Science in the Service of Medicine

Unique Targets.
Novel Mechanisms.
New Medicines.

Pepinemab (VX15) Antibody Treatment for Cancer and Huntington’s Disease
Evolution of multi-modal therapy in Cancer

SEMA4D Expression is Concentrated at Invasive Margin of Tumor

Colorectal (Colon26)

Mammary carcinoma (Tubo.A5)

SEMA4D at the invasive margin of the tumor forms a barrier that restricts the infiltration of anti-tumor immune cells.

Antibodies against SEMA4D neutralize this barrier and “open the gates” of the tumor to the immune system.
Semaphorin 4D (SEMA4D) Mechanism of Action

SEMA4D signals through PLXNB1 and PLXNB2 receptors to trigger dissociation of polymerized F-actin and collapse of cell’s cytoskeleton.

The cell cytoskeleton regulates process extension and cell migration.

Pepinemab (VX15 antibody) binds to SEMA4D and blocks its signaling activity.
SEMA4D Controls Infiltration of Antigen Presenting Dendritic Cells into Tumor

- Dendritic cells (DC) express PLXNB1 receptor for SEMA4D.
- Binding of SEMA4D immobilizes DC and restricts penetration into tumor.
- Antibody blockade of SEMA4D enhances migration and differentiation of DC within tumor.

- Colon26 tumor bearing mice were treated with control antibody or with anti-SEMA4D.
- Tumors were harvested 27 days post inoculation and stained for **CD11c** marker of DC lineage or **F4/80** marker of macrophage lineage.
Anti-SEMA4D Antibody Increases Cytotoxic T Cells in Tumor

T cell exclusion in Colon26 tumor

Control group
CD8+ T cells (red) do not penetrate the tumor. Most CD8+ cells are within the stroma and vessels

Anti-SEMA4D antibody
CD8+ T cells infiltrate the interior of the tumor
Anti-SEMA4D Antibody Enhances Activity of Immune Checkpoint Inhibitors (ICI)

Anti-CTLA-4 ICI in Combination with anti-SEMA4D

<table>
<thead>
<tr>
<th>Head &amp; Neck Cancer</th>
<th>Colorectal Cancer</th>
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<tbody>
<tr>
<td><strong>MOC1</strong></td>
<td><strong>Colon26</strong></td>
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- Control
- αSEMA4D
- αCTLA-4
- αSEMA4D + αCTLA-4

Significance:
- ****: p < 0.0001
- *: p < 0.05

Tumor Volume (mm³) + SEM

Days post implant vs. Day of Study

* November, 2019  I  7
Pepinemab rapidly promotes T cell infiltration into tumor bed

MSS Colorectal cancer metastasis to liver – neoadjuvant/"window of opportunity” study
Winship Cancer Institute, Emory University

Patients received neoadjuvant chemo therapy before immunotherapy and surgery
Combination immunotherapy in NSCLC following immunotherapy failure

Increase in CD8+ T cell infiltration, decrease in tumor burden

No or low tumor detected in these 2 biopsies from patients with PR

Tumor (Cytokeratin+)
CD8+ T cells
Pembrolizumab refractory
How does Vaccinex’s drug work in HD?

• Pepinemab antibody blocks SEMA4D, a molecule that triggers collapse of a cell’s cytoskeleton

• Why is SEMA4D important in HD?
  • SEMA4D is upregulated on neurons during underlying Huntington’s disease progression
  • Astrocytes express high levels of receptors for SEMA4D
  • SEMA4D triggers collapse of the astrocyte cytoskeleton which results in loss of normal astrocyte functions and gain of inflammatory activity
SEMA4D is progressively upregulated in NeuN+ neurons of HD mice

Q175 transgenic mouse model of HD

- SEMA4D expression is upregulated in HD mice as disease progresses, compared to low expression in normal controls.
- SEMA4D is upregulated early in disease, prior to onset of symptoms, which occurs ~ 5 months of age in Q175 HD transgenic mice.
- SEMA4D co-localizes with NeuN+ neurons.
Astrocytes express Plexin-B1 receptors for SEMA4D
SEMA4D triggers collapse of the astrocyte cytoskeleton

A  
Normal Control  
\[\text{PlexinB1 DAPI} \quad \text{PHALLOIDIN DAPI} \quad \text{PHALLOIDIN DAPI}\]  
rSEMA4D  

B  
\[\text{Mean phalloidin area/cell}\]  
\[\text{Untreated} \quad \text{rSEMA4D}\]  

\[\text{F-actin}\]
Astrocytes reach out to touch and interact with other brain cells

Astrocyte “arms” provide essential functional support to neurons.

• Fully cover capillaries and facilitate glucose uptake from circulation
• Cradle synapses and recycle glutamate
• Positioned to couple energy metabolism with neuronal activity
Treatment Rationale: Anti-SEMA4D Antibody can prevent inflammatory transformation of astrocytes that aggravates brain damage in HD

• Blocking SEMA4D signaling prevents collapse of the cell cytoskeleton

• This preserves normal astrocyte functions and prevents transition to inflammatory activity

  • Glucose transport in brain is one of several important normal astrocyte functions that are known to be compromised in HD

  • In a previous clinical study, Vaccinex has shown that treatment with pepinemab has a dramatic effect in preventing loss of glucose transport in brain
% Change from baseline for each treatment group (FDG-PET)

**Left panel (A):** Average change in FDG-PET signal for each brain region of interest (ROI) during 6 months of treatment in the placebo group (n=8) expressed as a % of baseline at start of treatment.

**Right panel (B):** Average change in FDG-PET signal for each ROI during 6 months of treatment in the VX15 group (n=11).

Each dot represents one of 31 ROI. Left and Right hemispheres were highly correlated with Pearson correlation coefficient = 0.976 at p<0.0001. Only the mean of Left and Right is plotted for each ROI.

- **frontal lobe (red)**
- **parietal lobe (green)**
Huntington’s Disease Clinical Trial Design: Cohort B

Cohort B Group 1

179 early manifest subjects randomized 1:1 Drug:Placebo

Double-blind treatment with VX15 (pepinemab)

Database lock and analysis for Cohort B

2020

18 months

1 month safety follow-up

Cohort B Group 2

86 late prodromal subjects randomized 1:1 Drug:Placebo

Double-blind treatment with VX15 (pepinemab)

Database lock and analysis for Cohort B

2020

18 or 36 months

1 month safety follow-up

Enrollment in Cohort B was completed on December 31, 2018
Last patient last visit anticipated late June, 2020

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