

Session 5: Persistence

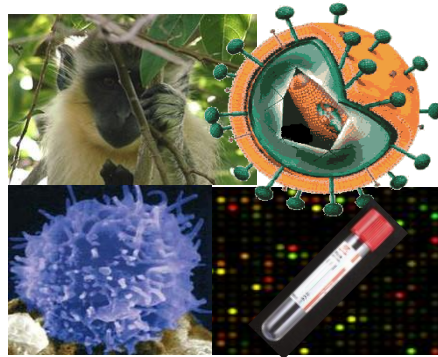
NK Cells

Michaela Müller-Trutwin, PhD
Institut Pasteur, France



NK cells and SIV reservoirs

Viral Infections and Inflammation, Viral education workshop
Washington DC, September 8-9th, 2022



Michaela Müller-Trutwin

Unité « HIV, Inflammation and Persistence »

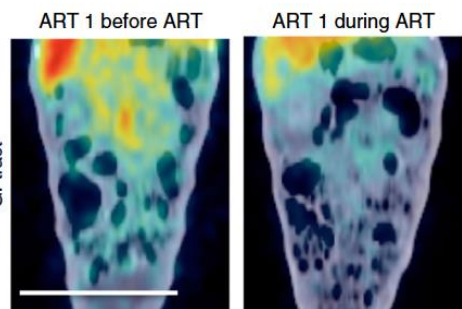
INSTITUT PASTEUR

Paris, France



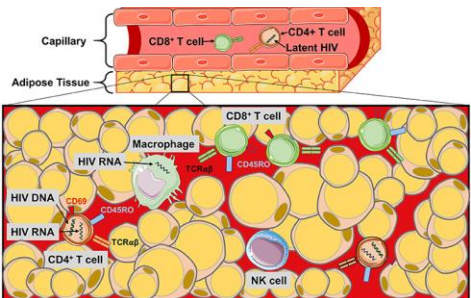
Viral reservoirs in tissues during HIV-1 and SIVmac infections

Whole body

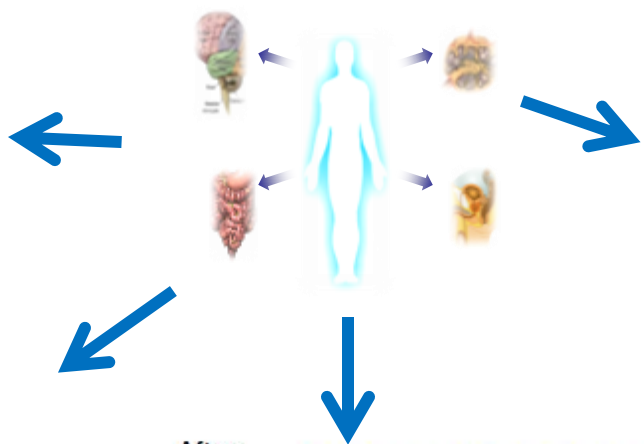


Santangelo, Nat Meth, 2015

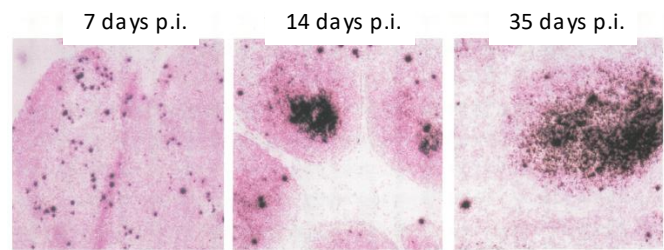
Adipose tissue



Damouche et al, Plos Path, 2015; Couturier et al AIDS 2015; Damouche et al, Eur J Imm, 2017

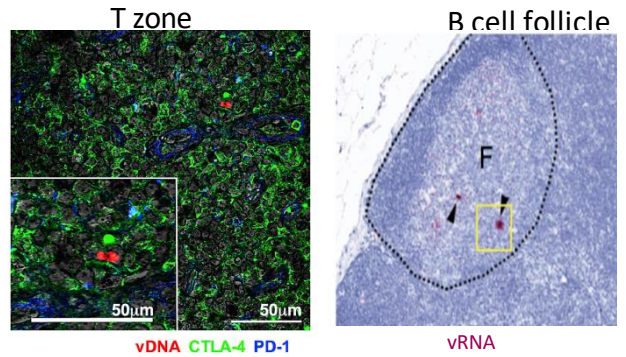


Lymph nodes (kinetics)

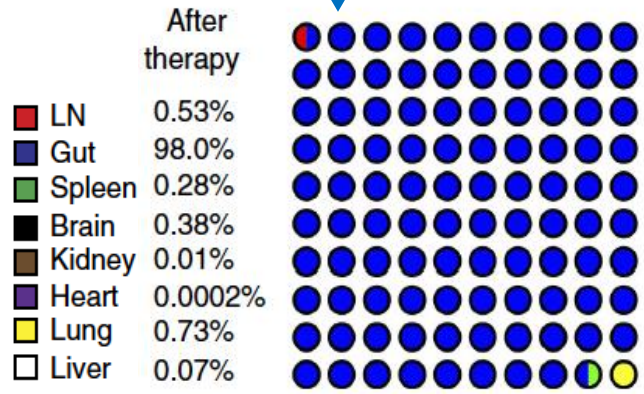


Chakrabarti L et al American Journal of Pathology, Vol. 144, No. 6, June 1994

Lymph nodes (ART)



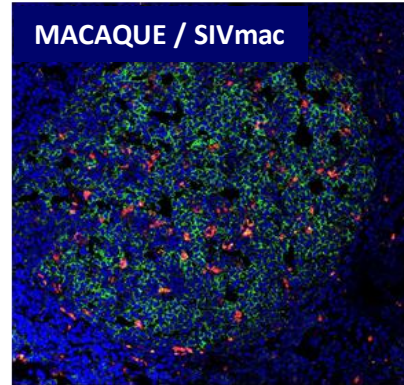
Fukazawa Y et al NMED 2015; Banga R et al NMED 2016; McGary et al, Immunity 2017; Huot et al, Front Immunol 2018



Estes et al, Nat Med, 2017

Strong viral control in lymph nodes (LN) of African green monkeys (AGM), a natural host of simian immunodeficiency virus (SIV)

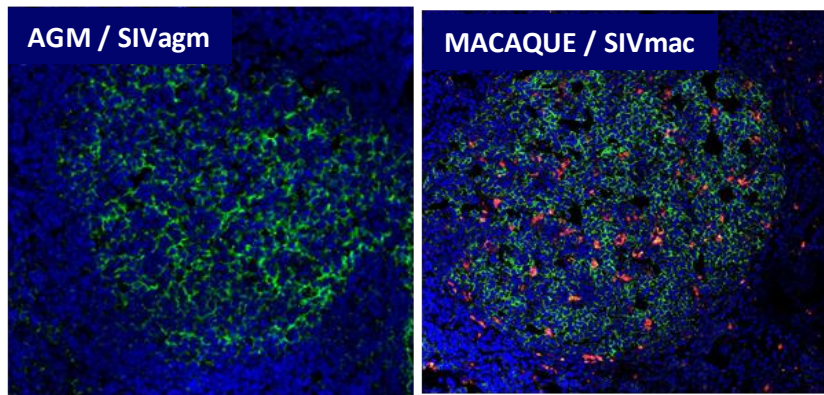
green: B cells; red: SIV



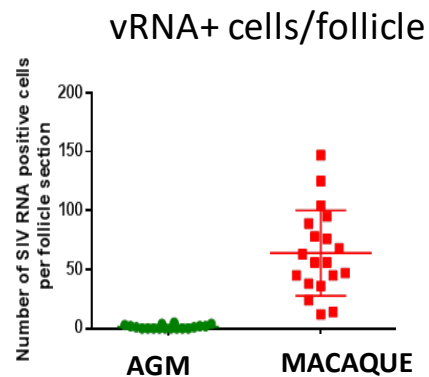
Lymph node B cell follicle
(chronic SIV infection)

Strong viral control in lymph nodes (LN) of African green monkeys (AGM), a natural host of simian immunodeficiency virus (SIV)

green: B cells; red: SIV



**Viral control in LN
(T and B zone)**



Lymph node B cell follicle
(chronic SIV infection)

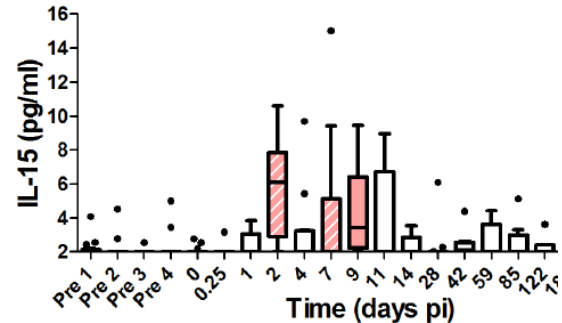
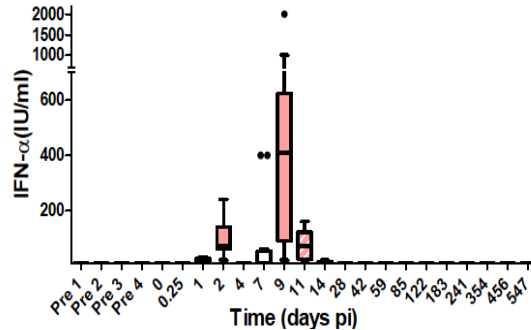
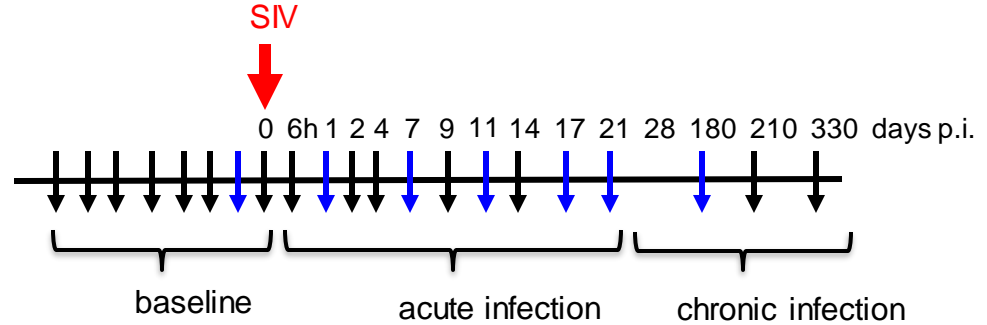
	Natural host / SIV	Human / HIV MAC / SIV
Viremia	+++	+++
Viral replication in gut	+++	+++
Chronic inflammation	-	+++

Sodora D et al, Nat Med, 2009
Huot N et al, Front Immunol, 2018

Strong early production in AGM/SIV of IFN- α and IL-15

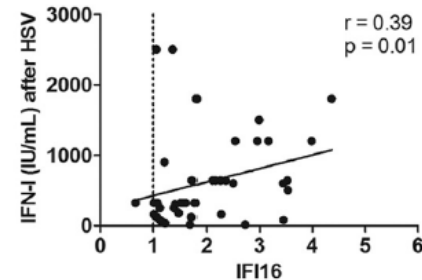
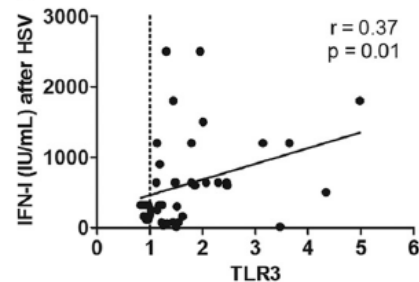
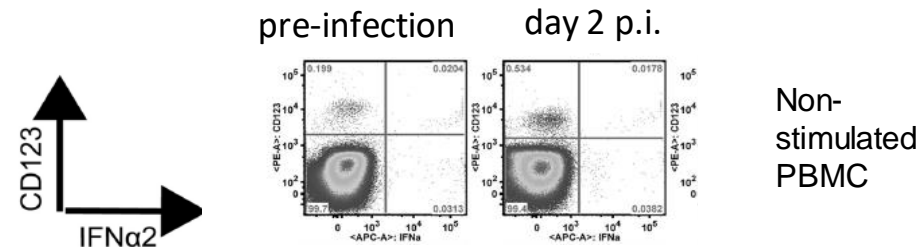
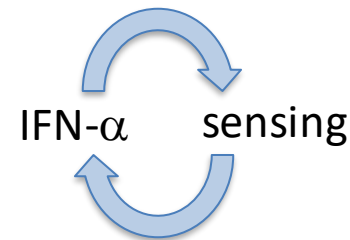
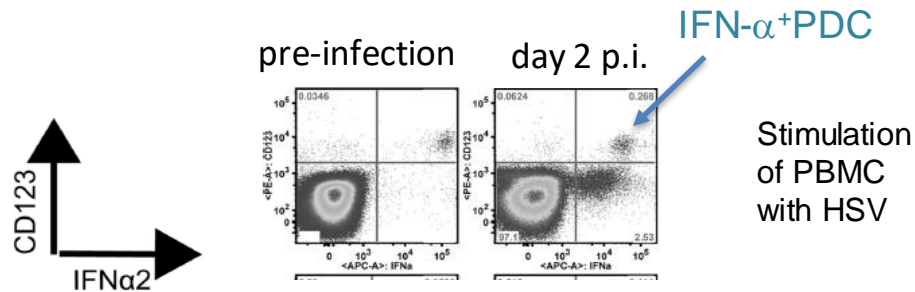
Order of appearance in acute infection (plasma)

Marker	AGM	HUMAN MAC
IL-15	+++	++
IFN- α	+++	+++
IP-10	+++	+++
MCP-1	+++	++
IFN-g	+	++
IL-18	+	+++
TNF-a	-	+
IL-8	-	+++
sTrail	-	+++
Il-6	-	+
IL-12	+	+
MIP1-a	-	++
MIP1-b	-	++
TGF-b	+	+++
IL-10	-	+
IP-10	-	+++
sCD14	-	+



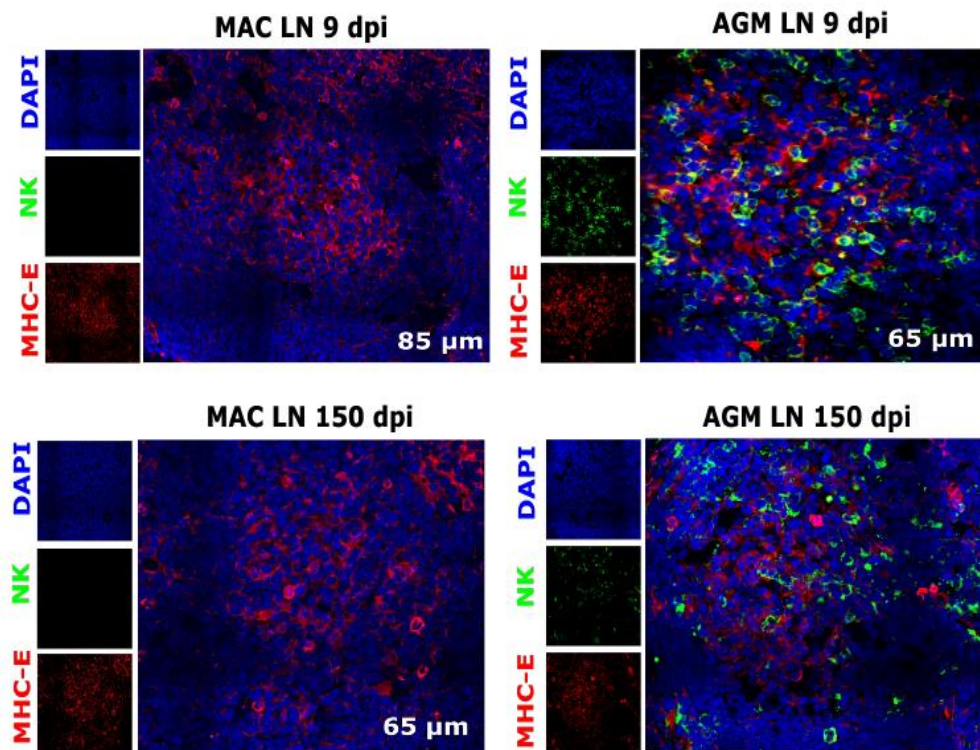
Diop OM et al, JVI 2008; Jacquelin B et al, JCI 2009; Jacquelin B et al, Plos Path 2014

Transient gain of blood cells other than pDC to produce IFN- α during primary SIVagm infection

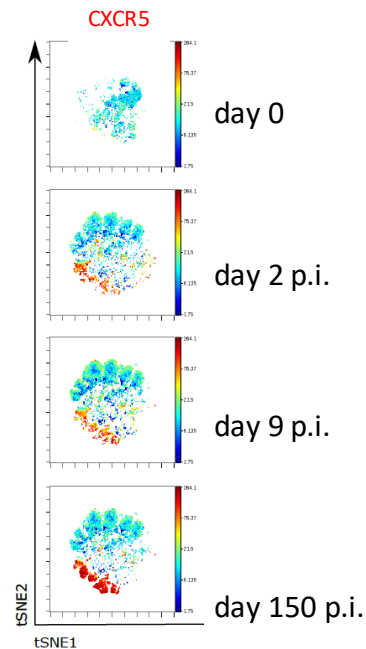


Mechanism to protect against re-activation of other chronic viral infections during primary HIV/SIV infection ?

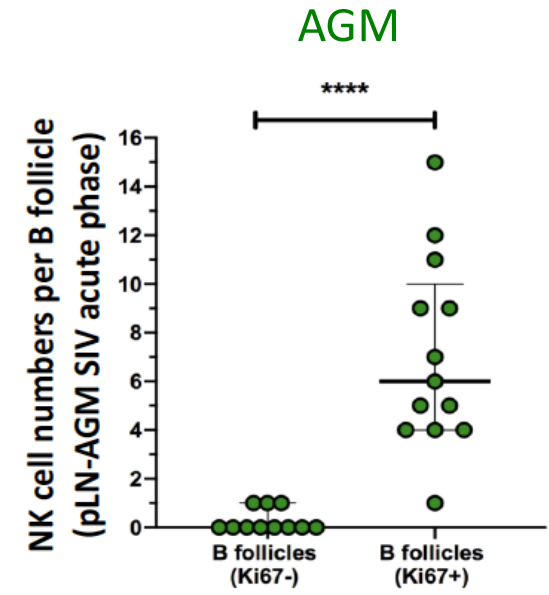
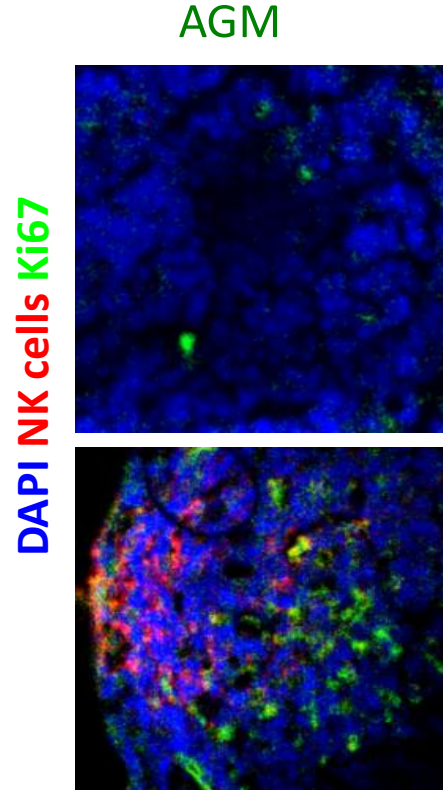
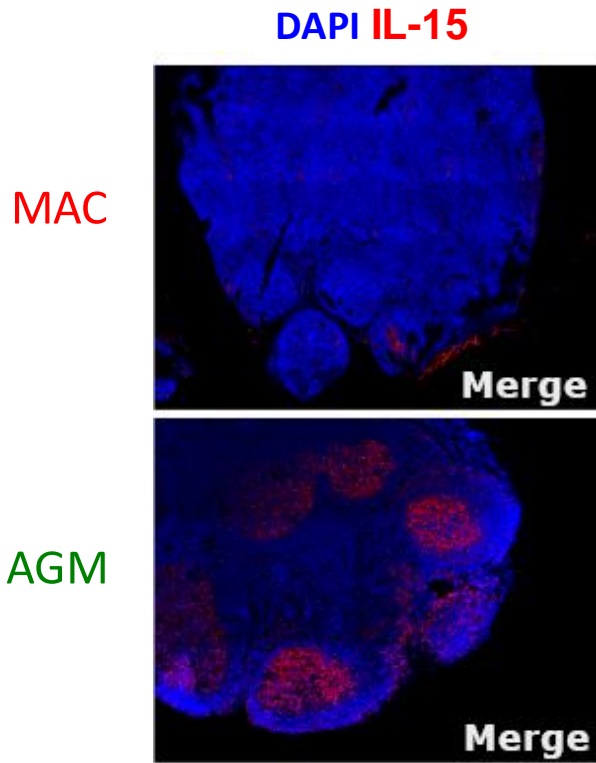
NK cells control of SIVagm replication in secondary lymphoid organs



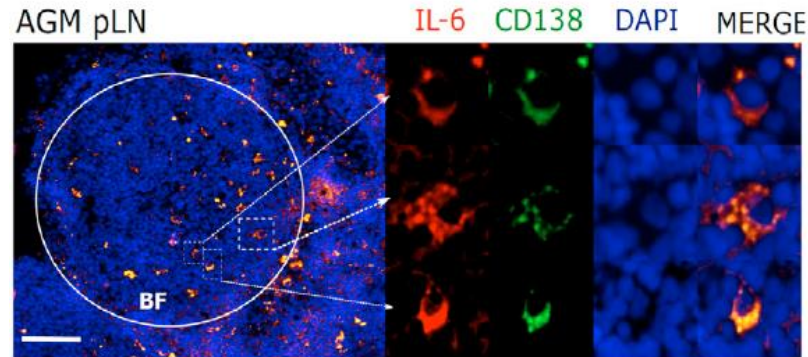
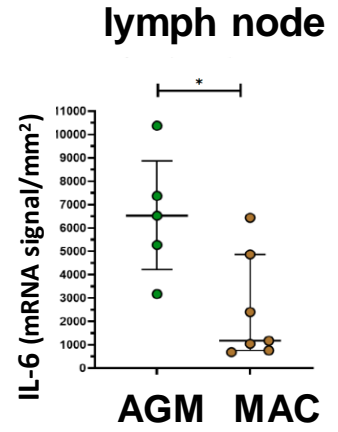
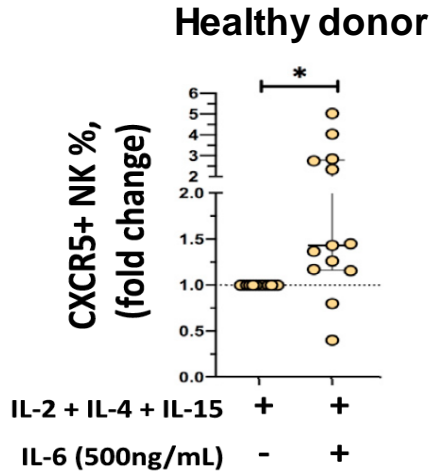
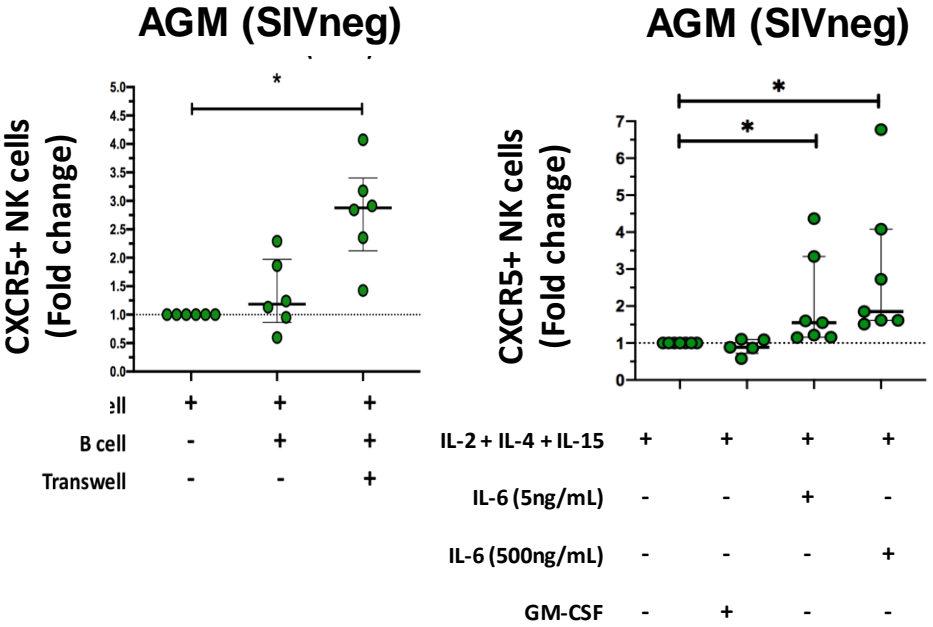
CXCR5⁺ NK cells (AGM, LN)



Preferential accumulation of NK cells in follicles with signs of B cell proliferation and high levels of FDC membrane-bound IL-15

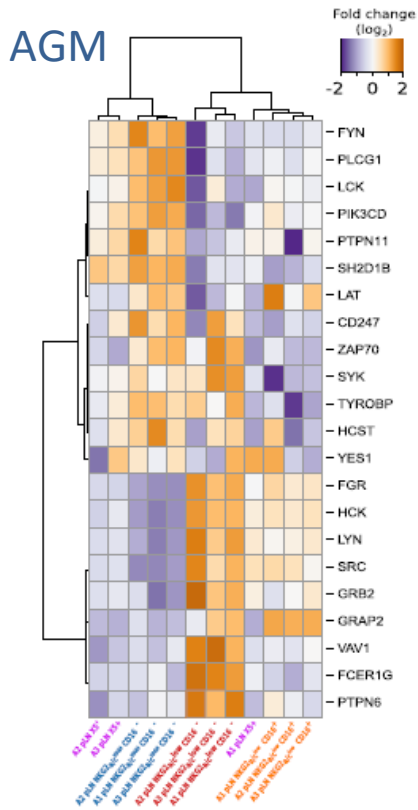


IL-6 induces CXCR5 on African green monkey (AGM) and human NK cells

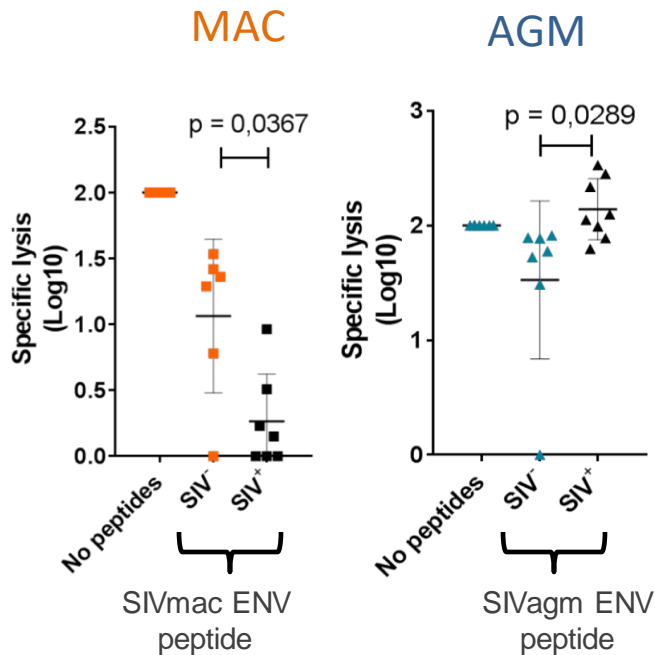


Terminally differentiated, adaptive profile of NK cells in secondary lymphoid organs of SIVagm-infected AGMs

Adaptive profile

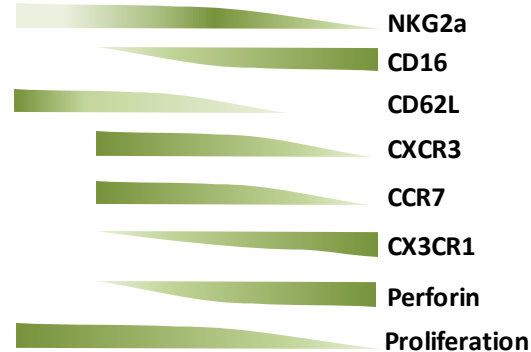


MHC-E-dependent NK cell activity

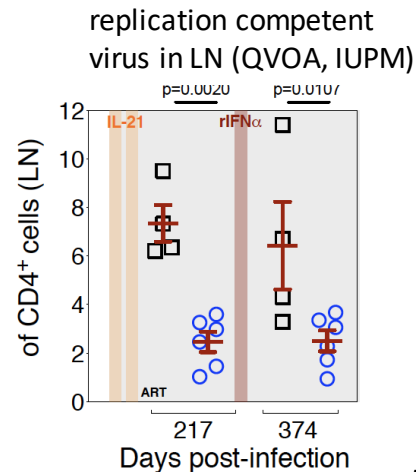
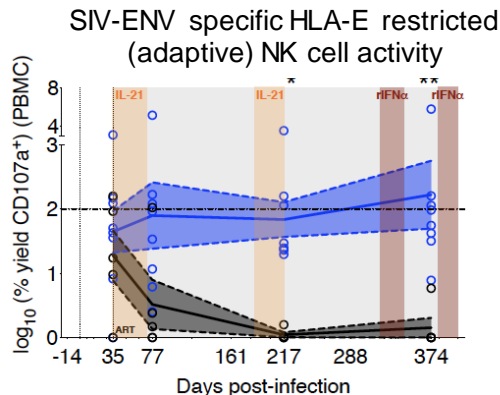
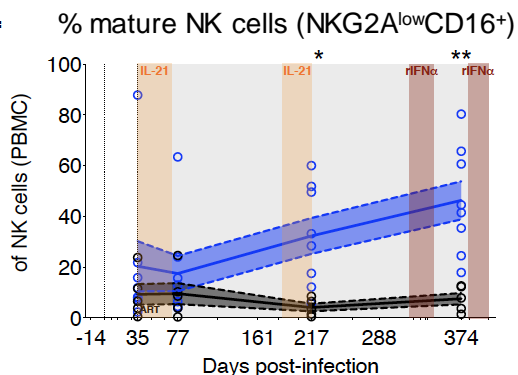
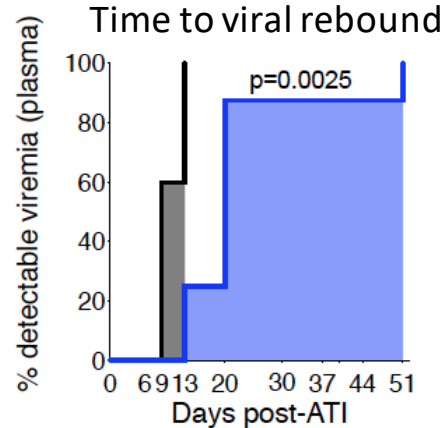
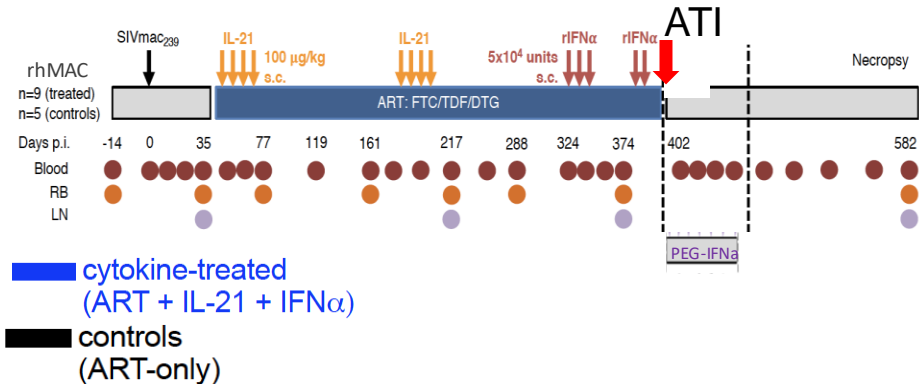


Adaptive NK cells : terminal differentiated phenotype

AGM



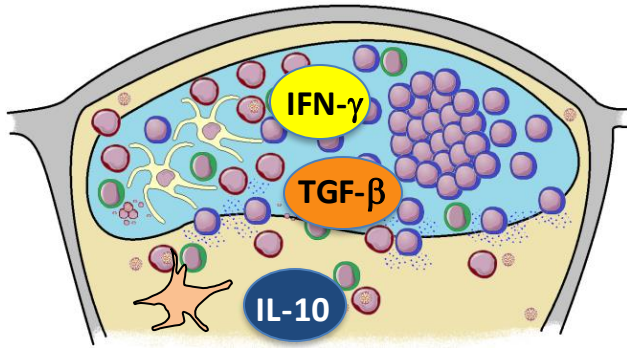
IL-21 in ART-treated SIVmac-infected macaques enhances MHC-E restricted activity of NK cells



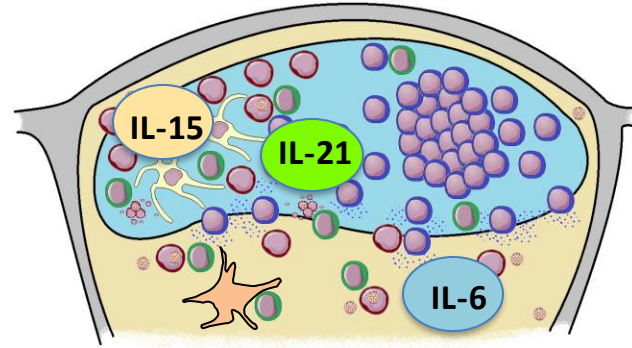
Mirko Paiardini

Tissue microenvironments : impact on NK cell differentiation ?

SIV, Lymph nodes



Humans, MAC



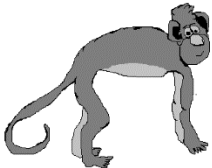
AGM

Tissue-specific viral control
Adaptive NK cells

Study on adaptive NK cells in the SARS-CoV-2/macaque model

Controls

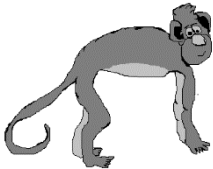
N = 7



No infection

N = 15

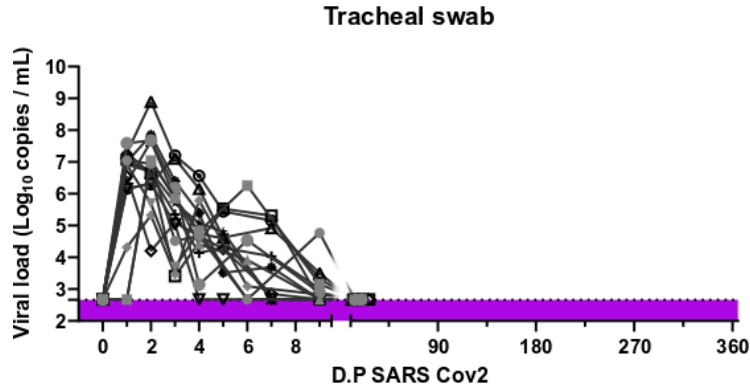
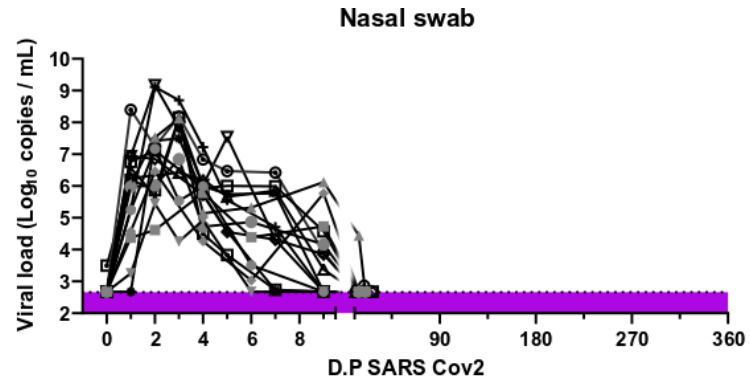
Infection with the Wuhan SARS COV-2 strain



Samples analysed 6-18 months p.i.

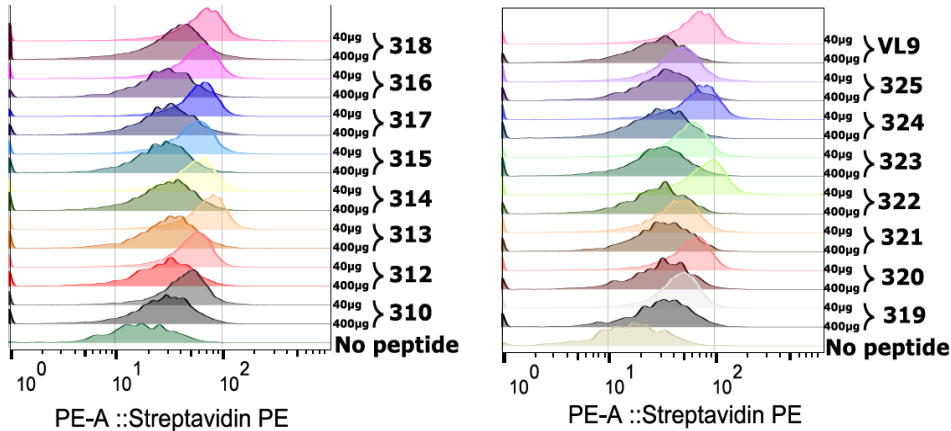
MAC (cynomolgus)

Resolution of the infection after 14 days p.i. (PCR)



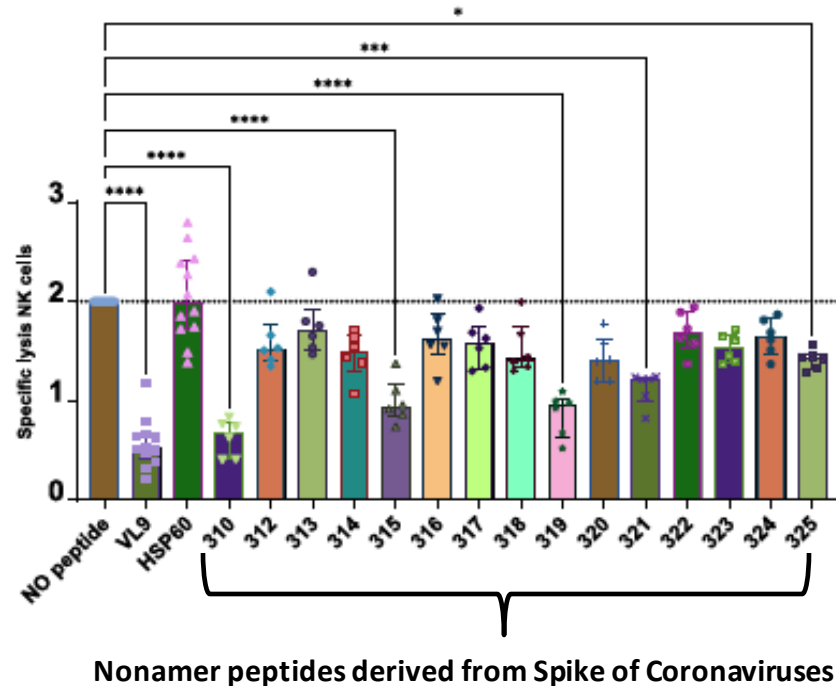
Measurement of the degranulation activity of NK cells exposed to peptides presented by HLA-E

Identification of Spike-derived nonamers that bind to HLA-E *in vitro*

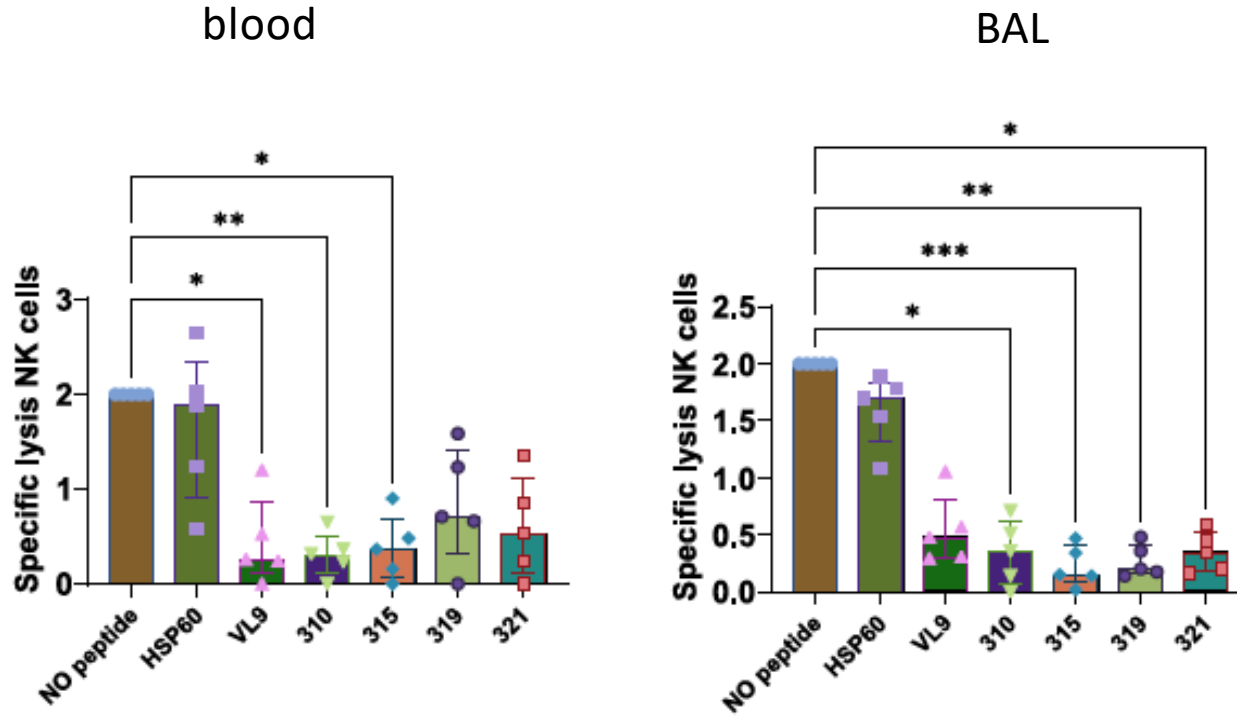


Identification of 4 Spike-derived nonamers that inhibit the HLA-E dependent degranulation activity of human NK cells

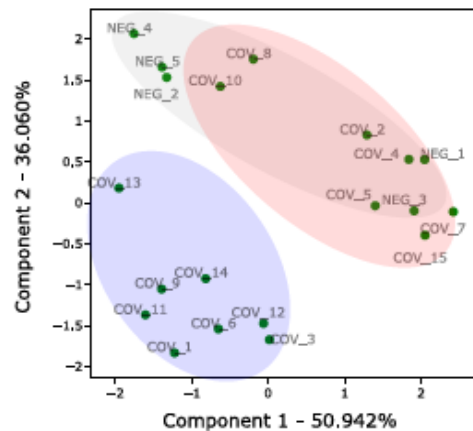
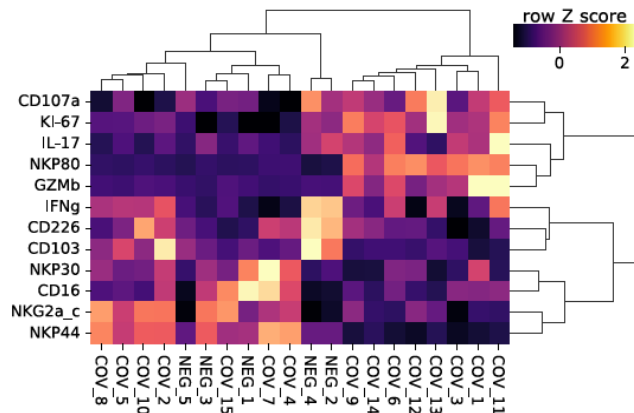
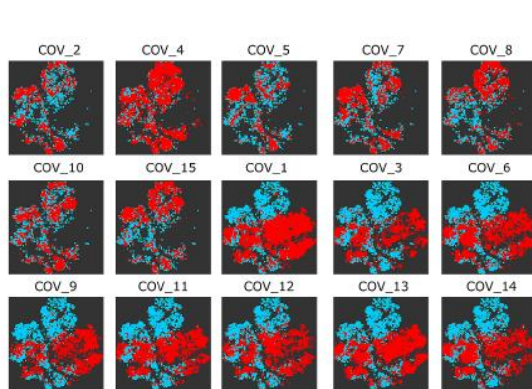
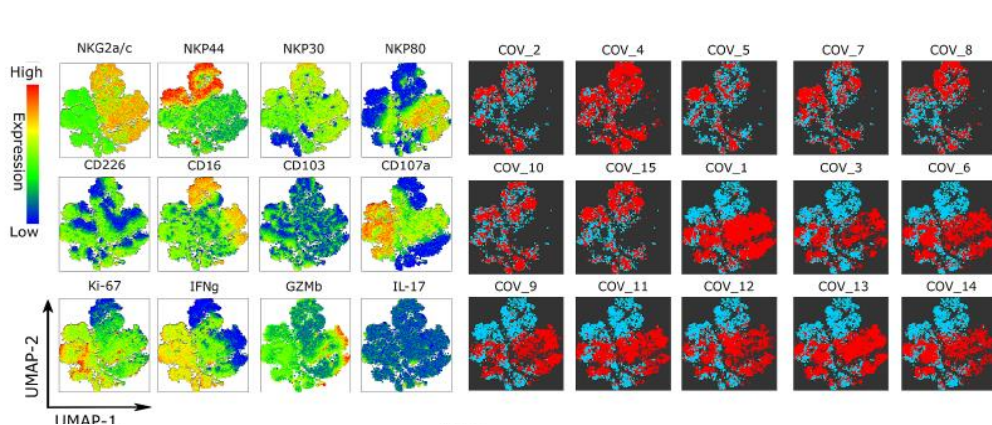
NK cells were isolated from human blood collected before 2019 (N=6 donors)



Spike-peptides inhibiting degranulation activity of NK cells from healthy macaques

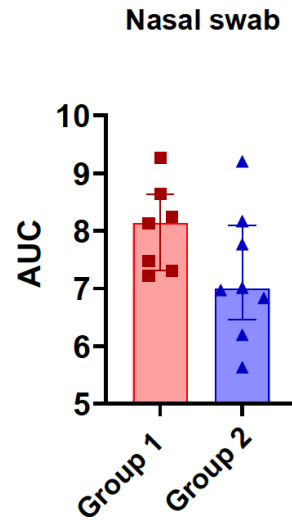
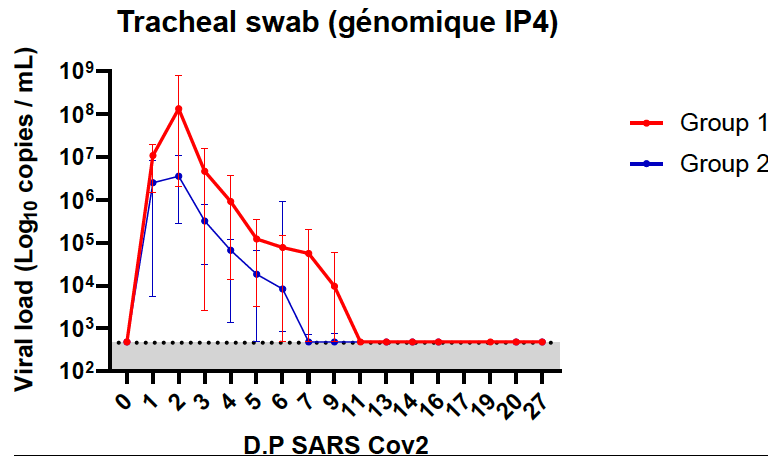


BAL NK cells segregate SARS-CoV-2 convalescent NHPs into two groups

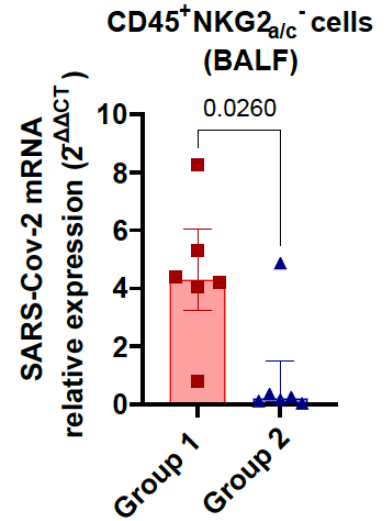
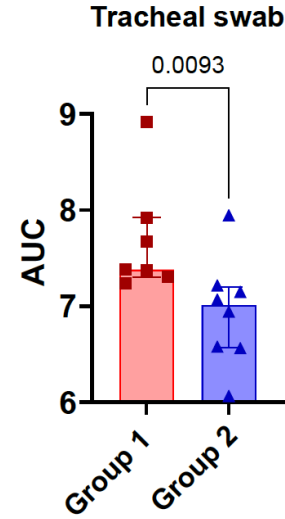


○ Control n= 7 ○ Group 1 n= 7 ○ Group 2 n= 8

Group 2 animals displayed lower viral load

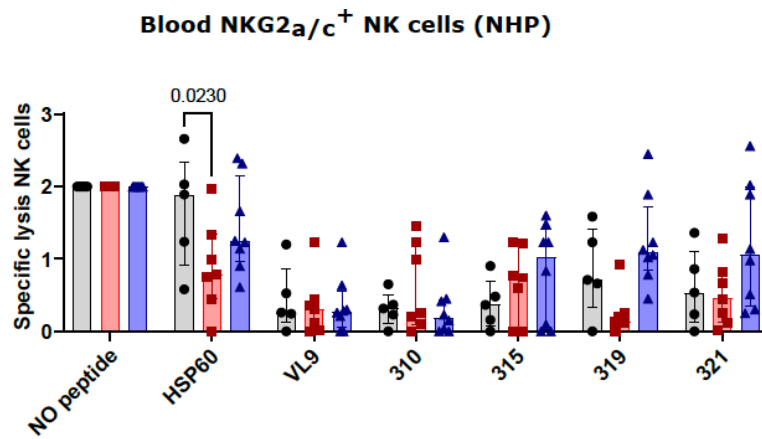
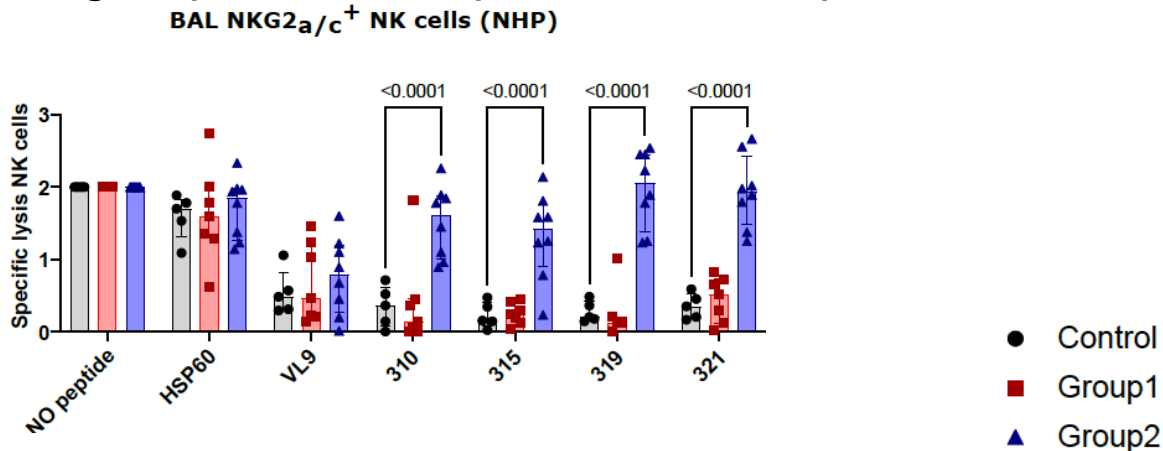


acute



convalescent

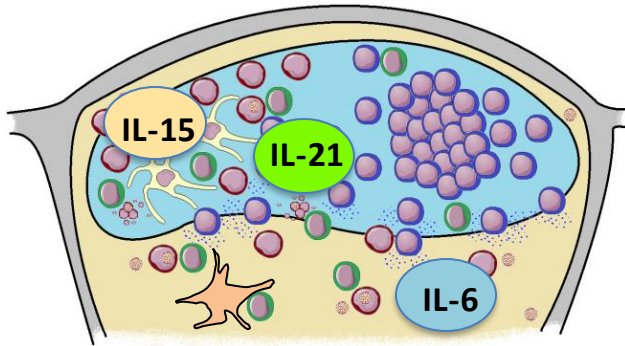
NK cells from BAL of group 2 show higher HLA-E dependent degranulation activity than group 1 when exposed to the Spike nonamers



Detection of adaptive NK cells in tissues

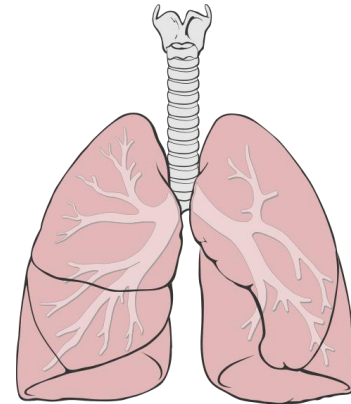
SIV, Lymph nodes

Adaptive NK cells
in SLT in SIVagm infection



SARS-CoV-2 (MAC), lung

Adaptive NK cells in BAL
of some animals



HIV, Inflammation and Persistence Lab



Institut Pasteur

Nicolas Huot

Beatrice Jacquelin
Caroline Petitdemange
Marie Lazzerini
Aurelio Orta Resendiz
Emma Beaumont

Asier Saez-Cirion

Anaïs Chapel
Amal Elfida
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