New insights about the biology of zika virus using iPS cells

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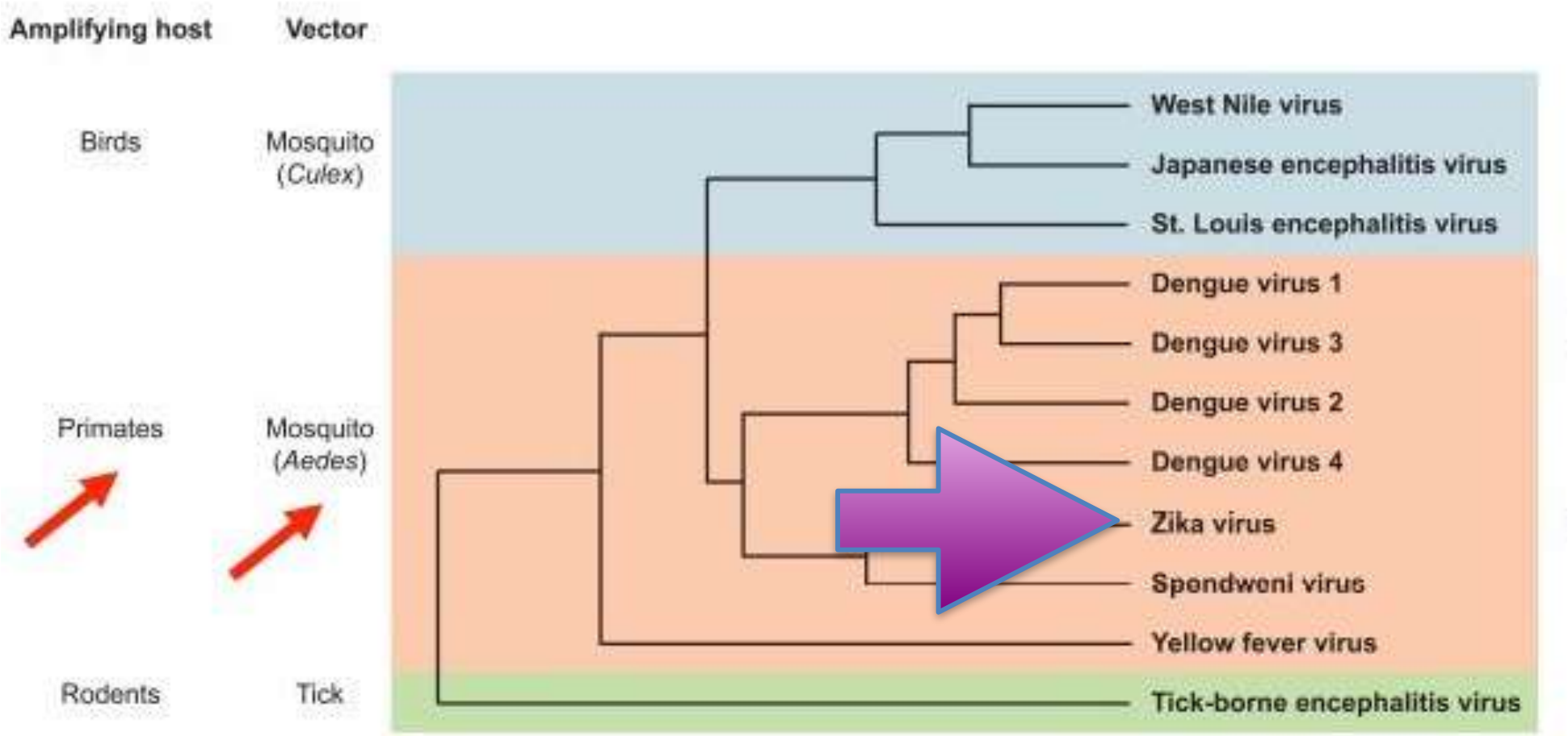
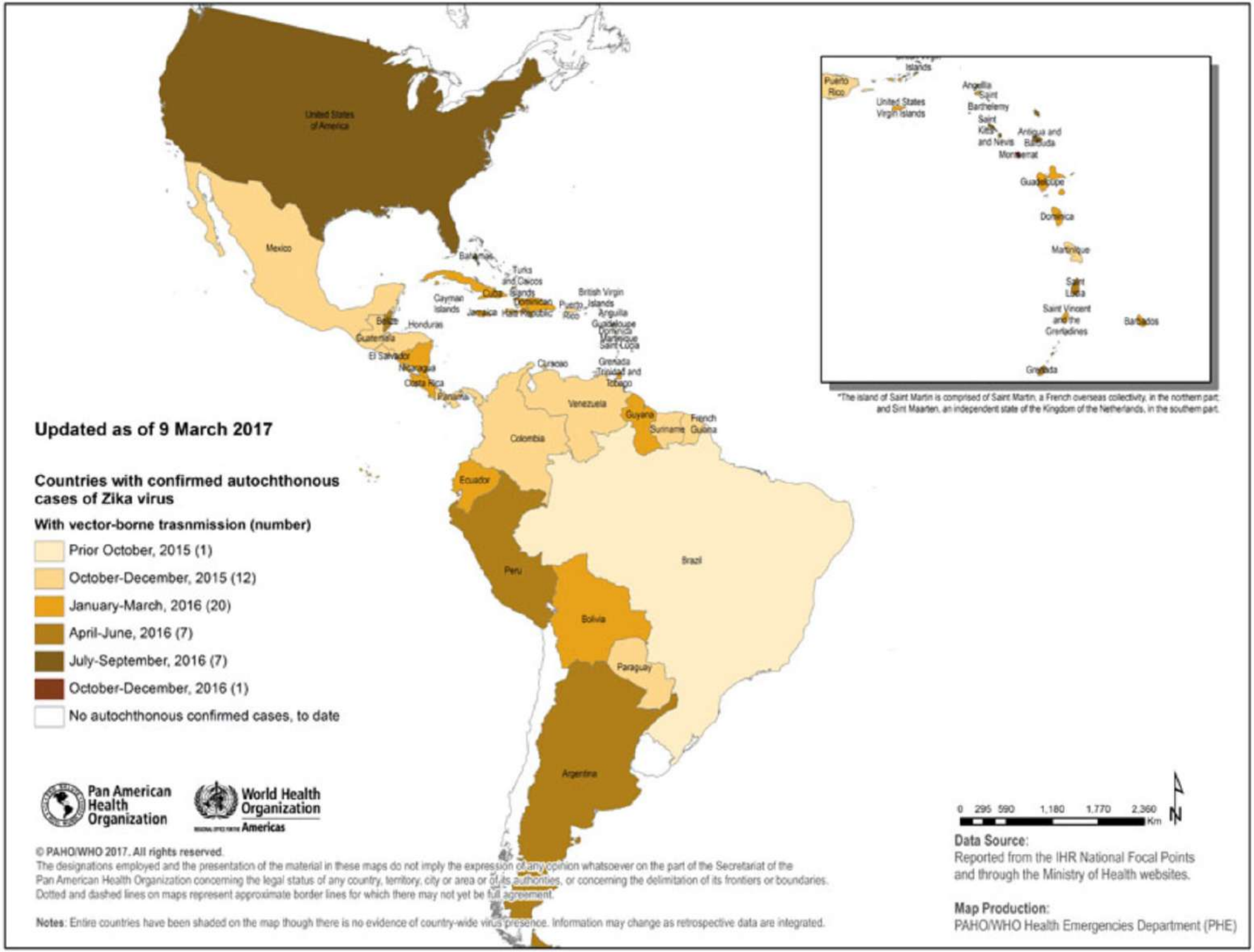
How iPS cells are helping to understand a global health security threat

@stevensrehen
Rio de Janeiro, Brasil

Flaviviruses



http://drrajivdesaimd.com/2016/05/12/zika/



*The island of Saint Martin is comprised of Saint Martin, a French overseas collectivity, in the northern part, and Sint Maarten, an independent state of the Kingdom of the Netherlands, in the southern part.

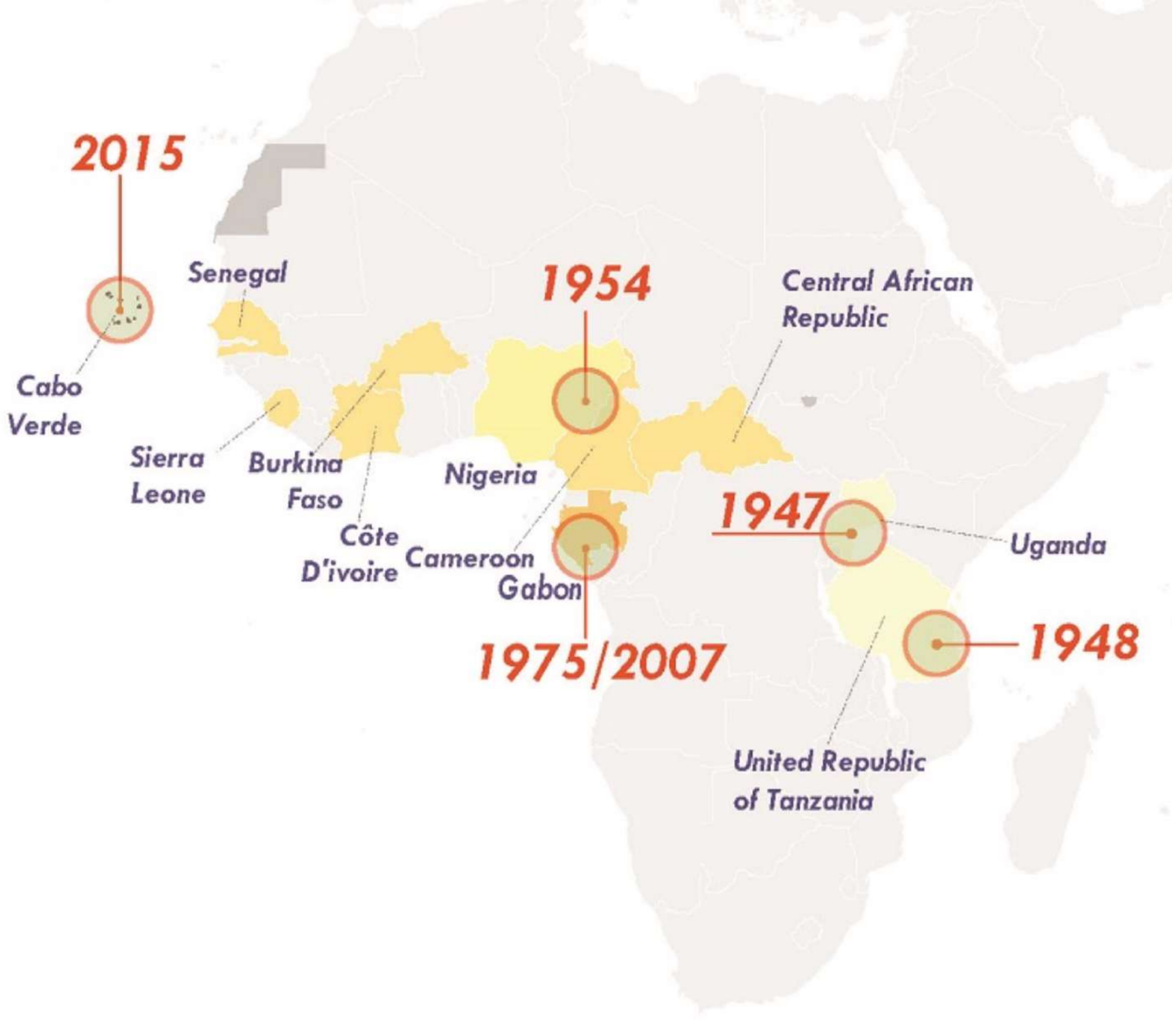
Notes: Entire countries have been shaded on the map though there is no evidence of country-wide virus presence. Information may change as retrospective data are integrated.

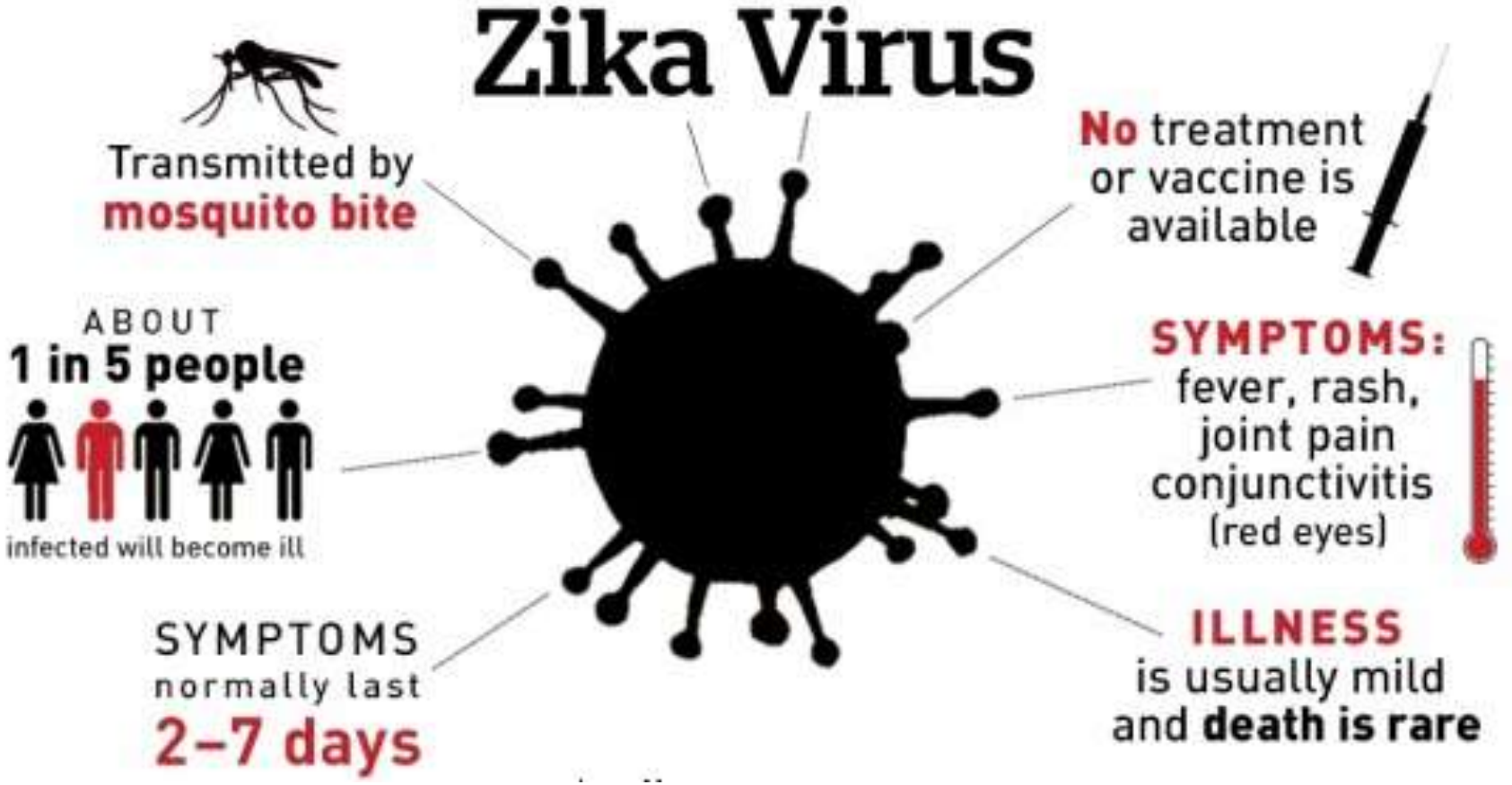
Data Source:
Reported from the IHR National Focal Points and through the Ministry of Health websites.

Map Production:
PAHO/WHO Health Emergencies Department (PHE)


Uganda


ZIIKA FOREST.


2015
Cabo Verde
Senegal
Sierra Leone
Burkina Faso
Côte D'ivoire
1954
Nigeria
Cameroon
Gabon
1975/2007
Central African Republic
1947
Uganda
1948
United Republic of Tanzania



http://drrajivdesaimd.com/2016/05/12/zika/


1977
Pakistan
Cambodia
Philippines
2007
Thailand
Malaysia
2016
Maldives
YAP(Micronesia (Federated States of))
Indonesia
1977/2012
Solomon Islands
Samoa
2013
Vanuatu
Fiji
Tonga
French Polynesia
Cook Islands
New Caledonia
2016

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

PLOS | NEGLECTED TROPICAL DISEASES

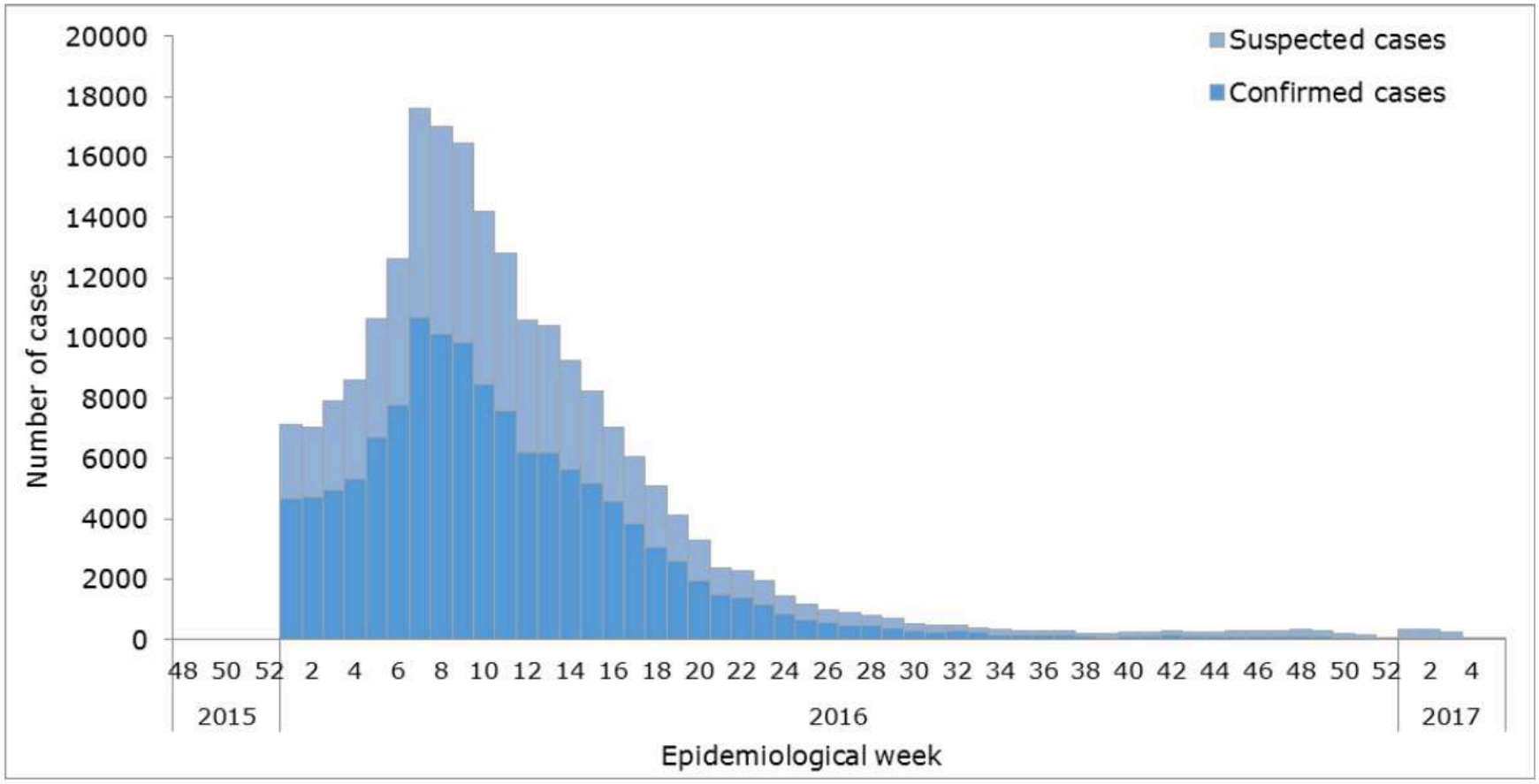

Haiti
Dominican Republic
Puerto Rico
Mexico
El Salvador
Saint Martin
Barbados
Nicaragua
United States
Virgin Islands
Curaçao
Guadeloupe
Martinique
Jamaica
Guatemala
Honduras
French Guiana
Guyana
Costa Rica
Panama
Suriname
2015
Colombia
2016
Ecuador
Brazil
Venezuela (Bolivarian
Republic of)
Bolivia (Plurinational
State of)
2014
EASTER ISLAND (Chile)
Paraguay

Zika-Epidemiological Report

Brazil

2 March 2017

Figure 1. Suspected and confirmed cases of Zika. Brazil. EW 1 of 2015 to EW 5 of 2017[1]



Source: Data reported by the Brazil Ministry of Health[2]

Zika and Sexual Transmission

Basics of Zika Virus and Sex

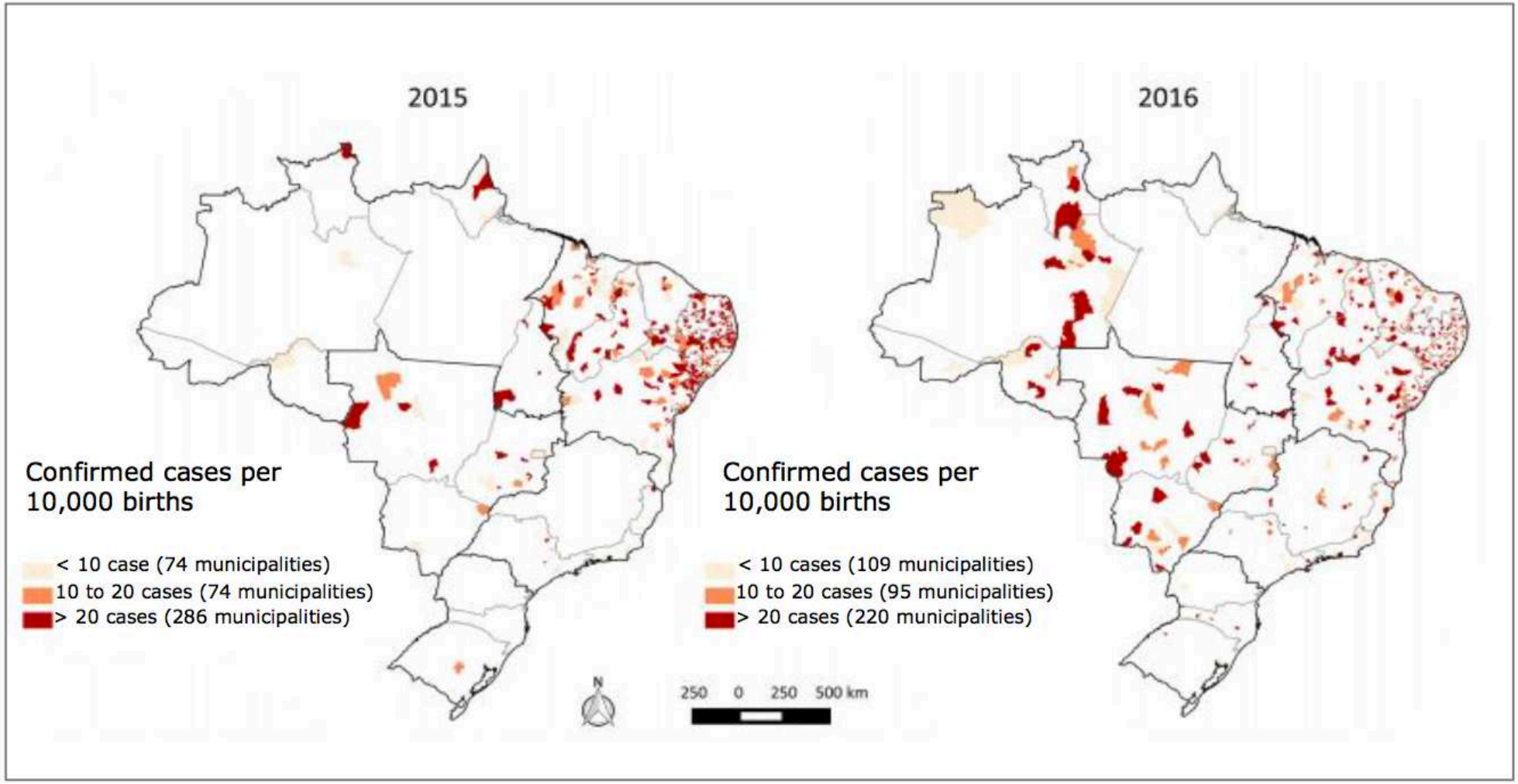
Transmission

- Zika can be passed through sex from a person who has Zika to his or her sex partners.
- Sex includes vaginal, anal, oral sex, and the sharing of sex toys.
- Zika can be passed through sex, even if the person does not have symptoms at the time.
  - It can be passed from a person with Zika before their symptoms start, while they have symptoms, and after their symptoms end.
  - Though not well documented, the virus may also be passed by a person who carries the virus but never develops symptoms.
- Studies are underway to find out how long Zika stays in the semen and vaginal fluids of people who have Zika, and how long it can be passed to sex partners. We know that Zika can remain in semen longer than in other body fluids, including vaginal fluids, urine, and blood.

Additional Guidance

- UPDATE: Interim Guidance for Prevention of Sexual Transmission of Zika Virus
- QA for Healthcare Providers: Sexual Transmission of Zika

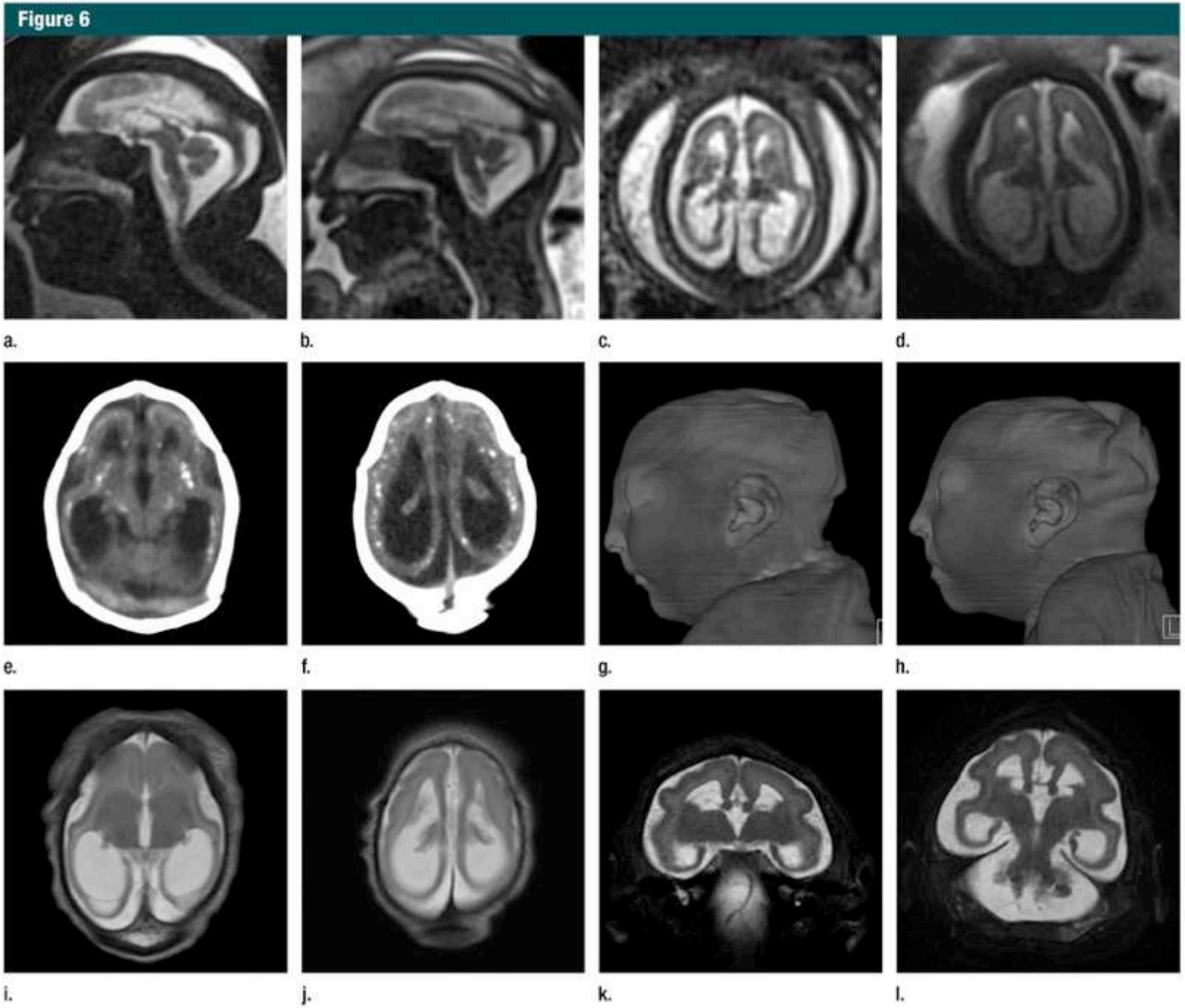
Figure 6. Confirmed cases (per 10,000 live births) of newborns and children with changes in growth related to Zika virus infection and other infectious etiologies, by municipalities of mother's residence. Brazil. 2015 and 2016.



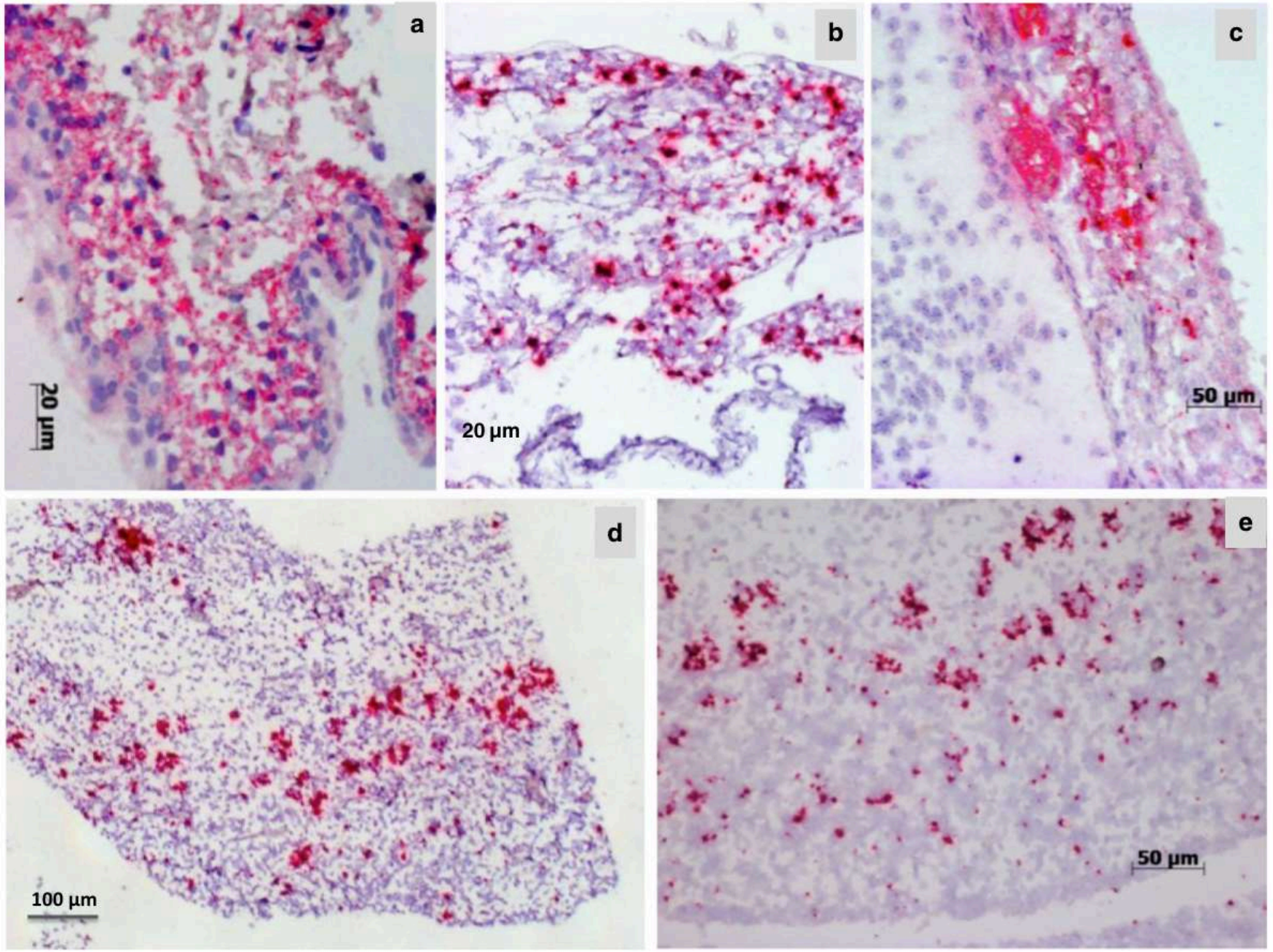
Source: Data published by the Brazil Ministry of Health[13]

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

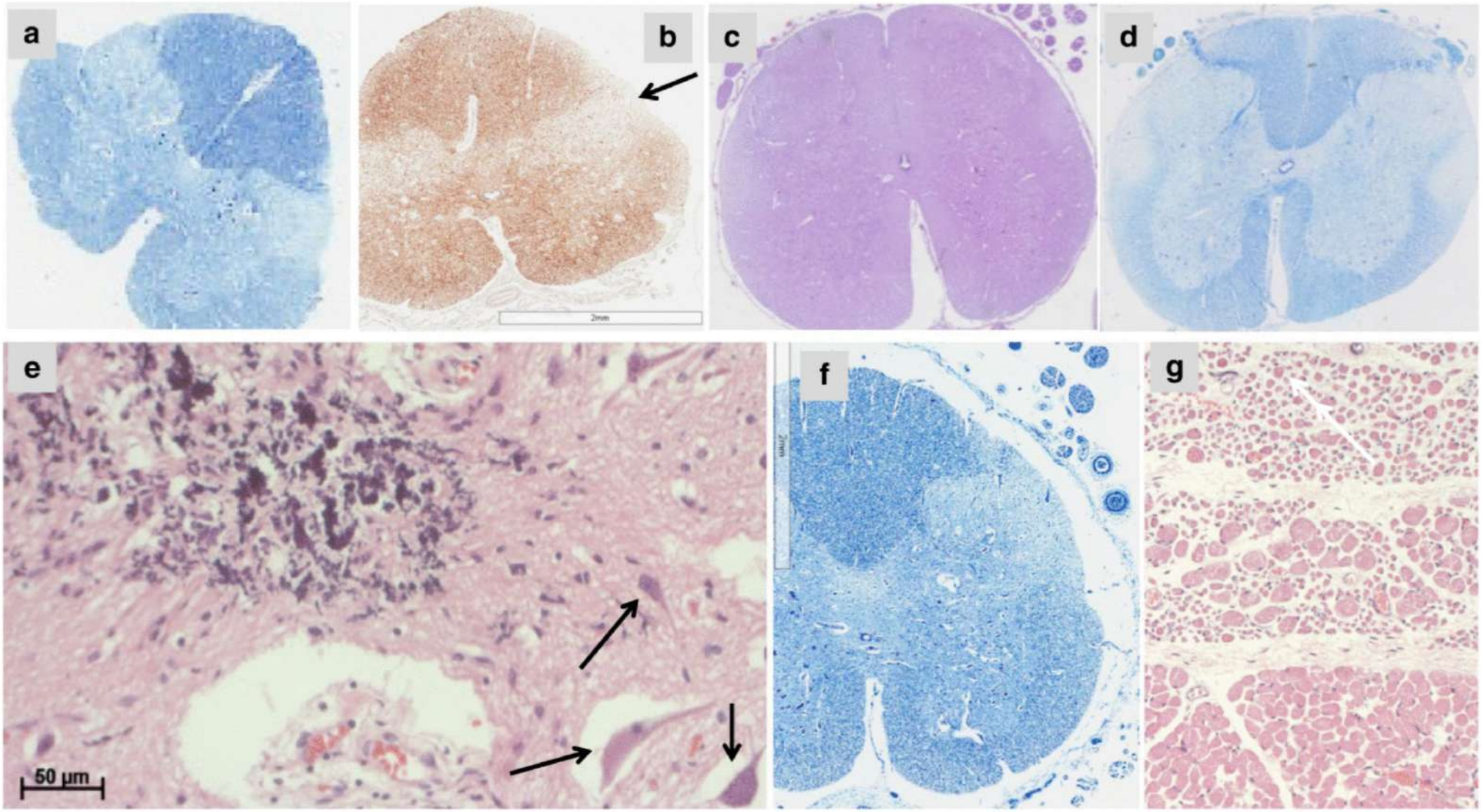
24 countries and territories in the Americas have reported confirmed cases of congenital syndrome associated with Zika virus infection



Oliveira-Szejnfeld et al, Radiology (2016)



Chimelli *et al*, Acta Neuropathologica (2017)



Chimelli *et al*, Acta Neuropathologica (2017)

Acta Neuropathol
DOI 10.1007/s00401-017-1699-5

ORIGINAL PAPER

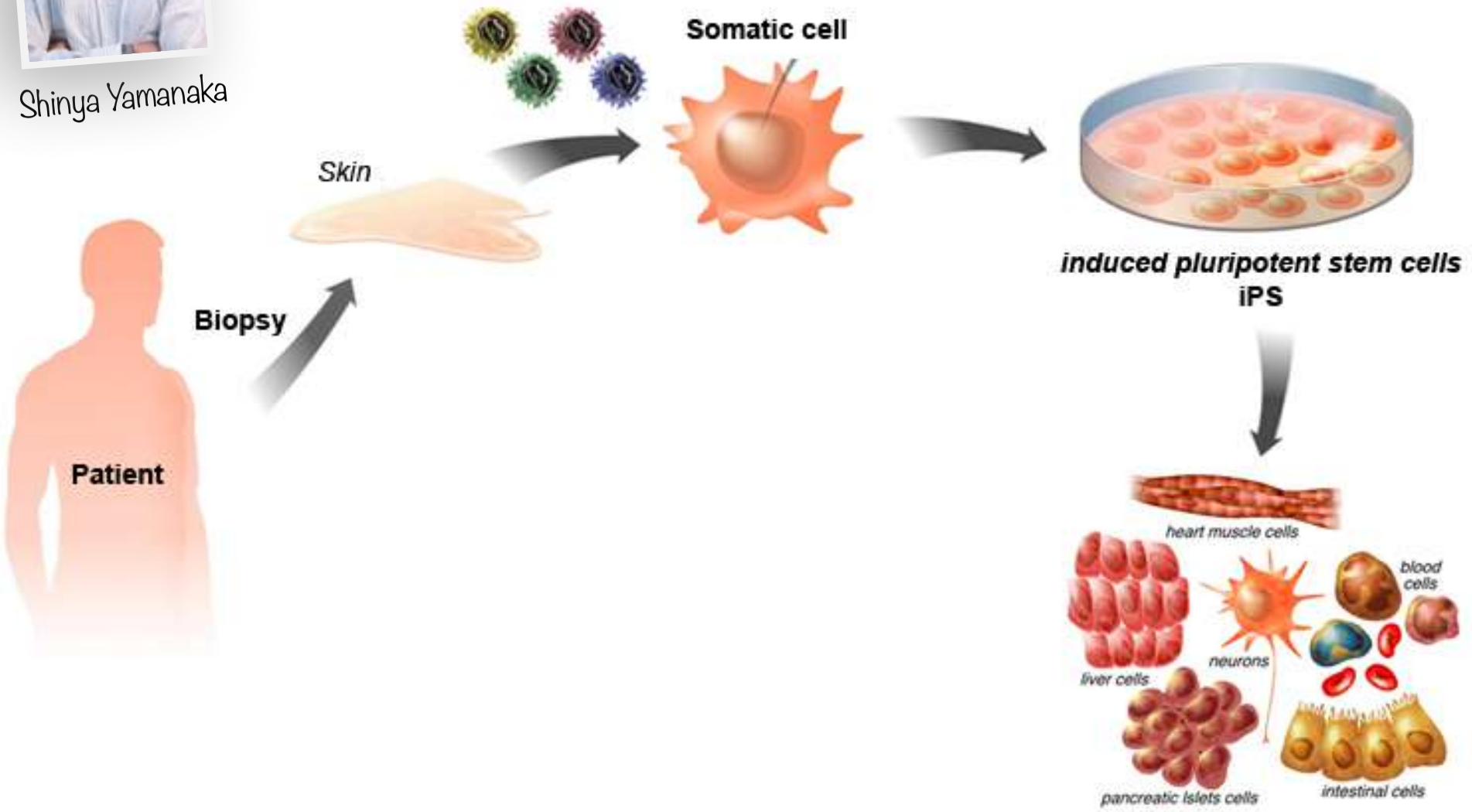
The spectrum of neuropathological changes associated with congenital Zika virus infection

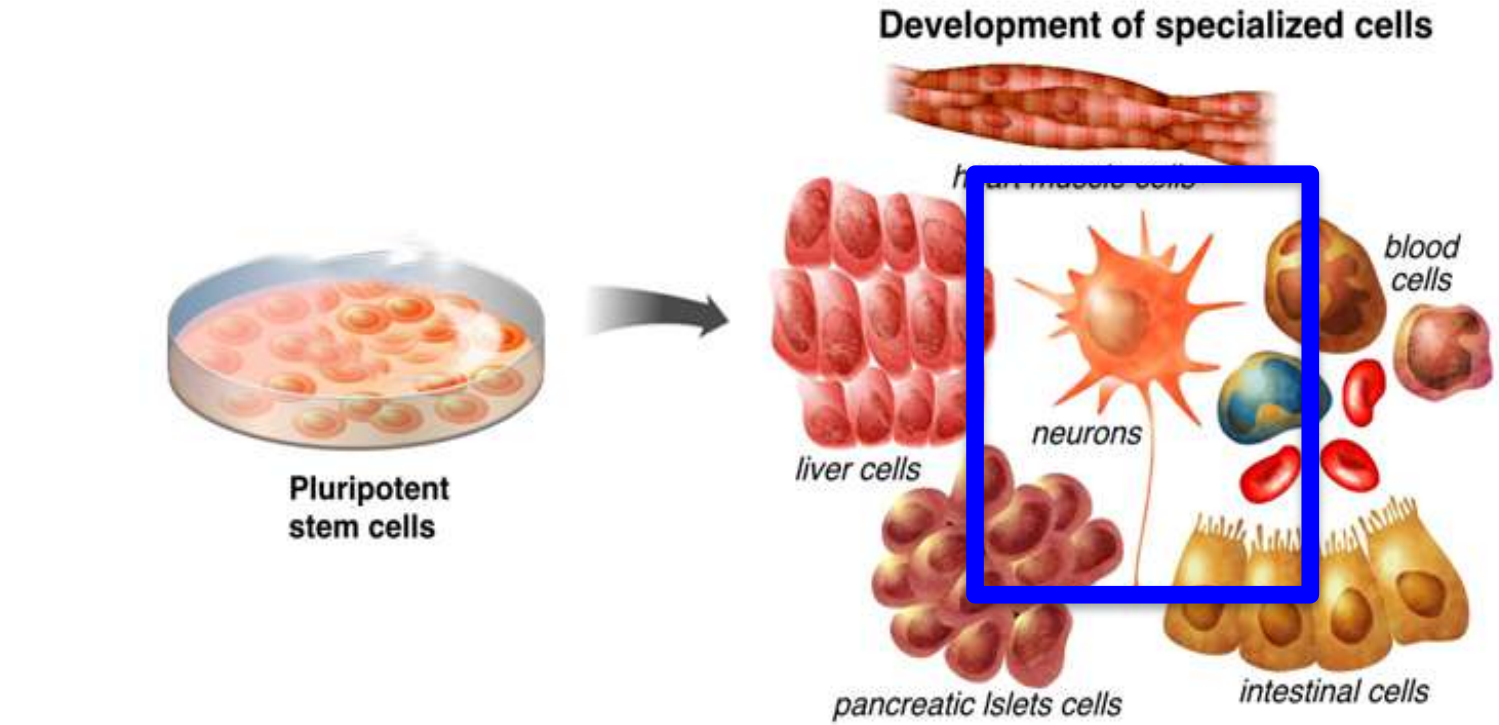
Leila Chimelli[1] · Adriana S. O. Melo[2,3] · Elyzabeth Avvad-Portari[4] · Clayton A. Wiley[5] · Aline H. S. Camacho[1] · Vania S. Lopes[6] · Heloisa N. Machado[4] · Cecilia V. Andrade[4] · Dione C. A. Dock[4] · Maria Elisabeth Moreira[4] · Fernanda Tovar-Moll[7] · Patricia S. Oliveira-Szejnfeld[8] · Angela C. G. Carvalho[6] · Odile N. Ugarte[6] · Alba G. M. Batista[3] · Melania M. R. Amorim[2] · Fabiana O. Melo[2] · Thales A. Ferreira[2] · Jacqueline R. L. Marinho[3] · Girlene S. Azevedo[2] · Jeime I. B. F. Leal[3] · Rodrigo F. Madeiro da Costa[7] · Stevens Rehen[7] · Monica B. Arruda[9] · Rodrigo M. Brindeiro[9] · Rodrigo Delvechio[9] · Renato S. Aguiar[9] · Amilcar Tanuri[9]

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

Human induced pluripotent stem cells

Shinya Yamanaka




Development of specialized cells
Pluripotent
stem cells
blood
cells
neurons
liver cells
pancreatic Islets cells
intestinal cells

Nº	Linhagem	Origem	Condição
1	CF-2	Fibroblasto	Controle
2	CF-1	Fibroblasto	Controle
3	CF-3	Fibroblasto	Controle
4	C-8	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	EZQ-3	Fibroblasto	Esquizofrenia
21	EZQ-4	Fibroblasto	Esquizofrenia
22	EZQ-9	Fibroblasto	Esquizofrenia
23	TOC-4	Urotélio	TOC
24	CF-4	Fibroblasto	Controle
25	CF-6	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-5	Urotélio	Controle
32	C-18	Urotélio	Controle

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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

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[d] 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

Jaroslaw Sochacki[a], Sylvie Devalle[a], Marcelo Reis[a], Paulo Mattos[a], Stevens Rehen[a, b]
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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

Jaroslaw Sochacki[a], Sylvie Devalle[a], Marcelo Reis[a], Renata de Moraes Maciel[a], Bruna da Silveira Paulsen[b], Helena Brentani[c, d], Paulo Silva Belmonte-de-Abreu[a], Stevens Rehen[a, b]
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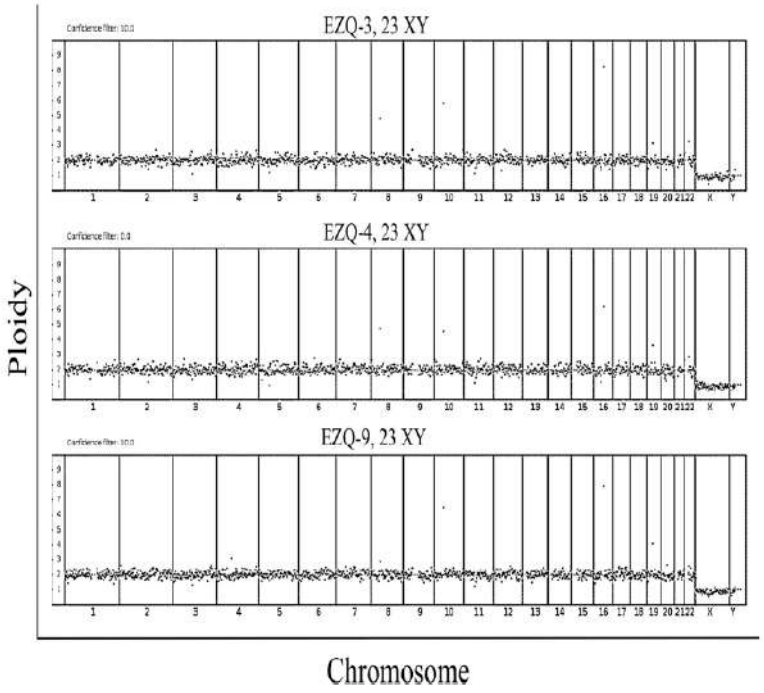
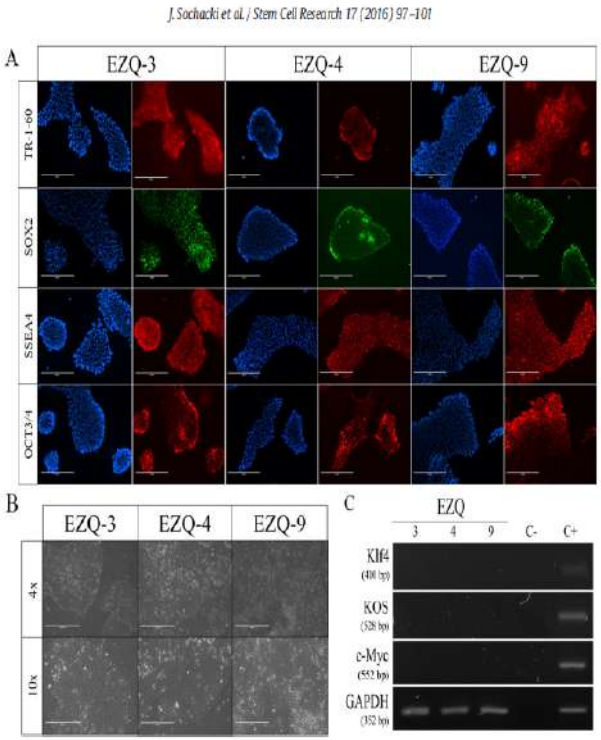
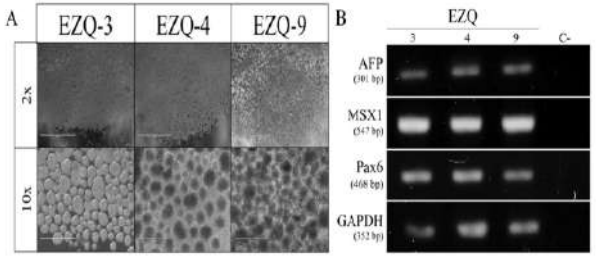
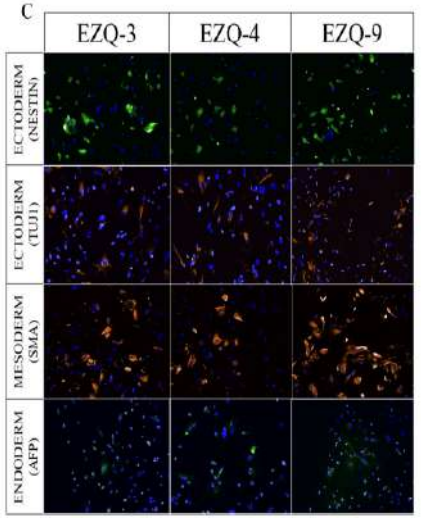
[d] Laboratory of Medical Investigation, Faculty of Medicine, São Paulo University (USP), Avenida Doutor Arnaldo, 455 – Cerqueira César, 01246-903 São Paulo, Brazil
[e] Department of Psychiatry, Faculty of Medicine, Federal University of Rio Grande do Sul (UFRGS), Rua Ramiro Barcelos 2400 – Floresta, Porto Alegre 90035-002, Brazil



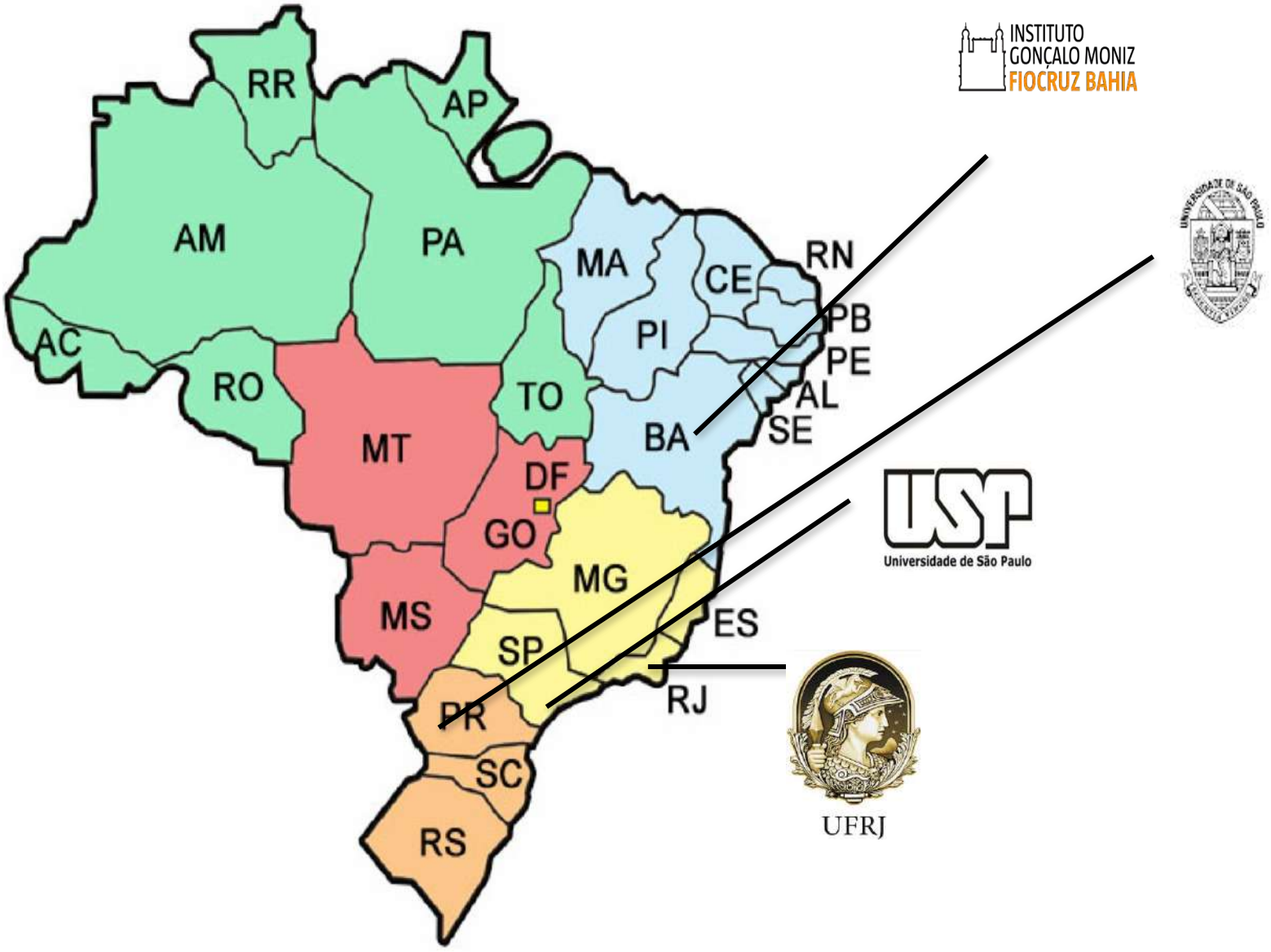
Sendai based reprogramming of urine-derived epithelial cells and fibroblasts to study mental and neurological disorders



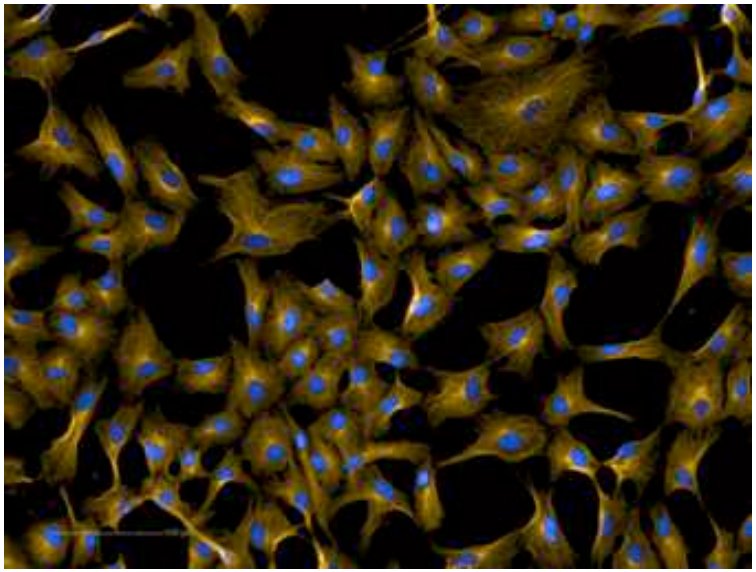


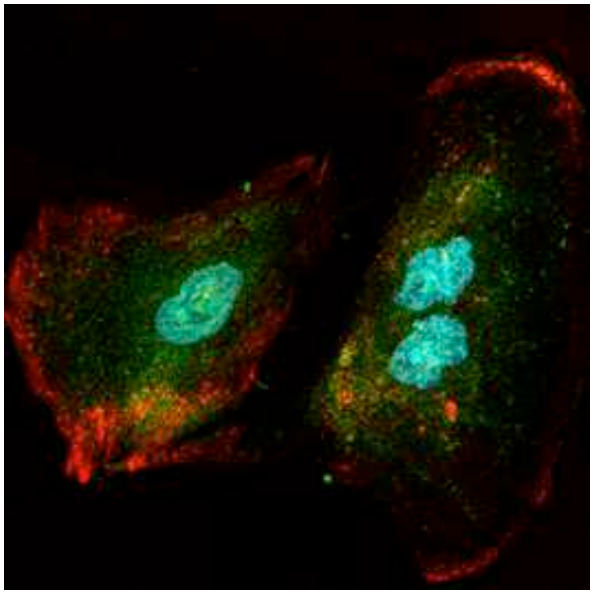


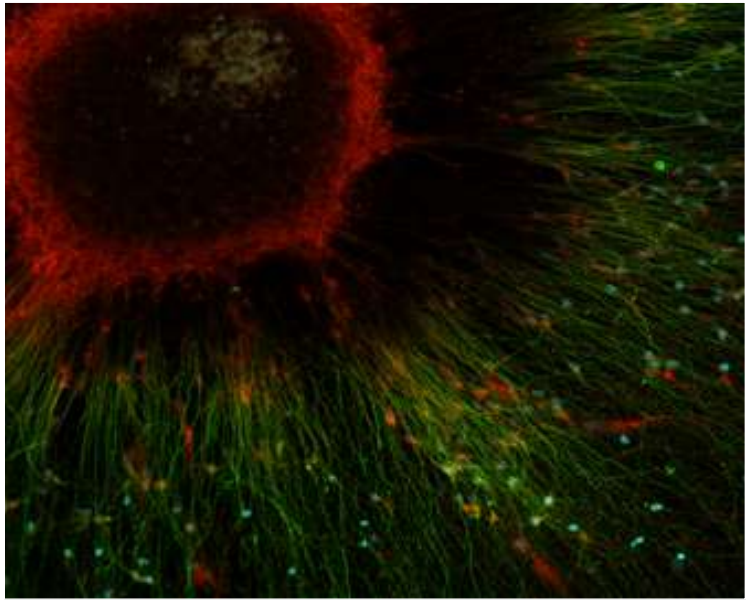
Brazilian iPS Biobank Initiative (17 diseases, 150 cell lines)



Cellular models to study brain development *in vitro*







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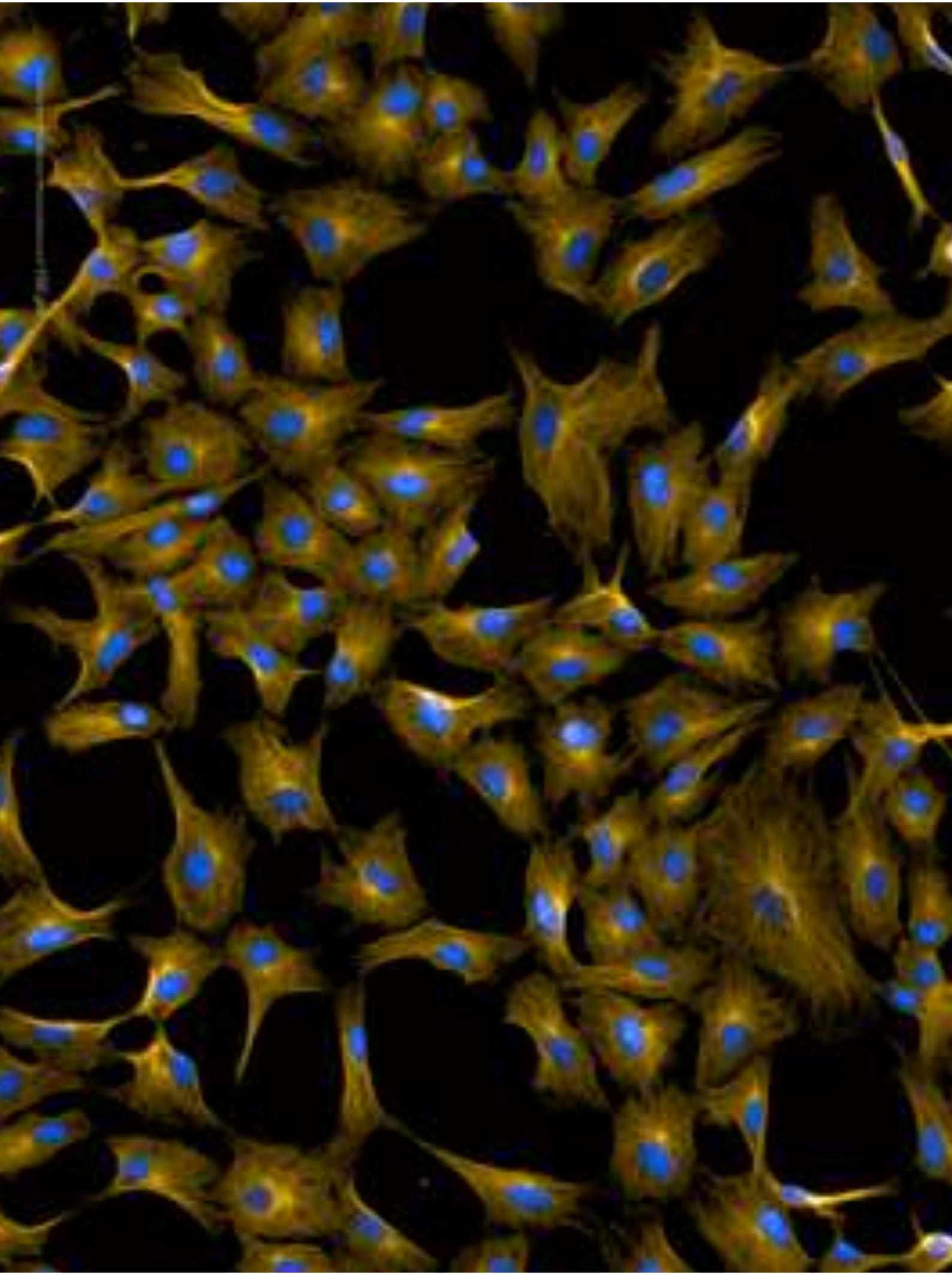
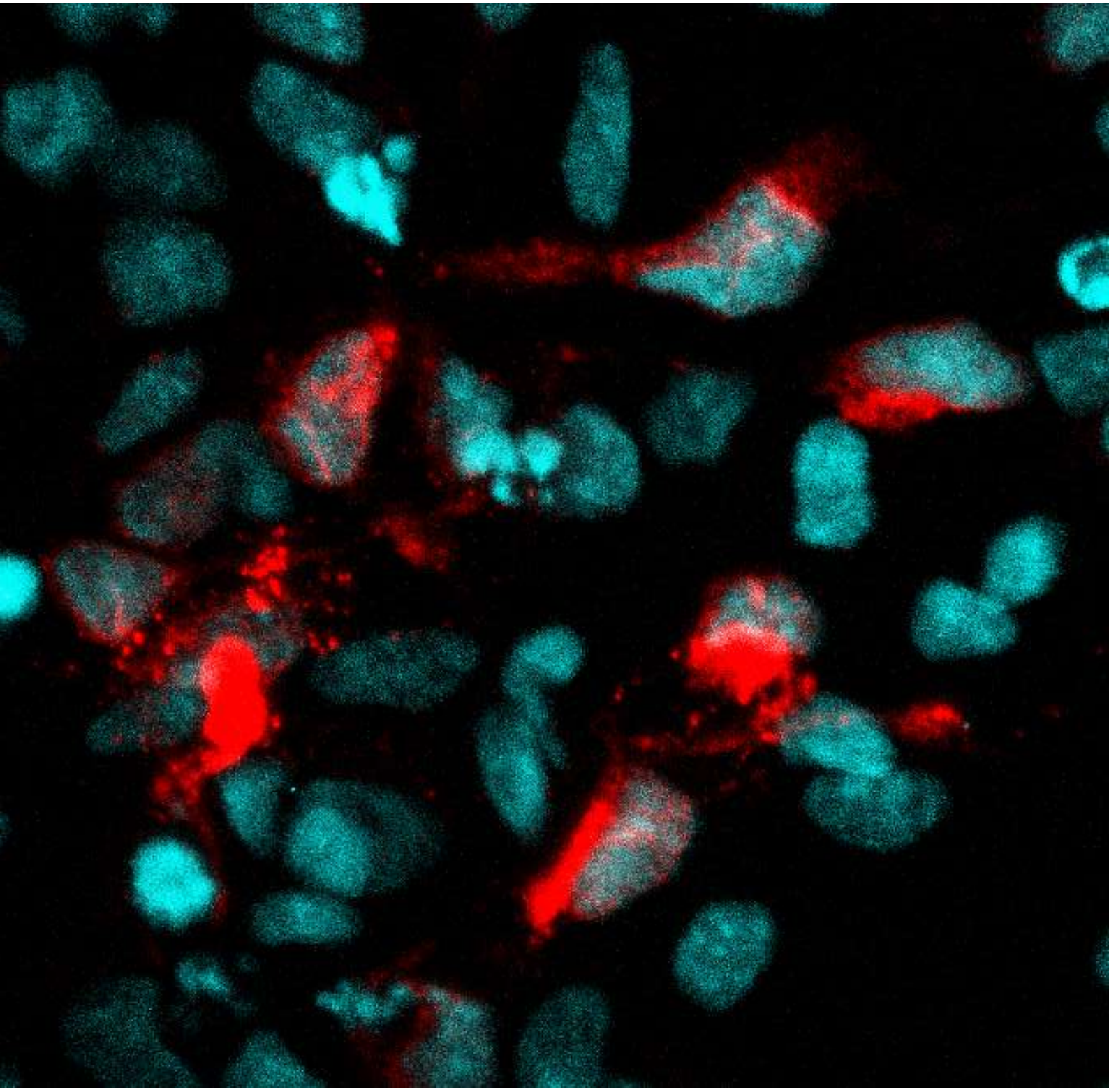
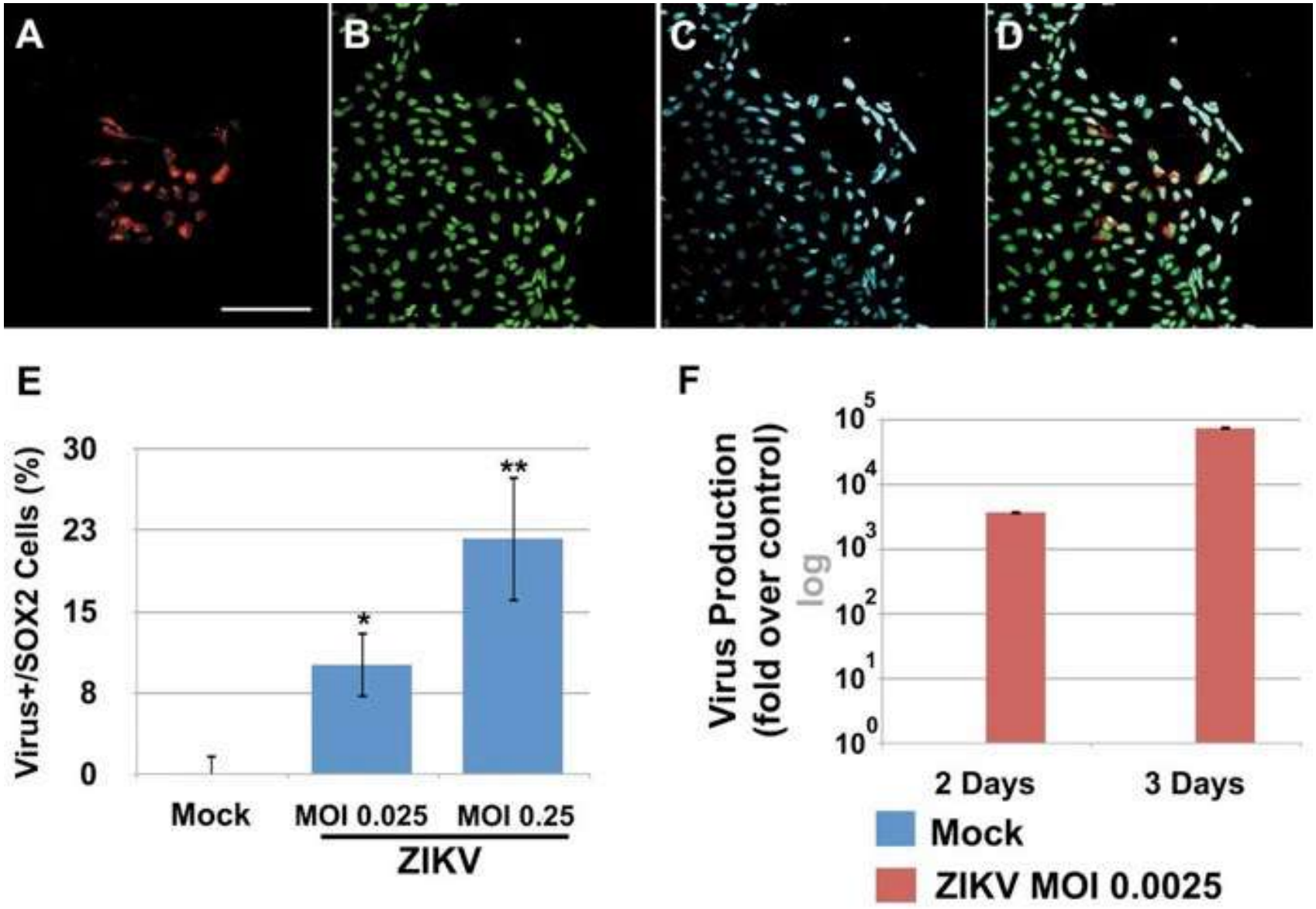
1) The consequences of ZIKV infection during neurogenesis and growth of human neurospheres and brain organoids
2) Insights about the molecular mechanisms of ZIKV infection
3) A platform based on iPS cell models to anticipate the consequences and to drug screen for TORCHES and other viruses





ZIKV infects human neural stem cells

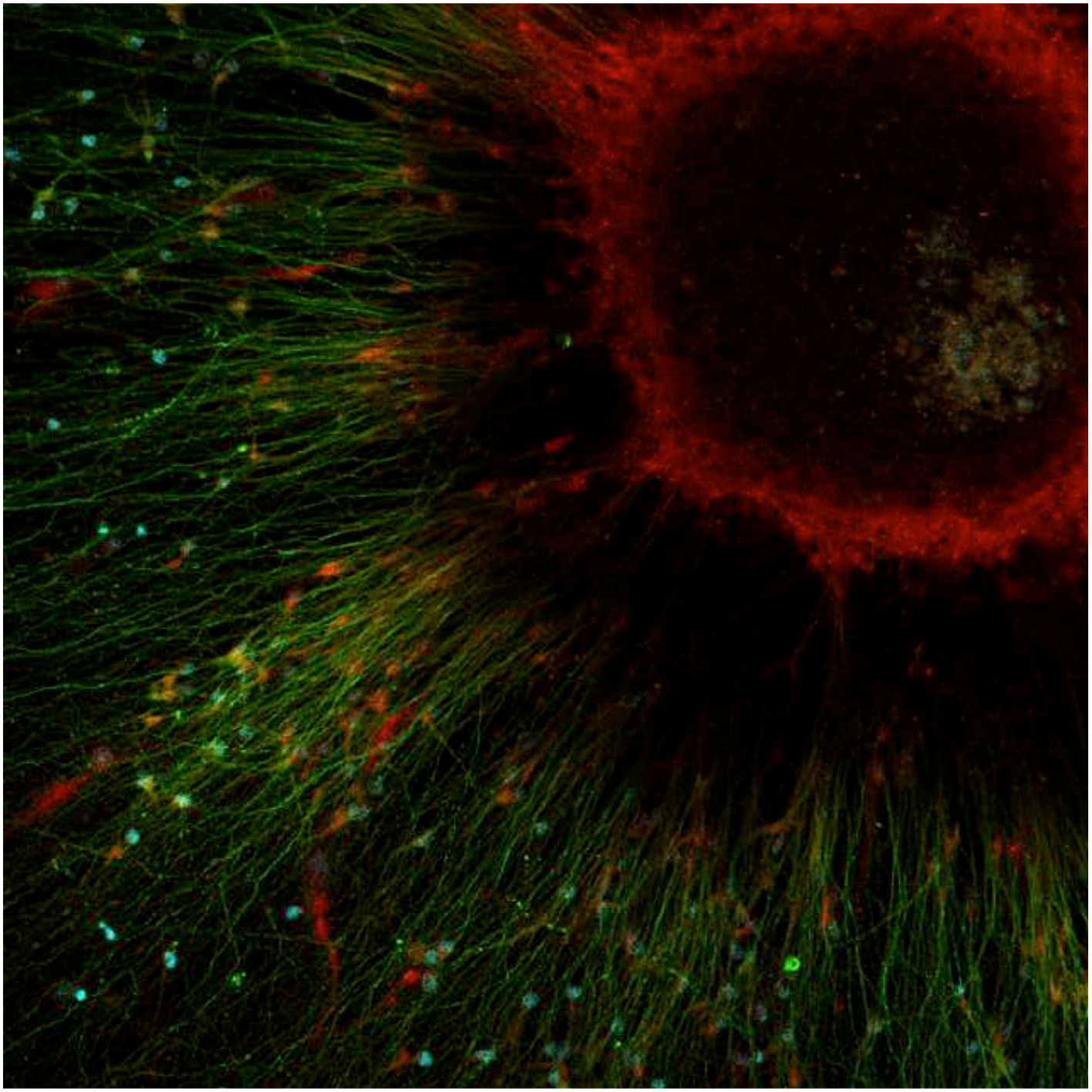


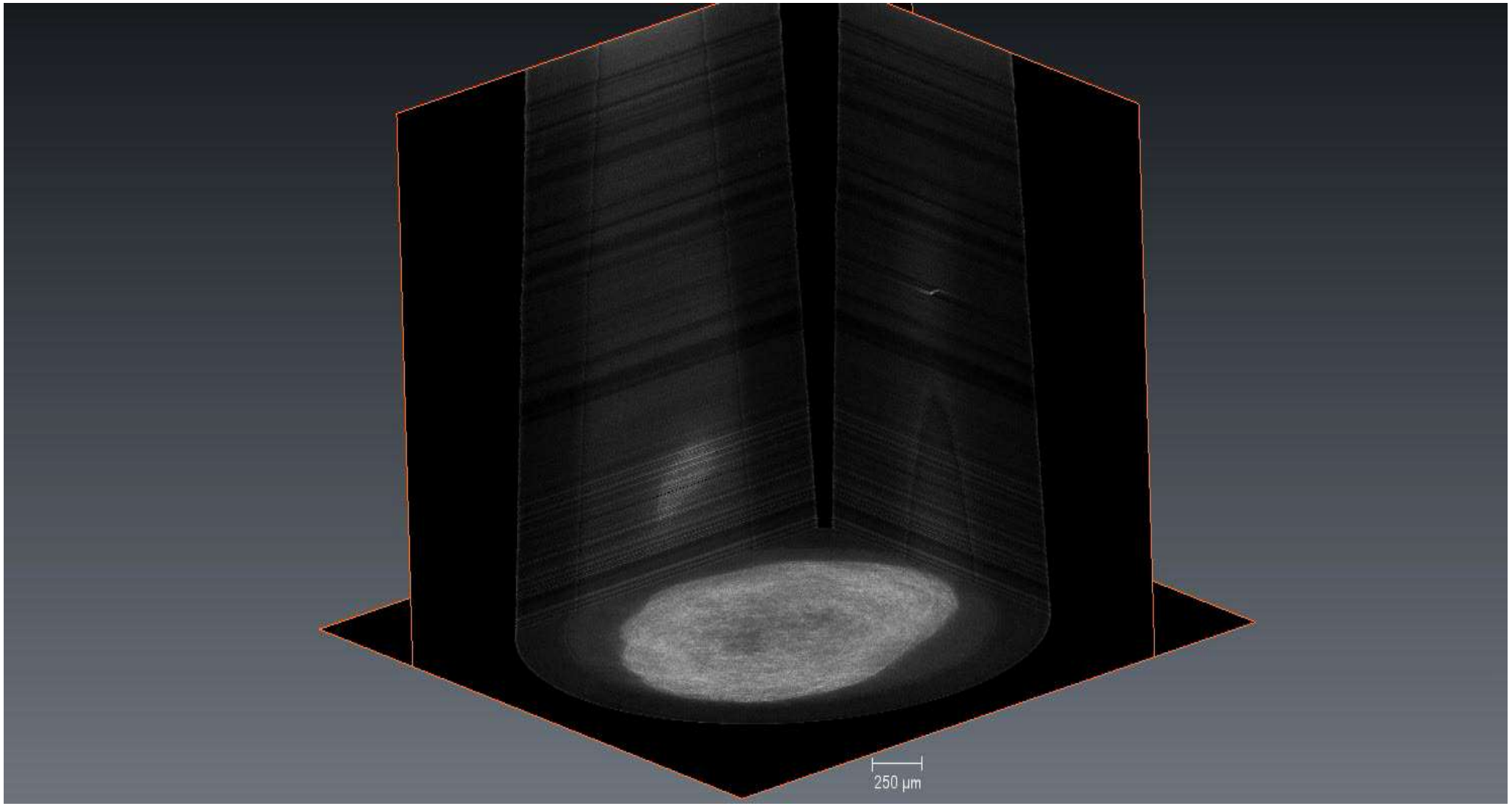
Garcez *et al*, Science (2016)

Radiology

Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally[1]

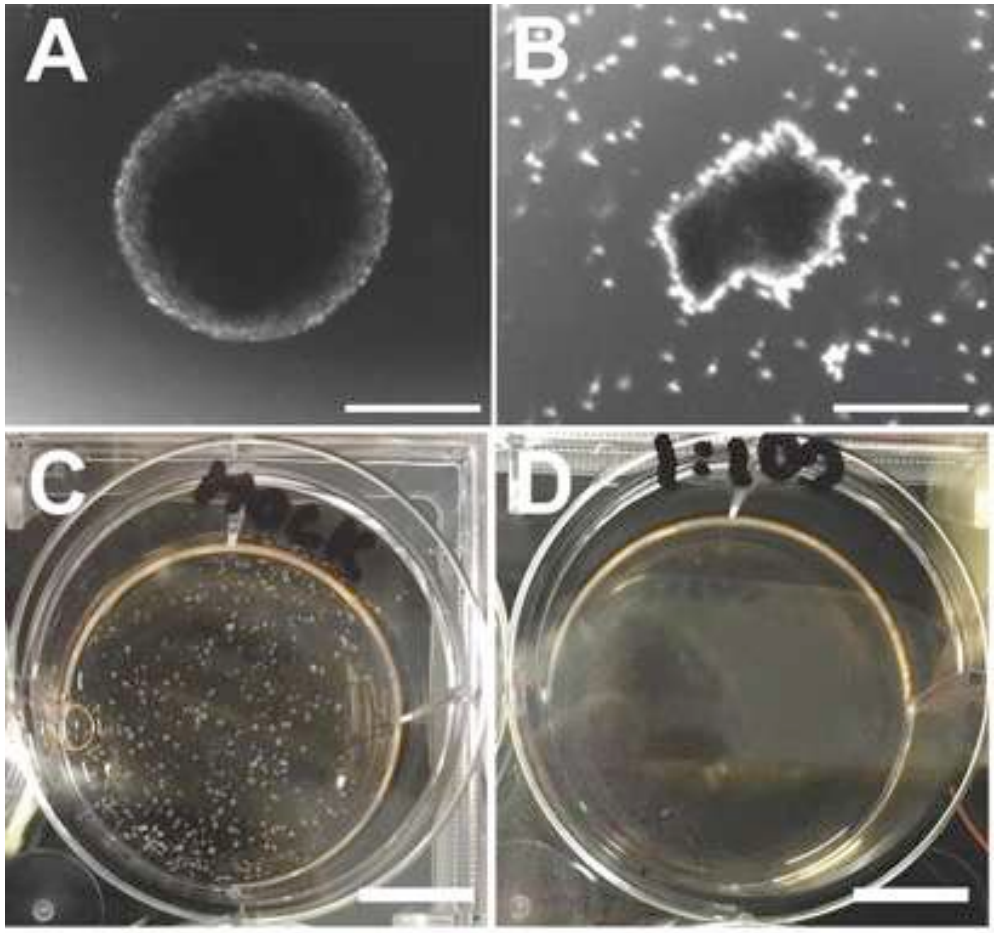
Patricia Soares de Oliveira-Szejnfeld, MD
Deborah Levine, MD
Adriana Suely de Oliveira Melo, MD, PhD
Melania Maria Ramos Amorim, MD, PhD
Alba Gean M. Batista, MD
Leila Chimelli, MD, PhD
Amilcar Tanuri, MD, PhD
Renato Santana Aguiar, PhD
Gustavo Malinger, MD, PhD
Renato Ximenes, MD
Richard Robertson, MD
Jacob Szejnfeld, MD, PhD
Fernanda Tovar-Moll, MD, PhD

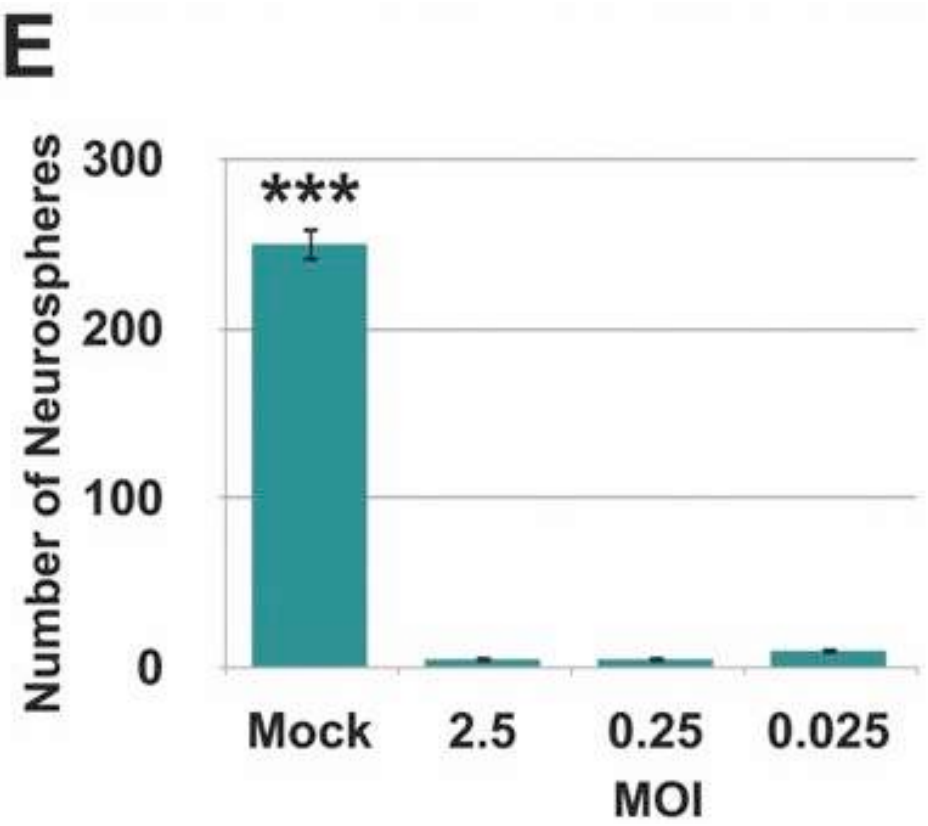




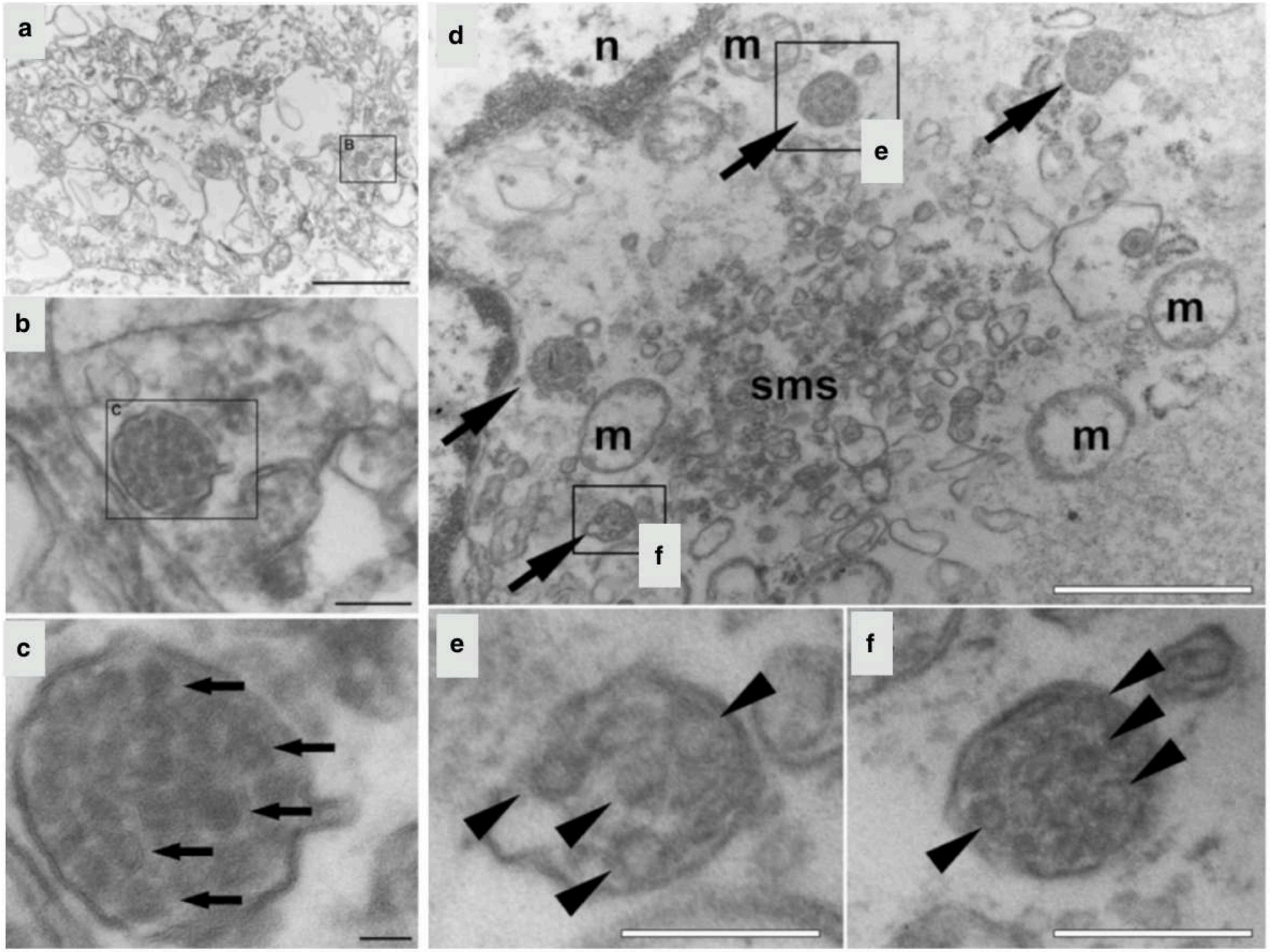
Cardoso et al (unpublished data)

ZIKV alters morphology and halts the growth of human neurospheres

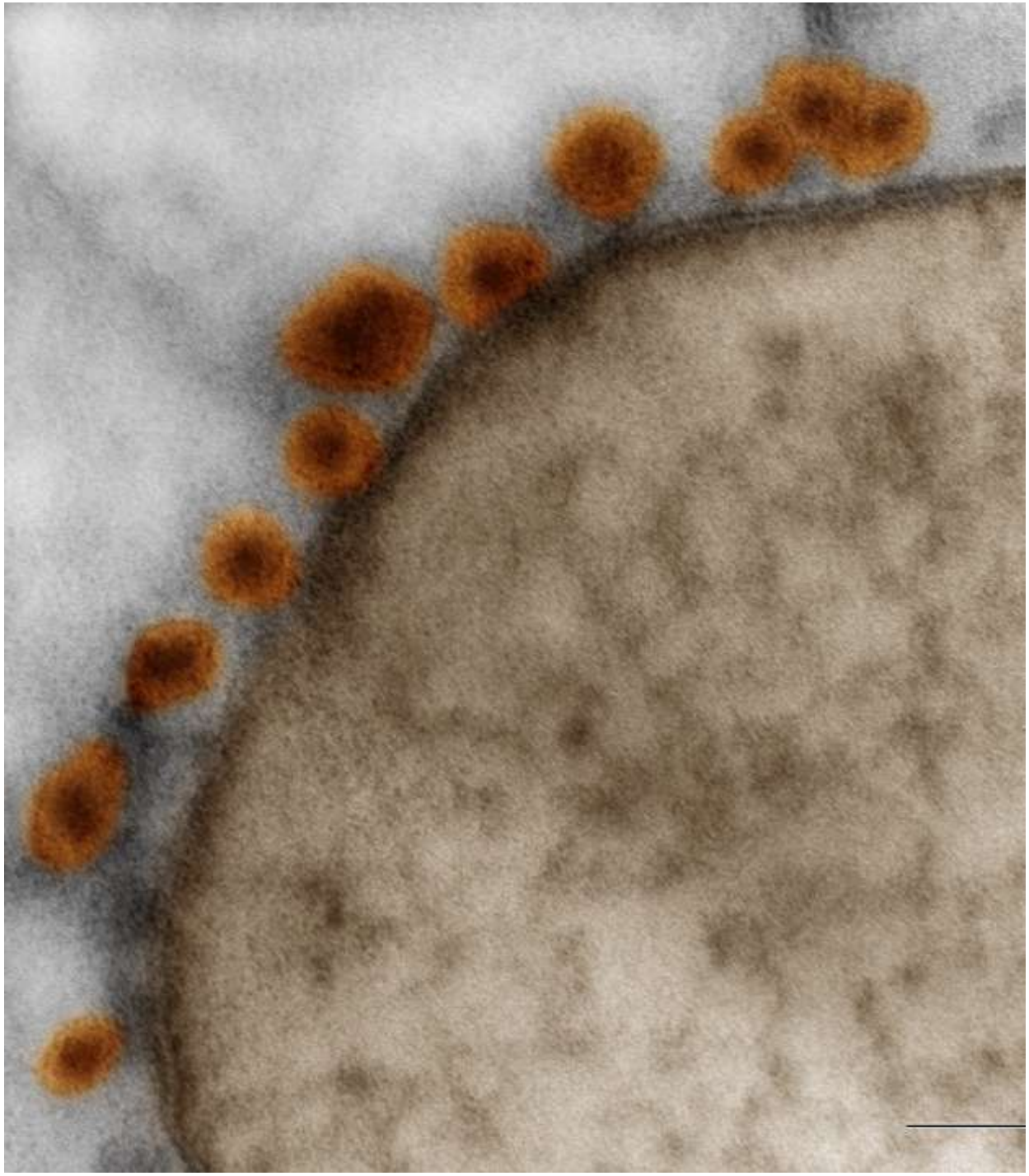




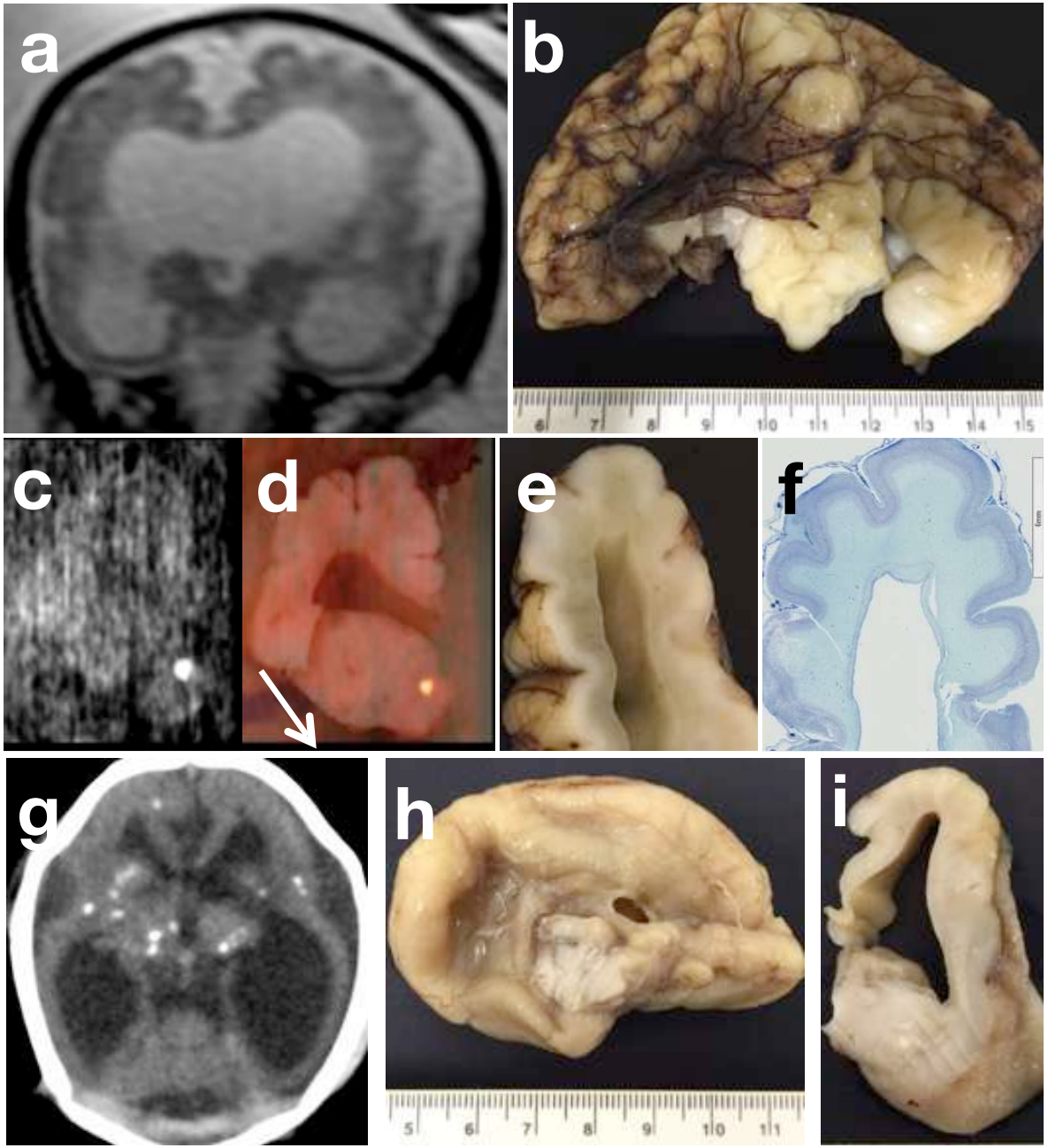
Garcez *et al*, Science (2016)



Chimelli *et al*, Acta Neuropathologica (2017)

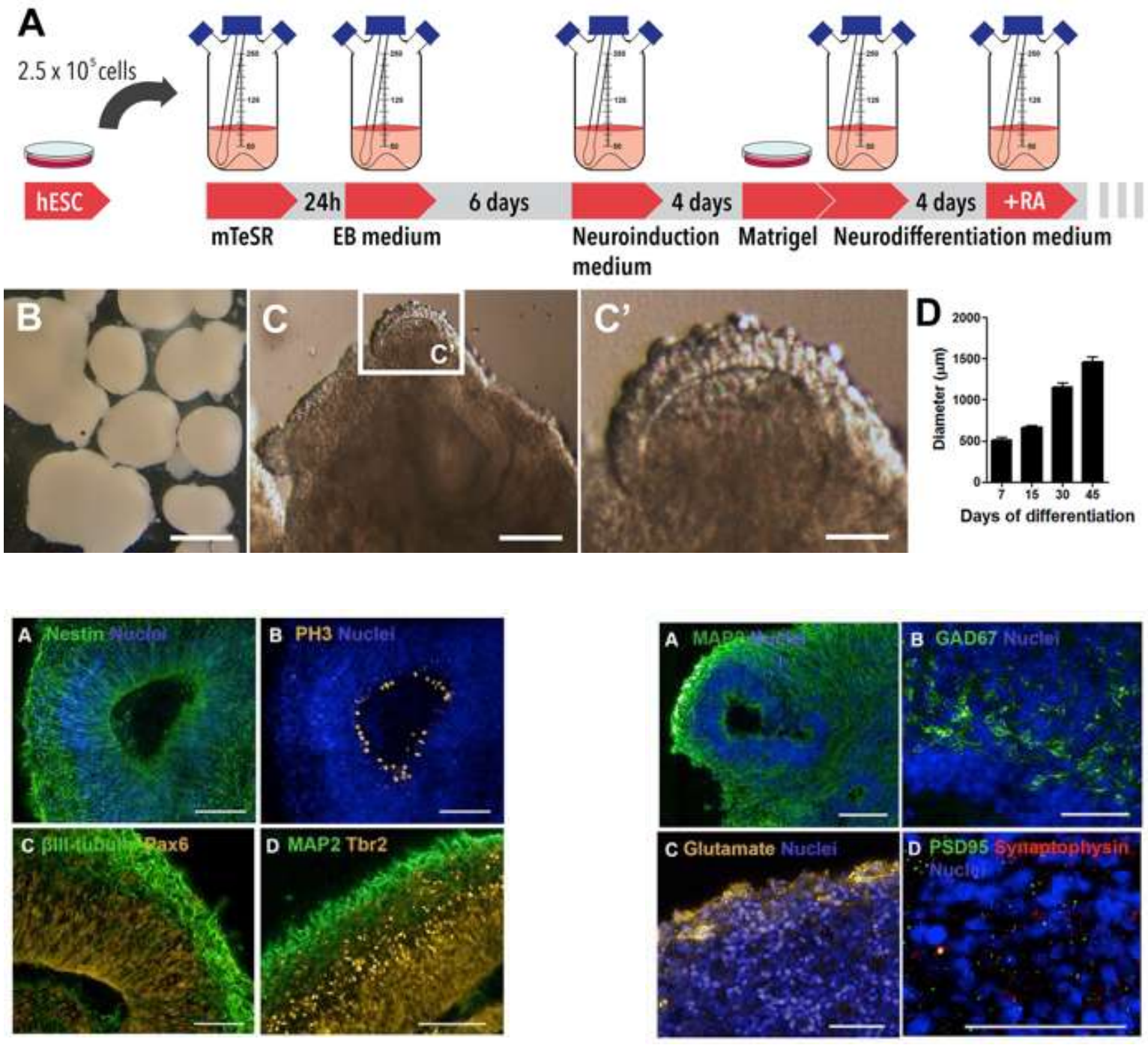


Garcez et al, Science (2016)

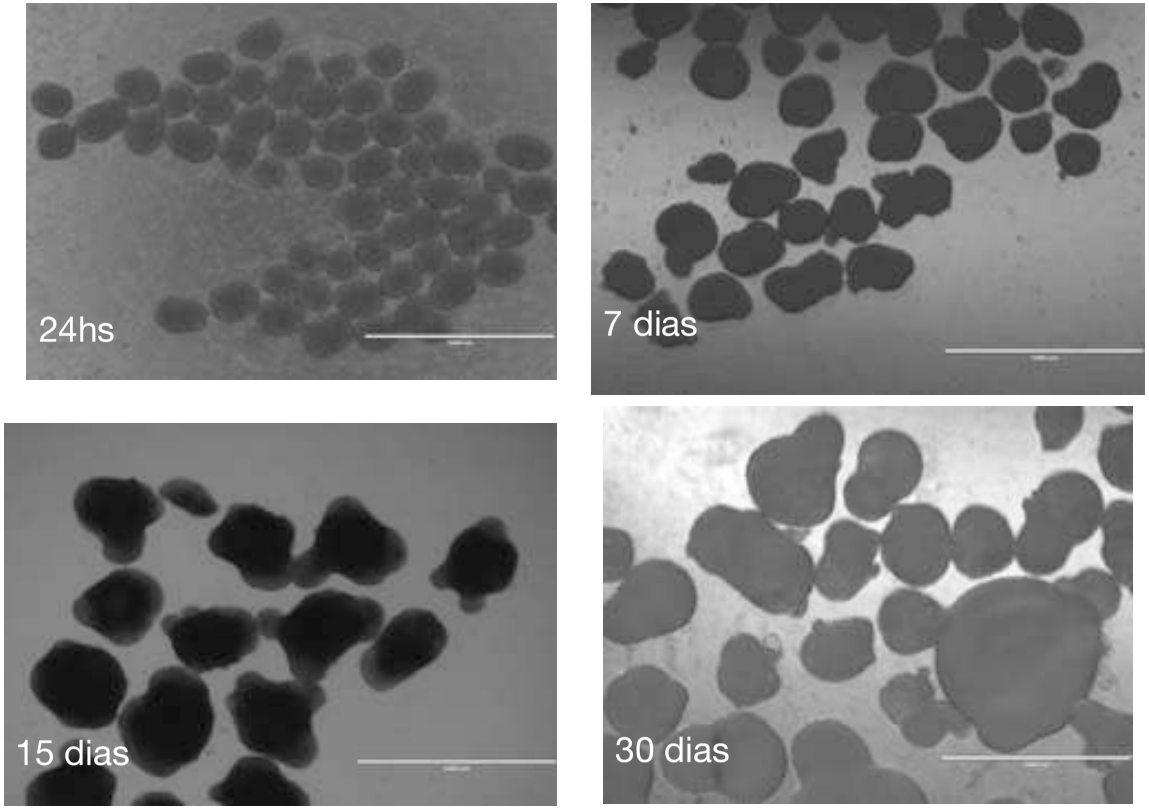


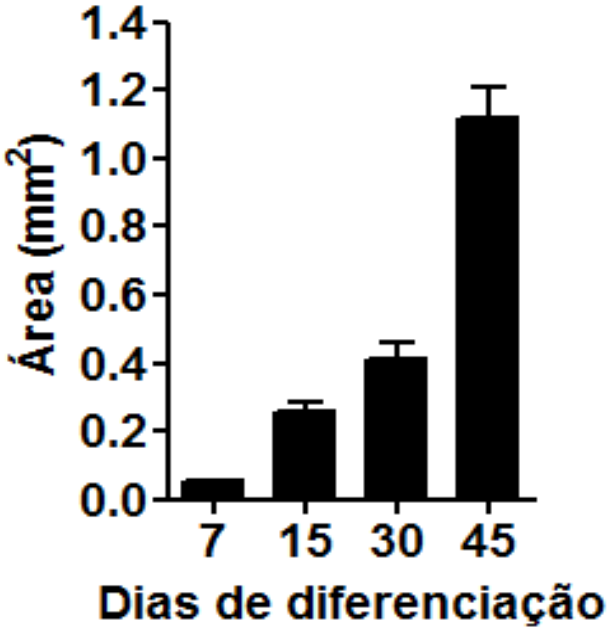
Chimelli *et al*, Acta Neuropathologica (2017)

Sartore *et al*, PeerJ (2017)

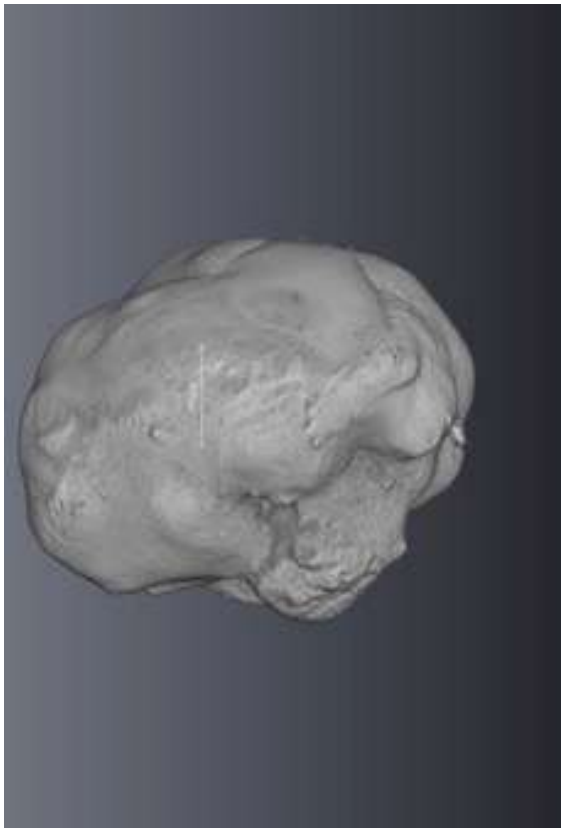


Sartore *et al*, PeerJ (2017)



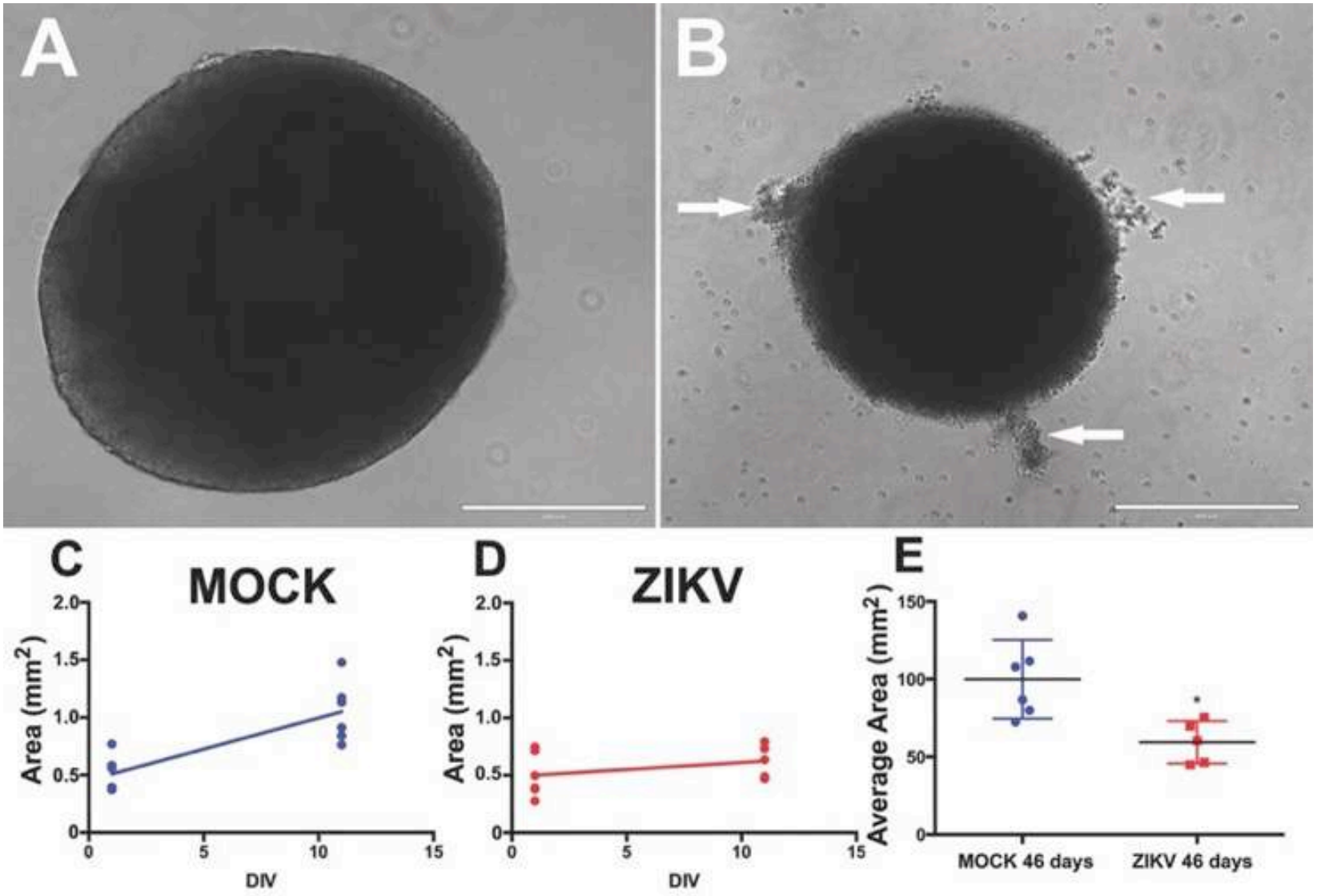


Sartore *et al*, PeerJ (2017)



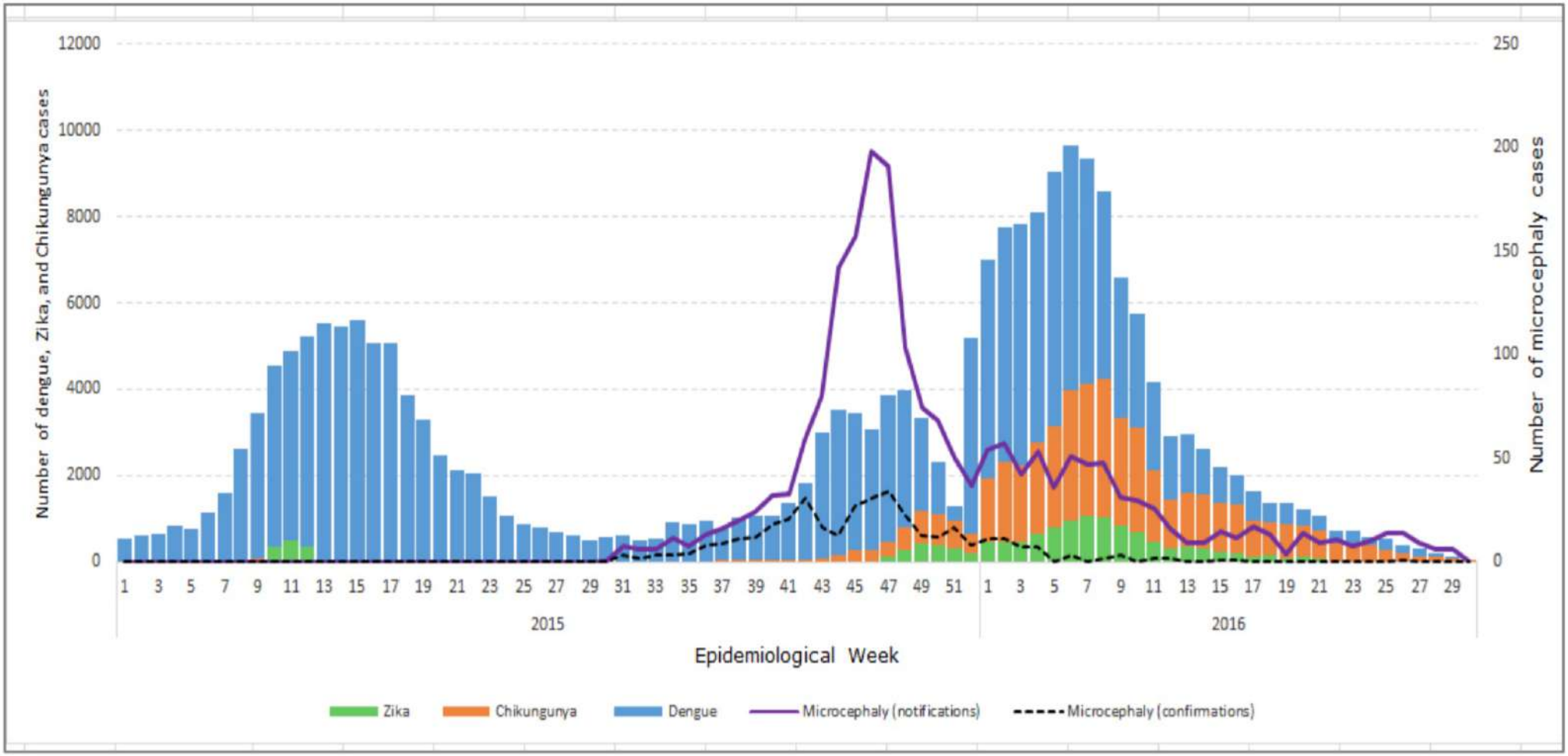
Sartore *et al*, PeerJ (2017)

ZIKV reduces the growth rate of human brain organoids

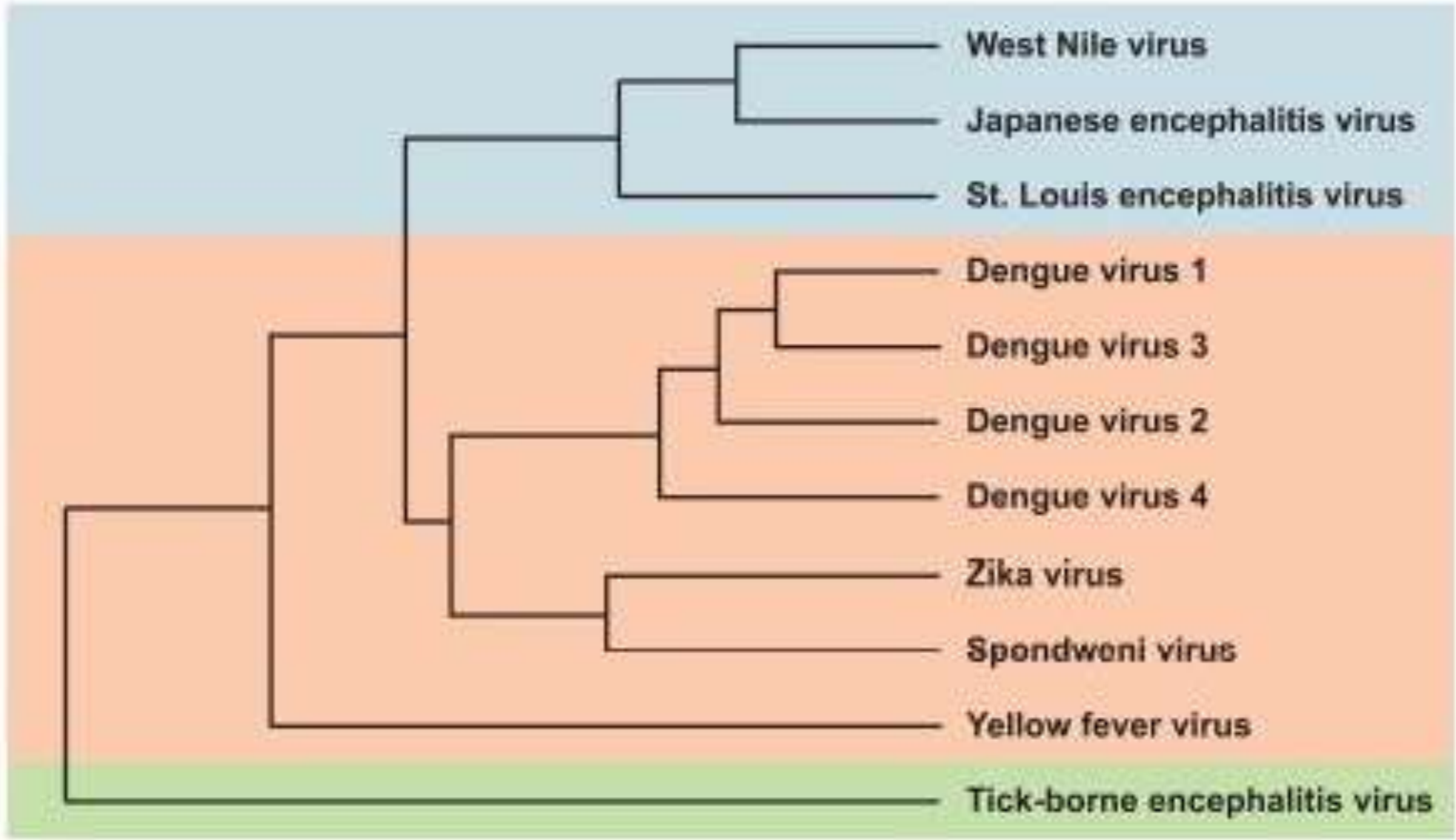


Garcez *et al*, Science (2016)

Figure 8. Chikungunya, dengue, Zika and microcephaly cases reported in the state of Pernambuco, by EW. Brazil. 2015 to EW 29 of 2016

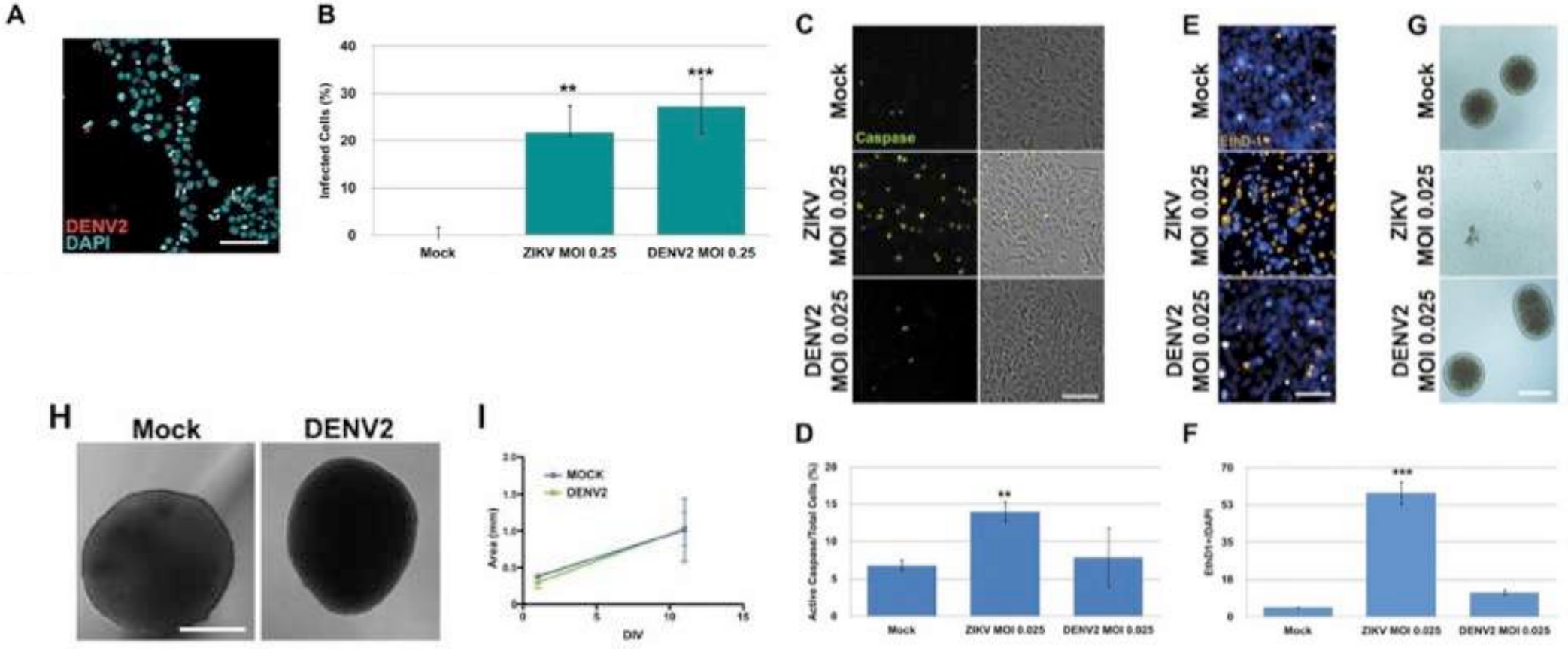


Source: Data provided by the Pernambuco Secretary of Health

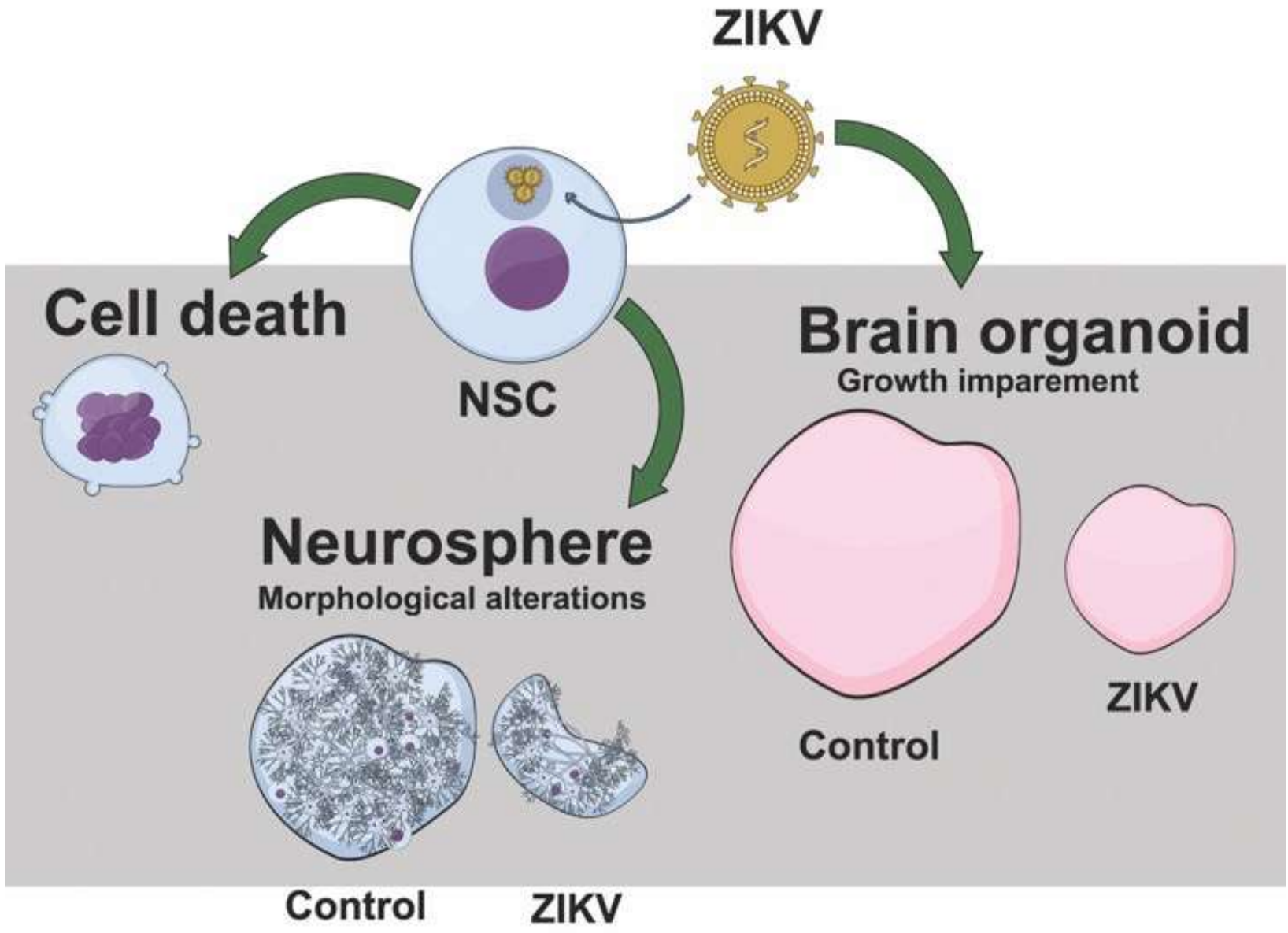


http://drrajivdesaimd.com/2016/05/12/zika/

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



Garcez *et al*, Science (2016)



Garcez et al, Science (2016)

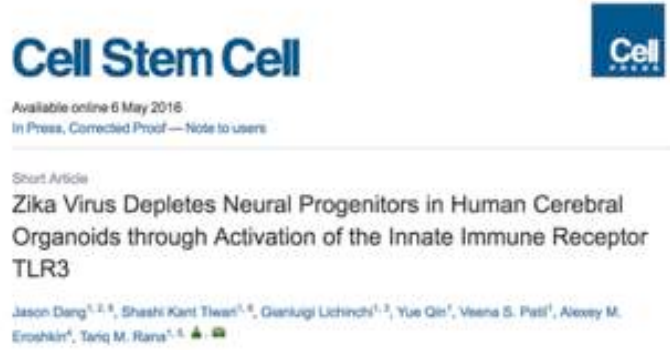
Science

REPORTS

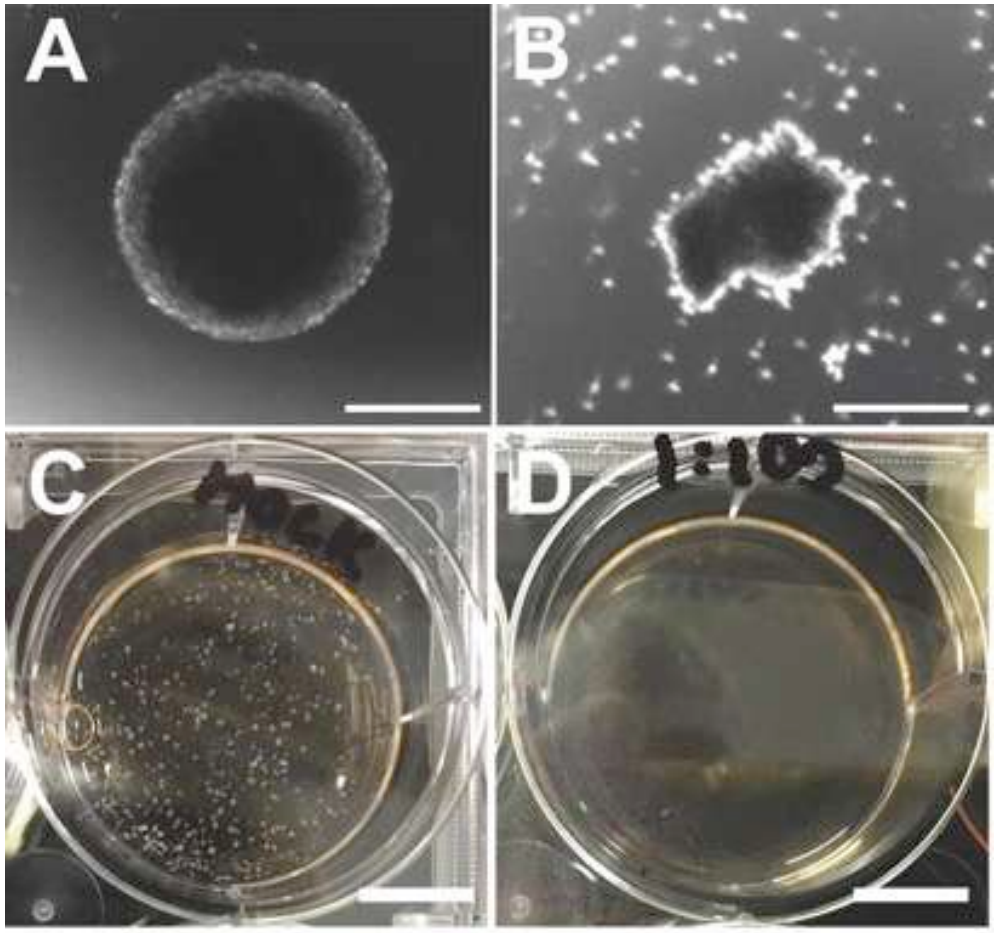
Cite as: Garcez *et al.*, *Science*
10.1126/science.aaf6116 (2016).

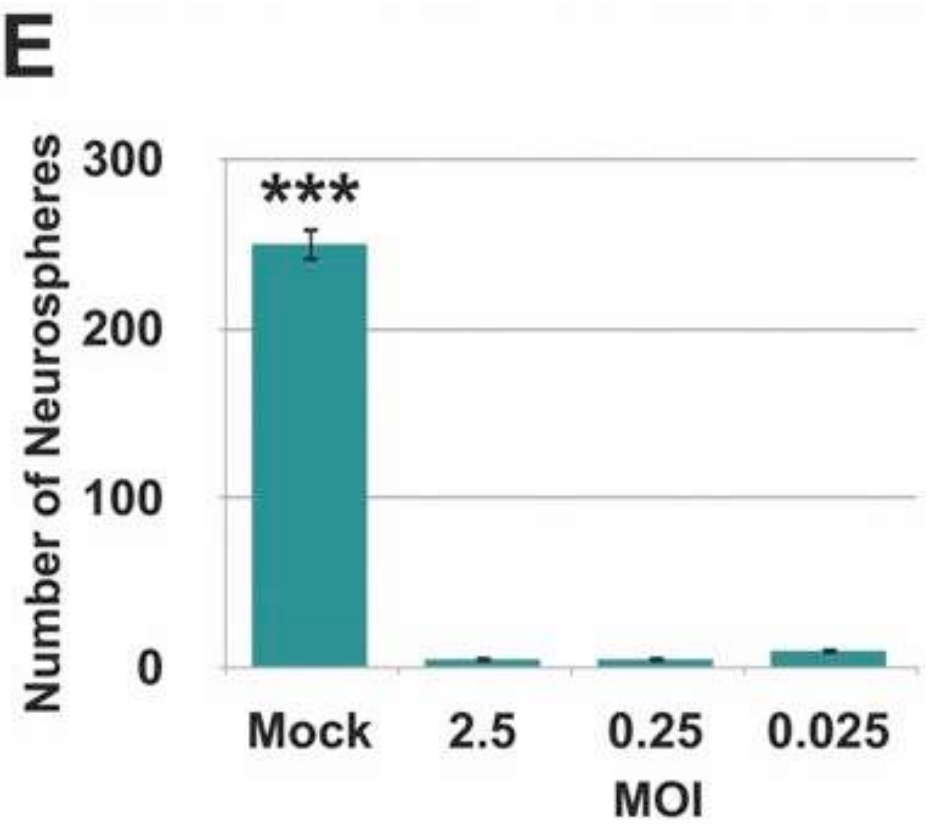
Zika virus impairs growth in human neurospheres and brain organoids

Patricia P. Garcez,[1,2*] Erick Correia Loiola,[2†] Rodrigo Madeiro da Costa,[2†] Luiza M. Higa,[2†] Pablo Trindade,[2†] Rodrigo Delvecchio,[3] Juliana Minardi Nascimento,[2,4] Rodrigo Brindeiro,[5] Amilcar Tanuri,[3] Stevens K. Rehen[2,1*]

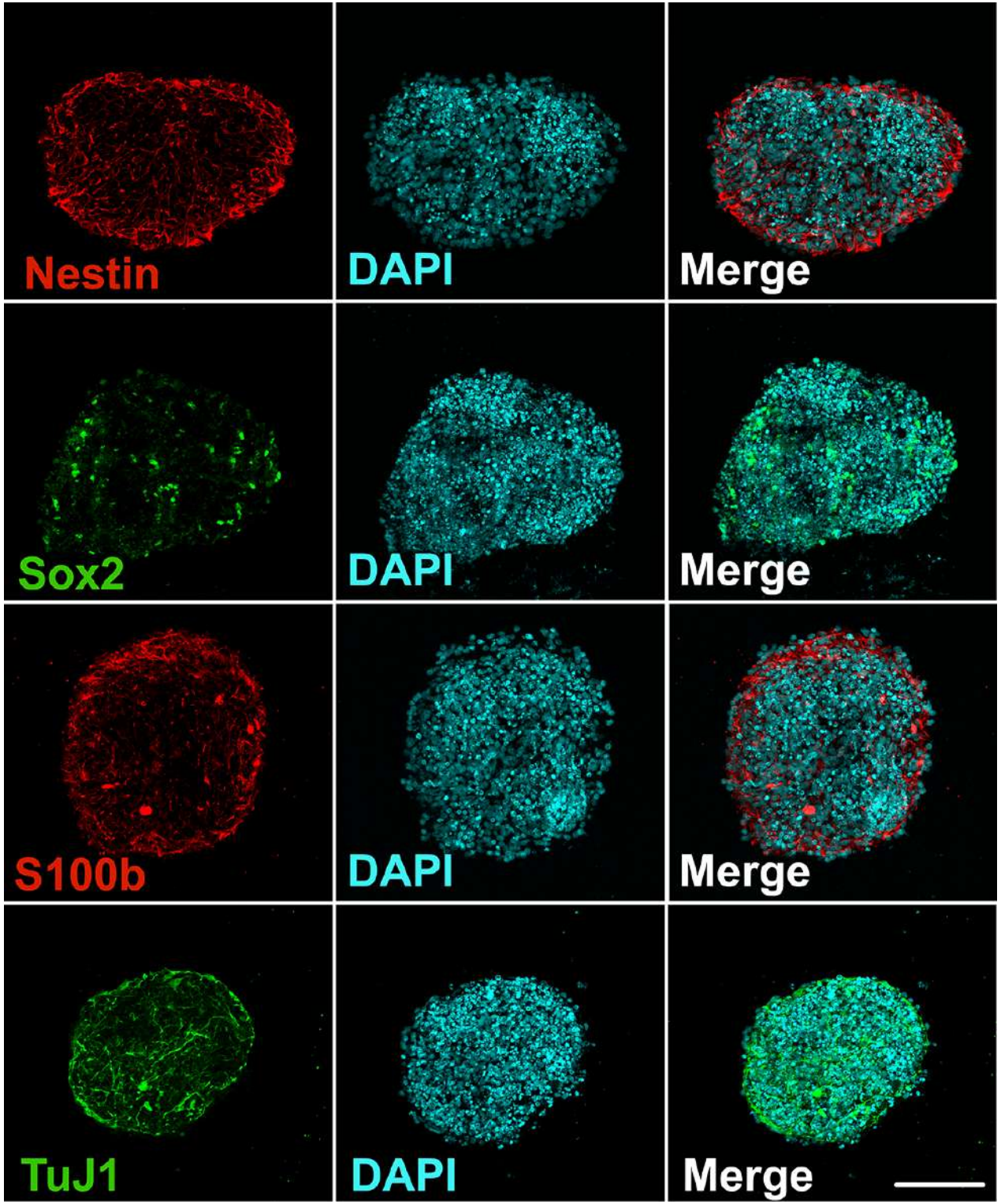


ZIKV alters morphology and halts the growth of human neurospheres





Garcez *et al*, Science (2016)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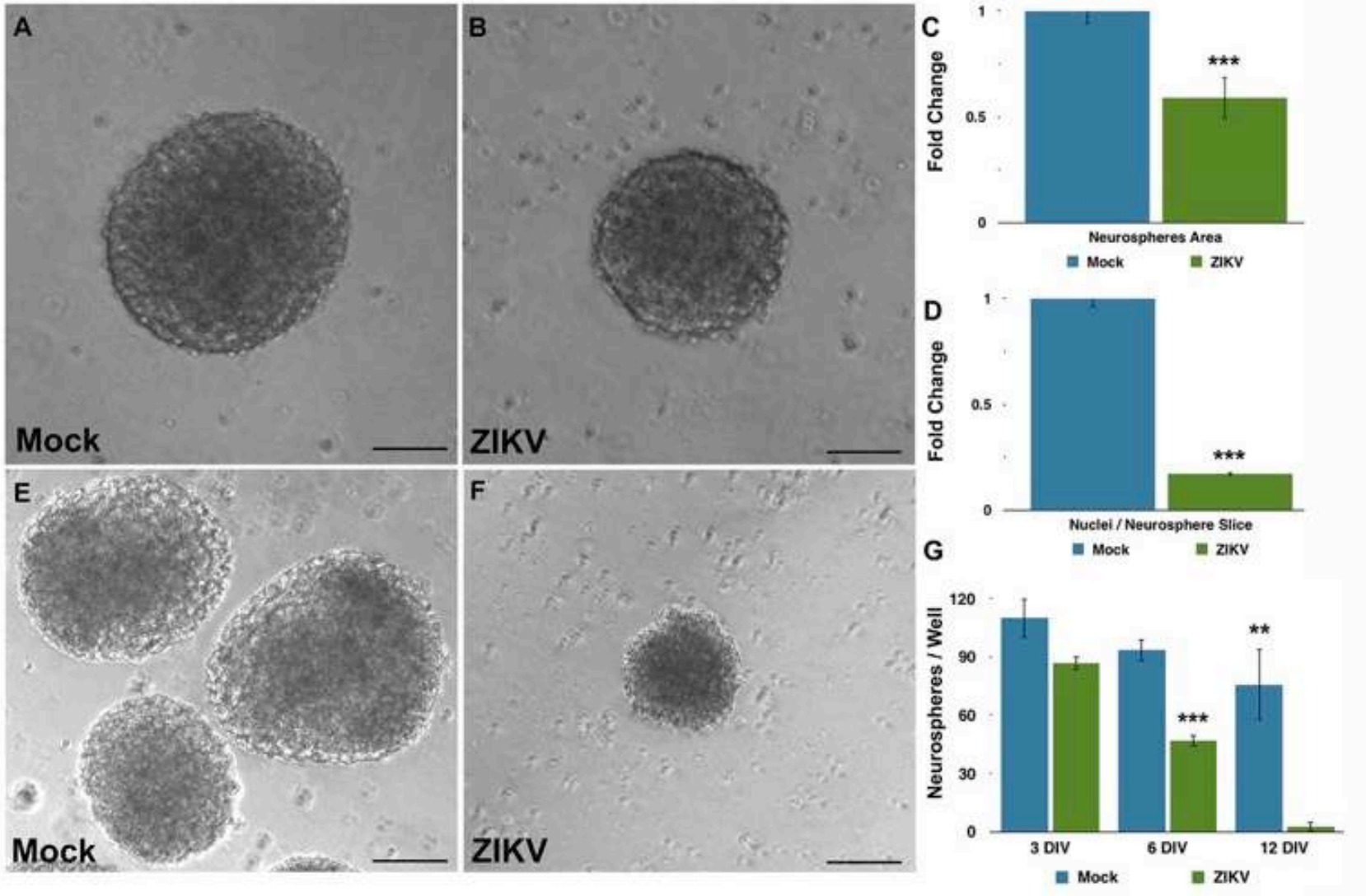
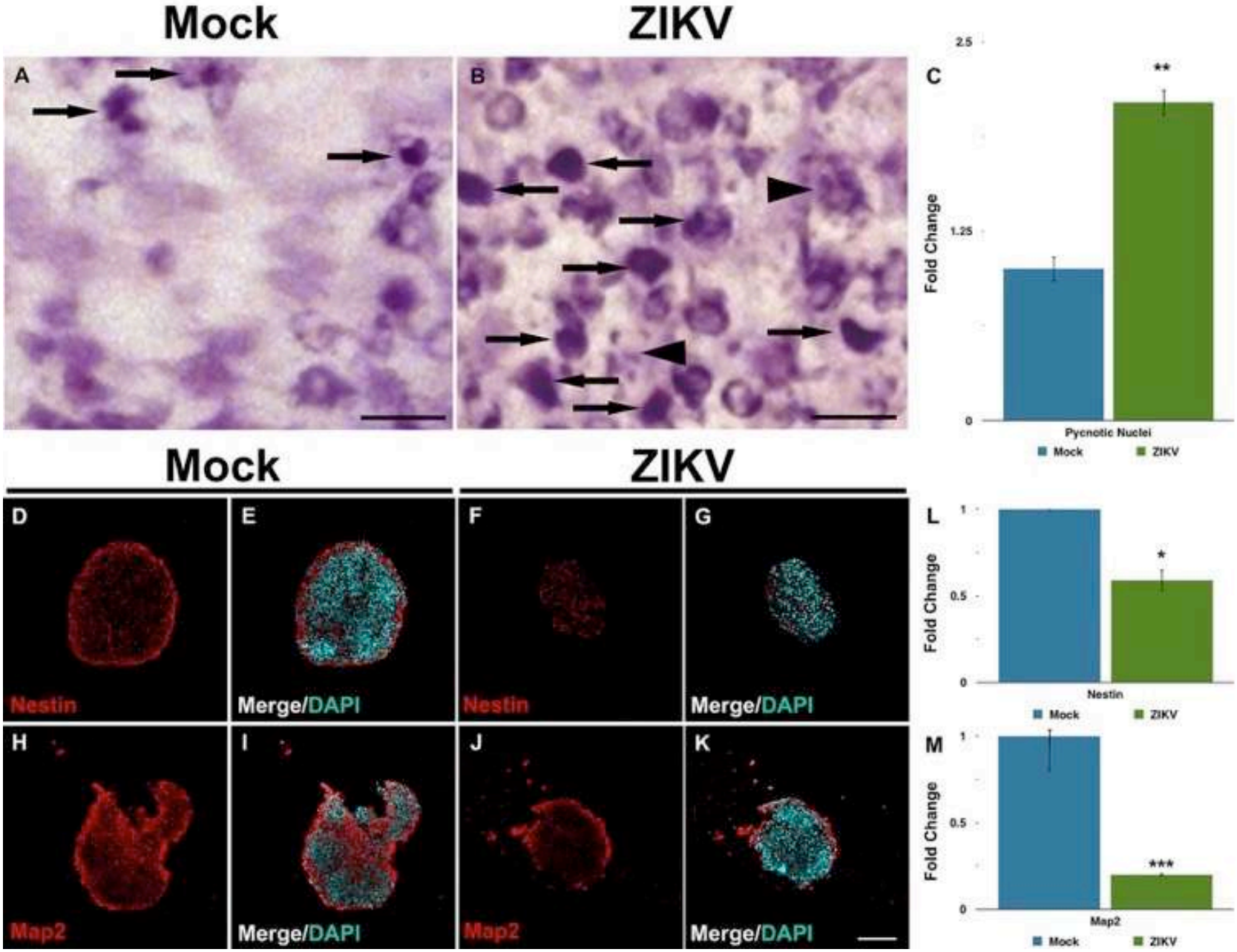
Br ZIKV reduces the growth of neurospheres



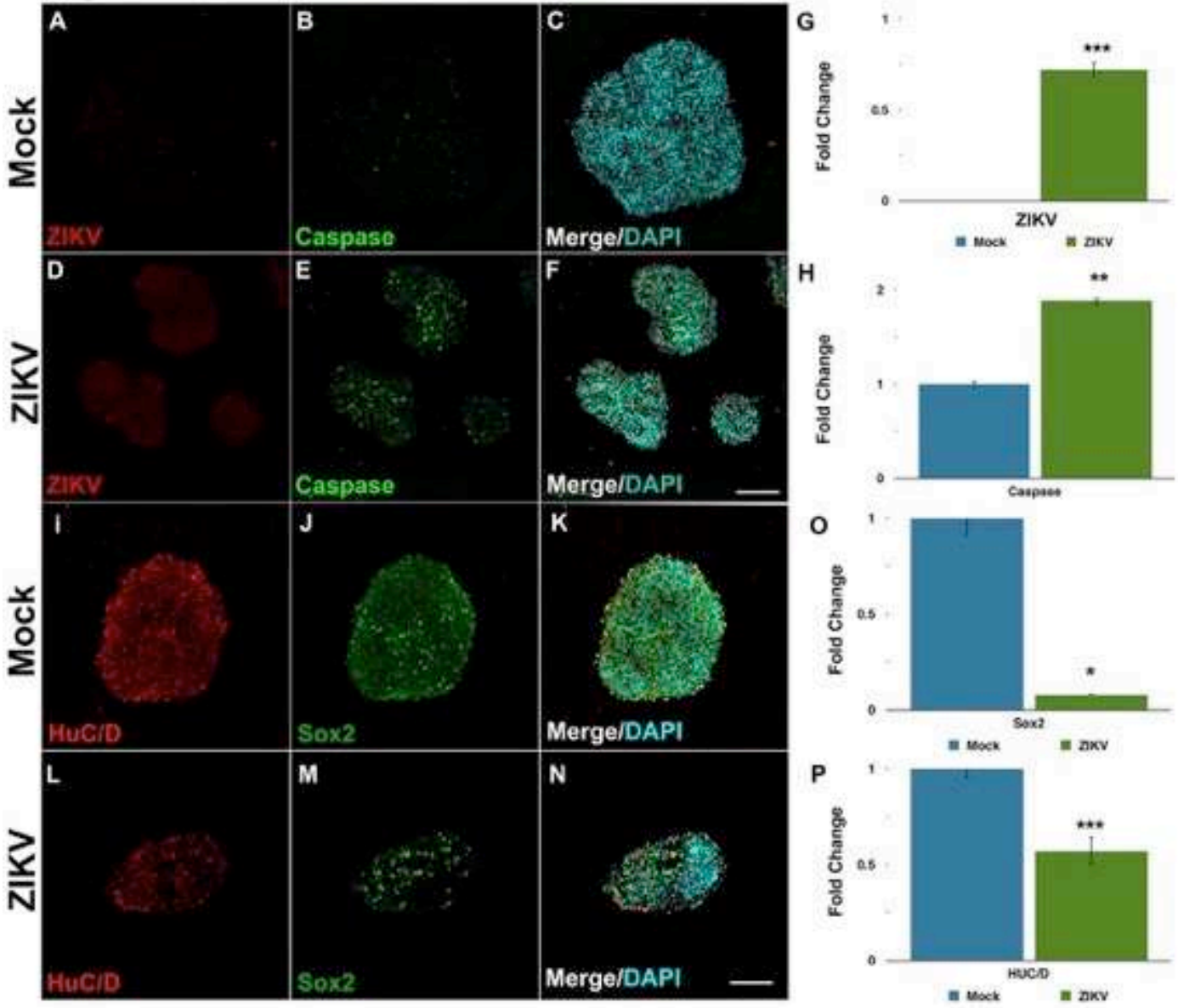
Garcez *et al*, Scientific Reports (2017)

BRZIKV triggers cell death in human neurospheres

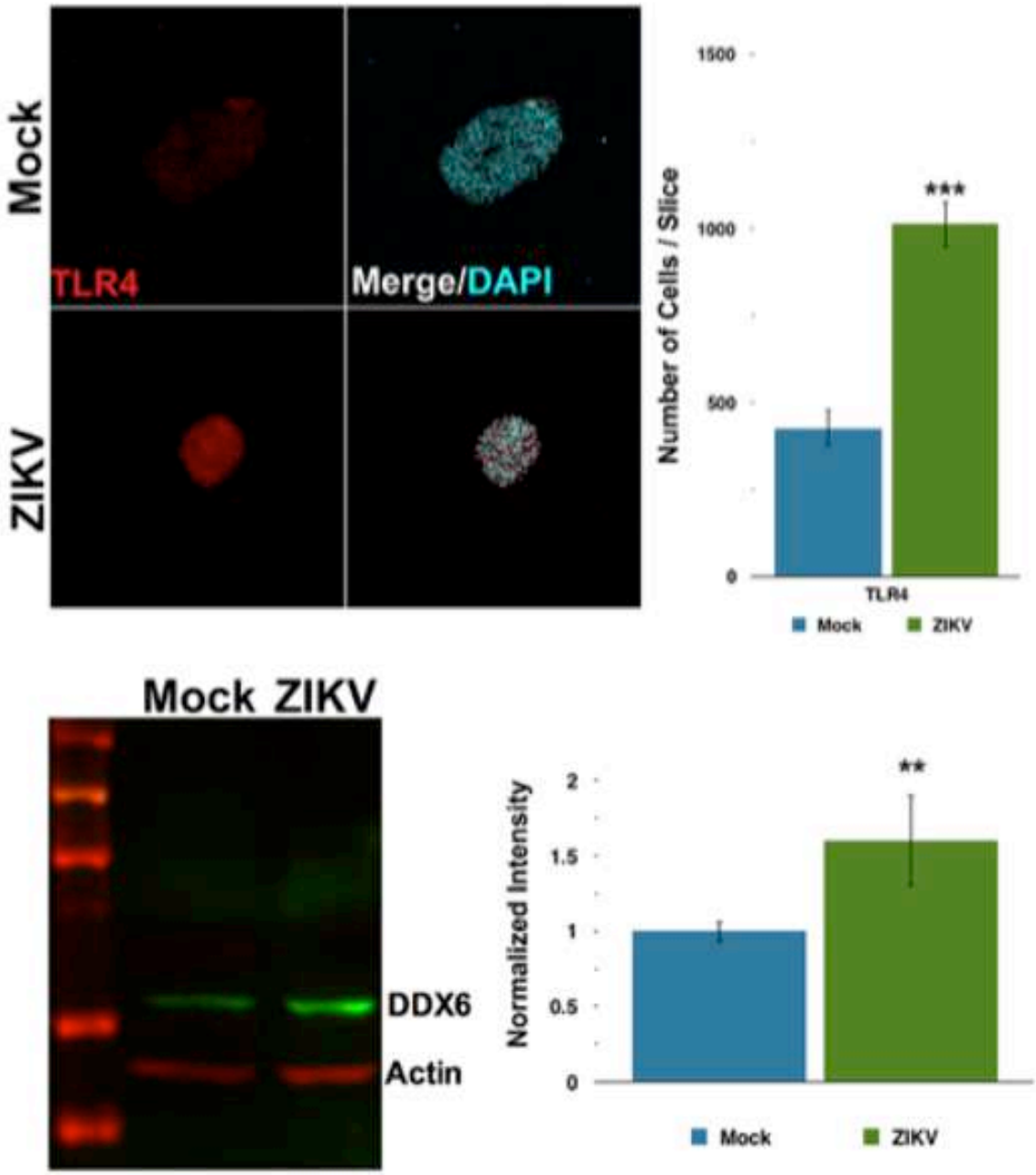


Garcez *et al*, Scientific Reports (2017)

Br ZIKV reduces the growth of neurospheres, by depleting the pool of neural progenitors and the generation of neurons

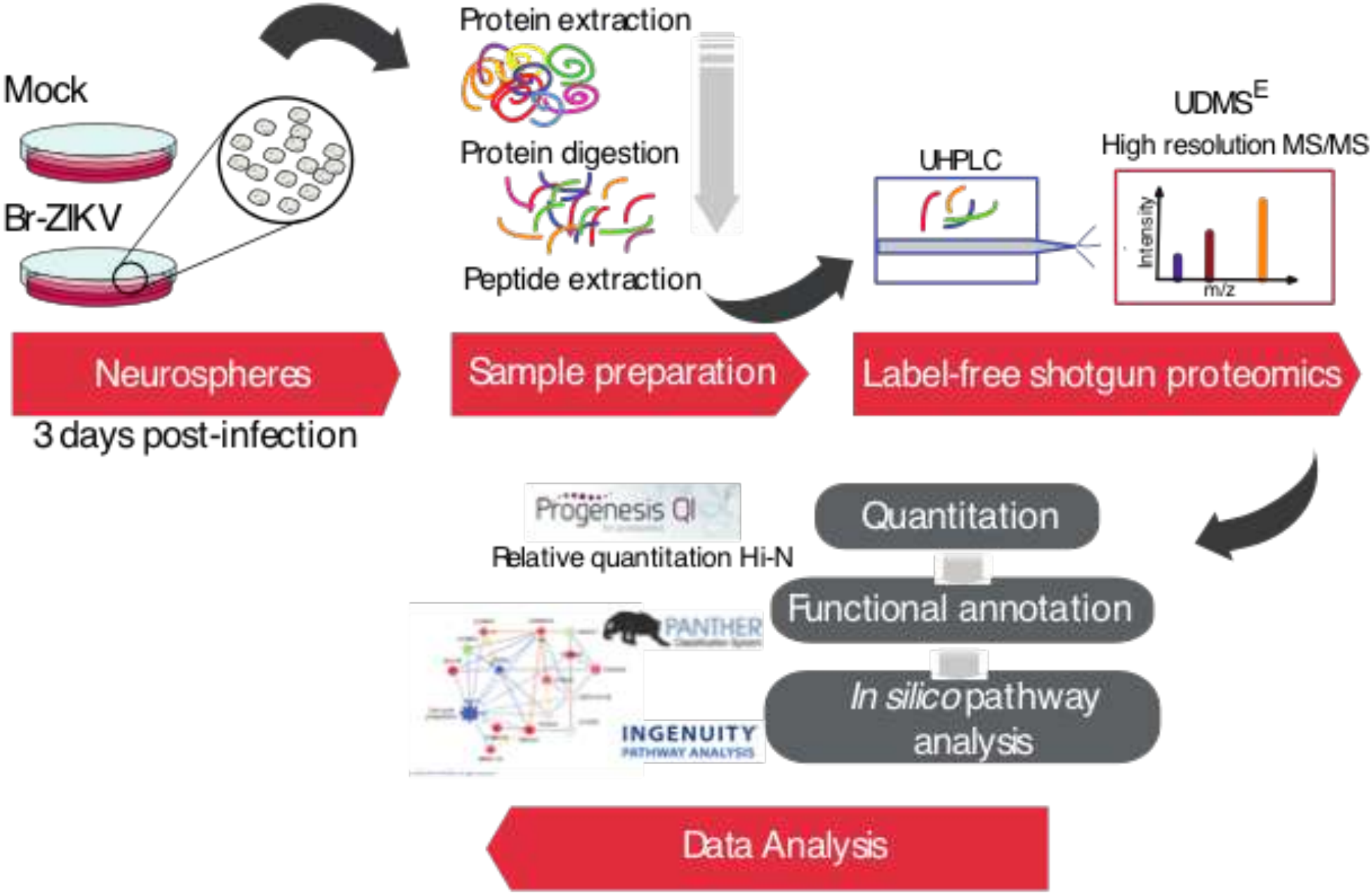


Garcez *et al*, 2016 (submitted)

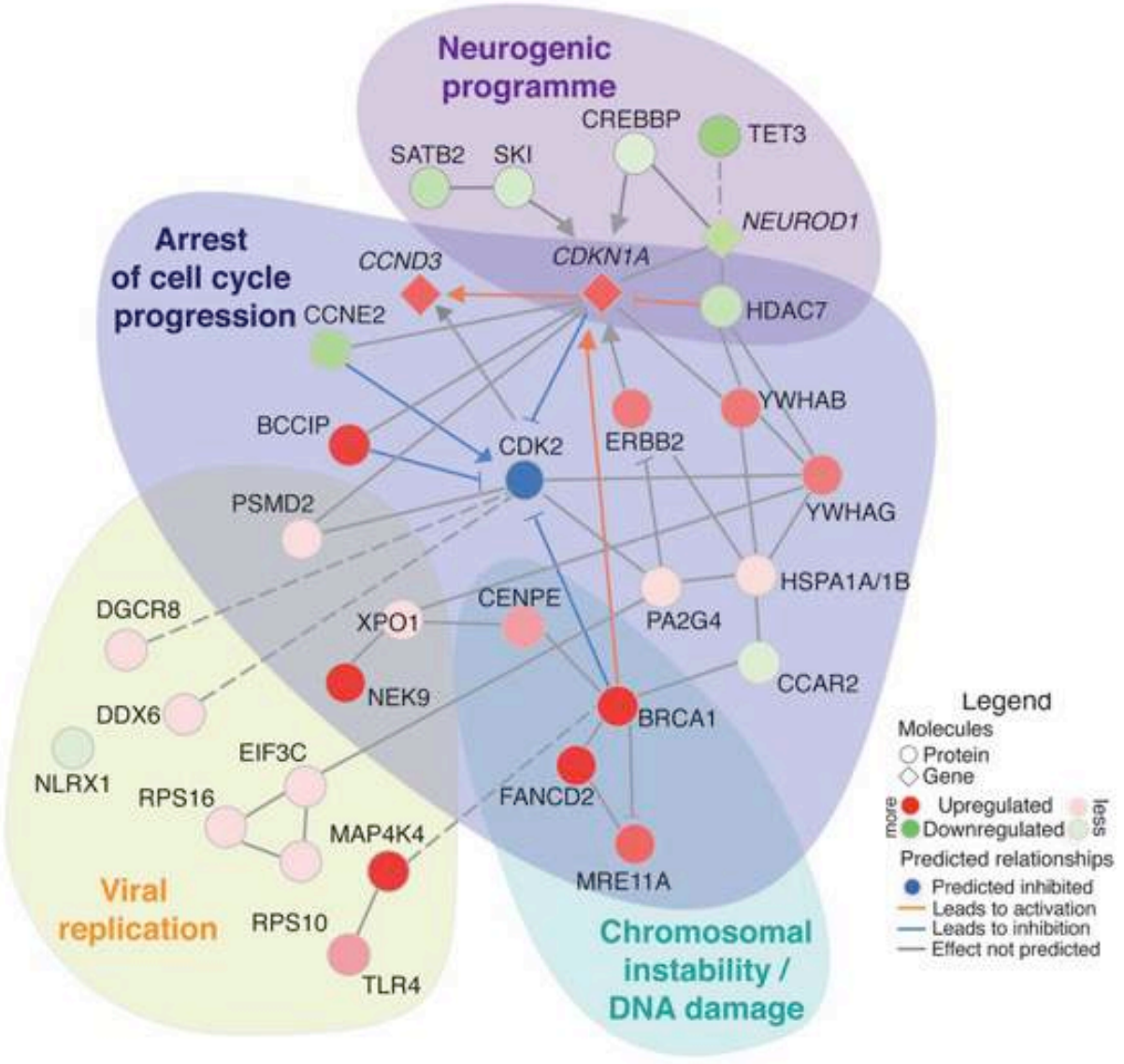


Garcez *et al*, Scientific Reports (2017)

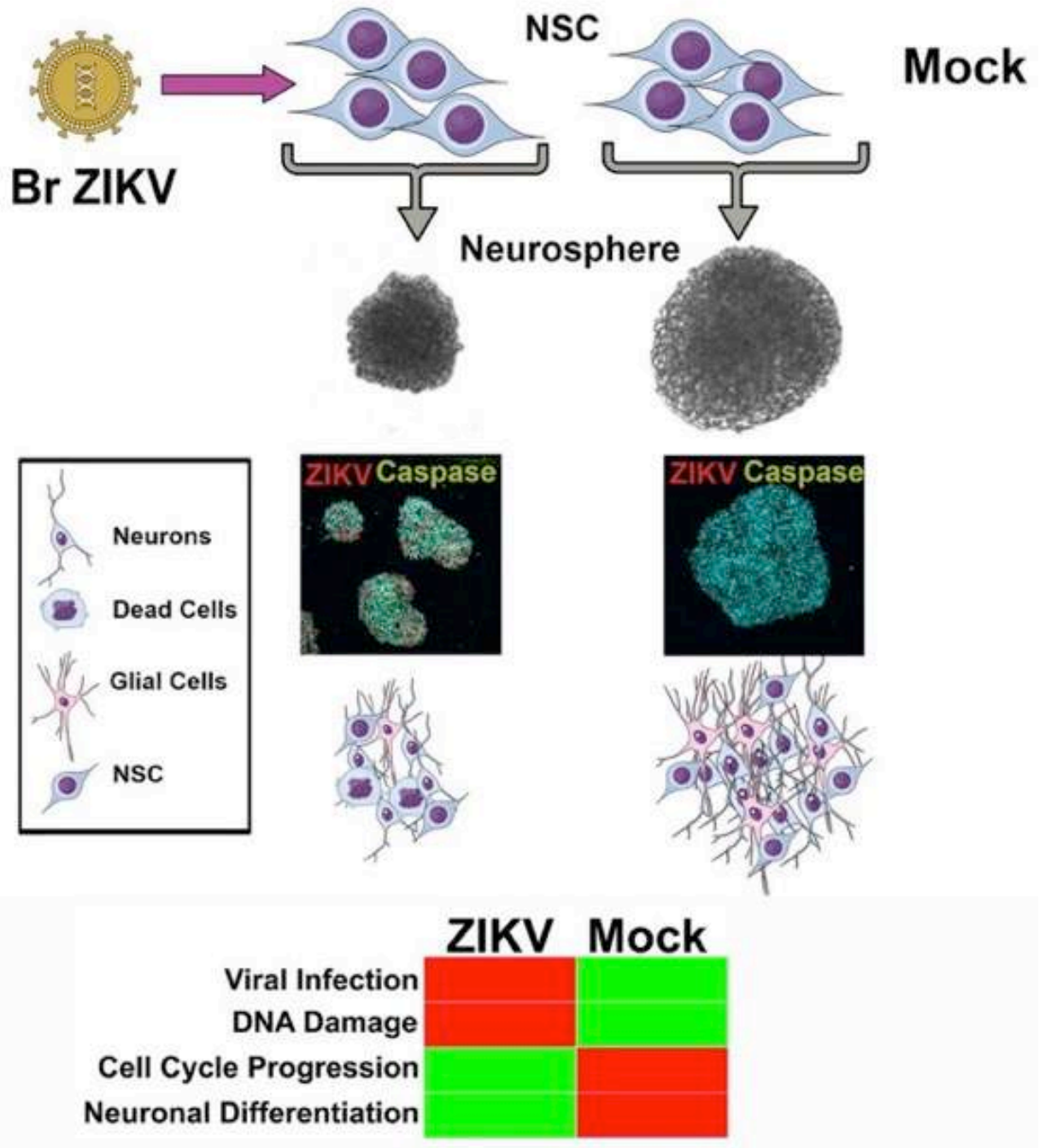
Shotgun proteomics



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



Garcez *et al*, Scientific Reports (2017)



Garcez *et al*, Scientific Reports (2017)

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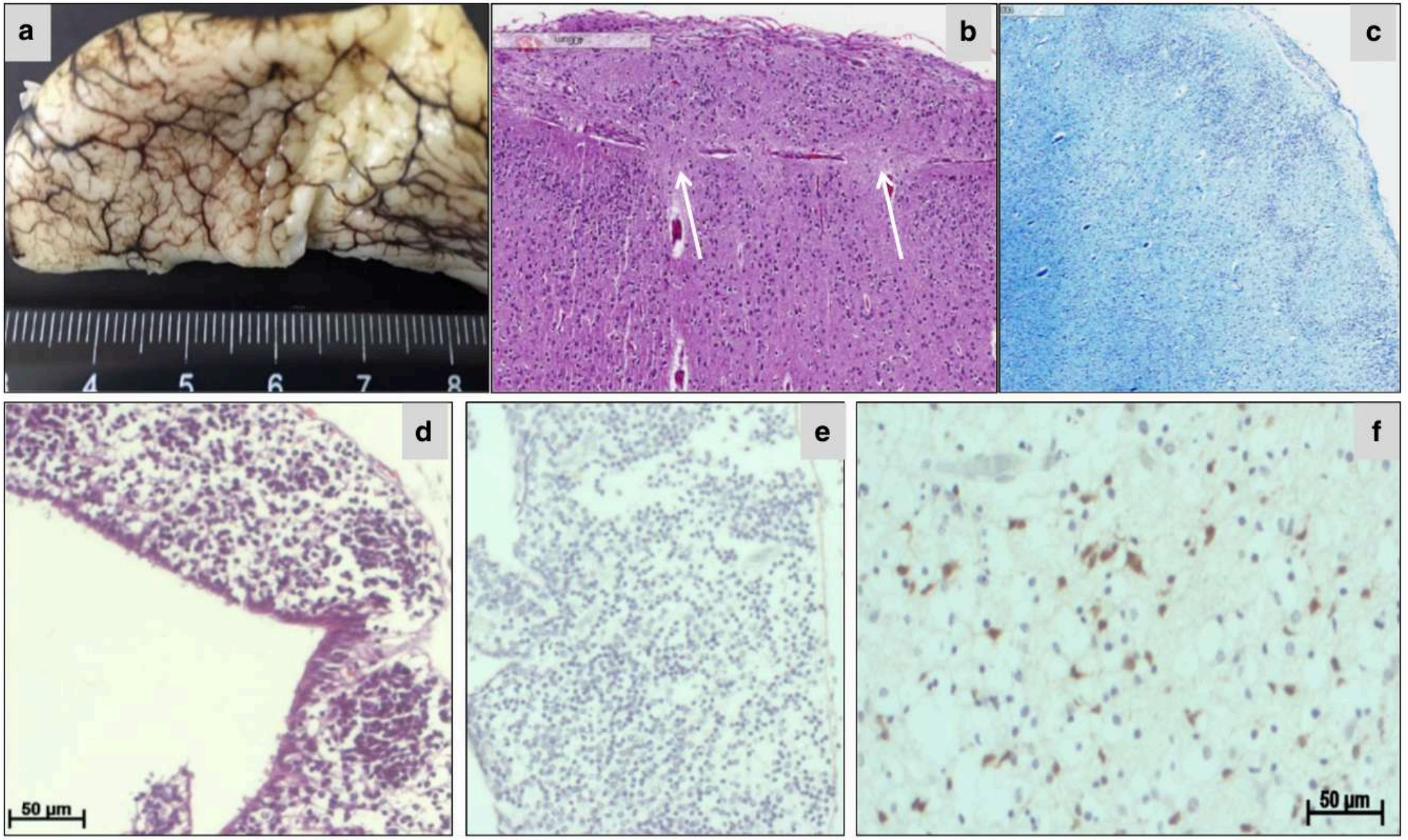
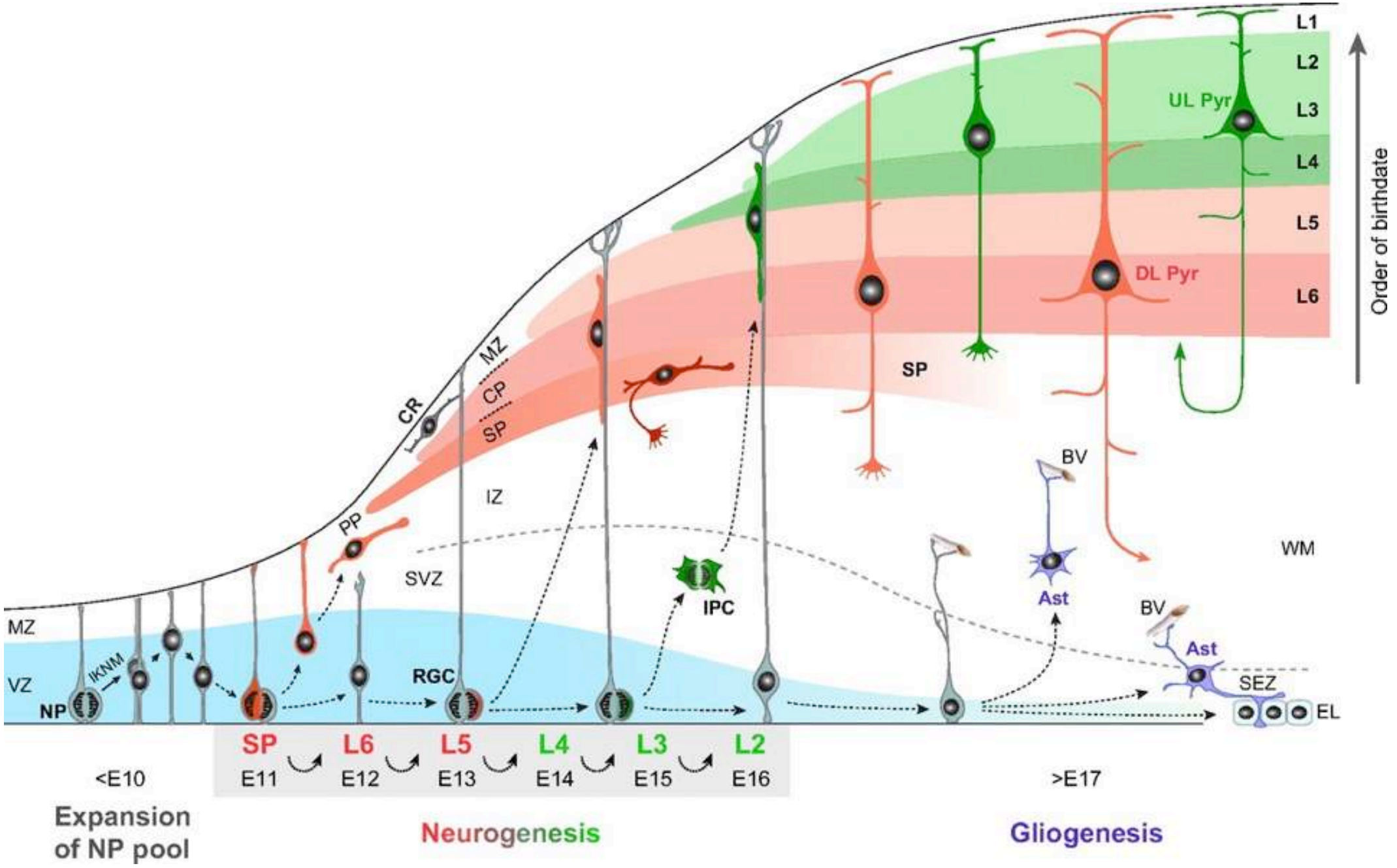
Zika virus disrupts molecular fingerprinting of human neurospheres

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

“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.”



Chimelli *et al*, Acta Neuropathologica (2017)


L1
L2
L3
L4
L5
L6
UL Pyr
DL Pyr
SP
Order of birthdate
CR
MZ
CP
SP
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IPC
BV
Ast
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MZ
VZ
NP
IKNM
RGC
SP
L6
L5
L4
L3
L2
<E10
E11
E12
E13
E14
E15
E16
>E17
Expansion
of NP pool
Neurogenesis
Gliogenesis

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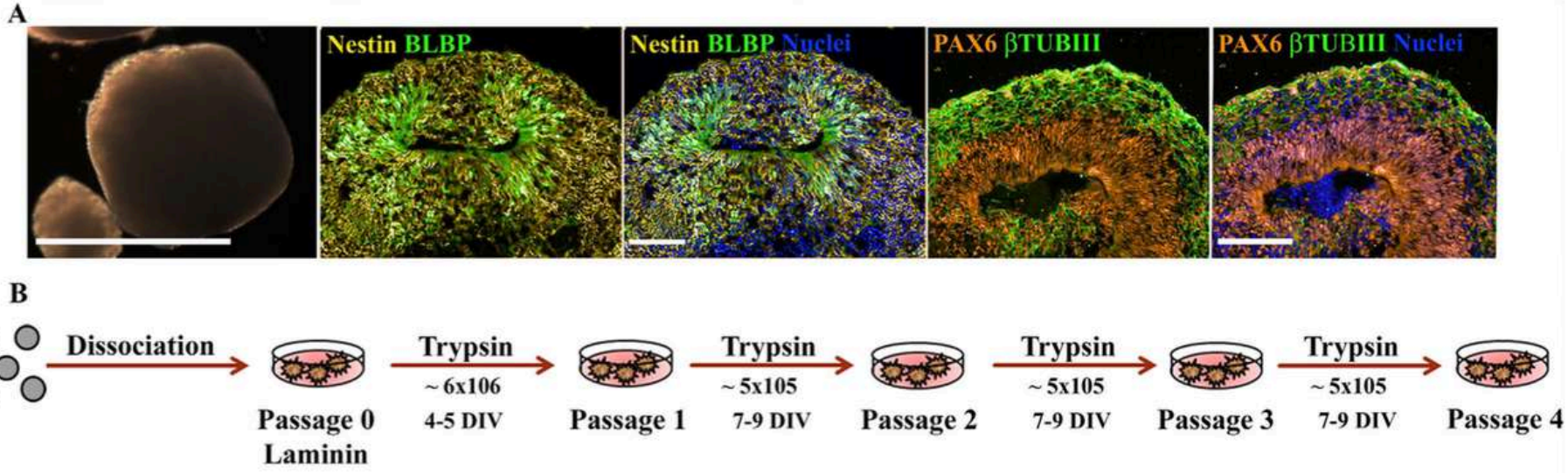
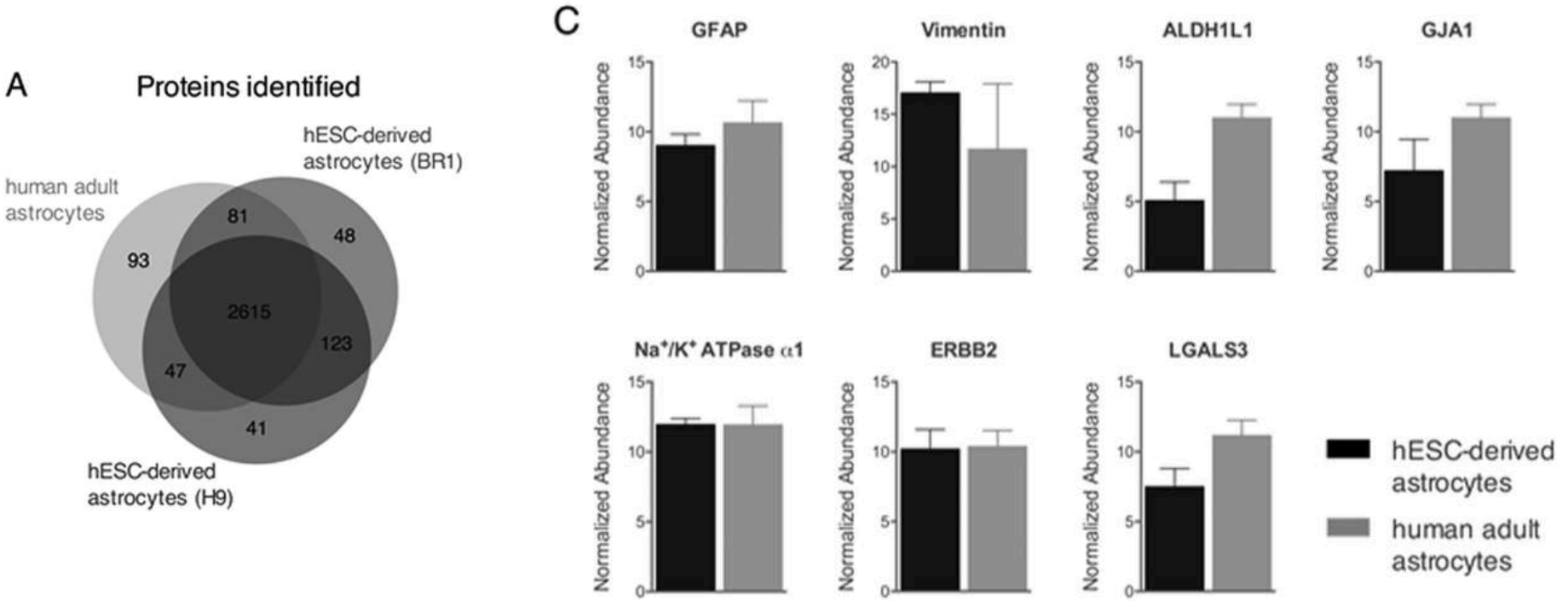
Derivation of Functional Human Astrocytes from Cerebral Organoids

Rômulo Sperduto Dezonne[1], Rafaela Costa Sartore[1,2], Juliana Minardi Nascimento[2,3], Verônica M. Saia-Cereda[3], Luciana Ferreira Romão[1,4], Soniza Vieira Alves-Leon[5], Jorge Marcondes de Souza[5], Daniel Martins-de-Souza[3], Stevens Kastrup Rehen[1,2] & Flávia Carvalho Alcantara Gomes[1]

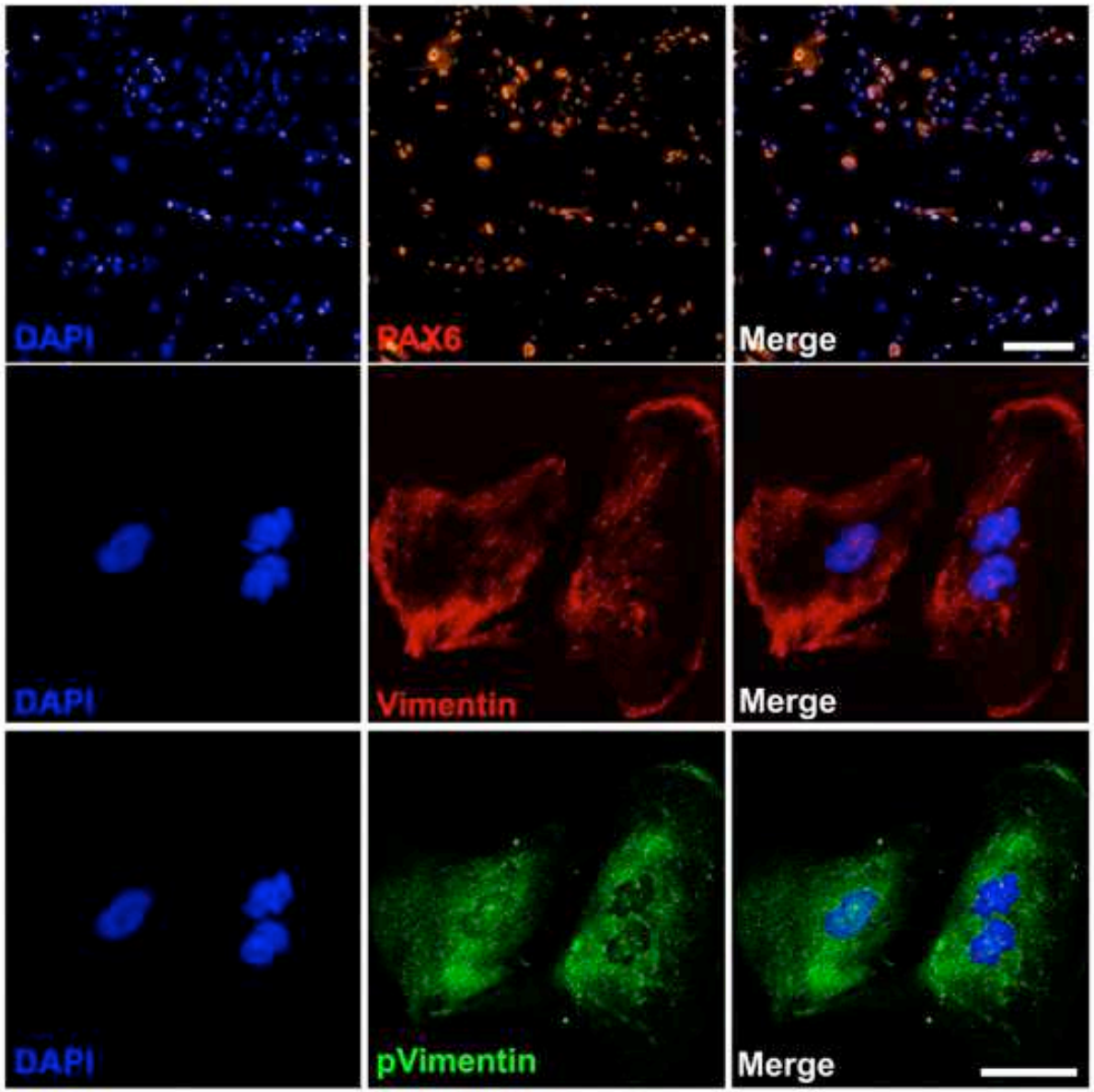
Received: 31 October 2016
Accepted: 15 February 2017

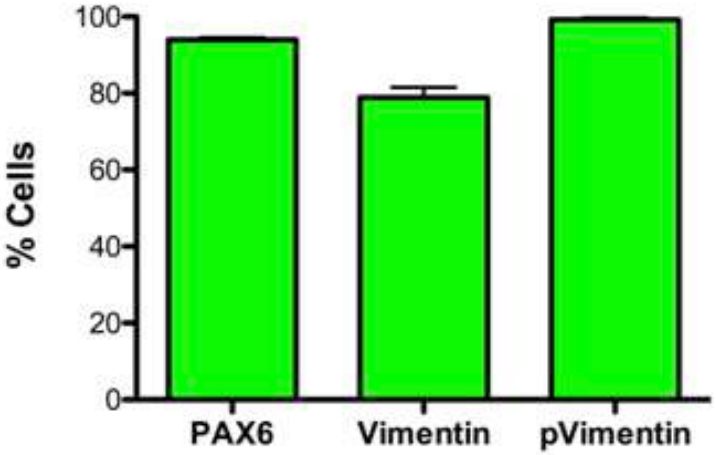




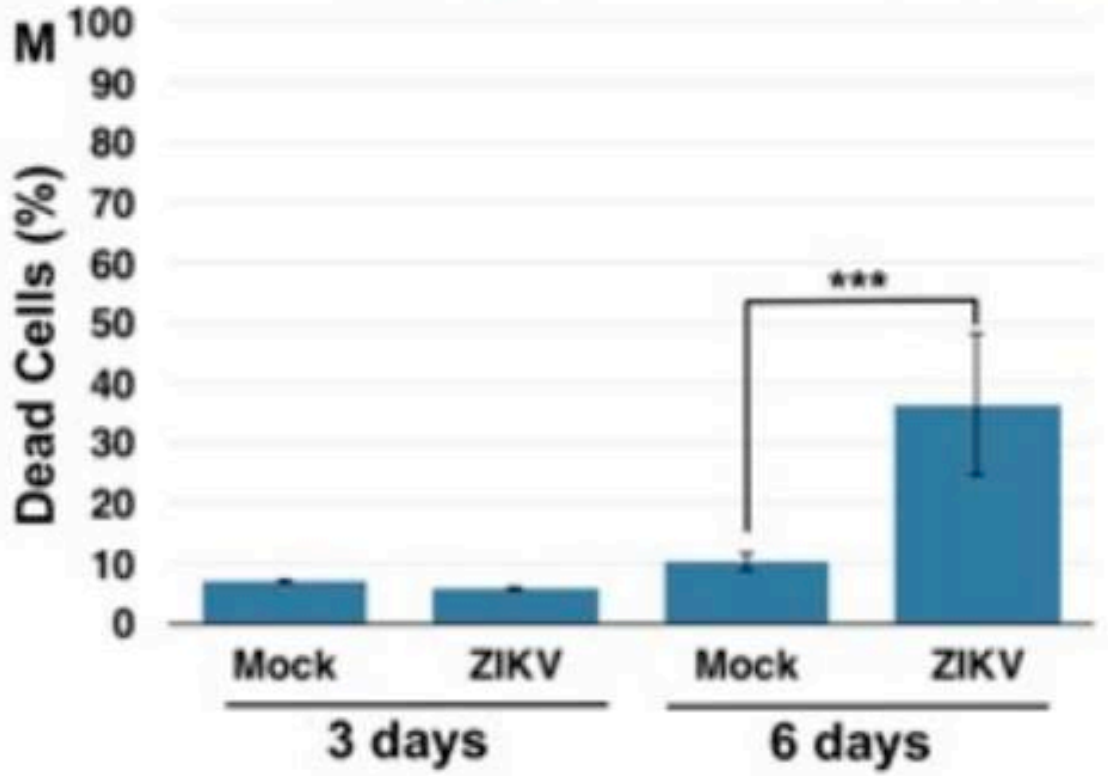
Dezonne *et al*, Scientific Reports (2017)

Generation of radial glial cells/astrocytes from human iPS cells



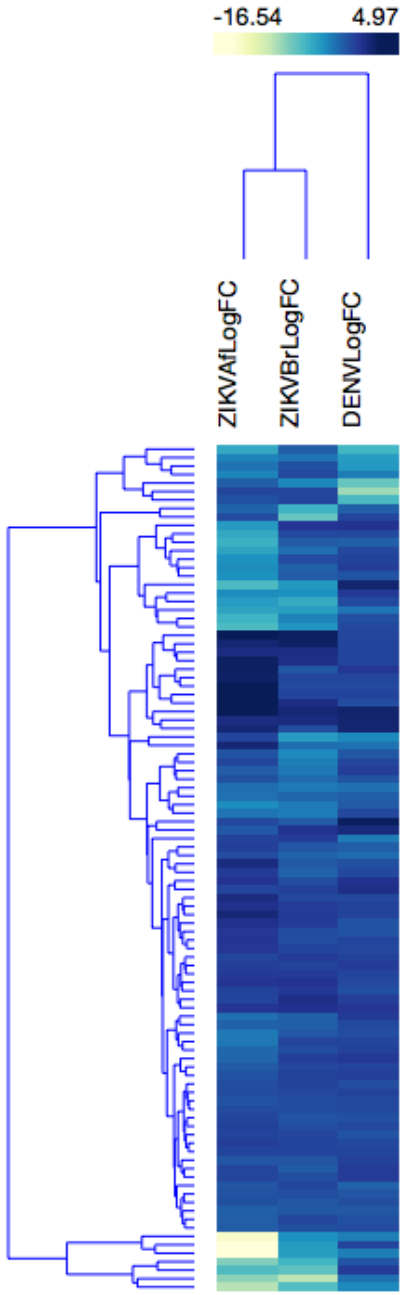


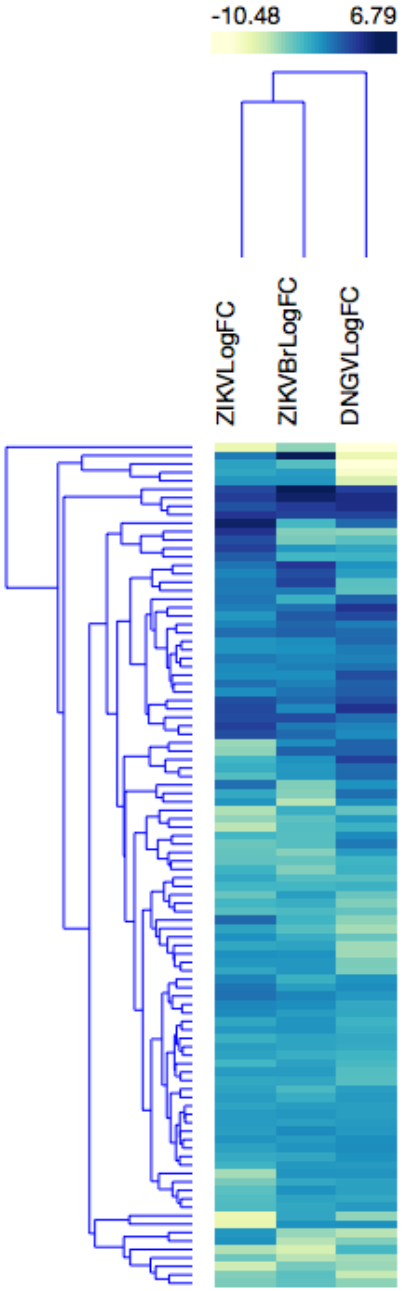
Garcez *et al*, Scientific Reports (2017)



Garcez *et al*, Scientific Reports (2017)

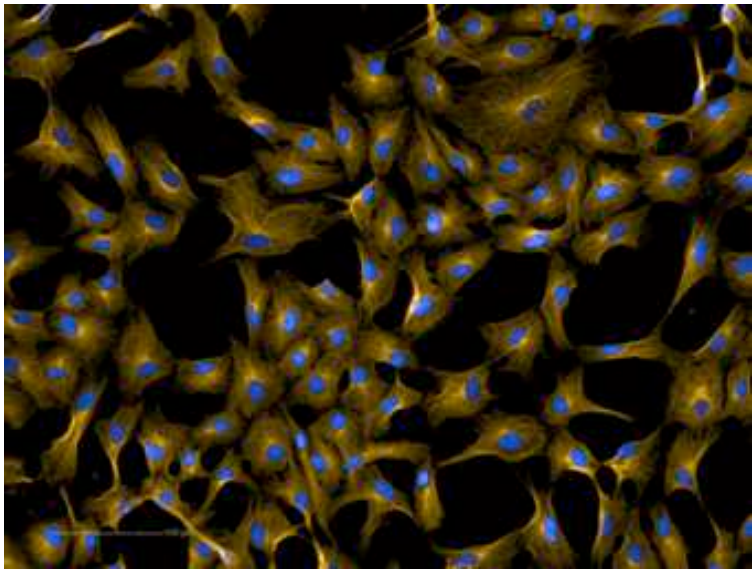
Proteomic analysis of Br ZIKV-infected different neural cells types

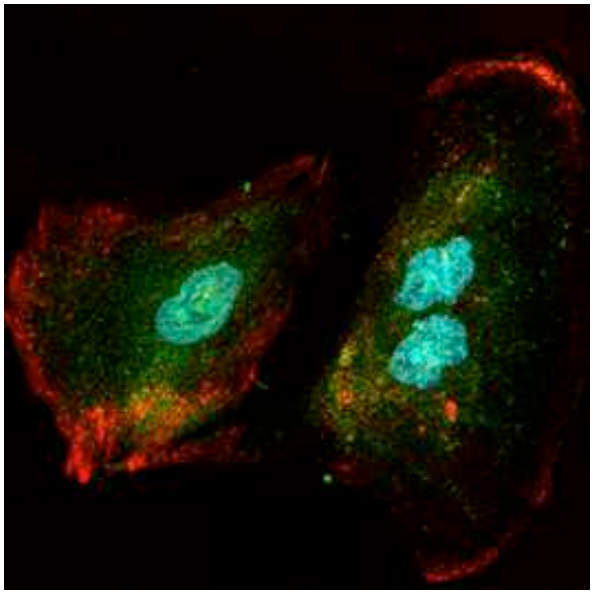


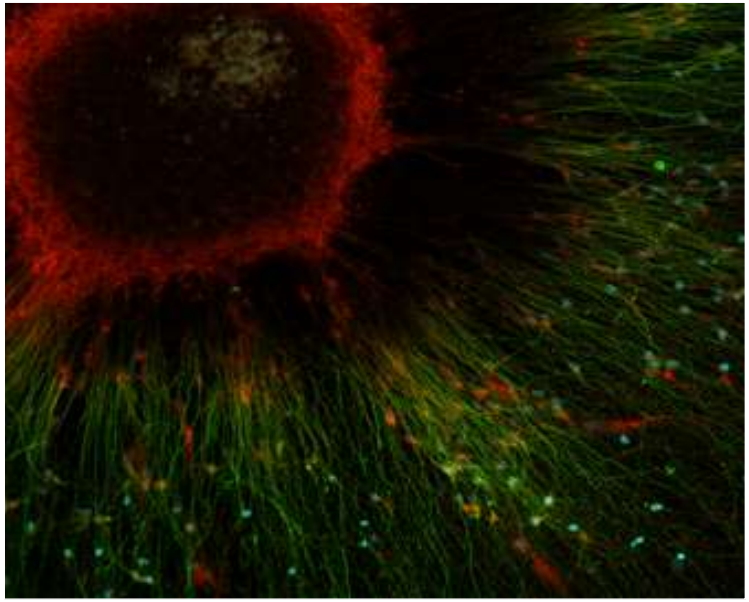


Minardi *et al* (unpublished data)

Human cellular models to identify leads for Zika virus







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Drug screen to identify leads for Zika virus

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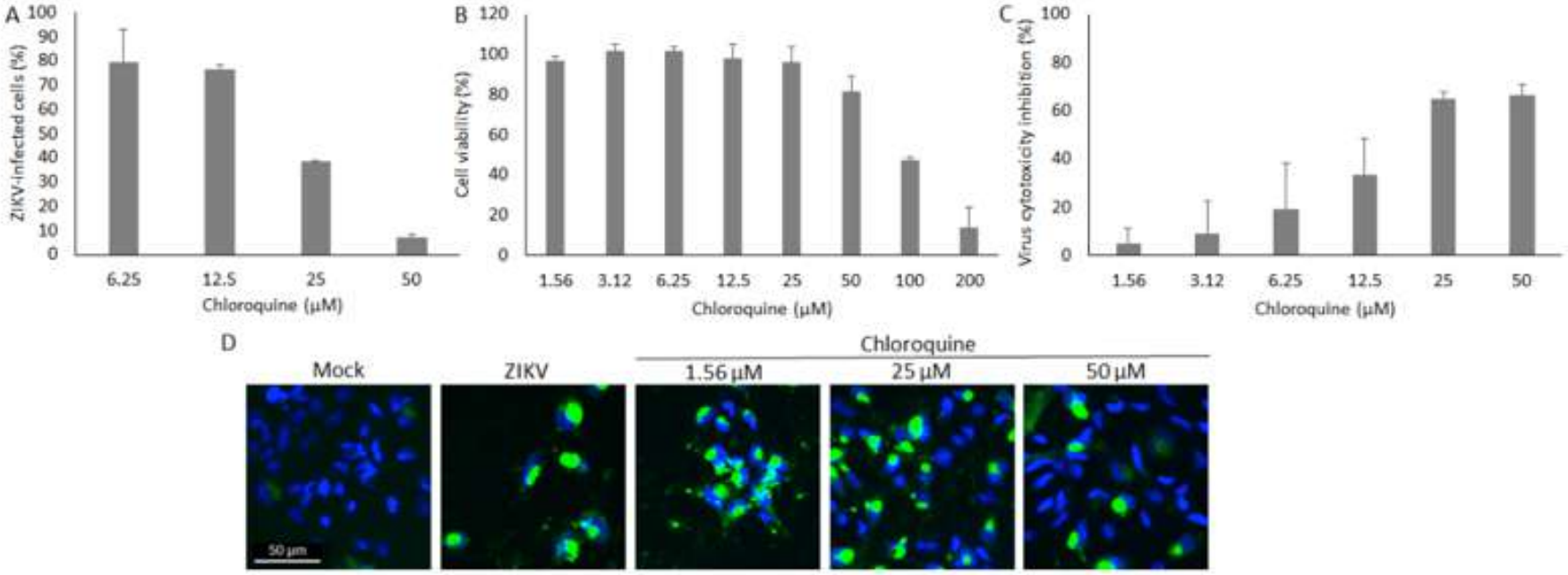
Screening to identify leads for Zika virus: Chloroquine (1934)



viruses

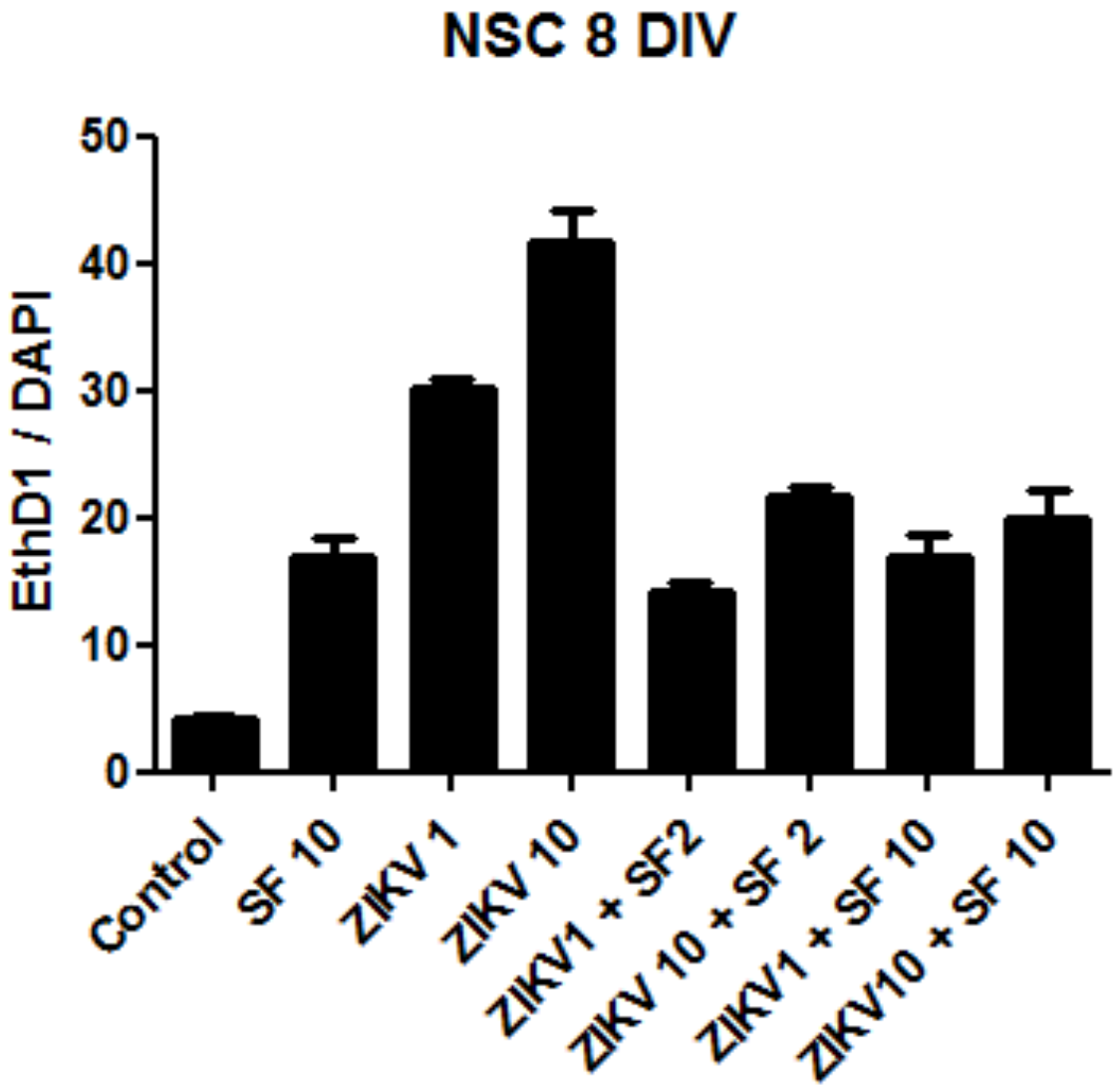
MDPI

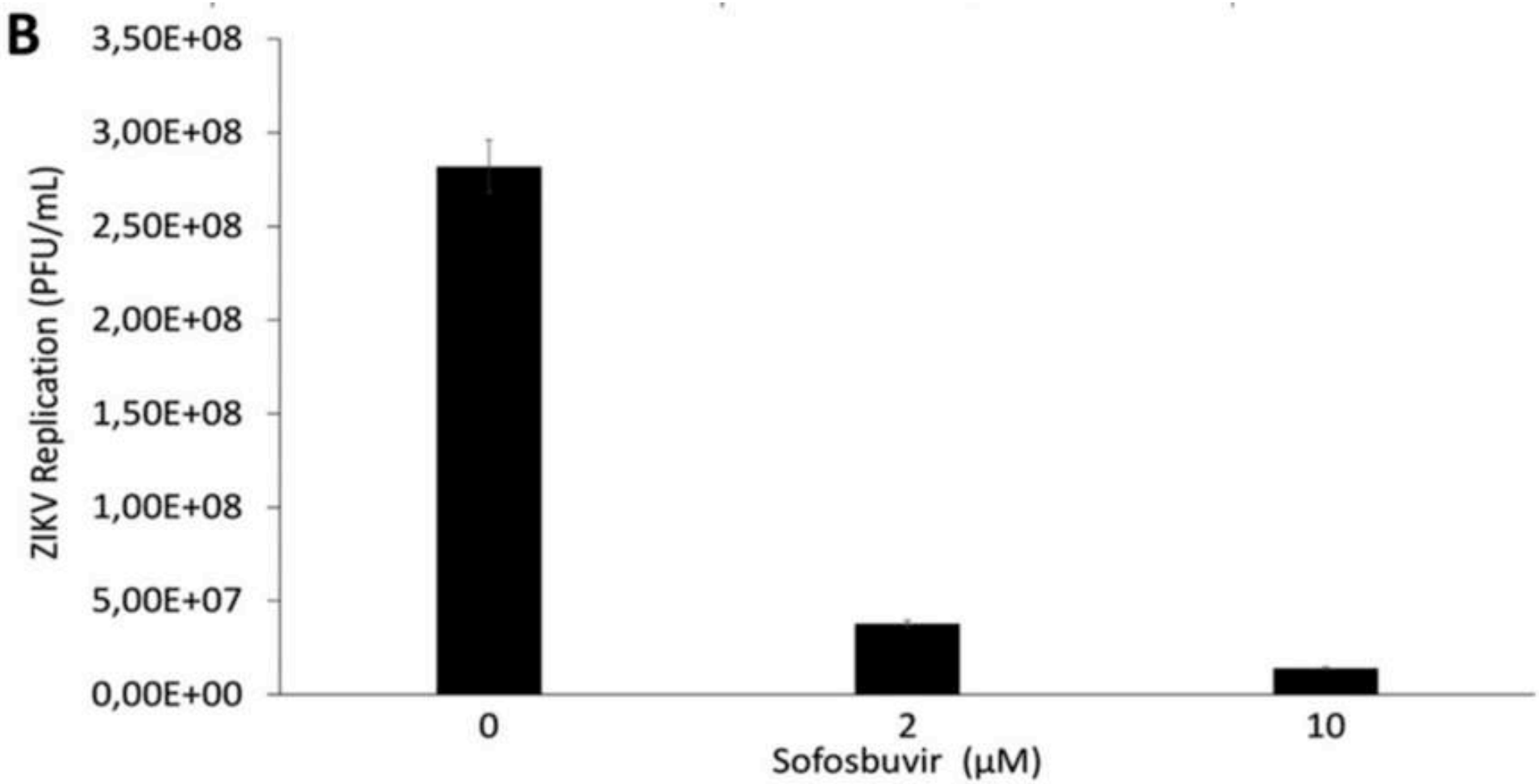
Article

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,*]

Screening to identify leads for Zika virus: Sofosbuvir (2013)

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1,00E+08
5,00E+07
0,00E+00
ZIKV Replication (PFU/mL)
0
2
10
Sofosbuvir (µM)

SCIENTIFIC REPORTS

Article | OPEN

The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication

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

Acta Neuropathol
DOI 10.1007/s00401-017-1699-5

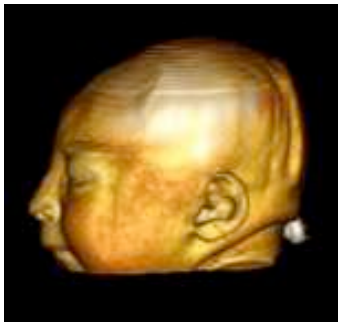
CrossMark

ORIGINAL PAPER

The spectrum of neuropathological changes associated with congenital Zika virus infection

Leila Chimelli[1] · Adriana S. O. Melo[2,3] · Elyzabeth Avvad-Portari[4] · Clayton A. Wiley[5] · Aline H. S. Camacho[1] · Vania S. Lopes[6] · Heloisa N. Machado[4] · Cecilia V. Andrade[4] · Dione C. A. Dock[4] · Maria Elisabeth Moreira[4] · Fernanda Tovar-Moll[7] · Patricia S. Oliveira-Szejnfeld[8] · Angela C. G. Carvalho[6] · Odile N. Ugarte[6] · Alba G. M. Batista[3] · Melania M. R. Amorim[2] · Fabiana O. Melo[2] · Thales A. Ferreira[2] · Jacqueline R. L. Marinho[3] · Girlene S. Azevedo[2] · Jeime I. B. F. Leal[3] · Rodrigo F. Madeiro da Costa[7] · Stevens Rehen[7] · Monica B. Arruda[9] · Rodrigo M. Brindeiro[9] · Rodrigo Delvechio[9] · Renato S. Aguiar[9] · Amilcar Tanuri[9]

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



Science

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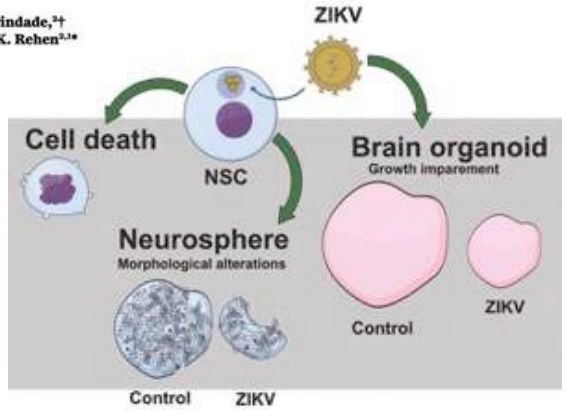
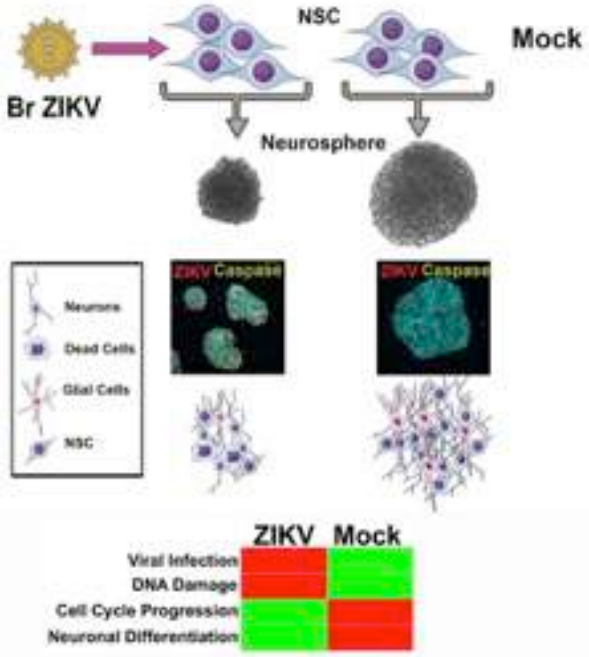
Cite as: Garcez *et al.*, *Science* 10.1126/science.aaf6116 (2016).

Zika virus impairs growth in human neurospheres and brain organoids

Patricia P. Garcez,[1,2]* Erick Correia Loiola,[2]† Rodrigo Madeiro da Costa,[2]† Luiza M. Higa,[2]† Pablo Trindade,[2]† Rodrigo Delvecchio,[2] Juliana Minardi Nascimento,[2,4] Rodrigo Brindeiro,[3] Amilcar Tanuri,[3] Stevens K. Rehen[2,1]*





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Zika virus disrupts molecular fingerprinting of human neurospheres

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viruses

MDPI

Article

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Our results provided the first experimental evidence connecting congenital ZIKV outbreak to the increased number of reports of brain malformations in Brazil

Combined proteomics and mRNA transcriptional profile analyses showed that Brazilian ZIKV, prior to induce cell death, triggers DNA damage response which alters cell cycle and halts neurogenic programmes

Cell types forming the developing human brain (e.g. neural stem cells, radial glial cells, astrocytes, neurons) should be considered in screening platforms for Zika virus drugs

It is not only about zika...

Plataform 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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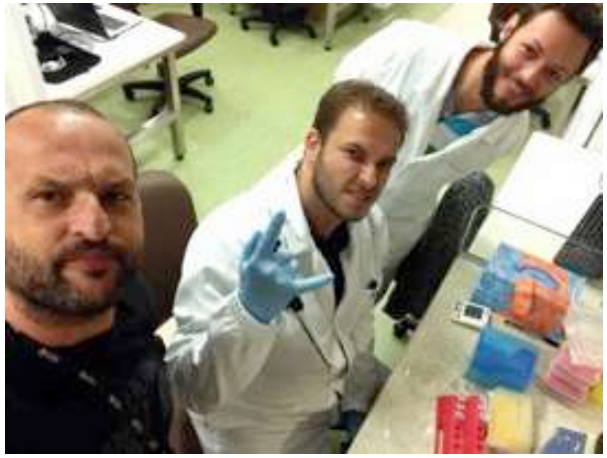

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Erick Loiola
Pítia Letur
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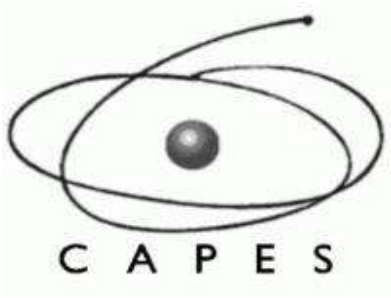
à Pesquisa do Estado do Rio de Janeiro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