

Interdisciplinary Technical Journal Club: special
series on Laboratory Animal Science

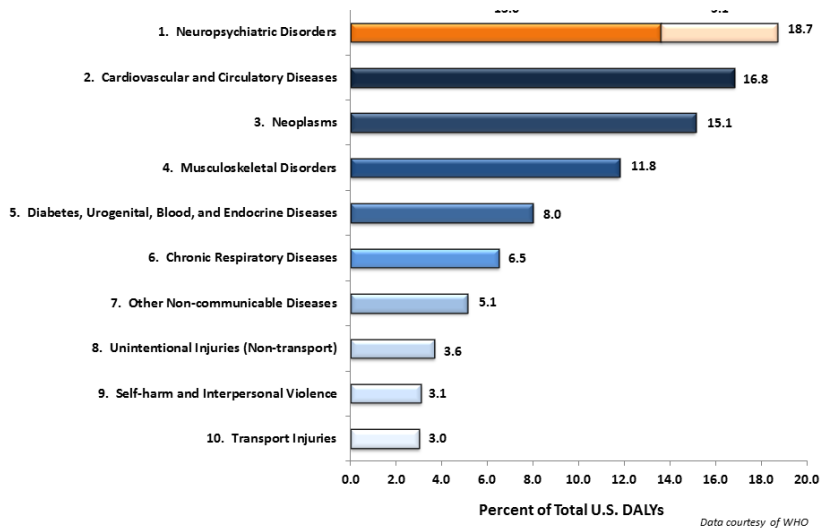
Human-mouse chimeric models for studying brain disorders

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07.05.2019

Brain disorders: challenges of drug discovery

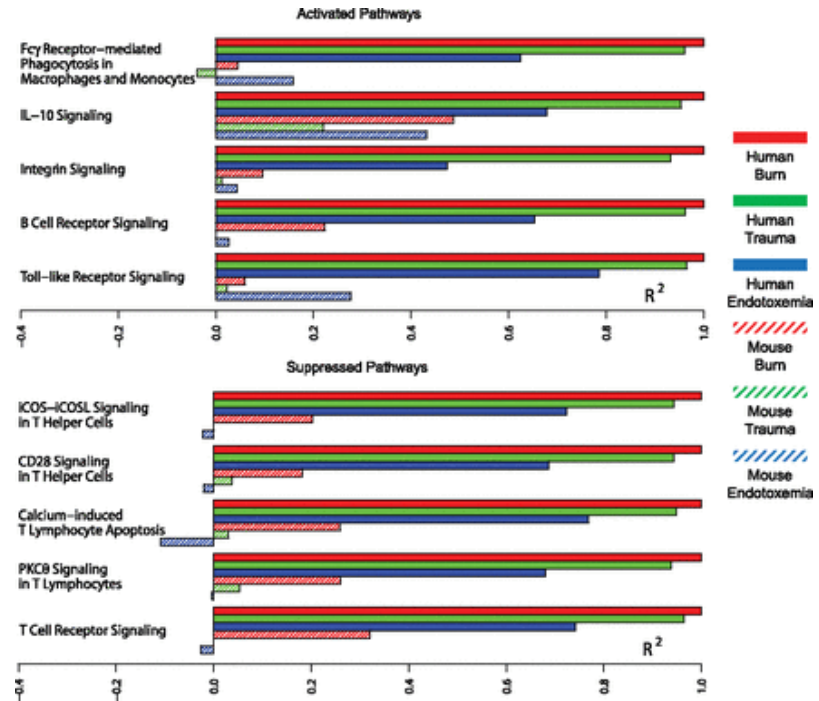
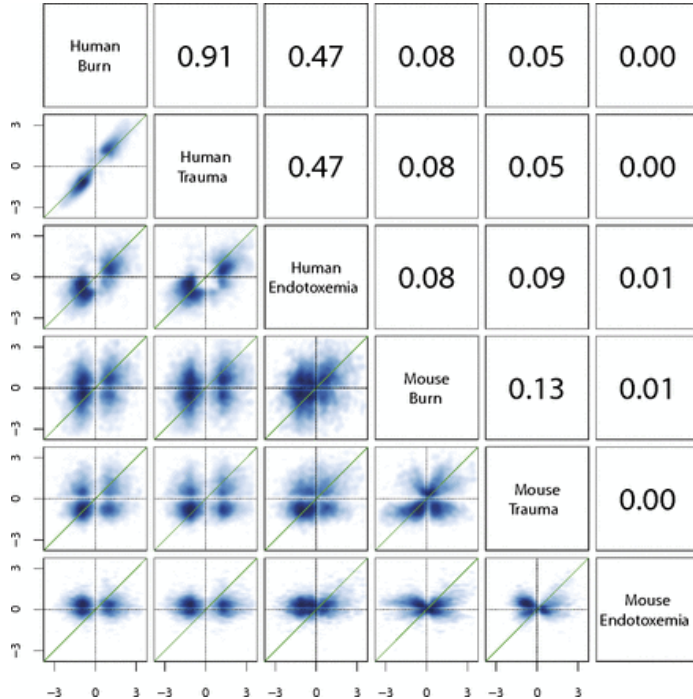
Top 10 Leading Disease/Disorder Categories Contributing to U.S. DALYs (2010)



- CNS drug discovery and development has been problematic, particularly in the area of acute and chronic neurodegenerative disorders.
- These difficulties have resulted in significant cutbacks in CNS drug programs.
- Drug targets must be better understood in terms of their role in normal CNS function and in disease.
- Animal models of disease and hypothetical drug regimens must better reflect the clinical condition.

DALYS (Disability-adjusted life-years): a summary metric of population health. DALYS measure the state of a population's health compared to a normative goal. The goal is for individuals to live the standard life expectancy in full health. DALYs are the sum of 2 components: years of life lost (YLLs) and years lived with disability (YLDs).

Genomic responses in mouse models poorly mimic human conditions during inflammation (and neurodegenerative diseases)



Junhee Seok, H. Shaw Warren, Alex G. Cuenca et al., *PNAS*, 2013
 Terry C. Burns et al., *European Journal of Pharmacology*, 2015

Making animal models that are better reflecting the human clinical condition? How?

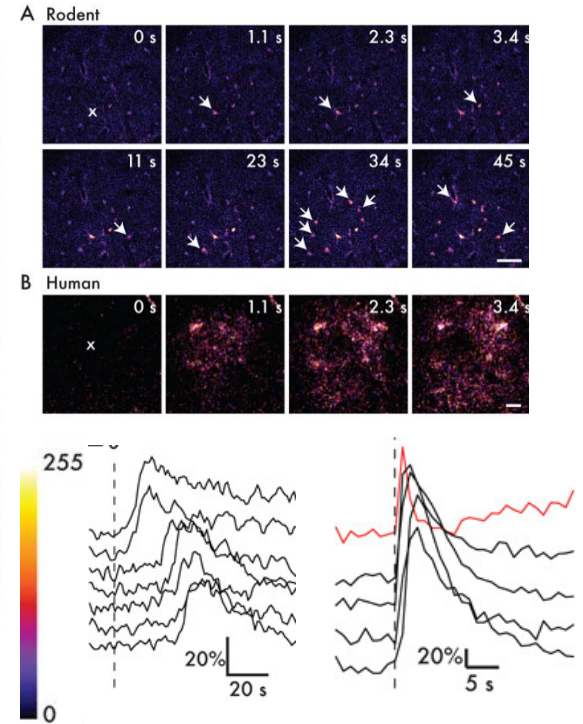
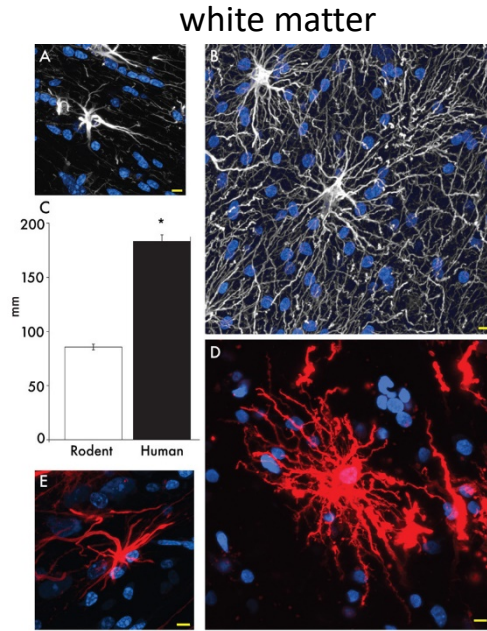
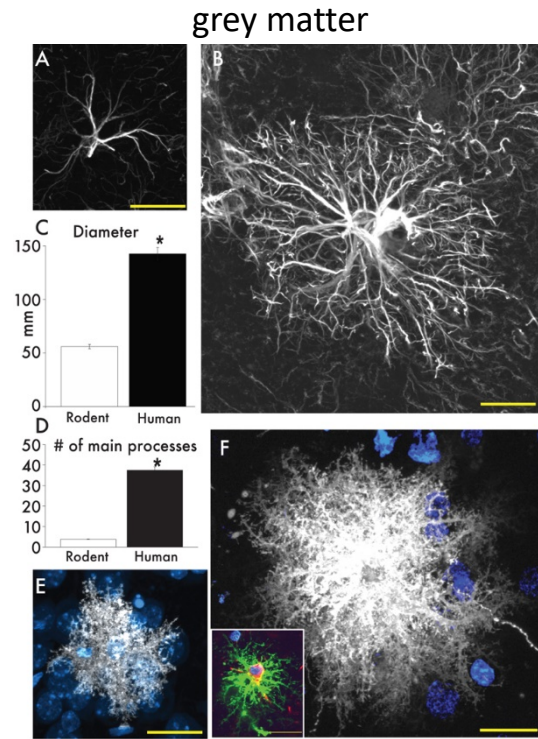
Using animal models more similar to humans

- Non-human primates
- Organoids
- ...

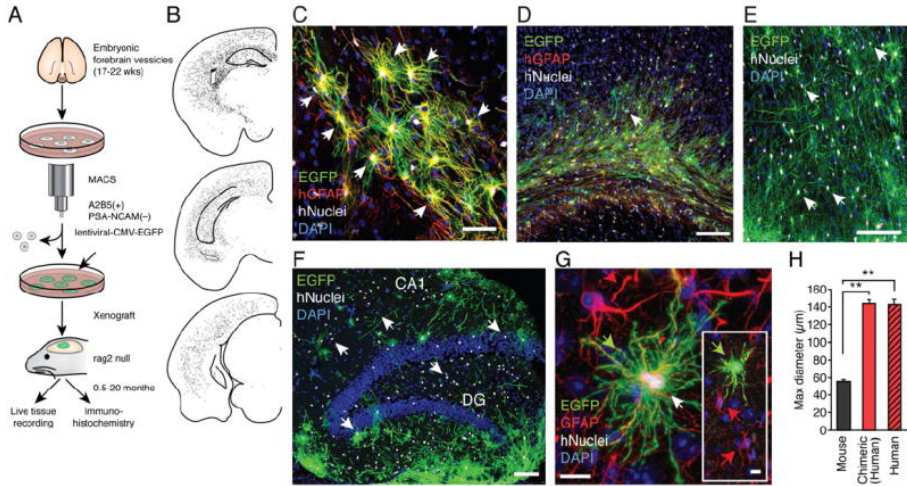
Humanize animal models

- Replace animal genes with their human versions
- Replace animal cells with human cells (ESC-derived or iPSC-derived)
- ...

Uniquely hominid features of adult human astrocytes

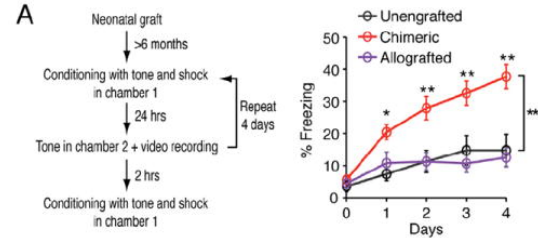


Human glial progenitor engraftment enhances synaptic plasticity and learning in adult mice

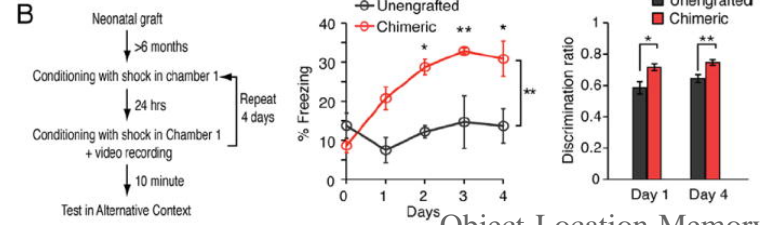


Xiaoning Han, Steven A. Goldman and Maiken Nedergaard et al., Cell Stem Cell, 2013

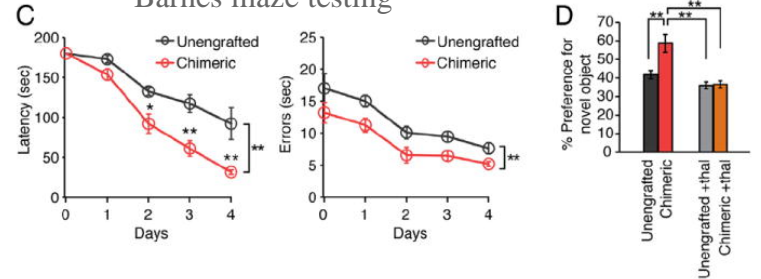
Auditory fear conditioning



Contextual fear conditioning



Object-Location Memory Task



Stem-Cell-Derived Human Neurons Transplanted into AD Mouse Brain

Alzheimer's disease

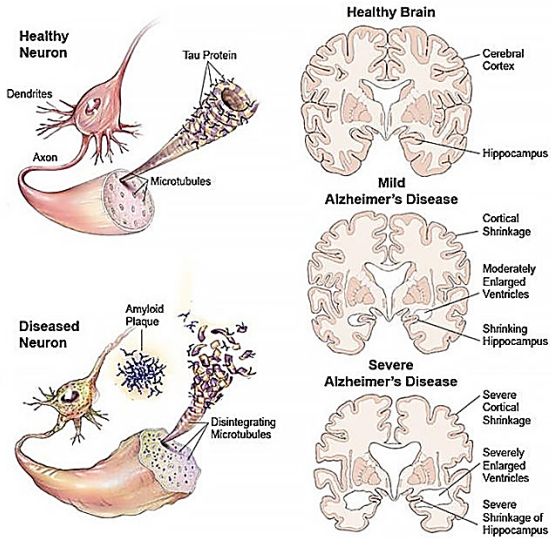
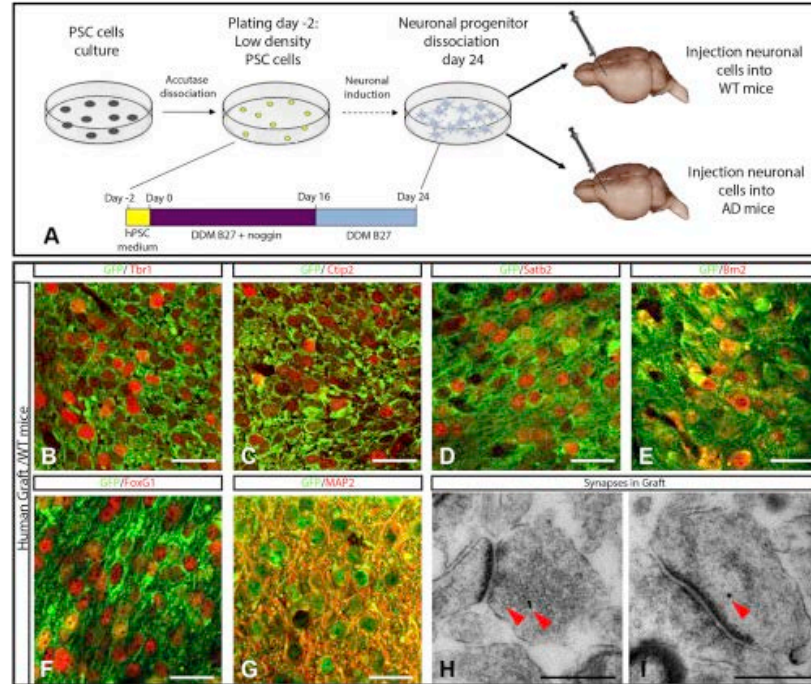
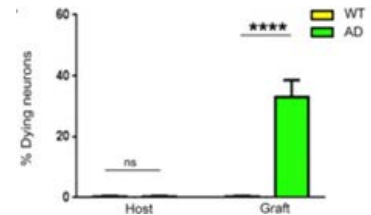
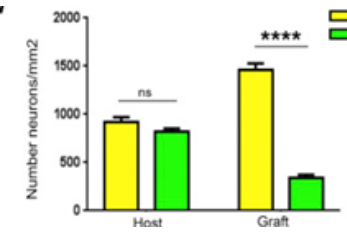
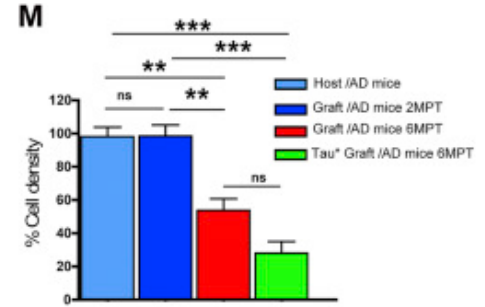
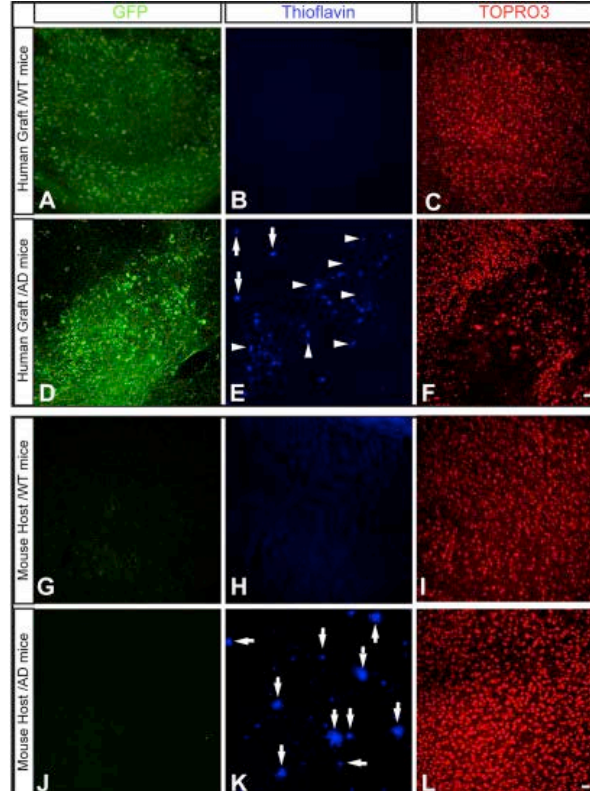
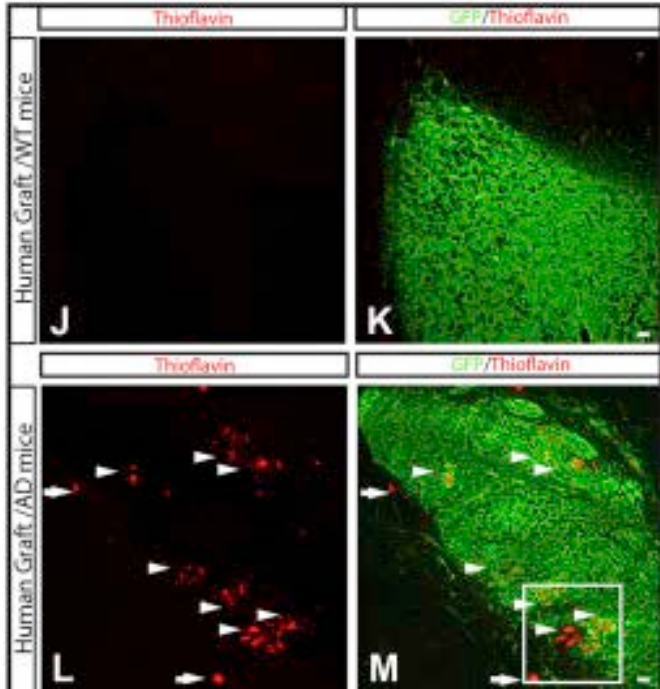


Illustration by Bob Morreale, provided courtesy of the BrightFocus Foundation

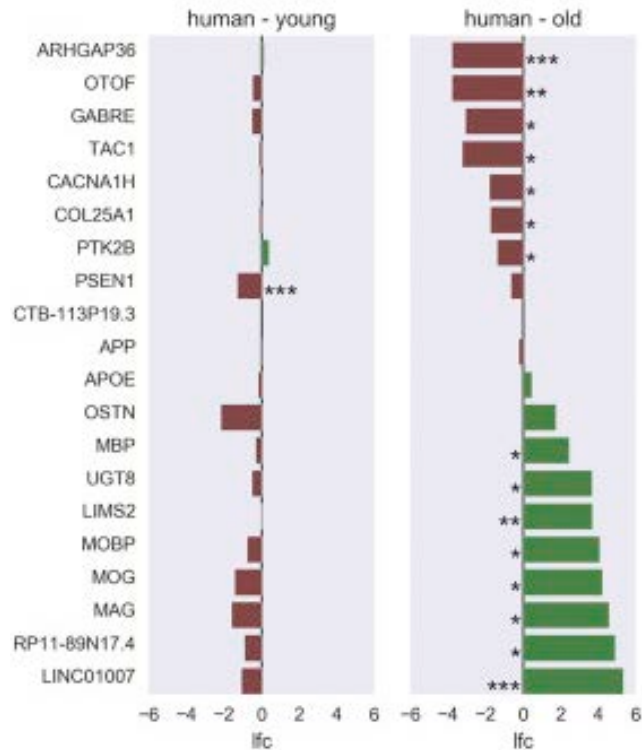
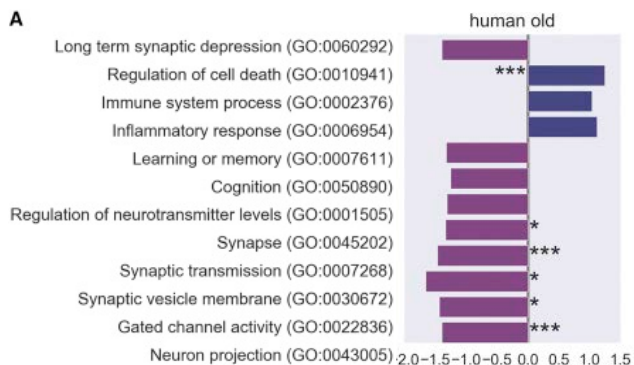
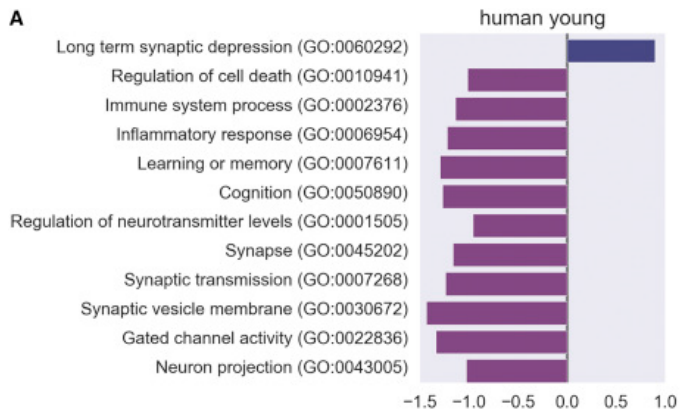


Espuny-Camacho I, Arranz AM, Vanderhaeghen P and De Strooper B et al., *Neuron*, 2017

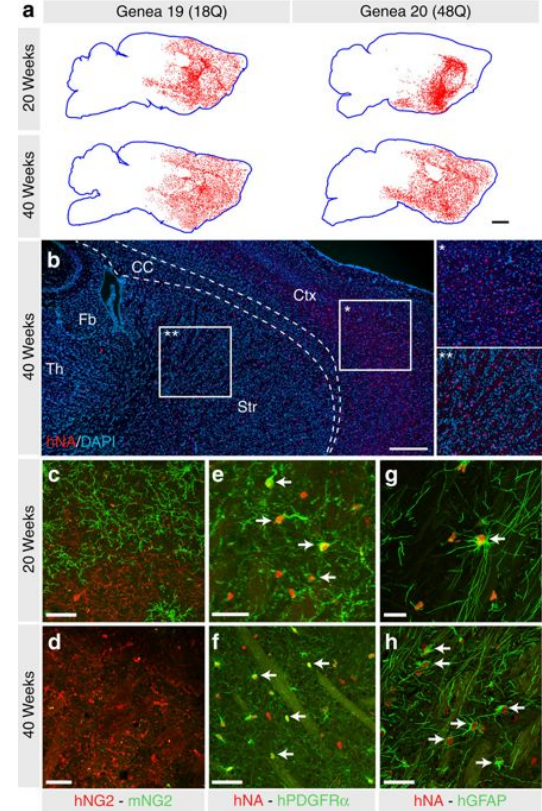
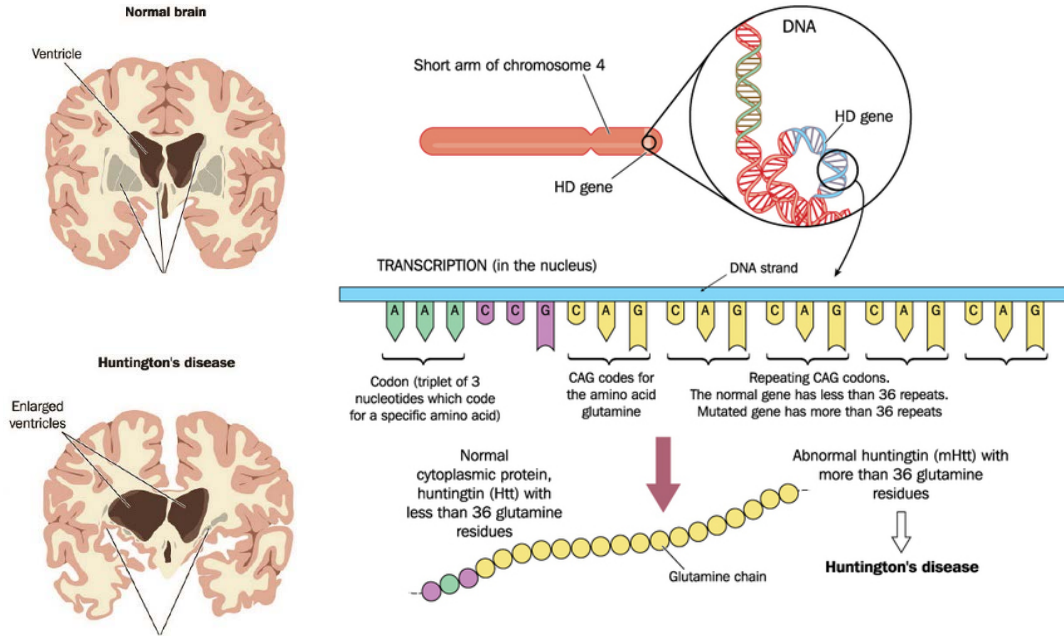
Severe degeneration of human neurons in the AD mouse brain

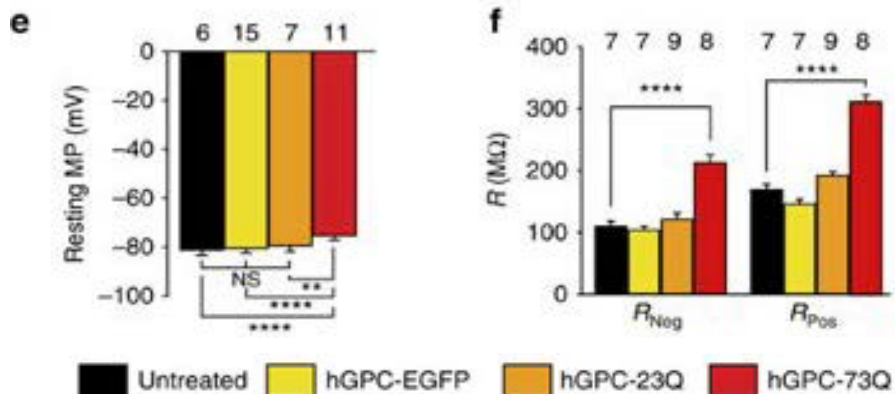
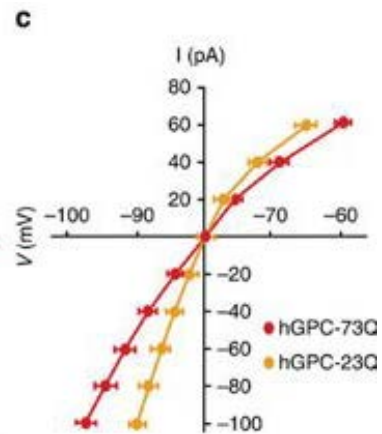
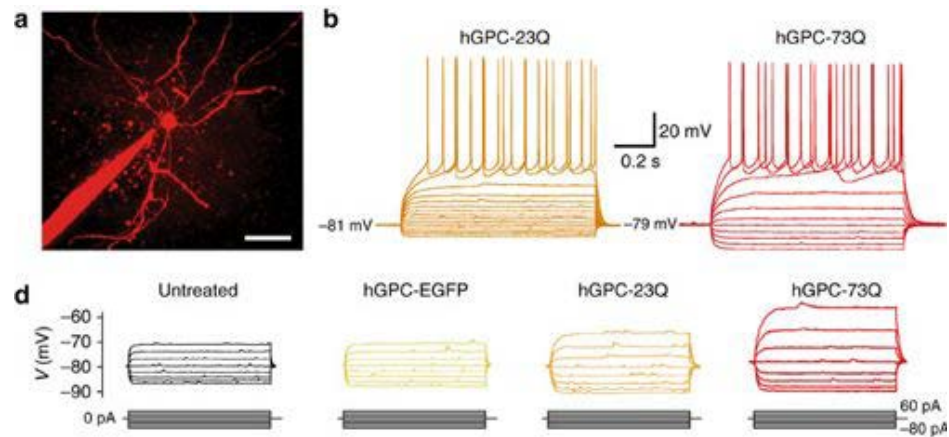
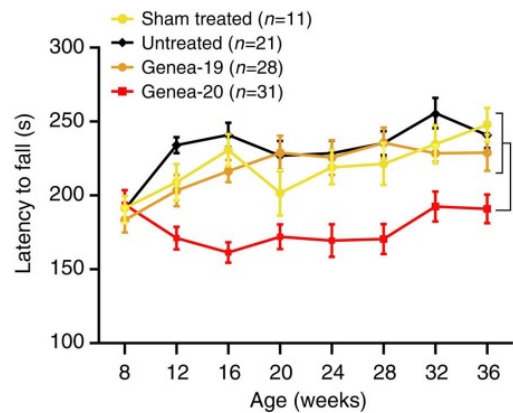


Studying human-specific gene expression changes *in vivo*

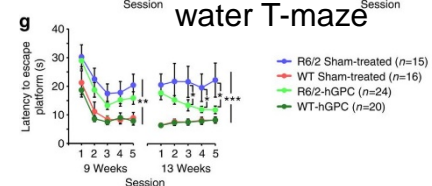
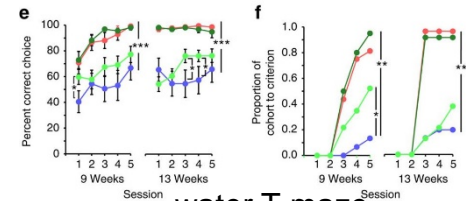
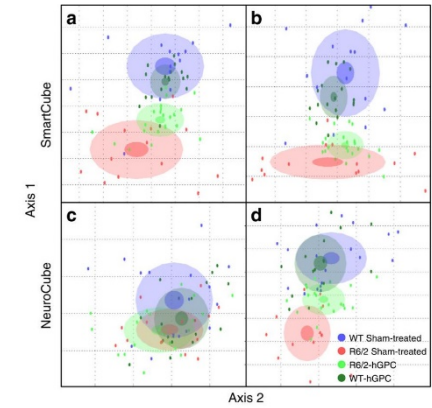
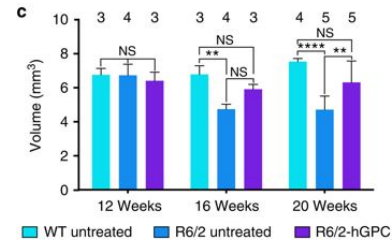
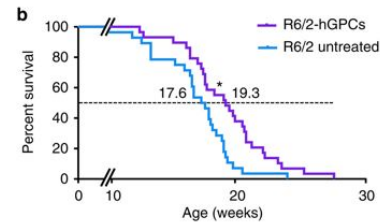
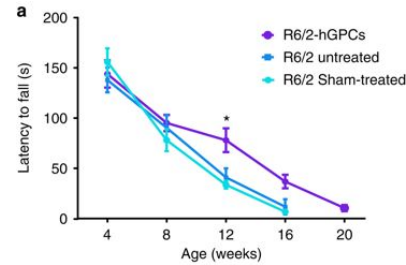
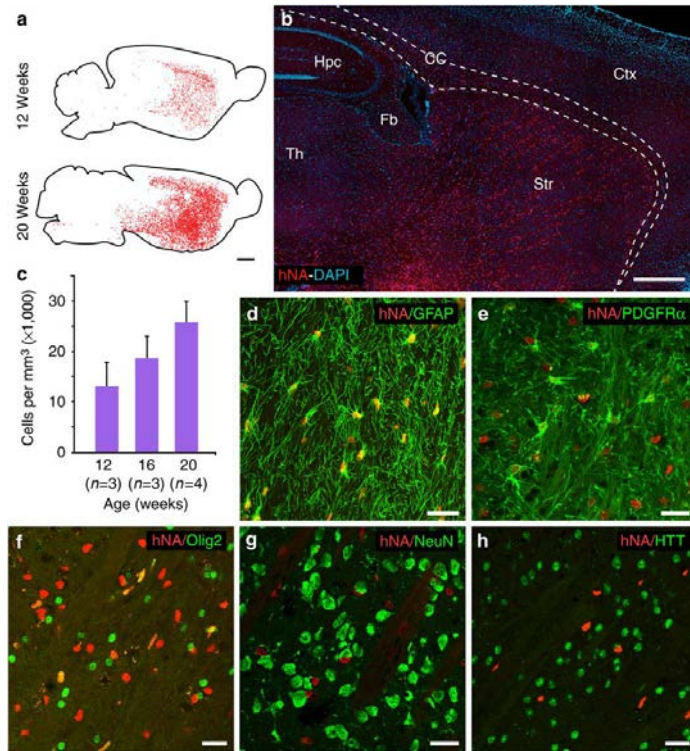


Human Huntington gliia induce aspects of Huntington disease phenotype in mice

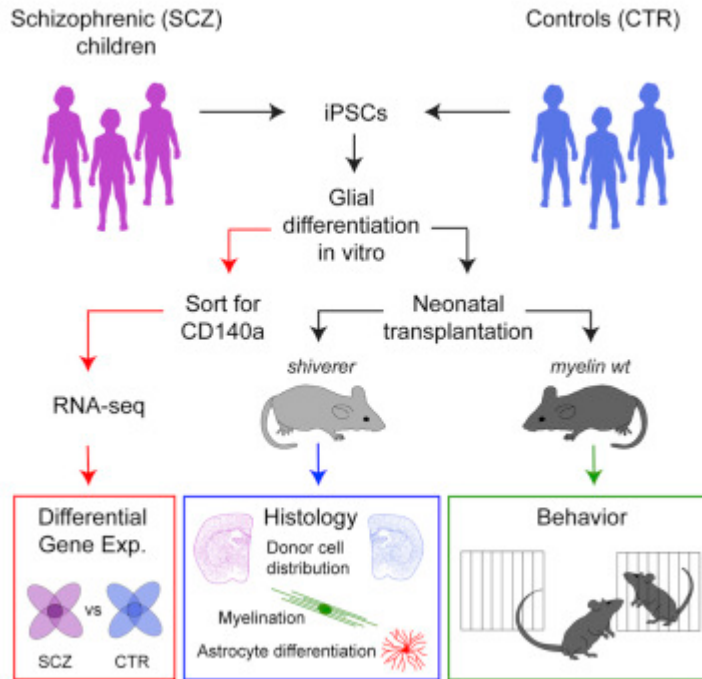




Human glia rescue aspects of Huntington disease phenotype in Huntington disease mouse models

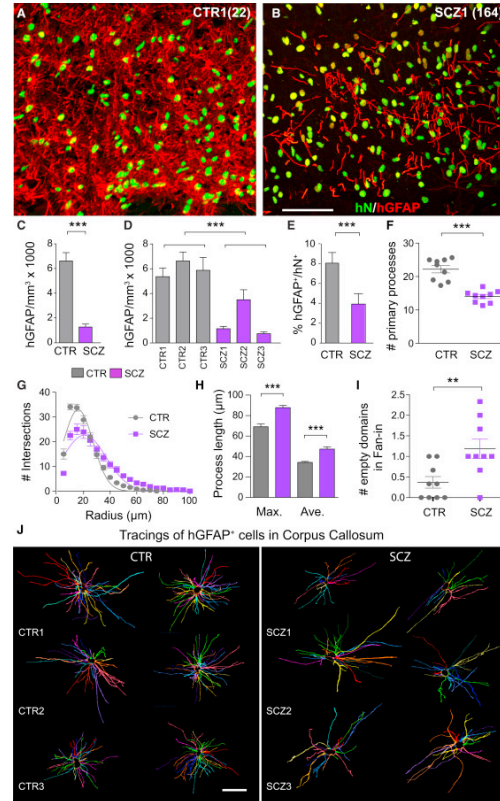
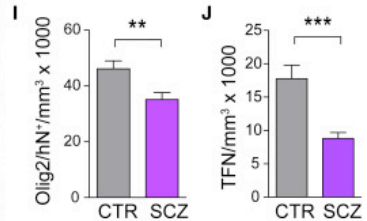
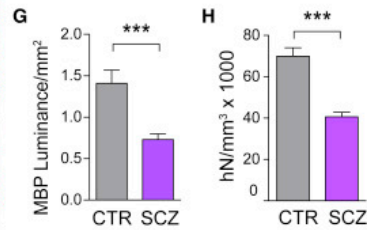
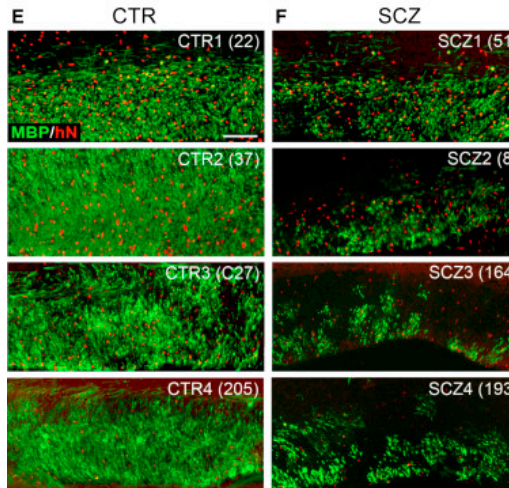
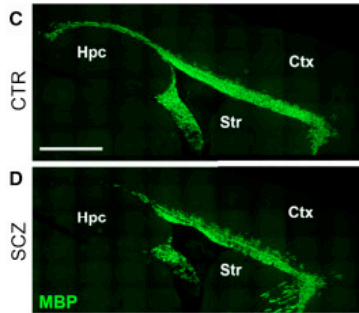
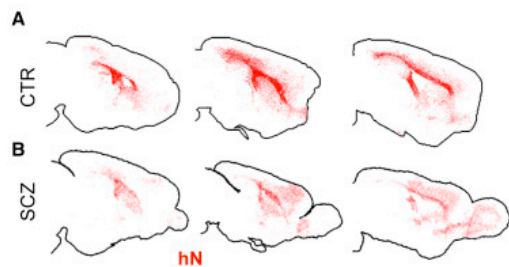


Human iPSC Glial Mouse Chimeras Reveal Glial Contributions to Schizophrenia

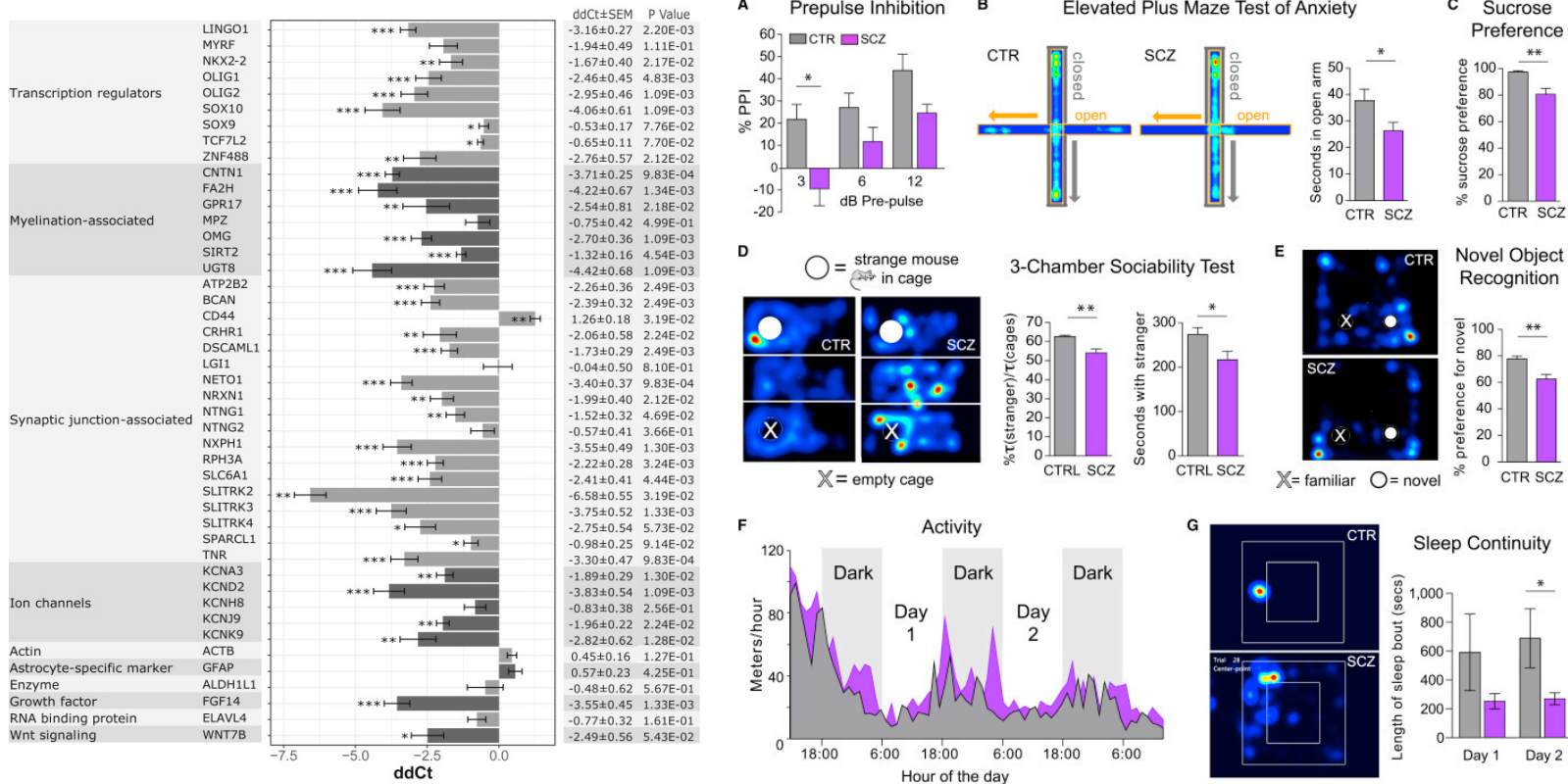


- Human glial chimeric mice were made using iPSCs derived from schizophrenic subjects
- SCZ glial chimeras develop abnormal astrocytic morphology and hypomyelination
- Differentiation-associated gene expression is impaired in SCZ glial progenitors
- SCZ glial chimeric mice have broad behavioral and sleep abnormalities

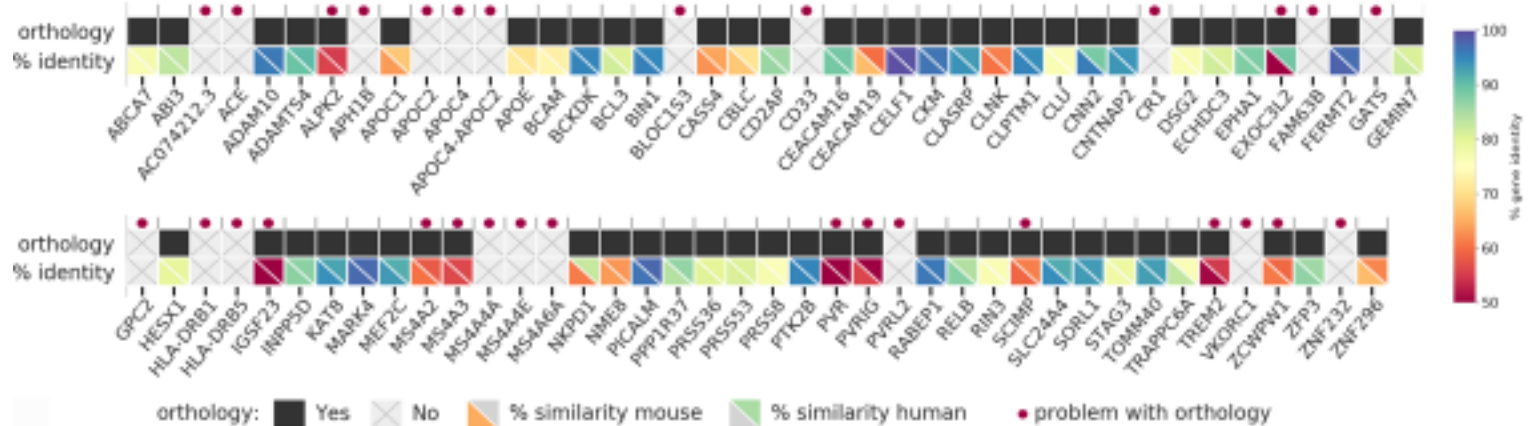
SCZ-Derived hGPCs Exhibit Aberrant Dispersal and Relative Hypomyelination



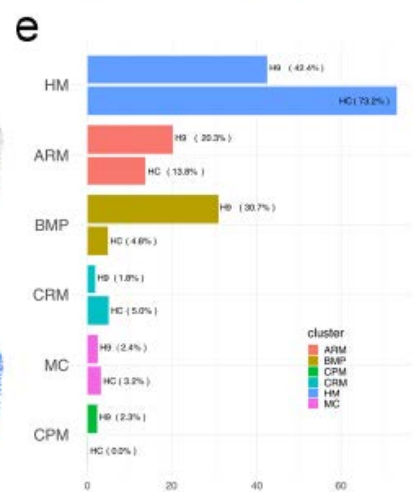
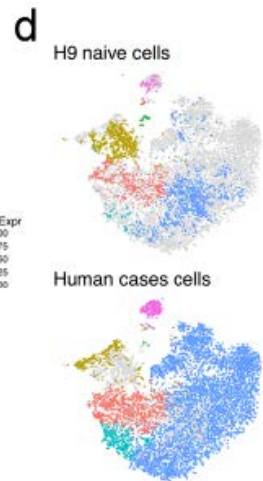
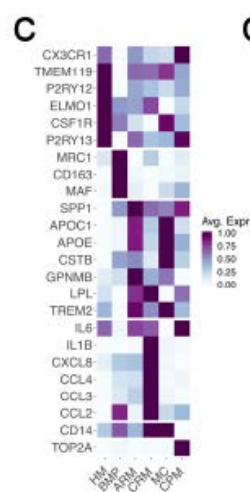
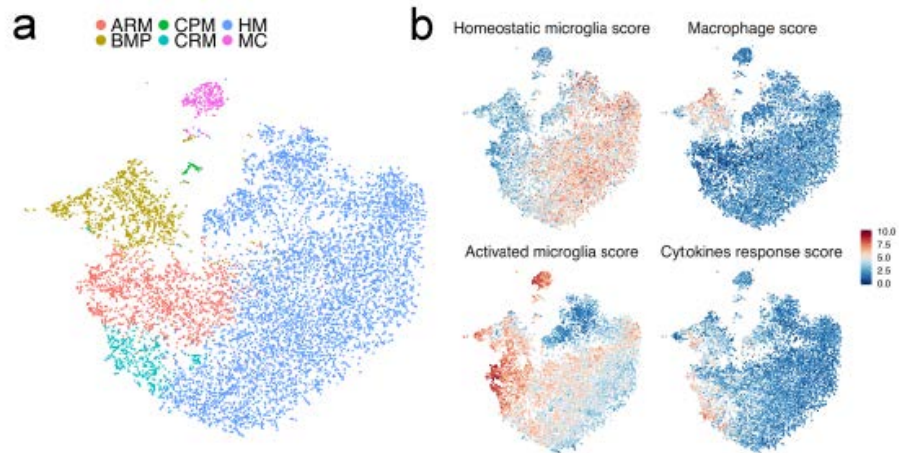
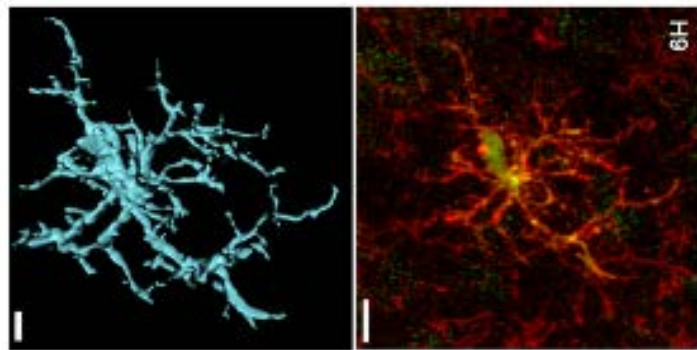
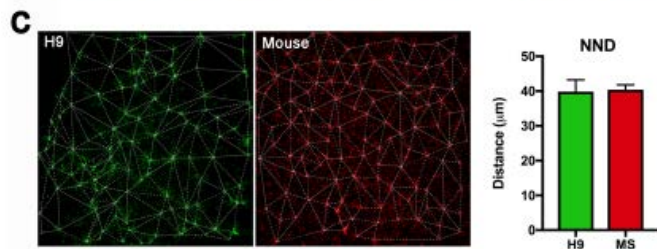
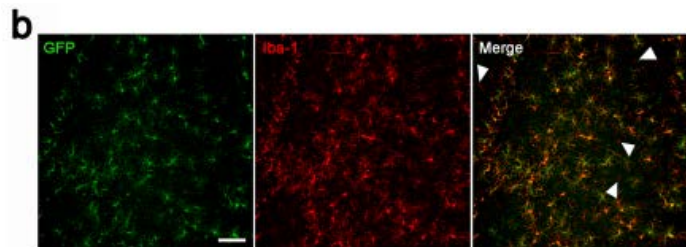
SCZ-Derived Human Glial Chimeras Have Significant Behavioral Abnormalities



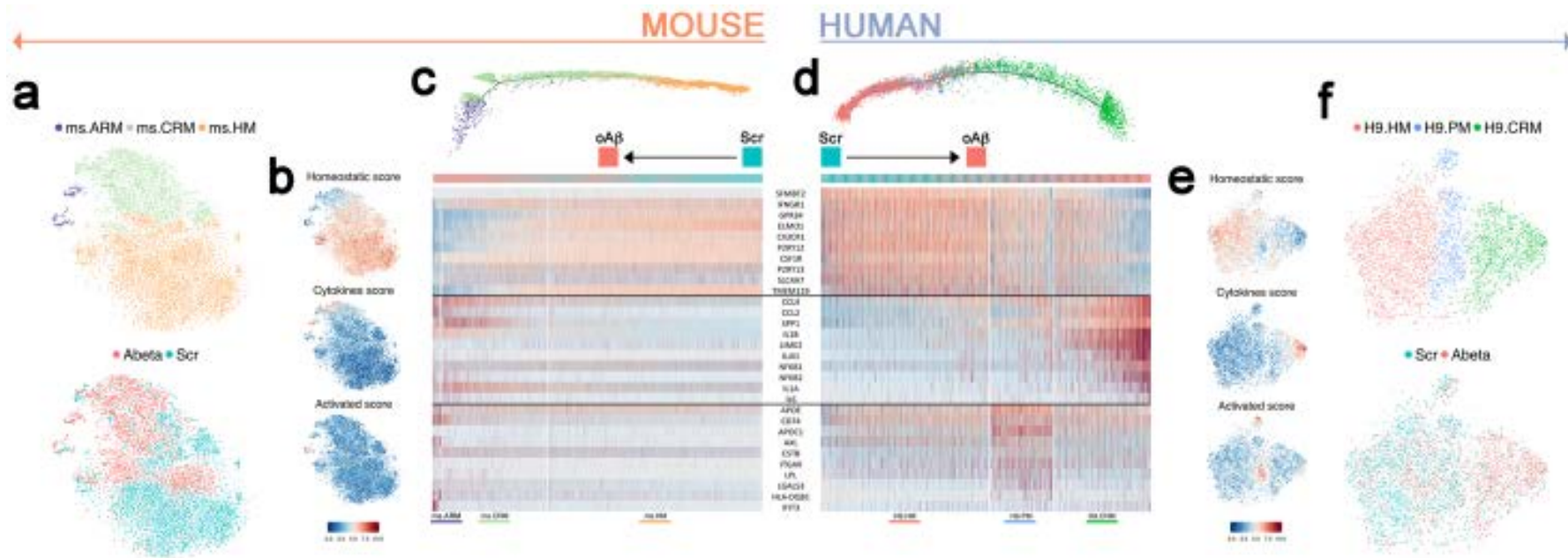
Human microglia transplantation into AD mouse



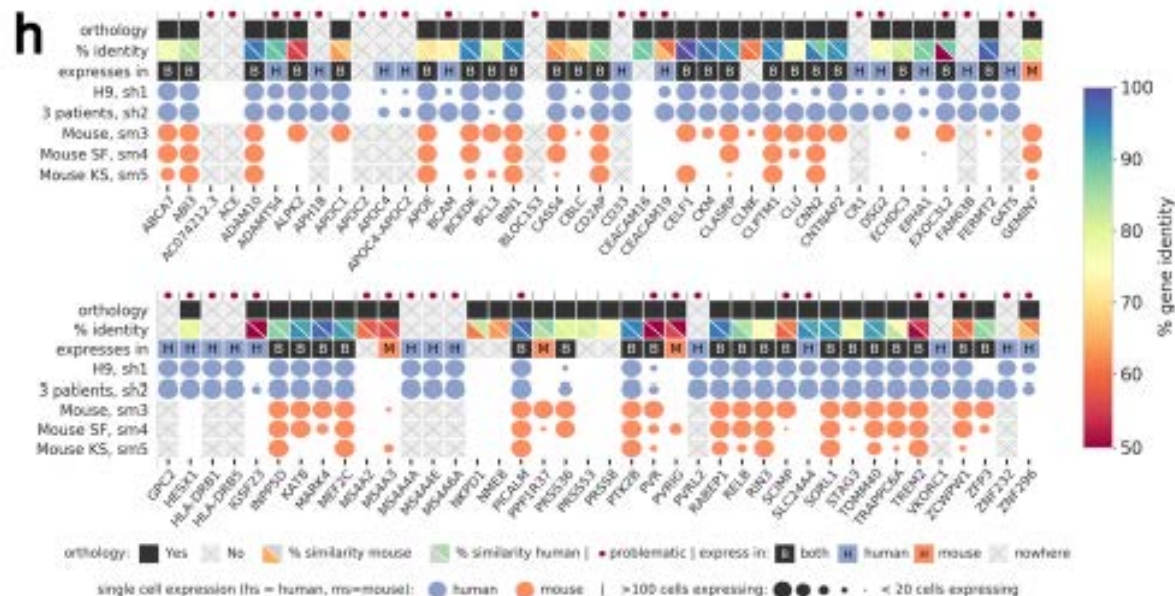
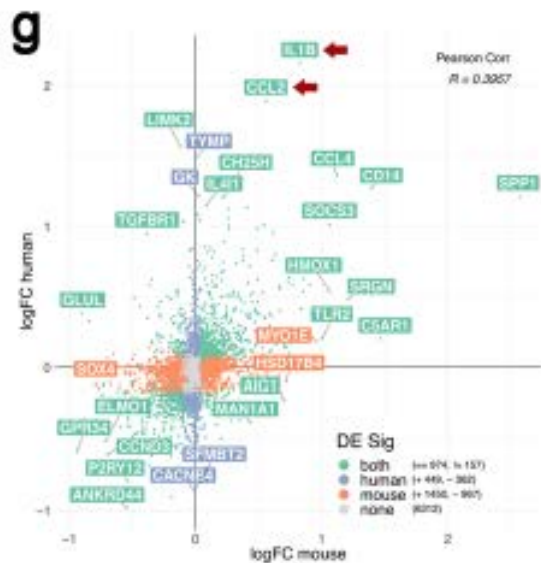
Limited orthology between human and mouse AD-related genes



Human and host mouse microglial response to oligomeric A β



Human microglia show a different response to A β



Thank you for your attention!