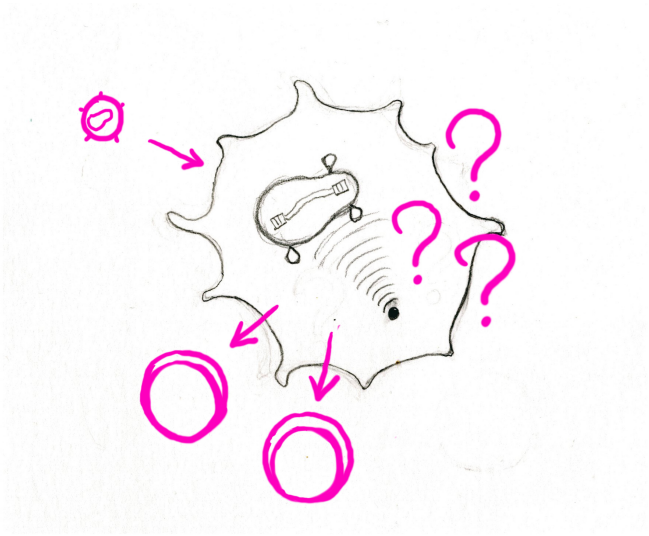
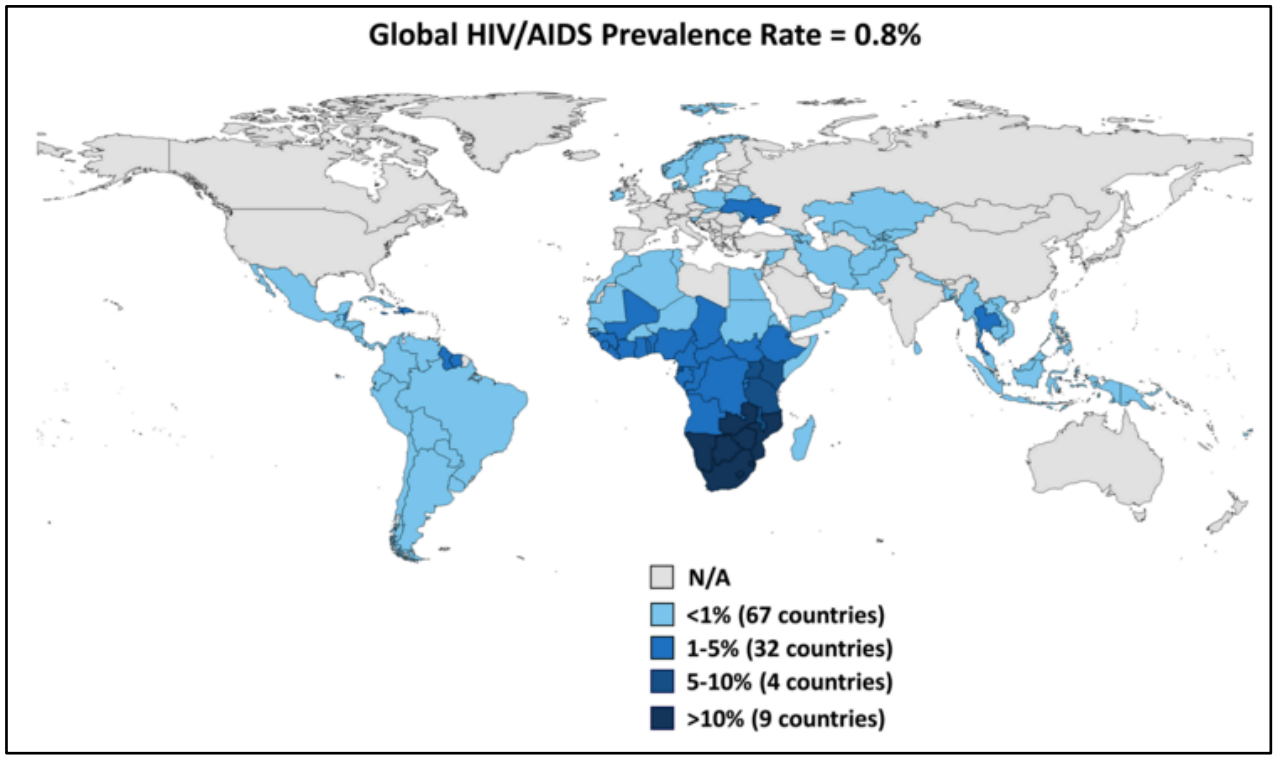
Induction of protective innate immune responses:
Lessons learned from HIV-2



Nicolas MANEL – INSERM U932 – Institut Curie

03/05/2016 – Fondation Mérieux

Current clinical strategy for HIV worldwide



Source: Kaise family / UNAIDS 2014

- Need to put all infected individual on therapies

- Need for a Cure due to several limitations of current drugs:
  - adherence to treatment
  - renal toxicity
  - neuropsychic effects
  - cost

HIV vaccine as a cure

Therapeutic (functional cure)

- Induce functional cytotoxic CD8+ T cells to kill actively infected cells
- Control viral load to prevent transmission
- Produce neutralizing antibodies to the virus

Prophylactic

- Induce functional cytotoxic CD8+ T cells residing at mucosal sites
- Produce neutralizing antibodies at mucosal surfaces

Main current vaccine strategies

- **Non-HIV viral vectors (Ad, MVA)**
  Limits: Dilution of HIV epitopes by vector epitopes
  Quality of the immune response dictated by the vector

- **Viral peptides coupled to x**
  Limits: Limited functional CD8/CD4 response
  Limited breadth to viral epitopes

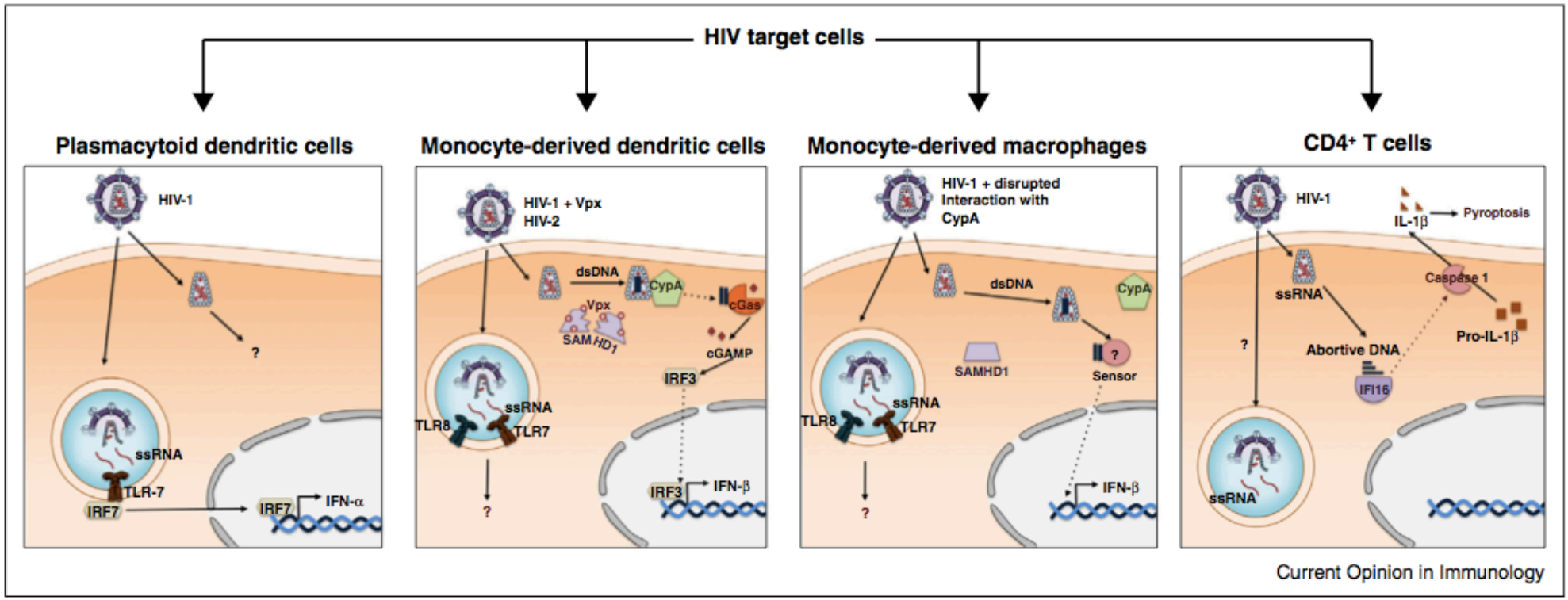
- **Viral proteins to raise bnAbs**
  Limits: Method of induction is unknown
  gp41/gp120 antigens

INNATE IMMUNITY IN HIV INFECTION

- unchecked induction of innate immune responses → ***Pathogenesis***

- avoidance of innate sensing pathways → ***Immune evasion***

Cell-extrinsic / Cell-intrinsic sensing in CD4+ target cells



Silvin & Manel, Current Opinion in Immunology, 2015

INNATE IMMUNITY IN HIV INFECTION

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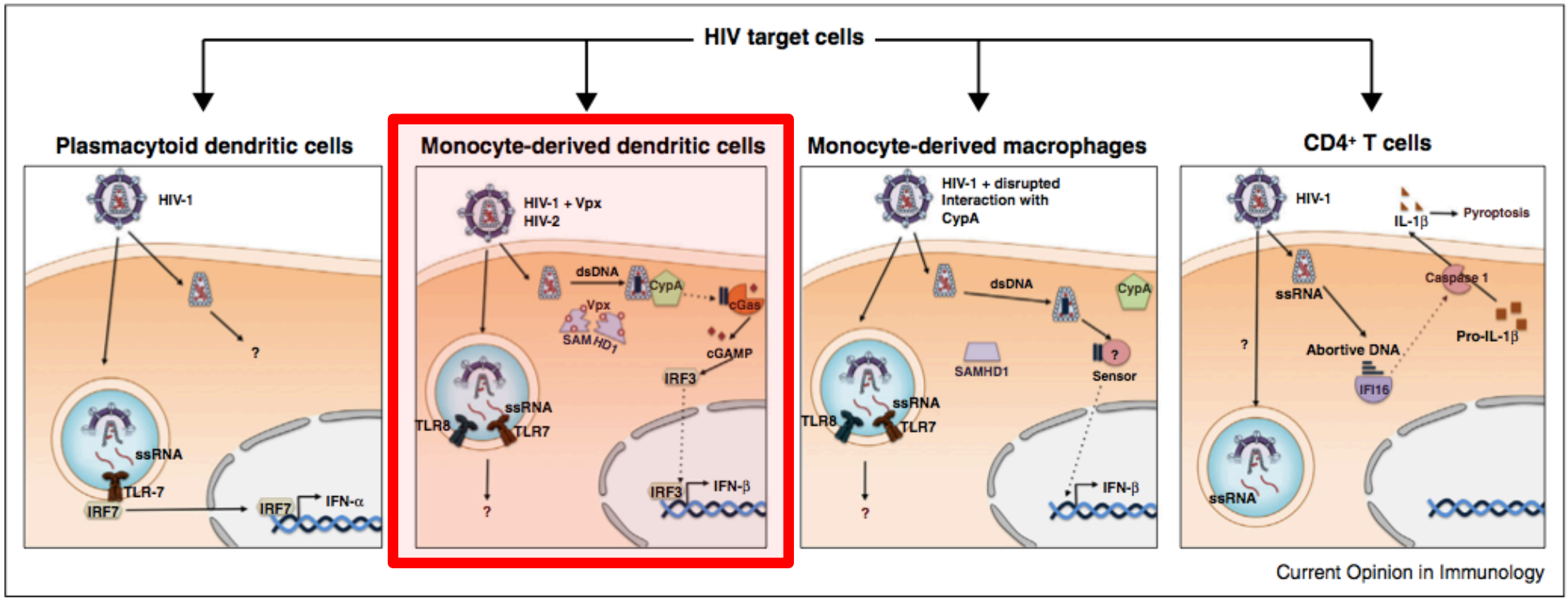
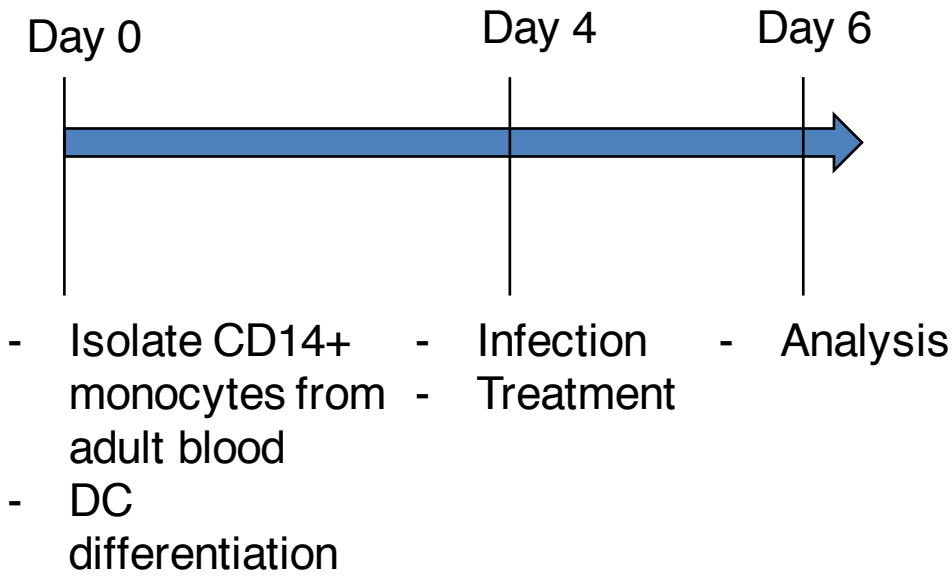
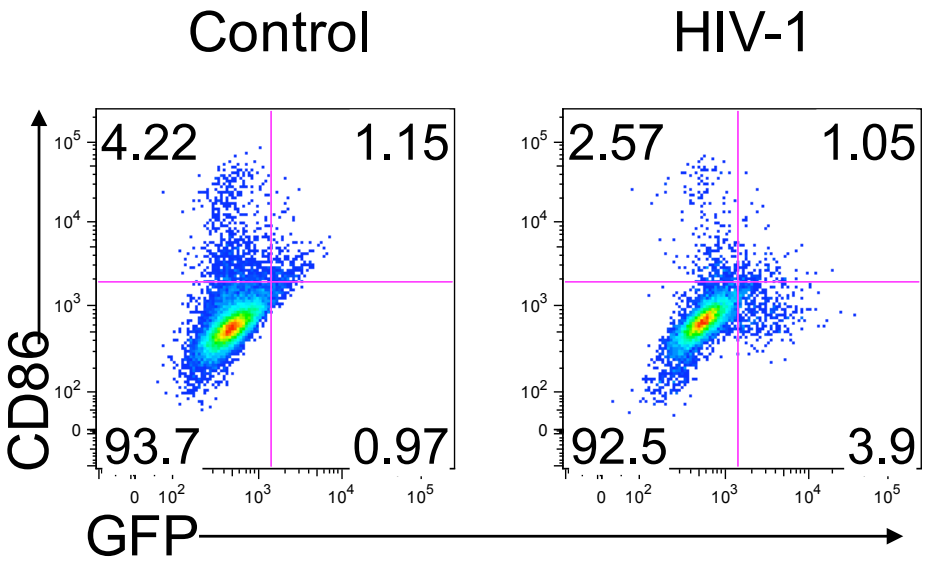


Silvin & Manel, Current Opinion in Immunology, 2015

DCs do not get activated in response to HIV-1 in vitro

"DCs do not sense HIV-1"

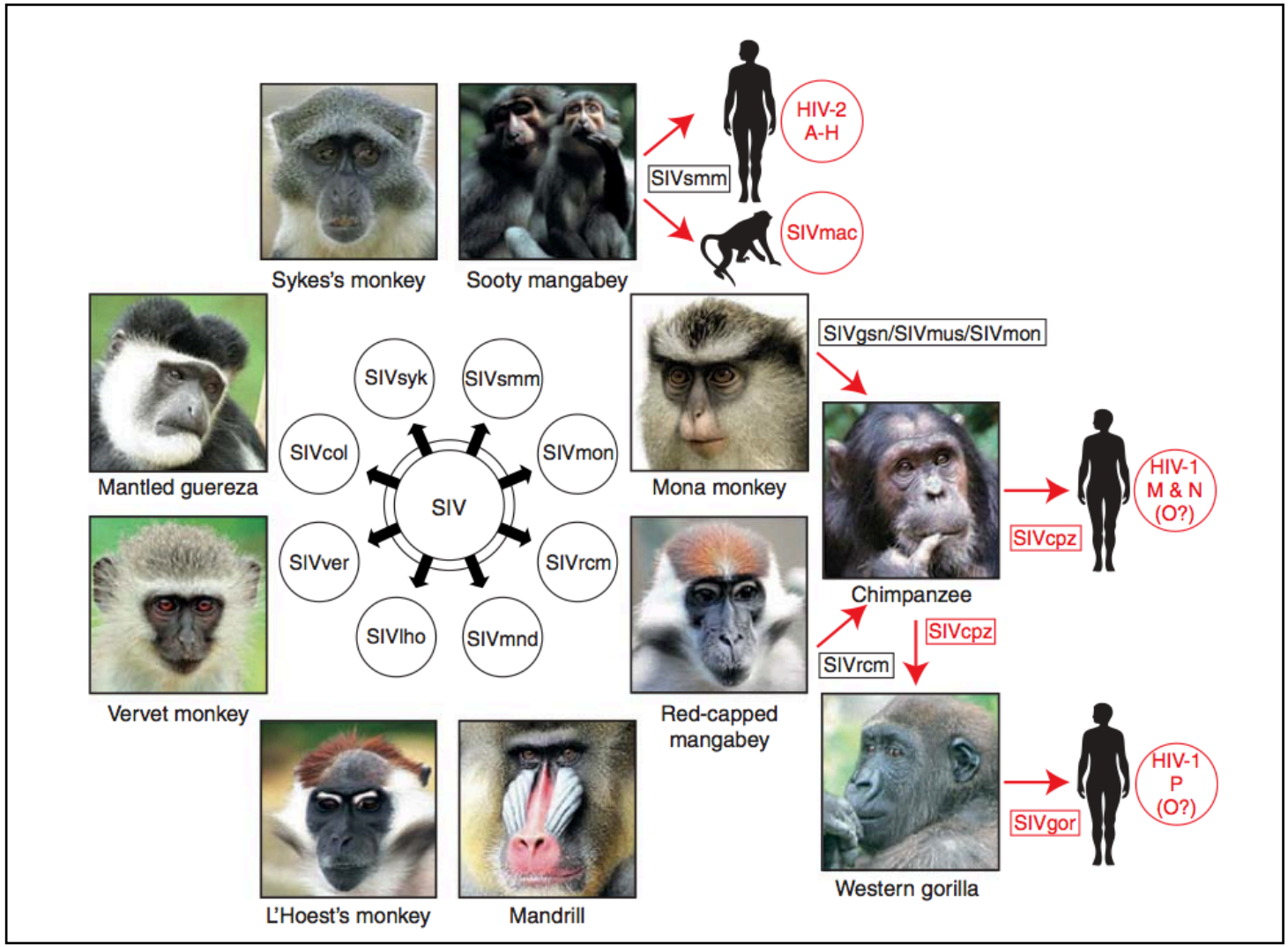




No machinery in DCs?

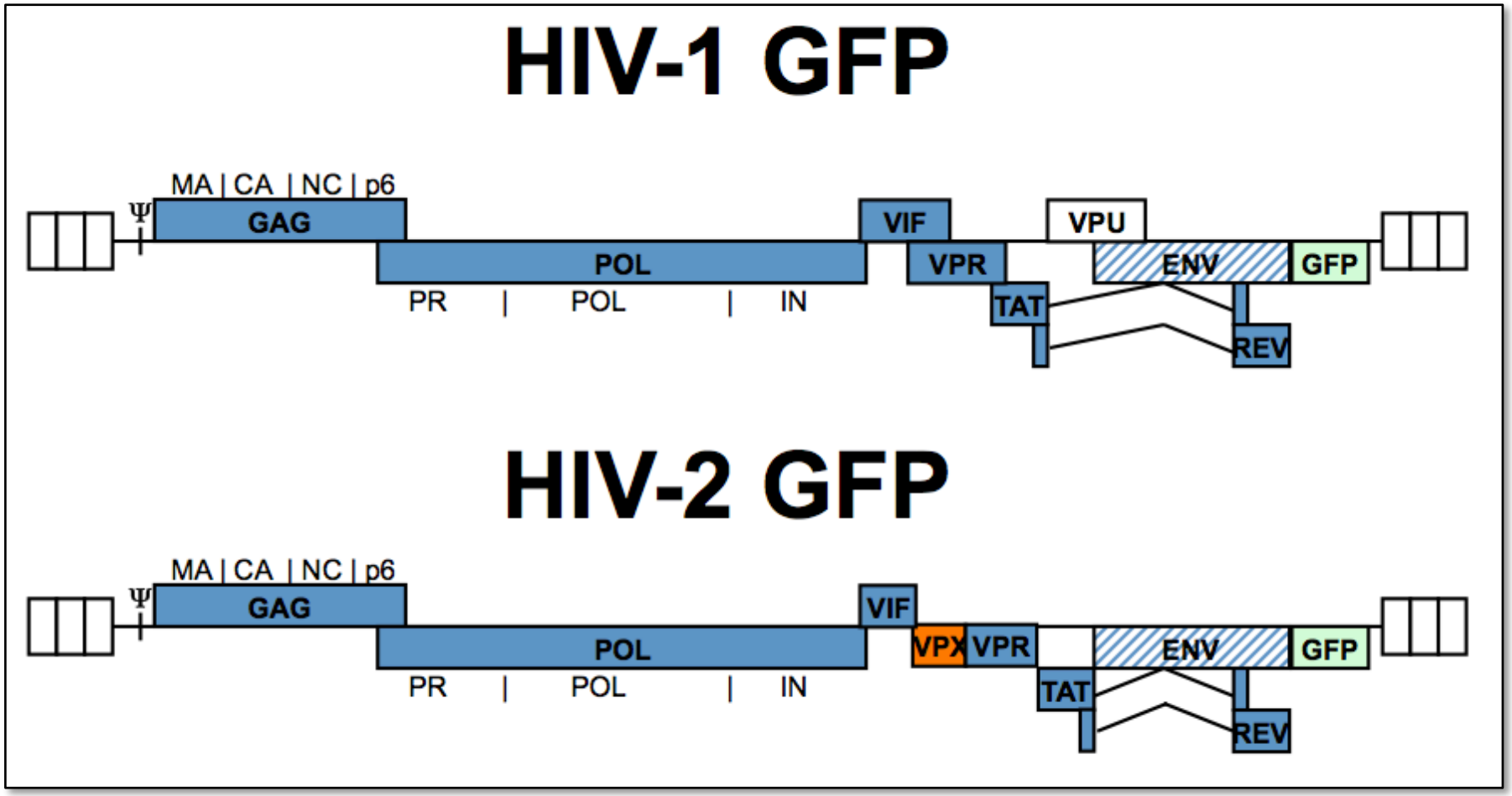
or **Viral escape?**

Primate lentiviruses

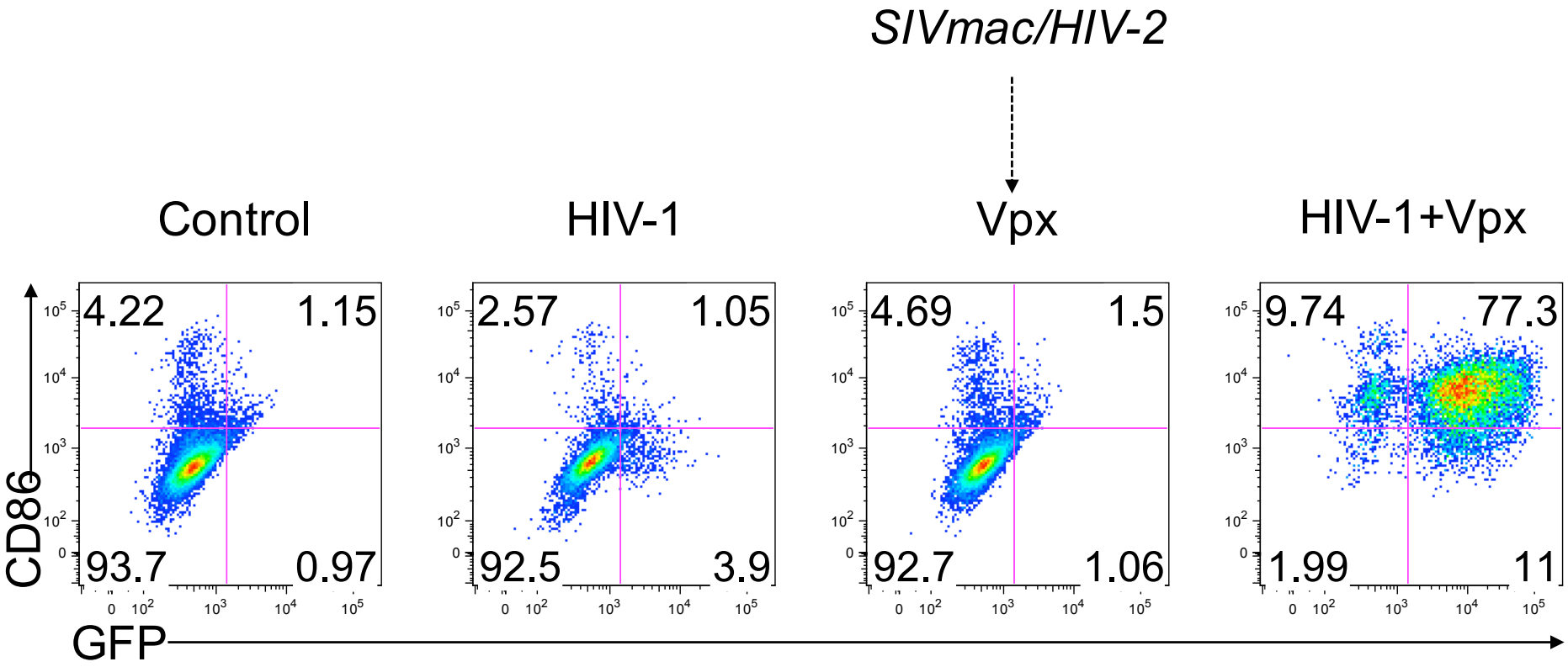


Sharp/Hahn 2011

HIV-2 encodes the Vpx protein, absent in HIV-1



DCs sense HIV-1 when replication blocked is removed



➔ existence of a DC-intrinsic, cytosolic, sensing machinery of HIV-1

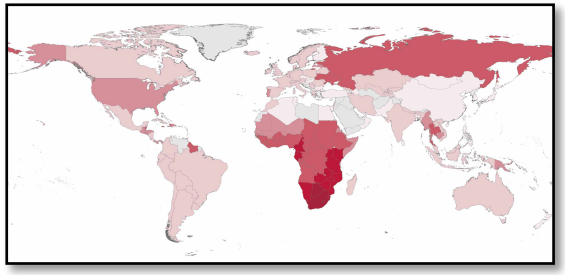
Manel et al., Nature 2010

HIV-2 is less pathogenic than HIV-1

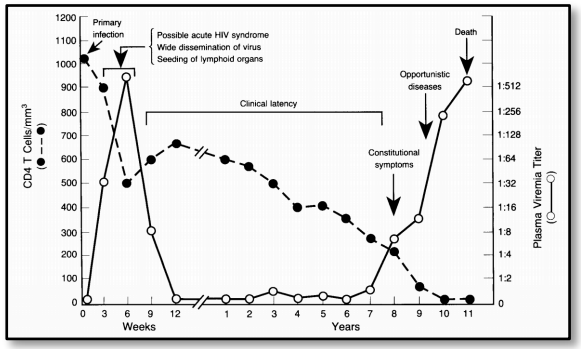
HIV-1

>98% AIDS

<2% control



UNAIDS



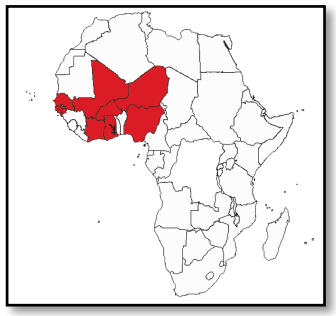
Pantaleo et al., NEJM 1993

Inability of the immune system to control the virus

HIV-2

<25% AIDS

>75% control

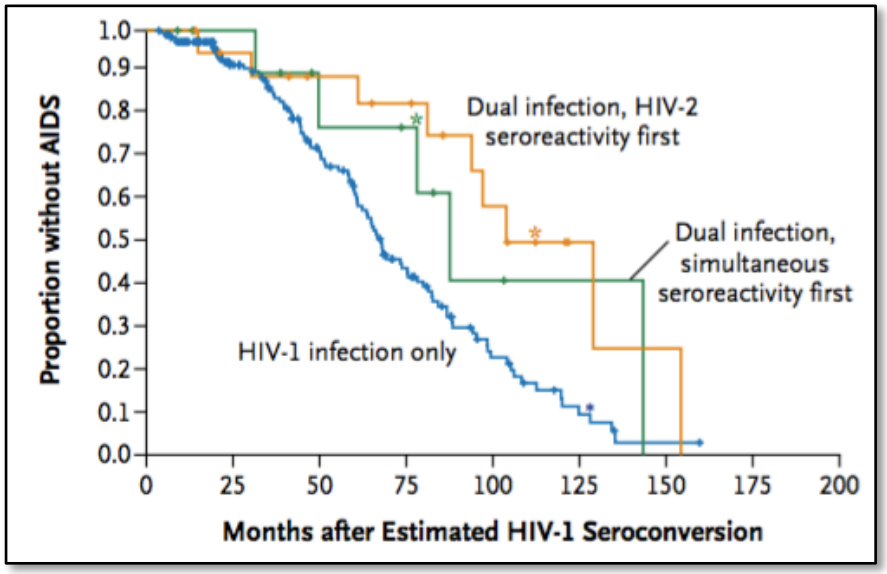


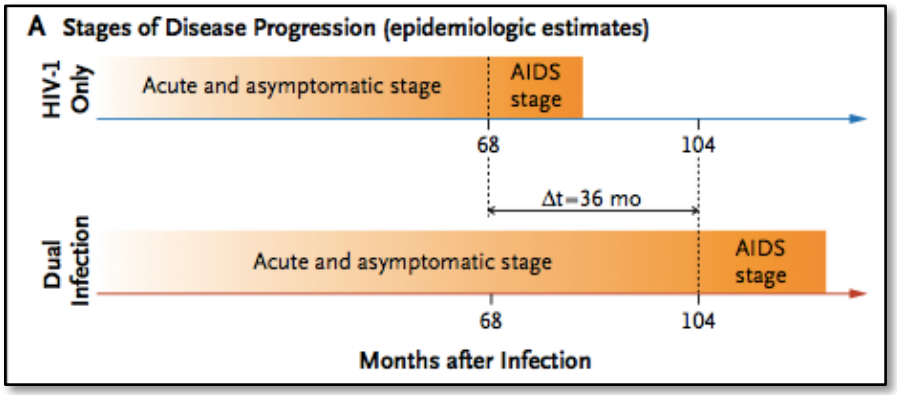
Apparent contribution of the immune system to control infection
(reviewed in Rowland-Jones et al., Nature Immunology 2007)

HIV-2 is not an attenuated virus,

but infected patients naturally exhibit characteristics of a desired response to an effective therapy against HIV.

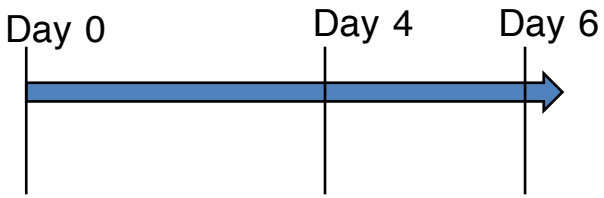
- Behave as Long-Term Non Progressors
- Low or no viral load detectable
- Proviral load is controlled
- Neutralizing antibodies for >15 years (Silva/Weiss JVI 2011)
- CTLs are more polyfunctional
- Larger breath of targeted epitopes
- Partial cross-protection against HIV-1 pathogenesis:



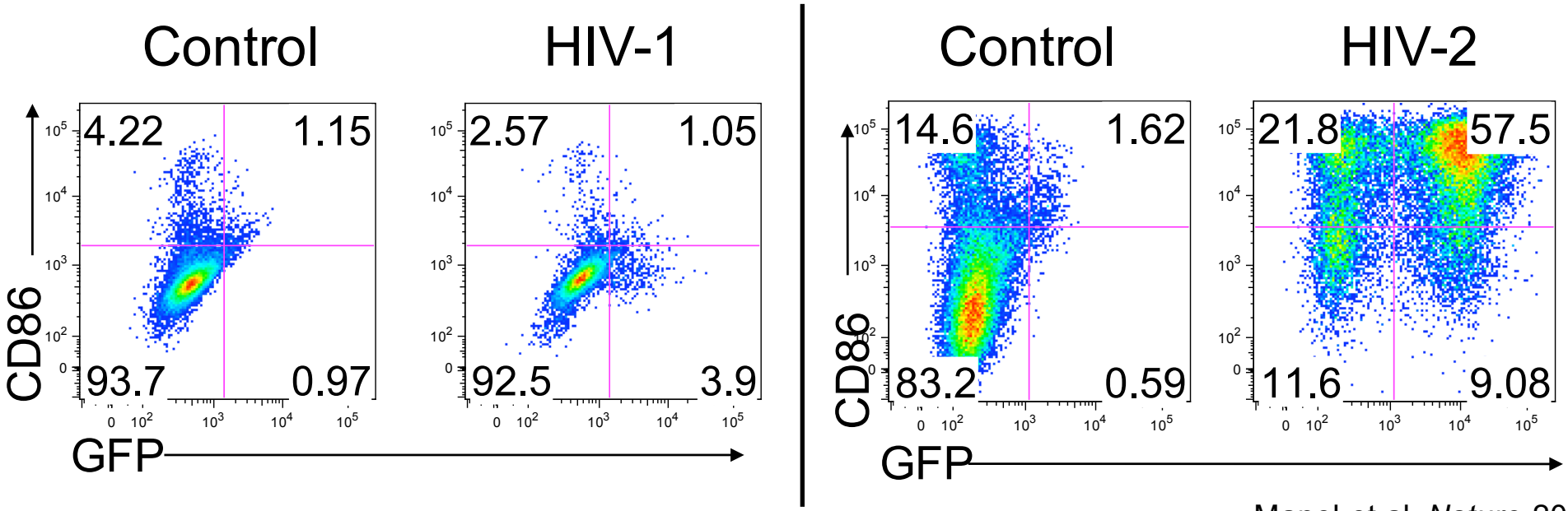


Esbjörnsson et al., NEJM, 2013

HIV-2 infects the DCs and DCs respond to the infection



- Isolate CD14+ monocytes from adult blood
- DC differentiation
- Infection
- Treatment
- Analysis



Manel et al, *Nature* 2010
Manel & Littman, *Cell* 2011

Stimulation of dendritic cells

HIV-2 or HIV-1+Vpx

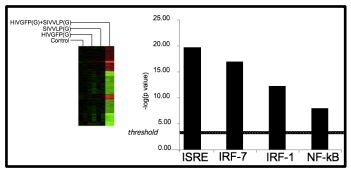
Rice et al., Nature Genetics 2009
Hrecka et al., Nature 2011
Laguette et al., Nature 2011
Goldstone et al., Nature 2011
Lahoussa et al., Nat Imm 2012

Degradation of SAMHD1

cGAS-mediated cytosolic innate sensing

Low dose IFN response
+ DC maturation

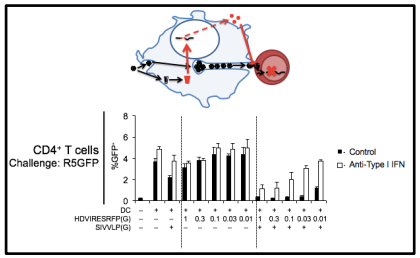
Manel et al. Nature 2010
Gao et al. Science 2013
Lahaye et al. Immunity 2013



Infection

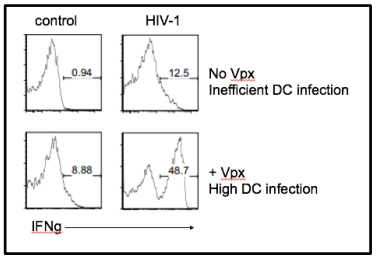
Increase in viral antigens

Protection of CD4+ T cells



Manel et al. Nature 2010

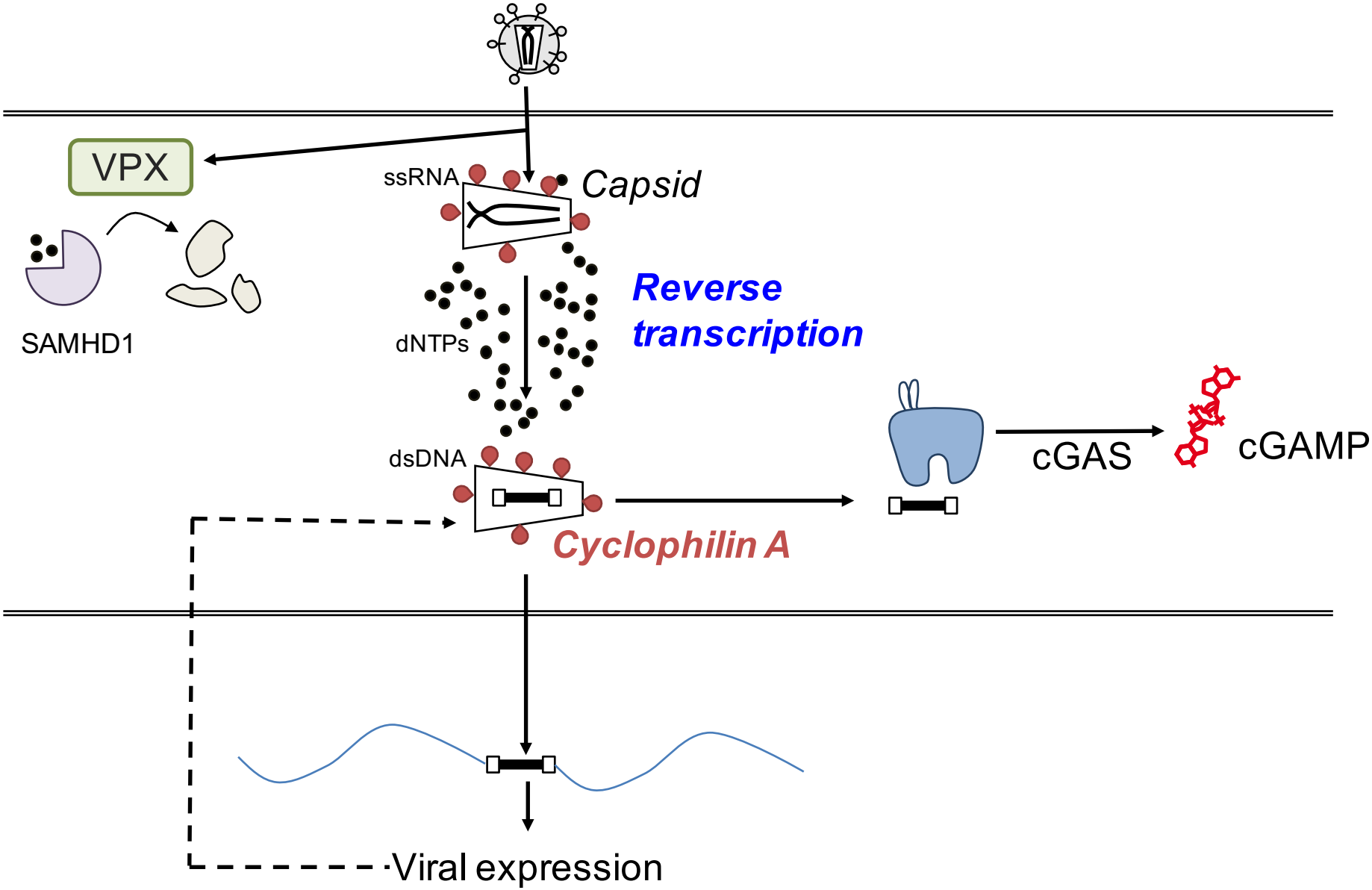
Antigen presentation to CD4+ and CD8+ T cells



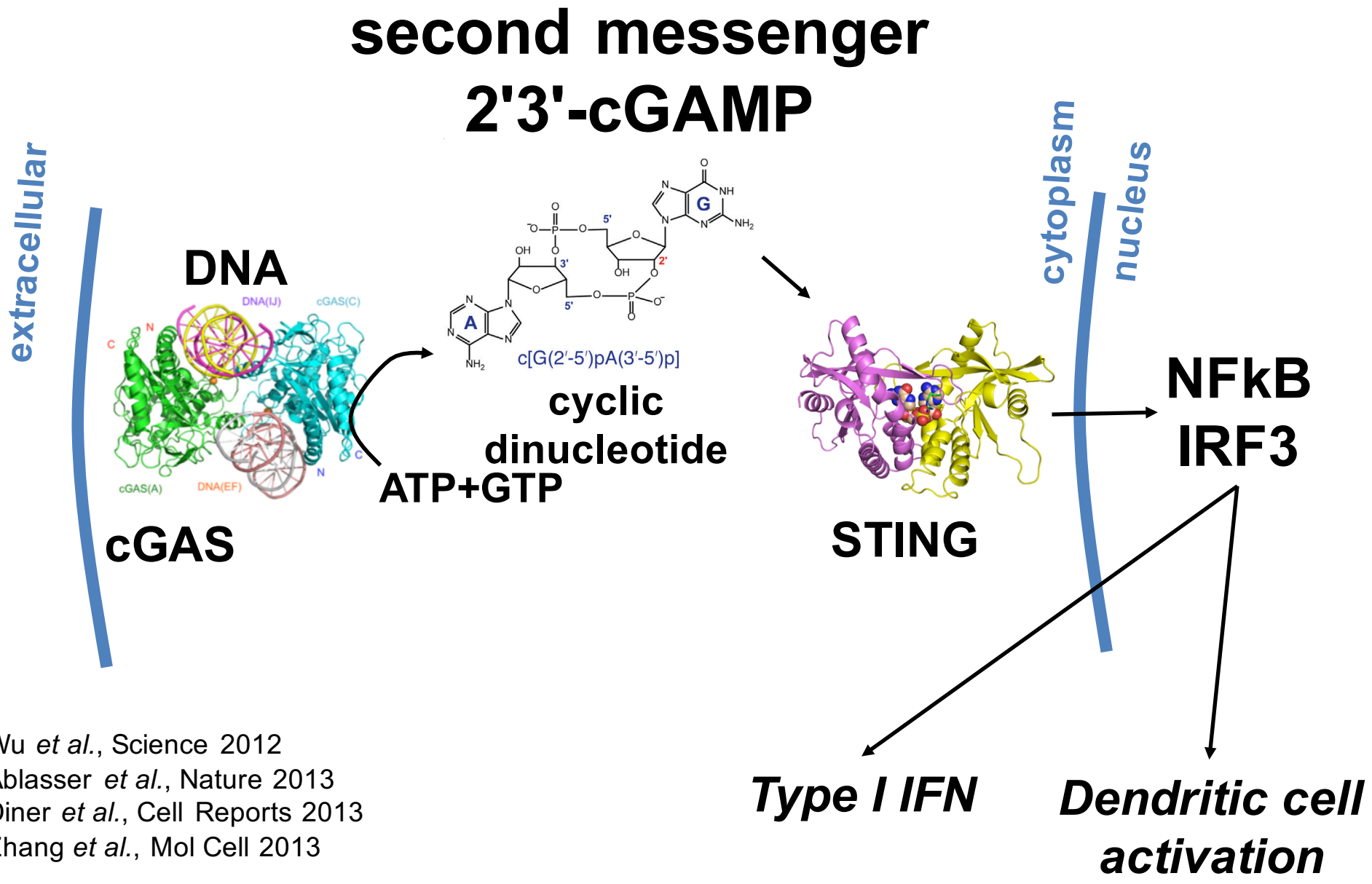
Manel et al. Nature 2010

Molecular mechanism of HIV sensing by dendritic cells

Manel & Littman, Cell 2011

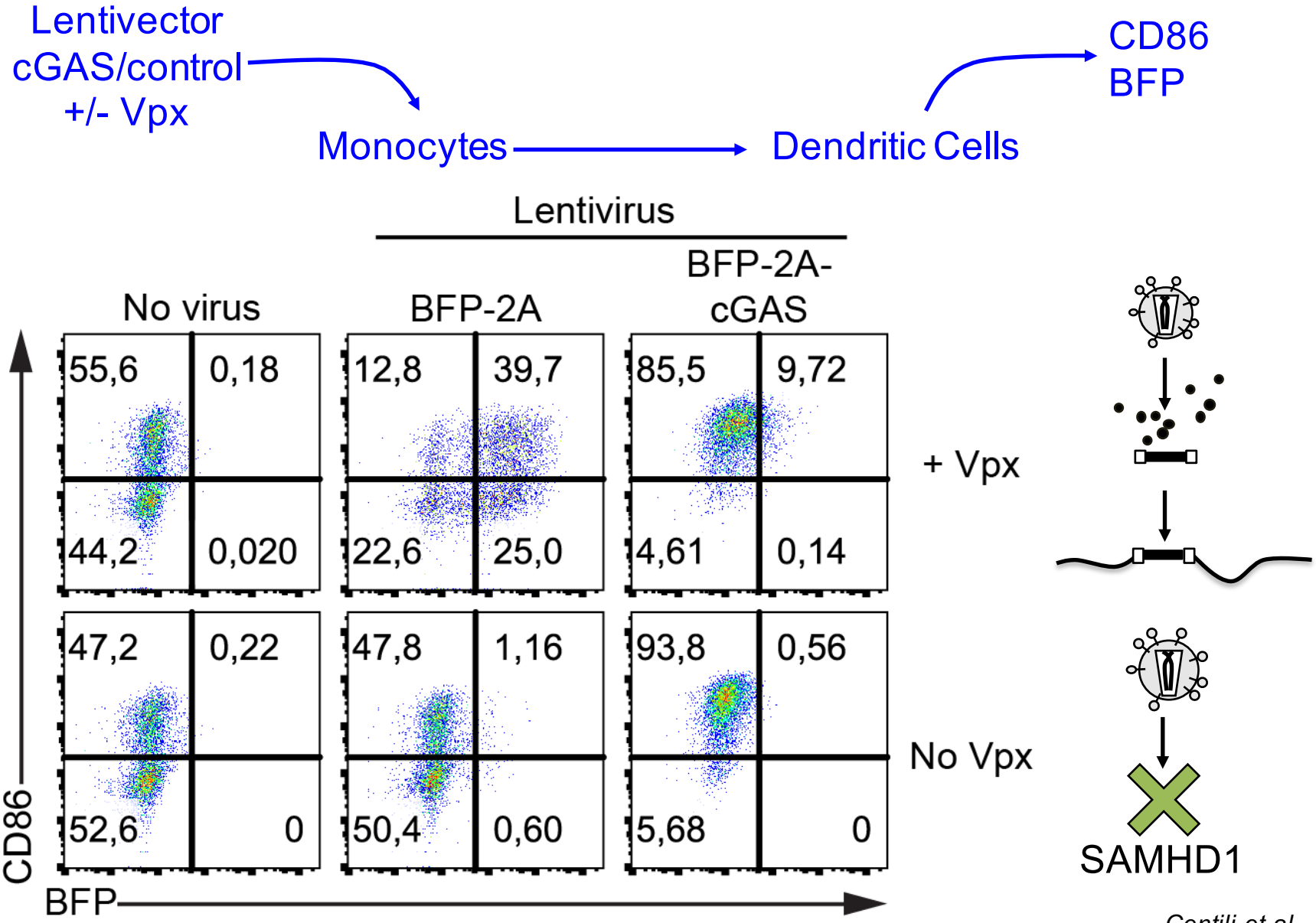


cGAS = cyclic GMP-AMP synthase



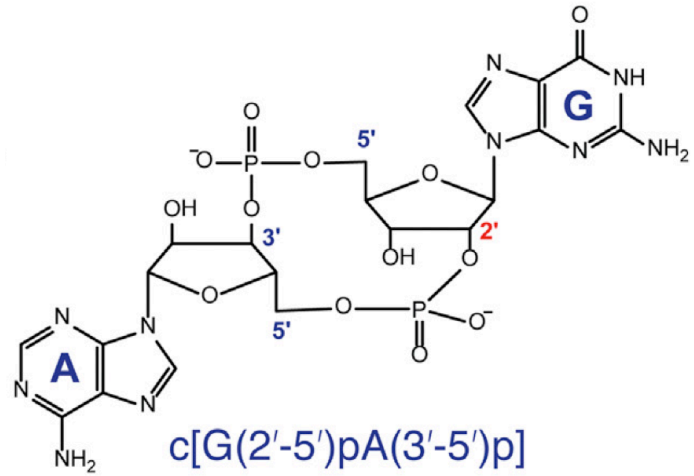
Wu *et al.*, Science 2012
Ablasser *et al.*, Nature 2013
Diner *et al.*, Cell Reports 2013
Zhang *et al.*, Mol Cell 2013

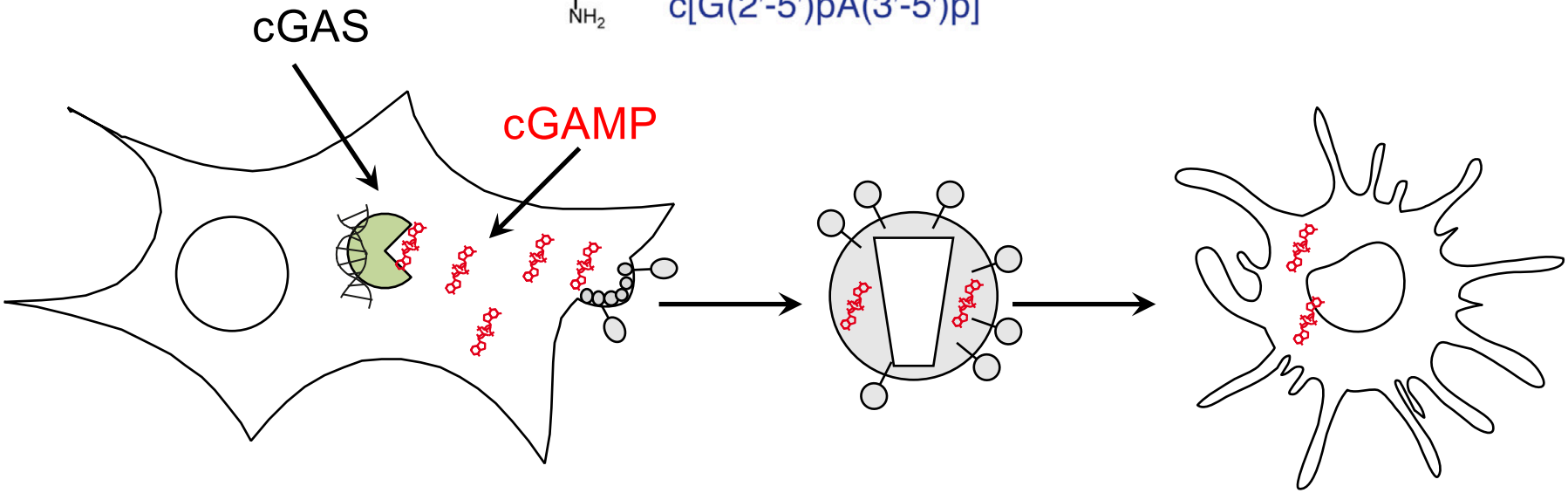
cGAS transduction activates MDDCs



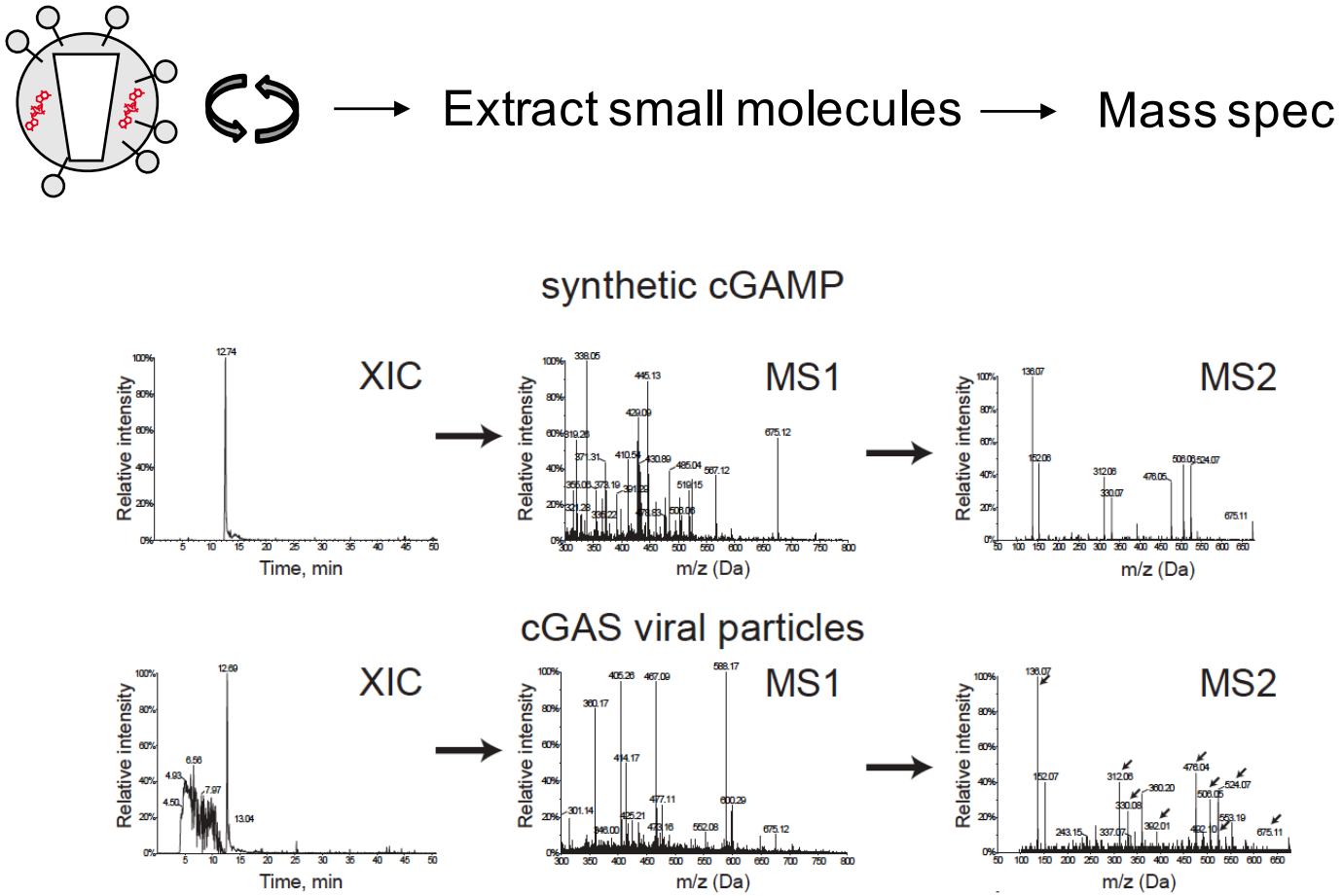
Gentili et al., Science 2015

Is cGAMP packaged into viral particles and transmitted to target cells?



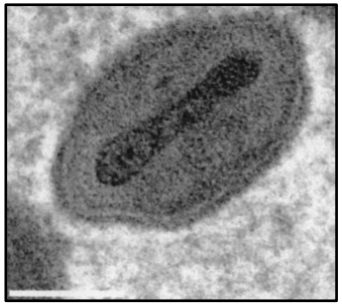


Detection of cGAMP presence in viral particles

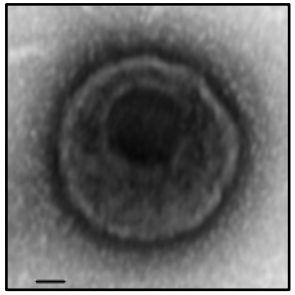


Gentili et al., Science 2015

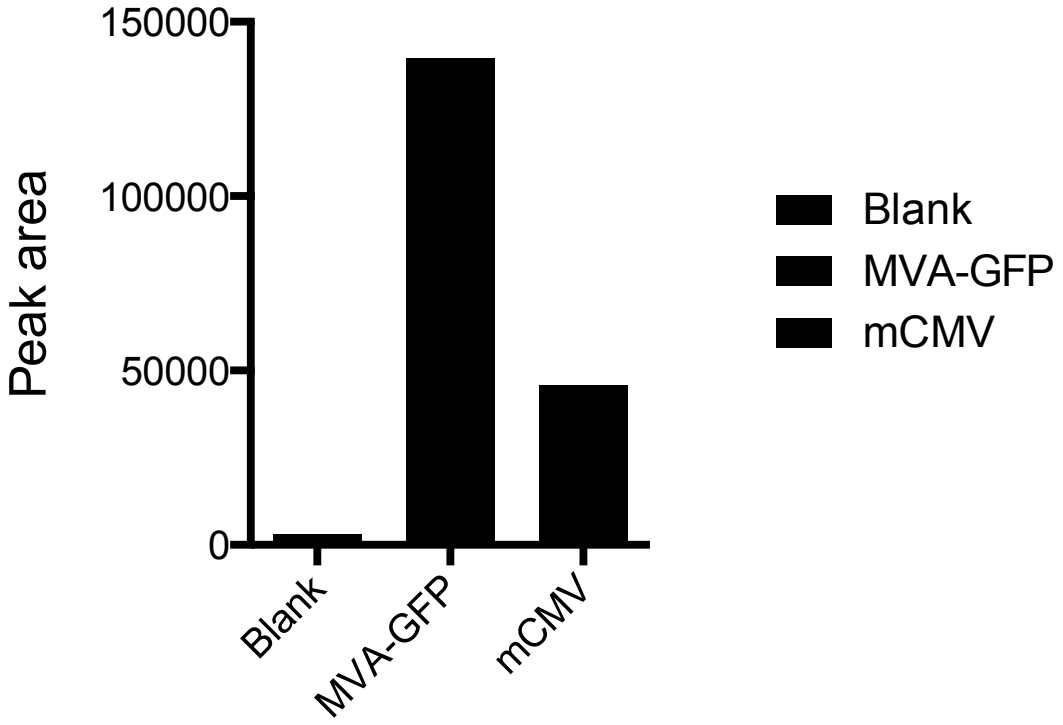
cGAMP is present in viral stocks of enveloped DNA viruses



Modified Vaccinia Ankara (MVA)
(bar 100 nm)
Gallego-Gómez, JVI 2003

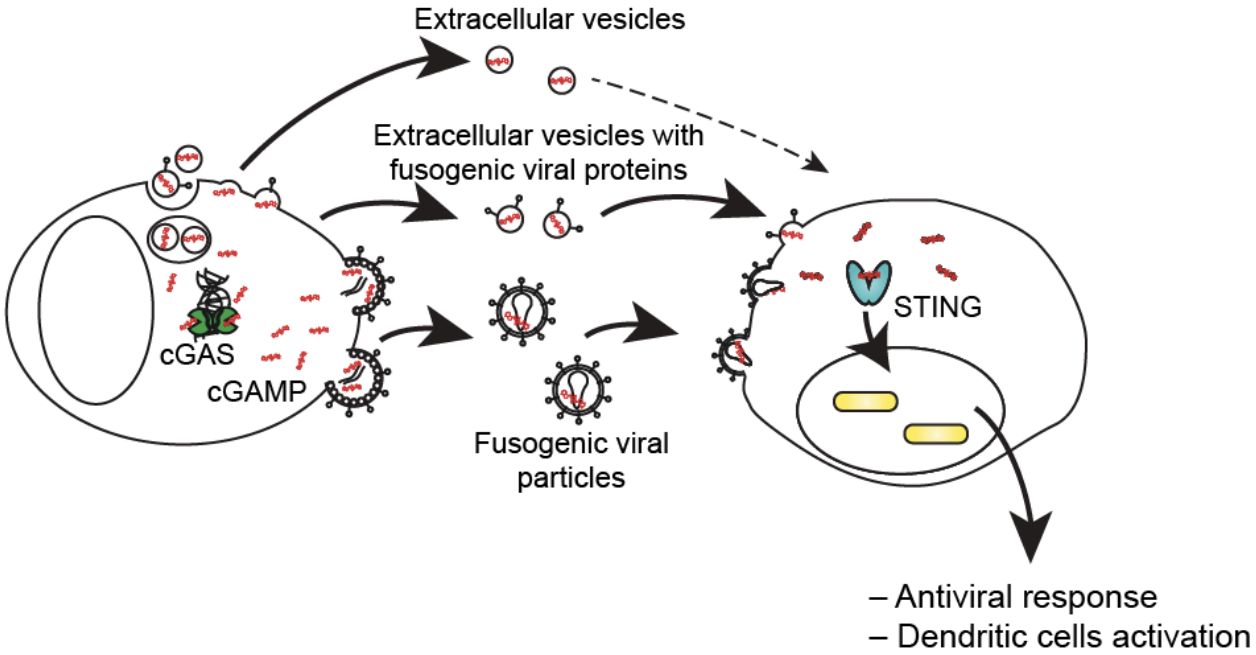


mCMV
(bar 100 nm)
Shaw-Wei, J. Biomed. Opt. 2012



Gentili et al., Science 2015

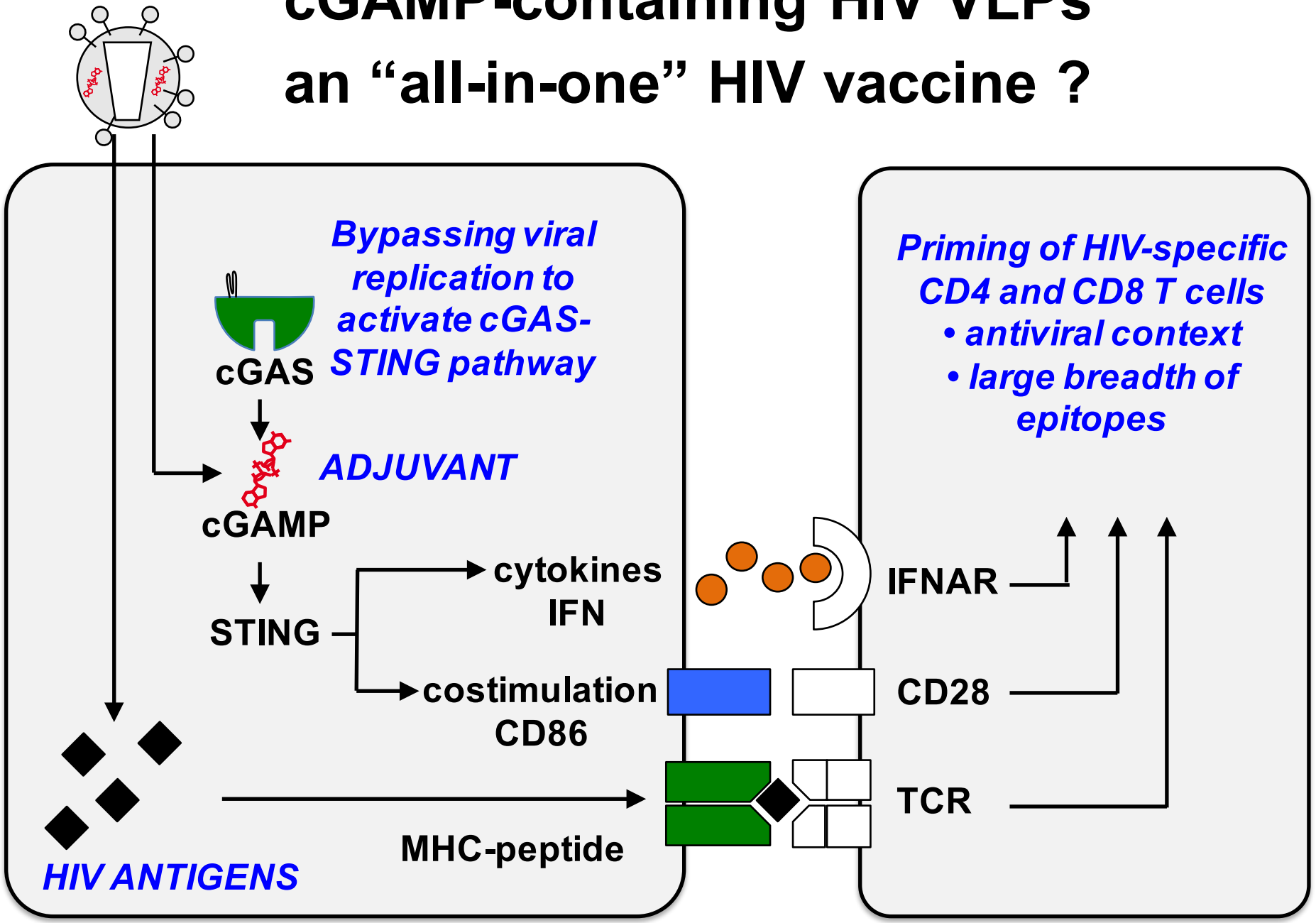
Transfer of innate immune signaling by packaging of cGAMP in viral particles



- Enveloped virues function as paratenic hosts for cGAMP
- Packaging of a DAMP in viral particles – "tagging" viruses as danger
- Spreads an immune signal that leads to DC maturation and antiviral protection
- HIV-1 normally escapes cGAS stimulation
- Provides a vectorization mean for cGAMP

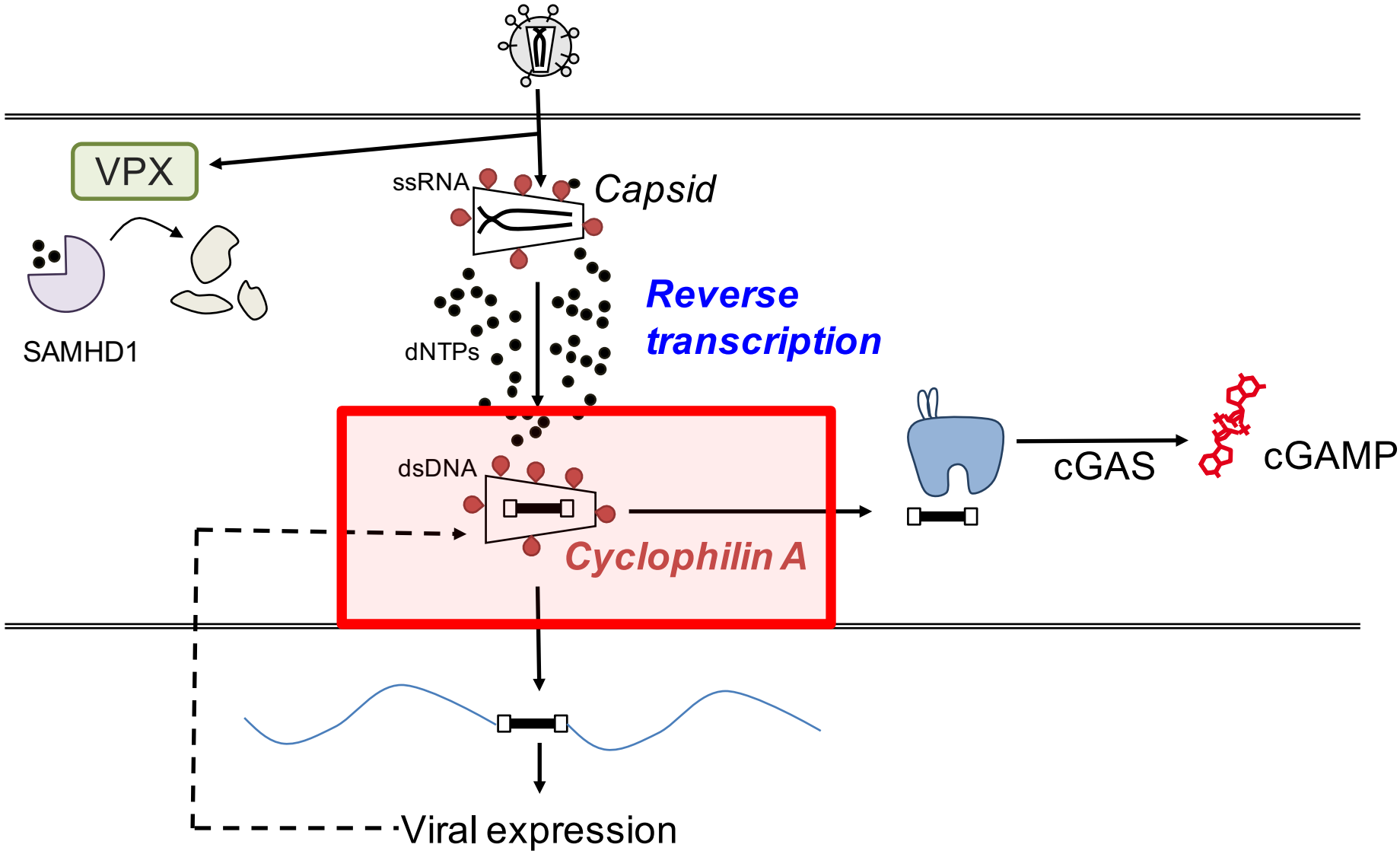
Gentili et al., Science 2015

cGAMP-containing HIV VLPs an "all-in-one" HIV vaccine ?

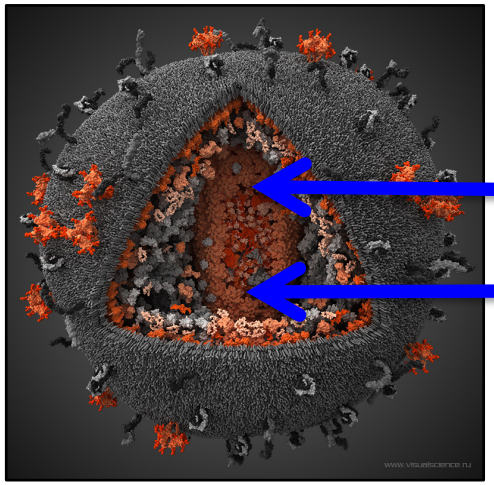


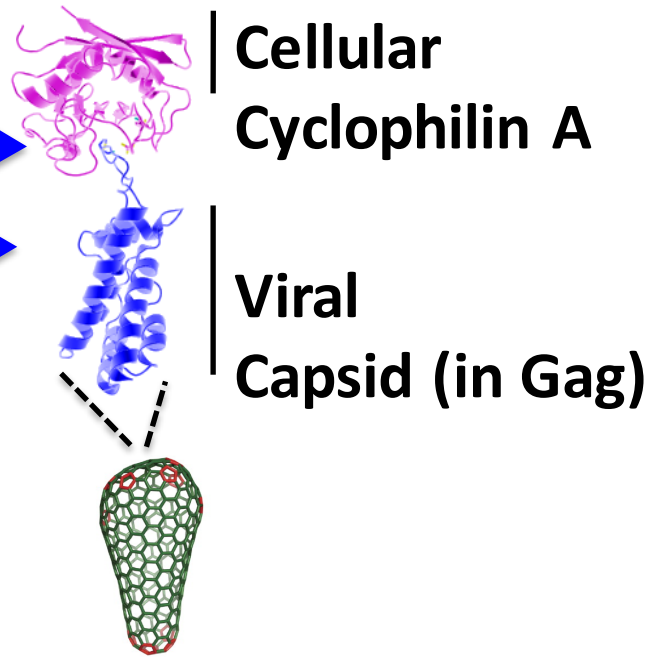
Capsid-cyclophilin A interactions play a critical role at the intersection of replication vs. innate sensing

What are the associated host factors ?



Cyclophilin A:
Host protein that binds the HIV capsid





Structure from Sundquist et al.

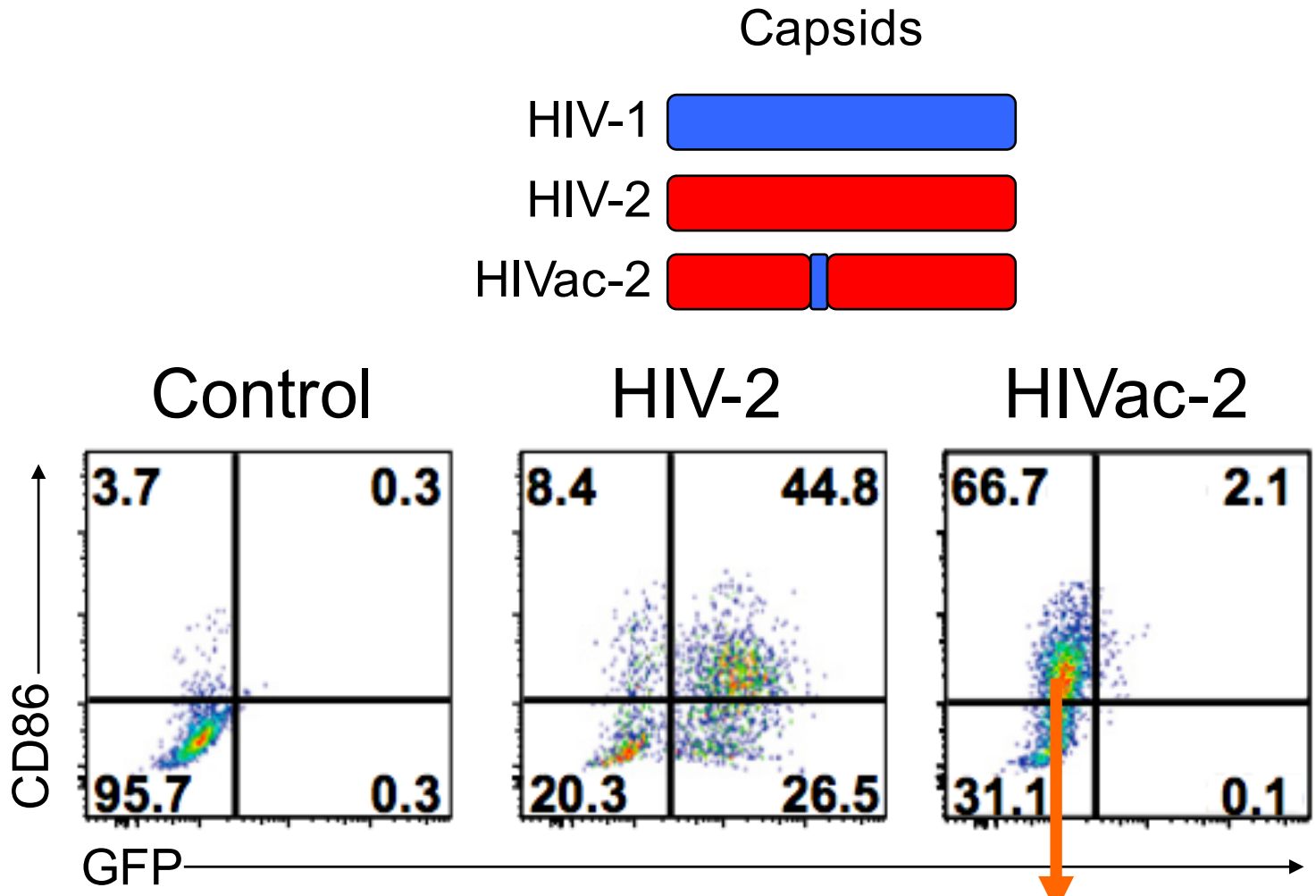
Identification: Luban et al., Cell 1993

Multiple regulatory activities on the virus:

- Uncoating
- Reverse transcription
- Nuclear entry
- Integration targeting
- Susceptibility to DNA sensors

Mechanism unclear & no host factor essential for CypA activities

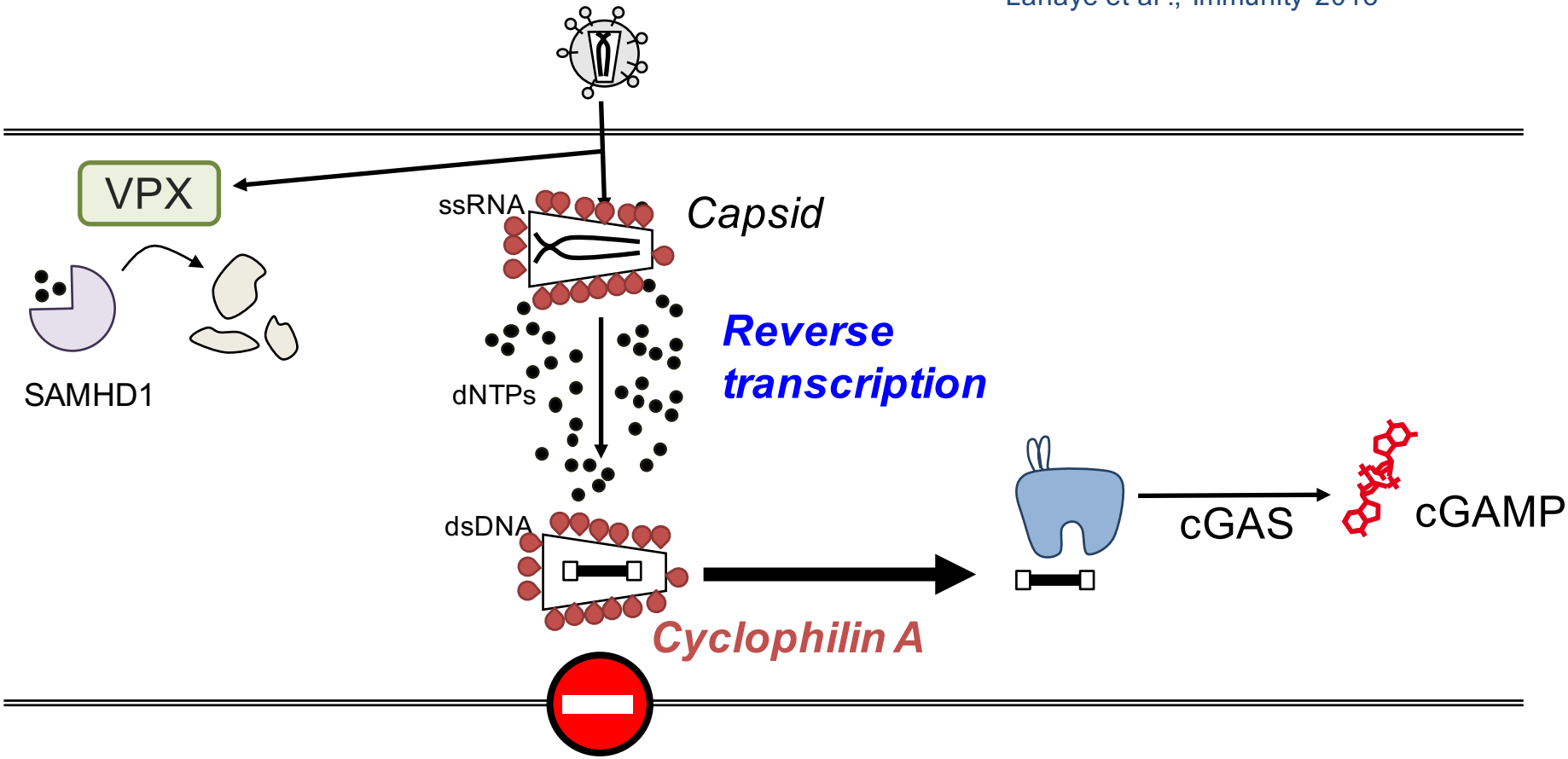
The viral capsid determines innate immune sensing of the virus



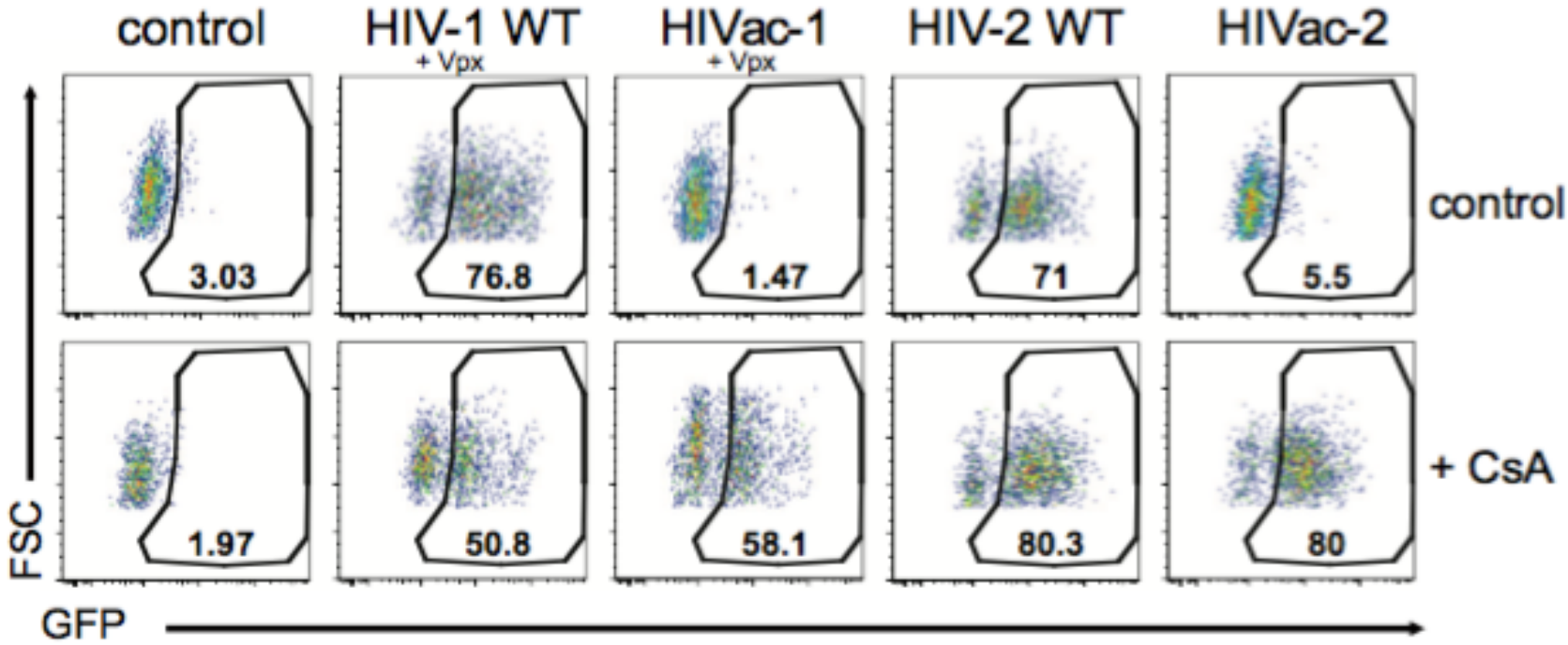
Mutant capsid: Genetic dissociation between productive infection and innate sensing

HIVac mutant capsids are blocked at nuclear import and increase cGAS sensing

Lahaye et al ., Immunity 2013



Restriction of HIVac capsids is mediated by CypA and can be rescued



➔ *Conserved restriction of HIV nuclear import by CypA in human, macaque and murine cells*

➔ *However, CypA is not sufficient (not shown)*

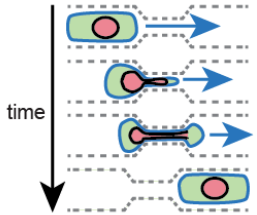
Lahaye et al., Cell Reports 2016

SUN2 is a candidate regulatory host factor of HIV at the nuclear envelope

CELL BIOLOGY

ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death

M. Raab,[1,2] M. Gentili,[3] H. de Belly,[1] H. R. Thiam,[1] P. Vargas,[1,2] A. J. Jimenez,[1] F. Lautenschlaeger,[1*] Raphaël Voituriez,[4,5] A. M. Lennon-Duménil,[3] N. Manel,[3] M. Piel[1,2†]

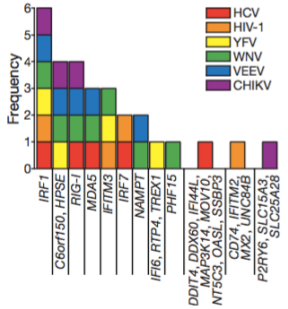


LETTER

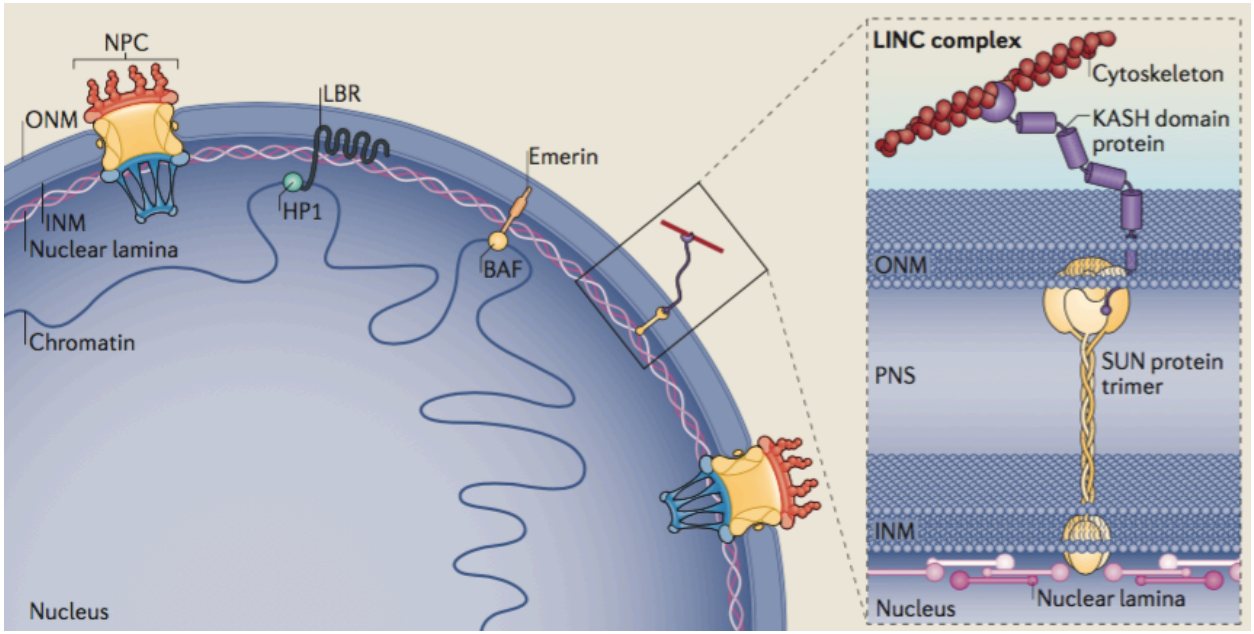
doi:10.1038/nature09907

A diverse range of gene products are effectors of the type I interferon antiviral response

John W. Schoggins[1], Sam J. Wilson[2], Maryline Panis[1], Mary Y. Murphy[1], Christopher T. Jones[1], Paul Bieniasz[2] & Charles M. Rice[1]

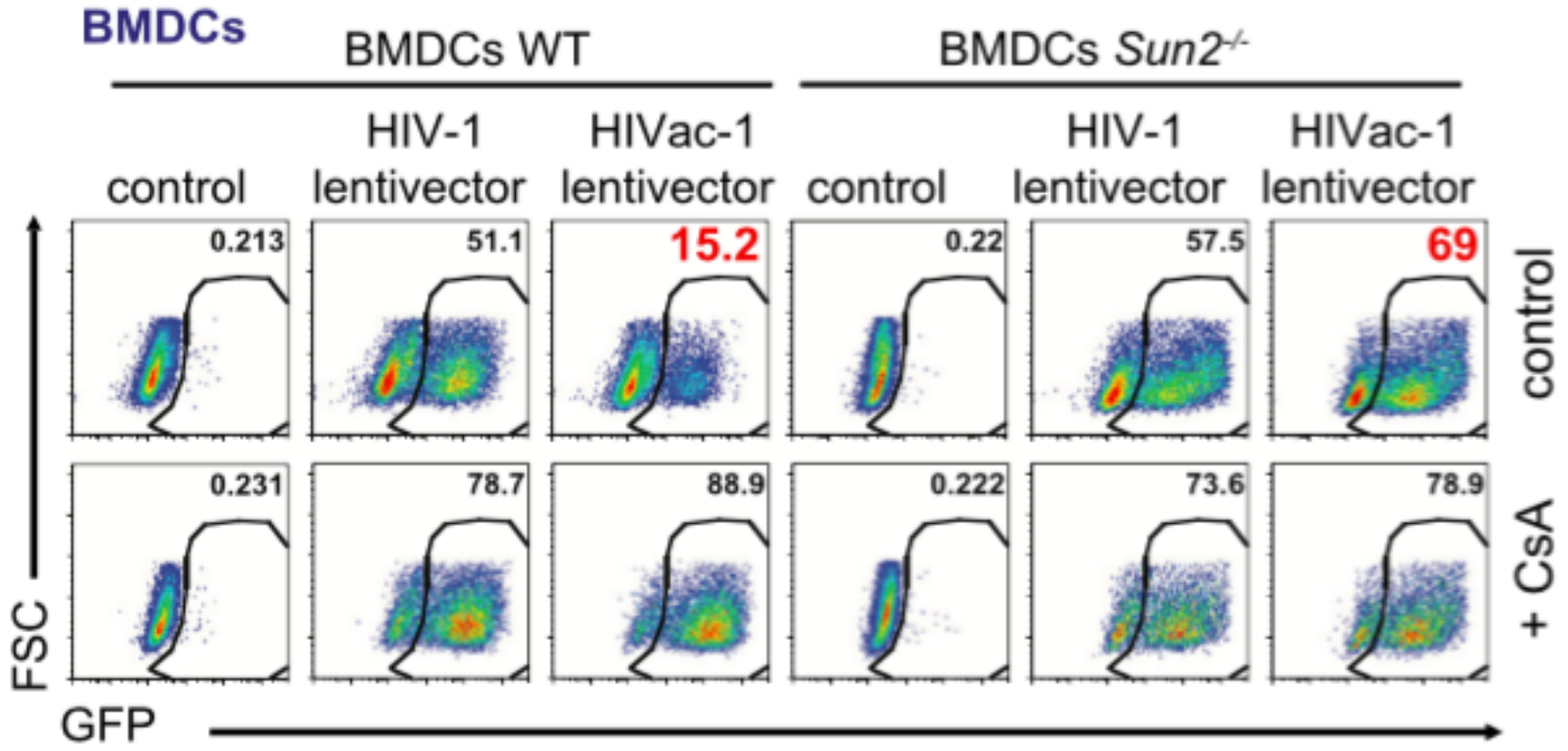


UNC84B = SUN2



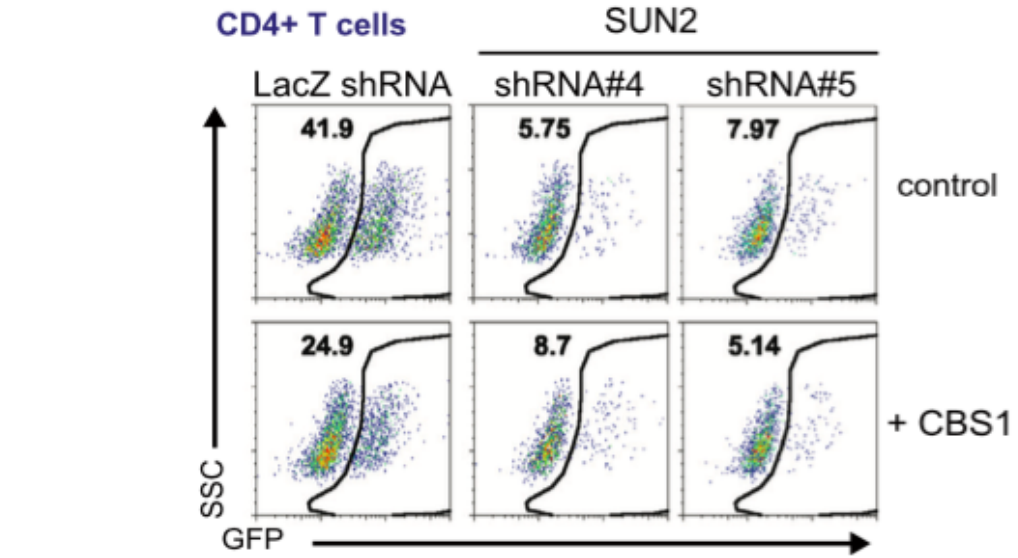
Burke & Stewart, NRMCB 2013

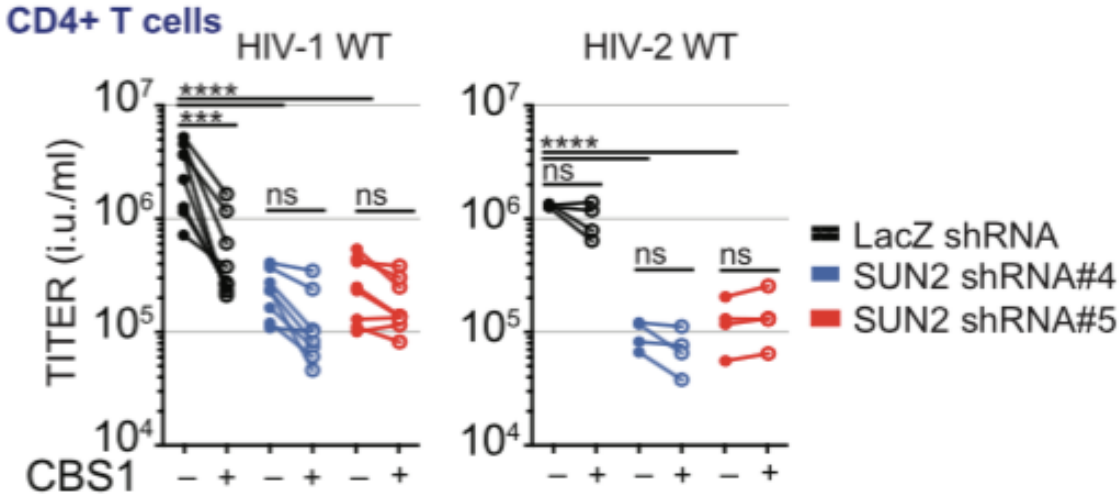
SUN2 participates to the CypA restriction



Lahaye et al., Cell Reports 2016

SUN2 is an essential host factor of HIV infection in CD4+ T cells and mediates CypA activities

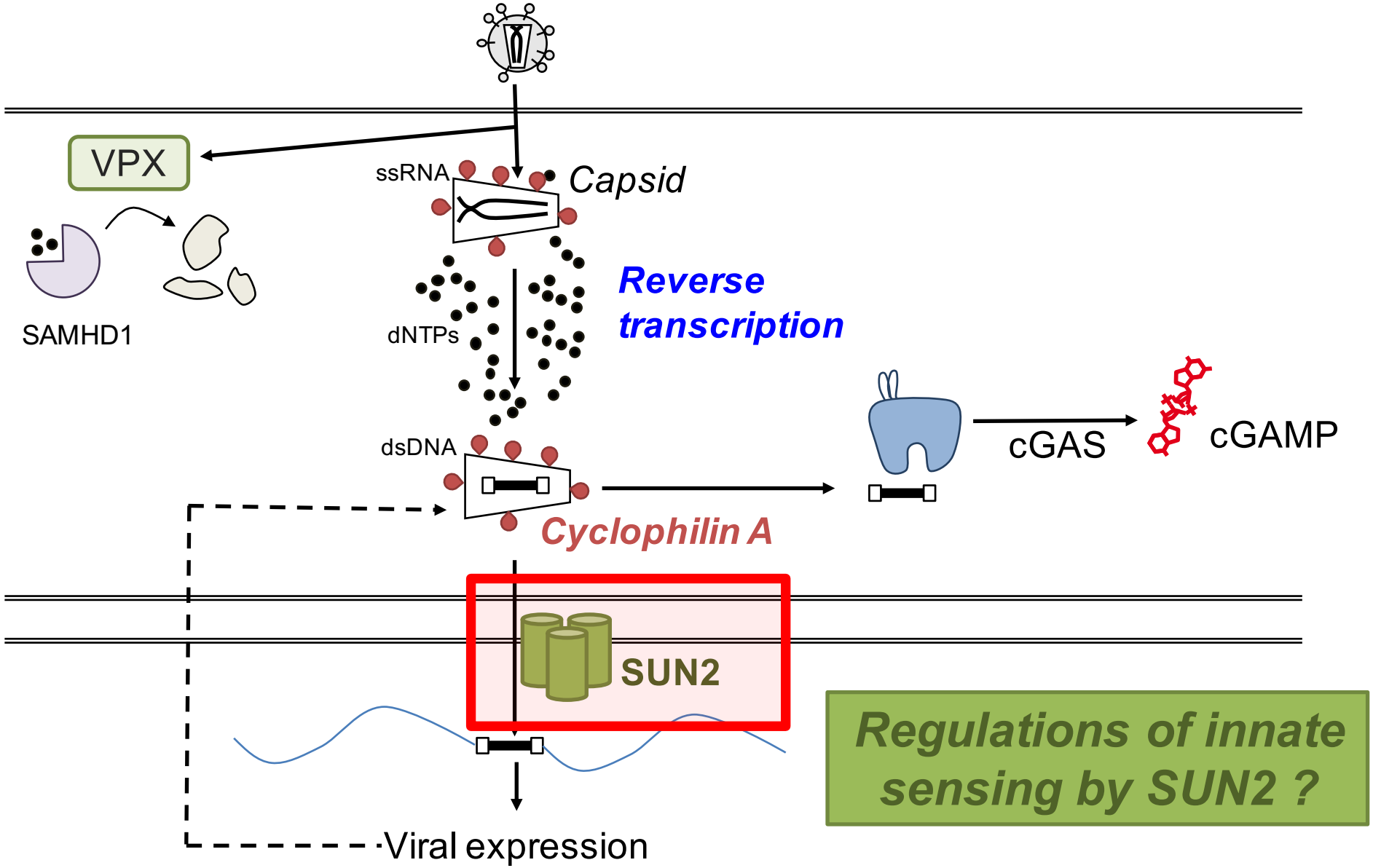




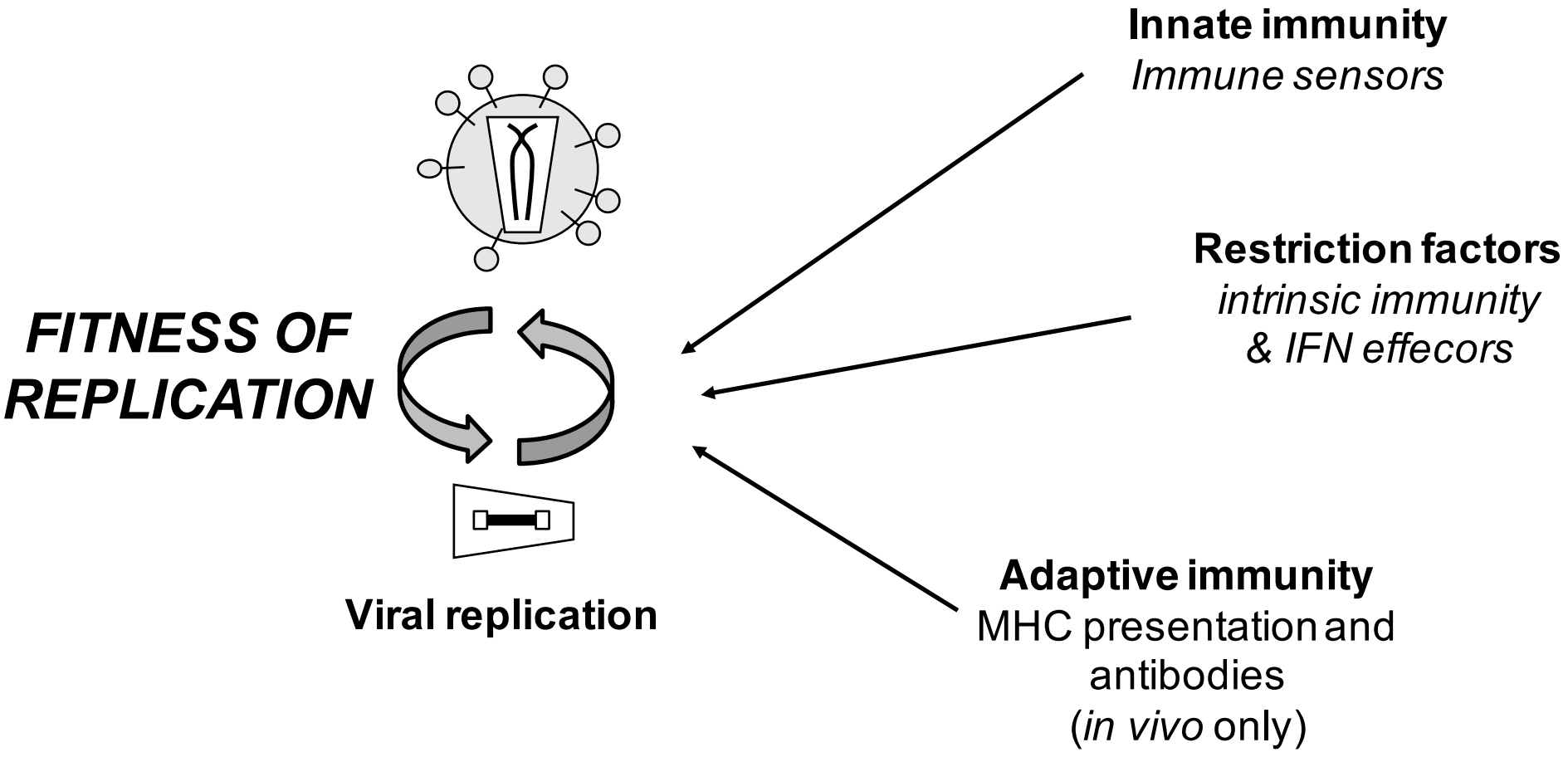
Lahaye et al., Cell Reports 2016

Identification of SUN2 as a new player in capsid-cyclophilin A interactions

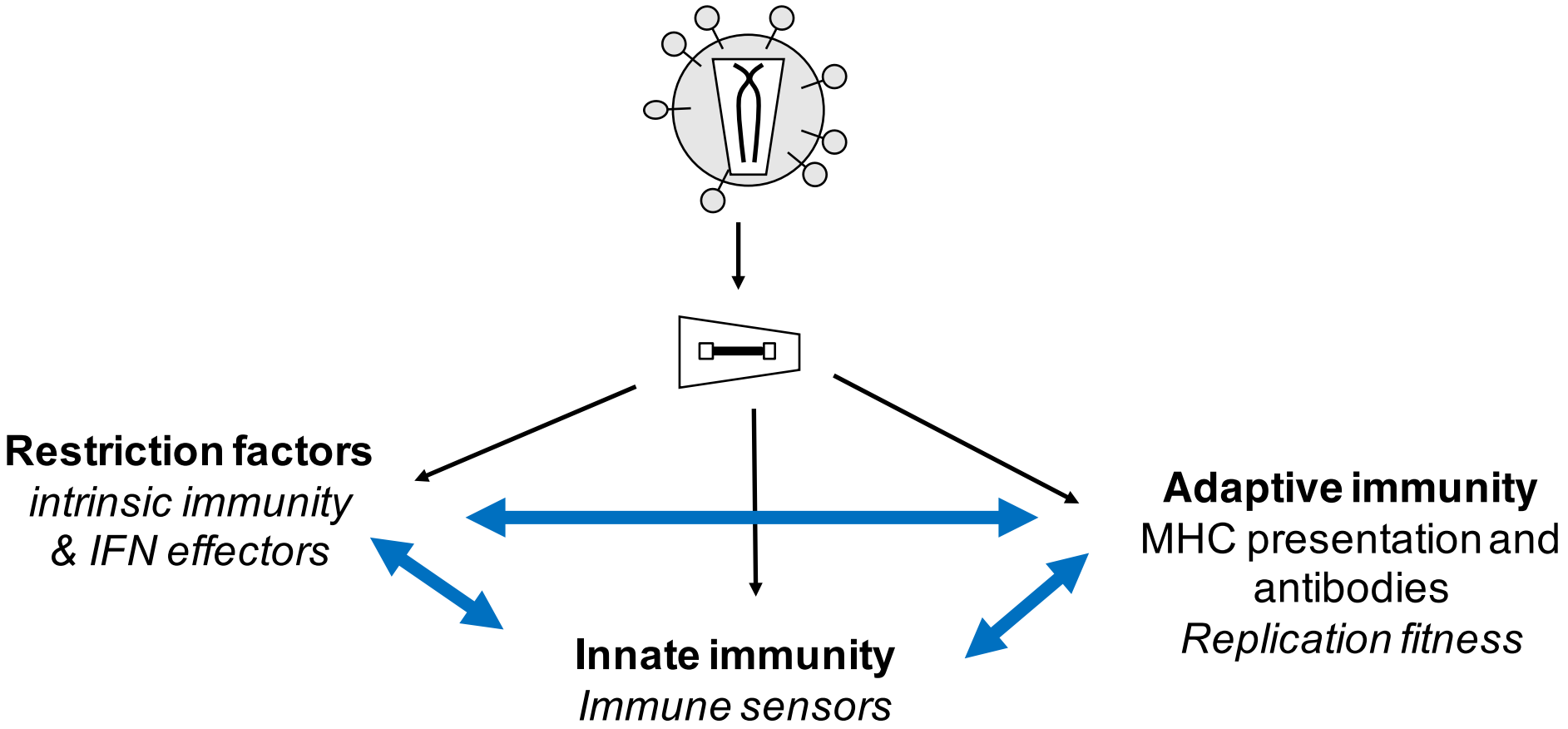
Lahaye et al., Cell Reports 2016



Innate immunity intersects innate sensors with other factors of viral replication



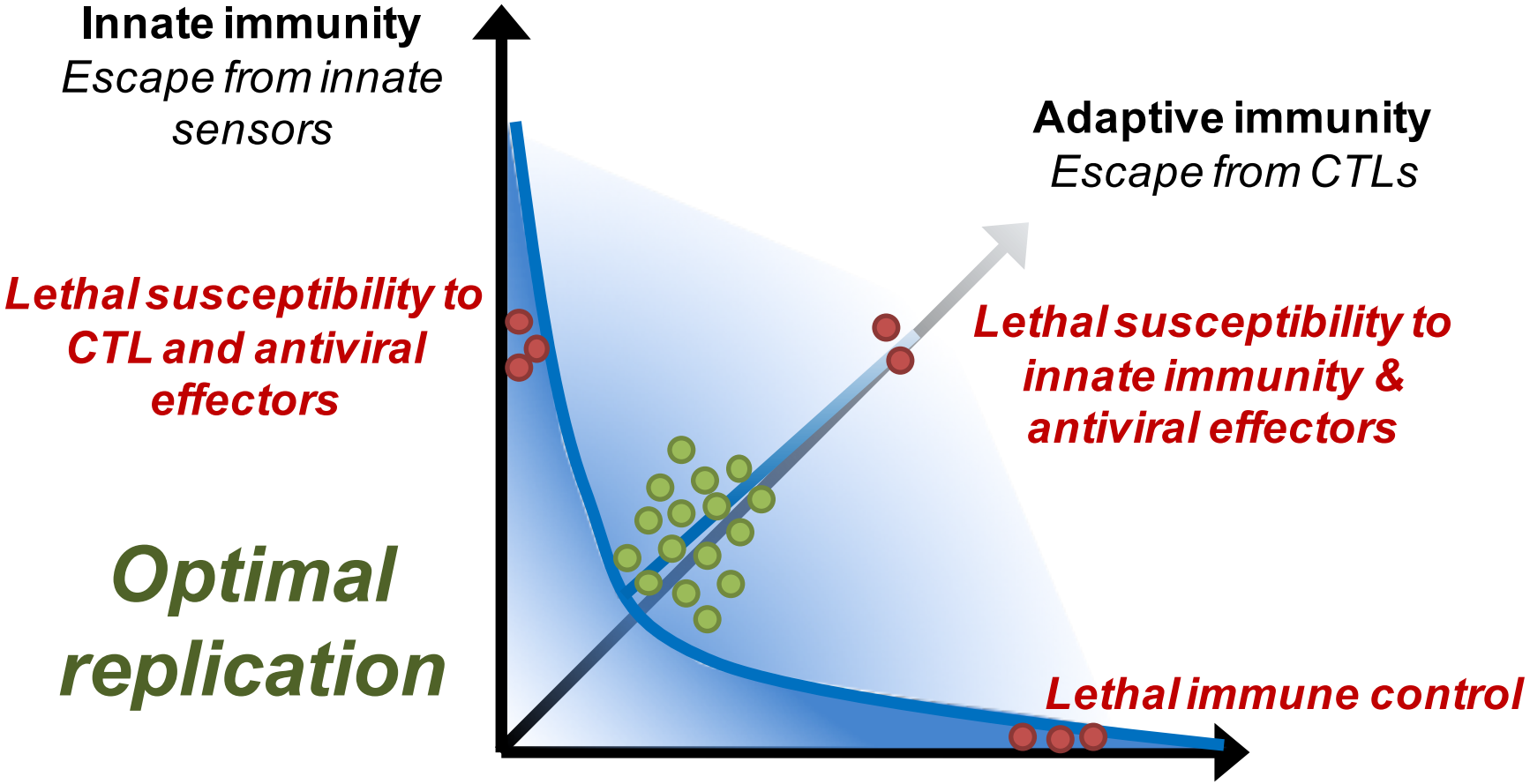
Restriction factors, innate & adaptive immunity are in interactions (genetic or biochemical)



- **Antagonism (competition)**
  e.g. SAMHD1 restricts viral replication but limits innate sensing
- **Synergism (cooperation)**
  e.g. Tetherin restricts viral budding and induce an innate signal
- **Neutral**

Cooperation and Conflict in Antiviral Immune Responses

Viral genotypes landscape:



Adapted from Chae et al., PLoS Pathogens 2016
Cooperation and Conflict in the Plant Immune System

Current members
Aymeric Silvin
Cécile Conrad
Xavier Lahaye
Silvia Cerboni
Matteo Gentili
Santy Marques-Ladeira
Laurent Zablocki
Nadia Jeremiah
Marius Döring
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