Targeting Neuroinflammation to Modulate Reactive Astrocytes for Treatment of Neurodegenerative Disease

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Chief Operating Officer
SVP Discovery & Translational Medicine

VACCINEX

Unique Targets
Novel Mechanisms
New Medicines

AD & PD Drug Development Summit
April 25, 2024

Disclosures

Elizabeth Evans is a full-time employee, executive officer and shareholder at Vaccinex, Inc.

This presentation involves discussion of unapproved, experimental or investigational use of pepinemab.

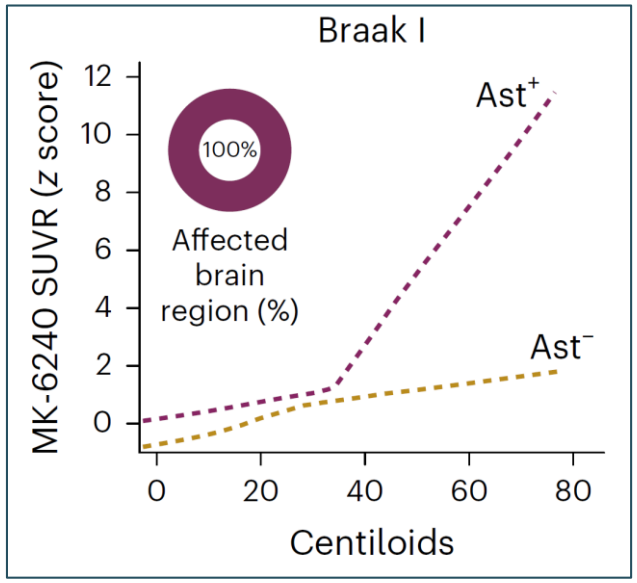
Forward Looking Statements

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited to, statements about the Company's plans, expectations and objectives with respect to the results and timing of clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Head and Neck cancer, Huntington's and Alzheimer's disease and other indications, and other statements identified by words such as "may," "will," "appears," "expect," "planned," "anticipate," "estimate," "intend," "hypothesis," "potential," "advance," and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of the Company's research and pre-clinical development programs, clinical development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties inherent in the execution, cost and completion of preclinical and clinical trials, uncertainties related to regulatory approval, the risks related to the Company's dependence on its lead product candidate pepinemab, the ability to leverage its ActivMAb® platform, the impact of the COVID-19 pandemic, and other matters that could affect the Company's development plans or the commercial potential of its product candidates. Except as required by law, the Company assumes no obligation to update these forward-looking statements. For a further discussion of these and other factors that could cause future results to differ materially from any forward-looking statement, see the section titled "Risk Factors" in the Company's periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in the Company's most recent year end Annual Report on Form 10-K and subsequent filings with the SEC.

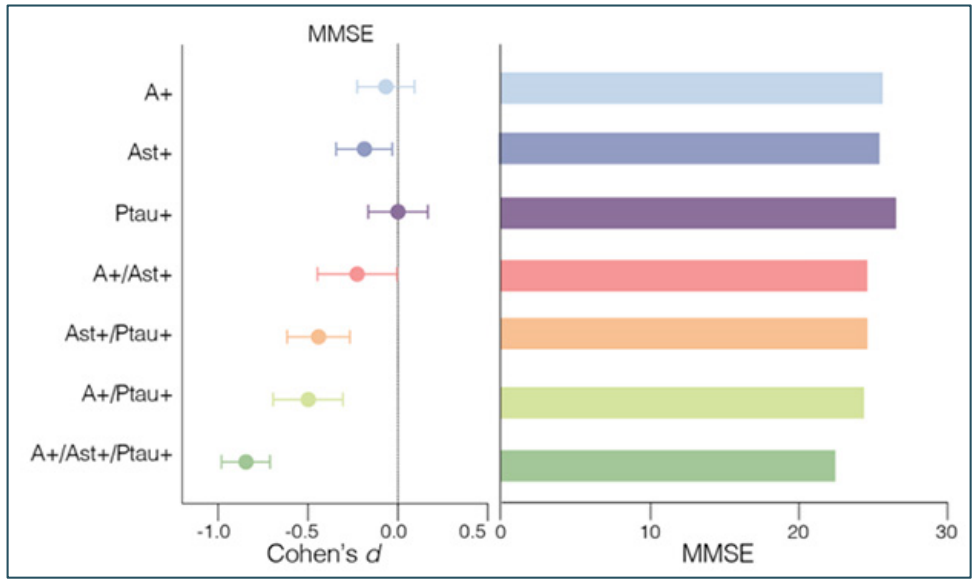
Inflammation is a key driver of pathology in neurodegenerative disease

"Fillit said that researchers have learned through autopsies of elderly patients that beta amyloid can be present in the brain without progressing to Alzheimer's. **If there's no strong immune reaction to the buildup, there's no inflammation and no progression of disease**."

(Howard Fillit, MD. Co-founder and CSO Alzheimer's Drug Discovery Foundation)
- Annalee Armstrong, Oct 16, 2023 Fierce Biotech



Bellaver et al. Nat Med 2023

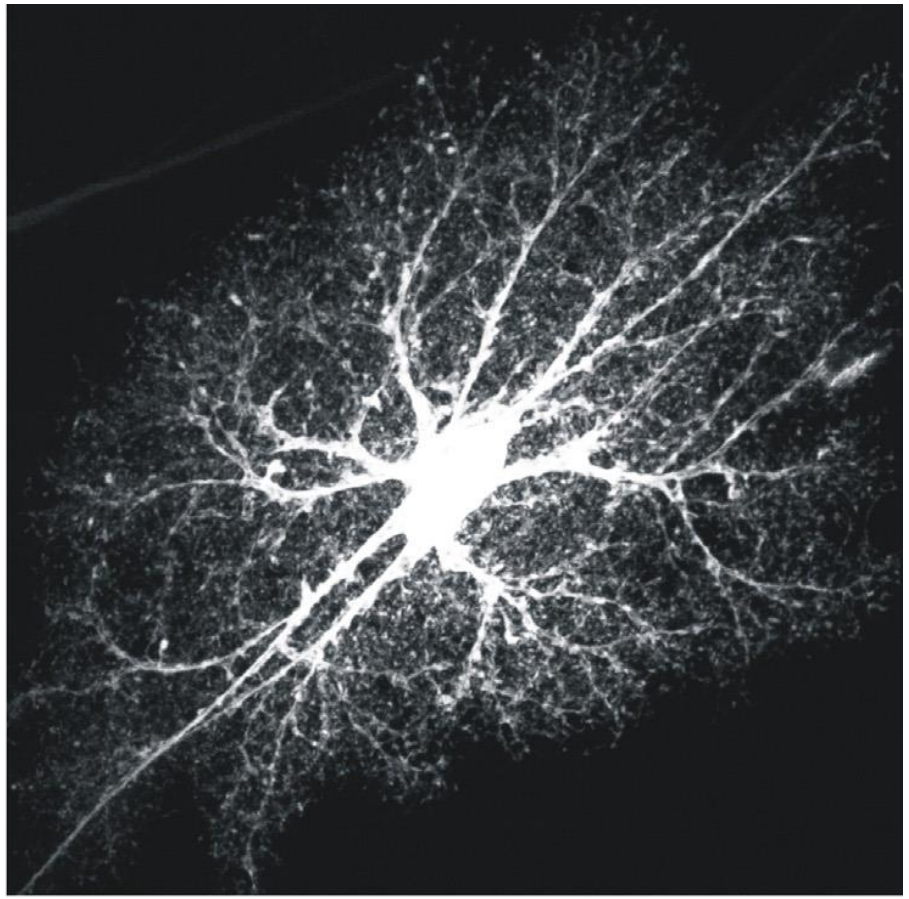


The Astrocyte Factor. *Astrocyte reactivity (Ast+) potentiates the effect of amyloid (A+) and/or p-tau217 (Ptau+) on cognition (MMSE). [Courtesy of Bruna Bellaver, University of Pittsburgh.]*

"Bellaver speculates that astrocytes change when they sense amyloid buildup in the brain. "**They get reactive and progressively lose neuroprotective functions and/or gain novel neurotoxic properties, disrupting brain homeostasis**," she wrote to Alzforum. This reactivity might preclude their ability to contain tau pathology, she speculated."

- Alzforum Series- AD/PD™ 2024, 12APR2024

Astrocytes reach out to touch and interact with other brain cells

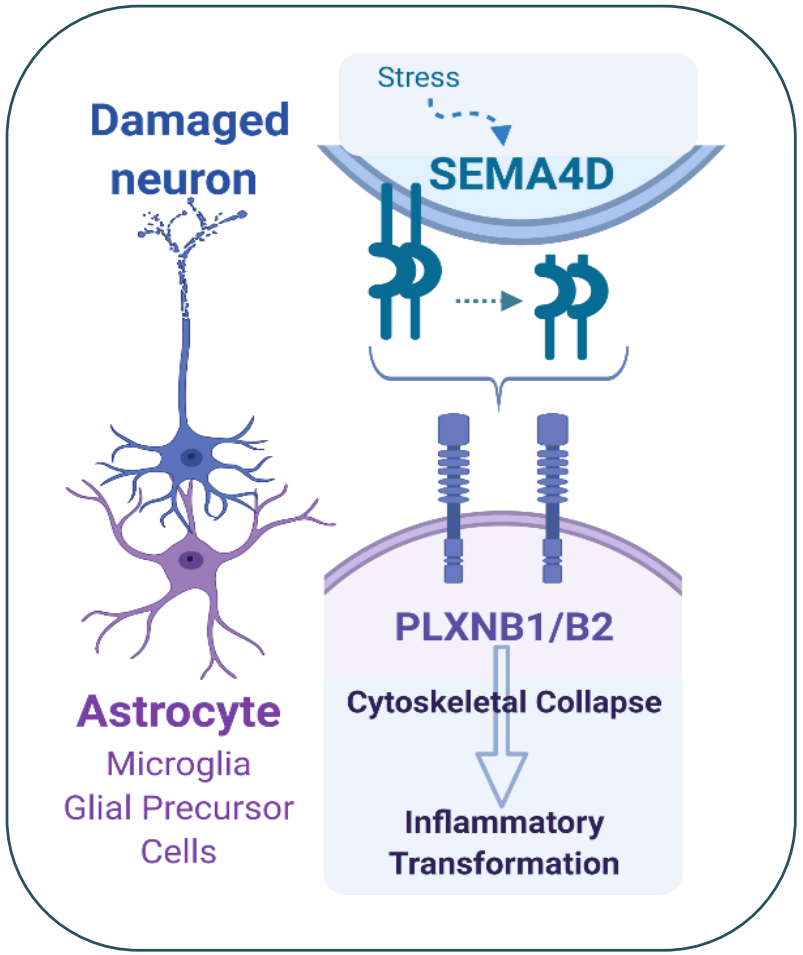


Astrocyte "arms" provide essential functional support to neurons.

- Fully cover capillaries and facilitate glucose uptake from circulation
- Cradle synapses and recycle glutamate
- Positioned to couple energy metabolism with neuronal activity

How do astrocytes sense damage and what triggers the conversion to reactive state?

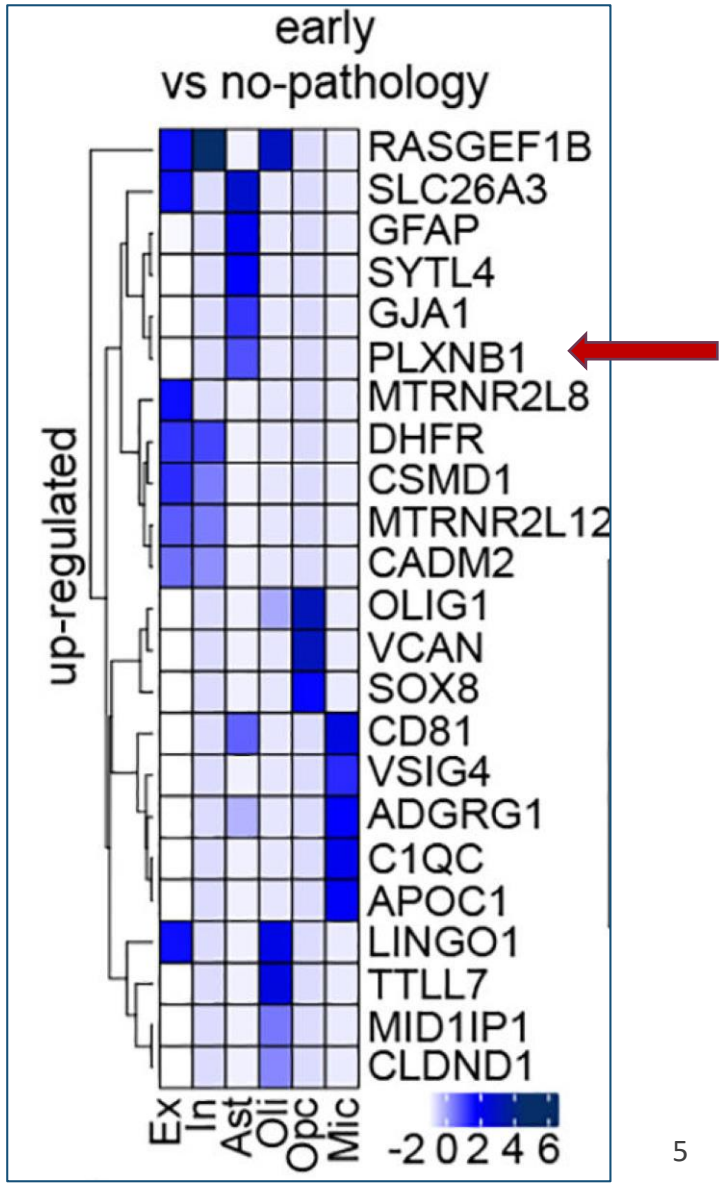
Semaphorin/Plexin neuro-immune signaling pathway is upregulated in early AD



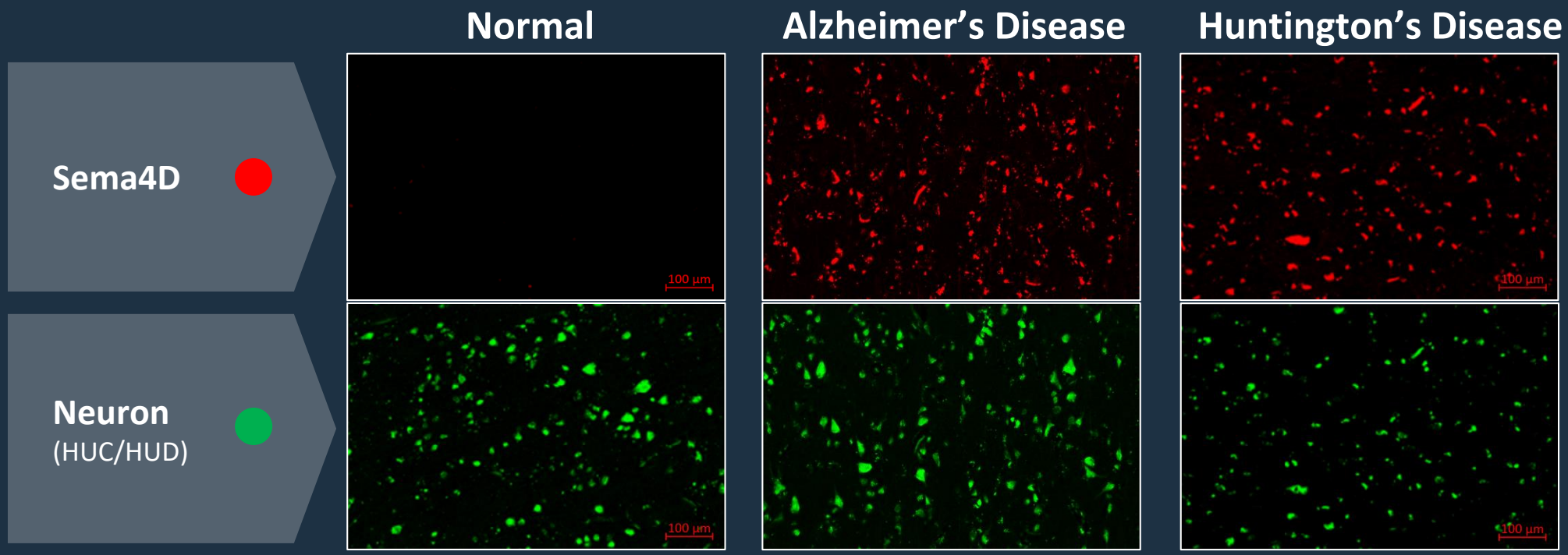
PlexinB1 is upregulated specifically in astrocyte cluster genes

Genetic profiles were determined from post-mortem human prefrontal cortex (Brodmann area 10), given its major role in AD affected traits, including cognition.

Mathys H et al. Nature 2019. Single-cell transcriptomic analysis of Alzheimer's disease



SEMA4D IS OBSERVED TO BE UPREGULATED IN NEURONS DURING DISEASE PROGRESSION



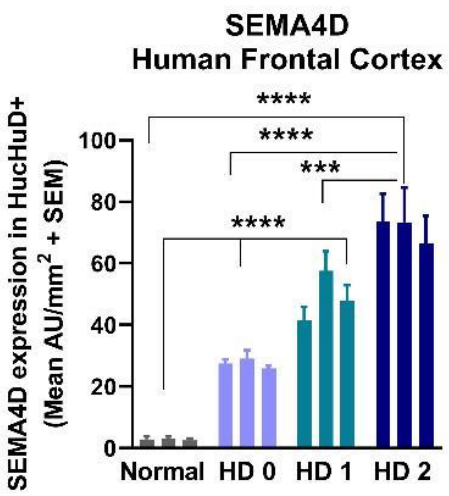
Human autopsy sections of frontal lobe

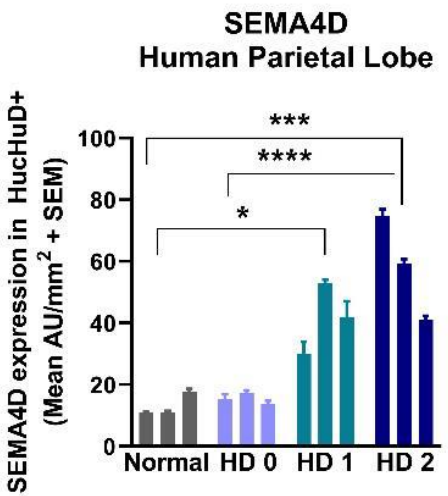
Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity
Elizabeth E Evans, Vikas Mishra, Crystal Mallow, Elaine Gersz, Leslie Balch, Alan Howell, Ernest S. Smith, Terrence L. Fisher, Maurice Zauderer*
Journal of Neuroinflammation, 2022

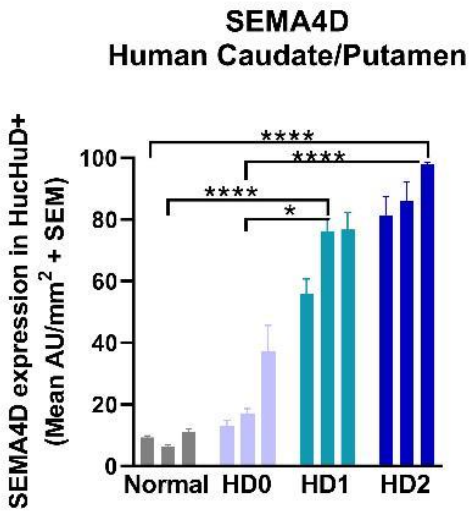
VACCINEX

SEMA4D IS PROGRESSIVELY UPREGULATED WITH INCREASING PATHOLOGIC STAGE OF HD

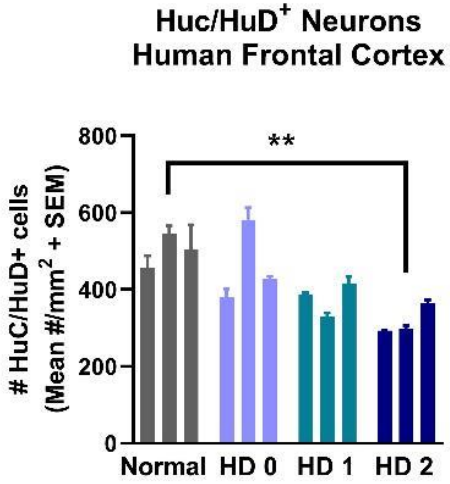
SEMA4D in neurons

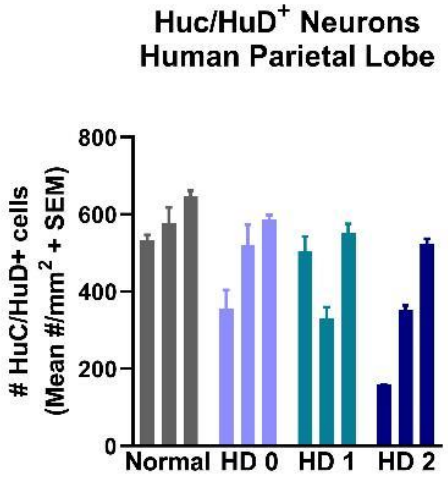


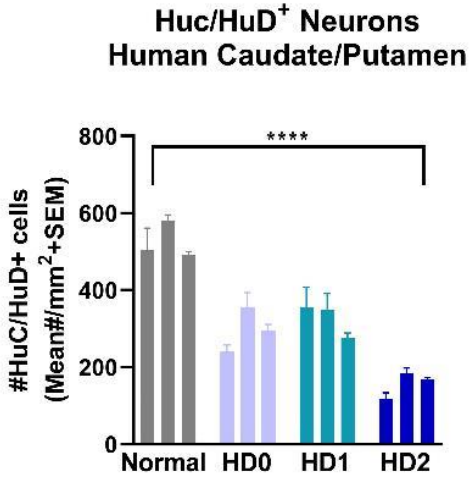




Neuron Density





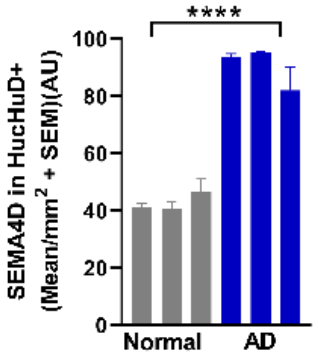


Evans et al. Journal of Neuroinflammation, (2022) 19:200.

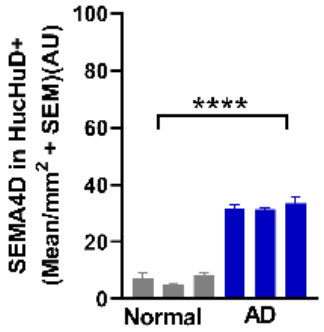
SEMA4D UPREGULATION is ASSOCIATED WITH NEURONAL LOSS AND ASTROCYTE ACTIVATION IN AD

SEMA4D in neurons

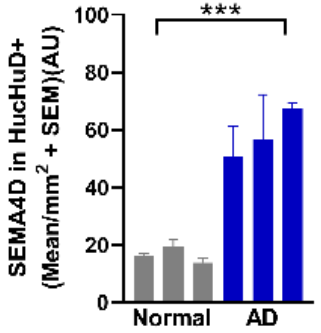
Thalamus Human



Temporal Lobe Human

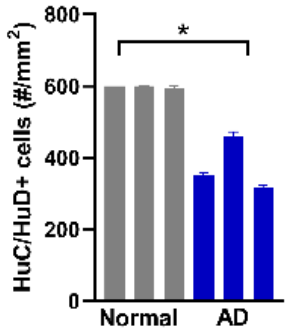


Frontal Cortex Human

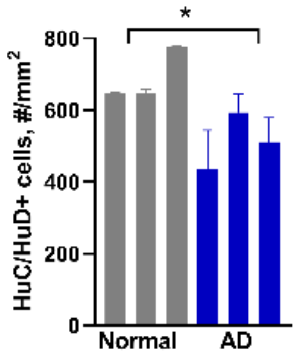


Neuron Density

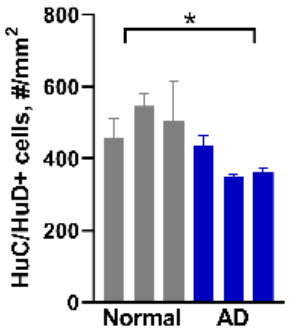
HuC/HuD+ Neurons Human Thalamus



HuC/HuD+ Neurons Human Temporal Lobe



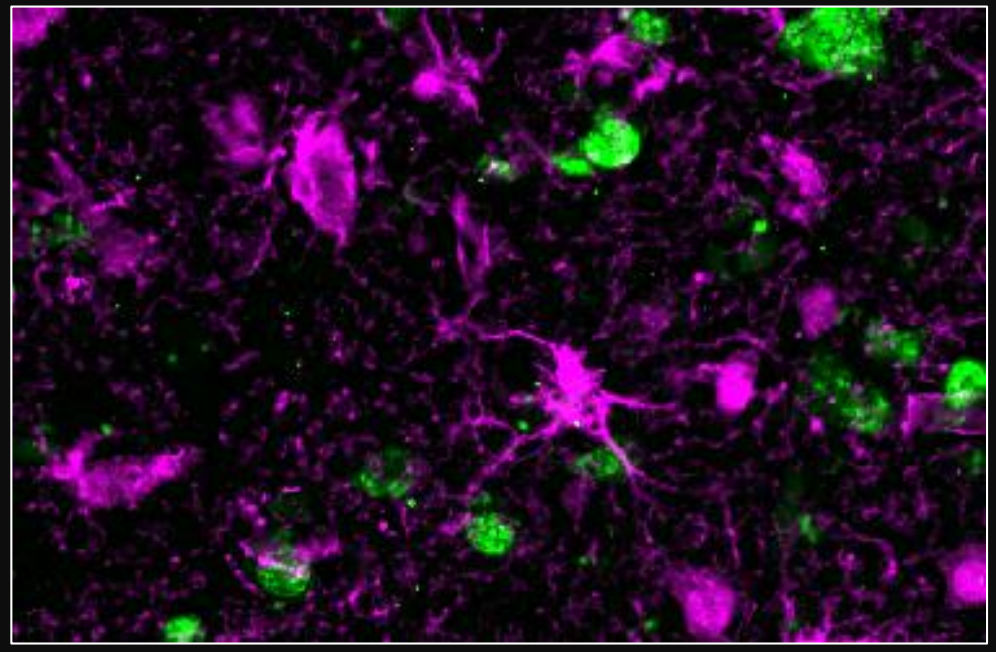
HuC/HUD+ Neurons Human Frontal Cortex



Evans et al. Journal of Neuroinflammation, (2022) 19:200.

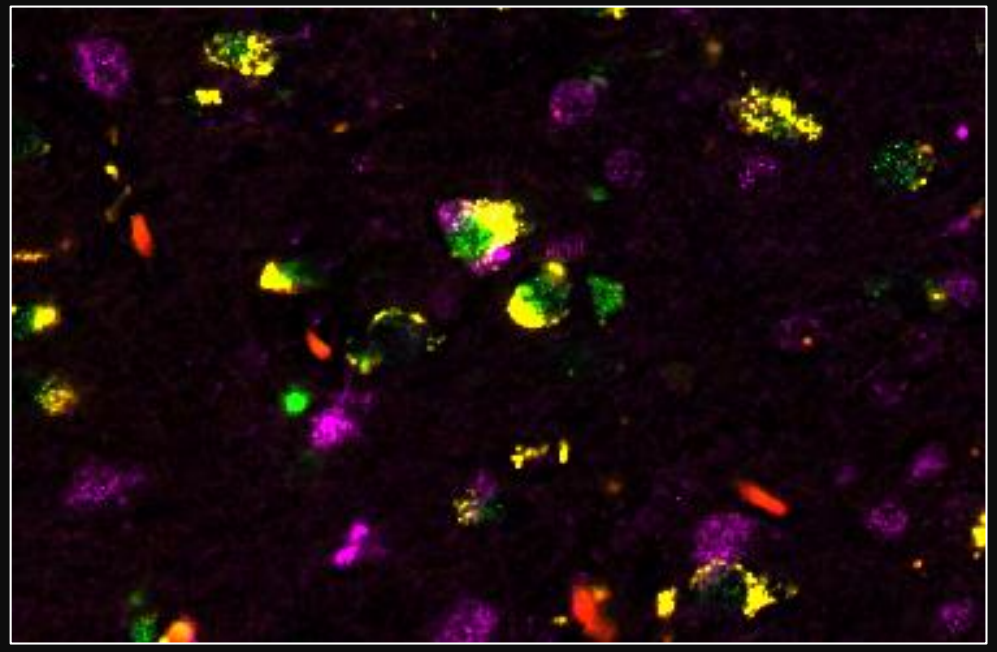
ASTROCYTES TRANSFORM TO REACTIVE STATE IN PRESENCE OF SEMA4D

Normal



Astrocyte
(Glutamine Synthetase expressed in astrocyte end feet)
Neuron
(HuC/HuD expressed in neuronal body)
SEMA4D

Early Huntington's Disease



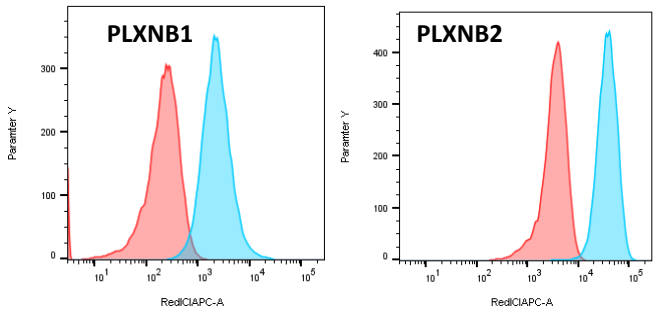
Astrocyte
SEMA4D **Neuron** **MERGE**

Evans et al. Journal of Neuroinflammation, (2022) 19:200.

ASTROCYTE FUNCTION:

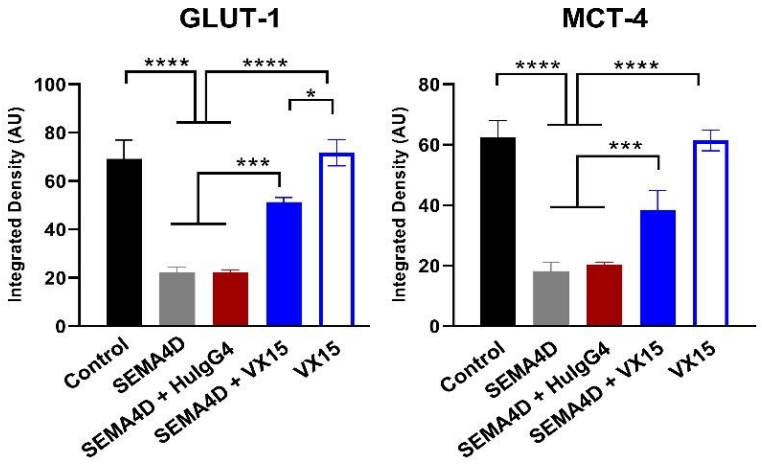
Astrocytes couple energy metabolism and synaptic activity

Astrocytes express receptors for SEMA4D



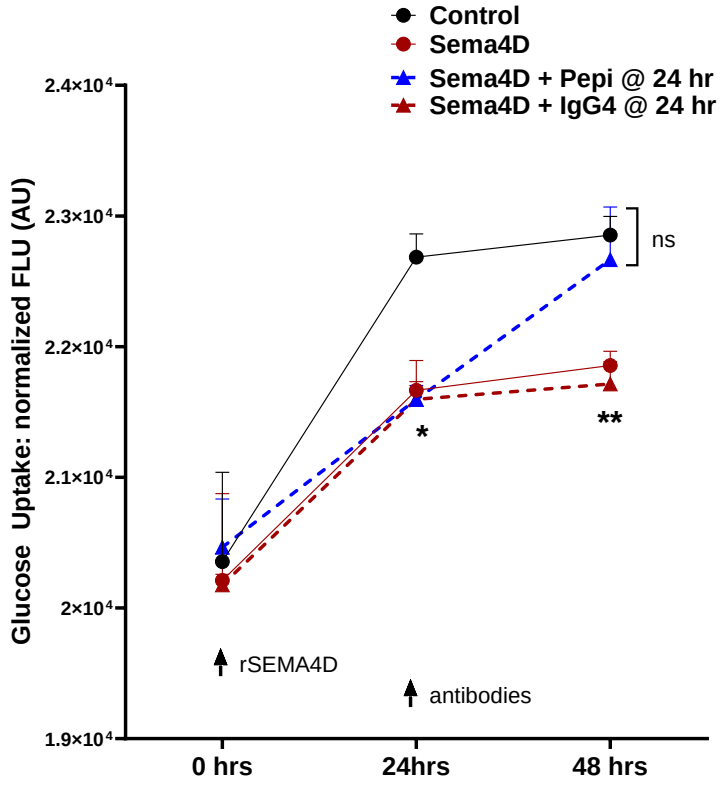
Blue= anti-PLXN
Red= isotype control

SEMA4D regulates Metabolic Transporters



Purified human astrocyte cultures
VX15 = pepinemab

Antibody blockade of SEMA4D reverses loss of metabolic function



Evans et al. Journal of Neuroinflammation, August 2022, 19:200.

PEPINEMAB: SEMA4D blocking antibody

Clinical Experience in HD

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01919-8

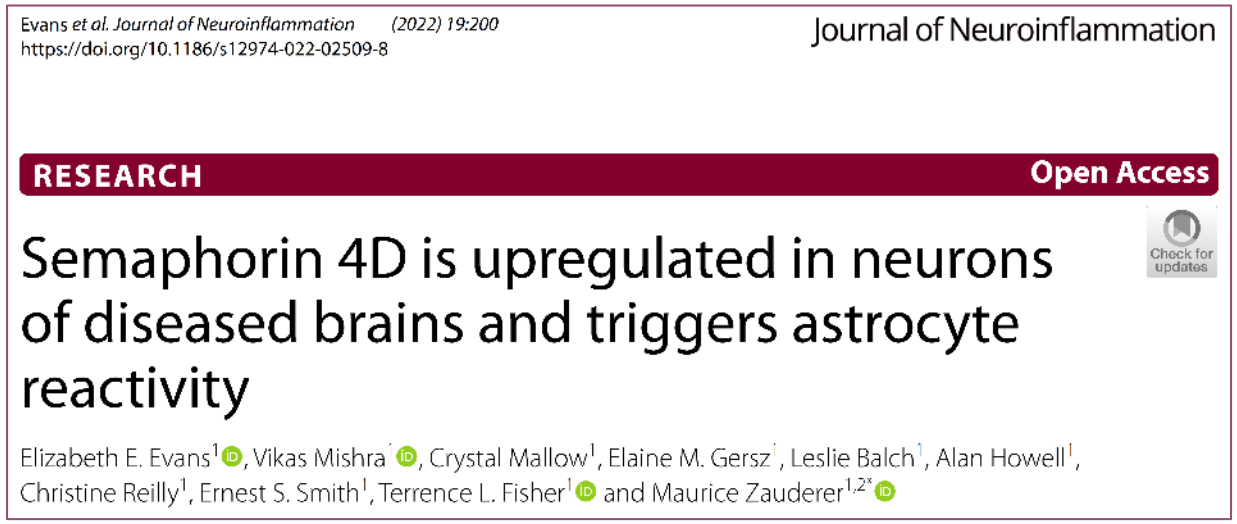
Check for updates

OPEN

Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial

Andrew Feigin[1], Elizabeth E. Evans[2], Terrence L. Fisher[2], John E. Leonard[2], Ernest S. Smith[2], Alisha Reader[2], Vikas Mishra[2], Richard Manber[3], Kimberly A. Walters[4], Lisa Kowarski[4], David Oakes[5], Eric Siemers[6], Karl D. Kieburtz[5], Maurice Zauderer[2]✉ and the Huntington Study Group SIGNAL investigators*

Preclinical Mechanism of Action



Evans *et al. Journal of Neuroinflammation* (2022) 19:200
https://doi.org/10.1186/s12974-022-02509-8

Journal of Neuroinflammation

RESEARCH Open Access

Check for updates

Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity

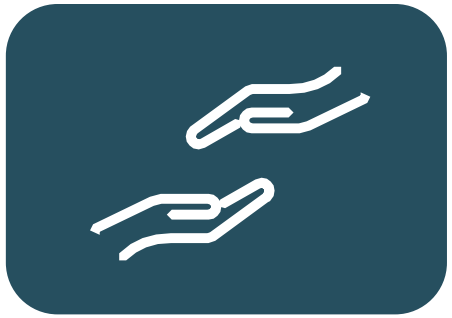
Elizabeth E. Evans[1], Vikas Mishra[1], Crystal Mallow[1], Elaine M. Gersz[1], Leslie Balch[1], Alan Howell[1], Christine Reilly[1], Ernest S. Smith[1], Terrence L. Fisher[1] and Maurice Zauderer[1,2*]

Pepinemab (VX15/2503):
Humanized IgG4 Mab with hinge mutation

HUNTINGTON'S DISEASE

Genetic Disease

HD is caused by dominant mutation in a single gene.



Unmet need

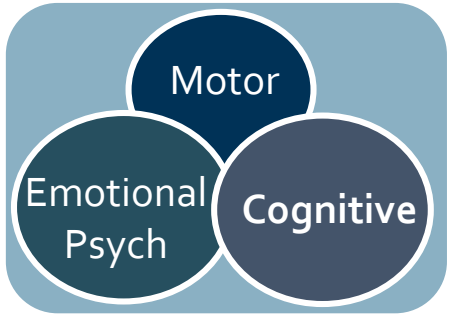
No approved treatments to alter the course of Huntington's Disease.

~40,000 individuals

with manifest disease in US

>150,000 more

at risk of inheriting mutation



Symptoms

Cognitive impairment = most significant impact on daily life (FDA Voice of the Patient)

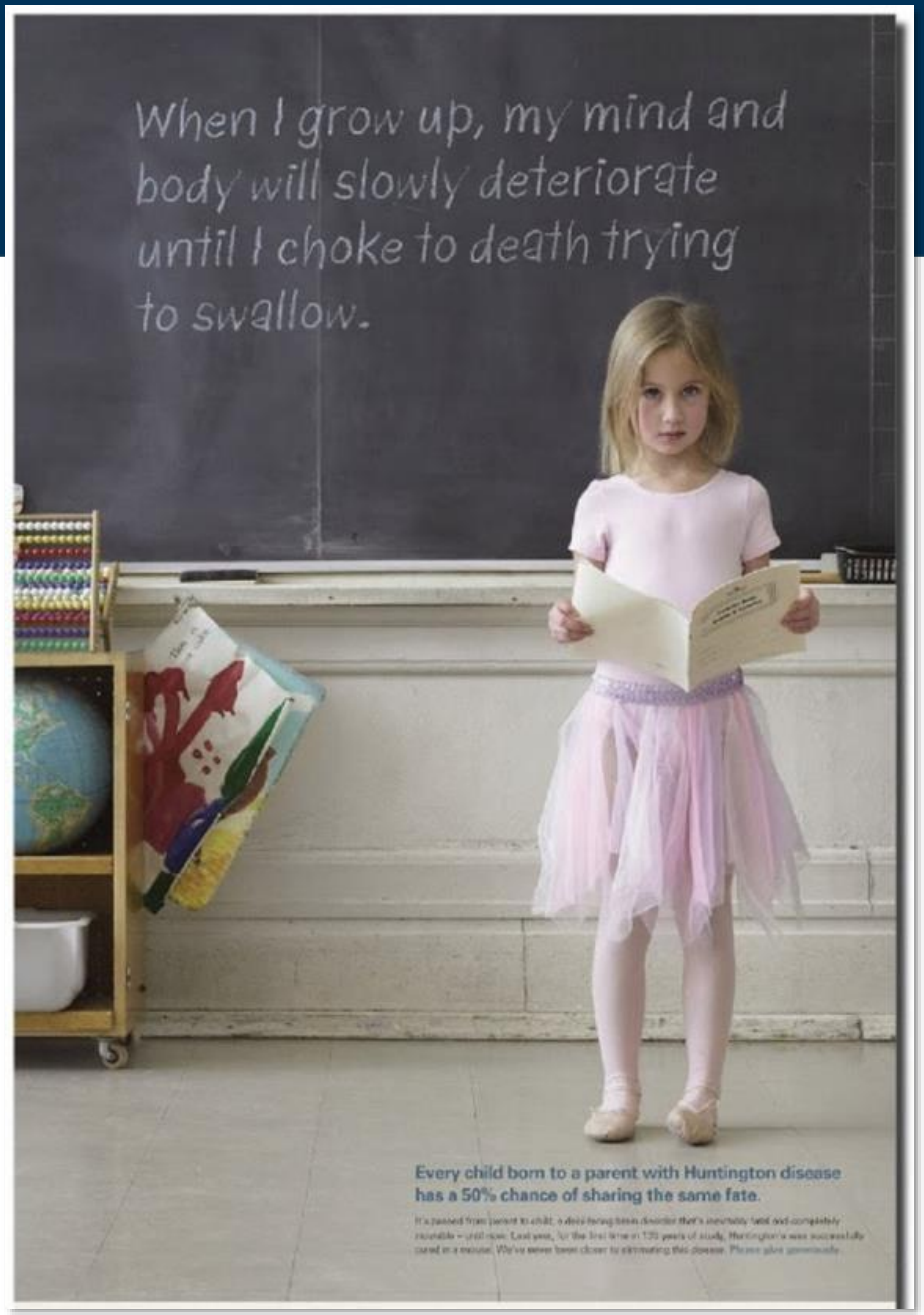


Photo credit: Huntington Society of Canada

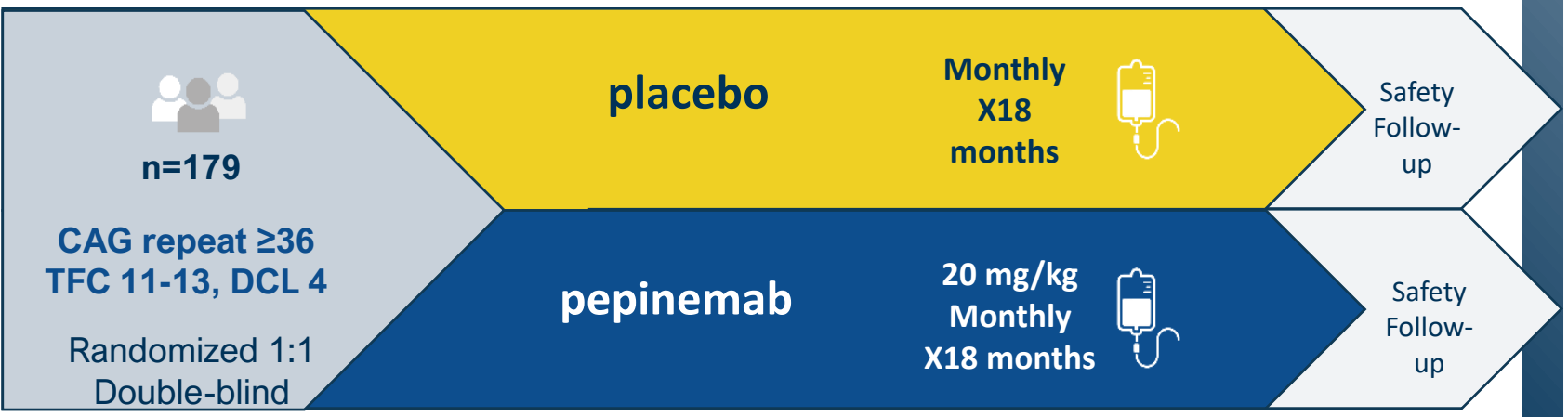
HUNTINGTON'S DISEASE

Clinical Trial Design

SIGNAL

Orphan Disease and Fast Track Designations

"Mild HD" Early Manifest HD



Data Analysis and Study Objectives

Safety and tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

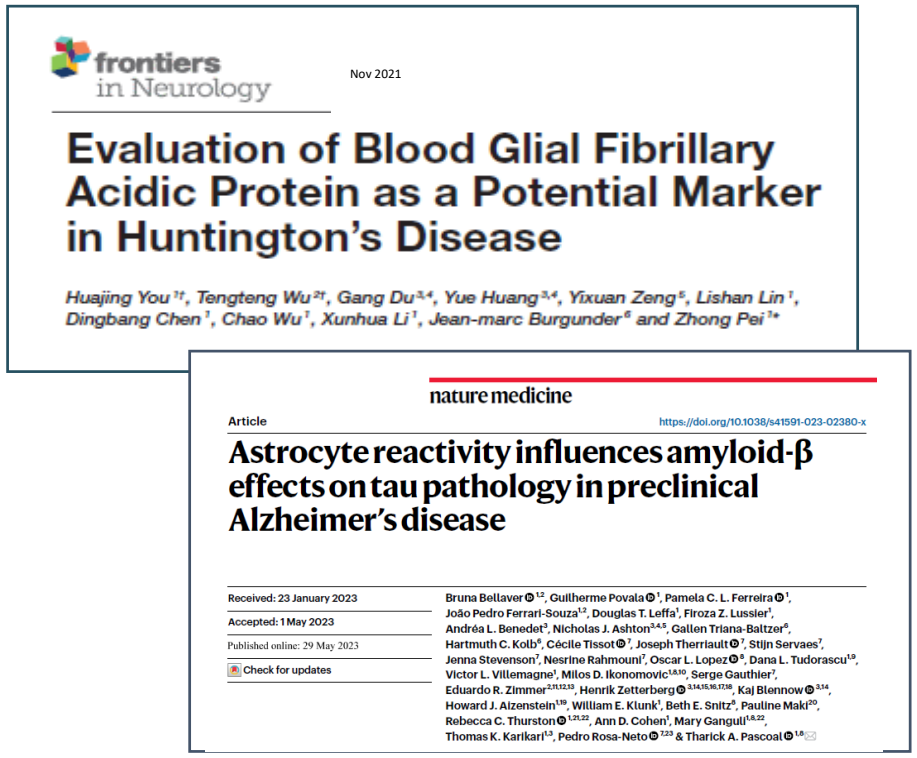
Key Exploratory and Biomarker Outcomes
Metabolic imaging (FDG-PET)
Brain Volume (vMRI)
Fluid Biomarkers: GFAP, etc

NCT02481674. *Note separate Prodromal Cohort (DCL 2 or 3, n=86) was also completed*

Glial Fibrillary Acidic Protein (GFAP):

Biomarker for astrocyte activation / dysfunction

- Correlates with cognitive decline
- Proposed as the key neuroinflammatory fluid biomarker for the revised AD staging classification



frontiers in Neurology

Nov 2021

Evaluation of Blood Glial Fibrillary Acidic Protein as a Potential Marker in Huntington's Disease

Huajing You [†], Tengteng Wu [2†], Gang Du [3,4], Yue Huang [3,4], Yixuan Zeng [5], Lishan Lin [1], Dingbang Chen [1], Chao Wu [1], Xunhua Li [1], Jean-marc Burgunder [6] and Zhong Pei [1]*

nature medicine

Article

https://doi.org/10.1038/s41591-023-02380-x

Astrocyte reactivity influences amyloid-β effects on tau pathology in preclinical Alzheimer's disease

Received: 23 January 2023

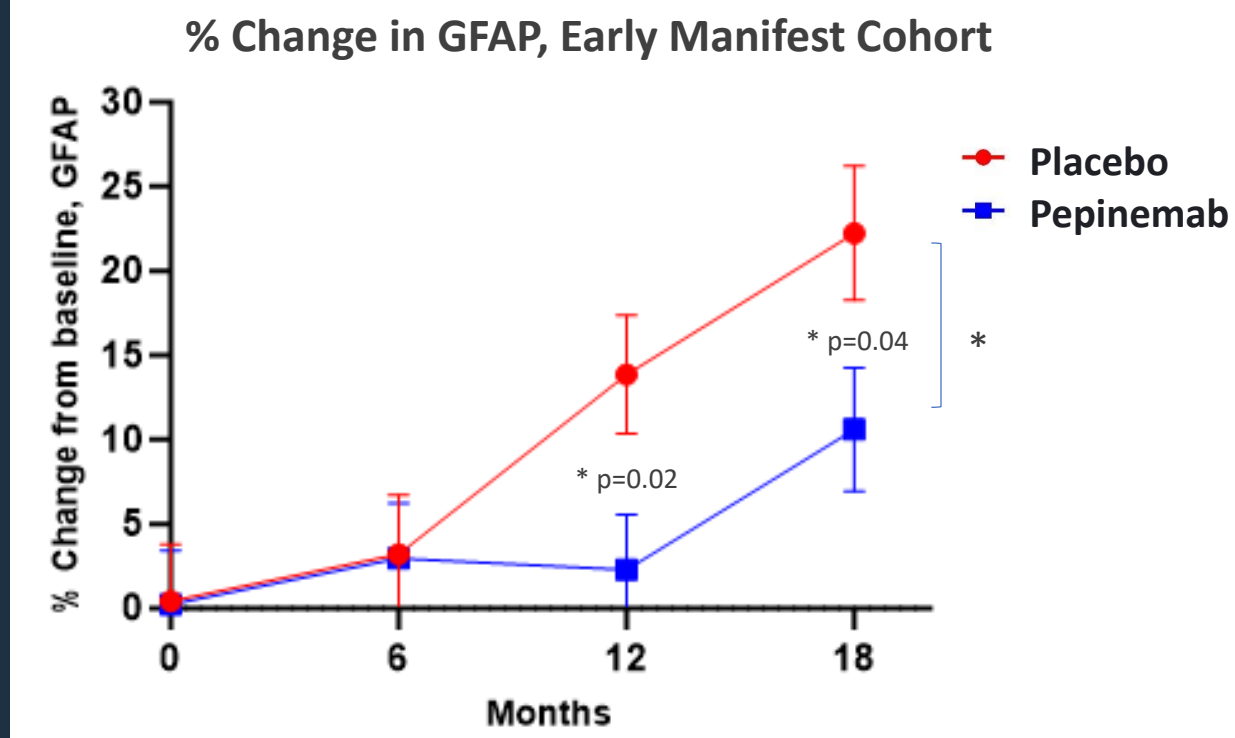
Accepted: 1 May 2023

Published online: 29 May 2023

Check for updates

Bruna Bellaver [1,2], Guilherme Povala [1], Pamela C. L. Ferreira [1], João Pedro Ferrari-Souza [1,2], Douglas T. Leffa [1], Firoza Z. Lussier [1], Andréa L. Benedet [3], Nicholas J. Ashton [3,4,5], Gallen Triana-Baltzer [6], Hartmuth C. Kolb [6], Cécile Tissot [7], Joseph Therriault [7], Stijn Servaes [7], Jenna Stevenson [7], Nesrine Rahmouni [7], Oscar L. Lopez [8], Dana L. Tudorascu [1,9], Victor L. Villemagne [1], Milos D. Ikonomovic [1,8,10], Serge Gauthier [7], Eduardo R. Zimmer [2,11,12,13], Henrik Zetterberg [3,14,15,16,17,18], Kaj Blennow [3,14], Howard J. Aizenstein [1,19], William E. Klunk [1], Beth E. Snitz [8], Pauline Maki [20], Rebecca C. Thurston [1,21,22], Ann D. Cohen [1], Mary Ganguli [1,8,22], Thomas K. Karikari [1,3], Pedro Rosa-Neto [7,23] & Tharick A. Pascoal [1,6]

Pepinemab reduced plasma GFAP in SIGNAL-HD



* % change from baseline over time was analyzed via MMRM after adjusting for baseline value and age. P values represent t-tests for significant difference (PEPI-PBO) at each timepoint.

FDG-PET CORRELATES WITH COGNITIVE FUNCTION

Measure of glucose uptake, Early Manifest cohort

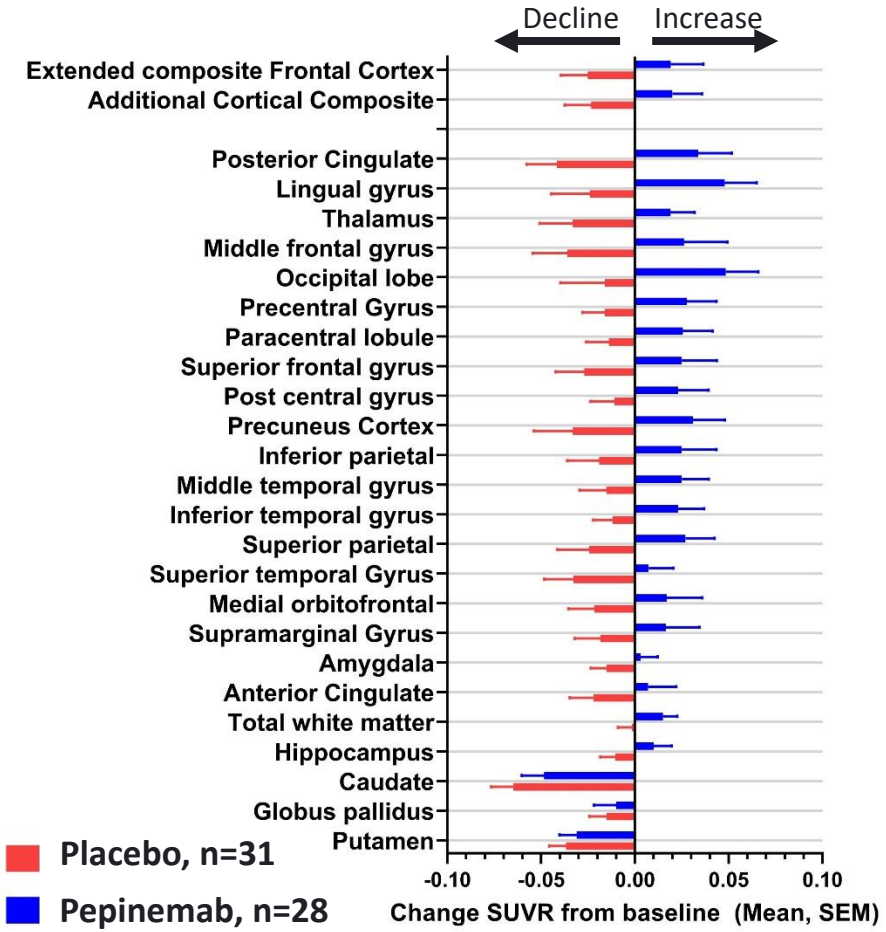
1 FDG-PET measures brain metabolic activity.

2 Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.

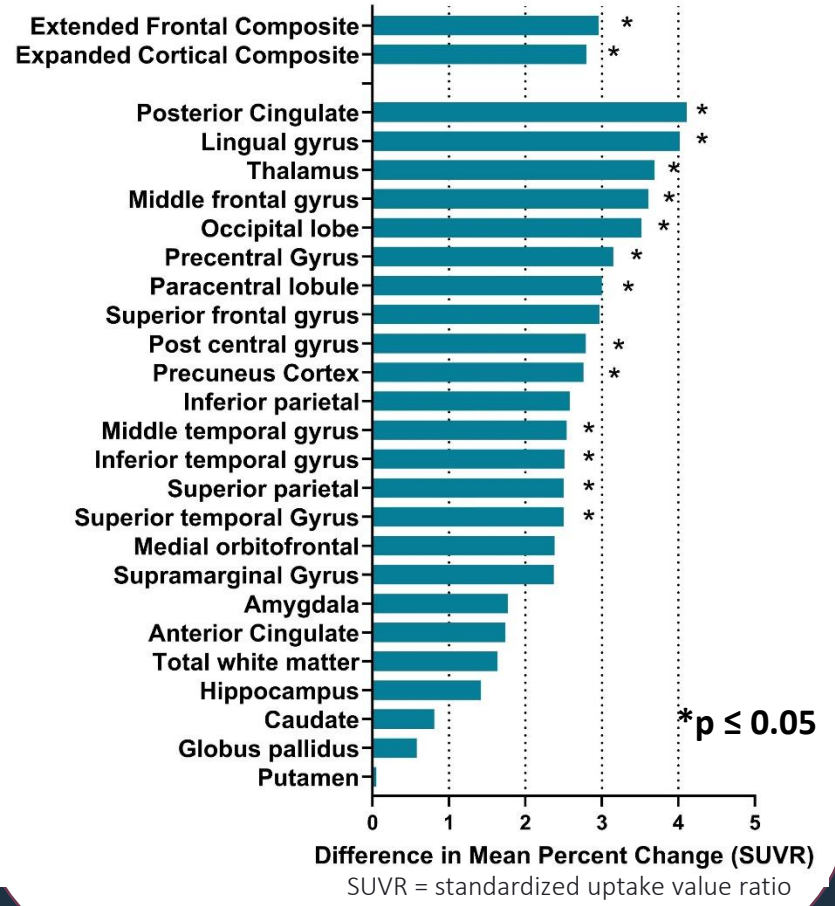
Pepinemab treatment appears to reverse loss of metabolic activity.

Nature Medicine (2022) 28:2183-2193

Change in FDG-PET at Month 18



Difference (PEPI-PBO) at Month 18



SUVR = standardized uptake value ratio

PRIMARY ENDPOINT:

Huntington's Disease Cognitive Assessment Battery (HD-CAB)

- The HD-CAB is a battery of cognitive tests designed specifically for use in late prodromal/ early HD clinical trials
  - Includes 6 tests selected based on representation of the cognitive domains affected in HD, along with their high reliability, sensitivity, practicality and tolerability
  - Developed and validated by experts and has become a robust measure of cognition for use in HD clinical trials

Executive Function Assessments

1. One Touch Stockings of Cambridge (OTS)
2. Symbol Digit Modalities Test (SDMT)
3. Trail Making Tests (TMT)

Psychomotor Function

4. Paced Tapping Test (PTAP)

Learning and Memory

5. Hopkins Verbal Learning Test (HVLT)

Social Cognition

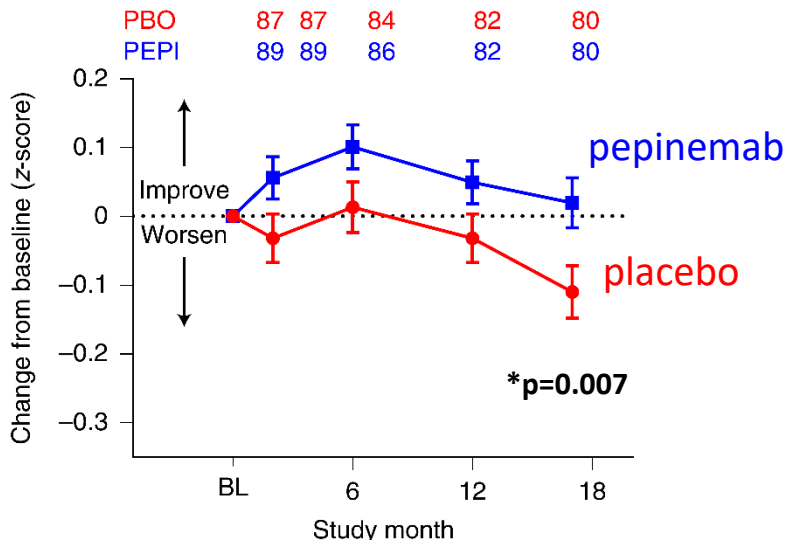
6. Emotion Recognition Test

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

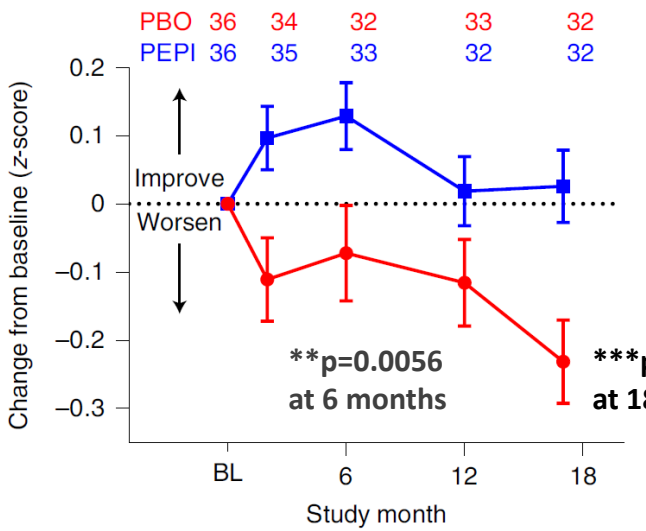
Exploratory and Post-hoc analysis

- Treatment effect is most evident in patients with early signs of cognitive deficits (MoCA<26)

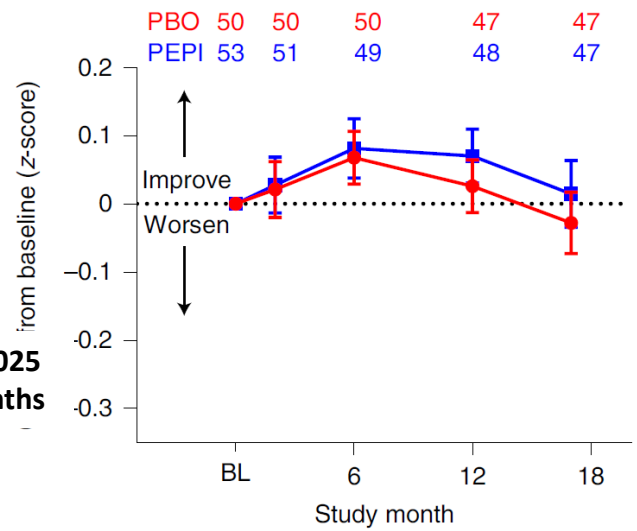
Early Manifest HD:
Intent to treat population (mITT)



MoCA <26, Early Manifest



MoCA ≥26, Early Manifest

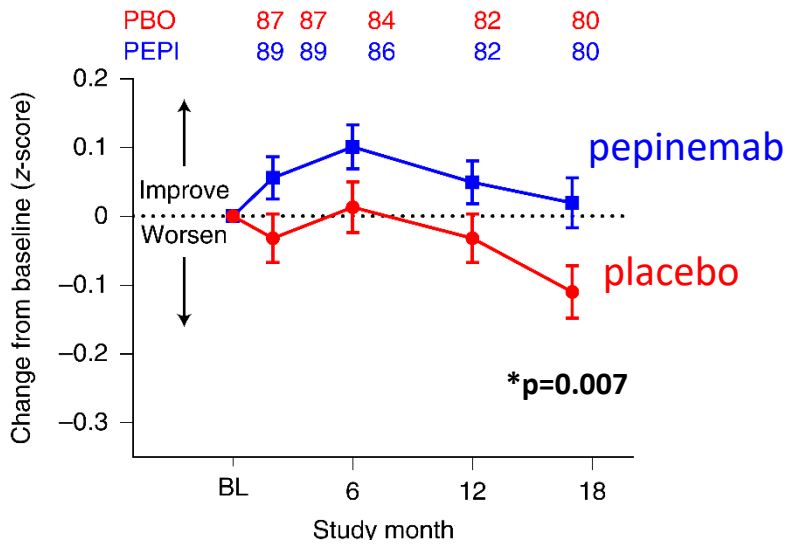


Feigin, A., Evans, E.E., Fisher, T.L. et al.
Nature Medicine (2022), 28: 2183-2193

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Exploratory and Post-hoc analysis

Early Manifest HD:
Intent to treat population (mITT)



- Highly significant improvement in HD-CAB Index score (p=0.007)
- A striking increase in brain metabolic activity, FDG-PET
- Significant reduction in plasma GFAP

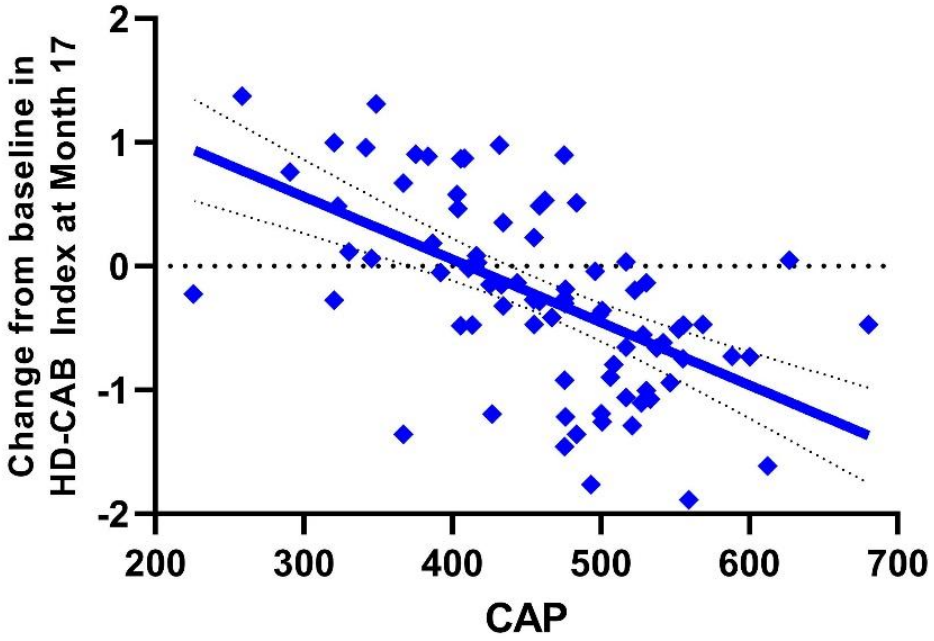
- Significant benefit in reducing apathy severity (p=0.017, 1-sided)
- Reduced atrophy in caudate region of striatum, vMRI (p=0.017)
- Confirmed target engagement in blood and CSF

Feigin, A., Evans, E.E., Fisher, T.L. et al.
Nature Medicine (2022), 28: 2183-2193

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Associated with Meaningful change

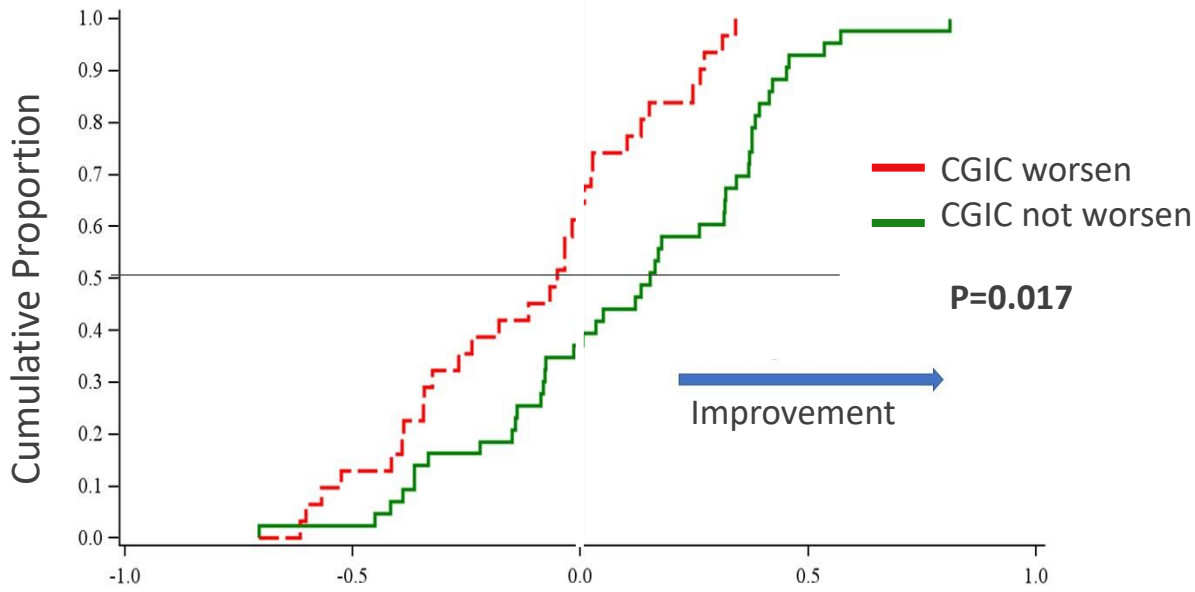
HD-CAB cognitive score correlates with CAP score



Pearson R^2=0.33, p<0.0001 (N=79).

The CAG:Age Product (CAP) Score, is a widely employed age-adjusted measure of Huntington's disease burden. The CAP score has been shown to correlate with multiple clinical features of HD, including age of disease onset, motor dysfunction, cognitive deficits, compromised daily living capacity, and neurodegeneration.

HD-CAB cognitive score correlates with Clinical Global Impression of Change (CGIC)

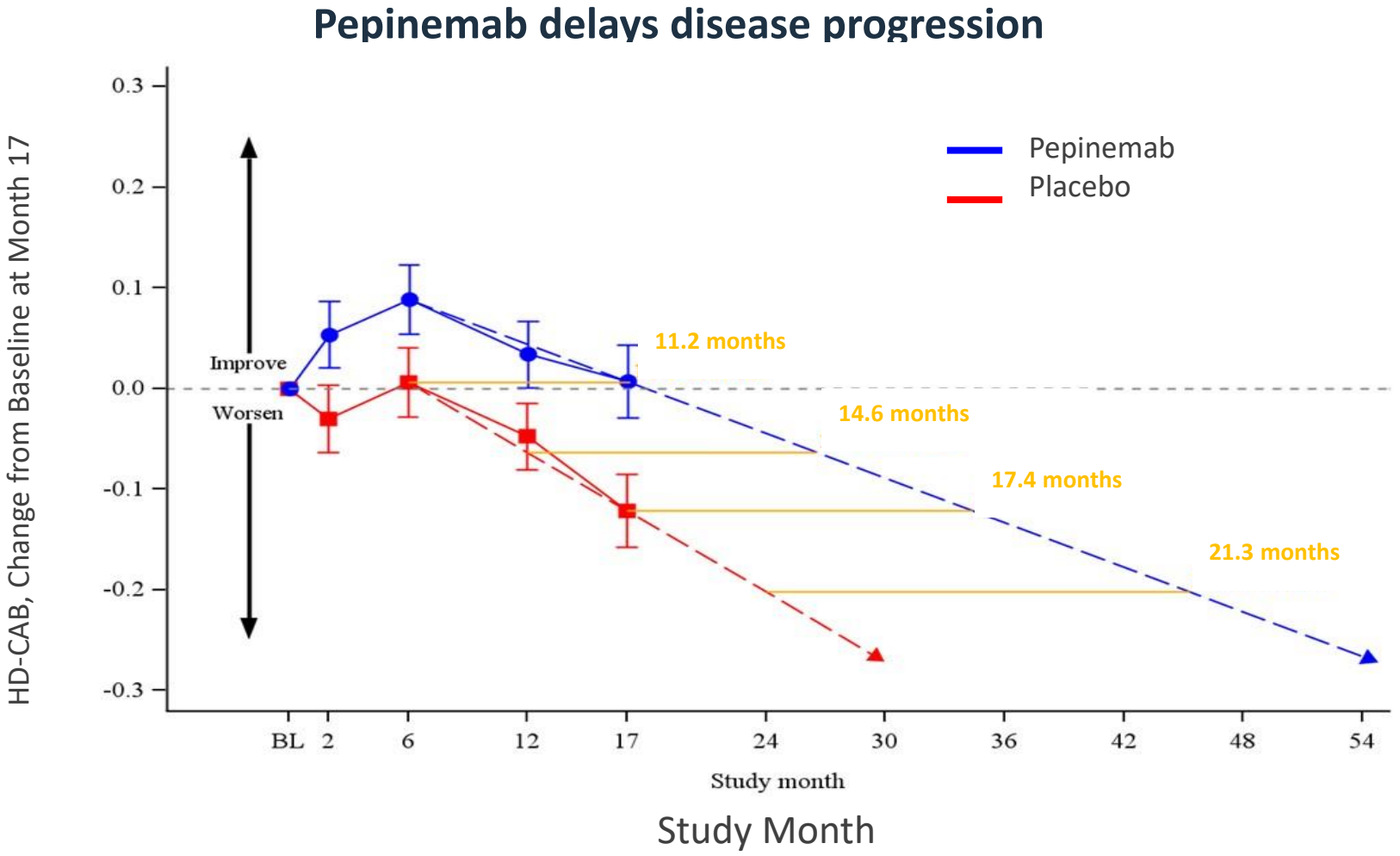


HD-CAB, Change from Baseline at Month 17

Early Manifest Cohort B1 treated with Pepinemab

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Associated with Meaningful change

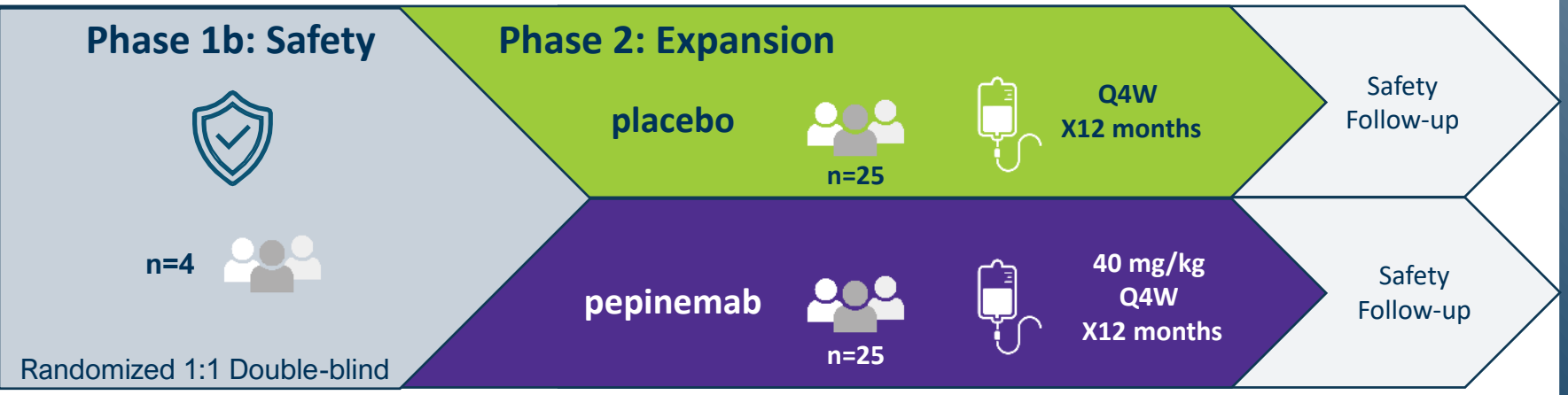


ALZHEIMER'S DISEASE

Phase 1b/2 Trial Design

SIGNAL-AD

Funding by alzheimer's association® Alzheimer's Drug Discovery Foundation



Mild AD
(CDR=0.5 or 1.0, MMSE 18-26)

Topline Data:

Safety and tolerability

Cognitive Function measures
CDR-SB, iADRS, ADAS-Cog13, ADCS-CGIC, MMSE, CDRS, etc

Biomarker Outcomes
Metabolic imaging (FDG-PET)*
GFAP, also Aβ, pTau, NfL, etc
Brain Volume (vMRI)

16 sites in US

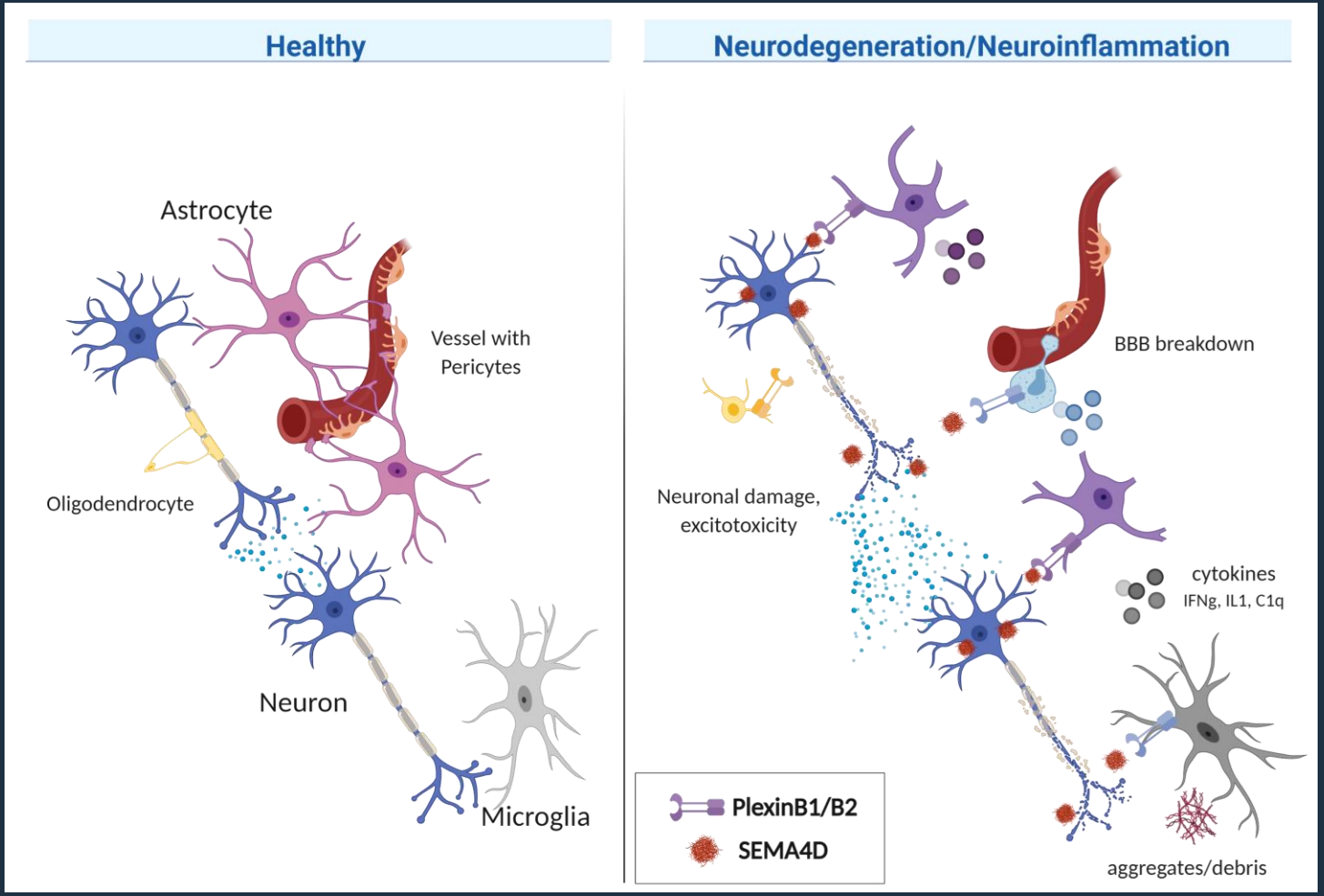
Data Safety Monitoring Board
5 meetings complete

APR 2023
Enrollment Complete

LPLV
June 2024
Topline Data Q3 2024

NCT04381468

GLIAL CELLS RESPOND TO DAMAGE IN THE BRAIN



Images created with Biorender.com

SEMA4D is upregulated on damaged neurons

SEMA4D binding to Plexin receptors triggers collapse of cytoskeleton and transformation to reactive inflammatory state

Reported effects of SEMA4D include astrocyte and microglial activation, survival and differentiation of glial precursor cells, integrity of BBB.

Evans et al. 2022, J Neuroinflammation
Smith et al. 2014 Neurobiology of Disease

Summary

- Pepinemab is designed to block neuroinflammatory SEMA4D pathway to reduce neuroinflammation and to protect and restore healthy astrocyte and neuronal functions
- SIGNAL-HD study established safety and proof of concept for pepinemab
  - Well tolerated
  - Target engagement and CNS penetration
  - Reduction in plasma GFAP and reversed loss of metabolic activity as determined by FDG-PET
  - SIGNAL-HD study informed study design for SIGNAL-AD
    - Patient population: data supports the potential cognitive benefit, particularly in patients with mild cognitive deficits
    - Key efficacy outcome measure: FDG-PET

- SIGNAL-AD is a placebo-controlled randomized Phase 1b/2 study to evaluate safety and activity of pepinemab treatment for people living with early AD.
  - Last patient last visit is anticipated in June 2024
  - Topline data expected in 3Q 2024 will include **safety** and key efficacy measures, i.e. impact of treatment on brain metabolic activity (**FDG-PET**), together with other biomarkers of disease progression (**GFAP**). Initial assessment of treatment effects on **cognition** employing several validated, clinically meaningful cognitive scales for AD.

Thanks and Gratitude

Participants, caregivers and their families!

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SIGNAL-AD

alzheimer's association®

Alzheimer's Drug Discovery Foundation

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