DukeNUS Medical School

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Antibody-dependent dengue virus infection: new insights, new challenges

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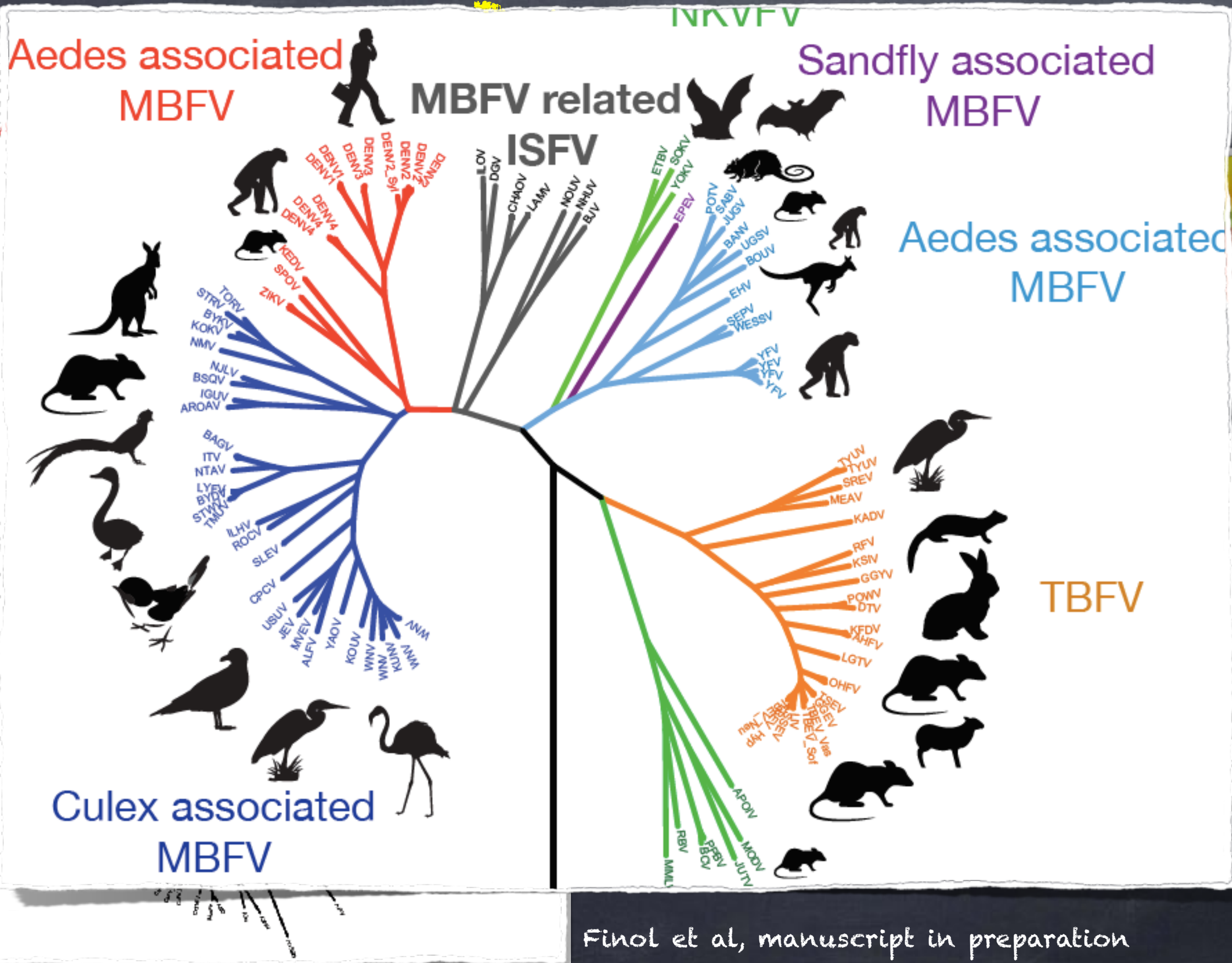
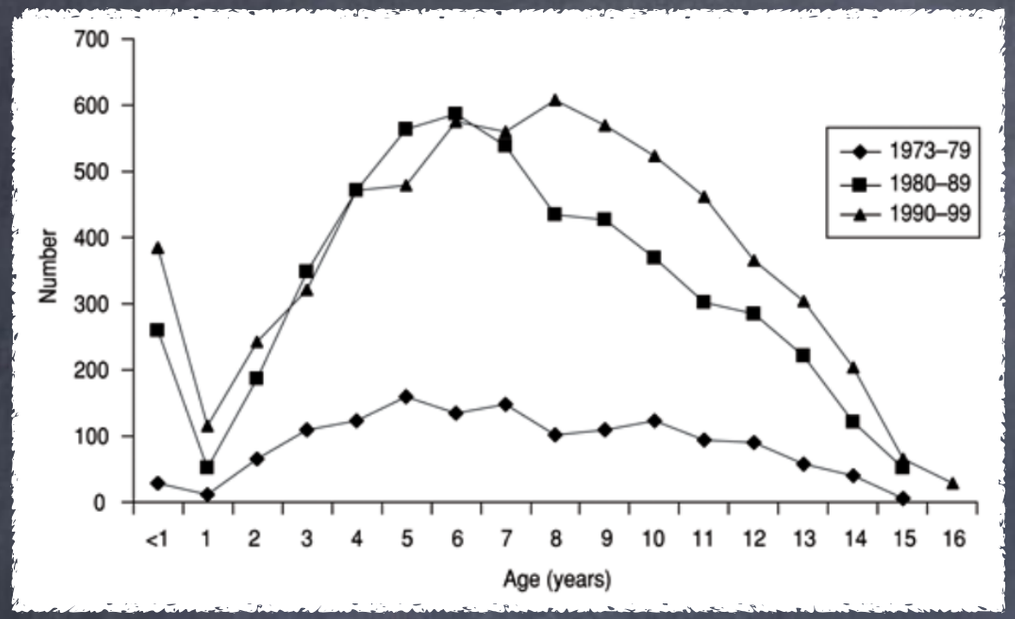


Finol et al, manuscript in preparation

Antibody-dependent enhancement (ADE)

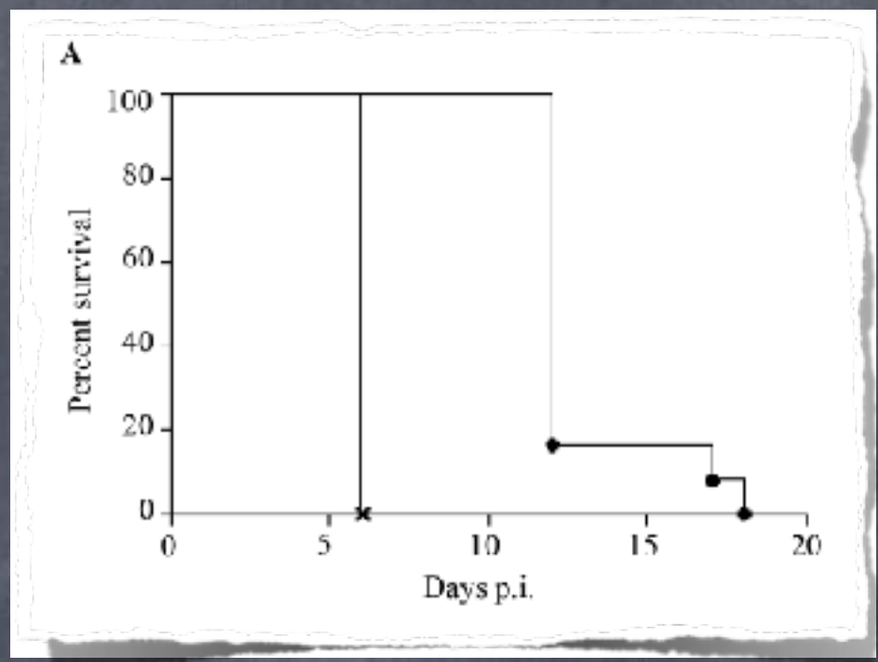


Halstead, Rev Panam Salud Publica 2006

Kliks et al, AJTMH 1988

Simmons et al, J Infect Dis 2007

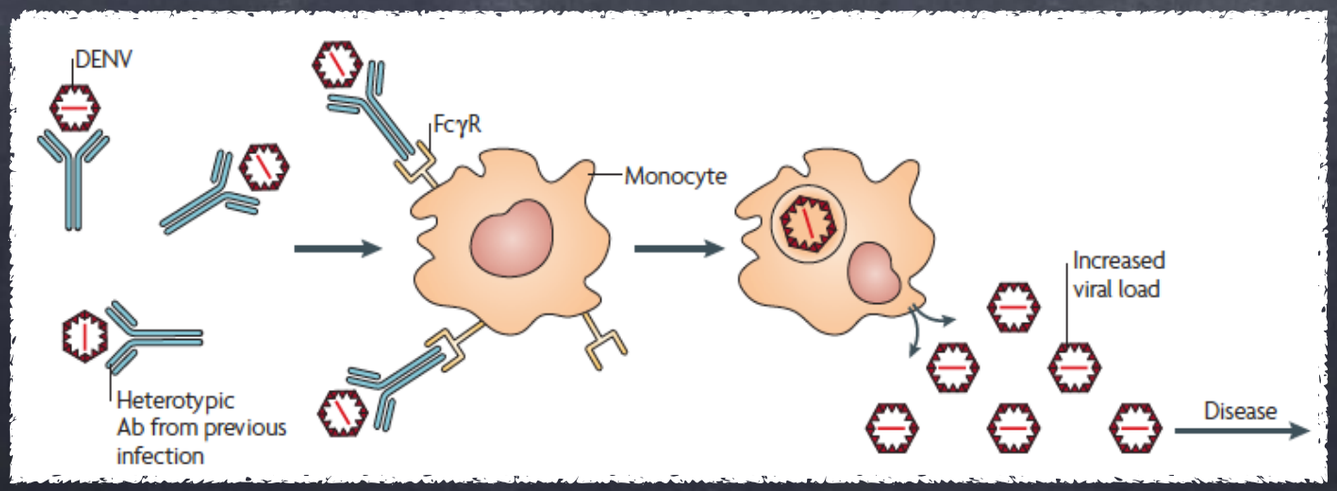
Libraty et al, PLoS Med 2009



Ng et al, PLoS Pathog 2014

Zellwegger et al, Cell Host Microbe 2010

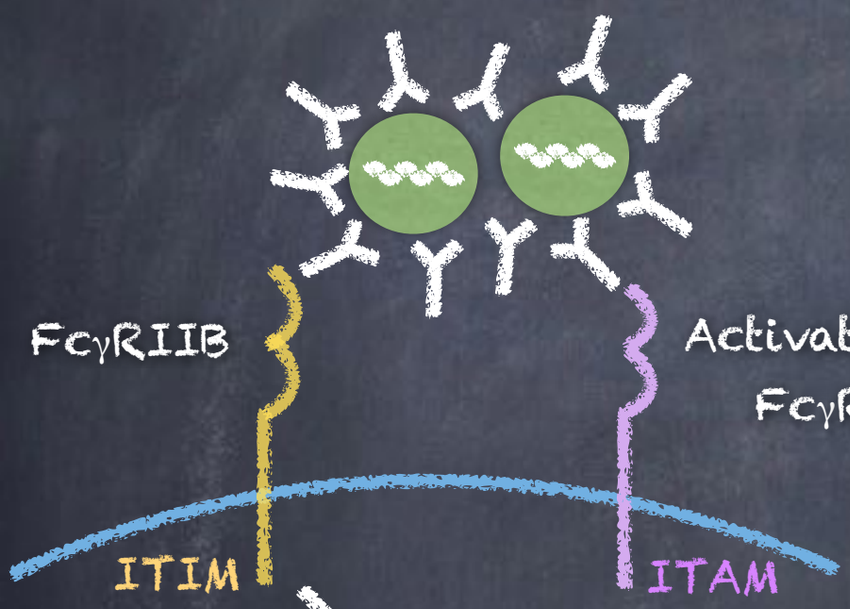
Balsitis et al, PLoS Pathog 2010,



Whitehead et al, Nat Rev Microbiol 2007

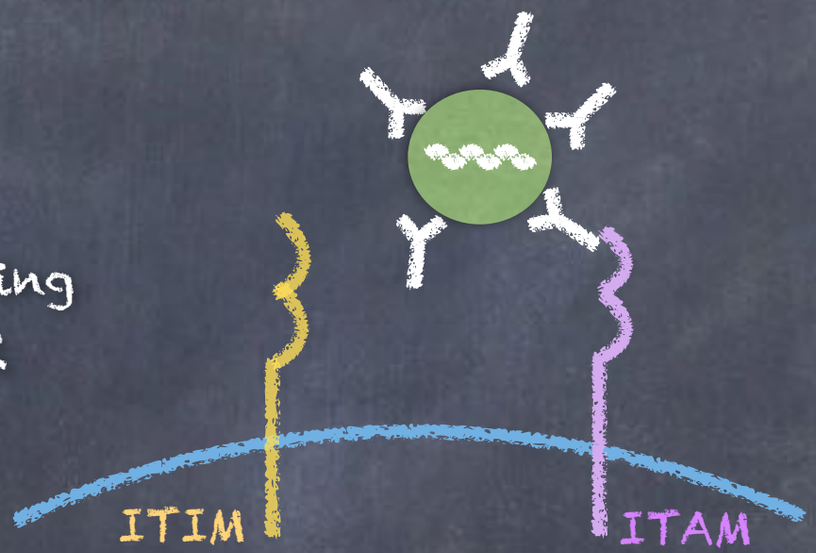
Antibody-dependent inhibition & enhancement of DENV infection

Infection inhibition ⟷ Infection enhancement



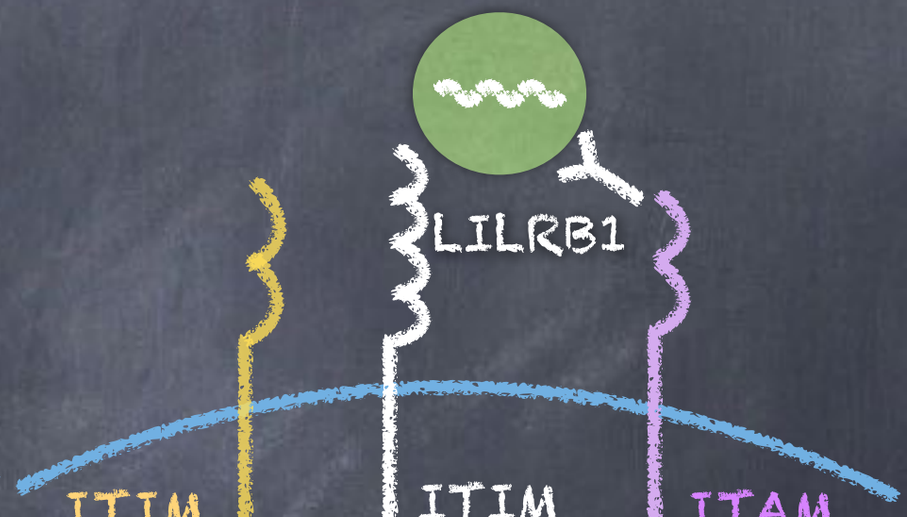
Phagocytosis
ISG induction

Chan et al, PNAS 2011
Boonnak et al, J Immunol, 2013



ISG induction

Dhodapkar et al, J Exp Med 2007
Wu et al, Antiviral Res 2012
Robinson et al, Cell 2016



ISG induction

Chan et al, PNAS 2014
Ong et al, Sci Rep 2017
Gan et al, EMBO J, in press

DENV is trafficked to lymph nodes post-inoculation

Intradermal/
subcutaneous virus/
vaccine inoculation

↓

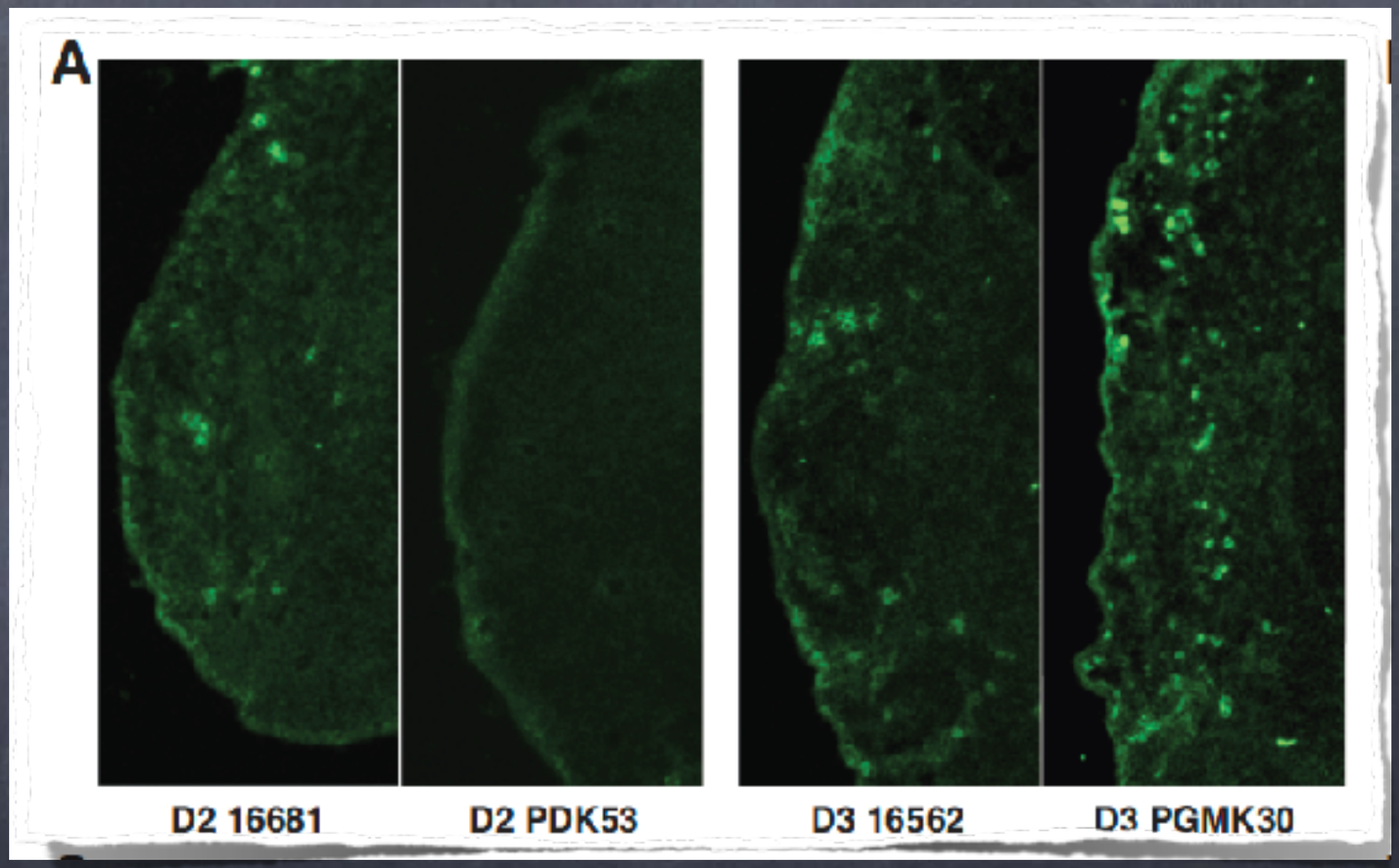
Uptake by antigen
presenting cells

↓

Draining lymph nodes

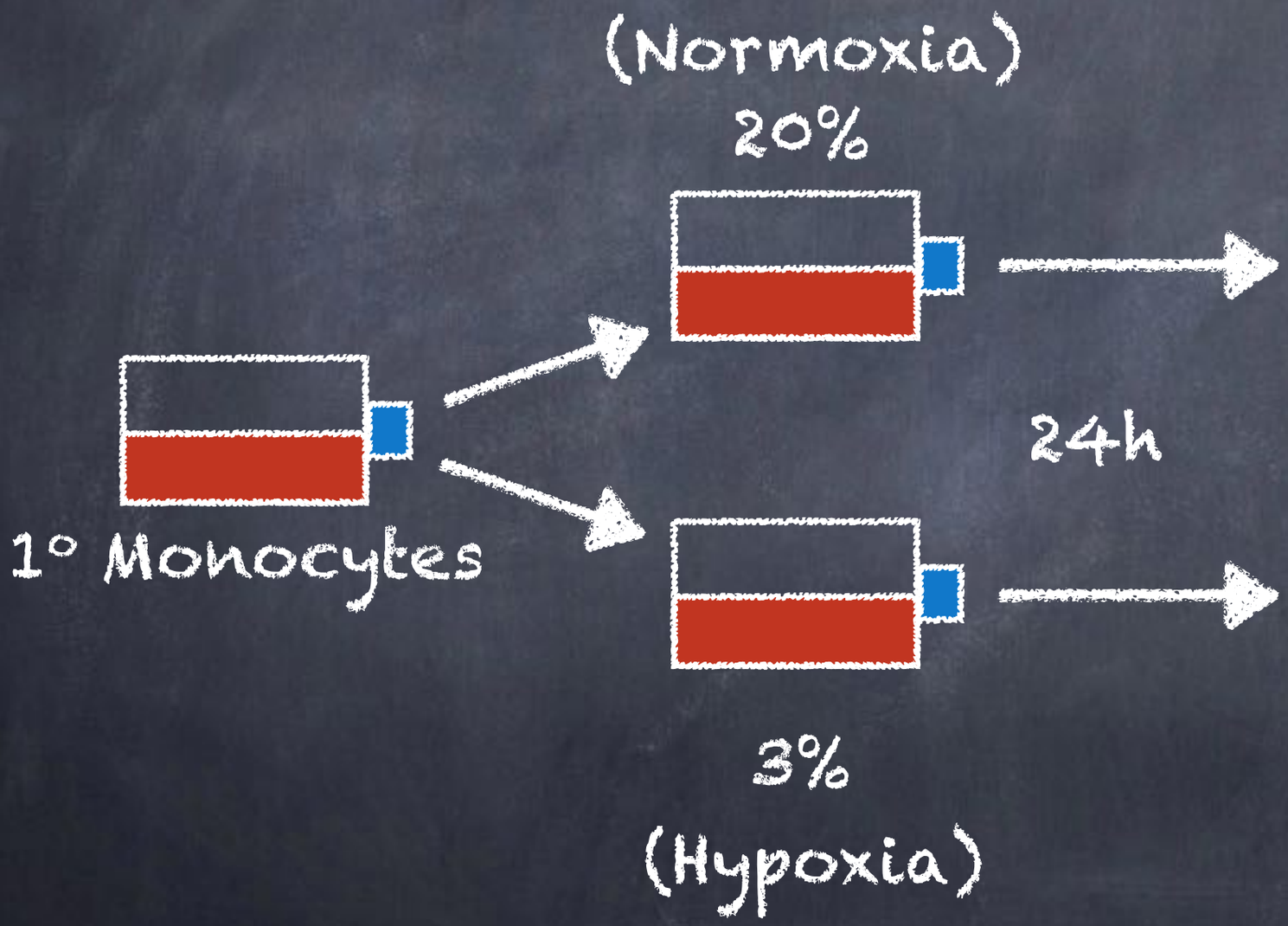
Physiological O2 levels ~3%

IFA of DENV in popliteal lymph nodes
24h post footpad inoculation



Goh et al, Scientific Reports 2016

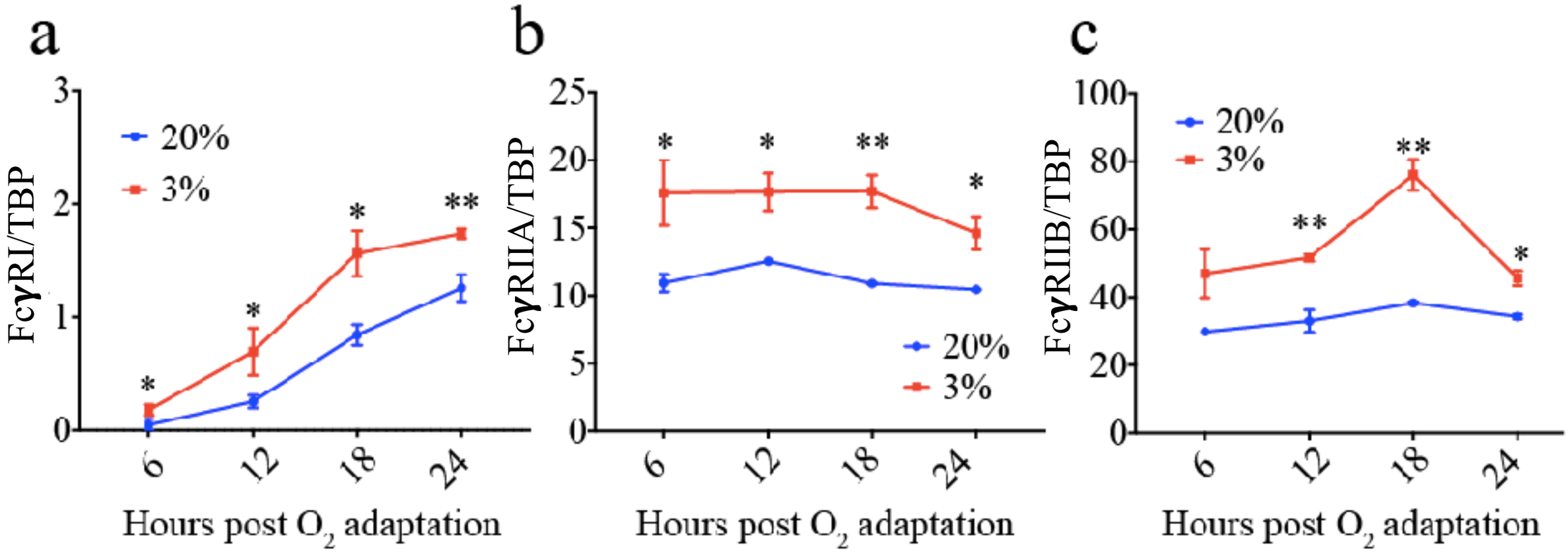
What is the effect of hypoxia on ADE?

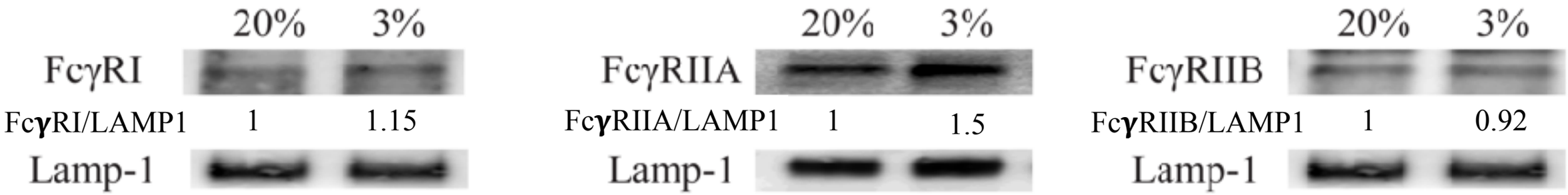


- FcγR expression?
- DENV infection?
- ADE?

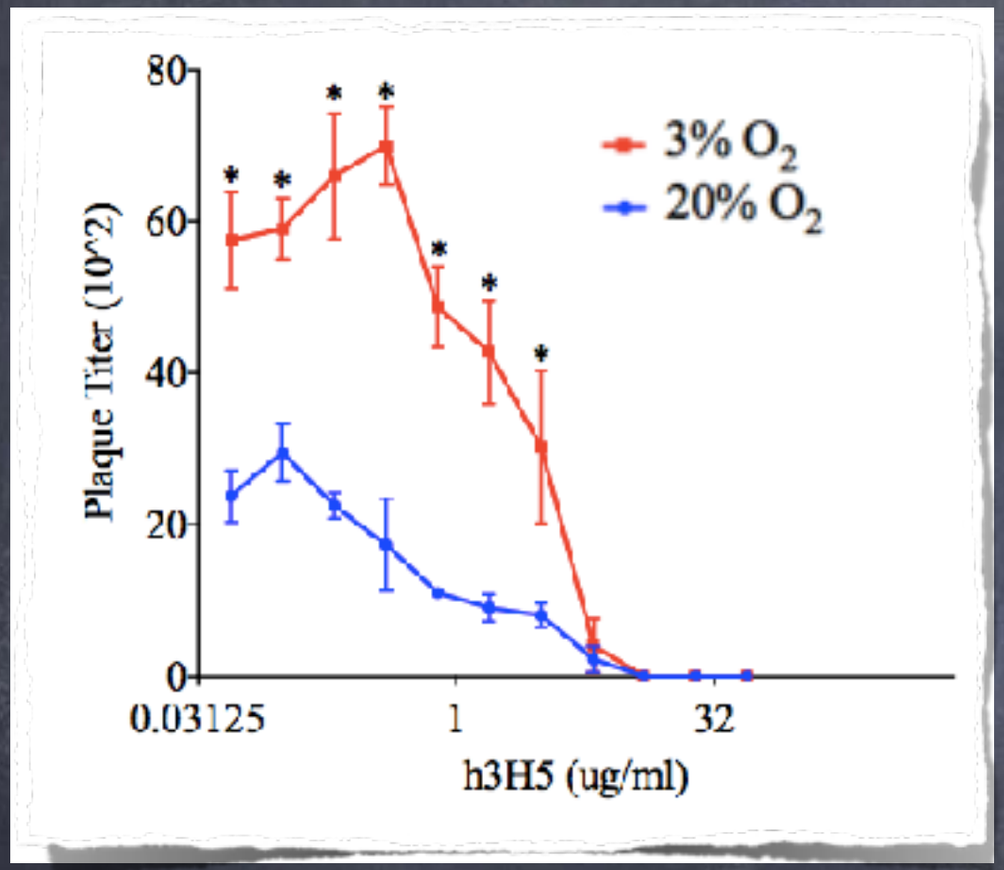
FcγRIIA expression increases under hypoxic conditions

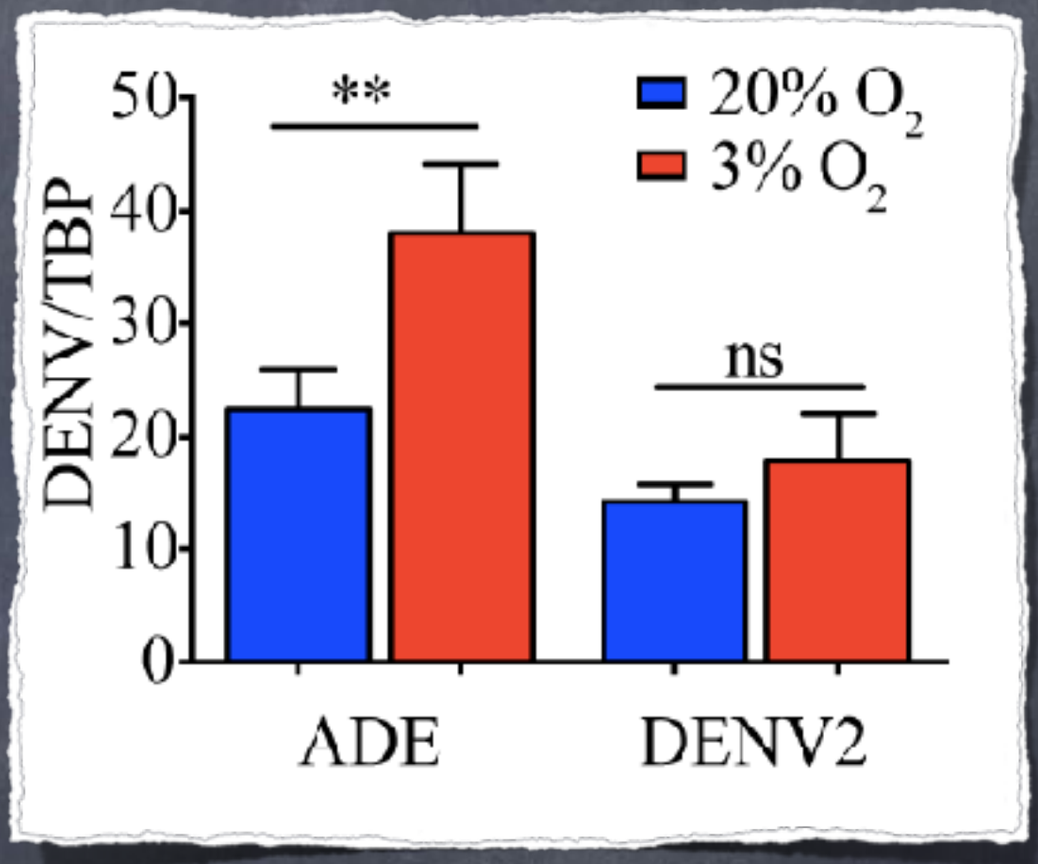
Primary Monocytes





Physiological O_2 levels in lymph nodes augment ADE



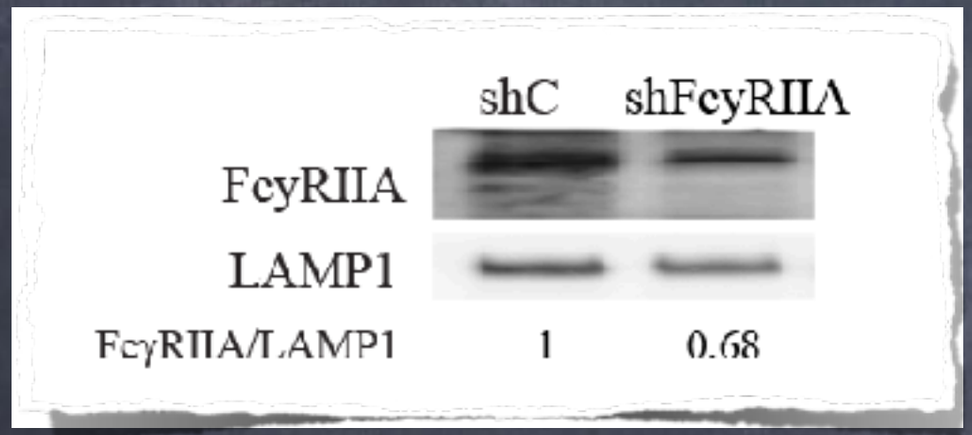


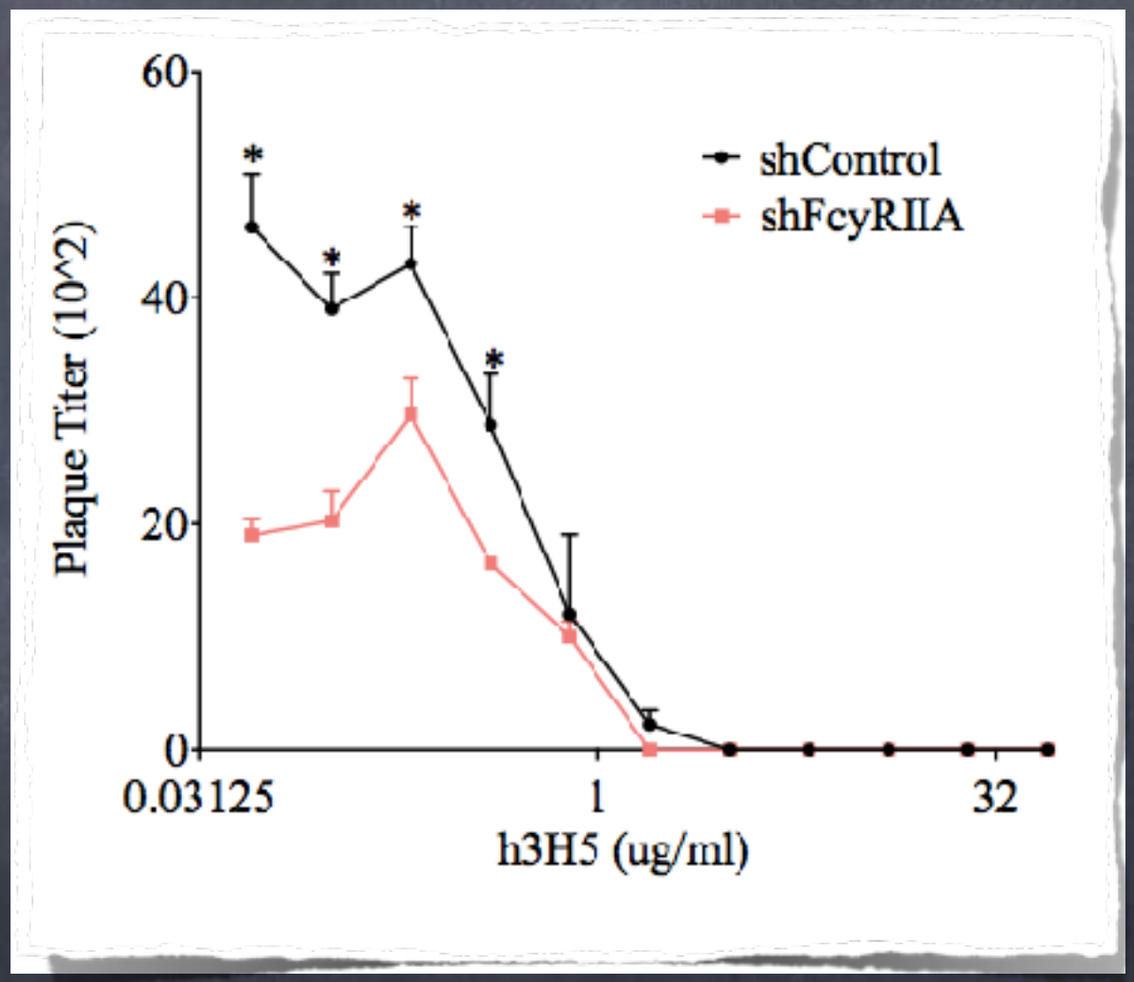
With pronase

→ Increased DENV entry 2h post-inoculation

Gan et al, EMBO J, in press.

Knocking down FcγRIIA leads to reduced ADE in hypoxia





Gan et al, EMBO J, in press.

HIF1α - master regulator of hypoxic response

20%

3%

DFX

Fe^{2+}

PHD

O_2

VHL

OH OH

Ub Ub Ub Ub

HIF1α

VHL

Fe^{2+}

PHD

O_2

HIF1α

nucleus

CBP/p300

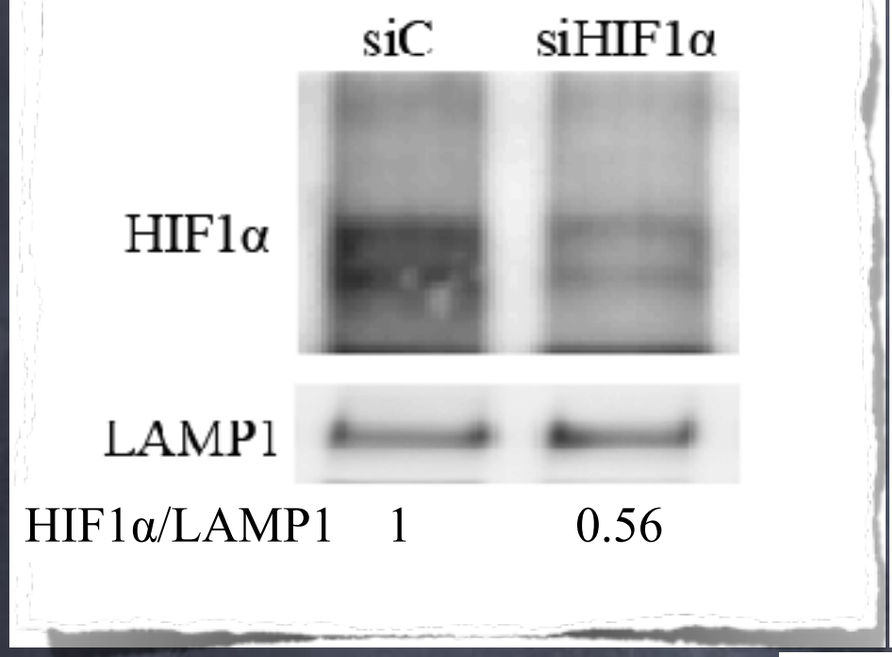
HIF1β

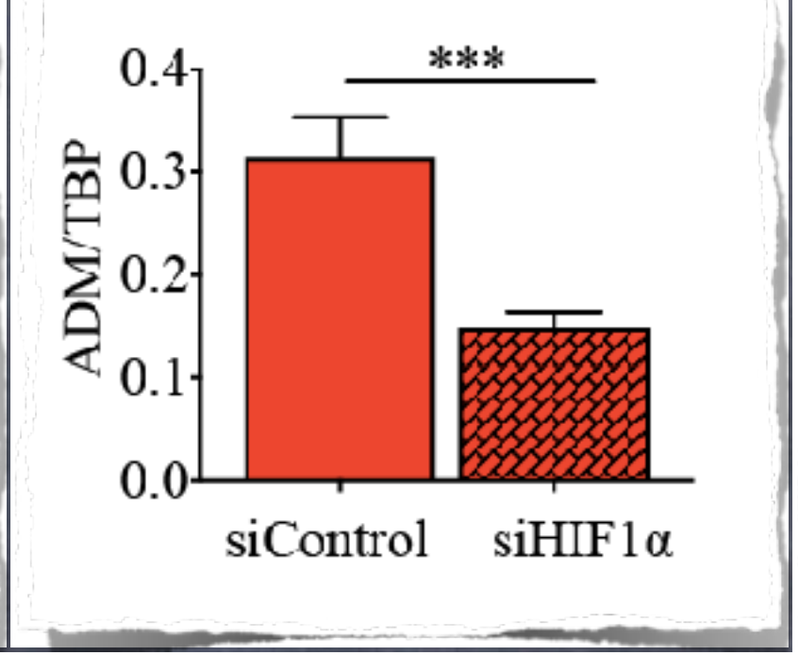
gene

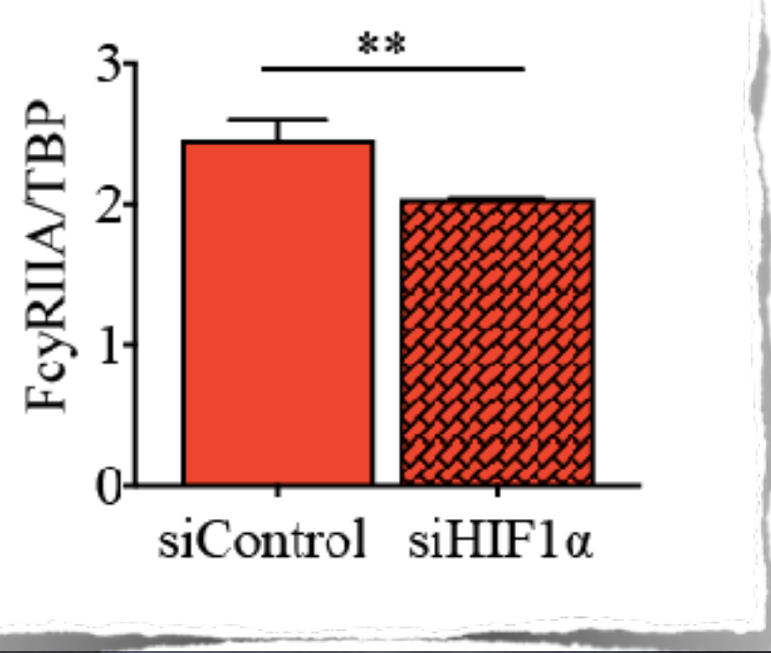
CGTG

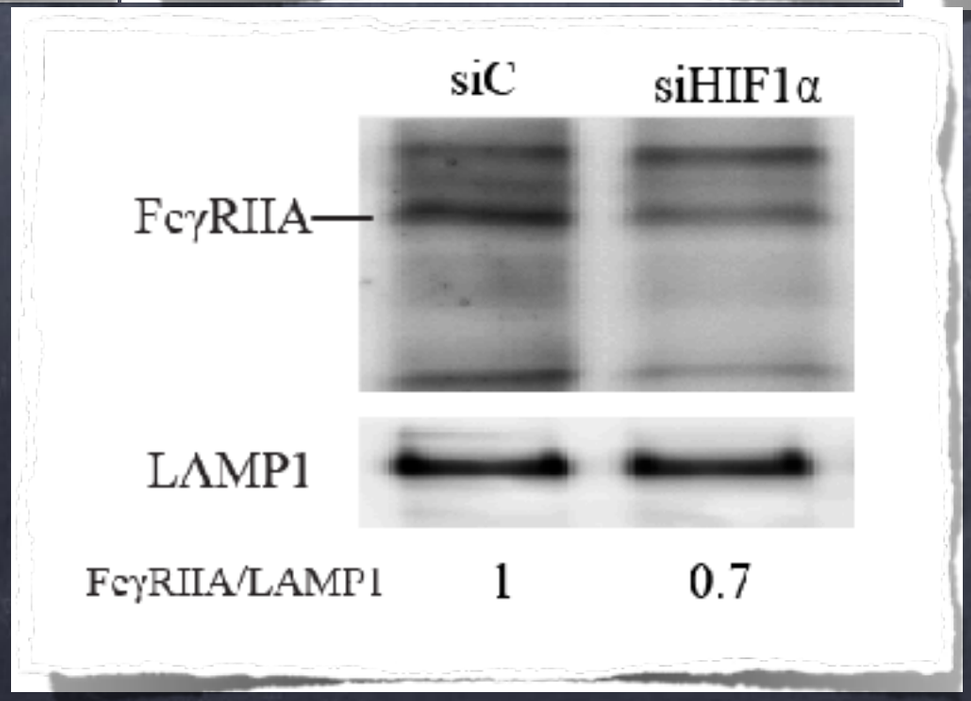
(HRE)

HIF1α knockdown reduces FcγRIIA expression under hypoxic conditions





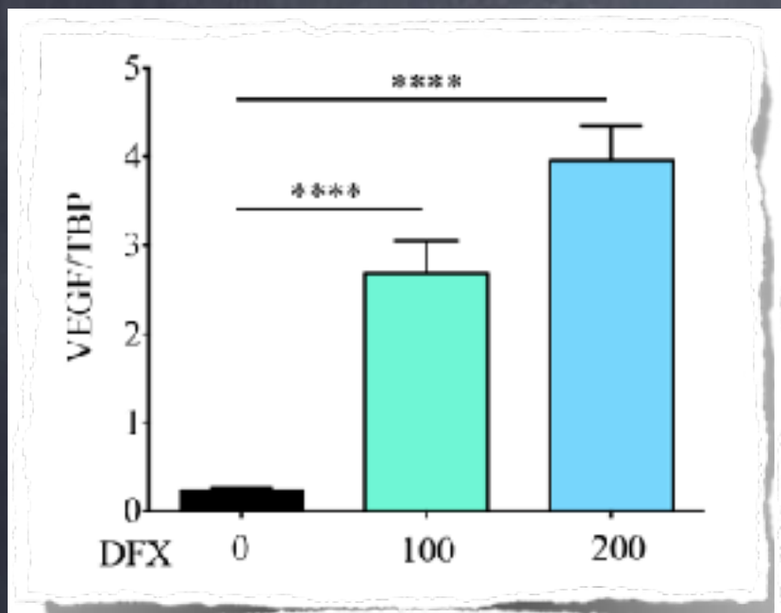


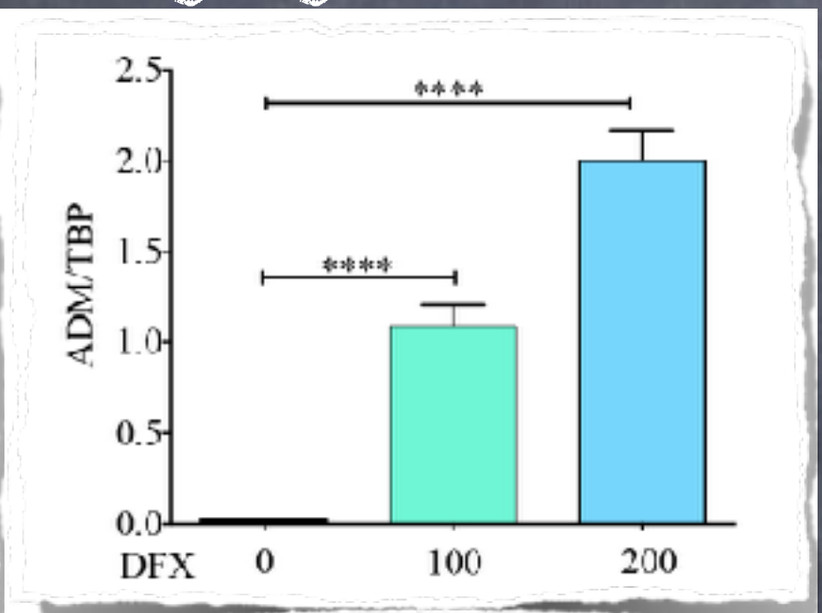


Gan et al, EMBO J, in press.

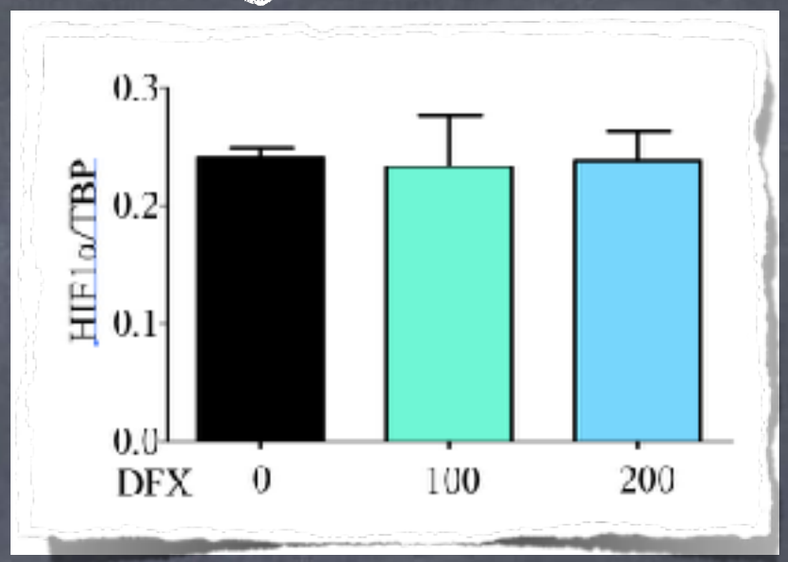
Stabilising HIF1α in normoxia with DFX treatment

Increase in HIF1α target genes

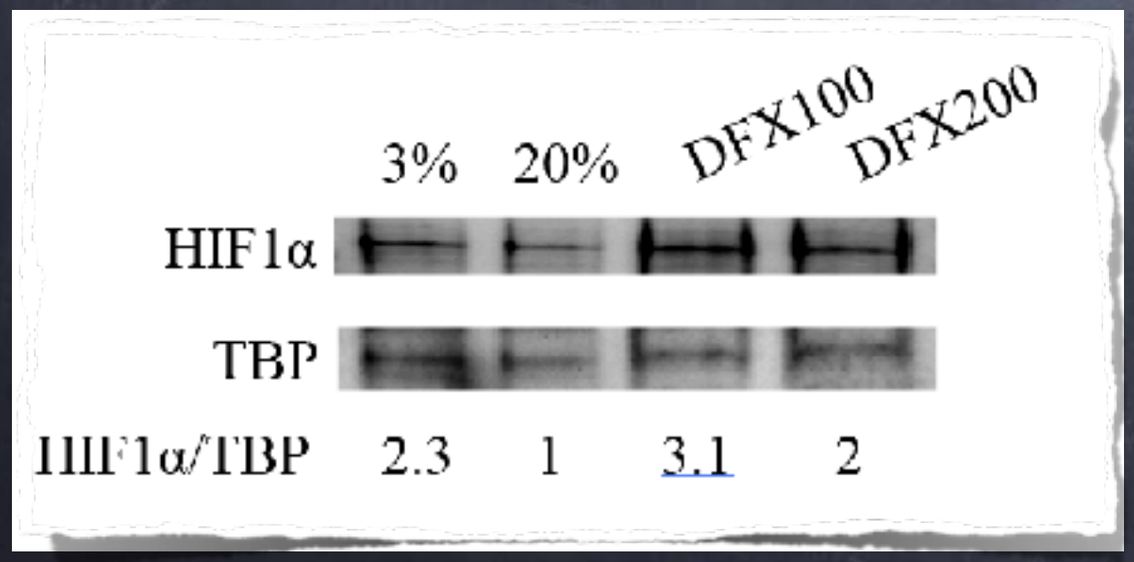




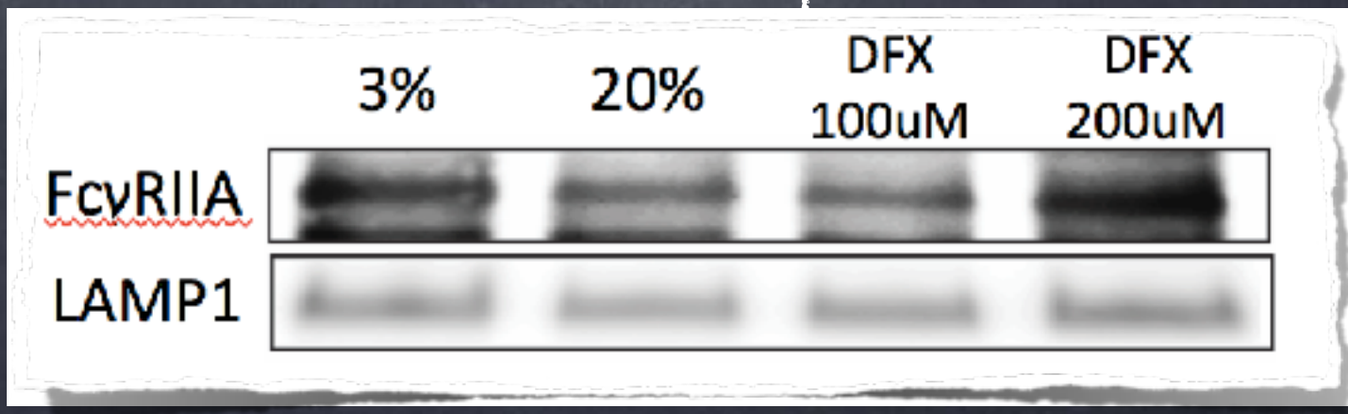
No change in HIF1α mRNA



Increase HIF1α nuclear translocation

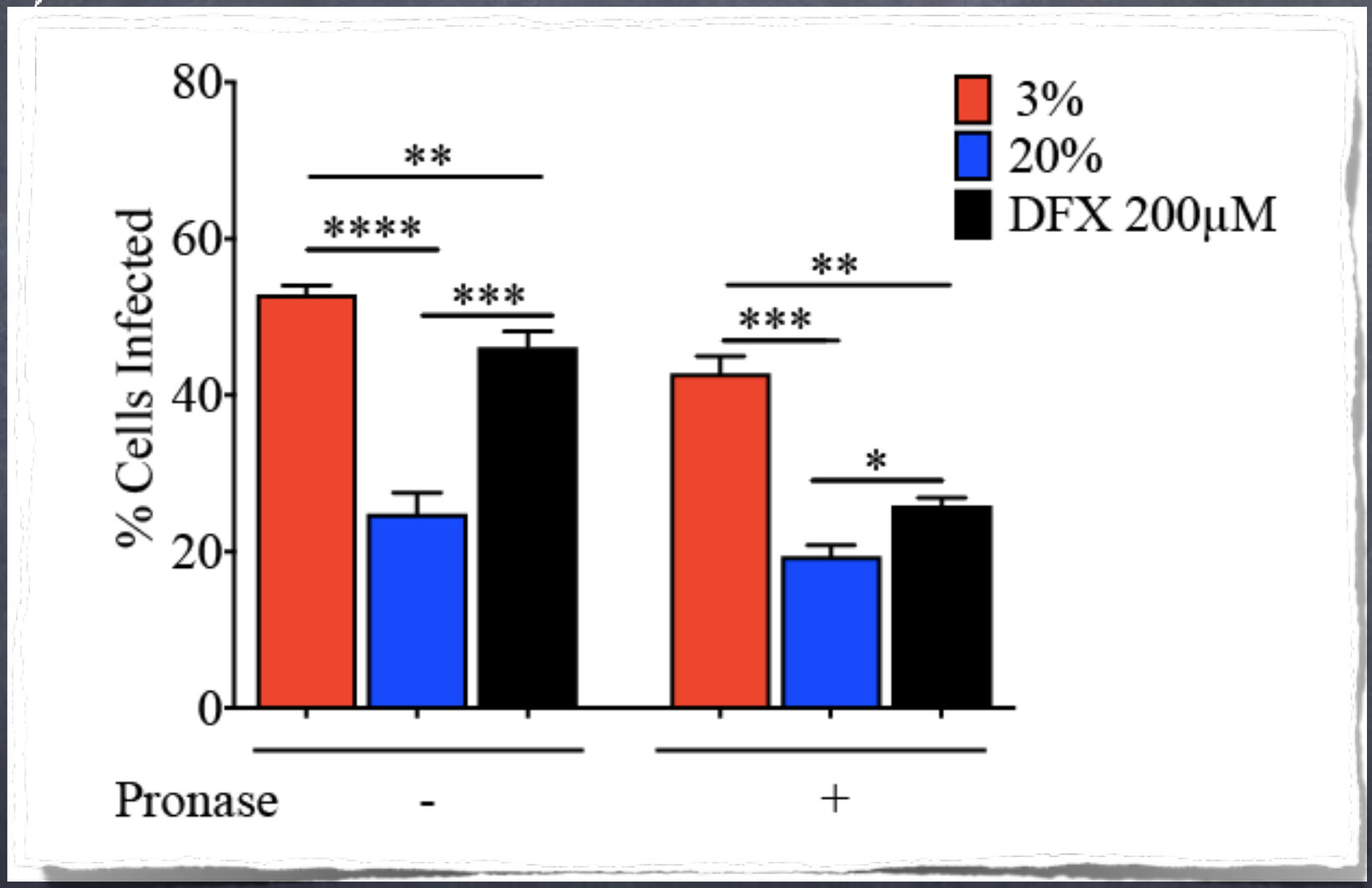


Dose-dependent increase in FcγRIIA expression



Increase in FcγRIIA increases binding but not internalization

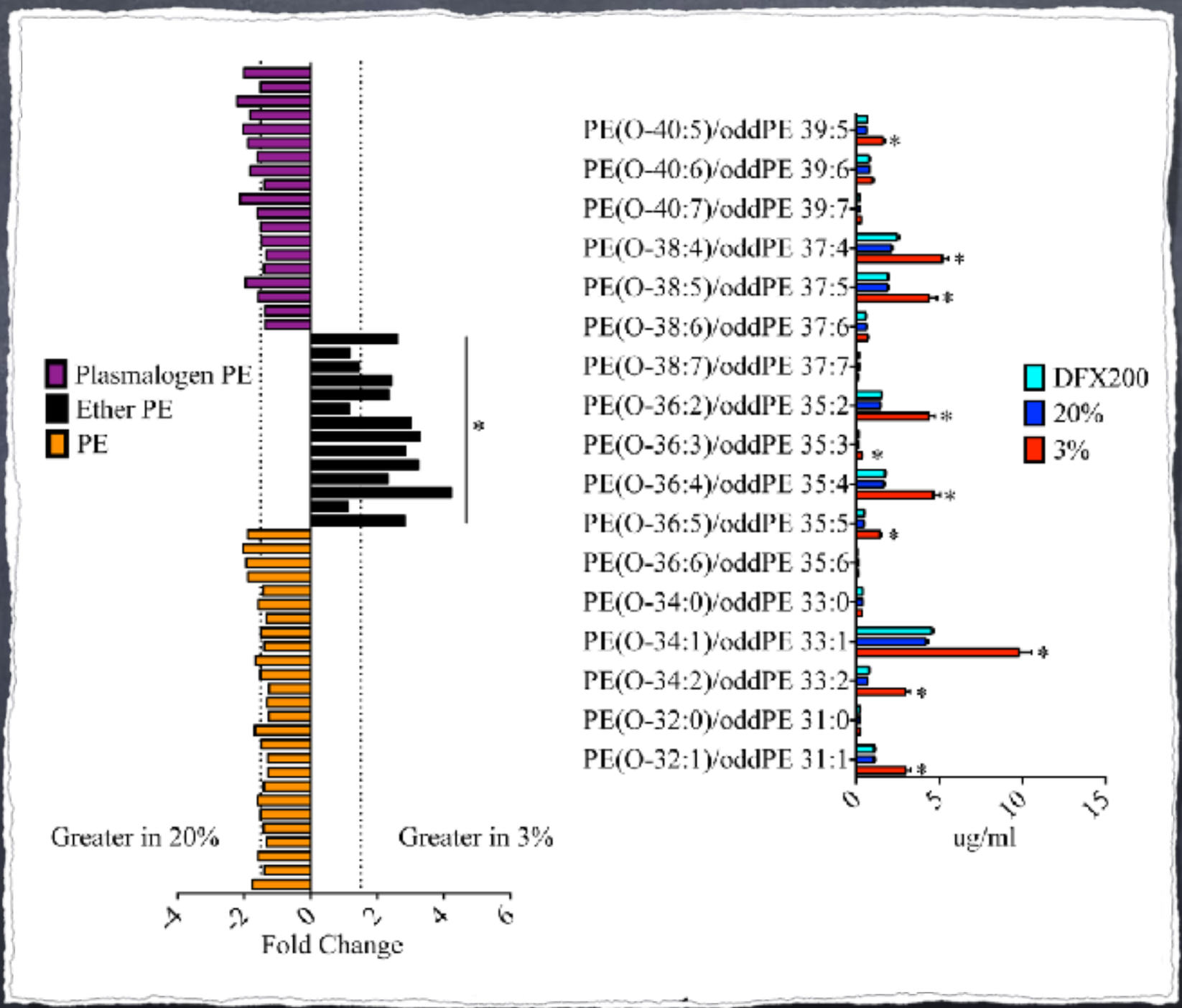
ADE infection with DFX treatment under normoxic conditions



ADE requires complementary hypoxia induced but HIF1α independent factors?

Gan et al, EMBO J, in press.

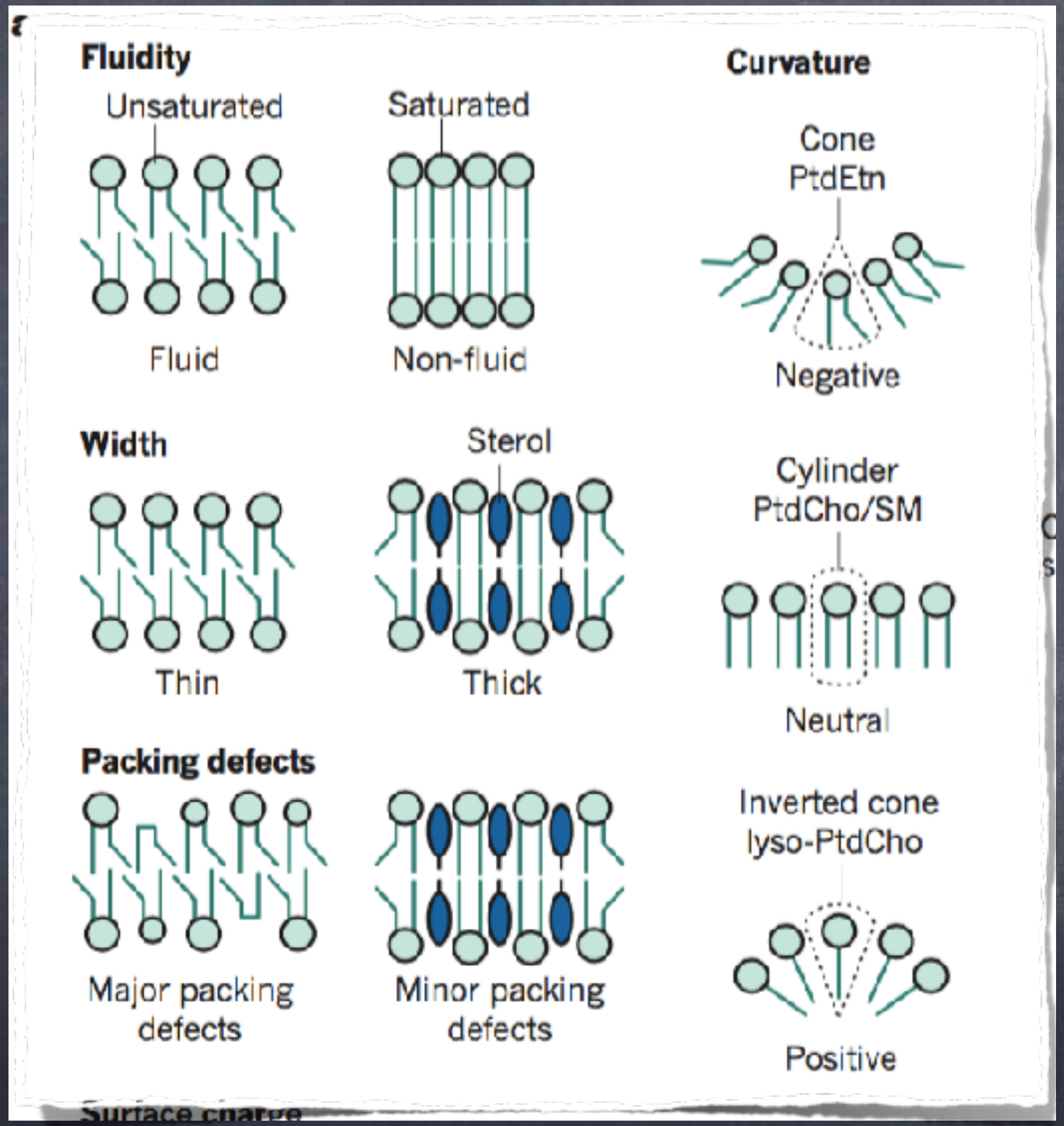
Ether phosphoethanolamines upregulated in HIF1α independent manner



in collaboration with Markus Wenk

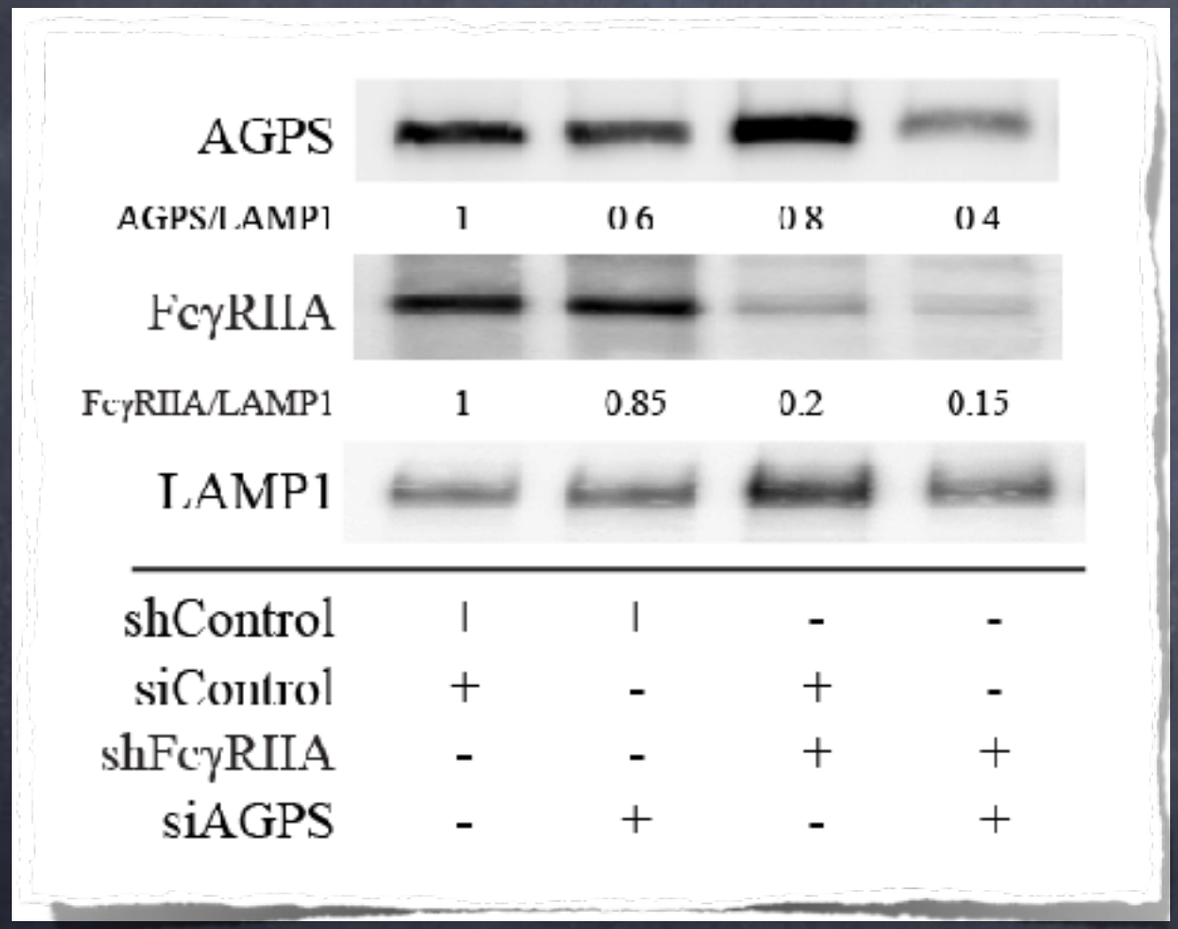
Lipids affect membrane properties

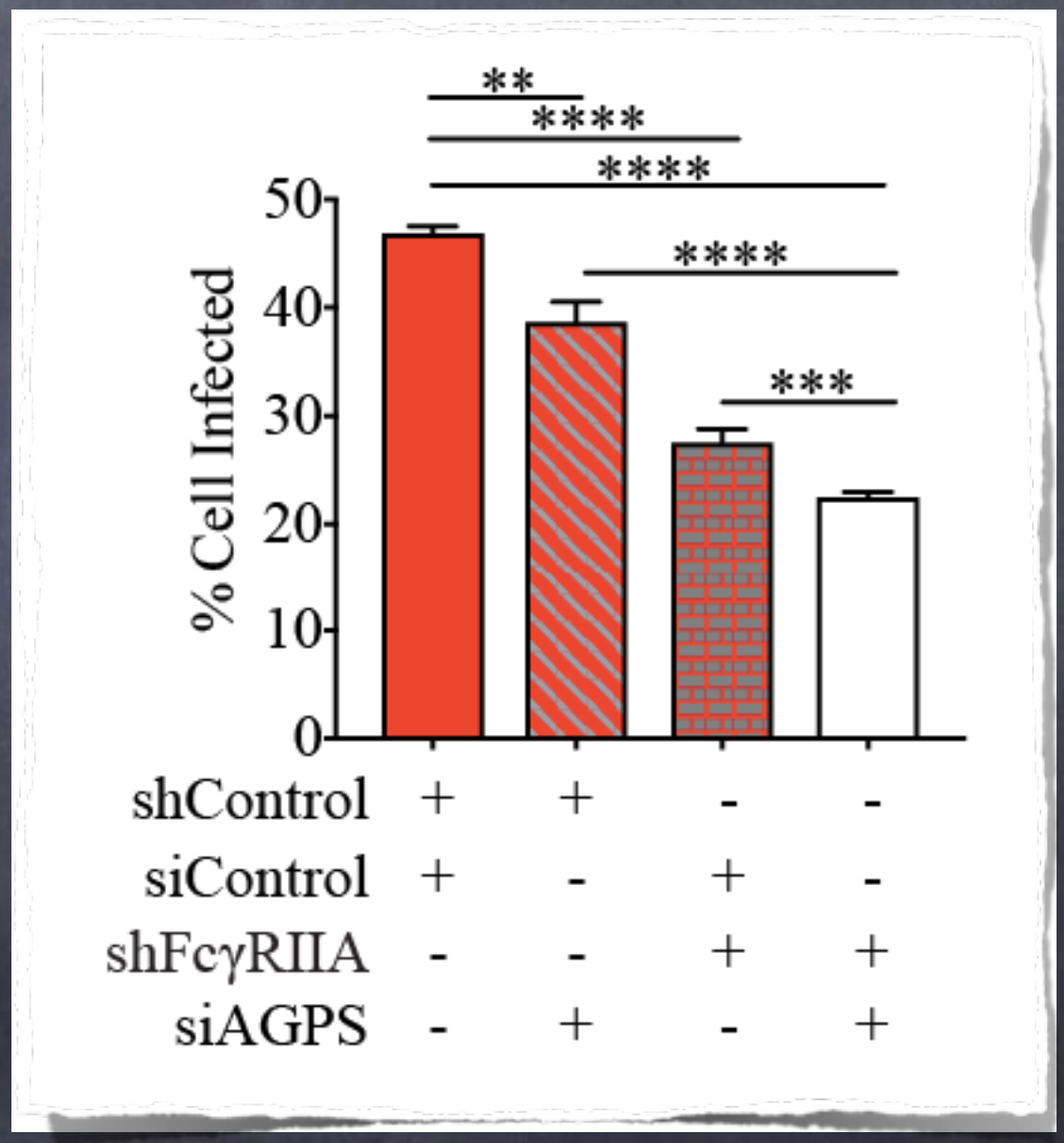
Ether PEs →



Holthuis et al, Nature 2014

Ether lipids and FcγRIIA act synergistically for ADE under hypoxic conditions





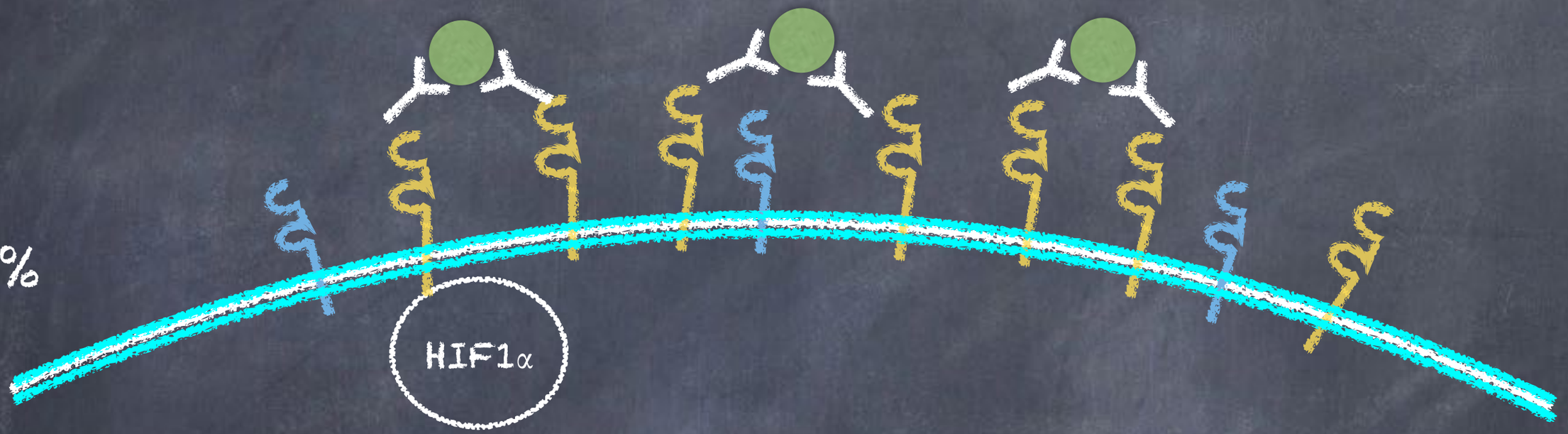
Gan et al, EMBO J, in press.

Summary I

FcγRI

FcγRIIA

Preferential Binding of FcγRIIA



Increase ether PE

Increased Internalisation

FcγRIIA

Increased DENV enhancement

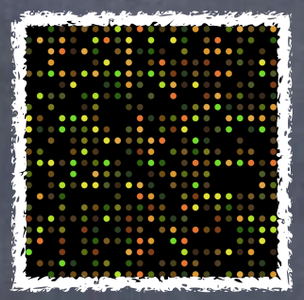
Is ADE clinically relevant?

Trial overview

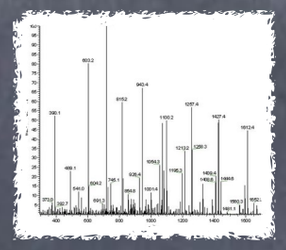
84 DENV IgG -

64 JE +YF vaccines

20 YF vaccine only



Microarray



Cytokines
Chemokines
Metabolome

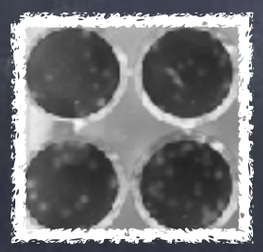
2nd JE dose

YF vaccination

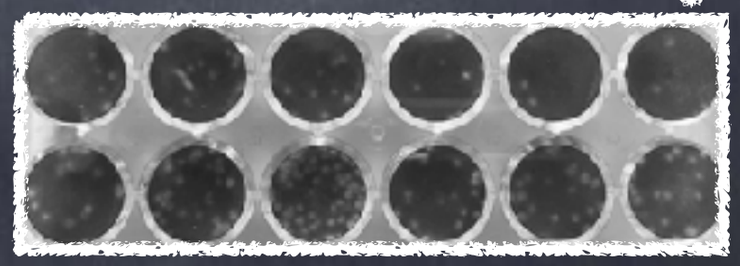
Primary endpoint

N 0 1 3 7 30 Days

N = 1, 4 or 9 months



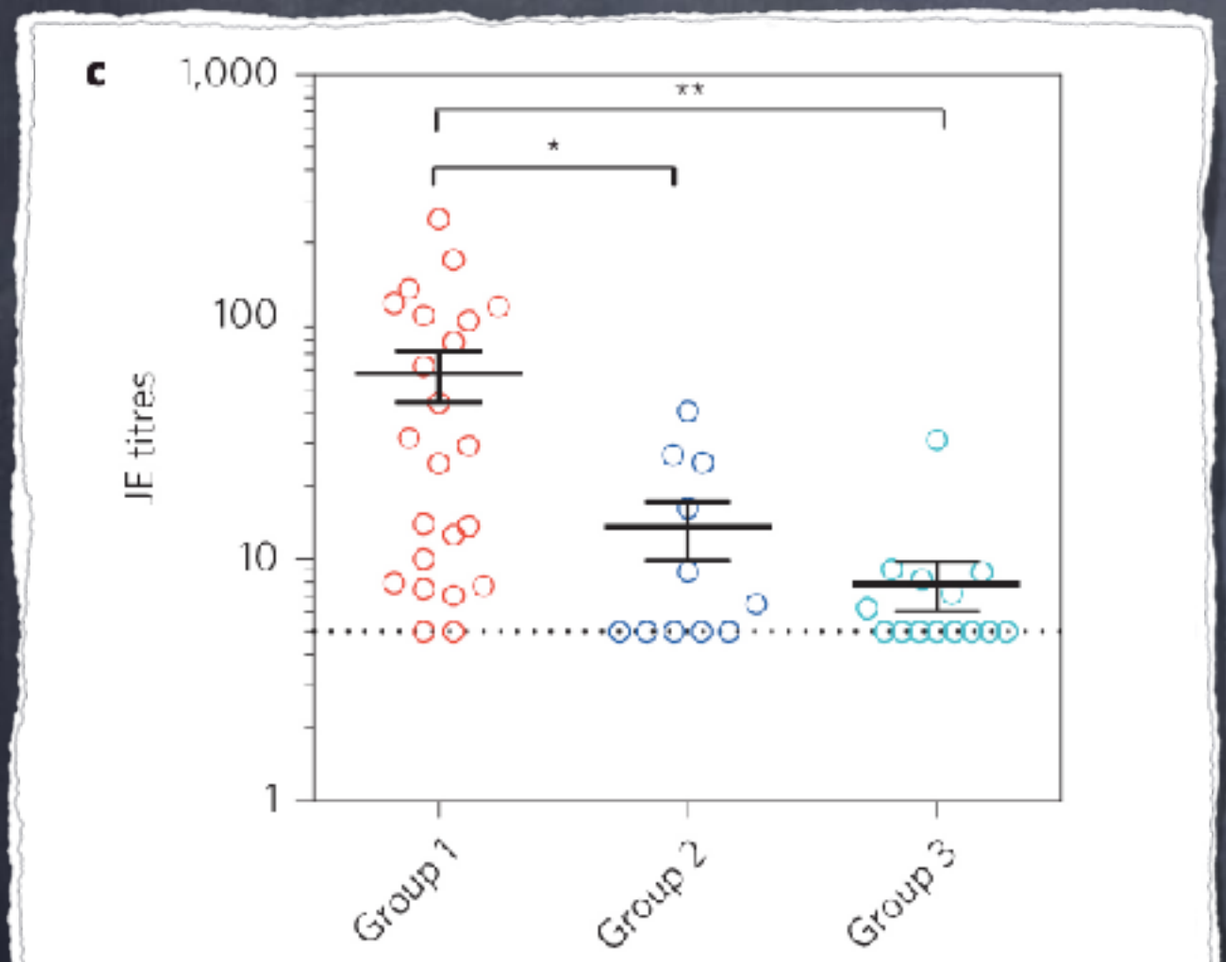
JEV PRNT

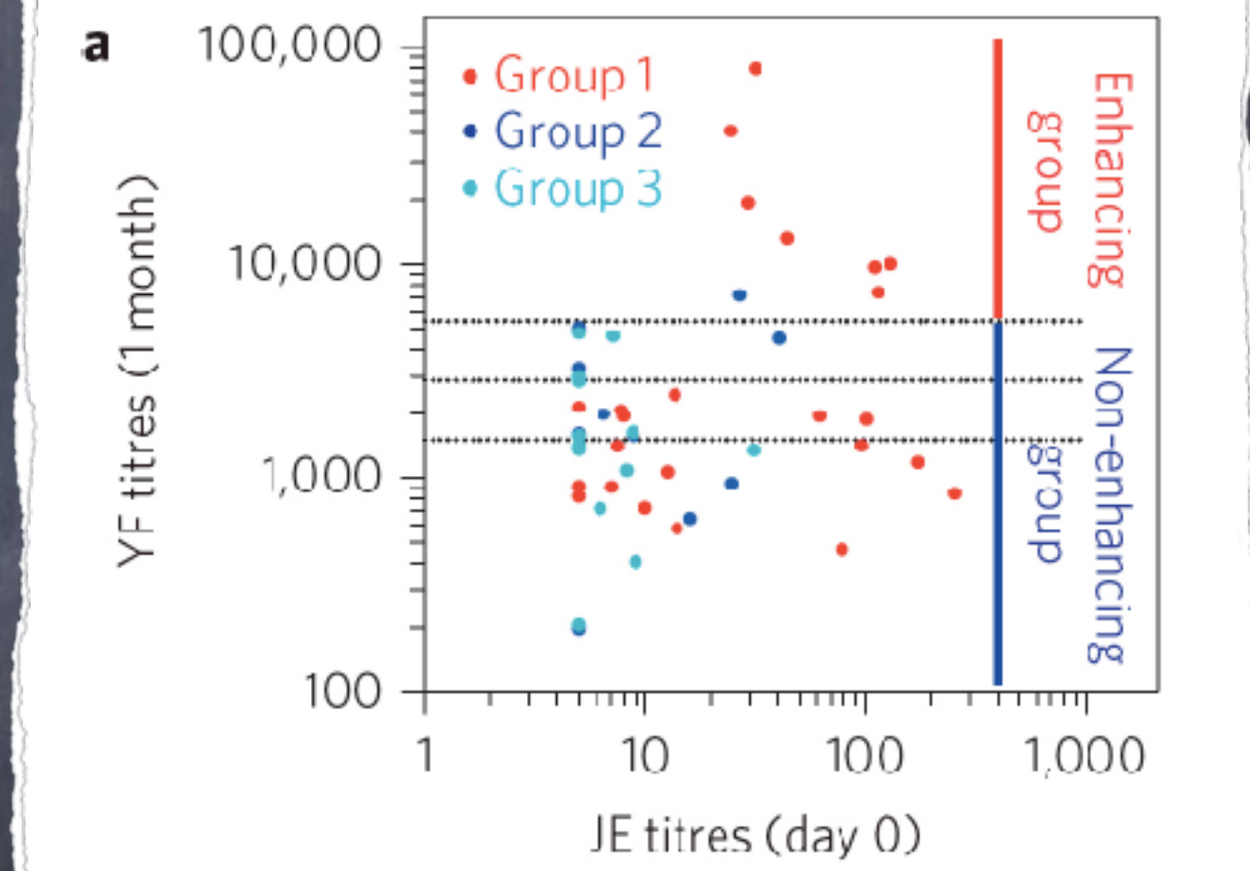


YF17D PRNT

Low et al, Trials 2015

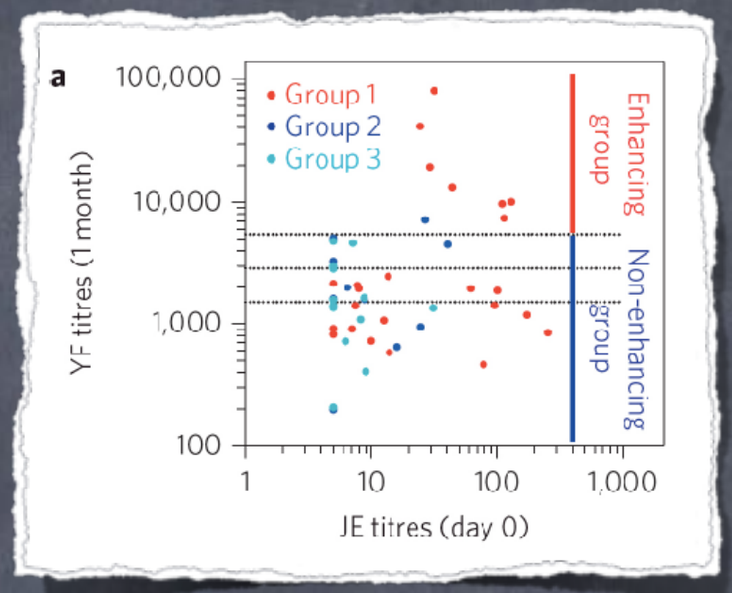
JE antibodies enhance YF17D immunogenicity

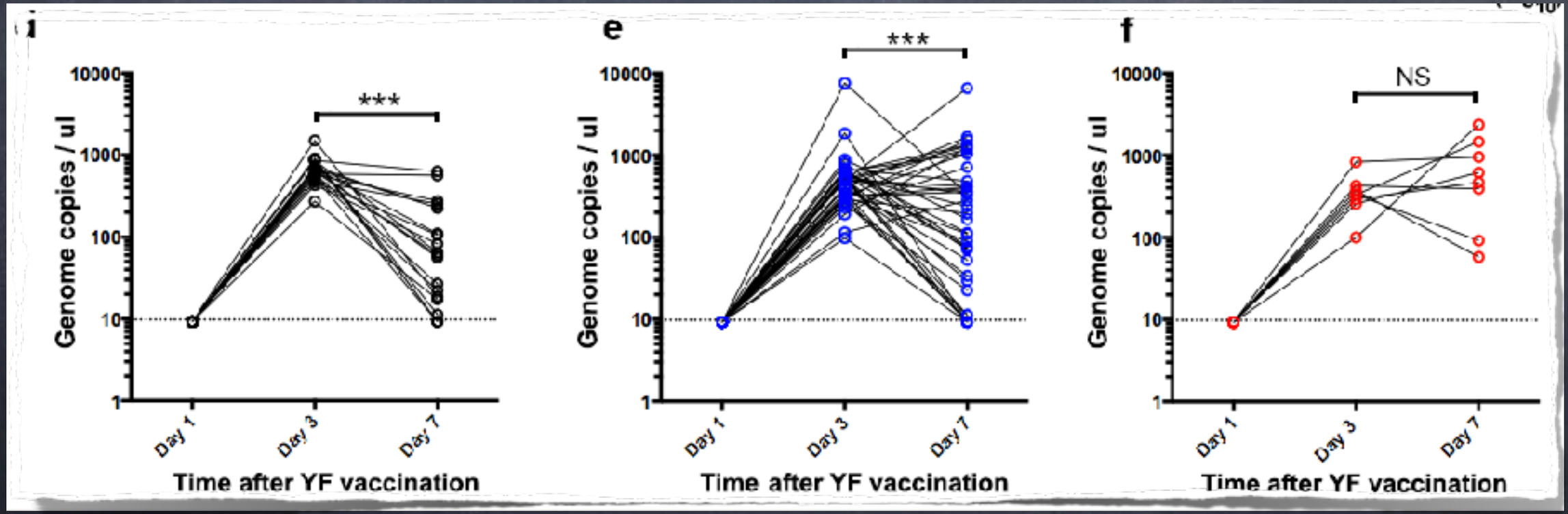




Chan et al, Nature Microbiology 2016

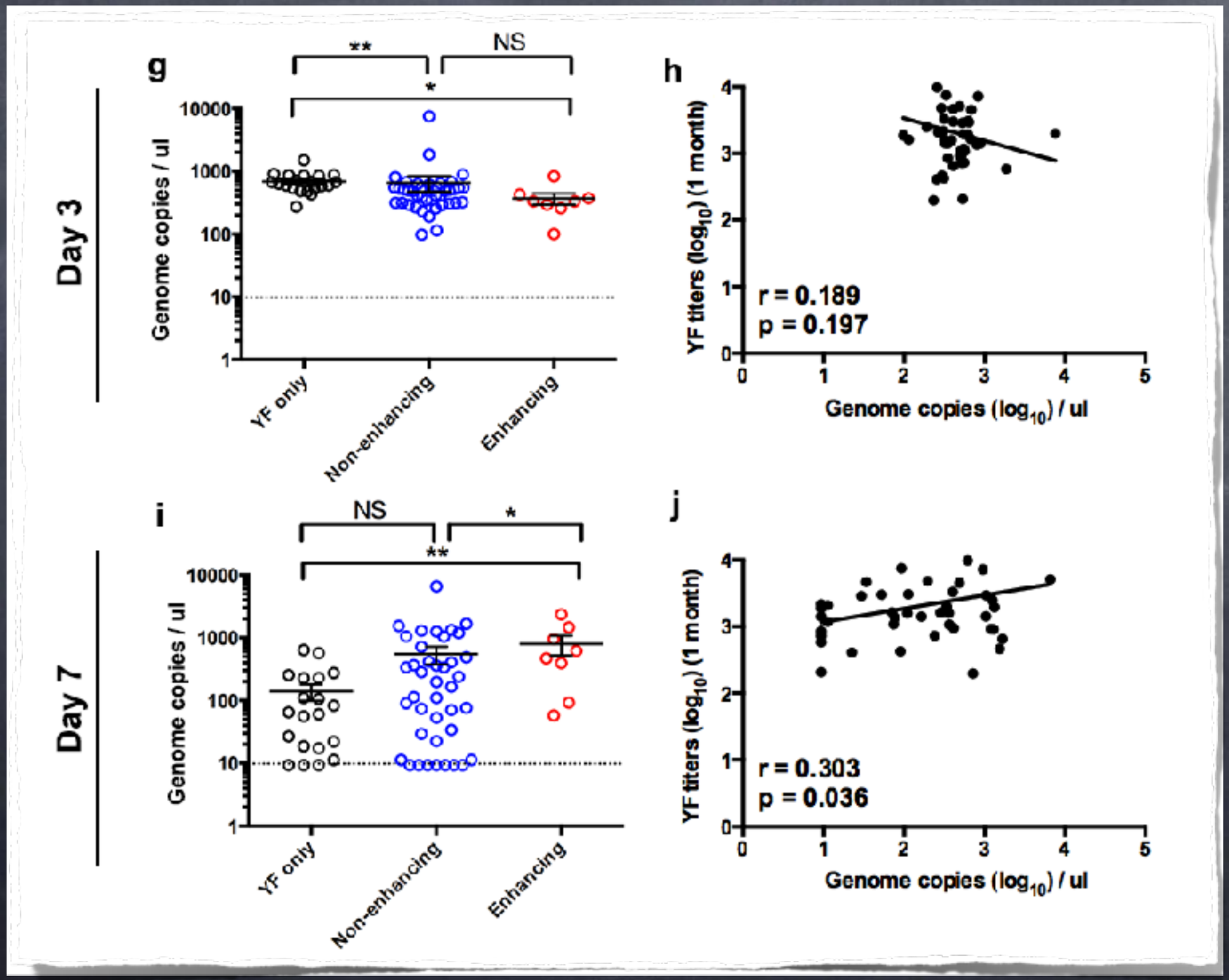
Sustained viremia associated with enhanced YF antibody response





YF17D only | Non-enhancing | Enhancing

YF17D viremia and its correlation with YF neutralising antibody titer



Summary II

- Cross-reactive antibodies enhance YF17D immunogenicity

- Cross-reactive antibodies prolonged YF17D viremia

- Host response to YF vaccination includes pathways intrinsic to activating FcγR

Chan et al, Nature Microbiology 2016

Acknowledgements

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Sue Tee

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Steven Tannenbaum
Yee Hou Lee
Cui Liang

NUS
Markus Wenk
Wei Fun Cheong

NMRC National Medical Research Council Singapore

A*STAR Biomedical Research Council