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Dec 16, 2024

NATIONAL ACADEMIES Sciences Engineering Medicine

BOARD ON HEALTH SCIENCES POLICY

Committee on Research Priorities for Preventing and Treating Alzheimer's Disease and Related Dementias

Meeting #3 and Public Workshop
January 16 and 17, 2023

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Panel IV

Molecular and Cellular Mechanisms of Alzheimer's disease (and related dementias)

Session Objectives

- Explore research priorities related to mechanistic hypotheses for AD/ADRD, including those that are shared across multiple forms of dementia and have great potential to illuminate the mechanistic underpinnings of brain health and disease and broaden approaches to AD/ADRD prevention and treatment.
- Discuss promising advances and remaining gaps in tools, technologies, and analytical methods needed to advance the identification of effective intervention strategies for AD/ADRD.

Making a case for investment in combining aging and AD/ADRD research

Perspective https://doi.org/10.1038/s43587-023-00402-4

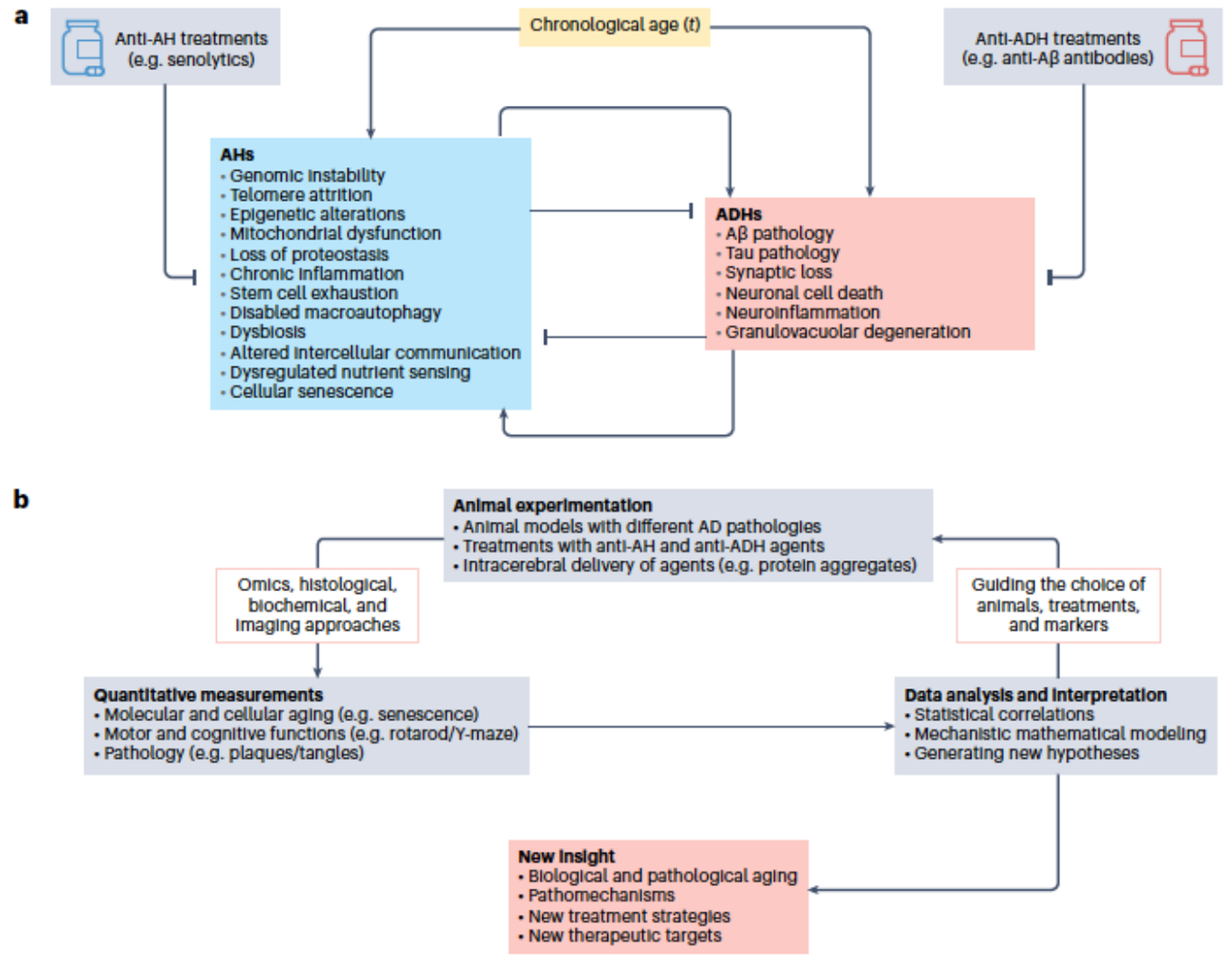


Fig. 3 | A framework to understand the interactions of the hallmarks of aging and Alzheimer's disease as a function of chronological age. a, Chronological age can independently accelerate the development of aging hallmarks (AHs) and Alzheimer's disease (AD) hallmarks (ADHs). Moreover, at any given age, these hallmarks could influence each other. In such a scenario, treatments that target an AH, such as senolytics targeting senescent cells, could affect ADHs, and those that target an ADH, such as anti-amyloid-β (Aβ) antibodies, could affect AHs. Arrows and T bars indicate activation and repression of hallmark expression, respectively. **b**, An iterative approach to investigate the inter-relationship between AHs and ADHs in animal models with chronological age.

(1) Hallmarks of health:
Integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, and repair and regeneration.

Lopez-Otin & Kroemer,
Cell 2021

(2) Hallmarks of ageing (AHs)

Lopez-Otin et al.,
Cell 2022

(3) Hallmarks of AD (ADHs)

Padmanabhan & Götz
Nature Aging 2023

Implementation of aging and health hallmarks to provide a framework for analyzing how AD-associated pathological aging manifests in different animal models, as well as in humans.

Making a case for studying brain/cognitive reserve and responders/non-responders

A few discussion points:

(1) Preclinical and clinical studies suggest dissociation between pathology and cognitive read-outs. Why is that?

New Results

Follow this preprint

Scanning ultrasound-mediated memory and functional improvements do not require amyloid-β reduction

Gerhard Leinenga, Xuan Vinh To, Liviu-Gabriel Bodea, Jumana Yousef, Gina Richter-Stretton, Tishila Palliyaguru, Antony Chicoteau, Laura Dagley, Fatima Nasrallah, Jürgen Götz

doi: https://doi.org/10.1101/2023.06.16.545394

Leinenga & Götz,
Science Transl Med 2015

Leinenga et al.,
bioRxiv 2023

(2) Brain reserve/cognitive reserve mechanisms in AD/ADRD underexplored.

Stern et al.,
Neurobiol Aging 2019

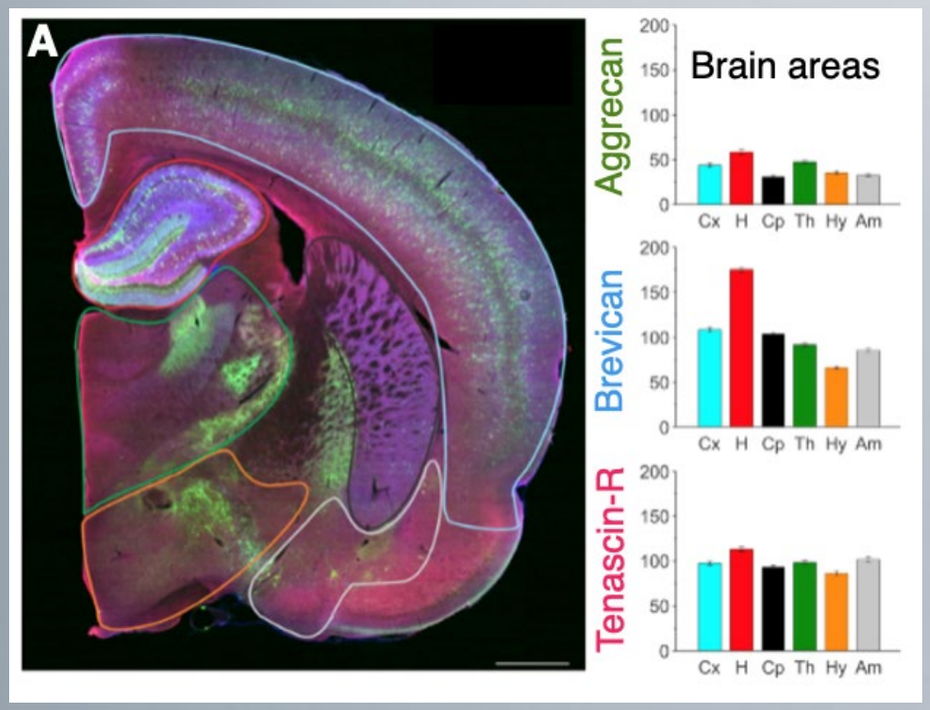
(3) Studies of responders/non-responders:

(i) Transgenic mouse colonies often include a few mice with no or little pathology
(ii) Transgenic colonies drift leading to reduced pathology. Can this be utilised?
(iii) Therapeutic interventions in mice: responders and non-responders
(iv) Therapeutic interventions in human study participants: responders and non-responders

➔ Coordinated activities to understand this segregation and use it to understand AD and ADRD mechanisms and improve therapies.

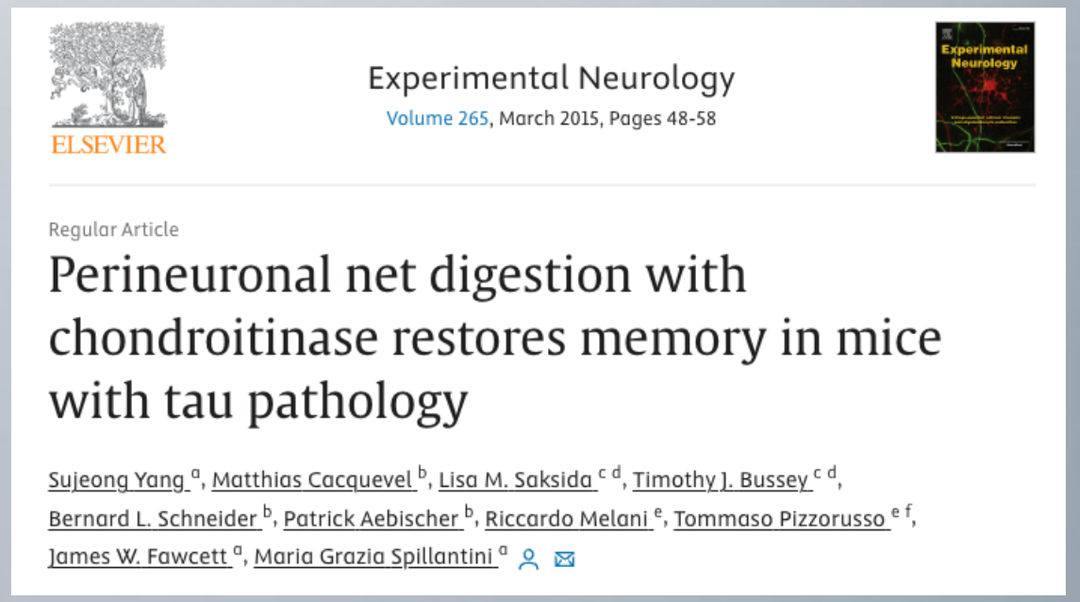
Making a case for studying the extracellular matrix and PNNs

ECM is hard to study and highly heterogeneous



Dauth et al.,
J Comp Neurol 2016

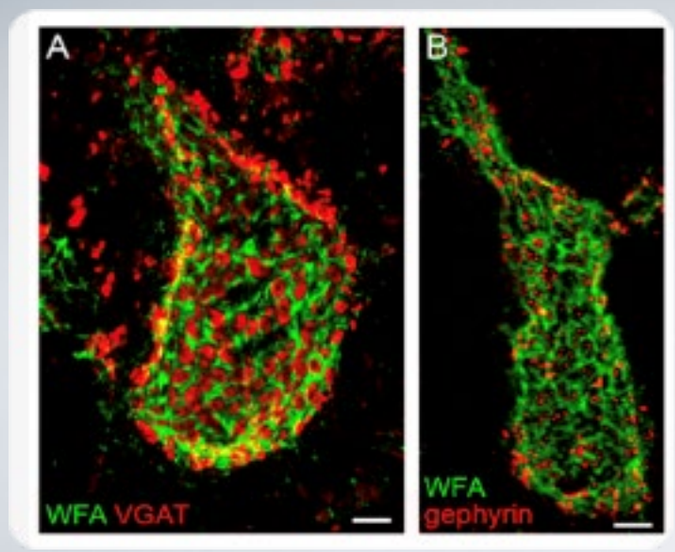
ECM in AD/ADRD is under-explored, but its digestion restores memory



Several barriers for drug-delivery: BBB, ECM (pore size of 38-64 nm) and plasma membrane:

e.g. Thorne & Nicholson,
PNAS 2006

Perineuronal nets



Carulli & Verhaagen,
Int J Mol Sci 2021

<u>SUMMARY:</u> Expand AD/ADRD research:

- ❑ **with aging hallmarks providing a framework for analzying AD pathology**
- ❑ **by investigating in mechanisms of brain/ cognitive reserve and responders/non-responders**
- ❑ **adressing pathology of ECM/PNNs and what the role is of the ECM for therapies.**