The background of the slide is a fluorescence microscopy image of neurons. The neurons are stained with green and red dyes, with some areas showing yellow/orange overlap. The green staining highlights the cell bodies and processes of the neurons, while the red staining appears to be more localized, possibly indicating specific protein expression or damage. The overall image has a dark, textured appearance with bright green and red spots.

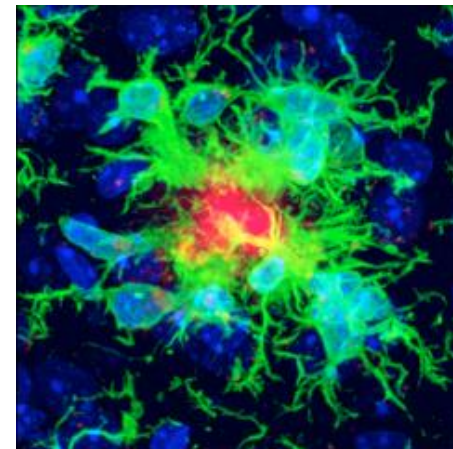
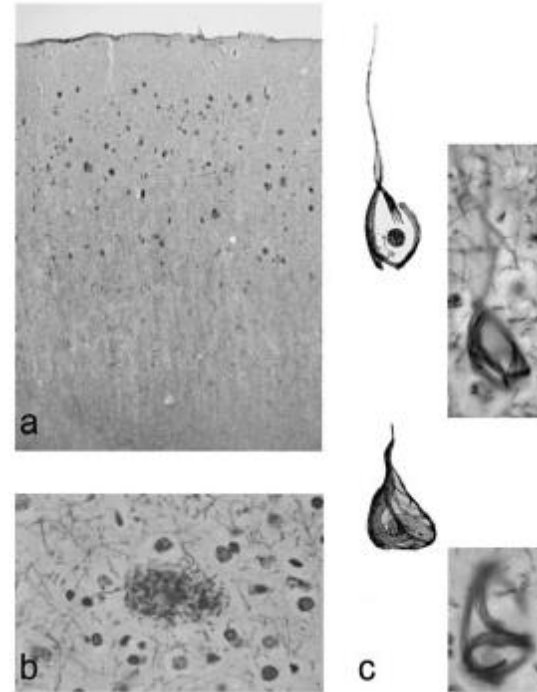
The Role of Innate Immunity in Neurodegenerative Disease Pathogenesis

Bruce Lamb
Department of Neurosciences
Lerner Research Institute
The Cleveland Clinic

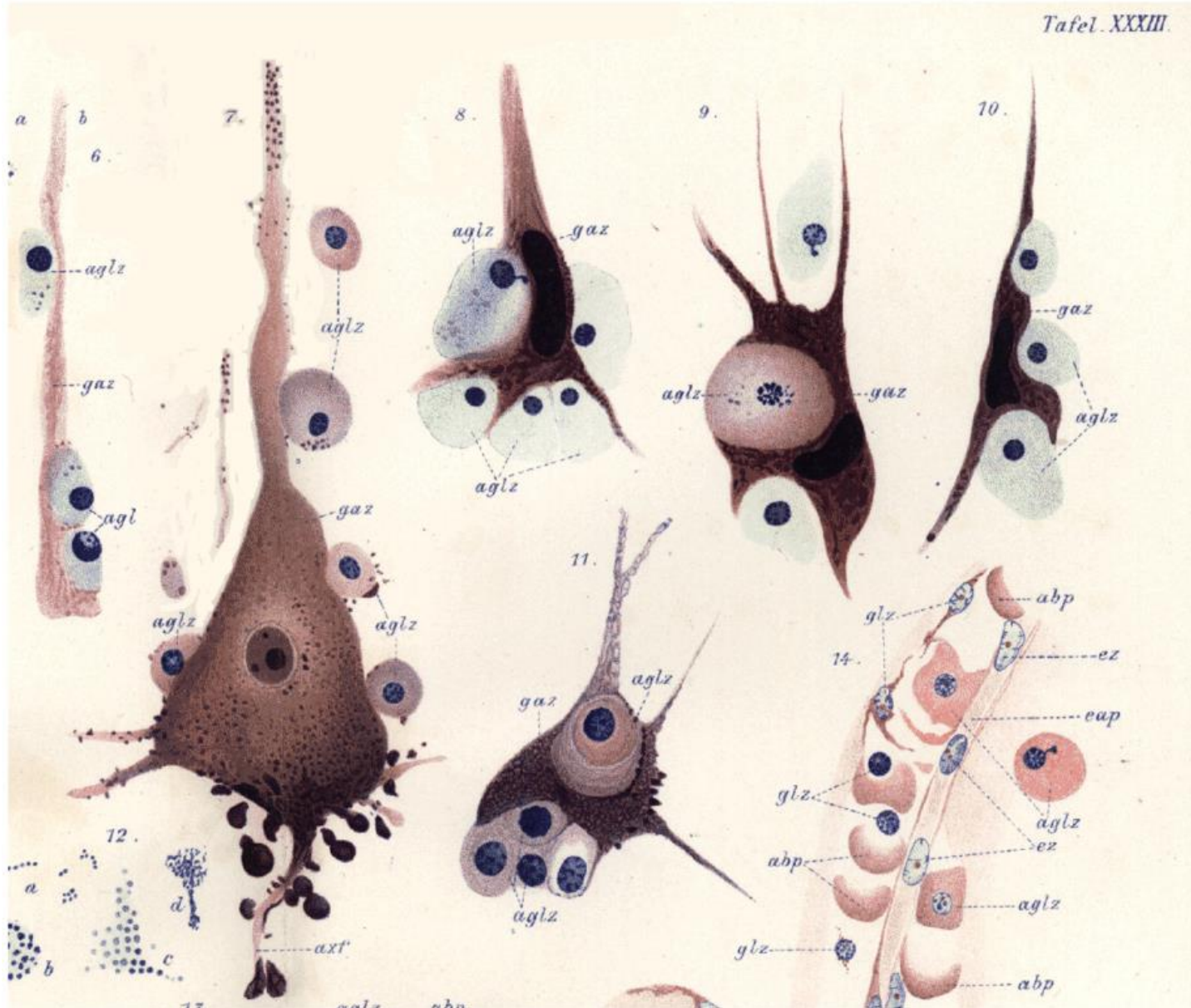
Parisi Lecture
American Association of Neuropathologists
91st Annual Meeting
June 12, 2015

Neuropathological Characteristics of Alzheimer's Disease

- ◆ **Senile Plaques**
 - Extracellular Deposition of Fibrillar β -Amyloid ($A\beta$) Peptide
- ◆ **Neurofibrillary Tangles (NFTs)**
 - Intracellular Accumulation of Hyperphosphorylated MAPT Protein
 - Also Observed in Other Neurodegenerative Diseases (FTDP, PSP, etc.)
- ◆ **Inflammation**
 - Activation of Microglia/Monocytes and Inflammatory Response



Innate Immune Cells in Neurodegeneration

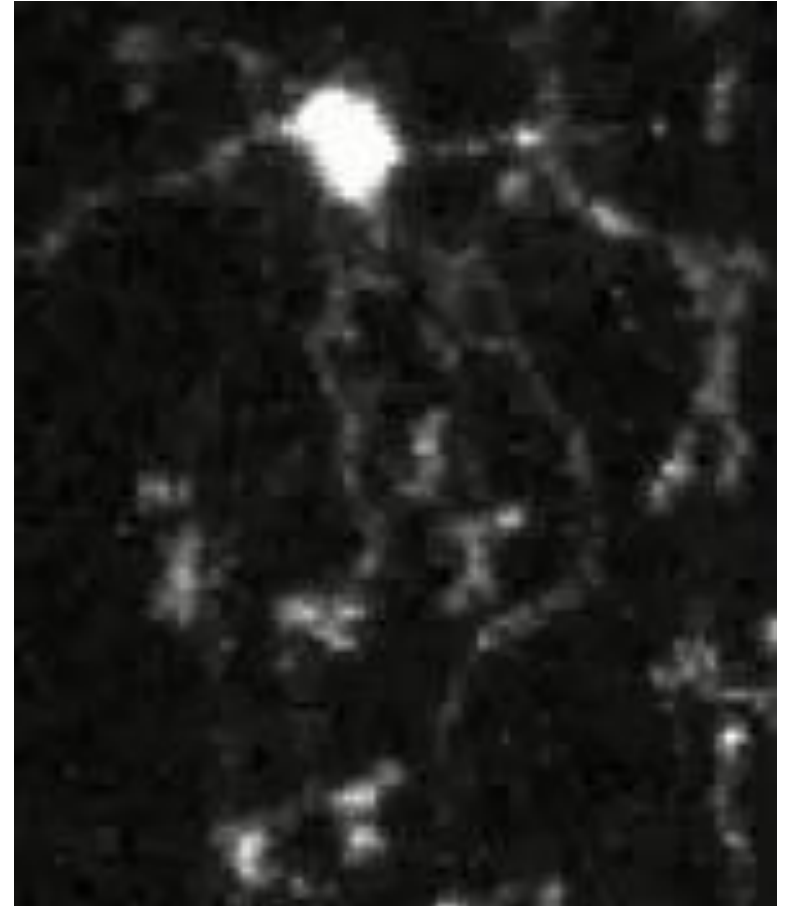


Microglia

(Gr. mikros, small; glia, glue)

◆ Microglia

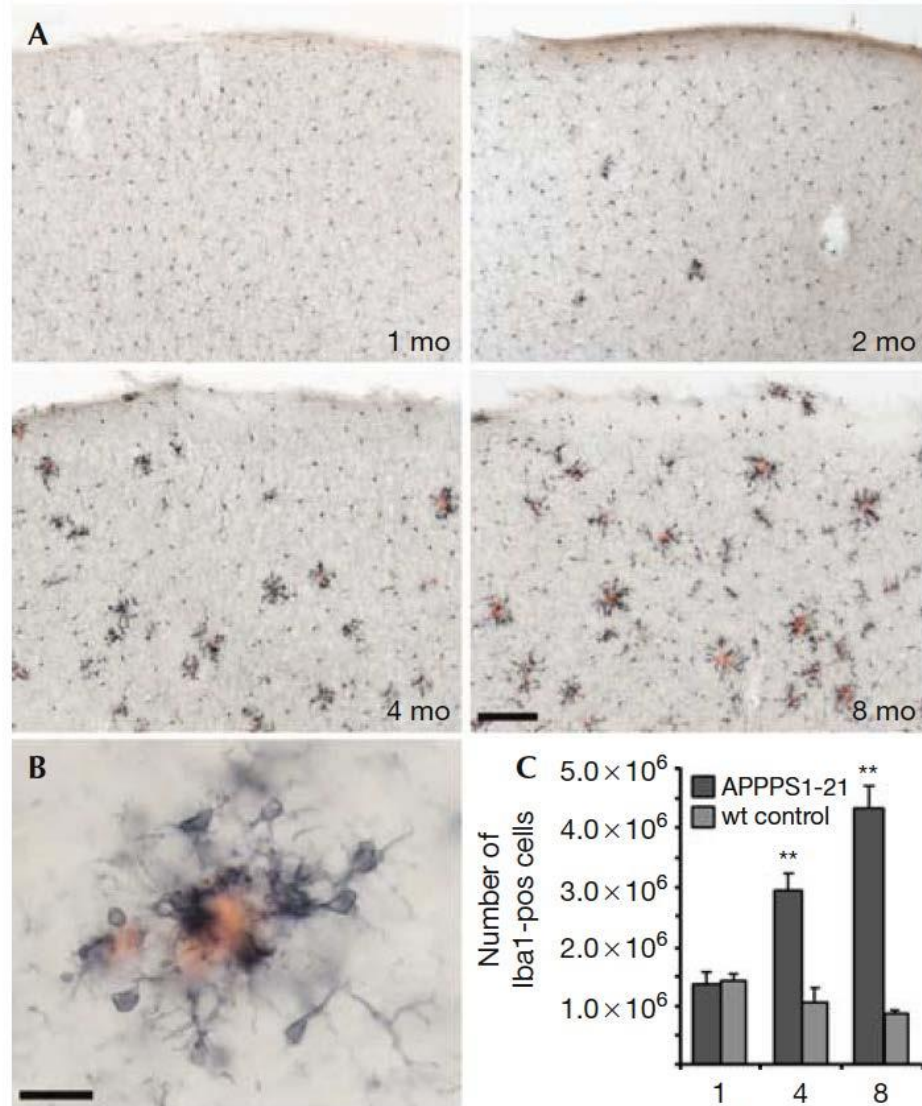
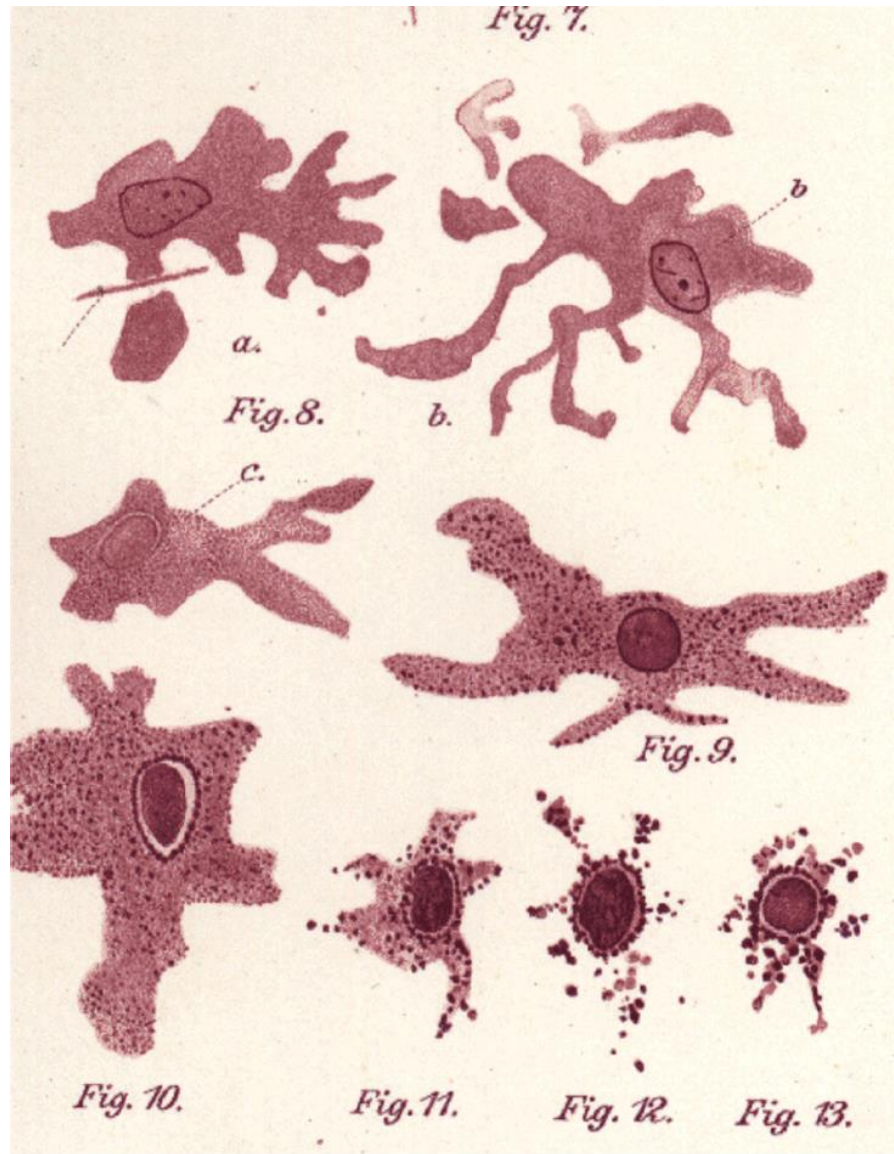
- Primary Immune Effector Cell Within the Brain
- Derived from Yolk Sac, Populate CNS During Embryogenesis
- Little Evidence for Brain Infiltration by Peripheral Immune Cells in Non-Pathological States
- Survey the Entire Brain for Damage Within Hours
- Different States of Activation



Cx3cr1^{+/GFP} Mice

Innate Immune Cells Exhibit Different States of Activation in Neurodegeneration

APPPS1 Mouse Model of AD



Iba1

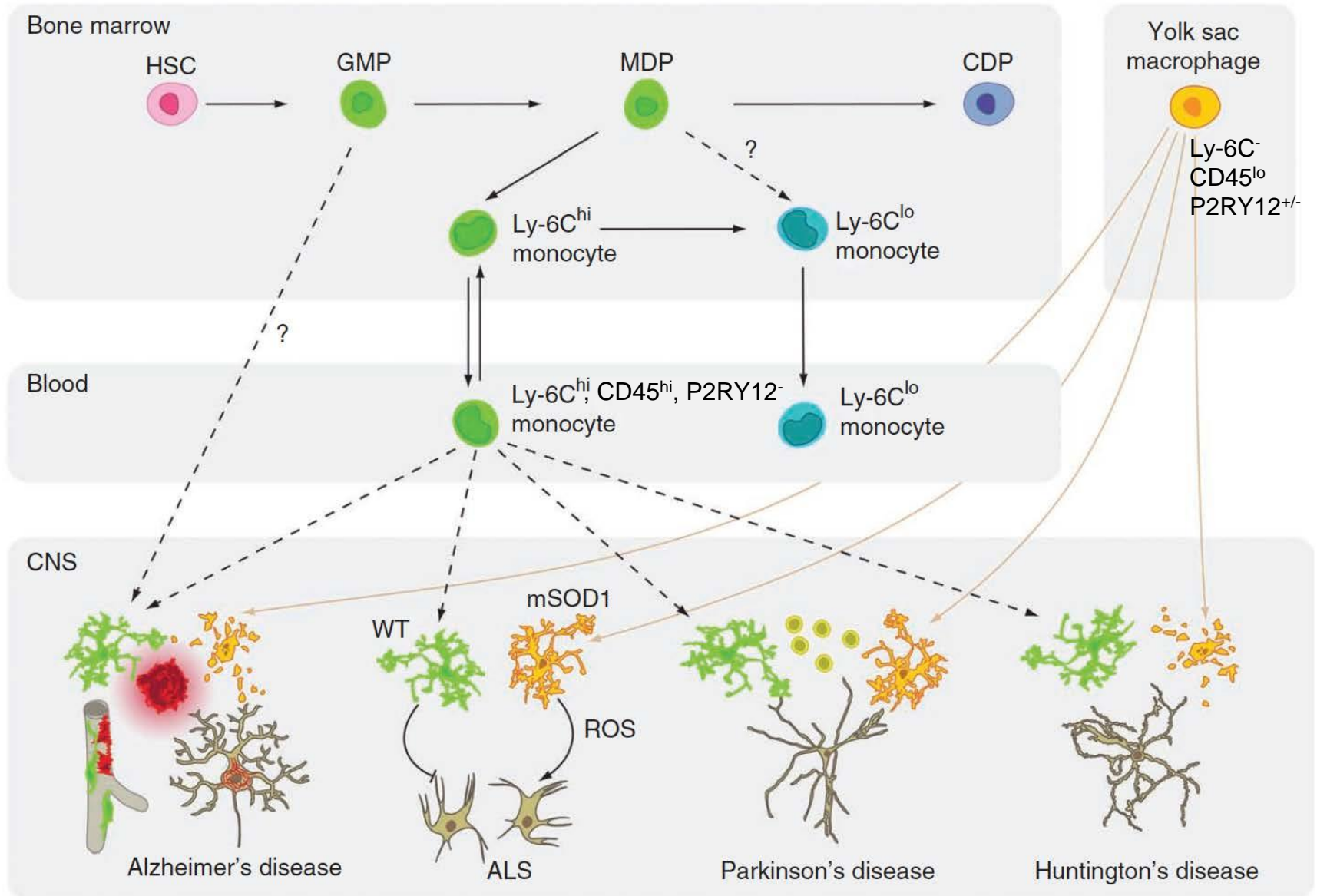
Kettenmann et al., *Phys. Rev.*, **91**: 461-553, 2011; Alzheimer A.U. *Z Neurol Psychiatrie* **4**:356-385, 1911; Radde et al., *EMBO Rep.*, **7**:940-946, 2006

Complexity of Innate Immune Cell Activation



Types of Innate Immune Cells in Neurodegeneration?

Innate Immune Cells In Neurodegeneration

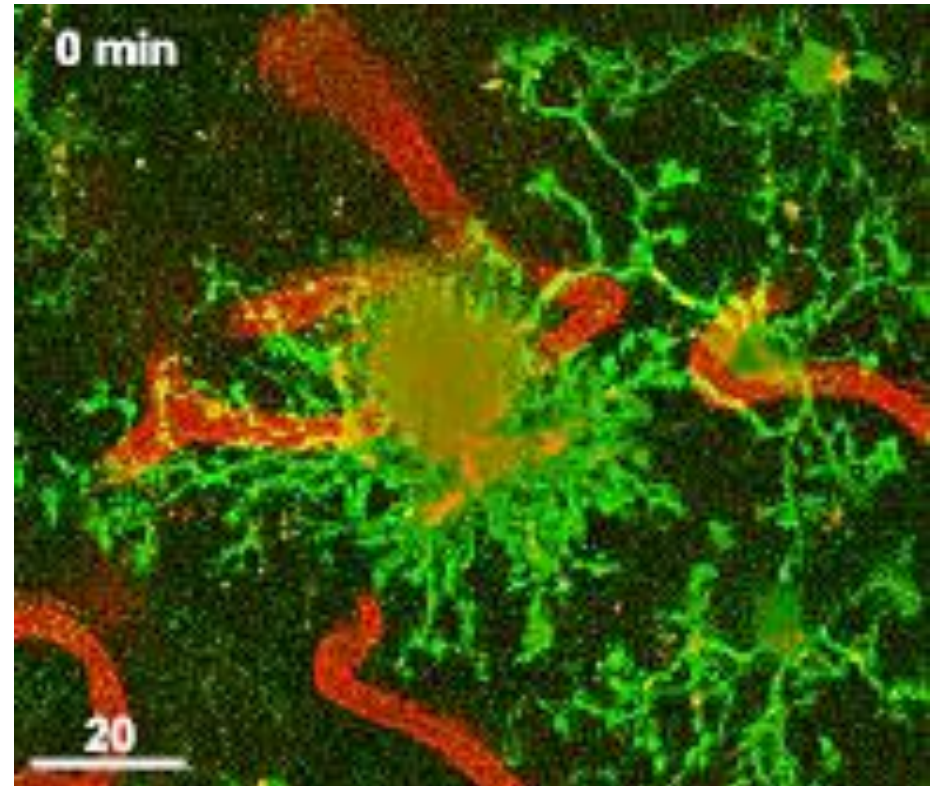


HSC-hematopoietic stem cells, GMP-granulocyte-myeloid progenitors, MDPs- monocyte-dendritic cell progenitors

Myeloid Cells and A β Pathology

◆ Myeloid Cells Activation Upon A β Deposition

- Myeloid Cells Rapidly Move and Surround A β Deposits
- Alteration in Morphology
- Expression of Cytokines and Chemokines
- Myeloid Cells Can Remove A β (Phagocytosis and Pinocytosis)



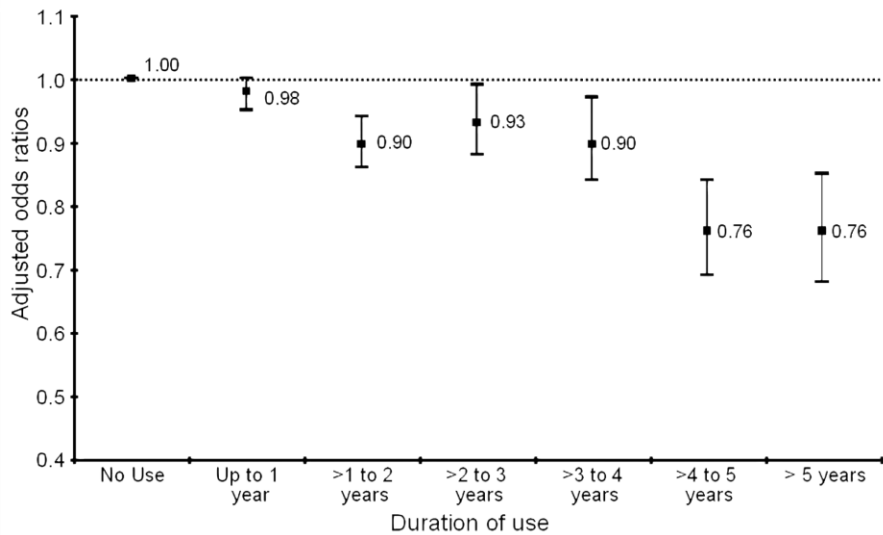
Cx3cr1^{+/GFP} Mice

Other Evidence for Role of Innate Immunity in AD?

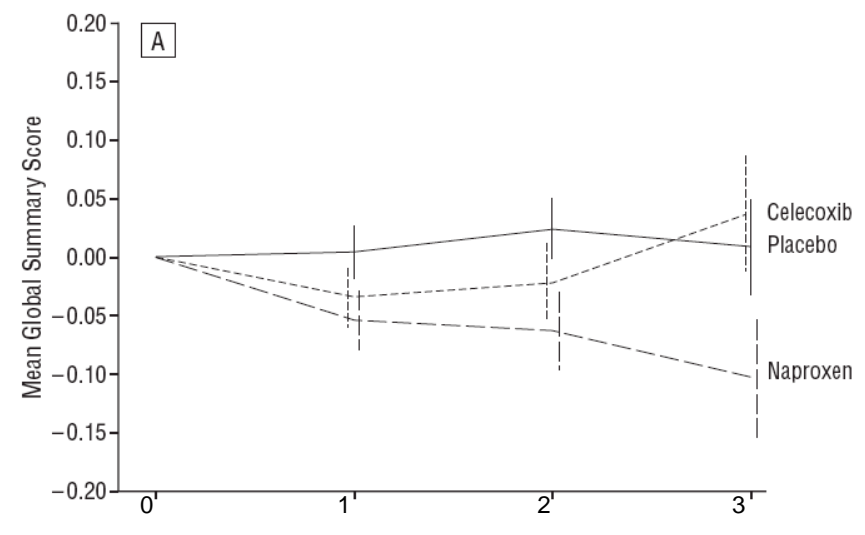
NSAIDs and Alzheimer's Disease

◆ Epidemiological Evidence

- Retrospective Studies Indicate NSAIDs Reduce AD Risk
- Prospective NSAIDs Studies Suggest Limited Efficacy



Vlad et al., *Neurology*, **70**:1672-1677, 2008

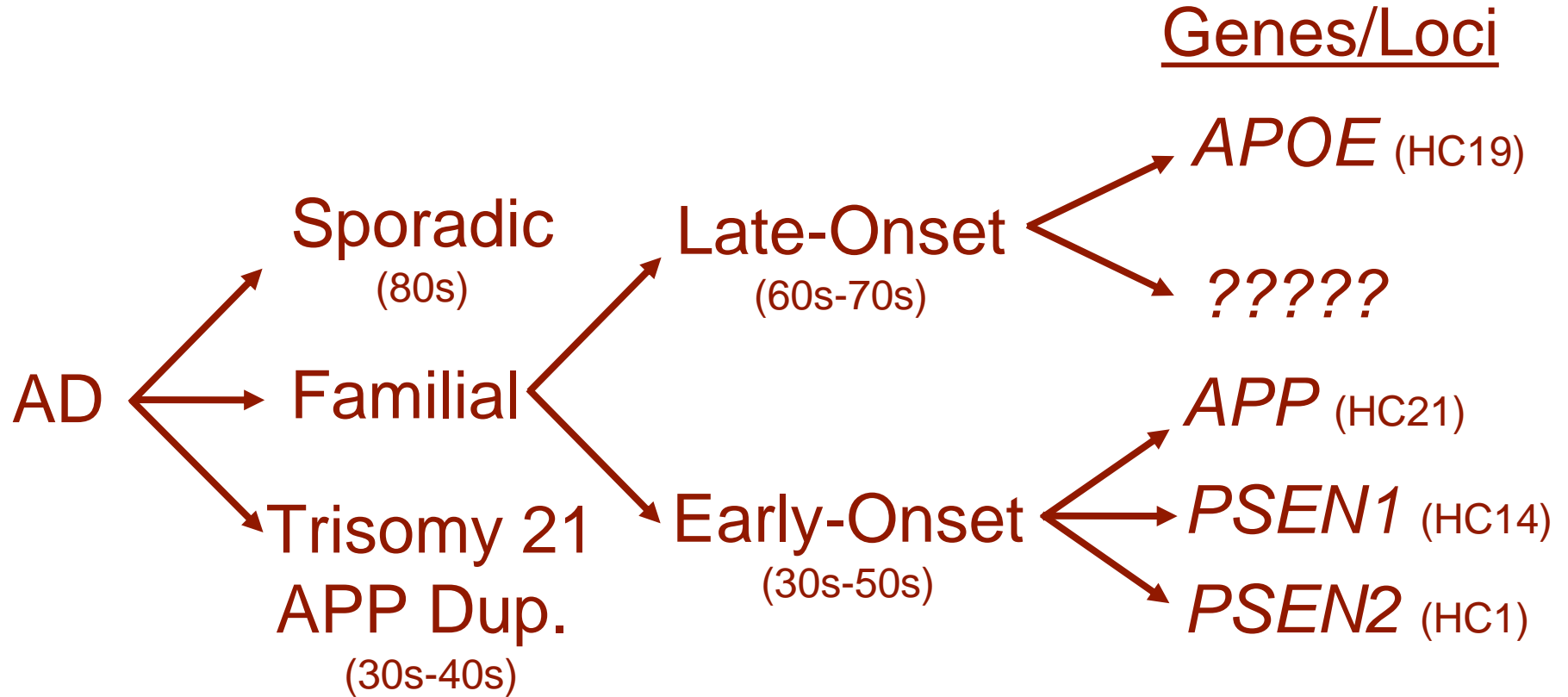


ADAPT, *Arch Neurol*, **65**:896-905, 2008

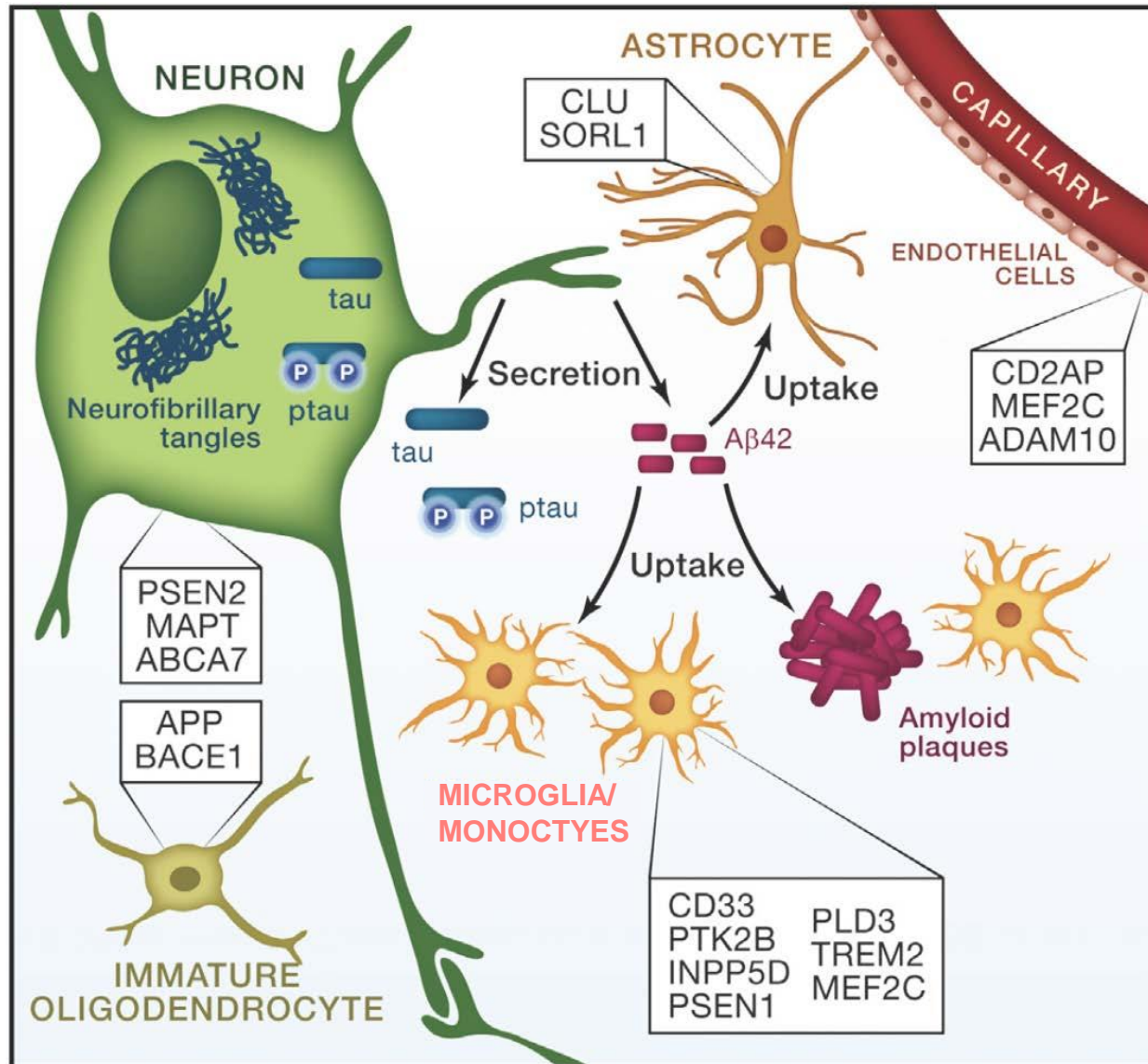
Role of Inflammation at Specific Stages of AD?

Other Evidence Implicating Innate Immunity in AD?

Alzheimer's Disease Genetics



Recent Genetic Studies of AD Implicate Innate Immune Pathways



Recent Genetic Studies Implicate Innate Immunity in Neurodegeneration

Triggering Receptor Expressed on Myeloid Cells 2

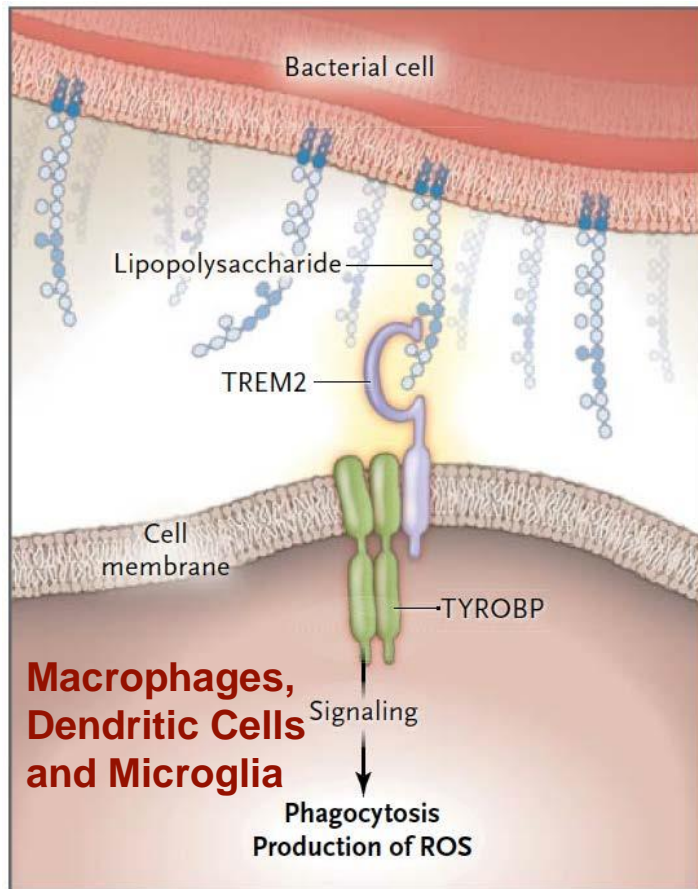


Table 1. Association between the rs75932628-T Variant and Alzheimer's Disease in Comparisons with Three Control Groups.

Control Group	No. of Participants	Frequency %	Odds Ratio (95% CI)	P Value
All population controls	110,050	0.63	2.26 (1.71–2.98)	1.13×10^{-8}
Population controls ≥ 85 yr of age	8,888	0.46	2.92 (2.09–4.09)	3.42×10^{-10}
Cognitively intact controls ≥ 85 yr of age*	1,236	0.31	4.66 (2.38–9.14)	7.39×10^{-6}

Table 2. Coding Variants Found in TREM2 through DNA Sequencing in Patients with Alzheimer's Disease and in Controls.*

Variant	SNP Number	Position†	Minor Alleles	Patients with Alzheimer's Disease		Controls		Reference Allele	P Value‡	Odds Ratio (95% CI)	PolyPhen-2§
				No. of Nonreference Alleles	No. of Cases	No. of Nonreference Alleles	No. of Controls				
All variants				60		38			0.02¶		
L211P	rs2234256	41126655	G	0	281	3	503	A	0.56	0	Benign (0.001)
H157Y	rs2234255	41127543	A	1	281	0	504	G	0.36	NA	Possibly damaging (0.7)
R136Q	rs149622783	41127605	T	1	281	1	501	C	1.00	1.8 (0.1–28.6)	Benign (0.0)
R98W	rs147564421	41129100	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
T96K	rs2234253	41129105	T	4	1091	3	1105	G	0.72	1.4 (0.3–6.0)	Probably damaging (1.0)
D87N	rs142232675	41129133	T	6	1091	0	1105	C	0.02	NA	Probably damaging (1.0)
N68K	NA	41129188	C	0	1090	1	1105	G	1.00	0	Benign (0.05)
T66M	rs201258663	41129195	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
R62H	rs143332484	41129207	T	25	1090	31	1104	C	0.50	0.8 (0.3–1.4)	Benign (0.02)
R47H	rs75932628	41129252	T	22	1091	5	1105	C	<0.001	4.5 (1.7–11.9)	Probably damaging (1.0)
Y38C	NA	41129279	G	3	1091	0	1107	A	0.12	NA	Probably damaging (1.0)
Q33X	rs104894002	41129295	A	2	1084	0	1103	G	0.25	NA	NA
Nasu-Hakola mutations	Q33X, Y38C, T66M			6		0			0.01	NA	Known damaging

TREM2 Also Risk For Other Neurodegenerative Diseases

Loss-of-Function TREM2 Mutations Cause Nasu-Hakola Disease

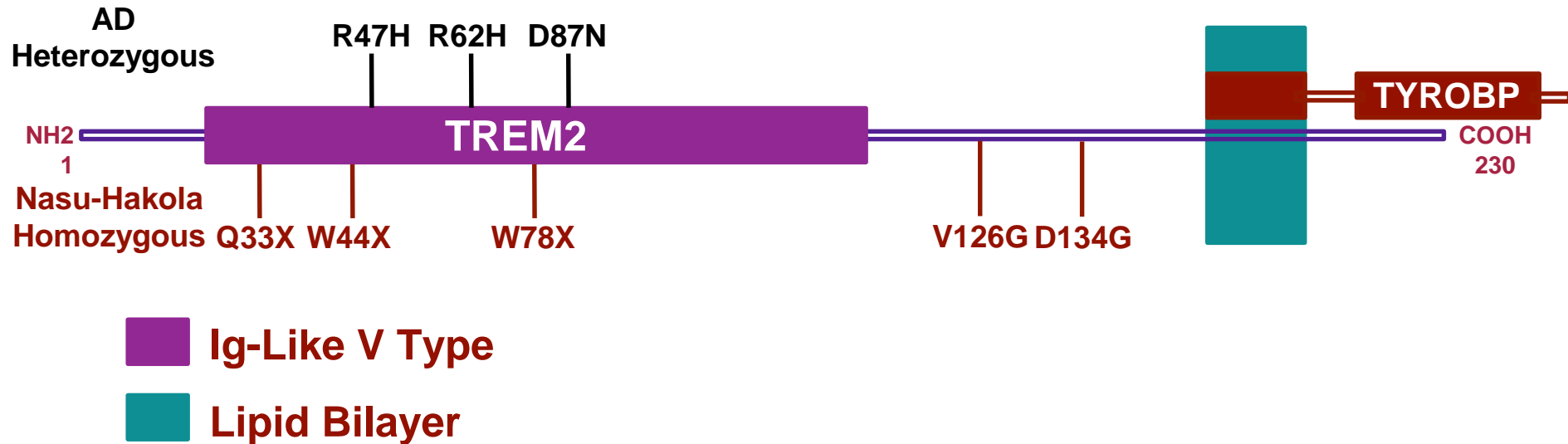
(Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy; PLOSL)

TREM2 Variants also Associated with Frontotemporal Dementia, Parkinson's Disease, Amyotrophic Lateral Sclerosis

Jonsson et al., *NEJM*, 368:107-116, 2012; Guerreiro et al., *NEJM*, 368:117-127, 2012; Neumann and Daly, *NEJM*, 368:182-184, 2012

Role of TREM2 In Neurodegeneration

Triggered Receptor Expressed on Myeloid Cells 2

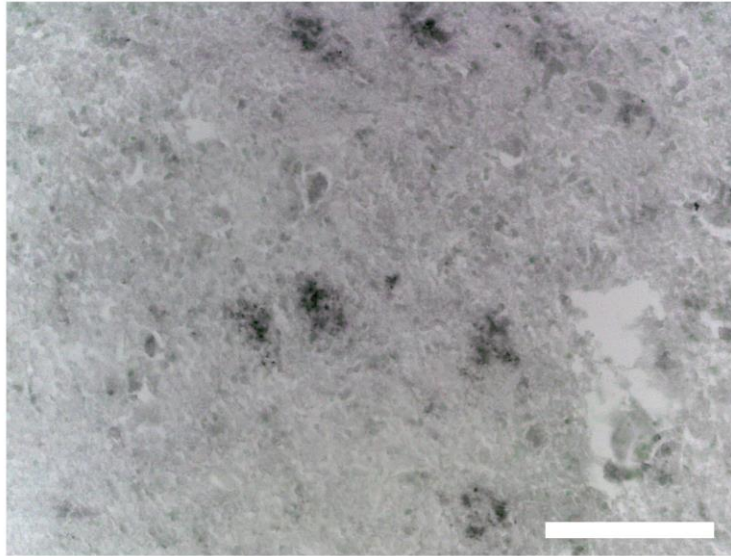


What Cells Promote TREM2-Dependent Risk?

TREM2 Expression Around A β Deposits in Human AD

AD

88 Year Old
Male



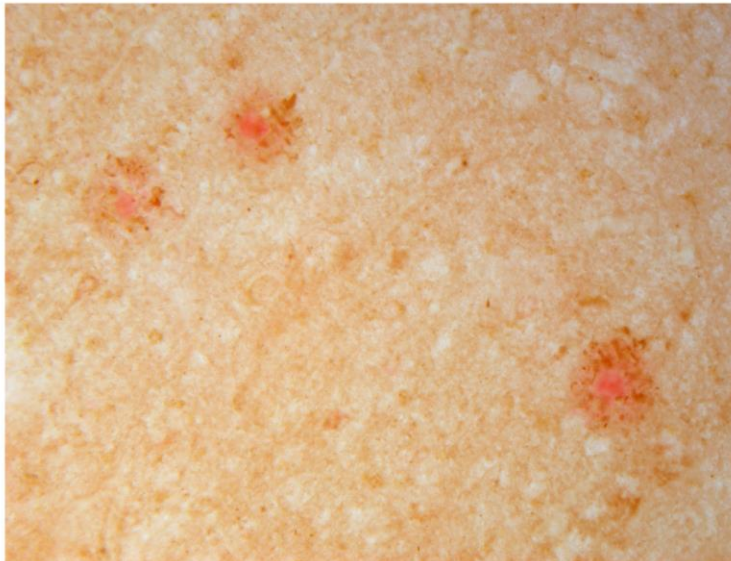
AD

78 Year Old
Male



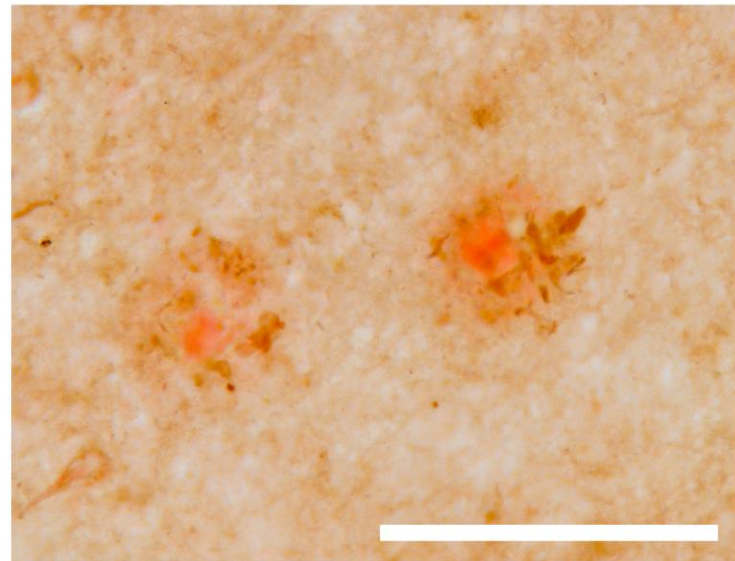
AD

78 Year Old
Male



AD

78 Year Old
Male



TREM2 IHC/Congo Red



Cleveland Clinic

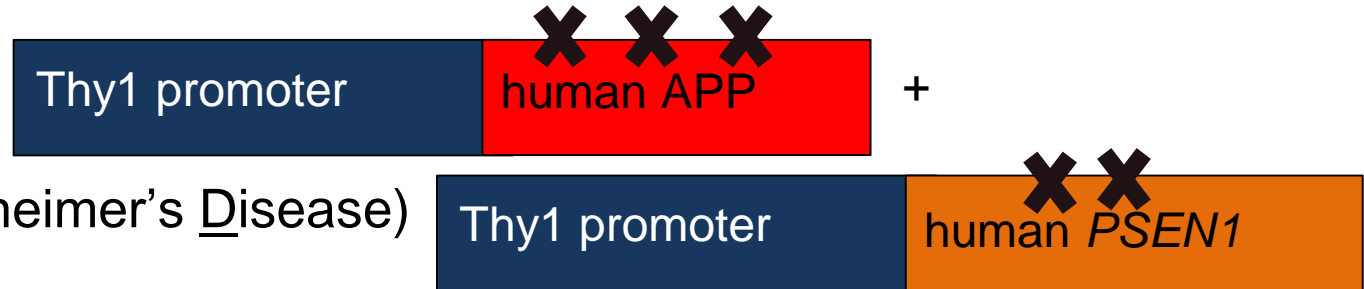
TREM2 Expression in Mouse Models of AD?

Jay et al., *J. Exp. Med.*, 212:287-297, 2005

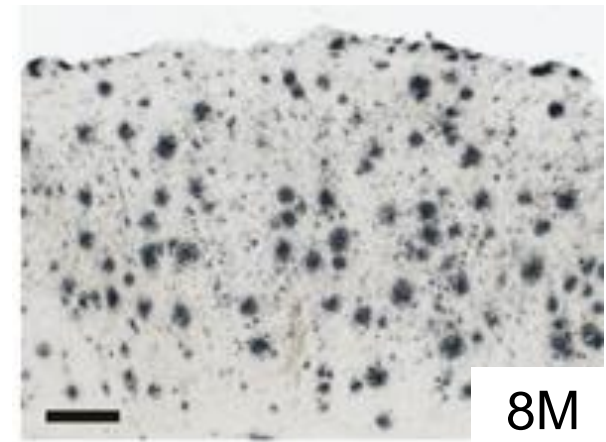
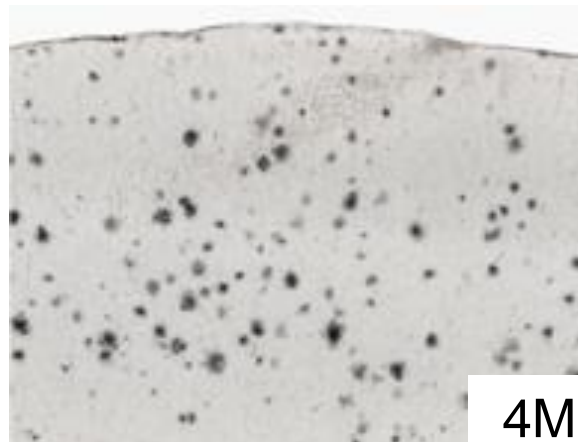
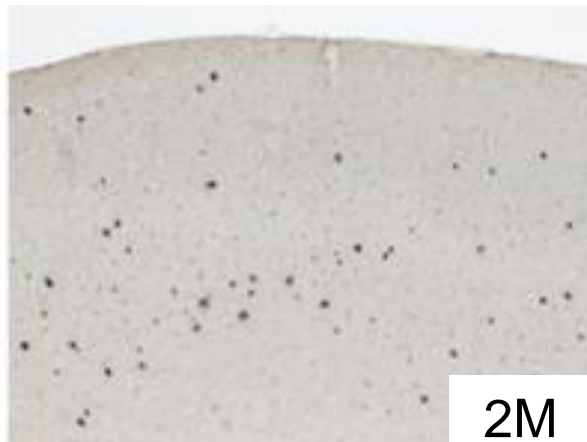
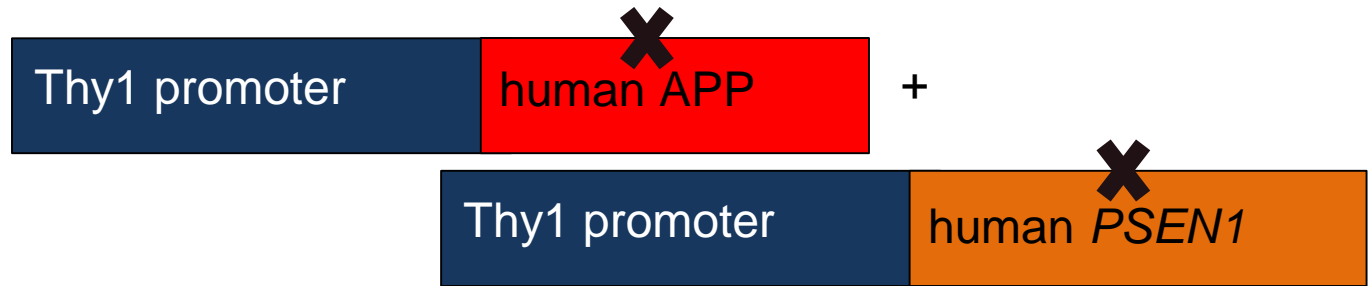
Mouse Models of AD With A β Deposits

5xFAD

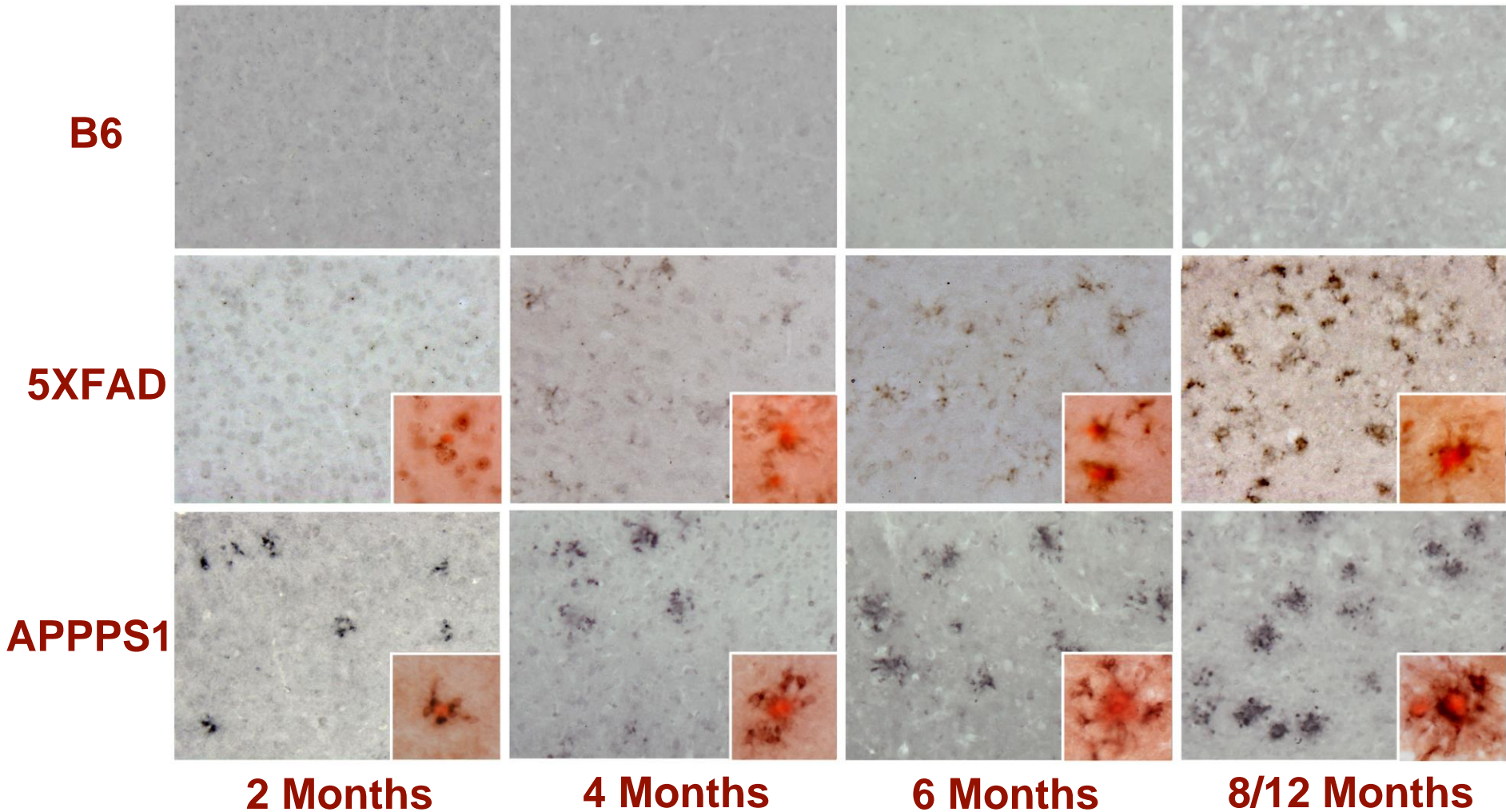
(Familial Alzheimer's Disease)



APPPS1



Age-Related TREM2 Expression Around A β Deposits in Mouse Models of AD



TREM2 IHC/Congo Red

Trem2 Knock-Out Confirms Antibody Specificity

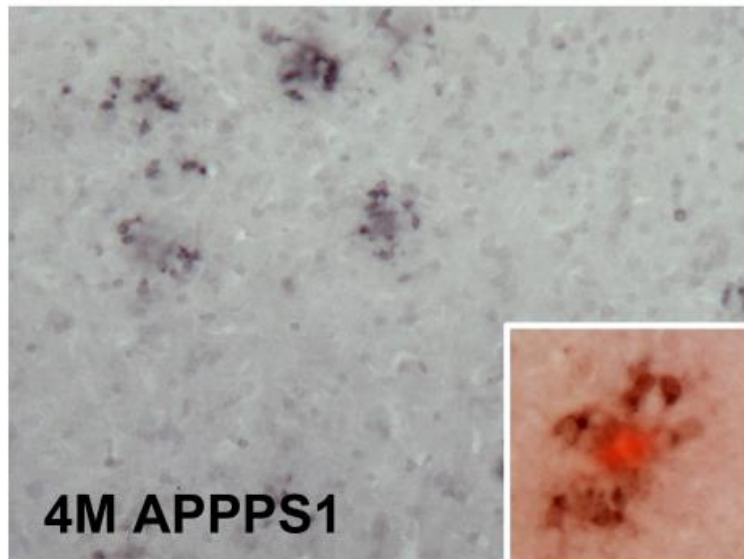
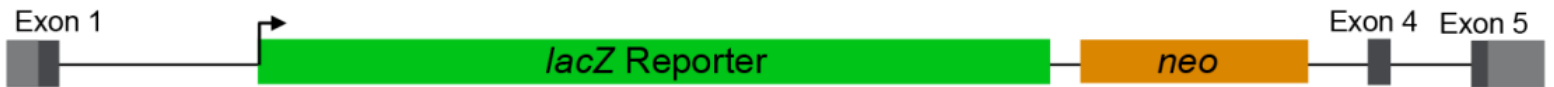
Trem2 gene



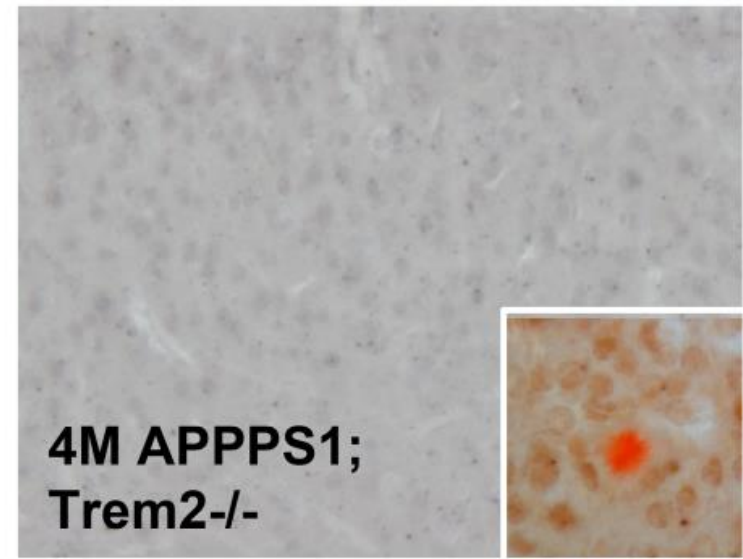
Trem2 targeting construct (ZEN-Ub1)



Trem2 knock-out/LacZ knock-in



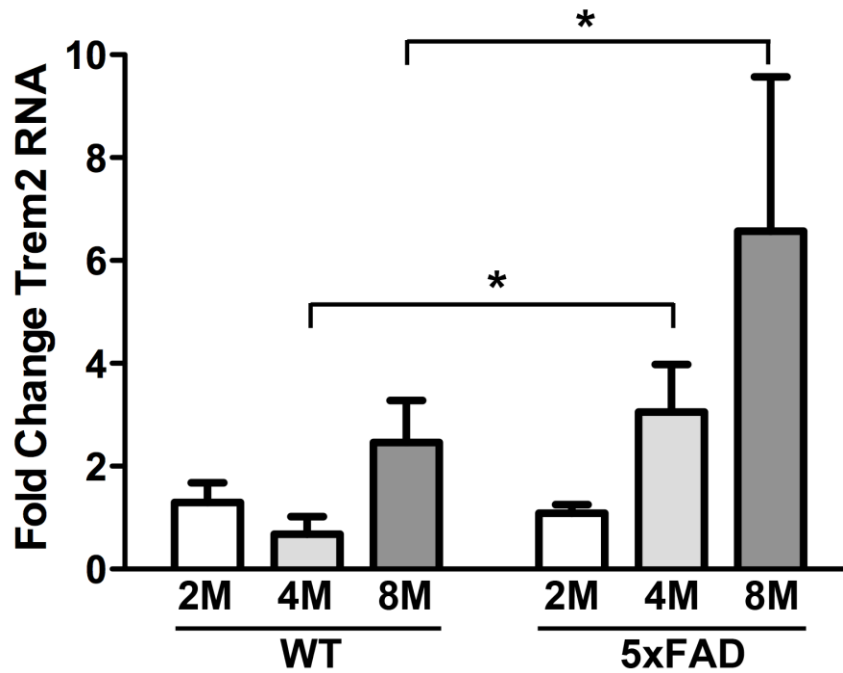
Location: Cortex



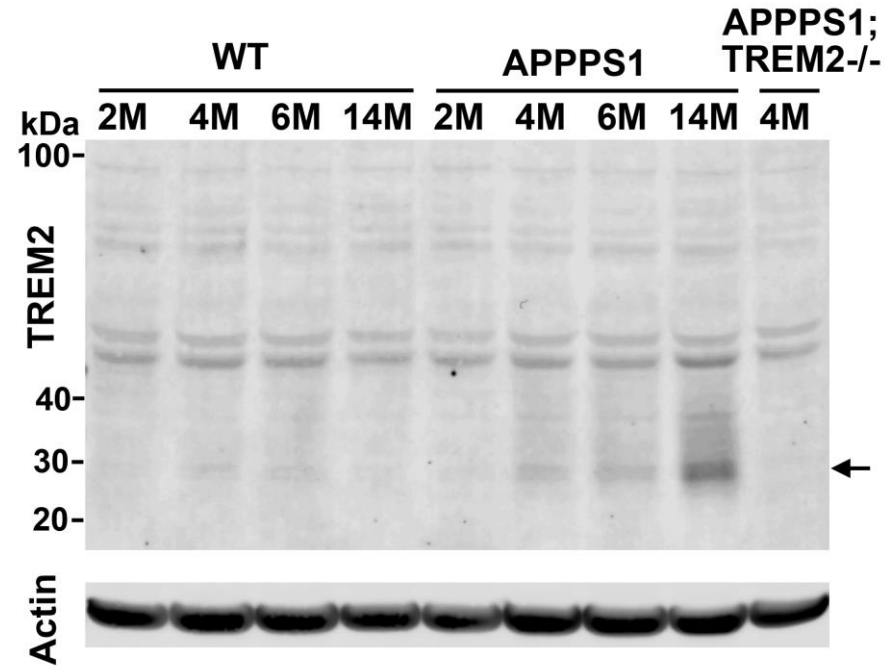
Markers: TREM2 Congo Red

Jay et al., *J. Exp. Med.*,
212:287-295, 2105

Age-Related Up-Regulation of TREM2 in Mouse Models of AD



TREM2 RNA

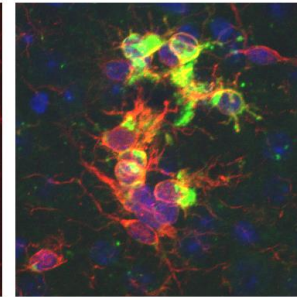
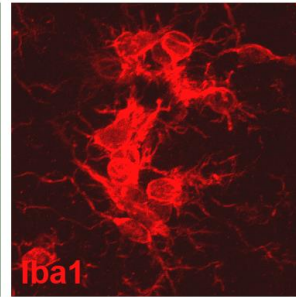
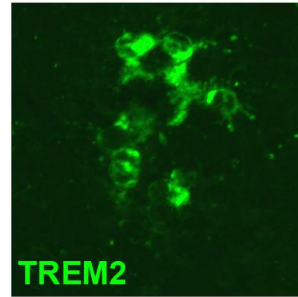


TREM2 Protein

What Cells Express TREM2?

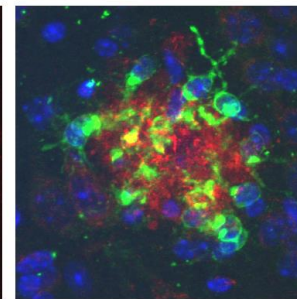
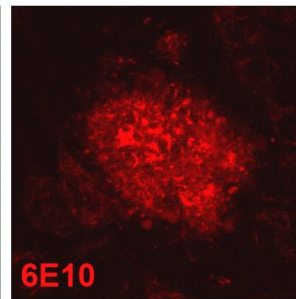
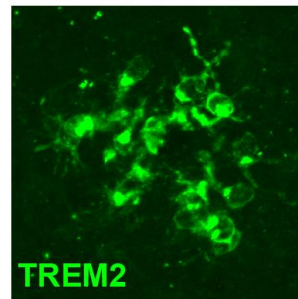
TREM2 Expression in Iba1⁺ Myeloid Cells Around A β Deposits in Mouse Models of AD

TREM2/
Iba1 IHC



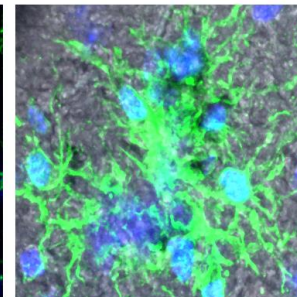
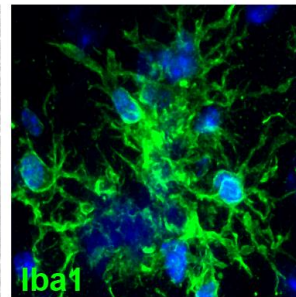
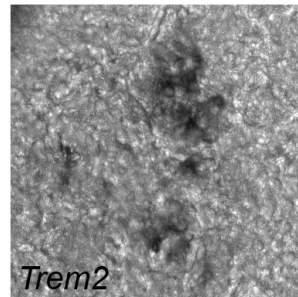
APP/PS1

TREM2/
6E10 IHC



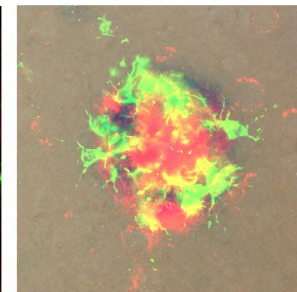
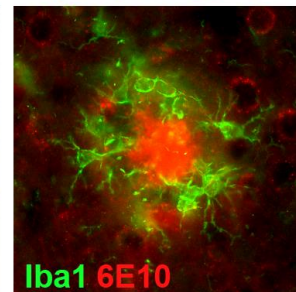
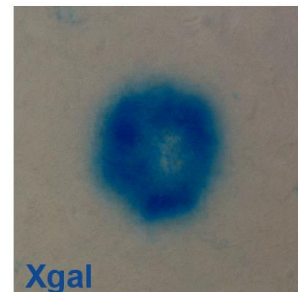
APP/PS1

TREM2 In-Situ/
Iba1 IHC



APP/PS1

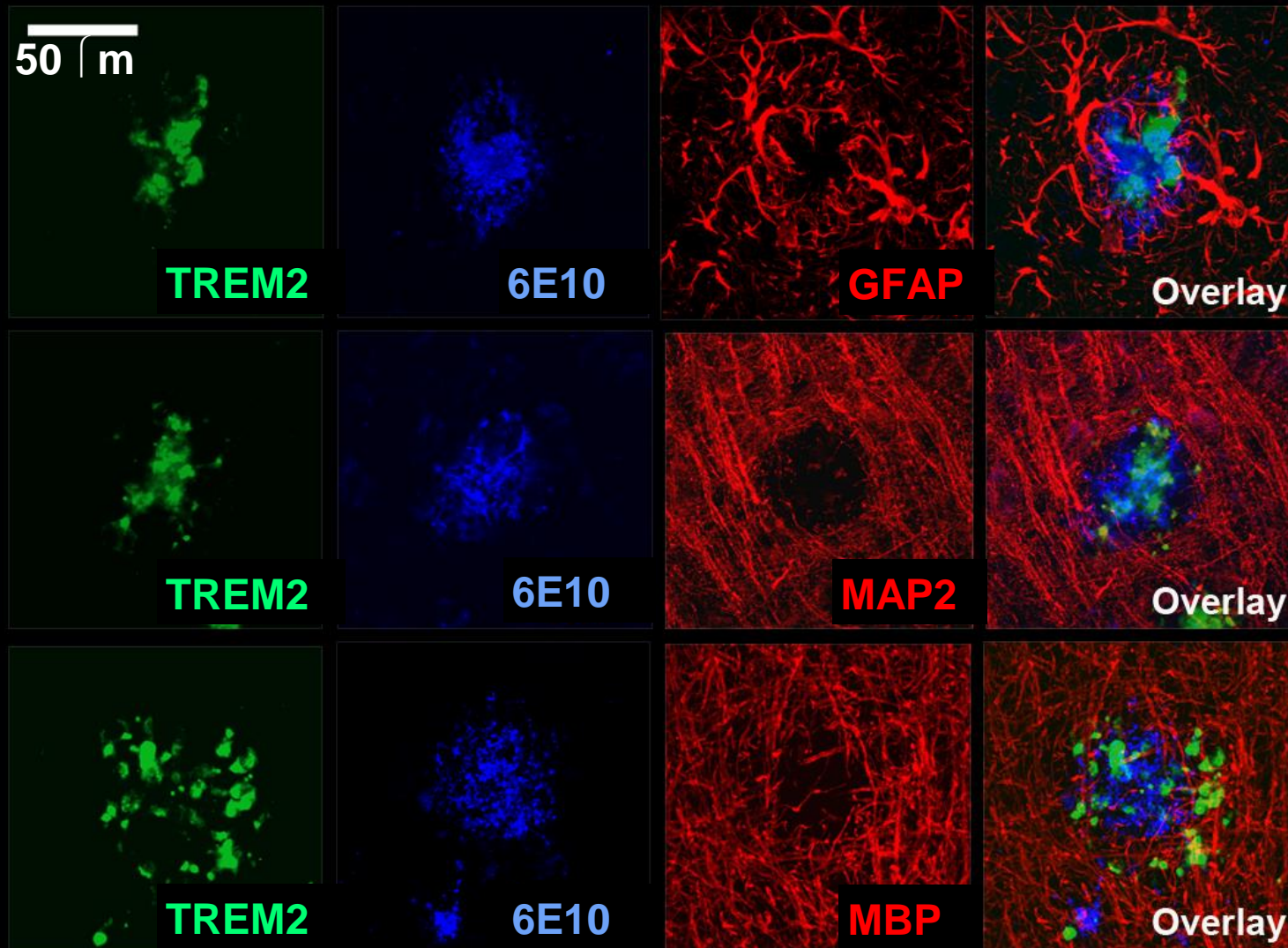
Xgal/
Iba1/6E10 IHC



APP/PS1/Trem2^{LacZ/+}

4 Month Old

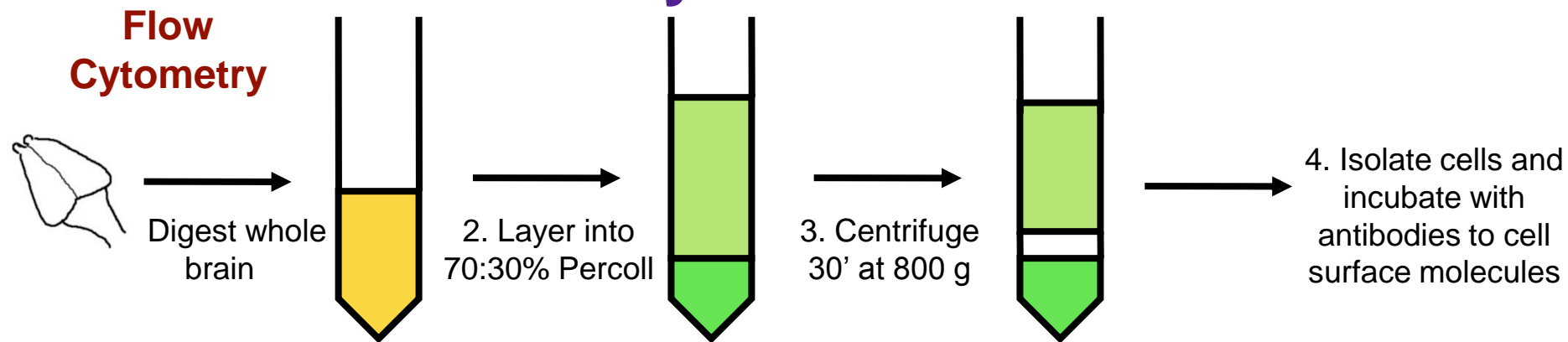
TREM2 is Not Detectable in Other Cell Types in the Brain



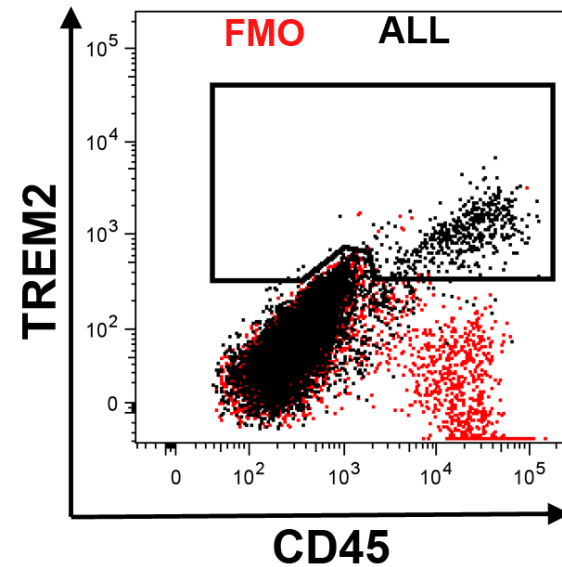
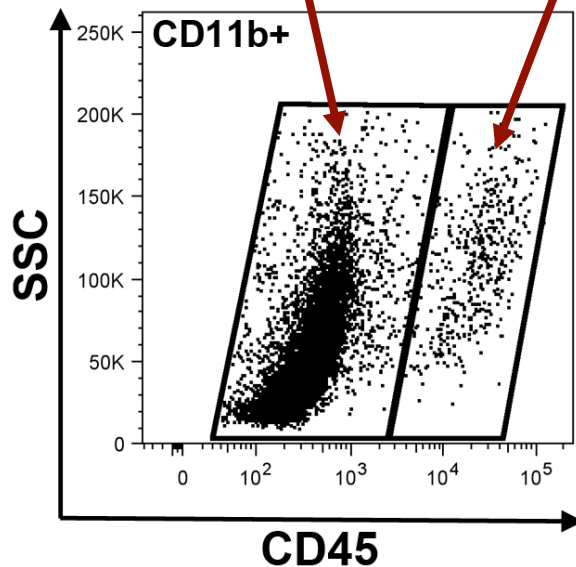
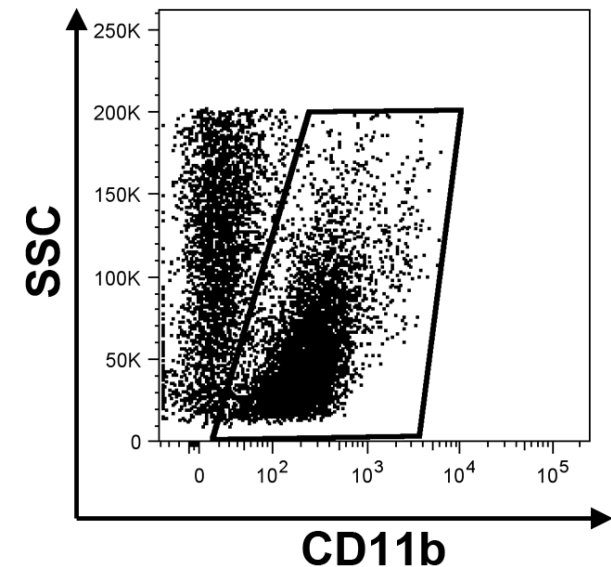
Location: Cortex

Age/Genotype: 4M APPS1

TREM2⁺ Cells Exhibit Markers Consistent with Peripherhal Monocytes in AD Mouse Models

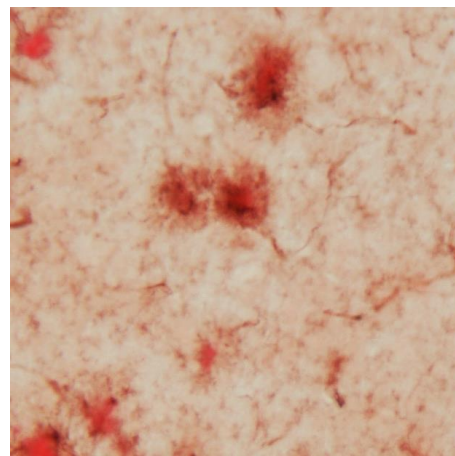
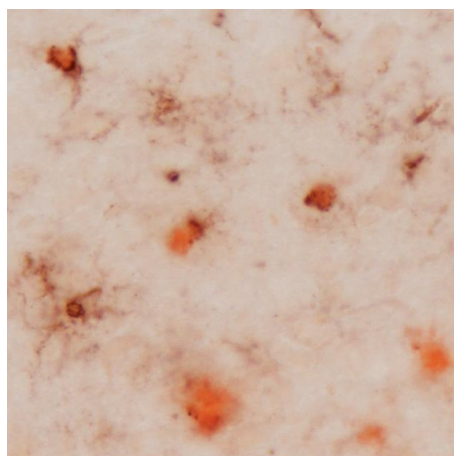
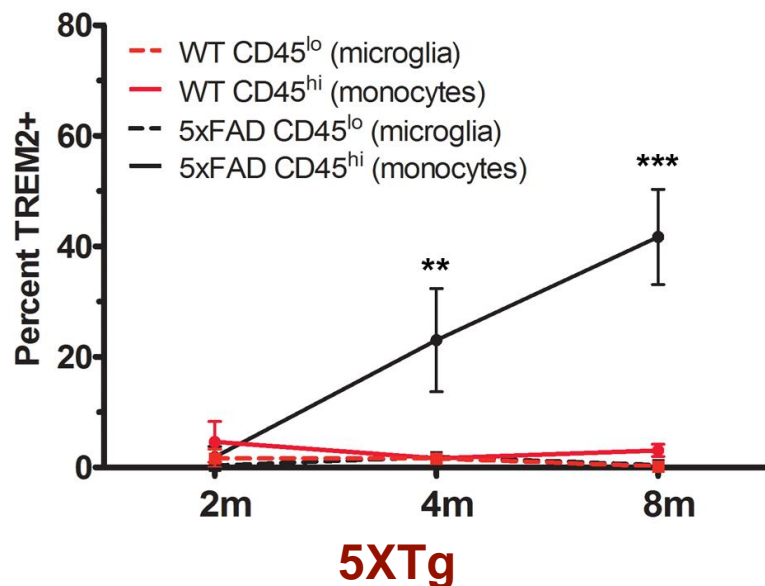
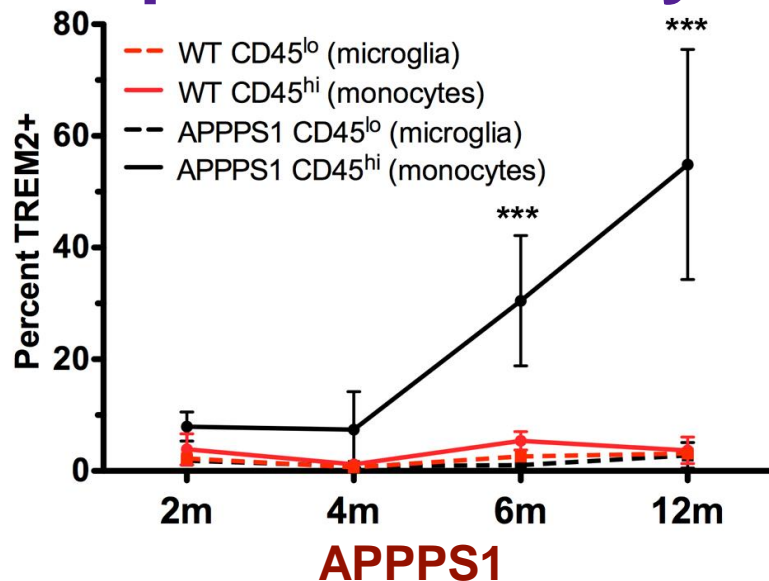


Microglia Monocytes



**5XTg
8 Months**

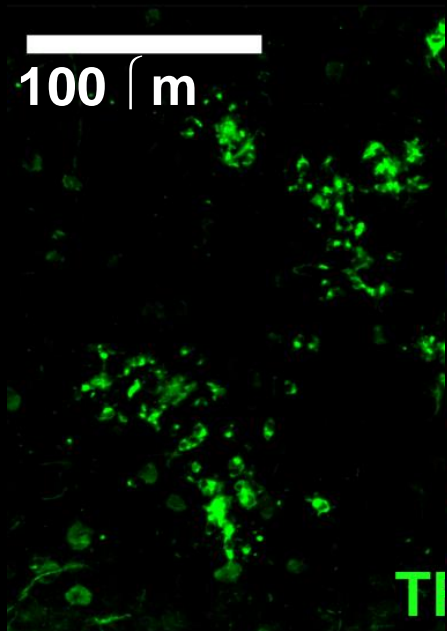
TREM2⁺ Cells Exhibit Markers Consistent with Peripheral Monocytes in AD Mouse Models



F4/80 Congo Red Ly6C Congo Red
Brain

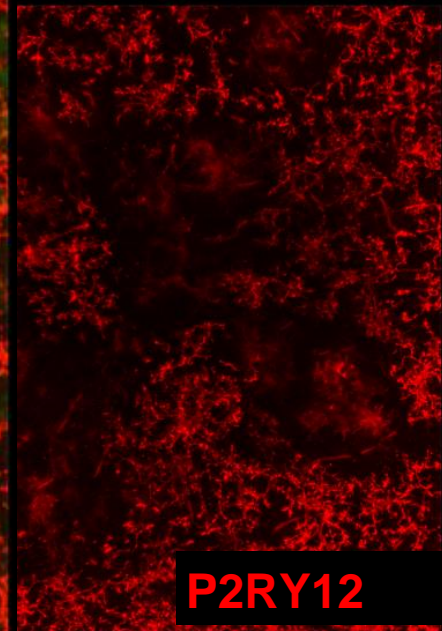
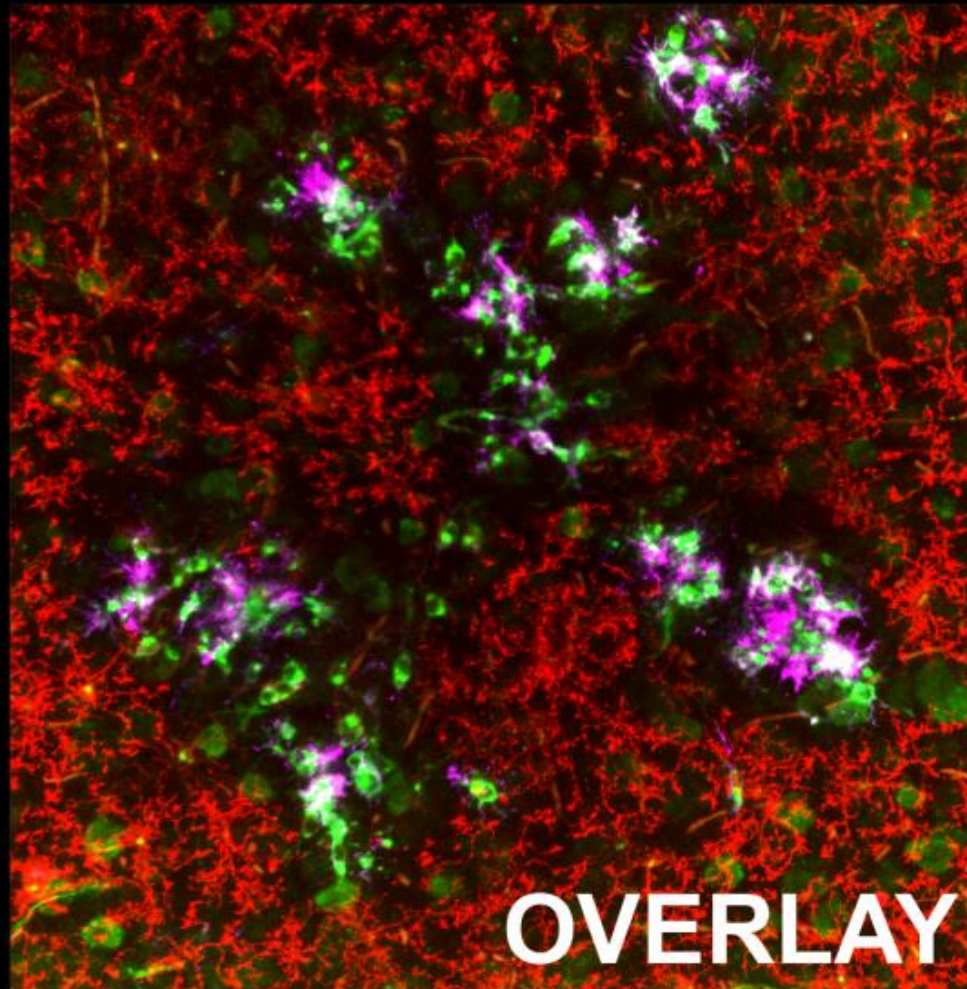
TREM2⁺ Cells Exhibit Markers Consistent with Peripheral Monocytes in AD Mouse Models

Jay et al., *J. Exp. Med.*,
212:287-295, 2105



Location

The Role of
TREM2 in AD?



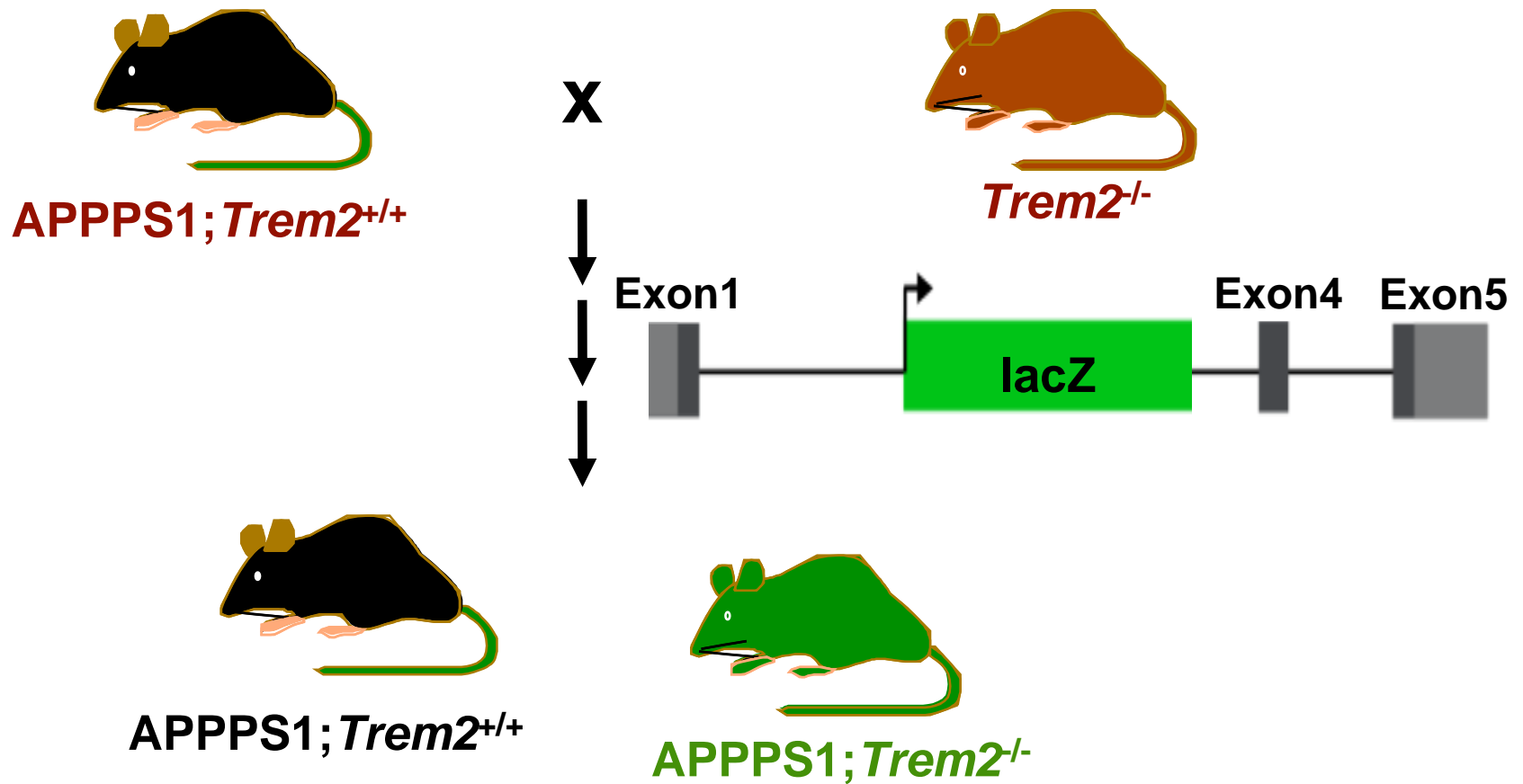
PPS1

TREM2

CD45

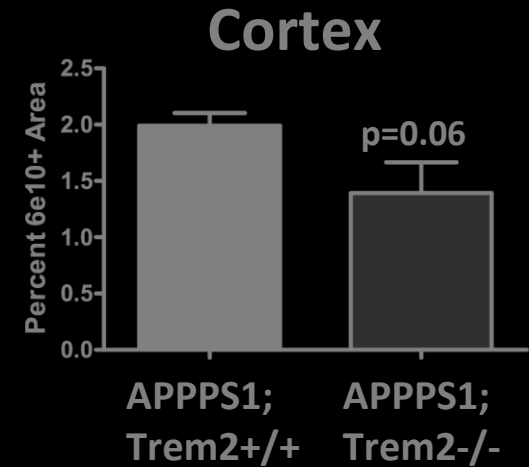
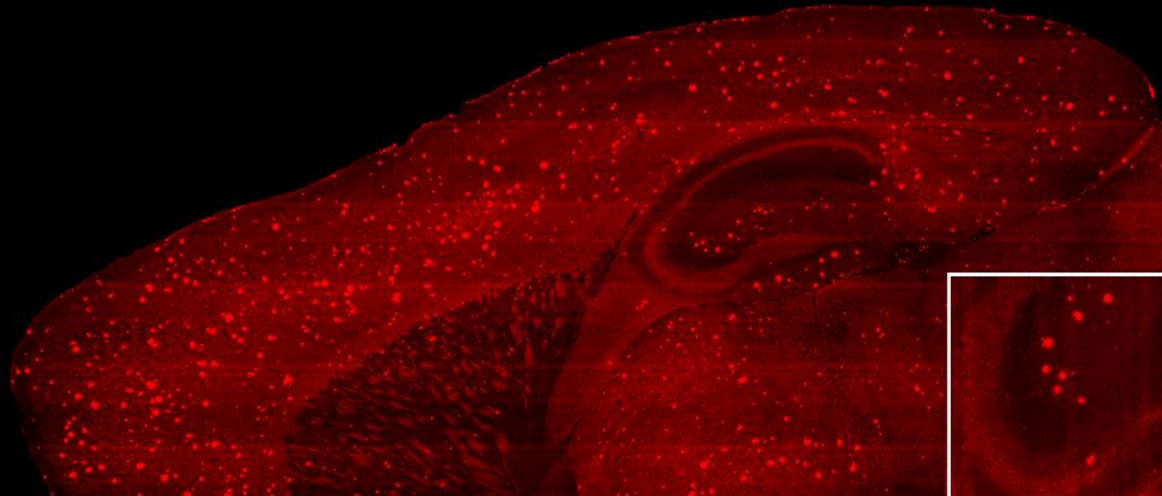
P2RY12

Generation of TREM2 Deficient Mouse Model of A β Pathology

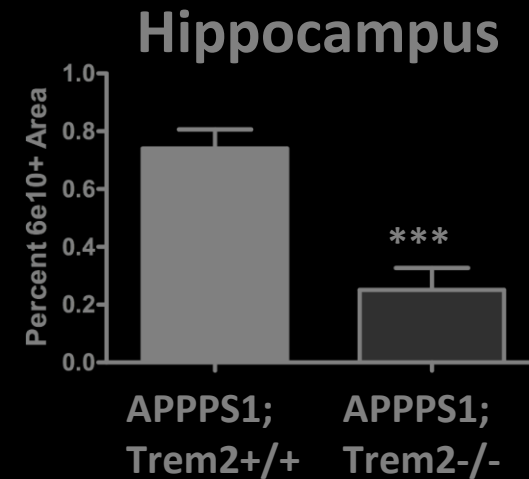
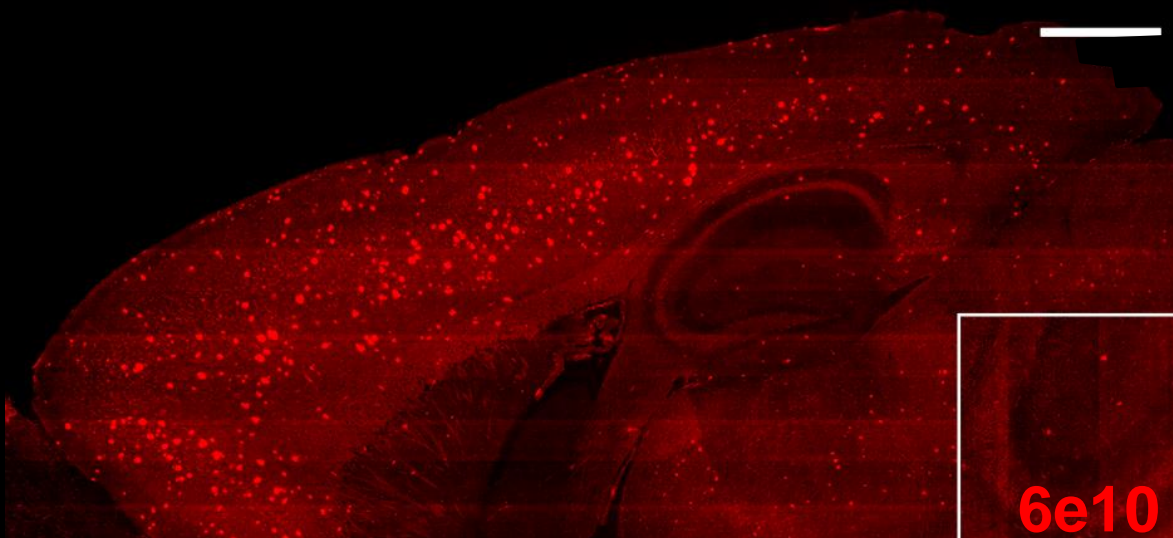


TREM2 Deficiency Reduces Hippocampal A β Deposition

APP^{PS1};Trem2^{+/+}

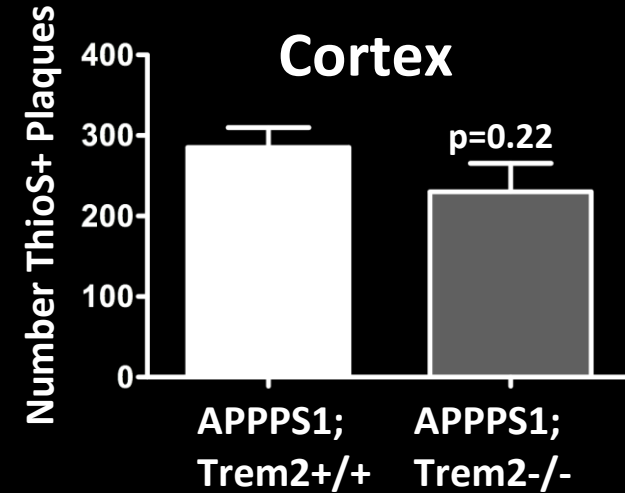
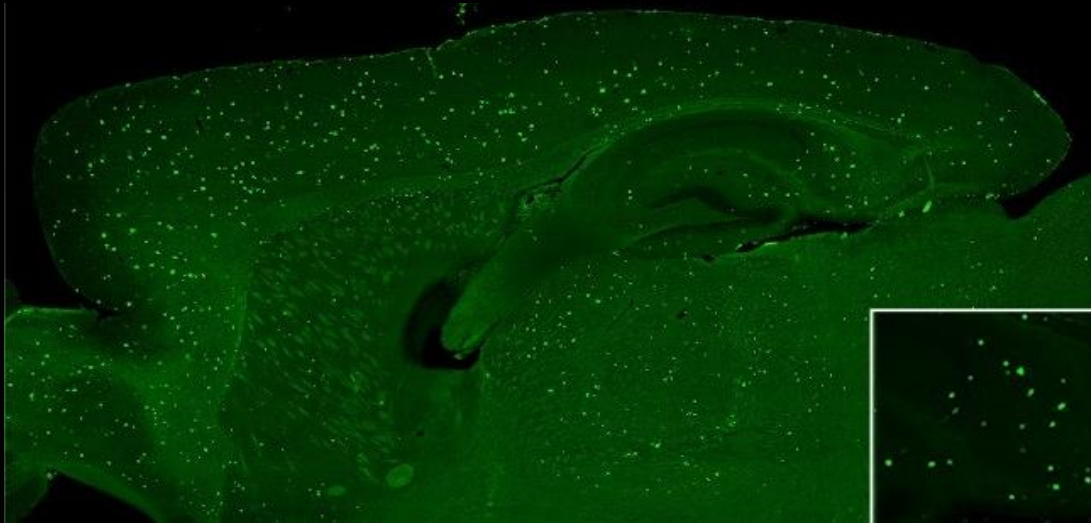


APP^{PS1};Trem2^{-/-}

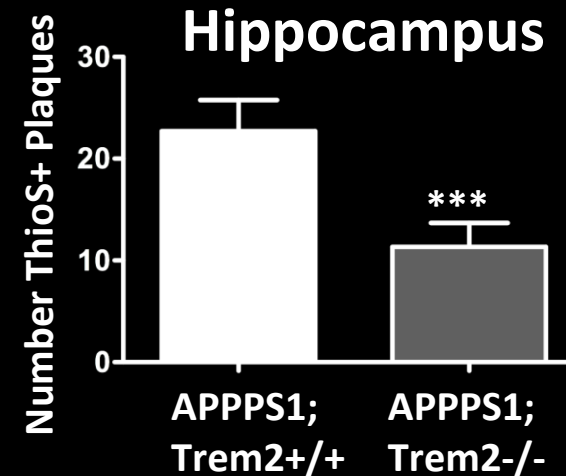
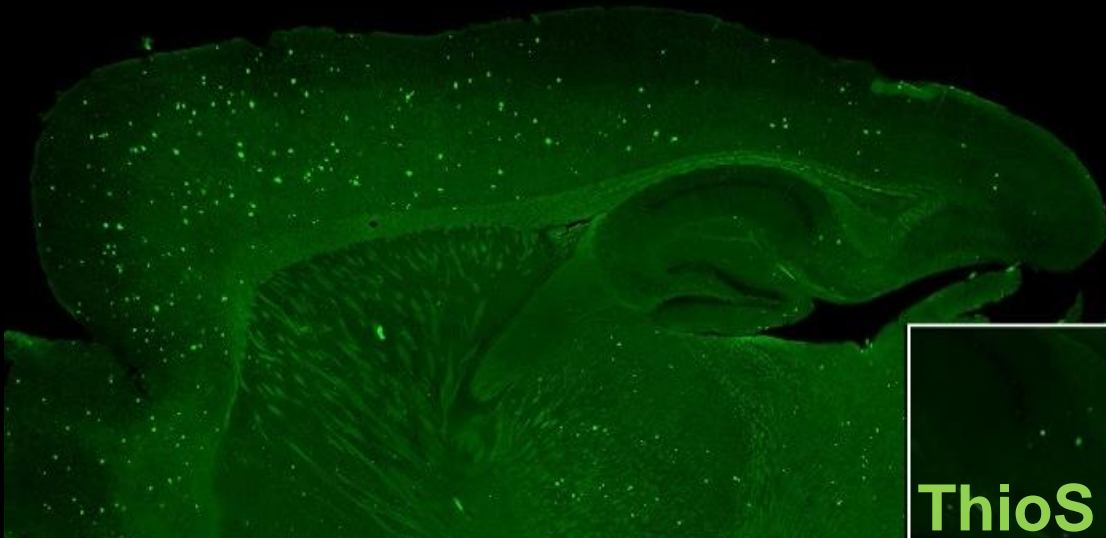


TREM2 Deficiency Reduces Hippocampal A β Deposition

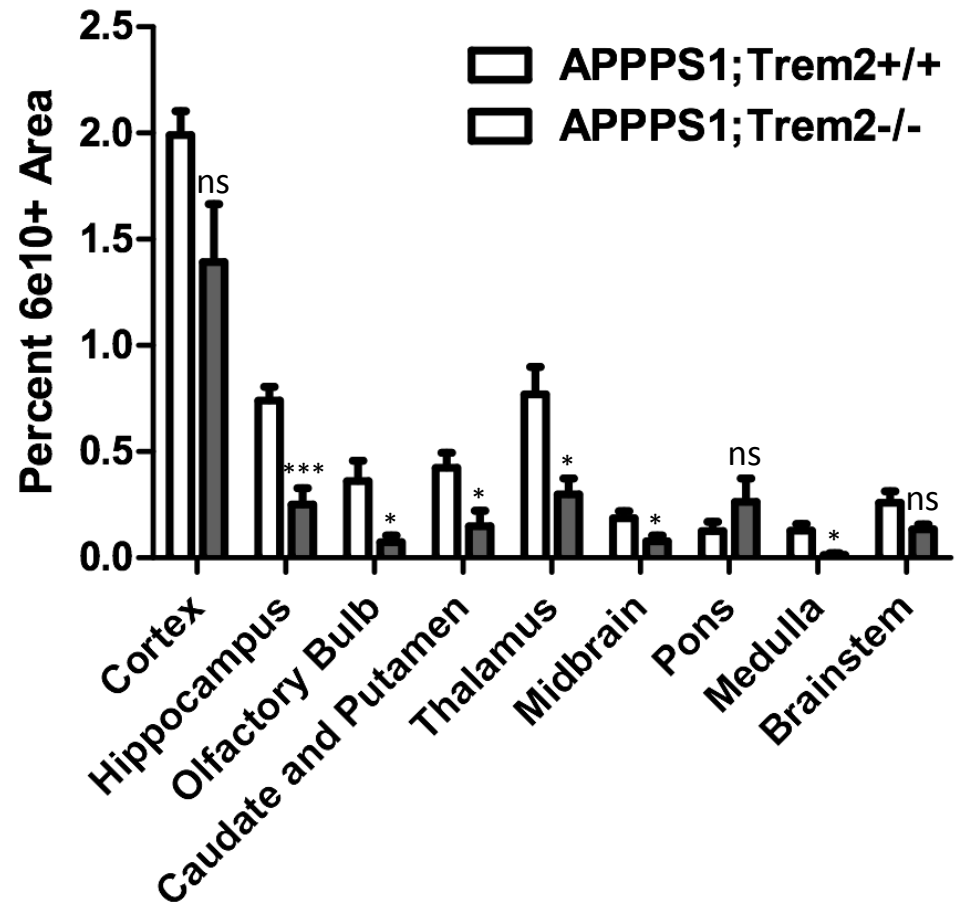
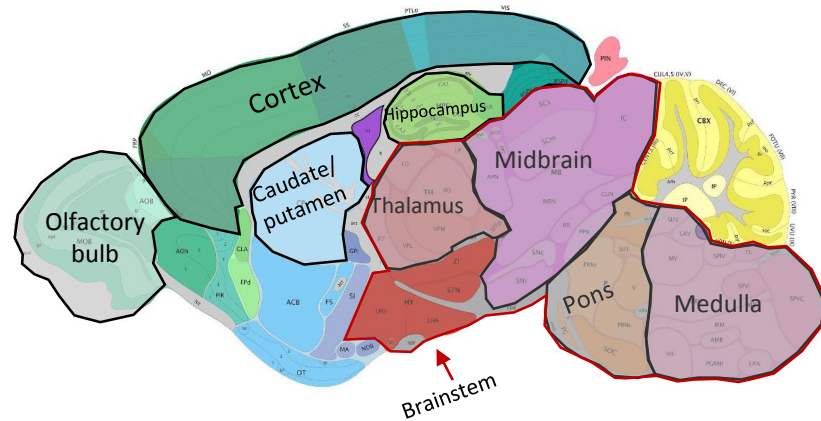
APP^{PS1};Trem2^{+/+}



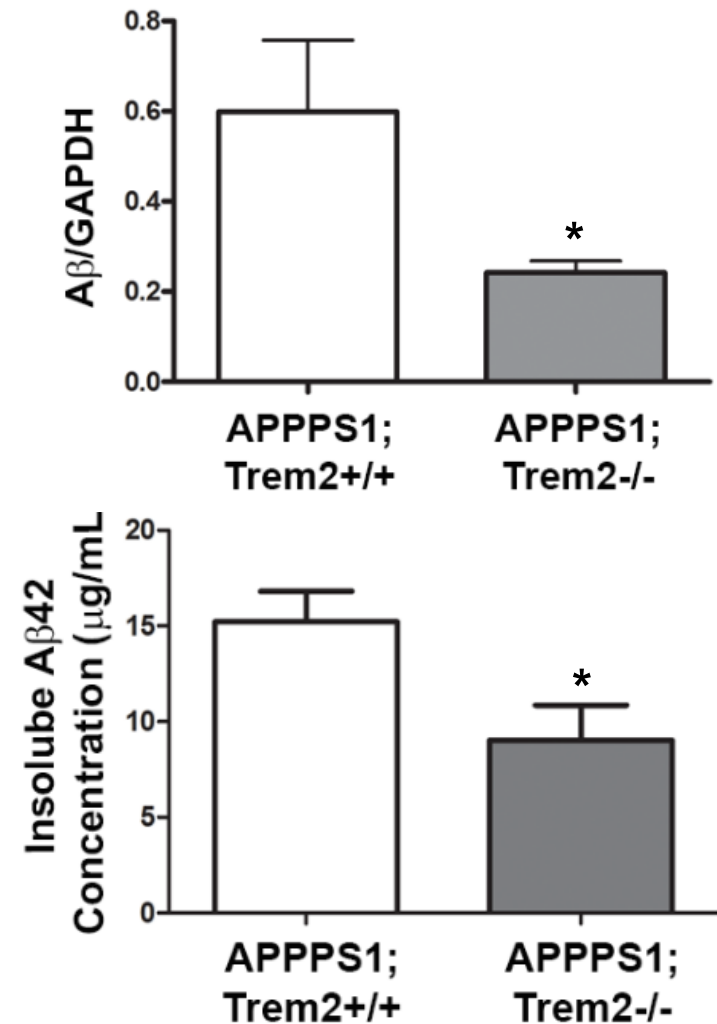
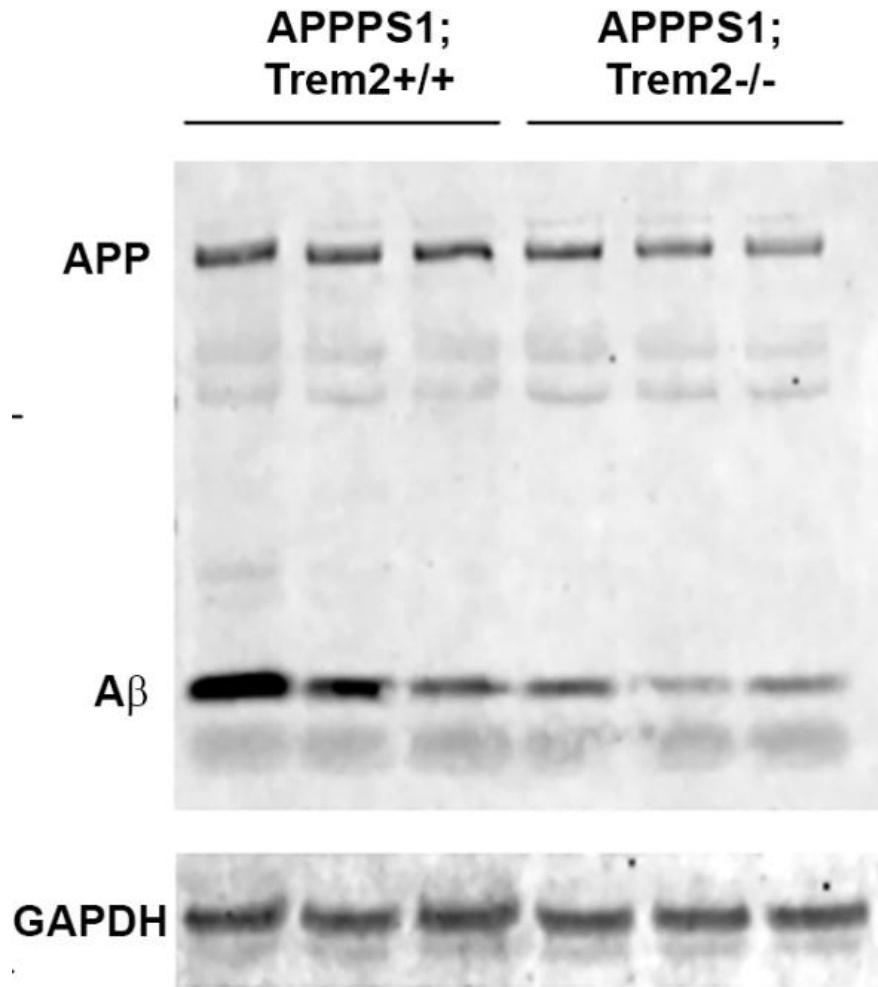
APP^{PS1};Trem2^{-/-}



TREM2 Deficiency Reduces A β Deposition in Multiple Brain Regions

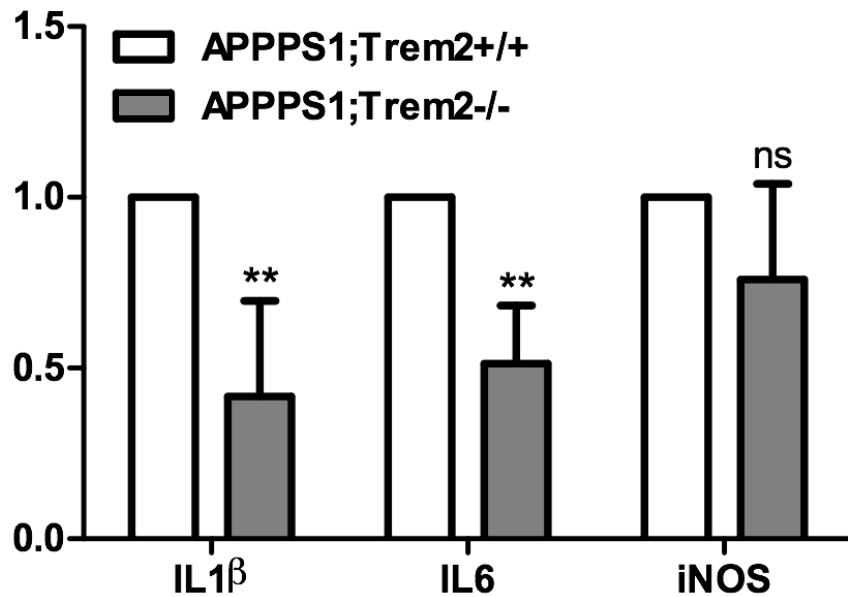


TREM2 Deficiency Reduces A β Deposition

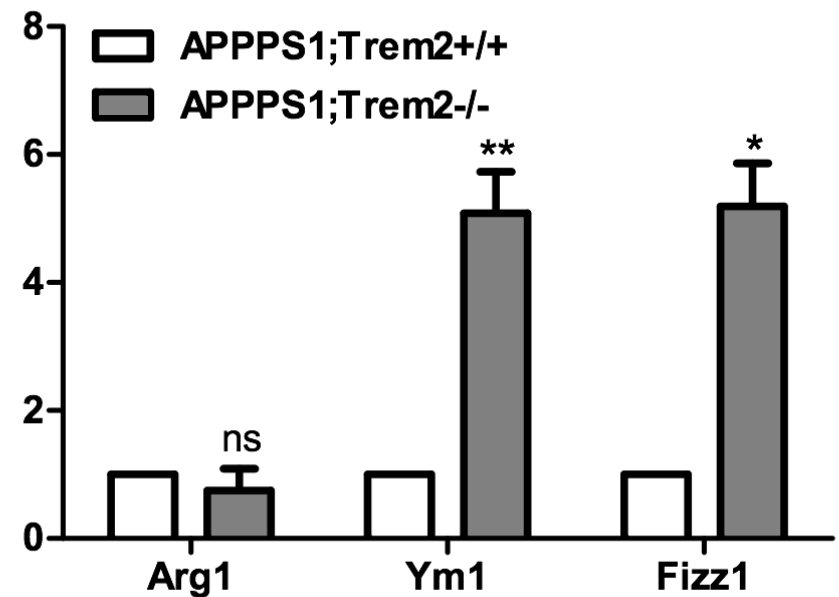


TREM2 Deficiency Reduces Inflammation Within the Brain of AD Mouse Models

Pro-inflammatory Gene Expression

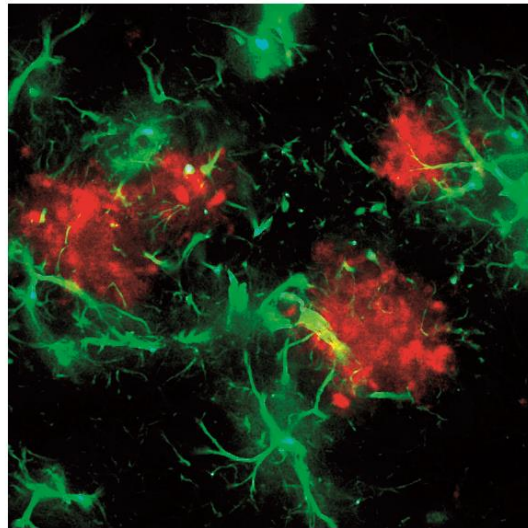


Anti-inflammatory Gene Expression

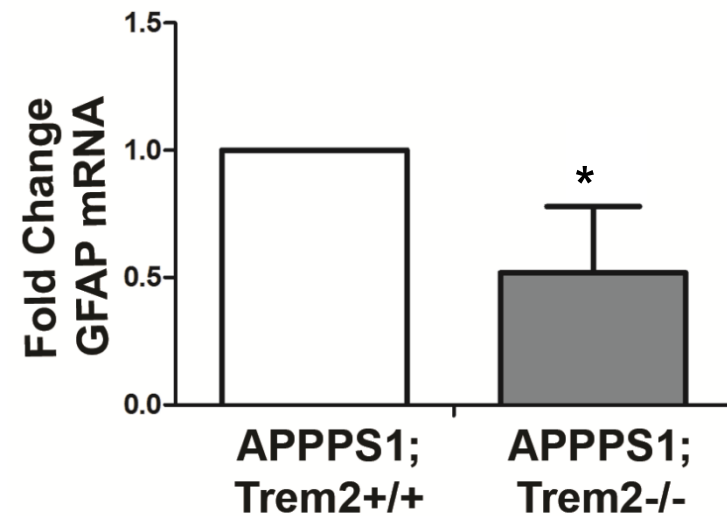
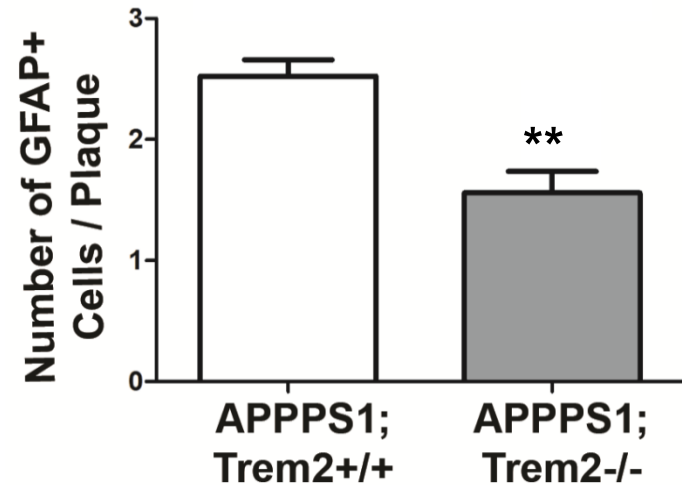
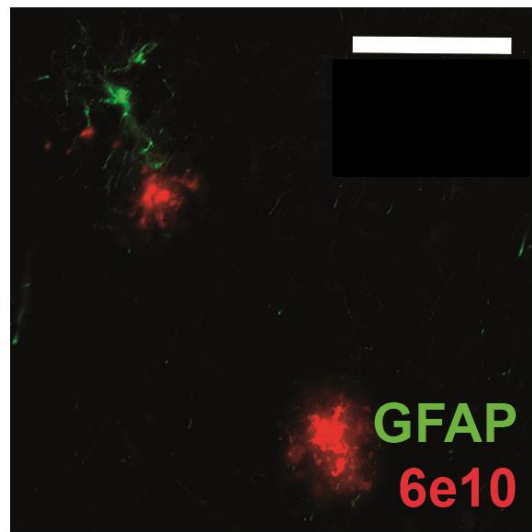


TREM2 Deficiency Reduces Astrogliosis Surrounding A β Deposits

APP^{PS1}; Trem2^{+/-}



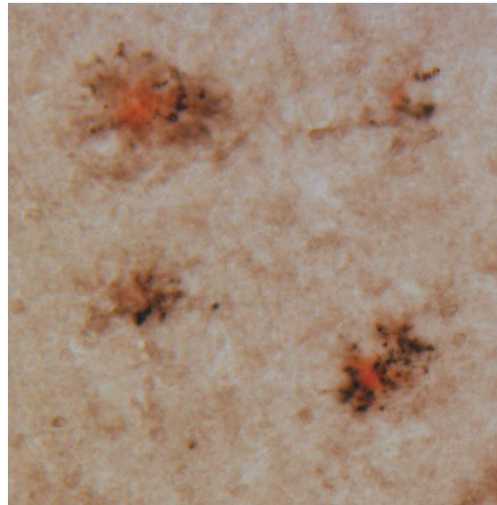
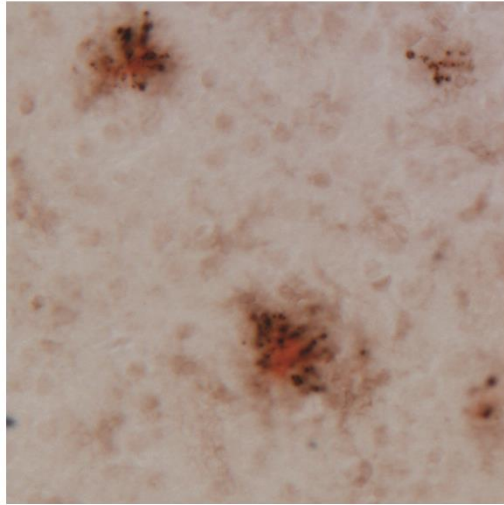
APP^{PS1}; Trem2^{-/-}



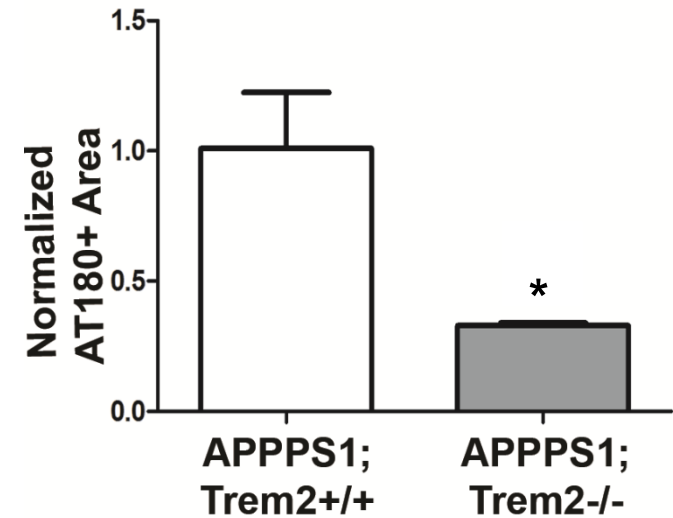
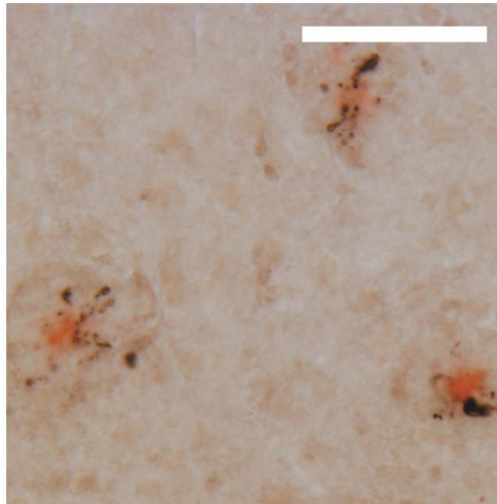
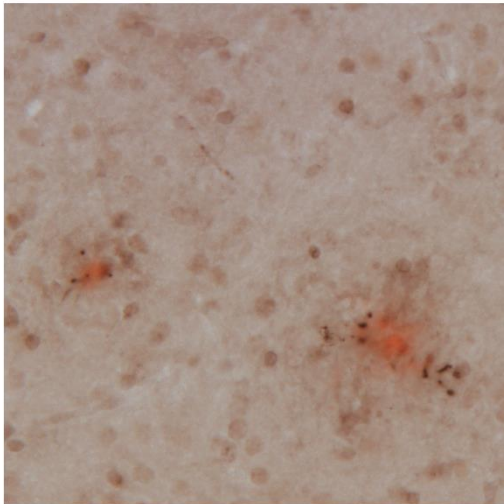
TREM2 Deficiency Reduces MAPT Phosphorylation Surrounding A β Deposits

AT8 / Congo Red AT180 / Congo Red

APPPS1; Trem2^{+/+}

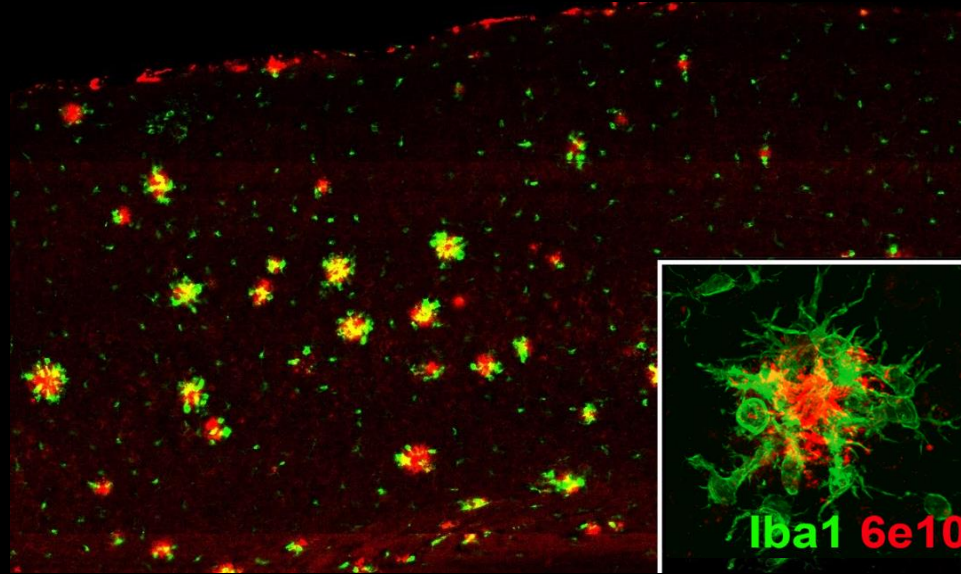


APPPS1; Trem2^{-/-}

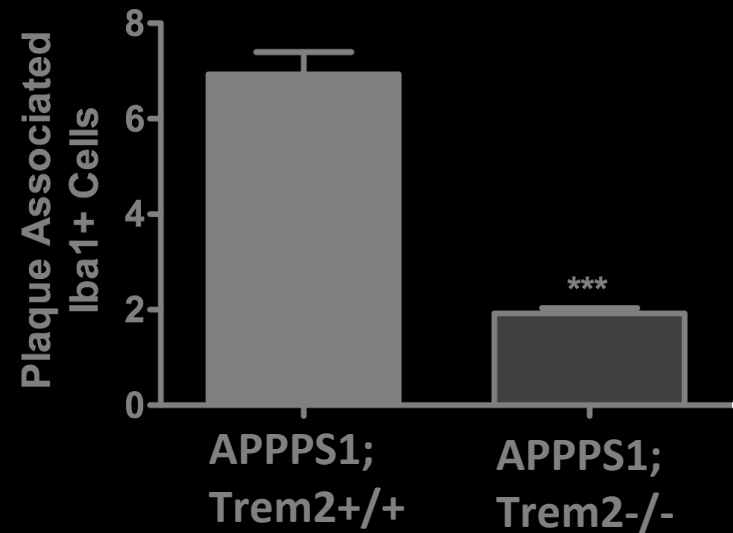
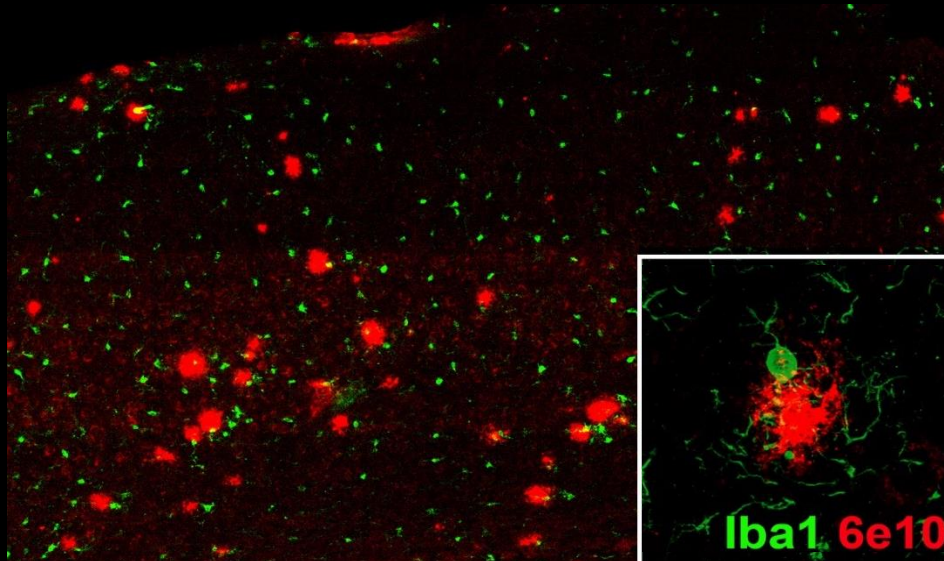


TREM2 Deficiency Reduces Myeloid Cell Accumulation Around A β Deposits

APPSP1;*Trem2*^{+/-}



APPSP1;*Trem2*^{-/-}

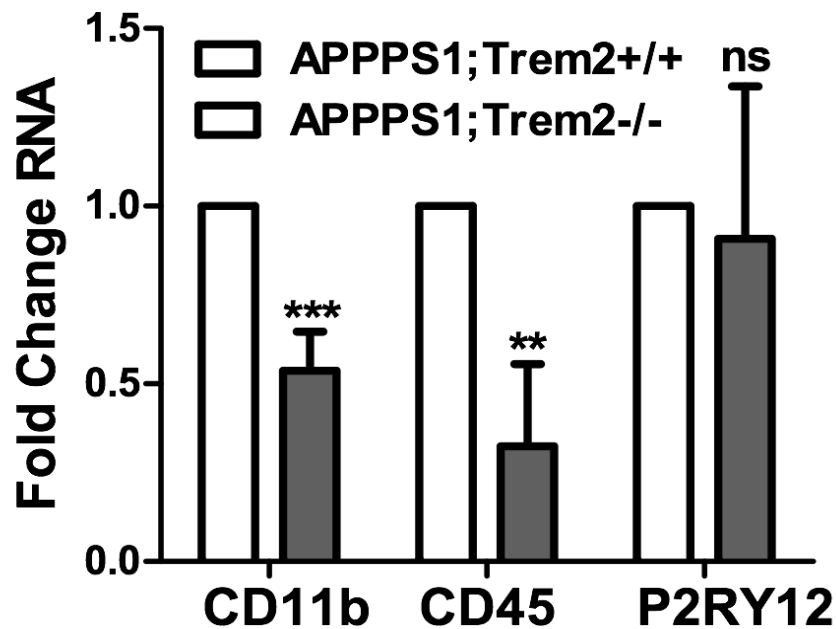


TREM2 Deficiency Blocks Appearance of CD45^{hi}Ly6C⁺P2RY12⁻ Cells Around A β Deposits

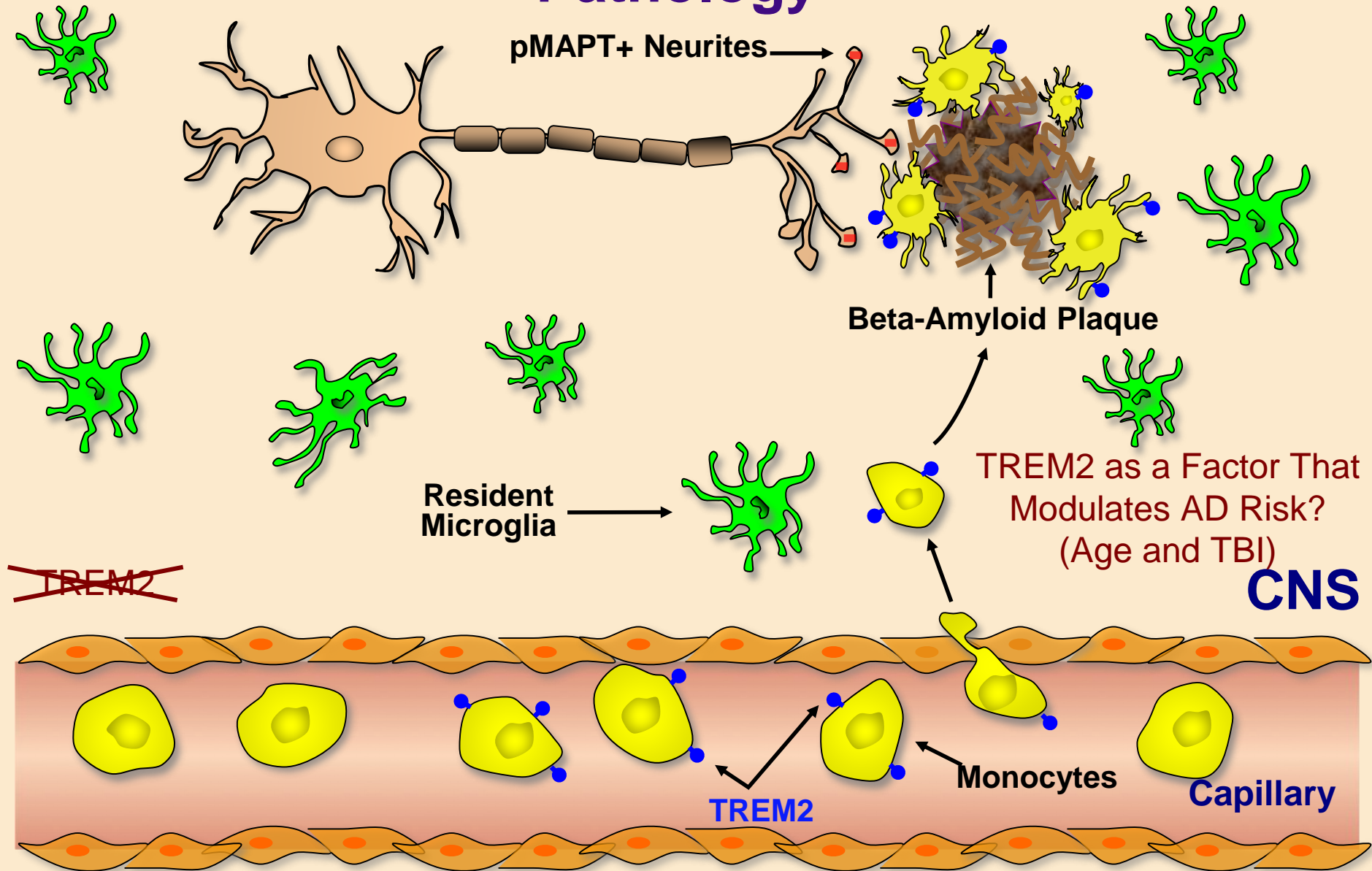
CD45 / Congo Red

Ly6C / Congo Red

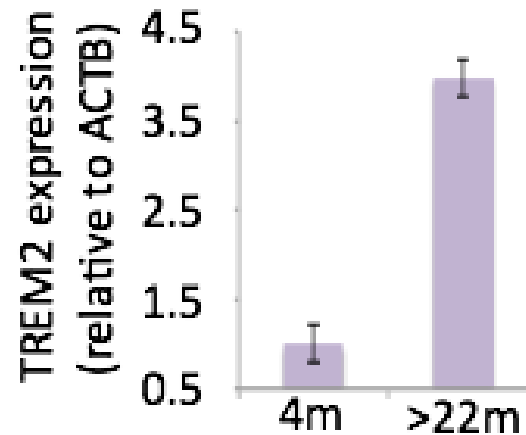
P2RY12 / Congo Red



The Role of TREM2 in Regulating Amyloid Pathology

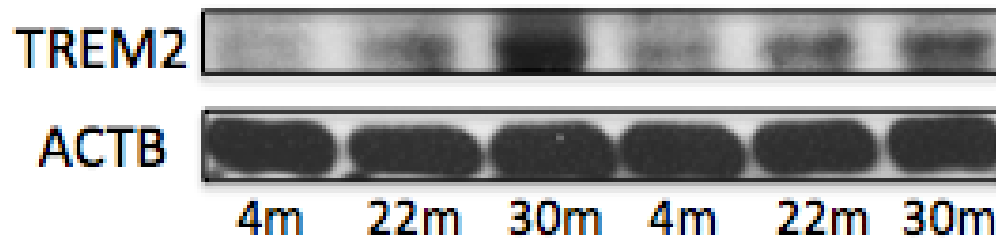


TREM2 Expressing Increases with Aging



C57BL/6

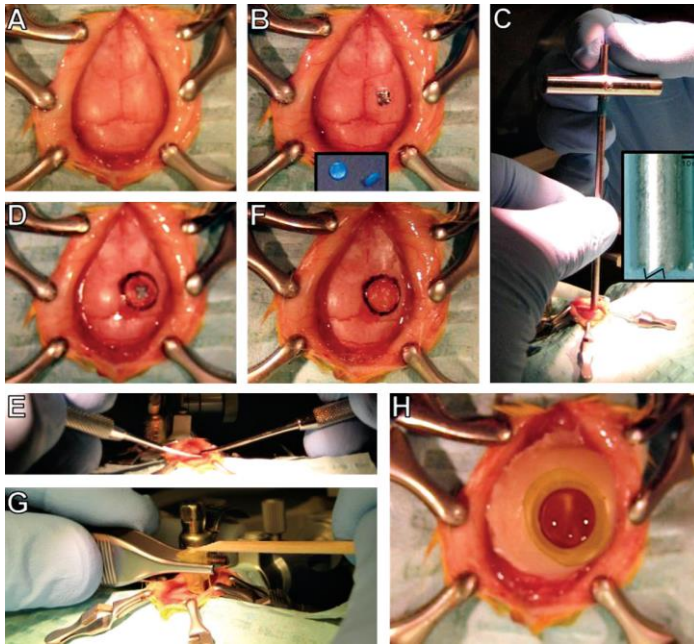
TREM2 RNA



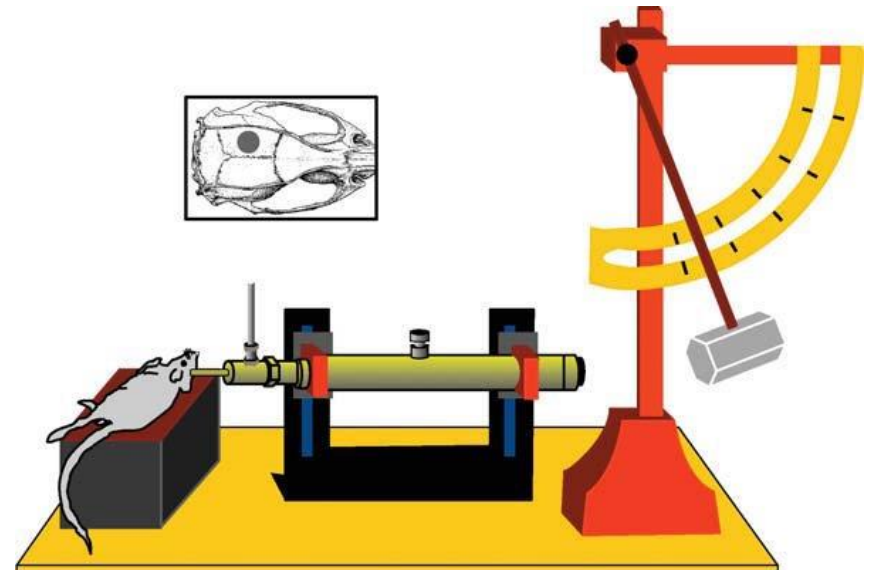
TREM2 Protein

Experimental Model of TBI

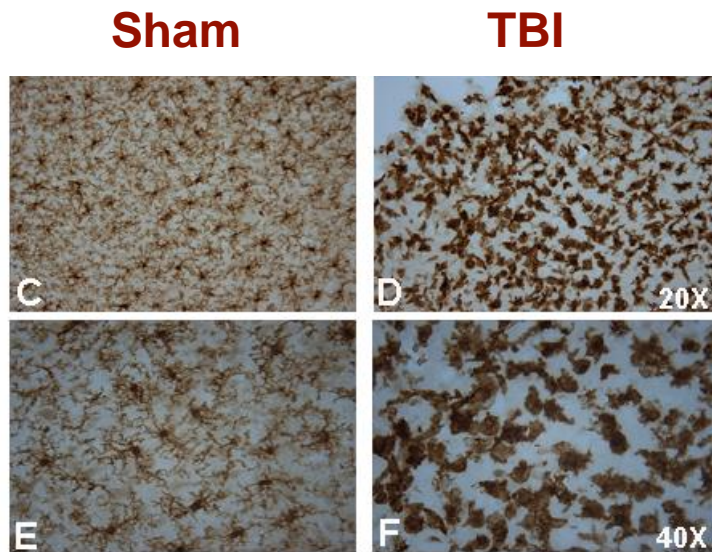
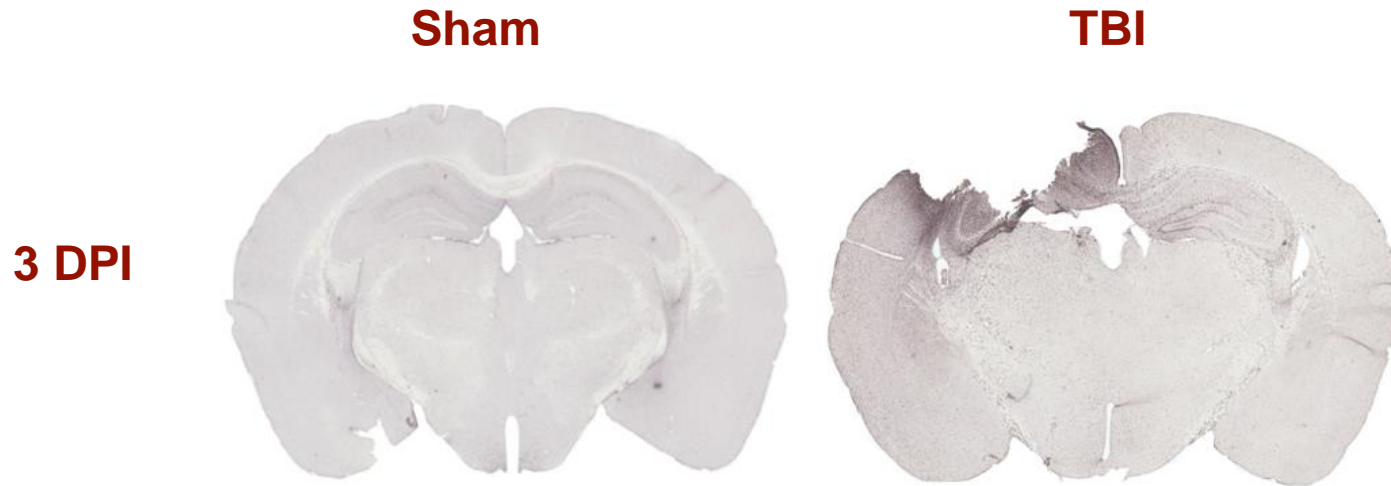
Surgical Preparation



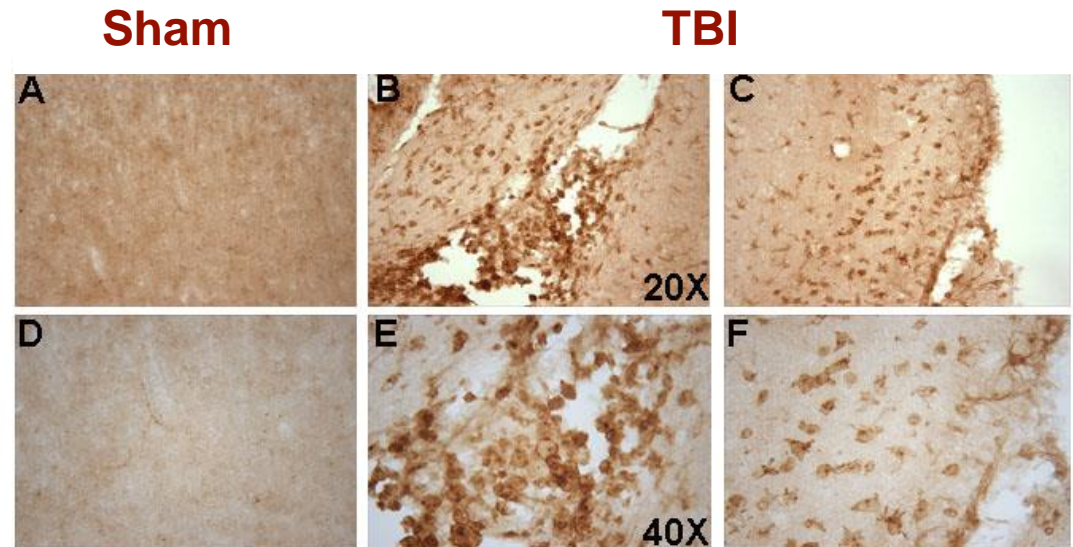
Fluid Percussion Injury



Expression of TREM2 Following TBI

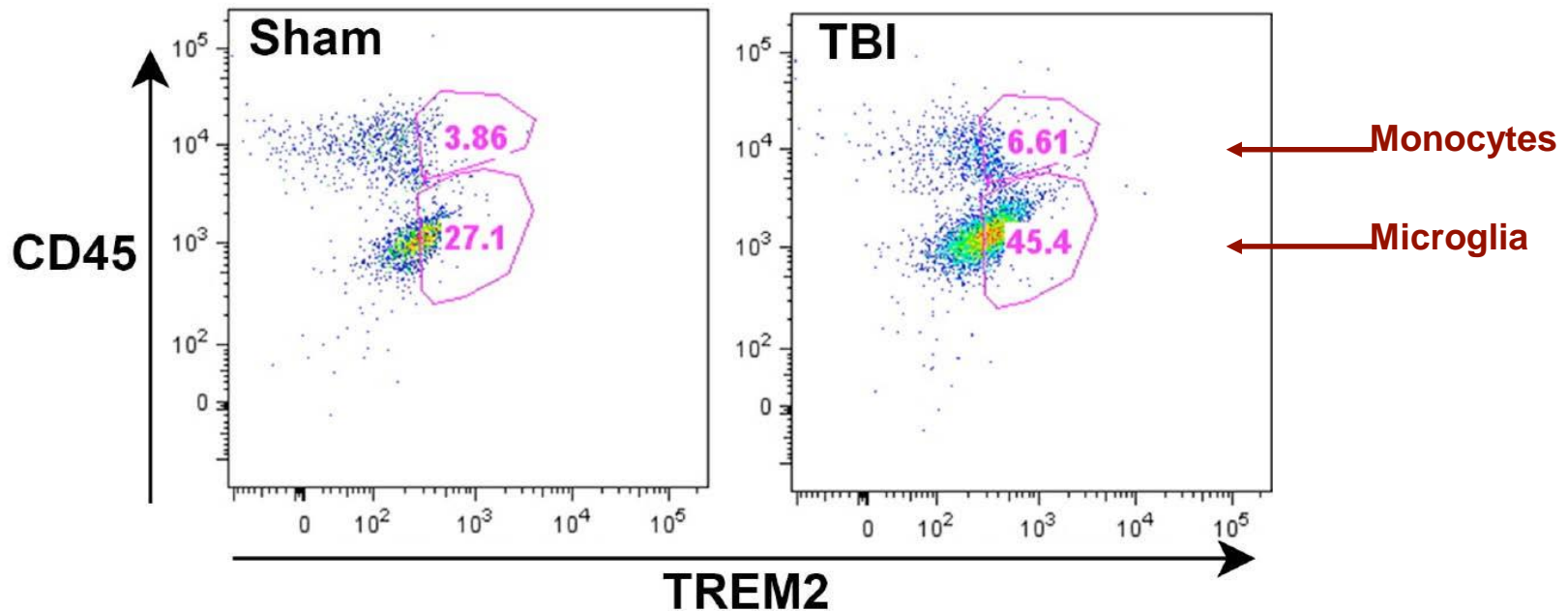
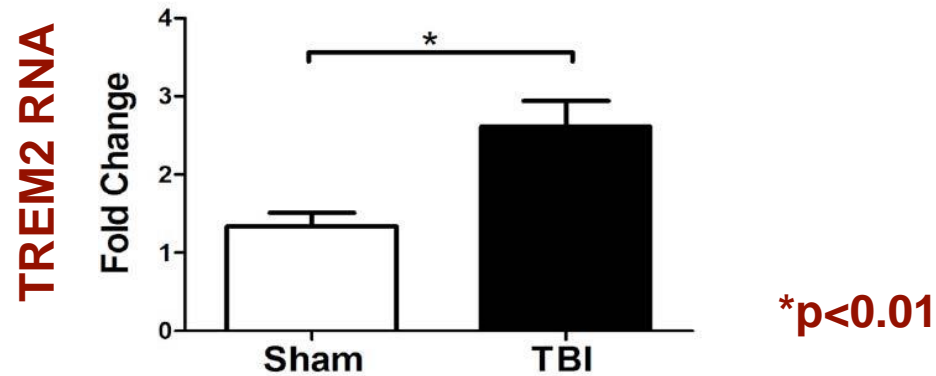


Iba1

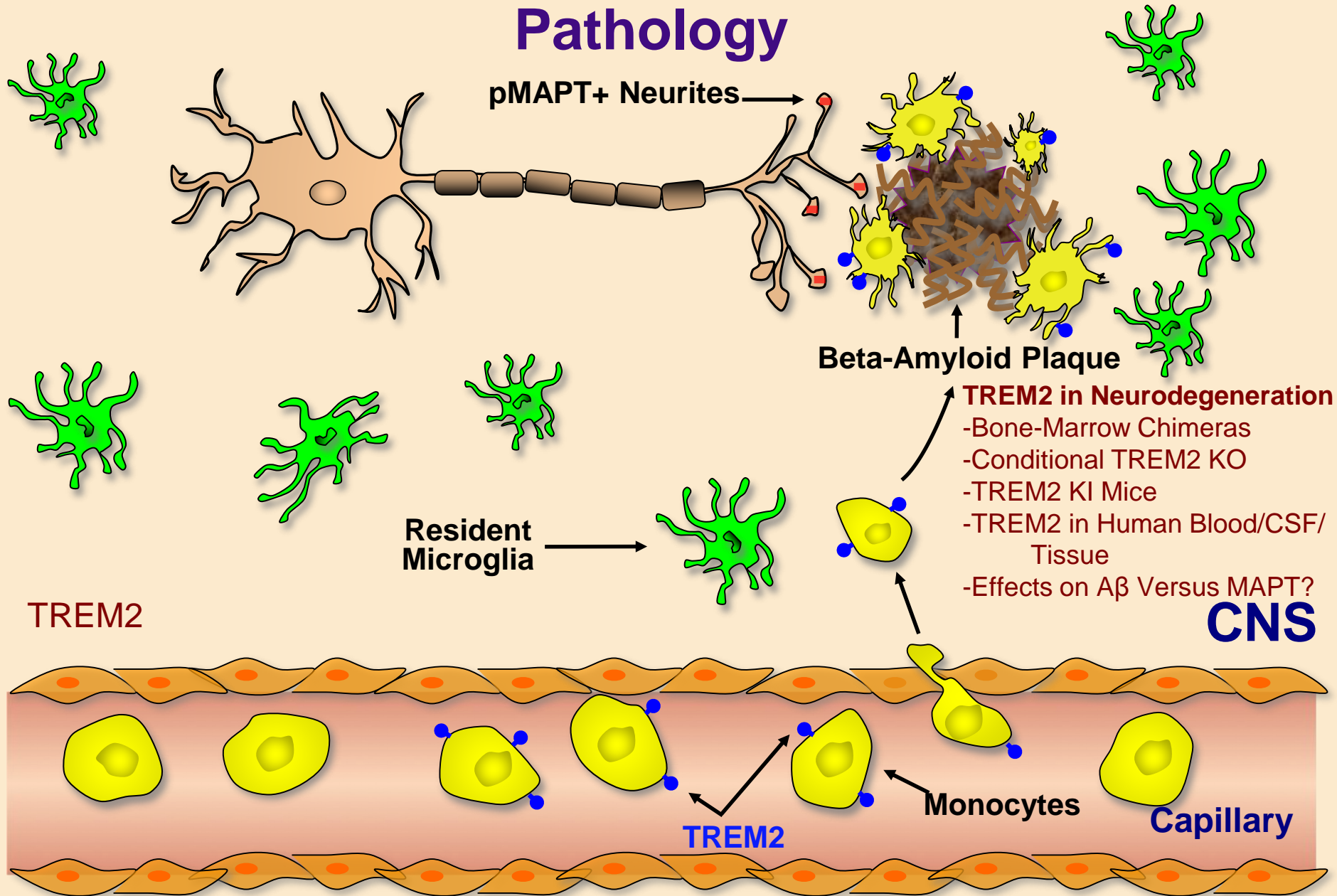


TREM2

Expression of TREM2 Following TBI



The Role of TREM2 in Regulating MAPT Pathology



The Team at the Laboratory



Collaborators/Funding

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