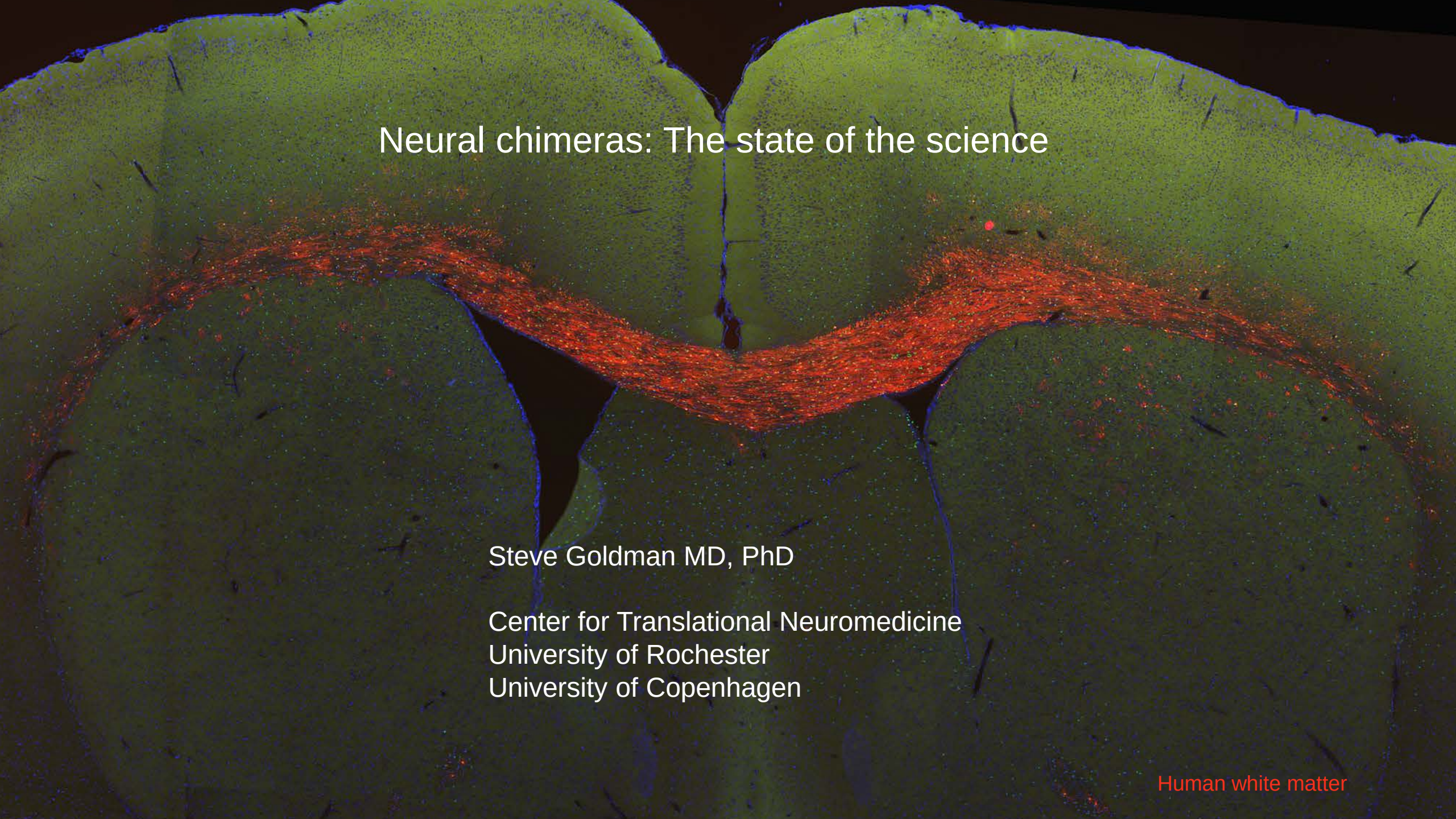
Neural chimeras: The state of the science



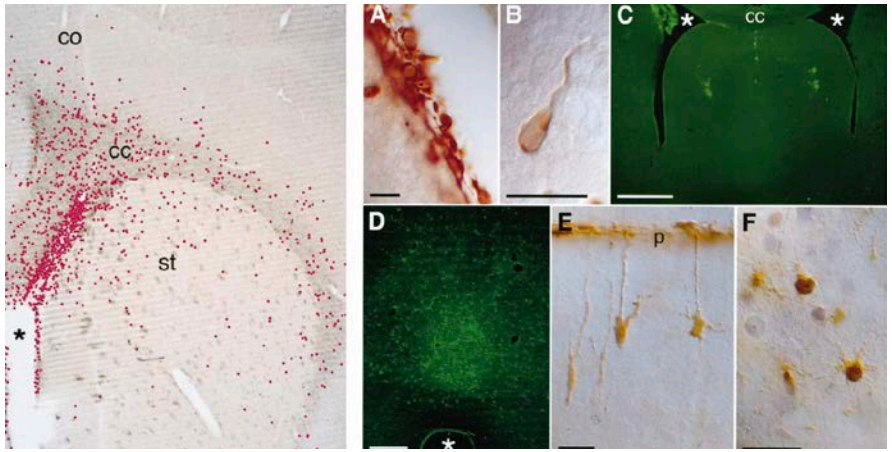
Steve Goldman MD, PhD

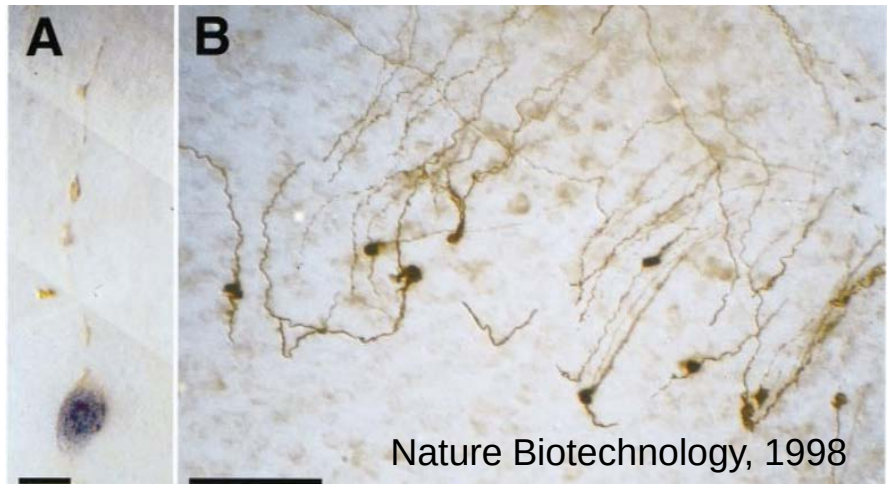
Center for Translational Neuromedicine
University of Rochester
University of Copenhagen

Human white matter

Chimeric brains generated by intraventricular transplantation of fetal human brain cells into embryonic rats

Oliver Brüstle[1,2*], Khalid Choudhary[1†], Khalad Karram[1,2†], Anita Hüttner[1], Kerren Murray[3], Monique Dubois-Dalcq[3], and Ronald D.G. McKay[1]





Nature Biotechnology, 1998

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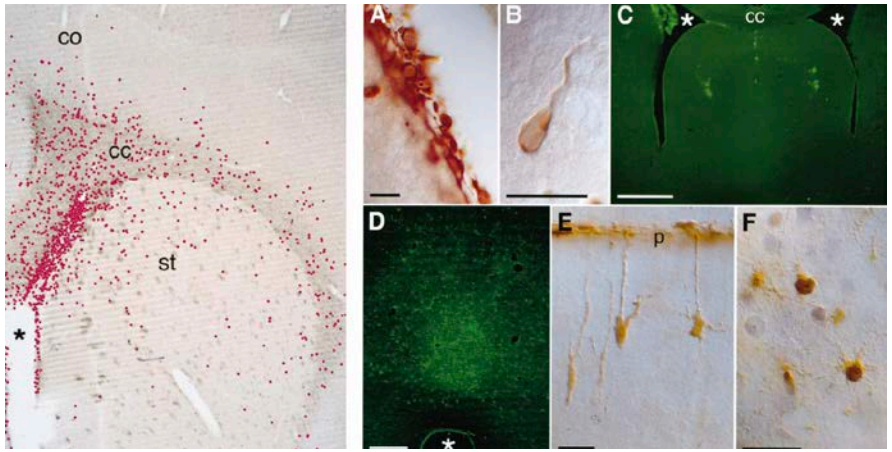
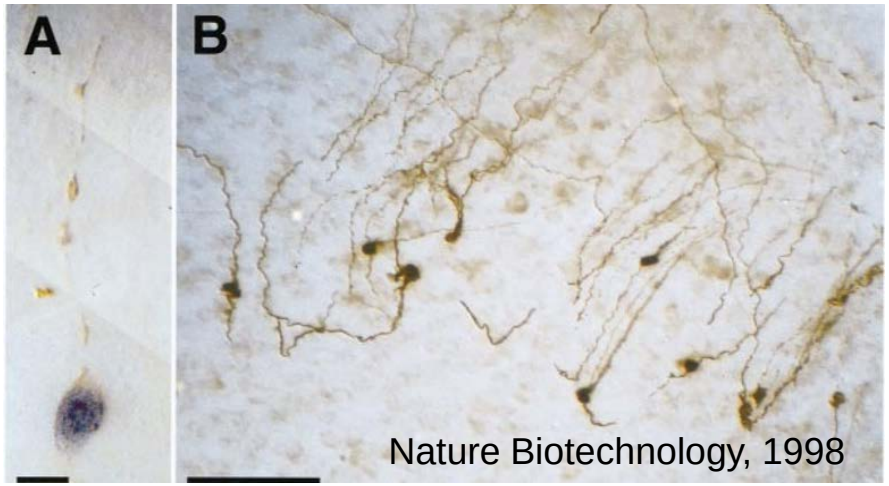
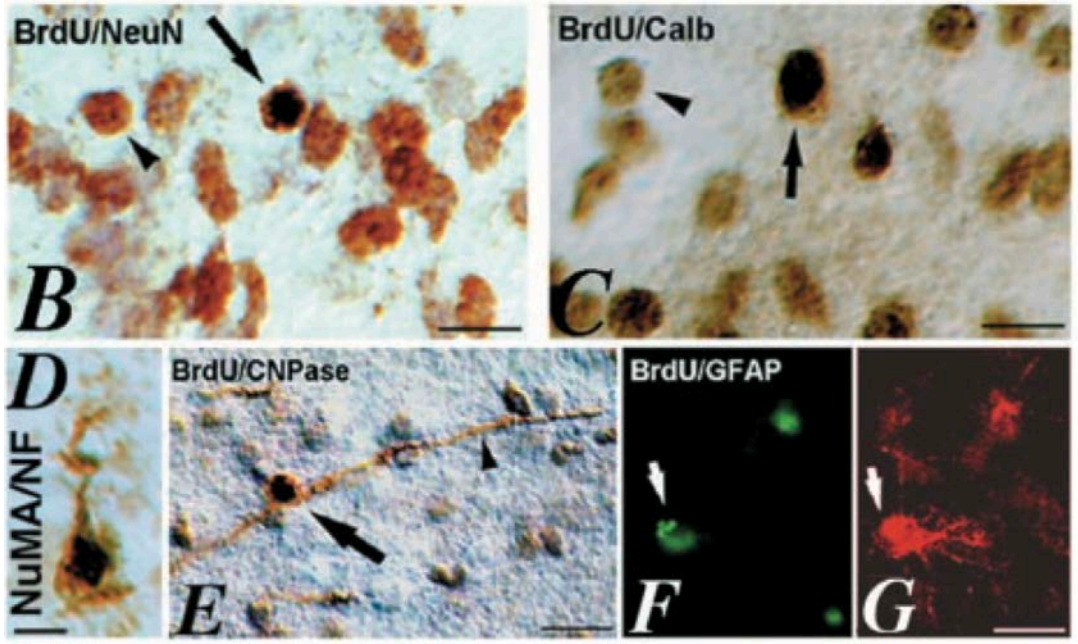




Nature Biotechnology, 1998

Segregation of Human Neural Stem Cells in the Developing Primate Forebrain

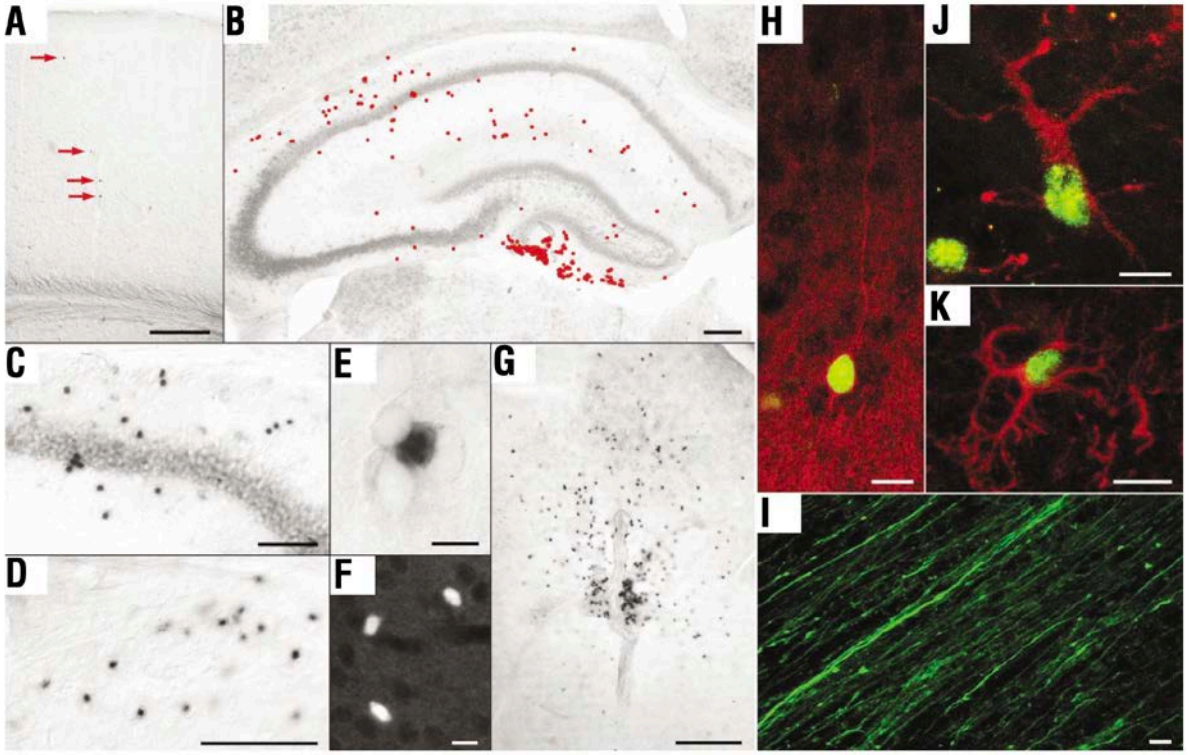
Václav Ourednik,[1*†] Jitka Ourednik,[1*] Jonathan D. Flax,[1] W. Michael Zawada,[2] Cynthia Hutt,[2] Chunhua Yang,[1] Kook I. Park,[1,3] Seung U. Kim,[4] Richard L. Sidman,[5] Curt R. Freed,[2‡] Evan Y. Snyder[1†‡]



Science, 2001

In vitro differentiation of transplantable neural precursors from human embryonic stem cells

Su-Chun Zhang[1,2,4*], Marius Wernig[5], Ian D. Duncan[3], Oliver Brüstle[5*], and James A. Thomson[1]

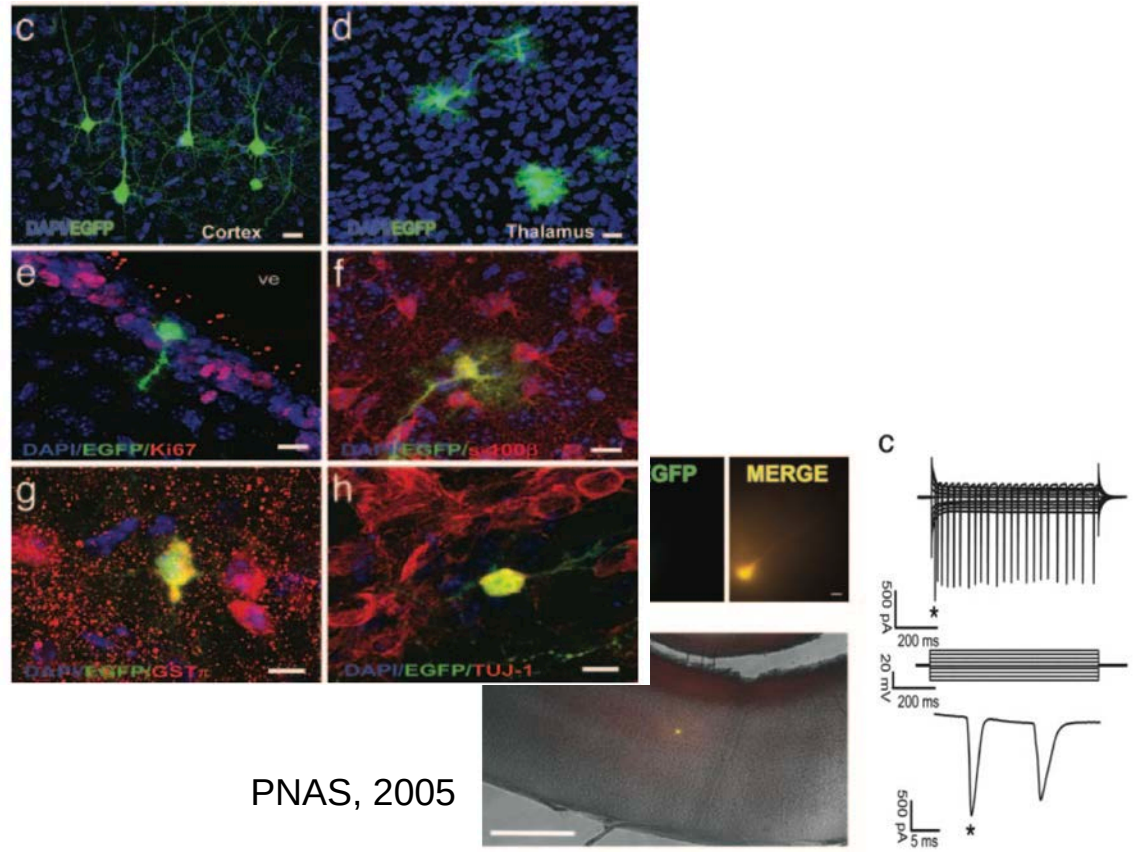


Nature Biotechnology, 2001

Development of functional human embryonic stem cell-derived neurons in mouse brain

Alysson R. Muotri*†, Kinichi Nakashima*†‡, Nicolas Toni*, Vladislav M. Sandler*, and Fred H. Gage*§

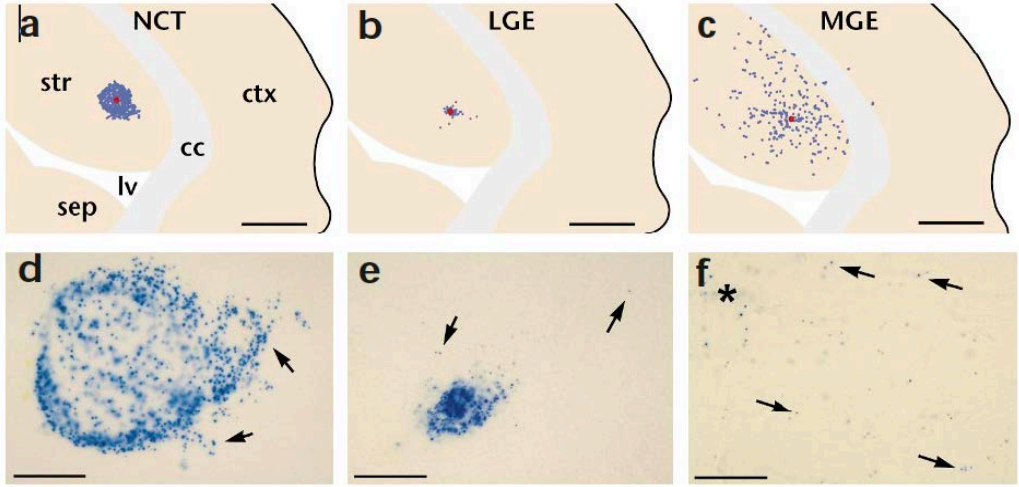
*Laboratory of Genetics, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037; and ‡Laboratory of Molecular Neuroscience, Graduate School of Biological Sciences, Nara Institute of Science and Technology, 8916-5 Takayama, Ikoma 630-0101, Japan



PNAS, 2005

Young neurons from medial ganglionic eminence disperse in adult and embryonic brain

Hynek Wichterle[1], Jose Manuel Garcia-Verdugo[2], Daniel G. Herrera[1,3] and Arturo Alvarez-Buylla[1]



Nature Neuroscience, 1999

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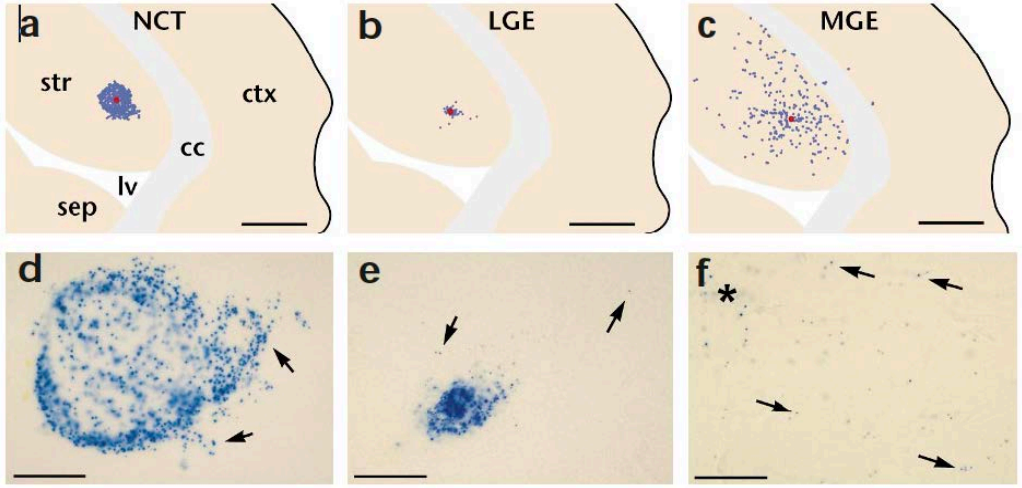

Nature Neuroscience, 1999

High-yield selection and extraction of two promoter-defined phenotypes of neural stem cells from the fetal human brain

H. Michael Keyoung[1†], Neeta S. Roy[1†], Abdellatif Benraiss[1], Abner Louissaint, Jr.[1], Akira Suzuki[3,4], Mitsuhiro Hashimoto[5], William K. Rashbaum[2], Hideyuki Okano[3,4,6], and Steven A. Goldman[1*]

Nature Biotechnology, 2001

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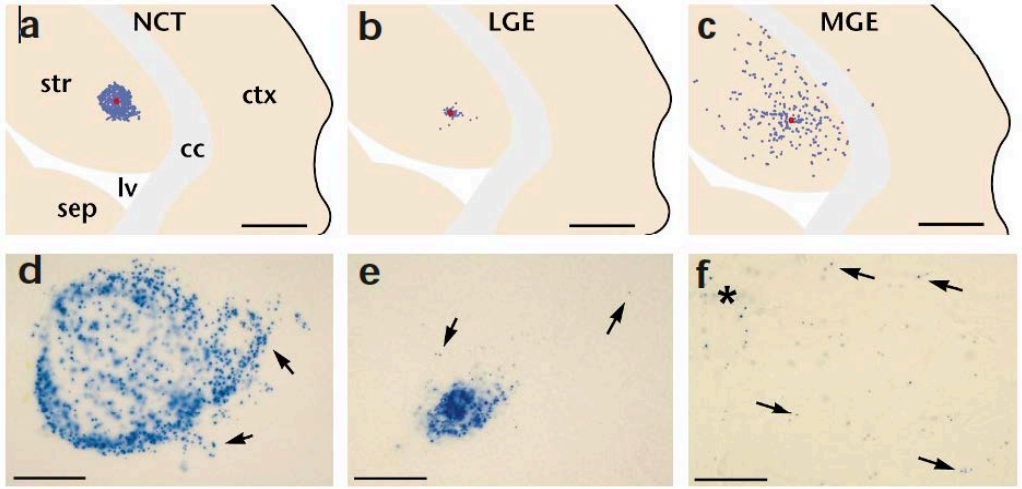
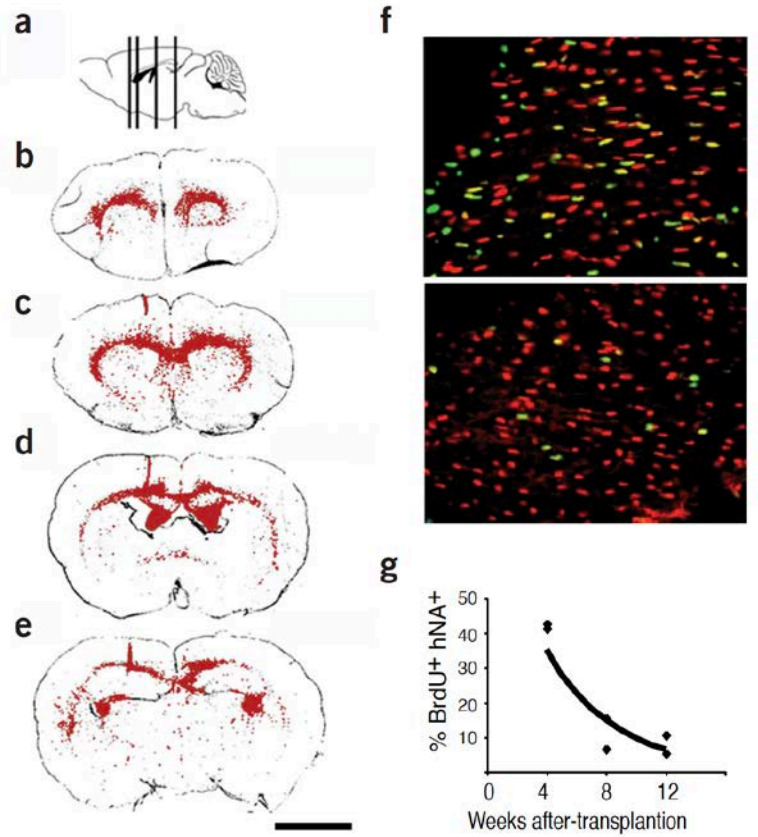


Nature Neuroscience, 1999

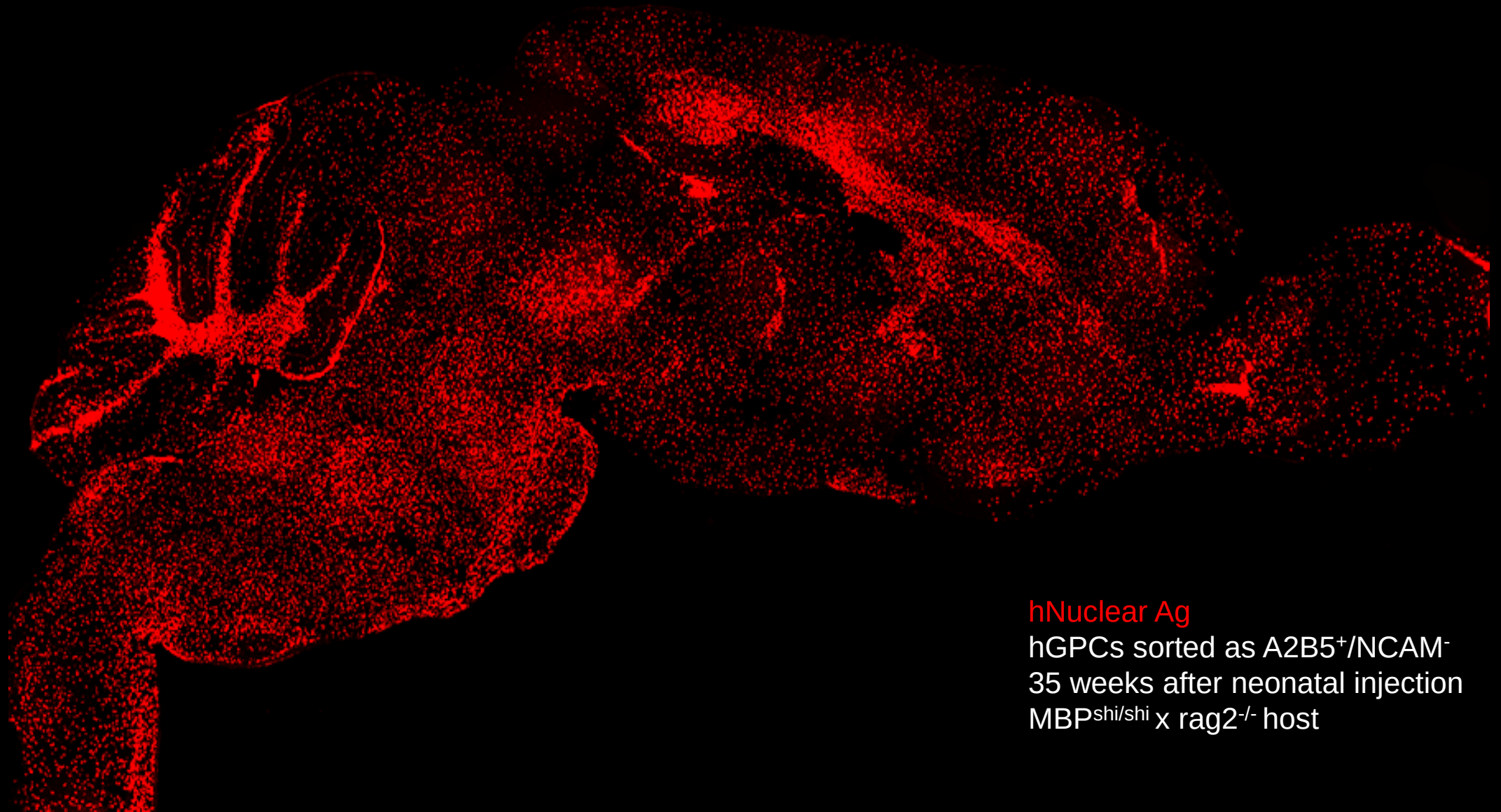
Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain

Martha S Windrem[1], Marta C Nunes[1], William K Rashbaum[2], Theodore H Schwartz[3], Robert A Goodman[4], Guy McKhann II[4], Neeta S Roy[1] & Steven A Goldman[1,5]



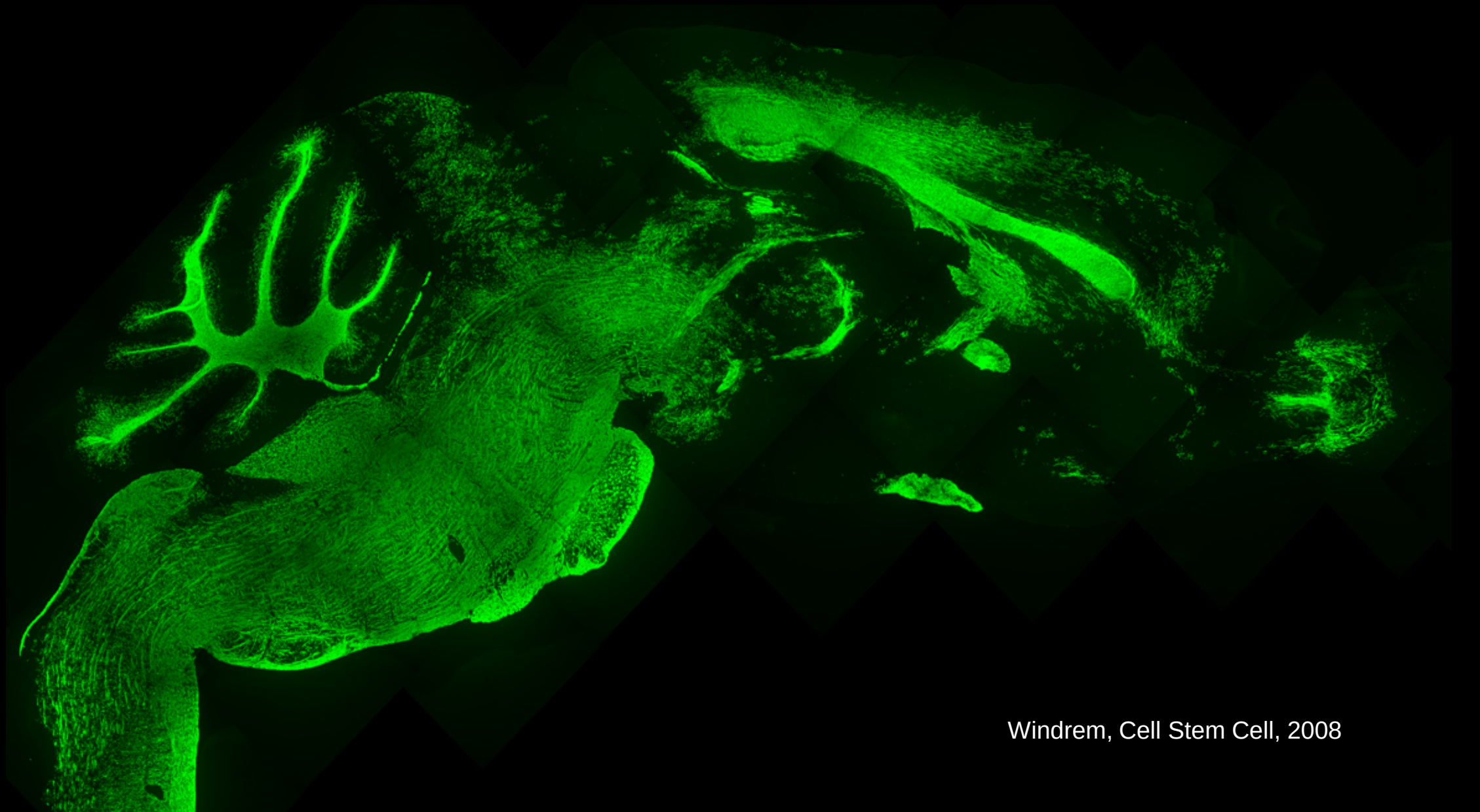
Nature Medicine, 2004

Human glial progenitor cells are highly migratory in vivo



hNuclear Ag
hGPCs sorted as A2B5^{+}/NCAM^{-}
35 weeks after neonatal injection
MBP$^{shi/shi}$ x rag2$^{-/-}$ host

Hypomyelinated mice can be remyelinated by human glial progenitors



Windrem, Cell Stem Cell, 2008

LETTER

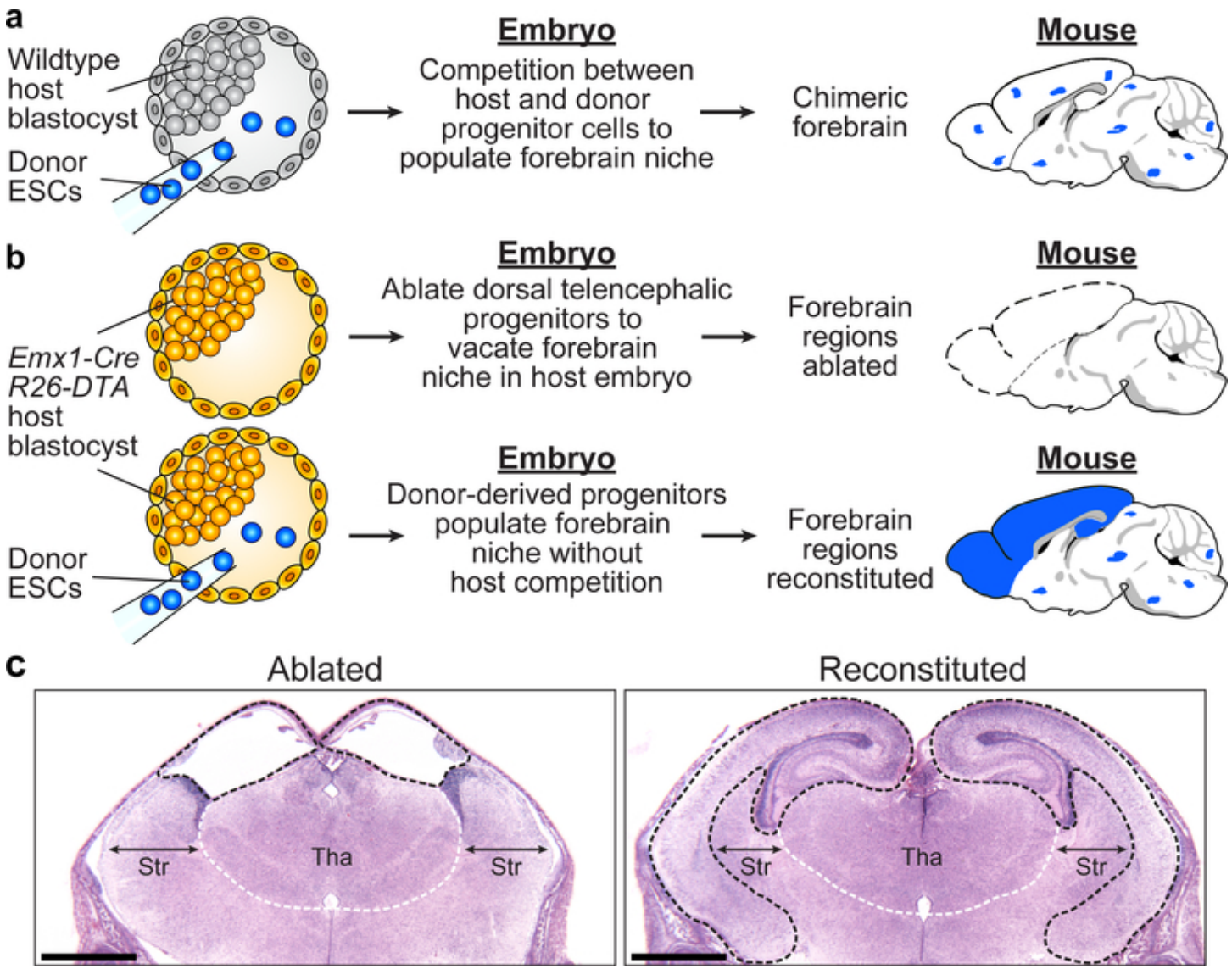
https://doi.org/10.1038/s41586-018-0586-0

Neural blastocyst complementation enables mouse forebrain organogenesis

Amelia N. Chang[1,5], Zhuoyi Liang[1,5], Hai-Qiang Dai[1,5], Aimee M. Chapdelaine-Williams[1], Nick Andrews[2], Roderick T. Bronson[3], Bjoern Schwer[4,6*] & Frederick W. Alt[1,6*]

Blastocyst complementation may be used to establish neural or glial chimeras defined whose specificity is defined by that of the conditional regulatory element that determines host cell deficiency

Pros: Complete replacement of the target phenotype



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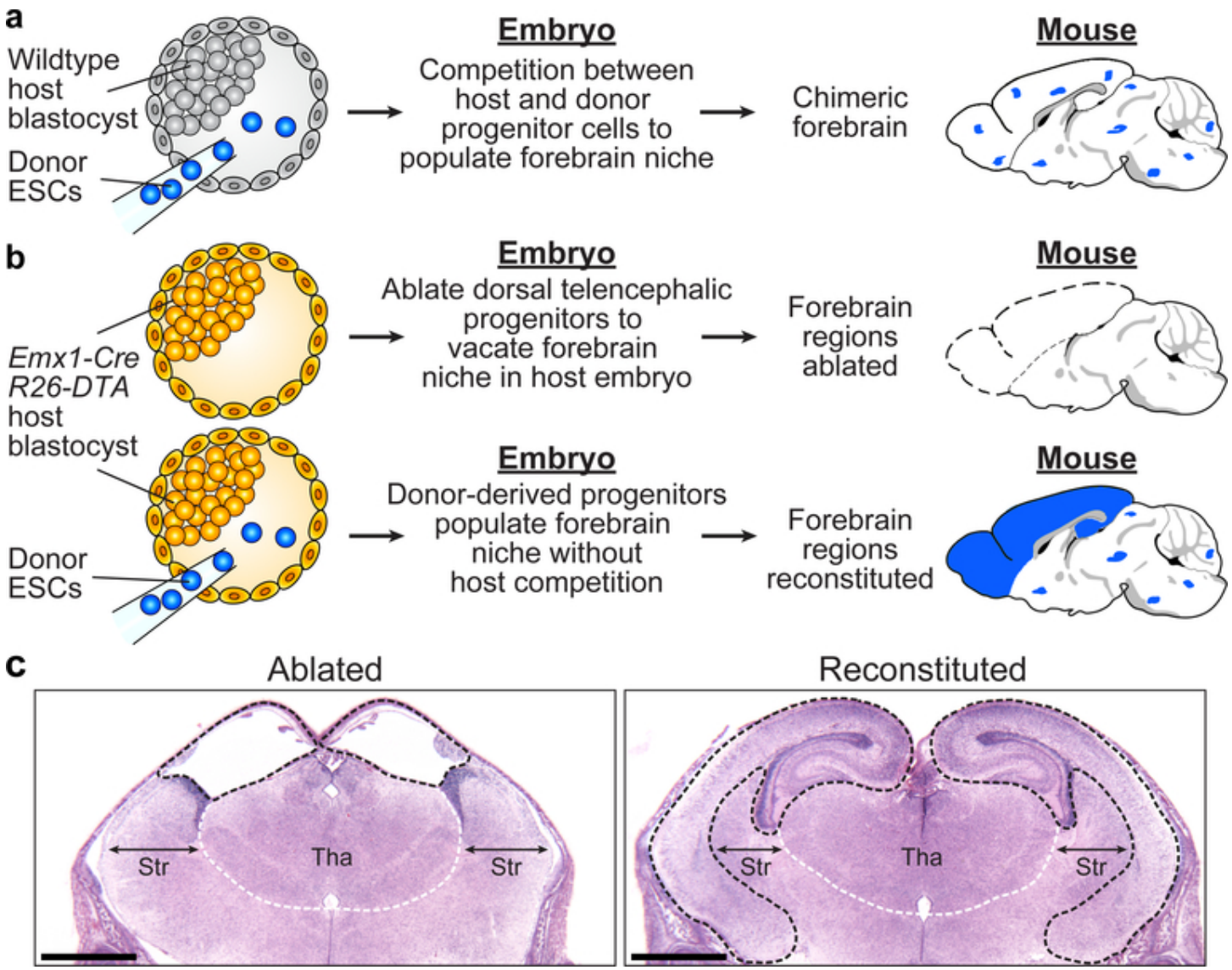
Blastocyst complementation may be used to establish neural or glial chimeras defined whose specificity is defined by that of the conditional regulatory element that determines host cell deficiency

Pros: Complete replacement of the target phenotype

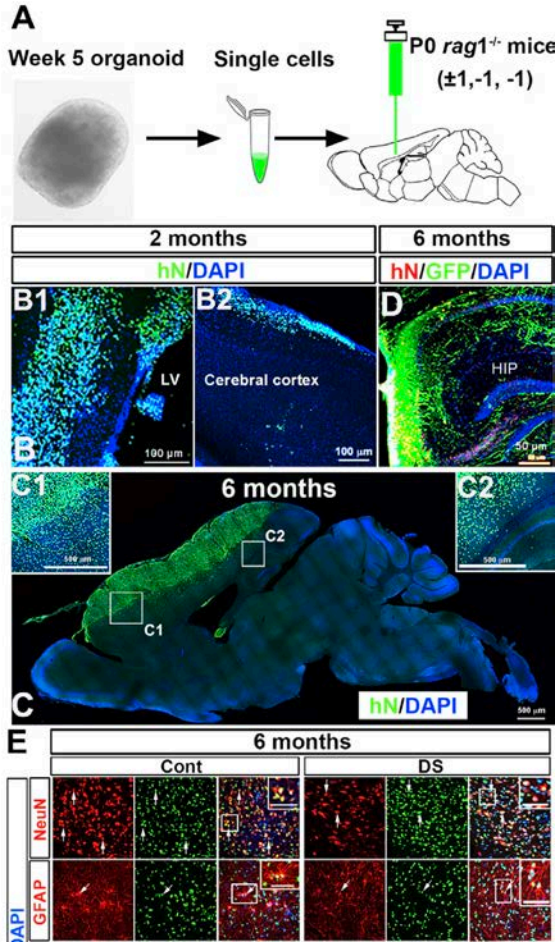
Con: Depending upon regulatory element used to direct DT expression, may not be limited to region of interest or to CNS

Con: Cannot humanize: mismatched cell cyclicity; risk of gonadal integration



OLIG2 Drives Abnormal Neurodevelopmental Phenotypes in Human iPSC-Based Organoid and Chimeric Mouse Models of Down Syndrome

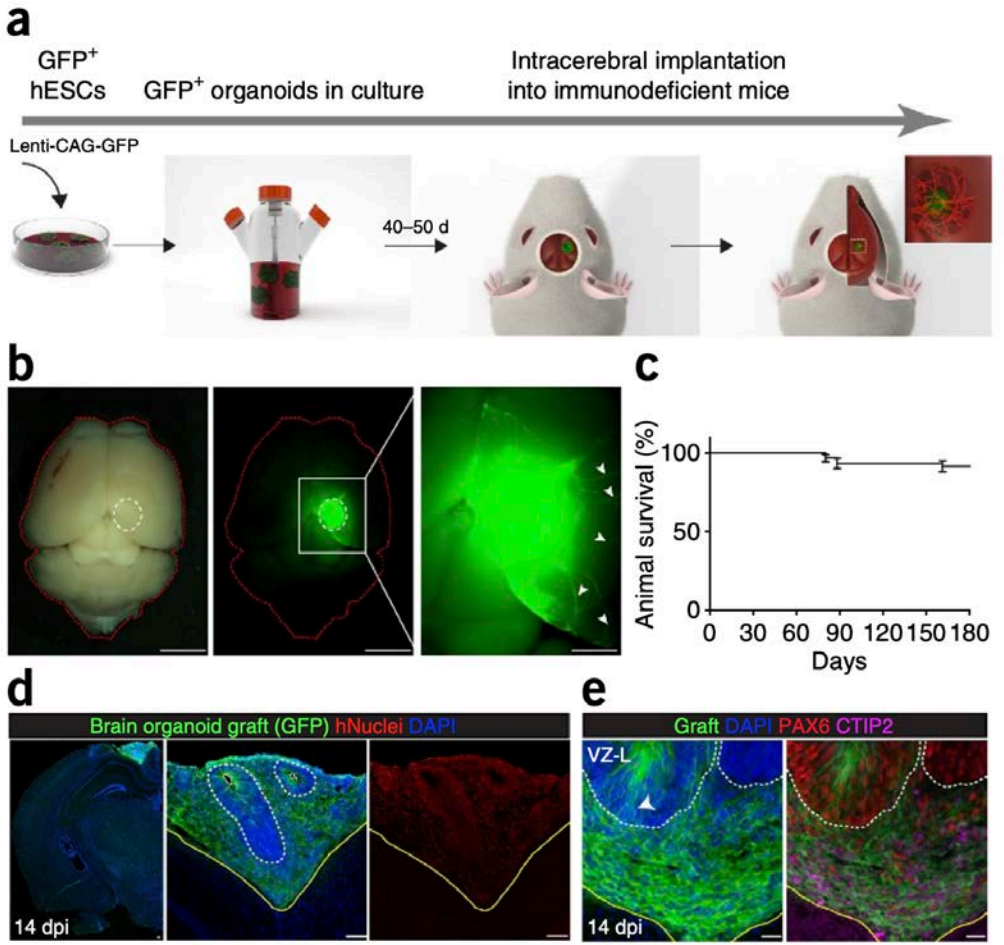
Ranjie Xu,[1,2] Andrew T. Brawner,[2] Shenglan Li,[3] Jing-Jing Liu,[4] Hyosung Kim,[1] Haipeng Xue,[3] Zhiping P. Pang,[4] Woo-Yang Kim,[5] Ronald P. Hart,[1] Ying Liu,[3] and Peng Jiang[1,2,6,*]
[1]Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, NJ 08854, USA
[2]Department of Developmental Neuroscience, Munroe-Meyer Institute and Mary & Dick Holland Regenerative Medicine Program, University of Nebraska Medical Center, Omaha, NE 68198, USA



Cell Stem Cell, 2019

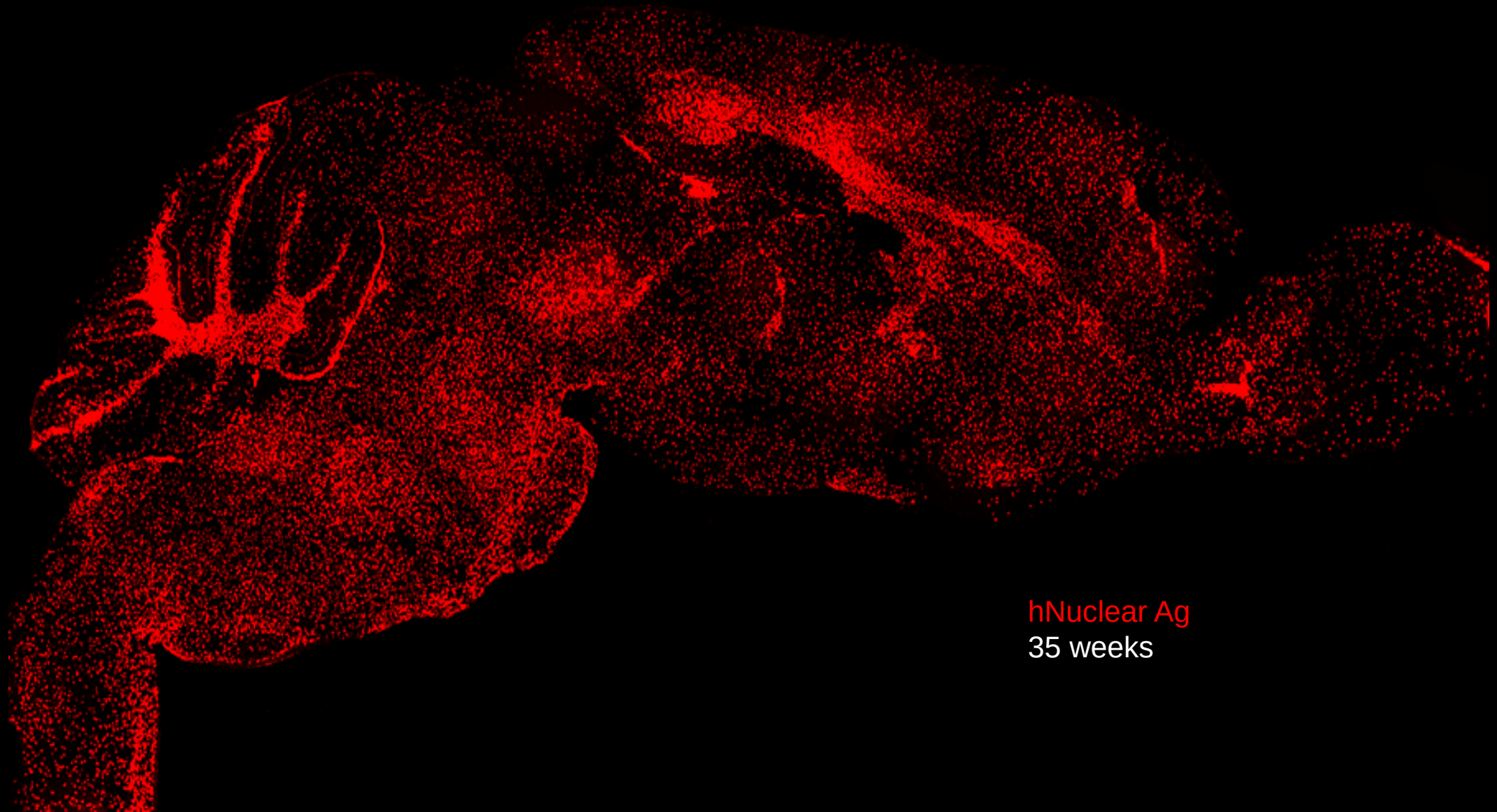
An *in vivo* model of functional and vascularized human brain organoids

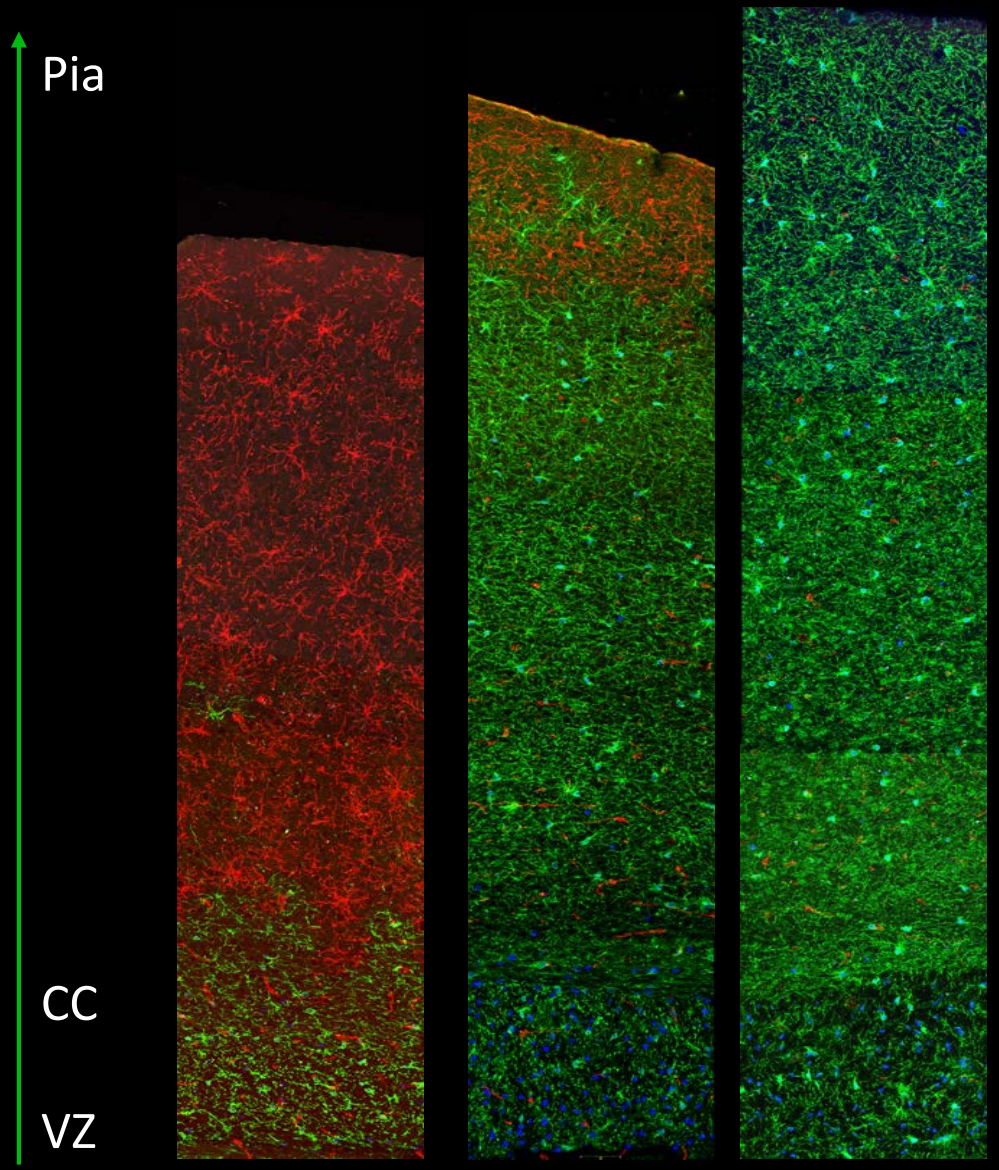
Abed AlFatah Mansour[1], J Tiago Gonçalves[1,4], Cooper W Bloyd[1], Hao Li[2], Sarah Fernandes[1,3], Daphne Quang[1], Stephen Johnston[1], Sarah L Parylak[1], Xin Jin[2] & Fred H Gage[1]



Nature Biotechnology, 2018

Mice neonatally-engrafted with human glial progenitor cells become substantially chimeric for human glia





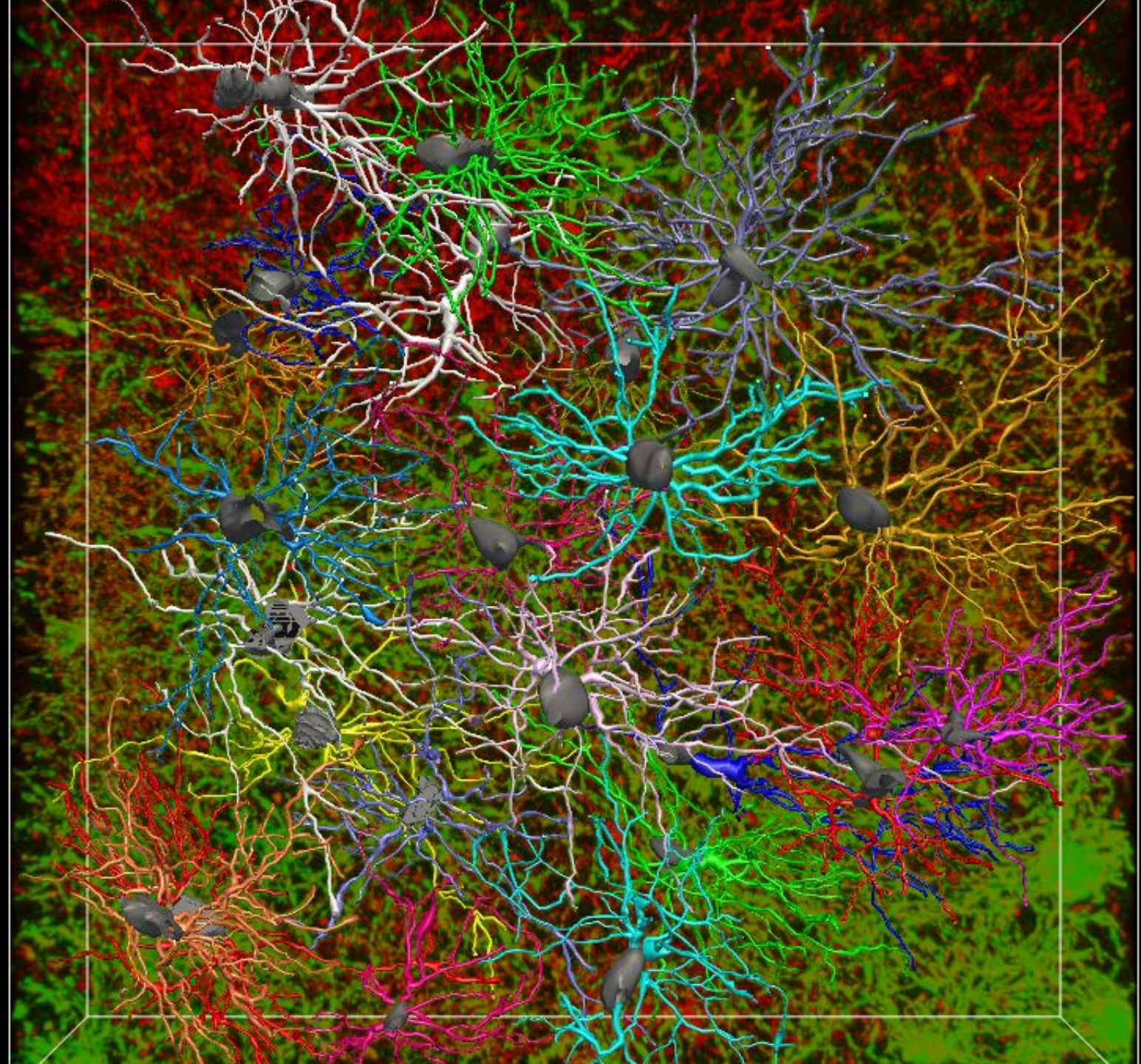
Human glial progenitors invade cortical parenchyma to displace and competitively replace mouse glial progenitors

hN
hNG2
msNG2

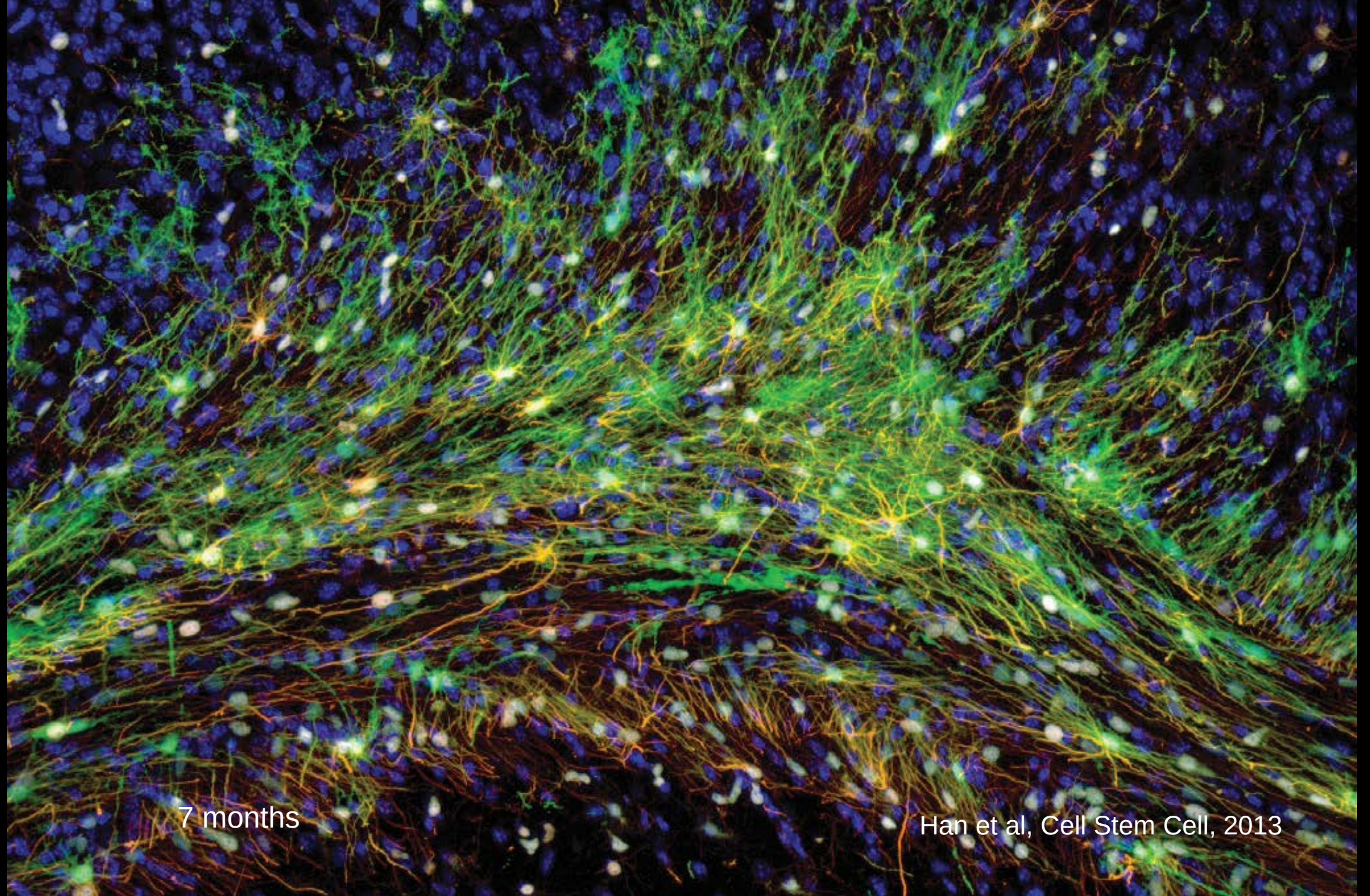
300 µm

Windrem et al. J. Neurosci., 2014

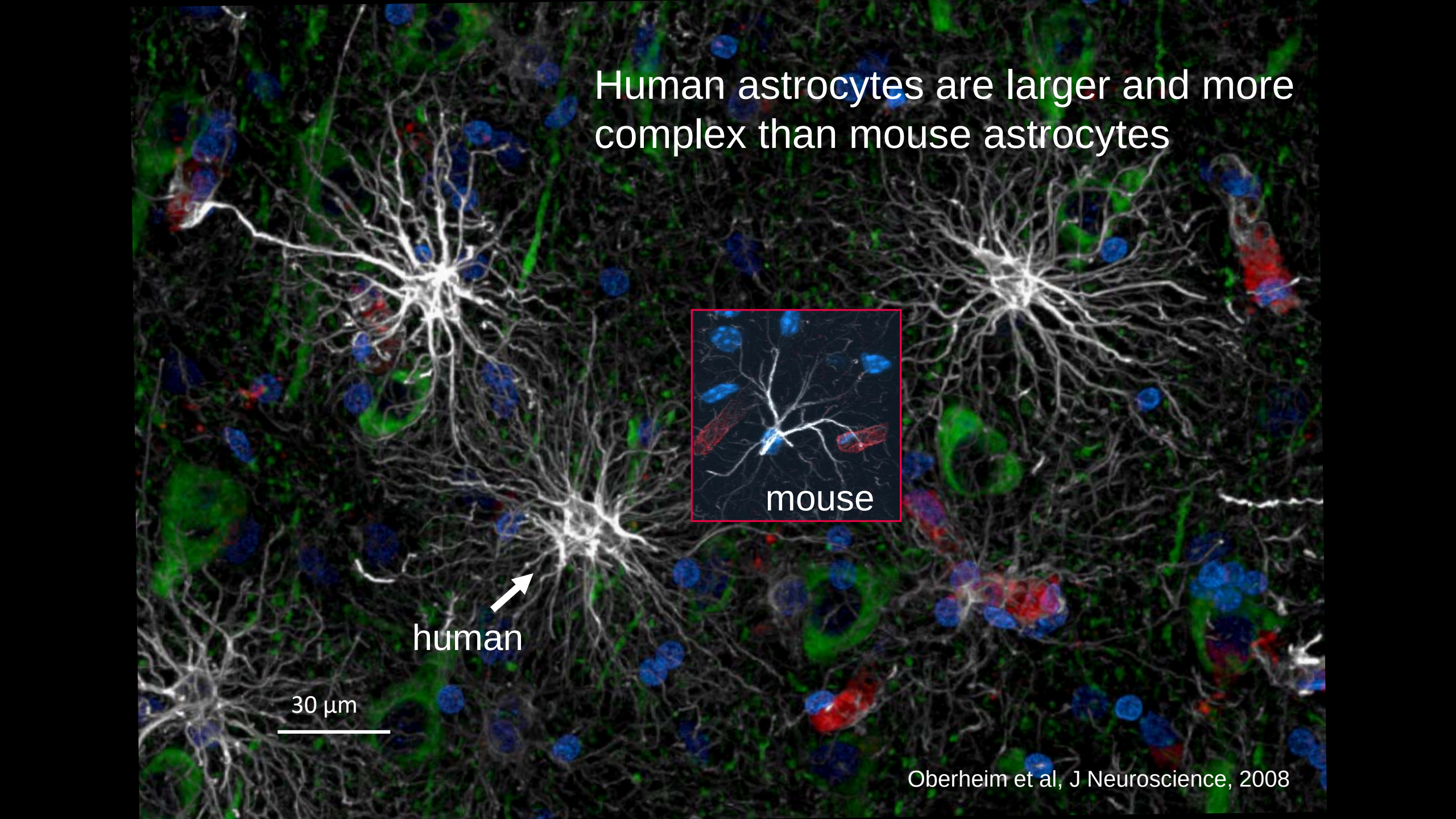
Human glial progenitor cells form dense networks in chimeric brains



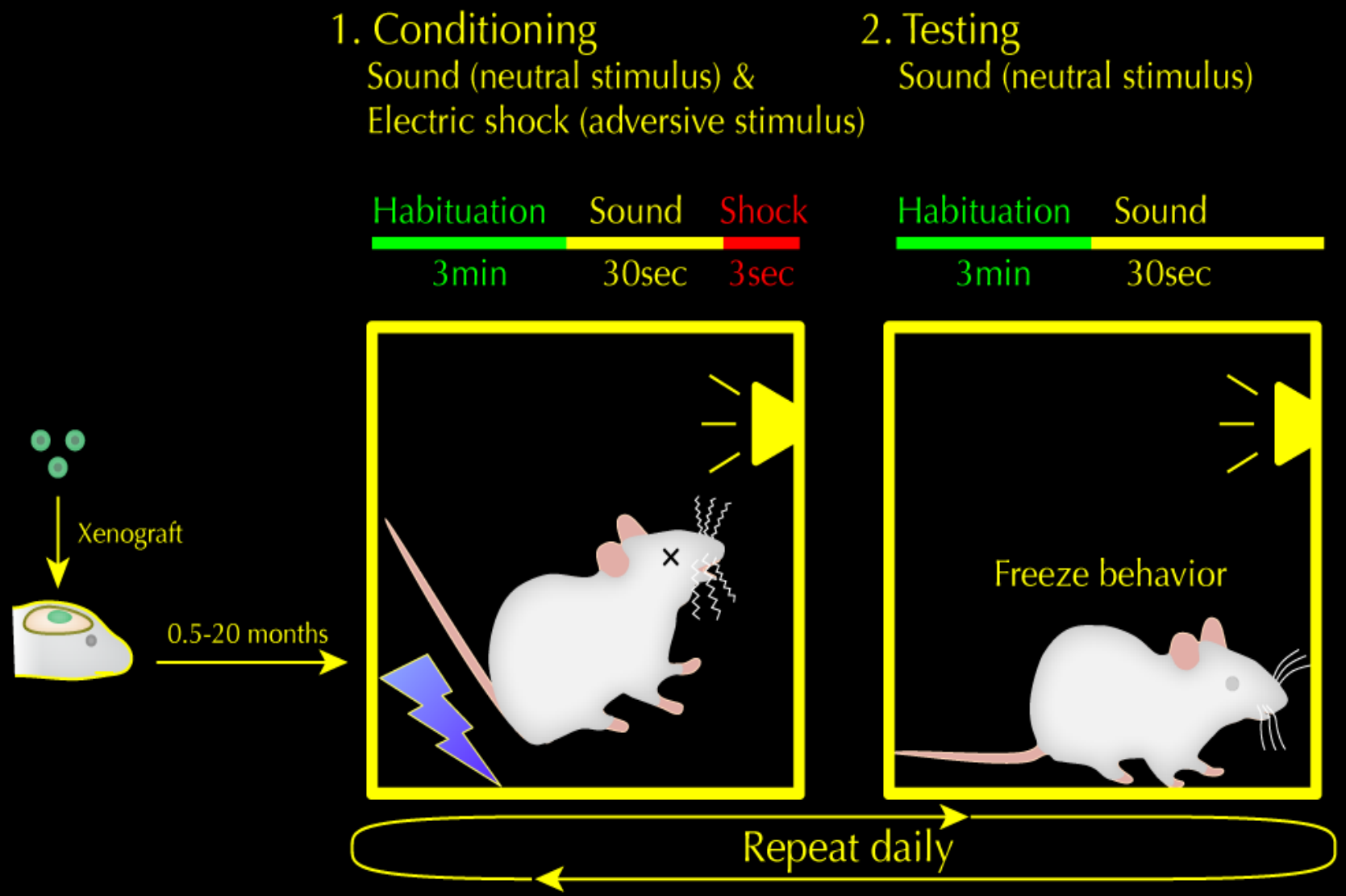
Joana Osorio, MD



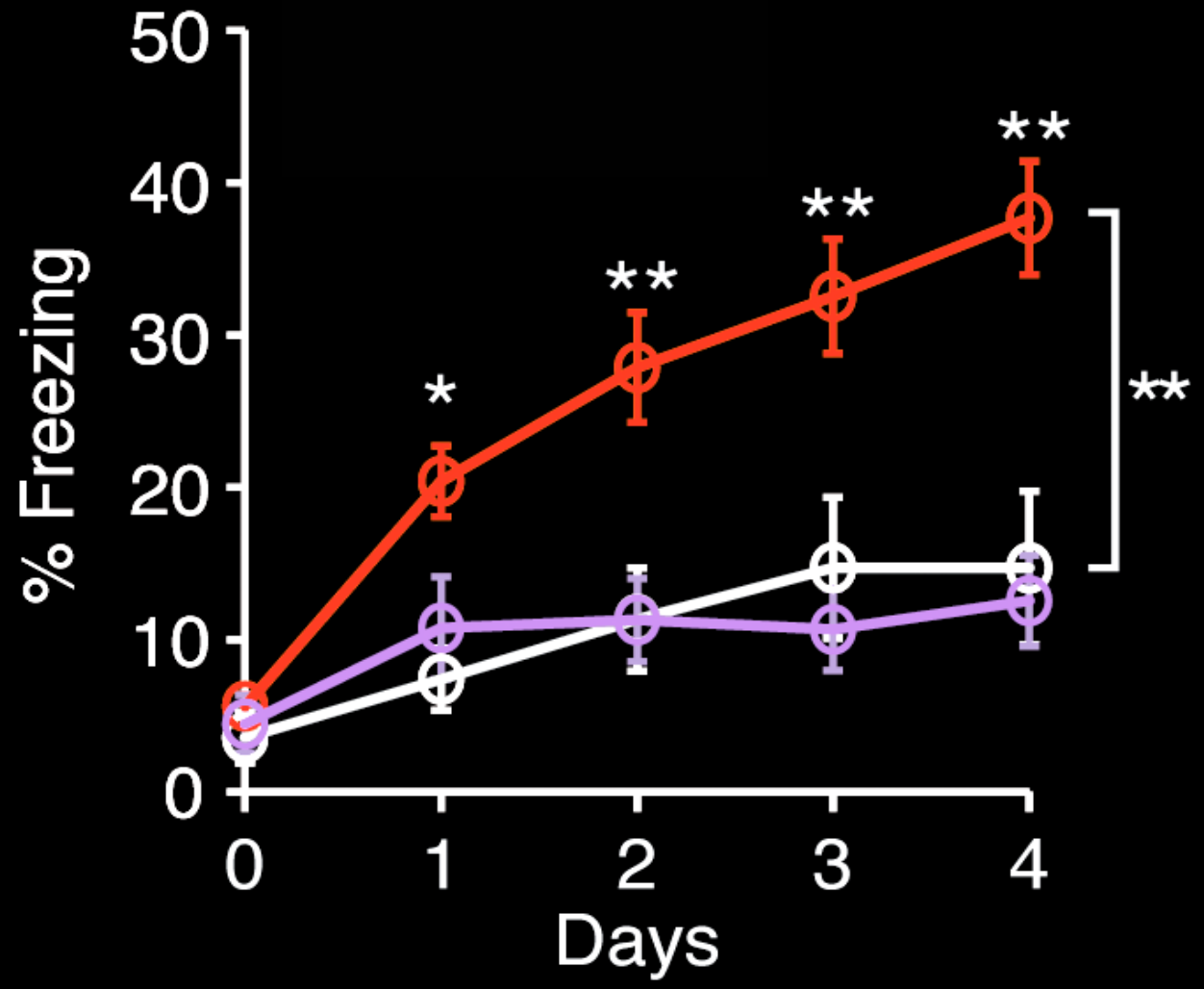
Han et al, Cell Stem Cell, 2013


Human astrocytes are larger and more complex than mouse astrocytes
mouse
human
30 µm
Oberheim et al, J Neuroscience, 2008

Are humanized glial chimeric mice smarter?



Human glial chimeric mice acquire conditioned fear more rapidly



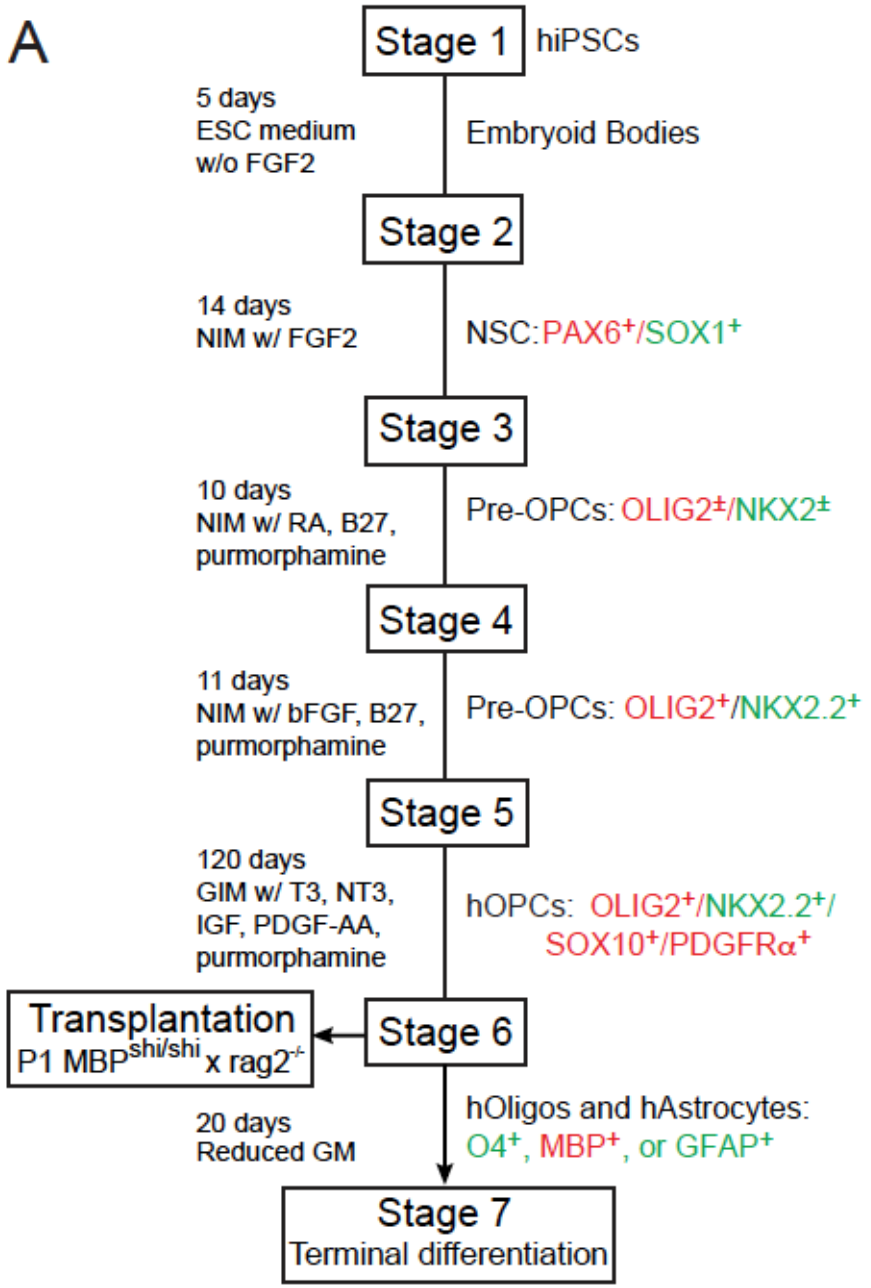
Human glial chimeric

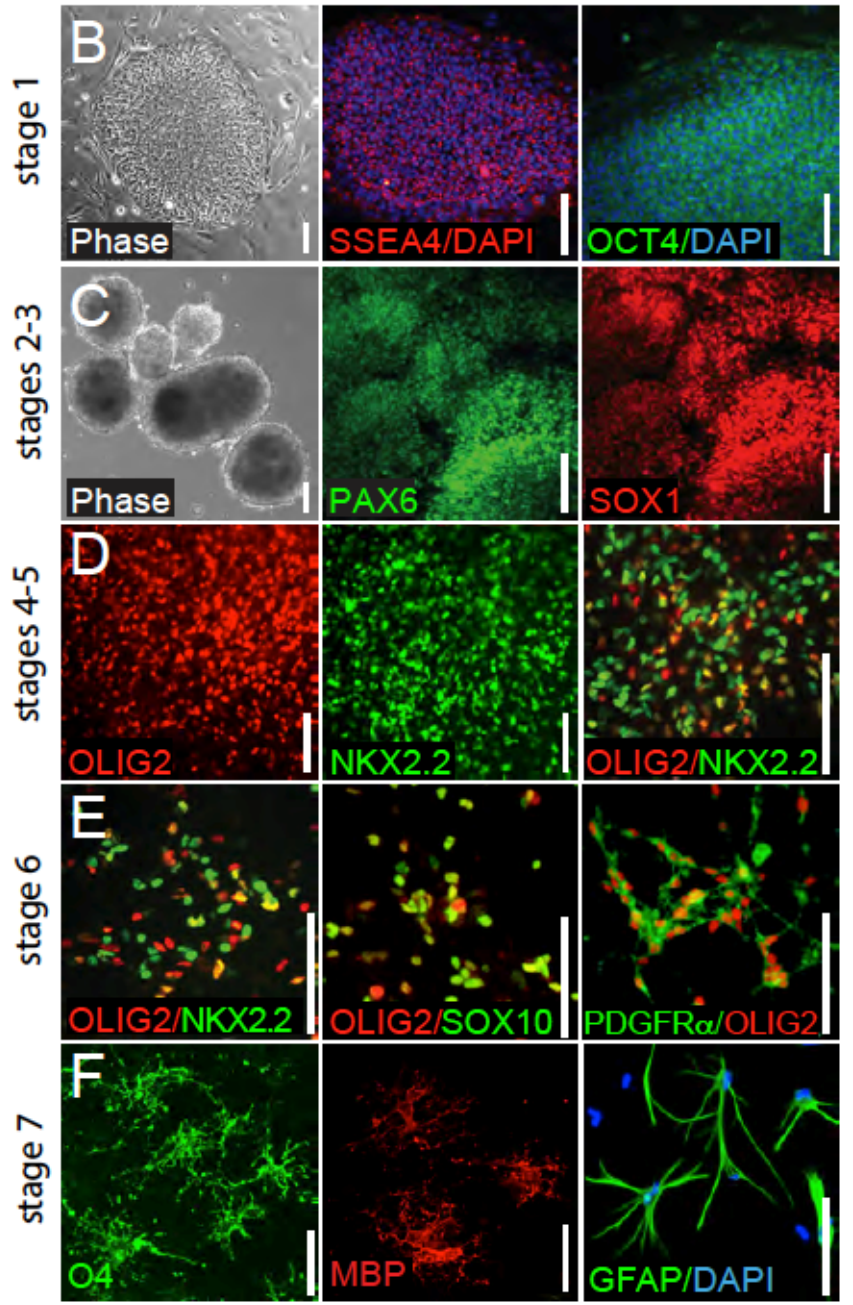
Mouse allograft control

Unengrafted control

Han et al., Cell Stem Cell, 2013

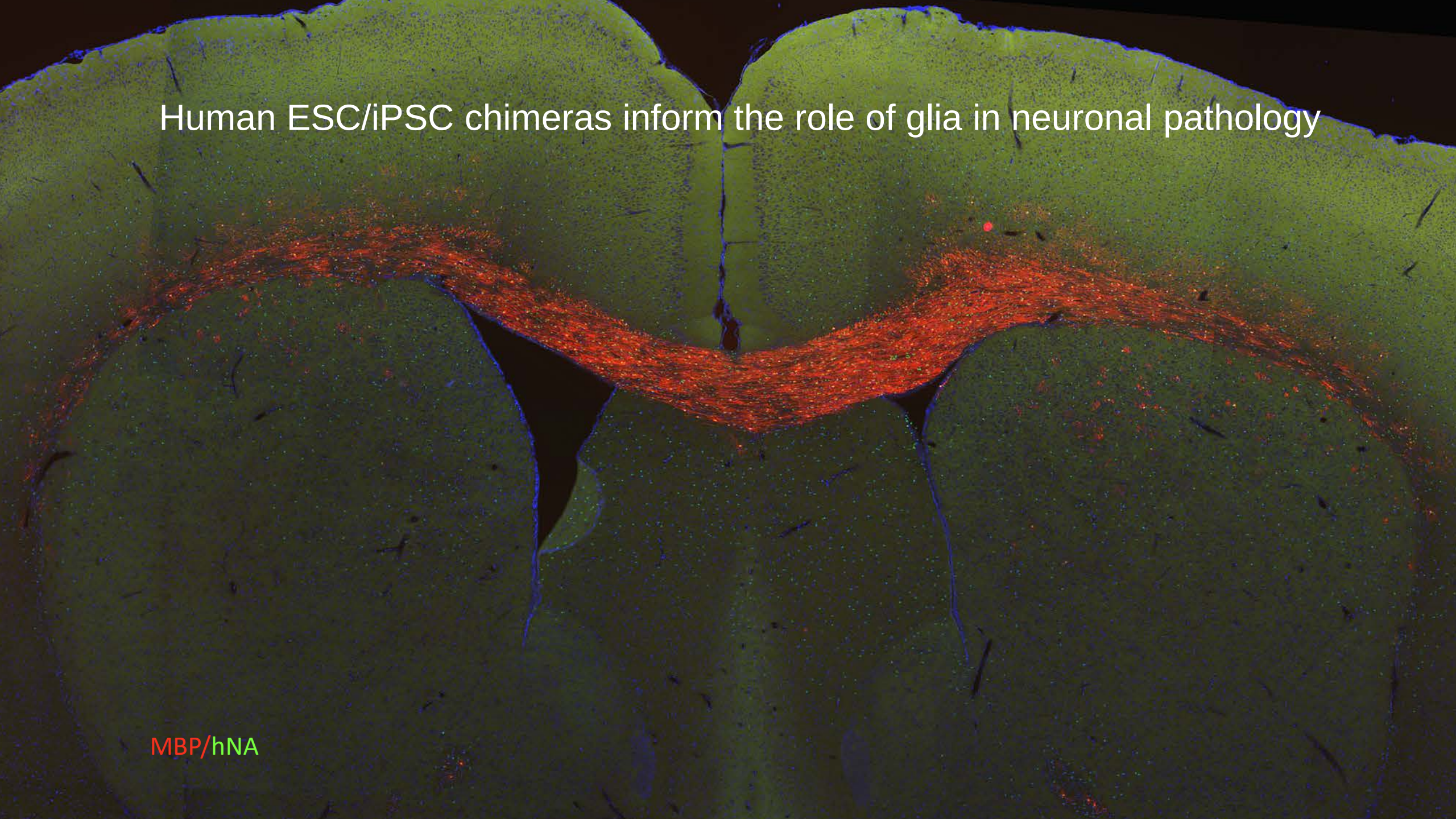
Production from pluripotent stem cells of patient- and disease-specific human glial progenitor cells





Wang et al, Cell Stem Cell, 2013

Human ESC/iPSC chimeras inform the role of glia in neuronal pathology



Human glial chimeras may be established with iPSC-derived GPCs to produce patient-specific human glial chimeric mice

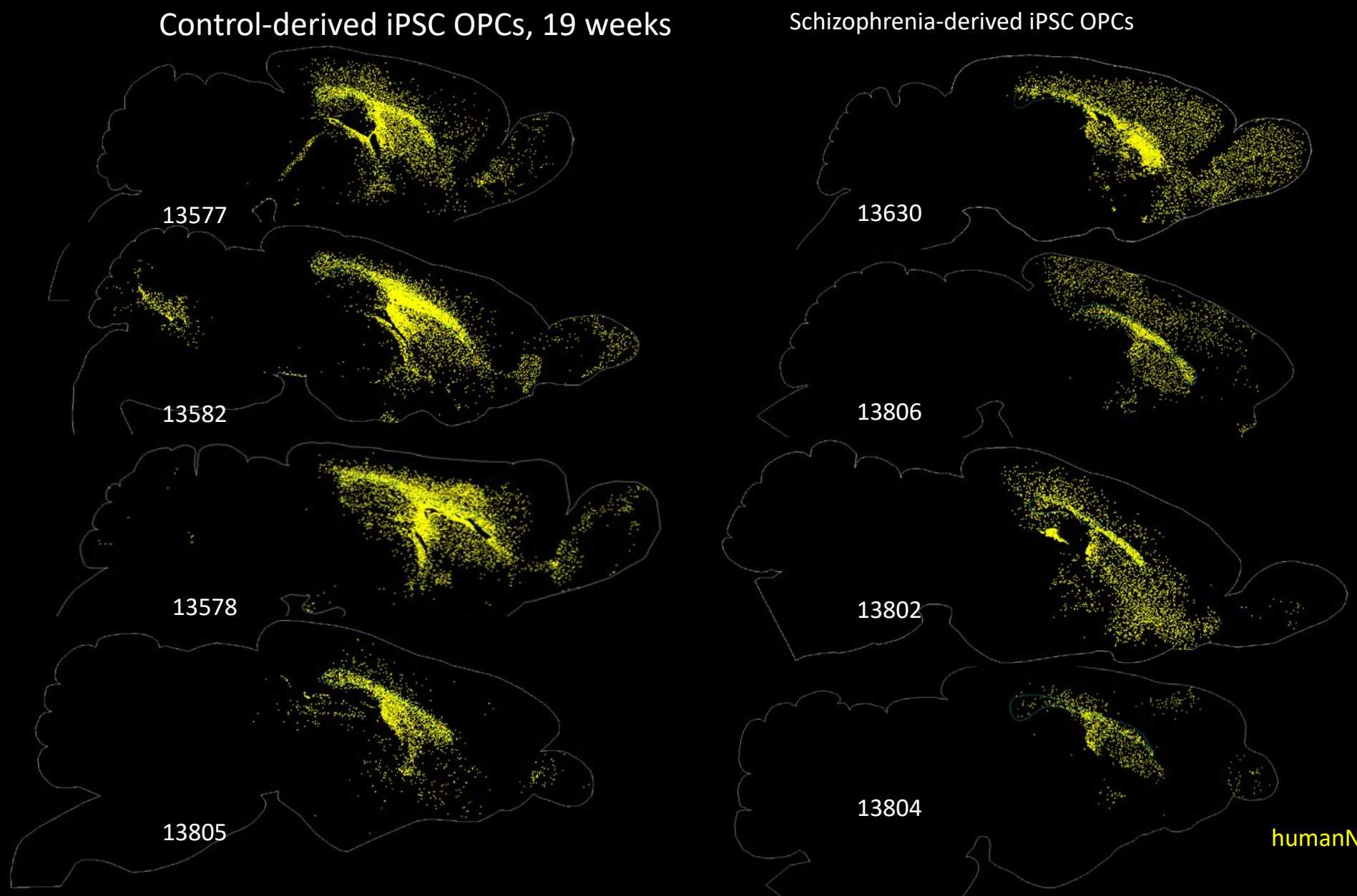
Patient-derived glial chimeras allow us to define the contributions of glial pathology to human-specific neurological disease

Neuropsychiatric disorders, such as schizophrenia, first appear in apes and humans, paralleling human glial evolution

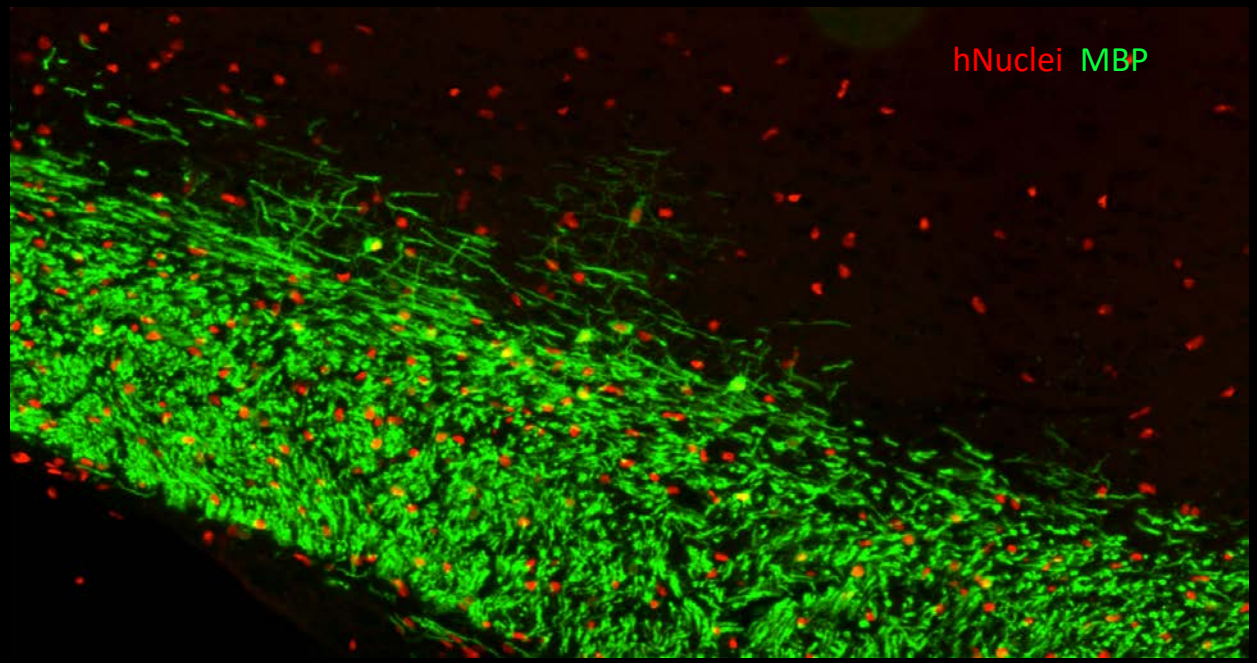
Is schizophrenia a glial disease?

Experiment: Compare chimeras established with iPSC GPCs from childhood-onset schizophrenics (n=8) to age/gender controls (n=6)

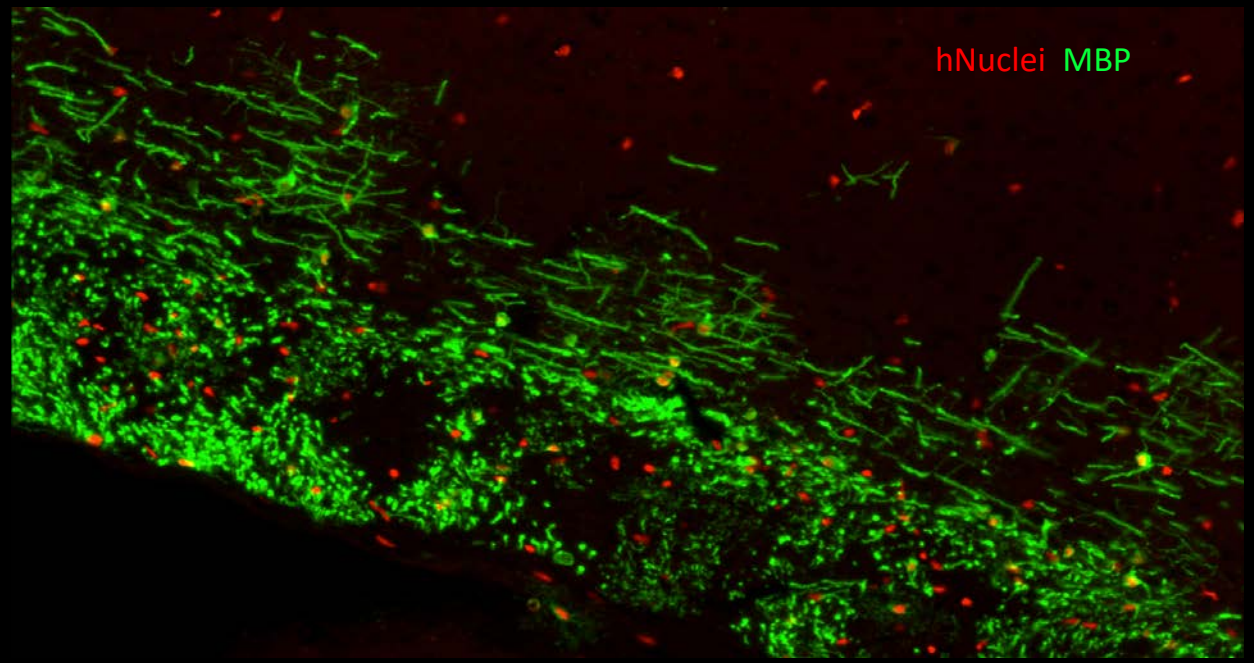
Juvenile-onset schizophrenic hiPSC OPCs exhibit abnormal migration



Myelination in hiPSC hGPC chimeras



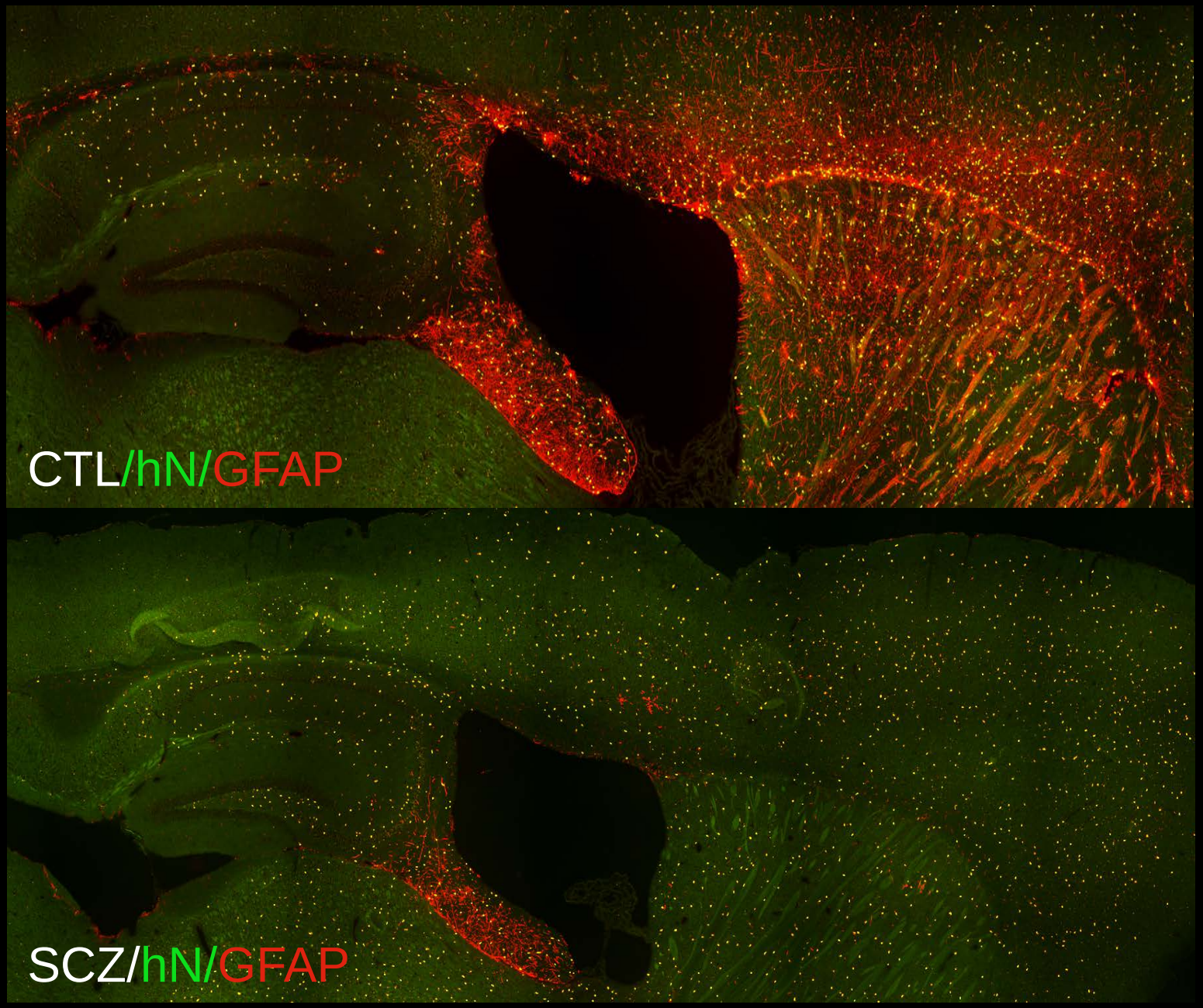
Control HGPC



SCZ hGPC

Windrem et al, Cell Stem Cell, 2017

Astrocytic differentiation by schizophrenia-derived GPCs is delayed in vivo



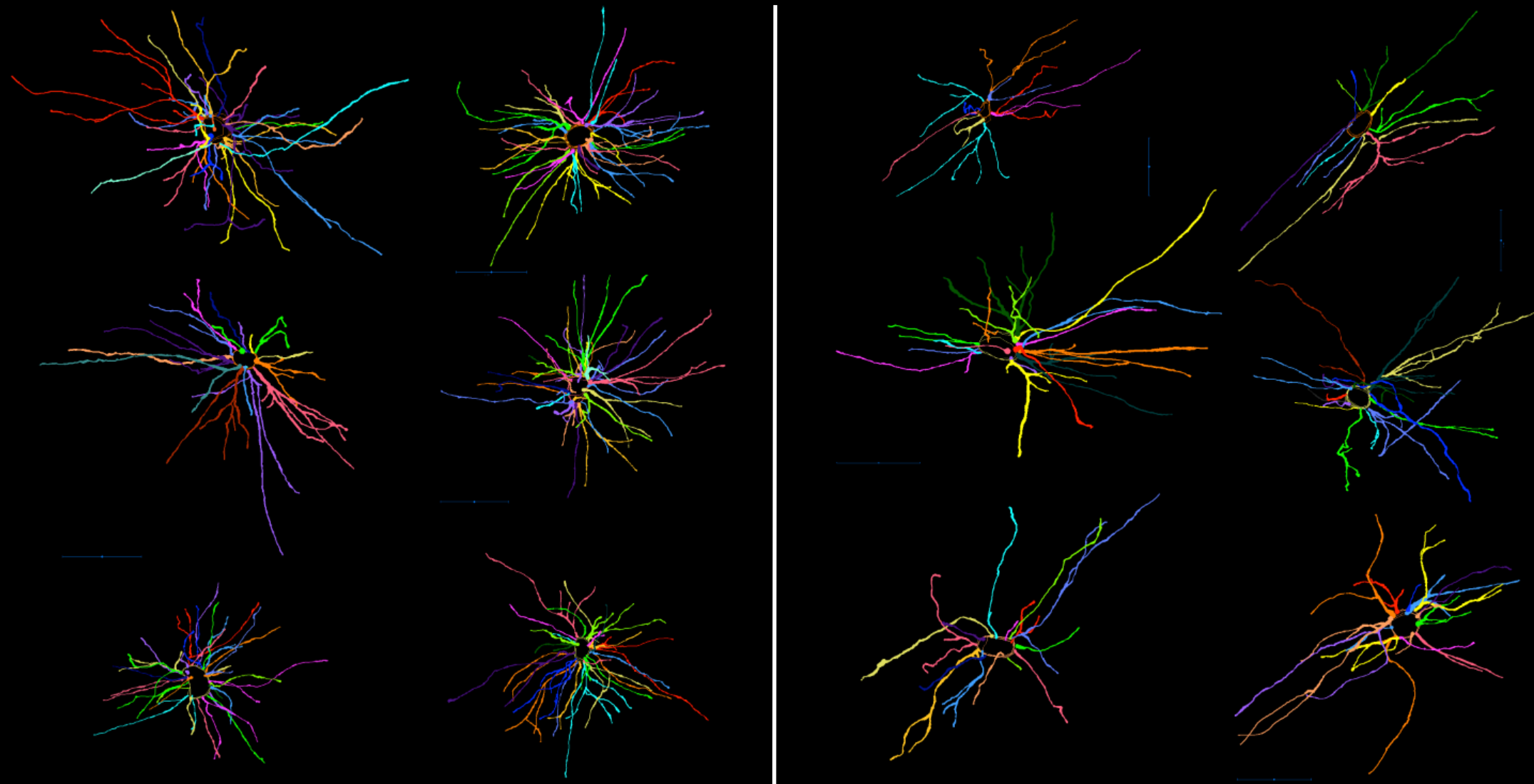
5 months after neonatal injection

Windrem et al., Cell Stem Cell, 2017

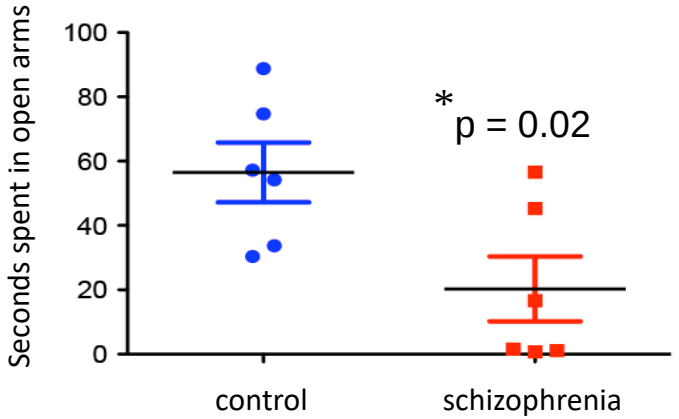
Schizophrenia-derived astrocytes are abnormal and occupy incomplete domains

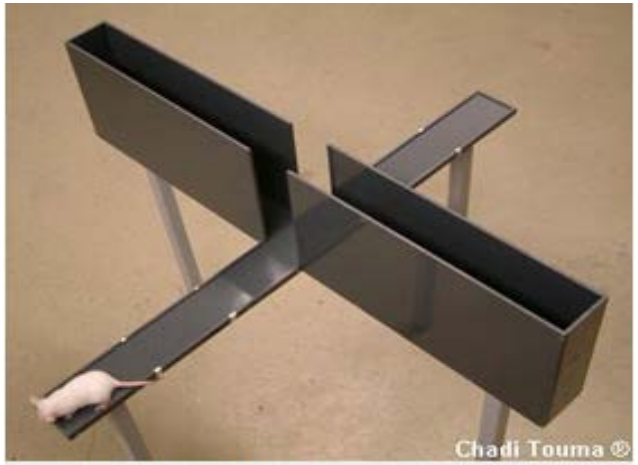
Control

Schizophrenia

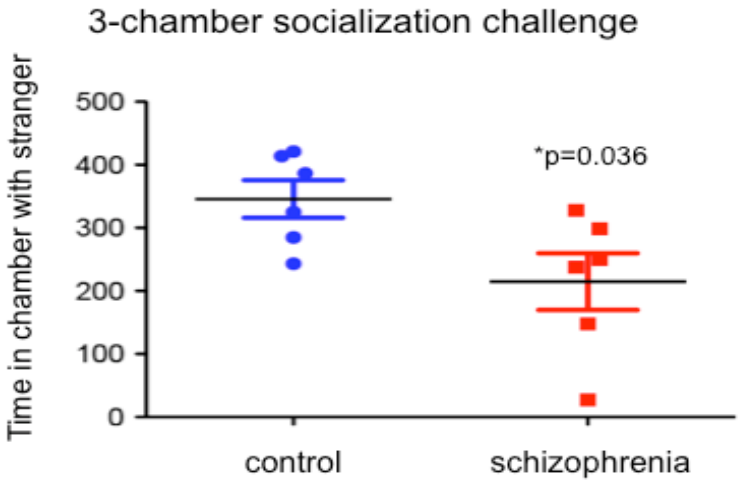


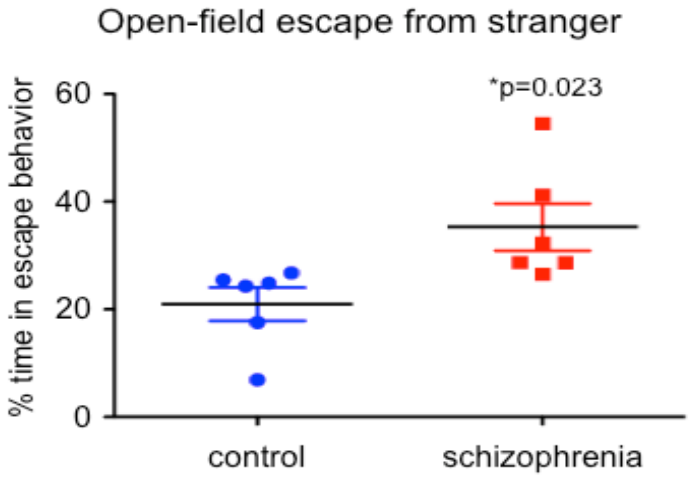
Schizophrenia-derived iPSC OPC-implanted mice exhibit markedly increased anxiety and antisocial behavior



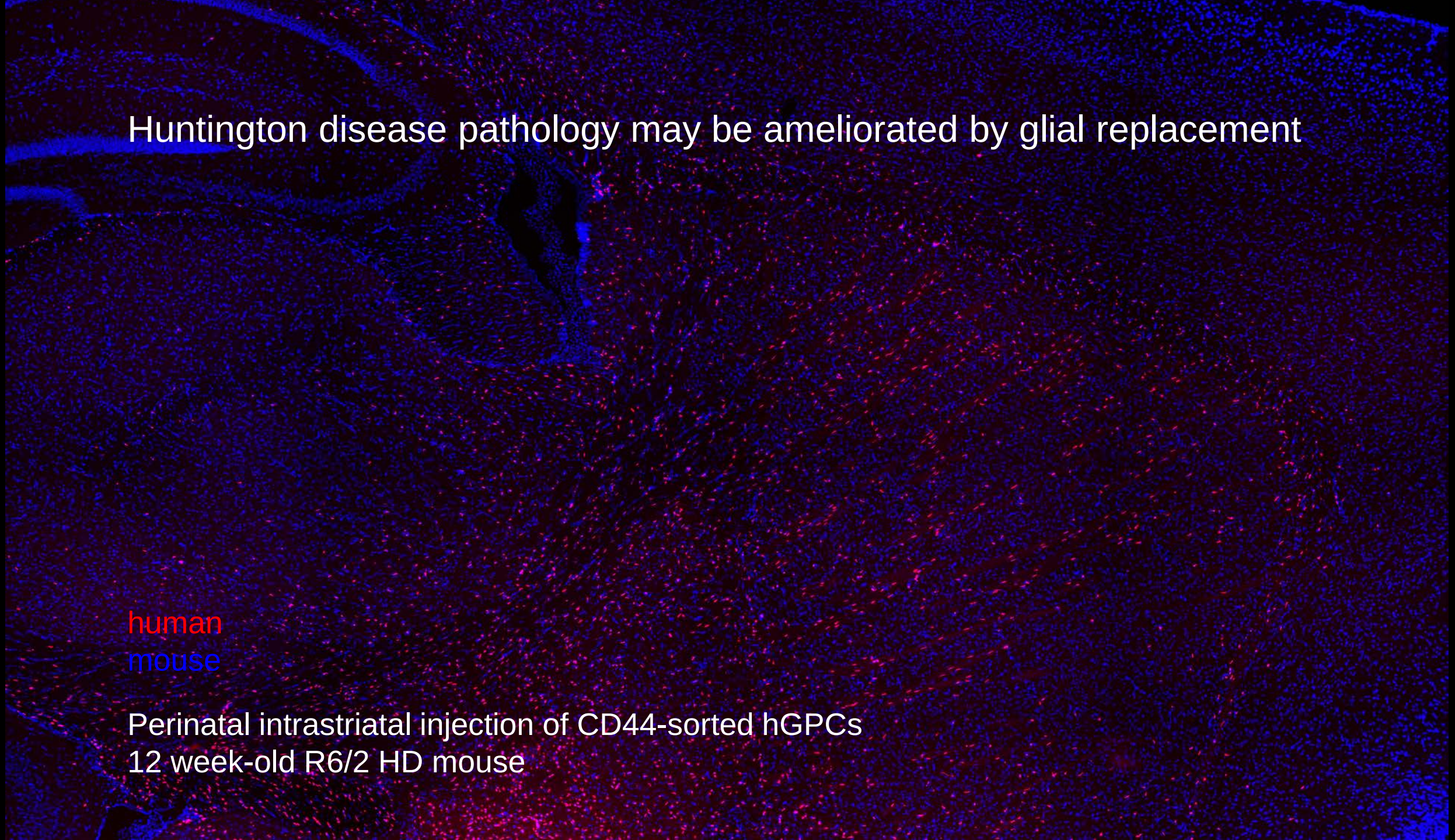


Elevated plus-maze test

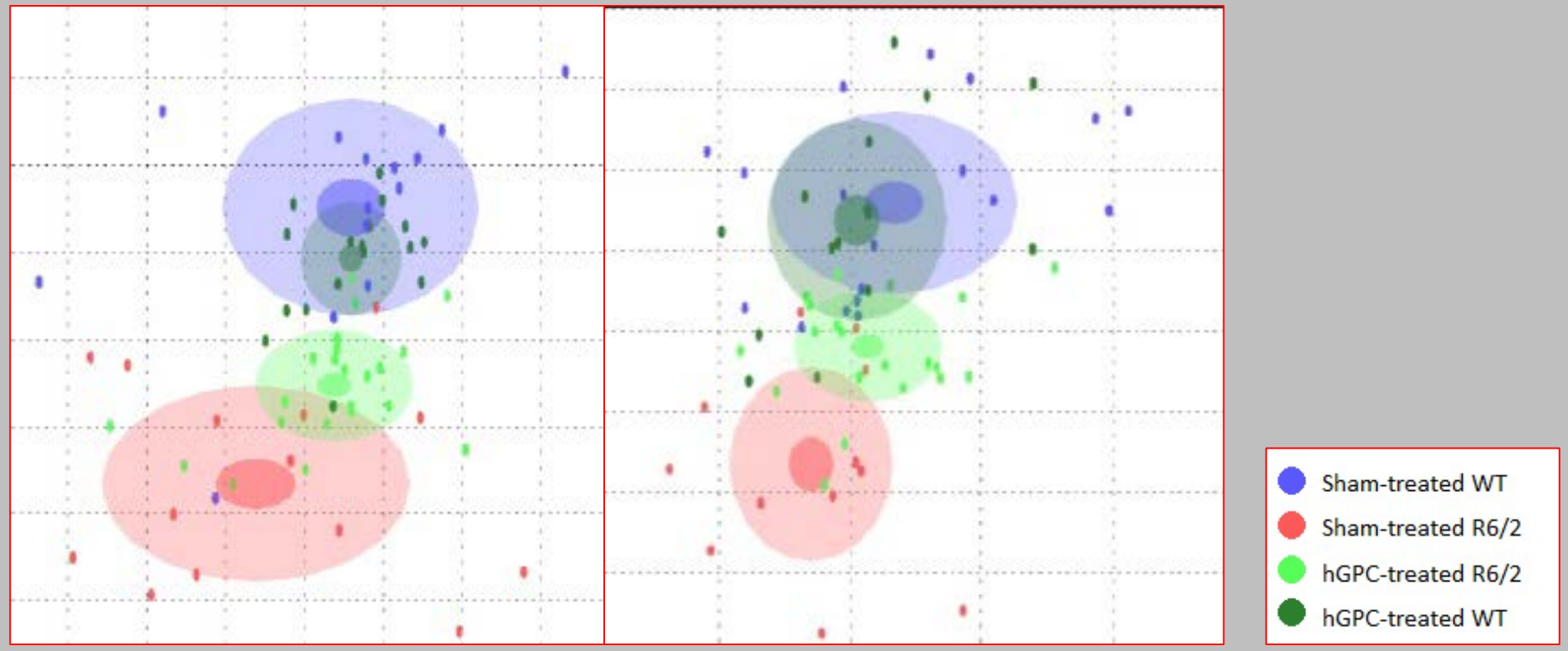




9 months old


Huntington disease pathology may be ameliorated by glial replacement
human
mouse
Perinatal intrastriatal injection of CD44-sorted hGPCs
12 week-old R6/2 HD mouse

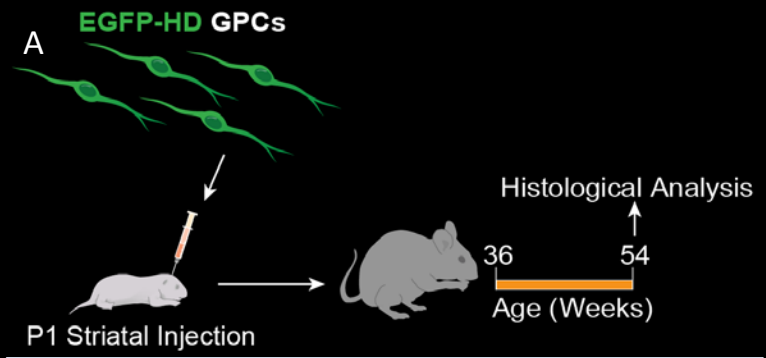
hGPC transplantation lessens HD-related cognitive and motor deficits in R6/2 HD mice

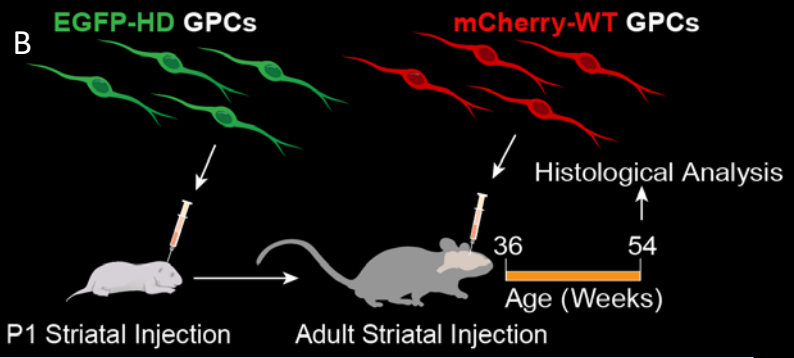


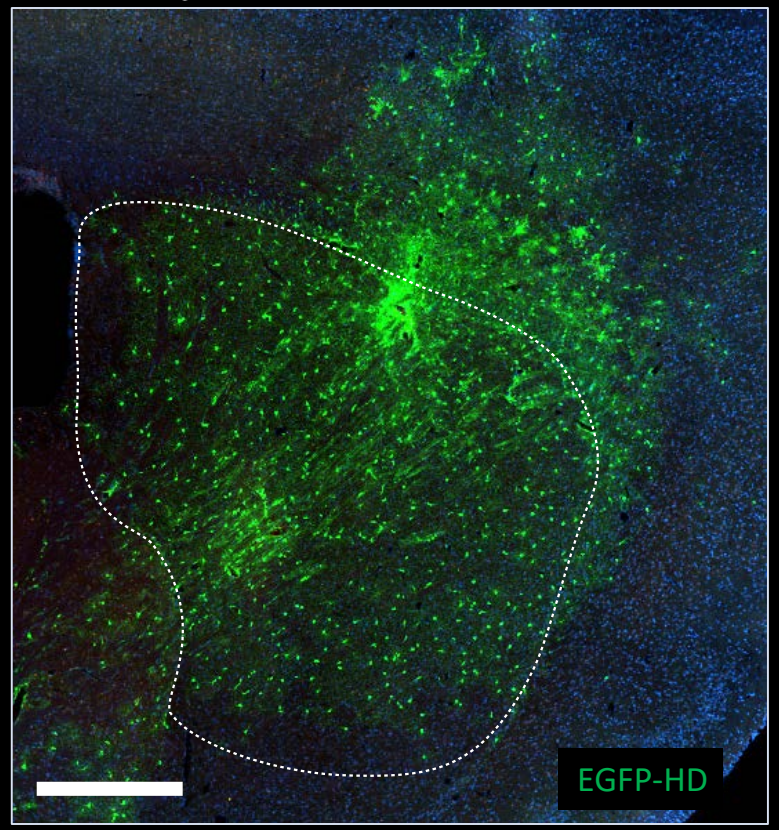
8 weeks post-transplant, SmartCube 11 weeks post-transplant, NeuroCube

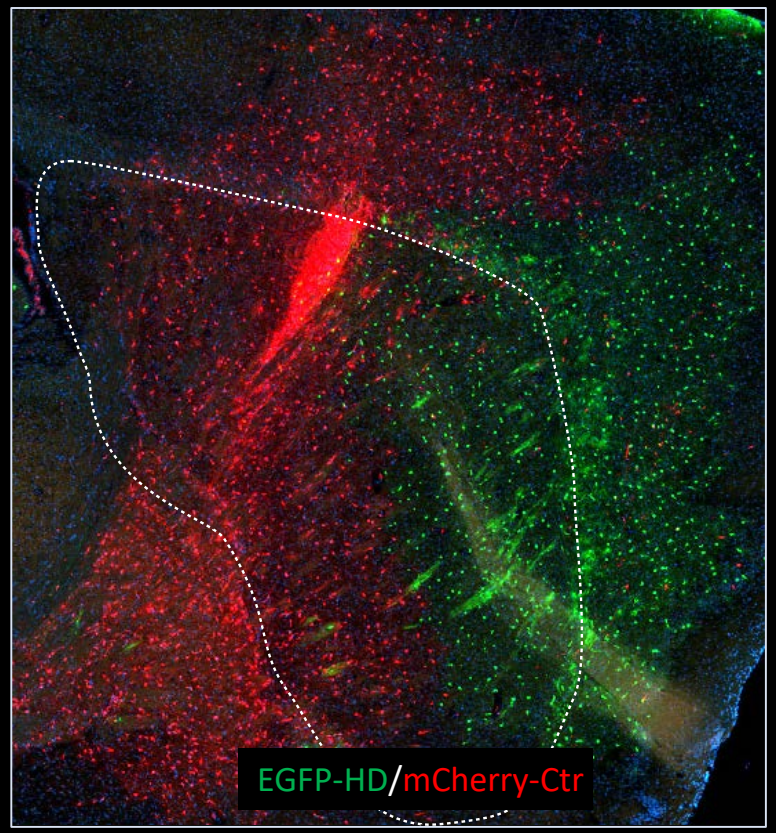
Benraiss et al, Nature Comm., 2016
Osipovitch et al., Cell Stem Cell, 2019

Therapeutic modeling: Human vs human competition may be assessed in mouse chimeras

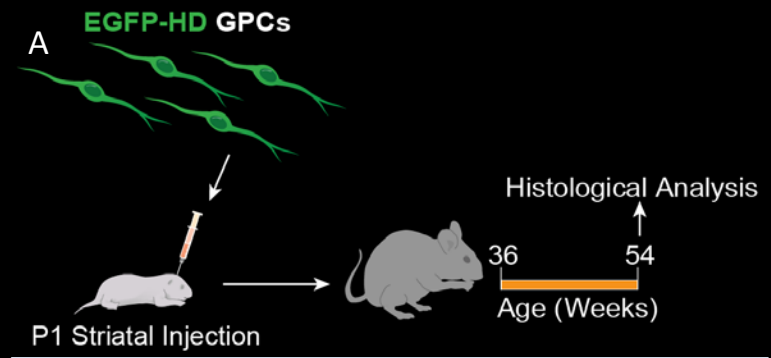


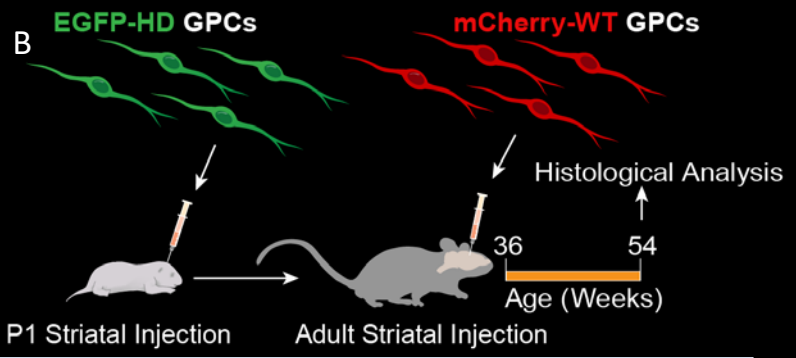


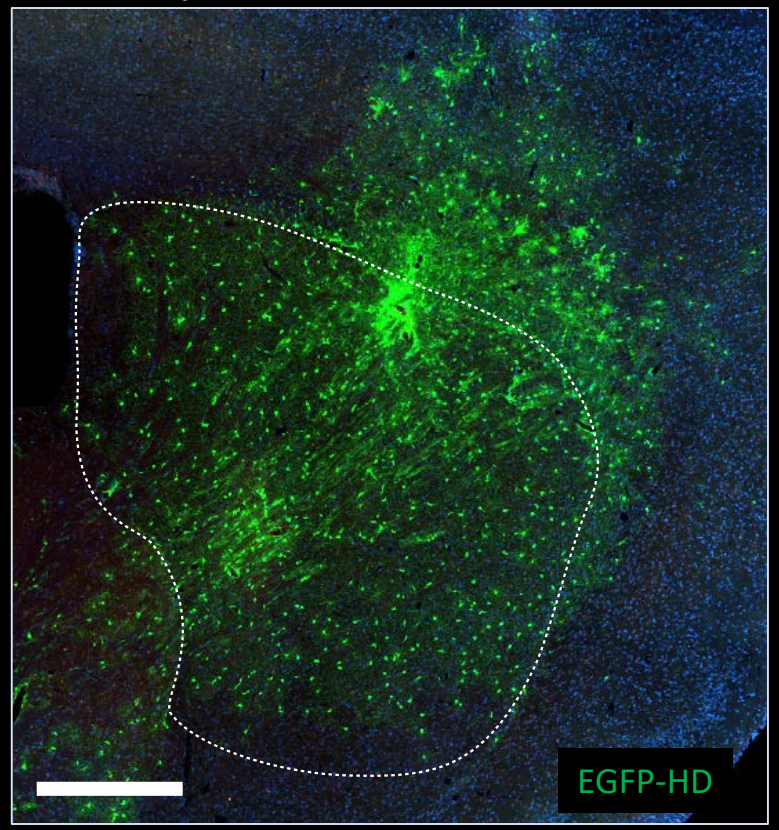


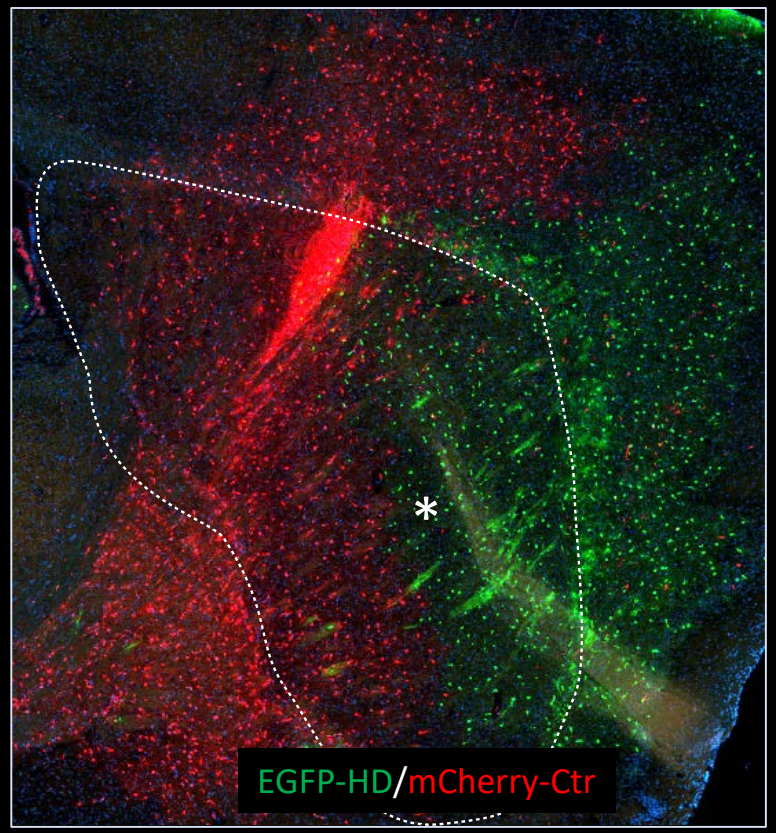


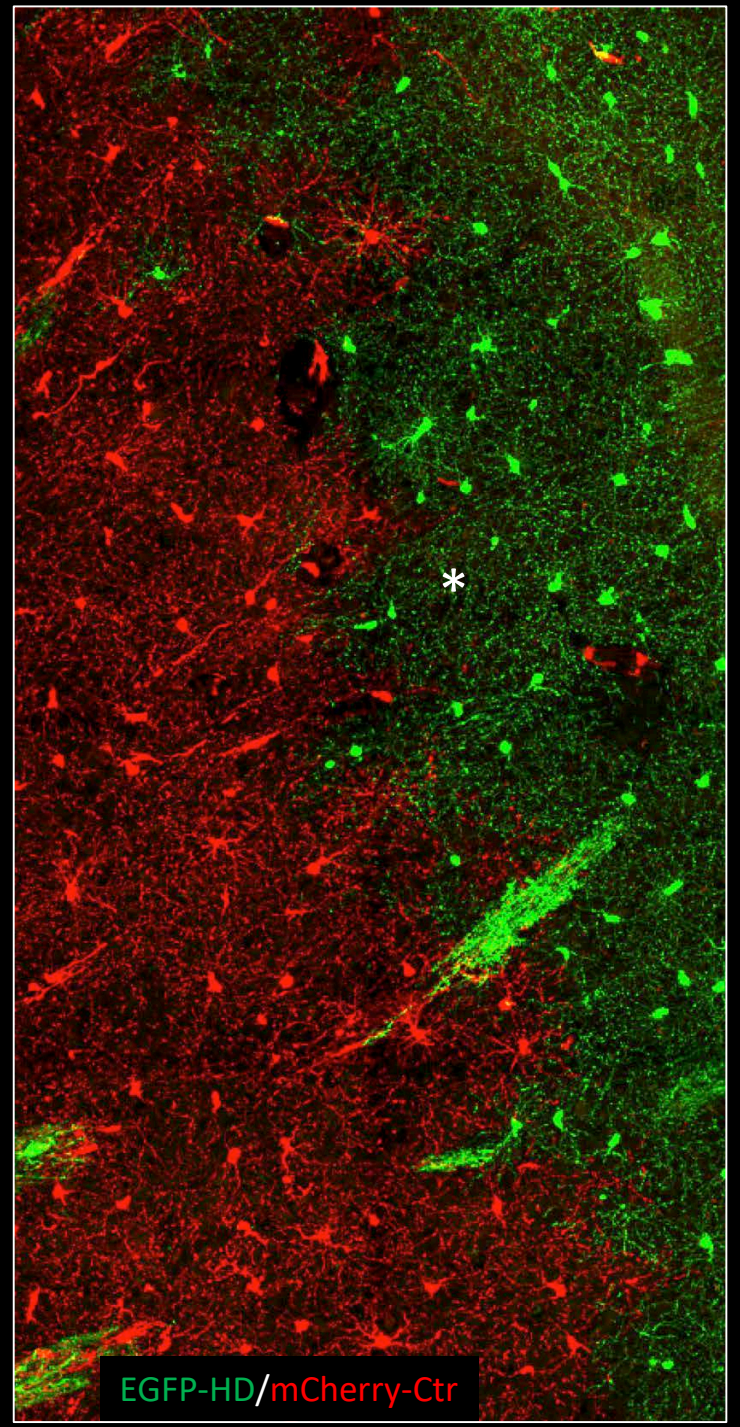
Human vs human competition may be assessed in mouse chimeras



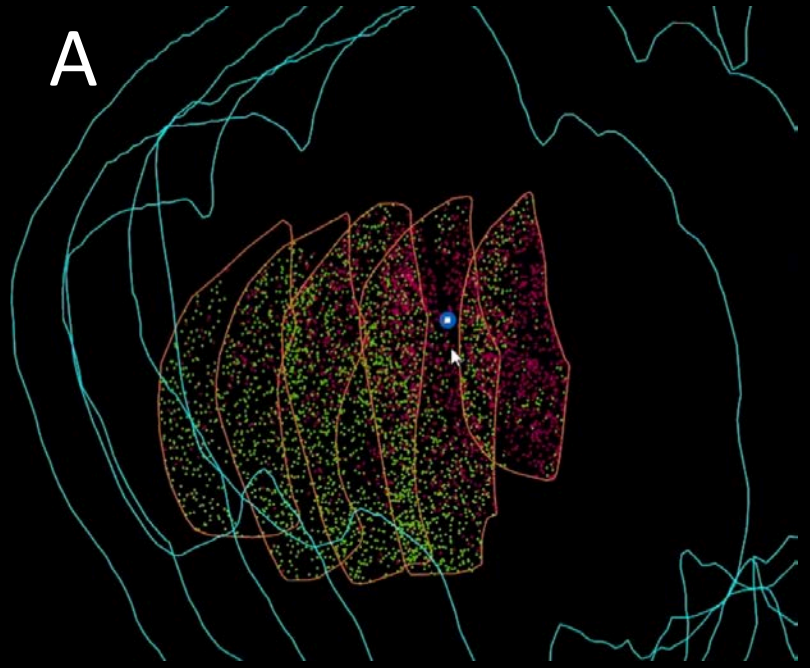


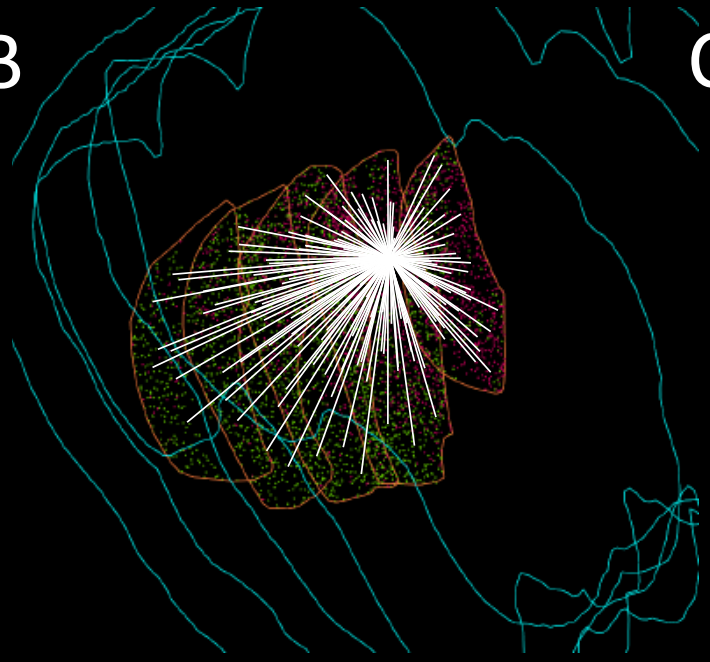


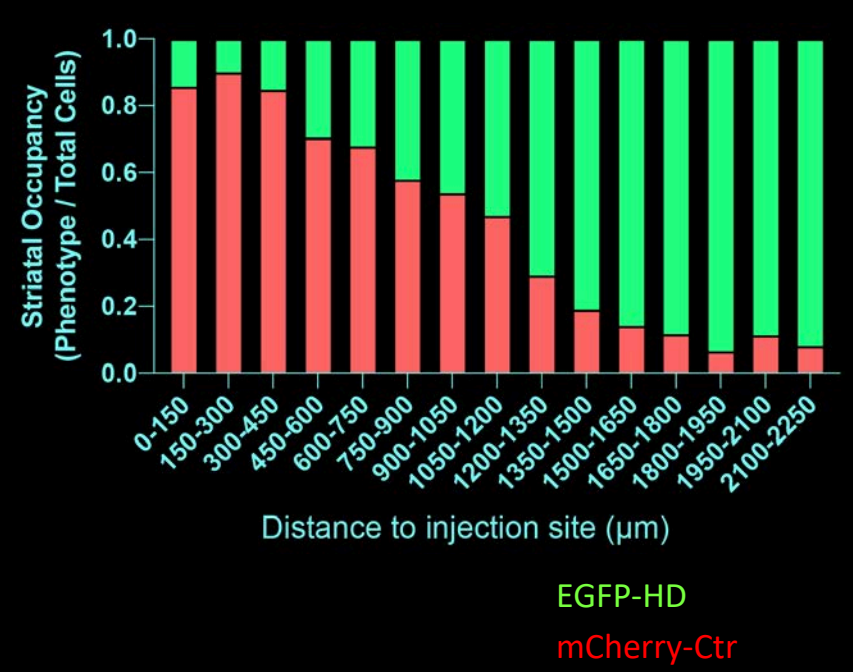




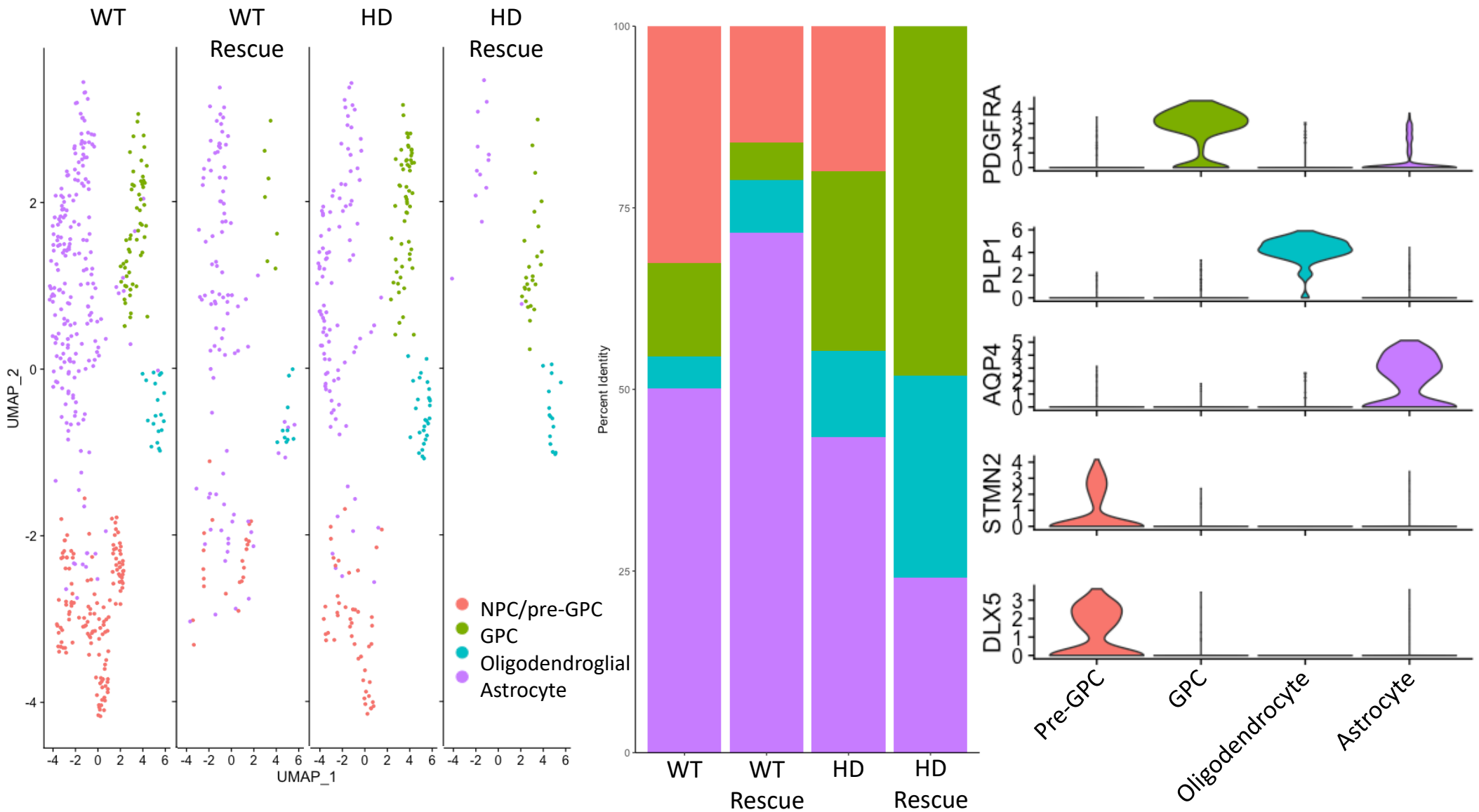
Healthy donor hGPCs confront and dominate mHTT-expressing hGPCs, as a function of time and distance





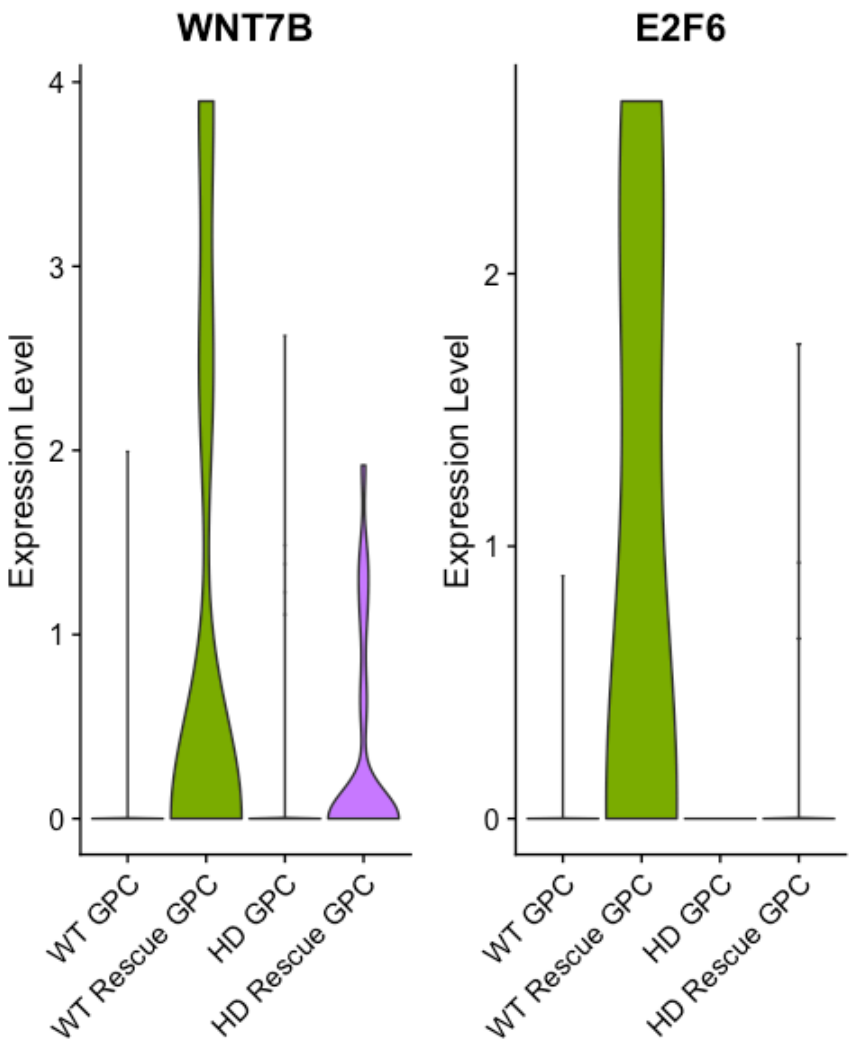


Allogenic human glial competition in a mouse: WT and HD glia from mouse striata - 54 weeks

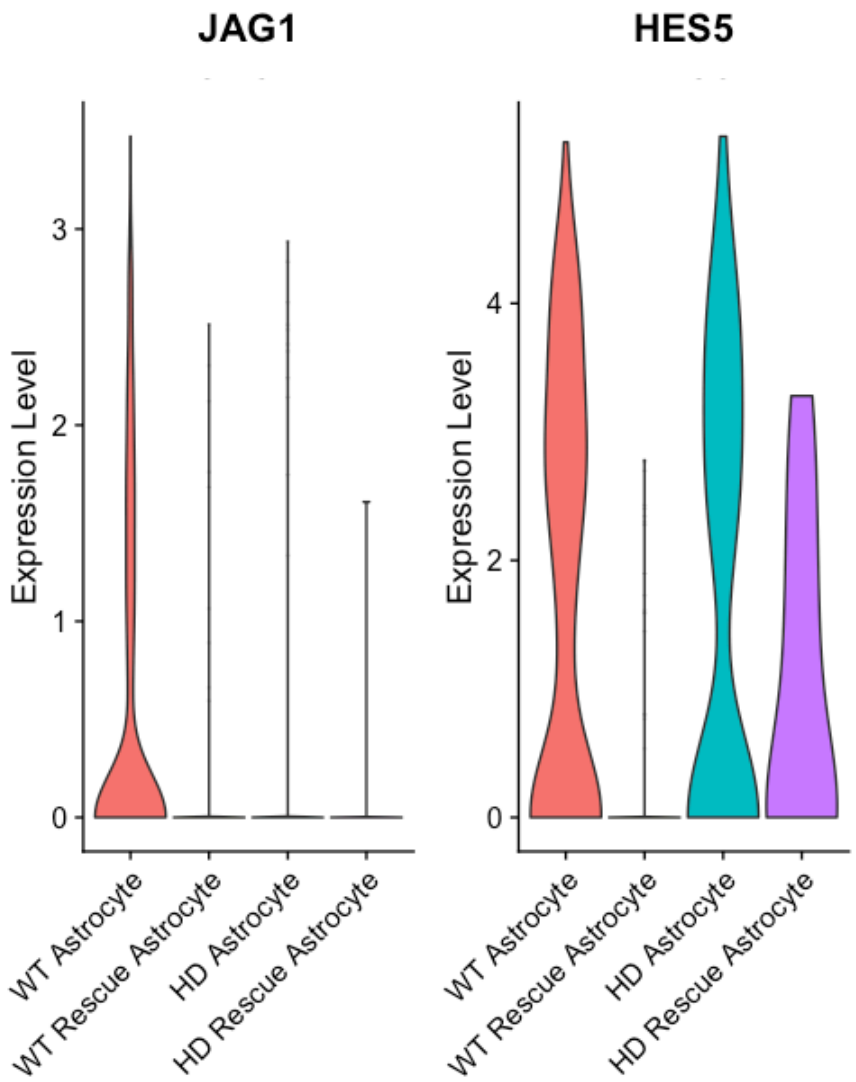


Differential gene expression of WT and HD glia during competition

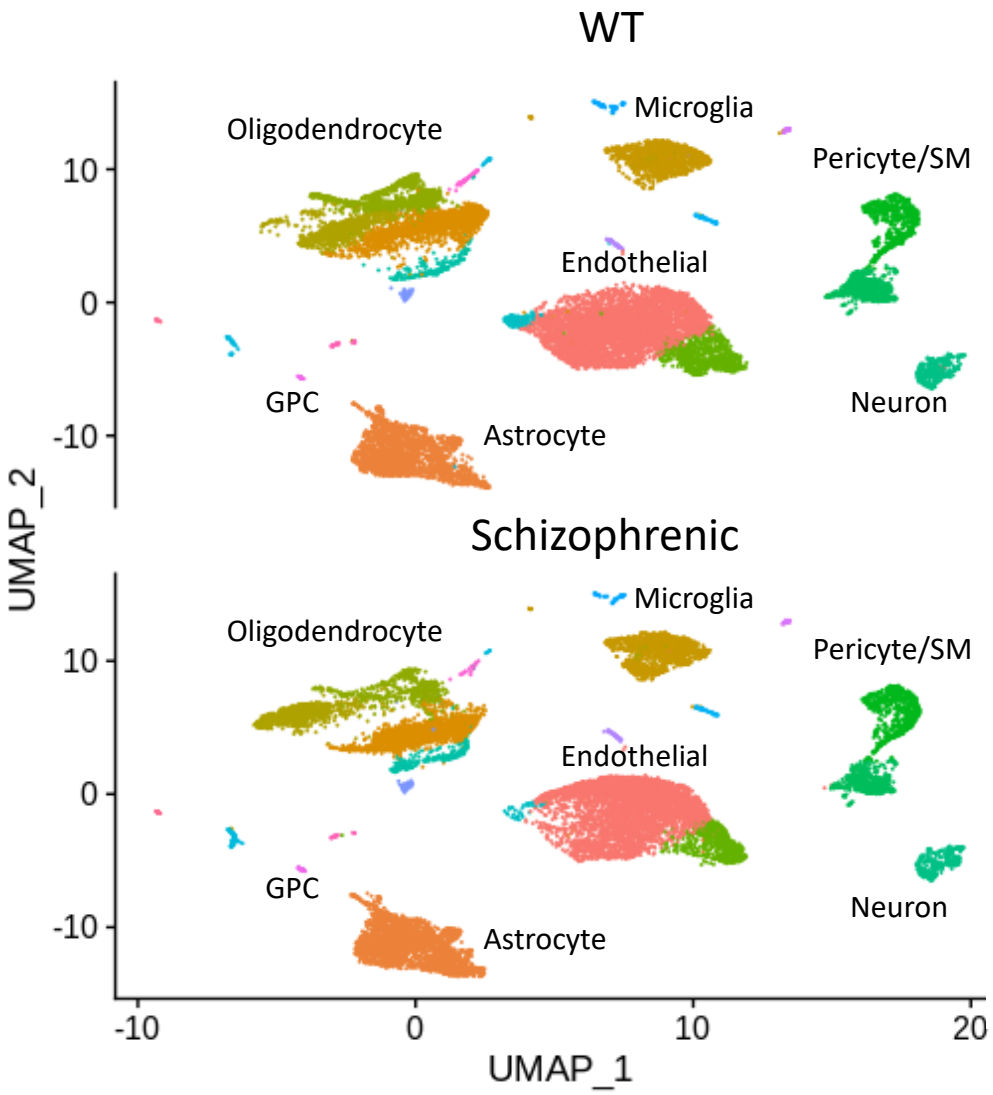
Differentially Expressed in Rescue GPCs

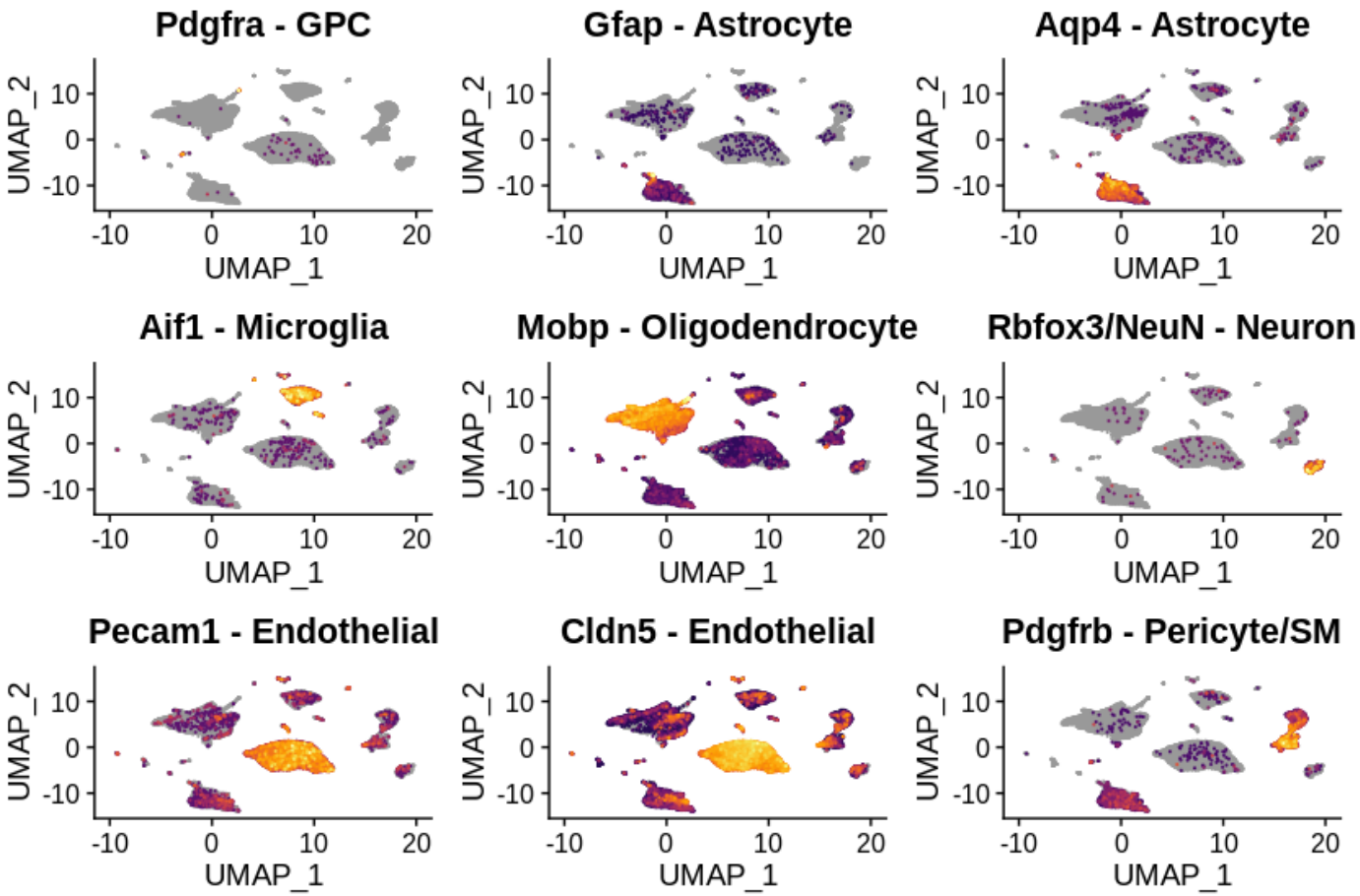


Differentially Expressed in Rescue Astrocytes



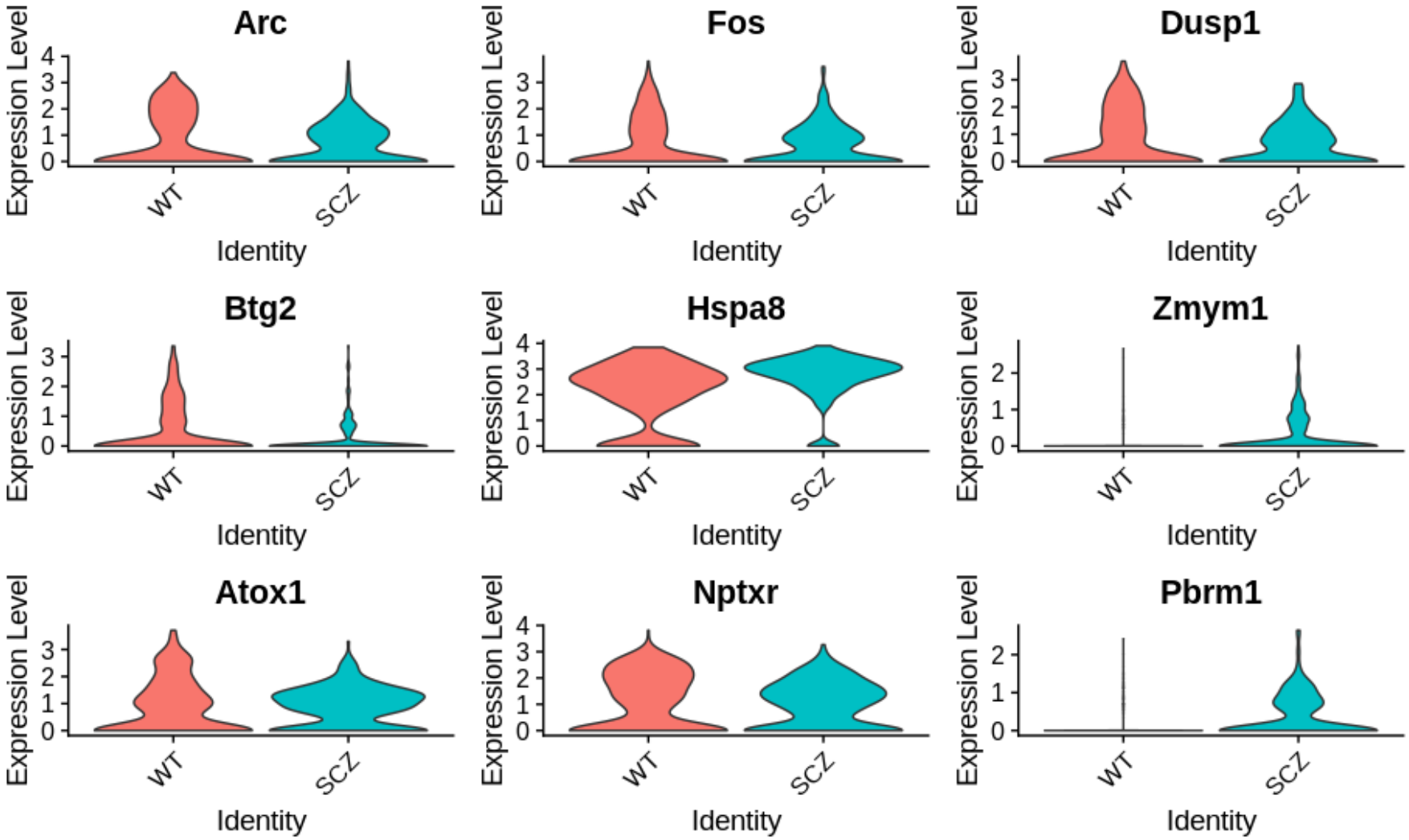
Effects of donor **on host**: Mouse cells in cortex of perinatally engrafted WT and SCZ hGPCs





1 year in vivo

Mouse neuronal genes dysregulated in the presence of human SCZ Glia



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Supported by:

- NIMH
- NINDS
- Novo Nordisk Foundation
- Lundbeck Foundation
- Adelson Medical Research Foundation
- Mathers Charitable Foundation

Oscine Therapeutics

Sana Biotechnology

Goldman lab

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