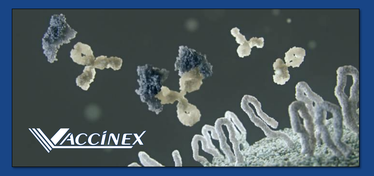
Evidence that semaphorin 4D is upregulated in neurons in Huntington's and Alzheimer's diseases, effects of a SEMA4D blocking antibody on FDG PET in a clinical trial, and treatment rationale for its use in AD.



E. Evans, T. Fisher, J. Leonard, A. Reader, Vikas Mishra, C. Mallow, L. Balch, A. Howell, E. Smith, M. Zauderer, E. Siemers and A. Feigin (for the Huntington Study Group SIGNAL investigators and coordinators), Vaccinex, Inc., Rochester, NY, USA and NYU Langone Health, New York, NY, USA

AAIC 2020, Poster #43971

Targeting common pathology in Neurodegeneration

Many current intervention strategies in diseases of the brain focus on a unique disease-associated biomarker. *Most have failed.*

What if we target a common pathology?

- Increasing interest in novel approaches and new targets to address underlying pathology and common pathways affecting neurodegeneration
- This strategy may be broadly applicable across many CNS diseases

Antibodies to Aβ amyloid

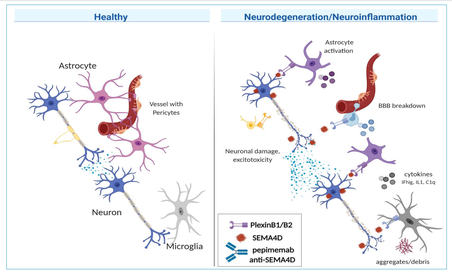
- Bapineuzumab -> mild Aβ reduction
- Crenezumab -> halted Aβ accumulation
- Gantenerumab -> Aβ plaque clearance

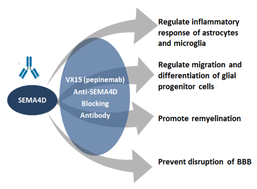
- **Most have not had significant disease modifying effects**
- Aducanumab -> Aβ plaque clearance. High doses may be beneficial, but controversial.

Pepinemab: Novel Target

- Neurons under stress during the course of underlying disease progression upregulate semaphorin 4D (SEMA4D)
- Astrocytes express high affinity plexin-B1 receptors for SEMA4D which triggers inflammatory transformation
- Vaccinex's pepinemab anti-SEMA4D antibody blocks its activity and prevents loss of normal astrocyte functions and support and the chronic inflammation that follows

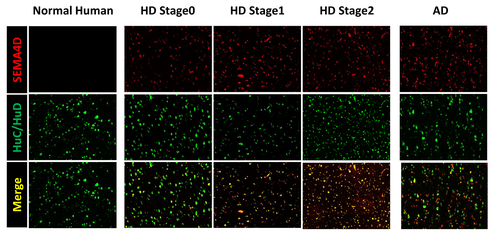
SEMA4D regulates Glial Cell Function

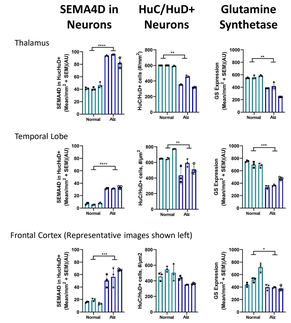




Smith, et.al. Neurobiology of Disease, 73:254–268. 2015

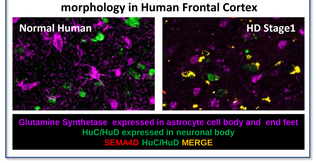
SEMA4D is upregulated in HD and AD and triggers transformation of astrocytes



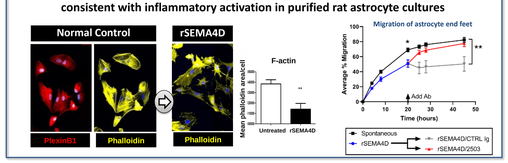


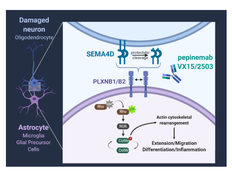
- Astrocytes undergo inflammatory transformation that aggravates brain damage in neurodegenerative diseases
- How do astrocytes recognize and respond to damage?
  - SEMA4D is upregulated on neurons during underlying Huntington's disease progression and in Alzheimer's Disease, coincident with neuronal loss
  - Astrocytes are in close proximity to neurons and express high levels of receptors for SEMA4D, including Plexin B1
  - SEMA4D triggers change in astrocyte morphology and altered gene expression which results in loss of normal astrocyte functions and gain of inflammatory activity

Disease-associated activated astrocytes have altered morphology in Human Frontal Cortex



SEMA4D induces changes in morphology and function consistent with inflammatory activation in purified rat astrocyte cultures





Treatment Rationale: SEMA4D Blocking Antibody will prevent inflammatory transformation of astrocytes that aggravate brain damage

- Blocking SEMA4D signaling prevents collapse of the cell cytoskeleton
- This should preserve normal astrocyte functions and prevent transition to inflammatory activity

- **BIOMARKER: Glucose transport in brain is one of several important normal astrocyte functions that are known to be compromised in HD and AD and can be measured with FDG-PET**

- **A clinical trial to evaluate safety and FDG-PET biomarker of metabolic activity in AD will be initiated in 2020**
- **Pepinemab is well tolerated and restores metabolic activity, as measured by FDG-PET, in clinical trial for HD**
- **Pepinemab is an antibody that targets a key driver of neurodegenerative disease pathology**
  - **SEMA4D is upregulated in Huntington's Disease (HD) and Alzheimer's Disease (AD) and triggers response to stress in CNS, where normal functions are lost and glia switch to inflammatory activity**
  - **Antibody blockade of SEMA4D can restore normal function of astrocytes that regulate metabolic activity**

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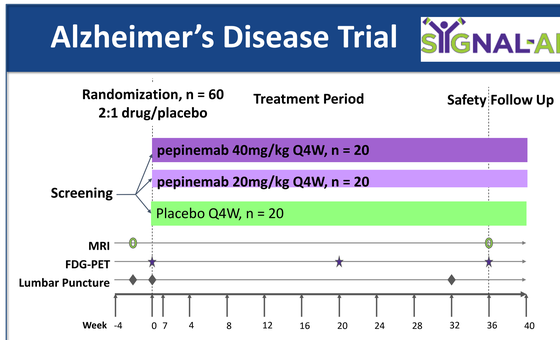
Hypothesis: Blocking F-actin depolymerization with anti-SEMA4D antibody pepinemab may reduce inflammatory transformation and increase glucose uptake, which can be measured by FDG-PET

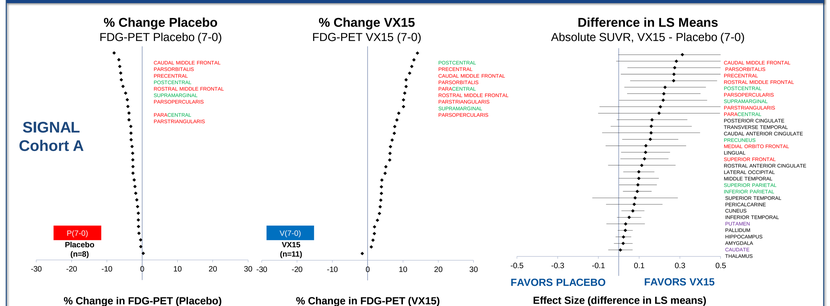
Alzheimer's Disease Trial

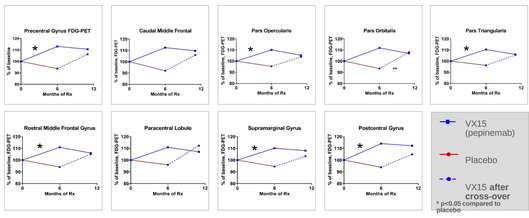


Program funding from Alzheimer's Association and Alzheimer's Drug Discovery Foundation (ADDF)
To be initiated Fall 2020

(NCT04381468)

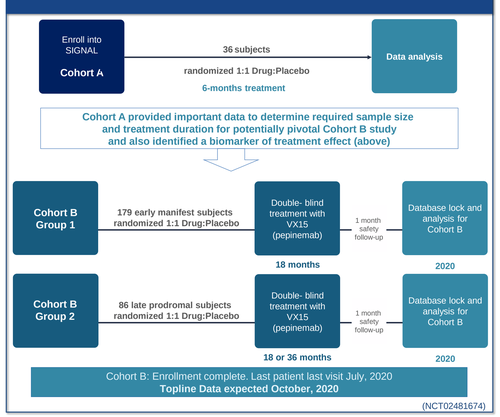
FDG-PET Declines During Natural Course of HD but is Increased in Response to Treatment





Orphan Drug and Fast Track Designation by the FDA Division of Neurology Products

Huntington's Disease Trial



(NCT02481674)

CONCLUSIONS:

- **Clinical investigation of pepinemab in AD is being planned based on preclinical MOA data, clinical safety data, as well as SIGNAL FDG-PET data that suggests treatment-induced increase in metabolic activity and glial health.**
- Previous studies in Alzheimer's Disease concluded that glucose metabolism is a sensitive measure of change in cognition and functional ability and has value in predicting future cognitive decline or as an outcome measurement to monitor clinically-relevant change over time (Landau et. al., Neurobiol Aging. 2011; 32(7): 1207–1218).
- While it is widely believed that neuronal loss is irreversible, other important elements that govern neurological activity, in particular glial cells and synapses, may be replenished or repaired with potentially significant impact on disease progression. We hypothesize that the imaging results from SIGNAL-HD Cohort A suggest a partial restoration of glial function and/or restoration of disrupted neural networks.
  - Pepinemab has been well-tolerated in in subjects with neurodegenerative disease, including those enrolled in SIGNAL-HD, and previously in a Phase 1 MS trial.
  - Pepinemab treatment resulted in an increase in FDG-PET signal relative to the decrease observed in placebo group in SIGNAL-HD Cohort A.