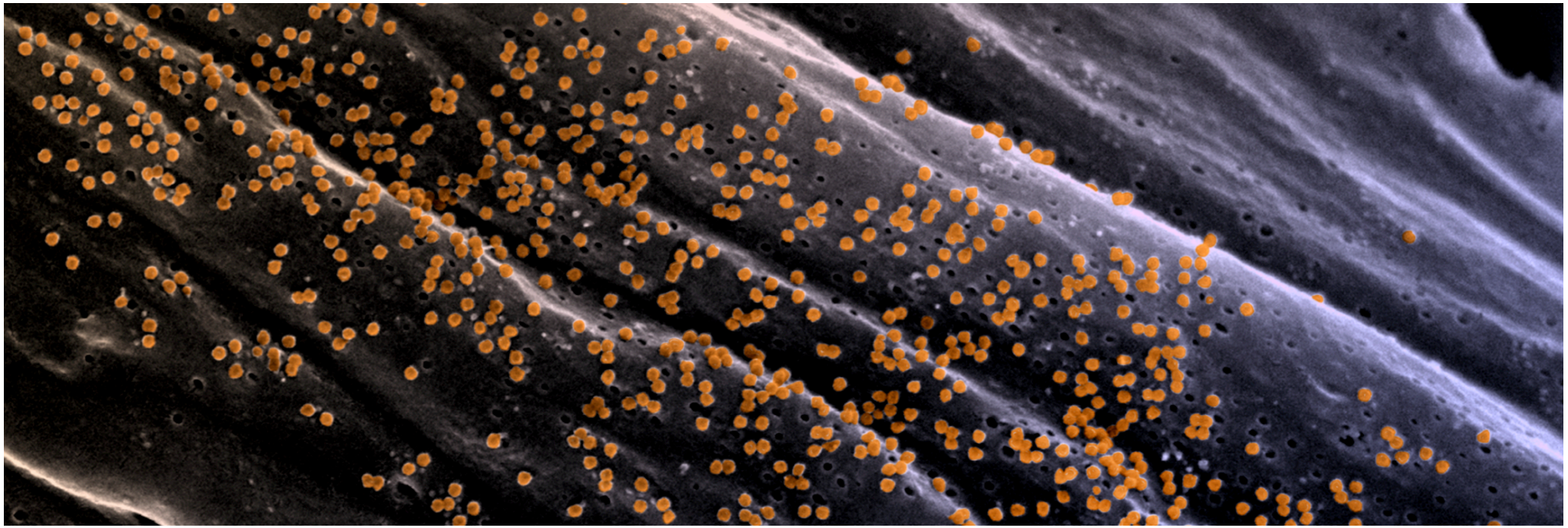


How Zika virus induces congenital microcephaly?

Marc LECUIT

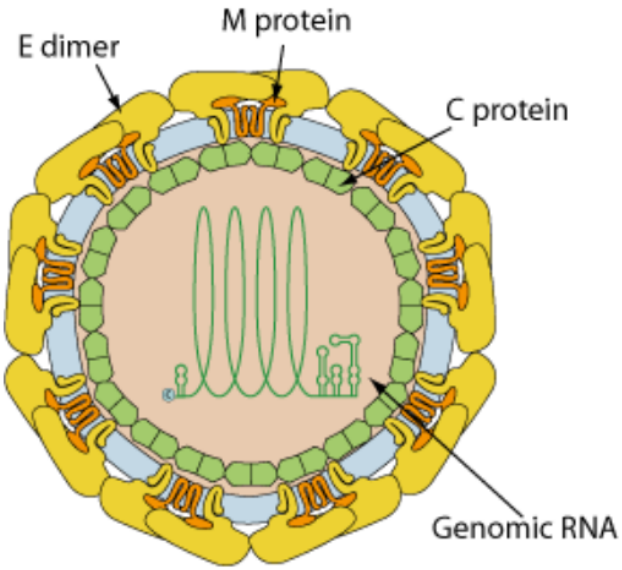
Institut Pasteur
Biology of Infection Unit, Inserm U1117

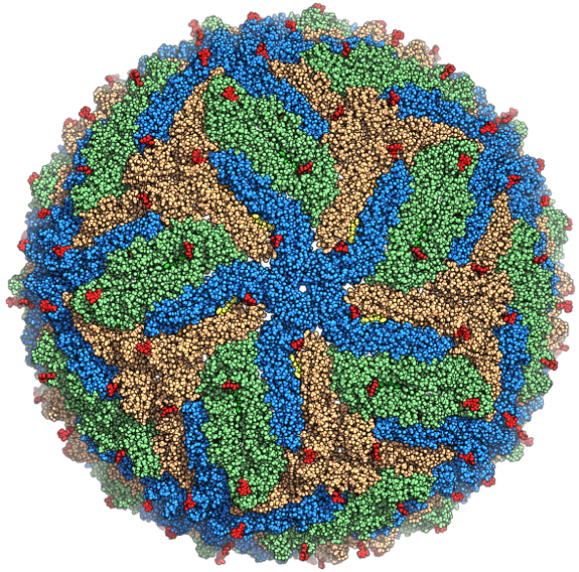
Department of Infectious Diseases and Tropical Medicine
Necker-Enfants Malades University Hospital
Paris Descartes University

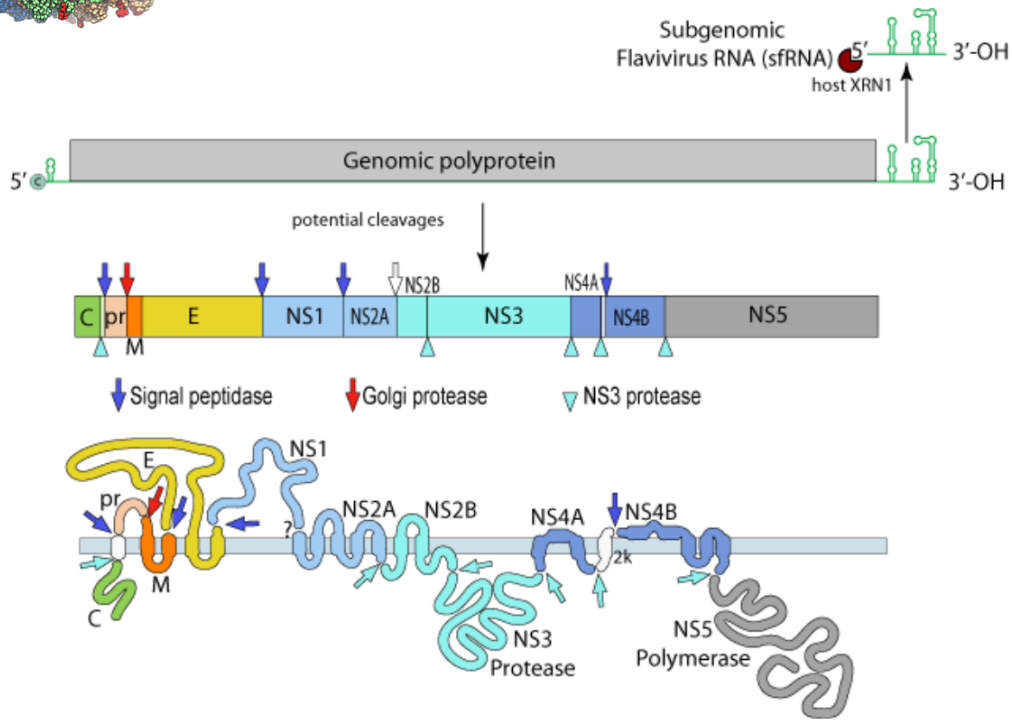
Inserm

Institut Pasteur

Zika virus, a typical flavivirus…







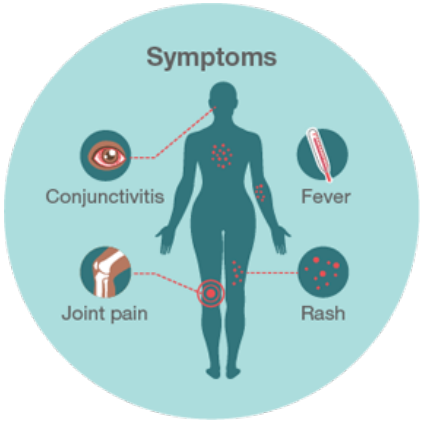
Zika virus vertical transmission and congenital microcephaly

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.



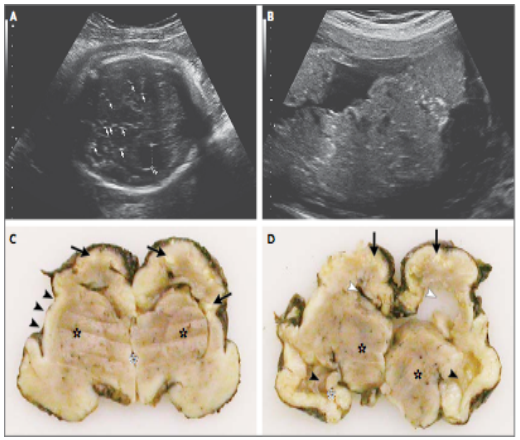
Lessler *et al.*, Science 2016

The NEW ENGLAND JOURNAL of MEDICINE

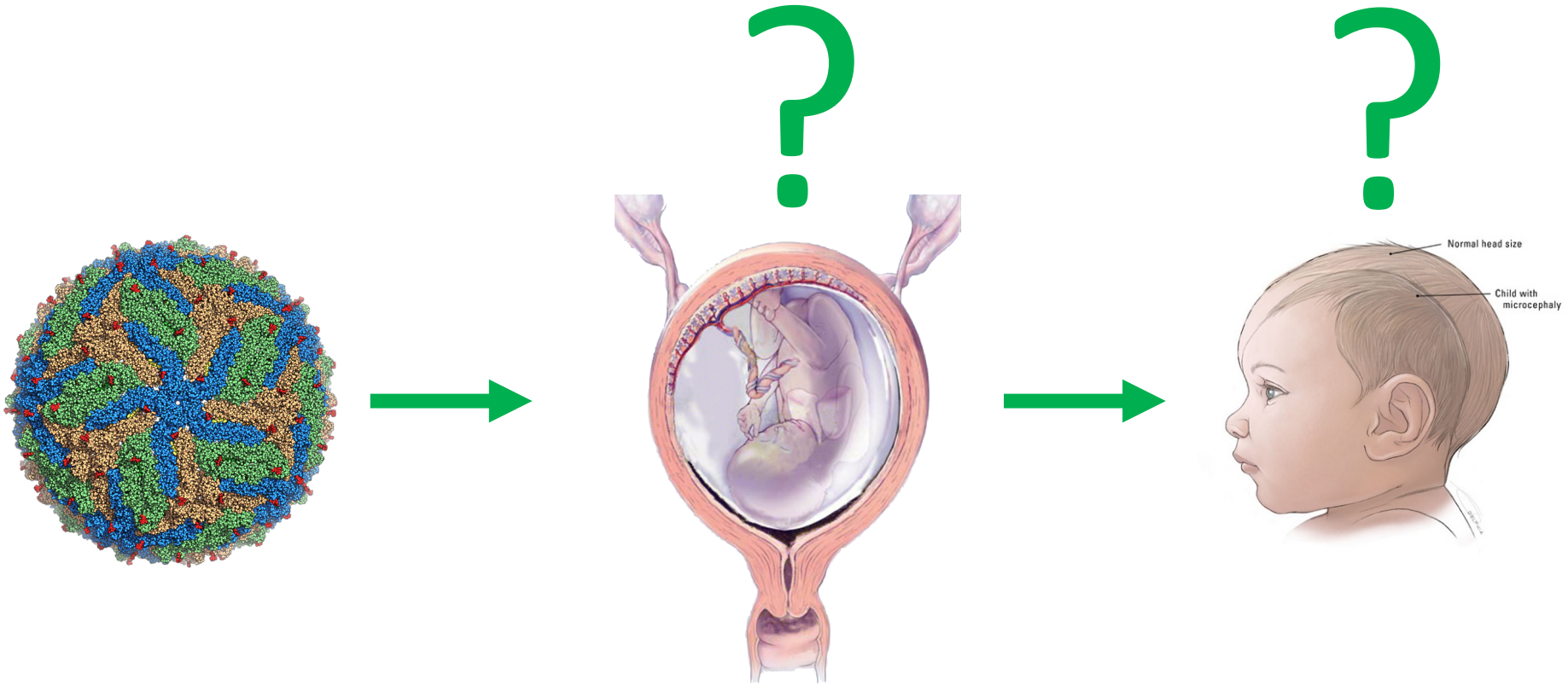
BRIEF REPORT

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities

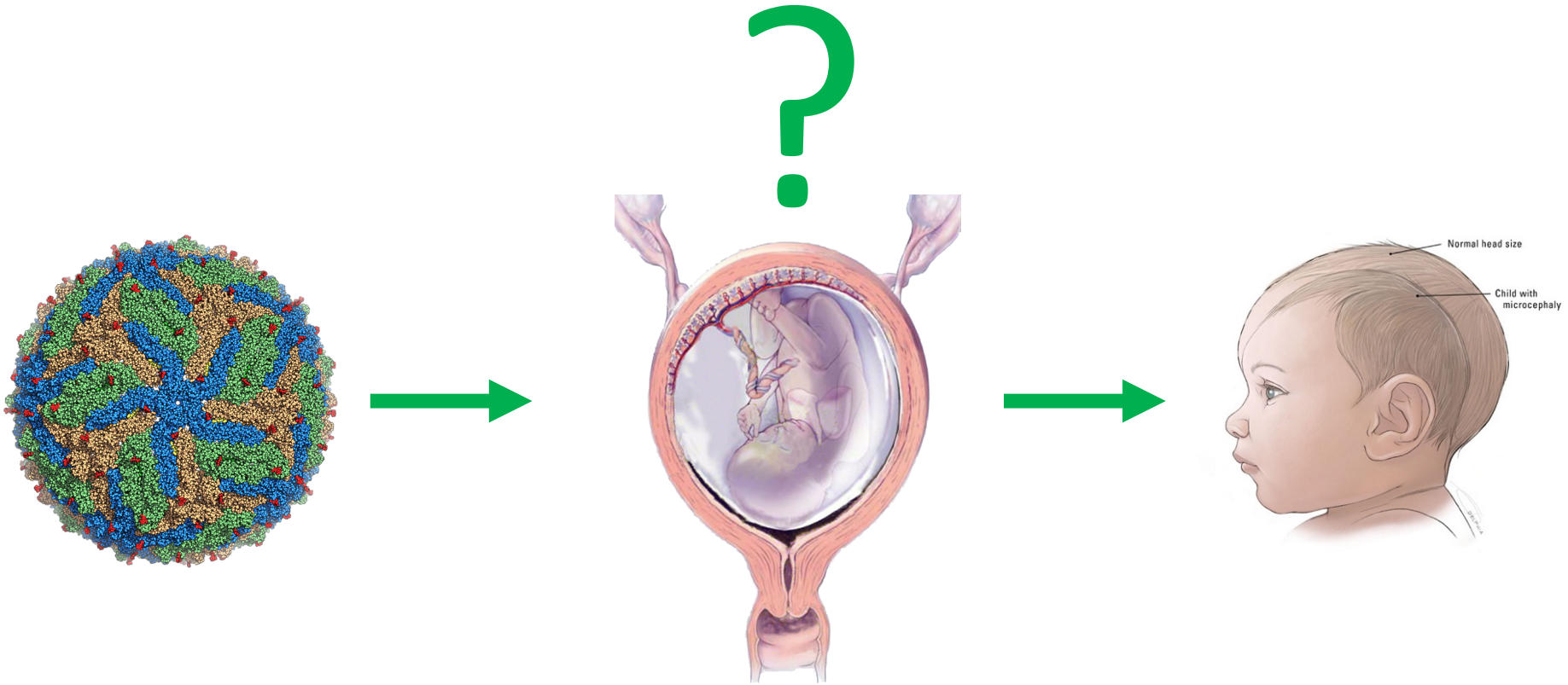
R.W. Driggers, C.-Y. Ho, E.M. Korhonen, S. Kuivanen, A.J. Jääskeläinen, T. Smura, A. Rosenberg, D.A. Hill, R.L. DeBiasi, G. Vezina, J. Timofeev, F.J. Rodriguez, L. Levanov, J. Razak, P. Iyengar, A. Hennenfent, R. Kennedy, R. Lanciotti, A. du Plessis, and O. Vapalahti



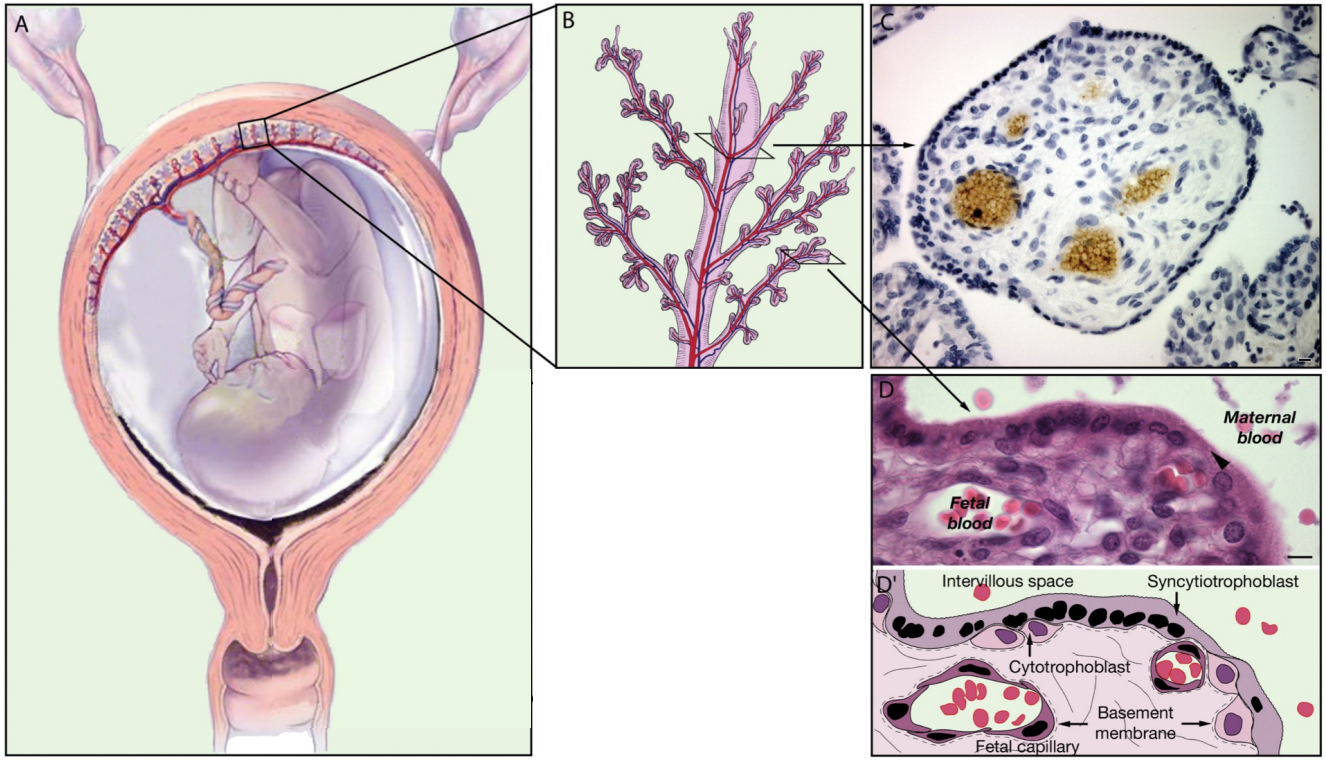
Zika virus vertical transmission and congenital microcephaly



Mechanisms of vertical transmission of Zika virus

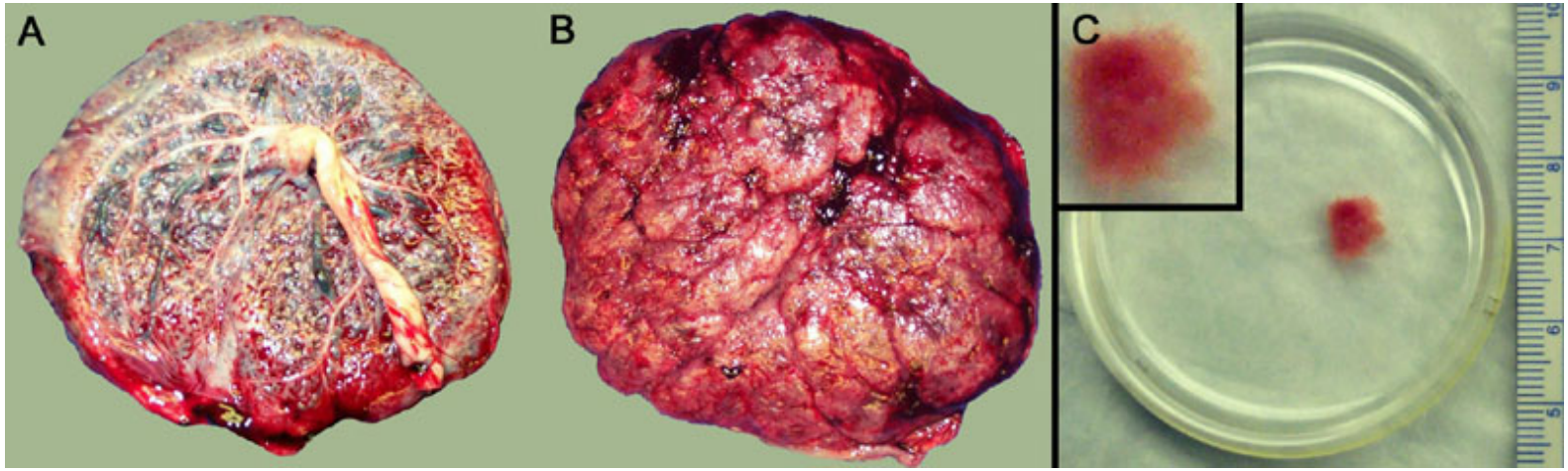


Anatomy of the maternal-fetal barrier

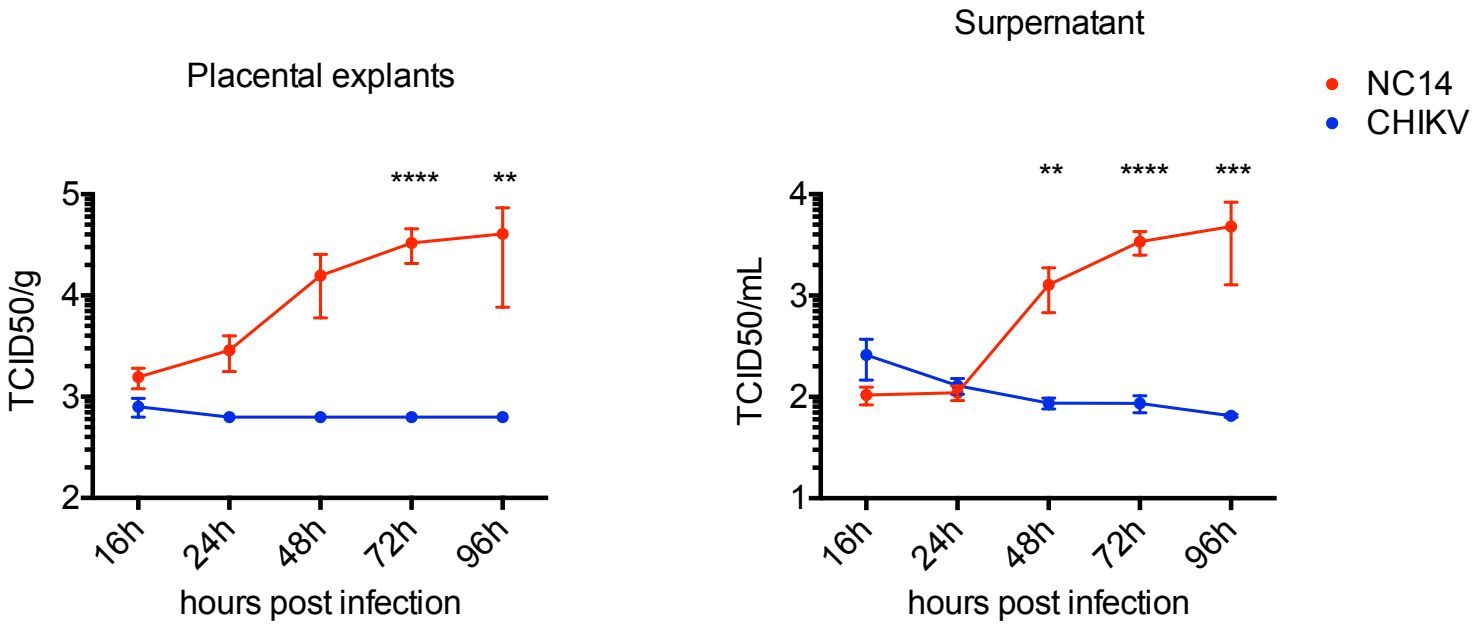


placental barrier

Ex vivo infection of human placental explants



ZIKV replicates in 3rd trimester human placental explants

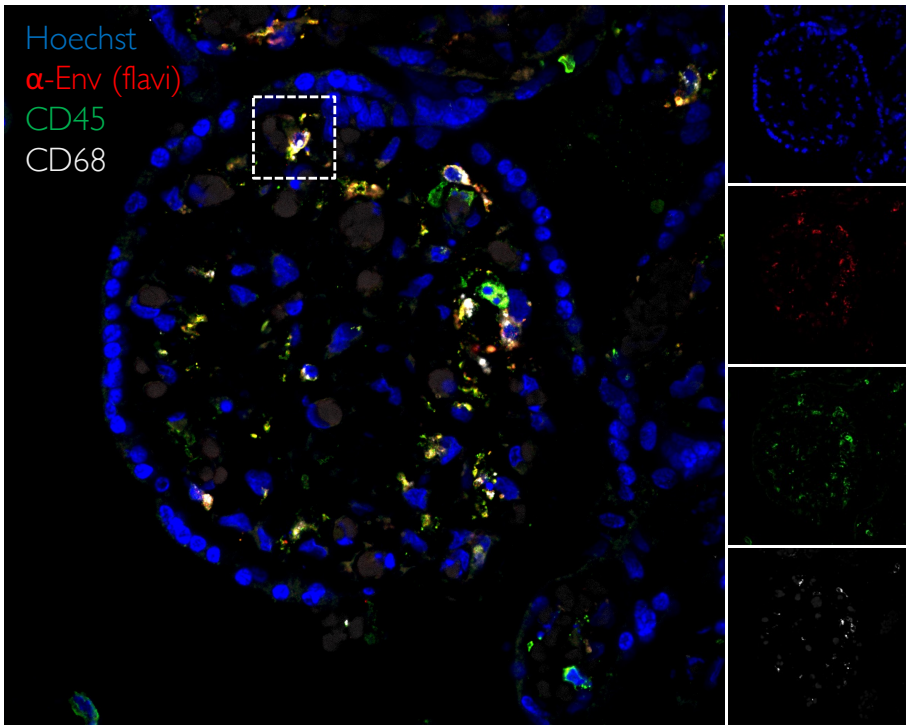


NB: CHIKV is a negative control, as it does not replicate in human placenta, and is transmitted vertically only in peripartum by viremic mothers

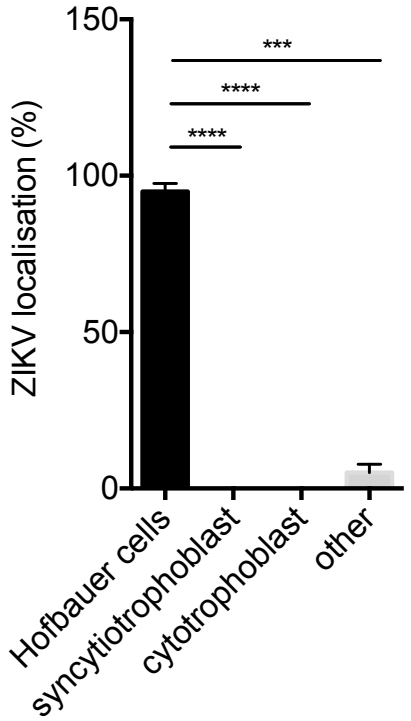
Couderc PLOS Pathog 2008, Gérardin PLOS Med 2008

ZIKV infects Hofbauer cells in human placental explants

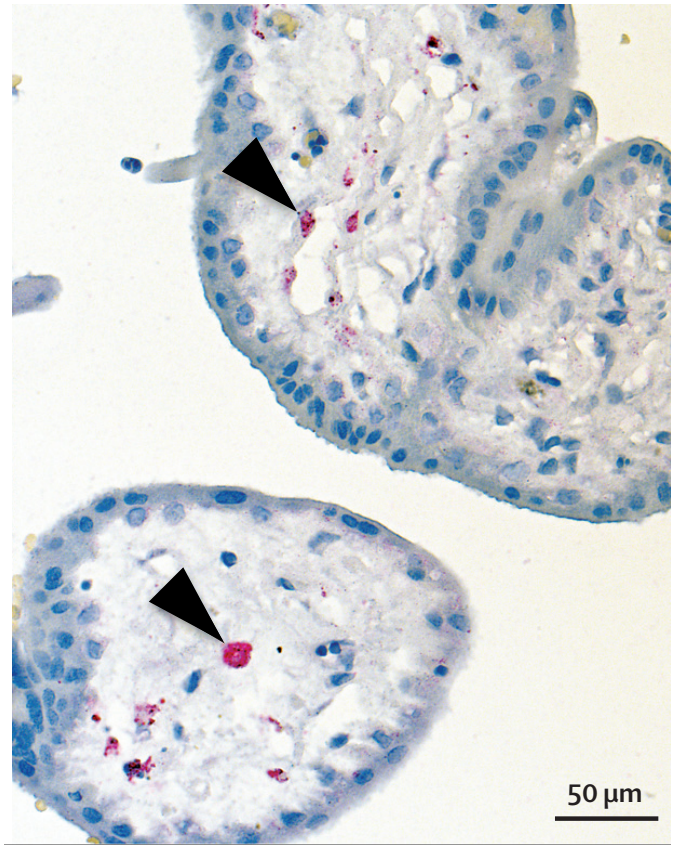
ZIKV Infected 72h



Infected cells are CD45+ and CD68+



Actual data from pregnant women with zika…



Pathology of congenital Zika syndrome in Brazil: a case series

Roosecelis Brasil Martines, Julu Bhatnagar*, Ana Maria de Oliveira Ramos, Helaine Pompeia Freire Davi, Silvia D'Andretta Iglezias, Cristina Takami Kanamura, M Kelly Keating, Gillian Hale, Luciana Silva-Flannery, Atis Muehlenbachs, Jana Ritter, Joy Gary, Dominique Rollin, Cynthia S Goldsmith, Sarah Reagan-Steiner, Yokabed Ermias, Tadaki Suzuki, Kleber G Luz, Wanderson Kleber de Oliveira, Robert Lanciotti, Amy Lambert, Wun-Ju Shieh, Sherif R Zaki*

www.thelancet.com **Vol 388 August 27, 2016**

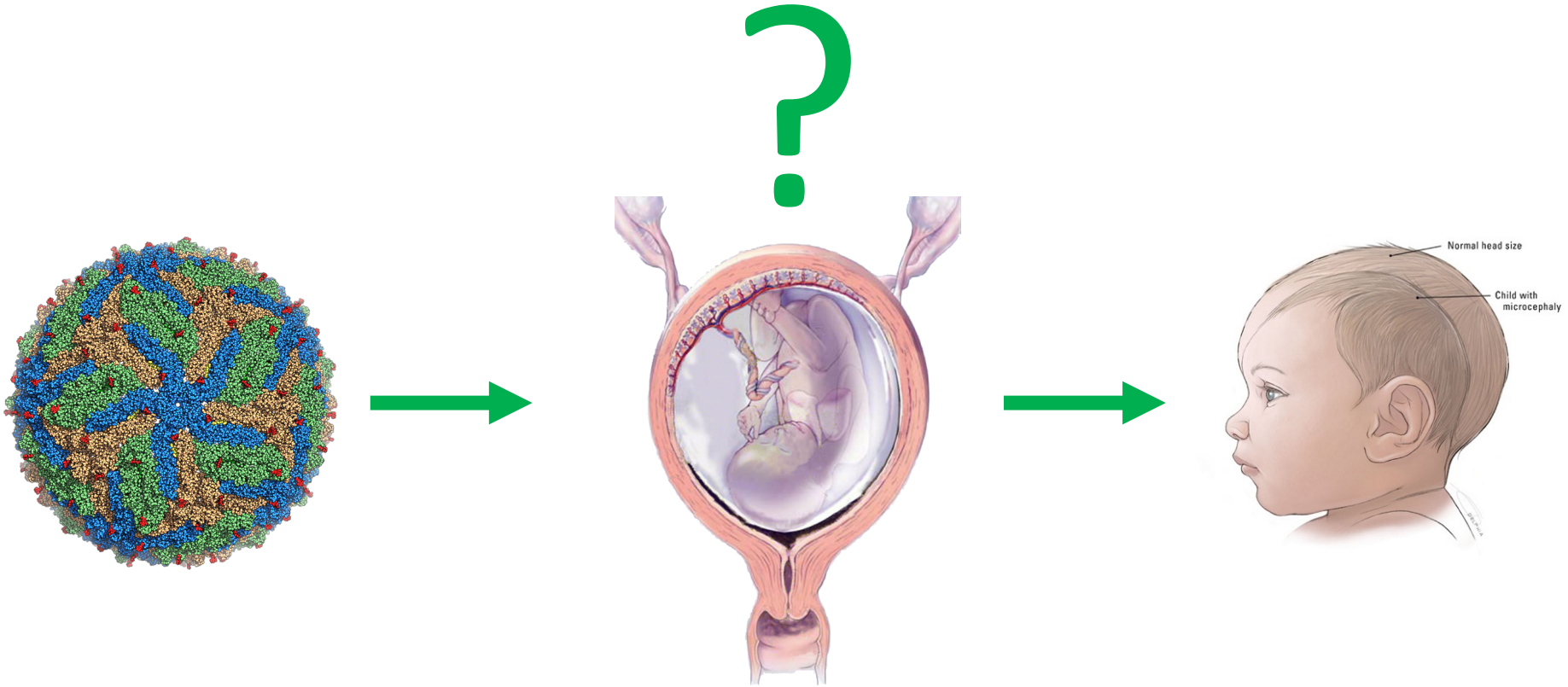
Mem Inst Oswaldo Cruz, Rio de Janeiro: 1-7, 2016

Zika virus damages the human placental barrier and presents marked fetal neurotropism

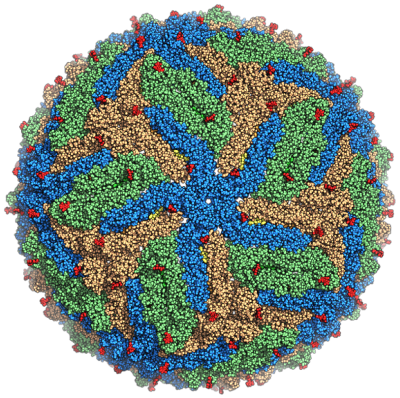
Lucia de Noronha[1], Camila Zanluca[2], Marina Luize Viola Azevedo[1], Kleber Giovanni Luz[3], Claudia Nunes Duarte dos Santos[2]/+

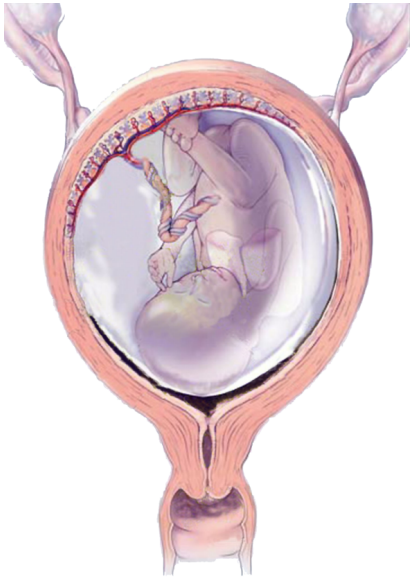
[1]Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brasil [2]Fundação Oswaldo Cruz, Instituto Carlos Chagas, Laboratório de Virologia Molecular, Curitiba, PR, Brasil [3]Universidade Federal do Rio Grande do Norte, Instituto de Medicina Tropical, Natal, RN, Brasil

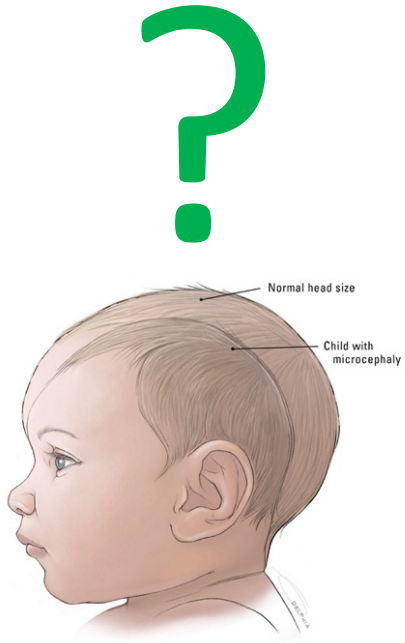
Molecular mechanisms of ZIKV crossing of the placental barrier



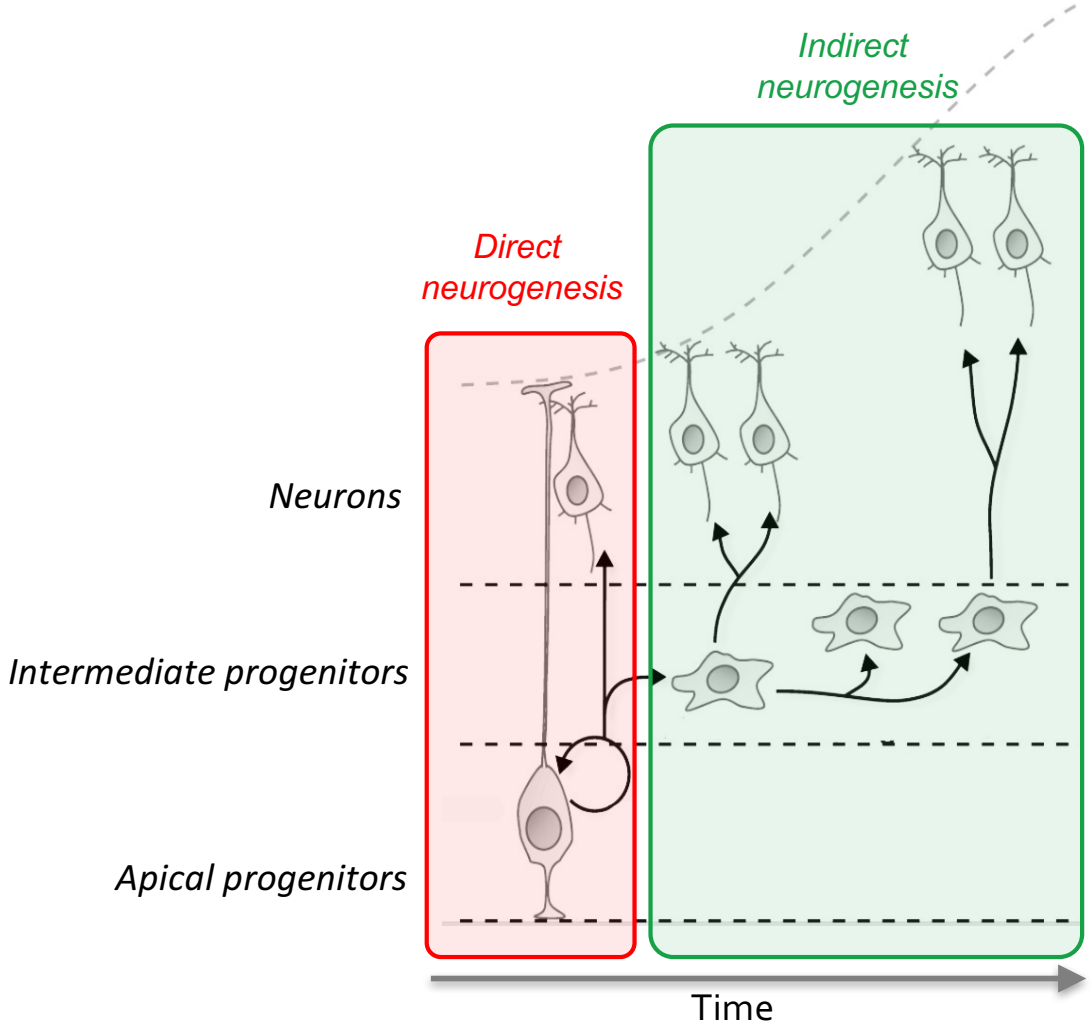
Molecular mechanisms of ZIKV-associated microcephaly





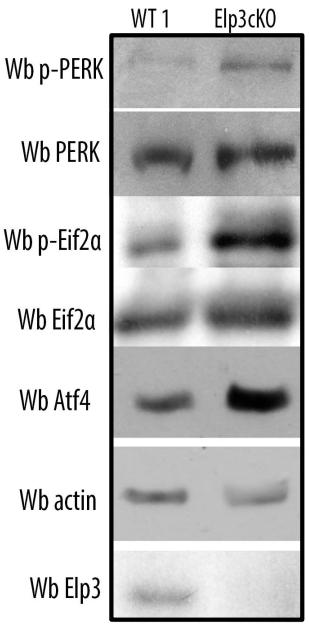


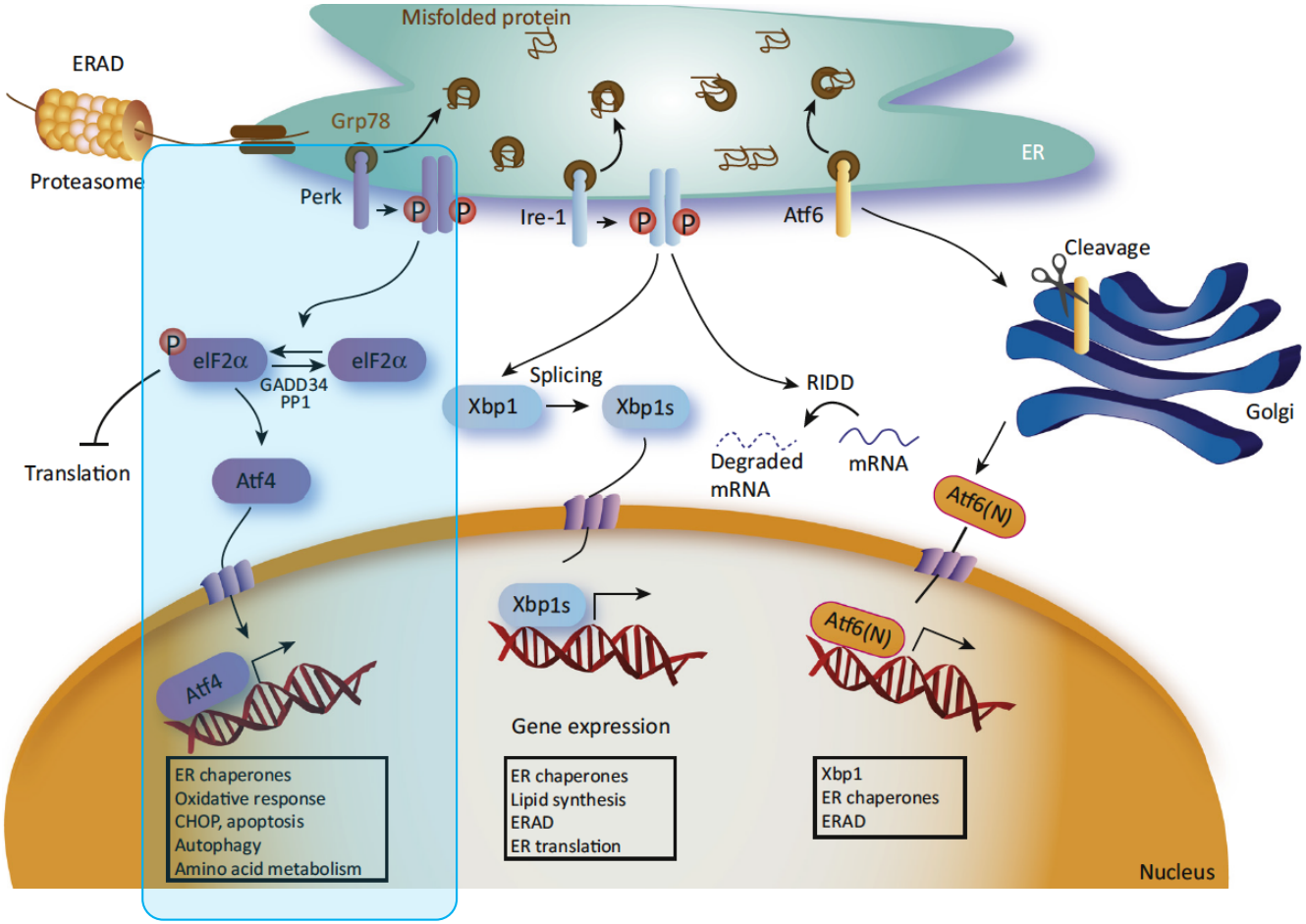
Birth of projection neurons

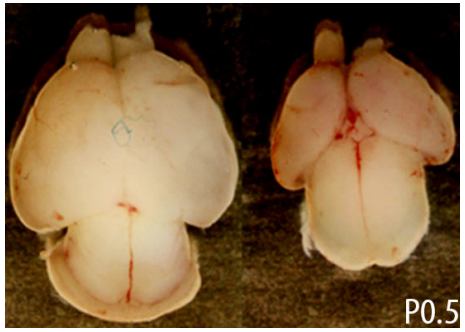


Adapted from Tiberi, Curr Opin Cell Biol 2012

ER stress can activate three distincts UPR pathways

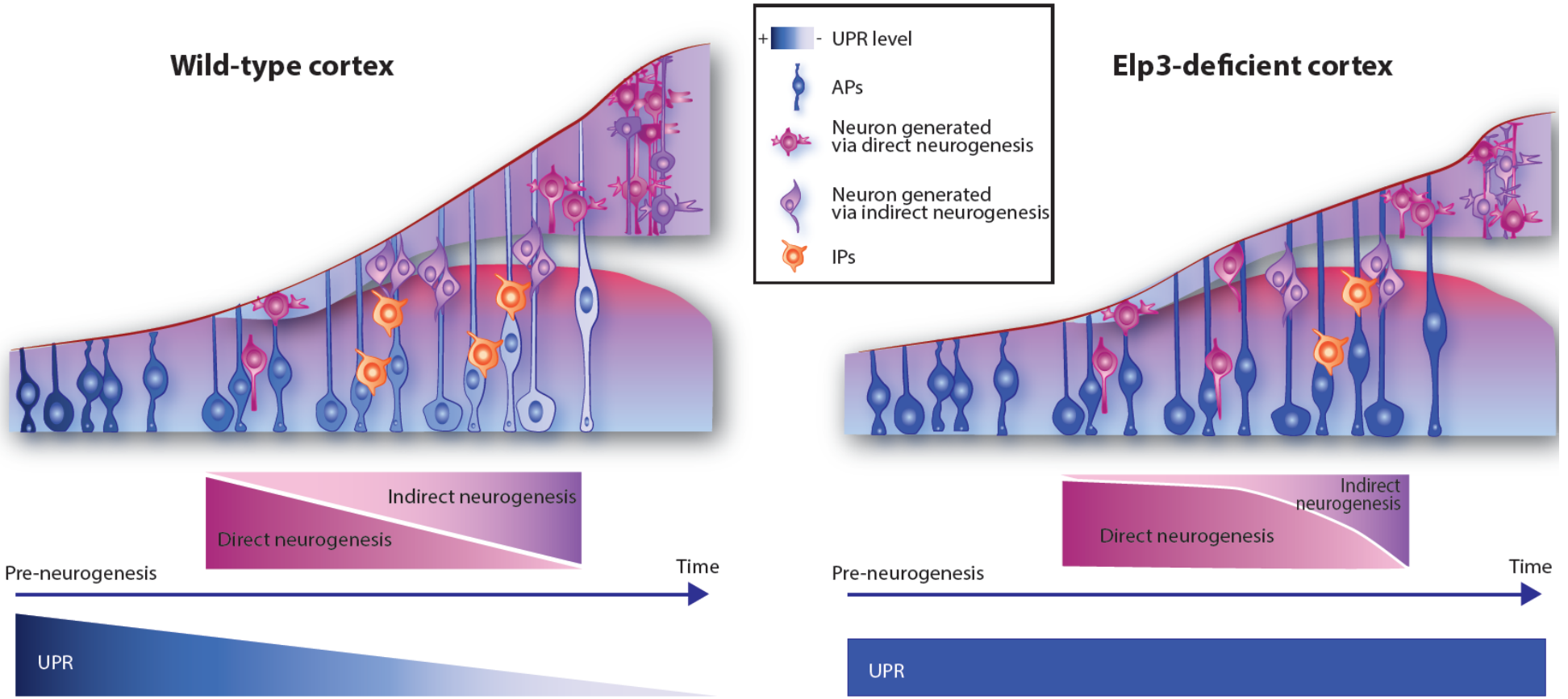


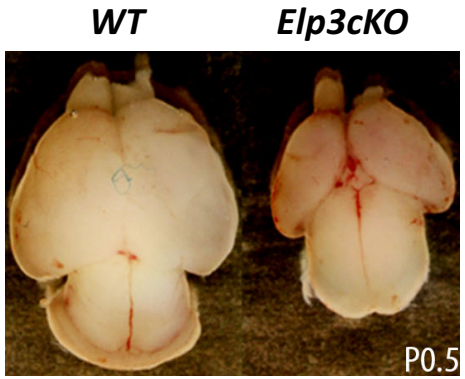




Laguesse *et al.*, Developmental Cell 2015
Godin *et al.*, Trends Neurosci 2016

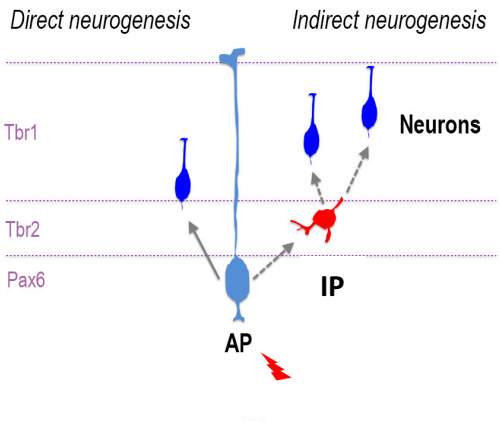
Working model

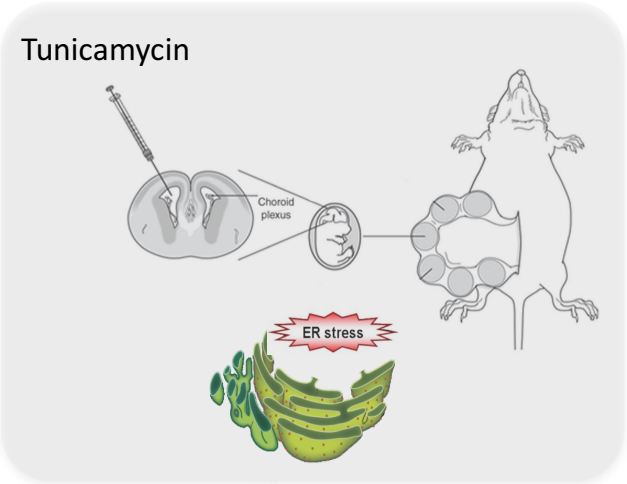




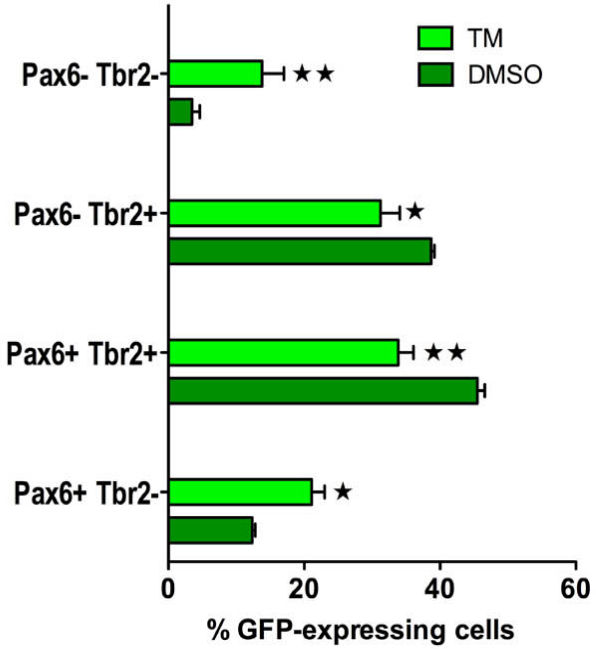
Laguesse *et al.*, Developmental Cell 2015
Godin *et al.*, Trends Neurosci 2016

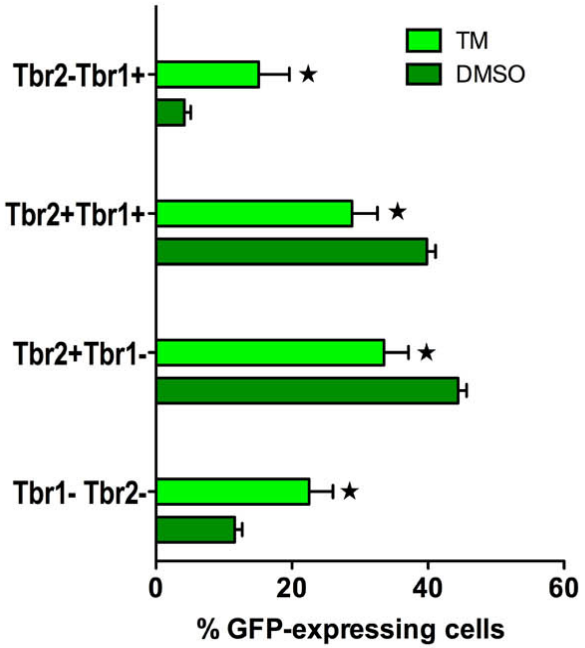
Chemical induction of ER stress impairs cortical neurogenesis

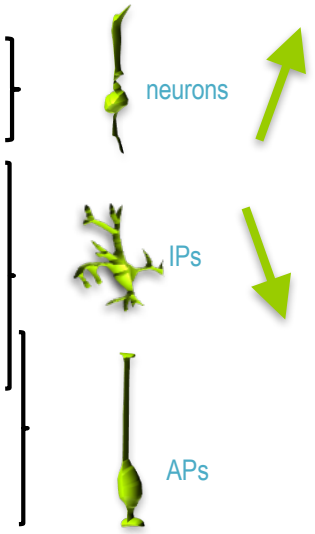




Direct neurogenesis *Indirect neurogenesis*



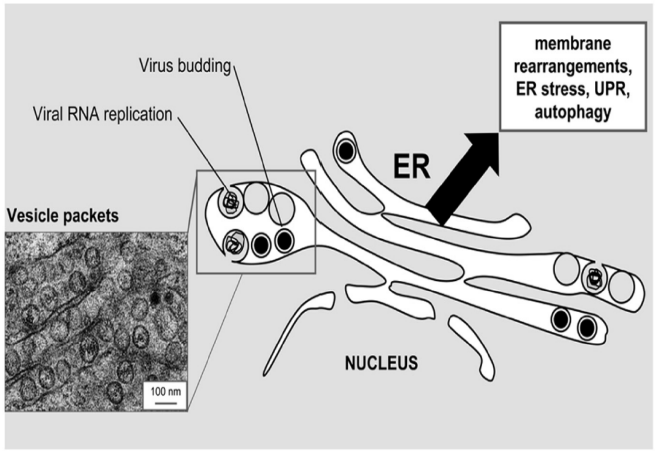




ZIKA-induced congenital microcephaly as a result of ER stress?

ZIKA targets cortical apical progenitors

Wu *et al.*, Cell Res 2016
Tang *et al.*, Cell Stem Cell 2016



Blazquez, Front Microbiol 2014

Science REPORTS

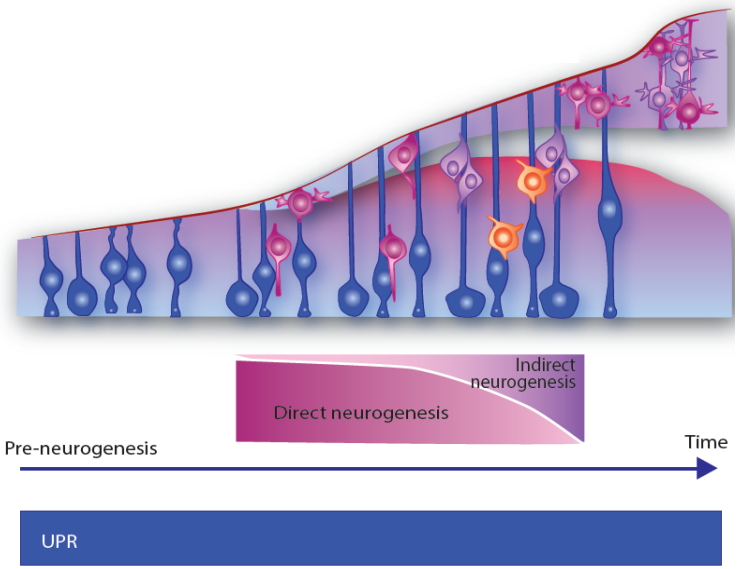
Cite as: P. L. Chavali *et al.*, *Science* 10.1126/science.aam9243 (2017).

Neurodevelopmental protein Musashi 1 interacts with the Zika genome and promotes viral replication

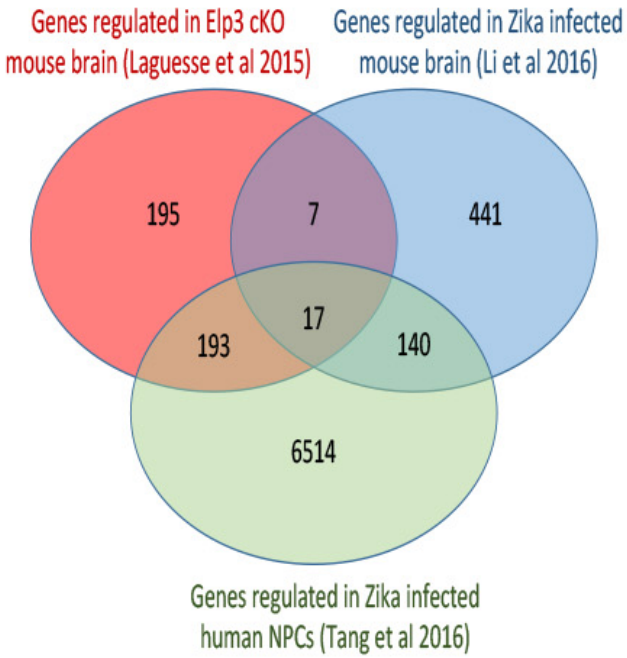
Pavithra L. Chavali,[1*†] Lovorka Stojic,[1*] Luke W. Meredith,[2] Nimesh Joseph,[1] Michael S. Nahorski,[3] Thomas J. Sanford,[2] Trevor R. Sweeney,[2] Ben A. Krishna,[4] Myra Hosmillo,[2] Andrew E. Firth,[2] Richard Bayliss,[5] Carlo L. Marcelis,[6] Susan Lindsay,[7] Ian Goodfellow,[2] C. Geoffrey Woods,[3] Fanni Gergely[1‡]

[1]Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Robinson Way, Cambridge CB2 0RE, UK. [2]Division of Virology, Department of Pathology, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK. [3]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Hills Road, Cambridge CB2 0XY, UK. [4]Department of Medicine, University of Cambridge, Hills Road, Cambridge CB2 2QQ, UK. [5]Faculty of Biological Sciences, Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, UK. [6]Department of Human Genetics, Radboud University Medical Centre, Nijmegen, Netherlands. [7]Institute of Genetic Medicine, Newcastle University, International Centre for Life, Central Parkway, Newcastle upon Tyne NE1 3BZ, UK.

UPR



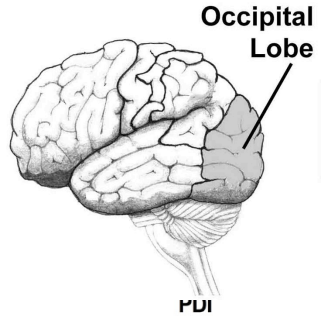
Gene expression profiles suggest that ZIKV activates UPR

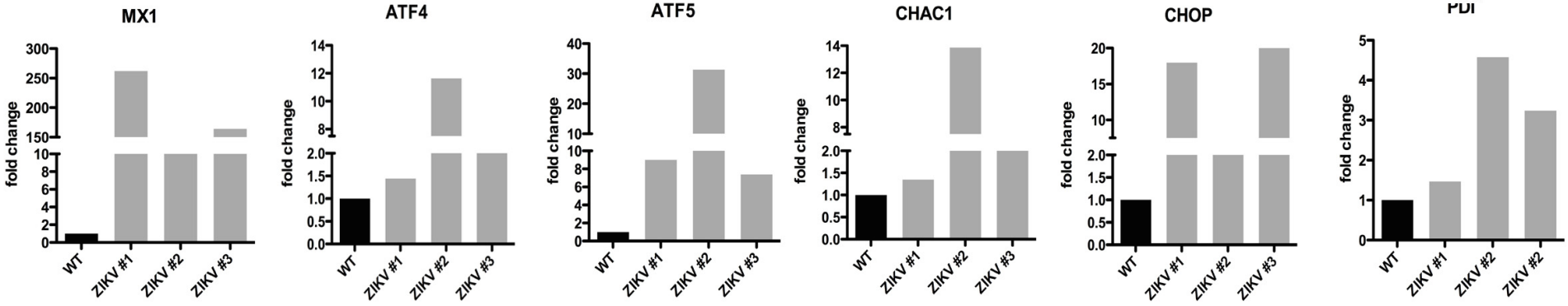


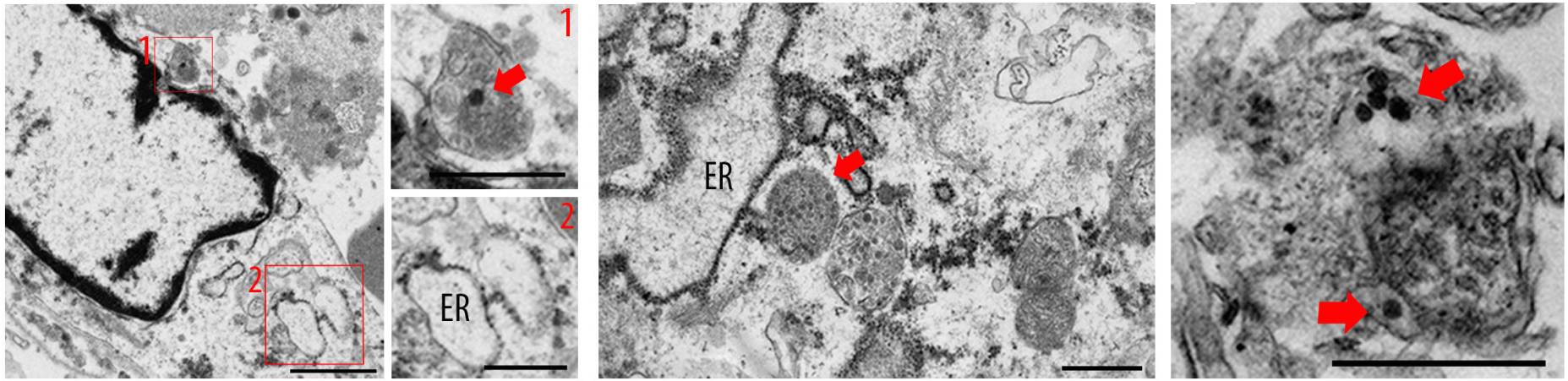
17common genes	FC Elp3 mBrain	FC Zika mBrain	FC Zika hNPCs
Slc7a3	9,62	2,38	2,46
Sesn2	7,66	2,15	4,16
Chac1	7,11	2,89	7,93
Eif4ebp1	6,64	2,72	3,73
Atf5	3,78	1,72	2,18
Slc6a9	3,11	1,49	1,63
Asns	2,88	1,55	4,32
Cenpf	2,50	0,80	0,43
Atf4	2,32	1,25	1,19
Cars	2,09	1,49	4,36
Mthfd2	1,80	1,46	4,71
Shmt2	1,68	1,41	3,18
Iars	1,62	1,23	2,39
Dpy19l1	0,72	0,79	0,57
Hn1	0,61	0,82	0,77
H19	0,60	1,31	0,45

Gladwynng *et al.* Nat Neurosci 2018

Human cortex from infected fetuses show signs of ER stress and UPR

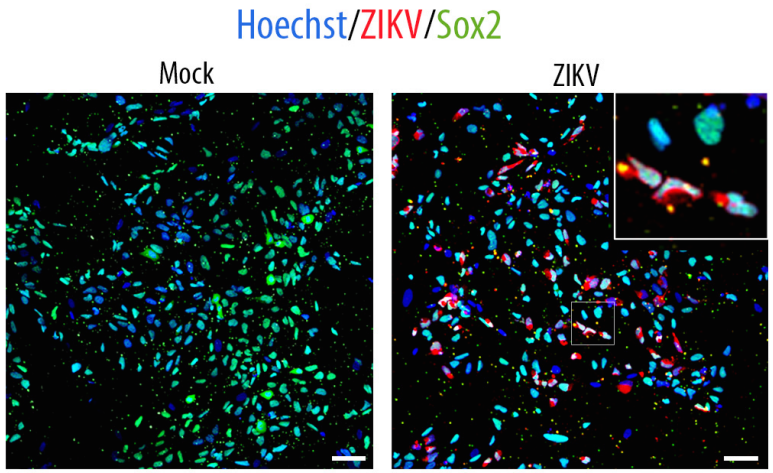


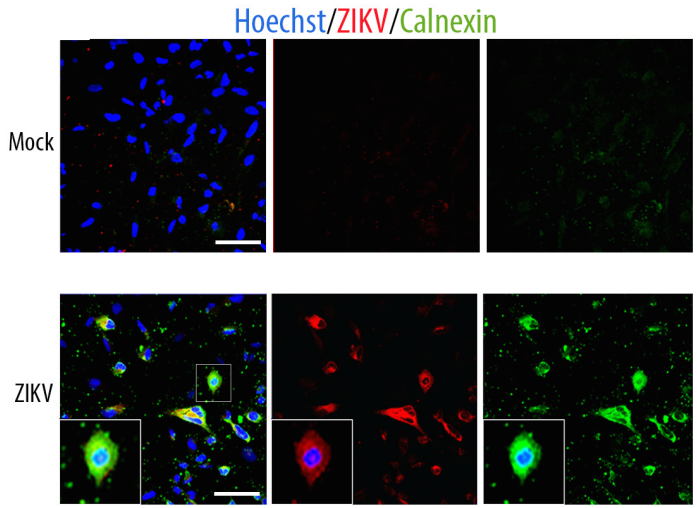


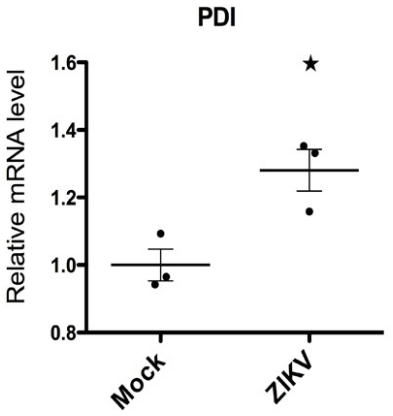


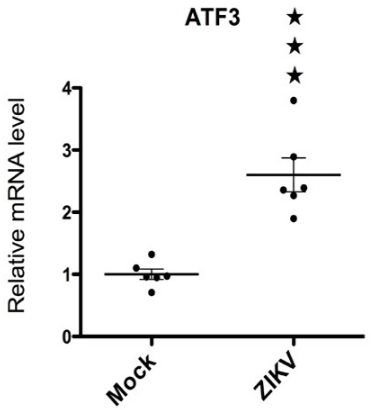
Gladwynng *et al.* Nat Neurosci 2018

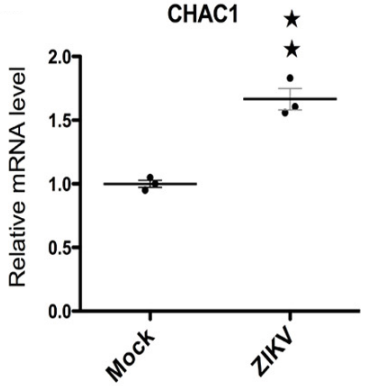
ZIKV induces ER stress and UPR activation in HiPSCs

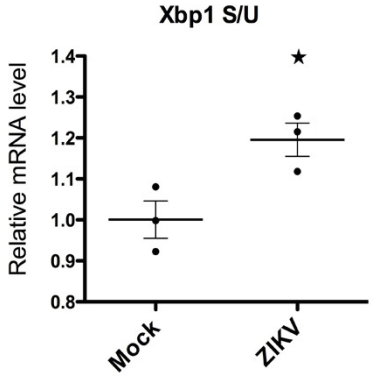






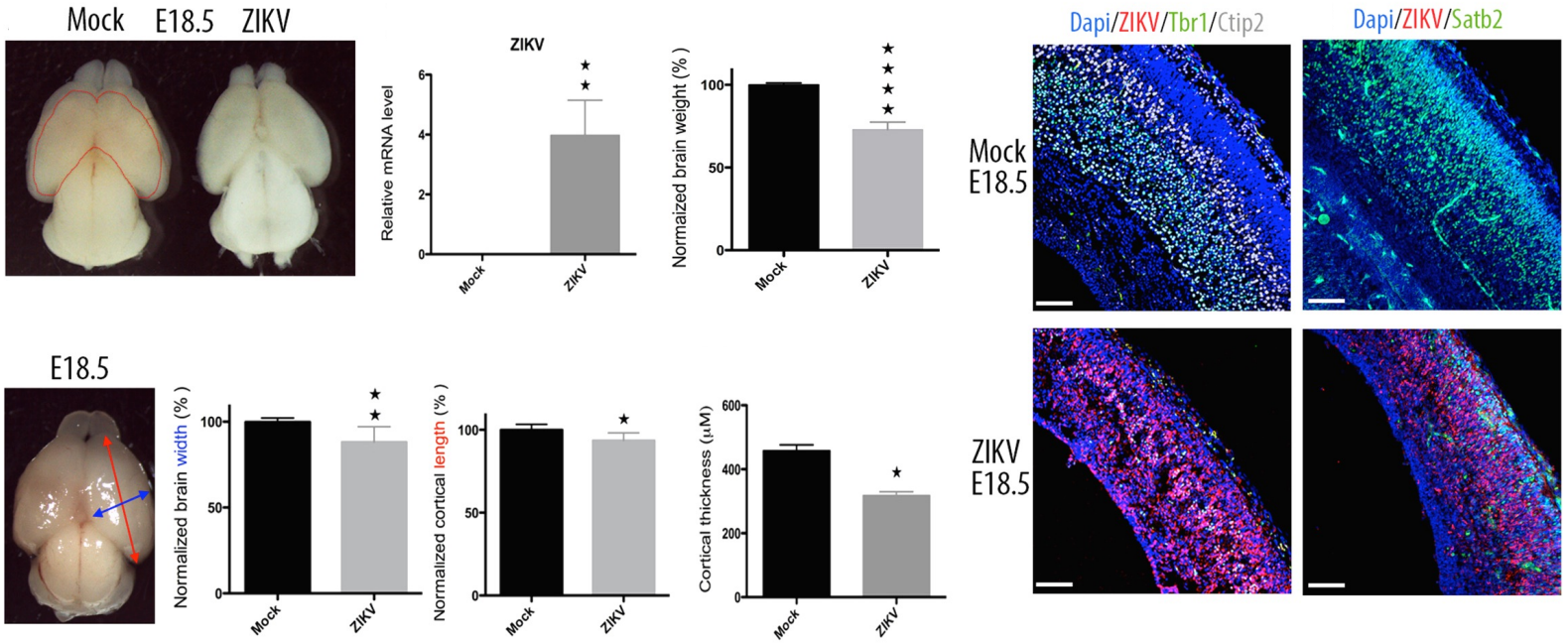


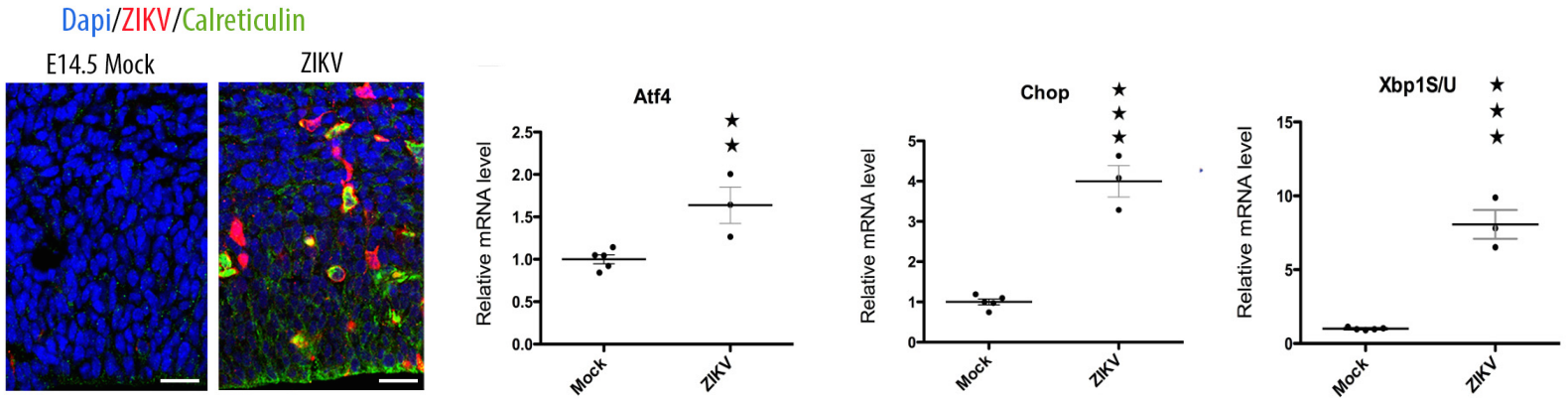




Gladwynng *et al.* Nat Neurosci 2018

ZIKA-induces ER stress and activates UPR in mouse embryos (ICV)





Gladwynng *et al.* Nat Neurosci 2018

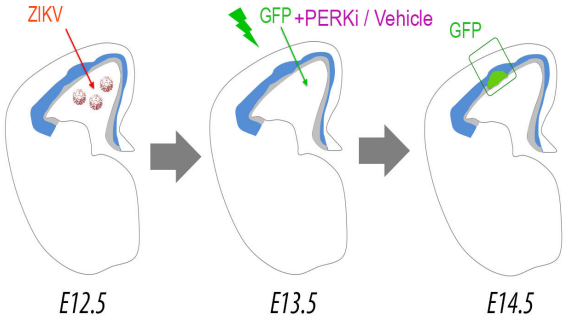
Does UPR induction by ZIKV-infection result in impairment of the neurogenic balance?

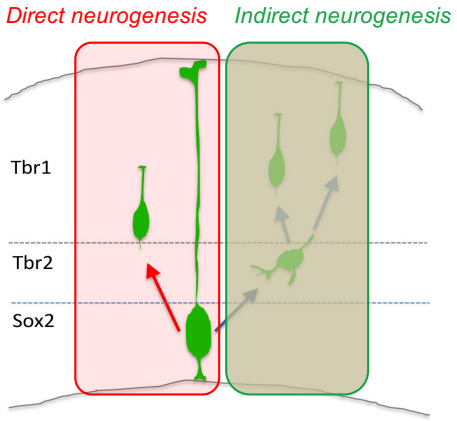
Fate mapping of apical progenitors and their direct cell progeny

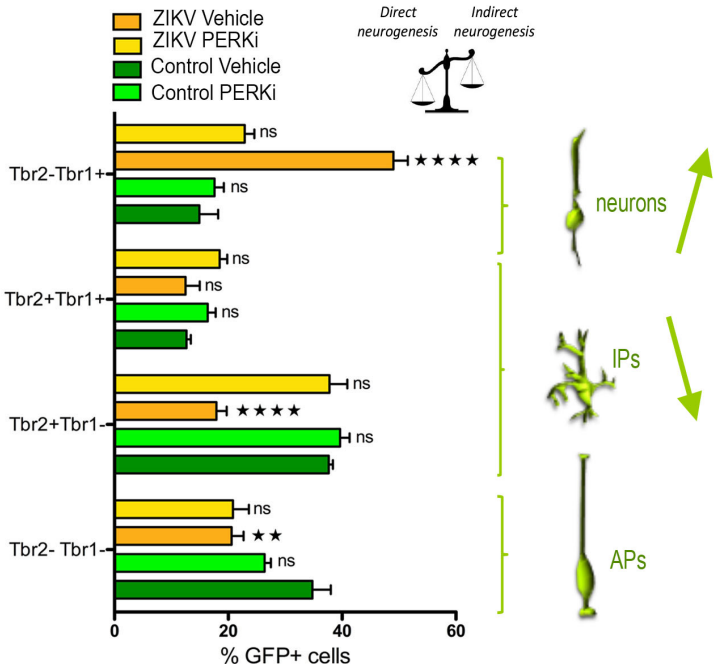
ICV injection of ZIKV in E12.5 mouse brains
In utero electroporation of GFP-expressing plasmids at day 13.5
Fate-mapping of APs and of their direct cell progenies at E14.5

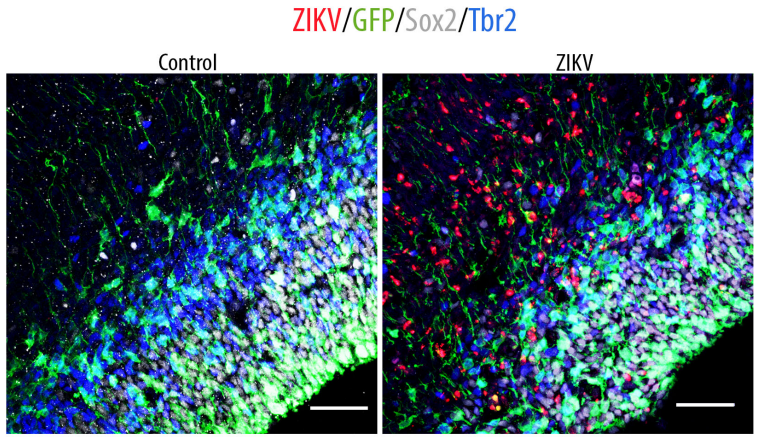
neurons	Tbr2-	Tbr1+
IPs	Tbr2+	Tbr1+
immature IPs	Tbr2+	Tbr1-
APs	Tbr2-	Tbr1-

ZIKV infection disrupts the UPR-dependent neurogenic balance









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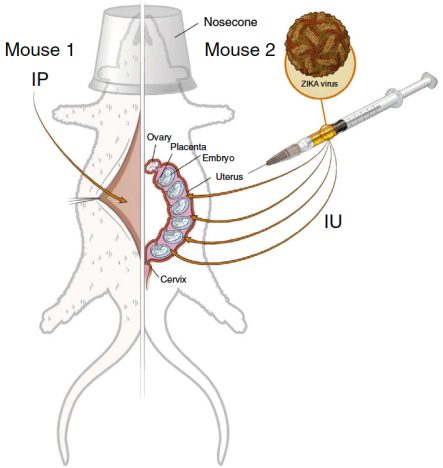
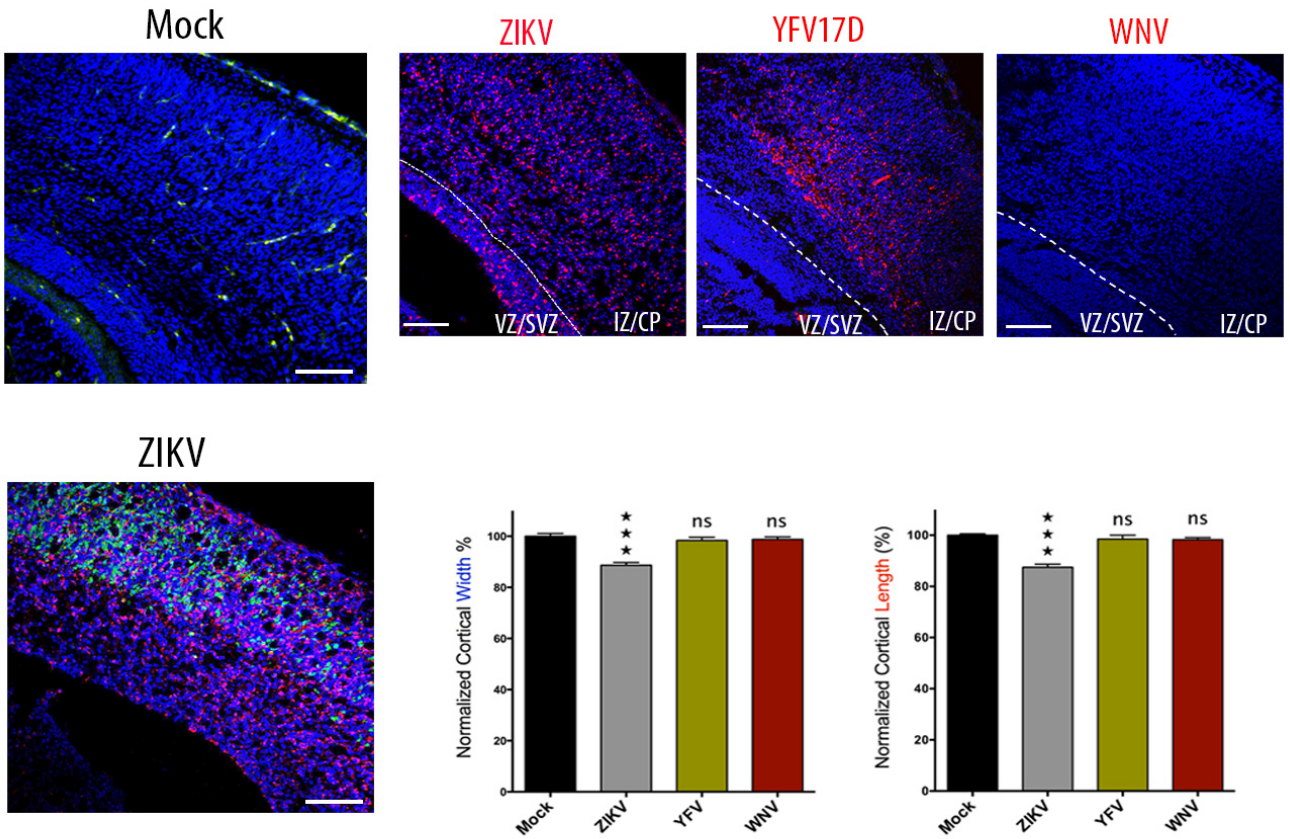
Specificity of ZIKA-induced microcephaly in mouse embryos (IPL)



Nature Commun (2017) Vermillion

ZIKV/ac-caspase 3/Dapi



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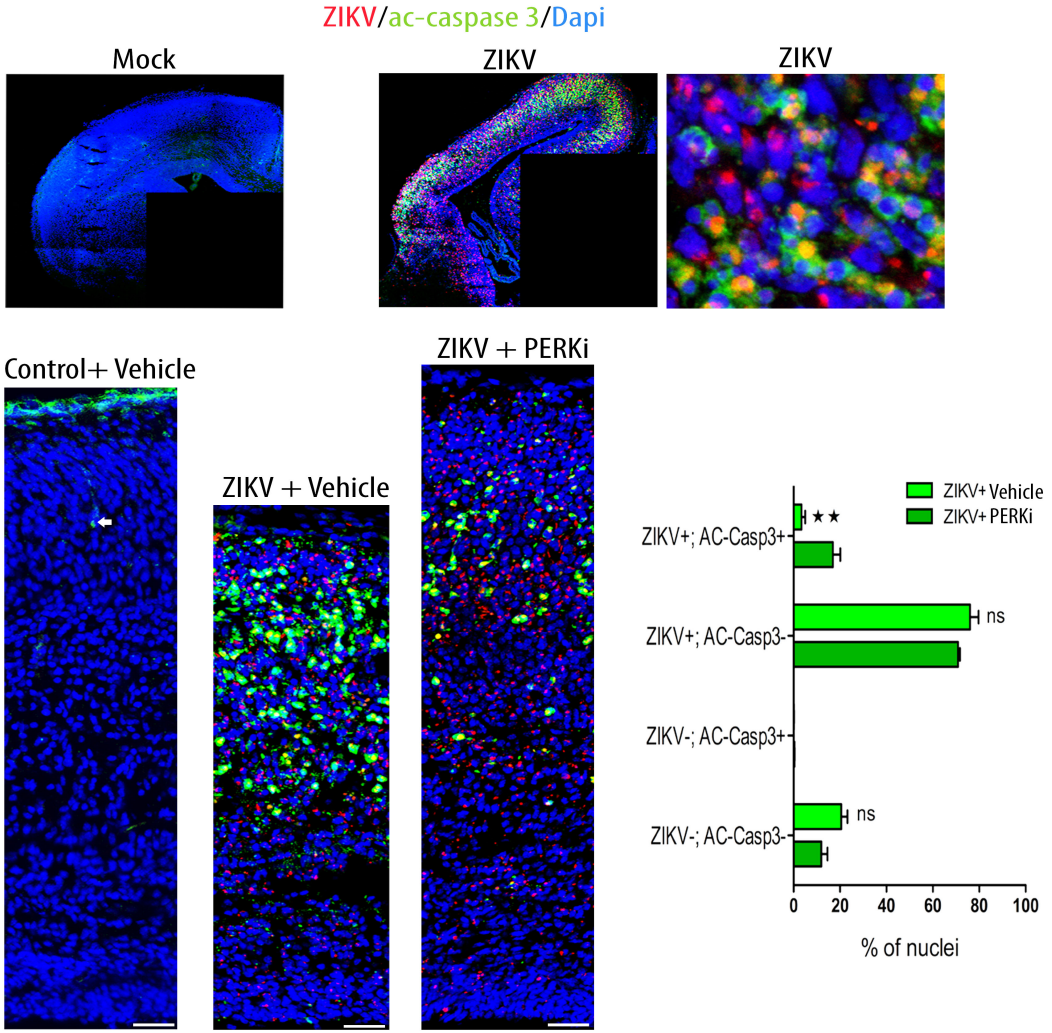
ZIKV promotes UPR-dependent apoptosis in newborn neurons



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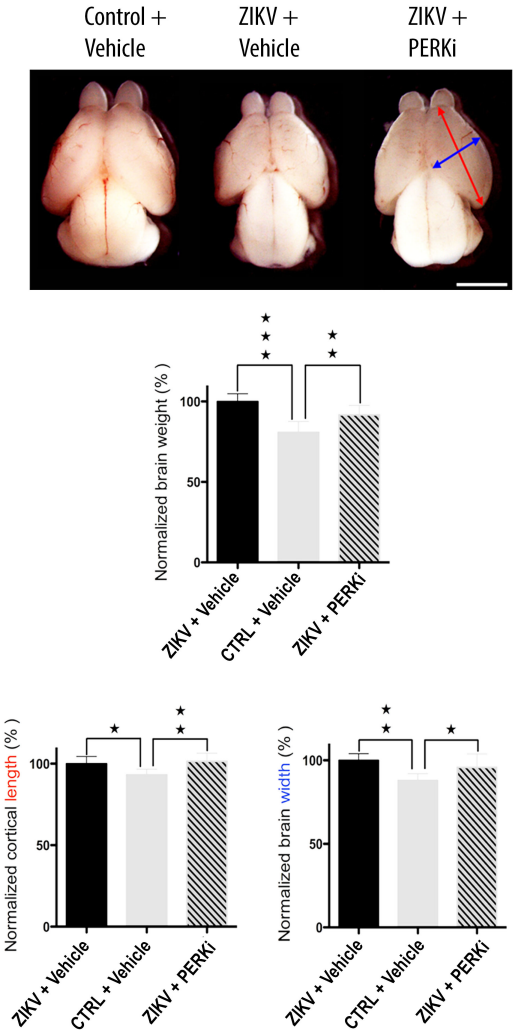
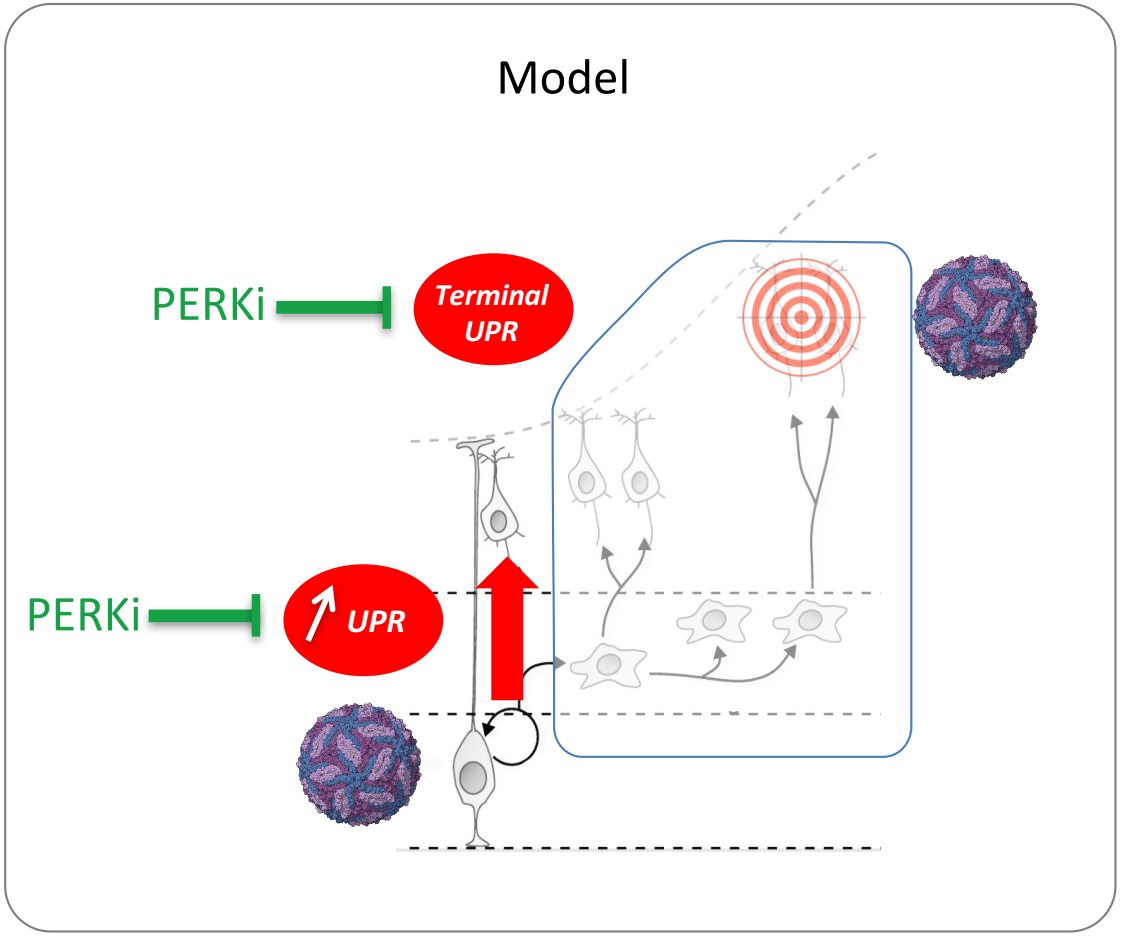
ZIKV promotes microcephaly by triggering ER stress





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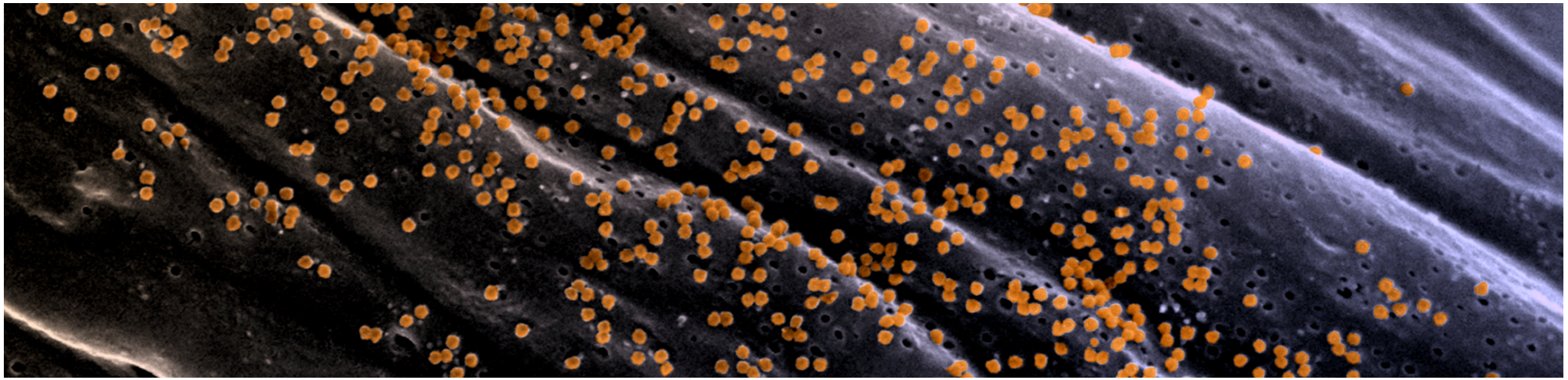

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