

New insights about Zika virus infection using iPS cells



@stevensrehen

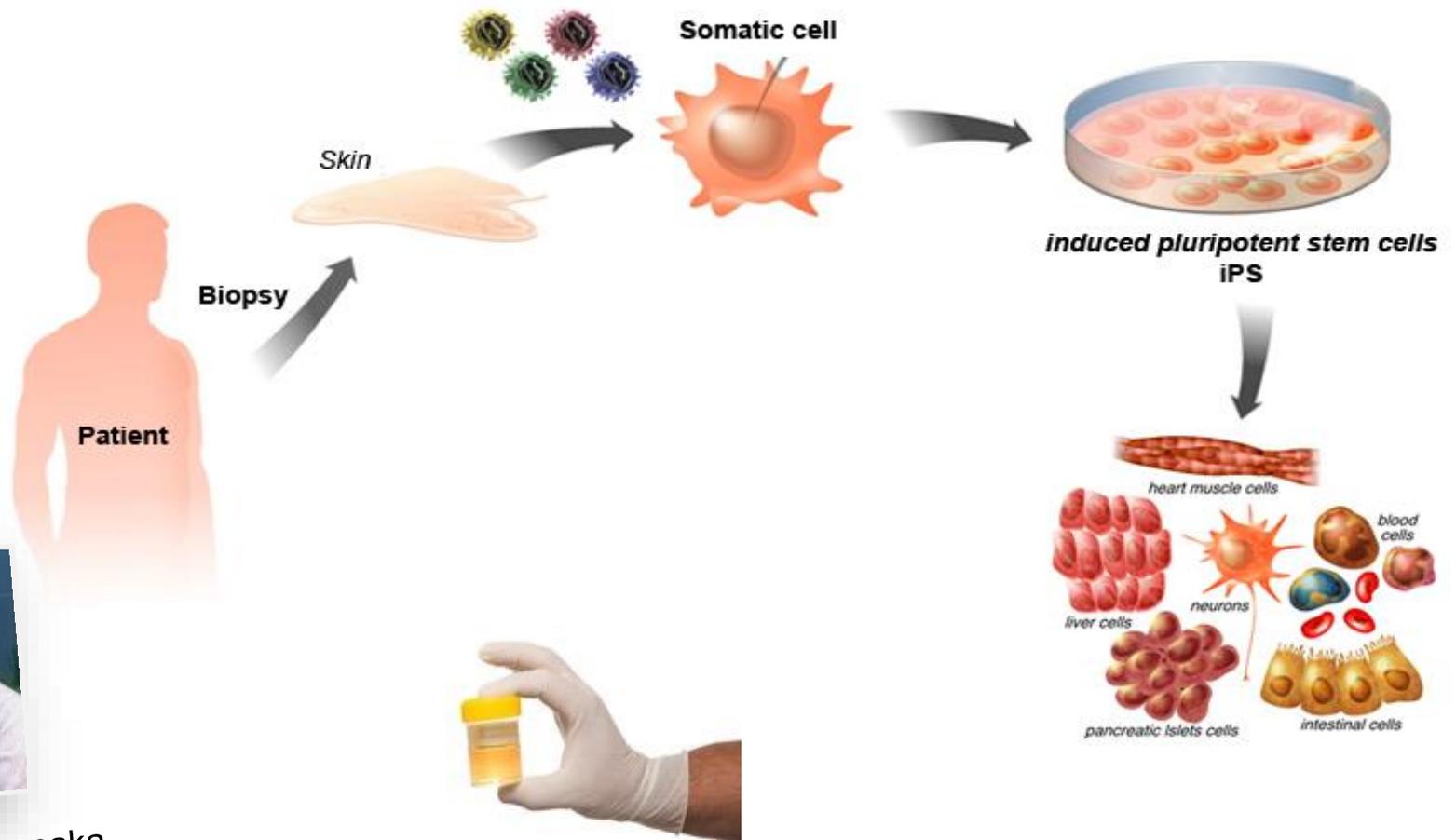
Rio de Janeiro, Brasil

INSTITUTO *D'OR*
PESQUISA E ENSINO



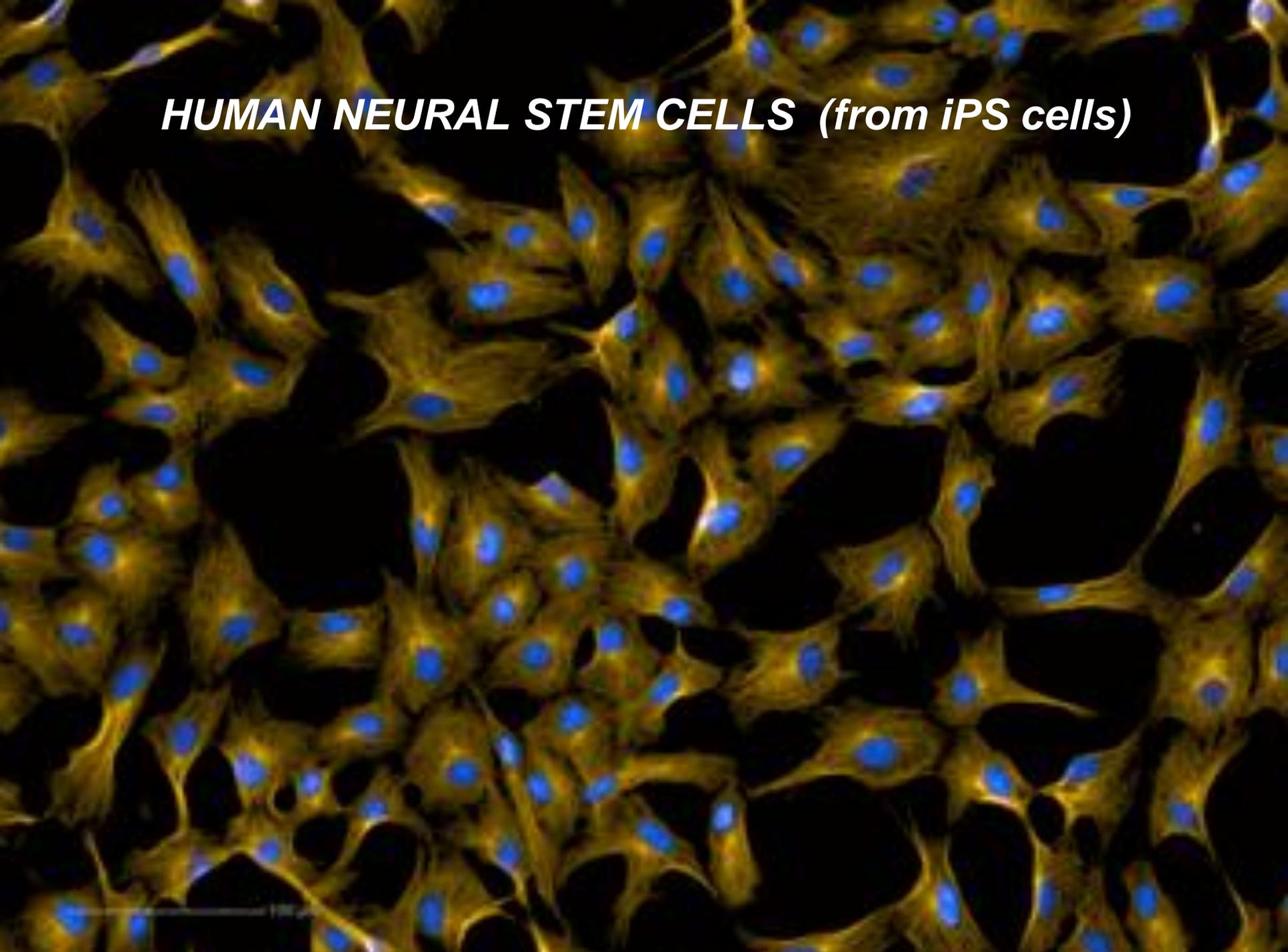
UFRJ

Human induced pluripotent stem cells



Shinya Yamanaka

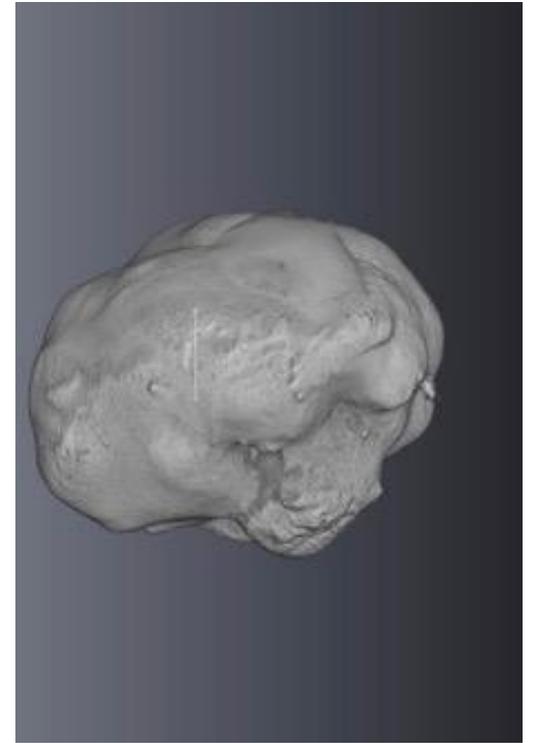
HUMAN NEURAL STEM CELLS (from iPS cells)



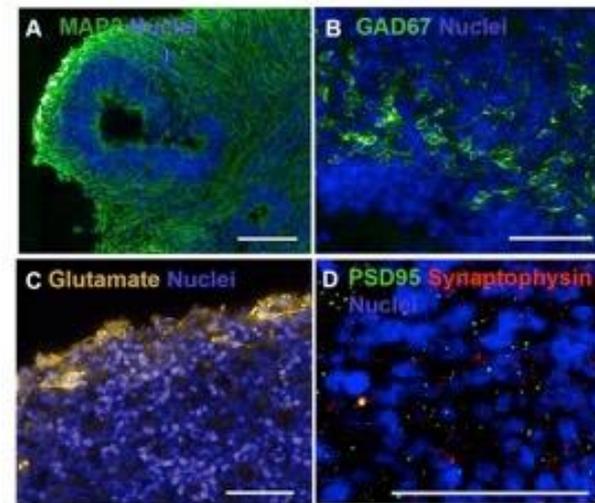
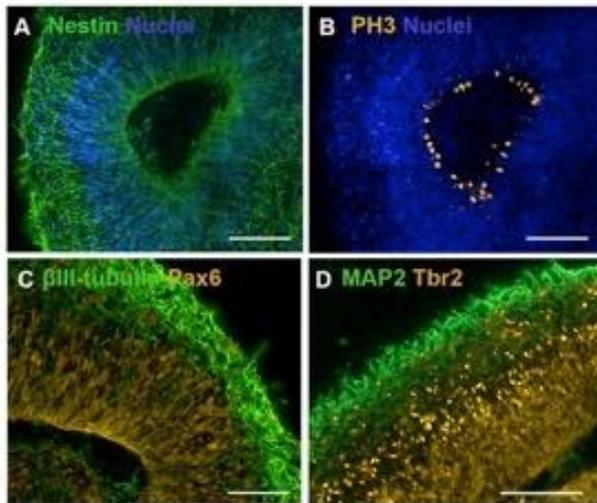
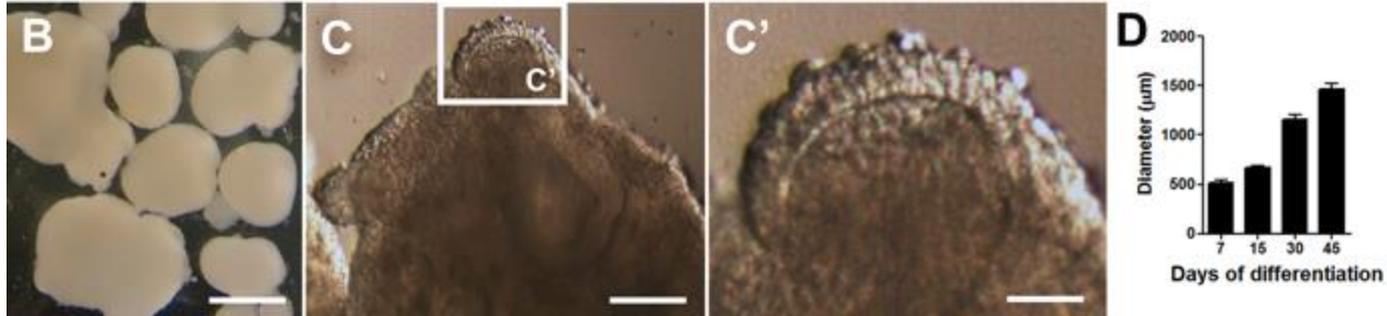
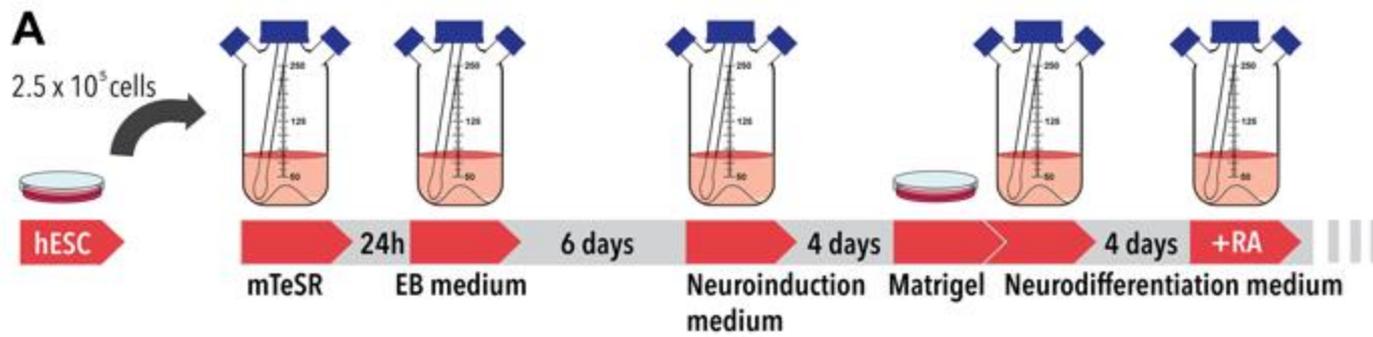
HUMAN BRAIN ORGANOIDS (MINIBRAINS)



Sartore *et al*, PeerJ (2017)

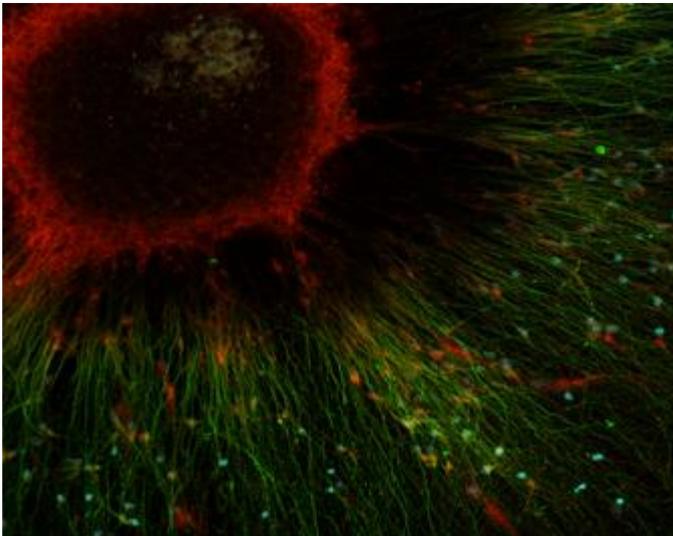
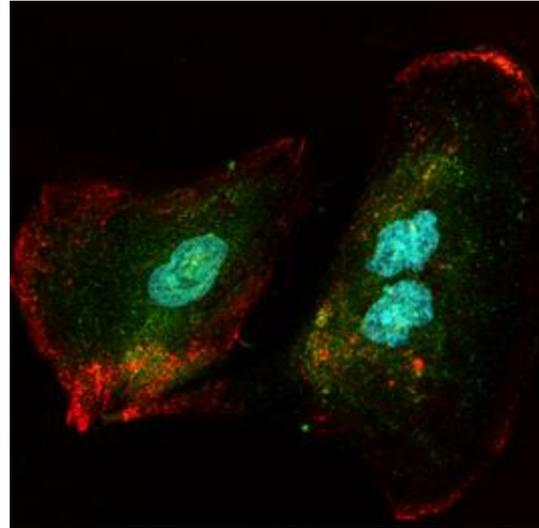
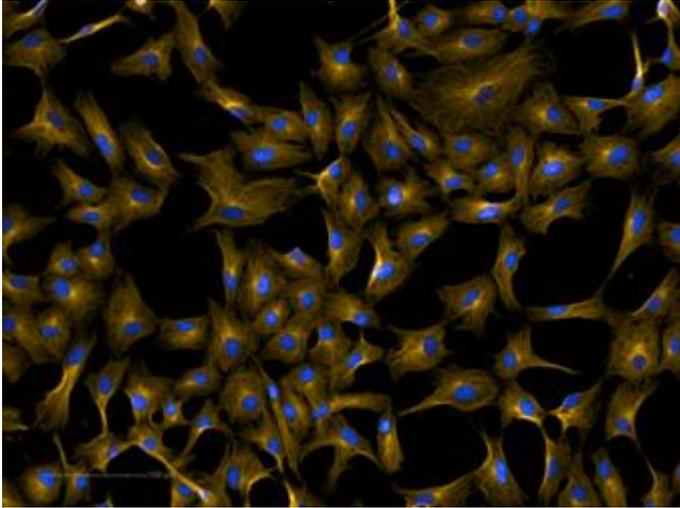


Sartore *et al*, PeerJ (2017)



Sartore *et al*, PeerJ (2017)

Cellular models to study brain development *in vitro*



| Nº | Linagem | Origem | Condição |
|----|---------|-------------|----------------------------|
| 1 | CF-2 | Fibroblasto | Controle |
| 2 | CF-1 | Fibroblasto | Controle |
| 3 | CF-3 | Fibroblasto | Controle |
| 4 | C8 | Urotélio | Controle |
| 5 | C-12 | Urotélio | Controle |
| 6 | C-13 | Urotélio | Controle |
| 7 | C-15 | Urotélio | Controle |
| 8 | C-16 | Urotélio | Controle |
| 9 | DRVT-1 | Urotélio | Síndrome de Dravet |
| 10 | DRVT-2 | Urotélio | Síndrome de Dravet |
| 11 | DRVT-3 | Urotélio | Síndrome de Dravet |
| 12 | ADHD-2 | Urotélio | Controle |
| 13 | ADHD-5 | Urotélio | TDAH |
| 14 | ADHD-24 | Urotélio | TDAH |
| 15 | C-1 | Urotélio | Controle |
| 16 | C-2 | Urotélio | Controle |
| 17 | ADHD-4 | Urotélio | TDAH |
| 18 | ADHD-10 | Urotélio | TDAH |
| 19 | DCC-4 | Urotélio | Controle |
| 20 | EZO-3 | Fibroblasto | Esquizofrenia |
| 21 | EZO-4 | Fibroblasto | Esquizofrenia |
| 22 | EZO-9 | Fibroblasto | Esquizofrenia |
| 23 | TOC-4 | Urotélio | TOC |
| 24 | CF-4 | Fibroblasto | Controle |
| 25 | CF-5 | Fibroblasto | Controle |
| 26 | CF-7 | Fibroblasto | Controle |
| 27 | ALZHp-1 | Fibroblasto | Alzheimer |
| 28 | DCC-1 | Urotélio | Controle |
| 29 | DCC-2 | Urotélio | Disgenesia do Corpo Caloso |
| 30 | C-3 | Urotélio | Controle |
| 31 | C-6 | Urotélio | Controle |
| 32 | C-18 | Urotélio | Controle |

Sendai based reprogramming of urine-derived epithelial cells and fibroblasts to study mental and neurological disorders



Stem Cell Research

Volume 17, Issue 1, July 2016, Pages 107–110



Lab Resource: Stem Cell Line

Generation of urine iPS cell line from a patient with obsessive-compulsive disorder using a non-integrative method

Jaroslav Sochacki^a, Sylvie Devaille^a, Marcelo Reis^a, Leonardo F. Fontenelle^{a, 4}, Stevens Rehen^{a, 5}, 
^a D'Or Institute for Research and Education (IDOR), Rua Diniz Cordeiro, 30, Rio de Janeiro 22228-1, Brazil
¹ Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), Avenida Carlos Chagas, 373, Rio de Janeiro 21941, Brazil
² Obsessive, Compulsive, and Anxiety Spectrum Program, Institute of Psychiatry of the Federal University of Rio de Janeiro, Brazil
³ Monash Institute of Clinical and Cognitive Neurosciences, Monash University, Melbourne, Australia



Stem Cell Research

Volume 17, Issue 1, July 2016, Pages 102–106



Lab Resource: Stem Cell Line

Generation of urine iPS cell lines from patients with Attention Deficit Hyperactivity Disorder (ADHD) using a non-integrative method

Jaroslav Sochacki^a, Sylvie Devaille^a, Marcelo Reis^a, Paulo Mattos^a, Stevens Rehen^{a, 5}, 
^a D'Or Institute for Research and Education (IDOR), Rua Diniz Cordeiro, 30, Rio de Janeiro 22228-1, Brazil
¹ Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), Avenida Carlos Chagas, 373, Rio de Janeiro 21941, Brazil



Stem Cell Research

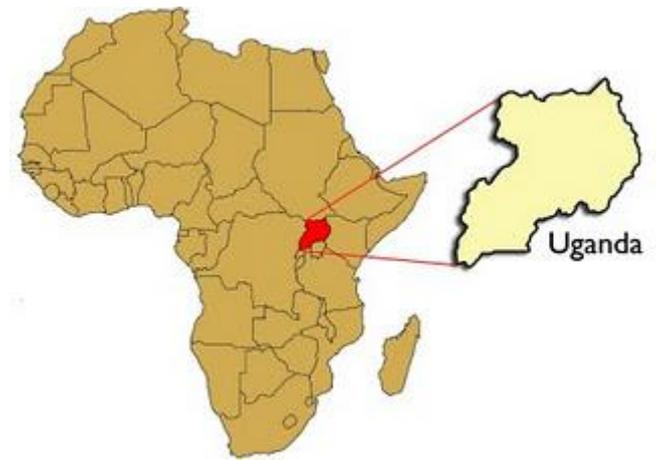
Volume 17, Issue 1, July 2016, Pages 97–101



Lab resource

Generation of iPS cell lines from schizophrenia patients using a non-integrative method

Jaroslav Sochacki^a, Sylvie Devaille^a, Marcelo Reis^a, Renata de Moraes Maciel^a, Bruna da Silveira Pauletti^a, Helena Bertani^{a, 2}, Paulo Silve Belmonte-de-Abreu^a, Stevens Rehen^{a, 5}, 
^a D'Or Institute for Research and Education (IDOR), Rua Diniz Cordeiro, 30, Rio de Janeiro 22228-1, Brazil
¹ Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), Avenida Carlos Chagas, 373, Rio de Janeiro 21941, Brazil
² Department of Psychiatry, Faculty of Medicine, São Paulo University (USP), Avenida Doutor Arnaldo, 455 – Cerqueira César, 01246-903 São Paulo, Brazil
³ Laboratory of Medical Investigation, Faculty of Medicine, São Paulo University (USP), Avenida Doutor Arnaldo, 455 – Cerqueira César, 01246-903 São Paulo, Brazil
⁴ Department of Psychiatry, Faculty of Medicine, Federal University of Rio Grande do Sul (UFRGS), Rua Ramiro Barcelos 2400 – Floresta, Porto Alegre 91003-002, Brazil



Zika Virus

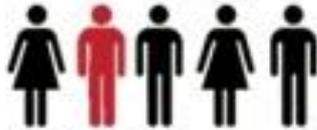


Transmitted by
mosquito bite

No treatment
or vaccine is
available



ABOUT
1 in 5 people



infected will become ill

SYMPTOMS:

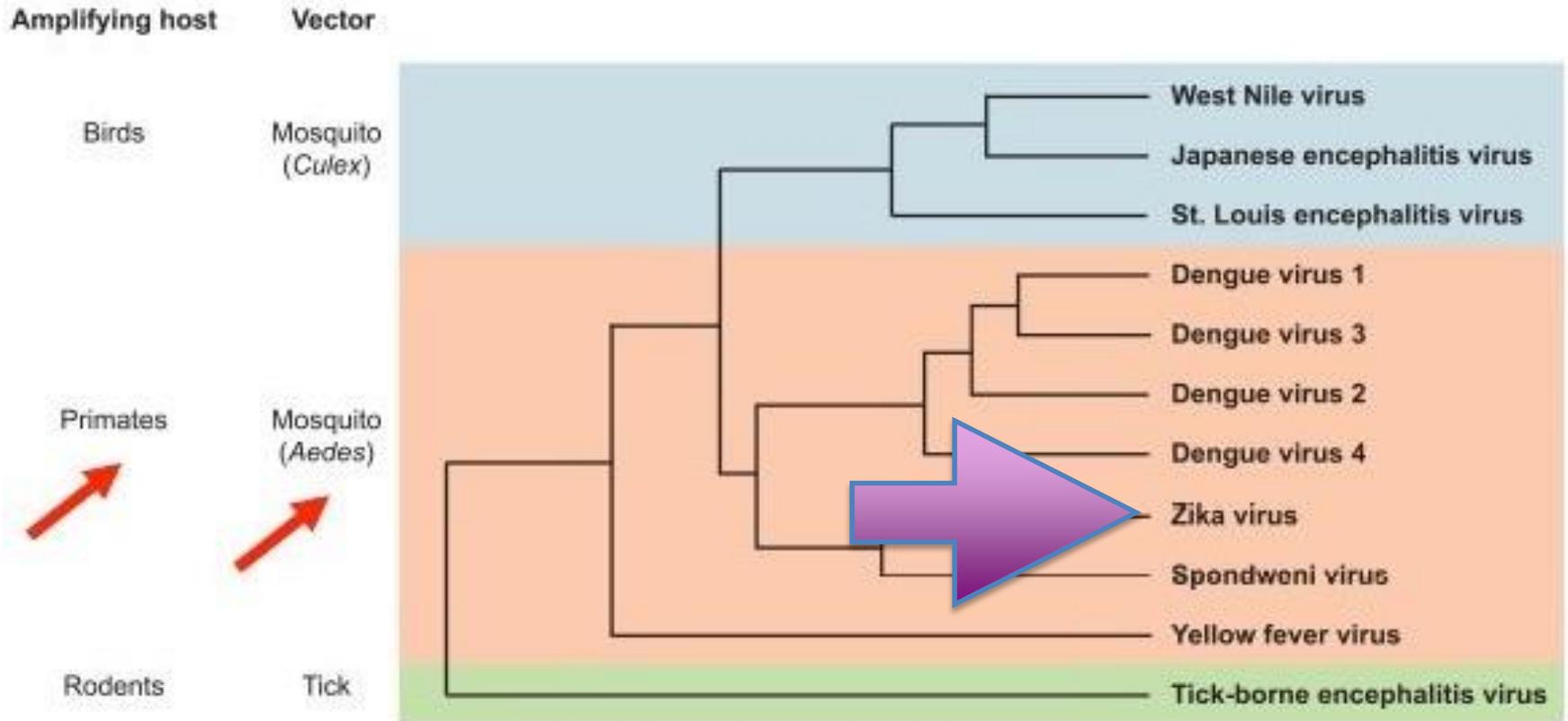
fever, rash,
joint pain
conjunctivitis
(red eyes)



SYMPTOMS
normally last
2-7 days

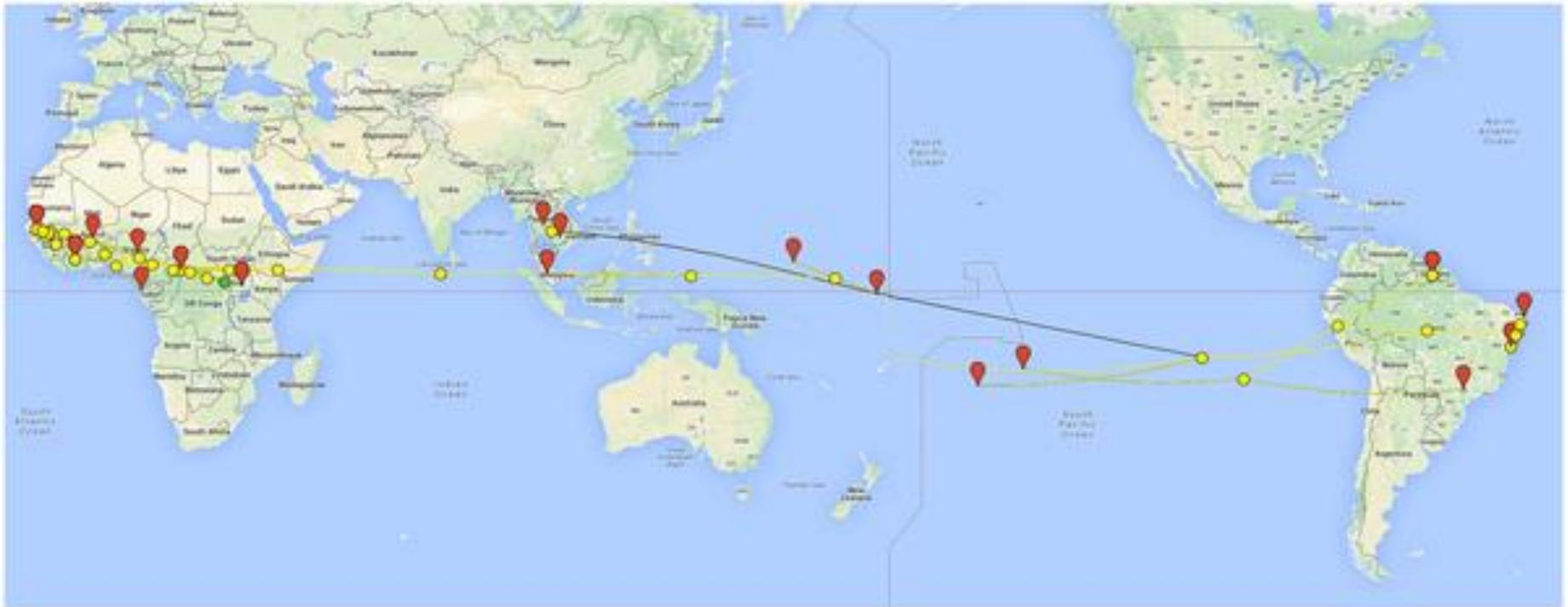
ILLNESS
is usually mild
and **death is rare**

Flaviviruses



Phylogeographic analyses illustrating the lineage of the Zika virus currently circulating in Brazil

Introduction of Zika virus in Brazil: May, 2013



Malone RW, PLoS Negl Trop Dis 2016



174,000 cases of zika in Brazil
11,059 in pregnant women

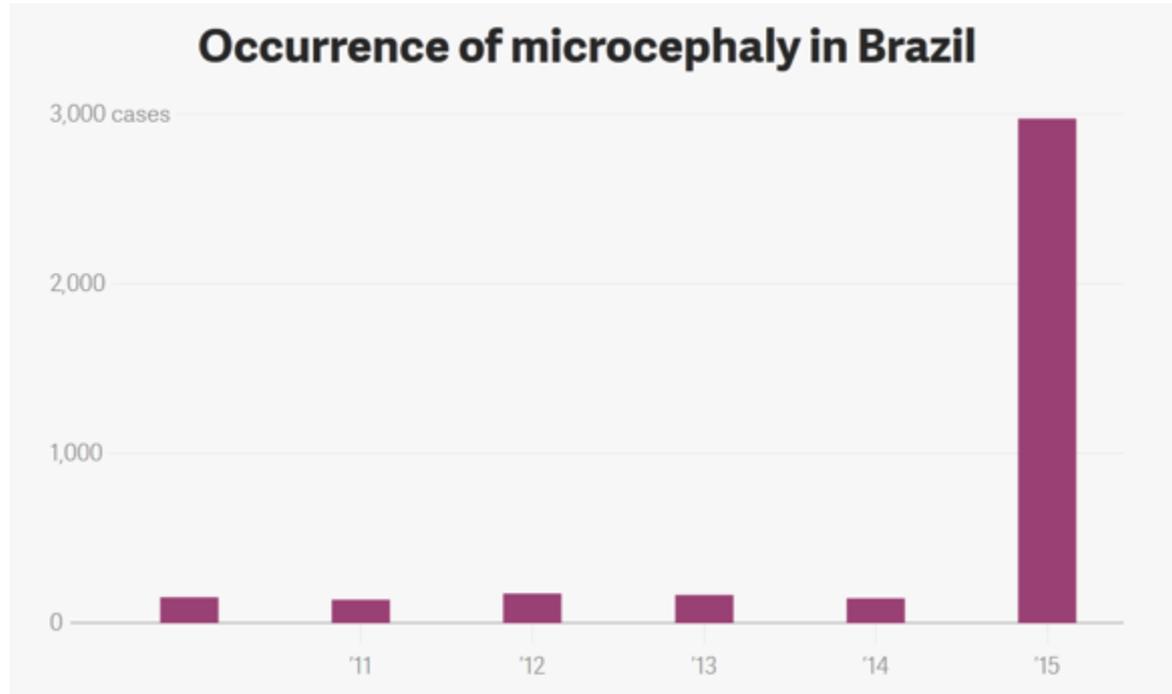
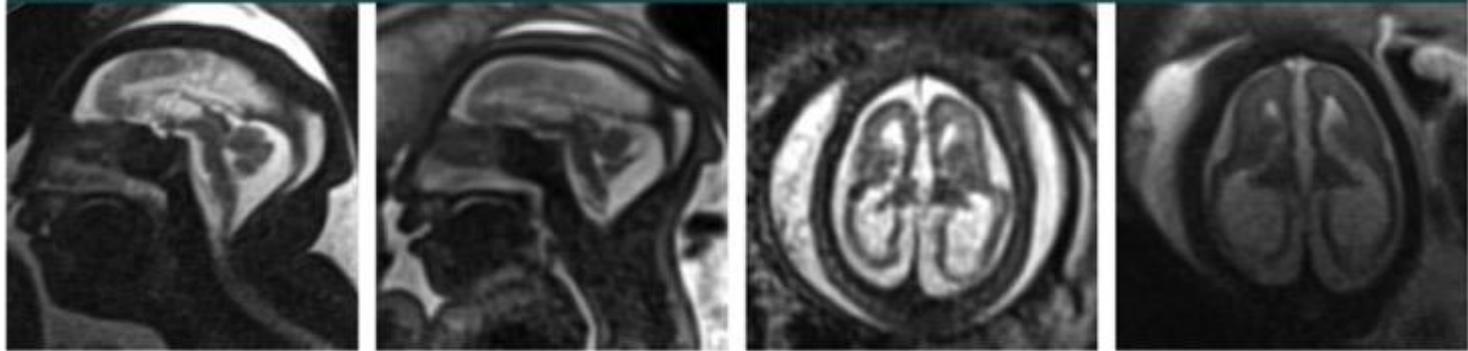


Figure 6

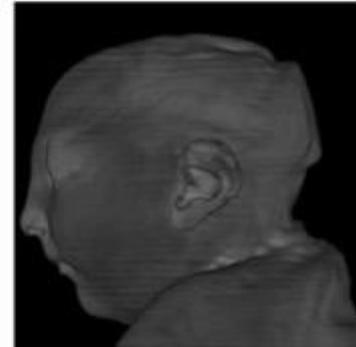
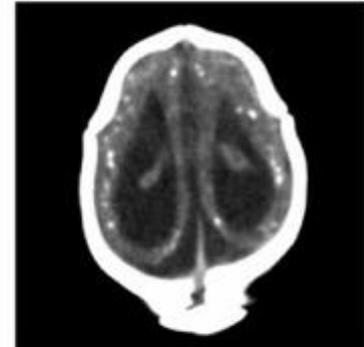
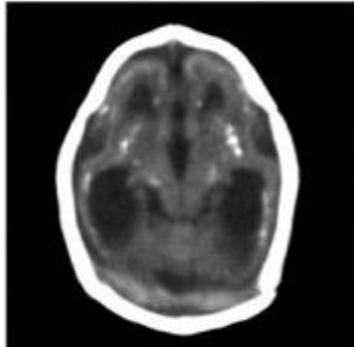


a.

b.

c.

d.

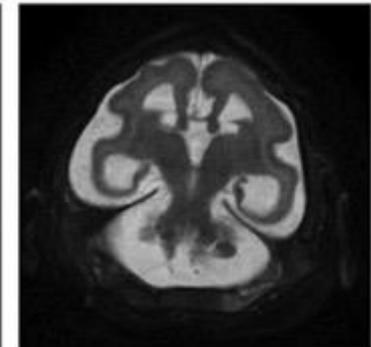
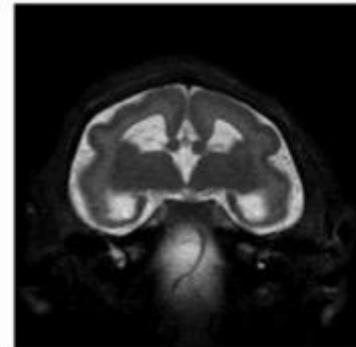
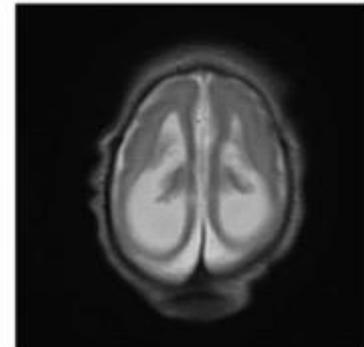
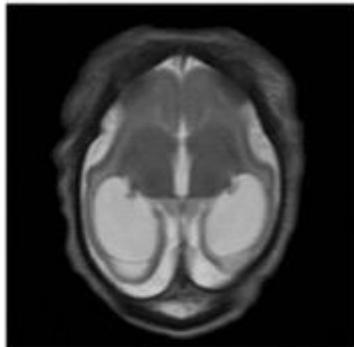


e.

f.

g.

h.



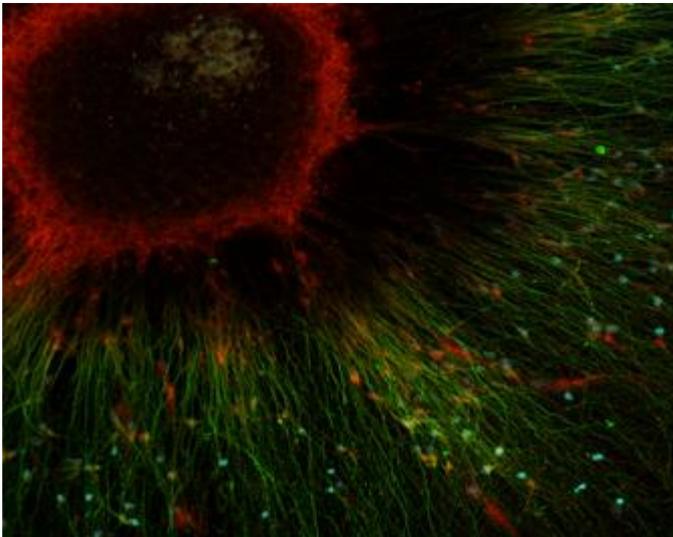
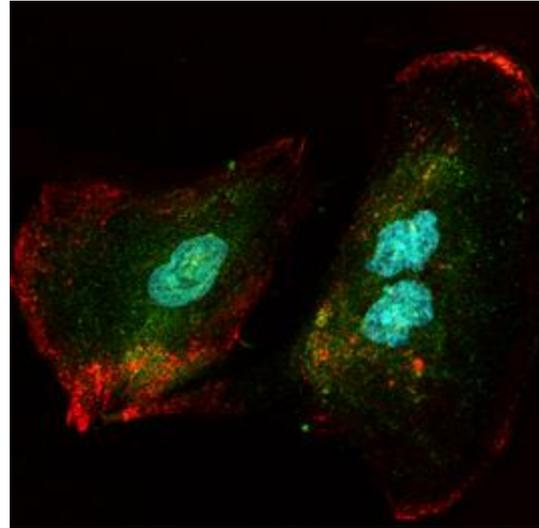
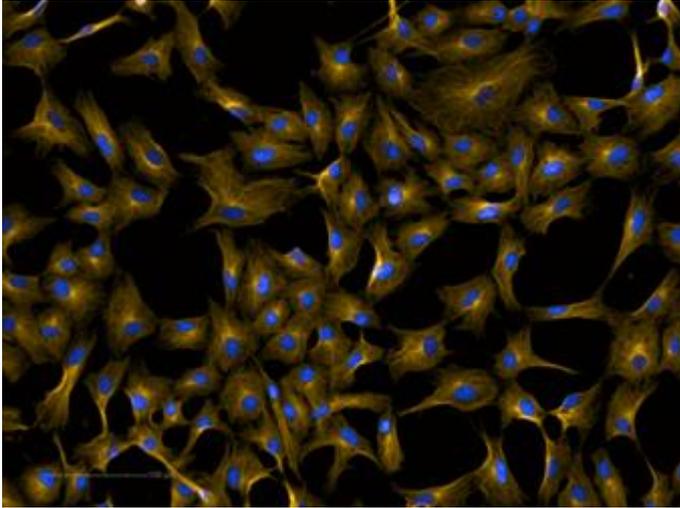
i.

j.

k.

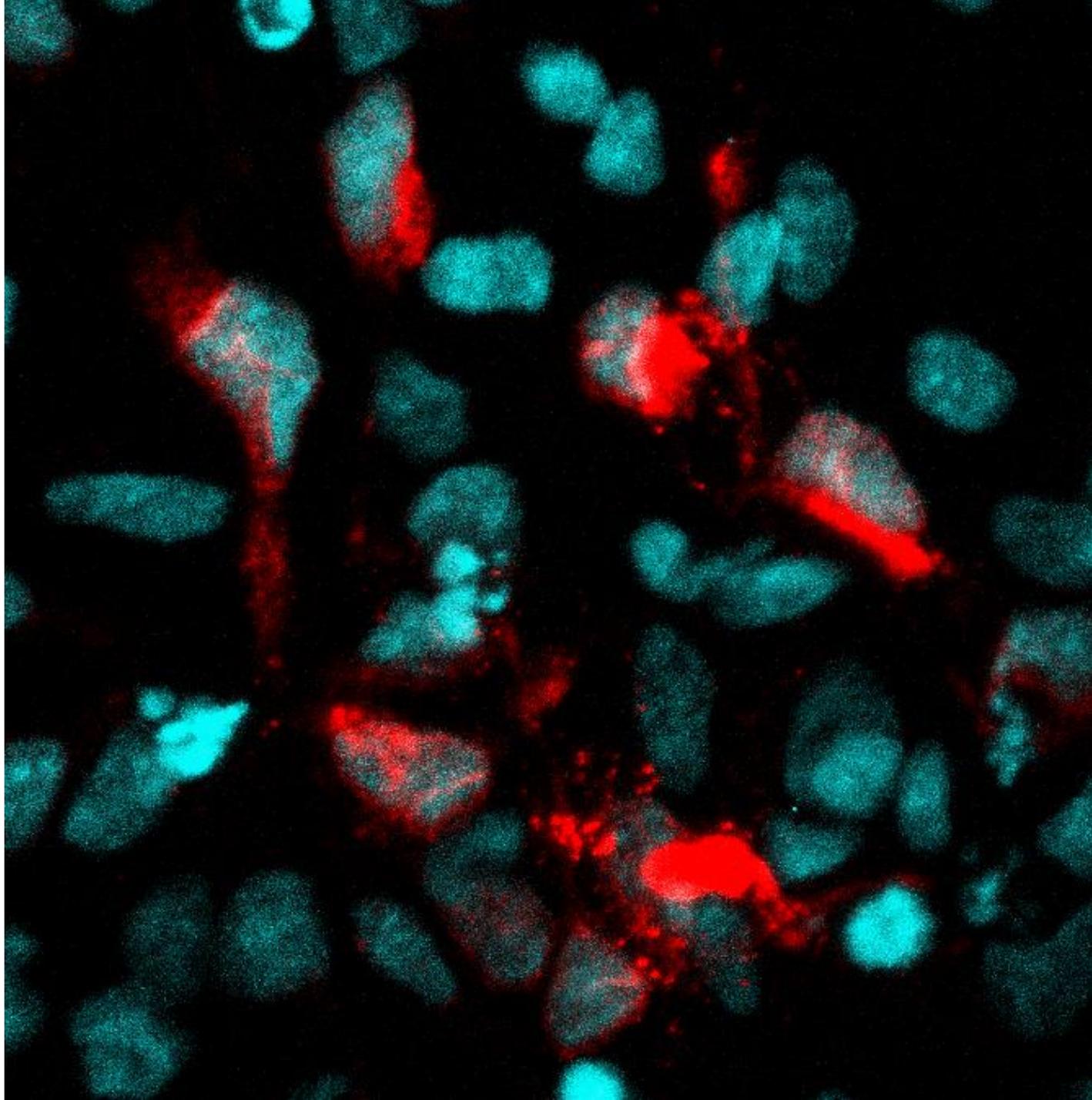
l.

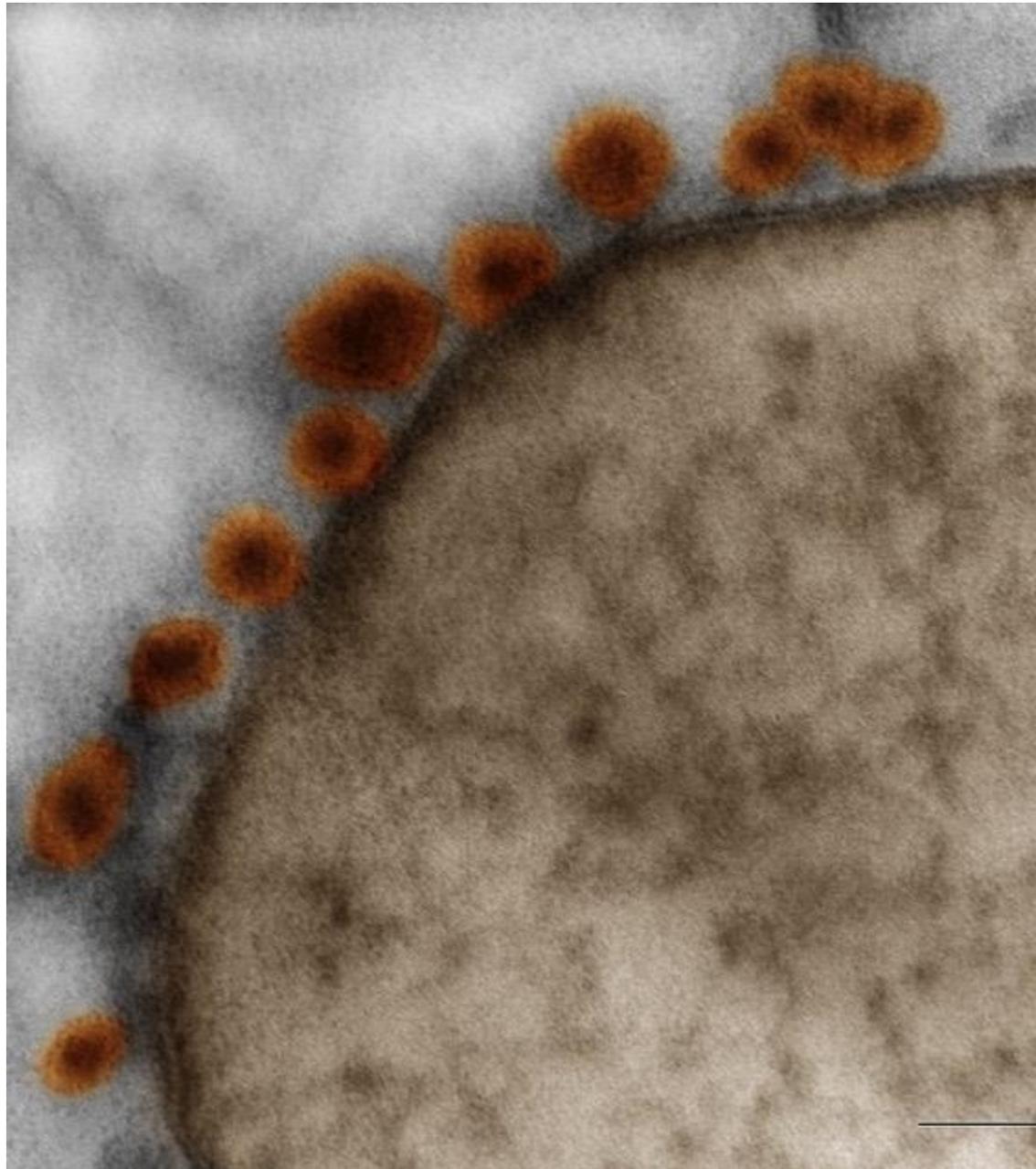
Cellular models to study brain development *in vitro*





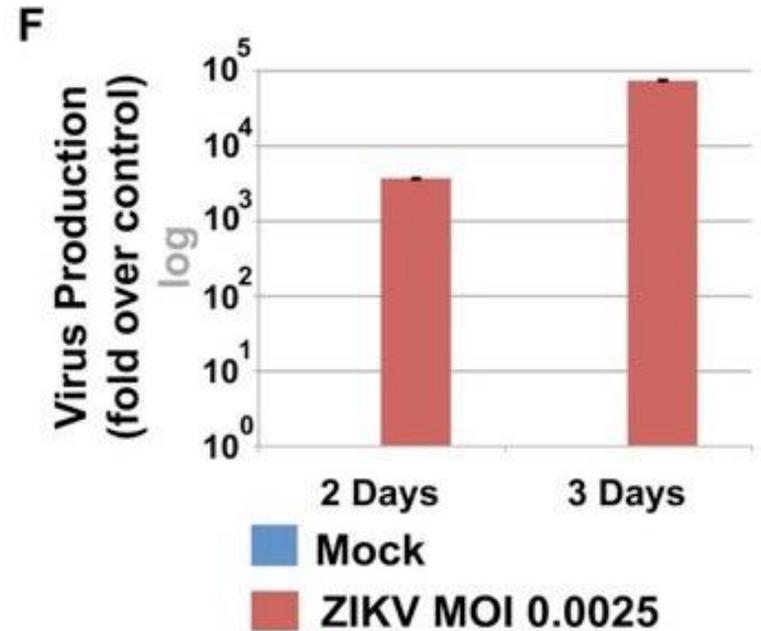
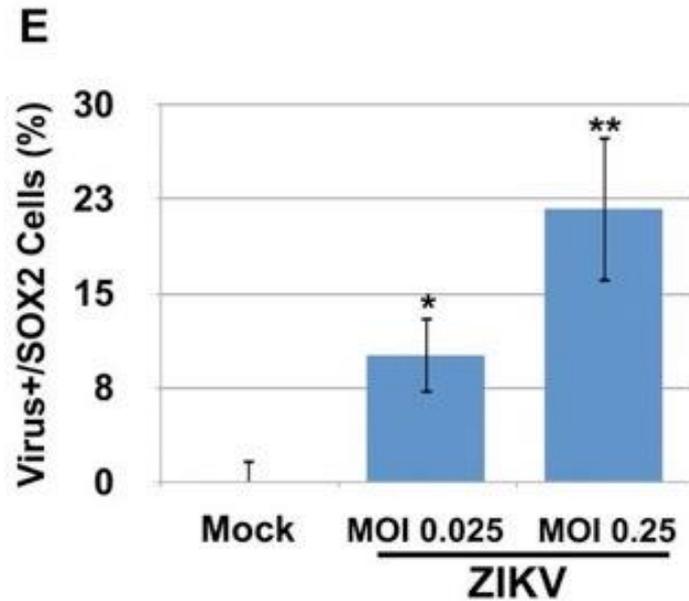
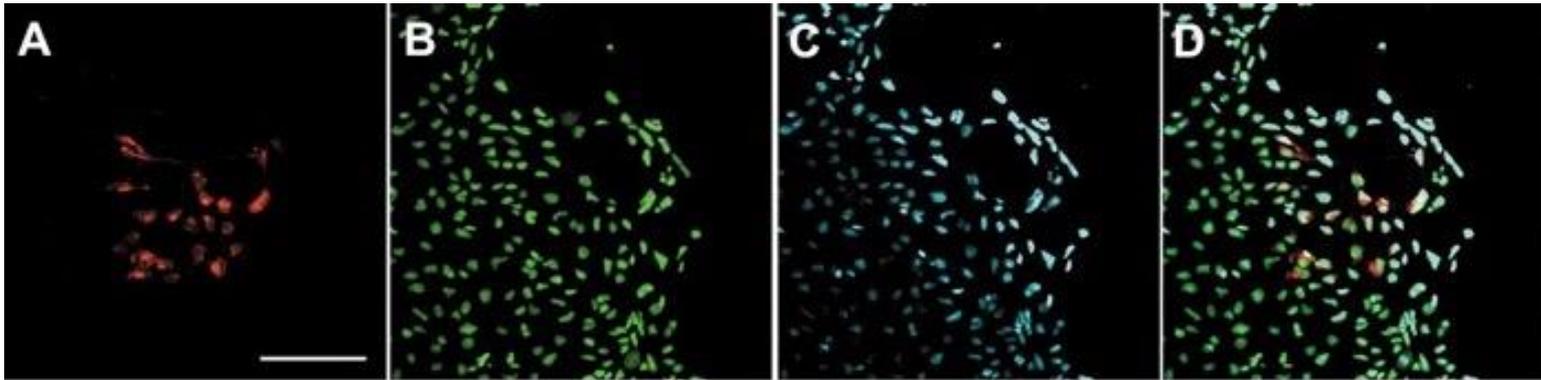
- 1) The consequences of ZIKV infection during neurogenesis and growth of human brain organoids
- 1) Insights about the molecular mechanisms of ZIKV infection
- 1) A platform based on iPS cell models to anticipate the consequences and to drug screen for TORCHES and other viruses

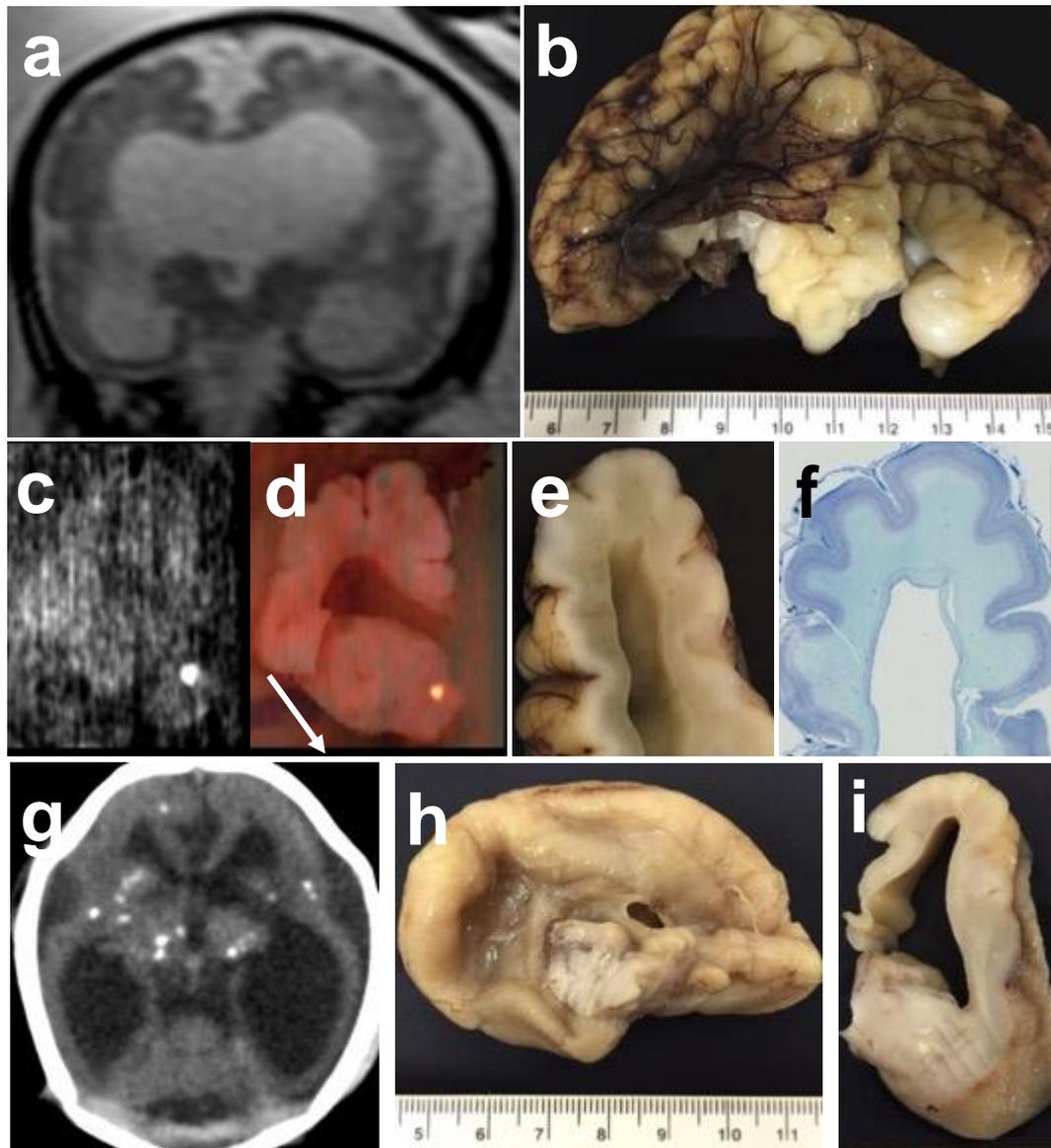




Garcez et al, Science (2016)

ZIKV infects human neural stem cells

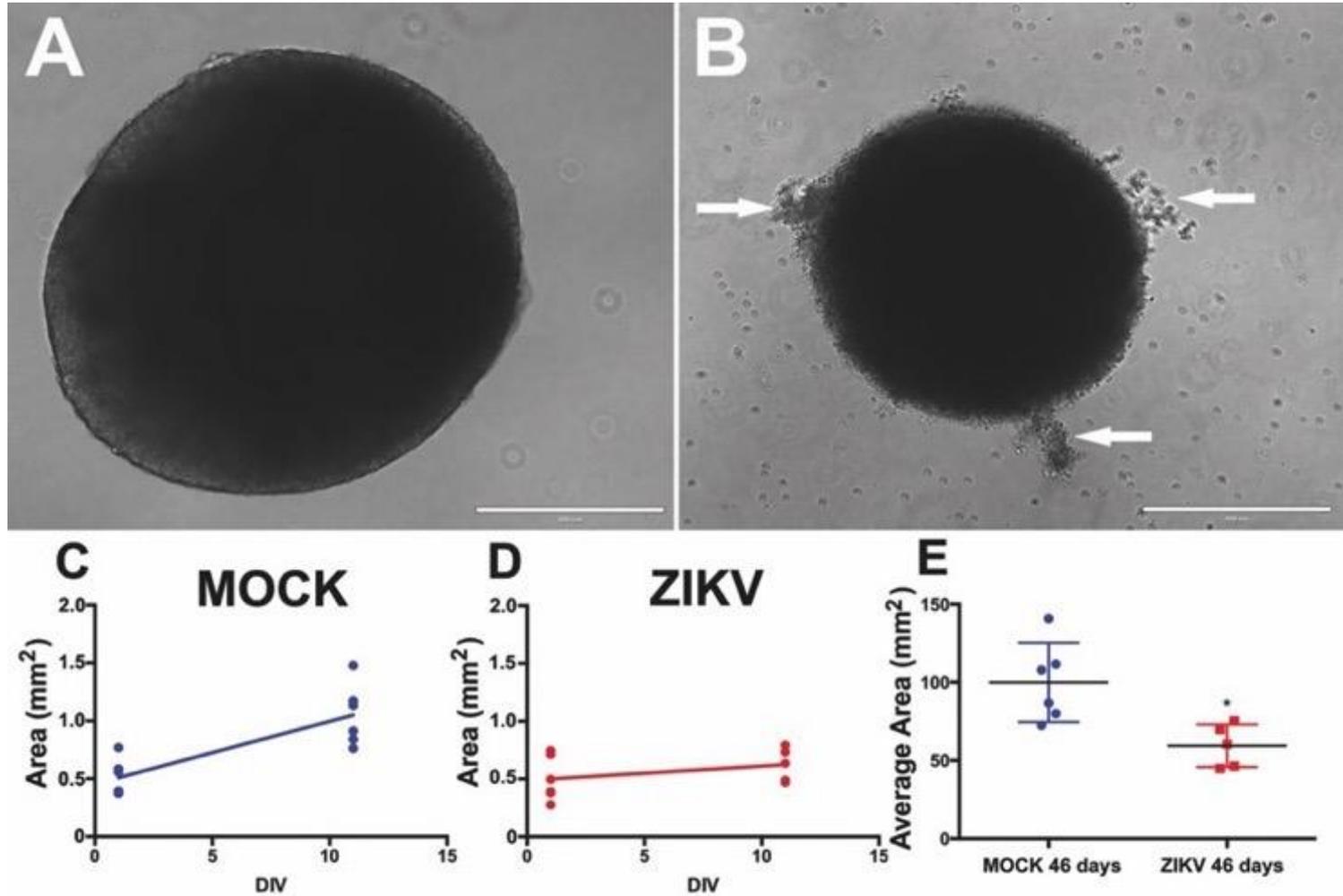






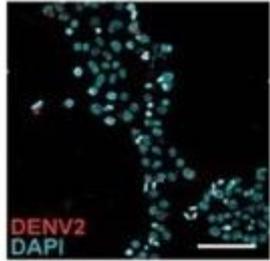
Sartore *et al*, PeerJ (2017)

ZIKV reduces the growth rate of human brain organoids

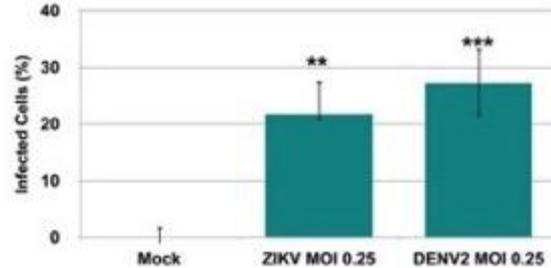


DENV2 infects human neural stem cells but does not impair growth in neurospheres and brain organoids

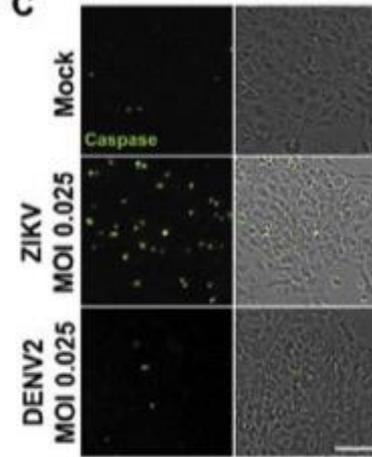
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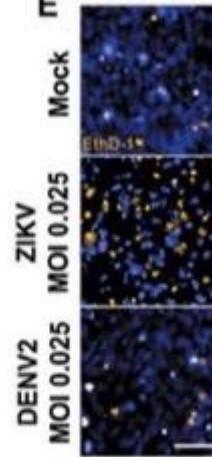
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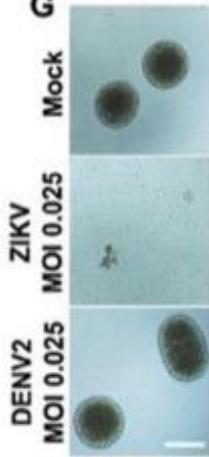
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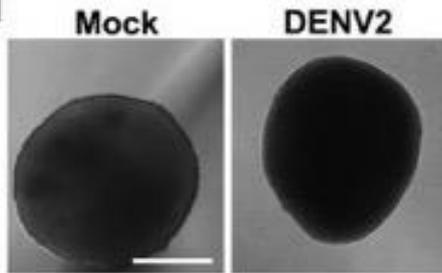
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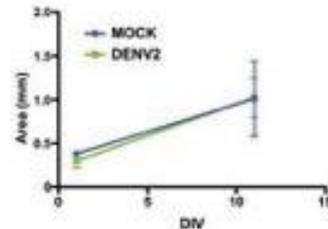
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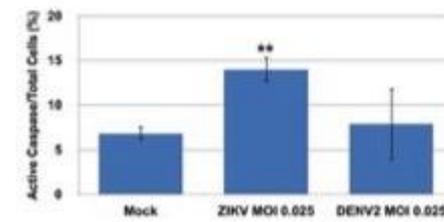
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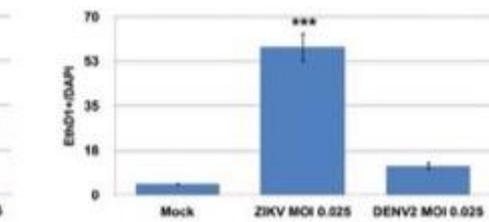
I



D



F



Cite as: Garcez *et al.*, *Science* 10.1126/science.aaf6116 (2016).

Zika virus impairs growth in human neurospheres and brain organoids

Patricia P. Garcez,^{1,2*} Erick Correia Loliola,^{3†} Rodrigo Madeiro da Costa,^{3†} Luiza M. Higa,^{3†} Pablo Trindade,^{3†} Rodrigo Delvecchio,³ Juliana Minardi Nascimento,^{2,4} Rodrigo Brindeiro,³ Amílcar Tanuri,³ Stevens K. Rehen^{3,1*}

Cell 

Volume 165, Issue 5, 19 May 2016, Pages 1238–1254

Resource
Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure

Xuyu Qian^{1,2,10}, Ha Nam Nguyen^{1,3,4,10}, Mingqi M. Song^{1,11}, Christopher Hadjilov^{1,11}, Sarah C. Ogden¹¹, Christy Hammack¹¹, Bing Yao¹², Gregory R. Hamersky¹, Fadi Jacob¹, Chun Zhong^{1,1}, Kijun Yoon^{1,1}, William Jeang^{1,14}, Li Lin¹⁵, Yujing Li¹⁵, Jai Thakor¹, Daniel A. Berg¹, Ce Zhang^{1,1}, Eunchal Kang^{1,1}, Michael Chickering¹, David Nauen^{1,1}, Cheng-Ying Ho^{16,18}, Zhenxing Wen^{1,1}, Kimberly M. Christian^{1,1}, Pei-Yong Shi¹⁷, Brady J. Maher^{1,1}, Hao Wu¹⁹, Peng Jin¹⁹, Hengli Tang¹⁹, Hongjun Song^{1,3,4,9}   Guo-Il Ming^{1,3,4,7,8}  

nature International weekly journal of science

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Advance Online Publication > Letters > Article

NATURE | LETTER *near-final version*  

The Brazilian Zika virus strain causes birth defects in experimental models

Fernanda R. Cugola, Isabella R. Fernandes, Fabiele B. Russo, Beatriz C. Freitas, João L. M. Dias, Kátia P. Guimarães, Cecilia Benazzato, Nathalia Almeida, Graciela C. Pignatari, Sarah Romero, Carolina M. Polonio, Isabela Cunha, Carla L. Freitas, Wesley N. Brandão, Cristiano Rossato, David G. Andrade, Daniele de P. Faria, Alexandre T. Garcez, Carlos A. Buchpiguel, Carla T. Brazoni, Erica Mendes, Amadou A. Sali, Paolo M. de A. Zanotto, Jean Pierre S. Peron, Alysson R. Monteiro & et al.

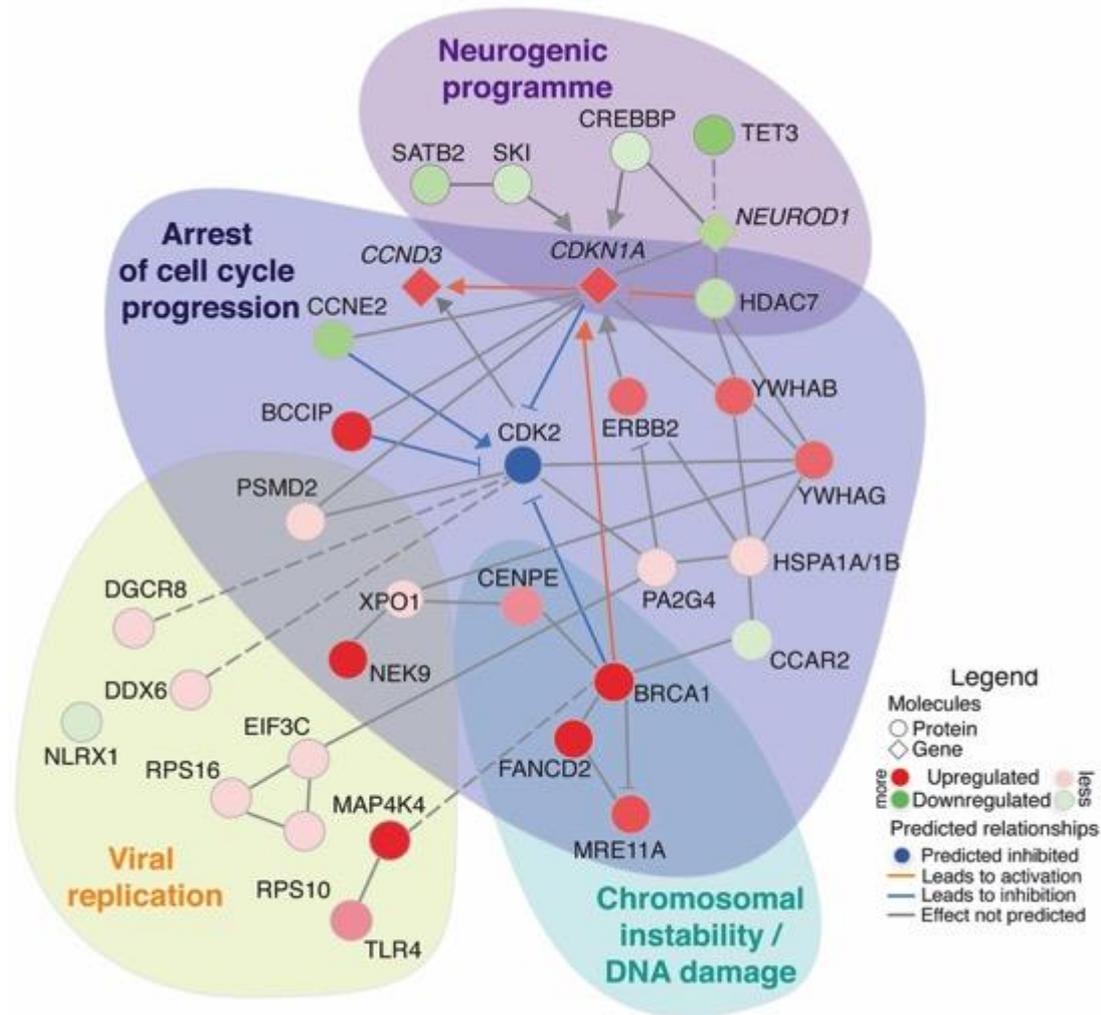
Cell Stem Cell 

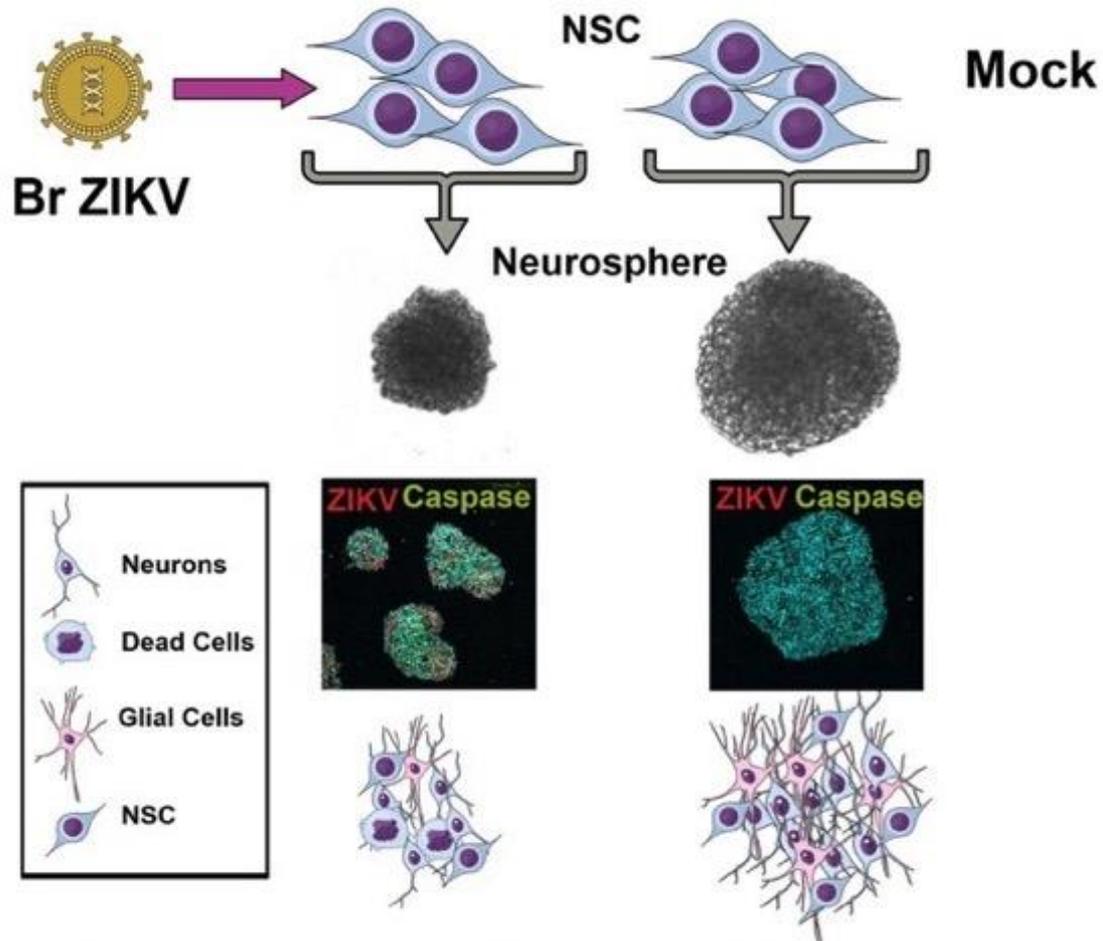
Available online 6 May 2016
 In Press, Corrected Proof — Note to users

Short Article
Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3

Jason Deng^{1,2,3}, Shashi Kant Tiwari⁴, Gianluigi Lichnerci¹, Yue Qin¹, Venna S. Patel¹, Alexey M. Eroshkin¹, Tariq M. Rana^{1,5}  

Network interactive representation of molecular relationship among regulated molecules in ZIKV-infected neurospheres





| | ZIKV | Mock |
|--------------------------|-------|-------|
| Viral Infection | Red | Green |
| DNA Damage | Red | Green |
| Cell Cycle Progression | Green | Red |
| Neuronal Differentiation | Green | Red |



Article | [OPEN](#)

Zika virus disrupts molecular fingerprinting of human neurospheres

Patricia P. Garcez , Juliana Minardi Nascimento, Janaina Mota de Vasconcelos, Rodrigo Madeiro da Costa, Rodrigo Delvecchio, Pablo Trindade, Erick Correia Loiola, Luiza M. Higa, Juliana S. Cassoli, Gabriela Vitória, Patricia C. Sequeira, Jaroslaw Sochacki, [Renato S. Aguiar](#), Hellen Thais Fuzii, Ana M. Bispo de Filippis, João Lídio da Silva Gonçalves Vianez Júnior, Amilcar Tanuri, Daniel Martins-de-Souza  & Stevens K. Rehen 

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0

Kill or be killed: The epic battle between Zika virus and cells revealed



Kwanghun Chung

[+ See all authors and affiliations](#)



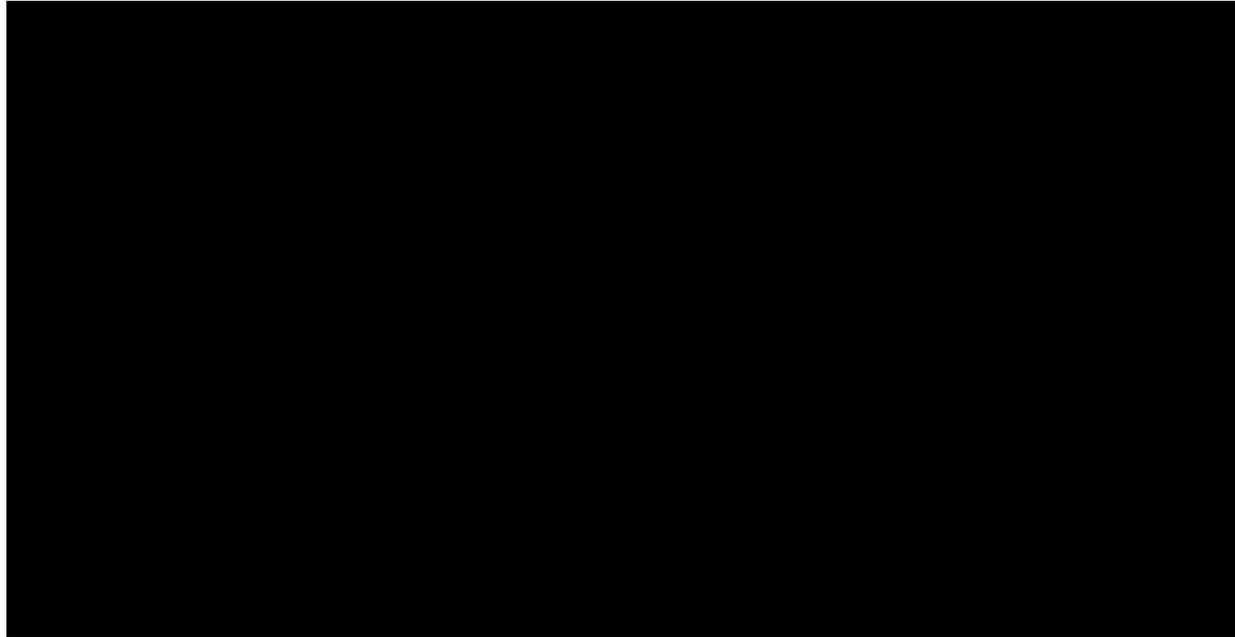
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Science Translational Medicine 08 Mar 2017:
Vol. 9, Issue 380, eaam9859
DOI: 10.1126/scitranslmed.aam9859

“This suggests that cell death in both radial glia-like cells, which are capable of generating neurons and nonneuronal cells, as well as neural stem cells might be associated with damaged DNA.”



Drug screen to identify leads for Zika virus



Article

Chloroquine, an Endocytosis Blocking Agent, Inhibits Zika Virus Infection in Different Cell Models

**Rodrigo Delvecchio ^{1,†}, Luiza M. Higa ^{1,†}, Paula Pezzuto ^{1,†}, Ana Luiza Valadão ^{1,†},
Patrícia P. Garcez ^{2,3}, Fábio L. Monteiro ¹, Erick C. Loiola ³, André A. Dias ⁴, Fábio J. M. Silva ²,
Matthew T. Aliota ⁵, Elizabeth A. Caine ⁵, Jorge E. Osorio ⁵, Maria Bellio ⁴, David H. O'Connor ⁶,
Stevens Rehen ^{2,3}, Renato Santana de Aguiar ¹, Andrea Savarino ⁷, Loraine Campanati ^{2,*}
and Amilcar Tanuri ^{1,*}**



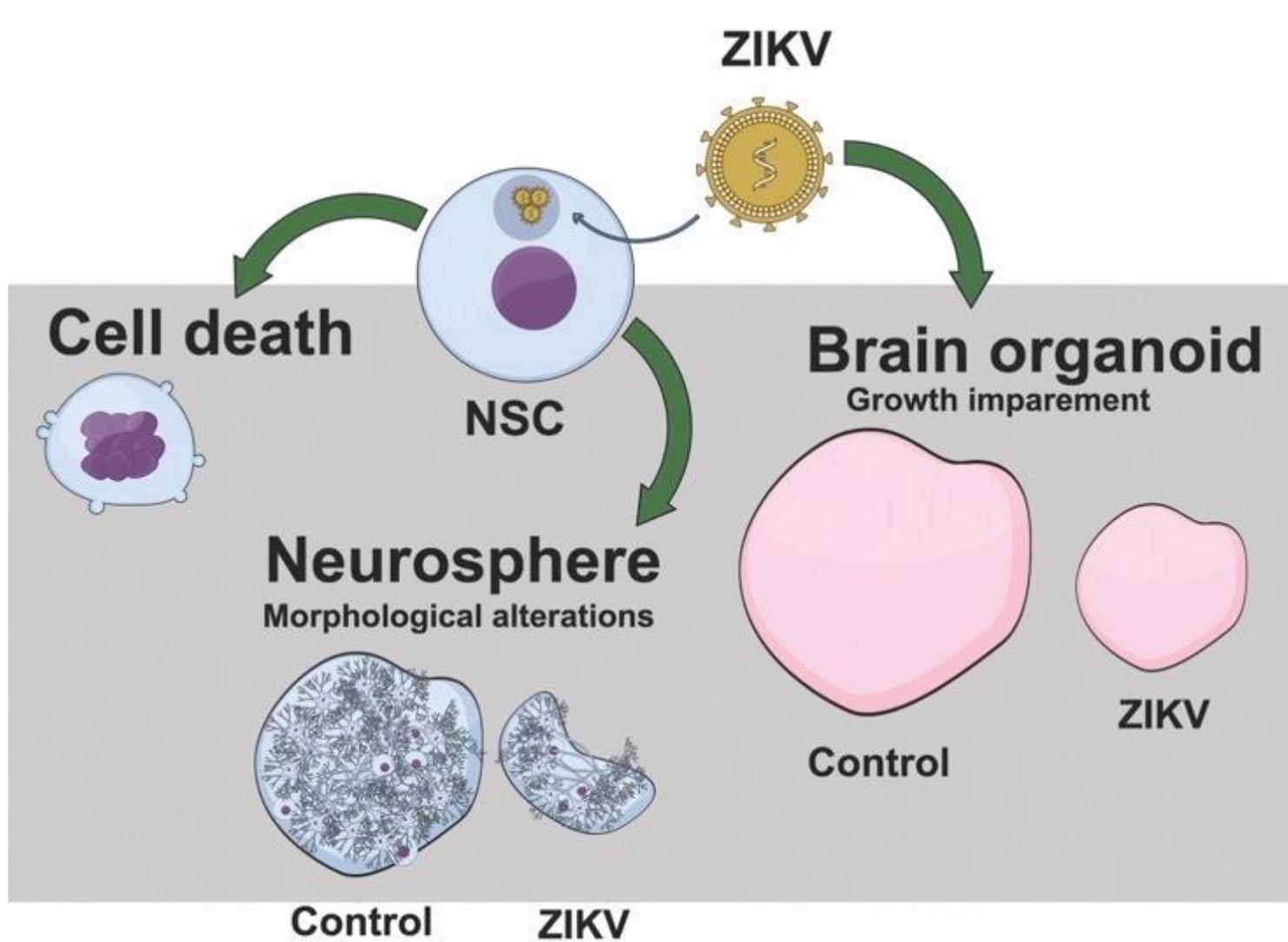
Altmetric: 108 Views: 4,950

[More detail >>](#)

Article | [OPEN](#)

The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication

Carolina Q. Sacramento, Gabrielle R. de Melo [...] Thiago Moreno L. Souza



The spectrum of neuropathological changes associated with congenital Zika virus infection

Leila Chimelli¹ · Adriana S. O. Melo^{2,3} · Elyzabeth Avvad-Portari⁴ · Clayton A. Wiley⁵ · Aline H. S. Camacho¹ · Vania S. Lopes⁶ · Heloisa N. Machado⁴ · Cecília V. Andrade⁶ · Dione C. A. Dock⁴ · Maria Elisabeth Moreira⁴ · Fernanda Tovar-Moll⁷ · Patrícia S. Oliveira-Szejnfeld⁸ · Angela C. G. Carvalho⁶ · Odile N. Ugarte⁶ · Alba G. M. Batista³ · Melania M. R. Amorim² · Fabiana O. Melo² · Thales A. Ferreira² · Jacqueline R. L. Marinho³ · Girlene S. Azevedo² · Jeime I. B. F. Leal³ · Rodrigo F. Madeiro da Costa⁷ · Stevens Rehen⁷ · Monica B. Arruda⁹ · Rodrigo M. Brindeiro⁹ · Rodrigo Delvecchio⁹ · Renato S. Aguiar⁹ · Amílcar Tanuri⁹

Received: 3 December 2016 / Revised: 15 March 2017 / Accepted: 15 March 2017
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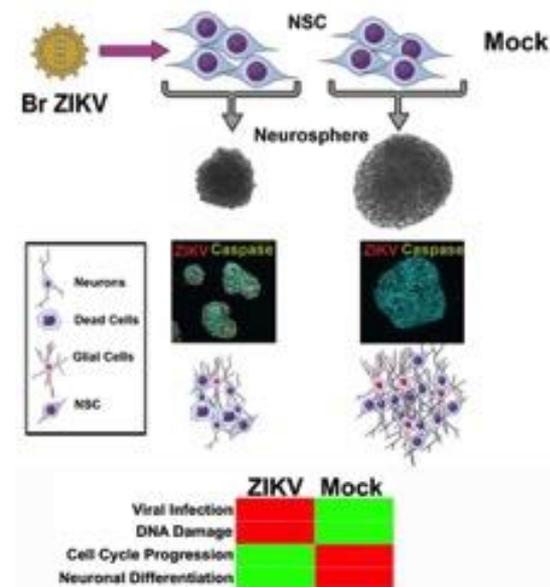
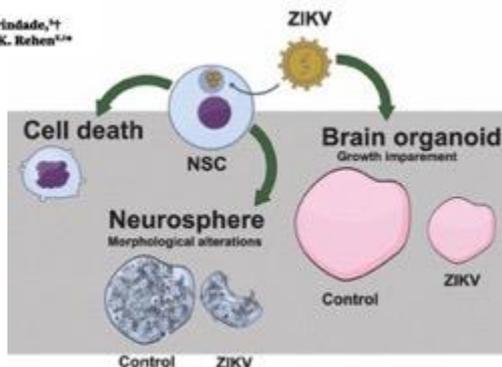
Science

REPORTS

Cite as: Garcez et al., *Science* 10.1126/science.aaf1116 (2016).

Zika virus impairs growth in human neurospheres and brain organoids

Patrícia P. Garcez^{1,2*} · Erick Correia Lotola^{3,4*} · Rodrigo Madeiro da Costa^{5,6*} · Luiza M. Higa^{4,7*} · Pablo Trindade^{4,8*} · Rodrigo Delvecchio⁹ · Juliana Minardi Nascimento¹⁰ · Rodrigo Brindeiro⁹ · Amílcar Tanuri⁹ · Stevens K. Rehen^{11,12*}



SCIENTIFIC REPORTS

Altmetric: 92 Views: 3,742

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Zika virus disrupts molecular fingerprinting of human neurospheres

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The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication

Carolina Q. Sacramento, Gabrielle R. de Melo [...] Thiago Moreno L. Souza

viruses

MDPI

Article

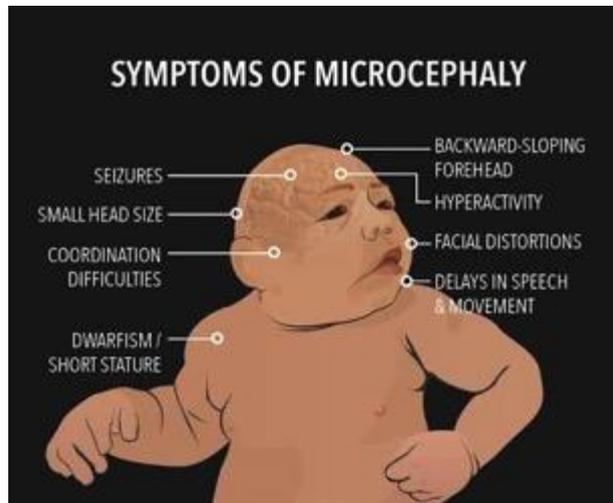
Chloroquine, an Endocytosis Blocking Agent, Inhibits Zika Virus Infection in Different Cell Models

Rodrigo Delvecchio^{1,2} · Luiza M. Higa^{1,2} · Paula Pezzuto^{1,2} · Ana Luiza Valadão^{1,2} · Patrícia P. Garcez^{2,3} · Fábio L. Monteiro³ · Erick C. Lotola³ · André A. Dias⁴ · Fábio J. M. Silva⁵ · Matthew T. Allota⁶ · Elizabeth A. Caine⁶ · Jorge E. Osorio⁶ · Maria Bellio⁶ · David H. O'Connor⁶ · Stevens Rehen^{2,3} · Renato Santana de Aguiar⁷ · Andrea Savarino⁷ · Loraine Campanati^{1,2} and Amílcar Tanuri^{1,2*}

It is not only about zika...

Platform based on iPS cell models to anticipate the consequences and to drug screen for TORCHES and other viruses

TORCHES Syndrome infection of a developing fetus or newborn
(T)oxoplasmosis, (O)ther Agents, (R)ubella, (C)ytomegalovirus, and (H)erpes Simplex, Syphilis)



Aedes aegypti is known to transmit dengue virus, yellow fever virus, chikungunya virus, Zika virus, Venezuelan Equine Encephalitis virus, West Nile virus etc.





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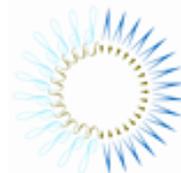


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