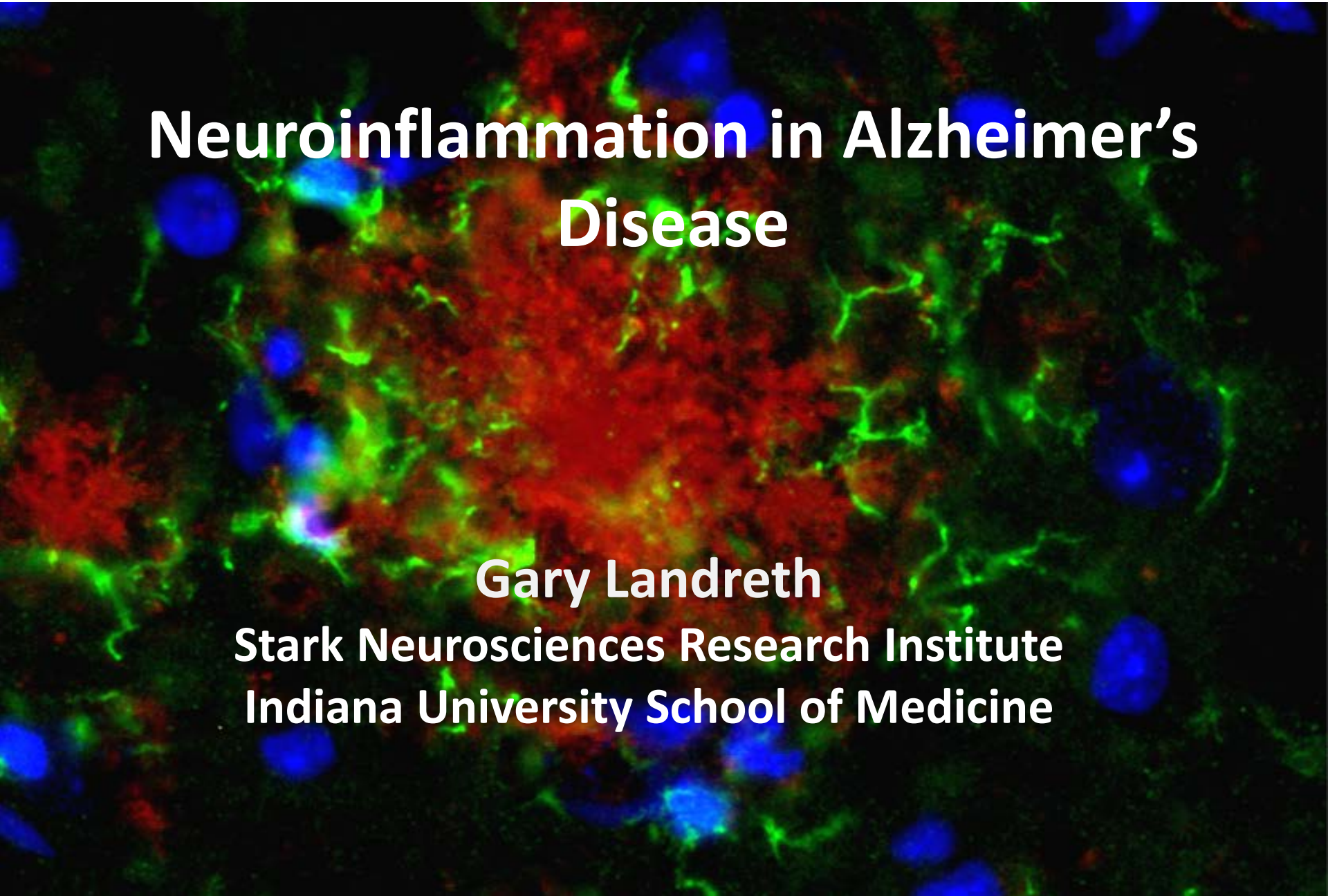
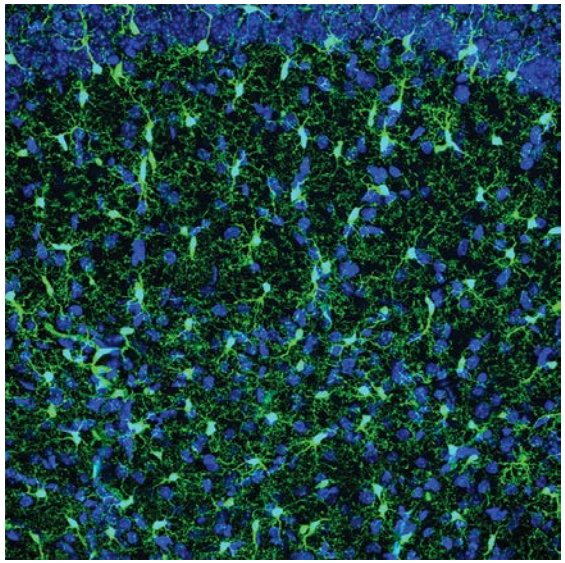
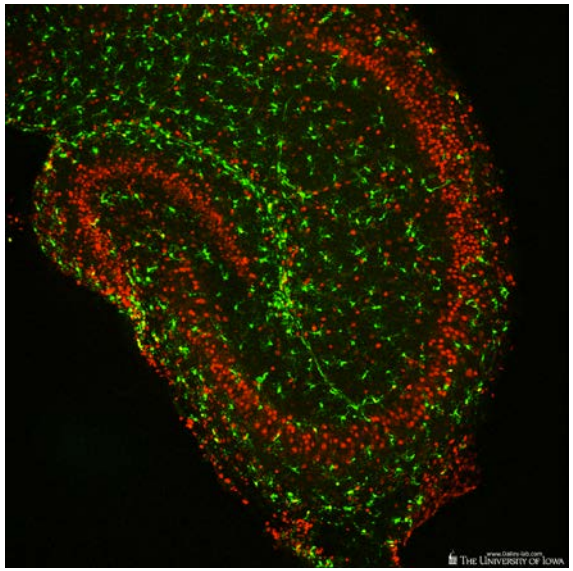
Neuroinflammation in Alzheimer's Disease



Gary Landreth
Stark Neurosciences Research Institute
Indiana University School of Medicine

Neuroinflammation is an Invariant Feature in Neurodegenerative Diseases





- Microglia, the brain's resident macrophage, performs immune surveillance, but is now understood to have a broad range of brain-specific functions.

- Microglia are highly dynamic and continuously extend and retract processes throughout the brain parenchyma

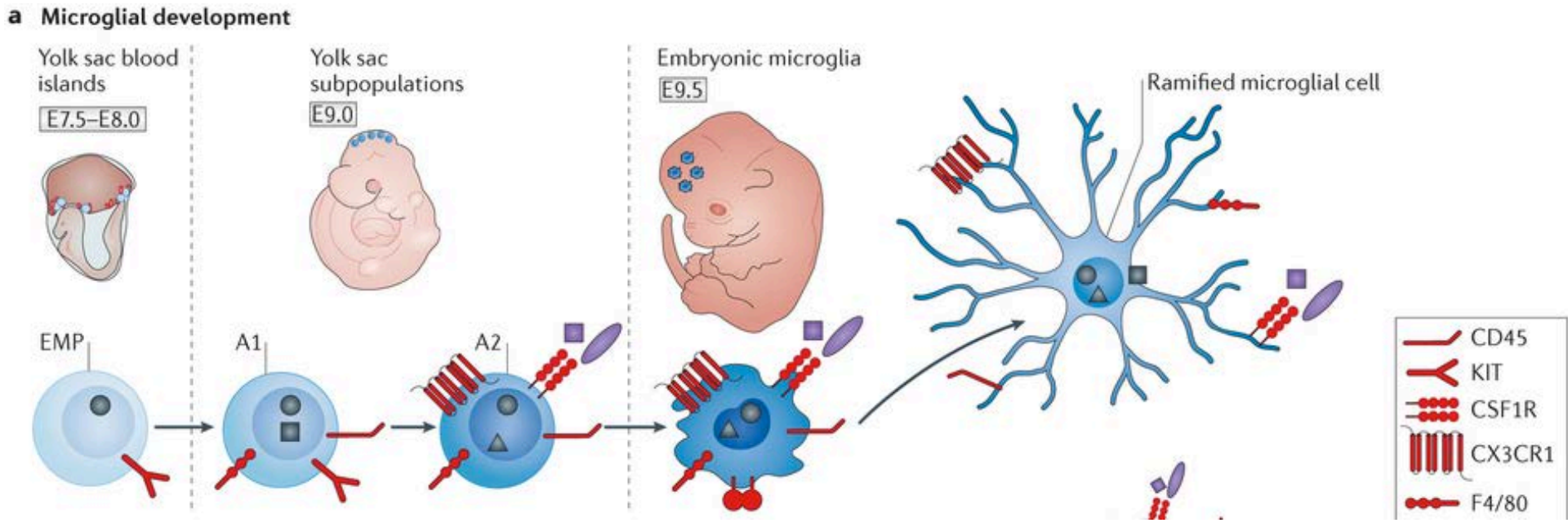
- The brain undergoes complete surveillance by microglia every few hours with each microglia surveying an area with a radius of about 80μm

- **Neuroinflammation arises from disease-related perturbations in the brain that subsequently induce a pro-inflammatory response by microglia, which exacerbates disease severity and accelerates disease progression, resulting in neuronal loss**.

Ontogeny of microglia:

Microglia are derived from early yolk sac derived myeloid precursors that invade and populate the developing brain

Microglia self renew from endogenous progenitors

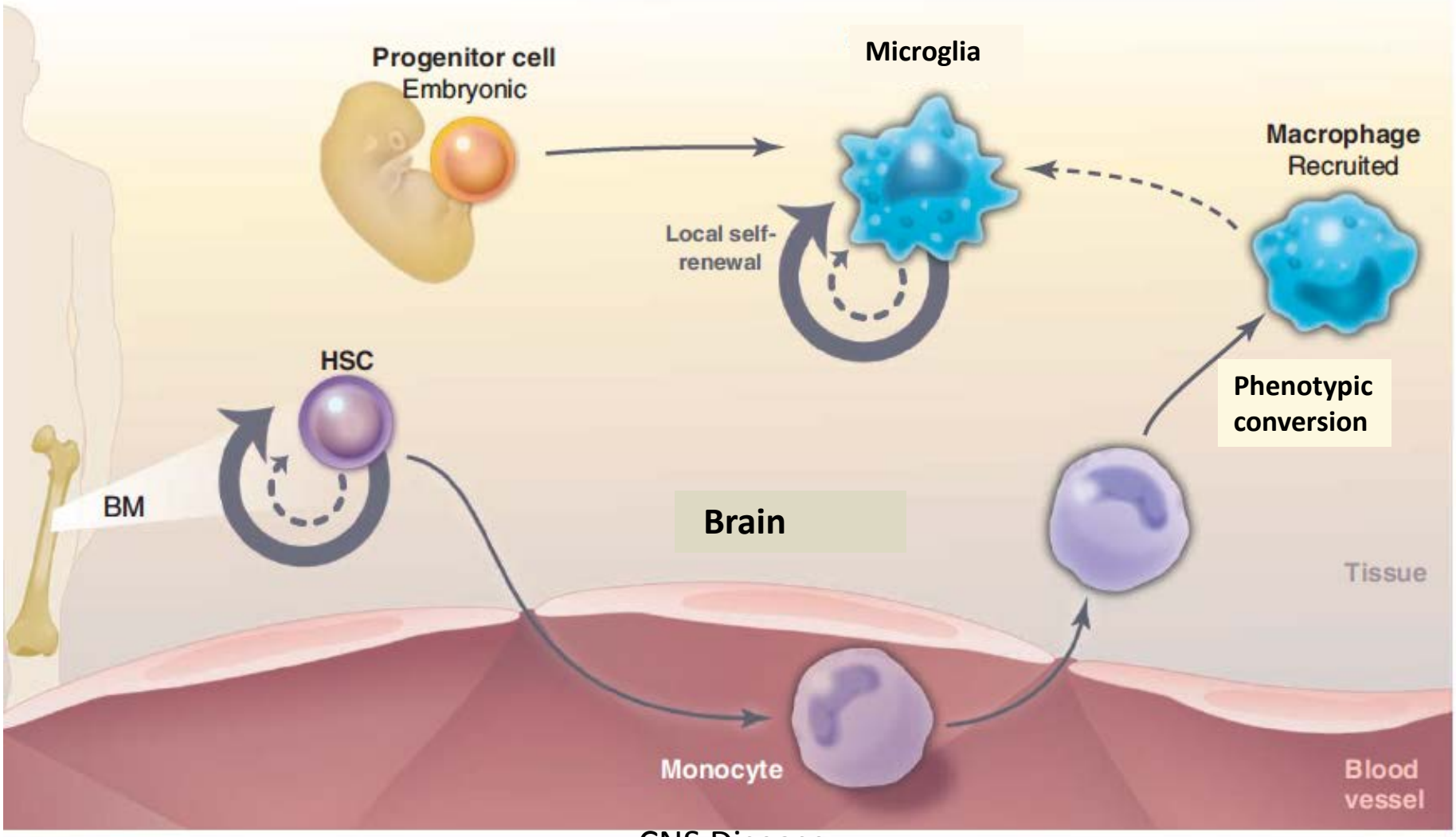


Expression of PU.1 and myeloid cell markers

Surface markers
Iba1
CX3CR1
P2RY12/13
CD45 ^{lo}
MerTK

Transcripts:
Sall1
Tmem119
Olfml3
C1qa
Gas6
Pros1
Fcrls
GPR34

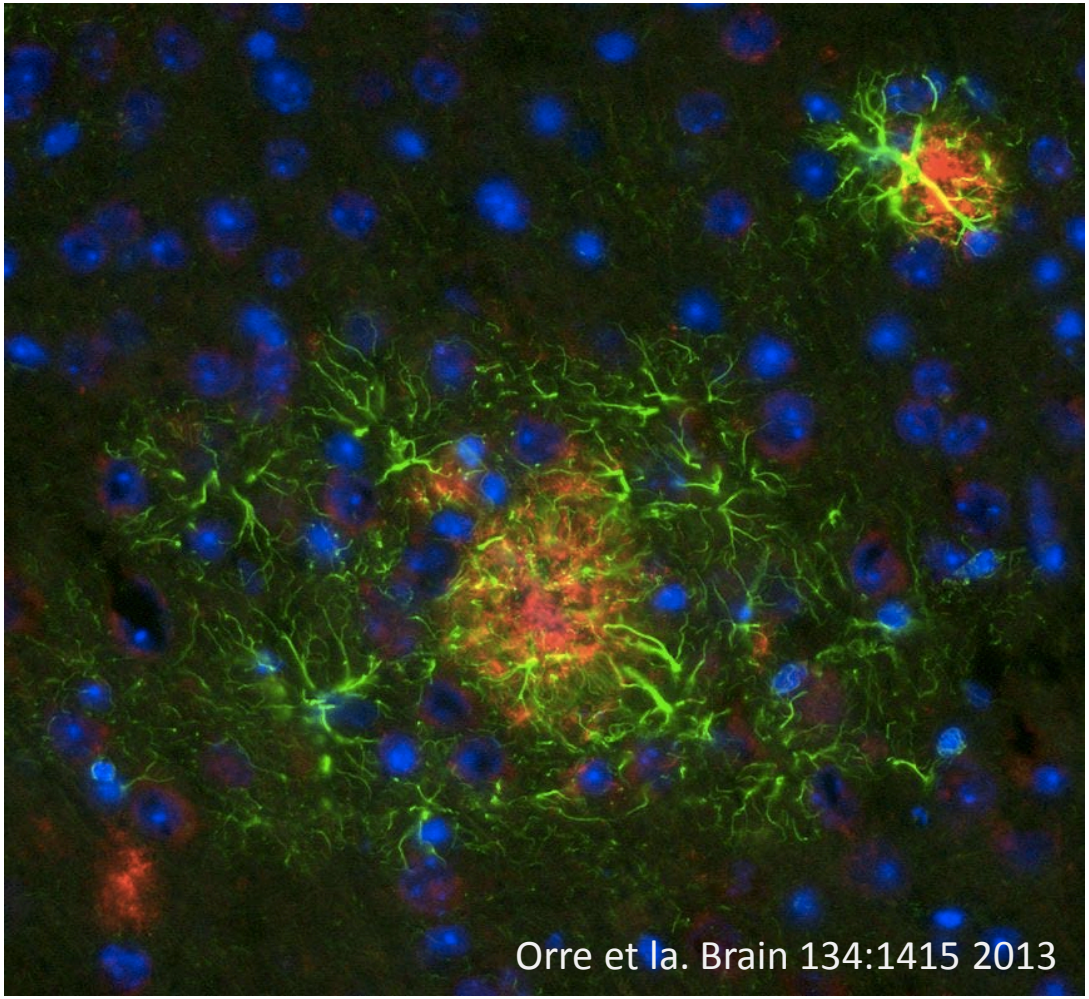
In many CNS disorders blood borne monocytes infiltrate the brain



Sieweke & Alan, 2013

CNS Disease:
CCL2-mediated infiltration of monocytes into the brain

Amyloid deposition results in the accumulation of macrophages on and around the plaque

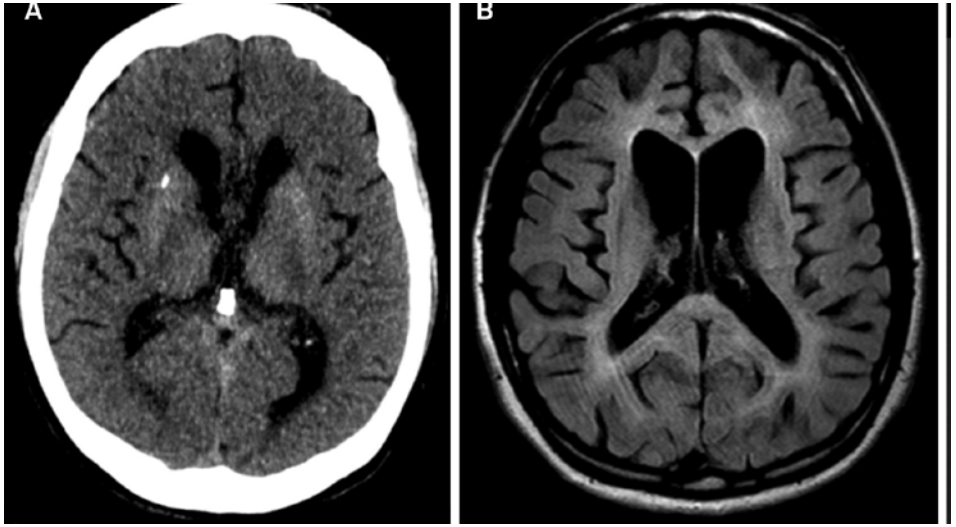


The plaque associated macrophages exhibit a proinflammatory phenotype but are inefficient phagocytes

Nasu-Hakola Disease: Demonstration that perturbation of microglia is alone sufficient to cause Neurodegenerative Disease

- Nasu-Hakola disease (aka PLOSL) is a progressive neurodegenerative disease that arises from mutation of the myeloid specific gene, TREM2 or its signaling adapter protein DAP12 (TyroBP)

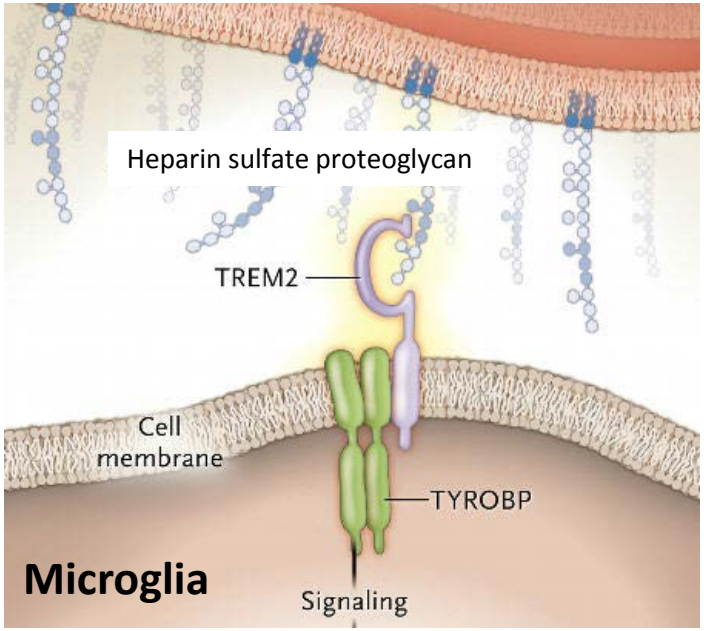
- In the brain TREM2 and DAP12 are exclusively expressed by microglia.



TREM2
Variants in the microglial receptor TREM2 confer risk for developing neurodegenerative diseases

TREM2 is expressed on myeloid cells
and exclusively on microglia in the brain

Its ligand(s) are unknown are are postulated to be
- Lipids, including phospolipids/ApoE.
- Cell surface proteins that interact with heparin sulfate-containing proteoglycans.



TREM2 phospholipid binding does not result in signaling,

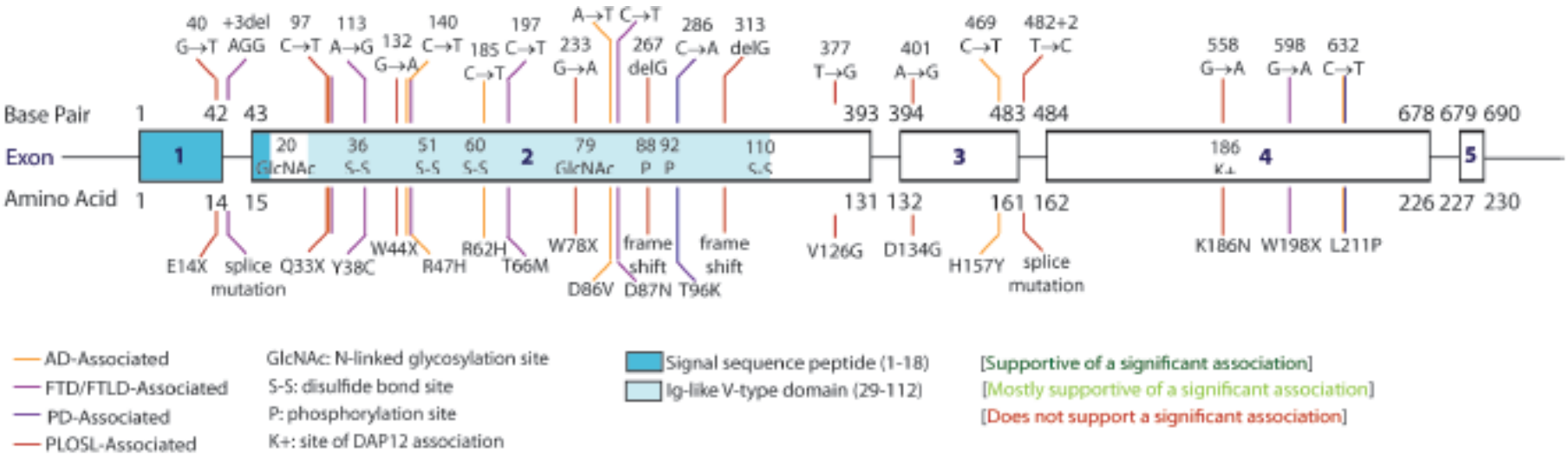
The function of TREM2 remains controversial:

It has been postulated to be a phagocytic receptor.

TREM2 has been shown in vitro to suppress inflammatory responses. However, this conclusion is not supported in several in vivo settings.

TREM2 variants are associated with neurodegenerative diseases

GWAS have identified a number of TREM2 variants linked to neurodgenerative diseases

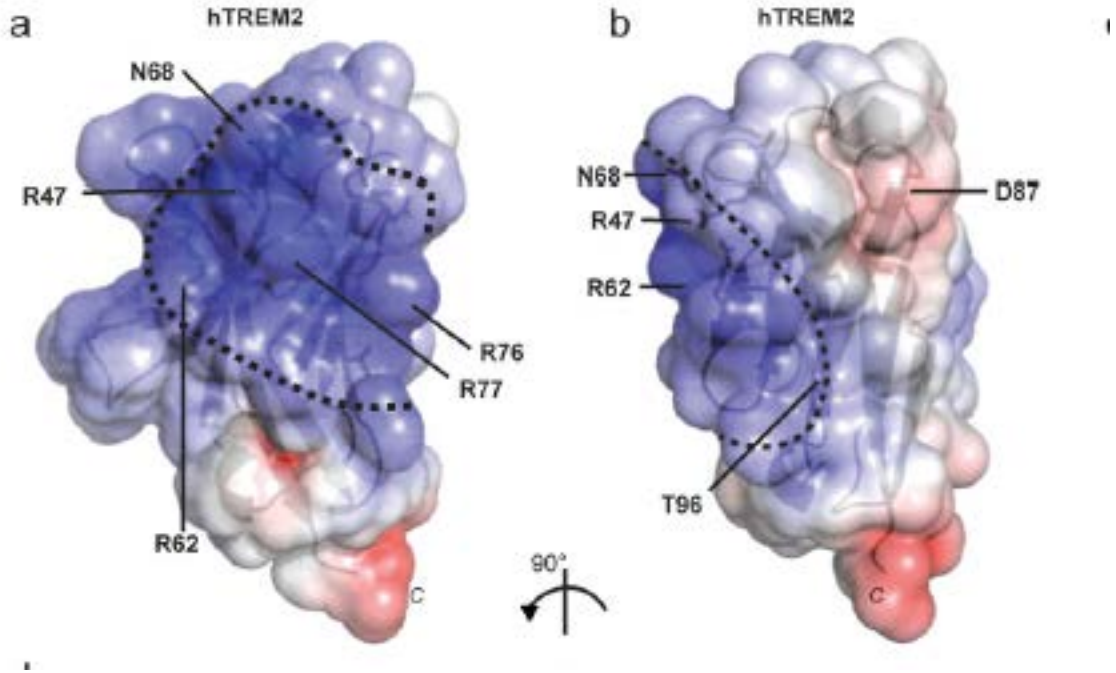


R47H increases the risk for AD by approximately 3 fold, an effect size similar to that observed with APOE4

The TREM2 R47H variant is linked to AD, FTD/FTLD, ALS.

AD-linked TREM2 mutations are confined to a surface ligand binding domain that alters binding affinity

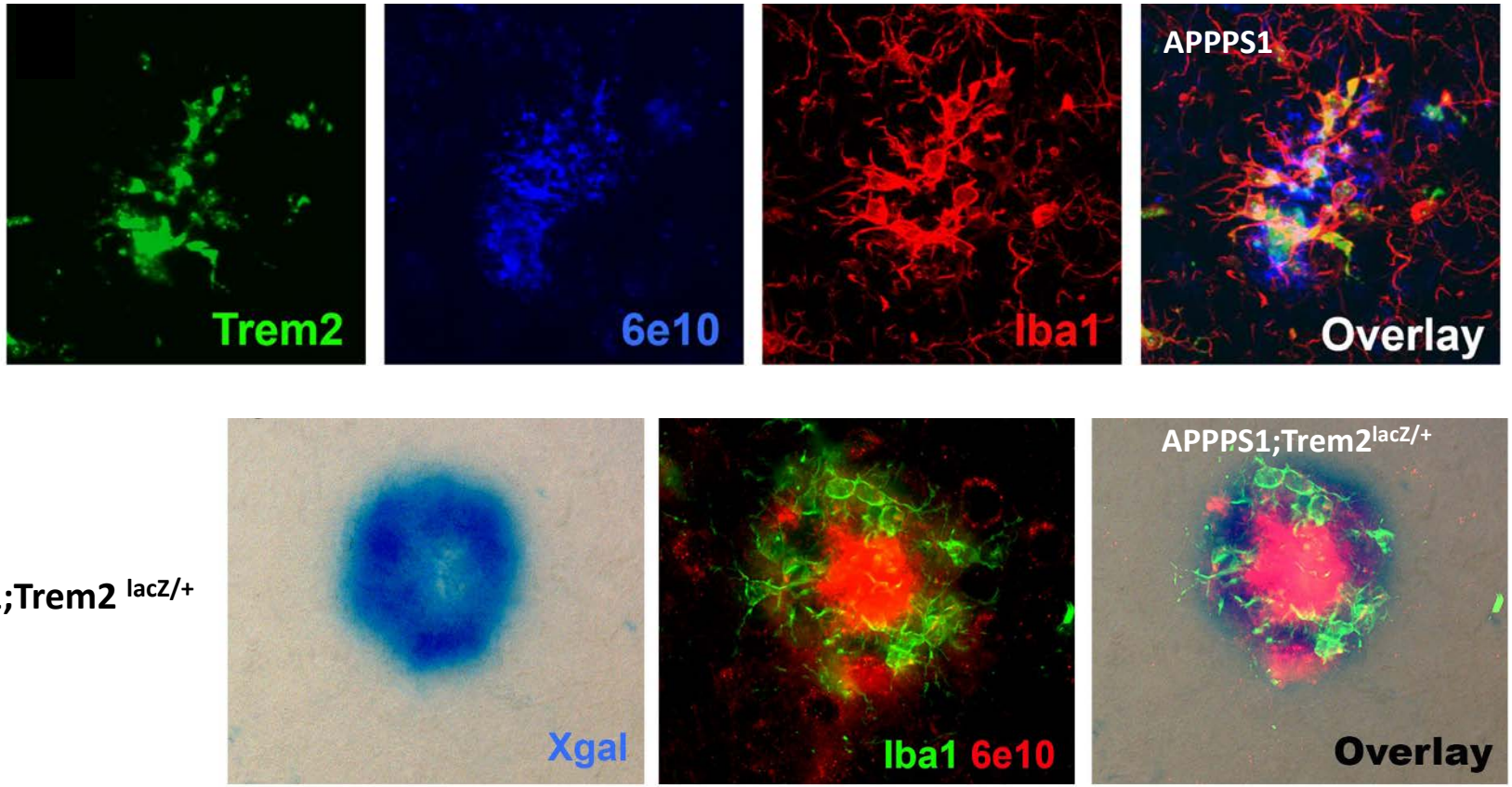
Nasu-Hakola and other LOF mutations are buried and affect folding and stability



TREM2 extracellular domain

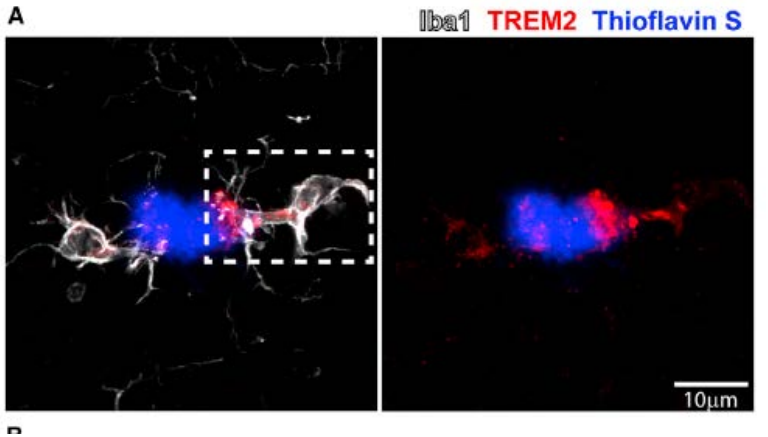
Kober et al. eLife 2016;5;e20391

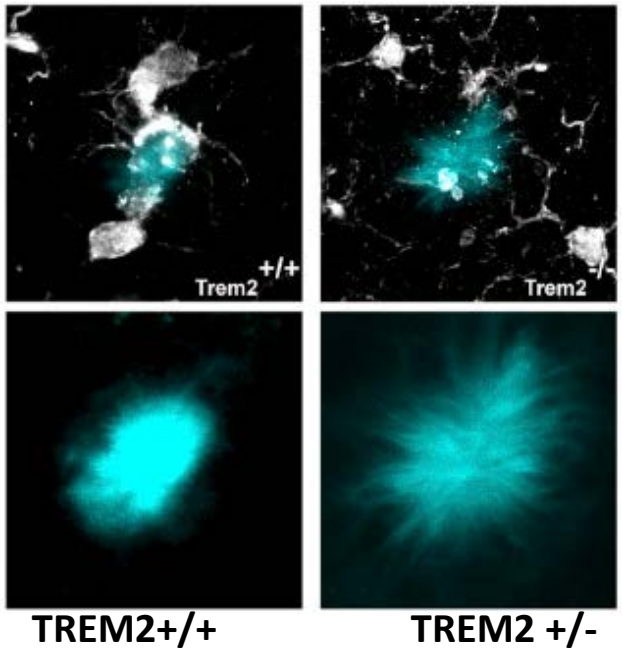
Plaque-associated macrophages express high levels of TREM2



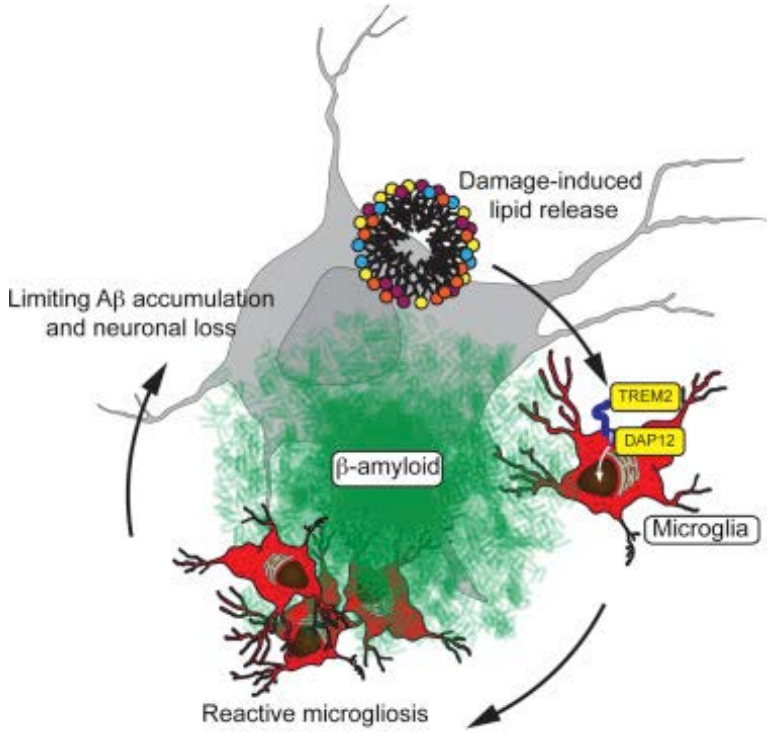
Jay et al. J Exp Med, 2015

TREM2 is focally expressed at plaque interface, curbing plaque growth and abrogating microglial barrier function





Iba1/ThioS



Yuan et al. Neuron 90:724, 2016

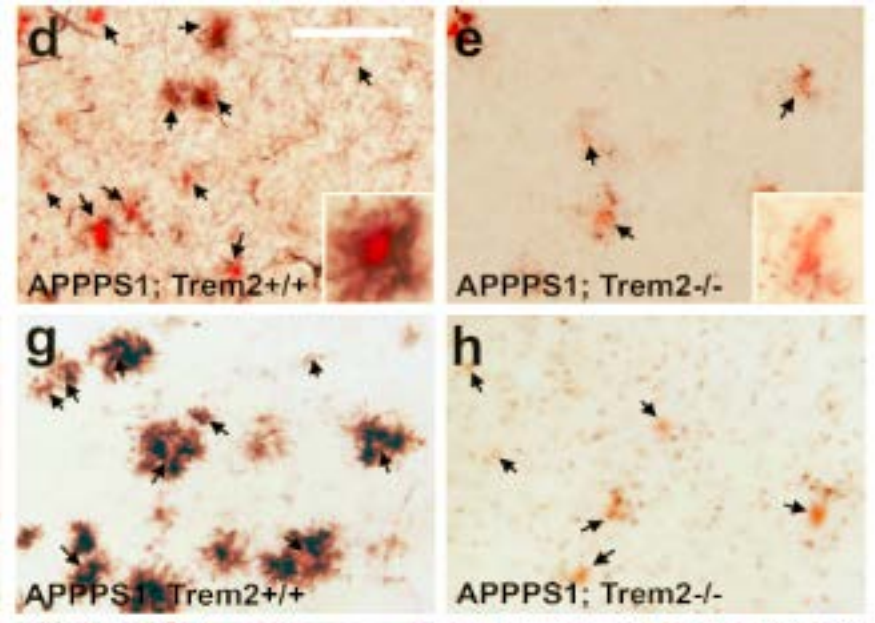
Plaque-associated macrophages bear markers of peripheral monocytes

APPPS1;*Trem2+/+*

APPPS1;*Trem2-/-*

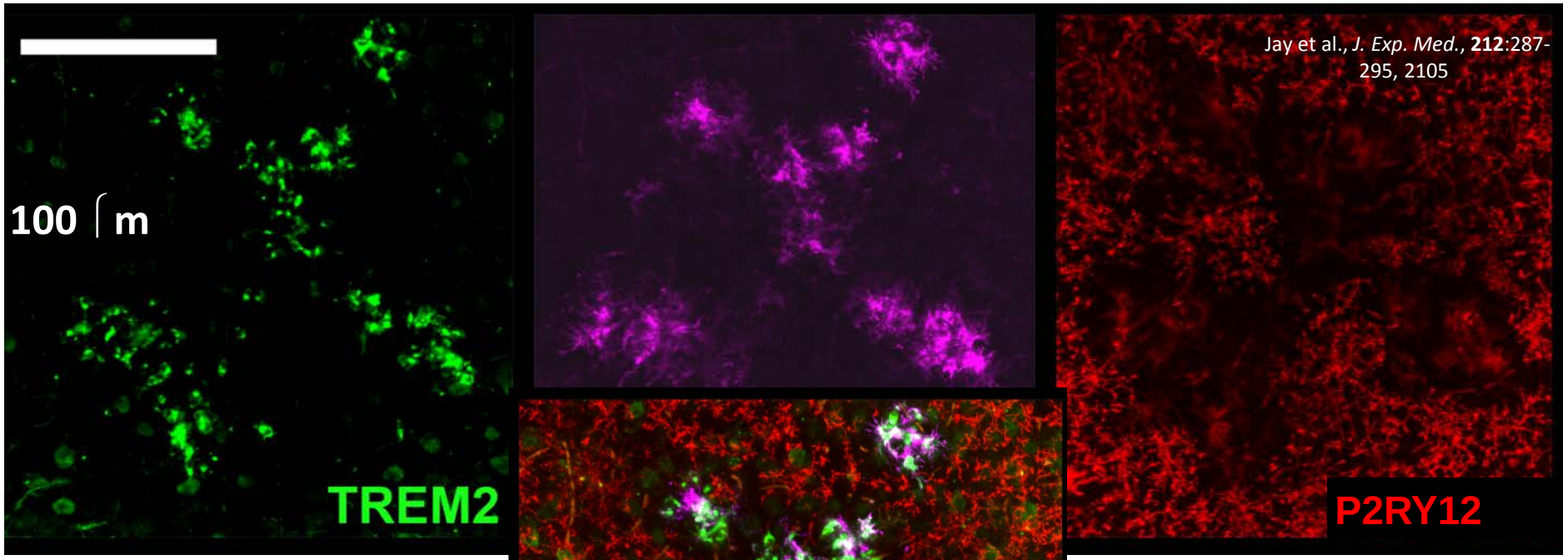
Ly6C

CD45



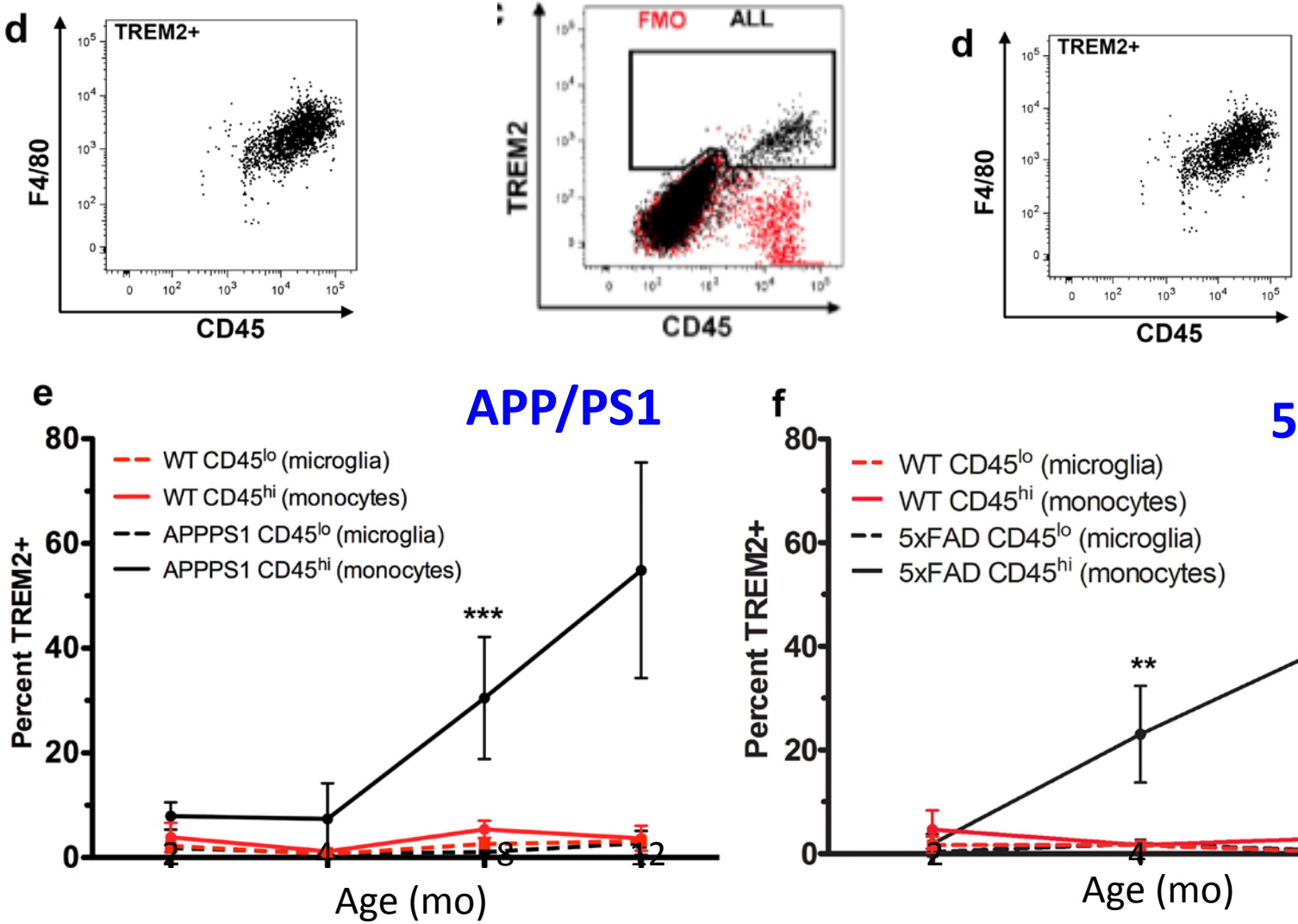
Jay et al. J Exp Med, 2015

Resident microglia do not associate with plaques in AD Mouse Models



TREM2
CD45
P2RY12

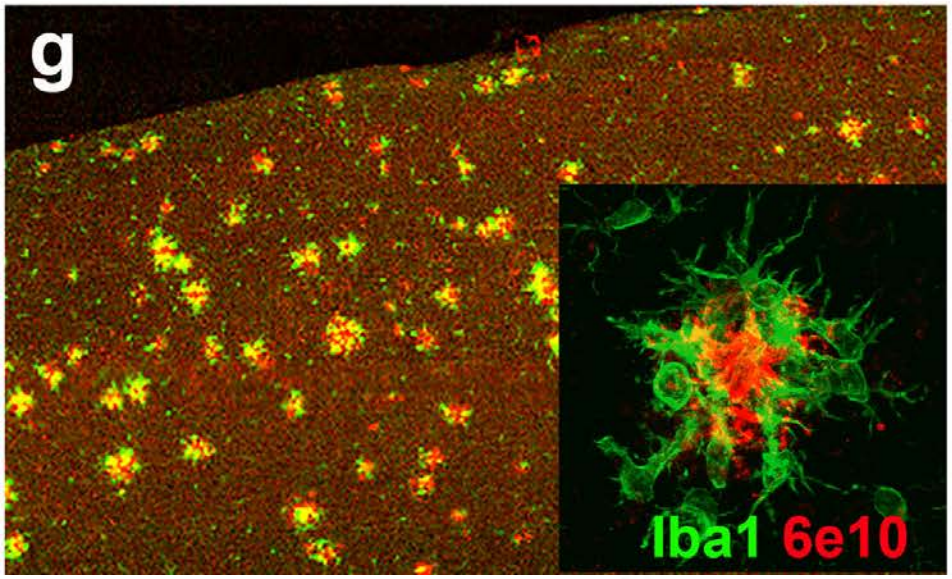
TREM2+, CD45^{hi} myeloid cells are elevated in the brains of 2 different AD models

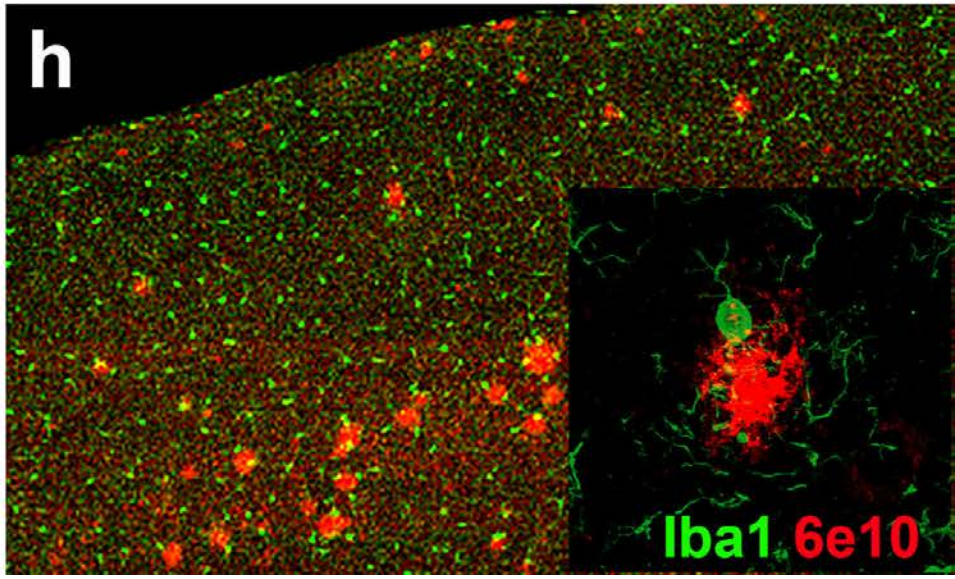


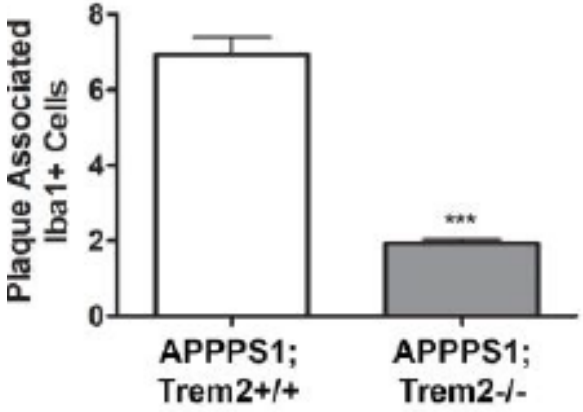
Plaque associated macrophages are absent in the TREM2 KO

APPPS1

APPPS1; TREM2-/-

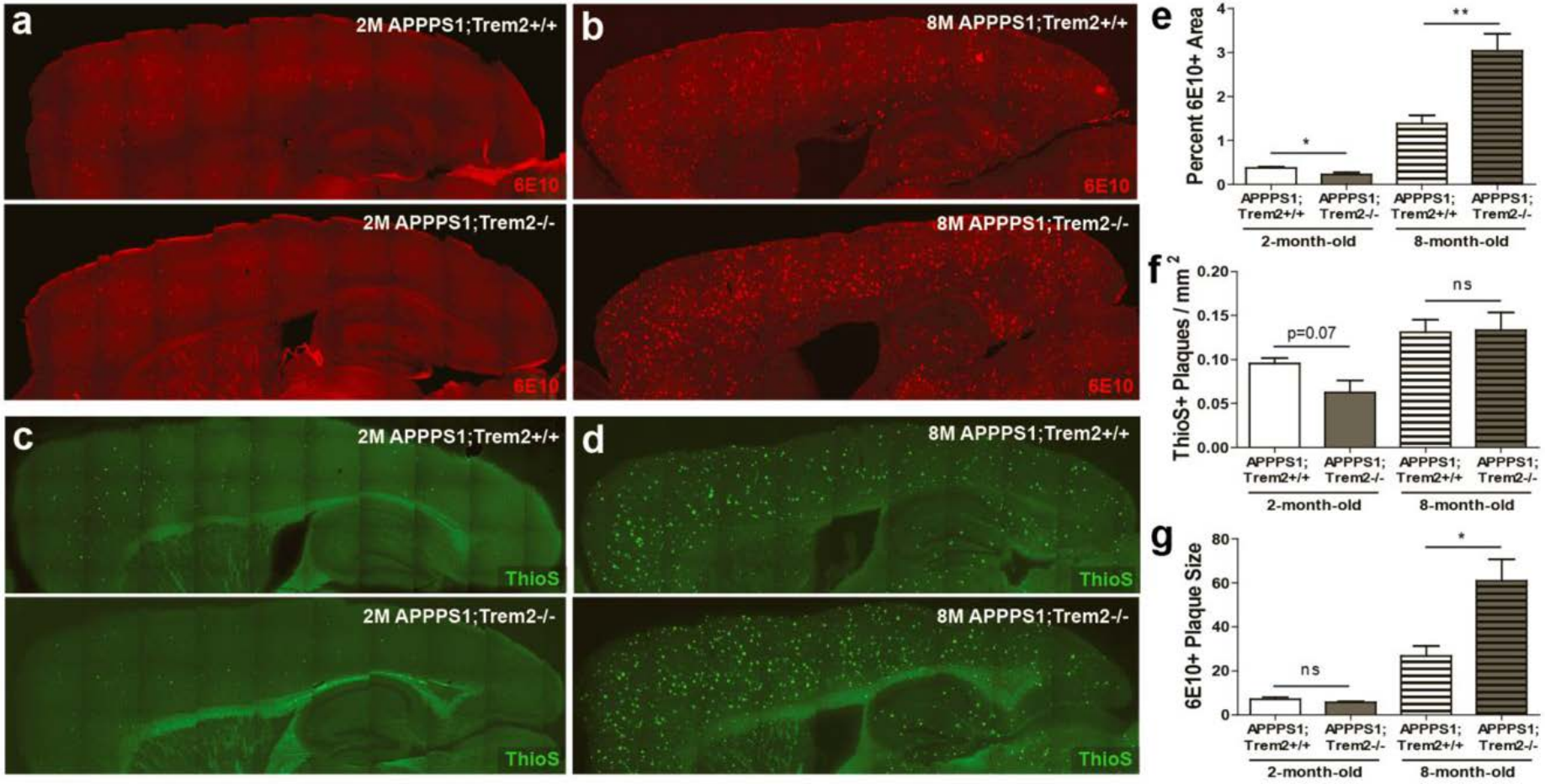




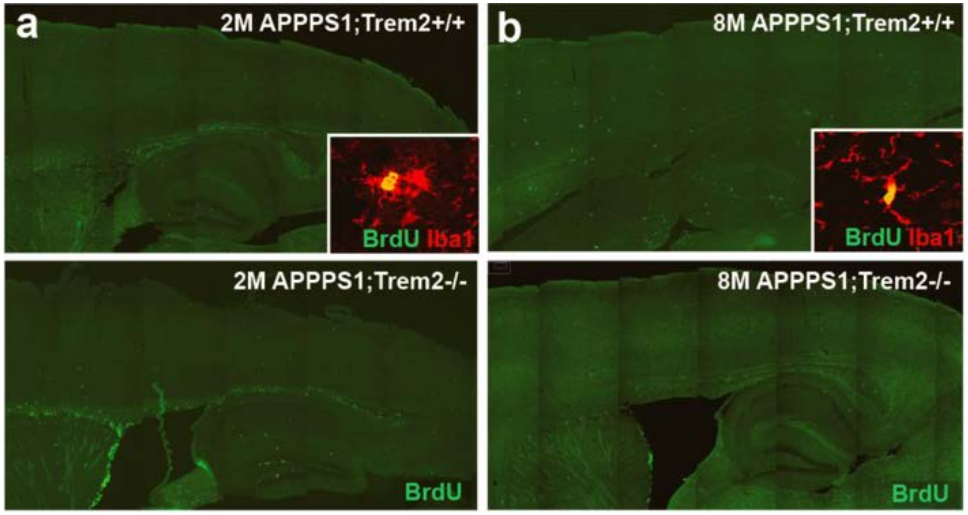


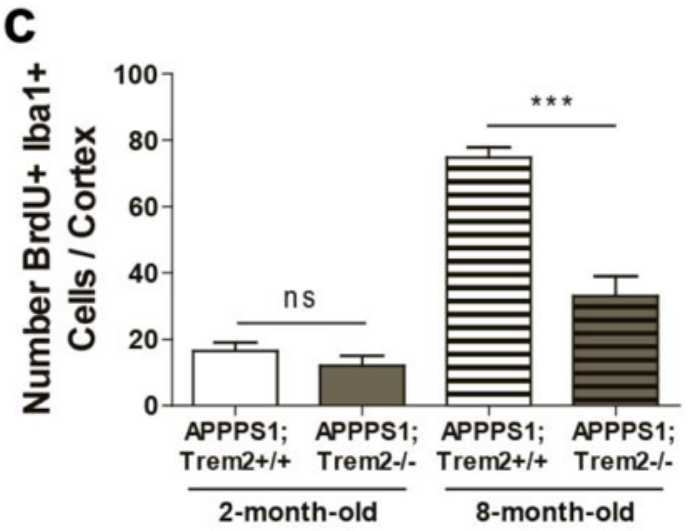
Jay et al. J Exp Med 2015

TREM2 Deficiency Regulates Aβ Deposition in an Age and disease progression-Dependent Manner

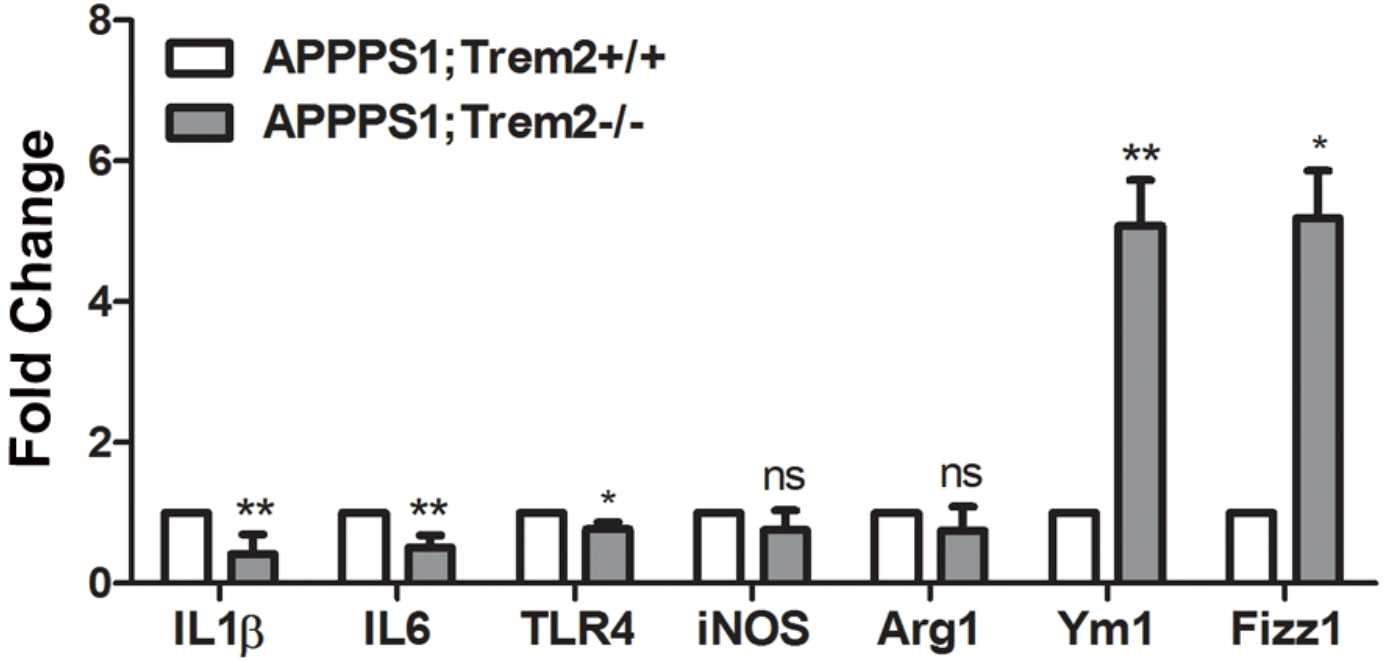


TREM2 Deficiency Reduces Proliferation of Resident Microglia At Late Disease Stages

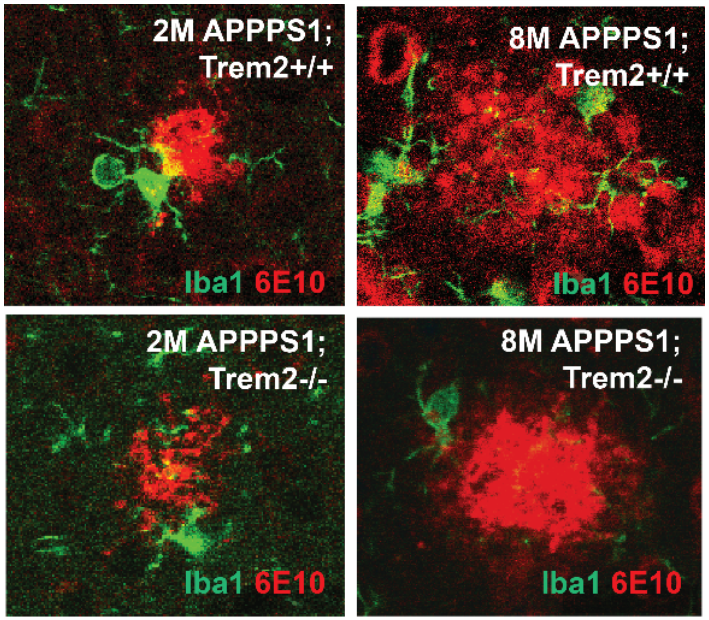


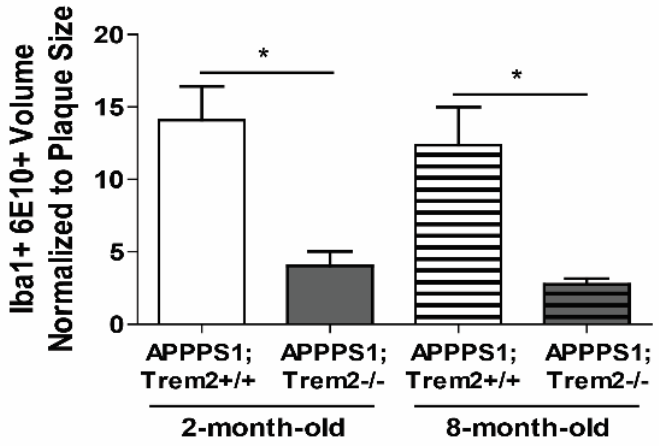


Trem2 deficiency is linked to microglial ‘alternative activation’ phenotype

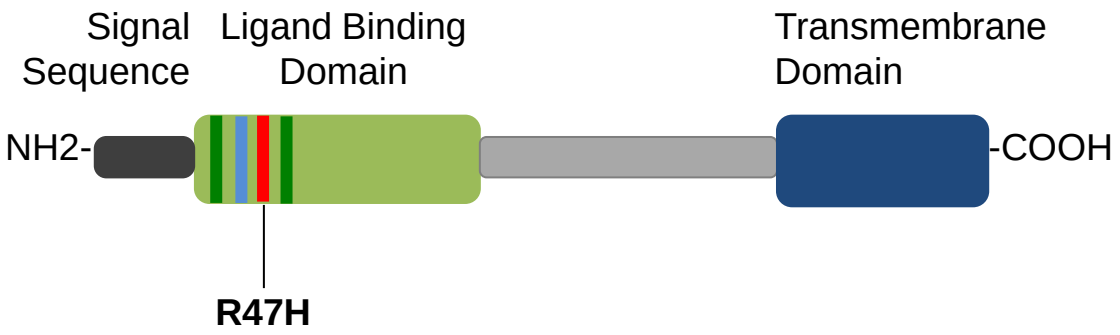


TREM2 deficiency reduces amyloid internalization in plaque associated macrophages



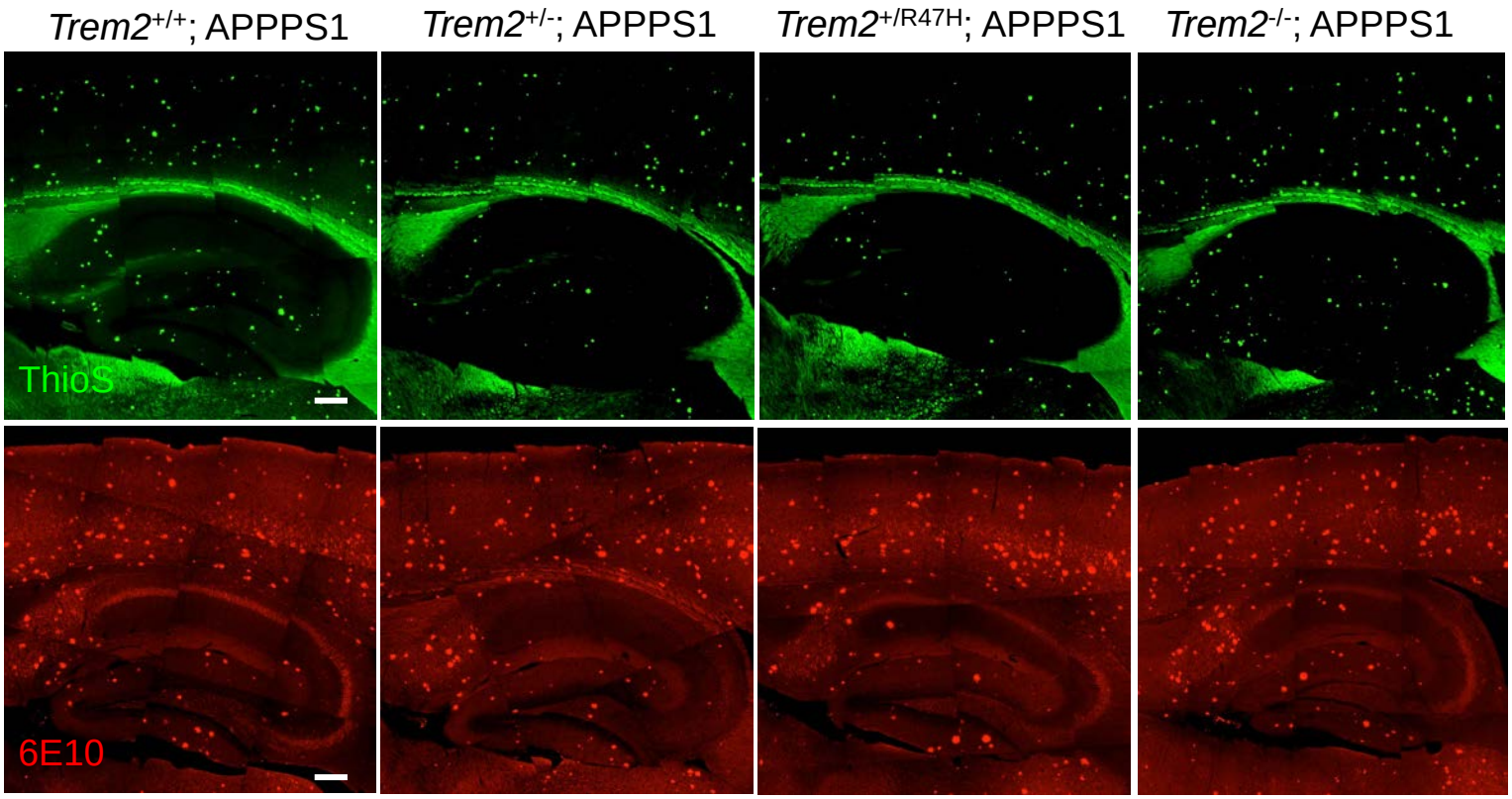


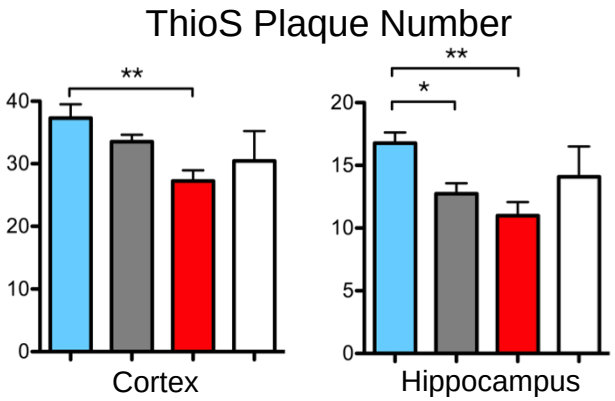
The TREM2 R47H Mutation Increases AD Risk

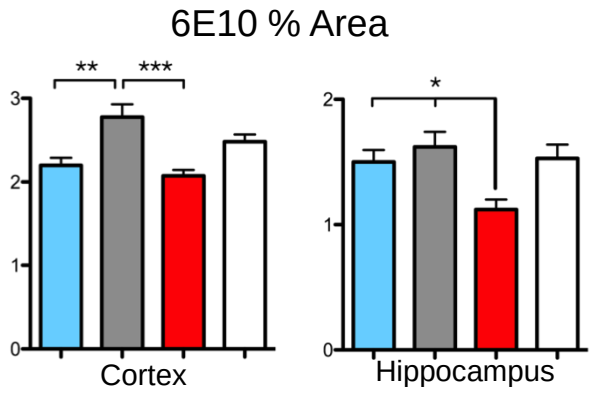


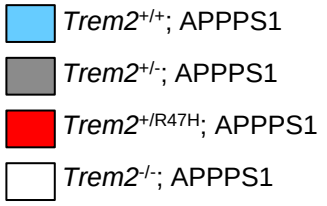
Population	OR	CI	*p* Value	Reference
European-North American	4.5	1.7-11.9	<0.001	Guerreiro et al., 2013
European	2.83	1.45-5.40	0.002	Jonsson et al., 2013
French	4.07	1.29-16.8	0.009	Pottier et al., 2013
European-North American	3.3	1.3-9.8	0.0044	Giraldo et al., 2013
North American	3.5	1.3-8.8	0.008	Murcia et al., 2013

Amyloid burden is modestly reduced in *Trem2*$^{+/R47H}$;APPPS1 mice

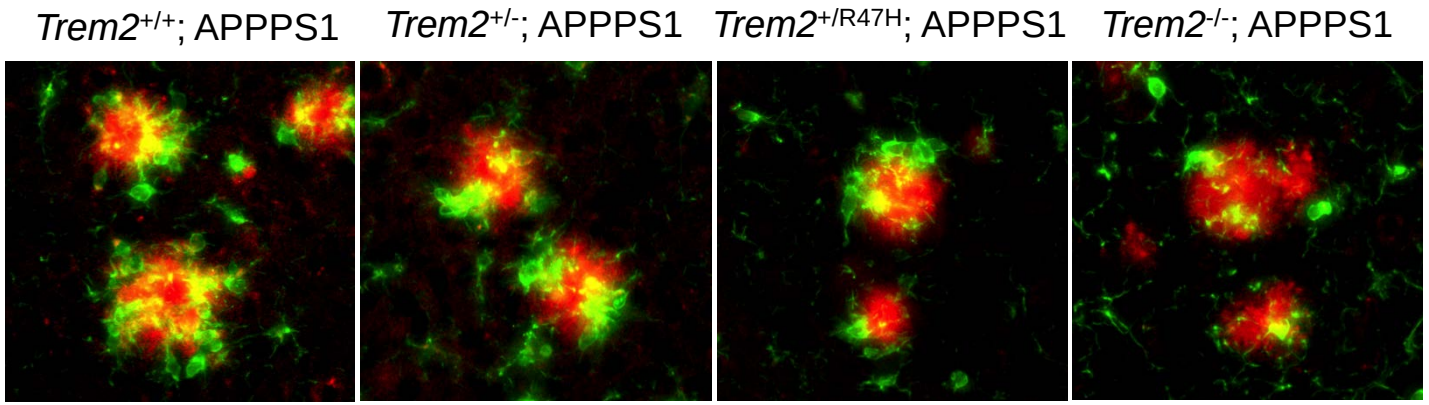


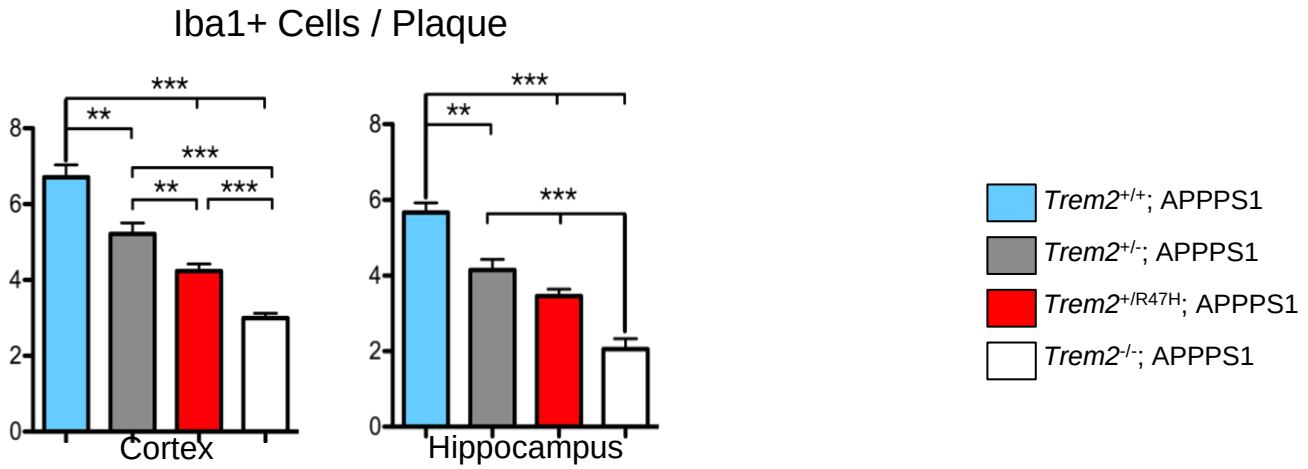




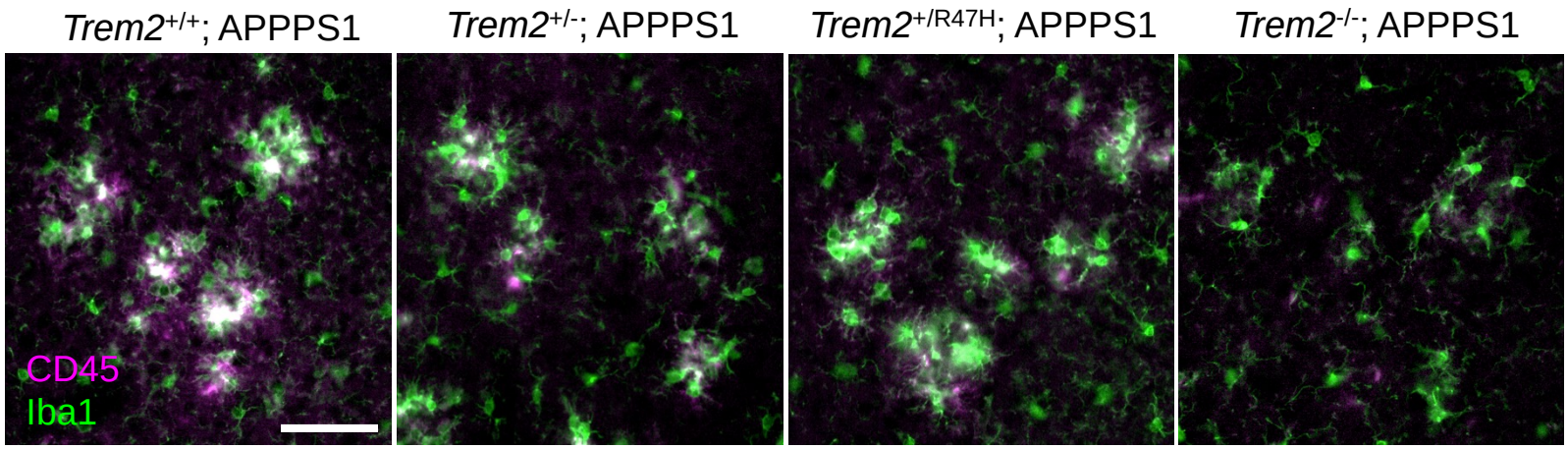


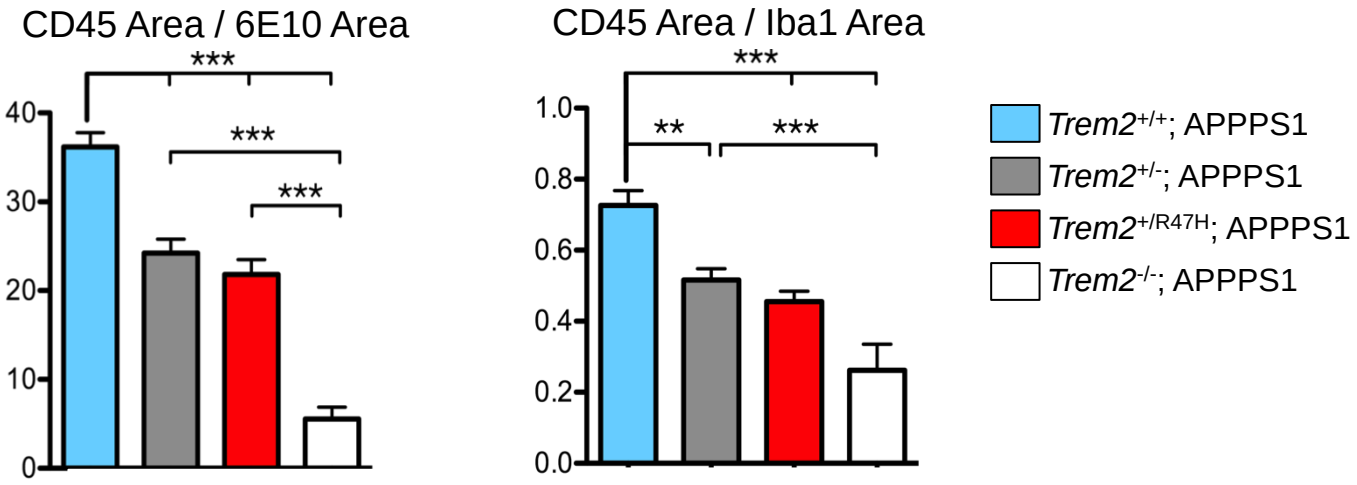
Plaque associated Iba1+ cells are significantly reduced in *Trem2*$^{+/R47H}$;APPPS1 mice





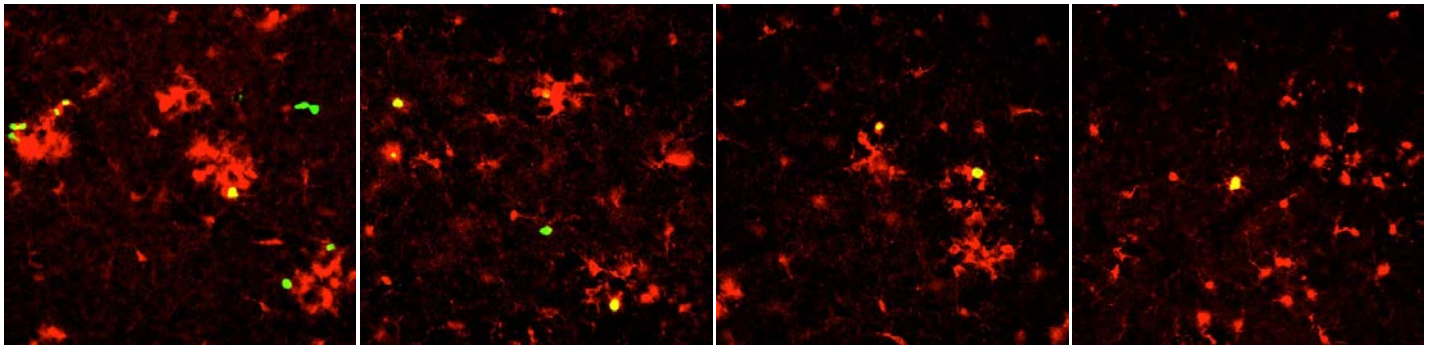
CD45, a marker of peripheral myeloid cells, is significantly reduced in *Trem2*$^{+/R47H}$;APPPS1 mice



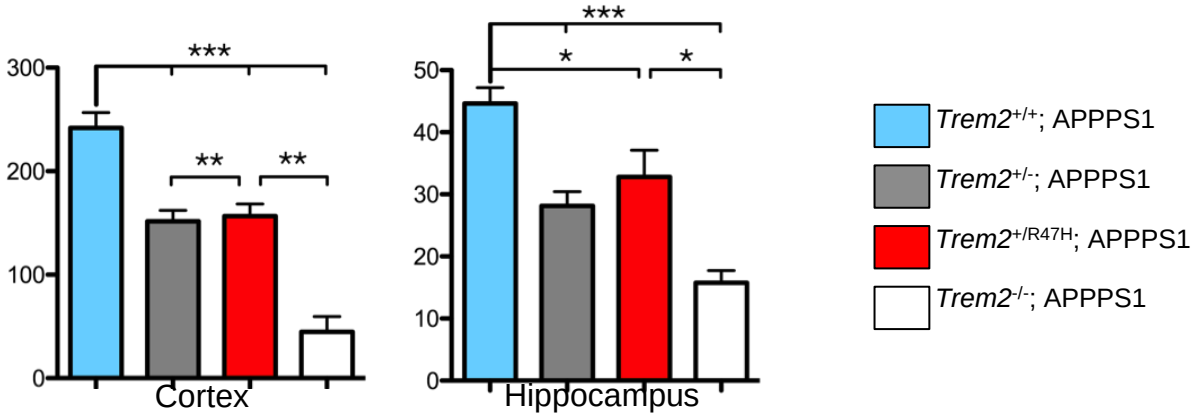


Plaque associated myeloid cell proliferation is significantly reduced in *Trem2*$^{+/R47H}$;APPPS1 mice

Trem2$^{+/+}$; APPPS1 *Trem2*$^{+/-}$; APPPS1 *Trem2*$^{+/R47H}$; APPPS1 *Trem2*$^{-/-}$; APPPS1

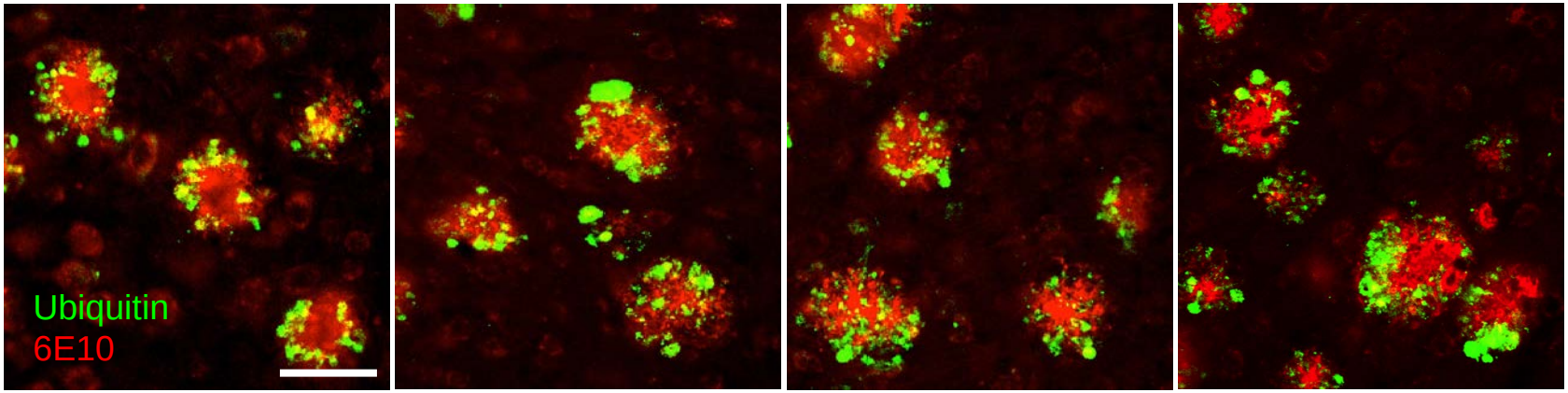


Total Ki67+ Iba1+ Cells

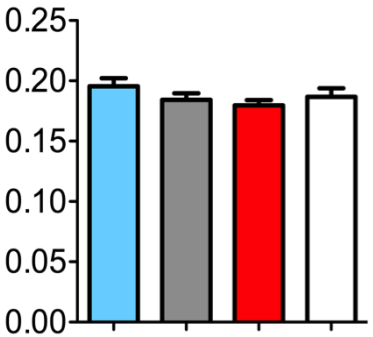


Plaque associated neuritic dystrophy is modestly increased in *Trem2*$^{+/R47H}$;APPPS1 mice

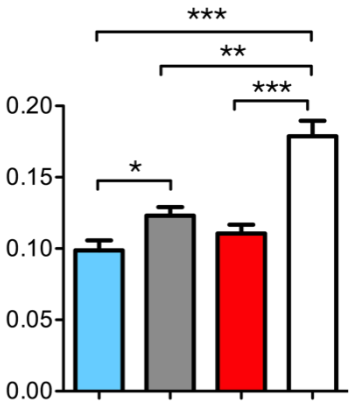
Trem2$^{+/+}$; APPPS1 | *Trem2*$^{+/-}$; APPPS1 | *Trem2*$^{+/R47H}$; APPPS1 | *Trem2*$^{-/-}$; APPPS1



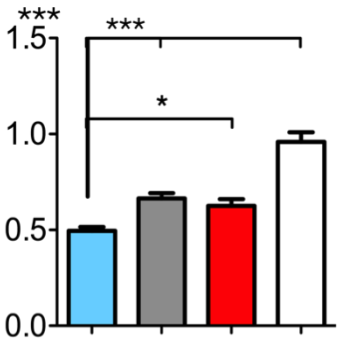
Plaque Size (AU)

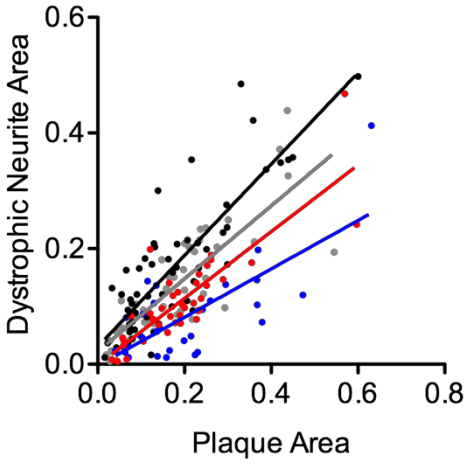


Ubiquitin Area (AU)



Ubiquitin Area / Plaque Size

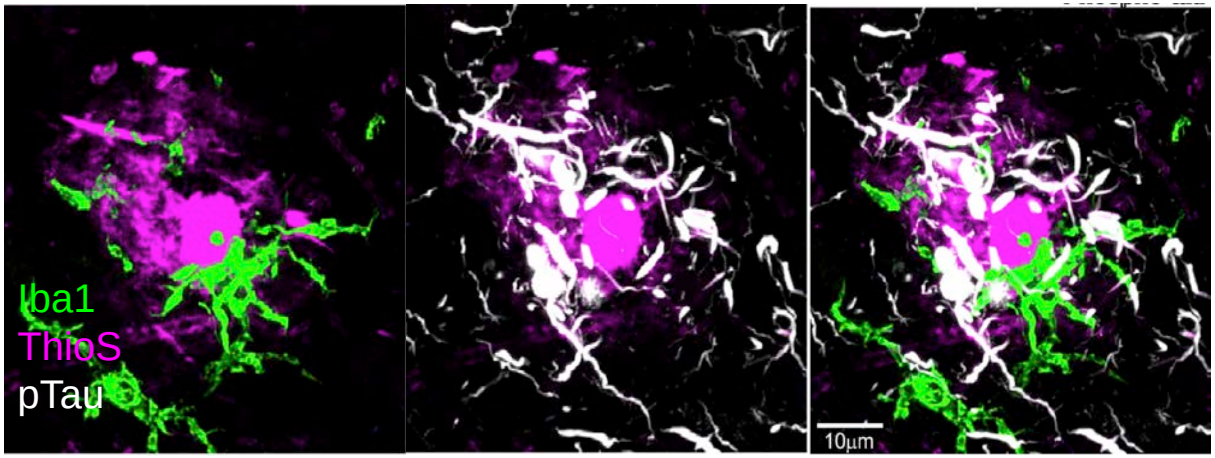




Trem2$^{+/+}$; APPPS1
Trem2$^{+/-}$; APPPS1
Trem2$^{+/R47H}$; APPPS1
Trem2$^{-/-}$; APPPS1

Trem2$^{+/+}$; APPPS1
Trem2$^{+/-}$; APPPS1
Trem2$^{+/R47H}$; APPPS1
Trem2$^{-/-}$; APPPS1

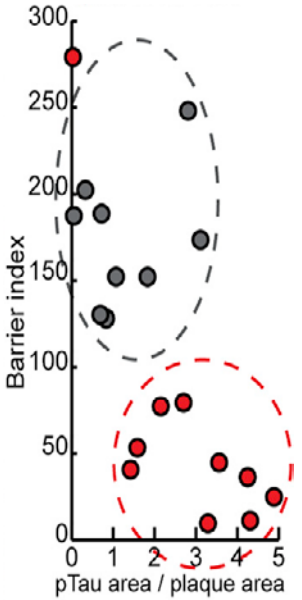
Human R47H carriers exhibit impaired Myeloid Cell Barrier and enhanced Plaque Associated Neuronal Dystrophy



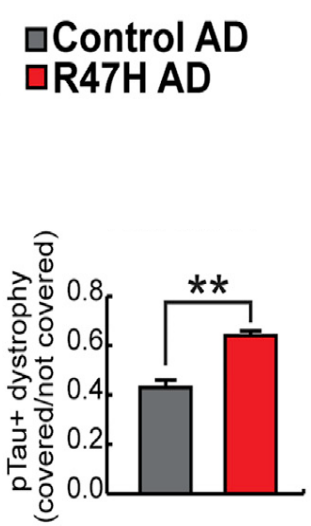
Plaque regions poorly covered by myeloid cell processes have more neuritic dystrophy

Yuan et al., Neuron (2016)

Barrier Function



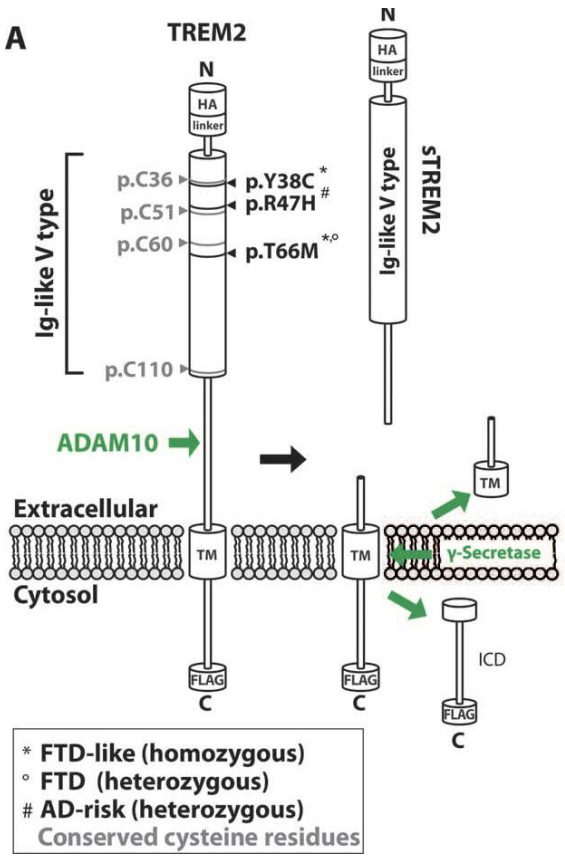
pTau



TREM2 R47H reduces myeloid barrier index and increases neuritic dystrophy

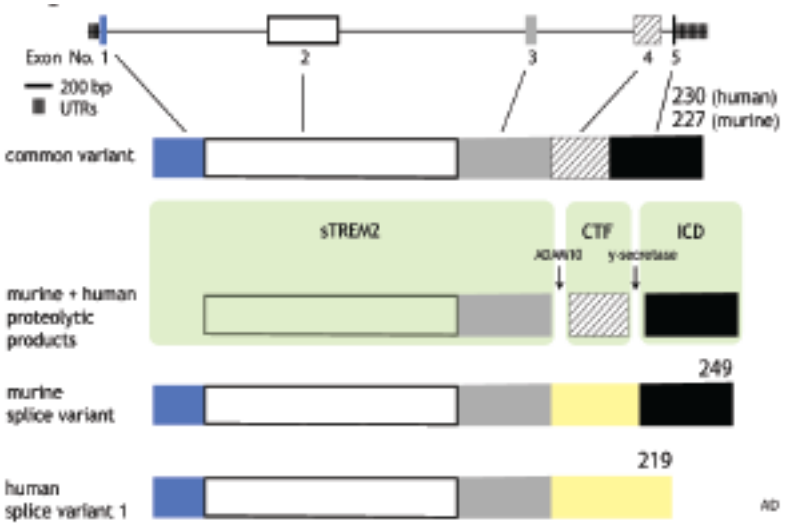
Soluble Trem2 extracellular domains are released from microglia

Proteolytic cleavage



Klineberger et al.

Alternatively spliced mRNAs

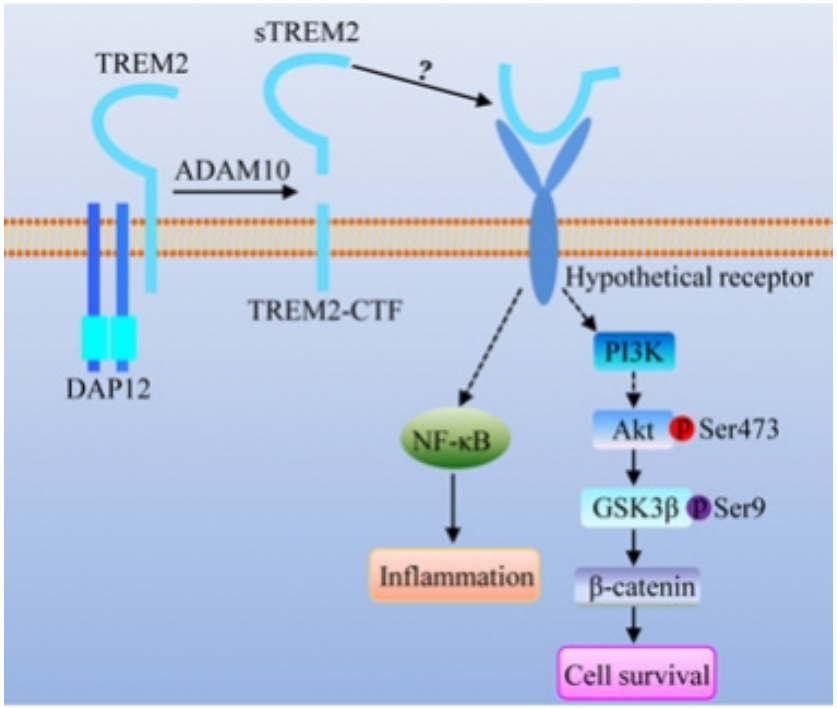


Alternatively spliced mRNAs have not been shown to be translated

Jin et al.

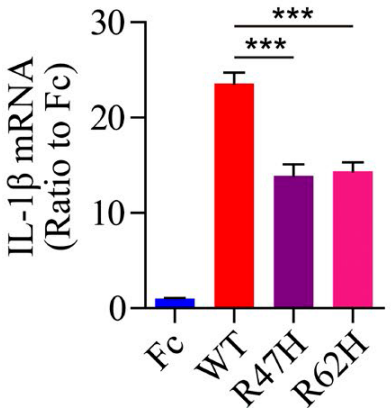
sTREM2 stimulates proinflammatory gene expression in microglia

sTREM2 acts in an autocrine or paracrine manner to drive microglial activation

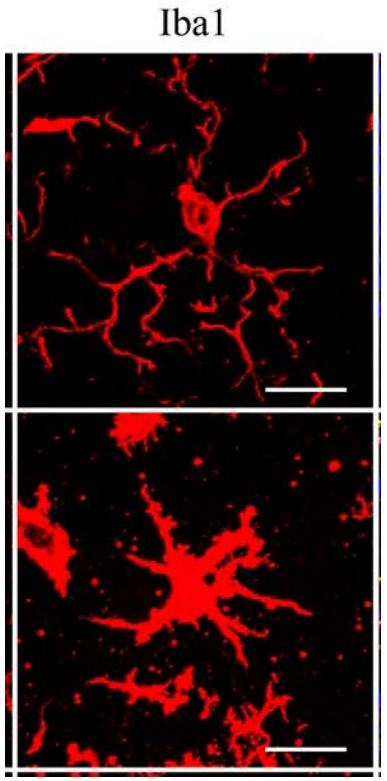


Zhong et al. JEM 2017

In vitro

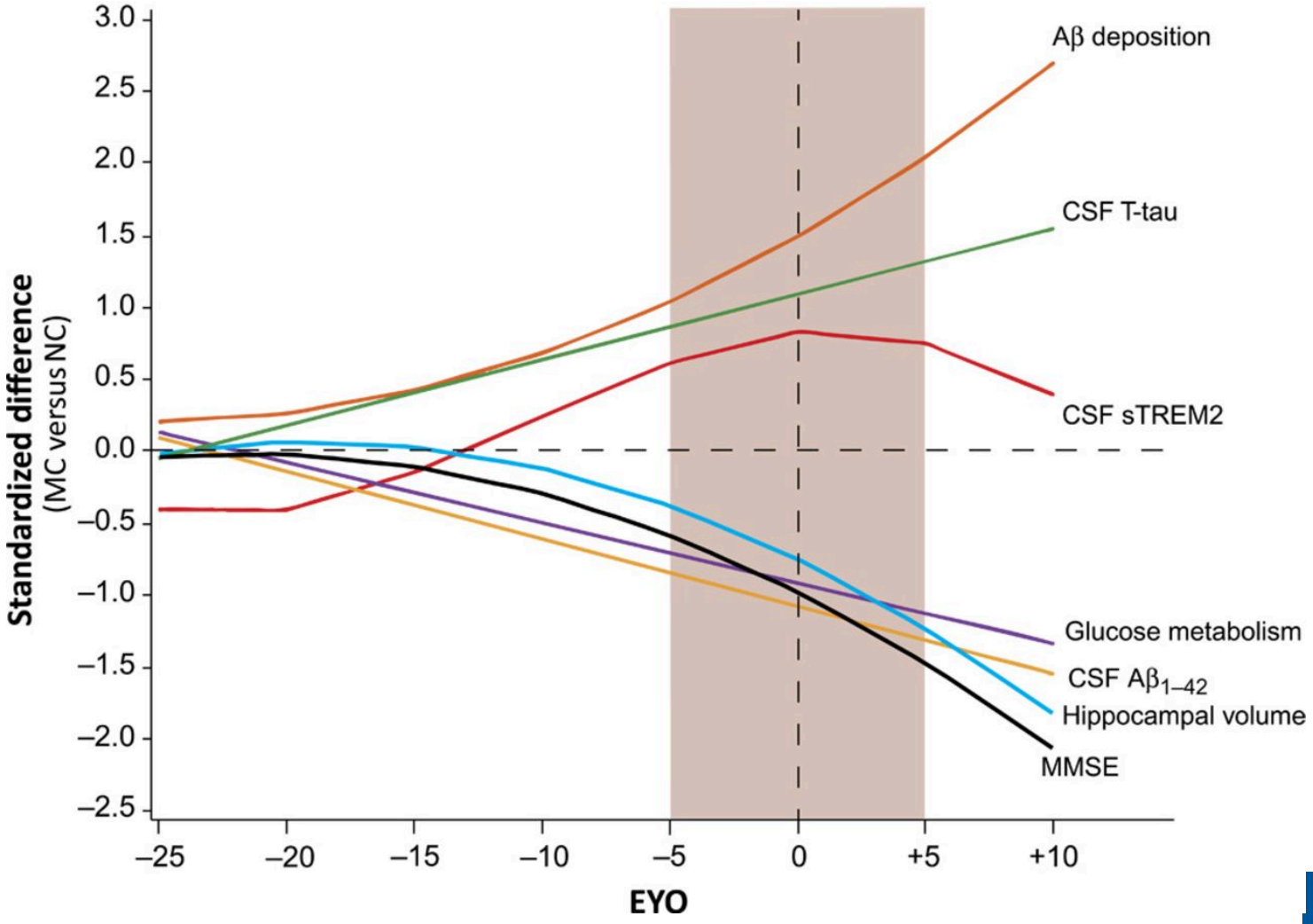


Ex vivo



These data force a reevaluation of TREM2 actions in the brain and its roles in neurodegenerative diseases

sTREM2 appears in CSF after amyloid deposition and concurrent with other disease markers in dominantly inherited forms of AD



Marc Suárez-Calvet et al., Sci Transl Med 2016;8:369ra178

Science Translational Medicine
AAAS

Summary

- Perturbation of microglial function through loss of TREM2 is sufficient to cause neurodegenerative disease
- TREM2 deficiency ($^{-/-} > {}^{+/-}$) reduces plaque associated peripherally-derived macrophages
- TREM2 deficiency results in reduced microglial proliferation
- Age and disease progression-dependent phenotypes preclude firm conclusions with regard to effect of $TREM2^{+/R47H}$ mutation on plaque and neuritic dystrophy
- The preliminary findings suggest the $TREM2^{R47H}$ variant appears to be LOF
- CSF levels of sTREM2 may be a useful biomarker for AD

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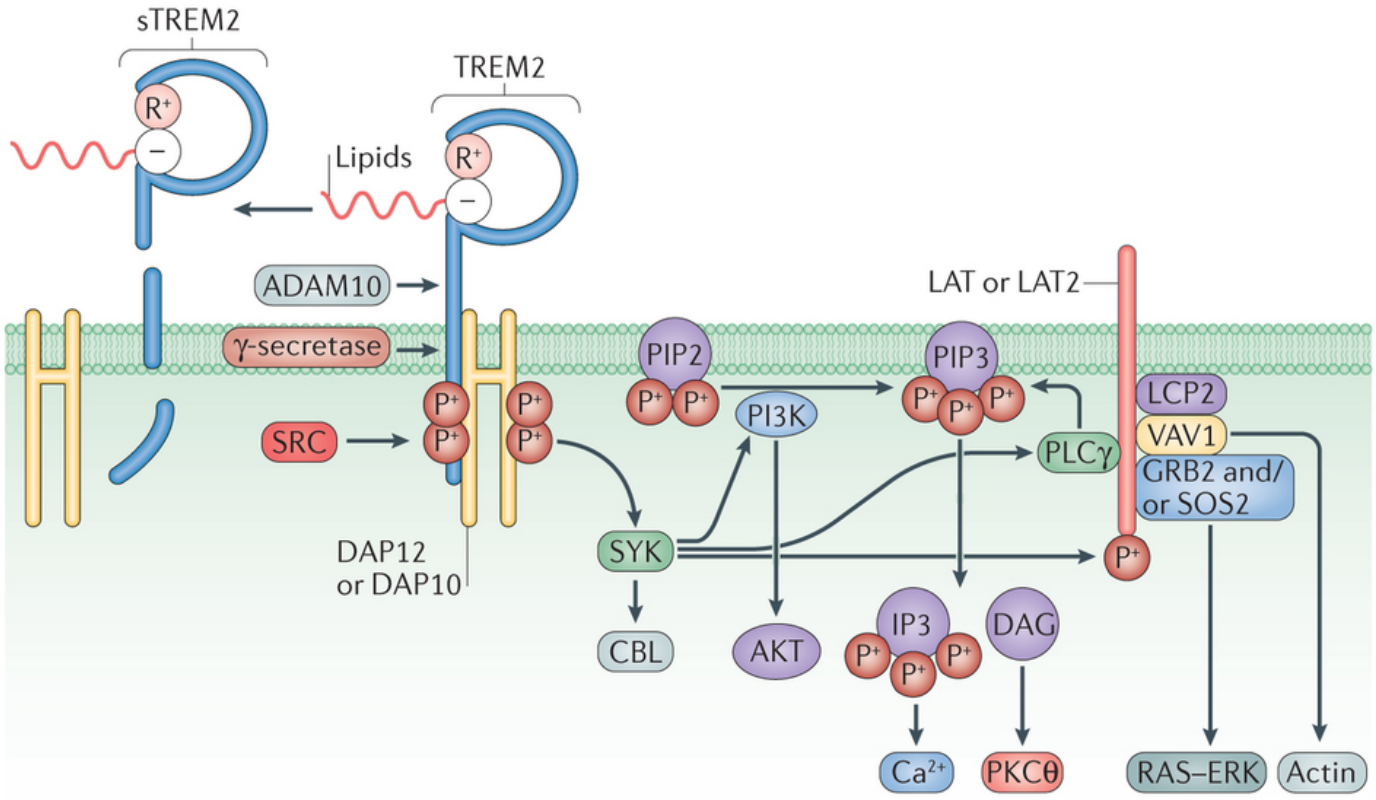
END


sTREM2
TREM2
R+
−
Lipids
ADAM10
γ-secretase
SRC
P+
DAP12
or DAP10
SYK
CBL
AKT
PI3K
PIP2
PIP3
LAT or LAT2
LCP2
VAV1
GRB2 and/
or SOS2
PLCγ
IP3
DAG
Ca2+
PKCθ
RAS–ERK
Actin