

Year of **Alzheimer's Disease** Research

Professor Rusty Gage

Joan Jacobs Science & Music Series
October 25, 2025



Rusty Gage, PhD

salk®

**Professor, Laboratory of Genetics
Vi and John Adler Chair**

Elected memberships

- American Academy of Arts and Sciences
- US National Academy of Medicine
- US National Academy of Sciences

Select awards

- Ogawa-Yamanaka Stem Cell Prize
- Taylor International Prize in Medicine
- W.M. Keck Foundation Award

Education

- Fulbright, University of Lund, Sweden
- MS and PhD, Johns Hopkins University
- BS, University of Florida



The Challenge

Alzheimer's disease is one of the most significant public health crises of our time. Despite more than \$30 billion in research funding since 1984, we still have no highly effective treatments.

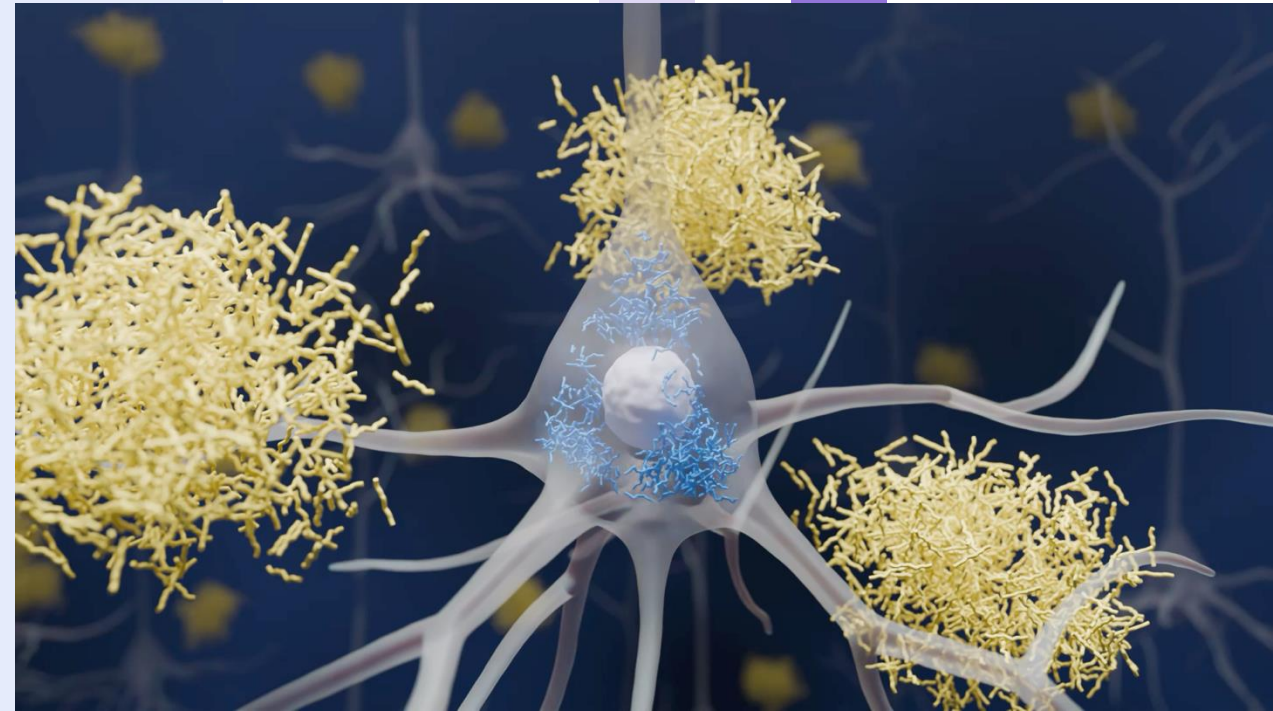
Why?

Limited research focus

- On amyloid plaques and tau tangles instead of earlier causes and signs
- On neurons instead of all brain cells

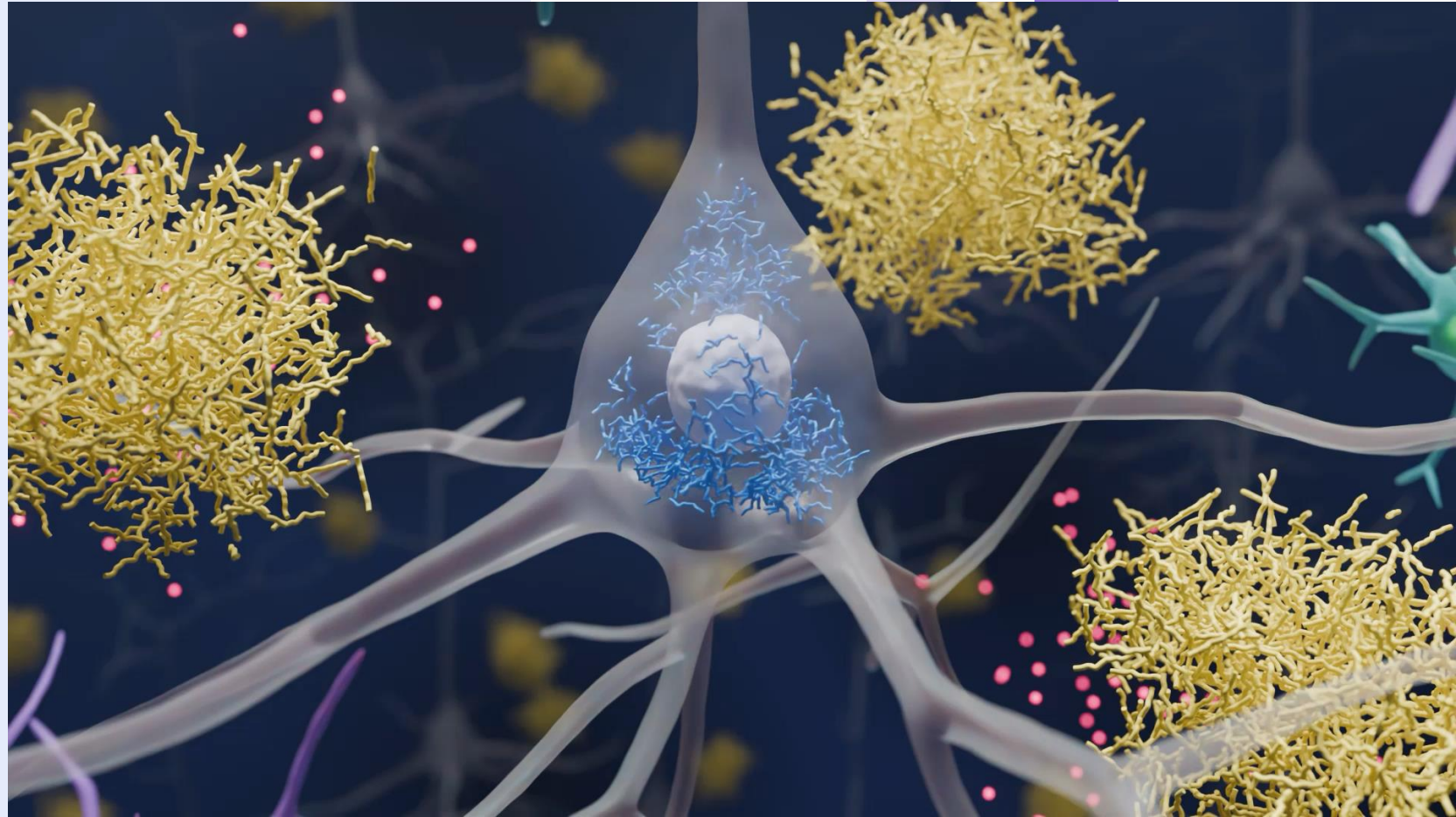
Disease variability

- Alzheimer's is not the same for everyone



Salk's Approach

Unlike traditional Alzheimer's research focused on the later stages of disease, **Salk's approach pulls back the lens** to study *earlier drivers* of the disease across the *whole brain*.



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Salk's Approach

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To get a more holistic view of Alzheimer's, we bring together scientists with different expertise.

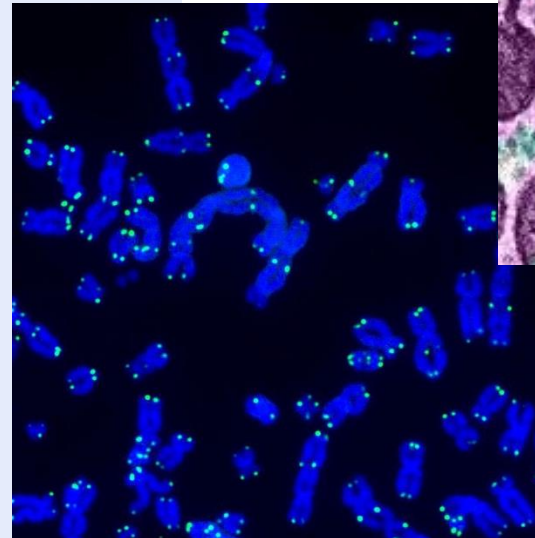
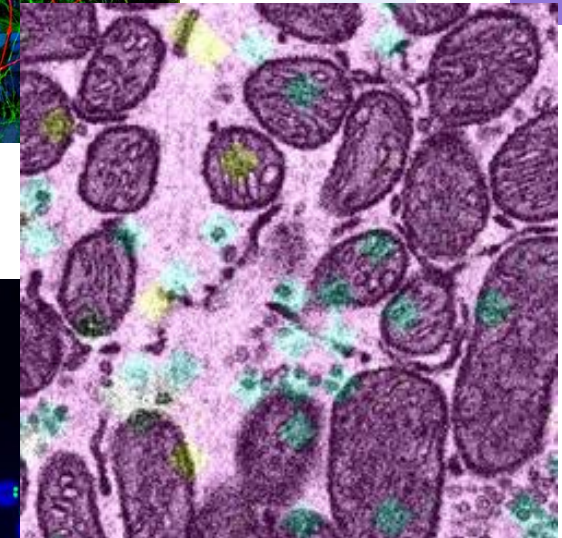
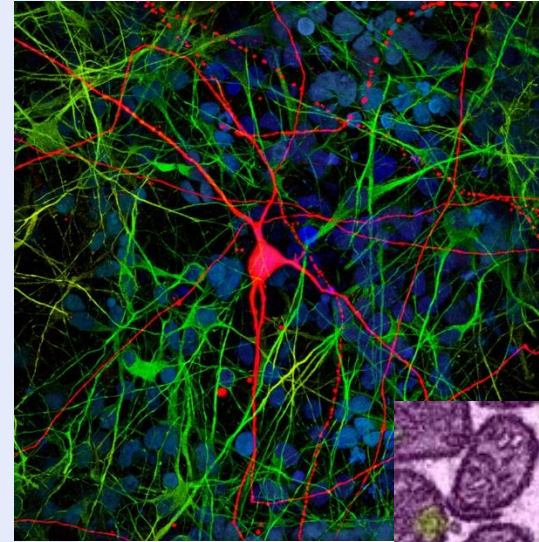
Thanks to these collaborations, **we've made discoveries that led to new ideas about Alzheimer's.**



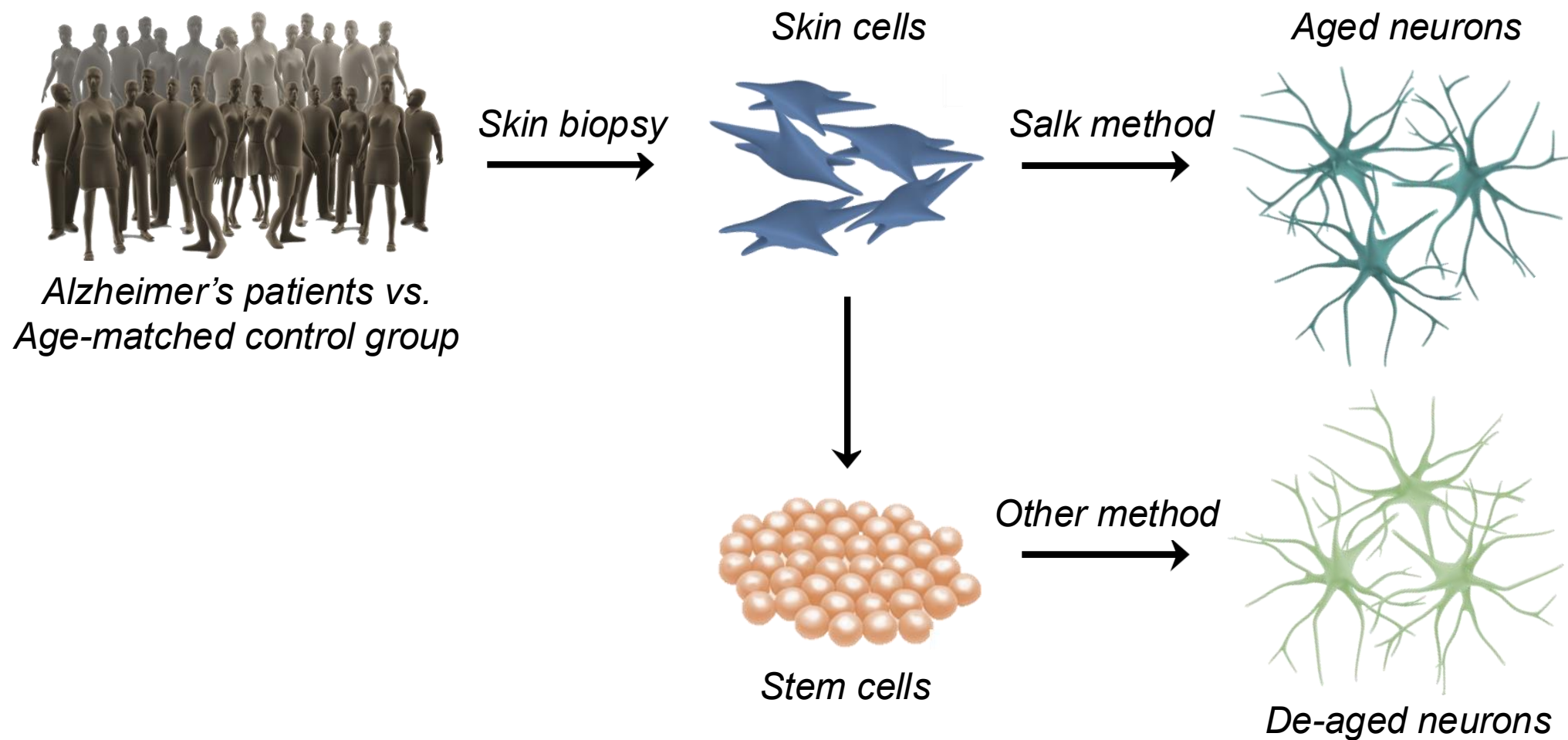
Salk's Approach

What drives Alzheimer's disease?

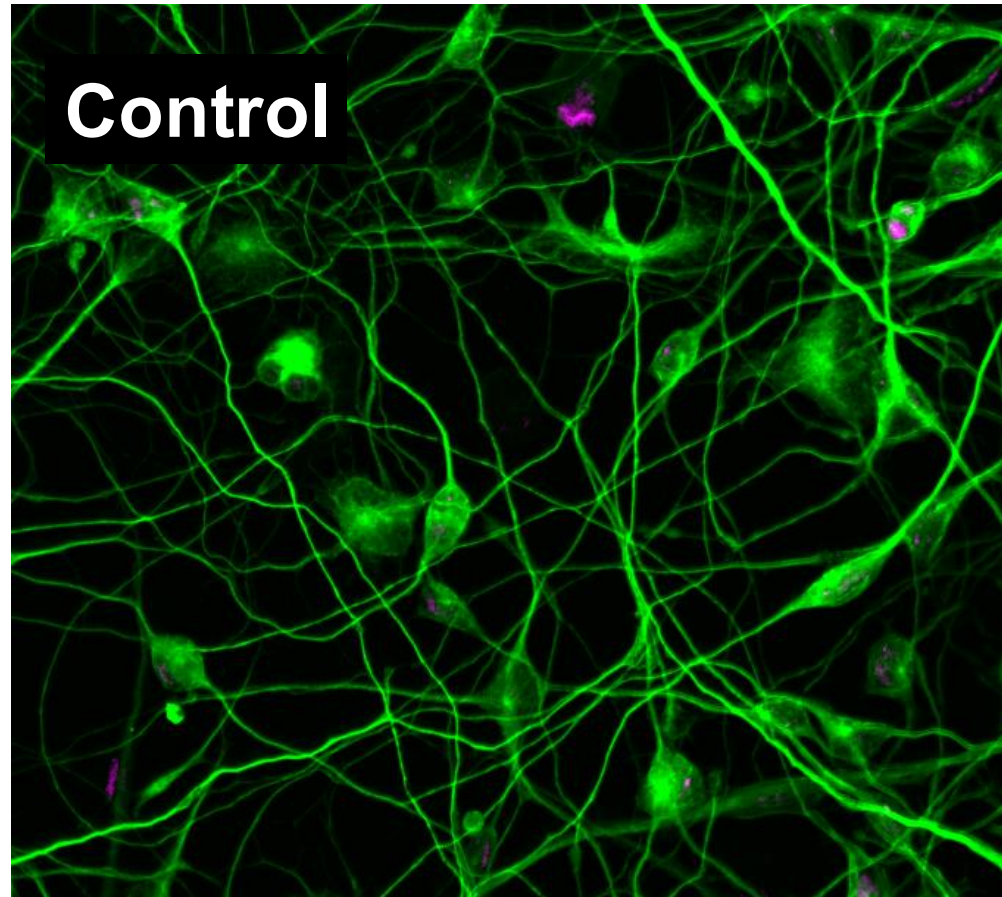
- ↑ *Chronic inflammation*
- ↑ *Impaired energy metabolism*
- ↑ *DNA damage*



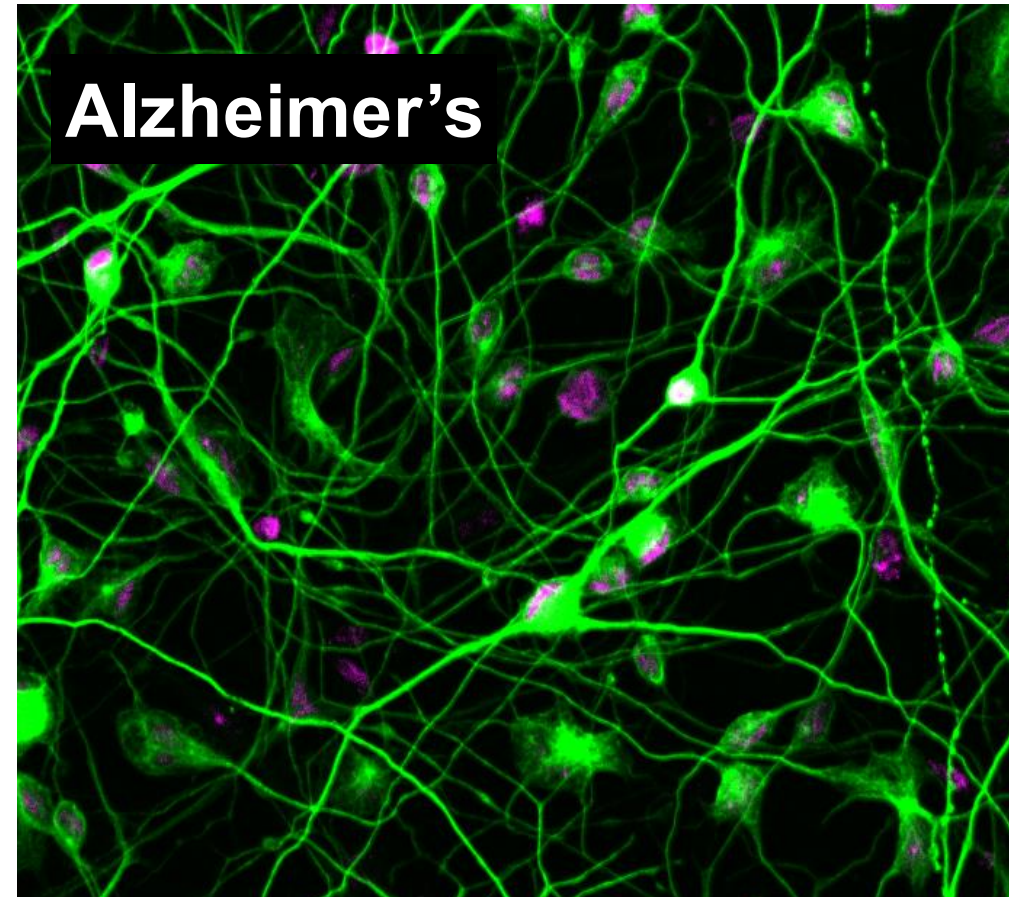
Better models of the Alzheimer's brain



Salk brain model reveals new signs of Alzheimer's



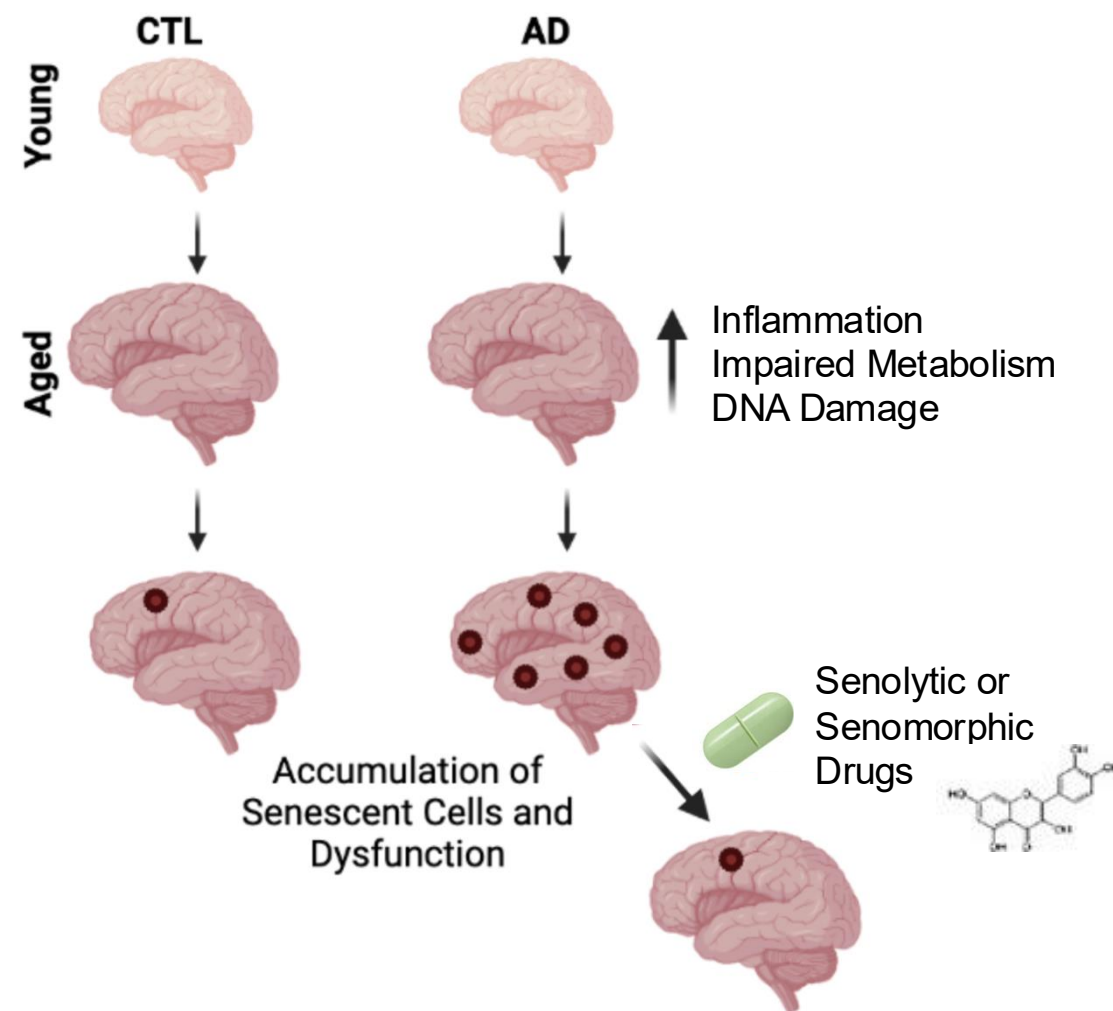
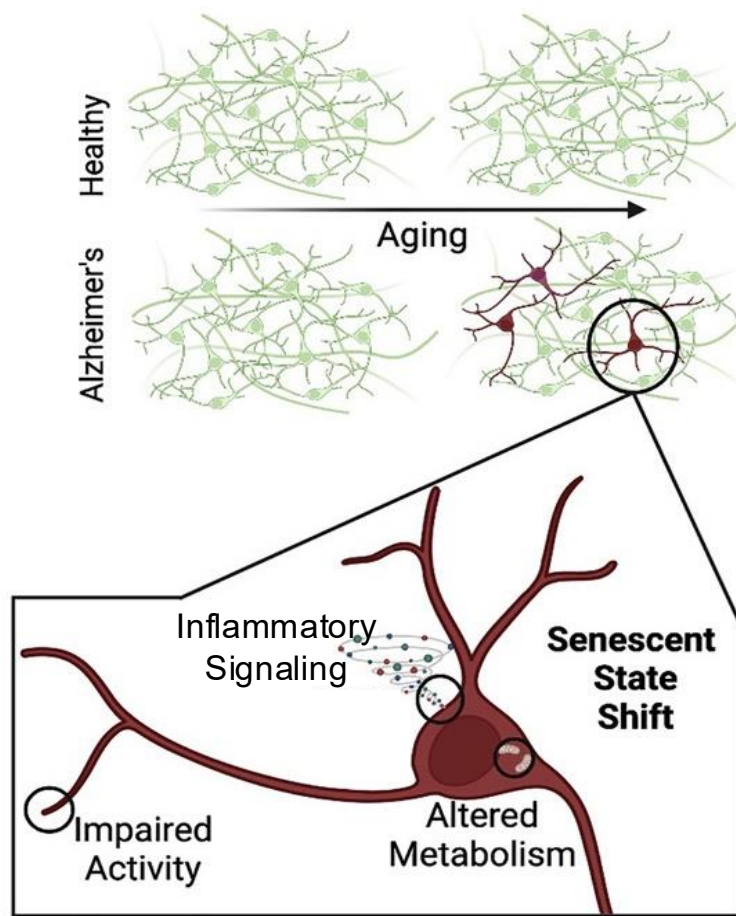
Control



Alzheimer's

*Senescent cells

Alzheimer's neurons become "senescent"



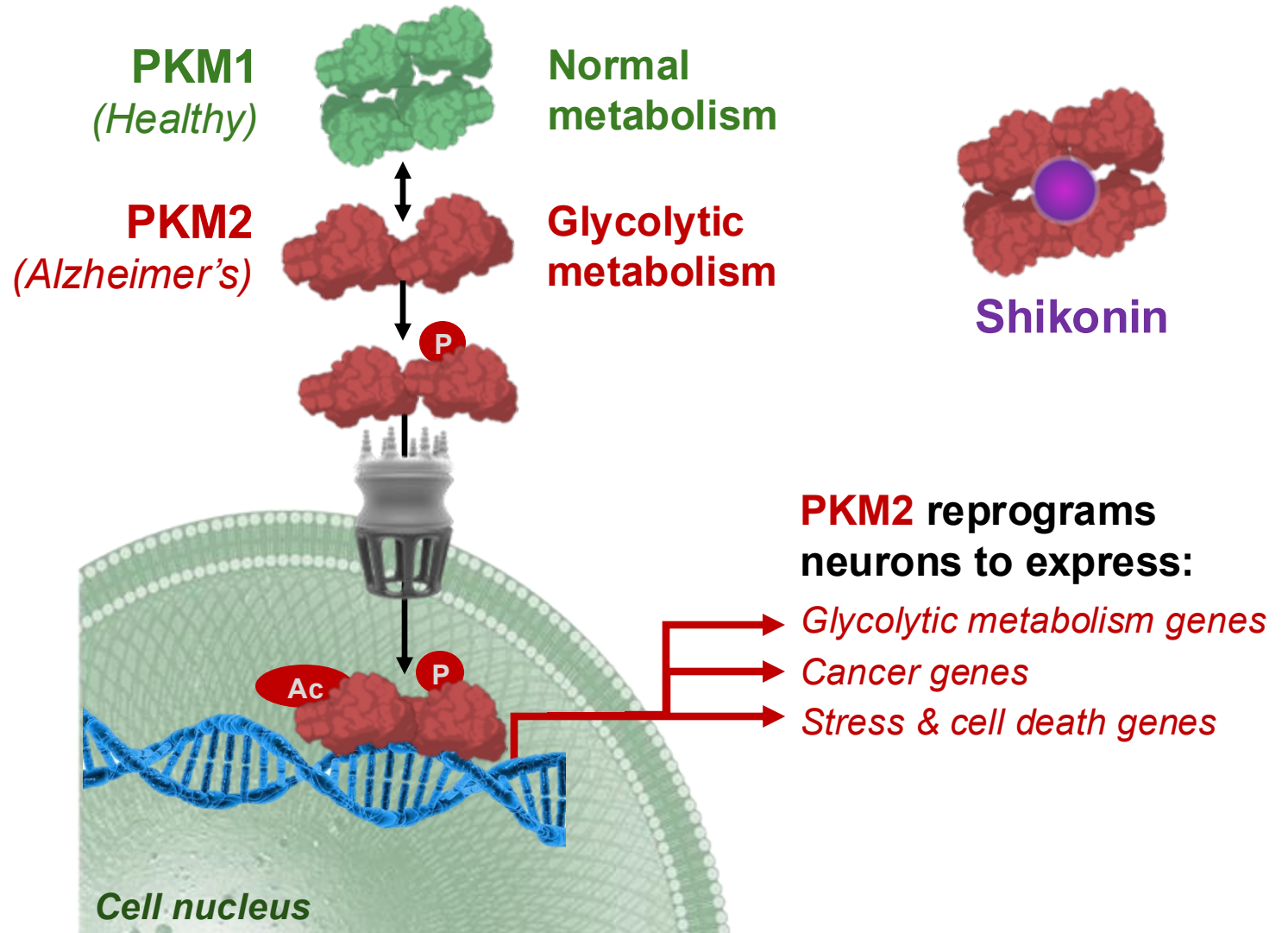
Alzheimer's neurons are low on energy

Alzheimer's neurons make **more PKM2 protein.**

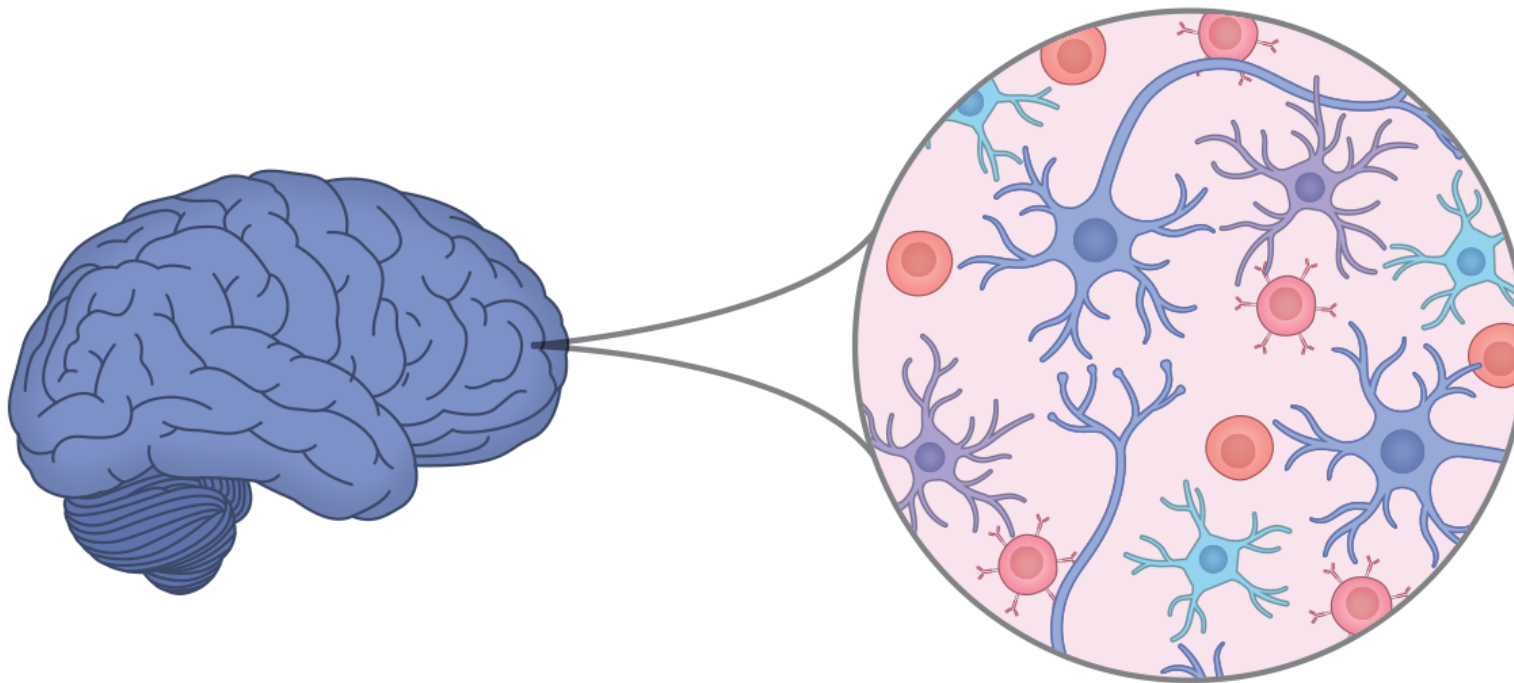
PKM2 makes neurons perform a different kind of cellular metabolism that **generates less energy.**

This causes neurons to **lose function and die.**

This neurodegeneration can be **rescued with Shikonin.**



To cure Alzheimer's, we need to look beyond neurons



NEURONS

Information conductors

ASTROCYTES

Neuron nurturers

MICROGLIA

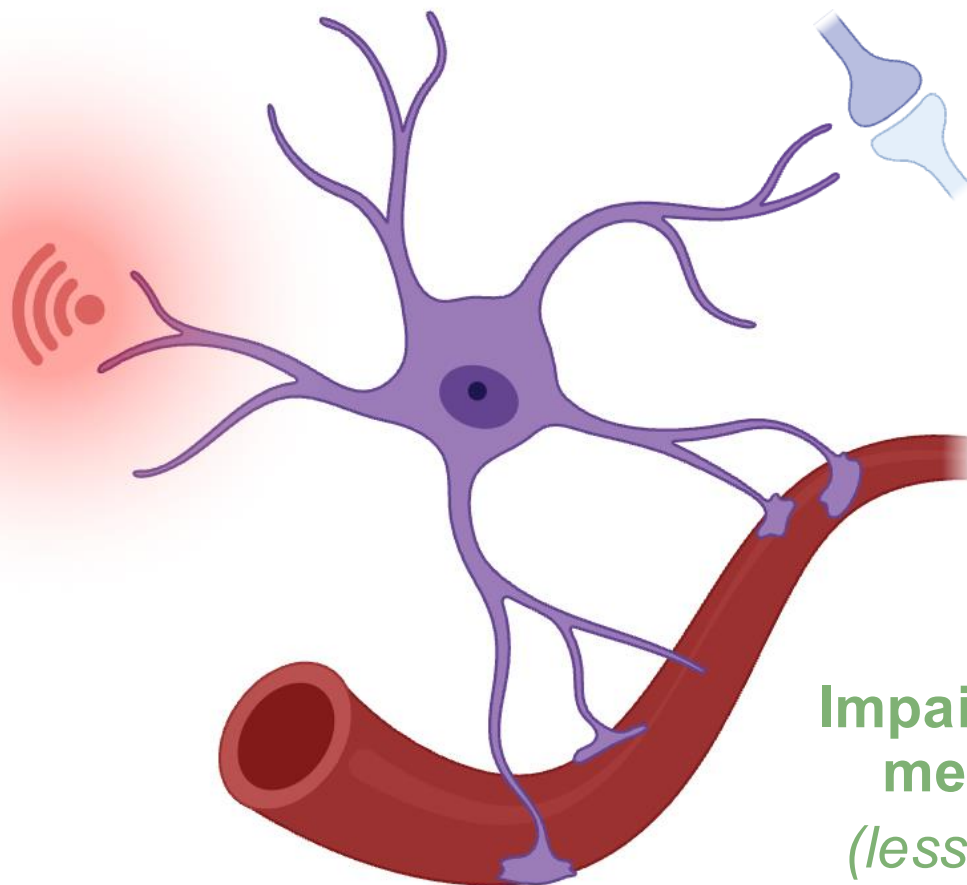
Defenders & custodians

IMMUNE CELLS

Infection fighters

Non-neuronal cells are also impaired in Alzheimer's

**Increased
inflammatory
signaling**
*(damages
surrounding
cells)*



**Weakened
connections
between neurons**
*(disrupts information
flow in the brain)*

**Impaired energy
metabolism**
(less brain fuel)

Repairing astrocytes can improve signs of Alzheimer's

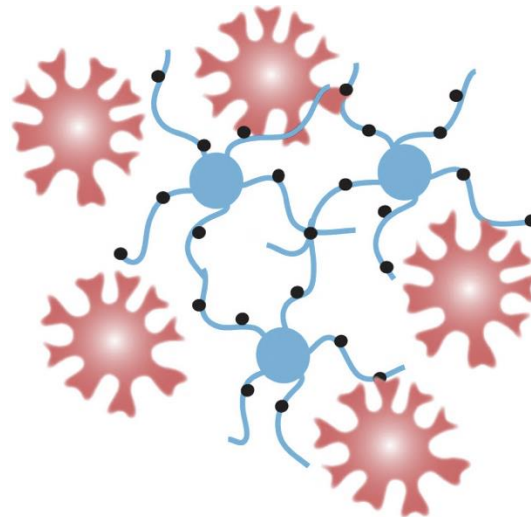
Alzheimer's astrocytes make **more IDO1 protein.**

IDO1 suppresses metabolism, so **astrocytes can't supply enough energy to neurons.**

This **disrupts communication** between hippocampal neurons.

Astrocyte metabolism and memory function can be **rescued with IDO1 inhibitors.**

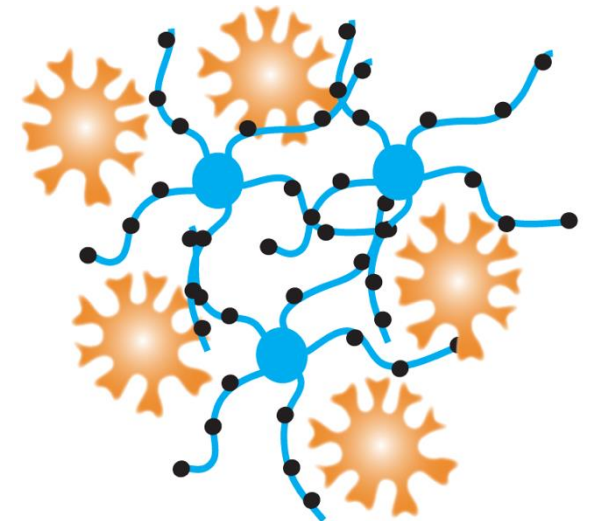
Alzheimer's Brain



Restore
astrocytes



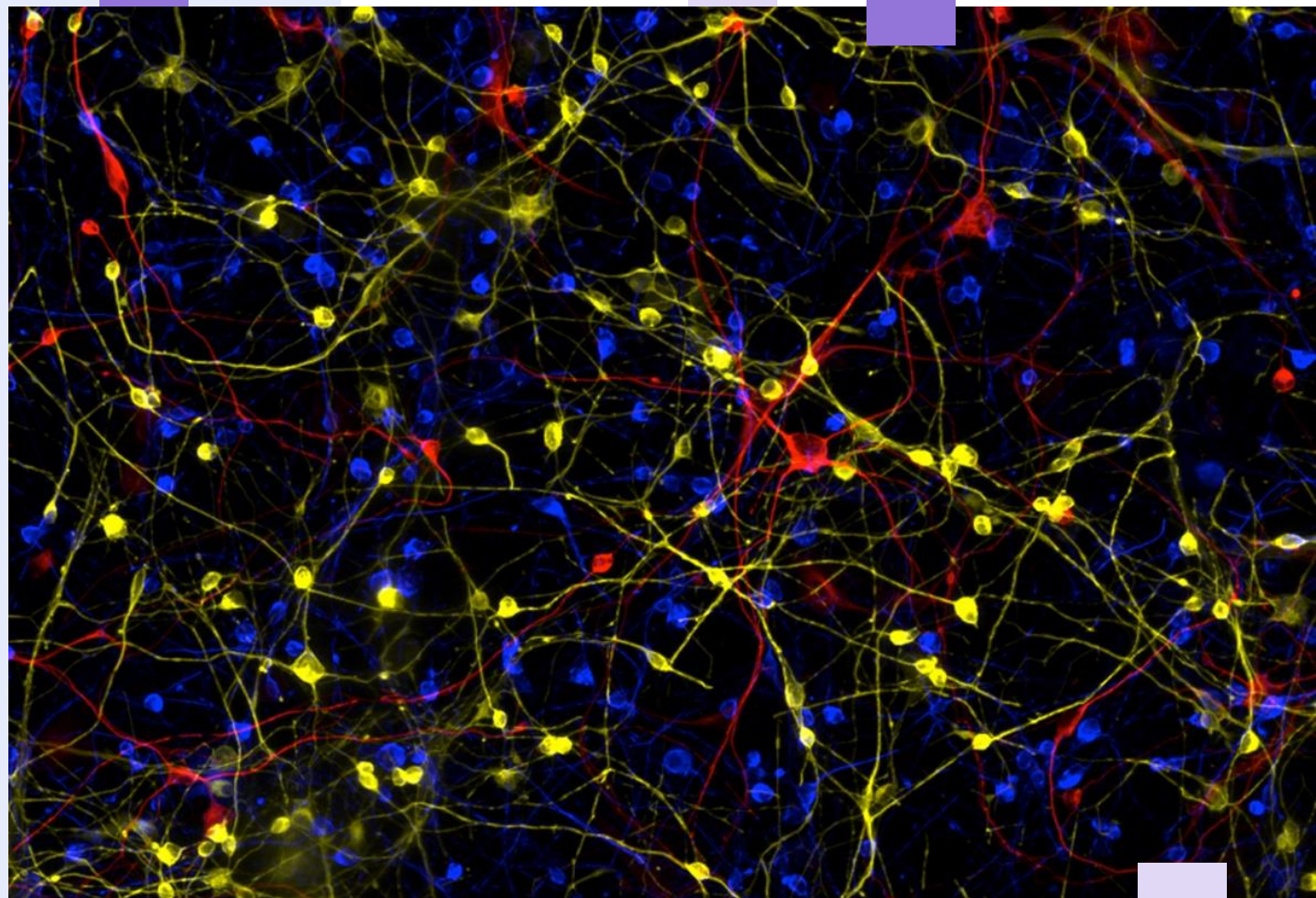
Rejuvenated Brain



In Summary

Salk Institute scientists are:

- Looking beyond plaques and tangles to consider **inflammation, impaired energy metabolism, and DNA damage** as critical drivers of Alzheimer's.
- Developing state-of-the-art tools to study these processes **in all brain cells**.
- Identifying new opportunities to **intervene earlier** with more **personalized and effective treatment plans**.



2025
Year of
Alzheimer's Disease
Research

Q & A

