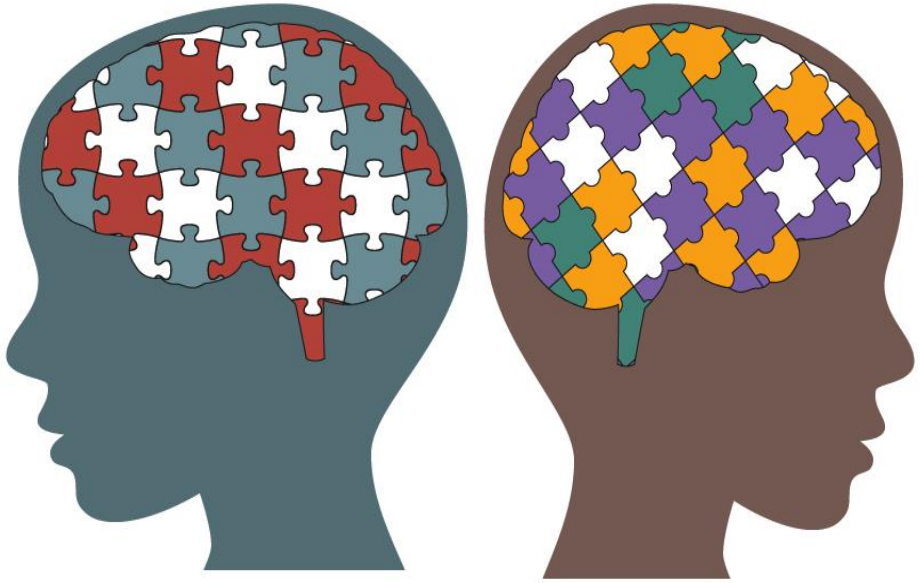
2nd PAN-AMERICAN Conference for Alternative Methods
August 23-24, 2018
Rio de Janeiro

The application of brain organoids to invetigate CNS diseases and test drugs

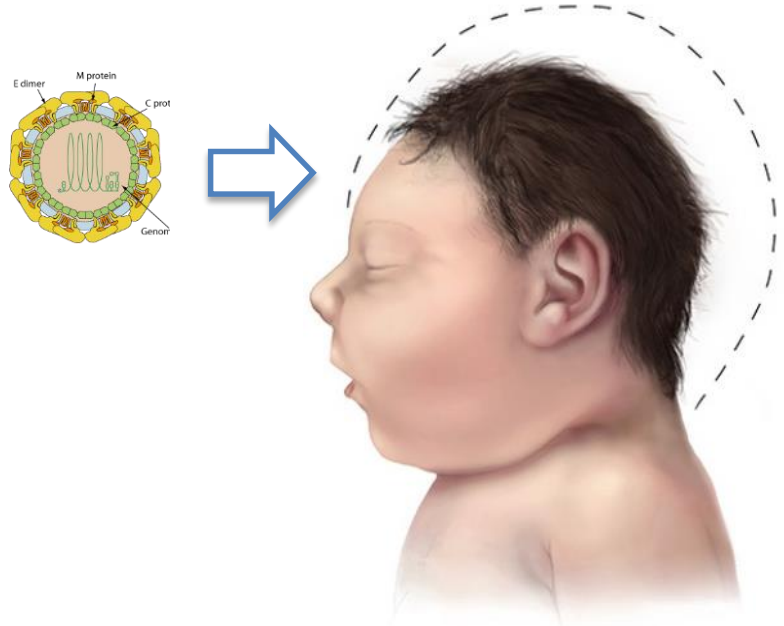
Prof. Patrícia Beltrão-Braga, Ph.D.

patriciacbbbraga@usp.br

Laboratory of Disease Modeling



ASD **DMD**



Congenital Zika Syndrome

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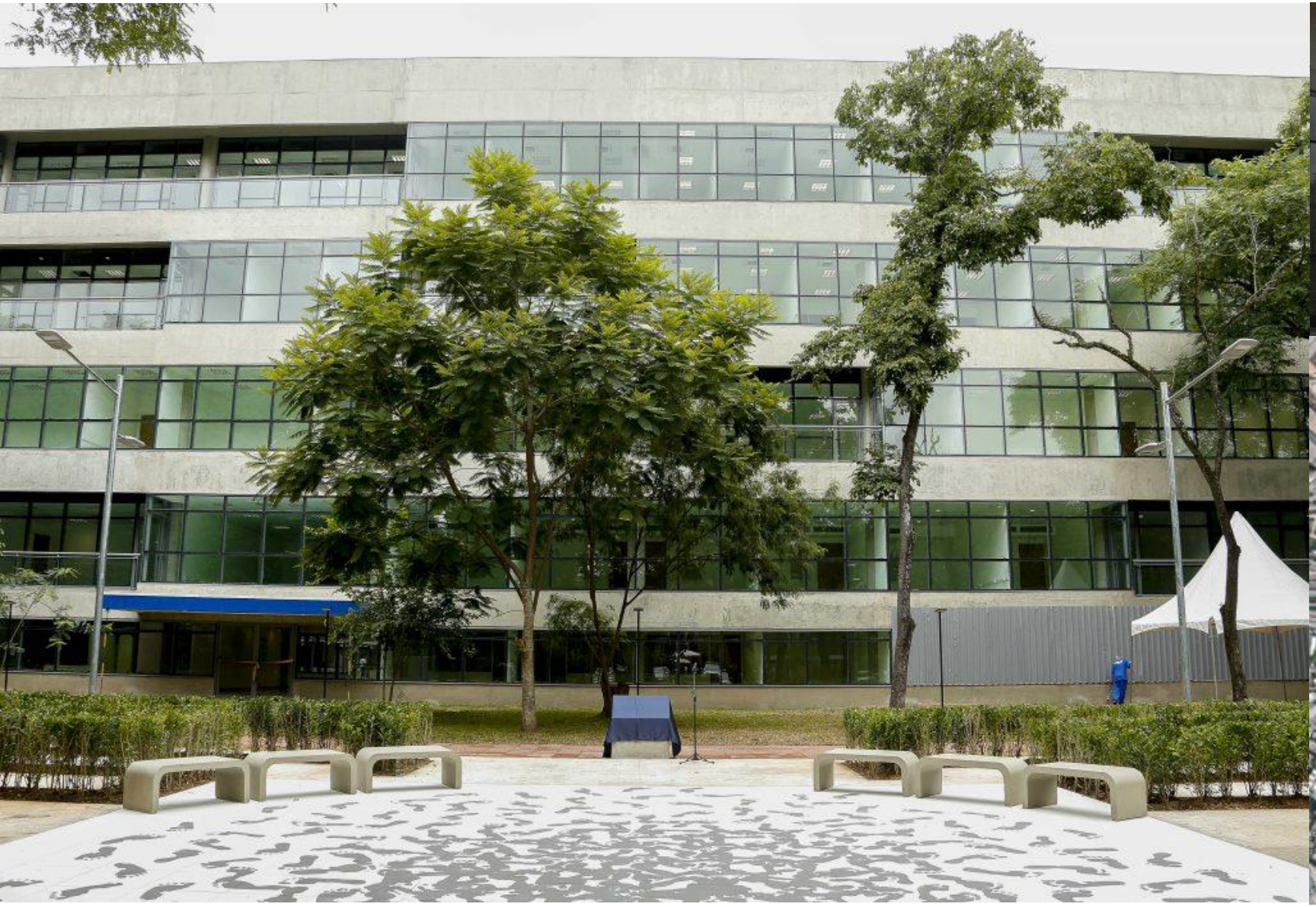
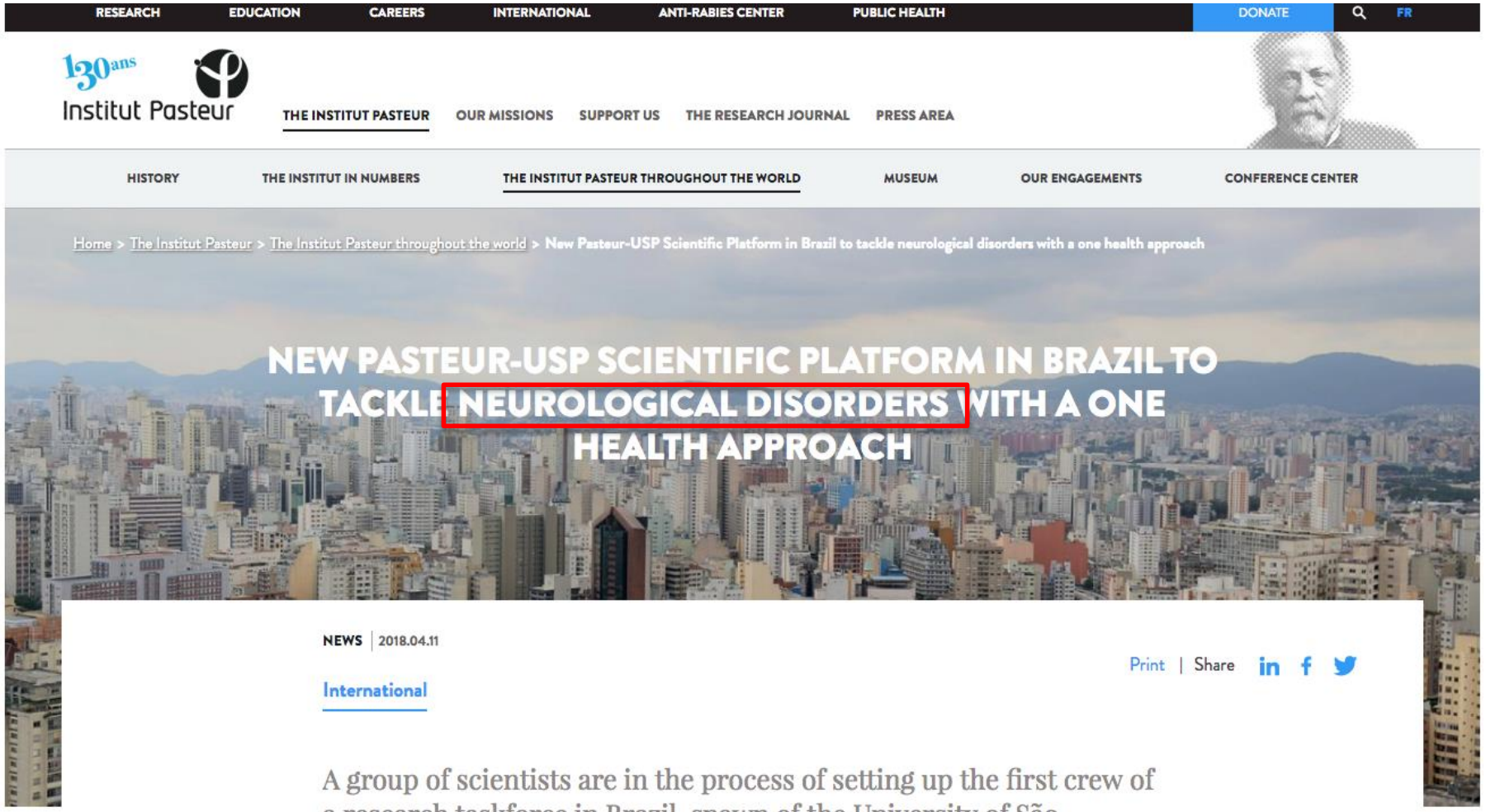
Scientific Plataform Pasteur-USP

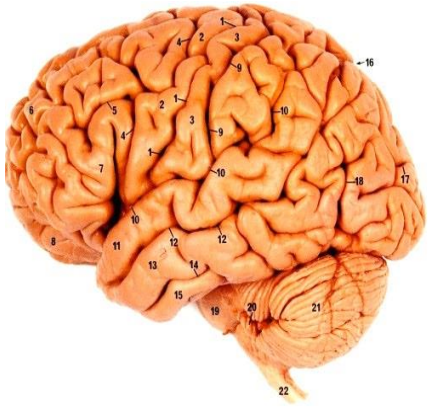


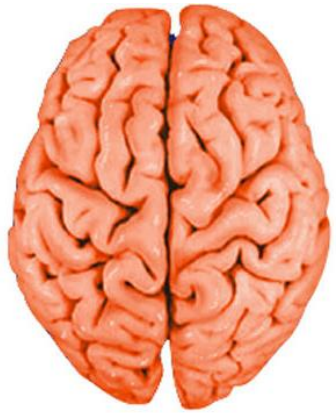
Scientific Plataform Pasteur-USP



Ways to investigate diseases that affects CNS

Post-mortem Brain



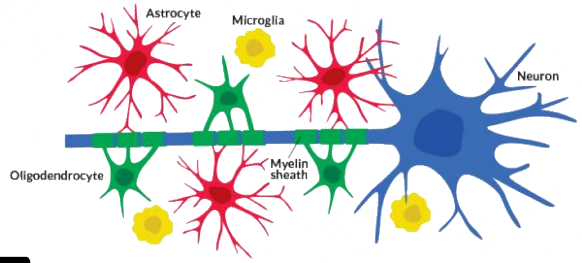


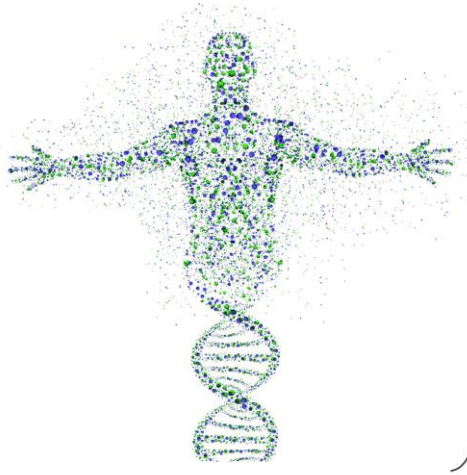
X

Animal model

CNS alive cells

+

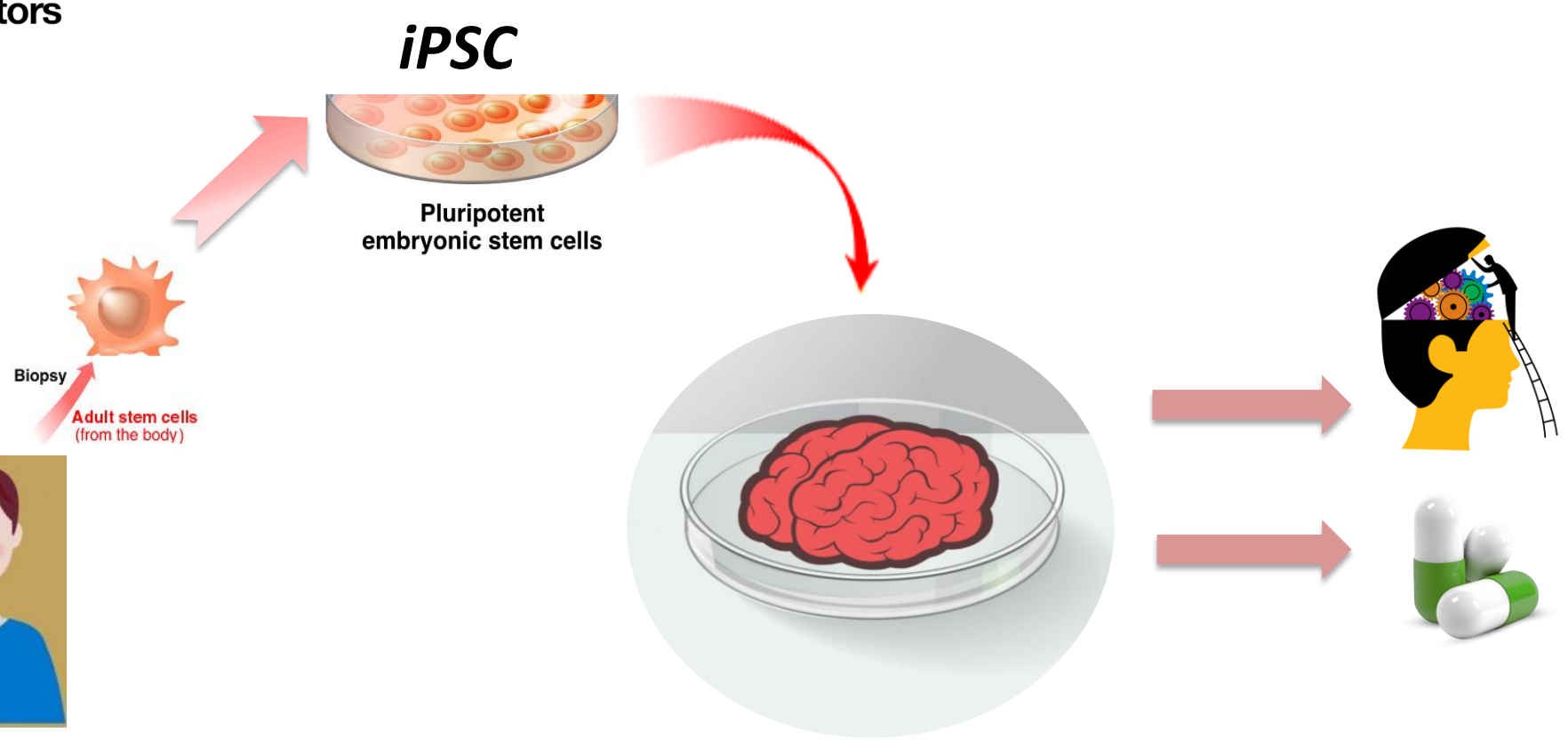




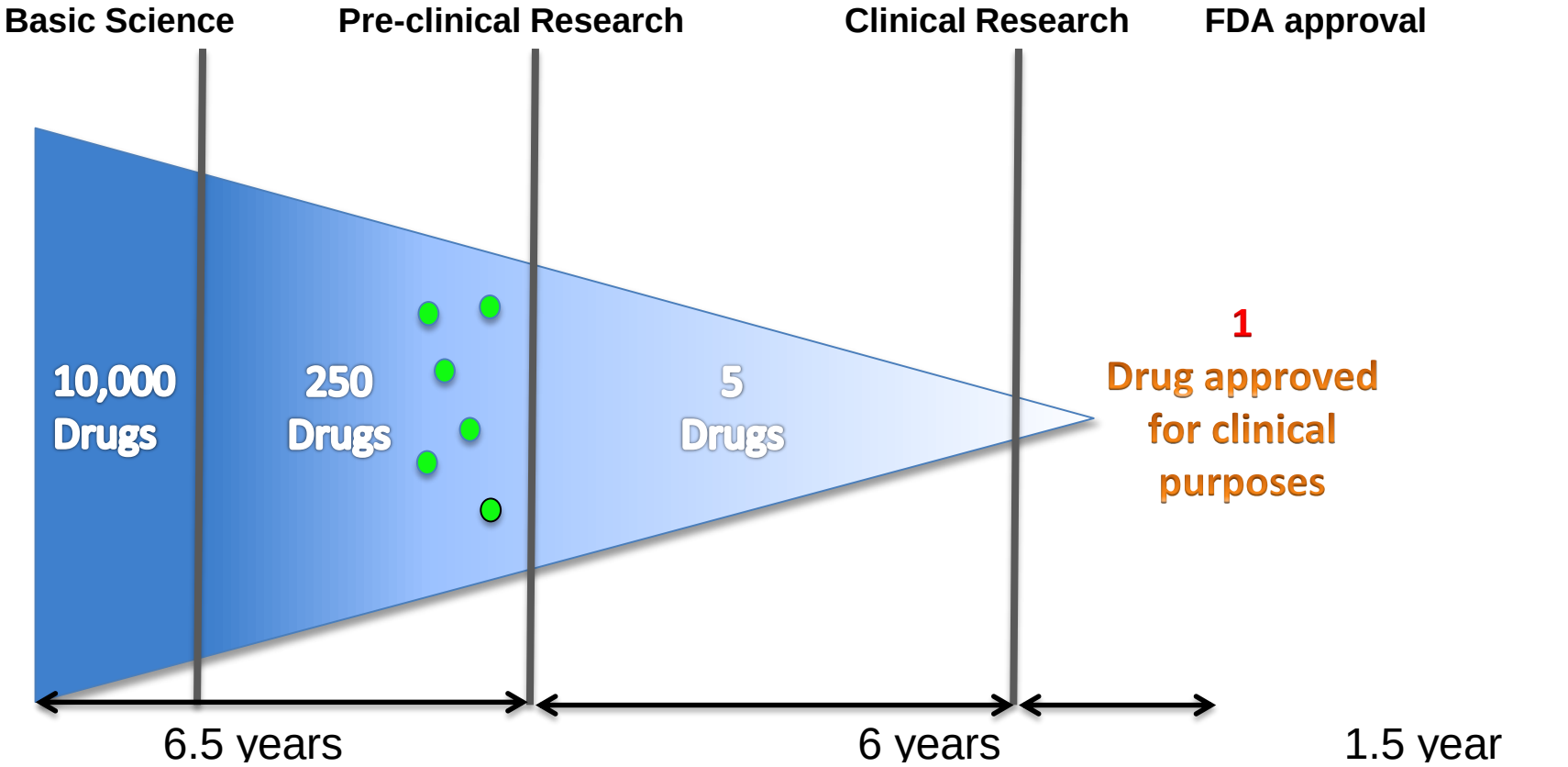
Producing human brain cells still keeping the genetic background

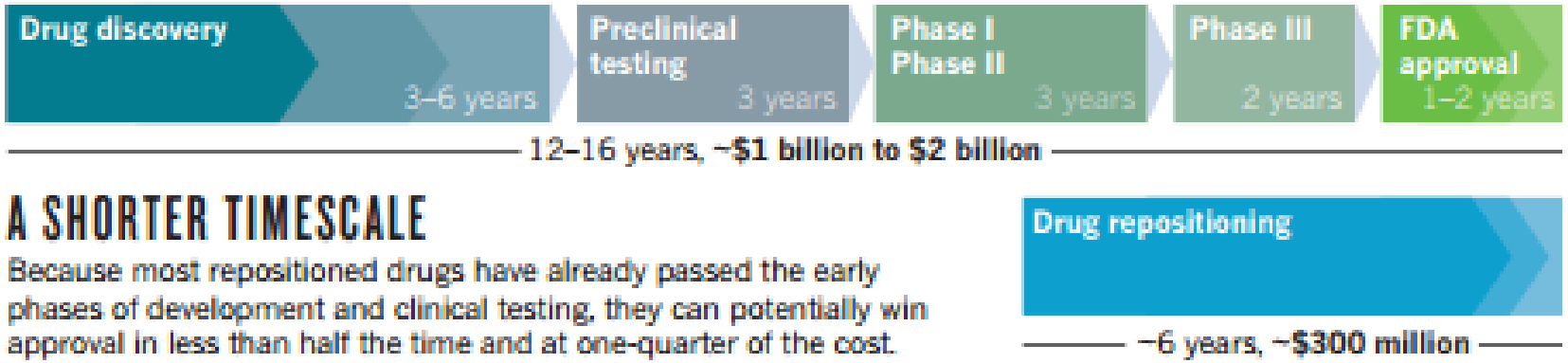
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

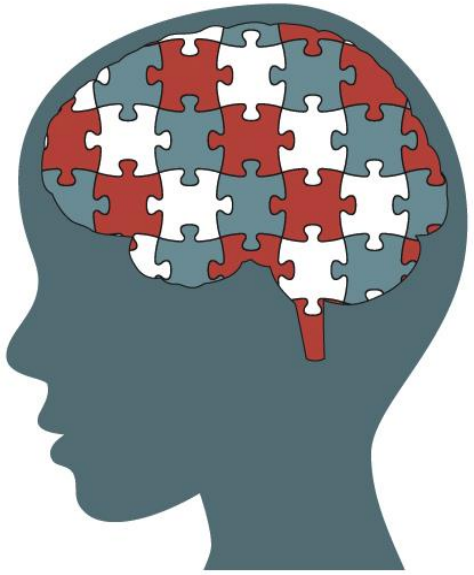
Takahashi, Yamanaka, Cell, 2006



Drug repurposing X Drug discovery







ASD

DMD

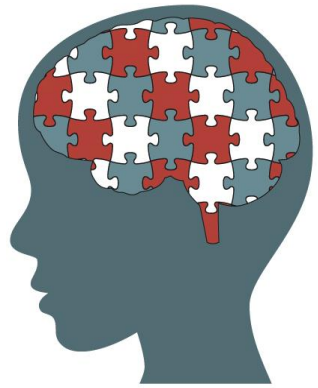
ZIKV

Congenital Zika Syndrome

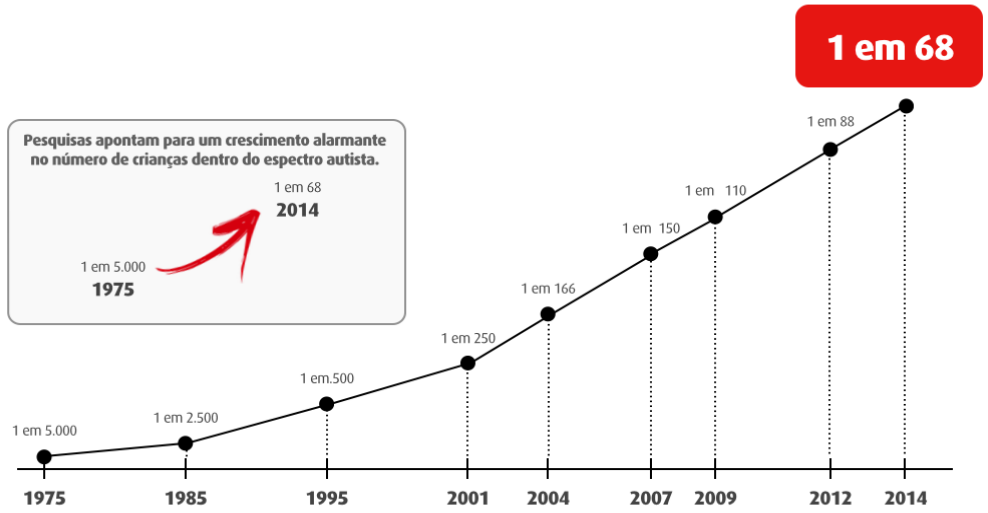
Autism Spectrum Disorder (ASD)

Social Skills

Genetic (1007 genes)
Enviromental factors (?)
Neuroinflamation



ASD



1 em 68

2018:
1 to 59

Baio et al., MMWR Surveill Summ. 2018

In 29 years prevalence increased ~7300%

World 1-2% ~2-4 K of brazilians

Economical Impact US$ 5.9 trillion

Table 3 | **Drug screening for neurological diseases using patient-derived induced pluripotent stem cell models**

Machado–Joseph disease (4)	*ATXN3*	Late	Neurons	Cellular	Candidate	ALLN, calpeptin	134
Neuronal ceroid lipofuscinosis (2)	*TPP1*	Early	NPCs and neurons	Cellular	Candidate	PTC124	135
Niemann–Pick disease (1–4)	*NPC1*	Early	NPCs and neurons	Molecular and cellular	Confirmation, candidate	Rapamycin, carbamazepine, verapamil, trehalose, 2-hydroxypropyl-b-cyclodextrin (HPBCD), 2-hydroxypropyl-c-cyclodextrin (HPGCD), VEGF, δ-tocopherol with HPBCD or methyl-β-cyclodextrin (MBCD)	136–139
Parkinson disease (1–5)	*PARK2*, *SNCA*, *PINK1* and *LRRK2*	Late	Neurons, midbrain dopaminergic neurons and cortical neurons	Molecular and cellular	Confirmation, candidate, HTS	Taxol, isoxazole, NAB2, GW5074, co-enzyme Q10	37,52, 140,141
Phelan–McDermid syndrome (PMDS) (2)	Complex	Early	Mature forebrain neurons	Molecular, cellular and electrophysiological	Confirmation, candidate	Insulin-like growth factor 1 (IGF1)	142
Rett syndrome (3–4)	*MECP2*	Early	Neurons and astrocytes	Cellular	Confirmation, candidate	Glypromate (GPE), IGF1, gentamicin	143,144
Schizophrenia (1–4)	Complex	Early and late	NPCs and neurons	Molecular and cellular	Confirmation	Loxapine, valproate (VPA)	33,145, 146
Spinal and bulbar muscular atrophy (SBMA) (1)	Androgen receptor	Late	Motor neurons	Cellular	Confirmation	Heat shock protein 90 (HSP90) inhibitor 17-AAG	147
Spinal muscular atrophy (SMA) (2)	*SMN1*	Early	Motor neurons	Molecular and cellular	Confirmation, candidate (drugs and ASOs)	Phosphorodiamidate morpholino oligonucleotides (PMOs), FasNT antibody, Z-DVED-FMK, salubrinal, guanabenz	99,102, 103
Timothy syndrome (2)	*CACNA1C*	Early	Cortical neurons	Molecular, cellular and electrophysiological	Candidate	Roscovitine	148
Wolfram syndrome (5)	*WFS1*	Early	Neurons	Cellular	Candidate	Dantrolene	149

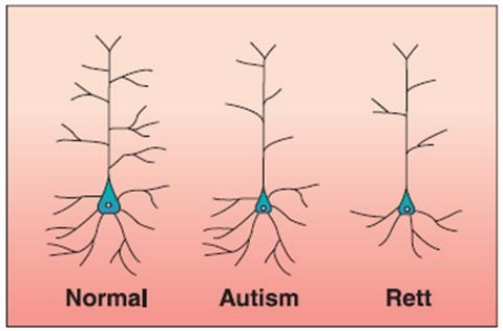
ABCD1, ATP-binding cassette D1; *APP*, amyloid precursor protein; ASOs, antisense oligonucleotides; *ATM*, ataxia telangiectasia mutated; *ATXN3*, ataxin 3; *C9ORF72*, chromosome 9 open reading frame 72; *CACNA1C*, calcium channel subunit α1C; *FMR1*, fragile X mental retardation 1; *FUS1*, fused in sarcoma 1; *FXN*, frataxin; *GLB1*, galactosidase-β1; HTS, high-throughput screening; *HTT*, huntingtin; *IKBKAP*, IKK complex-associated protein; *LRRK2*, Leu-rich repeat kinase 2; *MECP2*, methyl-CpG-binding protein 2; *NPC1*, Niemann–Pick type C1; *PARK2*, parkin RBR E3 ubiquitin protein ligase; *PINK1*, PTEN-induced kinase 1; PS, presenilin; *SMN1*, survival of motor neuron 1; *SNCA*, α-synuclein; *SOD1*, superoxide dismutase; *SPAST*, spastin; *TDB43*, TAR DNA-binding protein 43; *TPP1*, tripeptidyl peptidase 1; *TTR*, transthyretin; VEGF, vascular endothelial growth factor; *WFS1*, Wolfram syndrome 1. *The different phenotypes that have been analysed and ameliorated by the drugs belong to three categories: molecular (gene and protein expression, and DNA methylation); cellular (morphology (foci, synapses), mitochondrial functions, apoptosis and toxicity-induced reactions); and electrophysiological (currents, action potentials and ion fluxes).

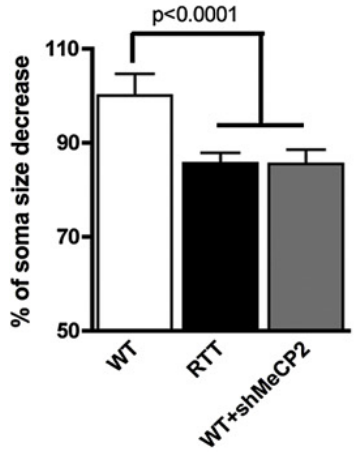
A Model for Neural Development and Treatment of Rett Syndrome Using Human Induced Pluripotent Stem Cells

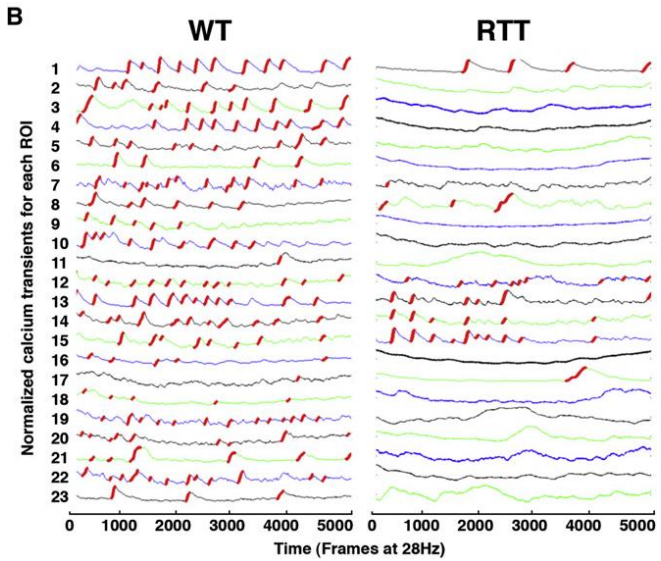
Maria C.N. Marchetto,[1,5] Cassiano Carromeu,[2,5] Allan Acab,[2] Diana Yu,[1] Gene W. Yeo,[3] Yangling Mu,[1] Gong Chen,[4] Fred H. Gage,[1] and Alysson R. Muotri[2,*]

Cell

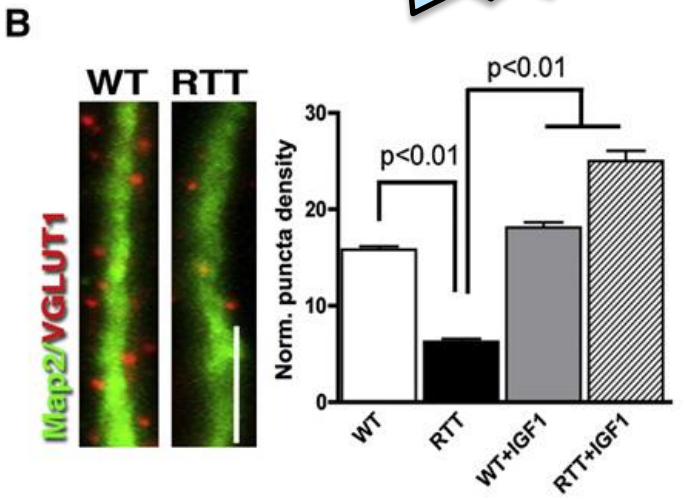
Less complex neurons







IGF-1



Marchetto et al., 2010

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed Has Results	Treatment of **Rett Syndrome** With **rhIGF-1** (**Mecasermin** [rDNA]Injection)	• **Rett Syndrome**	• Drug: **rhIGF-1**	• Boston Children's Hospital Boston, Massachusetts, United States
2	☐	Completed Has Results	Treatment of **Rett Syndrome** With Recombinant Human **IGF-1**	• **Rett Syndrome**	• Drug: Recombinant Human Insulin Growth Factor 1 (**rhIGF-1**) • Drug: Placebo	• Boston Children's Hospital Boston, Massachusetts, United States

Table 3 | **Drug screening for neurological diseases using patient-derived induced pluripotent stem cell models**

Disease name (number of patients)	Genetic basis	Onset	Differentiated cell	Analysed and corrected phenotype*	Screening type	Identified drug	Refs
Adrenoleuko-dystrophy (2)	*ABCD1*	Early and late	Neurons and oligodendrocytes	Molecular and cellular	Confirmation	4-phenylbutyrate (4PBA), lovastatin	114
Amyotrophic lateral sclerosis (ALS) (1–16)	*SOD1*, *C9ORF72*, *FUS1*, *TDP43*, complex	Late	Neurons, motor neurons and astrocytes	Molecular, cellular and electro physiological	Confirmation, candidate (drugs and ASOs), HTS	Retigabine, kenpaullone, digoxin, lanatoside C, proscillaridin A, anacardic acid, methotrimeprazine, fluphenazine, ASOs	36, 96–98, 111,113, 115
Alzheimer disease (1–6)	*APP*, *PS1*, *PS2*, complex	Late	Neurons	Molecular and cellular	Confirmation, candidate	γ-secretase inhibitor, compound E, compound W, GSM-4, Si-II,OM99-2, docosahexaenoic acid (DHA)	116–120
Ataxia telangiectasia (2)	*ATM*	Early	Neurons and glia	Cellular	Candidate	Geneticin (G418)	121
Autism spectrum disorder (ASD) (1–5)	15q11-q13.1 duplications, (3;11) (p21;q22) translocation	Early	Neurons	Molecular, cellular and electro physiological	Candidate	Hyperforin with flufenamic acid (FFA), mithramycin	108,122
Bipolar disorder (2)	Complex	Early	Neurons	Molecular and cellular	Candidate	CHIR-99021	123
Down syndrome (1–2)	Trisomy 21	Early	Neural progenitor cells (NPCs), neurons, astroglia	Molecular and cellular	Candidate	Minocycline, epigallocatechin gallate (EGCG), F127–*N*-butylidenephthalide (BDPH)	124–126
Familial dysautonomia (2–3)	*IKBKAP*	Early	Neural crest cells	Molecular and cellular	Confirmation, HTS	SKF-86466 hydrochloride, kinetin	43,44
Fragile X syndrome (FXS) (1–3)	*FMR1*	Early	NPCs, neurons	Molecular	Candidate, HTS	5-azacytidine, several other compounds (not specified)	92,127
Friedreich ataxia (2)	*FXN*	Early	Neurons	Molecular and cellular	Confirmation, candidate	Forskolin, RG2833	106,128
GN1 gangliosidosis (1)	*GLB1*	Early	NPCs	Molecular and cellular	Candidate	Z-YVAD-FMK	129
Hereditary spastic paraplegias (HSP) (1)	*SPAST*	Early and late	Forebrain glutamatergic neurons	Cellular	Confirmation	Vinblastine	130
Hereditary transthyretin amyloidosis (1)	*TTR*	Early and late	Neurons	Cellular	Candidate	Flufenamic acid	131
Huntington disease (1–2)	*HTT*	Late	NPCs, neurons, GABAergic neurons and medium spiny	Molecular and cellular	Confirmation, candidate	P110-TAT, KU-60019, X5050	109,132, 133

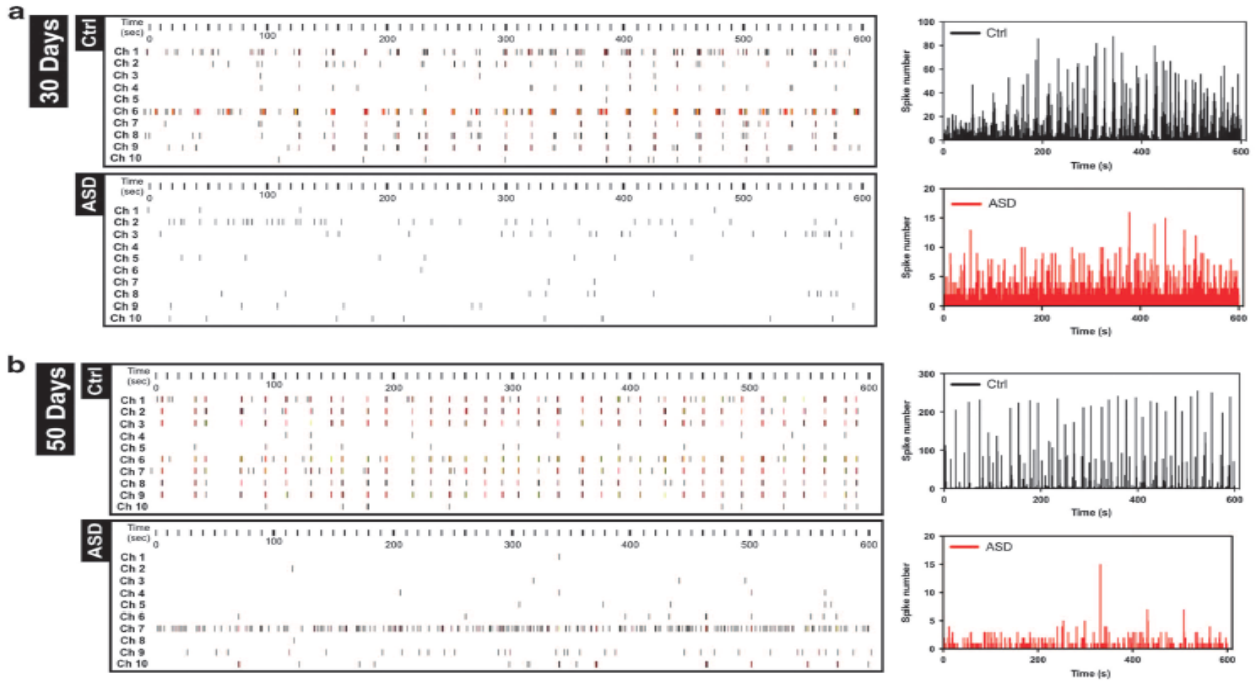
Molecular Psychiatry (2016) 00, 1–16

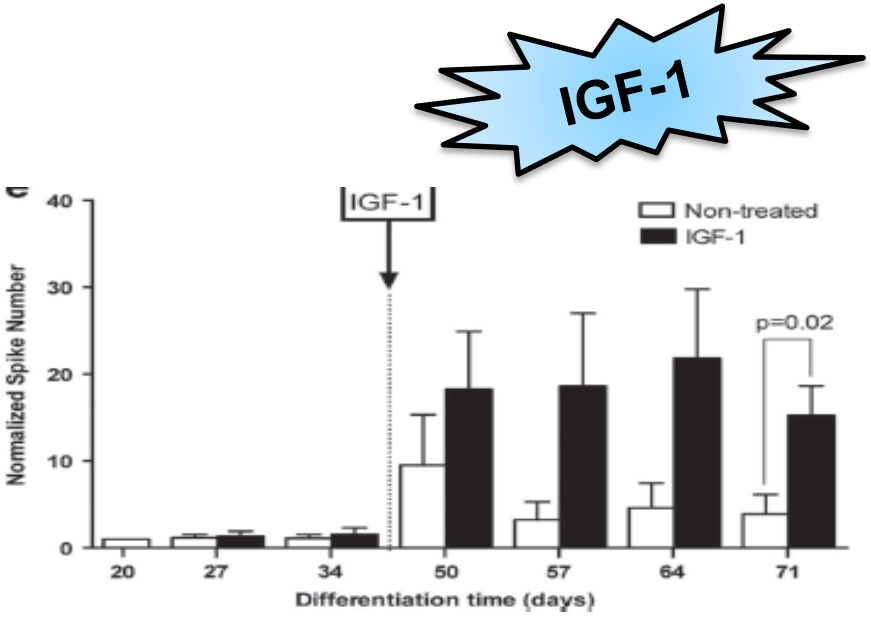
www.nature.com/mp

ORIGINAL ARTICLE

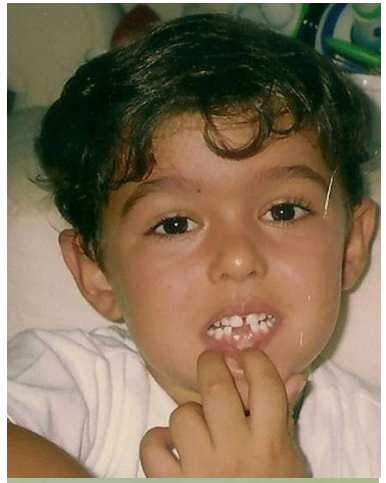
Altered proliferation and networks in neural cells derived from idiopathic autistic individuals

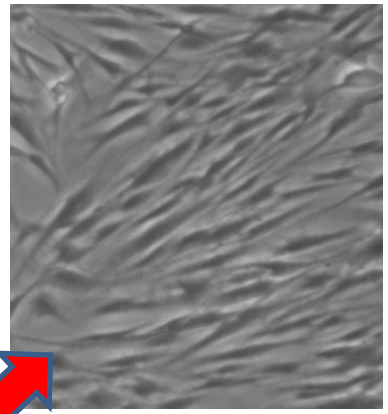
MC Marchetto[1,10], H Belinson[2,10], Y Tian[3], BC Freitas[4], C Fu[5], KC Vadodaria[1], PC Beltrao-Braga[4,6], CA Trujillo[4], APD Mendes[1], K Padmanabhan[7], Y Nunez[1,4], J Ou[3], H Ghosh[1], R Wright[1], KJ Brennand[8], K Pierce[9], L Eichenfield[9], T Pramparo[9], LT Eyler[9], CC Barnes[9], E Courchesne[9], DH Geschwind[3], FH Gage[1], A Wynshaw-Boris[2,5] and AR Muotri[4]

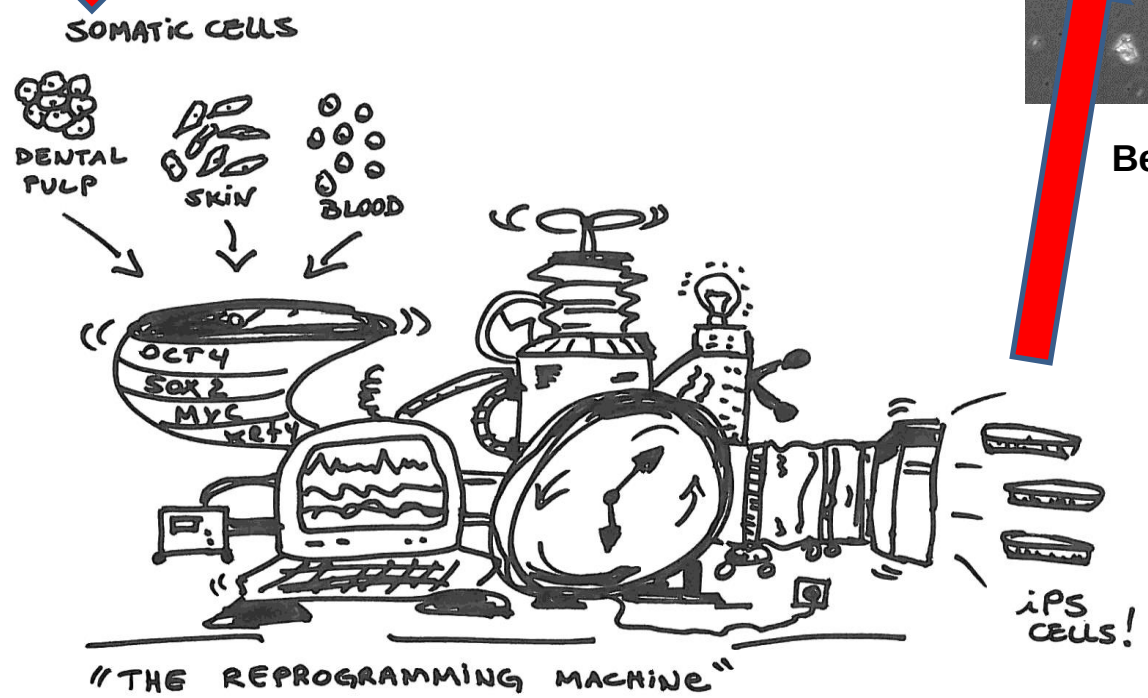


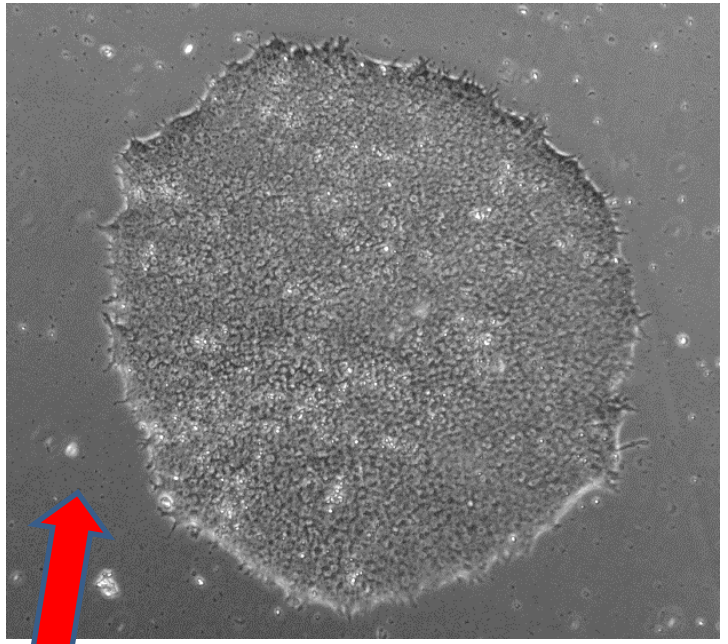


Disease modeling: using dental pulp stem cells to make iPSC









Beltrão-Braga *et al., Cell Transpl. 2011*

PROJETO a fada do dente

The Tooth Fairy Project

PROJETO
a fada do dente

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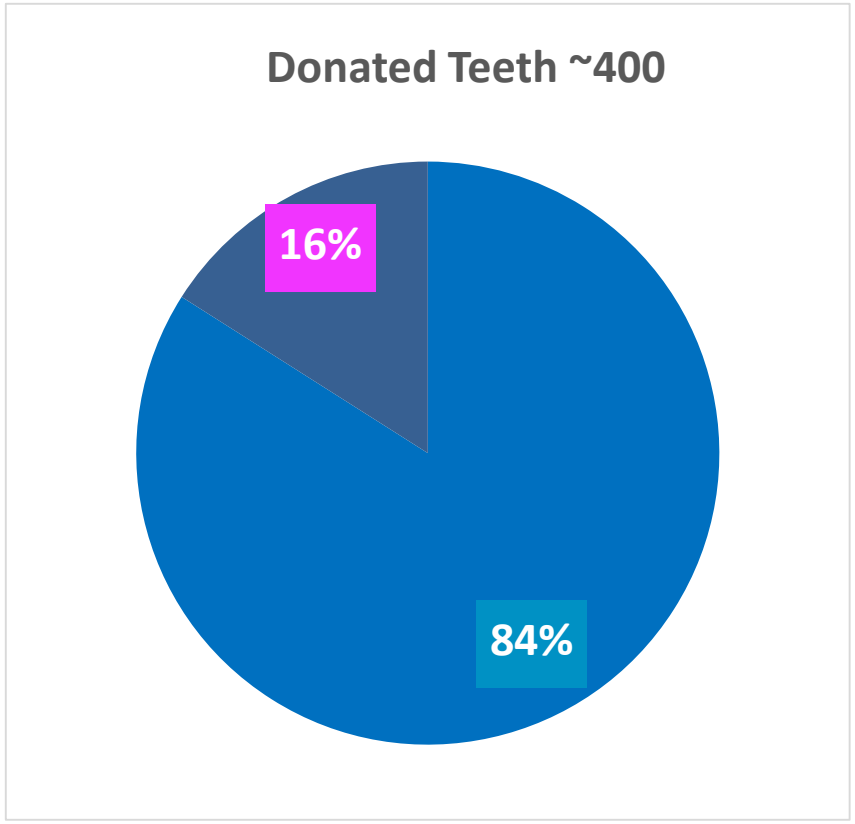
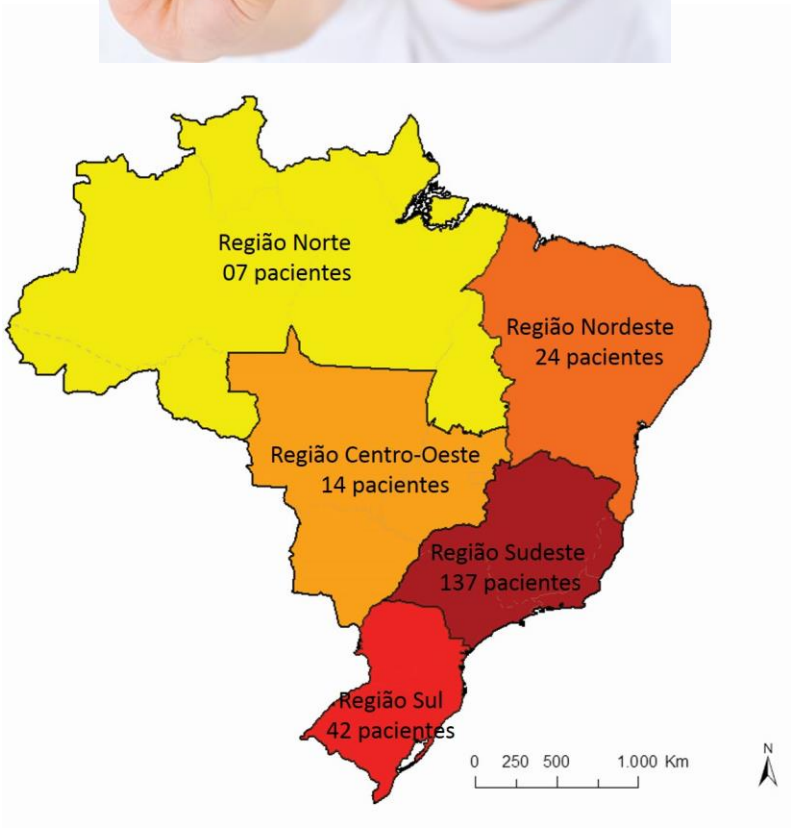




PROJETO a fada do dente

300 ASD cell lineages and controls

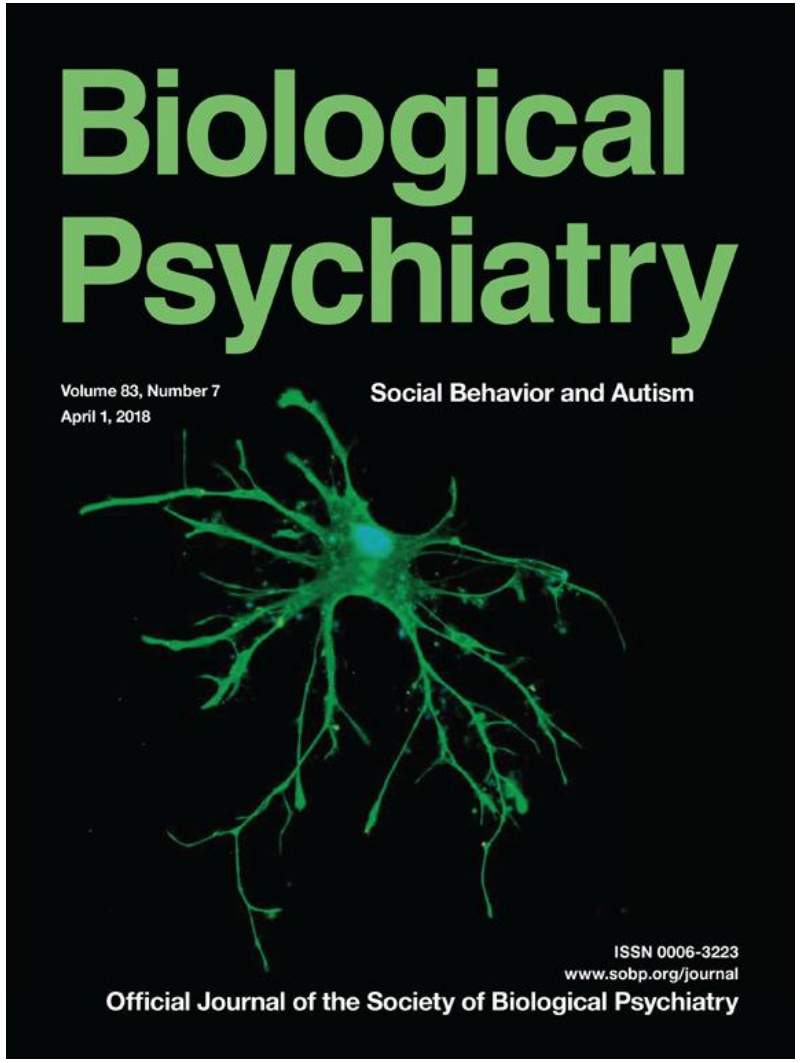
Modeling severe ASD

Fabiele Russo, PhD

Non verbal, cognitive impaired, with stereotypic behaviors, non aggressive, without seizures

WGS
No ASD related genes in common

Russo & Freitas et al., Biol Psy. 2018



ARTICLE IN PRESS

Archival Report

Biological Psychiatry

Modeling the Interplay Between Neurons and Astrocytes in Autism Using Human Induced Pluripotent Stem Cells

Russo & Freitas et al., Biol Psy. 2018

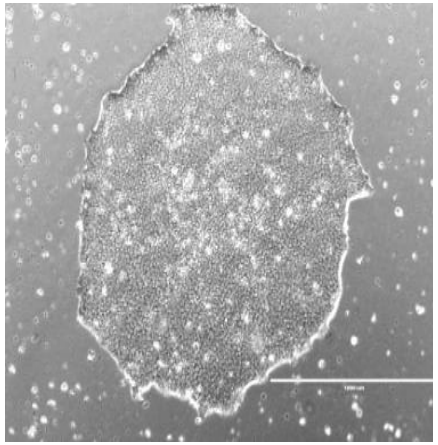
Modeling severe ASD

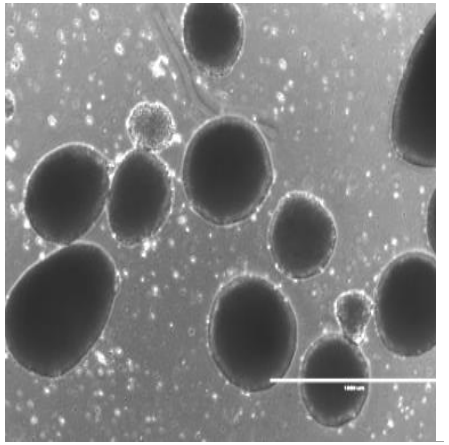
"The Tooth Fairy Project"

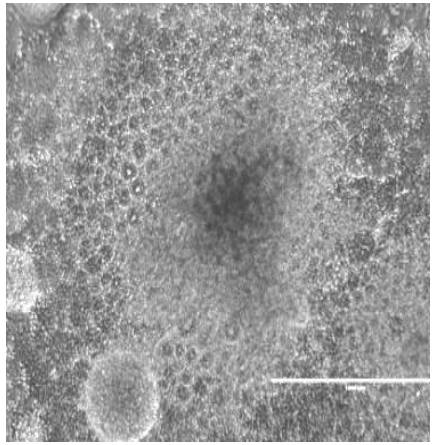
ASD

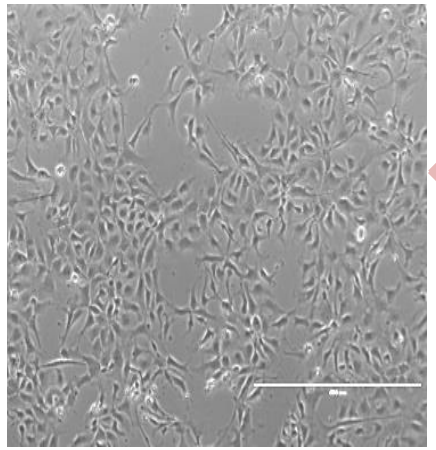
"Controls"

iPS cells → EB → Rosettes → NPC



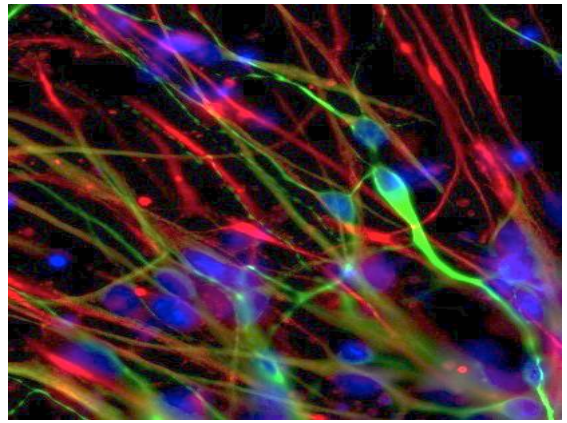


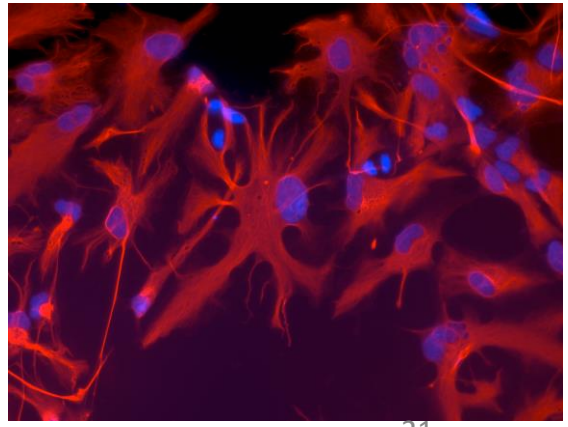




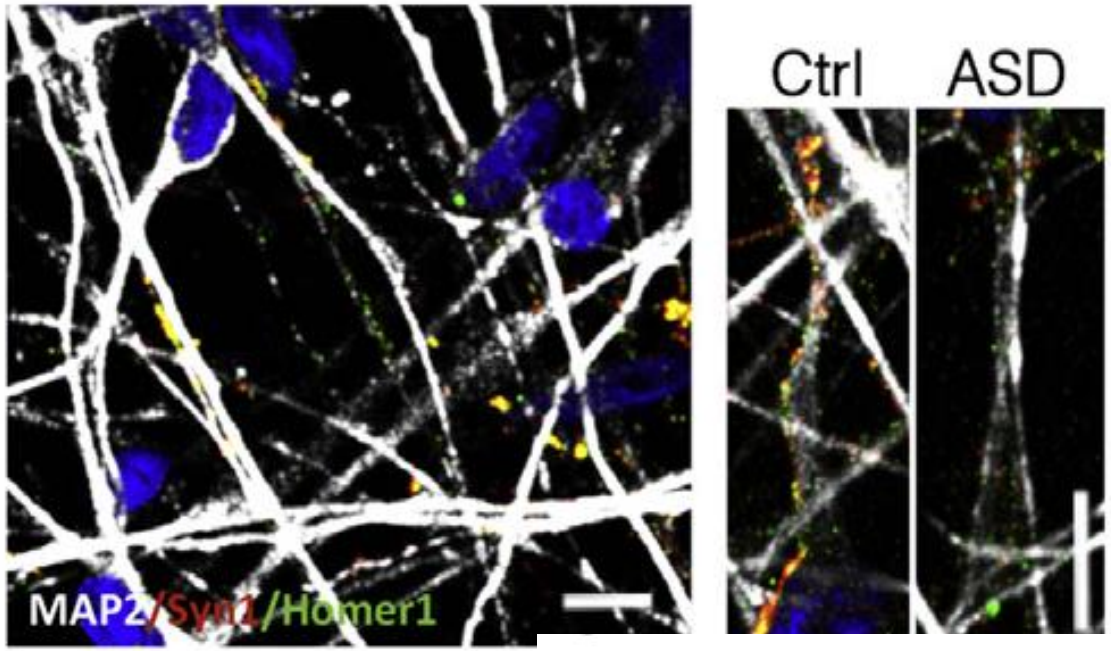
Neurons

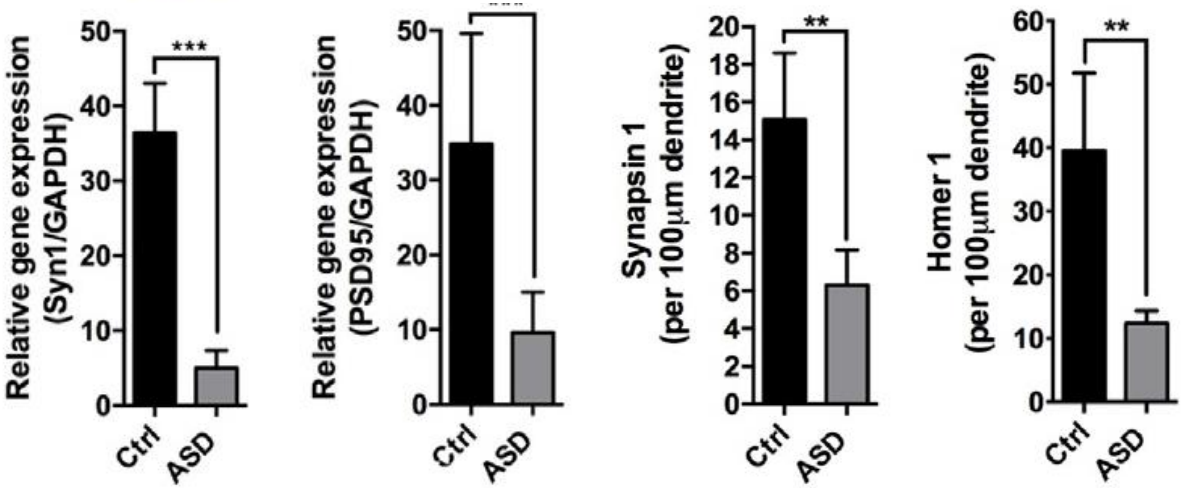
Astrocytes

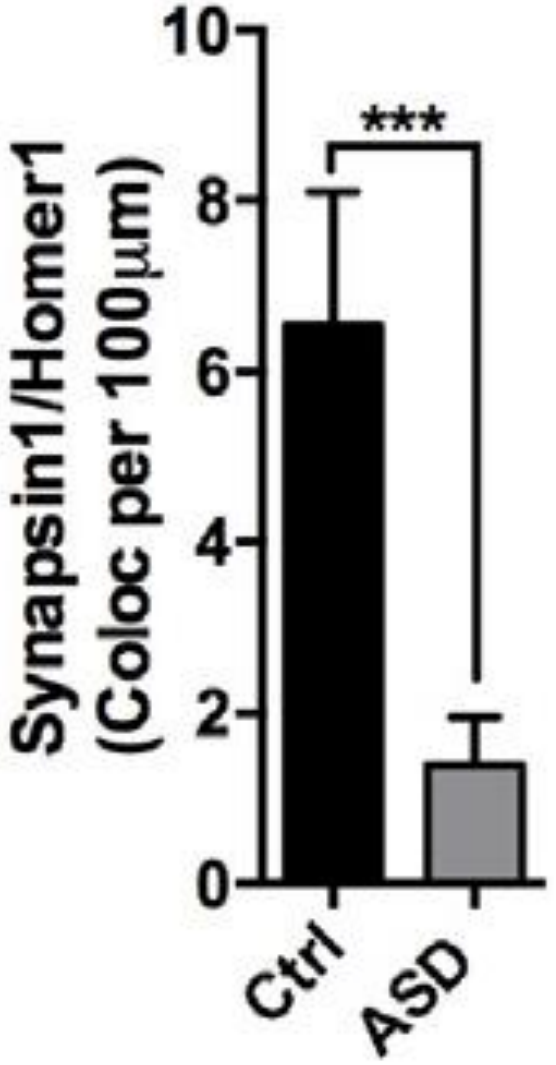




Autistic neurons have less synapses than controls

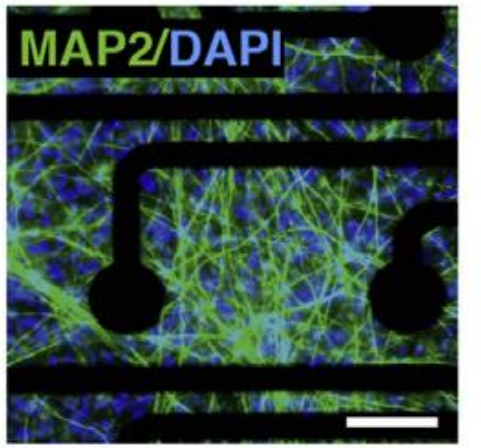


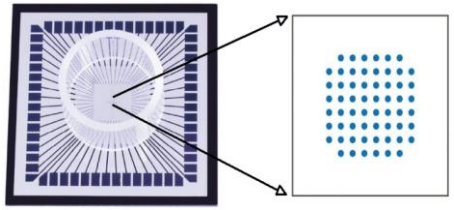


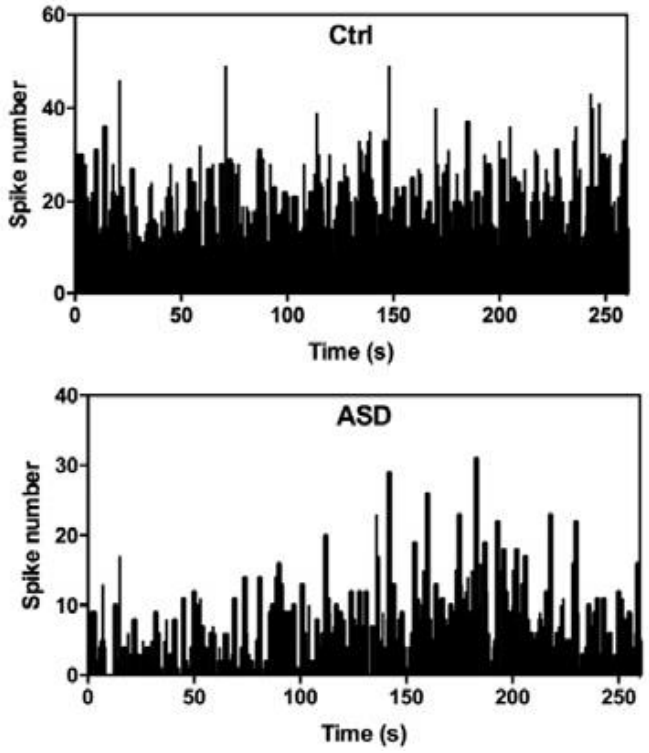


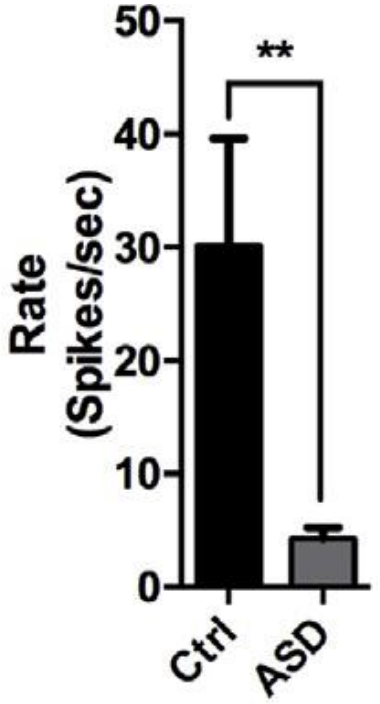
Autistic neurons have less spikes and produces less glutamate than controls

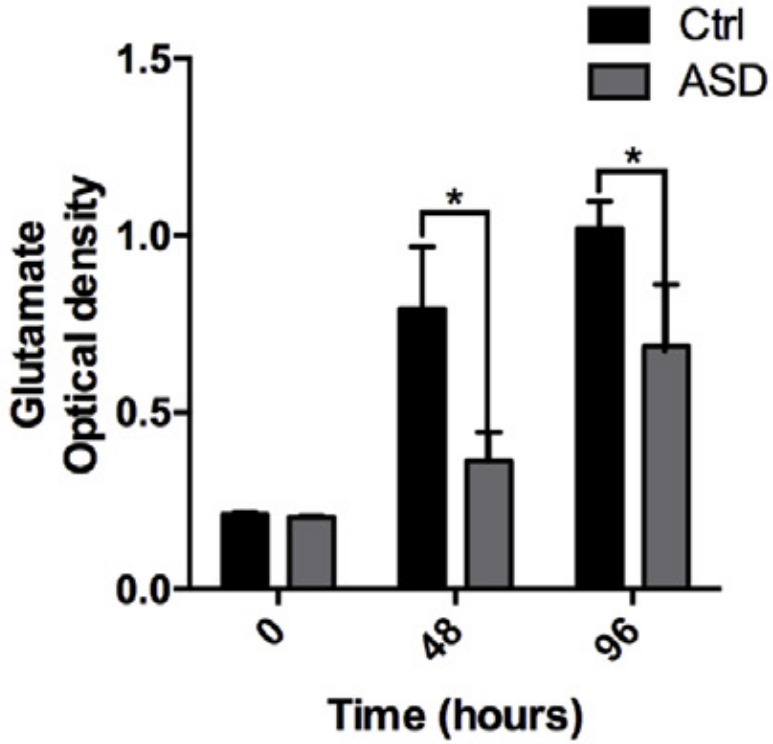
Multi-eletrode Array (MEA)



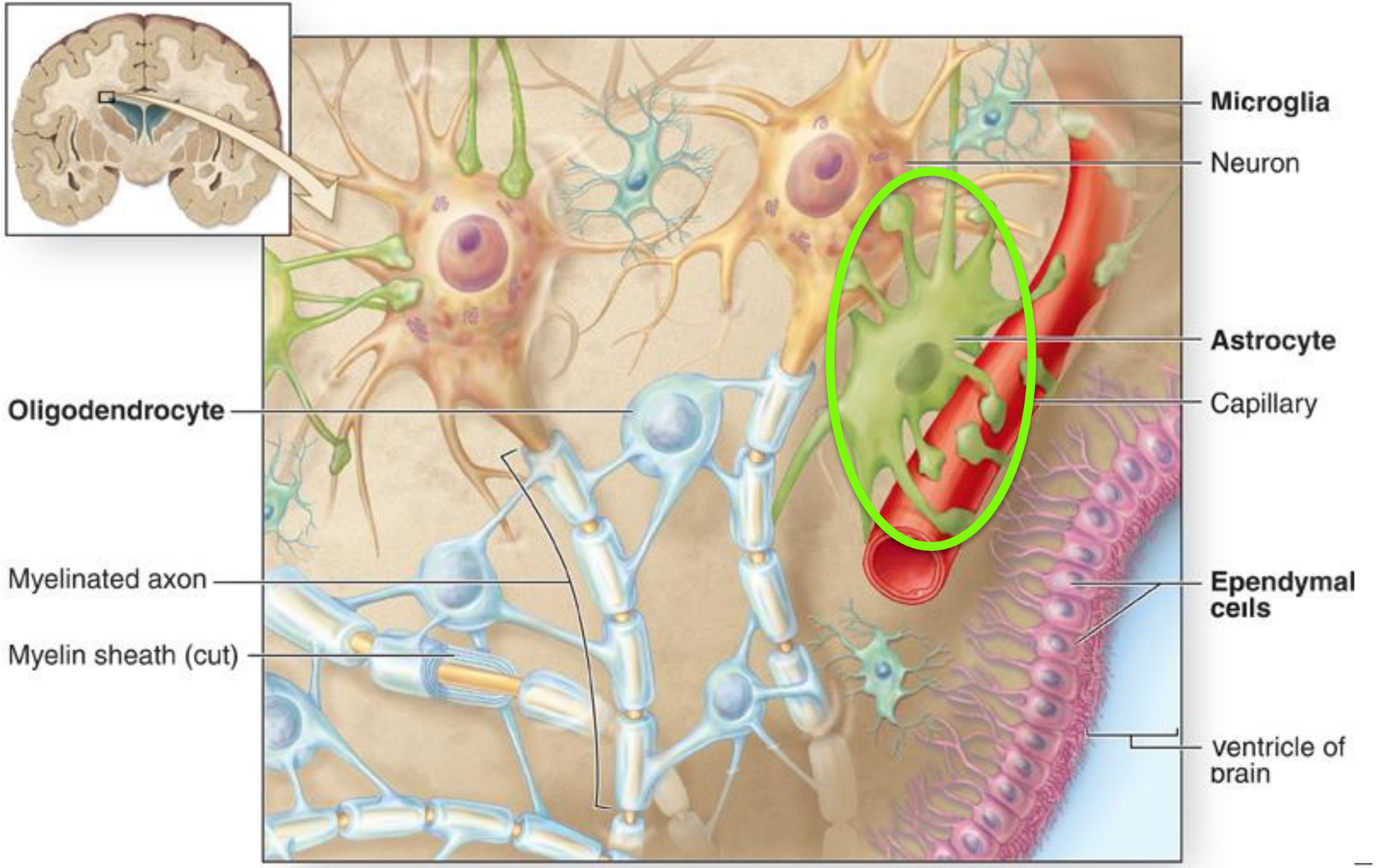


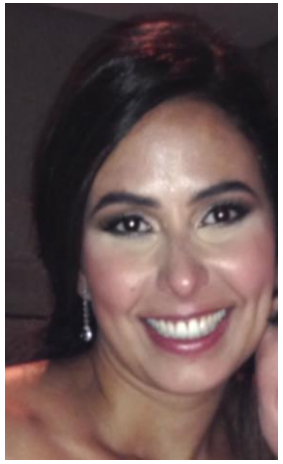




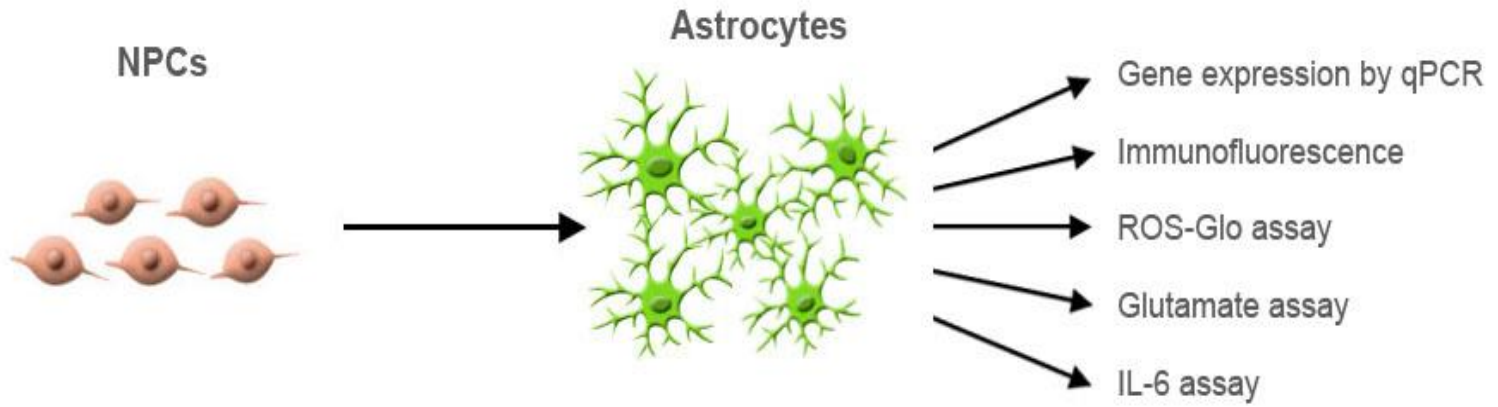


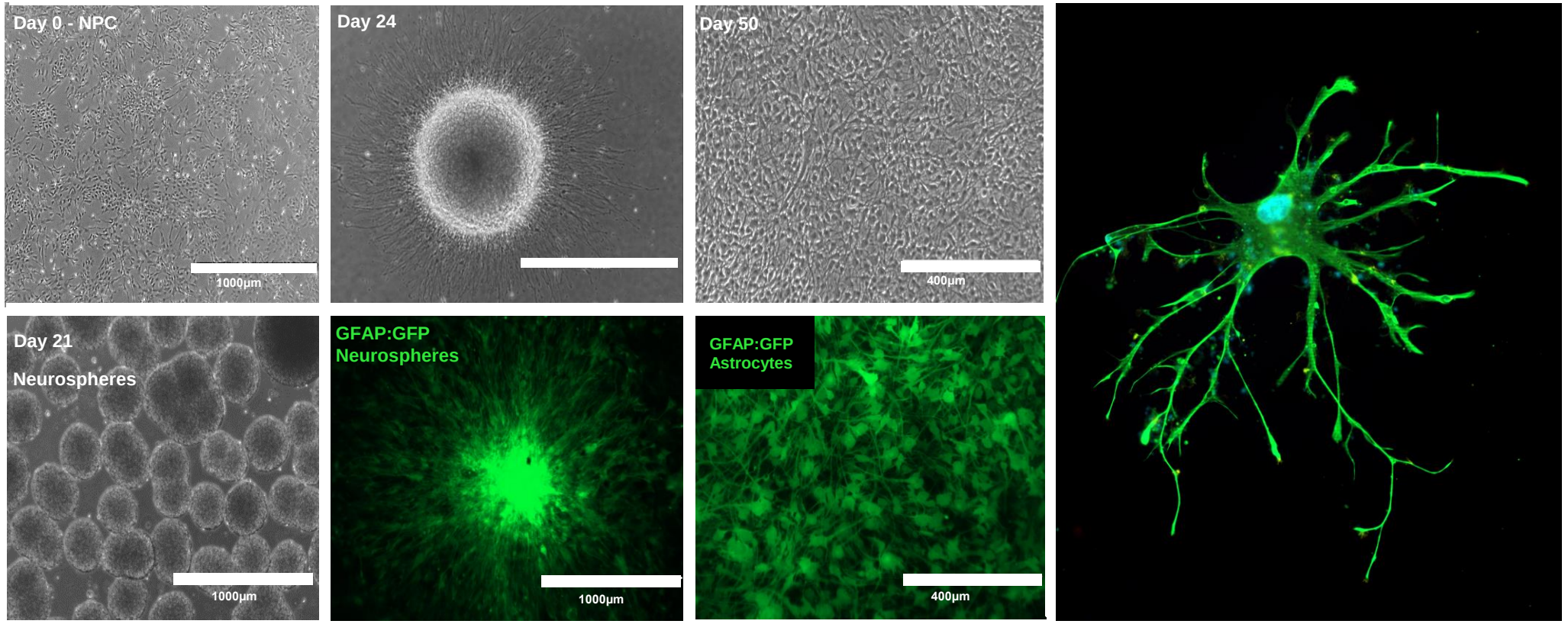
GLIA



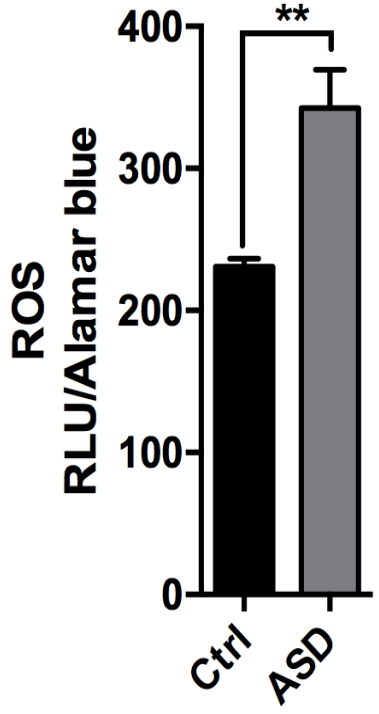


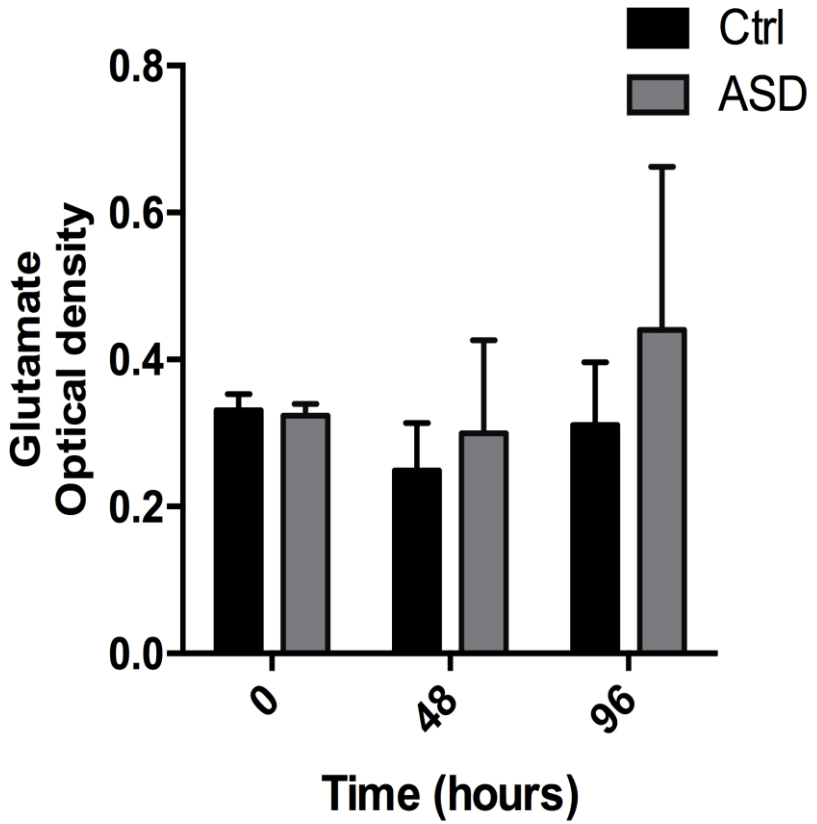
Bia Freitas, PhD

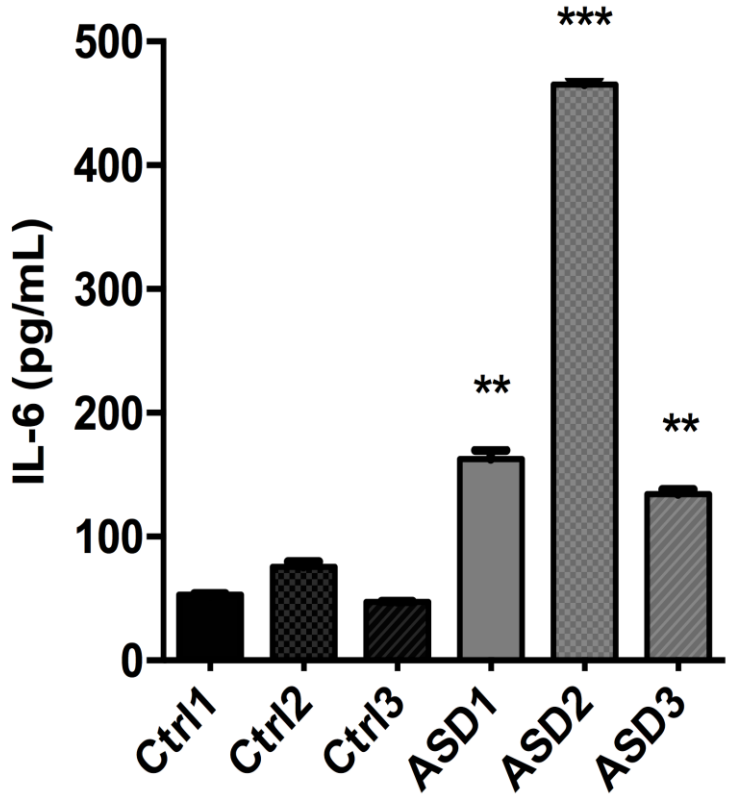


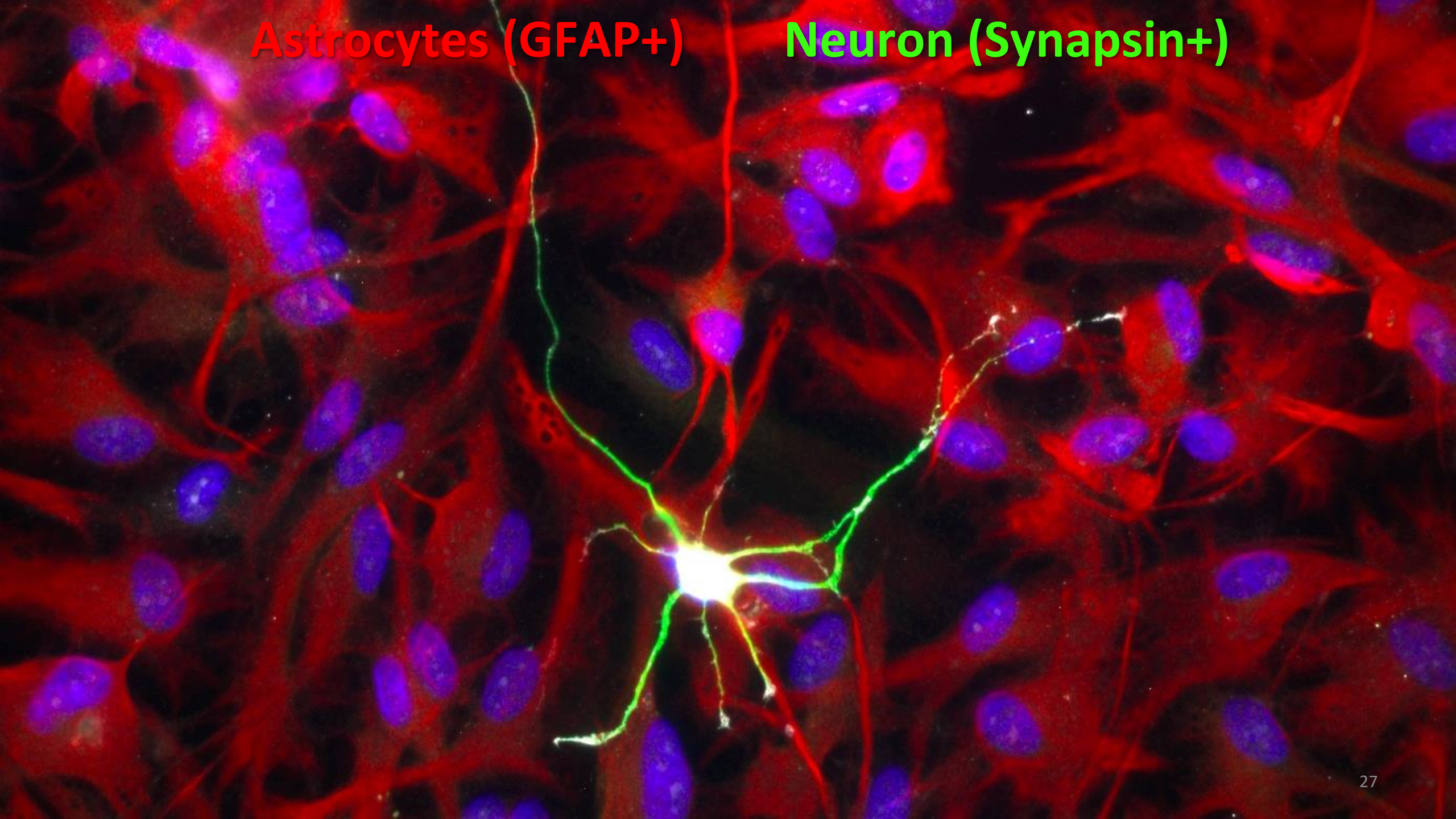


Autistic Astrocytes produce more ROS, glutamate and IL6 than controls

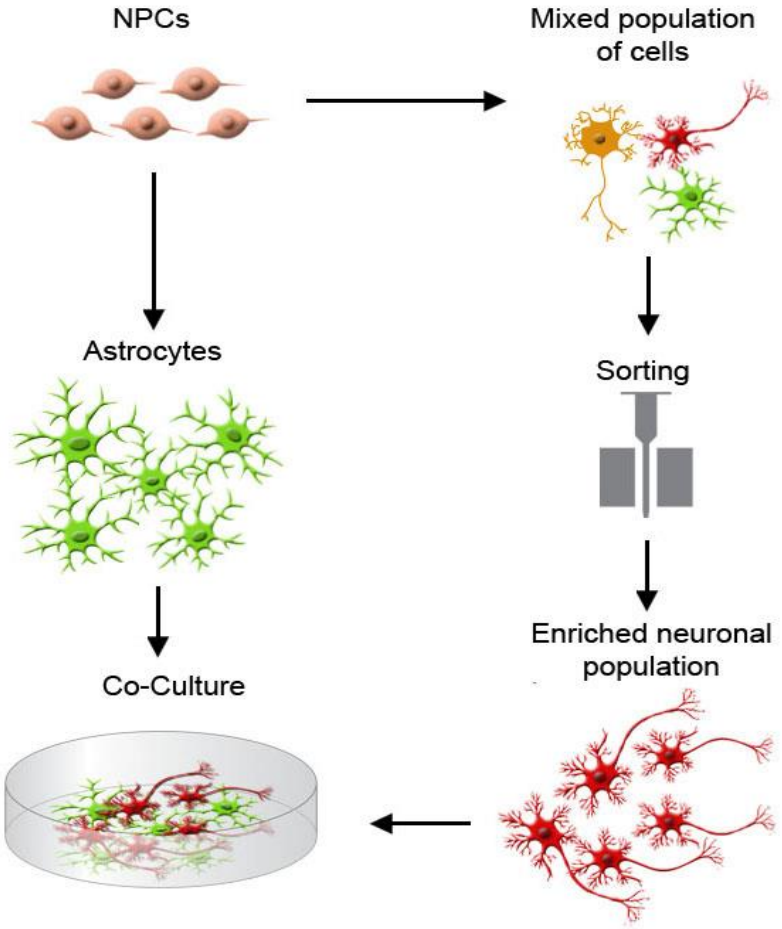


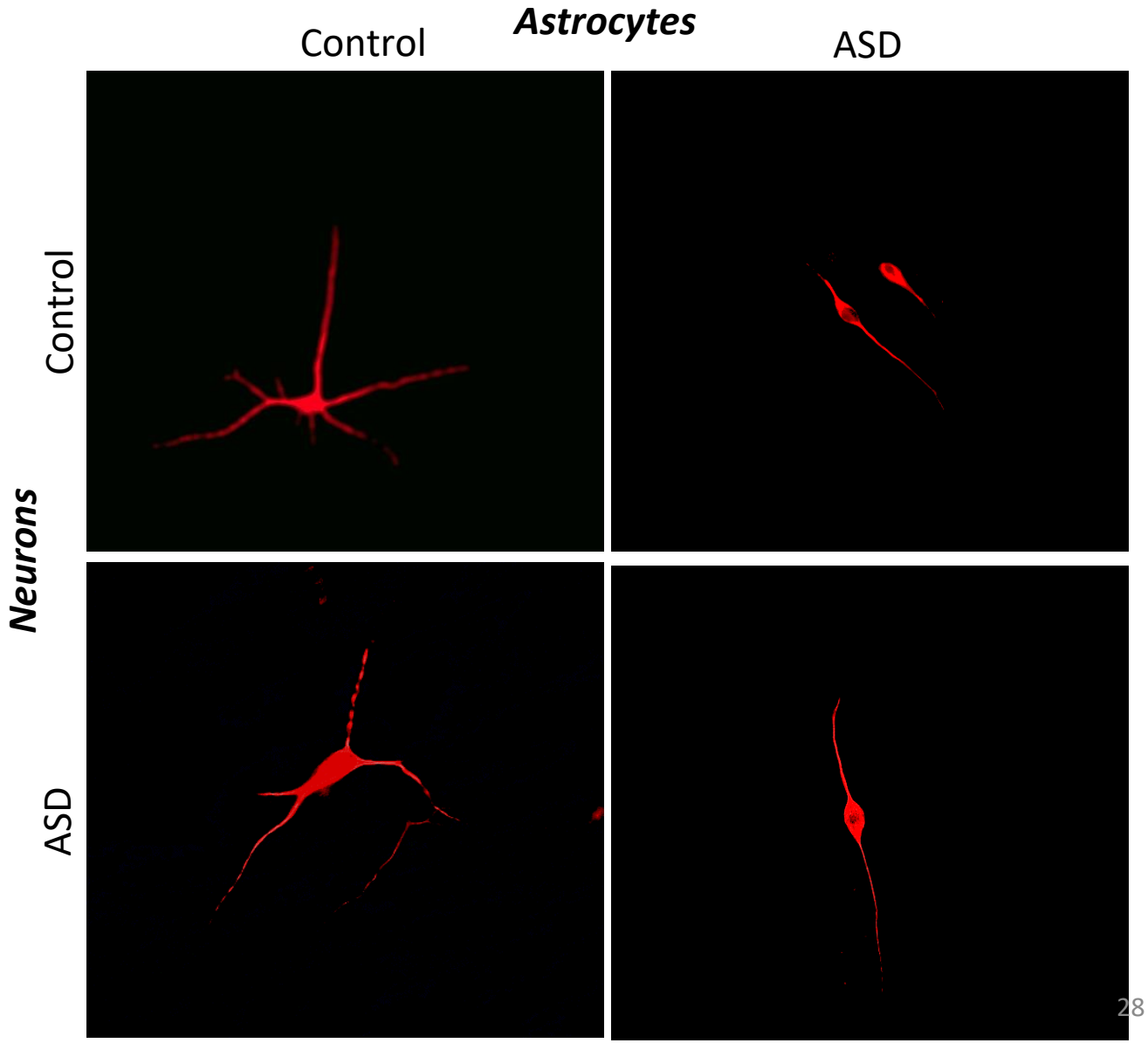




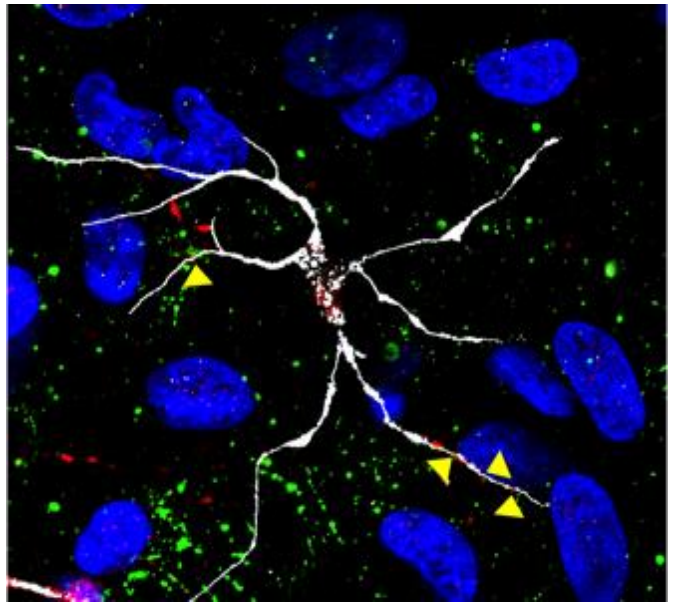

Astrocytes (GFAP+)
Neuron (Synapsin+)

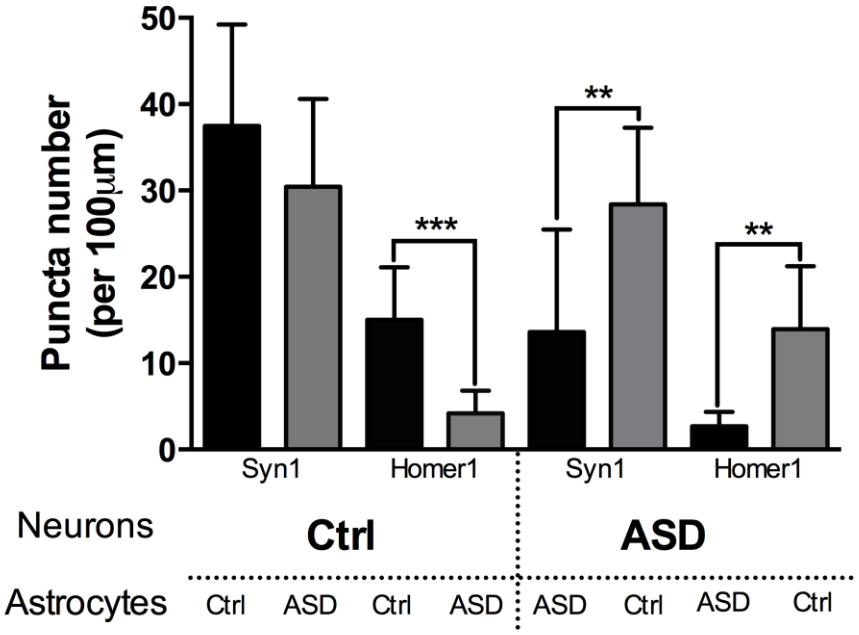
Control astrocytes improved ASD neurons morphology
ASD astrocytes make control neurons worse in terms of morphology

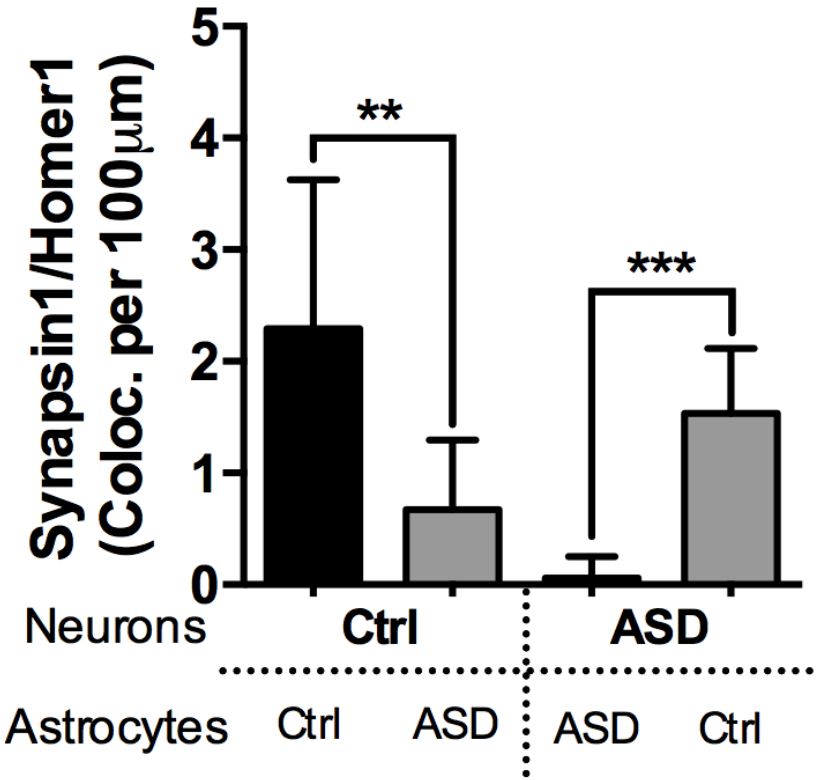




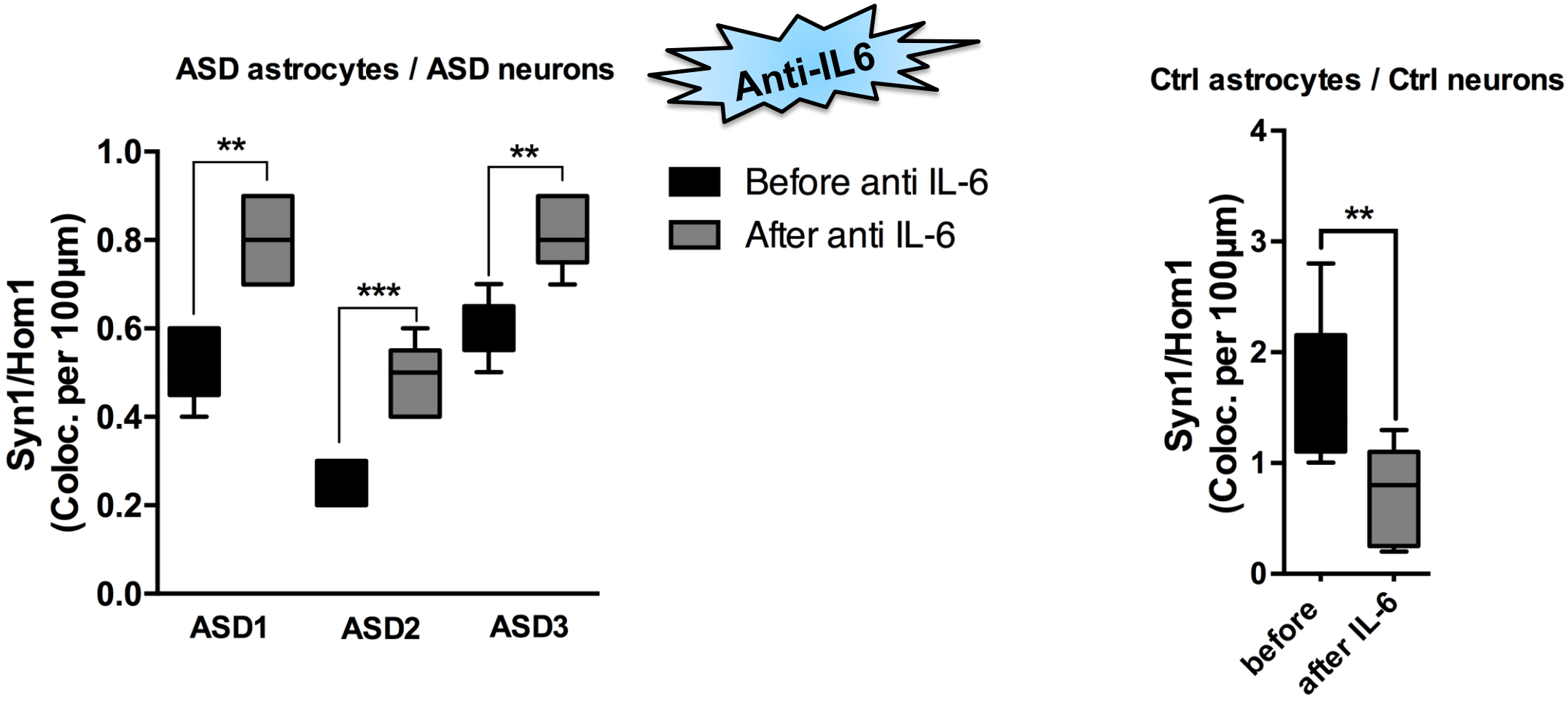
Control astrocytes improved synaptogenesis in ASD neurons



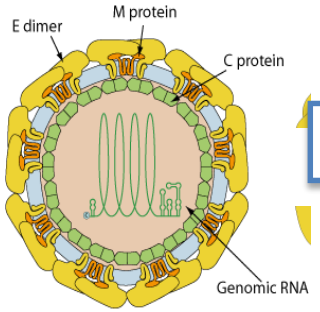




IL-6 blocking improves synaptogenesis
IL-6 decreases synaptogenesis



ASD DMD



ZIKV

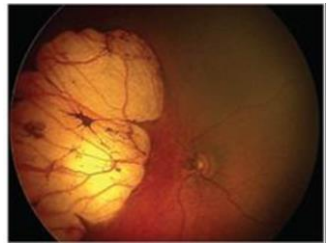
Congenital Zika Syndrome

Congenital Zika Syndrome

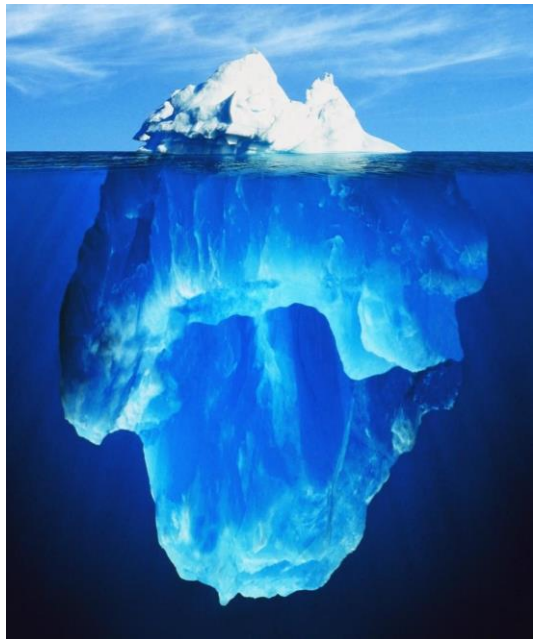
Microcephaly



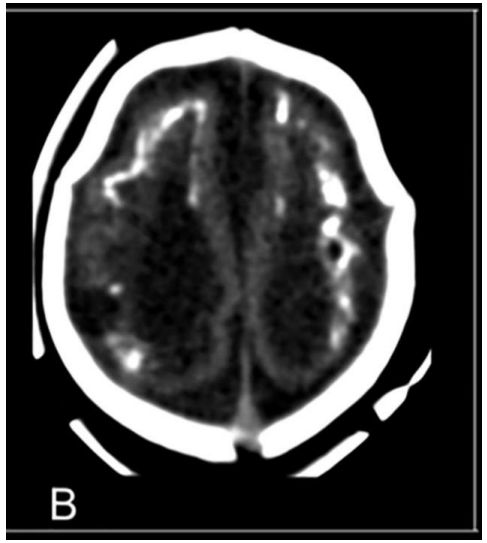
Eye abnormality



IUGR

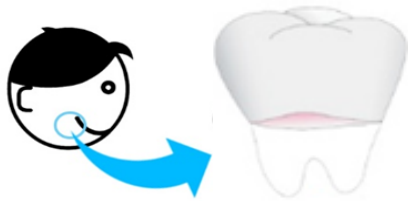


Microcalcifications

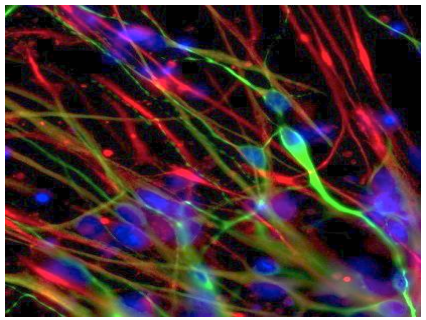


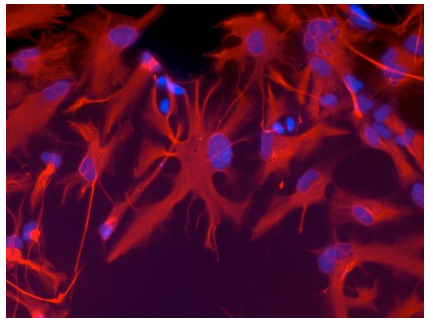
Arthrogriposis

“Disease in a dish”



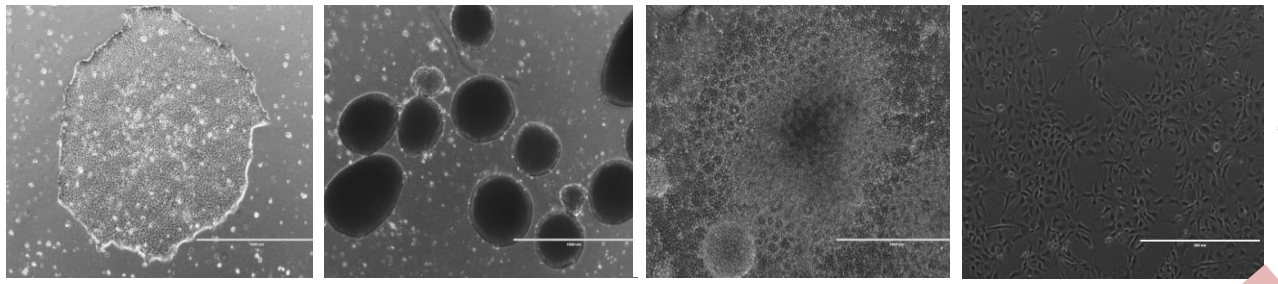
2D





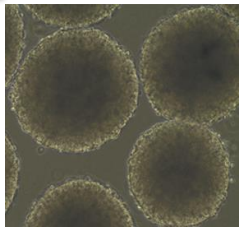
Neurons

Astrocytes



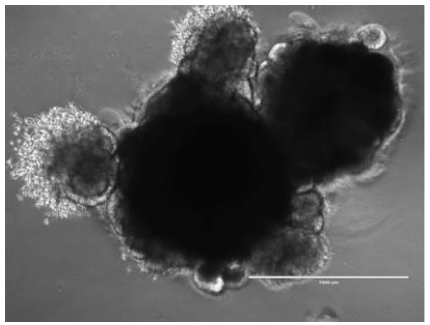
3D

Neurospheres



3D

Brain organoids



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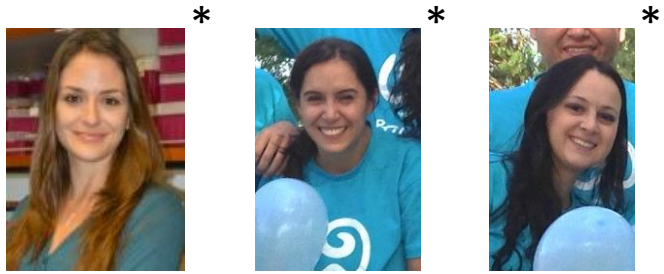
International weekly journal of science

LETTER

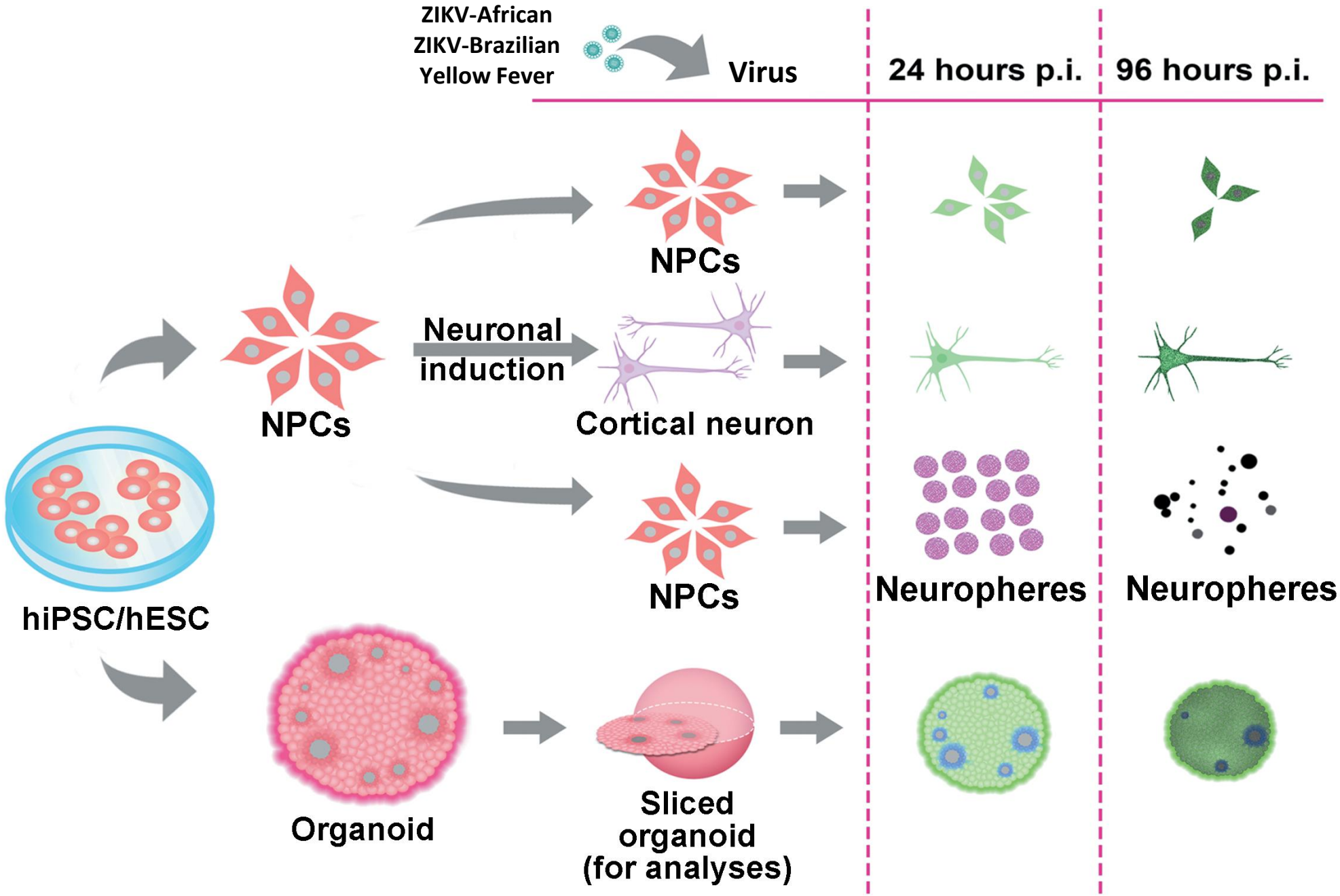
doi:10.1038/nature18296

The Brazilian Zika virus strain causes birth defects in experimental models

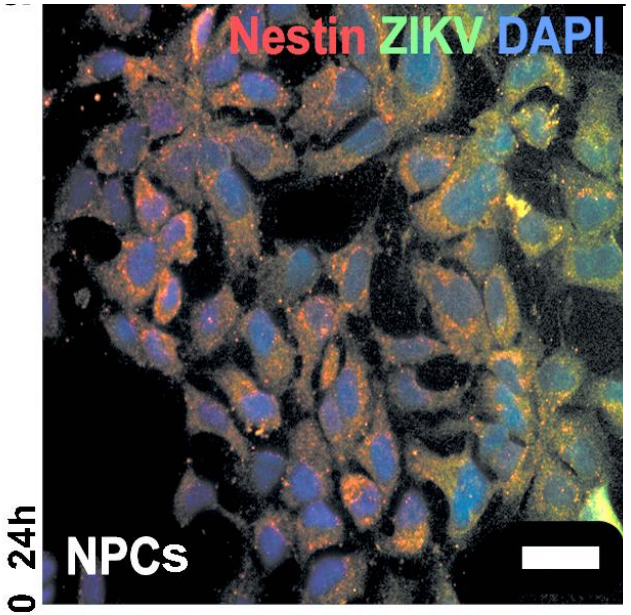
Fernanda R. Cugola[1]*, Isabella R. Fernandes[1,2]*, Fabiele B. Russo[1,3]*, Beatriz C. Freitas[2], João L. M. Dias[1], Katia P. Guimarães[1], Cecília Benazzato[1], Nathalia Almeida[1], Graciela C. Pignatari[1,3], Sarah Romero[2], Carolina M. Polonio[4], Isabela Cunha[4], Carla L. Freitas[4], Wesley N. Brandão[4], Cristiano Rossato[4], David G. Andrade[4], Daniele de P. Faria[5], Alexandre T. Garcez[5], Carlos A. Buchpigel[5], Carla T. Braconi[6], Erica Mendes[6], Amadou A. Sall[7], Paolo M. de A. Zanotto[6], Jean Pierre S. Peron[4], Alysson R. Muotri[2] & Patricia C. B. Beltrão-Braga[1,8]

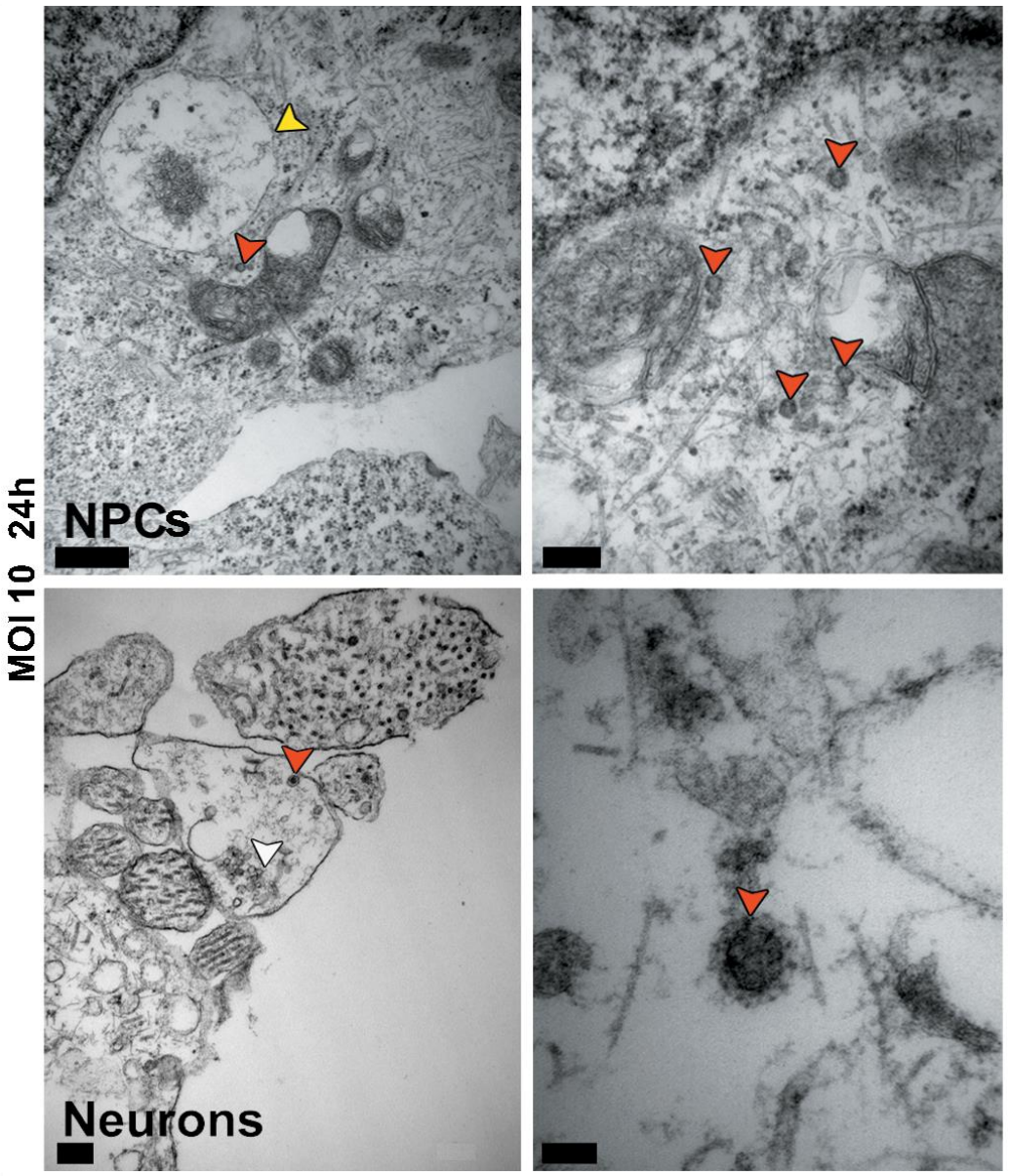


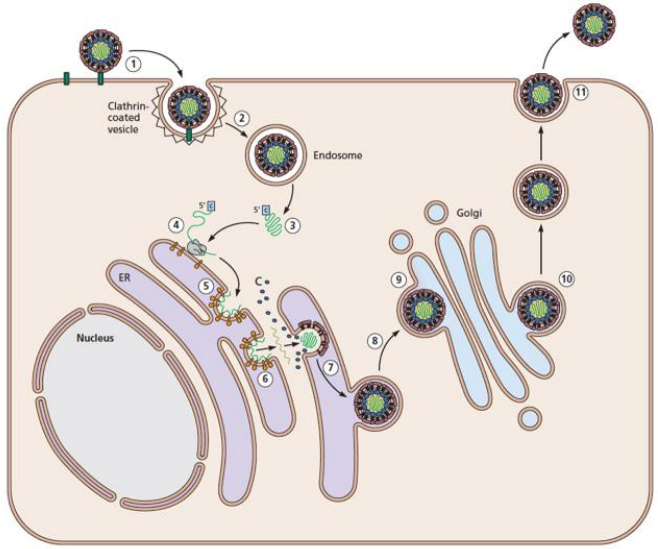
Cugola, Fernandes and Russo et al., Nature 2016


ZIKV-African
ZIKV-Brazilian
Yellow Fever
Virus
24 hours p.i.
96 hours p.i.
NPCs
Neuronal induction
Cortical neuron
NPCs
hiPSC/hESC
NPCs
Neuropheres
Neuropheres
Organoid
Sliced organoid (for analyses)

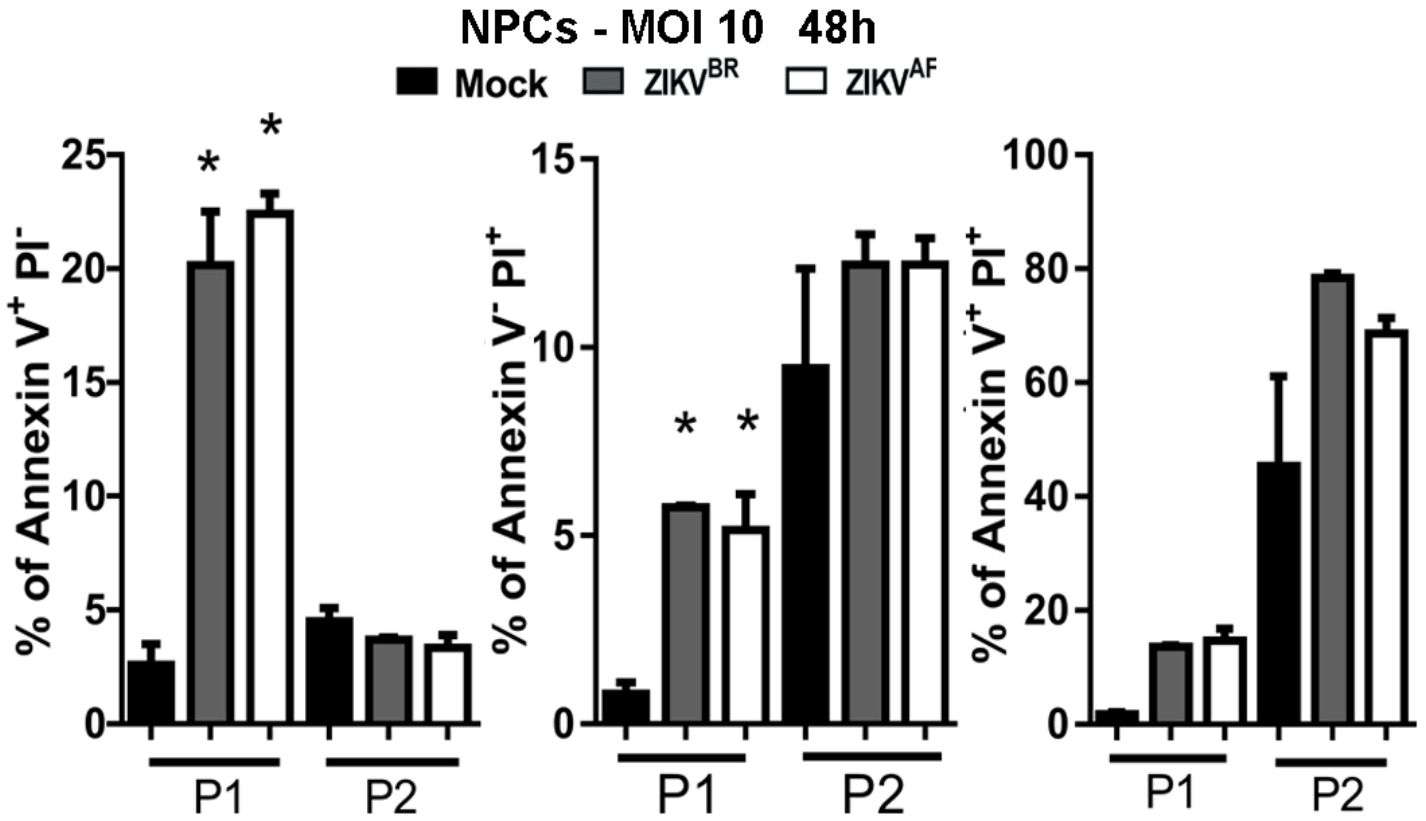
ZIKV infects NPC and neurons and replicates into vesicles



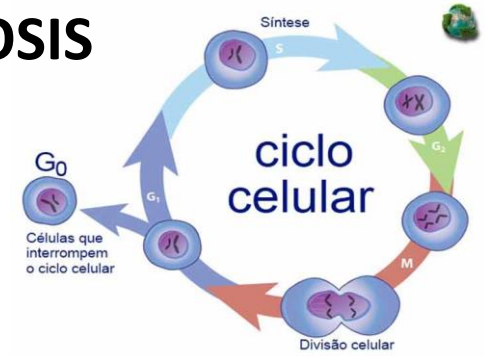


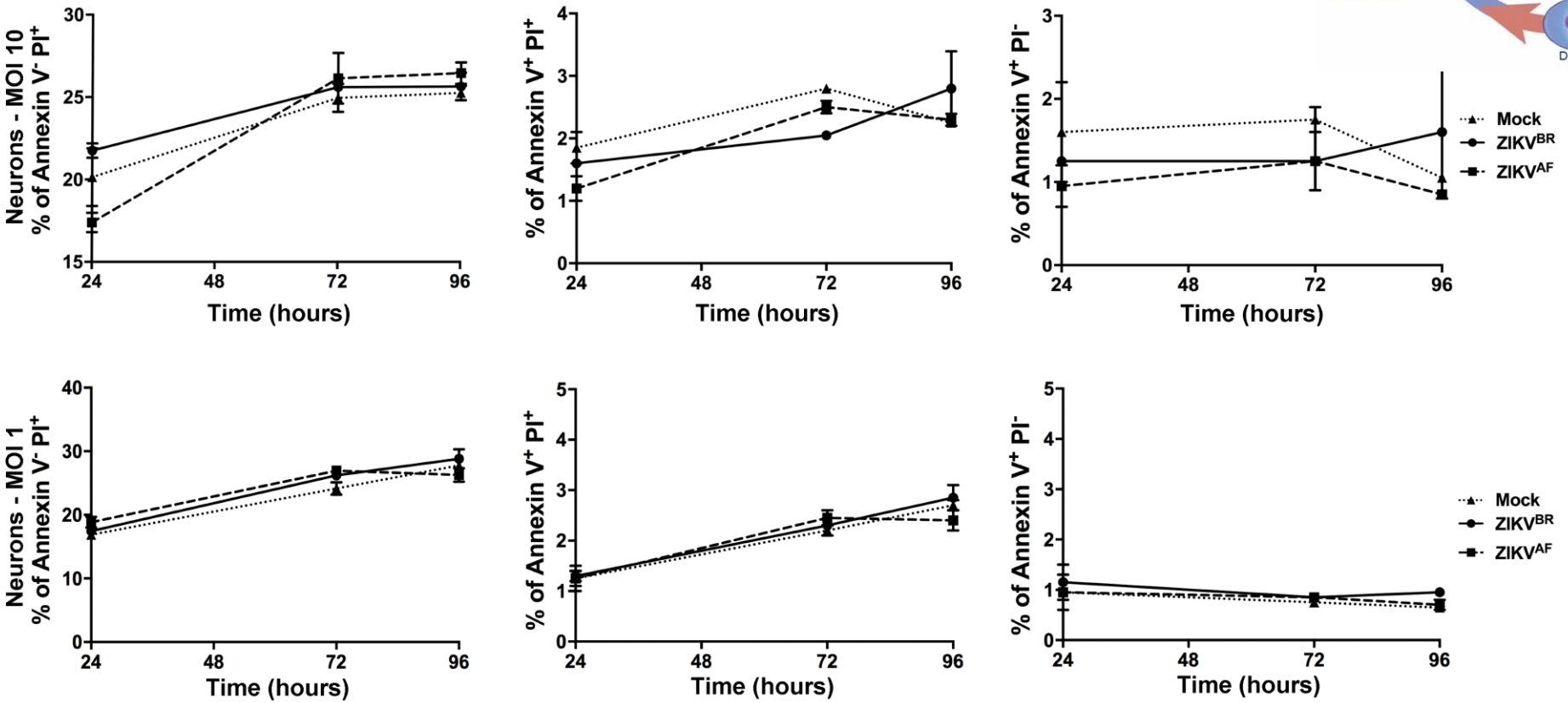


INFECTED NPCS COME INTO APOPTOSIS AND NECROSIS

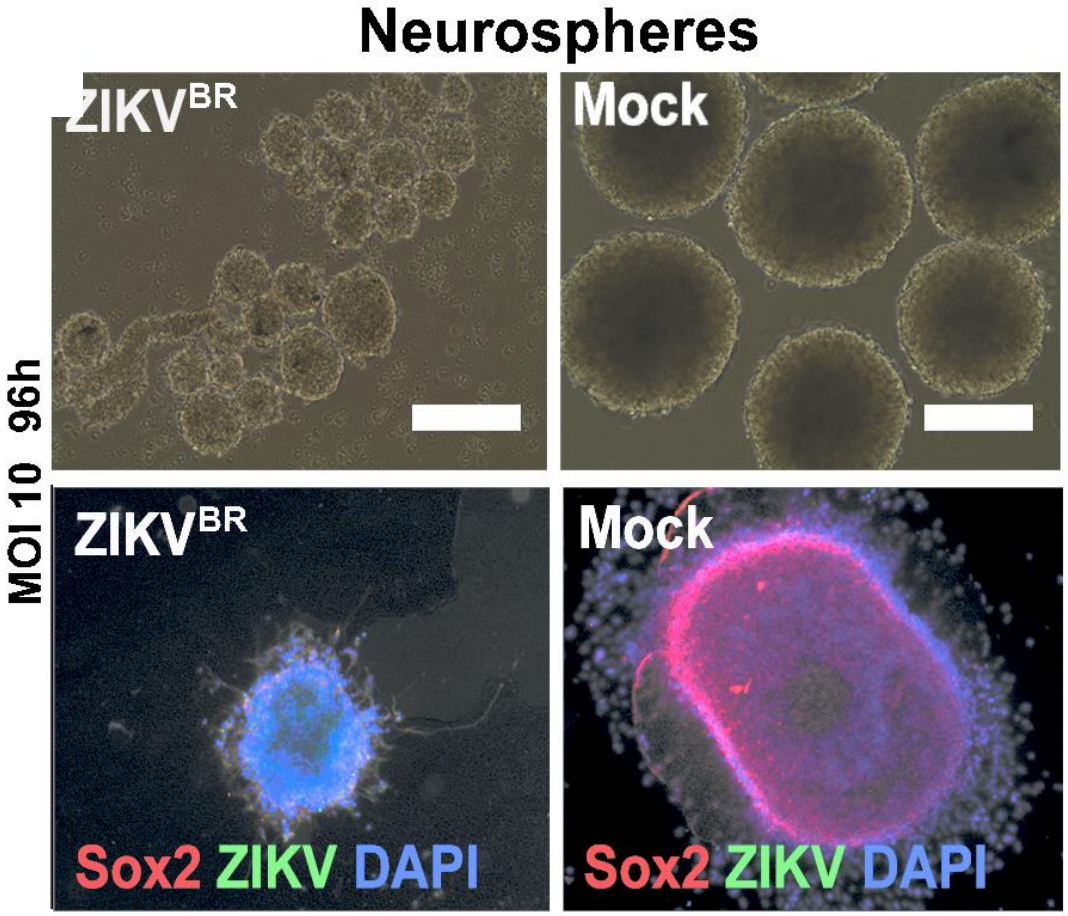


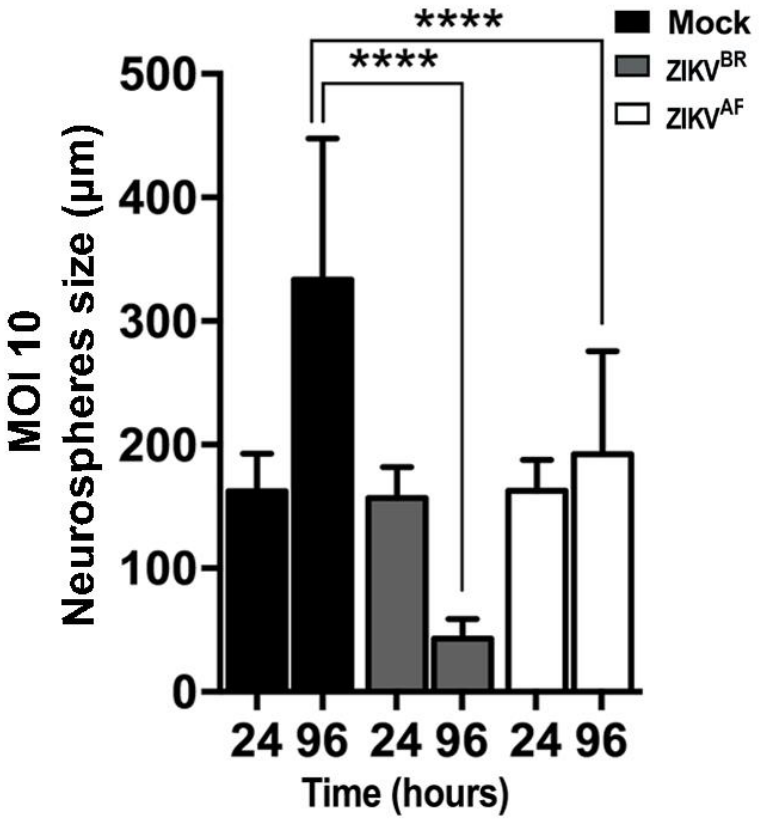
INFECTED NEURONS DID NOT COME INTO APOPTOSIS

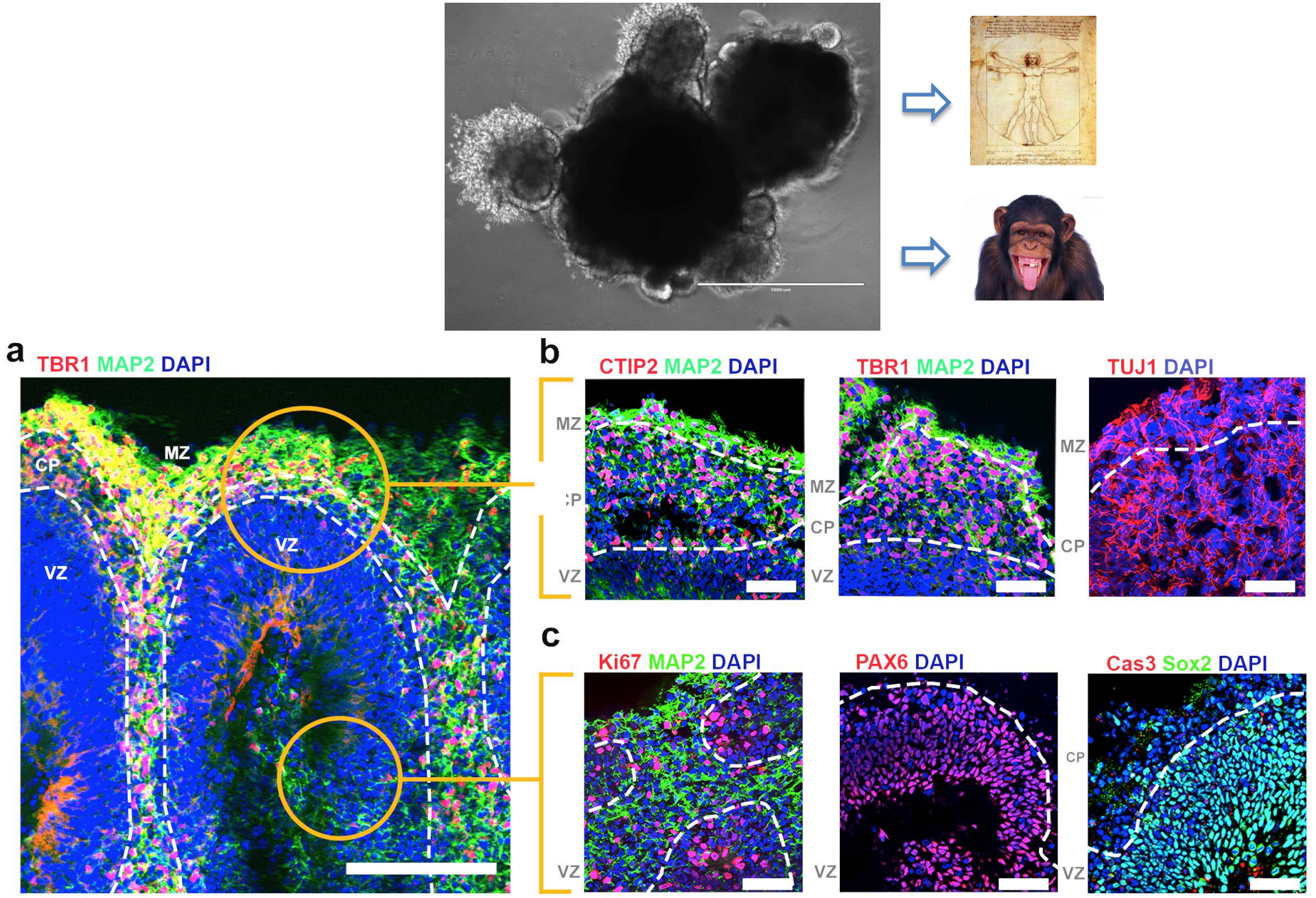




Neurospheres diminishes their size after 4 days and cells did not migrate

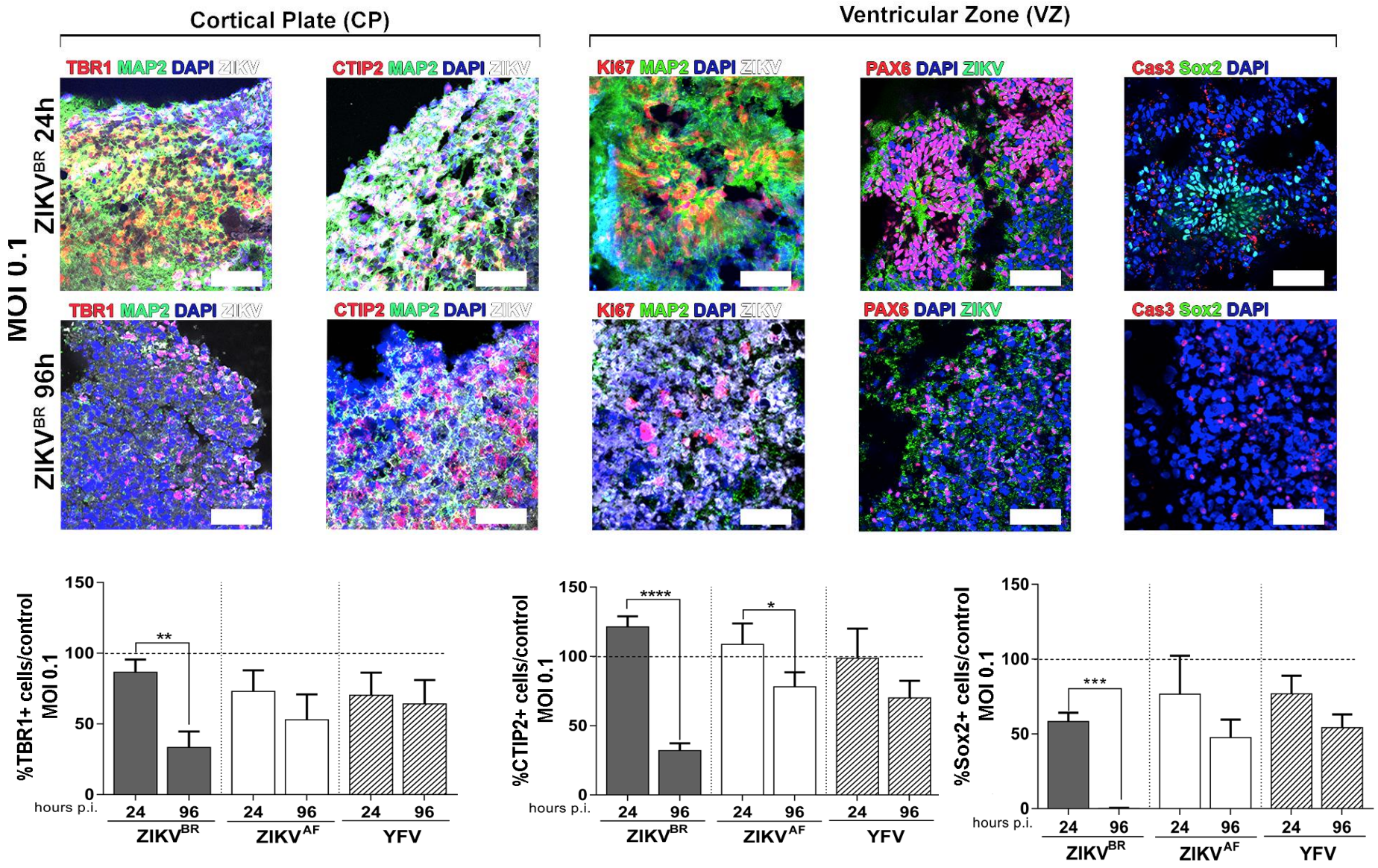




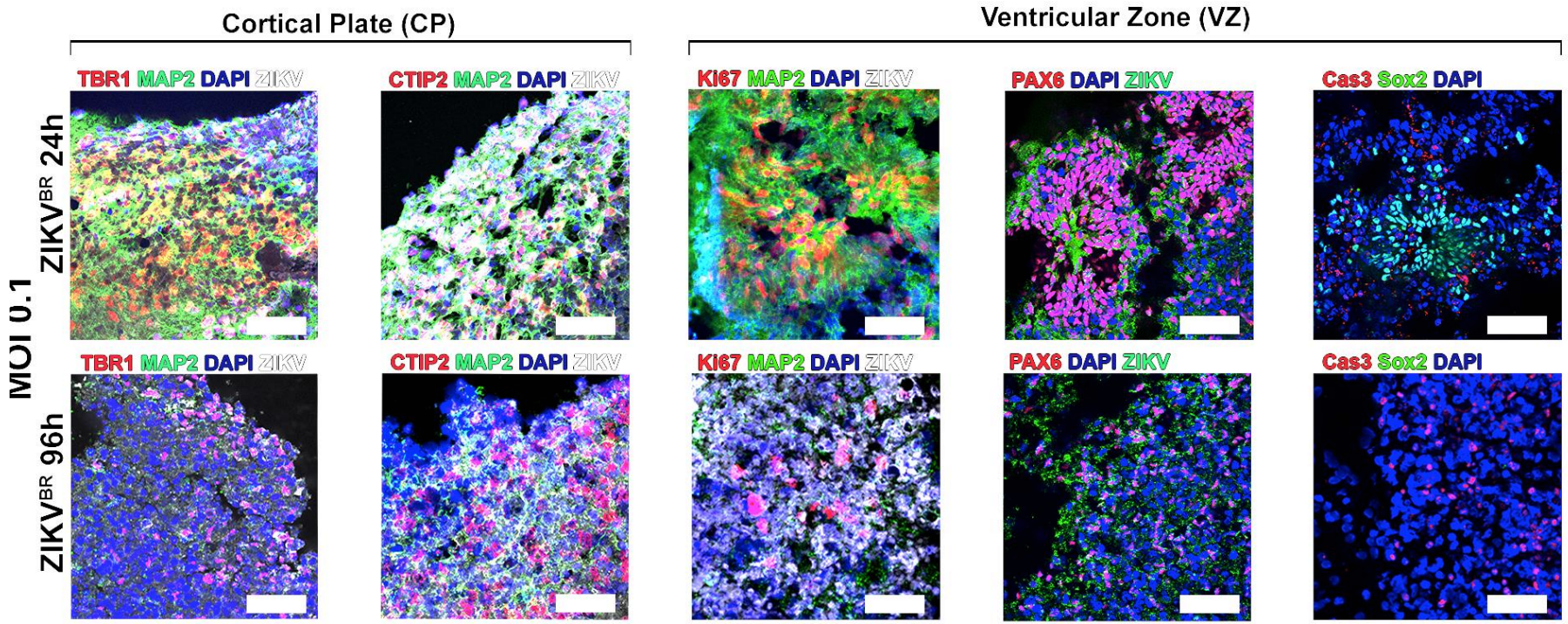


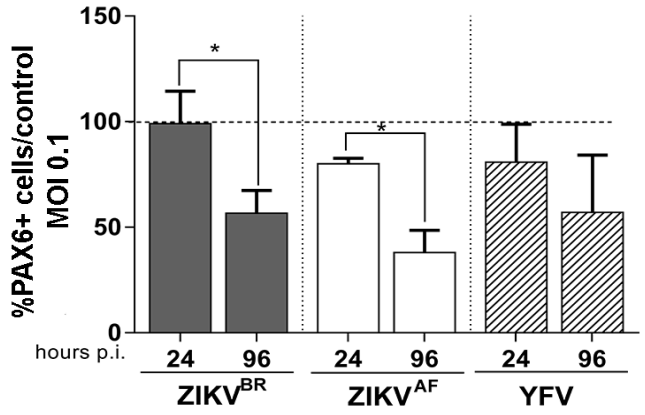
Cugola, Fernandes, Russo, et al. Nature 2016.

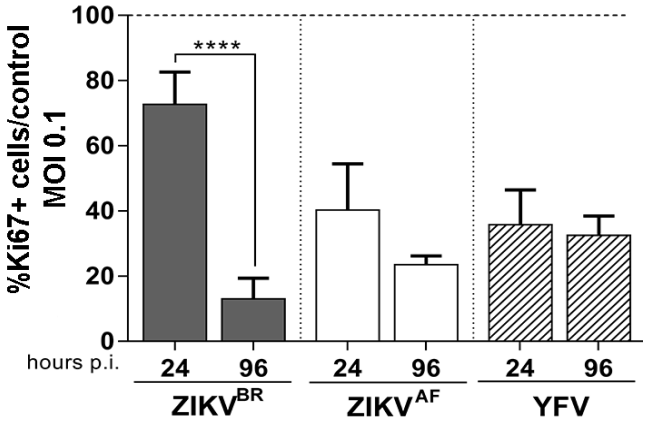
Cortex Progenitors cells and NPC had diminished in number 96 h p.i.



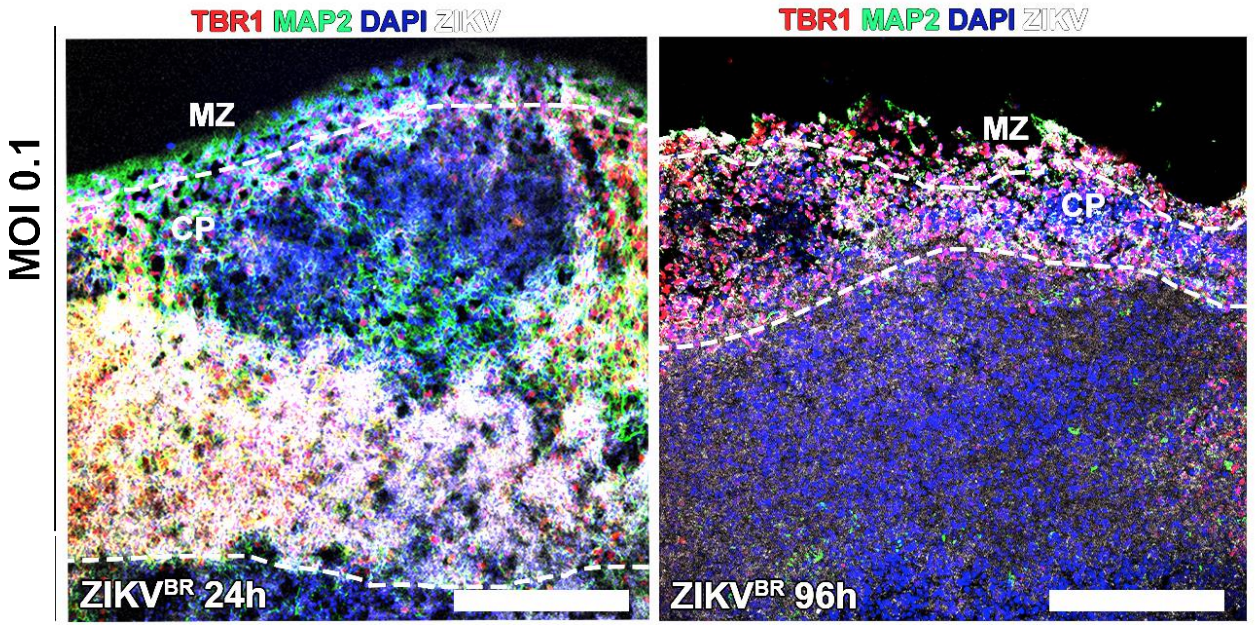
Mitotic cells had diminished in number after 96h p.i.

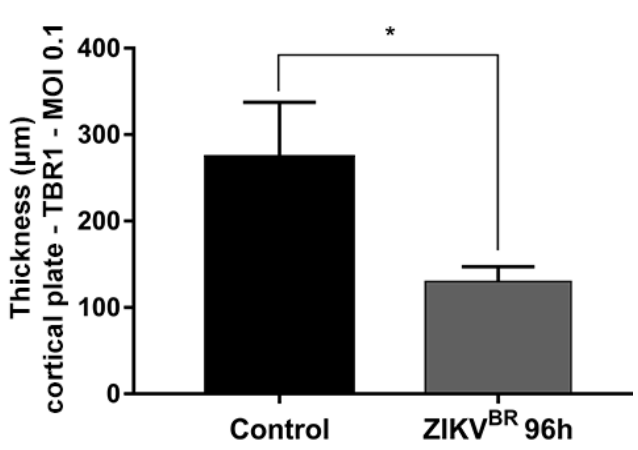


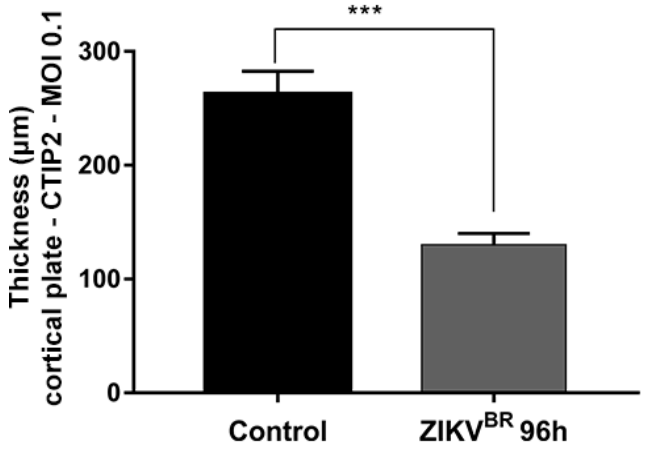




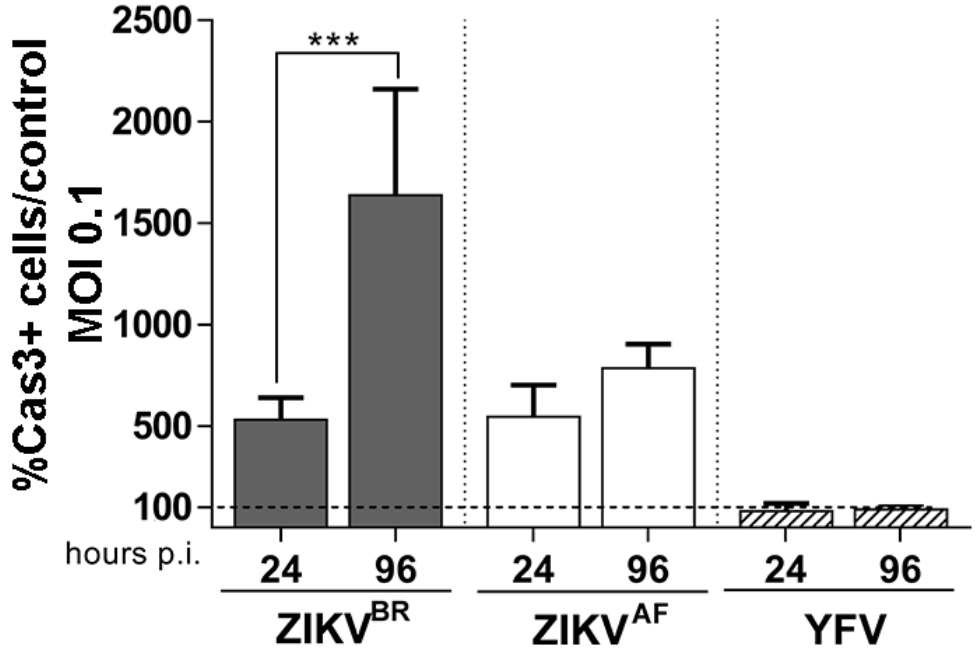
Cortical layer was thinner after 96h p.i.

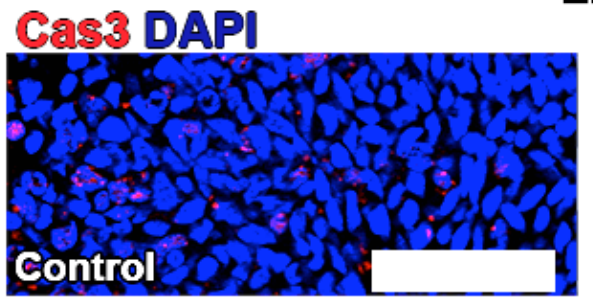


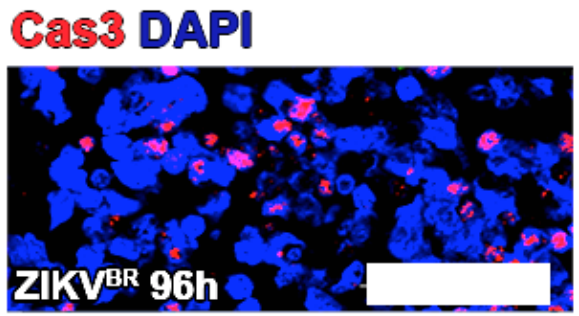


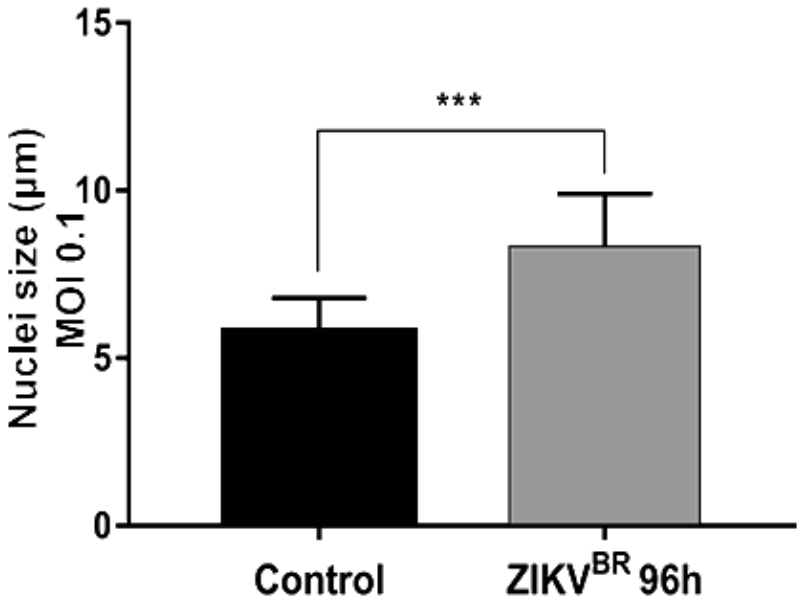


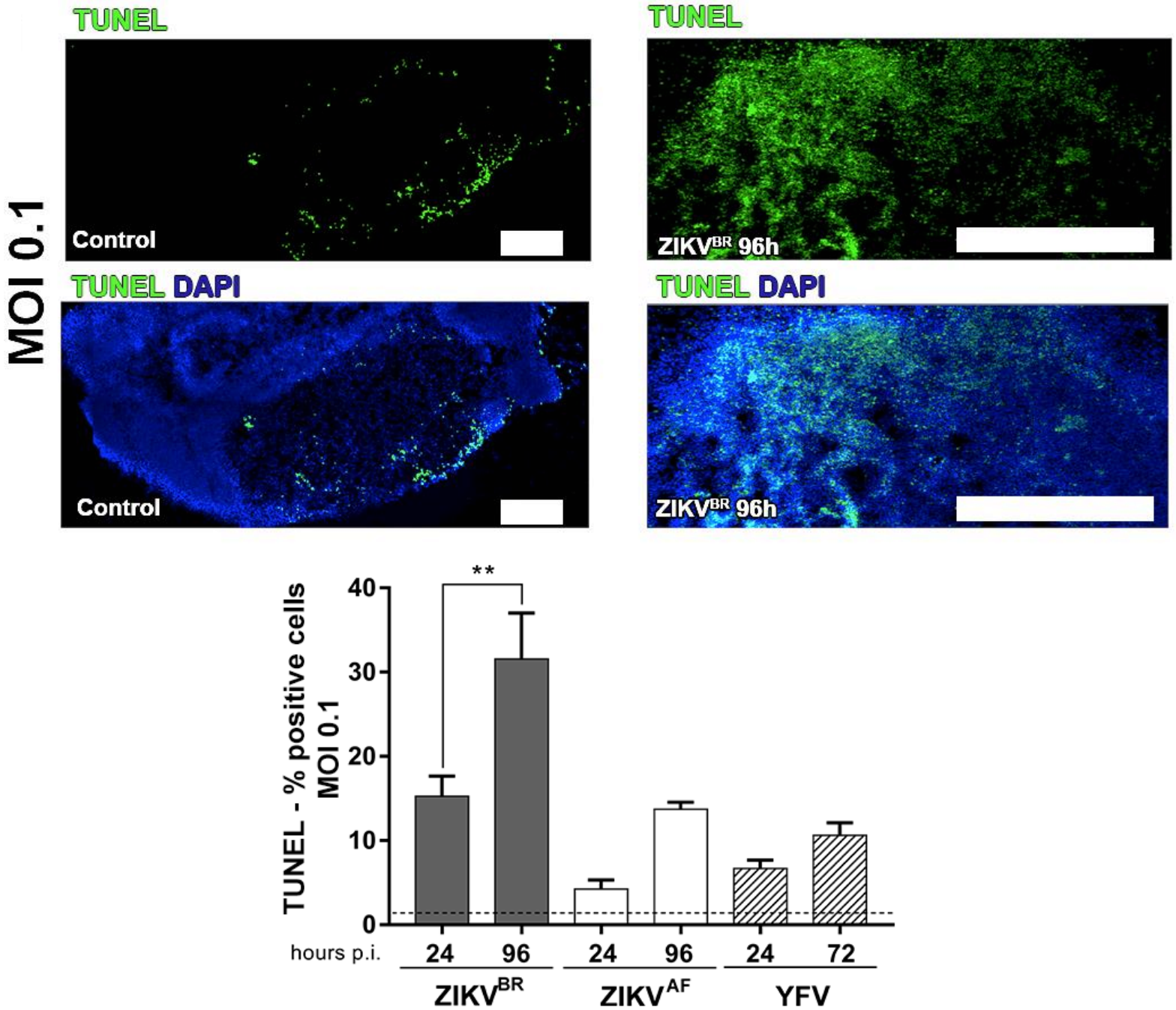
Number of apoptotic cells increased after 96h p.i.

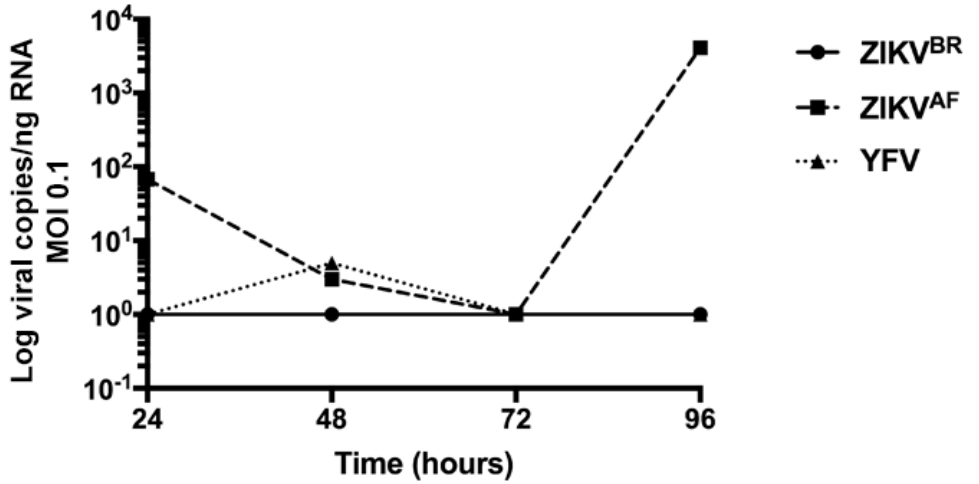


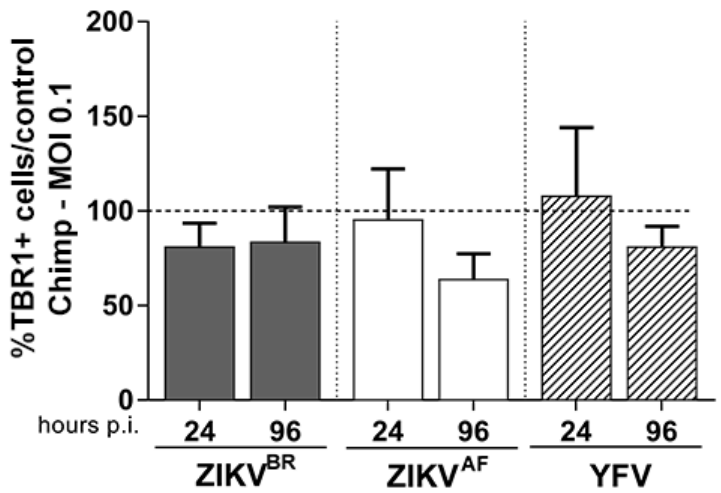







MOI 0.1
TUNEL
Control
TUNEL
ZIKV^BR 96h
TUNEL DAPI
Control
TUNEL DAPI
ZIKV^BR 96h
TUNEL - % positive cells
MOI 0.1
**
40
30
20
10
0
hours p.i.
24
96
24
96
24
72
ZIKV^BR
ZIKV^AF
YFV


Log viral copies/ng RNA
MOI 0.1
10^4
10^3
10^2
10^1
10^0
10^{-1}
24
48
72
96
Time (hours)
ZIKV^{BR}
ZIKV^{AF}
YFV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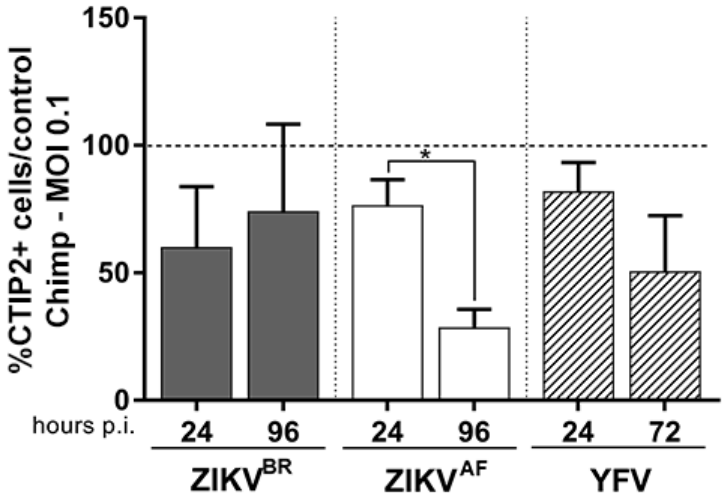
Chimp - MOI 0.1
200
150
100
50
0
hours p.i.
24
96
24
96
24
96
ZIKV^{BR}
ZIKV^{AF}
YFV


%CTIP2+ cells/control
Chimp - MOI 0.1
150
100
50
0
*
hours p.i.
24
96
24
96
24
72
ZIKV^{BR}
ZIKV^{AF}
YFV

Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

Hengli Tang,[1,11,*] Christy Hammack,[1,11] Sarah C. Ogden,[1,11] Zhexing Wen,[2,3,11] Xuyu Qian,[2,4,11] Yujing Li,[9] Bing Yao,[9] Jaehoon Shin,[2,5] Feiran Zhang,[9] Emily M. Lee,[1] Kimberly M. Christian,[2,3] Ruth A. Didier,[10] Peng Jin,[9] Hongjun Song,[2,3,5,6,7,*] and Guo-li Ming[2,3,5,6,7,8,*]

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,[3†] Pablo Trindade,[2†] Rodrigo Delvecchio,[3] Juliana Minardi Nascimento,[2,4] Rodrigo Brindeiro,[3] Amilcar Tanuri,[3] Stevens K. Rehen[2,1*]

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

Xuyu Qian,[1,2,18] Ha Nam Nguyen,[1,3,4,18] Mingxi M. Song,[1,9] Christopher Hadiono,[1,10] Sarah C. Ogden,[11] Christy Hammack,[11] Bing Yao,[12] Gregory R. Hamersky,[5] Fadi Jacob,[1] Chun Zhong,[1,4] Ki-jun Yoon,[1,4] William Jeang,[1,14] Li Lin,[12] Yujing Li,[12] Jai Thakor,[1] Daniel A. Berg,[1] Ce Zhang,[1,4] Eunchai Kang,[1,4] Michael Chickering,[1] David Nauen,[1,6] Cheng-Ying Ho,[15,16] Zhexing Wen,[1,4] Kimberly M. Christian,[1,4] Pei-Yong Shi,[17] Brady J. Maher,[5,7] Hao Wu,[13] Peng Jin,[12] Hengli Tang,[11] Hongjun Song,[1,3,4,8,*] and Guo-li Ming[1,3,4,7,8,*]

Brief Report

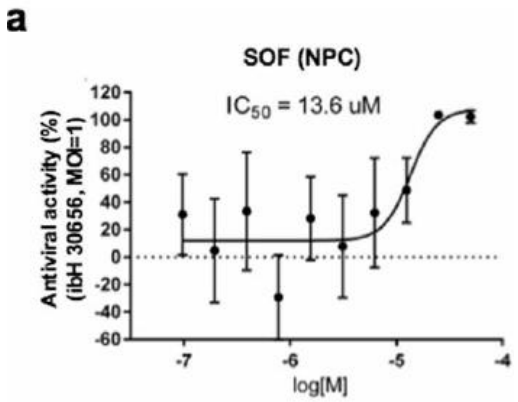
Cell Stem Cell

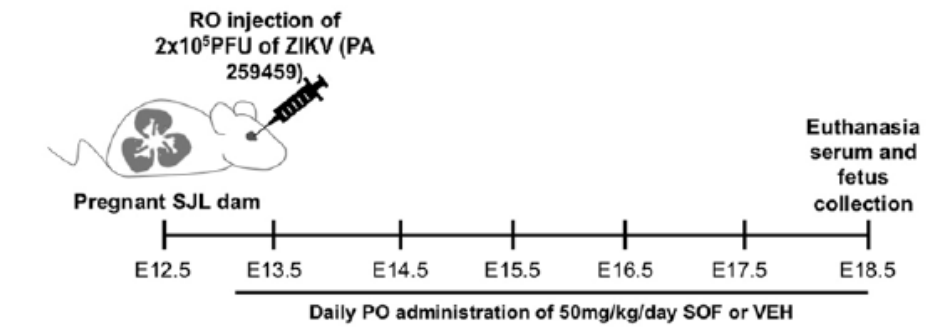
Expression Analysis Highlights AXL as a Candidate Zika Virus Entry Receptor in Neural Stem Cells

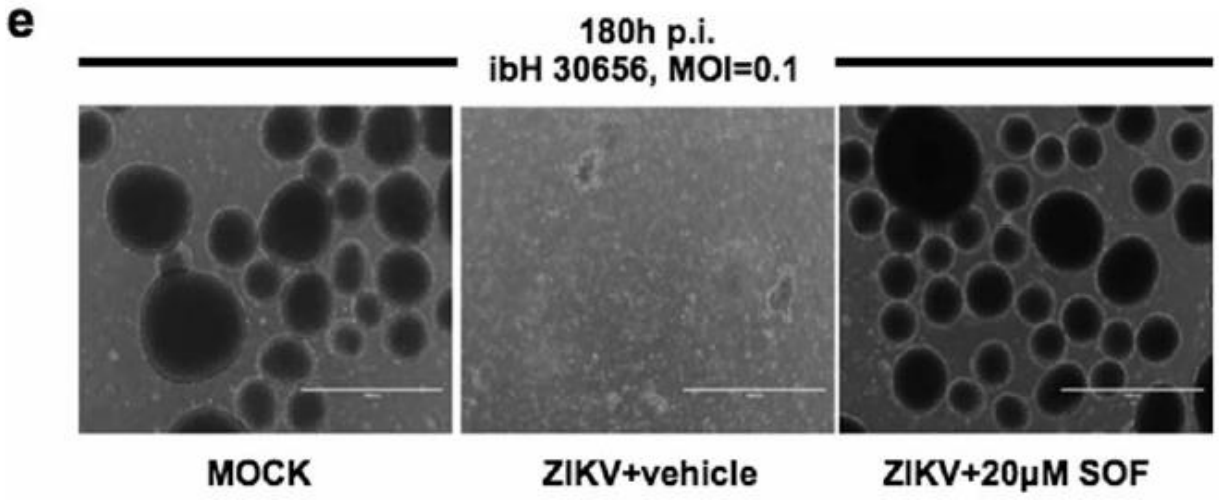
Blocking Zika virus vertical transmission

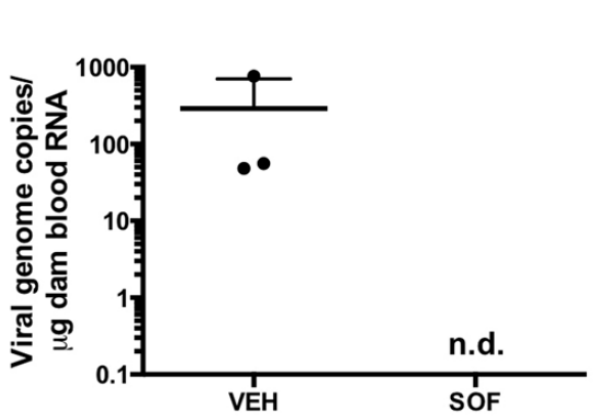
Pinar Mesci[1], Angela Macia[1], Spencer M. Moore[1], Sergey A. Shiryaev[2], Antonella Pinto[2], Chun-Teng Huang[2], Leon Tejwani[1], Isabella R. Fernandes[1], Nicole A. Suarez[1], Matthew J. Kolar[3], Sandro Montefusco[4], Scott C. Rosenberg[5,6], Roberto H. Herai[7], Fernanda R. Cugola[8,9,10], Fabiele B. Russo[8,9,10], Nicholas Sheets[11], Alan Saghatelian[3], Sujan Shresta[11], Jeremiah D. Momper[12], Jair L. Siqueira-Neto[4], Kevin D. Corbett[5], Patricia C. B. Beltrão-Braga[8,9,10], Alexey V. Terskikh[2] & Alysson R. Muotri[1]

Mesci et al., Sci Rep, 2018





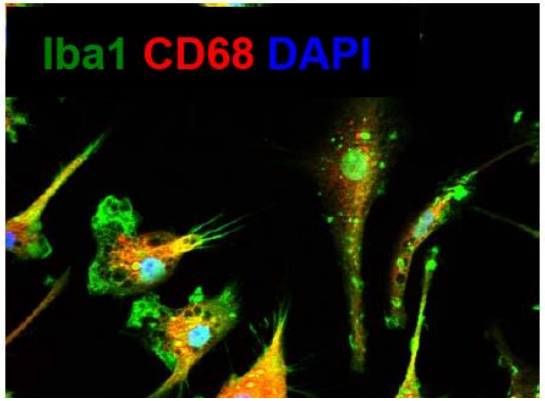




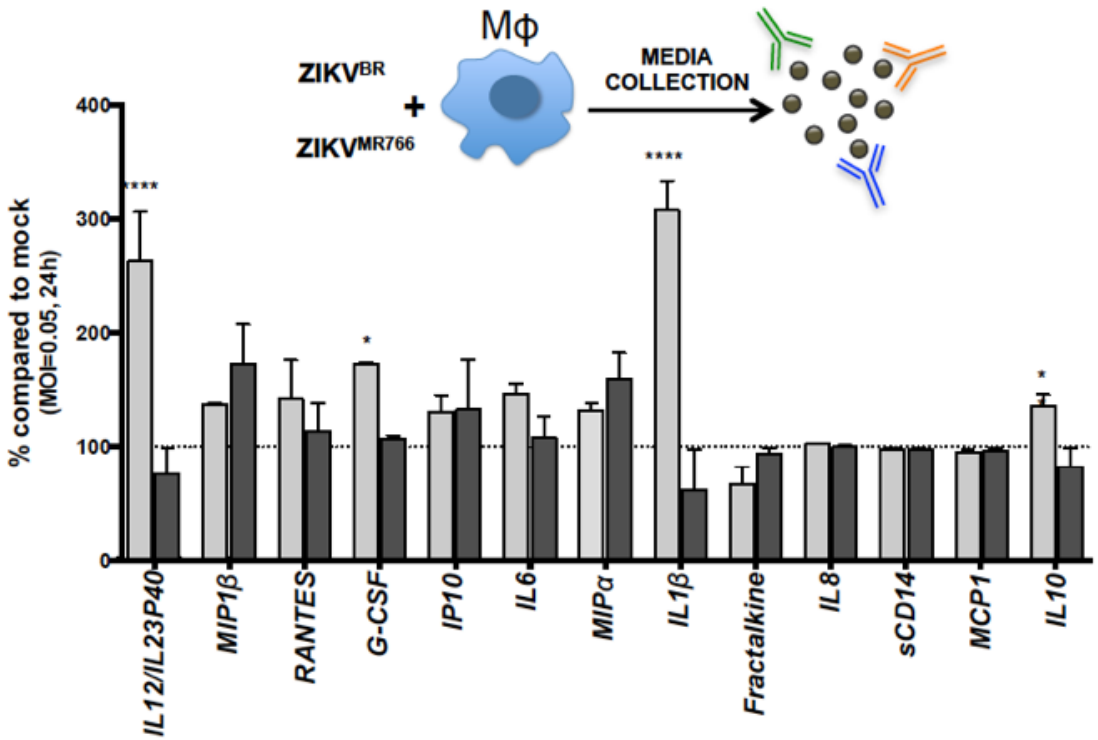
ORIGINAL ARTICLE

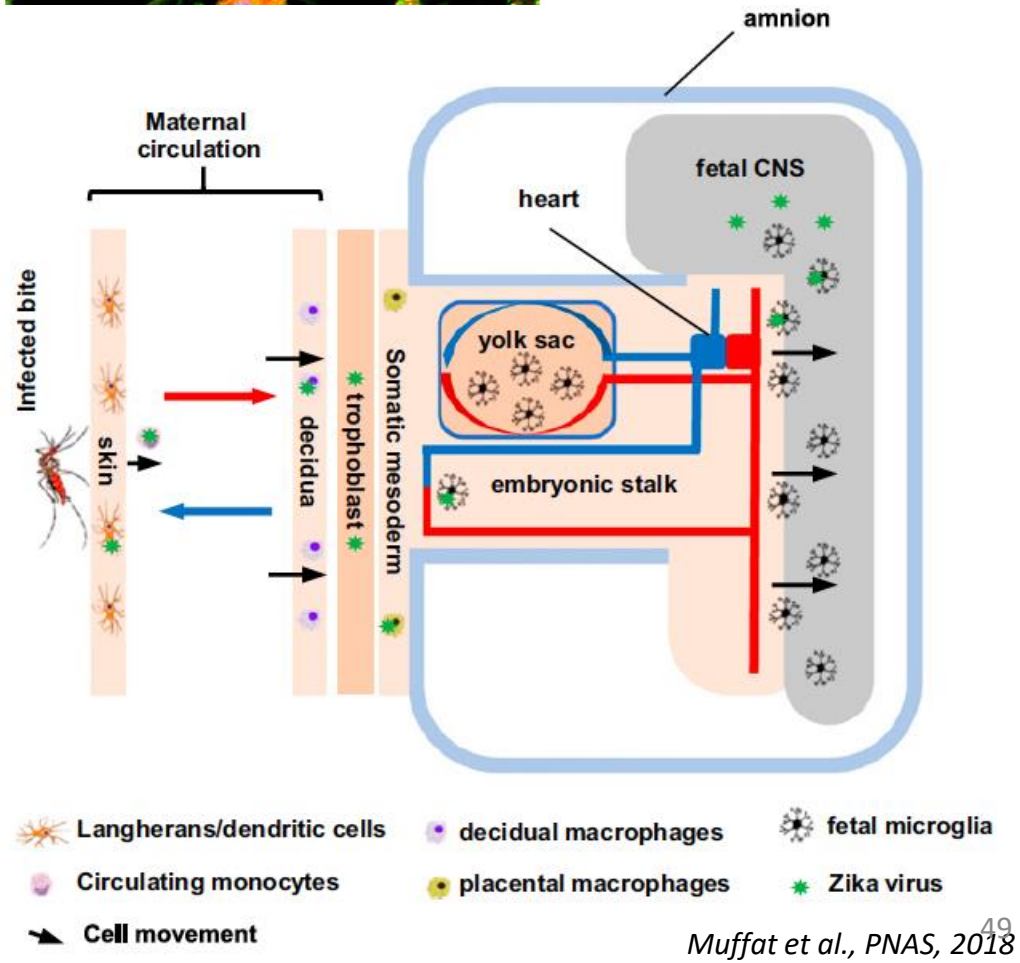
Modeling neuro-immune interactions during Zika virus infection

Pinar Mesci[1,2,†], Angela Macia[1,2,†], Christopher N. LaRock[3], Leon Tejwani[1,2], Isabella R. Fernandes[1,2], Nicole A. Suarez[1,2], Paolo M. de A. Zanotto[4], Patricia C.B. Beltrão-Braga[5,6,7], Victor Nizet[3] and Alysson R. Muotri[1,2,*]



Mesci et al., Hum Mol Gen, 2018

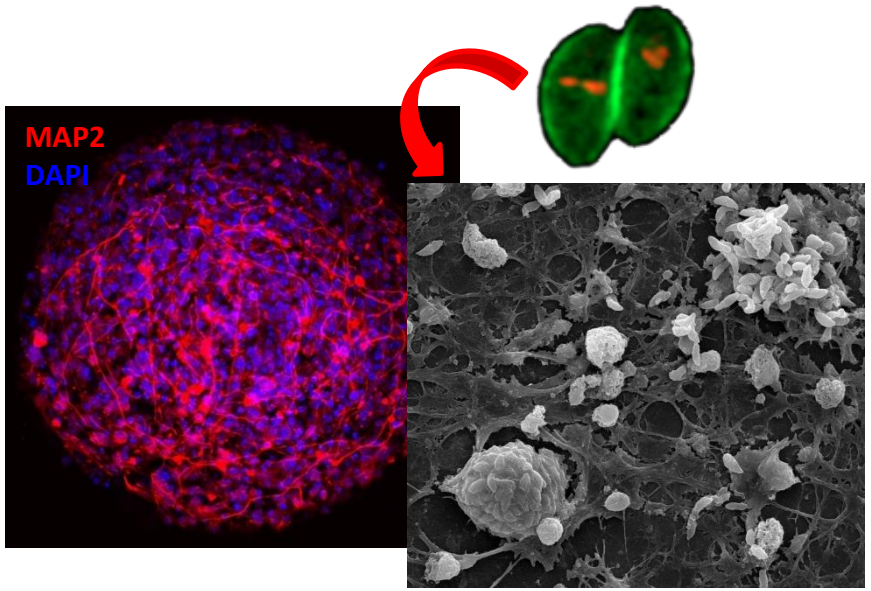




Muffat et al., PNAS, 2018

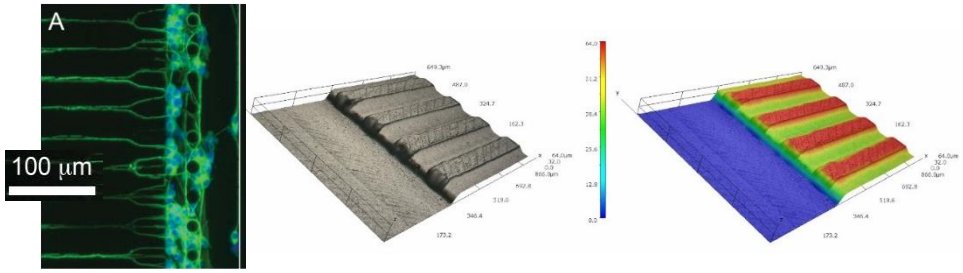
Application to other infection models (TORCHES) *Toxoplasma gondii*...

Collaboration: Paulo Emílio Corrêa Leite INMETRO/UFRJ

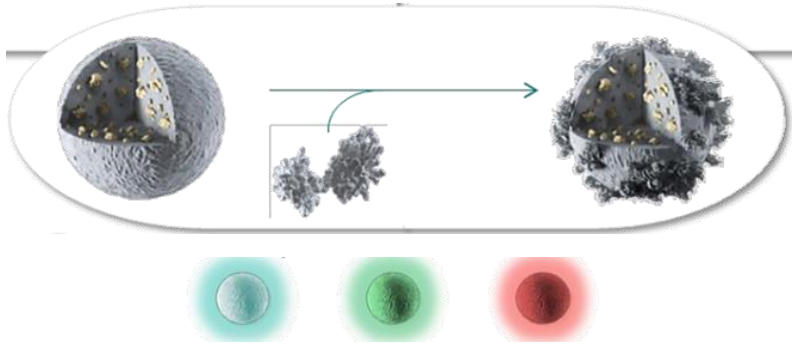


Development of microfluidic devices

COPPE UFRJ



Development of nanoparticles for selective drug delivery



Universidade de São Paulo

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Patricia Beltrão Braga

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Poul Hyttel (Univ. Copenhagen)
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Carlos Menck , ICB (USP)
Giuseppe Palmisiano, ICB (USP)
Lívia Rosa-Fernandes (SDU)
Paulo Leite (UFRJ)
Patricia Jungmann (UPE)

All donors and their families

FAPESP

CNPq

PROJETO a fada do dente