Targeting inflammation and impaired neuro-astro-glial communication through semaphorin 4D-plexin pathway for treatment of Huntington's Disease and Alzheimer's Disease

Elizabeth Evans, PhD
Sr VP, Discovery and Translational Medicine
Chief Operating Officer
eevans@vaccinex.com
VACCINEX
Rochester, New York

AAIC Advancements
AAIC Advancements: Immunity
March 24, 2023
Boston, MA

Disclosures

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

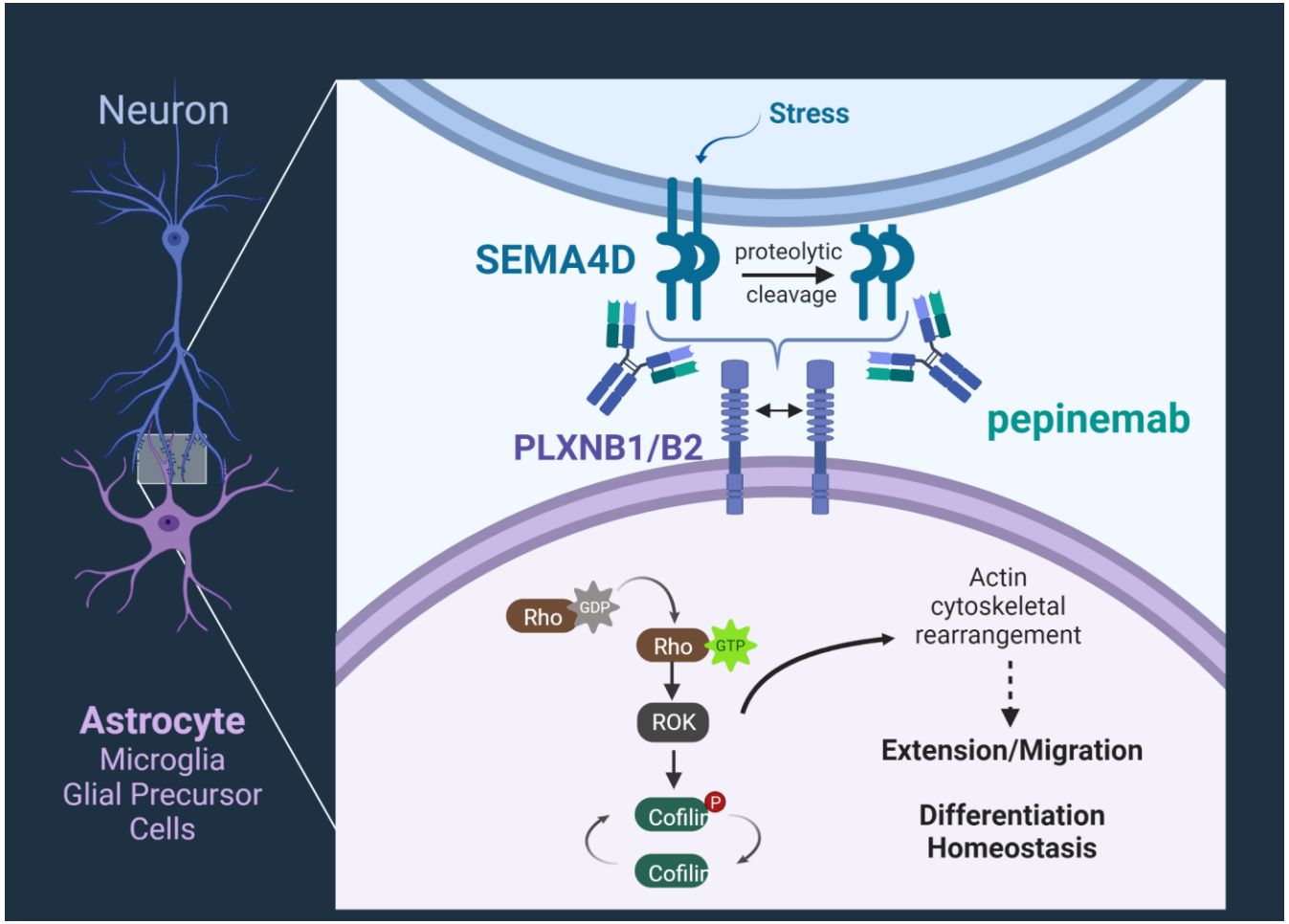
I will be discussing investigational drug and ongoing clinical trials.

Forward Looking Statements

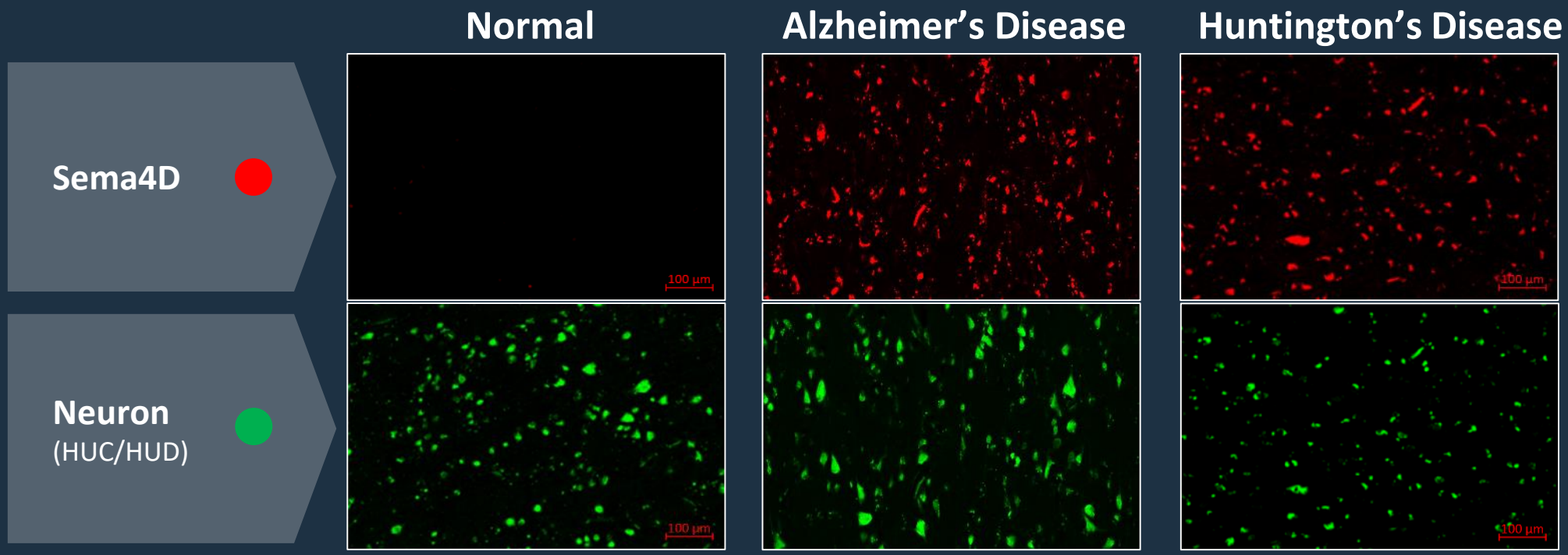
To the extent that statements contained in this presentation are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited 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.

Semaphorin 4D/Plexin signaling

- SEMA4D is upregulated in neurons in response to stress in the adult brain
- SEMA4D signals through PLXNB1 and PLXNB2 receptors to regulate the cell actin cytoskeleton and inflammatory transformation
- **Pepinemab antibody binds to SEMA4D and blocks its signaling activity. This preserves normal glial cell morphology and function and averts inflammatory transformation**
  - Pepinemab (VX15/2503): humanized IgG4 with hinge modification



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,.

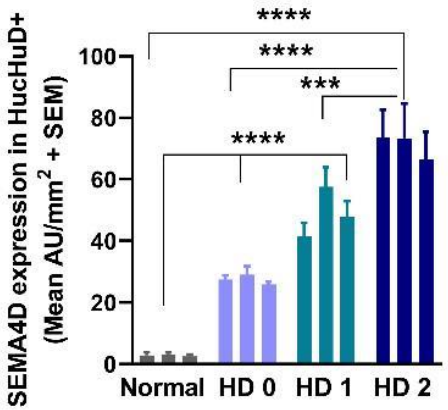
SEMA4D IS PROGRESSIVELY UPREGULATED WITH INCREASING PATHOLOGIC STAGES OF Huntington's Disease

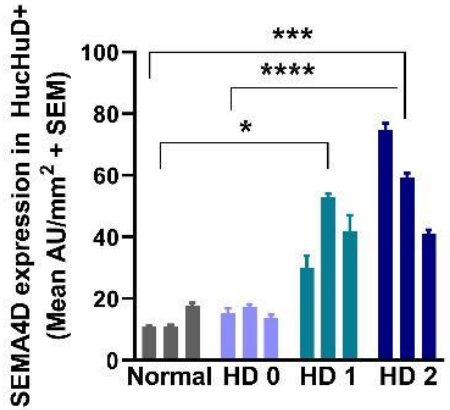
Frontal Cortex Human

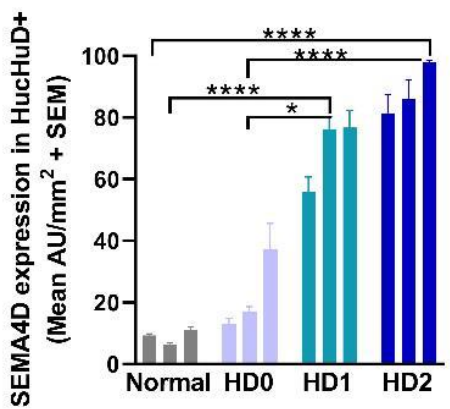
Parietal Lobe Human

Striatum (Caudate/Putamen) Human

SEMA4D in neurons





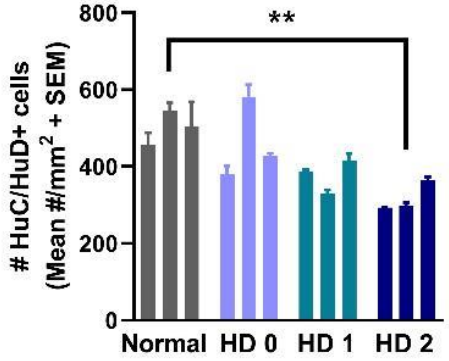


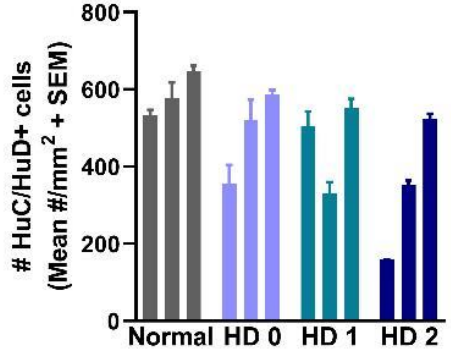
Huc/HuD⁺ Neurons
Human Frontal Cortex

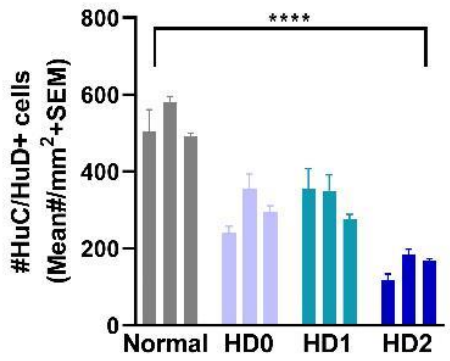
Huc/HuD⁺ Neurons
Human Parietal Lobe

Huc/HuD⁺ Neurons
Human Caudate/Putamen

Neuron Density





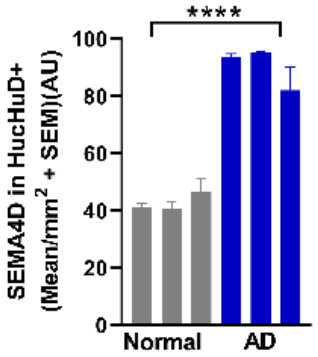


Evans et al. Journal of Neuroinflammation, (2022) 19:200.

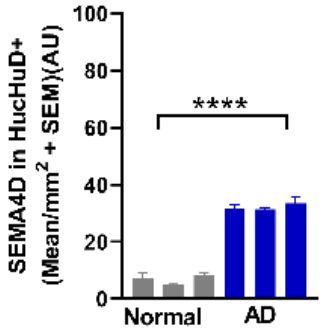
SEMA4D UPREGULATION is ASSOCIATED WITH NEURONAL LOSS AND ASTROCYTE ACTIVATION IN AD

SEMA4D in neurons

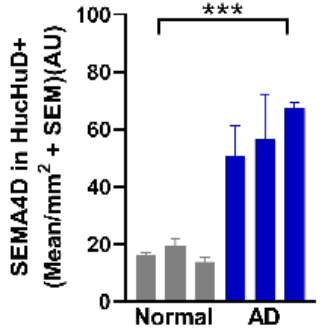
Thalamus Human



Temporal Lobe Human

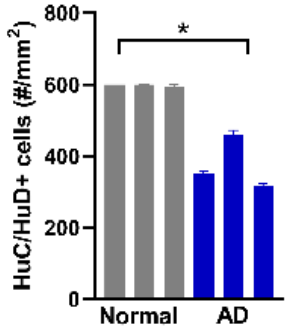


Frontal Cortex Human

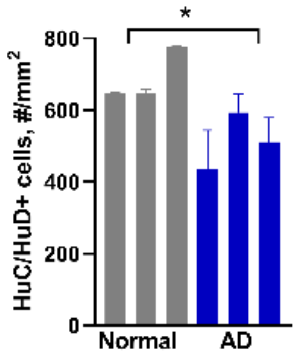


Neuron Density

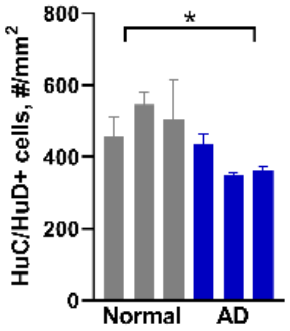
HuC/HuD+ Neurons Human Thalamus



HuC/HuD+ Neurons Human Temporal Lobe



HuC/HUD+ Neurons Human Frontal Cortex



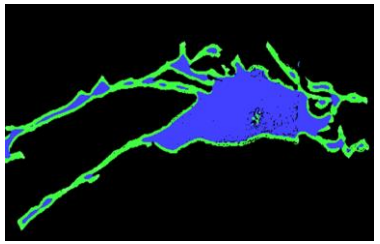
Evans et al. Journal of Neuroinflammation, (2022) 19:200.

ASTROCYTE FUNCTION:

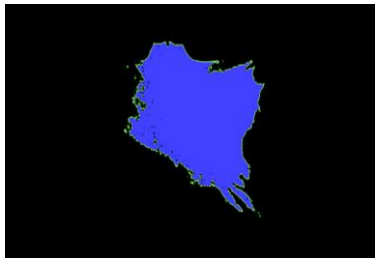
Astrocytes couple energy metabolism and synaptic activity

Cytoskeletal Collapse

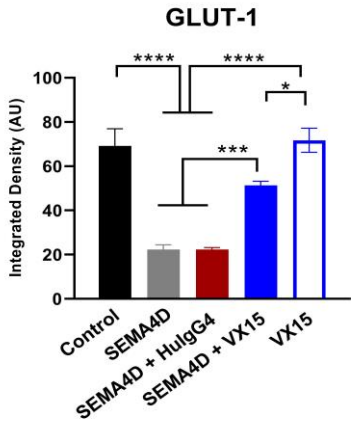
Control

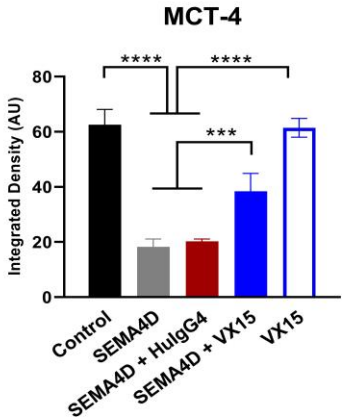


rSEMA4D

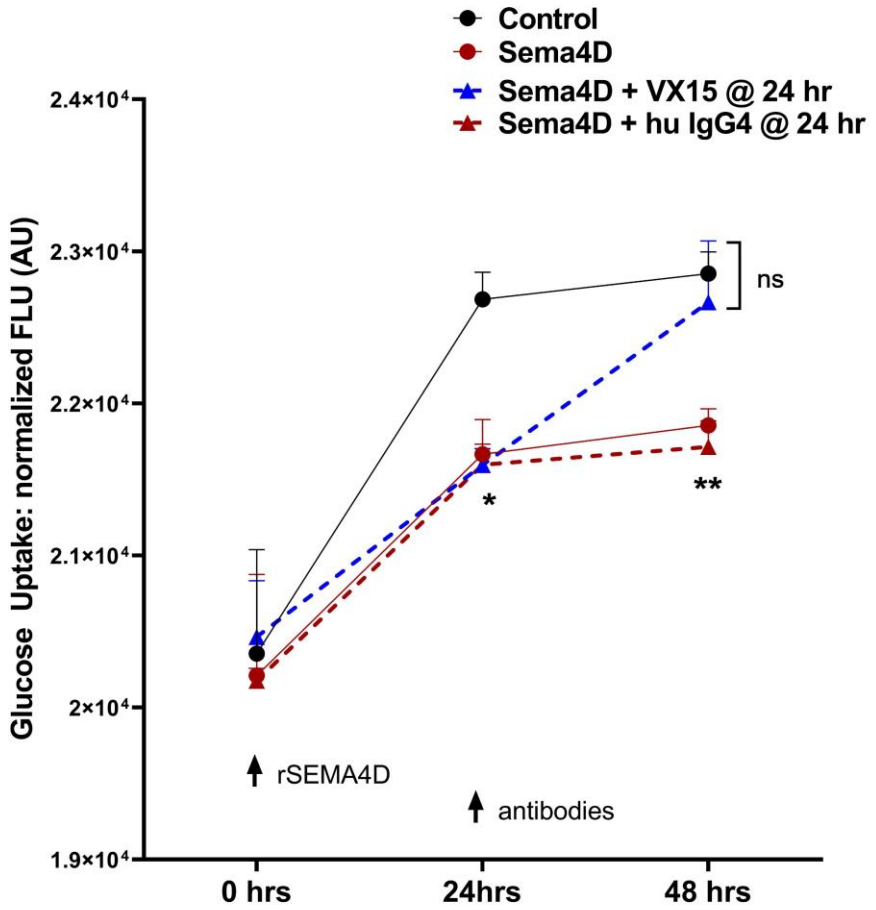


Metabolic Transport





Antibody blockade reverses loss of astrocytic function

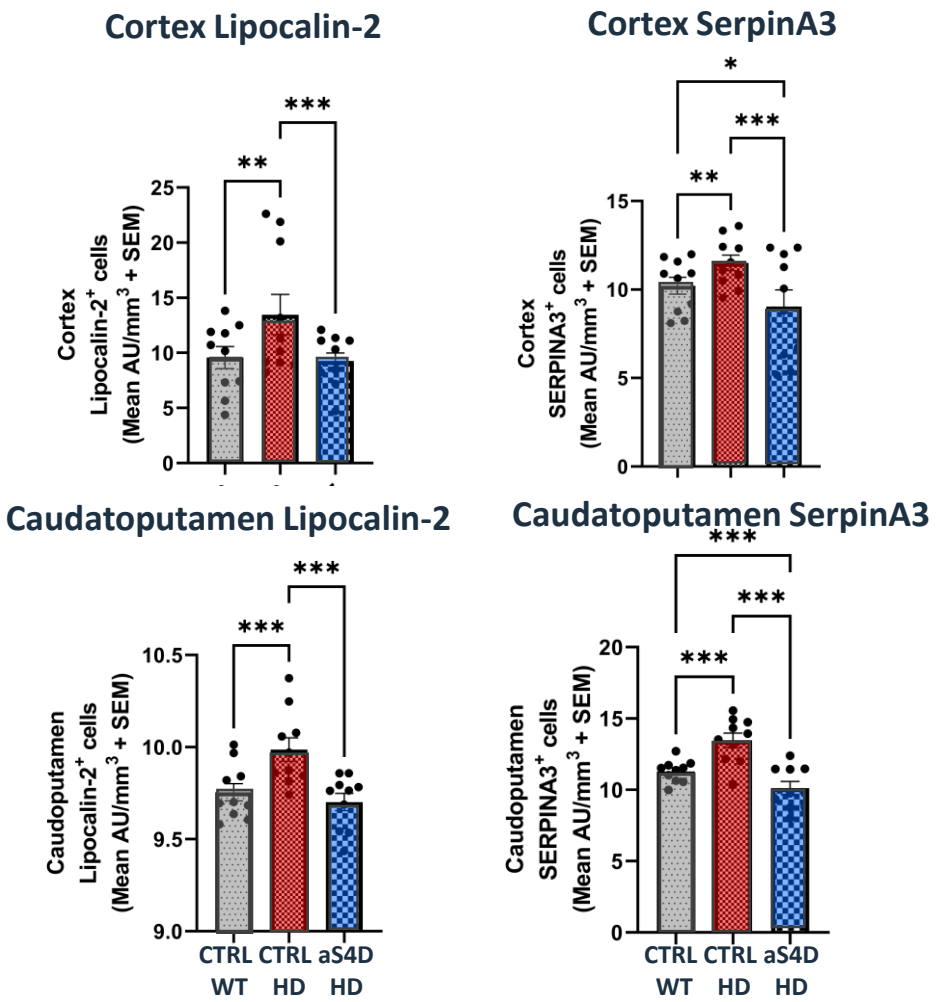


Evans et al. Journal of Neuroinflammation, August 2022, 19:200.

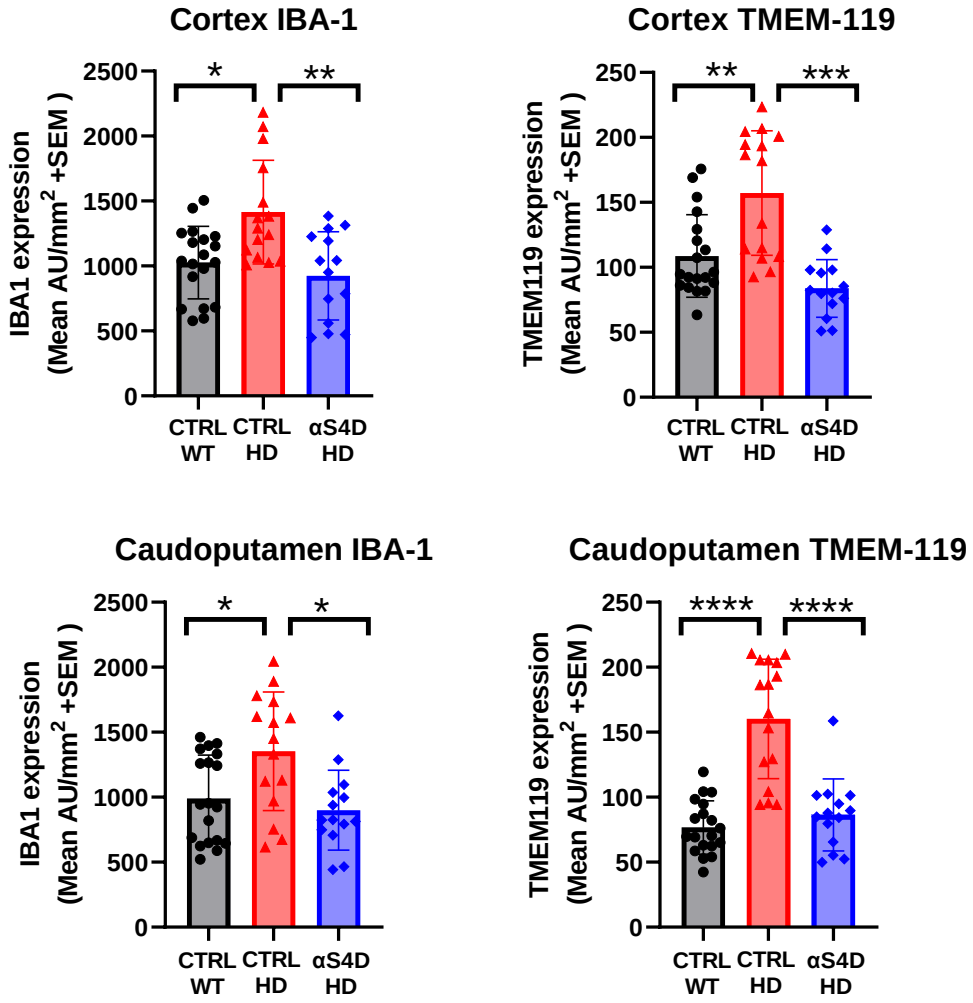
ANTI-SEMA4D ANTIBODY INHIBITS SEMA4D-INDUCED ACTIVATION OF ASTROCYTES AND MICROGLIA

Huntington's Disease Humanized Model: Hu97/18

ASTROCYTES



MICROGLIA



Hu18/18 WT control and Hu97/18 HD mice were treated weekly with MAb67/anti-SEMA4D or CTRL Ab, from 6 weeks – 12 months of age.

In collaboration with Amber Southwell, University of Central Florida

NEURO-IMMUNE COMMUNICATIONS

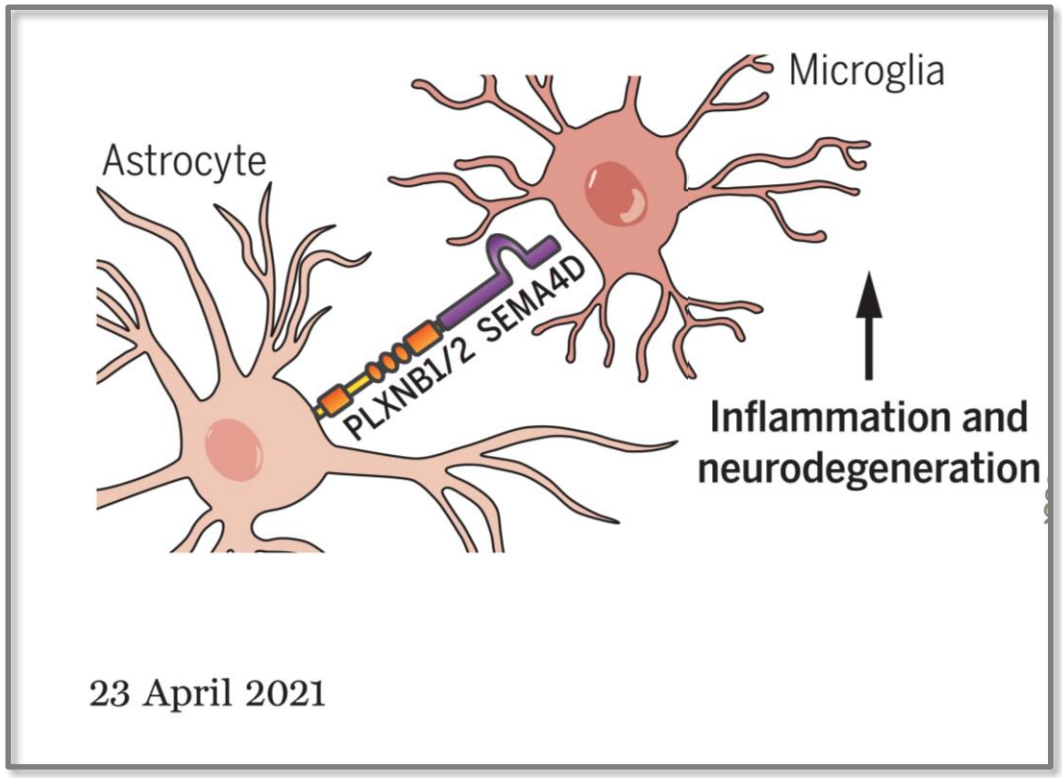
RESEARCH ARTICLE

Science 372, 360 (2021)

NEUROSCIENCE

Barcoded viral tracing of single-cell interactions in central nervous system inflammation

Iain C. Clark[1,2]†, Cristina Gutiérrez-Vázquez[1]†, Michael A. Wheeler[1,3]†, Zhaorong Li[1,3], Veit Rothhammer[1,4], Mathias Linnerbauer[1,4], Liliana M. Sanmarco[1], Lydia Guo[1], Manon Blain[5], Stephanie E. J. Zandee[6], Chun-Cheih Chao[1], Katelyn V. Batterman[7], Marius Schwabenland[8], Peter Lotfy[1,3], Amalia Tejeda-Velarde[1]‡, Patrick Hewson[1], Carolina Manganeli Polonio[1], Michael W. Shultis[1], Yasmin Salem[1], Emily C. Tjon[1], Pedro H. Fonseca-Castro[1], Davis M. Borucki[1], Kalil Alves de Lima[1], Agustin Plasencia[1], Adam R. Abate[9,10], Douglas L. Rosene[7], Kevin J. Hodgetts[1], Marco Prinz[8,11,12], Jack P. Antel[5], Alexandre Prat[6], Francisco J. Quintana[1,3]*



Elucidation of microglia-astrocyte interactions by rabies barcode interaction detection followed by sequencing (RABID-seq). Pseudotyped rabies virus expressing barcoded mRNA targets *Gfap*$^{+}$ astrocytes, where it replicates before infecting neighboring cells, leaving a barcoded trace. Single-cell RNA sequencing reads both cellular mRNAs and viral barcodes, allowing for the reconstruction of in vivo cell interactions and the transcriptional analysis of interacting cells with single-cell resolution.

Clark *et al.*, *Science* **372**, 360 (2021)

Mechanism of Action & Preclinical AD model

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

Journal of Neuroinflammation

RESEARCH Open Access

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*]

Southwell AL, Franciosi S, Villanueva EB, Xie Y, Winter LA, et al. Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 **mouse model of Huntington disease**. Neurobiol Dis. 2015 Feb 3; 76:46–56.

Mao Y, Evans EE, Mishra V, Balch L, Eberhardt A, Zauderer M, Gold WA. Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a **Rett Syndrome Mouse Model**. Int J Mol Sci. 2021 Aug 31;22(17):9465.

Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, et al. SEMA4D compromises **blood-brain barrier, activates microglia, and inhibits remyelination** in neurodegenerative disease. Neurobiol Dis. 2015 73 (2015) 254–268.

Clinical Experience in HD

nature medicine

ARTICLES

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

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*

HUNTINGTON'S DISEASE

Clinical Trial Design

SIGNAL

Orphan Disease and Fast Track Designations

Cohort B1 Early Manifest HD

n=179

CAG repeat ≥36
TFC 11-13, DCL 4

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Cohort B2 Prodromal HD

n=86

CAG repeat ≥36
DCL 2 or 3

randomized 1:1 double-blind

pepinemab or placebo

Monthly X18 months

Safety Follow-up 1 month

Data Analysis and Study Objectives

Safety and tolerability

Primary Efficacy Outcomes (mITT)
Cognitive Function
CGIC

Key Exploratory and Biomarker Outcomes
Brain Volume (vMRI)
Metabolic imaging (FDG-PET)

NCT02481674

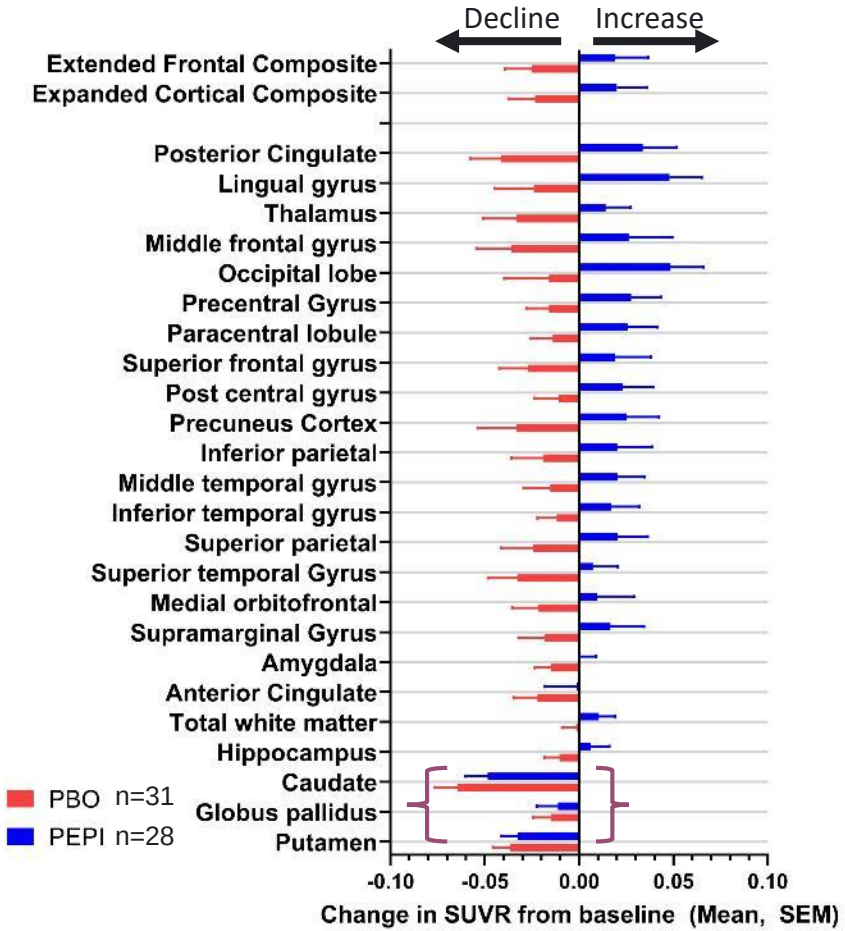
FDG-PET CORRELATES WITH COGNITIVE FUNCTION

Pre-specified Exploratory Endpoint, 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.

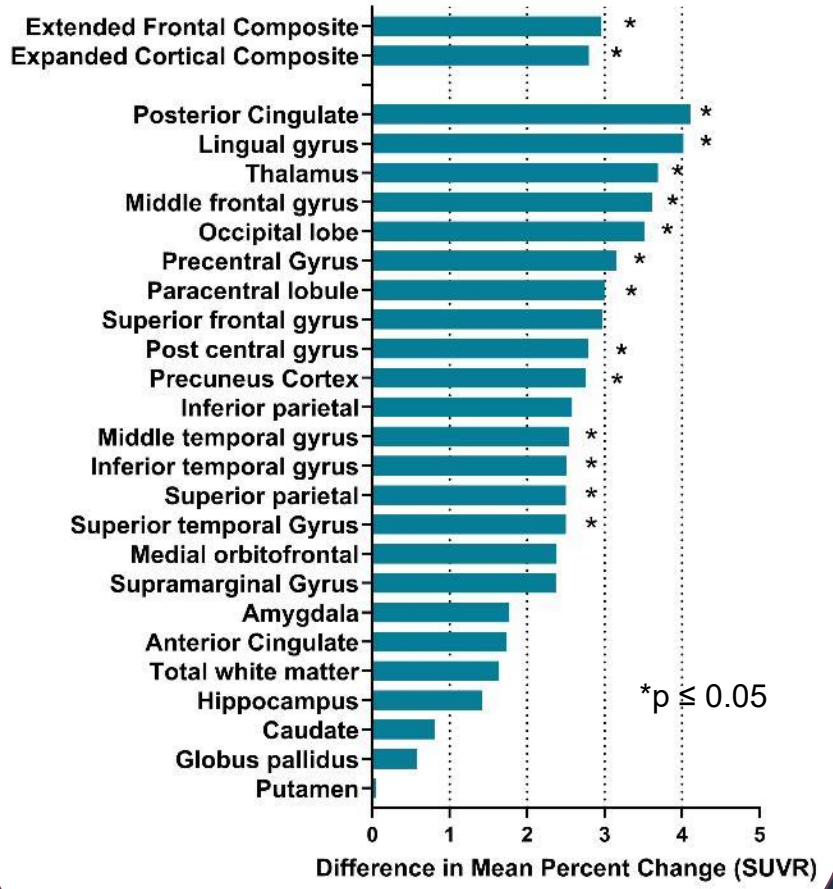
Pepinemab treatment appears to reverse loss of metabolic activity.

Change in FDG-PET at Month 18



SUVR = standardized uptake value ratio

Difference (PEPI-PBO) at Month 18

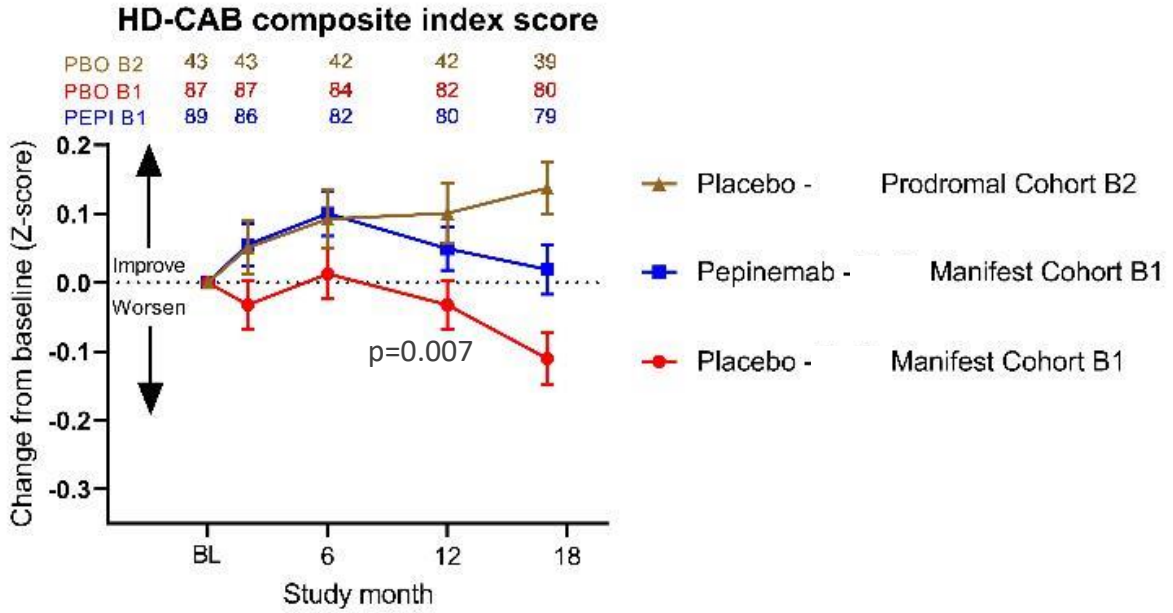


Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Exploratory and Post-hoc analysis

- "Learning effect" is lost when HD symptoms become manifest
- Pepinemab treatment restores the ability to benefit from experience (i.e., to learn)
- Pepinemab delays decline in cognitive performance in patients with manifest disease

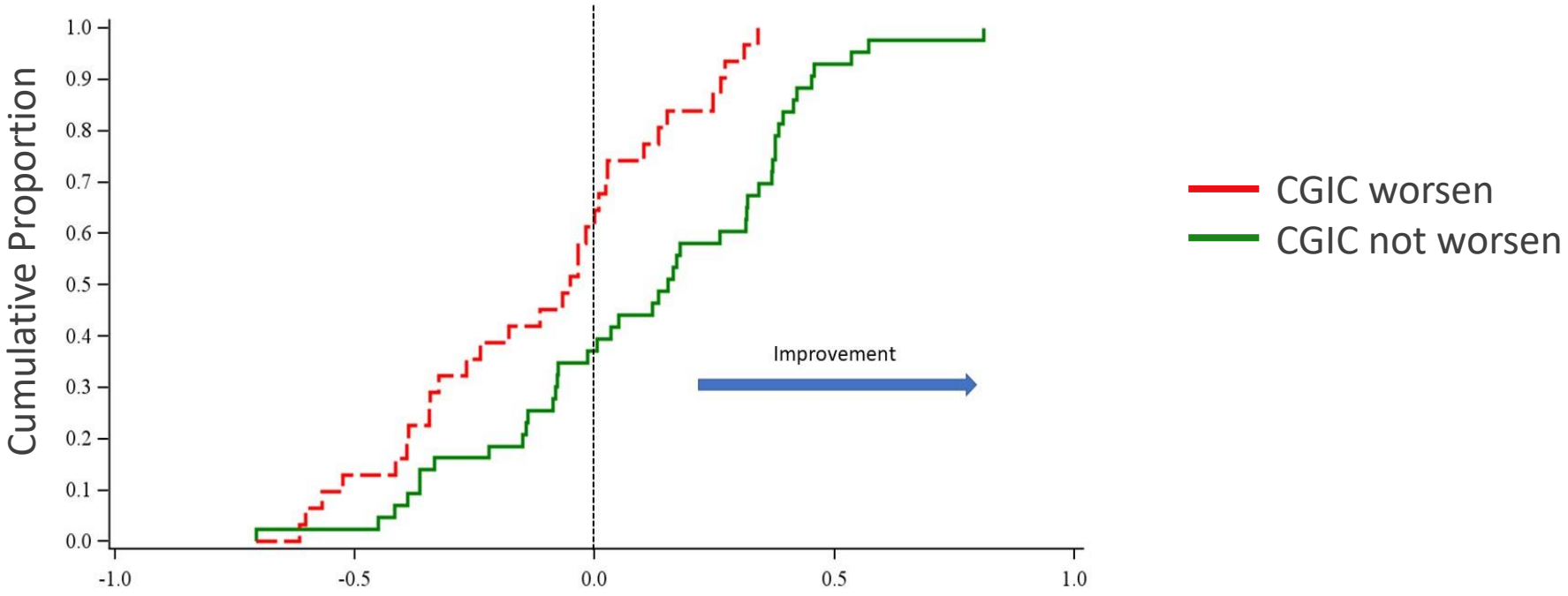


Feigin, A et al. *Nature Medicine* (2022)
https://doi.org/10.1038/s41591-022-01919-8

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Associated with Clinically Meaningful change

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

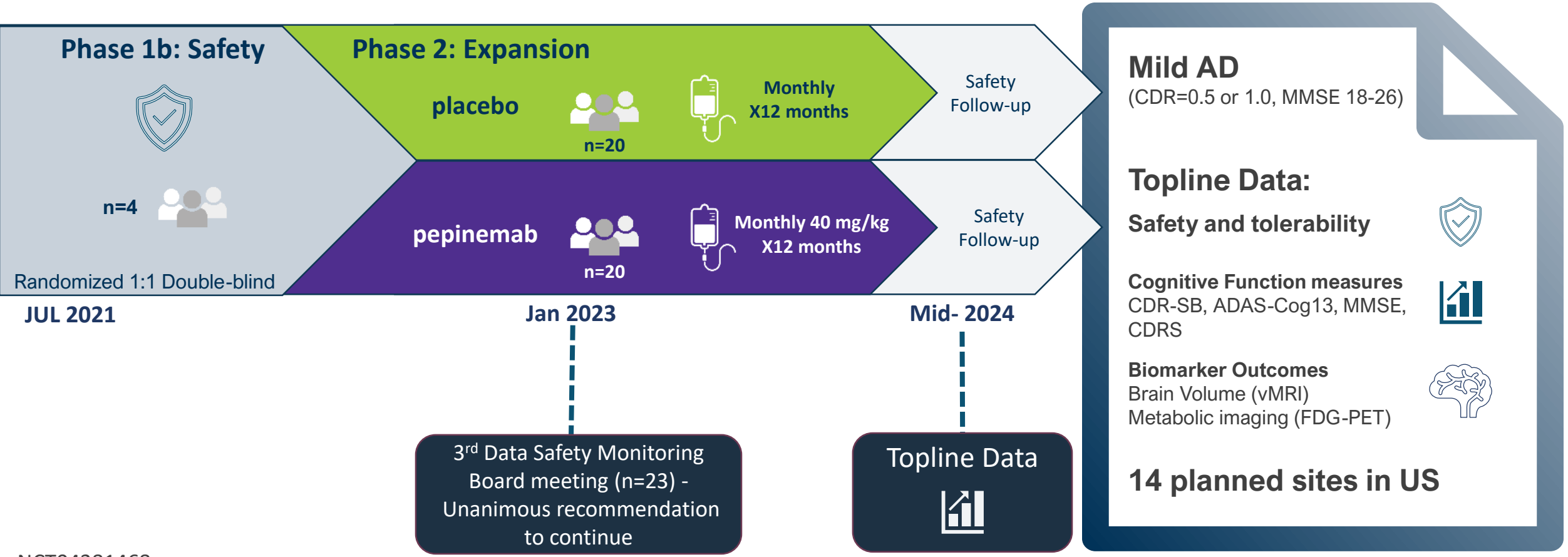


HD-CAB, Change from Baseline at Month 17

Early Manifest Cohort B1 treated with Pepinemab

ALZHEIMER'S DISEASE
Ongoing Phase 1b/2 Trial

SIGNAL-AD



NCT04381468

SUMMARY

Dysregulated cellular interactions and neuroinflammatory mechanisms contribute to disease pathology in HD, AD, etc.

- HYPOTHESIS:
  1. Disease associated stress/damage leads to upregulation of SEMA4D, as an alarm signal
  2. SEMA4D signals to receptors on astrocytes, resulting in reactive transformation and loss of normal homeostatic functions

- Antibody blockade of SEMA4D reduces reactive astrogliosis and inflammation, and reverses loss of normal homeostatic functions
- Results from SIGNAL-HD study provide evidence that pepinemab treatment reverses loss of metabolic activity, as measured by FDG-PET, and appears to delay cognitive impairment in people with early manifest Huntington's disease
- SIGNAL-AD is an ongoing trial to evaluate safety and efficacy of pepinemab in people with AD

Reprogramming neuroinflammatory interactions may provide therapeutic benefit in NDD

Thanks and Gratitude

Participants, caregivers and their families!

Andrew Feigin MD, and Huntington Study Group
Study investigators and staff

Vaccinex Clinical Development and Research Teams:

Maurice Zauderer, President and CEO
Terry Fisher, Sr VP Clinical Development
John Leonard, Sr VP Technical Operations
Eric Siemers, MD, Scientific Advisor
Karl Kieburtz, MD, MPH, Scientific Advisor
Vikas Mishra, PhD, Sr Research Scientist
Megan Boise and Amber Foster, Clinical Project Managers

Statistics Collaborative, Inc
Amber Southwell, PhD, University Central Florida

Funding support

Alzheimer's
Drug Discovery
Foundation

Appendix

Vaccinex Selected References, Neurology

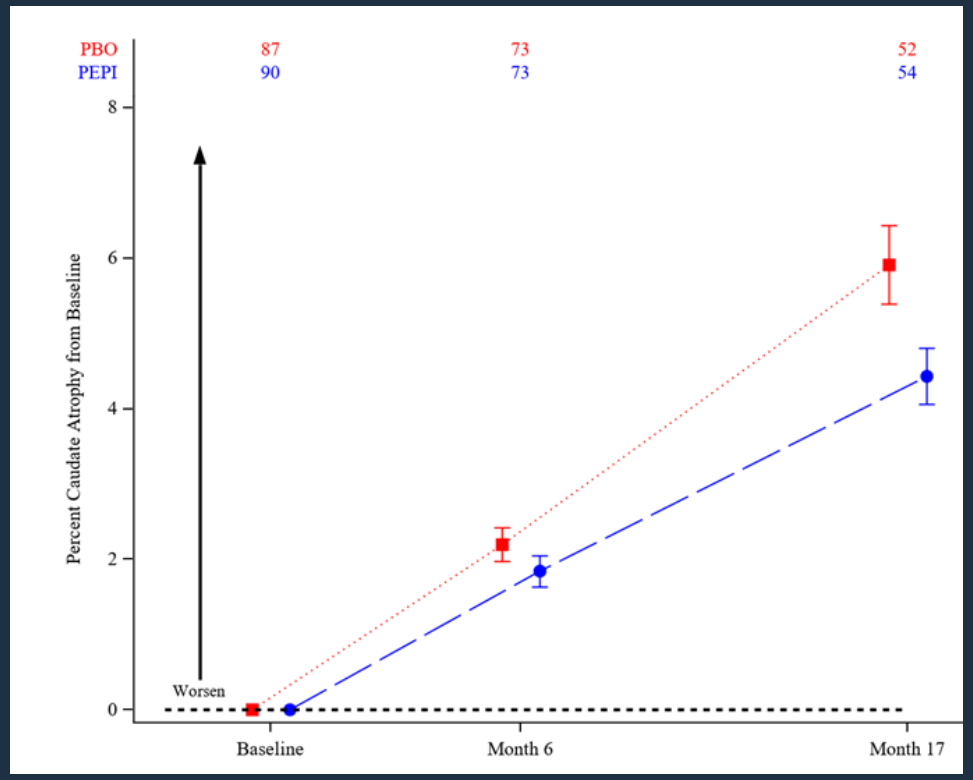
1. Feigin AS, Evans EE , Fisher TL, Leonard JE, Reader A, Wittes J, Oakes D, Smith ES, Zauderer M, and the Huntington Study Group SIGNAL investigators. **Pepinemab antibody blockade of SEMA4D in patients with early Huntington's Disease: a randomized, placebo-controlled, Phase 2 trial.** Nature Medicine, 2022 Aug 8;1-11. doi: 10.1038/s41591-022-01919-8.
2. Evans EE, Mishra V, Mallow C, Gersz EM, Balch L, Howell A, Reilly C, Smith ES, Fisher TL, Zauderer M.. **Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity**. Journal of Neuroinflammation, 2022 19:200. https://doi.org/10.1186/s12974-022-02509-8
3. Zauderer M, and Evans EE. **Conclusions of the SIGNAL study in Huntington and implications for treatment of other slowly progressive neurodegenerative diseases.** Clinical and Translational Medicine, 2022 DOI: 10.1002/ctm2.1169
4. Mao Y, Evans EE, Mishra V, Balch L, Eberhardt A, Zauderer M, Gold WA. **Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a Rett Syndrome Mouse Model.** Int J Mol Sci. 2021 Aug 31;22(17):9465. doi: 10.3390/ijms22179465. https://www.mdpi.com/1422-0067/22/17/9465
5. Southwell AL, Franciosi S, Villanueva EB, Xie Y, Winter LA, Veeraraghavan J, Jonason A, Felczak B, Zhang W, Kovalik V, Waltl S, Hall G, Pouladi MA, Smith ES, Bowers WJ, Zauderer M, Hayden MR. **Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease**. Neurobiol Dis. 2015 Feb 3; 76:46–56. http://www.sciencedirect.com/science/article/pii/S0969996115000145
6. Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, Doherty M, Klimatcheva E, Mallow C, Cornelius C, Leonard JE, Marchi N, Janigro D, Argaw AT, Pham T, Seils J, Bussler H, Torno S, Kirk R, Howell A, Evans EE, Paris M, Bowers WJ, John G, Zauderer M. **SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease**. Neurobiol Dis. 2015 73 (2015) 254–268. doi: 10.1016/j.nbd.2014.10.008. http://www.sciencedirect.com/science/article/pii/S0969996114003015
7. Fisher TL, Reilly CA, Winter LA, Pandina T, Jonason A, Scrivens M, Balch L, Bussler H, Torno S, Seils J, Mueller L, Huang H, Klimatcheva E, Howell A, Kirk R, Evans E, Paris M, Leonard JE, Smith ES, Zauderer M. **Generation and preclinical characterization of an antibody specific for SEMA4D**. Mabs. 2015 Oct 20. http://www.tandfonline.com/doi/abs/10.1080/19420862.2015.1102813
8. Leonard JE, Fisher TL2 Winter LA, Cornelius CA, Reilly C, Smith ES, Zauderer M. **Nonclinical Safety Evaluation of VX15/2503; a Humanized IgG4 Anti-SEMA4D Antibody**. Mol Cancer Ther. 2015 Feb 5 http://www.ncbi.nlm.nih.gov/pubmed/25657333
9. LaGanke, C., L. Samkoff, K. Edwards, L. Jung Henson, P. Repovic, S. Lynch, L. Stone, D. Mattson, A. Galluzzi, T. L. Fisher, C. Reilly, L. A. Winter, J. E. Leonard, and M. Zauderer. 2017. **Safety/tolerability of the anti-semaphorin 4D Antibody VX15/2503 in a randomized phase 1 trial**. Neurol Neuroimmunol Neuroinflamm 4: e367. https://www.ncbi.nlm.nih.gov/pubmed/28642891

Schematics created with BioRender.com

Pepinemab reduces brain atrophy

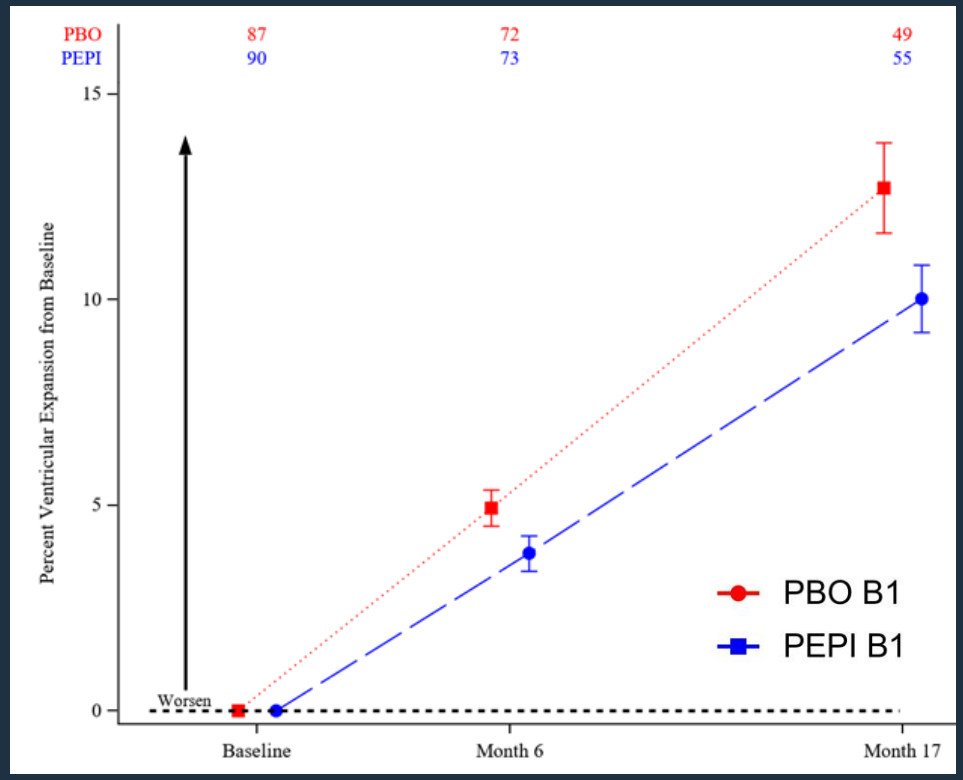
Volumetric MRI– Boundary Shift Integral Analysis
Early Manifest HD

CBSI (caudate atrophy)



LS Mean Difference Estimate (95% CI):
CBSI: -1.54 (-2.79, -0.29);
p = 0.017

VBSI (ventricular expansion)



VBSI:-2.47 (-5.04, 0.10);
p = 0.060

HD-COGNITIVE ASSESSMENT BATTERY (HD-CAB)

Associated with Clinically Meaningful change

Pepinemab delays disease progression