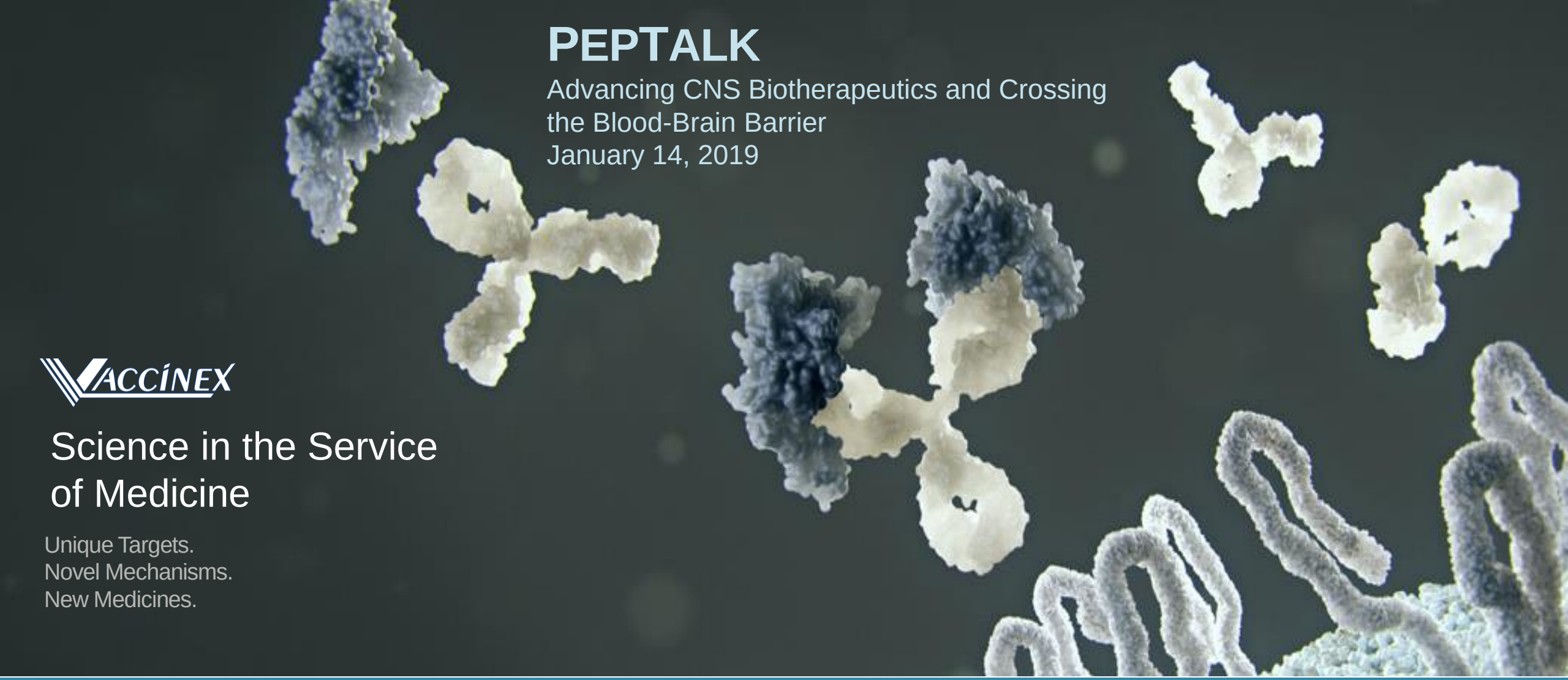


PEPTALK

Advancing CNS Biotherapeutics and Crossing the Blood-Brain Barrier
January 14, 2019

VACCINEX

Science in the Service of Medicine

Unique Targets.
Novel Mechanisms.
New Medicines.

An Emerging Role for Glial Cells and Guidance Molecules in Neurodegeneration

Elizabeth Evans, VP Preclinical Research

Disclosure Information

PEPTALK: Advancing CNS Biotherapeutics and Crossing the Blood-Brain Barrier

January 14, 2019

Elizabeth Evans, PhD

I have the following financial relationships to disclose:

Employee and shareholder of: Vaccinex, Inc

DISCLAIMER: *This document is provided for informational purposes only and does not constitute an offer to sell, or an invitation to subscribe for, purchase or exchange any securities of Vaccinex, Inc. or the solicitation of any vote or approval in any jurisdiction.*

Forward-Looking Statements*: To the extent that statements contained in this press release 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. Words such as "may," "will," "expect," "anticipate," "estimate," "intend," "potential," "advance," and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances) are intended to identify forward-looking statements. Forward-looking statements may involve substantial risks and uncertainties that could cause our 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, risks related to our dependence on our lead product candidate pepinemab (VX15), and other matters that could affect our development plans or the commercial potential of our product candidates. Except as required by law, we assume 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 our periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in our prospectus for our initial public offering dated August 9, 2018, filed with the SEC pursuant to Rule 424(b) under the Securities Act of 1933, as amended.*

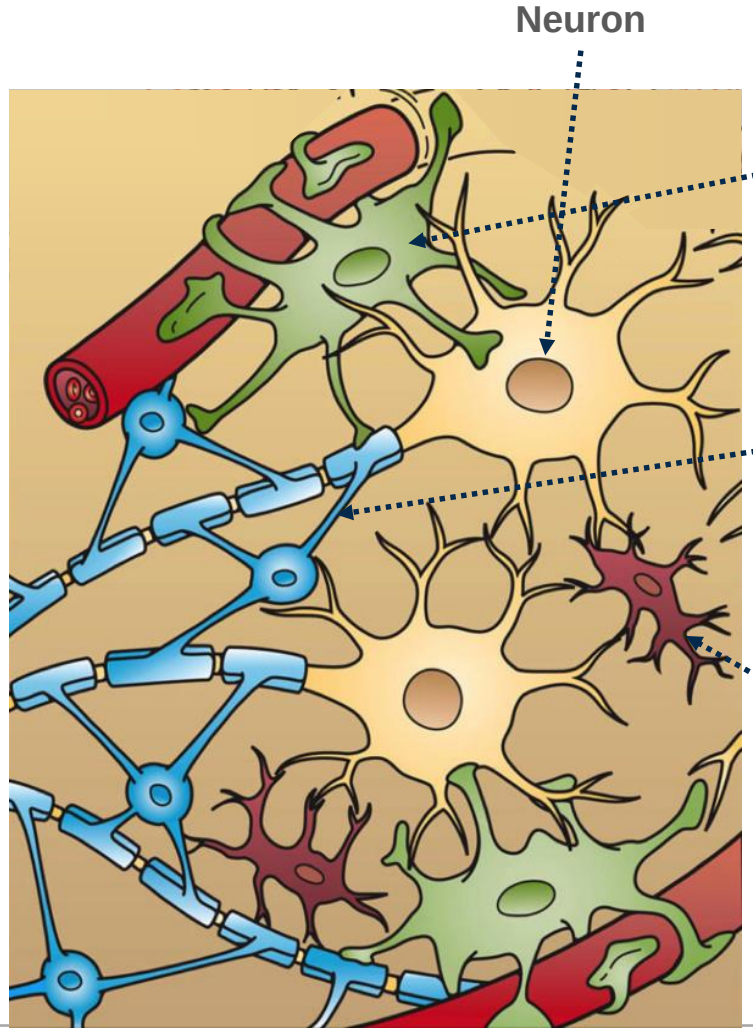
Glial cells undergo inflammatory transformation that aggravates brain damage in neurodegenerative diseases

Glial cells are the most abundant cells in the brain

1. **They provide essential functional support to neurons.** Glial cells couple glucose transport and metabolism to synaptic activity

2. **CNS damage triggers dramatic change in glial cell morphology and function** (a) Beneficial in the context of acute focal injury, but (b) maladaptive in broad chronic injury such as HD

3. **How do glial cells recognize and respond to damage?** Glial cells express plexin receptors. SEMA4D signals through plexin receptors to trigger glial transformation from normal to activated “inflammatory” state at sites of injury. Reactive glial cells secrete cytokines that activate other inflammatory cells.



Semaphorin 4D (SEMA4D)

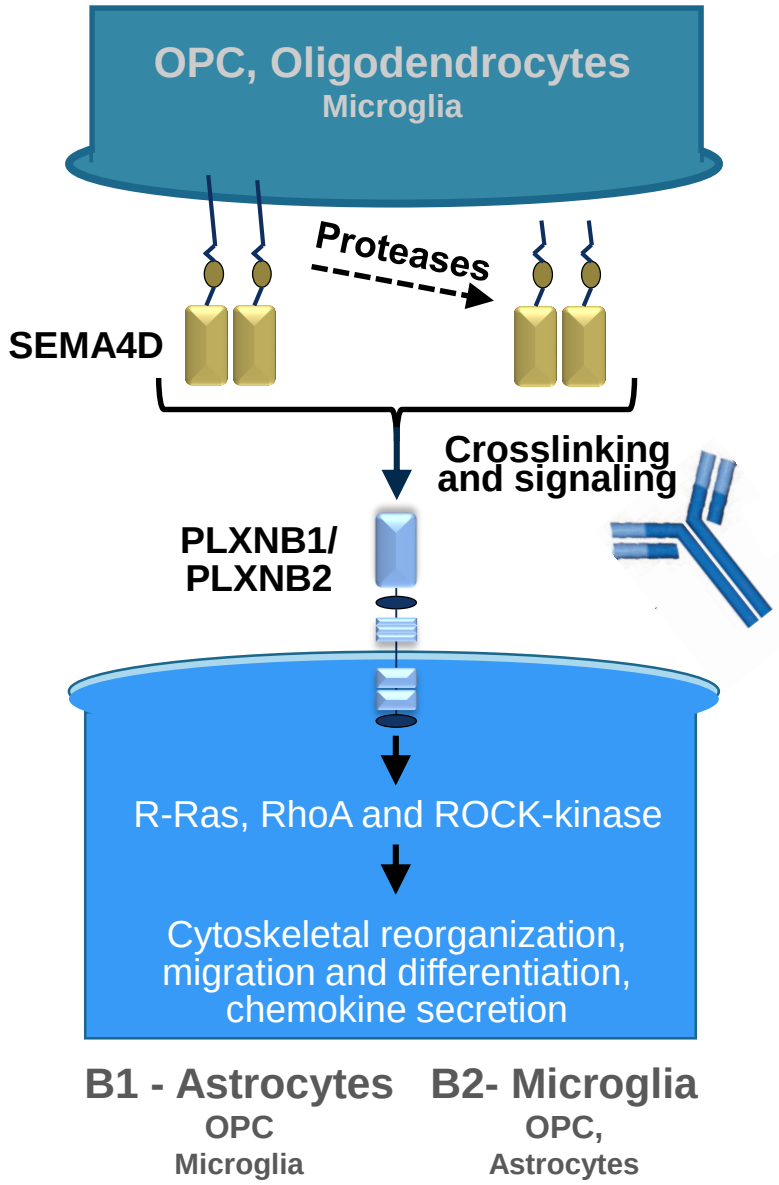
- SEMA4D is a guidance molecule that regulates the activity of inflammatory and glial cells at sites of injury
- SEMA4D signals through PLXNB1 and PLXNB2 receptors to regulate (1) cell cytoskeleton (2) cytokine synthesis and secretion

SEMA4D/Plexin signaling on glial cells:

- SEMA4D triggers partial depolymerization of F-actin in astrocytes and inhibits process extension and migration
- Glial progenitor cells express PLXN receptors and are inhibited from migrating and differentiating at sites of injury by SEMA4D.

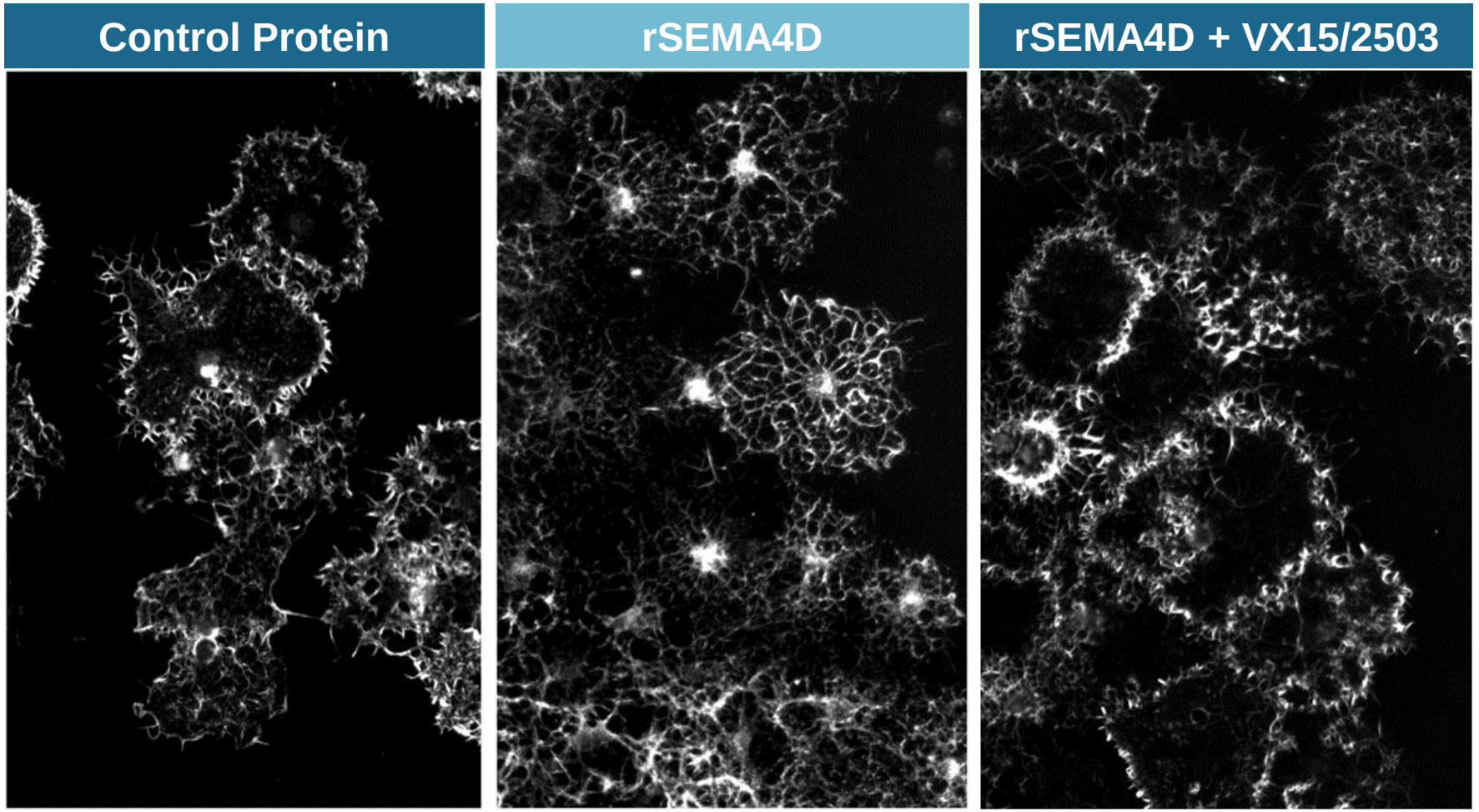
Antibody blockade of SEMA4D inhibits changes associated with glial cell activation, and promotes migration and differentiation of glial progenitor cells that can repair and remyelinate brain lesions

- MAb67: mouse IgG1, cross reacts with mouse and human SEMA4D
- Pepinemab (VX15/2503): humanized IgG4 with hinge modification



SEMA4D causes collapse of actin cytoskeleton in rat GPC cultures

- Anti-SEMA4D rescues glial precursor cells (GPC) from SEMA4D-induced cytoskeletal collapse

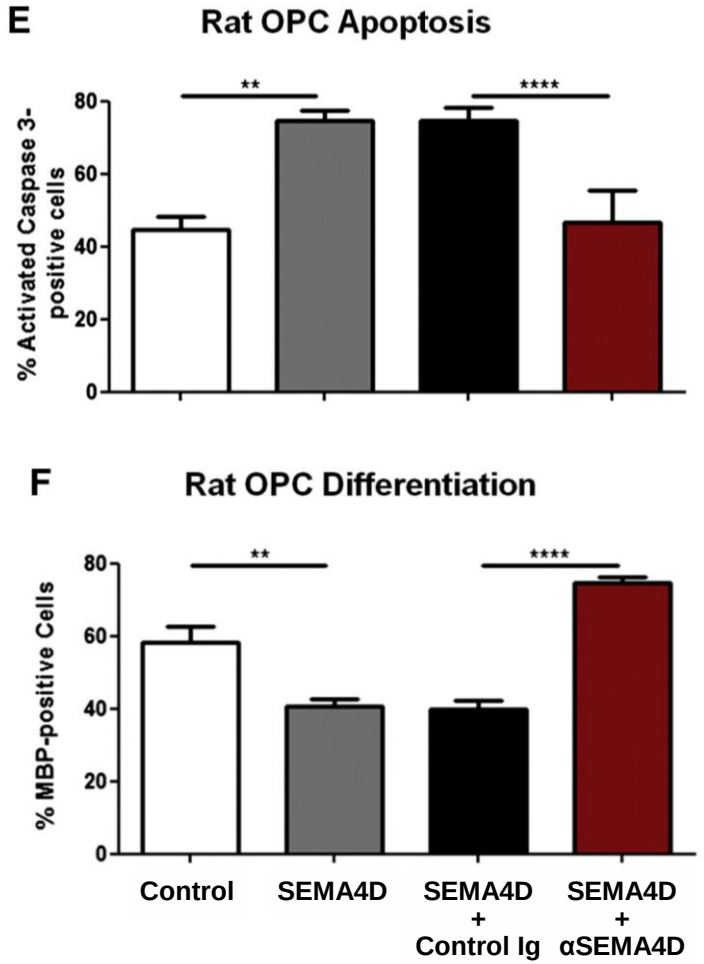


Smith et al. Neurobiology of Disease, 73:254-268, 2015

Anti-SEMA4D promotes survival & differentiation of GPC that can repair and remyelinate brain lesions

- Glial progenitor cells (GPCs) differentiate into oligodendrocytes and astrocytes.
- SEMA4D induces apoptosis and inhibits differentiation of GPC

- **Anti-SEMA4D rescues GPC from SEMA4D-induced apoptosis and inhibition of differentiation.**

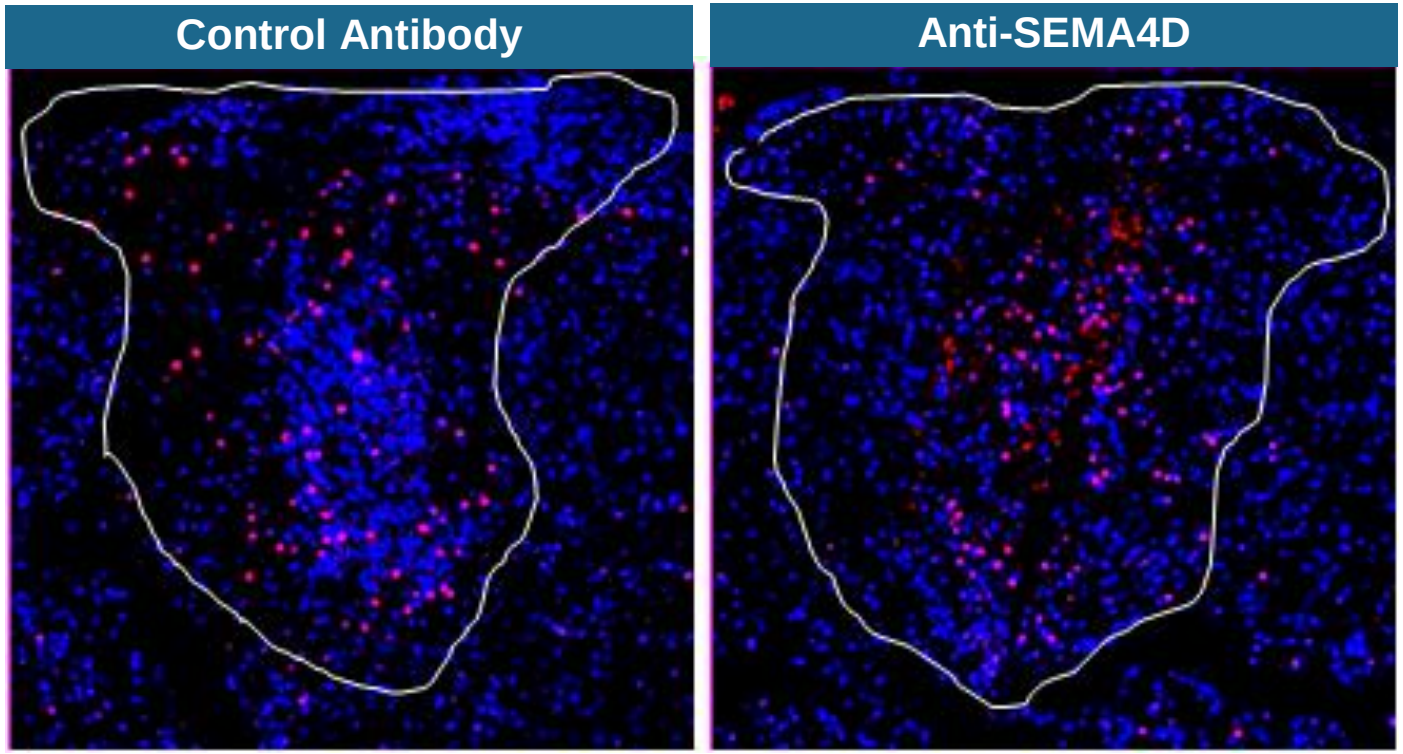


Smith et al. Neurobiology of Disease, 73:254-268, 2015

Anti-SEMA4D Antibody Promotes Migration of Glial Precursor Cells to Demyelinated Lesion

- **Antibody blockade of SEMA4D increases migration of NKX2.2+ glial progenitor cells to area of lysolecithin-induced lesions**

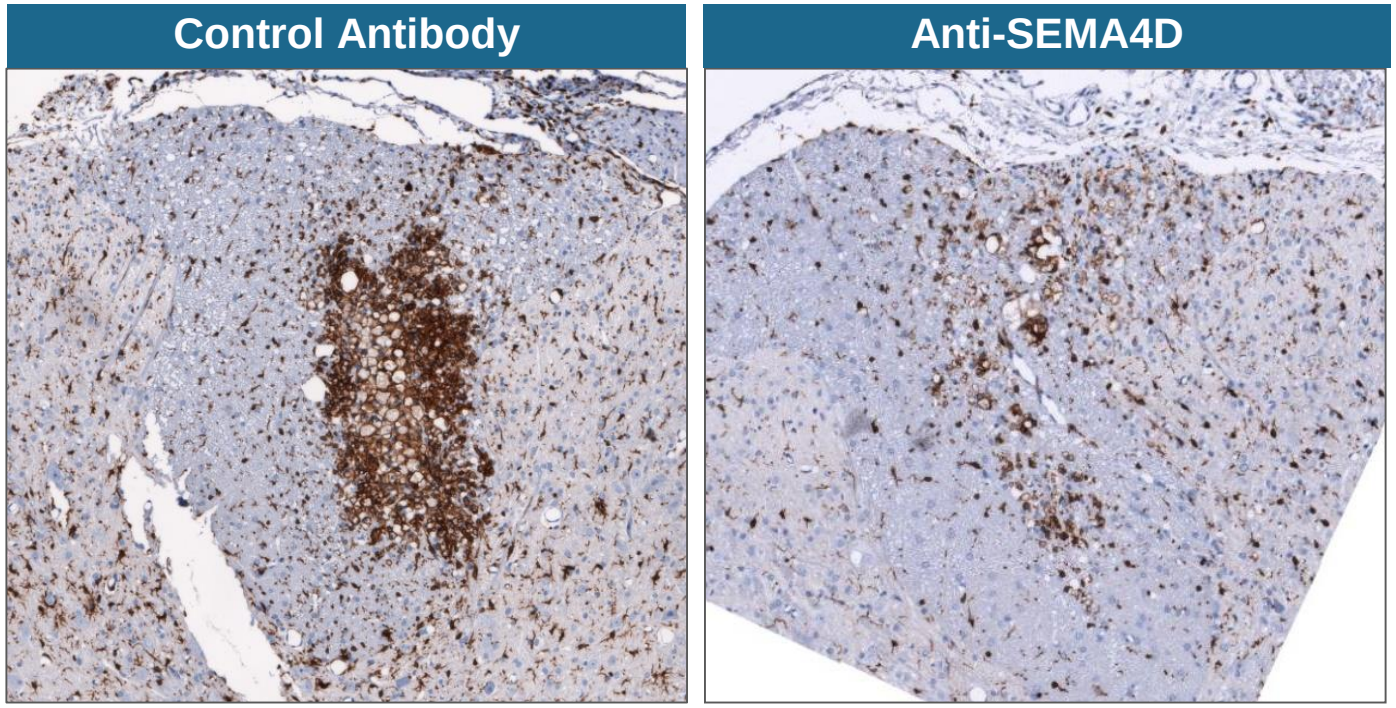
- Following injury, surrounding GPCs proliferate and migrate to the lesion area, where they can differentiate and replenish the injured area with new mature oligodendrocytes.
- Demyelination has been observed in acute injury, as well as neurodegenerative and neuroinflammatory diseases



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

Anti-SEMA4D Antibody Inhibits SEMA4D-induced Activation of Microglia

- **Anti-SEMA4D antibody treatment prevents activation of microglia in area of lysolecithin-induced demyelinated lesions in rat model**



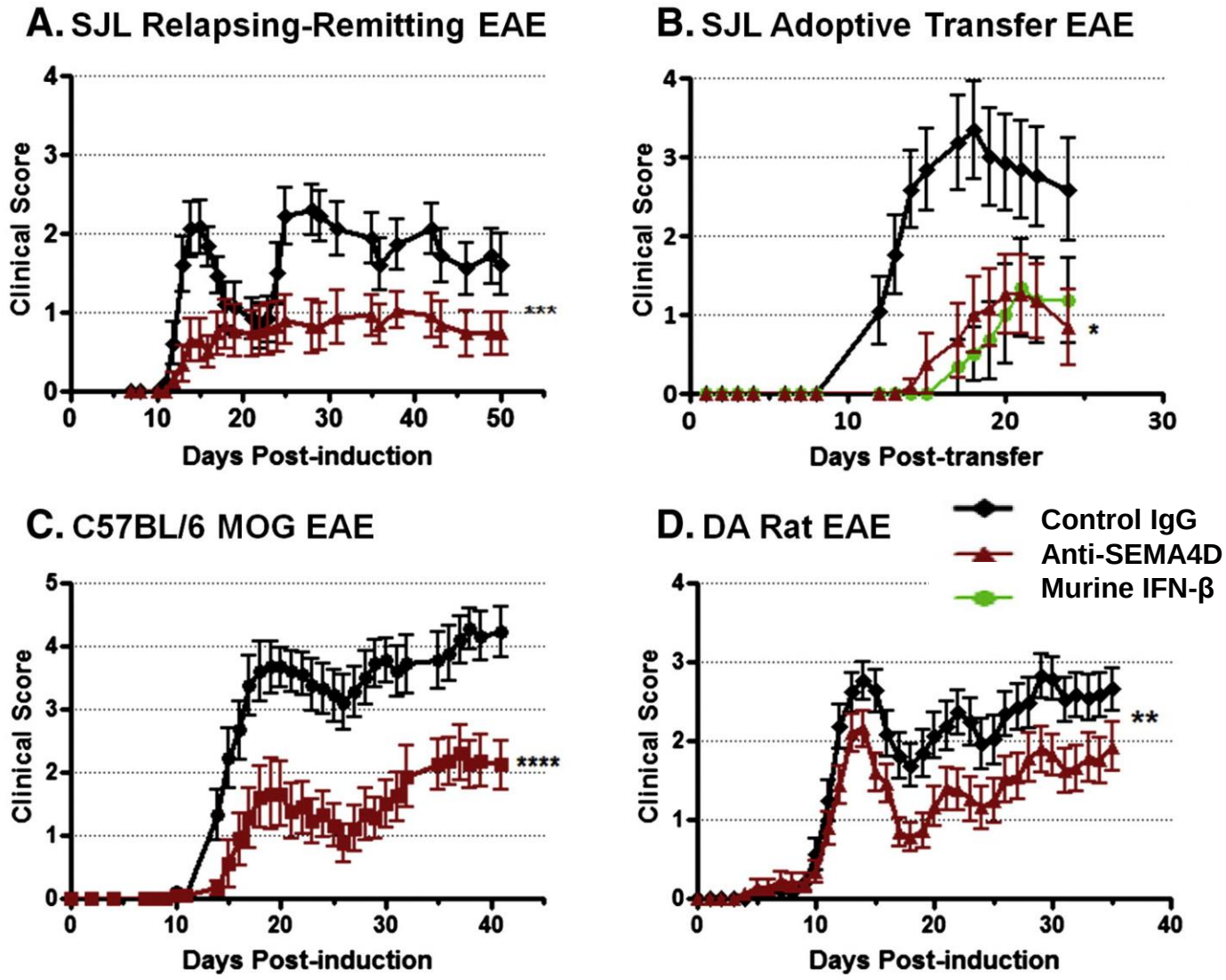
staining for Iba1 marker of microglial activation

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

Anti-SEMA4D improves clinical score in rodent Experimental Autoimmune Encephalitis (EAE) models of Multiple Sclerosis

- Activation of oligodendrocytes and microglia promotes demyelinating and inflammatory pathogenesis in Multiple Sclerosis

- **Ab blockade of SEMA4D can reduce symptoms in several preclinical EAE models.**
  - Phase 1 trial is MS was completed, well tolerated.



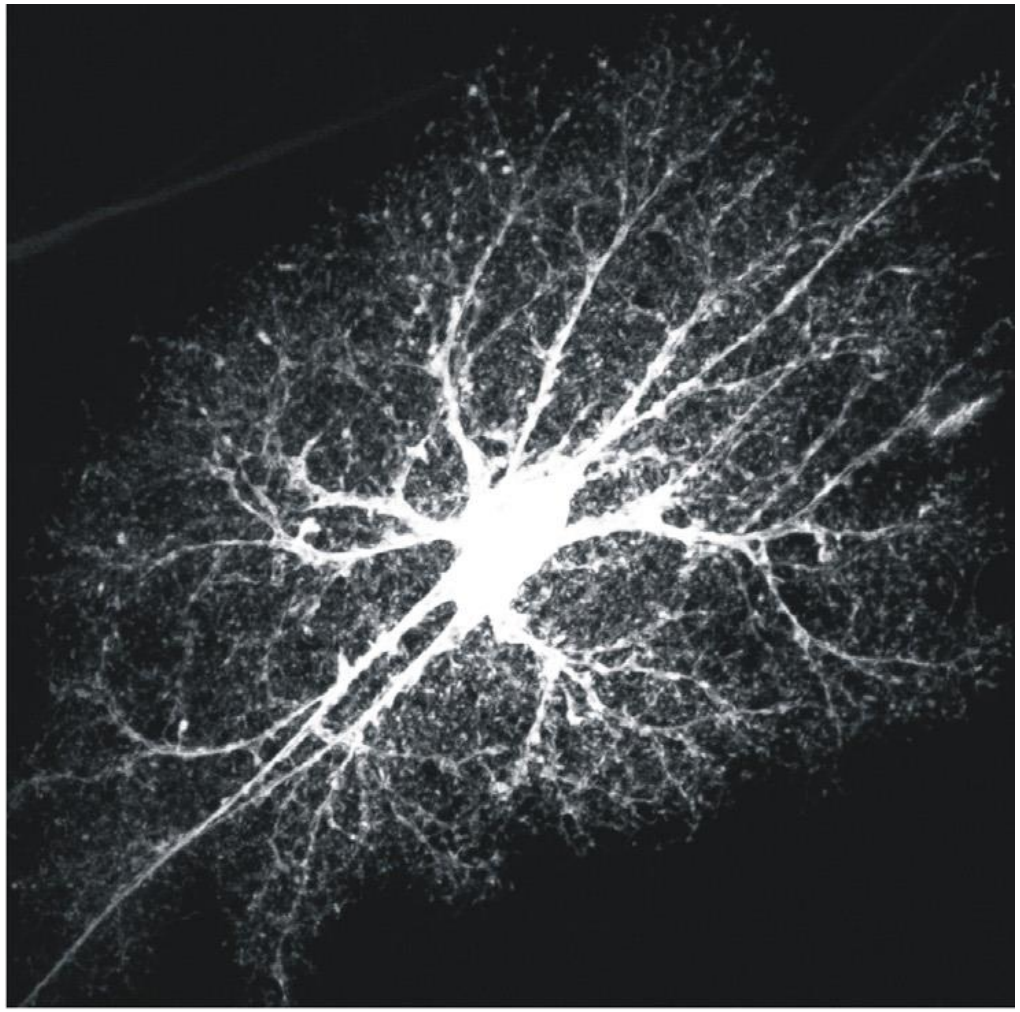
Smith et al. Neurobiology of Disease, 73:254-268, 2015

VACCINEX

Astrocytes Extend Numerous Processes to Interact with Other Brain Cells

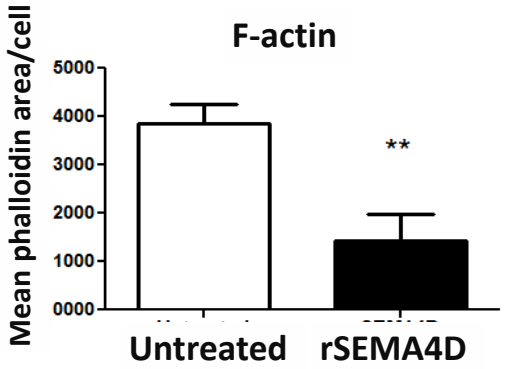
- A single human astrocyte can make as many as 1,000,000 contacts with capillaries, neurons, oligodendrocytes, and other astrocytes.
- Astrocyte process extensions cover brain capillaries and cradle synapses between neurons to support neural networks.
- Activated astrocytes dysregulate neuronal support

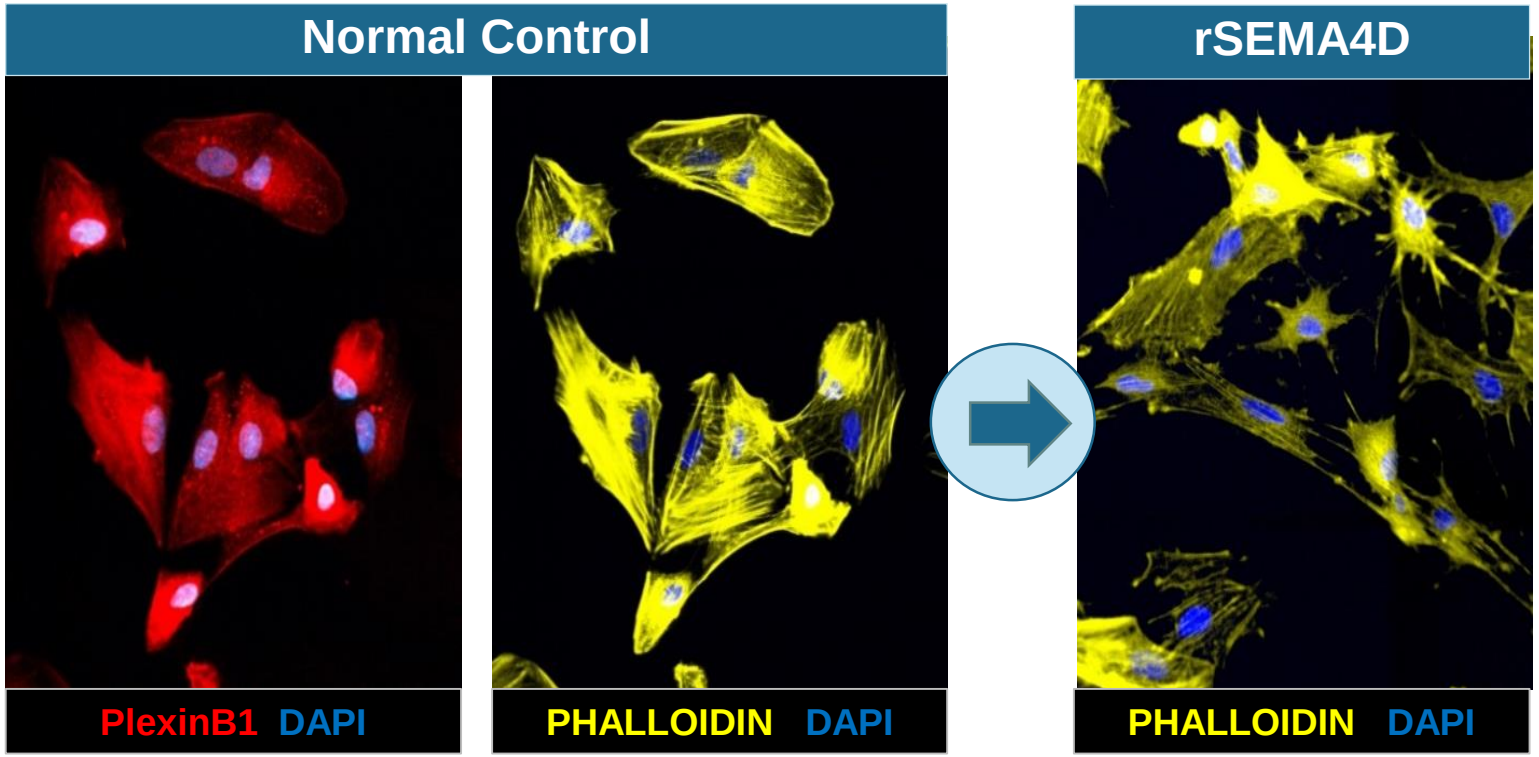
- Expression of mHtt in astrocytes alone has been shown to be sufficient to trigger the disease phenotype in an animal model for HD.
- Conversely, reconstitution of HD transgenic mice with normal human astrocytes ameliorates disease. (Benraiss et al. 2015 Nature Communication)
- Glial precursor cells derived from HD patients exhibit deficiencies in oligodendrocyte and astrocyte functions (Osipovitch et al. 2019 Cell Stem Cell)



SEMA4D Inhibits Astrocyte Migration and Process Extension

- Astrocytes express SEMA4D receptor, PlexinB1
- **SEMA4D induces cytoskeletal collapse of rat primary astrocytes by inducing F-actin depolymerization**





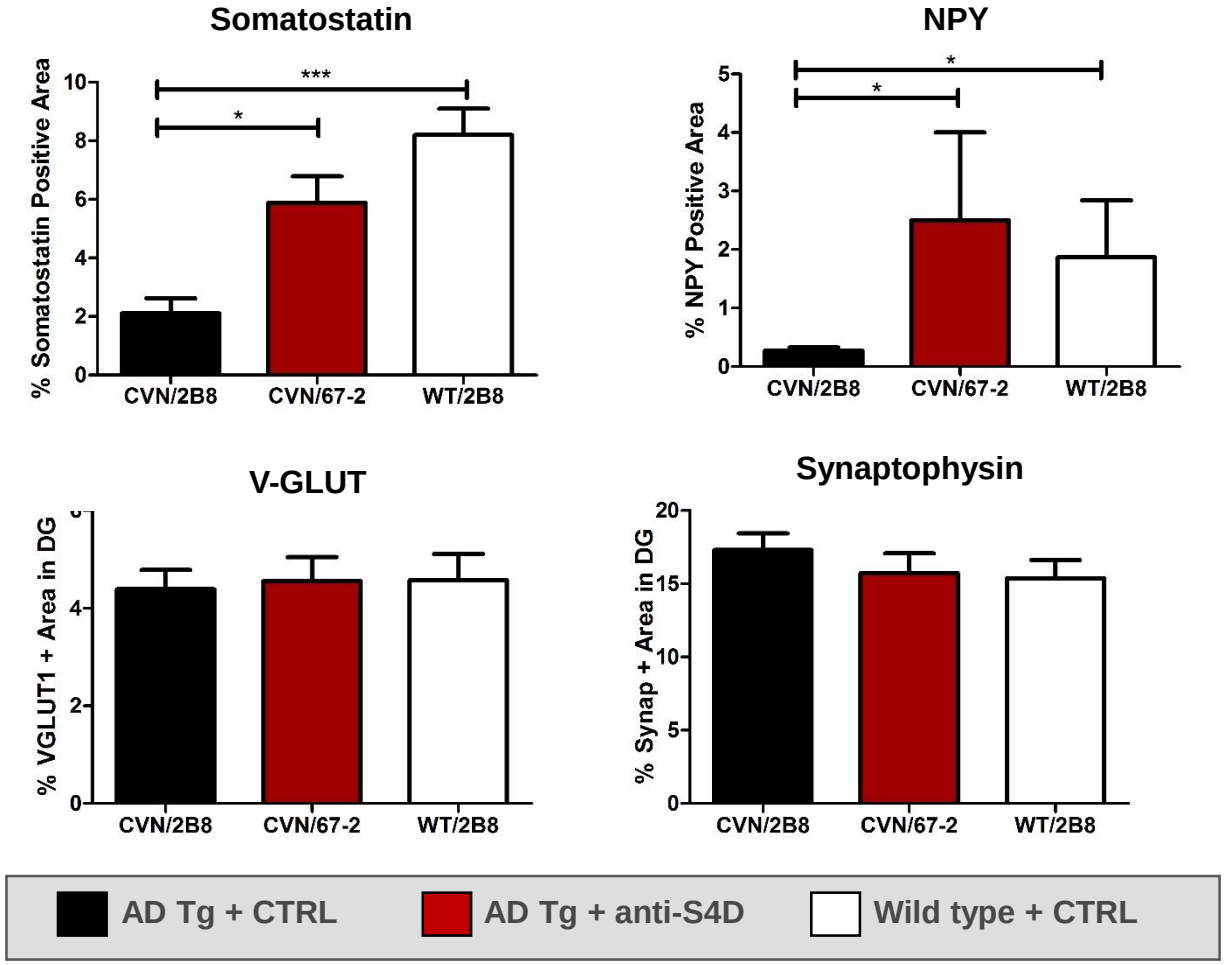
Primary rat astrocyte cultures were treated with recombinant SEMA4D for 1 hour, and were then stained for F-actin filaments (phalloidin) and nuclei (Dapi). Representative images are shown. Mean phalloidin-positive area/cell in a field of ~ 300 cells was quantified in 5 separate culture wells using ImagePro software.

Blocking SEMA4D protects against loss of inhibitory Neurons

CVN murine model of Alzheimer's Disease

- **Blocking SEMA4D protects against loss of inhibitory Neurons (Somatastatin+ or NPY+)**

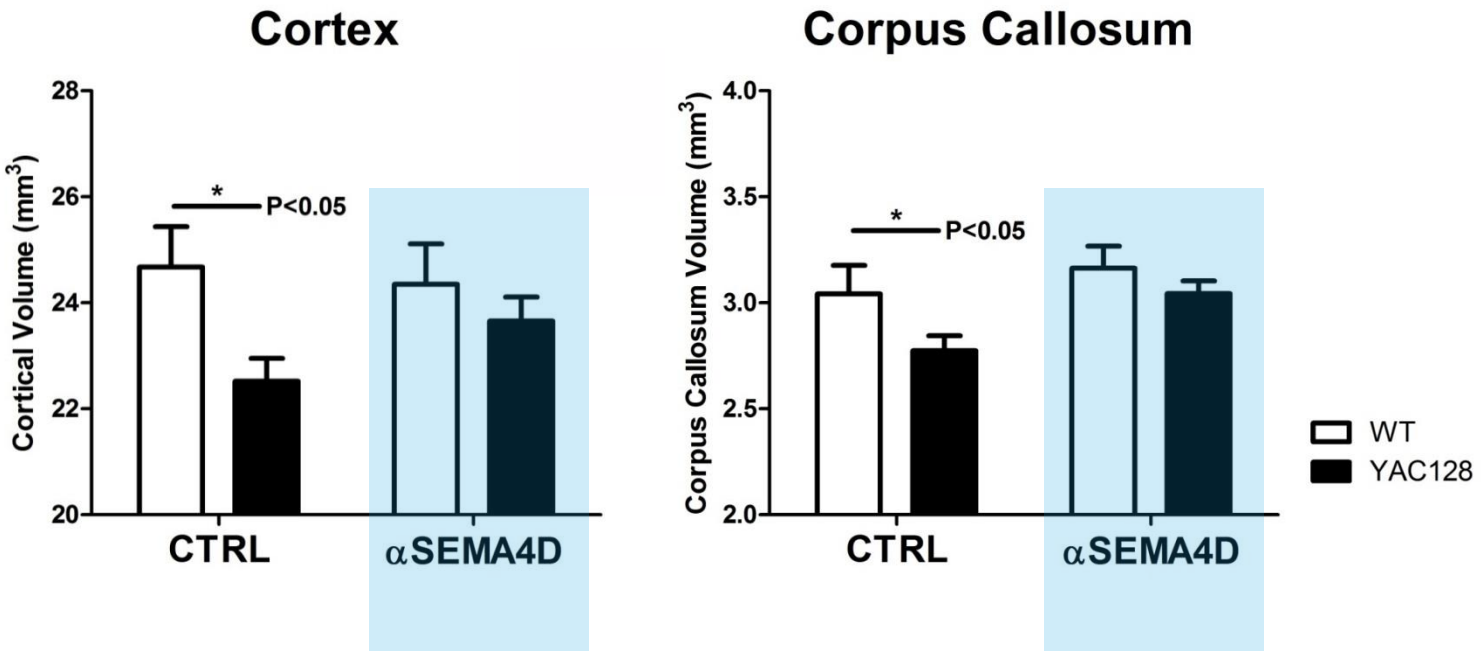
- No effects on excitatory synapses or total synapses were observed in diseased mice, as determined by staining for VGLUT-1 and Synaptophysin, respectively.



Preventive Treatment with Anti-SEMA4D Protects against Loss of Brain Volume

YAC128 transgenic model of Huntington's Disease

- **Anti-SEMA4D treatment inhibits significant cortical and corpus callosum degeneration in brains of 12 month-old YAC128 mice, a transgenic model of HD.**



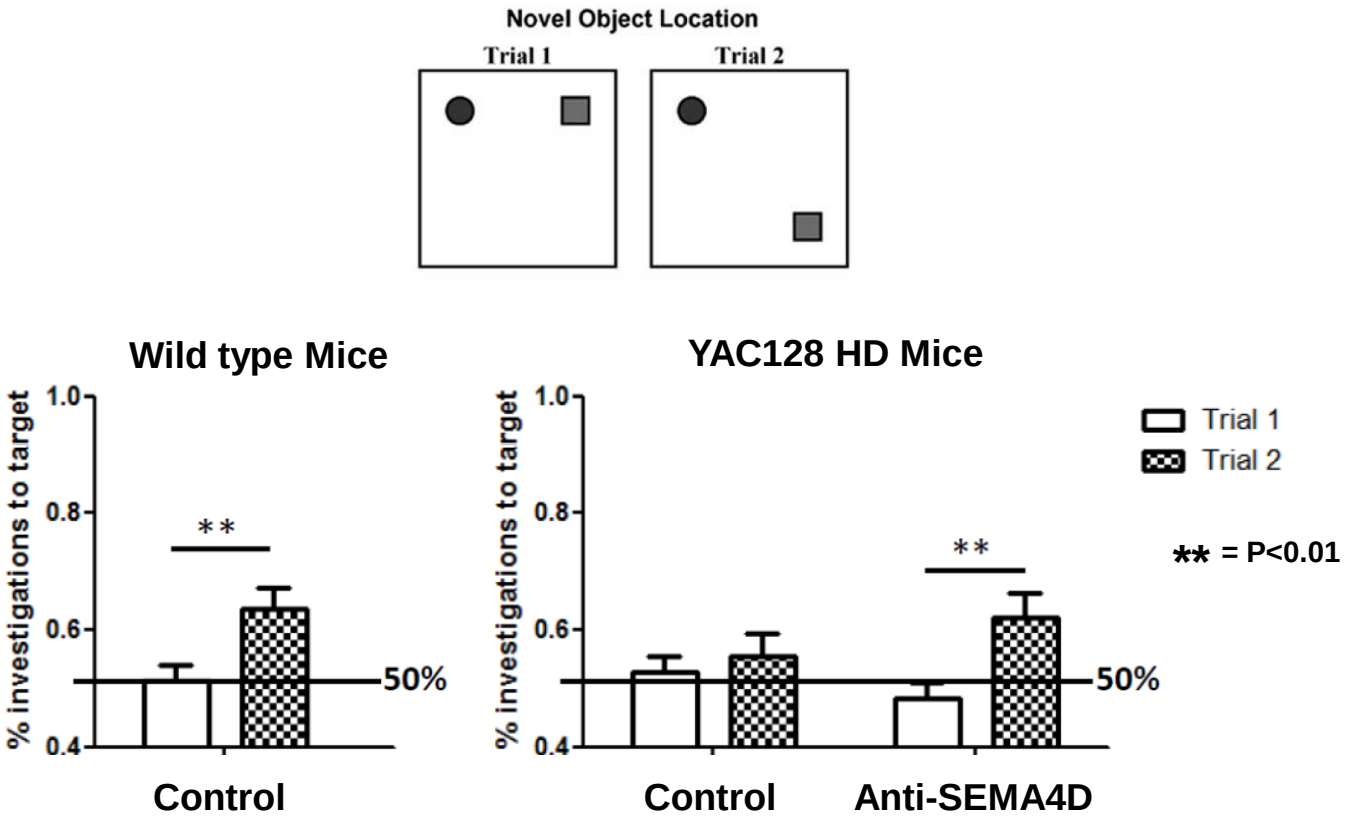
Southwell, et.al., Neurobiology of Disease, 76:46–56, 2015.

Anti-SEMA4D Antibody Improves Cognitive Function

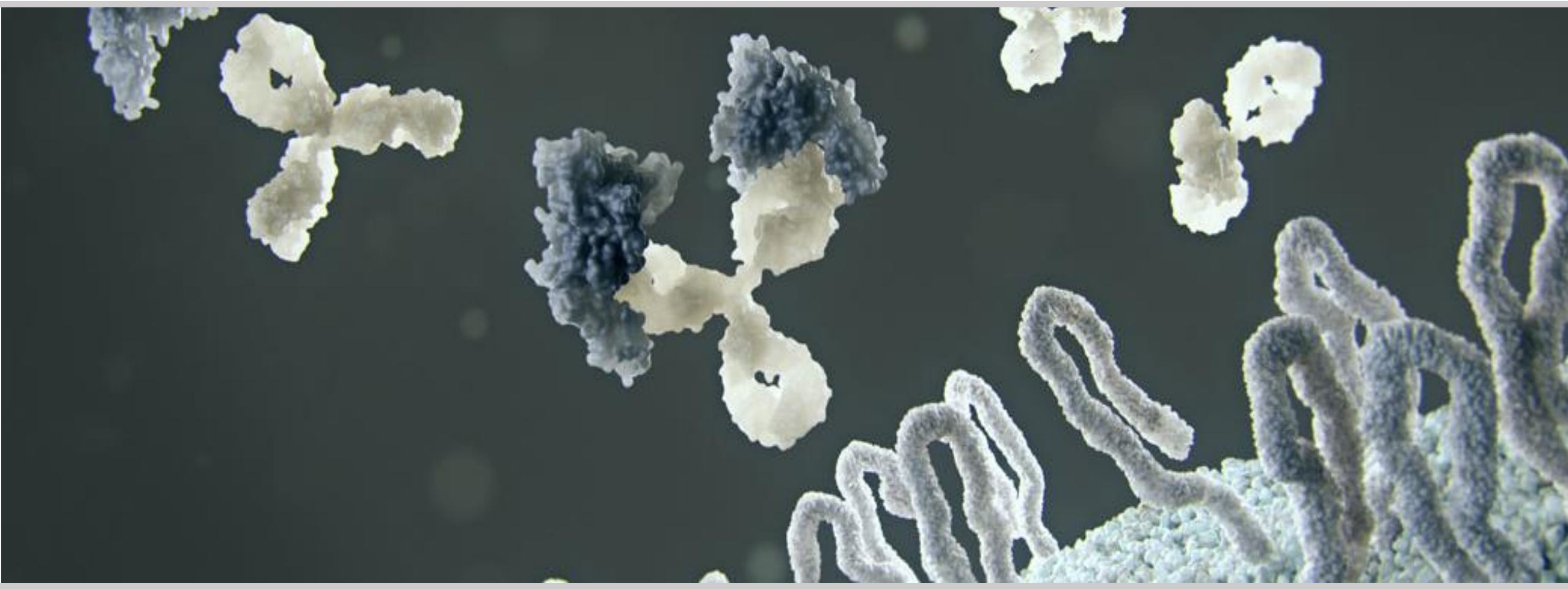
YAC128 transgenic model of Huntington's Disease

- **Anti-SEMA4D antibody improves spatial memory in HD model.**

- Wild type (WT) animals preferentially explore an object in a novel location, while control-treated YAC128 HD mice do not.
- Treatment with anti-SEMA4D MAb restores this behavior in YAC128 mice.



Southwell, et.al., Neurobiology of Disease, 76:46–56, 2015.

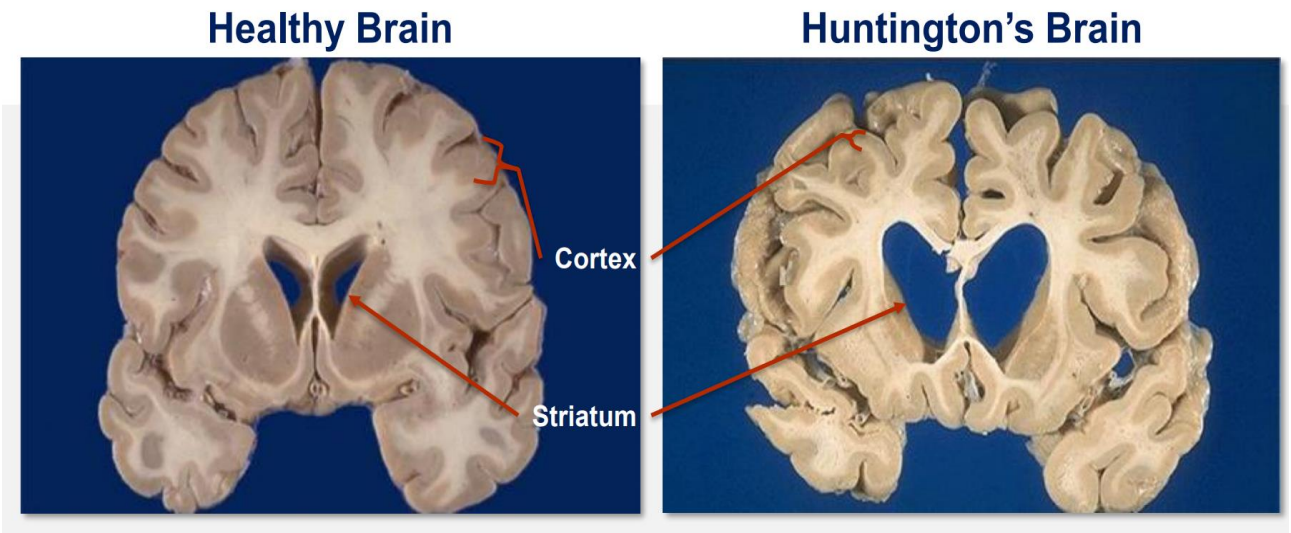


Pepinemab (VX15/2503)/Anti-Semaphorin 4D for Huntington's Disease

Huntington's Disease (HD)

HD is a fatal autosomal-dominant neurodegenerative disease based on a single mutated gene

- Symptoms usually appear between the ages of 30 to 50
- Neuronal degeneration and severe atrophy is observed in multiple brain regions



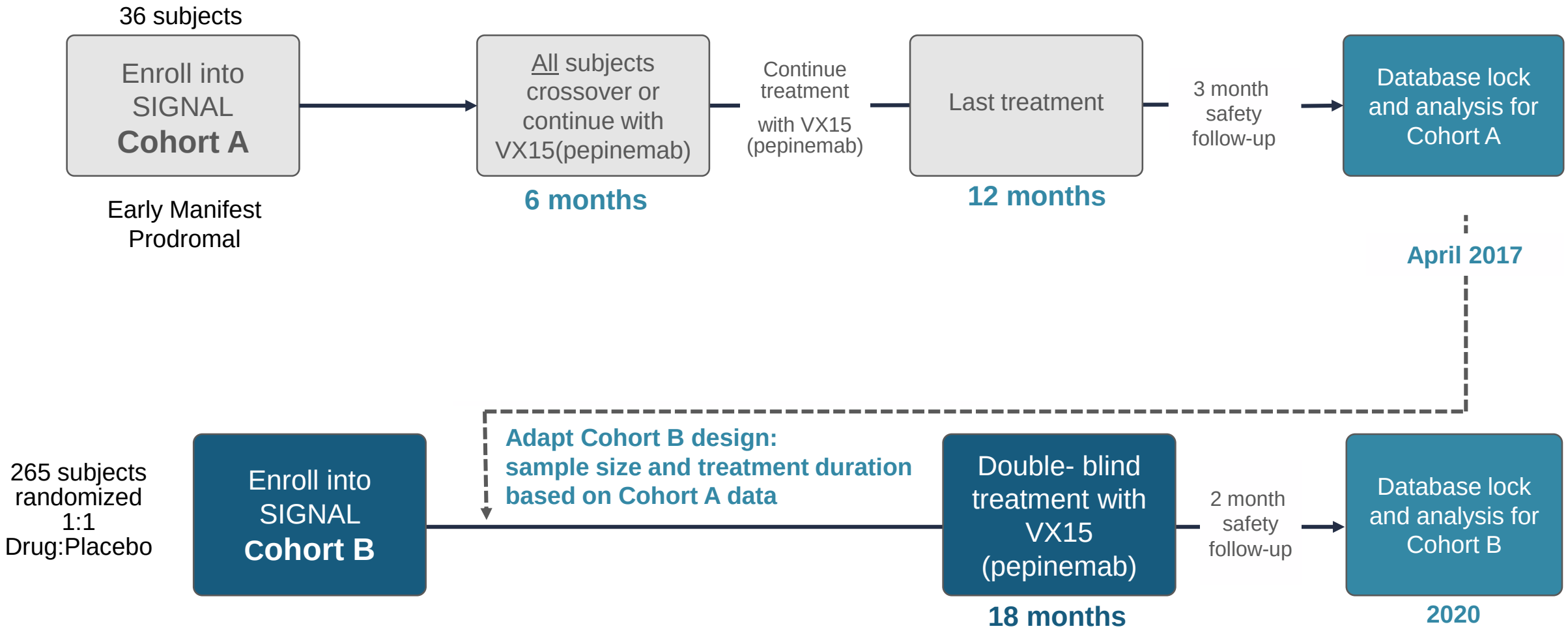
Estimated patient population ~30,000 manifest disease and 100,000 pre-manifest with inherited mutation (prodromal) in the U.S. Similar number in EU

Biomarkers of disease progression can be detected even during the pre-manifest stage of disease. This makes it possible to **test treatment benefit not only in manifest disease but also in the pre-HD prodromal phase** when intervention is most likely to be effective at delaying or preventing disease onset

There are currently no approved treatments to alter the course of HD

Huntington's Disease Clinical Trial Design

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



Huntington's Disease Clinical Trial Design

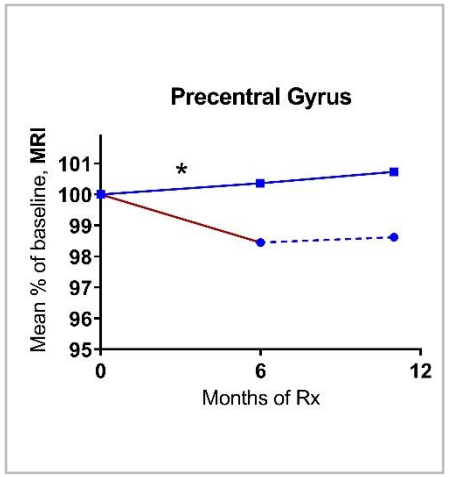
Endpoints

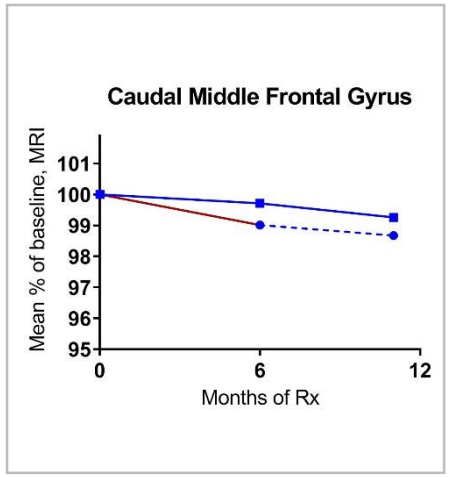
- Safety and Tolerability
- Imaging
  - A significant relationship between decreasing volumetric MRI and disease progression in HD was previously demonstrated in the much larger PREDICT-HD and TRACK-HD* natural history biomarker studies.
  - Therefore, a major focus of analysis in SIGNAL includes the use of brain imaging measures in 31 prospectively defined brain regions of interest (ROI)
  - **Volumetric MRI** as a measure of brain atrophy
  - **FDG-PET** reflecting glucose metabolism
- Quantitative motor and cognitive assessments were also performed and provided important guidance for projecting the group size required to detect clinical effects in the continuing Cohort B study
  - Q-motor, HD-CAB, UHDRS-Motor, Process Behavior Analysis, Total Functional Capacity, Patient Reported Outcomes
- PK, PD, sSEMA4D levels in CSF, serum cytokine and biomarker levels

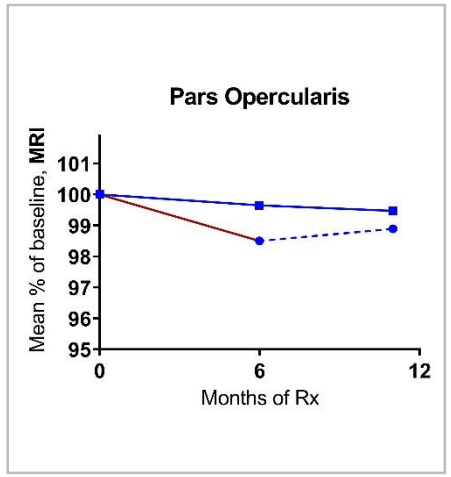
*Tabrizi, et.al. Lancet Neurology 2013; 12: 637–49

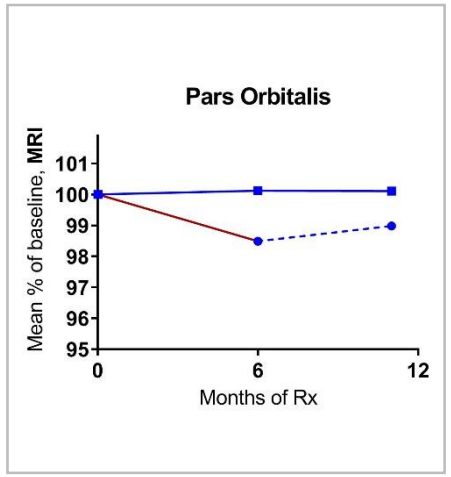
SIGNAL Study: Clinical Evidence of Brain Tissue Preservation

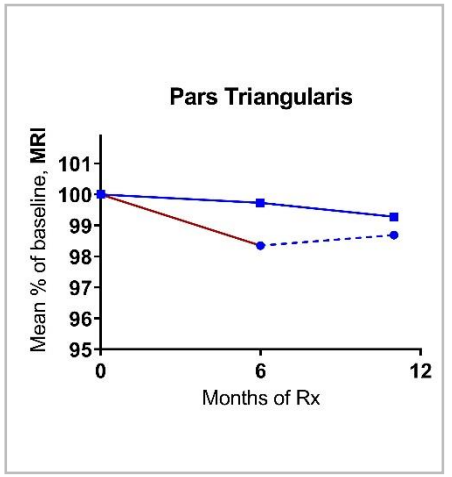
Volumetric MRI

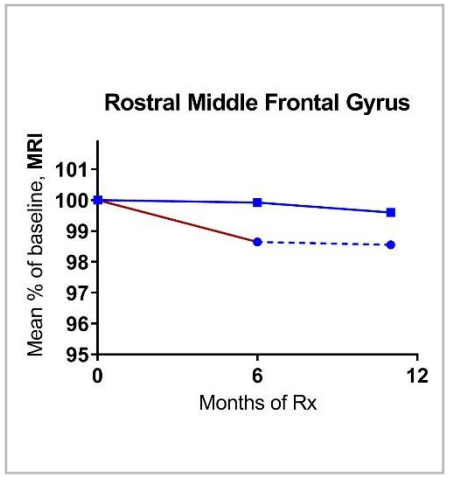


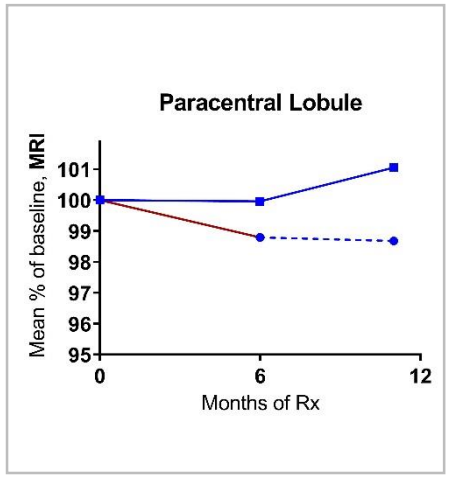


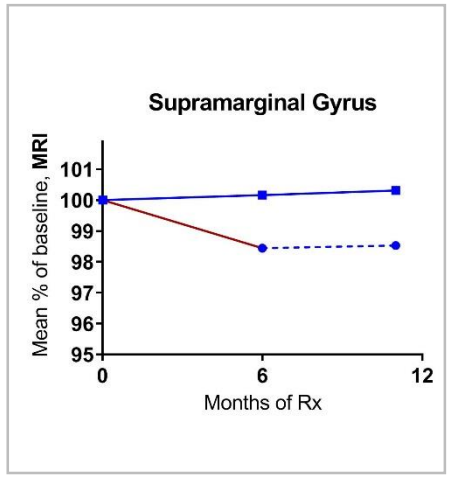


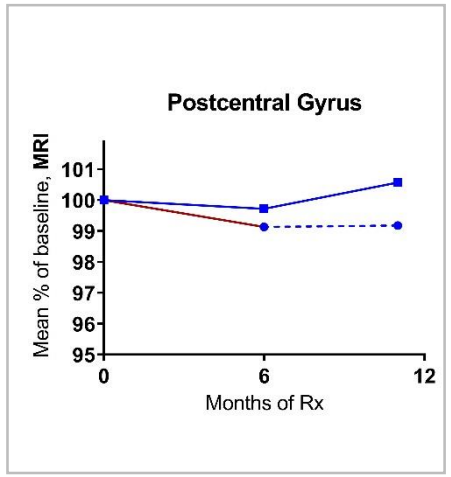












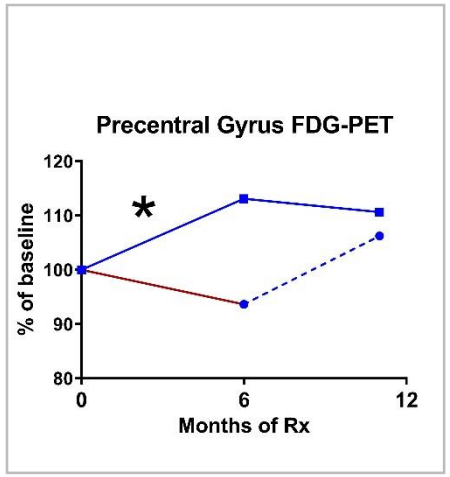
VX15

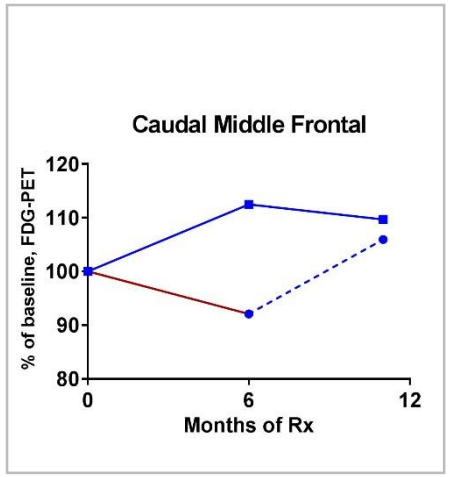
Placebo

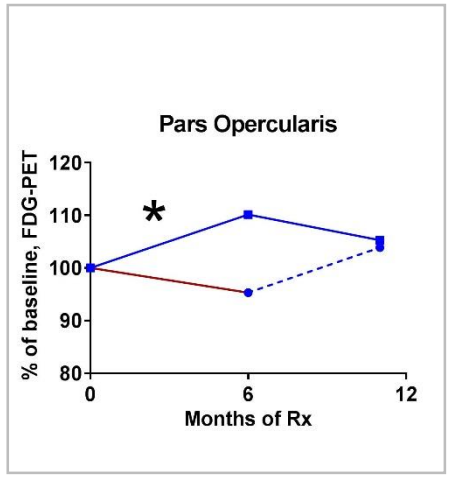
VX15 (pepinemab) after cross-over

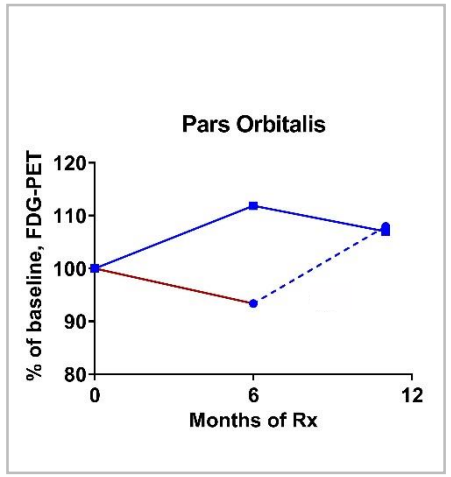
*** p<0.05 compared to placebo**

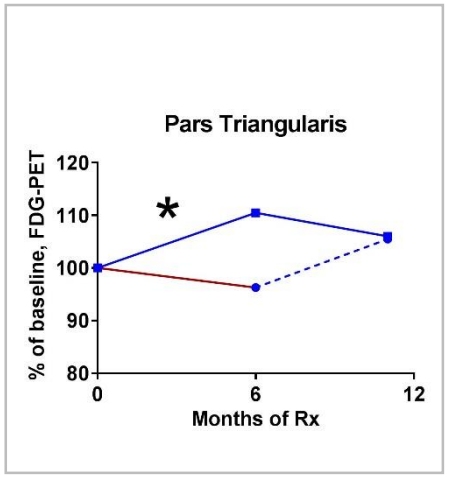
Clinical Evidence of Improved Brain Metabolic Activity in Frontal Lobe and Adjacent Parietal Regions: FDG-PET

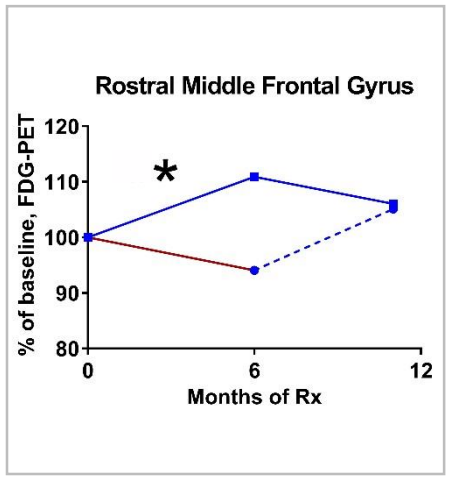


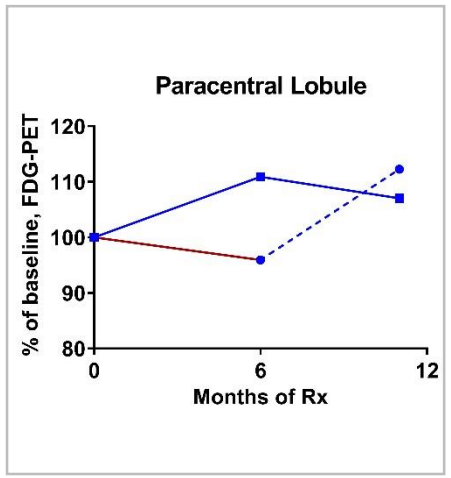


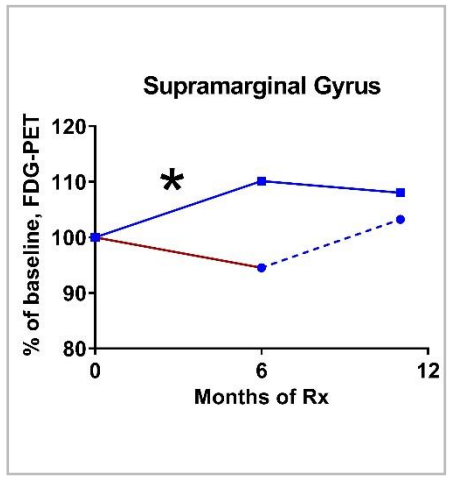


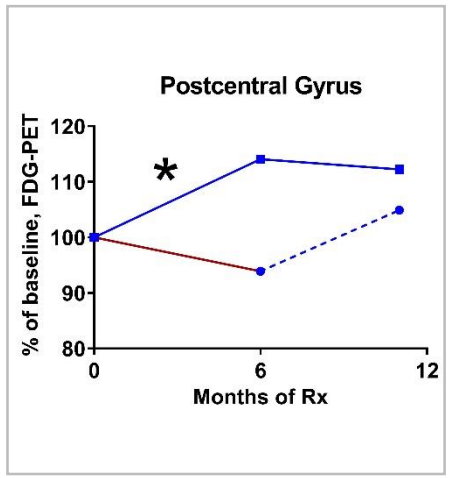


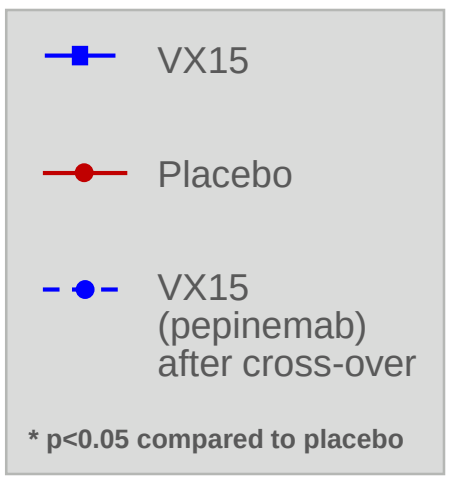












SIGNAL Cohort A Data Highlights

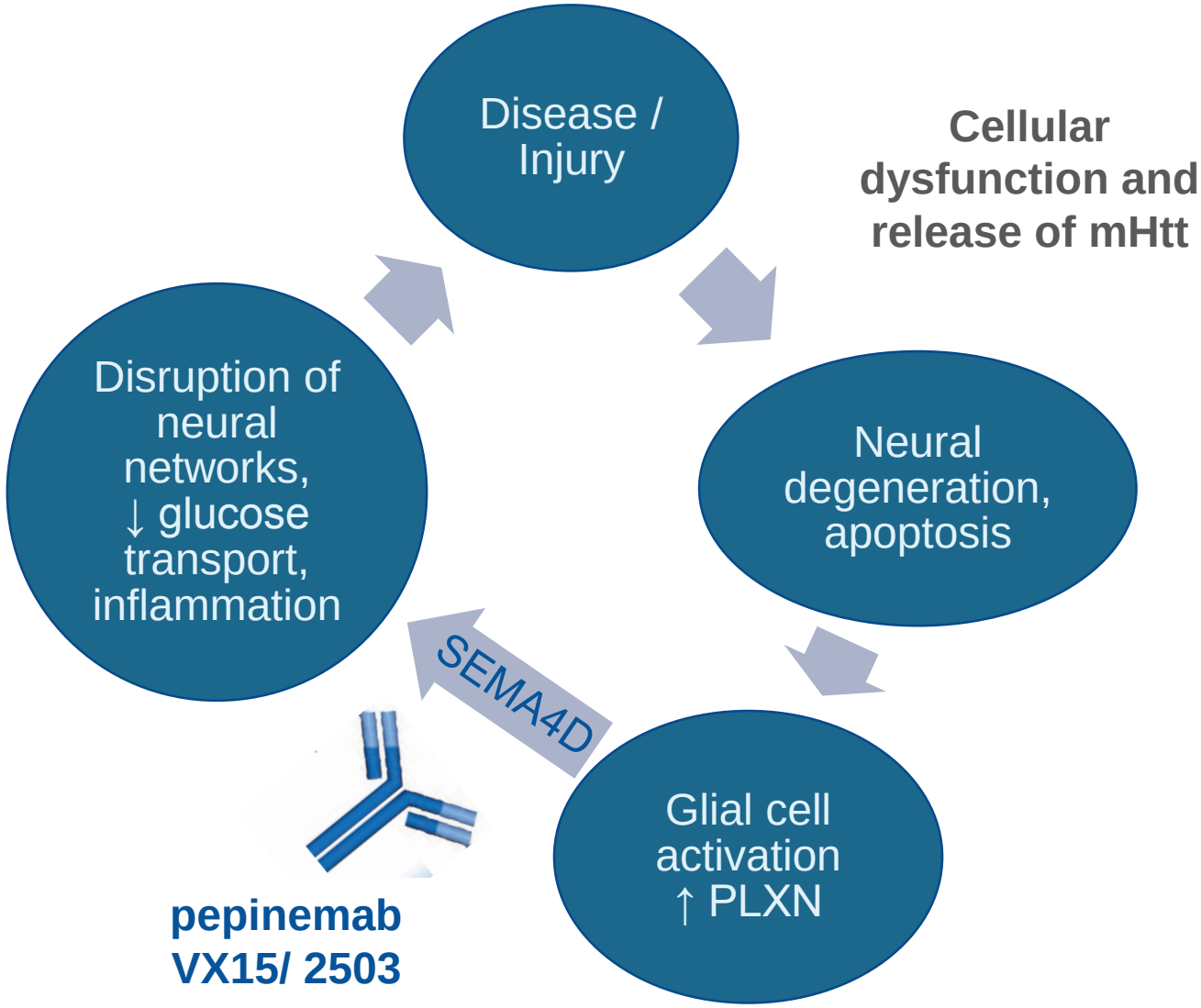
- **Cohort A** data included both brain imaging results (FDG-PET and volumetric MRI) as well as quantitative motor and cognitive assessments of treatment effects
  - **Pepinemab treatment was well tolerated**
  - **VX15 (pepinemab) treatment significantly increased metabolic activity as detected by FDG-PET**
    - FDG-PET favored pepinemab in all 31 ROI, with median increase in FDG uptake from baseline of 8.6% (range: 0.5-20.4%) compared to placebo control, achieving significance ($p<0.05$) in a majority of frontal and parietal brain ROI.
    - 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 for monitoring clinically-relevant change over time*.
  - Consistent and encouraging treatment effects on preservation of brain matter (reduced atrophy) and improvement in multiple motor and cognitive assessments were also seen in Cohort A but did not reach statistical significance
    - Pepinemab treatment trended toward stabilization of disease-related reduction in MRI volume and was favored over placebo in 24/31 ROI

- Cohort A data informed design of **Cohort B**: a total of 265 subjects consisting of two separate arms
  - 179 early manifest
  - 86 prodromal HD subjects
  - 15 to 35 months of randomized treatment without crossover

* Landau et. al., *Neurobiol Aging*. 2011; 32(7): 1207–1218

Possible Mechanism of Action in HD

- Under conditions of physiological stress or injury
  - Astrocytes and microglia transition from their normal function to an activated inflammatory state that can trigger or exacerbate neurodegeneration.
  - SEMA4D/PLXN signaling can trigger activation and cytoskeletal changes in glial cells
  - SEMA4D inhibits ability of glial precursor cells to replenish and repair damage
  - Expression of the Huntington disease mutation can induce injury and can be released by dying neurons to further activate glial cells
- **Blockade of SEMA4D can regulate glial cell activation and function, potentially restoring synaptic balance and metabolic activity**



Acknowledgements

Vaccinex, Research:

- Crystal Mallow
- Leslie Balch
- Alan Howell
- Christine Reilly

Vaccinex, Clinical Development:

- Terrence Fisher
- Alisha Reader
- Metodija Andonov
- John Parker
- Robert Parker
- Jason Condon
- William Bigham

Vaccinex Leadership:

- Maurice Zauderer, CEO
- Ernest Smith, CSO
- John Leonard, SVP
- Raymond Watkins, COO

Huntington Study Group, Andrew Feigin, Elise Kayson and Jody Goldstein and their staff at the University of Rochester Clinical Trials Coordination Center for their excellent operational support

Dr. David Oakes and his colleagues at the University of Rochester for Biostatistical and Computational analysis.

Finally, we wish to particularly thank the clinical investigators and staff at the thirty sites that are participating in the SIGNAL trial.

Patients and their families

eevans@vaccinex.com