

EDITION  
10<sup>th</sup>

# HIV PERSISTENCE DURING THERAPY™

Reservoirs & Eradication  
Strategies Workshop



DECEMBER 13-16, 2022  
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## Viral persistence and NK cells



*Painting: Françoise Petrovitch (Organoid / Institut Pasteur / Keza)*

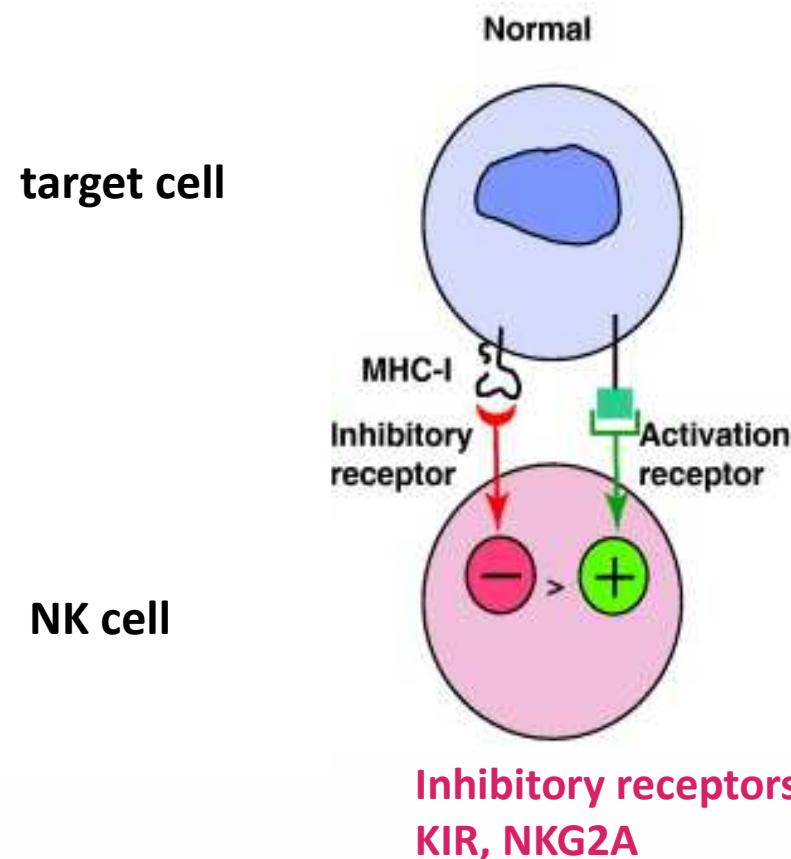
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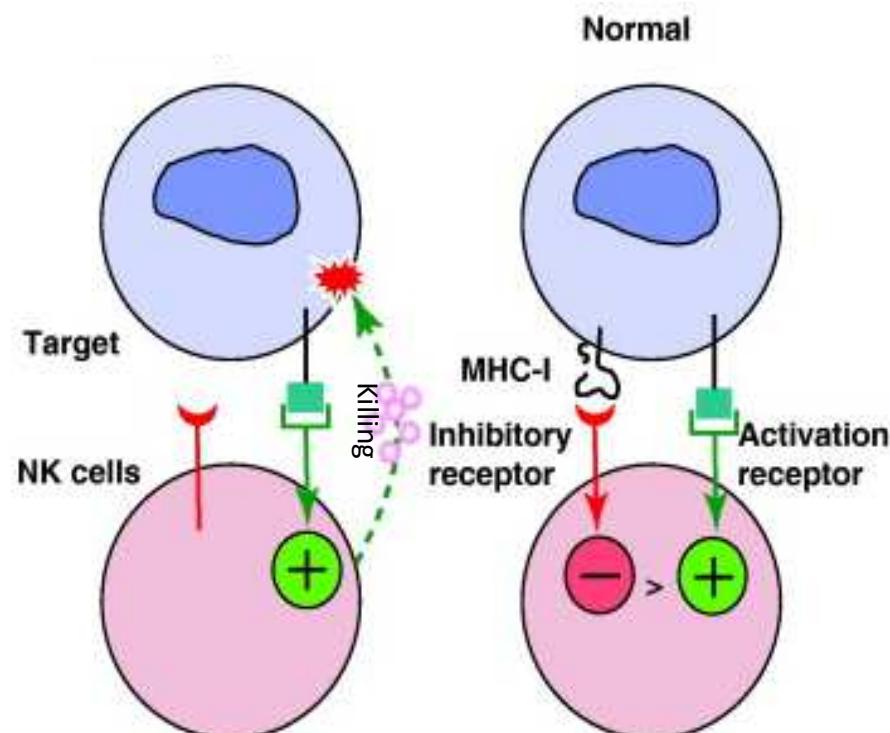


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# NK cells recognize and kill abnormal cells: potentially relevant for HIV reservoir reduction

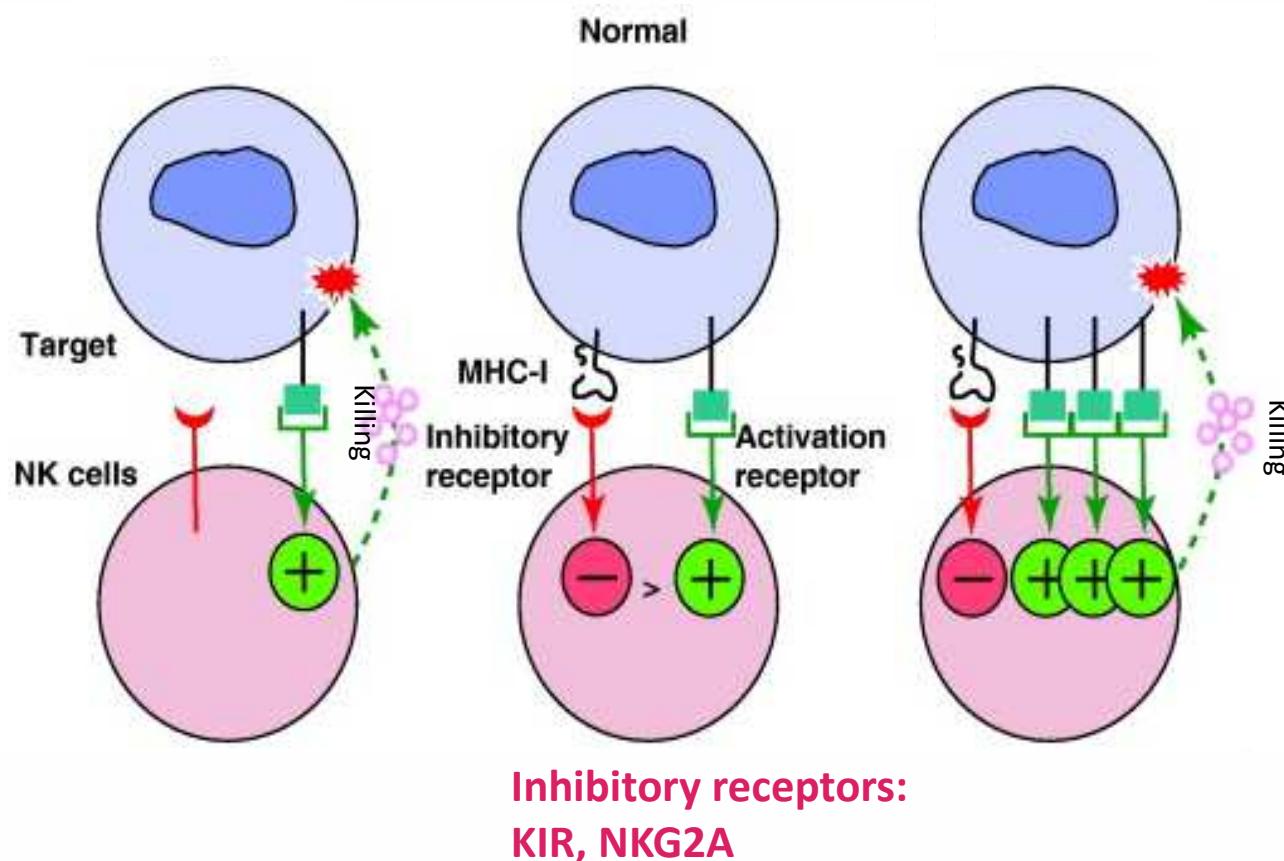


# NK cells recognize and kill abnormal cells: potentially relevant for HIV reservoir reduction

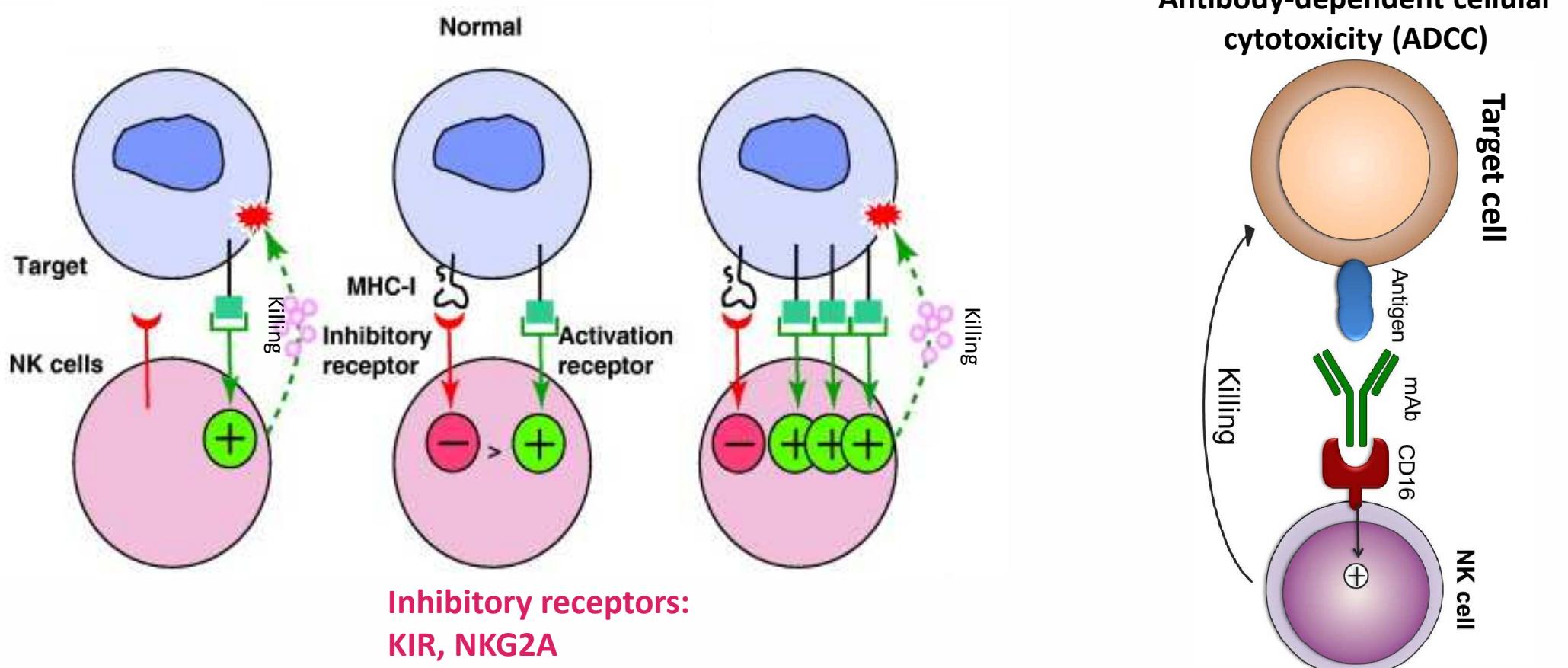


**Inhibitory receptors:**  
KIR, NKG2A

# NK cells recognize and kill abnormal cells: potentially relevant for HIV reservoir reduction



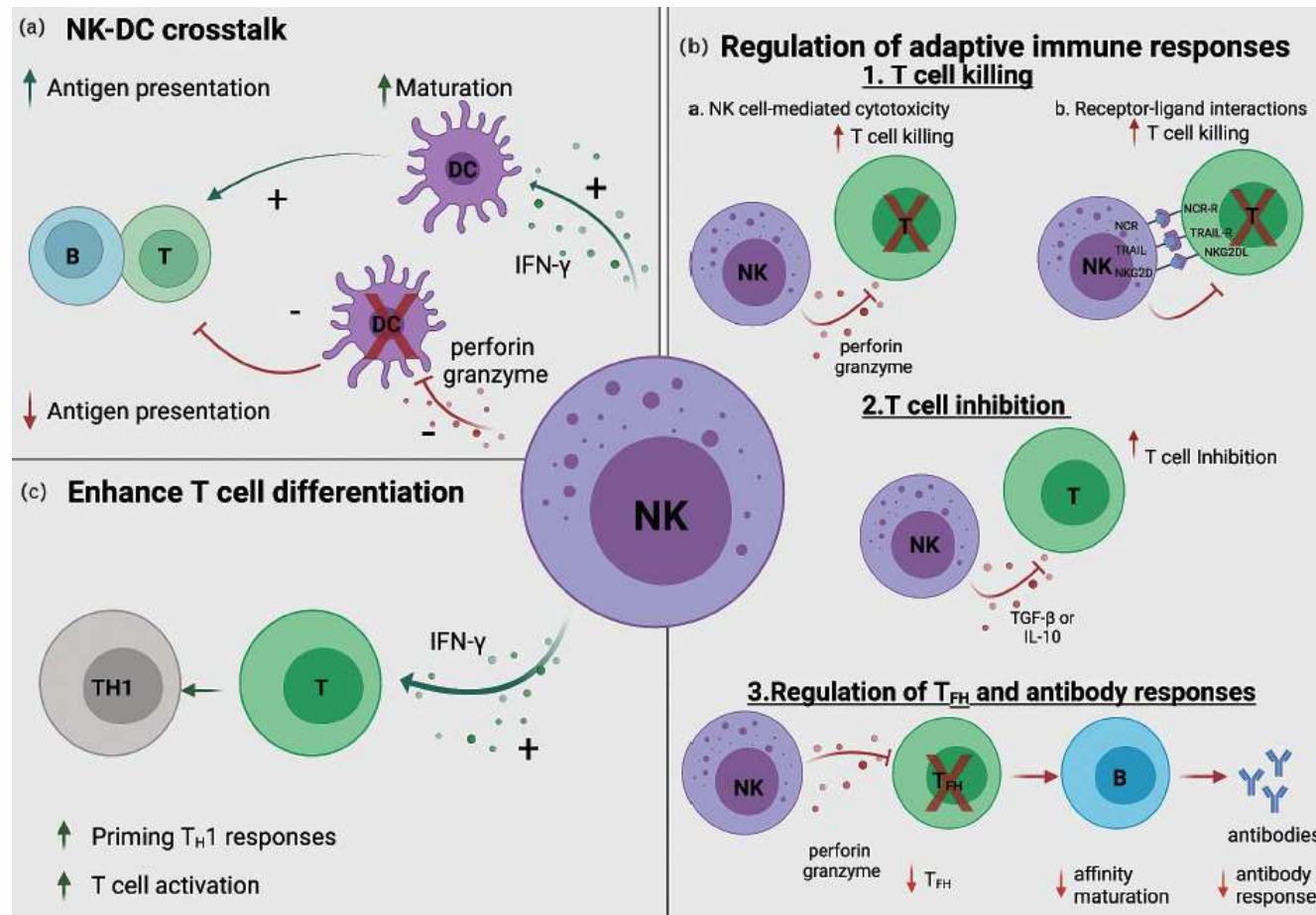
# NK cells recognize and kill abnormal cells: potentially relevant for HIV reservoir reduction



Elliott et al; *Trends in Immunology* 2011 32, 364-372 DOI: (10.1016/j.it.2011.06.001)  
Copyright © 2011 Elsevier Ltd [Terms and Conditions](#)

Siernicka et al, <http://www.stream.wum.edu.pl/en/knowledge-base/96-nk-cells-applications-in-immuno-oncology>

# NK cells : multiple impacts on adaptive antiviral responses

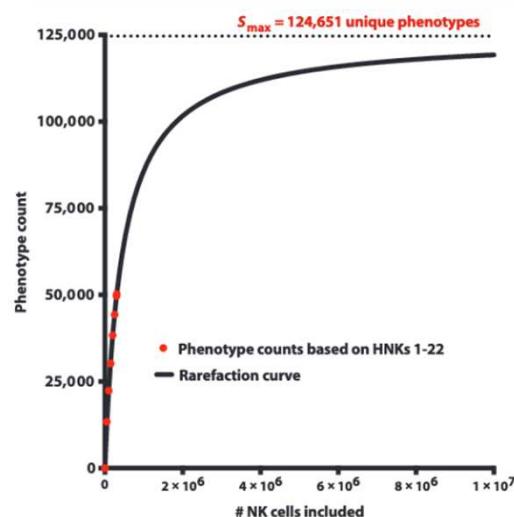


Alrubayyi et al, AIDS 2022

Ploquin M et al, AIDS 2022; Bradley et al, Cell 2018.

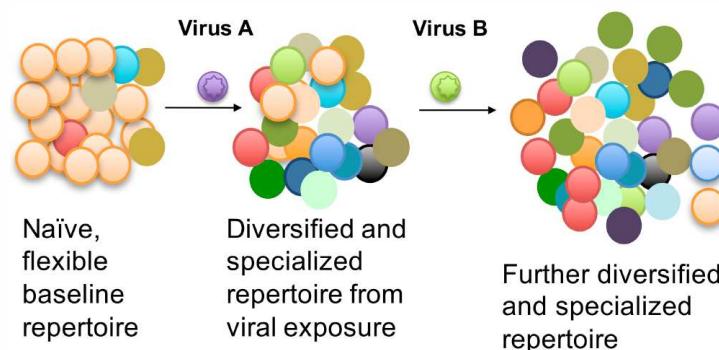
# NK cells: findings of the last decades modified our view on these innate immune cells

## Unprecedented diversity



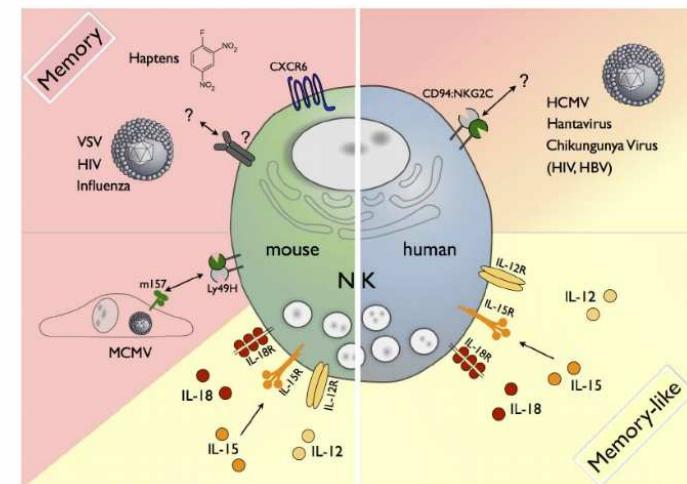
Horowitz et al, STM 2012

## NK cell diversity evolves over time with immune experience



C Blish. Plos Path 2016;  
Strauss-Albee et al, STM 2015

## Antigen-specificity and memory



Röller, Plos Path 2016; O'Leary et al, Nat Immunol 2006; Reeves et al, Nat Immunol 2015.

Which impact for HIV reservoirs ?

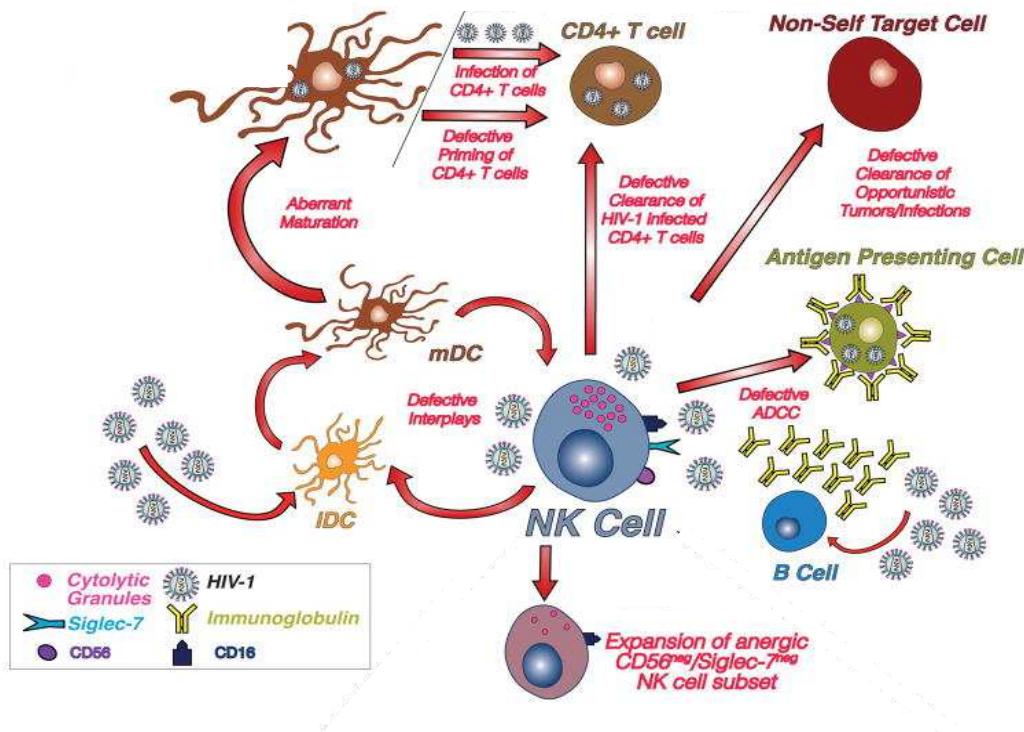
# NK cells in people living with HIV (i)

## NK cells contribute to the control of HIV replication

- Many studies demonstrating correlation between genetic factors and susceptibility to infection and viremia levels in PLWH
- HIV possesses mechanisms to escape NK cell responses
- Antigen-specific memory NK cells (SIV)
- Associations with HIV reservoir size in some studies
- HIV Cure approaches also target or exploit NK cells (IL-15, TLR7, bNAbs, IFN- $\lambda$ ,...)
- After early ART initiation, many but not all NK cell markers come back to normal

*Martin et al, Nat Gen 2002; Scott-Algara et al, JI 2003; Alter et al, JEM 2007; Thomas R et al, Nat Gen, 2009; Olesen et al, J Virol 2015; Reeves RK et al, Nat Immunol, 2015; Ramsuran et al, Science 2018; Garcia-Broncano et al, STM 2019; Pace et al, Front Immunol 2022; Fittje et al, PLoSPPath 2022*

## NK cells in people living with HIV (ii): NK cell activity is impaired in several ways

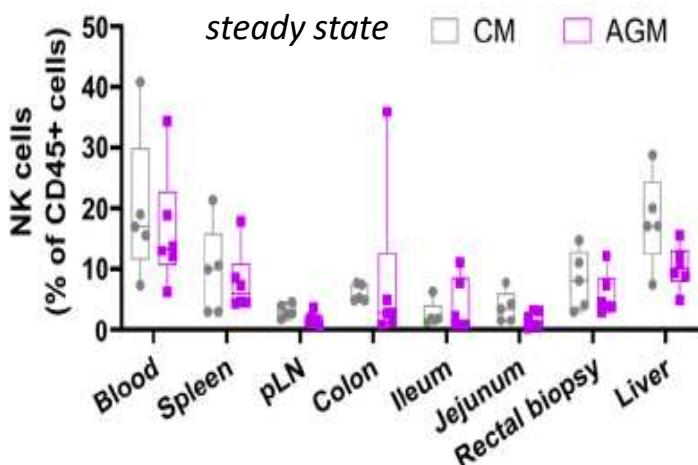


Mikulak et al, AIDS 2017

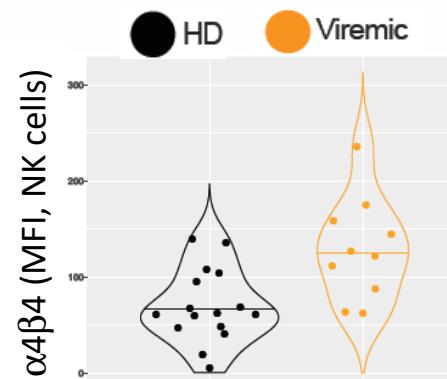
Mavilio et al, PNAS 2005; Alter et al, Blood 2005; Brunetta et al, Blood 2009; Schafer et al, JVI 2015; Adeniji et al, PlosPath 2021.

# NK cells in people living with HIV (iii): Alterations in NK cell tissue trafficking

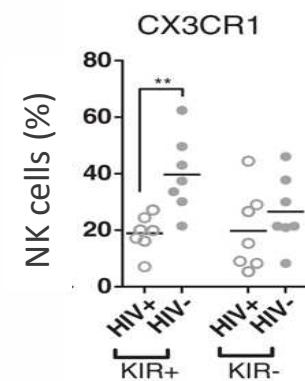
- enhanced trafficking toward the gut
- diminished capacity of LN homing and of KIR<sup>+</sup> NK cell recruitment to lymph nodes



Huot et al, *Front Immunol* 2020



Kroll et al, *BioRxiv* 2022

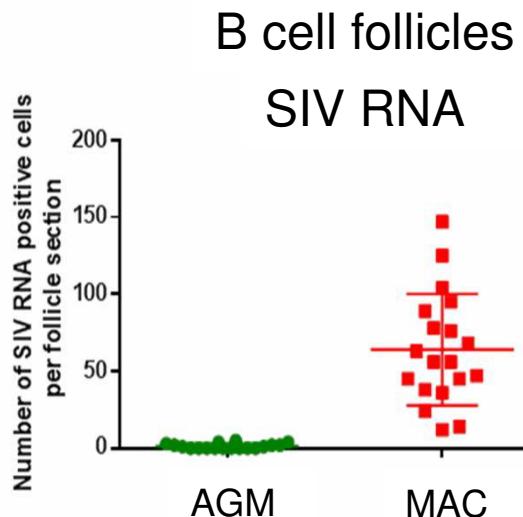


Luteijn et al, *EJ* 2011

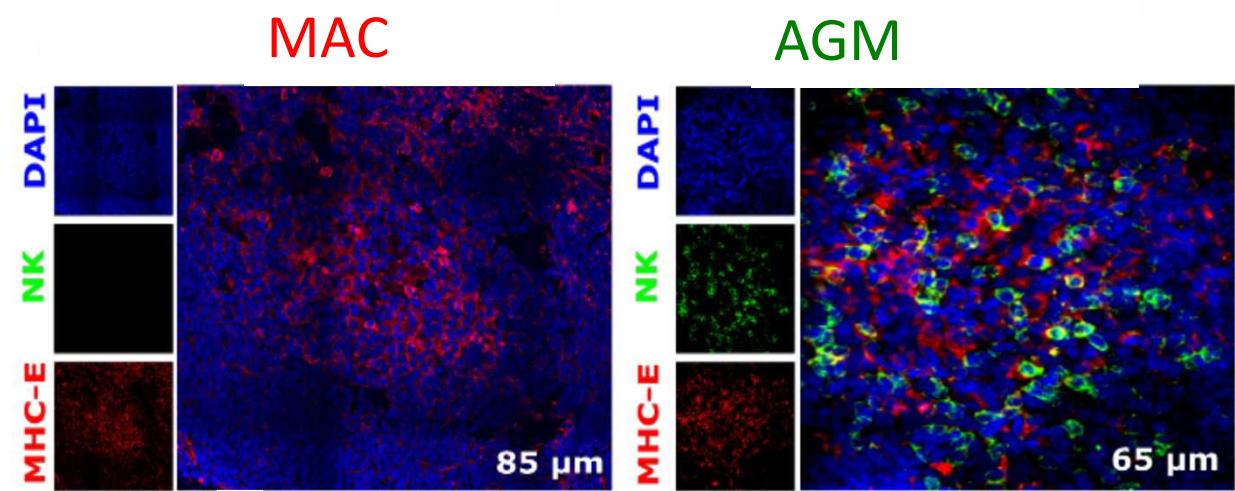
Reeves et al, *JVI* 2010; Sips M et al, *Mucosal Immunol* 2012; Schafer et al, *JVI* 2015; Huot et al, *Nat Med* 2017.

# NK cells mediate strong and long-term control of SIVagm in secondary lymphoid organs of African green monkeys (AGM)

**Strong control of SIV in LN of natural hosts  
T cell zone and B cell follicles**



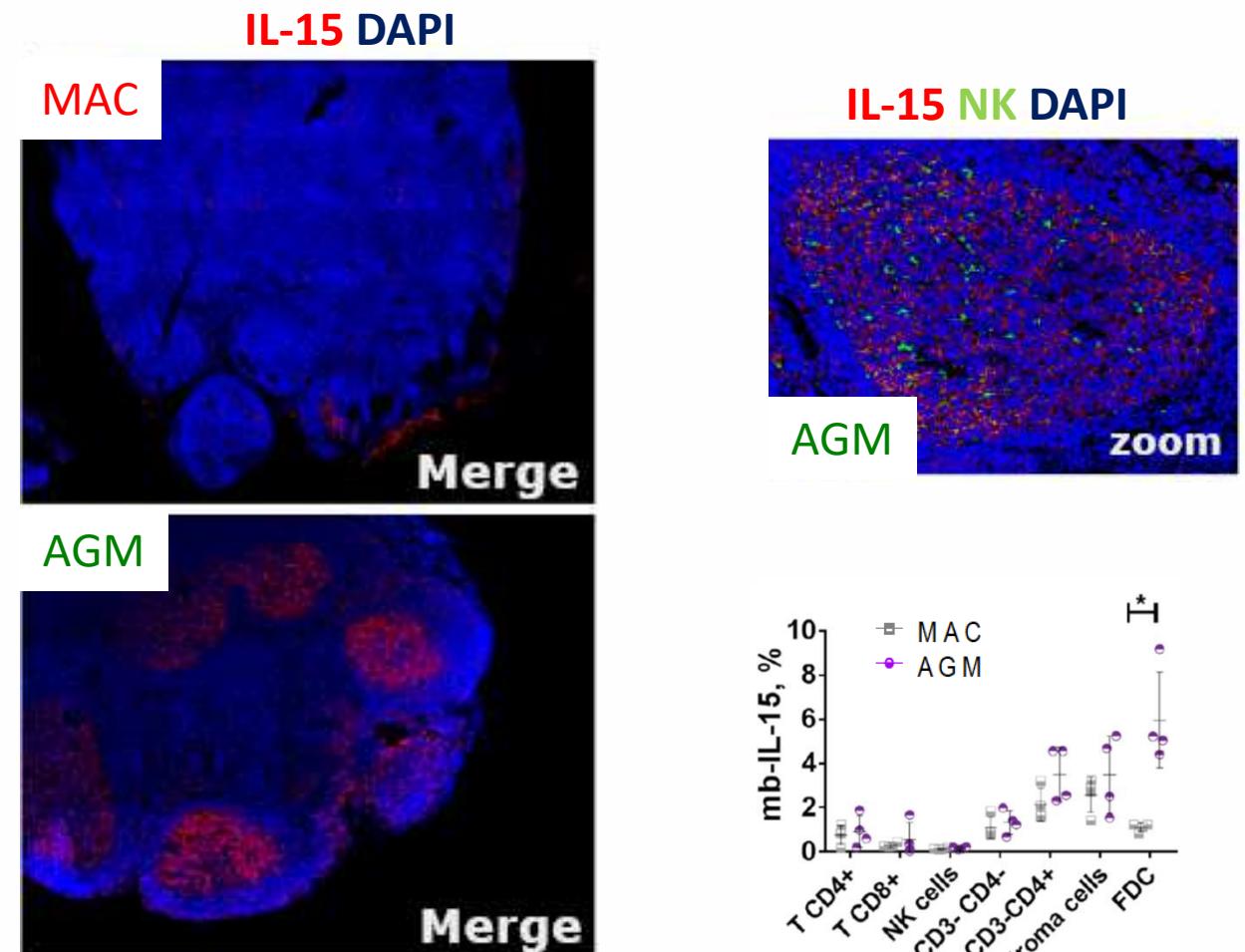
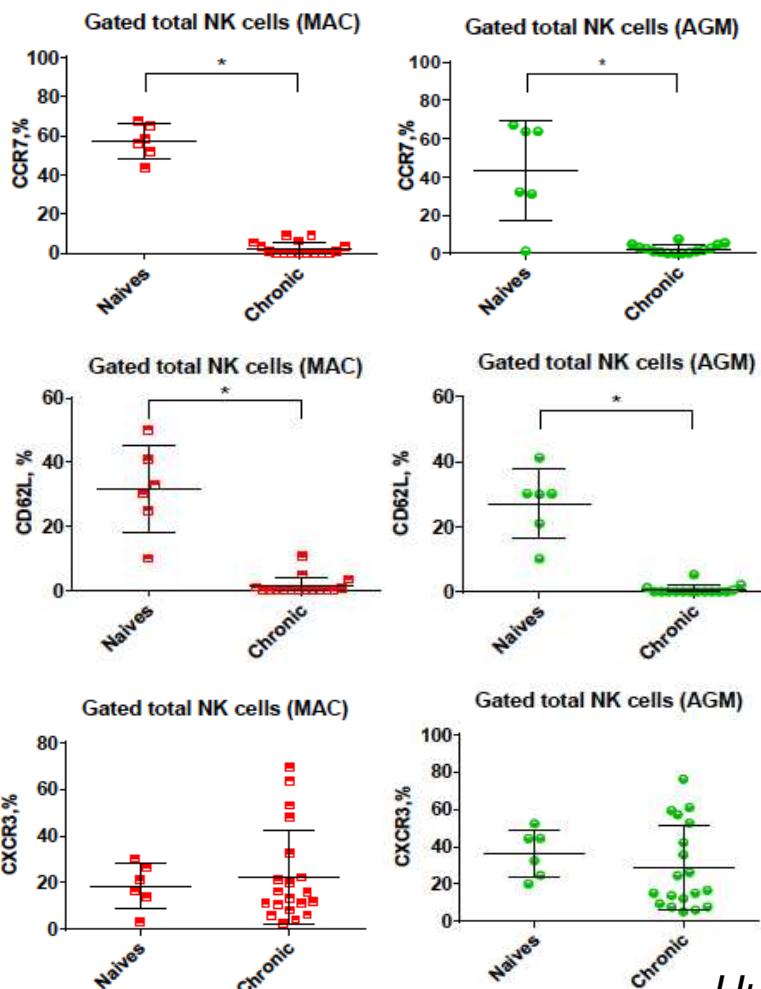
**NK cells mediate SIVagm control  
in peripheral lymph nodes and spleen**



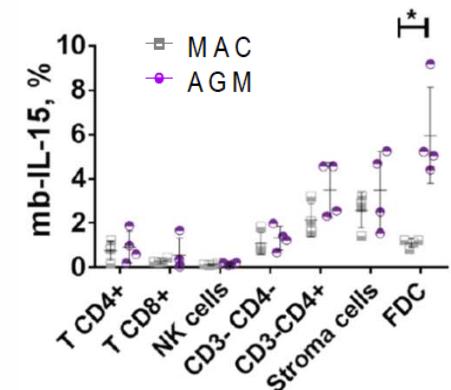
Diop OM et al, JVI 2000; Müller-Trutwin & Barré-Sinoussi, Frontiers Biosci 2003; Gueye A et al, JMP, 2004; Meythaler M et al, J Immunol, 2011; Brenchley et al, Blood 2012; Estes et al, Immunol Rev 2013

Jacquelin et al Plos Path 2014  
Huot et al, Nat Med 2017

# No enhanced migration to lymph nodes but local IL-15 production by follicular dendritic cells (FDC) during SIVagm infection

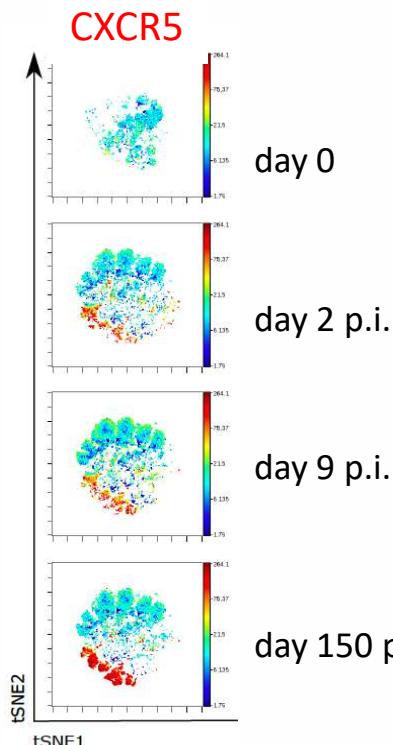


Huot et al, Nat Med 2017

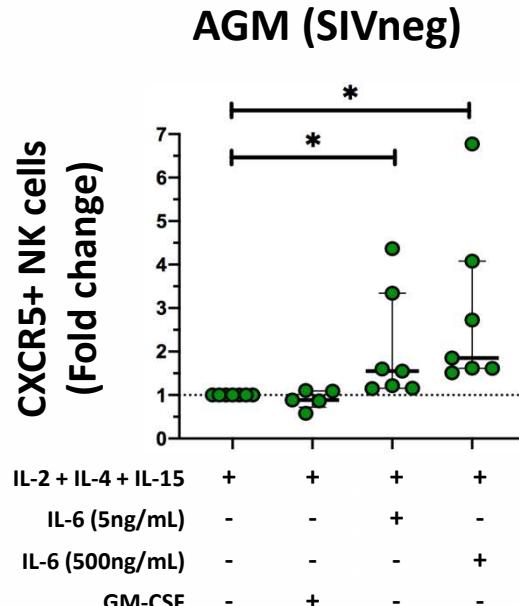


## B cell-mediated modulation of NK cells: IL-6 up-regulates CXCR5 on NK cells

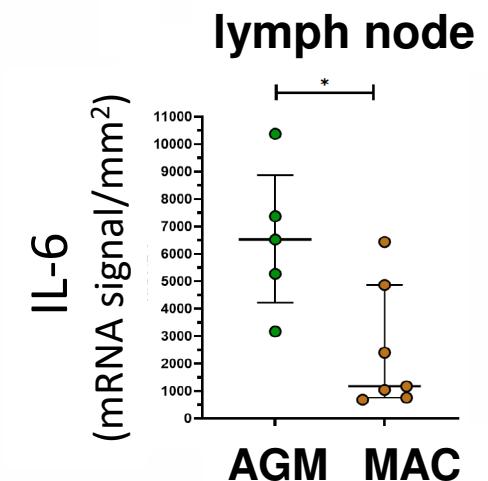
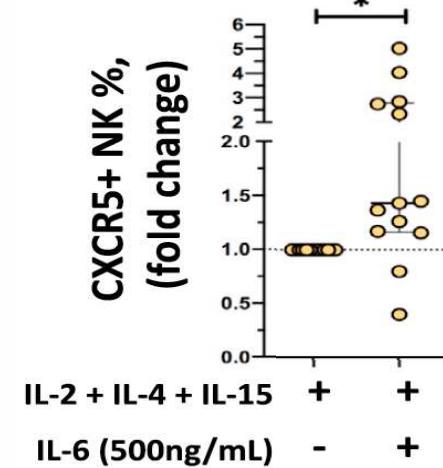
**CXCR5<sup>+</sup> NK cells  
(AGM, LN)**



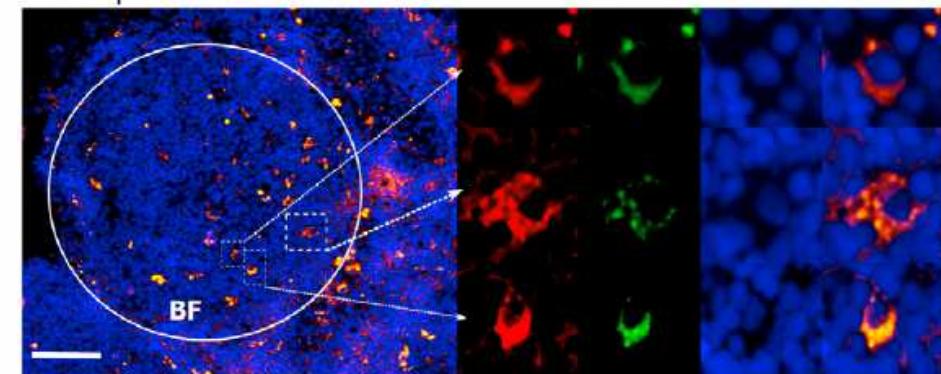
**CXCR5<sup>+</sup> NK cells  
(Fold change)**



**healthy human donor**

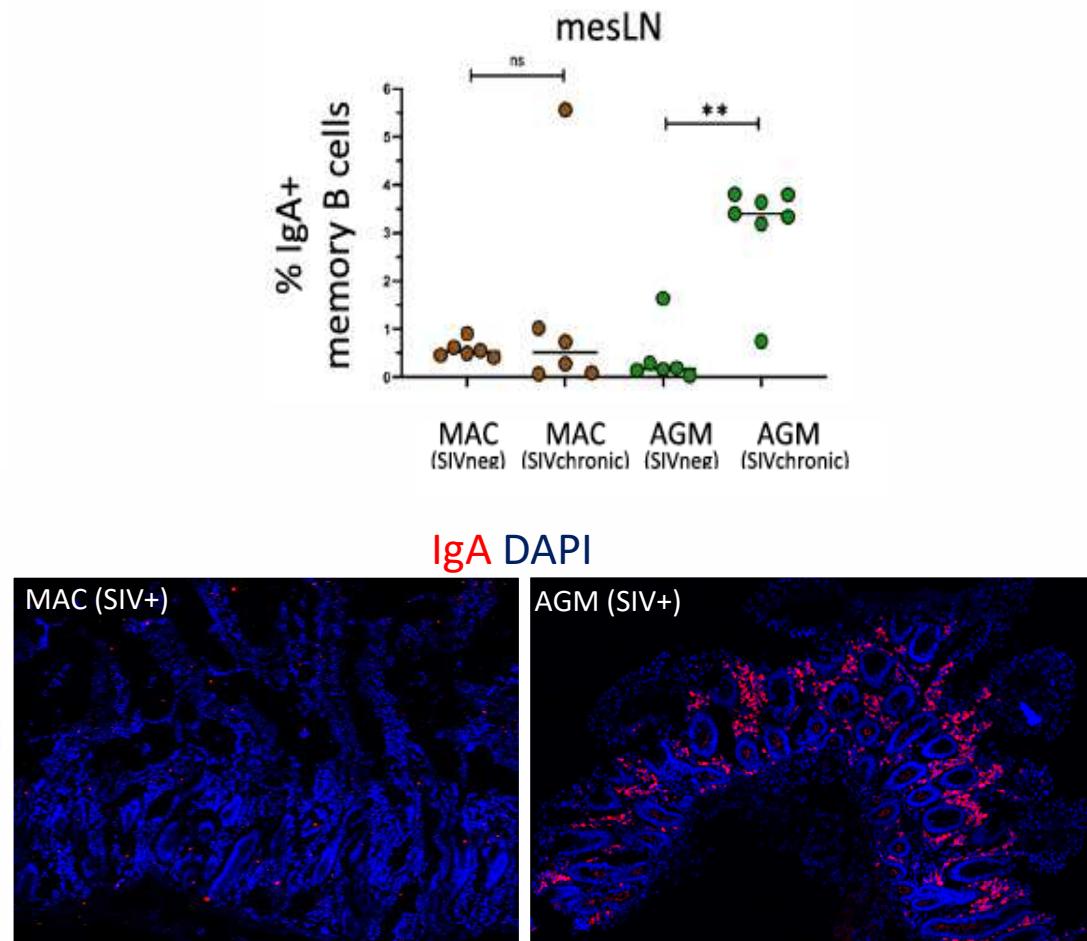
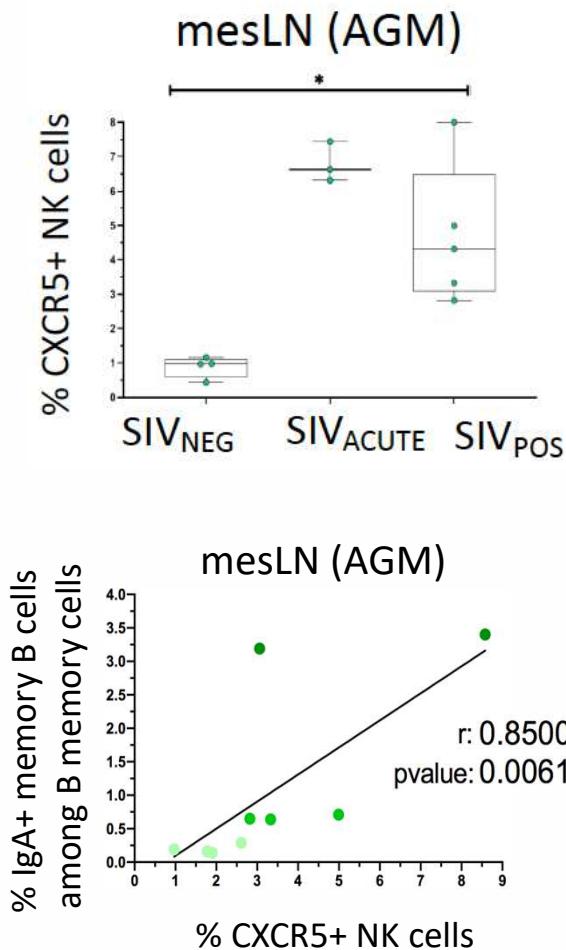
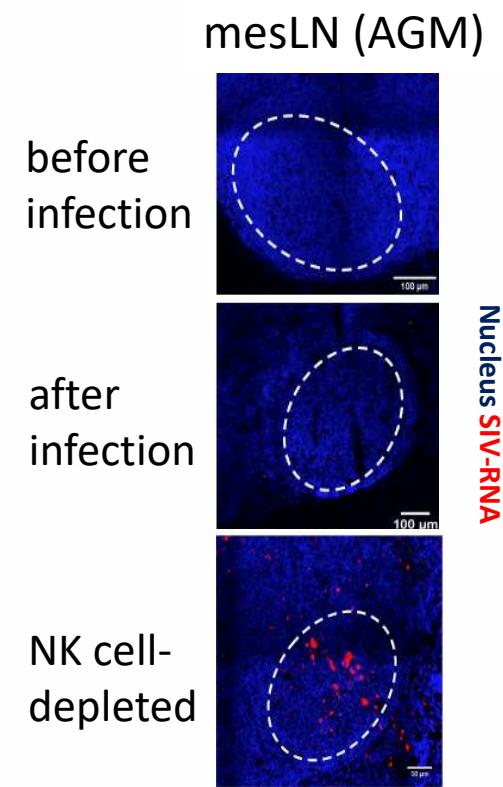


**AGM pLN**



*Rascole P et al, iScience 2021*

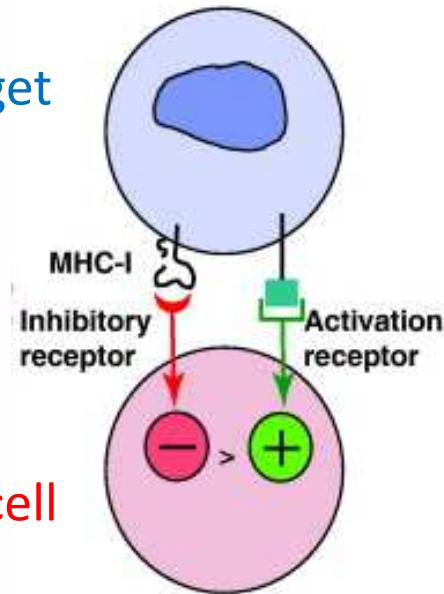
# Indirect effects of NK cell mediated control on B cell responses during SIVagm infection



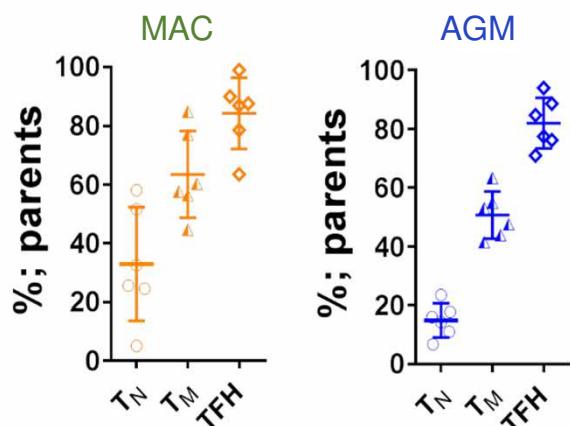
# How do NK cells suppress SIVagm in lymph nodes?

Target  
cell

NK cell

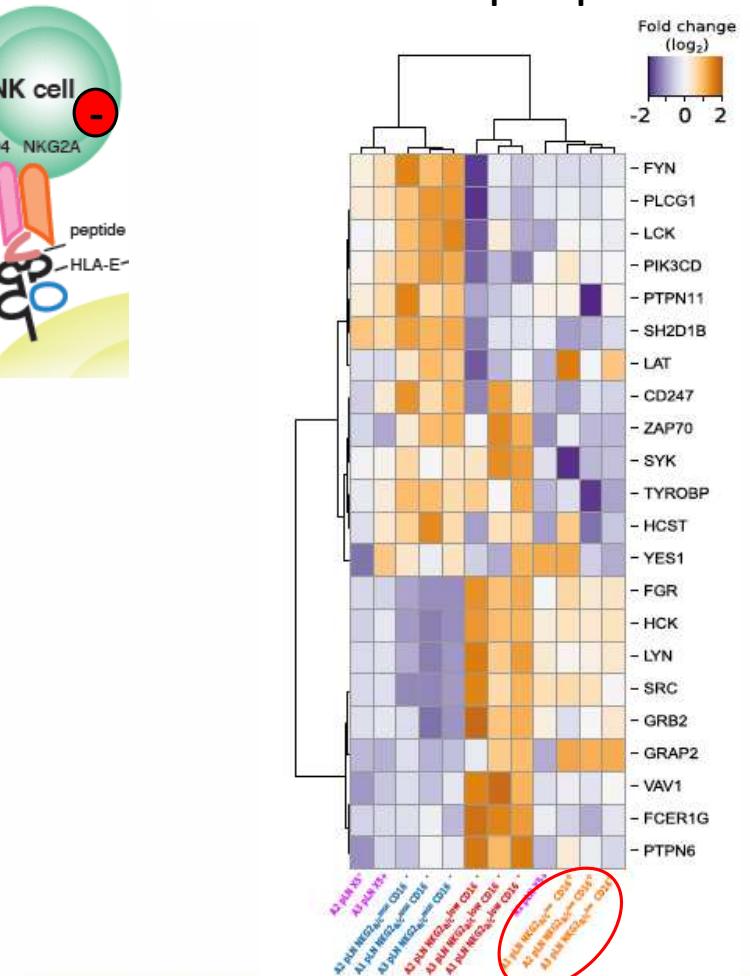


MHC-E<sup>+</sup> CD4<sup>+</sup> T cells in LN (SIV-)



T<sub>N</sub>: Naïve CD4<sup>+</sup> T cells  
T<sub>M</sub>: Memory CD4<sup>+</sup> T cells  
TFH: Follicular Helper (CD4) T cells

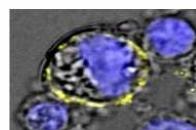
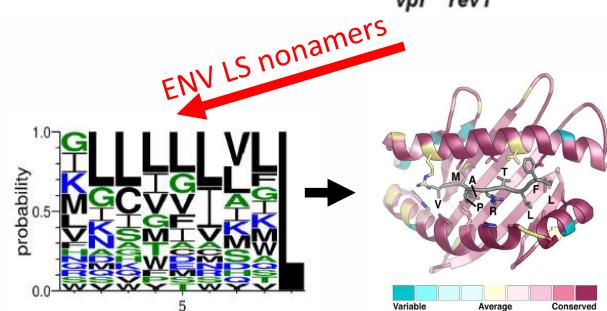
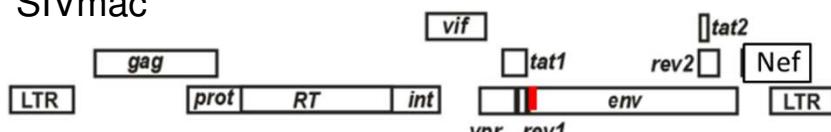
LN (SIVagm): expansion of NKG2A<sup>low</sup>CD16<sup>+</sup>  
NK cells with an adaptive profile



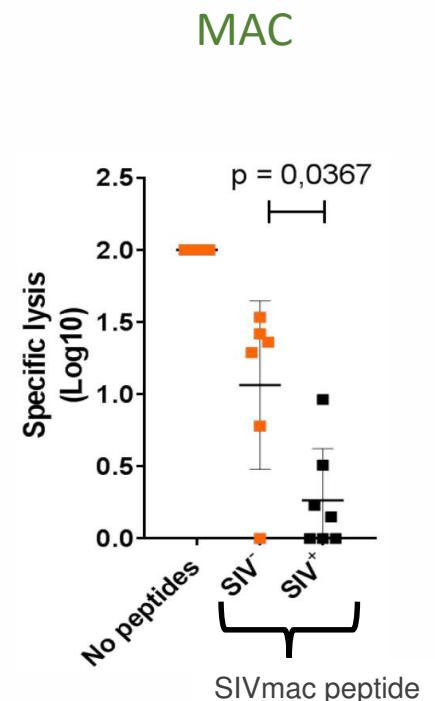
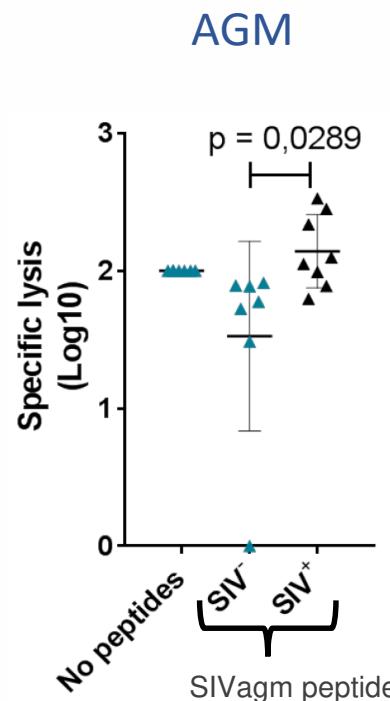
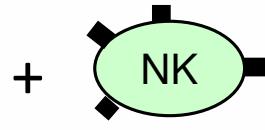
Huot et al, Nat Comm 2021

# MHC-E dependent NK cell suppressive activity increases in SIVagm infection and decreases in SIVmac infection

SIVagm,  
SIVmac

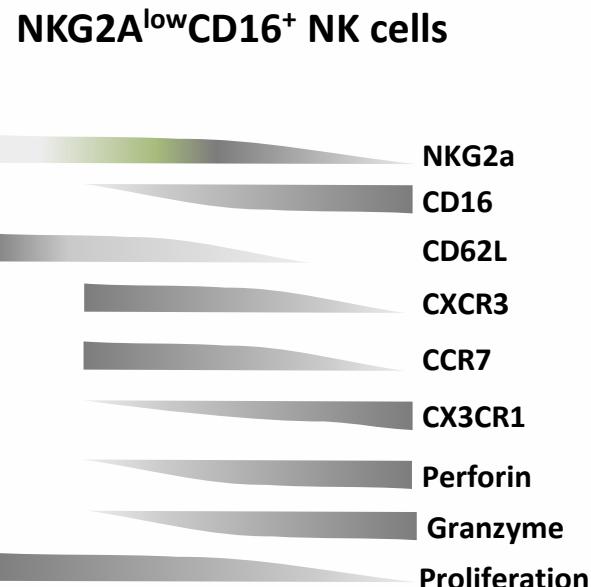
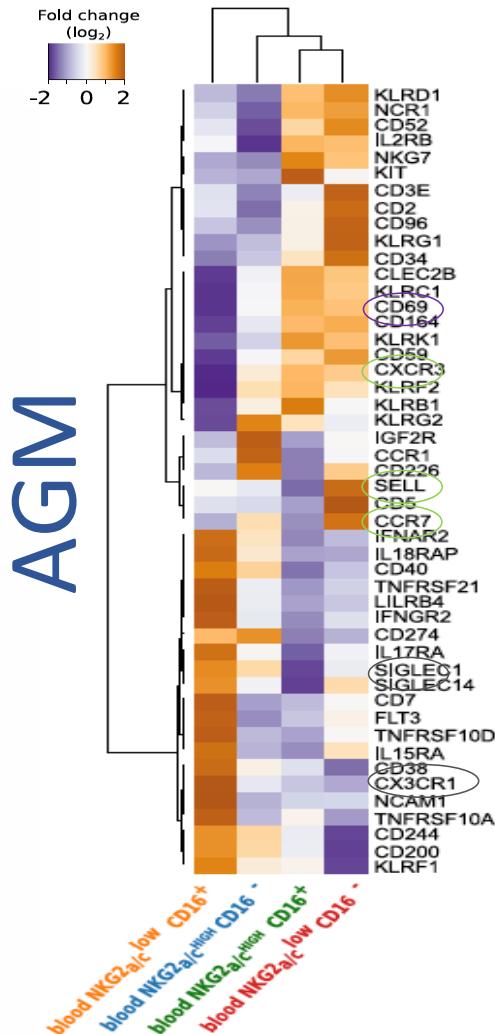


K562-MHC-E<sup>+</sup>  
+/- peptides  
(Env LS peptides)

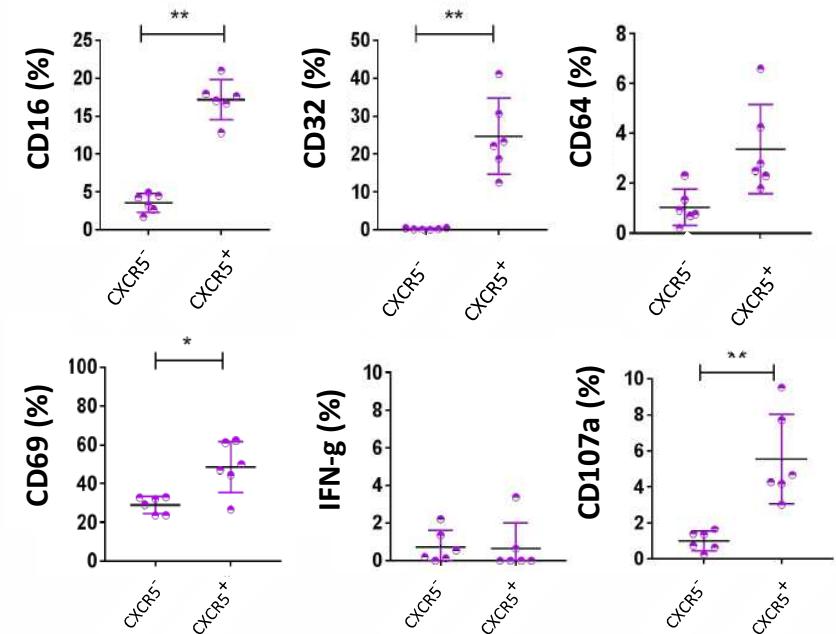


Huot et al, Nat Comm 2021

# The adaptive NK cells in lymph nodes from SIVagm infected AGM displayed a terminally differentiated phenotype



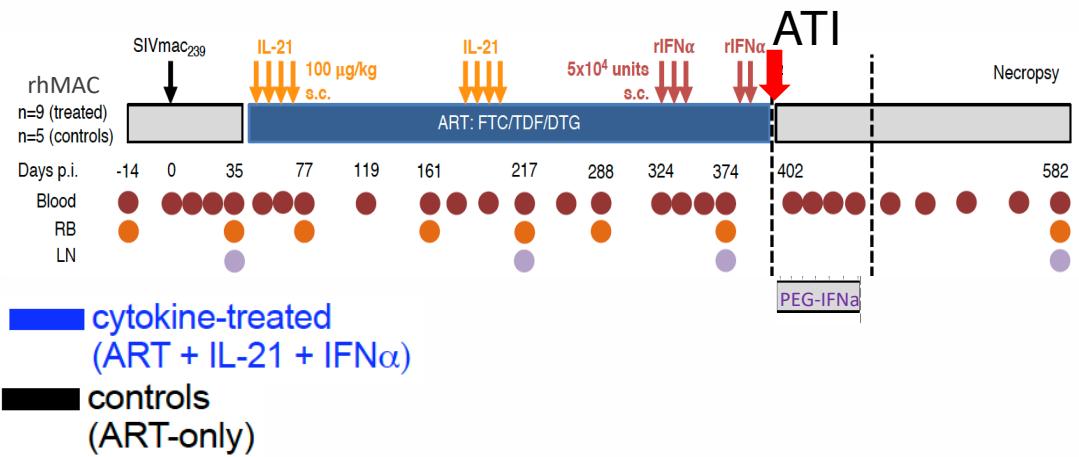
The terminal differentiated and the CXCR5<sup>+</sup> NK cells frequently expressed FcγRs



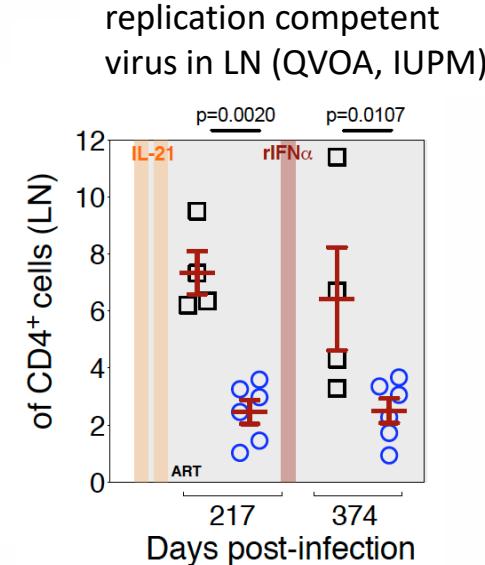
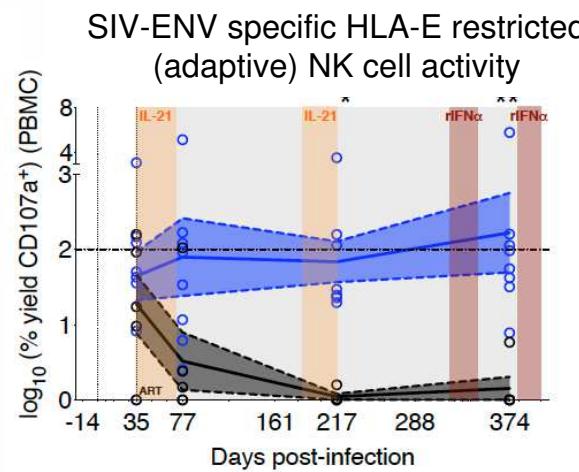
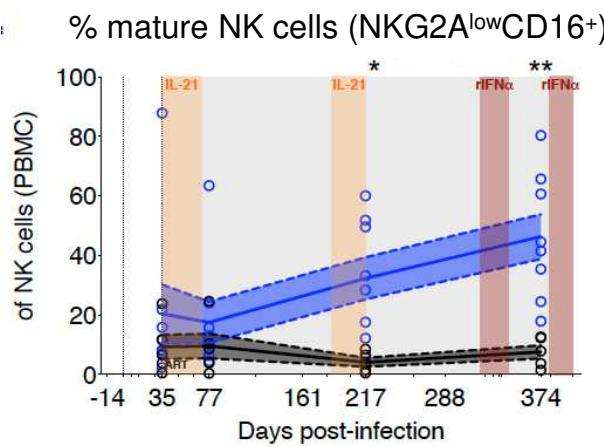
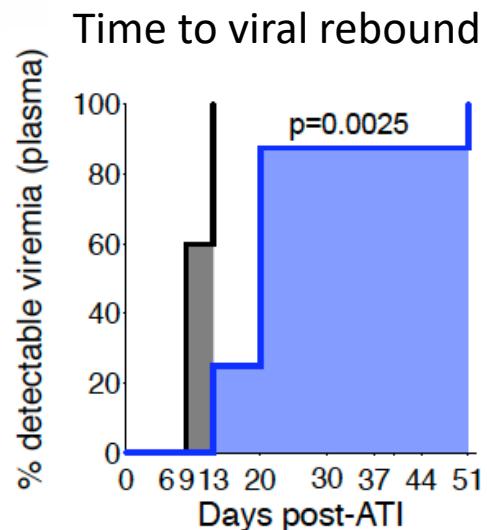
Doințin Tomescu<sup>1</sup>, Kyle Kroll<sup>4</sup>, Krystal Colon<sup>1</sup>, Emmanouil Papasavvas<sup>1</sup>, Ian Frank<sup>4</sup>, Pablo Tebas<sup>2</sup>, Karam Mounzer<sup>3</sup>, R. Keith Reeves<sup>4,5</sup>, Luis J. Montaner<sup>1,†</sup>

Identification of the Predominant Human NK Cell Effector Subset Mediating ADCC Against HIV-infected Targets Coated with BNabs or Plasma from PLWH. Eur. J. Immunol. August 2021

# IL-21 drives NK cell maturation and maintains adaptive activity under ART during SIVmac infection : associated with reservoir reduction in LN



Mirko Paiardini



Harper J et al,  
Nat Comm, 2021

# Summary

- NK cells by their own can strongly control SIV replication in a tissue (LN) throughout chronic infection
- The SIVagm control is tissue-specific (LN) and associated with a particular microenvironment
- Early IFN- $\alpha$  and IL-15 in SIVagm infection might favor NK cell activity
- IL-6 secreted by activated B cells (plasma cells) induces CXCR5 on NK cells allowing NK cells to migrate into B cell follicles
- Terminal differentiation of NK cells is associated with their adaptive profile and allows to escape HLA-E mediated inhibition



## COMMUNITY SUMMARY

- **Key question(s)** being asked

HIV persists in sanctuaries such as B cell follicles. Natural killer (NK) cells are known for their capacity to identify and eliminate infected cells. Can we teach NK cells how to reduce HIV reservoirs in B cell follicles?

- **Key finding(s)** and take-home message

We identified soluble factors that can modulate NK cells :

IL-6 induced the capacity of NK cells to migrate into HIV sanctuaries (B cell follicles).

Administration of the cytokine IL-21 during ART in SIVmac-infected macaques improved the maturation and antiviral function of NK cells. This was associated with a reduction of infectious virus in lymph nodes.

- **What are the next steps?**

To find strategies to durably maintain fully mature NK cells after treatment interruption.



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Post doc applications welcome

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