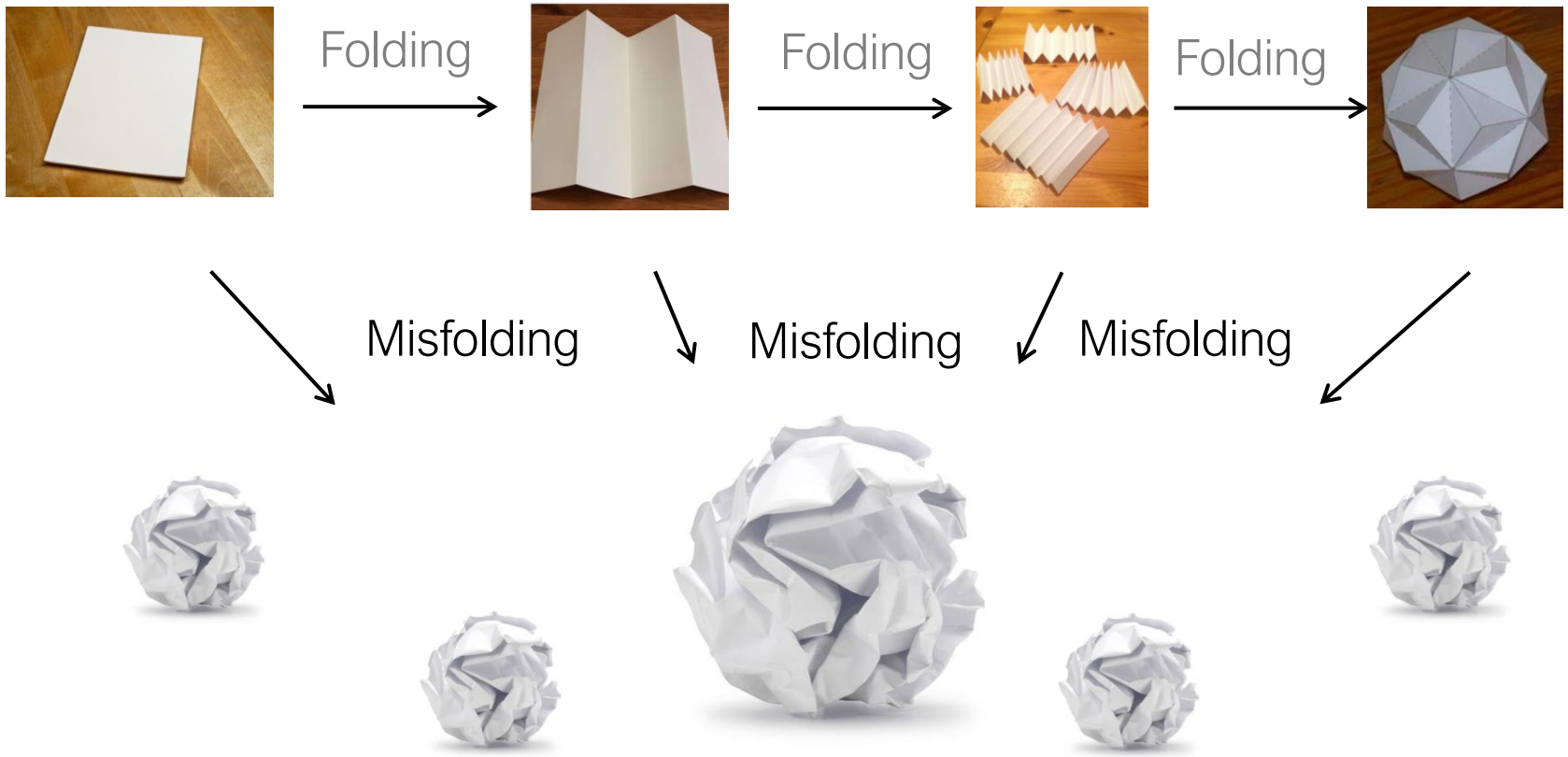
Amyloid-beta spreading from the olfactory bulb

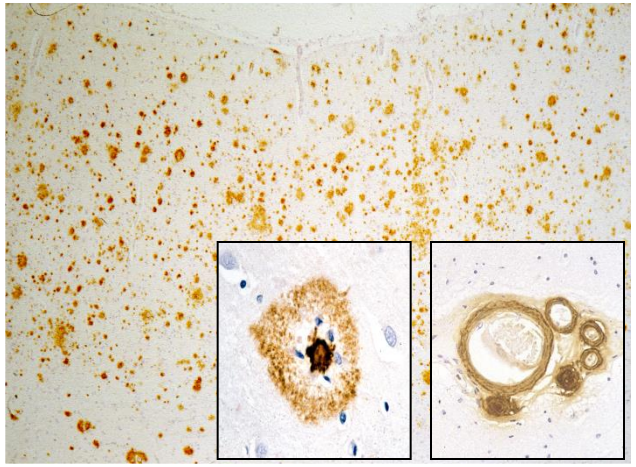
13.11.2024

Melanie Meyer-Luehmann

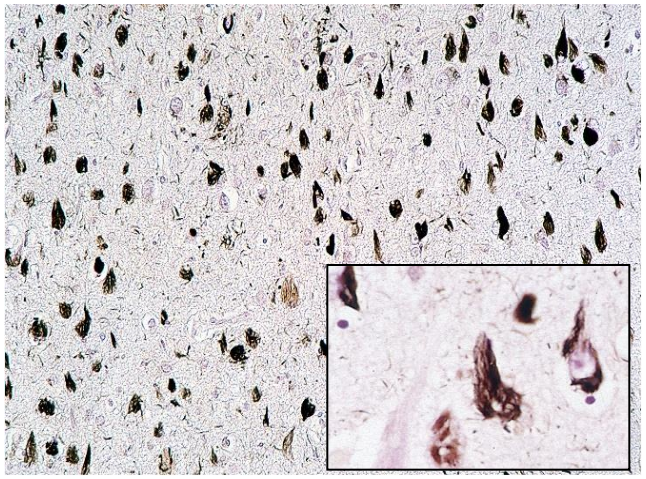
Alzheimer’s disease – protein misfolding disease



Alzheimer’s disease – Neuropathological hallmarks

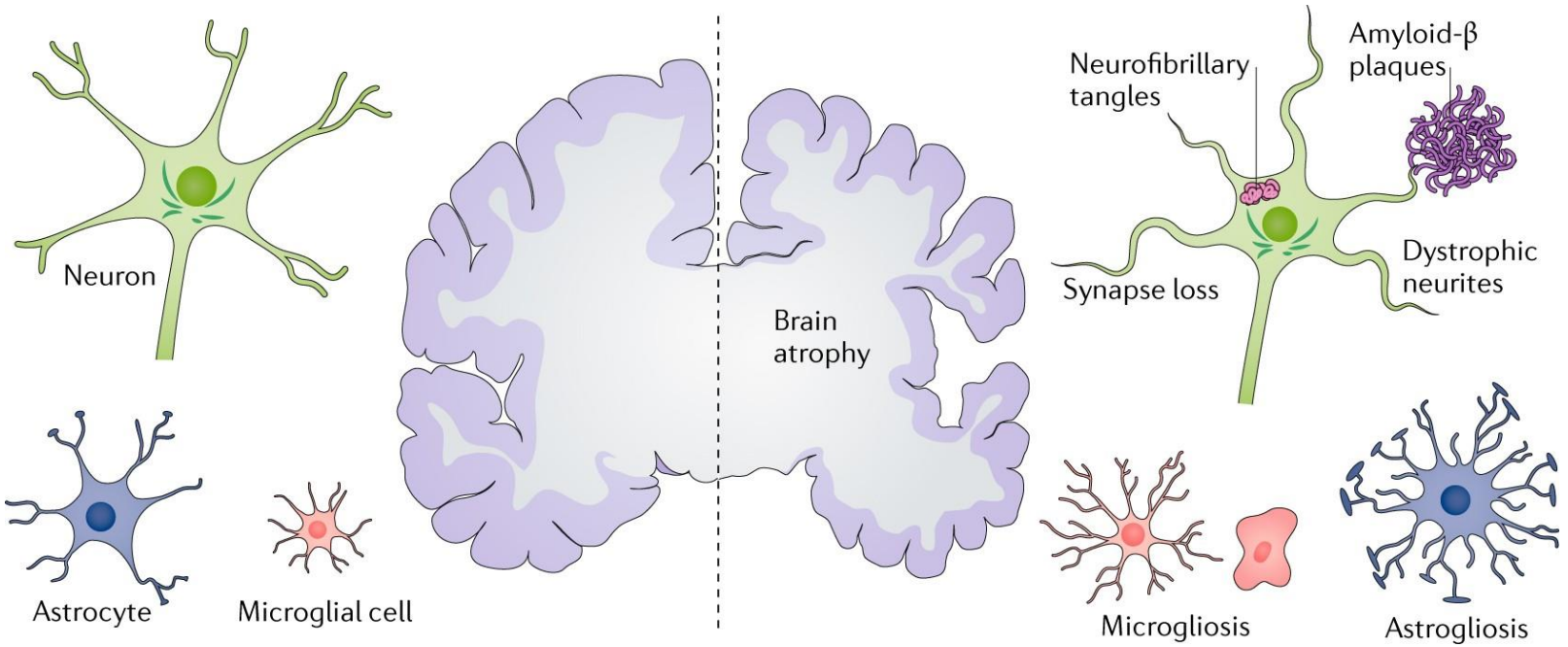


- amyloid-β plaques



- neurofibrillary tangles

AD – a complex multicellular disease



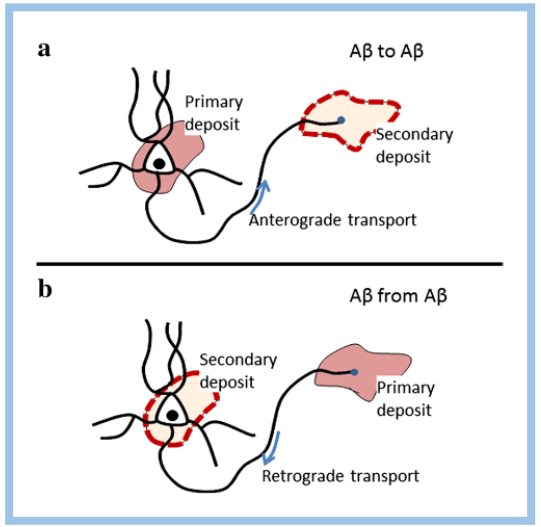
Congdon and Sigurdsson, 2018

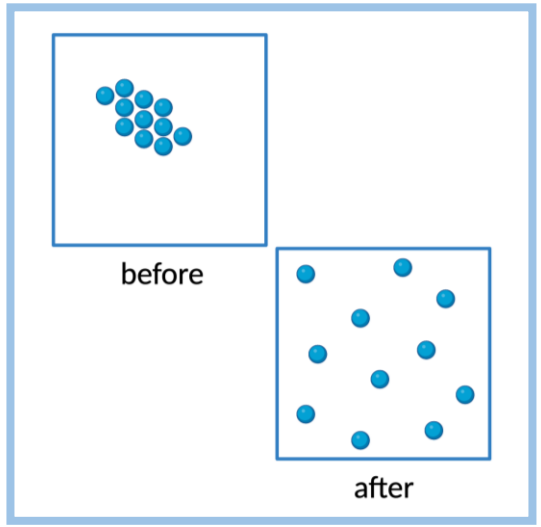
- microgliosis
- astrogliosis

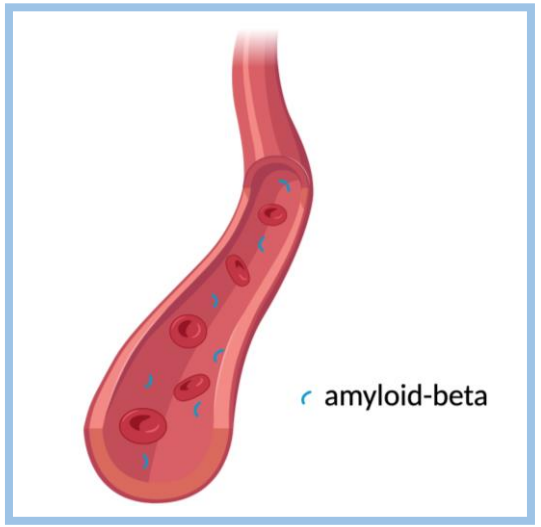
Possible spreading mechanisms

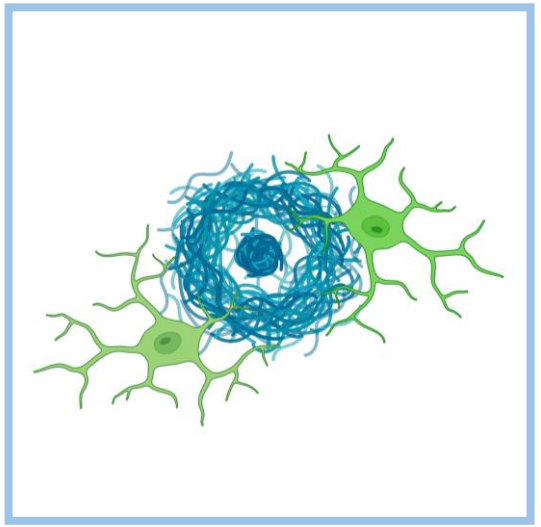
Proposed spreading routes:

- neuronal connections
- passive diffusion
- vasculature
- microglia?



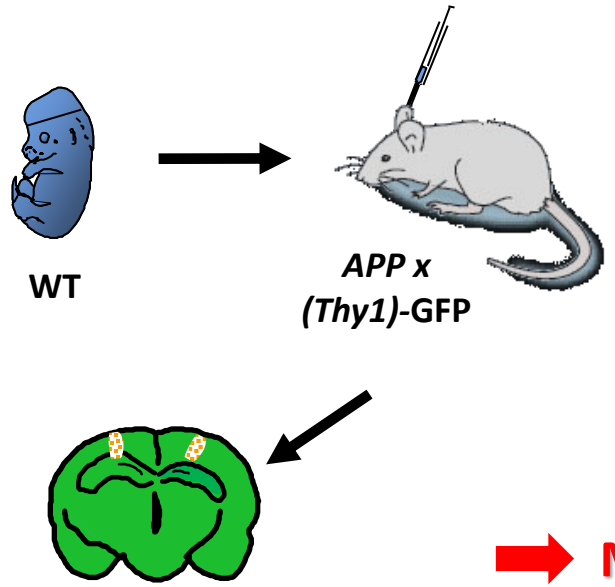


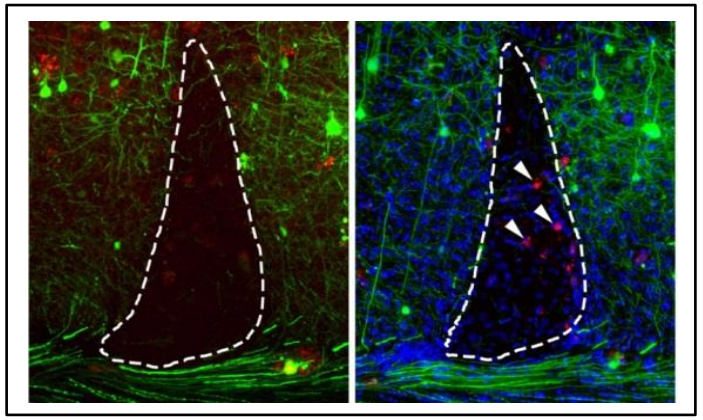




→ Are microglia involved the spread of Aβ pathology?

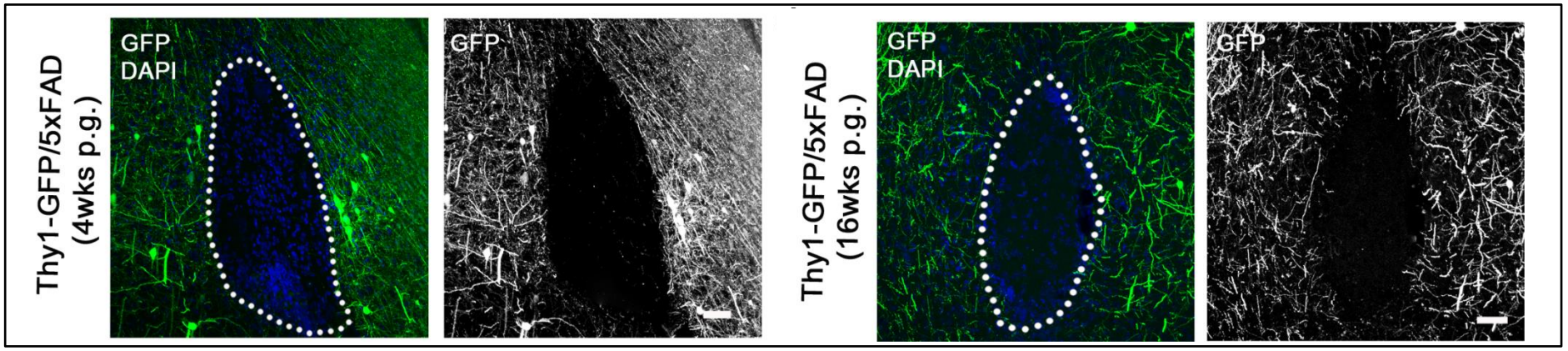
Aβ plaque formation in cortical WT transplants





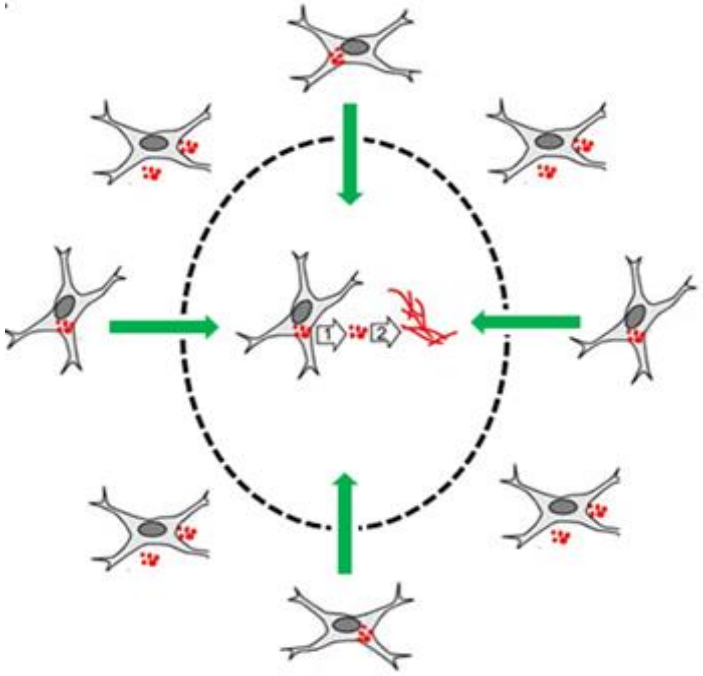
Meyer-Luehmann et al. Nat Neurosci, 2003
Bachhuber et al. Nat Med, 2015

Mechanism???



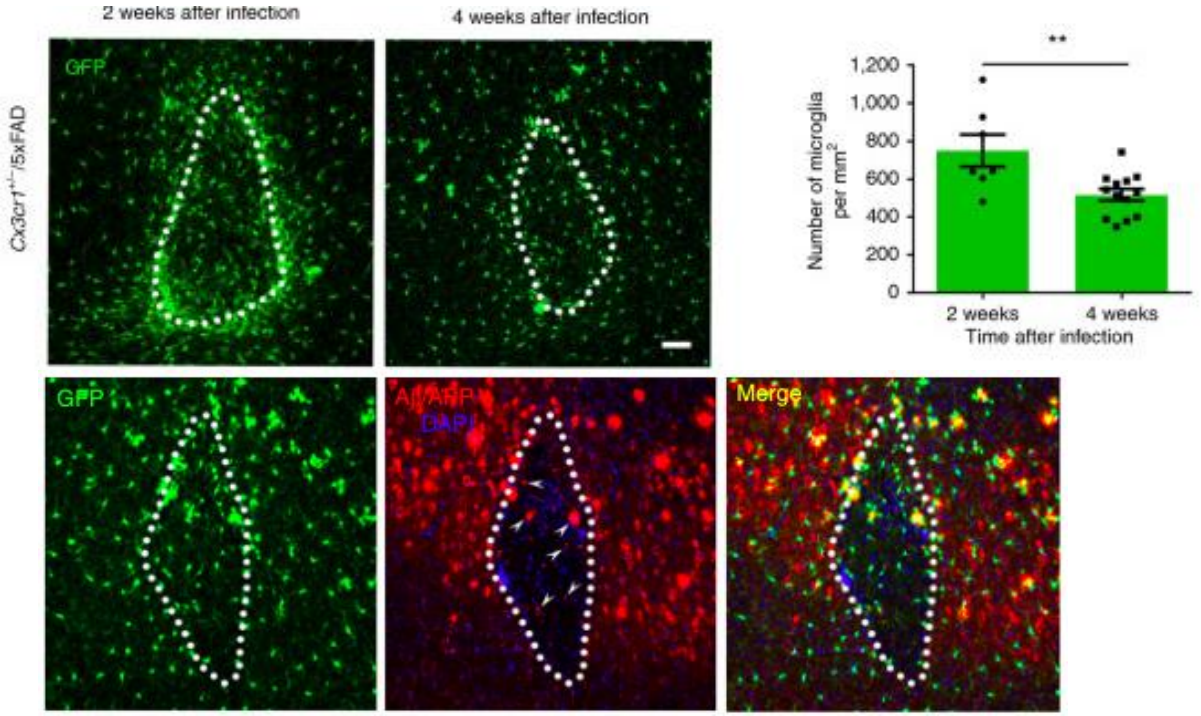
→ Axonal transport is not involved in the spread of Aβ pathology in WT grafts

Role of microglia during Aβ plaque formation in WT transplants



Do microglia act as an Aβ carrier?

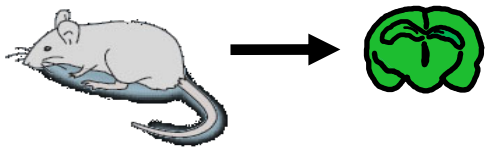
Microglia invasion into WT grafts



d'Errico P et al., Nat Neurosci 2022

→Do microglia act as an Aβ carrier?

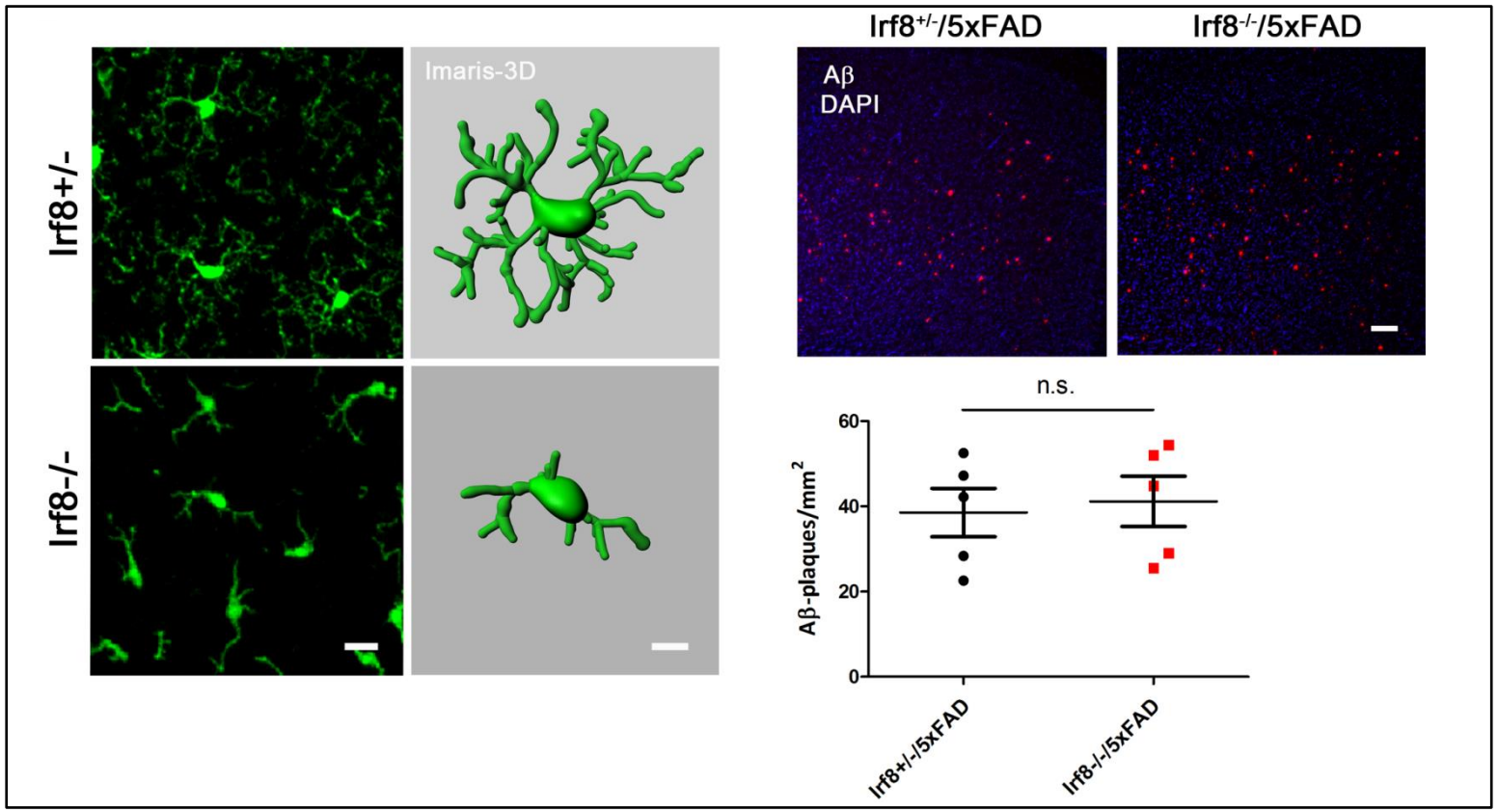
Characterization of Irf8$^{-/-}$ mice



Irf8$^{+/-}$
Irf8$^{-/-}$
***Irf8$^{-/-}$ x* 5xFAD**
***Irf8$^{-/-}$ x* 5xFAD**

Postmortem analysis

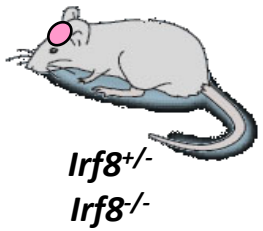
Irf8$^{-/-}$: defects in maturation, migration and process motility *(in vitro)*
(Masuda T. et al. Puirnergic Signal 2014; Minten C. et al. Plos One 2012)



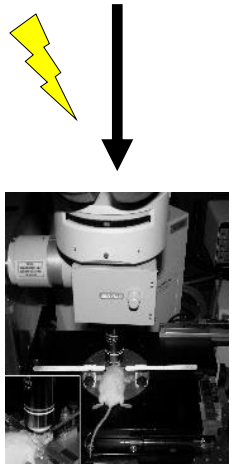
→ Irf8$^{-/-}$ microglia are less ramified and display shorter, swollen processes

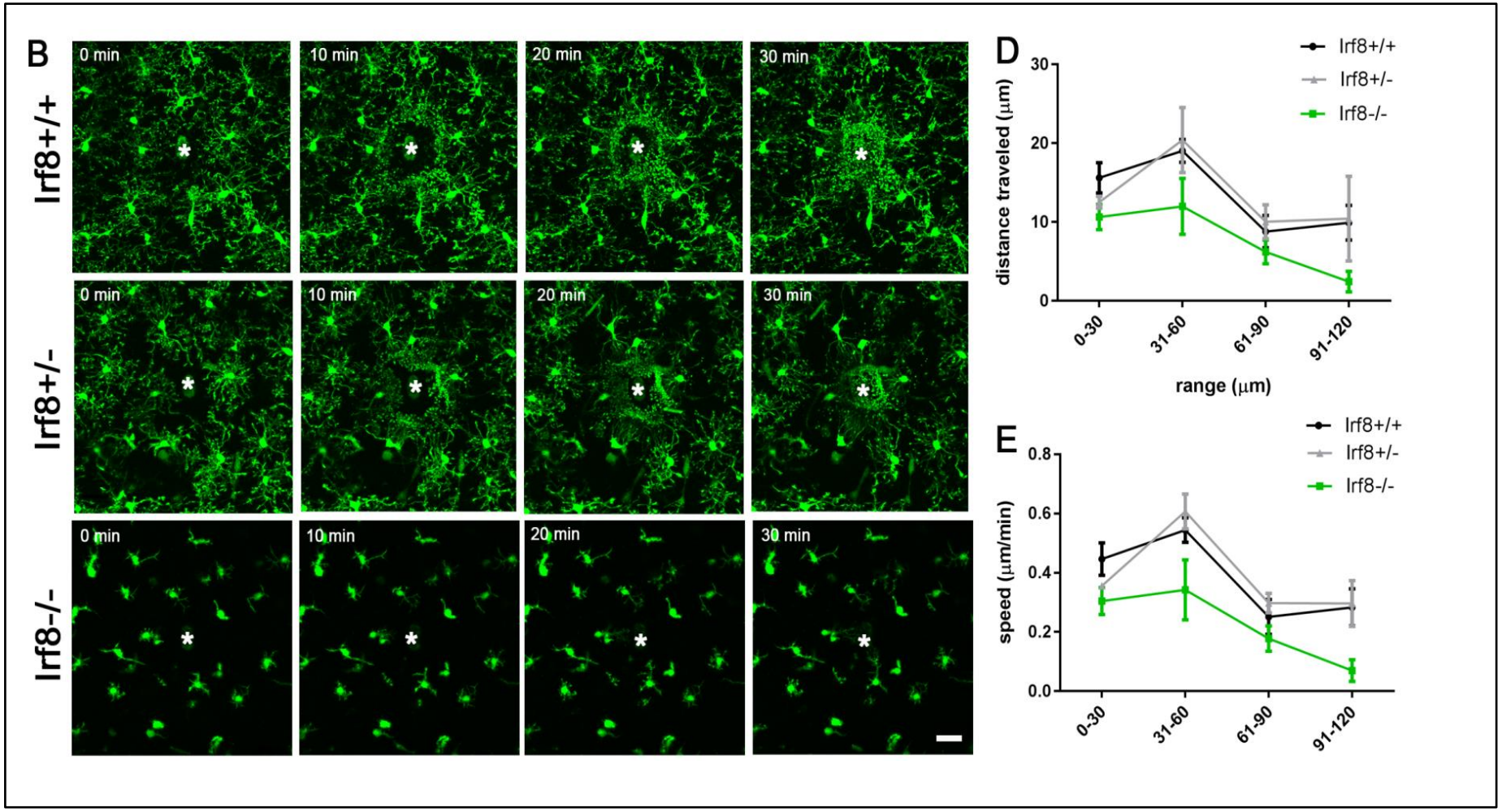
→ Plaque load in Irf8$^{-/-}$ x 5xFAD is similar

In vivo characterization of Irf8$^{-/-}$ mice



Irf8$^{+/-}$
Irf8$^{-/-}$

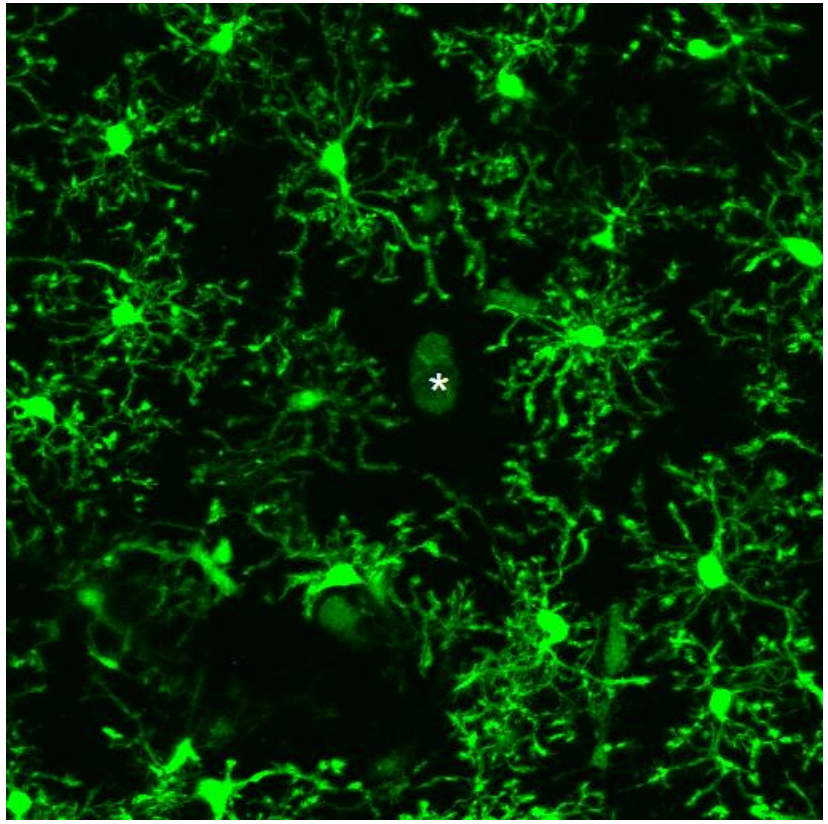




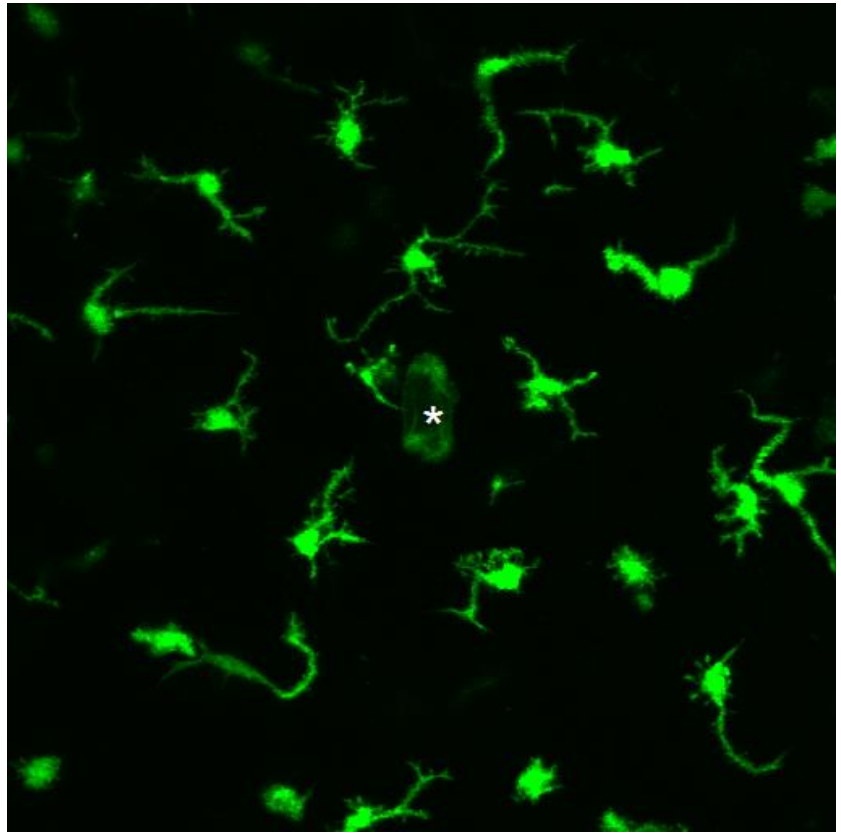
→ Reduced process motility and migration towards laser-induced injury

In vivo characterization of Irf8$^{-/-}$ mice

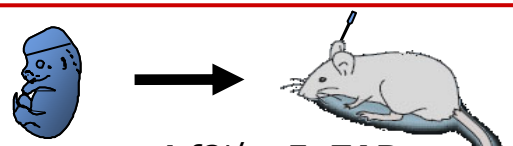
Irf8$^{+/-}$



Irf8$^{-/-}$



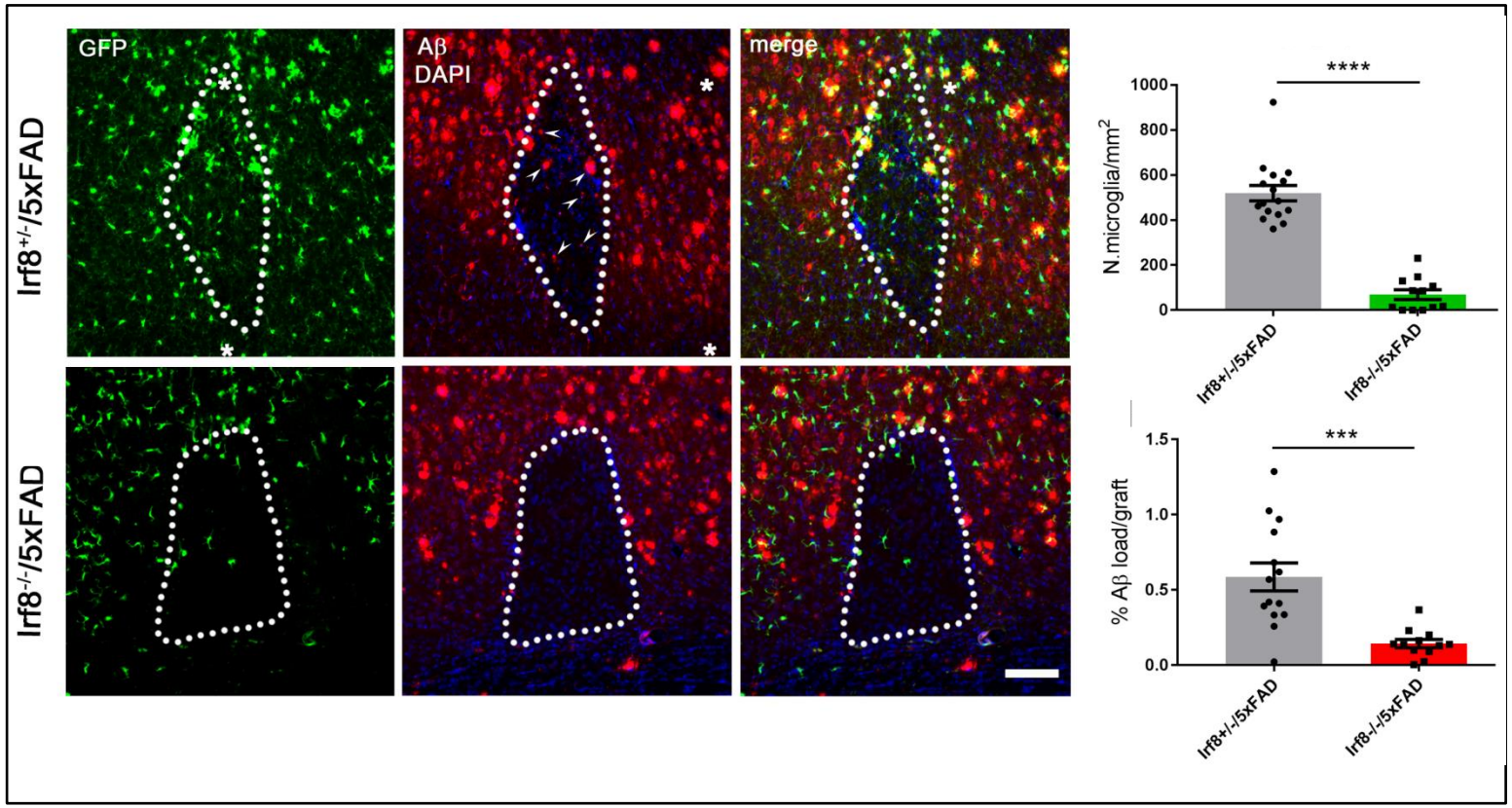
Reduced Aβ plaque deposition in cortical WT transplants (1)



WT

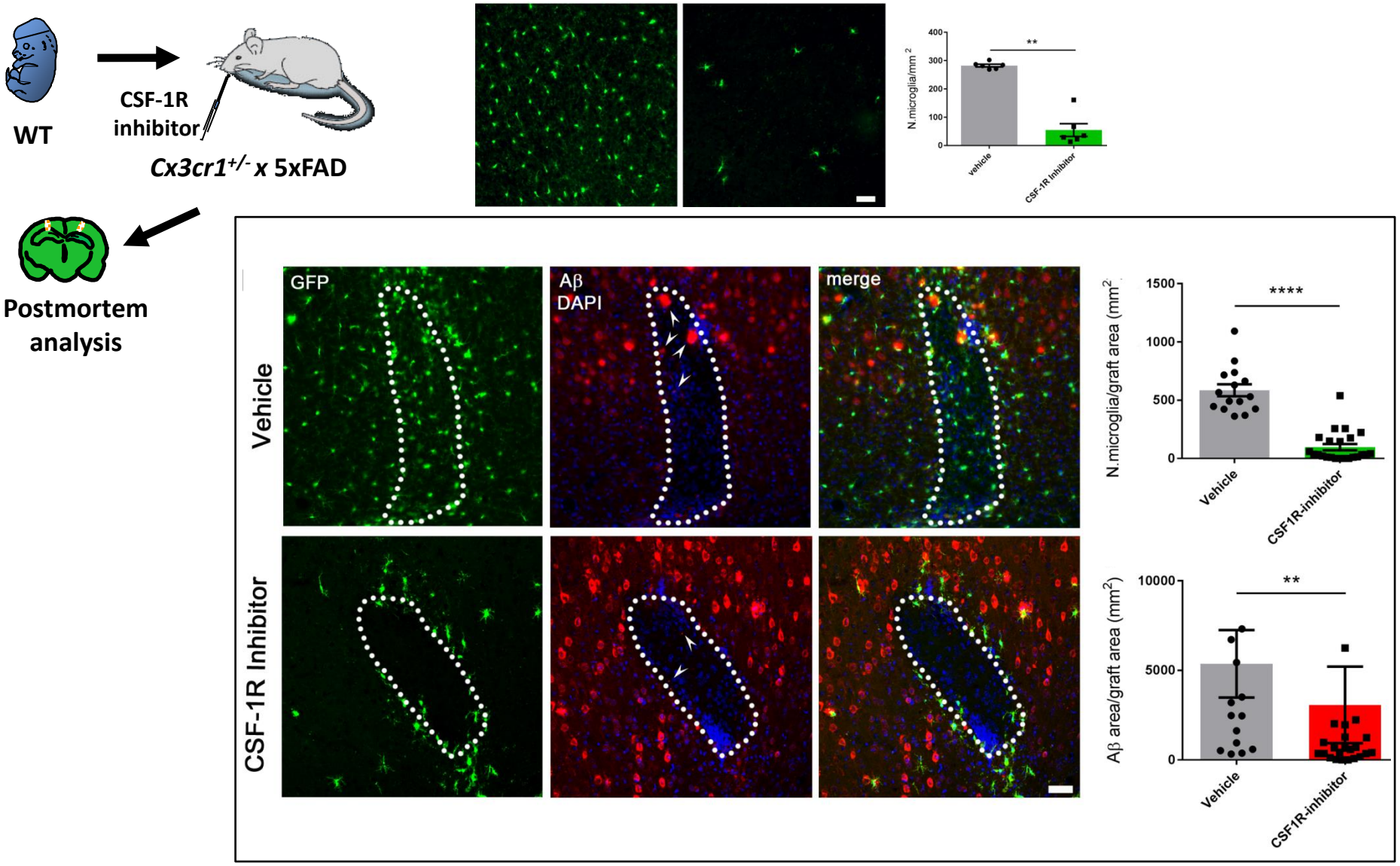
Irf8$^{+/-}$ *x* 5xFAD
Irf8$^{-/-}$ *x* 5xFAD

Postmortem analysis



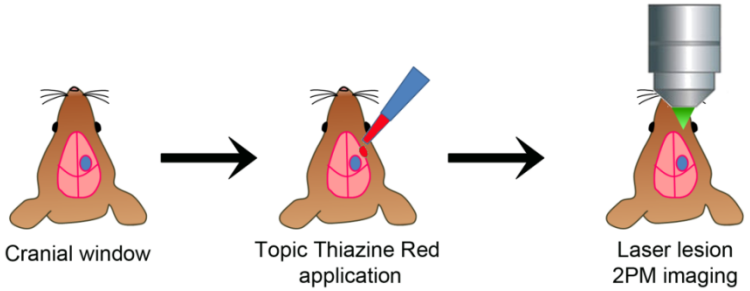
→ Microglia migration deficit reduces Aβ deposits in WT grafts

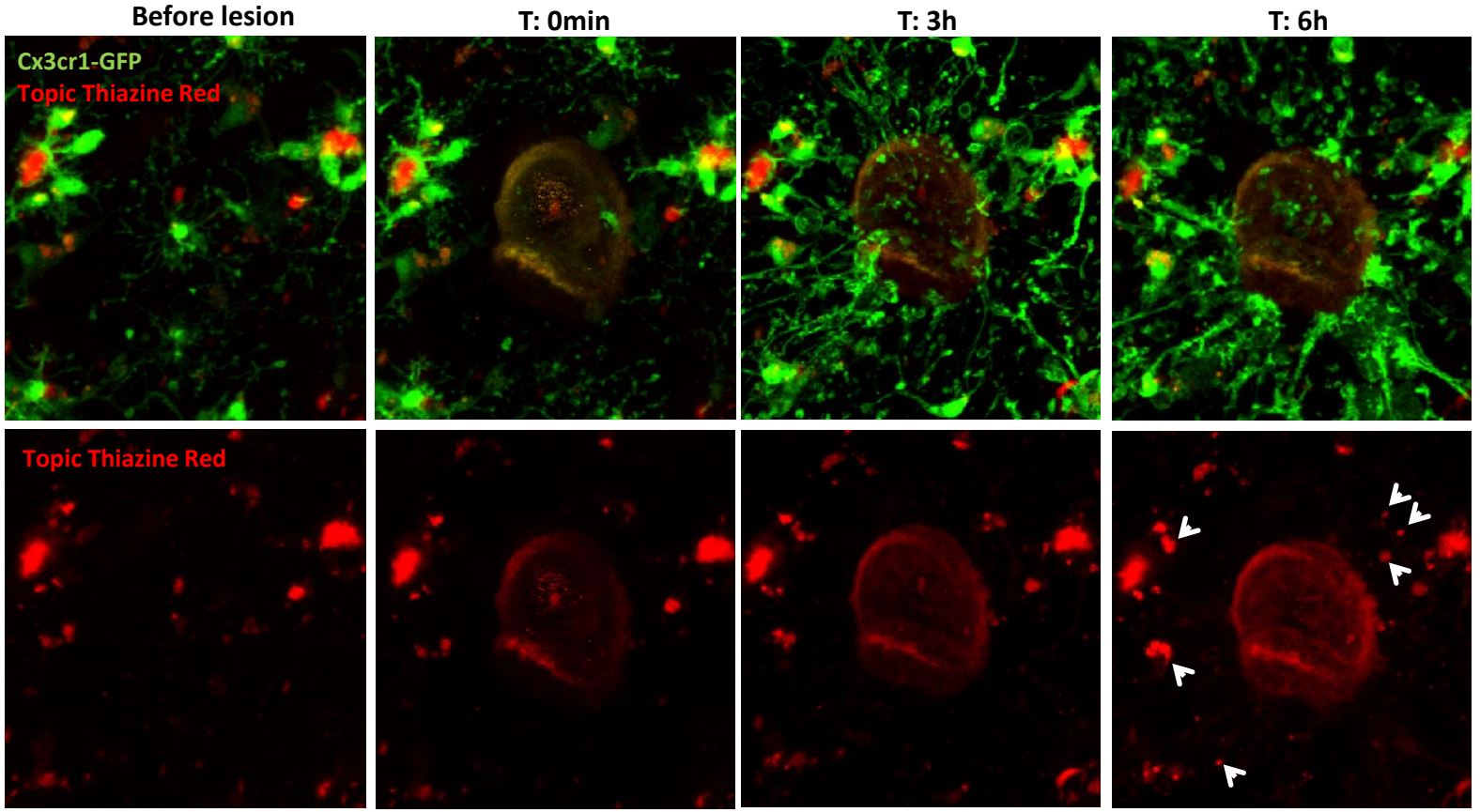
Reduced Aβ plaque deposition in cortical WT transplants (2)



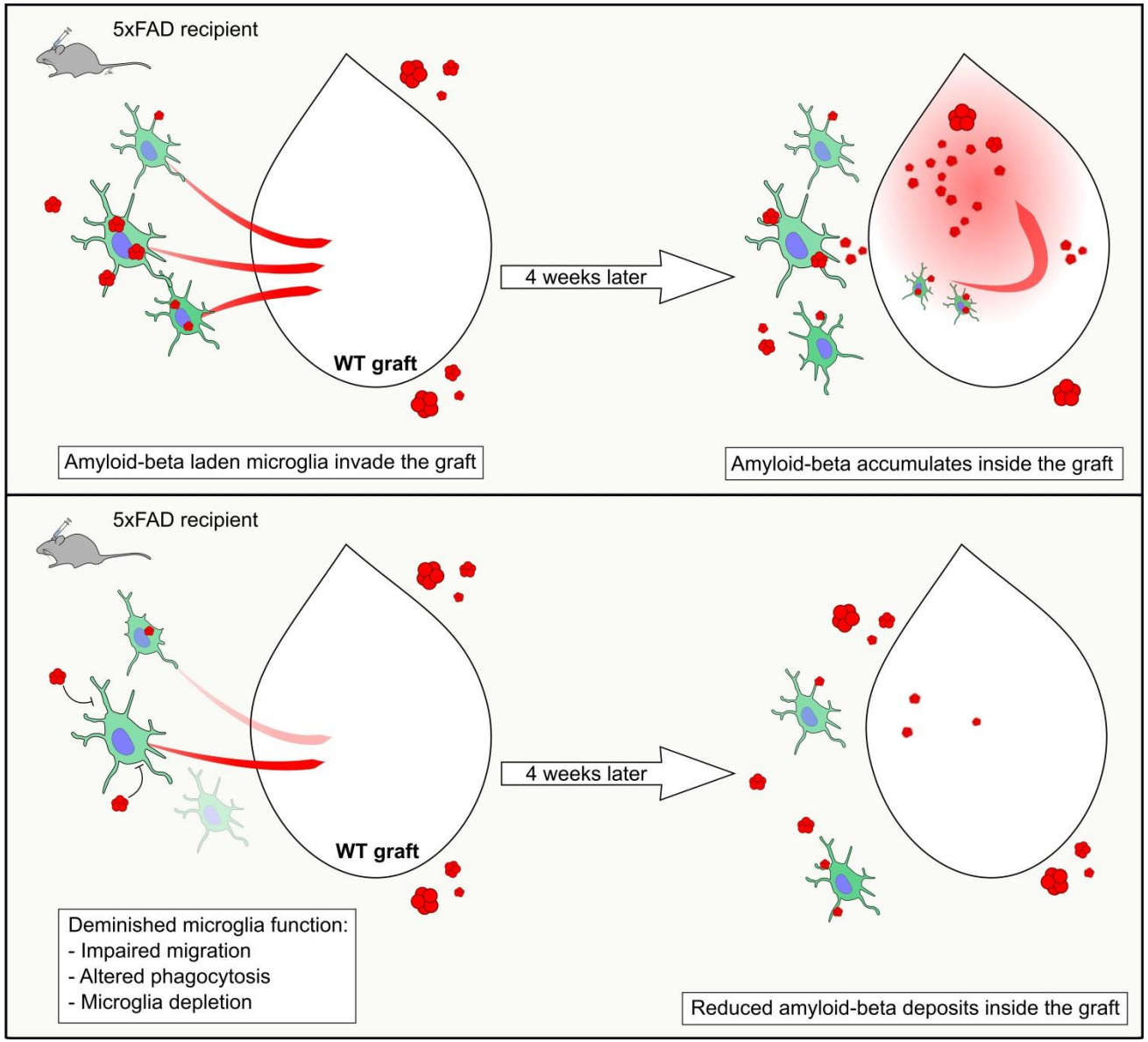
→ Microglia depletion reduces Aβ deposits in WT grafts

Laser-induced injury leads to Aβ deposits in vicinity

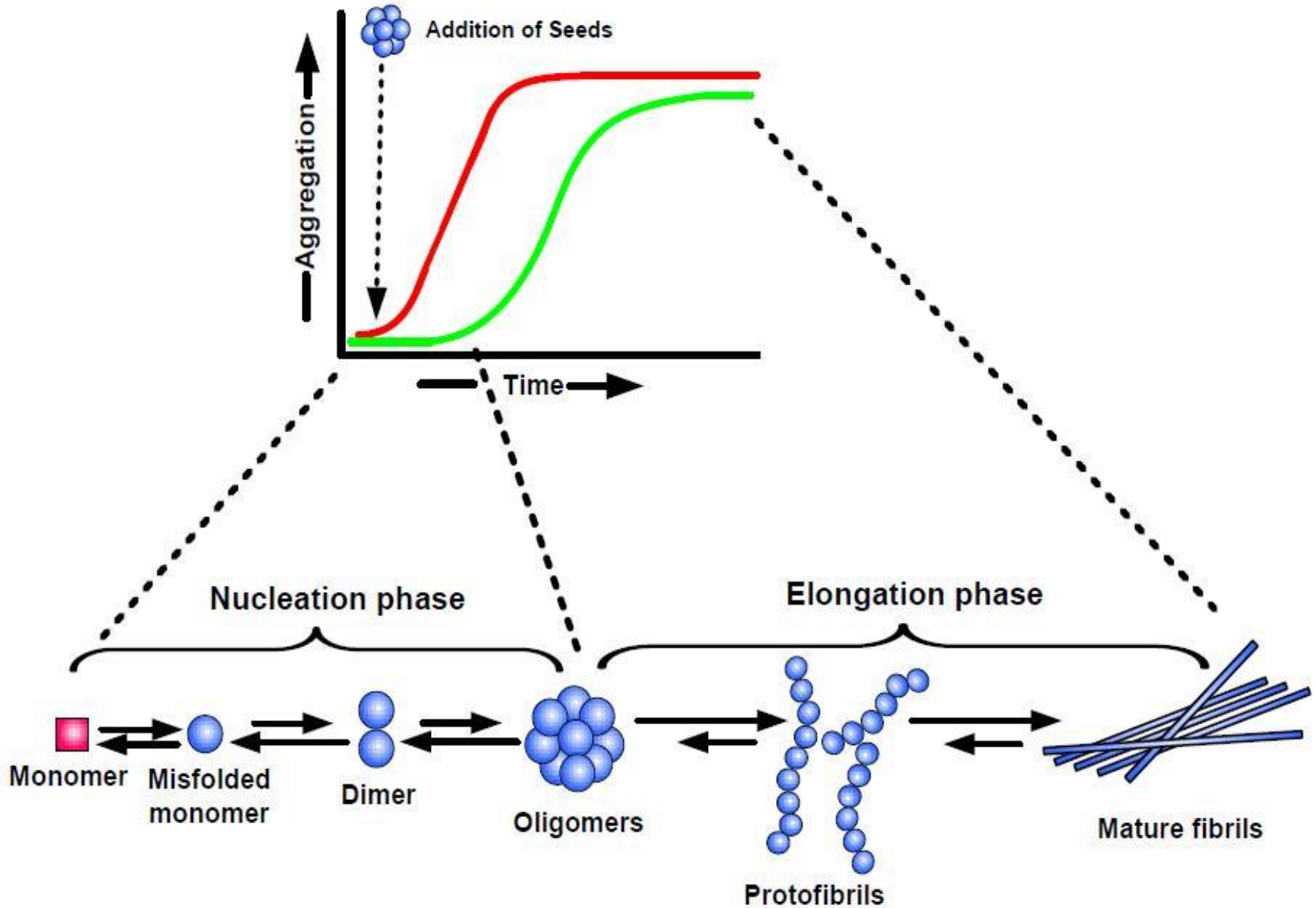




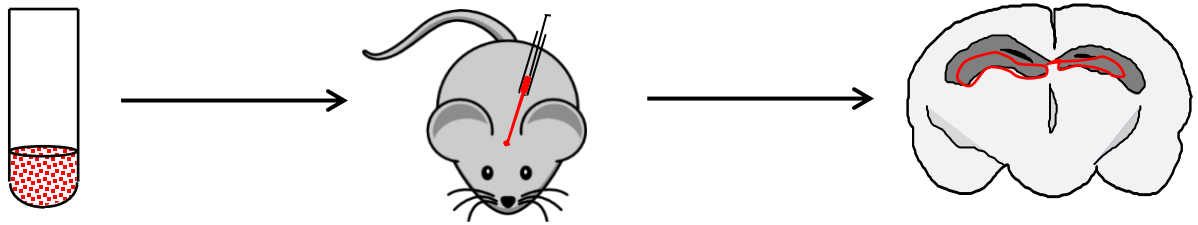
Summary I

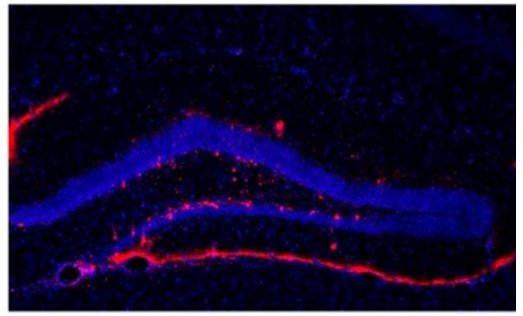

5xFAD recipient
WT graft
4 weeks later
Amyloid-beta laden microglia invade the graft
Amyloid-beta accumulates inside the graft
5xFAD recipient
WT graft
4 weeks later
Deminished microglia function:
- Impaired migration
- Altered phagocytosis
- Microglia depletion
Reduced amyloid-beta deposits inside the graft

Nucleation- dependent polymerization model

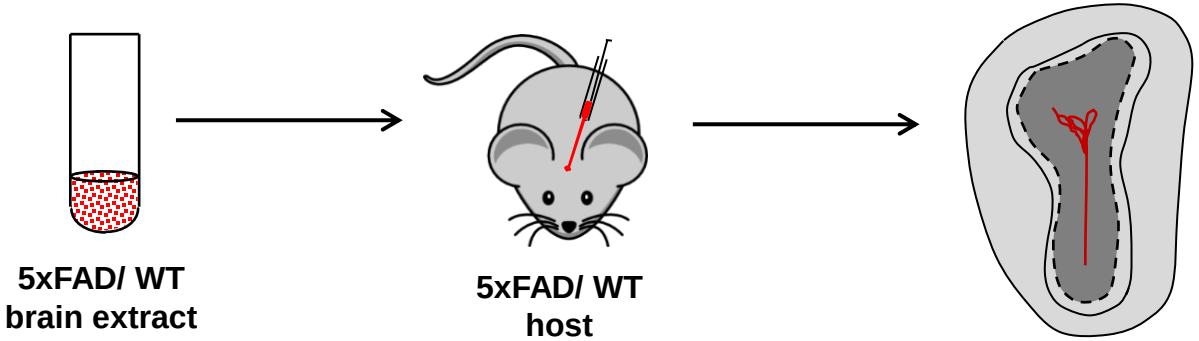


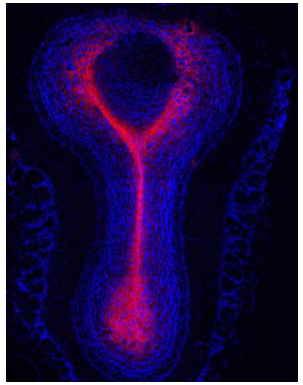
Induction of Aβ aggregation - seeding





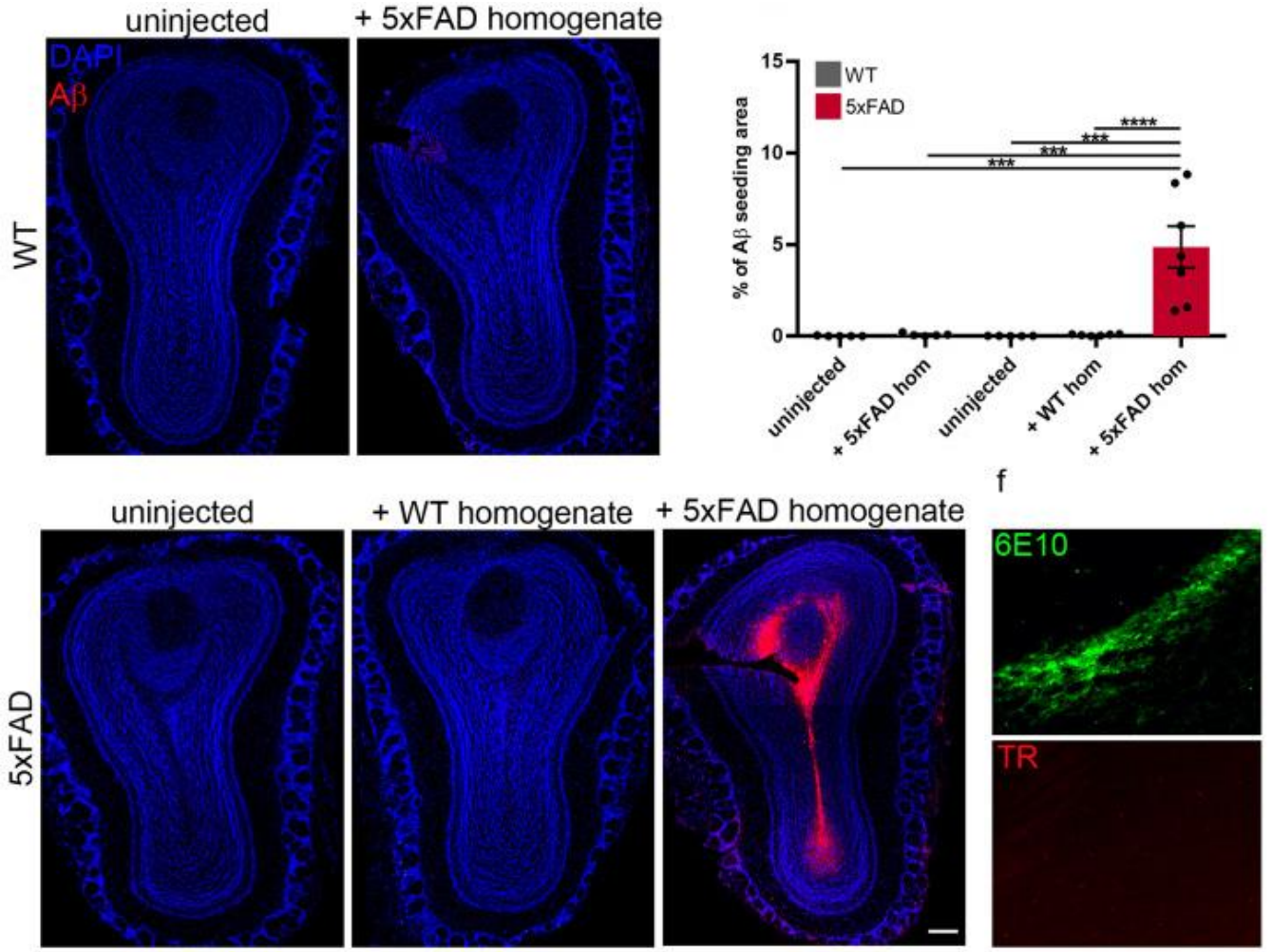
Meyer-Luehmann M et al., Science 2006
Bachhuber T et al., Nat Med 2015
Ziegler-Waldkirch S et al., EMBO J 2018
Parhizkar S et al., Nat Neurosci 2019





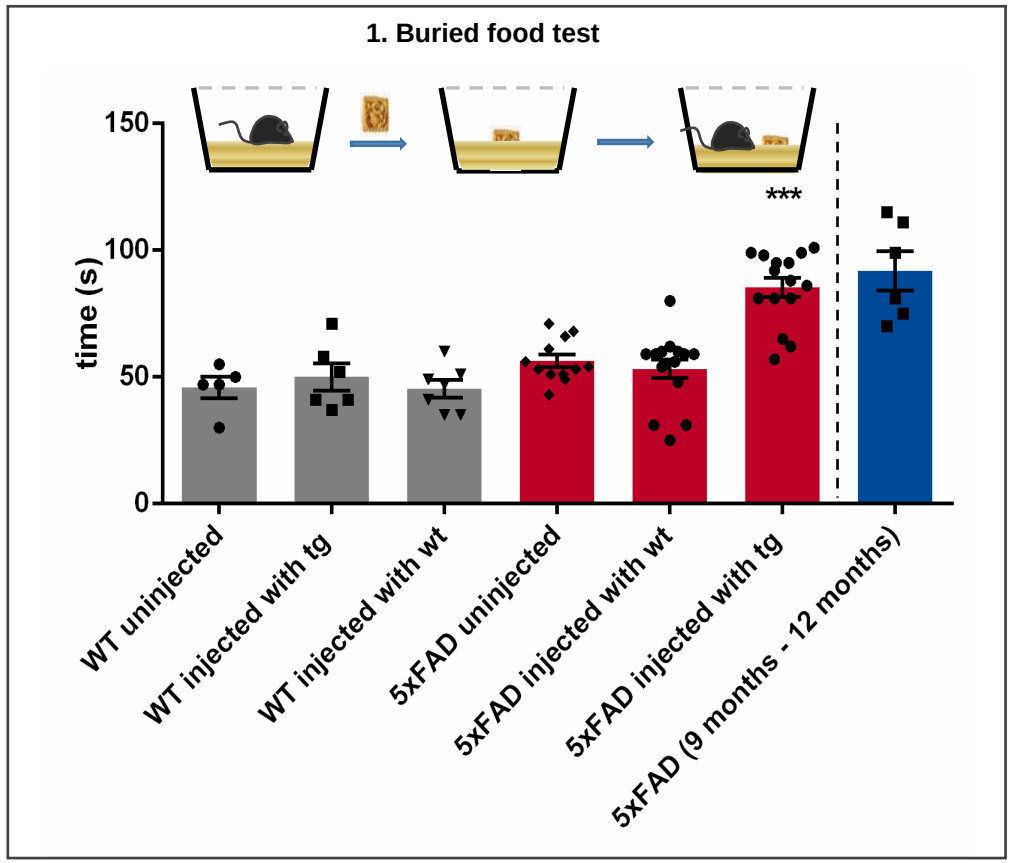
Friesen M et al., Brain Pathol 2022
Ziegler-Waldkirch S et al., Mol Psychiatry 2022

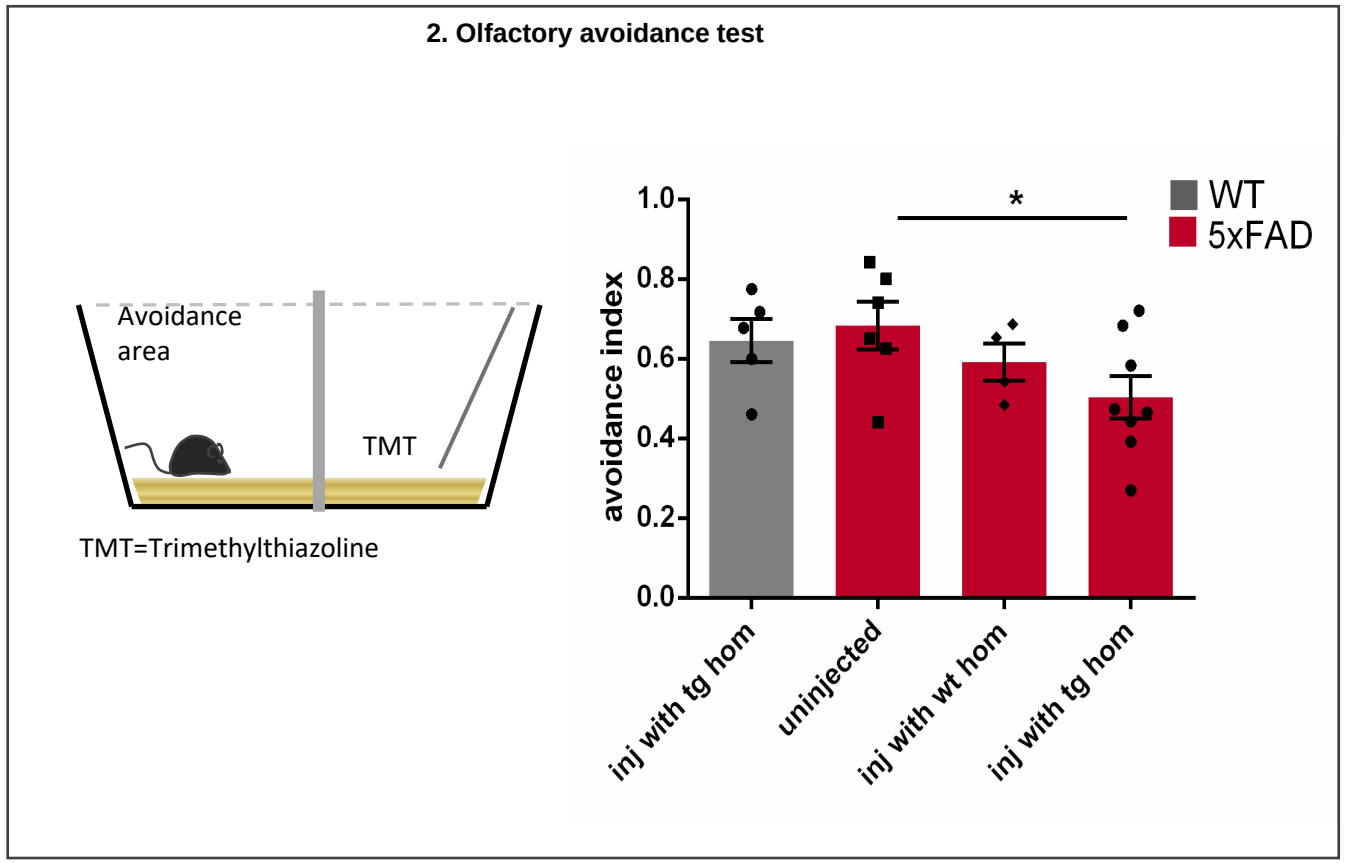
Aβ seeding in the olfactory bulb



Ziegler-Waldkirch et al., MolPsychiatry 2022

Aβ seeding in the olfactory bulb

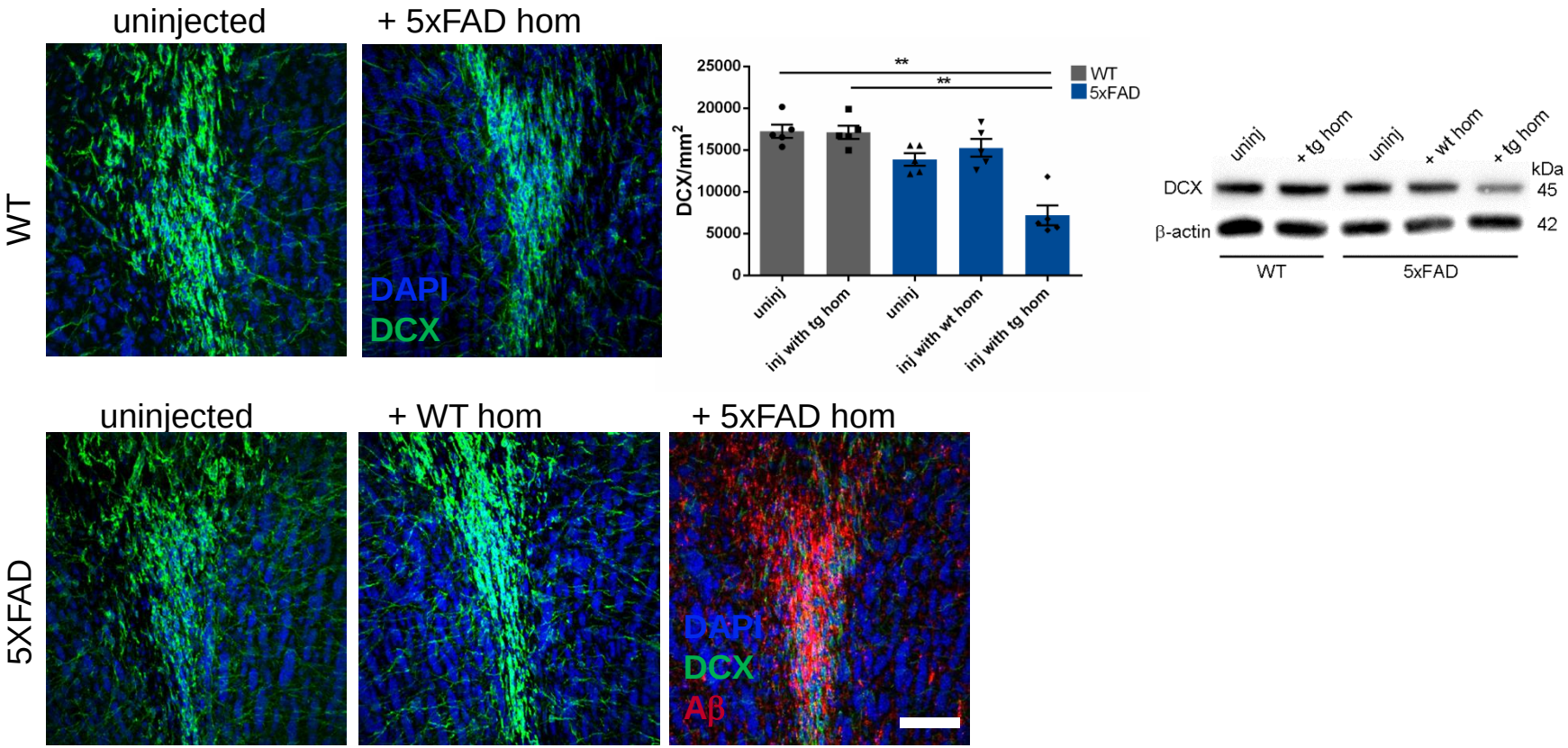




Ziegler-Waldkirch et al., MolPsychiatry 2022

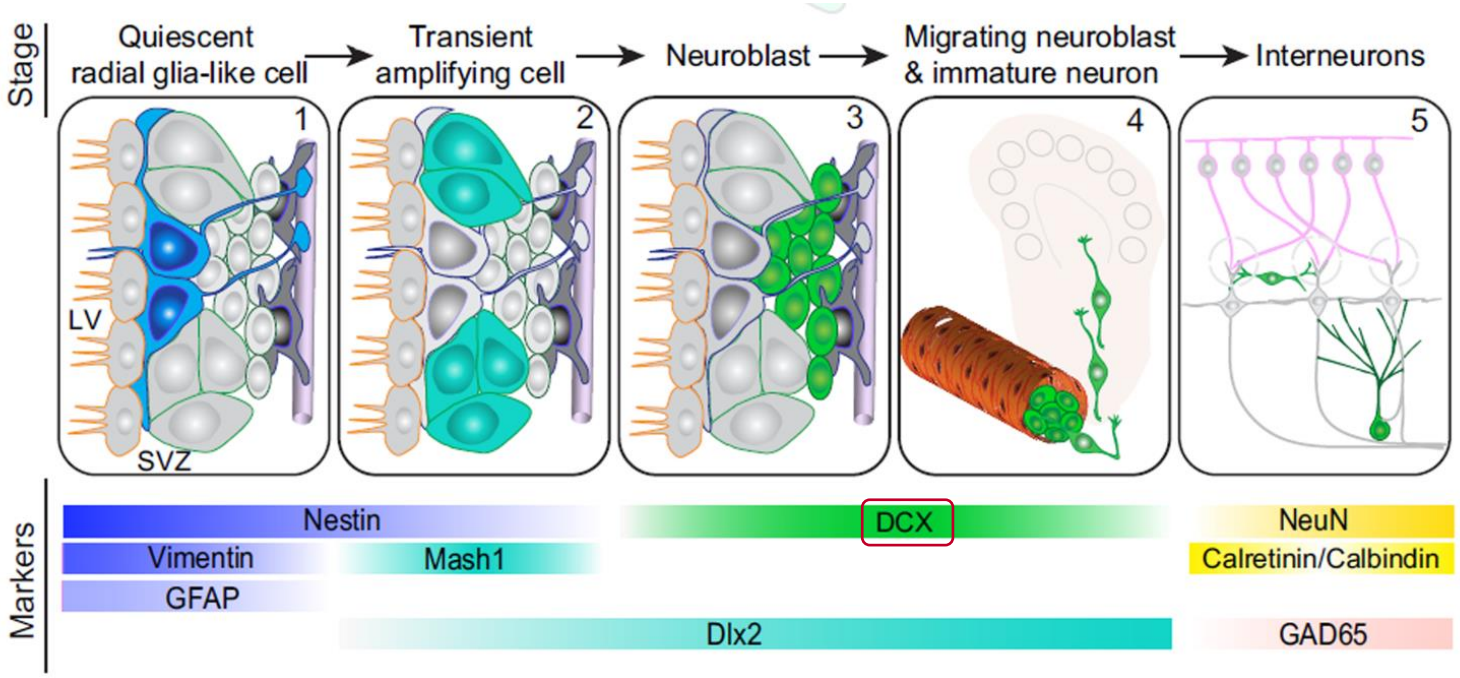
→ Seeded 5xFAD mice have a significant deficit in simple olfaction tests

Aβ seeding impairs adult neurogenesis



Ziegler-Waldkirch et al., MolPsychiatry 2022

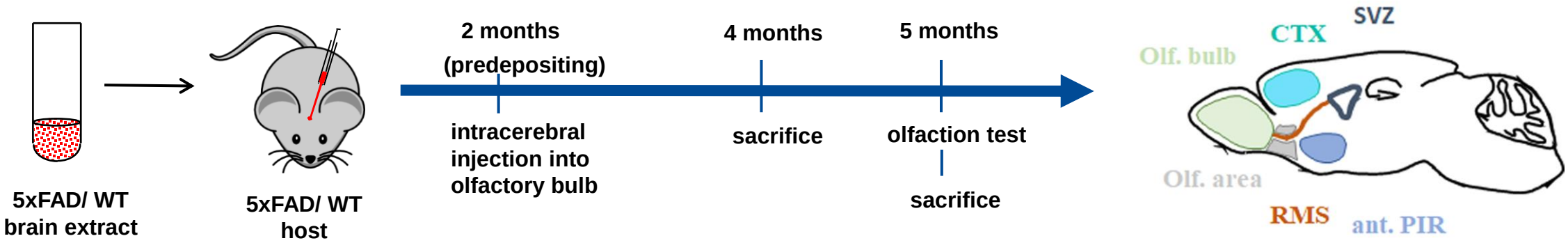
Adult neurogenesis in the SVZ

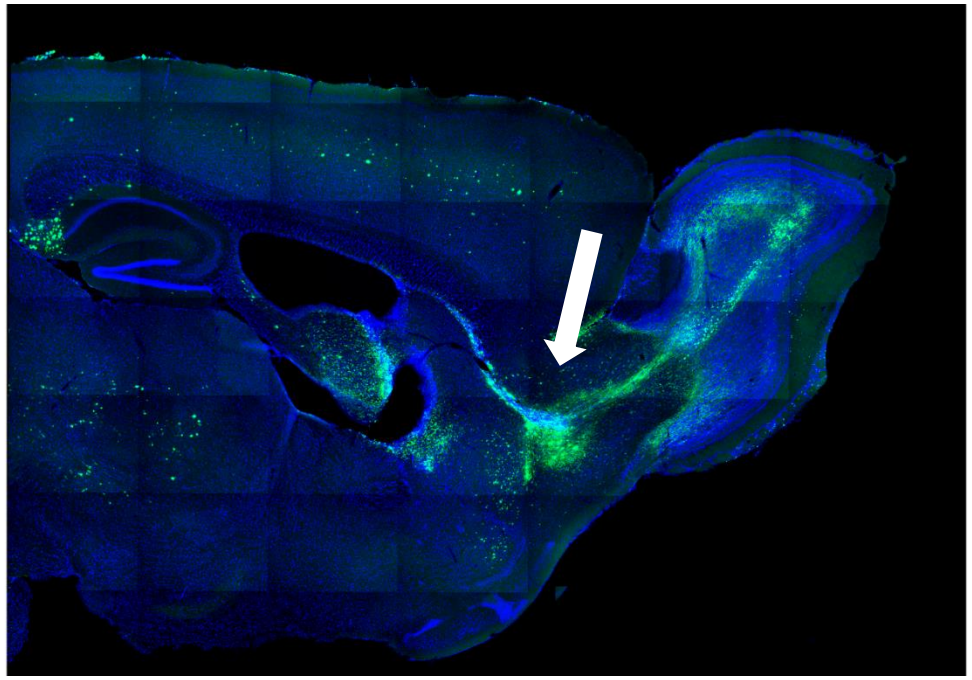


Ming GL, Song H, Neuron, 2011

- Neurogenesis occurs throughout life in restricted brain regions: **SGZ** of hippocampus and the **SVZ** of lateral ventricles
- Neural stem cells start to proliferate and differentiate in the SVZ
- Neuroblasts migrate from the SVZ in the **RMS** towards the olfactory bulb and mature to neurons.

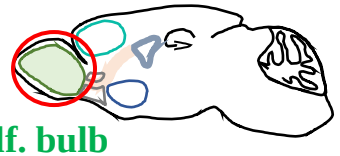
Aβ spreads via the rostral migratory stream (RMS)



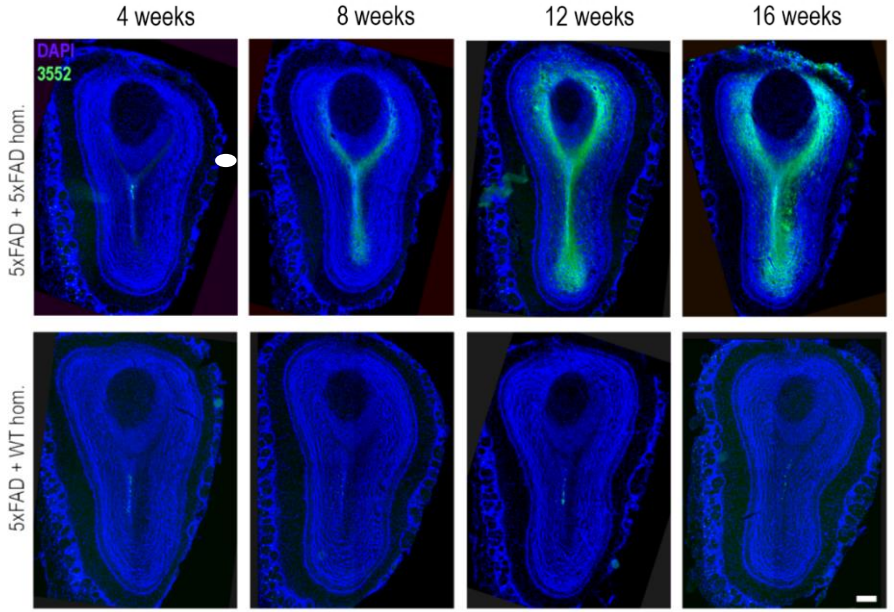


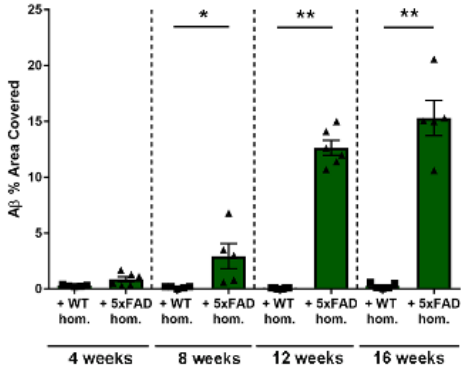
- The **RMS** is the major pathway by which neuroblasts migrate from the SVZ to the OB troughout adulthood

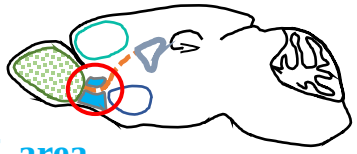
Aβ spreads via the rostral migratory stream (RMS)



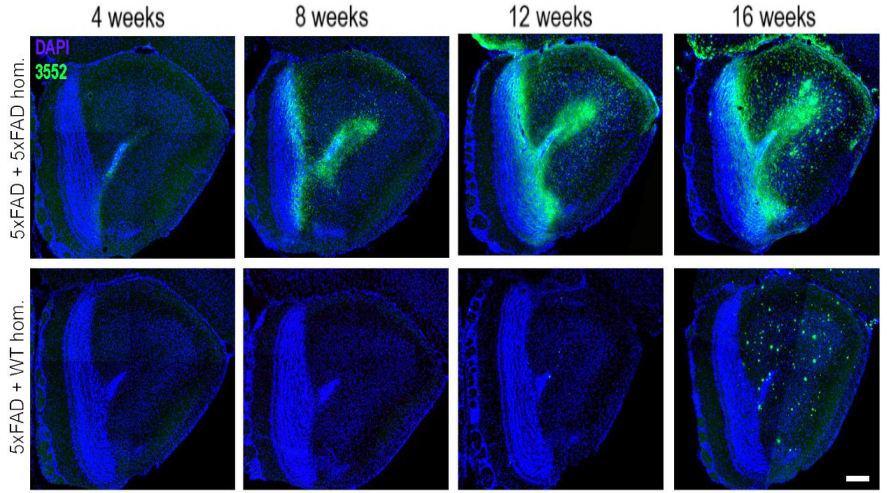
Olf. bulb

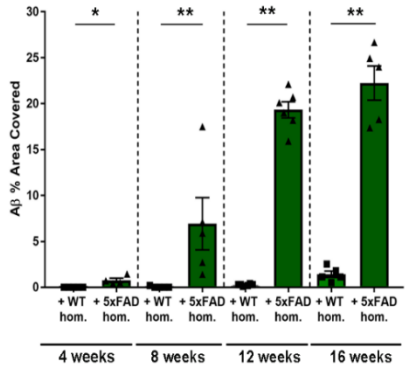




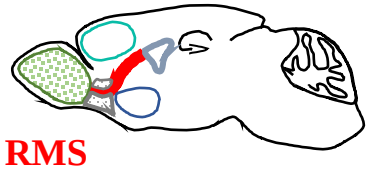


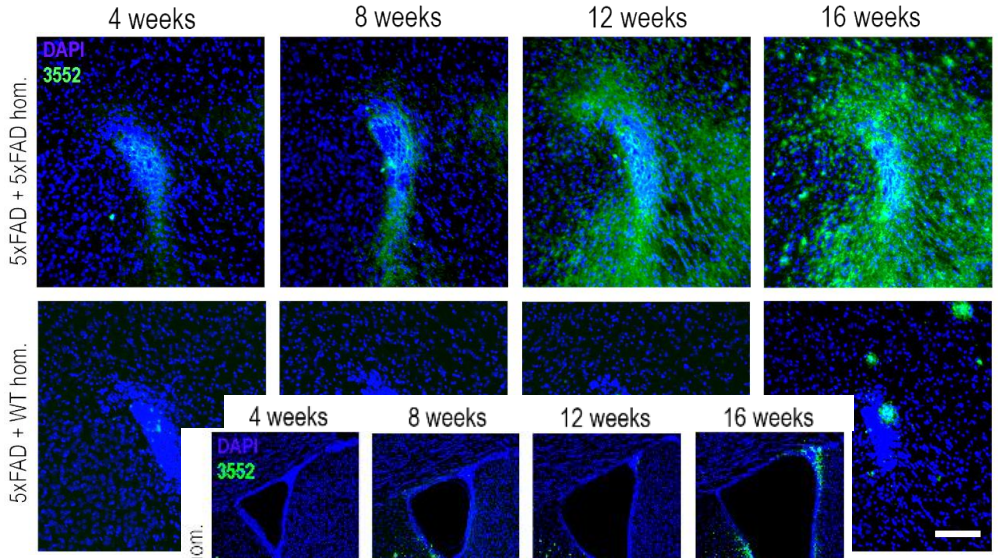
Olf. area

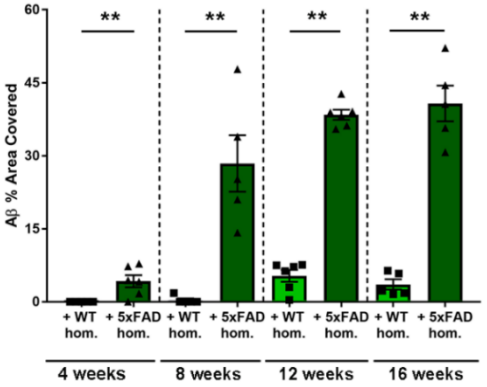


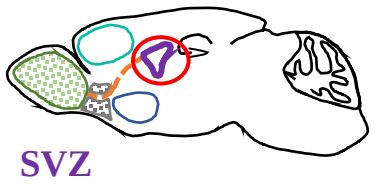


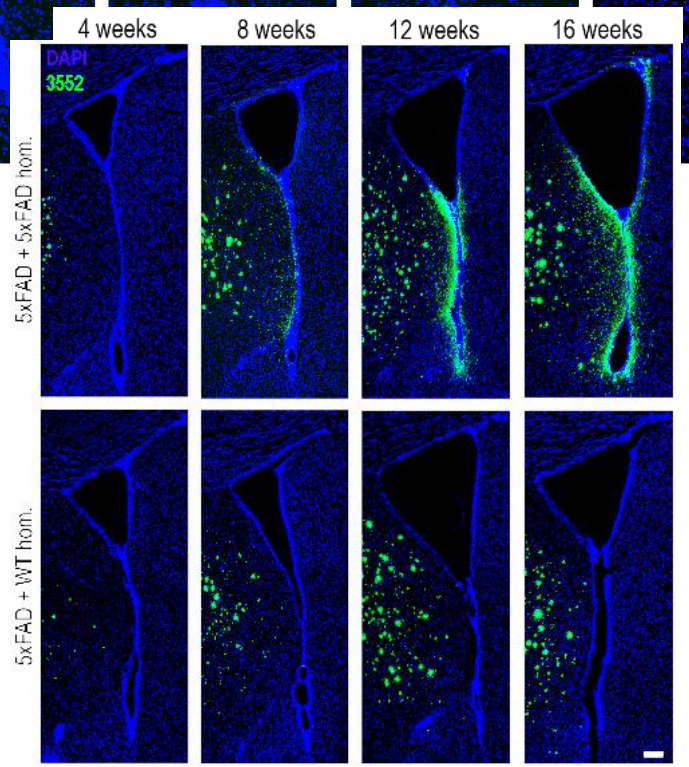
Aβ spreads via the rostral migratory stream (RMS)

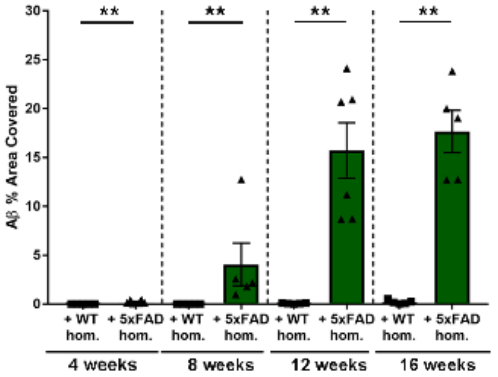




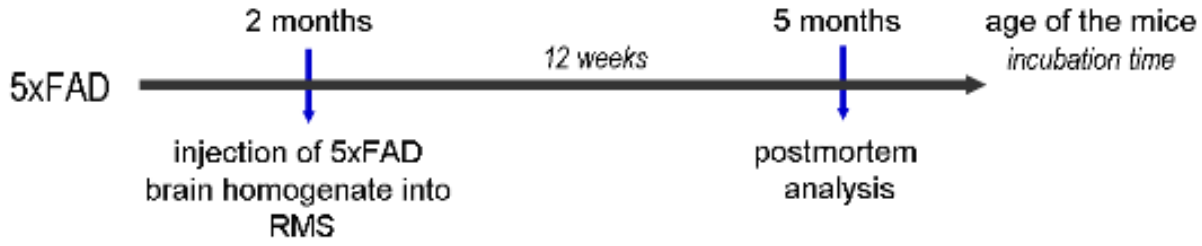


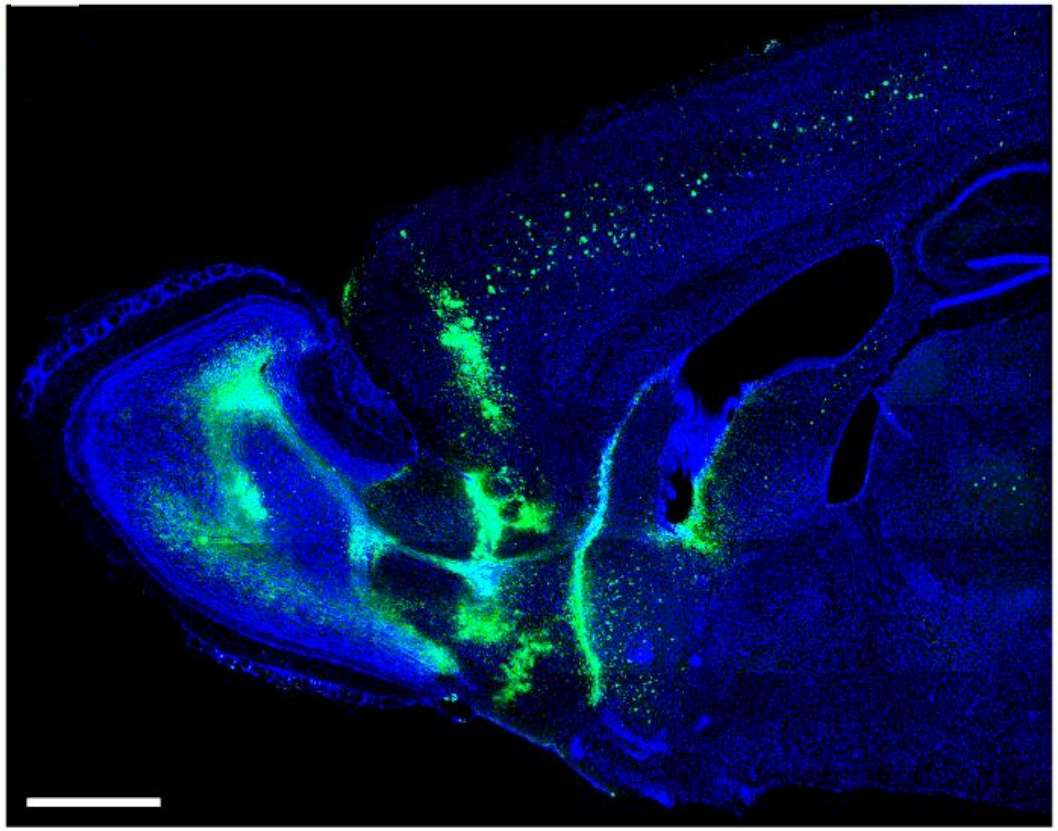


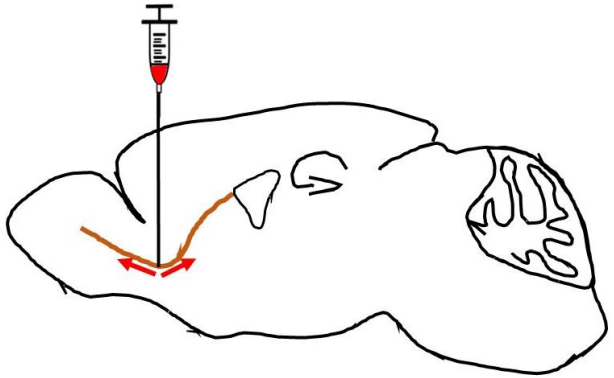




Bidirectional dissemination of Aβ seeds after injection into the RMS

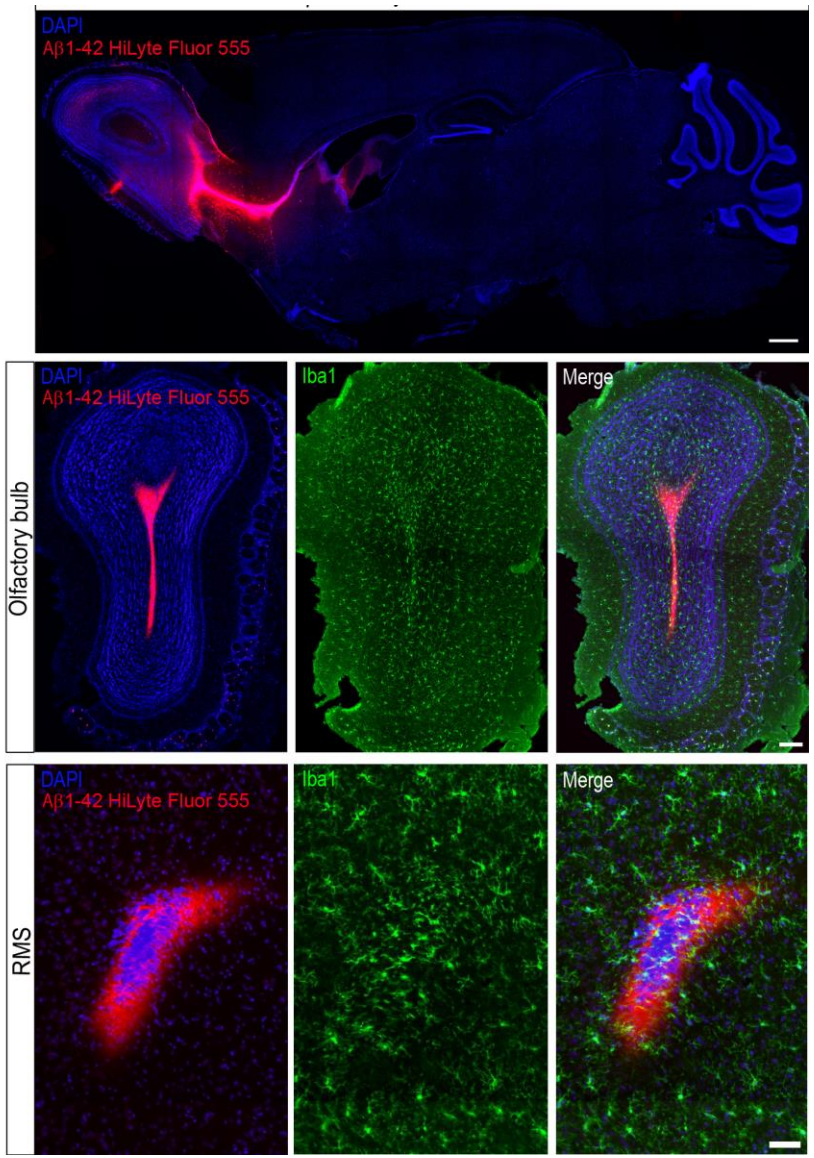




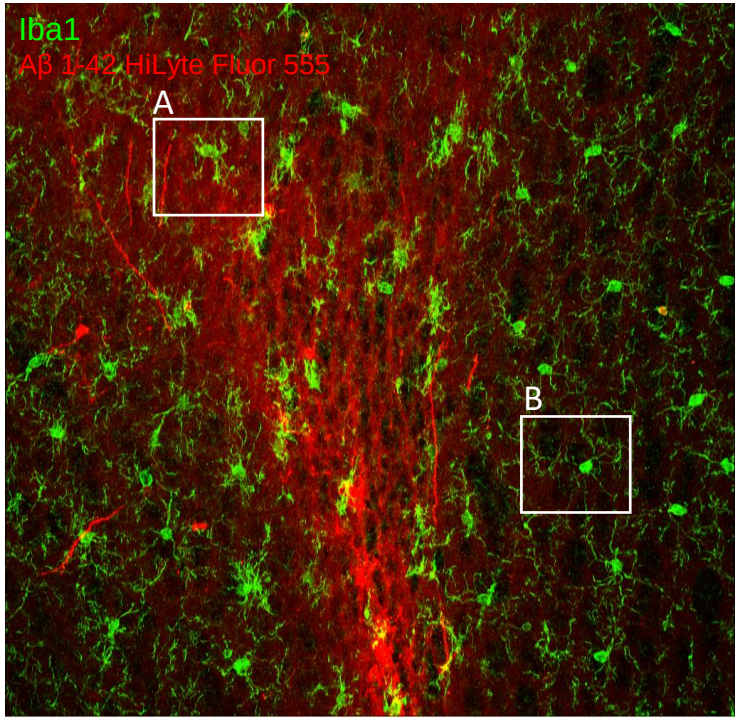


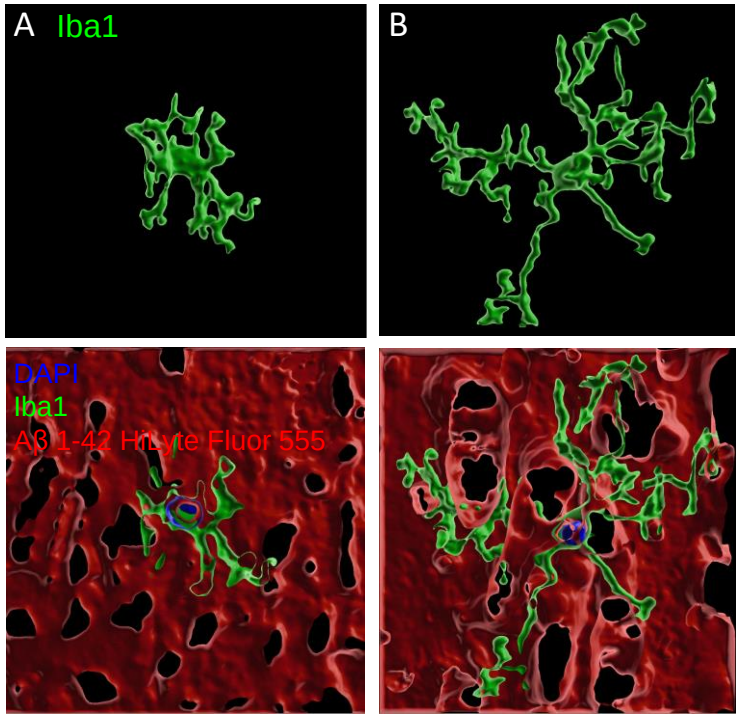
- Propagation of Aβ pathology via RMS towards olf. bulb **and** SVZ

Aβ spreads via the RMS – role for microglia?

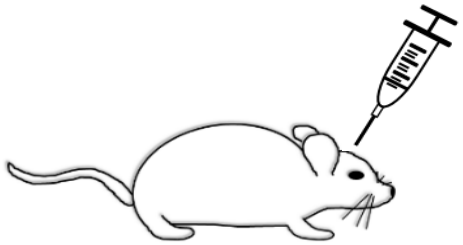


Olfactory bulb

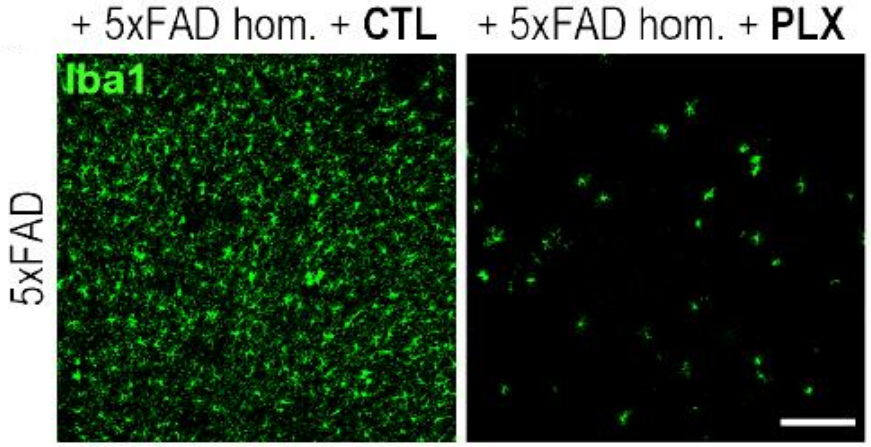


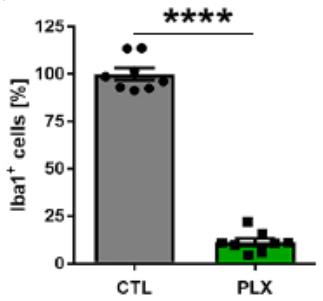


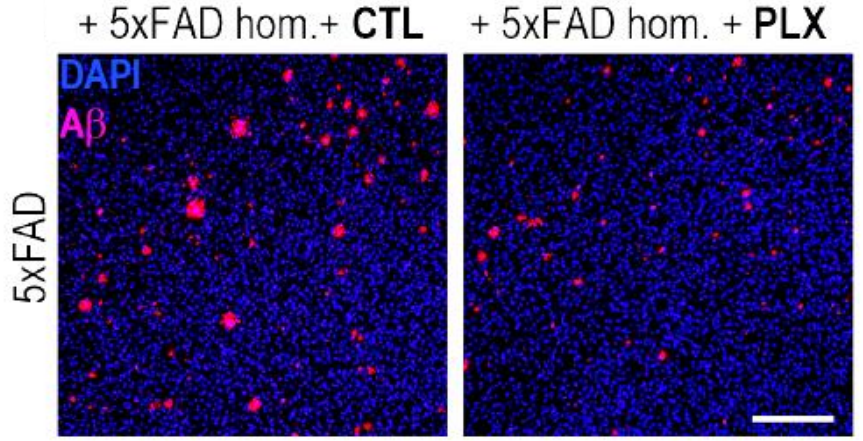
Depletion of microglial cells

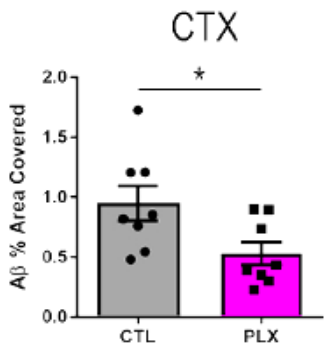


5xFAD

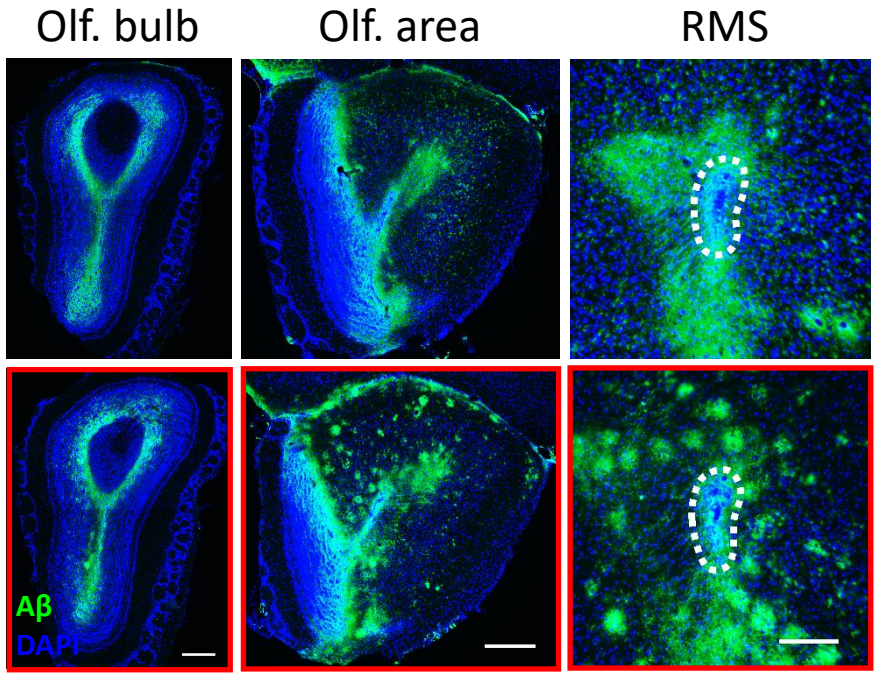


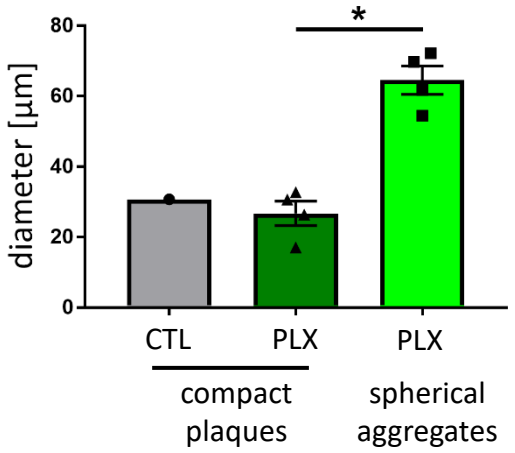




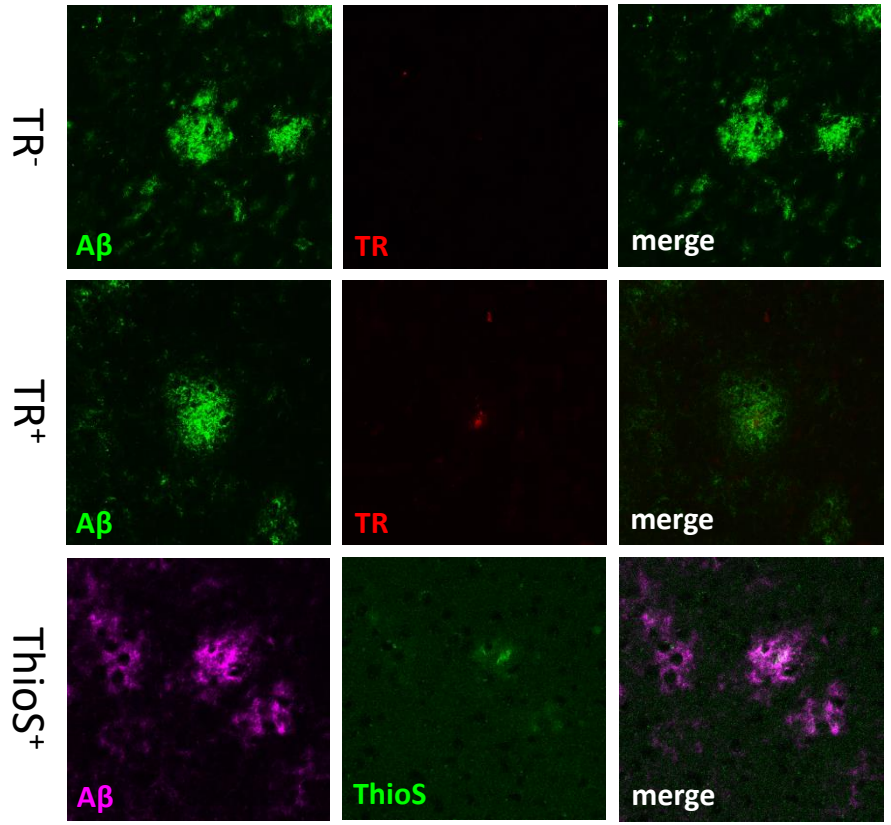


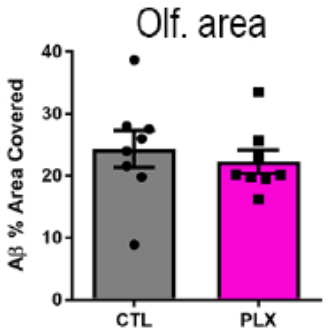
Modified aggregation pattern of seeded Aβ spread

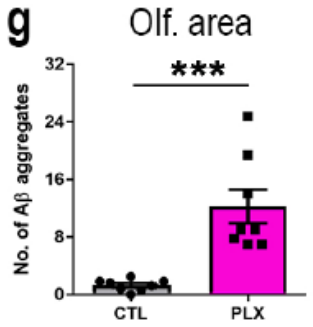




- bigger size

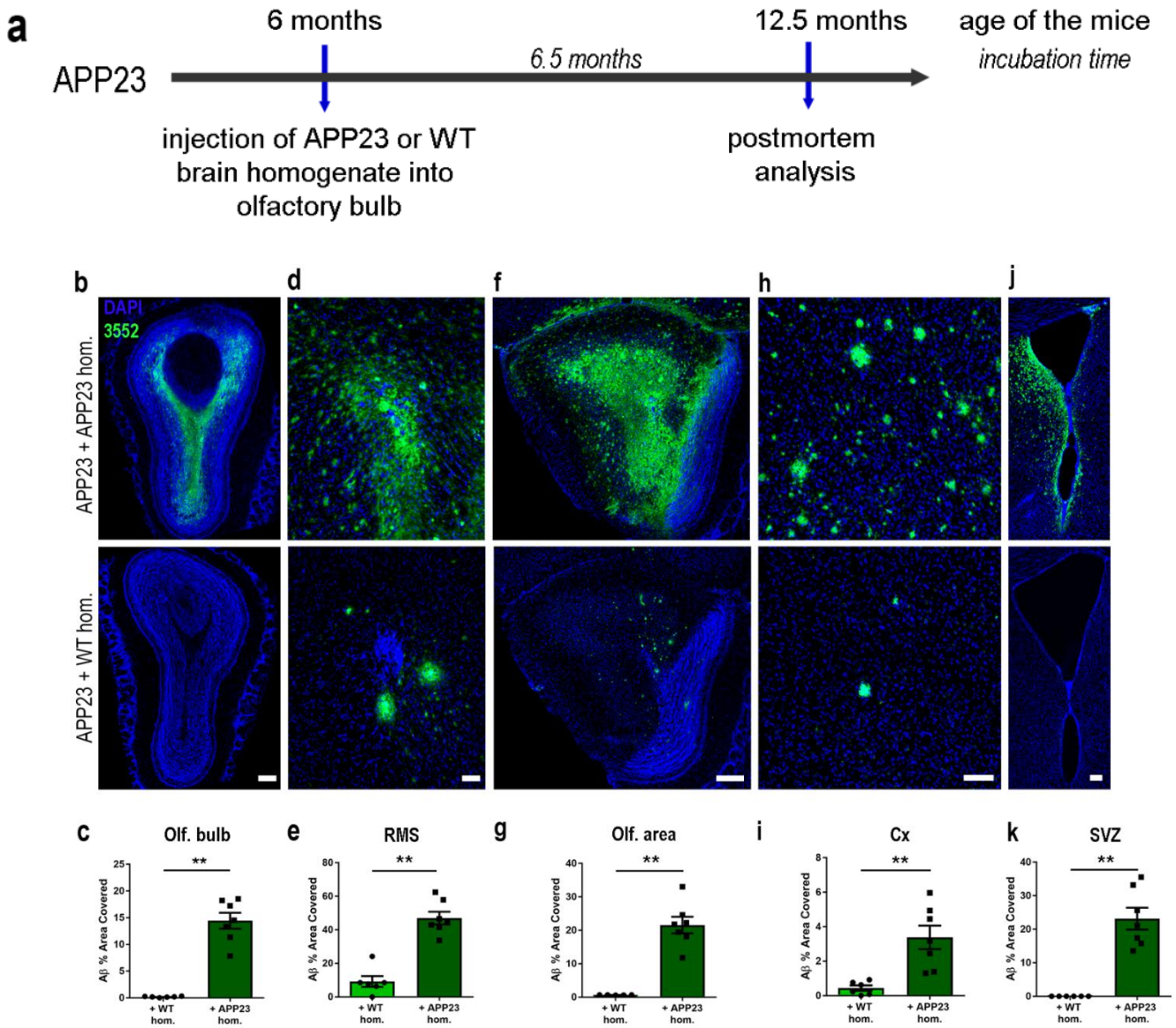


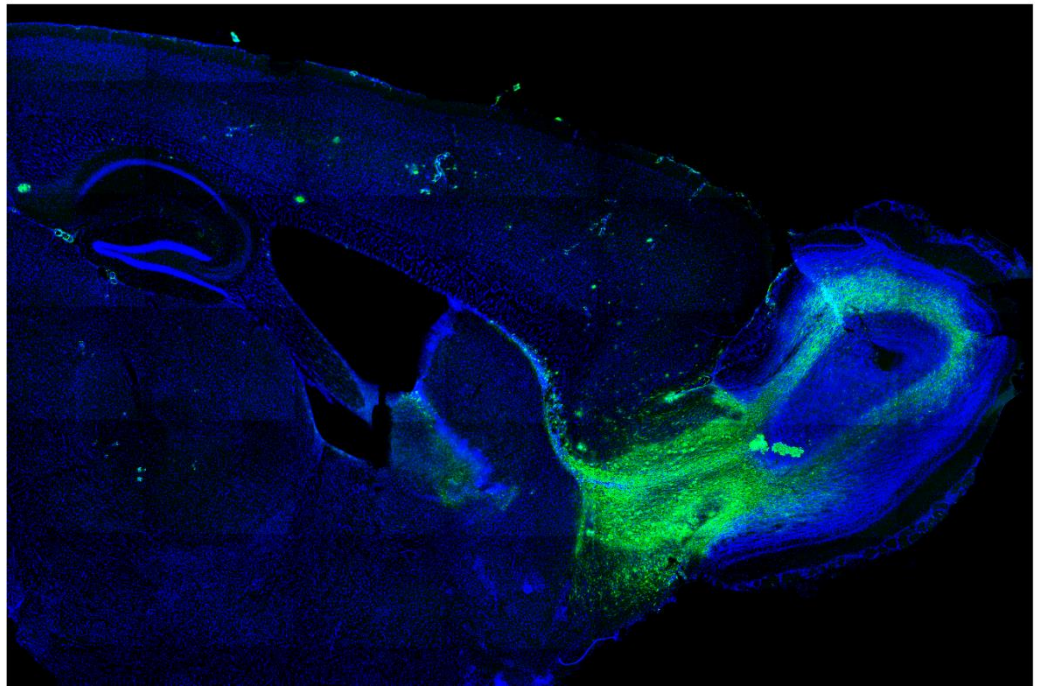




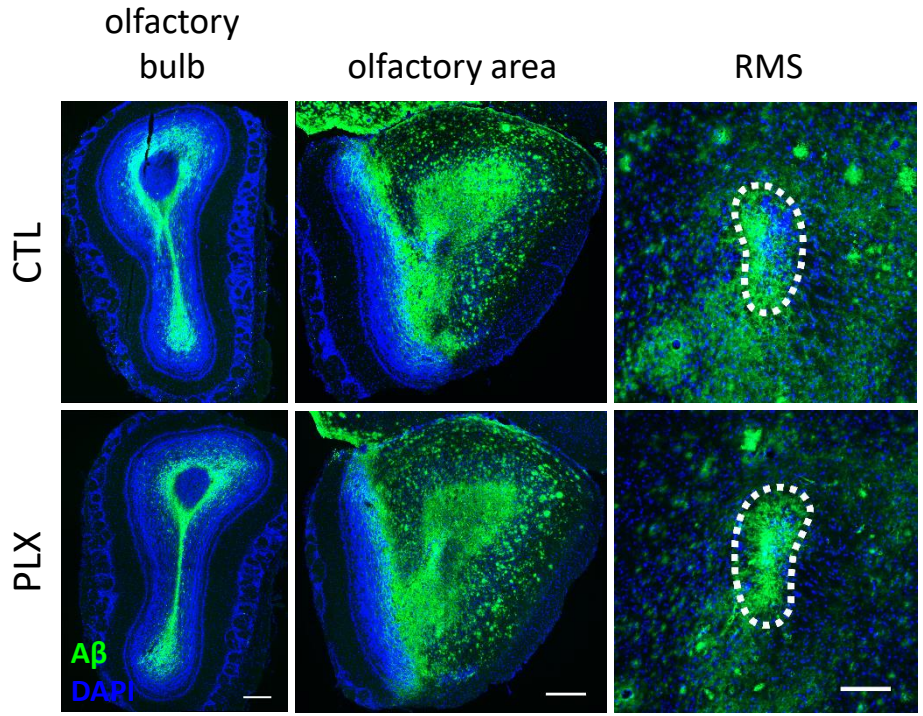
→ Some spherical aggregates have a compact core and are positive for TR⁺ and ThioS⁺

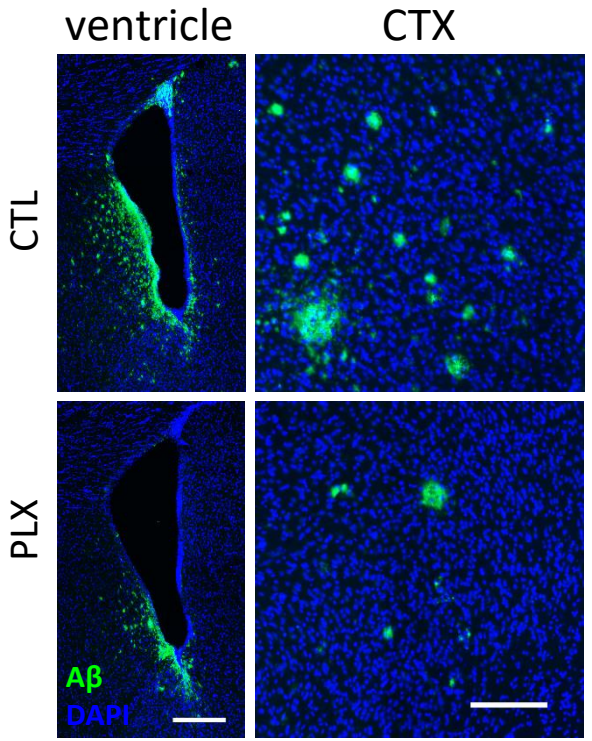
Aβ spreads via the RMS in APP23 mice

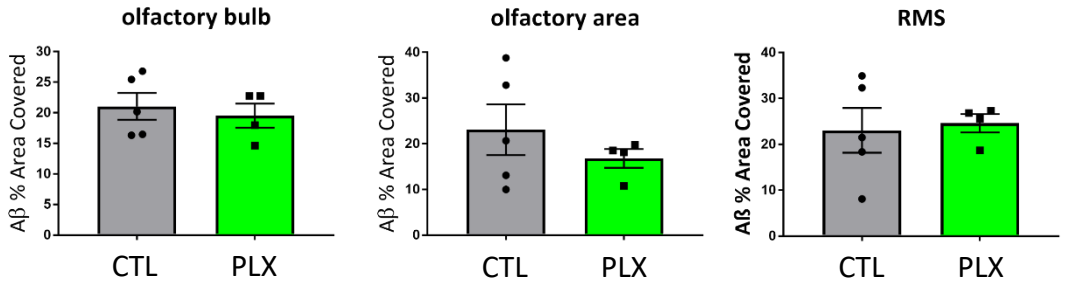


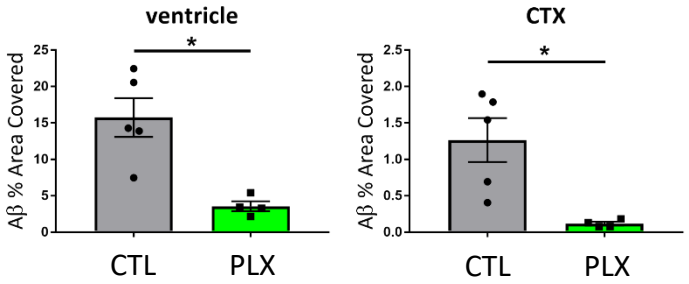


Microglia depletion in APP23 mice



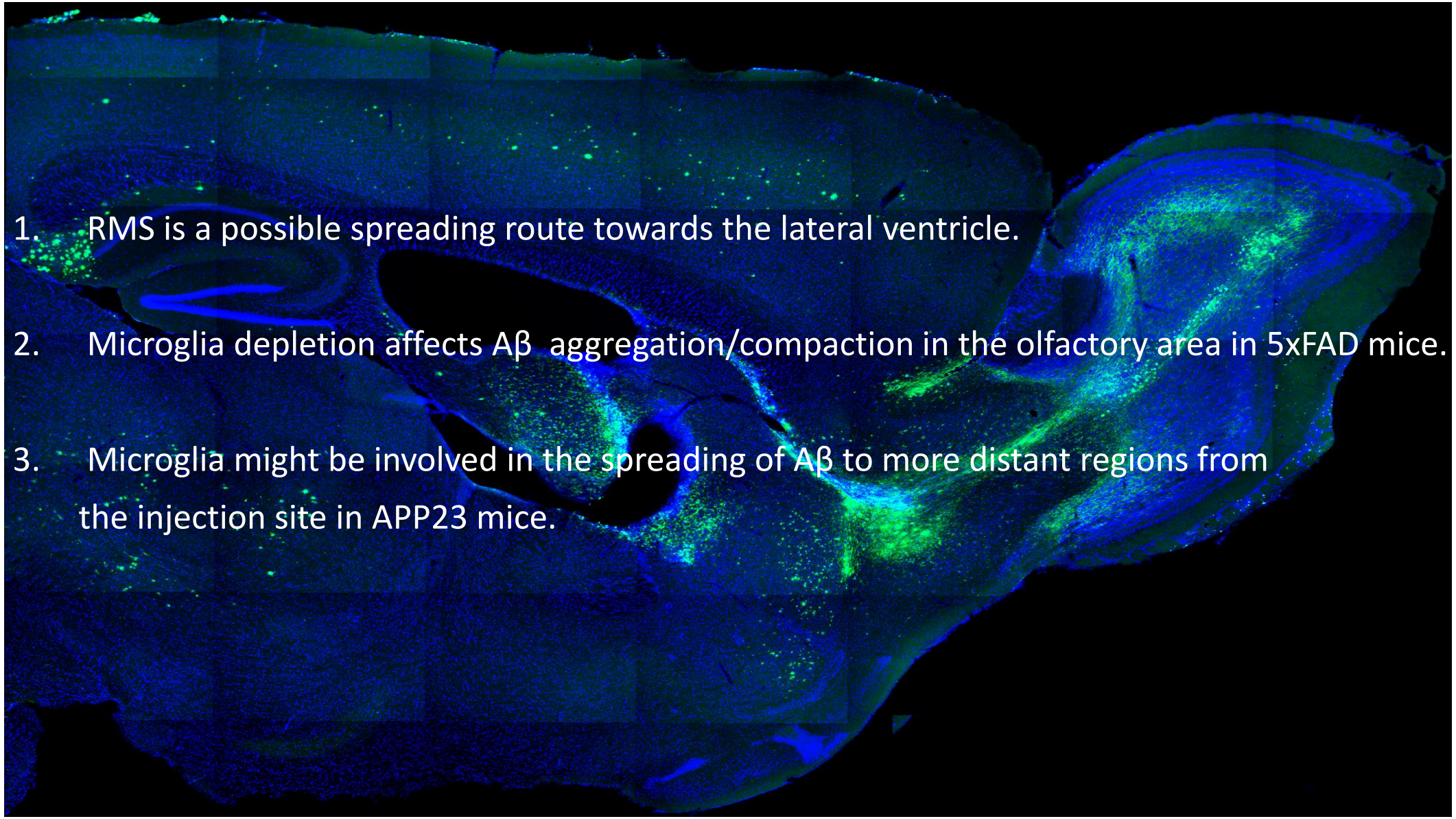






→ Microglia depletion has no effect on Aβ load in brain regions near the injection site

Summary II



1. RMS is a possible spreading route towards the lateral ventricle.

2. Microglia depletion affects Aβ aggregation/compaction in the olfactory area in 5xFAD mice.

3. Microglia might be involved in the spreading of Aβ to more distant regions from the injection site in APP23 mice.

Acknowledgements

AG Meyer-Luehmann

Members:

Hanna Küpper
Iris Früholz
Leoni Ottma

Dr. Paolo d'Errico
Dr. Stephanie Ziegler-Waldkirch
Dr. Marina Friesen
Dr. Vanessa Aires Mofreita
Dr. Jeannine Boudier
Katja Malfertheiner
Charlotte Oldenburg

Collaborators:

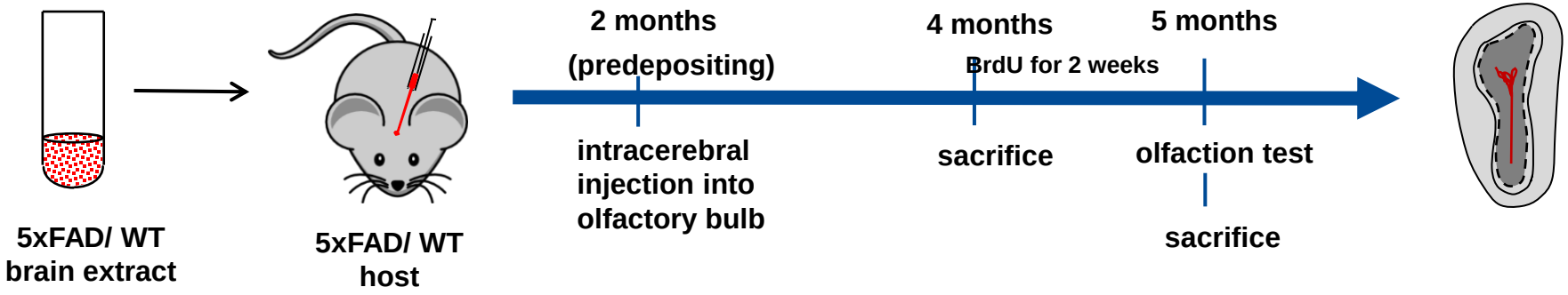
Prof. Marco Prinz, University of Freiburg
Prof. Marlene Bartos, University of Freiburg
Prof. Andreas Vlachos, University of Freiburg
Prof. Christian Haass, LMU Munich and DZNE

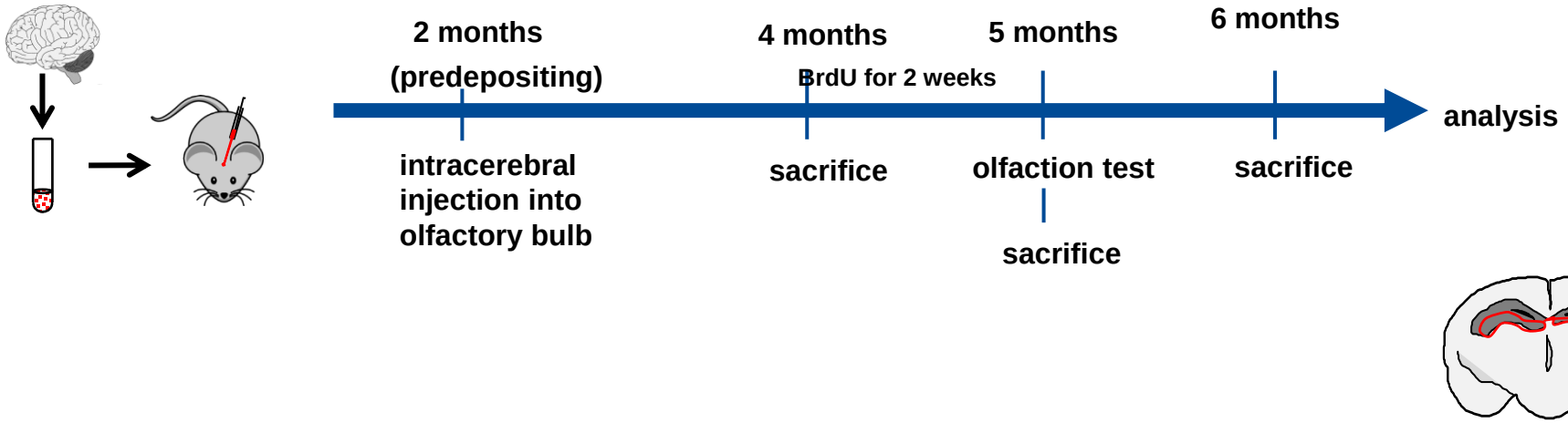
Alzheimer Forschung Initiative e.V.

NEURO MODUL BASICS
Center for Basics in NeuroModulation

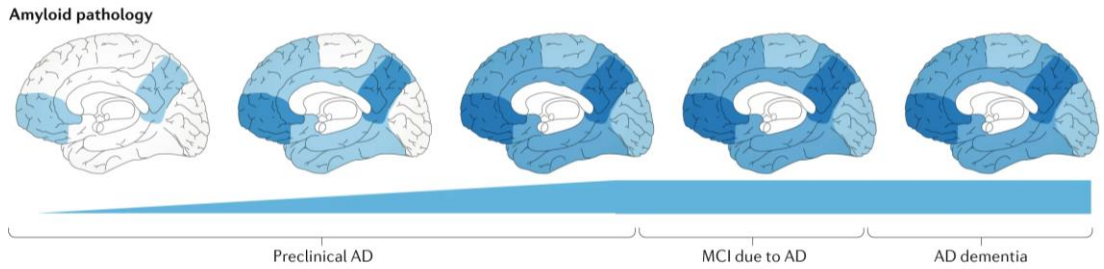
DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Induction of Aβ aggregation *in vivo* (seeding) HC and bulbes Stephi





Possible spreading mechanisms

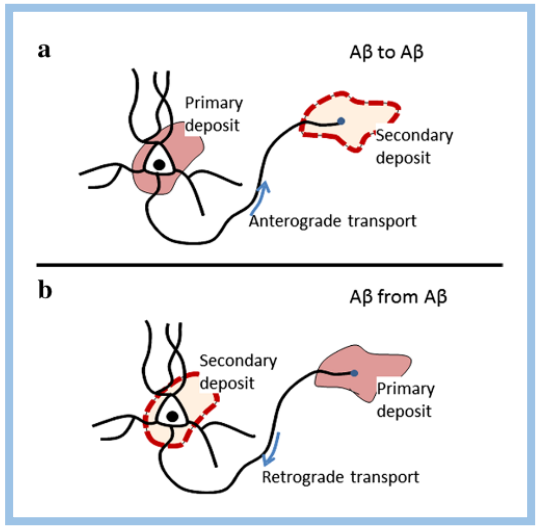


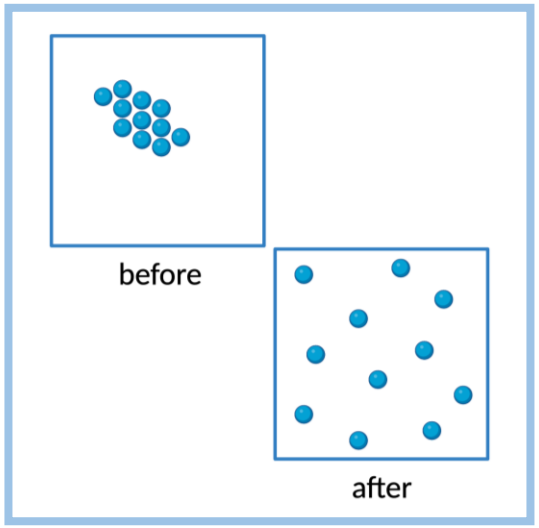
van der Kant et al., 2020

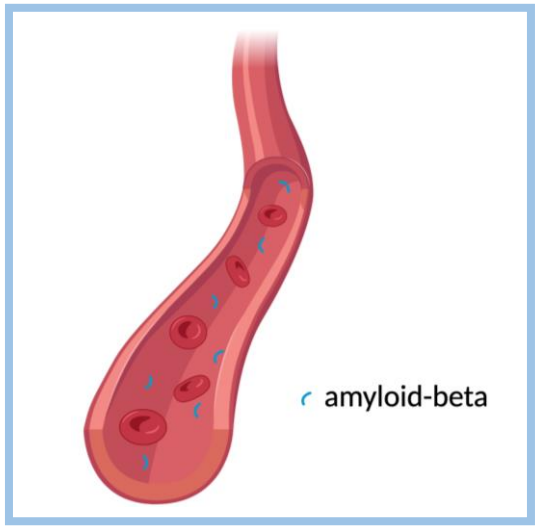
→ Aβ deposition occurs in a **stereotypical spatiotemporal distribution**

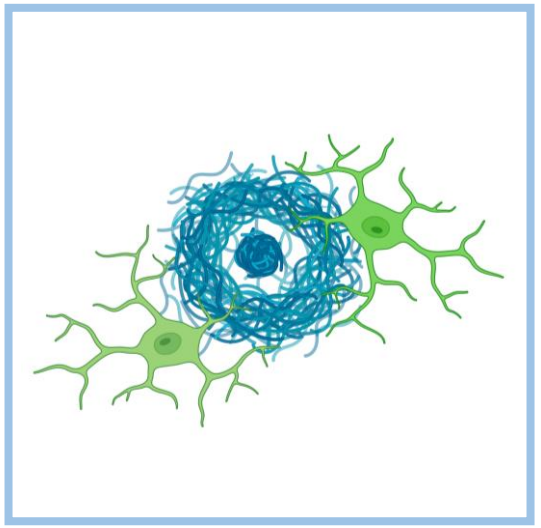
Proposed spreading routes:

- neuronal connections
- passive diffusion
- vasculature
- microglia?



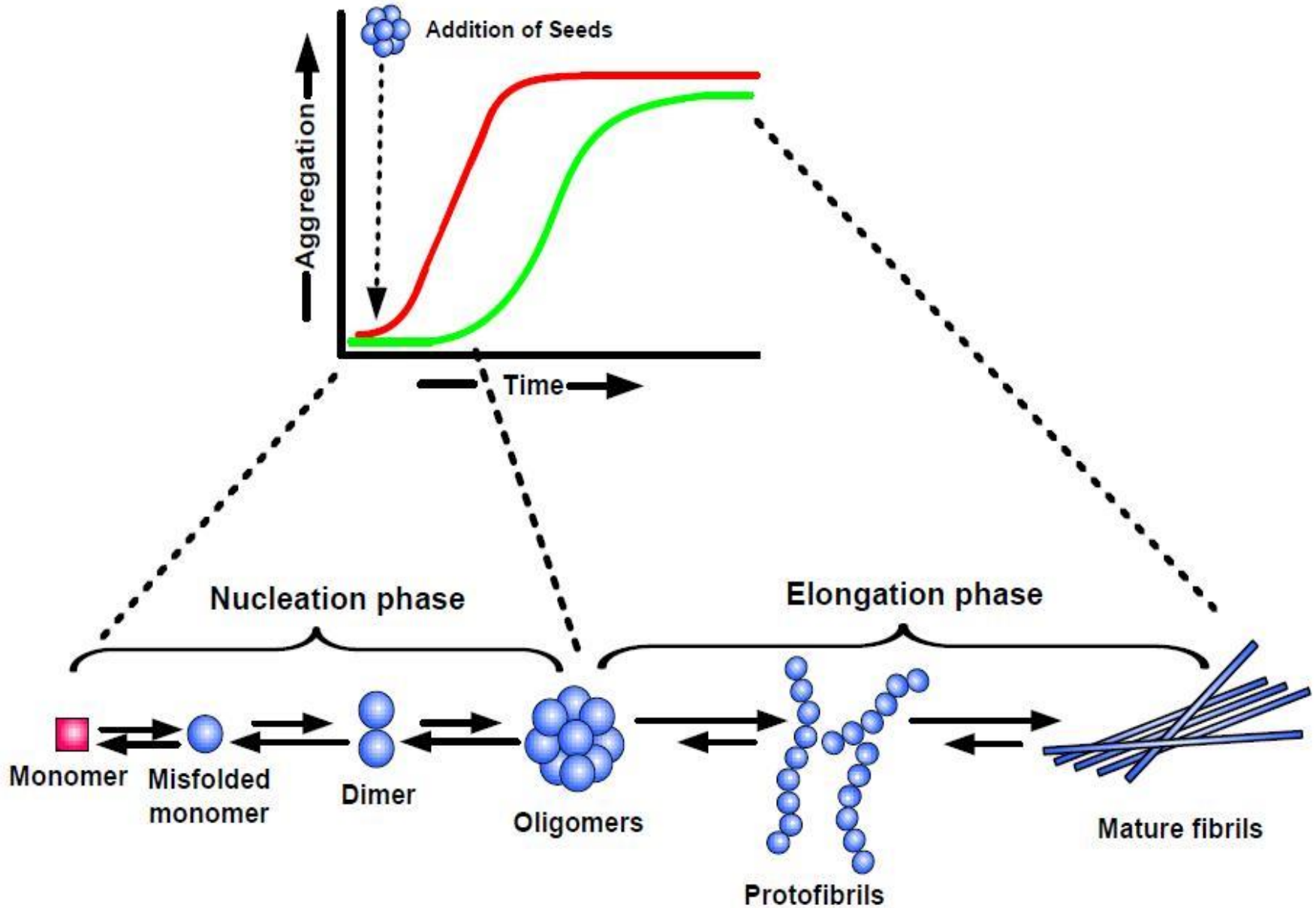




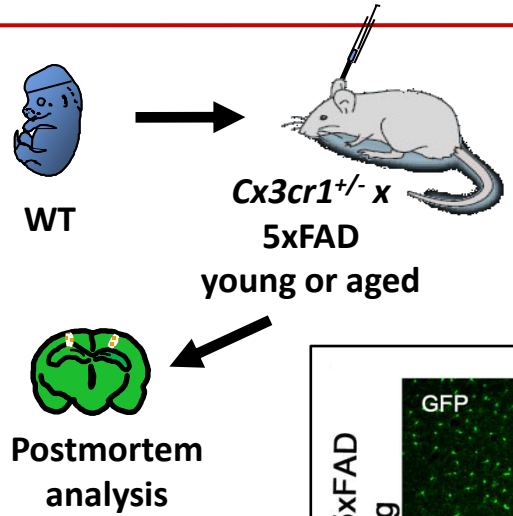


→ What are the mechanisms underlying the spread of Aβ pathology?

Nucleation- dependent polymerization model



Reduced Aβ plaque deposition in cortical WT transplants (1)

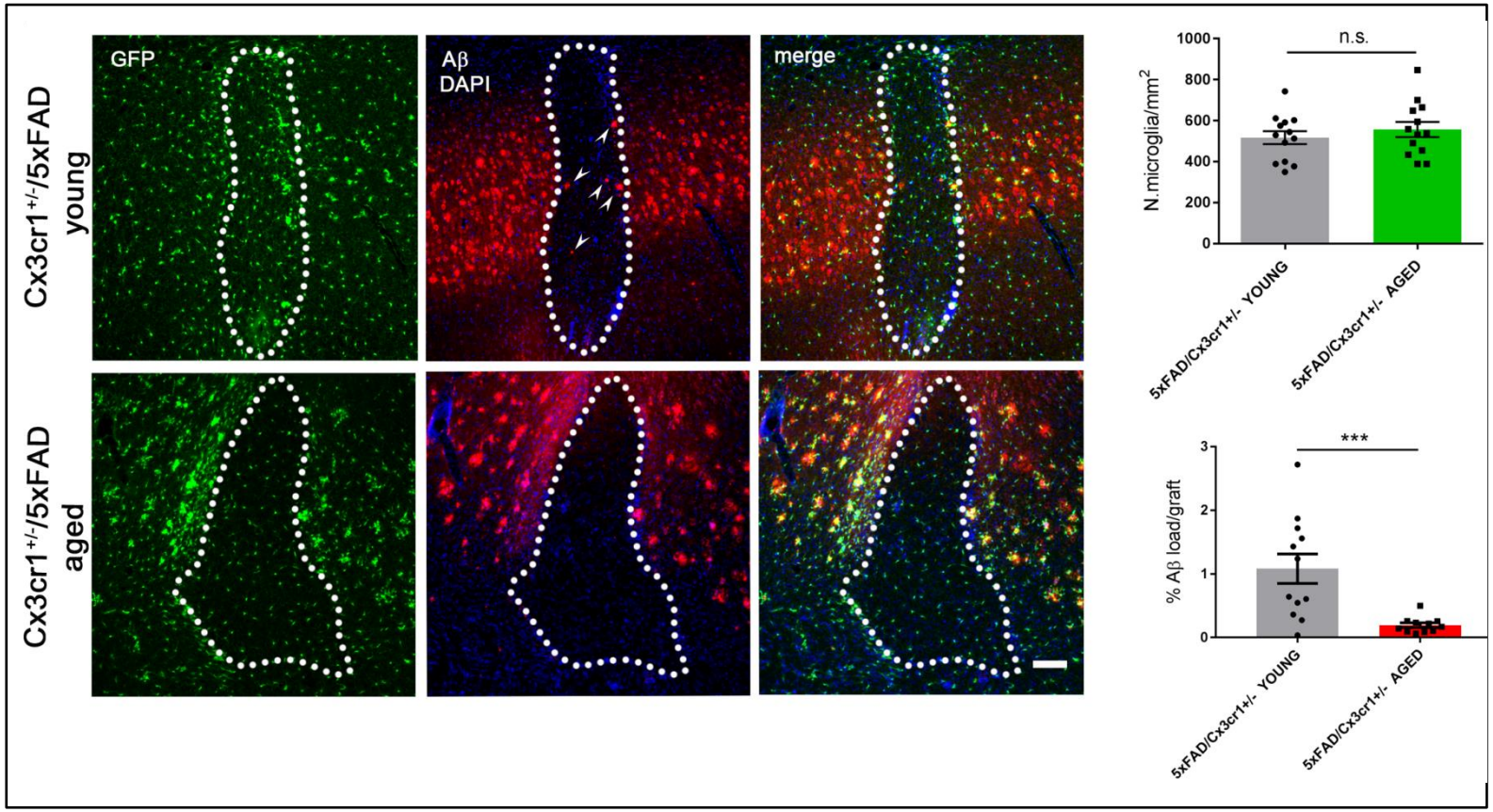


Age of 8 / 40 weeks

injection of
embryonic brain
tissue ED17

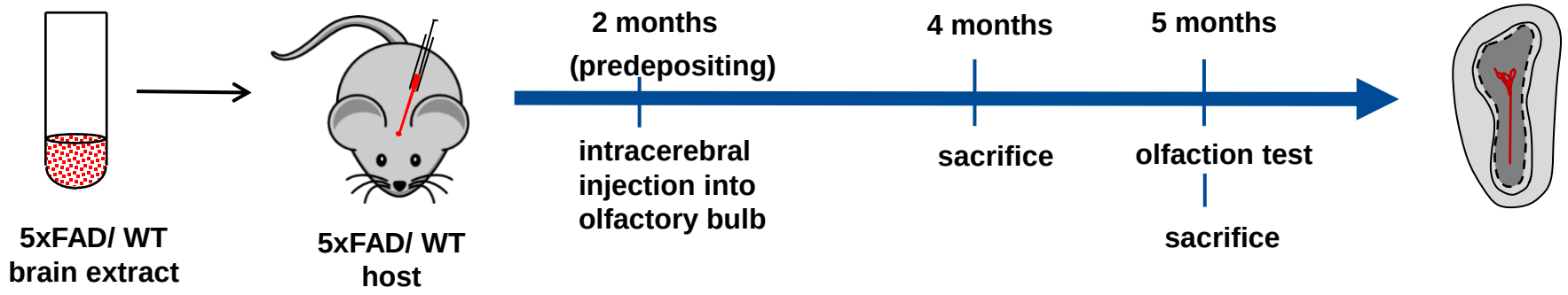
12 / 44 weeks

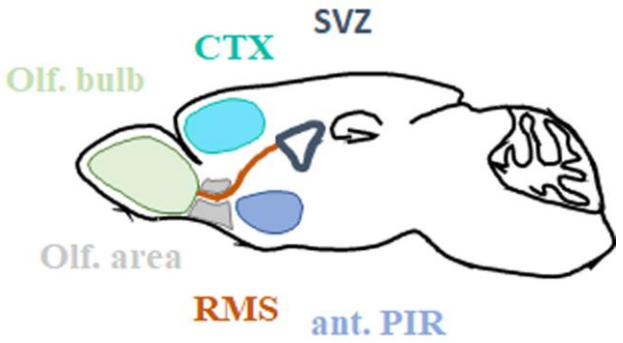
postmortem
analysis
IHC

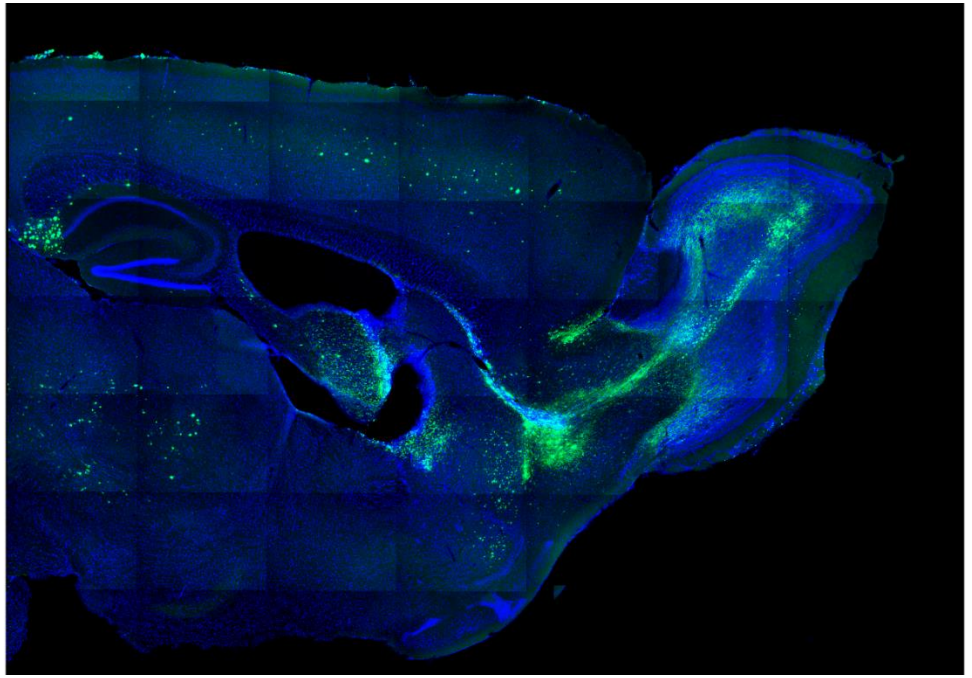


→ Less Aβ uptake by microglia reduces Aβ deposits in WT grafts

Aβ seeds spread via the rostral migratory stream (RMS)







- Neurogenesis occurs throughout life in restricted brain regions: **SGZ** of hippocampus and the **SVZ** of lateral ventricles

- The RMS is the major pathway by which neuroblasts migration from the SVZ to the OB troughout adulthood