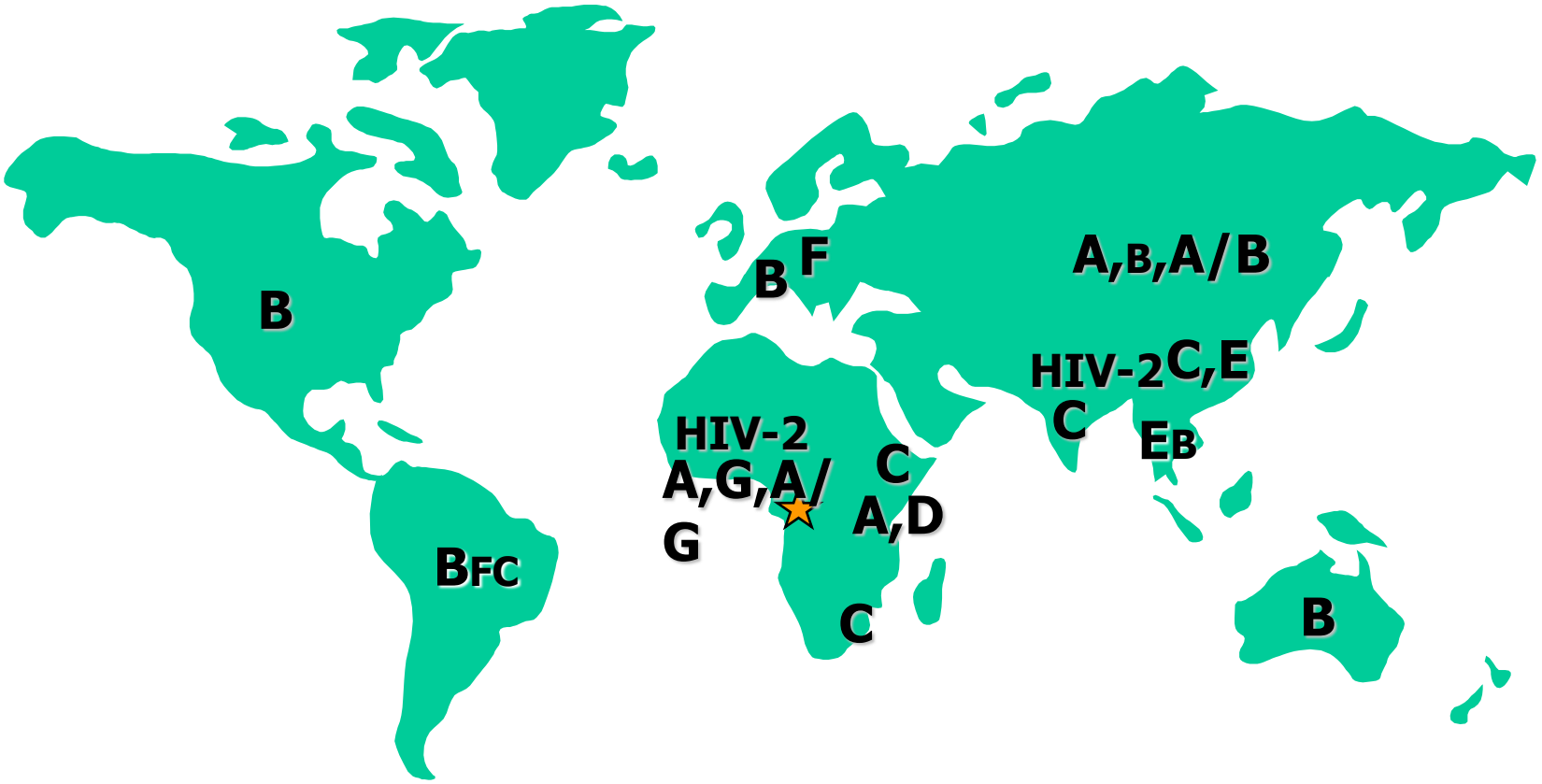


2006 TOTAL: 39,5 million

Children under 15 :
2.3 million (1,7-3,5)

Numbers not up to date

Geographic Distribution of HIV-1 Subtypes and HIV-2

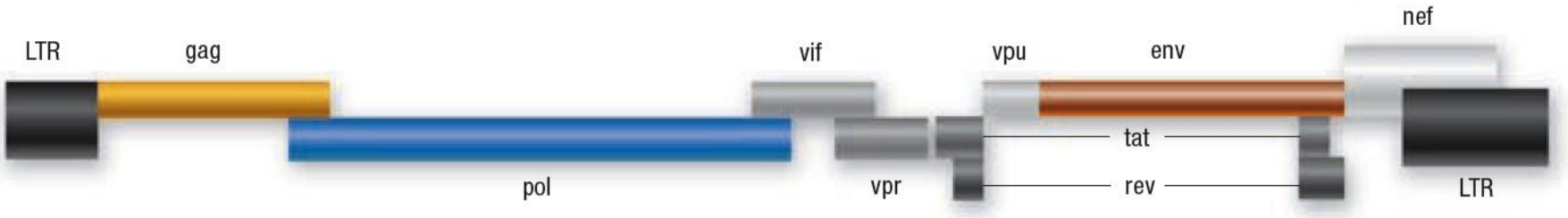


★ Subtypes A, B, C, D, "E", F, G, H, "I", J, K, CRFs, and untypable

CDC
Centers for Disease Control and Prevention

Human immunodeficiency virus type-1

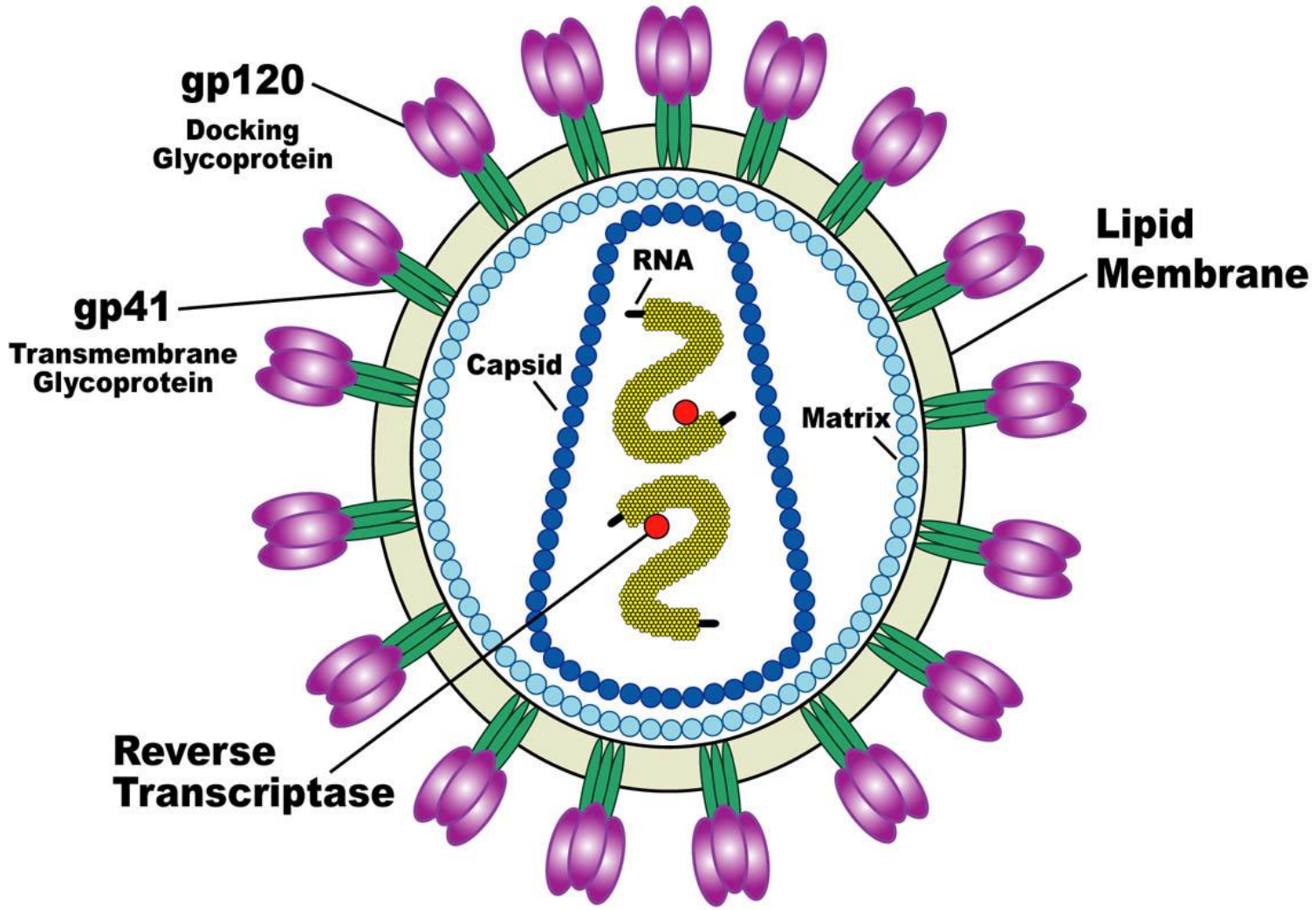
- **3 Structural genes (gag, pol and env)**
- **6 regulatory genes (vit, vpr, vpu, tat, rev and nef)**
- **LTR act as switches to control production of new viruses.**



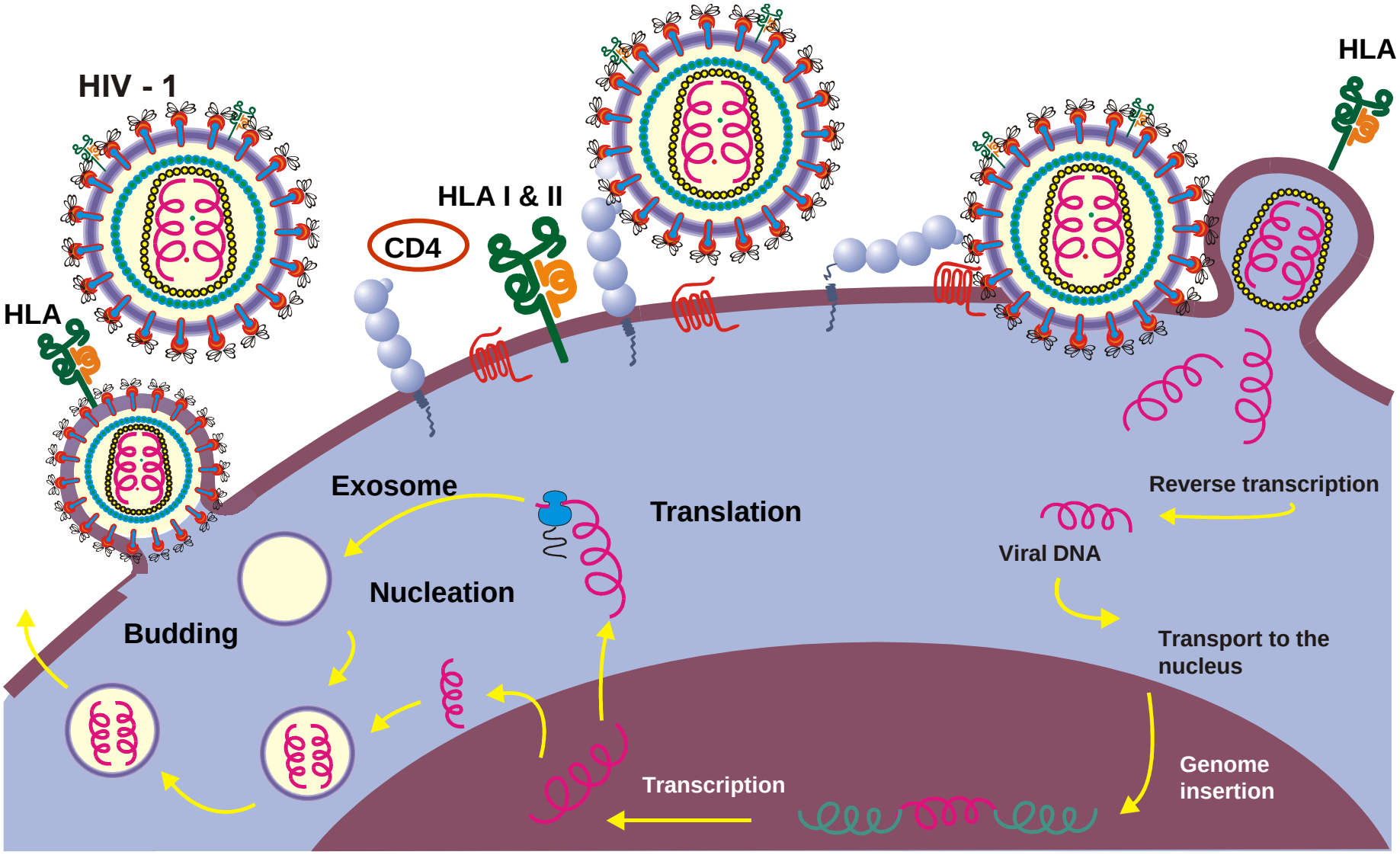
Human immunodeficiency virus type-1

- HIV is a retrovirus and has about 120nm in diameter.
- HIV contain 2 copies of positive single-stranded RNA that codes for the virus's nine genes
- The single-stranded RNA is tightly bound to nucleocapsid proteins and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase.
- HIV has an envelope which is taken from the membrane of a human cell. Embedded in the viral envelope are proteins from the host cell (MHC molecules).
- HIV has only 70 copies of a HIV env protein that protrudes through the surface of the virus particle.

Human immunodeficiency virus type-1



Human immunodeficiency virus type-1 cycle



Overall Objective of an AIDS Vaccine

- **Protect the individual from infection**
- **Protect or delay the individual from developing the disease**
- **Reduce virus in body fluids (e.g. genital) and decrease HIV transmission**
- **Reduce infection (transmission) of the population**

The Ideal HIV Vaccine

- **Induces cellular and humoral immune responses against virus-infected cells as well as conserved HIV sequences**
- **Induces antibodies that neutralize multiple strains of the virus and do not enhance HIV infection**
- **Does not induce autoimmune responses**
- **Induces local immunity at all entry sites (mucosal)**
- **Safe with long-lasting effects**

Current Model of HIV Vaccine Development

Pre-clinical studies

1. Development of HIV and SIV antigenic formulations → 2. Test HIV and SIV formulations in small animals → 3. GLP production of the antigens → 4. Test immunogenicity and/or protection of SIV e SHIV in non-human primates

4. Test immunogenicity and/or protection of SIV e SHIV in non-human primates ↕ 5. GMP production of the antigens

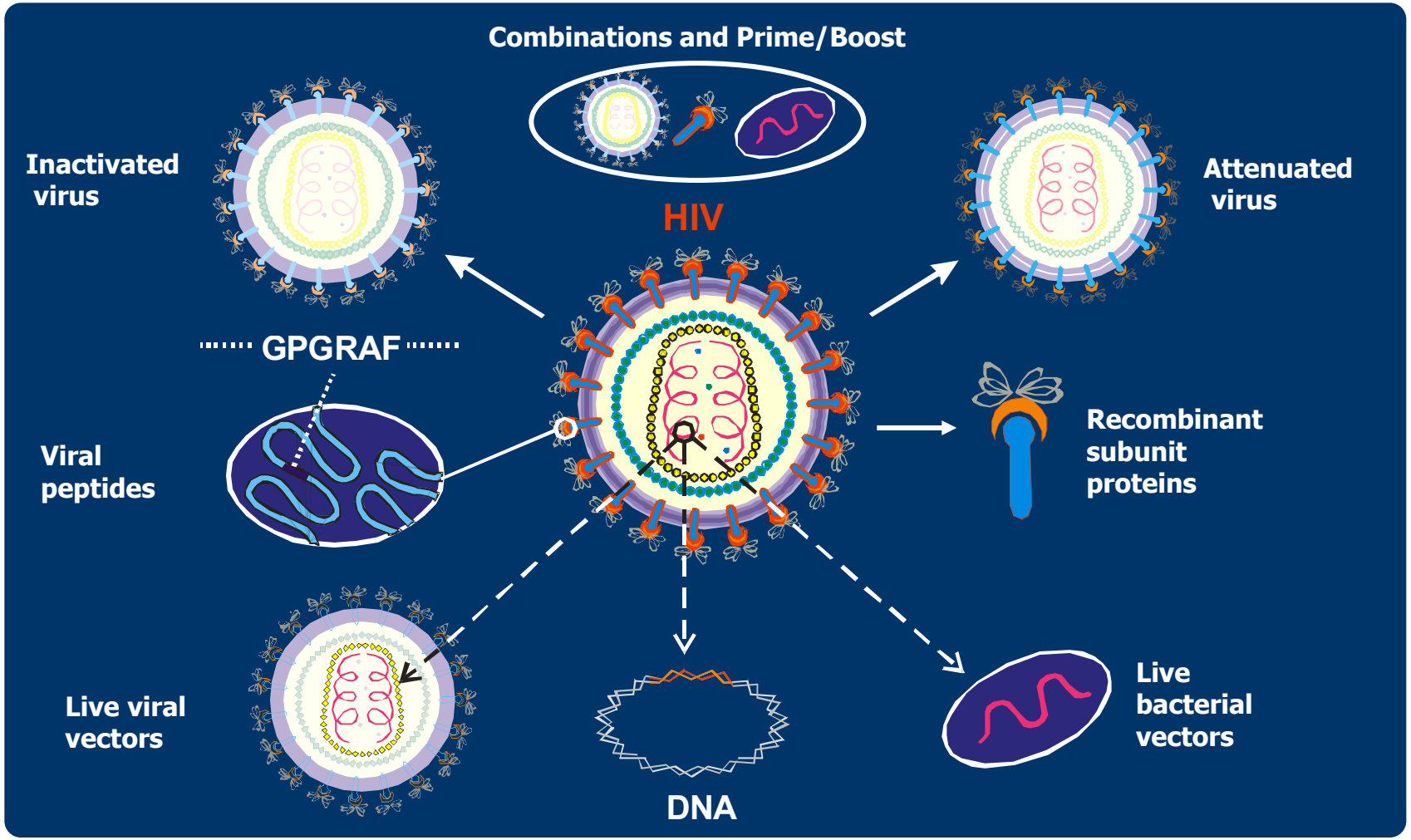
5. GMP production of the antigens → 6. Animal toxicity studies

Clinical studies

7. Phase I → 8. Phase II → 9. Phase III → 10. Phase IV

	7. Phase I	8. Phase II	9. Phase III	10. Phase IV
Primary objective:	Safety and immunogenicity	Safety and immunogenicity	Efficacy and protection	Safety and Efficacy
Subjects:	Health adult volunteers (10-100)	Target population (50-500)	Target population (1000-50,000)	Epidemiological surveillance

General overview of the strategies applied to development of anti - HIV/AIDS vaccine



Adapted from Basic Concepts in HIV Vaccinology; Gaston Djomand, MD; HVTN Core, FHCRC, October, 2003

DNA Vaccines – A Partial List

Clade B gag	MRK
A/B/C/env/gag/pol/nef Clade B	VRC
Env/gag/pol/nef/tat/rev	Emory
Env/gag/pol/nef/tat/rev Clade A/G	Emory
CTL epitopes of Clade A	Oxford/IAVI
CTL epitope multiclade	Epimmune
Env/gag/RT, nef/tat Clade C	SAAVI
Env (gp140) Clade B microparticles	Chiron
Env (gp140) Clade C microparticles	Chiron
Env + tat Clade B	ABL Corp.
Gag IL-12 Clade B	Wyeth
Gag IL-15 Clade B	Wyeth
Env/gag/pol Clade B	Univ of New S. Wales
Env/gag/pol Clade E	Univ of New S. Wales
Env/gag/pol/nef/IL-2 Clade B	VRC

Pox Virus Vectors

• ALVAC 1521 clade E env/gag-pol HXB-2	Aventis/WRAIR
• ALVAC clade A env/gag-pol HXB-2	Aventis/WRAIR
• MVA clade B env-LAI/gag-pol HXB-2	EuroVacc
• MVA clade B env/gag-tat-rev-nef RT (Wooster strain)	Therion
• MVA clade B env-ADA gp160/gag-pol HXB-2	B. Moss/NIAID
• MVA gag clade A + CTL epitopes	IAVI/Oxford
• MVA clade C env/gag RT-nef-tat	SAAVI
• MVA clade C env/gag pro HXB-2	EuroVacc
• MVA clade A/G env gp160/gag-pol HXB-2	B. Moss/NIAID
• MVA clade E	Walter Reed
• MVA CTL epitopes (multiclade)	Epimmune
• NYVAC clade B env-LAI/gag-pol HBx2	EuroVacc
• NYVAC clade C env/gag-pol	EuroVacc
• FPV clade B env/gag-tat-rev-nef RT	Therion
• FPV clade A/E+B env/gag	U of New S. Wales
• Vaccinia Poly Env 23 recombinant env vaccine	St. Judes ALVAC

Development of Licensed Vaccines

Vaccine	Discovery of etiologic agent	Vaccine developed or licensed in U.S.	Years elapsed
Typhoid	1884	1896	12 years
Pertussis	1906	1926	20 years
Polio	1908	1955	47 years
Measles	1953	1983	30 years
Hepatitis B	1965	1981	16 years
Rotavirus	1970	1998	28 years
Hepatitis A	1973	1995	22 years
Lyme Disease	1982	1998	16 years
HIV	1983	???	> 20 years

From Susan Buchbinder and Johathan Fuchs, S.F. Dept of Health

Why HIV is so variable?

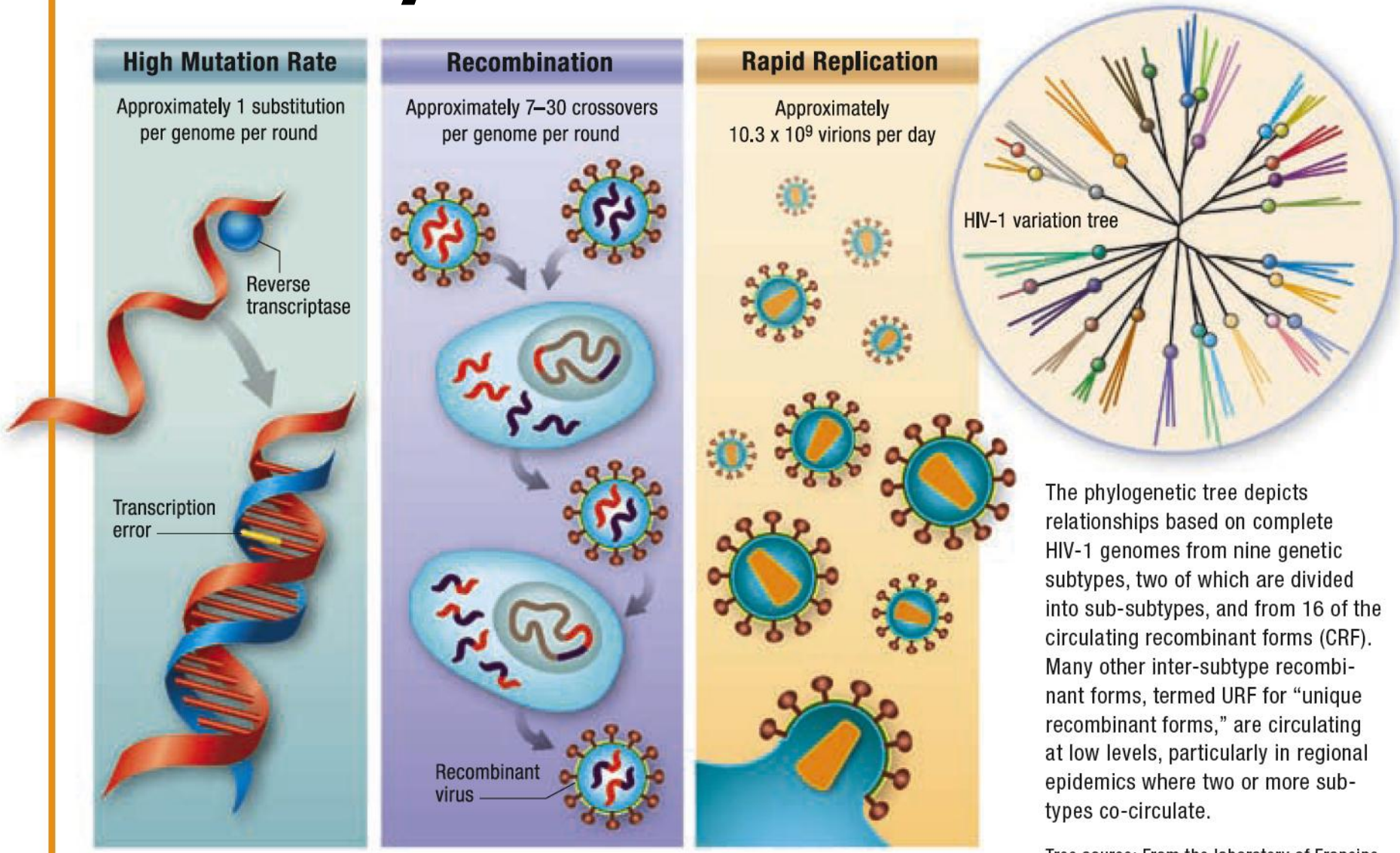


Figure 10 **Causes of HIV Variability and Impact on the Circulating Virus**

The phylogenetic tree depicts relationships based on complete HIV-1 genomes from nine genetic subtypes, two of which are divided into sub-subtypes, and from 16 of the circulating recombinant forms (CRF). Many other inter-subtype recombinant forms, termed URF for "unique recombinant forms," are circulating at low levels, particularly in regional epidemics where two or more subtypes co-circulate.

Tree source: From the laboratory of Francine McCutchan, Henry M. Jackson Foundation.

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PLoS MEDICINE: QUARTER-CENTURY OF PRIMATE RESEARCH FAILURE

"The only people who don't know in 2005 that animal research is irrelevant for human disease are those who don't understand it or those who benefit from it. Primates have failed as research models virtually whenever they have been used."

- **Forced smoking experiments, allowed cigarettes to be promoted widely**
- **Failure of a quarter-century of primate research on AIDS or the failure to identify even one useful AIDS drug from primate studies. VaxGen's AIDS vaccine (AIDSVAX) showed great success in primate studies, but was an abject failure in two human clinical trials.**
- **The false leads and dangerous vaccines produced during polio research (verified by Albert Sabin);**
- **The failure of primate studies to improve risks for birth defects and premature births;**
- **The failure of monkey studies to identify nonsteroidal anti-inflammatory drug cardiovascular risk.**

Pippin JJ (2005) PLoS Med 2(8): e278

Major problems with the HIV vaccine development model

1. No conclusive evidence of human immunity to HIV
2. Poorly defined correlates of protection
3. High cost of pre-clinical development, requires development of SIV antigens as surrogate for challenge protection models
4. Poor correlation of the SIV/SHIV non-human primate model with HIVAIDS human disease.=
5. Very long and costly efficacy studies (phase III)
6. Several difficult ethical issues regarding clinical design of the phase III studies.

Scientific challenges of an AIDS vaccine

Virus

- **Hypervariability**
- **Cell-cell transmission**
- **Genome integration**
- **Impair key immunological functions**

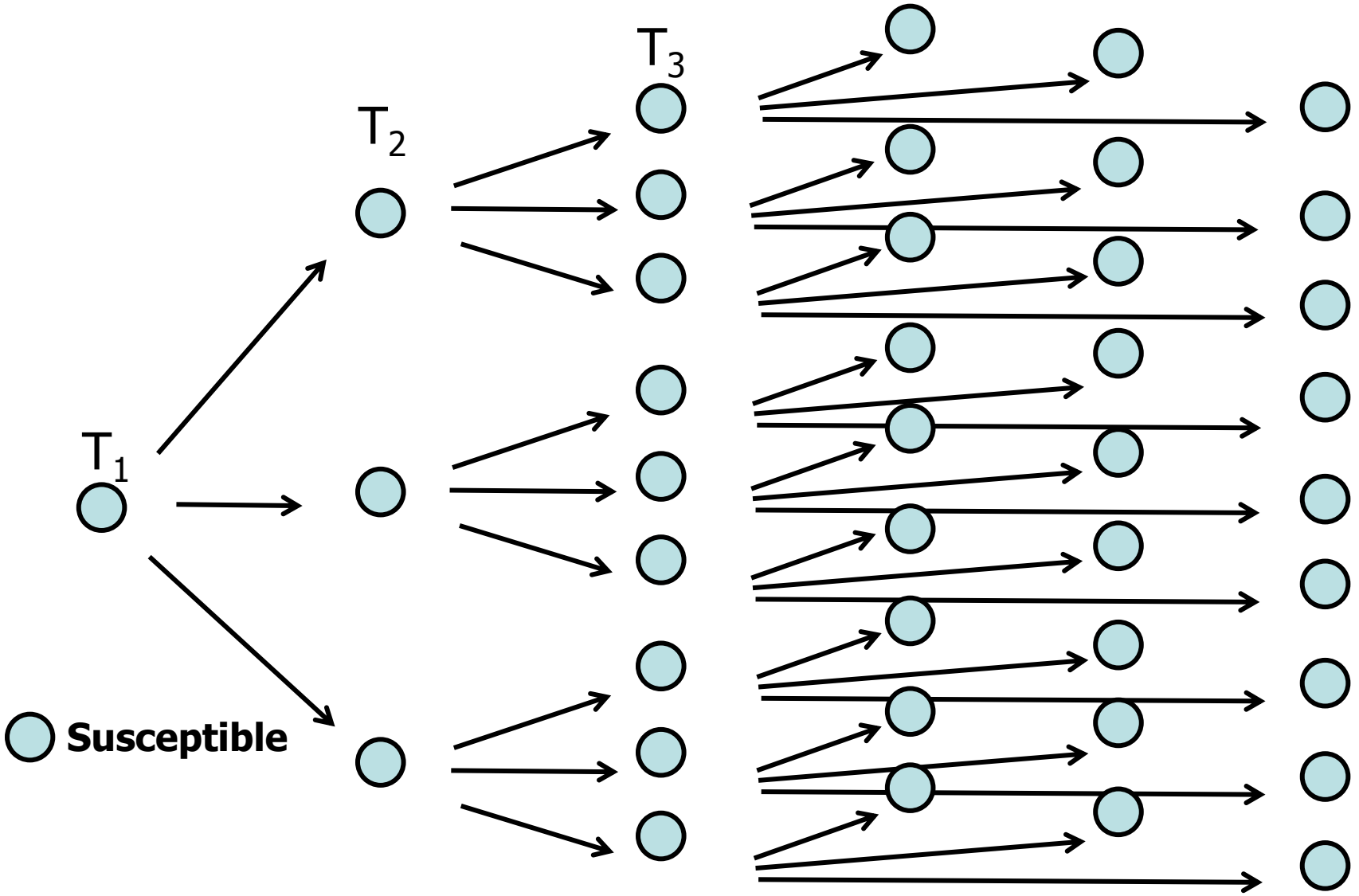
Immune responses

- **Natural immune responses do not clear the virus**
- **Lack of correlates of protection**
- **Role of innate immunity poorly defined**
- **Required protective epitopes undefined**
- **Lack of proven animal models**

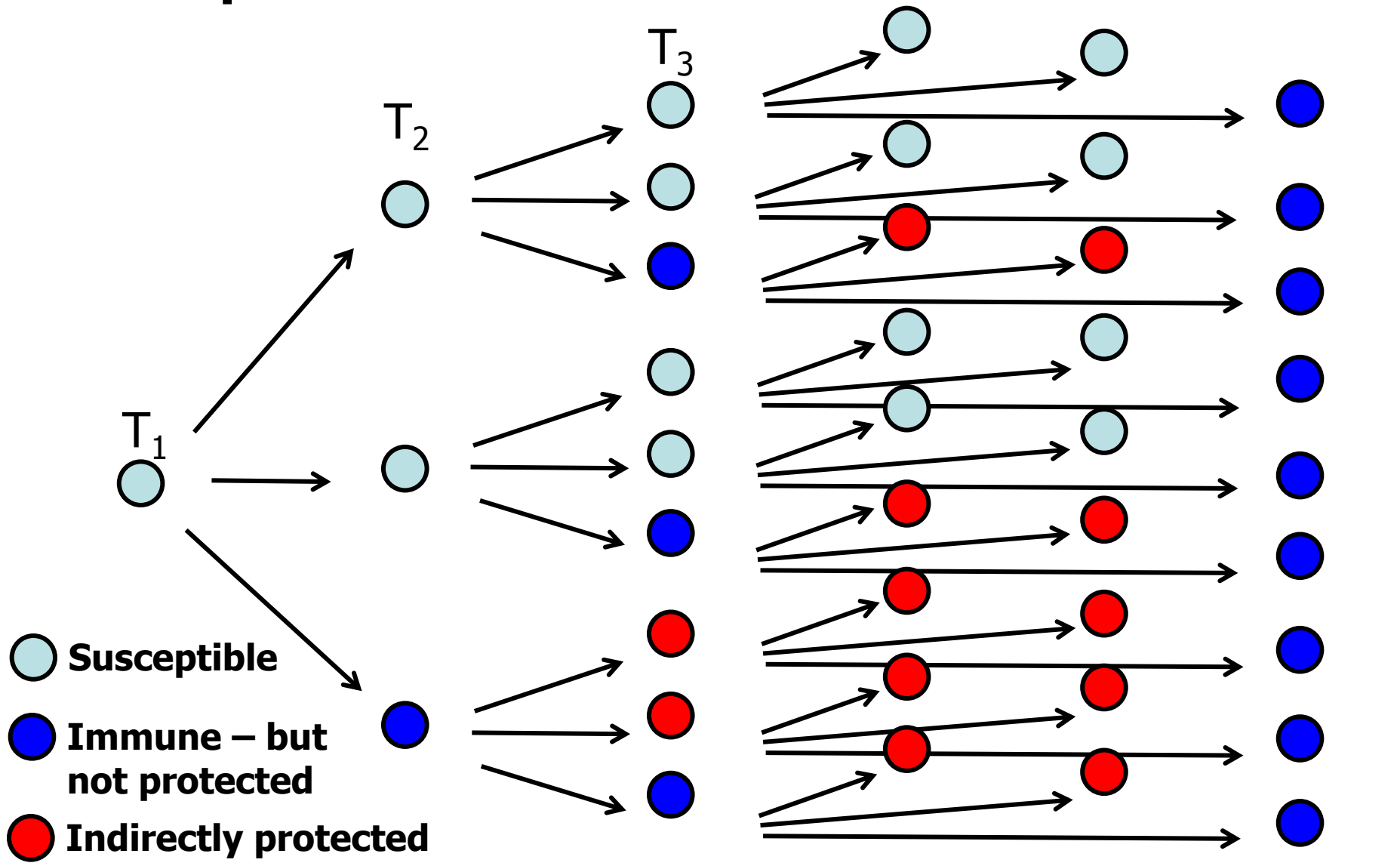
An HIV Vaccine is Possible?

- **Transmission is relatively inefficient (<1% contact)**
- **Natural or innate immunity can be elicited**
- **Highly exposed uninfected individuals have been reported**
- **Vaccines have shown some protection in animal studies**

Spread of Infection: All Susceptible



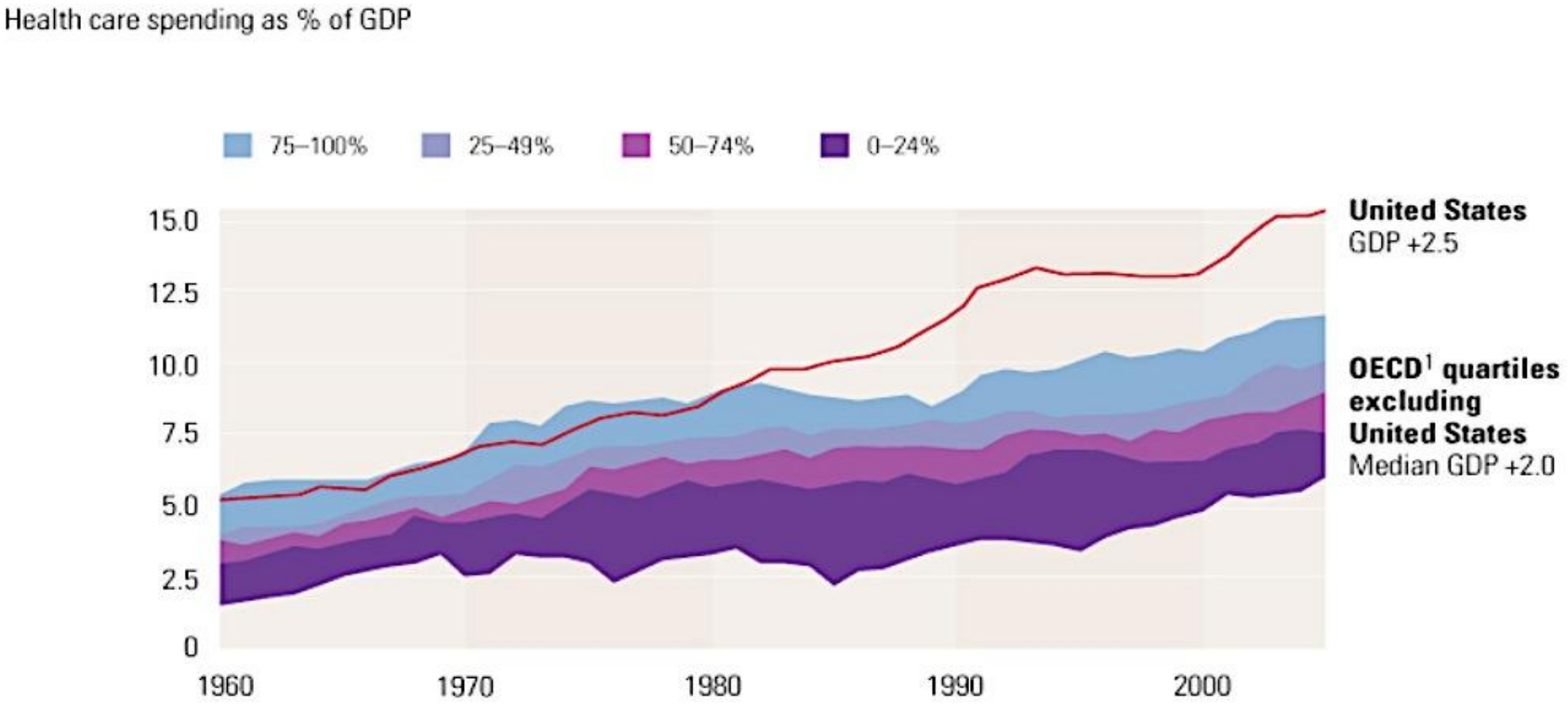
Spread of infection: 1/3 Immune



What's Needed? - Innovation

- **Innovation on antigen design**
- **Innovation on pre-clinical vaccine development**
- **Innovation on vaccine clinical testing**
- **Innovation on enabling the development of more HIV vaccine research in developing countries**
- **A new vaccine development paradigm**

Health care outstripped GDP



Translational Approach

Patient

Population

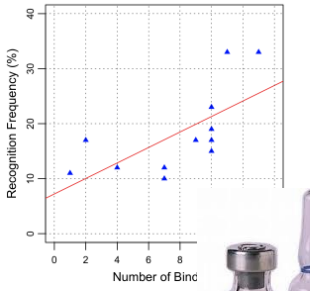
T1

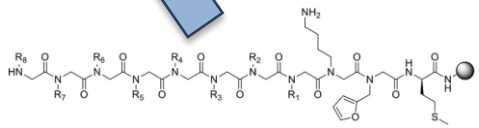
T2

Discovery

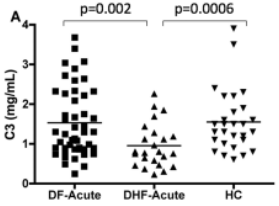
Transmission control

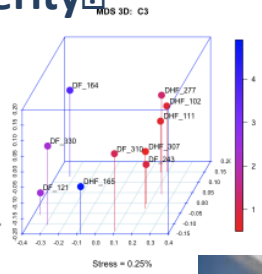
T-Cell Immunity





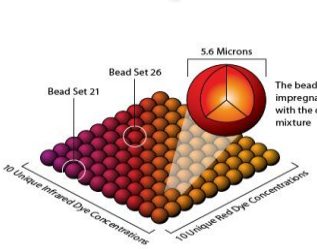
Disease Severity

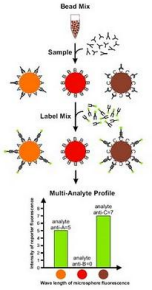




B-Cell Immunity

Hemobrás





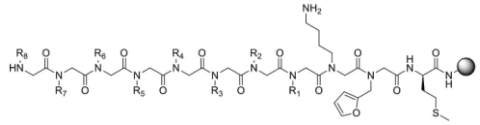
Incidence;
Efficacy;
HIV Recency

BILL & MELINDA GATES foundation

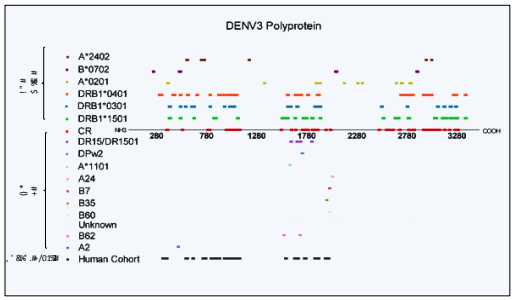
Diagnostics;
Vaccination (CYD);
Dengue Infection

SANOFI PASTEUR

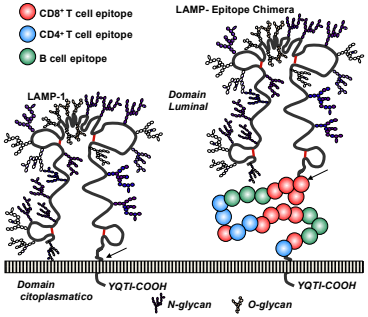
B-cell epitope discovery



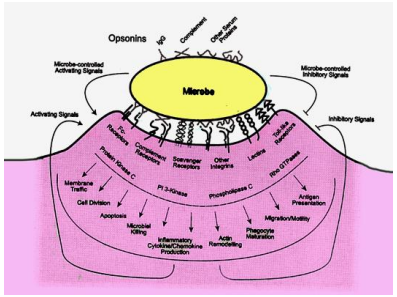
T-cell epitope discovery



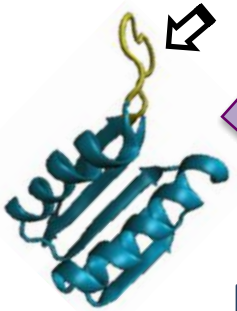
T-cell epitope LAMP



PRR Agonists



B-cell epitope -Top7



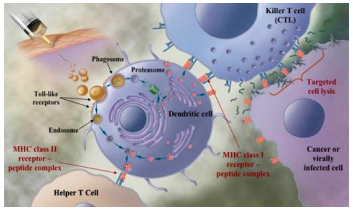
Immune Epitopes

Vaccines

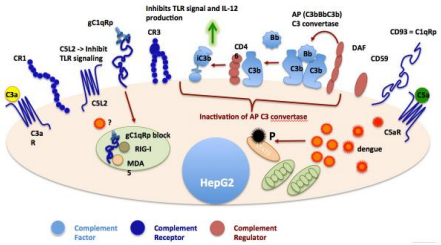
Antigen presentation

Adjuvants

Mucosal response

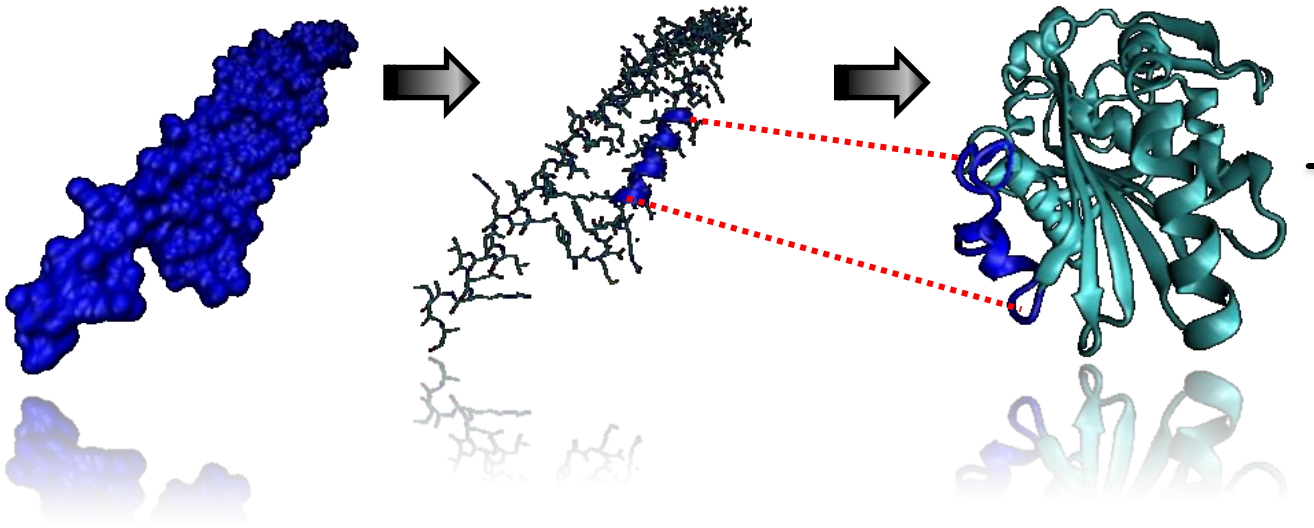


Complement receptors



Concept

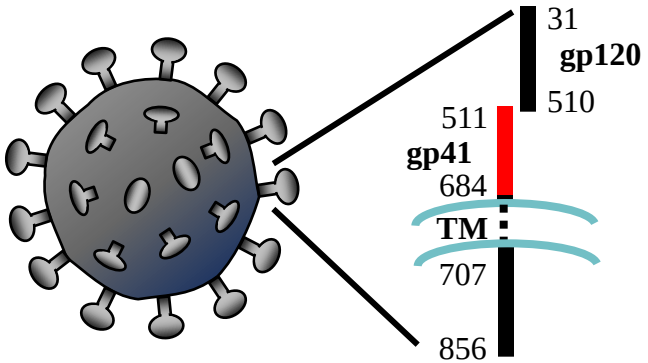
Protein grafting



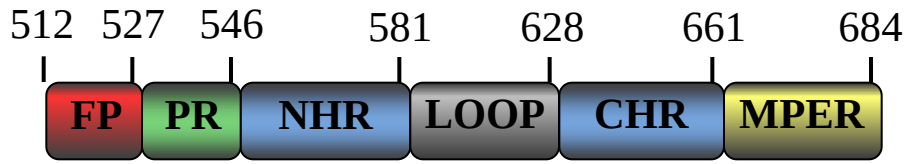
- Molecular Dynamics Simulation
- Structural characterization
- Immunological characterization

Target epitopes

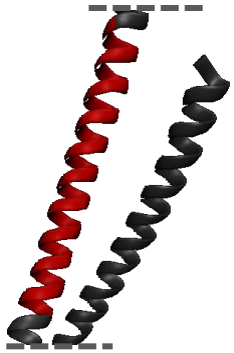
HIV-1



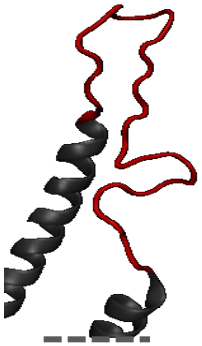
gp41 N-terminal



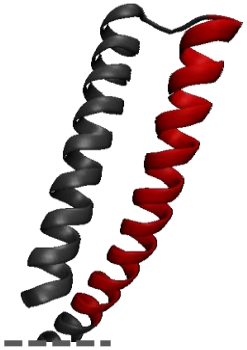
Secondary structure assignment



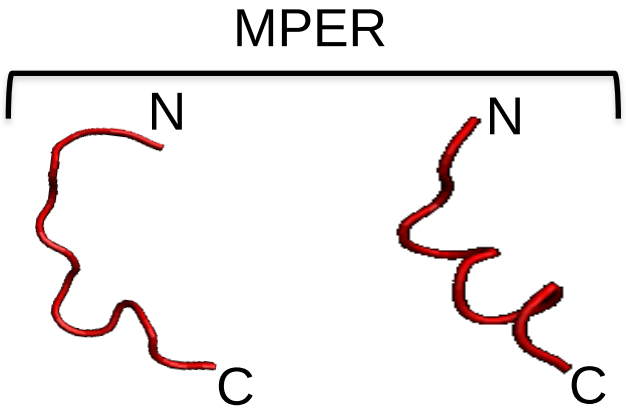
NHR
(1ENV)



Loop
(1IF3)



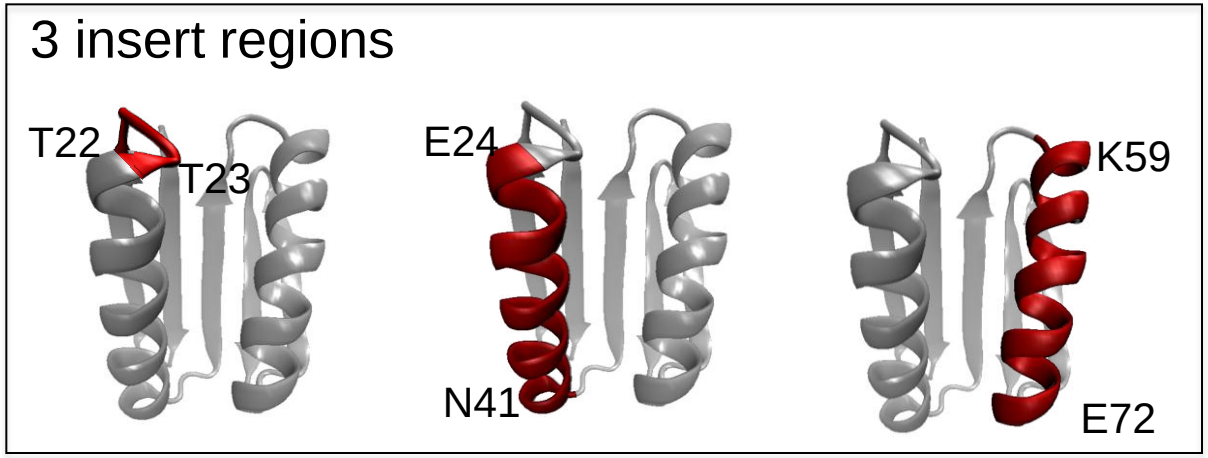
CHR
(3K9A)

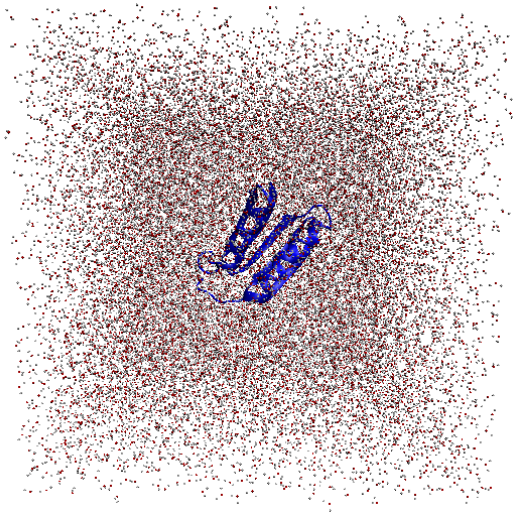


2F5
(1TJI)

4E10
(1TZG)

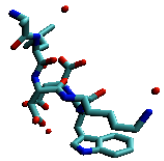
Epitope scaffold modeling and Molecular Dynamics Simulation



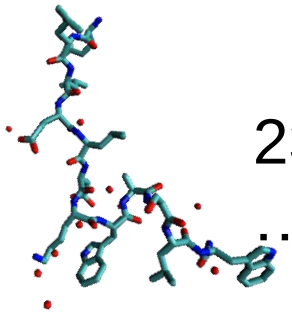


GROMOS 96 53a6 Force Field.
Data production was carried out for 50ns.

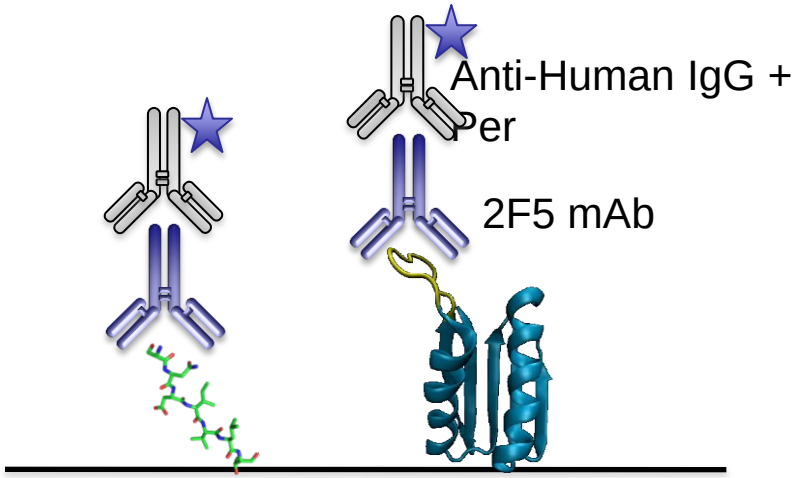
Immunological Characterization of Top7_E2F5

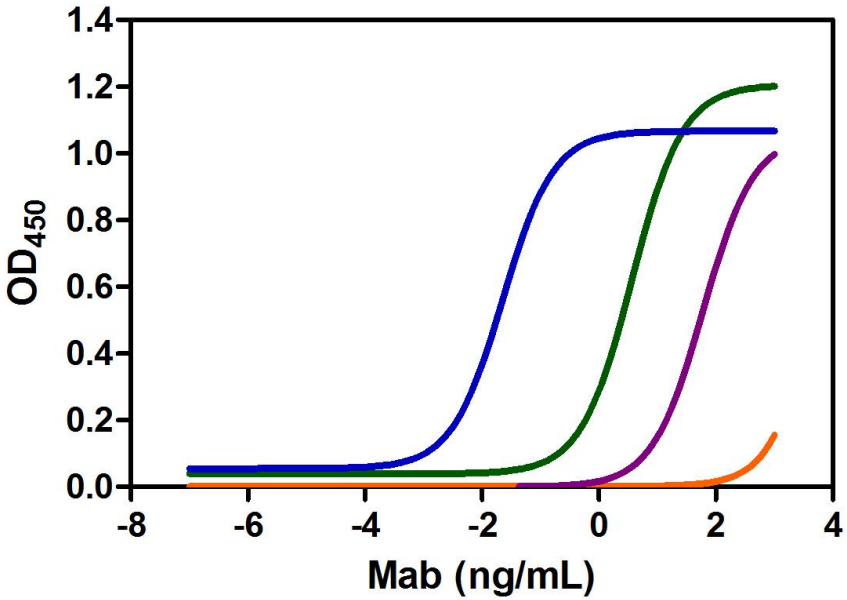


9-mer (ELDKWASL)

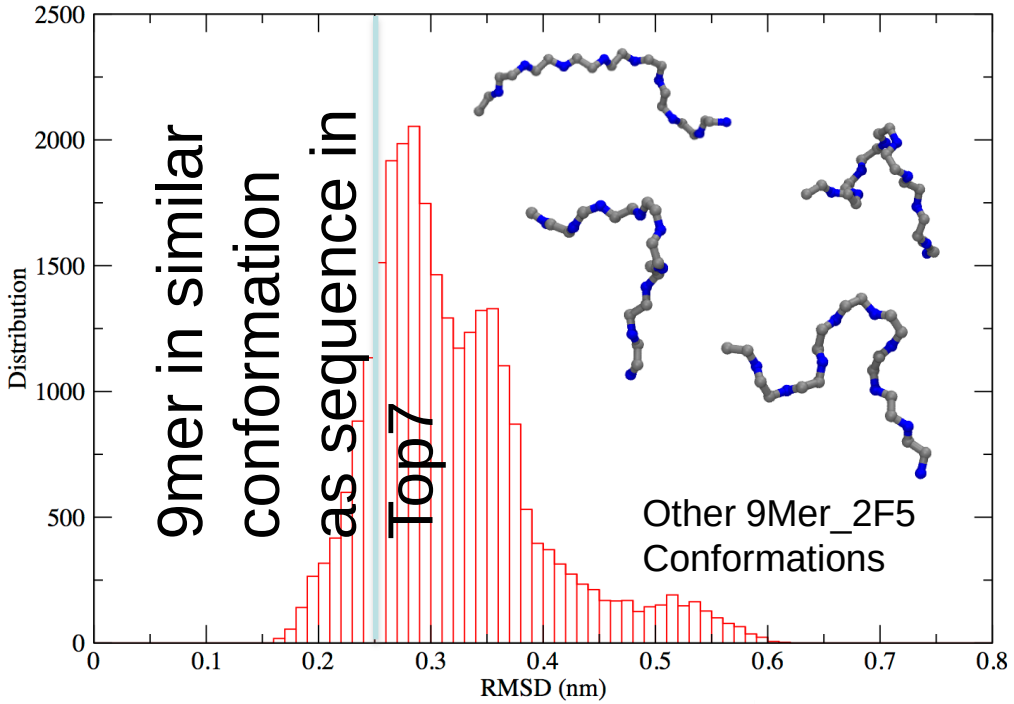


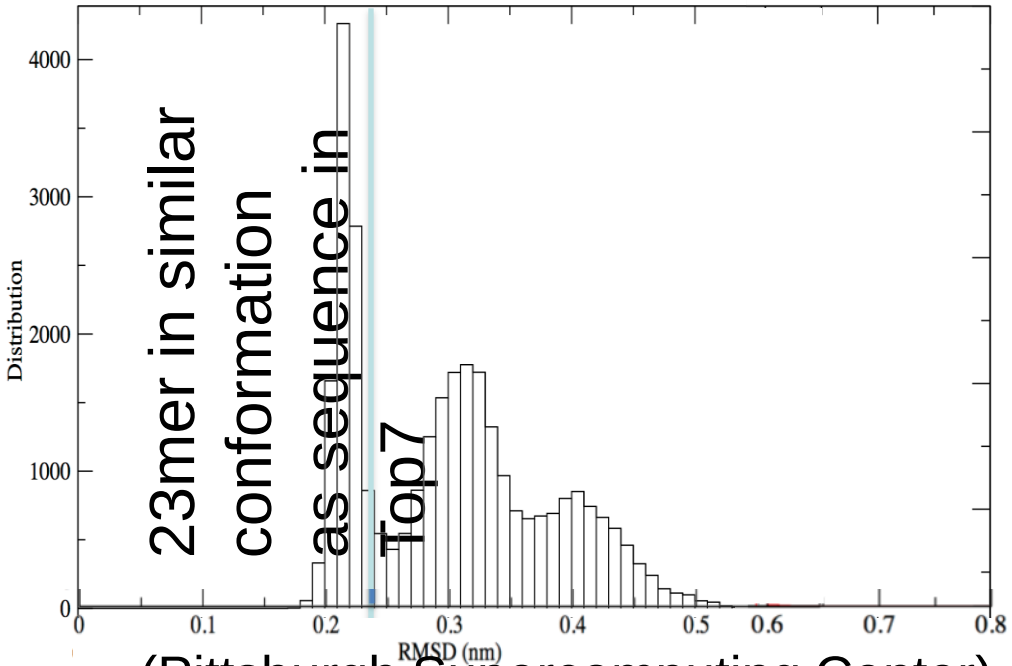
23-mer (MPER)
…ELDKWASL…





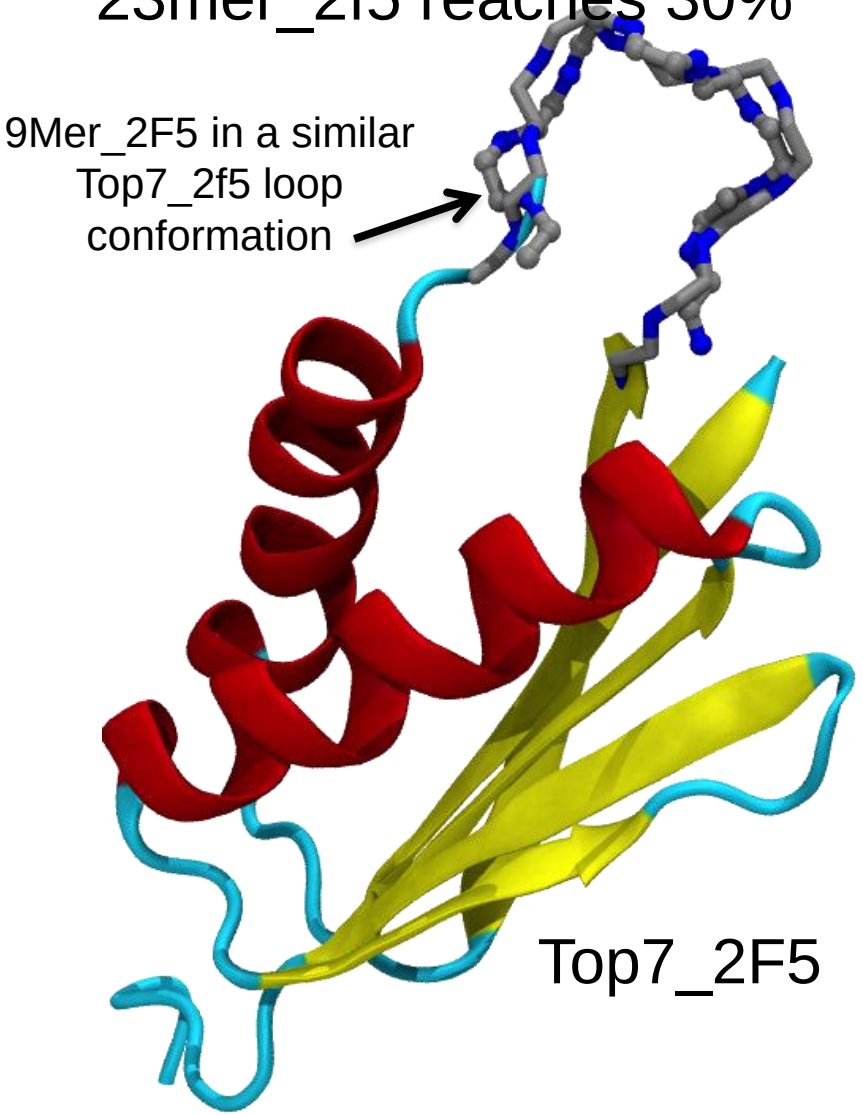
Top7_Original
Top7_E2F5 (EC50 = 0.036 nM)
MPER (EC50 = 3.954 nM)
E2F5 (EC50 = 59.74 nM)



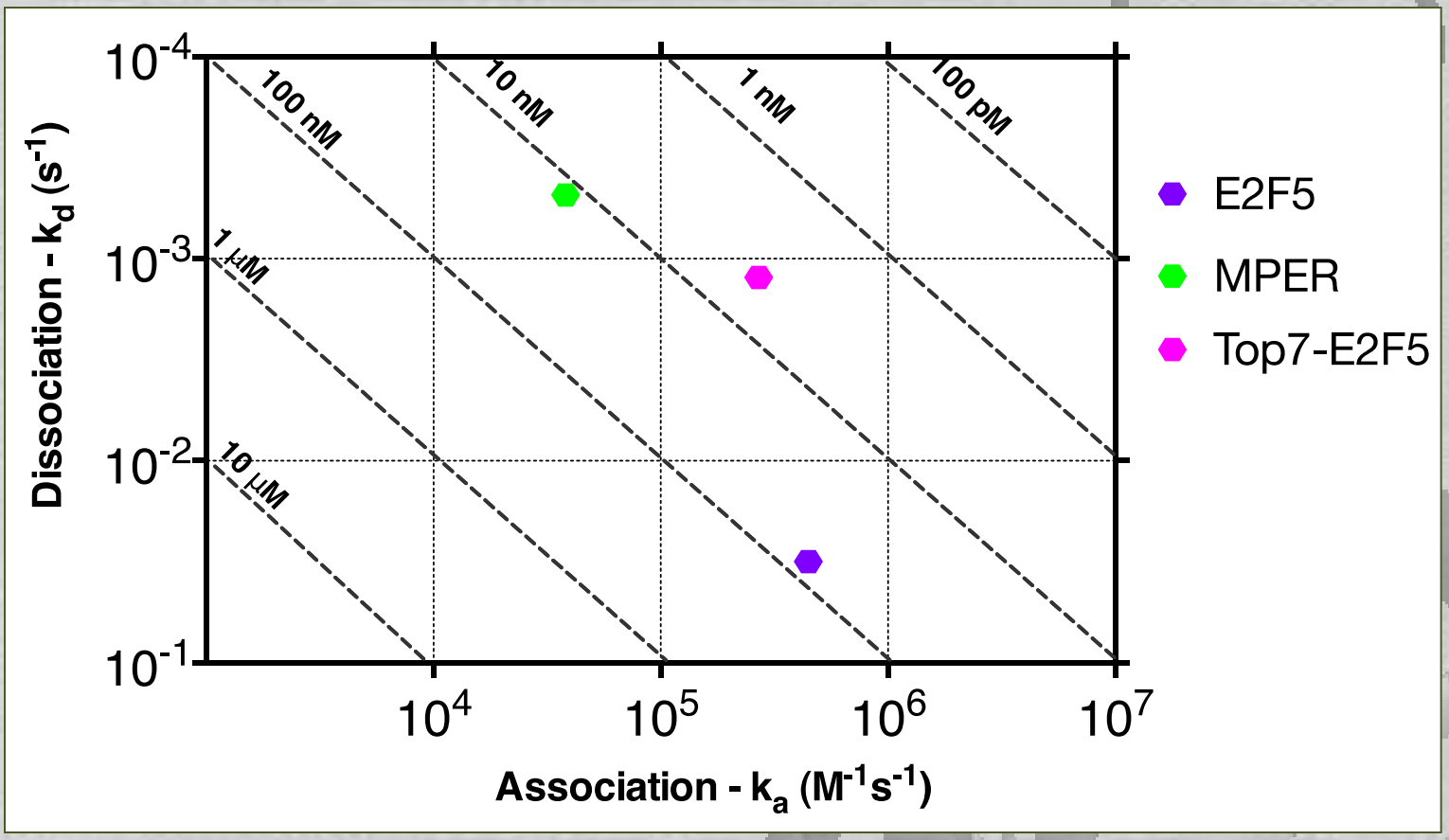


(Pittsburgh Supercomputing Center)

9Mer_2F5 is found 12% of the Time in a Similar Conformation, while 23mer_2f5 reaches 30%

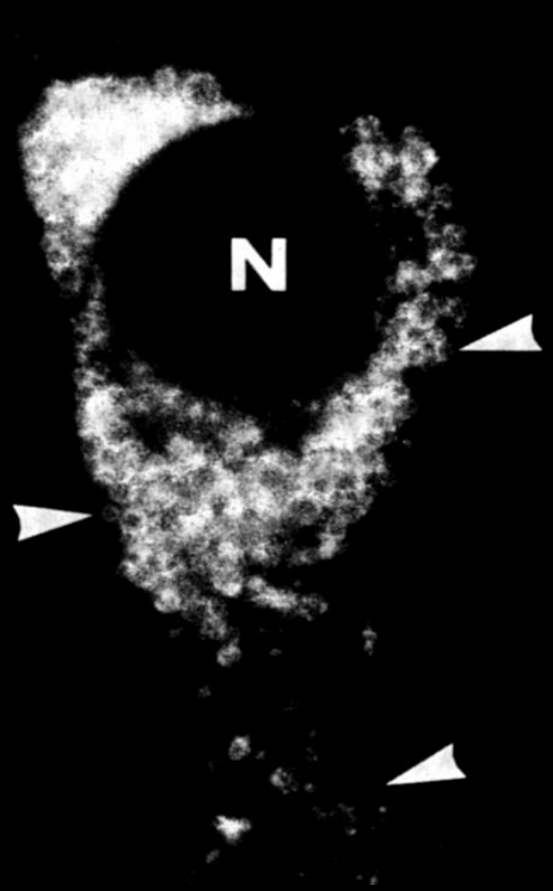


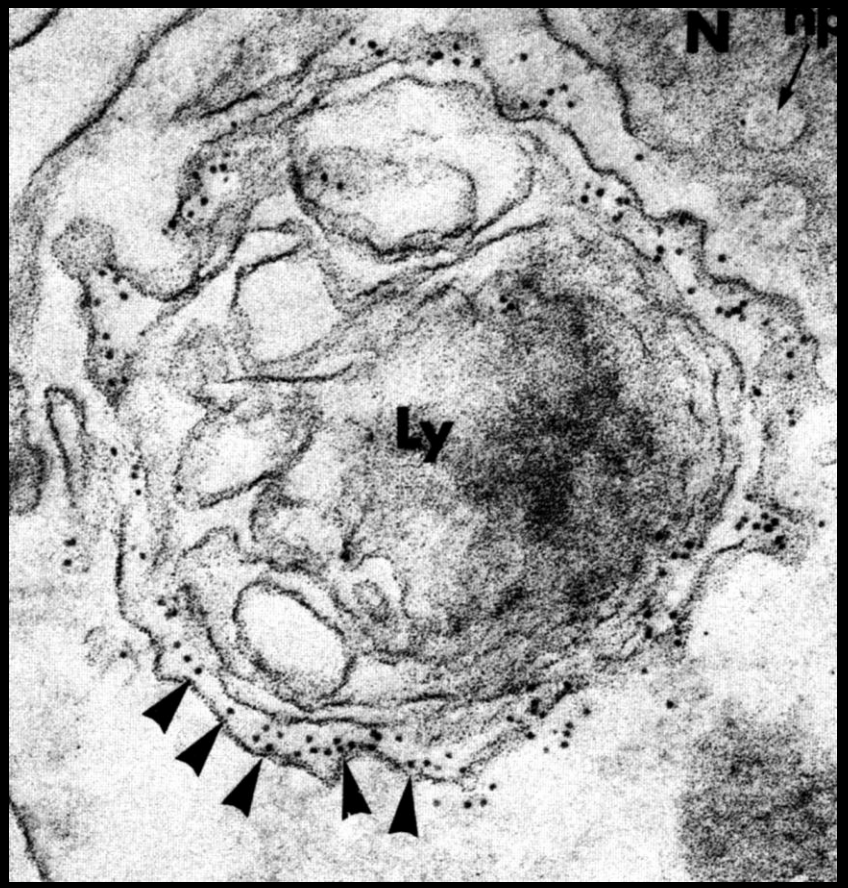
Kinetics map



Analyte	K_{on}(1/Ms)	K_{off} (1/s)	KD (Affinity) (M)	Chi^2
Top7_E2F5	4.97e5	6.98e-4	1.4e-9 (1log)	0.526
9-mer (E2F5)	4.47e5	0.0315	7.06e-8	0.727

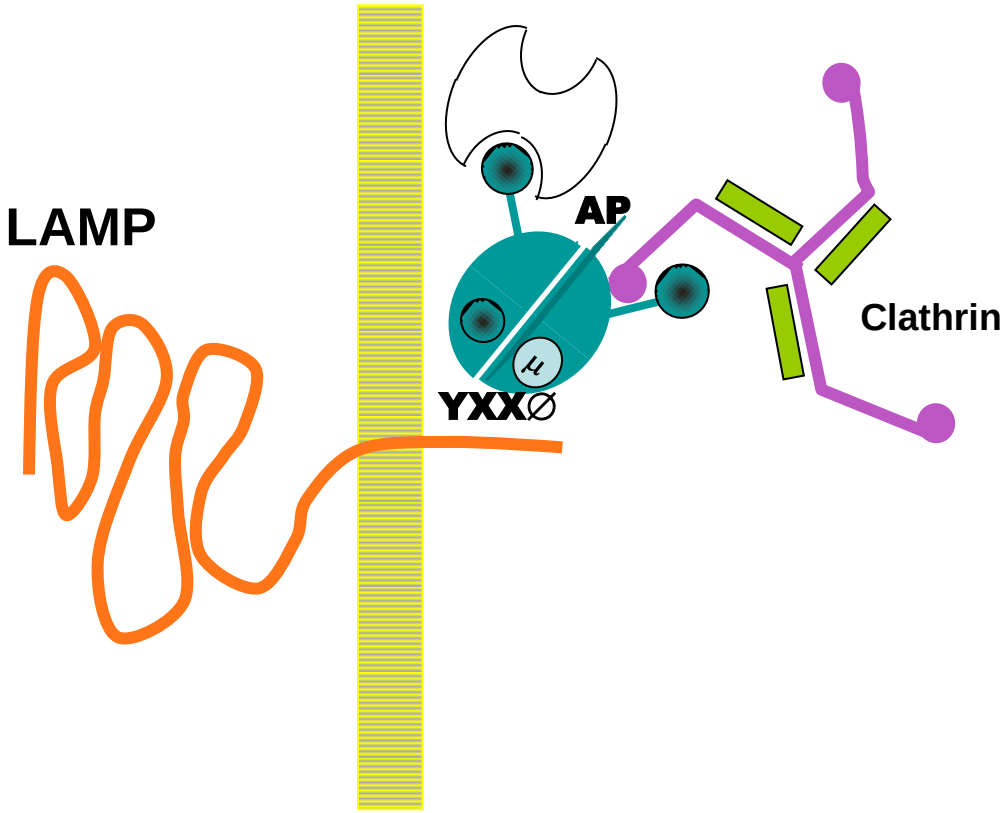
Lysosome-associated membrane protein (LAMP-1)





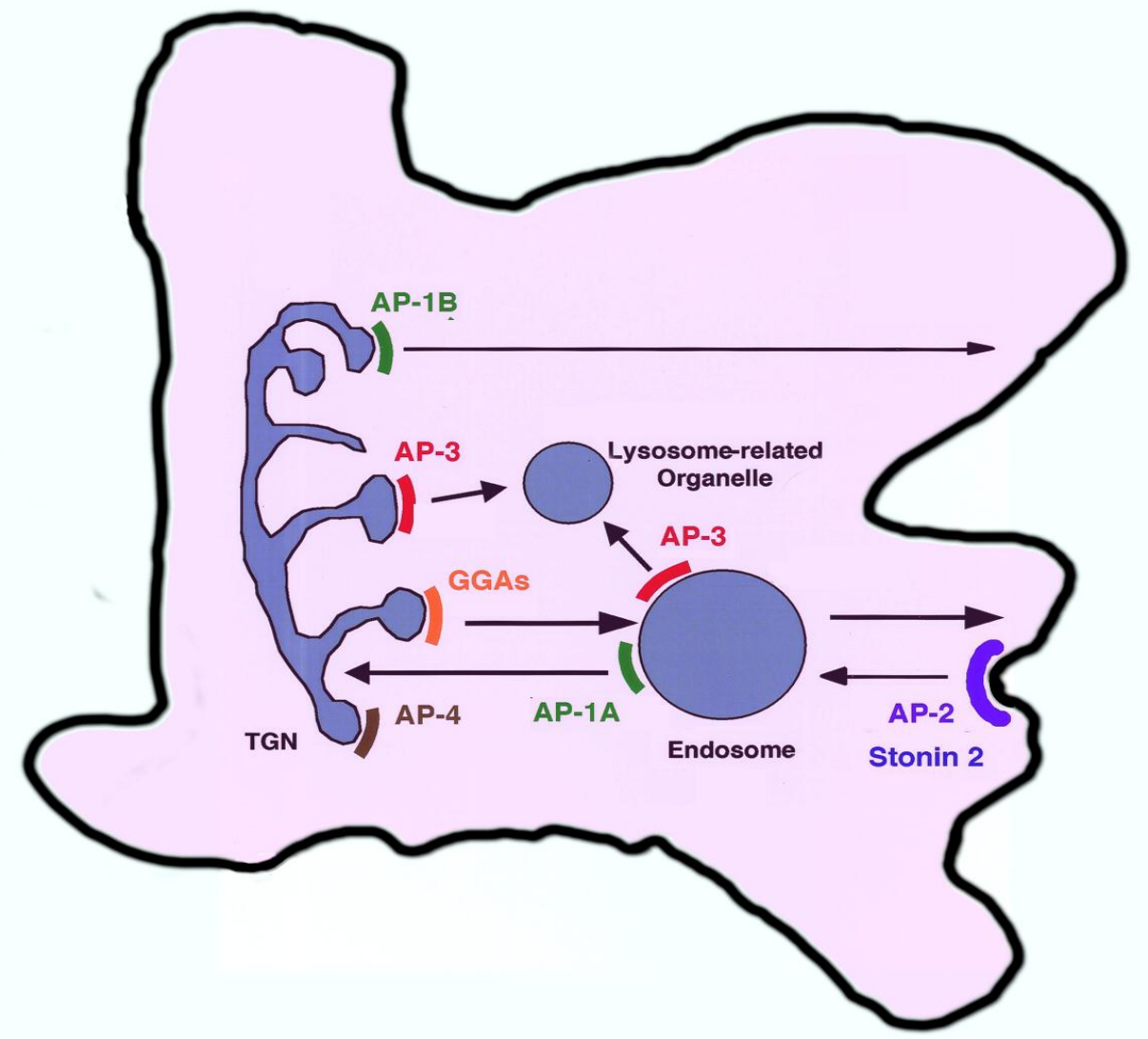
Chen et al, J Cell Bio ,101:85, 1985

Adaptor-proteins: vesicle formation, cargo selection and sorting



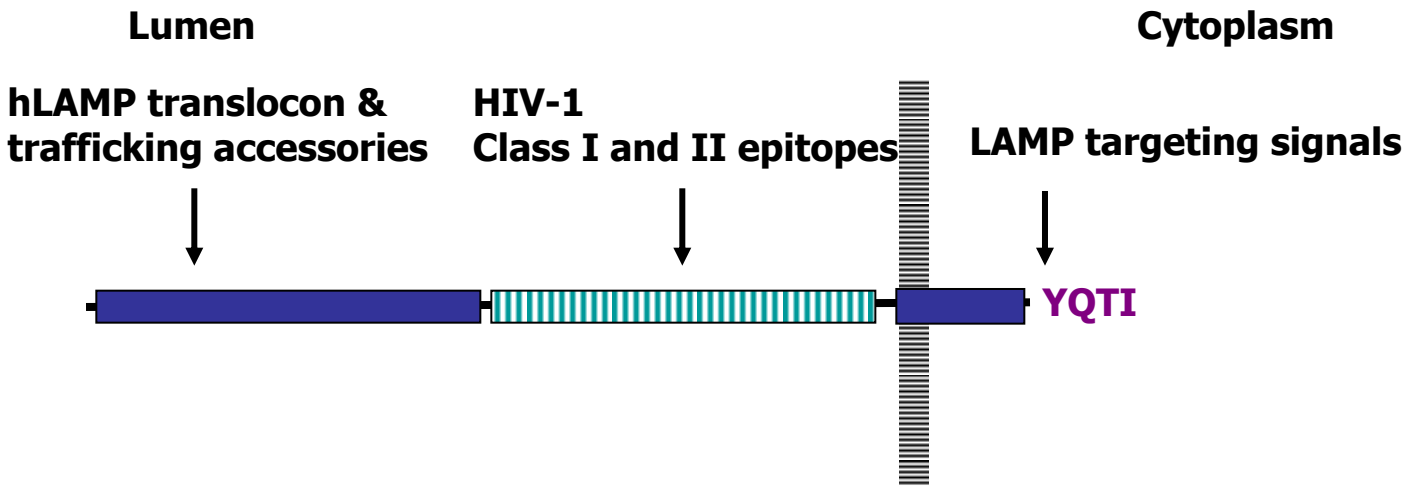
Adapted from "M. Robinson and J. S. Bonifacino *Cur. Op. in Cell Bio*. 2001 444-453

Adaptor-proteins and cell sorting

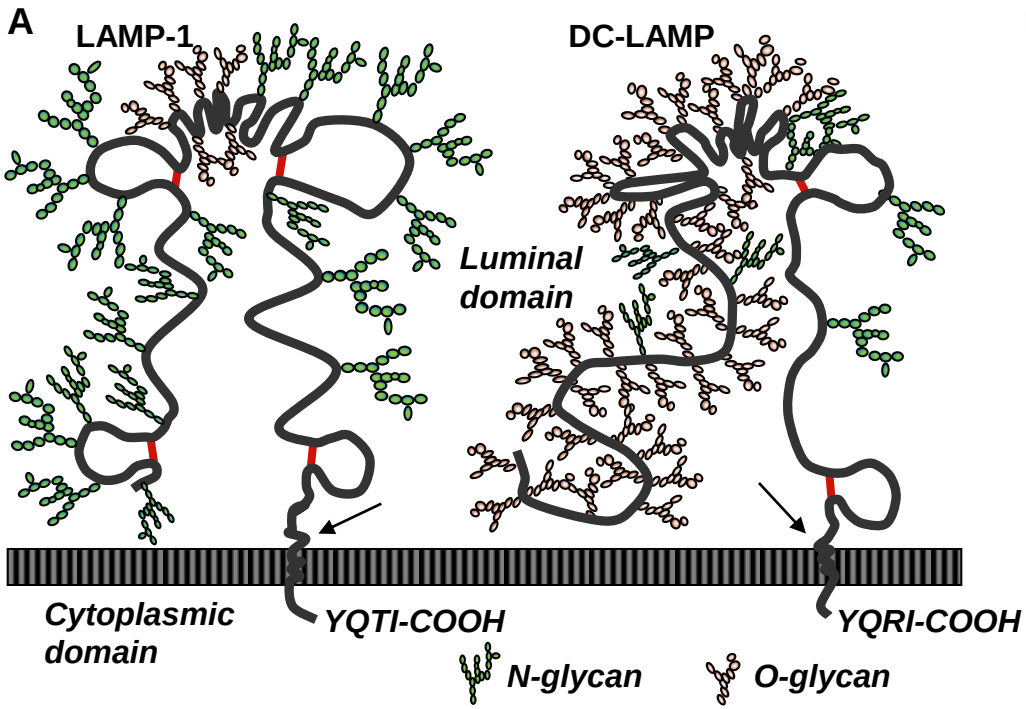


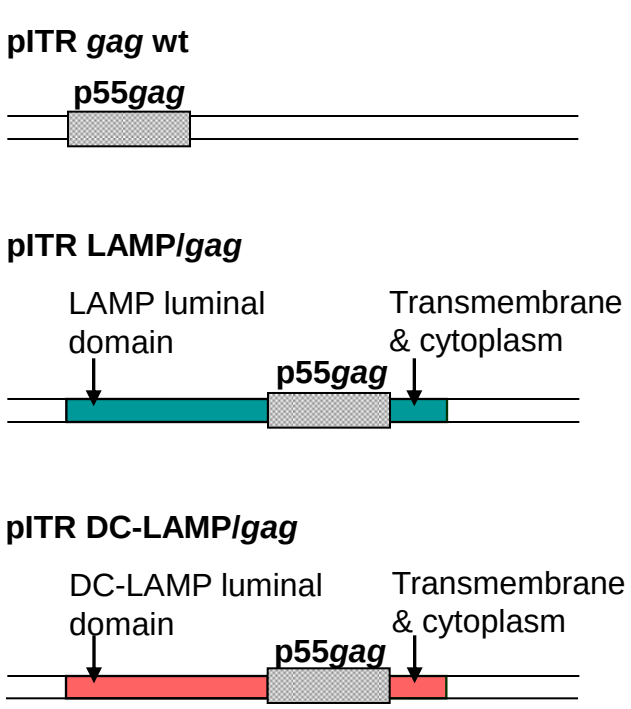
Adapted from "M. Robinson and J. S. Bonifacino *Cur. Op. in Cell Bio*. 2001 444-453

Human LAMP/Gag chimera DNA plasmid vaccine: MHC II compartment targeting as a molecular adjuvant

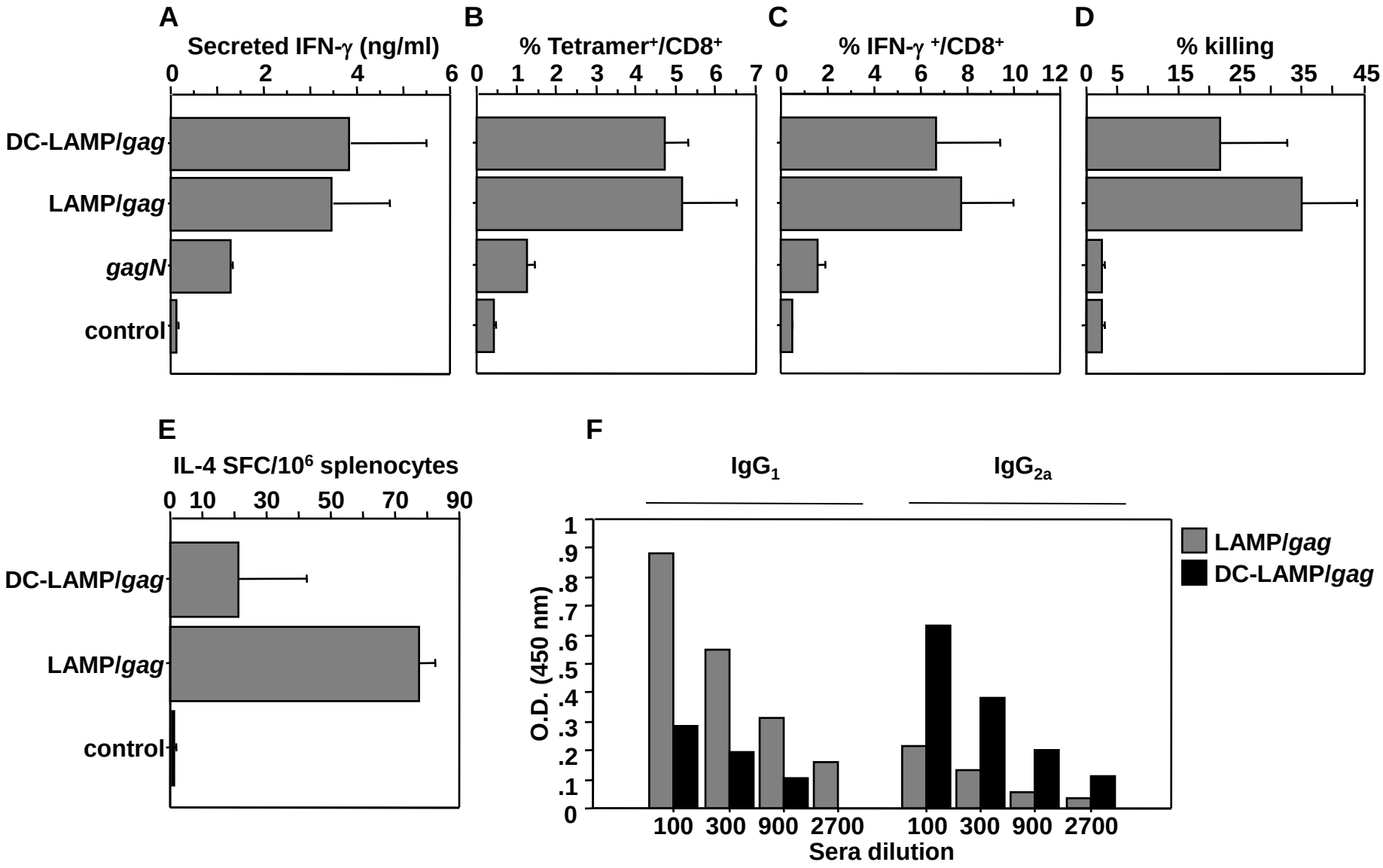


MIIC Targeting with LAMP and DC-LAMP

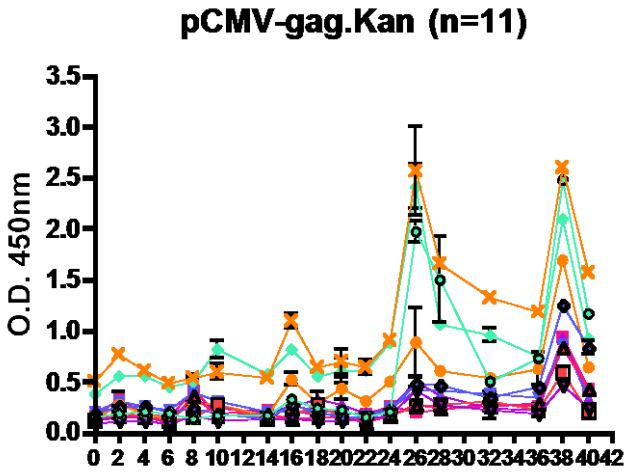


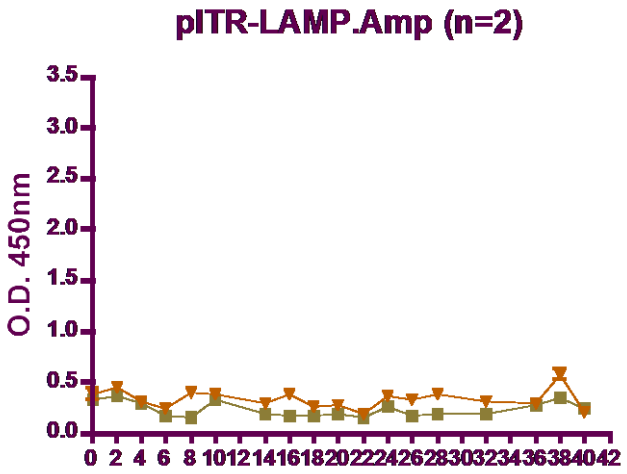


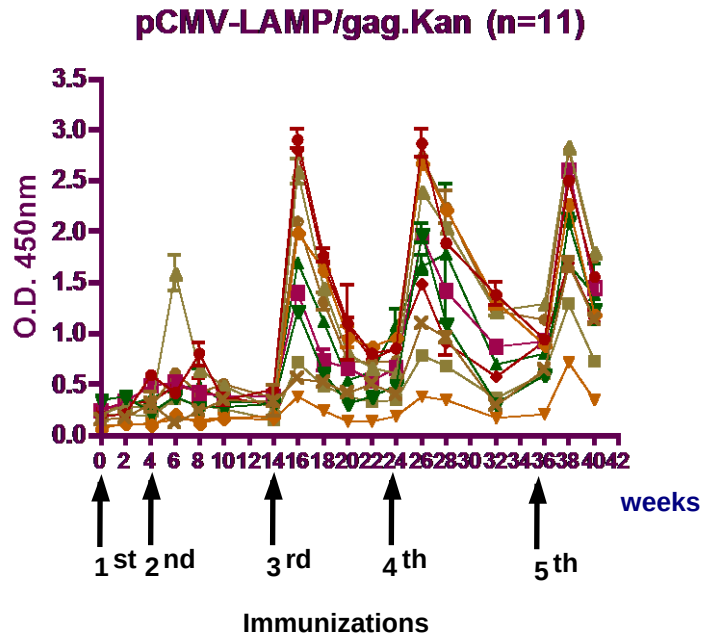
DC-LAMP/Gag and LAMP Immune responses

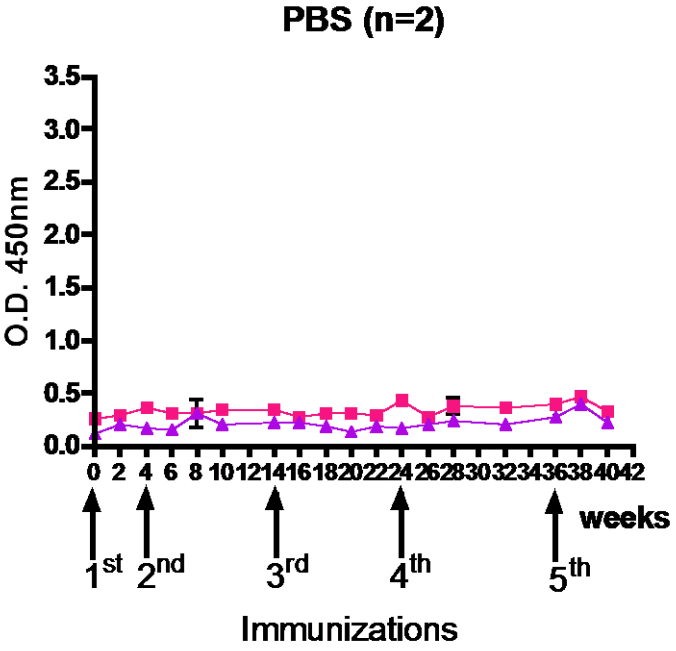


Strong humoral response in individual rhesus macaques (dilution 1:100)

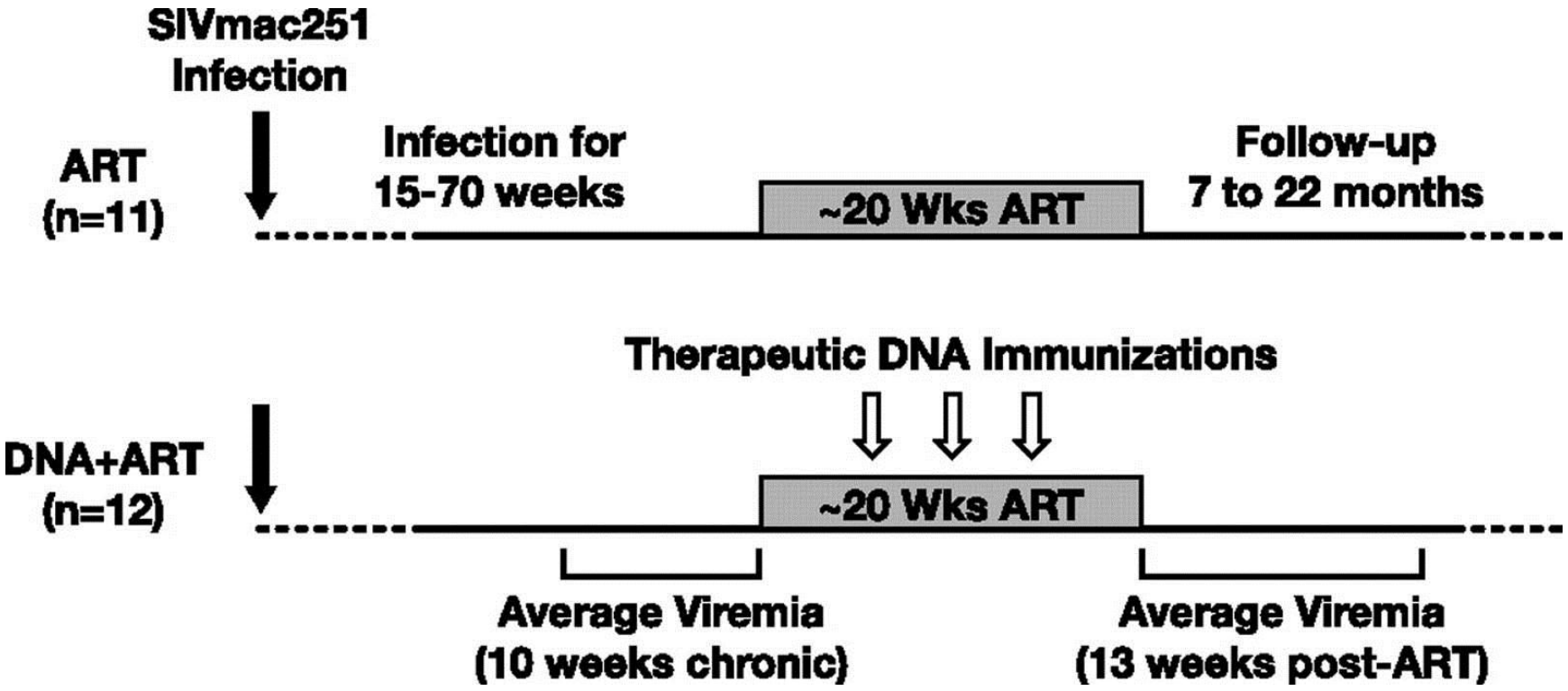






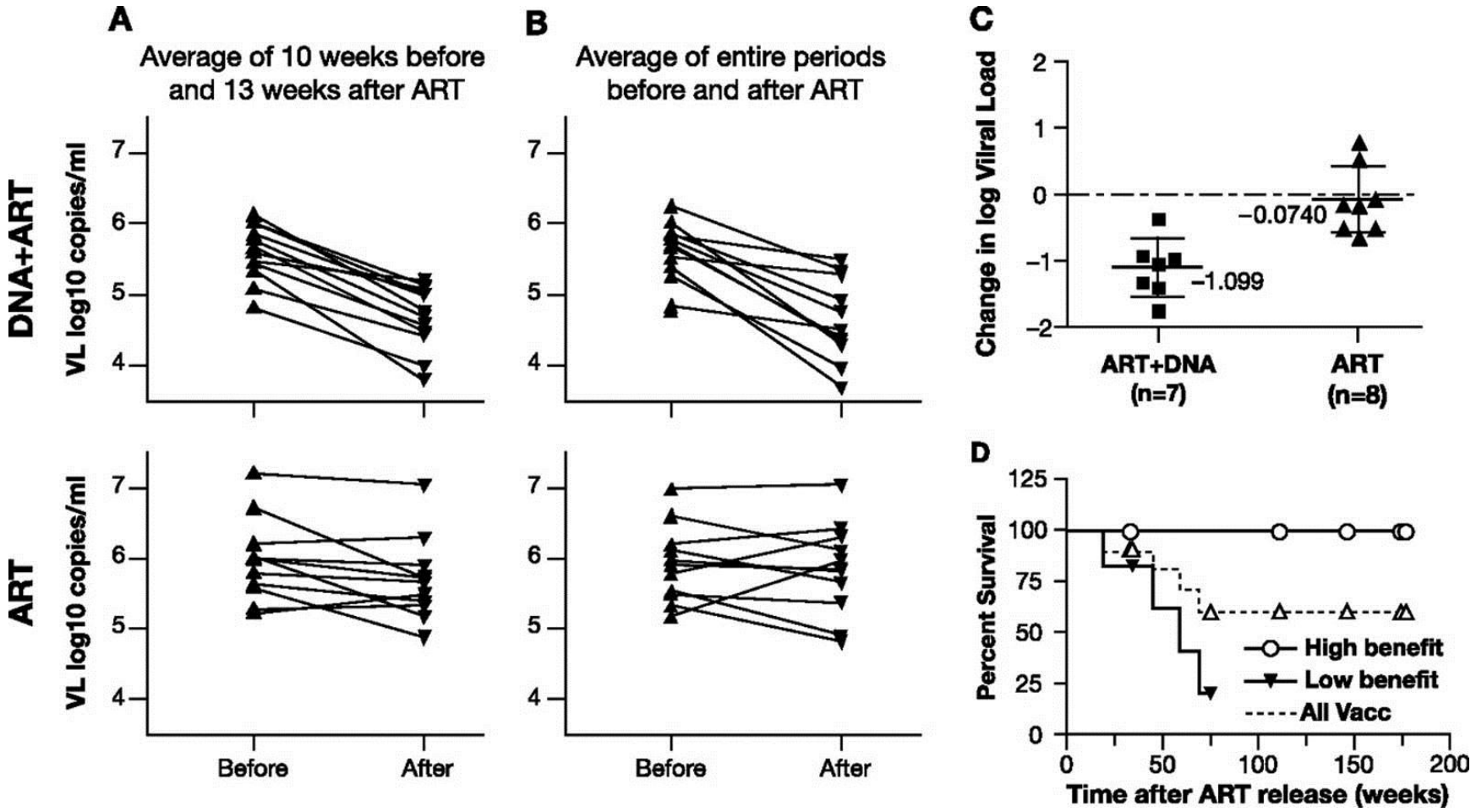


Long lasting control and lack of pathogenicity of the attenuated Rev-independent SIV in rhesus macaques.



J Virol. 2007 Feb;81(4):1972-9. von Gegerfelt at all

Long lasting control and lack of pathogenicity of the attenuated Rev-independent SIV in rhesus macaques.



J Virol. 2007 Feb;81(4):1972-9. von Gegerfelt at all