# Synthesis of key results and conclusions of the SIGNAL phase 2 study of pepinemab as a treatment for early HD

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Science in the Service of Medicine

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## Pepinemab antibody blocks a key driver of neurodegenerative disease pathology

### Mechanism of Action

Neuroimmune Semaphorin 4D (SEMA4D) is upregulated in neurons in Huntington's Disease (HD) and Alzheimer's Disease (AD) in response to stress associated with disease progression. SEMA4D signals to receptors on astrocytes to trigger reactive inflammation and loss of normal homeostatic functions (Evans et al., ***J. Neuroinflammation***, 2022)

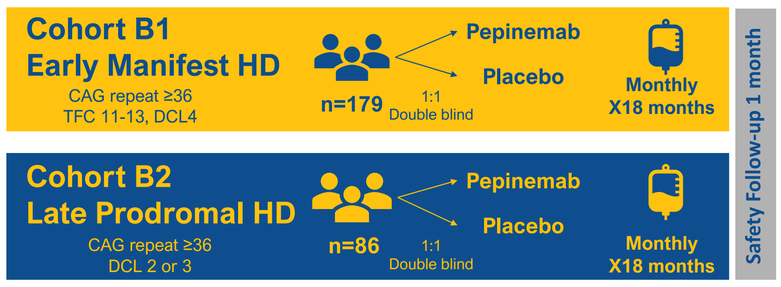
Antibody blockade of SEMA4D reduces neuroinflammation, preserves normal function of astrocytes, improves synaptic function, and prevents cognitive decline in early manifest HD (Feigin et al., ***Nature Medicine***, 2022).

### Aims

We predicted that treatment with SEMA4D blocking antibody would prevent reactive transformation of astrocytes and thereby reduce the decline in brain metabolic activity that is characteristic of HD progression. We investigated the impact of treatment on cognitive, functional and motor activity during clinical progression in the Phase 2 SIGNAL study (NCT02481674).

The ongoing Phase 1/2 SIGNAL-AD study is evaluating the safety, tolerability and effects of pepinemab treatment on cognition and brain metabolic activity in early Alzheimer's Disease (NCT04381468).

## SIGNAL Phase 2 Study Design and Key Findings




The Phase 2 randomized, double-blind, placebo-controlled SIGNAL trial of pepinemab in HD has been completed and we believe the program is Phase-3 ready.

While the Phase 2 study **did not meet the pre-specified primary endpoints**, multiple pre-specified exploratory and post-hoc analyses support the potential cognitive benefit of treatment with pepinemab in Early Manifest (EM) HD patients, particularly those with existing mild cognitive deficits. Findings have been published in *Nature Medicine*, Aug 2022

- Pepinemab was generally well tolerated, with a relatively low frequency of serious treatment-emergent adverse events of 5% with pepinemab, compared to 9% with placebo.
- Highly significant improvement (p=0.007) in the (Huntington's Disease Cognitive Assessment Battery (HD-CAB) Index
- Significant benefit in reducing apathy severity (p=0.017)
- Reduced atrophy (p=0.017) in caudate region of striatum
- A striking increase in brain metabolic activity as measured by FDG-PET in most brain regions of interest (ROI), with the important exception of caudate and putamen.

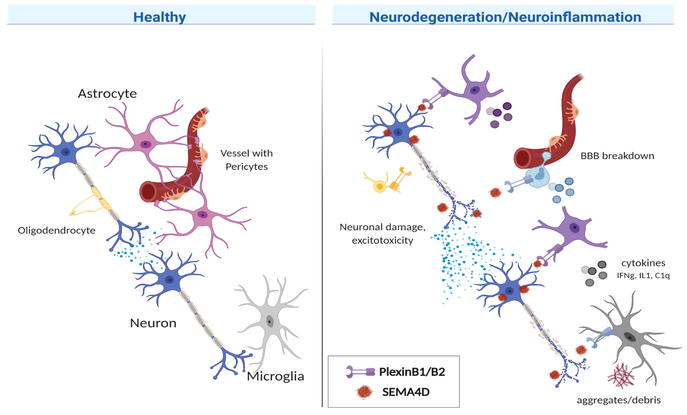
| Summary of SIGNAL endpoints | Early Manifest | Late Prodromal |
|---|---|---|
| **Functional and Global** | | |
| CGIC (Co-Primary) | No | No |
| CGIC subgroup TFC=11 (post hoc) | p#=0.04 | No |
| **Cognitive** | | |
| OTS (Co-Primary) | p#=0.028 | No |
| PTAP (Co-Primary) | p#=0.060 | No |
| HD-CAB Index (Exploratory) | YES, p=0.007 | No |
| HD-CAB Index subgroup MoCA<26 (post hoc) | YES, p=0.0025 | |
| Apathy Severity (post hoc) | YES, p=0.017 | |
| Learning effects (post hoc) | YES | |
| **Motor Activity** | | |
| TMS (Exploratory) | No | No |
| Q-motor (Secondary) | No | No |
| **Imaging** (Exploratory) | | |
| vMRI: caudate atrophy | YES, p=0.017 | No |
| FDG-PET SUVR | YES, cortical (but not striatum) | |

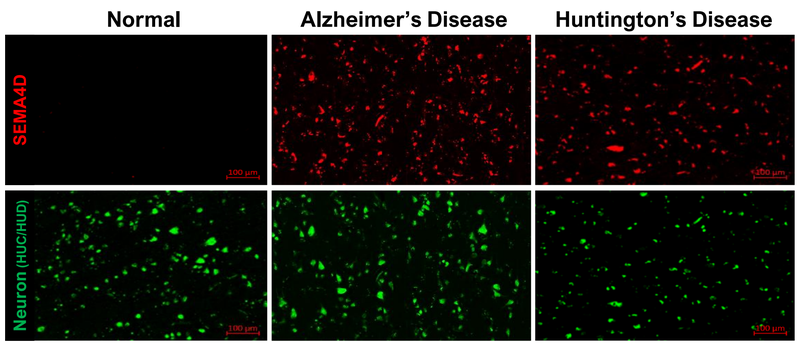
# sided p-value

## BACKGROUND

Many intervention strategies aimed at neurodegenerative disease-associated targets, such as mutant HTT and β-amyloid, have had limited efficacy.

**An *alternative and potentially complementary* strategy is to target inflammation and its role in underlying disease pathology.** Glial cells play a central role in support of brain homeostasis and synaptic function, as well as orchestrating potentially deleterious neuroinflammatory processes.

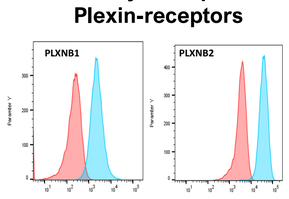



Human autopsy sections of frontal lobe

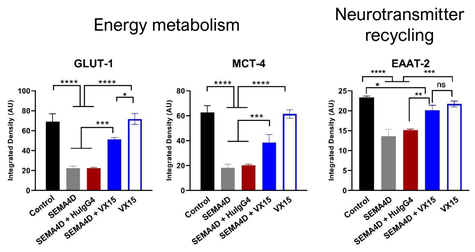
- Neurons under stress in disease upregulate SEMA4D ⬆
- Astrocytes and microglia express plexin B1/B2 receptors for SEMA4D, which triggers activation, loss of normal homeostatic function and inflammation
- **Pepinemab, SEMA4D antibody, blocks its activity and the glial cell activation that contributes to and aggravates pathogenesis** ⬇

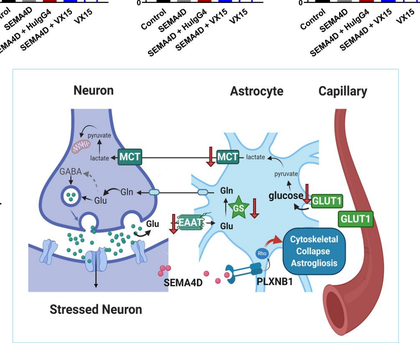
### Astrocytes express Plexin-receptors




Blue= anti-PLXN
Red= isotype control
Purified human astrocyte cultures

### Effect of SEMA4D on astrocyte functions



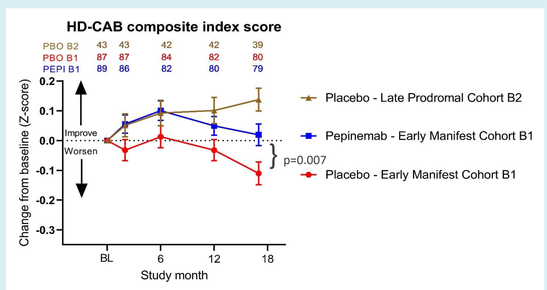

GLUT1 glucose transporter
MCT-4 lactose transporter

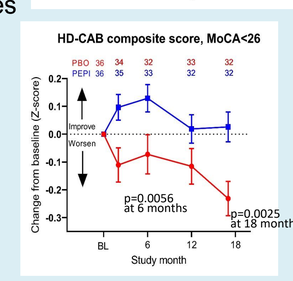
EAAT-2 glutamate transporter
GS glutamine synthetase

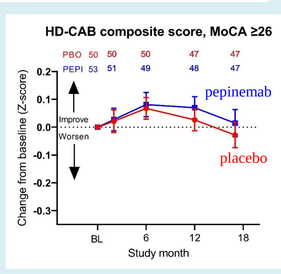
*Evans et al. J Neuroinflammation. 2022 Aug 6;19(1):200. doi: 10.1186/s12974-022-02509-8.*

## COGNITION and LEARNING

- "Learning effect" is lost when HD symptoms become manifest
- Pepinemab treatment restores the ability to benefit from experience (i.e. to learn)

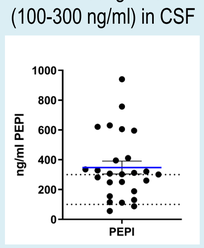


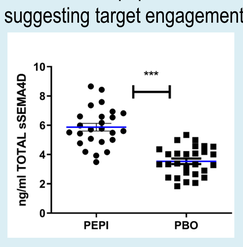




## TARGET ENGAGEMENT and BIOMARKERS

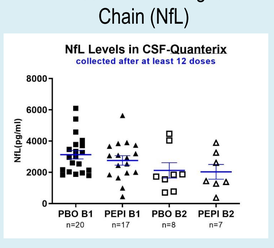
Most subjects dosed with pepinemab have ≥ saturating levels (100-300 ng/ml) in CSF




sSEMA4D / drug complexes increase in CSF of individuals dosed with pepinemab – suggesting target engagement



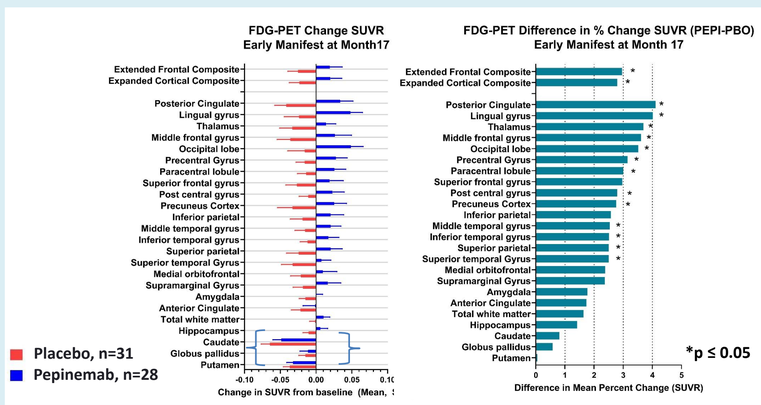

No significant change in CSF levels of Neurofilament Light Chain (NfL)



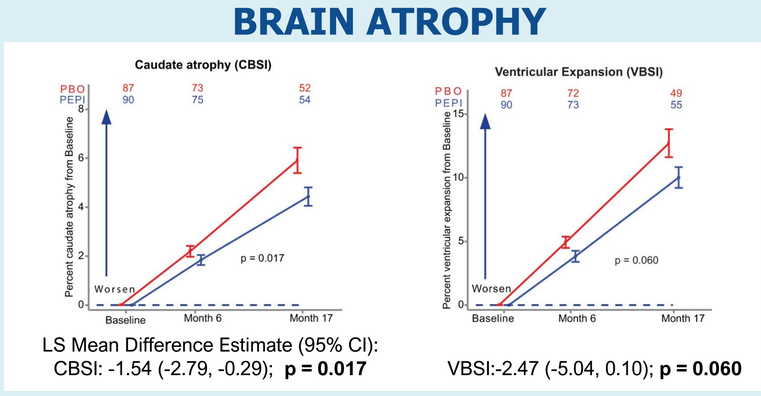

*Feigin et al. Pepinemab antibody blockade of SEMA4D in early Huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nat Med. 2022 Aug 8:1–11. doi: 10.1038/s41591-022-01919-8.*

## IMAGING in EARLY MANIFEST COHORT B1

### PEPINEMAB APPEARS TO REVERSE LOSS OF METABOLIC ACTIVITY




### PEPINEMAB APPEARS TO REDUCE BRAIN ATROPHY




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

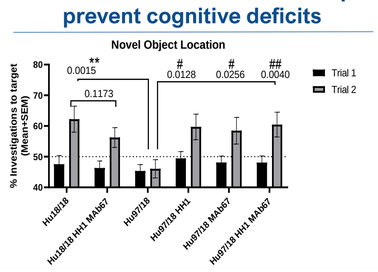
VBSI:-2.47 (-5.04, 0.10); **p = 0.060**

Pepinemab inhibits reactive astrogliosis and cognitive decline in early manifest HD, as well as preventing loss of metabolic activity in brain cortical regions as measured by FDG-PET SUVR. In contrast, pepinemab does not prevent early motor deficits (e.g. chorea) or loss of metabolic activity in striatum. This suggests that cognitive decline and loss of metabolic activity in cortex is due to a SEMA4D-dependent event reversed by pepinemab, but that a SEMA4D-independent mechanism that is not affected by pepinemab treatment in individuals with EM disease is responsible for loss of medium spiny neurons, decline in early motor activity and reduced FDG-PET-SUVR in striatum.

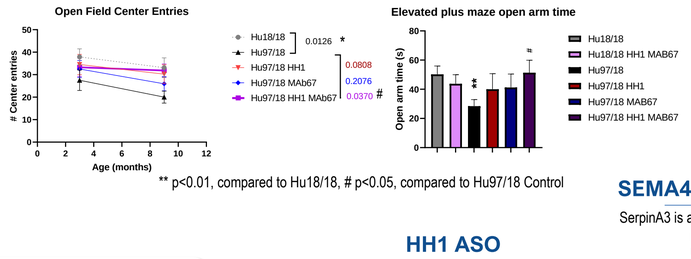
**Inhibition of both early striatal and later cortical pathology may require combination therapy.**

## CONTINUED RESEARCH: COMBINATION HTT-LOWERING and IMMUNOTHERAPY

### Individual and Combination therapies prevent cognitive deficits

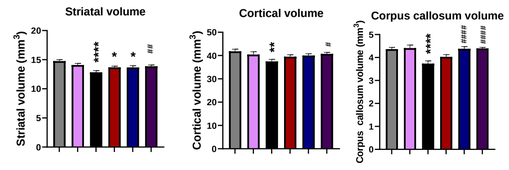



### Combination therapy improves anxiety like behavior

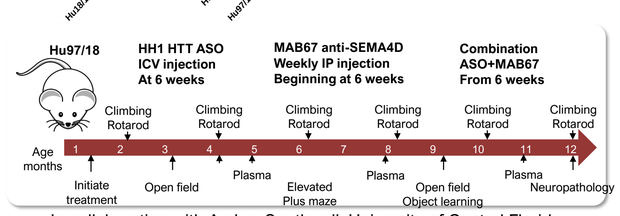



** p<0.01, compared to Hu18/18, # p<0.05, compared to Hu97/18 Control

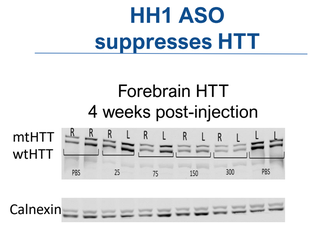
### Combination therapy prevents forebrain volume loss




### HH1 ASO suppresses HTT

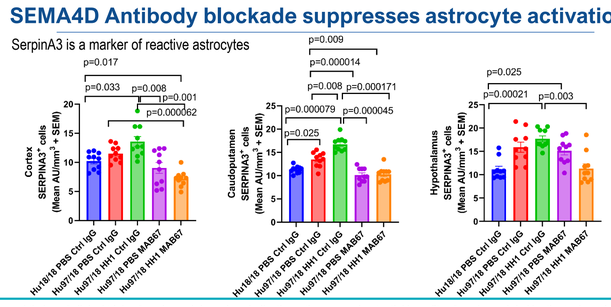



In collaboration with Amber Southwell, University of Central Florida




### SEMA4D Antibody blockade suppresses astrocyte activation

SerpinA3 is a marker of reactive astrocytes

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