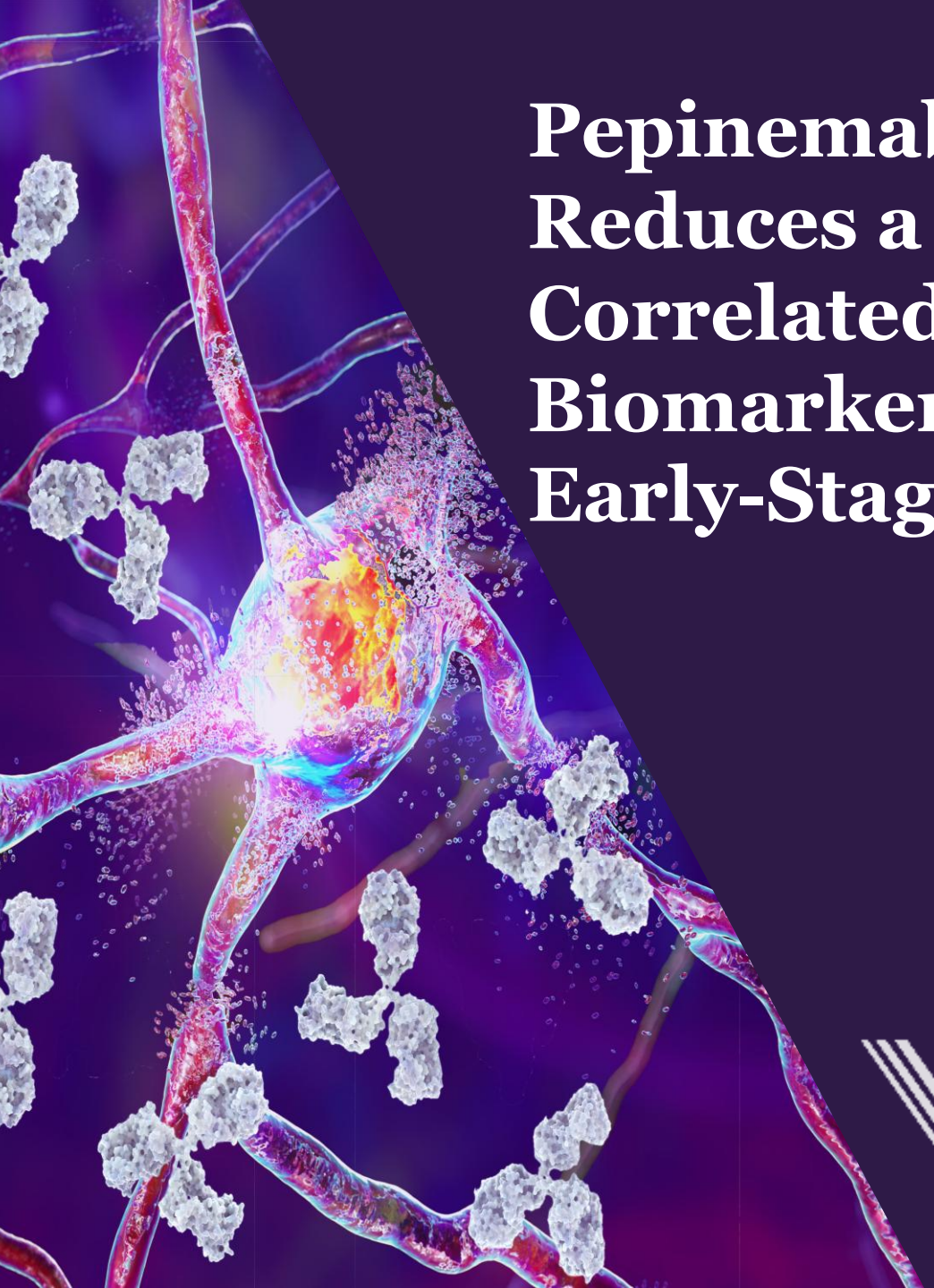


Pepinemab, SEMA4D Blocking Antibody, Reduces a Unique Astrocyte Subset (Ast10) Correlated with Cognitive Decline and Biomarkers of Synaptic Loss in People with Early-Stage AD

Elizabeth Evans, PhD

Sr VP Discovery and Translational Medicine

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VACCINEX

Unique Targets

Novel Mechanisms

New Medicines

CTAD 2026 Clinical Trials on Alzheimer's Disease

November 16-19, 2026

Boston, MA (USA)

Disclosures

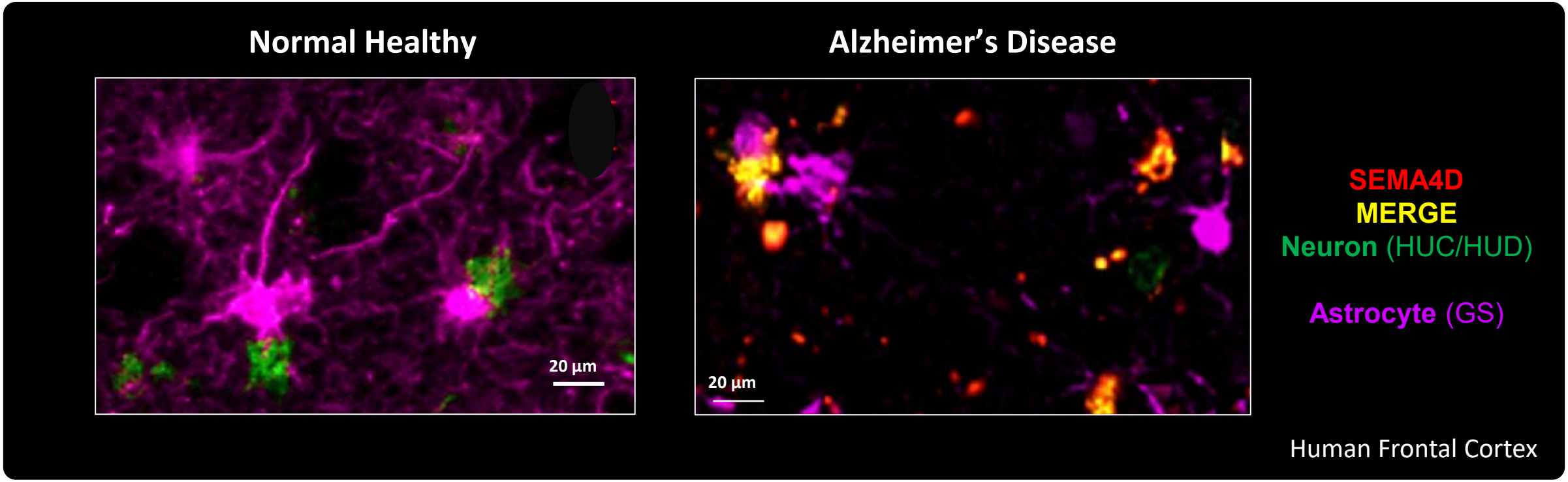
Elizabeth Evans, PhD
Sr VP Discovery and Translational Medicine
Chief Operating Officer

Current Employee and Stock Shareholder of 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, 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 and the other risks and uncertainties described in the Company's most recent year end Annual Report.



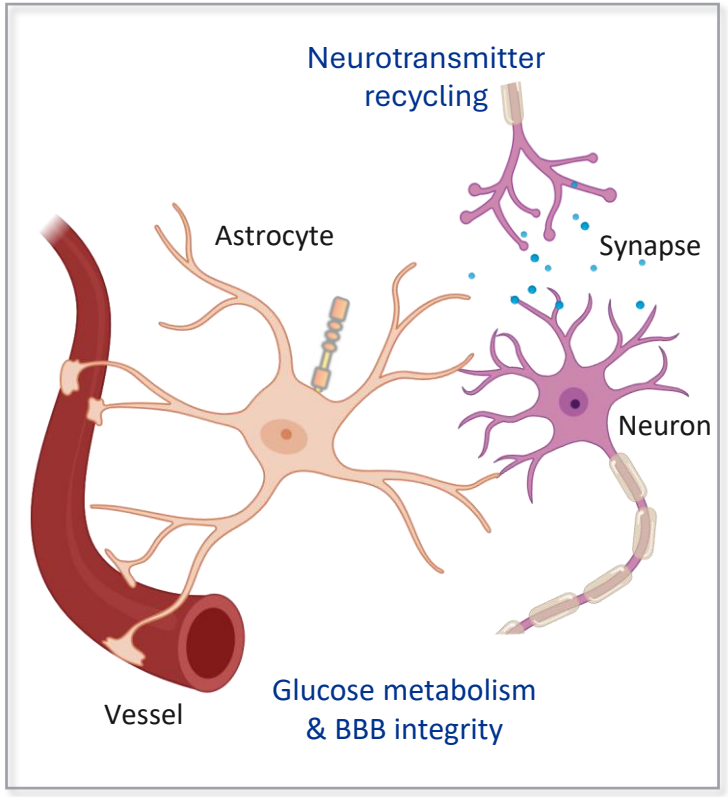
Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity

Evans, EE. et al., J Neuroinflammation, 2022. doi: 10.1186/s12974-022-02509-8

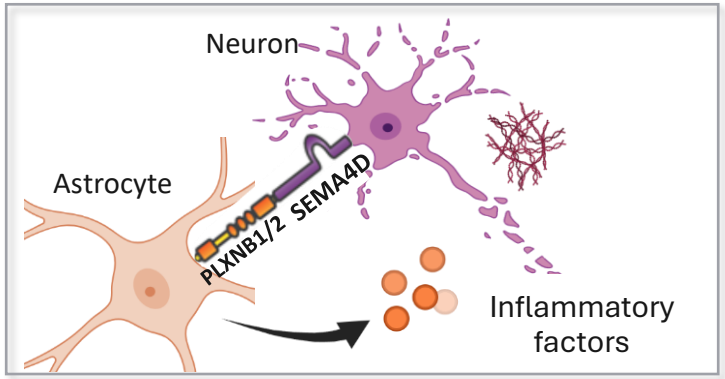
- SEMA4D triggers reactive state and loss of homeostatic functions in purified human astrocytes.
- Antibody blockade reduced reactive astrocytes, synaptic loss and cognitive decline in AD mouse model.

Reactive Astrocytes and microglia contribute to the Alzheimer's Cascade and cognitive decline

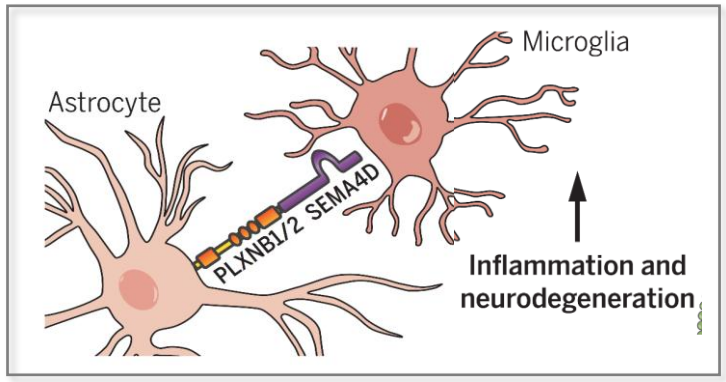
Homeostatic



Reactive / Inflammatory
SEMA4D+



Evans et al, J Neuroinflamm. 2022



Clark…Quintana et al, Science 2

Loss of homeostatic functions

- Excitotoxicity, synaptic loss
- Metabolic deficit & compromise to BBB

Gain of inflammatory functions

- Astrocyte-Microglia interactions
- Secretion of inflammatory factors

Genetic Evidence Links SEMA4D/PLXNB1/B2 Signaling to Neuropathology and Cognitive Decline in Alzheimer's Disease

SEMA4D/PLXN signaling associated with:	References
• Reactive astrocytes	1, 2, 4, 6-11
• Astrocyte – Microglia interactions	4, 6-7, 9
• Neuroinflammation	1, 4, 6, 9, 11
• Neuropathology and cognitive decline: • **associated with Aβ plaques and Tau tangles**	1-4, 7-9
• Vascular integrity and dementia	1 11
• Synaptic integrity and cognition	4, 5, 9, 10

	References
1	Mega Vascular Cognitive Impairment and Dementia (MEGAVCID) consortium. A genome-wide association meta-analysis of all-cause and vascular dementia. Alzheimers Dement. 2024
2	Mostafavi S, et al. A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease. Nat Neurosci. 2018
3	Yu L, et al. Targeted brain proteomics uncover multiple pathways to Alzheimer's dementia. Ann Neurol. 2018
4	Huang J et al. **SORLA up- regulation suppresses pathological effects in aged tauopathy mouse brain.** Sci Adv. 2026
5	Ku TS, et al. Proteomic Analysis in Alzheimer's Disease with Psychosis Reveals Separate Molecular Signatures for Core AD Proteinopathy and Postsynaptic Density Disruption. 2026.
6	Li M-M, et al. Programmed cell death signatures-driven microglial transformation in AD: single-cell transcriptomics and functional validation. Front. Immunol. 2025.
7	Huang Y. et al. Regulation of cell distancing in peri-plaque glial nets by Plexin-B1 affects glial activation and amyloid compaction in Alzheimer's disease. Nat Neurosci 2024
8	Mathys H et al. Single-cell transcriptomic analysis of Alzheimer's disease. Nature. 2019
9	Comandante-Lou N, …De Jager PL et al. **A systems approach uncovers drivers of the multifocal emergence of an astrocyte state contributing to cognitive decline in Alzheimer's disease**. bioRxiv 2025.02.24.639868;
10	Evans EE, et al. Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity. Journal of Neuroinflammation, 2022
11	Smith ES, et al. SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease. Neurobiol Dis. 2015

SCIENCE ADVANCES | RESEARCH ARTICLE

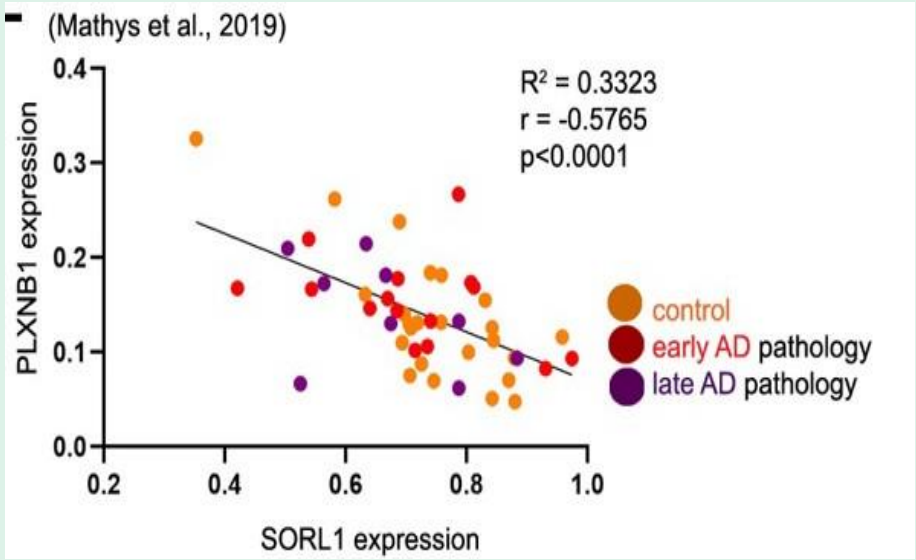
NEUROSCIENCE

SORLA up-regulation suppresses pathological effects in aged tauopathy mouse brain

Huijie Huang[1], Christina Huan Shi[2]†, Wenqi Yang[1]†, Juan C. Piña-Crespo[1], Jay Bhatnagar[1], Julian Curatolo[1], Rabi Murad[3], Palak Shah[1], Alex Campos[4], Alexandra Houser[1], Rebecca A. Porritt[5], Giau Van Vo[1], Qiang Xiao[6,7], Tongmei Zhang[1], Shengjie Feng[1], Kevin Y. Yip[1,2,8], Timothy Y. Huang[1]*

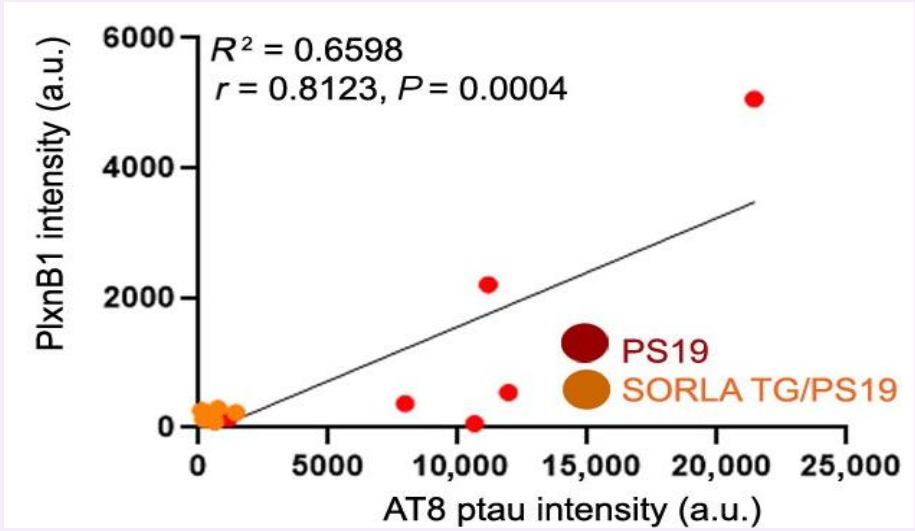
Human Brain Tissue

- PLXNB1 inverse correlation with SORL1
- PLXNB1 is upregulated in astrocytes in early AD (*Mathys et al. 2019*)



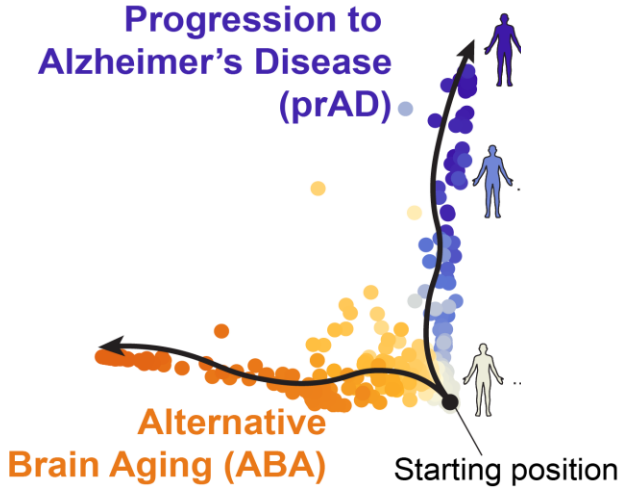
SEMA4D/PLXNB1/B2 identified as key receptor/ligand pair associated with SORLA-mediated effects

- SORLA regulates tau phosphorylation and seeding, glial hyperactivation, synapse loss in Tauopathy mouse model
- SEMA4D and PLXNB1/B2 correlate with pTau

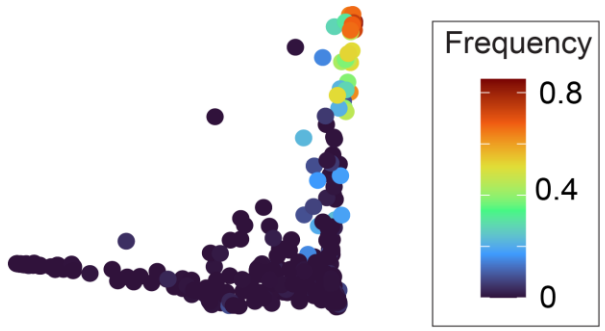


Ast10 Astrocytes are associated with AD disease progression – Aβ and tau load, and slope of cognitive decline

Cellular landscape overlaid by trajectories of cellular change (Green et al. Nature 2024)



Astrocyte 10 frequency in landscape



- Meta-analysis of single-nucleus transcriptomic datasets from 869 older individuals (ROSMAP and related RUSH studies)
- Unique cellular subset **Ast10 increase in frequency from <1% in cognitively normal individuals to as much as 25-80% of all astrocytes in AD**
- **Ast10** is strongly associated with **synaptic integrity (SNAP25) and cognitive impairment**

- Spatial transcriptomics identified and prioritized **SEMA4D/PLXNB1 as a key receptor/ligand pair driving Ast10 state**
- PLXNB1 knockout inhibited expression of Ast10 gene signature in human iPSC astrocytes and mouse models

Led by Philip De Jager, Columbia University

Pepinemab

Humanized IgG4 monoclonal antibody

Binds SEMA4D and blocks signaling through PLXNB1/B2 receptors

<u>Phase II RCT – Huntington's Disease</u>

- **Well tolerated**, n=301
- Reduced biomarkers of astrocyte reactivity -- FDG-PET metabolic imaging and plasma GFAP
- Evidence of slowing cognitive decline, HD-Cognitive Assessment Battery in Early Manifest HD
- *Feigin, A., Evans, E.E., Fisher, T.L. et al. Nature Medicine (2022), 28: 2183-2193*

<u>Phase I RCT – Alzheimer's Disease</u>

- **Well tolerated,** n=50
- Exploratory cognitive assessments and fluid biomarkers, including Olink proteomic panel

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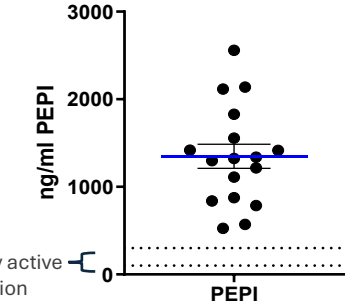
SIGNAL-AD

SIGNAL-AD: Phase 1 randomized clinical trial

- 50 patients, placebo controlled
- 48 weeks of treatment
- Safety, PK/PD, exploratory biomarker and cognitive assessments

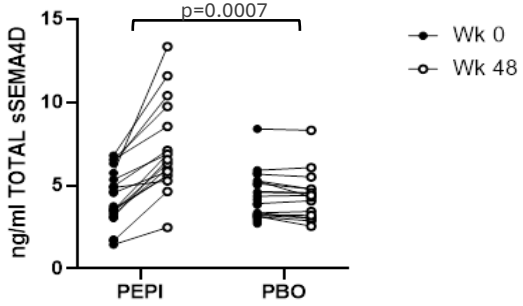
Topline Safety Results, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
	n (%)	n (%)	n (%)
TEAE	21 (87.5)	23 (88.5)	44 (88.0)
Serious TEAE	1 (4.2)	7 (26.9)	8 (16.0)
TEAE with CTCAE Grade ≥ 3	2 (8.3)	4 (15.4)	6 (12.0)
TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE Related to Treatment	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Related to Treatment	12 (50.0)	5 (19.2)	17 (34.0)
TEAE Leading to Treatment Discontinuation	0 (0.0)	1 (3.8)	1 (2.0)
TEAE of Special Interest (TEAESI)	3 (12.5)	0 (0.0)	3 (6.0)
Amyloid-related imaging abnormalities			
ARIA-E	0 (0.0)	0 (0.0)	0 (0.0)
ARIA-H	2 (8.3)*	0 (0.0)	2 (4.0)
* 1 patient at screening			
Any abnormal post-baseline value(s)			
Laboratory: Hematology	19 (79.2)	22 (84.6)	41 (82.0)
Laboratory: Chemistry	24 (100.0)	26 (100.0)	50 (100.0)

Subjects dosed with pepinemab contain ≥ saturating levels of drug in CSF

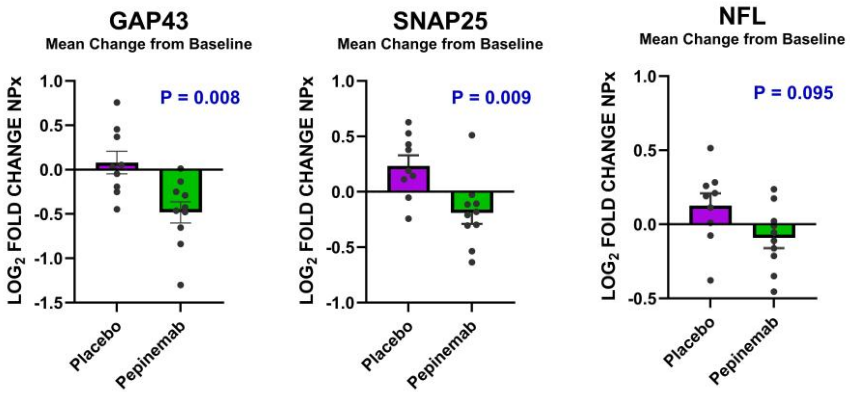


Lower limit biologically active concentration

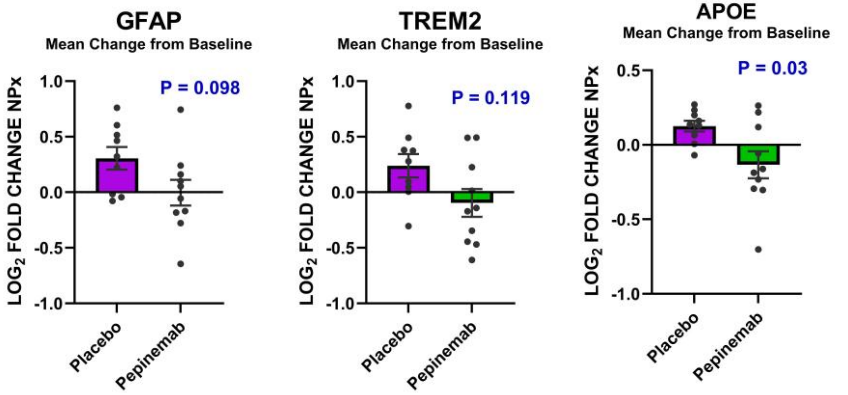
sSEMA4D:PEPI complexes in CSF of subjects dosed with pepinemab – *suggesting target engagement*



Synaptic-Related Biomarkers



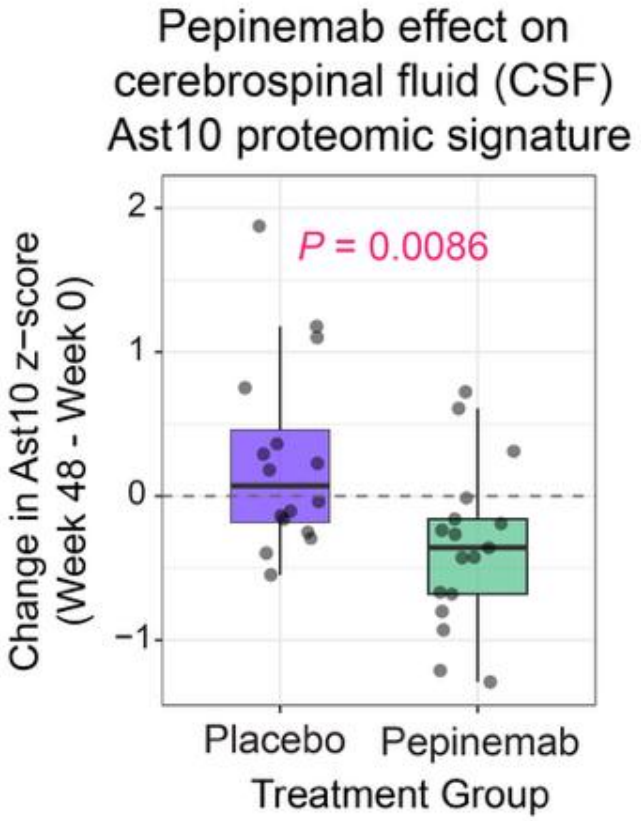
Inflammatory-Related Biomarkers



Olink 5000; Pre-specified subgroup analysis: MMSE22-26

Does pepinemab reduce Ast10 signature and slow damaging consequences of Ast10 astrocytes?

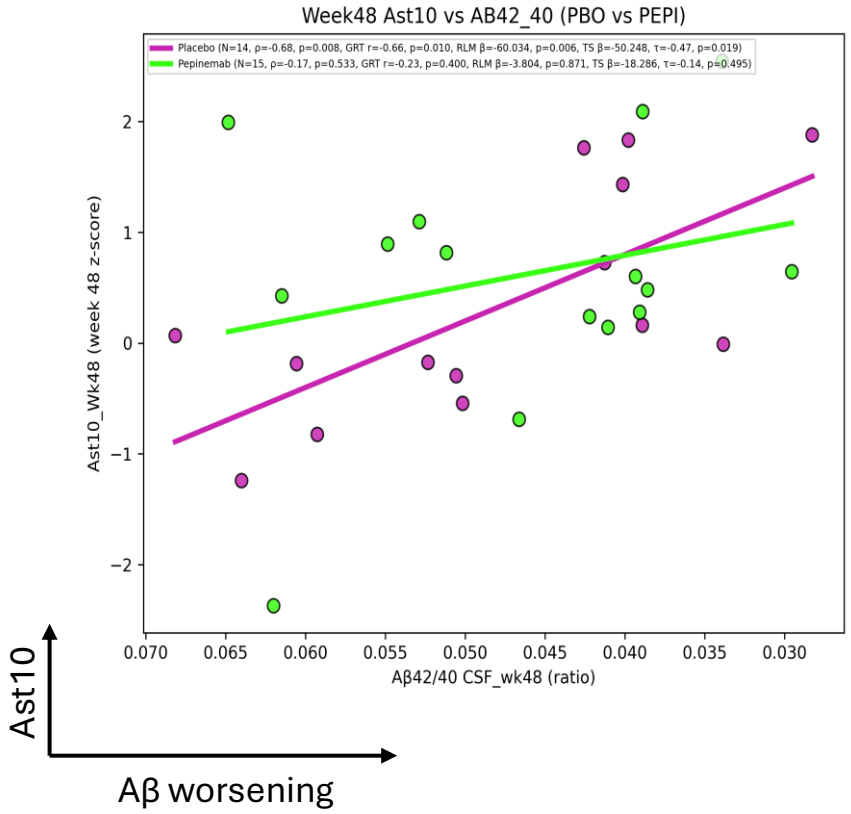
Pepinemab significantly reduced Ast10 proteomic signature



→ **Proteomic data (Olink®) from SIGNAL-AD confirmed that blocking SEMA4D/PLXNB1 with pepinemab reduced Ast10 phenotype**

In collaboration with Philip De Jager, Columbia University
Comandante-Lou, et al, submitted

Ast10 correlates with Tau and Aβ in Placebo group
Pepinemab treatment disrupts association of Ast10 with Tau and Aβ



	Placebo	Pepinemab
Aβ 42/40	**r_S = -0.68, p = 0.008**	r_S = -0.17, p = ns (0.5)
pTau-181	**r_S = 0.77, p <0.001**	r_S = 0.39, p = ns (0.1)

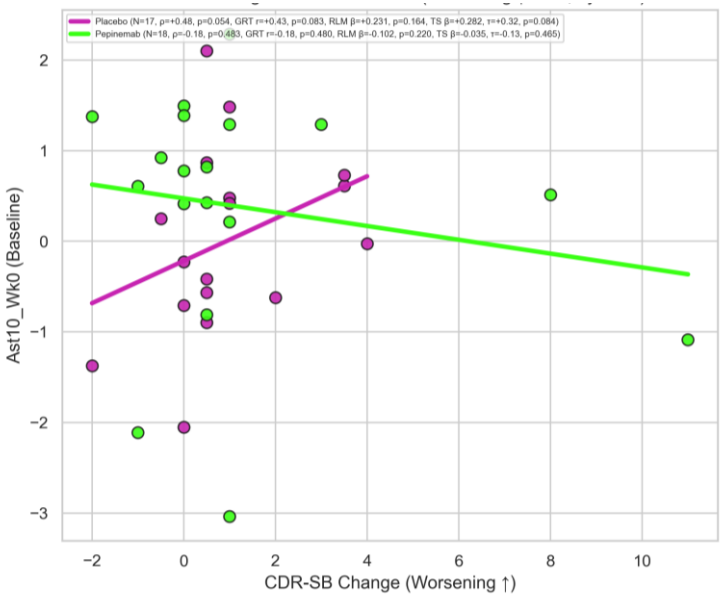
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SIGNAL-AD

Ast10 proteomic signature is associated with cognitive decline in Placebo cohort
→ Pepinemab disrupted correlations with cognitive decline

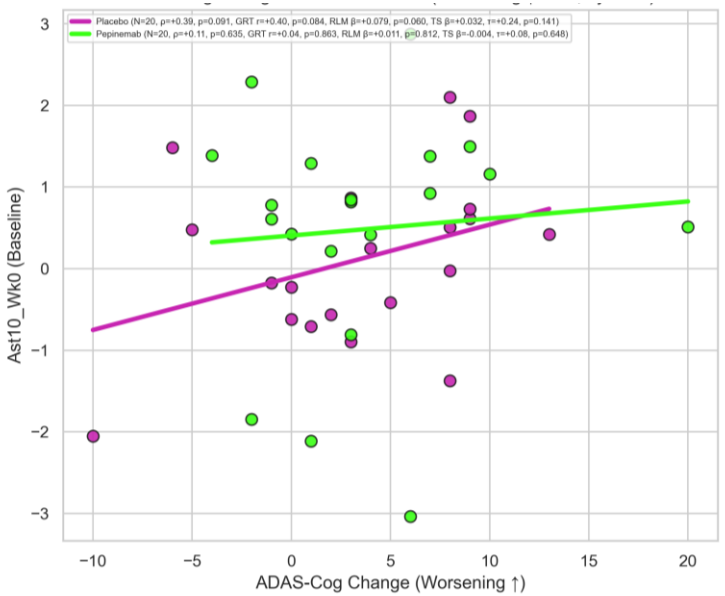
CDR-SB

● r_S = 0. 48, p = 0.05



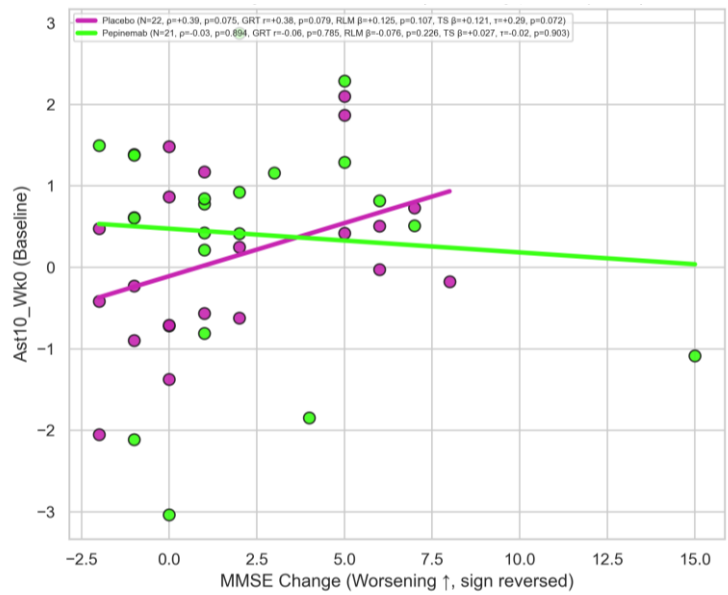
ADAS-Cog13

● r_S = 0. 39, p = 0.09



MMSE

● r_S = 0. 39, p = 0.07



BL Ast10

Δ COA 48 wks, worsening

● Placebo
● Pepinemab

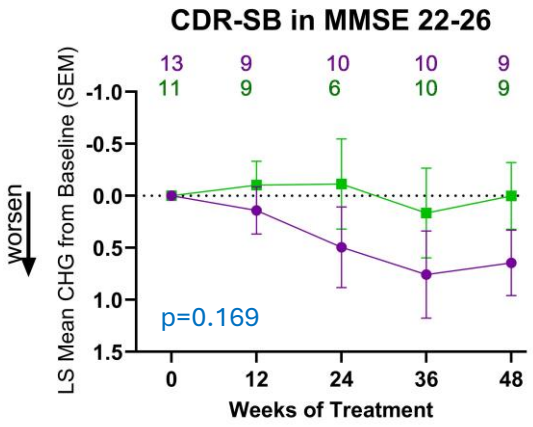
In collaboration with Philip De Jager, Columbia University

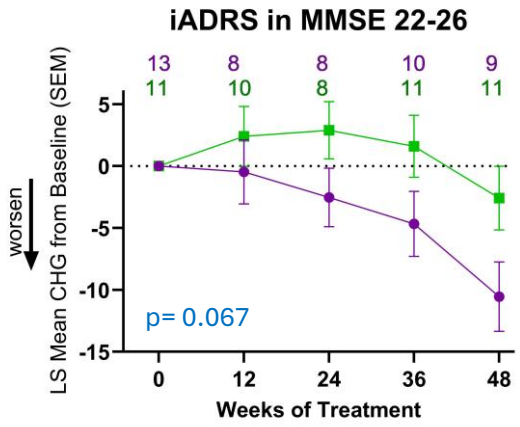
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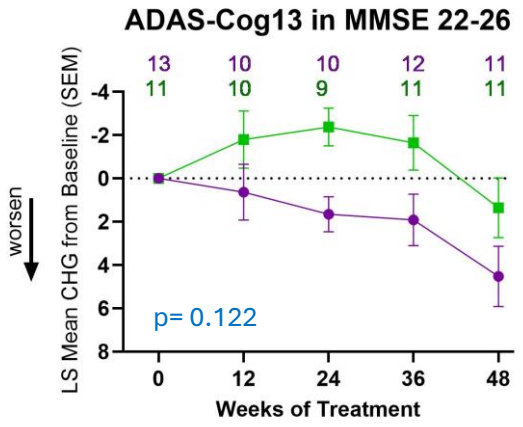
SIGNAL-AD: Phase 1 randomized clinical trial

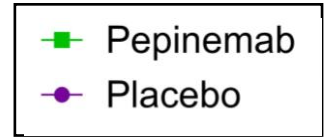
- Well-tolerated
- Evidence of target engagement and bioavailability
- Biomarkers associated with synaptic and cognitive change
- Refine patient population

Baseline MMSE 22-26

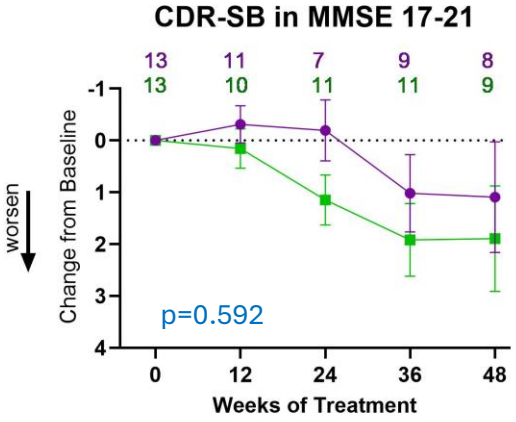


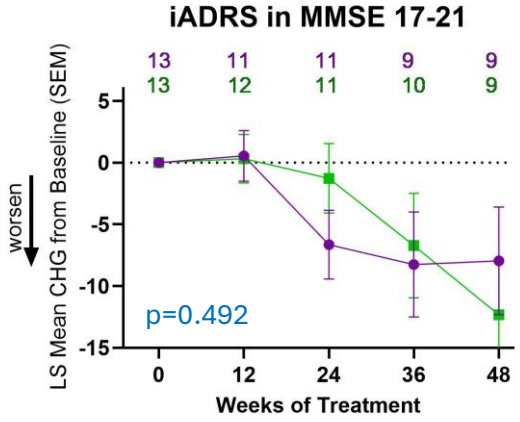


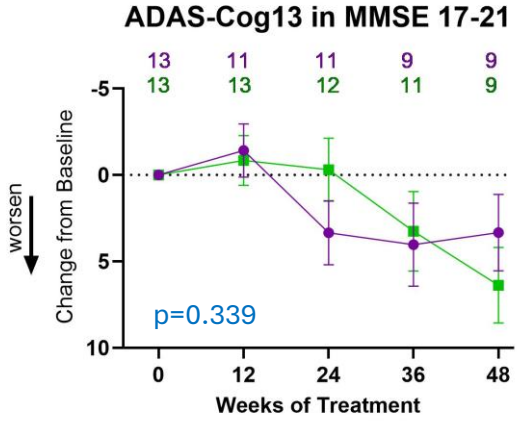




Baseline MMSE 17-21

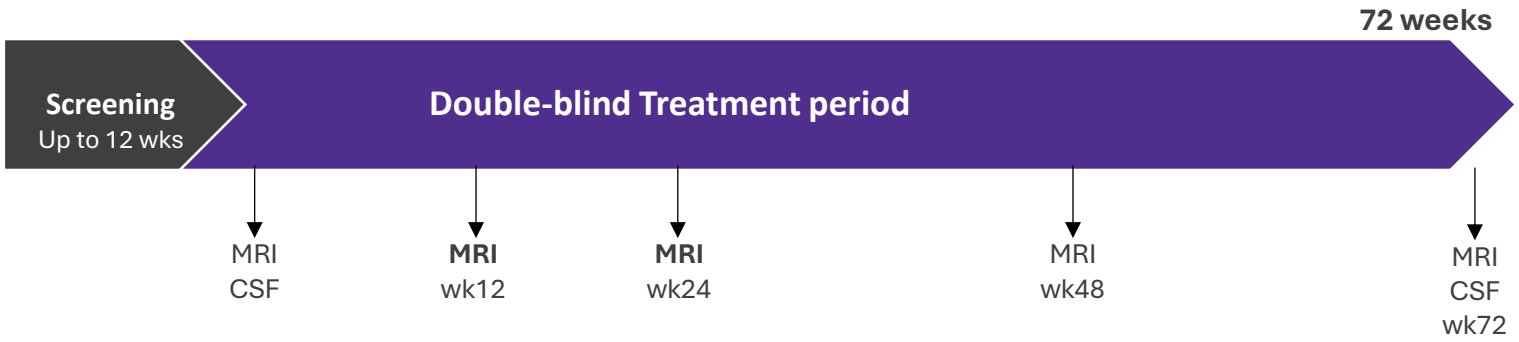






Prespecified subgroup analysis

Planned SIGNAL-AD2, Phase 2 trial design

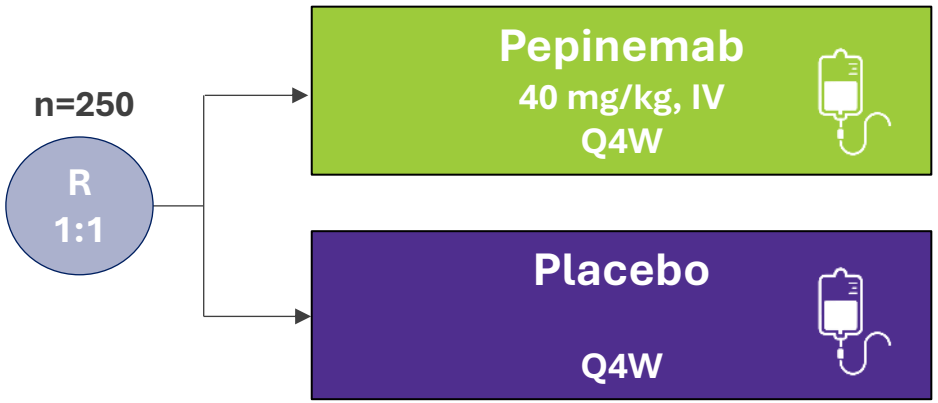


MCI and Mild AD dementia

Key eligibility criteria:

- **MMSE = 22-28**
- CDR-GS = 0.5 or 1.0
- Tiered Screening, Positive for both:

1. Plasma Lumipulse G p-tau217
2. Amyloid (CSF AB42/40)



Objectives:

Primary	**Efficacy : Change from baseline in CDR-SB**
Secondary	• Safety and tolerability, including ARIA assessments • Secondary efficacy endpoints: ADAS-Cog 13 and ADCS-ADL, using the Hochberg procedure
Exploratory	• Change in CSF biomarkers of neurodegeneration, synaptic function, inflammation (Ast10 z-score, pTau217, pTau205, Total tau, pTau181, eMTBR-tau243, Aβ, NRGN, SNAP25, GAP-43, YKL-40, PSD-95, GFAP, NfL) • Correlations among biomarkers, COAs, and Ast10 astrocyte signature • iADRS • PK/PD, Immunogenicity • Additional plasma biomarkers of neurodegeneration, synaptic function, inflammation (Aβ, pTau217, GFAP)

SIGNAL-AD2 Study Start-Up

1

Regulatory

Aligned with FDA on clinical outcome assessments and protocol

2

Site Activation

40 sites in US, Canada, United Kingdom, and Europe

3

Initiation Q1 2027

Screening and enrollment expected in Q1 2027

Summary

1 **Reactive astrocytes may be a key intermediary in the Alzheimer's cascade of amyloid plaques, tau accumulation, synaptic loss and cognitive decline**

2 **Multiple lines of evidence suggest SEMA4D/PLXN signaling as a key driver of reactive astrocytes in AD, including Ast10**

- Ast10 is strongly associated with AD progression, synaptic loss and cognitive impairment
- **Pepinemab** disrupted the correlation of Ast10 with Aβ, pTau, and cognitive decline

3 **SIGNAL-AD2, an expanded randomized, placebo-controlled Phase 2 trial, of pepinemab in early AD is planned to begin Q1 2027**

- Primary outcome assessment is CDR-SB
- Additional COAs and exploratory biomarker assessments as supporting evidence
- Safety and tolerability

Thank you!

1. **Participants, caregivers and their families!**
2. Vaccinex Research and Clinical Development Colleagues
3. PI David Watson, PsyD and Senior Medical Advisor Howard Feldman, MD and SIGNAL-AD and SIGNAL-AD2 study investigators and staff
4. Philip De Jager, Natacha Comandante-Lou, et al.

Charlotte Teunissen, Lisa Vermunt, UMC, Amsterdam Neuroscience

Funding support for SIGNAL-AD

Appendix



VACCINEX

Unique Targets

Novel Mechanisms

New Medicines

ALZHEIMER'S DISEASE

Abbreviated Demographics and Baseline Characteristics

NCT04381468
SIGNAL-AD

Topline Demographics, Number (%) of Patients	Pepinemab 40 mg/kg (N=24)	Placebo (N=26)	All Patients (N=50)
Age (years)			
Mean (SD)	72.4 (7.23)	72.1 (7.69)	72.3 (7.40)
Min, Max	55, 82	55, 83	55, 83
Sex [n (%)]			
Male	6 (25.0)	15 (57.7)	21 (42.0)
Female	18 (75.0)	11 (42.3)	29 (58.0)
Race [n (%)]			
White	20 (83.3)	23 (88.5)	43 (86.0)
Non-White	4 (16.7)	3 (11.5)	7 (14.0)
Baseline Mini Mental State Examination (MMSE)			
Mean (SD)	21.8 (4.31)	21.2 (3.20)	21.5 (3.75)
Min, Max	13.0, 29.0	14.0, 26.0	13.0, 29.0
Baseline Clinical Dementia Rating – Sum of Boxes (CDR-SB)			
Mean (SD)	3.9 (1.66)	4.8 (2.13)	4.4 (1.94)
Range(min, max)	1.0, 8.0	2.0, 11.0	1.0, 11.0
Baseline Clinical Dementia Rating – Global Score (CDR-GS)			
0.5	14 (58.3)	11 (42.3)	25 (50.0)
1.0	10 (41.7)	13 (50.0)	23 (46.0)
Baseline APOE-4 Carrier Status [n (%)]			
Non-carrier	9 (37.5)	6 (23.1)	15 (30.0)
Heterozygous	9 (37.5)	15 (57.7)	24 (48.0)
Homozygous	6 (25.0)	5 (19.2)	11 (22.0)
Duration of Disease (years)			
Mean (SD)	1.9 (1.83)	1.3 (1.28)	1.5 (1.57)
Min, Max	0.2, 8.7	0.0, 4.5	0.0, 8.7

Huntington's disease Phase 2 trial

NCT02481674

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*

Pepinemab was well tolerated in HD Phase 2 trial

NCT02481674 SIGNAL

Table 1 | Overview of TEAEs for the safety analysis period

Category	Cohort B1, $n=179$		Cohort B2, $n=86$		Cohort B, overall $n=265$	
	PBO, $n=87$	PEPI, $n=92$	PBO, $n=45$	PEPI, $n=41$	PBO, $n=132$	PEPI, $n=133$
Subjects with ≥1 TEAE, *n* (%)[a]	82 (94%)	84 (91%)	41 (91%)	41 (100%)	123 (93%)	125 (94%)
Probably or definitely related[b]	10 (11%)	16 (17%)	9 (20%)	17 (41%)	19 (14%)	33 (25%)
Study drug discontinuation	2 (2%)	5 (5%)	1 (2%)	0	3 (2%)	5 (4%)
Serious TEAE	8 (9%)	4 (4%)	4 (9%)	2 (5%)	12 (9%)	6 (5%)
Probably/definitely related[b]	0	0	0	0	0	0
Grade ≥3 TEAE[c]	14 (16%)	17 (18%)	6 (13%)	8 (20%)	20 (15%)	25 (19%)

Column header counts are the number of subjects in the safety population; TEAEs are those that occurred during the safety analysis period with onset on or after the date of the first exposure to study drug (PEPI or PBO). [a]Subjects are counted at most once in each cell, regardless of the number of events they may have had; denominators are the number of subjects in the safety population, unless otherwise specified. [b]Relatedness to study drug is defined as any of attribution of probable or definite as reported by the investigator. [c]Grade ≥3 refers to any severe, life-threatening or fatal event.

Feigin, A et al. *Nature Medicine* (2022) https://doi.org/10.1038/s41591-022-01919-8

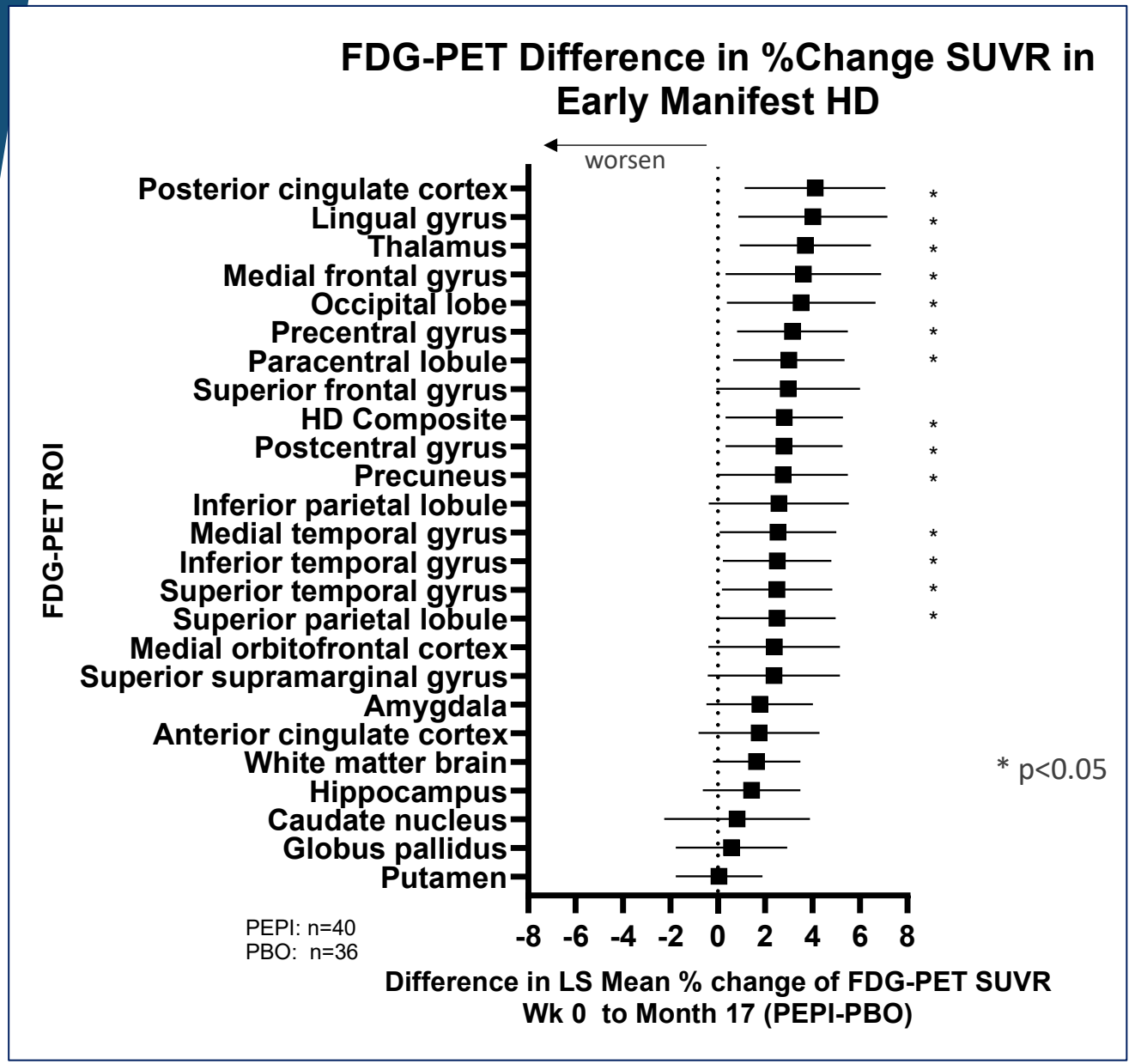
Pepinemab treatment reversed loss of brain metabolic activity

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Maintenance of metabolic activity is a key homeostatic function of astrocytes

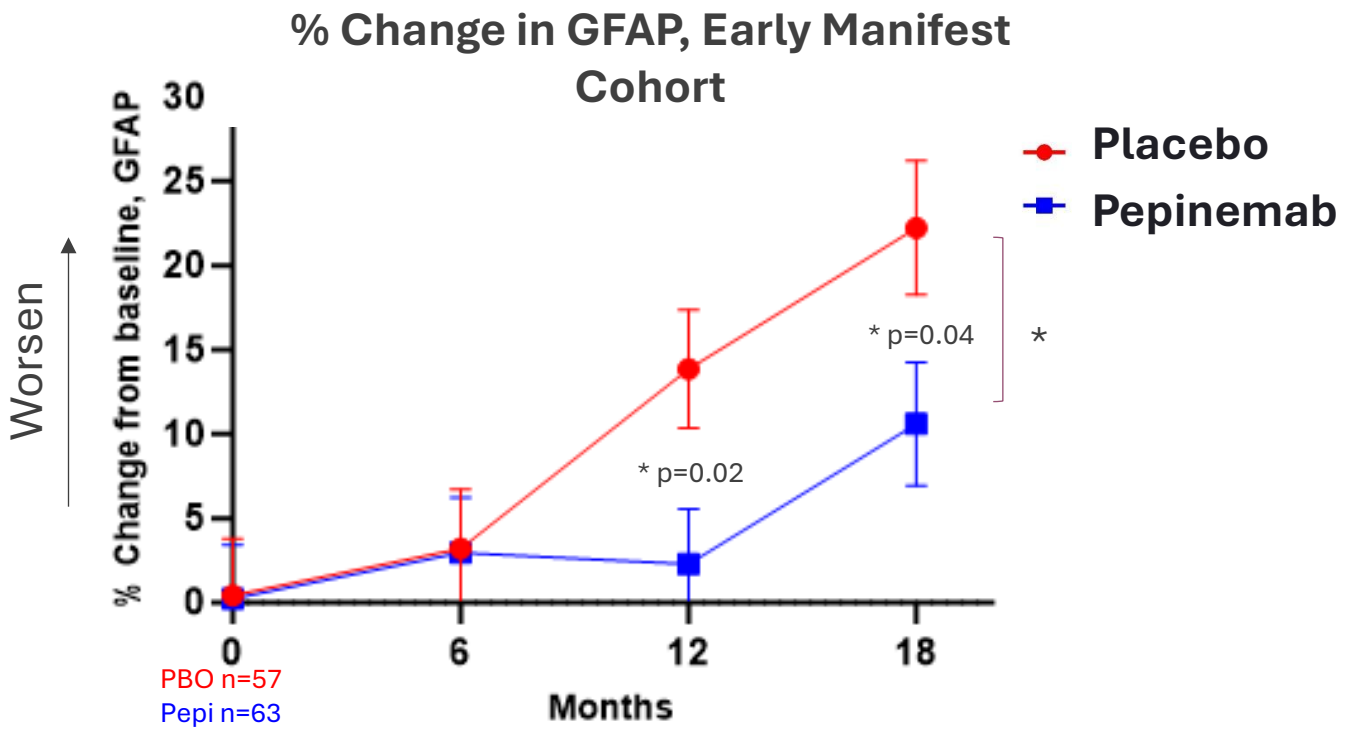
Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.



Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

Pepinemab treatment reduced levels of GFAP inflammatory biomarker in blood of Early HD patients

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* % 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.

Pepinemab reduced plasma GFAP in SIGNAL-HD

Glial Fibrillary Acidic Protein (GFAP) is a biomarker of neuroinflammation and reactive/dysfunctional astrocytes

Feigin AS, Evans EE, Fisher TL, and Zauderer M. ***Pepinemab: a SEMA4D antagonist for treatment of Huntington's and other neurodegenerative diseases.*** *Expert Opinion on Inv Drugs, 2025*

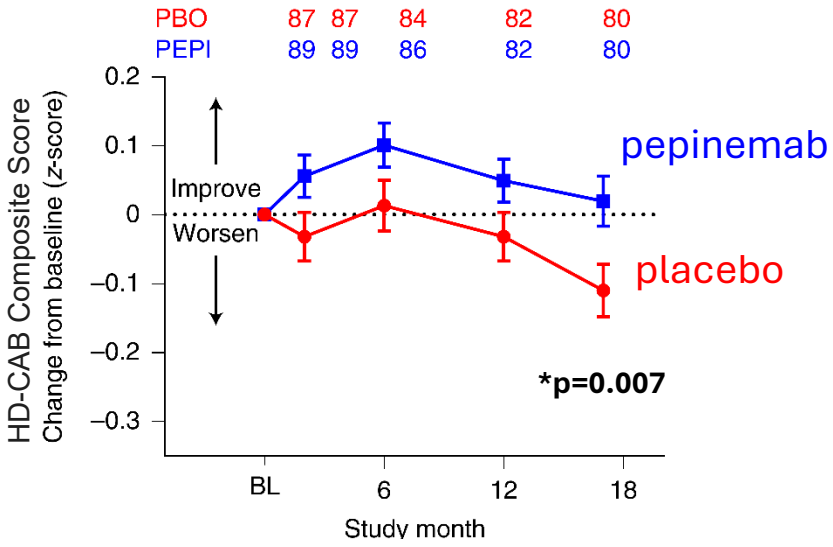
Pepinemab-induced Cognitive Change in Early Huntington's Disease patients

HD Cognitive Assessment Battery (HD-CAB), Early Manifest cohort

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Early Manifest HD:

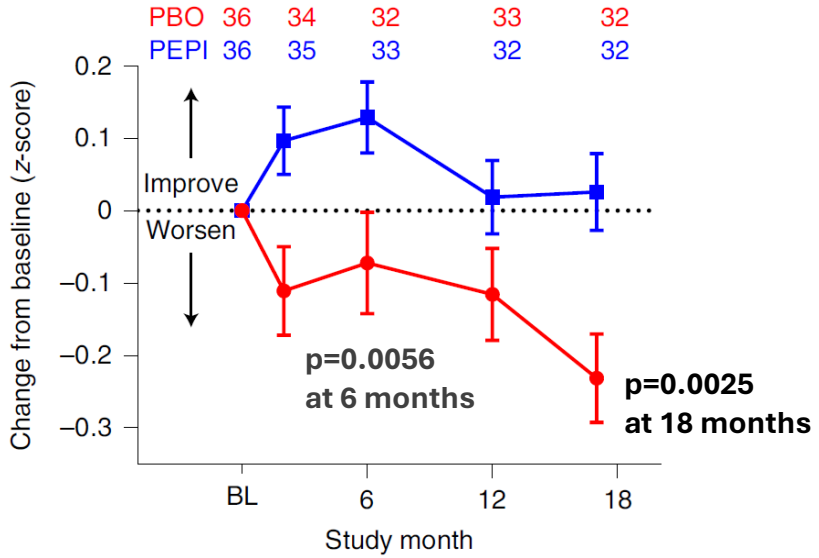
Intent to treat population (mITT)



Pre-specified exploratory analysis

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

MoCA <26, Early Manifest



Post-hoc analysis: Montreal Cognitive Assessment (MoCA) subgroups

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

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