Diving Deep into TREM2:

Uncovering its Potential as a Therapeutic Target for Alzheimer's Disease

Forward Looking Statement

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potentially," "predict," "should," "will" or the negative of these terms or other similar expressions. Forward-looking statements contained in this presentation also include, but are not limited to, statements regarding the beneficial characteristics, safety, efficacy, and therapeutic effects of our product candidates; our plans, timelines and expectations related to our product candidates and our other clinical and pre-clinical programs, including with respect to the availability of data, the initiation of future clinical trials and plans and expectations regarding planned regulatory filings with respect to such programs; expectations regarding the timing and financial benefit of our collaborations; and objectives of management for future operations, as well as statements regarding industry trends.

We, Alector, Inc. ("Alector"), have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: Alector's plans relating to its research programs and the development and manufacturing of its product candidates; the ability of Alector's clinical trials to demonstrate safety and efficacy of its product candidates, and other positive results; the timing and focus of Alector's clinical trials, and the reporting of data from those trials; Alector's plans relating to commercializing its product candidates, if approved, including the geographic areas of focus and sales strategy; the expected potential benefits of strategic collaborations with third parties and Alector's ability to attract collaborators with development, regulatory and commercialization expertise; Alector's estimates of the number of patients in the United States, the European Union and world-wide who suffer from the diseases it is targeting and the number of patients that will enroll in its clinical trials; the size of the market opportunity for Alector's product candidates in each of the diseases it is targeting; Alector's ability to expand its product candidates into additional indications and patient populations; the success of competing therapies that are or may become available; the beneficial characteristics, safety, efficacy, and therapeutic effects of Alector's product candidates; the timing or likelihood of regulatory filings and approvals, including Alector's expectation to seek special designations, such as orphan drug designation, for its product candidates for various diseases; Alector's ability to obtain and maintain regulatory approval of its product candidates; Alector's plans relating to the further development and manufacturing of its product candidates, including additional indications that it may pursue; existing and future regulations and regulatory developments in the United States and other jurisdictions; Alector's reliance on third parties to conduct clinical trials of its product candidates, and for the manufacture of its product candidates for preclinical studies and clinical trials; the impact of worldwide economic conditions, including macroeconomic downturns stemming from increased inflation, supply chain and other economic impacts of the coronavirus (COVID-19) pandemic and geopolitical events on our business; and the other risks, uncertainties and assumptions discussed in the public filings we have made and will make with the Securities and Exchange Commission ("SEC"). These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements.

This presentation also contains results based on data from our clinical trials. These clinical trials are ongoing and this presentation does not speak to, and you should make no assumptions about, any additional data. In addition, the information we have chosen to publicly disclose regarding our product candidates has been selected from a more extensive amount of available information. You or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise. If the initial data that we report differ from updated, late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

This presentation discusses certain investigational therapeutic agents which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of our product candidate for the therapeutic use for which it is being studied.

This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on our internal sources. We have not independently verified the accuracy or completeness of the data contained in these industry publications and other publidy available information. Accordingly, we make no representations as to the accuracy or completeness of that data.

Except as required by law, we undertake no obligation to update any statements in this presentation for any reason after the date of this presentation. We have filed Current Reports on Form 8-K, Quarterly Reports on Form 10-Q, Annual Reports on Form 10-K, and other documents with the SEC. You should read these documents for more complete information about us. You may obtain these documents for free by visiting EDGAR on the SEC website at www.sec.gov.

Today's Agenda

01	**Perspectives on Immuno-neurology and TREM2** *Arnon Rosenthal, Ph.D., Chief Executive Officer, Alector*	**9:00-9:15 am**
02	**TREM2: A Promising Target for Alzheimer's Disease** *Michael Heneka, M.D., Director of the Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg and Adjunct Professor, University of Massachusetts Chan Medical School*	**9:15-9:35 am**
03	**AL002 Overview and Clinical Development** *Gary Romano, M.D., Ph.D., Chief Medical Officer, Alector*	**9:35-9:55 am**
04	**Alzheimer's Disease Treatment Landscape: Beyond Anti-Amyloid Beta Therapies** *Reisa Sperling, M.D., Professor of Neurology, Harvard Medical School and Director of the Center for Alzheimer's Research and Treatment at Brigham and Women's Hospital and Massachusetts General Hospital*	**9:55-10:15 am**
05	**Closing Remarks and Q&A** *Arnon Rosenthal, Ph.D., Chief Executive Officer, Alector*	**10:15-10:30 am**

Perspectives on Immuno-neurology and TREM2

Arnon Rosenthal, Ph.D.

Chief Executive Officer

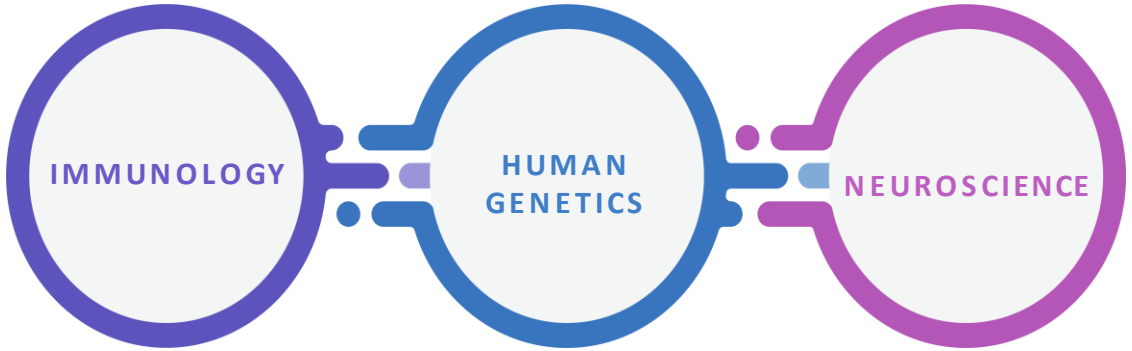
Alector

Alector: Pioneering the Potential of Immuno-neurology to Address Neurodegeneration

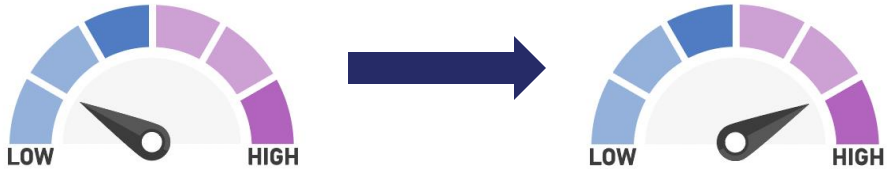
- Pioneering immuno-neurology as a novel therapeutic strategy
- Targeting immune dysfunction as a root cause of neurodegenerative disease
- Ongoing Phase 2 studies in AD (TREM2 & PGRN) and pivotal Phase 3 study in FTD (PGRN)

RESTORING MICROGLIA, THE BRAIN'S IMMUNE SYSTEM

Integrated Insight



Therapeutic Approach



Dysfunctional and damaging Microglia

Healthy disease fighting Microglia

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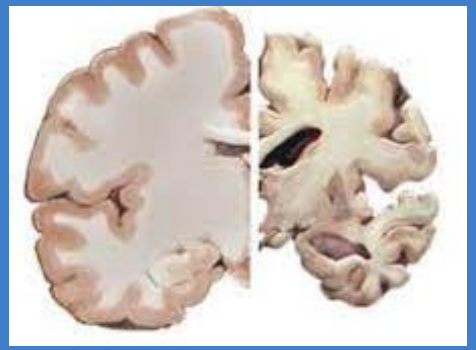
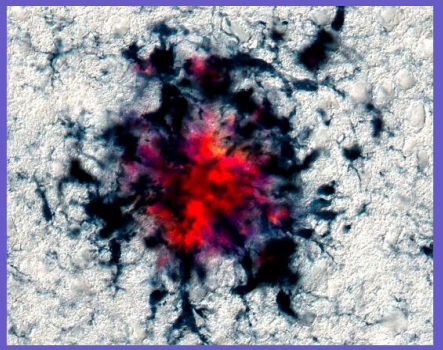
Alois Alzheimer Described 3 Pathologies in the AD Brain

- First AD diagnosis: Auguste Deter, 51-years old, Nov. 1901
- 37th Meeting of South-West German Psychiatrists:
  - *"minute miliary foci caused by deposition of a particular substance in the cortex", **Aß plaques***
  - *"quite striking changes of the neurofibrils", **Tau tangles***
  - *"The glia had abundant fibers, in addition, many glia showed large deposits... further, many glia include adipose inclusions", **Dysfunctional glia***

HEALTHY BRAIN SEVERE AD[1]

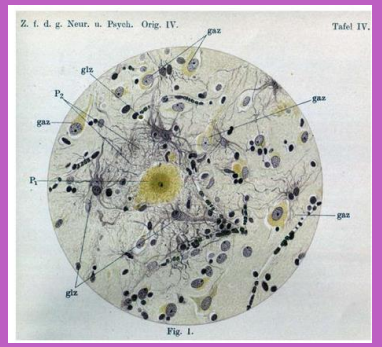


Aβ PLAQUE (RED) SURROUNDED BY MICROGLIA

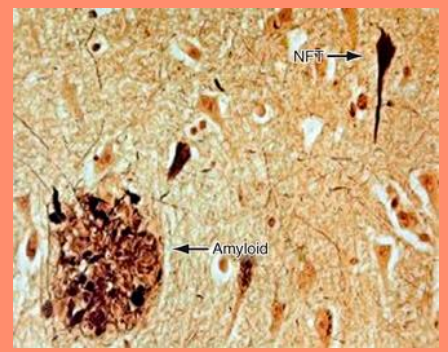


Neher lab/DZNE

DRAWING OF HYPERTROPHIED GLIA BY A. ALZHEIMER[2]



Aβ PLAQUES AND TAU TANGLES[3]



National Institute on Aging, Alzheimer's Disease Fact Sheet

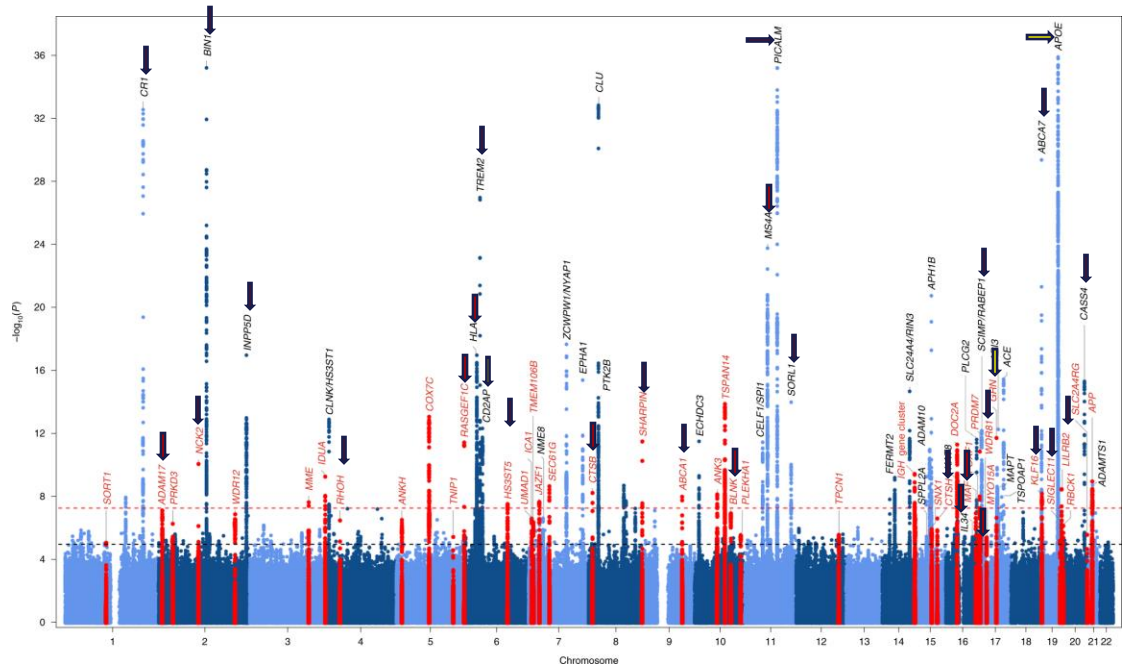
1. Kumar A, Sidhu J, Goyal A, et al. *Alzheimer Disease*. [Updated 2022 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Copyright © 2023, StatPearls Publishing LLC.

2. Ralf Dahm, *Alzheimer's discovery, Current Biology*, Volume 16, Issue 21, 2006, Pages R906-R910,
Used with permission of Elsevier from Alzheimer's Discovery, Dahm R, 16, 21, 2006; permission conveyed through Copyright Clearance Center, Inc.

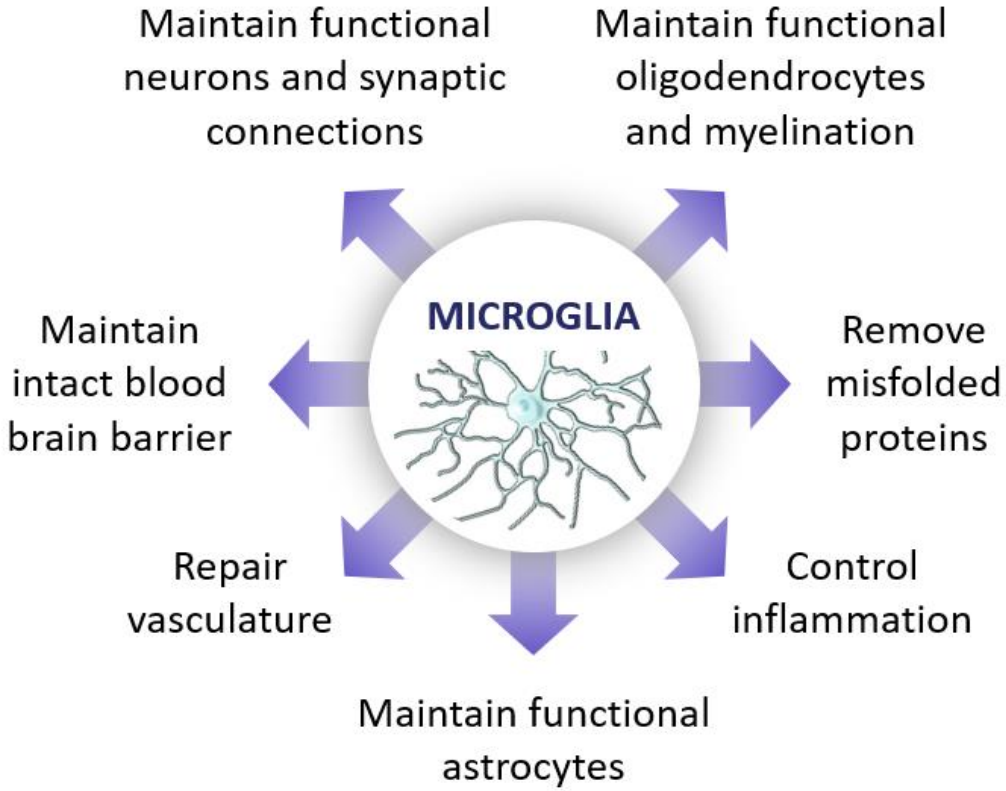
3. *Radiology Key*. Chapter 45. Neurodegeneration: Cerebrum.
Used with permission of Elsevier, from Neurodegeneration: Cerebrum, Ridha BH, 45, 2013; permission conveyed through Copyright Clearance Center, Inc.

Human Genetics and Biology Point to Healthy Microglia as Critical to Brain Health and AD

MANY AD RISK GENES ARE REGULATORS OF MICROGLIA[1]



MICROGLIA MAINTAIN BRAIN HEALTH THROUGHOUT LIFE[2]

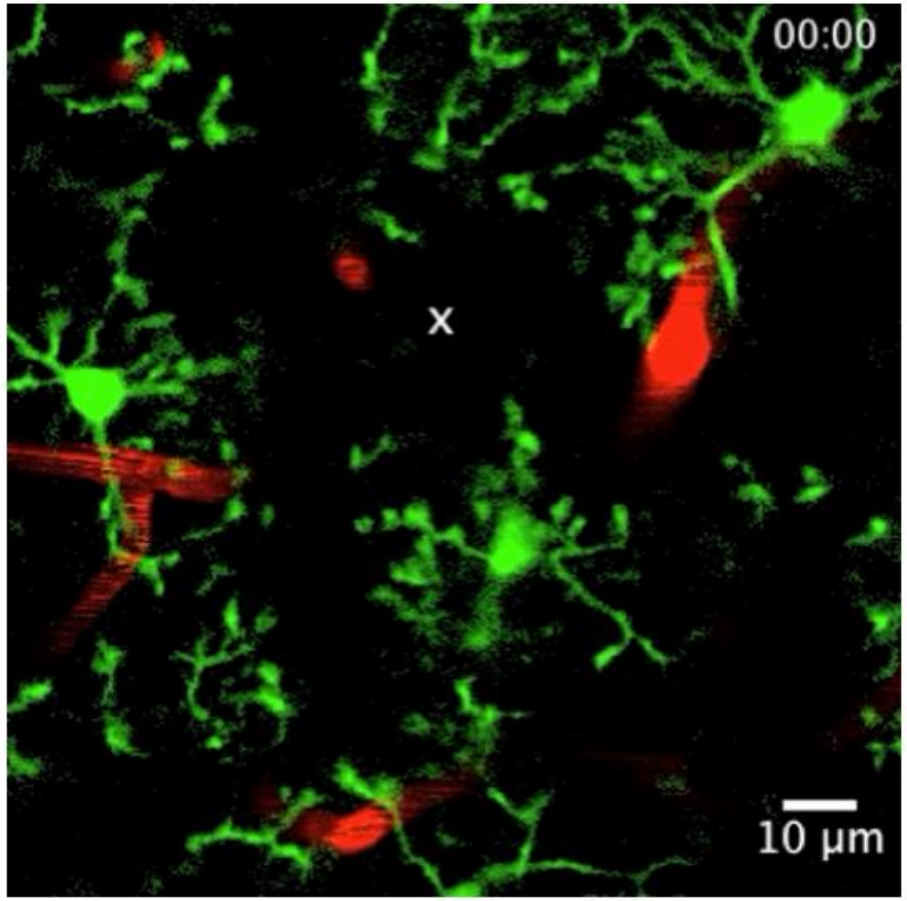


1. Bellenguez C, et al. *Nature Genetics*. 2022;54:412-436.; ©2022 Bellenguez C et all. Originally published in *Nature Genetics*.

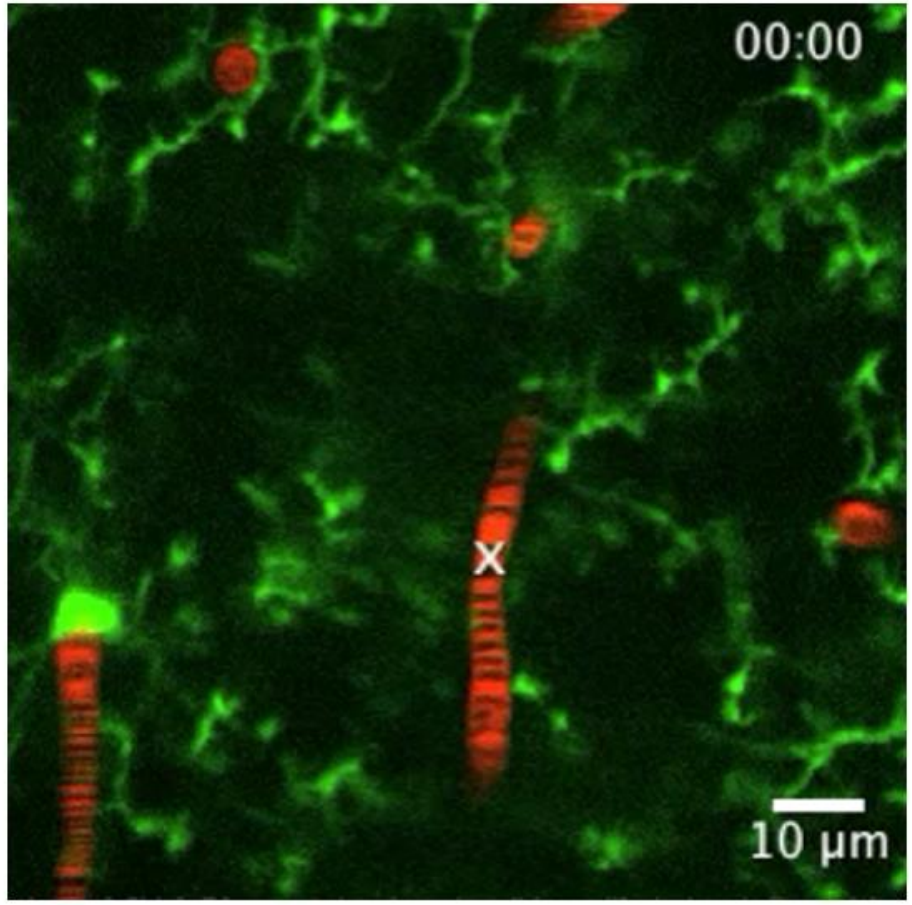
2. Hansen, D., et al., *J Cell Biol.* 2018 Feb 5; 217(2): 459–472.

Microglia Respond to Injury in Brain Tissues and Blood Vessels

MICROGLIA (GREEN) RESPOND TO LOCAL BRAIN DAMAGE (X)



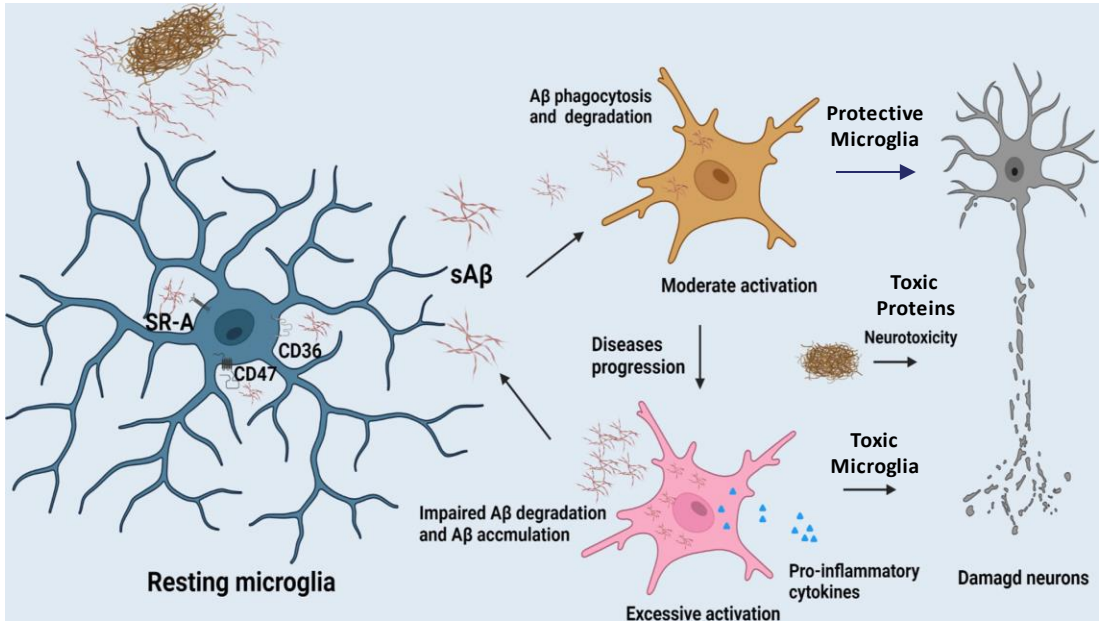
MICROGLIA (GREEN) SEAL DAMAGED BLOOD VESSELS (RED)



Lou, N, et al., *PNAS*. Jan. 2016; 113 (4) 1074-1079.
PNASPermissions@nas.edu.

Microglia May Become Dysfunctional With Age and AD and Require Restoration

AGING MICROGLIA MAY MALADAPT TO AD AND BECOME DYSFUNCTIONAL AND TOXIC



TREATMENT WITH IMMUNE CHECKPOINT-LIKE DRUGS MAY RESTORE MICROGLIA TO OPTIMAL STATE

- Microglia are initially beneficial but with age and disease may become dysfunctional
- Immune checkpoint like drugs are anticipated to "reverse microglia aging" and optimize their functionality
- Restoring -- instead of removing -- microglia is anticipated to be the better strategy

ALECTOR PIONEERED THE TREATMENT OF MICROGLIA AS A THERAPEUTIC STRATEGY, DESIGNATING IT AS IMMUNO-NEUROLOGY

Cai Y, et al., Microglia in the Neuroinflammatory Pathogenesis of Alzheimer's Disease and Related Therapeutic Targets. *Front Immunol.* 2022 Apr 26;13:856376.

Portfolio: Advancing Novel First-in-Class Programs with Major Rights Retained

TARGET	CANDIDATE	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ALECTOR'S COMMERCIAL OWNERSHIP	PARTNERS
PGRN	Latozinemab	FTD-*GRN*					U.S. 50-50 profit share with co-promote and tiered double-digit royalties ex-U.S.	GSK
	AL101	AD						GSK
TREM2	AL002	AD					Global 50-50 profit share with opt-in	abbvie
UD	ADP054-ABC	ALS, AD, PD						
UD	UD-ABC	AD, PD						
GCase	ADP050-ABC	PD, LBD						
GPNMB	ADP027-ABC	PD						
UD	ADP056-ABC	AD						

IP portfolio contains 50+ patent families, which include 73 issued patents and >500 pending patent applications directed to more than 20 targets and/or technologies

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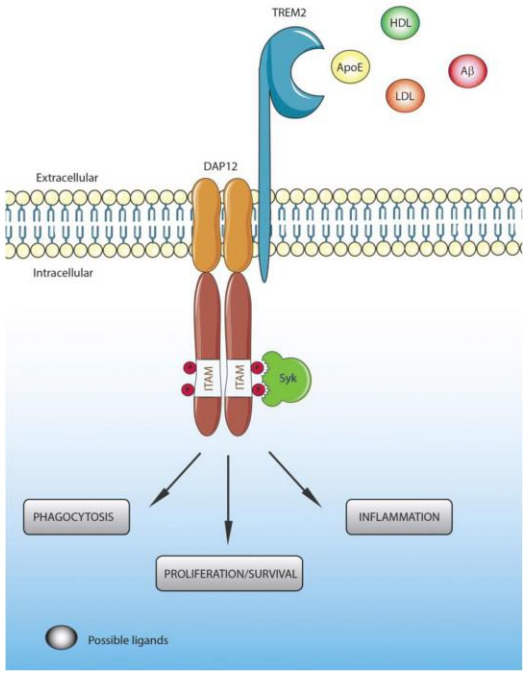
ABC = Alector Brain Carrier Technology
UD = undisclosed

TREM2: A Key Microglia Activating Immune Checkpoint/Immuno-neurology Receptor

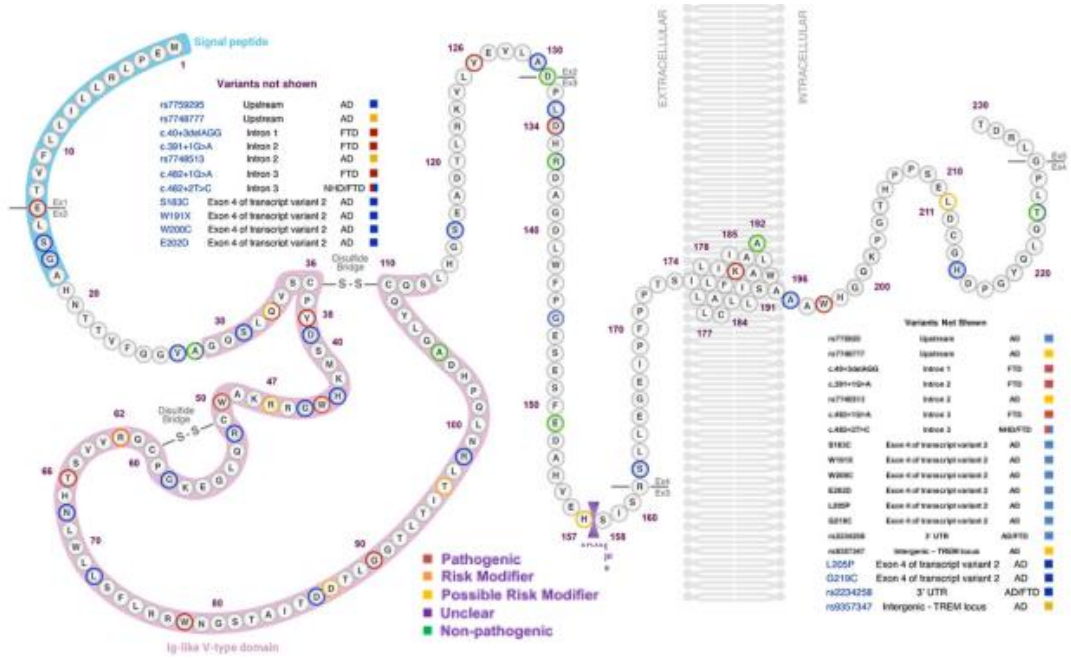
TREM2 IS A KEY MICROGLIA SIGNALING RECEPTOR

- TREM2 is a damage-sensing receptor
- Sustains microglia response to brain injury
- Stimuli, including apoptotic cells, myelin damage, and Aβ
- Regulates microglia survival proliferation, migration, function



TREM2 IS A KEY GENETIC RISK FOR AD

- Homozygous mutations cause dementia (NHD, FTD)
- Heterozygous mutations increase risk for AD by threefold
- 40 TREM2 mutations related to AD have been identified
- May modify the risk of developing PD and ALS



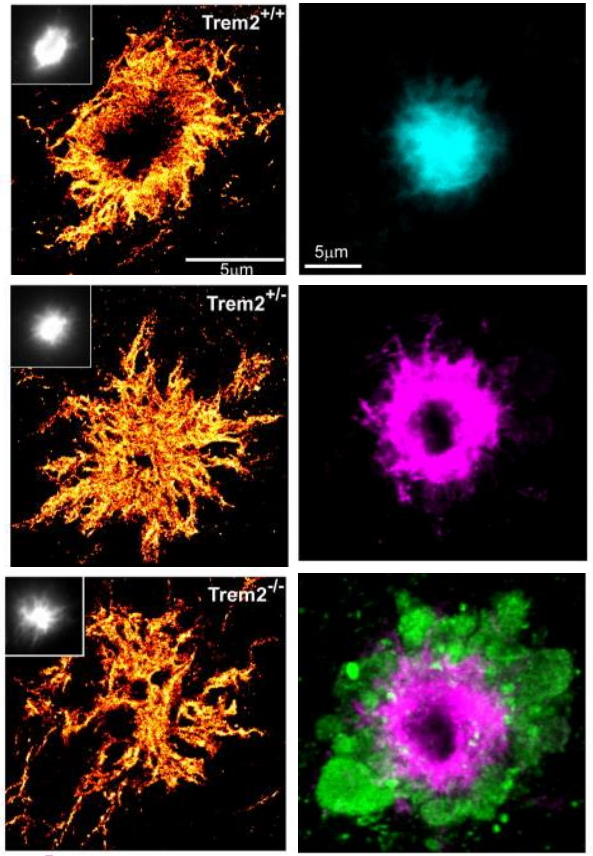
Gratuze, M, et al., New insights into the role of TREM2 in Alzheimer's disease. *Mol Neurodegeneration* 13, 66 (2018).

Mutations TREM2 | Alzforum. (n.d.). Retrieved November 29, 2023, from https://www.alzforum.org/mutations/trem2

Functional Microglia Insulate Aβ Plaques From Nerve Cells and Prevent Neuronal Dystrophy

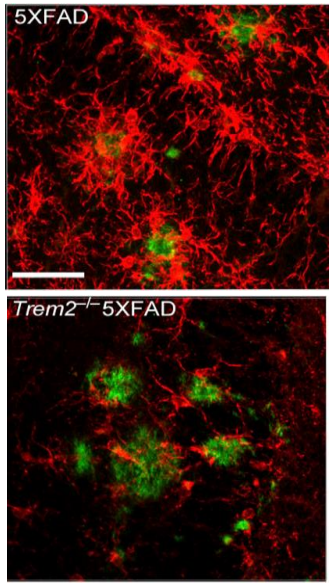
TREM2 DEFICIENT MICROGLIA DO NOT COMPACT AB PLAQUES, LEADING TO NEURONAL DYSTROPHY IN A MOUSE AD MODEL[1]

AB PLAQUES = BROWN, BLUE, PURPLE
NEURONAL DYSTROPHY = GREEN



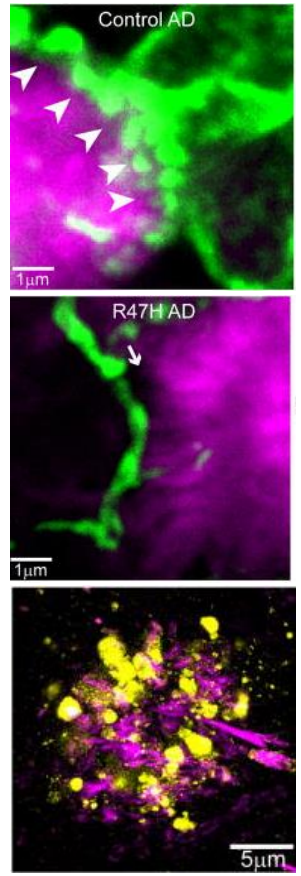
TREM2 DEFICIENT MICROGLIA DO NOT MIGRATE TO A BETA PLAQUES IN A MOUSE AD MODEL[2]

TREM2 DEFICIENT MICROGLIA = RED
AB PLAQUES = GREEN



TREM2 R47H MUTANT MICROGLIA DO NOT COMPACT AB PLAQUES, LEADING TO NEURONAL DYSTROPHY IN HUMAN AD[1]

AB PLAQUES = PURPLE
NEURONAL DYSTROPHY = YELLOW



1. Yuan P, et al., *Neuron*. 2016 May 18;90(4):724 39.
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2. Wang Y, et al., *Cell*. 2015 Mar 12;160(6):1061-71.
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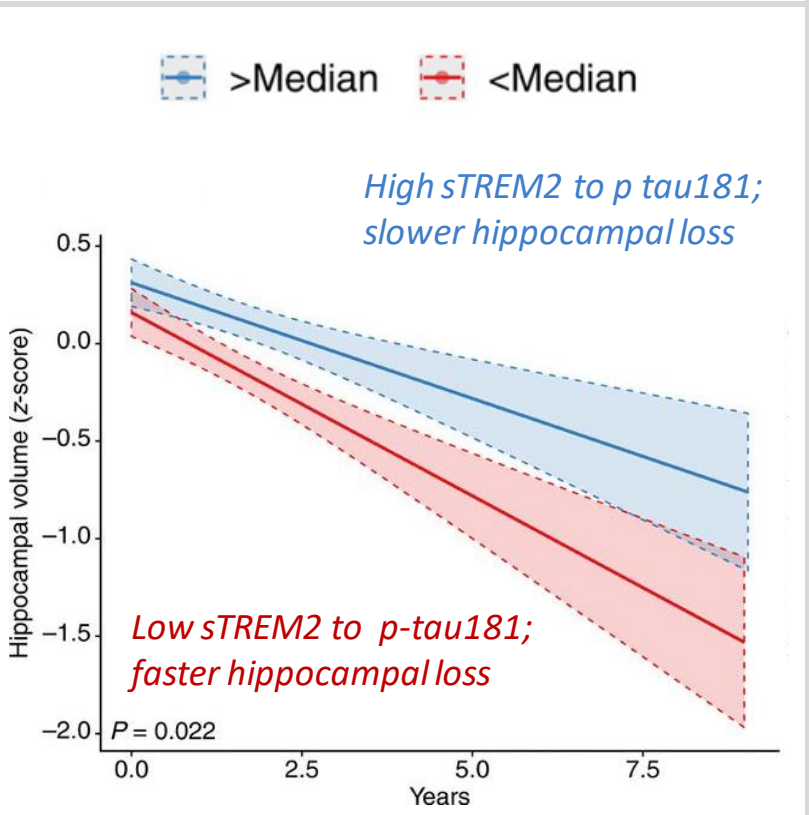
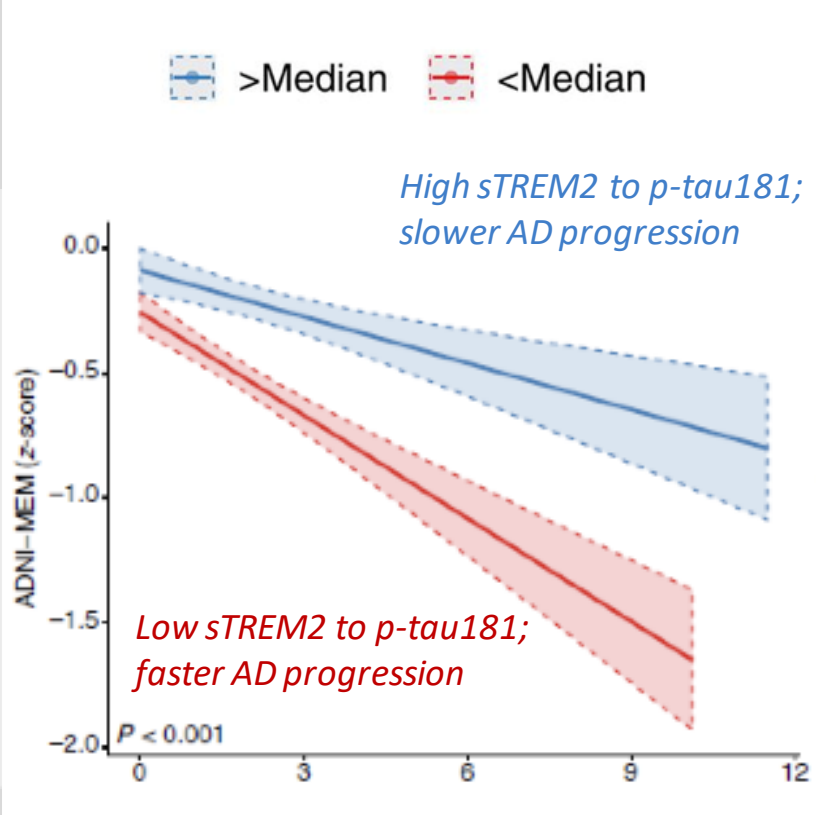
High Levels of TREM2/sTREM2 Are Associated with Protection from AD

High levels of TREM2, as measured by sTREM2 in the CSF, were shown to slow down cognitive decline, brain tissue loss, and the accumulation of Aβ and Tau, delay the conversion from mild cognitive inhibition to AD, and improve survival with AD

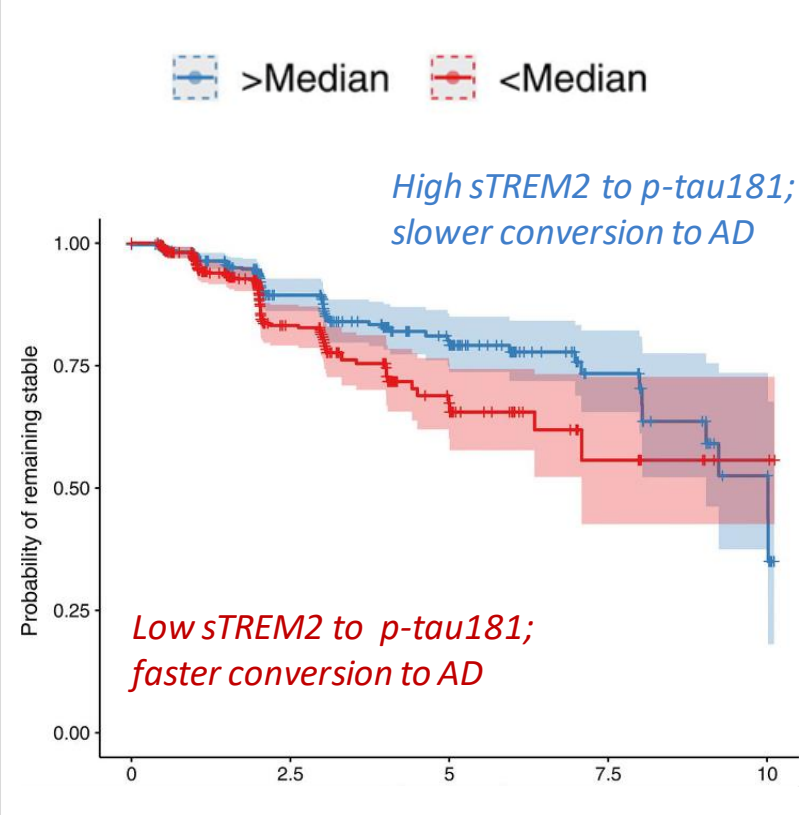
HIGH TREM2/sTREM2 CORRELATES WITH PRESERVATION OF HIPPOCAMPAL VOLUME



HIGH TREM2/sTREM2 CORRELATES WITH DELAYED COGNITIVE DECLINE



HIGH TREM2/sTREM2 CORRELATES WITH SLOWER CONVERSION FROM MCI TO AD



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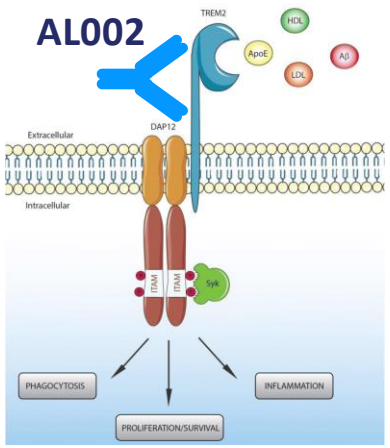
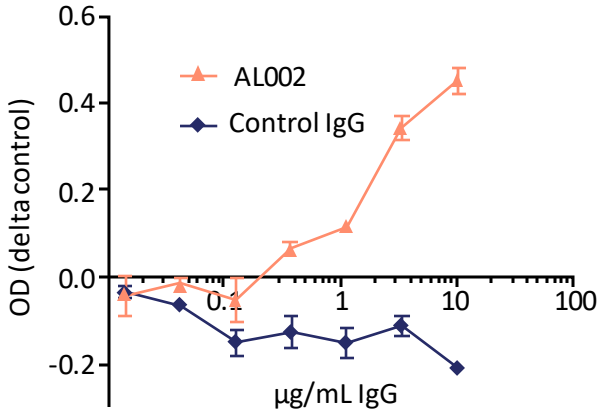
Requested from Publisher on 11/30/23.

AL002: A TREM2 Activating Antibody That Shows Multiple Downstream Effects

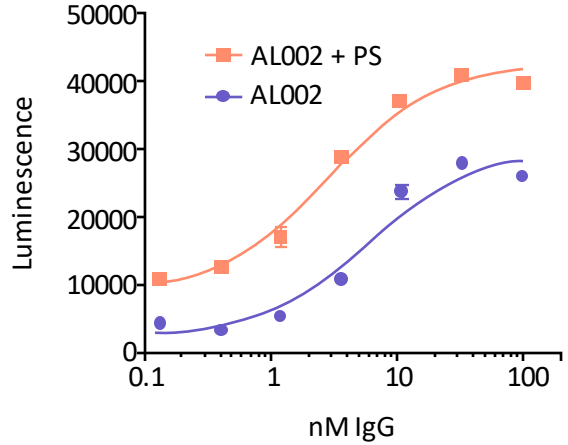
ENGINEERED AL002 BINDS THE STALK REGION[1]



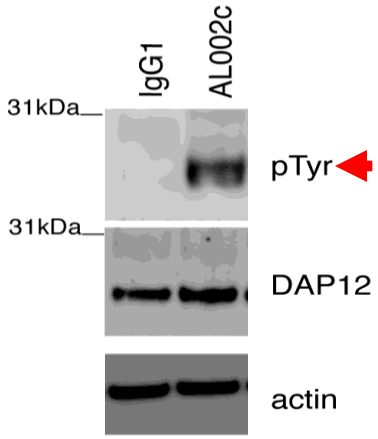
ENHANCES BINDING TO APOE



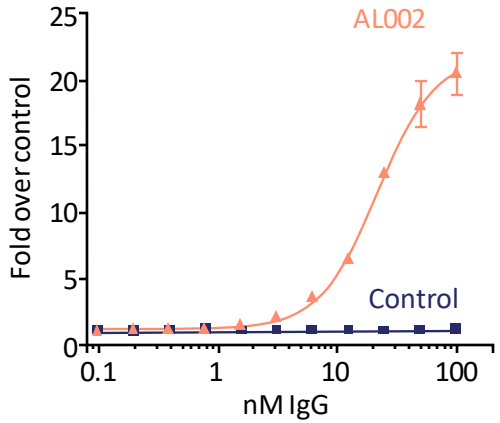
ENHANCES BINDING TO PHOSPHOLIPIDS



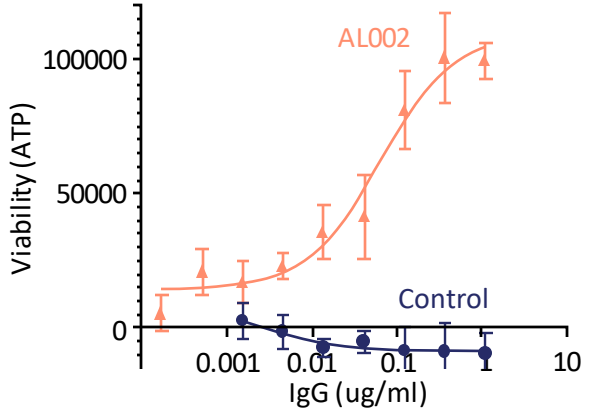
ACTIVATES TREM2 SIGNALING



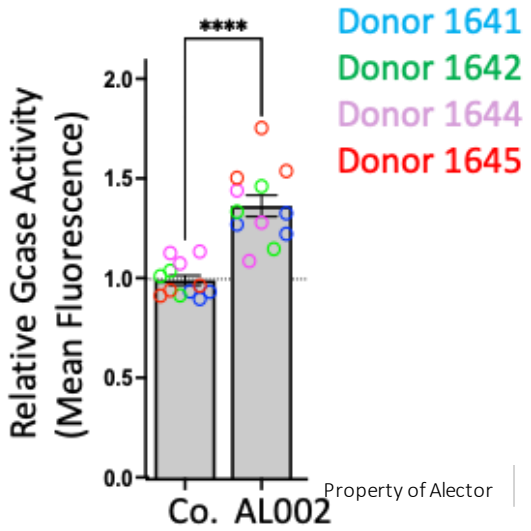
PROMOTES GENE EXPRESSION



PROMOTES CELL VIABILITY



INDUCES LYSOSOMAL ENZYMES

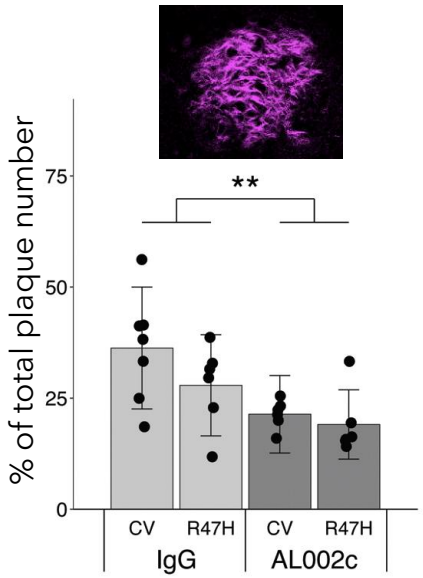


Gratuze, M, et al., New insights into the role of TREM2 in Alzheimer's disease. *Mol Neurodegeneration* 13, 66 (2018).

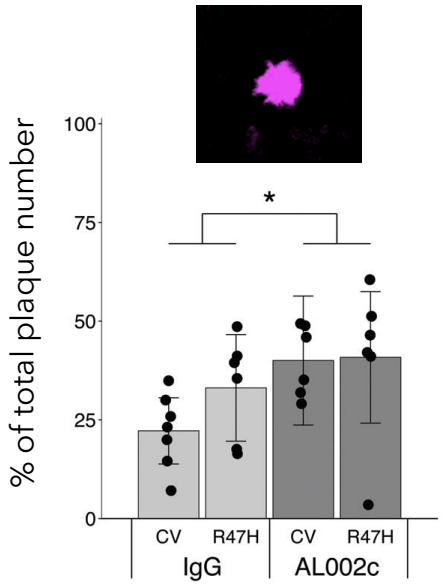
AL002c Reduces Toxic Plaques and Neuronal Damage in AD Mouse Model

COMPACTION OF AMYLOID PLAQUE[1]

Filamentous Plaque



Inert Plaque



Filamentous plaque is considered detrimental

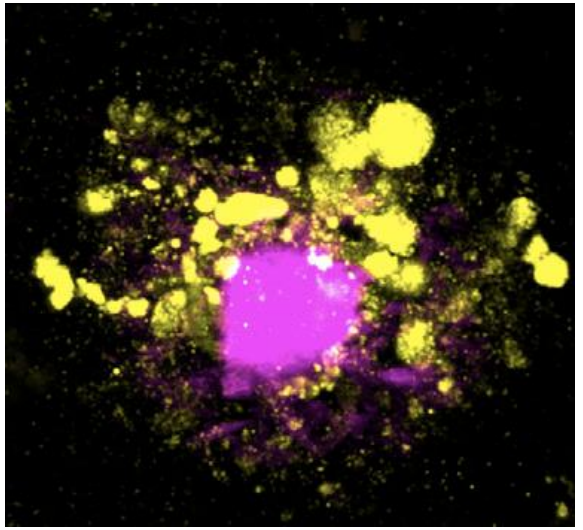
CV- mice expressing WT human TREM2

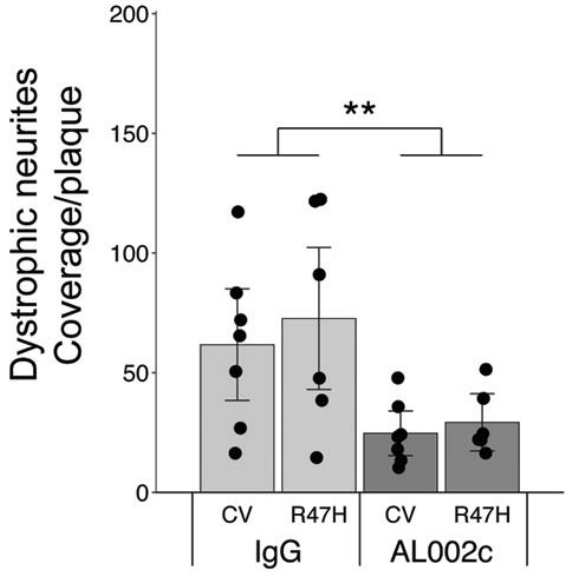
R47H- mice expressing R47H mutant TREM2

alector Studies conducted with AL002c, a murine version of AL002.

REDUCTION OF NEURONAL DAMAGE[2]

Neurite dystrophy surrounding a plaque





1. Yuan P, et al., *Neuron.* 2016 May 18;90(4):724-39.
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2. Wang Y, et al., J Exp Med. 2020 Sep 7; 217(9): e20200785.

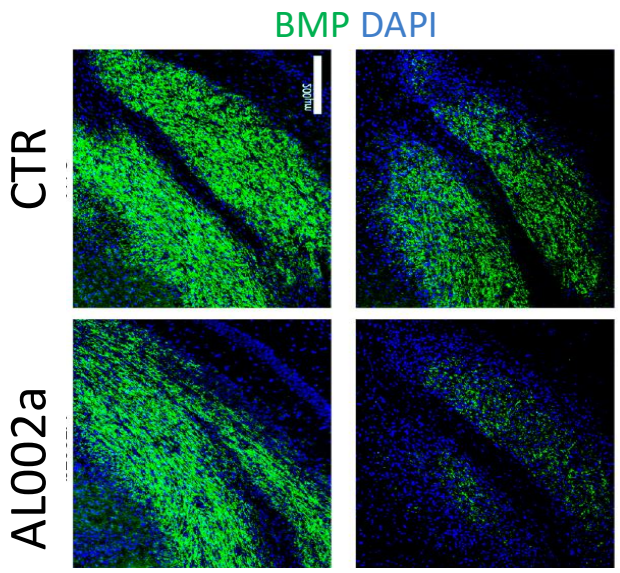
AL002a Promotes Re-myelination in a Model of Myelin Damage

"Myelin impairment may play an important role in AD pathology." Archives of Medical Science[1]

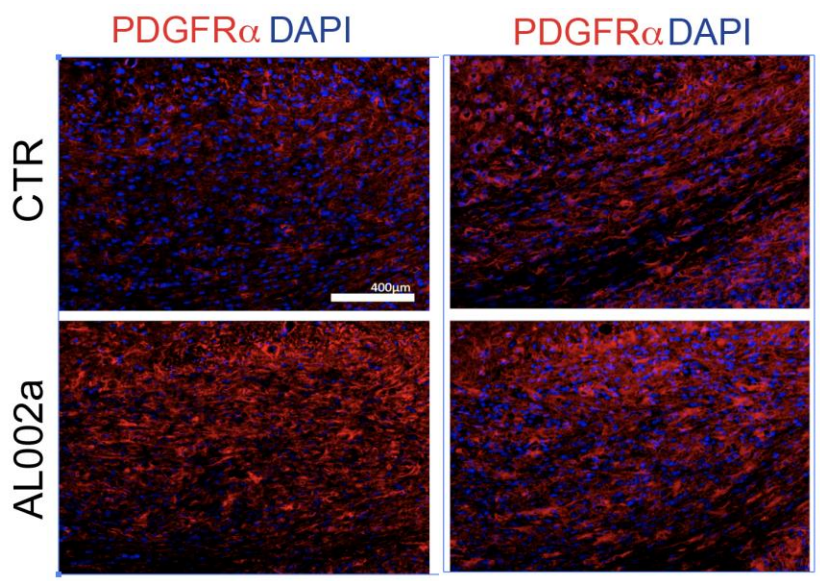
"We conclude that white matter abnormalities, and in particular myelin and oligodendrocytes, could be mechanistically important in AD pathology and could be potential treatment targets." Acta Neuropathologica Communications[2]

"There is also evidence that myelin pathology may even precede Aß and tau pathologies." Archives of Medical Science[3]

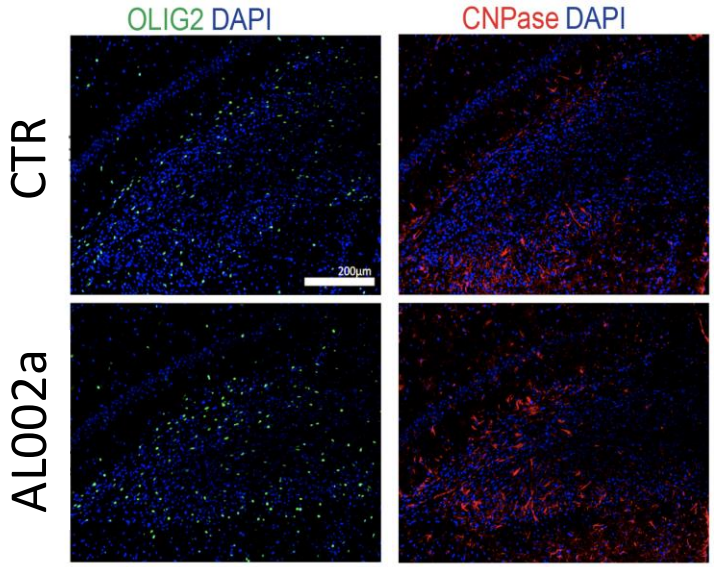
ACCELERATES THE CLEARANCE OF MYELIN DEBRIS[4]



PROMOTES THE RECRUITMENT OF OLIGODENDROCYTES PRECURSOR CELLS[4]



ACCELERATES OLIGODENDROCYTES MATURATION[4]

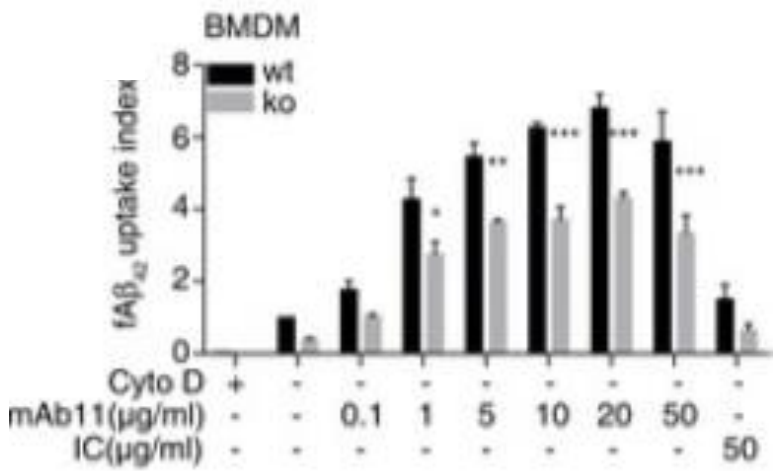


1. Papuc, E, et all, *Arch Med Sci.* 2020; 16(2): 345–351.; 2. Nasrabady, S, et al., *Acta Neuropathologica Communications* volume 6, Article number: 22 (2018).; 3. Papuc, E, et al., *Arch Med Sci*. 2018 Aug 28; 16(2):345-351.; 4. Cignarella, F, et al., *Acta Neuropathol. 2020; 140(4): 513–534.;* AL002a is a surrogate antibody that is active in the mouse system.

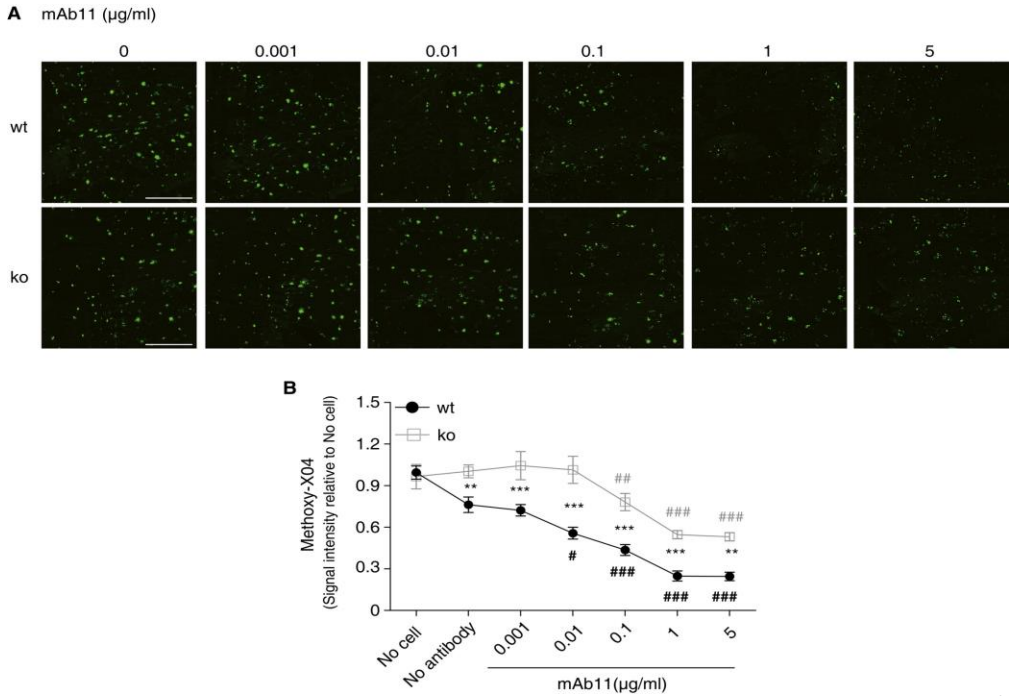
Opportunity to Explore Combination with Anti-Amyloid Beta Antibodies

"TREM2 deficiency reduces the efficacy of immunotherapeutic amyloid clearance"
EMBO Molecular Medicine, 2016

Phagocytosis of $fA\beta_{42}$ by primary microglia from wt and *TREM2* KO animals in the presence or absence of mAb11, or an isotype control antibody (IC)



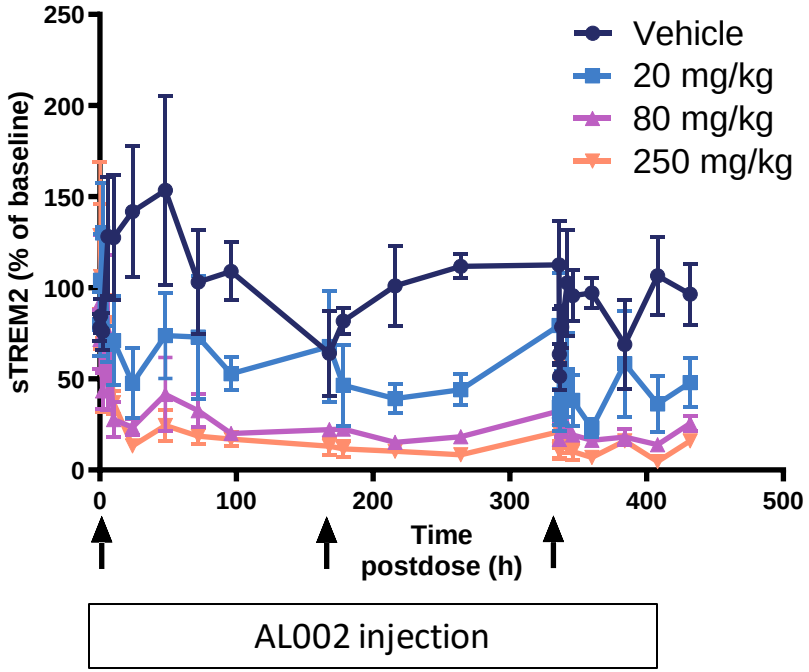
Aβ plaques staining from APP/PS1 mice that were treated with different concentrations of anti-amyloid antibodies with or without functional TREM2



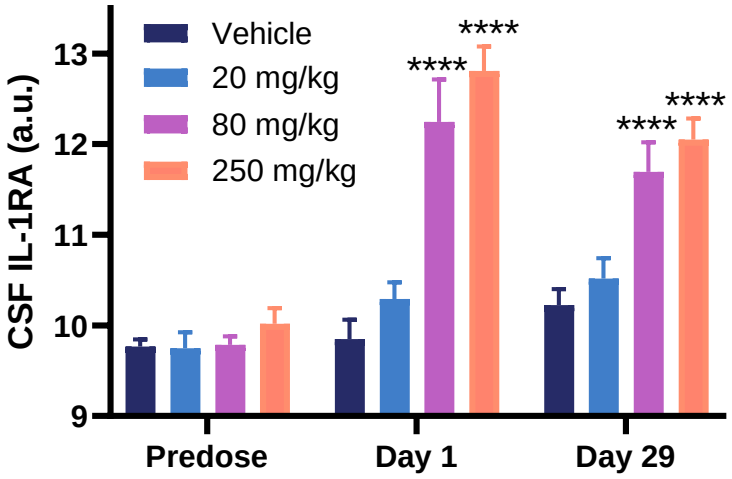
Xiang X et al., *EMBO Mol Med.* 2016 Sep 1;8(9):992-1004.

AL002 Shows Evidence of Target Engagement and Microglia Signaling with Decreases in sTREM2 and Increases in IL-1RA and sCSF1R in the CSF of NHPs

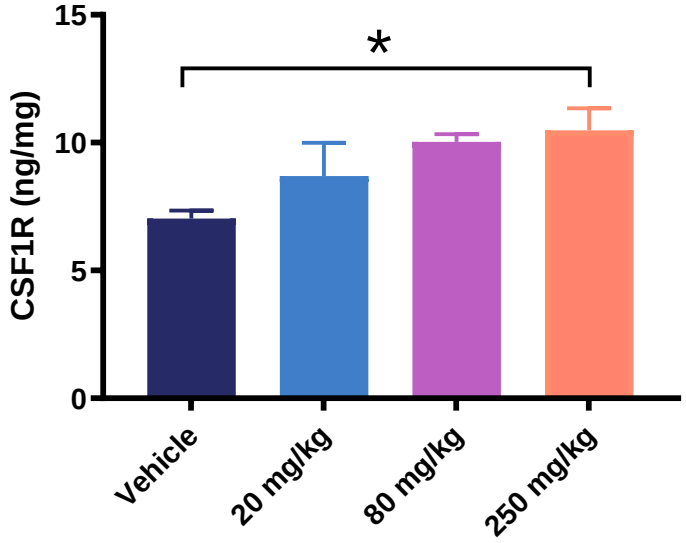
AL002 DECREASES STREM2 IN THE CSF OF NHPS IN A DOSE-DEPENDENT MANNER



AL002 INCREASES IL-1RA IN THE CSF OF NHPS IN A DOSE-DEPENDENT MANNER



AL002 INCREASES CSF1R PROTEIN IN THE FRONTAL CORTEX OF NHPS



Alector data on file

*$p < 0.05$

AL002 is Currently Partnered in an Option Agreement with AbbVie

AL002

$205M upfront payment
$20M equity investment
$17.8M milestone payment received (2023)
Up to $12.5M to support enrollment (2023)
$250M opt-in payment (anticipated early 2025)
$237.5M in potential additional milestones
Global 50-50 profit share

TREM2 and the Immuno-neurology Hypothesis: Possible Upsides

THE HYPOTHESIS

Microglia broadly and constantly counteract multiple AD pathologies, and AL002 may enhance these activities throughout the disease cascade

POTENTIAL THERAPEUTIC BENEFITS

Superior efficacy as stand-alone based on the broad mechanism

Clinical benefit at multiple disease stages based on the broad mechanism and effect of high TREM2/sTREM2 on disease progression

Superior efficacy in combination with anti-Aβ antibodies based on their dependence on functional microglia

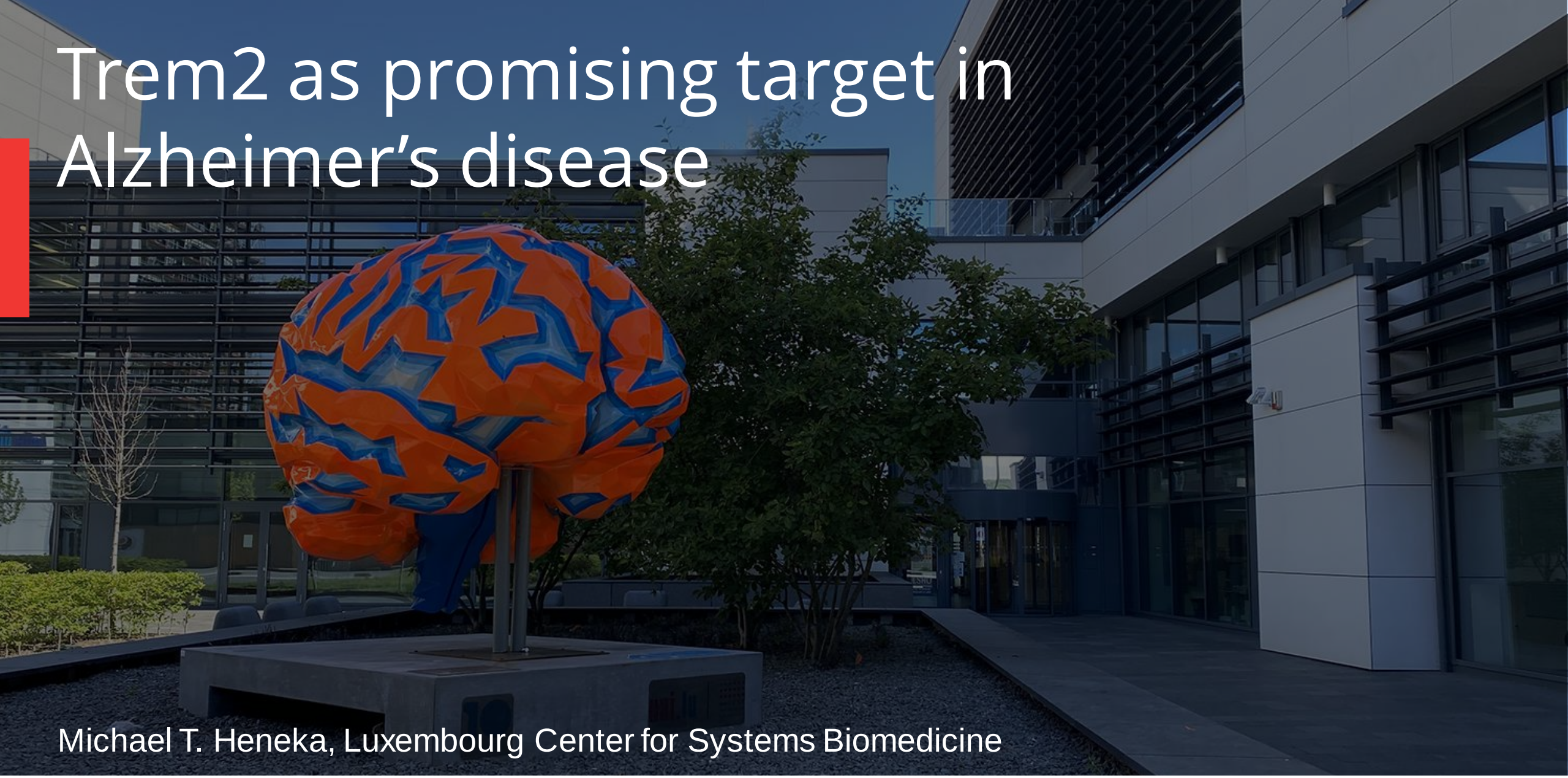
Benefit independent of Aβ removal based on the broad mechanism and microglia's ability to insolate Aβ plaques

TREM2: A Promising Target for Alzheimer's Disease

Michael Heneka, M.D.

Director of the Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg and
Adjunct Professor, University of Massachusetts Chan Medical School

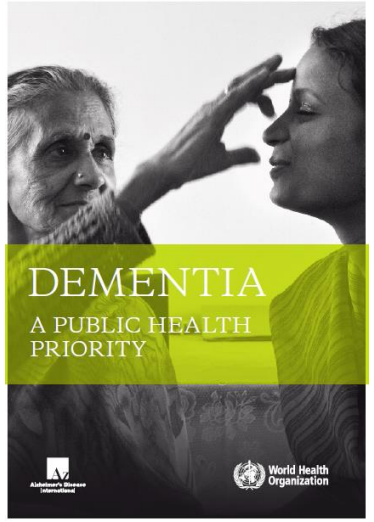
Trem2 as promising target in Alzheimer's disease



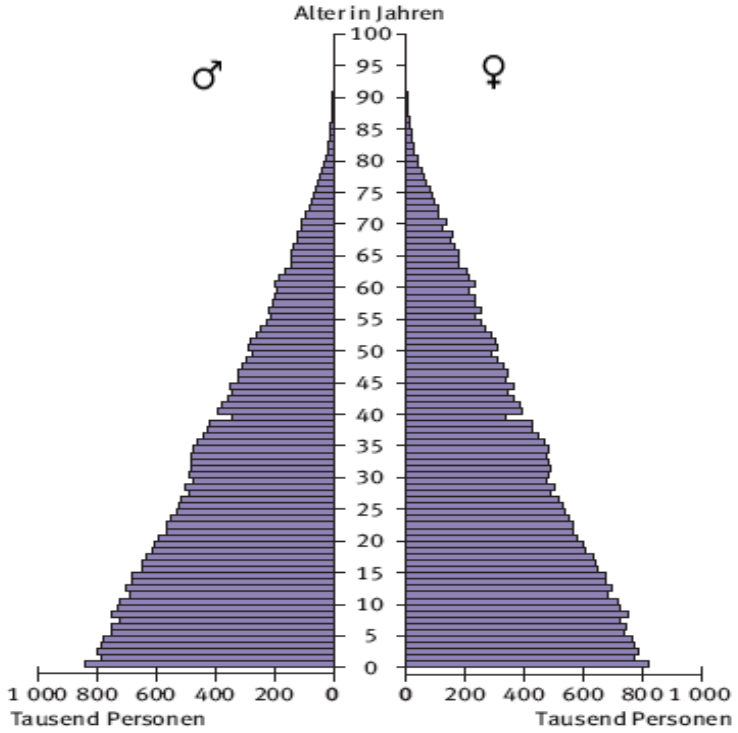
Michael T. Heneka, Luxembourg Center for Systems Biomedicine

Virtual 7.12.2023

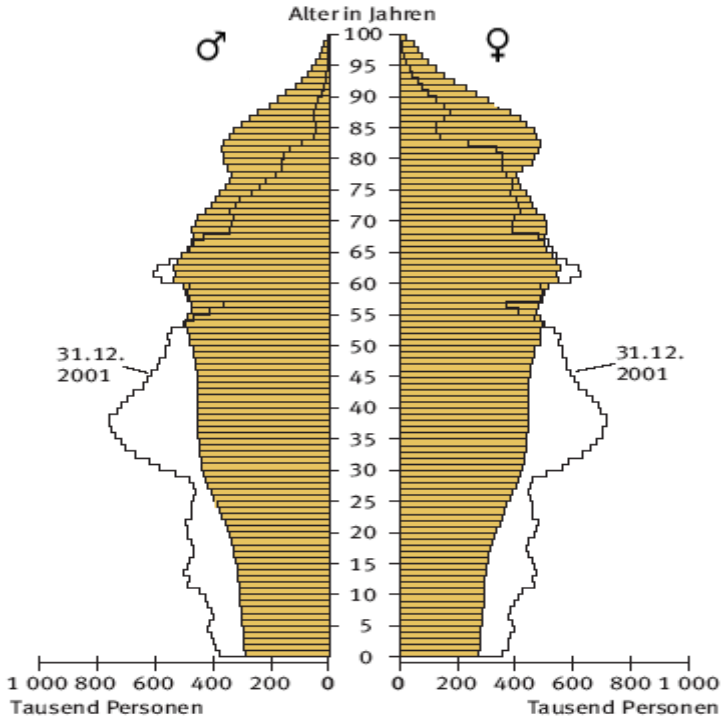
Increasing incidence of neurodegenerative disease



31.12.1910



31.12.2050



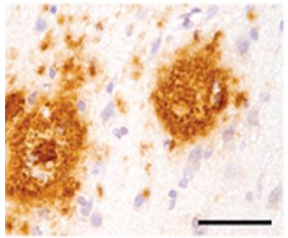
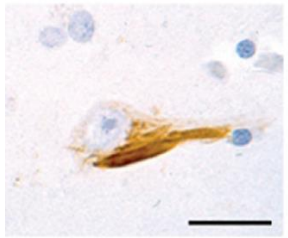
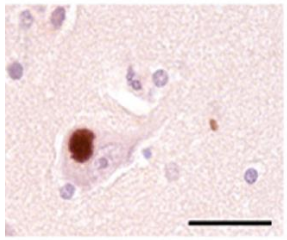
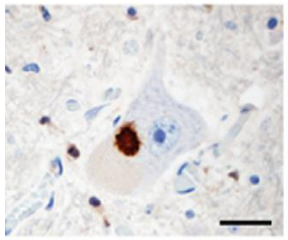
AD: 3x

PD: 2.4x

ALS: 2x

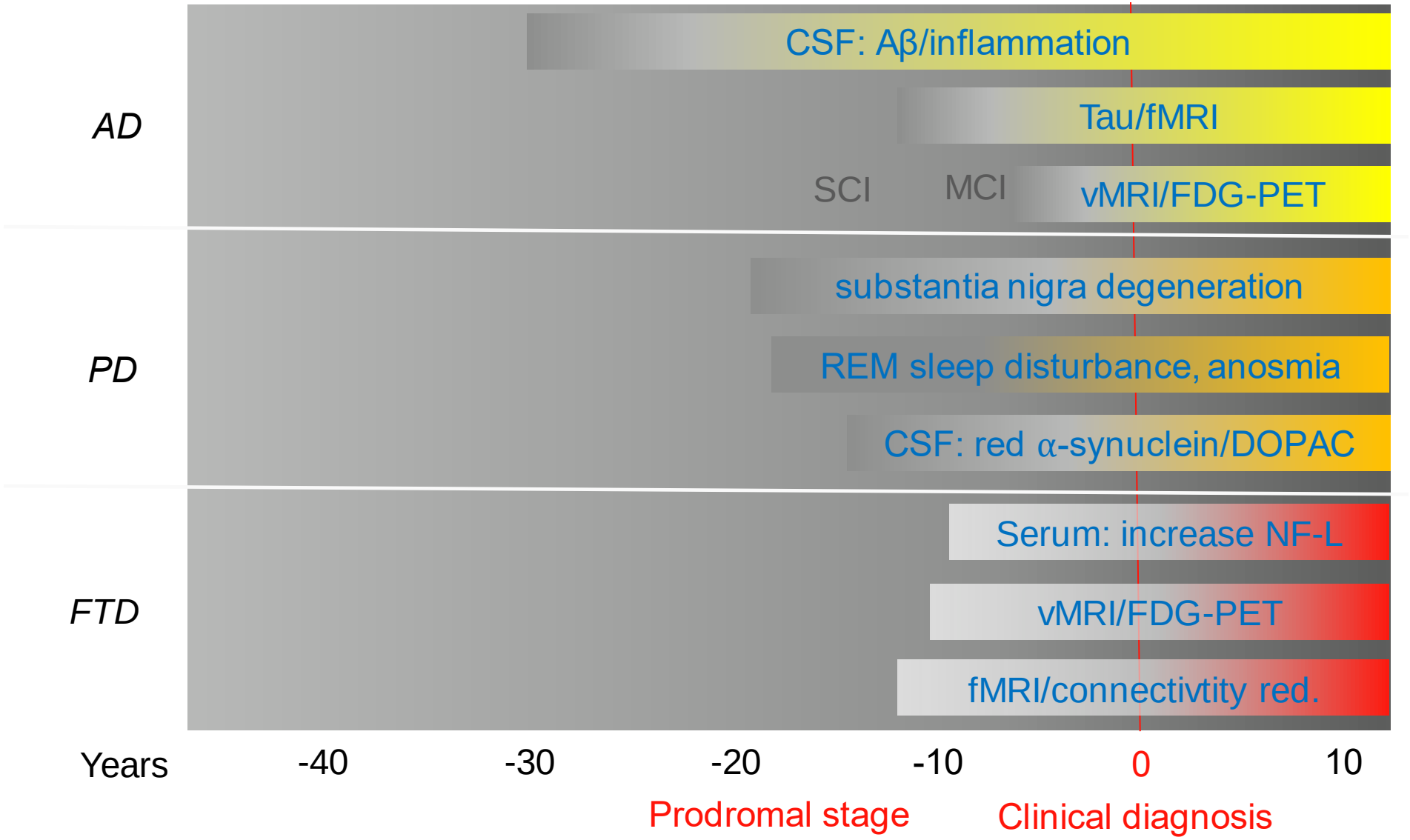
Source: Statistisches Bundesamt 2003-15-0220, World Alzheimer Report

Pathological protein aggregation and spread

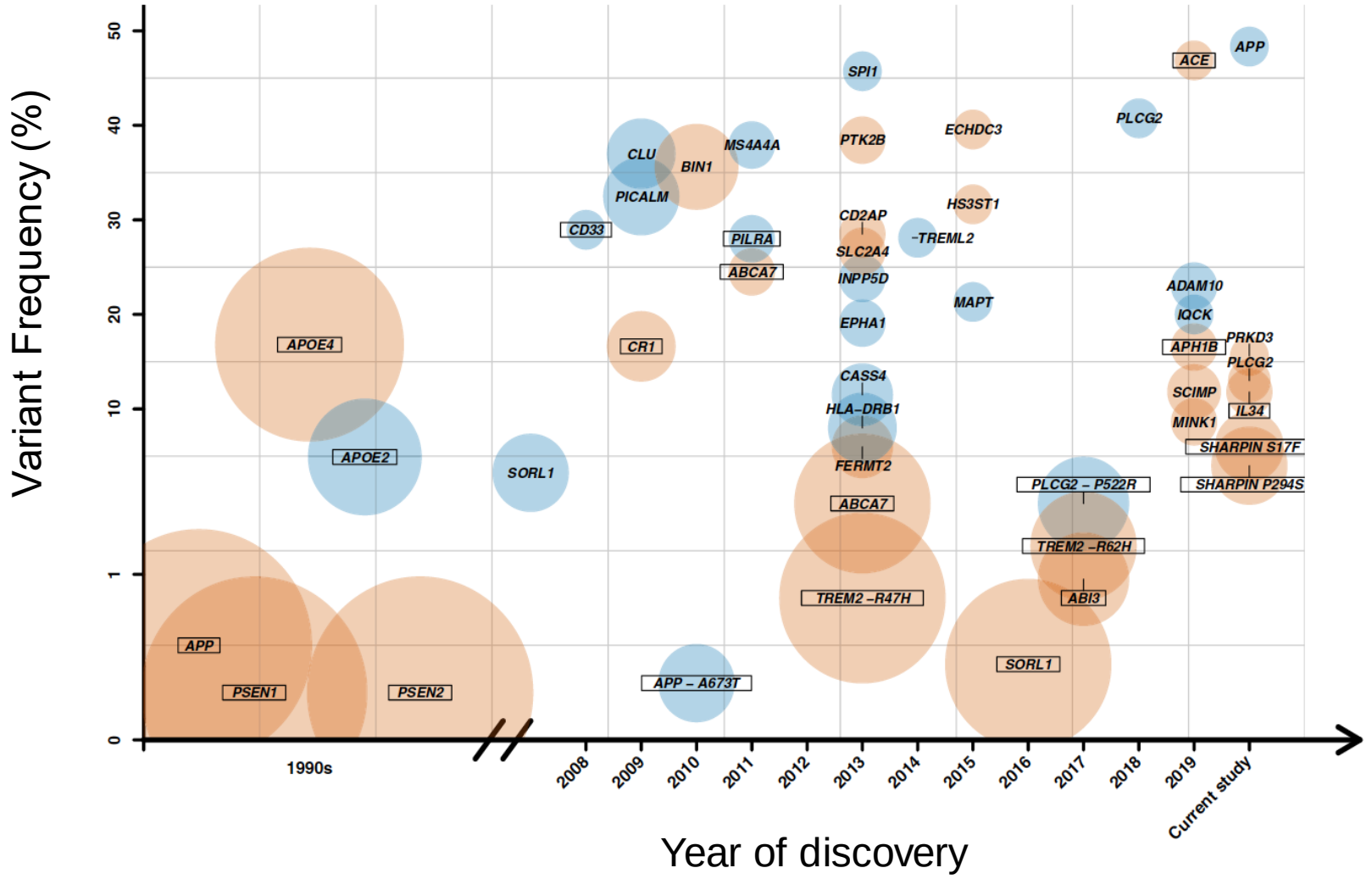
Aβ		*APP, PS1, PS2*	*AD*
Tau		*MAPT*	*Tauopathies, AD*
α-synuclein		*SNCA, PINK1, DJ-1, Parkin, ATP13A2, LRRK2, GBA*	*PD/LBD*
TDP-43		*TARDBP, C9orf72, VCP, TBK1* *MAPT, GRN, C9orf72, UBQLN2, TBK1*	*ALS* *FTD*

Walker&Jucker, 2013 *Nature* PMID: 24005412

Pathobiology starts years and decades prior to clinical symptoms



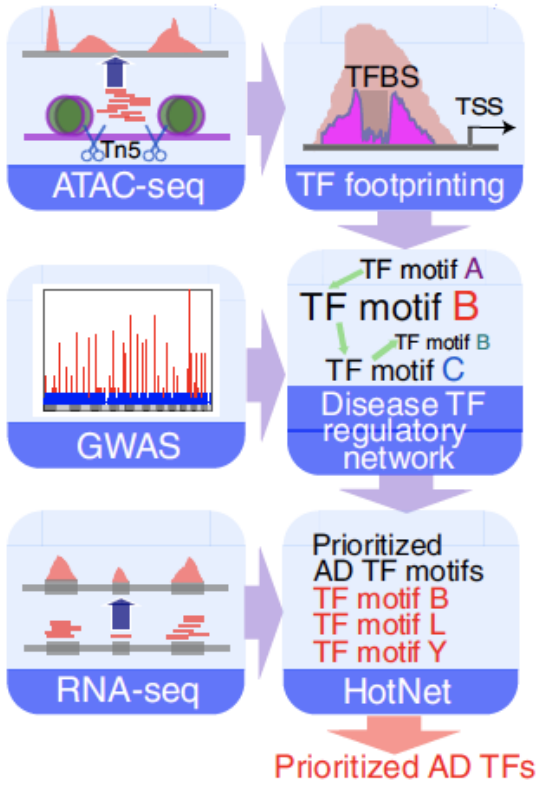
GWAS analysis provides mechanistic hints

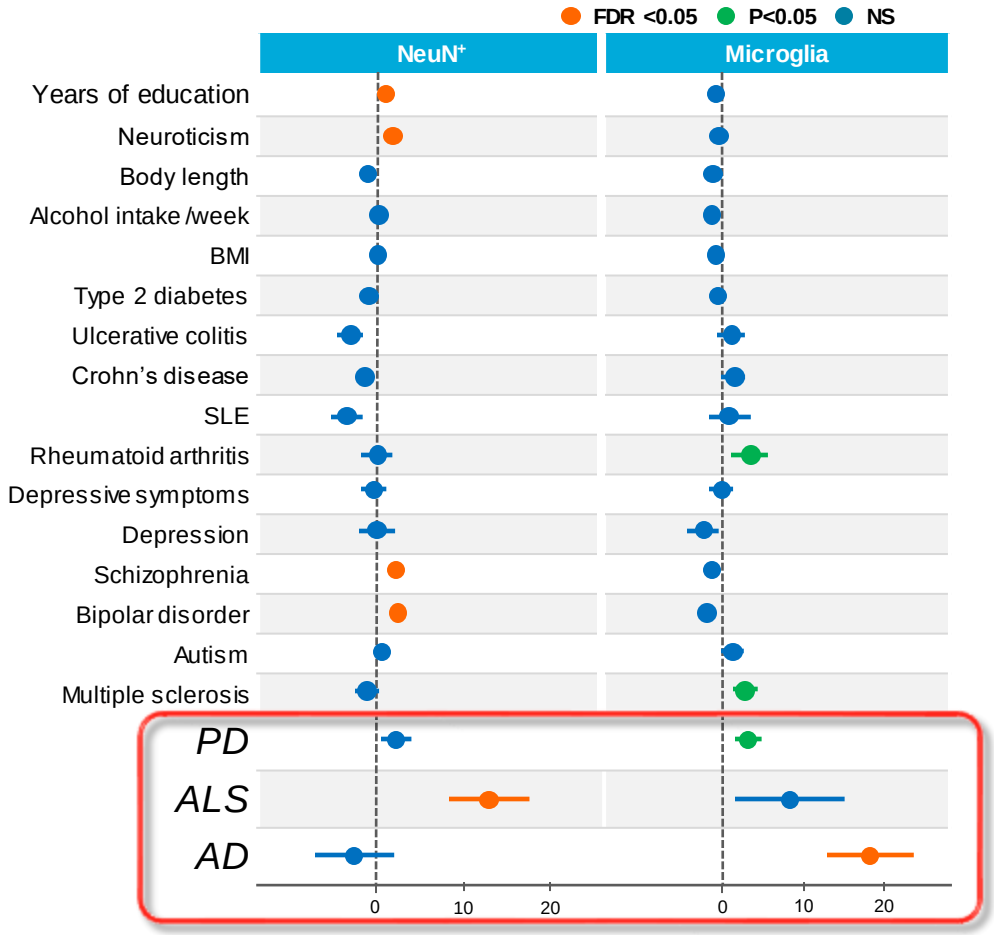


- Lipid metabolism
- Synapse: Structure and function
- Lysosomal function
- Immunological mechanisms (50%)

de Rojas et al. 2021, *Nat Gen* PMID: 34099642

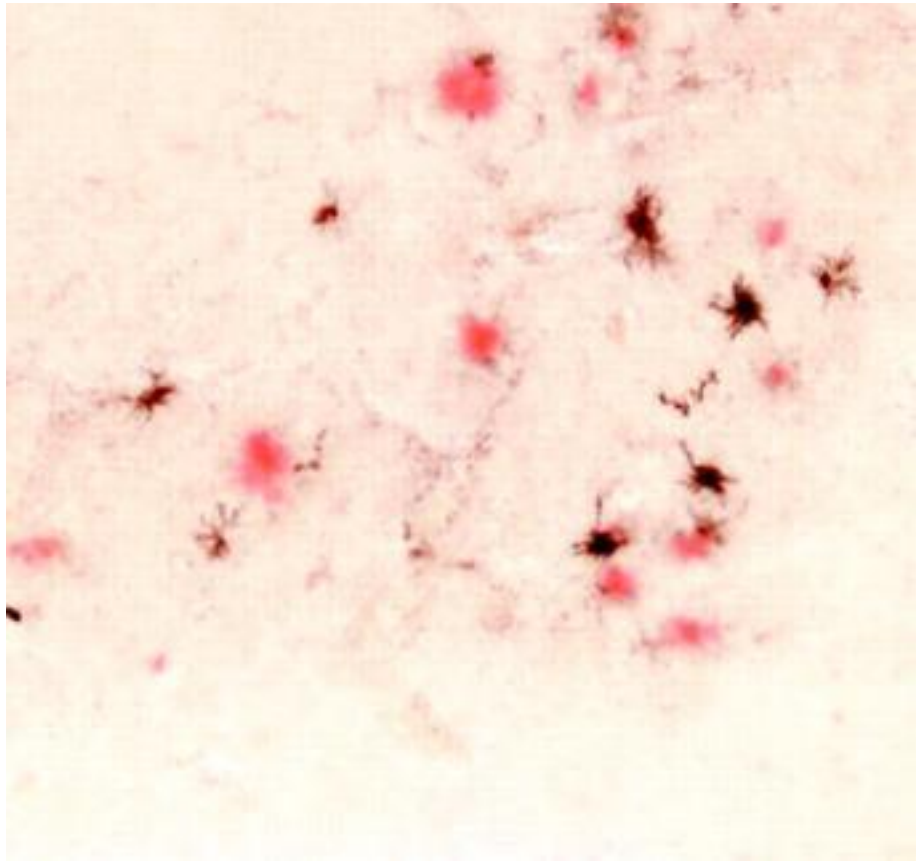
Which cell plays a role in which disease ?



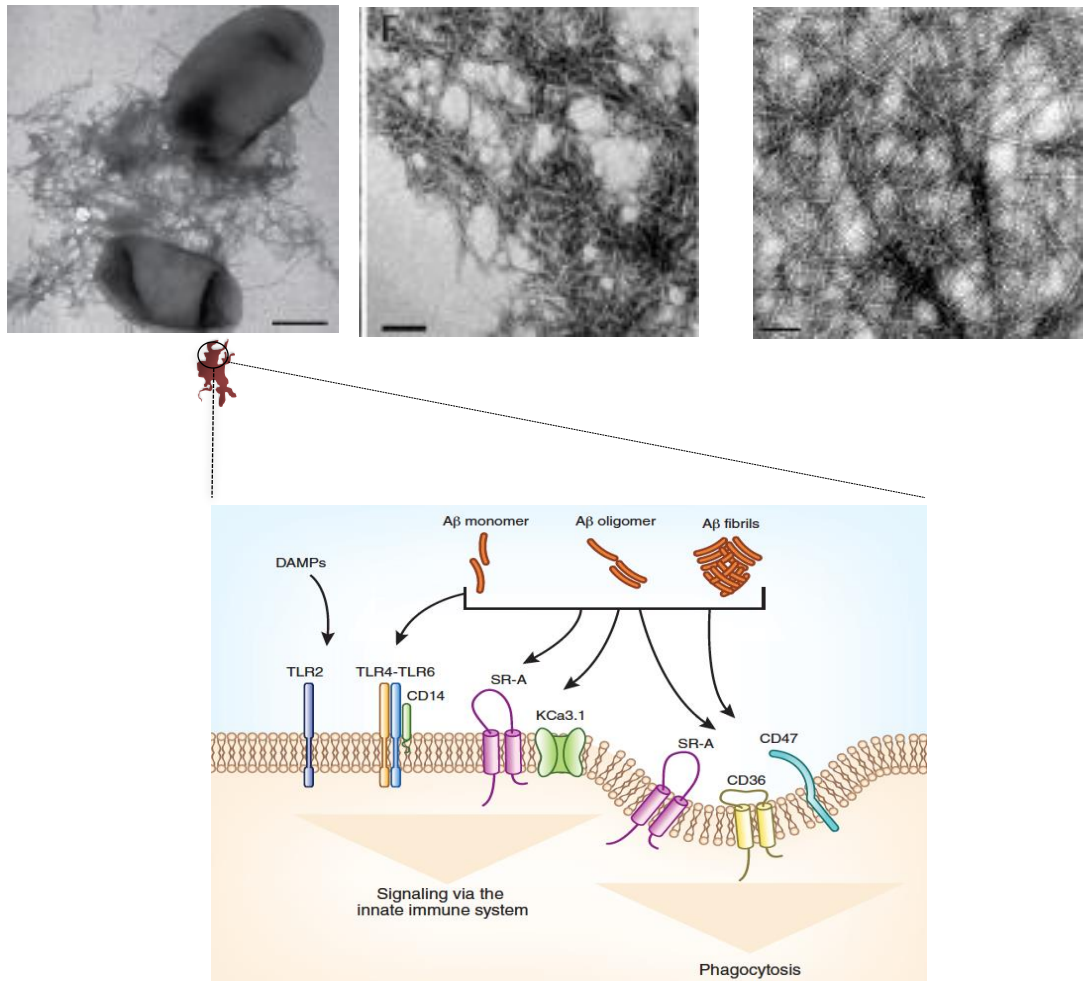


Kosoy et al. *Nat Gen*, 2022 PMID: 35931864

Activation of immunological processes

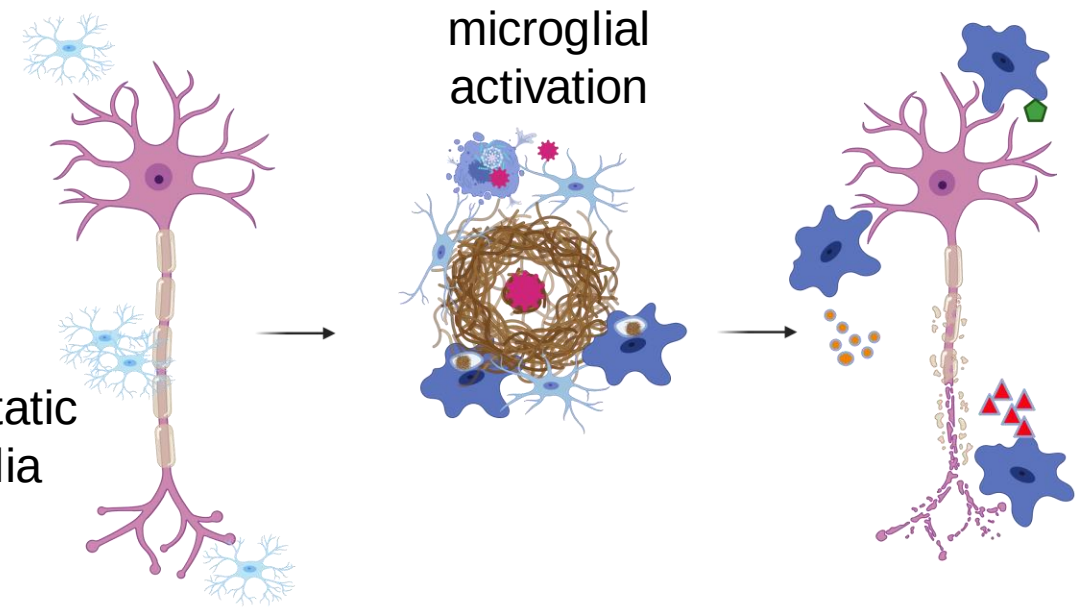


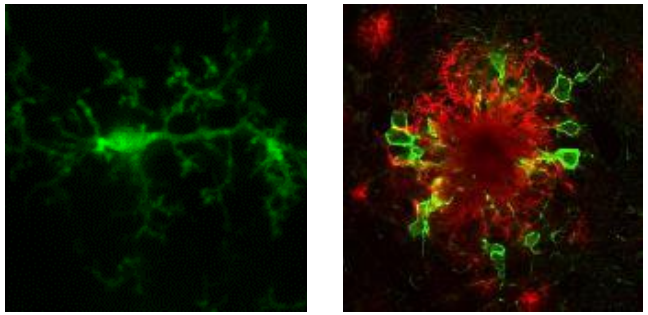
Congo red: Aβ / MHC-II: Microglia



Chapman et al. Science 2002, PMID:11823641

Consequences of cerebral innate immune activation





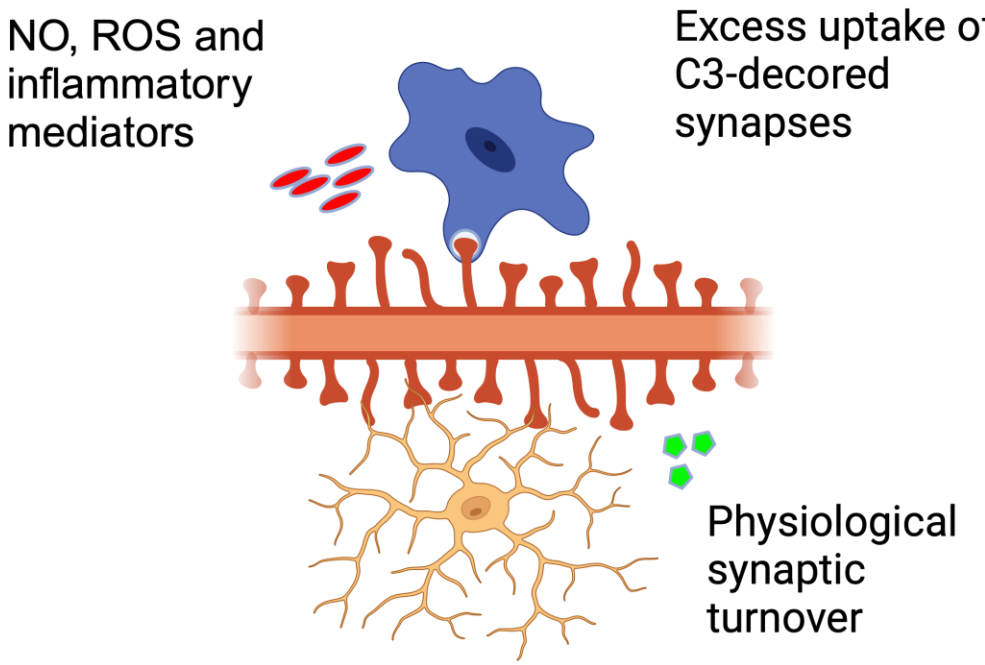
Inflammatory reaction
Complement
Cytokine
Chemokine
NO und ROS

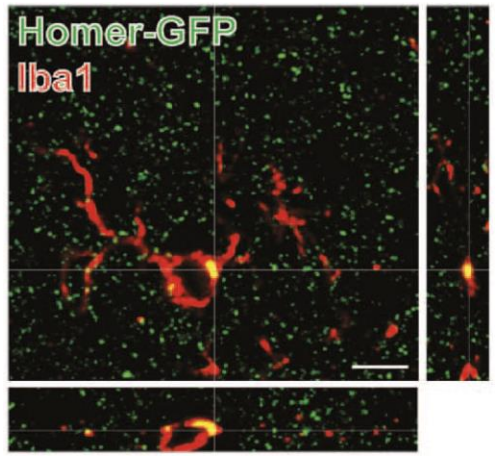
Loss of benefical functions
Reduced synaptic scaling and pruning
Reduced generation and release of neurotrophic factors (e.g. BDNF)
Decreased debris clearance

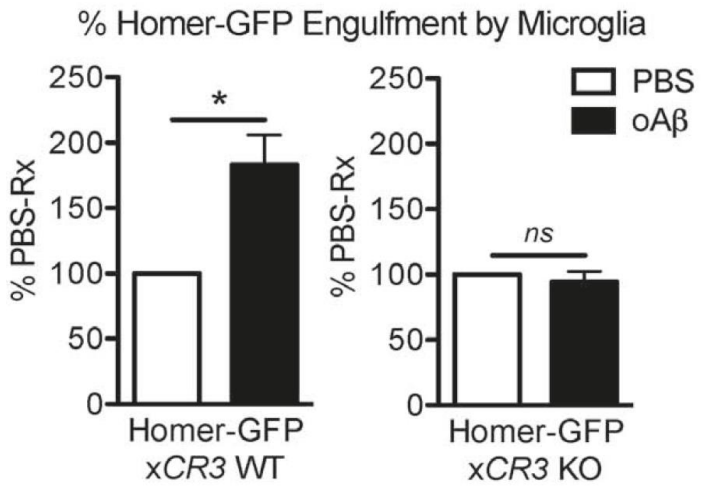
Heneka et al. 2015, *Lancet Neurol* PMID: 25792098

Immune activated microglia remove synapses through C3

Immune activation by oAβ causes excess uptake of synapses

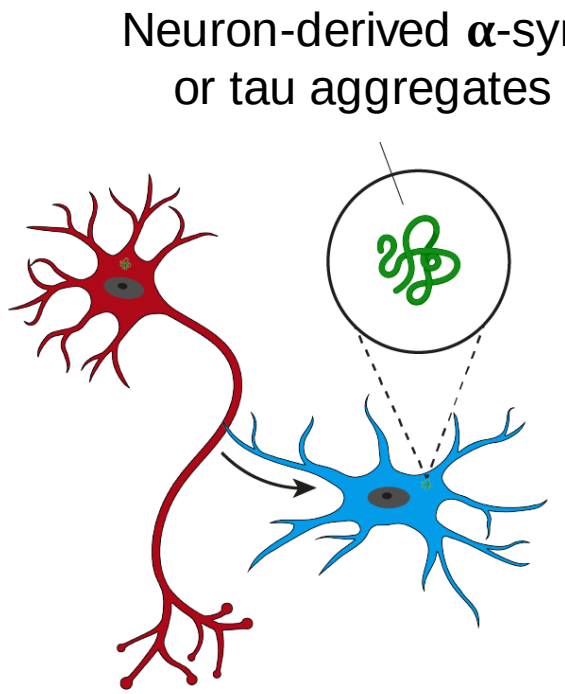


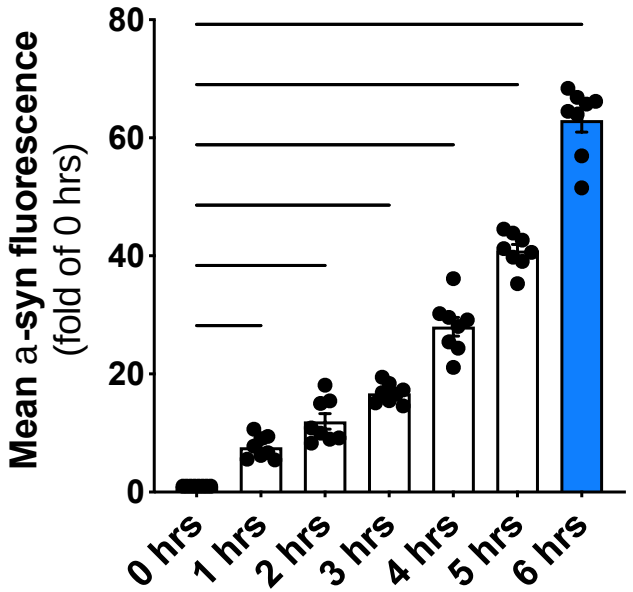


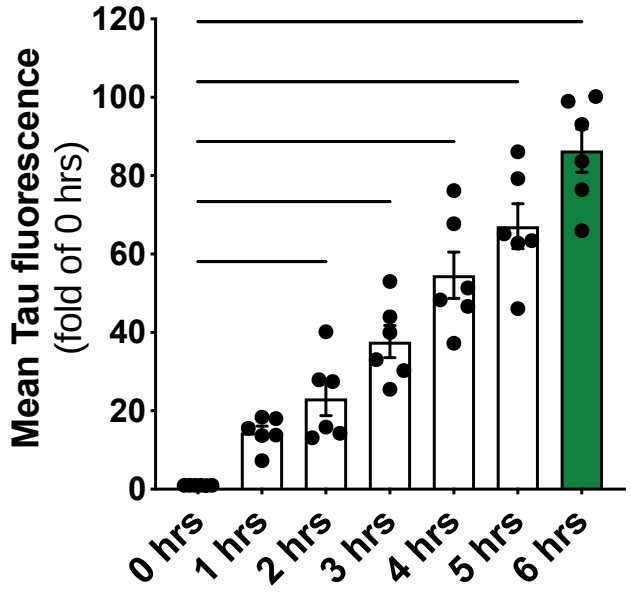


Hong et al. *Science* 2016, PMID: 27033548

α-syn and tau aggregate transfer from neurons to microglia

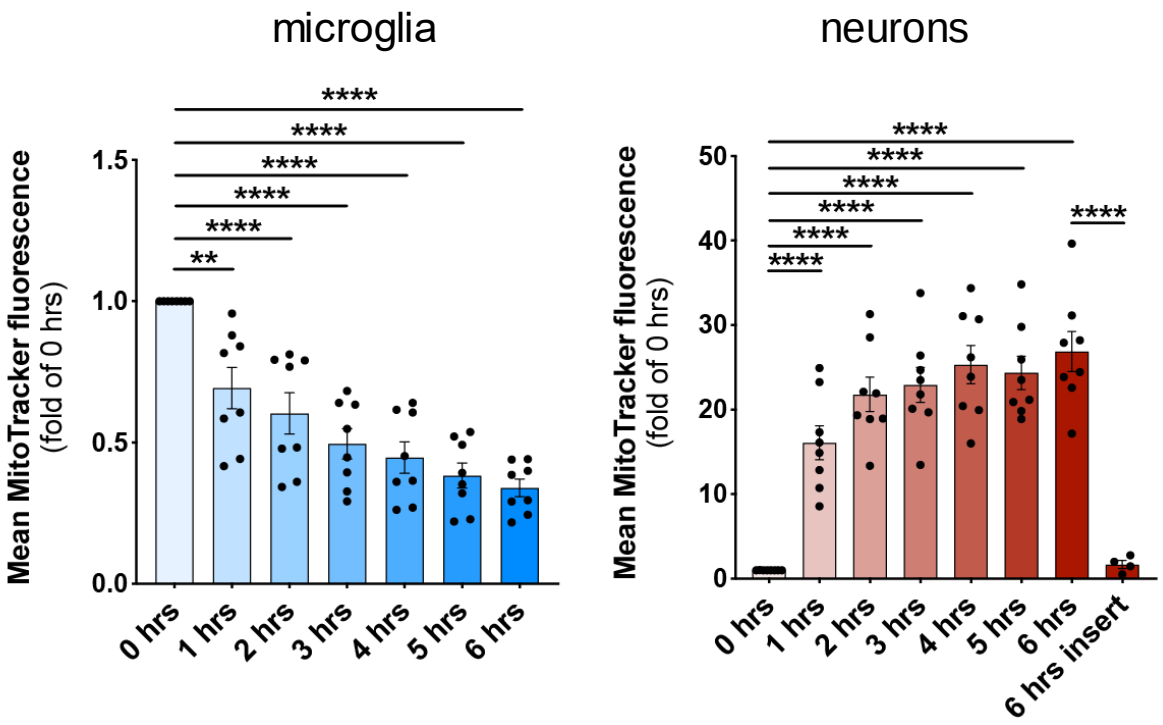




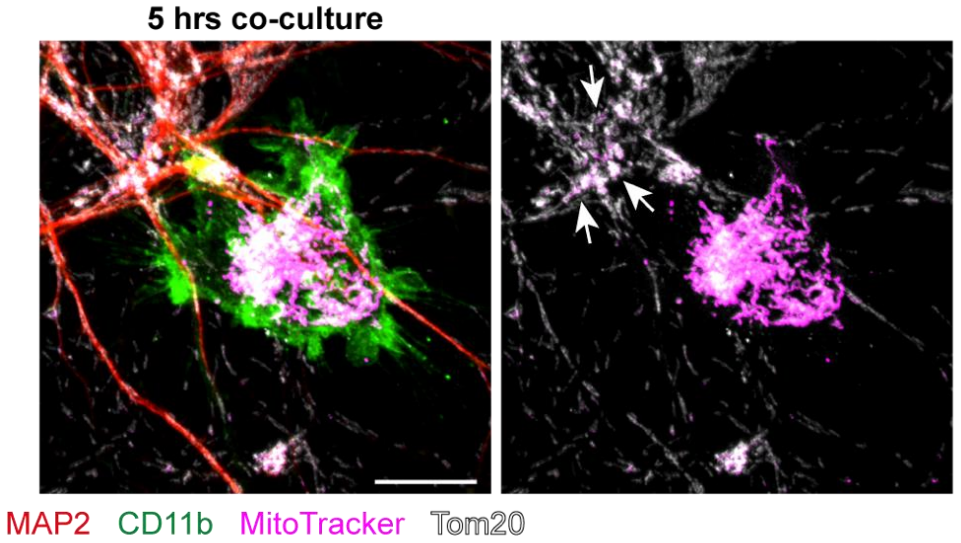


Microglia rescue neurons through transfer of functionally intact mitochondria

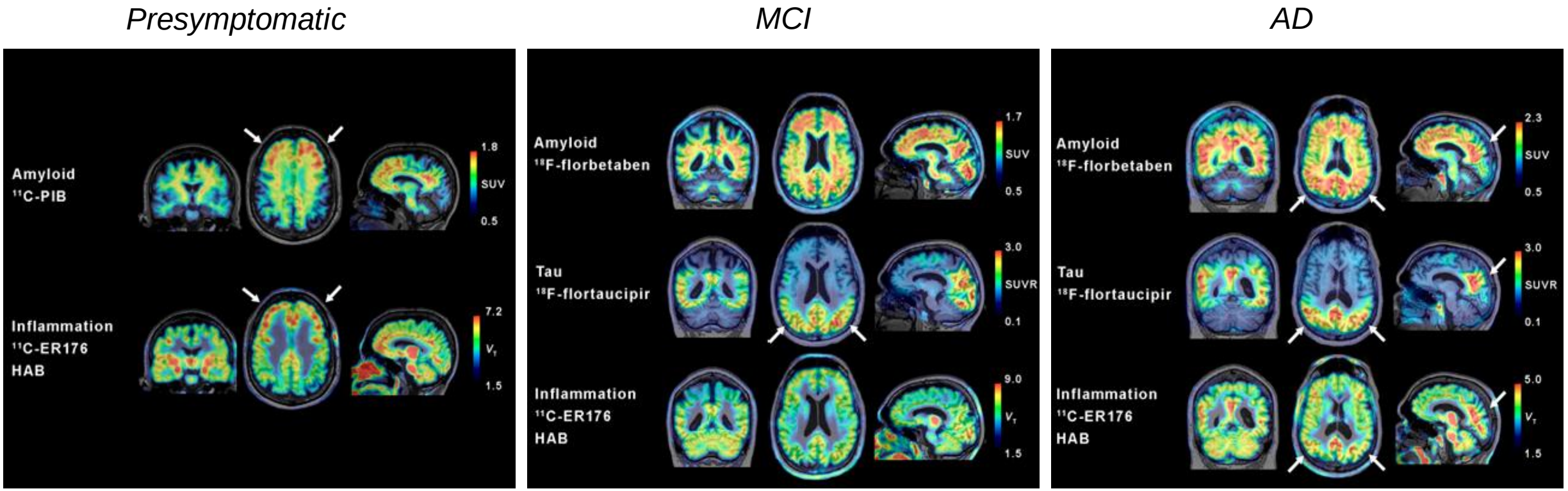
Microglia donate functionally intact mitochondria to neurons



Microglia-derived mitochondria integrate into mitochondrial network of neurons



TSPO-PET: Detecting chronic cerebral inflammation

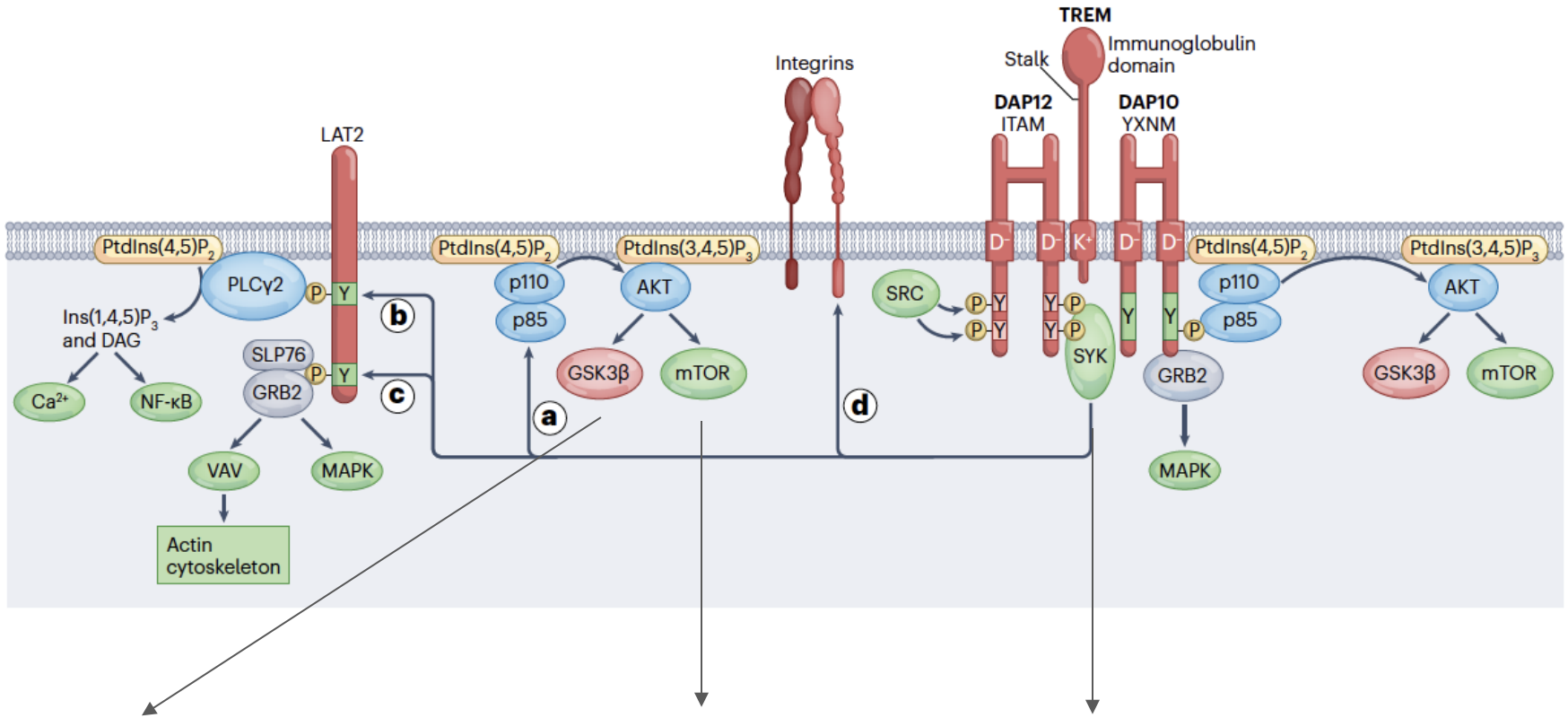


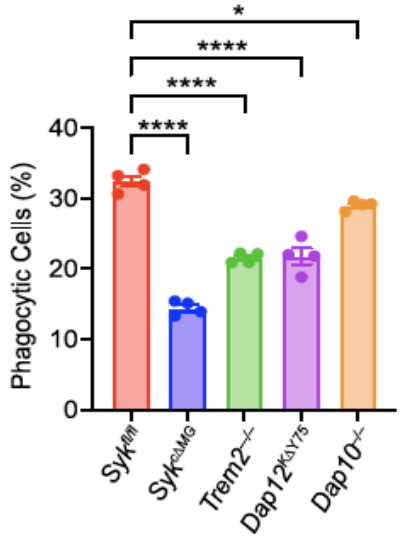
Progressing disease

Masdeu et al. 2022, *J Nucl Med* PMID: 35649654

Ising et al. *Nature*, 2019, PMID: 31748742

Trem2 signaling pathways and function





Proliferation

Key to maintain microglia metabolic fitness

Microglia survival

DAP10/SYK required for microglial response to Aβ

Restriction of Aβ pathology

Wang et al. 2022 *Cell* PMID: 36306735

Colonna, 2023 *Nat Rev Immunol* PMID: 36750615

Trem2 function

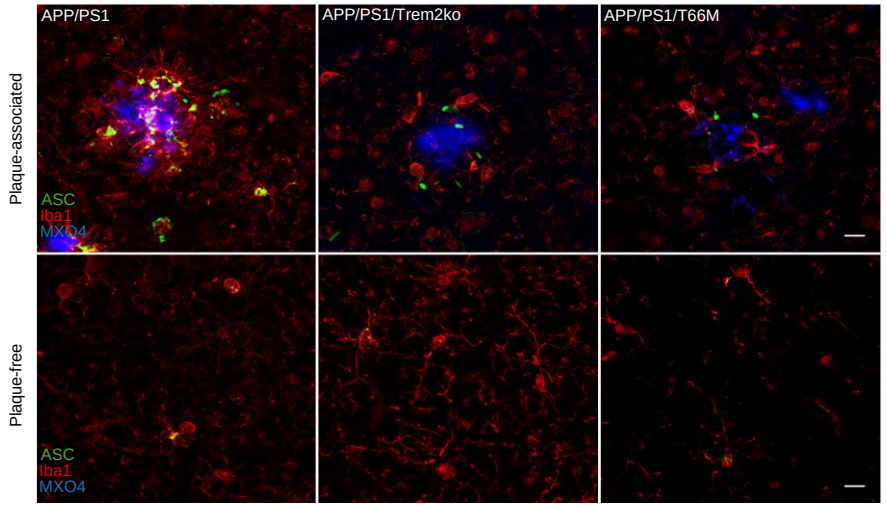
Trem2 overexpression

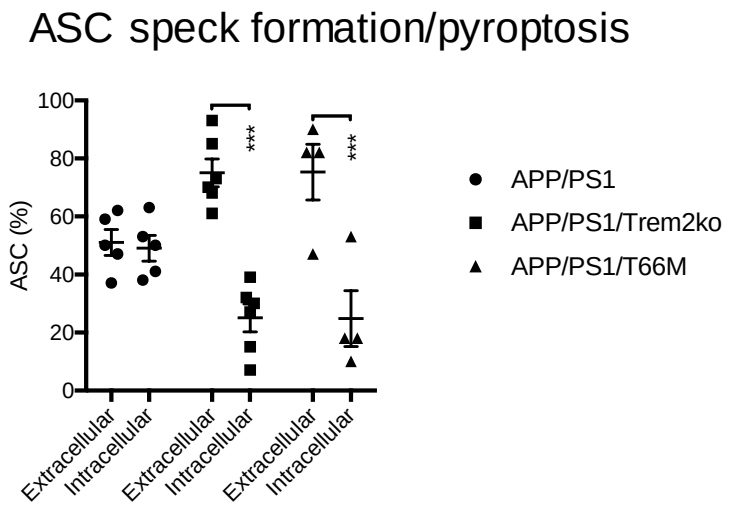
enhanced chemokine receptor expression, migration, phagocytosis

Attenuation of endogenous Trem2

reduced phagocytosis of apoptotic cells, increase in inflammatory gene transcription

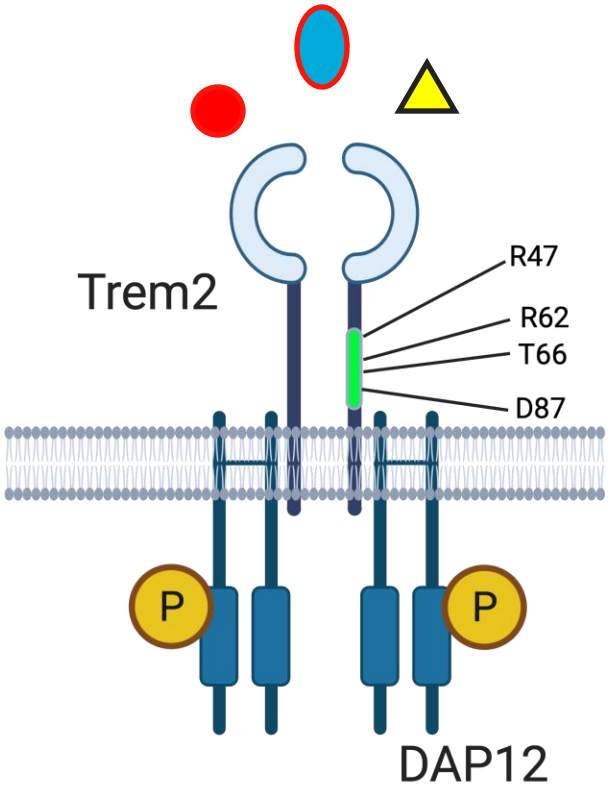
reduced engulfment of Aβ plaques, facilitation spreading and neurotoxicity of Aβ





Castro Gomez, *in preparation*

Endogenous Trem2 ligands



Potential ligands: ApoE –depending on its lipidation status

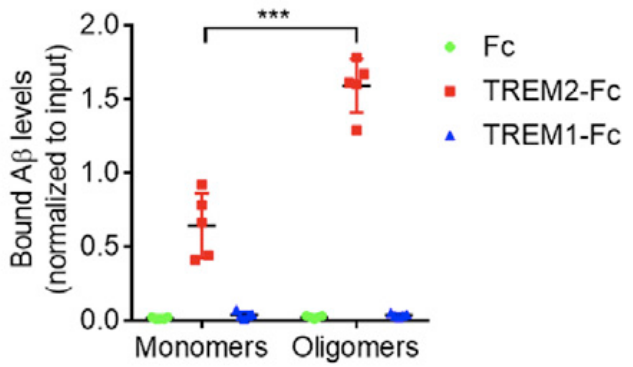
(unknown whether different for ApoE2, 3 or 4)

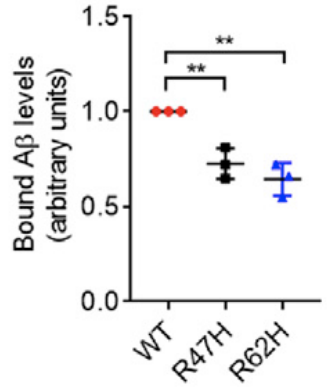
Clu/ApoJ

Myelin

Apoptotic neurons

Aβ:

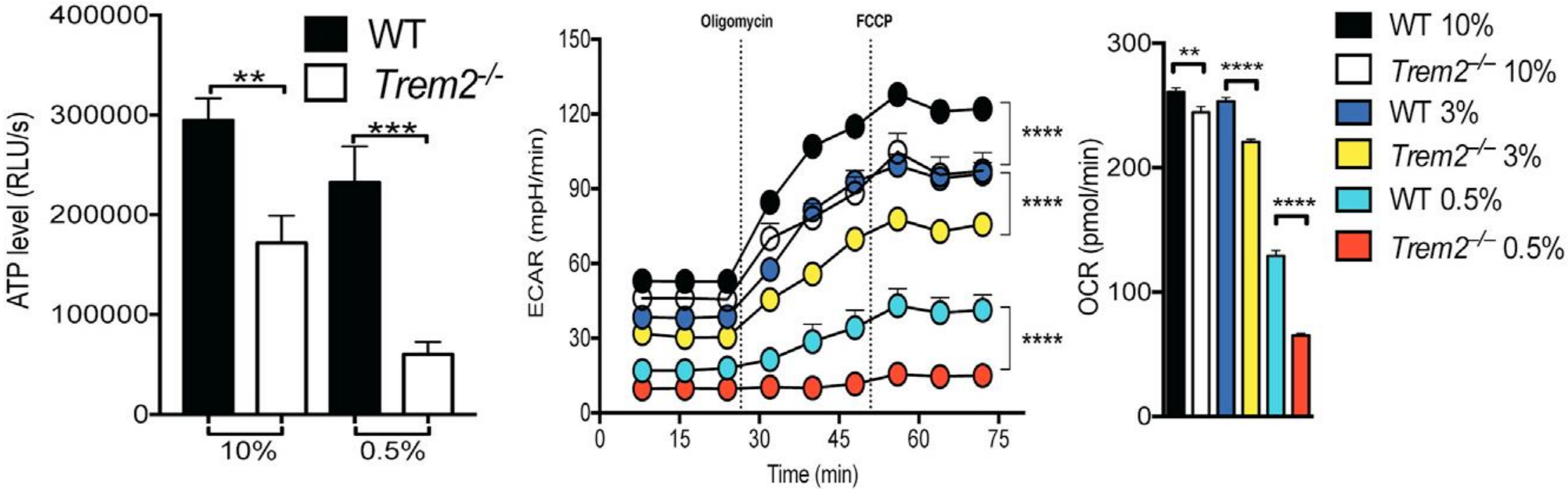




Zhao et al. 2018, *Neuron* PMID: 29518356

Yeh et al. 2016, *Neuron* PMID: 27477018

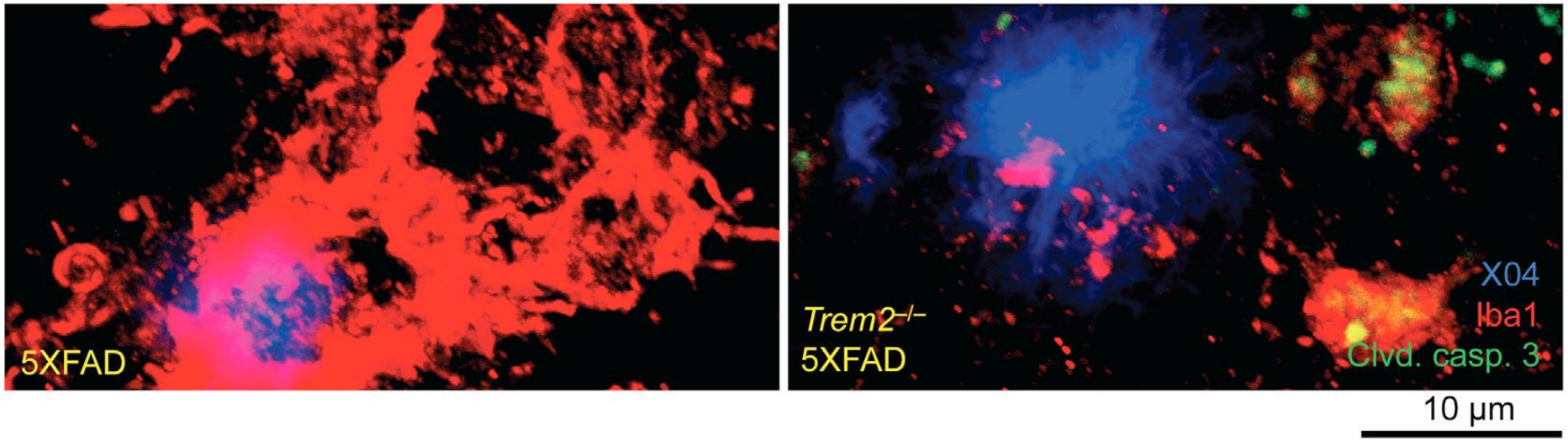
Trem2 insufficiency (ko or loss of function variant) impairs microglial metabolic fitness

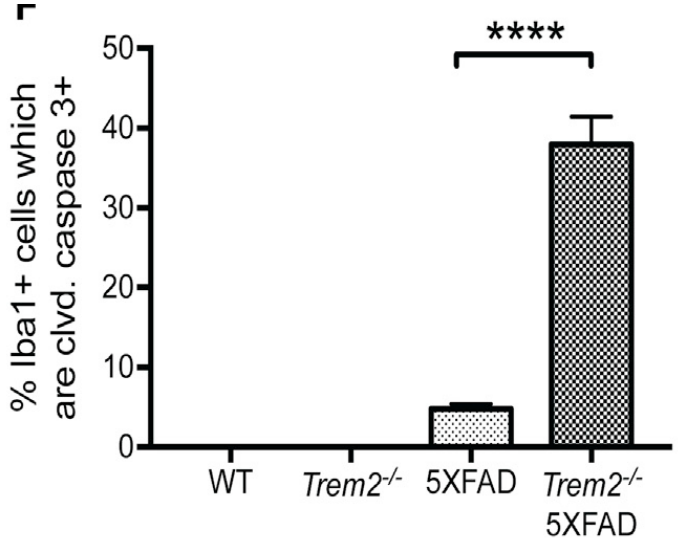


Reduction of anabolic and energetic metabolism in microglia

Ulland et al. 2017, *Cell* PMID: 28802038

Trem2 insufficiency causes microglial cell death



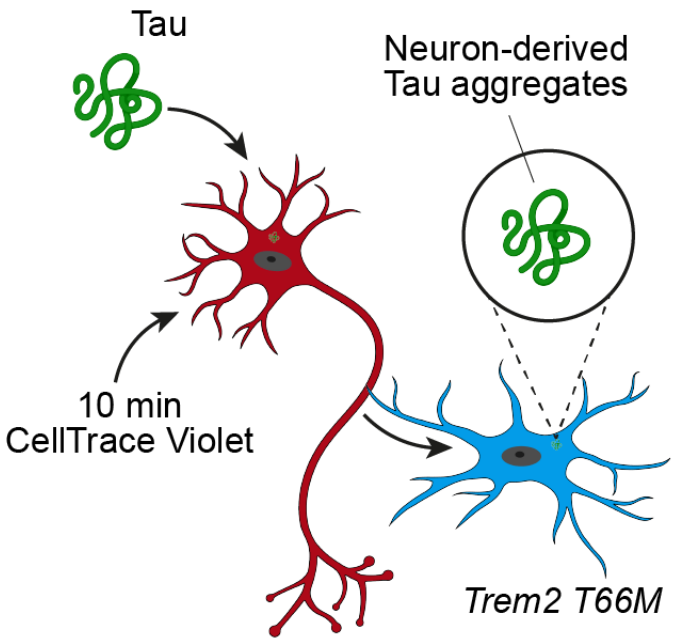


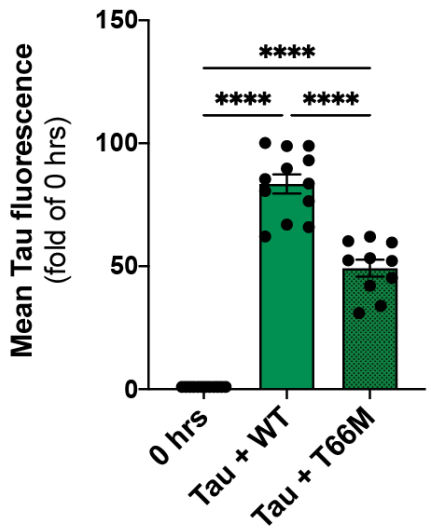
Similar data with TUNEL⁺
In Wang et al. 2015

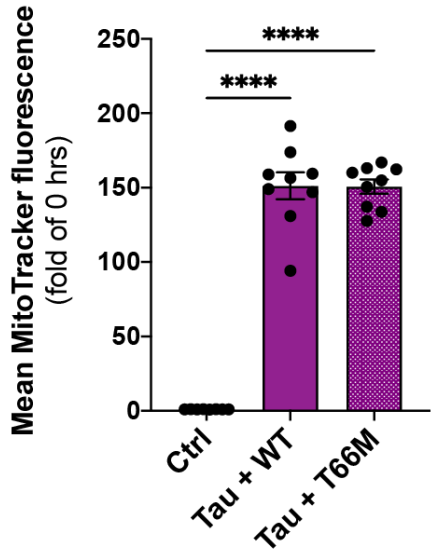
Ulland et al. 2017, *Cell* PMID: 28802038

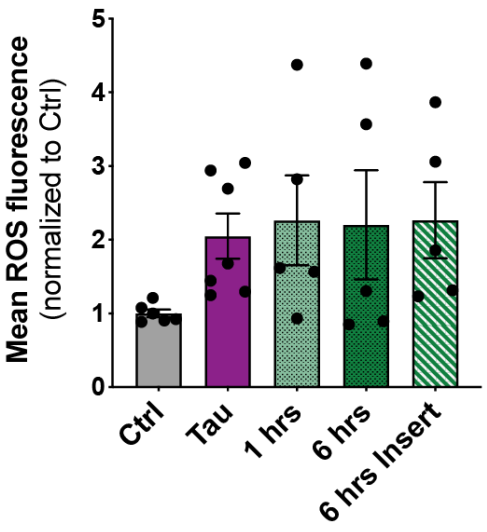
Wang et al. 2015, *Cell* PMID: 25728668

Effect of Trem2 T66M variant microglia on neuronal rescue





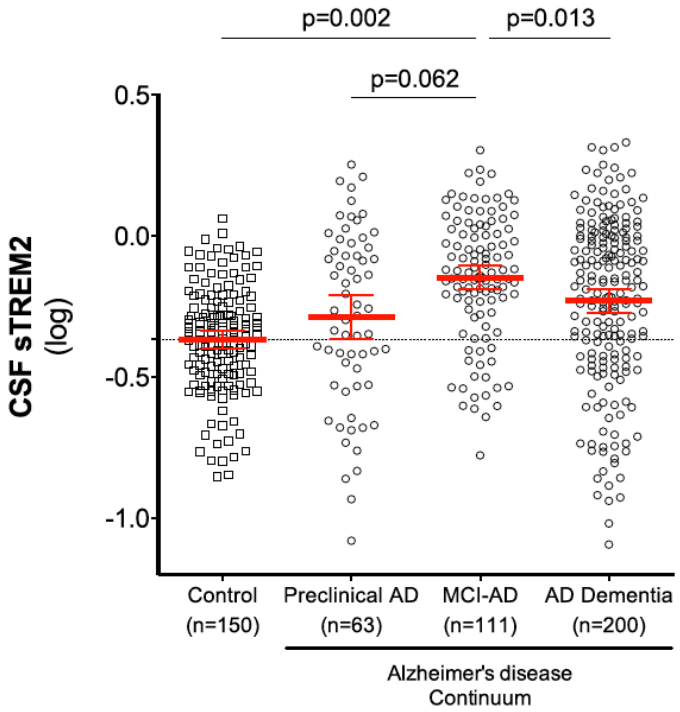


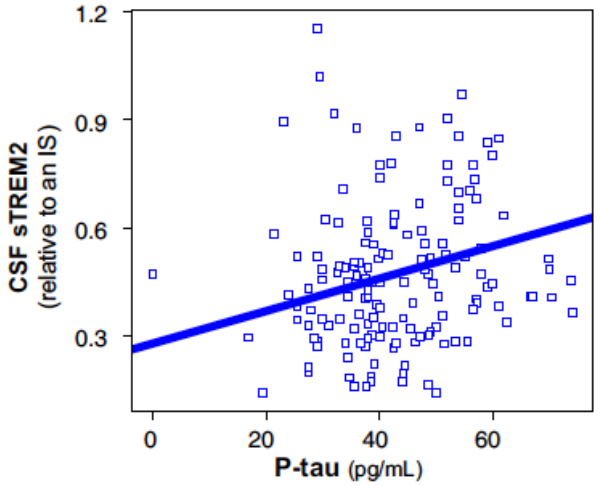


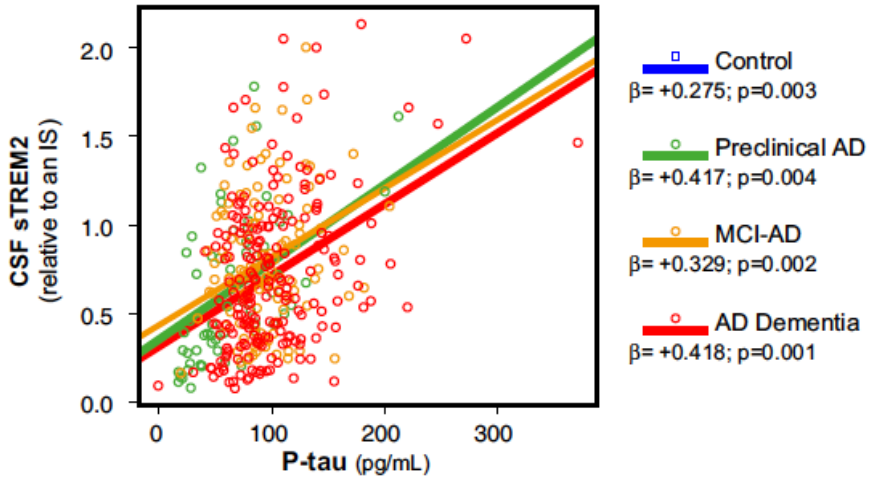
Loss-of-function mutation in the **Triggering Receptor Expressed on Myeloid Cells 2 (Trem2)**

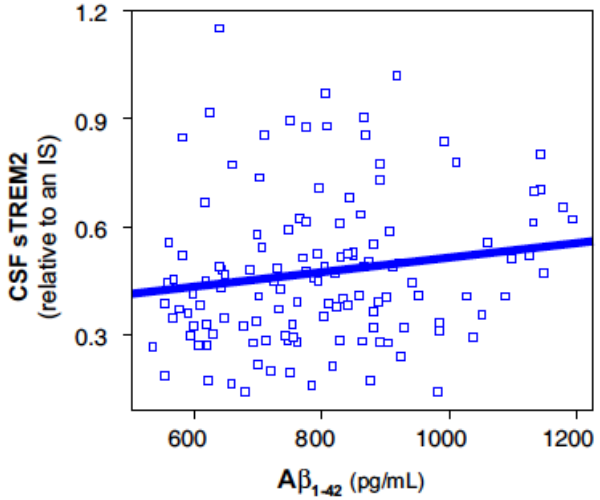
- impaired microglia function (phagocytosis, chemotaxis, proliferation)
- increased deposition of cytotoxic proteins

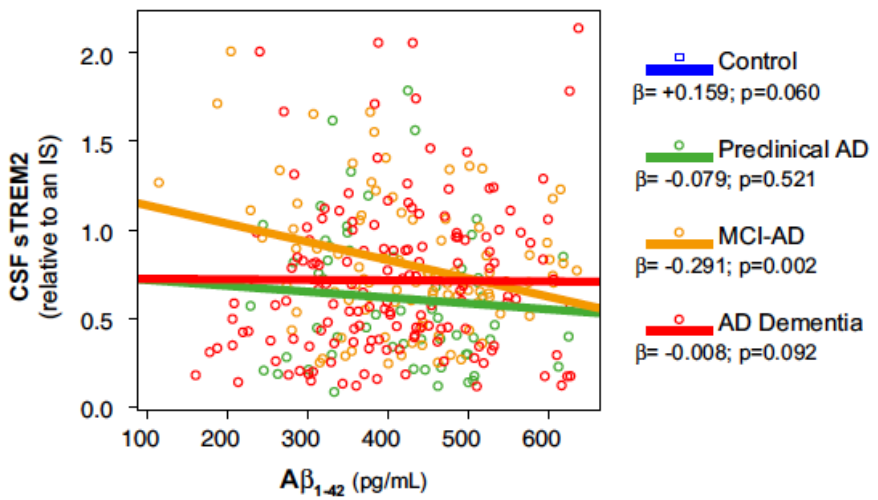
sTrem2 as biomarker in AD-relation to pTau and Aβ





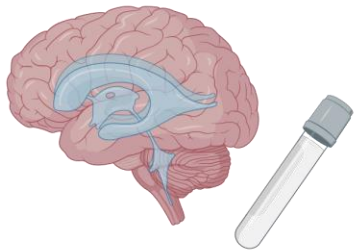






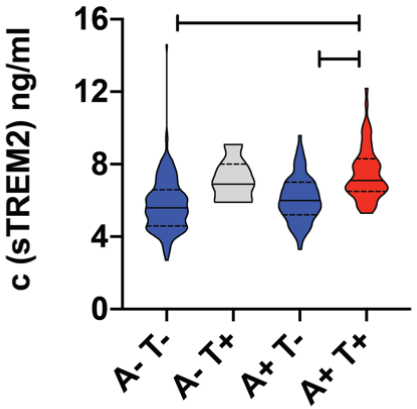
Suarez Calvet et al. 2016, *Embo Mol Med* PMID: 26941262

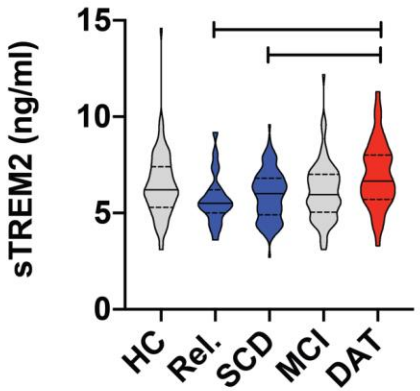
When is Trem2 upregulated/activated?

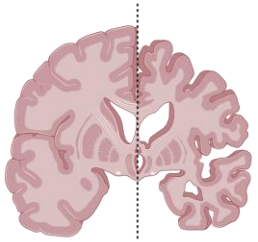


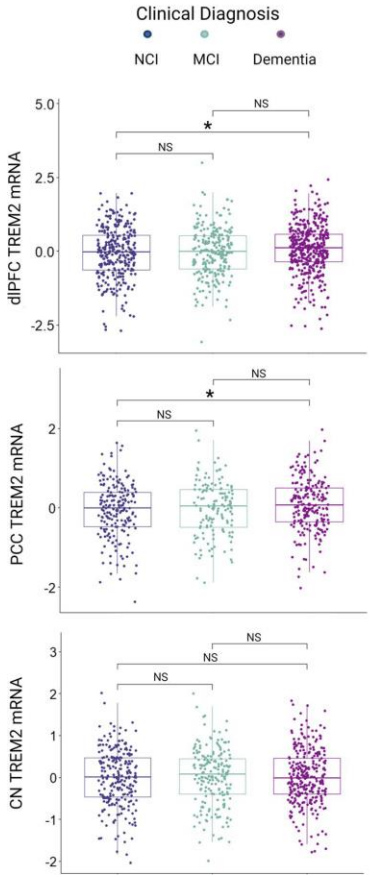
DELCODE

DZNE - Longitudinale Studie zu Kognitiven Beeinträchtigungen und Demenz





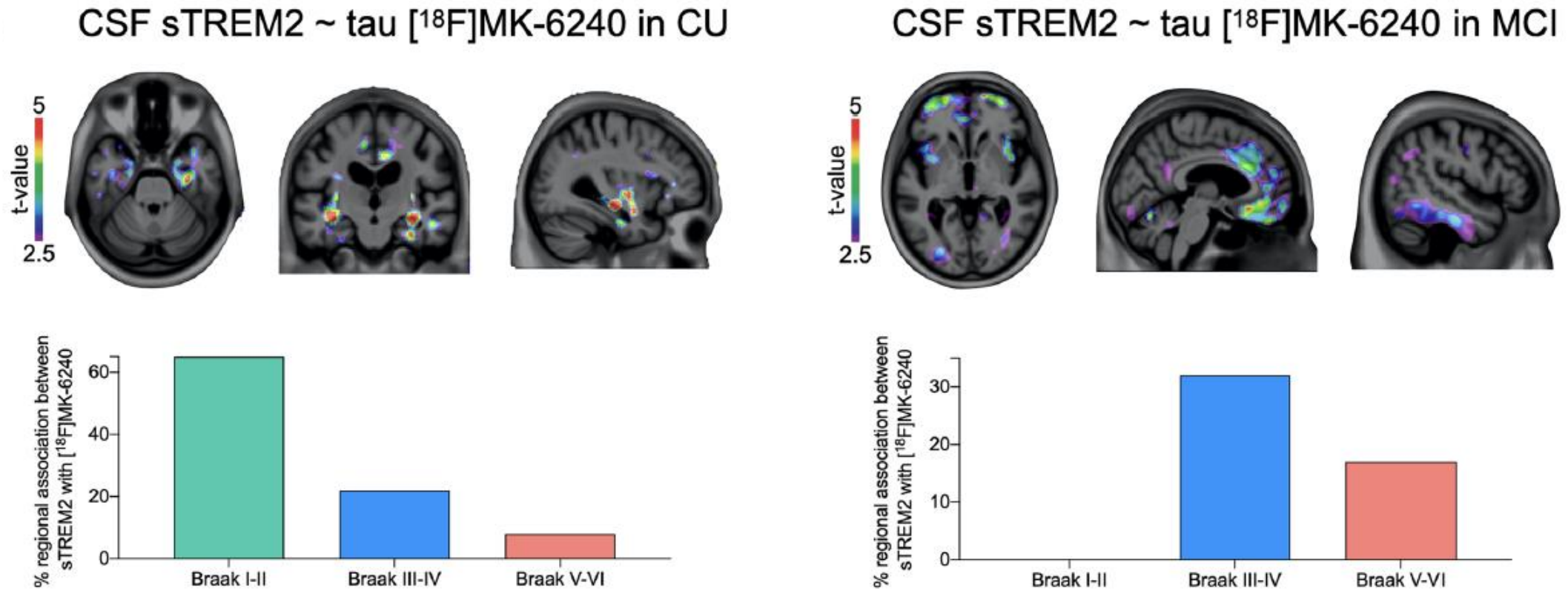




Brosseron et al. 2023, *Neuron* PMID: 34995486

Winfree et al. 2023, *Acta Neuropathol* PMID: 36966244

sTrem2 correlates with tau in later Braak stages



Microglia activation correlates with tau pathology → Suggesting an active role of Trem2 during this stage

Pascoal et al. 2021, *Nat Med* PMID: 34446931

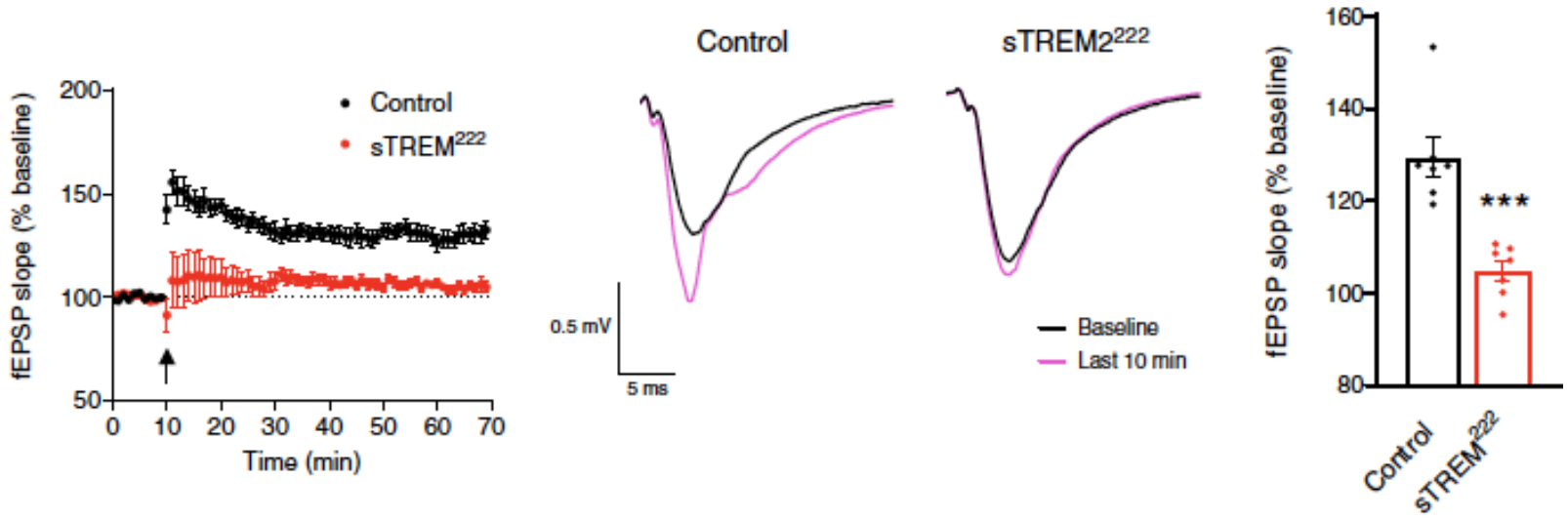
Trem2 and sTrem2 at the synapse

As a potential beneficial effect, microglia removal of oAβ-induced hyperactive synapses normalizes plaque-associated neuronal hyperactivity Rueda Carrasco et al. 2023, *Embo J* PMID: 37575021

Trem2 binds to C1q and thereby inhibits classical complement activation Zhong et al. 2023, *Immunity* PMID: 37442133

Overexpression of the R47H Trem2 variant in BV2 cells increased microglial synapse uptake and neuronal loss Popescu et al. 2022, *Glia* PMID: 36480007

Trem2 full length and splice variant derived sTrem2 suppresses hippocampal long-term potentiation

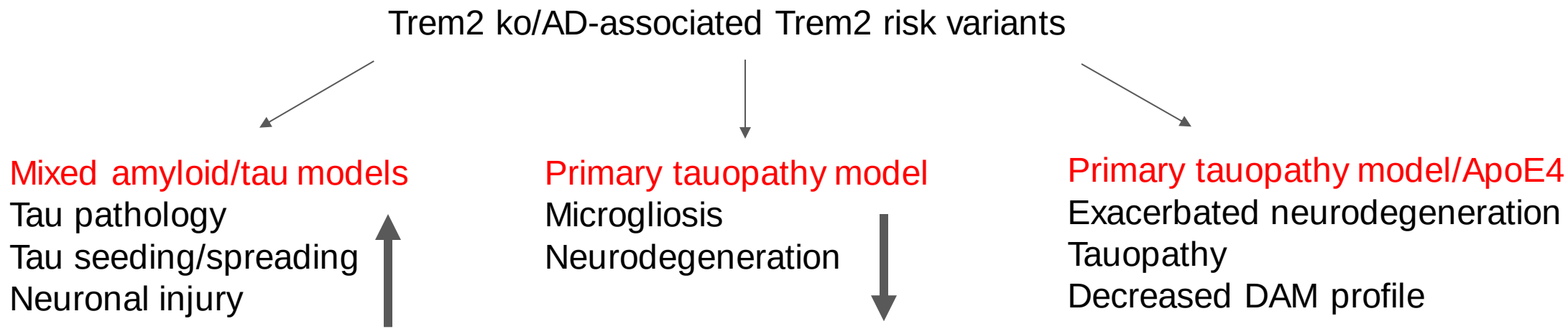


Moutinho et al. 2023, *Genome Med* PMID: 36805764

Trem2's tau games

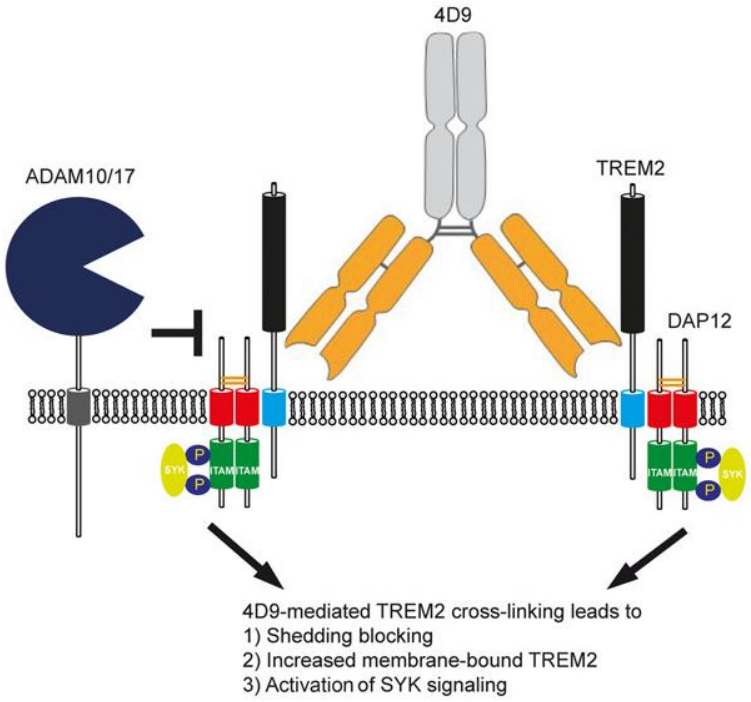
Lentiviral induced upregulation of Trem2 protein levels reduces tau hyperphosphorylation (Ser199, Ser396) in APP/PS1 transgenic mice
(Peng et al. 2023 *Mol Neurobiol* PMID:)

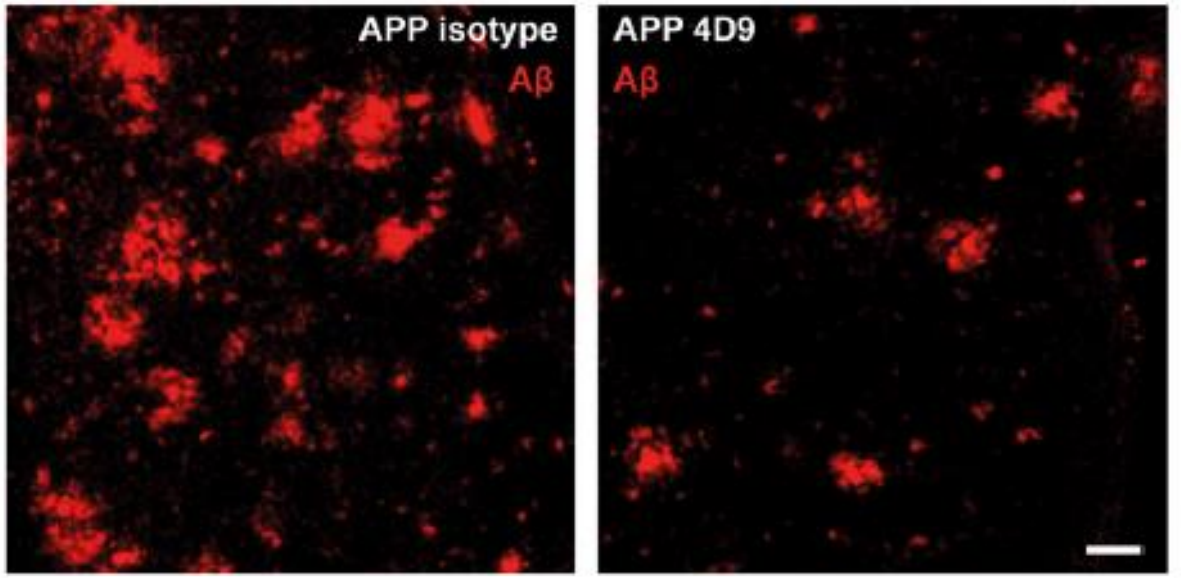
Trem2 R47H risk variant carrying mice show more neuritic plaque pathology upon AD-tau injection as wt
(Leyns et al. 2019 Nature Neurosci PMID:)

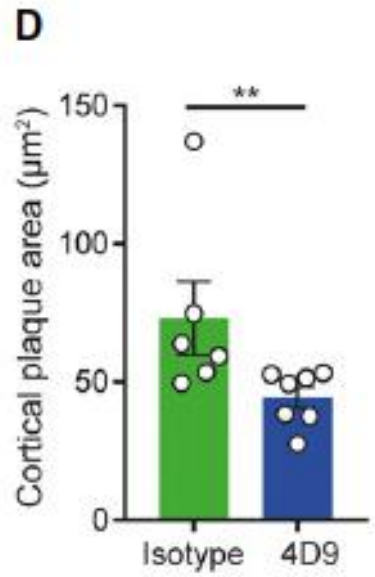


Gratuze et al. 2022, *Neuron* PMID: 36368315

Trem2 antibody action on microglia and Aβ clearance







Schlepkow et al. 2021, *EMBO Mol Med.* PMID: 32154671

Summary

Genetic findings link Trem2 gene variants to an increased risk for neurodegeneration, most prominently Alzheimer's disease

Trem2 function includes removal of cellular debris, restriction of Aβ deposits, synapse protection and maintenance of microglial homeostasis

Trem2 risk variants result in a loss of function, facilitated microglial death and consequently an increased disease risk.

sTrem2 detection in CSF and human brain pathology suggest an activation in MCI to early AD stages

Modulation of Trem2 has proven beneficial in preclinical models. Trem2 antibody ligation represents an efficient way to modulate the receptor

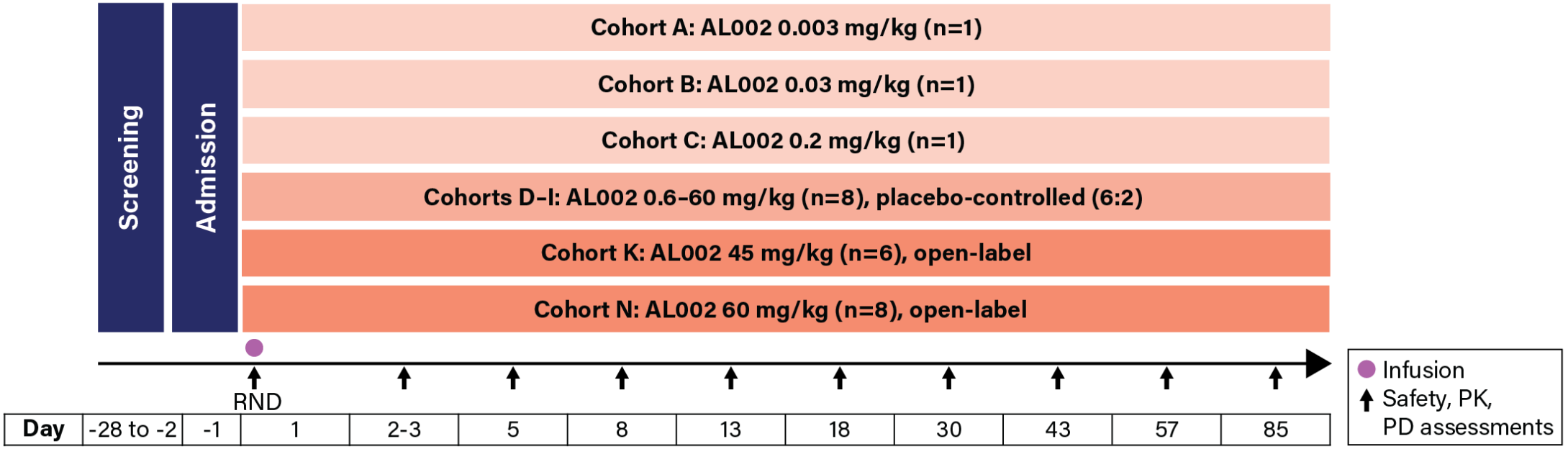
AL002
Clinical
Development

Gary Romano, M.D., Ph.D.

Chief Medical Officer
Alector

Phase 1 Study of AL002 in Healthy Volunteers

Figure 1. AL002-1 Study Design



AL002 Phase 1: Single Ascending Dose Study

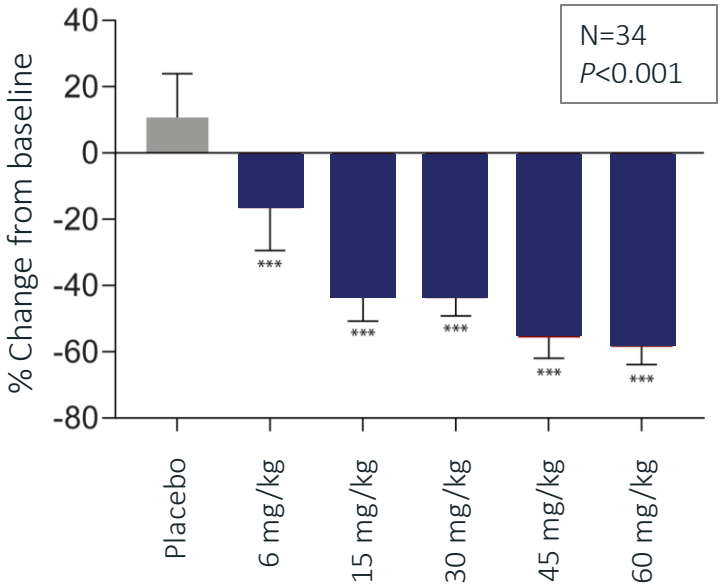
Well Tolerated in Healthy Volunteers

System Organ Class Preferred Term	AL002 0.003-0.2 mg/kg (n=3) n (%)	AL002 0.6 mg/kg (n=6) n (%)	AL002 2 mg/kg (n=6) n (%)	AL002 6 mg/kg (n=6) n (%)	AL002 15 mg/kg (n=6) n (%)	AL002 30 mg/kg (n=6) n (%)	AL002 45 mg/kg (n=6) n (%)	AL002 60 mg/kg (n=14) n (%)	Pooled Placebo (n=11) n (%)
Participants with ≥1 TEAE	2 (66.7%)	3 (50.0%)	2 (33.3%)	5 (83.3%)	5 (83.3%)	4 (66.7%)	6 (100.0%)	10 (71.4%)	9 (81.8%)
Participants with ≥1 treatment-related TEAE[b]	2 (66.7%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	5 (83.3%)	7 (50.0%)	6 (54.5%)
Treatment-related TEAEs in ≥5% of participants in the total AL002 group									
Headache	1 (33.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	4 (66.7%)	2 (33.3%)	2 (14.3%)	4 (36.4%)
Dizziness postural	1 (33.3%)	0	1 (16.7%)	0	0	1 (16.7%)	0	0	1 (9.1%)
Nausea	0	0	1 (16.7%)	1 (16.7%)	0	0	1 (16.7%)	6 (42.9%)	2 (18.2%)
Vomiting	0	0	0	0	0	0	0	3 (21.4%)	2 (18.2%)
Any TEAE leading to study drug withdrawal	0	0	0	0	0	0	1 (16.7%)	1 (7.1%)	0

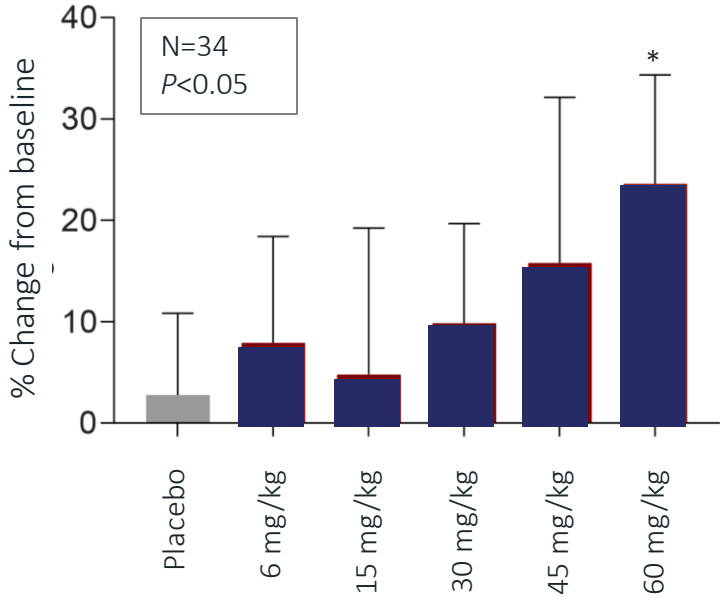
- No drug-induced or drug-related SAEs or DLAEs occurred during the study
- 1 participant in the pooled placebo group experienced an SAE that was not considered related to study drug
- 2 participants experienced AEs considered probably related to AL002 that led to withdrawal of study drug; one participant (AL002 45 mg/kg) experienced nausea (mild), and one participant (AL002 60 mg/kg) experienced paresthesia (moderate), nausea (mild), and retching (mild)

AL002 Phase 1: Dose-Related Target Engagement and Increase in Microglial Signaling

Dose-Dependent Reduction of Soluble TREM2 in the CSF (Mean +-SD)



Dose-Dependent Elevation of sCSF-1R in the CSF(Mean +-SD)

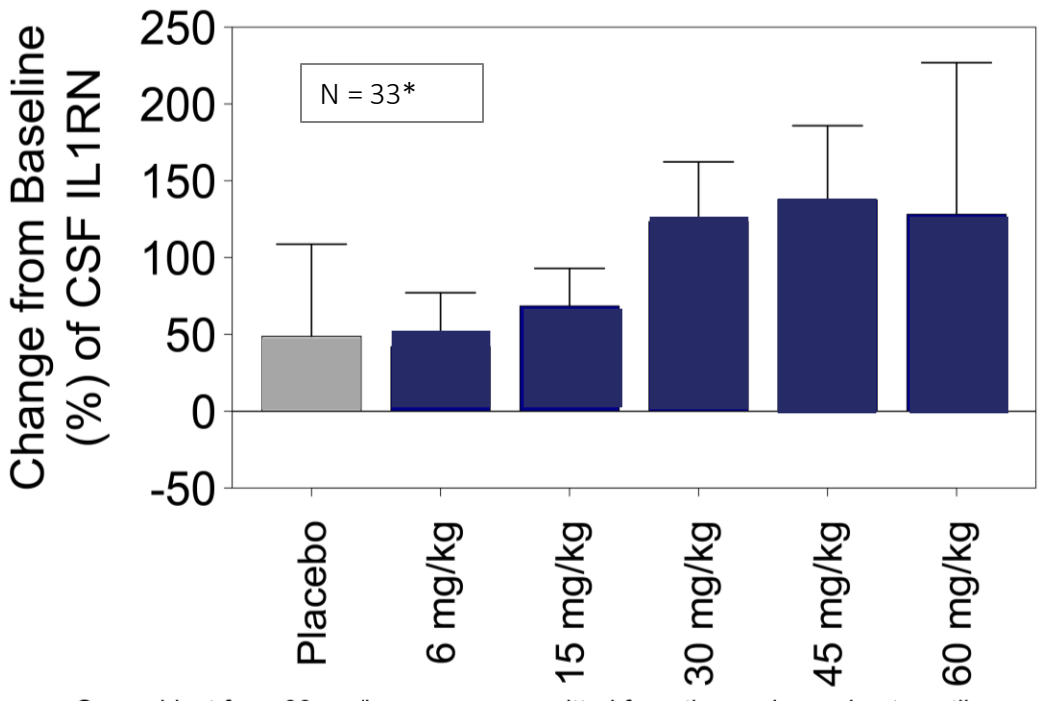


*P=0.026 at 60 mg/kg vs pooled placebo. ***P=0.0001 for 6 mg/kg and P<0.0001 for all other doses vs pooled placebo control.

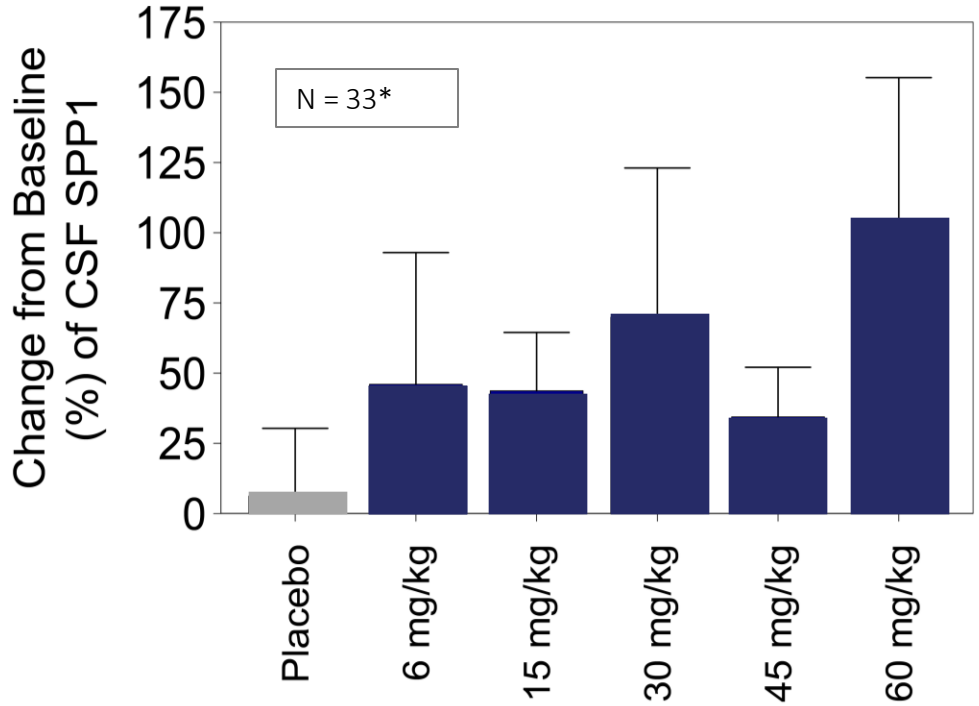
AAIC 2021; NCT03635047. 2. Wang S, et al. *J Exp Med*. 2020;217(9):e20200785.

AL002 Phase 1: Dose-Related Increase in Microglial Signaling

Dose-Dependent Elevation of IL1RN in CSF (Mean +-SD)



Dose Dependent Elevation of SPP1 in CSF (Mean +-SD)



At doses 6mg/kg – 45 mg/kg, N=6/cohort. N=14 in the 60 mg/kg cohort. Pooled placebo N=11.
*Outlier value (1280.3% above baseline at Day 3 from 1 participant in the 30 mg/kg dose group) were omitted from the graph.
Phase 1 data presented at AAIC 2021; NCT03635047.

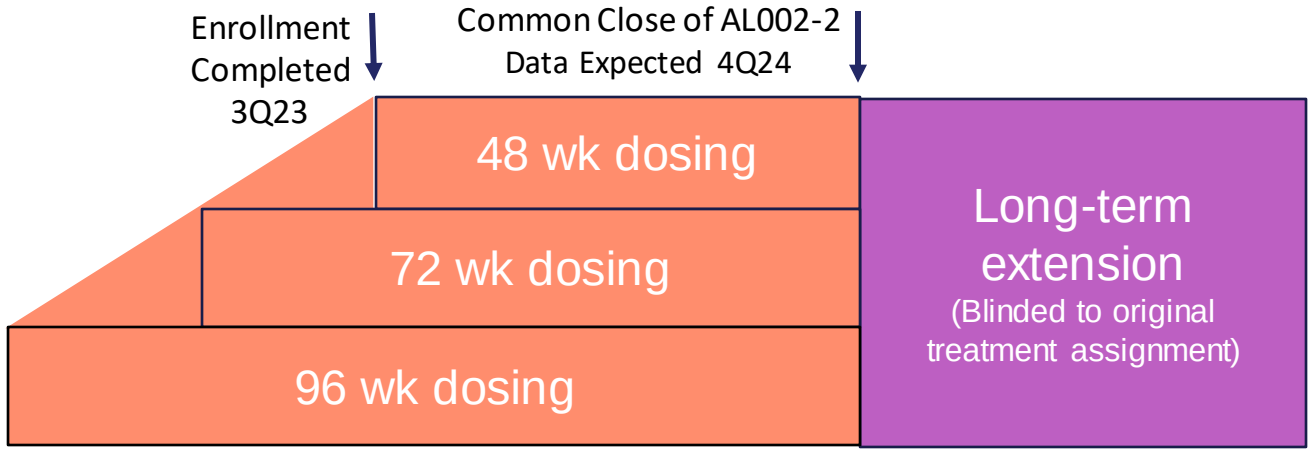
IL1RN = interleukin 1 receptor antagonist
SPP1 = secreted phosphoprotein 1
CSF = cerebrospinal fluid

INVOKE-2: AL002 Phase 2 Study in Participants with Early Alzheimer's Disease

Phase II Design: Randomized, double-blind, placebo-controlled 4-arm, common close study (48-96 weeks); randomized 381 participants (1:1:1:1) with early Alzheimer's disease

Treatment Arms

- AL002, 15mg/kg IV/q4w
- AL002, 40mg/kg IV/q4w
- AL002, 60mg/kg IV/q4w
- Placebo



INVOKE-2: Clinical and Functional Outcome Measures

- **Primary Outcome Measure:**
  - Clinical Dementia Rating Scale – Sum of Boxes
    - Primary endpoint of lecanemab Phase 3 trials

- **Secondary Clinical and Functional Outcome Measures**
  - RBANS
  - ADAS-Cog 13
  - ADCS-ADL-MCI
  - MMSE

} Items extracted for the iADRS, the primary endpoint of the donanemab Phase 3 trial

- **Proportional analysis**
  - Enables using ALL of the data collected in this common close design trial

Proportional constrained longitudinal data analysis models for clinical trials in sporadic Alzheimer's disease

Guoqiao Wang[1,2] | Lei Liu[1] | Yan Li[2] | Andrew J. Aschenbrenner[2] | Randall J. Bateman[2] | Paul Delmar[3] | Lon S. Schneider[4] | Richard E. Kennedy[5] | Gary R. Cutter[6] | Chengjie Xiong[1,2]

Alzheimer's & Dementia
Translational Research & Clinical Interventions

iADRS = Integrated Alzheimer's Disease Rating Scale
RBANs= Repeatable Battery for the Assessment of Neuropsychological Status
ADCS-ADL-MCI = Activities of Daily Living for Mild Cognitive Impairment
MMSE = Mini-Mental State Examination

INVOKE-2: Biomarkers of Target Engagement, Microglial Signaling and AD Pathophysiology

TARGET ENGAGEMENT AND MICROGLIAL SIGNALING

CSF sTREM2	CSF markers of Microglial Signaling
Reflects levels of TREM2 on microglial membrane Lower levels of sTREM2 correlate with AL002 binding and internalization of receptor	**CSF-1R:** Microglial proliferation **SPP1:** Microglial phagocytosis **IL1-RN:** Microglial immune regulation Markers of Microglial Subtypes / Activity

ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

Amyloid/Tau Pathology	Astrogliosis	Neuronal and Synaptic injury
Amyloid PET **Tau PET** **Plasma pTau^{217}** **CSF/Plasma MTBR-tau243** **CSF/Plasma Aß 42/40**	**Plasma GFAP** **CSF YKL40**	**Nfl** **Neurogranin** **Total Tau** **Volumetric MRI**

OPN = osteopontin protein
CSF1R = colony stimulating factor 1 receptor
IL1RN = interleukin-1 receptor antagonist
GFAP = glial fibrillary acidic protein
AD = Alzheimer's disease

YKL40= protein named YKL-40 based on its three N-terminal amino acids tyrosine (Y), lysine (K) and leucine (L), and its molecular mass of 40 kDa 14.
NfL = neurofilament light chain
CDR-SB = Clinical Dementia Rating Sum Boxes

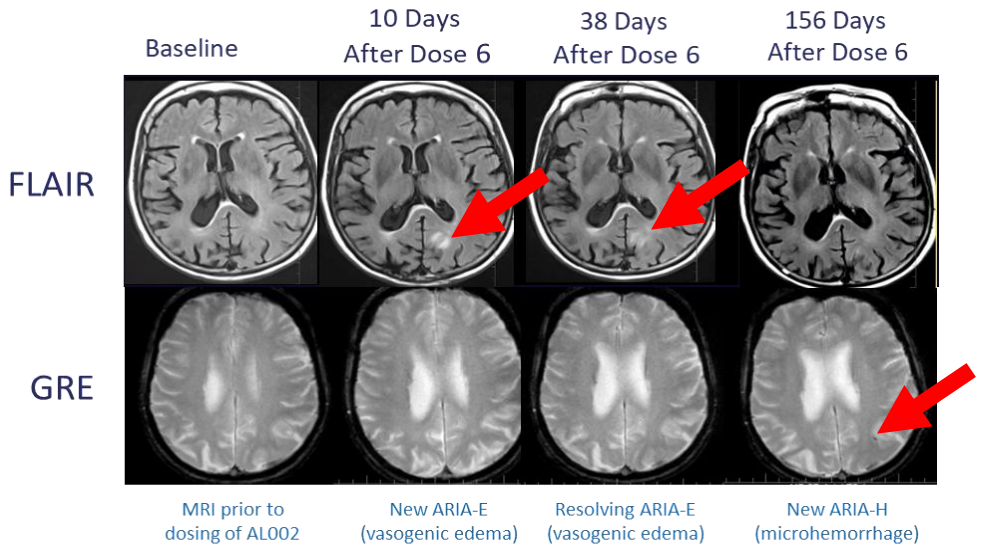
Treatment-related MRI findings resembling Amyloid Related Imaging Abnormalities Occurred in a Subset of Participants in the INVOKE-2 Trial

- MRI findings resemble ARIA reported with anti-amyloid antibodies with regard to:
  - MRI features, incidence, timing of onset/resolution, relatedness to number of ApoE ε4 alleles
  - Frequency and spectrum of associated clinical manifestations

- Early in the trial the more severe radiographic and clinically serious cases occurred exclusively in Apo ε4/ε4
  ➡ ApoE ε4/ε4 s were excluded from study participation

- An Independent Data Monitoring Committee reviews data regularly and has recommended to continue the trial

77 y/o (ApoE ε3/ε4) female participant with ARIA-E and ARIA-H



ARIA Incidence and Radiographic Severity Were Reduced After Exclusion of ApoE ε4/ε4

ARIA-E	ApoE ε4/ε4†	Current Study Population (Non–ApoE ε4/ε4)
ARIA-E incidence, n/N (%)	8/15 (71)*	49/337 (19)*
Radiographic severity (scale of 1-5), mean (SD)	2.5 (1.6)	2.2 (1.3)

ARIA-H	ApoE ε4/ε4†	Current Study Population (Non–ApoE ε4/ε4)
ARIA-H incidence, n/N (%)	8/15 (71)*	57/337 (23)*
ARIA-H radiographic severity (%)		
Mild	1/8 (12.5)	25/57 (44)
Moderate	2/8 (25)	16/57 (28)
Severe	5/8 (62.5)	16/57 (28)

This study remains blinded to treatment assignment.

*Placebo controlled; assumes all ARIA occurs in active treatment arms.

†Voluntarily discontinued APOE e4 homozygote trial participation.

Most Participants with Radiographic ARIA in the Trial Population (Excludes ApoE ε4/ε4) Have Been Asymptomatic and Clinically Serious Cases Have Been Uncommon

Symptomatic ARIA in Current Trial Population†	
Total participants dosed (excluding ApoE ε4/ε4)†	337
Participants with ARIA-E (%)	49 (19)*
Asymptomatic (%)	43/49 (88)
Symptomatic (%)	6/49 (12)
Clinically serious ARIA (%)	2/337 (<1)

This study remains blinded to treatment assignment.

*Placebo controlled; assumes all ARIA occurs in active treatment arms.

†Voluntarily discontinued APOE e4 homozygote trial participation.

AL002: Summary

- **Phase 1:** Completed in healthy volunteers.
  - Favorable safety profile at all doses tested
  - Demonstrated dose-dependent target engagement
  - Demonstrated evidence of dose-dependent effects on microglia signaling
- **Phase 2:** Completed enrollment of placebo-controlled Phase 2 study in early AD in Q3 2023 , with data readout expected in Q4 2024
  - Randomized, double-blind, placebo-controlled 4-arms, common close study; randomized 381 participants with early Alzheimer's disease
  - Favorable safety profile at all doses tested
  - MRI changes resembling ARIA in a subset of participants, which may indicate biological activity

What to Expect From the INVOKE-2 Trial?

- Therapeutic restoration of microglial function may slow Alzheimer's disease progression by:
  - Enhancing the clearance of misfolded proteins, including amyloid
  - Enhancing other beneficial effects of microglia on brain health:
    - maintenance of synaptic connections, support of astrocyte and oligodendrocyte function, maintenance and repair of the BBB and vasculature, and preservation of immune tolerance
- Potential differences from anti-amyloid trials with regard to:
  - Biomarker responses
    - E.g., lowering cerebral amyloid PET signal to the 24 centiloid threshold may not be required for efficacy of AL002 because its MOA may go beyond amyloid clearance
  - Optimal disease stage(s) for intervention: microglia decrease vulnerability of brain to pathogens and disease throughout life. Thus, the window for effectiveness may not be as narrow as for anti-amyloid therapeutics.
  - Temporal dynamics of treatment effects
    - Some improved microglia functions may manifest early in treatment (e.g., amyloid clearance, maintenance of synaptic function), while others may become apparent later (e.g., support of astrocyte and oligodendrocyte function, repair of vasculature and BBB)

Alzheimer's Disease Treatment Landscape: Beyond Anti-Aβ Therapies

Reisa Sperling, M.D.

Professor of Neurology, Harvard Medical School and Director of the Center for Alzheimer Research and Treatment, Brigham and Women's Hospital and Massachusetts General Hospital

*Dr. Sperling's slides are not included.

Closing Remarks

AL002 What To Look For: Will it be the **Keytruda** of Alzheimer's Disease?

THE HYPOTHESIS	POTENTIAL THERAPEUTIC BENEFITS	
Microglia broadly and constantly counteract multiple AD pathologies, and AL002 may enhance these activities throughout the disease cascade	Superior efficacy as stand-alone based on the broad mechanism	Clinical benefit at multiple disease stages based on broad mechanism and effect of high TREM2 on disease progression
	Superior efficacy in combination with anti-Aβ antibodies based on their dependence on functional microglia	Benefit independent of Aβ removal based on the broad mechanism and microglia's ability to insolate Aβ plaques

AL002 STATUS

- ✓ Most advanced, well-tolerated, TREM2-activating candidate in clinical development worldwide.
- ✓ Completed enrollment in Phase 2 clinical trial.
- ✓ Data readout expected in Q4 2024.
- ✓ Multiple microglia-specific biomarkers and treatment-emergent MRI findings that resemble ARIA may suggest AL002 is biologically active.
- ✓ AbbVie opt-in decision in early 2025.