The effects of chronic exposure to ambient traffic-related air pollution on Alzheimer's disease phenotypes in wildtype and genetically predisposed male and female rats

Pamela J. Lein, Ph.D.
Department of Molecular Biosciences
UC Davis School of Veterinary Medicine
UC Davis Environmental Health Sciences Center
UC Davis MIND Institute

Individual risk for Alzheimer's disease (AD) is determined by gene-environment interactions

- **Fewer than 5% of AD cases can be attributed solely to genetic factors; twin studies indicate a strong role for environmental factors in AD etiology**
  - **Lifestyle factors, disease history, educational background**
  - **Environmental and occupational exposures to chemicals**
- **Environmental risk factors can be remediated**
  - **Identifying specific environmental factors that increase AD risk is critical for implementing effective public health policies**
- **Near roadway exposures have emerged as a strong candidate risk factor for AD, AD-related dementia (ADRD) and age-related cognitive decline**

Key data gaps

- Impact of chronic exposures to ambient TRAP on AD risk
- Influence of sex on brain response to TRAP
- Identity of pollutants/components of TRAP that contribute to increased AD risk
- Mechanisms by which TRAP modifies AD risk

Preclinical animal models will be needed to address data gaps

- However, most published animal studies employed exposure paradigms that do not capture the complexity and spatiotemporal dynamics of real-world near roadway exposures
  - Composition, dose and timing of TRAP exposures can influence biological outcomes

Our solution

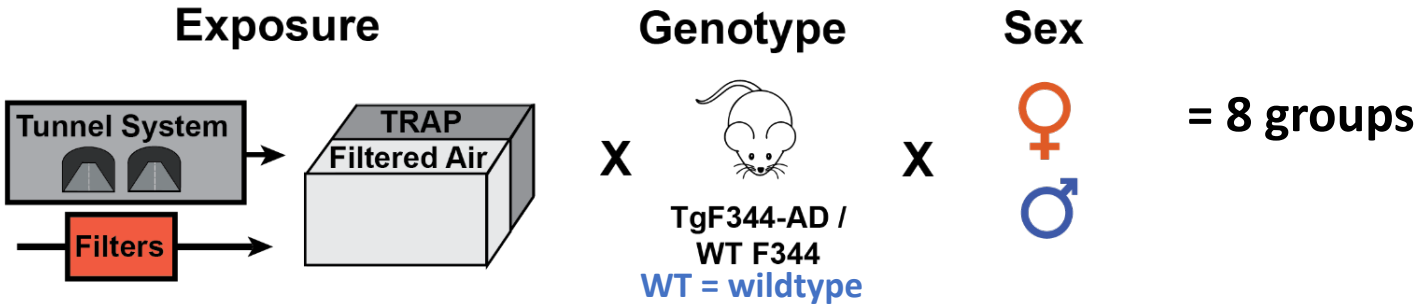
Bein et al. (2022) Emulating near-roadway exposure to traffic-related air pollution via real-time emissions from a major freeway tunnel system. ***Environ Sci Tech*** **56(7):7083-7095**. https://pubs.acs.org/doi/10.1021/acs.est.1c07047

Central Hypothesis

Chronic exposure to Traffic-Related Air Pollution (TRAP) triggers inflammatory responses in the brain that initiate or accelerate the progression of AD depending on

- **sex (AD more prevalent in women)**
- **age (incidence and severity increase with age)**
- **genetic background**

Experimental design



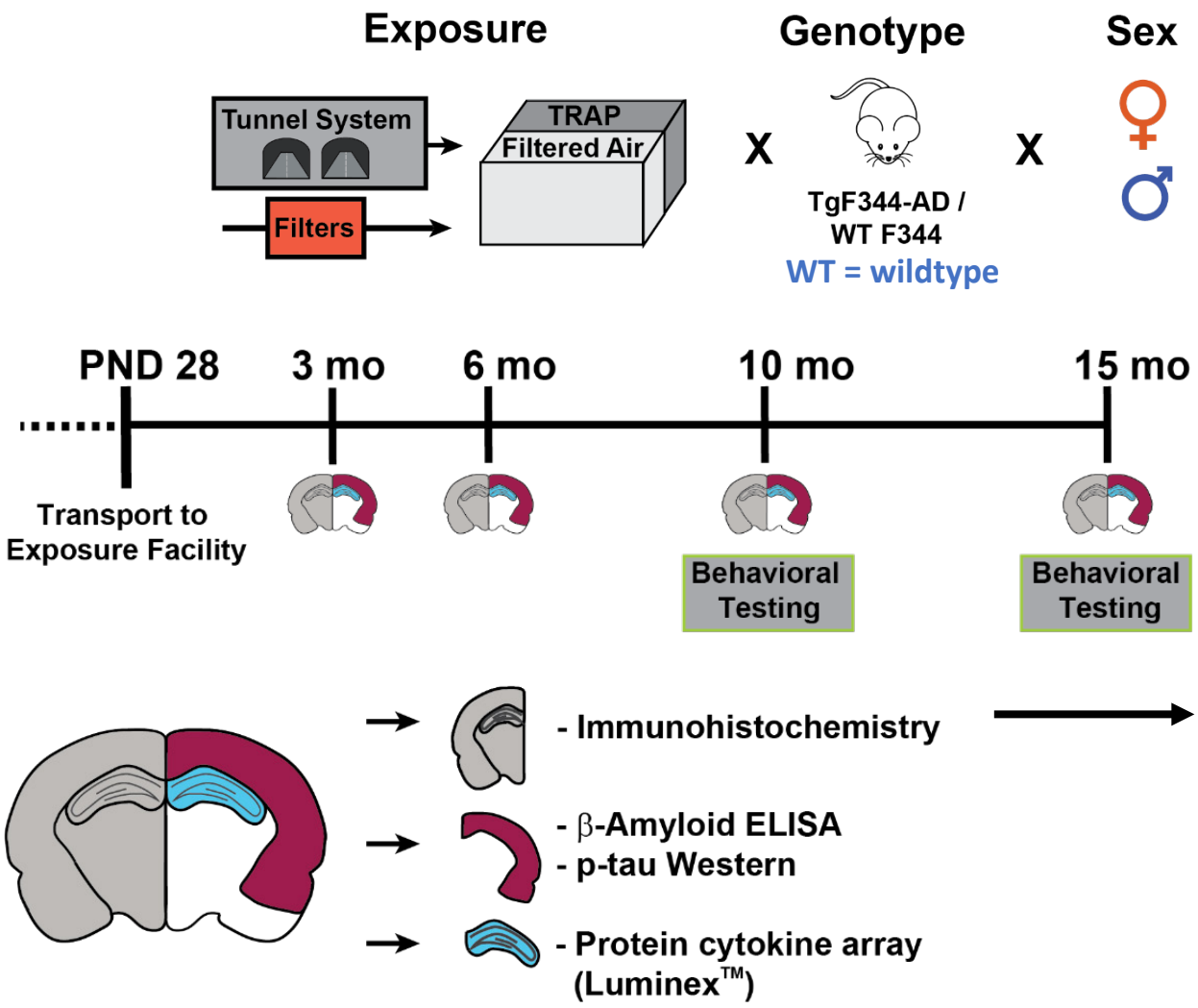
TgF344-AD rat model

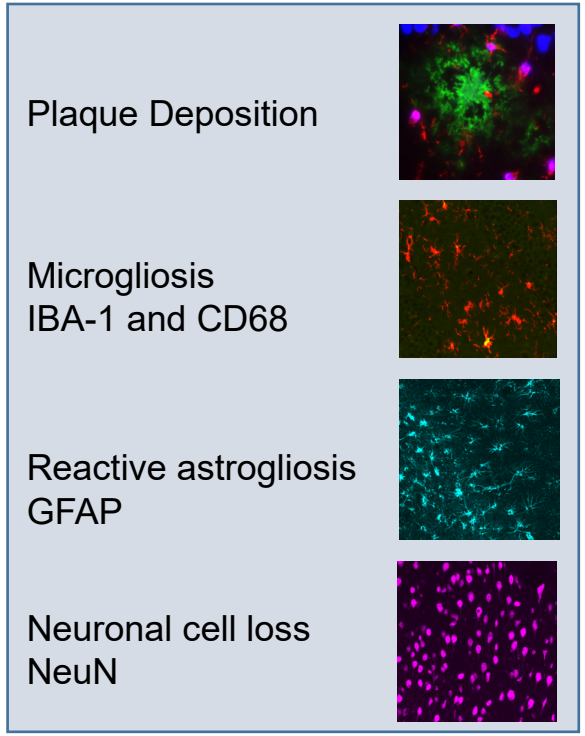
- Overexpresses two human AD risk genes on Fischer 344 background
  - APPswe (K670N, M671L)
  - PS1ΔE9

Cohen, R. M. et al., J Neurosci 33, 6245-6256, (2013)

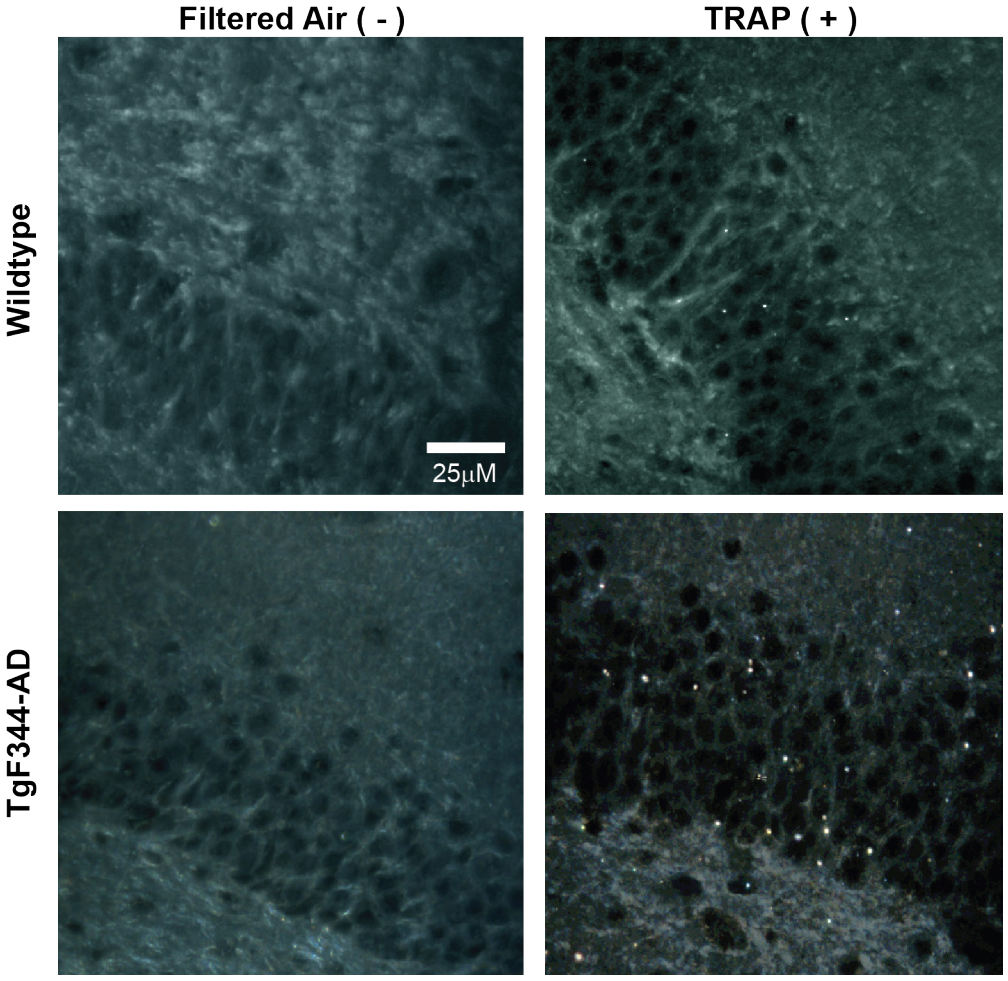
- Recapitulates temporal progression of AD pathology observed in humans

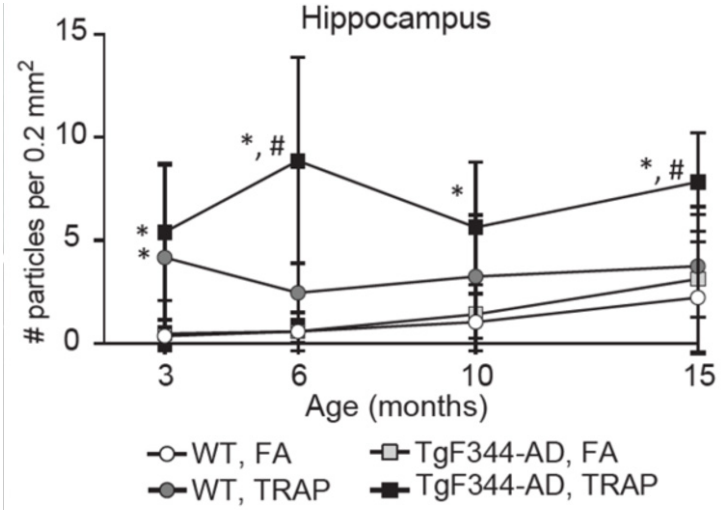
Experimental design

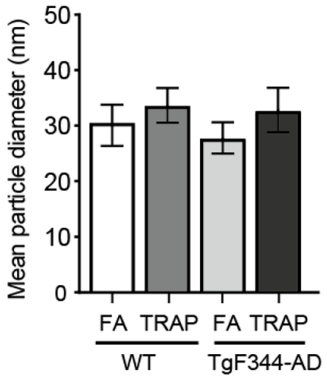


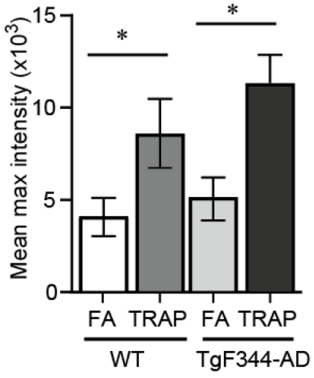


Refractive particles were present in the hippocampus





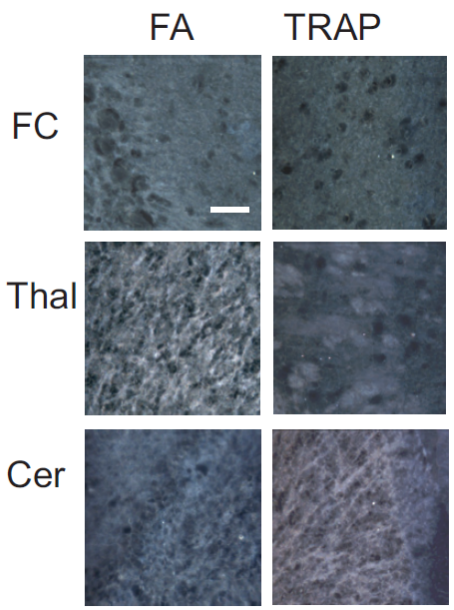




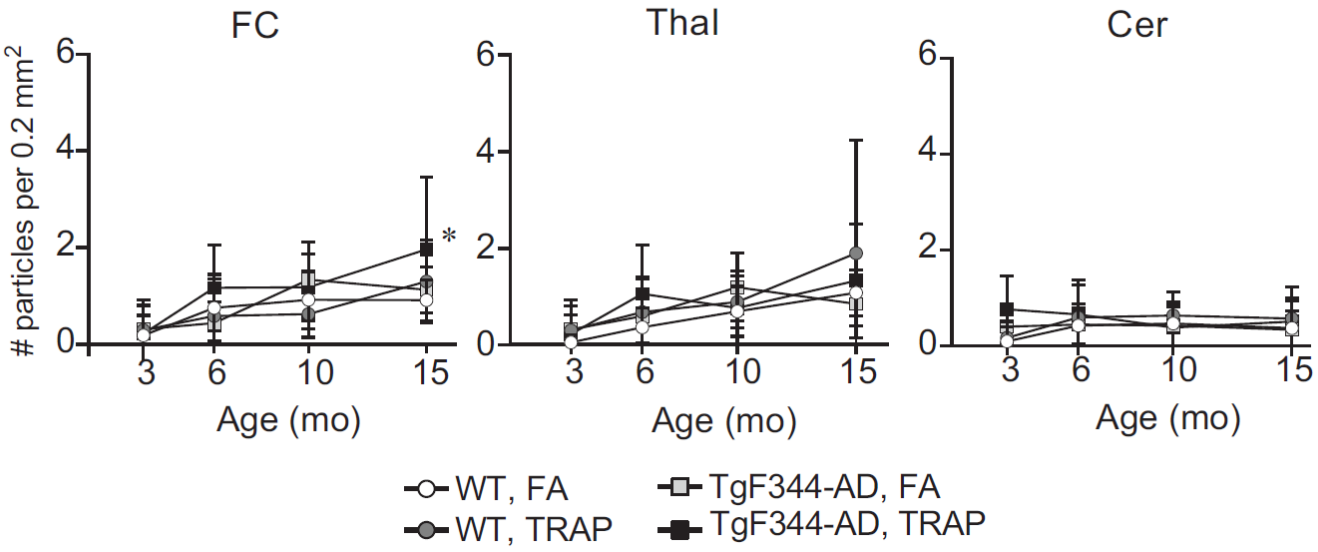
Representative images from 6 mo dentate gyrus (DG)

Patten et al., 2021, *Environ Health Perspect*

Significantly fewer refractive particles were detected in other brain regions of TRAP-exposed animals



FC = Frontal cortex; Thal = thalamus; Cer = cerebellum

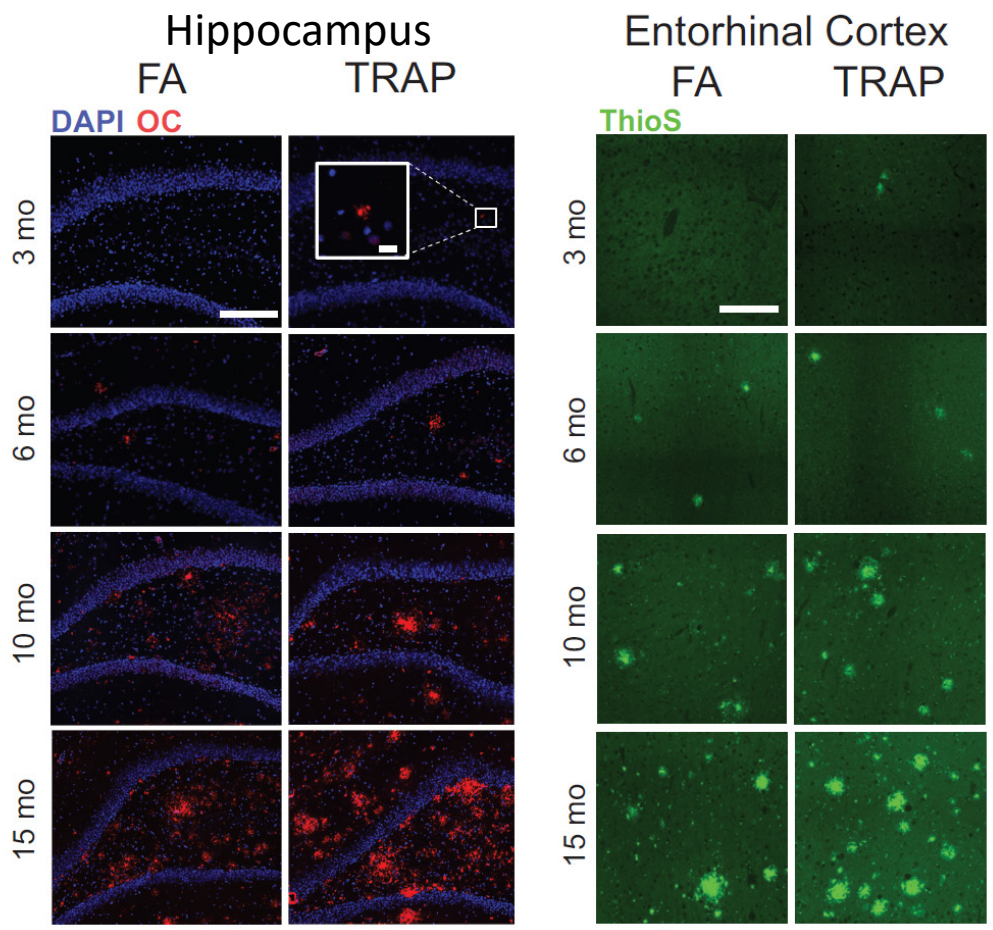


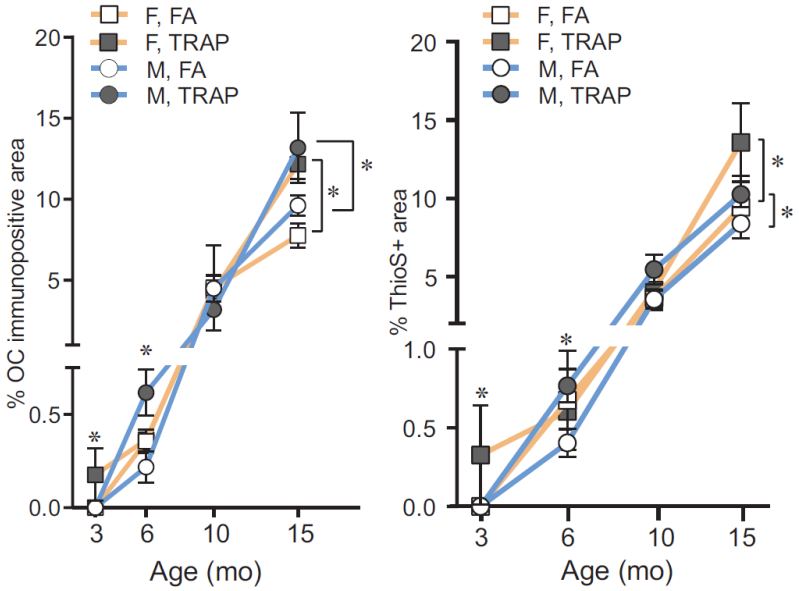
The significantly decreased number of particles in the frontal cortex relative to the hippocampus suggests retrograde transport of particles from the nose to the olfactory bulb is not the predominant route by which particles are accessing the brain.

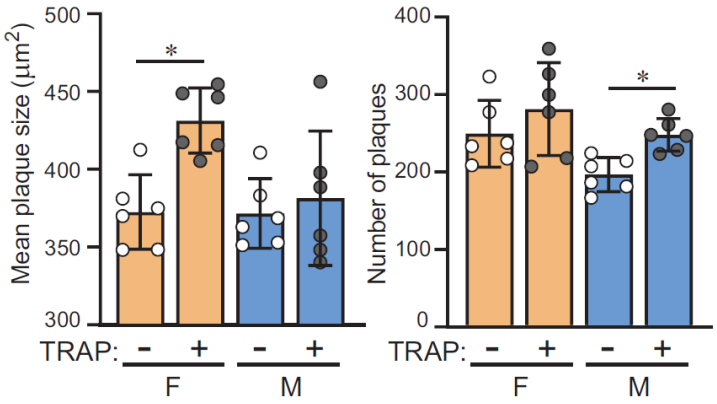
Patten et al., 2021, *Environ Health Perspect*

TRAP exposure accelerated and exacerbated plaque burden in TgF344-AD rats

- **No plaques found at any age in wildtype animals**







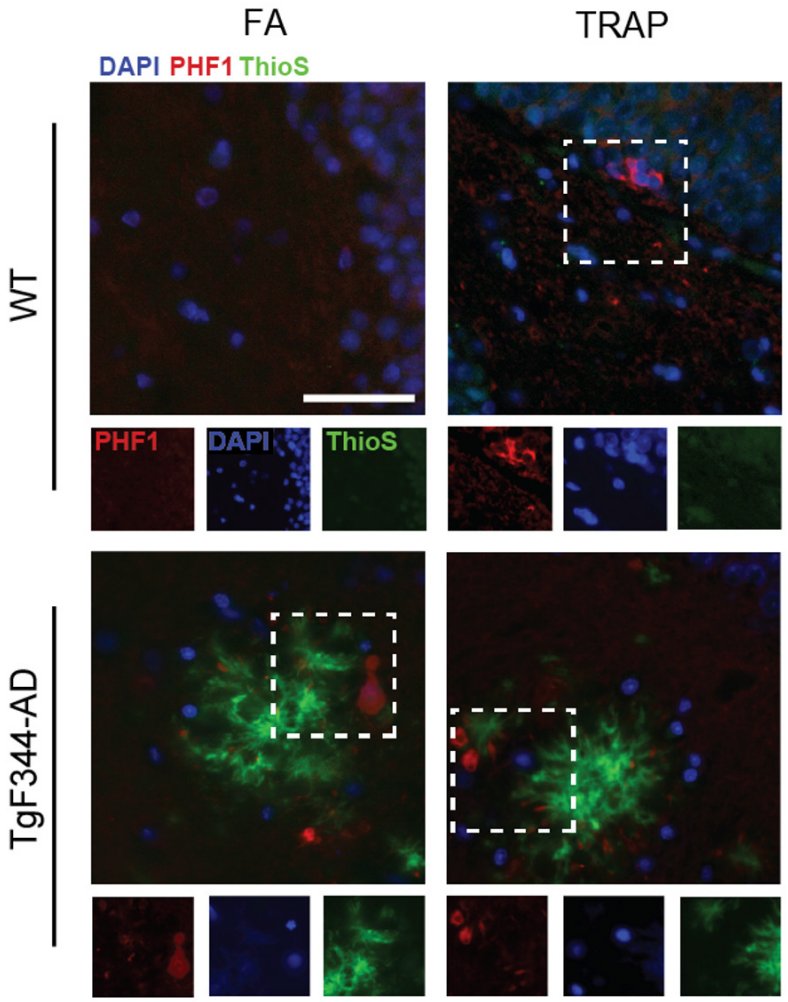
Patten et al., 2021, *Environ Health Perspect*

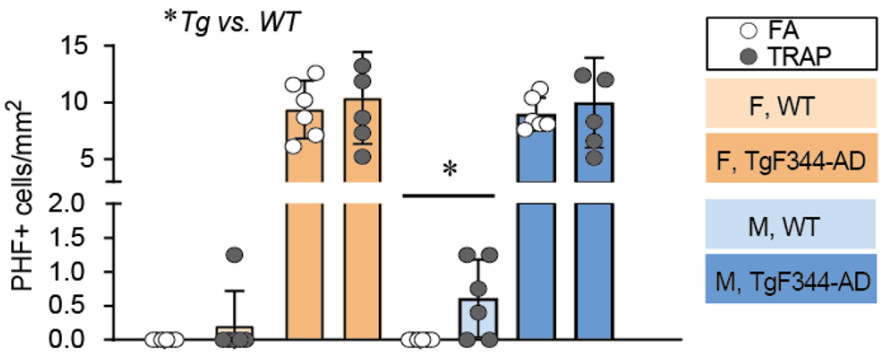
TRAP exposure increased soluble Aβ 42:40 ratio in cortical tissue of Tg3444-AD rats

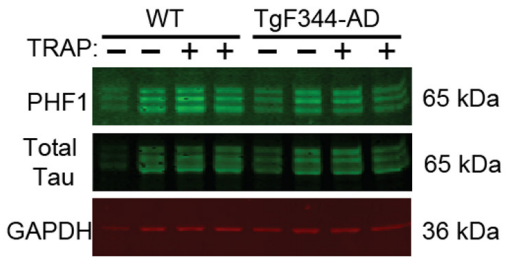
- **Aβ 1-42 is thought to be more neurotoxic than Aβ 1-40**
- **Ratio of Aβ 42:40 often used in diagnosis of human AD**
  - **Correlates better with cognitive decline/pathology than Aβ42 alone**
- **TRAP significantly increased Aβ 42:40 ratio**
  - **At 15 months in female Tg rats**
  - **At 10 and 15 months in male Tg rats**

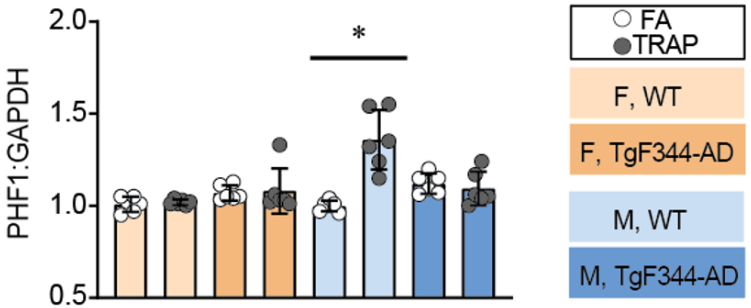
Patten et al., 2021, *Environ Health Perspect*

TRAP increased tau phosphorylation (pTau) in 15 month old male wildtype (WT) rats



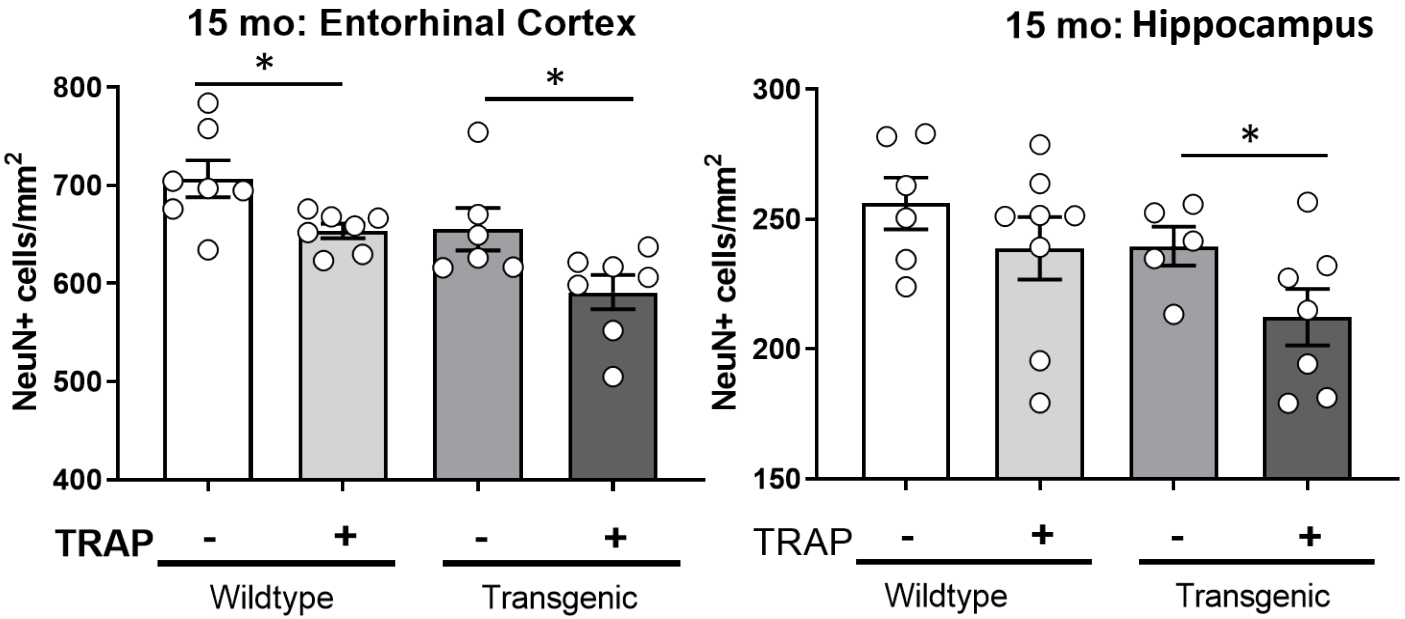






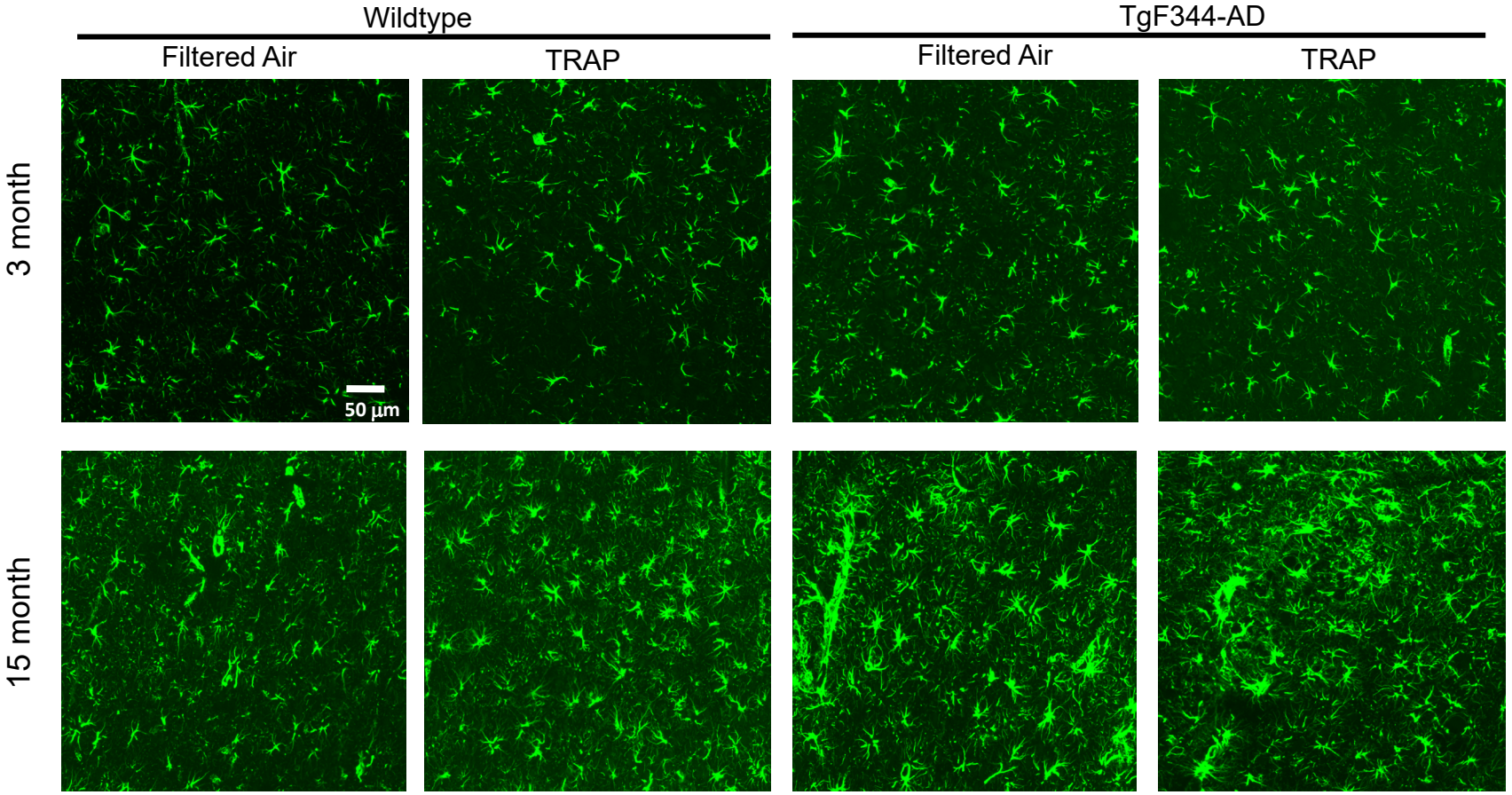
Patten et al., 2021, *Environ Health Perspect*

TRAP exposure exacerbated neuronal cell loss in 15-month-old rats (male and female)



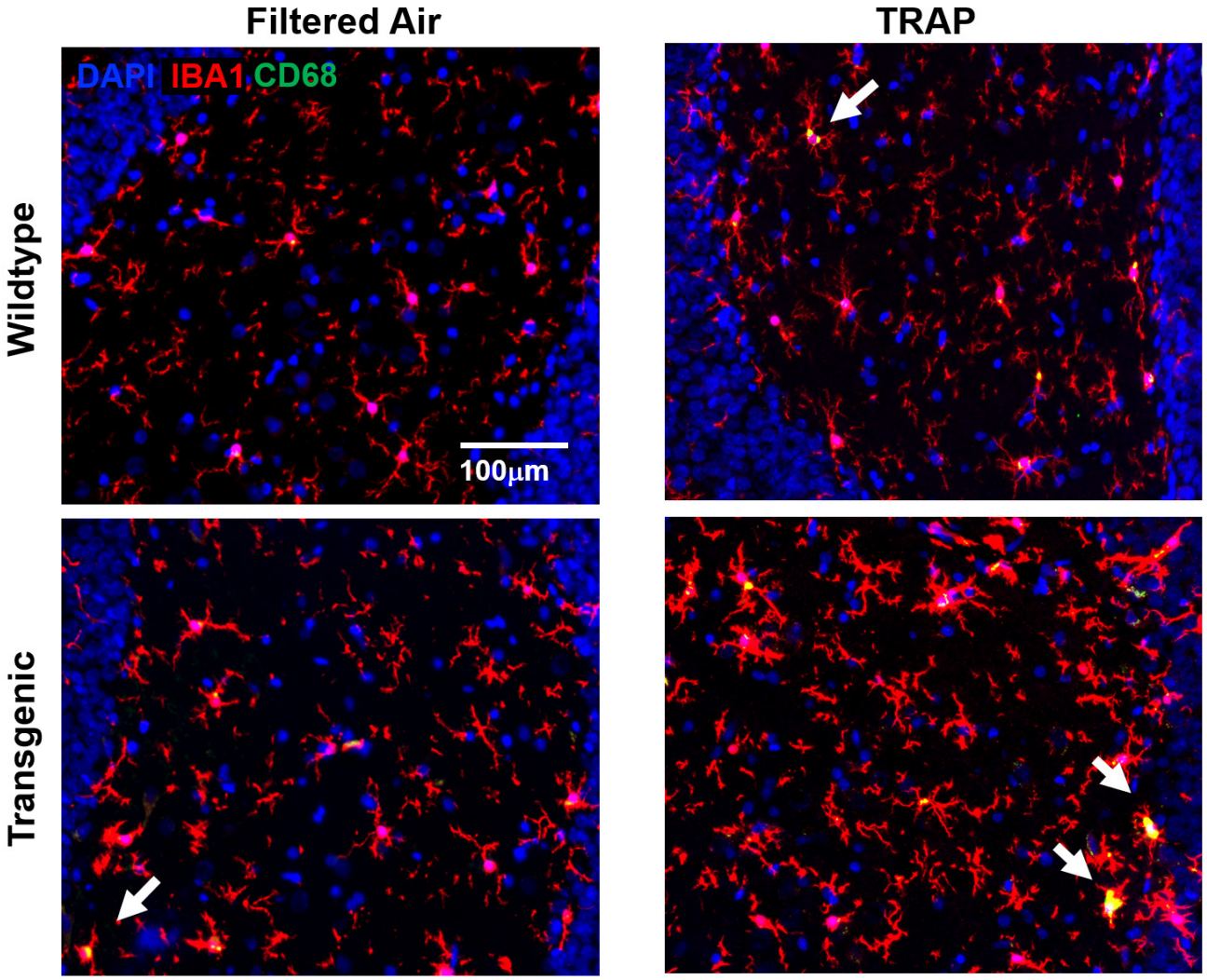
Patten et al., 2021, *Environ Health Perspect*

Genotype and age, but not TRAP exposure, increased GFAP immunoreactivity



Patten et al., 2021, *Environ Health Perspect*

In contrast, TRAP activated microglia



Representative images of hippocampus in 6 mo old female; IBA1-immunopositive cells (microglia) co-labeled for CD68 – a marker of phagocytic cells

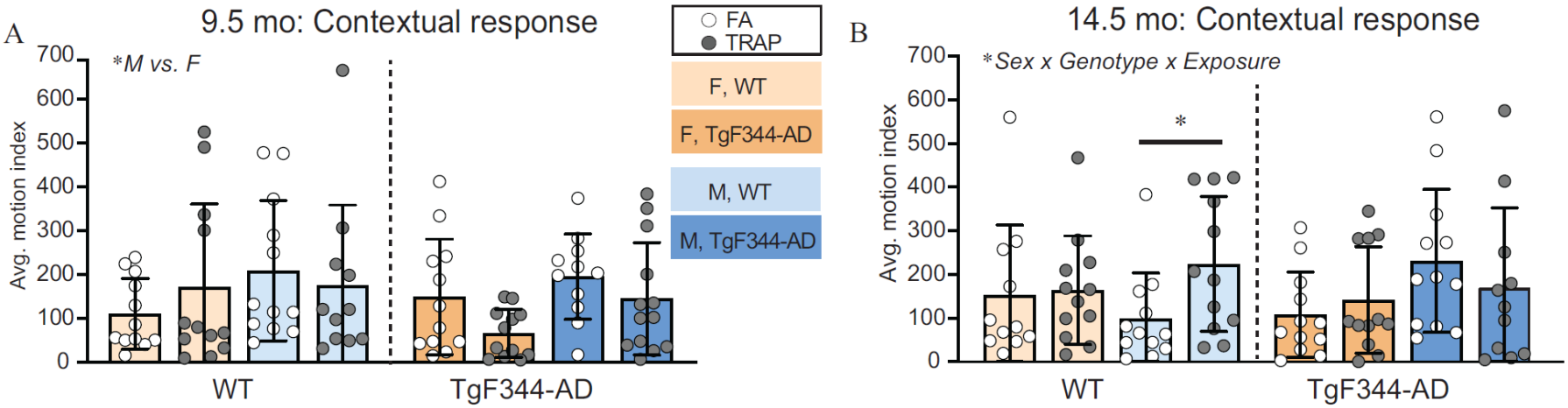
Patten et al., 2021, *Environ Health Perspect*

Summary of TRAP effects on microglia

- **TRAP did not change the number of microglial cells per unit area in the hippocampus**
- **However, TRAP increased the % of microglia that were phagocytic (CD68+)**
  - **TRAP *increased microglial activation* in both male and female wildtype and TgF344-AD rats at younger ages**
  - **TRAP *decreased microglial activation* in female wildtype and TgF344-AD rats at older ages, but *increased microglial activation* in male wildtype and TgF344-AD rats**

Patten et al., 2021, *Environ Health Perspect*

TRAP promoted cognitive deficits in male wildtype rats



Learning and memory tested using fear conditioning

Increase in average motion index indicates deficit in learning and memory

Patten et al., 2021, *Environ Health Perspect*

Summary of TRAP effects in TgF344-AD (Tg) and wildtype (WT) rats

Female	3 mo	6 mo	10 mo	15 mo
Plaque Deposition	↑ (Tg)			↑ (Tg)
Aβ42:40 ELISA				↑ (Tg)
Neuronal Cell Loss*				↑ (Tg, WT)
pTau				
Memory Deficits				
CD68/IBA1	↑ (Tg, WT)	↑ (Tg)		↓ (Tg, WT)

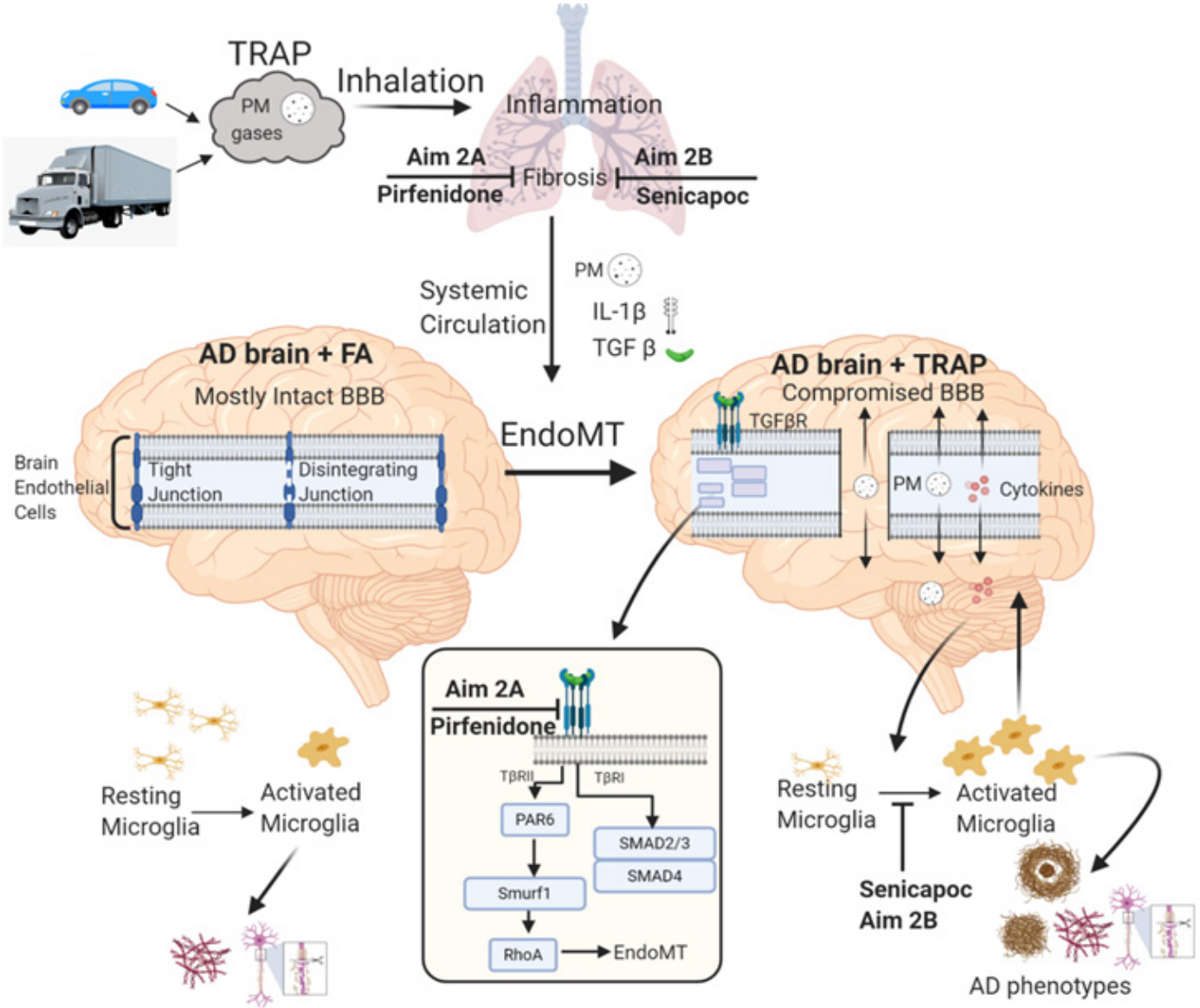
Male	3 mo	6 mo	10 mo	15 mo
Plaque Deposition		↑ (Tg)		↑ (Tg)
Ab42:40 ELISA			↑ (Tg)	↑ (Tg)
Neuronal Cell Loss*				↑ (Tg, WT)
pTau				↑ (WT)
Memory Deficits				↑ (WT)
CD68/IBA1		↑ (Tg)		↑ (Tg, WT)

*only measured at 15 months (mo)

Key data gaps

- **Impact of chronic exposures to ambient TRAP on AD risk**
- **Influence of sex on brain response to TRAP**
- **Identity of pollutants/components of TRAP that contribute to increased AD risk**
- **Mechanisms by which TRAP modifies AD risk**

Ongoing studies……



Overall Conclusions

- **Chronic exposure to ambient TRAP promoted AD phenotypes in wildtype and genetically susceptible rats**
  - **As observed in humans, specific effects are age, genotype and sex-dependent**
- **Evidence implicated microglial activation in TRAP effects but it is complicated…..**
- **Findings suggest that current PM2.5 regulations are insufficient to protect the aging brain**

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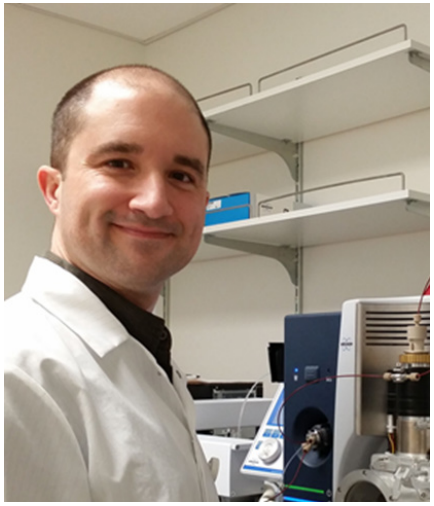

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Questions?