Modeling autism spectrum disorders with mini-brains

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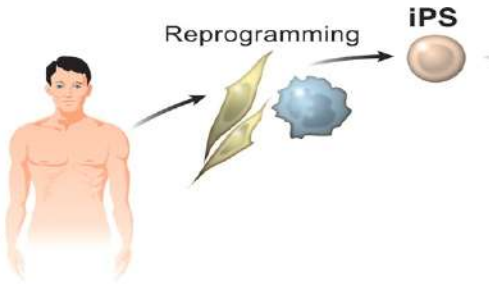
Autism in a dish



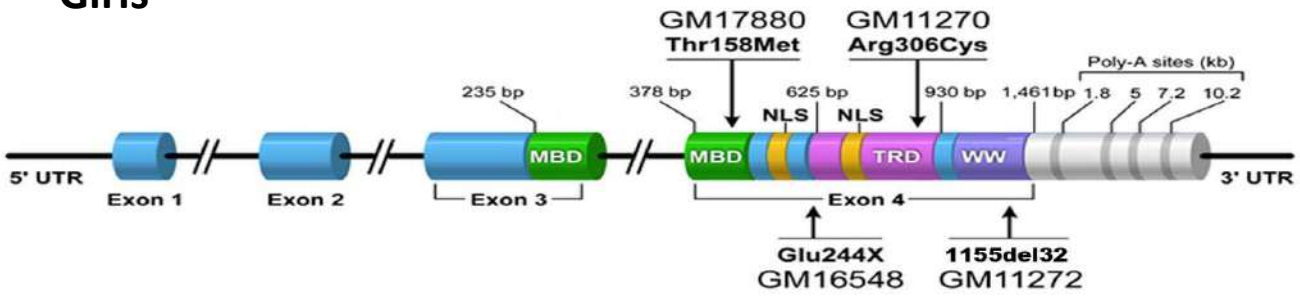
Marchetto *et al*, 2010

MeCP2 mutants

(X-LINKED GENE)

Rett Syndrome (RTT)

Girls

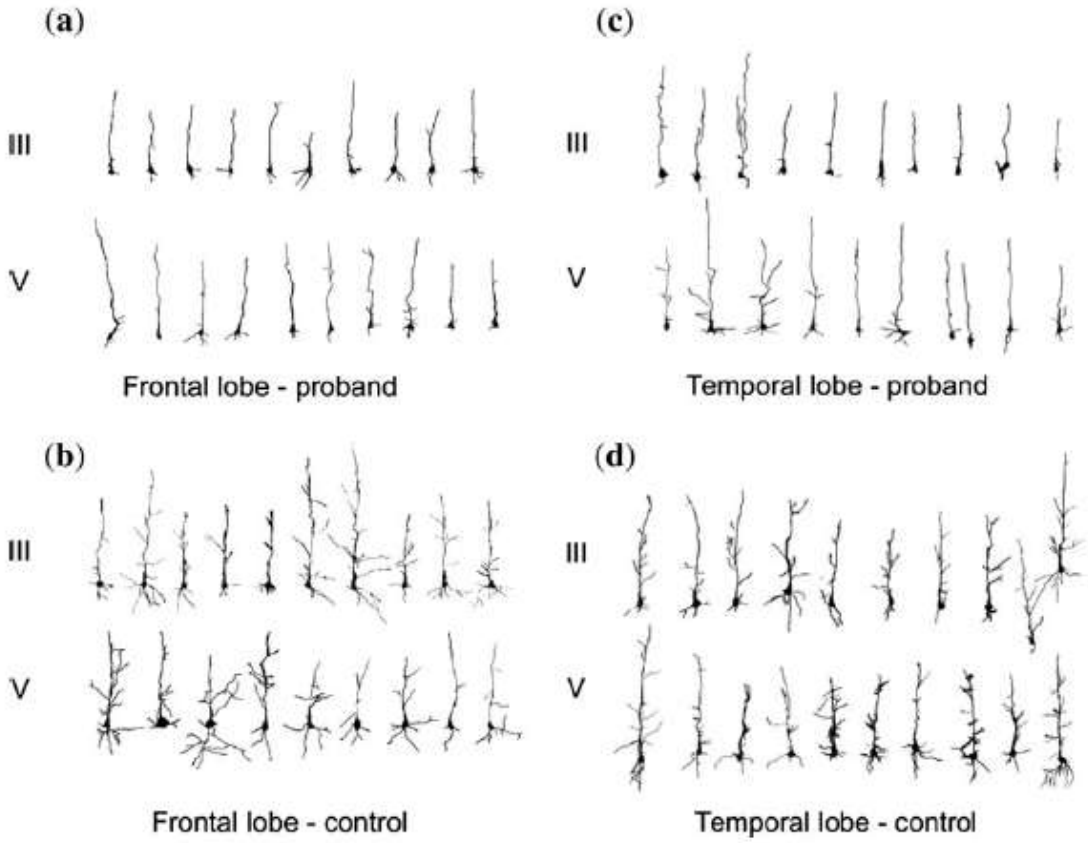


Boys

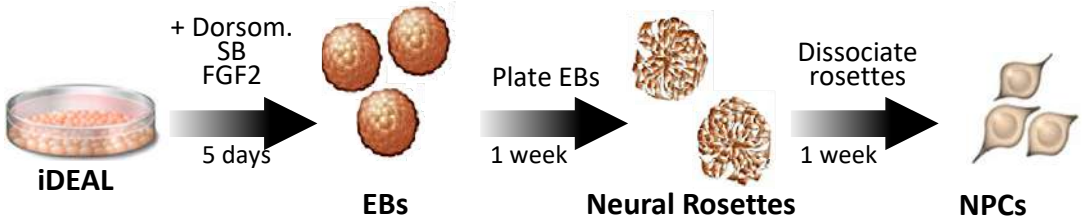
Postmortem brain tissues

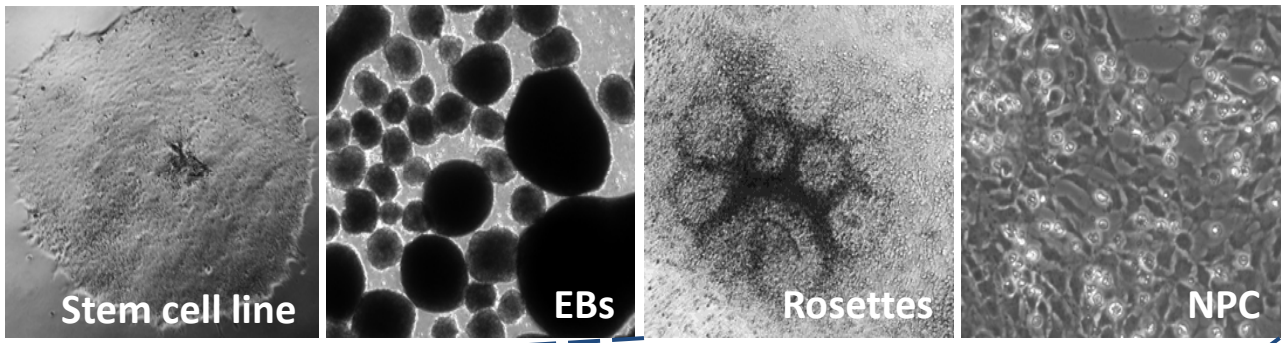
Schüle et al.

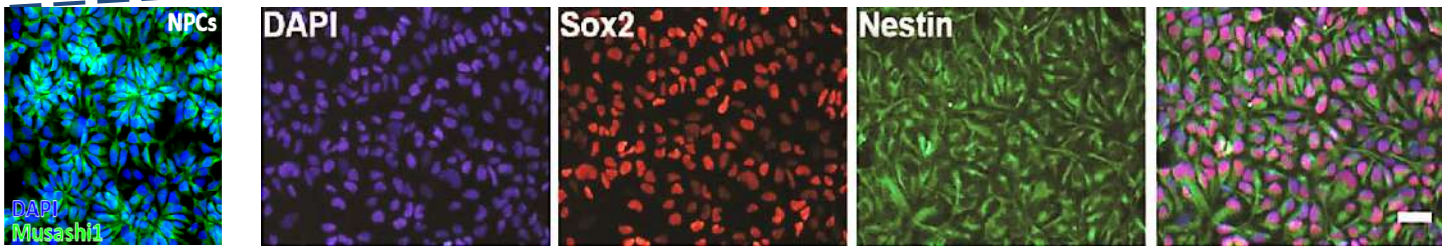
MECP2 null mutations in males



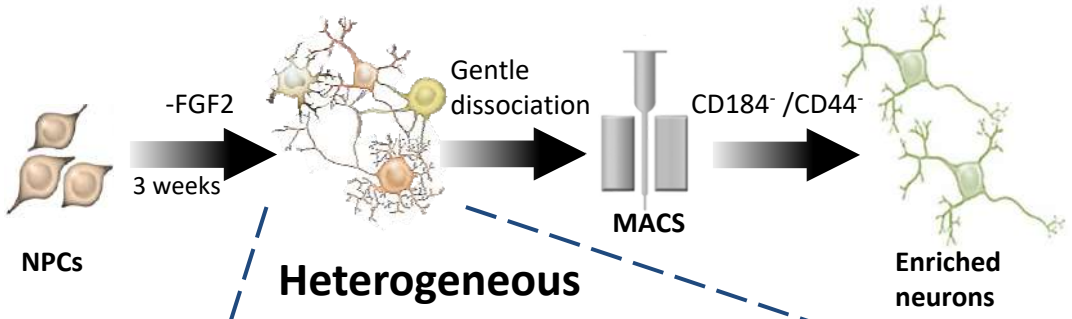
Neural Progenitor Cell (NPC) Production

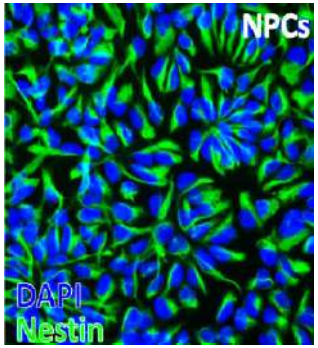


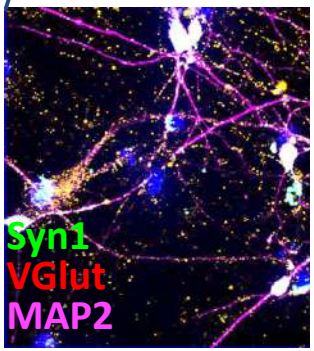


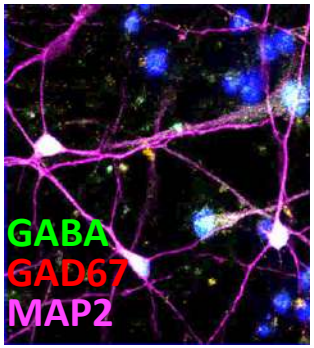


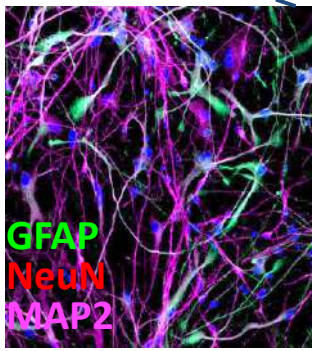
Neuron Differentiation

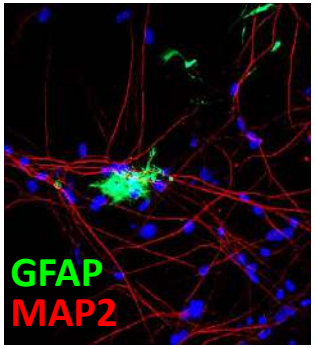




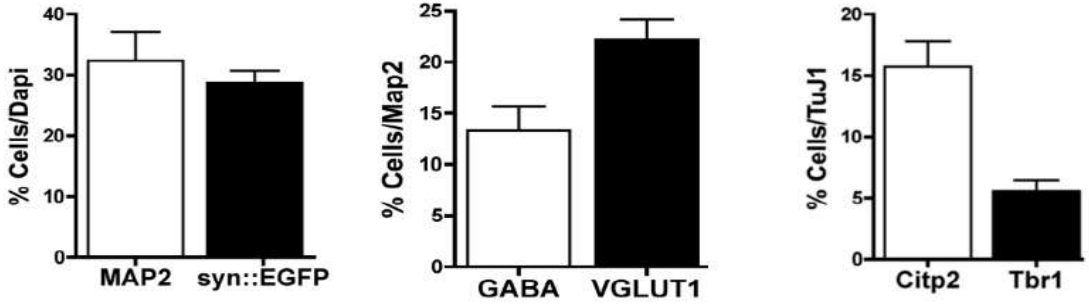






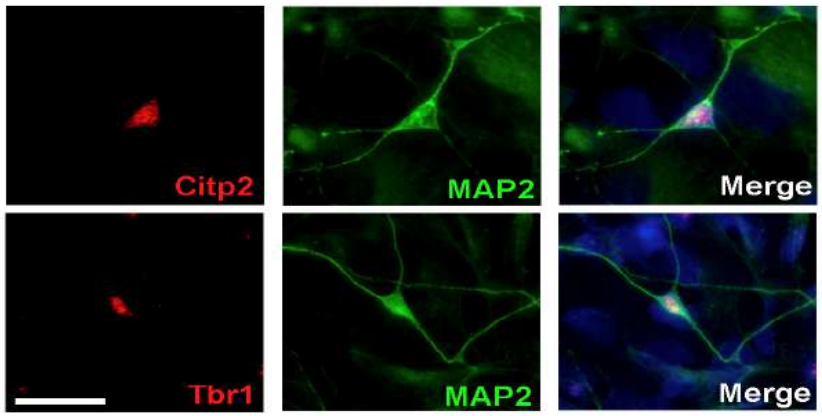


iPSC-derived cortical neurons



Layers V, VI

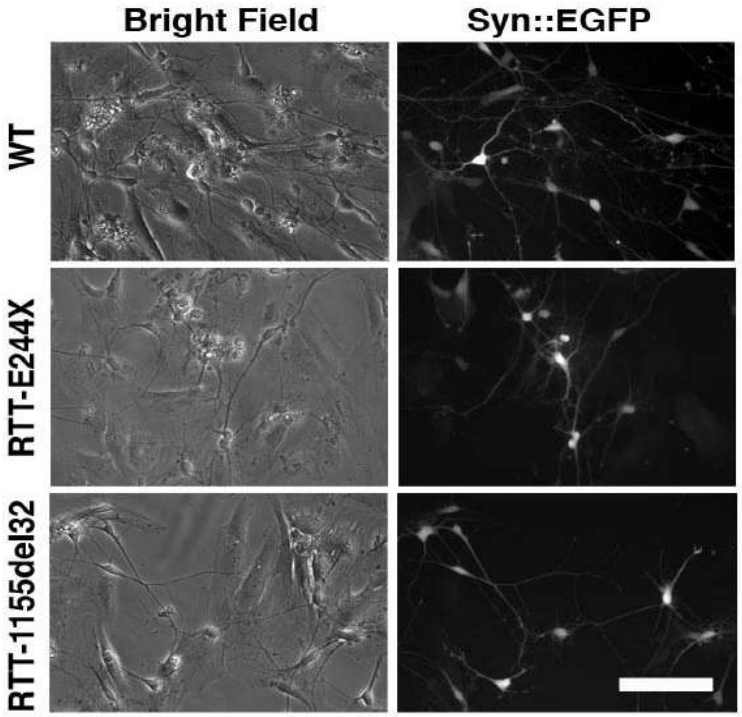
Layers I, IV

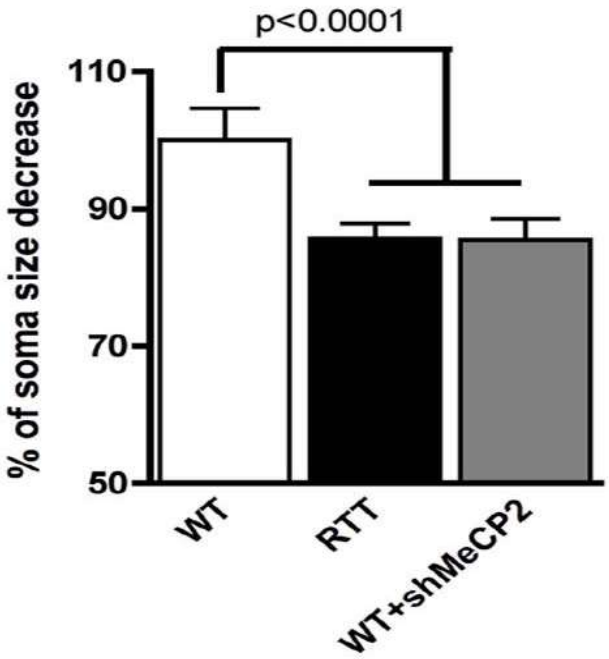


*Expression of Peripherin and En1 (midbrain) were not detected.

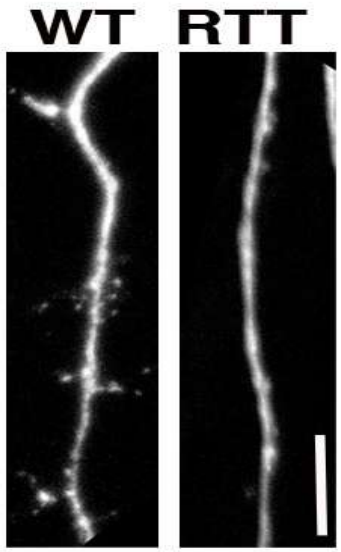
Carol

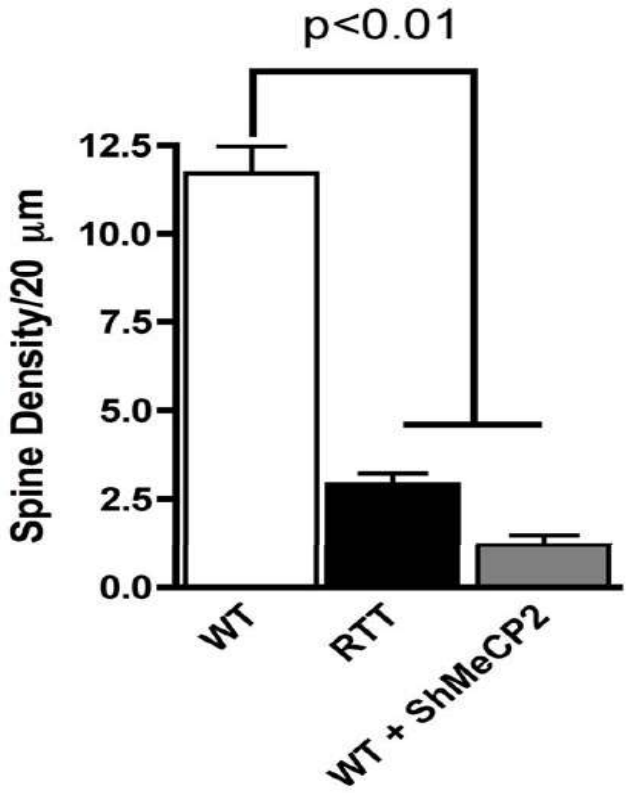
RTT neurons have smaller cell neuronal soma



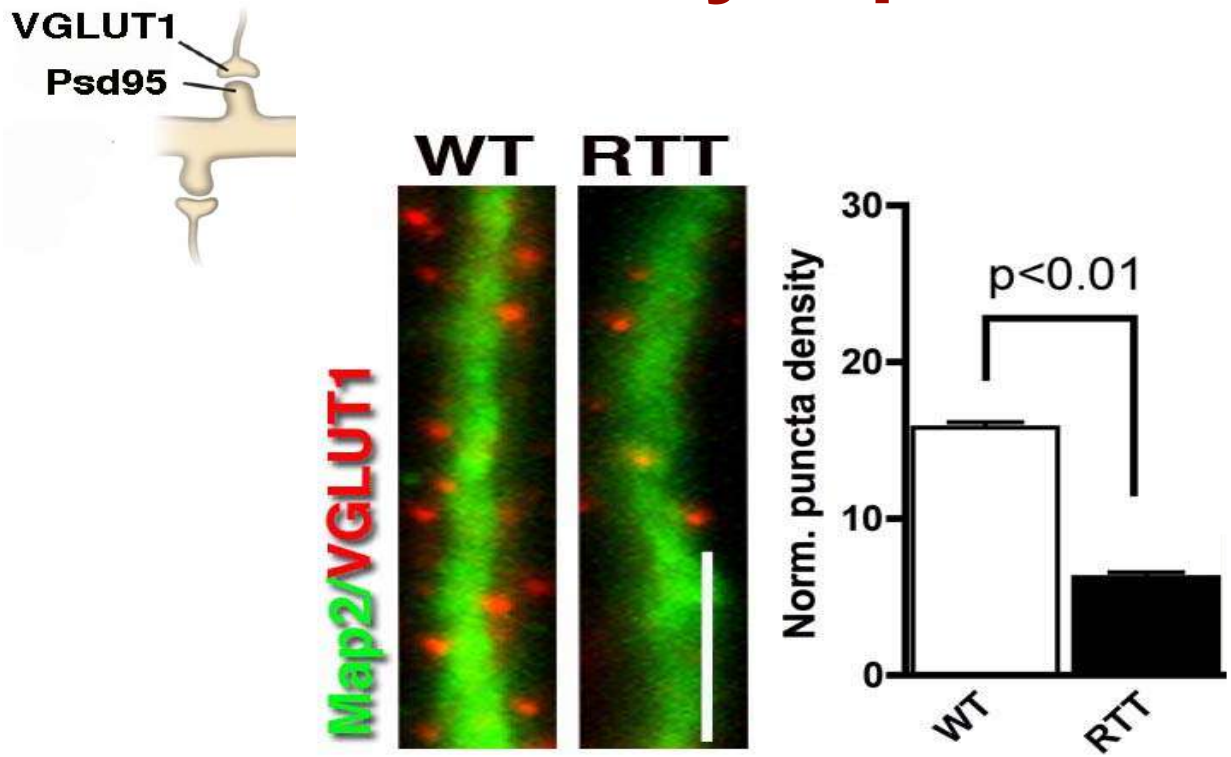


RTT neurons have lower spine density

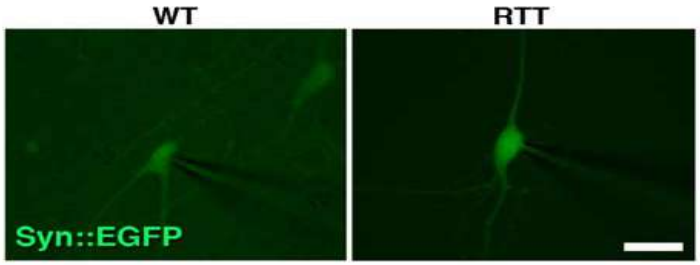


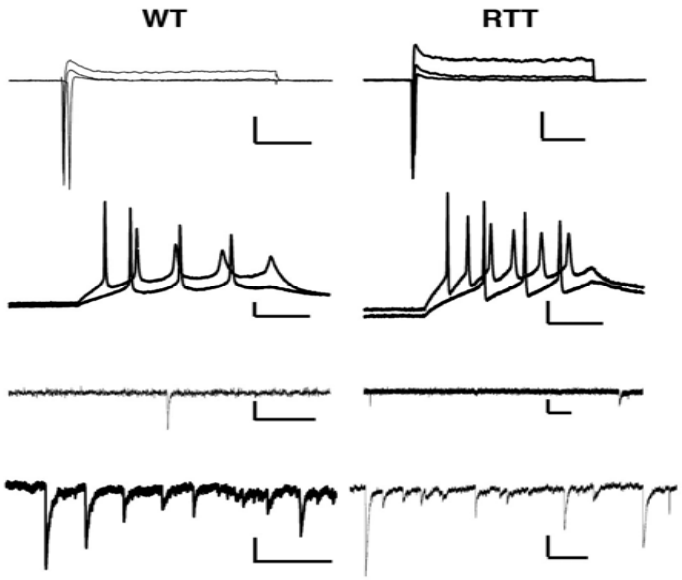


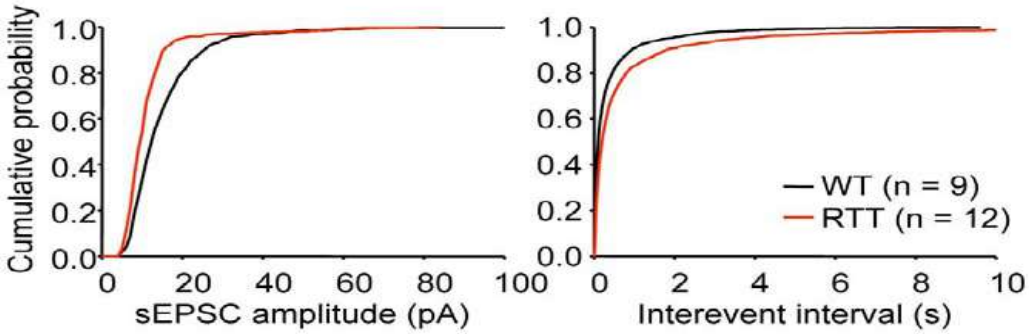
RTT neurons have fewer glutamatergic synapses

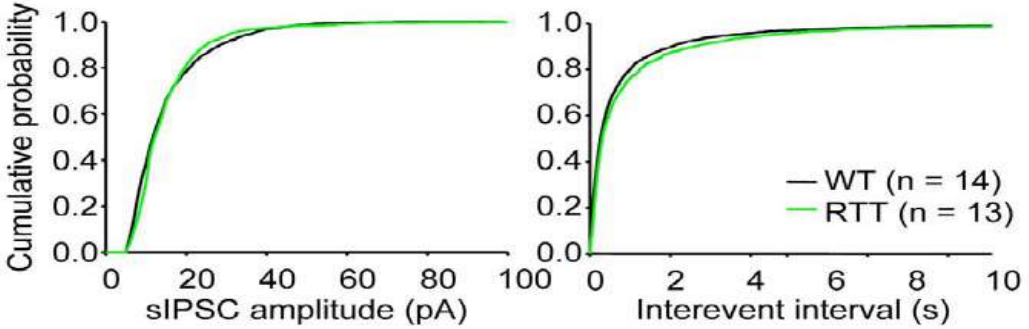


Decrease frequency of spontaneous postsynaptic currents in RTT neurons





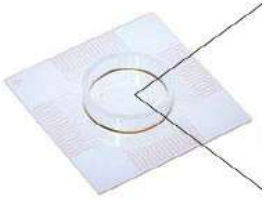


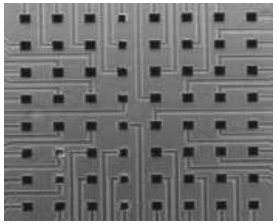


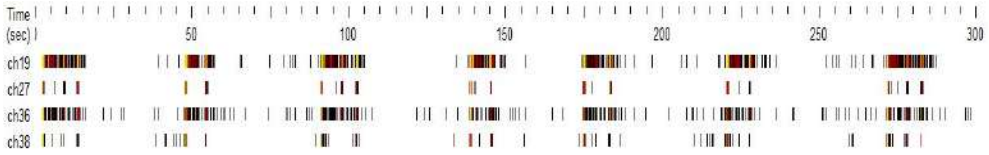
Gong Chen

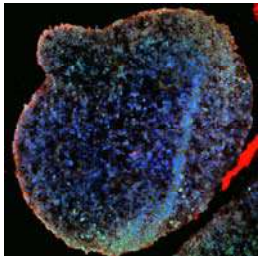
RTT neuronal networks are not synchronized

Cassiano

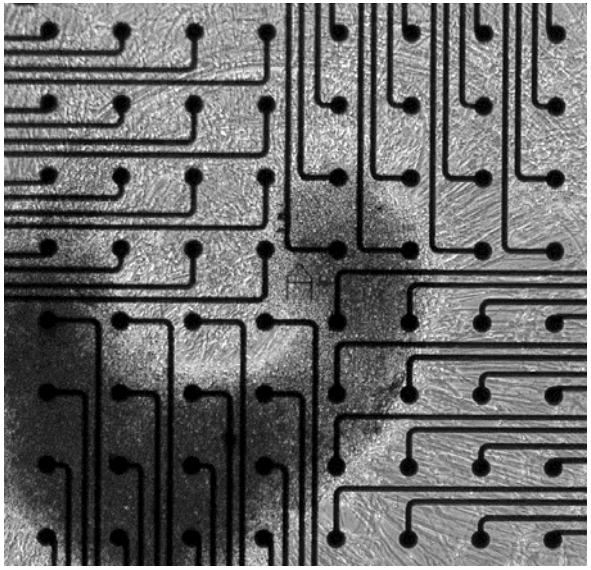


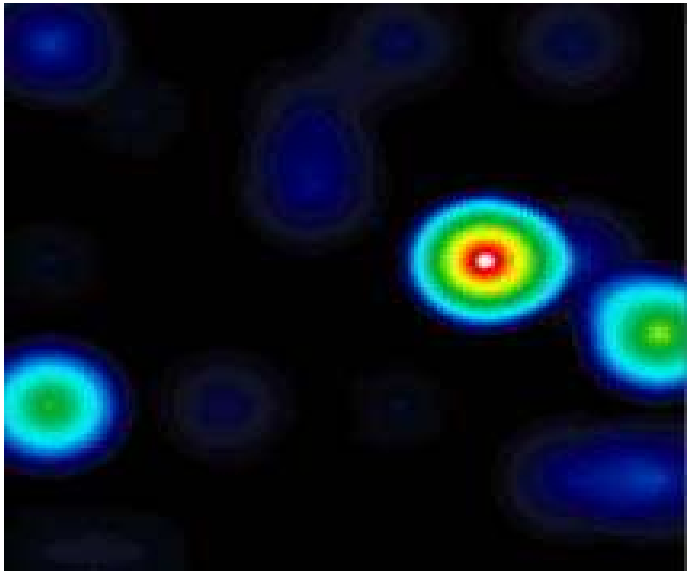






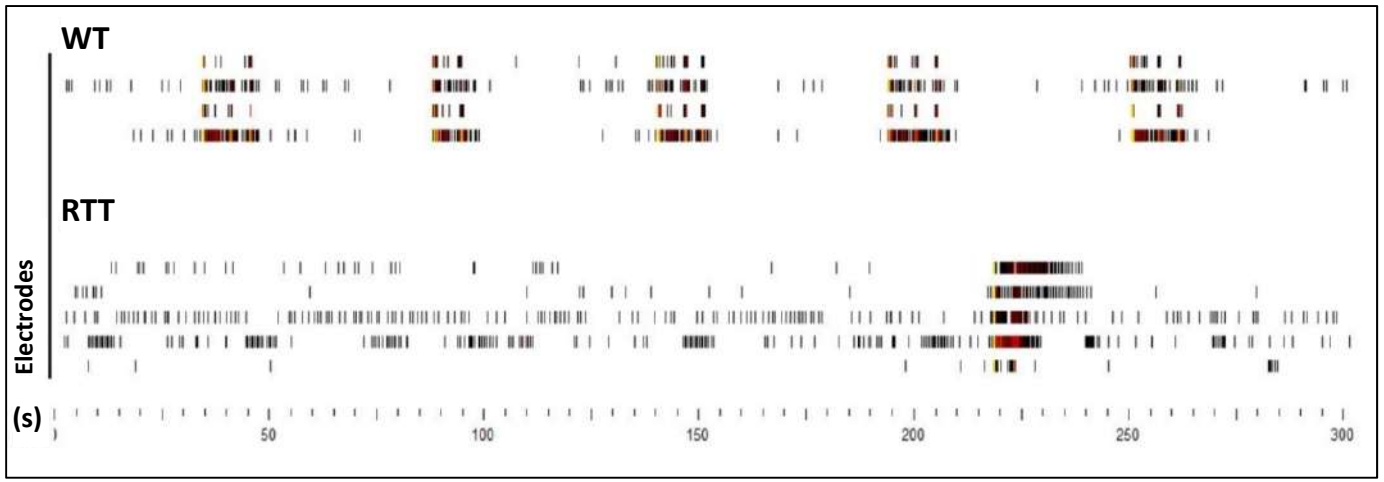
3D corticoids

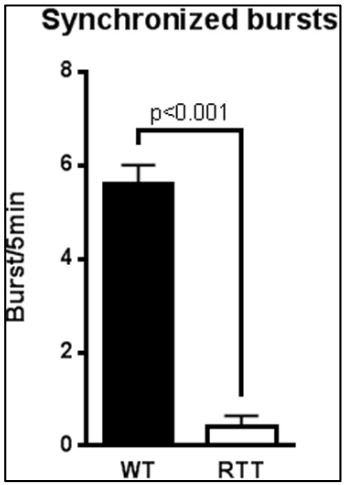




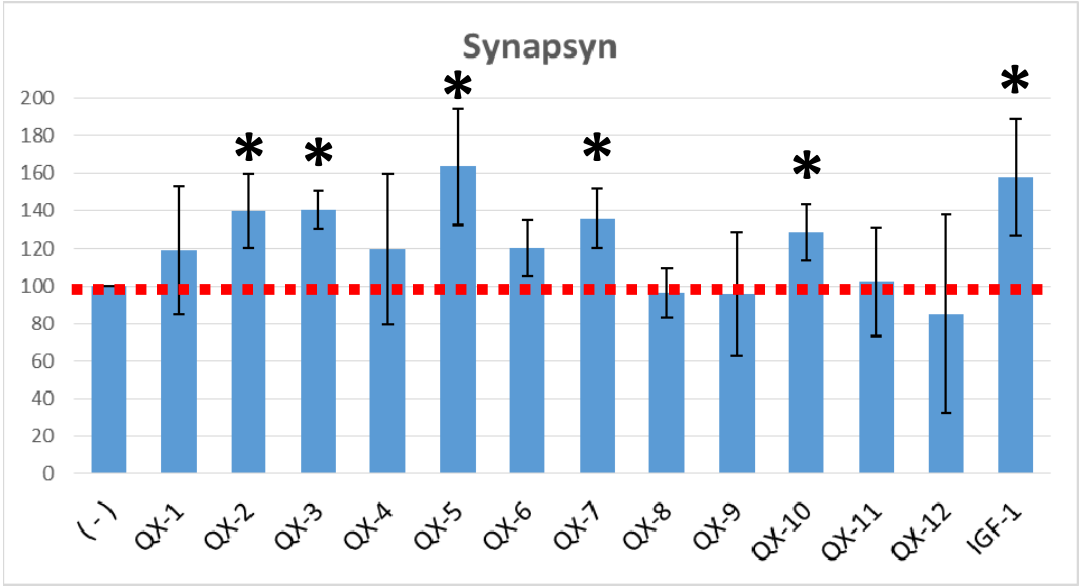
Activity Map

RTT neuronal networks are not synchronized

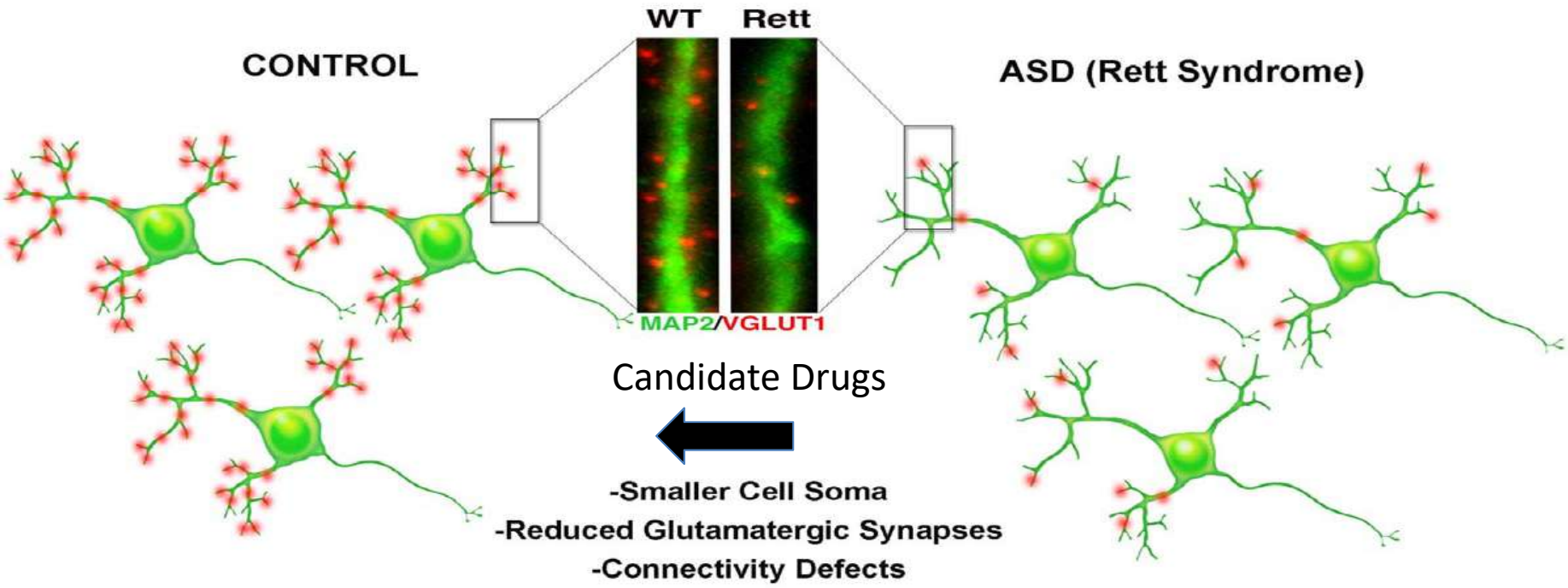




Repurposing drugs for RTT

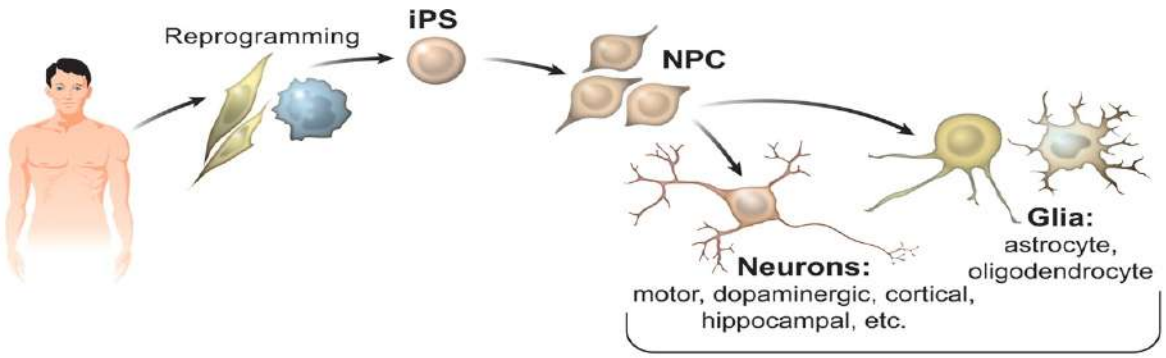


Summary

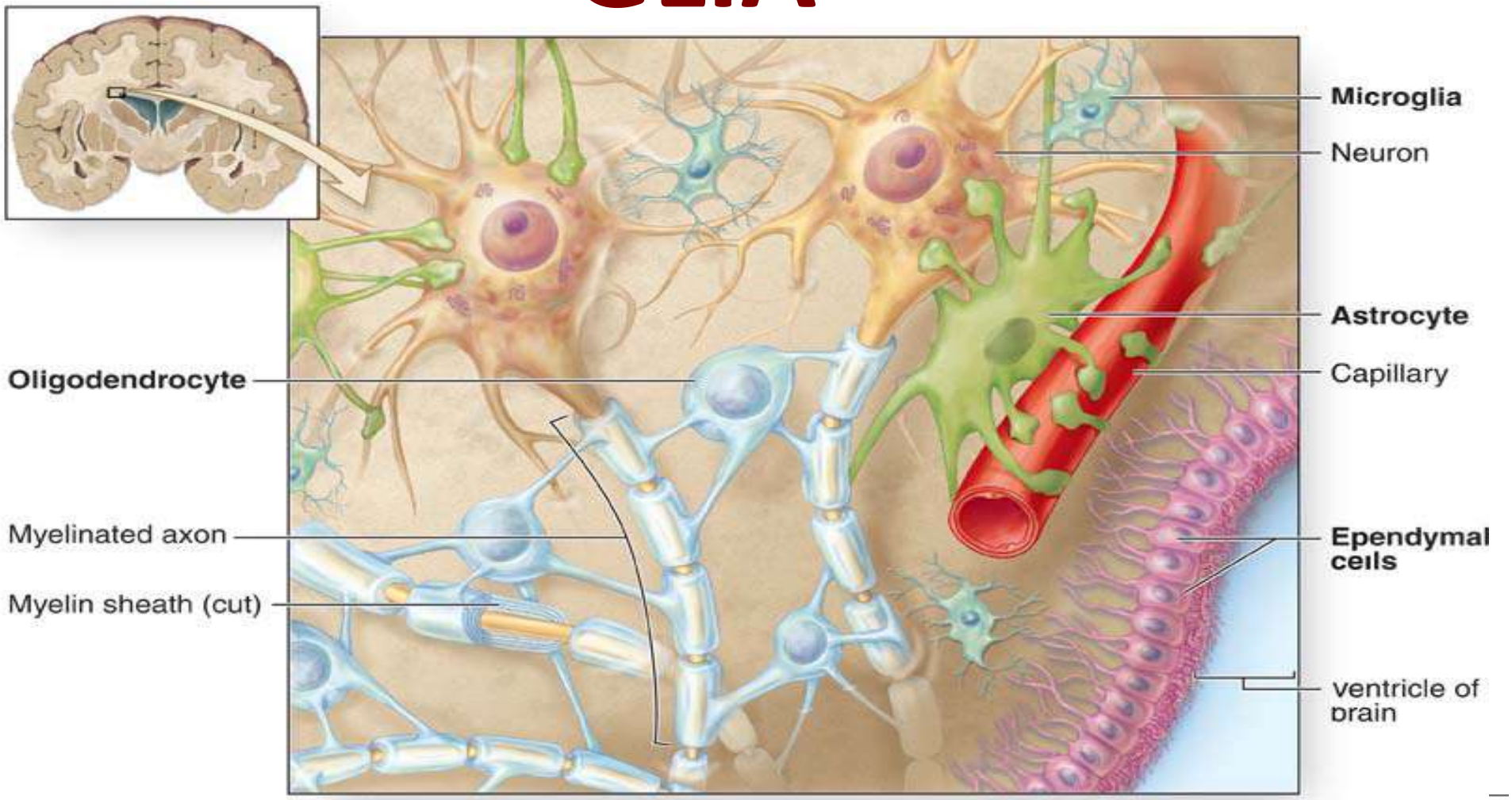


Cell, 2010

RTT in a dish


Reprogramming
iPS
NPC
Glia:
astrocyte,
oligodendrocyte
Neurons:
motor, dopaminergic, cortical,
hippocampal, etc.

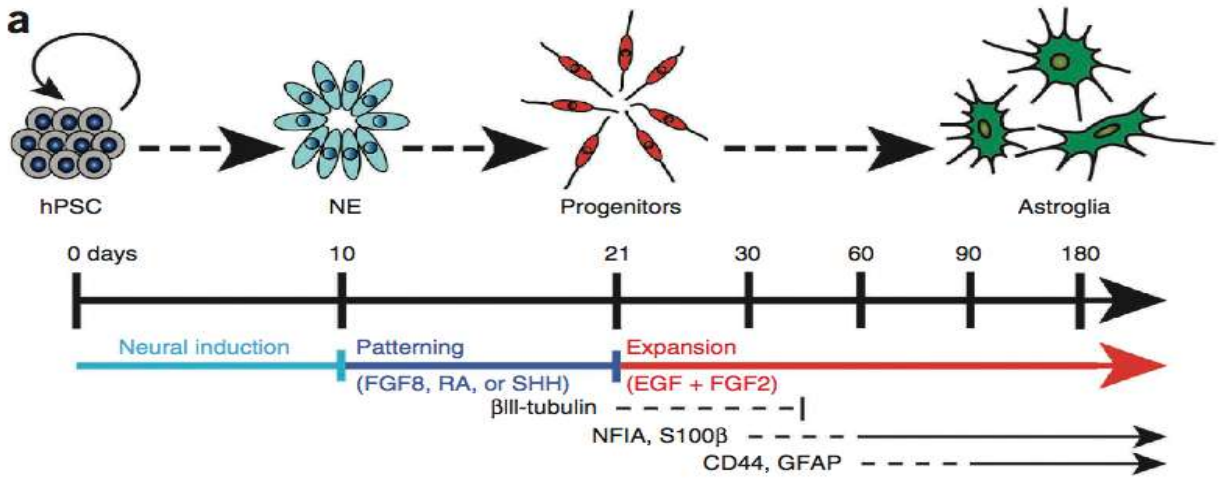
GLIA



iPSC-derived astrocytes

Specification of transplantable astroglial subtypes from human pluripotent stem cells

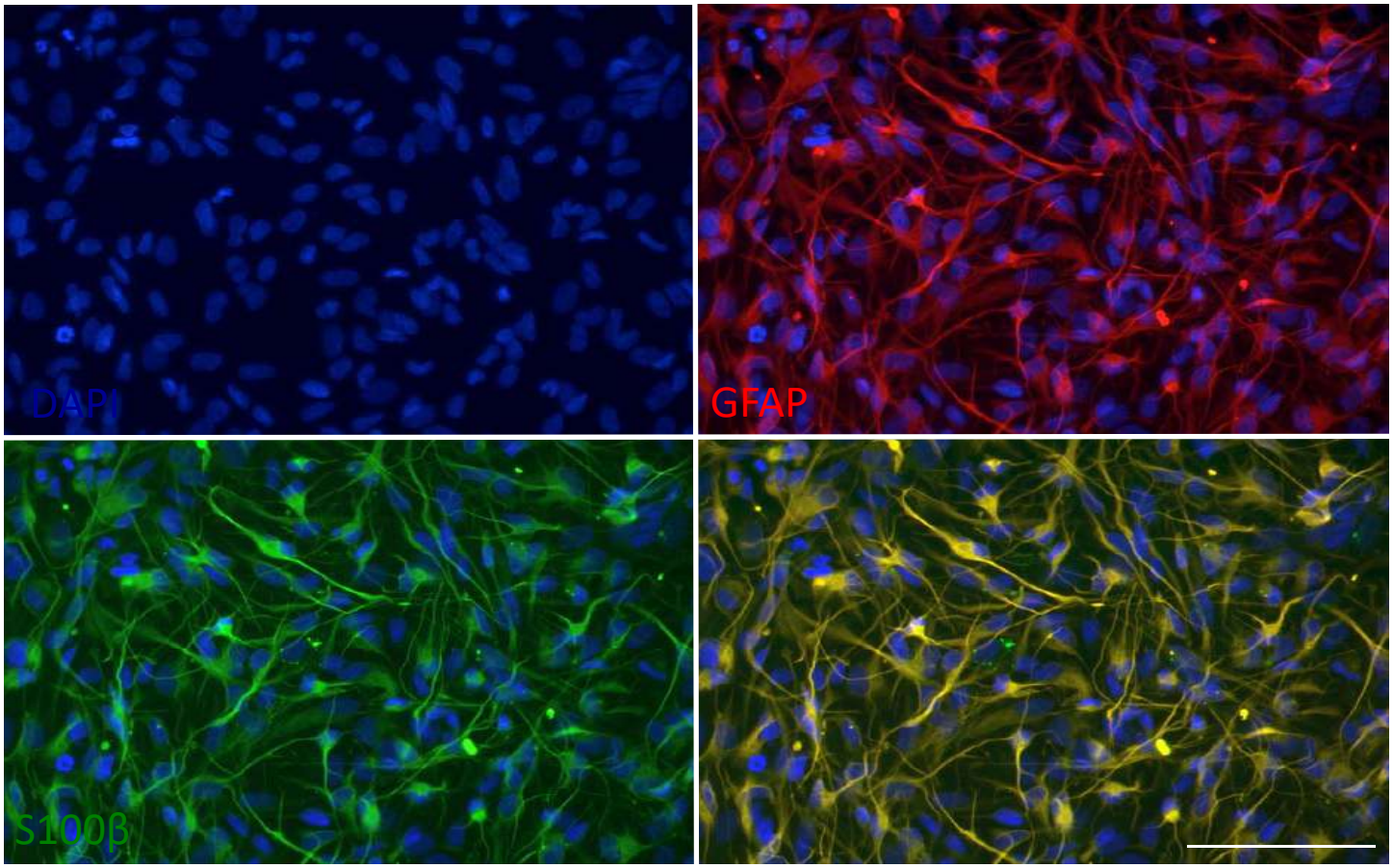
Robert Krencik[1,2], Jason P Weick[2,6], Yan Liu[3,6], Zhi-Jian Zhang[2] & Su-Chun Zhang[1–5]



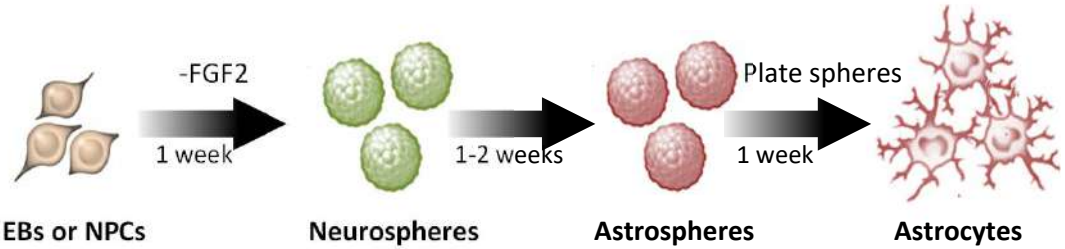
Muotri lab iPSC astrocyte protocol (30 days, no growth factors)

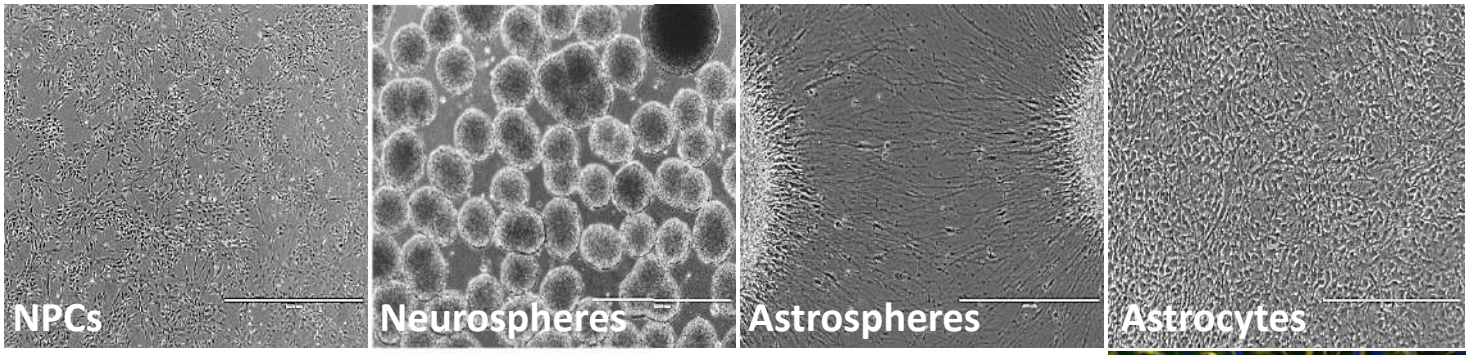
Cassiano

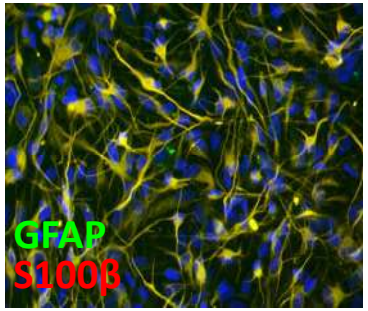
Bia



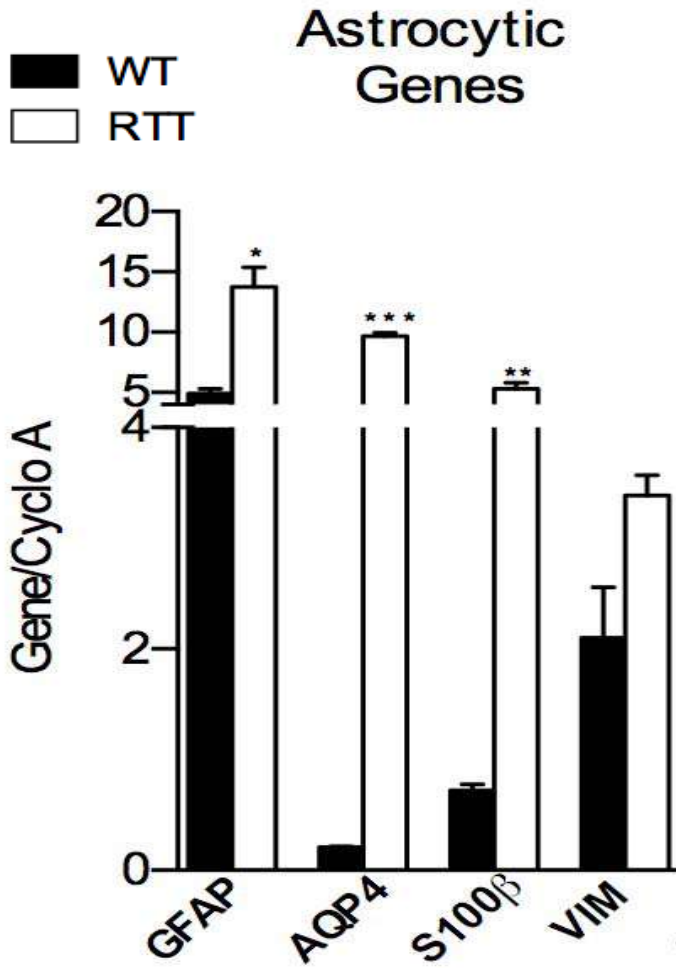
Astrocyte Differentiation



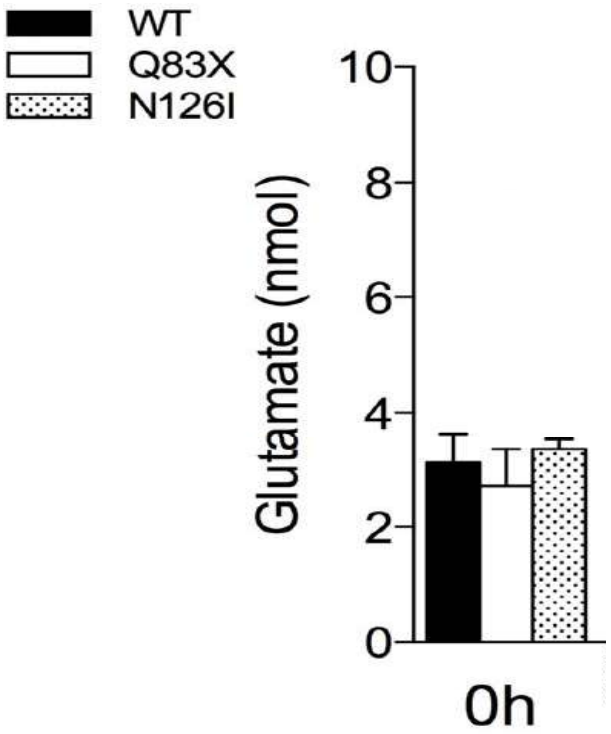




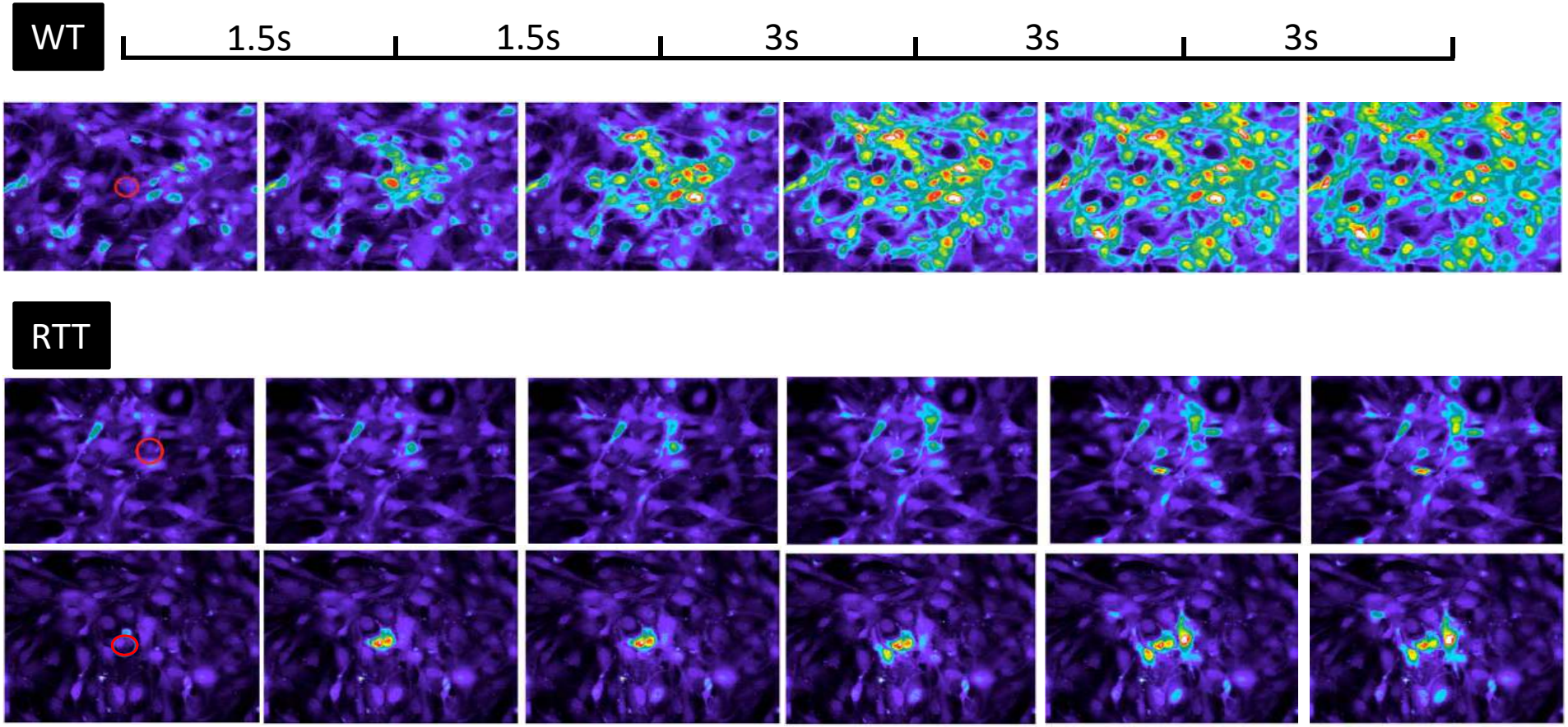
RTT astrocyte altered gene expression



RTT astrocytes have slower glutamate clearance



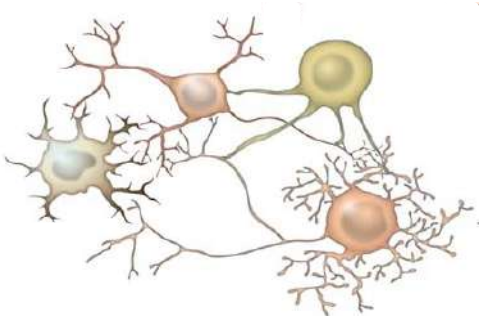
RTT astrocytes have impaired calcium waves



Hang Yao, PhD

Bia

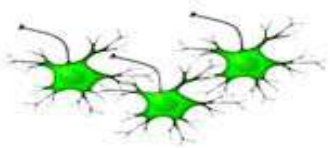
Effect of RTT astrocytes on human neurons



Mixed cell population
4 weeks of neuronal induction

Magnetic sorting

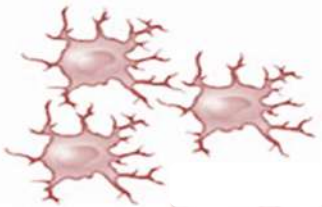
CD44 -
CD184-



WT
RTT

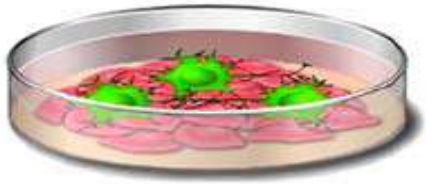
Neuron enriched population

WT
RTT



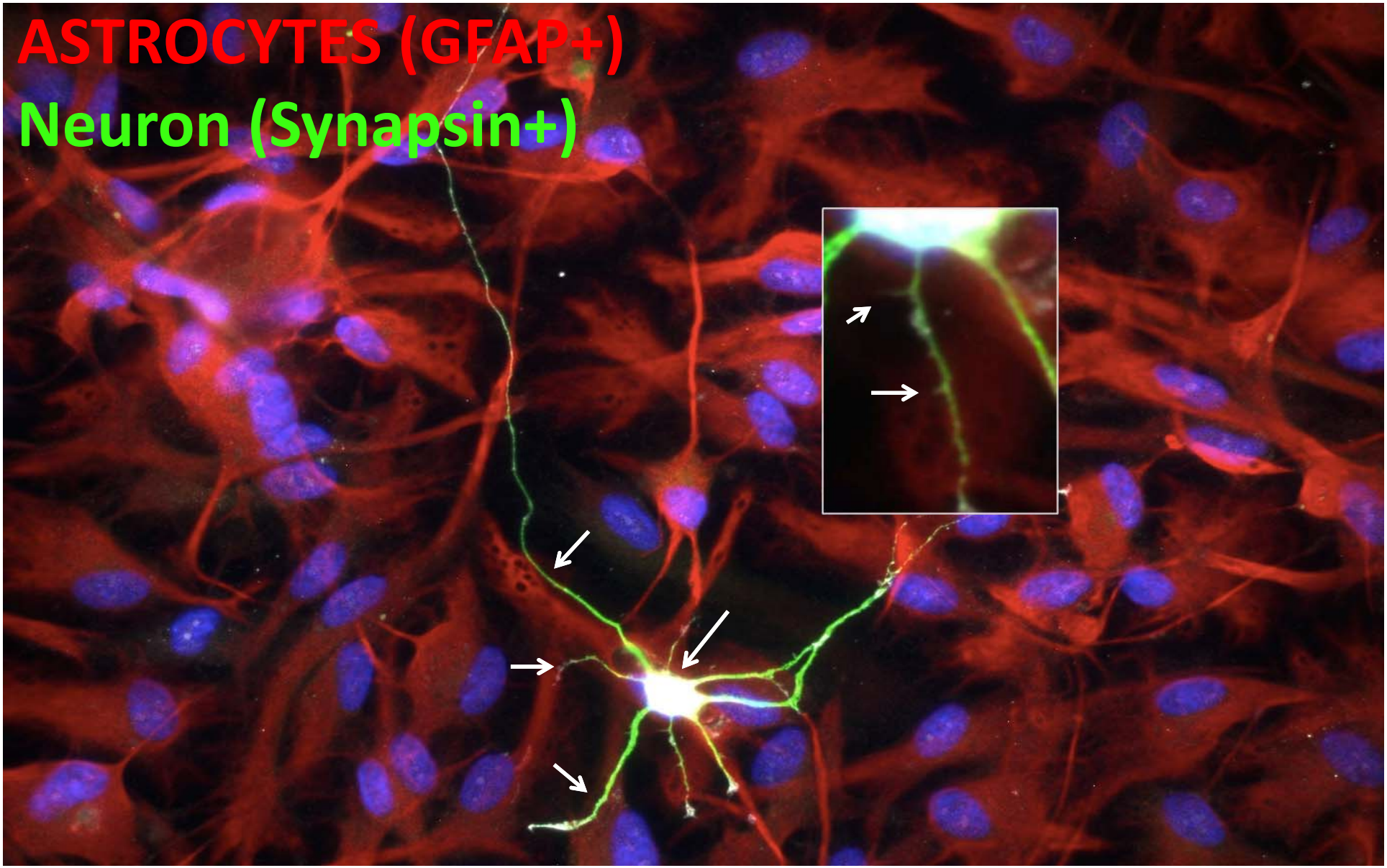
Astrocytes

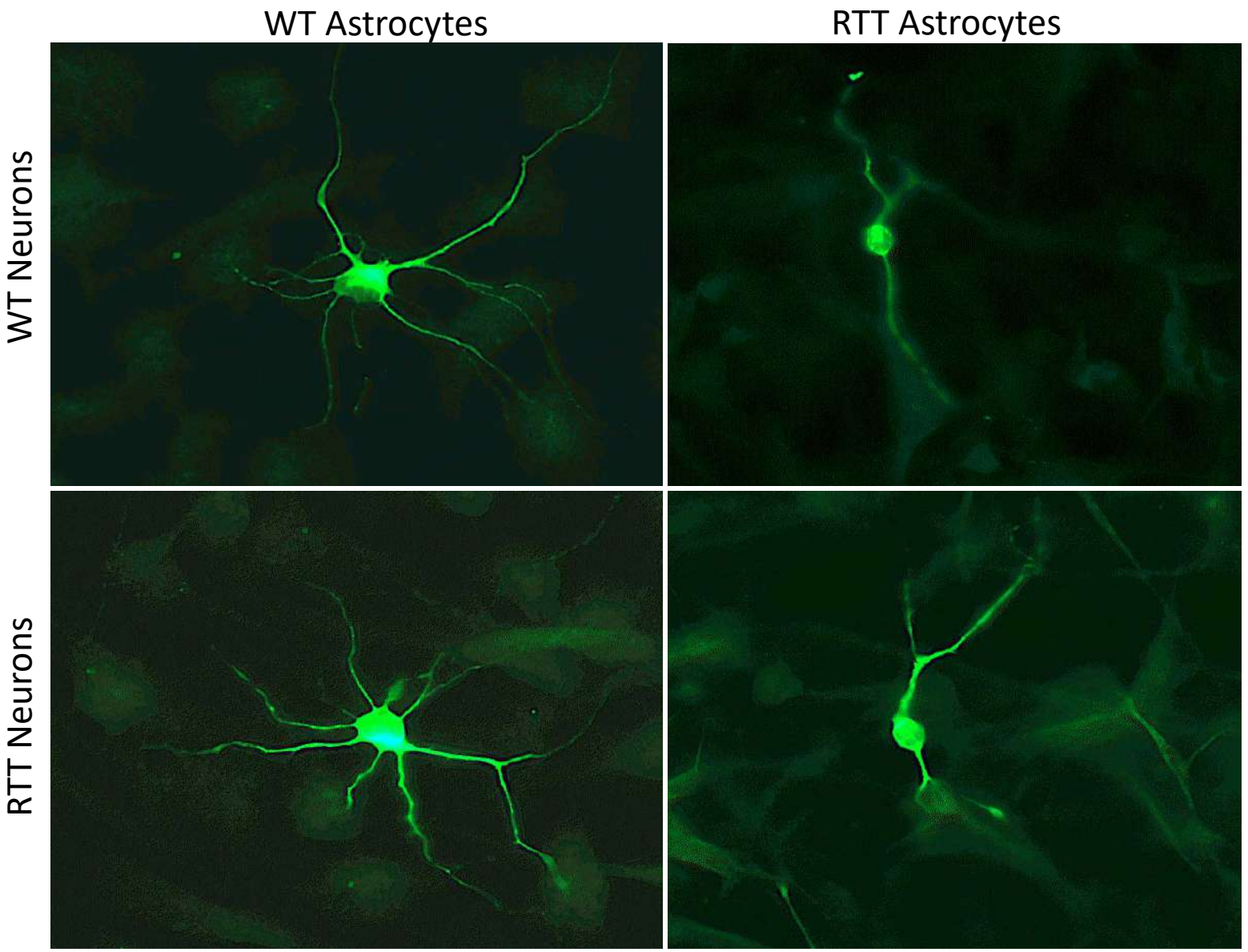
Plated on coverslips



2w

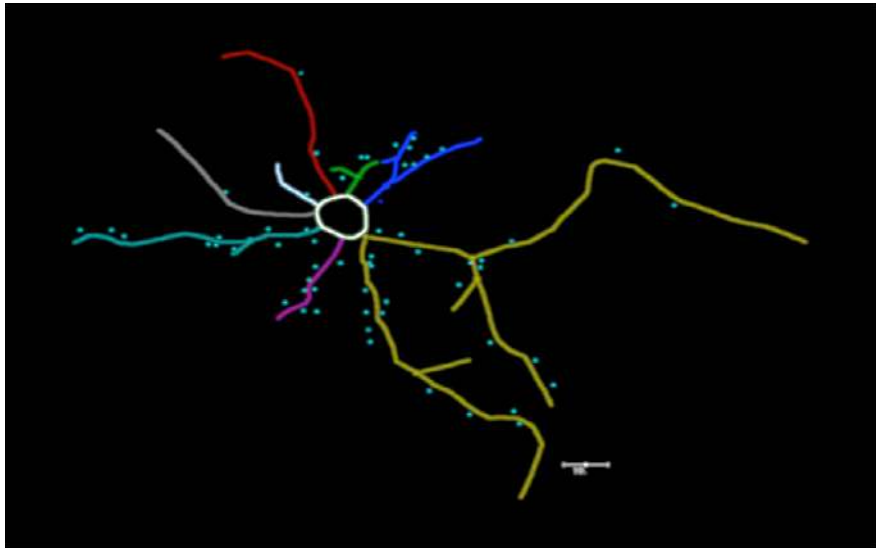
Fix
&
Stain

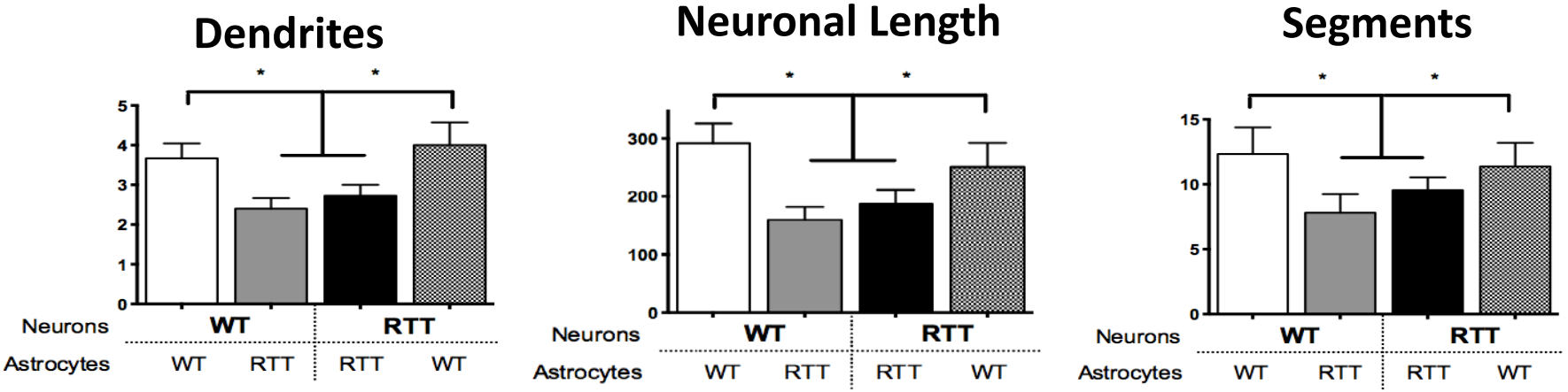

ASTROCYTES (GFAP+)
Neuron (Synapsin+)


WT Astrocytes
RTT Astrocytes
WT Neurons
RTT Neurons

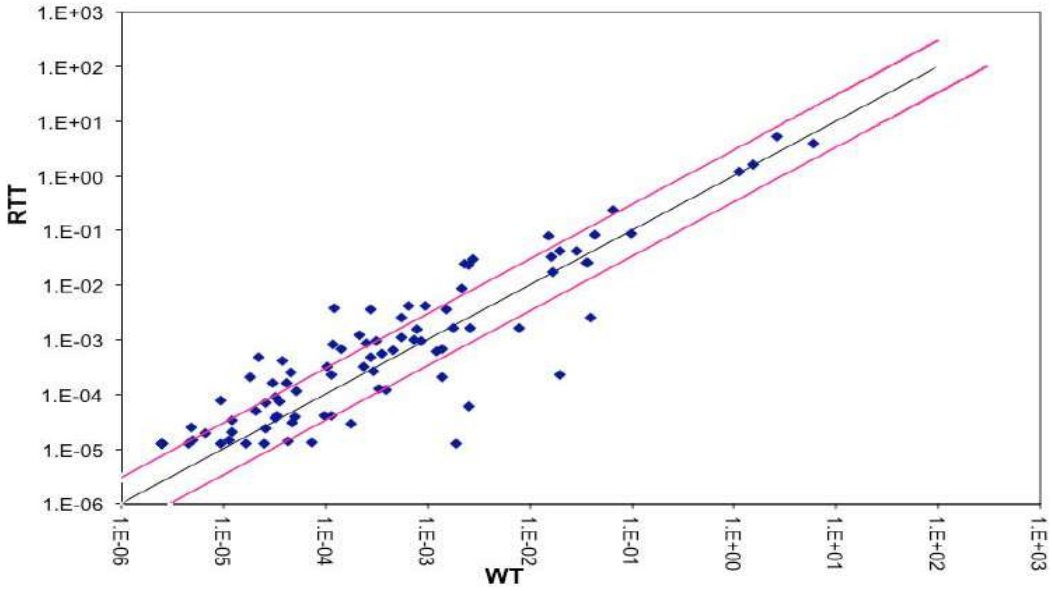
RTT neuronal rescue by astrocytes

Branka





RTT astrocytes cytokines

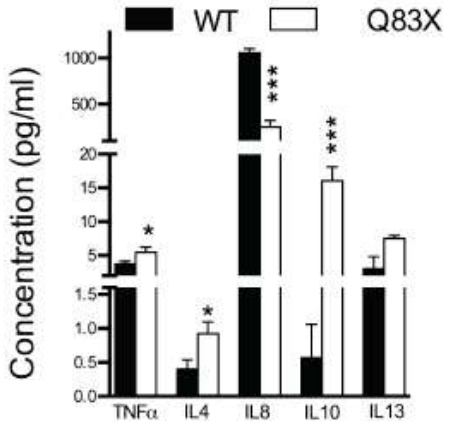


Up-regulated

Symbol	Fold dif.
BMP5	4.68
CD40LG	5.36
CSF2	2.29
CSF3	3.89
IFNA4	2.97
IL13	2.69
IL15	6.58
IL23A	2.98
IL3	2.97
IL4	5.42
IL5	5.62
INHBA	5.34
LIF	9.24
TGFB1	1.89
TGFB2	3.55
TGFB3	10.64
TNFSF12	3.98
TNFSF13B	3.39
TNFSF8	5.18
TXLNA	2.15

Down-regulated

Symbol	Fold dif.
BMP2	0.15
BMP3	0.01
BMP4	0.5
CD70	0.06
IL10	0.17
IL17B	0.32
IL18	0.2



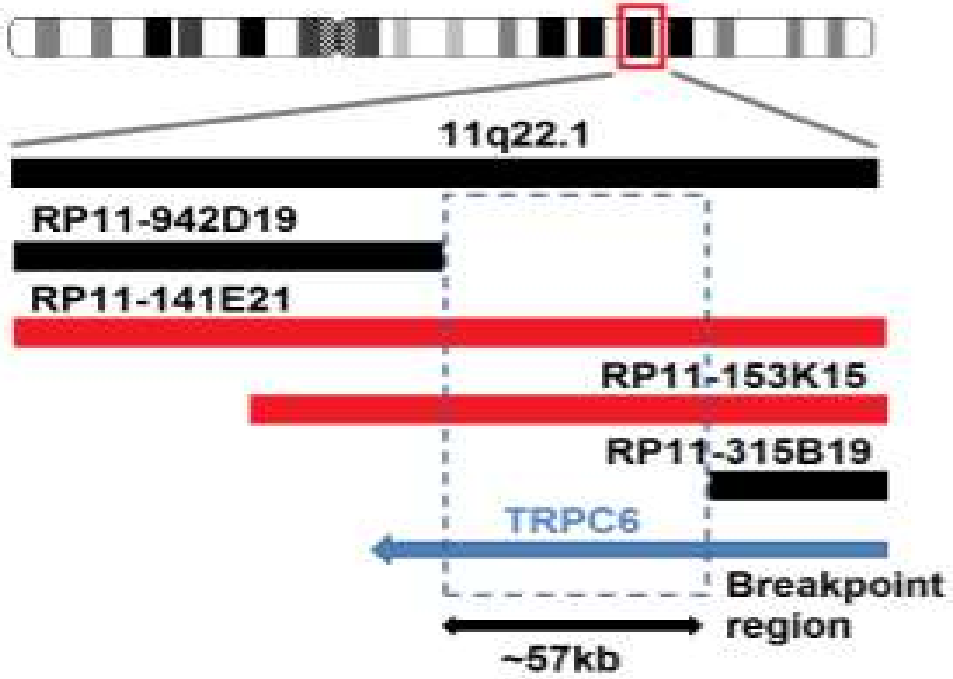
The Tooth Fairy Kit Collection

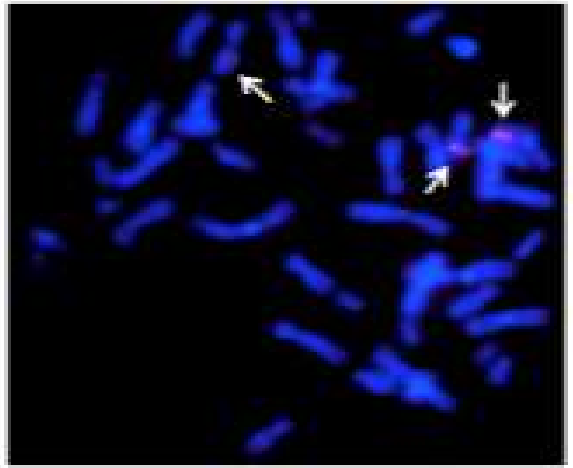



Beltrão-Braga et al, *Cell Transplantation* 2011

Karina

Reduced levels of TRPC6





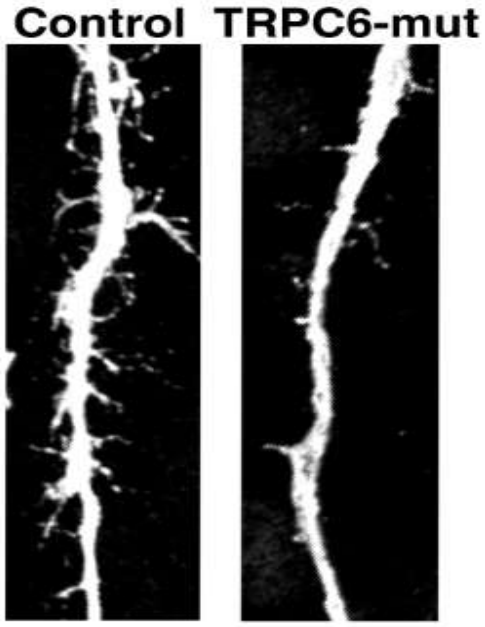
Maria Rita Passos-Bueno/Matt State

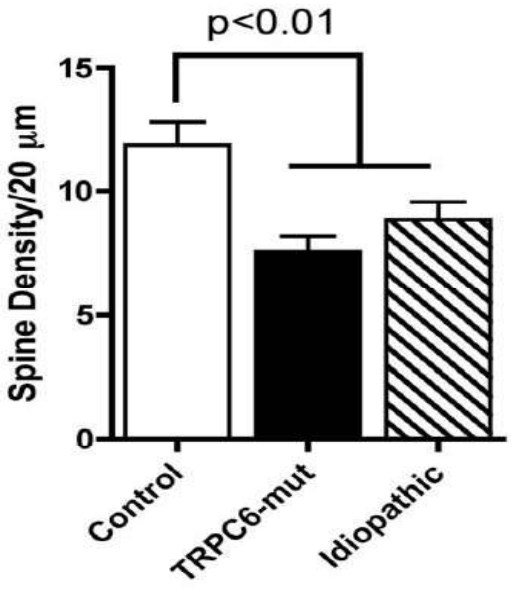
Gene expression revealed CREB targets

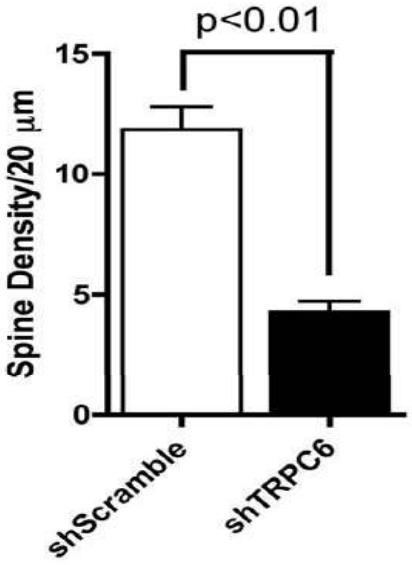
Functionally relevant genes differentially expressed between *TRPC6*-disrupted patient and controls

Gene	Fold change*	Gene Ontology	Regulation by CREB**	qPCR validation
INA	-2.639988194	nervous system development; neurofilament cytoskeleton organization	ChIP-on-chip	0.0198
NPTX1	-2.855578291	growth of neurites; synaptic transmission; central nervous system development	In silico	0.0885
MAP2	-2.789671289	growth of neurites; development and elongation of neurites; patterning of cerebral cortex; polarization of hippocampal neurons	ChIP-on-chip	0.0363
EPHA4	2.362428255	guidance of axons; formation of pyramidal tract; axon guidance	ChIP-on-chip; In silico	0.4305
CLDN11	4.066602785	axon ensheathment; calcium-independent cell-cell adhesion; migration of neuroglia	In silico Lui *et al.*, 2007	0.0005
PCDH10	-4.318180517	cell adhesion; establishment and function of specific cell-cell connections in the brain	ChIP-on-chip; In silico	0.3331
CLDN1	4.171417178	calcium-independent cell-cell adhesion; myelinization of cells	In silico	
PTGS2	-3.49316255	activation of astrocytes; activation of neuroglia; memory; positive regulation of synaptic plasticity; negative regulation of synaptic transmission, dopaminergic; positive regulation of synaptic transmission, glutamatergic	ChIP-on-chip Gosh *et al.*, 2007	
CDH6	-2.675463010	cell-adhesion; establishment and function of specific cell-cell connections in the brain	No evidence	0.0418
SEMA3A	2.314408538	nervous system development; axonal fasciculation; regulation of axon extension involved in axon guidance; distribution of neurons; migration of neuroglia; growth of neurites; chemorepulsion of sympathetic neuron	No evidence	0.1828
CASP1	2.545250054	activation of astrocytes; activation of neuroglia	No evidence	
VCAM1	4.546975557	growth of neurites; distribution of neurons; cell adhesion; guidance of axons	No evidence	

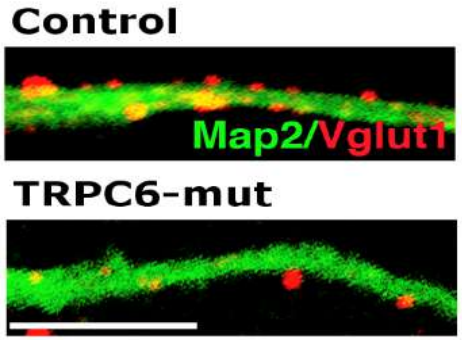
TRPC6 levels regulate cortical spine density

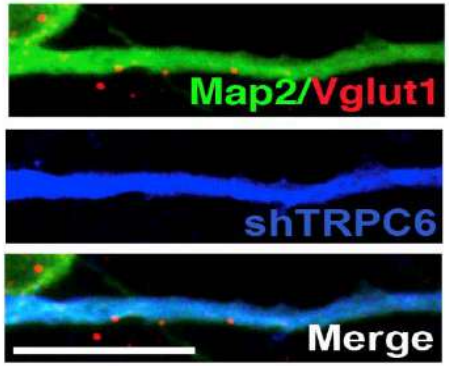


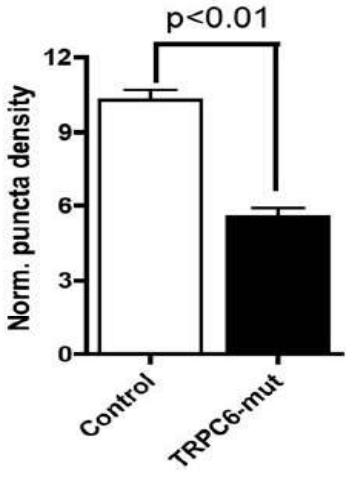


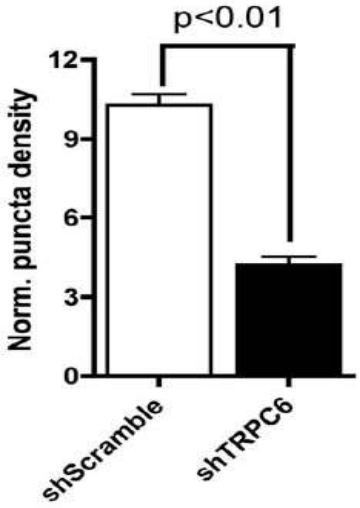


TRPC6 levels regulate glutamatergic synapses numbers









Personalized Therapy

The FASEB Journal • Research Communication

Hyperforin—a key constituent of St. John's wort specifically activates TRPC6 channels

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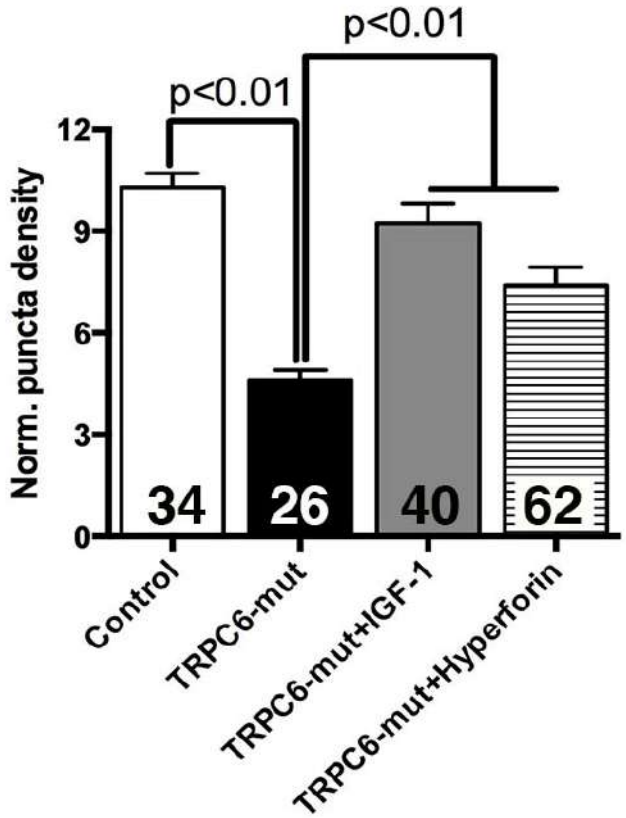
Hyperforin rescues synaptic puncta in TRPC6 haploinsuficent neurons



Mol. Psy, 2014

Take Home Messages:

-Loss of MeCP2/TRPC6 function is involved in glutamatergic synapses formation, revealing common molecular pathways between ASDs.

-RTT astrocytes have impaired metabolism and display an inflammatory cytokine signature. The morphology of RTT neurons can be rescued by WT astrocytes.

-iPSC-derived neurons can be used in a drug-screening platform to search for new ASD medicine and even personalized medicine.

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Families and patients

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