

The Third Coast CFAR Ripple Effect or how the CFAR helped me launch my independent career

Jeffrey Schneider
Assistant Professor
Rush University
Feb 12th, 2024



Seminar Series 2015-16

Thursday
March 31, 2016

1st Annual Third Coast CFAR Symposium

1:30 – 7:00 PM
Baldwin Auditorium
Lurie Cancer Center
Northwestern University
303 E. Superior Street

*Building Academic-Public Health Partnerships to
End the HIV Epidemic*

Schedule and presenters available at
<http://www.thirdcoastcfar.org/symposium>

Monday
September 26, 2016

Dan Barouch

Professor of Medicine, Harvard Medical School
Director, Center for Virology and Vaccine Research at Beth
Israel Deaconess Medical Center

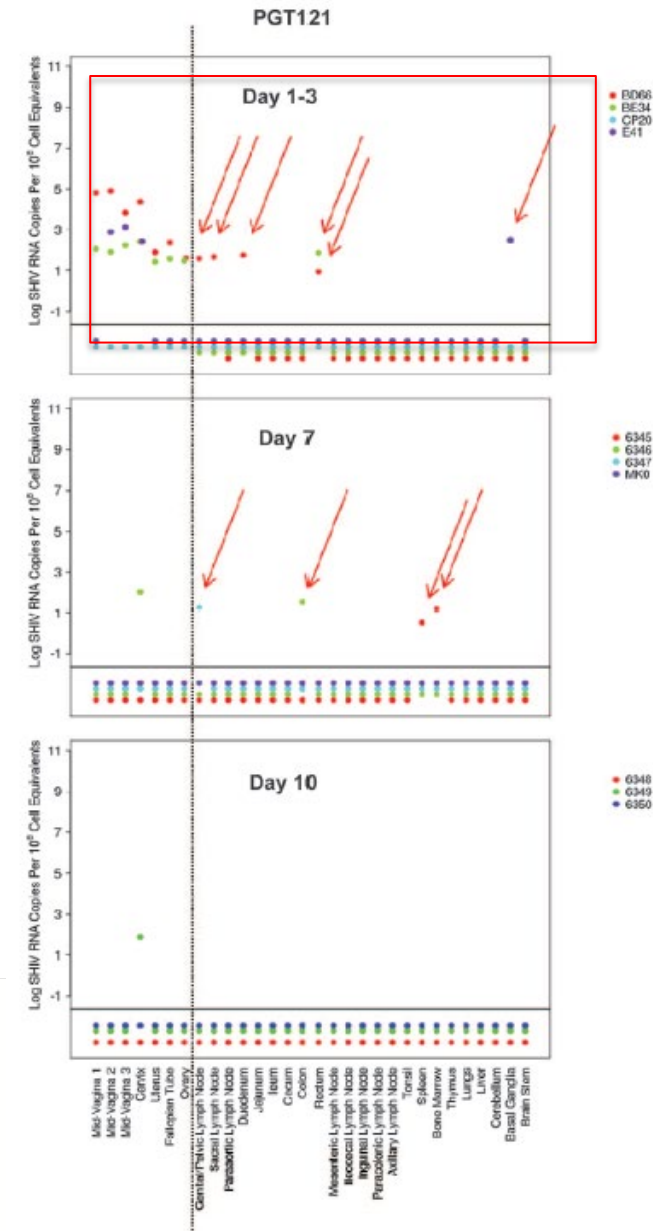
12:00-1:00 PM
Wieboldt Hall, Room 421
Northwestern University
Chicago Campus

*videoconference available

Antibody-mediated protection against SHIV challenge includes systemic clearance of distal virus

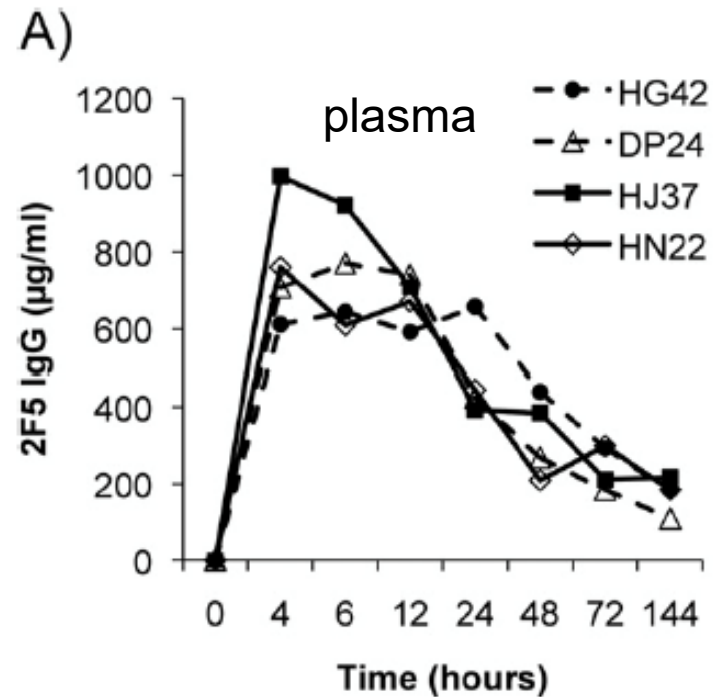
Jinyan Liu,¹ Khader Ghneim,² Devin Sok,³ William J. Bosche,⁴ Yuan Li,⁴ Elizabeth Chipriano,⁴ Brian Berkemeier,⁴ Kelli Oswald,⁴ Erica Borducchi,¹ Crystal Cabral,¹ Lauren Peter,¹ Amanda Brinkman,¹ Mayuri Shetty,¹ Jessica Jimenez,¹ Jade Mondesir,¹ Benjamin Lee,¹ Patricia Giglio,¹ Abishek Chandrashekar,¹ Peter Abbink,¹ Arnaud Colantonio,⁵ Courtney Gittens,⁶ Chantelle Baker,⁶ Wendeline Wagner,⁶ Mark G. Lewis,⁶ Wenjun Li,⁷ Rafick-Pierre Sekaly,^{2*} Jeffrey D. Lifson,^{4*} Dennis R. Burton,^{3,8*} Dan H. Barouch^{1,8,*†}

Distal Site accumulation of SHIV-SF162P3 even with IV PGT121 antibody given 24 hours prior to intravaginal challenge in rhesus macaques!



Can we track antibodies in vivo and how long does it take antibodies to get to mucosal surfaces following IV injection?

Antibody circulation following IV injection in rhesus macaques



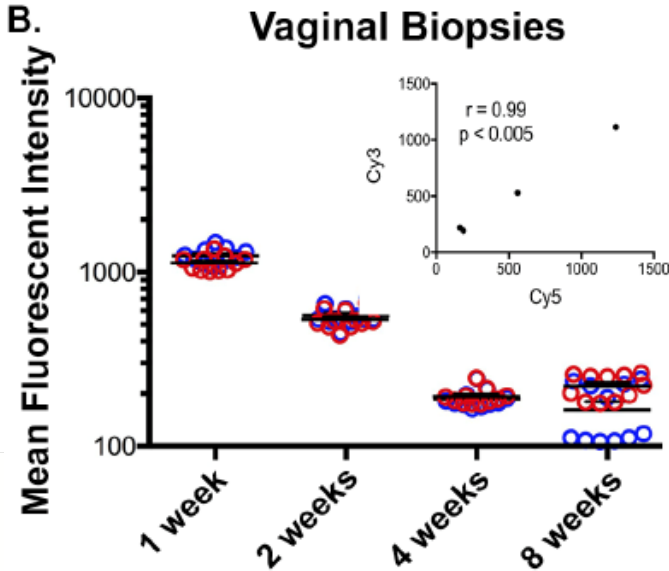
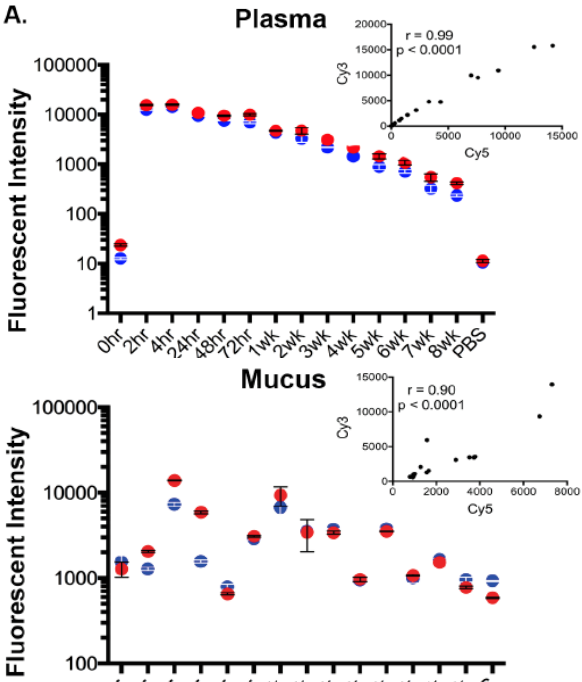
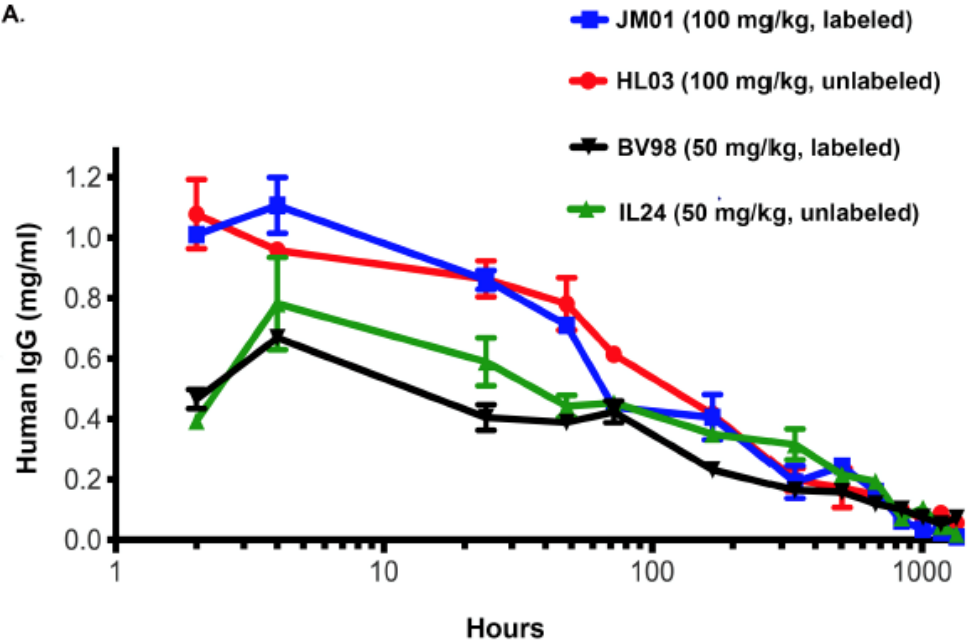
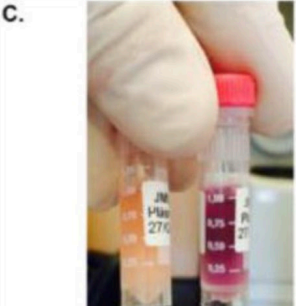
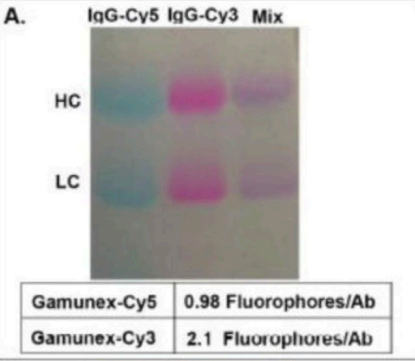
How long does it take for antibody to achieve peak levels in the tissue?



Research paper

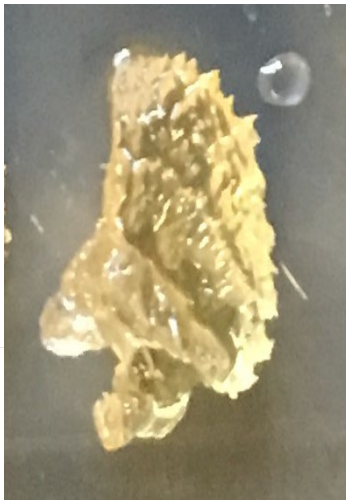
Long-term direct visualization of passively transferred fluorophore-conjugated antibodies

Jeffrey R. Schneider^{a,1}, Ann M. Carias^{a,1}, Arangaserry R. Bastian^b, Gianguido C. Cianci^a, Patrick F. Kiser^{b,c,d}, Ronald S. Veazey^e, Thomas J. Hope^{a,b,c,d,*}

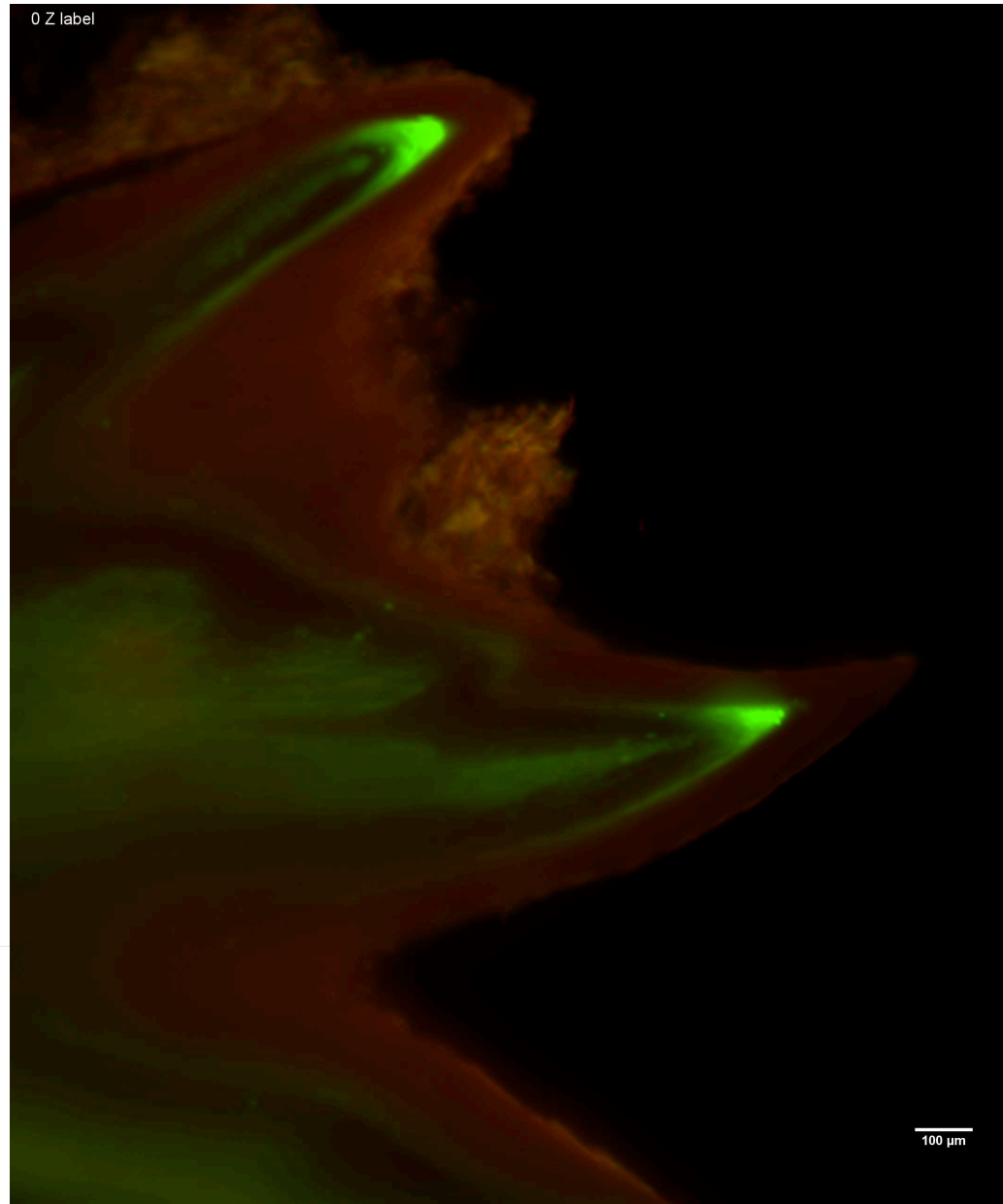


Antibody delivery to vaginal epithelium

Red=background
Green=VRC01



clarified tissue



VRC01
Background



This information is current as of June 23, 2021.

Anatomic Distribution of Intravenously Injected IgG Takes Approximately 1 Week to Achieve Stratum Corneum Saturation in Vaginal Tissues

Ann M. Carias, Jeffrey R. Schneider, Patrick Madden, Ramon Lorenzo-Redondo, Mariluz Araínga, Amarendra Pegu, Gianguido C. Cianci, Danijela Maric, Francois Villinger, John R. Mascola, Ronald S. Veazey and Thomas J. Hope

J Immunol published online 23 June 2021

<http://www.jimmunol.org/content/early/2021/06/23/jimmunol.2100253>



Tom Hope

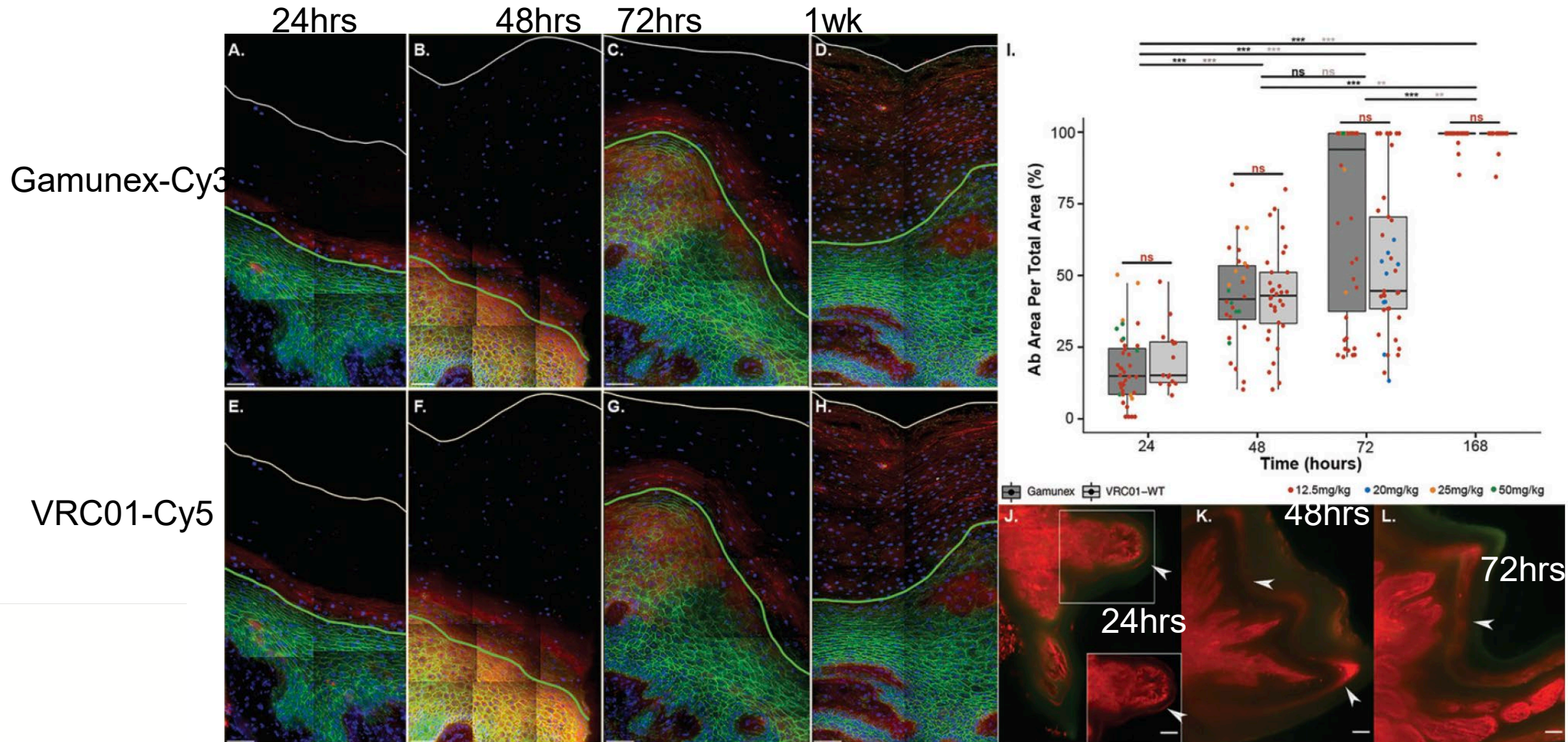


Ann Carias

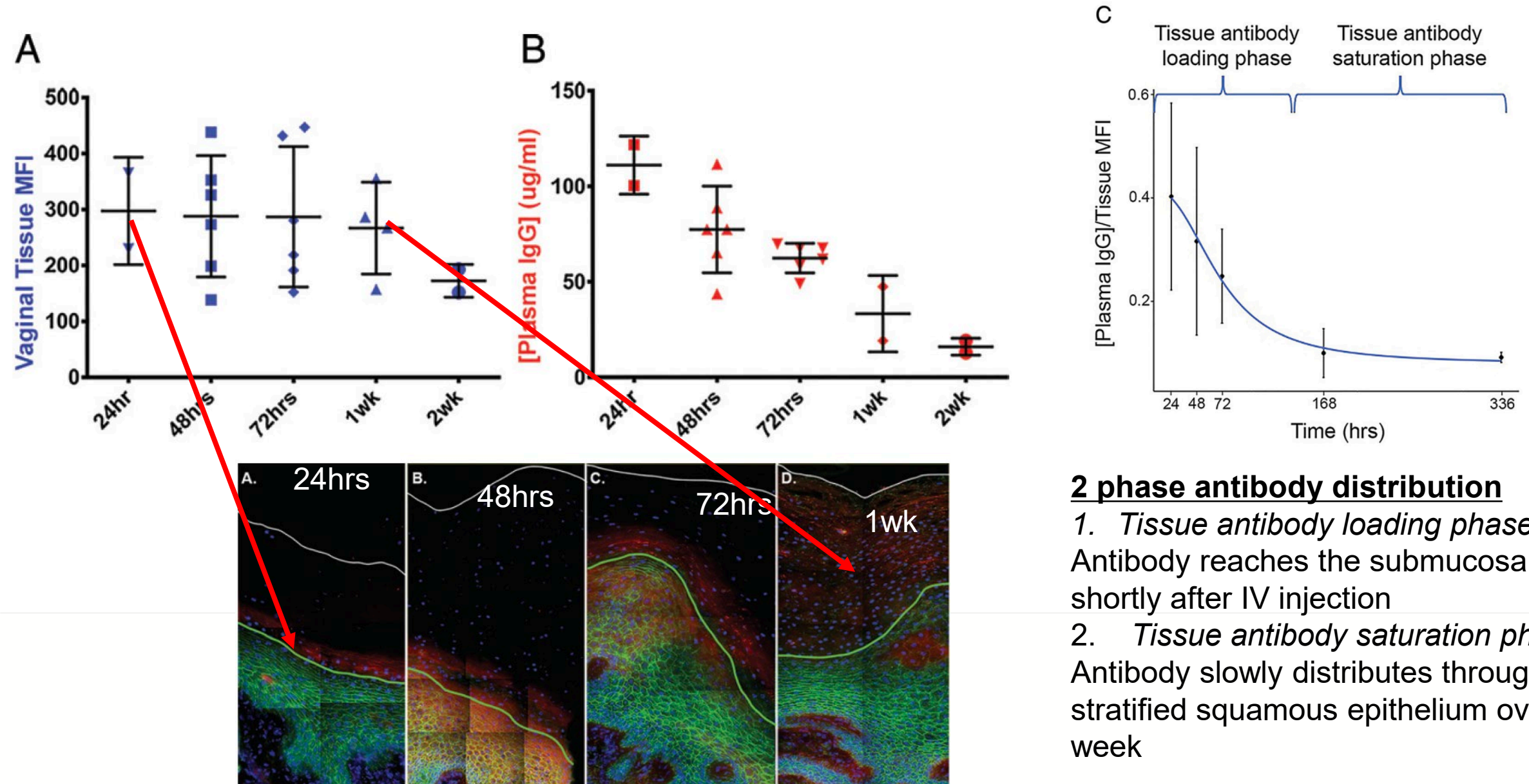


Ramon Lorenzo-Redondo

VRC01(Anti-HIV monoclonal) and gamunex both
take 1 week to fully saturate epithelium



Antibody leaves the plasma and enters tissue

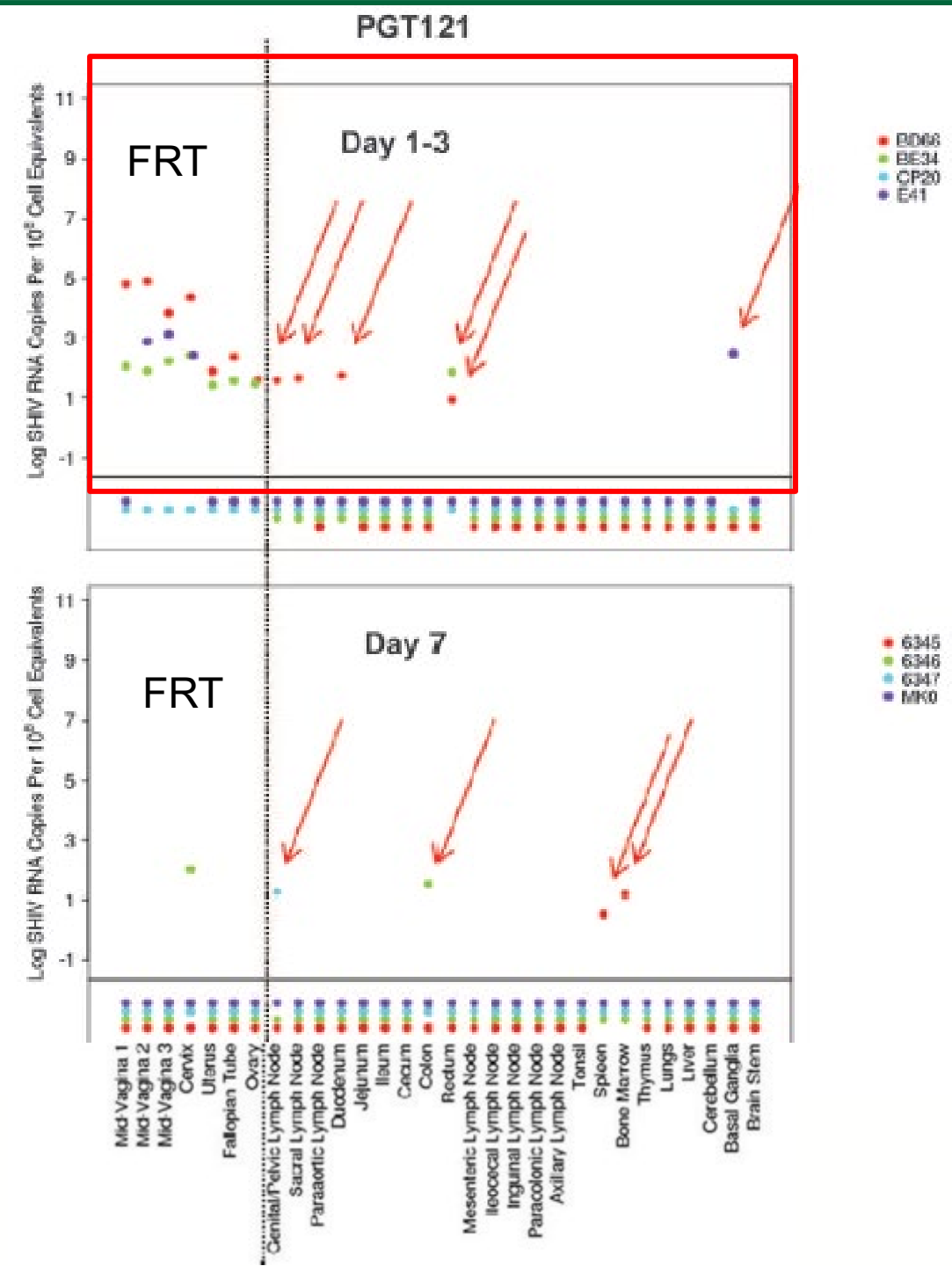
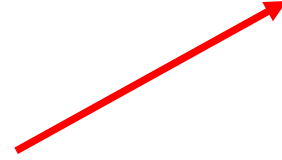


2 phase antibody distribution

1. *Tissue antibody loading phase:*
Antibody reaches the submucosa shortly after IV injection

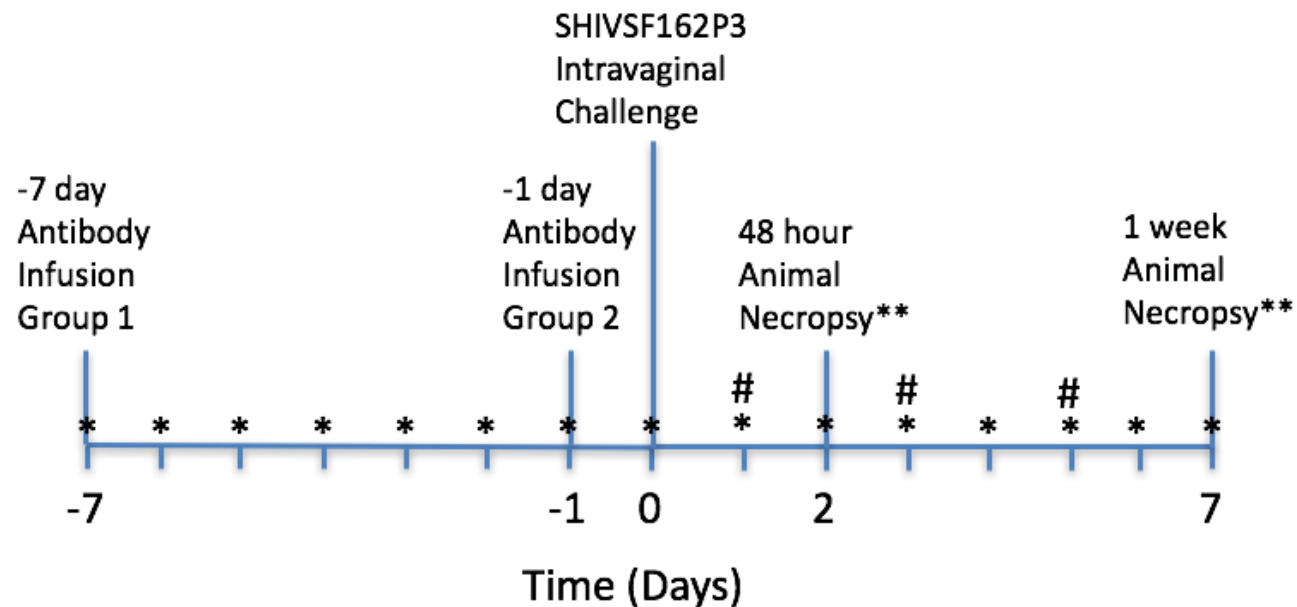
2. *Tissue antibody saturation phase:*
Antibody slowly distributes through the stratified squamous epithelium over 1 week

Can we block accumulation of virus 1-3 days after challenge at the site of challenge and distal sites by changing the timing of antibody injection to give antibody more time to fill the stratified squamous epithelium of the vagina?



Mentorship Team: Tom Hope and Ron Veazey

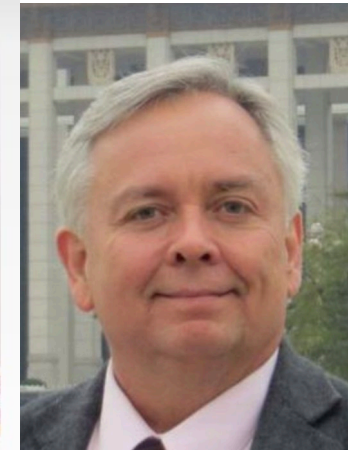
K01: The role of steady state broadly neutralizing antibody tissue levels in preventing distal site SHIV replication



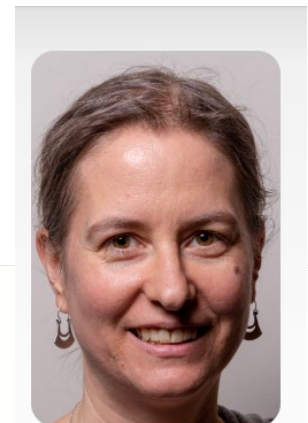
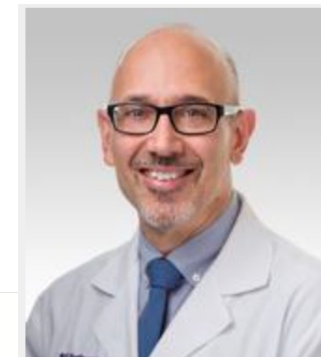
IV-Infusion groups consist of either Cy5-PGT121 or Cy5-DEN3 given at 2mg/kg at either -1 or -7 days prior to challenge



K01 advisor:
Rich D'Aquila



Tech:
Flora Engelmann



A. PGT121-Cy5 or sham DEN3-Cy5 (2mg/kg)

Cy5-IgG IV
injection at -1
or -7 days

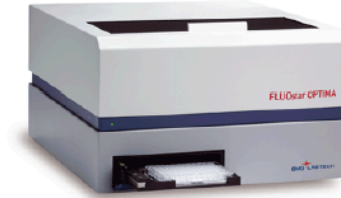
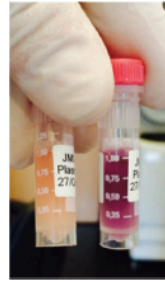


Intravaginal
challenge at
day 0 with
SHIV-SF162P3

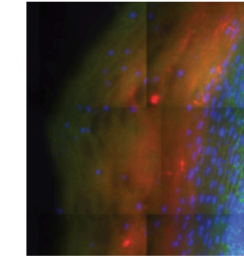
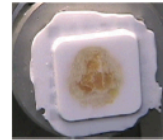


Necropsy at day 2

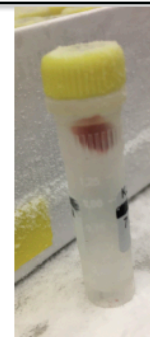
B.



C.



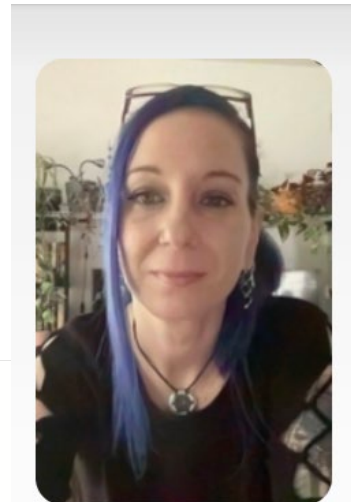
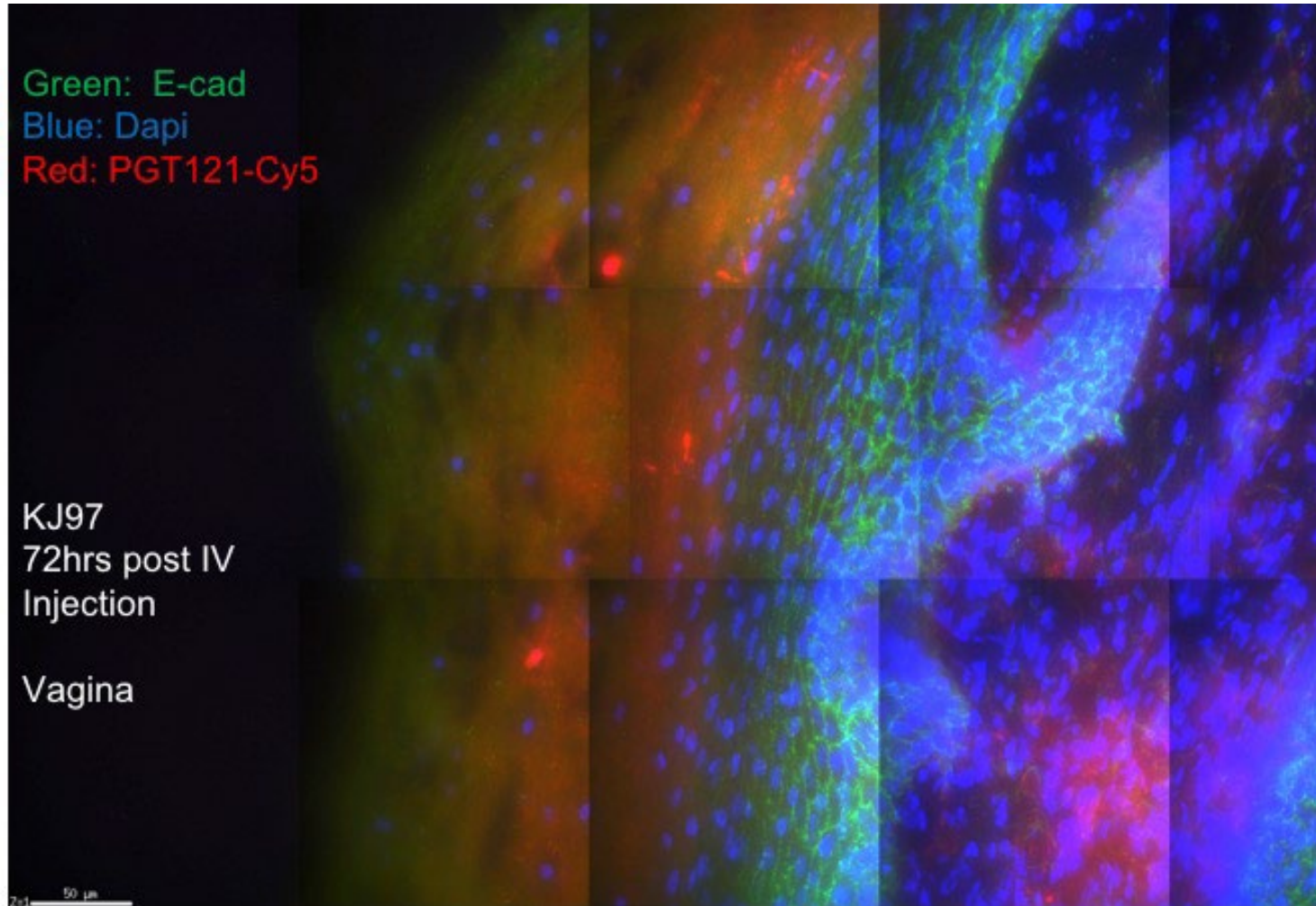
D.



Trizol isolation
of RNA and
DNA for viral
gag qPCR



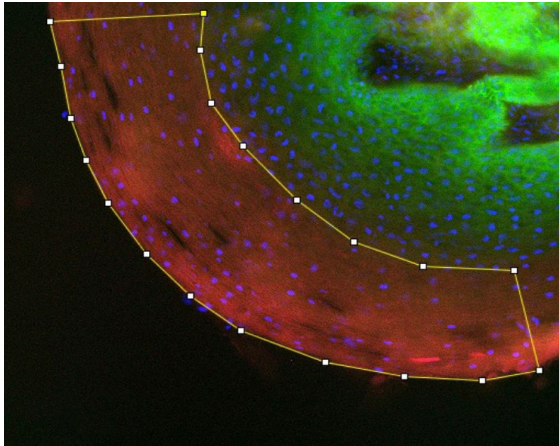
PGT121 fluorescence in the vagina at 2mg/kg



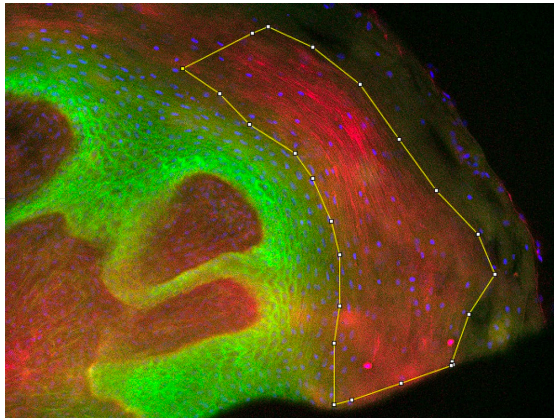
Ann Carias

More antibody occupancy in vaginal epithelium in -7 day animals

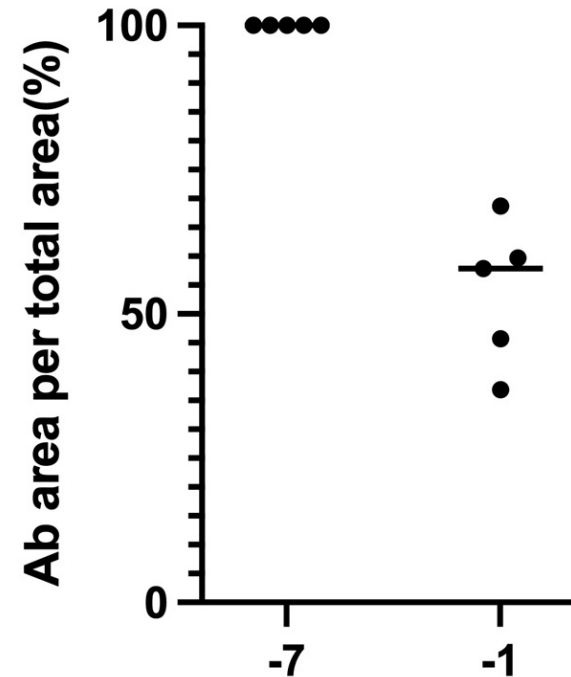
Example of -7day animal at necropsy



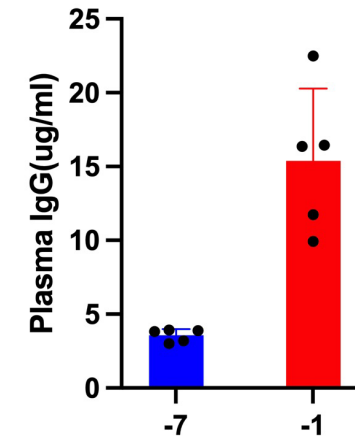
Example of -1 day animal at necropsy



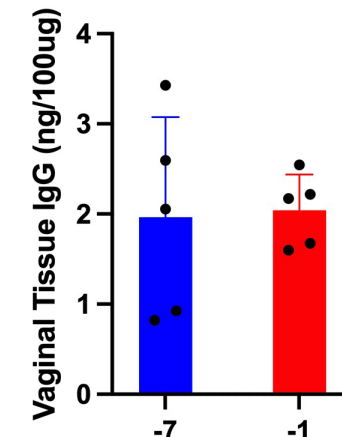
Antibody occupancy 48hrs after challenge in vaginal epithelium



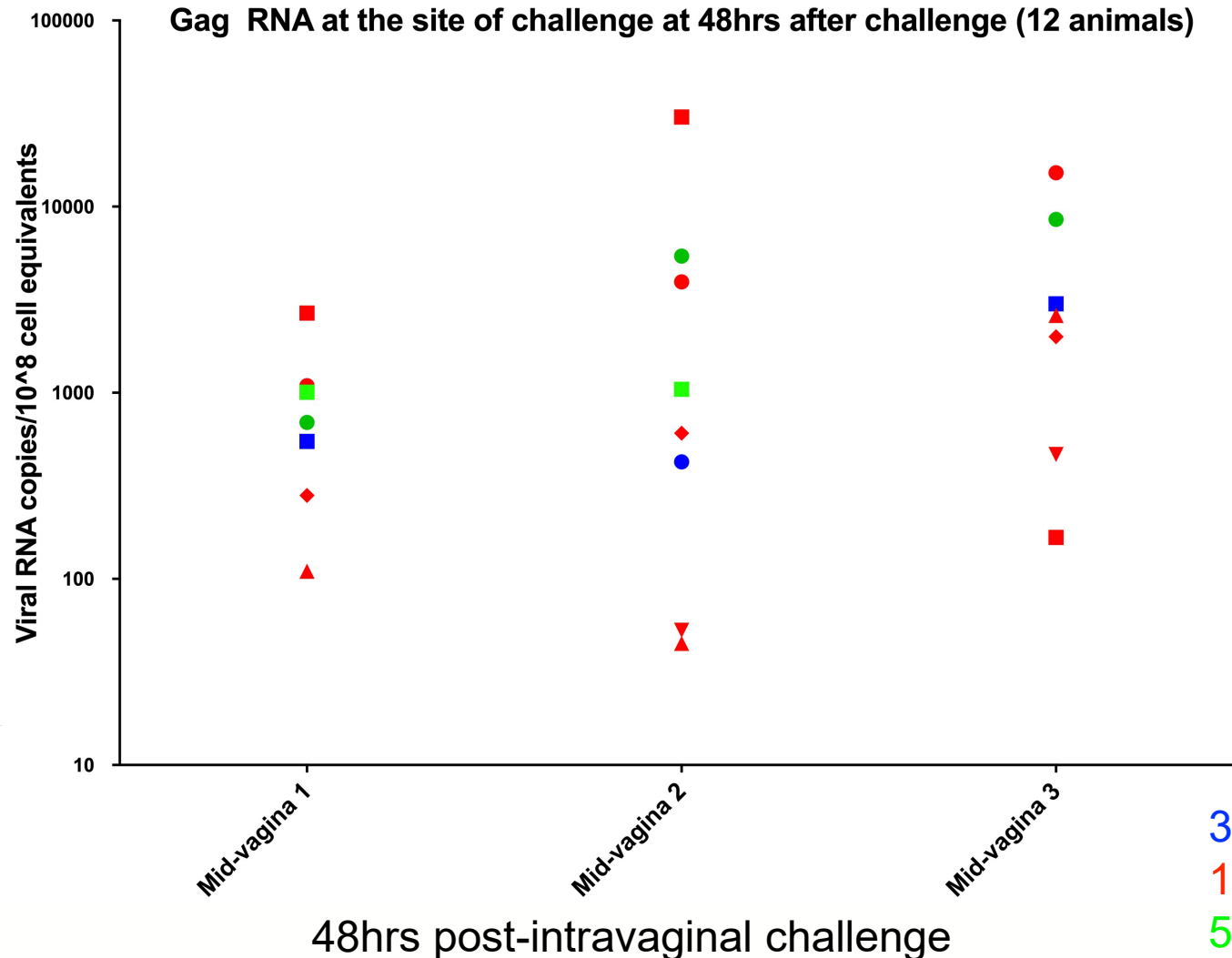
Plasma levels at time of challenge



Vaginal tissue lysate at time of necropsy



Enhanced protection at the site of challenge in animals that get PGT121 1 week before challenge



-7 day group, n=5

- JB21 -7 day PG121
- JT95 -7 day PG121
- ▲ HG63 -7 day PG121
- ◆ IJ32 -7 day PG121
- ▼ LH97 -7 day PG121

-1 day group, n=5

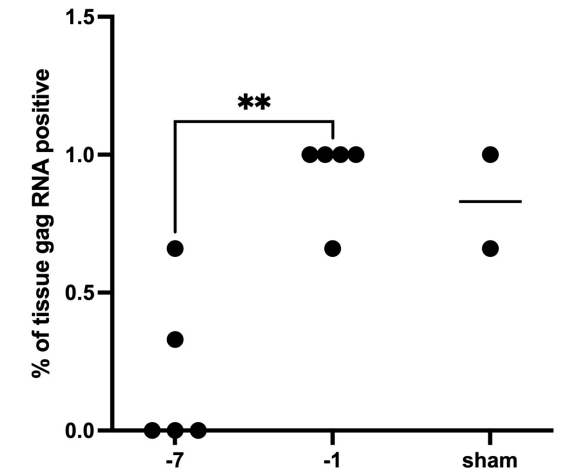
- KJ97 -1 day PG121
- KK15 -1 day PG121
- ▲ KF31 -1 day PG121
- ◆ KA61 -1 day PG121
- ▼ KG33 -1 day PG121

Sham group, n=2

- HE07 -7 day DEN3 (sham)
- HP54 -1 day DEN3 (sham)

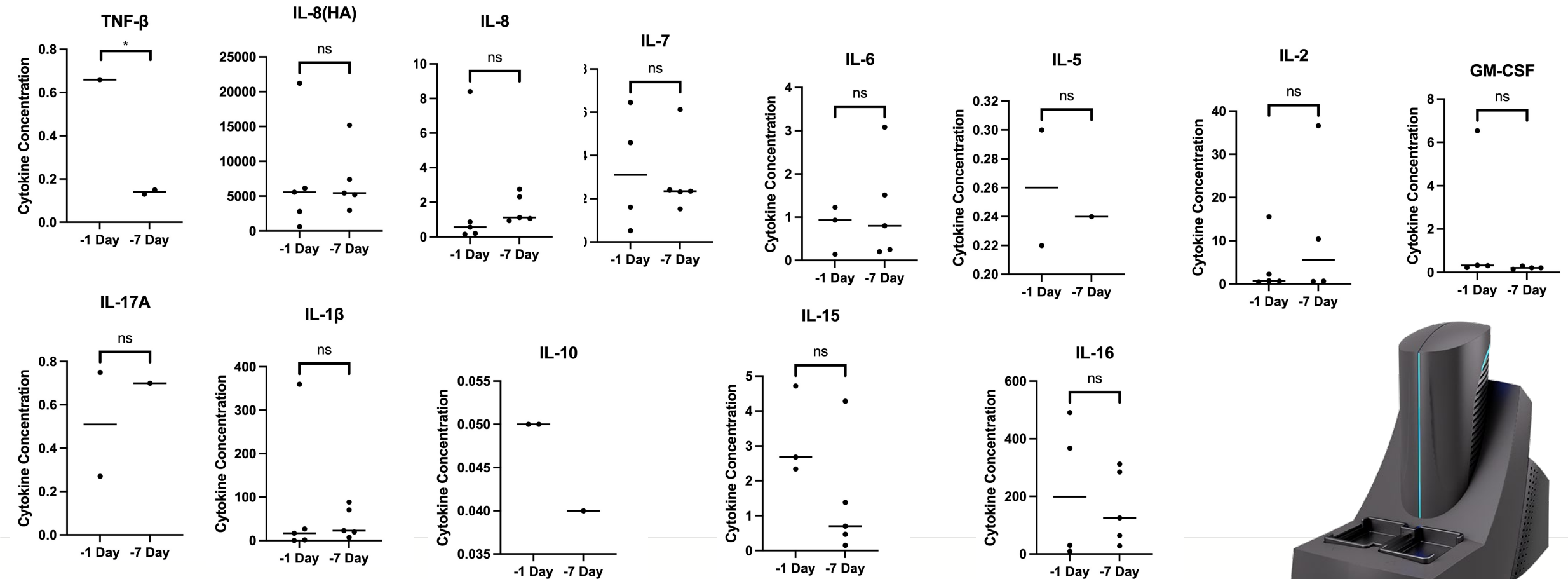
3 pieces of vaginal tissue assessed per animal (n=5 per group)

Percent of tissue per animal that is gag RNA positive



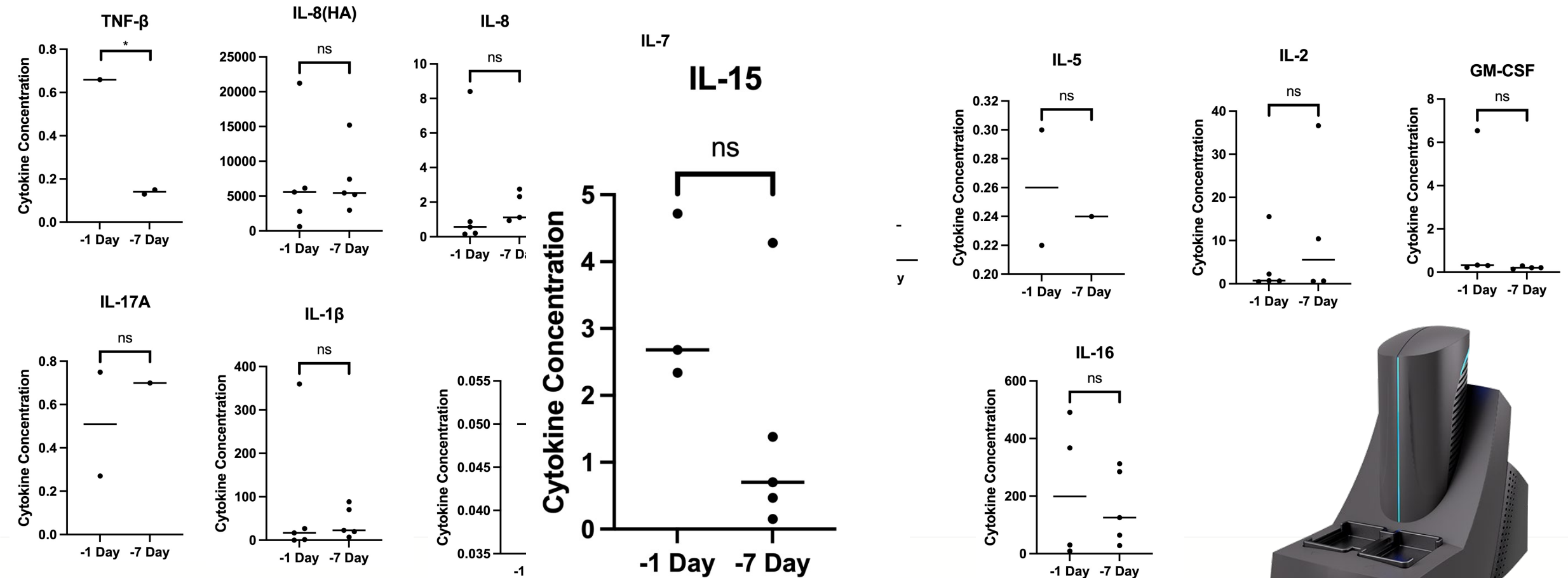
3/15 tissues among -7 day group gag RNA positive
14/15 tissues among -1 day group gag RNA positive
5/6 tissues among sham group gag RNA positive

Cytokine levels in vaginal weck cells at 48hrs

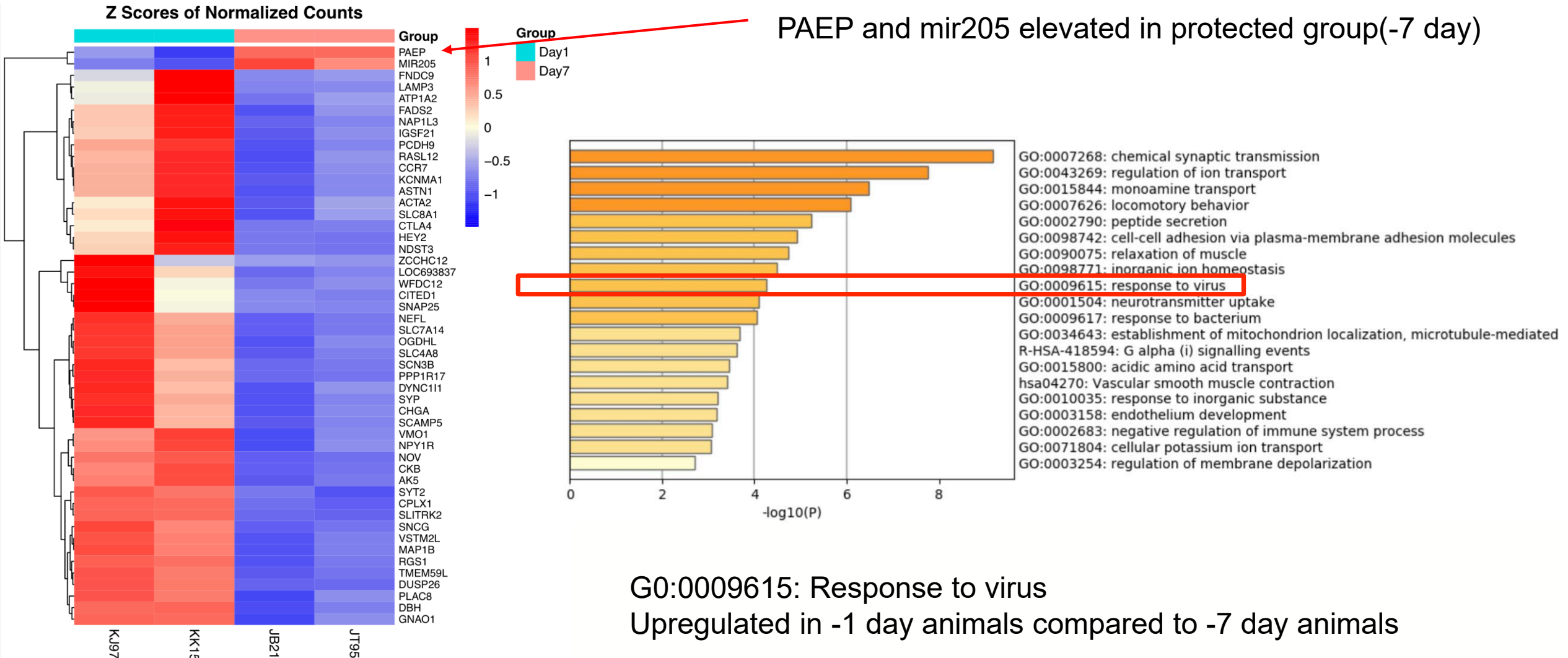


Mesoscale diagnostics (MSD) available in viral pathogenesis core

IL-15 elevated, close to significance

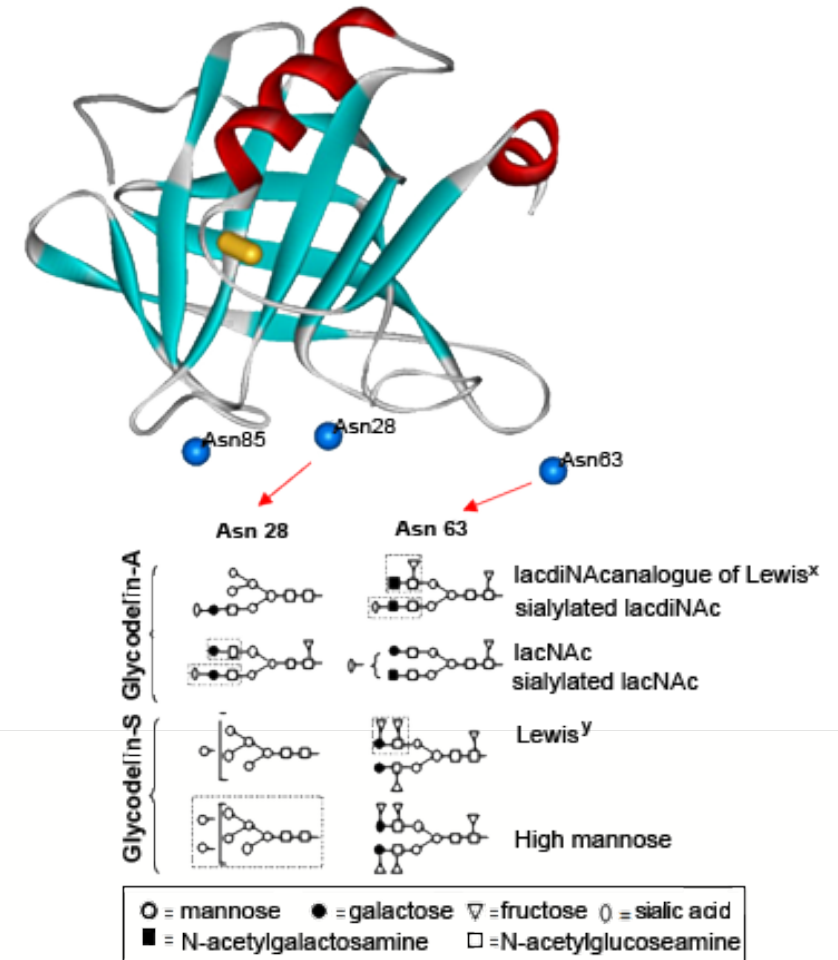


More response to virus genes upregulated in -1 day group





PAEP(progestagen-associated endometrial protein)

- Member of the kernel Lipocalin family of Small transporters
- also known as human placental protein 14 (PP14) and glycodeclin
- multiple glycosylation sites leading to different glycoforms



PAEP and NK cells

FULL TEXT ARTICLE

Glycodelin regulates the numbers and function of peripheral natural killer cells  

[Akanksha Dixit](#) and [Anjali A. Karande](#)

Journal of Reproductive Immunology, 2020-02-01, Volume 137, Article 102625, Copyright © 2019 Elsevier B.V.

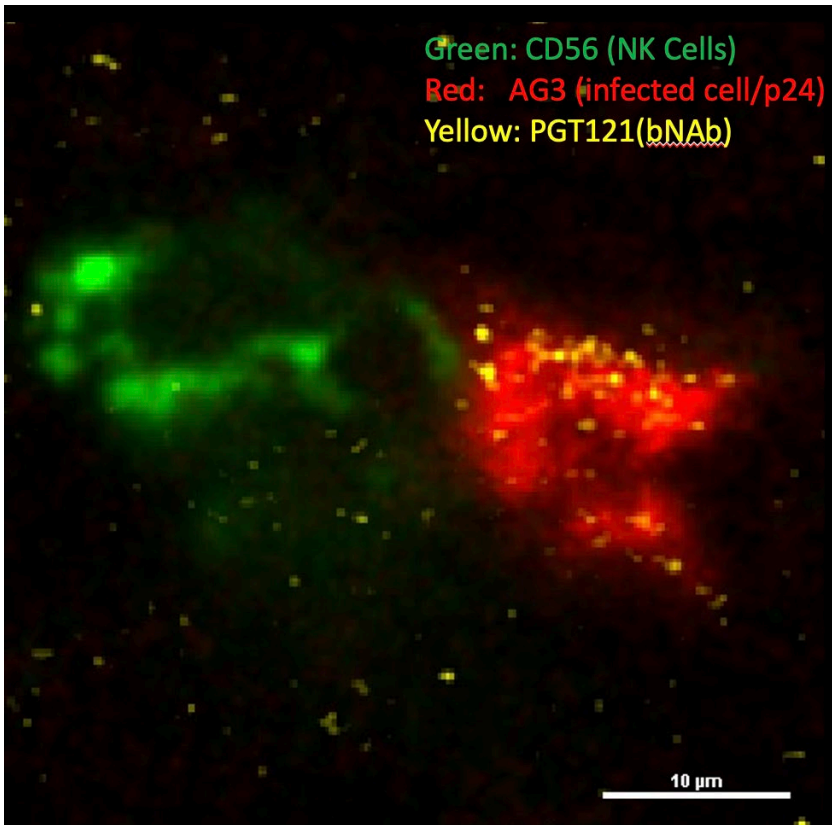
> [Hum Reprod.](#) 2019 Apr 1;34(4):689-701. doi: 10.1093/humrep/dey378.

Glycodelin-A stimulates the conversion of human peripheral blood CD16-CD56bright NK cell to a decidual NK cell-like phenotype

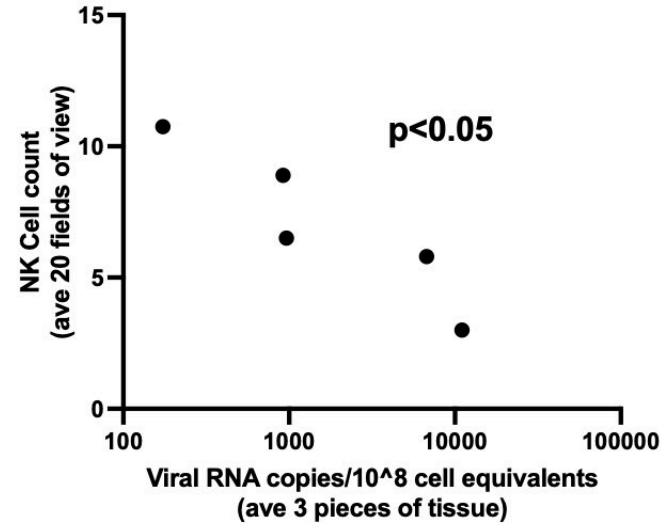
> [Am J Reprod Immunol.](#) 1991 Dec;26(4):137-42. doi: 10.1111/j.1600-0897.1991.tb00713.x.

Suppression by human placental protein 14 of natural killer cell activity

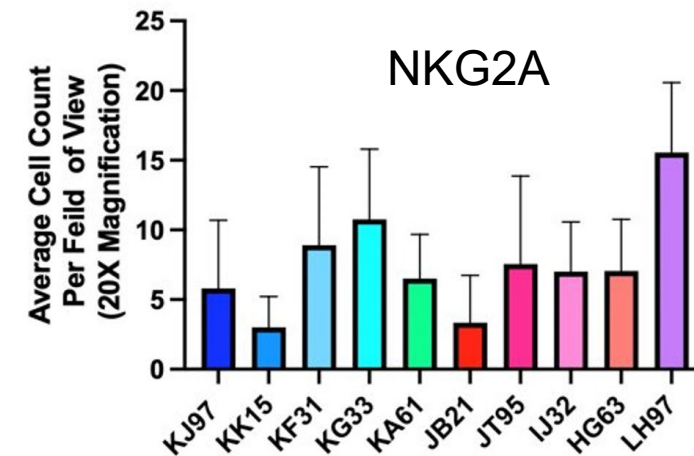
Increased NK cells correlates with less virus



NK cell count vs viral RTqPCR in -1 day animals



NK⁺ CELL COUNT

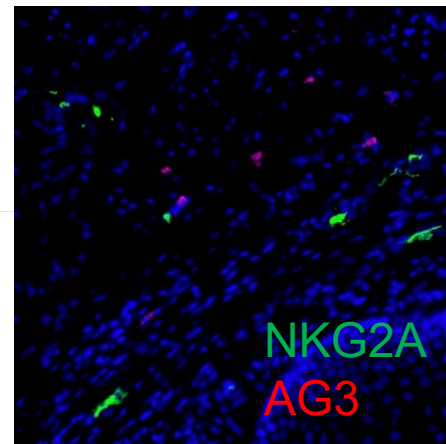


Counted 1440 NK cells across 30 tissues and 10 rhesus macaques

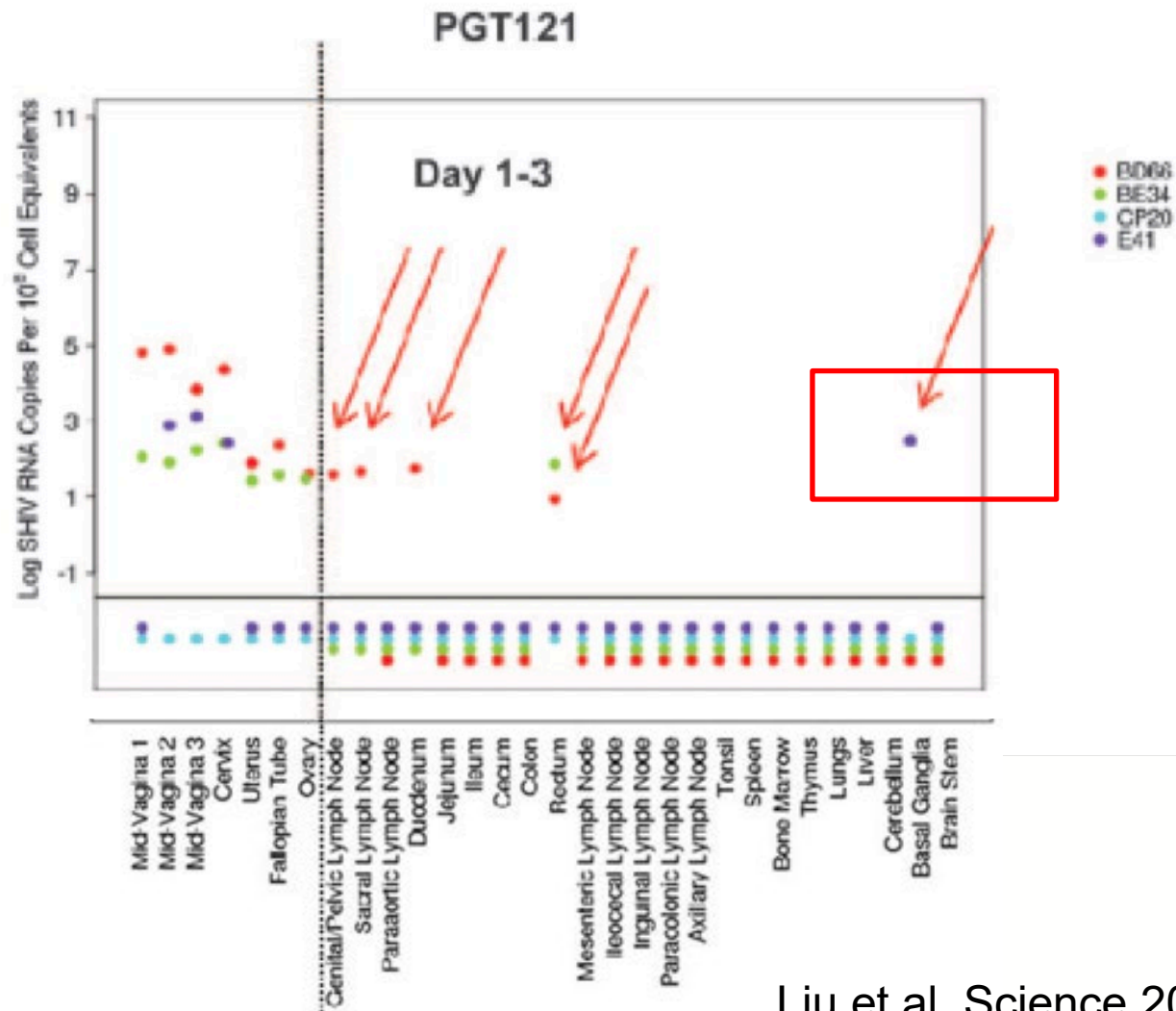
Evan Madden Will Howell Anjelica Reyes



Nikon A1
Spectral Imager



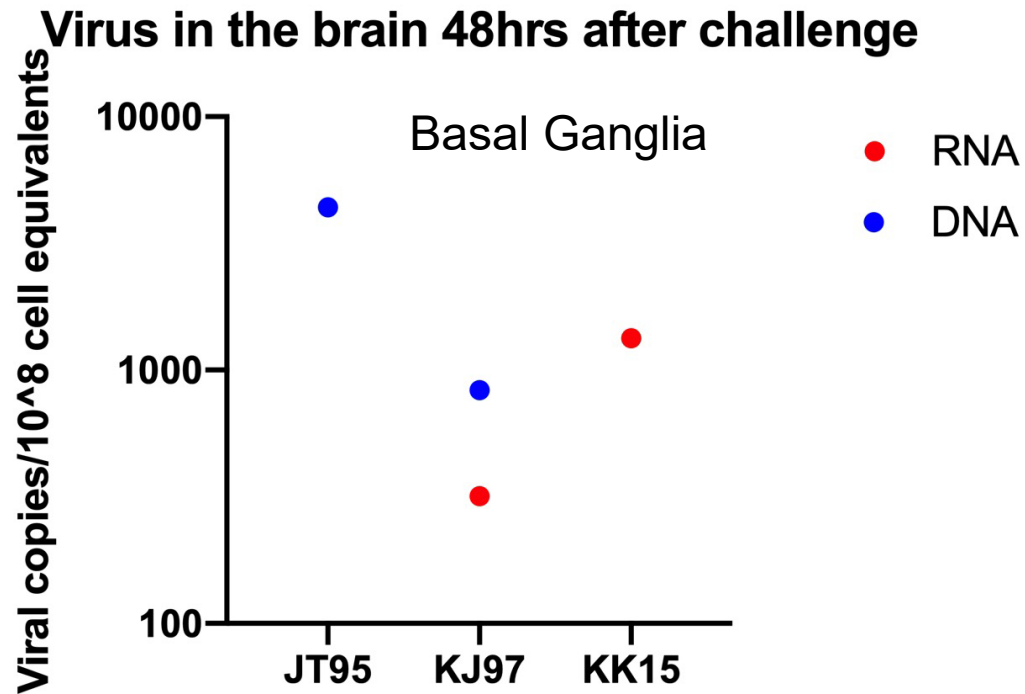
What about virus in the brain?



Basal Ganglia is positive for gag RNA 3 days after intravaginal challenge with SHIV-SF162P3

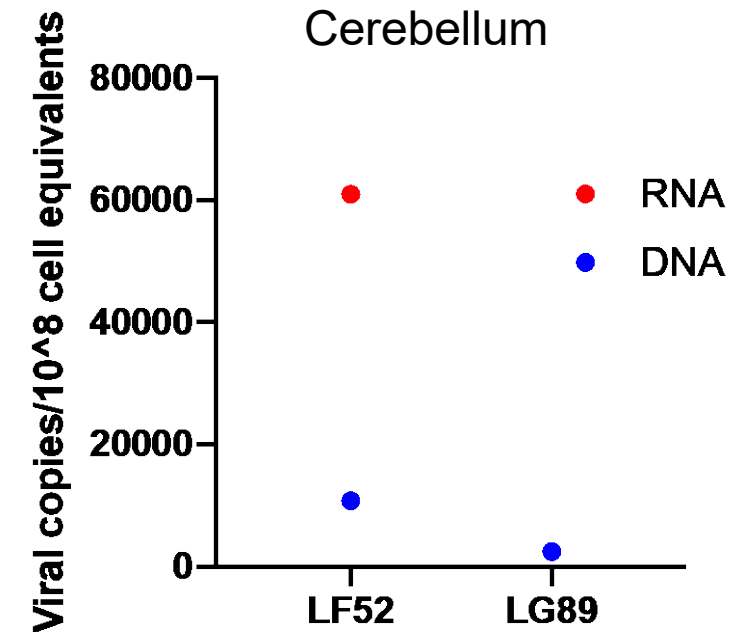
This is only seen in the PGT121 treated animals so perhaps Ab mediated

Virus in the brain 48hrs and 1 week after challenge, mostly in -1 day animal group



2/3 animals got -1 day IV ab infusion

Virus in the brain 1 week after challenge



2/2 animals got -1 day IV ab infusion

4/5 total animals where virus was found in the brain was from -1 day animals

Review Article | Published: 11 April 2018

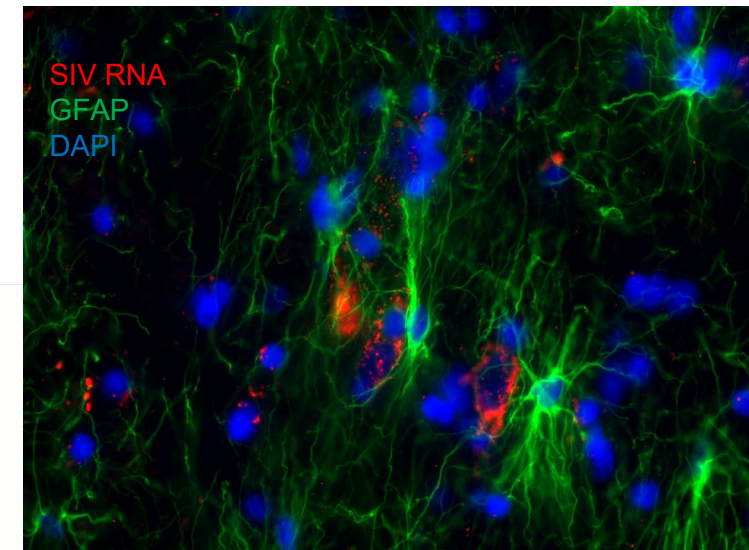
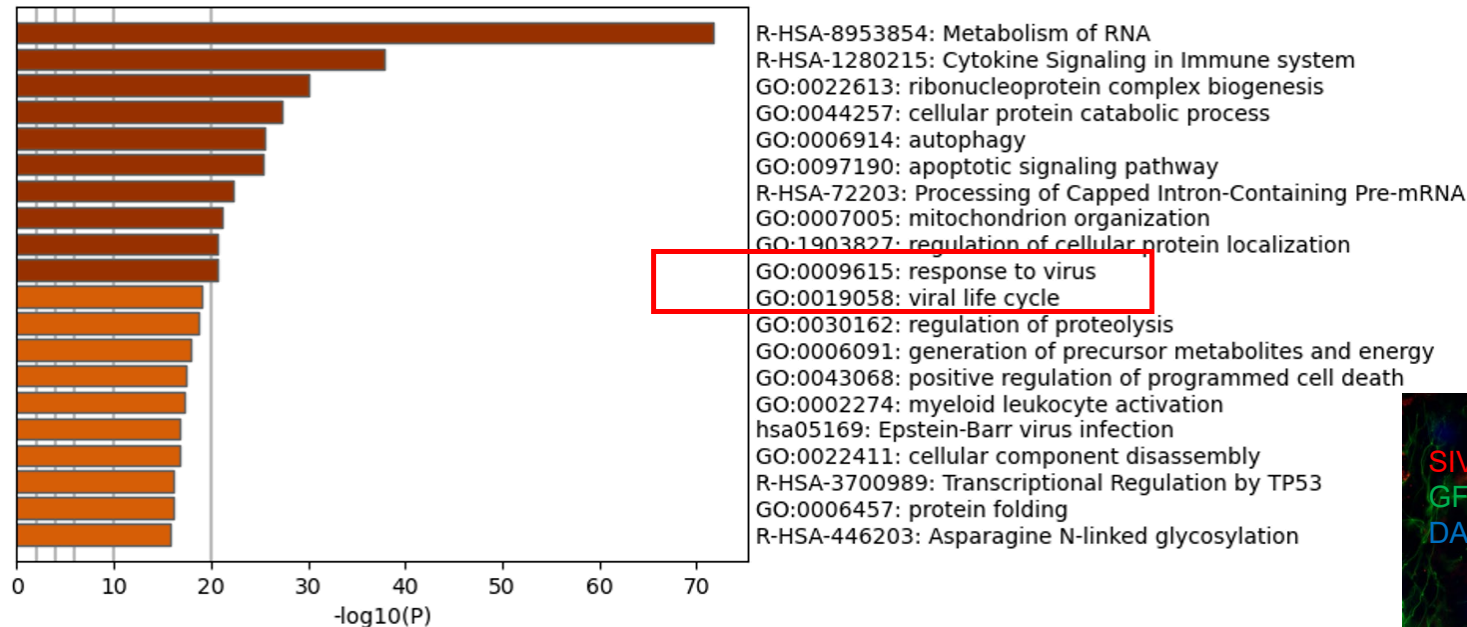
The basal ganglia and the cerebellum: nodes in an integrated network

Andreea C. Bostan & Peter L. Strick

Nature Reviews Neuroscience 19, 338–350(2018) | Cite this article

Response to virus/viral life cycle genes upregulated in positive tissue

RNA seq of RTqPCR positive vs negative tissue in CNS



Conclusions

- Viral RNA was detected in 5/5 animals at the site of challenge in animals that only had 1 day of PGT121 prior to challenge as opposed to 2/5 animals that received antibody 7 days prior.
- Transcriptomic differences were found in the vaginal tissue of these animals with increased response to virus genes in the animals that only had 1 day of PGT121 prior to challenge.
- PAEP, known to regulate NK cells, was elevated in protected -7 day group, showed NK cell number correlated with less virus
- Trends towards increased viral RNA in the CNS of animals that received PGT121 1 day prior to challenge but need to increase the sample number

RADAR Cohort Symposium

Fostering interdisciplinary collaborations on HIV and substance use among
young men who have sex with men in Chicago

Wednesday, February 27, 2019 1 – 5:30 PM Baldwin Auditorium 303 E. Superior St. Chicago, IL 60611

We invite you to join a symposium on February 27, 2019 highlighting the **RADAR** cohort's scientific contributions to HIV research and success in catalyzing over two dozen additional studies.

Presentations will highlight some of the latest findings on PrEP, HIV incidence, viral suppression, and substance use. Speakers will also describe findings from some of the 25 additional projects built out of RADAR, encompassing implementation science, biomedical prevention science, and innovative network modeling techniques. The symposium is an opportunity for us to disseminate the diversity of findings from both this NIDA U01 cohort and the breadth of sub-studies, discuss emerging methodologies, and inspire new collaborations.



- Met Lena Al-Harthi who told me about faculty positions available at Rush
- Takeaway go to meetings not just for science but for networking too!

Thanks

K01 mentors

Thomas Hope
Ronald Veazey

Veazey Lab

Meagan Watkins

Hope Lab

Flora Engelmann
Ann Carias
Mike McRaven
Gianguido Cianci
Lisette Corbin

Northwestern

Ramon Lorenzo-
Redondo
Richard D'Aquila
Elena Martinelli

VRC

John Mascola
Amarendra Pegu

Schneider Lab

Michelle Ash
Anjelica Reyes
Evan Madden
Gabrielle Kooi
Sam Welninksi
Pavan Bhimali

K01 Supplies

Dan Barouch-SHIV-SF162P3
Dennis Burton and Devin Sok-
PGT121/DEN3
Jeff Lifson-assistance with qPCR
protocol

Rush University

Lena Al-Harthi
Joao Mamede
William Howell
Billy Nguyen

NUseq Core

Ryan Embry
Matthew Schipma

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R21MH125339

