



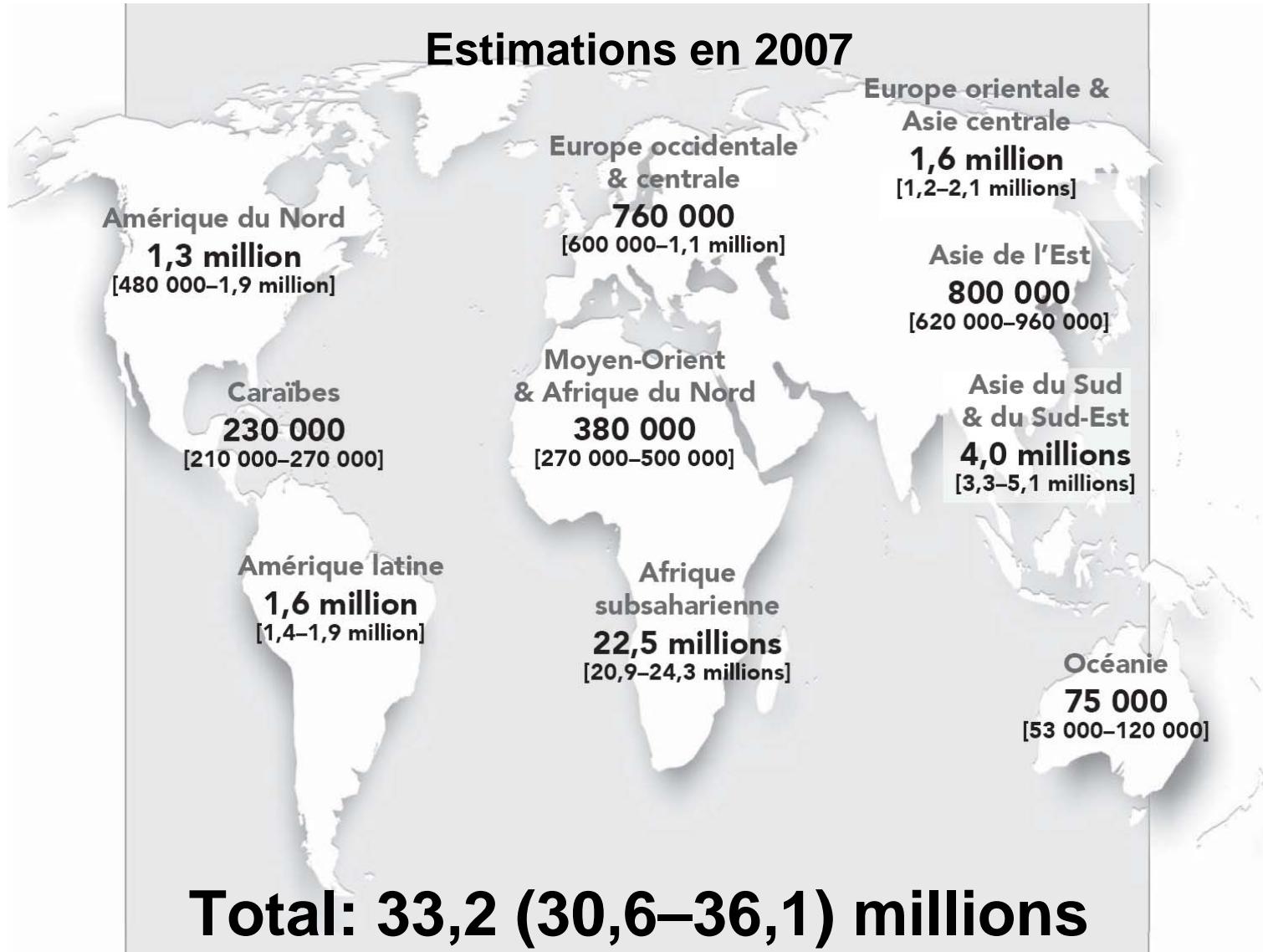
VIH : stratégies vaccinales innovantes

Roger LE GRAND

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(iMETI)*

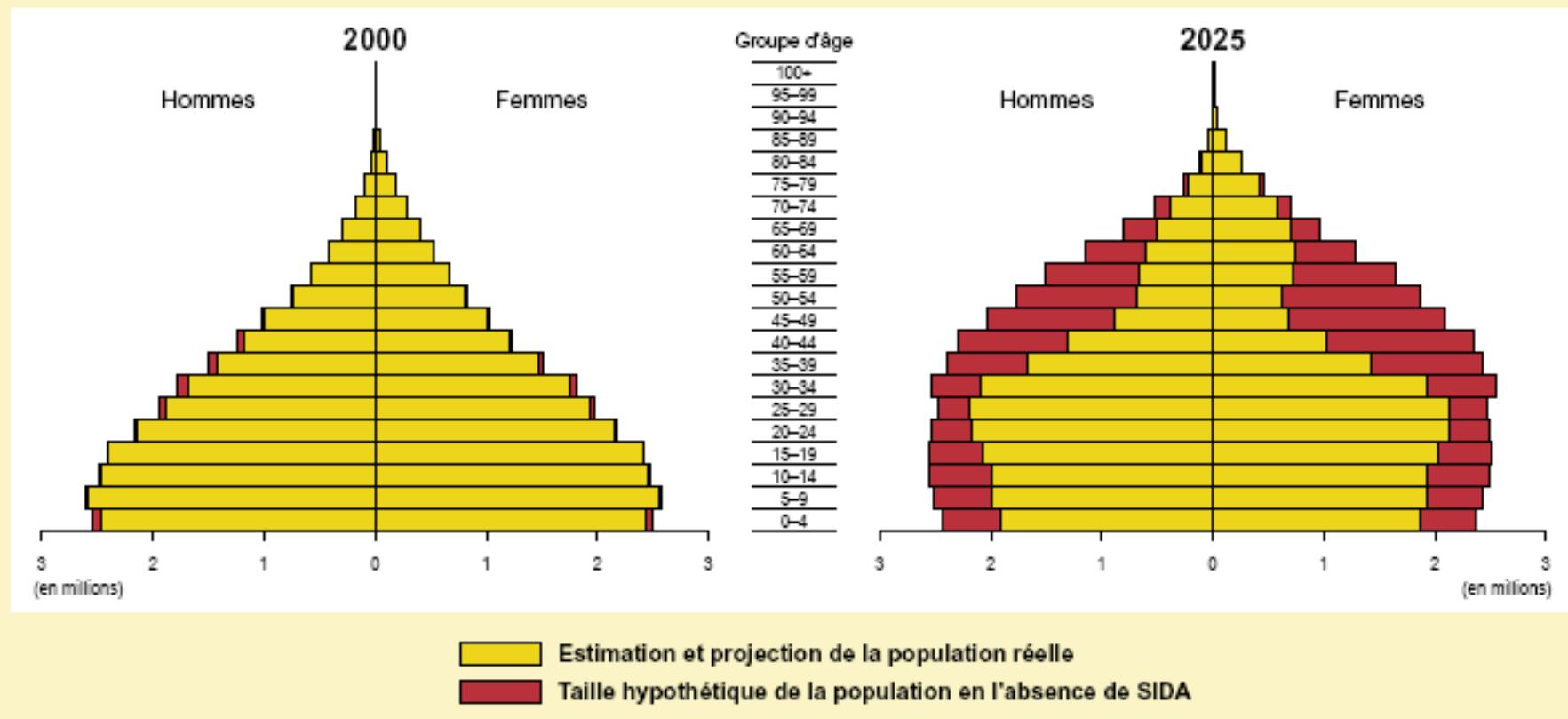
Direction des sciences du vivant du CEA

Adultes et enfants vivant avec le VIH



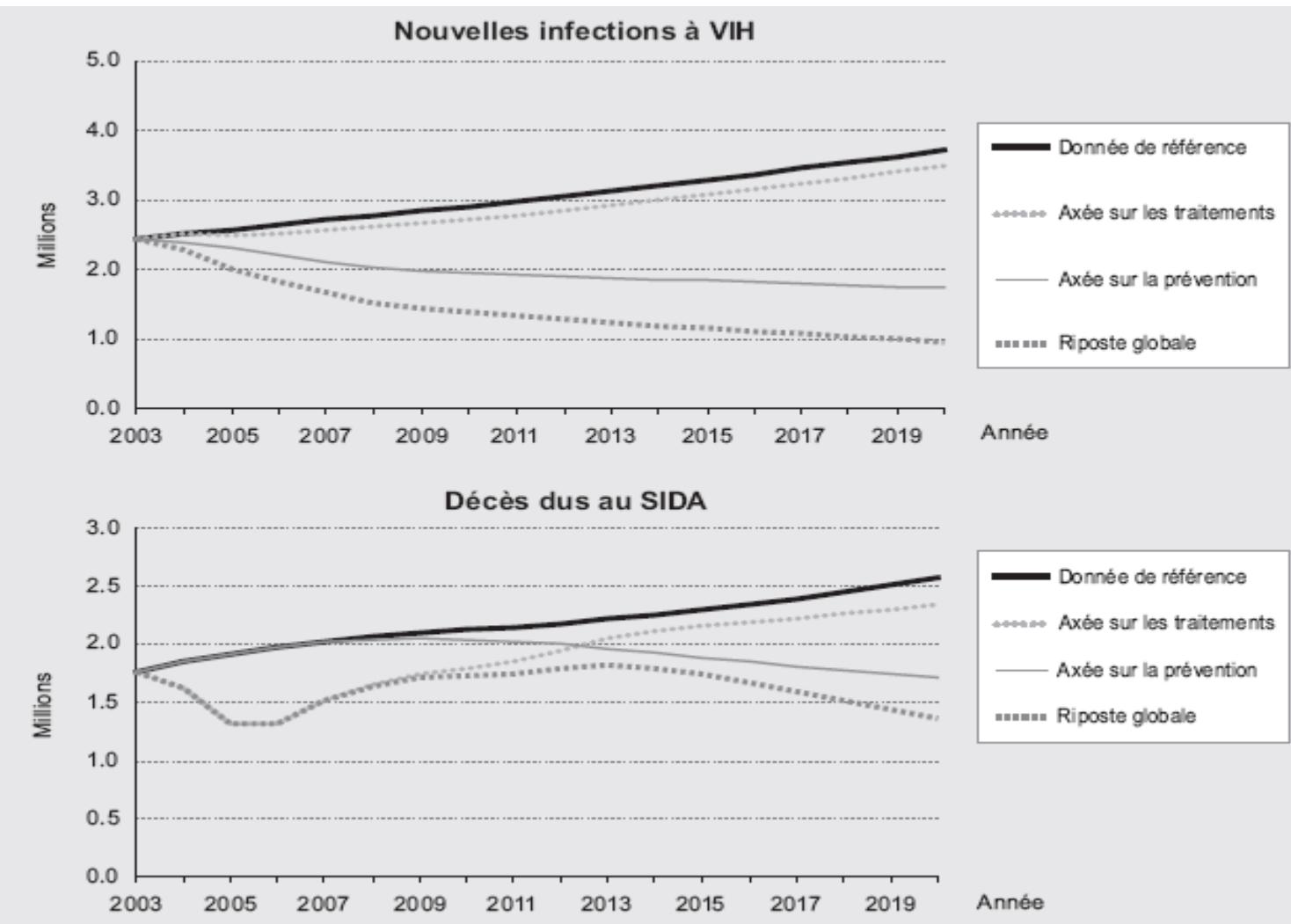
Impact du SIDA sur les populations africaines

Taille de la population avec et sans SIDA, Afrique du Sud, 2000 et 2025



Nécessité de développer de nouvelles stratégies de prévention

Projection en Afrique subsaharienne d'ici à 2020

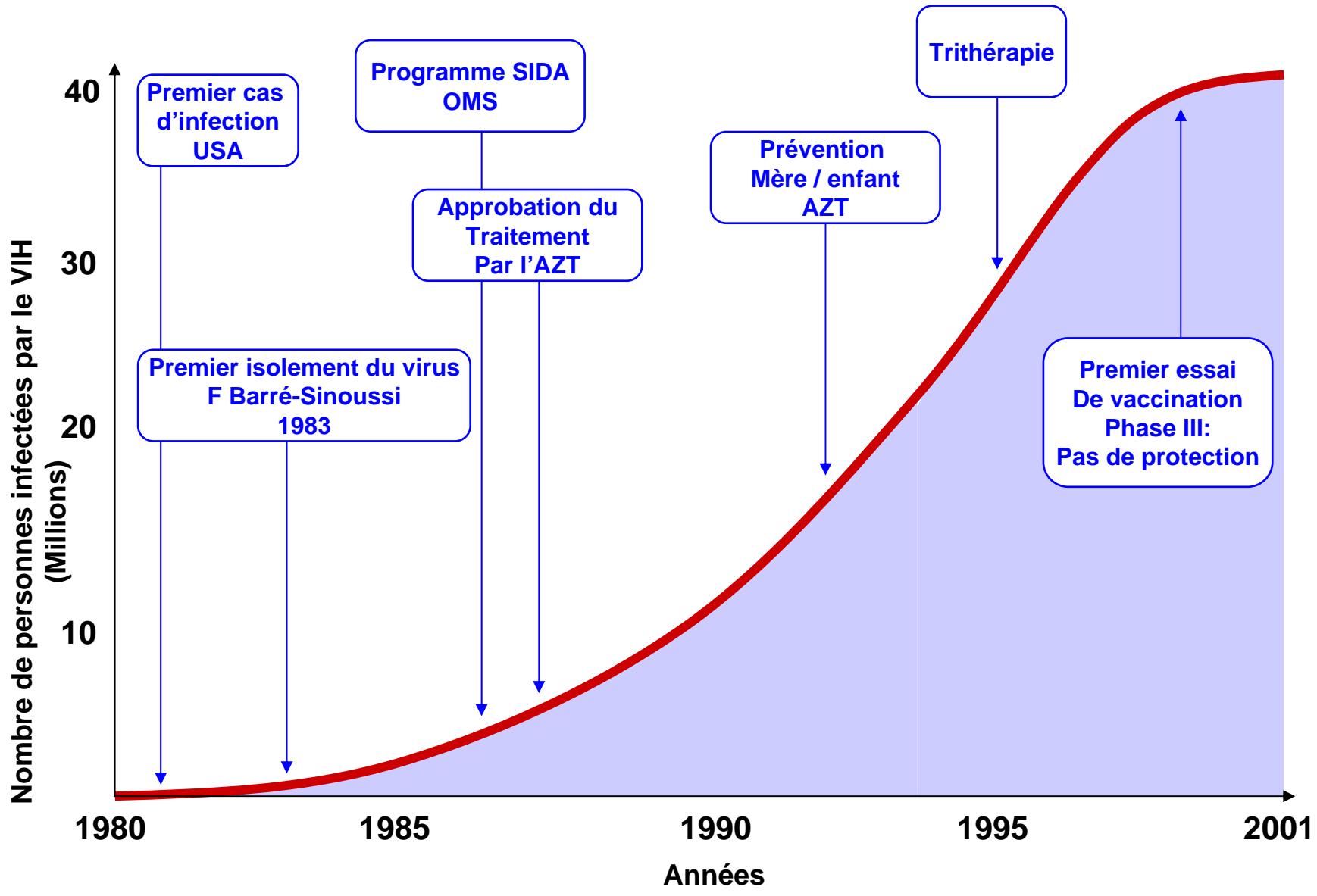


(Salomon JA et al, PLoS Medicine, 2005)

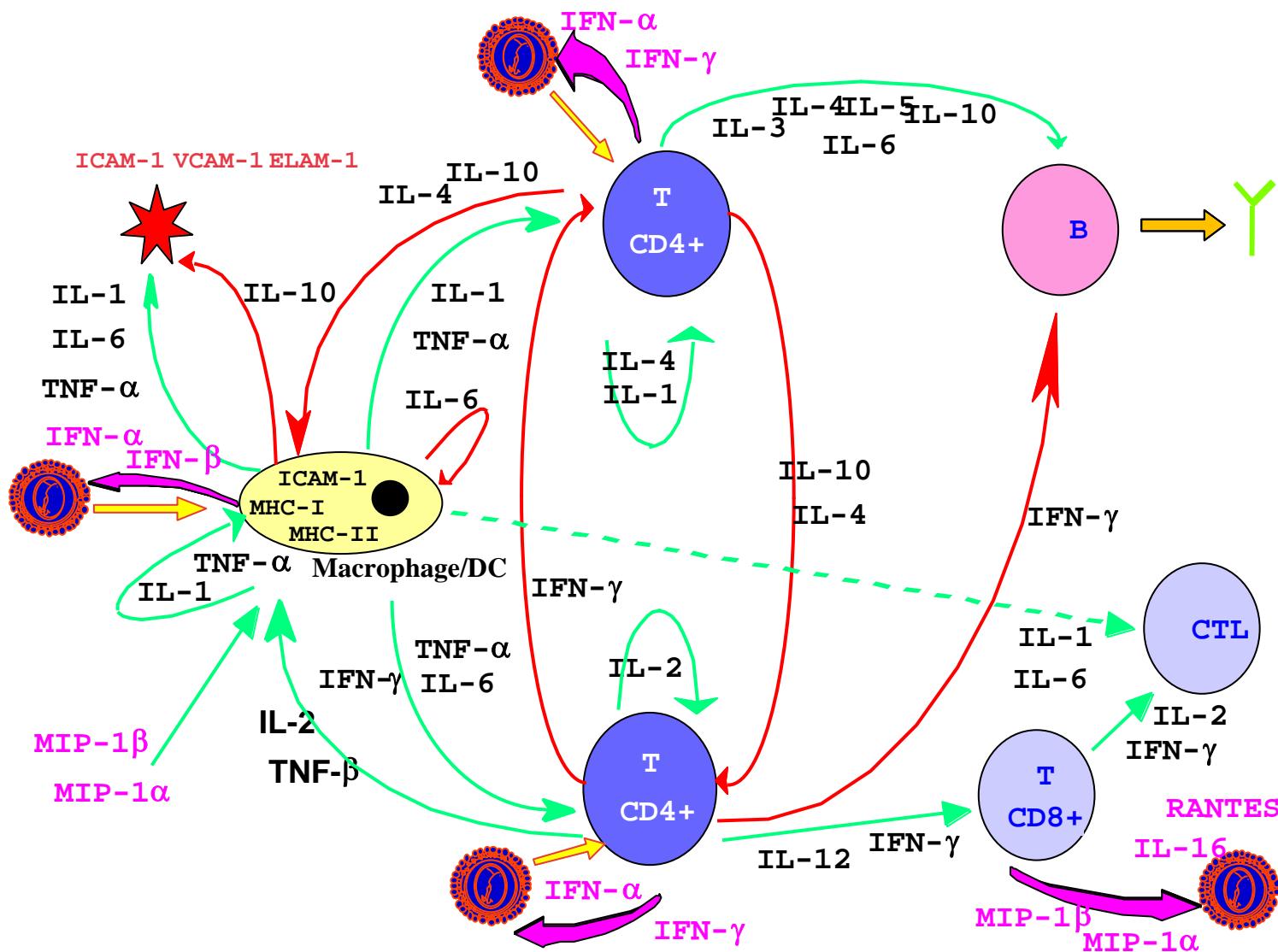
Prévention de la transmission du VIH

- Rapports sexuels protégés
 - Prophylaxie post-exposition au virus par les antiviraux
 - Microbicides vaginaux ou rectaux
 - La vaccination
-

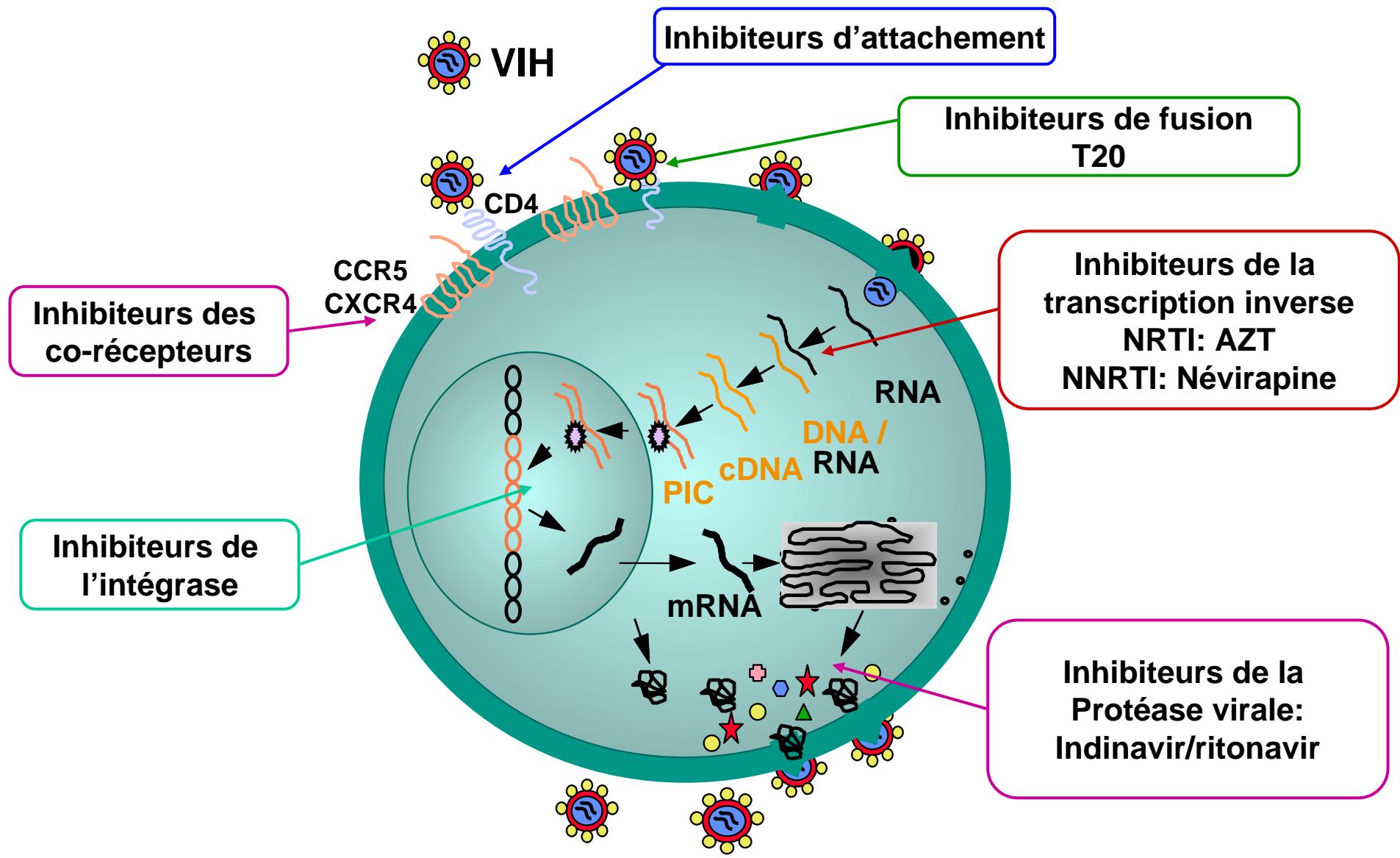
Plus de 25 années d'infection par le VIH



Le VIH infecte les cellules du système immunitaire



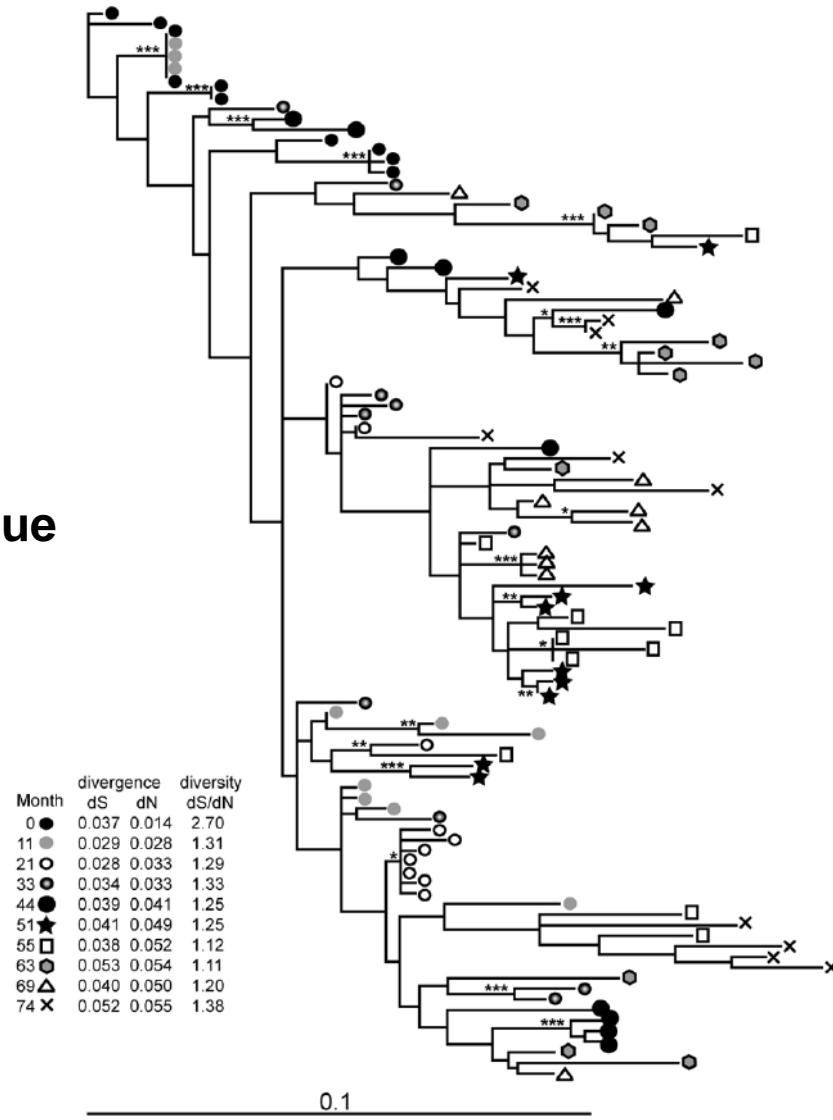
Cycle de réplication du VIH et cibles des antiviraux



Diversité et variabilité du VIH-1 au sein d'un individu

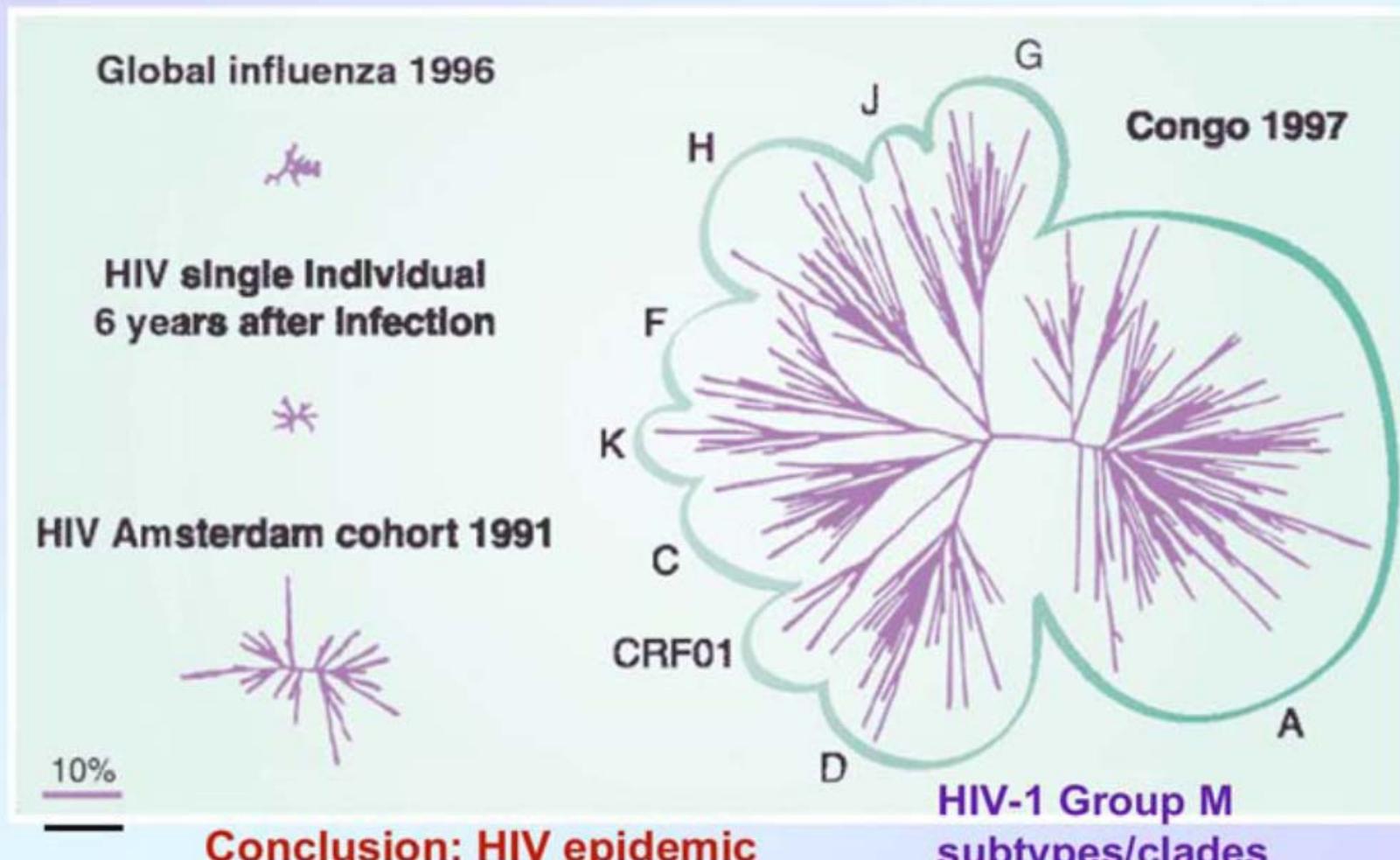
(Troyer *et al*, 2005)

Analyse phylogénétique env C2V3



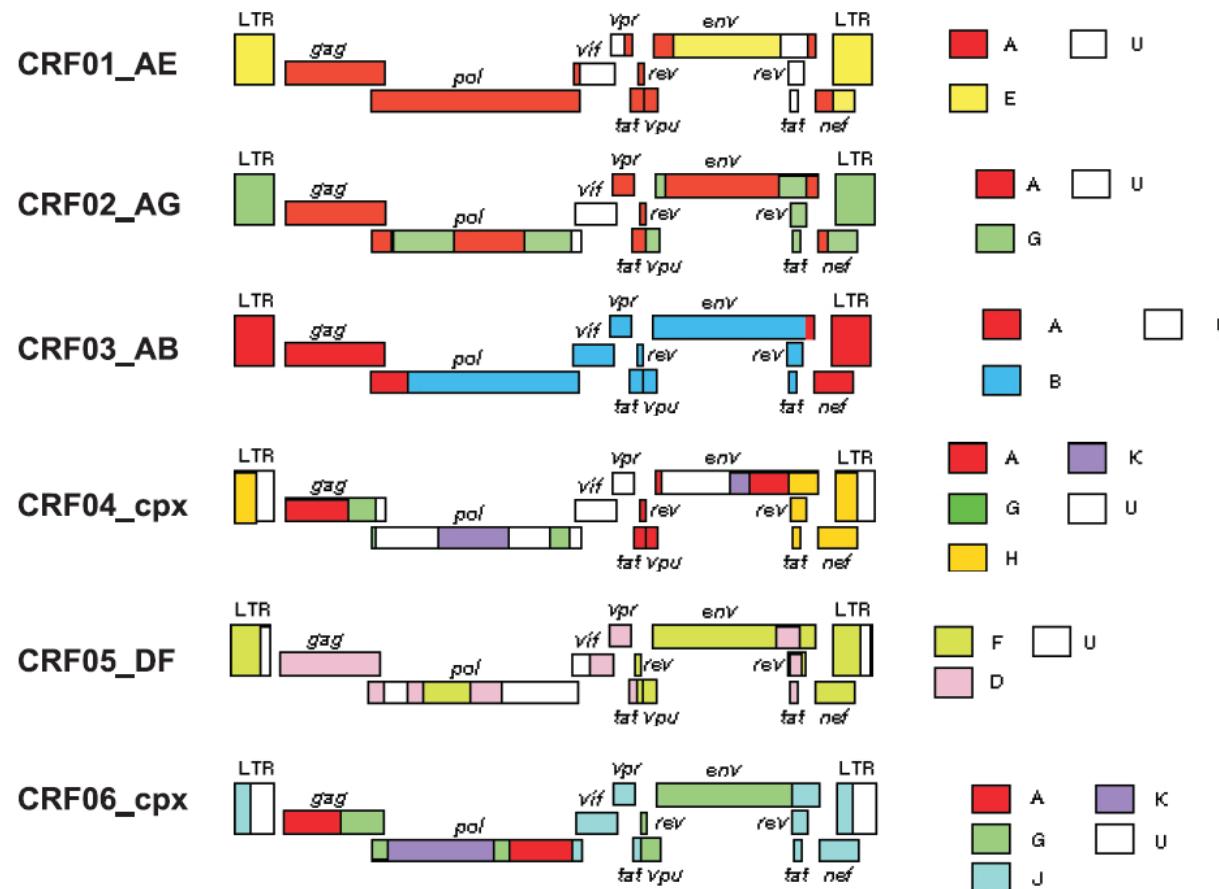
Diversité et variabilité du VIH-1

HIV-1 Genetic Diversity Increases with Time

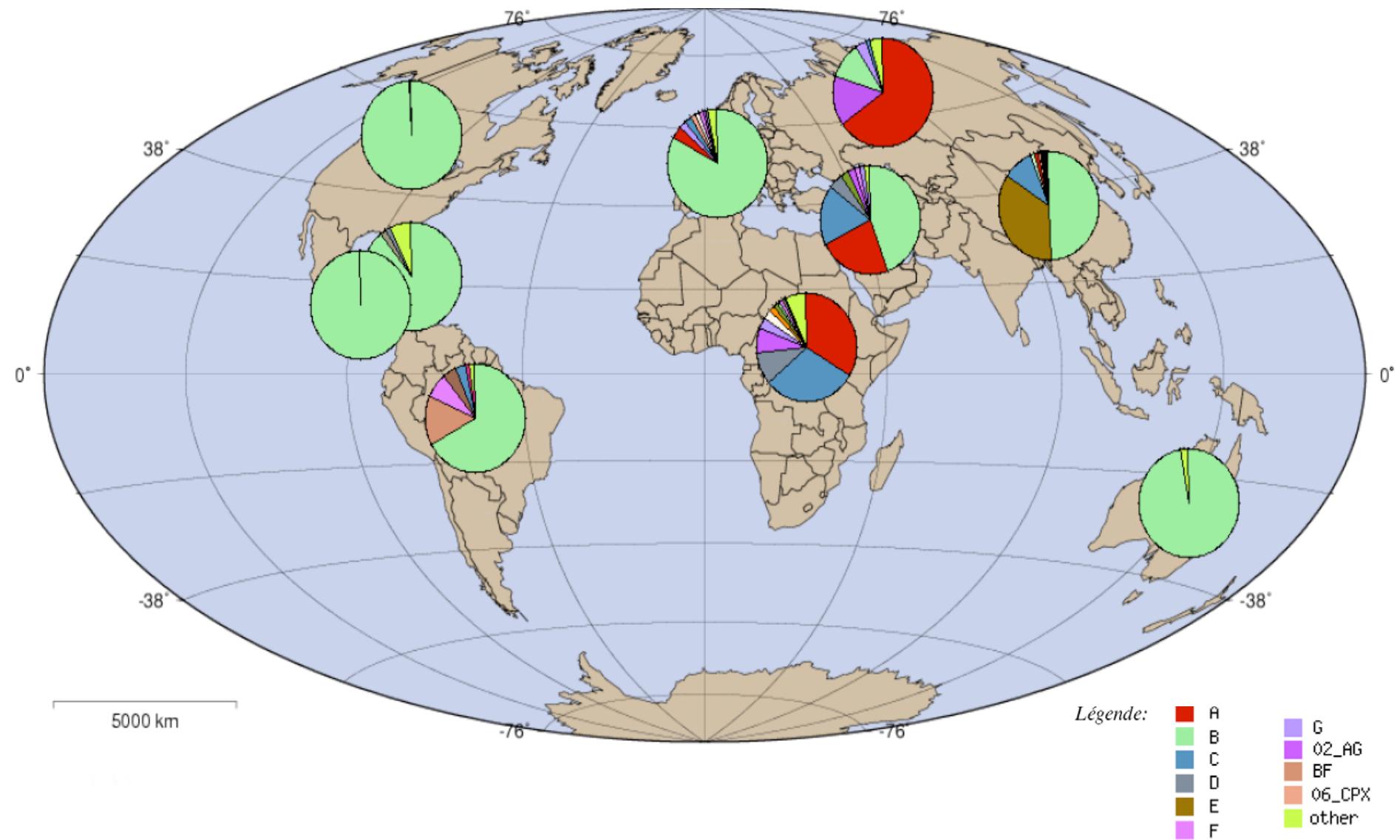


Diversité et variabilité du VIH: la recombinaison

(Lal *et al*, 2005)



Répartition à travers le monde des sous-types du VIH-1



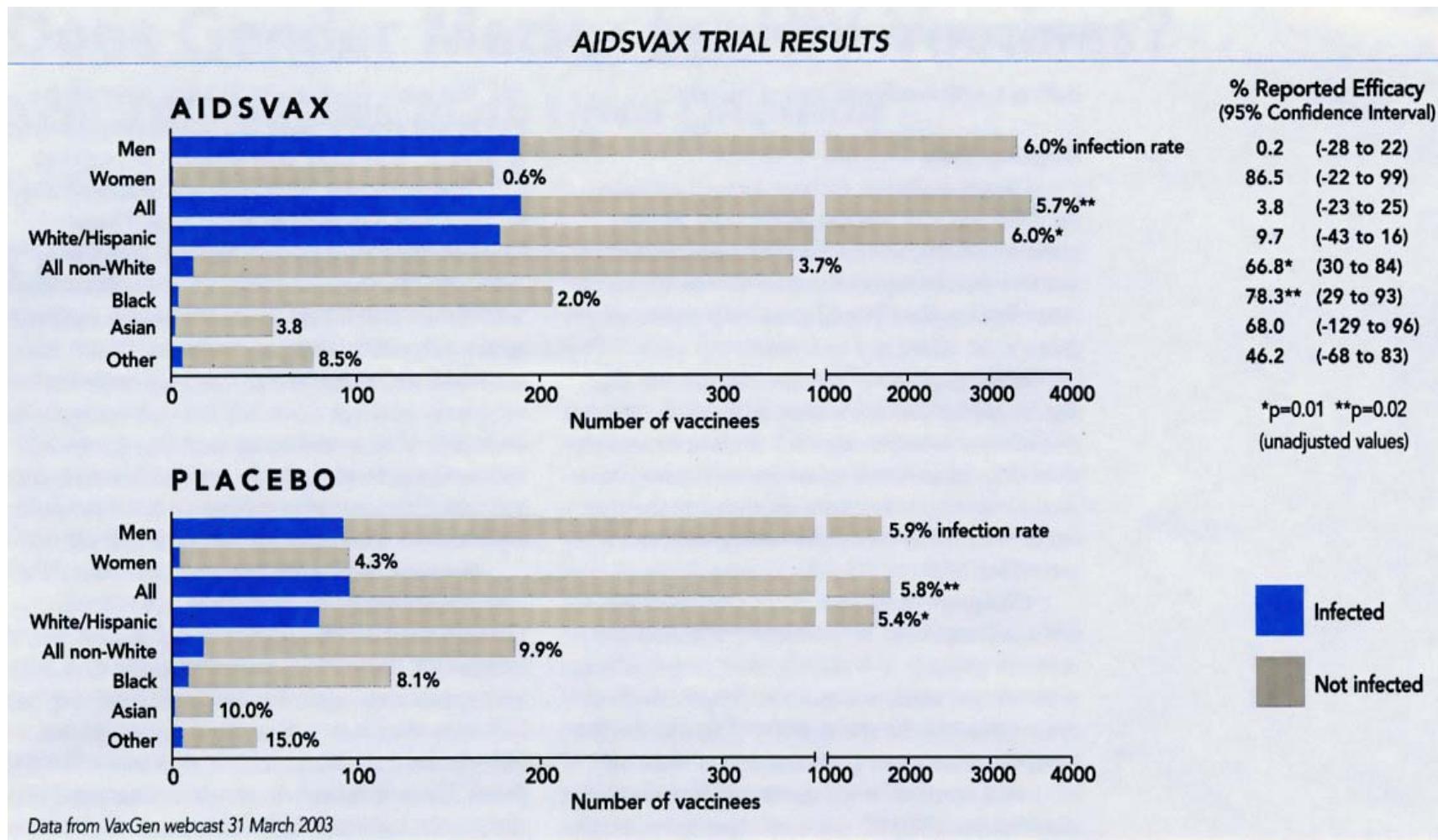
D'après Los Alamos HIV Sequence Database (www.hiv.lanl.org)

Essais de vaccination contre le VIH

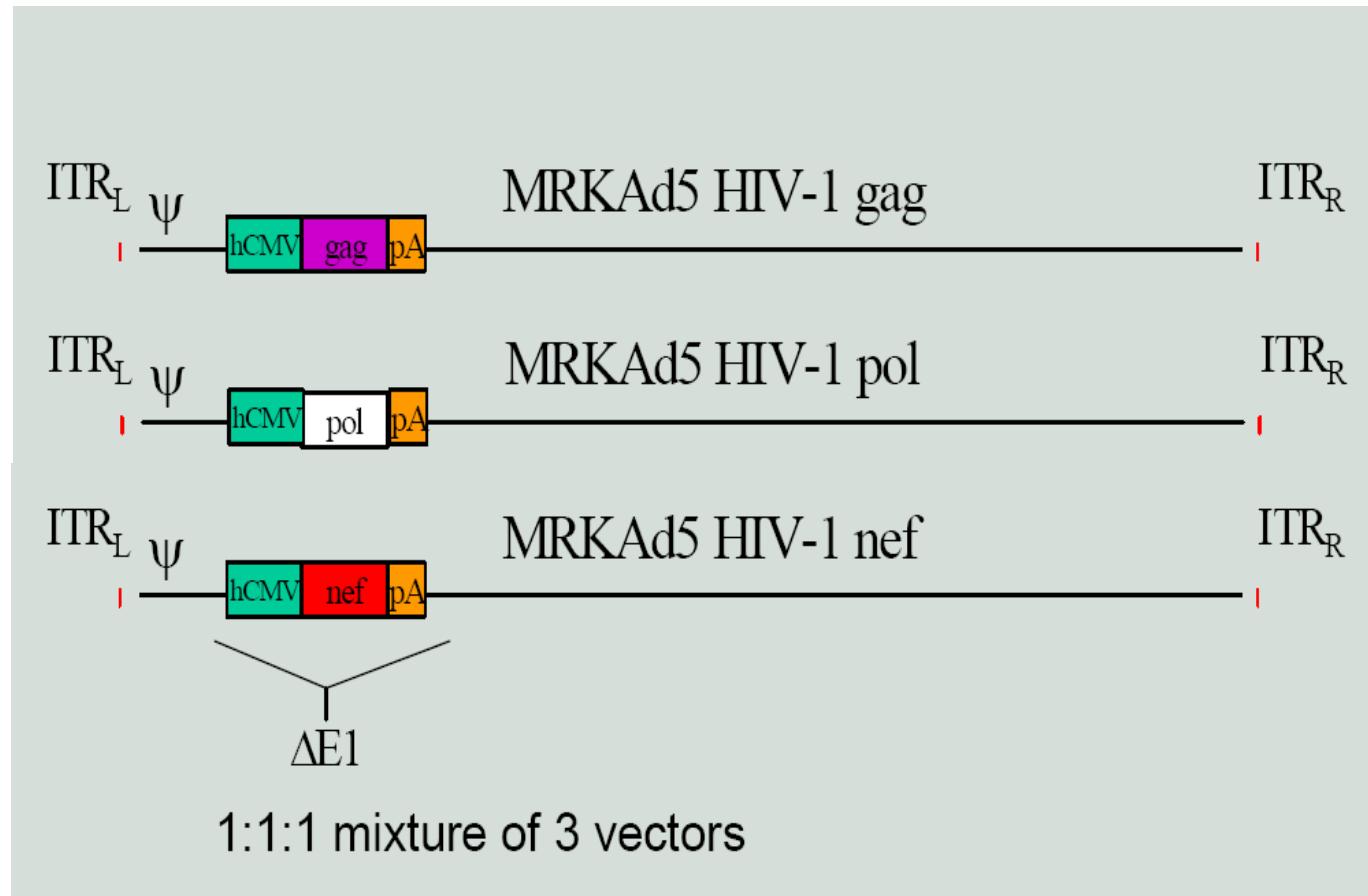
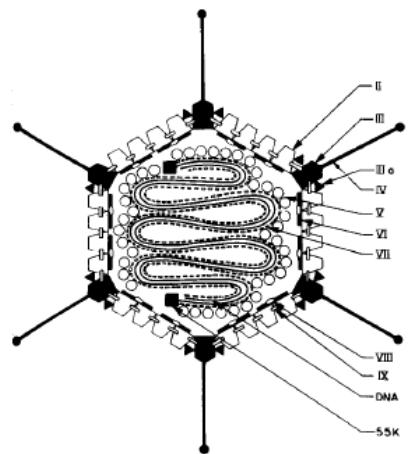
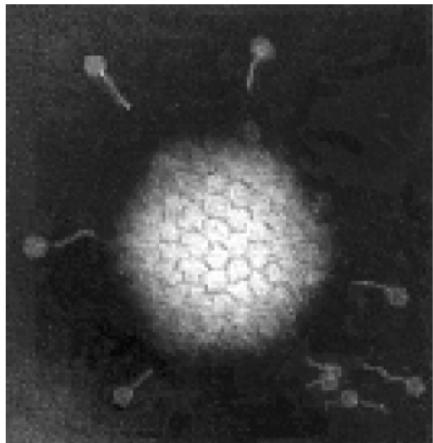
- **Essais chez l'animal** (primates non humains)
 - Plus de 300 essais d'immunogénicité/efficacité
- **En développement chez l'homme:**
 - Environ 10 candidats vaccins
- **Phase I/IIa et IIb:**
 - Plus de 40 essais en cours dont STEP
- **Phase III:**
 - Un essai terminé: AIDSVAX
 - (Vaxgene)
 - 5000 volontaires (USA, Europe)
 - Un essai en cours: vCP1552 et gp120
 - (Sanofi Pasteur, Walter Reed)
 - 15 000 volontaires en Thaïlande



Neutralizing antibody based-vaccine: AIDSVAX

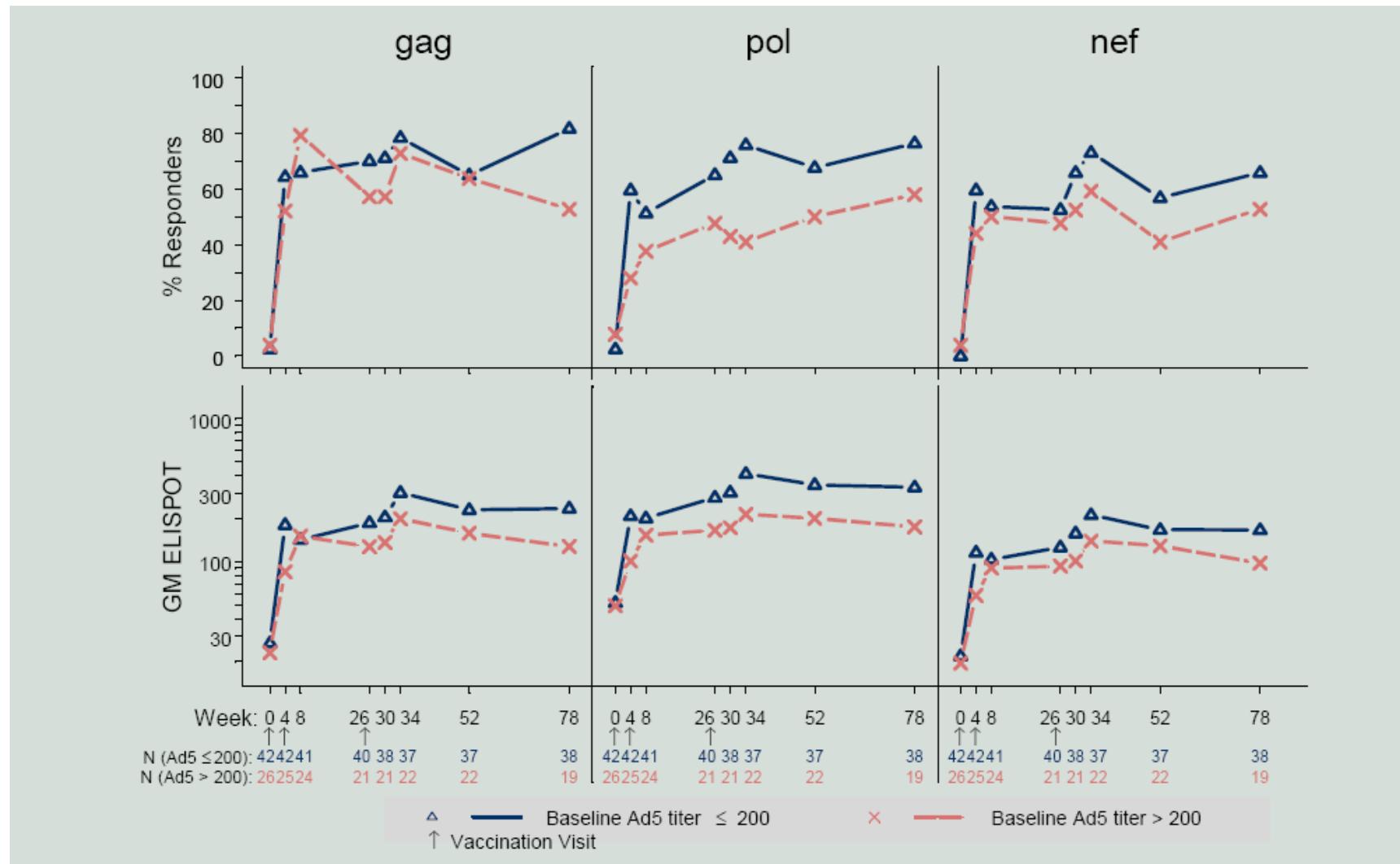


MRKAd5 Trivalent Vaccine: T-cell based vaccine



Longevity of Induced Cellular Immunity of MRKAd5 Trivalent Vaccine

Subjects Receiving 3×10^{10} or 1×10^{11} vp/d



HIV vaccine confirmatory trial

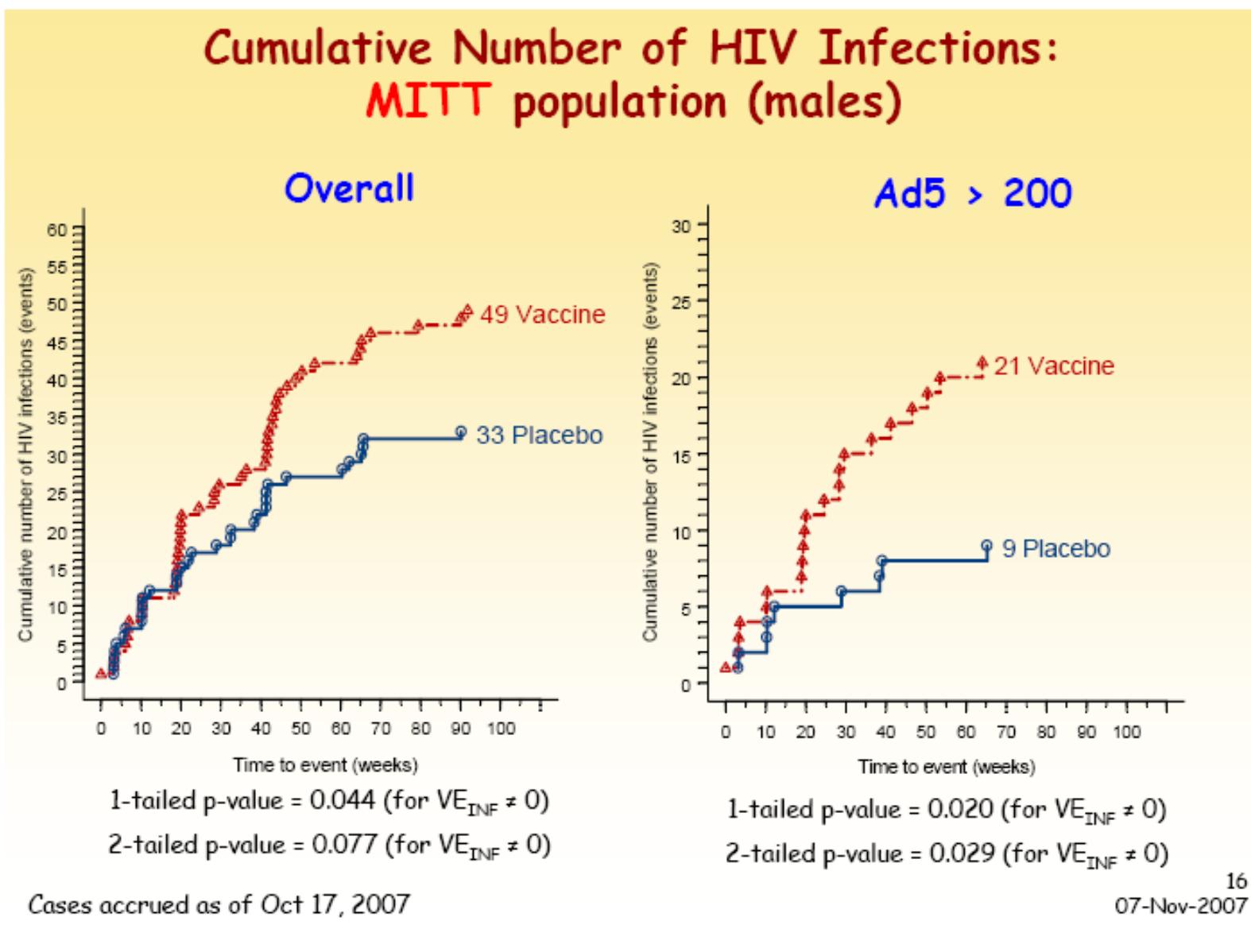
- Design assumptions:
 - Event rates in control group (annualized)
 - HIV seroincidence = 2%
 - Progression to ART initiation trigger* = 12%
 - Progression from ART initiation to ADE/Death** = 4%
 - Trial size
 - N = 25,000-50,000
 - Note: 4.8 years to enroll (at rate of 100/week)
 - Timeline for definitive efficacy results
 - Precise characterization of VES ~4-5 years (eg distinguish VES 40% vs 30%)
 - Precise characterization of impact on ART initiation ~8 years (eg, 25% reduction in median time to ART initiation)
 - Final primary efficacy analysis of ADE endpoint ~11-13 years
 - Timeline for safety results
 - Acute safety profile based on 12,500 vaccines ~5.5 years
 - Powered to detect serious safety events at absolute rates of 3/10,000 or greater
 - Controlled nature of safety database allows rigorous separation of “background” from vaccine-induced events
-

STEP: Test du Concept

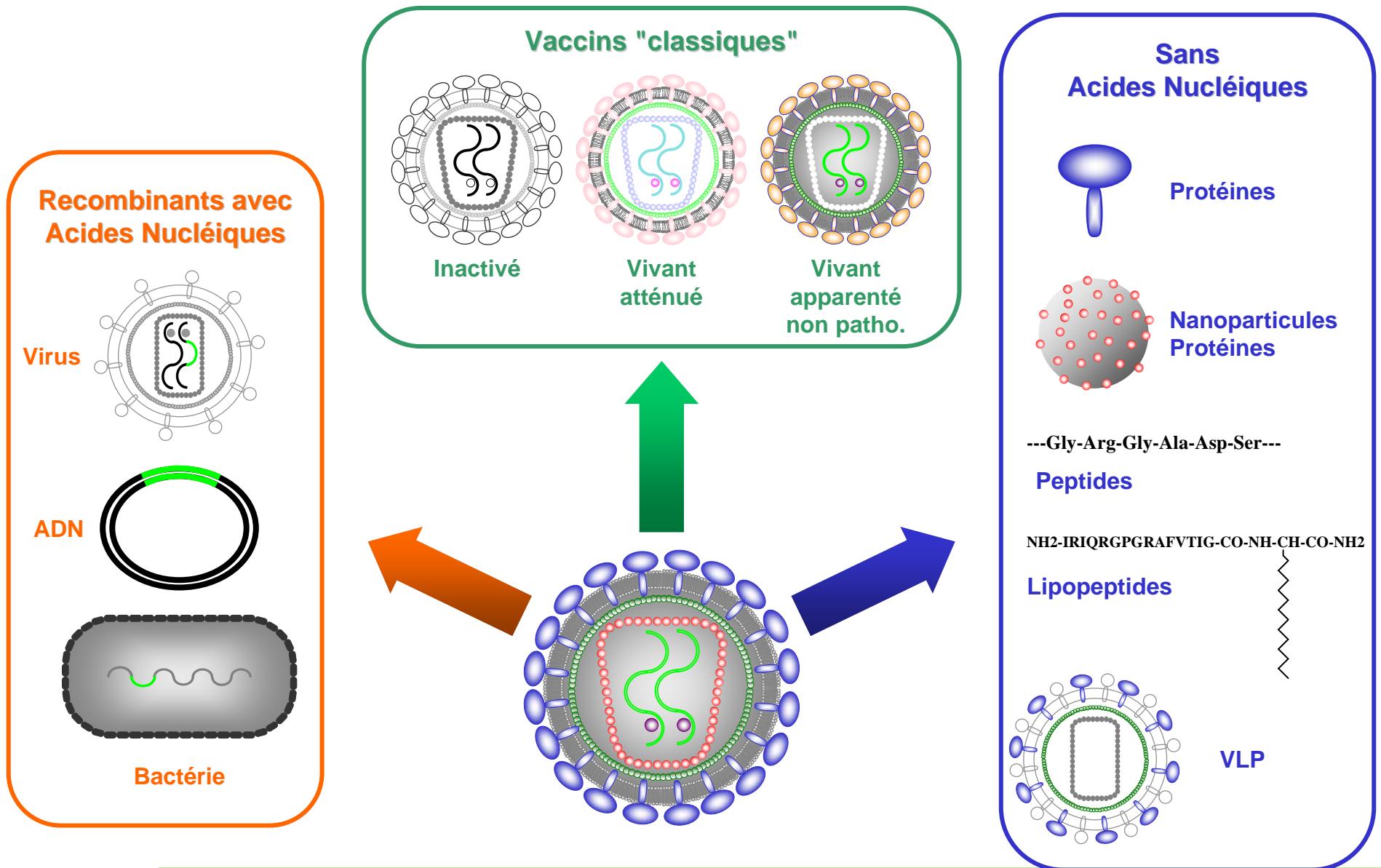
Merck Protocol 023/HVTN 502

- Phase IIb, test-of-concept (TOC), vaccin Merck V520
- Co-sponsors : Merck, NIAID (NIH)
- Multicentrique, double aveugle, randomisé, contre placebo
- n= 3000 volontaires sains à risque élevé d'infection par le VIH âgés de 18 à 45 ans, environ 2/3 hommes homosexuels, 1/3 femmes
 - Deux bras:
 - 1500 volontaires: Ad 5 titres <200
 - 1500 volontaires: Ad 5 titres >200
 - Sites : USA, Amérique du Sud, Caraïbes, Australie
 - Inclusions : Décembre 2004 - Mars 2007
 - Schéma d'immunisation : 3 injections (prime/boost homologue)
 - 2 end-points primaires :
 - prévention de l'infection
 - diminution de la CPp chez les individus infectés

STEP trial: vaccine induced enhancement of infection



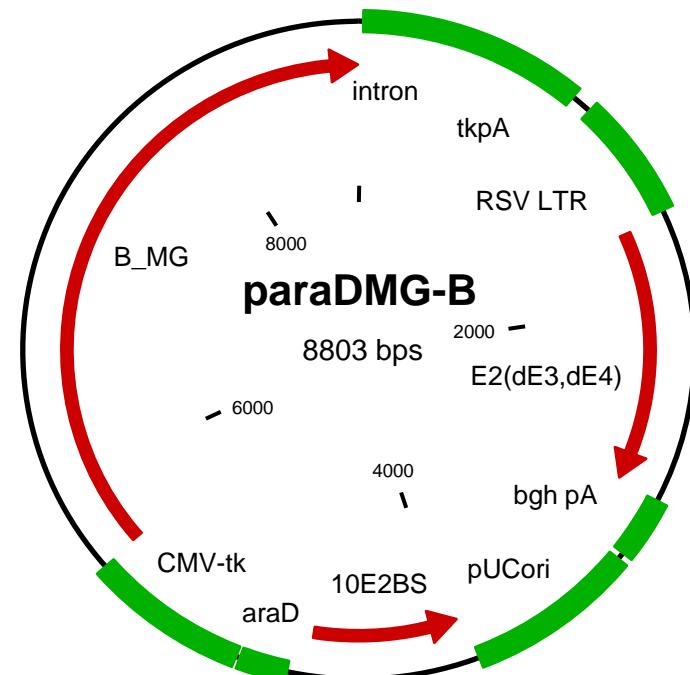
Stratégies de vaccination antivirale: choix du vecteur



Feature of the DNA vaccine

- Contains HIV genes :
 - *rev*
 - *nef*
 - *tat*
 - *gag* (p17 + p24 codon optimized)
 - (Stretch of known human CTL epitopes)
- Encodes a fusion protein corresponding to consensus sequences from clade B
- Encodes the bovin papillomavirus E2 protein

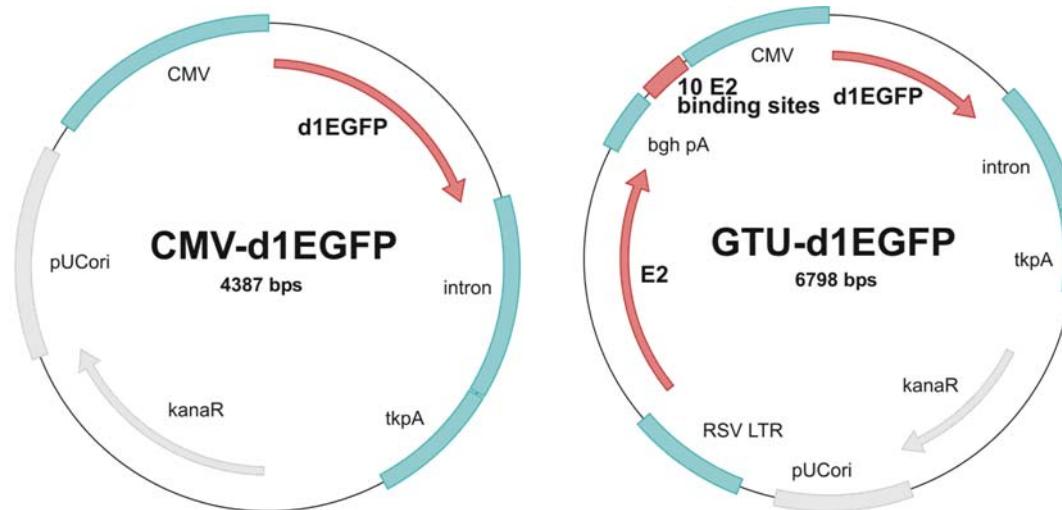
Auxo GTU-MultiHIV B plasmid



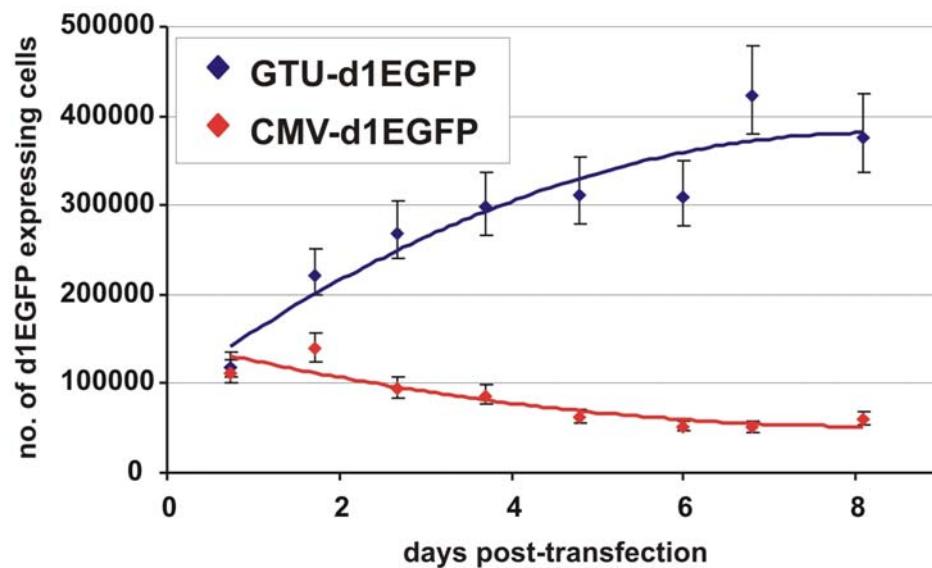
- ➡ 1 mg DNA per vaccination and per animal split in 10 injection sites in the back skin, on the basis of 100 µl at 1 mg/ml per injection site

E2 avoids plasmid loss in transfected cells

A.

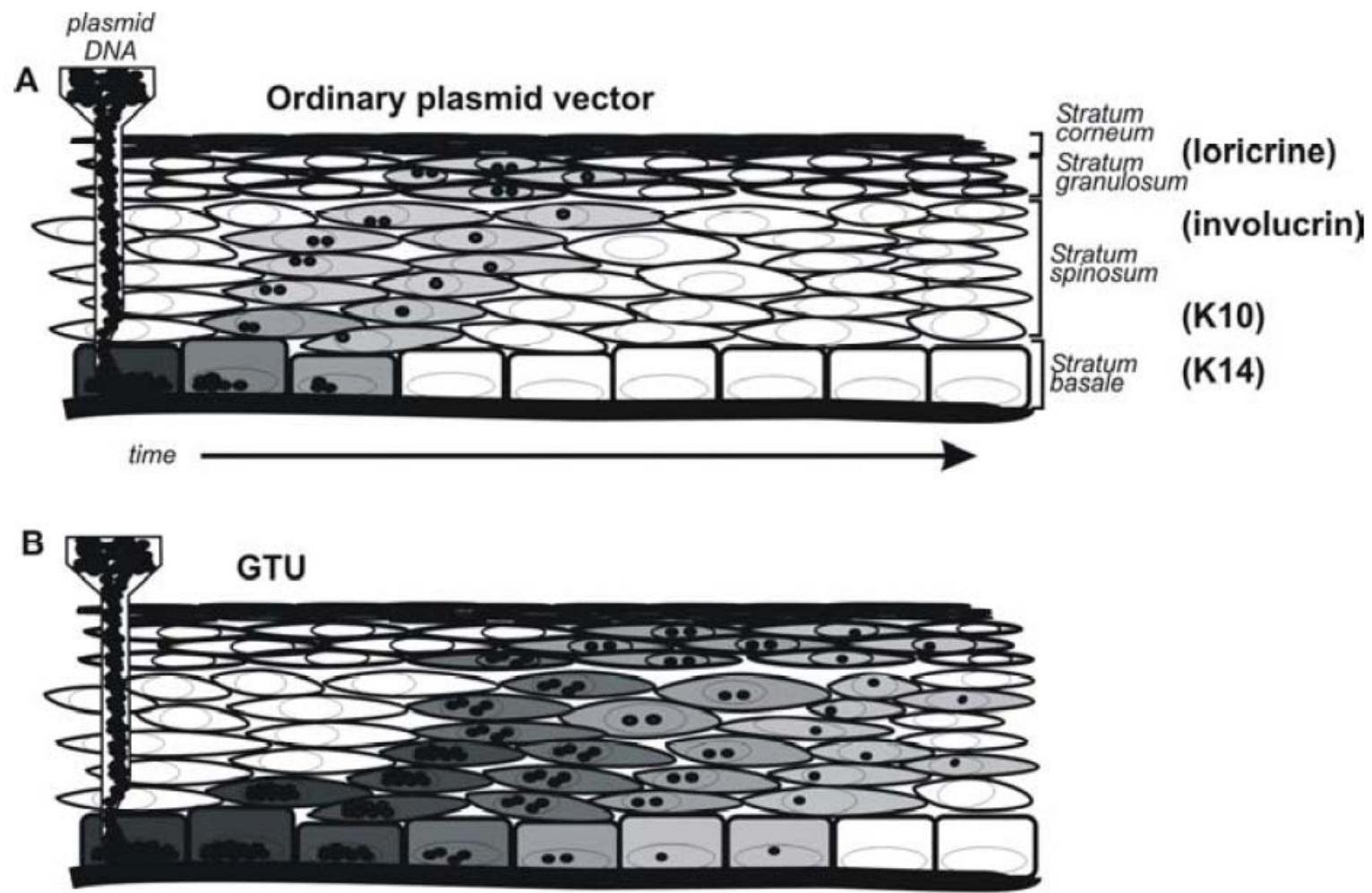


B.



Plasmid loss assay demonstrating the segregation/partitioning function of the GTU® vector. (A) Schematic maps of the CMV and GTU plasmids expressing the destabilized form of the EGFP (d1EGFP). (B) Changes in number of the d1EGFP-expressing cells in the Jurkat cell line transfected with 1 μ g of the GTU-d1EGFP vector or with an equimolar amount of the CMV-d1EGFP plasmid.

Persistence of vaccine DNA expression in skin cells



Electroporation at the injection site

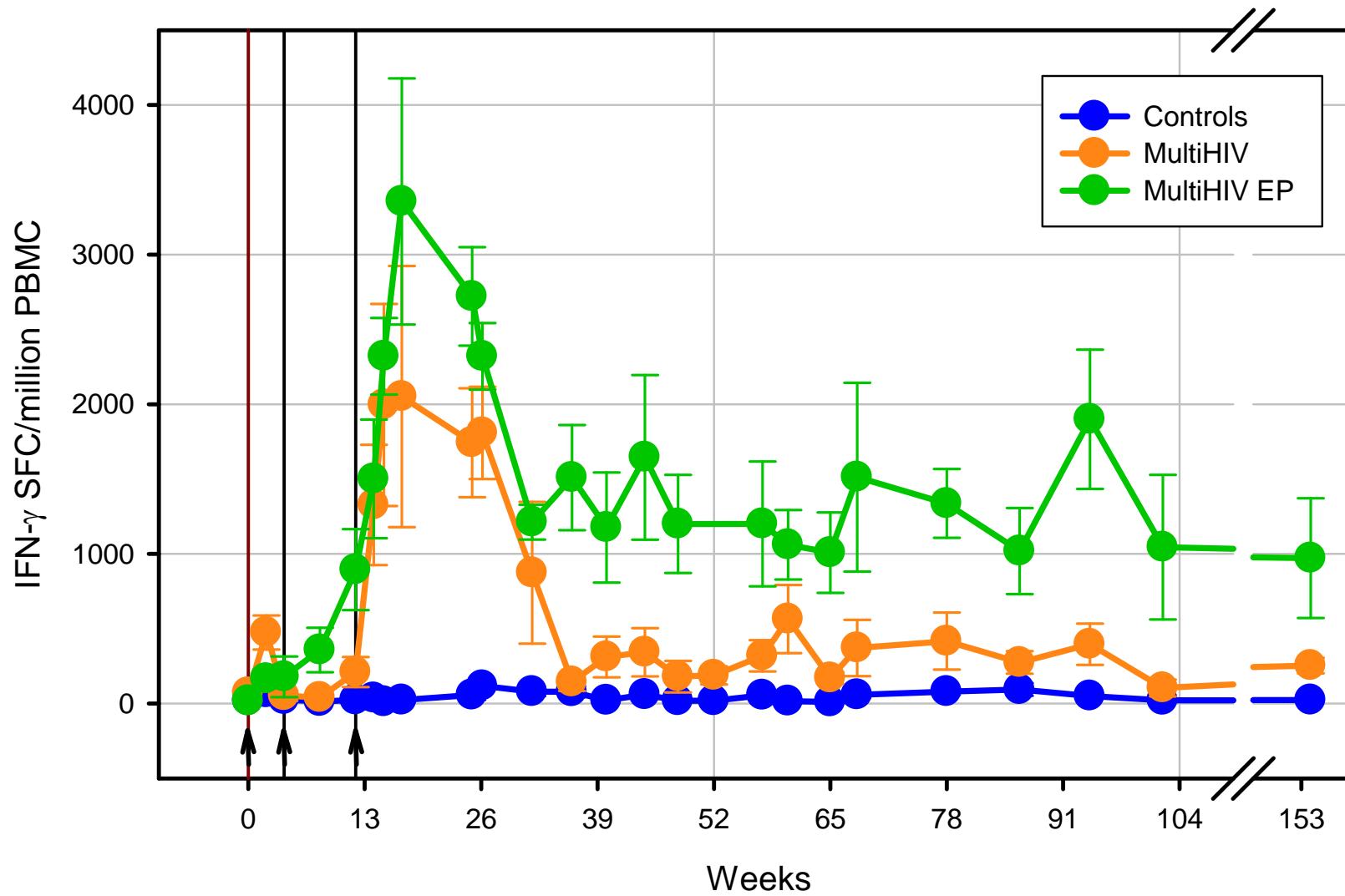


Optimal conditions for macaque skin

- Intra-dermal injection of plasmid encoding eGFP and Luciferase
- Test of 4 parameters for electroporation

- 300-600 mA output current
- 6 pulses
- 10 ms/pulse
- 90 ms interval

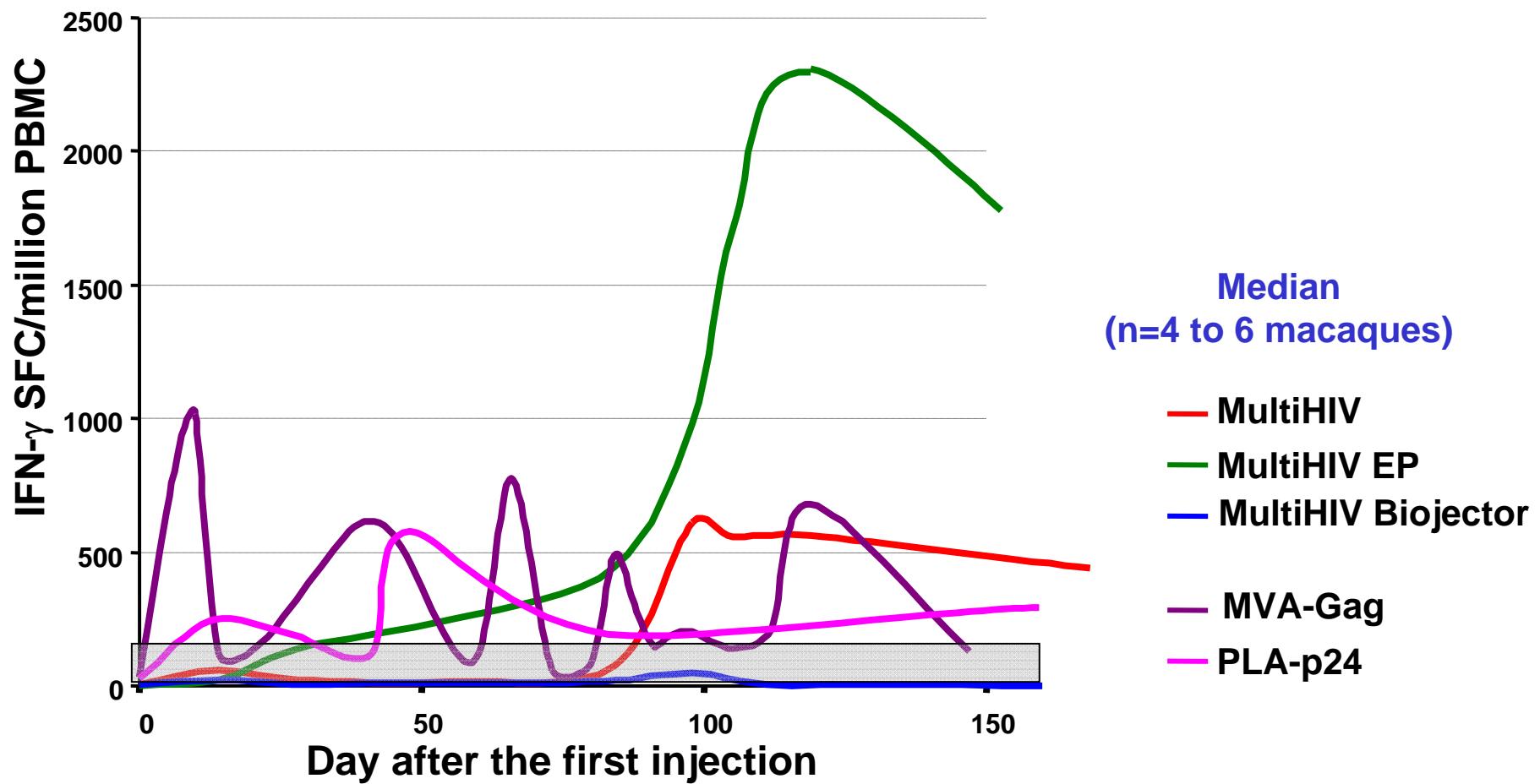
Cumulative T cell responses to all four HIV antigens



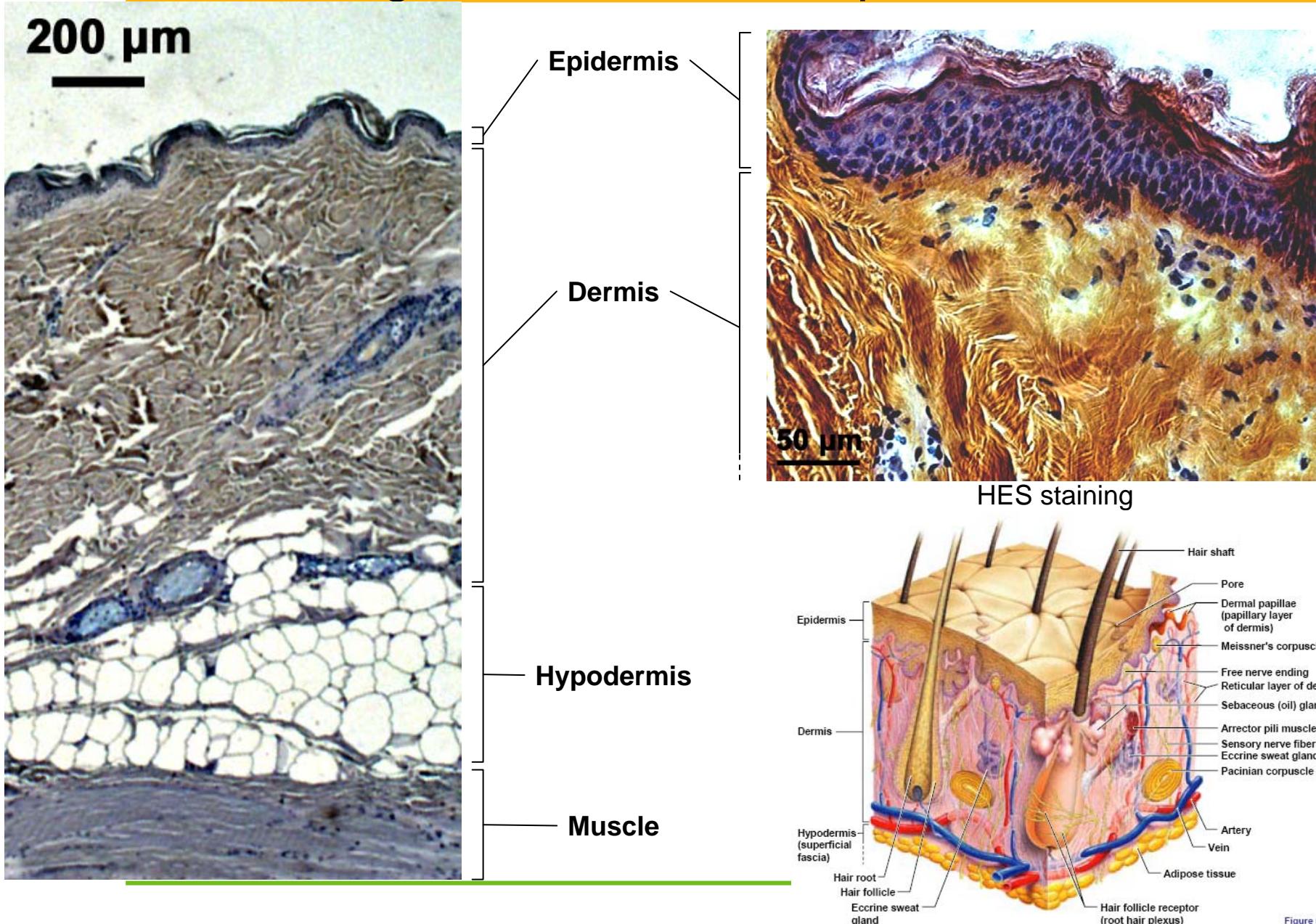
Mechanisms of vaccine induced cell-mediated long term memory

Vaccine induced anti-Gag responses

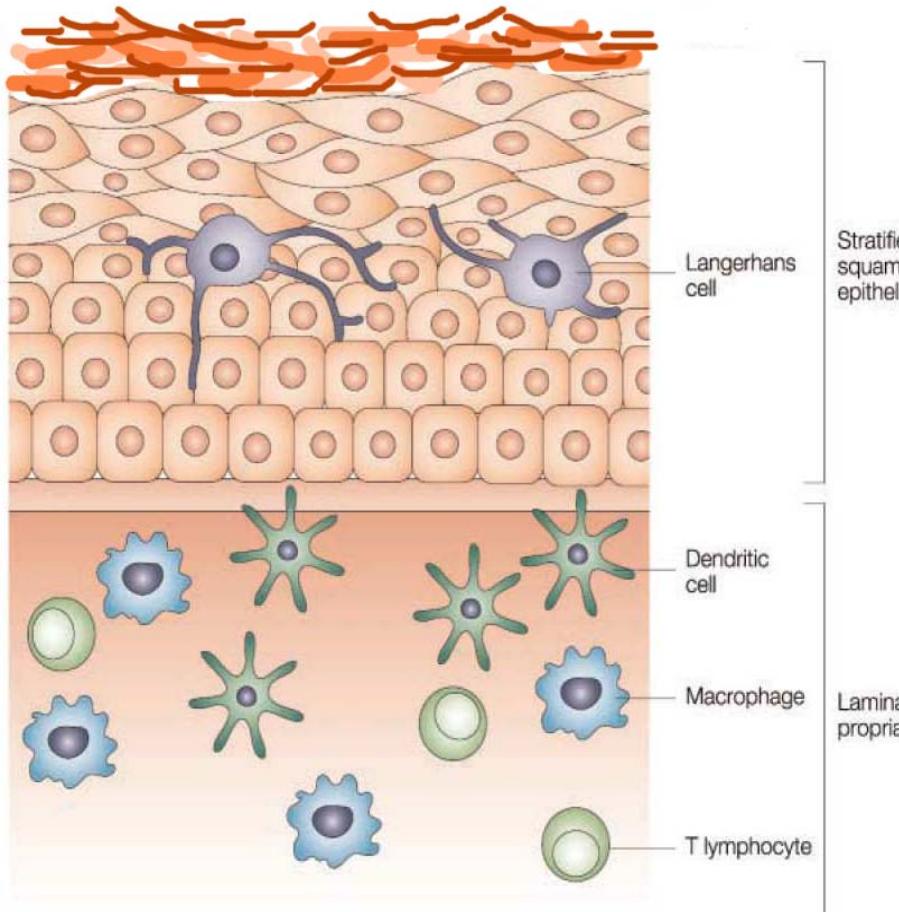
Comparison of priming with different vectors



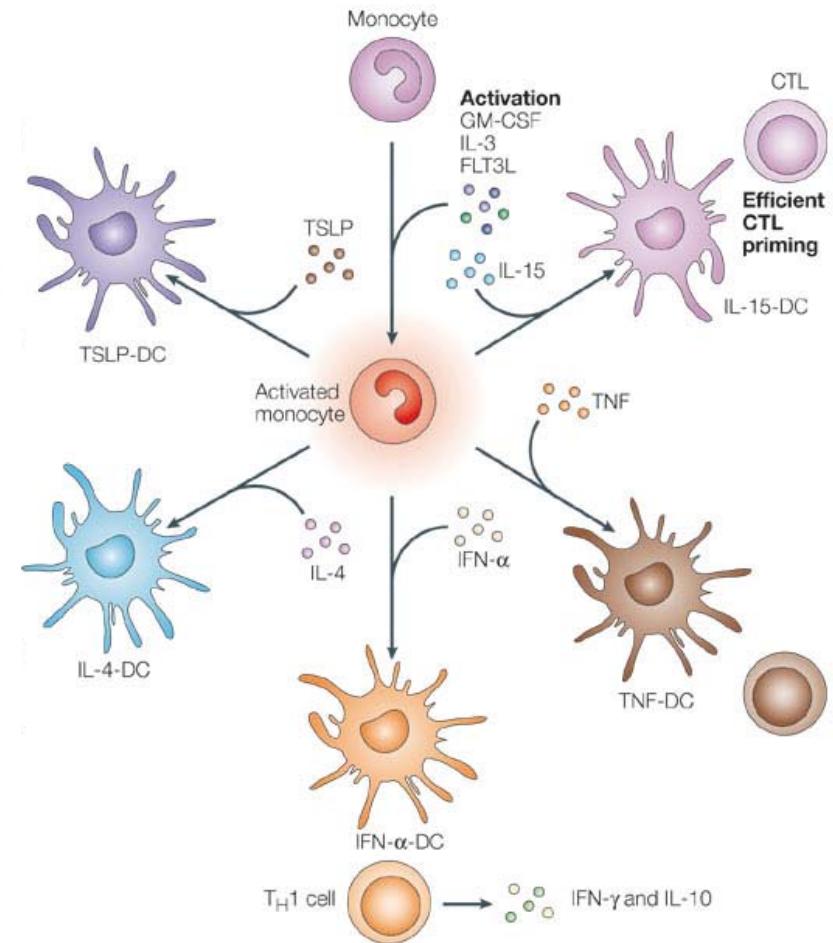
General organisation of macaque skin



Immune cells in the skin



(Adapted from Shattock et al., 2004)

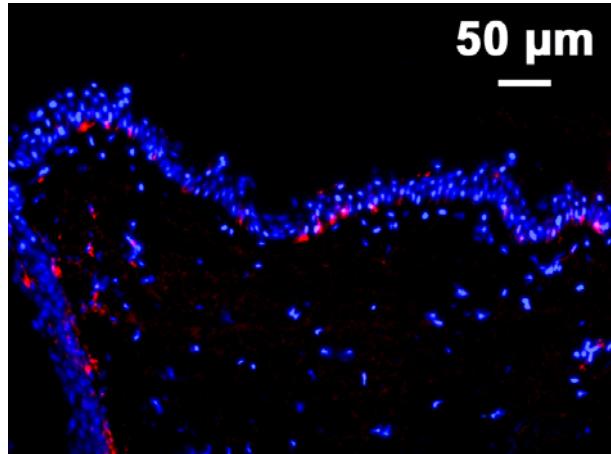


Nature Reviews | Immunology

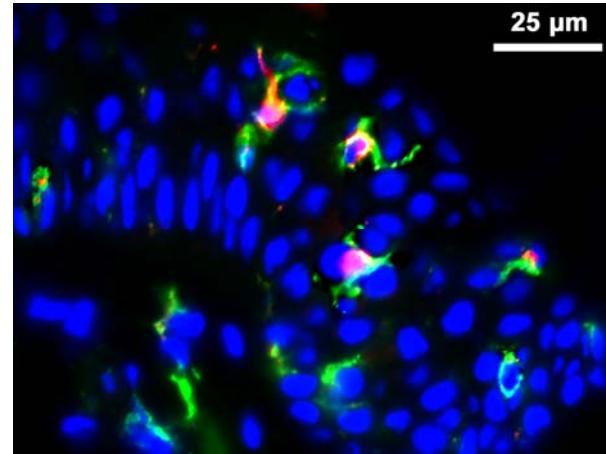
(From Banchereau et al., 2005)

Dendritic cells in macaque skin

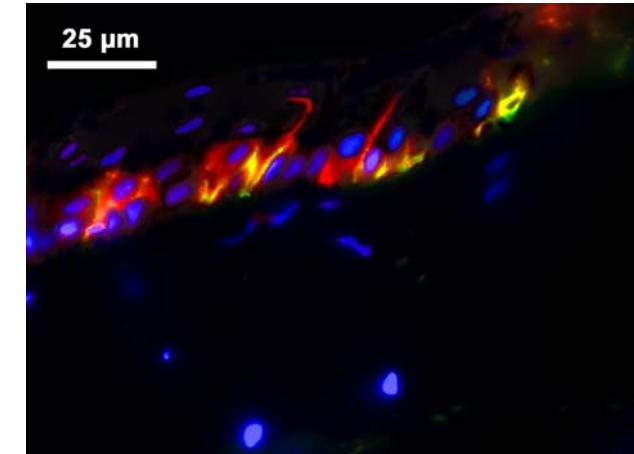
Langerhans cells: **CD207**



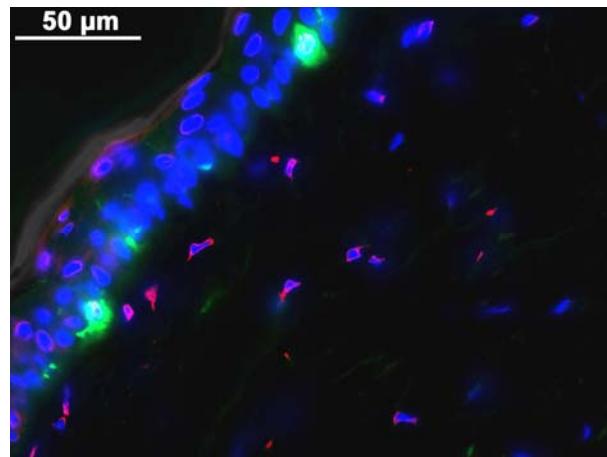
LC: **CD207 / MHC II**



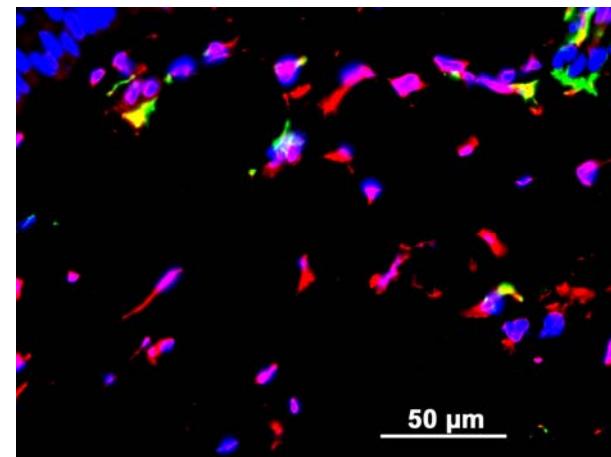
LC: **CD207 / CD1a**



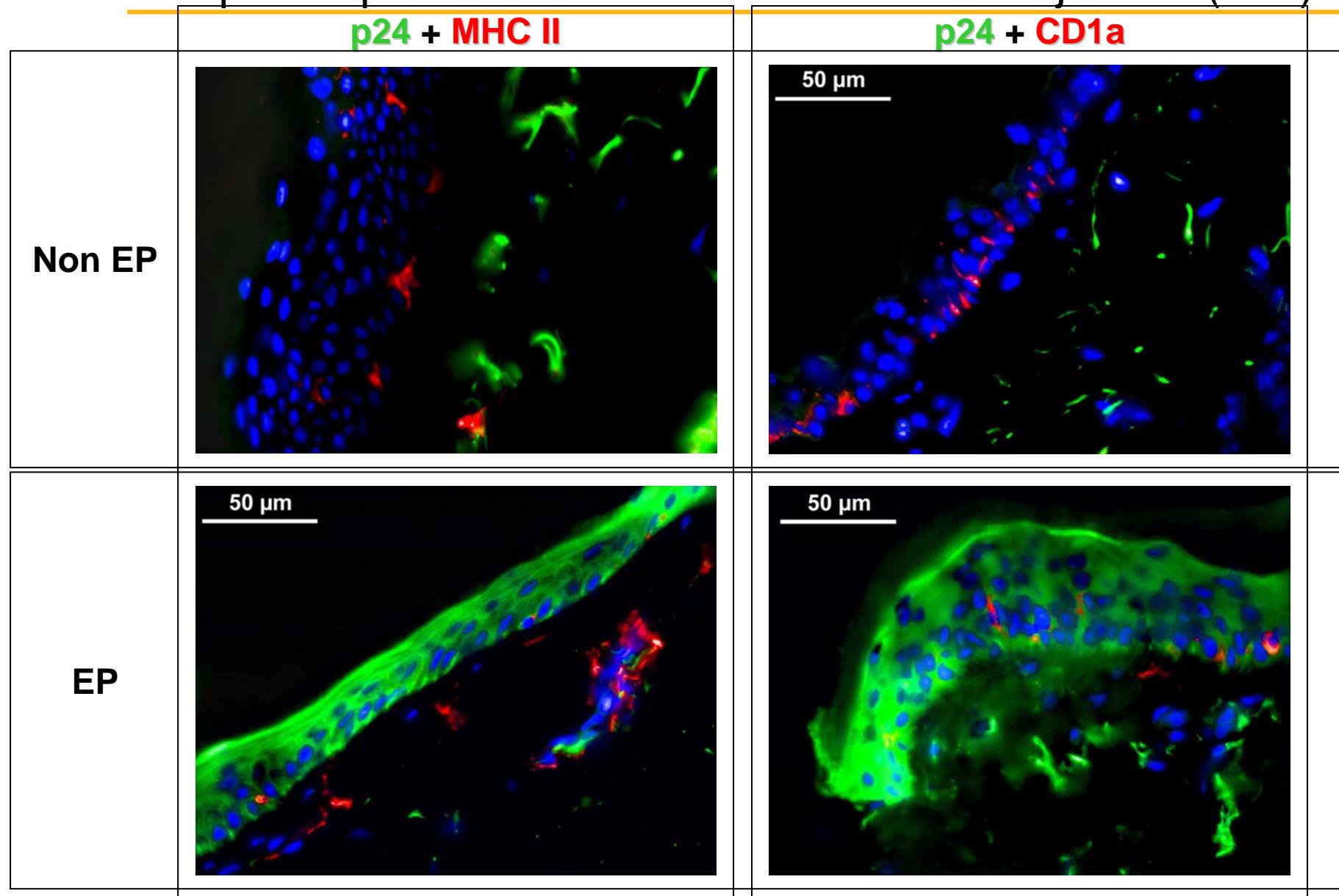
Dermal DC(**CD209**) / LC(**CD1a**)



Dermal DC: **CD209 / MHC II**



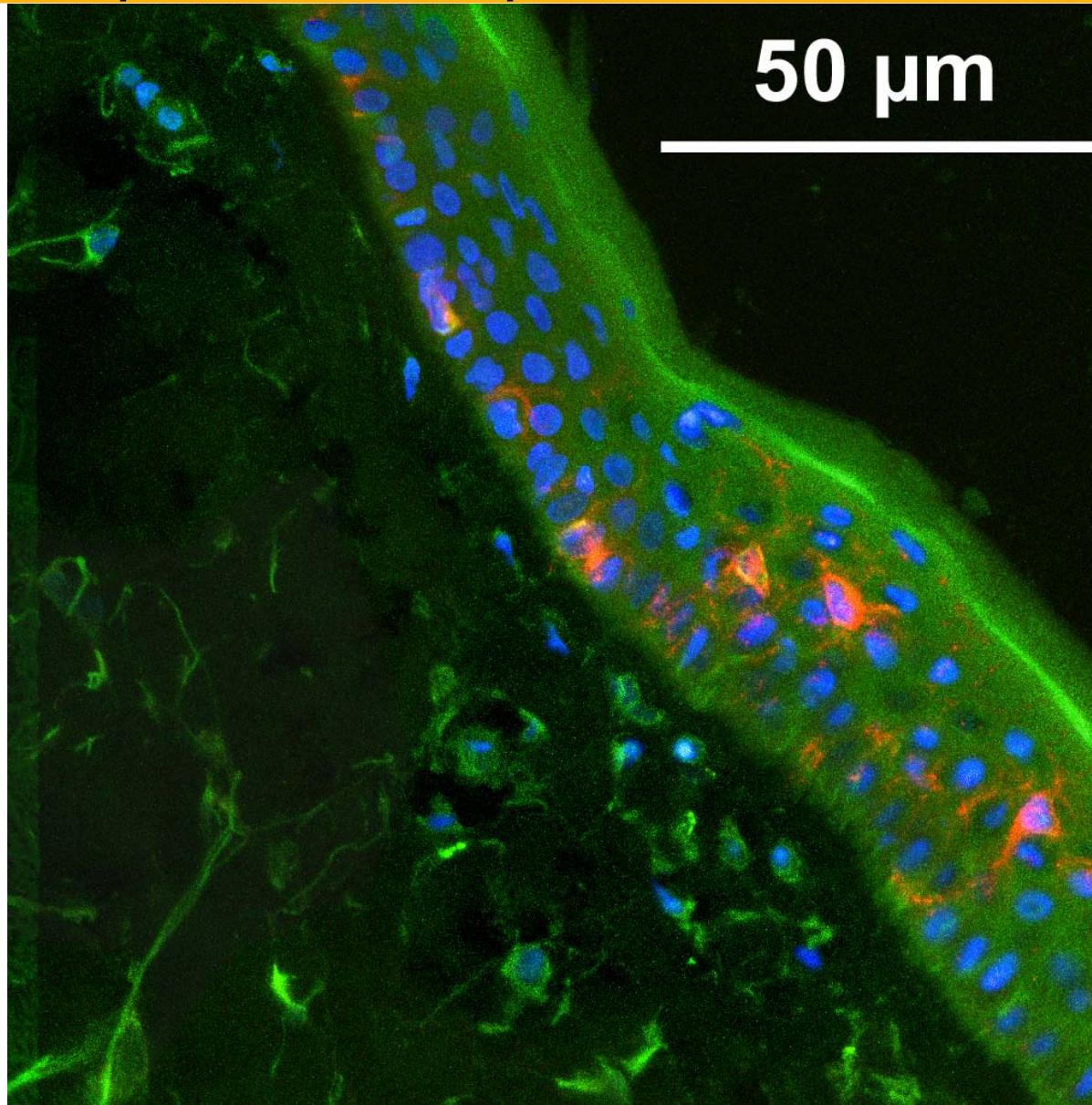
HIV p24 expression after DNA intradermal injection (24h)



- EP increase p24 expression in epidermis after MultiHIV DNA intradermal injection

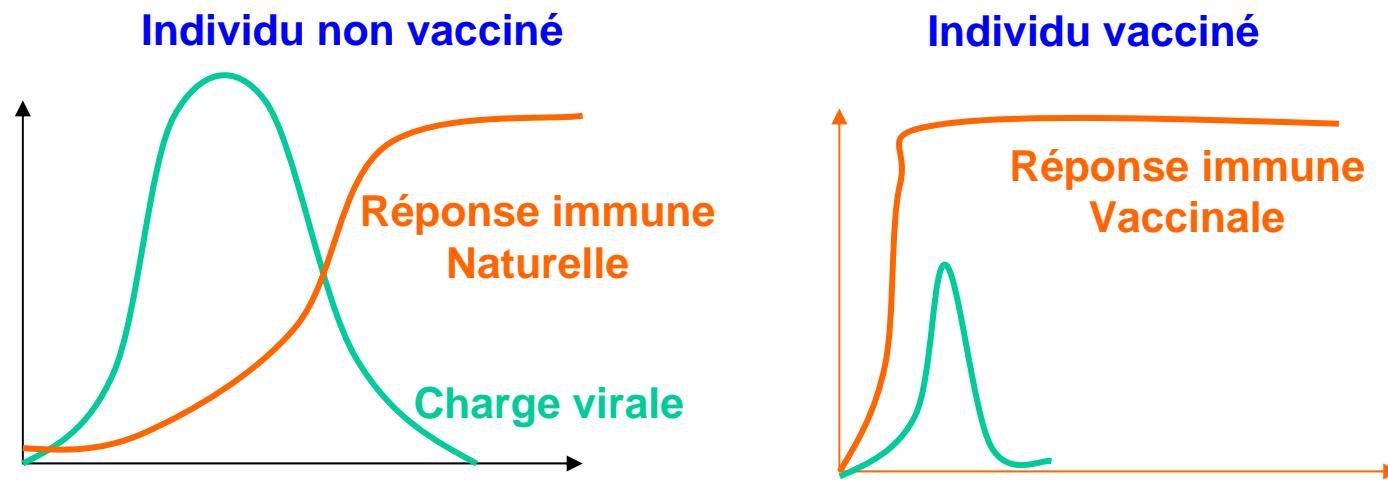
HIV p24 expression in epidermis

MultiHIV i.d. + EP
p24 + CD1a

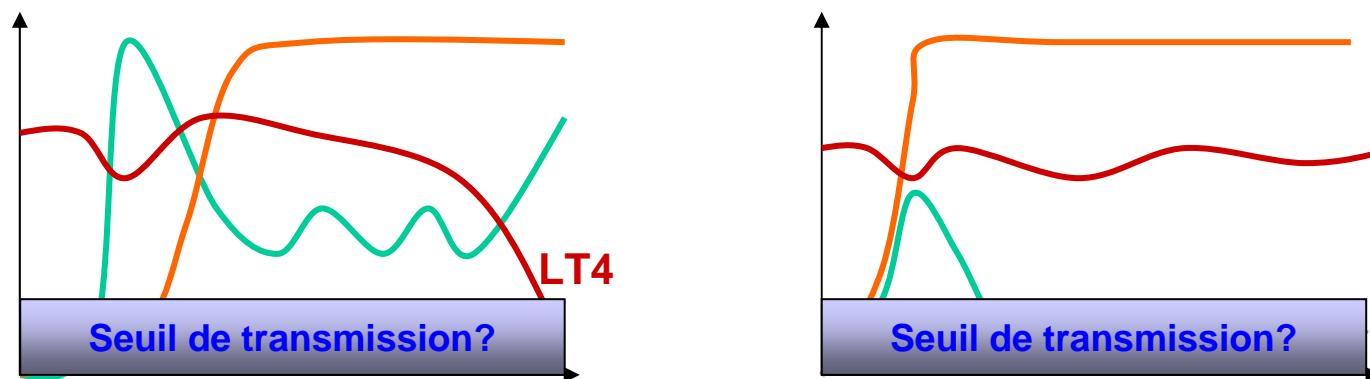


Vaccination et contrôle des infections virales

Infections spontanément résolutives: Les anticorps neutralisants protègent

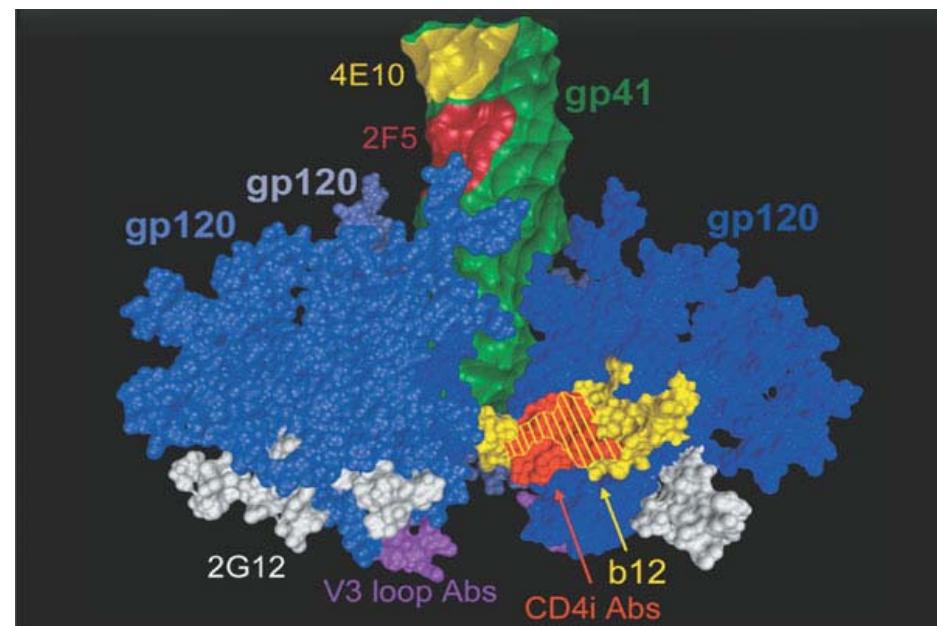


Infections chroniques: Nécessité d'une réponse cellulaire T cytotoxique?



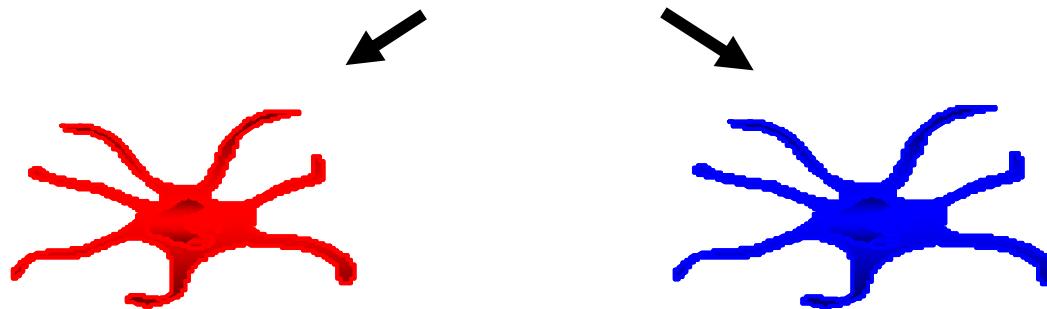
Neutralizing antibodies & protection of SHIV vaginal transmission

- 2G12: IgG1 recognizing an conformational glycosylation-dependant epitope overlapping the CD4 binding site of gp120 (C3-V4 region)
- 2F5: IgG1 recognizing the conserved ELDKWA sequence of membrane proximal external region (MPER) of gp41
- 4E10: IgG1 recognizing the conserved NWFDITNWLWYIK sequence of MPER of gp41
- Only a combination of NAb allows cross-clade neutralization of HIV-1 isolates *in vitro*
(Binley, J Virol, 2004, 78, 13232)



From Burton et al, Nat Immunol, 2004, 5, 233

Skin dendritic cells



*Interstitial DC
B cells and
Tfh priming*

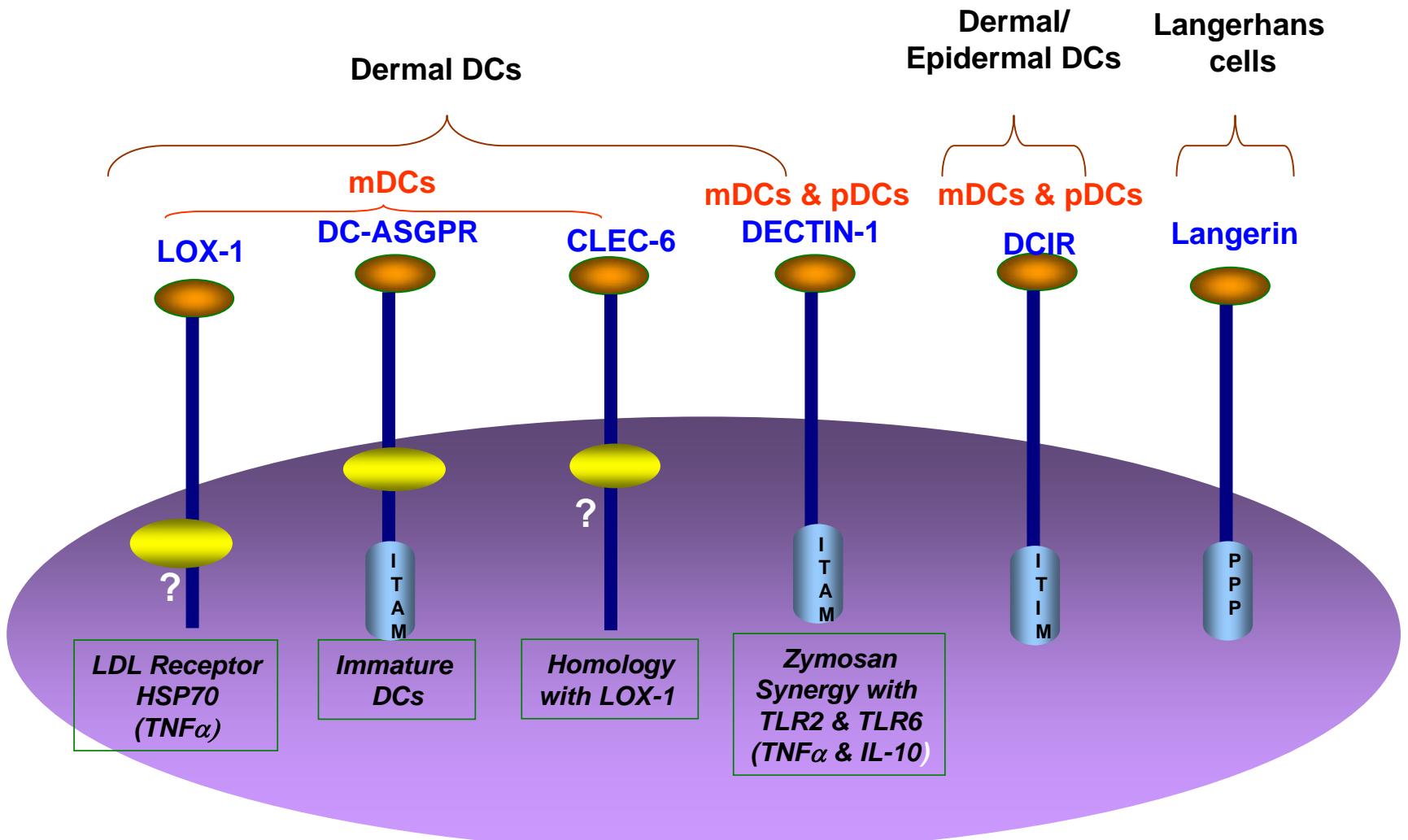
*Langerhans DC
CD4⁺ and CD8⁺ T cell priming*

HUMORAL IMMUNITY

CELLULAR IMMUNITY

Activation of memory T and B cells

Expression of DC-lectins in subsets of DCs

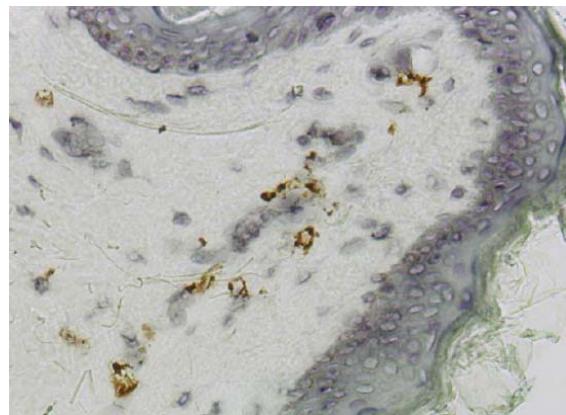


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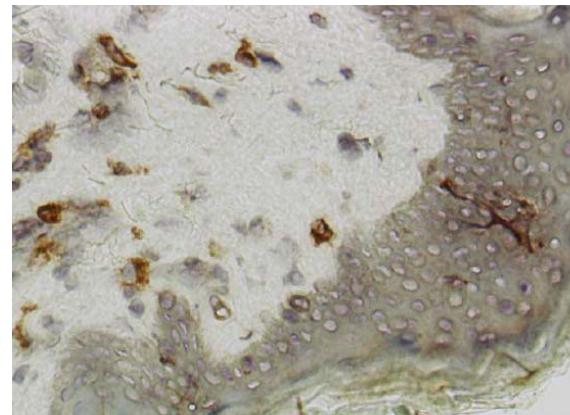
: CRD or CRD-like domain : Tyrosine-based motif for targeting to coated pits and internalization

LOX-1 and DC-ASGPR are mainly expressed in dermal cells

Anti-LOX-1



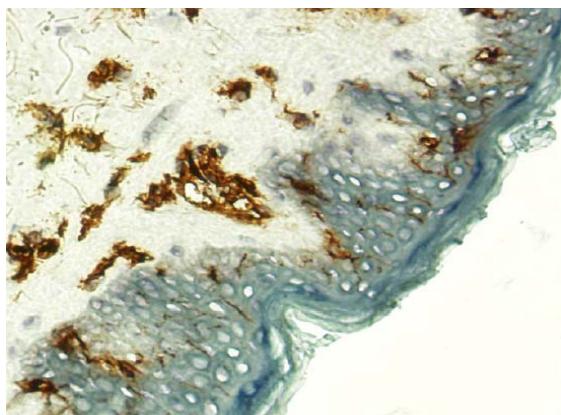
Anti-DC-ASGPR



x40

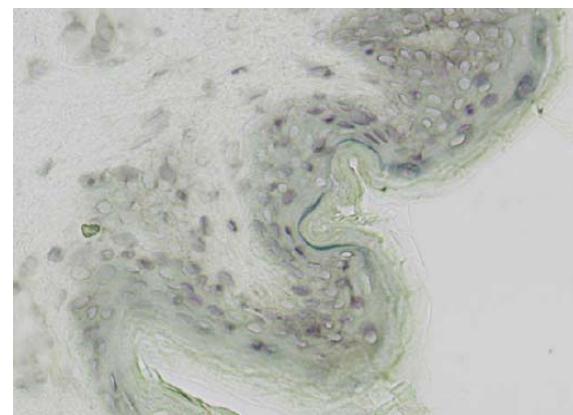
x40

Anti-HLA-DR

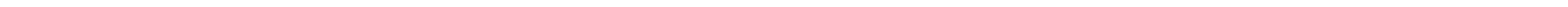


x40

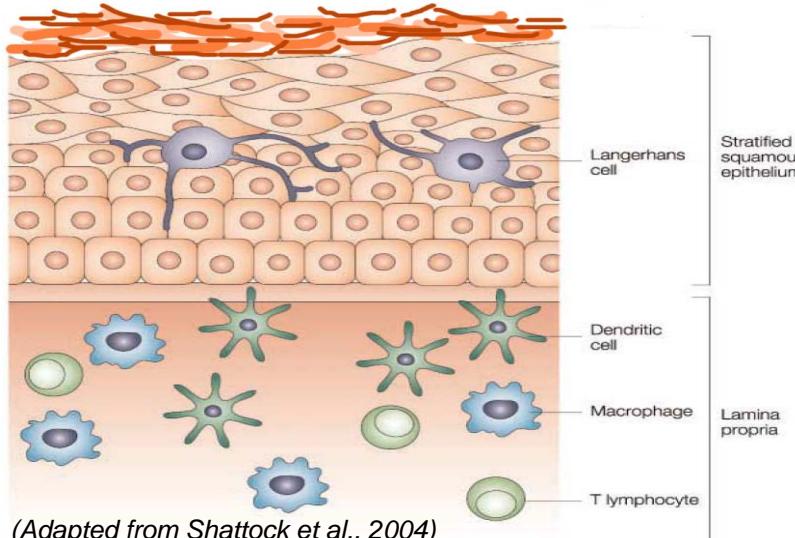
Isotype control Ig



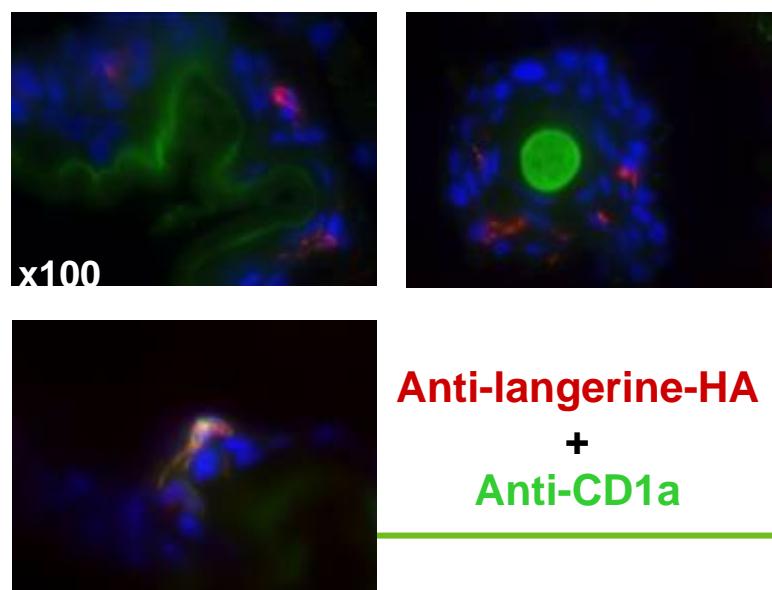
x40



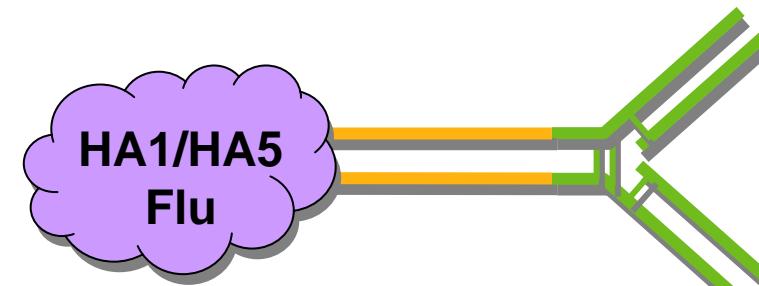
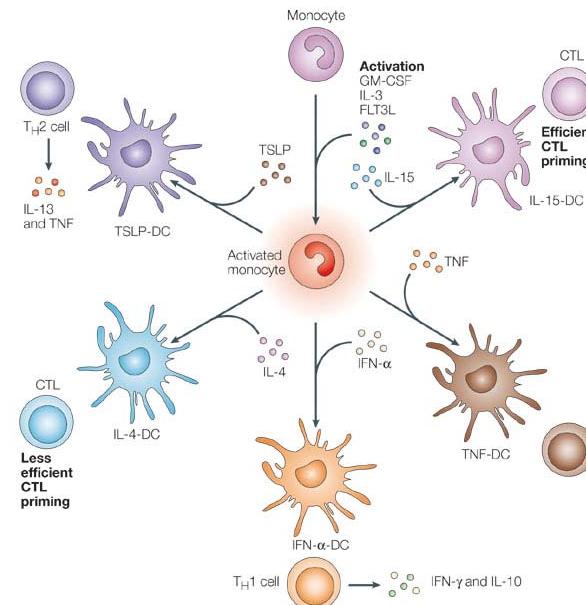
Ciblage des antigènes du virus de la grippe



(Adapted from Shattock et al., 2004)

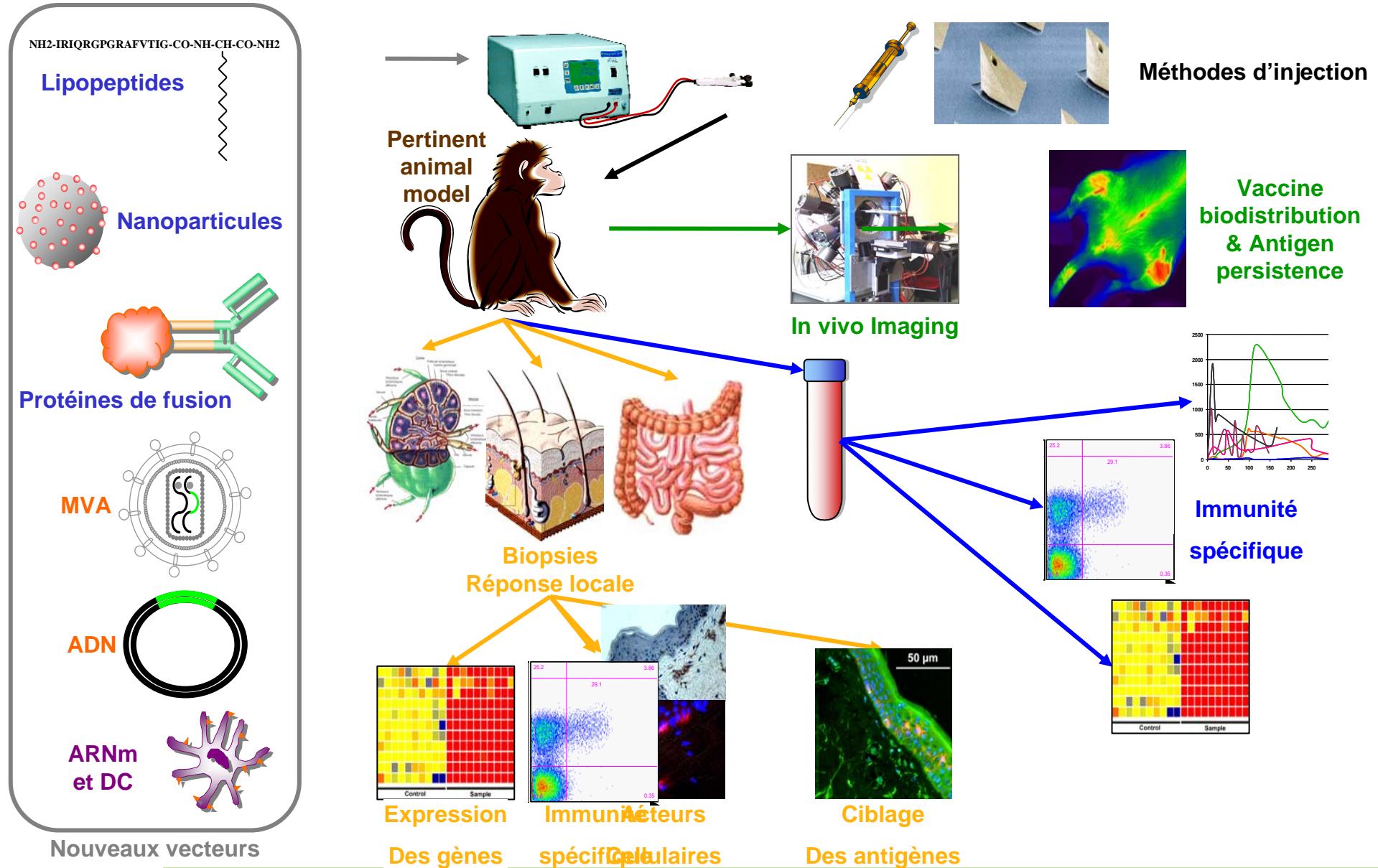


Anti-langerine-HA



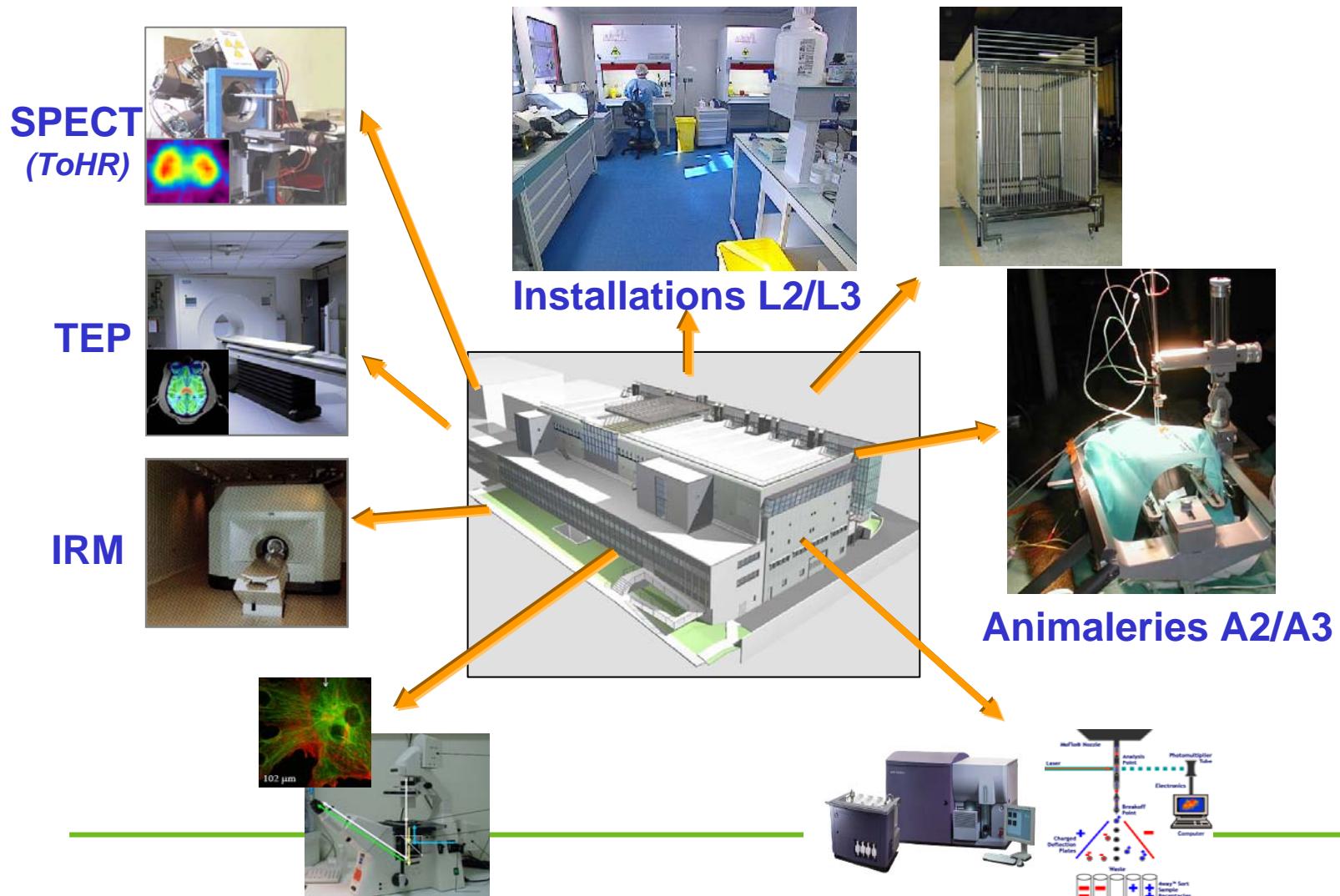
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Bases fondamentales de la vaccination



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