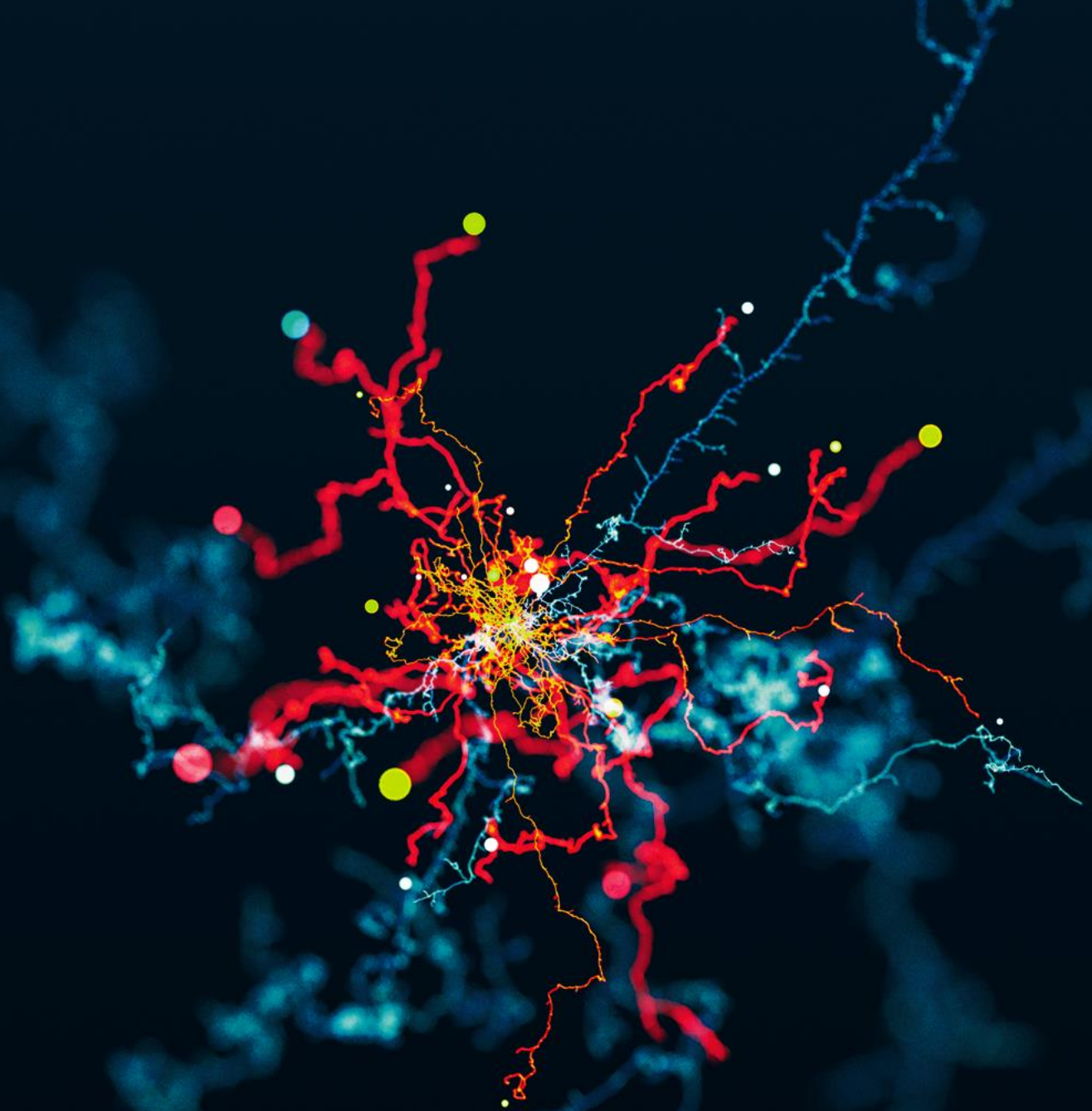
December 13, 2019

Alector R&D Day



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Meeting Information

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, 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.

We 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: the ability of our clinical trials to demonstrate safety and efficacy of our product candidates, and other positive results; the timing and focus of our future clinical trials, and the reporting of data from those trials; our plans relating to commercializing our product candidates, if approved; the expected potential benefits of strategic collaborations with third parties and our ability to attract collaborators with development, regulatory and commercialization expertise. 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, as discussed in greater detail in our filings with the Securities and Exchange Commission (SEC), including without limitation in our Annual Report on Form 10-Q, as filed on November 12, 2019 with the SEC. 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. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this presentation, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

Alector R&D Day 2019: Presenters

Arnon Rosenthal, PhD	Chief Executive Officer, Co-Founder, Alector
Robert Paul, MD, PhD	Chief Medical Officer, Alector
Sabah Oney, PhD	Chief Business Officer, Alector
Mario Masellis, MSc (Pharm), MD, PhD, FRCPC	Associate Professor, Department of Medicine, Institute of Medical Sciences Co-director, Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre
Elizabeth M. Bradshaw, PhD	Adler Assistant Professor of Neurology, the Taub Institute for Research on Alzheimer's Disease and the Aging Brain and the Institute for Genomic Medicine, Columbia University
Carlos Cruchaga, PhD	Professor of Psychiatry and Neurology, Director of NeuroGenomics and Informatics Washington University in St. Louis

Agenda

Section	Presenter	Time
Welcome and introduction to Alector	Arnon Rosenthal (CEO)	8:00 – 8:10 am
Alector's corporate strategy	Sabah Oney (CBO)	8:10 – 8:20 am
Clinician's view: Frontotemporal Dementia (FTD)	Mario Masellis (KOL)	8:20 – 8:40 am
AL001 / AL101: Scientific overview	Arnon Rosenthal (CEO)	8:40 – 8:50 am
AL001: Clinical data and update	Robert Paul (CMO)	8:50 – 9:10 am
Q&A		9:10 – 9:25 am
The human genetics of Alzheimer's disease:TREM2 and SIGLEC 3	Elizabeth Bradshaw (KOL)	9:25 – 9:55 am
Break		

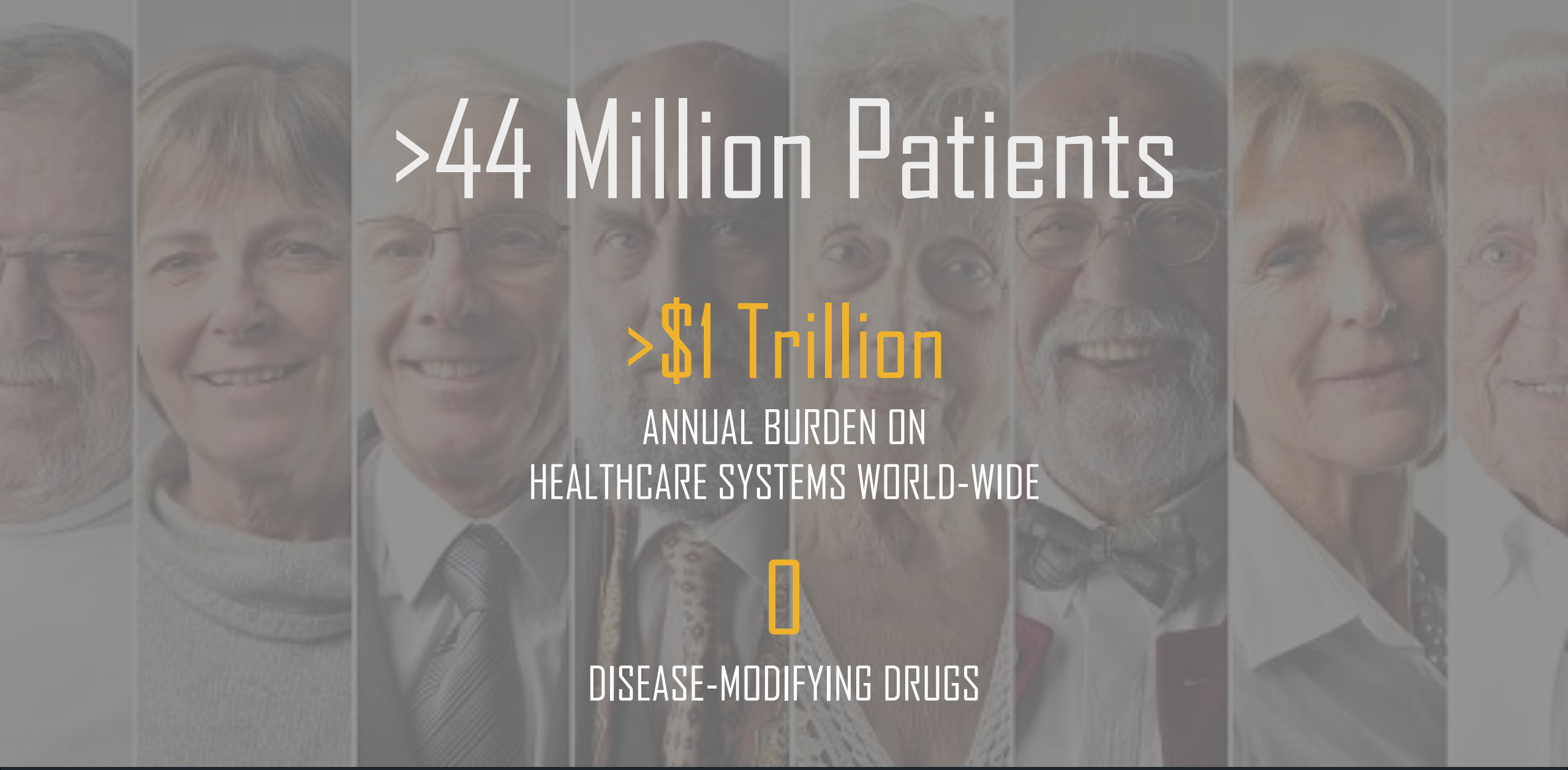
Agenda (cont'd)

Section	Presenter	Time
ALO02: Scientific overview	Arnon Rosenthal (CEO)	10:10 – 10:20 am
ALO02: Clinical data and update	Robert Paul (CMO)	10:20 – 10:30 am
ALO03: Scientific overview	Arnon Rosenthal (CEO)	10:30 – 10:40 am
ALO03: Clinical update	Robert Paul (CMO)	10:40 – 10:50 am
Q&A		10:50 – 11:05 am
New Alector program: Scientific overview	Carlos Cruchaga	11:05 – 11:20 am
New Alector program: Introduction and overview	Arnon Rosenthal (CEO)	11:20 – 11:30 am
Q&A		11:30 – 11:55 am
Closing remarks	Arnon Rosenthal (CEO)	11:55 – 12:00 pm

Welcome and Introduction

Our vision

At Alector we envision a world where dementia and neurodegeneration are illnesses of the past, just as smallpox and polio have become.



>44 Million Patients

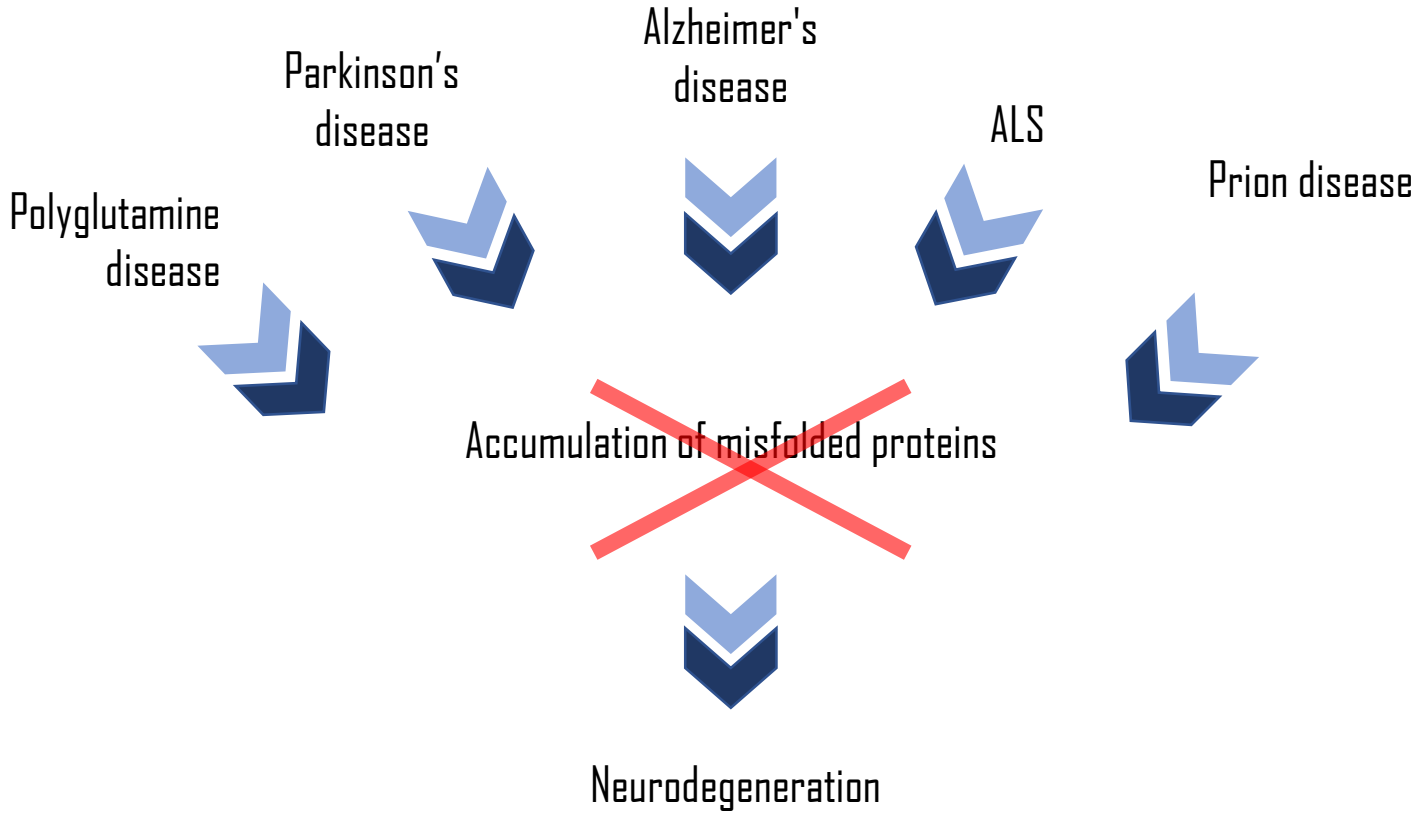
>$1 Trillion

ANNUAL BURDEN ON
HEALTHCARE SYSTEMS WORLD-WIDE

0

DISEASE-MODIFYING DRUGS

The prevailing approach to neurodegeneration to date: Remove or prevent production of misfolded proteins

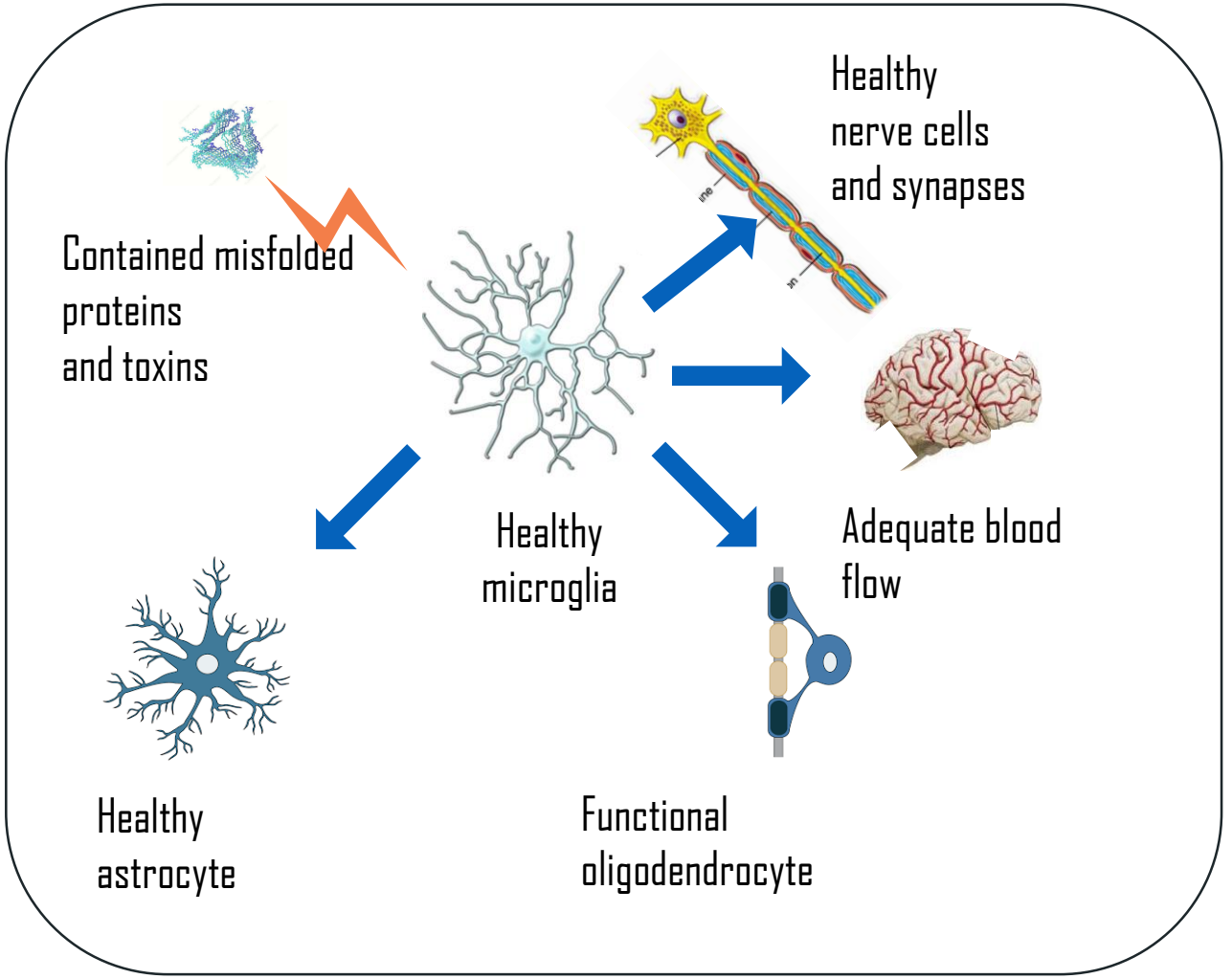


Targeting misfolded proteins drove therapeutic approaches for the last thirty years

Alector's immuno-neurology approach: Harness the brain's immune system to treat neurodegenerative diseases

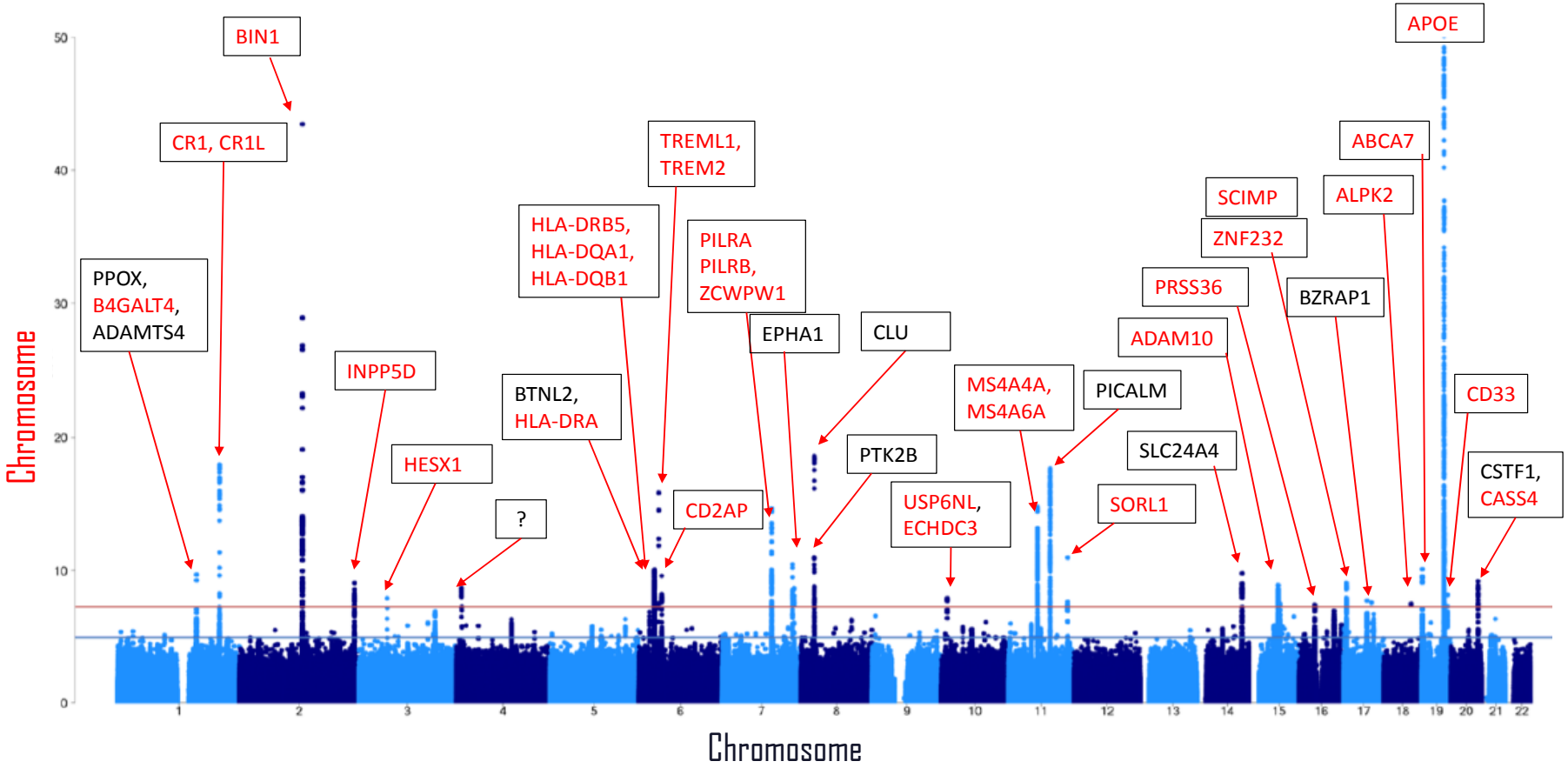
Degenerative Pathologies

- Misfolded proteins
- Destruction of synapses
- Death of nerve cells
- Dysfunction of support cells
- Insufficient blood flow



A strong scientific rationale underlies our strategy

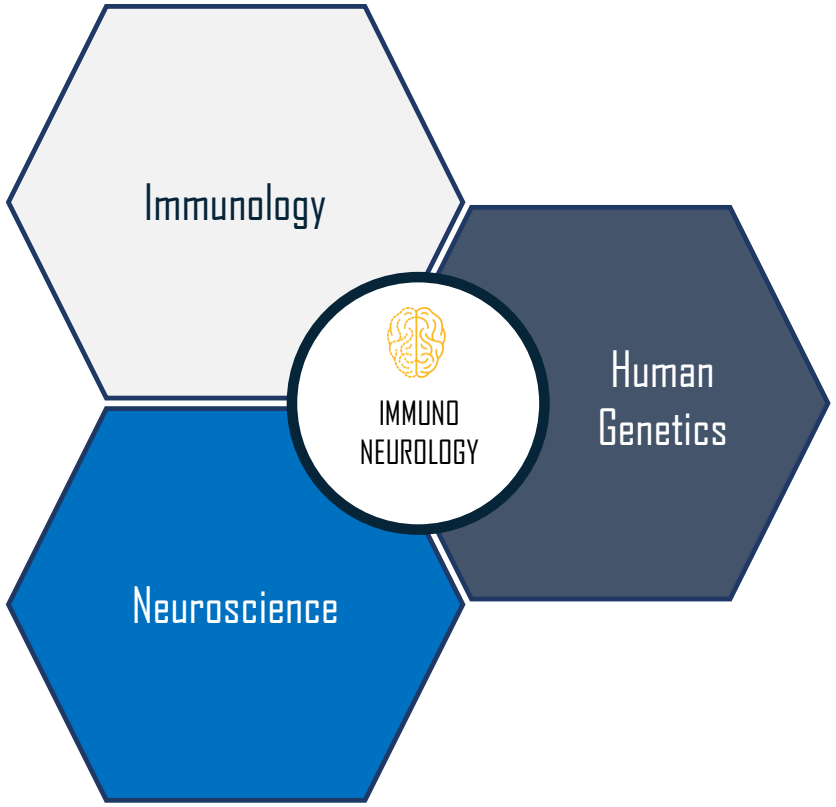
Most risk genes for Alzheimer's disease (AD) are brain immune check points



Annotated from Nature Genetics 2019 Mar;51(3):404-413

- 22/ 30 AD risk genes are immune genes
- Filed ~185 patent applications covering 30 patent families

We combine deep neuroscience expertise with genetics to target immune dysfunction as a root cause of neurodegeneration



- Integrating separate biological fields opened new therapeutic opportunities previously
- Targets, drugs, and biomarkers that are based on human genetics* increase the probability of technical success significantly
- Human genetics enables coherent patient populations for clinical trials

*Nat Rev Drug Discov. 2014 Jun;13(6):419-31.

Product candidates that functionally counteract genetic deficits

Genetic mutations that cause neurodegeneration	Our drugs functionally counteract the genetic or physiological shortfalls
Genetic mutations that reduce PGRN lead to frontotemporal dementia (FTD)	ALO01 restores PGRN back to the normal range
Genetic mutations or aging reduce TREM2 functionality and increase risk of AD	ALO02 increases TREM2 activity
Genetic mutations cause excessive activity of SIGLEC3 and increase risk of AD	ALO03 blocks SIGLEC3 activity

Since founding Alector six years ago - we have delivered substantial progress

Advanced multiple first-in-class programs into clinic

- ✓ AL001 in Phase 2 for FTD with pivotal Phase 3 in 2020
- ✓ AL002 in Phase 1b for AD with biomarker data
- ✓ AL003 in Phase 1b for AD with target engagement data
- ✓ AL101 entering Phase 1

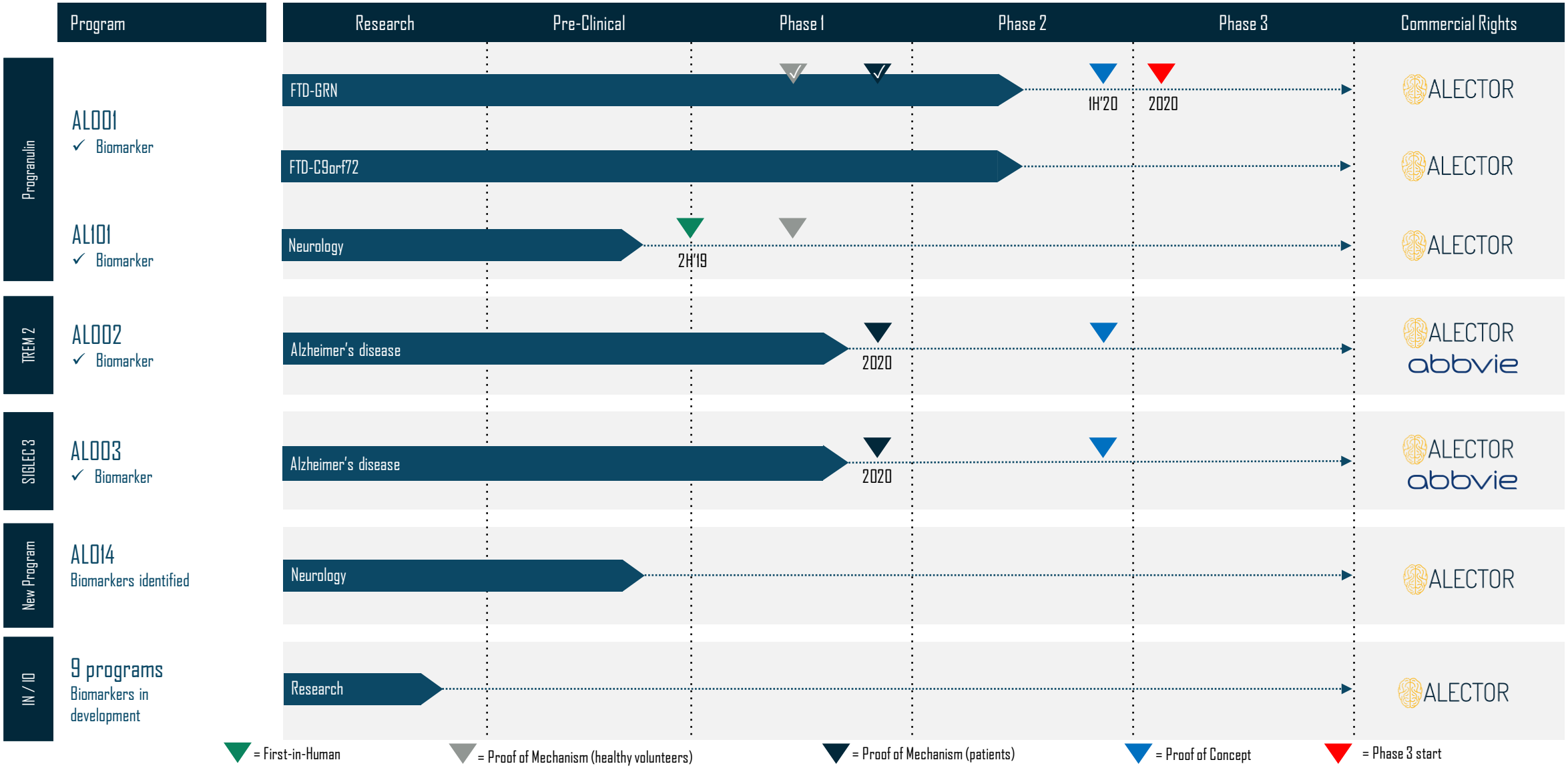
Robust Discovery and Research Pipeline

- ✓ Differentiated discovery platform
- ✓ Interrogating >150 targets
- ✓ 9 Active Late Stage / Research programs across diverse indications

Solid Company Fundamentals

- ✓ Over 185 patent applications, 30 patent families
- ✓ Cash balance of >$380M
- ✓ Global partnership with AbbVie for AL002 and AL003
- ✓ Fully integrated and efficient organization with >115 FTEs

Current pipeline has five prioritized programs in development



Corporate Strategy

Presenting:
Sabah Oney, Ph.D.
Chief Business Officer, Alector

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Large unmet medical need

First-in-class, innovative science

Exceptional people

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Our goal

Become a fully integrated biotech company with approved drugs by 2023

- Continue to discover, develop and commercialize innovative medicines to cure neurodegeneration
  - Build an exceptional organization that can translate our vision into reality
- Partner with investors and companies that support our vision
- Create significant value for patients, investors, partners and Alector team

Our company strategy

- Discovery platform to generate numerous high PTS program candidates
- Strong in-house clinical organization to accelerate development

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- Lead development through approval and commercialization initially for some indications
- Leverage strong industry partnerships for other indications

Our differentiated approach to drug development centers on increasing the probability of success – both technical and commercial

Human Genetics

- Target selection
- Patient selection
- Biomarker selection

Portfolio Approach

- Multiple targets
- Multiple programs
- Parallel development

Accelerated Timelines

- Accelerate readouts
- Advance early successes
- Kill early failures

Decrease impact of single program failure

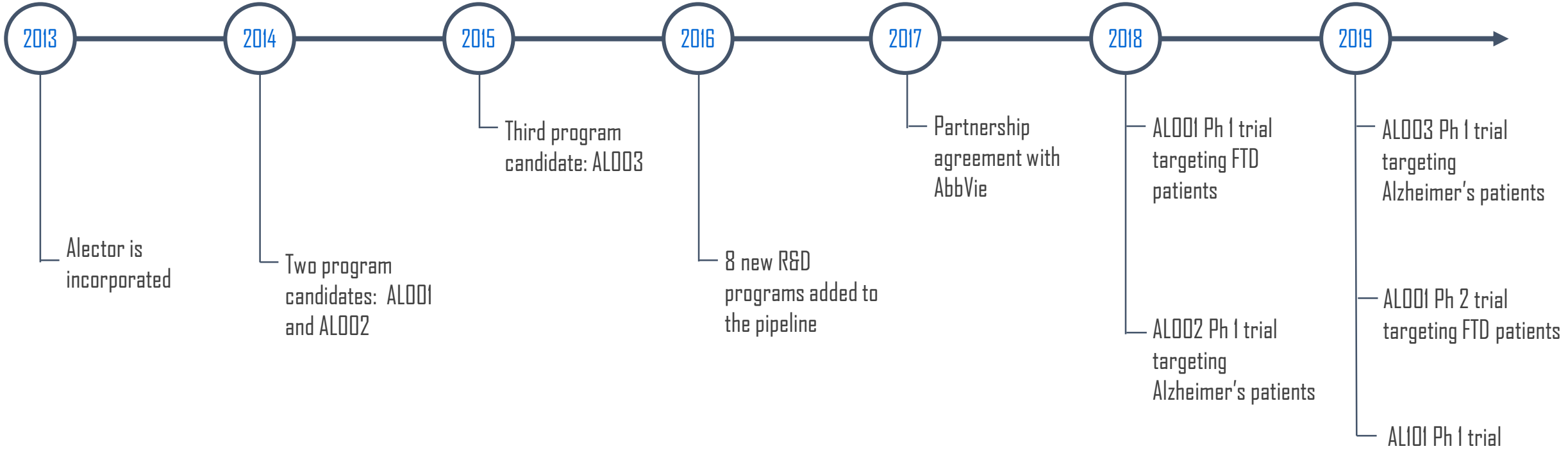
Learn of success and/or failure as soon as possible

Alector has made significant clinical progress over the last six years

14 programs created

4 programs moved into clinic*

>160 subjects dosed



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* AL101 program FIH December 2019.

Successful track record of financing our growth and development through both equity and partnership capital sources

EQUITY INVESTORS

>$400M

- Venture investors
- Crossover investors
- Strategic investors
- Institutional investors

- Raised >$400M in equity in private and public rounds
- Funding the development of AL001, AL101, nine programs in research and development, and discovery platform

ALECTOR

Up to $1.3B

abbvie

- Partnered two Alzheimer's disease programs, AL002 & AL003
- Upfront and development milestones of up to $1.3B
- 50/50 WW profit and cost share for both programs

INDUSTRY PARTNERSHIPS

Strategic collaboration with AbbVie: Advancing two Alzheimer's disease programs

abbvie

Financial Terms

$205M upfront +

$20M equity +

Up to $986M milestones +

Global profit / cost share

Programs

Partnership covers the global development and potential commercialization for our TREM2 and SIGLEC 3 programs

Key Highlights

Alector responsible for Phase 1 and 2 of both programs

Allows Alector to continue to build its clinical infrastructure

All remaining R&D programs wholly owned

Alector's leadership team

LEADERSHIP

Arnon Rosenthal, PhD CEO, CO-FOUNDER	Genentech, RiNAT, annexon biosciences
Shehnaaz Suliman, MD COO, President	Genentech, Theravance Biopharma
Sabah Oney, PhD CBO	Genentech, Ariosa Diagnostics, Stanford University, Duke University
Robert Paul, MD PhD CMO	LMU Ludwig-Maximilians-Universität München, Genentech
Robert King, PhD CDO	COR Therapeutics, SciClone Pharmaceuticals, RiNAT, Bayhill Therapeutics
Stephanie Yonker, PhD VP Legal	Morrison Foerster, Harvard Law, Genentech
Calvin Yu VP Finance	Stemcentrx, FivePrime
Omer Siddiqui VP Clinical Operations	Allakos, Johns Hopkins University, Genentech

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Terry McGuire	polarispartners
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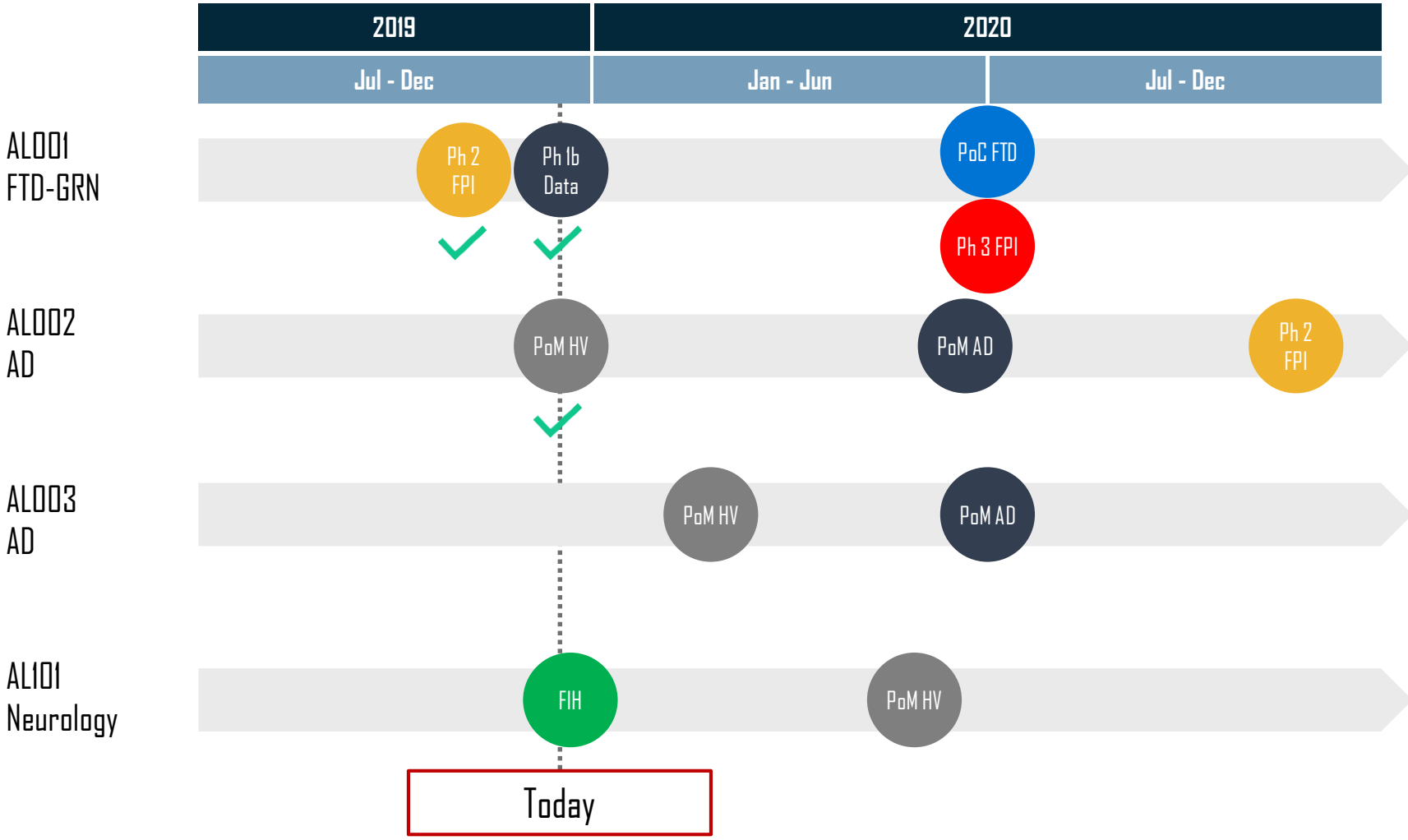
Marco Colonna, MD	National Academy of Sciences, Washington University in St. Louis School of Medicine
Michael Heneka, MD	Universität Bonn
Robert Vassar, PhD	Northwestern Medicine Feinberg School of Medicine

Exceptional people

Key anticipated milestones through 2020

Cash runway to the first half of 2022



- PoM = Proof of mechanism
- PoC = Proof of concept
- FPI = First patient in
- FIH = First in human

Clinician's view: Frontotemporal Dementia (FTD)

Presenting:
Mario Masellis, MSc (Pharm), MD, PhD, FRCPC
Associate Professor, Department of Medicine, Institute of Medical Sciences
Co-director, Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre

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Genetic frontotemporal dementia: Focus on Granulin (*GRN*) mutations

Mario Masellis, MSc, MD, PhD, FRCPC
Clinician-Scientist & Associate Professor
Department of Medicine (Neurology)
University of Toronto
Staff Neurologist
Sunnybrook Health Sciences Centre

Alector R&D Day
December 13, 2019

Objectives

- Case presentations
- Review the most common genetic causes of FTD and related pathology
- Focus on *GRN*-related FTD
- Clinical FTD diagnosis – cognitive, behavioural and language features
- Outcomes - clinical, neuroimaging, and other biomarkers
- Treatments

Case 1

Case 1

- Identifying data: 57 y.o. R-handed M; working as engineer; 18 years of education (M.Sc. Engineering); bilingual, fluent English
- Issue: “progressive language disturbance”
  - Age at onset 55 y.o.
- Past medical history:
  - High cholesterol
- Family history:
  - +ve for FTD

Case 1

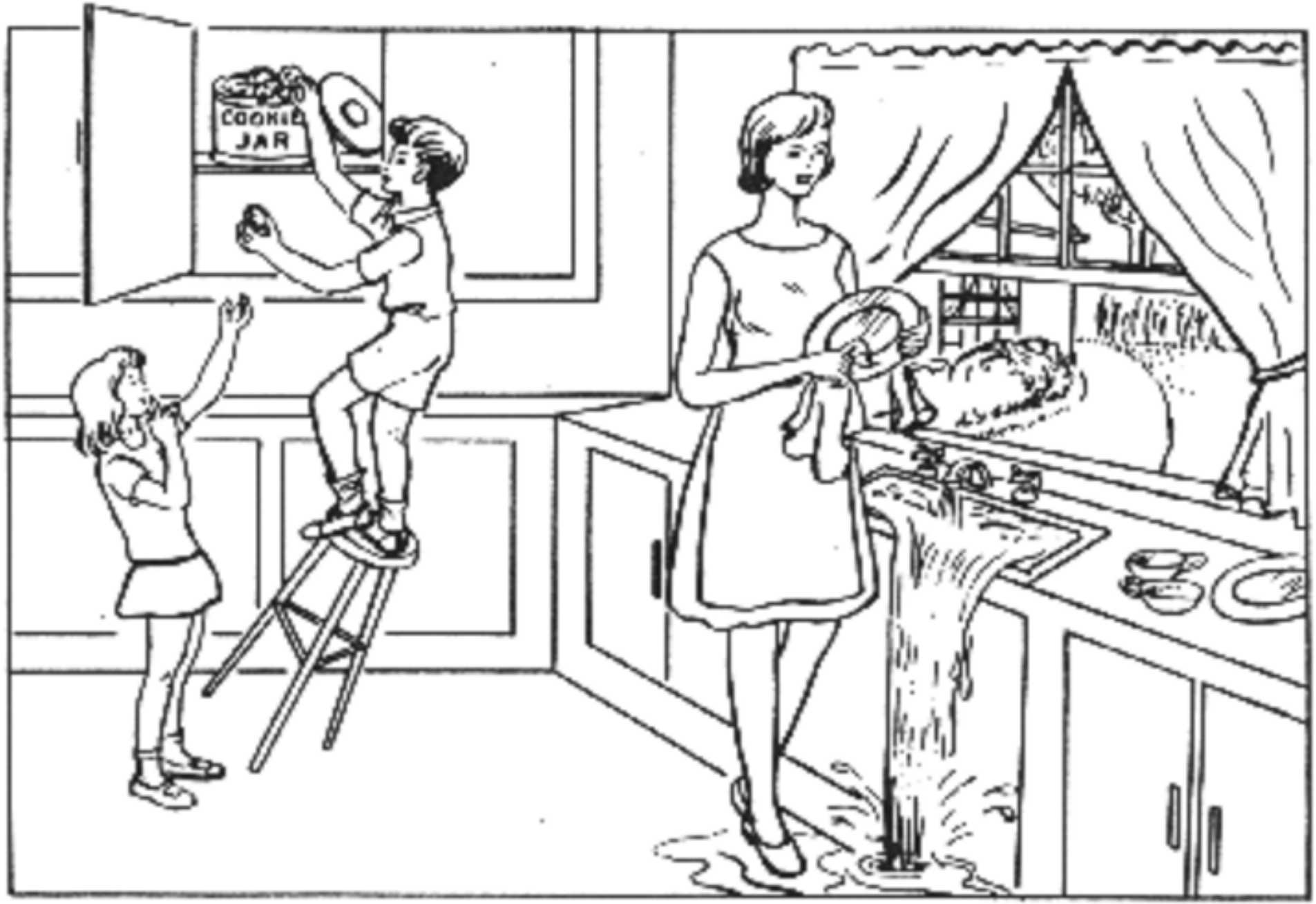
History of Presenting Illness (age 57):

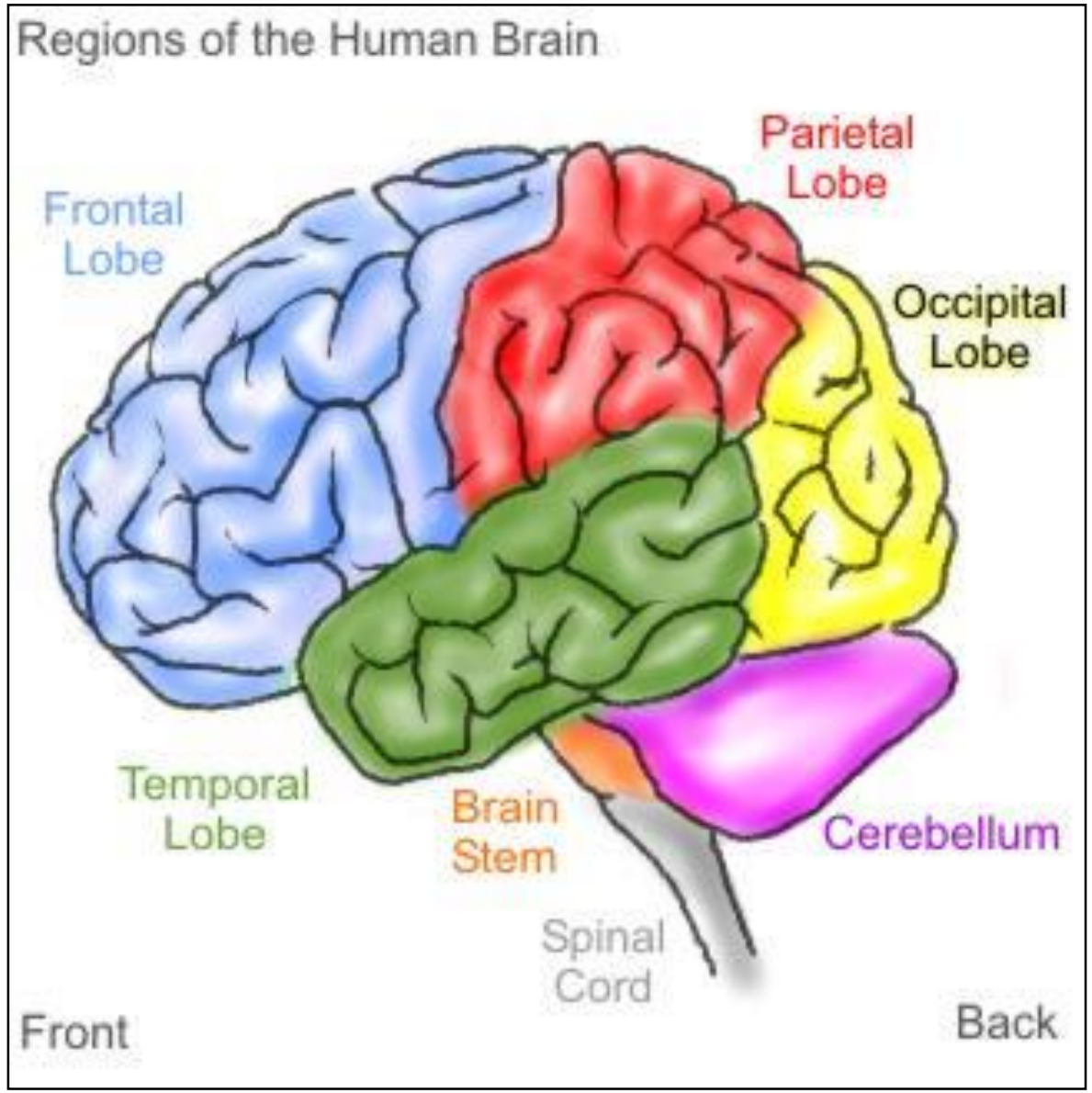
- Insidious onset and gradual decline in speech fluency for two years
- Frequent word-finding difficulties - interrupted verbal output
- Intermittent repetition of what others said
- No loss of word meaning
- No behavioural or personality change
- No neuropsychiatric symptoms
- No memory or visuospatial troubles

Case 1

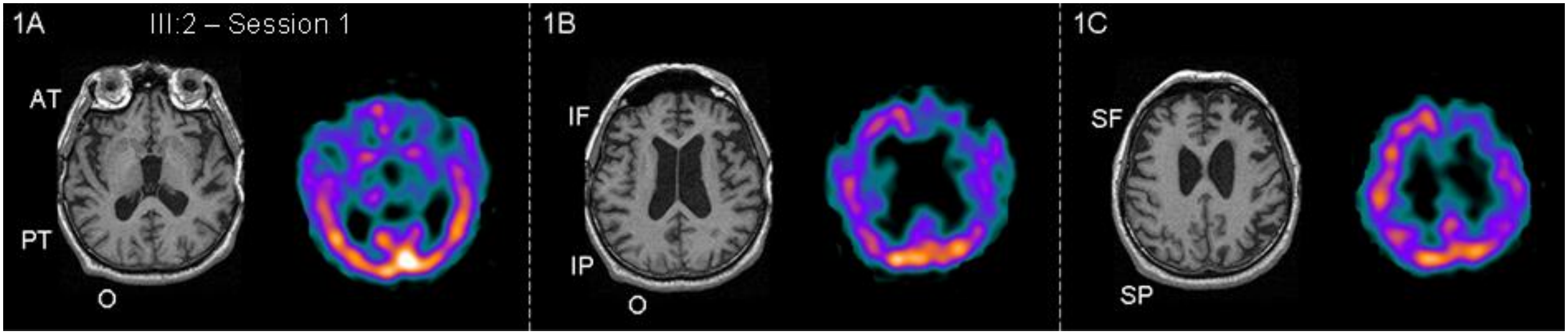
Examination (age 57):

- Mini-Mental State Exam = 22/30 (limited by language issues)
- Behavioural Neurology Assessment-short form:
  - Spontaneous speech output reduced; struggled to find words
  - Comprehension, sentence repetition, naming and reading – intact
  - Ability to generate a list of animals and f-words in 1 min – impaired
  - Written description of cookie theft picture – use of simplified sentences with sparse, but accurate description; agrammatical
  - Mild impairment of working memory and executive functions
- Daily functions – intact except for those reliant on language
- General and neurological exam - normal


COOKIE
JAR


Regions of the Human Brain
Parietal Lobe
Frontal Lobe
Occipital Lobe
Temporal Lobe
Brain Stem
Cerebellum
Spinal Cord
Front
Back

Neuroimaging



What is the clinical diagnosis?

- Primary Progressive Aphasia – Progressive Non-fluent Aphasia (PNFA)

Case 2

Case 2

- Identifying data: 64 y.o. R-handed M; working as managing director; 16 years of education
- Chief complaint: “slowness, apathy, and somnolence”
  - Age at onset 62 y.o.
- Past Medical History:
  - None
- Family history:
  - +ve for FTD

Case 2

History of Presenting Illness (age 64):

- Insidious onset and gradual change in personality and behaviour for two years
- Initially withdrawn; less talkative
- Gave up his hobbies
- Troubles with handling familiar objects
- Months later, social judgement deteriorated:
  - Breakdown in formalities – poor table manners
  - Disinhibited – went outside without his clothes on
  - Irritability when opposed

Case 2

Examination (age 64):

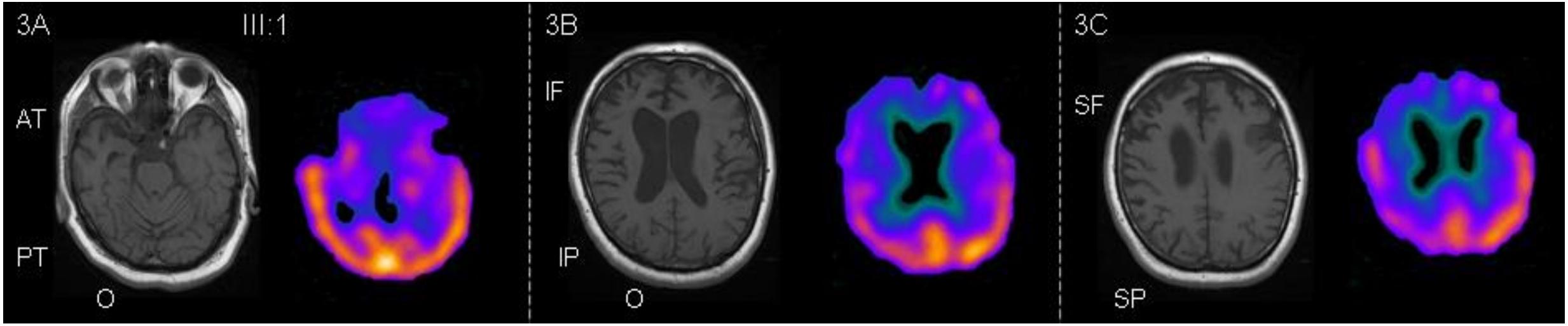
- Cognitive testing:
  - Impaired executive functions
  - Difficulties switching between categories
  - Poor attention
  - Visuospatial difficulties
  - F-word list generation – perseverated on “specific F word”
  - Relatively intact delayed memory
  - Neuropsychiatric Inventory = 23/144
- Impaired daily functions

Case 2

Examination (age 64):

- General exam - normal
- Neurological exam:
  - moderately impaired monotone, slurred speech
  - minimal loss of expression on his face
  - Tremor at rest of upper extremities, moderate in amplitude
  - moderate rigidity/stiffness
  - severe motor slowness of gait
  - multi-step turning with postural instability

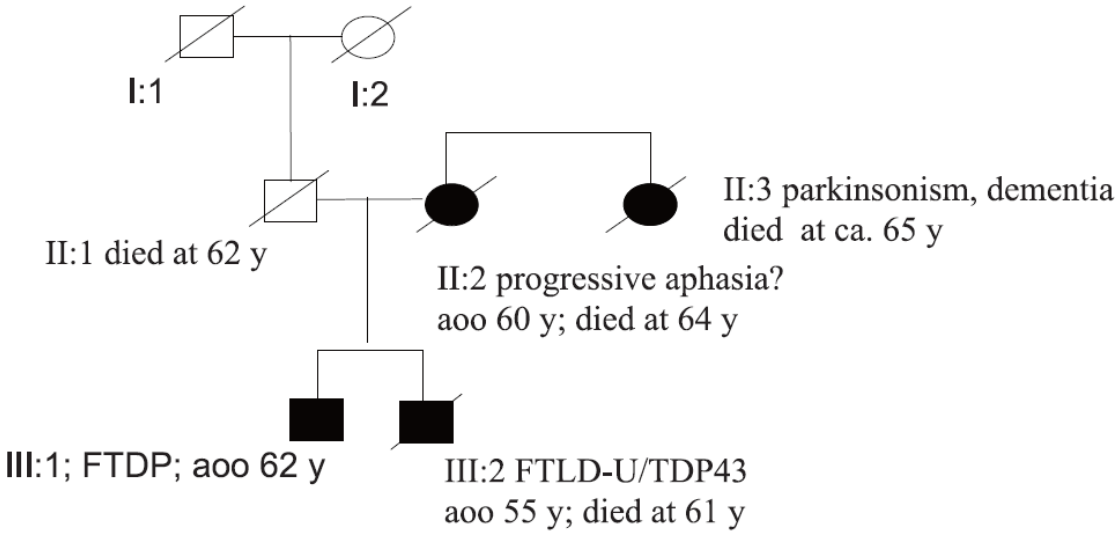
Neuroimaging



What is the clinical diagnosis?

- Behavioural variant FTD with parkinsonism

Family-genetic study



Journal of Alzheimer's Disease 22 (2010) 1123–1133
DOI 10.3233/JAD-2010-101413
IOS Press

Intra-Familial Clinical Heterogeneity due to FTLD-U with TDP-43 Proteinopathy Caused by a Novel Deletion in Progranulin Gene (*PGRN*)

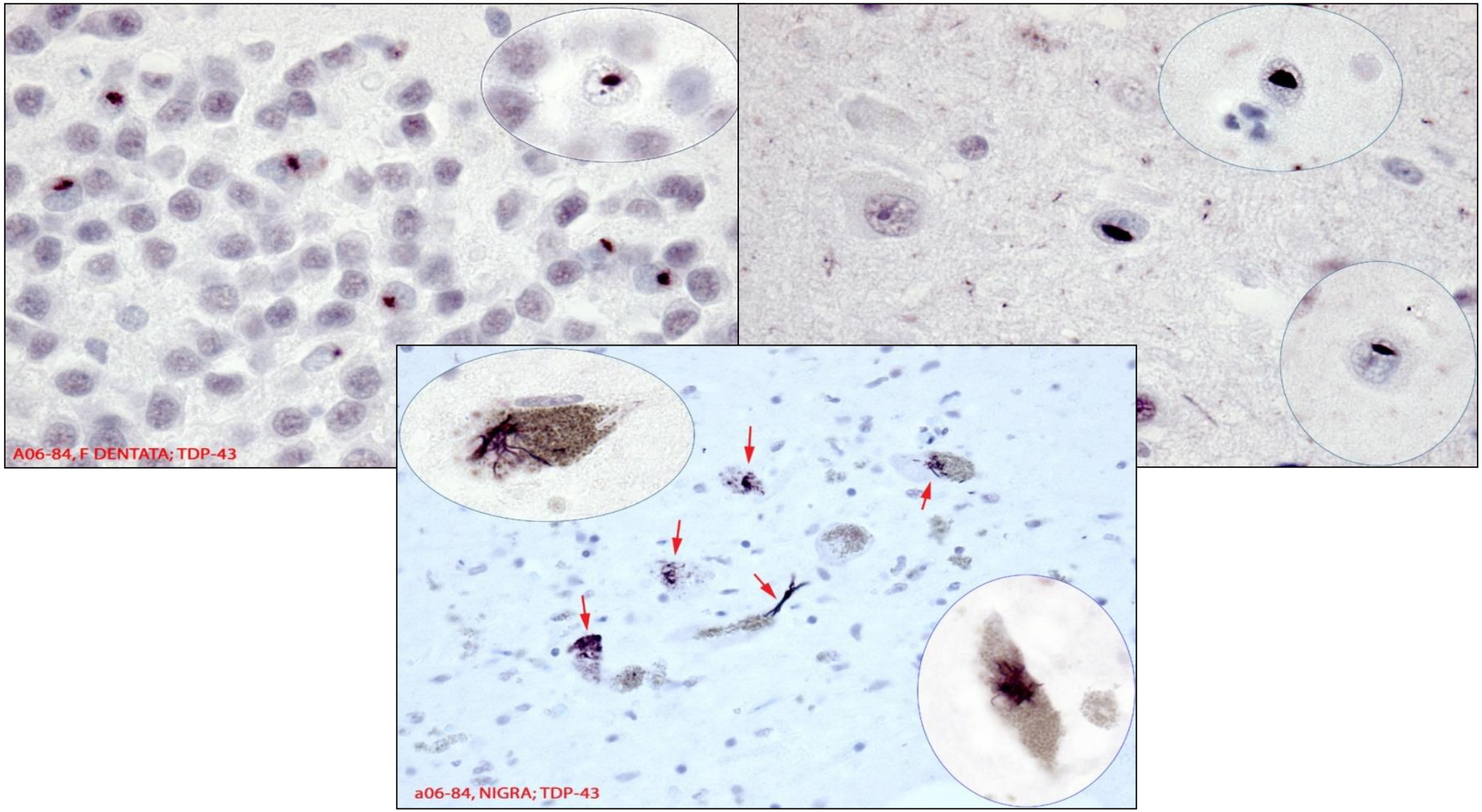
Tomasz Gabryelewicz[a,1], Mario Masellis[b,c,d,1], Mariusz Berdynski[a,1], Juan M. Bilbao[e], Ekaterina Rogaeva[f], Peter St. George-Hyslop[c,f,g], Anna Barczak[a], Krzysztof Czyzewski[a], Maria Barcikowska[a], Zbigniew Wszolek[h], Sandra E. Black[b,c,2,*] and Cezary Zekanowski[a,2]

Novel *GRN* mutation – CA dinucleotide deletion

g.2988_2989delCA, c.1536_1537delCA,
P439_R440fsX6

Pathology

TDP-43 Neuropathology of Case 1



Frontotemporal Dementia

- Second most common cause of dementia under age 65
  - Age At Onset = 45 to 65
- Predominant frontal and/or temporal lobe symptoms:
  - Behavioural variant
  - Language variant (Neary et al., 1998)
- May be associated with motoneuron disease and/or Parkinsonism
- Up to 40% of cases are familial (Seelar et al., 2011)

doi:10.1093/brain/awr179 Brain 2011: 134; 2456–2477 | 2456

BRAIN
A JOURNAL OF NEUROLOGY

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky,[1] John R. Hodges,[2] David Knopman,[3] Mario F. Mendez,[4,5] Joel H. Kramer,[6] John Neuhaus,[7] John C. van Swieten,[8] Harro Seelaar,[8] Elise G. P. Dopper,[8] Chiadi U. Onyike,[9] Argye E. Hillis,[10] Keith A. Josephs,[3] Bradley F. Boeve,[3] Andrew Kertesz,[11] William W. Seeley,[6] Katherine P. Rankin,[6] Julene K. Johnson,[12] Maria-Luisa Gorno-Tempini,[6] Howard Rosen,[6] Caroline E. Prioleau-Latham,[6] Albert Lee,[6] Christopher M. Kipps,[13,14] Patricia Lillo,[2] Olivier Piguet,[2] Jonathan D. Rohrer,[15] Martin N. Rossor,[15] Jason D. Warren,[15] Nick C. Fox,[15] Douglas Galasko,[16,17] David P. Salmon,[16] Sandra E. Black,[18] Marsel Mesulam,[19] Sandra Weintraub,[19] Brad C. Dickerson,[20] Janine Diehl-Schmid,[21] Florence Pasquier,[22] Vincent Deramecourt,[22] Florence Lebert,[22] Yolande Pijnenburg,[23] Tiffany W. Chow,[24,25] Facundo Manes,[26] Jordan Grafman,[27] Stefano F. Cappa,[28,29] Morris Freedman,[24,30] Murray Grossman[1,*] and Bruce L. Miller[6,*]

Table 3 International consensus criteria for behavioural variant FTD (FTDC)

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

The Banana Lady

and other stories of curious behaviour and speech

ANDREW KERTESZ

Classification of primary progressive aphasia and its variants

M.L. Gorno-Tempini, MD, PhD
A.E. Hillis, MD
S. Weintraub, PhD
A. Kertesz, MD
M. Mendez, MD
S.F. Cappa, MD
J.M. Ogar, MS
J.D. Rohrer, MD
S. Black, MD
B.F. Boeve, MD
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N.F. Dronkers, PhD
R. Vandenberghe, MD, PhD
K. Rascovsky, PhD
K. Patterson, PhD
B.L. Miller, MD
D.S. Knopman
J.R. Hodges, MD*
M.M. Mesulam, MD*
M. Grossman, MD*

Neurology® 2011;76:1006-1014

Table 2 Diagnostic features for the nonfluent/agrammatic variant PPA

I. Clinical diagnosis of nonfluent/agrammatic variant PPA
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

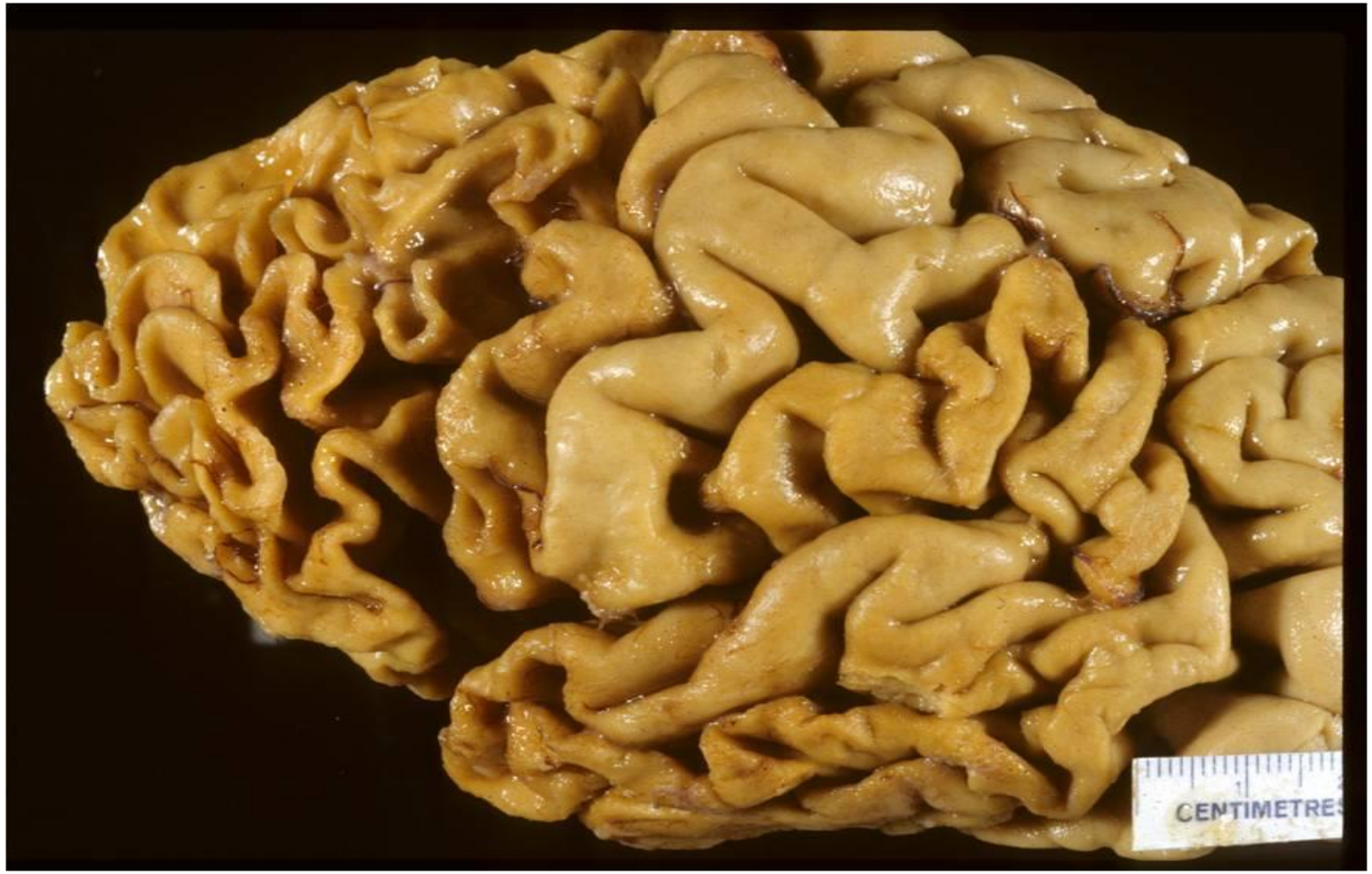
Table 3 Diagnostic criteria for the semantic variant PPA

I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

How common is FTD?

- Prevalence ranges from 0.01 to 4.61 per 1000
  - 2.7% (range 0-9.1%) of all dementia cases older than 65 years of age
  - 10.2% (2.8-15.7%) in those younger than 65 and approaches the prevalence of Alzheimer's disease in this age group
- Incidence rate 0.00 to 0.33 per 1000 person-years
- Behavioural variant presentation is 4 times more common than the language variant (Hogan et al., 2016)
- Rare disease but impact to society is huge

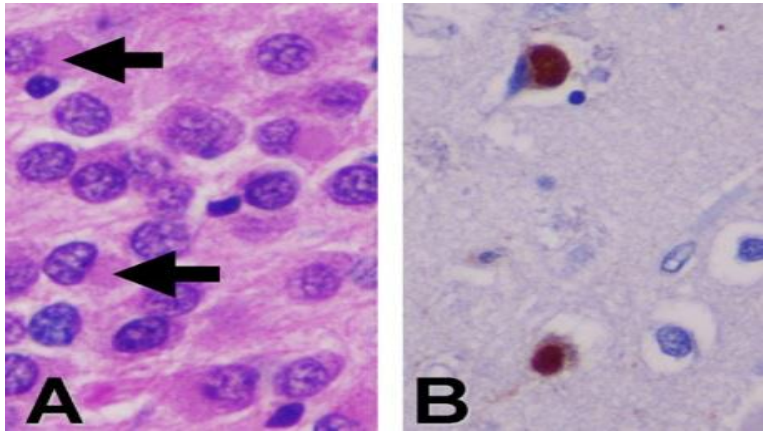
Frontotemporal shrinkage



Genetics of FTD and neuropathology

Tauopathies

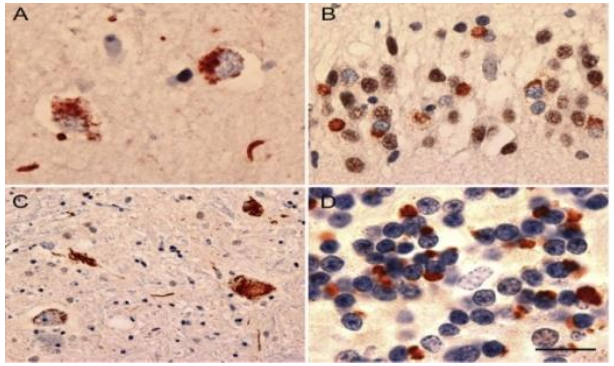
MAPT mutations



Montine et al., 2014

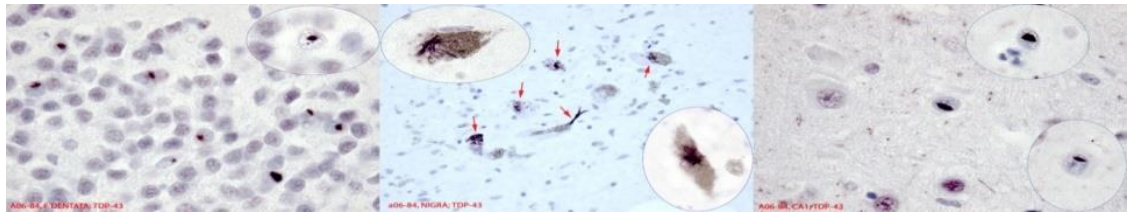
TDP43 proteinopathies

C9orf72 G_4C_2 repeat expansions



DeJesus-Hernandez et al., 2011

GRN mutations



doi:10.1038/nature05016

LETTERS

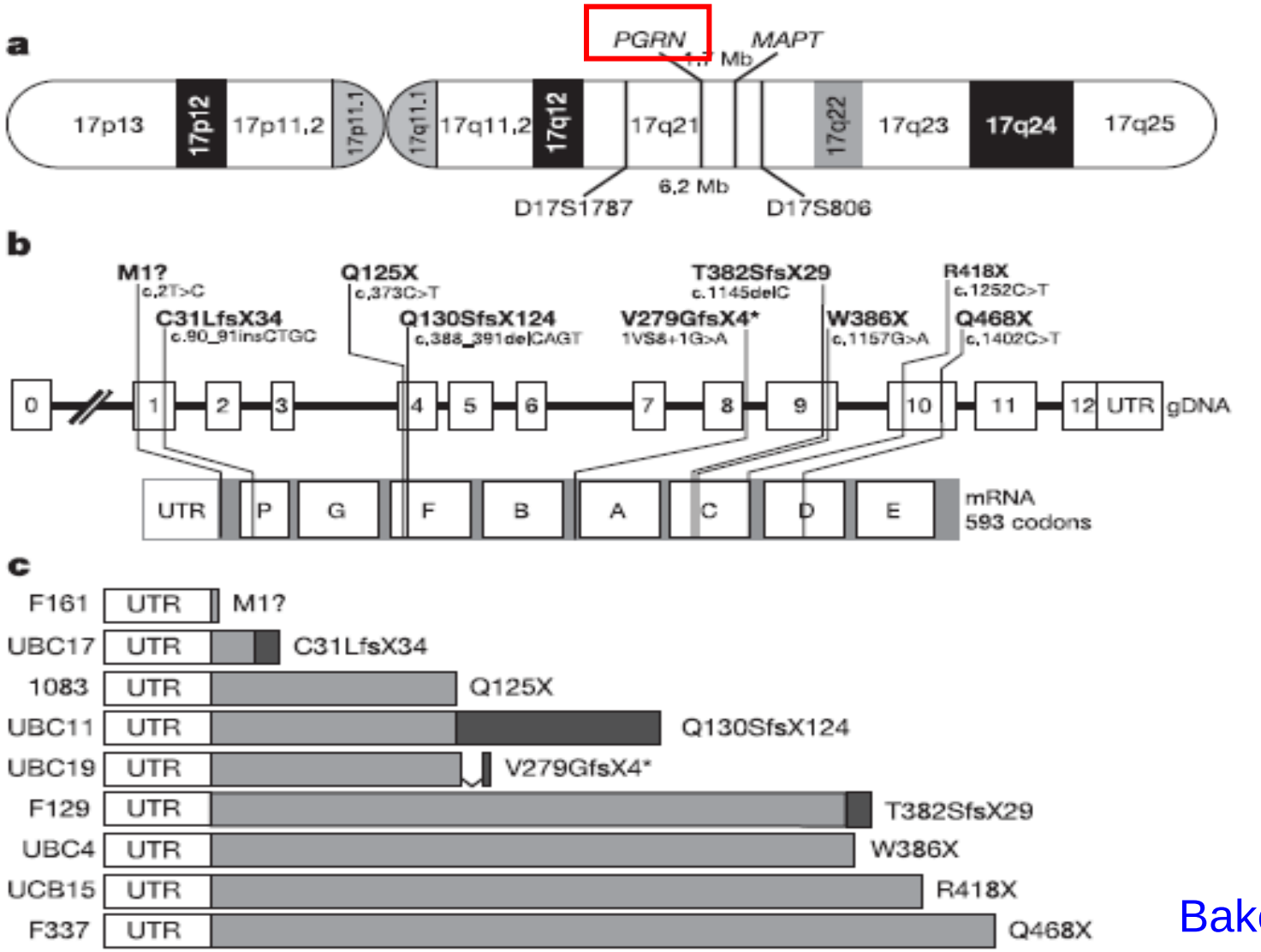
Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17

Matt Baker[1]*, Ian R. Mackenzie[2]*, Stuart M. Pickering-Brown[5,6]*, Jennifer Gass[1], Rosa Rademakers[1], Caroline Lindholm[3], Julie Snowden[6], Jennifer Adamson[1], A. Dessa Sadovnick[3,4], Sara Rollinson[5], Ashley Cannon[1], Emily Dwosh[4], David Neary[6], Stacey Melquist[1], Anna Richardson[6], Dennis Dickson[1], Zdenek Berger[1], Jason Eriksen[1], Todd Robinson[1], Cynthia Zehr[1], Chad A. Dickey[1], Richard Crook[1], Eileen McGowan[1], David Mann[6], Bradley Boeve[7], Howard Feldman[3] & Mike Hutton[1]

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

GRN-related FTD



Baker et al., 2006

Granulin (GRN)

Central Nervous System (Ahmed et al., 2007)

- Involved in embryonic forebrain development
- GRN - neurotrophic factor to promote growth of certain neuronal cells (Van Damme et al., 2008; Gass et al., 2012)
- Produced by activated microglia and may play a role in neuroinflammation → Granulins (Gass et al., 2012)

- Reduced GRN from haploinsufficiency is the likely cause of FTD

doi:10.1093/brain/awl276 *Brain* (2006), **129**, 3115–3123

Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome

Mario Masellis,[1,2,*] Parastoo Momeni,[7*] Wendy Meschino,[6] Reid Heffner Jr,[8] Joshua Elder,[7] Christine Sato,[3] Yan Liang,[3] Peter St George-Hyslop,[2,3,4] John Hardy,[7] Juan Bilbao,[5] Sandra Black[1,2] and Ekaterina Rogaeva[2,3]

The study of presymptomatic mutation carriers compared to non-carriers affords a unique opportunity to understand more about the natural history of genetic frontotemporal dementia during the preclinical phases.

Biomarkers

Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis

Jonathan D Rohrer, Jennifer M Nicholas, David M Cash, John van Swieten, Elise Dopper, Lize Jiskoot, Rick van Minkelen, Serge A Rombouts, M Jorge Cardoso, Shona Clegg, Miklos Espak, Simon Mead, David L Thomas, Enrico De Vita, Mario Masellis, Sandra E Black, Morris Freedman, Ron Keren, Bradley J MacIntosh, Ekaterina Rogaeva, David Tang-Wai, Maria Carmela Tartaglia, Robert Laforce Jr, Fabrizio Tagliavini, Pietro Tiraboschi, Veronica Redaelli, Sara Prioni, Marina Grisoli, Barbara Borroni, Alessandro Padovani, Daniela Galimberti, Elio Scarpini, Andrea Arighi, Giorgio Fumagalli, James B Rowe, Ian Coyle-Gilchrist, Caroline Graff, Marie Fallström, Vesna Jelic, Anne Kinhult Ståhlbom, Christin Andersson, Håkan Thonberg, Lena Lilius, Giovanni B Frisoni, Michela Pievani, Martina Bocchetta, Luisa Benussi, Roberta Ghidoni, Elizabeth Finger, Sandro Sorbi, Benedetta Nacmias, Gemma Lombardi, Cristina Polito, Jason D Warren, Sebastien Ourselin, Nick C Fox, Martin N Rossor

Lancet Neurol 2015

Case 3

Neurobiology of Aging 62 (2018) 245.e9–245.e12

Contents lists available at ScienceDirect

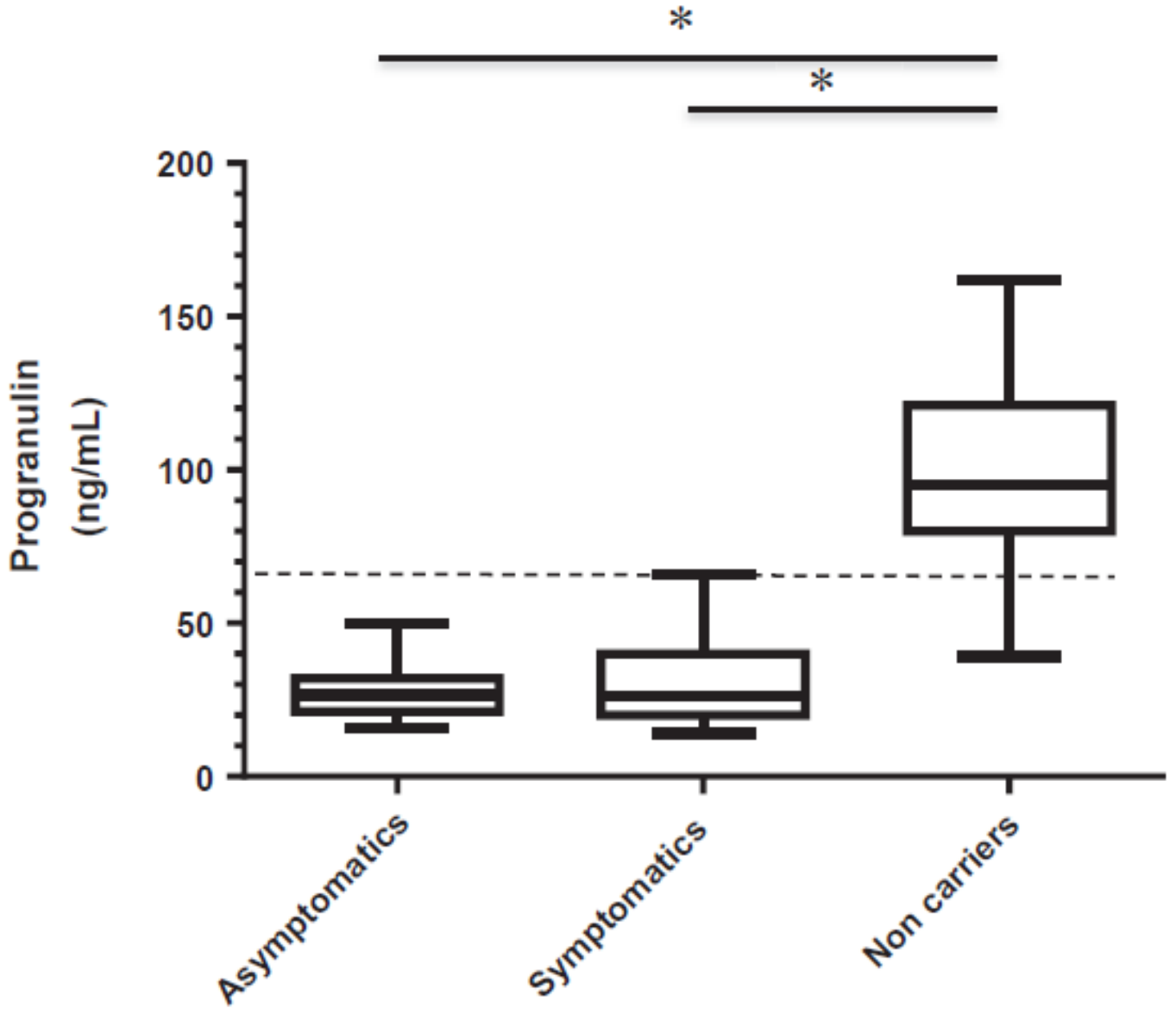
Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Progranulin plasma levels predict the presence of *GRN* mutations in asymptomatic subjects and do not correlate with brain atrophy: results from the GENFI study

Daniela Galimberti [a,*], Giorgio G. Fumagalli [a,b,1], Chiara Fenoglio [a,1], Sara M.G. Cioffi [a], Andrea Arighi [a], Maria Serpente [a], Barbara Borroni [c], Alessandro Padovani [c], Fabrizio Tagliavini [d], Mario Masellis [e], Maria Carmela Tartaglia [e], John van Swieten [f], Lieke Meeter [f], Caroline Graff [g,h], Alexandre de Mendonça [i], Martina Bocchetta [j], Jonathan D. Rohrer [j], Elio Scarpini [a], on behalf of the Genetic FTD Initiative (GENFI)[2]

Plasma GRN levels in *GRN* mutation carriers



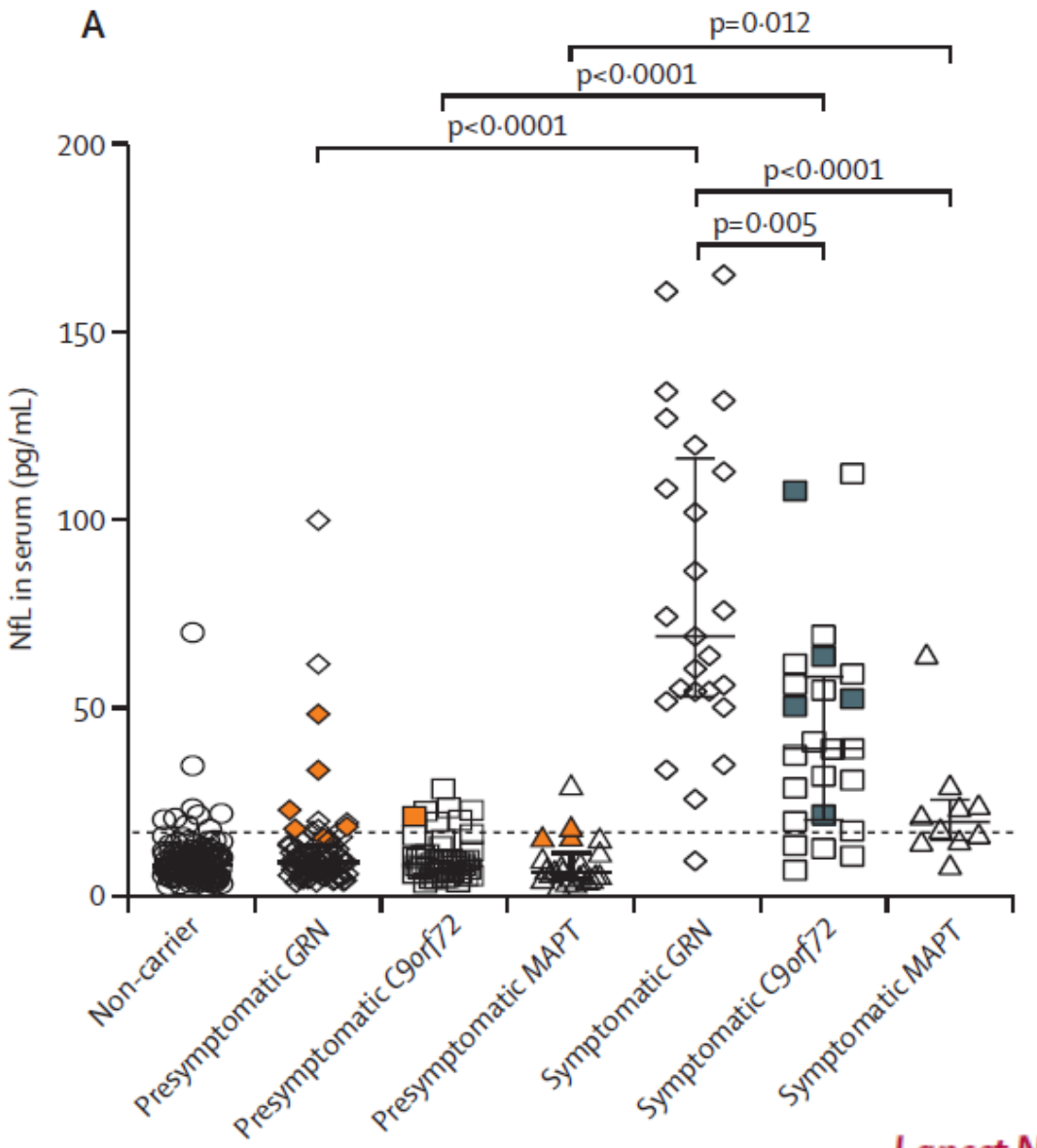
D. Galimberti et al. / Neurobiology of Aging 62 (2018) 245.e9–245.e12

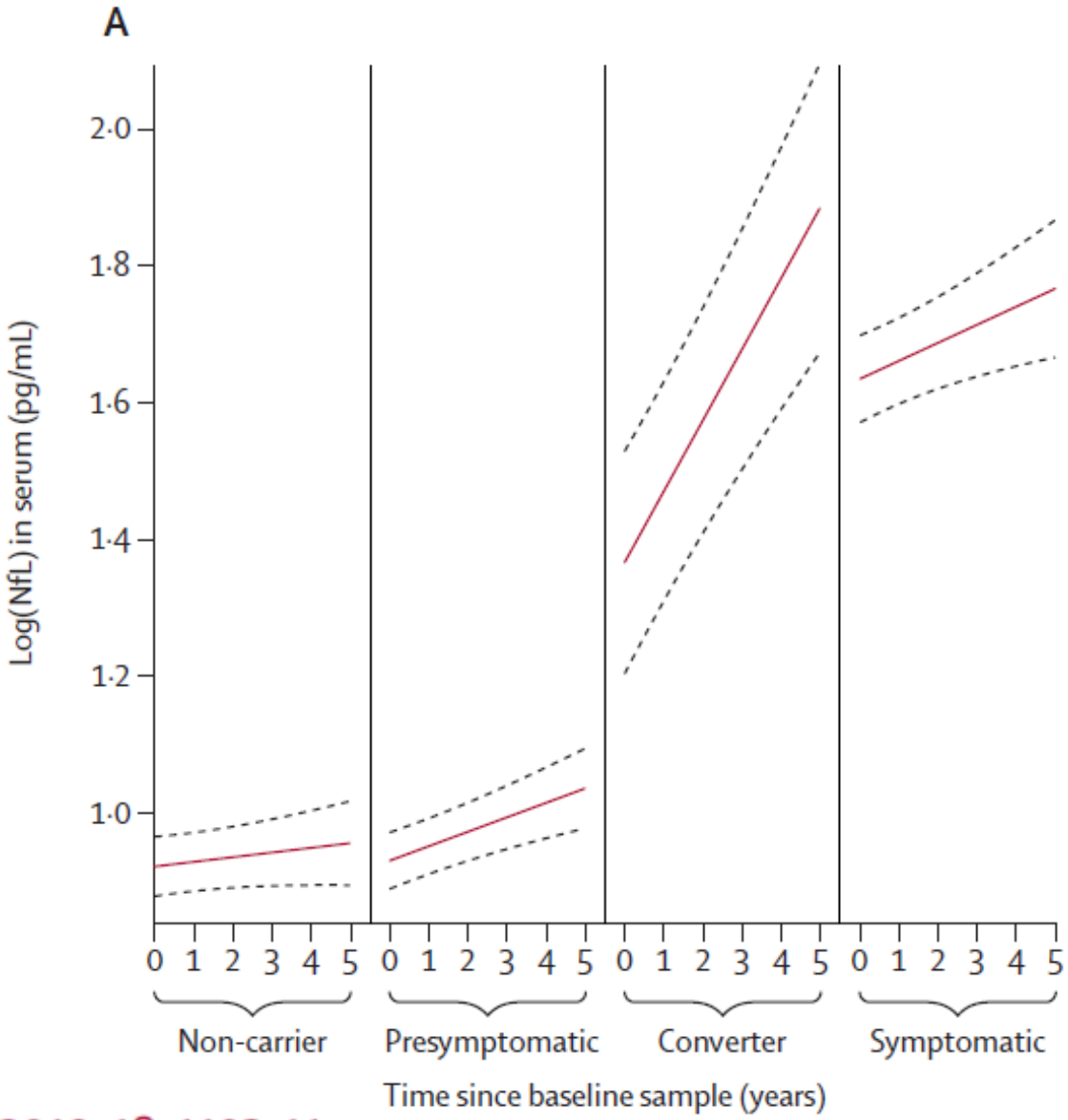
Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study

*Emma L van der Ende, Lieke H Meeter, Jackie M Poos, Jessica L Panman, Lize C Jiskoot, Elise G P Dopper, Janne M Papma, Frank Jan de Jong, Inge M W Verberk, Charlotte Teunissen, Dimitris Rizopoulos, Carolin Heller, Rhian S Convery, Katrina M Moore, Martina Bocchetta, Mollie Neason, David M Cash, Barbara Borroni, Daniela Galimberti, Raquel Sanchez-Valle, Robert Laforce Jr, Fermin Moreno, Matthis Synofzik, Caroline Graff, Mario Masellis, Maria Carmela Tartaglia, James B Rowe, Rik Vandenberghe, Elizabeth Finger, Fabrizio Tagliavini, Alexandre de Mendonça, Isabel Santana, Chris Butler, Simon Ducharme, Alex Gerhard, Adrian Danek, Johannes Levin, Markus Otto, Giovanni B Frisoni, Stefano Cappa, Yolande A L Pijnenburg, Jonathan D Rohrer, John C van Swieten, on behalf of the Genetic Frontotemporal dementia Initiative (GENFI)**

Lancet Neurol 2019; 18: 1103–11

Serum neurofilament light chain in genetic FTD: A promising biomarker





Lancet Neurol 2019; 18: 1103–11

Treatments

Treatment of FTD

- There are no drugs approved specifically for use in managing the symptoms
- There is limited evidence that selective serotonin reuptake inhibitor antidepressants can help with behavioural and mood symptoms
- In cases of extreme behavioural symptoms, antipsychotics could also be considered
- There are no disease-modifying or curative therapies available

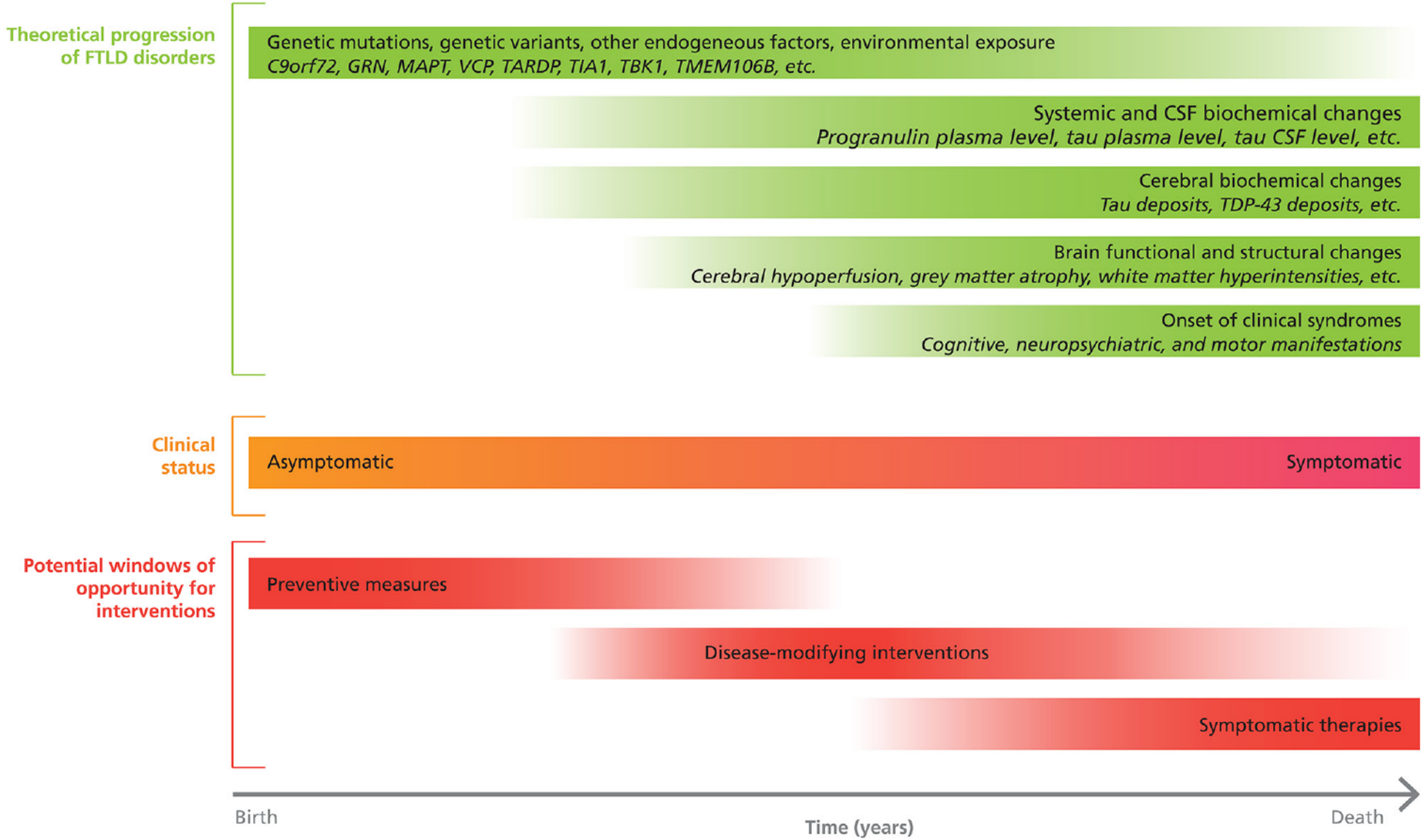
Tsai and Boxer, 2016

REVIEW

Therapeutic trial design for frontotemporal dementia and related disorders

Philippe Desmarais,[1,2,3,4] Jonathan D Rohrer,[5] Quoc Dinh Nguyen,[6] Nathan Herrmann,[7] Donald T Stuss,[3,4,8,9] Anthony E Lang,[4,10] Adam L Boxer,[11] Bradford C Dickerson,[12] Howie Rosen,[11] John Cornelis van Swieten,[13] Lieke H Meeter,[13] Barbara Borroni,[14] Maria Carmela Tartaglia,[4,10,15] Howard H Feldman,[16,17] Sandra E Black,[2,3,4,15] Mario Masellis[1,2,3,4,15]

Desmarais P, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**90**:412–423. doi:10.1136/jnnp-2018-318603

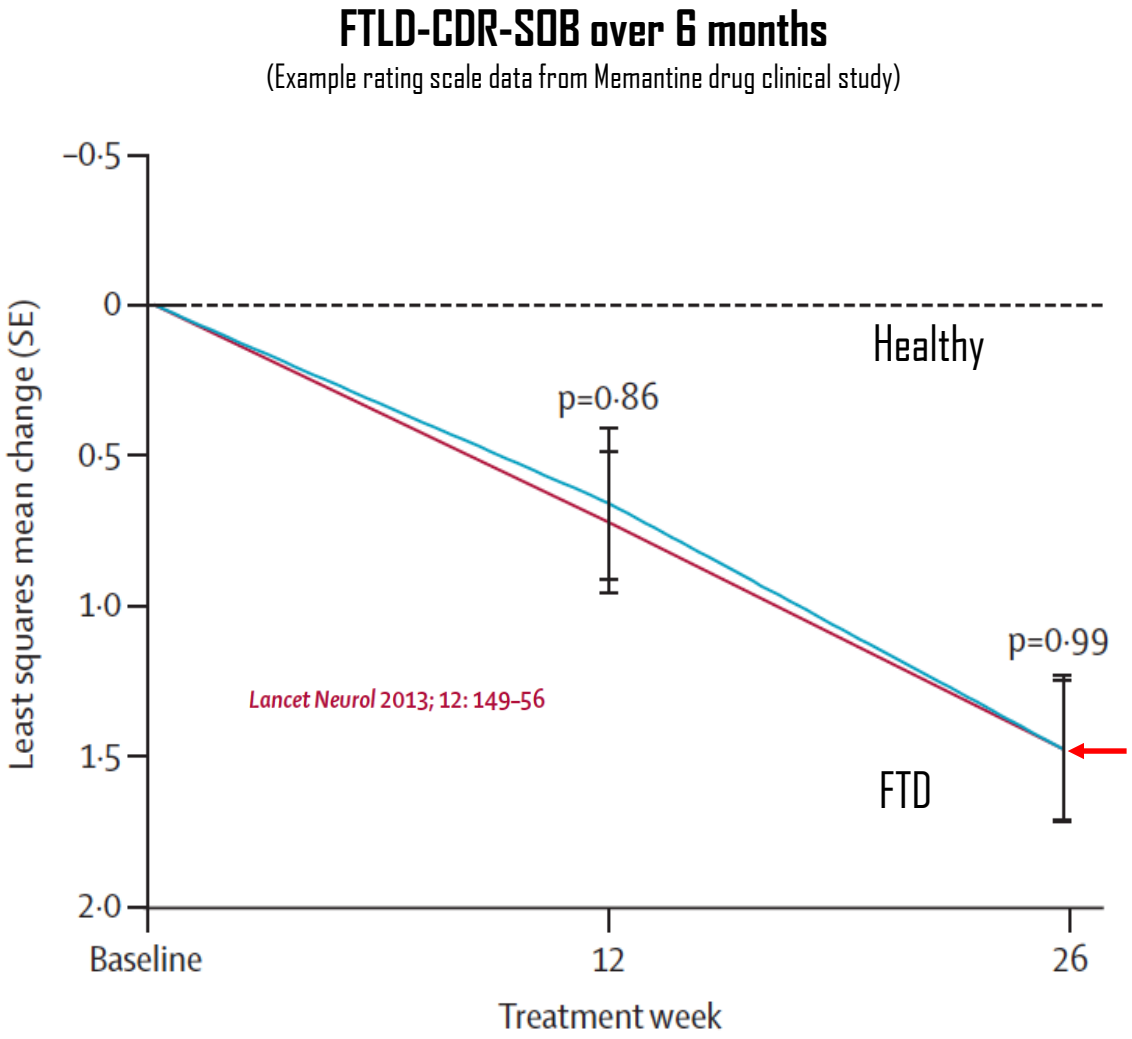

Theoretical progression of FTLD disorders
Genetic mutations, genetic variants, other endogeneous factors, environmental exposure
C9orf72, GRN, MAPT, VCP, TARDP, TIA1, TBK1, TMEM106B, etc.
Systemic and CSF biochemical changes
Progranulin plasma level, tau plasma level, tau CSF level, etc.
Cerebral biochemical changes
Tau deposits, TDP-43 deposits, etc.
Brain functional and structural changes
Cerebral hypoperfusion, grey matter atrophy, white matter hyperintensities, etc.
Onset of clinical syndromes
Cognitive, neuropsychiatric, and motor manifestations
Clinical status
Asymptomatic
Symptomatic
Potential windows of opportunity for interventions
Preventive measures
Disease-modifying interventions
Symptomatic therapies
Birth
Time (years)
Death

Outcome measures: CDR-FTLD

Section 1: Clinical Dementia Rating (CDR) Instrument

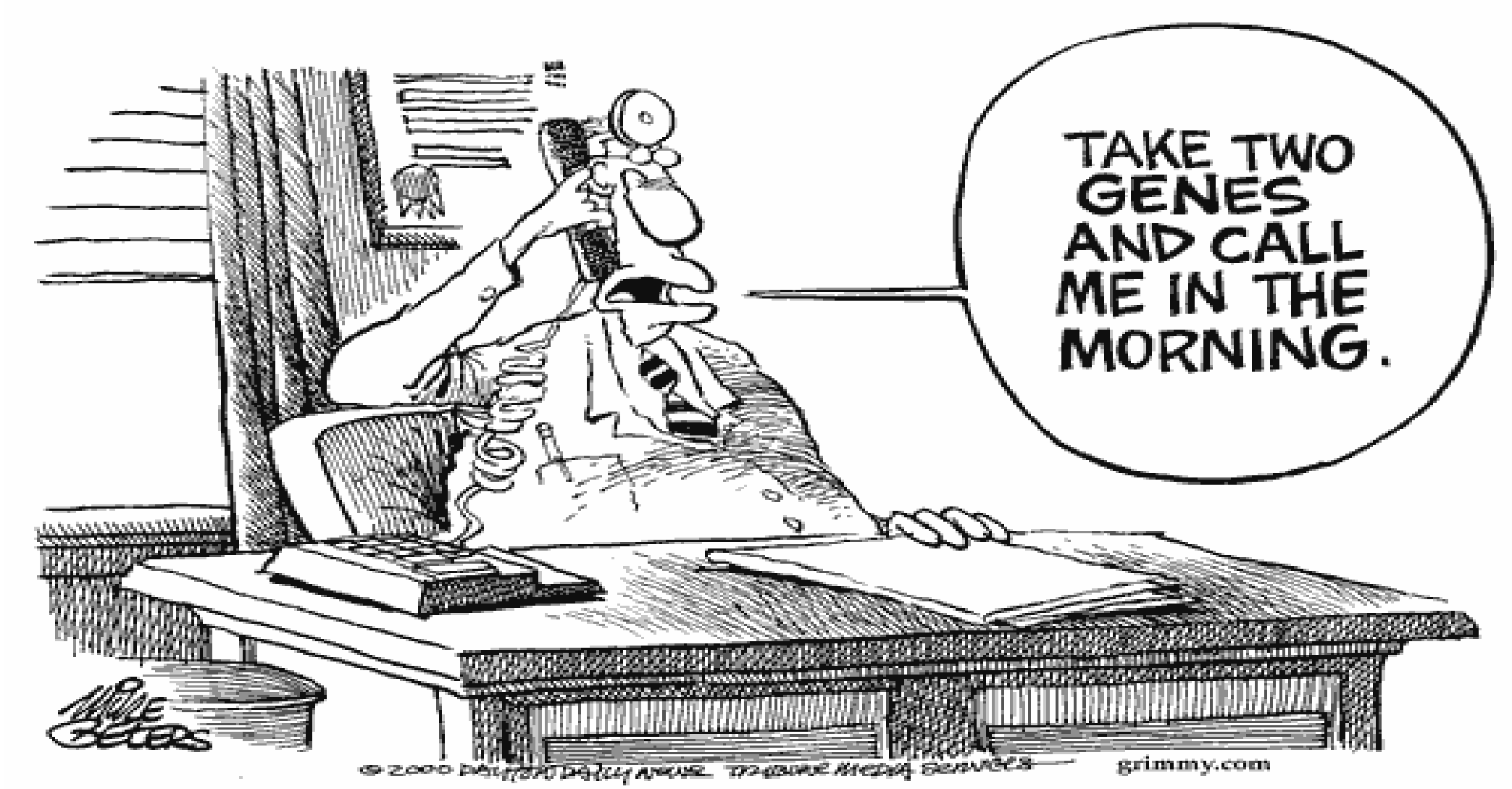
Section 2: Frontotemporal lobar degeneration (FTLD) behaviour & language domains

Change in both FTLD-CDR-SOB is rapid and dramatic



Conclusions

- FTD is a devastating disorder affecting patients and families during the prime of their lives, often in the height of their career and as they are raising young children
- It progresses relentlessly until death
- *GRN*-related FTD is particularly aggressive and affords an opportunity for targeting individuals during the presymptomatic phase
- Several clinical measures and biomarkers are available that can be used as outcome measures in clinical trials
- Natural history data from GENFI and ALLFTD will enhance the design of these clinical trials increasing the chances for success


TAKE TWO GENES AND CALL ME IN THE MORNING.
grimmy.com

Acknowledgements

- Henk-Jan Mutsaerts
- Bradley MacIntosh
- David M. Cash
- Martina Bocchetta
- David Thomas
- Katrina M Dick
- John van Swieten
- Barbara Borroni
- Daniela Galimberti
- Maria Carmela Tartaglia
- James Rowe
- Caroline Graff
- Fabrizio Tagliavini
- Giovanni Frisoni
- Robert Laforce Jr
- Elizabeth Finger
- Alexandre de Mendonça
- Sandro Sorbi
- Martin N Rossor
- Sebastien Ourselin
- Jonathan D Rohrer

GENFI Participants

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Sunnybrook RESEARCH INSTITUTE

WESTON BRAIN INSTITUTE

GENFI GENETIC FTD INITIATIVE

CIHR STAGE Strategic Training for Advanced Genetic Epidemiology

UK Medical Research Council
The Italian Ministry of Health

Alzheimer Society CANADA

AL001:
Scientific overview

Presenting:
Arnon Rosenthal, Ph.D.
Chief Executive Officer, Alector

AL001: In Phase 2 for frontotemporal dementia, a fast progressing degenerative brain disease with no treatment

AL001	**Target**: Progranulin (PGRN), regulator of microglial activity **Product candidate**: An antibody that is designed to increase PGRN levels **Status**: Phase 2 clinical trial ongoing, clinical PoC 1H 2020

- Initially targeting a monogenic patient population suffering from FTD (FTD-GRN)
  - ~15,000 patients with GRN mutations in US+EU with potential expansion to sporadic FTD and ALS
- Program supported by relevant biomarkers
- Expect to start Phase 3 in 2020

Orphan drug & Fast Track designation from FDA

Scientific Rationale: PGRN deficiency causal for dementia and FTD

Goal: Increase PGRN in brains of FTD patients

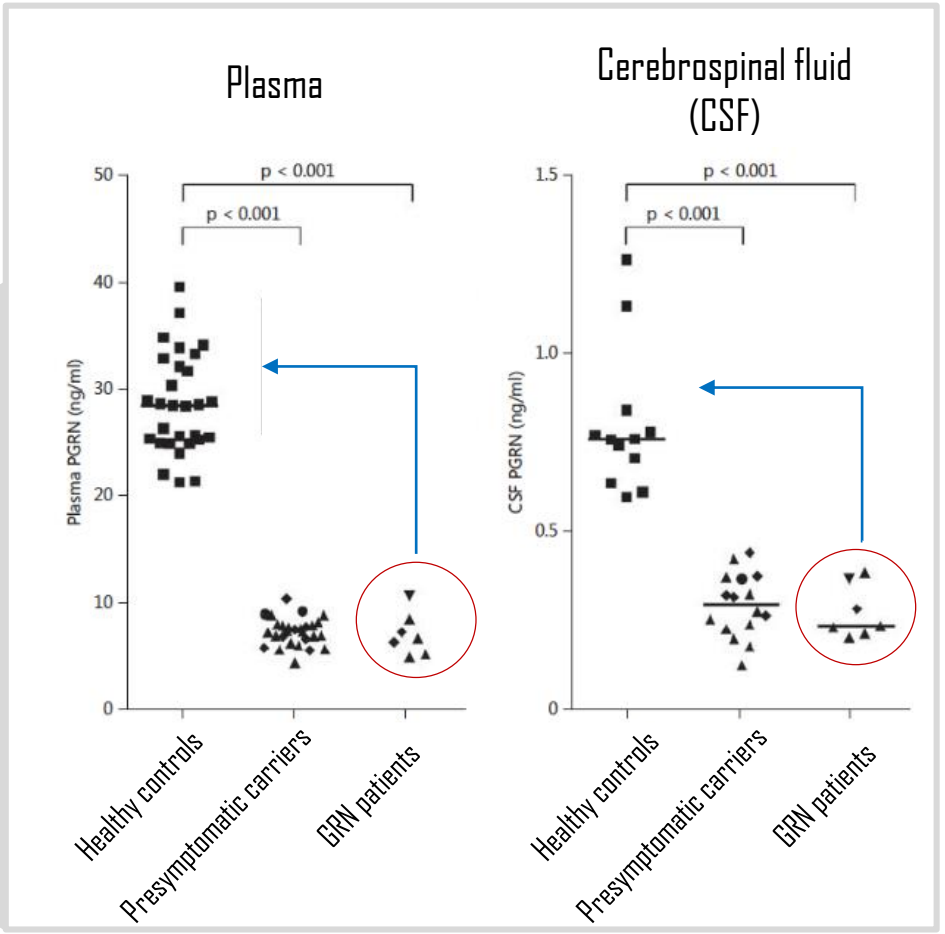
Homozygous mutations

- 100% decrease in PGRN levels
- Results in dementia, cerebellar atrophy, vision loss, epilepsy, death

Heterozygous mutations

- >50% decrease in PGRN levels
- FTD with >90% penetrance
- Onset of symptoms at ~58 years old, rapidly progressive, death within 7-10 years

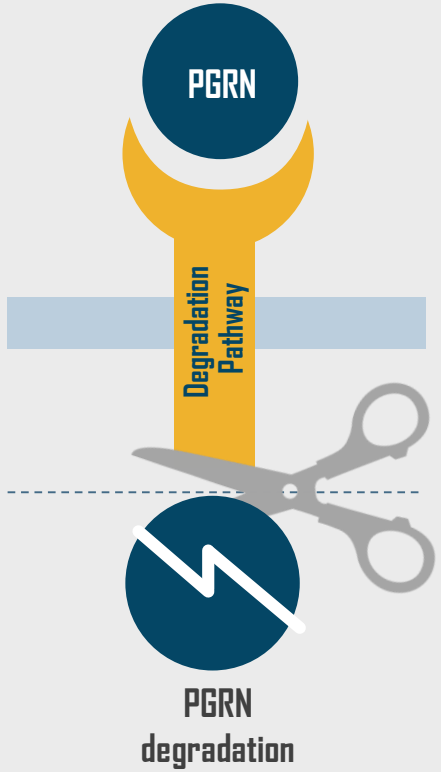
PGRN levels are reduced in FTD patients

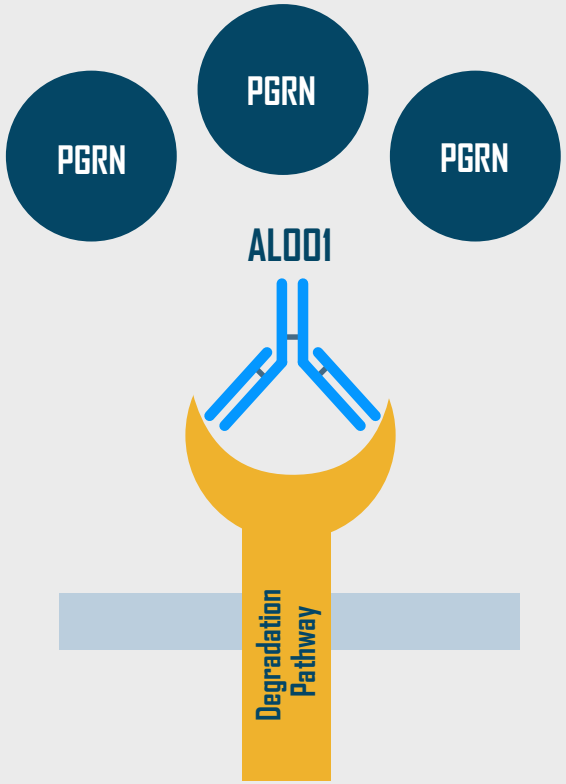


Dement Geriatr Cogn Disord Extra 2016;6:330-340; Eur J Neurol. 2013 Dec;20(12):1571-3; Gene. 2014 Jun 1;542(2):141-5; Sci Transl Med. 2017 Apr 12;9(385)

AL001 is an antibody product candidate designed to provide therapeutic levels of PGRN

Counteracting decreased production of PGRN by increasing its half life



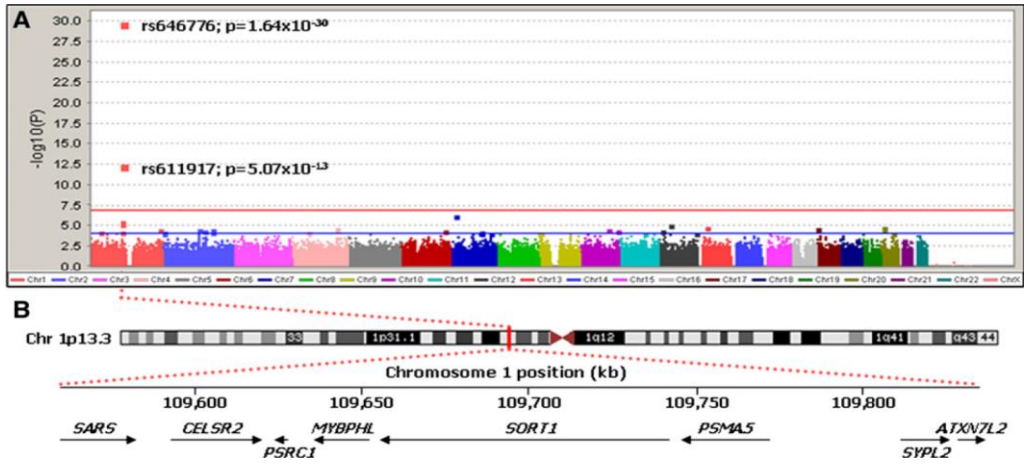


Our Approach:

- Increase PGRN level by blocking its degradation
- Restores PGRN to physiological levels in FTD patients

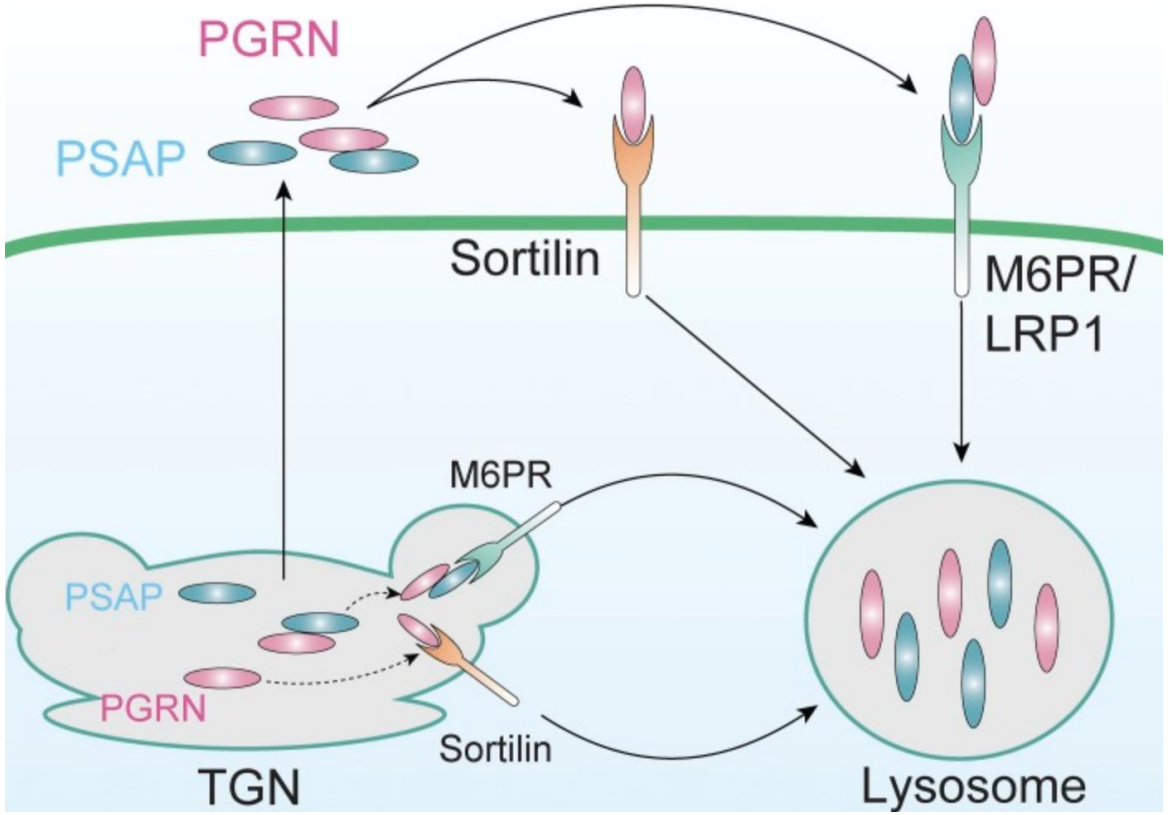
SORTILIN: A degradation but not an essential signaling receptor for PGRN

- SORT1 is receptor that degrades PGRN
- Expression of SORT1 inversely correlates with PGRN
- Lower levels of SORT1 not reported to be associated with adverse effects



Carrasquillo et al, AJHJ 2010

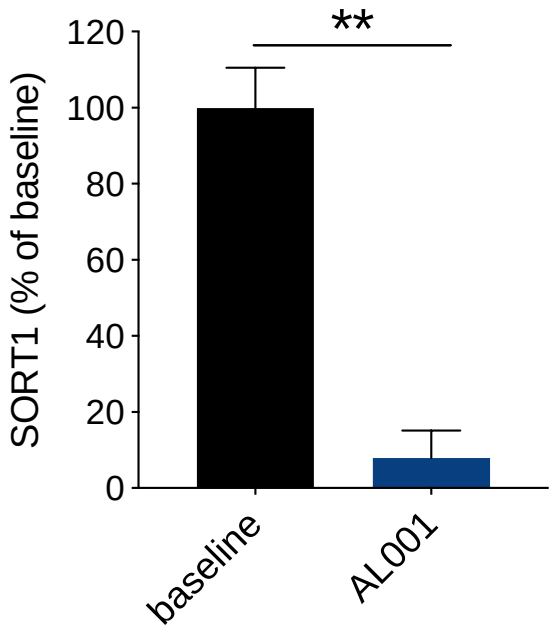
PGRN has multiple access routes to the lysosome



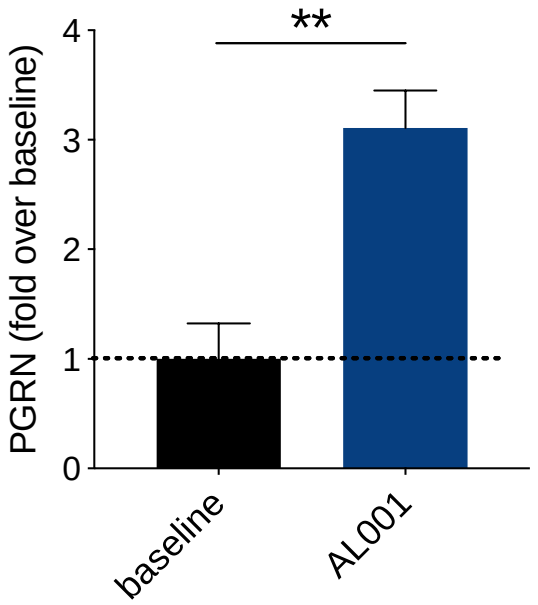
J. Cell Biol. Vol. 210 No. 6 991–1002

AL001 shown to increase PGRN in non-human primates (NHP)

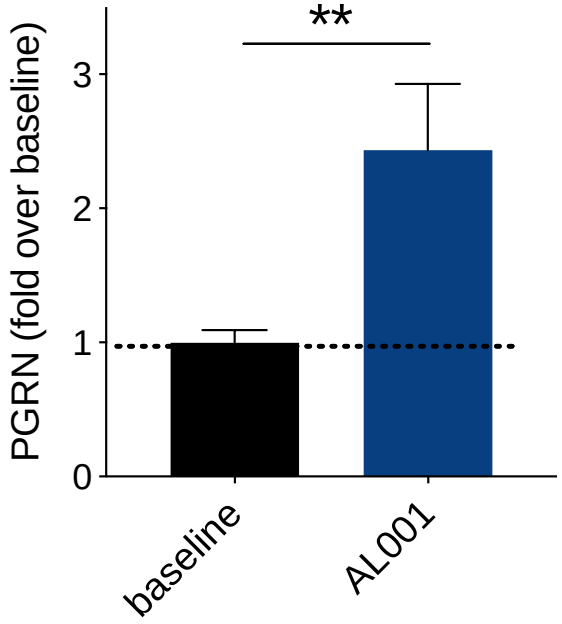
Blockade of functional SORT1



Significant increase in plasma PGRN

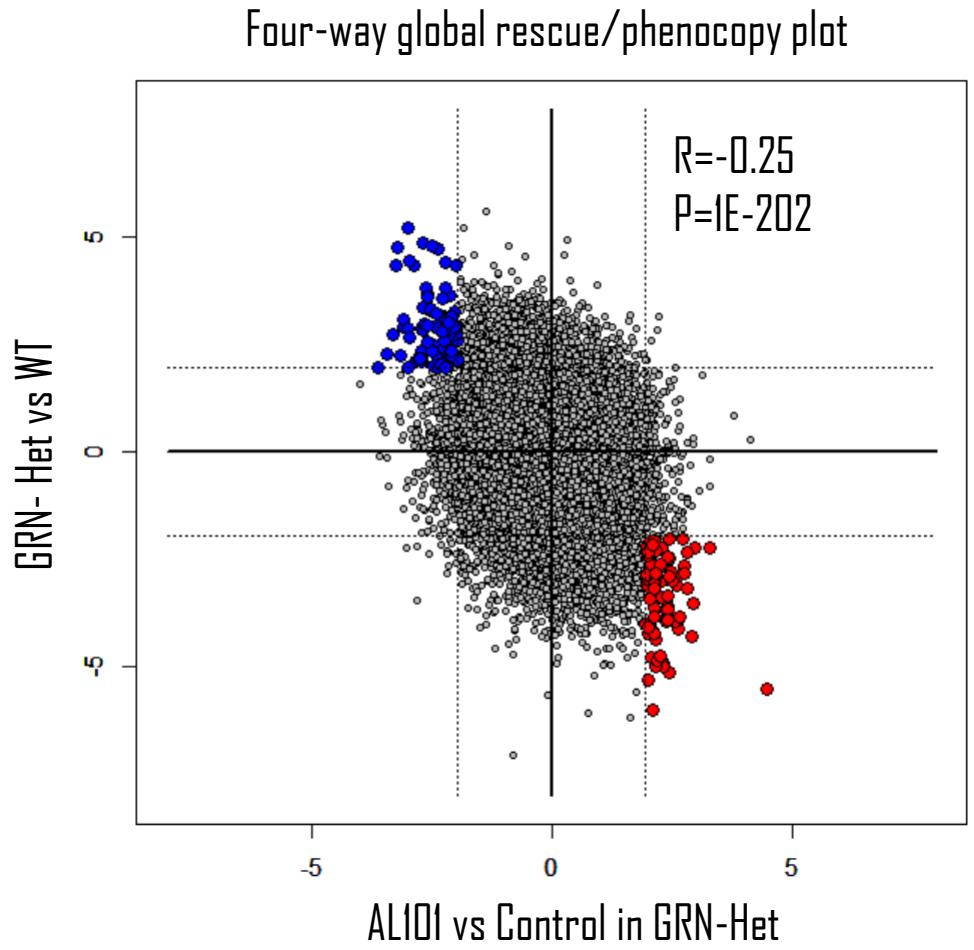


Significant increase in CSF PGRN



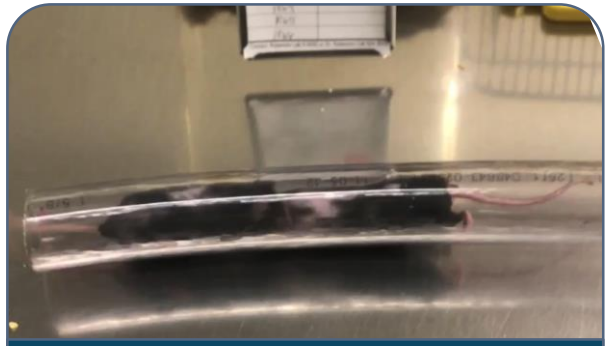
** indicates p< 0.01 by T-test.

Our antibodies counteract disease gene signature in the rodent FTD model



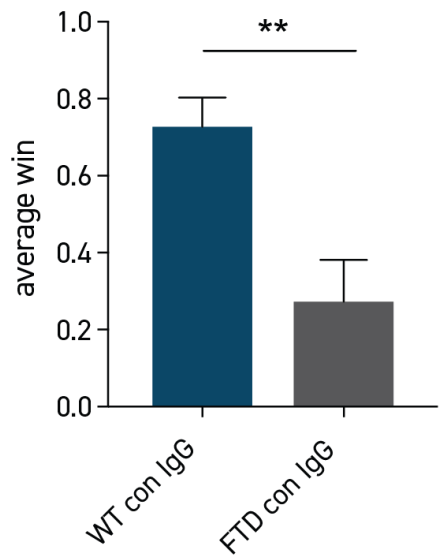
- AL001 down regulates transcripts that are up regulated in FTD (blue)
- AL001 up regulates transcripts that are down regulated in FTD (red)

Our antibodies rescue behavioral deficit in aged FTD mice

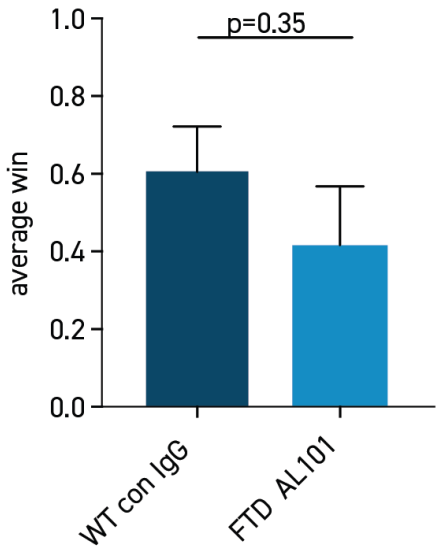


Our antibodies rescue behavioral deficit in FTD-GRN mice

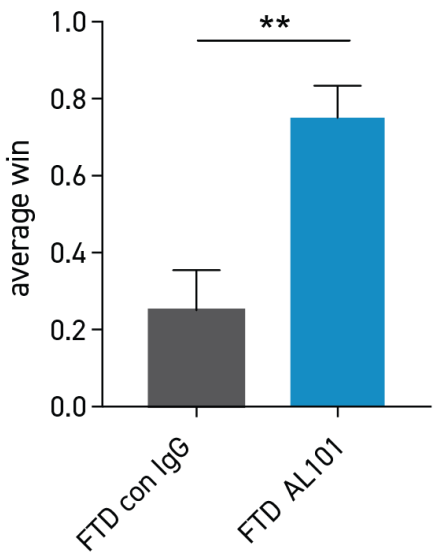
After 4 weeks of treatment



Control treated FTD mice lost majority of matches against control treated WT mice



Drug treated FTD mice won a similar number of matches as control treated WT mice



Drug treated FTD mice won majority of matches against control treated FTD mice

Mice treated with AL101, a mouse cross-reacting SORT1 blocking antibody.

AL001:
Clinical data and update

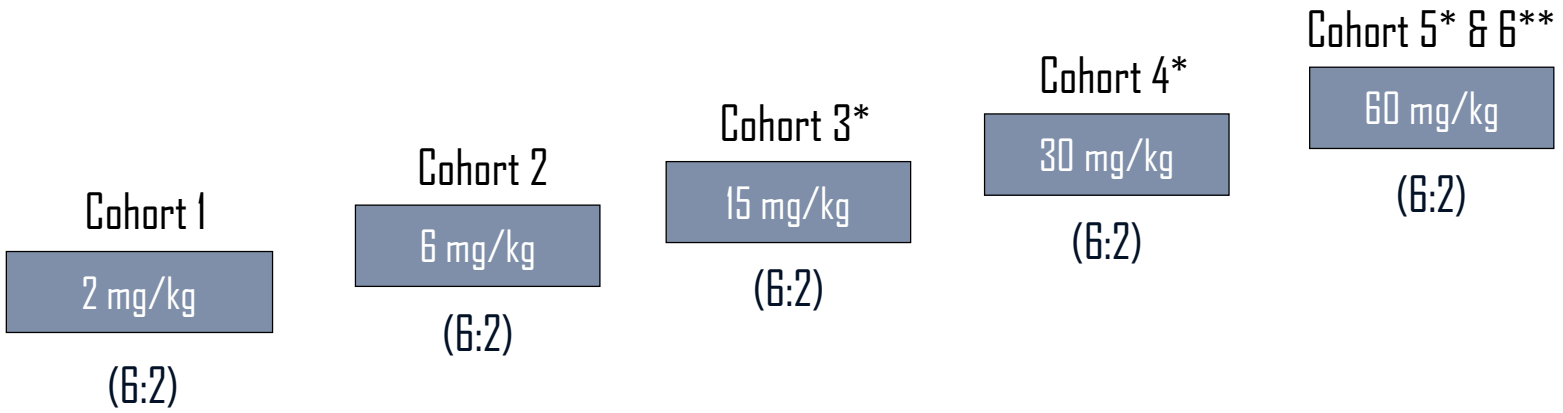
Presenting:
Robert Paul, M.D., Ph.D.
Chief Medical Officer, Alector

ALECTOR

AL001 Phase 1 summary

- Fifty (50) healthy volunteers (HV) received a single dose, with five escalating dose levels
- Six (6) asymptomatic FTD-GRN mutation carriers (aFTD-GRN) received a single dose
- Eight (8) FTD-GRN patients received three doses over one month
- AL001 was generally safe and well tolerated in HVs and GRN mutation carriers
- AL001 restored CSF PGRN level in GRN mutation carriers back to normal range

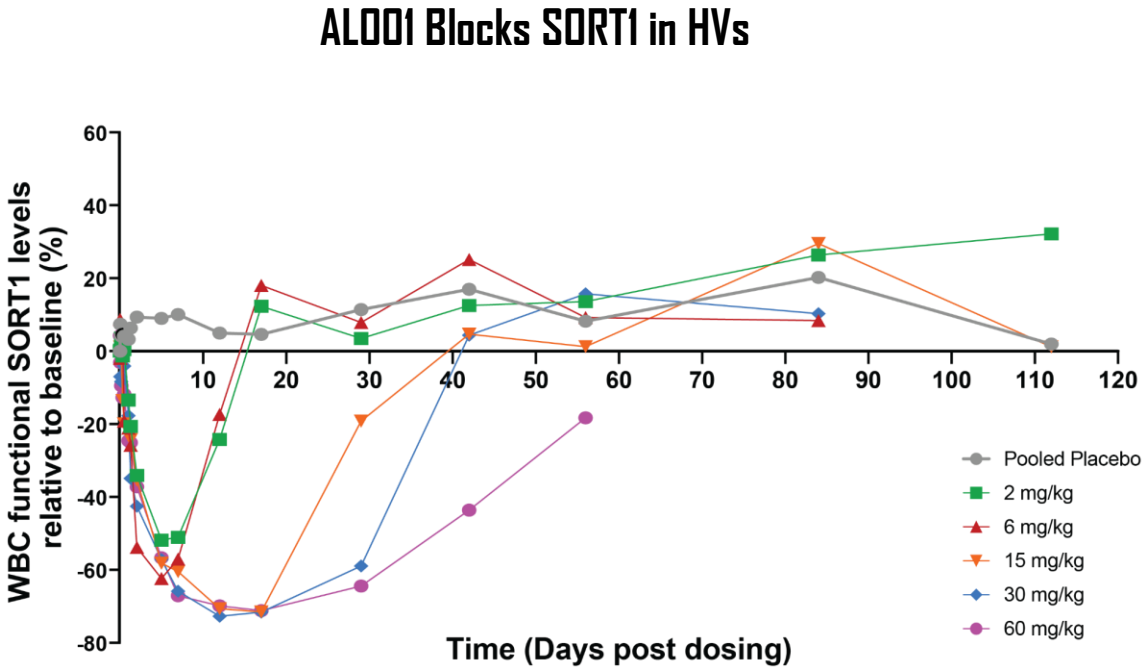
AL001 Phase 1a: Single ascending IV dose in healthy volunteers, placebo-controlled



*CSF on Day 2 and 13
**CSF on Day 25 and 43

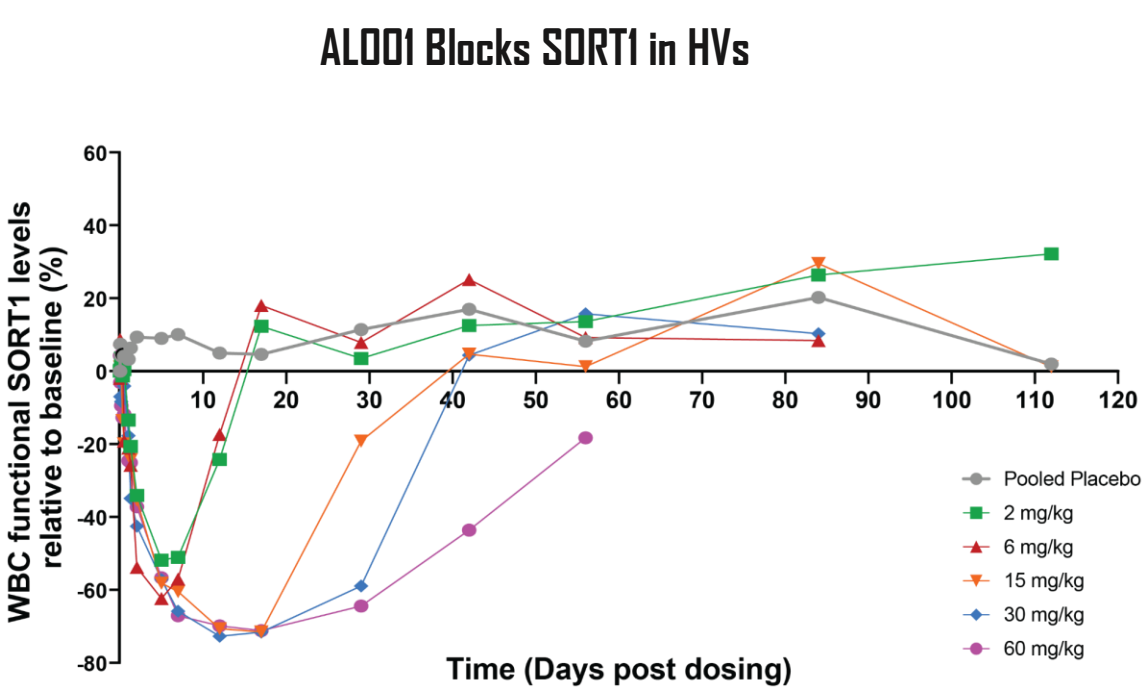
ALO01 triples PGRN levels in healthy volunteers in plasma

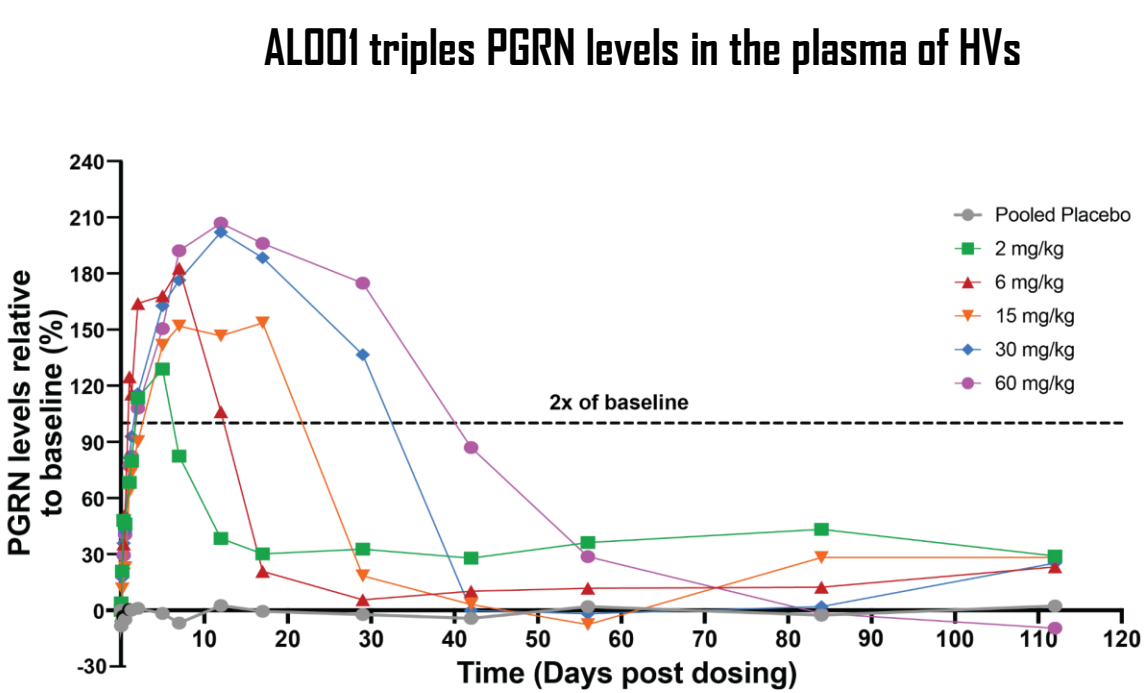
Dose dependent drug activity after a single dose in healthy volunteers



ALO01 triples PGRN levels in healthy volunteers in plasma

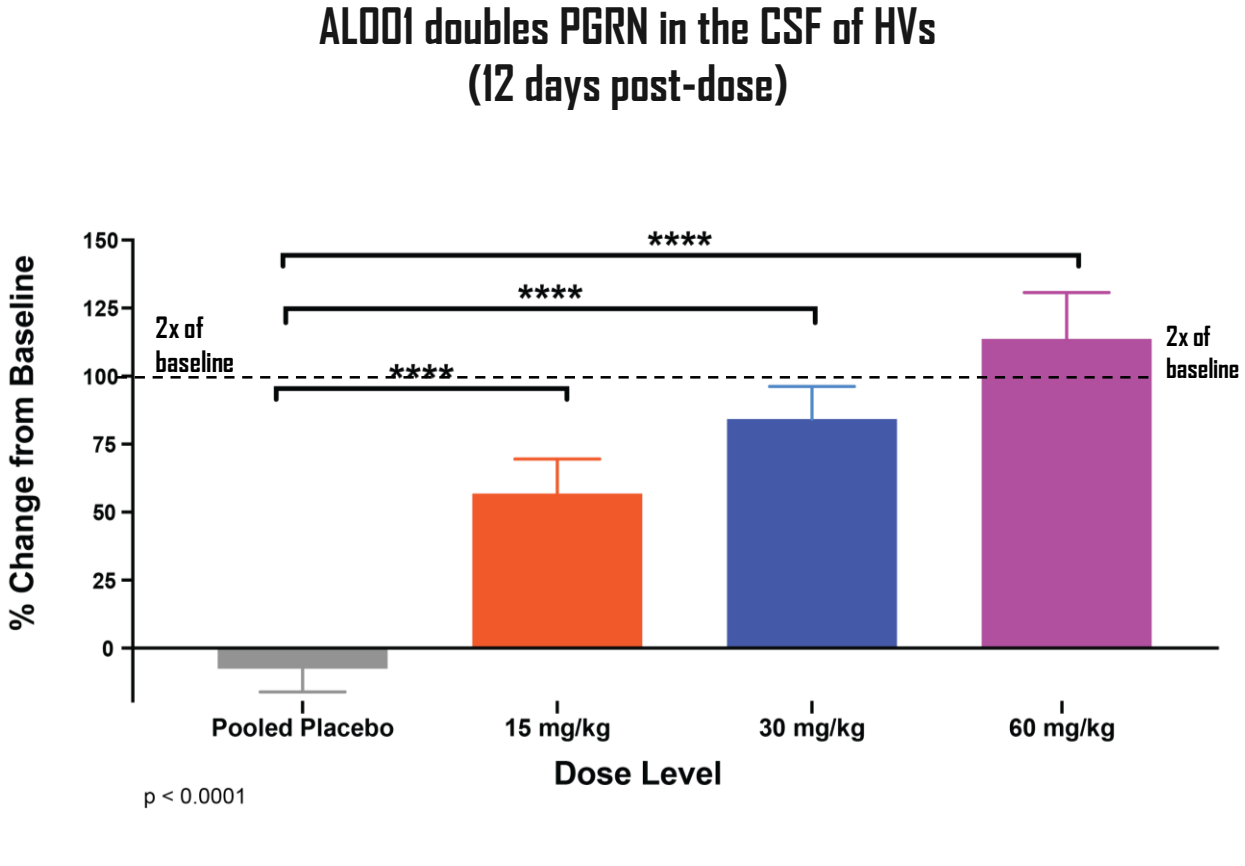
Dose dependent drug activity after a single dose in healthy volunteers





ALO01 doubles PGRN levels in healthy volunteers in CSF

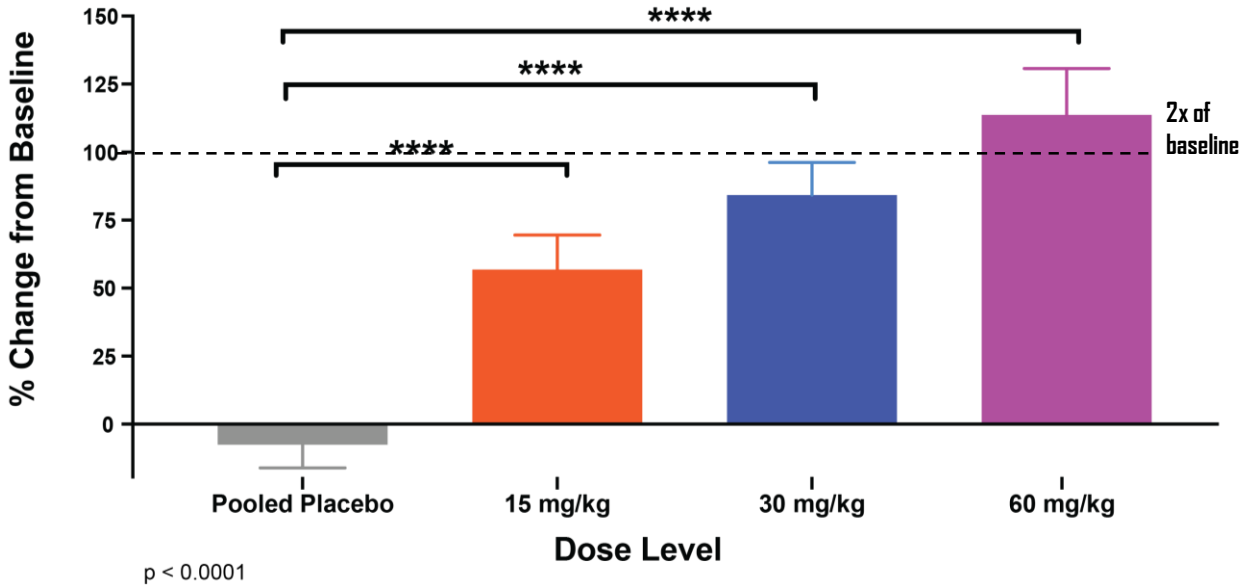
Dose dependent drug activity is significant and long lasting – expected to allow once monthly dosing



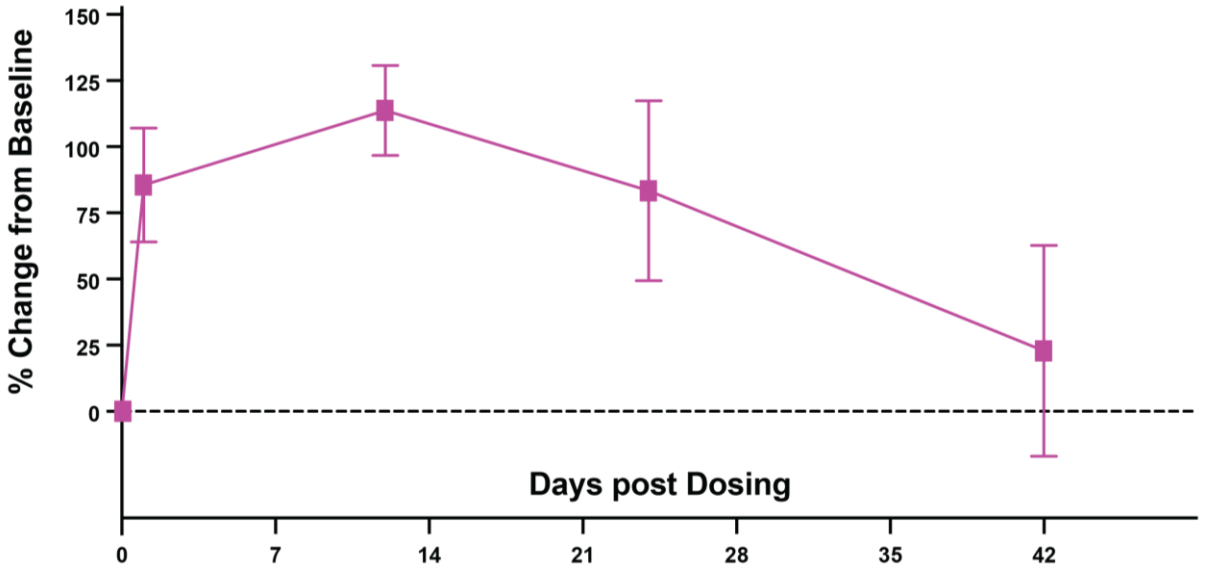
ALO01 doubles PGRN levels in healthy volunteers in CSF

Dose dependent drug activity is significant and long lasting – expected to allow once monthly dosing

ALO01 doubles PGRN in the CSF of HVs (12 days post-dose)



ALO01 treated HVs retain high levels of PGRN in the CSF



Phase Ib: Single IV dose in asymptomatic GRN mutation carriers (aFTD-GRN) and multiple IV doses in FTD-GRN patients

Study Design

- Open label
- Single IV dose, 60mg/kg
- CSF samples pre-dose, Day 13 and 35

- Open label
- Three IV doses, Q2W, 30mg/kg
- CSF samples pre-dose and Day 57

Objectives:

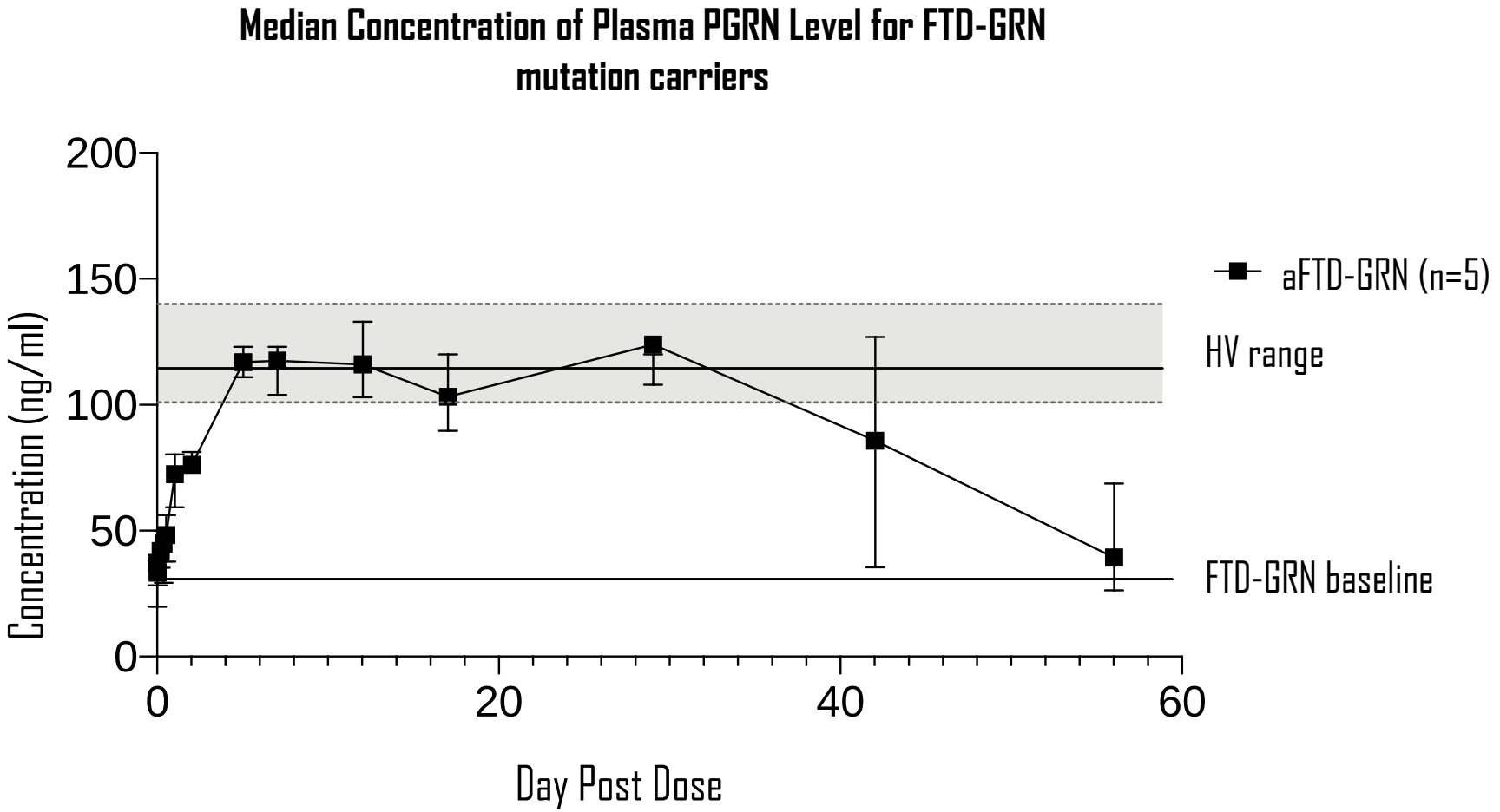
- Primary: Safety, tolerability, PK and PD
- Exploratory: Biomarkers

Safety outcome:

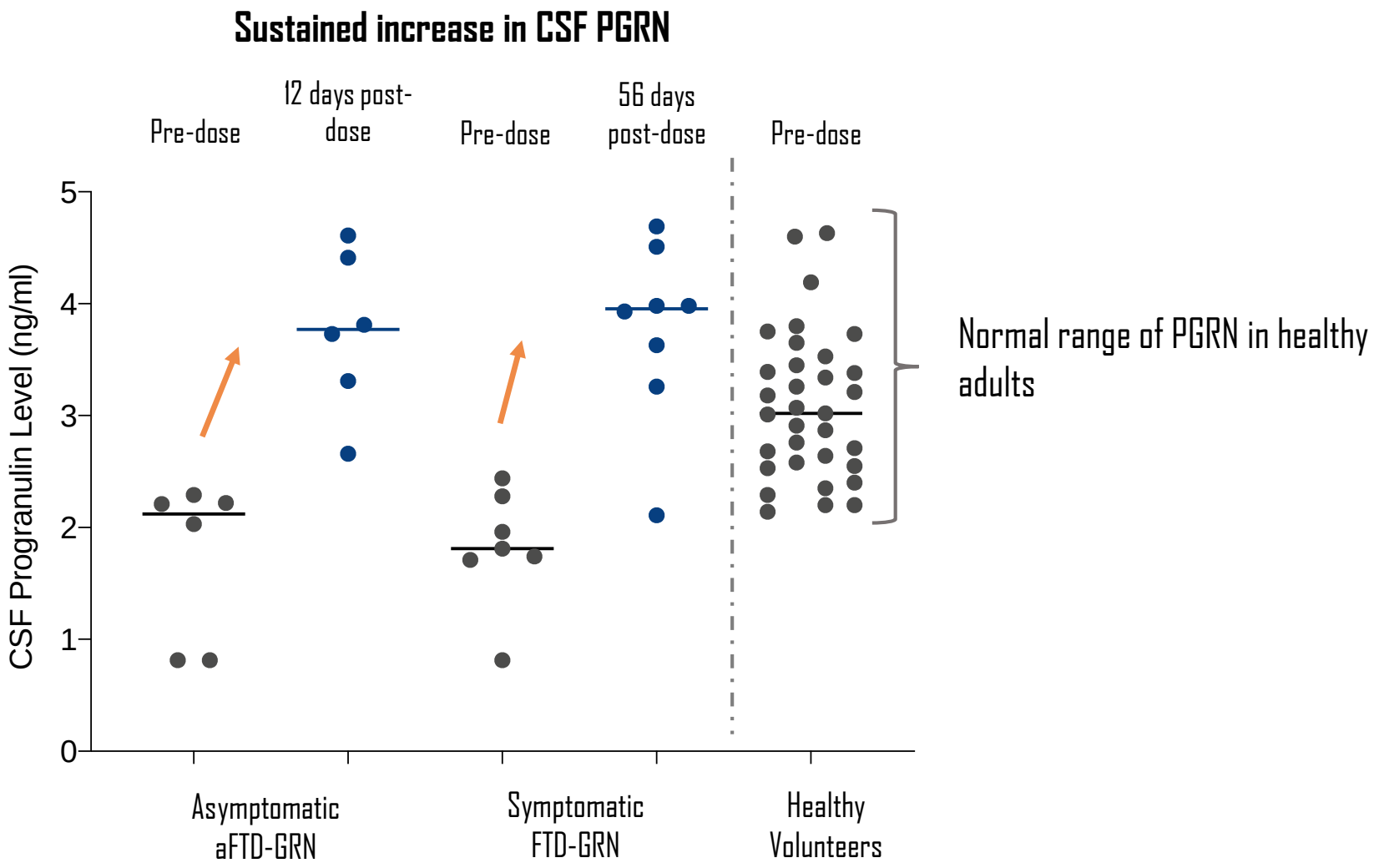
- No drug related SAEs, no discontinuations due to AEs, and all AEs were mild

*aFTD-GRN refers to asymptomatic GRN mutation carriers.

AL001 increases plasma PGRN in FTD-GRN mutation carriers

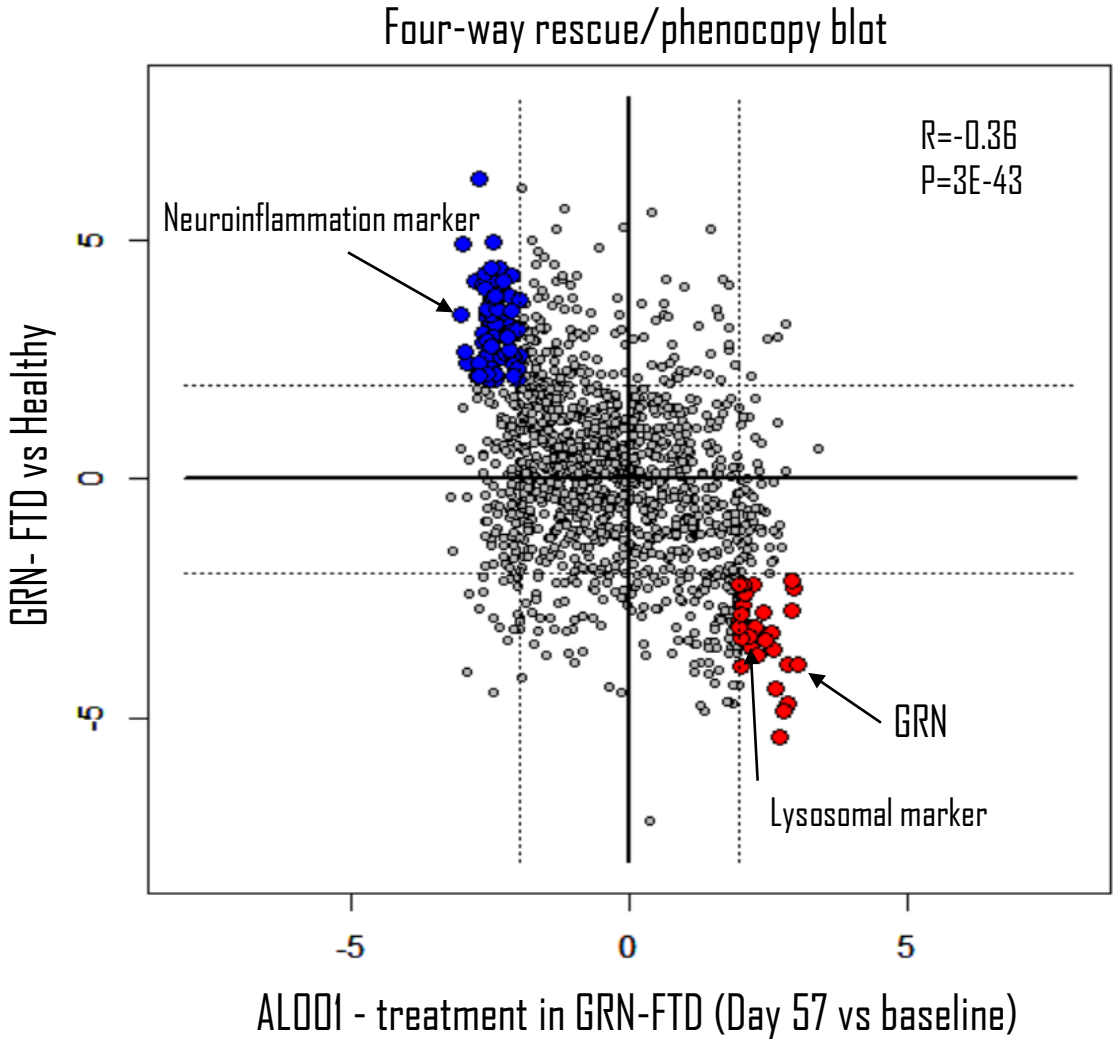


ALO01 restored PGRN in the CSF of FTD-GRN patients back to normal range



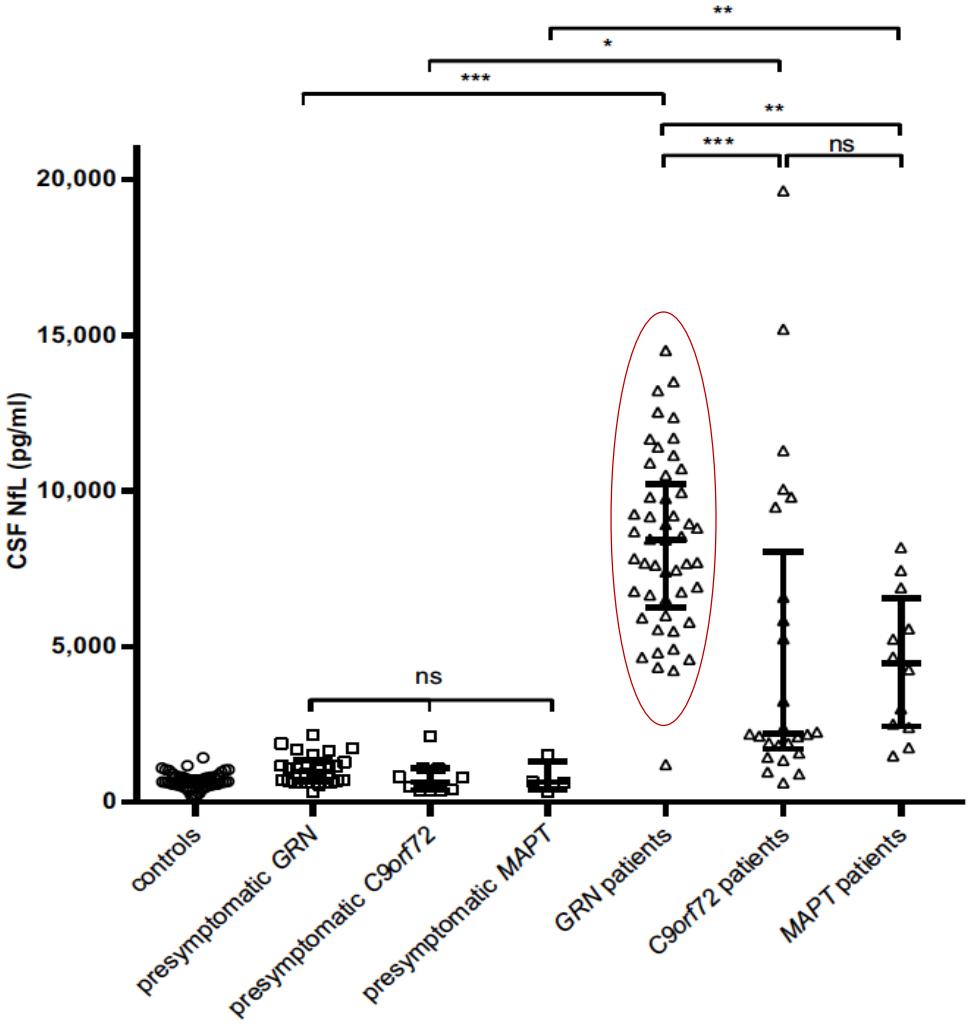
One symptomatic subject has a not reportable CSF PGRN result at baseline per Core lab SOP.

ALO01 counteracts disease protein signature in FTD patients



- ALO01 reduces inflammatory markers of disease (blue)
- ALO01 increases proteins associated with lysosomal function (red)

Decreasing clinical risk with neurofilament as a key biomarker of neurodegeneration

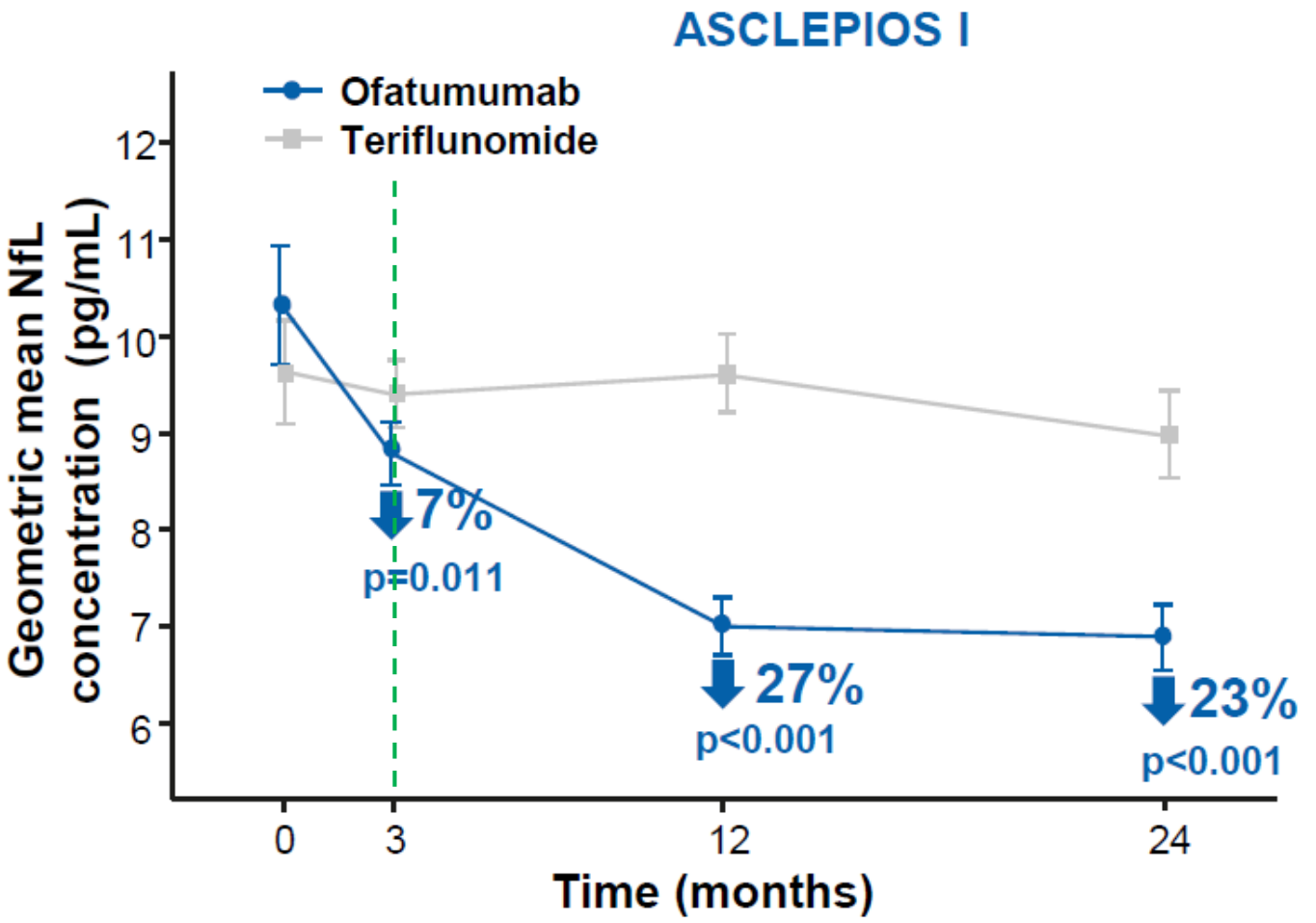


- Neurofilament light (NfL) is a biomarker of neuronal cell death
- NfL levels in FTD-GRN patients are 5-7x elevated compared to controls
- Targeting early and objective efficacy reads

Annals of Clinical and Translational Neurology 2016; 3(8): 623–636

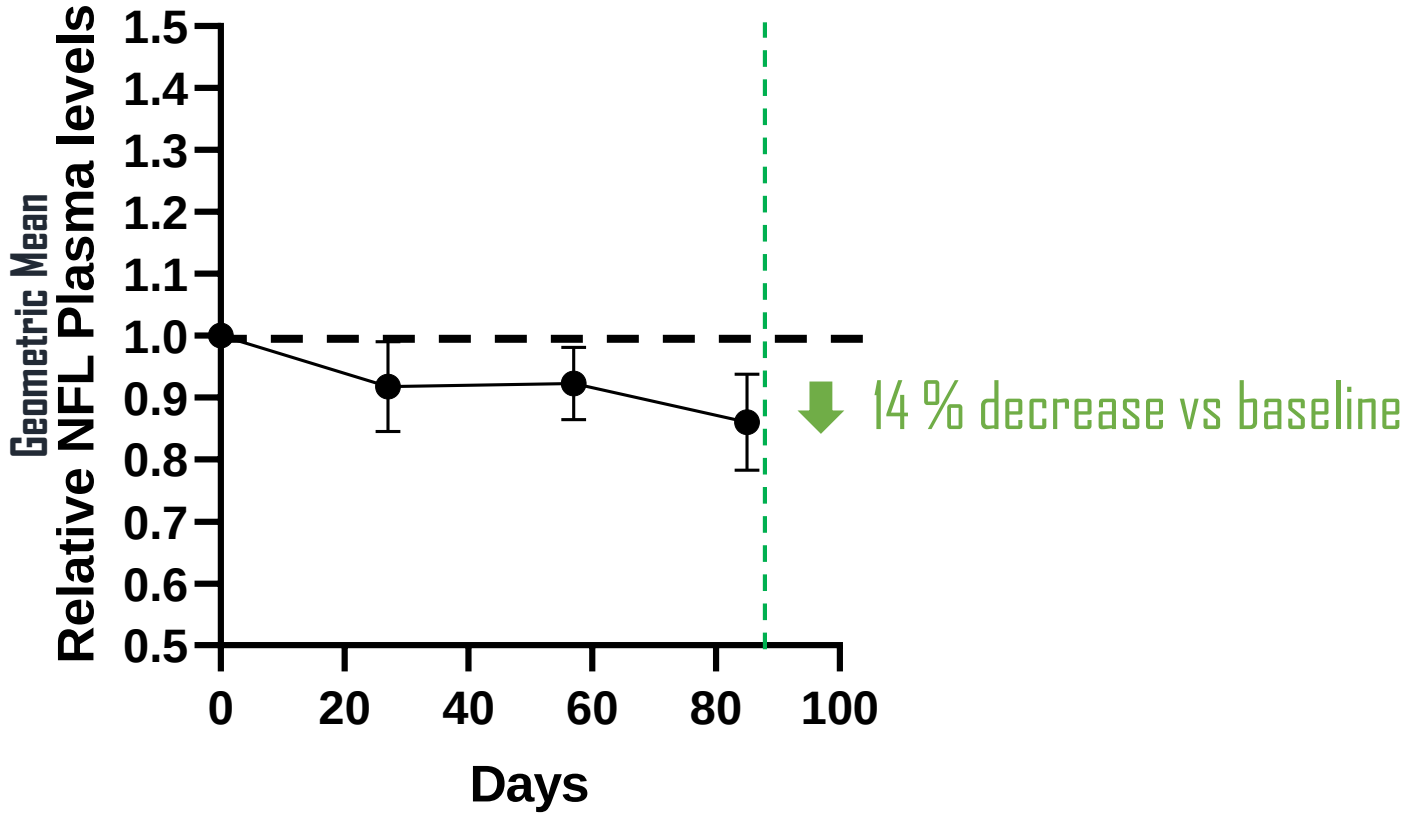
NfL levels shown to decrease with an effective MS drug

Neurofilament changes in MS patients post treatment



New data show reduction of NfL after one month of dosing

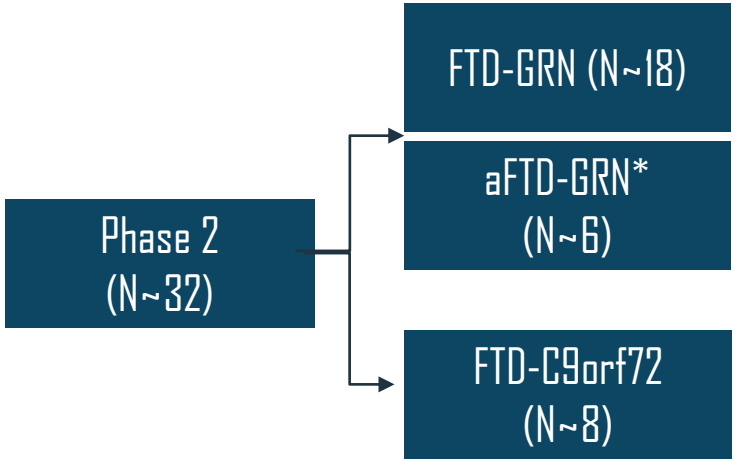
- Data are from five (5)* patients' blood samples taken three months after start of treatment
- We observed an average reduction in neurofilament levels of ~14% compared to baseline



*Out of eight (8) total FTD-GRN patients treated in the Phase 1b, two patients rolled into Phase 2 prior to the three-month blood draw and one patient finished Phase 1b but was not available for three-month blood draw due to logistics

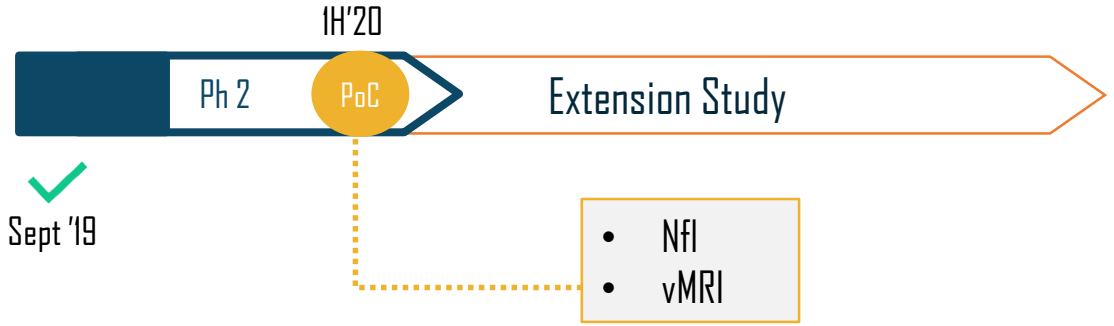
Phase 2 clinical trial ongoing, PoC in FTD in first half of 2020

Phase 2 Study Design



Phase 2 objectives:

- Primary: Safety and tolerability
- Secondary: PK and PD
- Exploratory: Biomarkers



*Pre-symptomatic FTD-GRN (aFTD-GRN)

Pivotal Phase 3 study to start in 2020

Phase 3 Study Design

Double-Blind Placebo Controlled Randomized in FTD-GRN Patients

Interim analysis (IA)

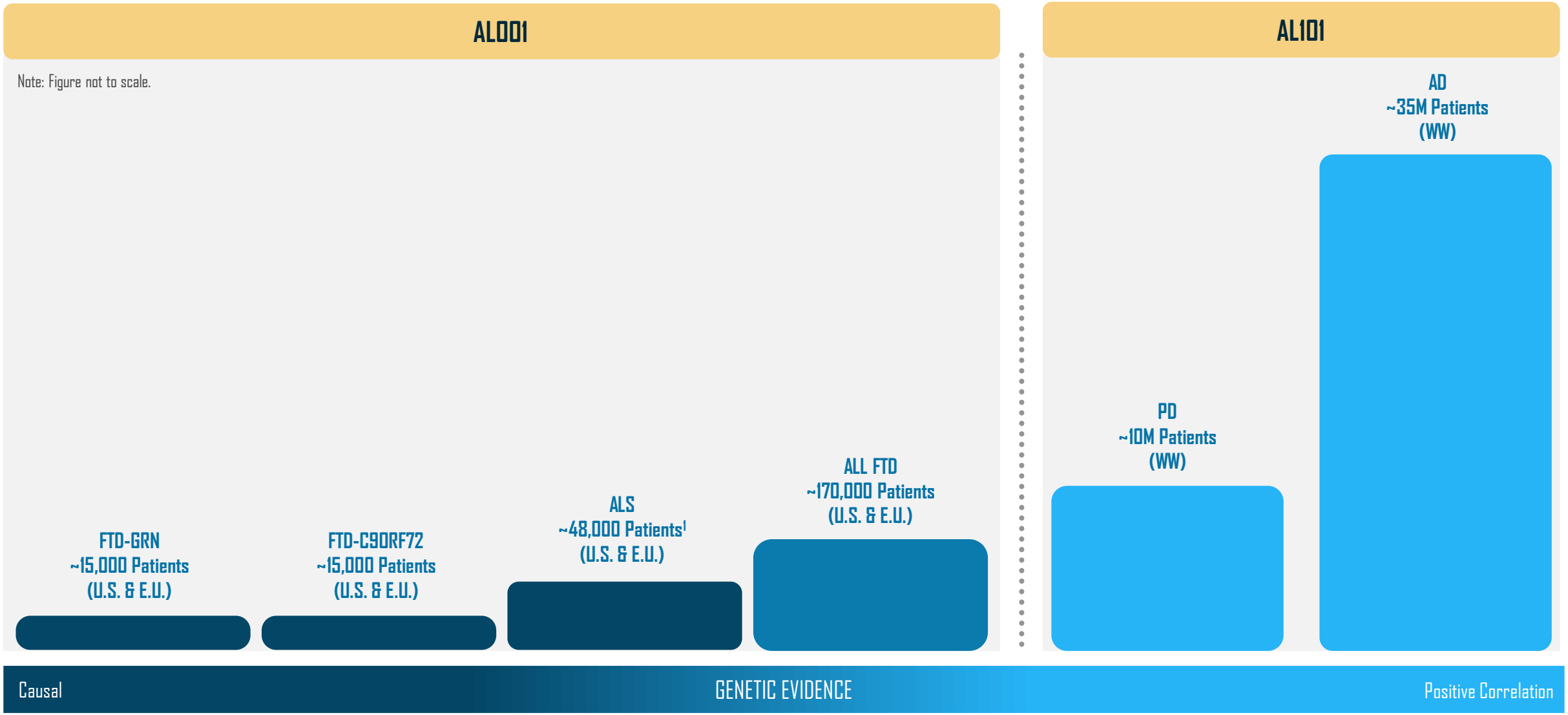
- Primary Efficacy Endpoint: CDR® plus NACC FTLD-SB
- NfL
- vMRI

Multiple interim analyses in pivotal study to potentially allow for early success

AL001: Summary

- AL001 restores PGRN levels in CNS of FTD-GRN mutation carriers
- Phase 1b data indicate that restoration of PGRN levels:
  - Counteracts the disease signature in the CNS
  - Reduces biomarkers of inflammation
  - Increases biomarkers of lysosomal function
- Phase 1b data indicate an initial trend of a decrease in plasma NfL levels 3 months after the first dose
- Currently in Phase 2 and expect PoC data in 1H 2020
- Start of Phase 3 in 2020

AL001 and AL101 programs have broad therapeutic potential



1. Nat Commun. 2016 Aug 11;7:12408.

Q&A

ALECTOR

The human genetics of Alzheimer's disease:TREM2 and SIGLEC 3

Presenting:
Elizabeth M. Bradshaw, PhD
Adler Assistant Professor of Neurology, the Taub Institute for Research on Alzheimer's Disease and the Aging Brain and the Institute for Genomic Medicine, Colombia University

ALECTOR

Genetics of Late-Onset Alzheimer's Disease: a Microglia Story

Elizabeth M. Bradshaw, PhD

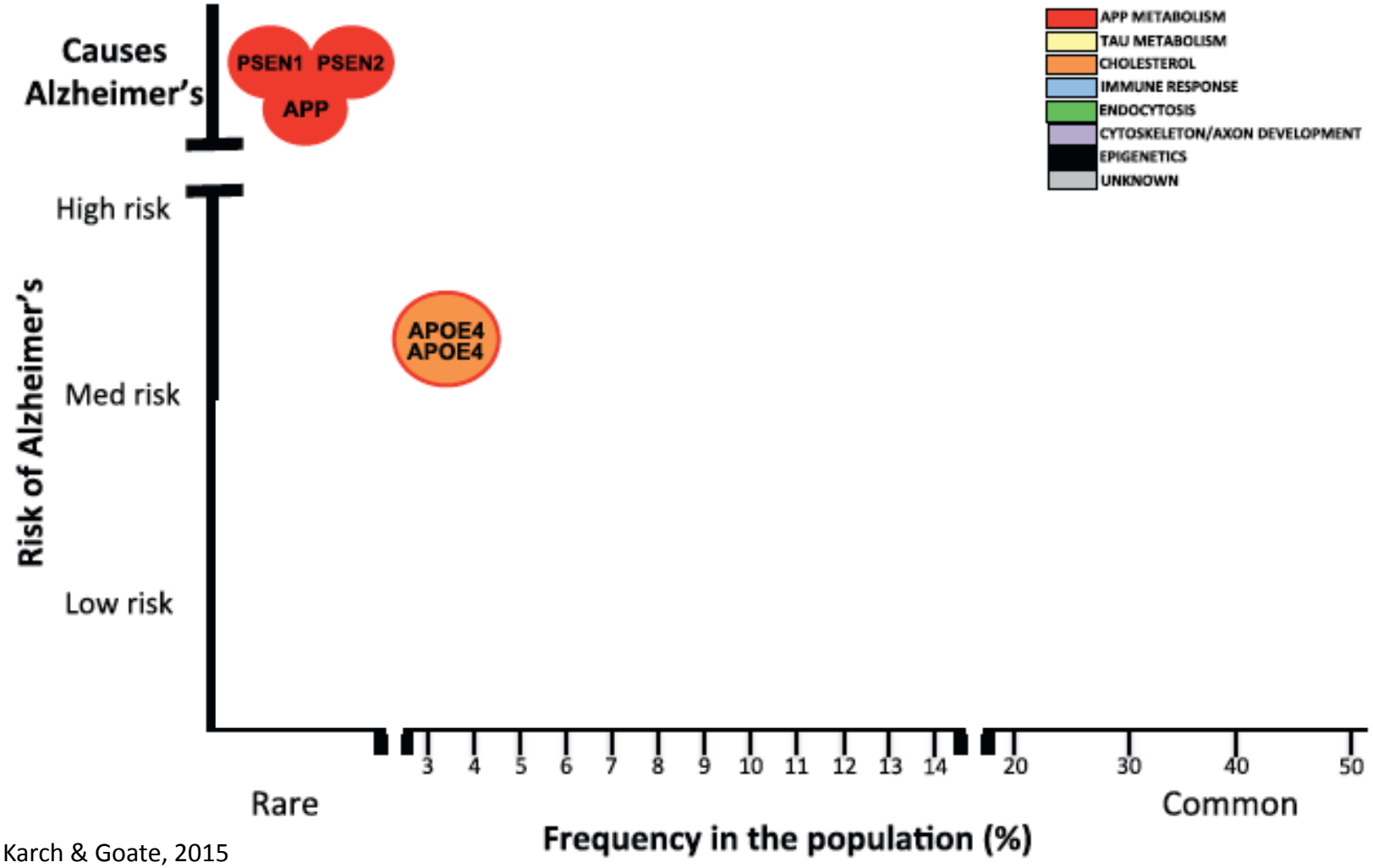
Columbia University Medical Center

Alector Science Day

12-13-19

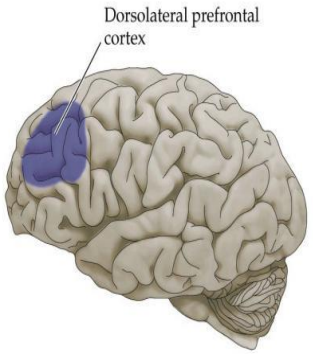
Genetics implicate the immune system

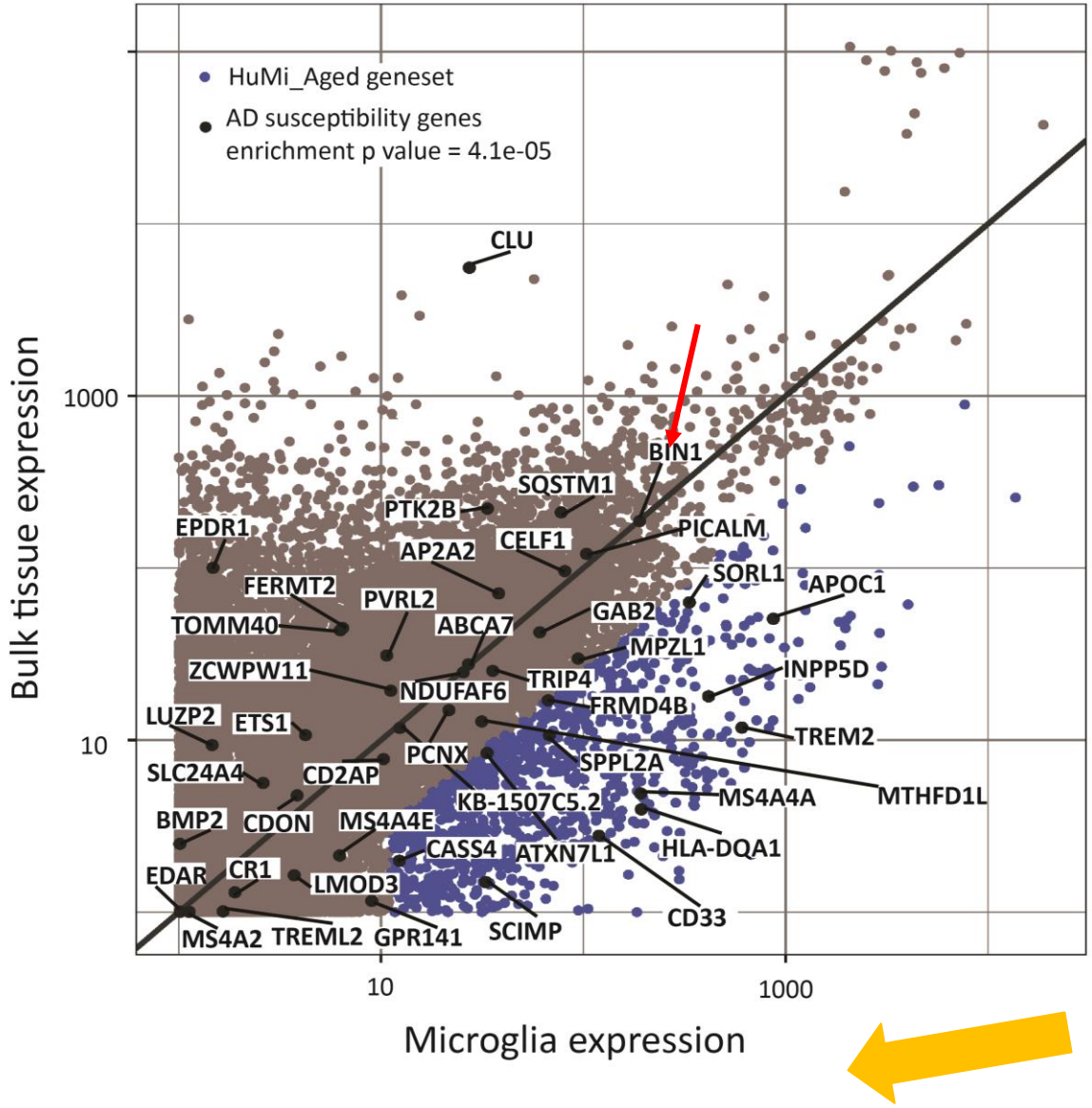
- GWAS focused on late-onset AD, not early-onset or familial AD
- We now have 29 genetic loci associated with AD

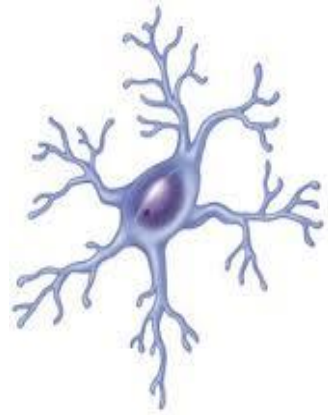


Karch & Goate, 2015

GWAS genes are enriched in microglia





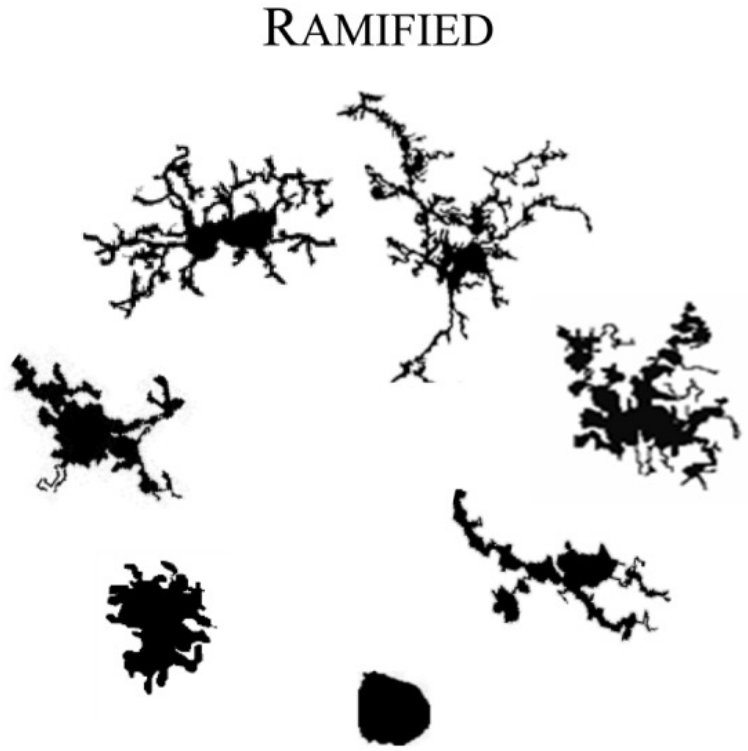


Olah et al. Nature Communications 2018

Microglia are the resident immune cell of the CNS

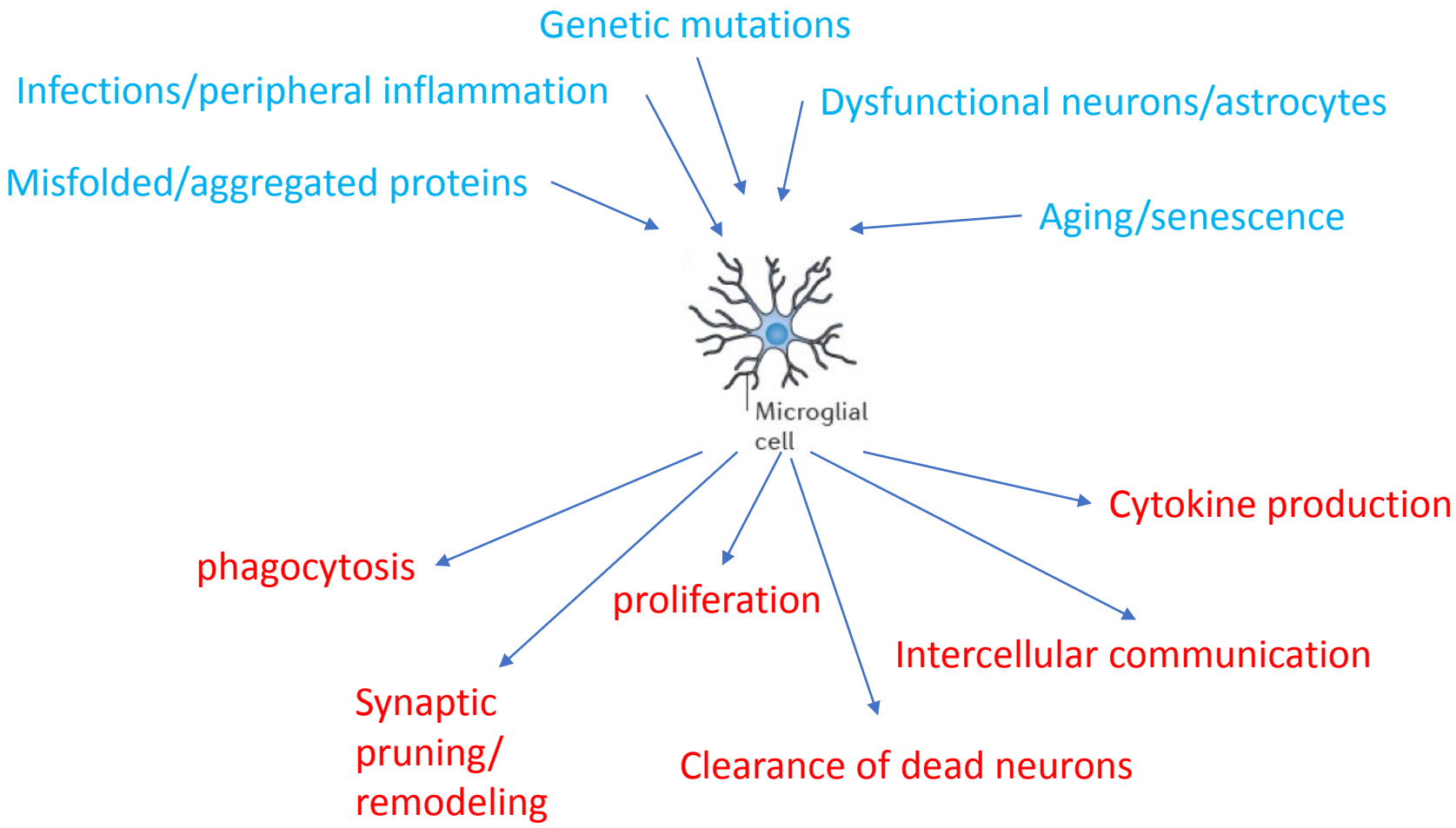
Microglia functions

- Immune surveillance – tissue macrophage
- Phagocytosis of pathogens and dying cells
- Cytokine production
- Synaptic plasticity



Karperien, et al Frontiers Cell Neurosci, 2013

Microglia in neurodegeneration

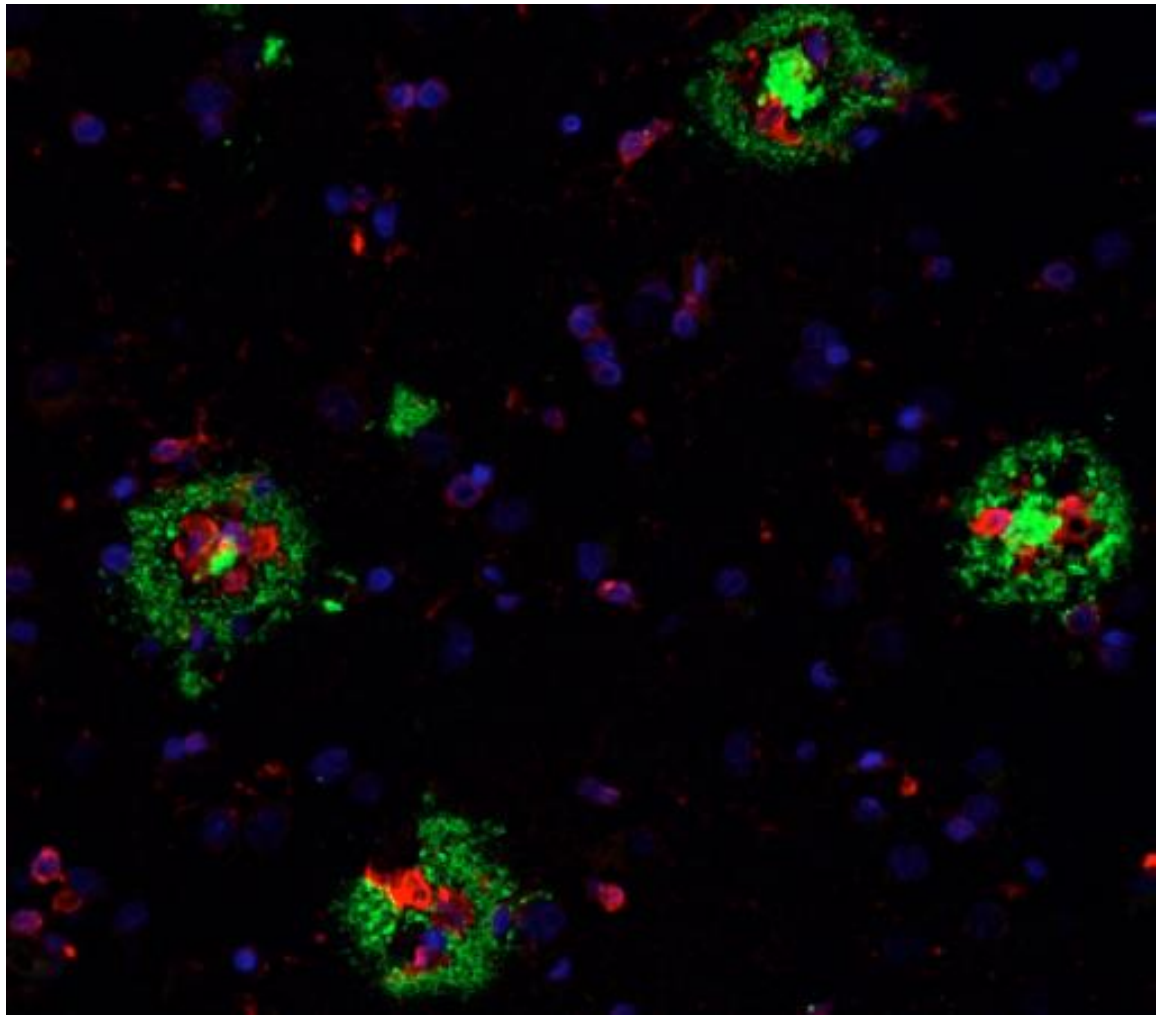


Microglia surround amyloid plaques

Do microglia sequester ‘toxic’ species into inert plaques?

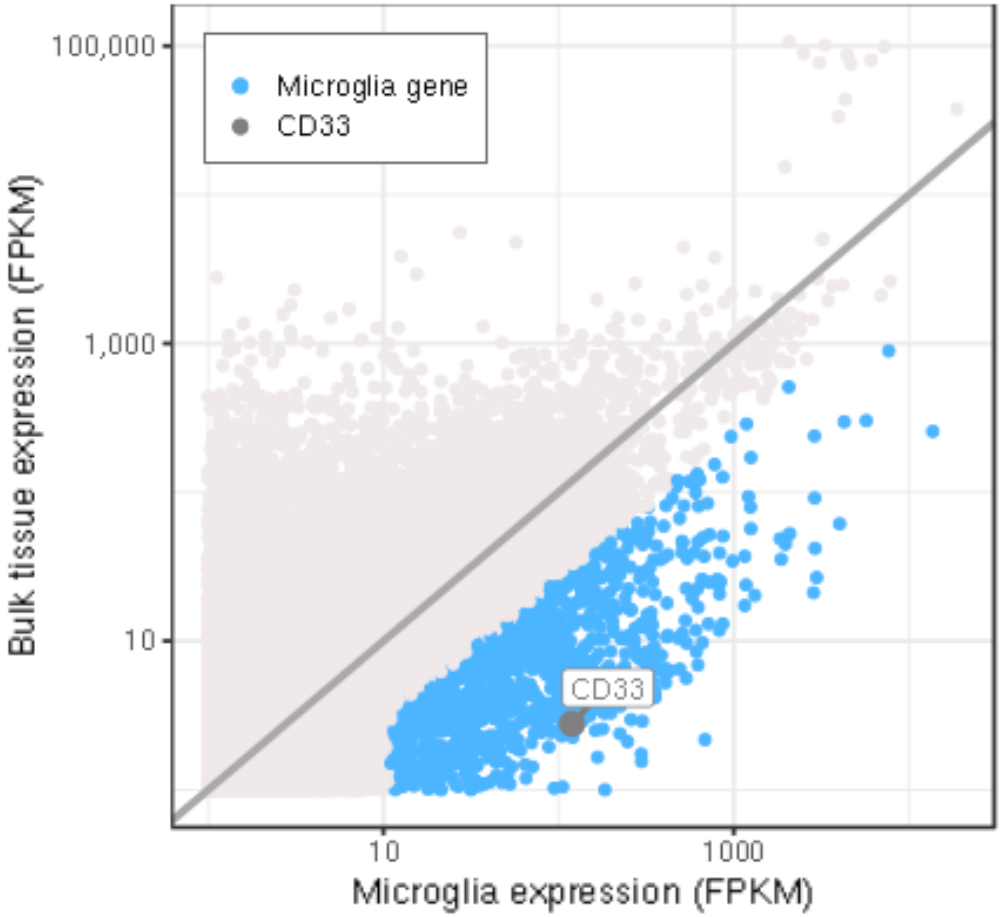
Do microglia seed plaques?

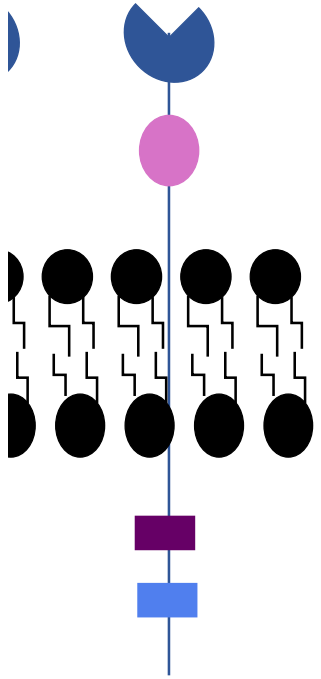
Are plaques formed due to microglia’s inability to clear amyloid?



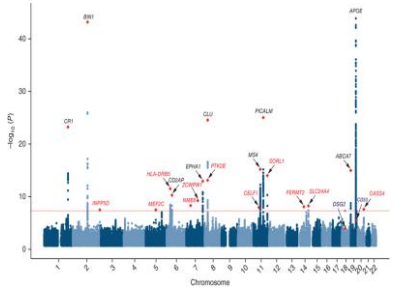
Alzheimer's risk gene: CD33/Siglec-3

- CD33/Sig
  transme
  expresse
  - Often
    marke
  - Conta
    tyrosi
    motif
    domai
- Binds sia
  ligand ur



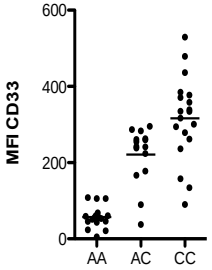


Experimental pipeline: genetics to therapeutic targets

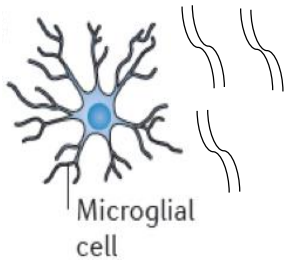


Patient derived unbiased datasets

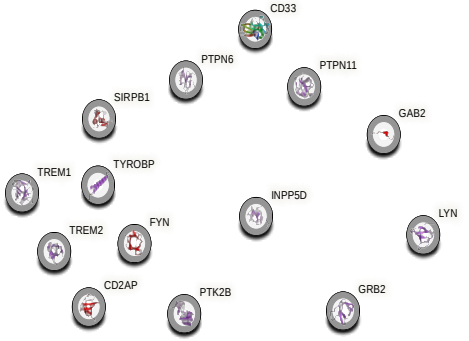
Identify gene/protein and cell type modulated by genetic variance or disease state



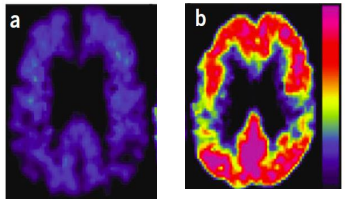
Molecular outcome of genetic variation



Cellular function



Binding Partners and Pathway identification



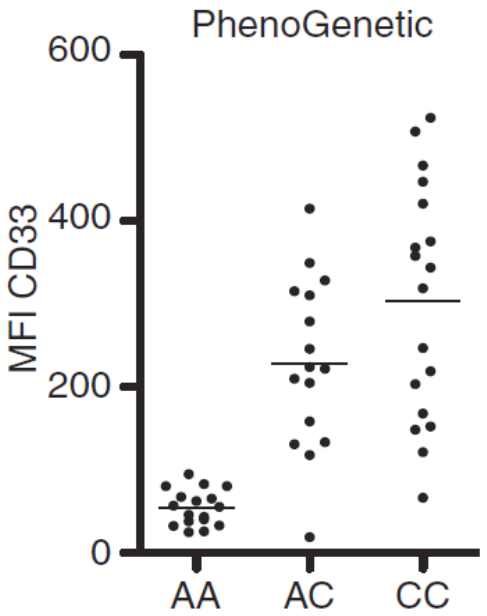
Endophenotype associations

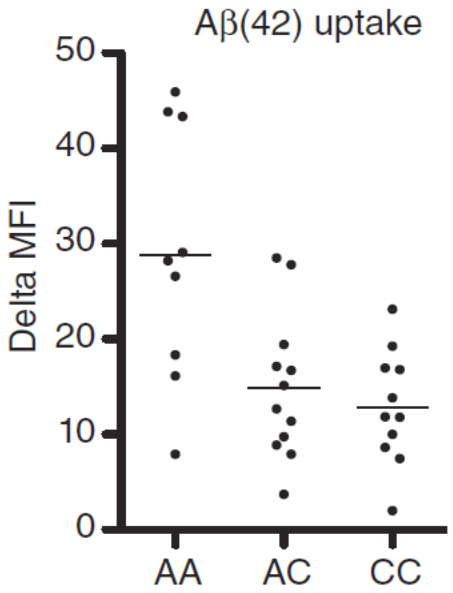
Is the genetic hit or pathway member a therapeutic target?

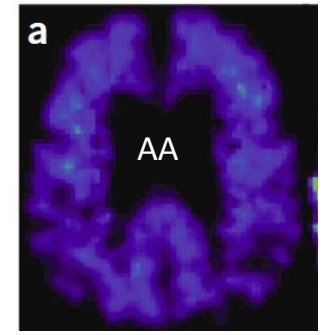
Siglec-3 risk leads to increased Siglec-3 function

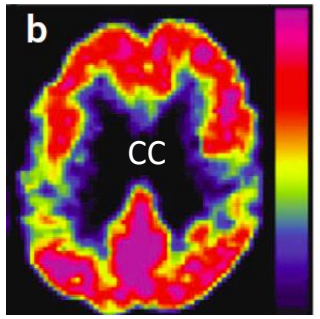
rs3865444^{C} risk allele → Greater expression of CD33 → Less Aβ uptake → More Aβ burden in brain

Reference SNP Cluster ID



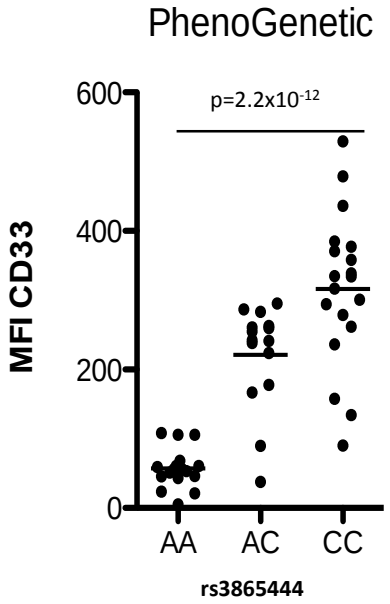


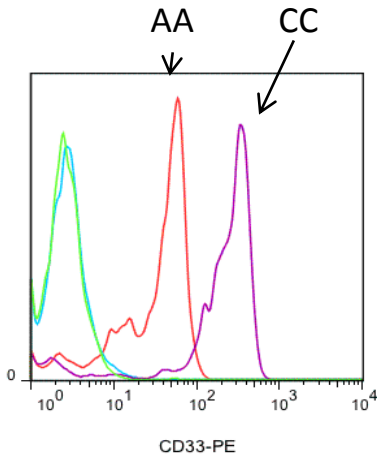




C= risk – increase of inhibitory molecule

Siglec-3 risk allele is associated with greater expression of exon 2

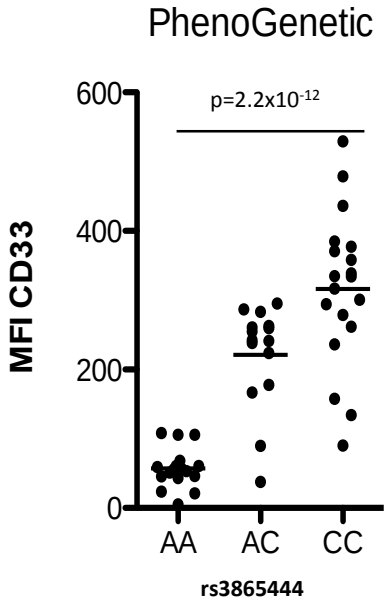


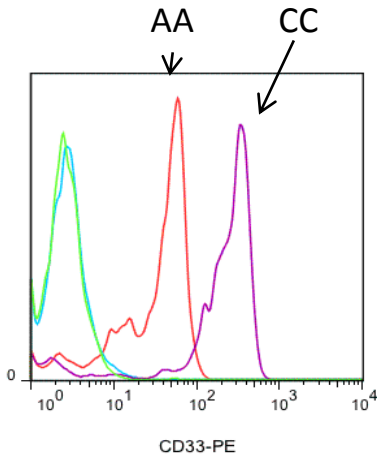


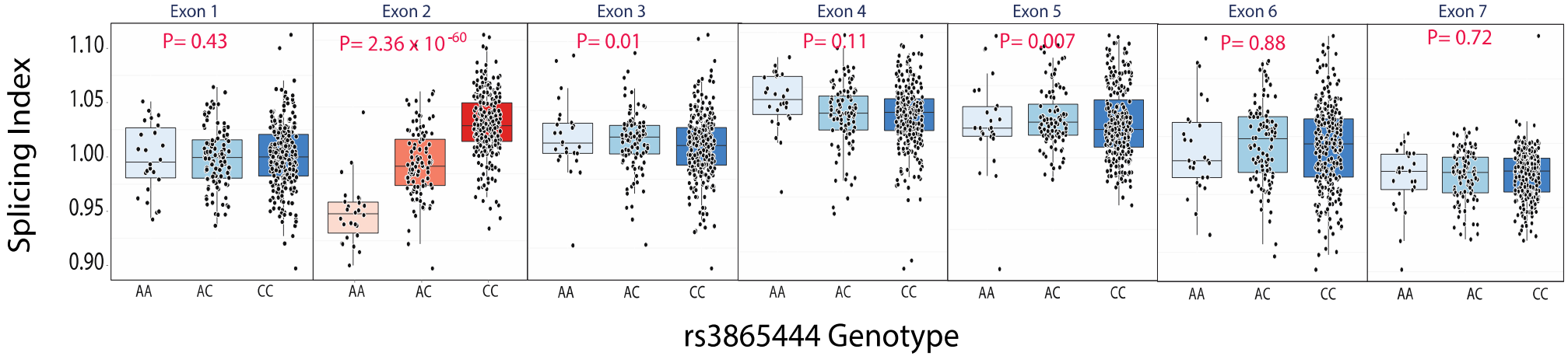
Raj et al. Human Molecular Genetics (2013).

Bradshaw *et al. (*2013) *Nat. Neurosci*.

Siglec-3 risk allele is associated with greater expression of exon 2







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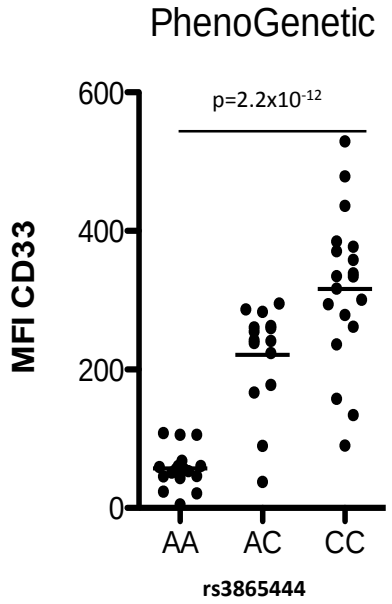
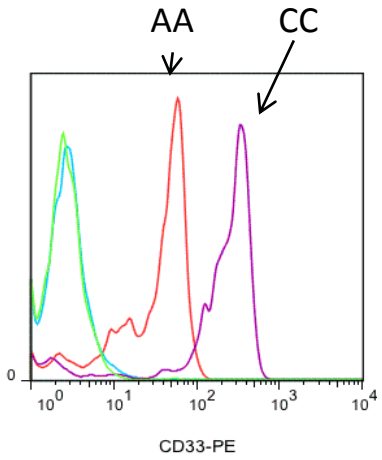
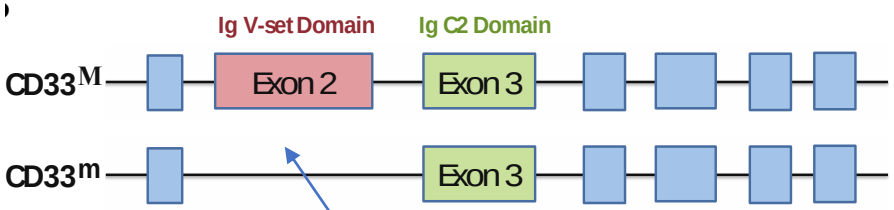
Siglec-3 risk allele is associated with greater expression of exon 2

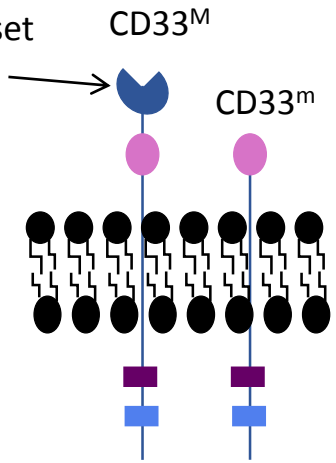


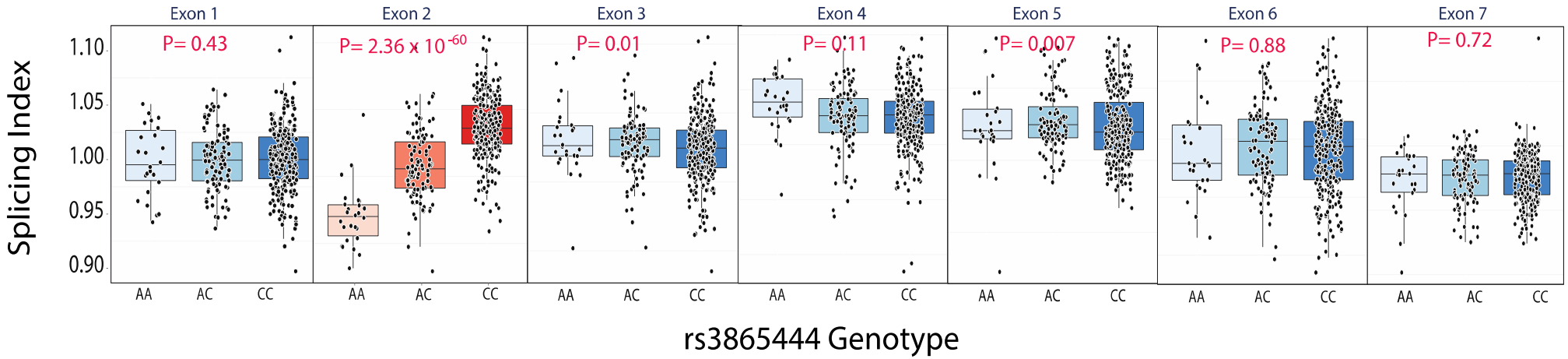


CC=risk allele



Sialic-acid Ig V-set binding domain





Raj et al. Human Molecular Genetics (2013).

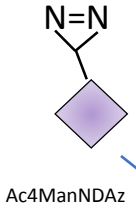
Bradshaw *et al.* (2013) *Nat. Neurosci*.

Unbiased screen of sialic acid dependent Siglec-3 binding partners

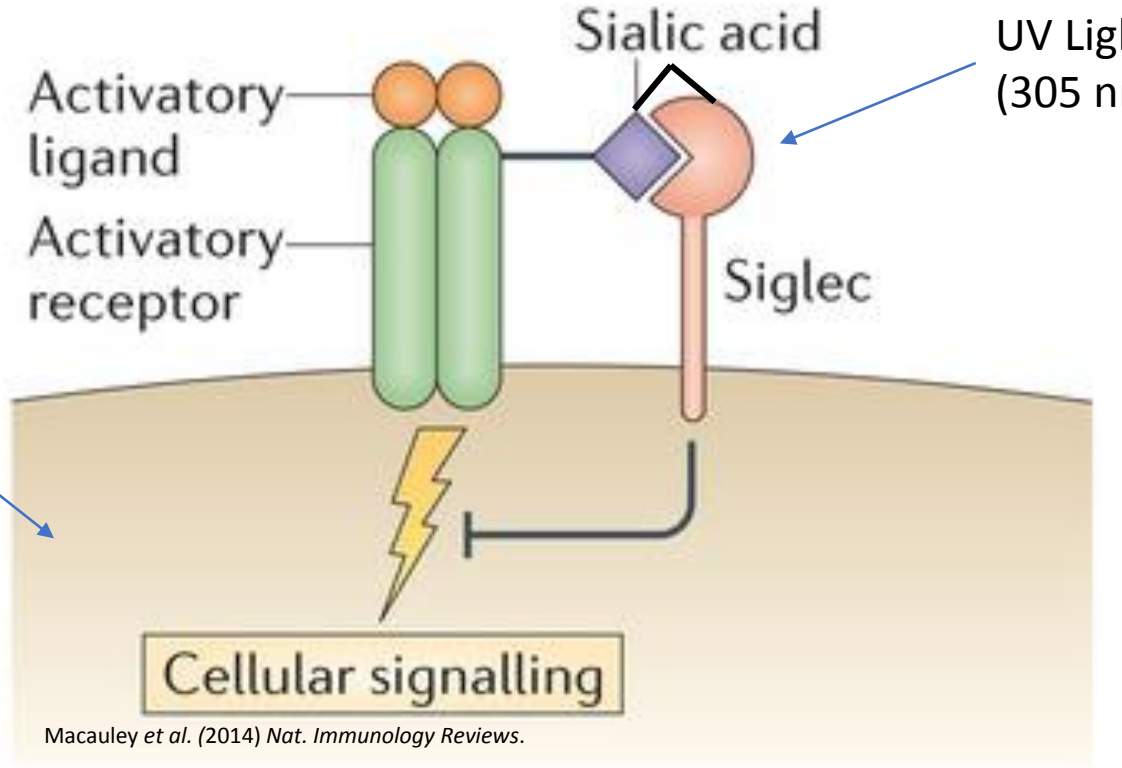
In collaboration with Steve Carr and Monica Schenone

Broad Institute

Identification of Siglec-3 sialic acid specific binding partners

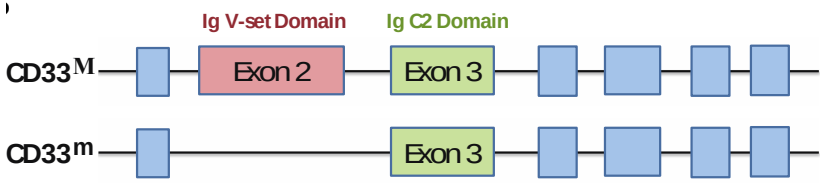


Ac4ManNDAz



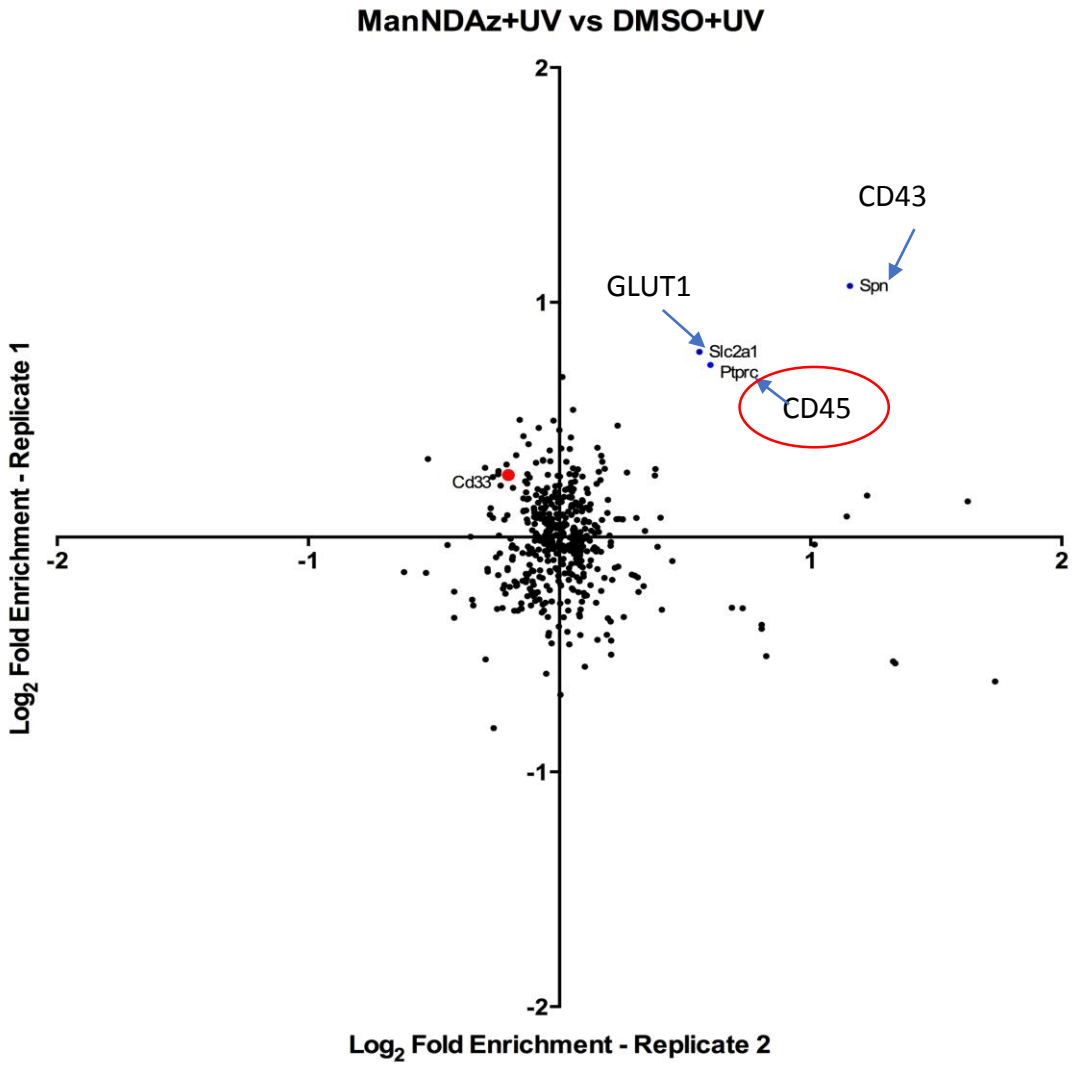
Macauley *et al.* (2014) *Nat. Immunology Reviews*.

Prototypical *cis* interaction of Siglecs



Cory Rillahan and Jennifer Kohler, UT Southwestern

CD45 is a Siglec-3 sialic acid specific binding partner



Cory Rillahan

CD45/PTPRC/LCA

- Immune cell specific transmembrane protein-tyrosine phosphatase

CD45/PTPRC/LCA

- Immune cell specific transmembrane protein-tyrosine phosphatase
- Expression level is markedly increased in frontal cortex and hippocampus of patients with AD

CD45/PTPRC/LCA

- Immune cell specific transmembrane protein-tyrosine phosphatase
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- CD45 deficient murine microglia are defective in amyloid-β uptake

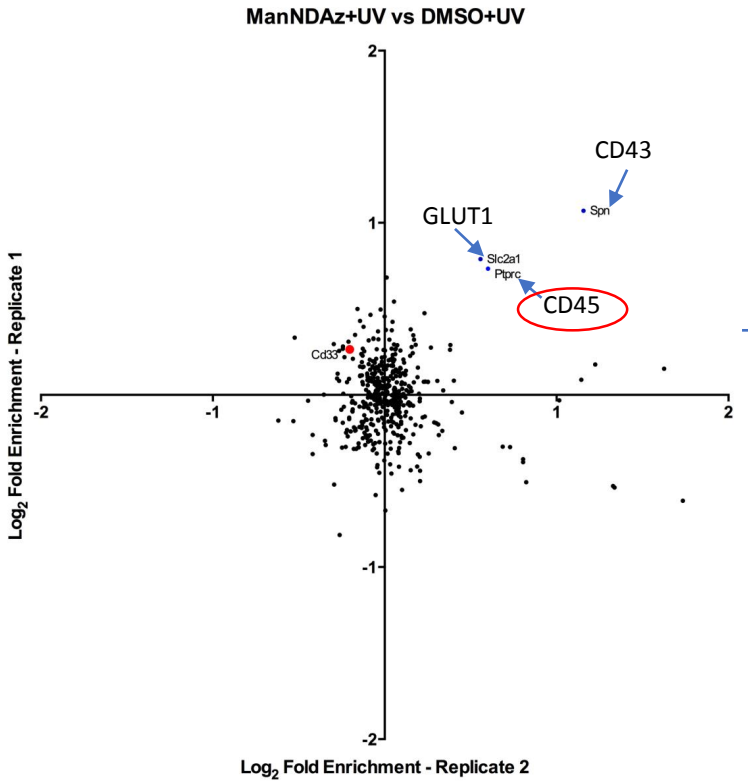
CD45/PTPRC/LCA

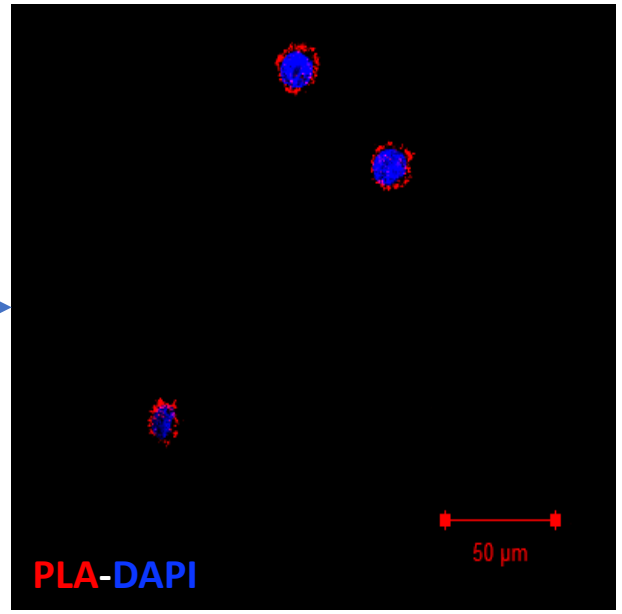
- Immune cell specific transmembrane protein-tyrosine phosphatase
- Expression level is markedly increased in frontal cortex and hippocampus of patients with AD
- CD45 deficient murine microglia are defective in amyloid-β uptake
- Recently identified as a key driver of AD by transcriptomics

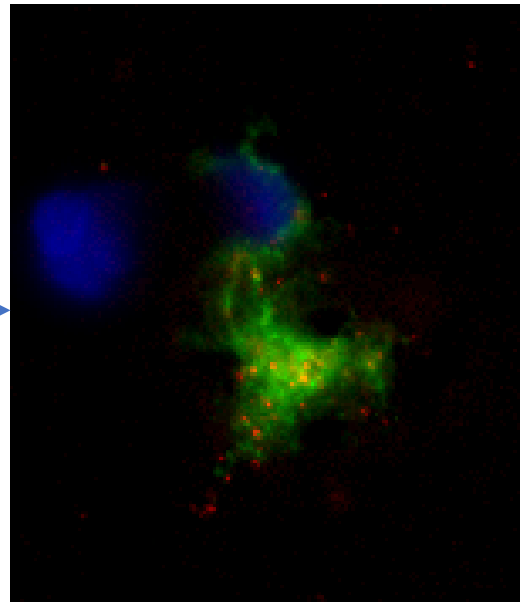
CD45/PTPRC/LCA

- Immune cell specific transmembrane protein-tyrosine phosphatase
- Expression level is markedly increased in frontal cortex and hippocampus of patients with AD
- CD45 deficient murine microglia are defective in amyloid-β uptake
- Recently identified as a key driver of AD by transcriptomics
- May be genetically associated in women

Validating CD45 as a siglec-3 sialic acid specific partner

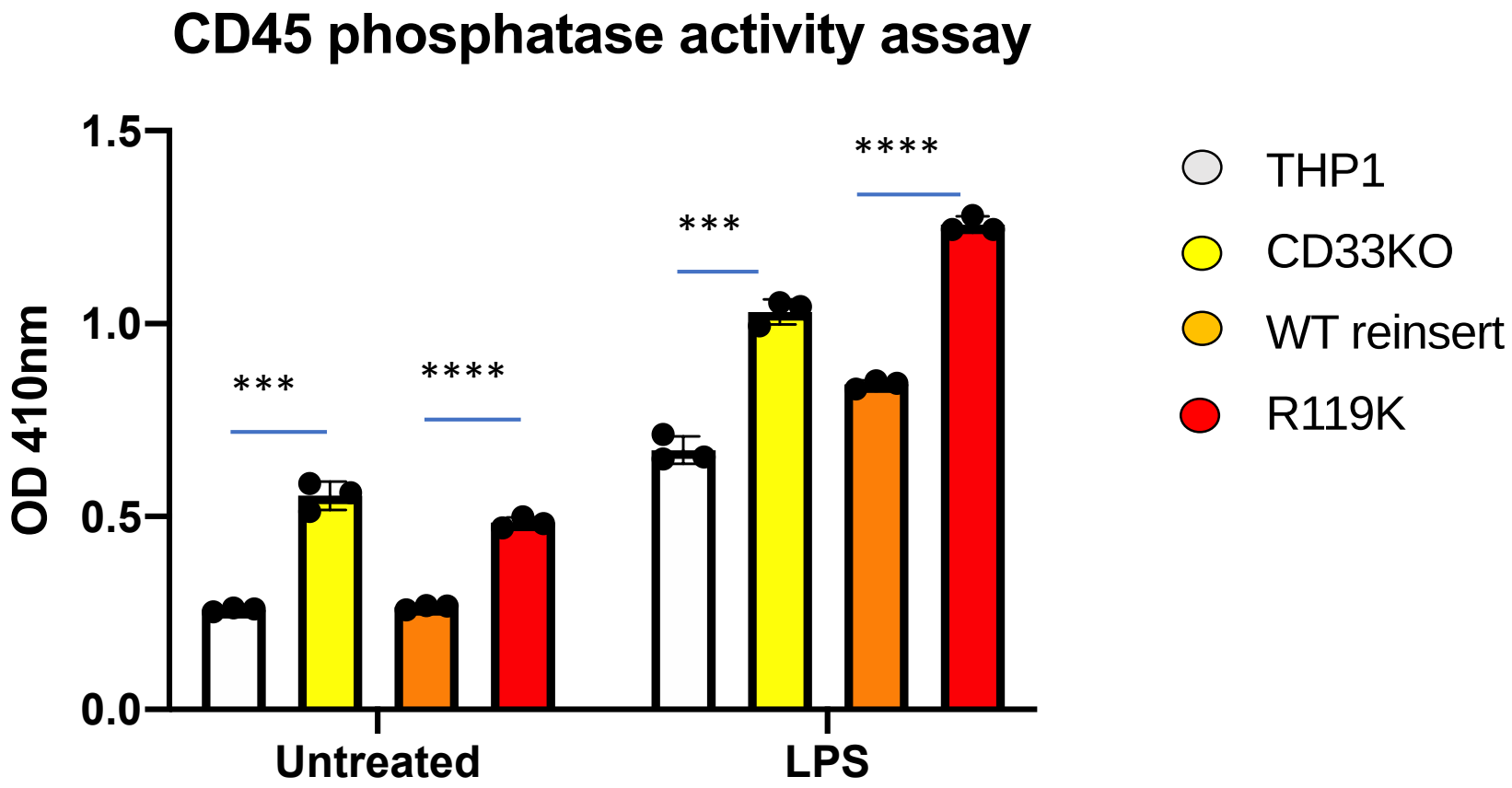






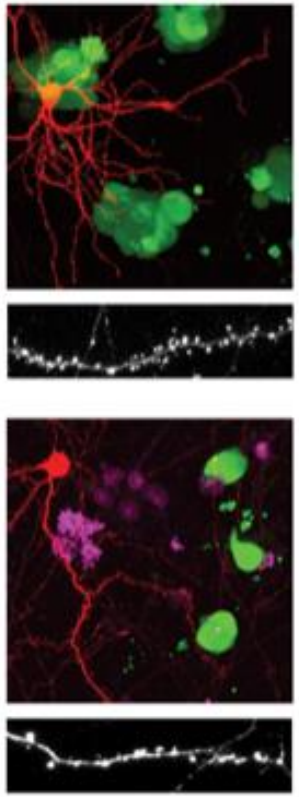
Nicole Vo

Siglec-3 influences CD45 phosphatase activity

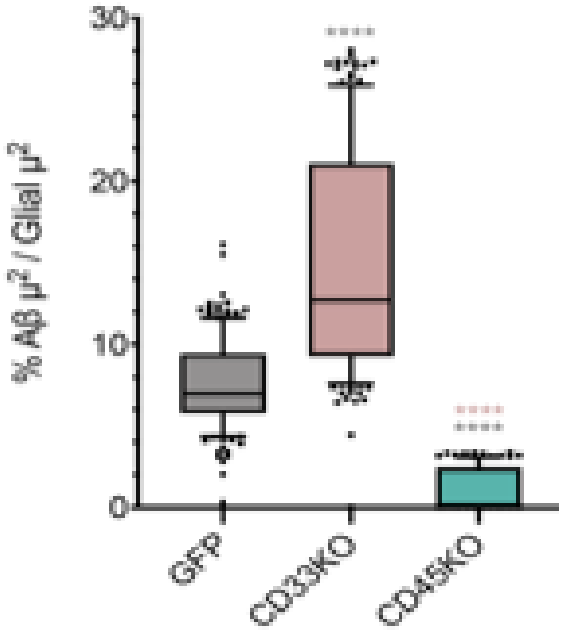


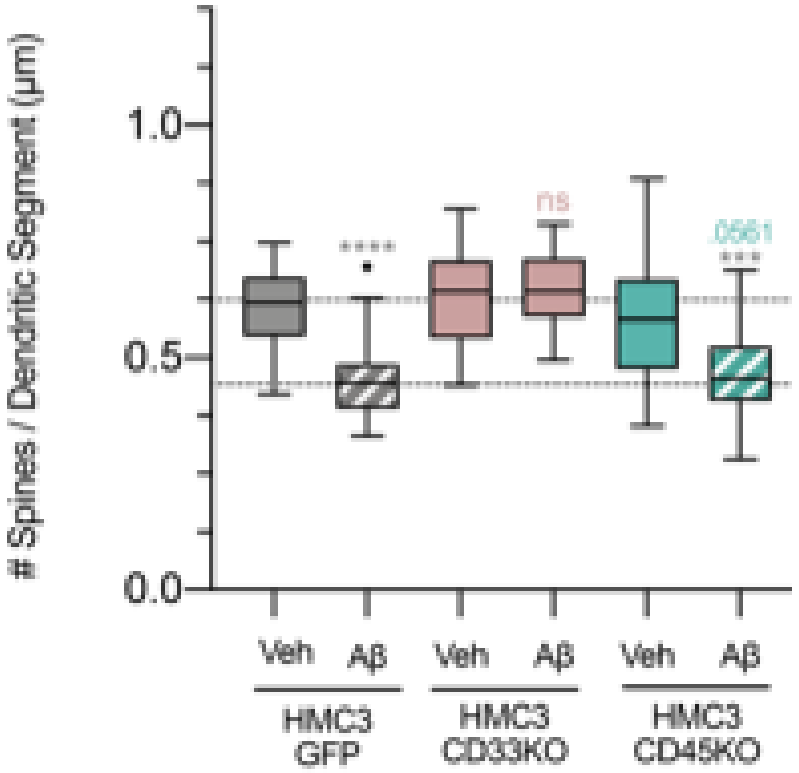
Nicole Vo

Siglec-3 KO protects synaptic density from A-beta



+ A-beta

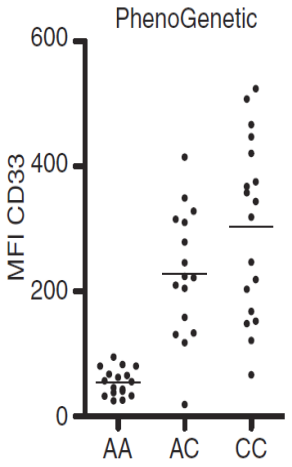


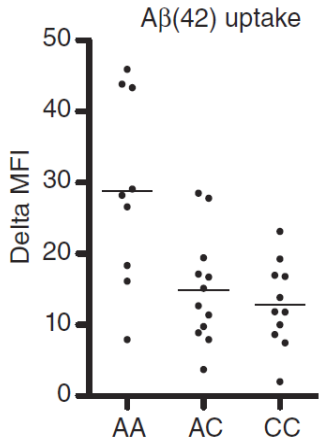


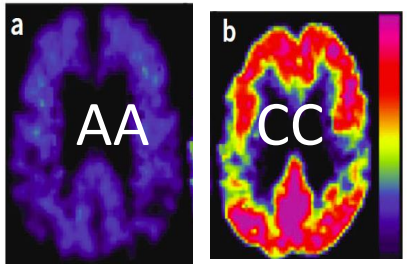
Nicole Vo Daniel Varga and Franck Polleux

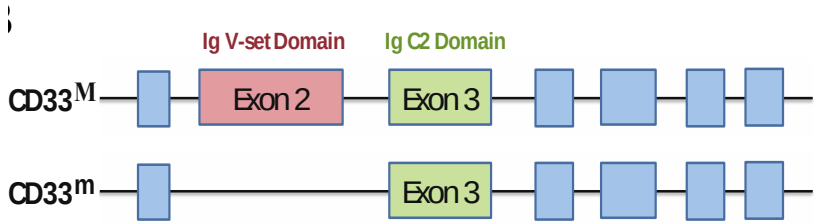
Summary

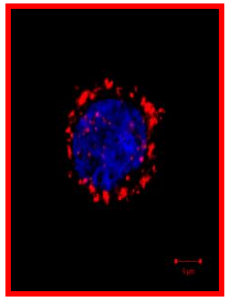
rs3865444^{C} risk allele → Greater expression of CD33M → Less Aβ uptake → More Aβ burden in brain → Genetic association is the sialic acid binding domain



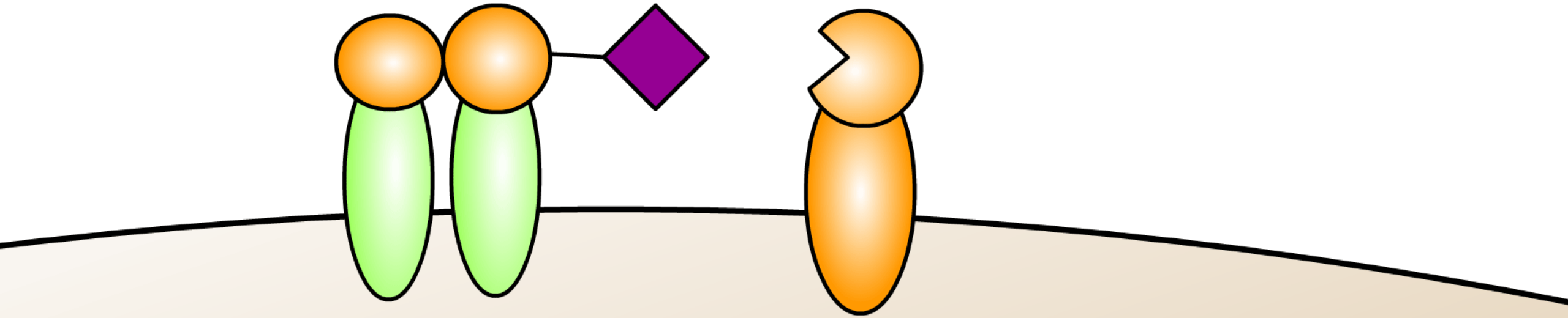


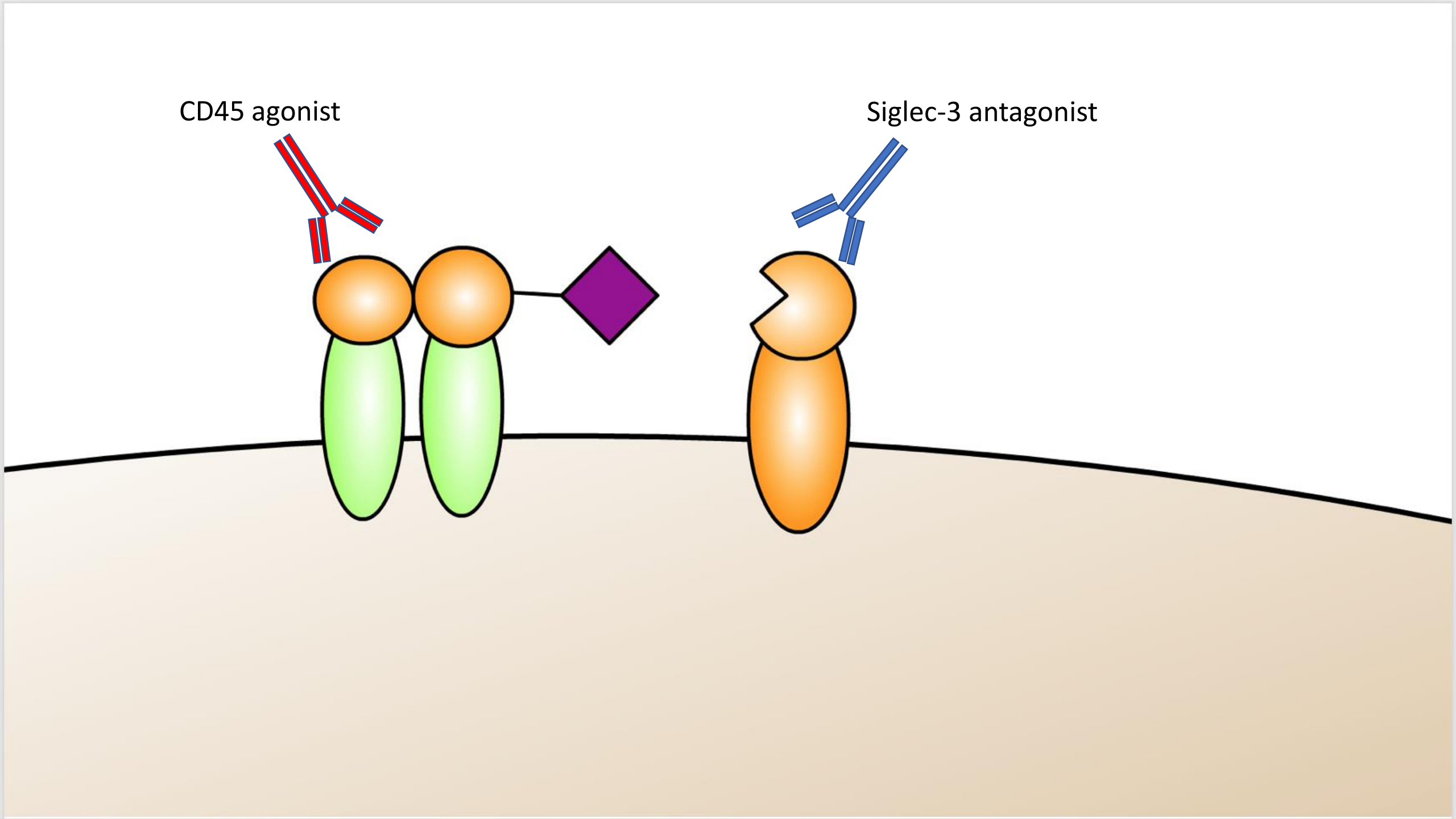




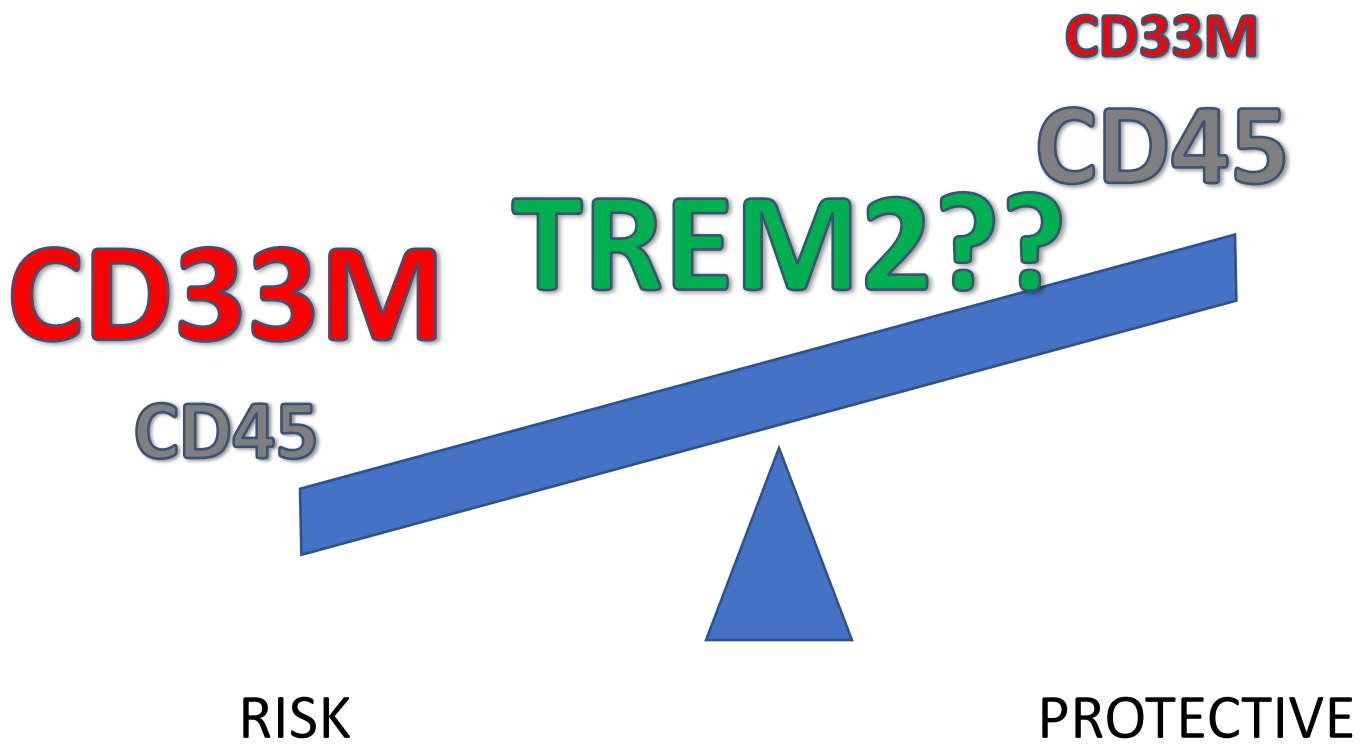


Identification of Sialic acid binding domain specific partners → New potential therapeutic targets



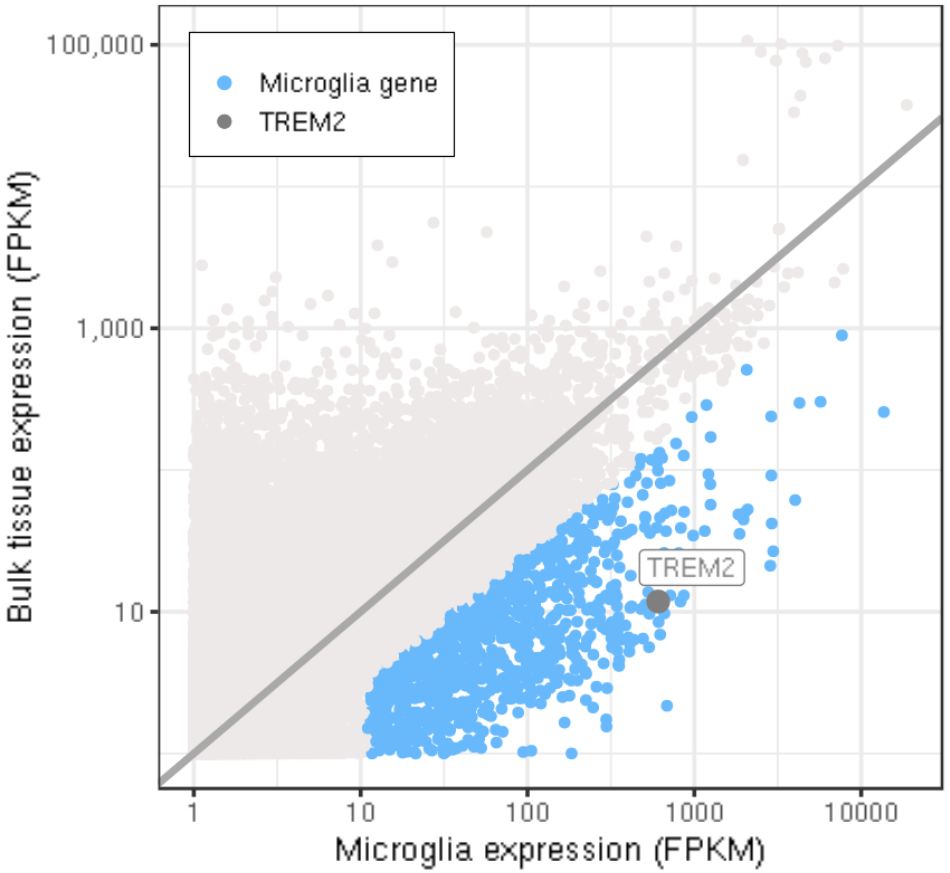

CD45 agonist
Siglec-3 antagonist

Summary

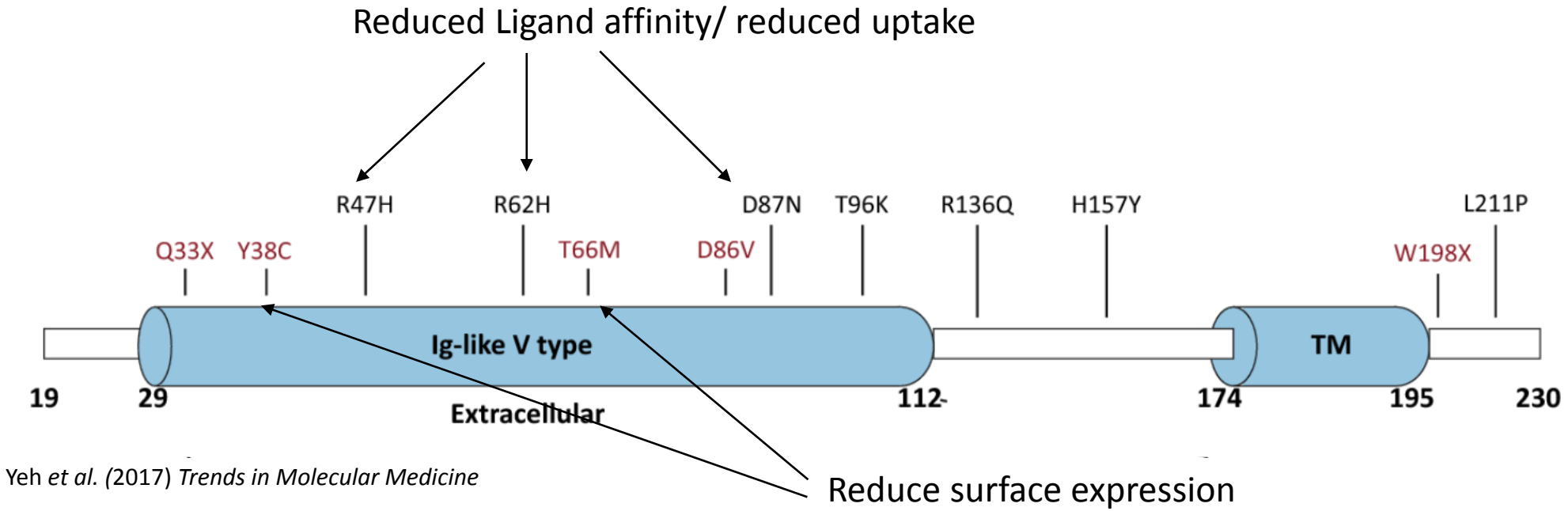


TREM2: Triggering receptor expressed on myeloid cells 2

- Signals through the adaptor protein TYROBP/DAP12
- Expressed by granulocytes, monocytes, macrophages, **microglia**, dendritic cells and osteoclasts
- Anti-inflammatory molecules enhance TREM2 expression
- Inhibits cytokine responses induced by TLR signaling
- Promotes phagocytosis



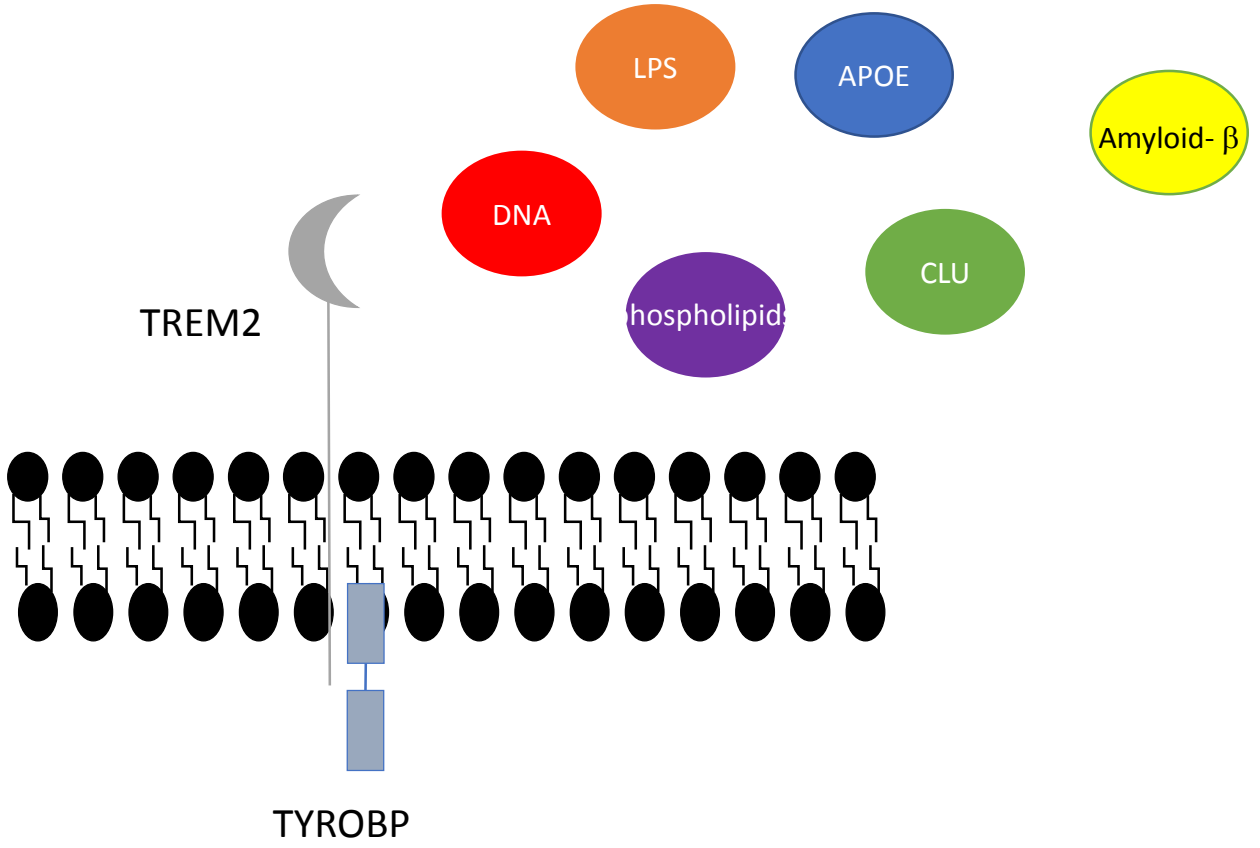
Whole genome and whole exome sequencing identified coding mutations in TREM2



Yeh *et al. (*2017) *Trends in Molecular Medicine*

Black = AD mutations
Red = FTD and NHD (Nasu–Hakola disease) mutations

What are the ligands for TREM2?

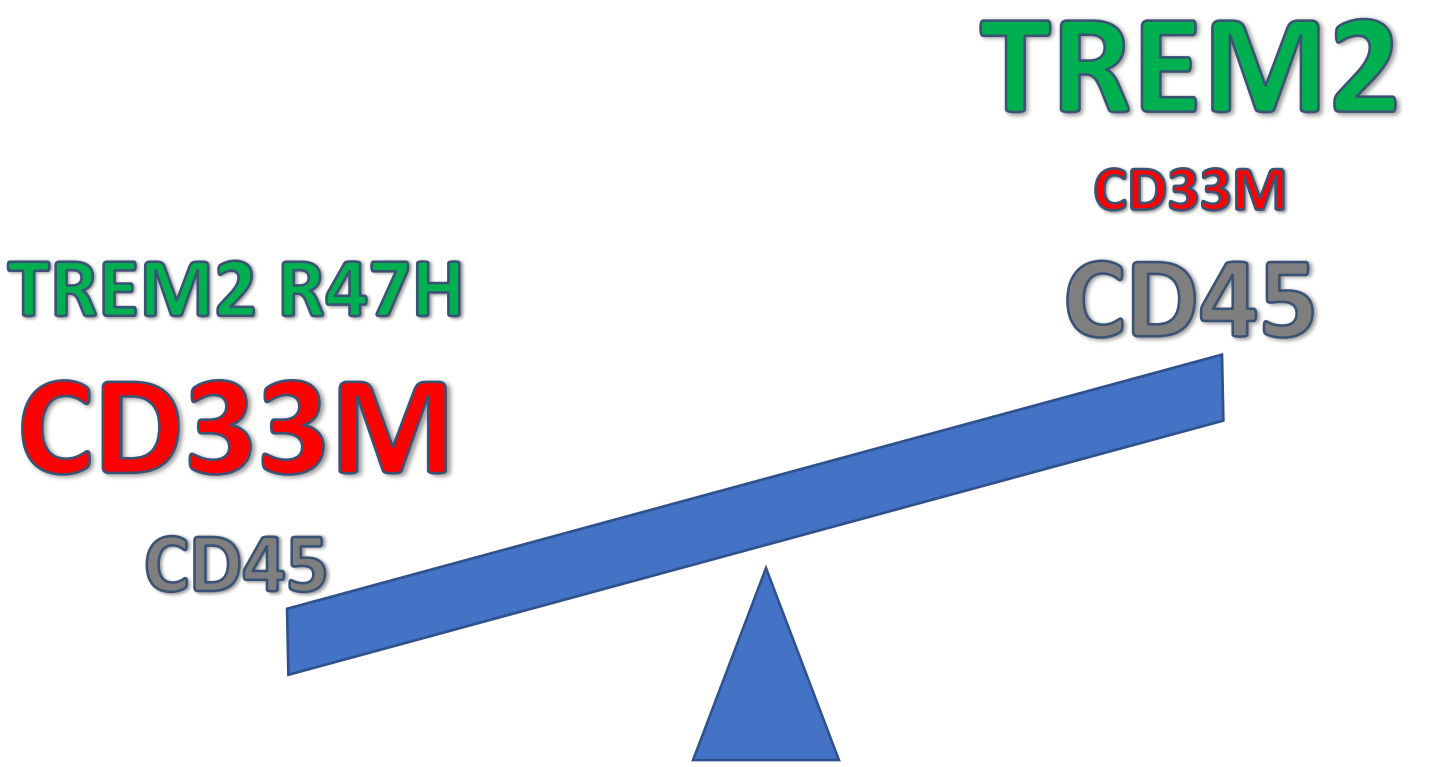


In vivo ligands in AD: APOE? Amyloid? Apoptotic cells? Myelin debris?

TREM2 KO mice phenotype

- crossed with amyloidosis model
- Microglia don’t cluster around plaques/Failed migration to lesions
- Impaired amyloid uptake
- Plaques have more dystrophic neurites with TREM2 KO (also seen in people with mutations)
- Impaired microglial activation
- R47H mutation is not as detrimental as full KO
- Accumulation of autophagic vesicles – defective energetic metabolism
- Over expression is protective

Summary



CUMC CENTER FOR TRANSLATIONAL AND COMPUTATIONAL NEUROIMMUNOLOGY

Break

ALECTOR

AL002: First-in-Class TREM2 Agonist in Alzheimer's Disease

Scientific Overview

Presenting:
Arnon Rosenthal, Ph.D.
Chief Executive Officer, Alector

ALECTOR

ALO02: In Phase 1b for Alzheimer's disease

Genetically validated target and defined patient population

ALO02	**Target**: TREM2, an activating receptor for brain immune system **Product candidate**: An antibody that is designed to increase & enhance immune response **Status**: Phase 1a SAD completed, Phase 1b in AD patients initiated

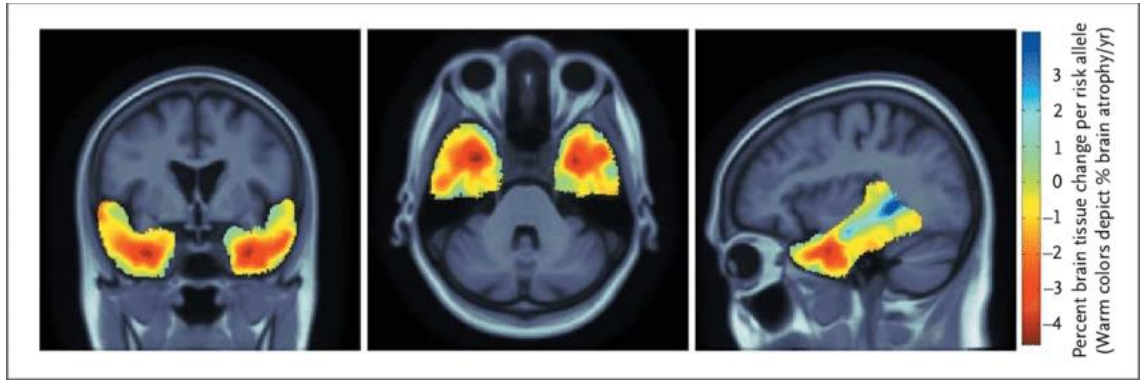
- Immune check point for microglia
- Strong genetic rationale
- Impact on both disease initiation and progression

>35M Alzheimer's disease patients globally

Scientific rationale: TREM2 causal for dementia

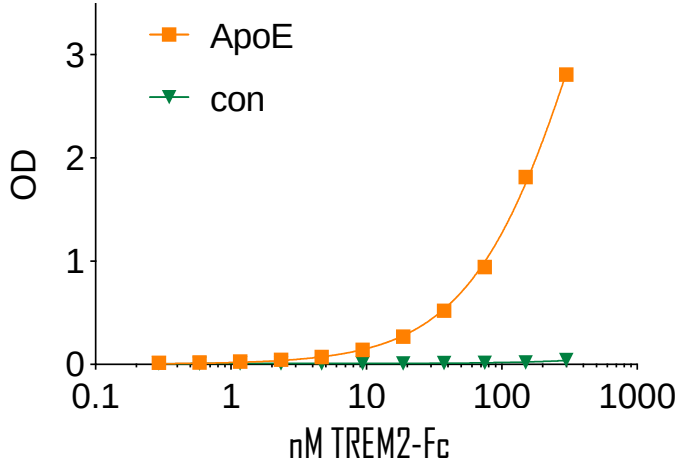
- Homozygous mutations:
  - Dementia at 100% penetrance
- Heterozygous mutations:
  - Increase risk for AD by 3x
  - Increase risk for PD
  - Double the rate of brain tissue loss
- Gain of function mutations:
  - Protective from AD
- APOE, amyloid-beta are ligands for TREM2

Brain Atrophy in Carriers of the TREM2 Risk Allele on MRI at 24 Months



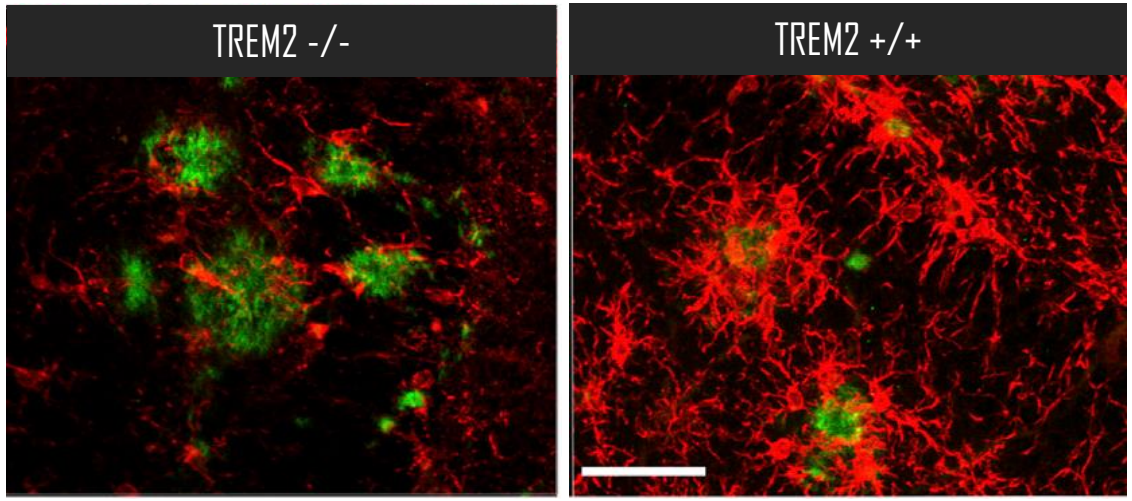
The New England Journal of Medicine 2013

APOE Binding to TREM2



TREM2 signaling is important for microglia to respond to pathology

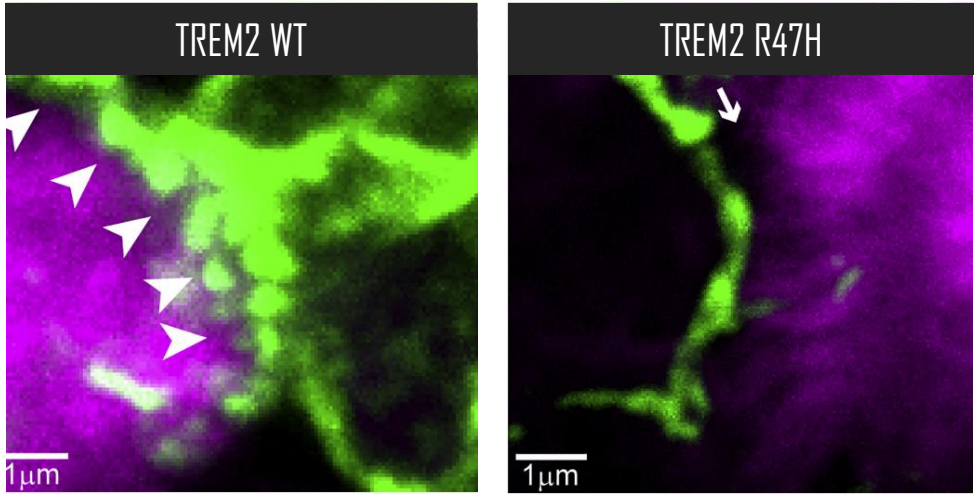
Mouse AD model



microglia
plaques

Wang et al., Cell 2015

Human AD patient

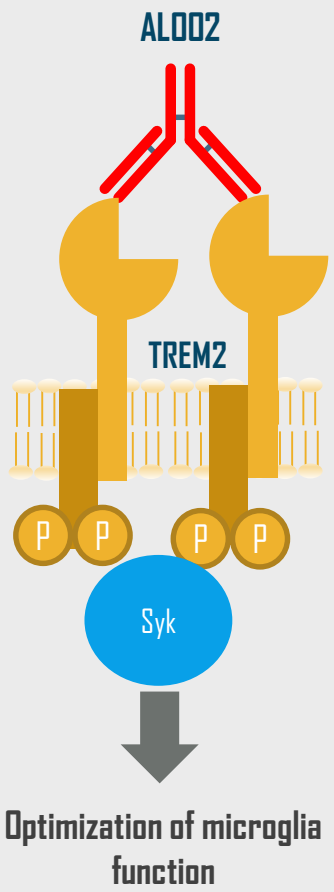


microglia
plaques

Yuan et al., Neuron 2016

- TREM2 deficiency leads to reduced microgliosis in AD model
- Human R47H TREM2 variant impairs the microglia barrier and worsens axonal dystrophy

AL002 is an antibody product candidate designed to optimize microglial function through activating TREM2



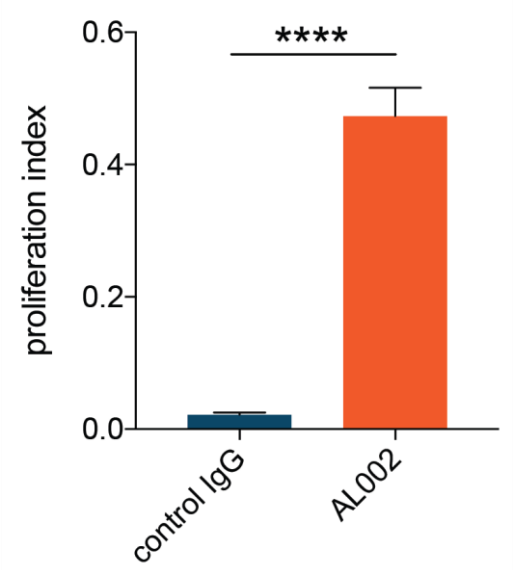
Counteracting decrease functionality of microglia by boosting TREM2 activity

Our Approach:

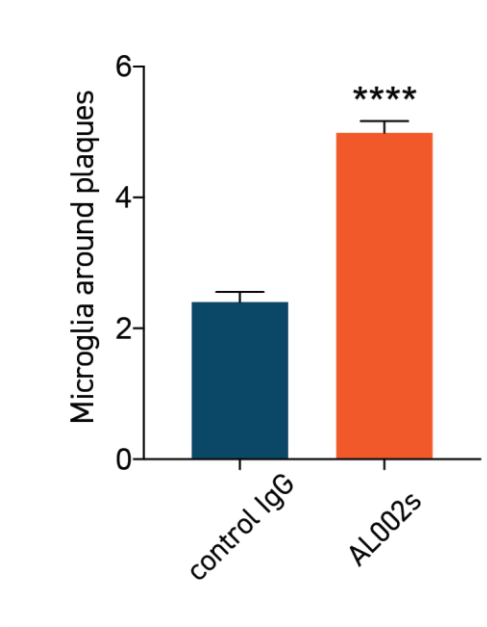
- Optimize TREM2 signaling
- Improve survival, proliferation, functionality of microglia
  - Decrease damage by disease causing proteins
  - Increase nourishment and survival of neurons
  - Optimize connections between neurons

AL002 recruit microglia to sites of Alzheimer's disease pathology

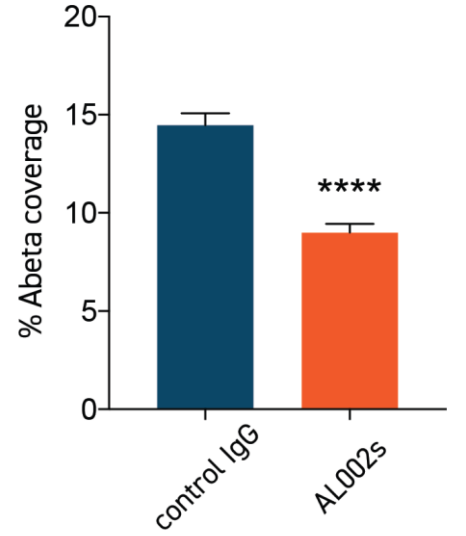
AL002s induces microglia proliferation by 5x



AL002s recruit microglia to plaques

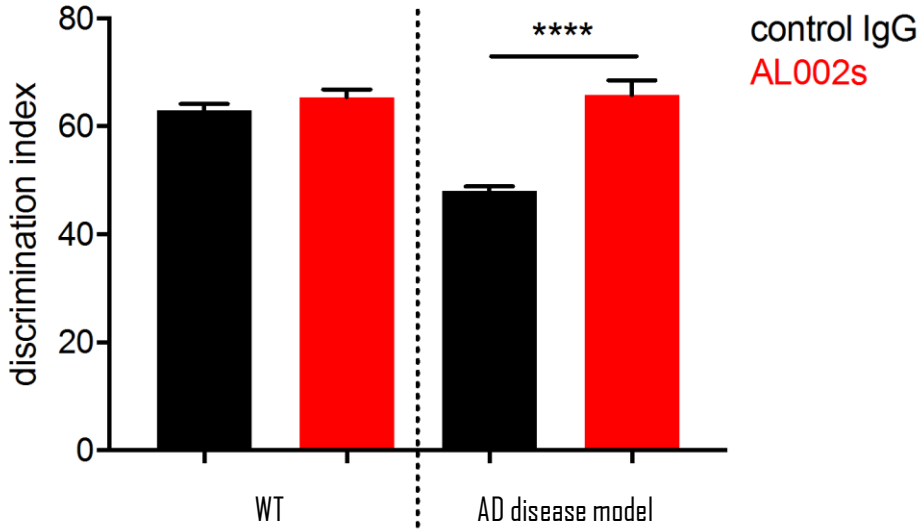


AL002s reduces area occupied by plaques



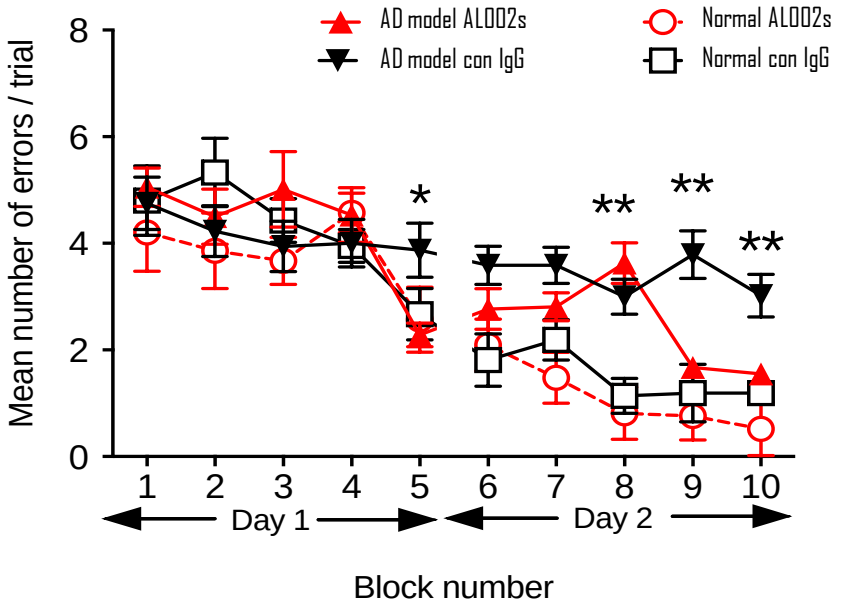
AL002s improves cognitive behavior in mouse model of AD

AL002s improves memory in novel object recognition test



****p<0.0001, One way ANOVA

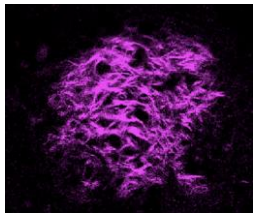
AL002s improves learning in radial arm water maze test

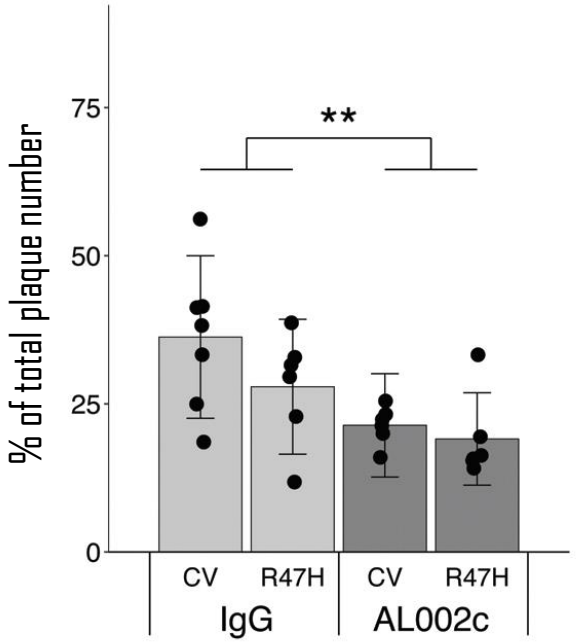


*p<0.05, Two way ANOVA

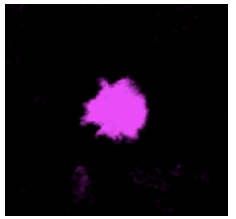
AL002c* reduces toxic filamentous plaques in a TREM2 mouse model of AD

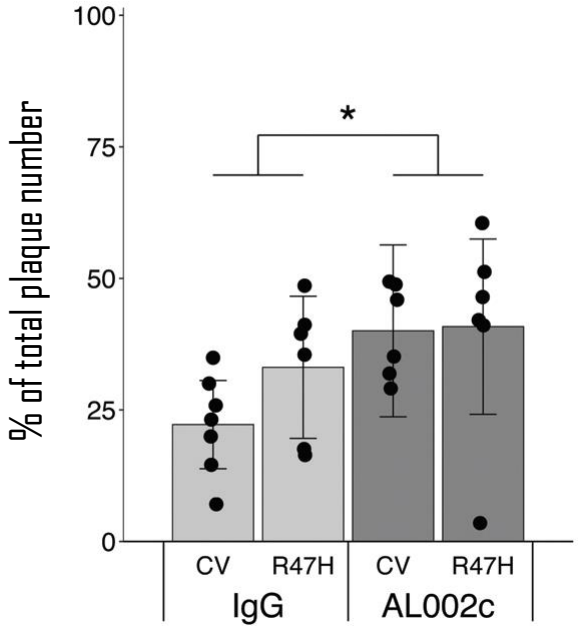
Filamentous





Inert Plaque

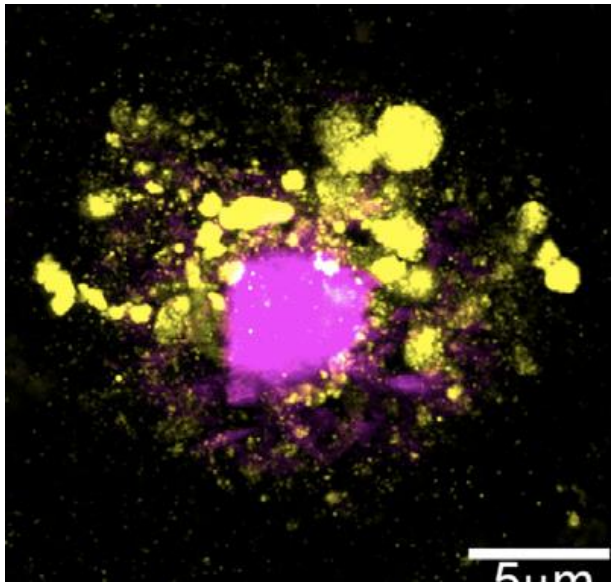




*AL002c is a variant of AL002.
Colonna et al., unpublished data

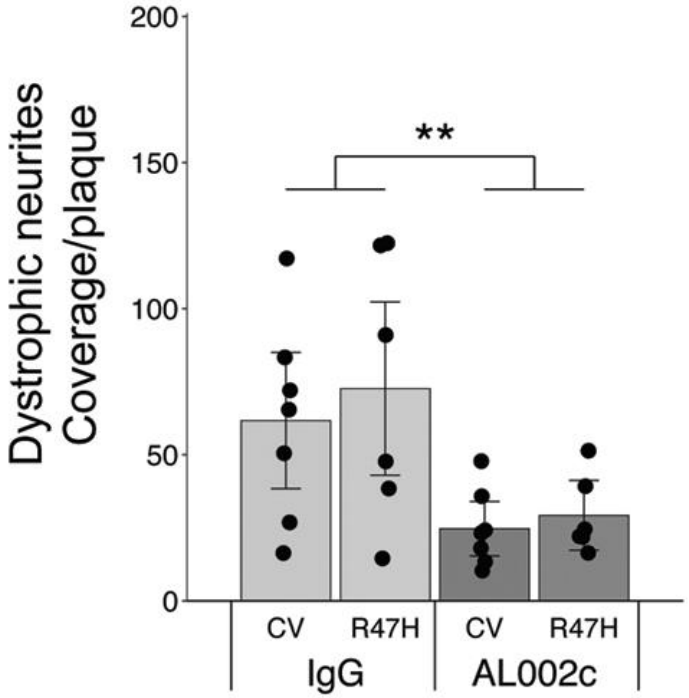
AL002c* activates microglia and reduces neurite dystrophy in a TREM2 mouse model of AD

Neurite dystrophy



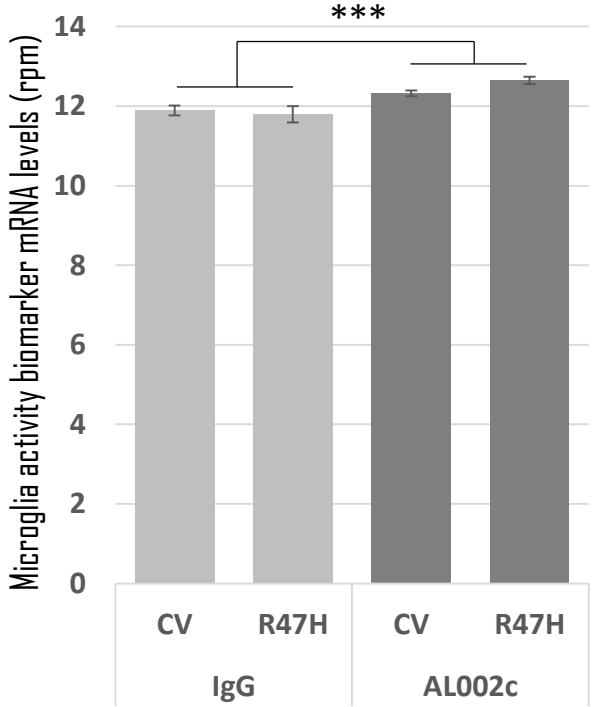
Yuan, Neuron 2016

Reduction of neurite dystrophy



CV stands for common variant

AL002c increases microglia activity biomarker in the mouse brain



CV stands for common variant

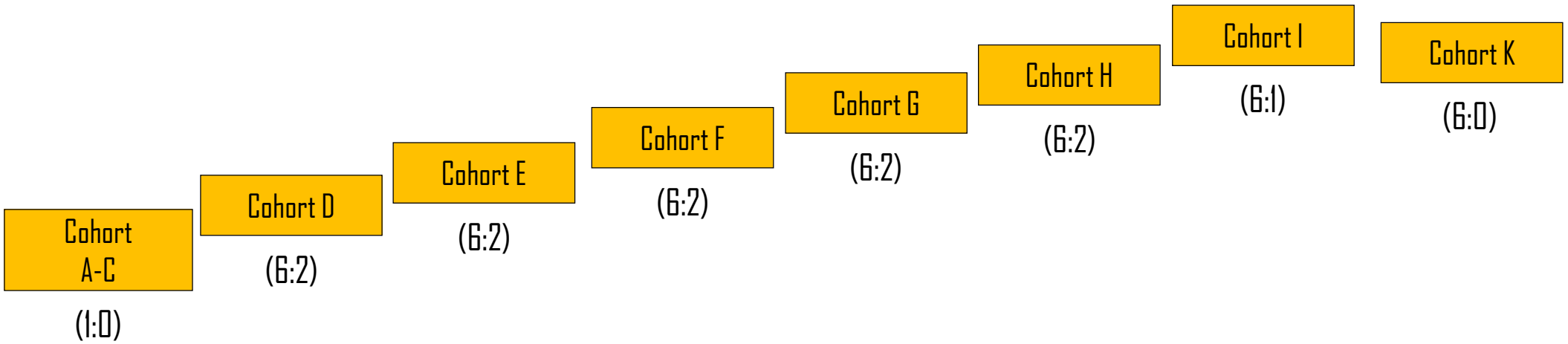
AL002:
Clinical Data and Update

Presenting:
Robert Paul, M.D., Ph.D.
Chief Medical Officer, Alector

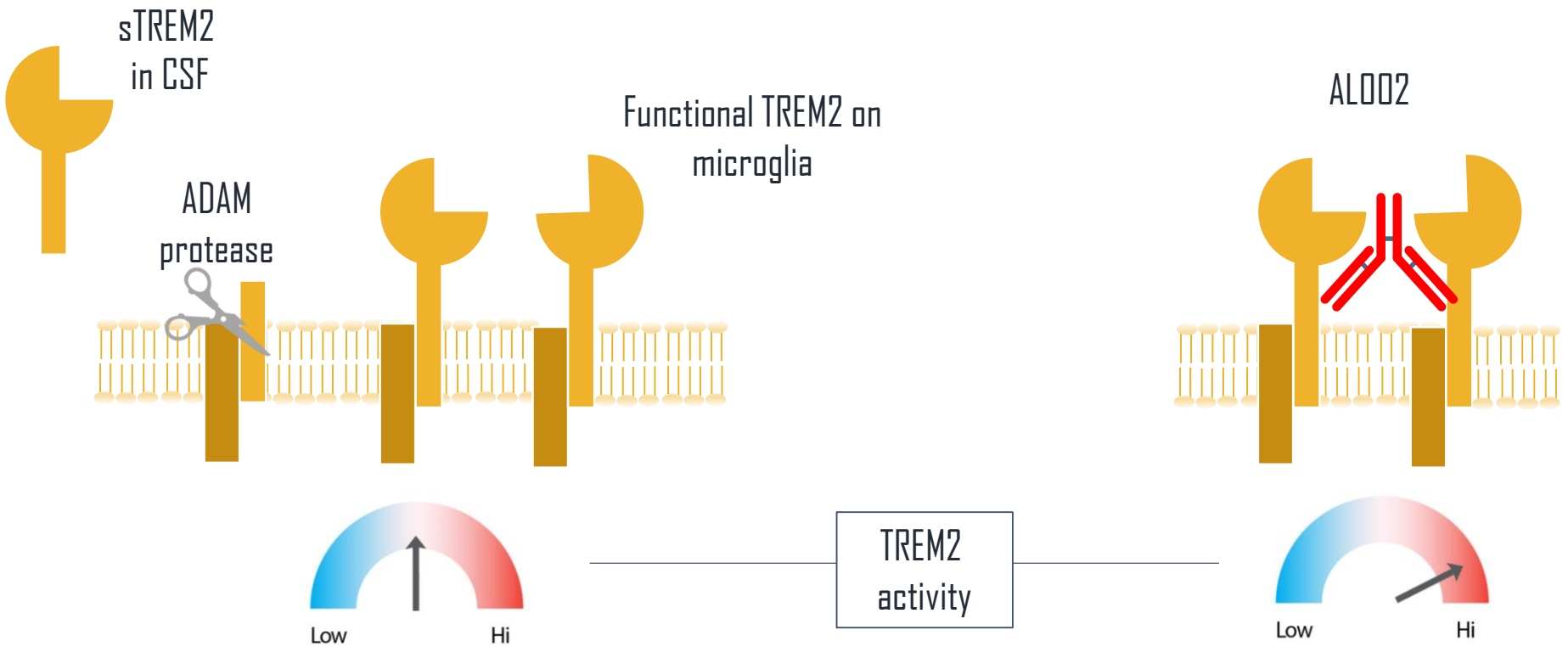
ALECTOR

ALO02 Phase 1a summary

- Fifty-six (56) healthy volunteers (HV) dosed with nine escalating doses
- ALO02 was generally safe and well tolerated in HVs
- ALO02 reduced CSF sTREM2 level in a dose dependent manner demonstrating proof-of-target engagement in the brain
- ALO02 increased a biomarker for microglia activity in the CSF, indicating proof-of-mechanism



AL002 intervention: Less sTREM2 means more TREM2 activity



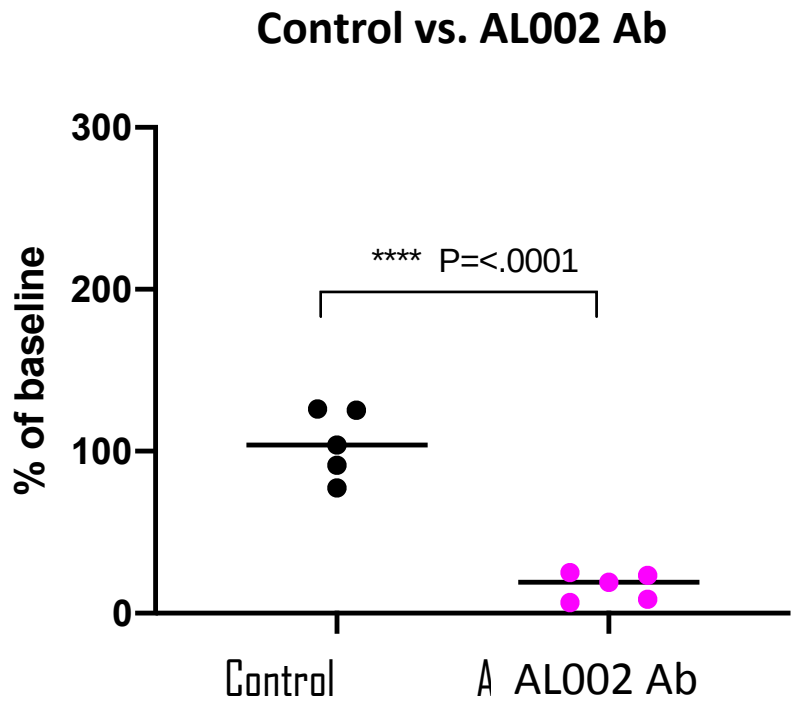
- sTREM2 is produced by TREM2 shedding

- AL002 activates TREM2 signaling
- Decreases sTREM2

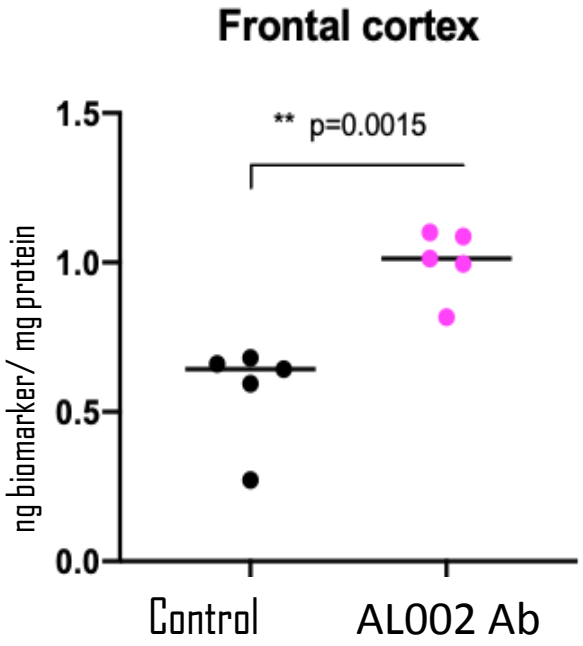
Soluble TREM2 does not have any known therapeutic function only membrane TREM2 does

AL002 reduces sTREM2, and increases microglia activity in brains of non-human primate (NHP)

AL002 decreases CSF sTREM2



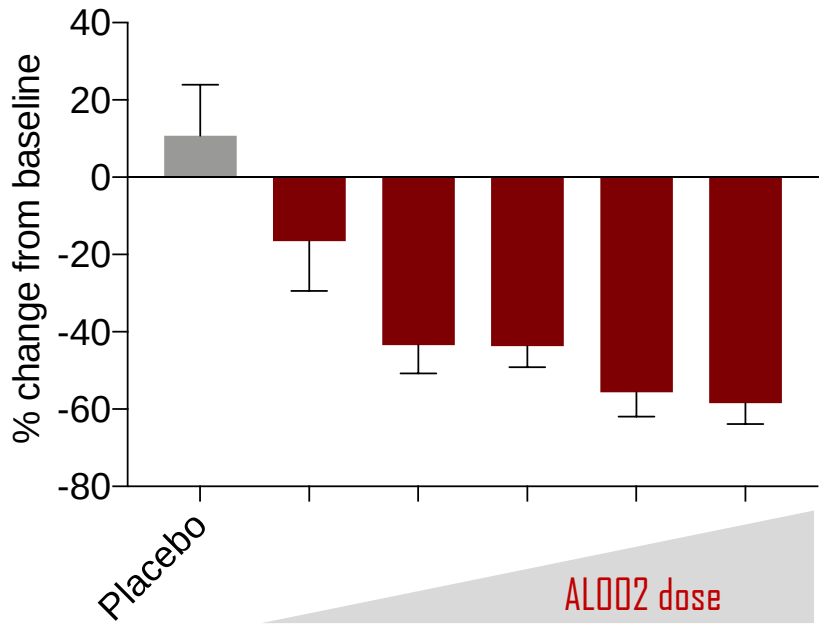
AL002 increases microglia activity biomarker in the NHP brain



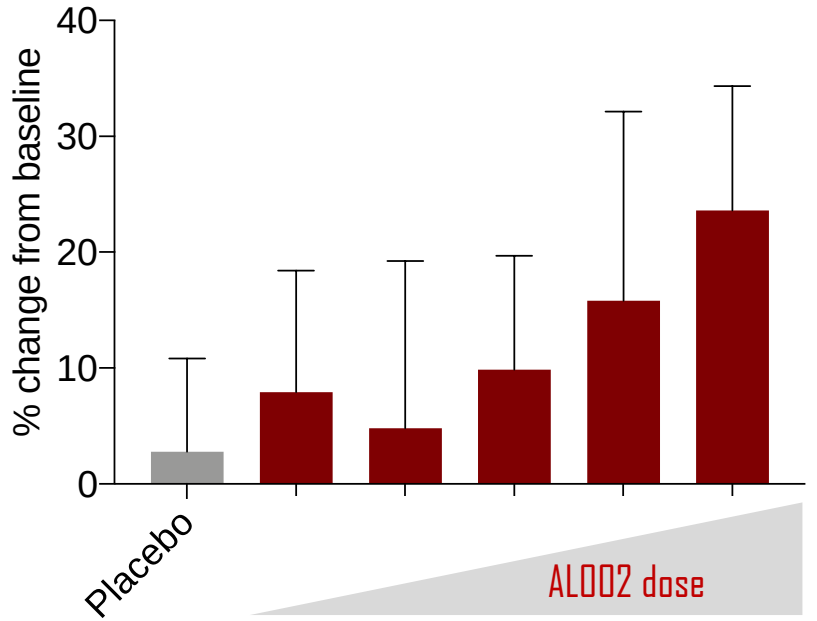
AL002 Ab: AL002 variant (different F_c)

ALO02 demonstrated target engagement and proof-of-mechanism in the CSF of HVs

ALO02 decreases CSF sTREM2

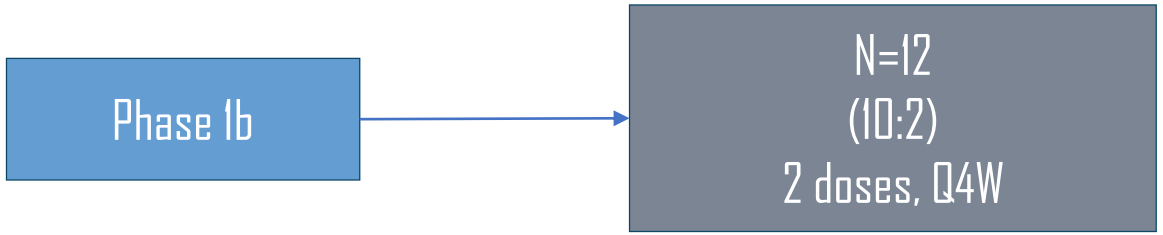


ALO02 increases microglia activity biomarker in CSF



Ongoing ALO02 Phase 1b study: One-month multiple-dose cohort

Objectives: Safety, PK, PD in mild to moderate Alzheimer's disease patients

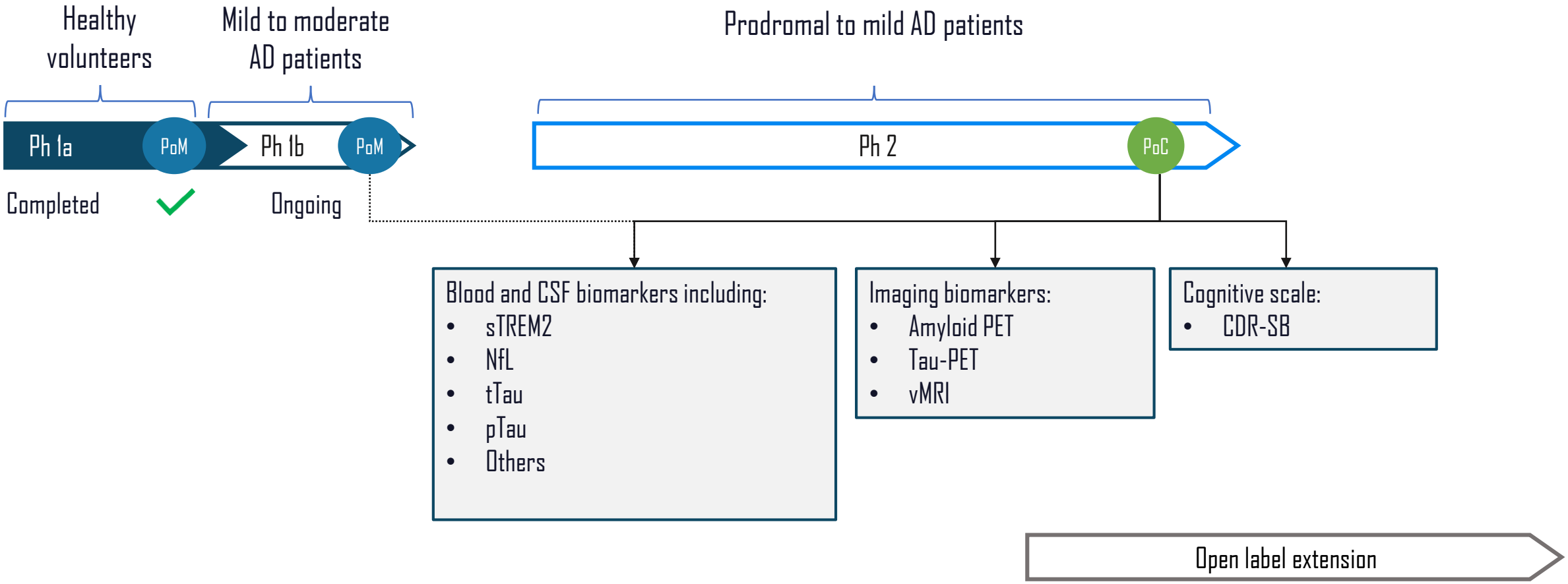


Biomarker assessments:
- CSF biomarkers including sTREM2
- MRI

Key inclusion criteria:
- Age 50-85 years, inclusive
- MMSE 16-28
- CDR-GS of 0.5, 1.0, or 2.0
- Positive amyloid-PET

AL002: PoC trial in Alzheimer's disease starting second half of 2020

AL002 Clinical Development Plan



AL002: Summary

- AL002 is the first TREM2 agonist antibody in clinical development for Alzheimer's disease
- AL002 was generally safe and well tolerated in the single ascending dose part of Phase 1
- AL002 demonstrated proof-of-target engagement in the brain of HVs by decreasing CSF sTREM2
- AL002 demonstrated proof-of-mechanism in the brain of HVs by increasing a microglia activity biomarker
- Safety, target engagement and proof-of-mechanism support continued development of AL002

AL003: First-in-class SIGLEC 3 antibody for Alzheimer's disease

Scientific Overview

Presenting:
Arnon Rosenthal, Ph.D.
Chief Executive Officer, Alector

ALECTOR

AL003: In Phase 1b for Alzheimer's disease

Genetically validated target and defined patient population

AL003	**Target**: SIGLEC 3, an inhibitory receptor expressed on microglia **Product candidate**: An antibody that is designed to optimize immune response in the brain **Status**: Phase 1a completed, initiated screening for Phase 1b in AD patients

- A SIGLEC 3 AD risk allele is present in 80% of AD patients
- Loss of function allele is protective in AD patients in addition to animal models

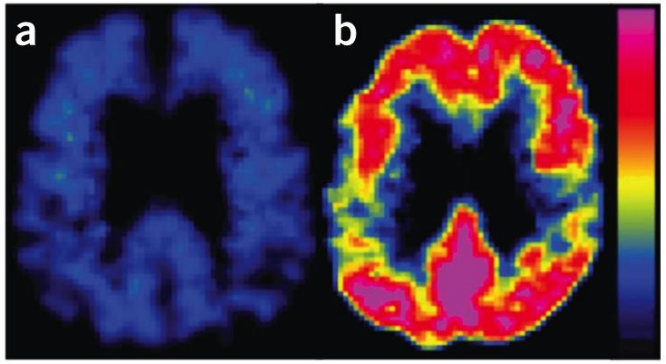
---

> 35M Alzheimer's disease patients globally

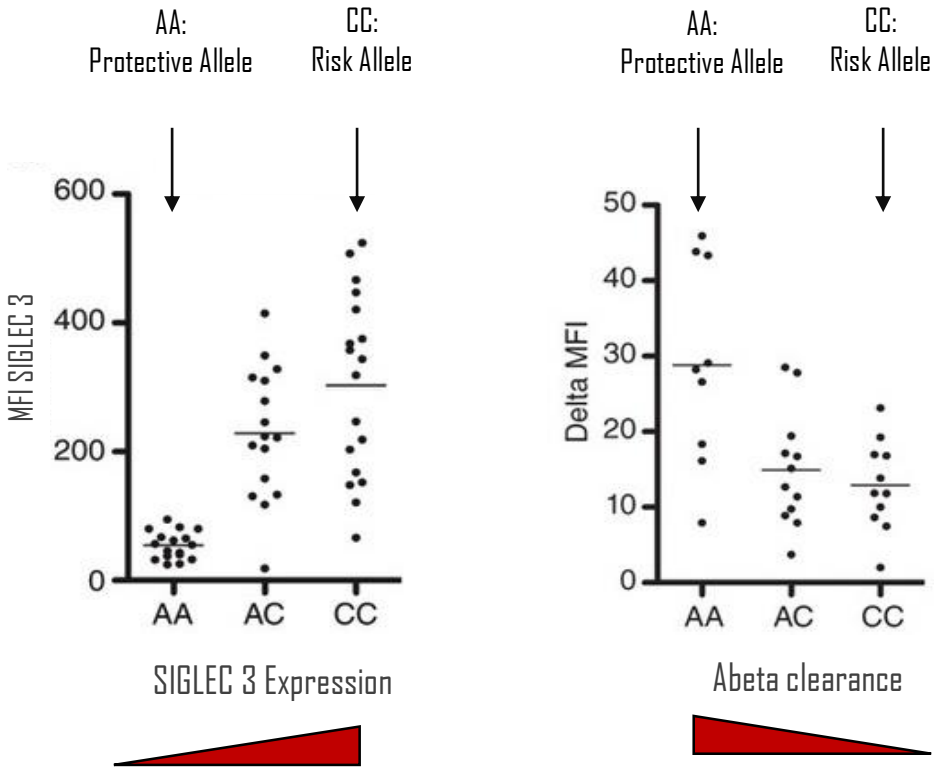
Scientific Rationale for ALO03: SIGLEC 3 is a risk gene for AD

- A receptor expressed on microglia and myeloid immune cells
- Prevalent risk allele in AD*:
  - Increased risk for AD**
  - Decreased amyloid-beta plaque clearance**
  - Smaller brain volume***

Protective Risk

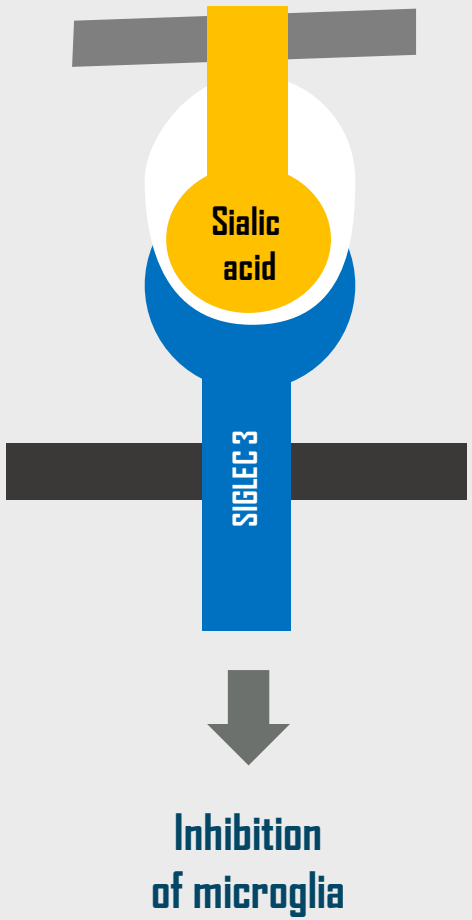


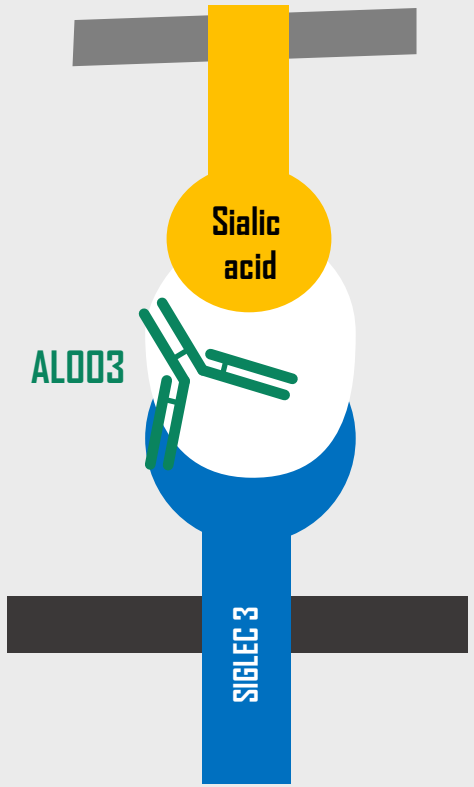
High-risk allele (right) shows increase in amyloid-beta pathology **



*Neurobiol Aging. 2015 Apr;36(4):1765.e7-1765.e16. **Nature Neuroscience volume 16, pages 848–850 (2013). ***Neurobiol Aging. 2015 Apr;36(4):1765.e7-1765.e16

ALO03 is an antibody product candidate designed to block SIGLEC 3 function in the brain



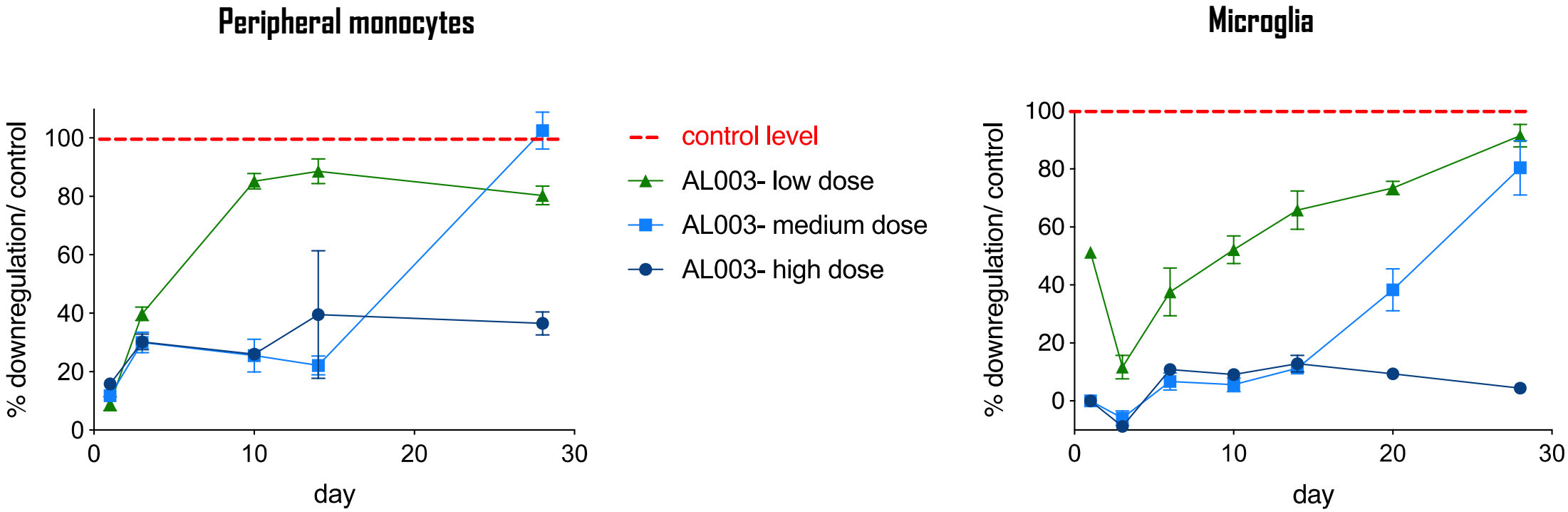


Increasing functionality by releasing the brakes on microglia

Our Approach:

- ALO03 mimics the protective allele of SIGLEC 3
- Block SIGLEC 3 inhibition of microglial function
- Improves functionality of microglia

AL003 shows similar dose dependent target engagement in monocytes and microglia in mice



Target engagement in blood predicts target engagement in brain

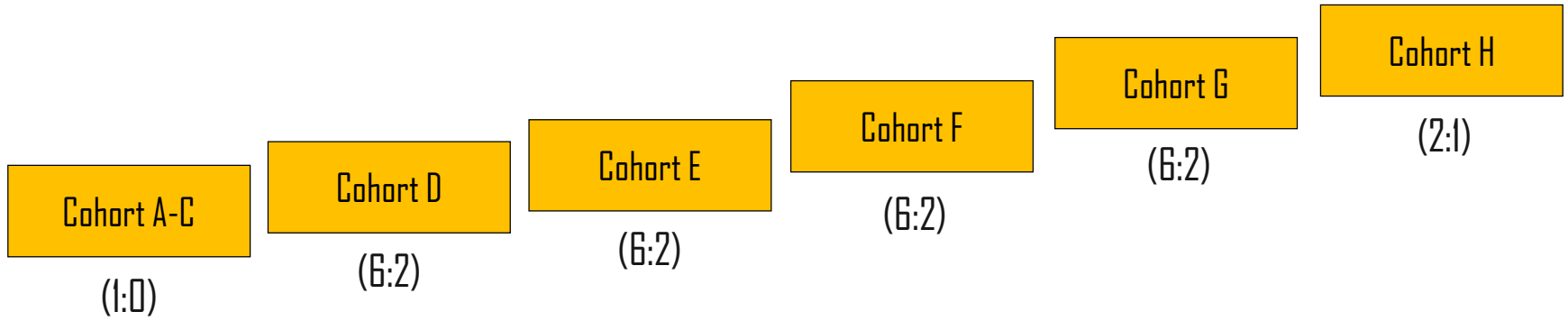
AL003:
Clinical Update

Presenting:
Robert Paul, M.D., Ph.D.
Chief Medical Officer, Alector

ALECTOR

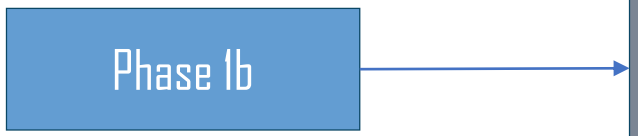
AL003 Phase 1 study update

- Thirty-eight (38) healthy volunteers (HV) dosed with eight escalating doses
- AL003 showed robust target engagement in the periphery at low doses
- Initiated screening for Phase 1b in AD patients
- AL003 was generally safe and well tolerated at all doses except for the top two doses:
  - Two serious adverse events (SAEs) observed and considered related to AL003
  - Both subjects responded to treatment with steroids, SAEs have resolved
- Maximum Tolerated Dose (MTD) established that will be carried forward to Phase 1b



Ongoing AL003 Phase 1b study: One-month multiple-dose cohort

Objectives: Safety, PK, PD in mild to moderate Alzheimer's disease patients



N=12
(10:2)
2 doses, Q4W

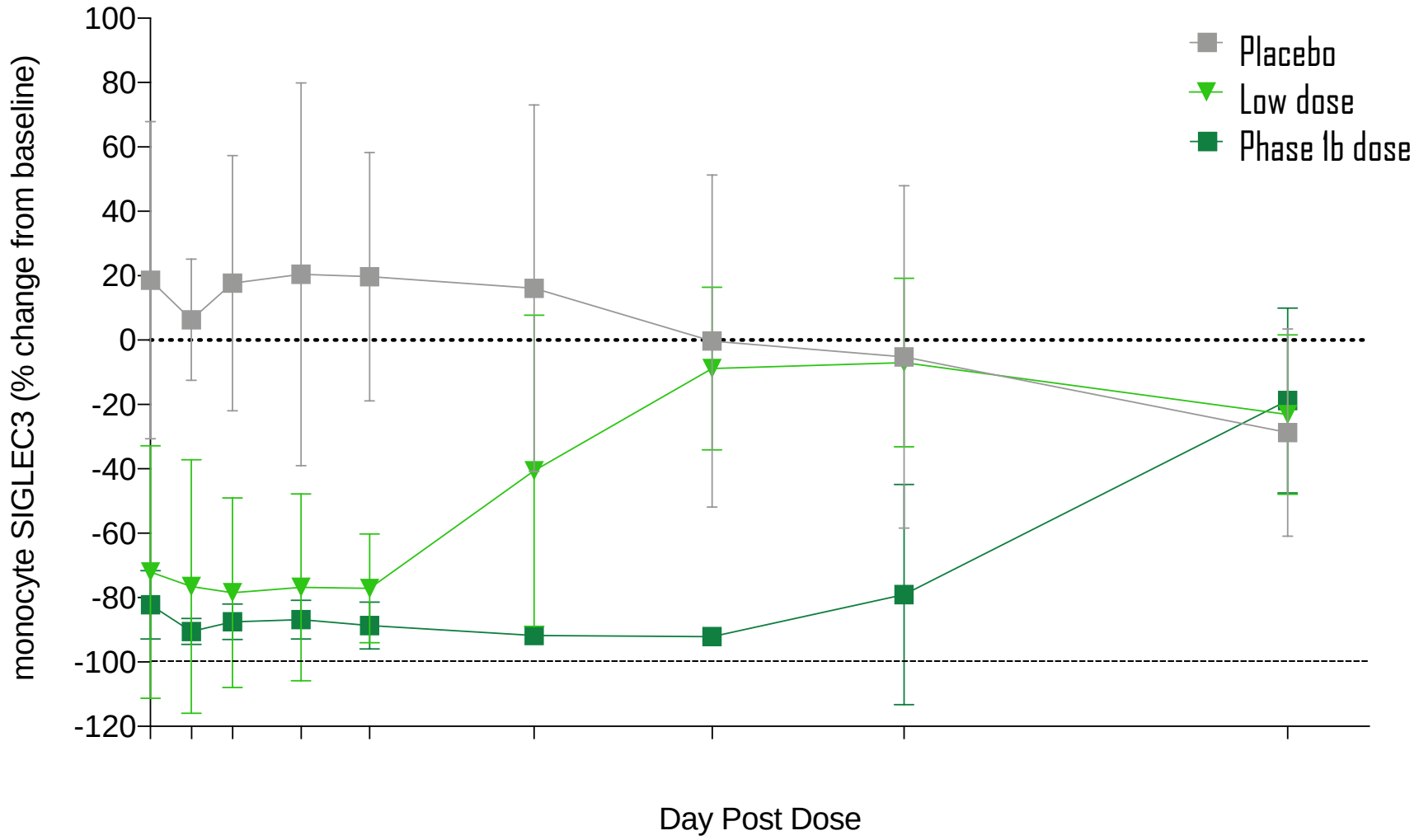
Key inclusion criteria:

- Age 50-85 years, inclusive
- MMSE 16-28
- CDR-GS of 0.5, 1.0, or 2.0
- Positive amyloid-PET
- Carrier of risk allele

Biomarker assessments:

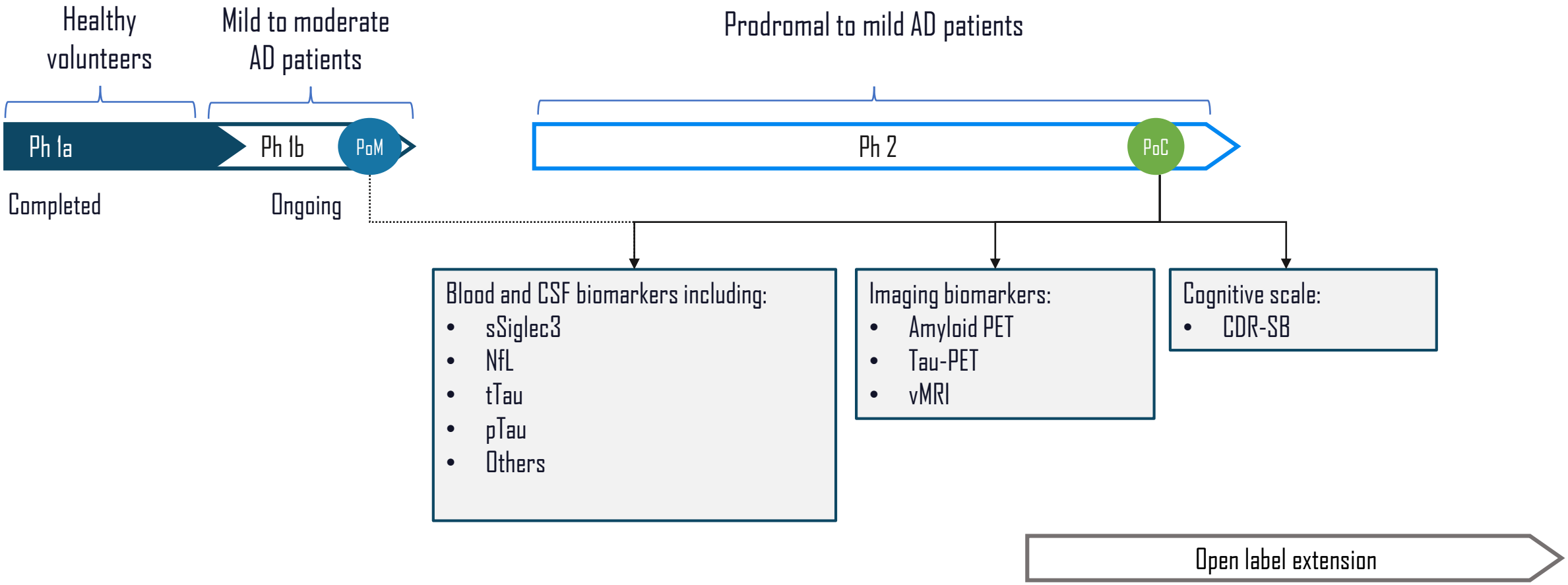
- CSF biomarkers including sSIGLEC3
- MRI

AL003: Phase 1a peripheral biomarker data in healthy volunteers



AL003: Phase 1b proof-of-mechanism data coming in 2020

AL003 Clinical Development Plan



AL003: Summary

- AL003 is the first Siglec 3 blocking antibody in clinical development for Alzheimer's disease
- Maximum Tolerated Dose (MTD) established that will be carried forward to Phase 1b
- AL003 showed robust target engagement in the periphery at low doses
- Phase 1b in AD patients initiated with proof-of-mechanism data coming in 2020

Q&A

ALECTOR

New Alector program: Scientific overview

Presenting:
Carlos Cruchaga, PhD
Professor of Psychiatry and Neurology, Director of NeuroGenomics and Informatics Washington University in St. Louis

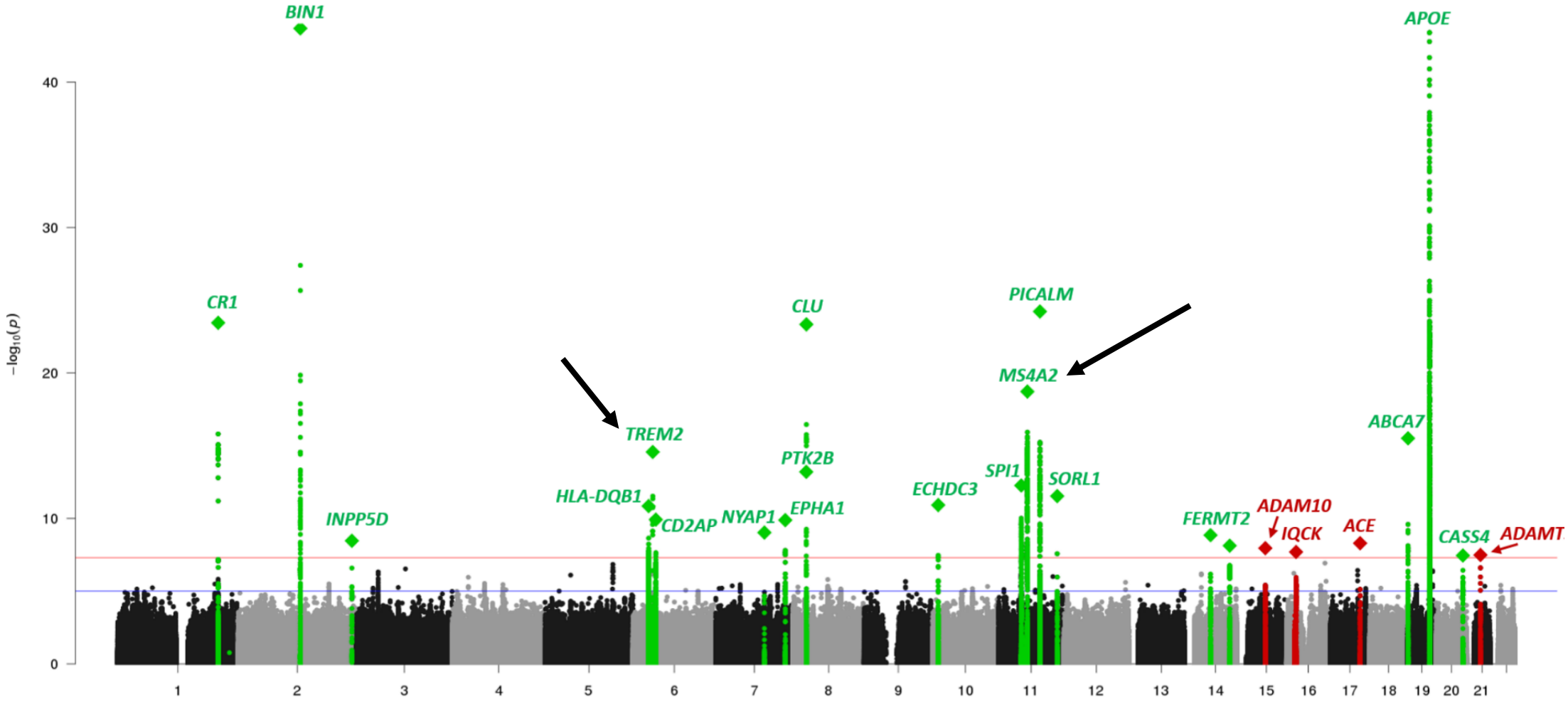
The MS4A gene cluster is a key modulator of soluble TREM2 and Alzheimer's disease risk

Carlos Cruchaga

Neurogenomics & Informatics

Washington University in St. Louis

Genome-wide association study for Alzheimer's disease



Kunkle et al, 2019, N=89,769

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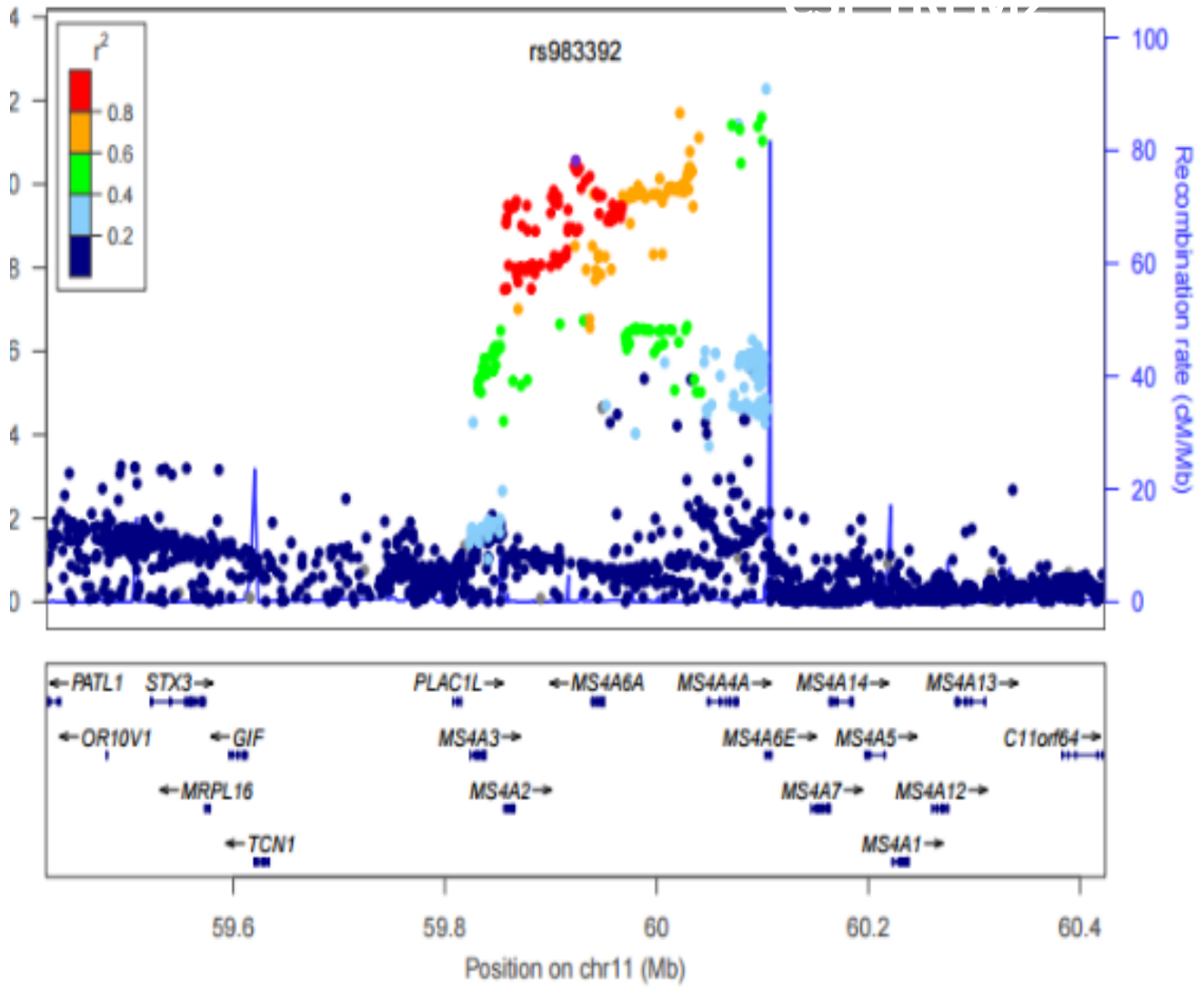
Some GWAS SNPs implicate a region but not a specific gene



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Multi-omics: from gene to Function

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D.,
Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D.,
Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D.,
Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D.,
Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D.,
Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D.,
Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D.,
Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D.,
for the Alzheimer Genetic Analysis Group*

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg Ph.D., Ingileif Jonsdottir, Ph.D.,
Palmi V. Jonsson, M.D., Jon Snaedal, M.D., Sigurbjorn Bjornsson, M.D., Johanna Huttenlocher, B.S.,
Allan I. Levey, M.D., Ph.D., James J. Lah, M.D., Ph.D., Dan Rujescu, M.D., Harald Hampel, M.D.,
Ina Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Knut Engedal, M.D., Ph.D., Ingun Ulstein, M.D., Ph.D.,
Srdjan Djurovic, Ph.D., Carla Ibrahim-Verbaas, M.D., Albert Hofman, M.D., Ph.D., M. Arfan Ikram, M.D., Ph.D.,
Cornelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D., Augustine Kong, Ph.D.,
and Kari Stefansson, M.D., Ph.D.

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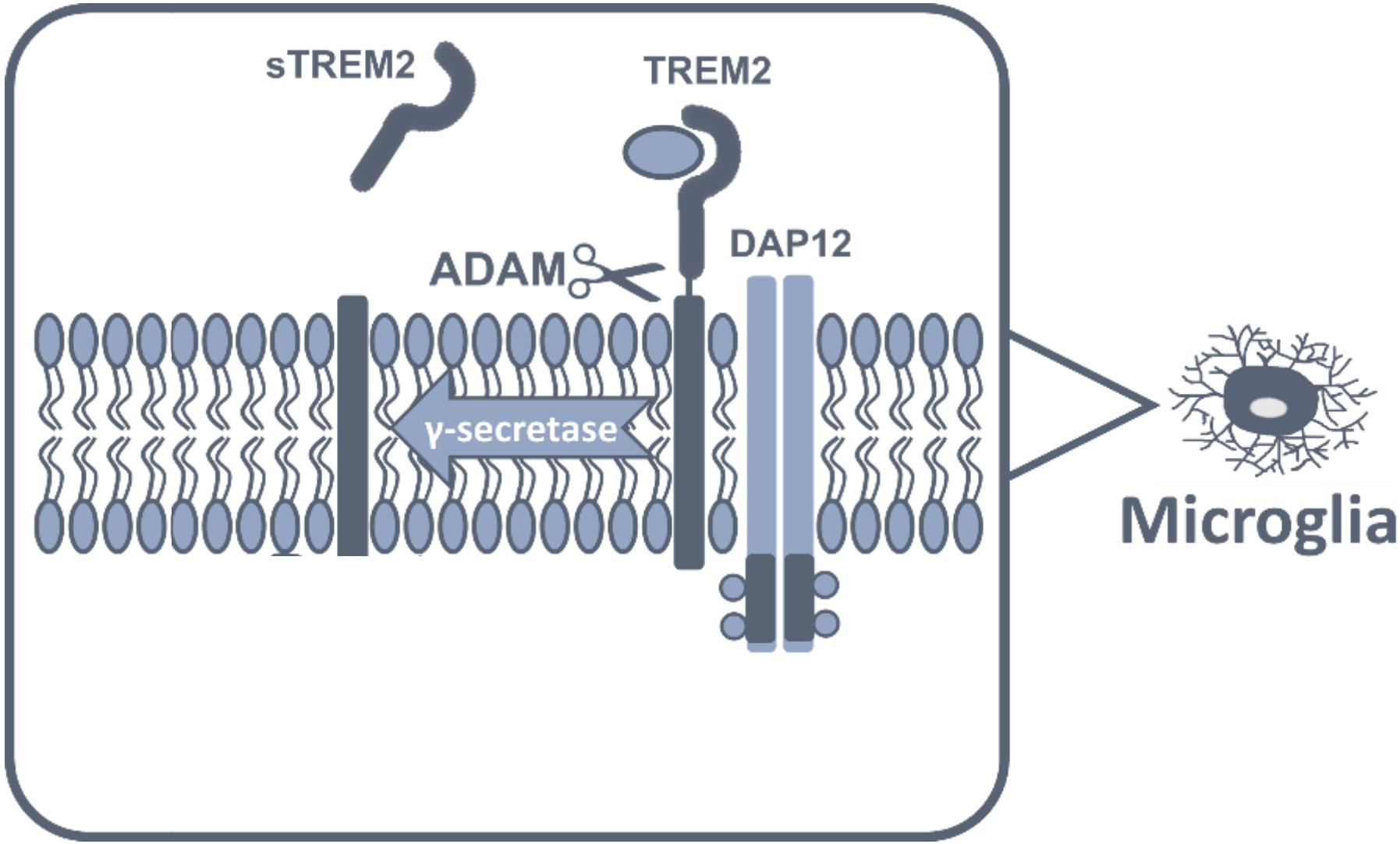
sTREM2



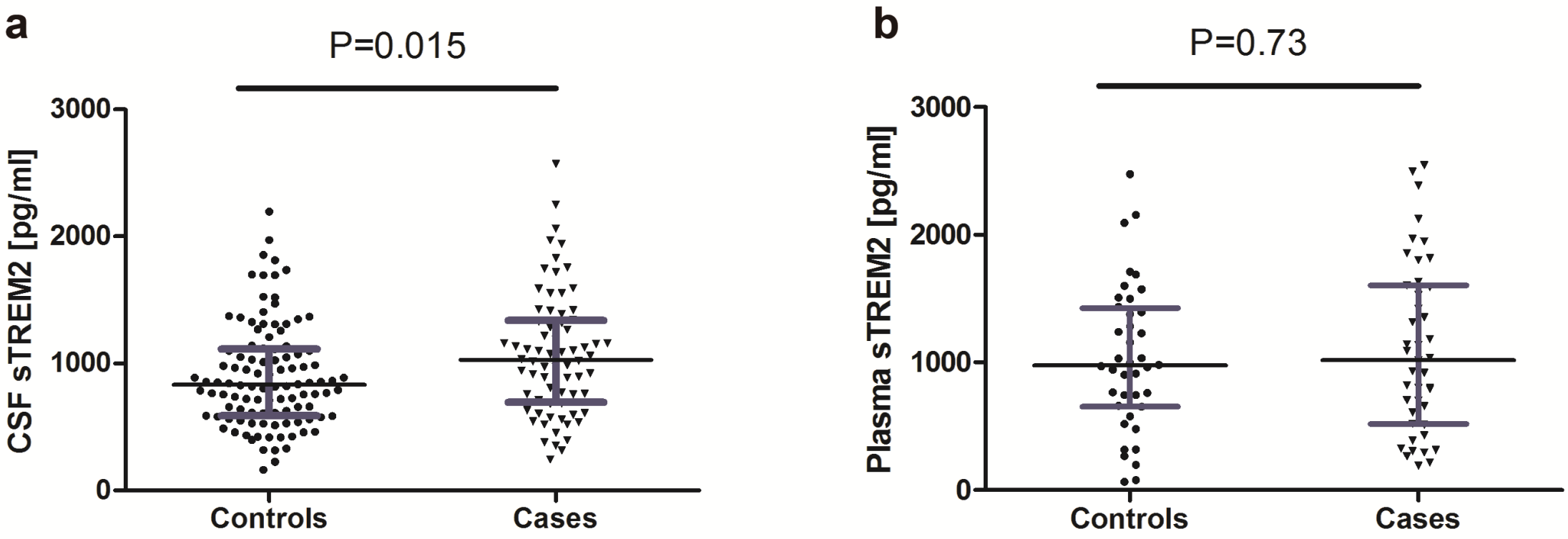
CSF TREM2 levels: study design

- **We measured CSF TREM2 levels in:**
  - **107 controls**
  - **73 AD cases**
  - **40 TREM2 variant carriers**

- **We have:**
  - **CSF tau and Aβ levels available to all individuals**
  - **And GWAS data**

Piccio et al, Acta Neuropath 2017

CSF TREM2 levels: Results



Piccio et al, Acta Neuropath 2017

CSF TREM2 as Biomarker

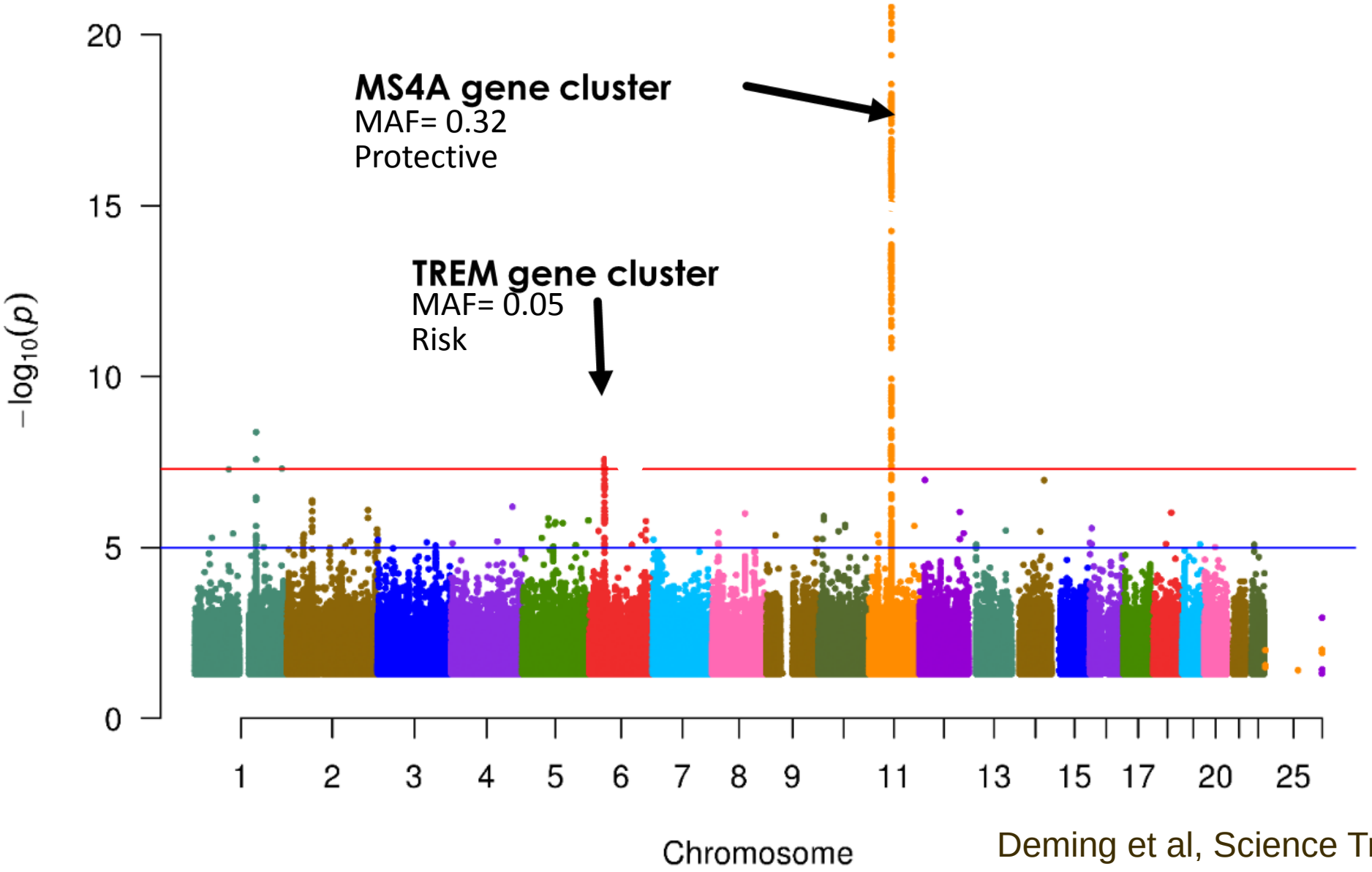
- **CSF TREM2 is increased in early stages of AD and correlates with CSF ptau levels**
- **TREM2 risk variants present different functional mechanism**
  - **NSK pathogenic variants are not expressed on the cell surface**
- **CSF TREM2 levels may be an informative biomarker for AD**

Piccio et al, Acta Neuropath 2017

Genome-wide screening CSF TREM2

	AD Cases	Controls	P
N	606	207	
age (years, mean ± SD)	73.09 ± 7.73	73.13 ± 6.07	0.955
females (%)	252 (41.6)	108 (52.2)	0.010
APOE ε4+ (%)	337 (55.6)	55 (26.6)	< 0.001
CDR at LP (%)			
0	41 (6.8)	197 (95.2)	
0.5	466 (76.9)	10 (4.8)	
1	99 (16.3)	0 (0)	
WashU sTREM2 (pg/mL mean ± SD)	2413.99 ± 730.13	2430.05 ± 764.84	0.783
LMU sTREM2 (pg/mL mean ± SD)	3910.94 ± 1932.31	3879.98 ± 1884.00	0.841
CSF $A\beta_{42}$ (pg/mL mean ± SD)	774.20 ± 333.58	1093.69 ± 365.18	< 0.001
CSF tau (pg/mL mean ± SD)	309.87 ± 139.66	230.15 ± 82.28	< 0.001
CSF $ptau_{121}$ (pg/mL mean ± SD)	30.38 ± 15.67	20.91 ± 8.13	< 0.001

CSF sTREM2: GWAS analyses



Deming et al, Science Translational Medicine

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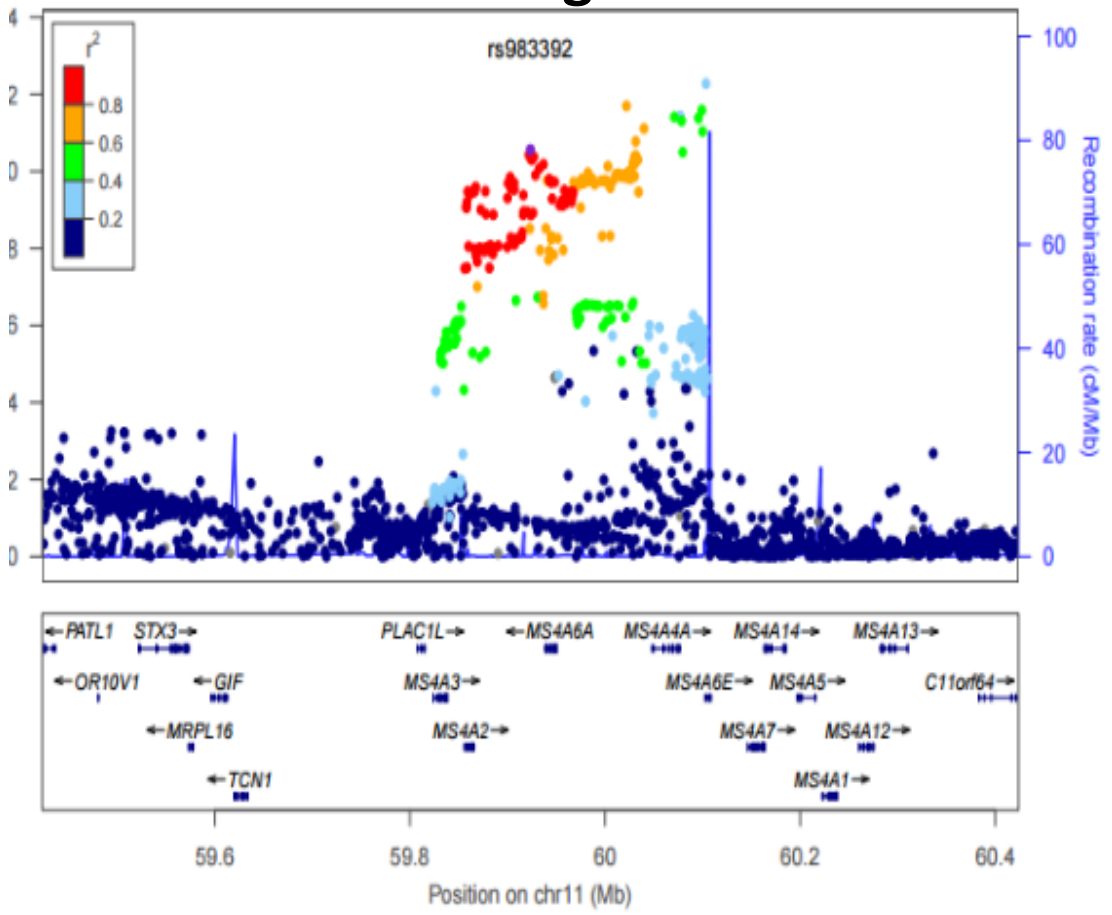
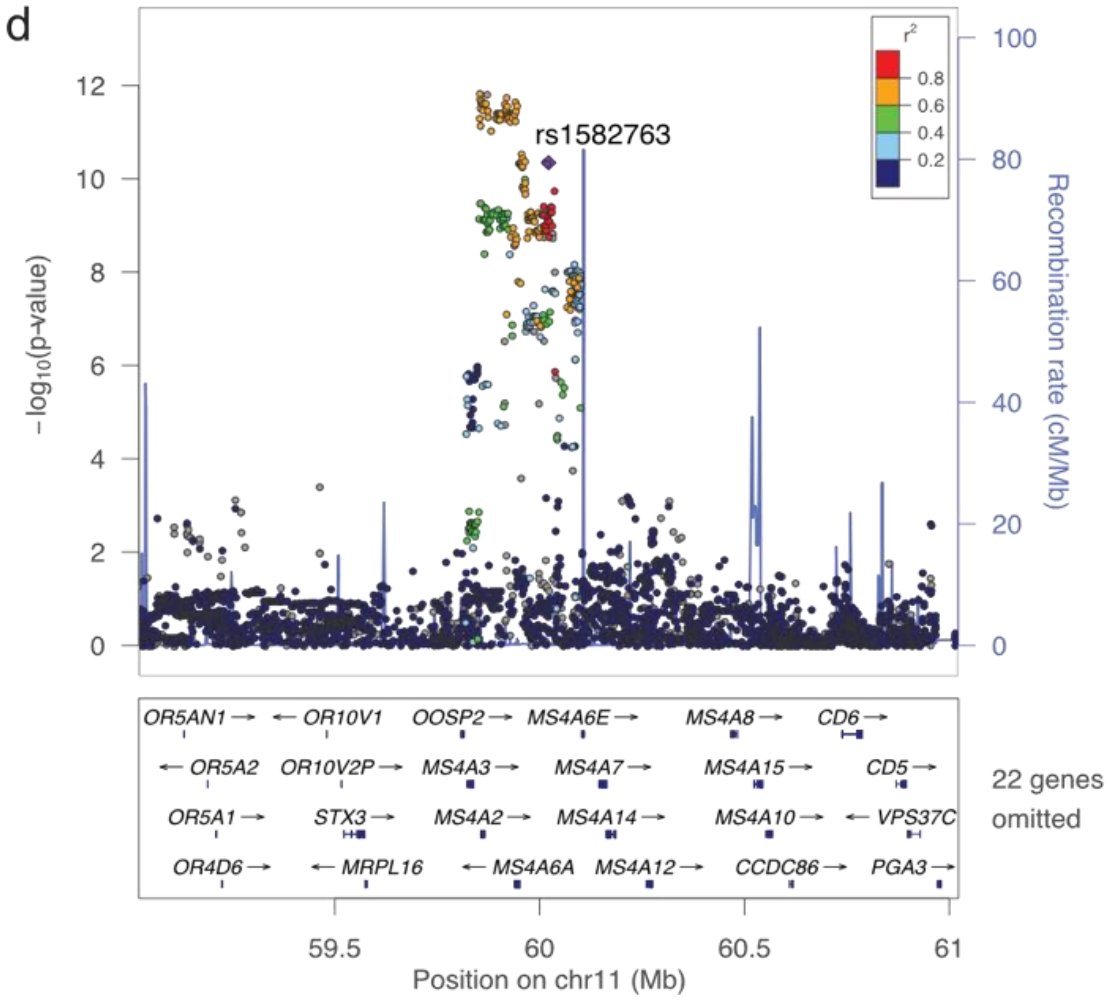
AD risk vs CSF TREM2

AD risk Signal

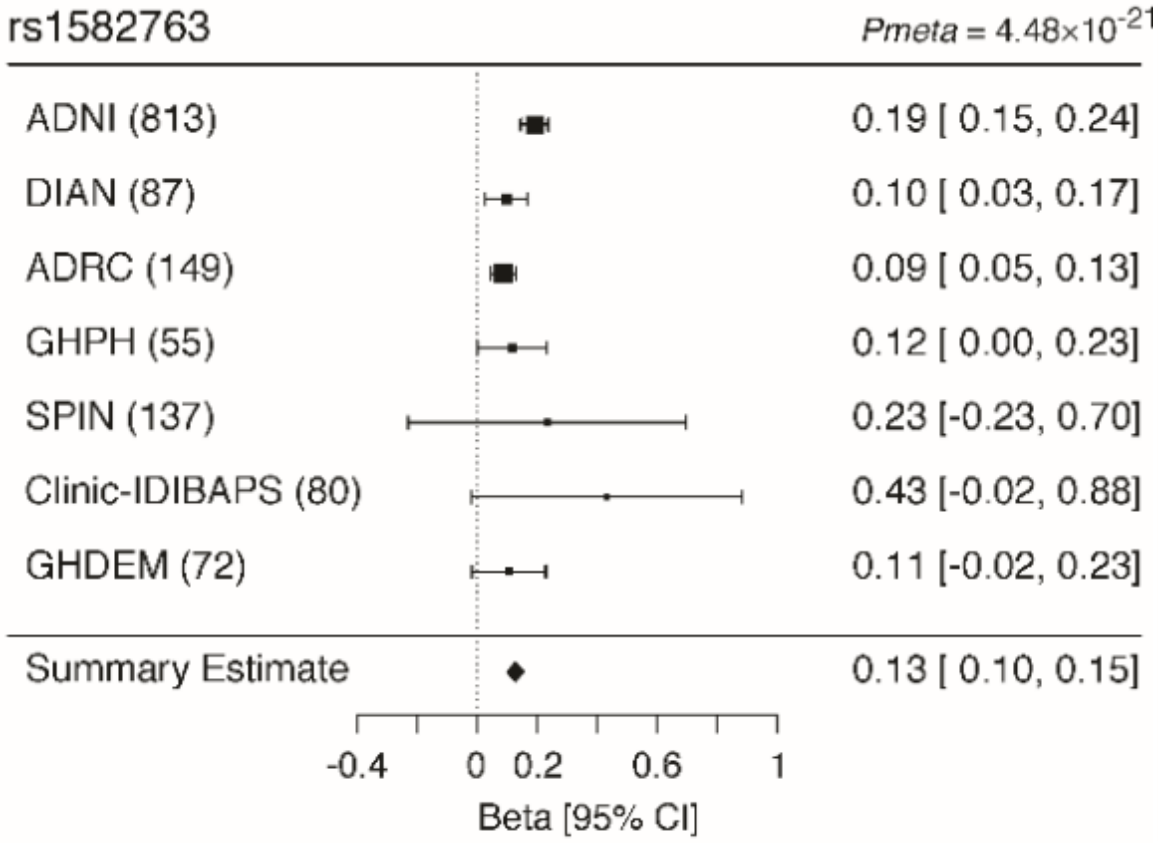


CSF TREM2 Signal

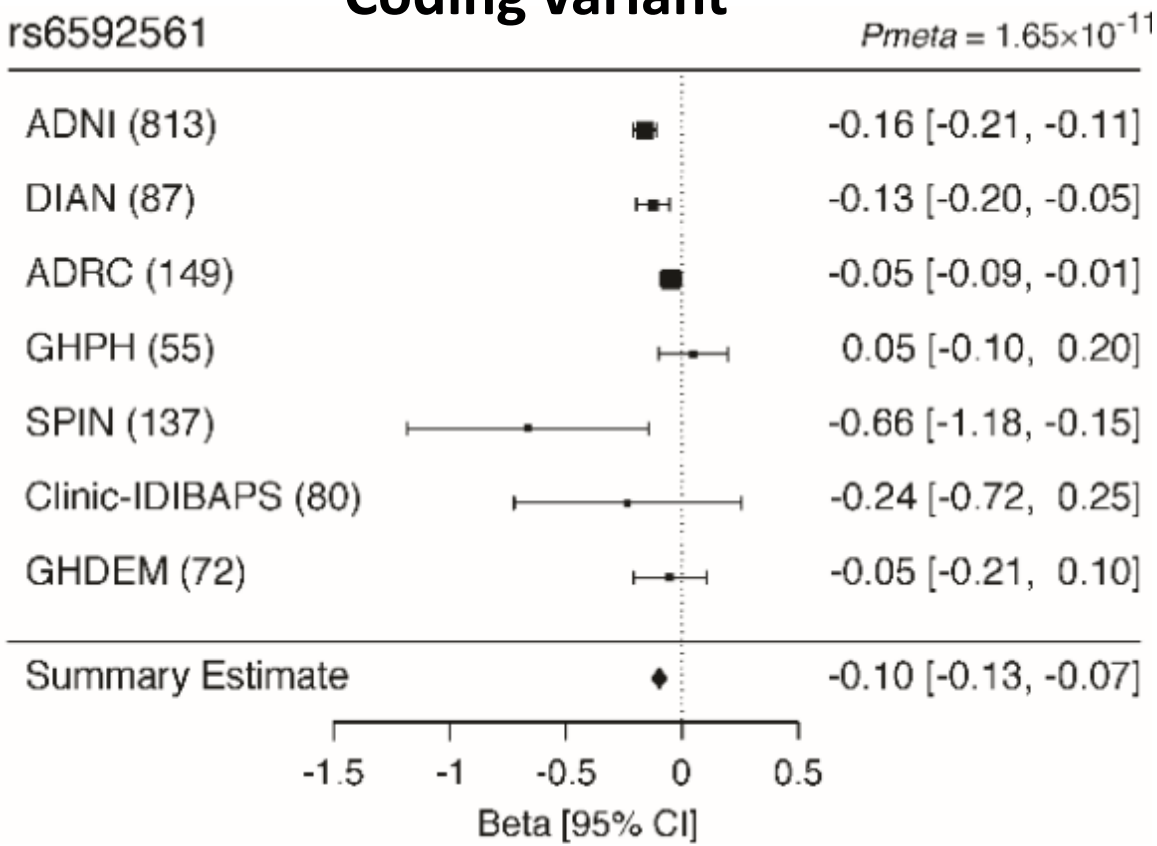


There are two replicable signals in the MS4A region

Non-Coding variant



MS4A4 p.M159V
Coding variant



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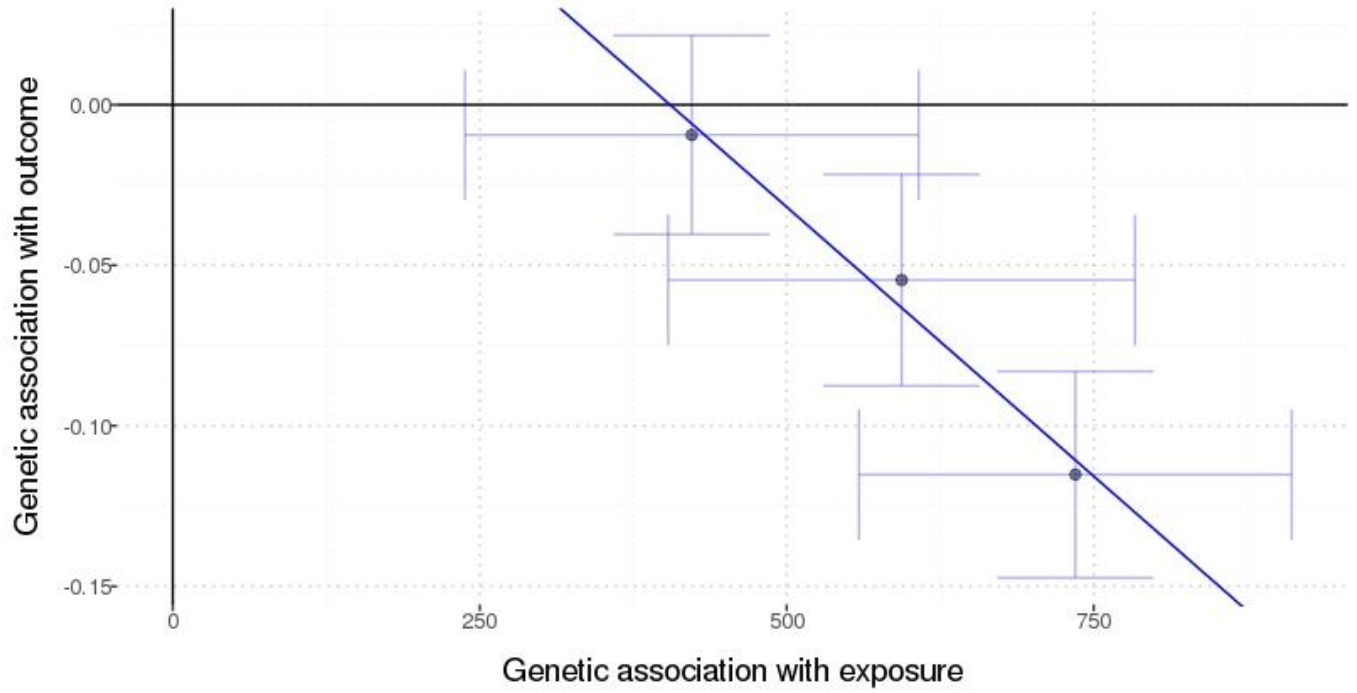
TREM2 is implicated in the pathology of sporadic AD

Mendelian Randomization analyses for CSF sTREM2 vs. AD risk

Method	Estimate	S.E	95% CI		*P*
MR-Egger	-3.35×10^{-04}	7.26×10^{-05}	-4.77×10^{-04}	$-1.92\times10-^{04}$	3.97×10^{-06}
Penalized MR-Egger	-3.35×10^{-04}	7.26×10^{-05}	-4.77×10^{-04}	-1.92×10^{-04}	3.97×10^{-06}
Robust MR-Egger	-3.35×10^{-04}	1.93×10^{-05}	-3.73×10^{-04}	-2.97×10^{-04}	$<1.00\times10^{-06}$
Penalized robust MR-Egger	-3.35×10^{-04}	1.93×10^{-05}	-3.73×10^{-04}	-2.97×10^{-04}	$<1.00\times10^{-06}$

Residual Standard Error : 0.934
Residual standard error is set to 1 in calculation of confidence interval when its estimate is less than 1.
Heterogeneity test statistic = 0.3884 on 1 degrees of freedom, (*P* = 0.533).
I^2_GX statistic: 60.0%

B



TREM2 is implicated in the pathology of sporadic AD

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALZHEIMER'S DISEASE

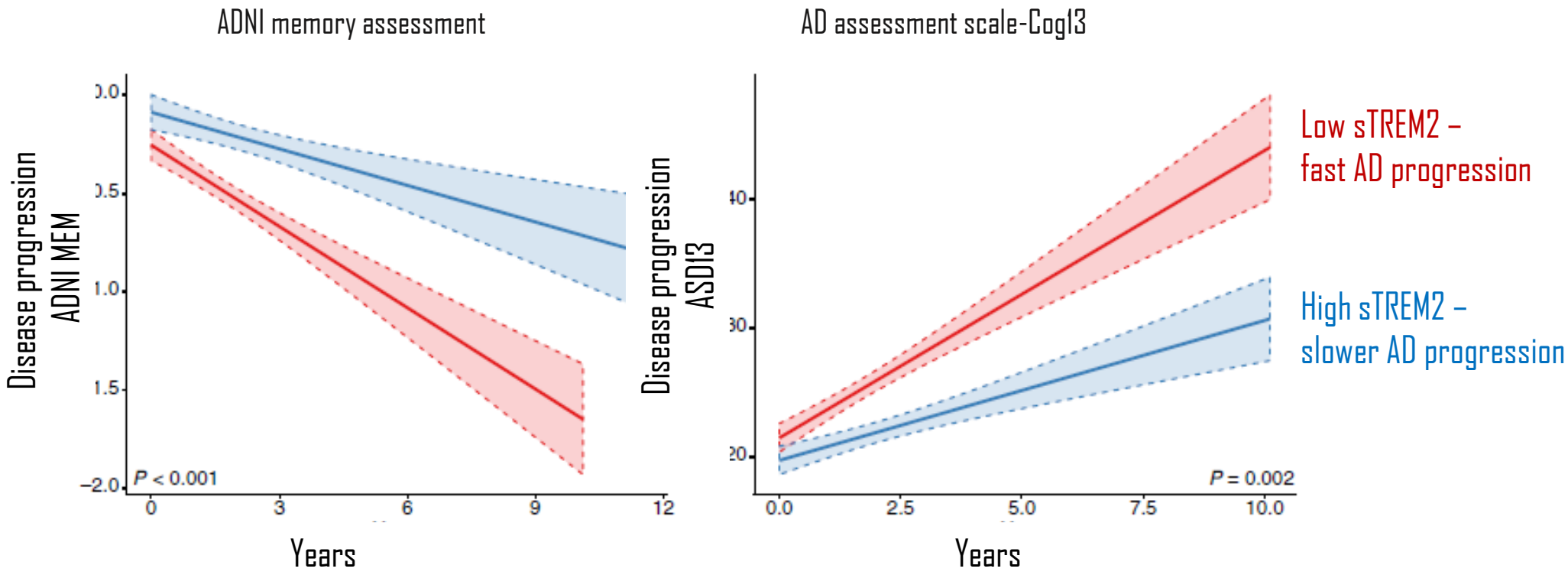
Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease

Michael Ewers[1*†], Nicolai Franzmeier[1*], Marc Suárez-Calvet[2,3,4,5*‡], Estrella Morenas-Rodriguez[2,6], Miguel Angel Araque Caballero[1], Gernot Kleinberger[2,7,8], Laura Piccio[9,10,11], Carlos Cruchaga[10,12], Yuetiva Deming[10,12], Martin Dichgans[1,3,7], John Q. Trojanowski[13], Leslie M. Shaw[14], Michael W. Weiner[15], Christian Haass[2,3,7†], for the Alzheimer's Disease Neuroimaging Initiative

Cruchaga LAB

TREM2 is implicated in the pathology of sporadic AD

"... associated with a slower rate of decline in episodic memory or cognition ... up to 11.5years"



Science Transl. Med. 2019: 11 (507) eaav6221

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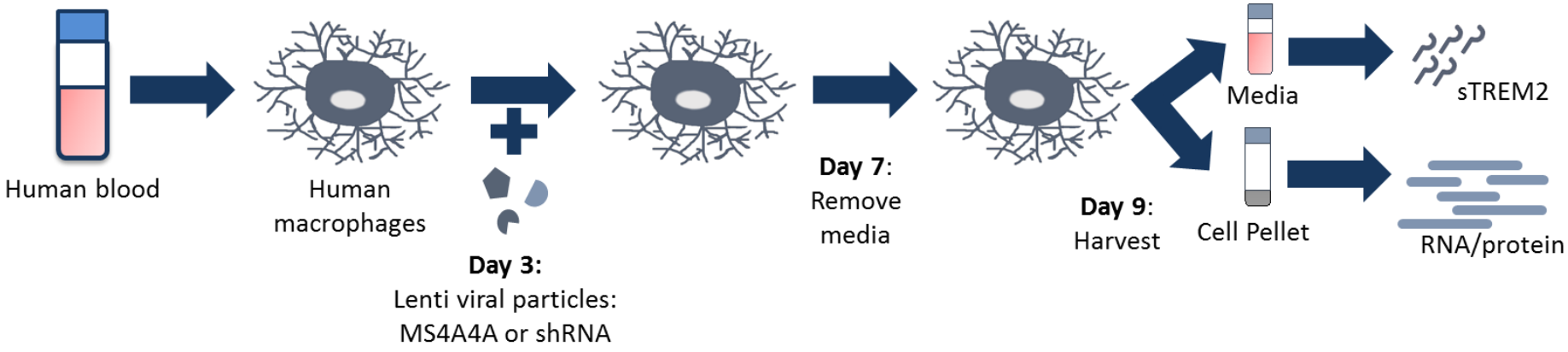
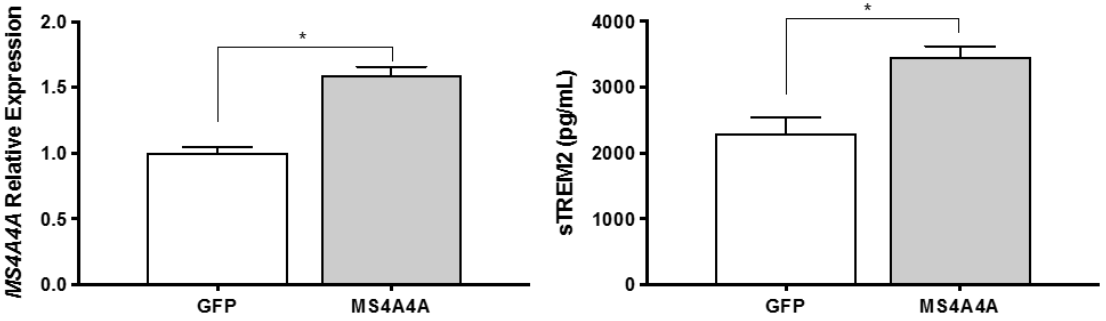
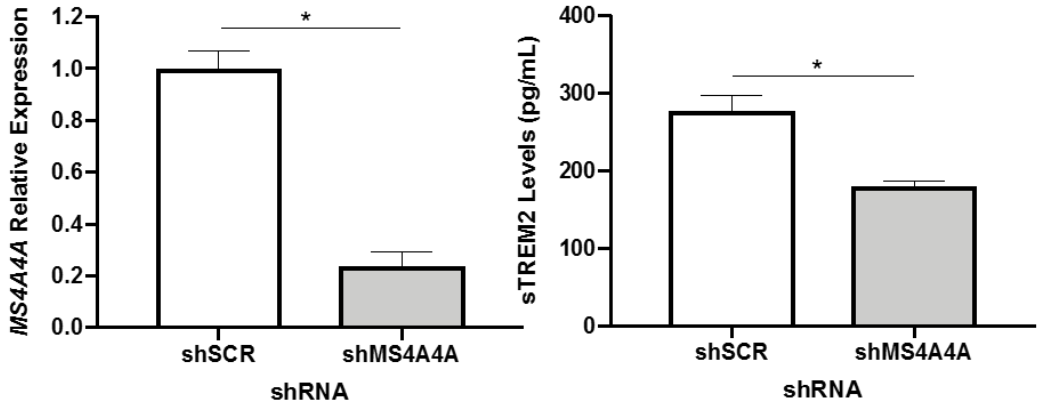
Modulation of TREM2 by targeting *MS4A4A*



Increased *MS4A4A* leads to more sTREM2

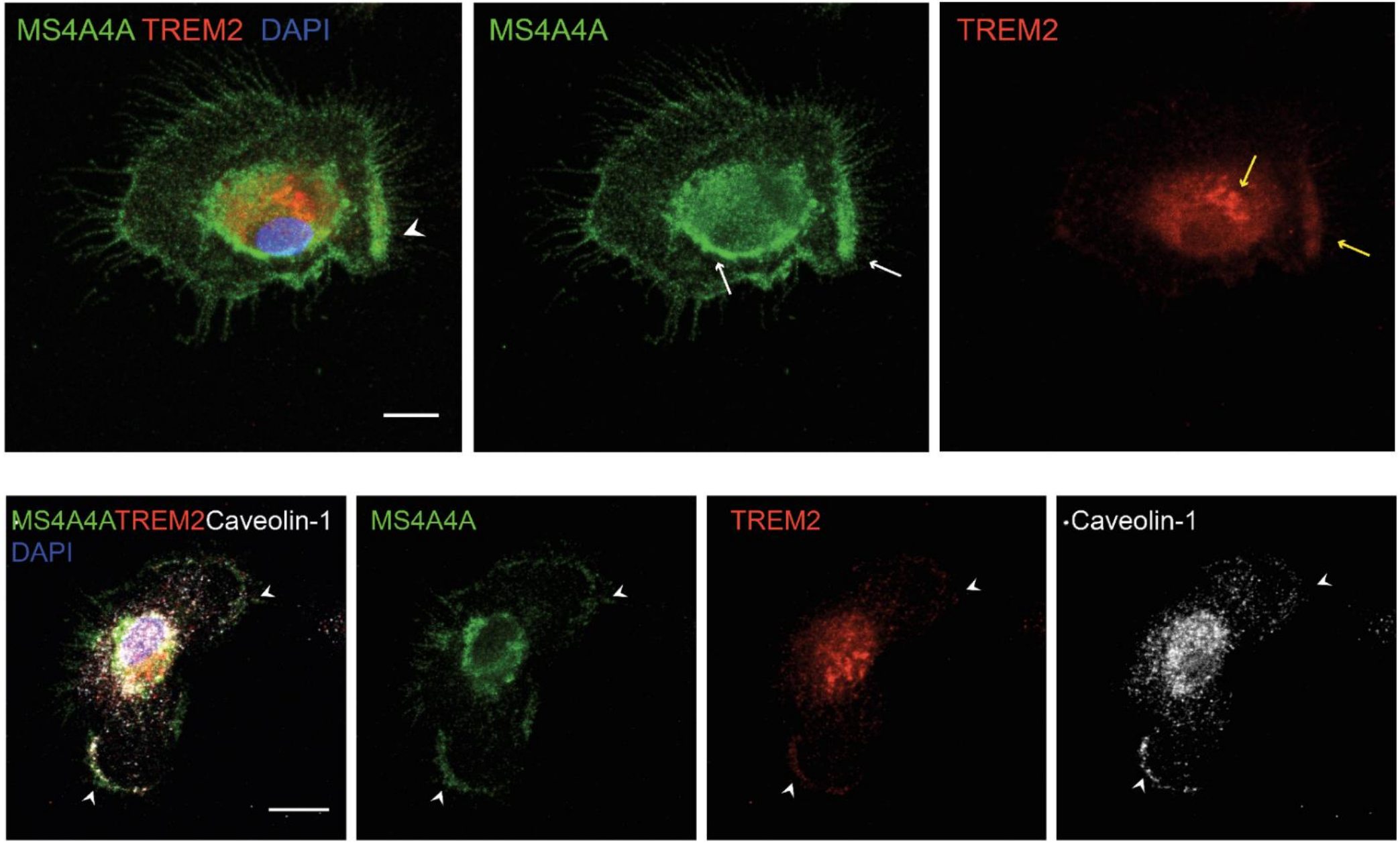


Silencing *MS4A4A* leads to less sTREM2



Deming et al, Science Translational Medicine.

TREM2 and MS4A4A co-localize in lipid rafts



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CSF sTREM2. Conclusions

- ***MS4A4A* represents the major regulator for sTREM2**
  - There are two independent signals in *MS4A4A*.
  - The strength of the association is comparable to APOE for CSF Aβ42
  - *MS4A4A* is also associated with AD risk.

- **Provide a biological context of the association of *MS4A4A* with AD risk**

- **Indicate that TREM2 play a role in AD in general**

- ***MS4A4A* co-express and co-localize with TREM2**

- **Pharmacologic or genetic modification of MS4A4A affect TREM2 biology and increase microglia activity/ fitness**
  - New therapeutic target-> molecules that mimic the MS4A4A protective allele will lead to lower AD risk

NeuroGenomics and Informatics Group

Neurogenomics
& Informatics

Washington
University in St. Louis

Cruchaga LAB

AL014:
Scientific Overview

Presenting:
Arnon Rosenthal, Ph.D.
Chief Executive Officer, Alector

ALECTOR

AL014: Targeting Alzheimer's disease

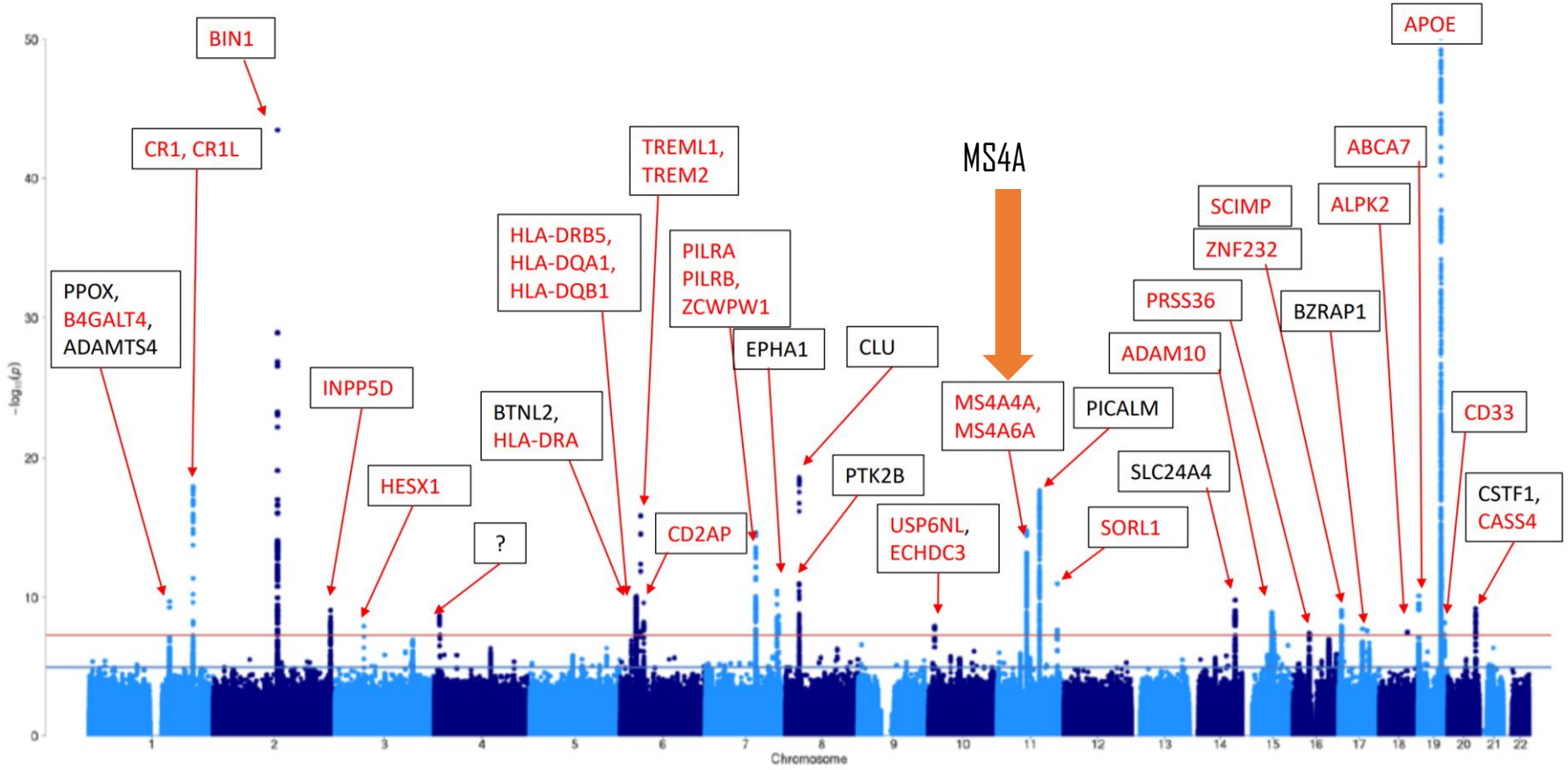
AL014	**Target**: MS4A, 4 trans-membrane protein expressed on microglia **Product candidate**: An antibody that is designed to mimic the MS4A4A protective allele **Status**: Pre-clinical development

- Among top risk genes for AD
- Protective allele decreases prevalence of AD in a copy number dependent manner
- Protective allele increases age of onset
- Acts on microglia
- Modulates TREM2 as one of its functions

> 35M Alzheimer's disease patients globally

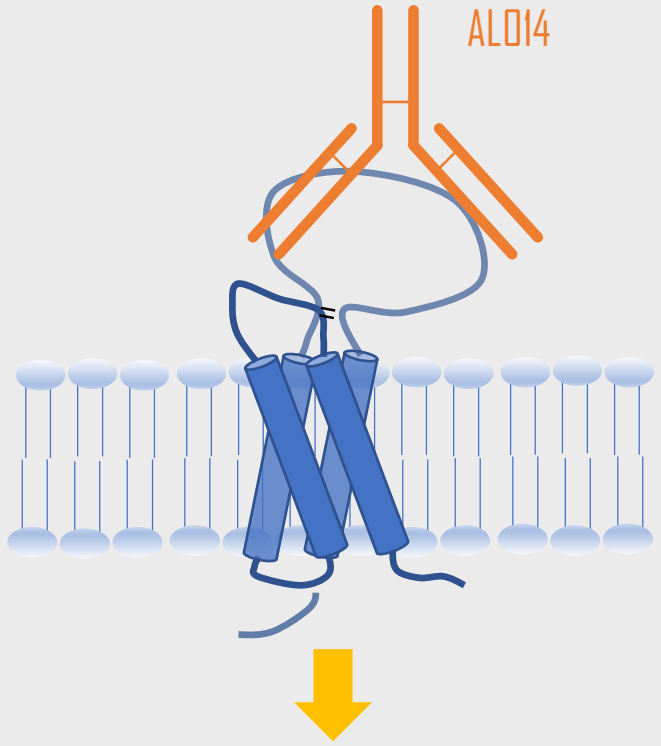
MS4A gene family as Alzheimer's disease risk loci

Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease



Annotated from Nature Genetics 2019 Mar;51(3):404-413.

AL014 is an antibody product candidate designed to mimic and exceed the protective variant of MS4A4A



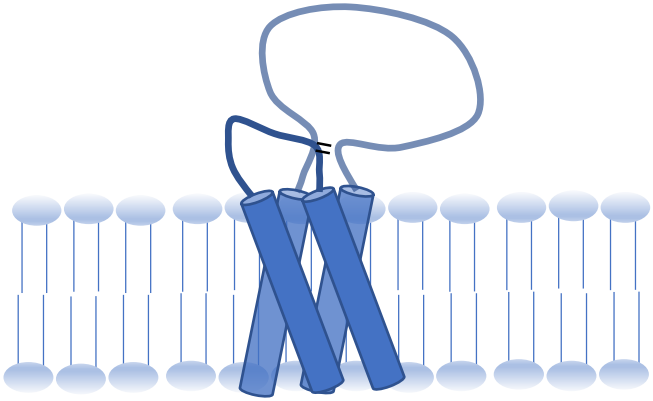
Improve functionality of microglia

Our Approach:

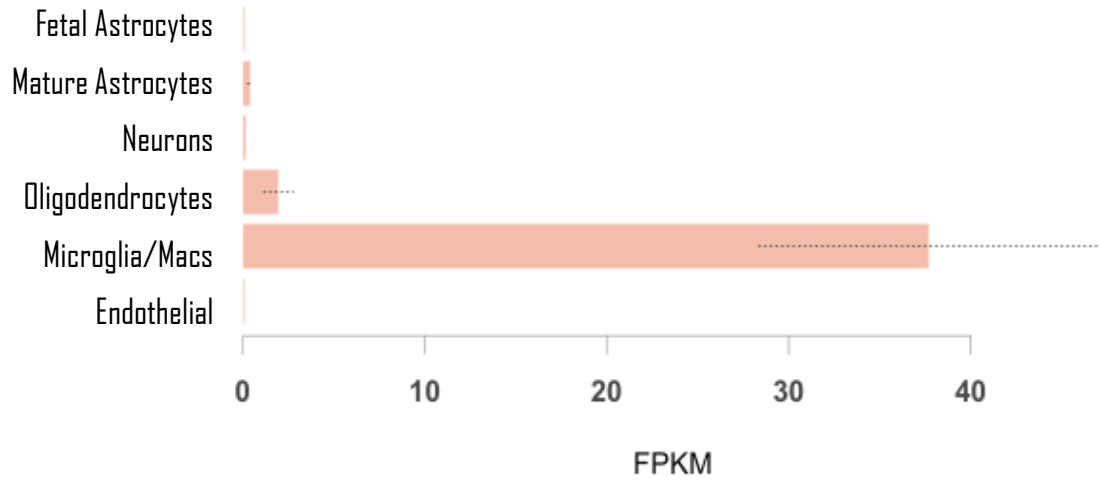
- Increases viability and functionality of microglia
- Enhances the levels of TREM2
- Functionally converts the risk variant of MS4A4A to the protective allele
- Slows disease progression

Background on MS4A4A

- Risk variant increase the probability of developing Alzheimer's disease risk and decrease the age of onset
- Member of ~22, membrane-spanning 4A family
- Structurally related to CD20, the target of Rituxan
- Expressed on microglia, perivascular macrophages
- Controls the levels of TREM2
- May form heterodimers with other MS4A family members

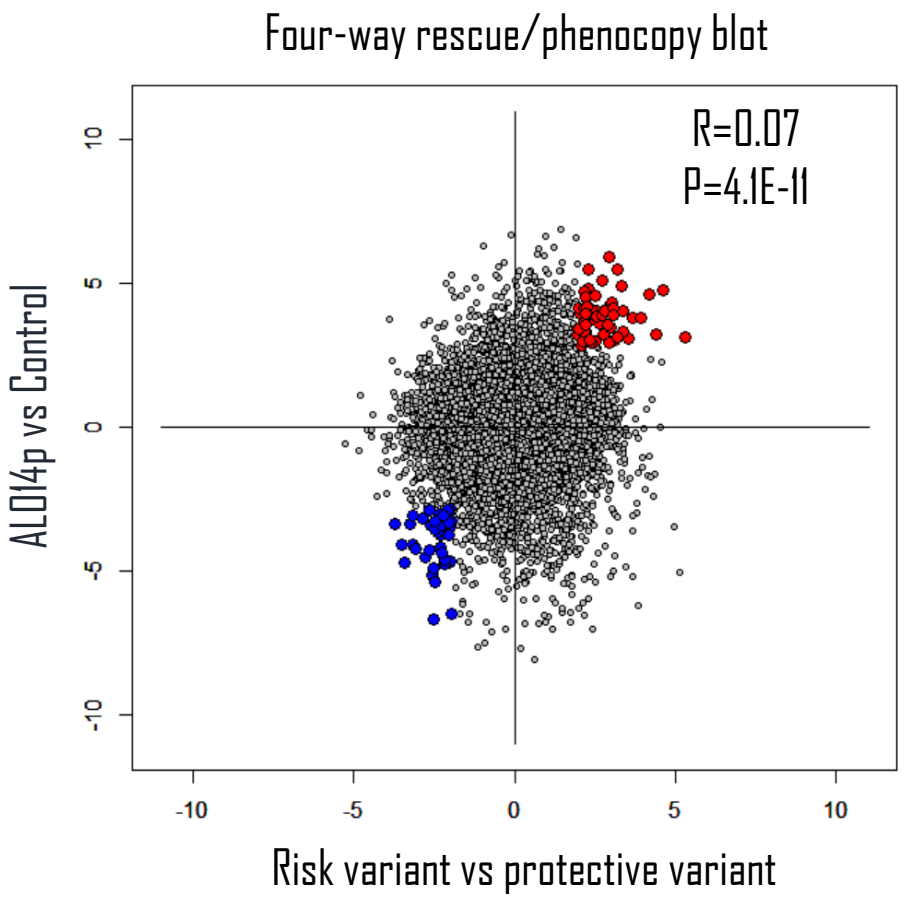


MS4A4A expression on human brain cell types



https://www.brainrnaseq.org/

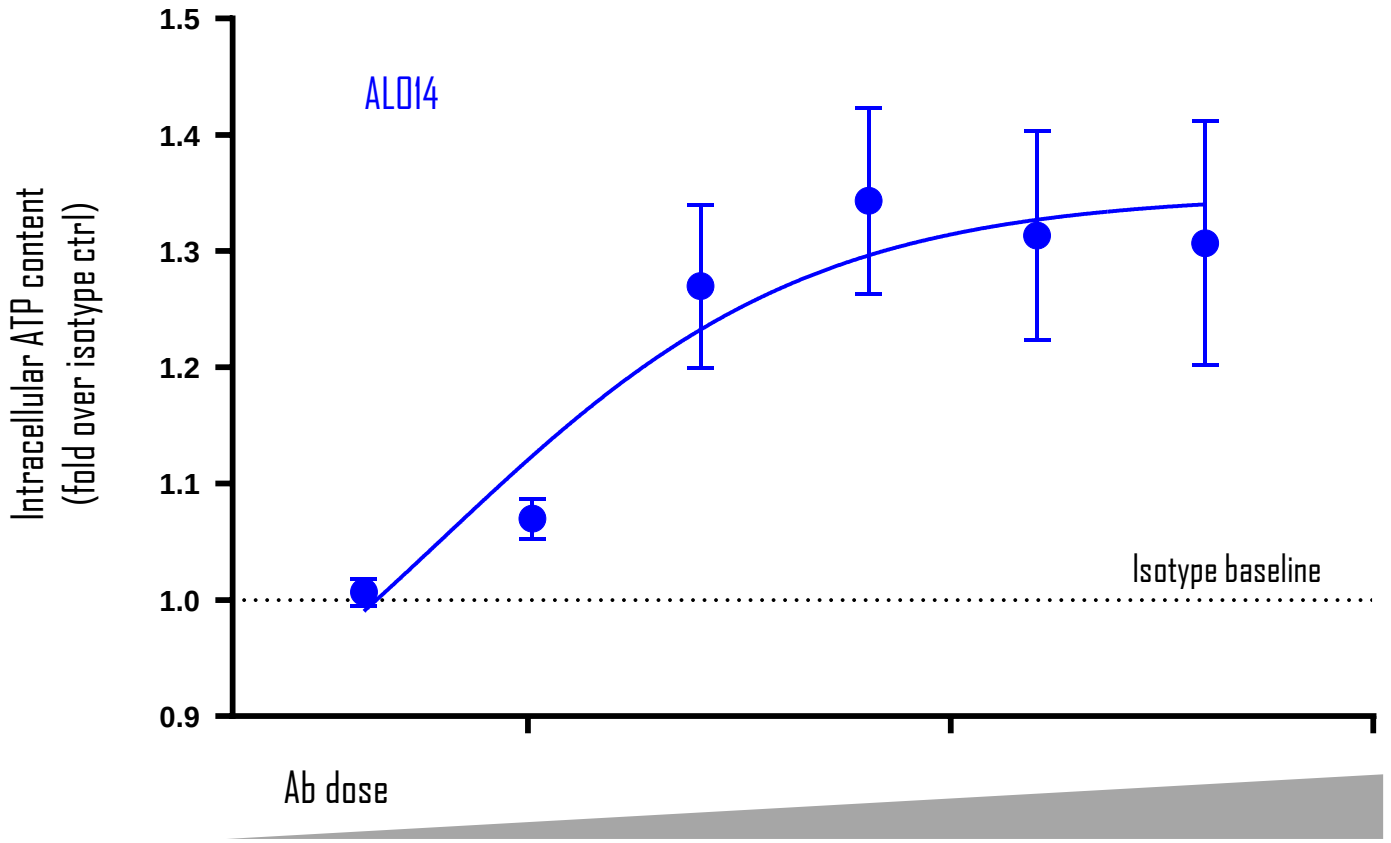
AL014 antibodies phenocopy the protective allele gene expression signature



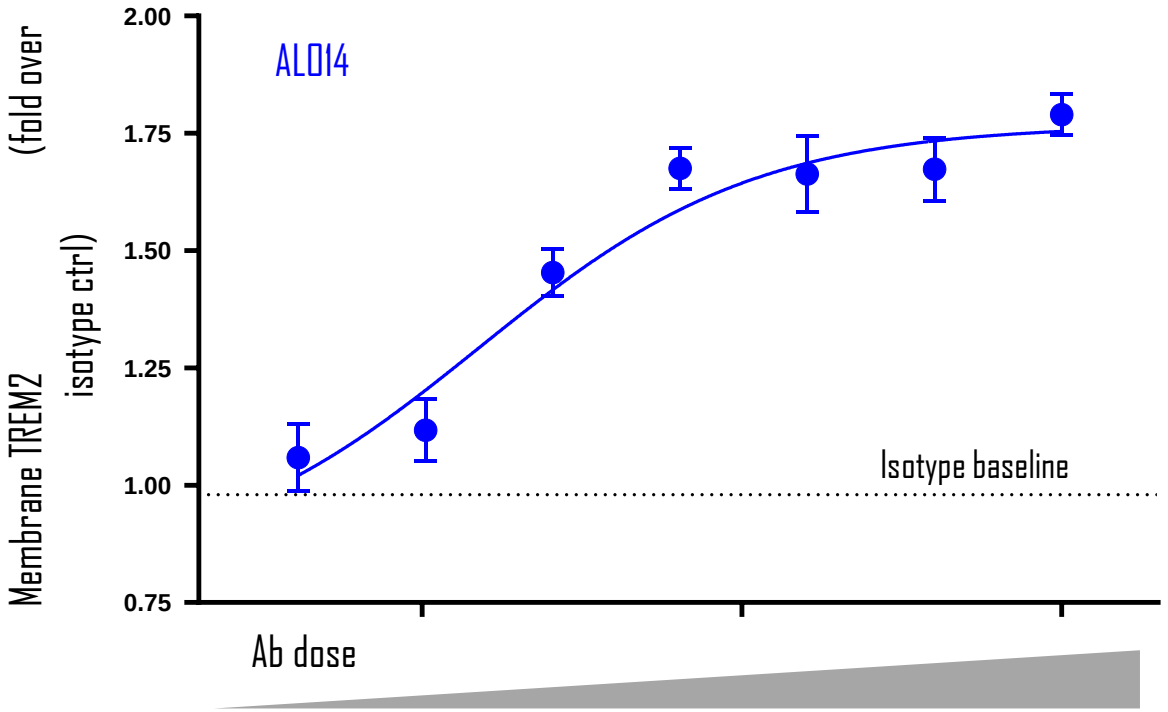
Analysis of >10,000 mRNA in human macrophages

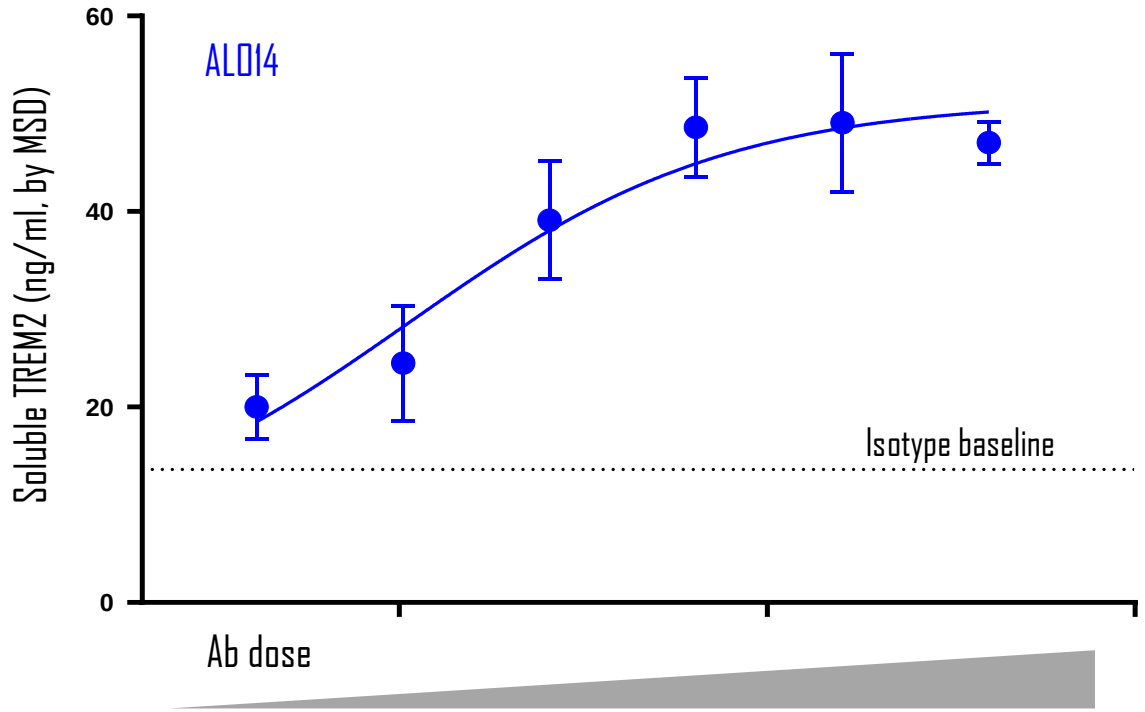
- AL014 increases genes that are increased by the protective allele of MS4A (red)
- AL014 decreases genes that are decreased by the protective allele of MS4A (blue)

AL014 increases the viability of primary human myeloid cells in a dose dependent manner



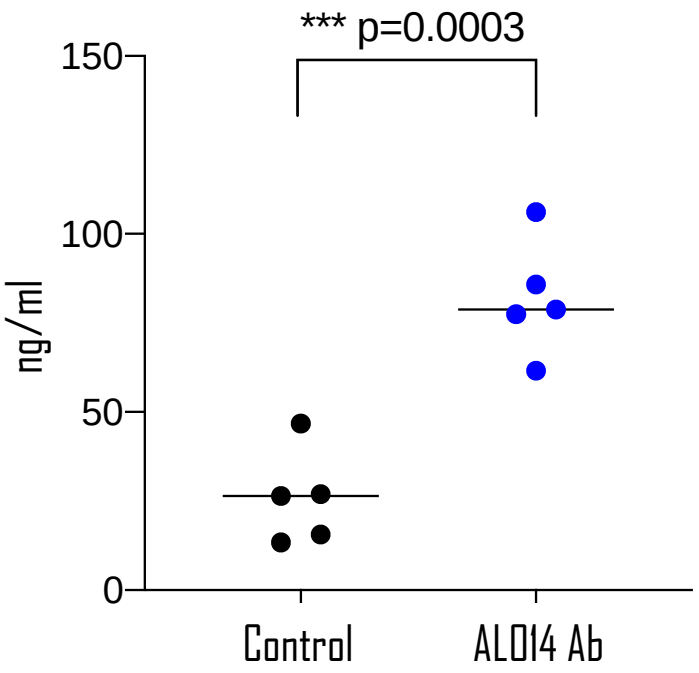
ALO14 increases the levels of TREM2 in primary human myeloid cells in a dose dependent manner



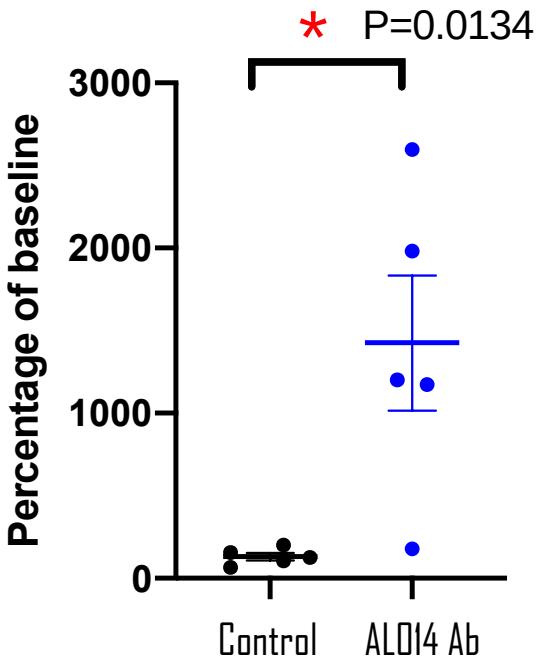


AL014 increases microglia activity biomarkers in non-human primates (NHP)

AL014 increases sTREM2 in NHP CSF

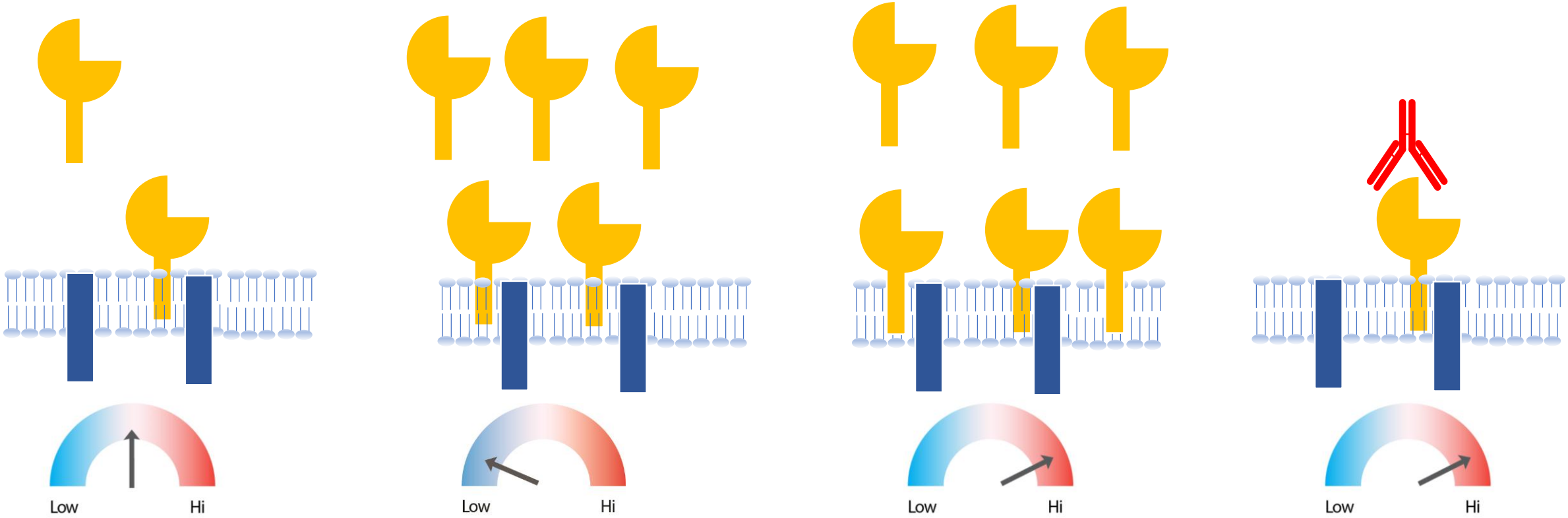


AL014 increases a microglia activity biomarker in NHP microglia

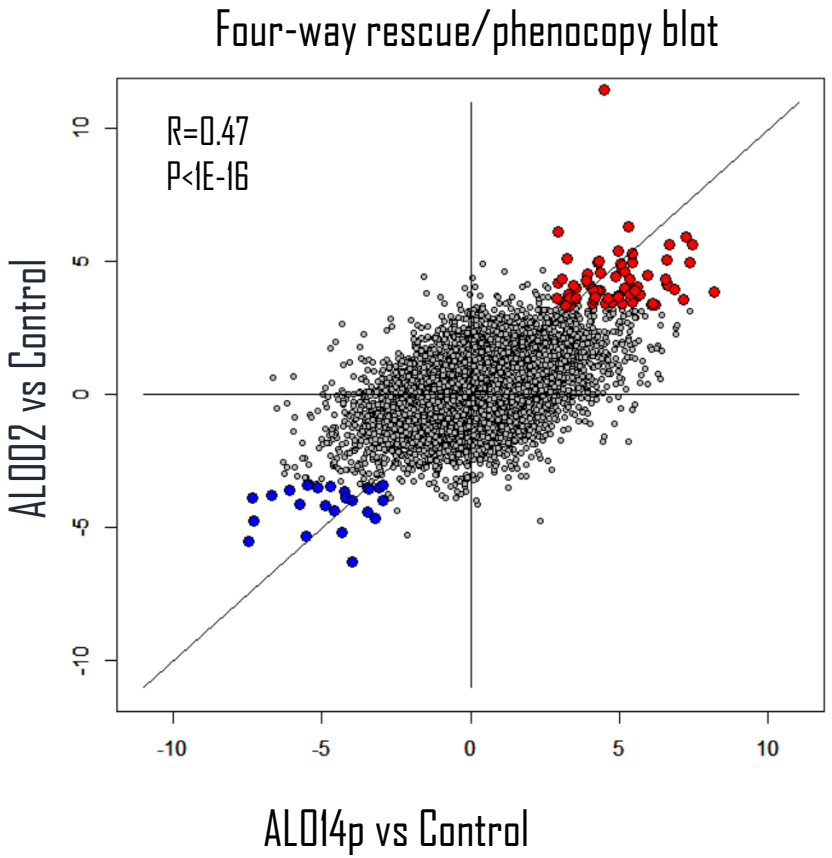


The levels of sTREM2 are context dependent

Normal State	Genetic risk mutations	MS4A4A protective allele and AL014	AL002



AL002 and AL014 have overlapping but unique gene expression signatures



AL014 increases genes that are increased by AL002 (red)

AL014 decreases genes that are decreased by AL002 (blue)

	AL002	AL014p	Control
Number of differentially expressed genes FDR 5%	144	853	0

AL014: Summary

- FIH targeted in the next 12-18 months
- Broad patent coverage
- MS4A4A is a top risk gene for AD
- MS4A4A impacts both disease initiation and disease progression
- AL014 mimics the protective allele
- Drug effect appears different then other immuno-neurology drugs
- Identified biomarkers to assist with clinical development

Q&A

ALECTOR

Closing remarks

Presenting:
Arnon Rosenthal, Ph.D.
Chief Executive Officer, Alector

ALECTOR

Our vision

At Alector we envision a world where dementia and neurodegeneration are illnesses of the past, just as smallpox and polio have become.