# *Identifying perspective therapeutic targets in Alzheimer's disease: Understanding the cascading effects of cellular deterioration*

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# Acknowledgements

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Société Alzheimer Society CANADA

*Cell signalling cascades that direct microglial activation outcome in AD*

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- Christian Humphreys
- Albert Yeung (MSc/MD)
- Deepthi Thomas

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- Shubham Tanwar
- Triston Eastman

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- Alana Lamont (MSc)
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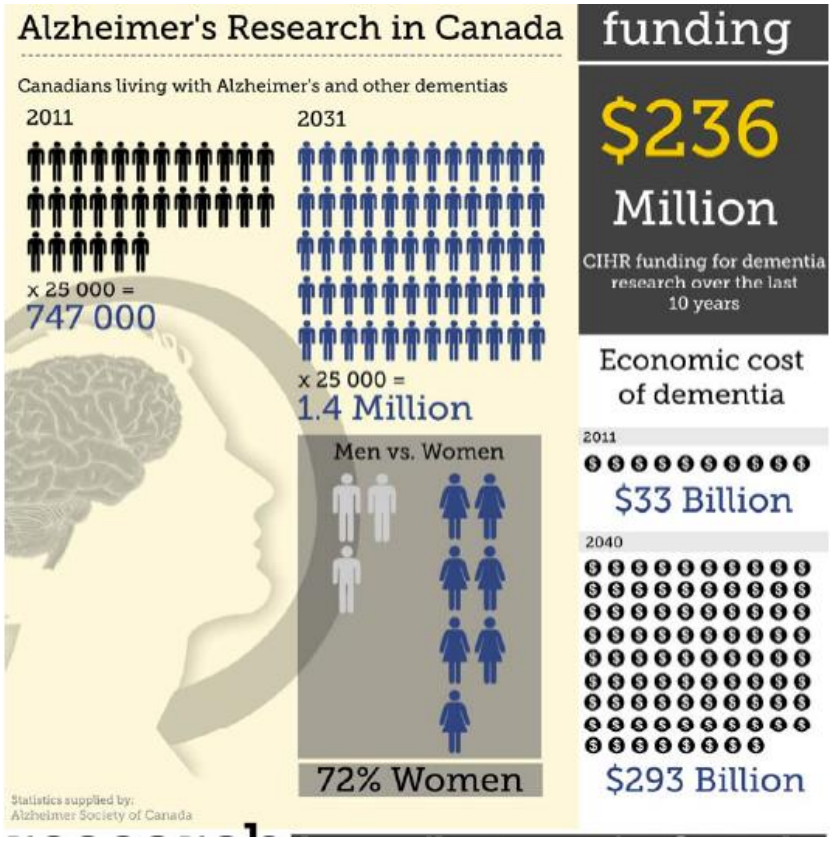
# Alzheimer's disease (AD)

- Most common neurodegenerative disease with over 20 million cases worldwide

**alarming facts**

1) increasing prevalence with aging population



# Alzheimer's disease (AD)

- Most common neurodegenerative disease with over 20 million cases worldwide

**alarming facts** 

1) increasing prevalence with aging population
2) no treatment is able to alter the course of disease

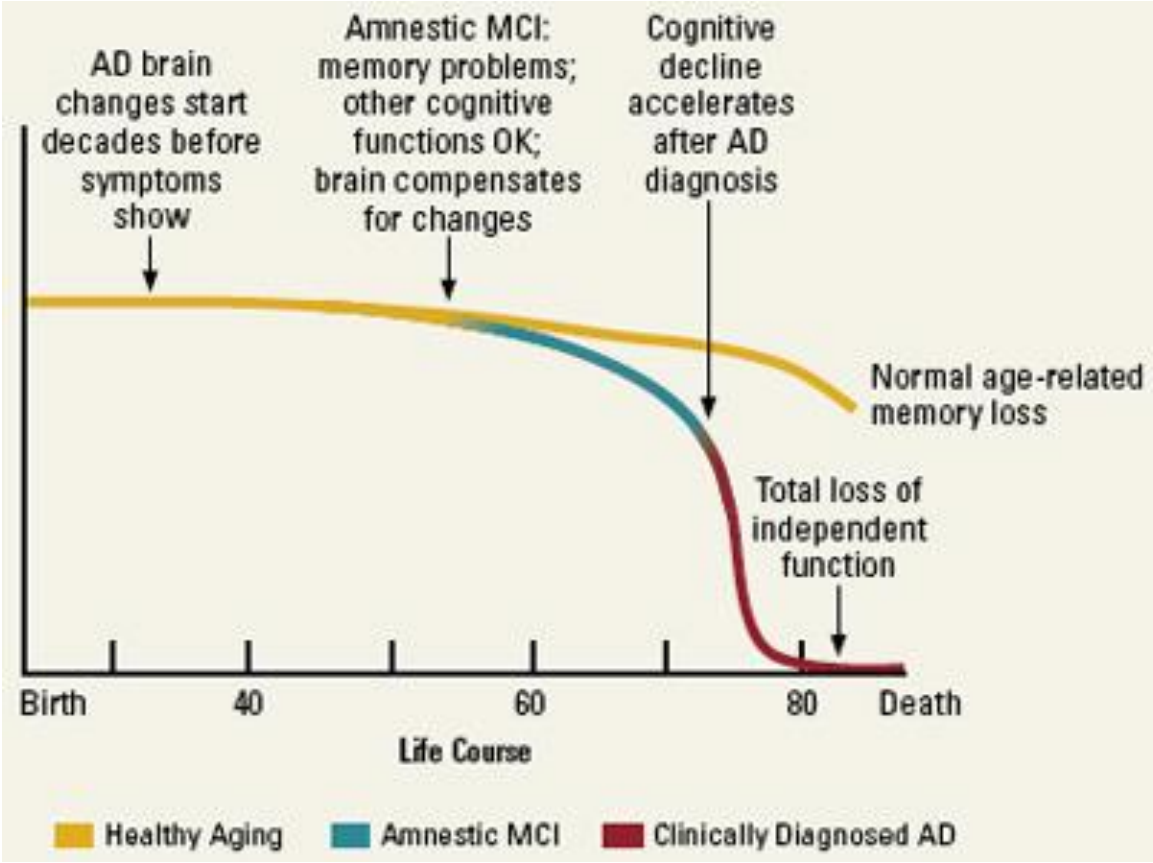
## Drugs currently approved

NMDA receptor antagonist
- Ebixa (Memantine)

Cholinesterase Inhibitors
- Aricept (Donepezil )
- Exelon (Rivastigmine)
- Reminyl (Galantamine)

} of modest benefit

# Alzheimer's disease is a progressive degenerative disease




treatments able to delay symptom onset by as little as one year could reduce the global prevalence of disease by ~9 million cases over 40 years

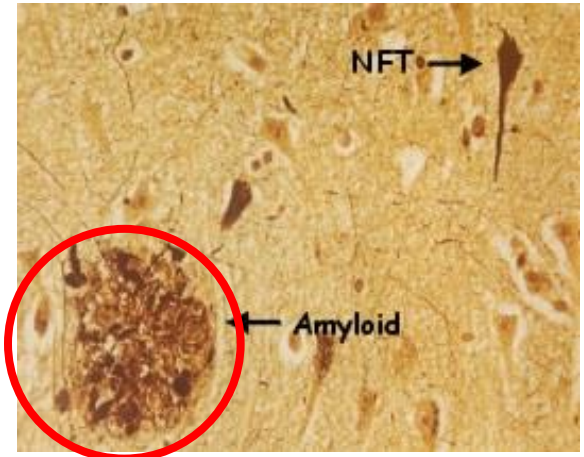
*Brookmeyer et al Alzheimer's & Dementia (2007)*

Research goal: to identify molecular mechanisms that cause disease as potential targets for development of novel therapeutics

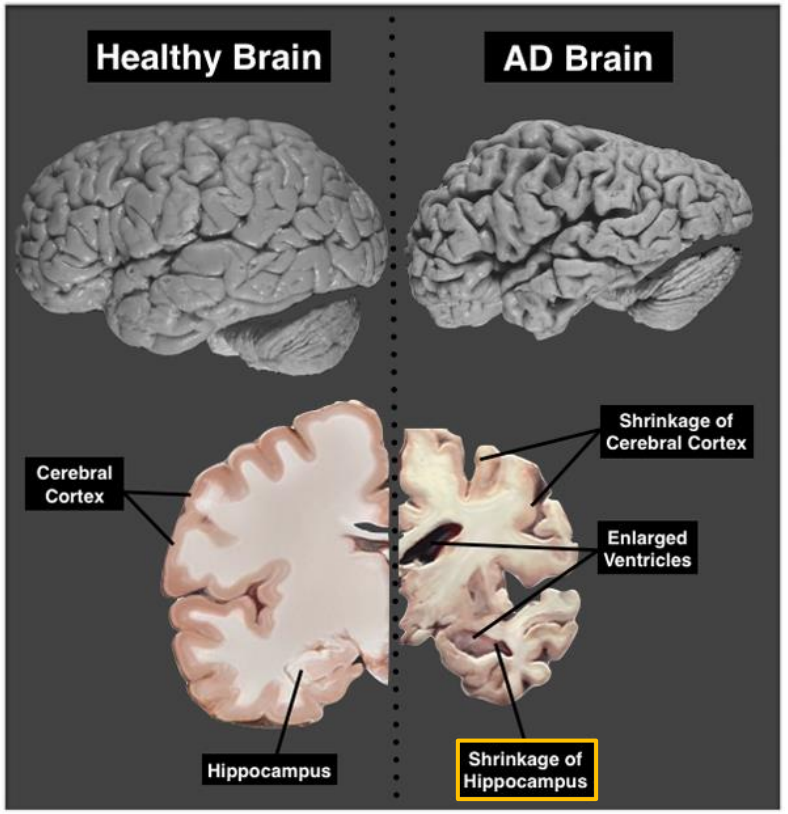
*what do we know about Alzheimer's pathology?*

# Alzheimer's disease: pathology hallmarks

Alois Alzheimer (1907)




Amyloid-beta (Aβ)
isolated from plaques (1985)



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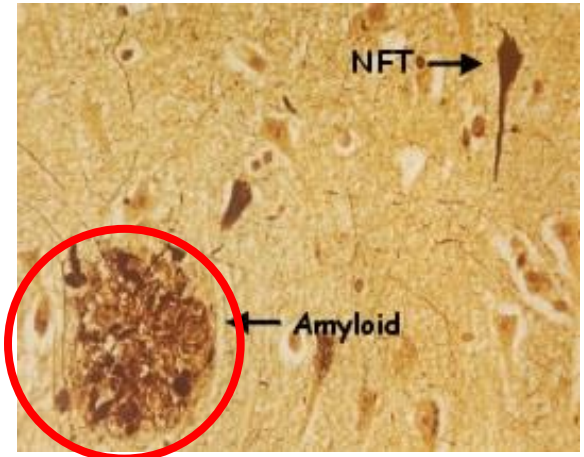
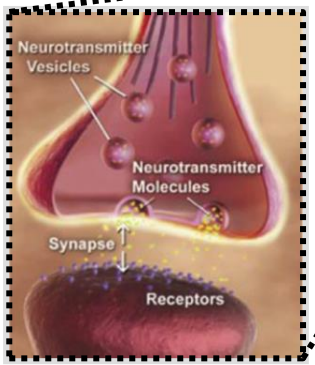
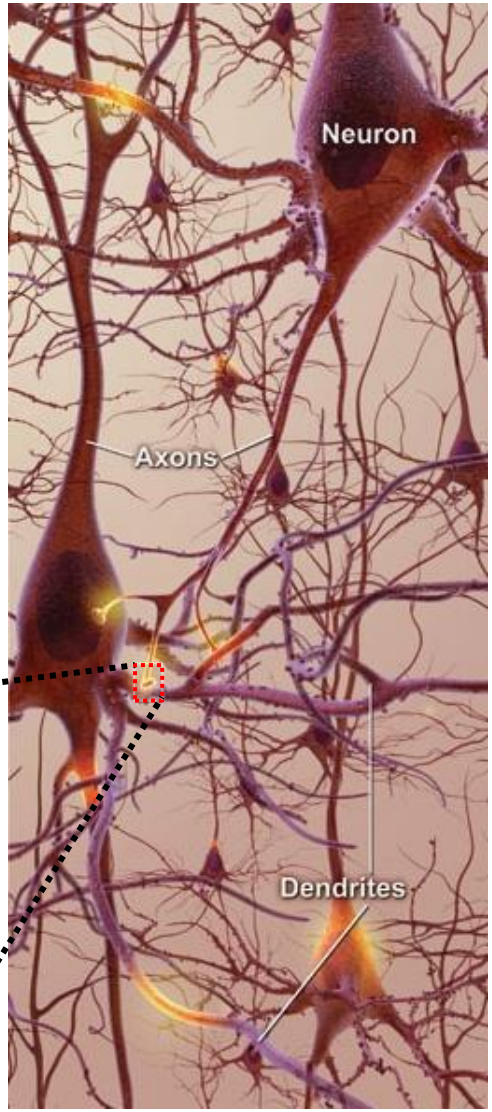



Amyloid-beta (Aβ)
isolated from plaques (1985)

Aβ is synaptotoxic
*(especially soluble oligomers)*



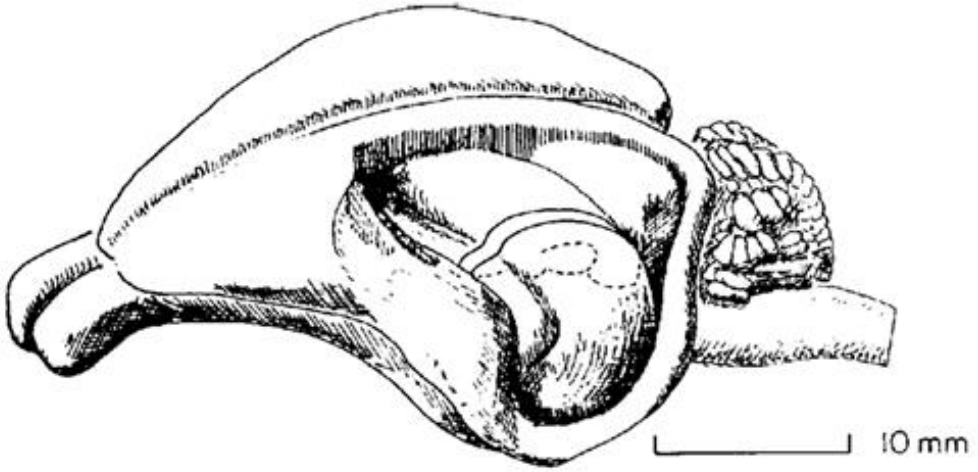



# Hippocampus and neuroplasticity

- important in humans for episodic memory (what-when-and-where) and in rodents for recognition memory
- one of the first areas to degenerate in Alzheimer's
- *important area for studying neuroplasticity*

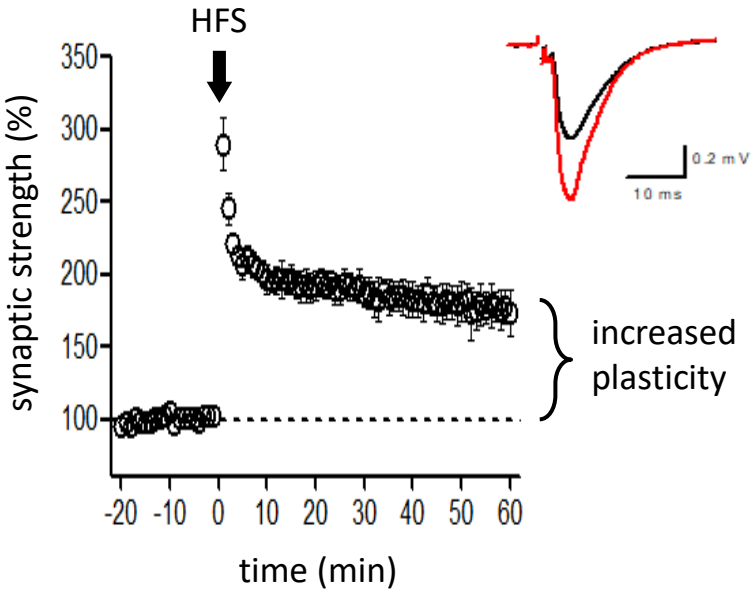
*Neuroplasticity: refers to the brains ability to adapt*

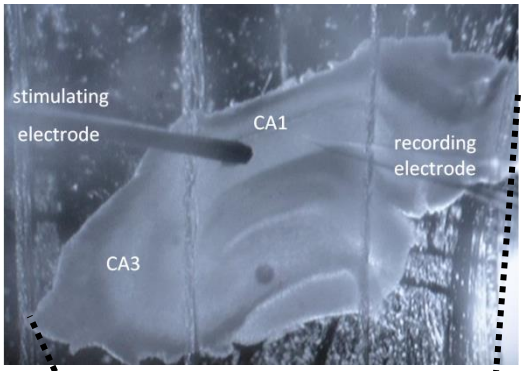
- basis learning and memory
- due to increased strength of communication between neurons

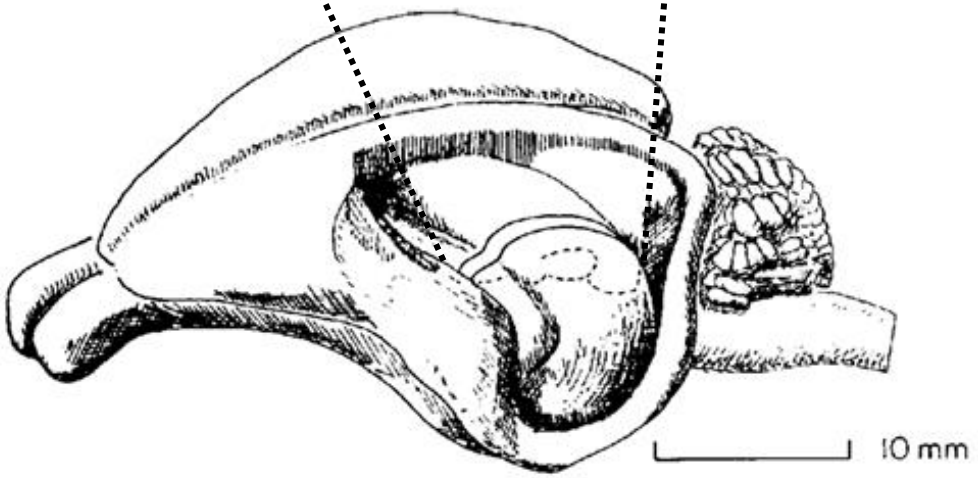



rodent hippocampal brain slice preparation

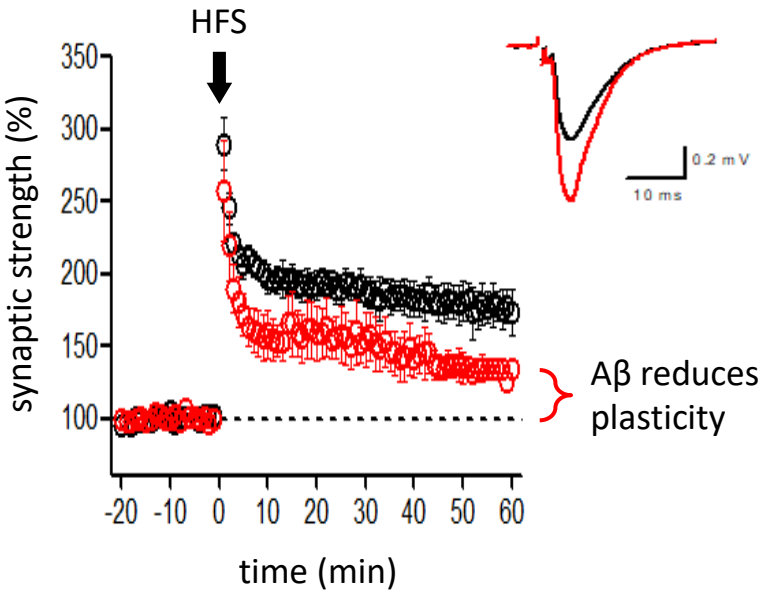
# Hippocampus and neuroplasticity

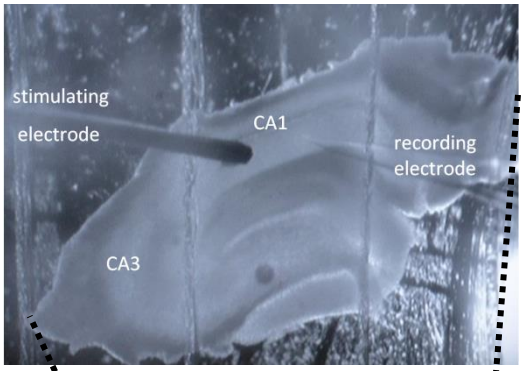


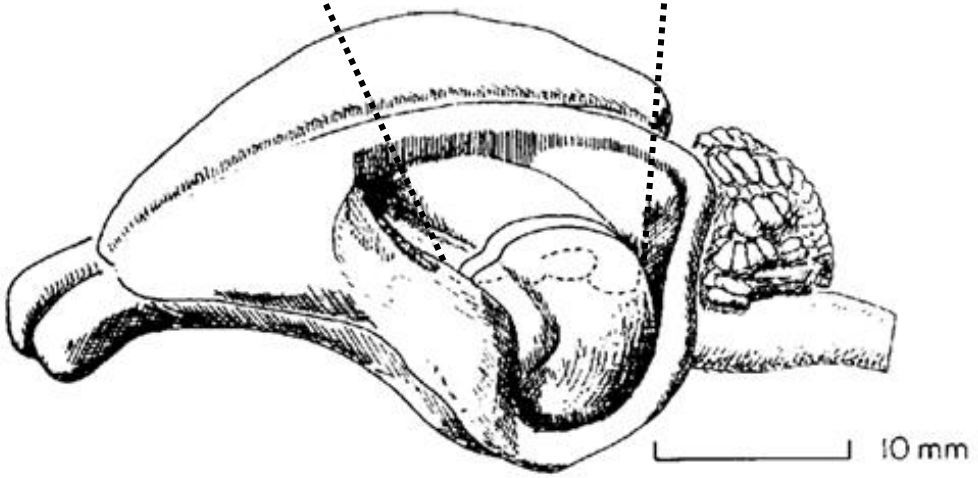



# Hippocampus and neuroplasticity

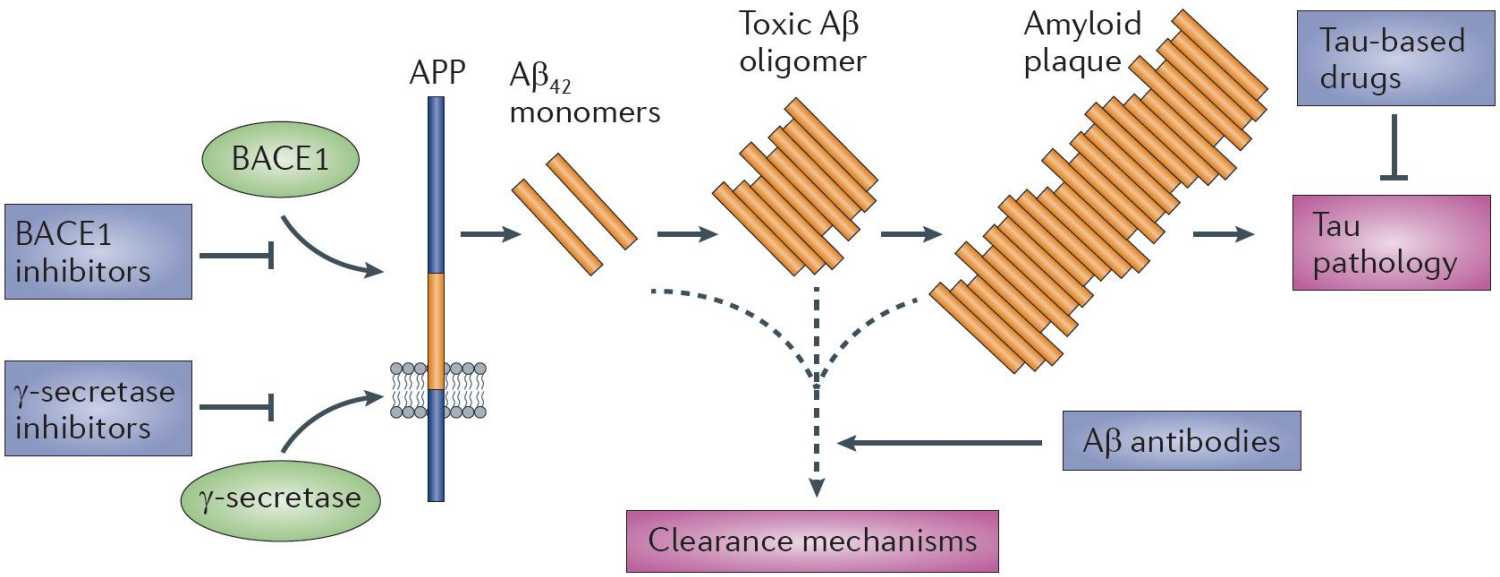



Amyloid Cascade Hypothesis (1992)



# Aβ targeted therapies in AD clinical trials




- All approaches targeting Aβ production or clearance have failed clinical trials
- Most common reason for Phase III failure is lack of efficacy and toxicity
- Identifying new therapeutic targets is of paramount importance

# Neuroinflammation theory of AD

- Reduced risk of AD in patients on long-term anti-inflammatory medication (NSAIDs)

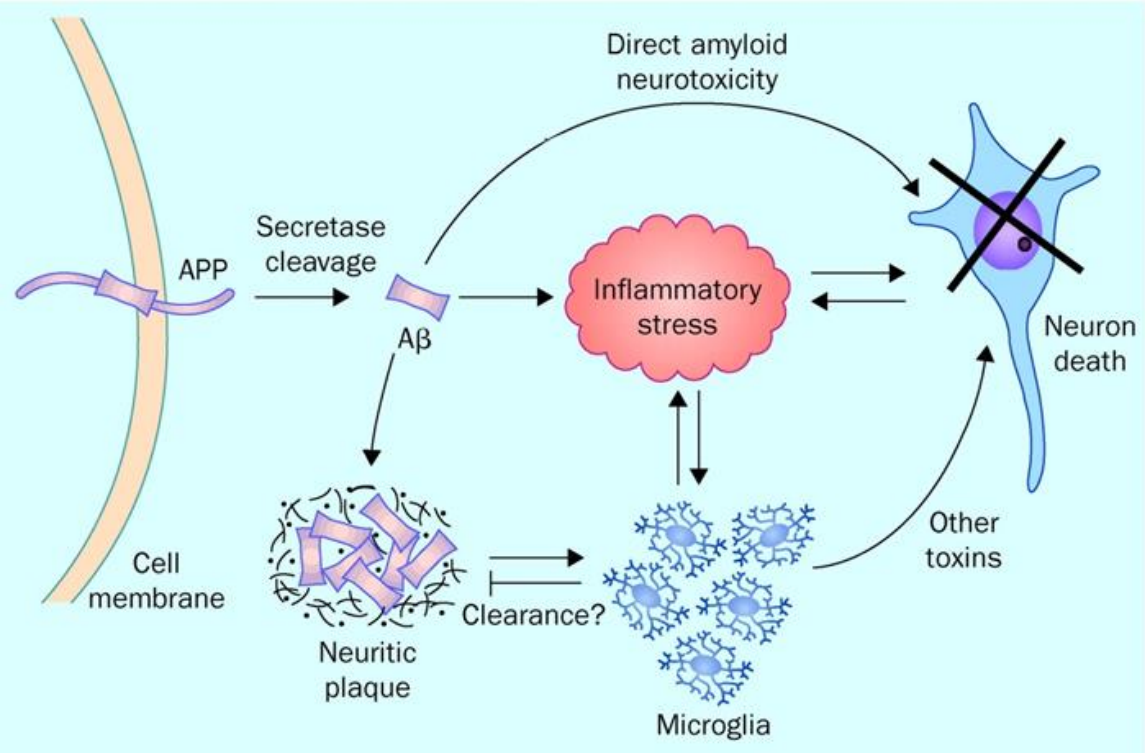
- Genetics studies (GWAS) have identified gene variants in AD patients:

  1) linked to dysfunction of *microglia* the immune cells of the brain

  *and*

  2) associated with a major increased in the risk of developing late-onset AD (LOAD)

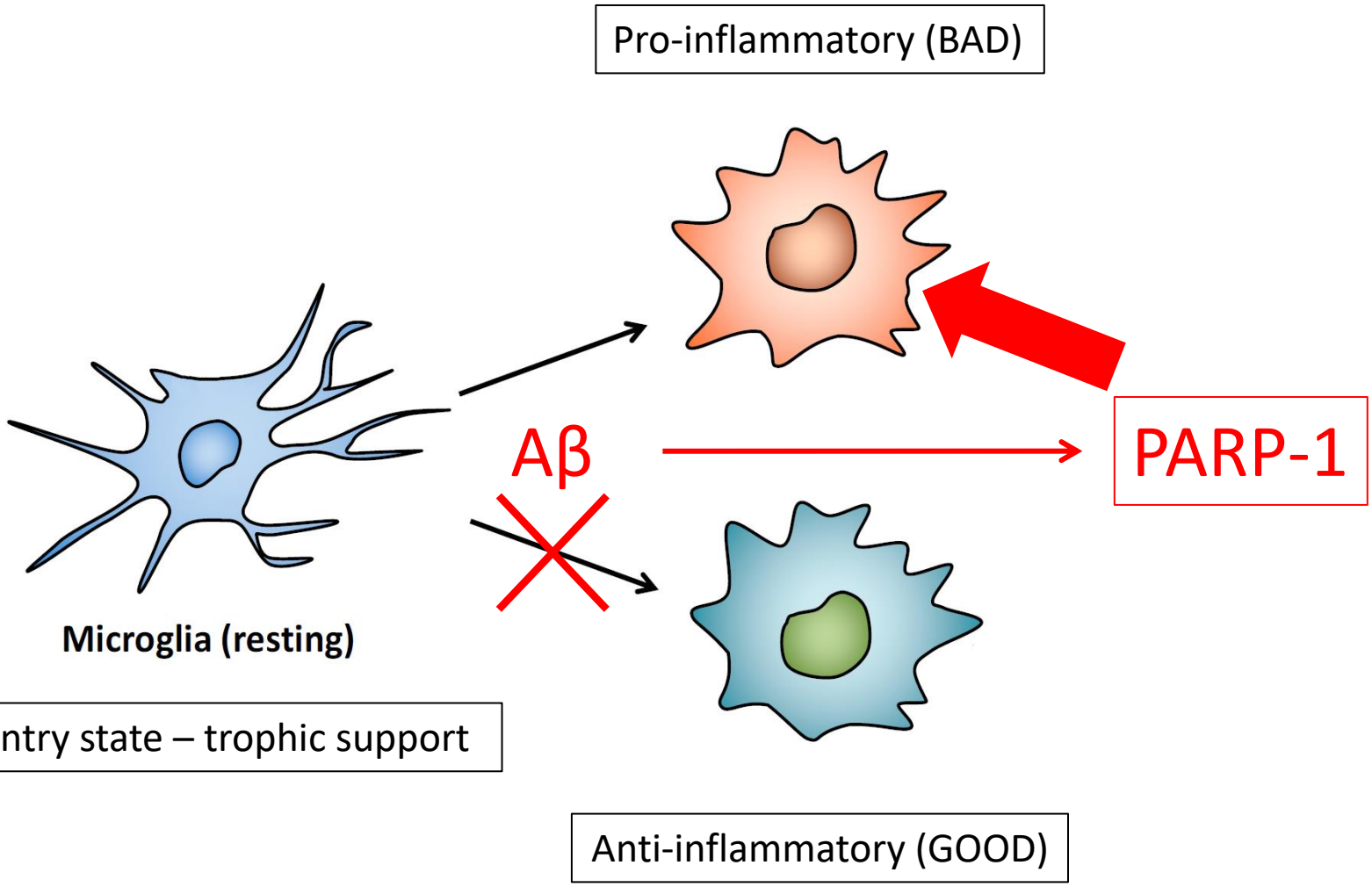
# Neuroinflammation theory of AD




In AD: the beneficial roles of microglia are corrupted leading chronic neuroinflammation

How can we reduce chronic inflammation in AD?

# Microglia: role of PARP-1



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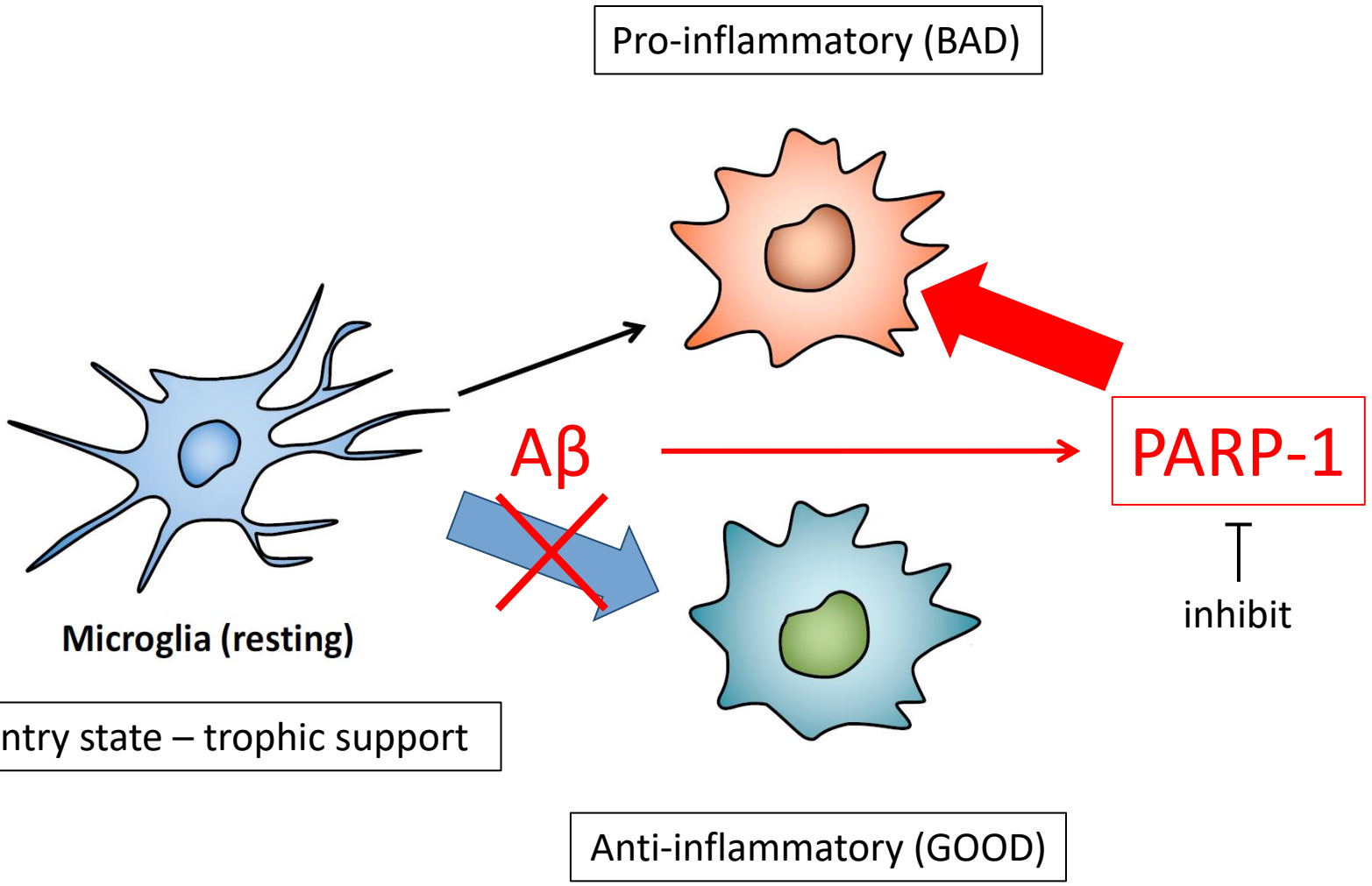

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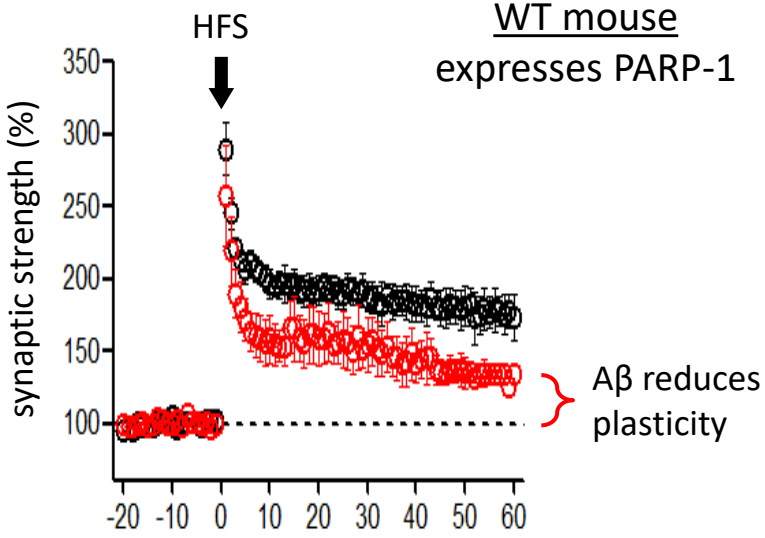


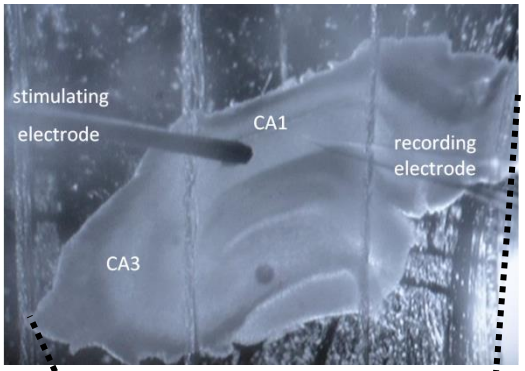


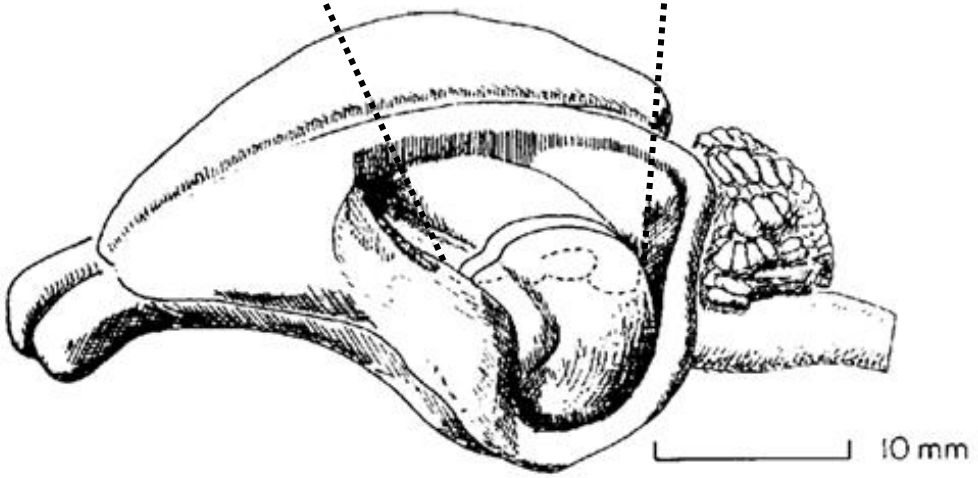

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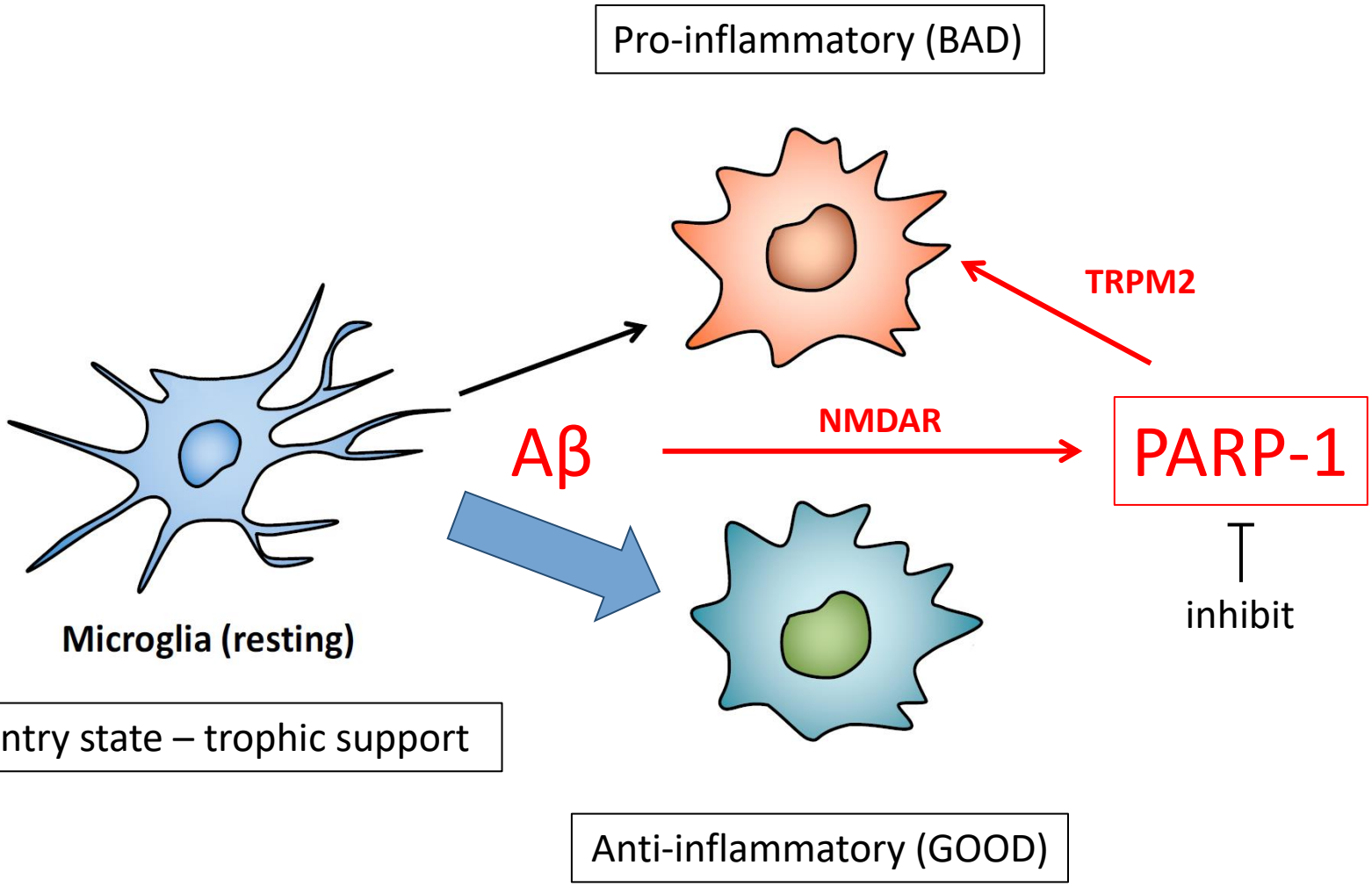

# Acknowledgements


research team:

*University of Manitoba (past and present)*
- Natalie Lavine (research associate)
- Dr. Dali Zhang (research associate)
- Olya Myhalatyuk (MSc)
- Alana Lamont (MSc)
- Chetan Patil (PhD)
- Christian Humphreys (MSc)
- Prajwal Raghunatha (MSc)
- Deepthi Thomas (MSc)
- Albert Yeung (MD/MSc)
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- Dr. Harish Gangadharappa (postdoc)

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- Dr. Mark Reed

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} Drug Discovery

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