VI CONGRESO INTERNACIONAL DE AUTISMO EN MURCIA

"INCLUSIÓN EN LAS PERSONAS CON AUTISMO: PRÁCTICAS BASADAS EN LA EVIDENCIA"

12 y 13 de marzo de 2026
Auditorio y Centro de Congresos Víctor Villegas
www.congresoautismo.es

NEURON DEVELOPMENT FROM BABY TEETH: A CELL MODEL FOR STUDYING THE CAUSES OF ASD.

DESARROLLO DE NEURONAS A PARTIR DE DIENTES DE LECHE: UN MODELO CELULAR PARA ESTUDIAR LAS CAUSAS DEL TEA.

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Experimental Models for the Study of Autism

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication and the presence of restricted or repetitive behaviors. The etiology of ASD involves a combination of genetic and environmental factors affecting early brain development. Because direct experimental studies in humans are limited, experimental models have become essential tools for understanding the biological mechanisms underlying autism and for testing potential therapeutic strategies.

Experimental model	Type of model	Main purpose in ASD research	Key advantages	Limitations	Representative references
Genetic mouse models (e.g., SHANK3, CNTNAP2, FMR1, MECP2)	Animal model	Study the effects of ASD-associated gene mutations on brain development, synaptic function, and behavior	Well-characterized genetics; ability to manipulate genes; behavioral assays available	Mouse social behavior differs from humans; models reproduce only some ASD features	Silverman et al., 2010; Bourgeron, 2015
Valproic acid (VPA) prenatal exposure model	Environmental rodent model	Investigate environmental risk factors affecting embryonic brain development and ASD-like phenotypes	Reproducible behavioral and neuroanatomical alterations; widely used	Represents only one environmental pathway to ASD	Roullet et al., 2013
Non-human primate models (gene-edited macaques)	Animal model	Study ASD-related genes in species with complex social cognition and brain organization closer to humans	High similarity to human brain and social behavior	Ethical issues; high cost; limited availability	Tu et al., 2019
Zebrafish genetic models	Vertebrate animal model	Investigate early neurodevelopmental processes and gene function in ASD-related pathways	Rapid development; transparent embryos; high-throughput genetic screening	Simpler brain structure than mammals	Stewart et al., 2014
Human induced pluripotent stem cells (iPSCs)	Cellular model	Study neuronal development and synaptic alterations using patient-derived cells	Human genetic background; patient-specific models	Limited ability to model complex neural circuits	Marchetto et al., 2017
Brain organoids (3D cortical cultures)	Cellular model	Model early human brain development and neuronal network formation in ASD	Mimic aspects of cortical organization; useful for studying developmental mechanisms	Lack full vascularization and brain connectivity	Lancaster & Knoblich, 2014; Quadrato et al., 2017
Computational and systems biology models	In silico model	Analyze large genetic datasets and neural network dynamics associated with ASD	Integrates multi-omics and large datasets	Requires validation with biological models	Geschwind & State, 2015

ASD NEUROBIOLOGY: SYNAPTIC FUNCTIONAL ALTERATIONS

Review 17 January 2023

Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy

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Review

Experimental Models to Study Autism Spectrum Disorders: hiPSCs, Rodents and Zebrafish

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REVIEW

Autism spectrum disorder: neuropathology and animal models

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•Bourgeron, T. (2015). From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nature Reviews Neuroscience*, 16, 551–563.
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•Roullet, F. I., Lai, J. K. Y., & Foster, J. A. (2013). In utero exposure to valproic acid and autism. *Neurotoxicology and Teratology*, 36, 47–56.
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•Stewart, A. M., et al. (2014). Zebrafish models for translational neuroscience research. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 55, 94–104.
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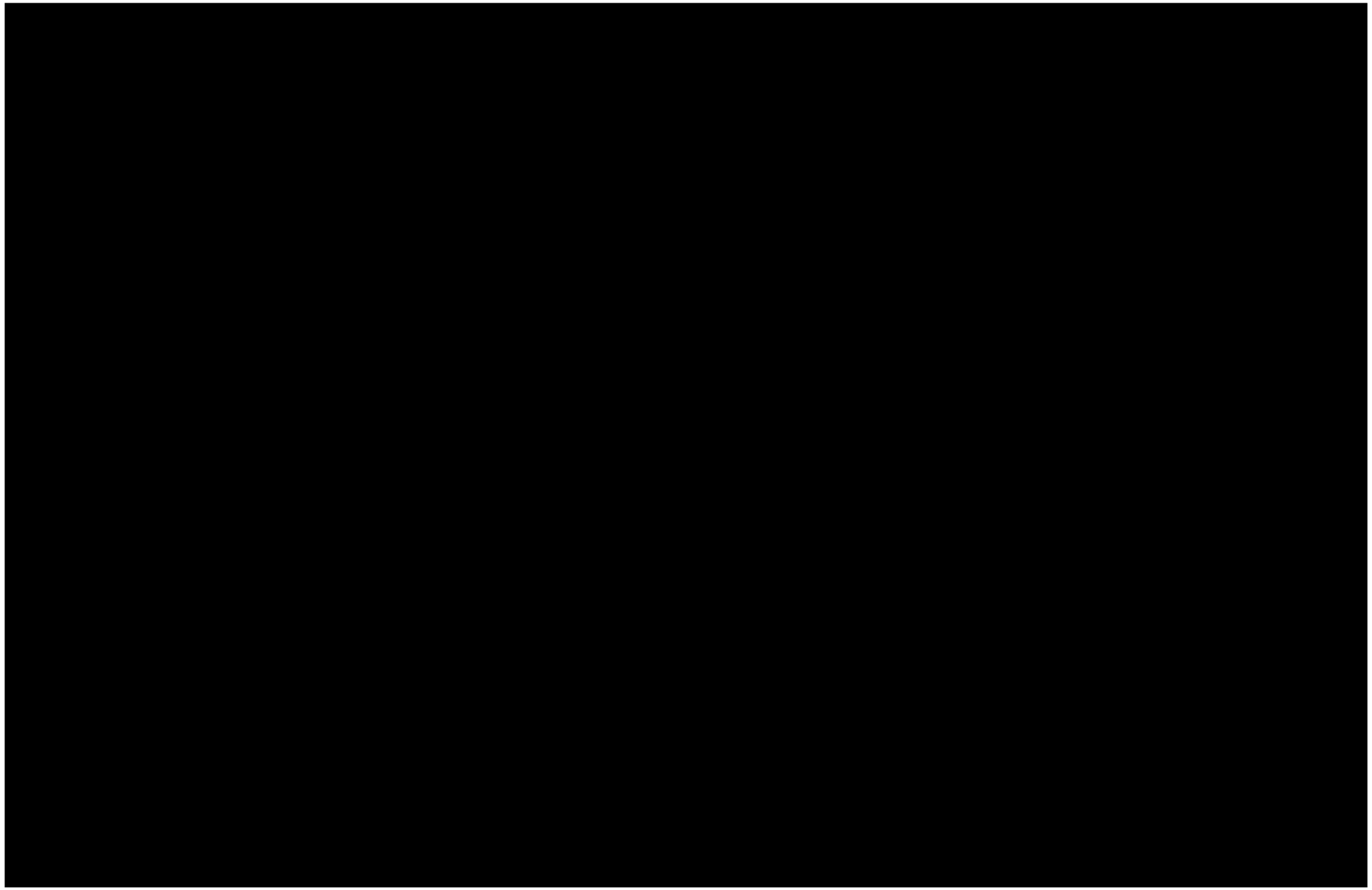
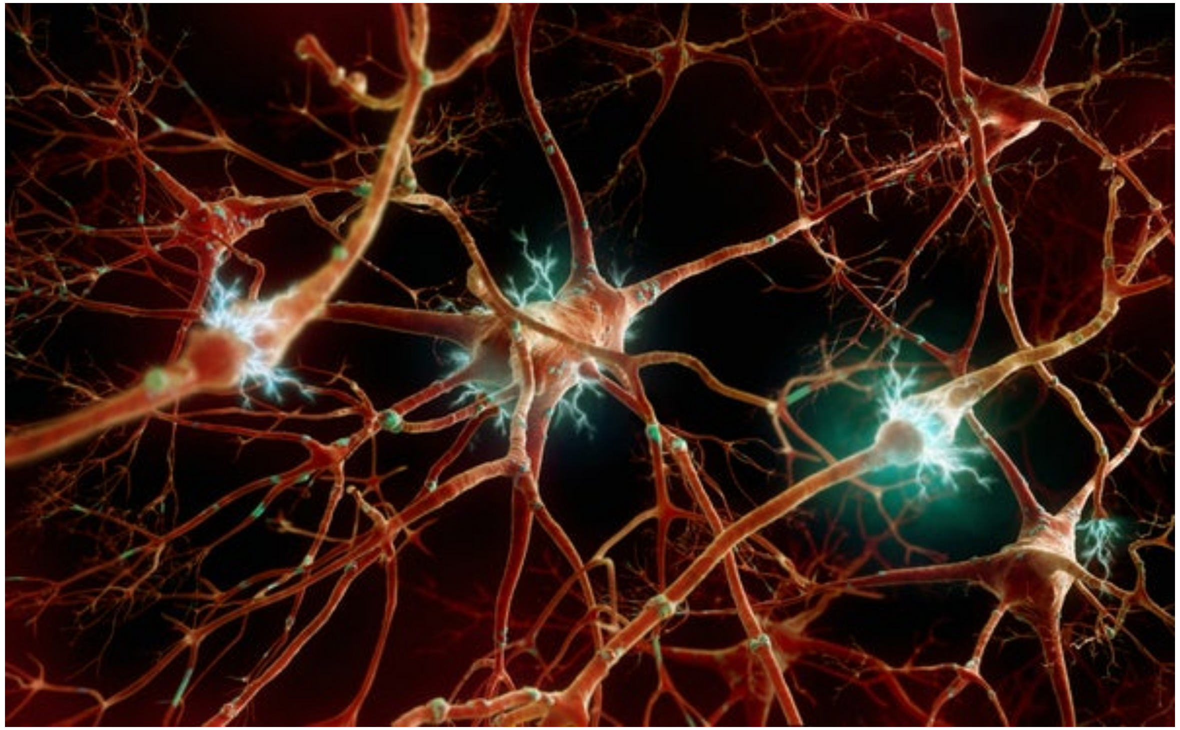


Limitations and perspectives

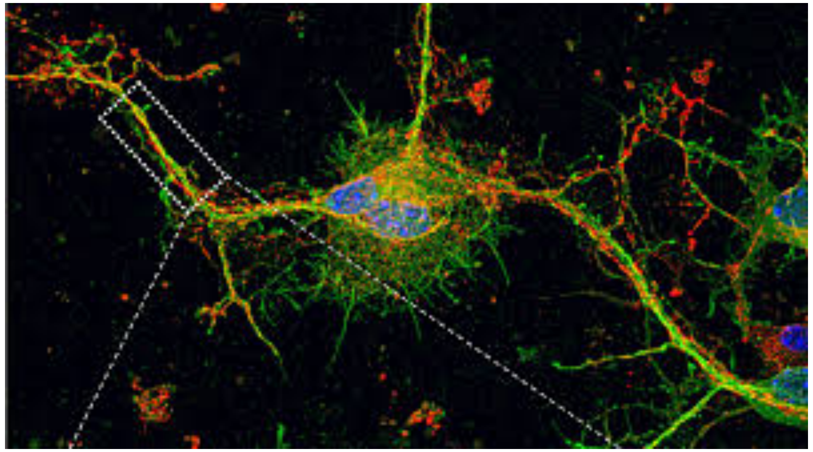
Despite their value, experimental models cannot fully reproduce the complexity and heterogeneity of ASD in humans. Animal models may capture only specific aspects of the disorder, and cellular models lack the full organization of the developing brain. Therefore, integrating findings from multiple experimental systems is essential for understanding the neurobiological basis of autism.

ASD NEUROBIOLOGY:

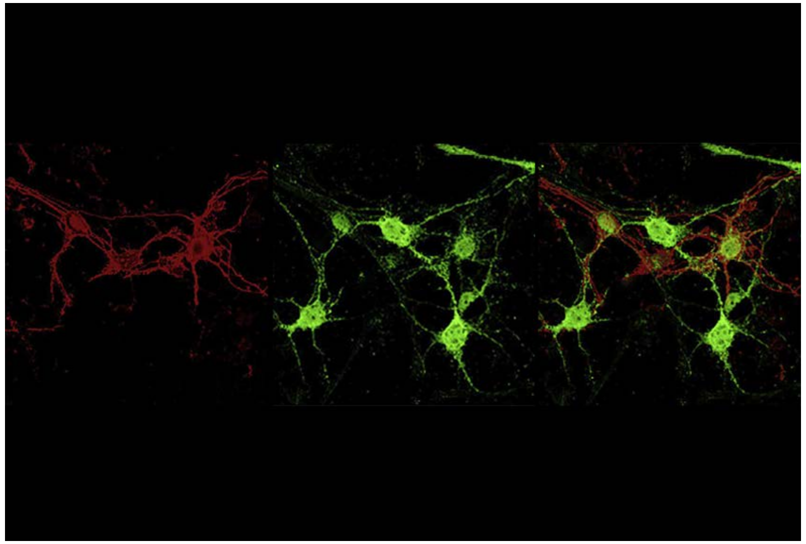
SYNAPSES



NEURONS



NEURONAL CIRCUITS



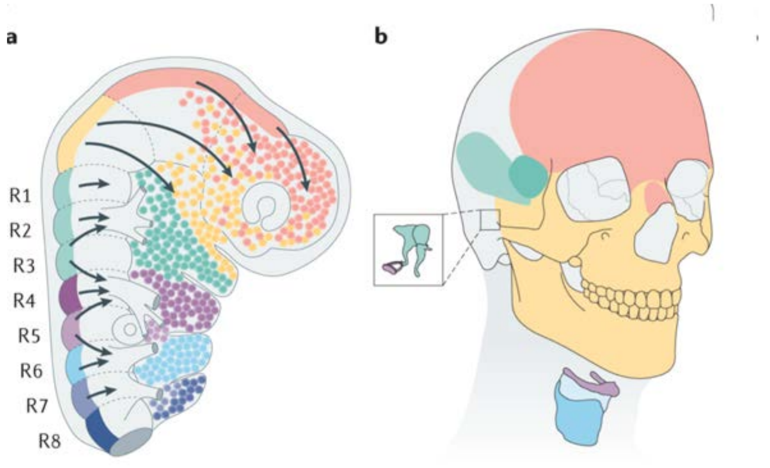
We need better models that are:

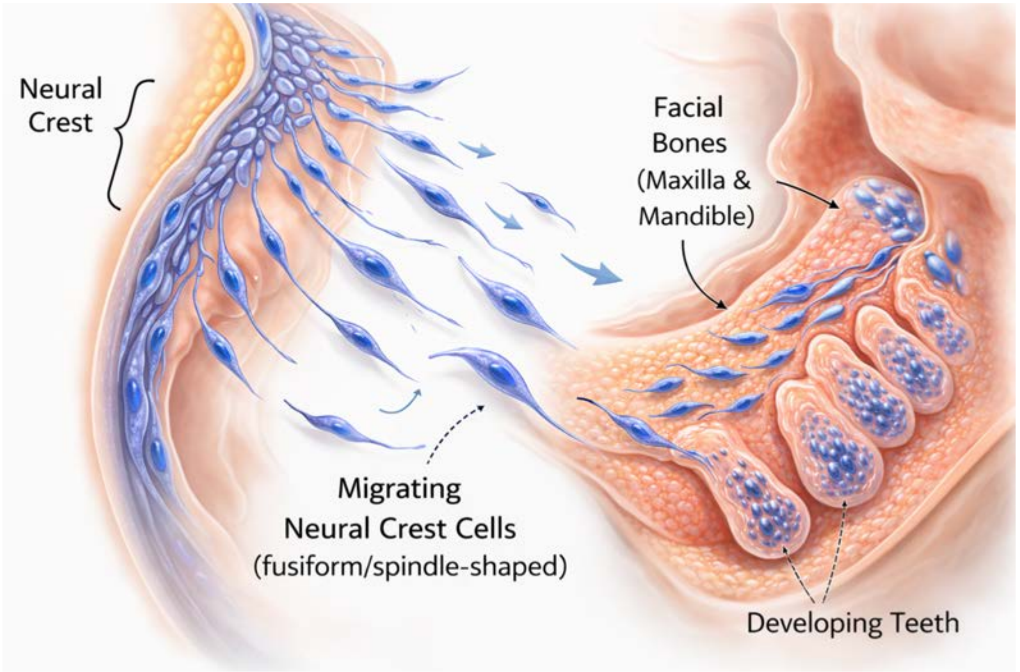
- as reliable as possible and as minimally invasive to obtain as possible.

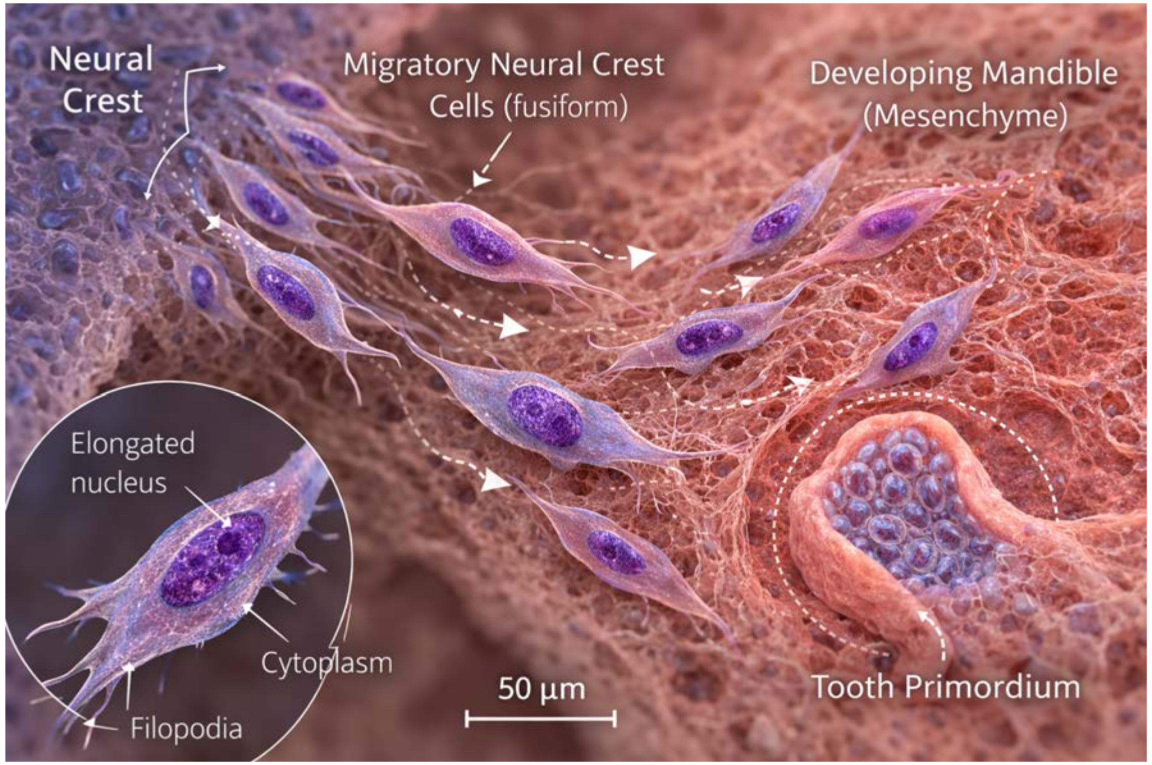
- If they are of human origin, we will be closer to understanding the pathogenic mechanisms of autism spectrum disorder (ASD).

Ideally, these models should be of neural origin, consisting of human neurons in which synapses, neuronal properties, and neural circuits can be studied.

During embryonic development, neural crest cells migrate toward the cephalic regions and give rise to sensory neurons, neurons of the autonomic nervous system, and craniofacial skeletal structures, including the tissues that form the teeth.





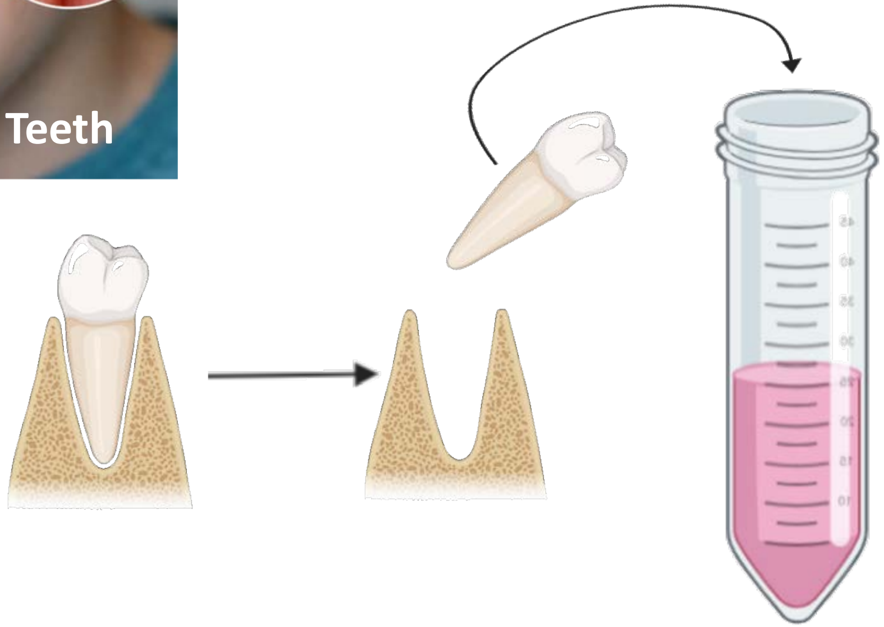


Neurons derived from neural crest:
- DRG sensorial neurons
- Vegetative neurons in visceral plexus

Selection of milk teeth donors

genetic report

Collection of samples



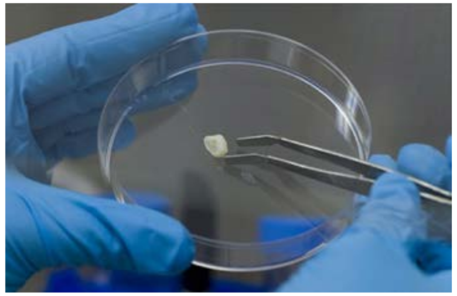
Inclusion criterion:
Genetic report showing a genetic alteration classified as a pathogenic variant affecting the central nervous system (CNS)

HOW TO JOIN THE STUDY:

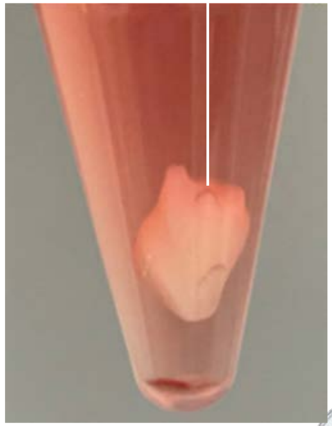
By email: send a donation proposal, genetic report, informed consent.

By courier: deliver the culture media and collect the sample within 24 hours (Sapain an Portugal)

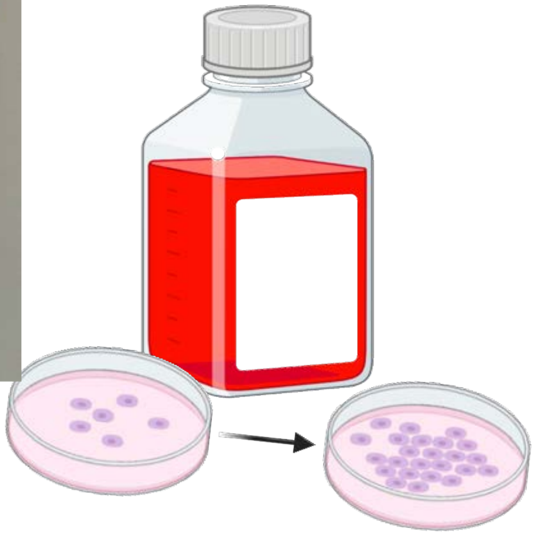
Objetivo general | **STUDY DEVELOPMENT** | Resultados preliminares

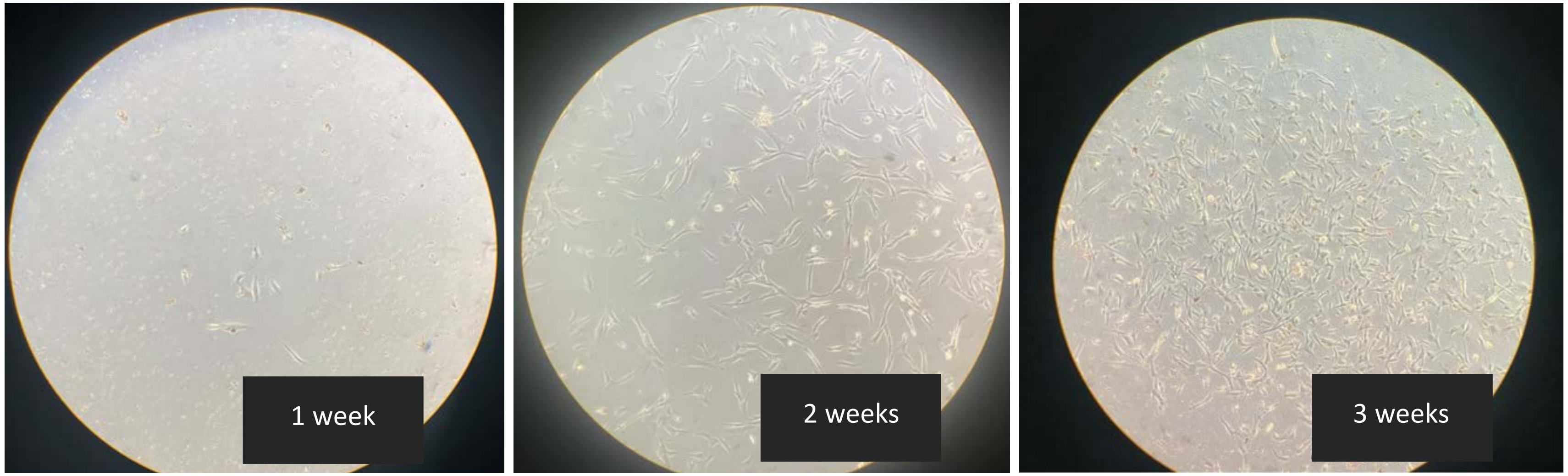


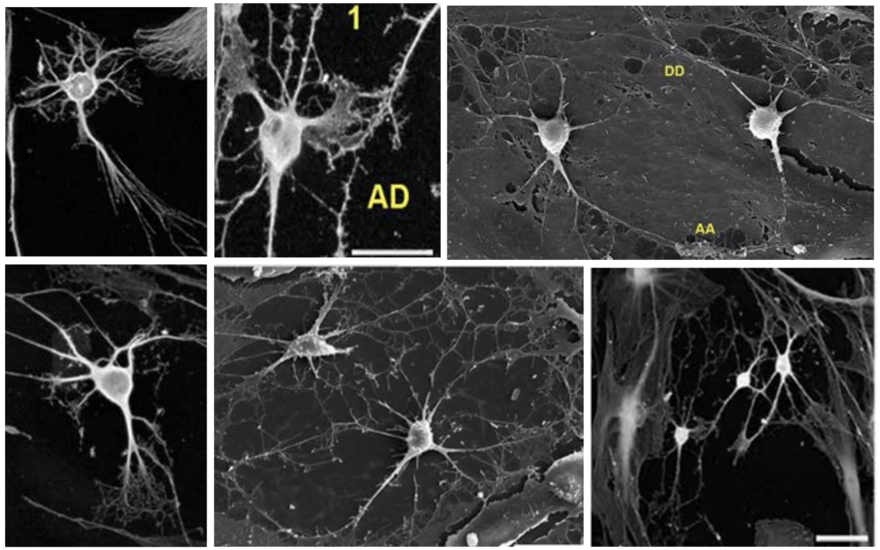
Dental pulp



Cell culture medium

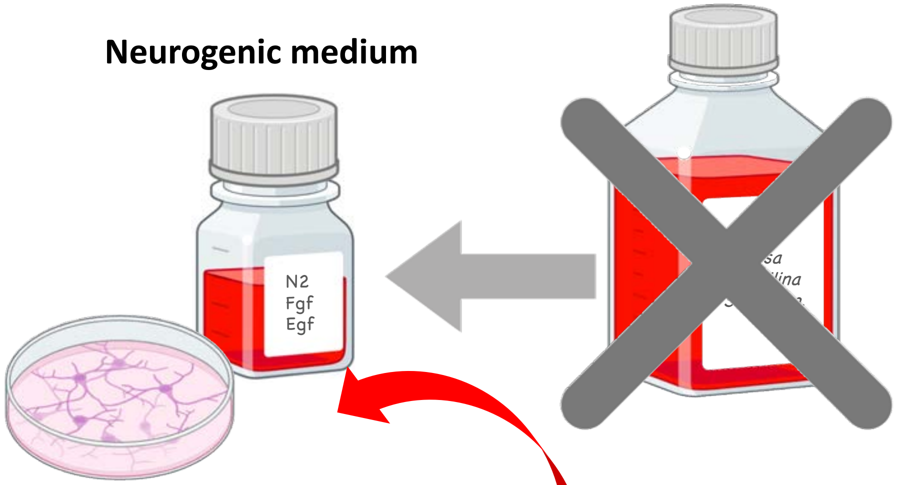




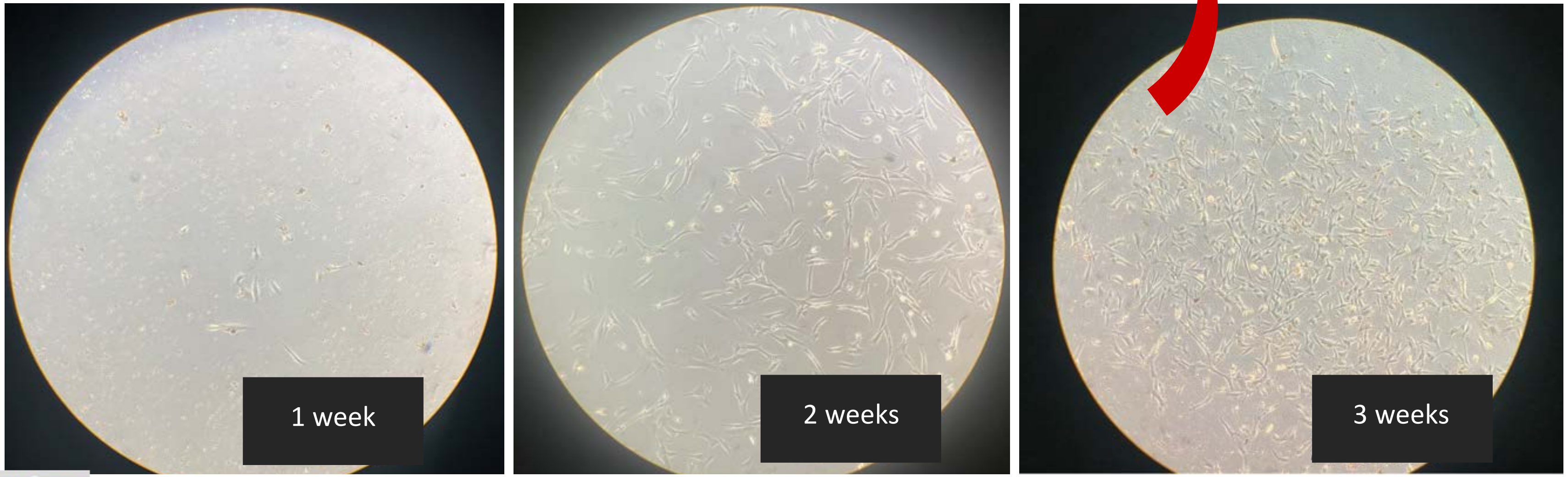


Cell culture medium

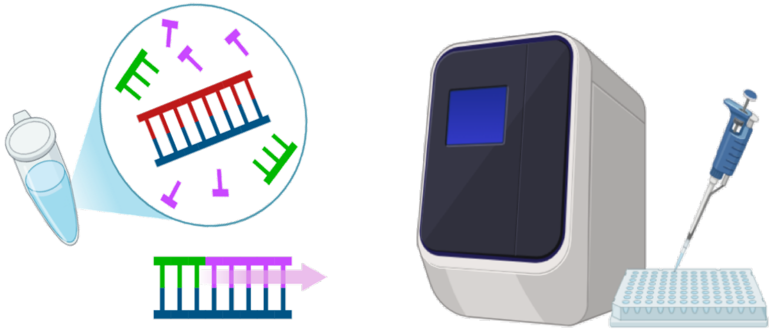
Neurogenic medium



4-6 days



MARKERS EXPRESSION STUDIES:

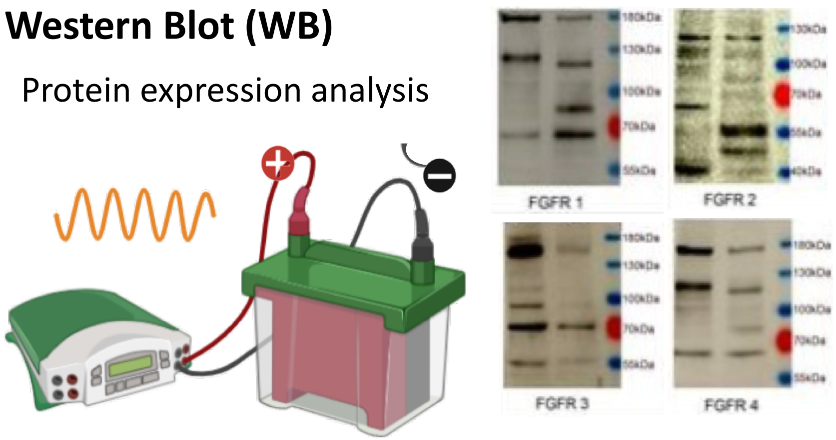


cuantitative PCR

Gene expresión analysis

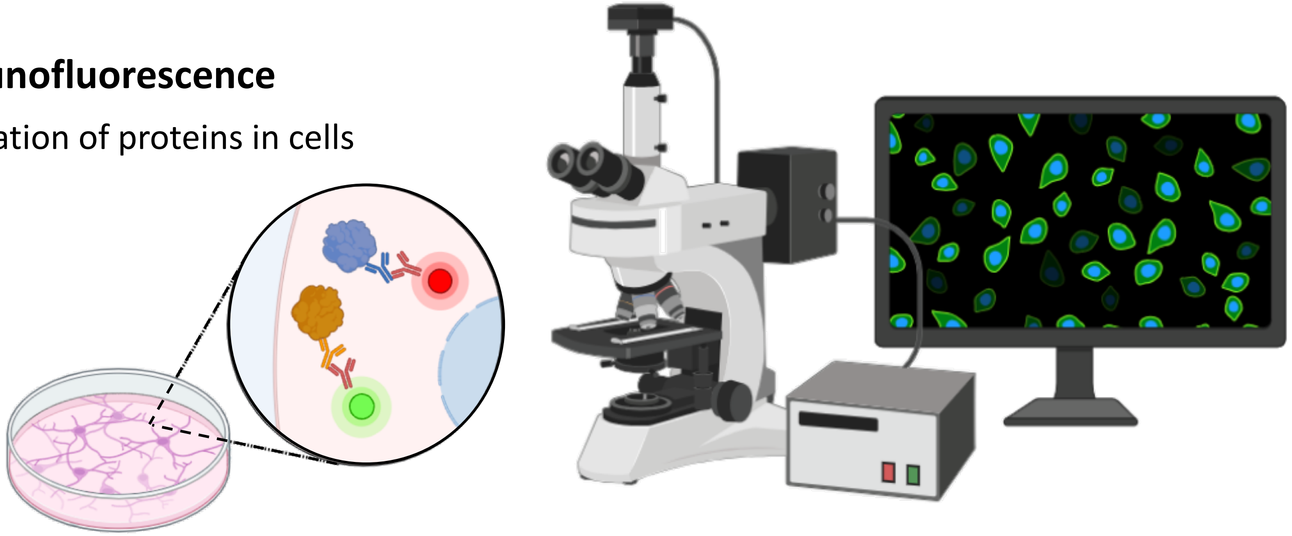
Western Blot (WB)

Protein expression analysis

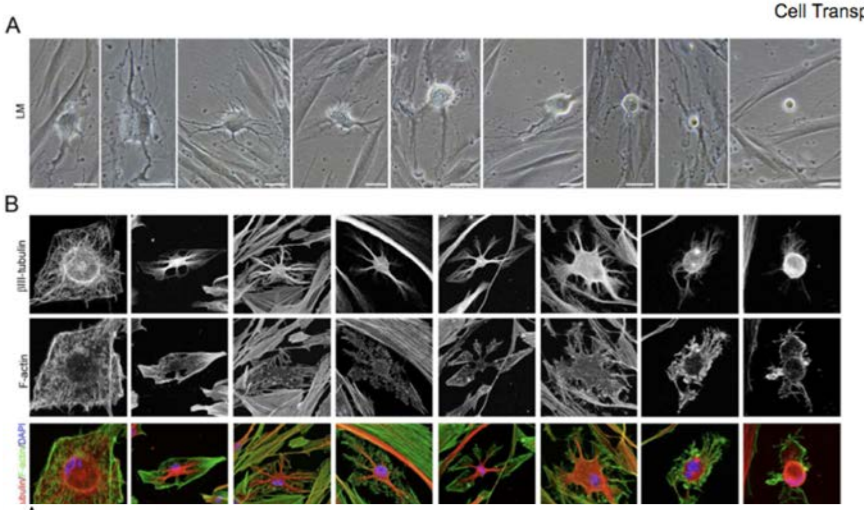


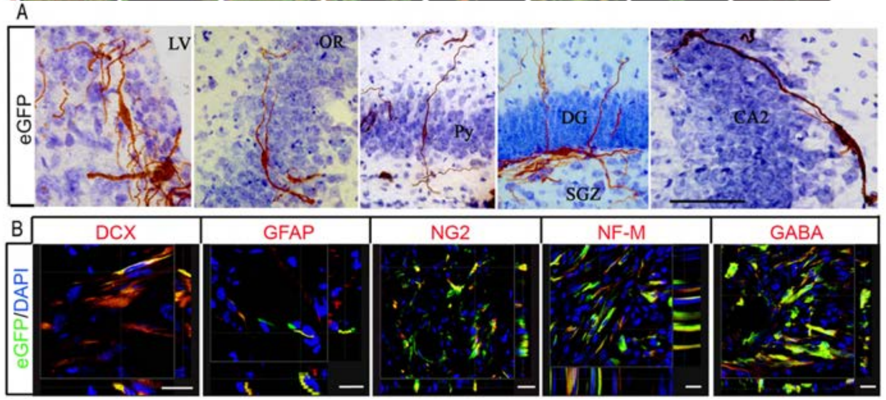
Immunofluorescence

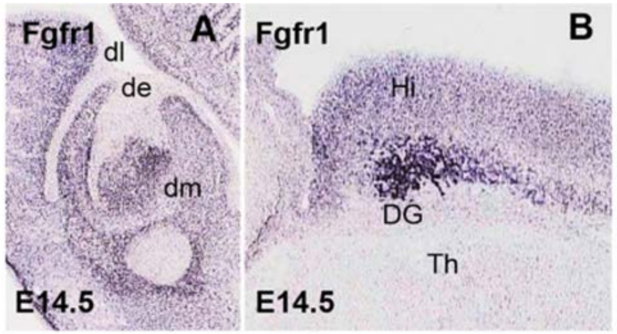
Localization of proteins in cells



DPSCs CULTURE
NEURAL DIFFERENTIATION



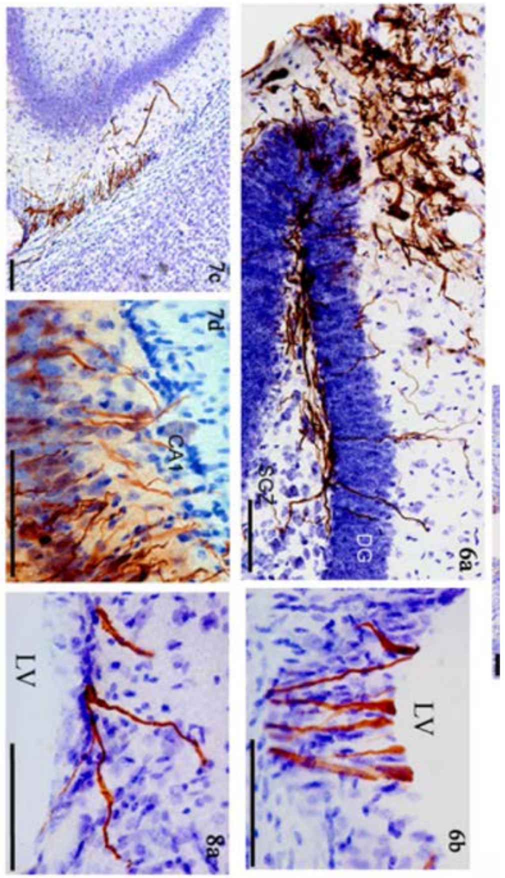




[Human adult periodontal ligament-derived cells integrate and differentiate after implantation into the adult mammalian brain.]

Bueno C, Ramirez C, Rodríguez-Lozano FJ, Tabarés-Seisdedos R, Rodenas M, Moraleda JM, Jones JR, **Martinez S**.

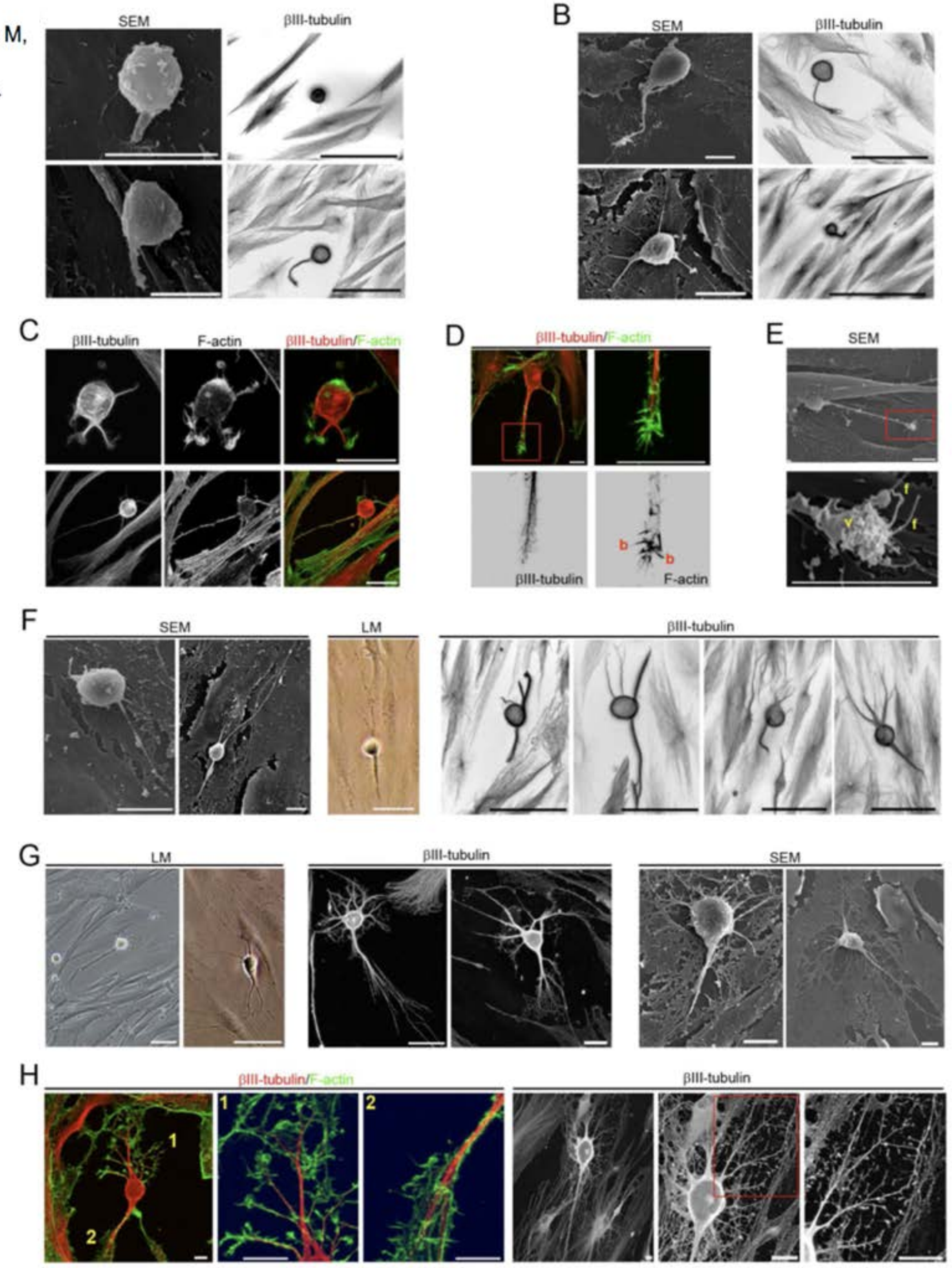
Cell Transplant. 2013;22(11):2017-28. doi: 10.3727/096368912X657305. Epub 2012 Oct 3.



[Human **Dental Pulp** Stem Cells and Gingival Mesenchymal Stem Cells Display Action Potential Capacity In Vitro after Neuronogenic Differentiation.]

Li D, Zou XY, El-Ayachi I, Romero LO, Yu Z, Iglesias-Linares A, Cordero-Morales JF, Huang GT.

Stem Cell Rev. 2018 Oct 15. doi: 10.1007/s12015-018-9854-5. [Epub ahead of print]



NEURONS DERIVED FROM DENTAL PULP OF DECIDUOUS TEETH

Cell Transplantation
Impact Factor: 3.2
5-Year Impact Factor: 3.4
Journal H
Free access | Research article | First published online November 1, 2013

Human Adult Periodontal Ligament-Derived Cells Integrate and Differentiate aft Mammalian Brain

Carlos Bueno, Carmina Ramirez, [...], and Salvador Martinez, Ph.D. +5 View all authors and affiliations

SCIENTIFIC REPORTS
natureresearch

OPEN **Non-proliferative neurogenesis in human periodontal ligament stem cells**

Carlos Bueno[1*], Marta Martinez-Morga[2] & Salvador Martinez[1]

scientific reports

OPEN **Differentiation of human adult-derived stem cells towards a neural lineage involves a dedifferentiation event prior to differentiation to neural phenotypes**

Carlos Bueno[1✉], Marta Martinez-Morga[2], David Garcia-Bernal[3], José M. Moraleda[3] & Salvador Martinez[1]

original article

Mesenchymal Stem Cells Improve Motor Functions and Decrease Neurodegeneration in Ataxic Mice

Jonathan Jones[1], Alicia Estirado[1], Carolina Redondo[1], Jesus Pacheco-Torres[1], Maria-Salomé Sirerol-Piquer[2,3], José M Garcia-Verdugo[2,3] and Salvador Martinez[1,4]

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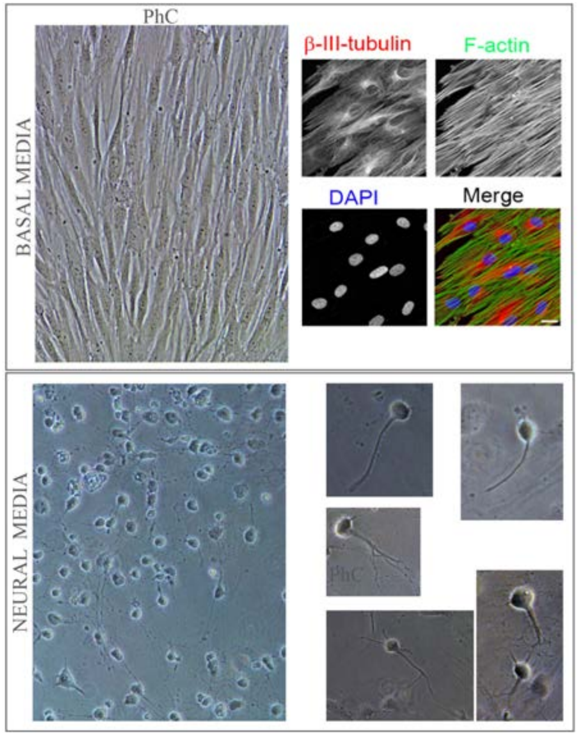
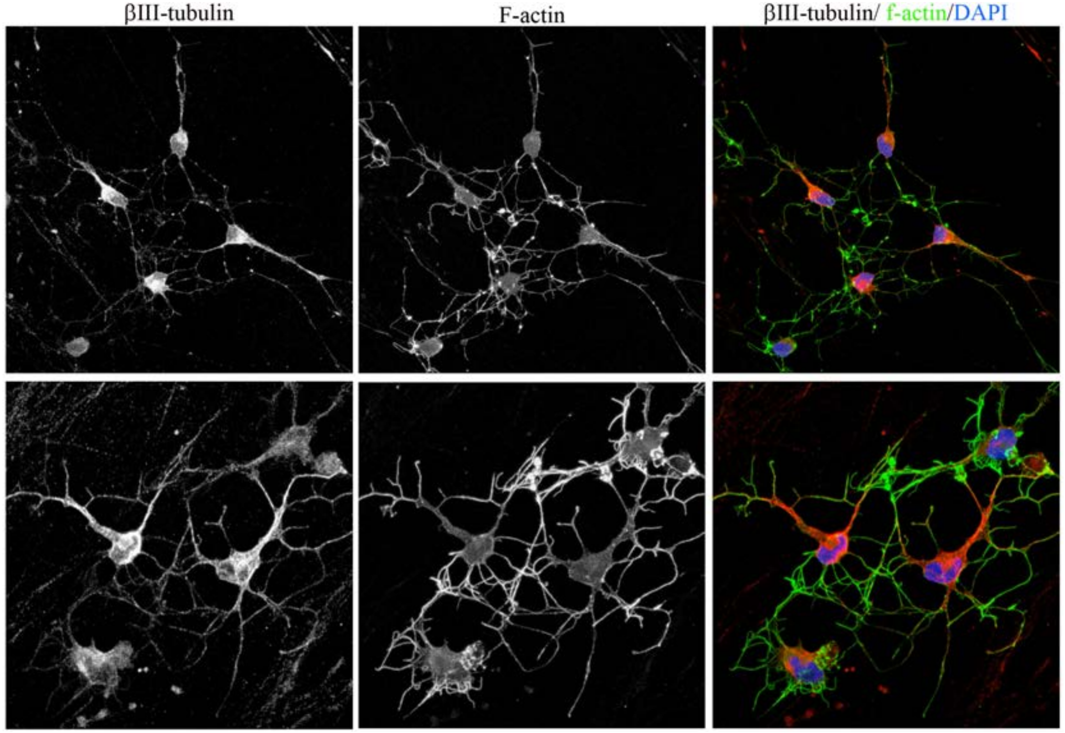
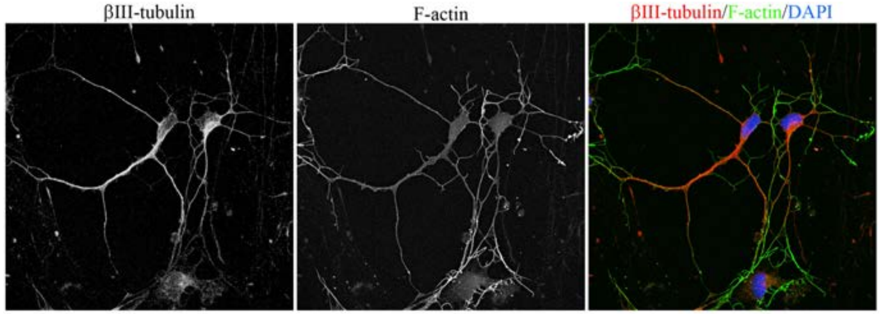
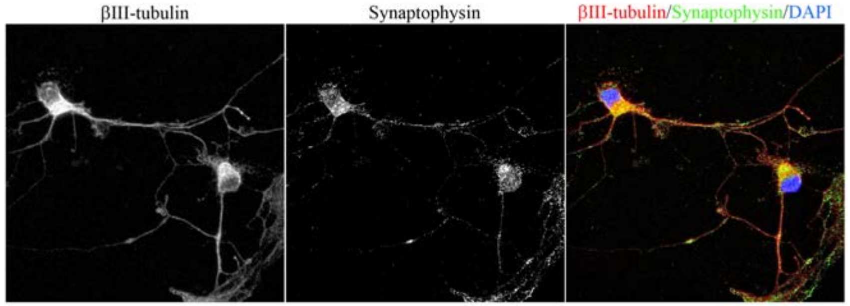
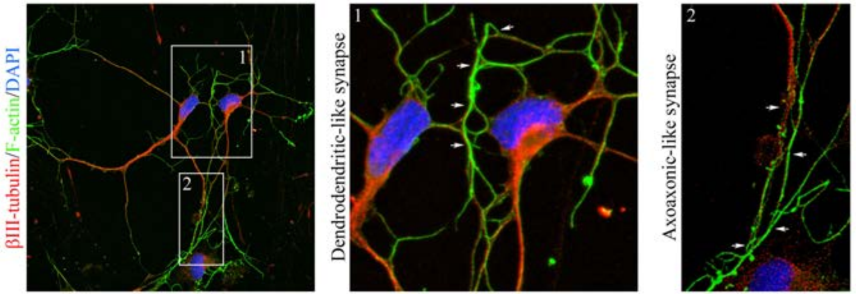
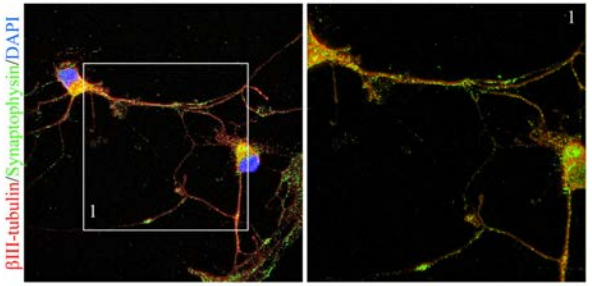




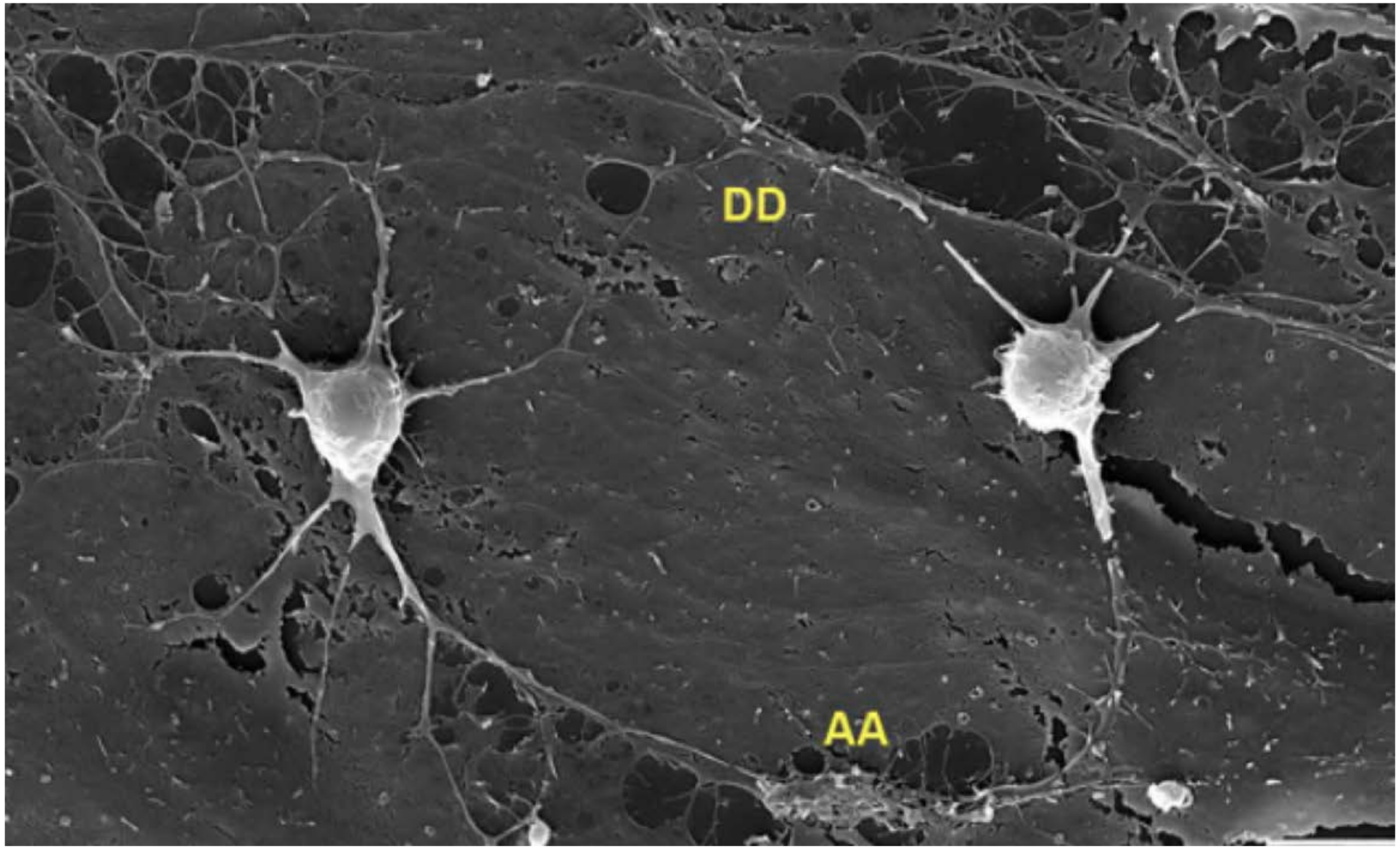








This approach allows us to obtain human neurons (from individuals with and without ASD) that establish synaptic connections and develop functional neural circuits.



RATONCITO PEREZ DE LAS ER

October 2024

193 potential donor families

Paciente	PATOLOGIA CLINICA	Estado actual
#6	Gen KMT5B	En cultivo tto
#13.1	diente procesado	contaminado
#25	TEA y síndrome Phelan-McDermid por mutación del gen SHANK-3	contaminado
#26	diente procesado	contaminado
#27	diente procesado	contaminado
#30	SINDROME de RETT	En cultivo tto
#31	SINDROME DE FEINGOLD (GEN MYCN)	En cultivo tto
#36	ADRENOLEUCODISTROFIA LIGADA A X	En cultivo tto
#39	TEA GRADO 2 celulas extraidas	Stock 3 viales
#42	Atrofia cerebelo congénita	En cultivo tto
#59	TEA	En cultivo tto
#82	Enfermedad congénita mutación del genSLC6A8 ligado al cromosoma X	En cultivo tto
#83	Síndrome de West sintomático con microcefalia	En cultivo tto
#91	TEA	En cultivo tto
#103	NO HALLAZGOS PATOLOGICOS	En cultivo tto
#107	Ceroidolipofuscinosis tipo 6	En cultivo tto
#113	TEA	contaminado
#123	MUTACION GEN GATAD2B	En cultivo tto
#130	TEA	contaminado
#131	TEA GRADO 1	En cultivo tto
#135	SINDROME DE RETT	En cultivo tto
#139	NO INFORME GENETICO	En cultivo tto
#148	Leucodistrofia metacromática- MLD	contaminado
#151	NO INFORME GENETICO	En cultivo tto

120 dientes con TEA

4 dientes con KMT5B
10 dientes con Rett
2 dientes con Nowat Wilson
2 dientes con AMSC1
2 dientes con KGB

Cromosomas

1 dientes con C17q11
1 diente con C8p23
1 diente con C16p11.2
……

Genes

3 diente con SHANK 3 (TEA)
1 diente con DNA H3
1 diente con SGC
1 diente con SLC6A8
1 diente con Med 13L
1 diente con CIRF2BPL
1 diente SNC8A
1 diente de GATA2B
…..

Síndromes con 1 diente

1 diente con Phelan-McDermid (SHANK3)
1 diente con Prader Willi
1 diente con Angelman
1 diente con X frágil
1 diente con 5p-
1 diente con Dandy Walker
1 diente con Moore
1 diente con Kleefast
1 diente con MLD
1 diente con X-ALD
1 diente con Tatton Brown-Rahman
1 diente con Dias Logan
1 diente con West
1 diente con muerte súbita
1 diente con HIBICH
1 diente con NEDAMSS
1 diente con A. Webber
1 diente con Webber Wolf
1 diente con Ondine
1 diente con Med13l
1 diente con Pitt Hopkings
1 diente con HDC (GPC3)
1 diente con CAPOS/CAOS (ATP1A3)
1 diente con atrofia Cerebelosa
2 dientes con mutación en SLC6A1
….

Controles: sanos y hermanos no diagnosticados

OUR STABLISHED CELL BANC: 23 SAMPLES HAVE DERIVED CELLS

VI CONGRESO INTERNACIONAL DE AUTISMO EN MURCIA

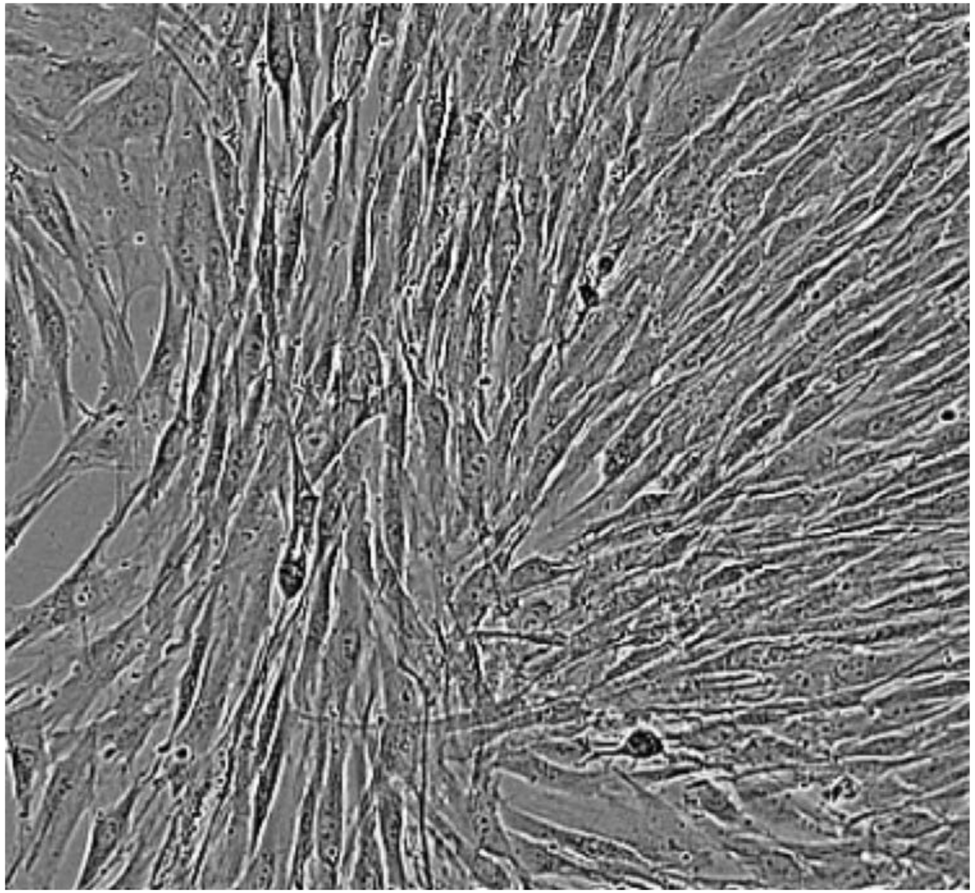
"INCLUSIÓN EN LAS PERSONAS CON AUTISMO: PRÁCTICAS BASADAS EN LA EVIDENCIA"

BANCO DE CELULAS LP RATONCITO PEREZ				
# Muestra	Nº pase	Fecha congelacion	Nº viales en N2L	Patologia
#39	1	5/7/2024	1	TEA grado 2
#39	1	25/7/2024	2	
#142	1	08/11/2024	1	Síndrome de microdeleción 15q24
#142	1	11/11/2024	2	
#148	1	27/11/2024	2	Leucodistrofia Metacromática
#148				
#31	1	05/12/24	3	Sindrome de Feingold
#31	2	12/12/2024	3	
#Control	1	02/12/2024	4	control sano 9 años
	2	9/12/2024	2	
	1	11/4/2025	3	control sano 12 años
#91	1	12/12/2024	2	Sindrome Mowat-Wilson
	2	20/12/2024	2	
#143	1	16/12/2024	2	Sindrome Tatton-Brown GenDNMT3A
	2	20/12/2024	2	
#129	1	20/12/2024	2	Distrofia muscular congenita gen LAMA2
	2	13/1/2025	2	
#154	1	16/01/2025	3	Gen SLC6A8 Deficiencia del transportador de creatina
	2	20/1/2025	2	
# 164	1	03/02/2025	2	Sindrome Rett
#157	1	06/02/2025	3	Gen ANKRD11.C Sindrome KBG
	2	12/2/2025	2	
# 1	1	19/02/2025	3	Sindrome microduplicacion 15q11-q13
	2	24/2/2025	2	
# 97	1	10/02/2025	5	Sindrome Mowat-Wilson
	2	17/2/2025	2	
# 42	1	14/03/2025	2	Atrofia cerebelo congénita
	2	18/3/2025	3	
#178	1	10/06/2025	1	Gen IRF2BPL
	2	26/6/2025	2	
#86		creciendo		Asociacion española Sindrome KBG
#181	1	10/06/2025	1	
	2	26/6/2025	2	
#175	1	27/05/2025	4	Sindrome Mowat-Wilson
#94	1	27/05/2025	4	Asociacion española Sindrome KBG
#150	1	20/06/2025	1	TEA
#103		creciendo		
#179		creciendo		
#135	1	13/06/2025	3	RETT
	2	17/6/2025	2	
#189		CRECIENDO		

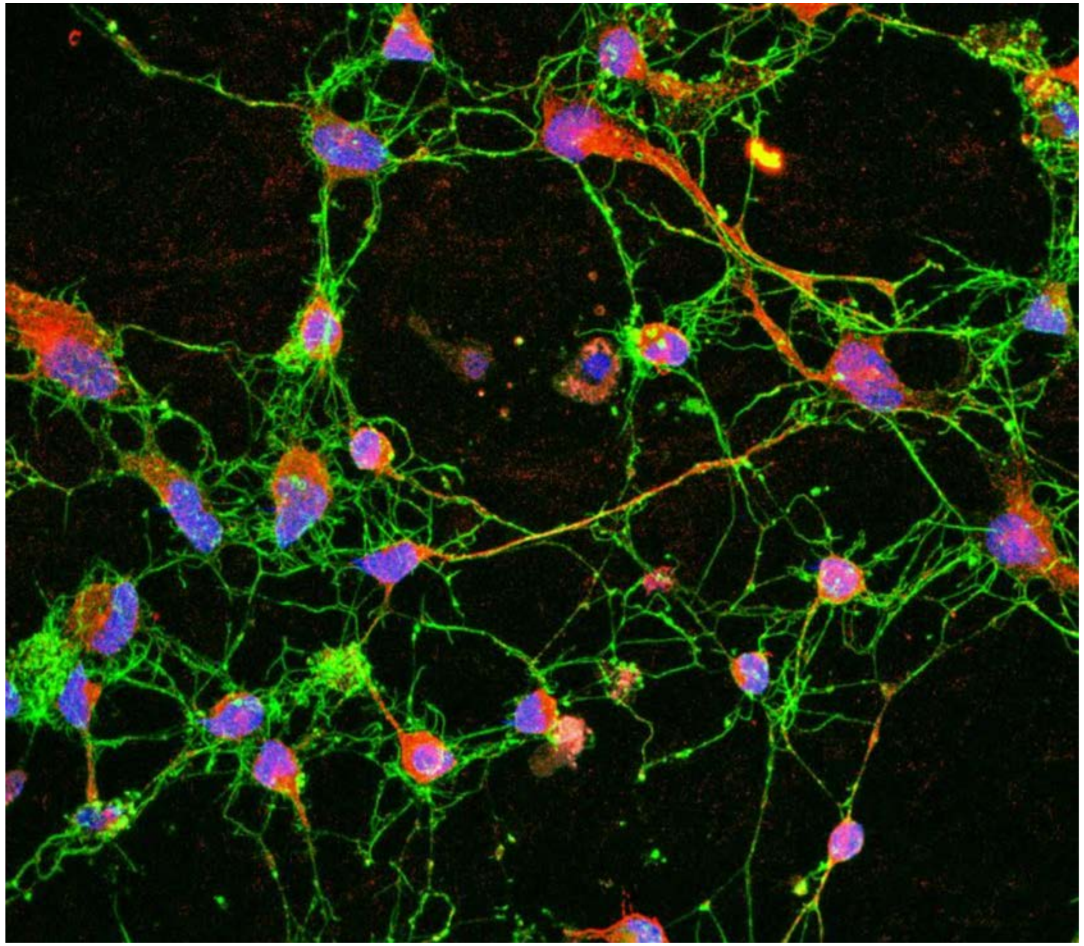
193 posibles donantes

32 casos se han conseguido aislar celulas

Banco de células



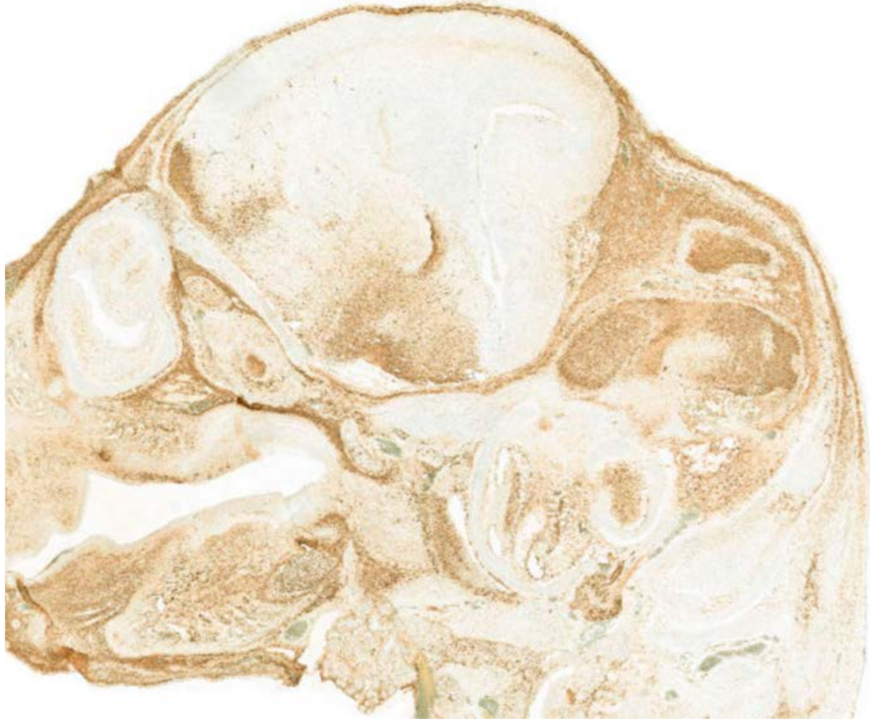
DERIVED NEURONS FROM ONE SAMPLE OF
SLEC6A1 PROJECT



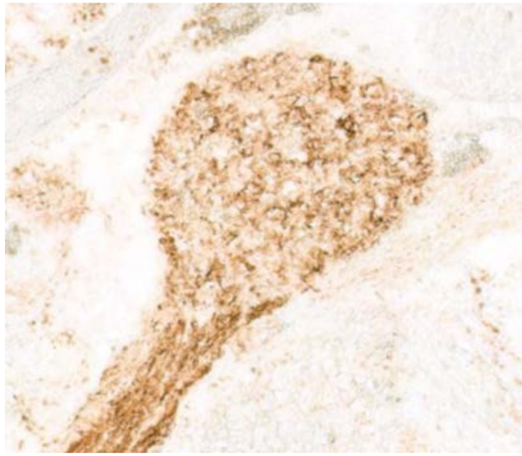
Why can we expect that neurons derived from dental pulp cell cultures will express SLC6A1?

GENSAT GENE EXPRESSION NERVOUS SYSTEM ATLAS

Expression of Slc6a1



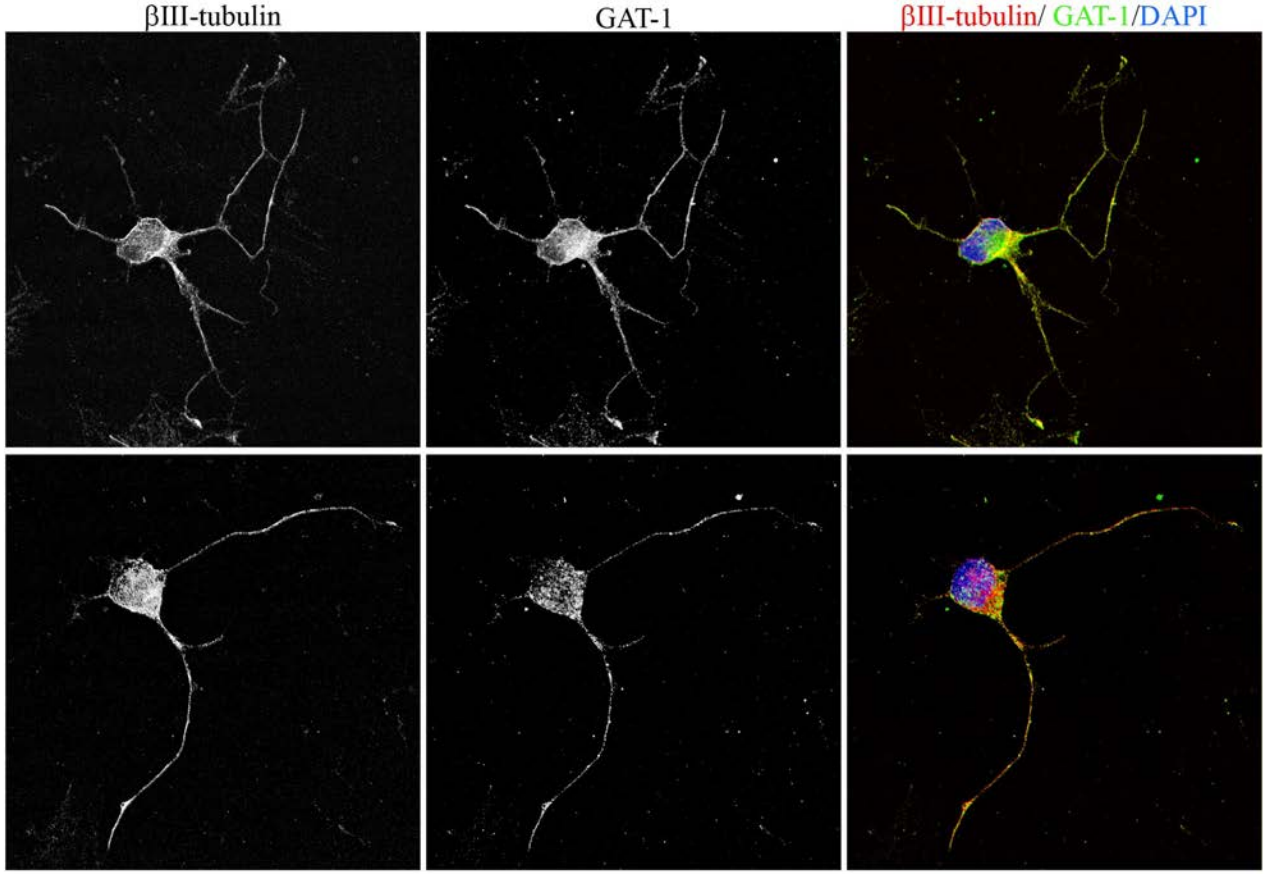
Sensory neurons

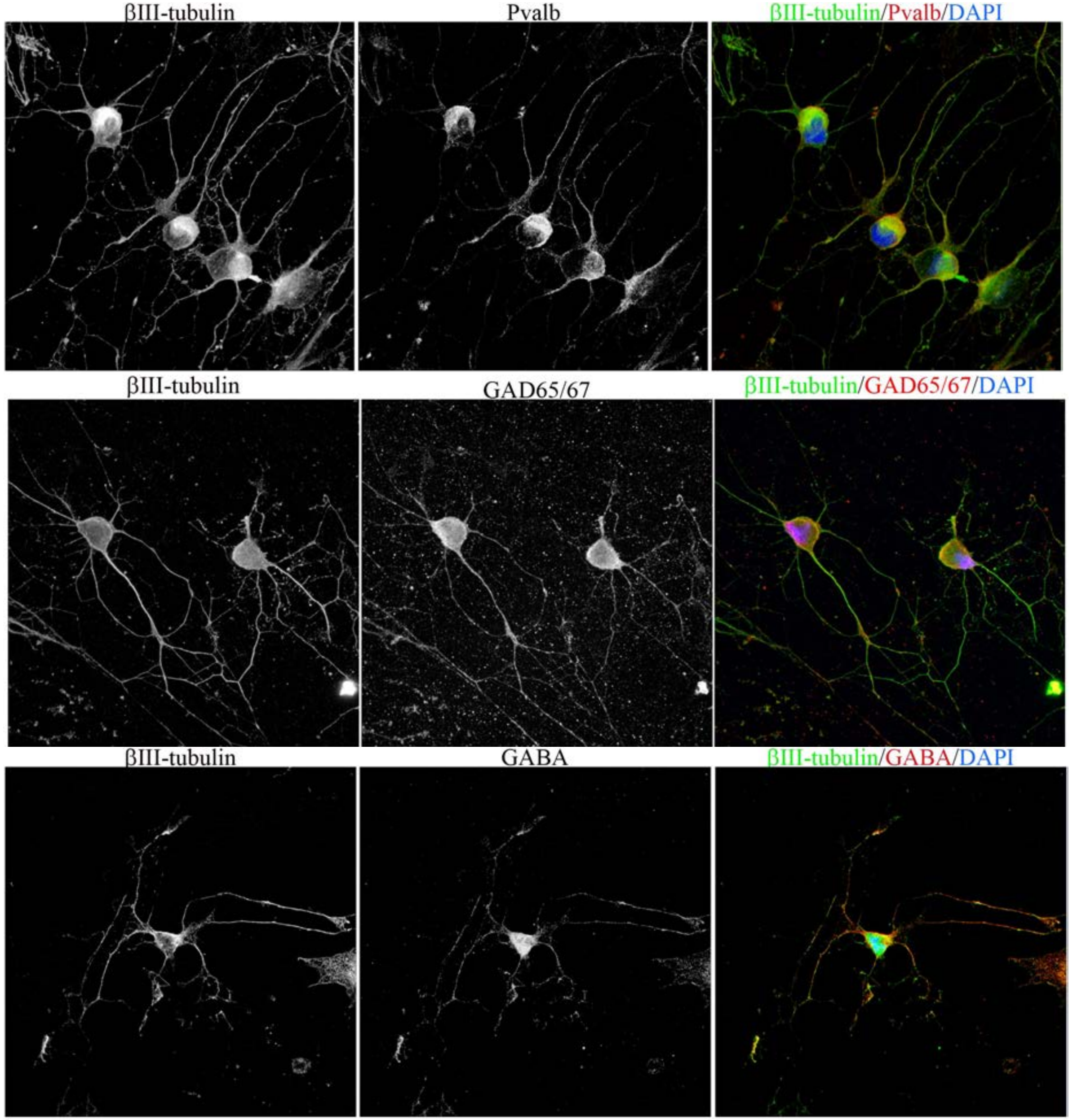


Dental Pulp cells

Novak B, Schulten R, Lübbert H. 2011 *revealed by RT-PCR the expression of GAT-1 and GAT-3, DRG sensory neurons cultures.*

GABAergic neurons from Fairy Theeth

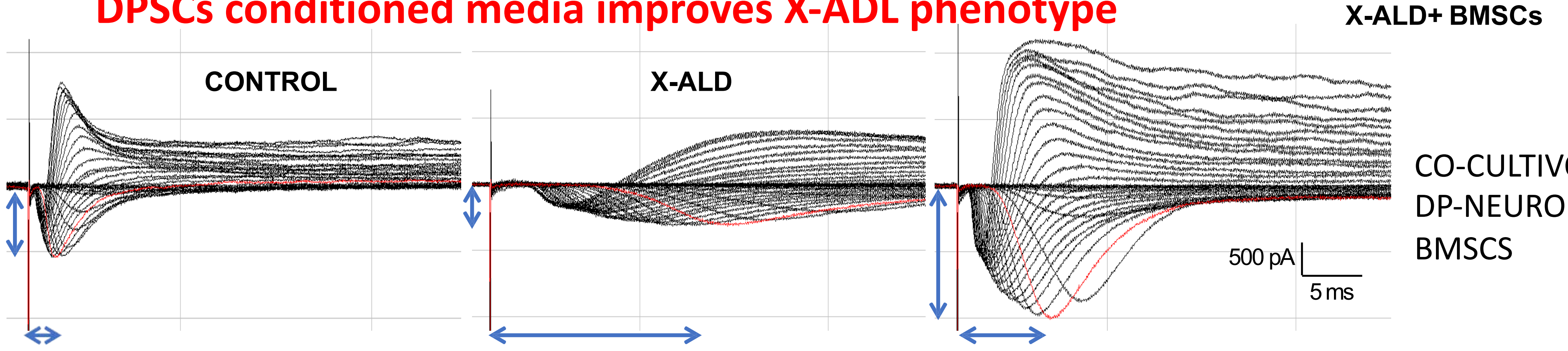




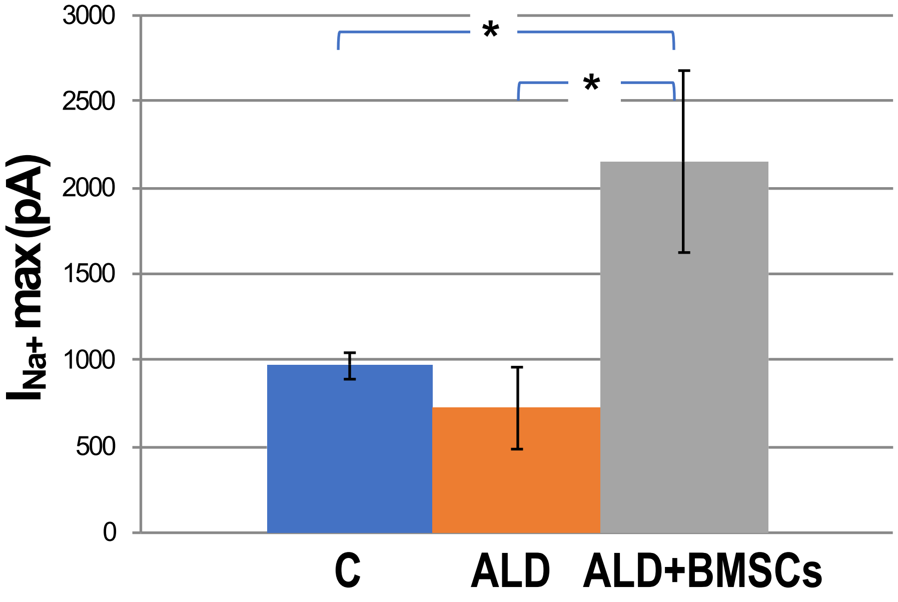
Co-culture with BMSCs increases maximum sodium currents and reduces time to peak.

IN VITRO THERAPEUTIC STUDIES

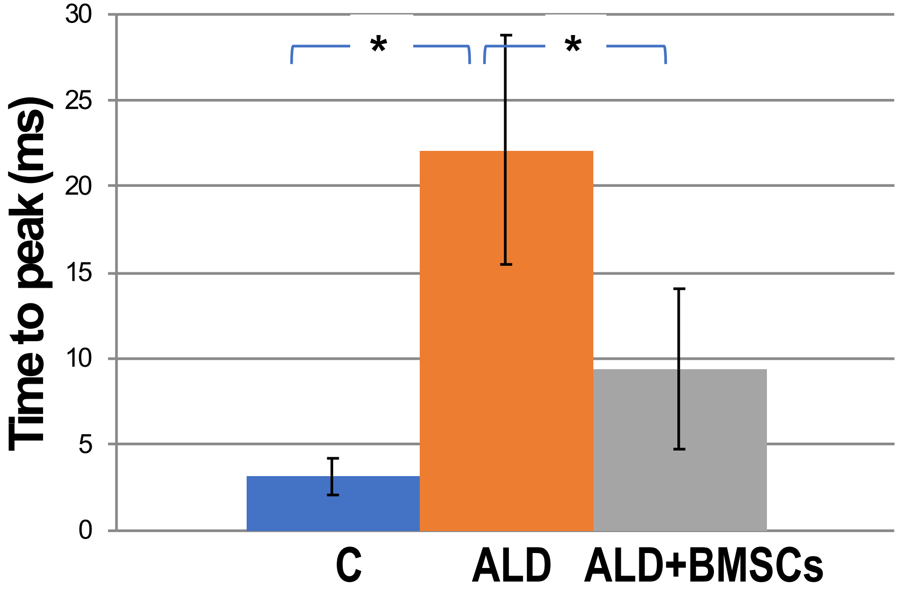
DPSCs conditioned media improves X-ADL phenotype



CO-CULTIVO:
DP-NEURONS
BMSCS



(N=3-6; p<0,05)



Gene expression analysis results

Development of the neural and brain tube:
EN1, EN2

Structure and function of the synapse:
SIRT1, SHANK, RORA, GAD1, SYNGAP, NR3C1, CD42

Cellular metabolism and control of cellular activity:
miRNA123

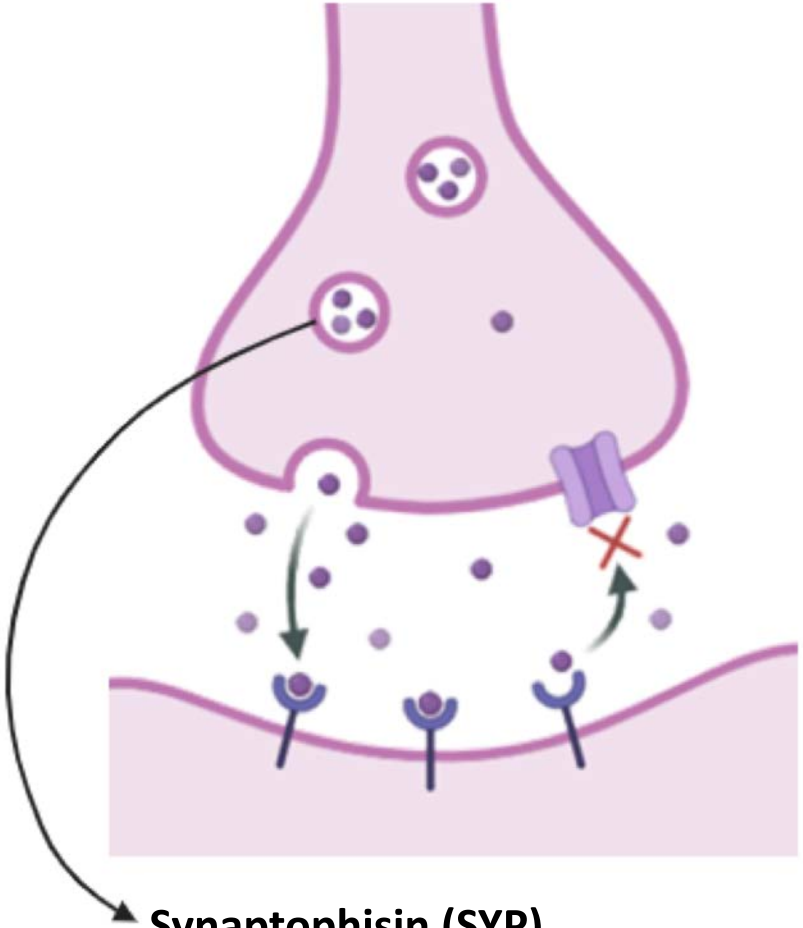
Microtubule stabilization:
CDC42

		EN1	NESTIN	MeCP2	SHANK3	SIRT1	GAD1	CASP3
LP	Prolif.	LPC < LPA (p<0,001)	LPC > LPA (p<0,037)	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)	ND	LPC > LPA (p<0,001)	LPC < LPA (p=0,002)
	Difer.	LPC > LPA (p<0,026)	LPC < LPA (p<0,001)	LPC < LPA (p<0,020)	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)	ND	LPC < LPA (p<0,001)
PD	Prolif.	X	ND	PDC < PDA (p=0,001)	PDC < PDA (p<0,015)	ND	LPC < LPA (p<0,015)	PDC < PDA (p<0,001)
	Difer.	X	PDC > PDA (p<0,001)	PDC < PDA (p<0,001)	PDC < PDA (p<0,001)	PDC < PDA (p<0,001)	X	PDC < PDA (p<0,001)

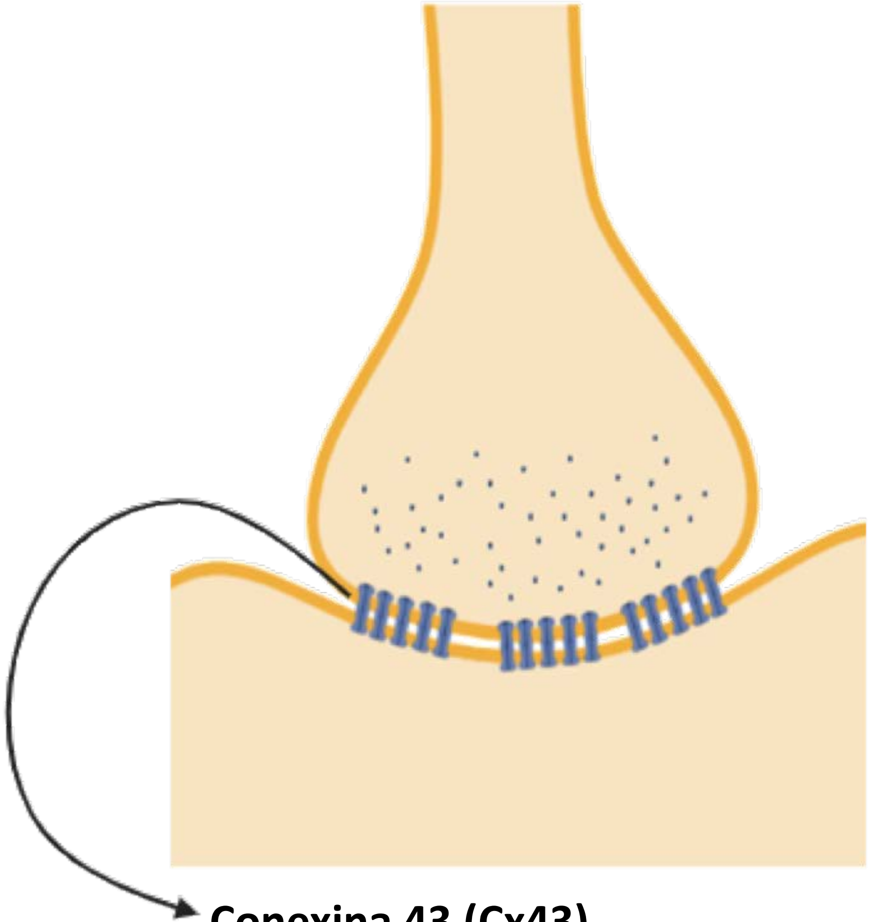
		MIKI67	SHANK2	RORA	RHOA	RAC1	BDNF	SYNGAP1
LP	Prolif.	LPC > LPA (p<0,001)	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)	LPC < LPA (p<0,012)	ND	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)
	Difer.	LPC > LPA (p<0,001)	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)	LPC < LPA (p<0,048)	ND	ND	LPC < LPA (p<0,002)
PD	Prolif.	PDC > PDA (p<0,001)	PDC > PDA (p<0,001)	ND	ND	PDC < PDA (p<0,001)	PDC < PDA (p<0,001)	PDC < PDA (p<0,002)
	Difer.	PDC > PDA (p<0,001)	PDC < PDA (p<0,001)	PDC < PDA (p<0,001)	ND	PDC < PDA (p<0,001)	PDC < PDA (p<0,017)	PDC < PDA (p<0,001)

		NR3C1	CDC42	CC2D1A	MBD3	RELN	NTRK2	MiRNA123
LP	Prolif.	LPC < LPA (p<0,001)	LPC < LPA (p<0,033)	LPC < LPA (p<0,001)	ND	LPC > LPA (p<0,001)	ND	LPC > LPA (p<0,001)
	Difer.	LPC < LPA (p<0,001)	LPC < LPA (p<0,002)	LPC < LPA (p<0,001)	LPC < LPA (p<0,001)	X	LPC > LPA (p<0,001)	LPC < LPA (p<0,001)
PD	Prolif.	PDC < PDA (p<0,001)	PDC > PDA (p<0,001)	ND	PDC > PDA (p<0,027)	X	PDC > PDA (p<0,001)	ND
	Difer.	ND	PDC < PDA (p=0,001)	PDC < PDA (p<0,001)	LPC < LPA (p<0,001)	X	PDC < PDA (p<0,008)	LPC < LPA (p<0,001)

Protein detection study results

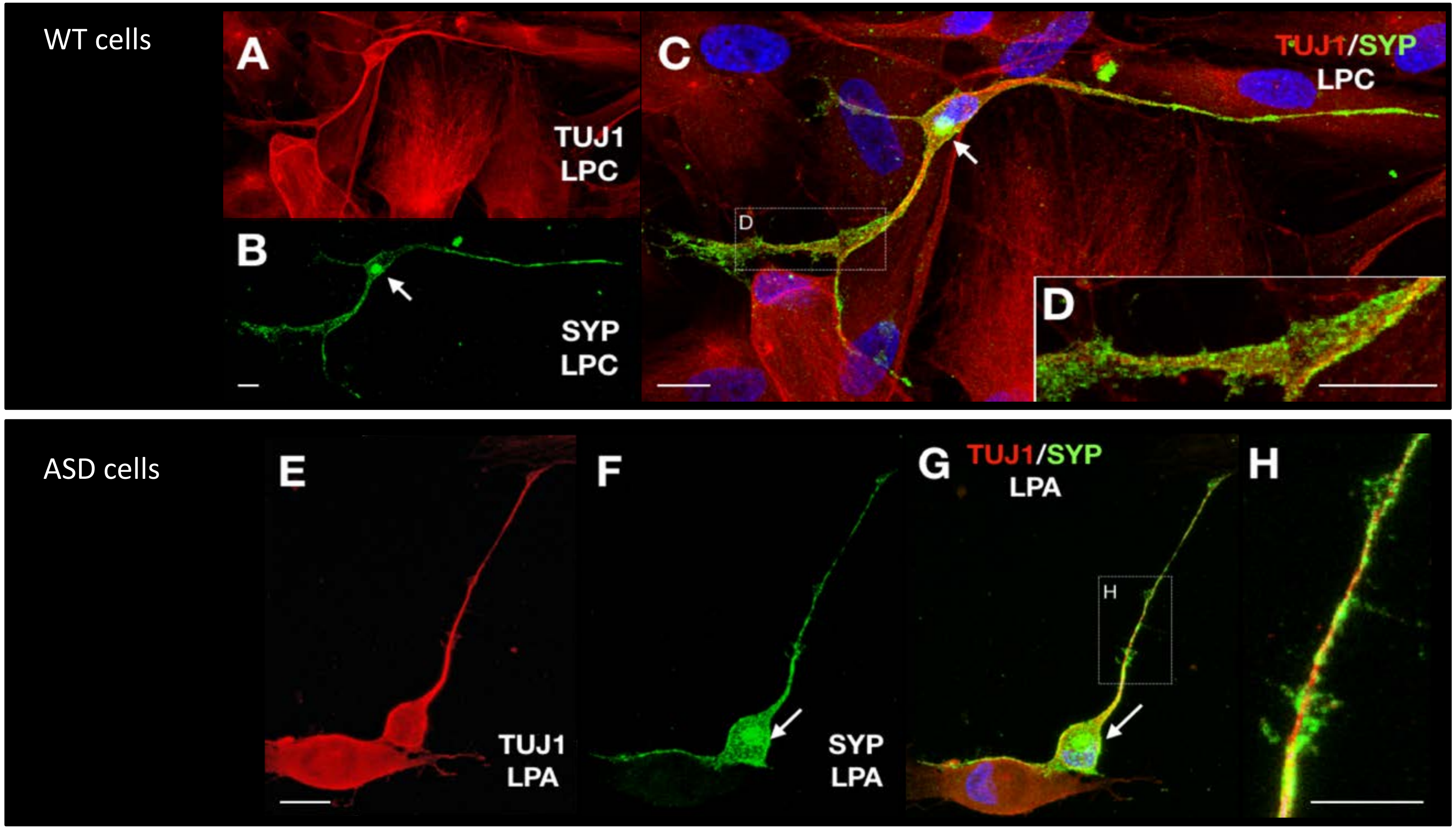


Synaptophisin (SYP)

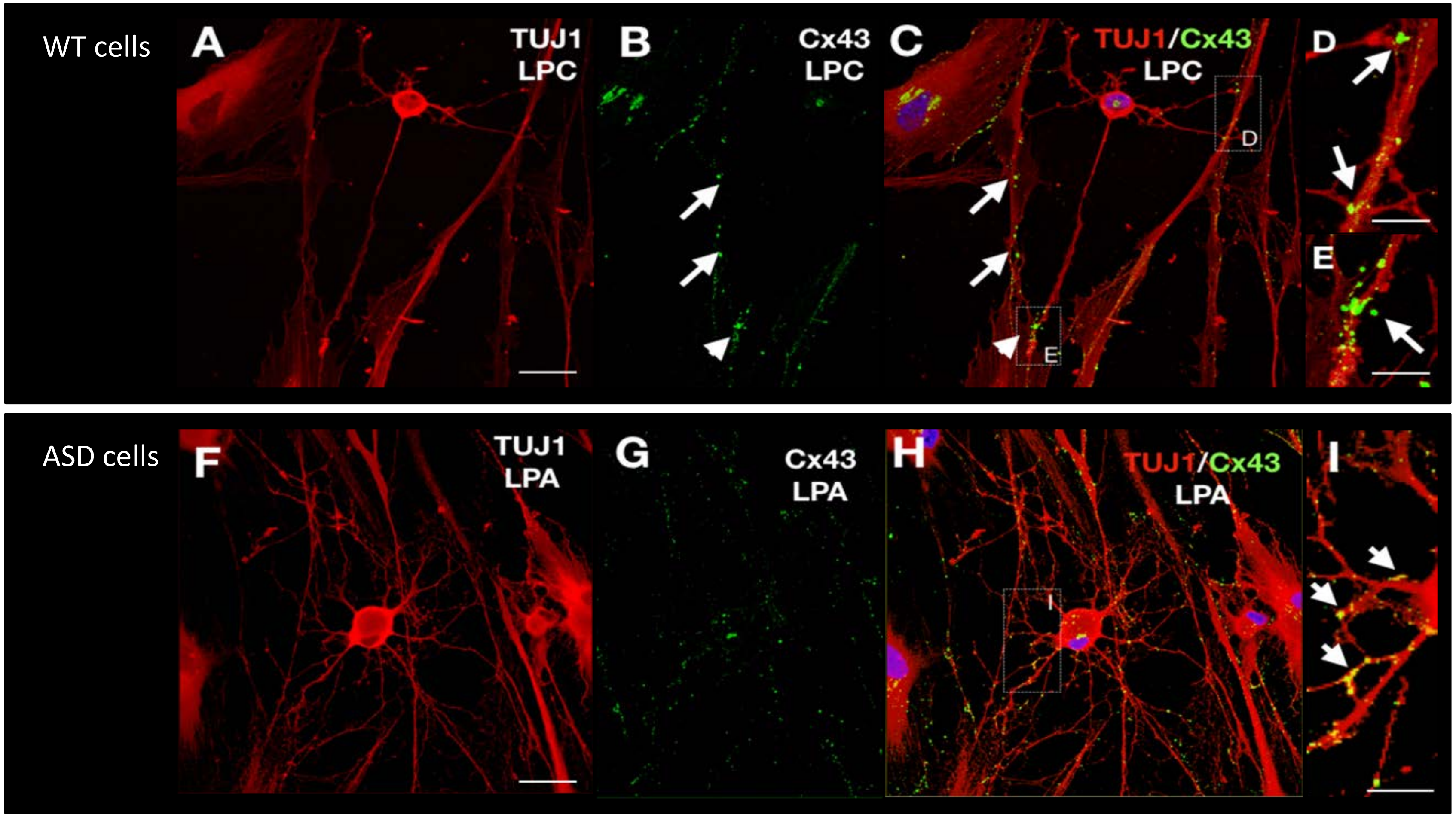


Conexina 43 (Cx43)

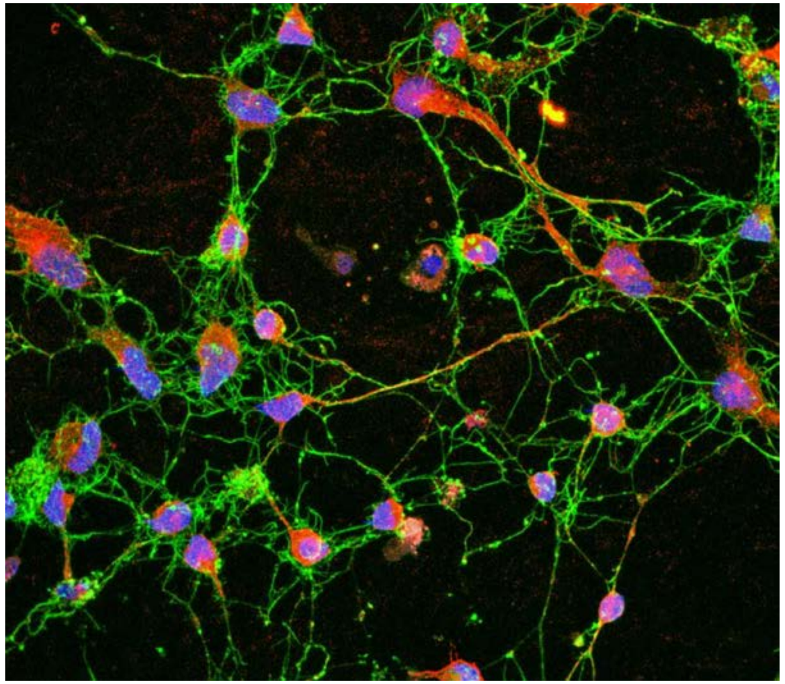
Tuj1 · Núcleos · **Sinaptofisina (SYP)**

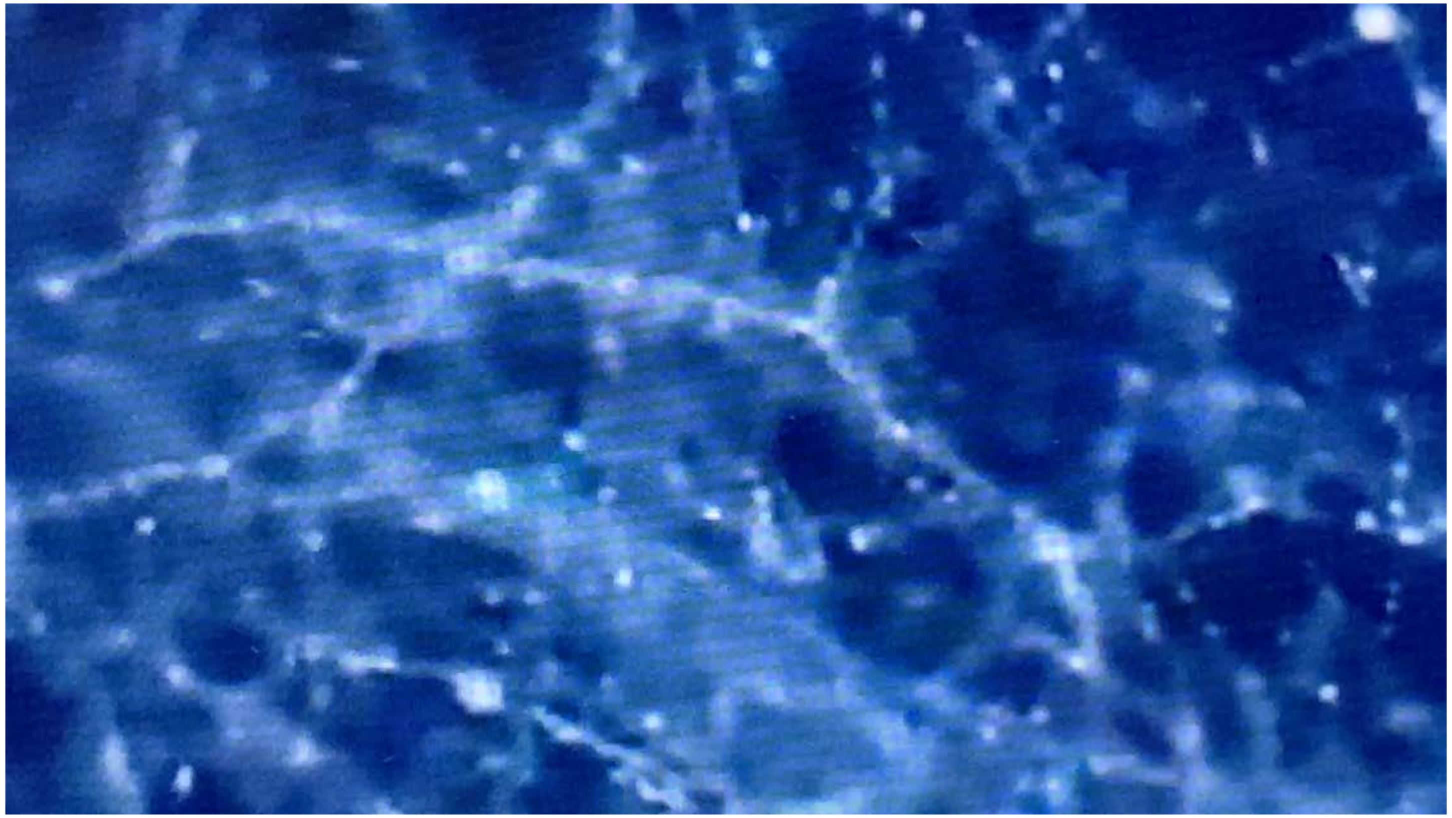


Tuj1 Nucleos **Conexina 43 (Cx43)**



Neuronal activity revealed through free calcium fluorescence imaging





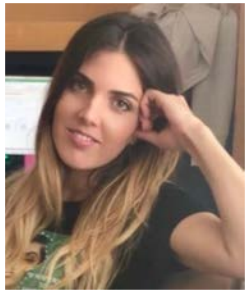
Proyecto "Ratoncito Pérez" de las enfermedades genéticas poco frecuentes

Terav+

Terav ISCIII
Red Española de Terapias Avanzadas - TerCel
GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

WALK ON PROJECT

C. Perez



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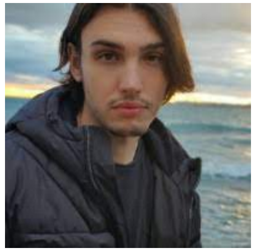
MP Quesada

C. Redondo

P. Cruz



T. Almenar

C. Medina

SEVENTH FRAMEWORK PROGRAMME

FEDER

ASOGAF

The amazing lab team