



ARISTOTLE
UNIVERSITY
OF THESSALONIKI

Stem-cell-derived human microglia transplanted in mouse brain to study human disease

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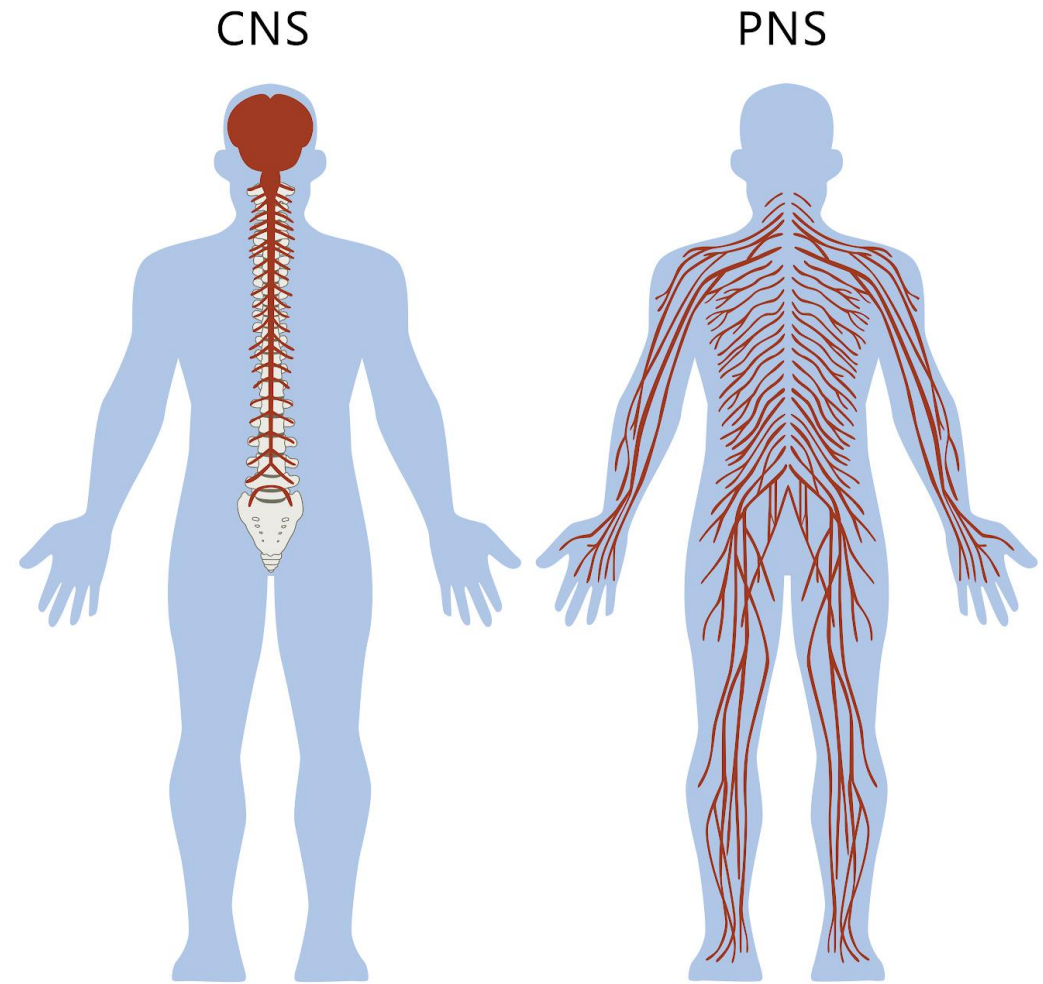
The Nervous System

Control

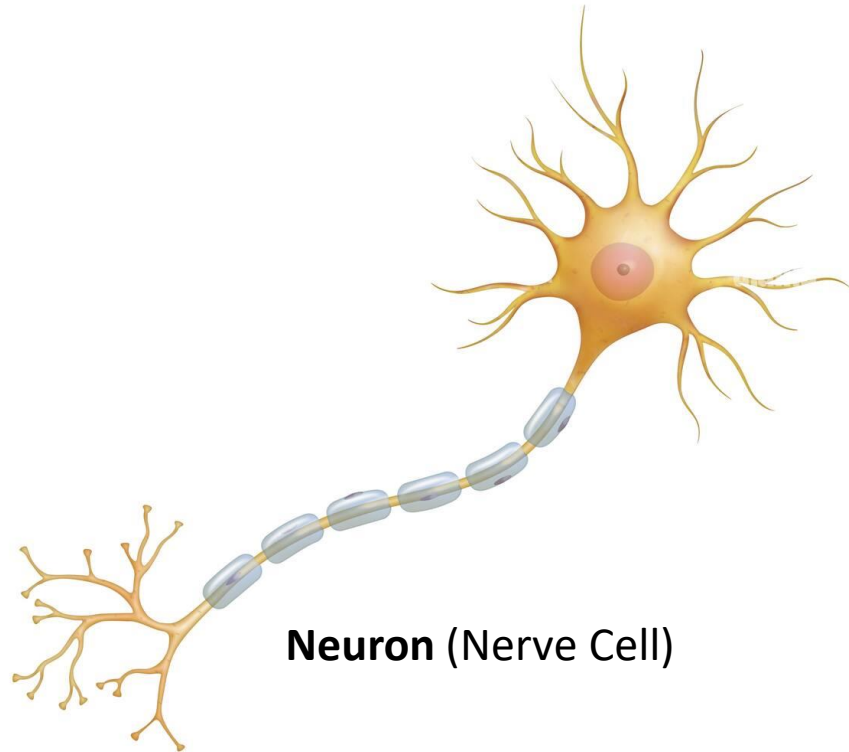
Regulation

Communication

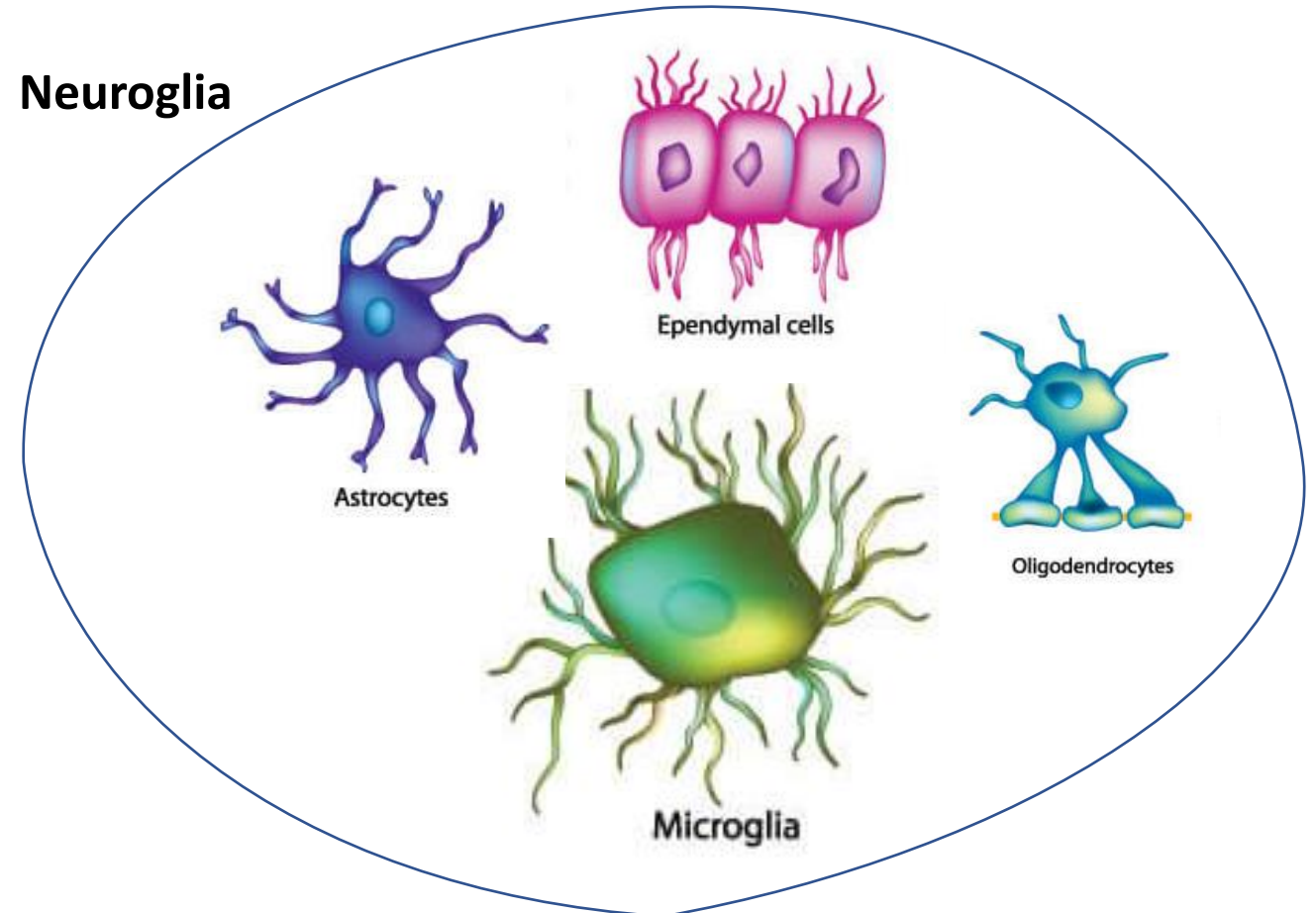
Homeostasis



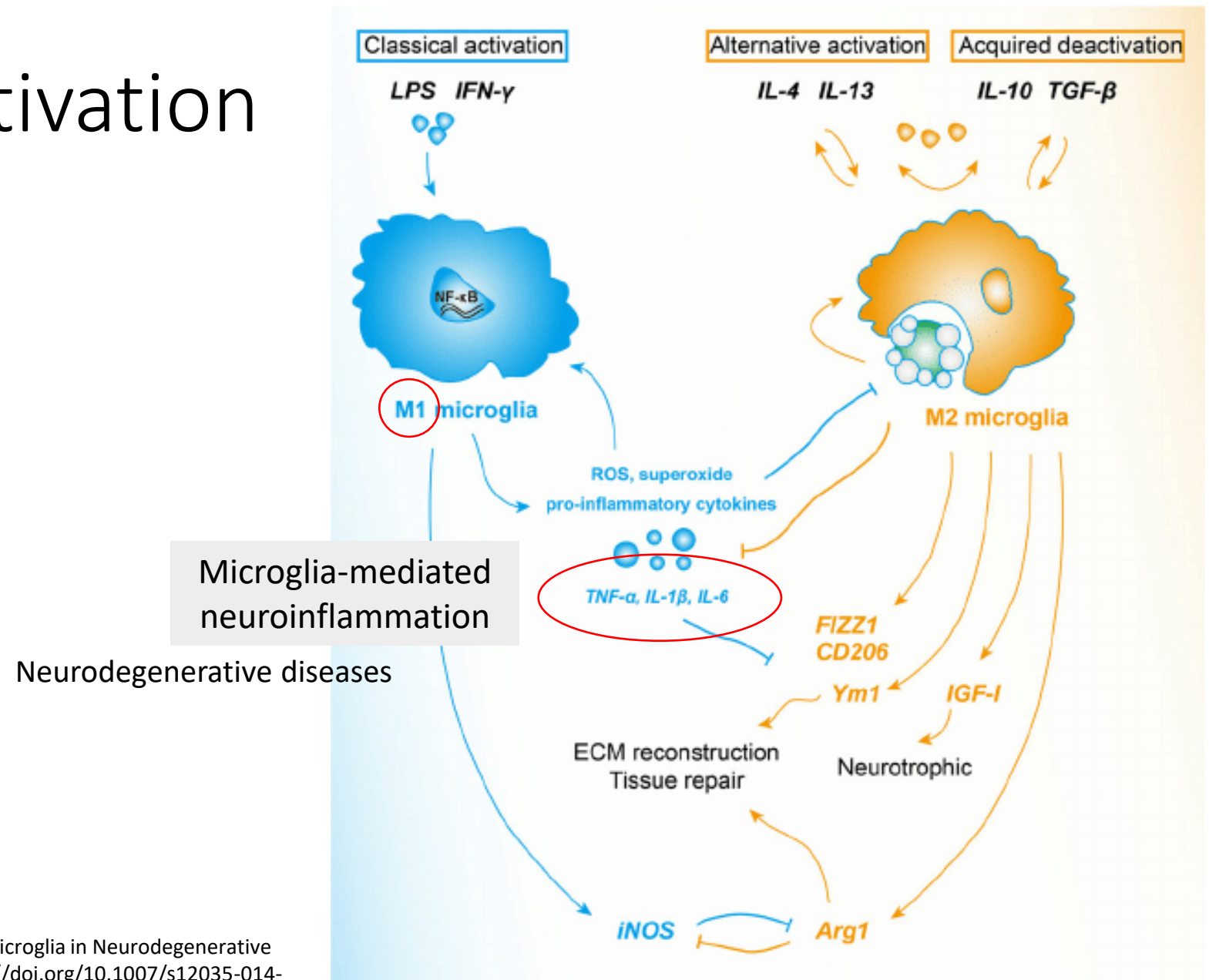
Central Nervous System's Cells



Neuroglia



Microglial Activation

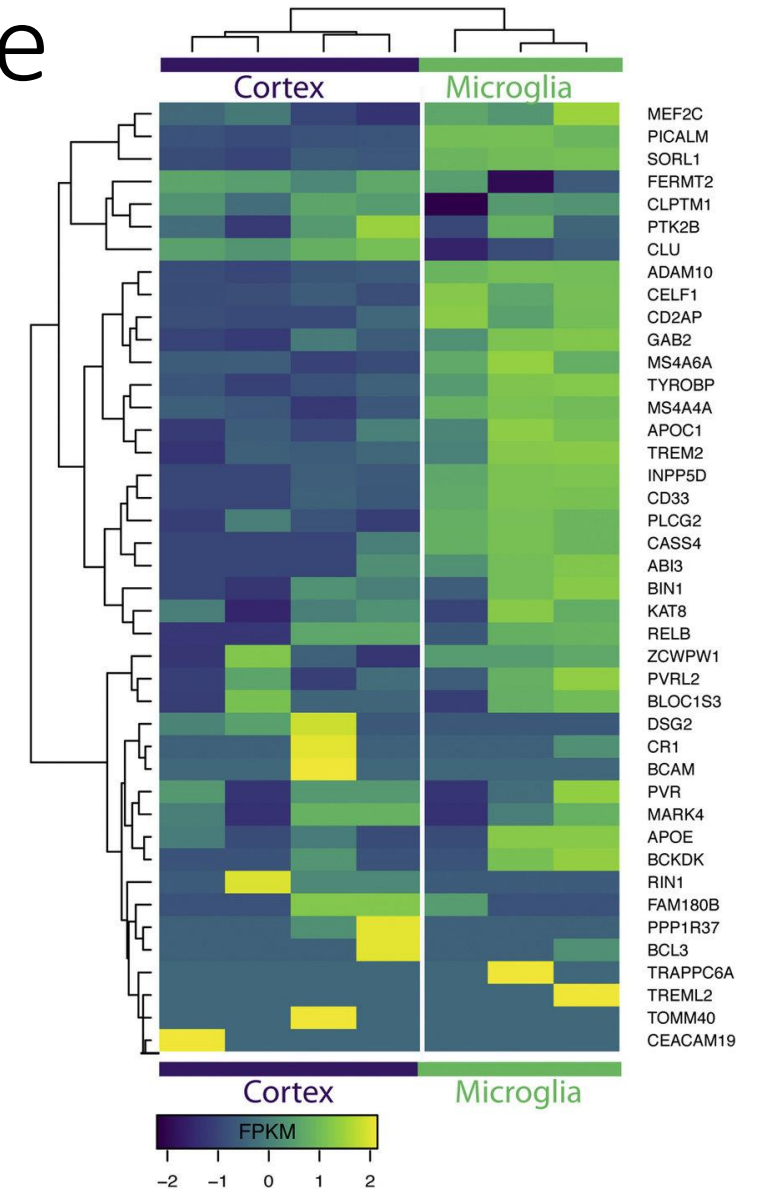


Microglia & Alzheimer's Disease

Alzheimer's Disease

- The leading cause of dementia
- Accumulation of the **β -amyloid peptide & protein tau.**

M1 Activation

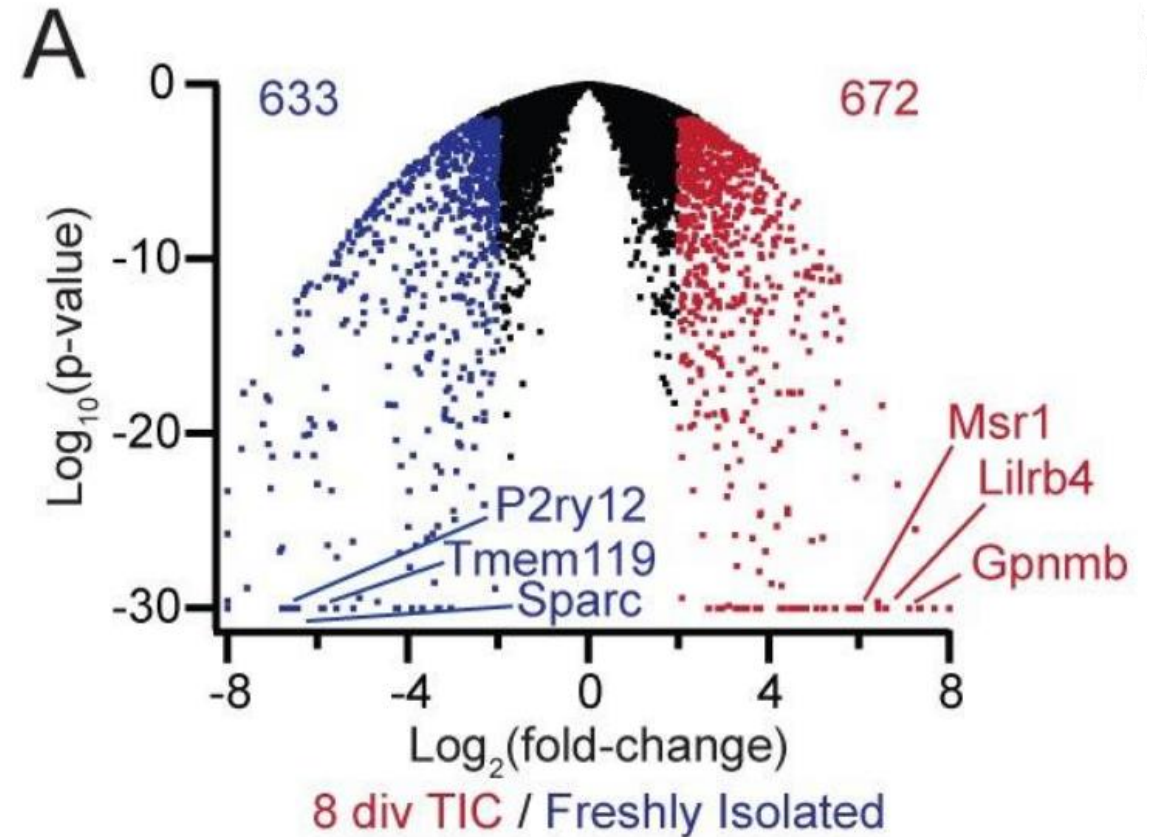


Microglia in Alzheimer's Disease: Exploring How Genetics and Phenotype Influence Risk - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Alzheimers-risk-genes-are-enriched-in-microglia-over-total-cortex-expression_fig2_330995187 [accessed 2 Mar, 2022]

Limitations of Classic Studies on Microglia

In Vitro

- No **Microenvironment**
 - Microglial Activation
 - Cellular Interplay
- Artificially induced transcriptional signatures



Limitations of Classic Studies on Microglia

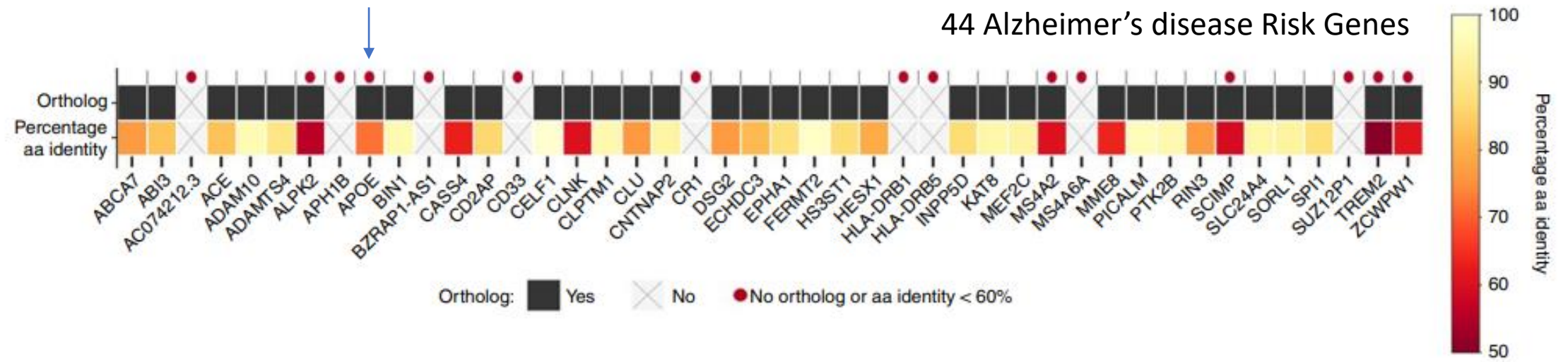
Mouse Model

No 1:1 mouse orthologs for 41% of genes

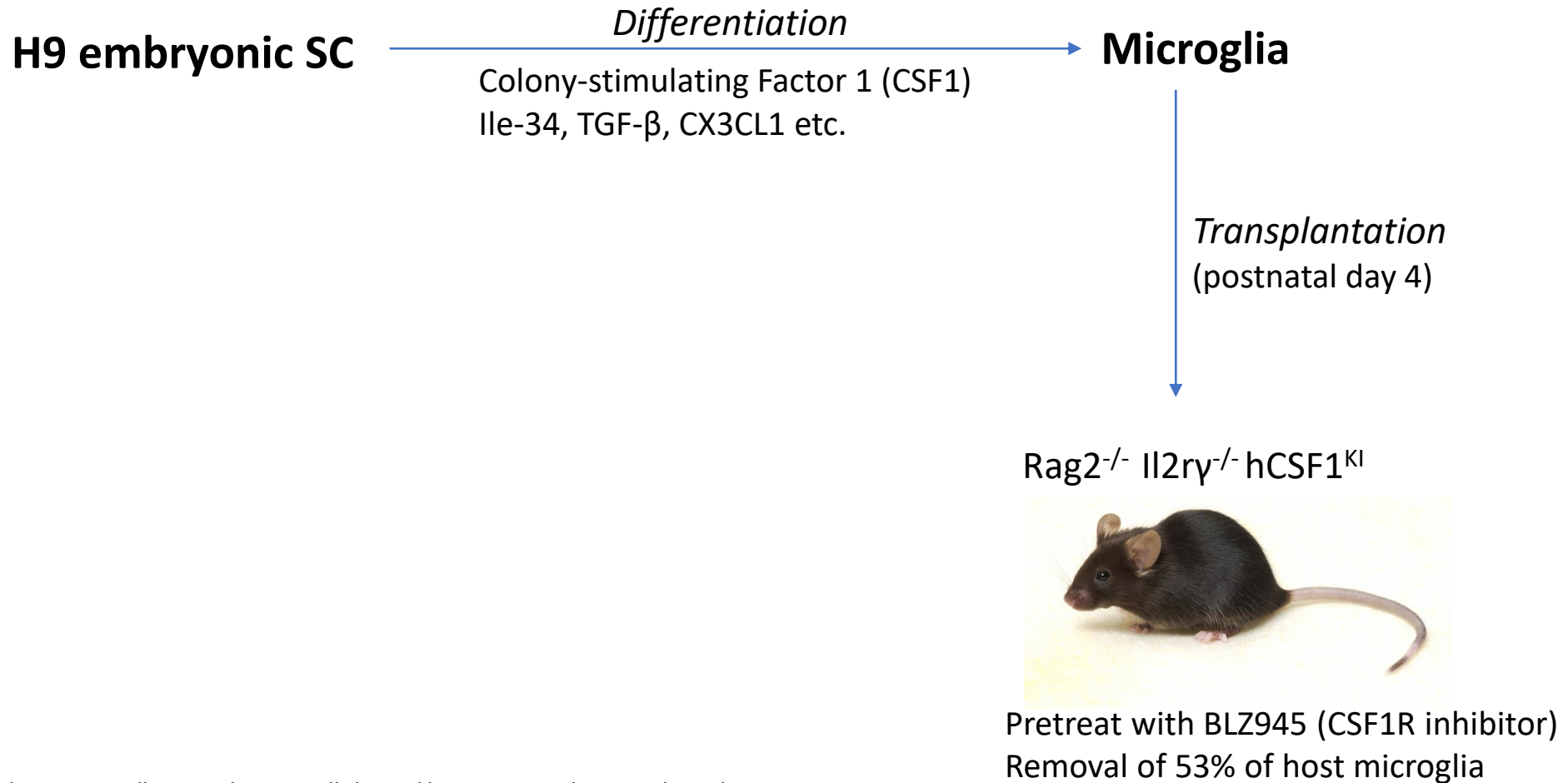
eg.

CR1, APOC lack a clear mouse ortholog

CD33, MS4A4 have many-to-many orthology



The Process



Mancuso, R., Van Den Daele, J., Fattorelli, N. et al. Stem-cell-derived human microglia transplanted in mouse brain to study human disease. Nat Neurosci 22, 2111–2116 (2019).

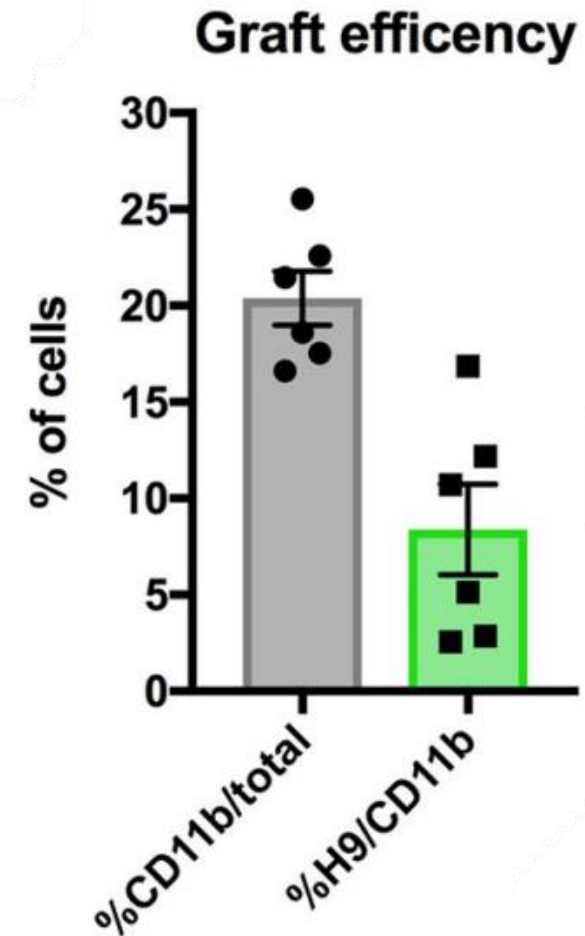
<https://doi.org/10.1038/s41593-019-0525-x>

<https://www.yourgenome.org/>

Results

Embryonic Stem cell-derived microglia survive and integrate in mouse brain.

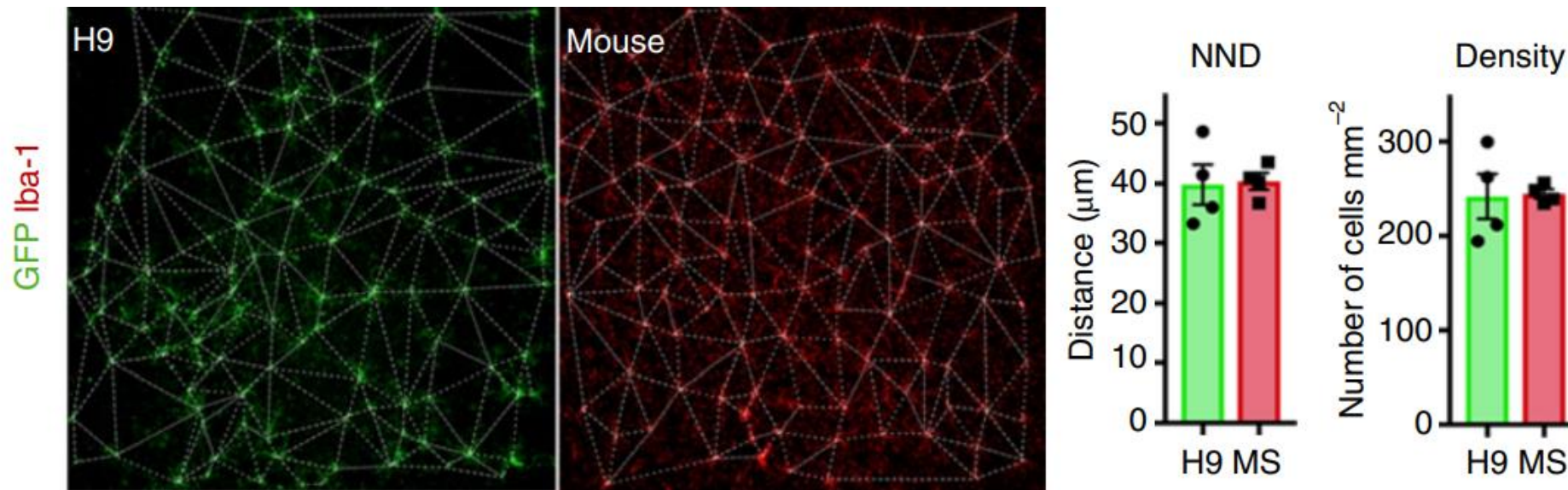
- After 8 weeks, H9-microglia represents $9\% \pm 5\%$ of the total microglia population



Results

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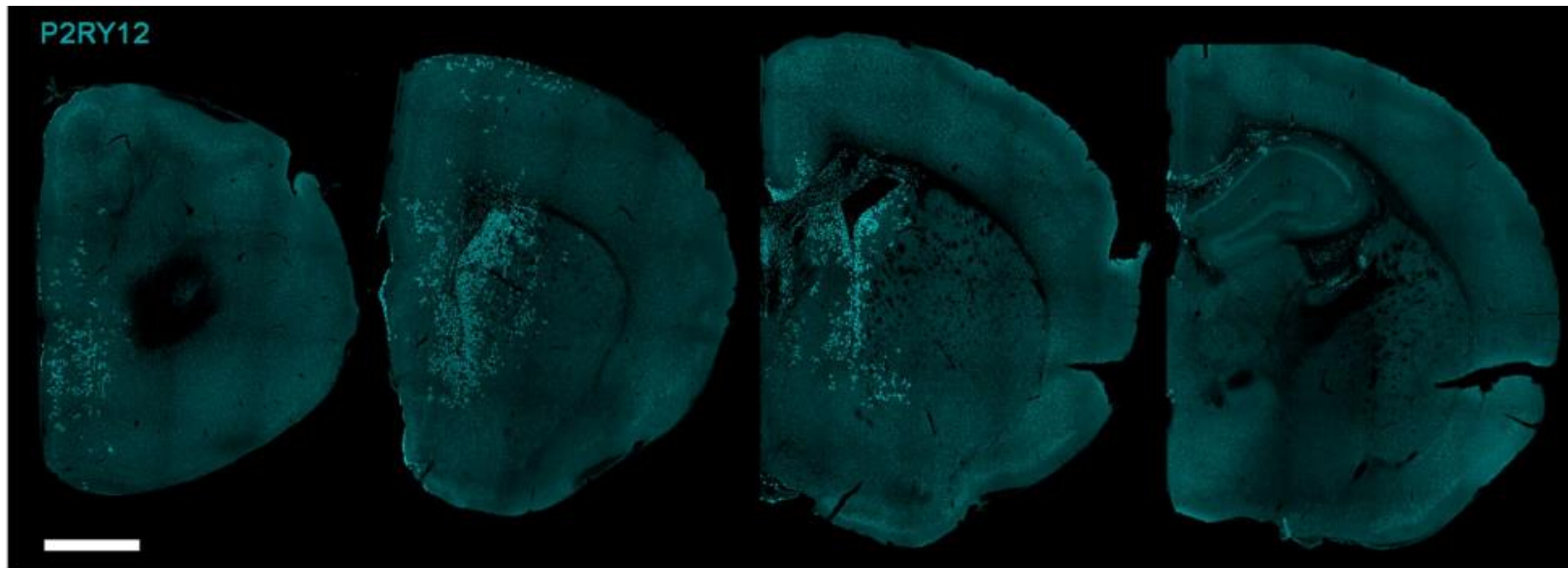
- Mosaic distribution, Nearest Neighbor Distance and density similar to host mouse cells.



Results

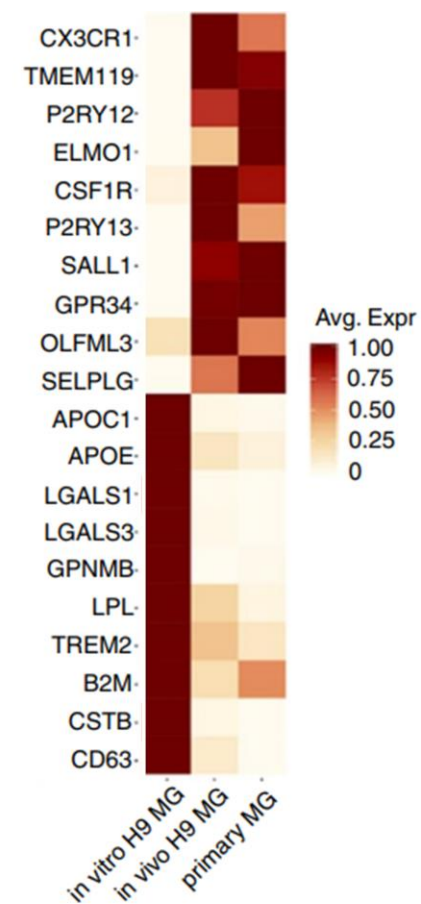
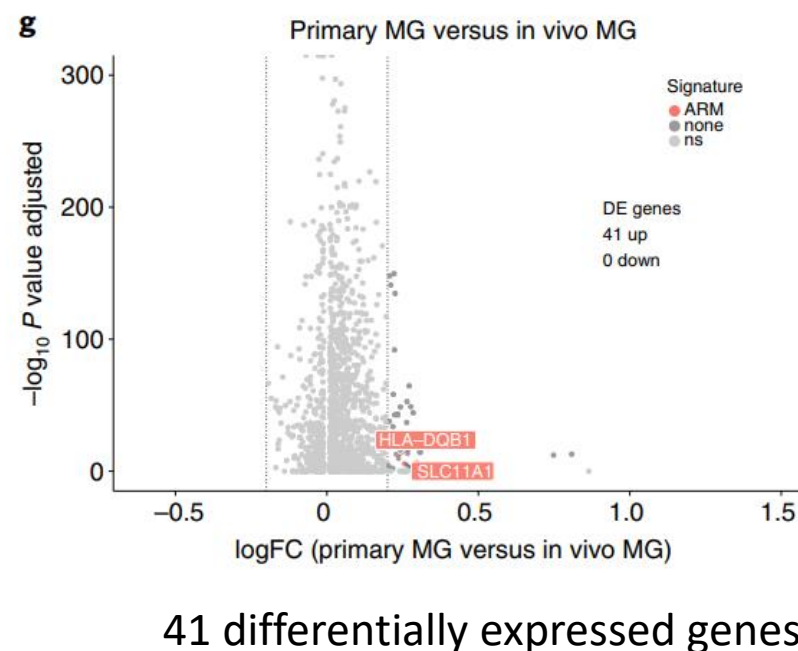
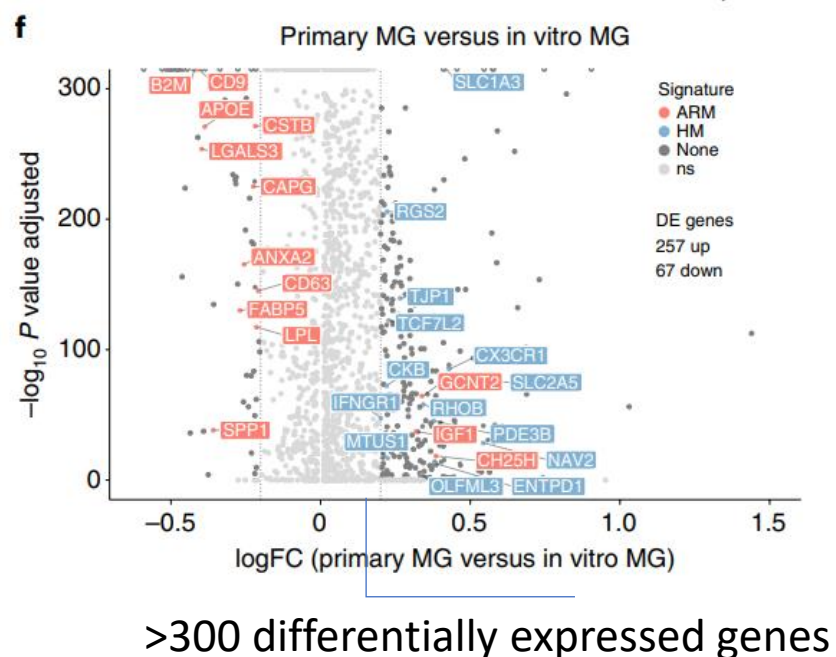
Embryonic Stem cell-derived microglia survive and integrate in mouse brain.

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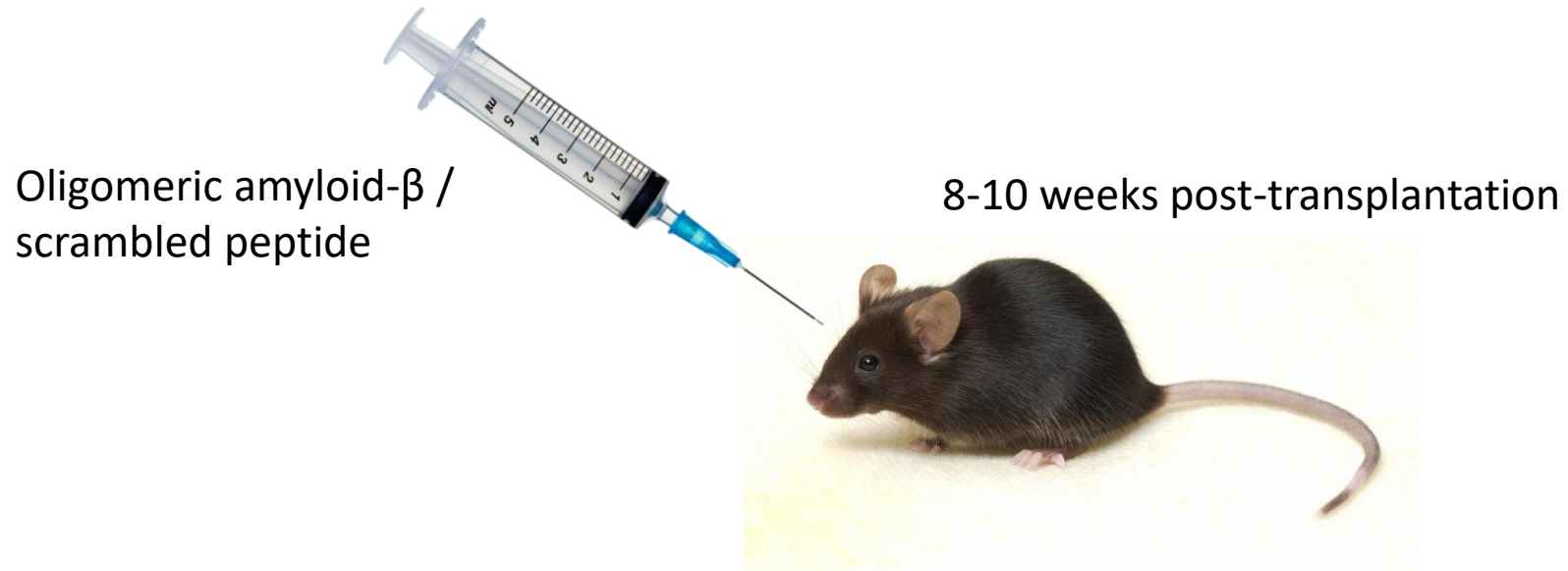
Results

ESC-derived microglia mimic primary human cells at the transcriptome level.



Results

Human ESC-derived and host mouse microglia display a divergent response to oligomeric amyloid- β .



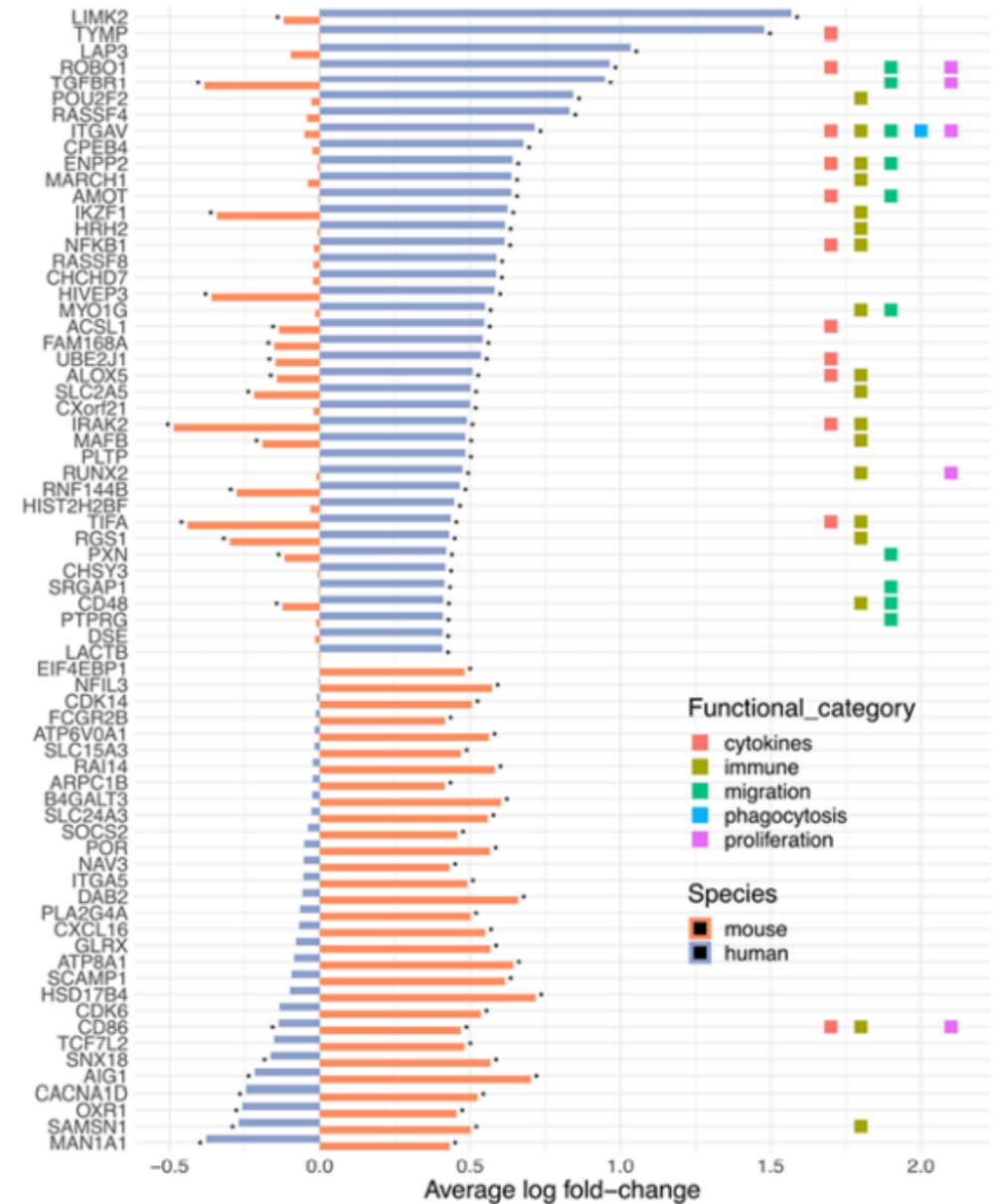
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<https://levelup.gitconnected.com/>

Results

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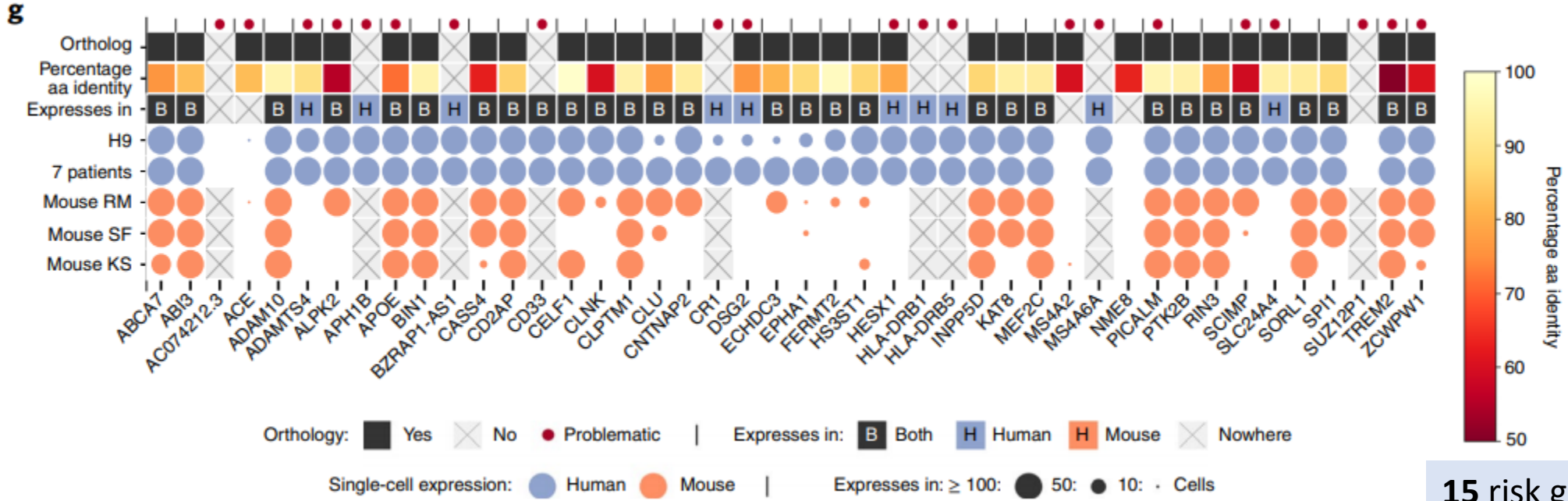
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Evaluation

- Does this chimeric model cover the human expressome better than the classical mouse models?



15 risk genes
 + humans
 - mice
 + H9 transplanted

Discussion and Limitations

Useful Alternative, but...

- Lack of adaptive immune system
- Variability in the grafting efficiency of different PSCs and iPSCs

New Approaches: **CRISPR/Cas9**

References

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Thank you for your attention!

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