Biological Aging as a Mechanistic Link Between Brain and Body:

Aging of the Immune System

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The Intersection of MCC and AD/ADRD
March 6-7, 2025; 9:50-10:05 AM

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Reconciling Conventional Wisdom with Clinical Reality

Conventional Wisdom

Alzheimer's Disease:

- A brain disease involving a unique and distinct biological process that results in plaques (Amyloid) and tangles (Tau)
- Disease-modifying therapies designed to target a single target (Amyloid or Tau)

As Regards Other Diseases:

- Each disease originates in and mostly affects one single tissue via a unique and distinct biological process
- Disease-modifying therapies designed to target that specific disease process

Clinical Reality

Nearly everything about aging is multifactorial

- Common chronic diseases of aging (AD etc)
- Geriatric syndromes (falls, delirium etc)
- Other causes of functional decline

Later in life such conditions almost never occur in isolation from other diseases and geriatric syndromes (MCC)

- Numbers of MCCs increase with aging
- Clusters of conditions contributing to MCCs are highly heterogeneous

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Has our devotion to Occam's Razor misled us?

- Problem-solving principle that recommends searching for explanations constructed with smallest possible set of elements
- William of Ockham, a Franciscan theologian and philosopher
- How could multifactorial conditions for which everything is highly heterogeneous be "cured" using any single therapy?

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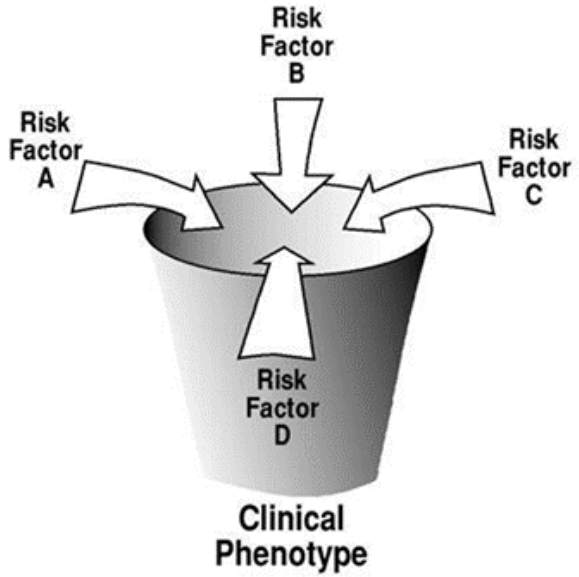

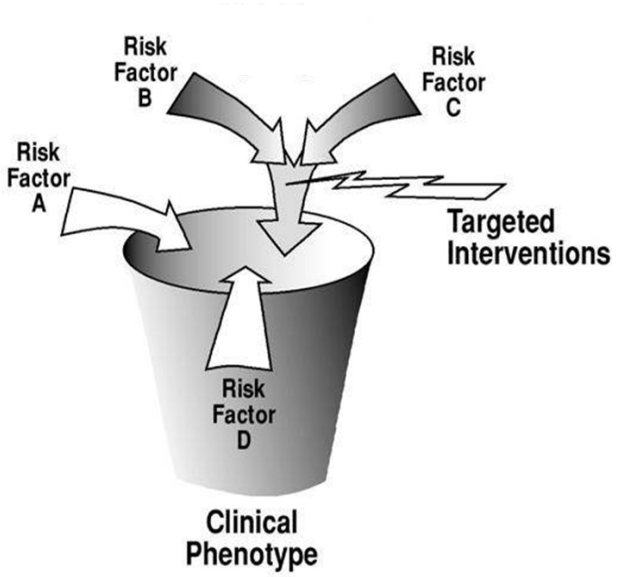

Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept
Inouye SK, Studenski S, Tinetti ME, Kuchel GA. *JAGS*. 2007

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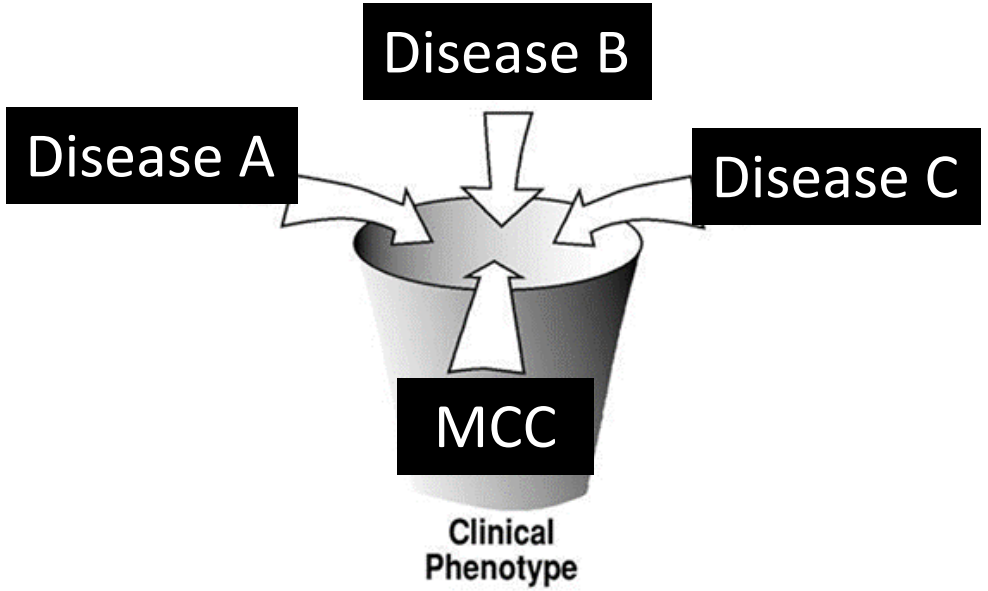

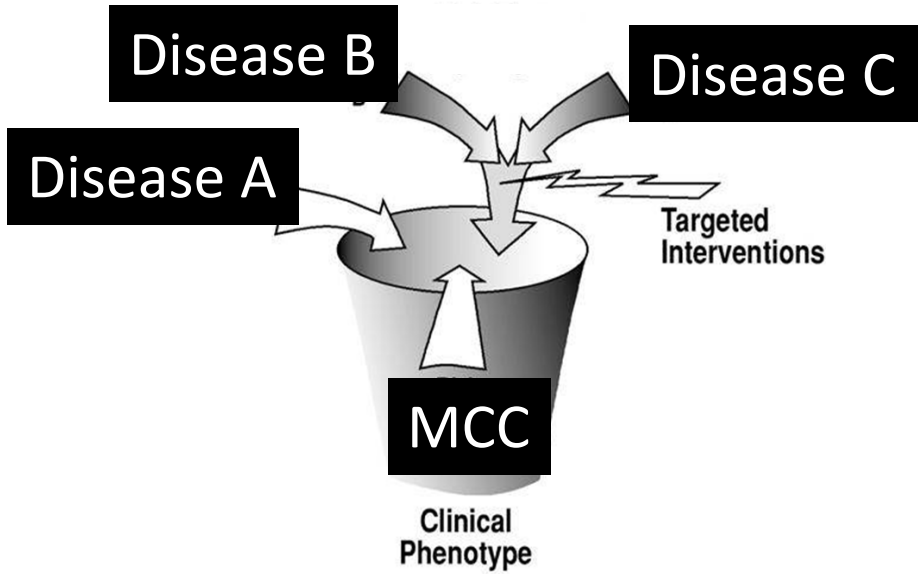

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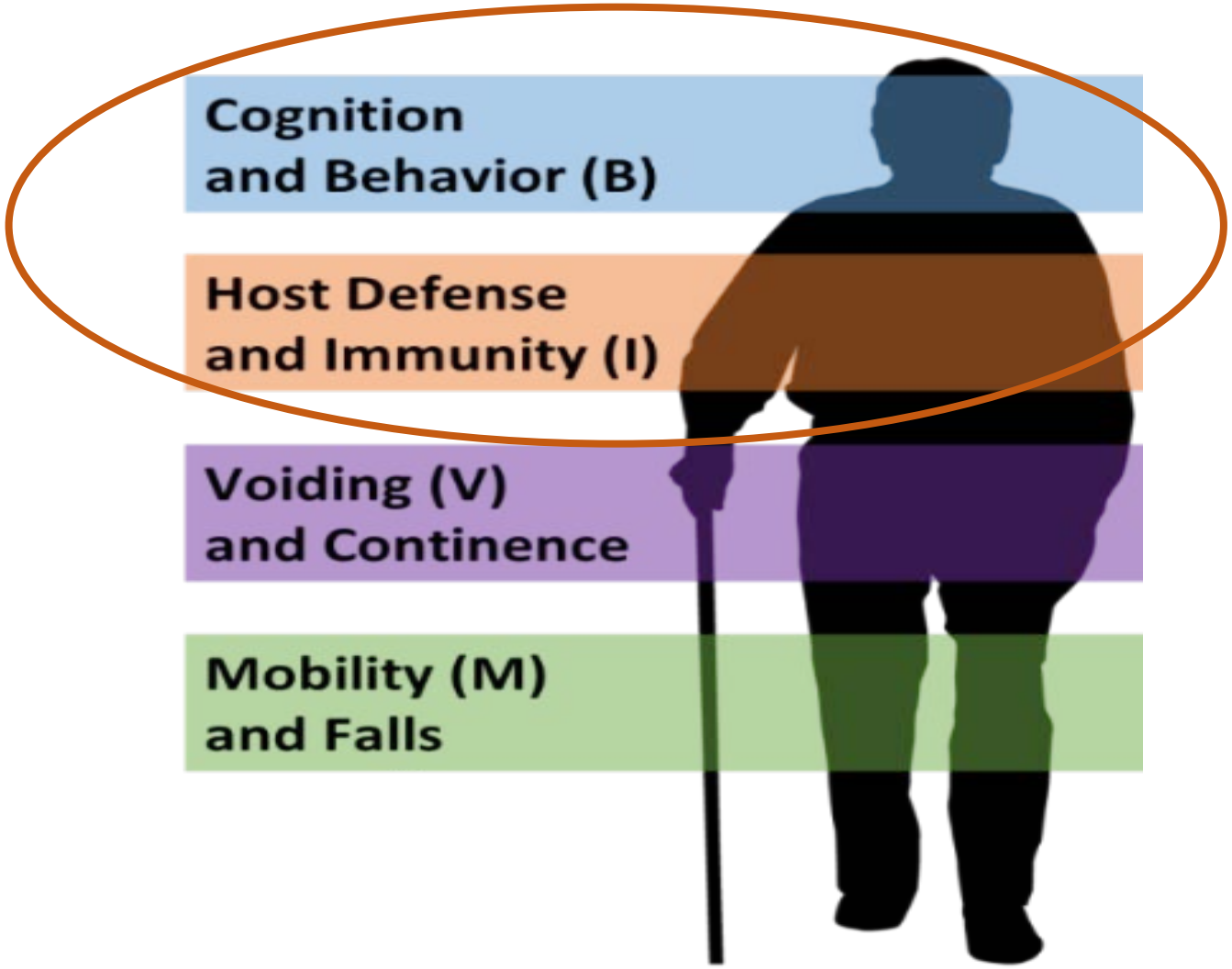
Enhancing Independence by Targeting Shared Risk Factors



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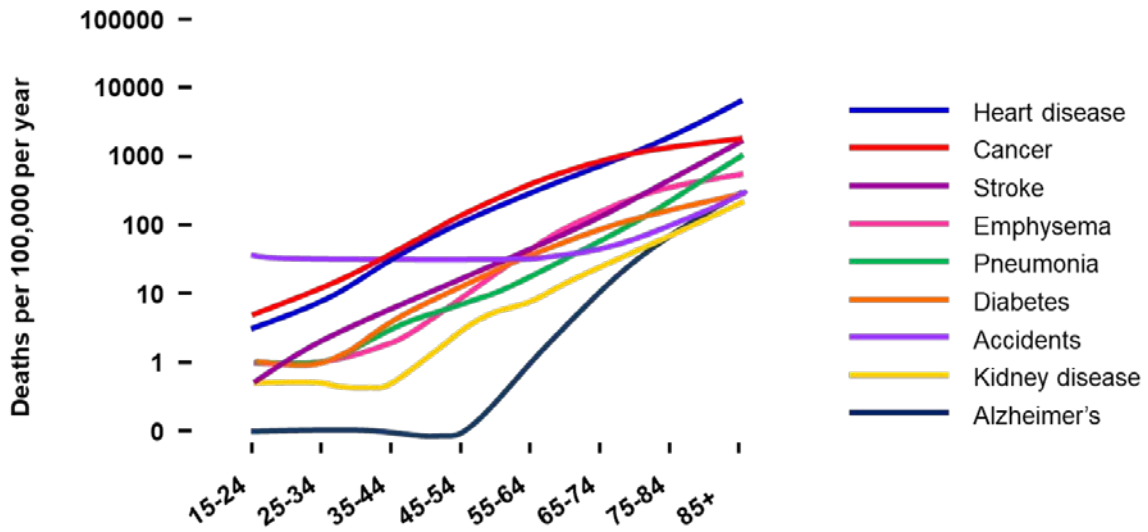
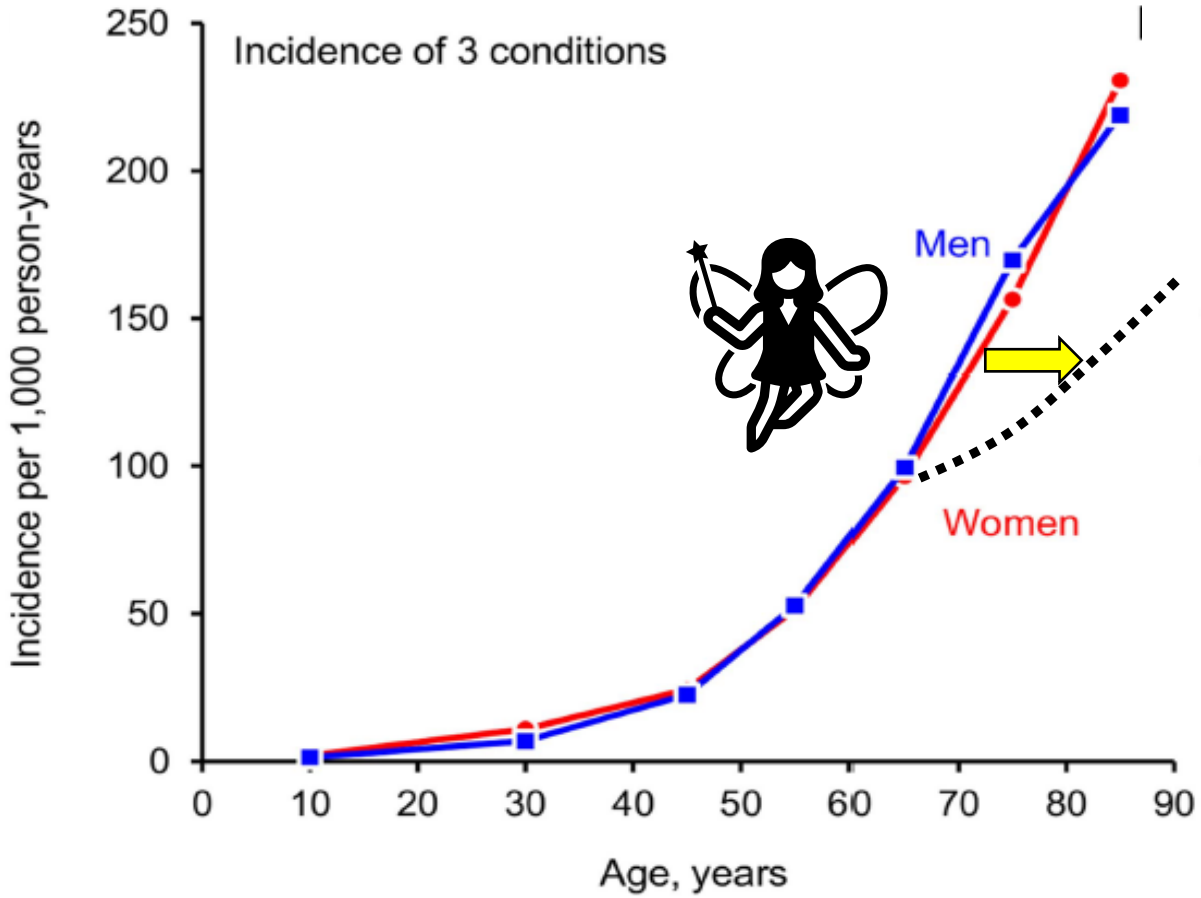
Moving Gerotherapeutics from an Idea to Reality



Espinoza, Justice, Newman, Pignolo and Kuchel;
Chapter 40 Applied Clinical Geroscience,
Hazzard's Geriatric Medicine and Gerontology, 8th edition



St Sauver JL *et al. BMJ Open 2015*

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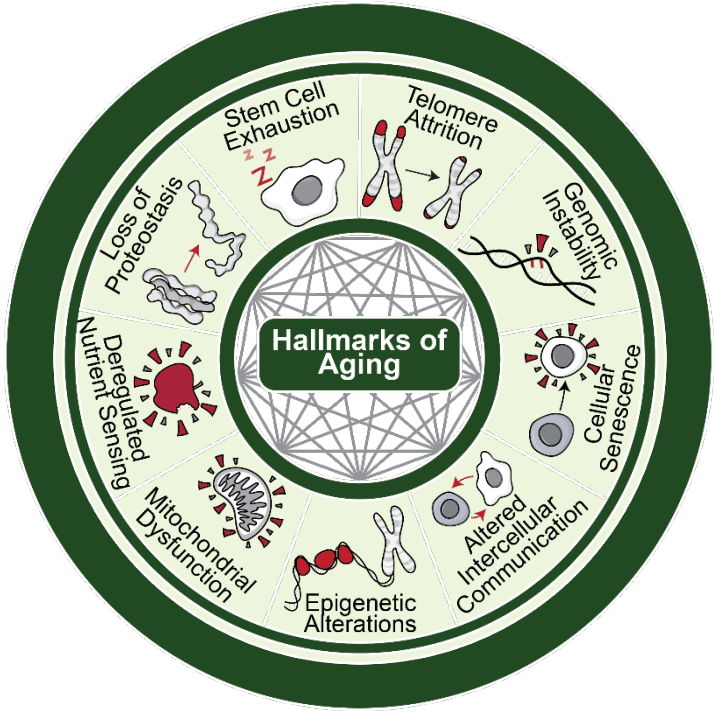

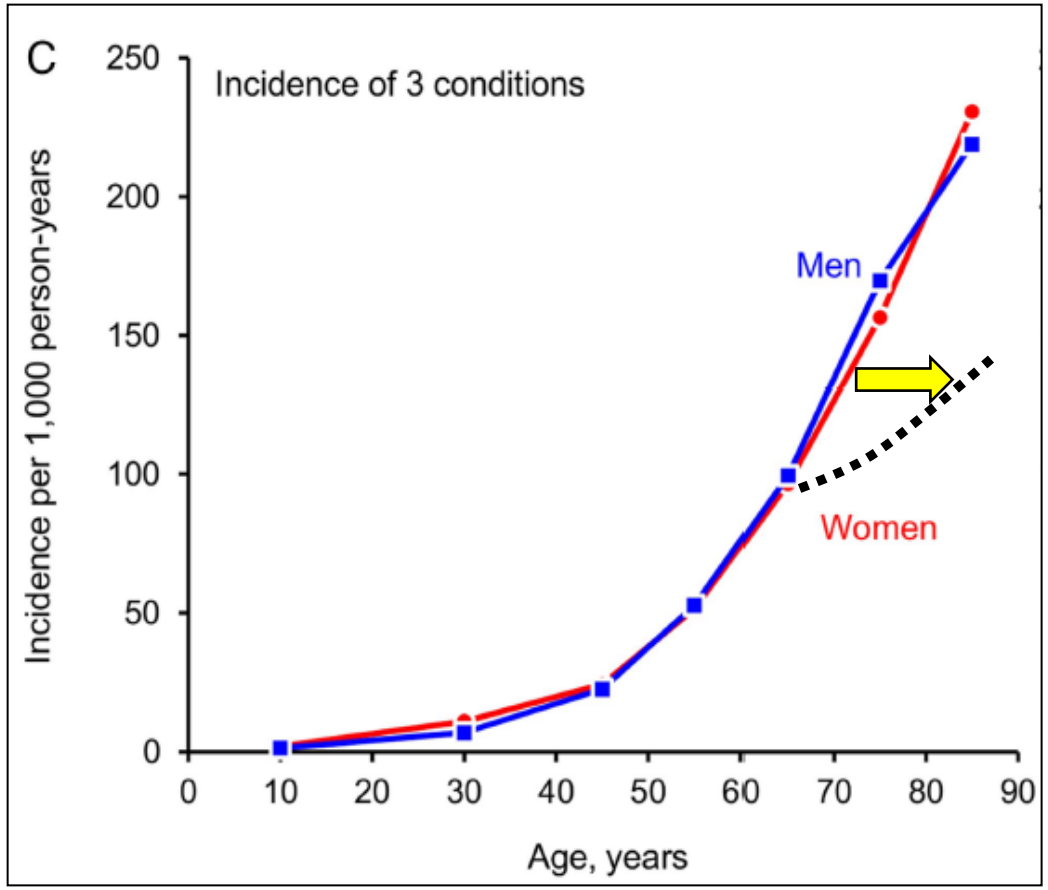

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Role of Inflammation in AD

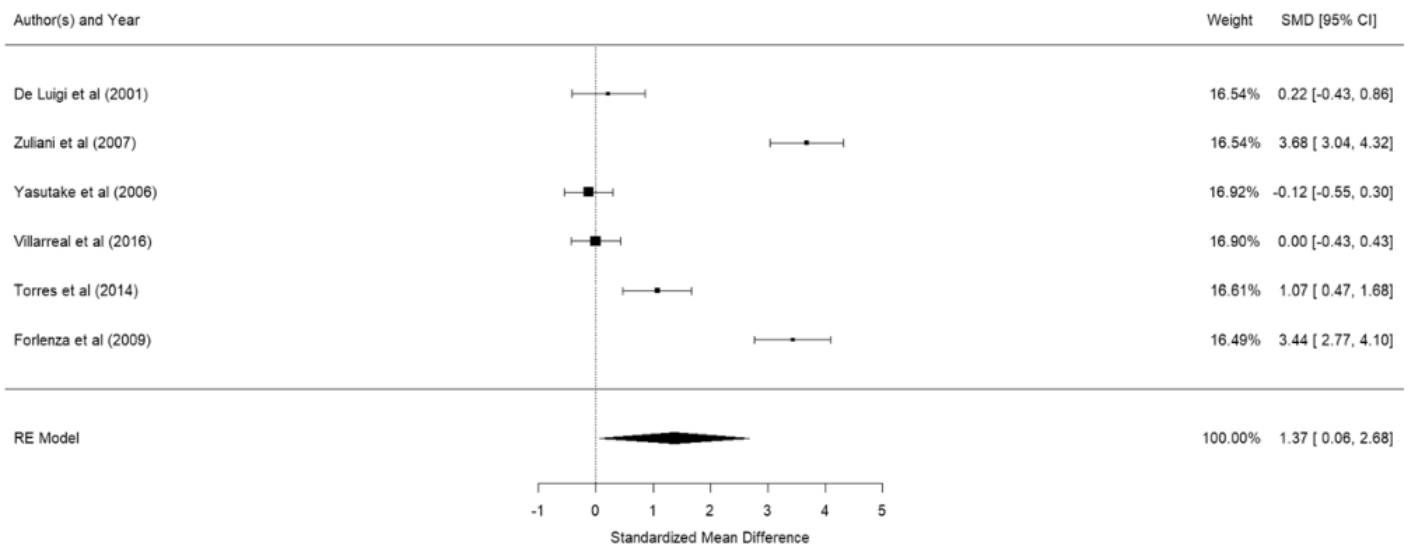

Figure 6. Forest plot of studies comparing peripheral IL-1β levels between elderly suffering from Alzheimer's disease and controls.

Ng *et al. Sci.Rep.* 2018

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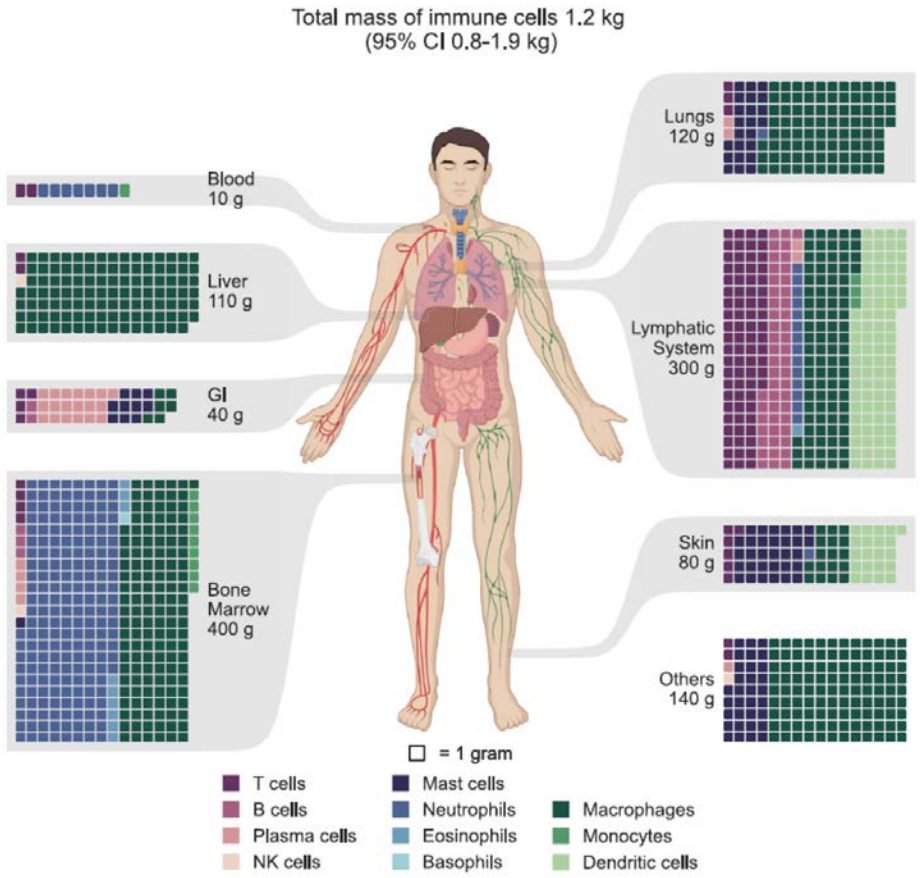
Role of Inflammation and the Immune System in AD



Sender *et al. PNAS* 2023

- Peripheral blood contains only 0.8% of all immune cells in the body!
- Inflammatory marker levels vary with time of day, eating, stress, etc.
- Venous levels reflect mostly liver efflux
- Composite measures (e.g. SASP Index) often perform much better (Breno Diniz)

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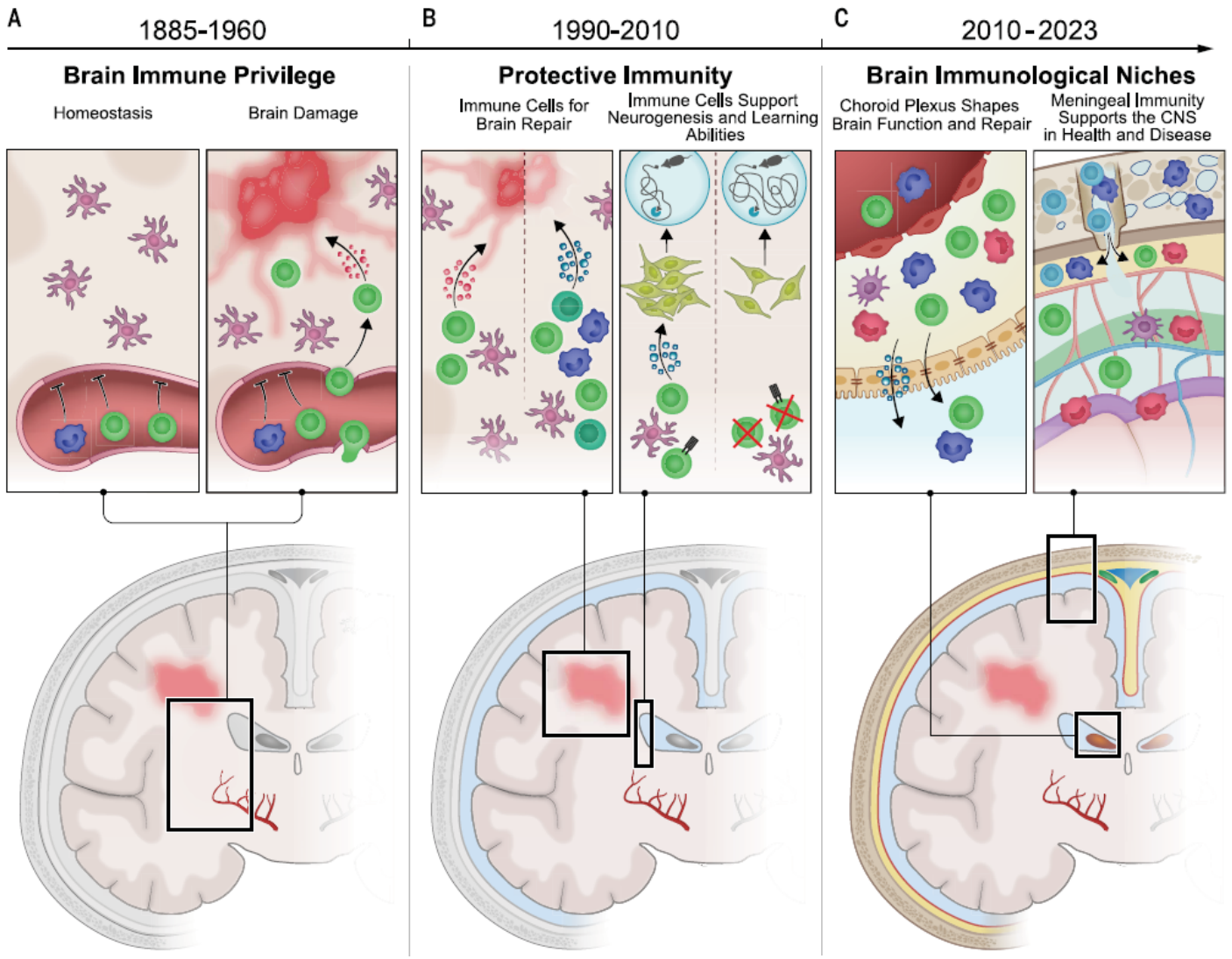
Immune Control of Brain Physiology



Castellani *et al. Science* (2023)

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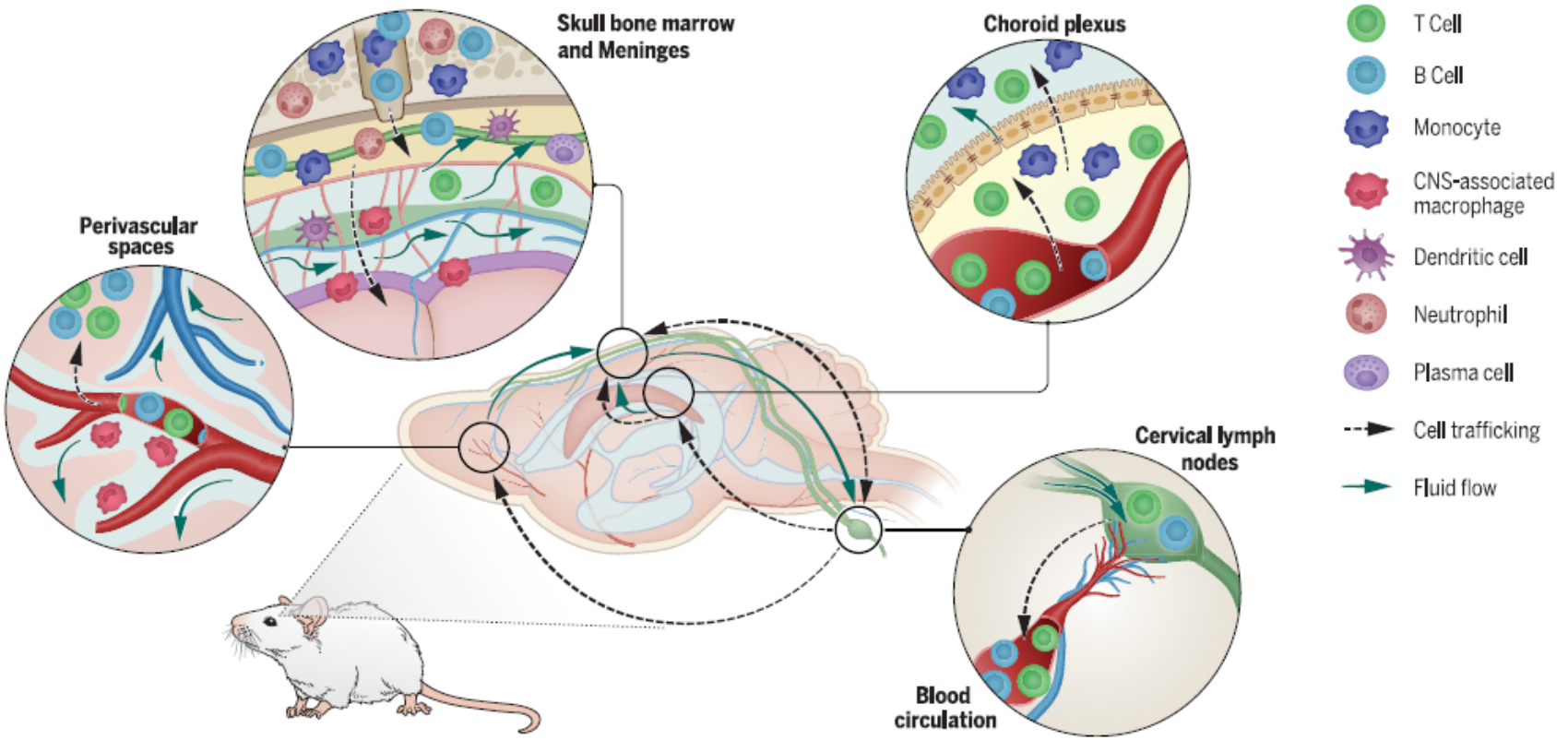
Immune Control of Brain Physiology



New perception of brain immunity. Shown is a representation of the communication network allowing fine-tuned brain immunosurveillance. The immune cells are strategically positioned in immunological niches, where they are constantly exposed to CNS cues transported by the intracranial interstitial, cerebrospinal, and lymphatic fluid. Upon sensing brain signals, the immune cells can migrate toward the CNS to exert their effector functions.

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Castellani *et al. Science* (2023)

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Immune-Brain Communication

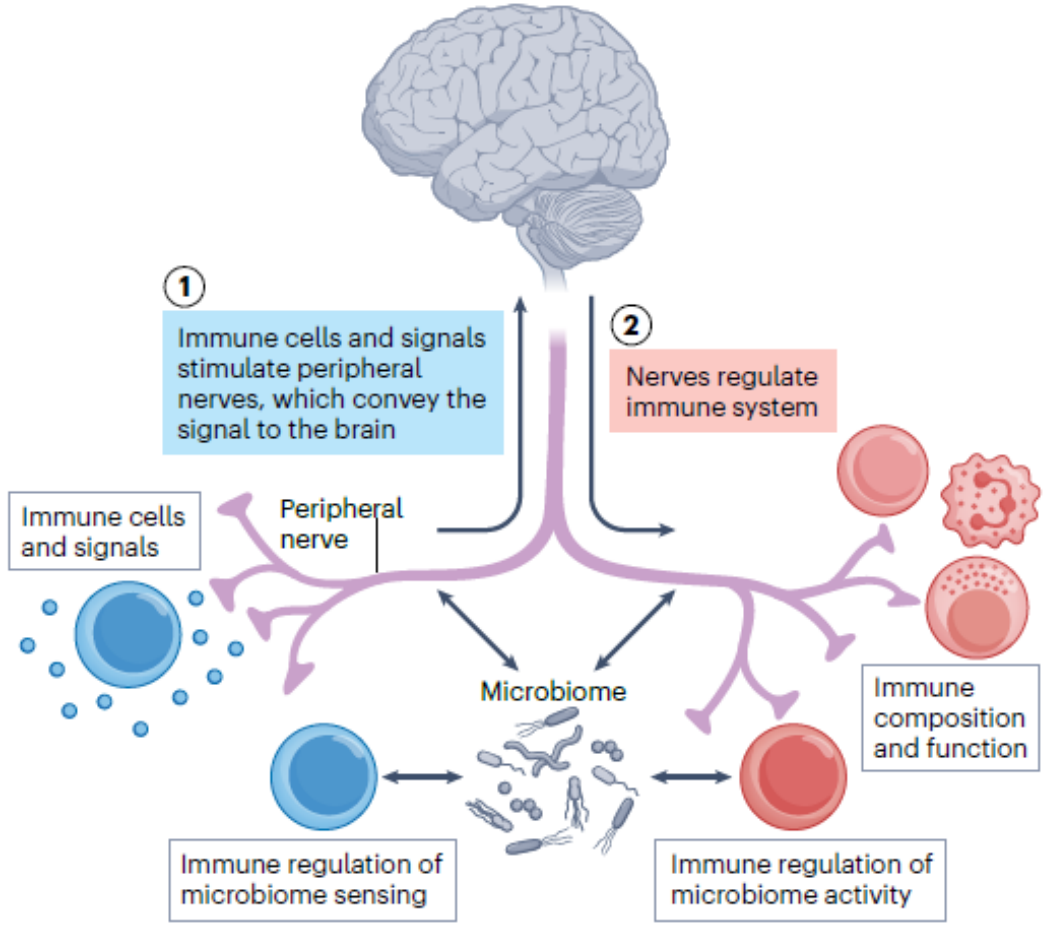

Fig. 5 | Immune–brain communication along peripheral nerves. (1) Peripheral nerves sense immune cues and transmit the information on immune status to distinct brain areas near-instantaneously. (2) In turn, the brain can regulate immune responses. In addition, the immune system can shape the ability of nerves to sense other stimuli, such as microbial products.

Kovacs et al. *Nature Rev. Imm.* (2025)

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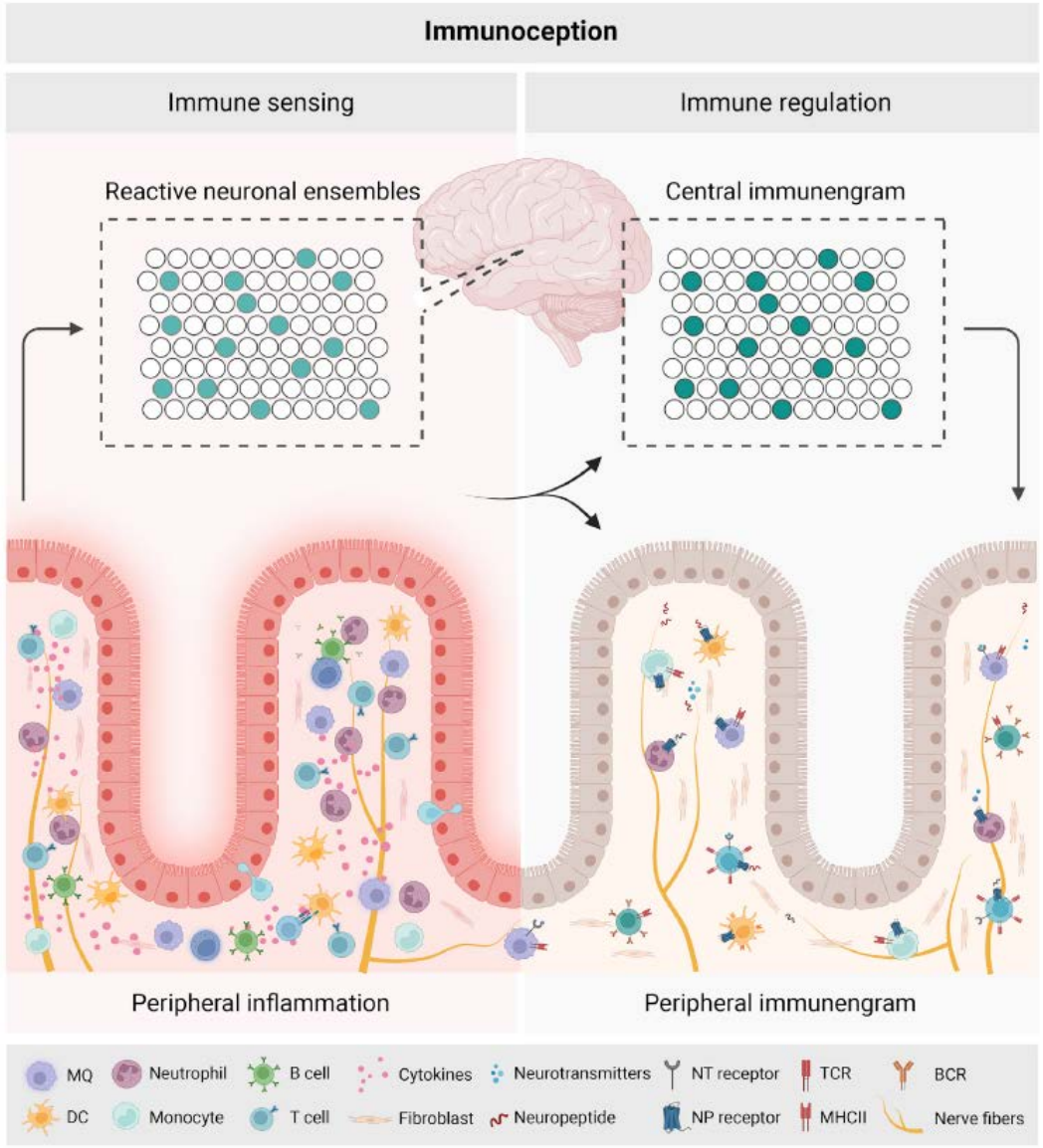
Immunoception: Brain-regulated Immunity



Koren and Rolls *Neuron* (2022)

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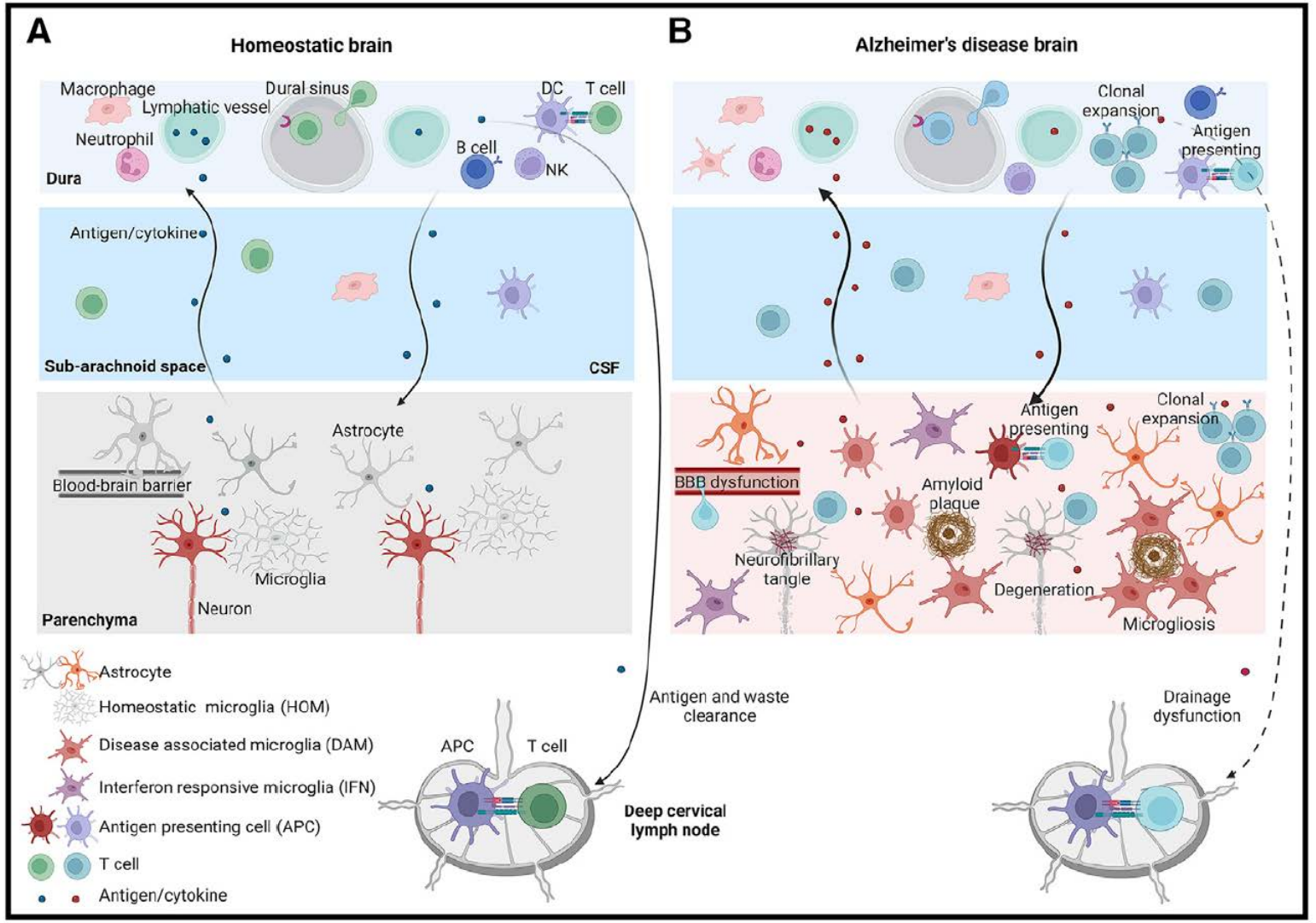
Role of Immunity in AD



Chen and Holtzman *Immunity* (2022)

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Conclusions

- Need to move from single disease paradigms to real-world clinical reality
- Address role of multifactorial complexity, MCCs, heterogeneity of aging
- Aging is the major shared risk factor for MCC and AD/ADRD
- Immune aging offers accessible yet imperfect insights into biological aging
- The immune system influences brain function
- The nervous system influences immune function
- Brain-Immune Dysregulation – a major contributor to AD (and other diseases)
- Major opportunities for geroscience-guided interventions

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