Age-related changes in brain-body communication

Brain-Body Interaction Workshop
National Academy of Sciences
October 23, 2025

Tony Wyss-Coray, Ph.D., D. H. Chen Professor
Director, Phil and Penny Knight Initiative for Brain Resilience

Stanford University School of Medicine, Department of Neurology

A·D·R·C for healthy brain aging

Wu Tsai Neurosciences Institute Stanford University

Knight Initiative for Brain Resilience
WU TSAI NEUROSCIENCES INSTITUTE
STANFORD UNIVERSITY

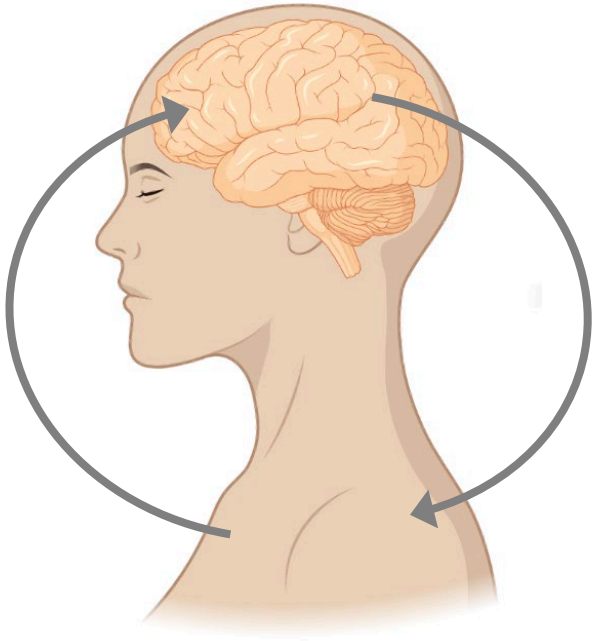
Disclosures

Co-founder and scientific advisor of
Teal Rise, Vero Biosciences, Qinotto, Alkahest

Brain-organismal communication

What goes in?

- molecules
- cells

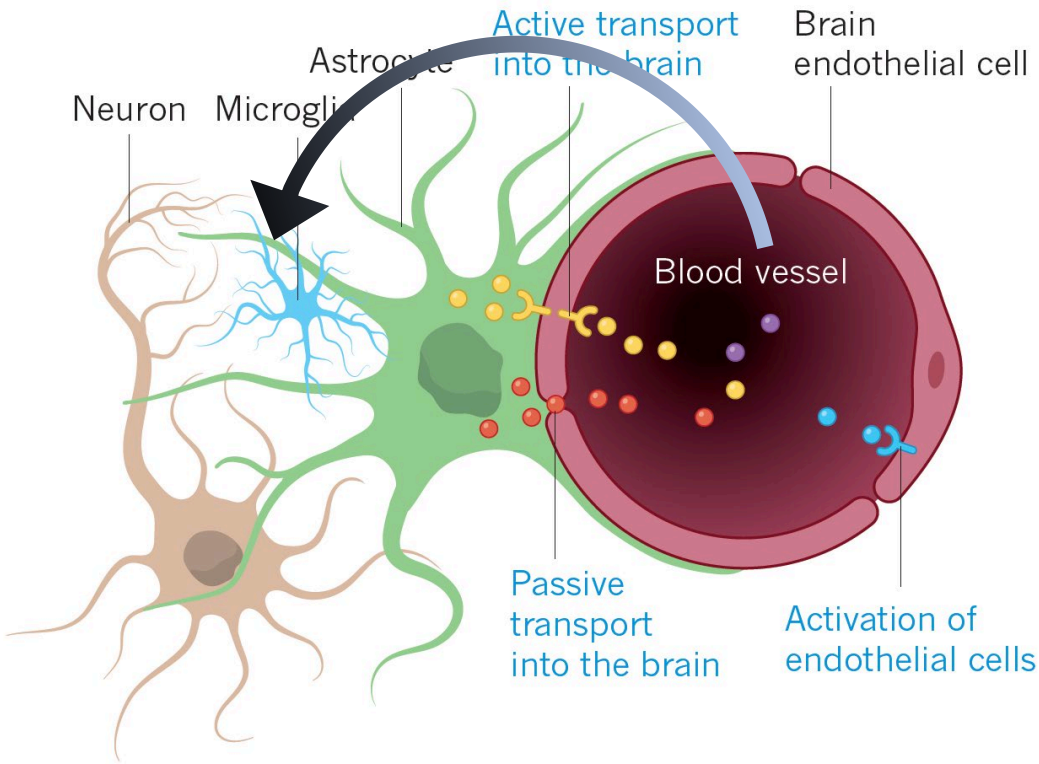


What comes out?

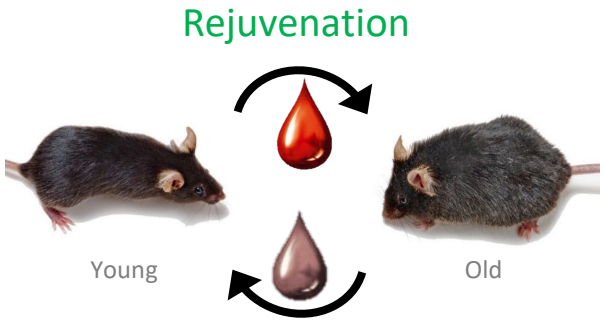
- molecules
- cells

- Understanding of brain physiology with aging and disease
- Exploit transport mechanism for therapeutic use
- Discover biomarkers
- Understand individual variation (genetic, environmental)

What goes from the circulation into the brain ?

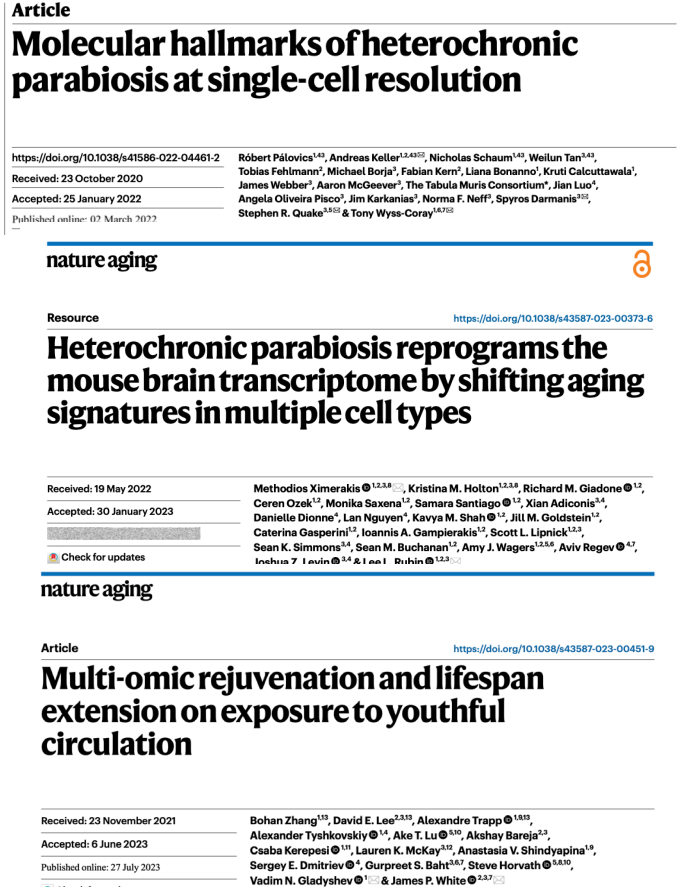


Functional and molecular evidence that circulatory factors modulate brain aging



- increased neural stem cell activity
- increased synaptic plasticity
- less brain inflammation
- **improved memory function**

Conboy 2005, Villeda 2011, Villeda 2014; Ruckh 2012; Katsimpardi 2014; Khrimian 2017; Yousef 2019; Kim 2020; Iram 2022, Hahn 2023



Article

Molecular hallmarks of heterochronic parabiosis at single-cell resolution

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Róbert Pálovics[1,43], Andreas Keller[1,2,43], Nicholas Schaum[1,43], Weilun Tan[2,43], Tobias Fehlmann[2], Michael Borja[3], Fabian Kern[2], Liana Bonanno[1], Kruti Calcuttawala[1], James Webber[3], Aaron McGeever[3], The Tabula Muris Consortium*, Jian Luo[4], Angela Oliveira Pisco[3], Jim Karkanias[3], Norma F. Neff[3], Spyros Darmanis[3], Stephen R. Quake[3,5] & Tony Wyss-Coray[1,6,7]

nature aging

Resource

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Heterochronic parabiosis reprograms the mouse brain transcriptome by shifting aging signatures in multiple cell types

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Methodios Ximerakis[1,2,3,8], Kristina M. Holton[1,2,3,8], Richard M. Gladone[1,2], Ceren Ozek[1,2], Monika Saxena[1,2], Samara Santiago[1,2], Xian Adiconis[3,4], Danielle Dionne[4], Lan Nguyen[4], Kavya M. Shah[1,2], Jill M. Goldstein[1,2], Caterina Gasperini[1,2], Ioannis A. Gampierakis[1,2], Scott L. Lipnick[1,2,3], Sean K. Simmons[3,4], Sean M. Buchanan[1,2], Amy J. Wagers[1,2,5,6], Aviv Regev[4,7], Joshua Z. Levin[3,4] & Lee L. Rubin[1,2,3]

nature aging

Article

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Multi-omic rejuvenation and lifespan extension on exposure to youthful circulation

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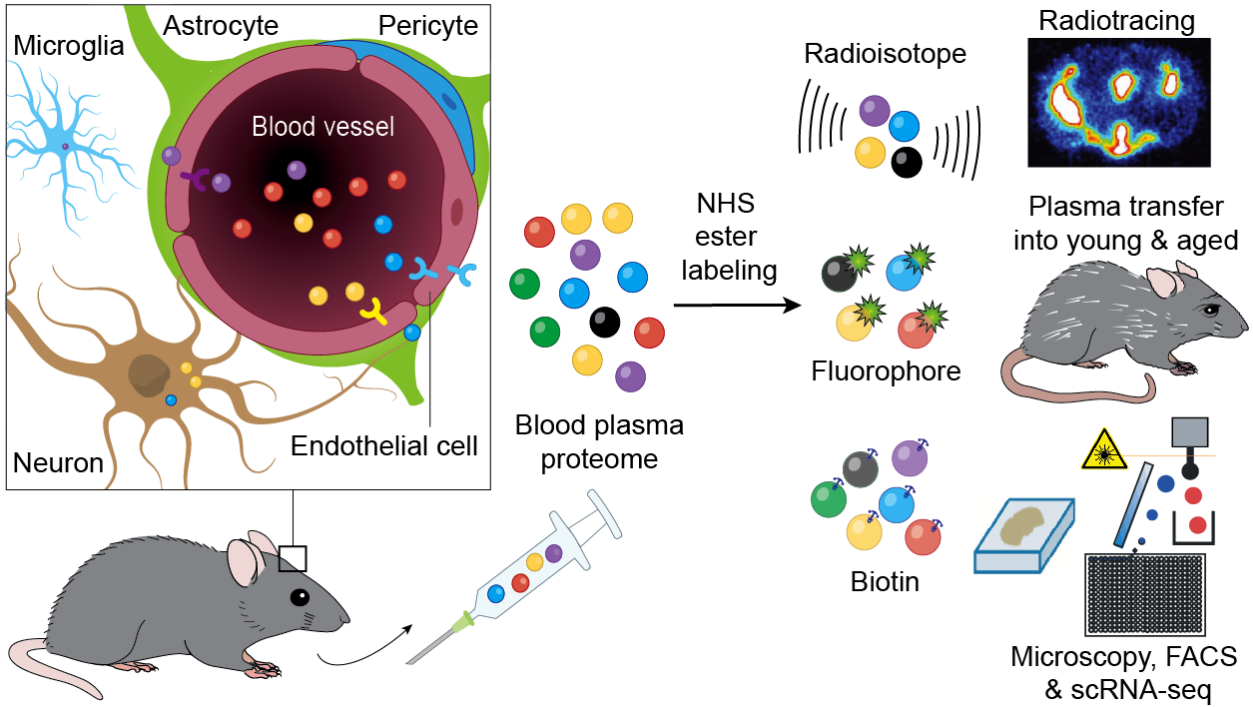
Bohan Zhang[1,13], David E. Lee[2,3,13], Alexandre Trapp[1,8,13], Alexander Tyshkovskiy[1,4], Ake T. Lu[5,10], Akshay Bareja[2,3], Csaba Kerepesi[1,11], Lauren K. McKay[3,12], Anastasia V. Shindyapina[1,9], Sergey E. Dmitriev[4], Gurpreet S. Baht[3,6,7], Steve Horvath[5,8,10], Vadim N. Gladyshev[1] & James P. White[2,3,7]

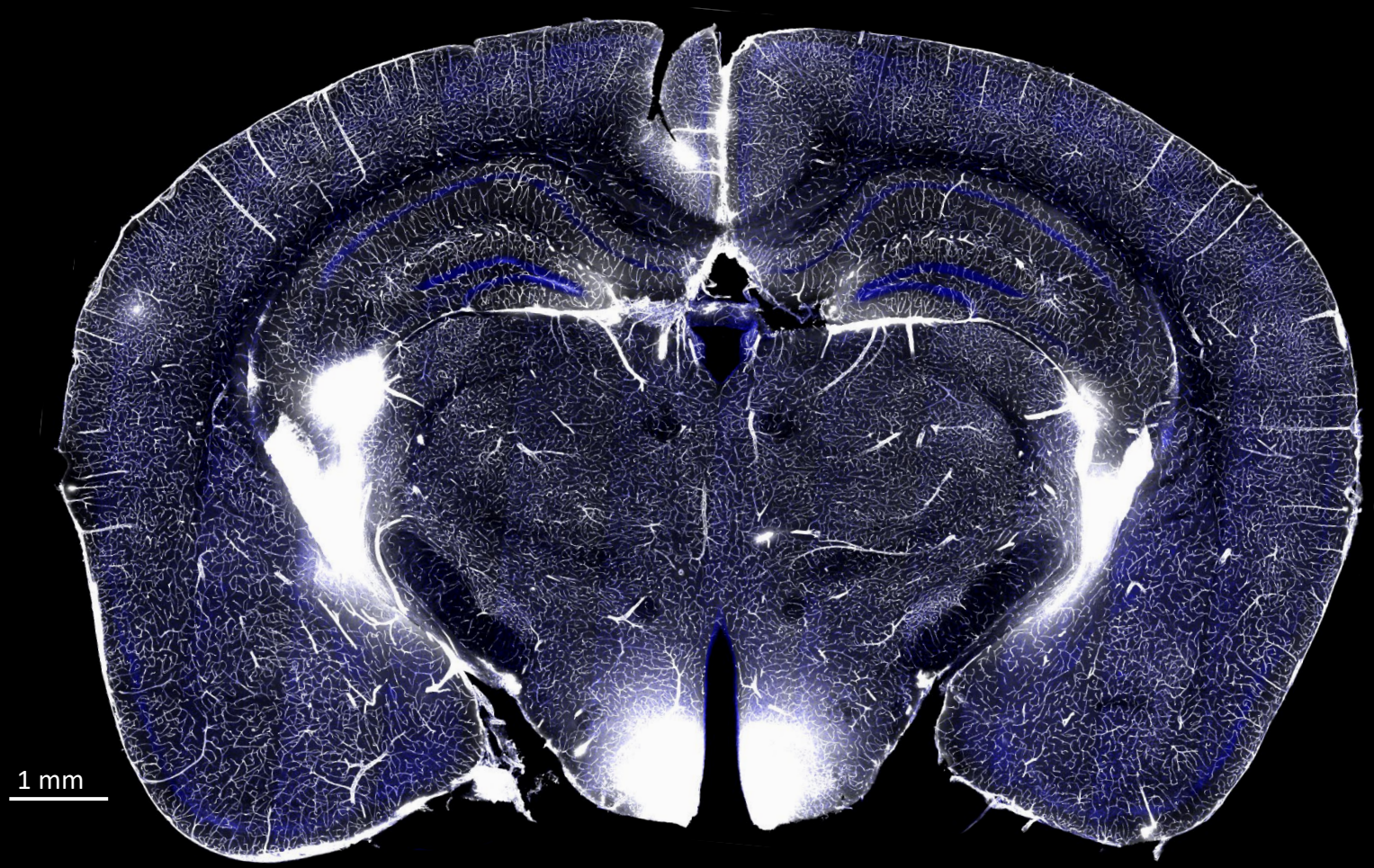
Plasma proteome labeling to study brain protein uptake



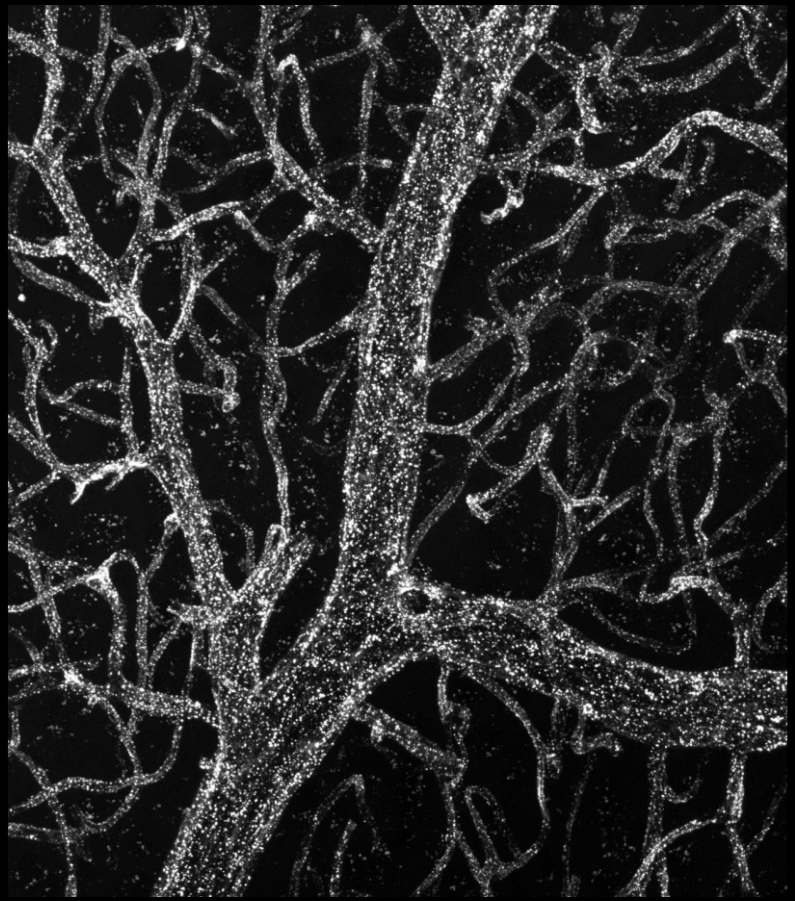
Andrew Yang
Asst. Prof.,
Gladstone/UCSF

Yang et al., Nature 2020

Plasma proteins permeate the healthy adult brain

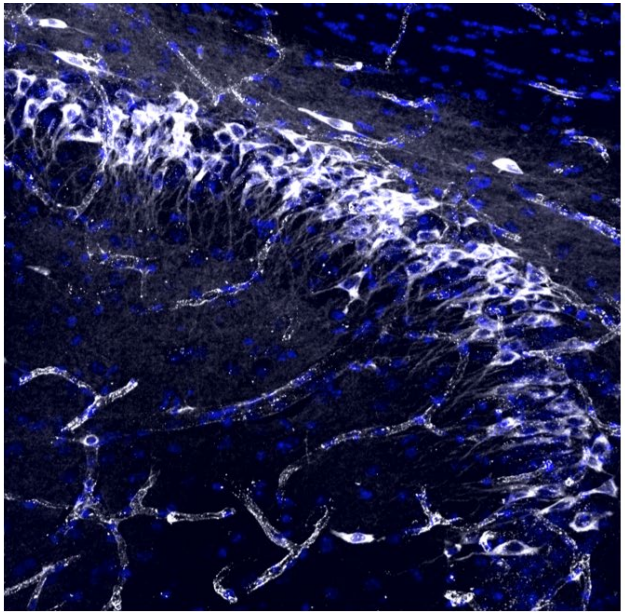


Extensive vesicular staining of vascular tree



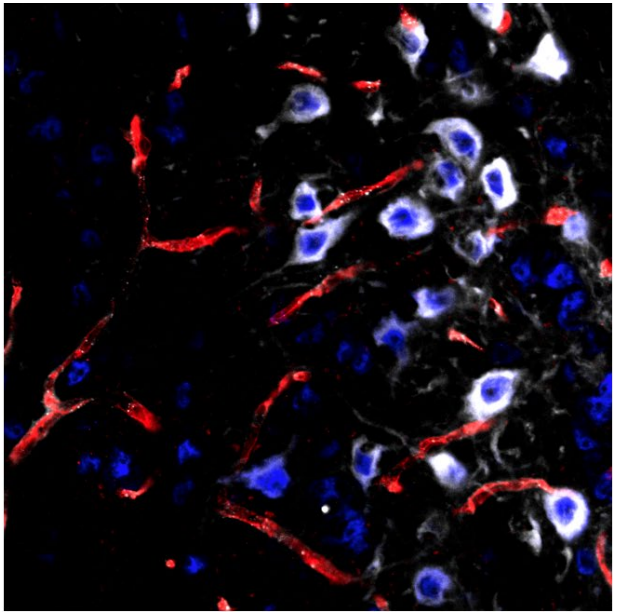
Plasma proteins accumulate in different brain cells

Neurons in hippocampus



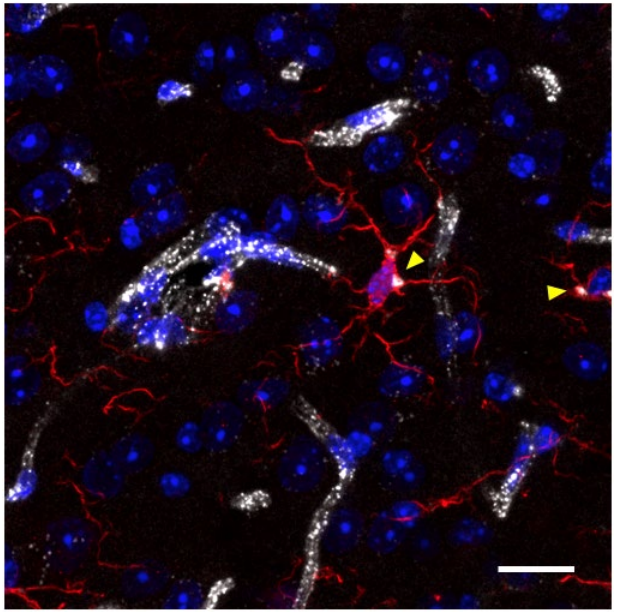
Hoechst/DNA Plasma

Neurons in neocortex



NeuN/Neuron Plasma
CD31/endothelial cell

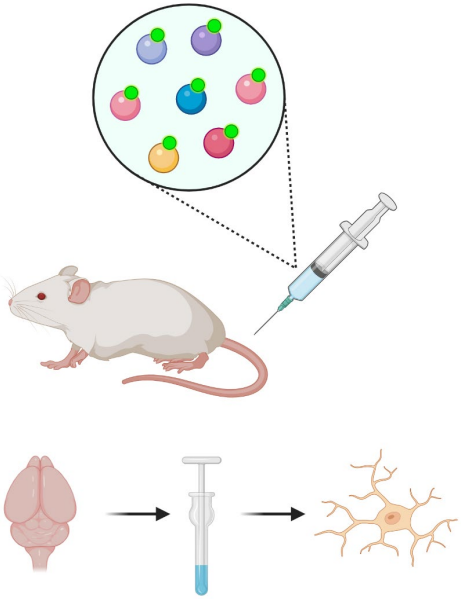
Microglia in hippocampus

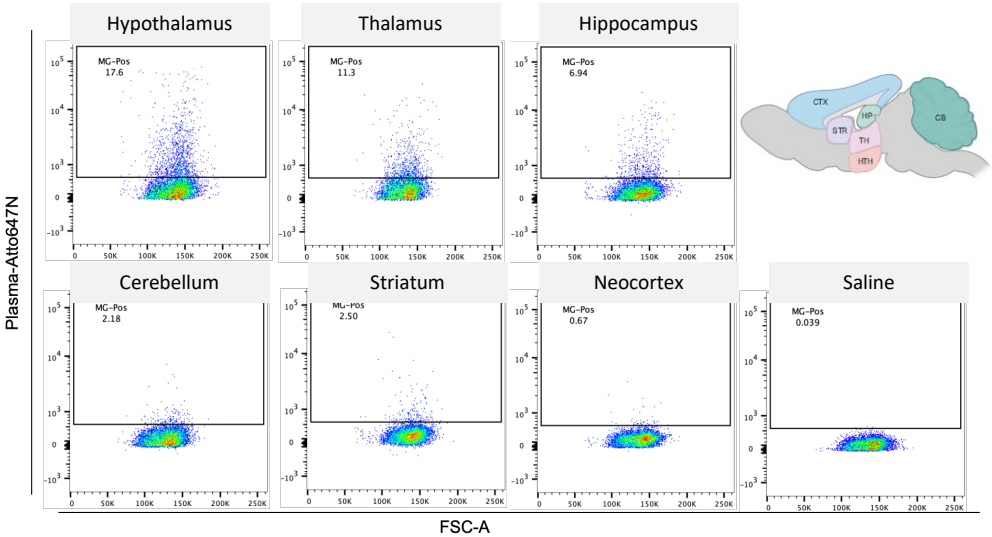


Hoechst/DNA Plasma Iba1/microglia

Yang et al., Nature 2020

Regional heterogeneity of plasma uptake into microglia of young mice

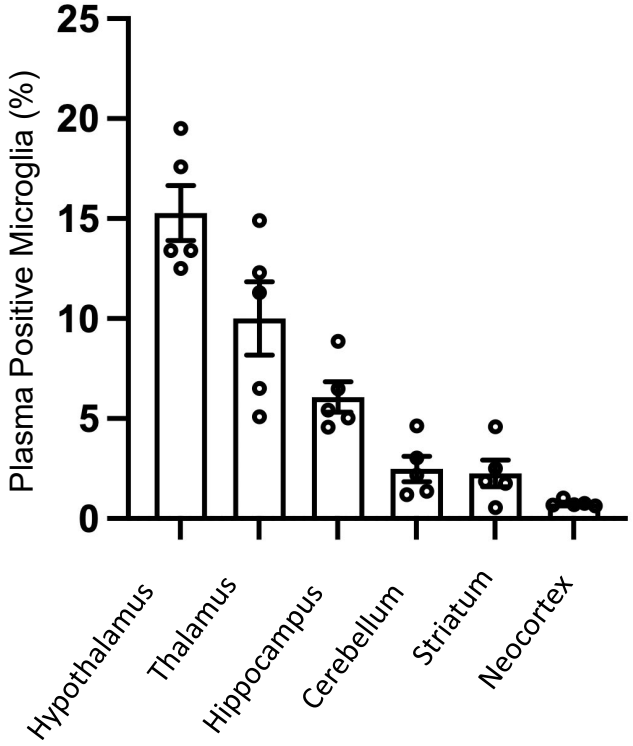




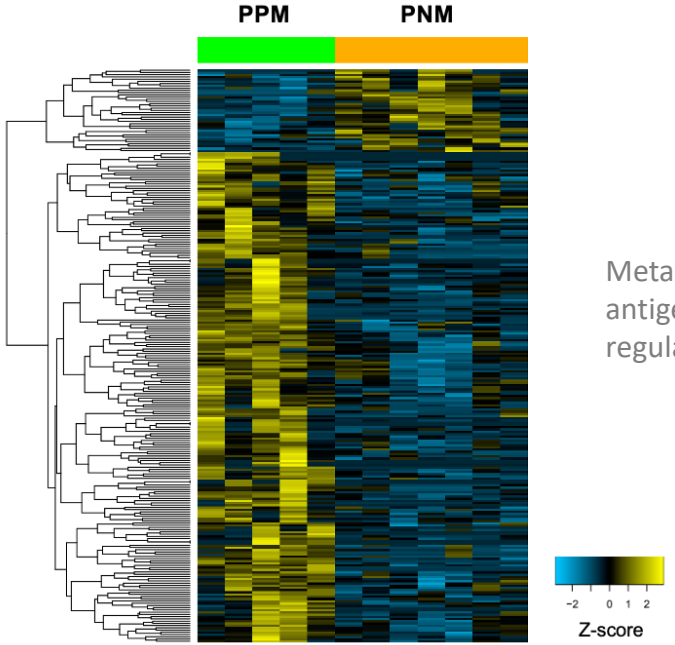
Nannan Lu
Instructor

Lu et al., In revision, BioRxiv

Plasma positive microglia are enriched in thalamus/hippocampus and specialized in phagocytosis and antigen presentation



Proteome of plasma-positive vs plasma-negative microglia in hypothalamus



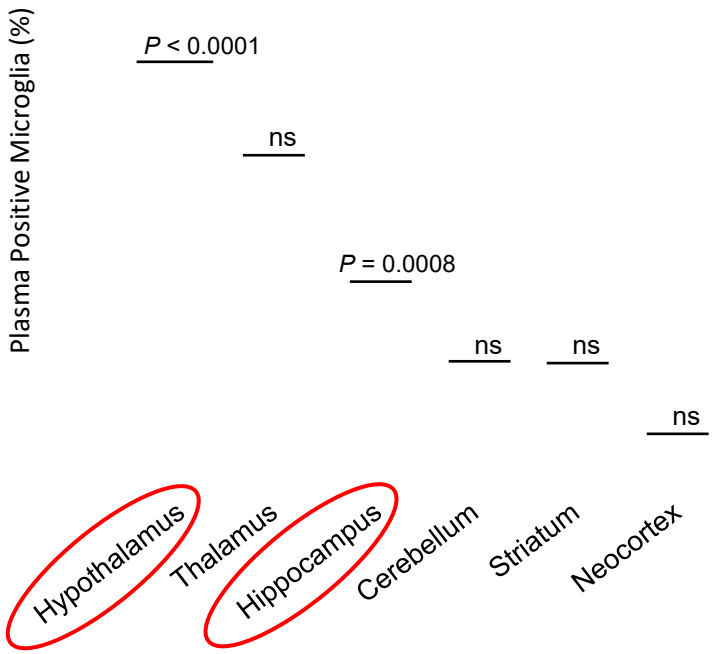
(n=5 for PPM and n=7 for PNM)

Metabolic/catabolic process
antigen presentation
regulation of transport

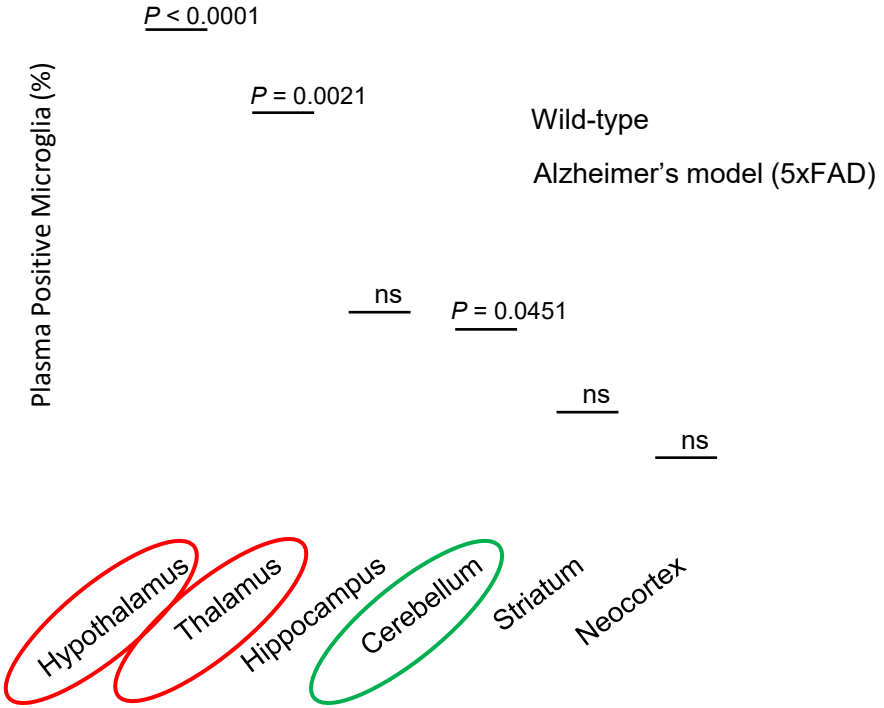
Lu et al., In revision, BioRxiv

Number of plasma positive microglia changes prominently with age and in Alzheimer's amyloidosis mice

Plasma Positive Microglia with aging

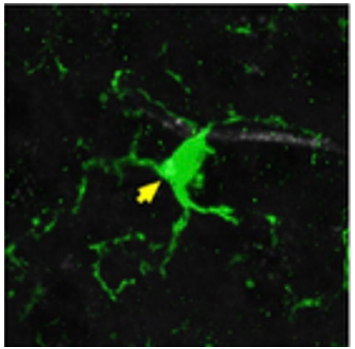


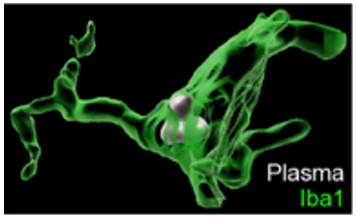
Plasma Positive Microglia with amyloidosis



Lu et al., In revision, BioRxiv

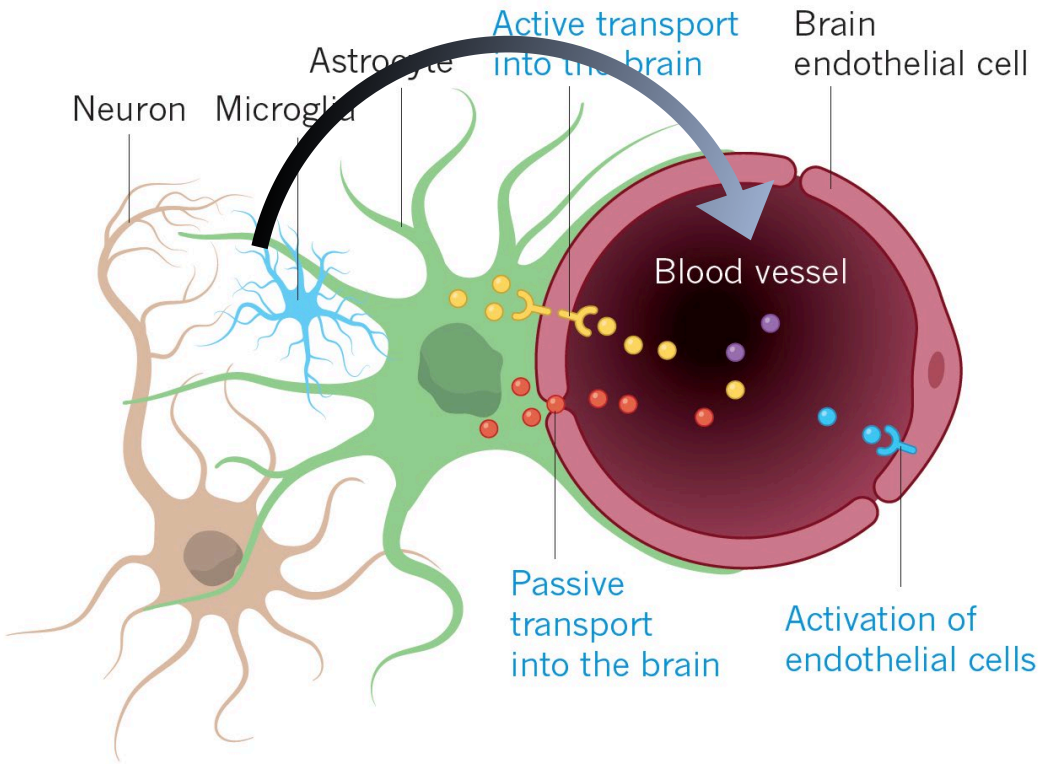
Plasma positive microglia represent a new way of communication between brain, circulation, and body



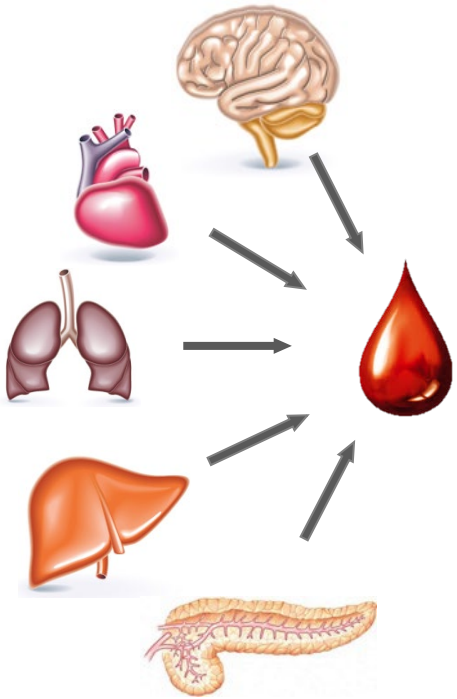


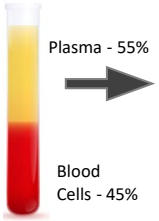
- Circulatory proteins are taken up readily into the brain — uptake shifts from receptor mediated to non-specific with age
- Specialized microglia take up plasma proteins in region specific way
- Plasma positive microglia appear specialized for phagocytosis and antigen presentation
- ApoA1 is taken up from the blood by microglia and facilitates this phagocytic, antigen presenting state

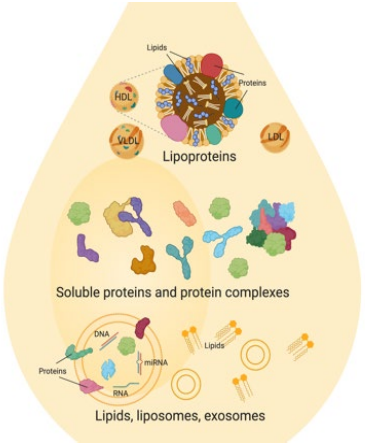
What comes out of the brain into the circulation?

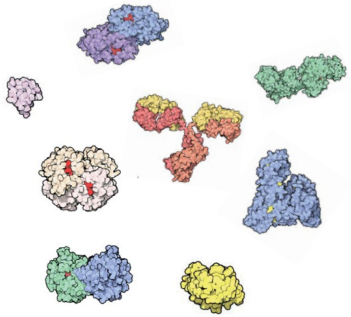


Brain and other organ-derived molecules can be measured in the blood







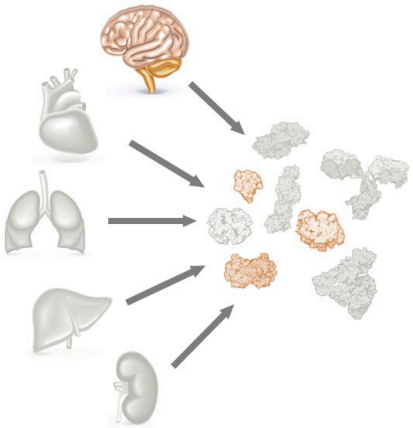


Blood plasma contains 10’000s of molecular species

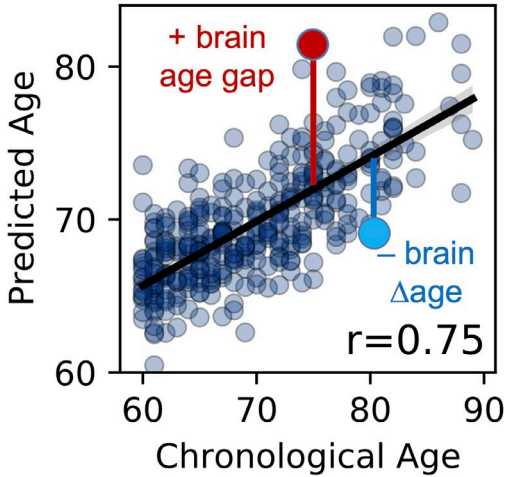
Focus on proteins derived from specific organs based on gene expression

Blood protein-based machine-learning models measure brain age

Brain-derived proteins accumulate in blood

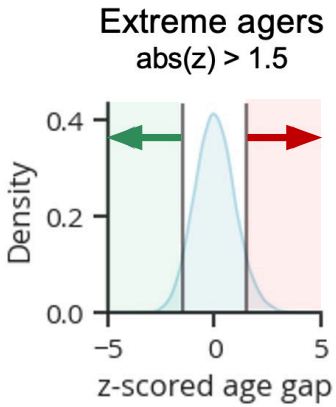


Brain-derived proteins estimate brain age

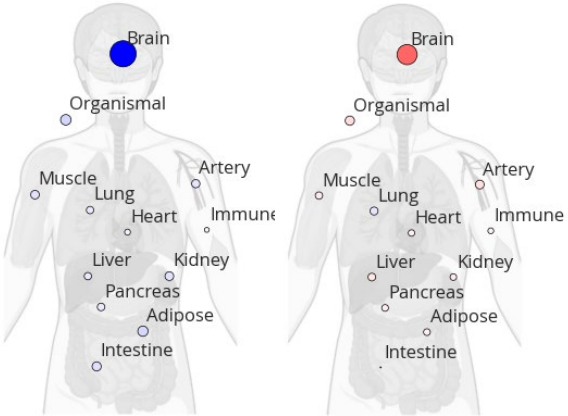


Brain age gaps predict disease and mortality

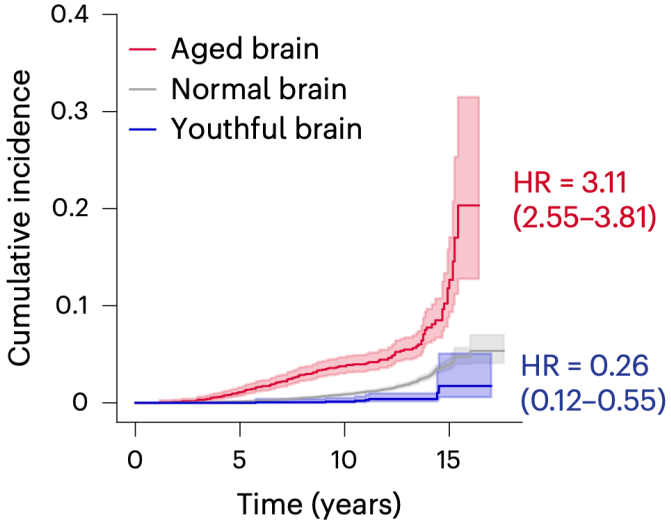
Oldest brains are 12 times more likely to develop Alzheimer's disease within 15 years



Youngest brains (1.4%) Oldest brains (1.2%)



Risk to develop Alzheimer's Disease

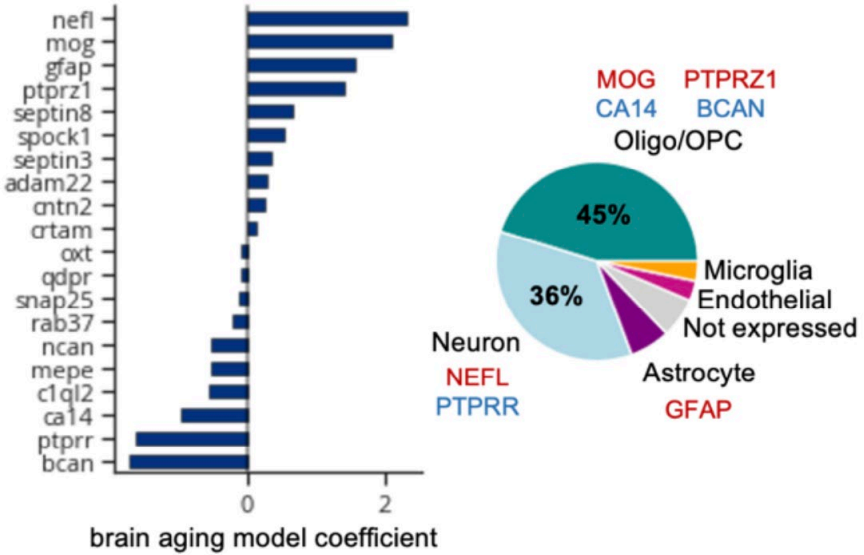


44,498 people, age 40-70 years Olink
3,000 proteins in plasma

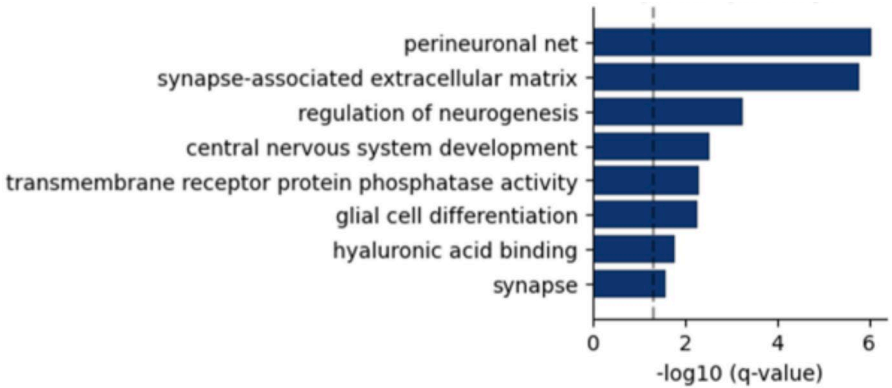
Oh et al. Nature Medicine, 2025b

Brain age is captured by proteins from neurons, oligos and the synaptic extracellular matrix, measured in the circulation

Brain age model composition



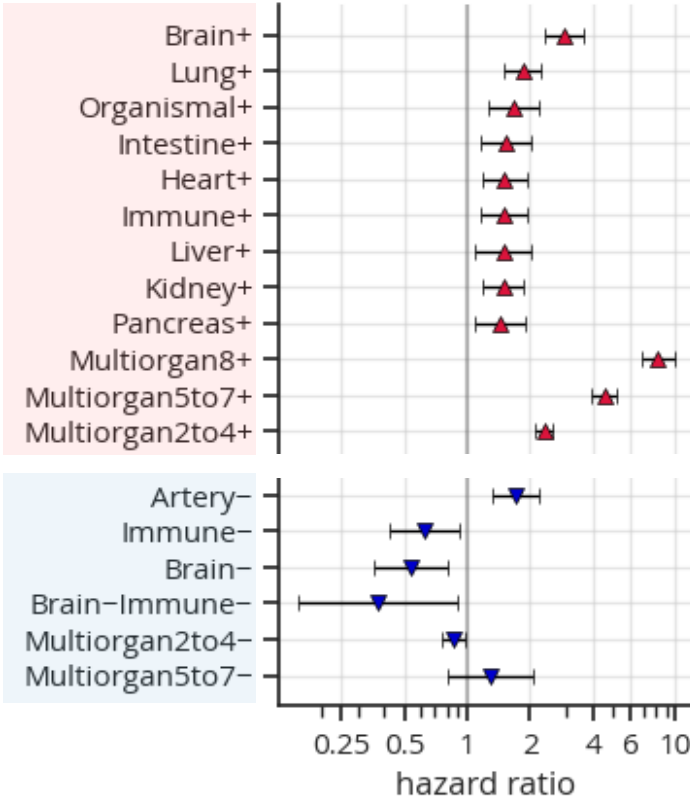
Biological pathways implicated by top brain longevity proteins

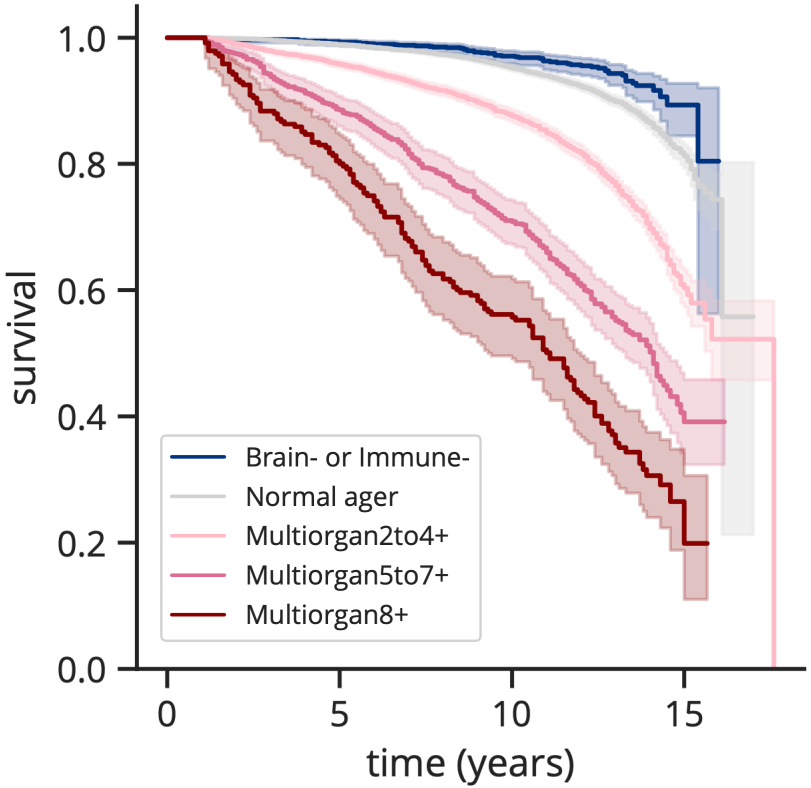


Oh et al. Nature Medicine, 2025b

Extreme organ age predicts mortality

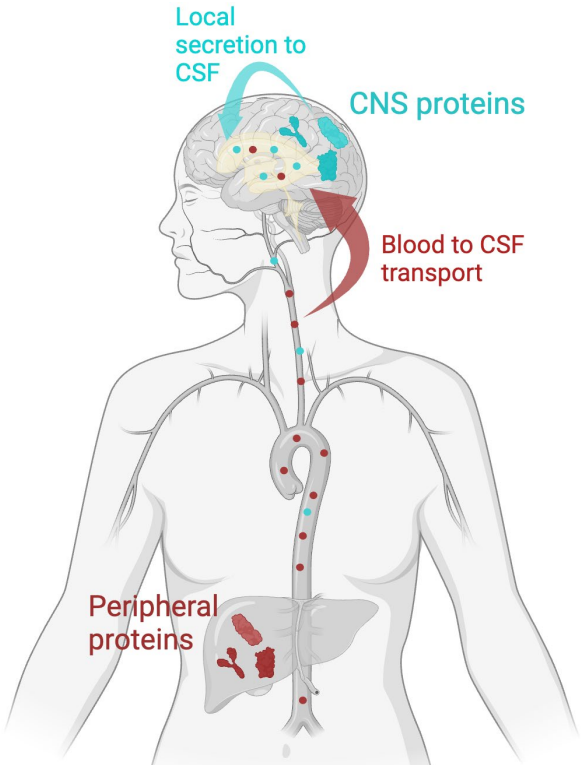
(models trained on chronological age in healthy people)



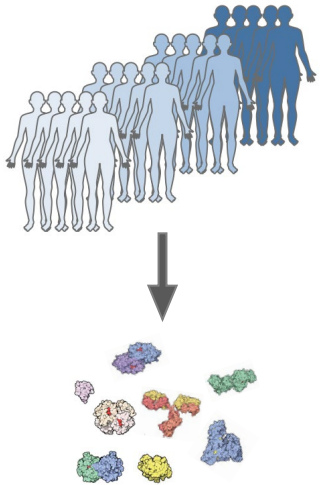


Oh et al. Nature Medicine, 2025b

Communication between brain and blood



Paired CSF and plasma from 2,171 healthy people and patients with cognitive impairment and dementia (age ~50–90 years old)



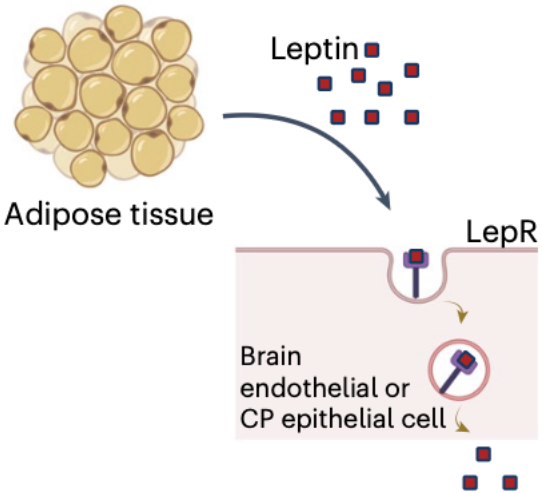
Measure 7K proteins
(Somalogic platform)

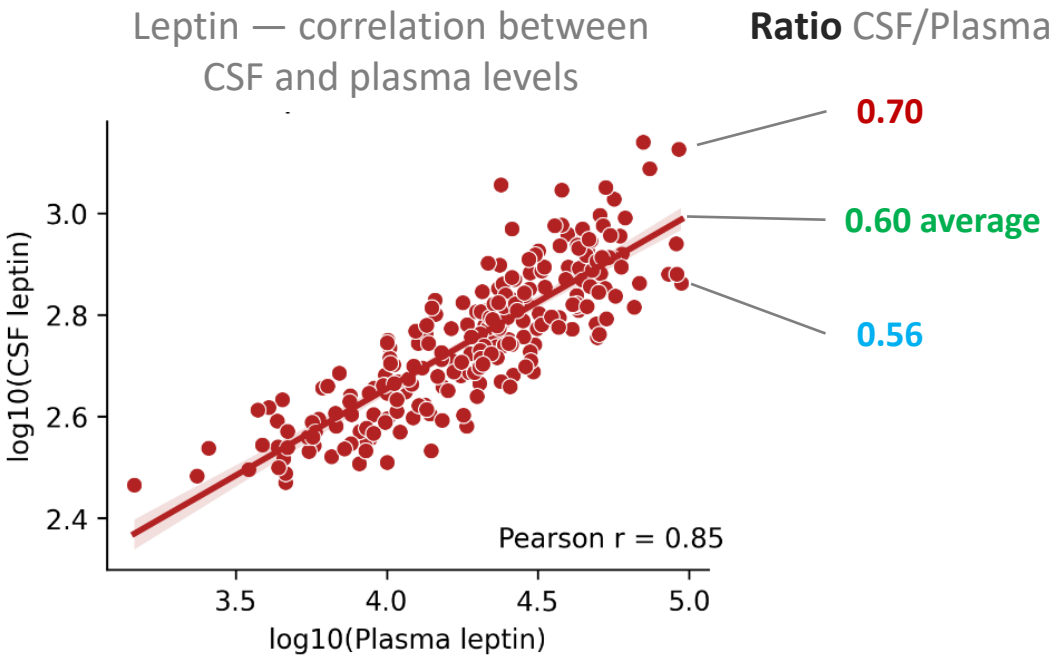
Amelia Farinas
Graduate Student

gnpc Global Neurodegeneration Proteomics Consortium

Farinas et al. Nature Medicine 2025

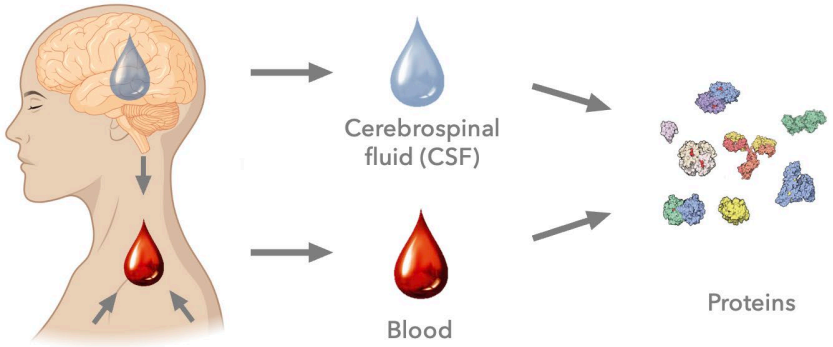
Correlation between CSF and plasma protein levels

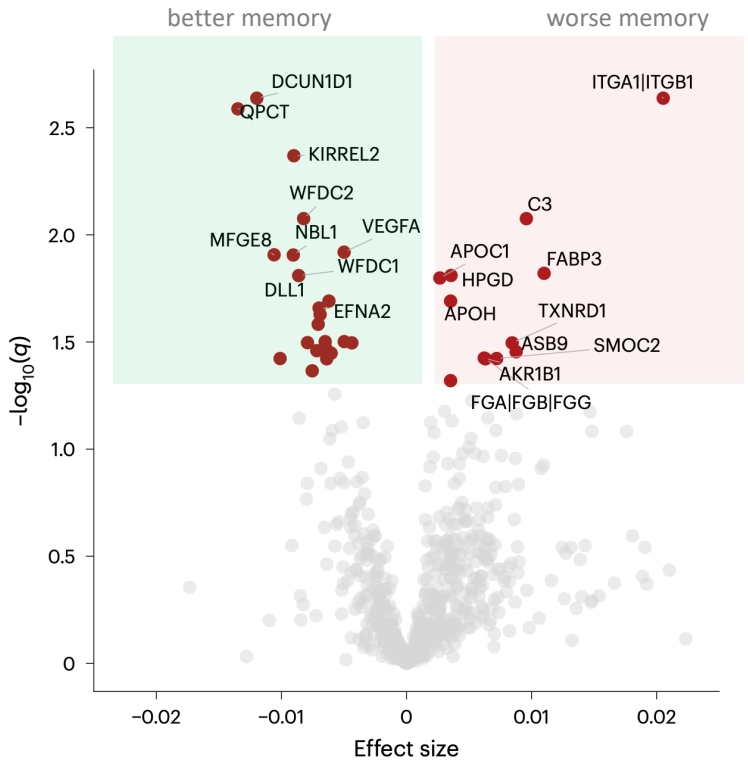




Farinas et al. Nature Medicine 2025

Calculation of CSF/plasma ratios for each protein: ratios change with cognitive function





DCUN1D1 – protein neddylation/degradation

ITGA1/ITGB1 – immune cell adhesion/extravasation

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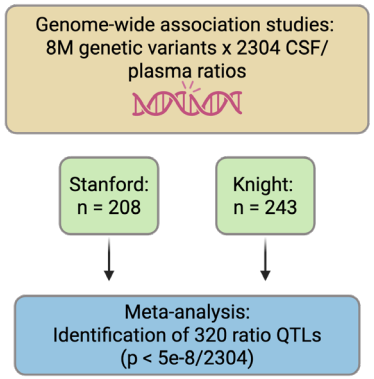
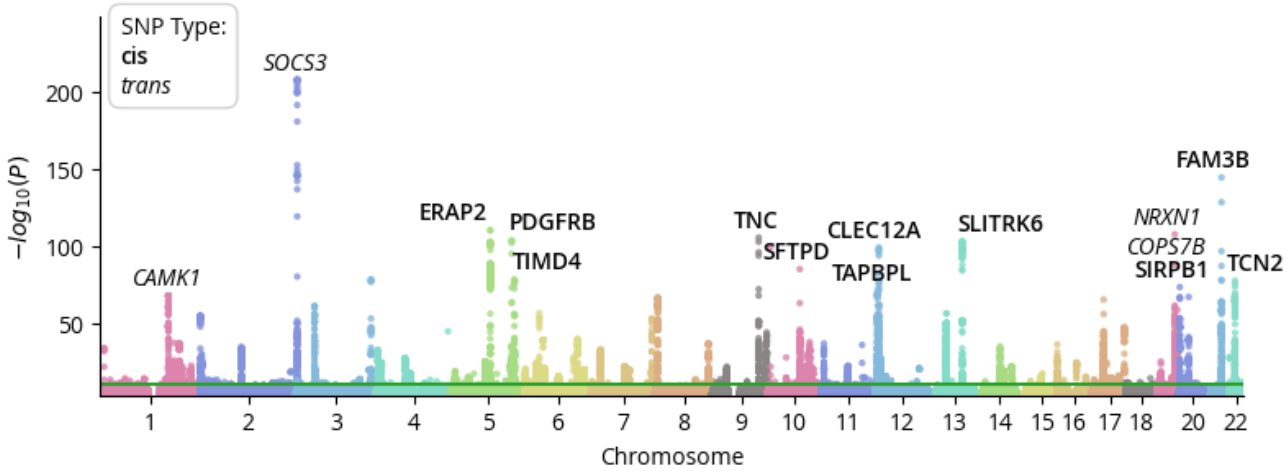
Genetic associations with CSF/plasma ratios





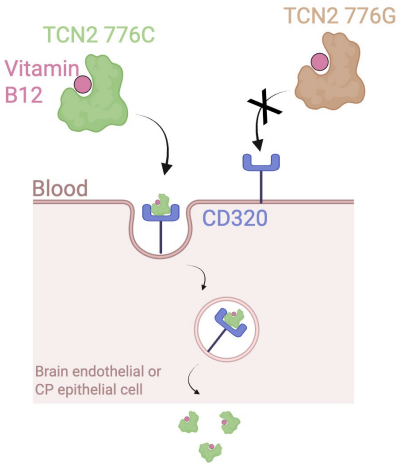
With Carlos Cruchaga

Farinas et al. Nature Medicine 2025

Genetic association of transcobalamin 776C/G genotype with CSF/plasma ratio – possible link to Vitamin B12 deficiency

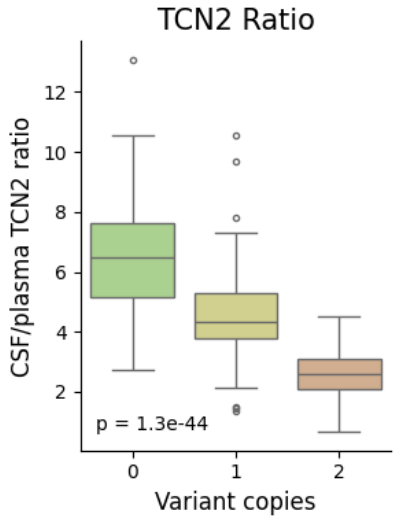
Vitamin B12 Binding Protein

Transcobalamin (TCN2)



Pluvinage et al. 2024: autoantibodies against CD320 result in brain B12 deficiency

Transcobalamin (TCN2) CSF/plasma ratio



Farinas et al. Nature Medicine 2025

Summary

- Plasma protein changes reflect physiological state but are also drivers of that state as shown by rejuvenating effect of young plasma and uptake into microglia
- Aging of the brain, risk for AD, and mortality can be predicted based on levels of neuronal, synaptic and oligodendroglial proteins in blood
- Ratios of protein levels between CSF and plasma change with age, cognitive function and some are linked to genetic variants
- Advanced plasma proteomics opens the possibility for unprecedented insight into human cell and organ physiology on an individual basis

Acknowledgments

TWC Lab

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Knight Initiative for Brain Resilience
WU TSAI NEUROSCIENCES INSTITUTE
STANFORD UNIVERSITY
gnpc Global Neurodegeneration Proteomics Consortium
Hong Kong Center for Neurodegenerative Diseases
香港神經退行性疾病中心
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