2018 Feb DNA Repair Video Conference

NAD^+ supplementation and DNA repair as therapeutic strategies in Alzheimer's disease

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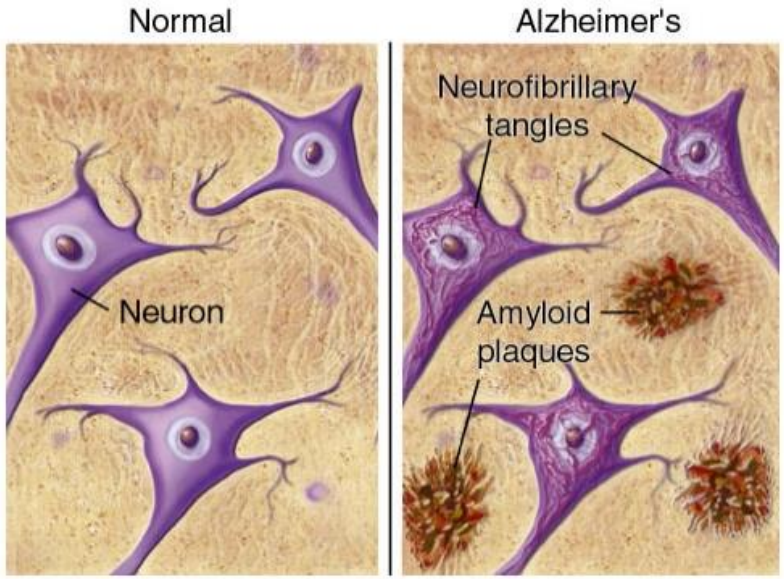
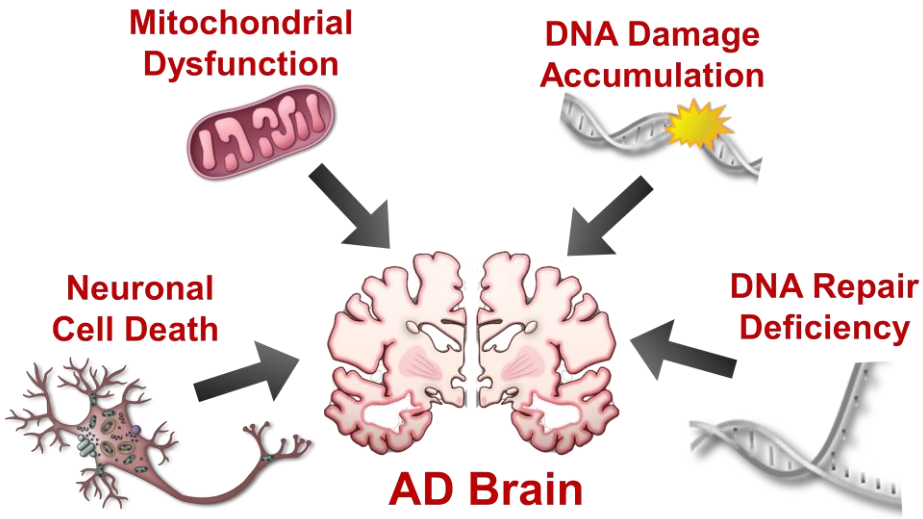
Mentor: Vilhelm A. Bohr

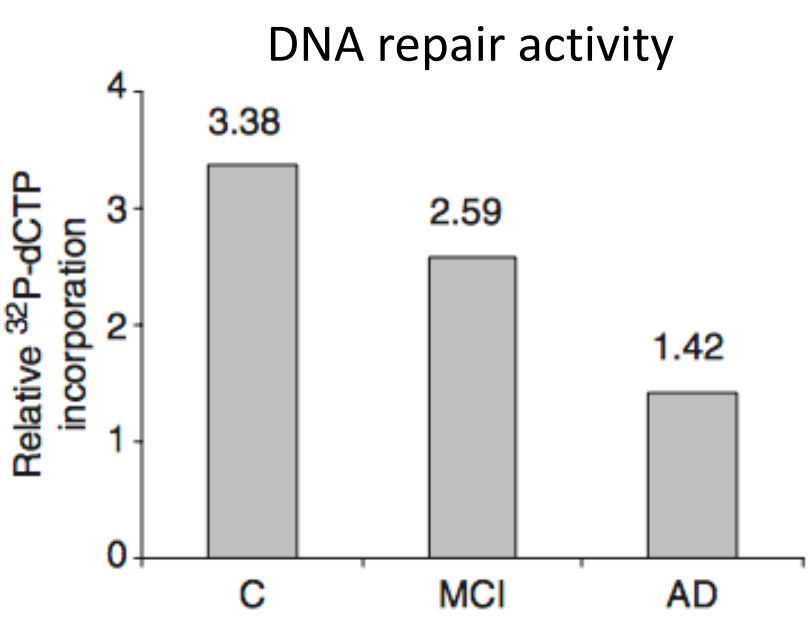
2/20/2018

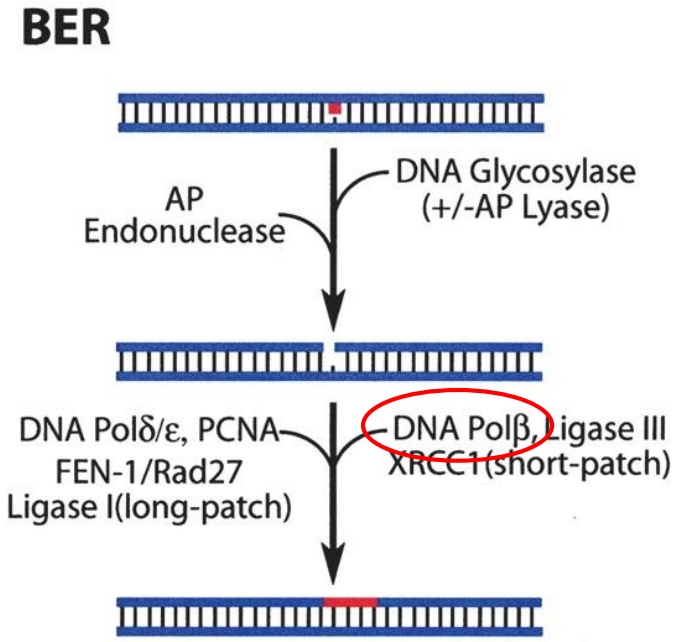
Alzheimer’s disease (AD)





Alzheimer's disease and DNA repair

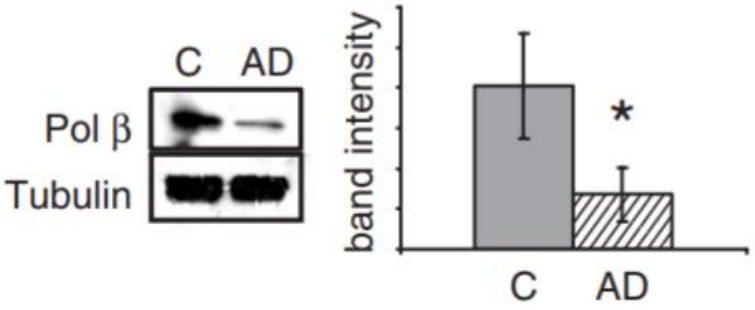




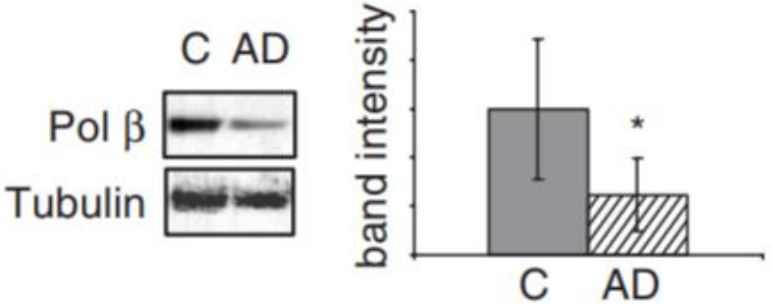
Weissman et al, 2007, NAR

DNA polymerase β in human brain

Inferior parietal lobule



Cerebellum

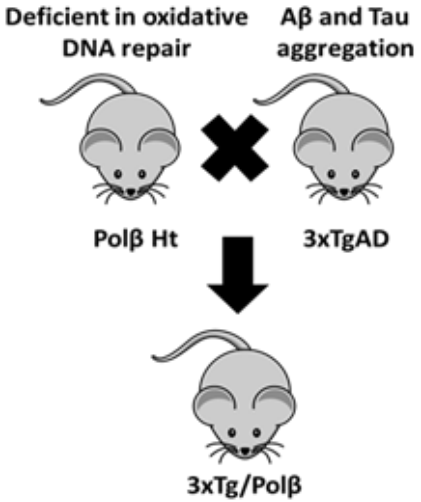


Polymerase $\beta^{+/-}$

Weissman et al, 2007, NAR
Sykora et al, 2015, NAR.

A New AD Mouse

3xTgAD/Polβ$^{+/-}$ mice have many more similarities to human AD than 3xTgAD mice

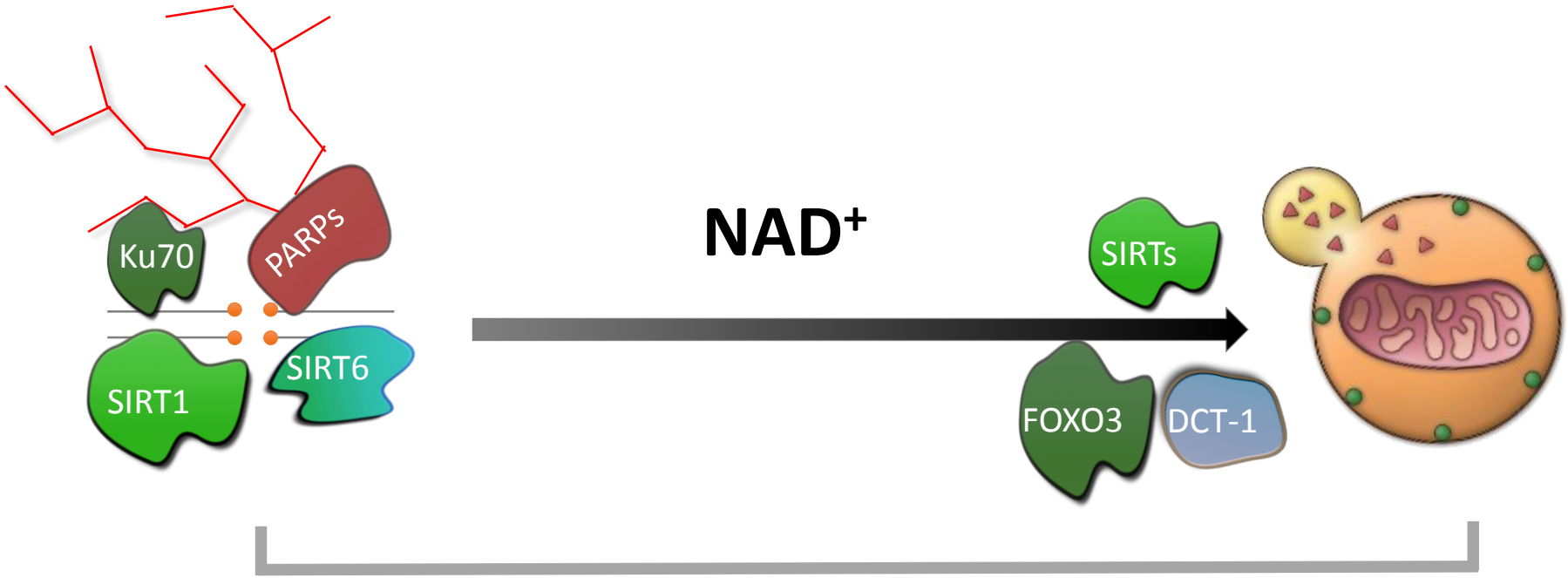


3xTgAD is mutated in APP, Tau and Presenilin1

- Synergistic loss of hippocampal volume
- Deficient neurogenesis
- Neuronal cell death
- Loss of synaptic plasticity
- Memory loss
- Higher similarity to human diseases
- Higher similarity to human AD
- Breakdown of mitochondrial bioenergetics
- Diabetes profile
- Deficient sense of smelling

Sykora et al NAR 2015
Misiak et al, Aging Cell 2016

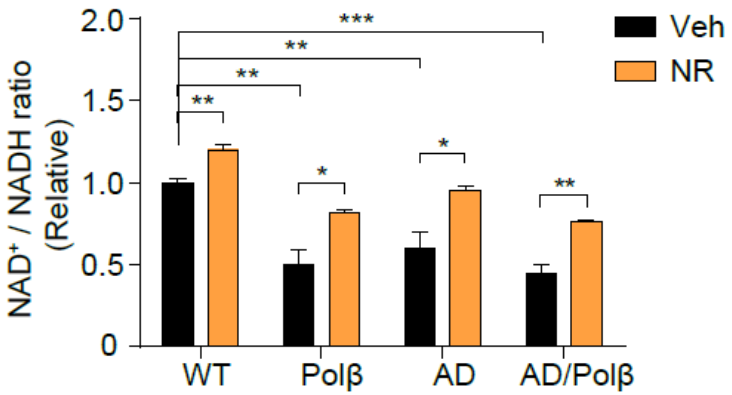
NAD^+ links DNA repair and mitophagy to mitochondrial maintenance

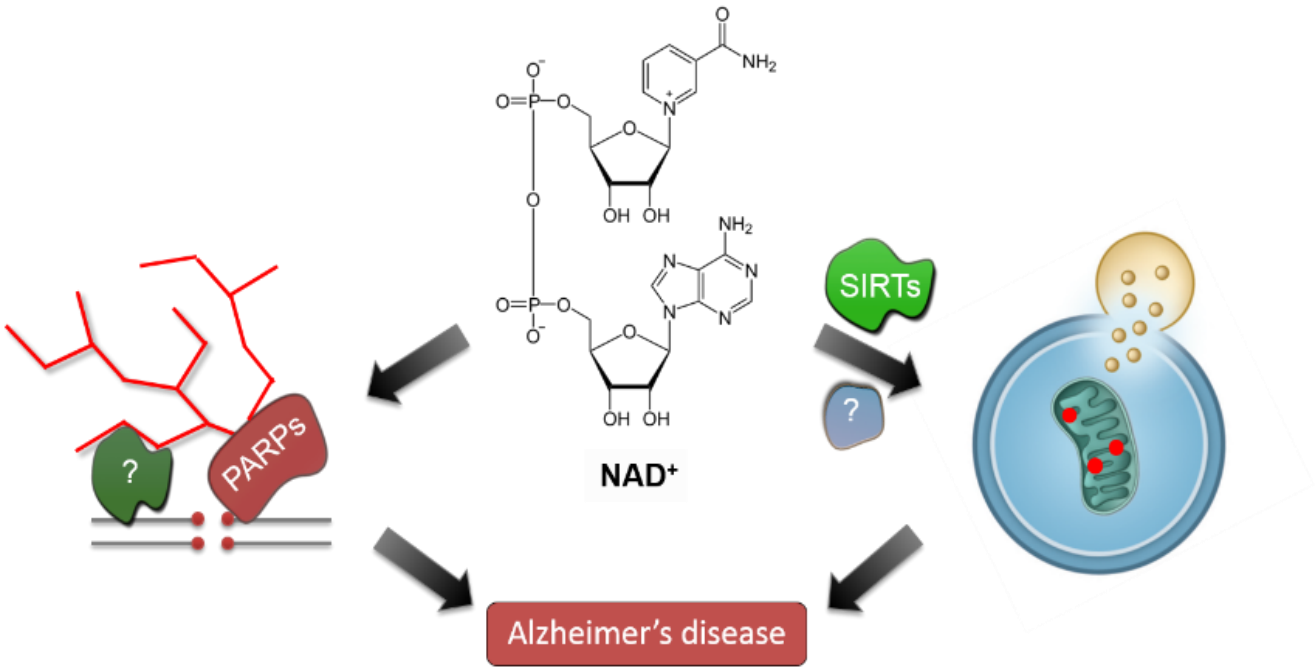


Genome maintenance
Mitochondrial homeostasis
Healthy aging

Fang EF et al., Nature Reviews MCB, 2016
Fang EF and Bohr VA, Autophagy, 2016

NAD⁺/NADH ratio is lower in AD mice and increases after NR treatment

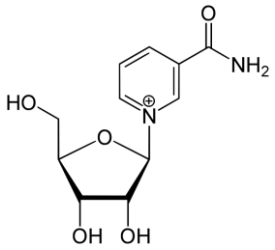




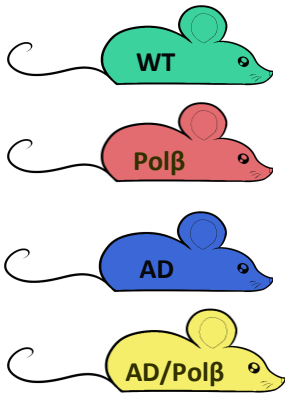
Modified from Fang et al, 2016, Cell Metabolism.

Experimental Design

Nicotinamide Riboside (NR)



Treatment



NR

Or

Veh

16-18
months

Behavior Tests

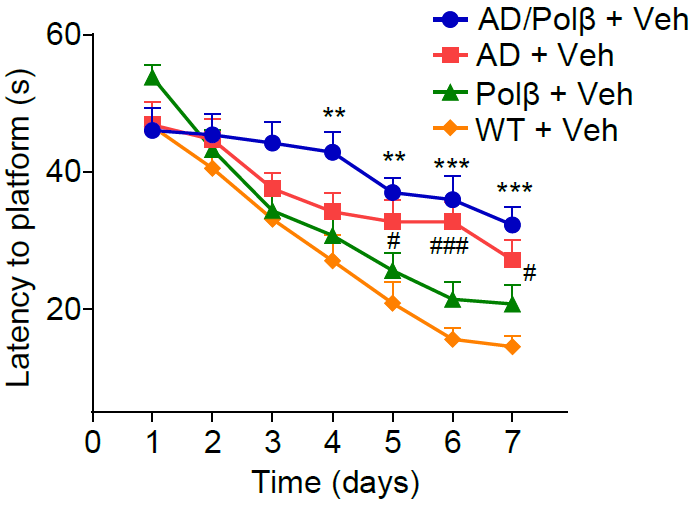
Cognitive Tests
Locomotor Tests
Metabolic Tests
Anxiety Tests
Motor Tests

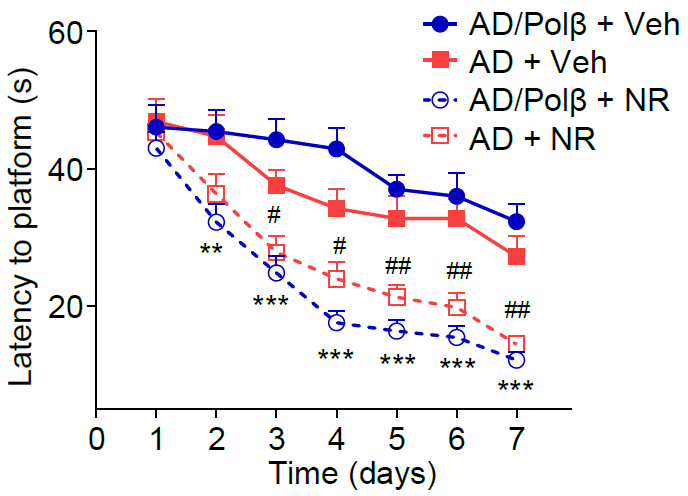
Mechanism

Electrophysiology
Biochemistry
Immunostaining
Microarray
…

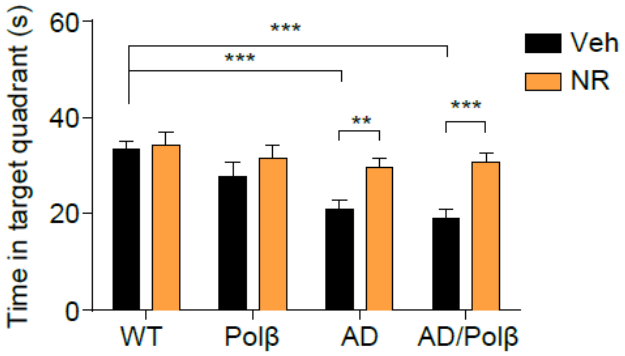
NR improves learning and memory in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

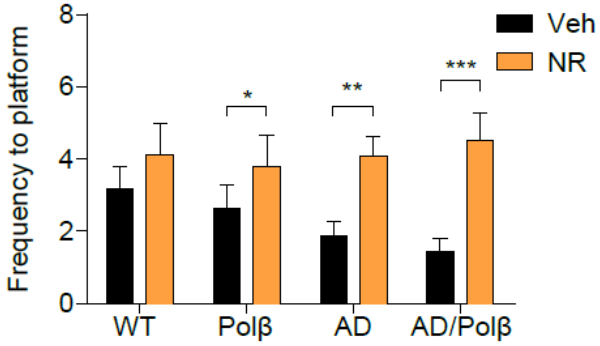
Morris Water Maze test





Morris Water Maze test – Probe trial

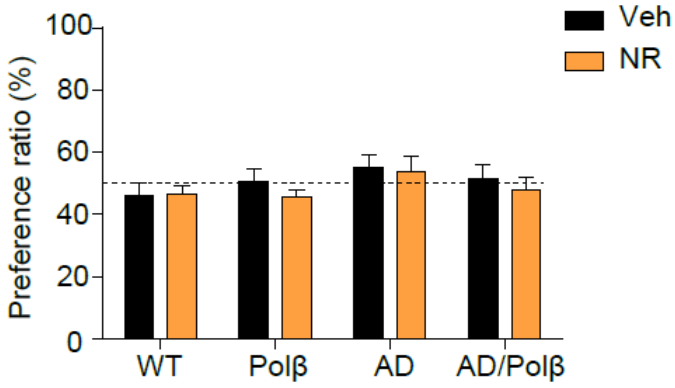


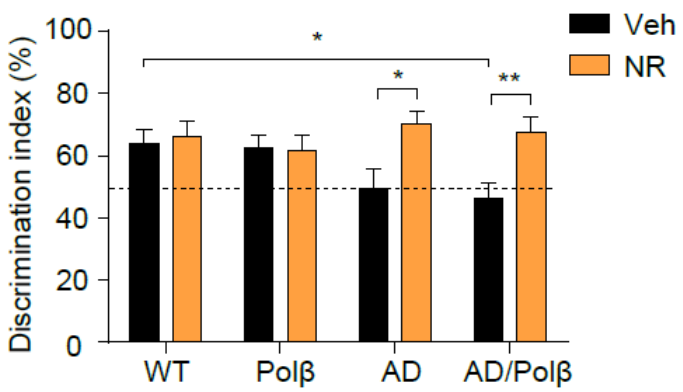


Hou Y et al., PNAS, 2018

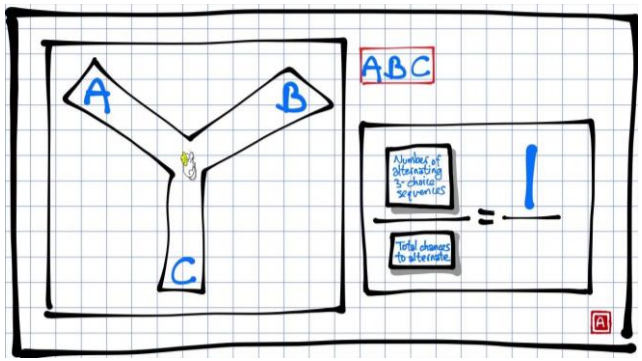
NR ameliorates cognition and memory deficiency in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

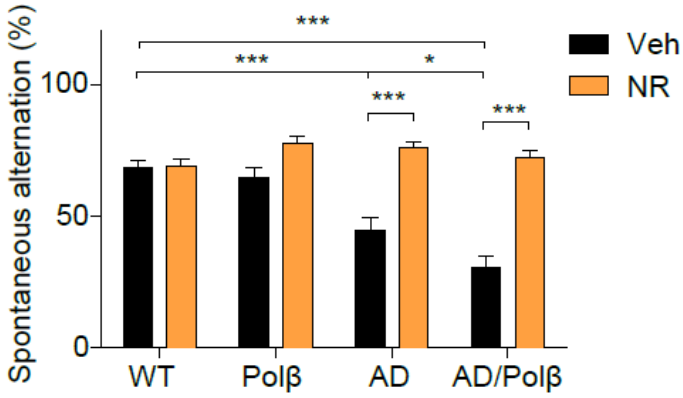
Object Recognition test





Y-maze

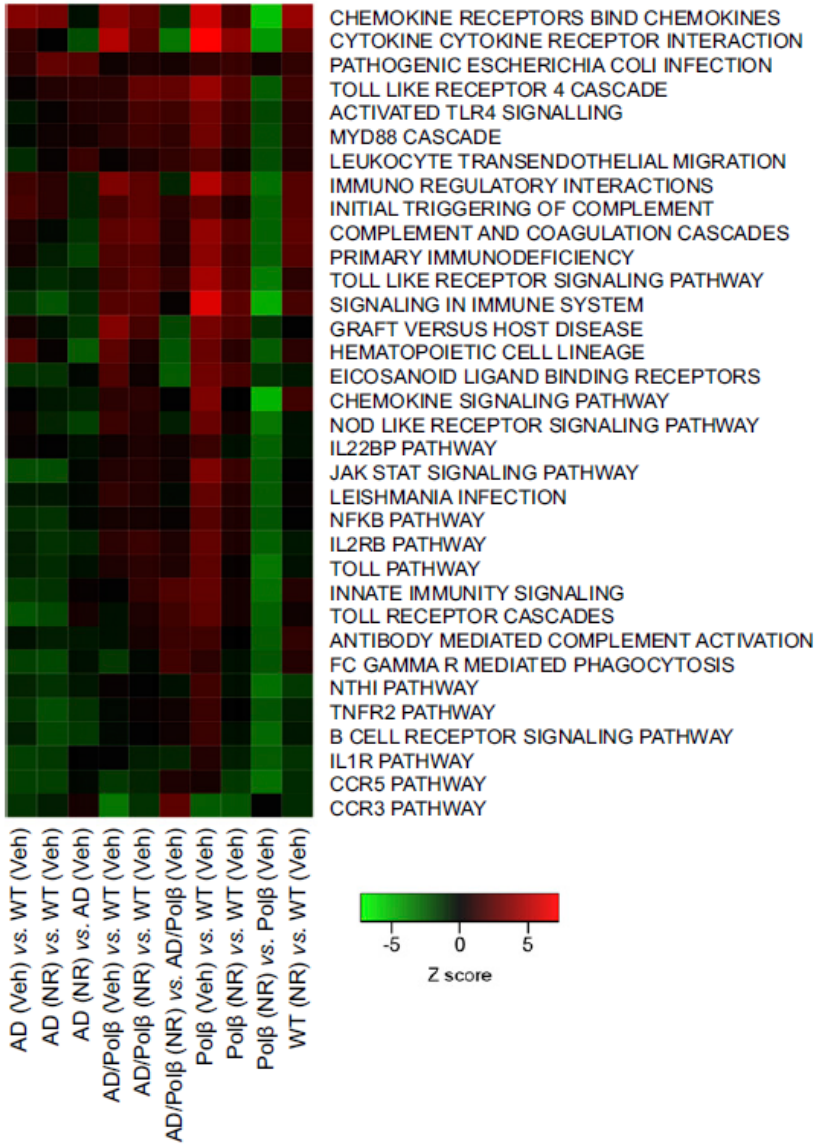




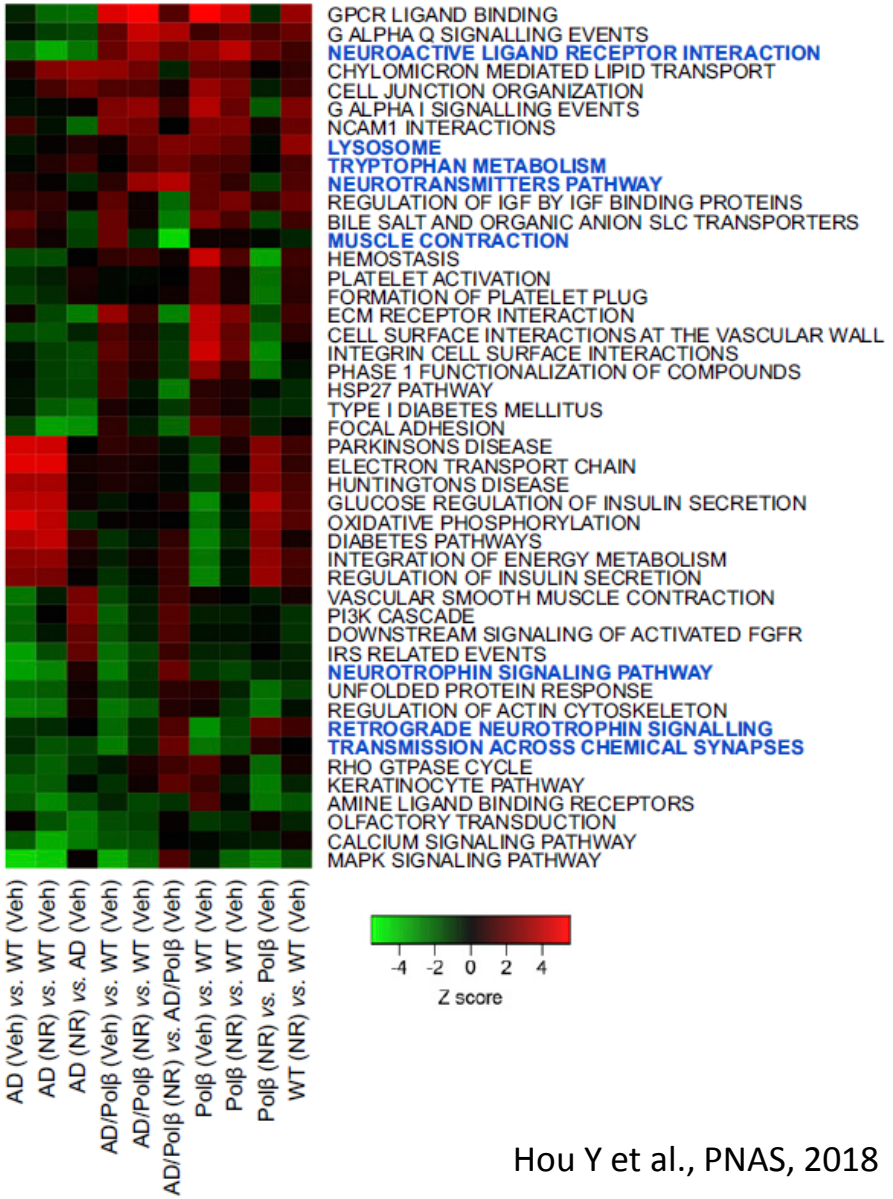
Hou Y et al., PNAS, 2018

Pathway analysis bases on gene expression changes

Hippocampus immune-related pathways

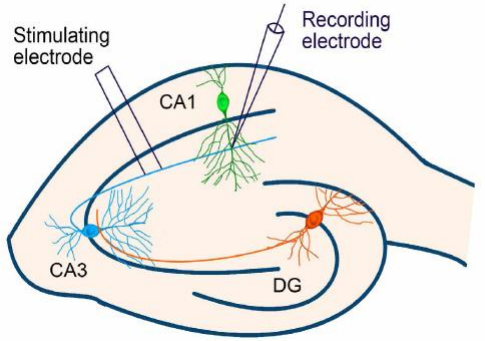


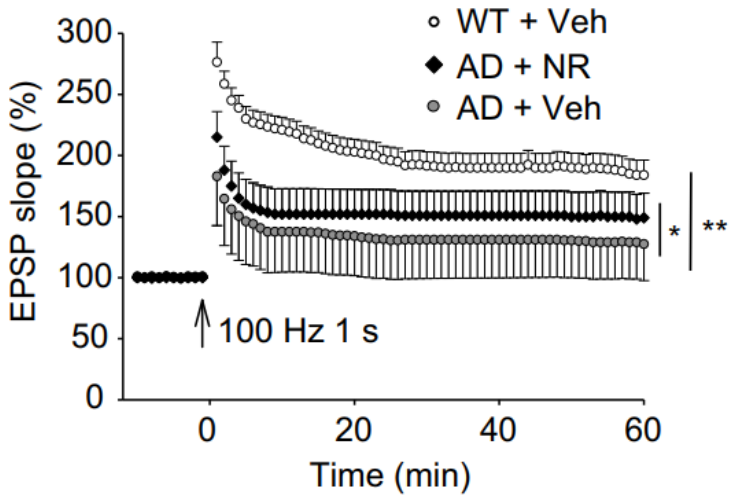
Hippocampus all other pathways

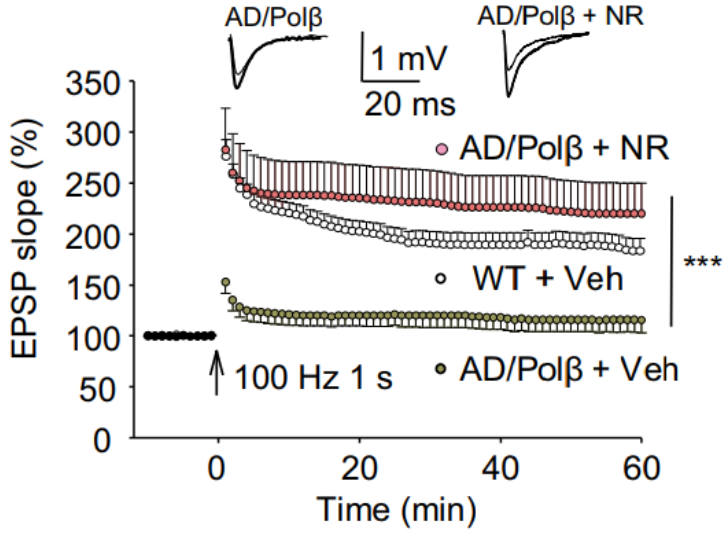


Hou Y et al., PNAS, 2018

NR improves synaptic function in long-term potentiation



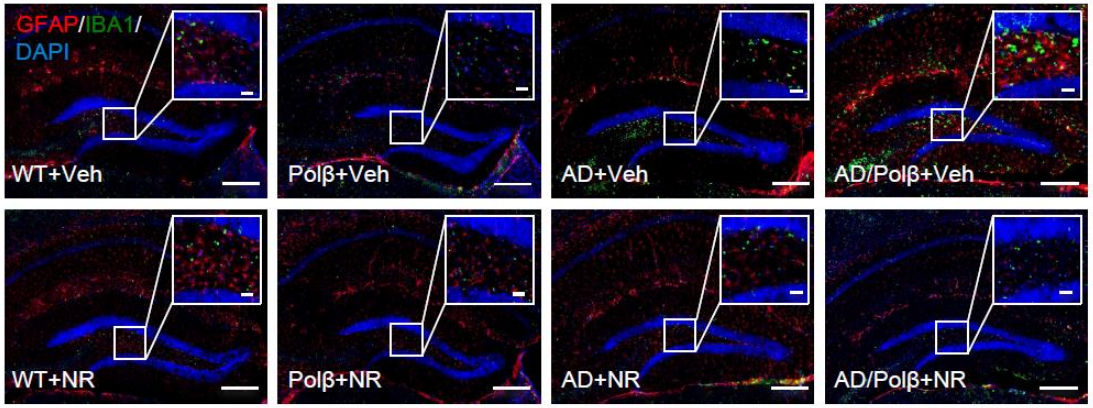


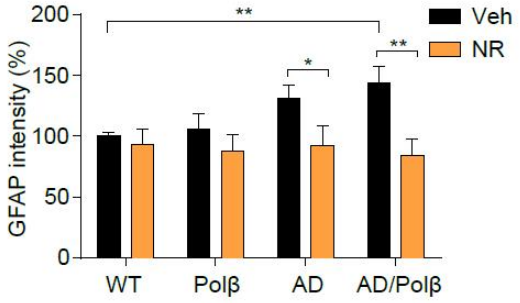


Hou Y et al., PNAS, 2018

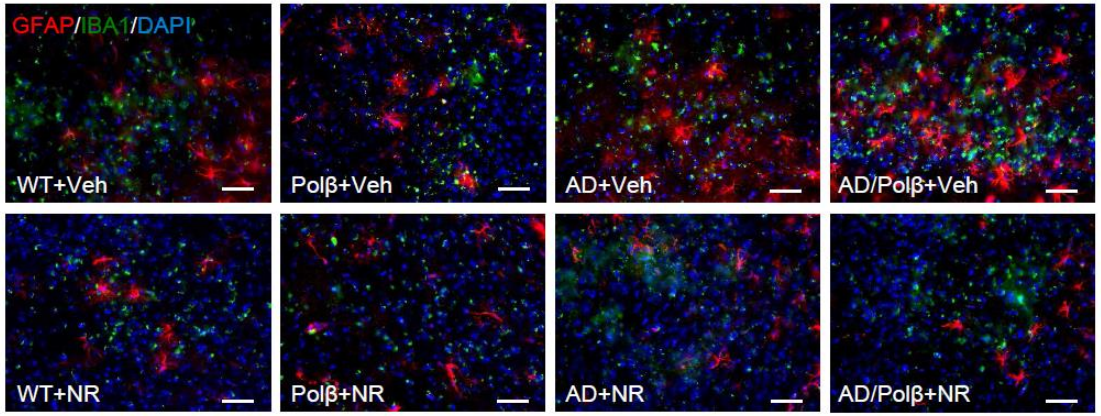
NR decreases neuroinflammation in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

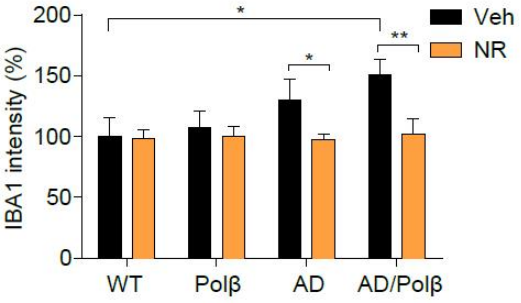
Hippocampus





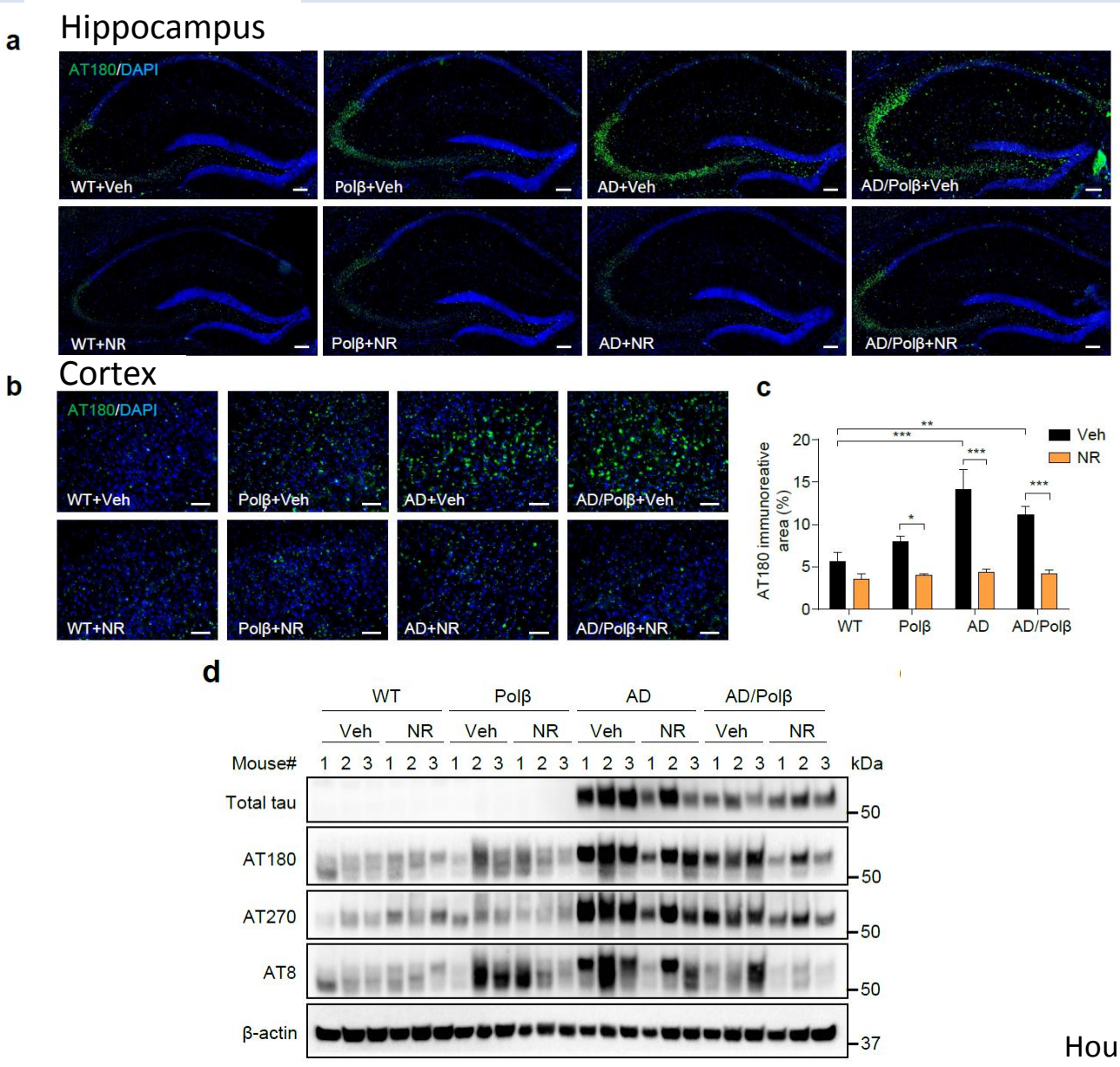
Cortex





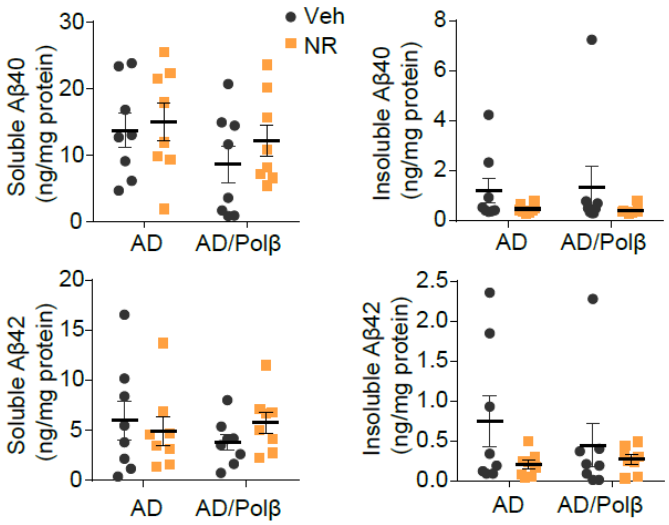
Hou Y et al., PNAS, 2018

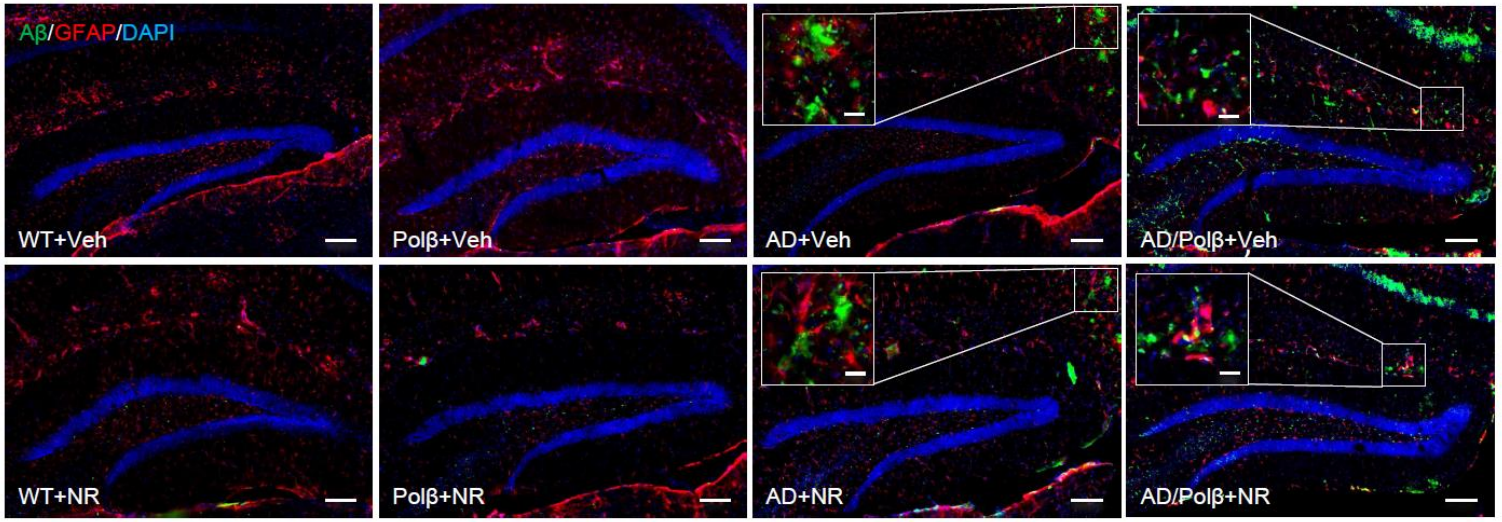
NR decreases tau phosphorylation in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice



Hou Y et al., PNAS, 2018

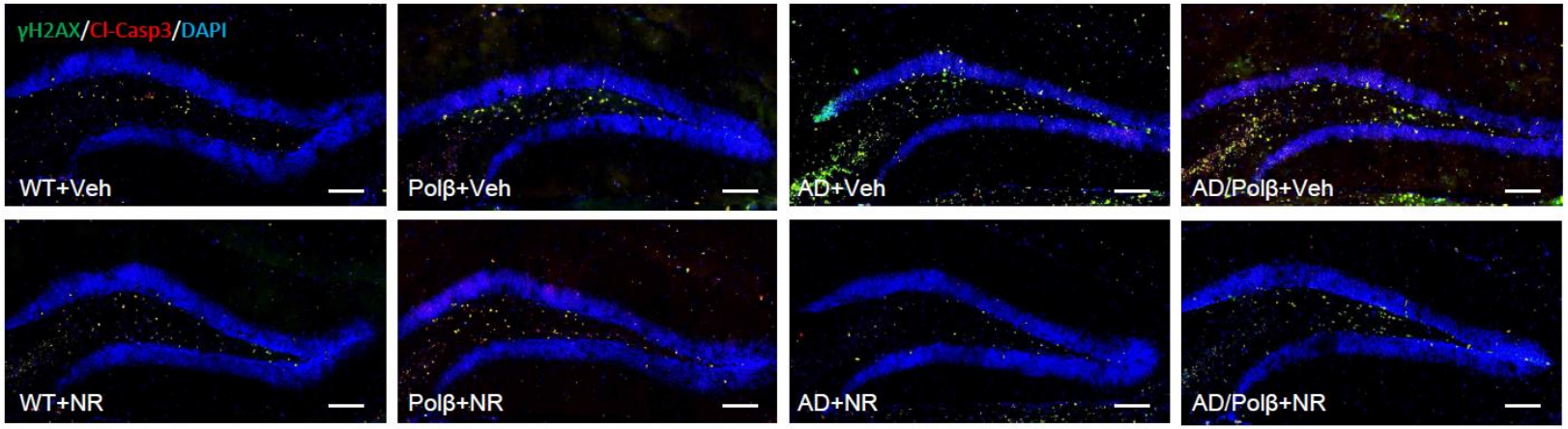
NR doesn't decrease Aβ in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

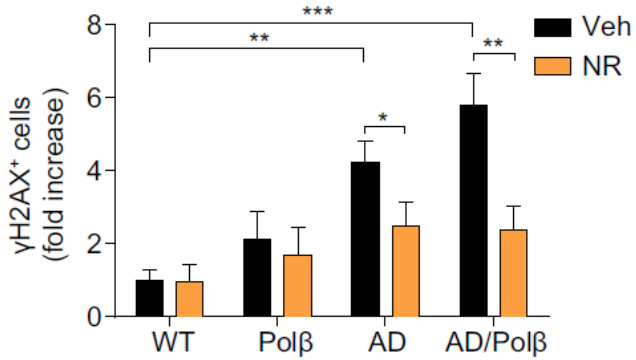


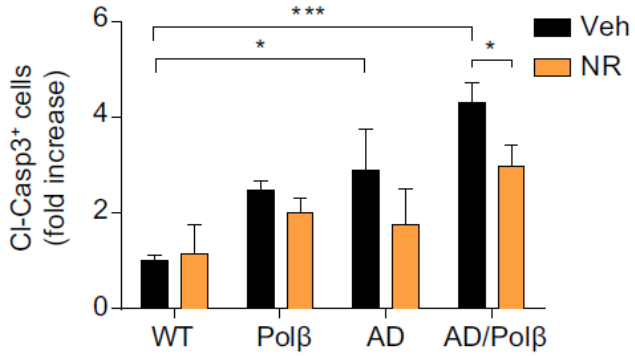


Hou Y et al., PNAS, 2018

DNA damage was decreased after NR treatment in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice

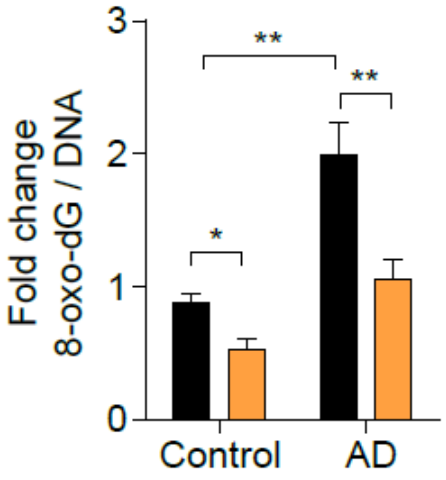


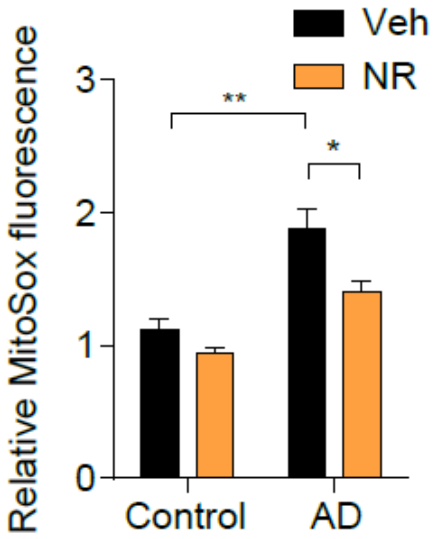




Hou Y et al., PNAS, 2018

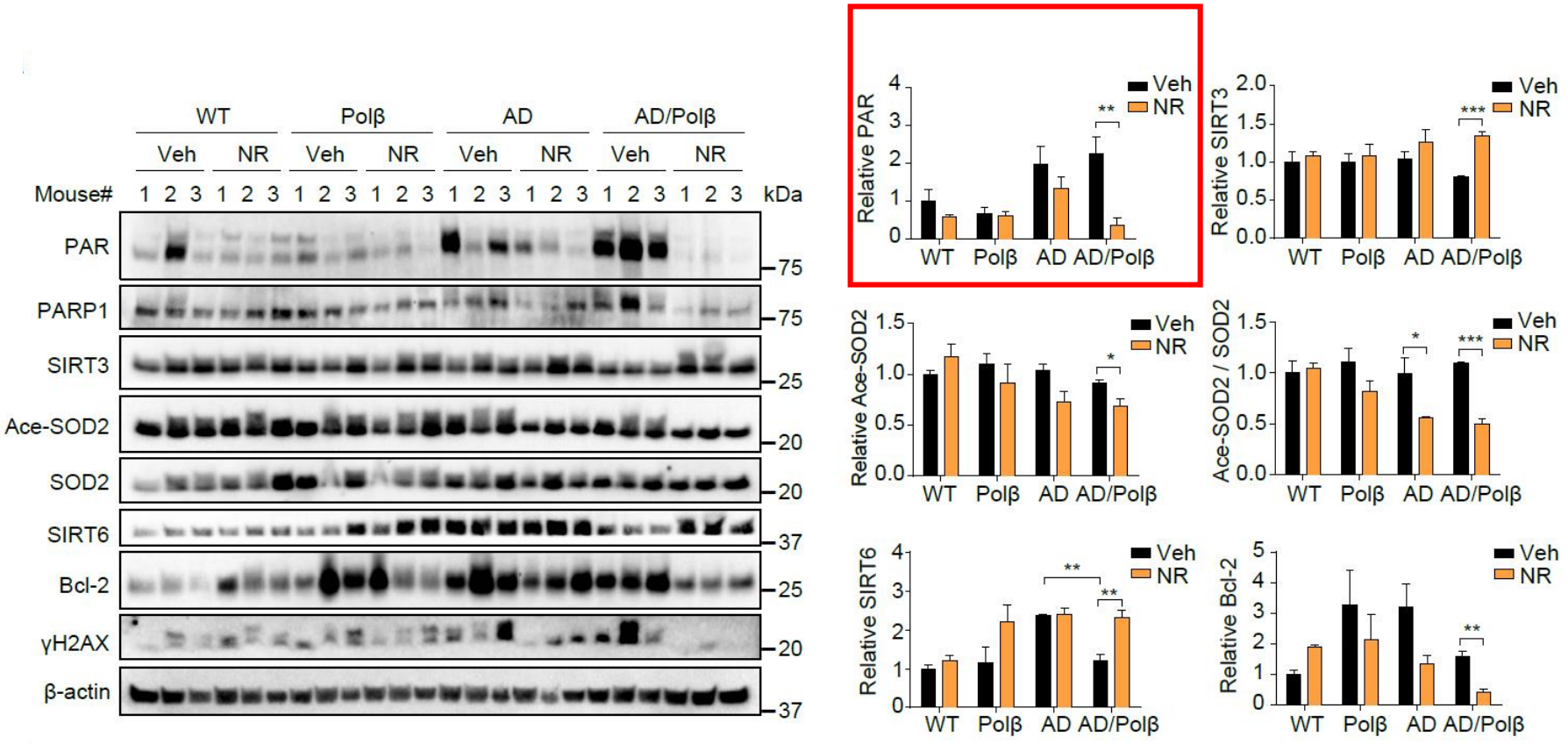
Oxidative damage and mitochondrial ROS was decreased after NR treatment in AD human fibroblasts





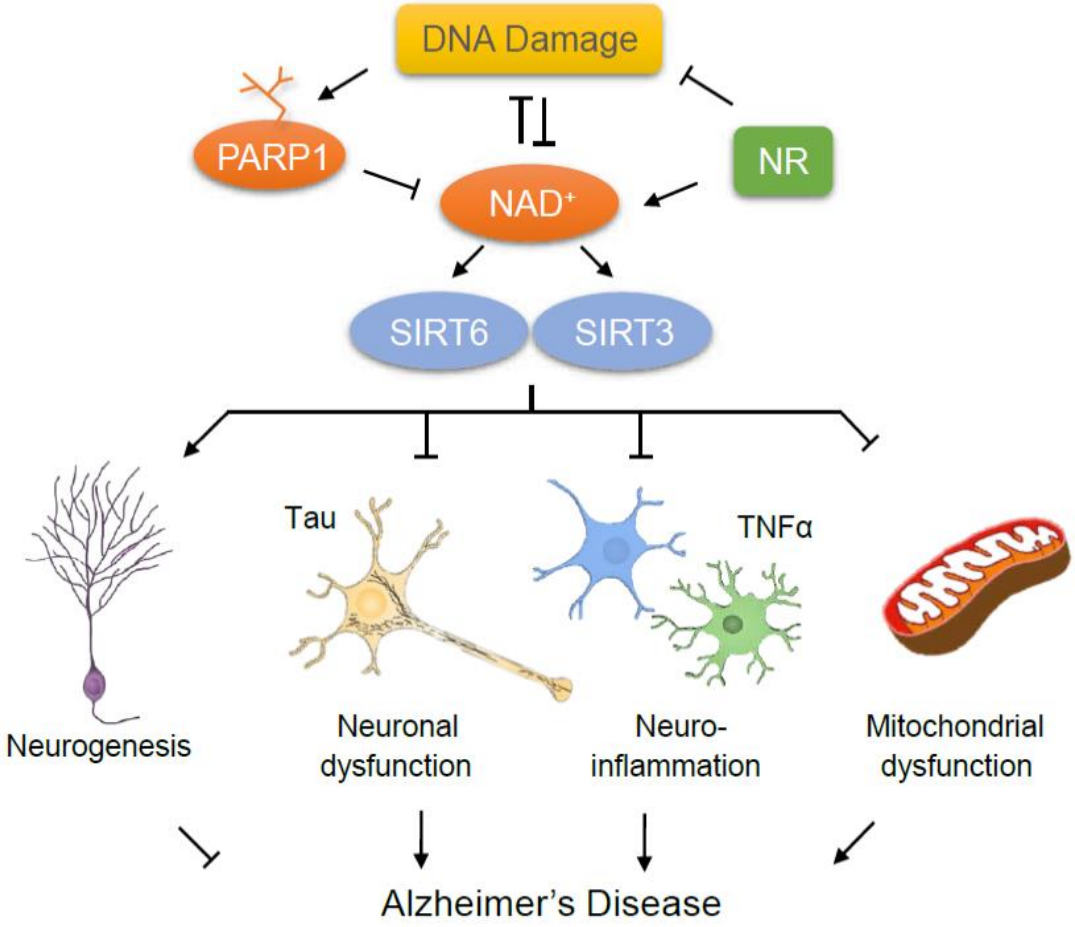
Hou Y et al., PNAS, 2018

SIRT3 and SIRT6 levels are restored after NR treatment in 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice



Hou Y et al., PNAS, 2018

Summary



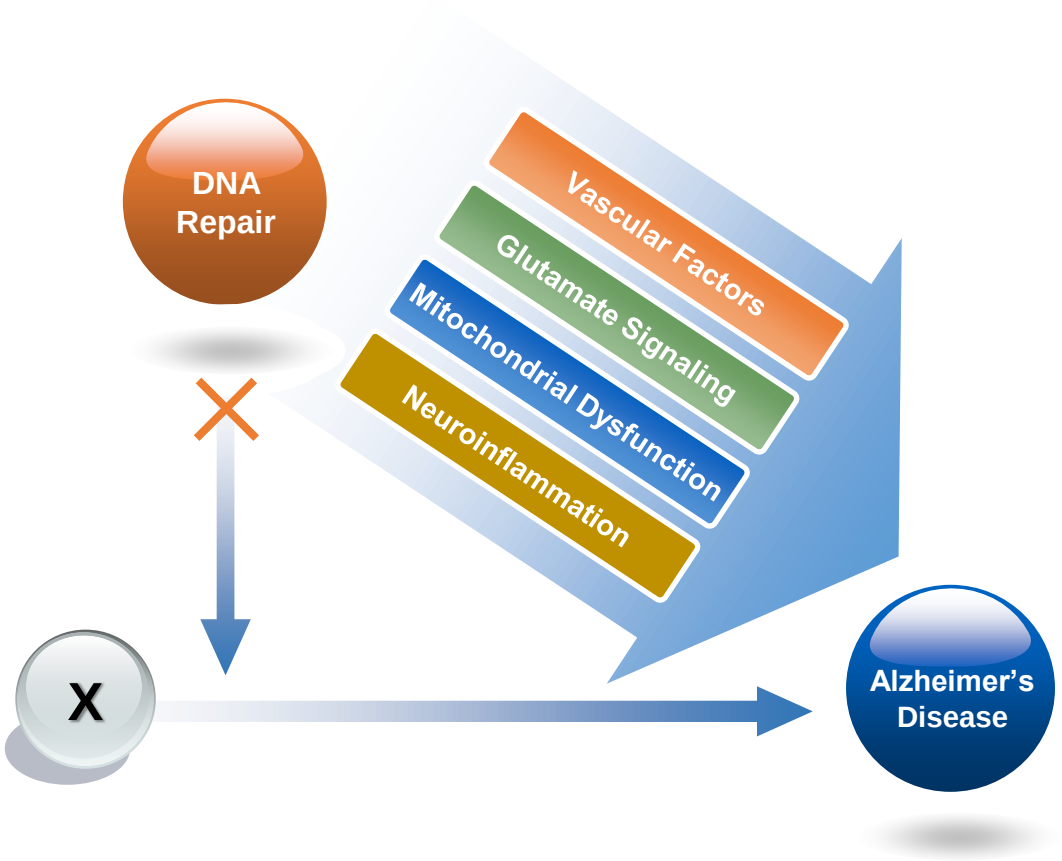
Hou Y et al., PNAS, 2018

Summary

- NAD^+/NADH ratio decreases in $Pol\beta^{+/-}$, 3xTgAD and 3xTgAD/$Pol\beta^{+/-}$ mice and increases after NR treatment
- NAD^+ supplementation improves learning and memory
- NAD^+ supplementation dramatically improve long-term potentiation
- NAD^+ supplementation decreases neuroinflammation and tau phosphorylation but not Aβ in 3xTgAD and 3xTgAD/$Pol\beta^{+/-}$ mice
- DNA damage was decreased after NR treatment in 3xTgAD and 3xTgAD/$Pol\beta^{+/-}$ mice

*Red means NR has better effects in 3xTgAD/$Pol\beta^{+/-}$ than 3xTgAD mice

Future plan



- Investigate neuroinflammatory mechanisms in Polβ deficiency or AD models. Investigate the ability of NR or mitophagy inducers to specifically inhibit neuroinflammation.
- Investigate the effects of mitophagy inducers on mitochondrial function in AD mice.
- Generate another way to determine the role of BER by deleting another BER gene in an AD mouse model.

Modified from **Hou** *et al*., Mechanisms of Ageing and Development, 2016

Acknowledgement

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LCI
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LMBI
Kanako Moritoh

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Thank you for your attention!