

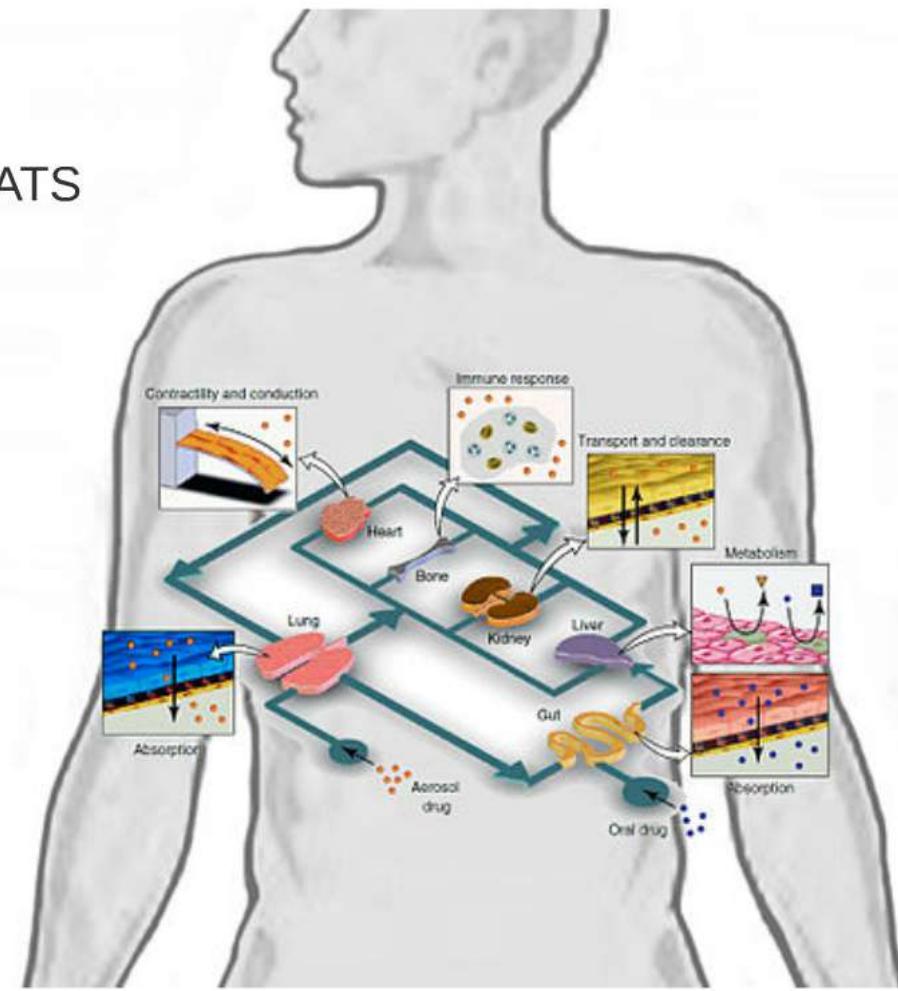
Updates in CAAT Brain Microphysiological System

David Pamies

HUMAN-ON-A-CHIP

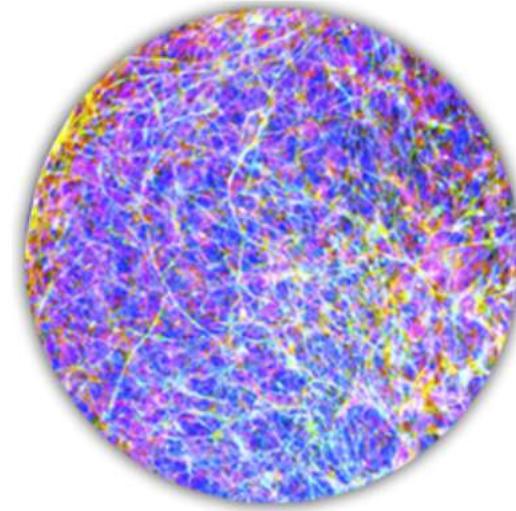


Funded by the NCATS

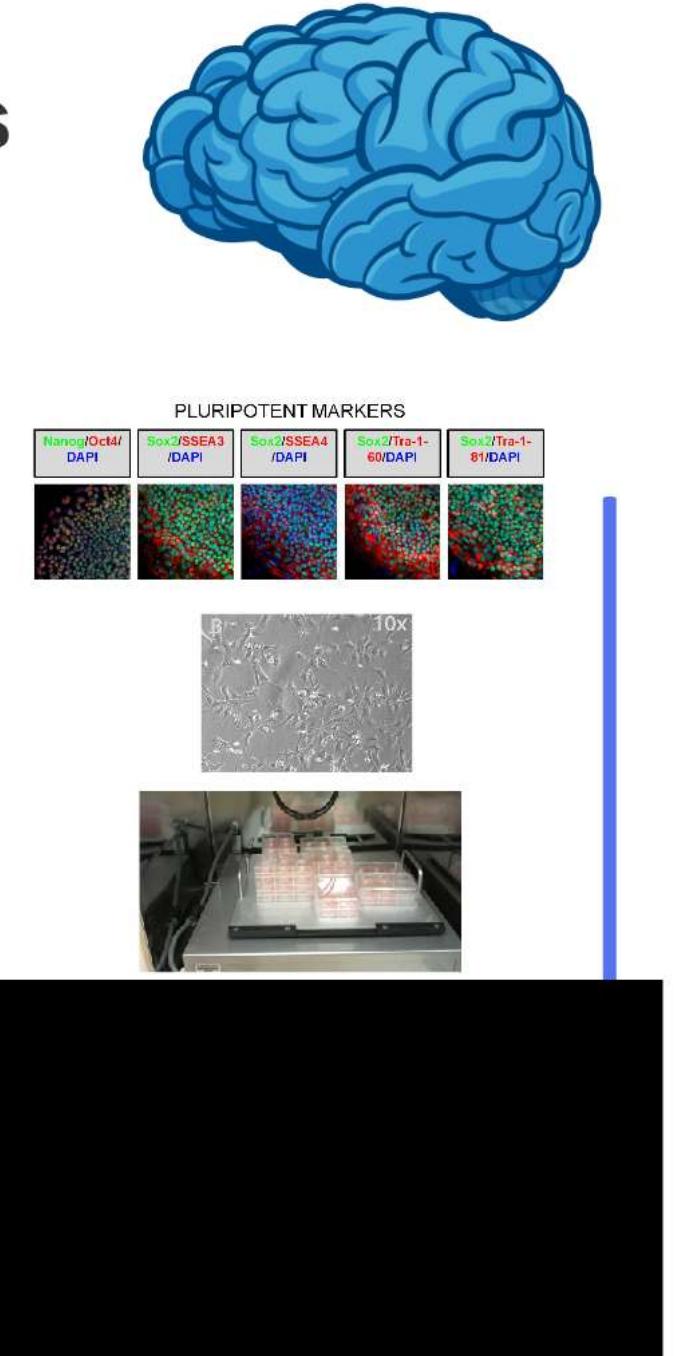
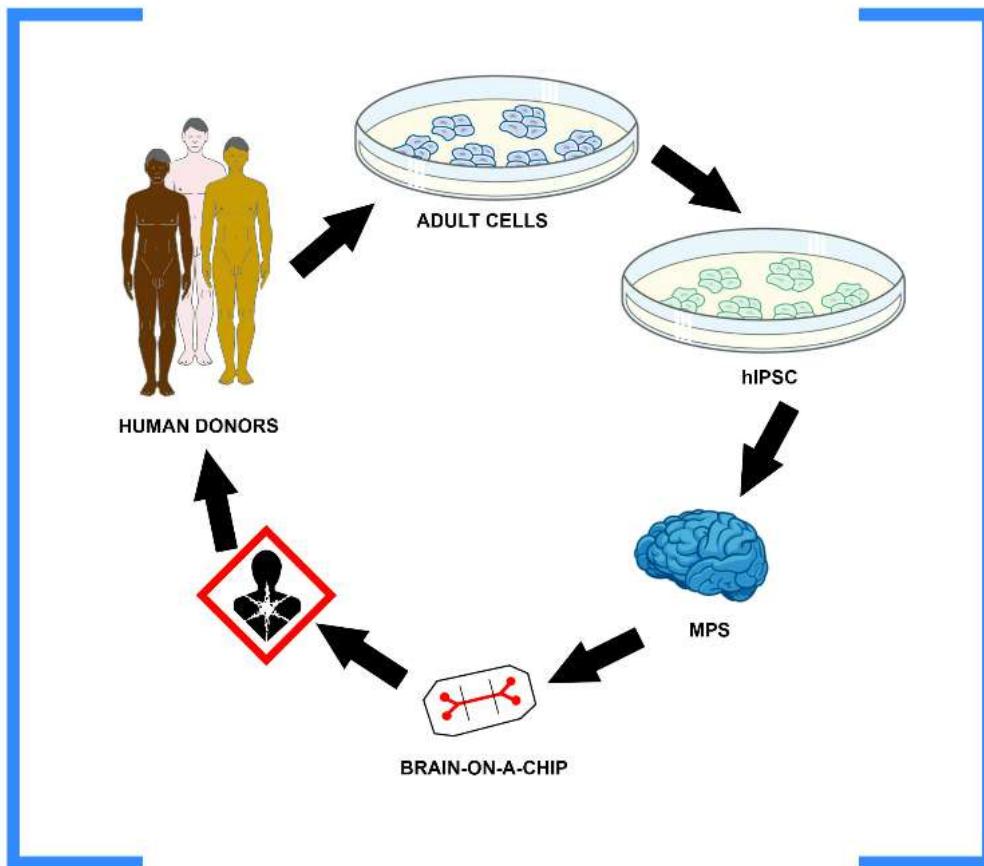


Human Brain Micropysiological System

- Multicellular
 - Cellular interaction
- 3D culture
 - Faster differentiation
 - Interactions
 - Survival
 -
- Represent a functional part of an organ.



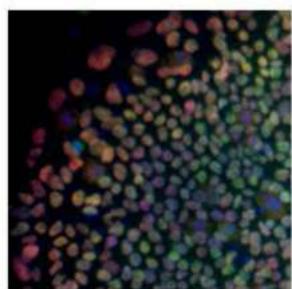
Materials and methods



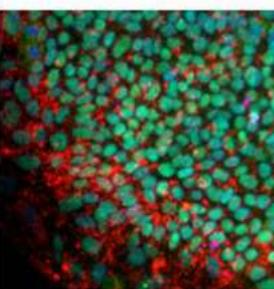


PLURIPOTENT MARKERS

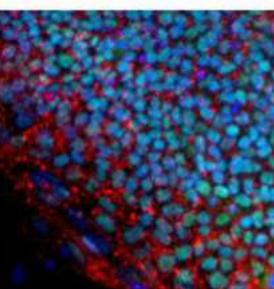
Nanog/Oct4/
DAPI



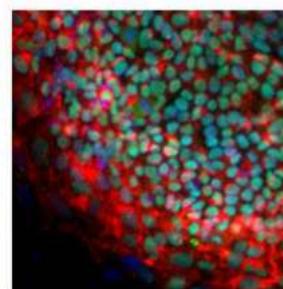
Sox2/SSEA3
/DAPI



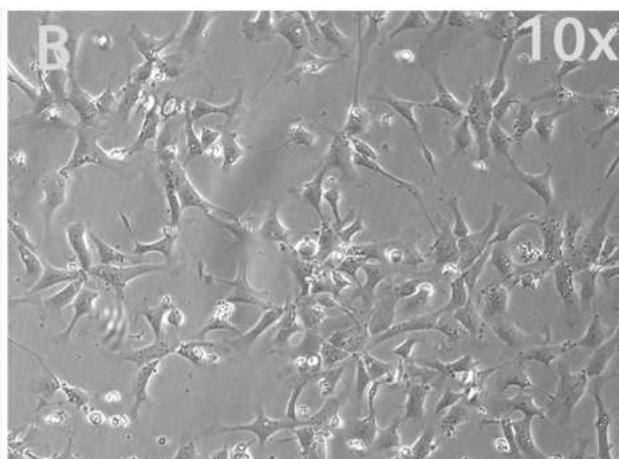
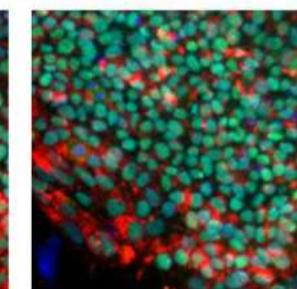
Sox2/SSEA4
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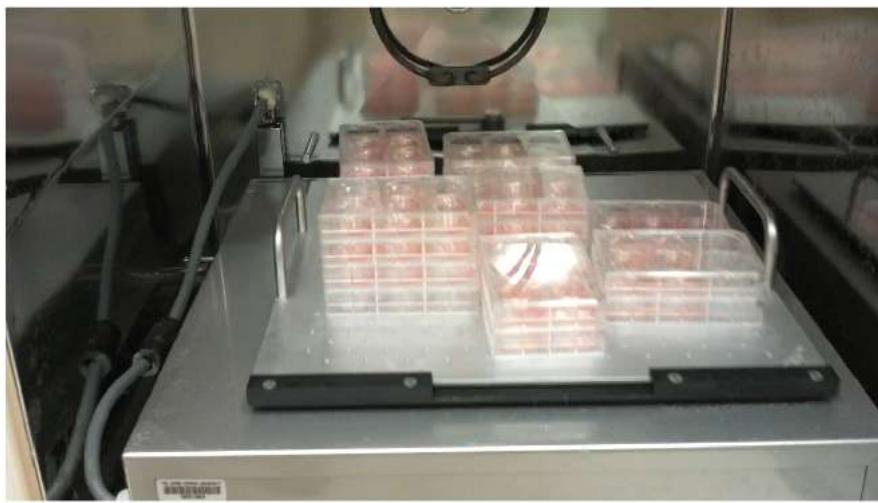
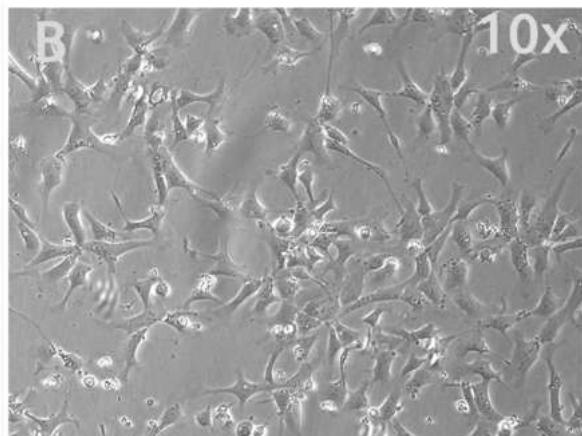
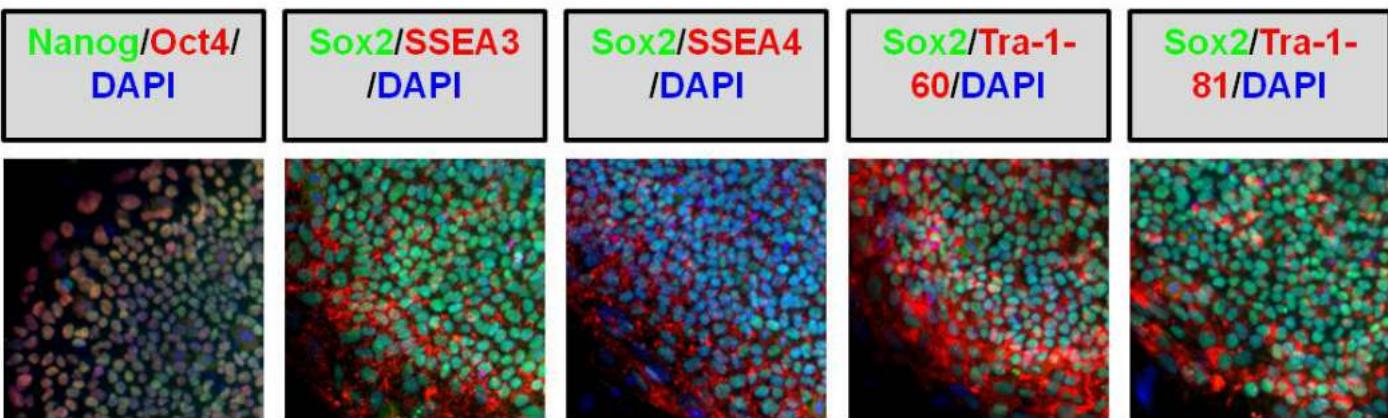
Sox2/Tra-1-
60/DAPI

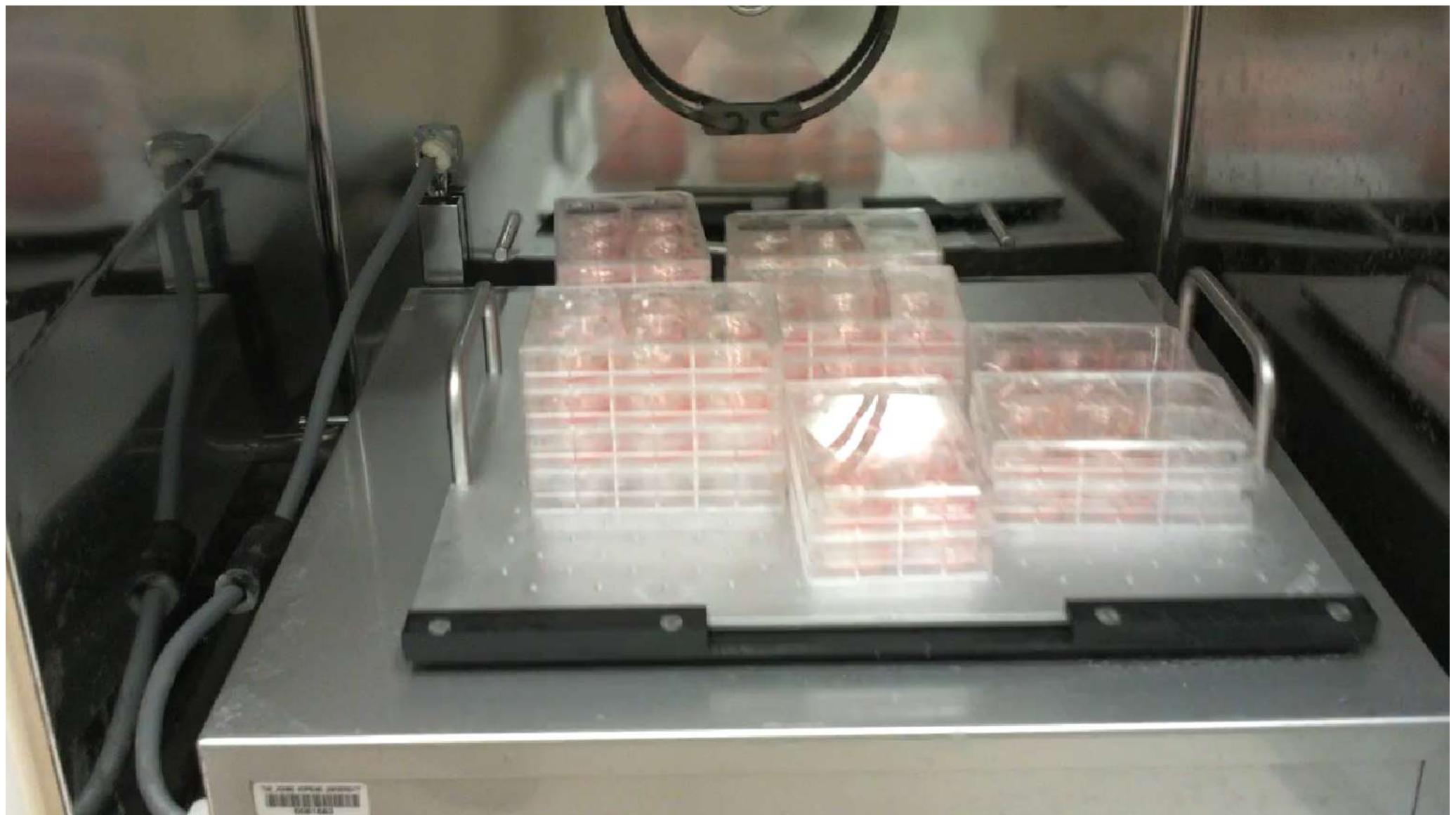


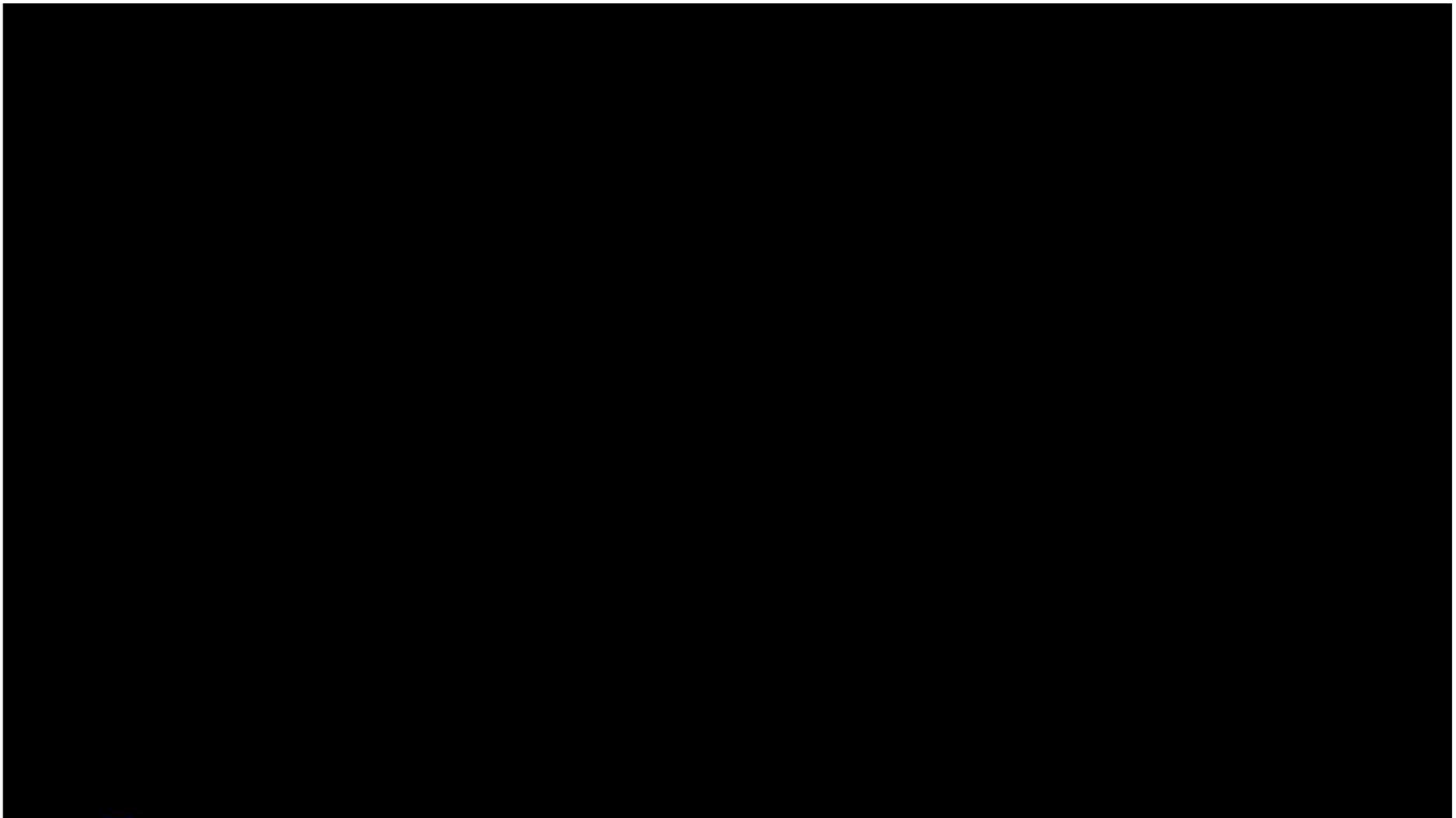
Sox2/Tra-1-
81/DAPI

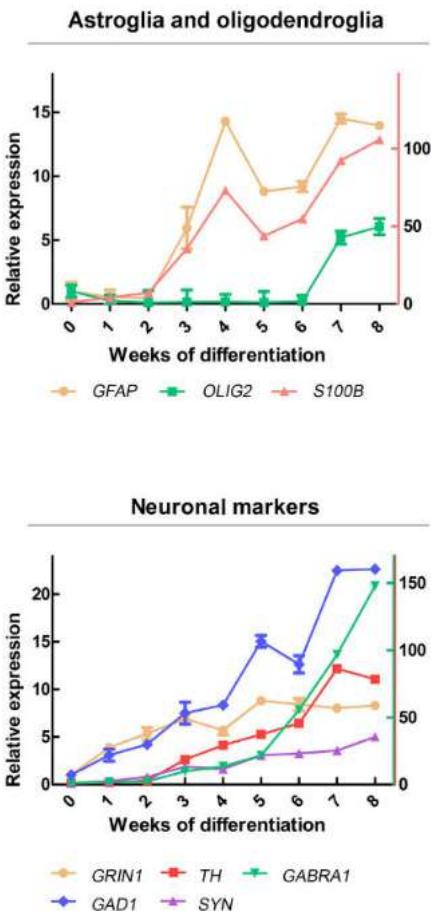
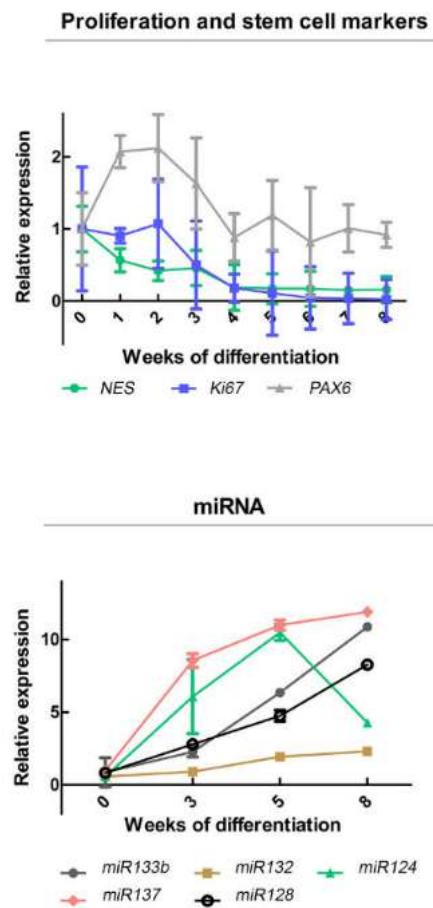
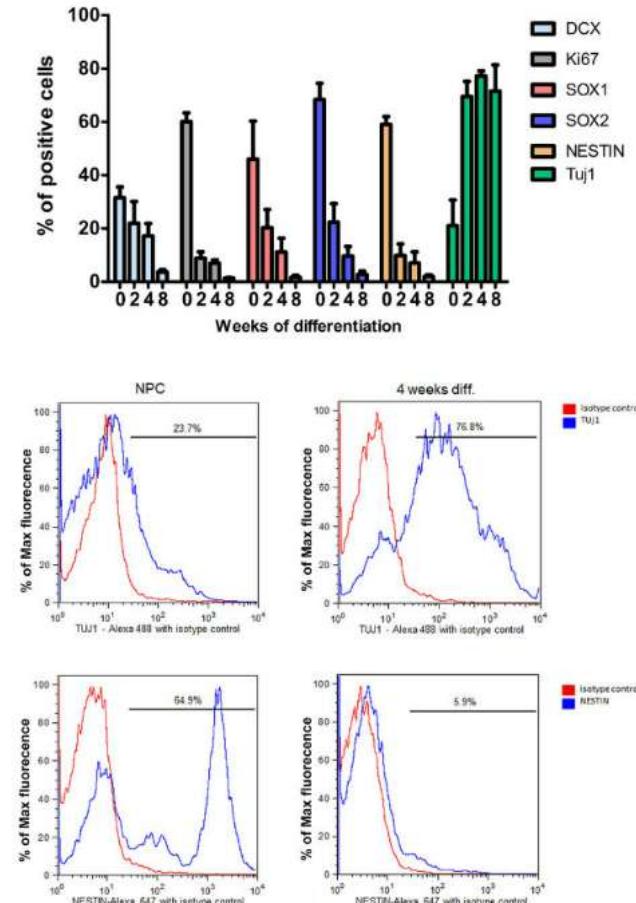


ESD-101 STEM MARKERS







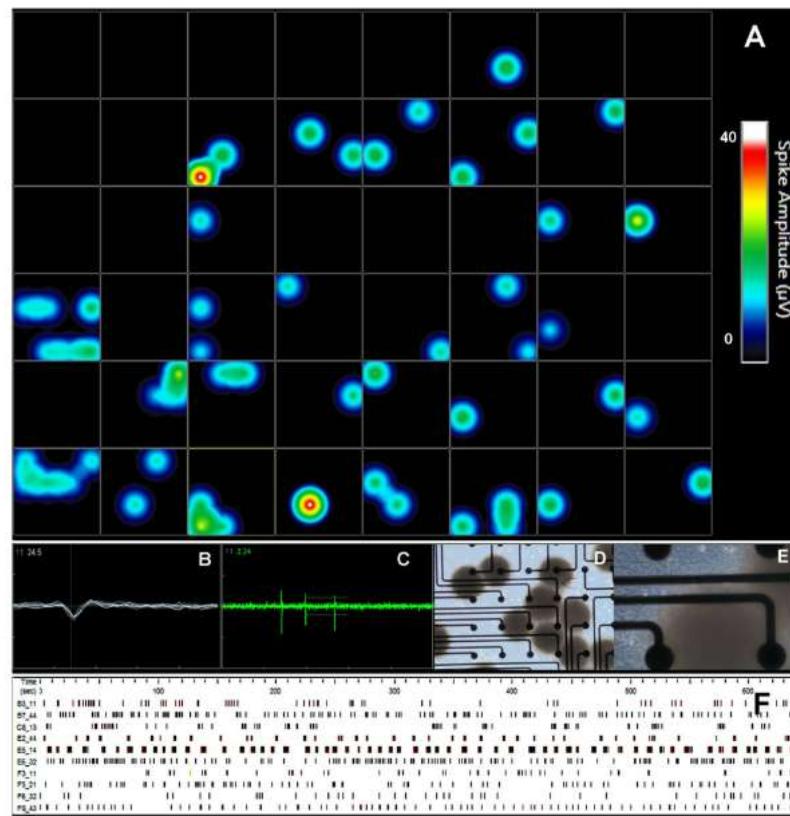
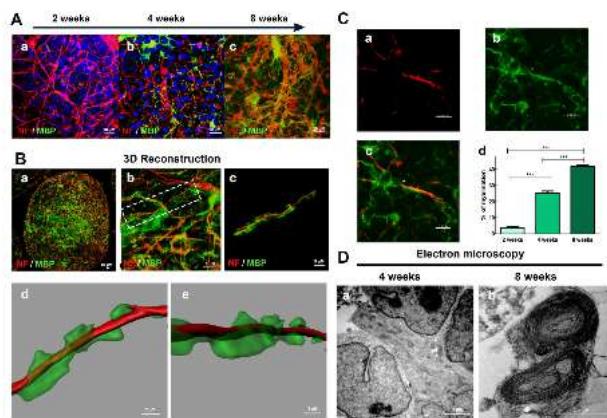
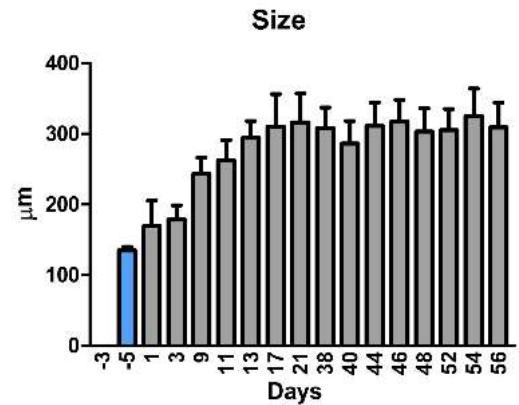
D**E****Flow cytometry**

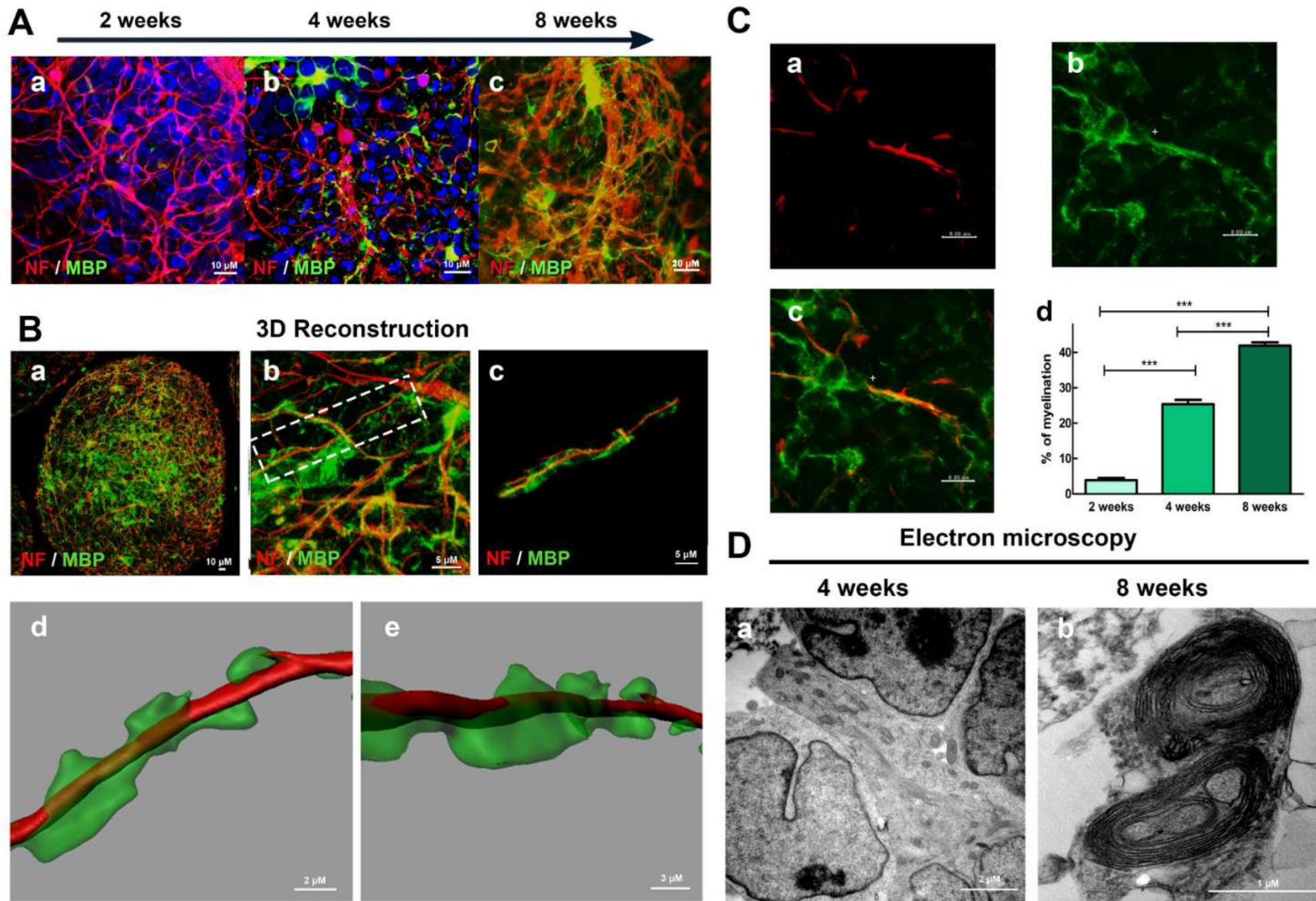
ALTEX. 2016 Nov 24. doi: 10.14573/altex.1609122. [Epub ahead of print]

A human brain microphysiological system derived from induced pluripotent stem cells to study neurological diseases and toxicity.

Pamies D¹, Barreras P^{2,3}, Block K¹, Makri G^{2,4}, Kumar A^{2,3}, Wiersma D¹, Smirnova L¹, Zhang C^{2,4}, Bressler J⁵, Christian KM^{2,4}, Harris G¹, Ming GL^{2,4,6}, Berlinicke C⁷, Kyro K⁸, Song H^{2,4,6}, Pardo CA², Hartung T^{1,9}, Hogberg HT¹.

Characterization

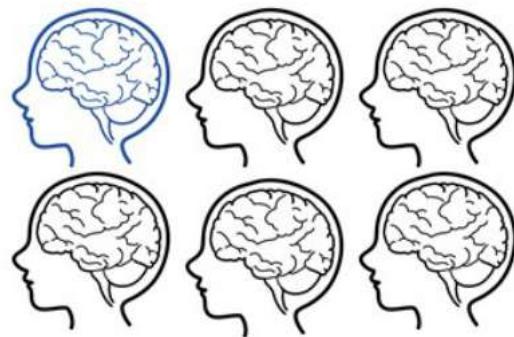




Applications



- Developmental neurotoxicity
- Parkinson model
- Virus infection
- Cancer Research
- Nanoparticles
- Multiple sclerosis
- Malaria
- Dysmyelination and demyelination
- **Autism**



1 in 6
children
was diagnosed
with a
developmental
disability from
2006 to 2008



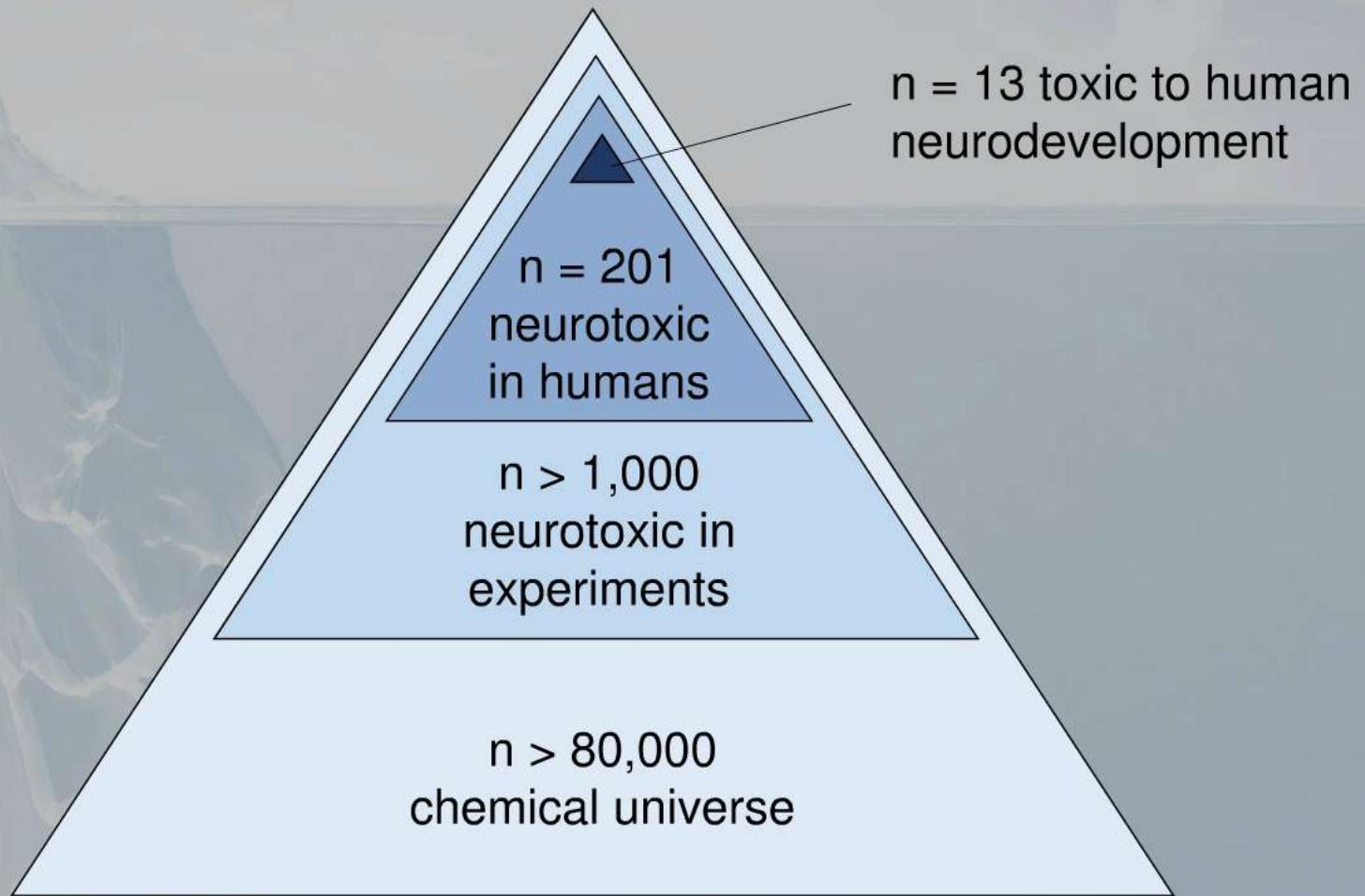
**1 in 68 children was diagnosed with
autism spectrum disorder (ASD) in
2012**



**1 in 10 children was diagnosed with
attention deficit / hyperactivity
disorder (ADHD) in 2011**

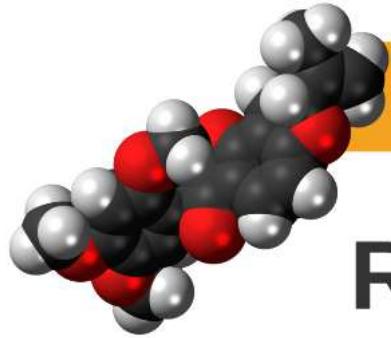


The chemical iceberg



Grandjean and Landigan 2006, 2014; Aschner et al. 2017

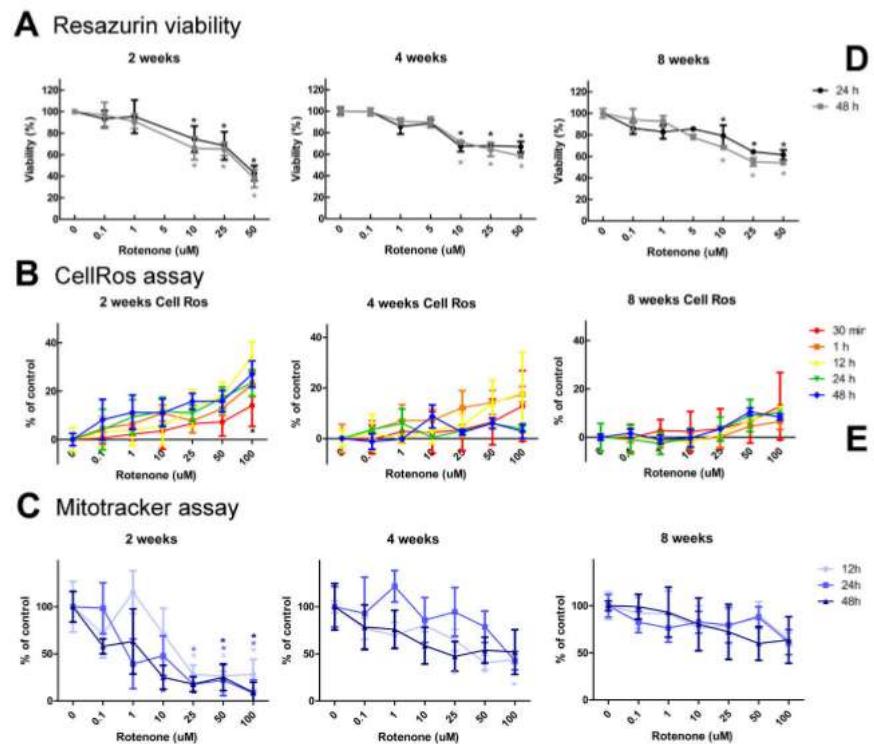




Rotenone

it was used as house hold insecticide

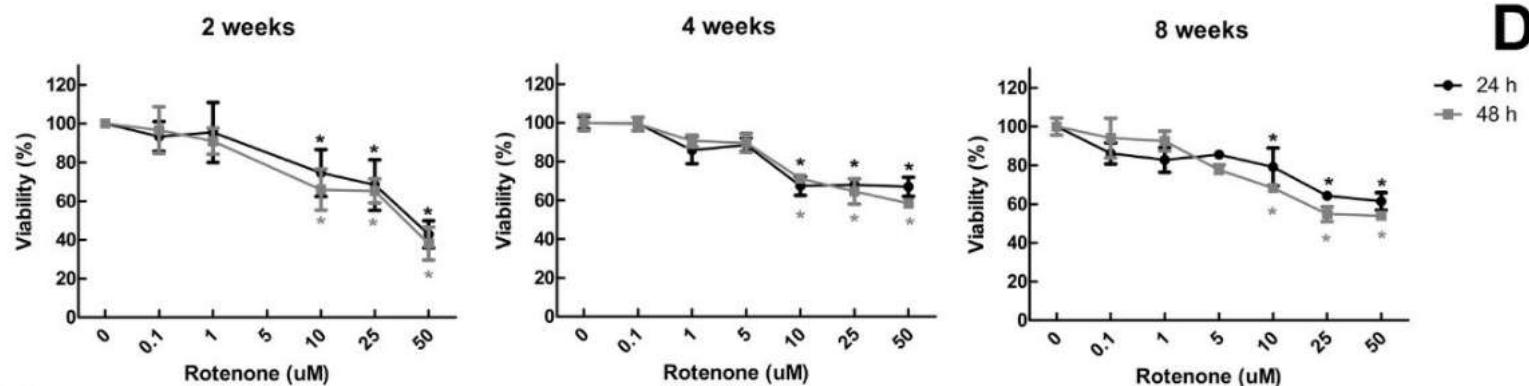
Progressive degeneration of dopaminergic neurons.



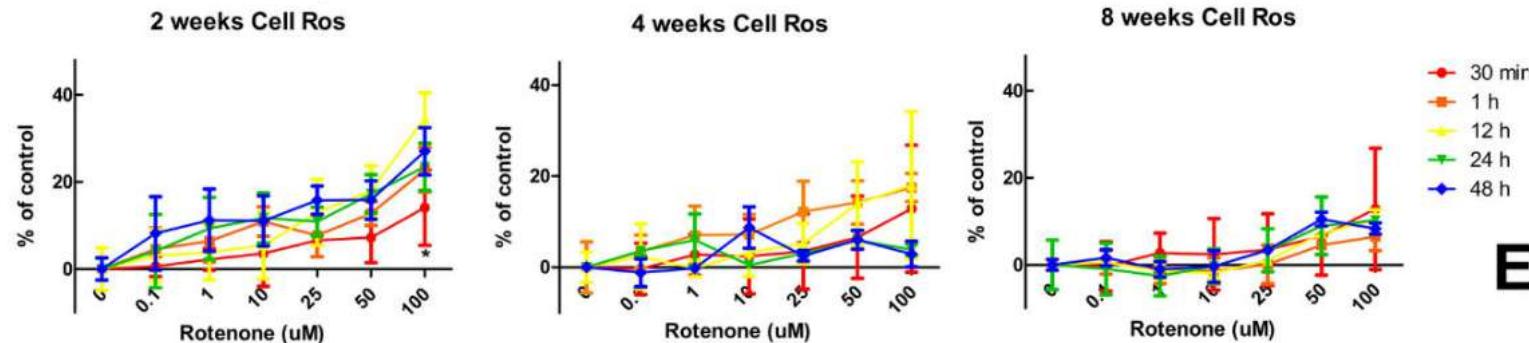
1

e

A Resazurin viability



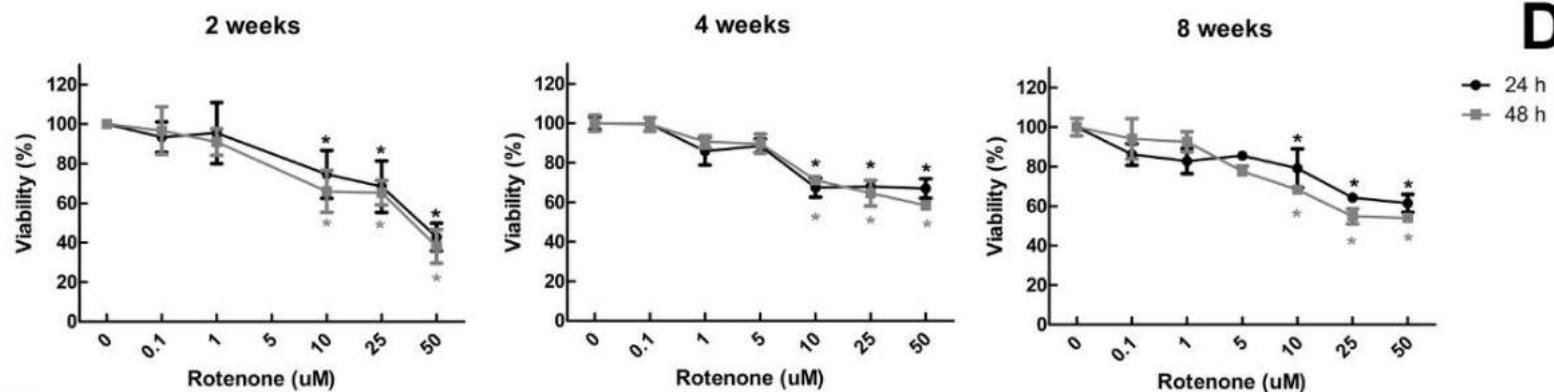
B CellRos assay



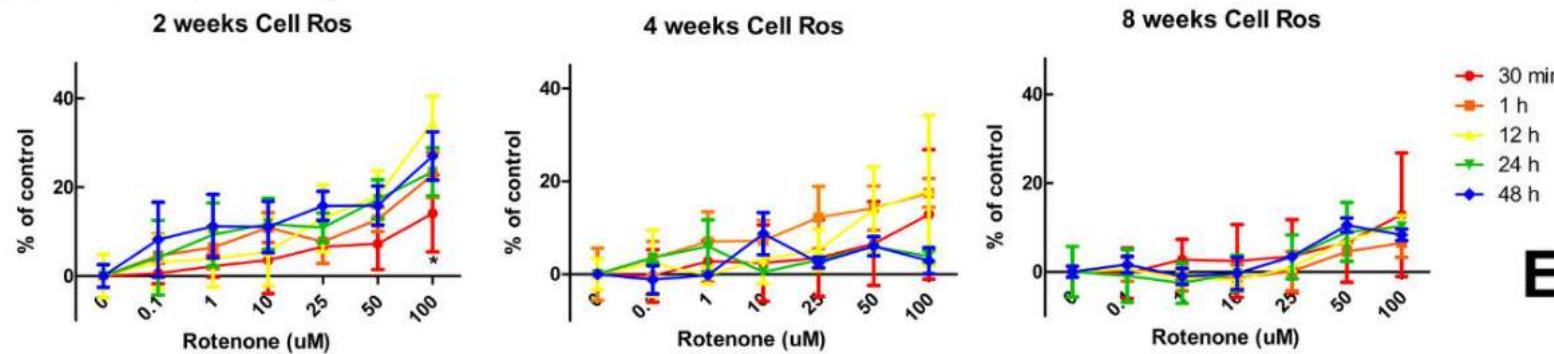
C Mitotracker assay



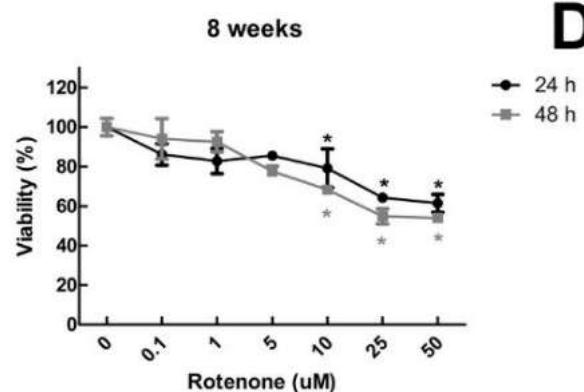
A Resazurin viability



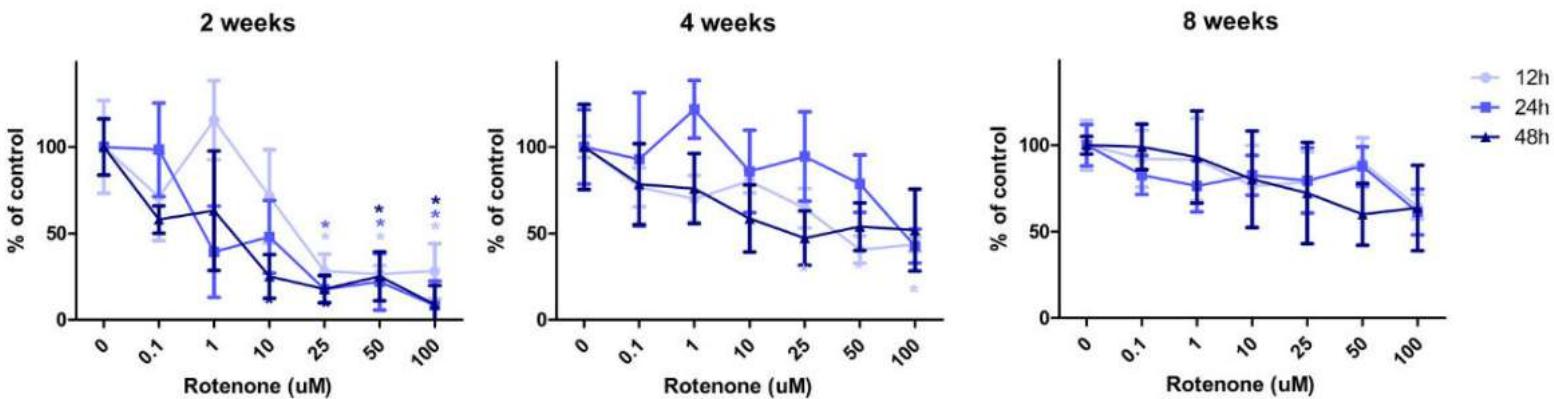
B CellRos assay



D

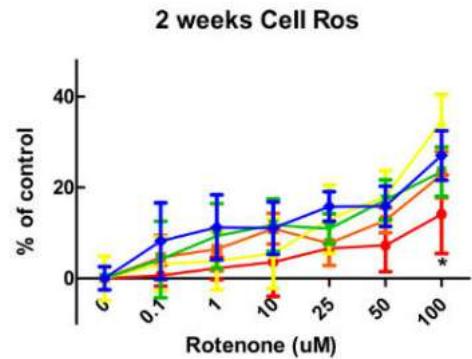


C Mitotracker assay

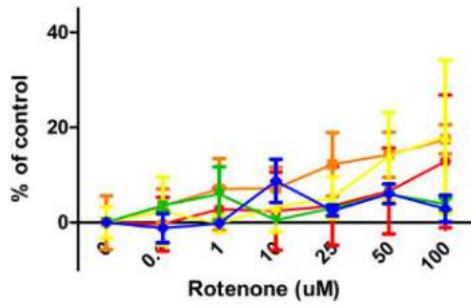


E

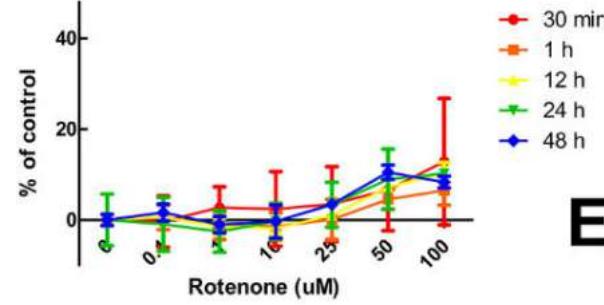
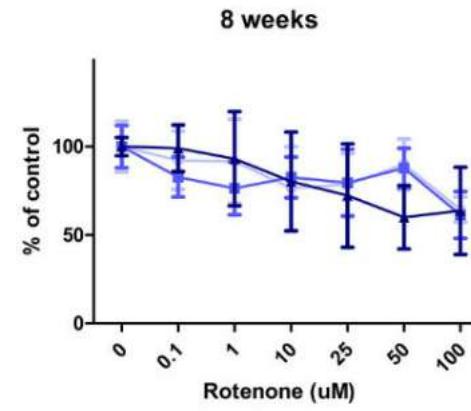
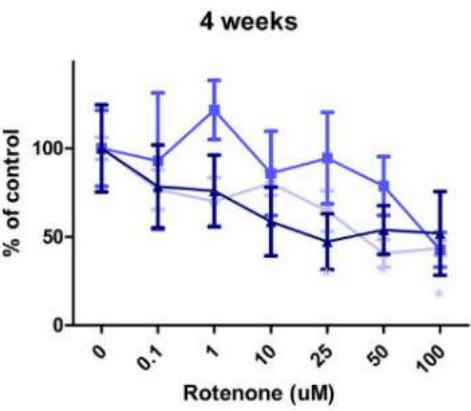
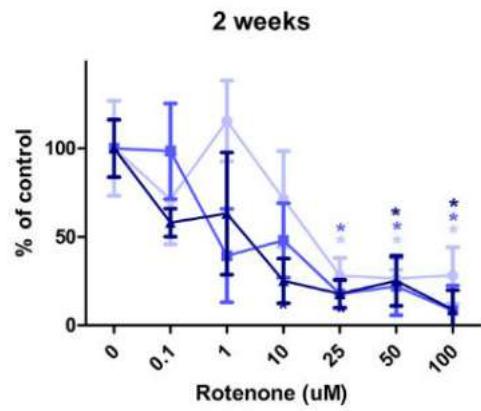
Rotenone (uM)

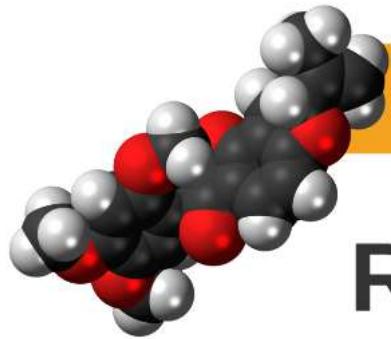
B CellRos assay

Rotenone (uM)

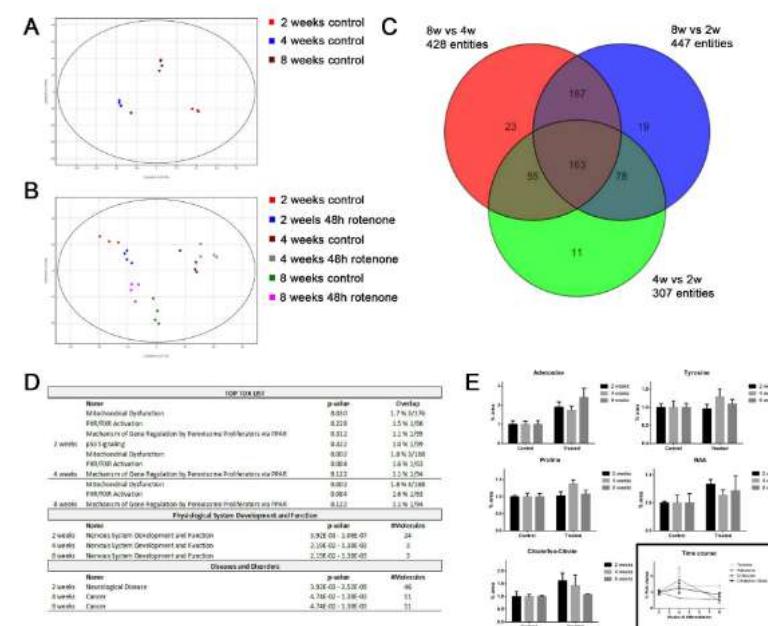
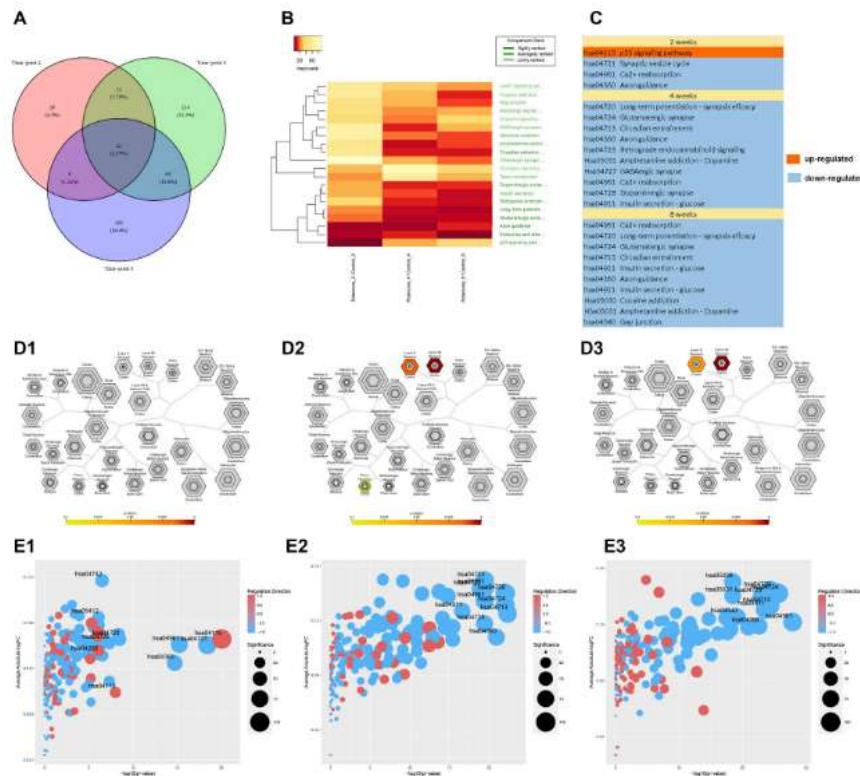
4 weeks Cell Ros

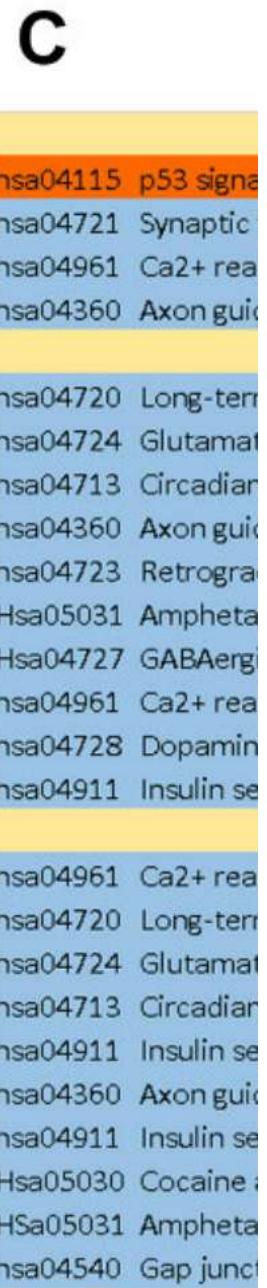
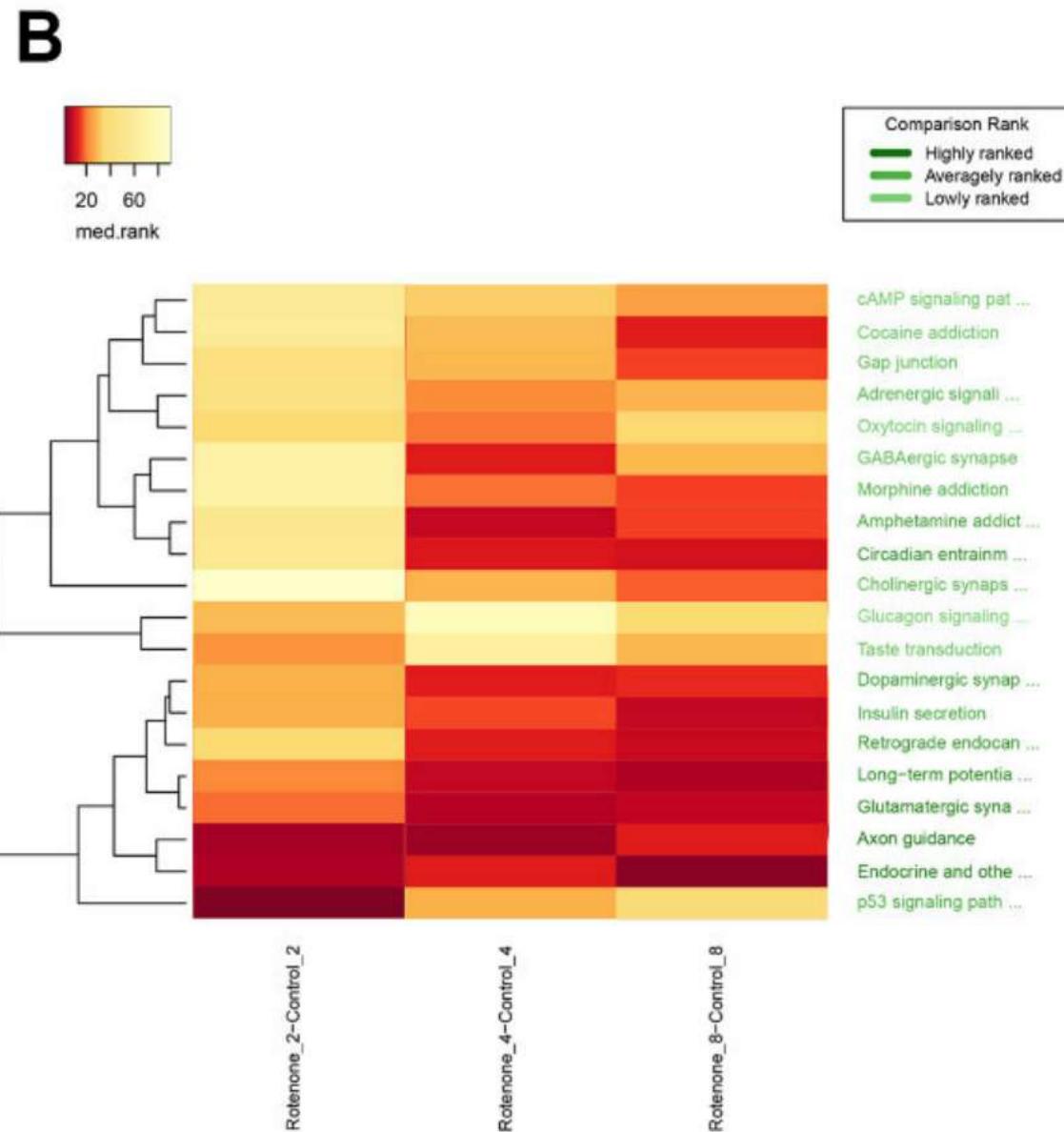
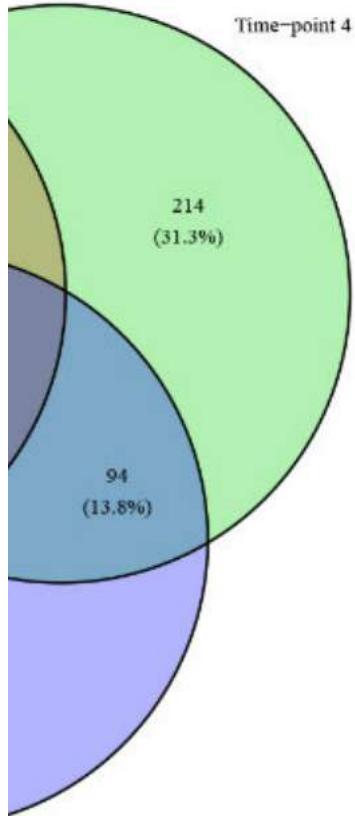
Rotenone (uM)

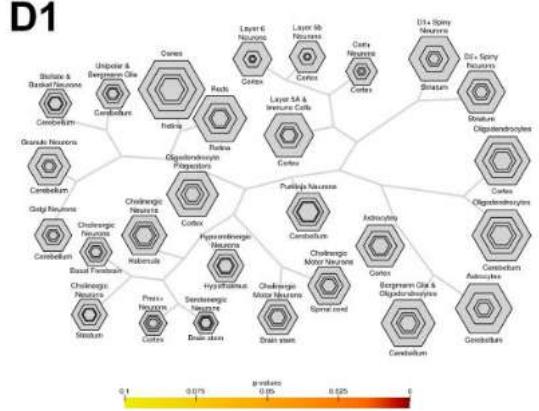
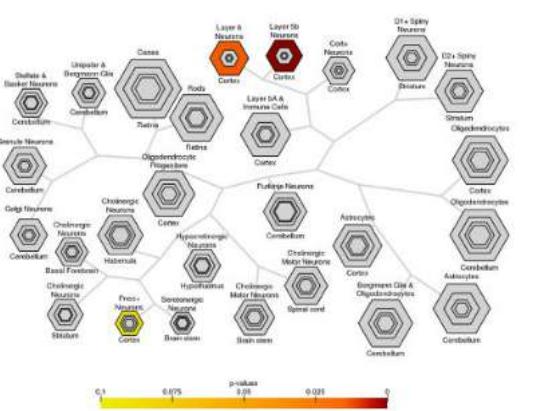
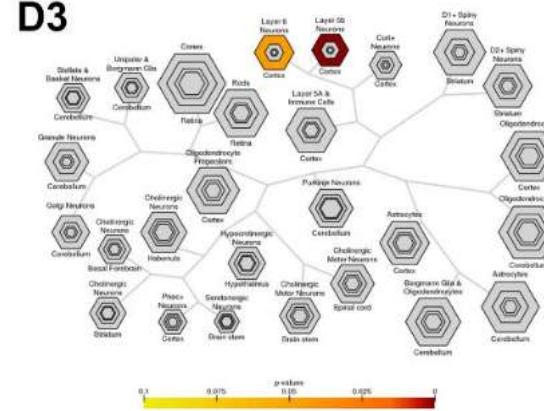
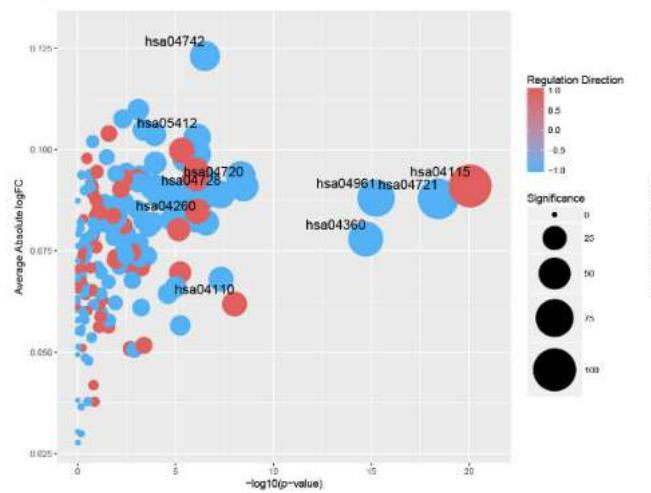
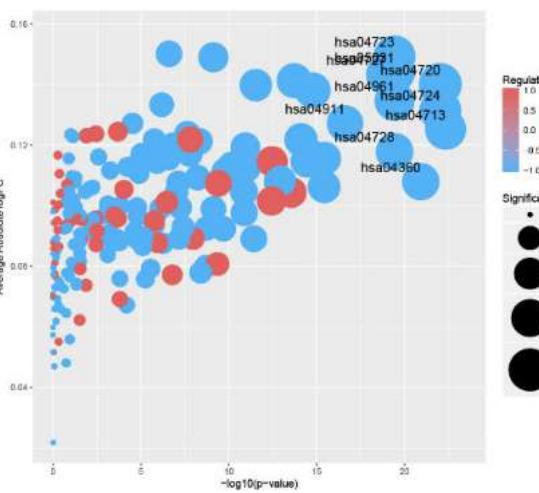
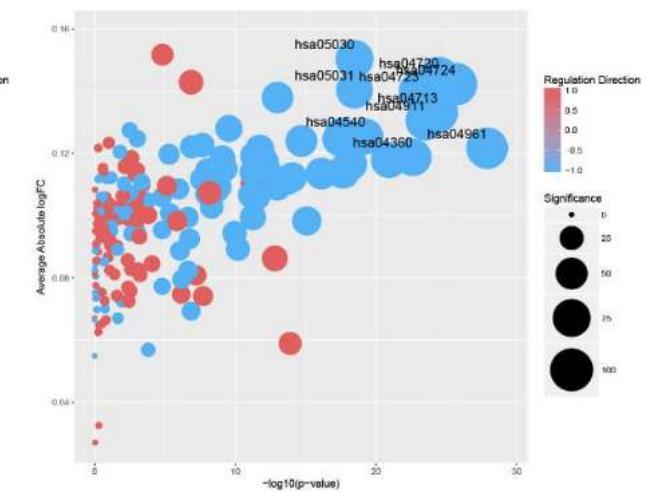
8 weeks Cell Ros**E****C Mitotracker assay**



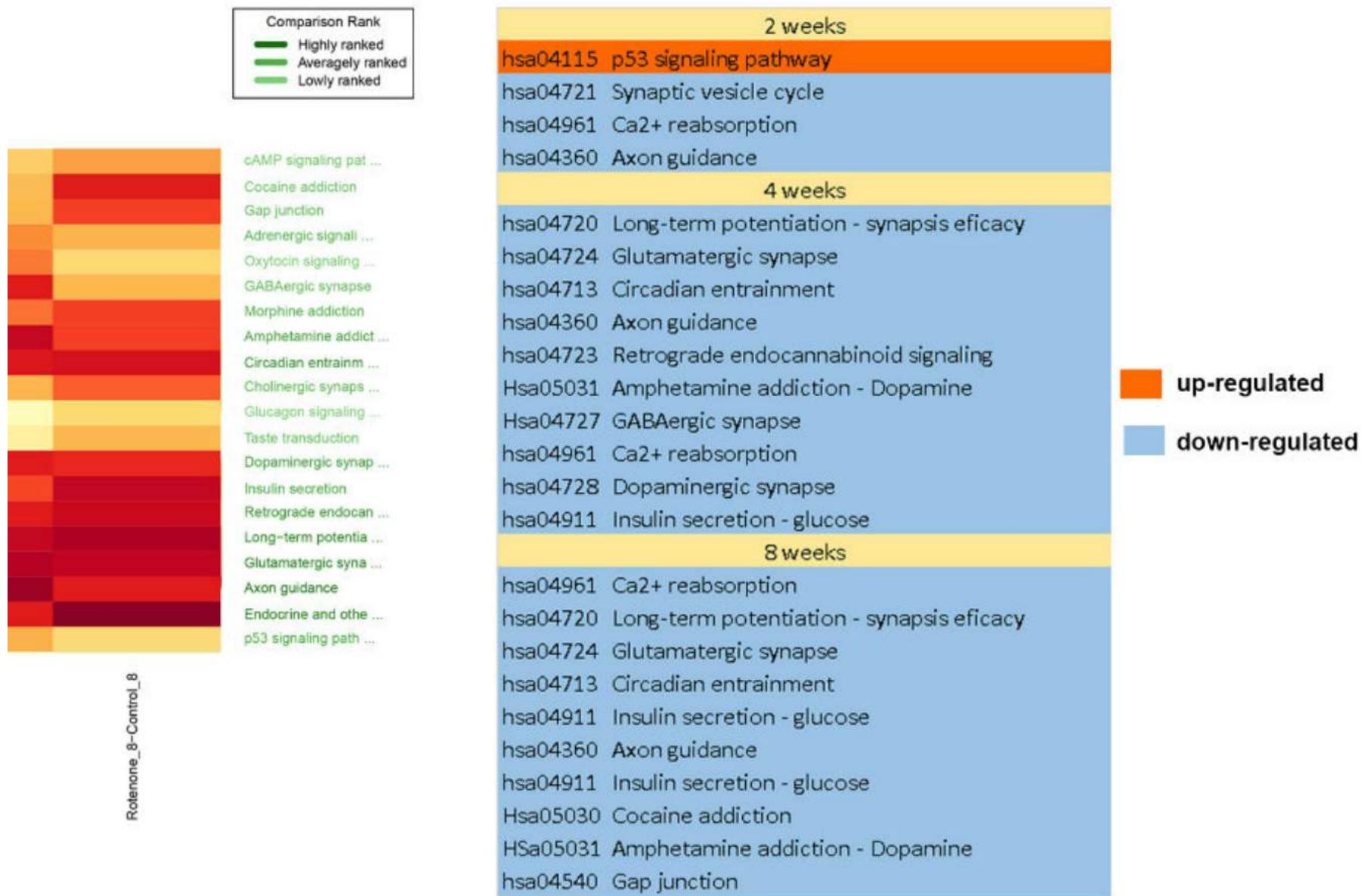
Rotenone





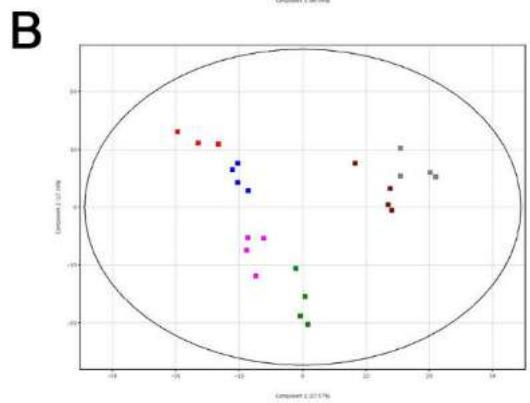
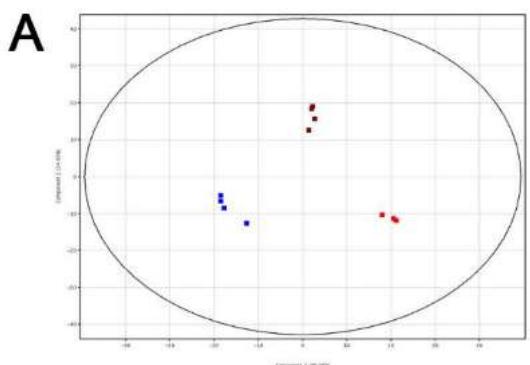
D1**D2****D3****E1****E2****E3**

C



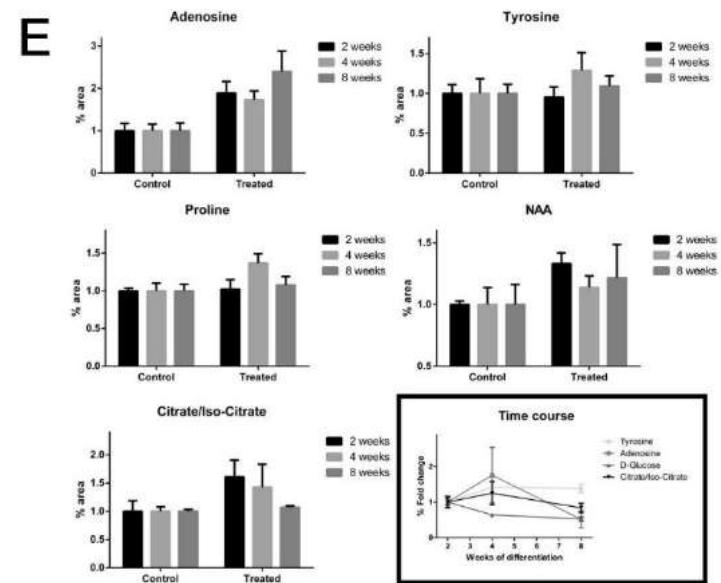
D3

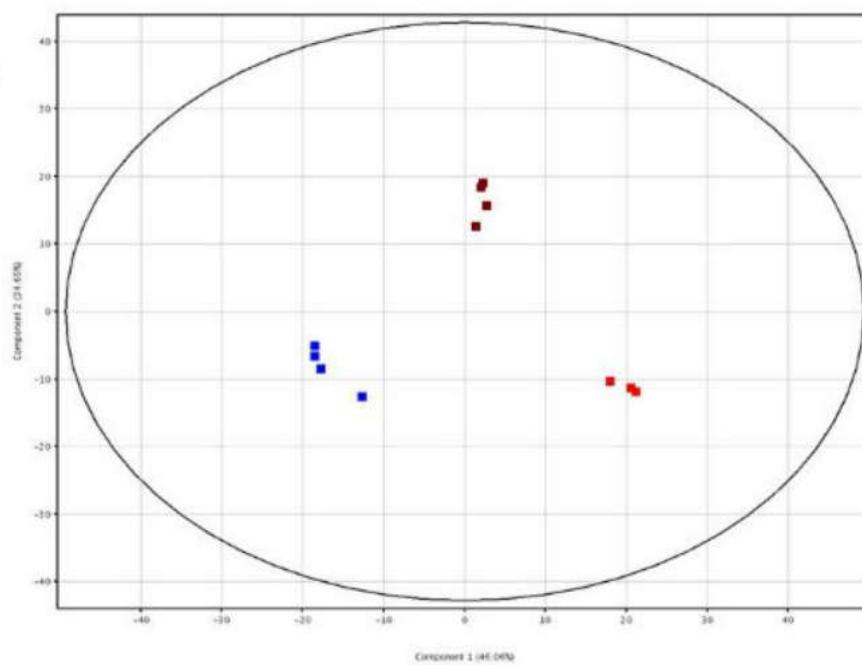




D

TOP TOX LIST				
	Name	p-value	Overlap	
2 weeks	Mitochondrial Dysfunction	0.030	1.7 % 3/176	
	PXR/RXR Activation	0.228	1.5 % 1/66	
	Mechanism of Gene Regulation by Peroxisome Proliferators via PPAR	0.312	1.1 % 1/95	
4 weeks	p53 Signaling	0.322	1.0 % 1/99	
	Mitochondrial Dysfunction	0.002	1.8 % 3/168	
	PXR/RXR Activation	0.084	1.6 % 1/63	
8 weeks	Mechanism of Gene Regulation by Peroxisome Proliferators via PPAR	0.122	1.1 % 1/94	
	Physiological System Development and Function			
	Name	p-value	#Molecules	
2 weeks	Nervous System Development and Function	3.92E-03 - 1.06E-07	24	
4 weeks	Nervous System Development and Function	2.19E-02 - 1.38E-03	3	
8 weeks	Nervous System Development and Function	2.19E-02 - 1.38E-03	3	
Diseases and Disorders				
Name	p-value	#Molecules		
2 weeks	Neurological Disease	3.92E-03 - 2.52E-09	46	
4 weeks	Cancer	4.74E-02 - 1.38E-03	11	
8 weeks	Cancer	4.74E-02 - 1.38E-03	11	

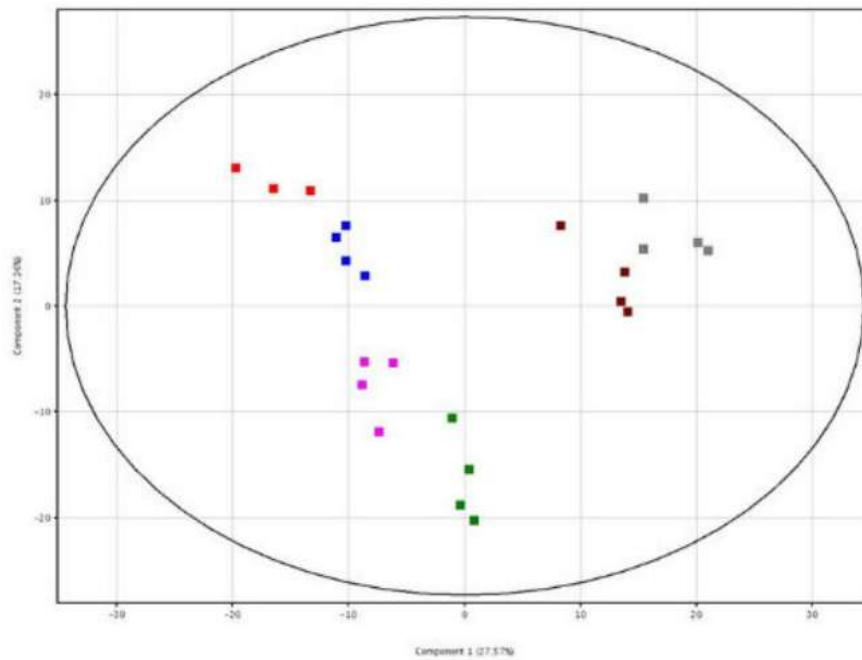


A

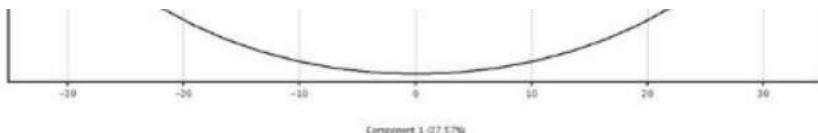
- 2 weeks control
- 4 weeks control
- 8 weeks control

C

8w vs 4w
428 entities

**B**

- 2 weeks control
- 2 weeks 48h rotenone
- 4 weeks control
- 4 weeks 48h rotenone
- 8 weeks control
- 8 weeks 48h rotenone



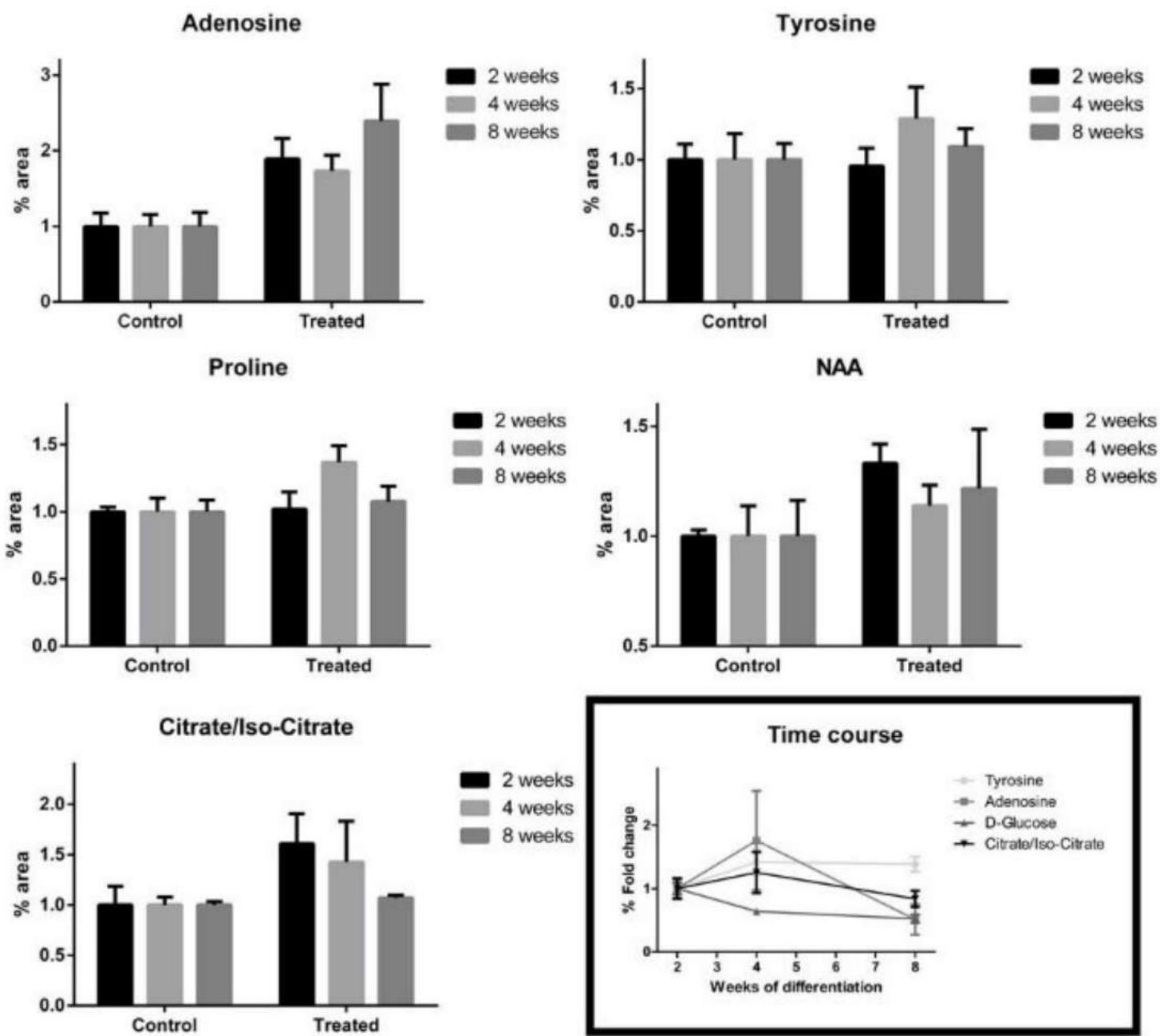
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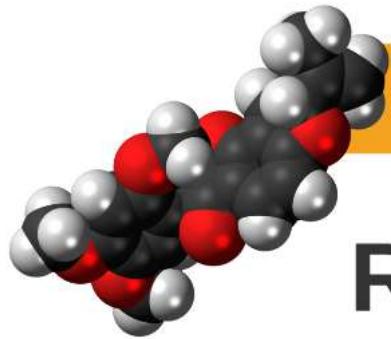
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E

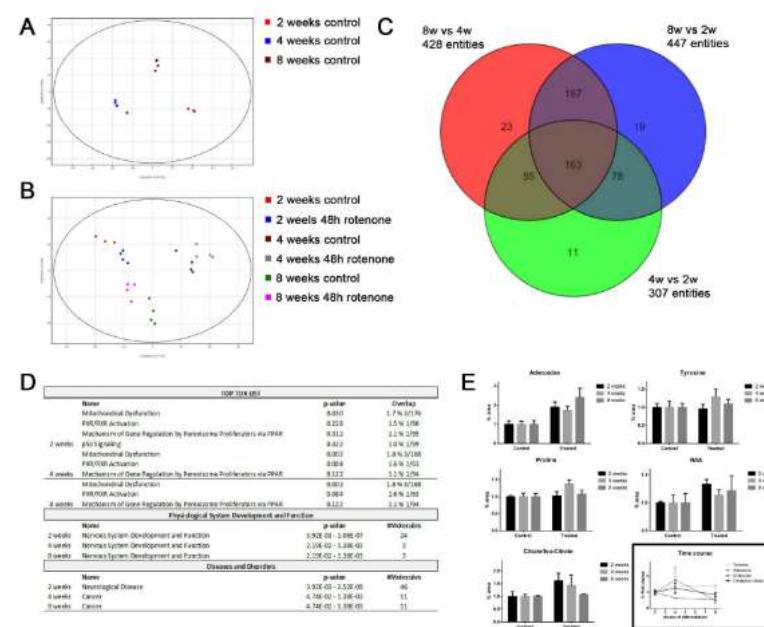
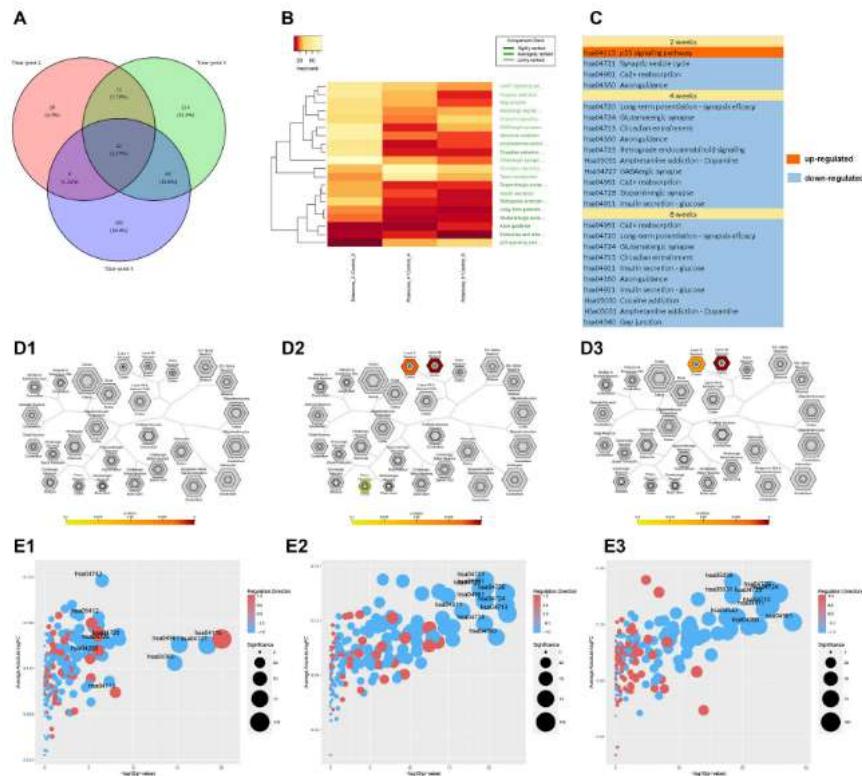
Eap
/176
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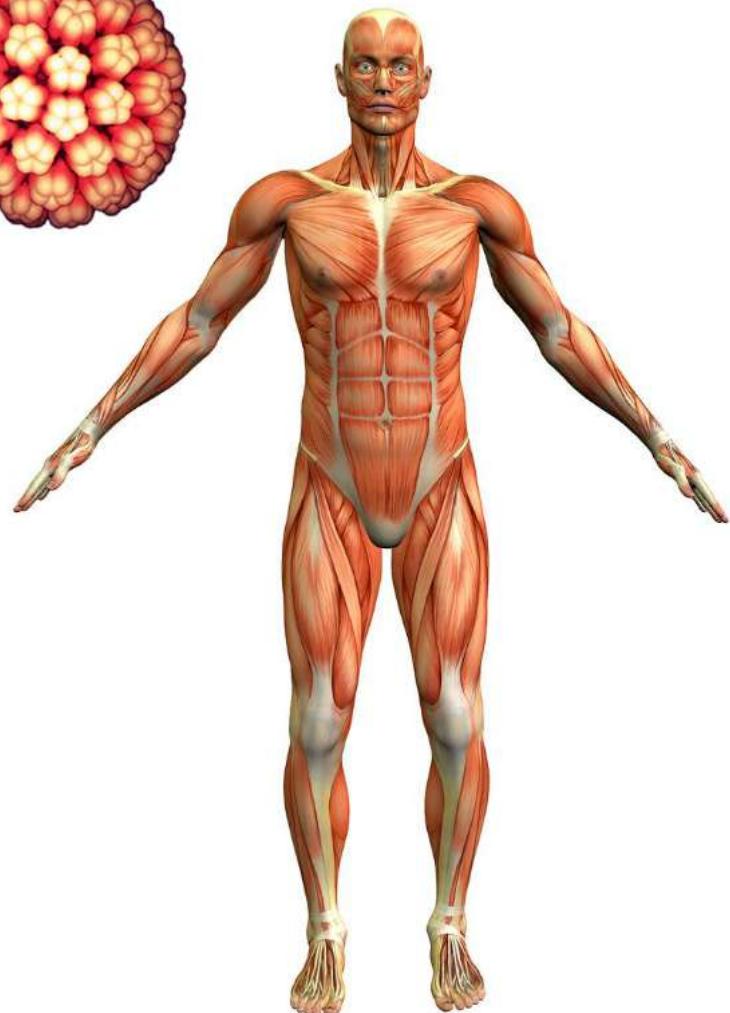
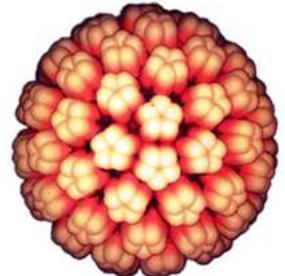




Rotenone



Virus



Virus

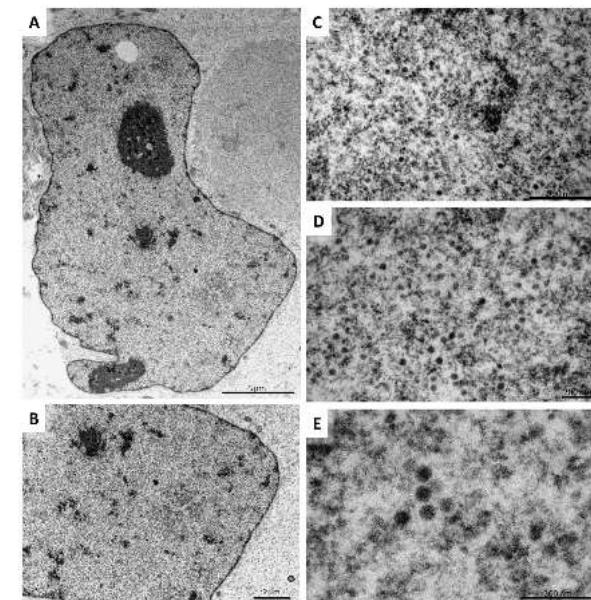
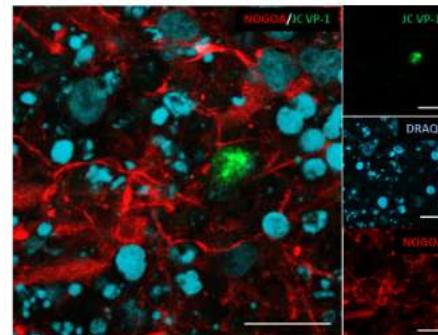
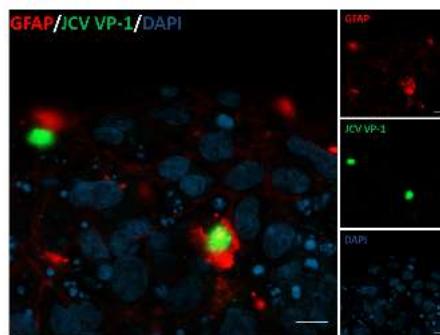
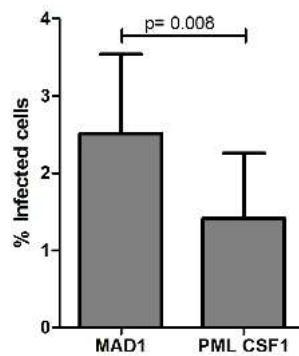
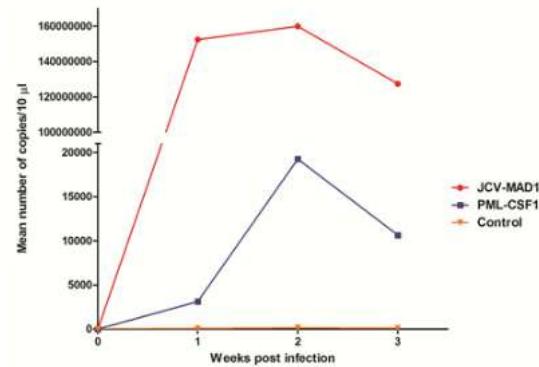
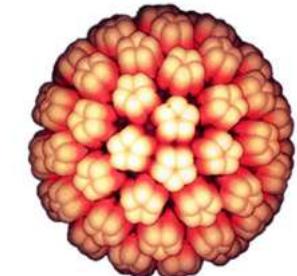
John Cunningham virus

Common in the general population, infecting 70% to 90% of humans

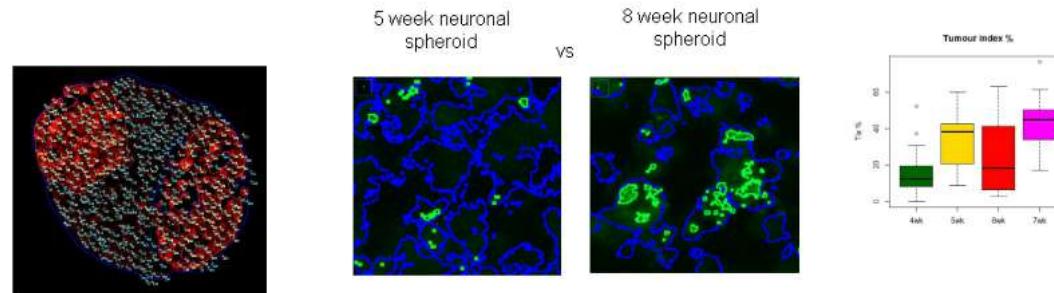
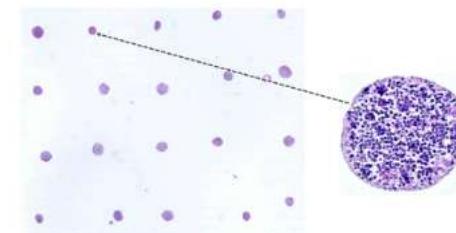
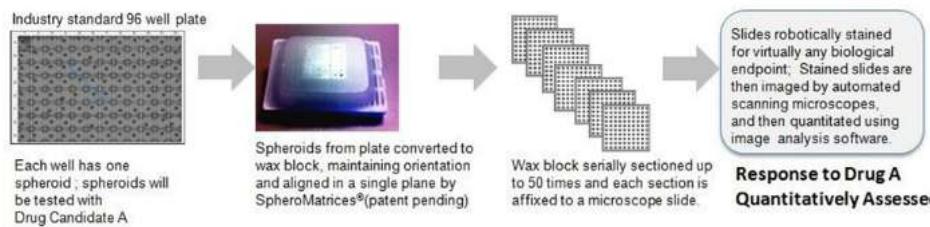
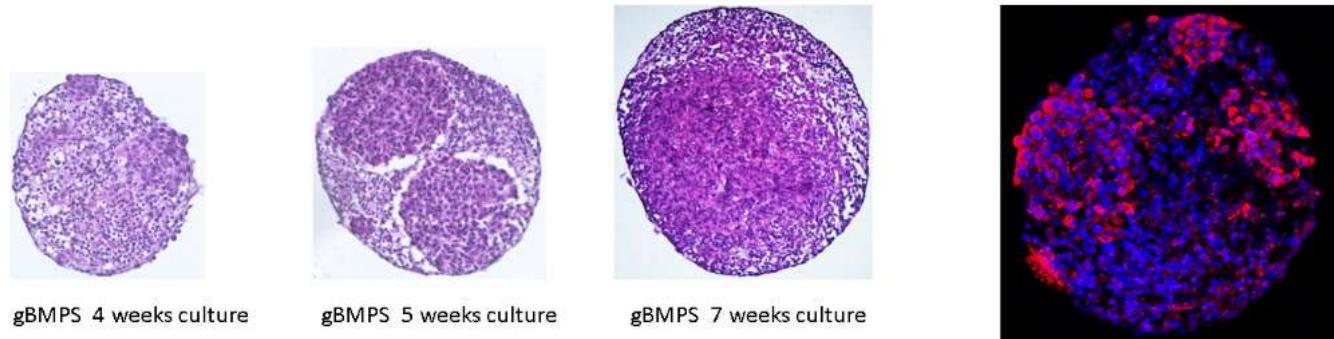
Contaminated water is the typical route of infection

Immunodeficiency or immunosuppression allows JCV to reactivate

Progressive multifocal encephalopathy



CANCER



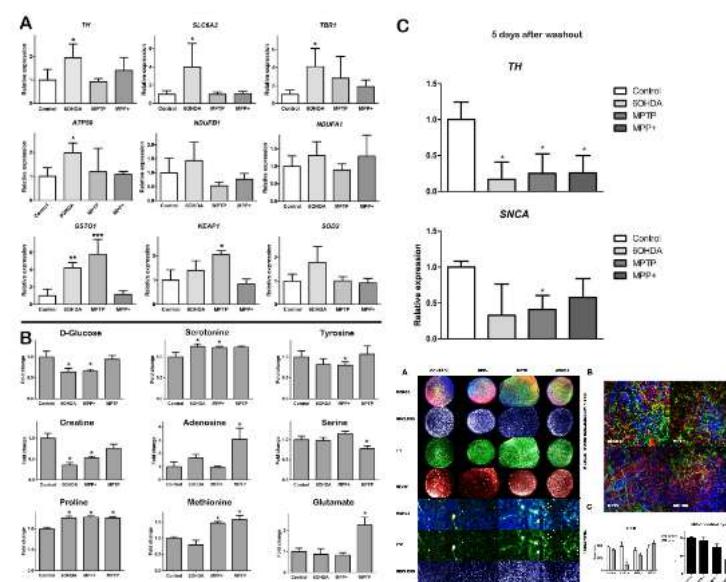
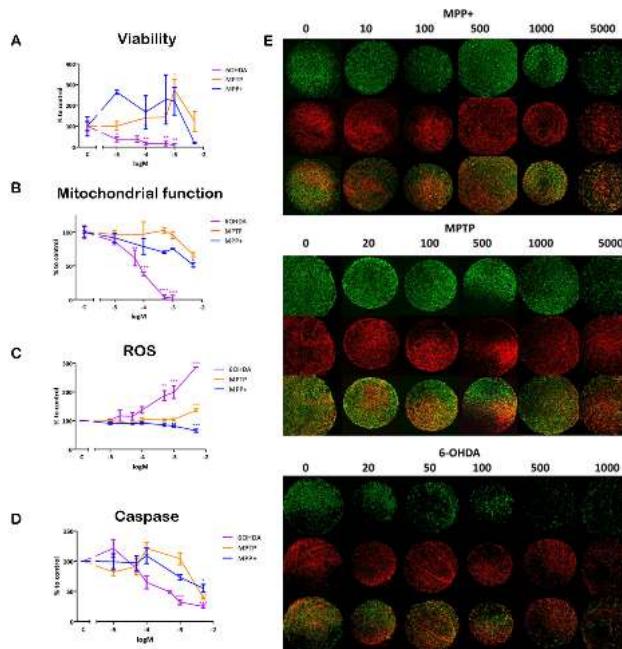
Capability	Whole Mount	Spheroidization
Analytical Imaging	X-Only periphery	y-Complete Spheroid
Automated staining (or high throughput)	X-No	y- Yes
Pathology via H&E (or cytotype QC)	X-No	y- Yes
Complex drug response (please see our mechanism studies)	X-No	y- Yes

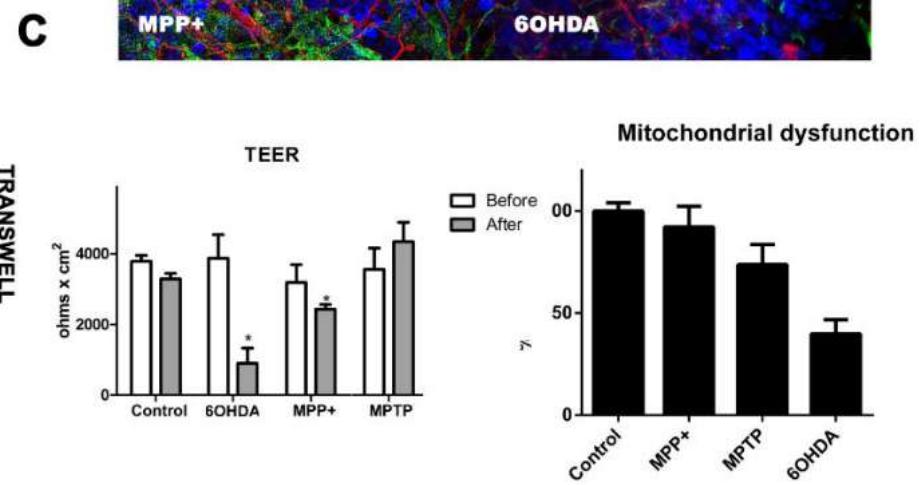
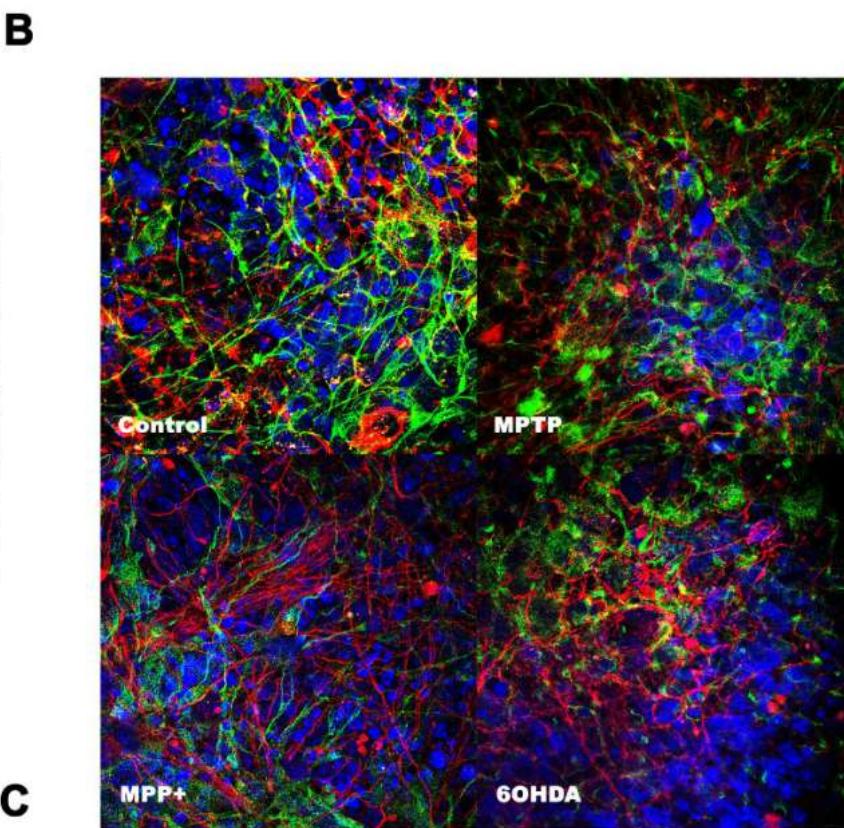
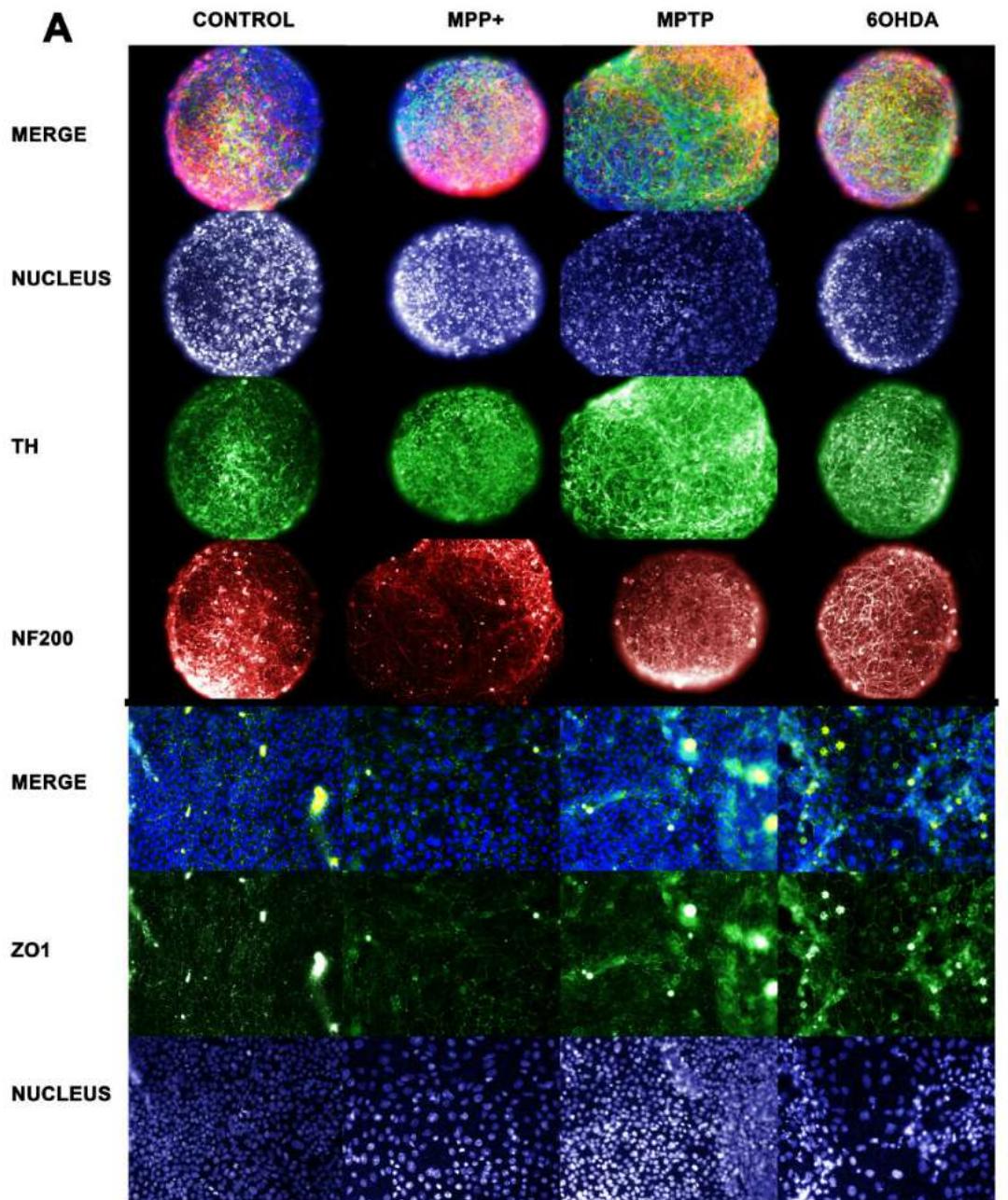
PD

Parkinson Model Chemical induction

Treatment

6OHDA
MPP+
MPTP





Thank you!

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