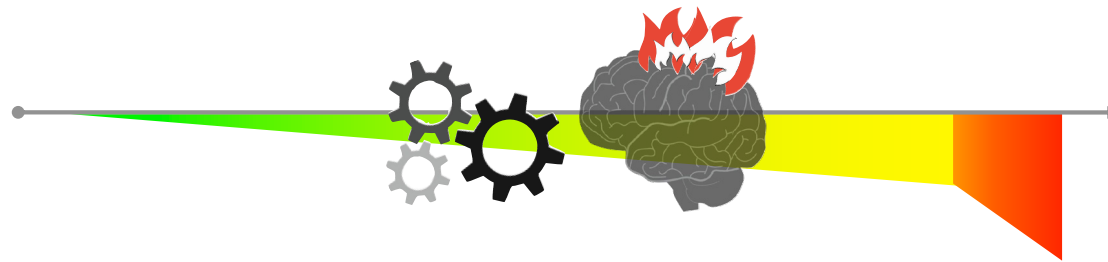


Mechanisms linking brain aging and neurodegeneration



Tom LaRocca

Dept. of Health & Exercise Science

Center for Healthy Aging

Molecular, Cellular & Integrative Neurosciences Program

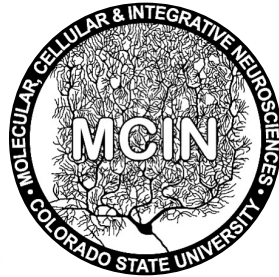
Colorado State University



HEALTH &
EXERCISE
SCIENCE



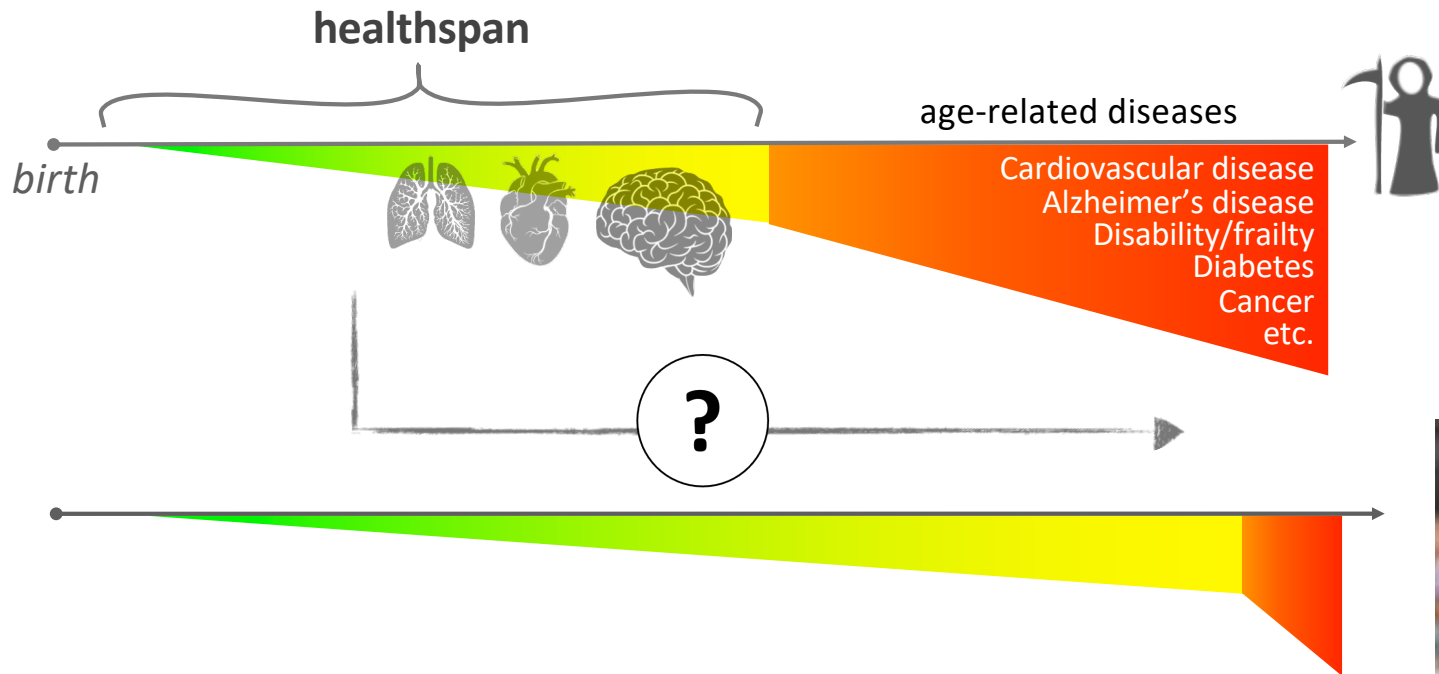
Columbine Health Systems
Center for Healthy Aging
COLORADO STATE UNIVERSITY



HEALTHSPAN BIOLOGY LAB



Key goal: increase healthspan

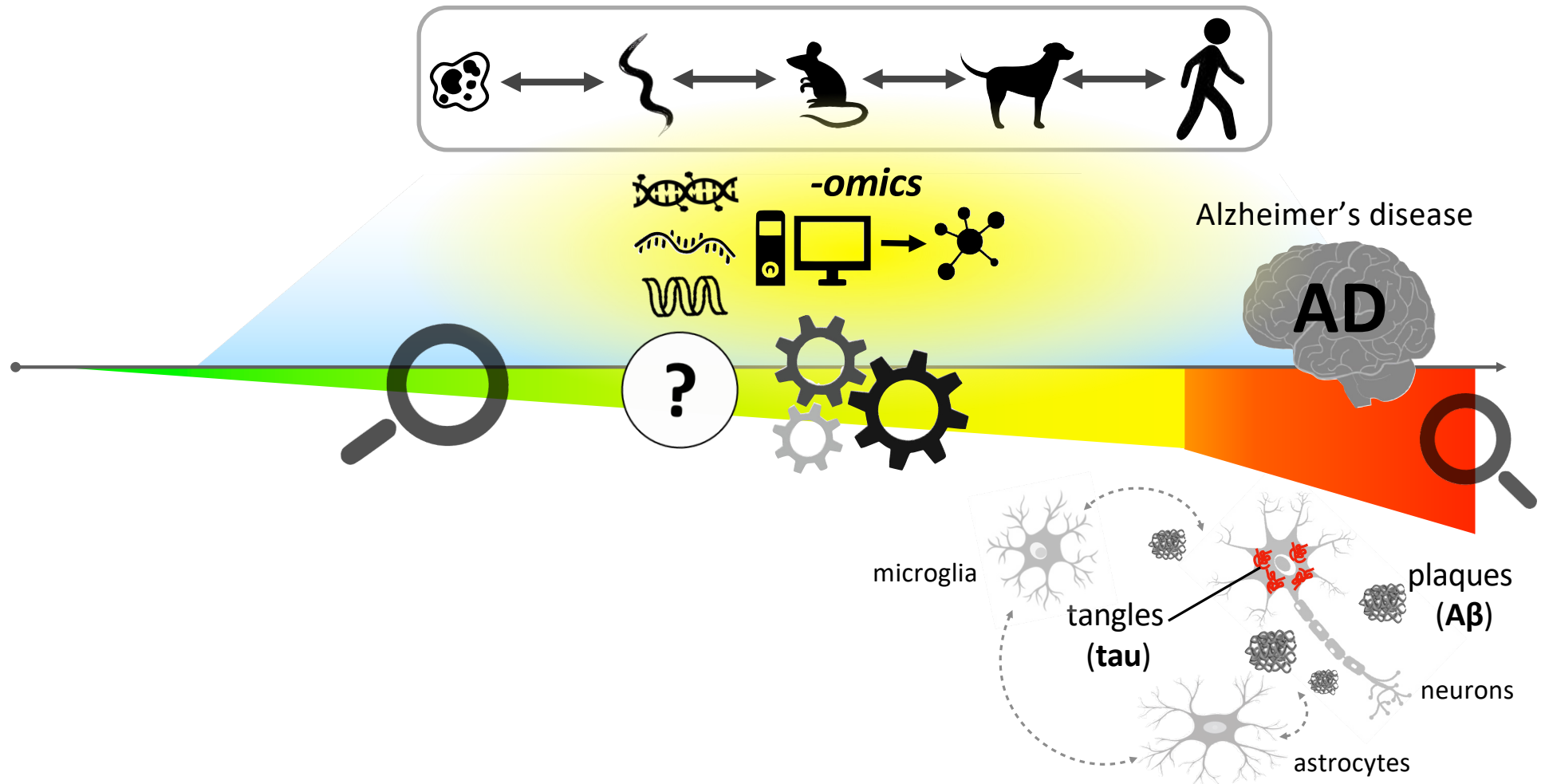


Johanna Quaas, age 94

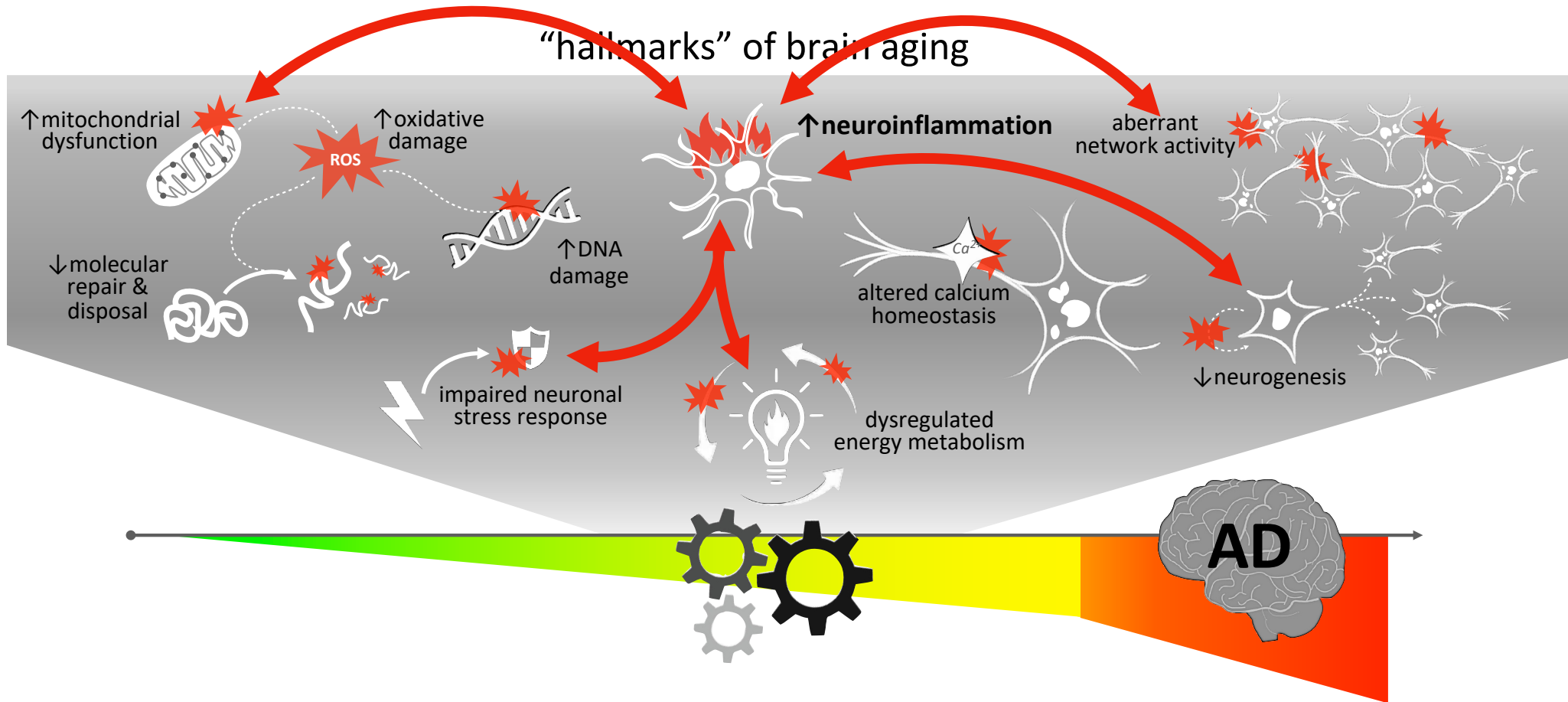


Seals, Justice, & LaRocca, *J Physiol* 2016

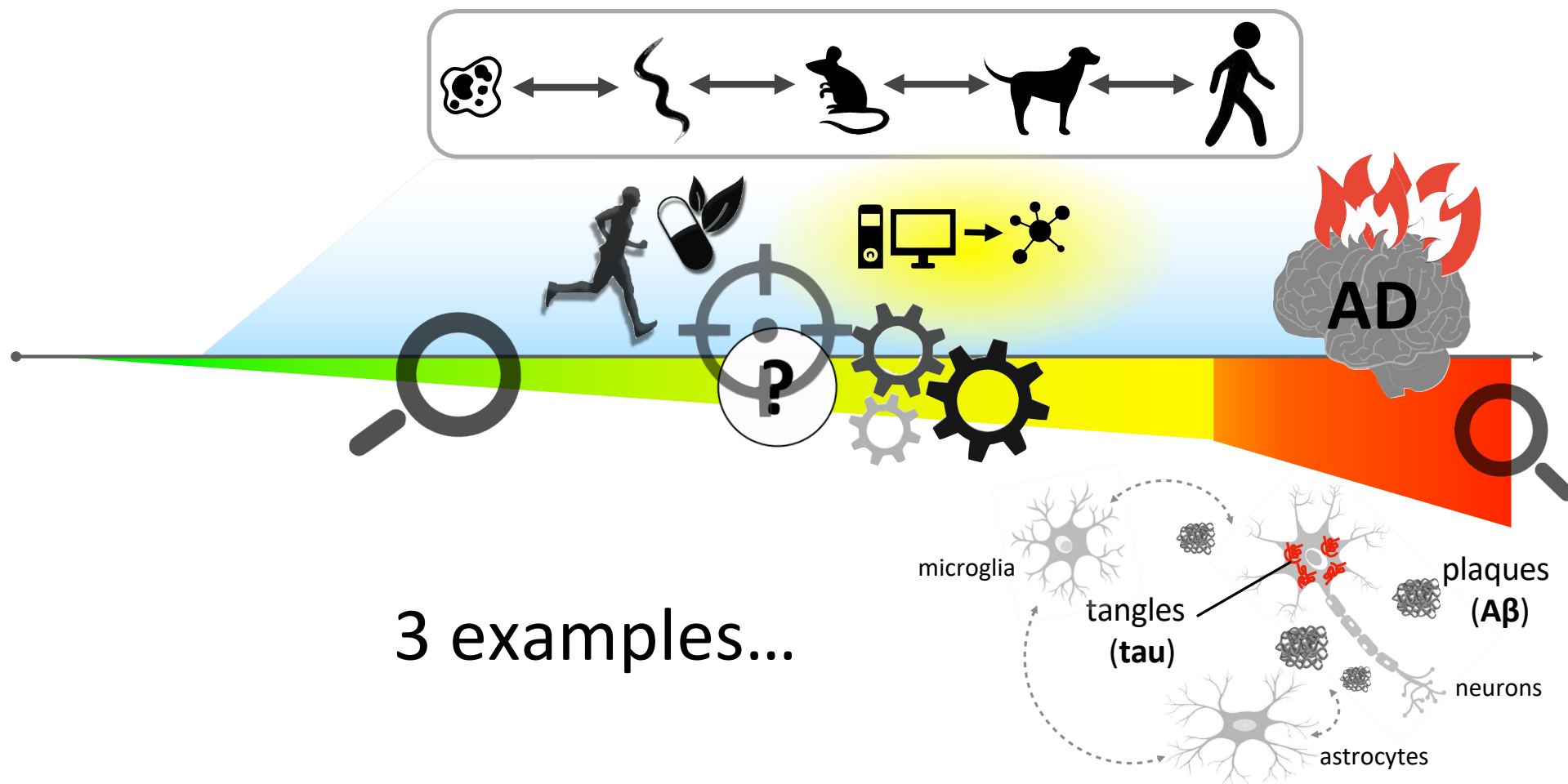
Our approach: mechanisms-focused translational research



Key target: **neuroinflammation**



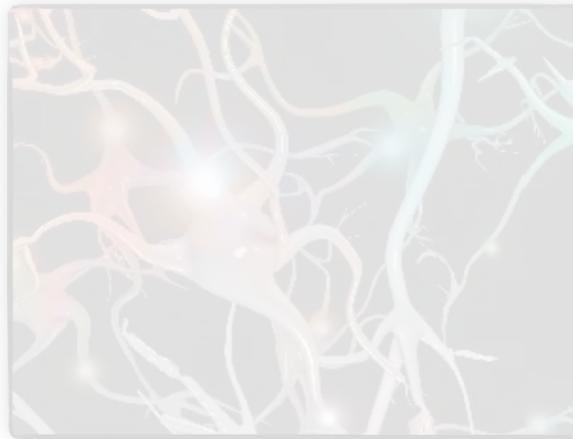
What puts the “age” in age-related neurodegeneration?



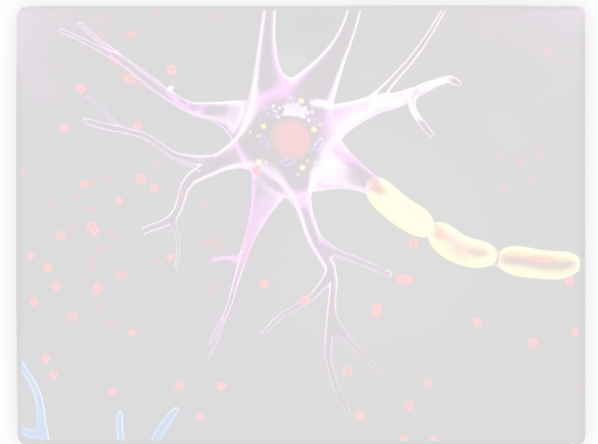
virus-like “self” RNAs,
brain aging and AD



inflammatory signaling,
brain aging and AD



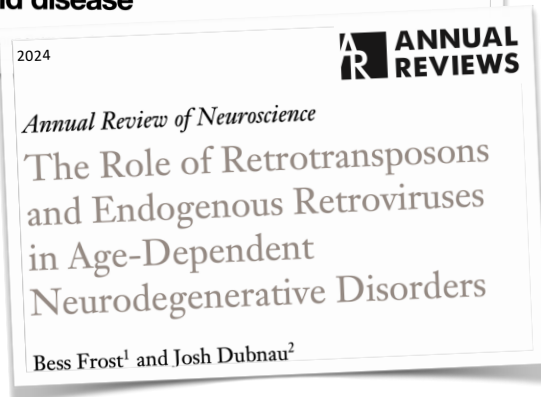
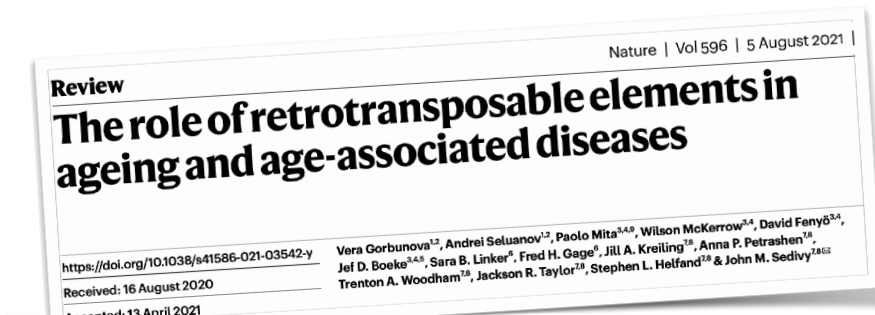
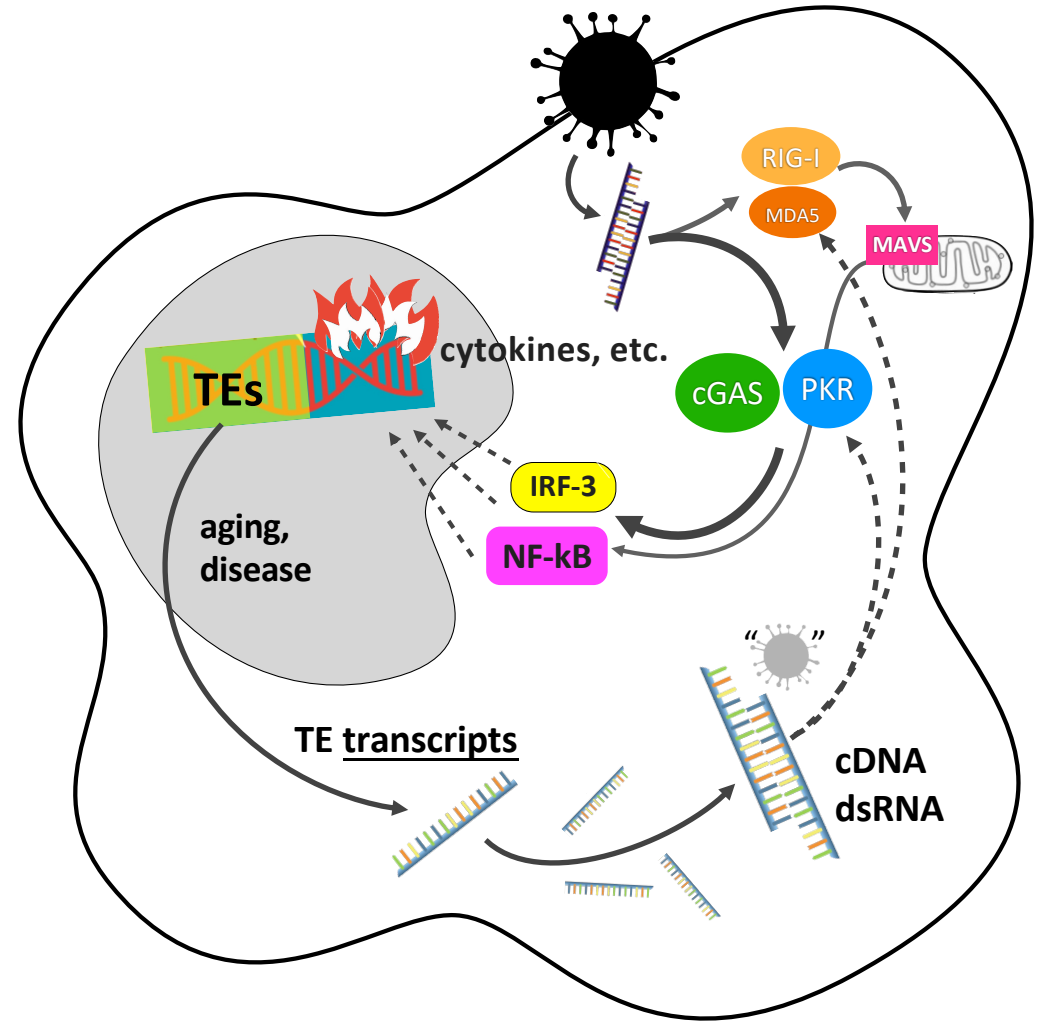
extracellular vesicles,
brain aging and AD



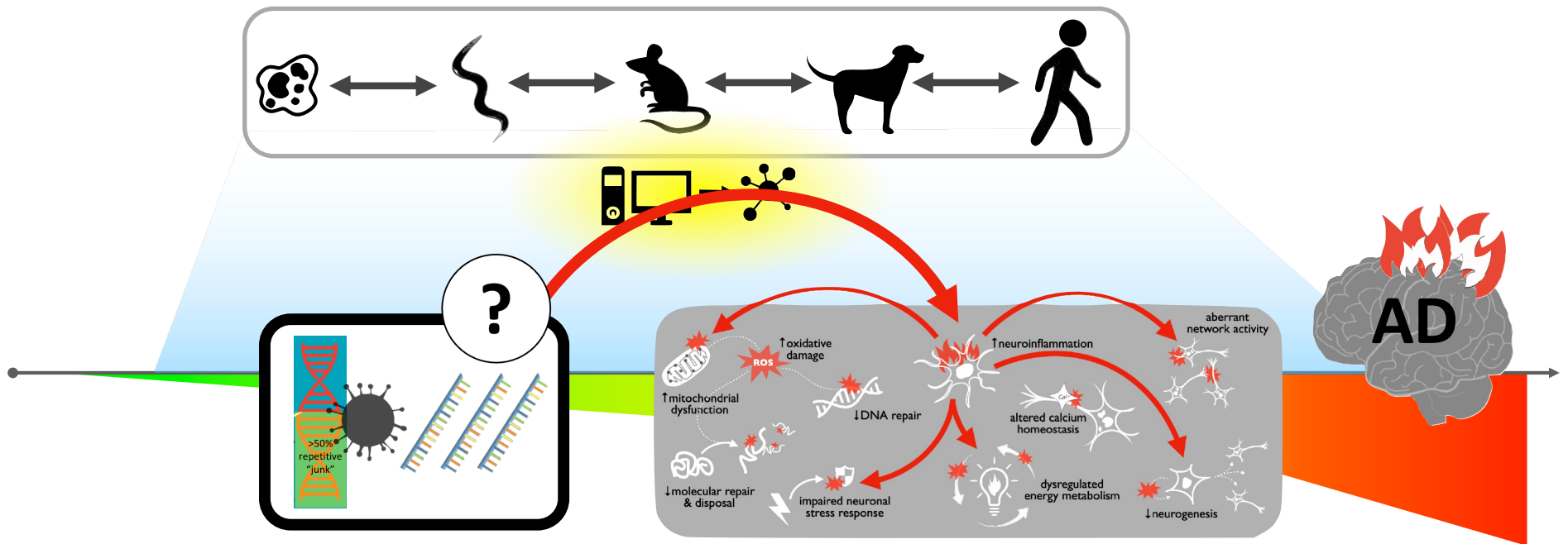
3 examples...
^
semi-related

Transposable elements (TEs)...

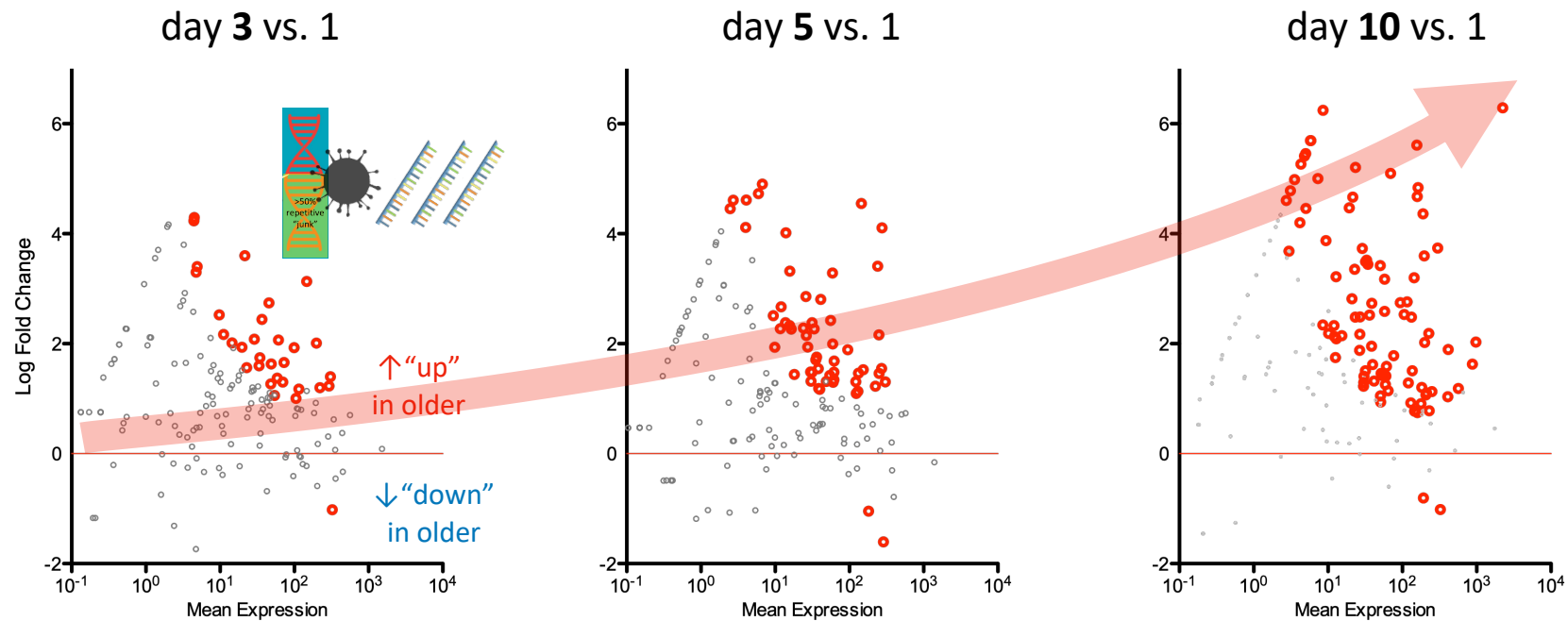
- Emerging roles in genome function
- Can form “virus-like” nucleic acids



Do TE transcripts play a role in brain aging?

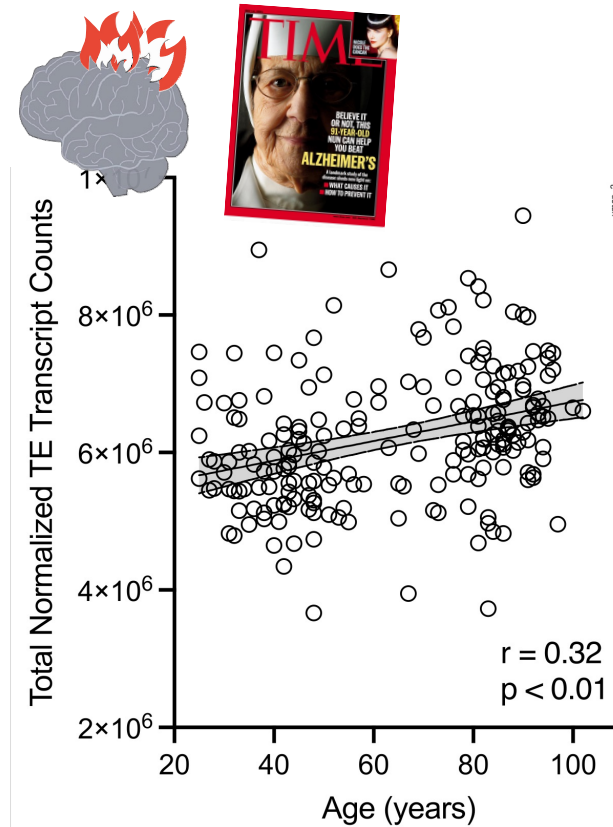
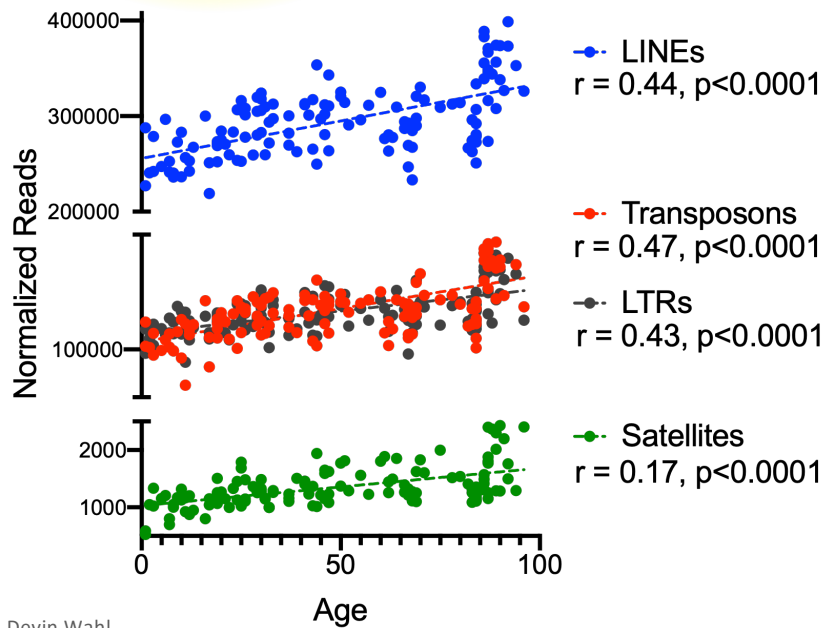
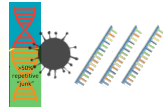
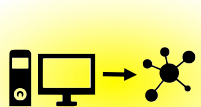


TE transcripts **increase** with aging.

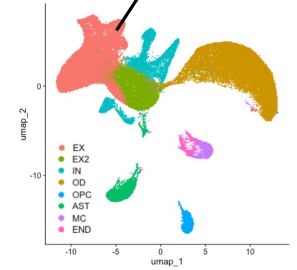


LaRocca et al., *Aging Cell* 2020
Wahl et al., *J Gerontol Biol Sci* 2021

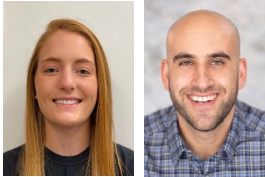
TE transcripts **increase** with aging...  including in the brain.



↑↑ in AD...
& in neurons!



Cali McEntee Devin Wahl



LaRocca et al., *Aging Cell* 2020
Wahl et al., *Aging Cell* 2023
McEntee et al., *Mol Neurobiol* 2025

Are TEs relevant to healthspan?

Chronological vs. biological age

45

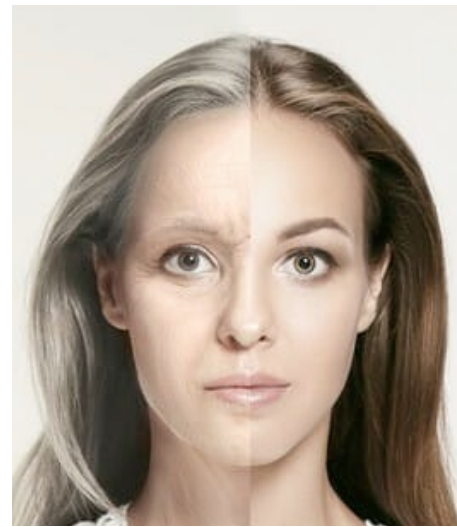
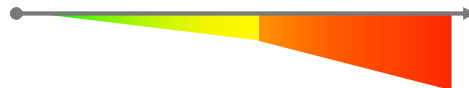
75

75

45



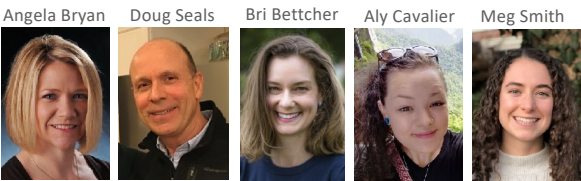
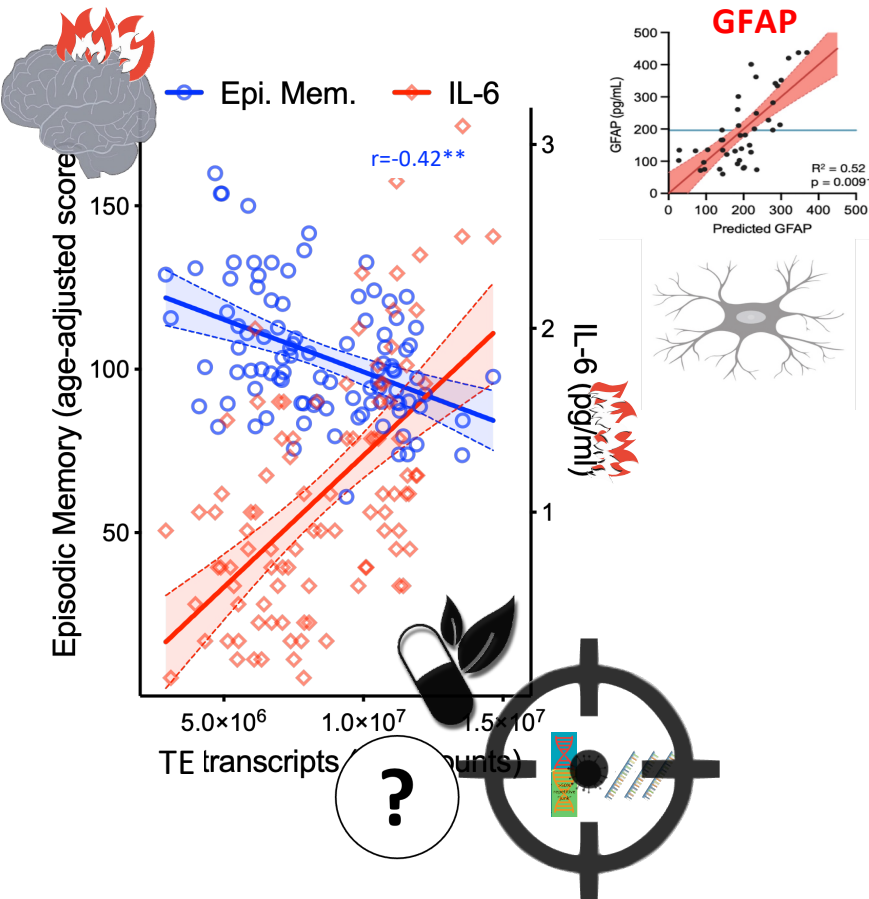
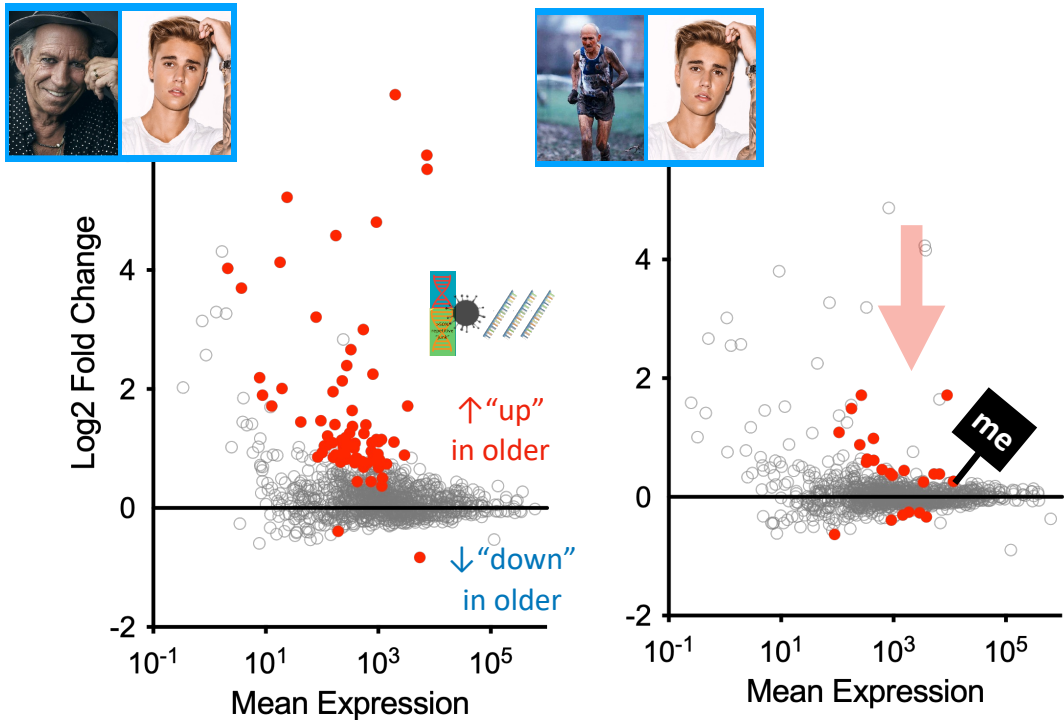
Smoker, poor sleep,
avid TikTok user, etc...



Vegetarian, sleeps well,
Swiftie, etc...

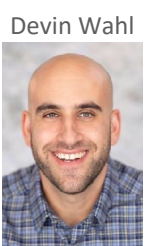
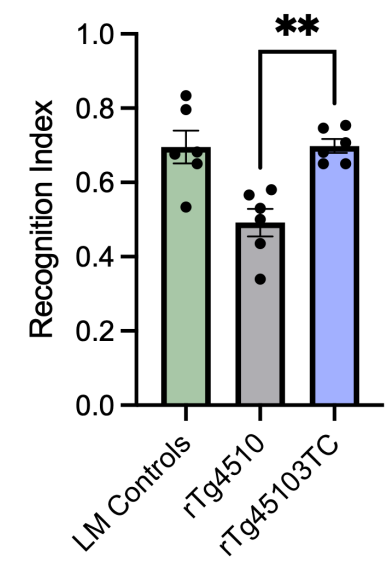
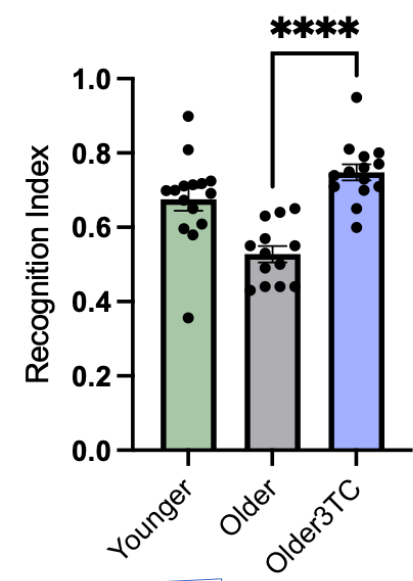
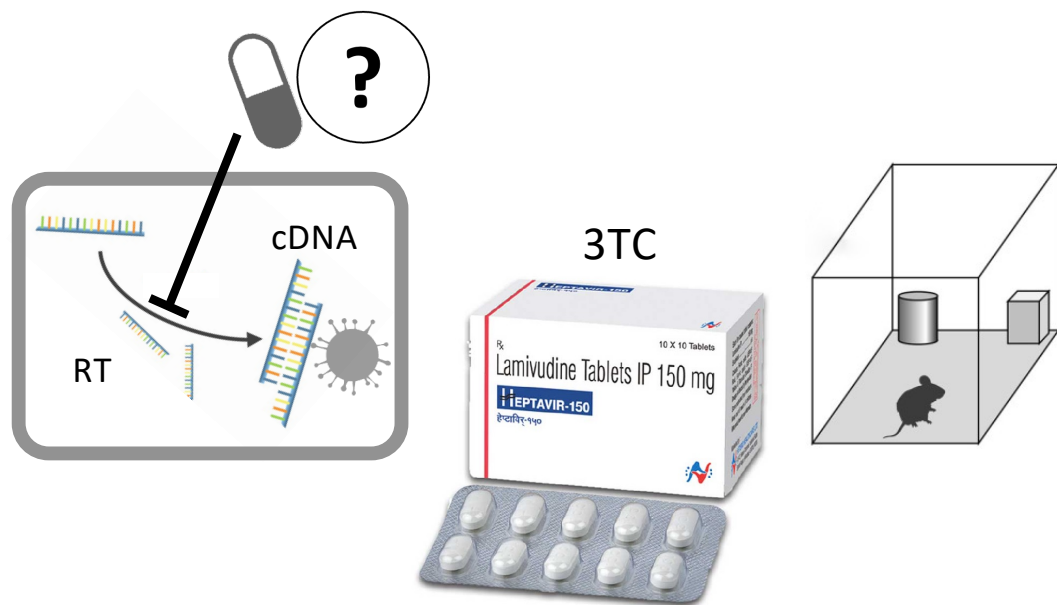


TE transcripts **decrease** with healthy aging interventions...
and are related to $\uparrow$ inflammation & $\downarrow$ memory.



Wahl et al., *J Gerontol Biol Sci* 2021
Smith et al., *Geroscience* 2024
Cavalier et al., *Geroscience* 2025

Inhibiting TE activity *in vivo* improves cognitive function.

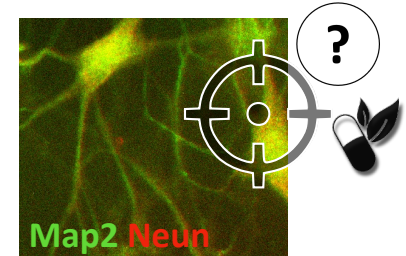
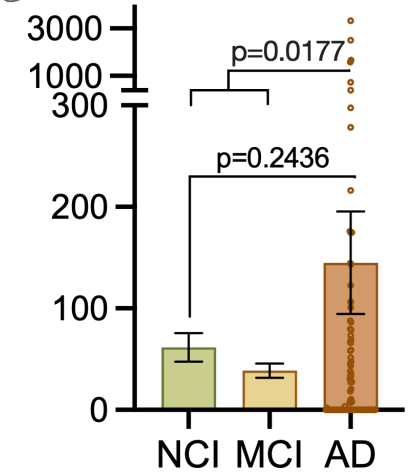
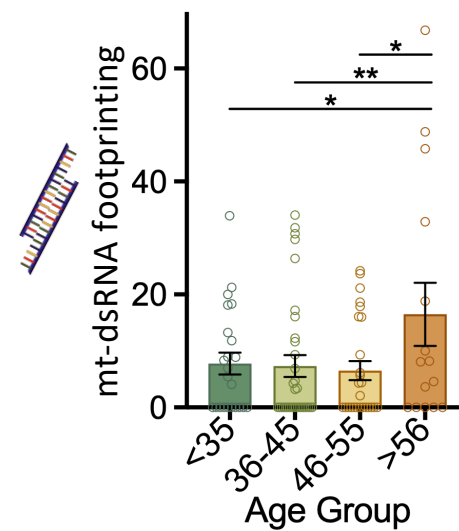
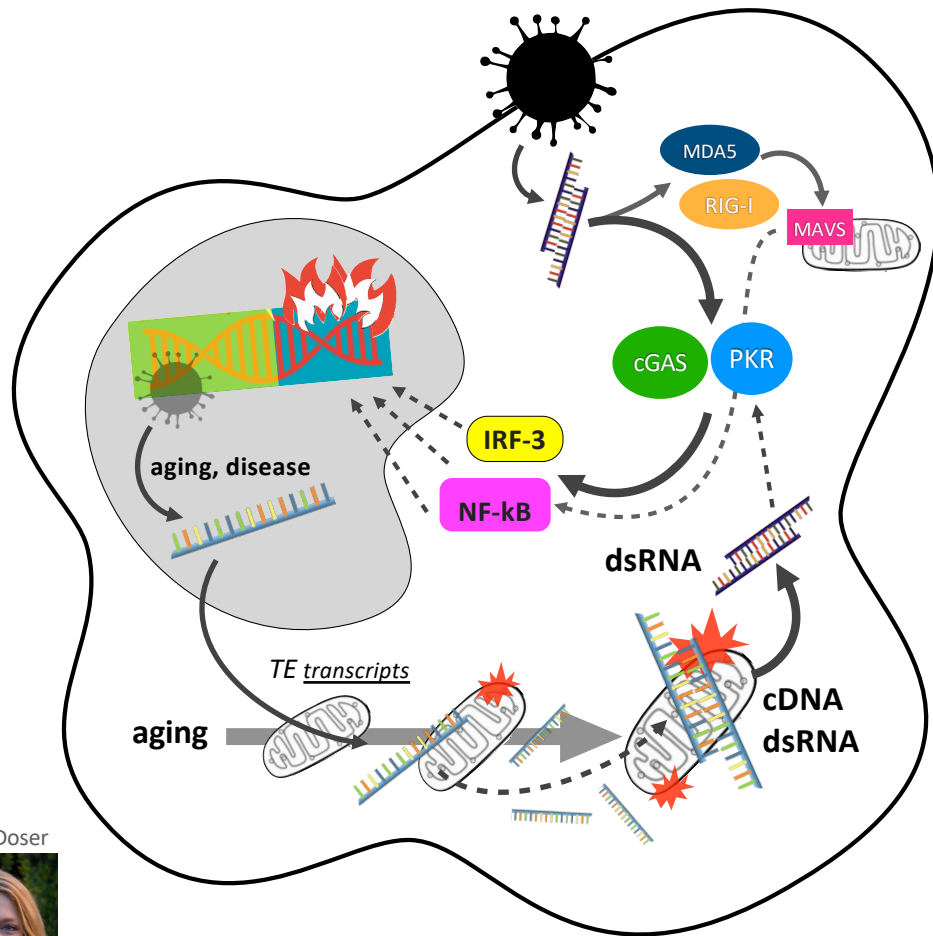


Devin Wahl



Wahl et al., *Aging Cell* 2023

Mitochondria (and other?) sources of cytosolic RNA...

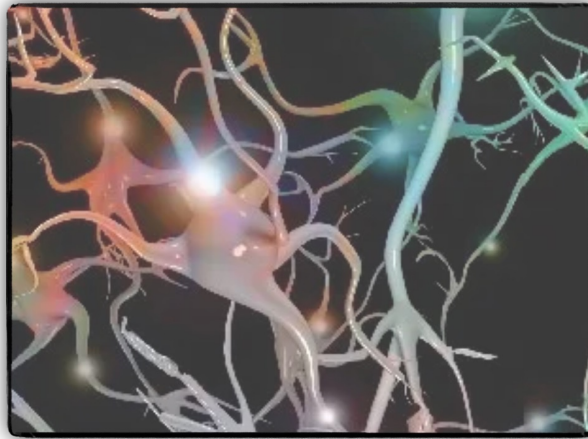


Doser et al., *Aging Cell* 2026

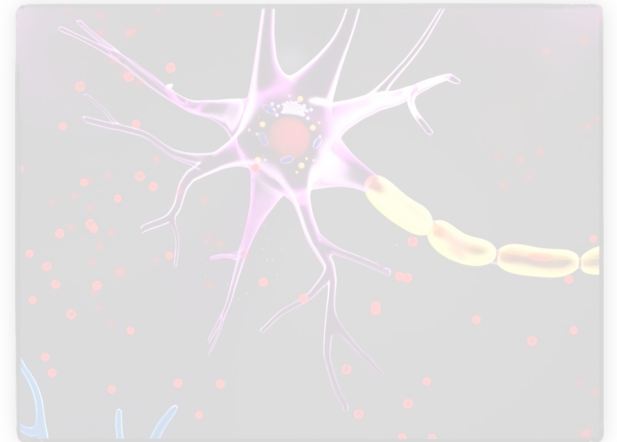
virus-like “self” RNAs,
brain aging and AD



inflammatory signaling,
brain aging and AD

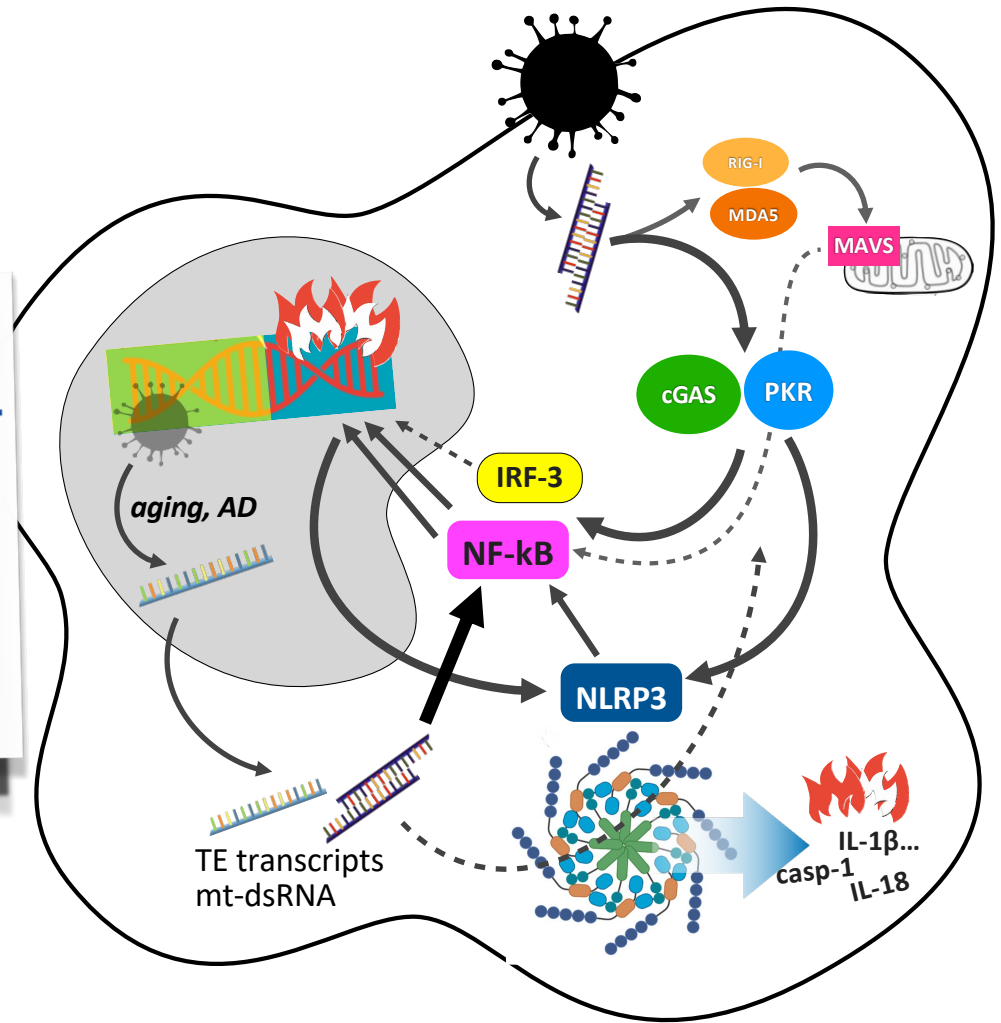


extracellular vesicles,
brain aging and AD



3 examples...
^
semi-related

NF- κ B, NLRP3, and inflammaging



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nature > nature immunology > review articles > article

Review Article | Published: 19 July 2017

Limiting inflammation—the negative regulation of NF- κ B and the NLRP3 inflammasome

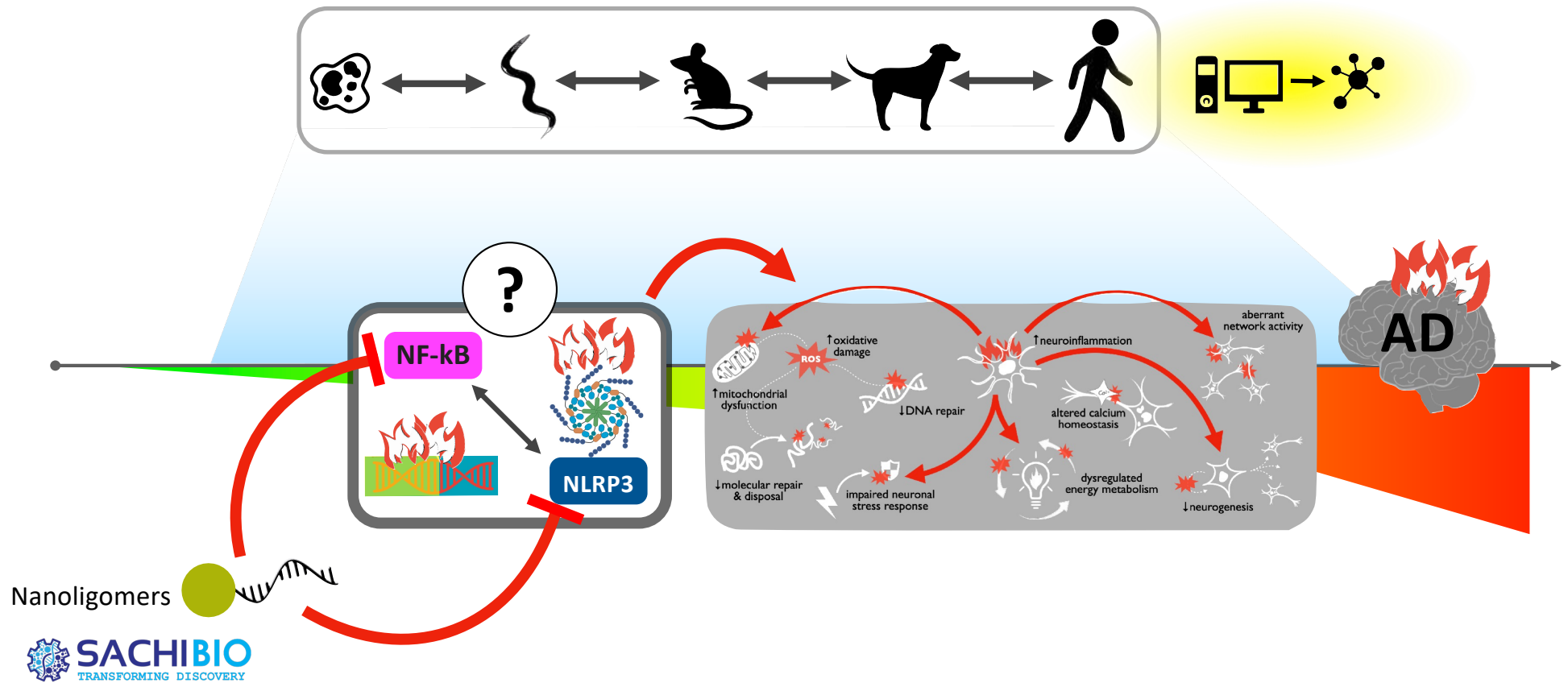
Inna S Afonina, Zhenyu Zhong, Michael Karin & Rudi Beyaert ✉

Nature Immunology 18, 861–869 (2017) | Cite this article

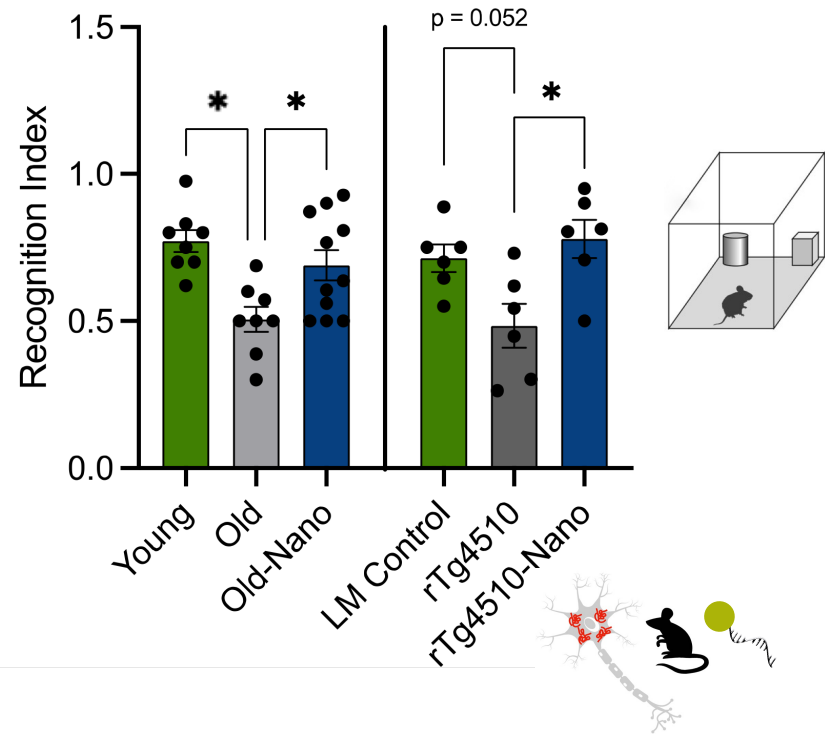
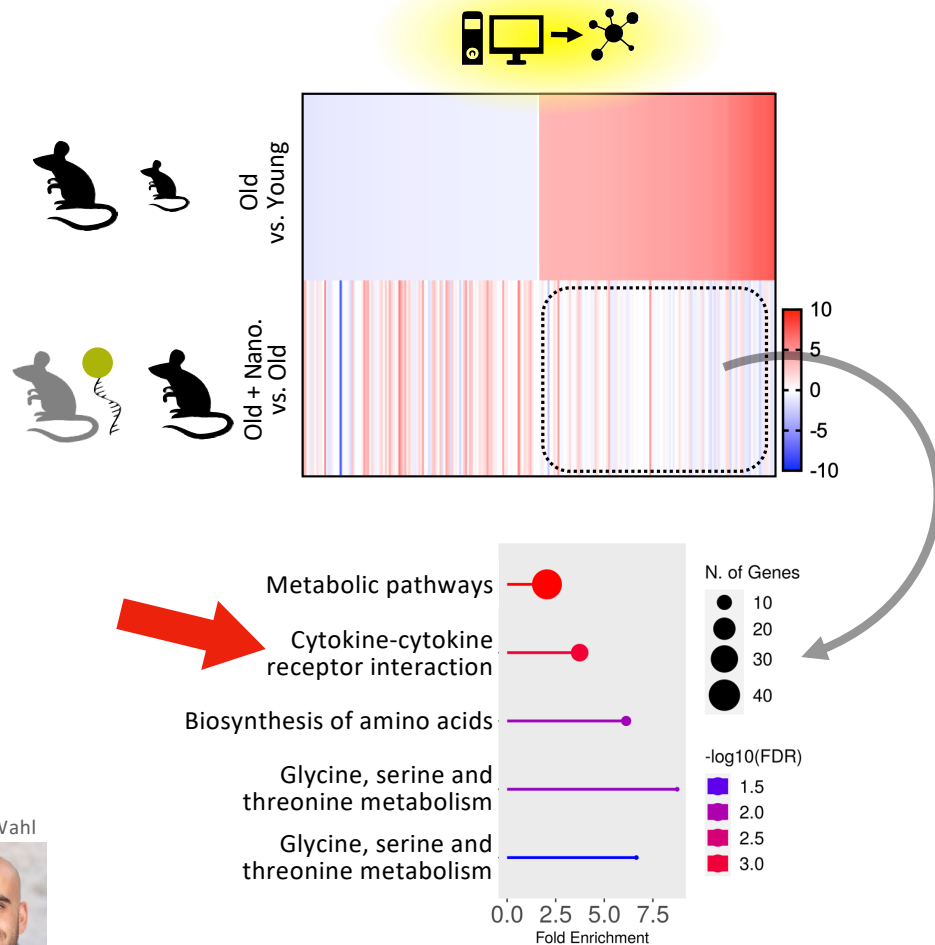
The NLRP3 inflammasome triggers sterile neuroinflammation and Alzheimer's disease

Mark T Milner¹, Madhavi Maddugoda¹, Jürgen Götz², Sabrina S Burgener^{1,3} ✉, Kate Schroder^{1,3} ✉

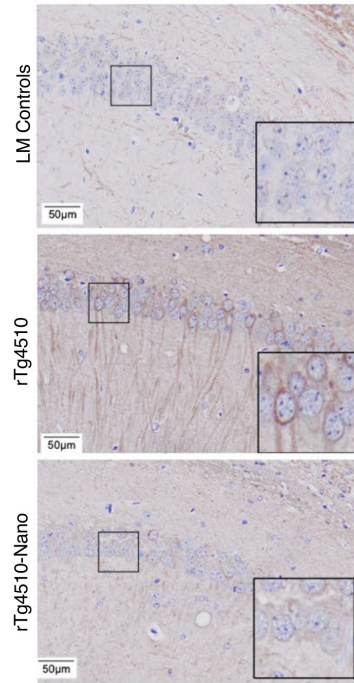
Does inhibiting NF- κ B/NLRP3 protect against brain aging/AD?



Inhibiting NF- κ B/NLRP3 reduces neuroinflammation, improves cognitive function...



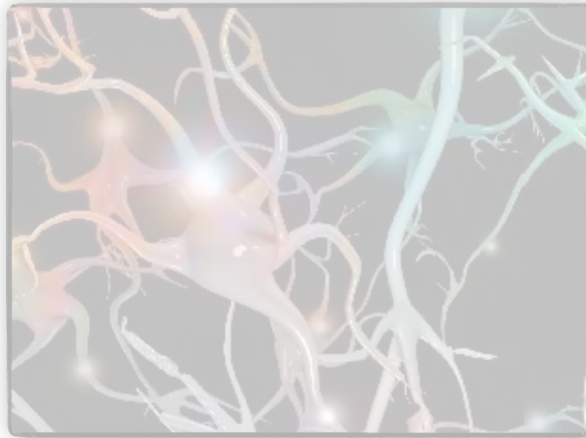
Devin Wahl



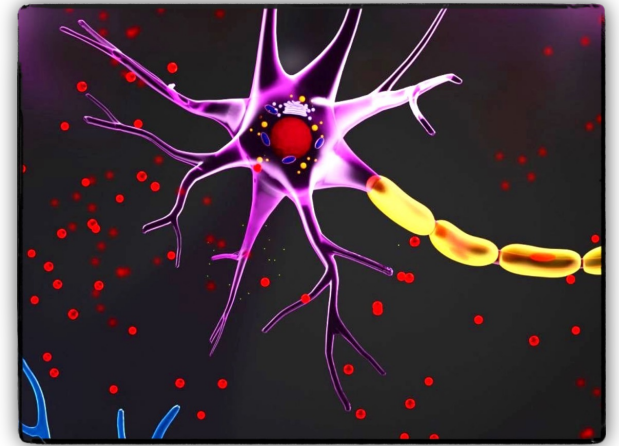
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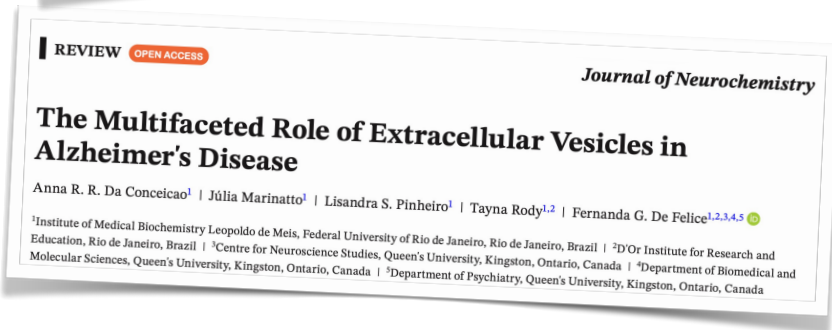
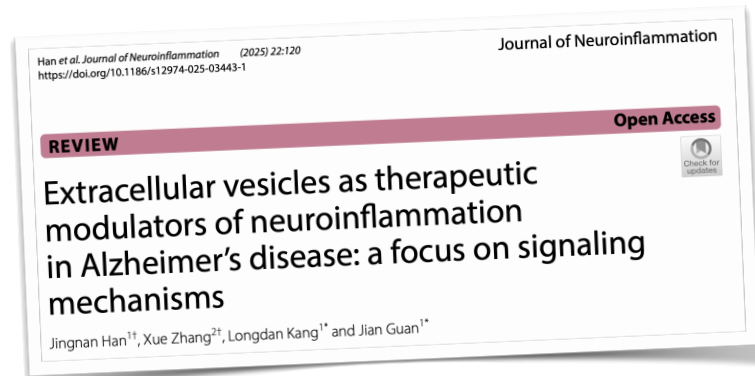


extracellular vesicles,
brain aging and AD

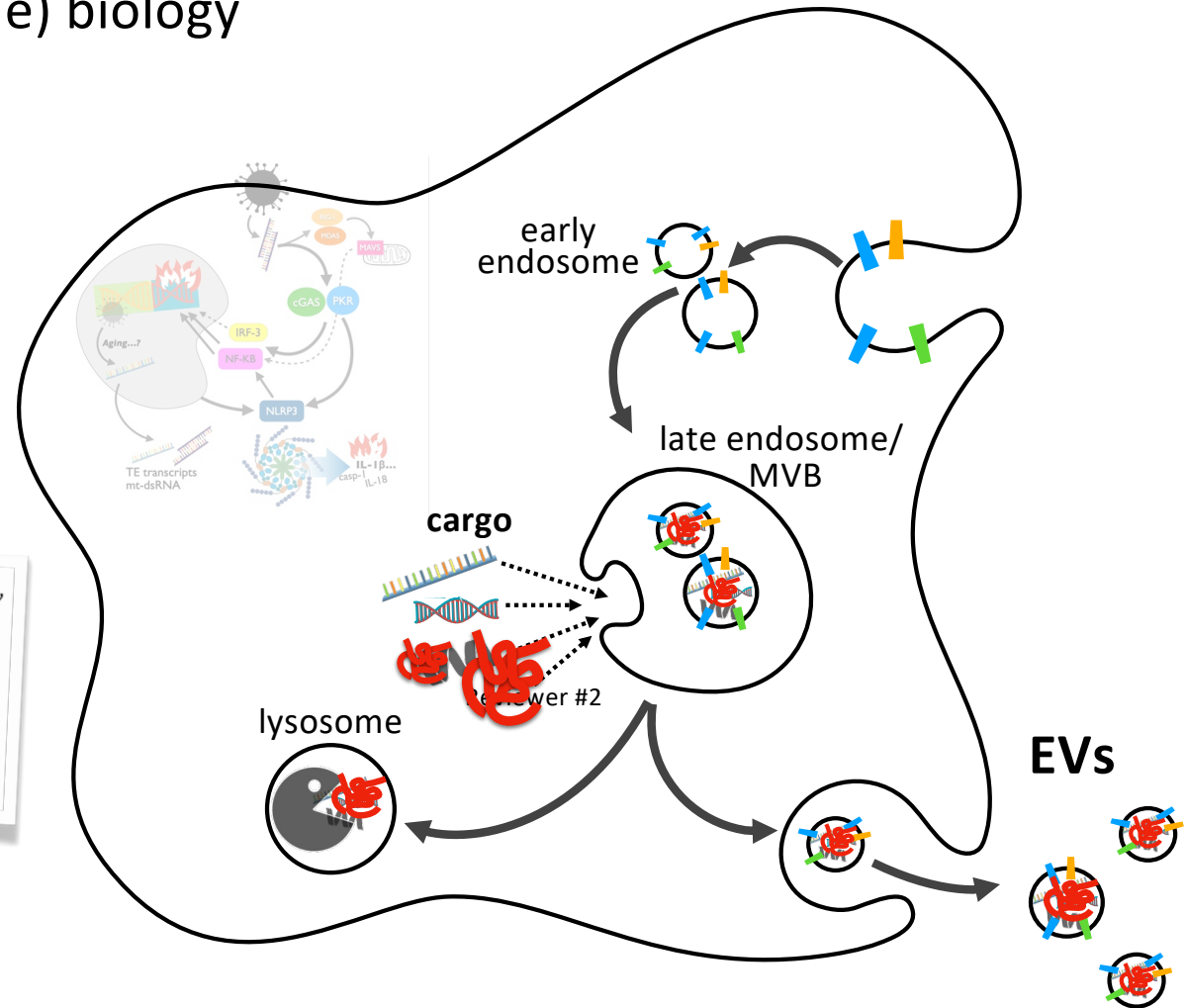


3 examples...
^
semi-related

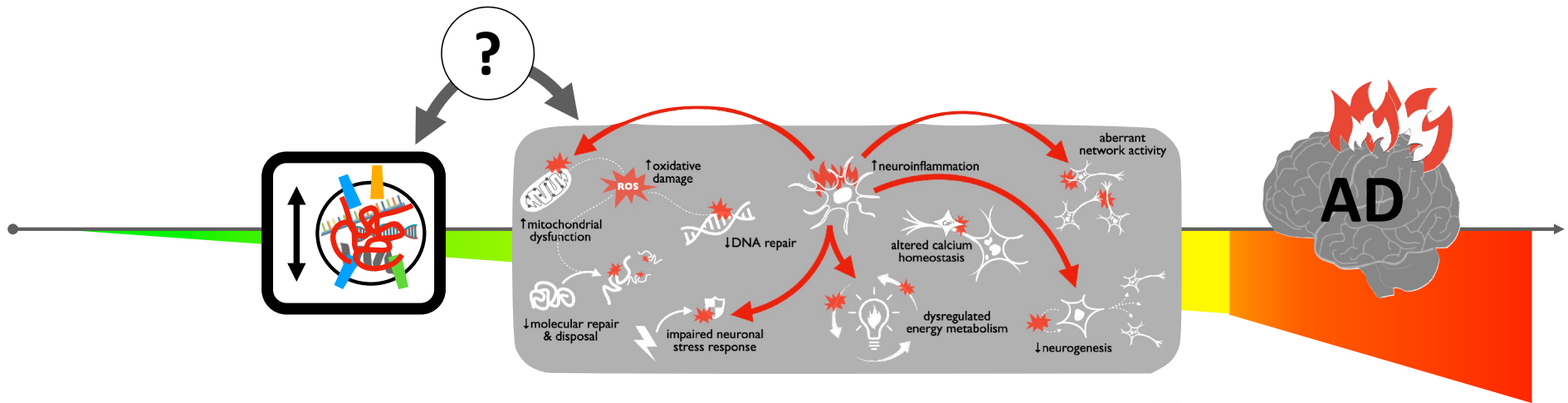
Extracellular vesicle (EV, exosome) biology



Dan Lark



Do changes in EV biology contribute to brain aging/AD?



[nature](#) > [genes & immunity](#) > [review articles](#) > article

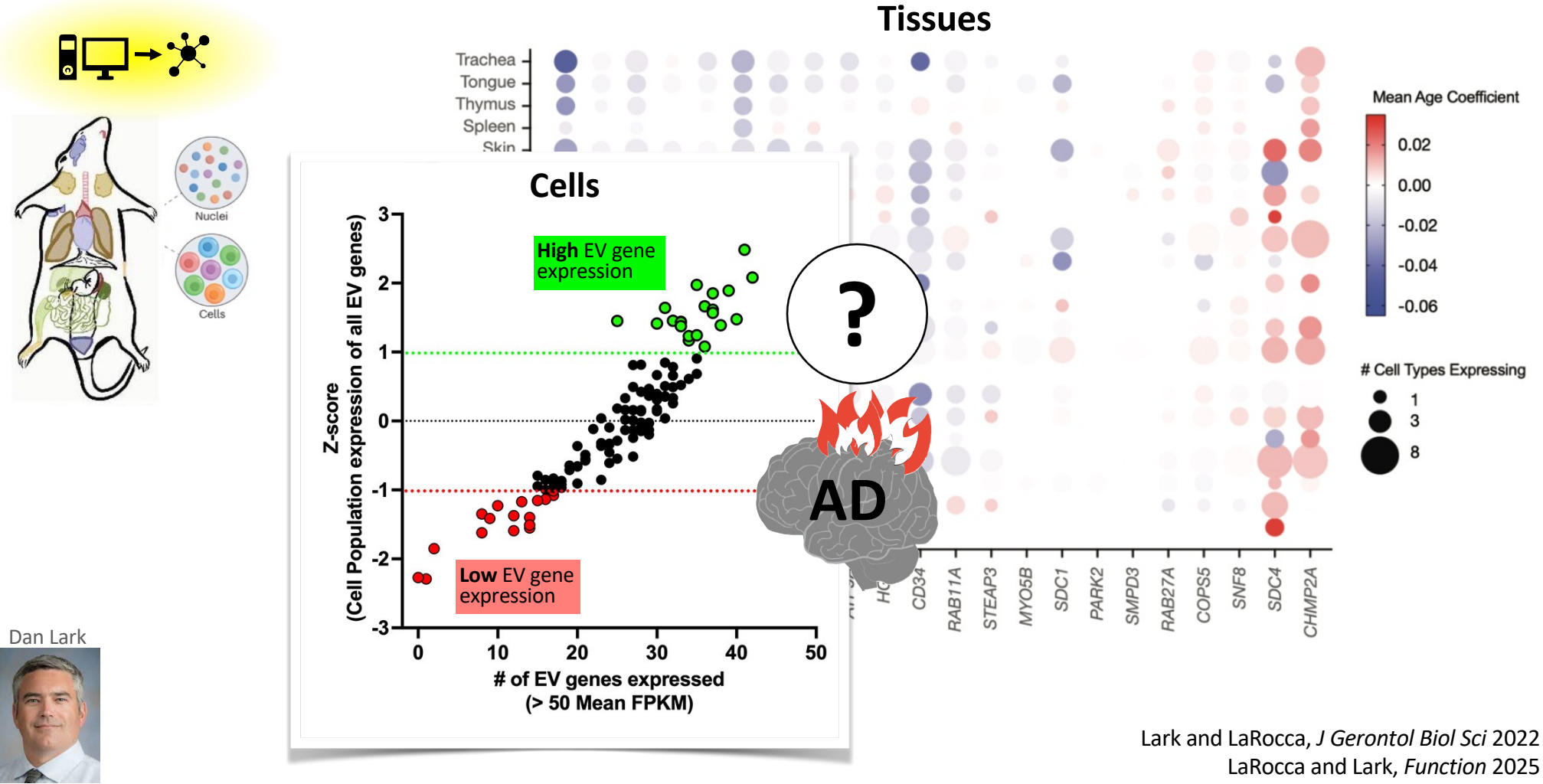
Review Article | Published: 03 October 2020

Tau at the interface between neurodegeneration and neuroinflammation

[Alessandro Didonna](#)

[Genes & Immunity](#) 21, 288–300 (2020) | [Cite this article](#)

Does cell type-specific EV gene expression matter in (brain) aging?

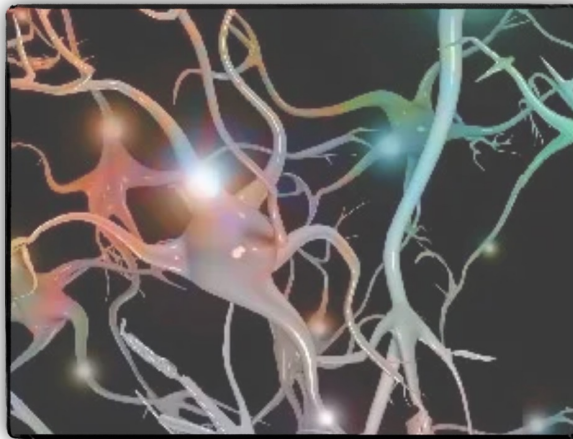


Lark and LaRocca, *J Gerontol Biol Sci* 2022
LaRocca and Lark, *Function* 2025

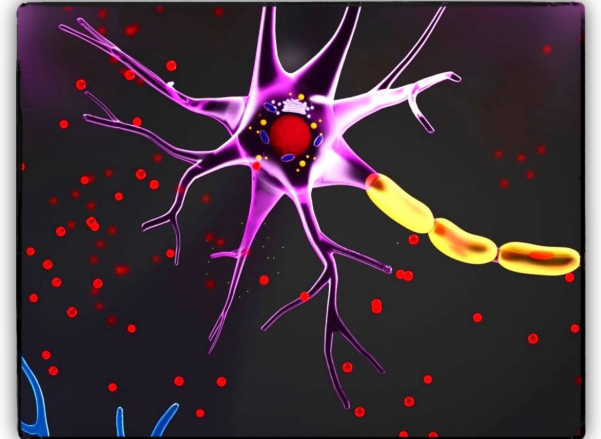
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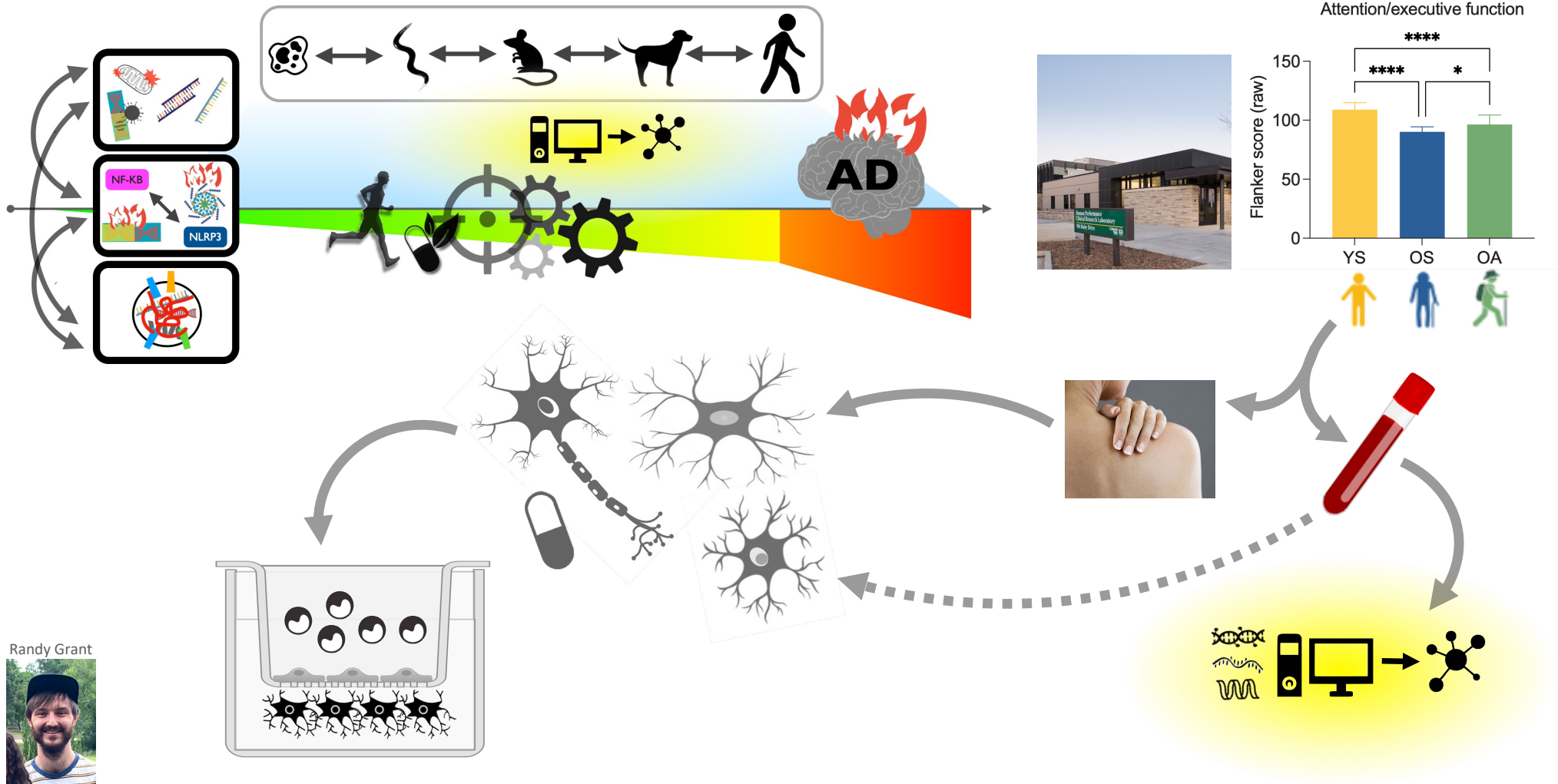


extracellular vesicles,
brain aging and AD



3 examples...
^
semi-related

Future lab directions...



Randy Grant



HEALTHSPAN BIOLOGY LAB



Current lab members

Rachel Doser
Randy Grant
Lauren Park
Alexa Pacheco
Dakota Peart
Faith Miles
Seth Nuncio-Cagle
Alex Grief
Lal Durmaz
Christina Cheng
Greta Runge

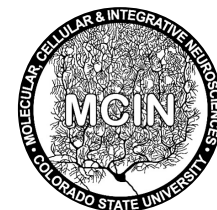
Alums

Devin Wahl	Hannah Martin
Shelby Osburn	Sam Burke
Cali McEntee	Toby Emge
Aly Cavalier	Ethan Cantrell
Meg Smith	Acacia Sack
Nate Bachman	Liz Talalai
Amanda Boyd	Gabbie McWilliams

Many thanks!



HEALTH &
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SCIENCE




Columbine Health Systems
Center for Healthy Aging
COLORADO STATE UNIVERSITY



National Institute
on Aging

Collaborators

Chris Link (CU Boulder)
Doug Seals (CU Boulder)
Angela Bryan (CU Boulder)
Brienne Bettcher (CU Anschutz)
Zach Clayton (CU Anschutz)
Dan Lark (CSU)
Julie Moreno (CSU)
Karyn Hamilton (CSU)
Stephanie McGrath (CSU)
Prashant Nagpal (Sachi Bioworks)