Targeting SEMA4D/PLXN signaling through reactive glia as a common pathology for the treatment of neurodegenerative disorders

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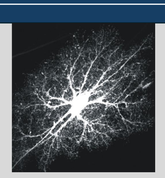
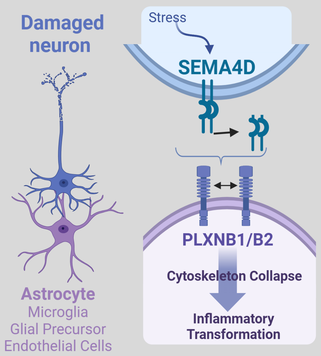
Background

- Accumulation of toxic protein aggregates, (Aβ in AD, αSyn in PD, mHtt in HD) are believed to trigger a series of pathogenic events, including gliosis, neuroinflammation, compromised blood brain barrier (BBB), and synaptic loss. These events are key drivers of neurodegeneration and cognitive dysfunction.
- Semaphorin 4D (SEMA4D) and its receptors are upregulated in damaged/diseased brains & correlate with amyloid plaque load, tau tangle density, and cognitive decline in AD (1-4). We have previously reported that **SEMA4D is upregulated in diseased or damaged neurons** during progression of Alzheimer's and Huntington's Disease (AD, HD), triggering astrocyte reactivity and gain of inflammatory processes (5). A genome wide association study identified SEMA4D as a novel genetic locus having strong interaction with known AD genes identified as risk factors of all-cause dementia and vascular dementia (6). Interestingly, we previously discovered that SEMA4D disrupts tight junctions in brain endothelial cells (8). We and others have described beneficial effects of blocking SEMA/PLXN signaling to inhibit damaging effects of astrogliosis, facilitate productive astrocyte/microglial interactions in AD models (7), and restore vascular integrity (8).
- **Pepinemab**, human SEMA4D blocking antibody, was **well-tolerated and appears to reduce biomarkers of reactive astrocytes and to slow or prevent cognitive decline in clinical studies of AD and HD** (10,11).



Healthy Astrocyte

Interacts with other brain cells : neurons. microglia, pericytes, endothelial cells



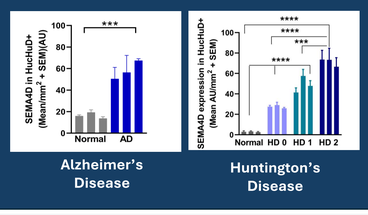
Role of SEMA4D in Neuroinflammation and Neurodegeneration

SEMA4D and its receptors, Plexin B1/B2, are upregulated in damaged neurons[1-5]

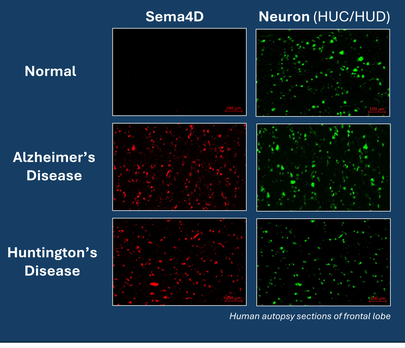
- Loss of glial homeostatic functions[7]
- Gain of inflammatory processes
- ≠ Disruption of vascular integrity[6,8]

Semaphorin 4D is upregulated in neurons of diseased brains[5]

SEMA4D in neurons
Human Frontal Cortex



Alzheimer's Disease | Huntington's Disease



Human autopsy sections of frontal lobe

Pepinemab for the treatment of neurodegenerative diseases

Pepinemab is a humanized IgG4 **antibody** that blocks Semaphorin 4D (SEMA4D)- induced astrocyte reactivity and **neuroinflammation**, as well as disruption of brain vascular integrity.

Pepinemab was **well-tolerated** in multiple clinical trials, including Alzheimer's Disease, Huntington's Disease and Multiple Sclerosis.

Data from a recently completed **SIGNAL-AD study in early Alzheimer's Disease** and a **Phase 2 study in Huntington's Disease** suggest that **pepinemab** treatment appears to **slow cognitive decline** with favorable effects on **biomarkers** related to disease progression.

Pepinemab has broad application in multiple indications in which inflammation contributes to disease pathology.

Pepinemab in the Clinic

NCT02481674
SIGNAL Huntington's Disease

- A larger randomized Phase 2 study (n=179), including ~ 90 patients/group with early manifest disease (Total Functional Capacity 11-13, HD diagnostic confidence level 4)
- Pepinemab (20mg/kg, Q4W) was **well tolerated** and demonstrated **target engagement** in CSF.
- Pepinemab **significantly improved cognition**, using HD-CAB (cognitive assessment battery), particularly in patients with evidence of mild cognitive impairment (MoCA <26) at baseline
- Pepinemab significantly **regulated biomarkers of reactive astrocytes: GFAP and FDG-PET**

Early Manifest HD:
Intent to treat population (mITT)

Early Manifest HD:
Baseline MoCA <26 subgroup

nature medicine ARTICLES

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] and Maurice Zauderer[2]

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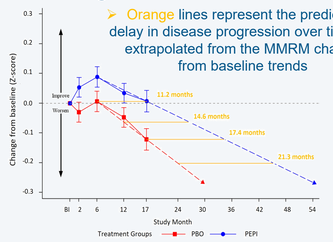
DRUG EVALUATION OPEN ACCESS

Pepinemab: a SEMA4D antagonist for treatment of Huntington's and other neurodegenerative diseases

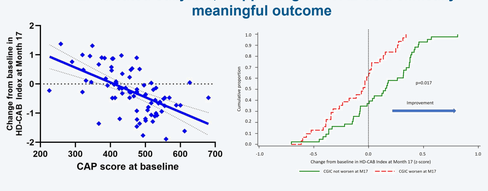
Andrew Feigin[a,b], Elizabeth E. Evans[c], Terrence L. Fisher[c] and Maurice Zauderer[c]

Clinical Meaningfulness

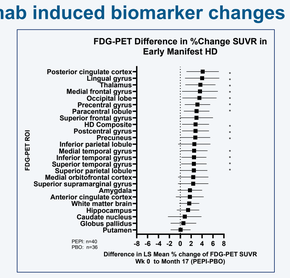
Orange lines represent the predicted delay in disease progression over time, as extrapolated from the MMRM change from baseline trends



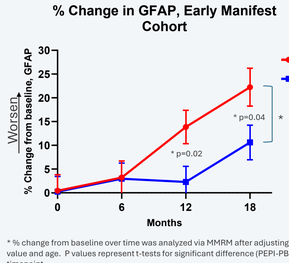
HD-CAB is correlated with both CAP score at baseline (measure of disease burden) and CGIC (global functioning) in PEPI treated subjects, supporting HD-CAB as a clinically meaningful outcome



Pepinemab induced biomarker changes



% Change in GFAP, Early Manifest Cohort



* % 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.

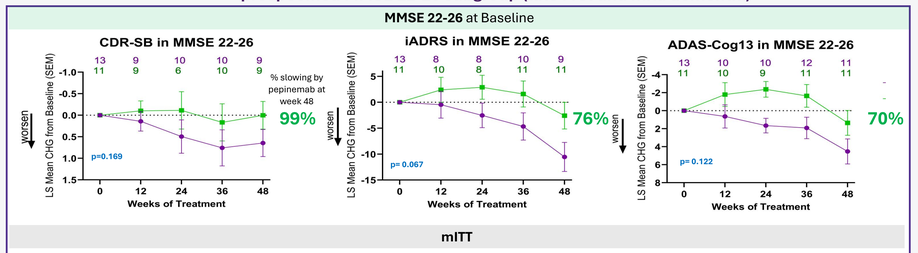
NCT04381468
SIGNAL-AD Alzheimer's Disease

- A placebo-controlled randomized Phase 1b/2 study enrolling **50** amyloid-positive patients, including MCI and mild dementia due to AD (CDR-GS 0.5-1; MMSE 17-26).
- Pre-specified subgroup analysis to assess activity during disease progression: baseline MMSE scores of 22-26 and 17-21.
- Pepinemab (40mg/kg. Q4W) was **well-tolerated** and **appears to improve multiple assessments of cognition** and function in the MMSE 22-26 subgroup of patients with MCI and mild dementia due to AD. Pepinemab also appeared to beneficially affect plasma biomarkers GFAP and p-Tau217 in early disease.
- Multiplex proteomics analysis of CSF via **Olink** suggest treatment induced reduction of AD-related biomarkers in CSF and regulation of immune related and metabolic pathways, consistent with mechanism of action

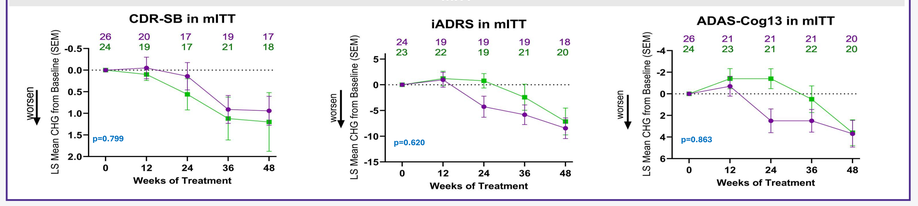
Pepinemab improved assessments of cognition and function in Alzheimer's Disease

prespecified MMSE 22-26 subgroup (late MCI and mild dementia)

MMSE 22-26 at Baseline

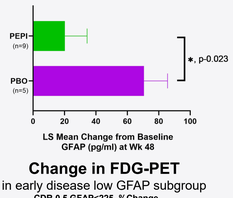


mITT

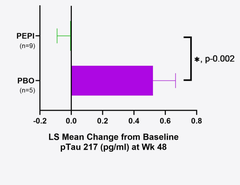


Pepinemab induced biomarker changes in early stage Alzheimer's Disease

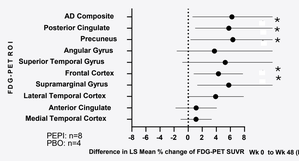
Change in plasma GFAP
in early disease low GFAP subgroup



Change in plasma pTau-217
in early disease low GFAP subgroup



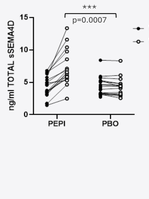
Change in FDG-PET
in early disease low GFAP subgroup
CDR 0.5 GFAP<225, %Change



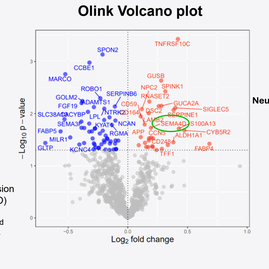
Pepinemab reduced plasma GFAP, pTau217, and brain hypometabolism in patients at early stage of disease
(baseline CDR 0.5,GFAP<225ng/ml)

CSF Olink analysis: pepinemab reduced levels of AD-related proteins associated with tau pathology and synaptic loss in patients with mild dementia

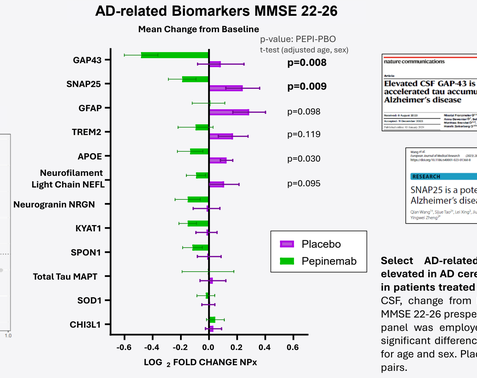
sSEMA4D:PEPI complexes in CSF– demonstrating target engagement



Olink Volcano plot

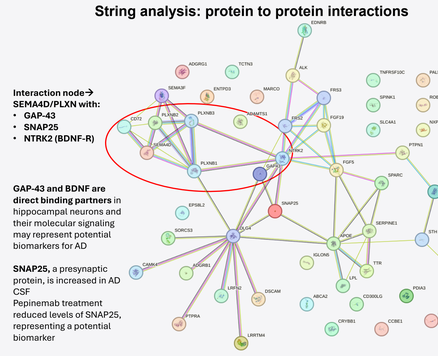


AD-related Biomarkers MMSE 22-26



Select AD-related biomarkers reported to be elevated in AD cerebrospinal fluid (CSF) are reduced in patients treated with pepinemab. Olink analysis of CSF, change from baseline at 48 weeks in Baseline MMSE 22-26 prespecified subgroup. Olink Explore 5400 panel was employed. P values represent t-tests for significant difference (Pepinemab - Placebo), adjusted for age and sex. Placebo n=8, Pepinemab n=7 matched pairs.

String analysis: protein to protein interactions



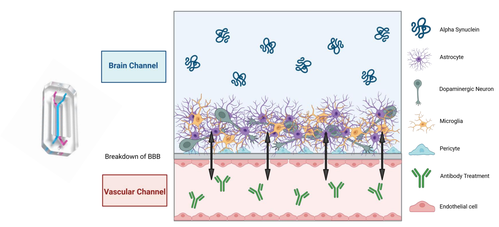
Interaction node→ SEMA4D/PLXN with:
- **GAP-43**
- **SNAP25**
- **NTRK2 (BDNF-R)**

GAP-43 and BDNF are direct binding partners in hippocampal neurons and their molecular signaling may represent potential biomarkers for AD

SNAP25, a presynaptic protein, is increased in AD CSF.
Pepinemab treatment reduced levels of SNAP25, representing a potential biomarker

Pepinemab in 3D "Brain on a chip" model of Neurodegeneration

Study Design

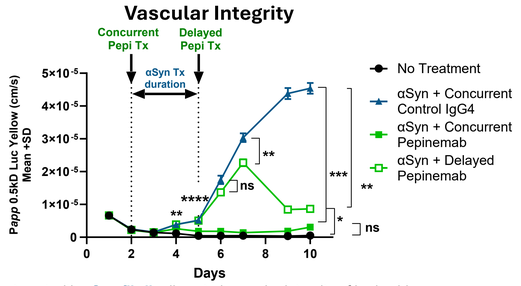


Brain and vascular channels (Emulate) are maintained under continuous flow, exchanging metabolites/ molecules across the brain vascular barrier in both directions.

Vascular permeability (*Papp*) can be determined by injection of high and low molecular weight dyes in vascular channel and measure how much leaks to brain side.

Soluble factors can also be measured in supernatants.

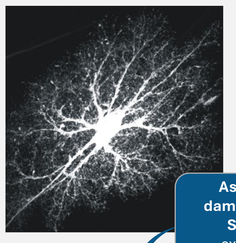
Vascular Integrity



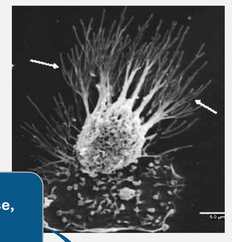
- Treatment with **αSyn fibrils** disrupted vascular integrity of brain chip
- Concurrent **pepinemab** treatment significantly **inhibited** effects of αSyn
- Delayed (+3 days) **pepinemab** treatment significantly **reversed** effects of αSyn
- αSyn is a co-pathology in AD and a key component of Lewy body pathology, including Lewy Body Dementia and Parkinson's Disease
- Effects of **pepinemab** in **Aβ amyloid model** are currently under investigation

SEMA4D plays a fundamental role in regulation of cellular morphology and communication in both the nervous and immune systems

Healthy Astrocyte
Reaches out to touch and interact with Neurons and other brain cells



Mature Dendritic Cell
Facilitates interactions with T cells and other immune cells



As a result of damage/disease, SEMA4D is expressed by

- Stressed or Damaged Neurons
- Activated T cells

Astrocytes in brain and **Dendritic Cells** in immune system express PlexinB1/B2 receptors and *change form and function* in response to SEMA4D upregulated during disease, "SEMA4D Reactive Regulators"

REFERENCES:
1. Mostafavi et al., Nat Neurosci. 2018 Jun;21(6):811-819. (ROS-MAP cohort)
2. Yu et al. Ann Neurol. 2018 Jul;84(1):78-88.
3. Mathys et al., Nature (2019) 570:332-337
4. Grubman et al. 2019 Dec;22(12):2087-2097
5. Evans et al. J Neuroinflammation, (2022) 19:200-216
6. Mega Vascular Cognitive Impairment and Dementia (MEGAVCID), Alzheimer's & Dementia (2024)
7. Huang et al. Nat Neurosci (2024) 27, 1489–1504
8. Smith et al. Neurobiology of Disease (2015) 73:254-268
9. Clark et al. Science. 2021 Apr 23;372(6540):eabf1230.
10. Feigin et al. Nat Med. 2022 Oct;28(10):2183-2193.
11. Feigin, A., Evans, E. E., Fisher, T. L., & Zauderer, M. 2025. Expert Opinion on Investigational Drugs, 34(3), 109–119.

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