



EMERGING TECHNOLOGY TOWARD PATHWAY-
BASED HUMAN BRAIN RESEARCH



Modeling Autism Spectrum Disorder using Human neurons

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AUTISM SPECTRUM DISORDER (ASD)



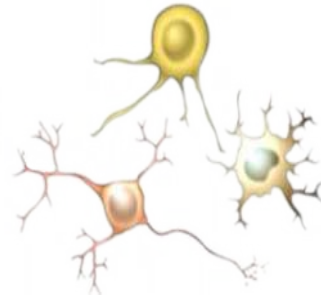
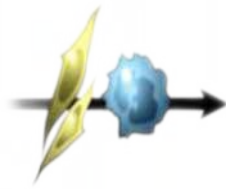
BEHAVIOR

1:68

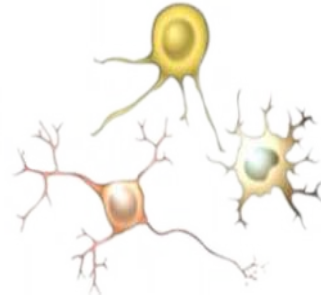
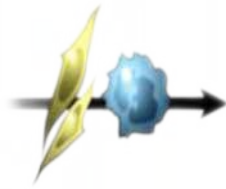
iPSC/ASD Disease Modeling



patient



control



Are they
different?

Disease Modeling using Dental Pulp Stem Cells

www.projetoafadadodente.org.br



Logo: PROJETO a Fada do dente

Navigation: Quem Somos | O que fazemos | Participe | Contato

Social media: Facebook, Twitter

Sobre o projeto

A primeira ONG brasileira inteiramente dedicada à pesquisa do autismo.

[SAIBA MAIS](#)

Projeto

A Fada do Dente é um importante projeto científico que visa a compreender os mecanismos biológicos existentes por trás do autismo. Conhecê-los é essencial para tratar o distúrbio, que atinge milhares de crianças brasileiras.



[→ CONHEÇA](#)

Como Participar

Podem participar do projeto pais de filhos diagnosticados com autismo, assim como pessoas interessadas em apoiar de outras formas.

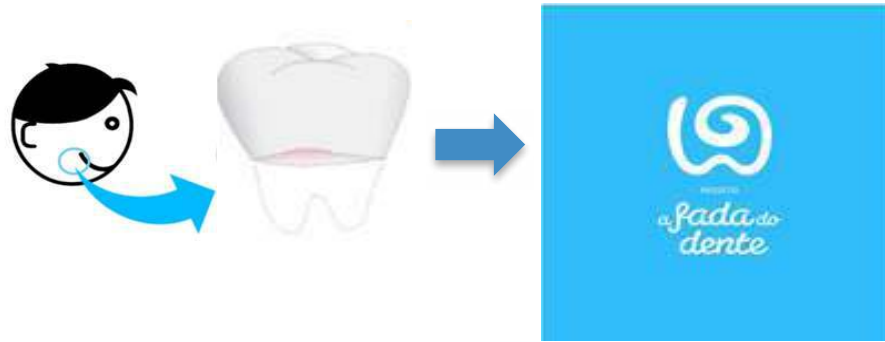


[→ SAIBA COMO](#)

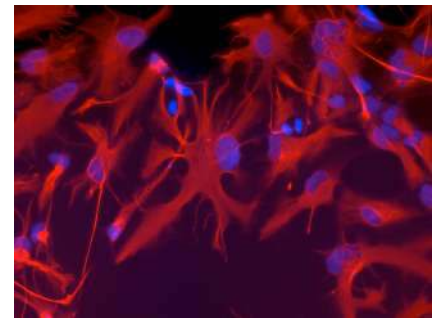
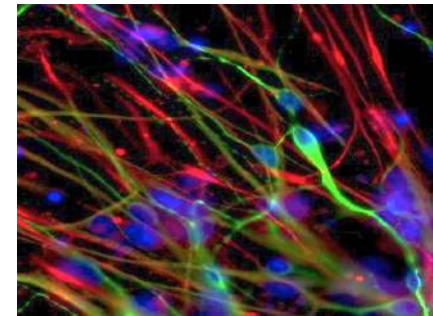
[O que é autismo](#)

[Notícias](#)

"Disease in a dish"



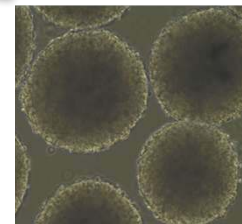
2D



Neurons

Astrocytes

3D
Neurospheres

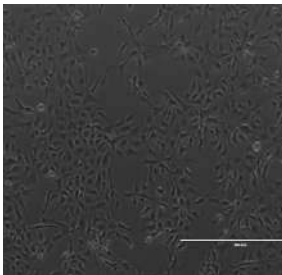
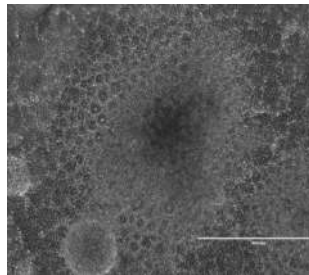
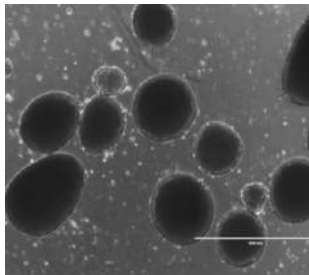
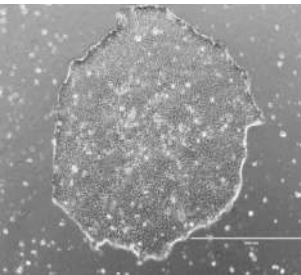


iPS cells

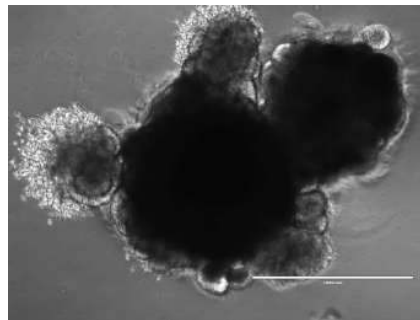
EB

Rosettes

NPC



3D
Brain organoids



Non-Syndromic ASD modeling



Fabiele Russo
PhD



Trait	Participants ID number					
	ASD1	Ctrl1	ASD2	Ctrl2	ASD3	Ctrl3
General Information						
Gender/Age (years)	M/10	M/10	M/7	M/6	M/11	F/7
Ethnicity	Caucasians	Caucasians	Caucasians	Caucasians	Caucasians	Caucasians
Diagnosis						
ASD	+	-	+	-	+	-
CARS score	<u>33</u>		<u>49</u>		<u>32</u>	
Genetic informations						
ASD related genes	-	x	SETD5 (NM_001080517:exon9: c.A894G:p.I298M)	x	-	x
Other genes	SKIV2L (NM_006929:exon16:c .T1811C:p.L604P)	x	ERP44 (NM_015051:exon6:cG4 73A;p.R158H)	x	-	x
Pathogenic CNVs identified	-	x	-	x	-	x
Developmental History						
Language delay	+	-	+	-	+	-
Age (months) start single words/phrases	36	18	non verbal	18	48	15
Cognitive delay	+	-	+	-	+	-
Walking ability	NE	NE	NE	NE	NE	NE
Abnormal behaviors						
Anxiety and depression, Aggression (self injurious), Obsessive-compulsive disorder (OCD), ADHD*	ADHD	-	ADHD	-	ADHD	-
Stereotypic Behavior	+	-	+	-	+	-
Birth History						
Birth length (cm)/weight (kg)	47,0/2.890	51,0/3.050	48,5/3.140	50,0/3.800	52,0/3.500	47,0/3.305
Frontal-occipital circumference (cm)	36,5	36,0	35,0	NA	34,0	NA
Dysmorphism, Macrocephaly, Microcephaly	NE	NE	NE	NE	NE	NE
Pregnancy History						
Mother Age (years)	36	30	36	36	32	28
Length/weight for gestational age	NE	NE	NE	NE	NE	NE
Maternal fever, Infection, medication	NE	NE	NE	NE	NE	NE
Family History						
Family member with neurologic diseases, Mental retardation, intellectual disability, behavior changes, Attention deficit hyperactivity disorder (ADHD)	Great uncle with intellectual disability (etiology unknown)	NE	Half brother with behavioral changes (etiology unknown)	NE	NE	NE
Additional Diagnosis						
Primary seizure disorder/epilepsy	-	-	-	-	-	-
Identifiable syndromes (e.g. Fragile X)	-	-	-	-	-	-
Sleep disturbance	+	-	+	-	+	-
Cardiovascular abnormality	-	-	-	-	-	-
Motor coordination alterations	+	-	-	-	-	-
Medication prescribed	Melatonin	-	-	-	Melatonin, clonidine	-

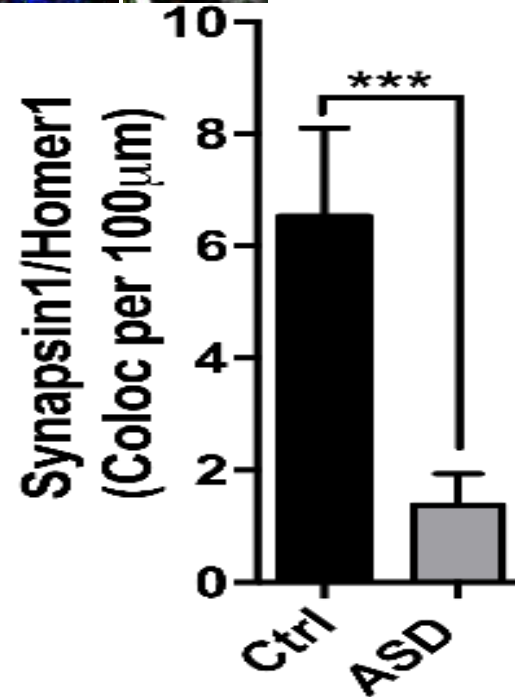
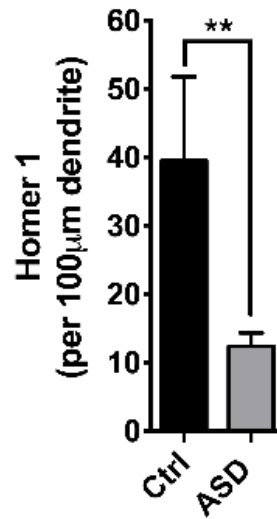
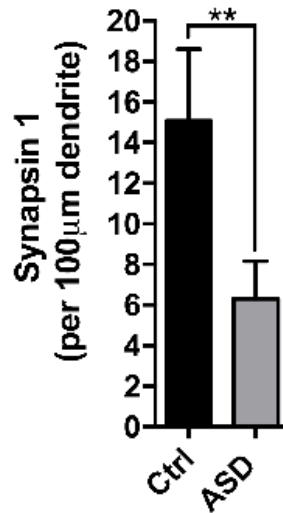
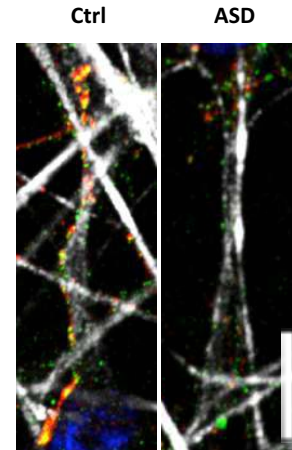
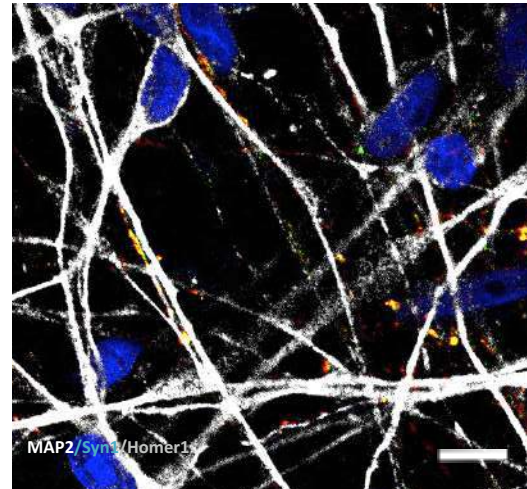
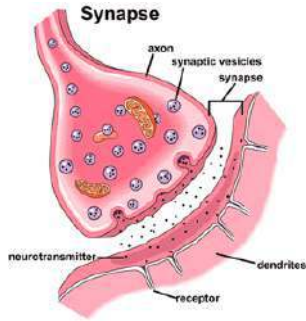
NE = Normal on examination

NA= N/A: Clinical data not available.

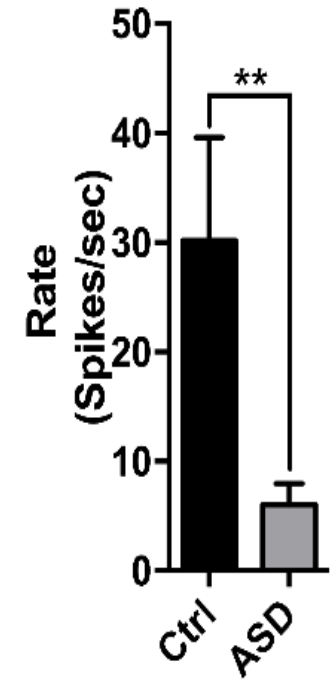
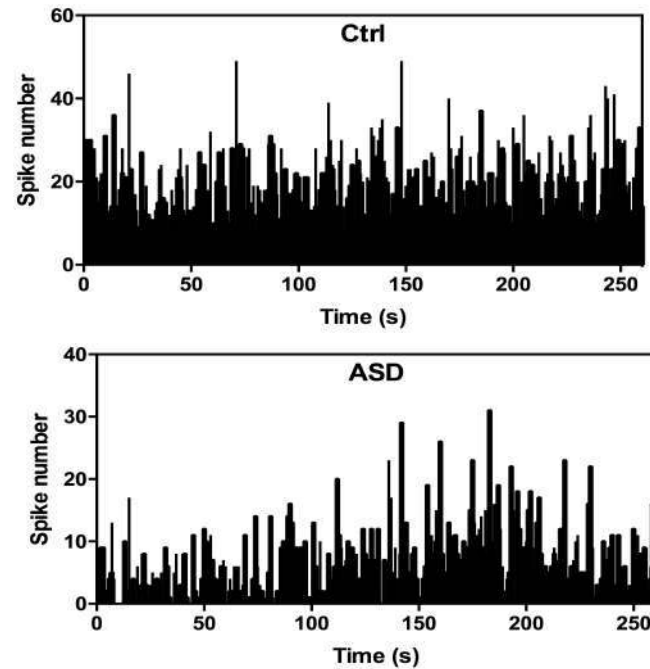
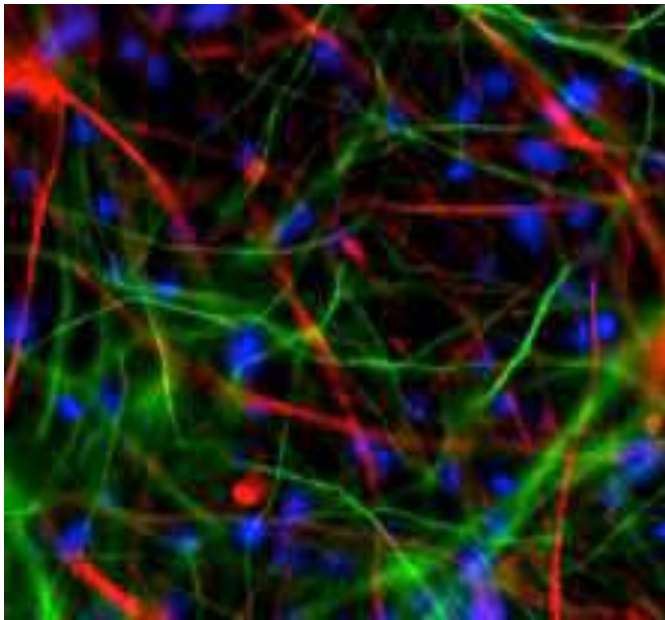
X= Not applicable

Russo and Freitas et al., submitted

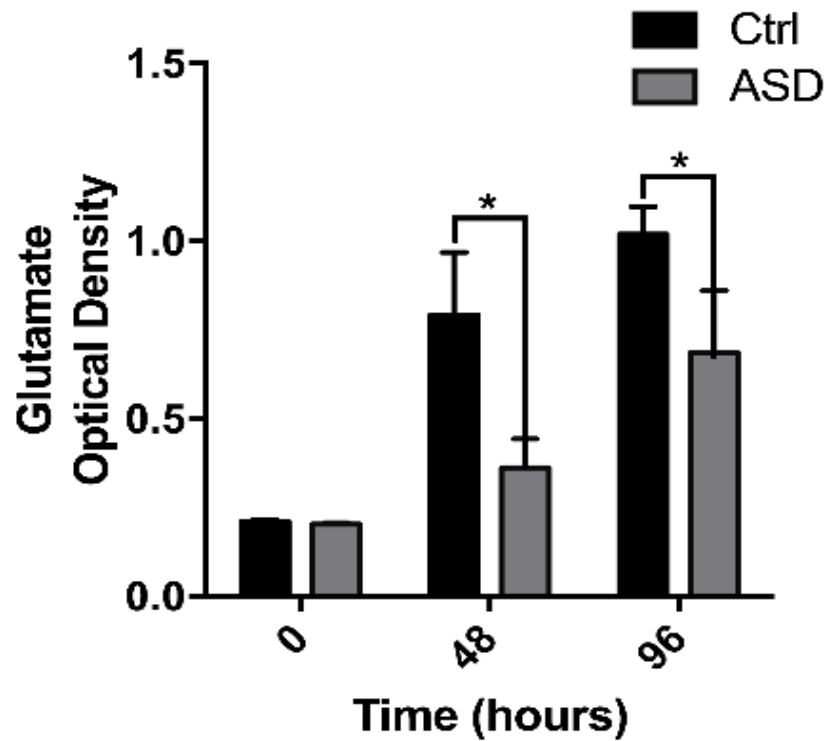
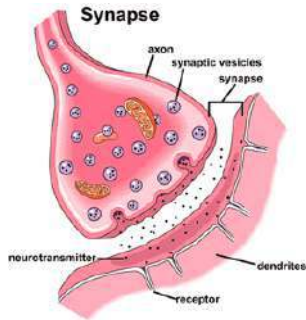
Neurons from ASD present less synapses



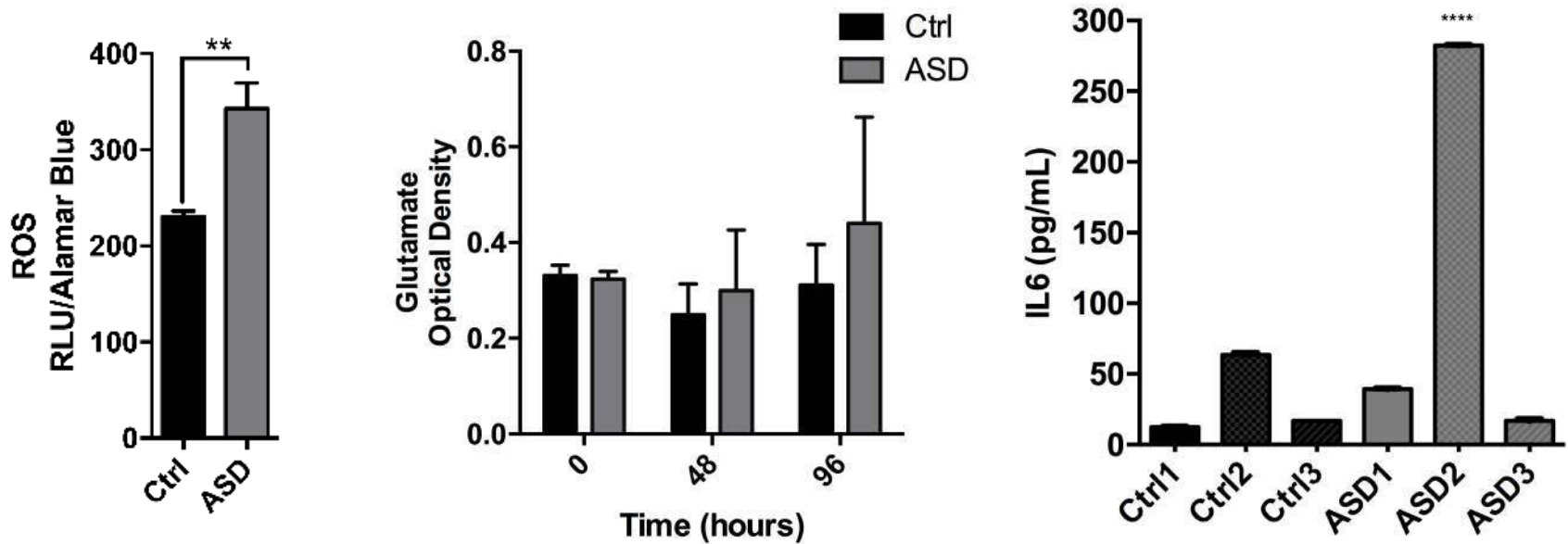
Neurons from ASD are less functional



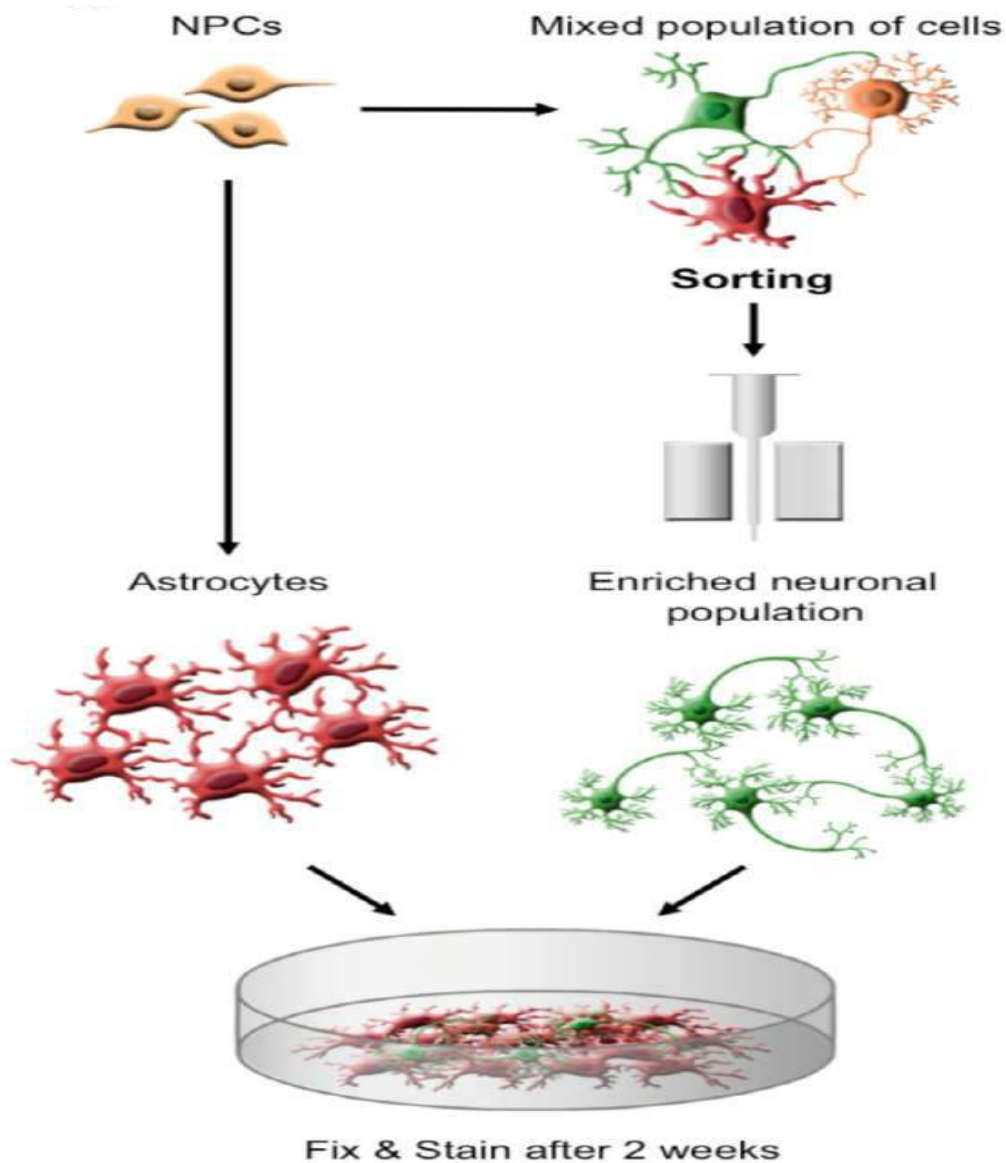
Neurons from ASD produces less Glutamate



Astrocytes from ASD produces more ROS, Glutamate and IL6



Coculture experiments

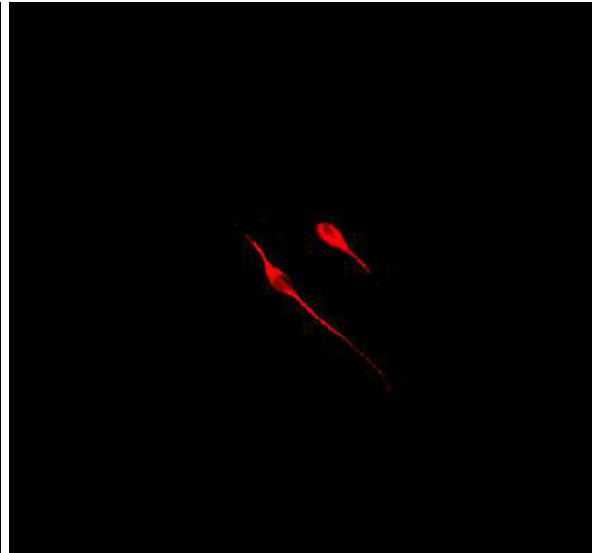
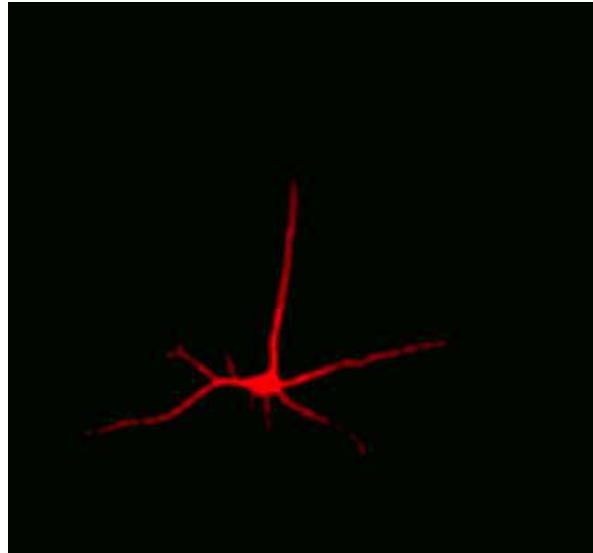


Control astrocytes recover ASD neurons

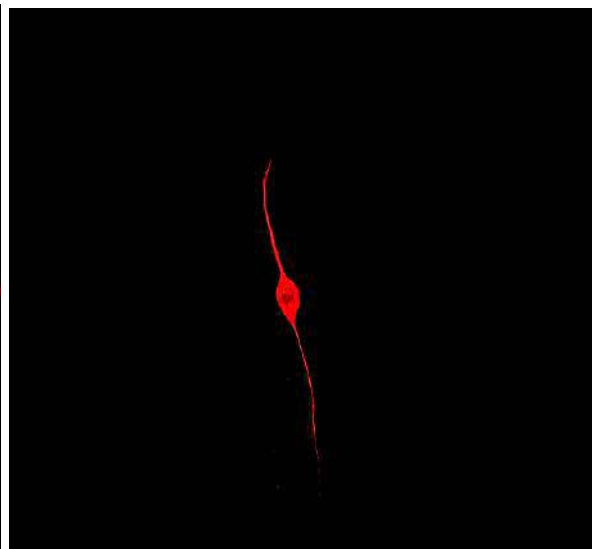
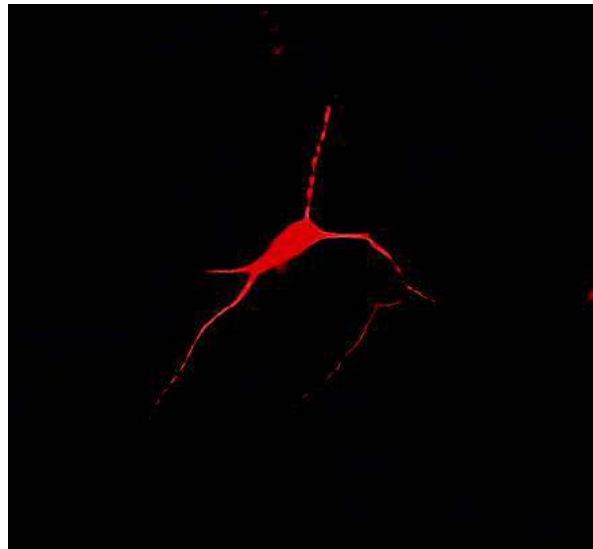
WT Astrocyte

ASD Astrocyte

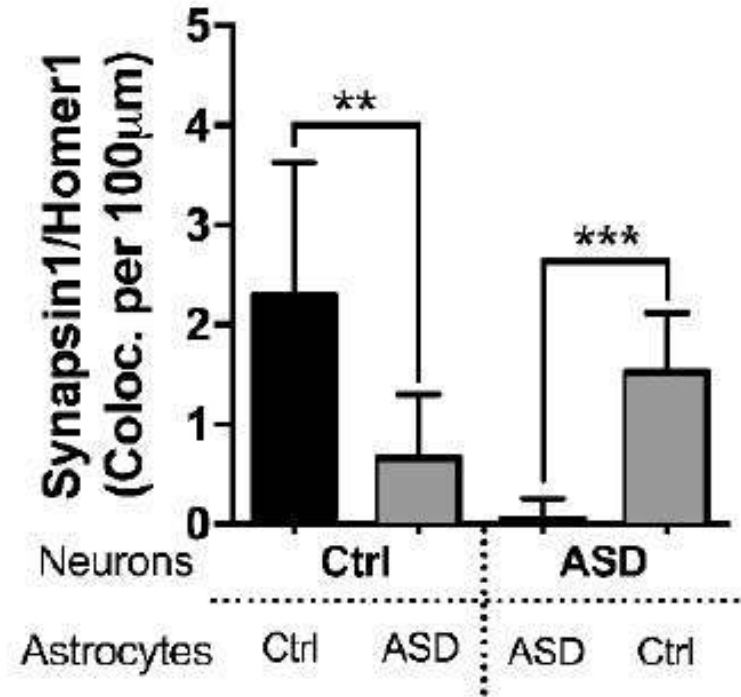
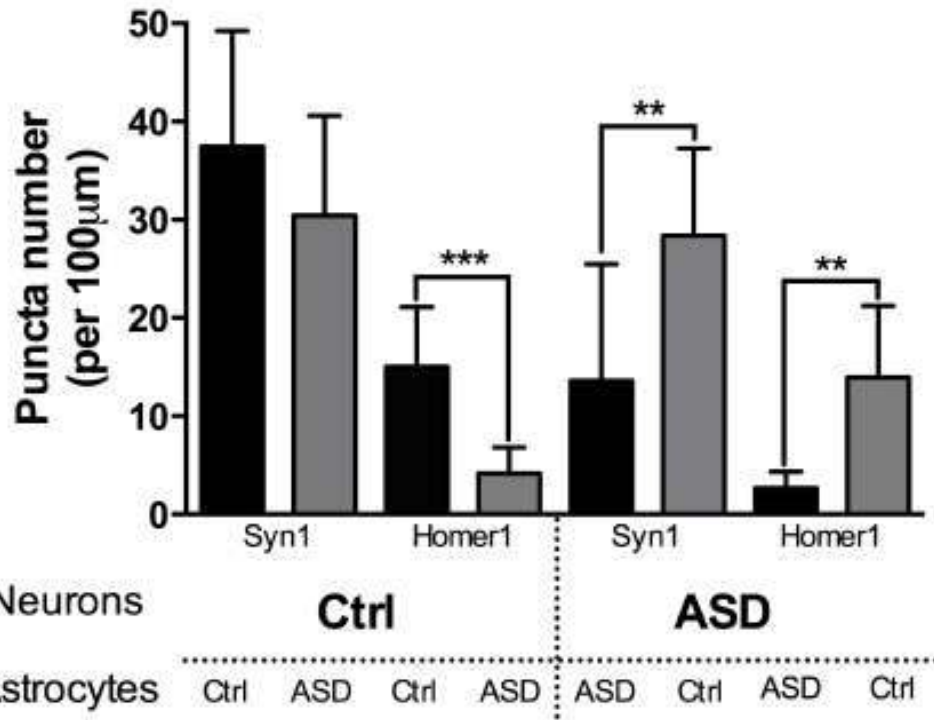
WT Neuron



ASD Neuron

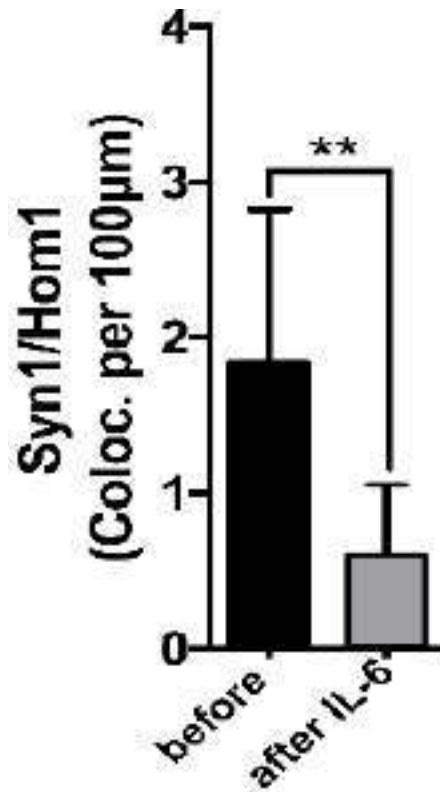


Control astrocytes recover ASD neurons

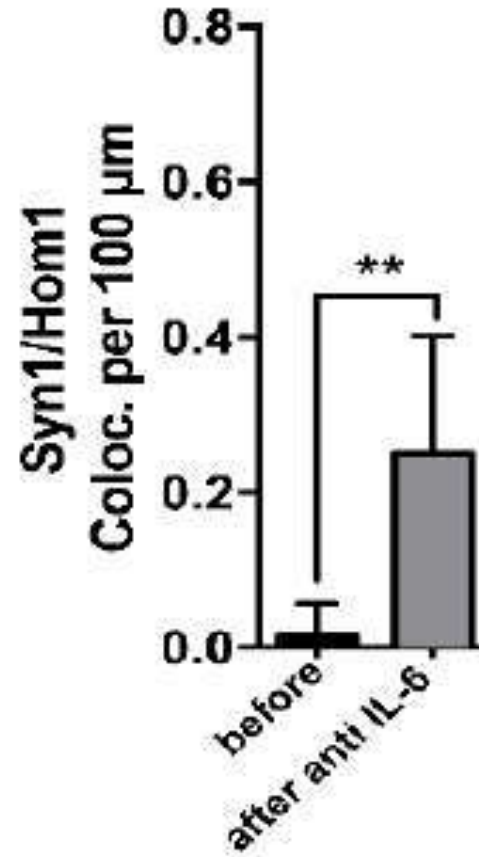


IL-6 impairs synaptogenesis in ASD neurons

Ctrl astrocytes / Ctrl neurons



ASD astrocytes / ASD neurons



TAKE HOME MESSAGE

- ASD neurons are less functional
- ASD neurons undergo less synaptogenic process
- Healthy astrocytes can recover neuronal functionality
- IL6 blocking could rescue ASD neurons

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. Freitas², João L. M. Dias¹, Katia P. Guimarães¹, Cecília Benazzato¹, Nathalia Almeida¹, Graciela C. Pignatari^{1,3}, Sarah Romero², Carolina M. Polonio⁴, Isabela Cunha⁴, Carla L. Freitas⁴, Wesley N. Brandão⁴, Cristiano Rossato⁴, David G. Andrade⁴, Daniele de P. Faria⁵, Alexandre T. Garcez⁵, Carlos A. Buchpiguel⁵, Carla T. Braconi⁶, Erica Mendes⁶, Amadou A. Sall⁷, Paolo M. de A. Zanotto⁶, Jean Pierre S. Peron⁴, Alysson R. Muotri² & Patricia C. B. Beltrão-Braga^{1,8}



*



*



*

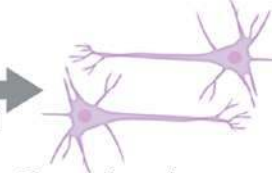


hiPSC/hESC



NPCs

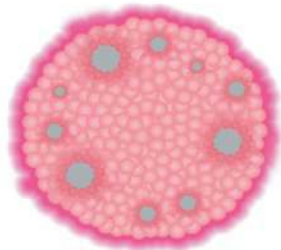
Neuronal
induction



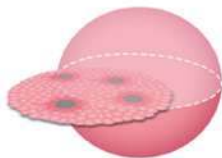
Cortical neuron



NPCs



Organoid



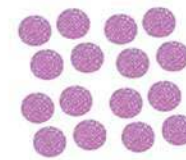
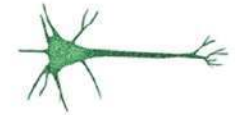
Sliced
organoid
(for analyses)



ZIKV

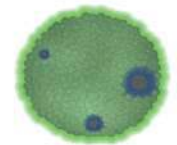
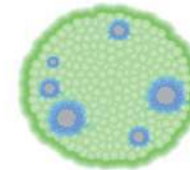
24 hours p.i.

96 hours p.i.

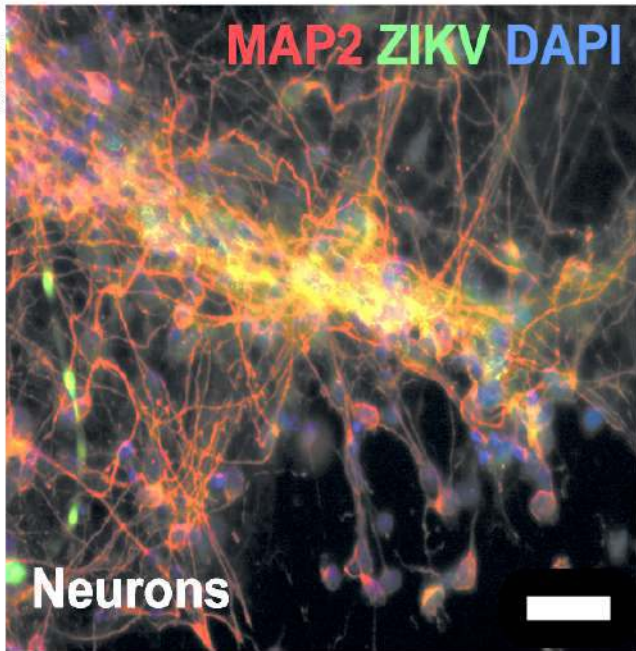
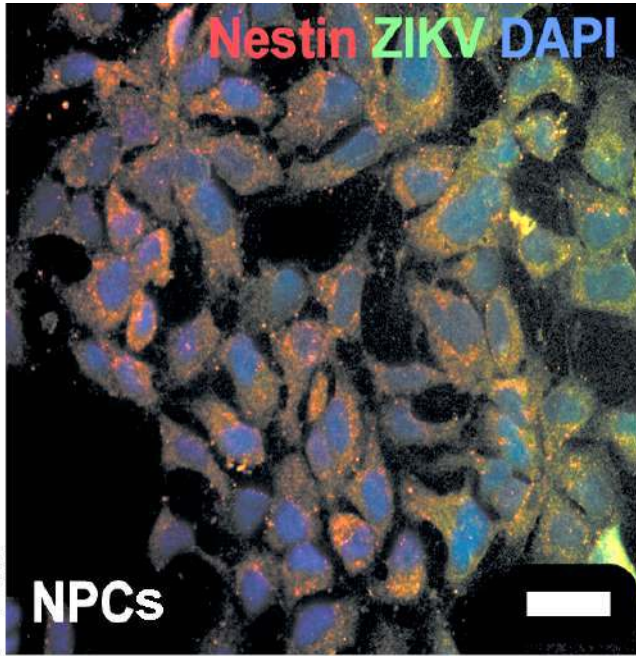


Neurospheres

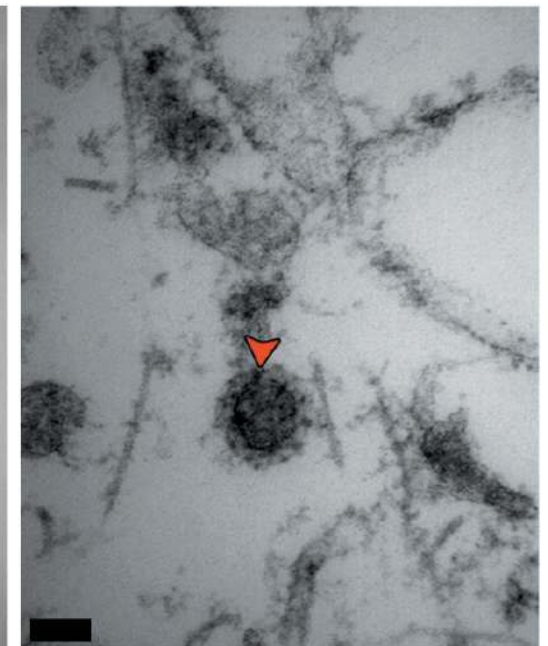
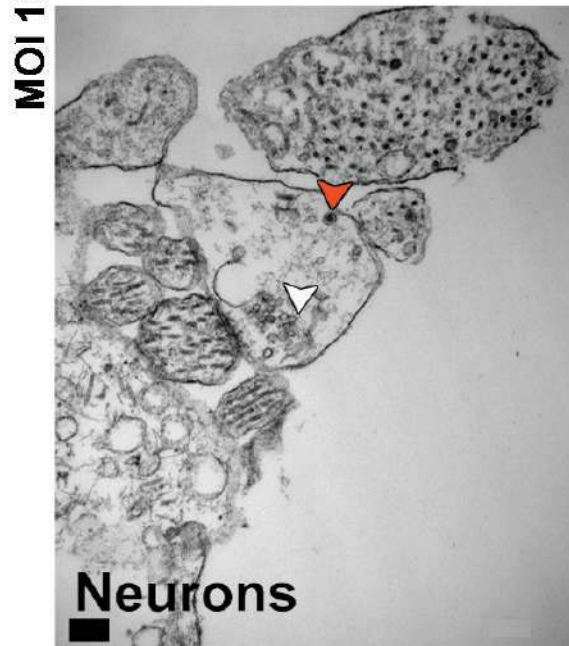
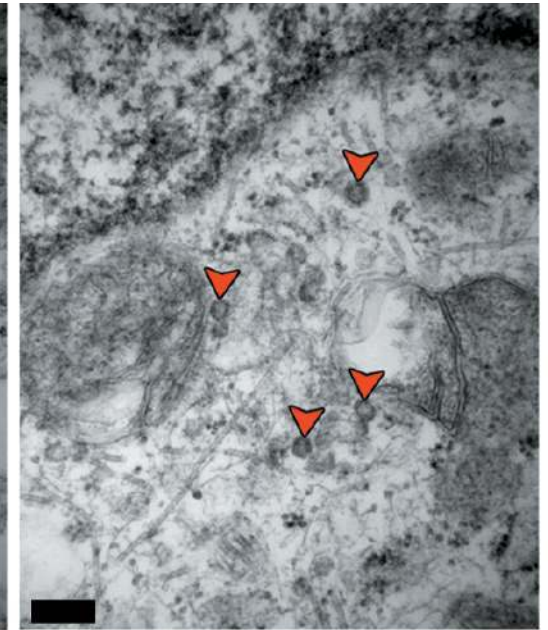
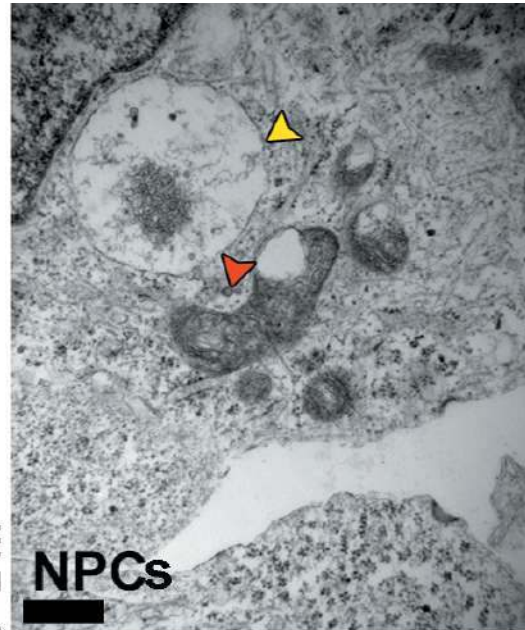
Neurospheres



MOI 10 24h

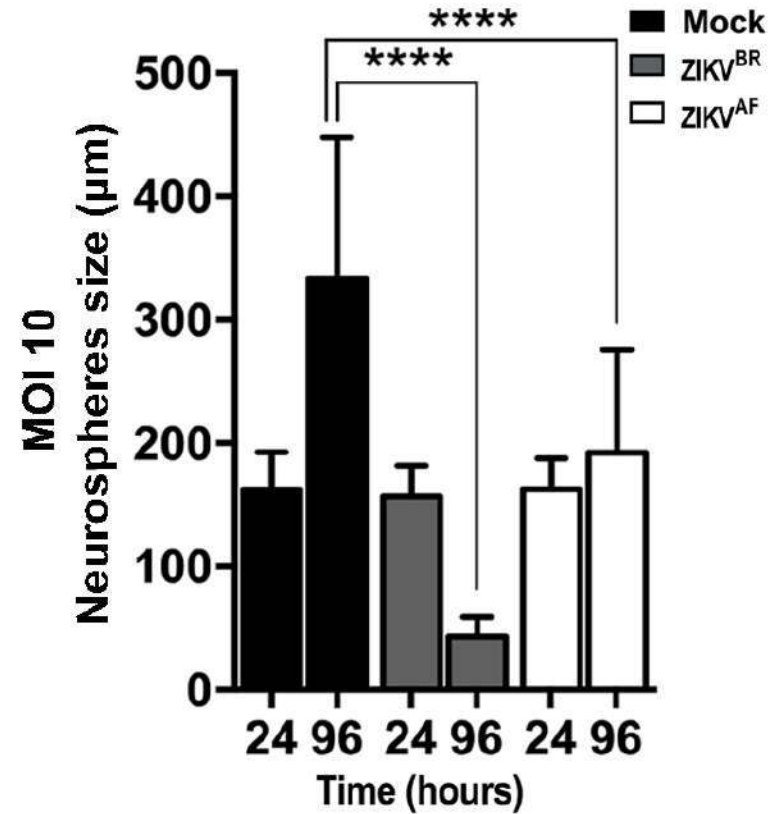
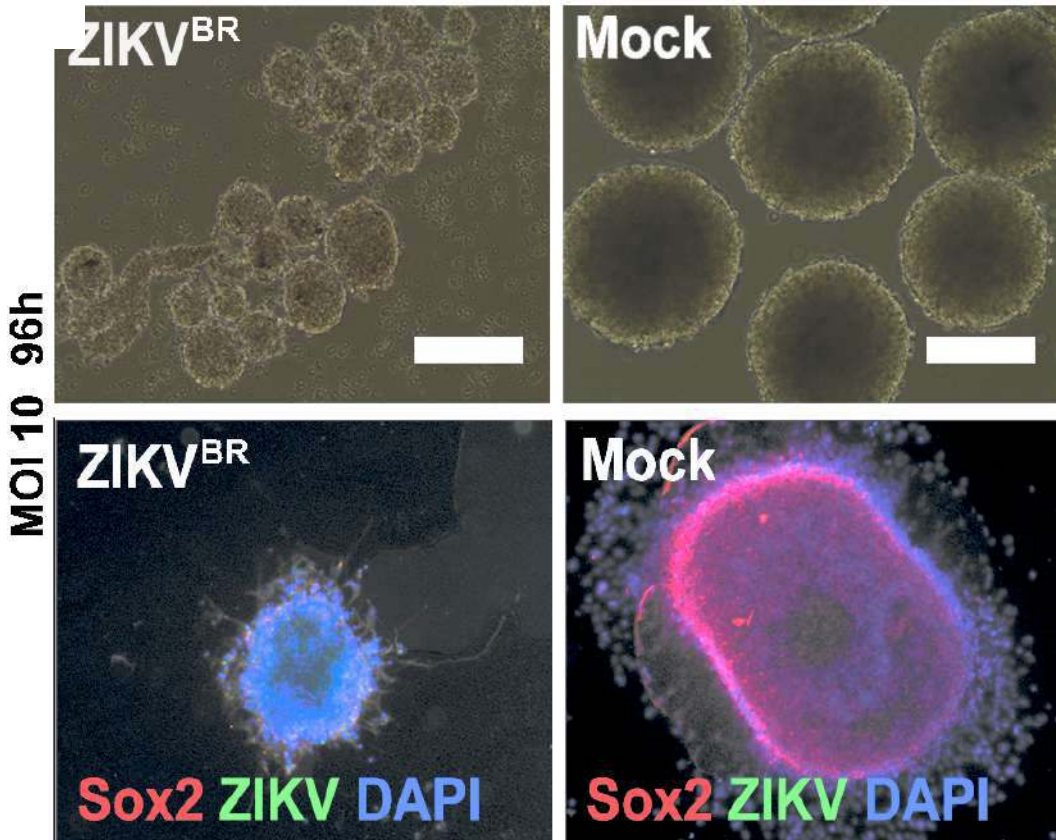


MOI 10 24h

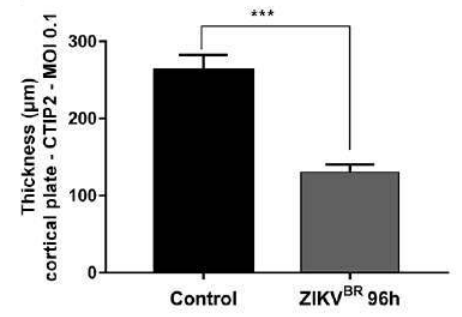
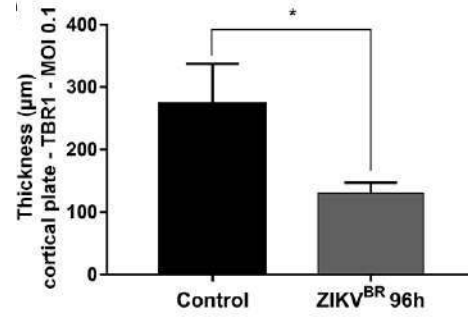
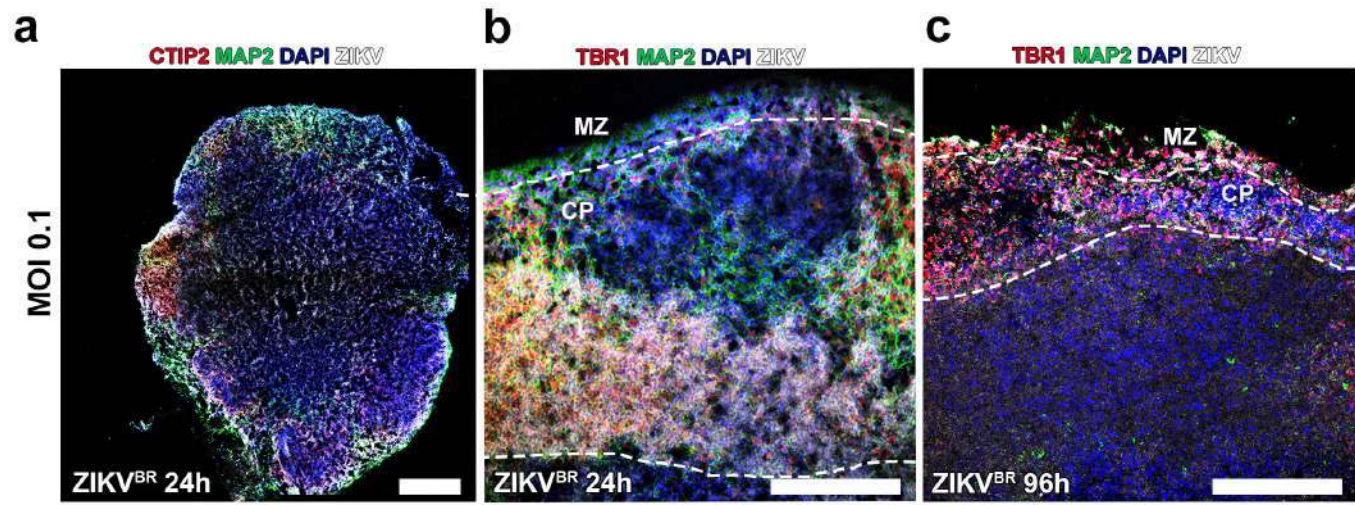
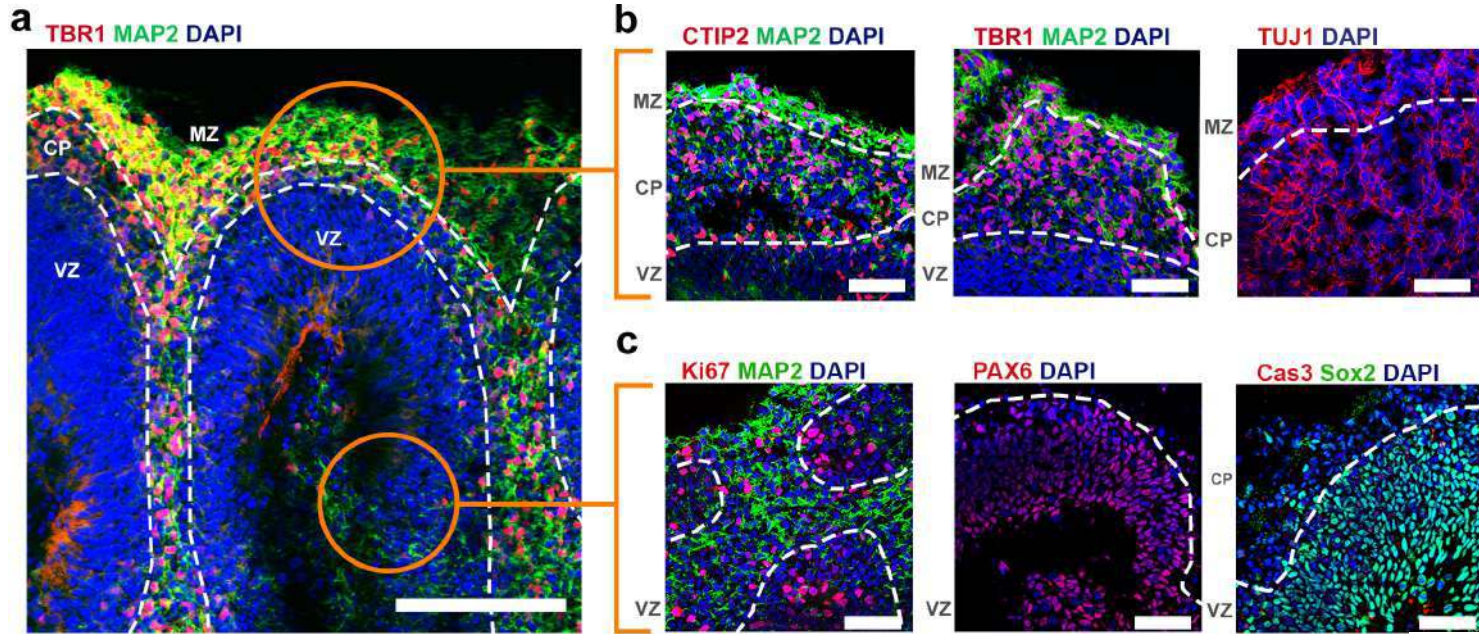


Neurospheres diminishes their size after 4 days and cells did not migrate

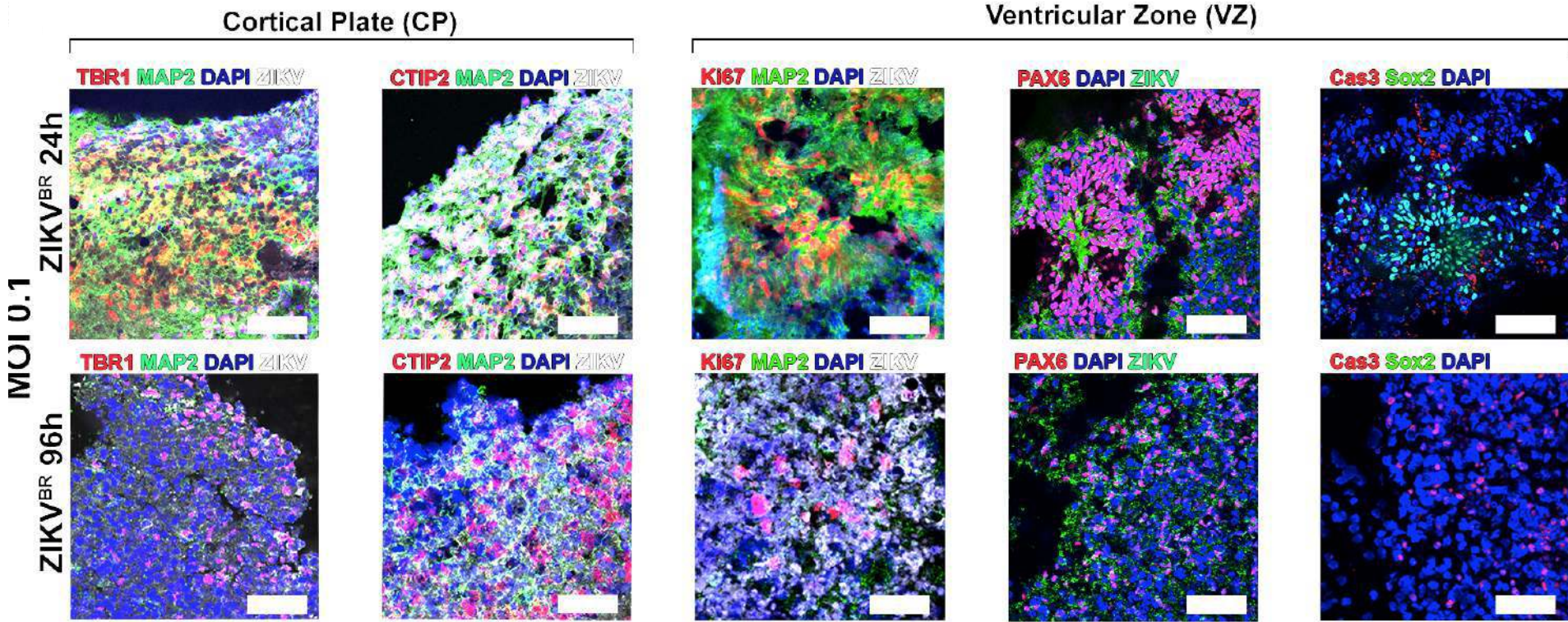
Neurospheres



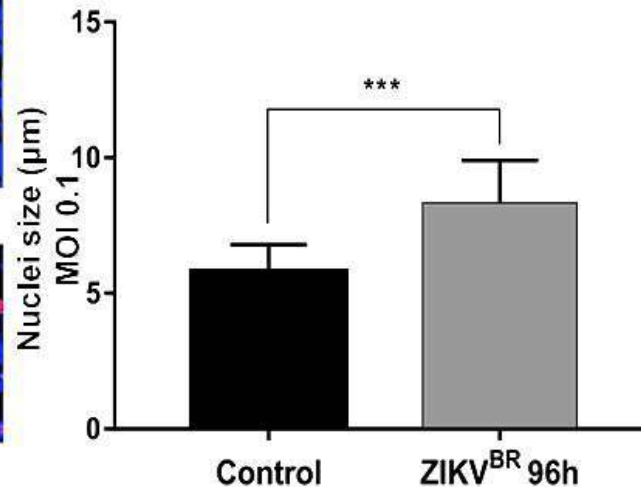
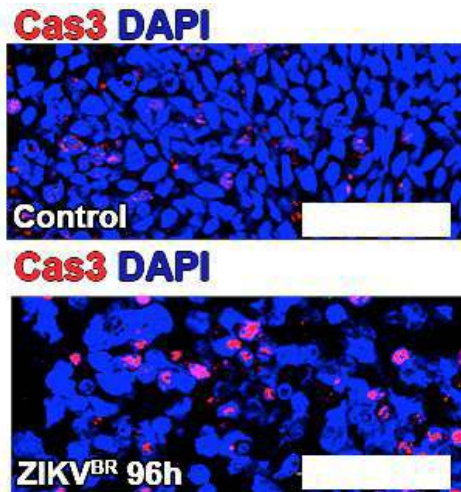
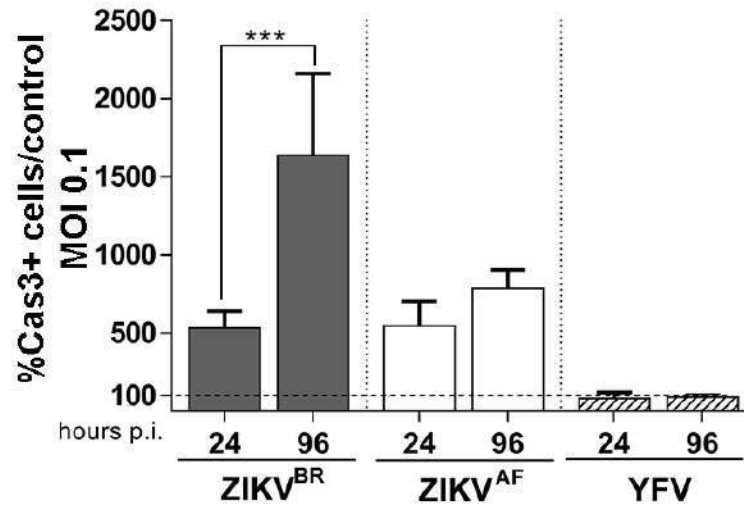
Cortical layer diminished after ZIKV infection



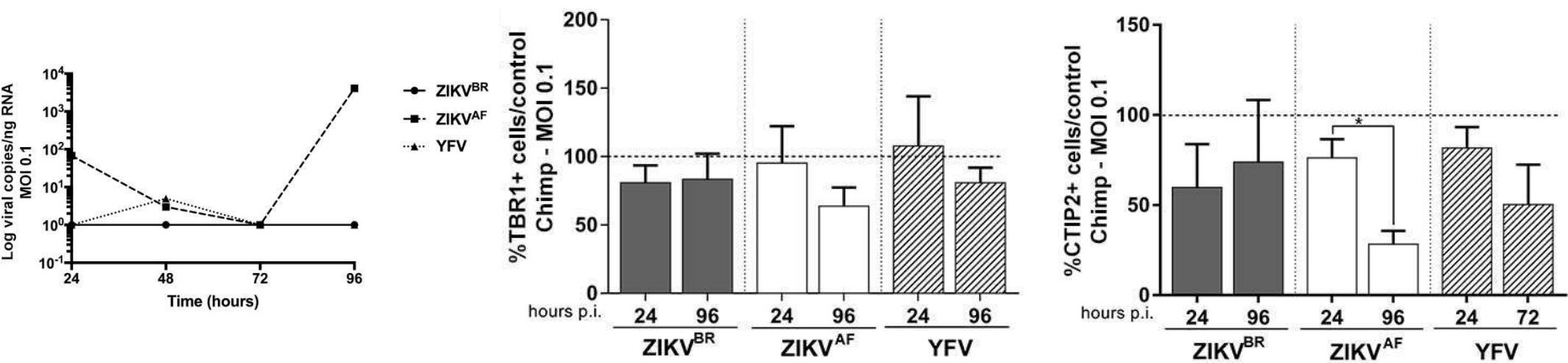
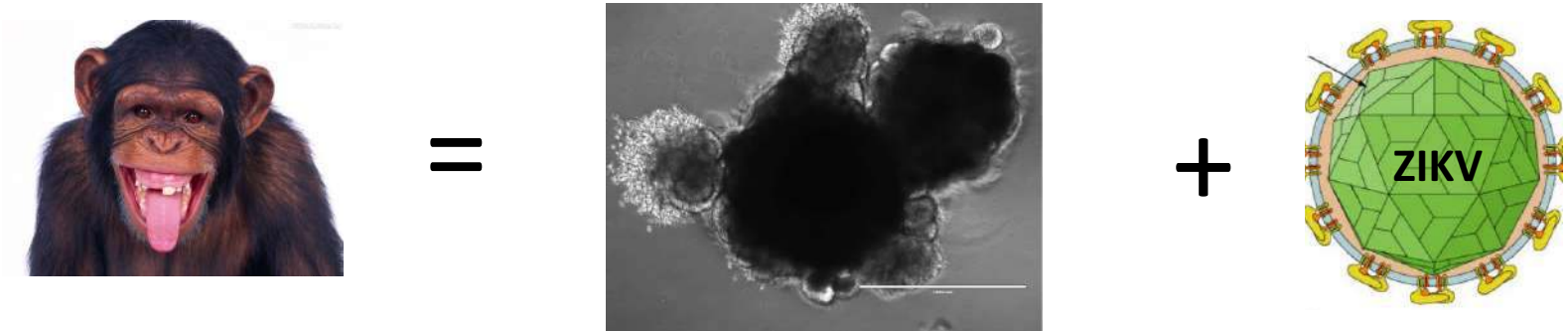
Not only Cortical plate, but ventricular zone was affected by ZIKV infection

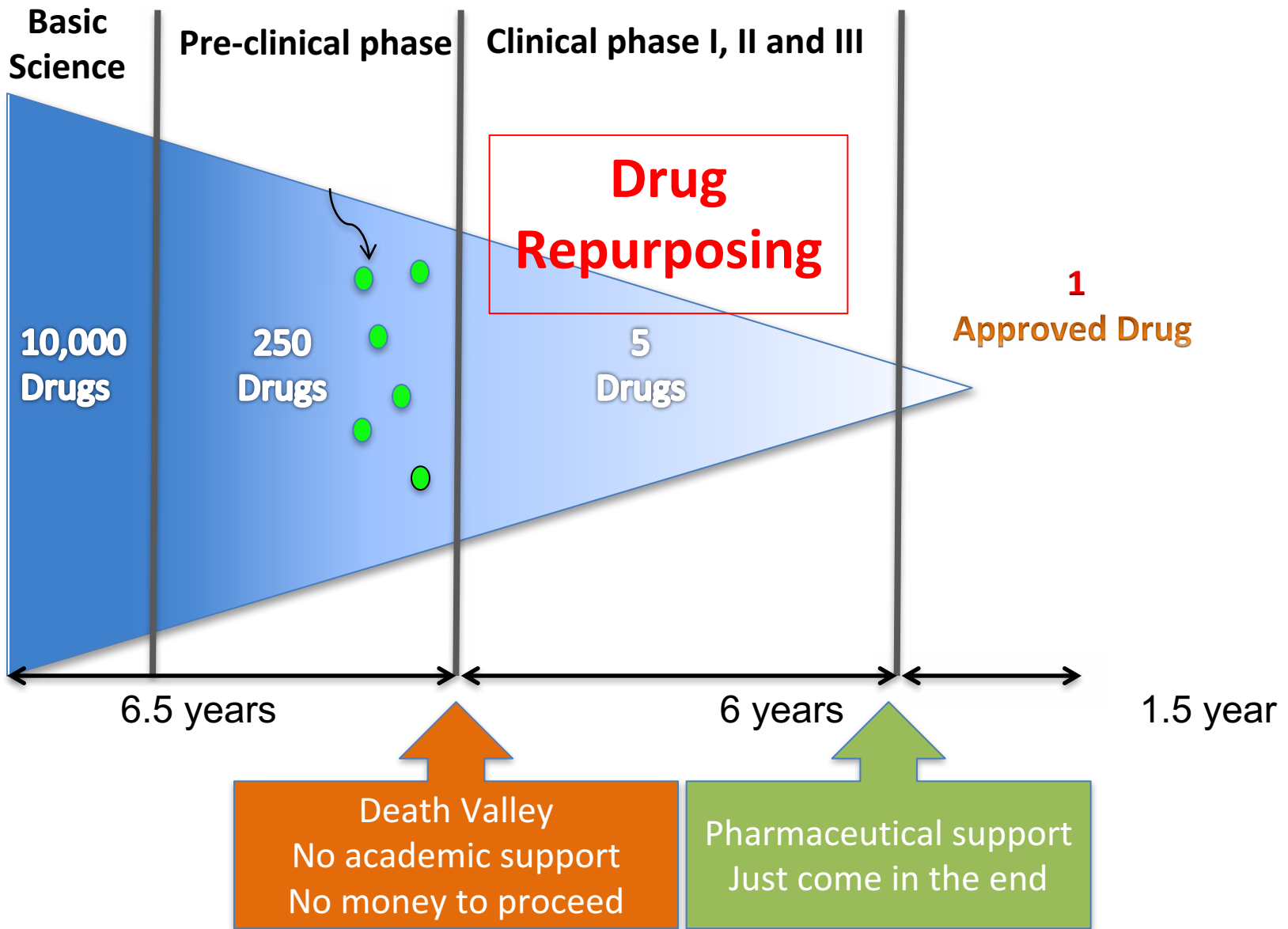


Number of apoptotic cells increased after 96h p.i. and the nuclei of cells get bigger and with an empty aspect



Brain organoids from chimps were more susceptible to African ZIKV strain than the Brazilian wild strain







Universidade de São Paulo



Lab of stem cells and disease modeling

Patricia Beltrão Braga

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Luiz Fernando Zerbini

