

# Pepinemab – Anti-SEMA4D Antibody for Cancer Immunotherapy and Neurodegenerative Disease



Unique Targets

Novel Mechanisms

New Medicines

## Corporate Presentation

February 2022

VCNX

# Forward Looking Statements

To the extent that statements contained in this presentation 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. Such statements include, but are not limited to, statements about the Company’s plans, expectations and objectives with respect to the results and timing of clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Huntington’s and Alzheimer’s disease and other indications, and other statements identified by words such as “may,” “will,” “appears,” “expect,” “planned,” “anticipate,” “estimate,” “intend,” “hypothesis,” “potential,” “advance,” and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of the Company’s 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, the risks related to the Company’s dependence on its lead product candidate pepinemab, the ability to leverage its ActivMAb® platform, the impact of the COVID-19 pandemic, and other matters that could affect the Company’s development plans or the commercial potential of its product candidates. Except as required by law, the Company assumes 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 the Company’s periodic reports filed with the Securities and Exchange Commission (“SEC”) and the other risks and uncertainties described in the Company’s most recent year end Annual Report on Form 10-K and subsequent filings with the SEC.



# NOVEL ANTIBODY THERAPEUTICS TO TARGET UNMET NEEDS



## ✓ Novel Mechanistic Approach

Lead product: Pepinemab

First in class: Blocks a unique target, Semaphorin 4D

Humanized IgG4 monoclonal antibody,

## ✓ Clinical Proof of Concept

## ✓ Advanced clinical programs with near-term opportunities for monetization by partnering

### Pepinemab

SEMA4D is activated

in immune and central nervous systems in response to stress/disease

#### Cancer Immunology

- ❖ Facilitates infiltration of T cells and reduce immunosuppression to potentially overcome immune resistance
- ❖ Data suggest pepinemab may **complement immune checkpoint therapies without added toxicity**
- ❖ Completed Phase 2 trial in lung cancer
- ❖ Ongoing Phase 1b/2 trial in head and neck cancer, collaboration with Merck







#### Neurologic Diseases

- ❖ Targets underlying disease pathology
- ❖ Data suggest ability to repair and restore normal functions
- ❖ **Broad application**
- ❖ Completed Phase 2 trial in Huntington's Disease - *Phase 3-ready asset*
- ❖ Ongoing Phase 1/2a trial in Alzheimer's Disease



# PIPELINE and MILESTONES



Research/Preclinical	Phase 1	Phase 2	Phase 3	Partner/Funding	Milestone
<b>Pepinemab Antibody Platform (anti-Semaphorin 4D Mab)</b>					
<b>Oncology</b>					
Pepinemab COMBO with Avelumab in <b>Non Small Cell Lung Cancer</b>			<b>CLASSICAL -Lung</b>	 Merck, KGaA Darmstadt	Complete, Published 2021
Pepinemab COMBO with Pembrolizumab in <b>Head and Neck Cancer</b>			<b>KEYNOTE- B84</b>	 Merck, MSD	Ongoing <b>Next data Q2 2022</b>
Phase 1b Safety: Complete					
<b>Neurology</b>					
Pepinemab in <b>Huntington's Disease</b> (Orphan Drug and Fast Track Designations)					Complete, <b>Publish 2022</b>
Pepinemab in <b>Alzheimer's Disease</b>				 	Ongoing <b>Data H1 2023</b>

All Studies Sponsored by:



# PEPINEMAB, IMMUNO-ONCOLOGY



Unique mechanism of action

Neutralizes the SEMA4D barrier at tumor boundary and inhibits immune suppressor cells to facilitate anti-tumor immune cells

Data suggests synergy with immune checkpoint therapy

Well tolerated

## Status

## Summary

### Complete



#### Phase 1b/2 Non Small Cell Lung Cancer (NSCLC)

Data published in Clinical Cancer Research, 2021  
Pepinemab Combination with Bavencio™

Sponsored by:



Co-funded by:

EMD Serono/Merck KGaA, Darmstadt



### CLASSICAL-Lung

- Well tolerated
- Anti-tumor activity observed in some patients with challenging PD-L1 negative or low tumors
- Anti-tumor activity observed in some patients whose cancer was resistant to prior therapy with single-agent checkpoint inhibitors
- Increased penetration of cytotoxic T cells following treatment

### Initiated Q2 2021



#### Phase 1b/2 Head and Neck Cancer (R/M HNSCC)

Phase 1b complete  
Phase 2 data expected 2H 2022

Pepinemab Combination with Keytruda™

Sponsored by:



Collaboration with: Merck, MSD



### Head and Neck Cancer (Keynote B84)

- RATIONALE: High levels of myeloid derived suppressor cells (MDSC) are induced by SEMA4D and are a source of resistance to immune checkpoint therapy
- First line treatment for recurrent or metastatic HNSCC
- 18 sites, US, n=62
- Phase 1b: Among 3 patients enrolled, 2 complete responses (CR)

Currently exploring pharma collaboration

# PEPINEMAB, NEURODEGENERATIVE DISEASE

## Unique mechanism of action

We believe pepinemab has the potential to block chronic glial activation and restore their normal support functions.

## Broadly applicable approach

Targets common trigger of reactive inflammation which contributes to & amplifies neurodegeneration



## Status

## Summary

### Complete



**Phase 2 Huntington's Disease**  
Double-blind, Placebo-controlled

Sponsored by:



Granted Orphan Disease  
and Fast Track Designation by FDA

### Huntington's Disease (SIGNAL)

- Well tolerated
- Co-primary endpoints did not achieve statistical significance (CGIC and family of 2 cognitive assessments)
- Improvements observed in cognitive assessments
- Observed reduced brain atrophy (vMRI) and restored loss of metabolic activity (FDG-PET)
- *Phase 3-ready asset*



### Initiated Q2 2021



**Phase 1/2a Alzheimer's Disease**  
Double-blind, Placebo-controlled

Data expected H1 2023

Sponsored by:



Funding by:



### Alzheimer's Disease (SIGNAL-AD)

- Primary endpoint: Safety
- Key efficacy assessments: Cognition and metabolic activity (FDG-PET)
- 14 sites, US
- 40 participants (n=20/treatment arm)

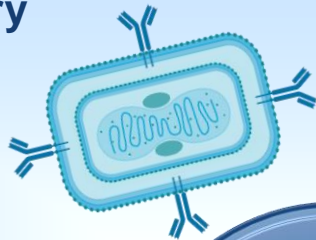


Currently exploring pharma collaboration

# ActivMab Discovery Solutions

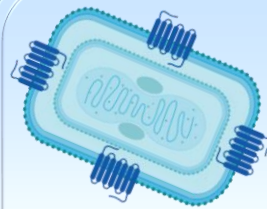
## Antibody Library

Diverse Antibody Library ( $10^{10}$ )  
Screened as Human IgG in Mammalian Cells



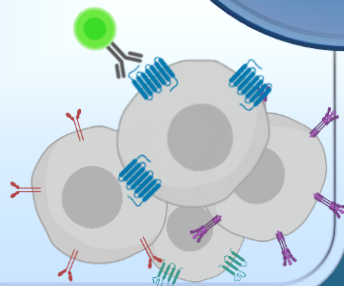
## Antigen Virus

Virions expressing Complex Membrane Proteins for Antibody Discovery



## Target Identification

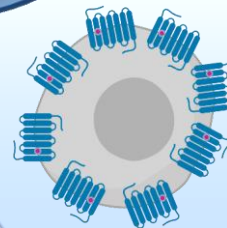
Large cDNA library expressed in Mammalian Cells



**ActivMab**  
Technology  
Discovery Solutions

## Protein Optimization

Mammalian expression of mutant libraries to enhance expression



Unique capability for selection of high value antibodies against hard-to-target multi-pass membrane receptors (i.e. GPCRs, ion channels)

Designed as a sustainable engine for value creation through pipeline expansion and strategic collaborations

Active collaborations with two major pharma and multiple biotech partners

A large, dark blue, semi-transparent rectangular area covers the center of the slide. Inside this area, the text "Pepinemab Antibody for Cancer Immunotherapy" is written in white. The background of this area is a faint, grayscale microscopic image showing various cell-like structures, including some that appear to be clusters of cells and others that are more elongated and fibrous.

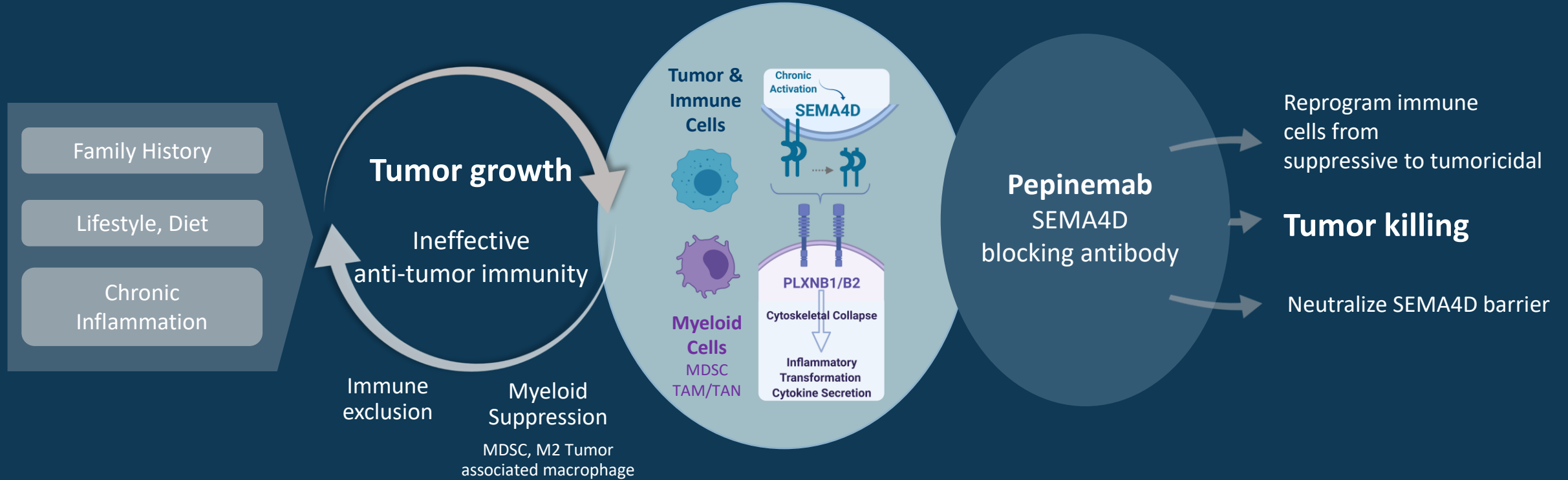
# Pepinemab Antibody for Cancer Immunotherapy

■ Unique Targets ■ Novel Mechanisms ■ New Medicines



# PROPOSED MECHANISM OF ACTION:

Preclinical and clinical evidence suggests pepinemab may reprogram underlying pathology in cancer

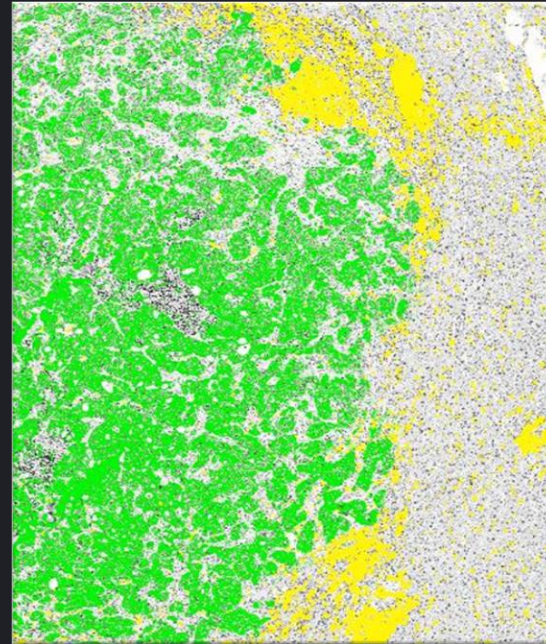


# WHY DOES IMMUNE RESPONSE FAIL IN TUMORS?

## Immune Exclusion

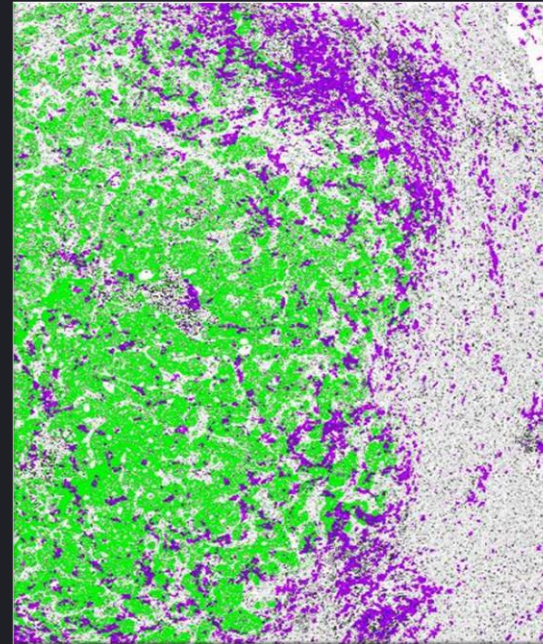
Activated T-cells and dendritic cells can't penetrate tumor

Sema4D is expressed at tumor margin



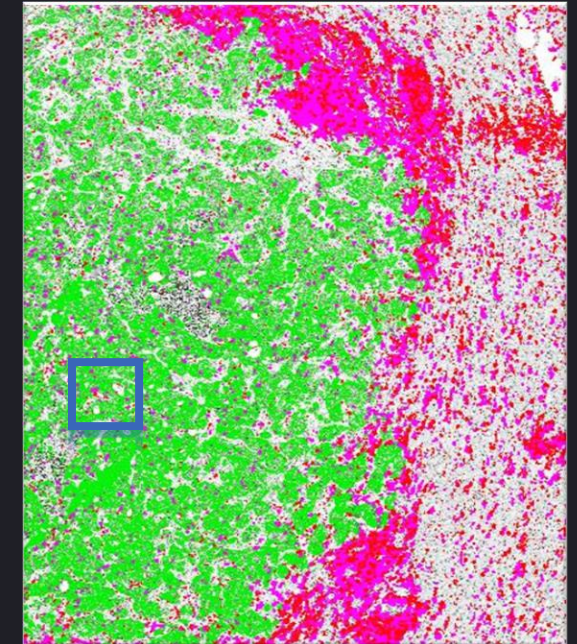
● Tumor ● SEMA4D

Sema4D binds PLXN receptors on DCs and restricts penetration



● Tumor ● Dendritic Cells (CD11c)

T-cells are excluded from tumor



● CD8+ ● CD4+ T Cells

**Pro-inflammatory cells are excluded from tumor and build up at the invasive edge**

CD8 T cells align with Sema4D at the invasive edge of the tumor. Most of these excluded T-cells express Sema4D.

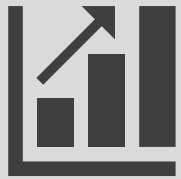
Dendritic Cells express receptors for SEMA4D and are heavily excluded at the invasive edge.

*Human metastatic colorectal tumor, in collaboration with Emory University (NCT03373188)*

# UNIQUE MECHANISM

Pepinemab:

1



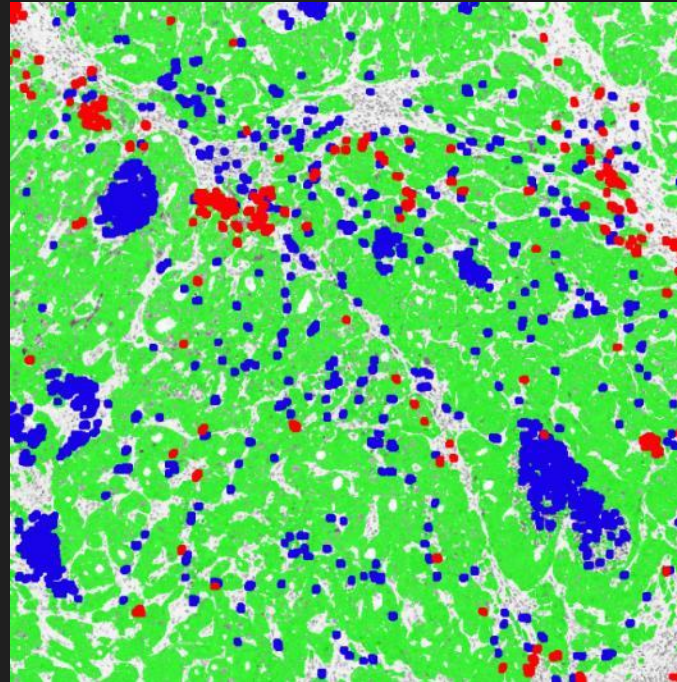
↑ cytotoxic T cells

2



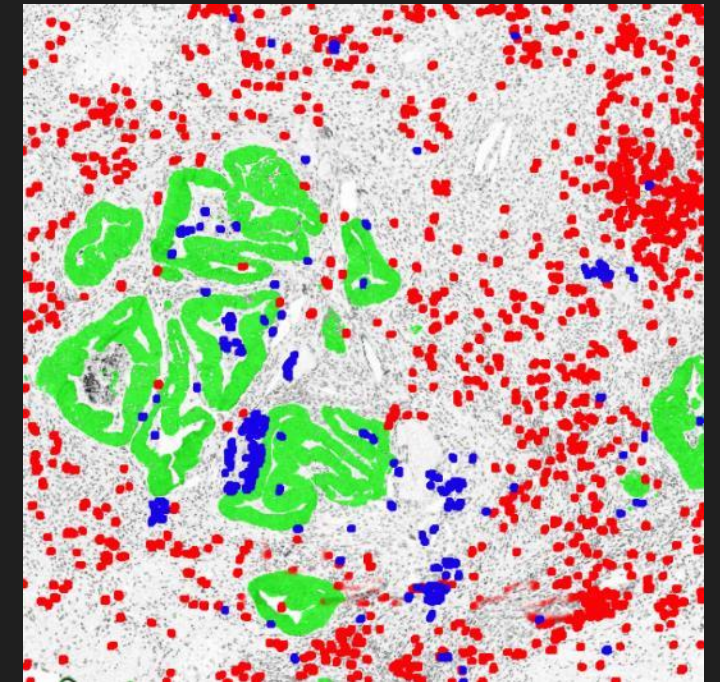
↓ inhibitory suppressor cells

**No treatment**  
Low CD8+ T cells  
High Tumor content and MDSC



● Myeloid Derived Suppressor Cells (MDSC)

**Pepinemab**  
High CD8+ T cells  
Low tumor content and MDSC



● Tumor ● T Cells

**Biopsies from patients with metastatic MSS Colorectal Cancer**

*Human metastatic colorectal tumor, in collaboration with Winship Cancer Institute, Emory University integrated biomarker study (NCT03373188), Wu et al. Ann Surg Oncol. 2021*

# COMBINATION THERAPY

Preclinical data suggests that pepinemab complements other immunotherapies

## Pepinemab

Facilitates T-cell infiltration  
Reduces immune suppression



## Immune Checkpoint Inhibitors

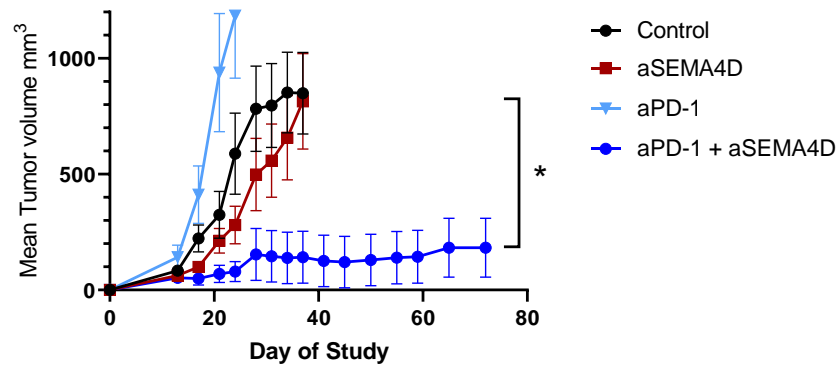
Sustain T-cell activity



Combination therapy to overcome multiple immune resistance mechanisms

## Combination therapy: Preclinical Data

Colon26 Mouse Tumor Model



Data suggest that SEMA4D blockade complements other immune-activating therapies, including

- anti-PD-1/L1
- anti-CTLA-4
- anti-LAG3
- anti-TGF- $\beta$
- DC vaccine, etc

Research Article

### Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function

Paul E. Clavijo<sup>1</sup>, Jay Friedman<sup>1</sup>, Yvette Robbins<sup>1</sup>, Ellen C. Moore<sup>1</sup>, Ernest Smith<sup>2</sup>, Maurice Zauderer<sup>2</sup>, Elizabeth E. Evans<sup>2</sup>, and Clint T. Allen<sup>1,3</sup>

Cancer Immunology Research



Research Article

### Antibody Blockade of Semaphorin 4D Promotes Immune Infiltration into Tumor and Enhances Response to Other Immunomodulatory Therapies

Elizabeth E. Evans, Alan S. Jonason Jr, Holm Bussler, Sebold Torno, Janaki Veeraraghavan, Christine Reilly, Michael A. Doherty, Jennifer Seils, Laurie A. Winter, Crystal Mallow, Renee Kirk, Alan Howell, Susan Giralico, Maria Scrivens, Katya Klimatcheva, Terrence L. Fisher, William J. Bowers, Mark Paris, Ernest S. Smith, and Maurice Zauderer

Cancer Immunology Research

# CLINICAL POC

## Phase 1b/2 CLASSICAL-Lung

- Well tolerated.** Pepinemab does not appear to increase immune-related toxicities of partner drug
- Unmet Need: *PD-L1 low/negative tumors***
  - Reported single agent anti-PDx:  
**ORR ~10-15%**
  - Combination with pepinemab:  
**ORR 25-33%**
- Unmet Need:** Antitumor activity observed in *immune checkpoint resistant/refractory tumors*

Sponsored by:



Co-funded by:



NCT03268057

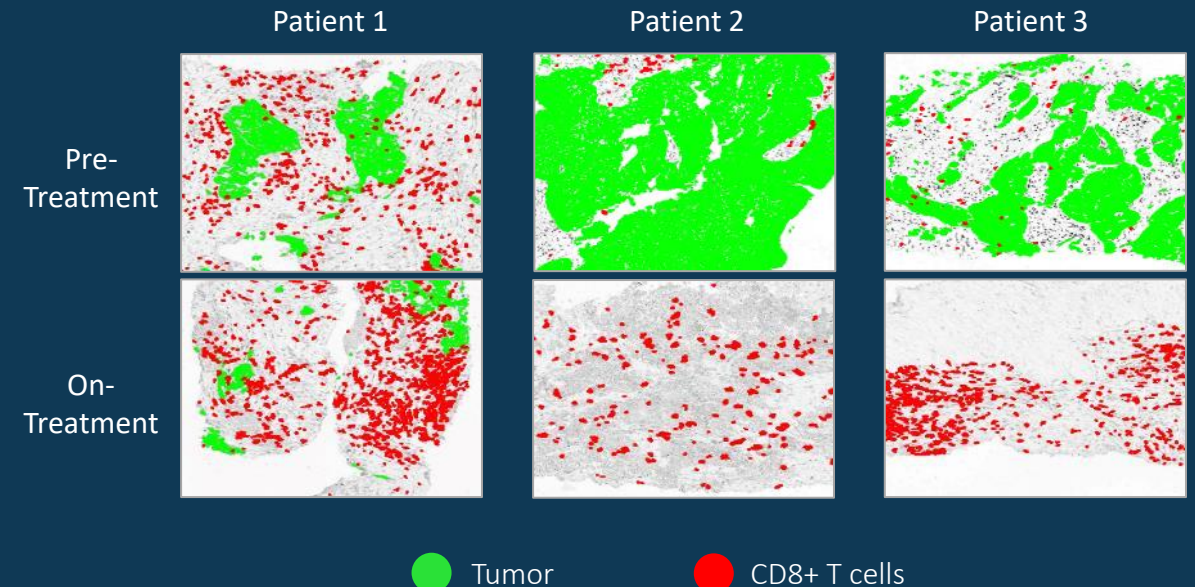


### A Phase 1b/2 Study of Pepinemab in Combination with Avelumab in Advanced Non-Small Cell Lung Cancer

Michael Rahman Shafique<sup>1</sup>, Terrence Lee Fisher<sup>2</sup>, Elizabeth E. Evans<sup>2</sup>, John E. Leonard<sup>2</sup>, Desha Rae Electa Pastore<sup>2</sup>, Crystal L. Mallow<sup>2</sup>, Ernest Smith<sup>2</sup>, Vikas Mishra<sup>2</sup>, Andreas Schröder<sup>3</sup>, Kevin M. Chin<sup>4</sup>, Joseph Thaddeus Beck<sup>5</sup>, Megan Ann Baumgart<sup>6</sup>, Ramaswamy Govindan<sup>7</sup>, Nashat Y. Gabrail<sup>8</sup>, Alexander I. Spira<sup>9</sup>, Nagashree Seetharamu<sup>10</sup>, Yanyan Lou<sup>11</sup>, Aaron Scott Mansfield<sup>12</sup>, Rachel E. Sanborn<sup>13</sup>, Jonathan W. Goldman<sup>14</sup>, and Maurice Zauderer<sup>2</sup>



Data suggests increased penetration of cytotoxic T cells.



# RATIONALE FOR TREATMENT OF HNSCC

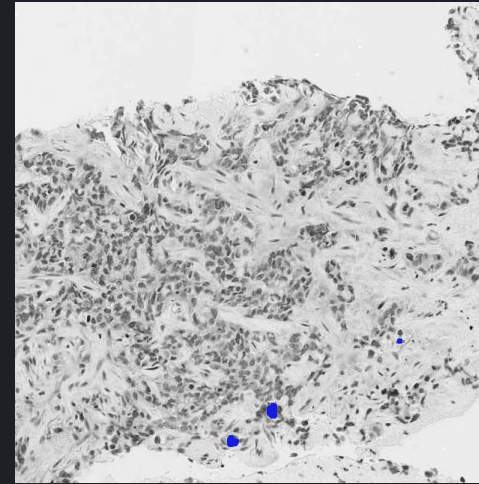
## Head and Neck cancer (HNSCC)

- Data suggest that SEMA4D is strongly expressed in HNSCC & induces high levels of myeloid derived suppressor cells (MDSC)
- Relatively low (17-19%) response rate to immune checkpoint therapy in HNSCC

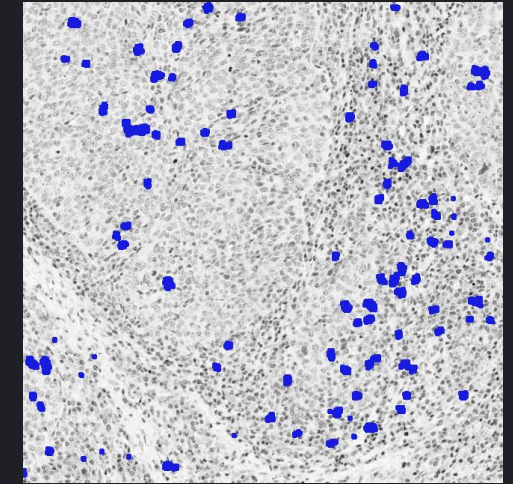


**Hypothesis:** Inhibiting MDSC with pepinemab may enhance response to pembrolizumab in HNSCC

### ● Myeloid Derived Suppressor Cells (MDSC)

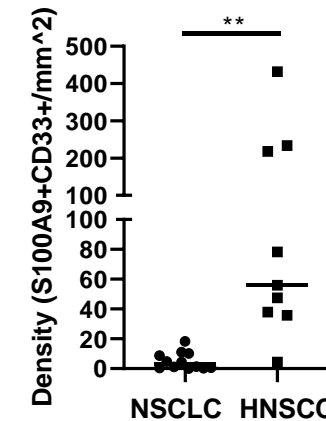


NSCLC



HNSCC

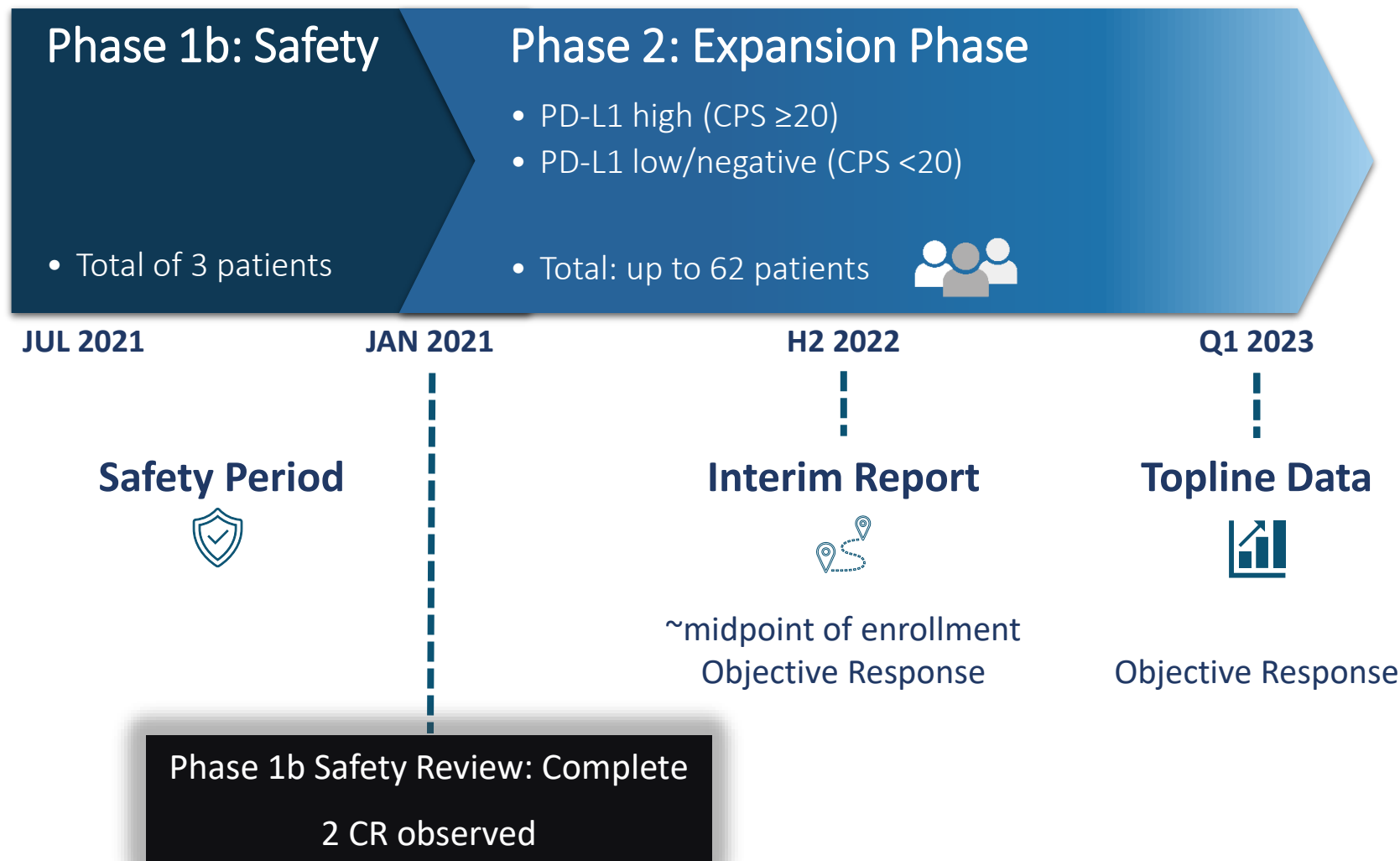
### MDSC Density NSCLC vs HNSCC



# HEAD AND NECK CANCER TRIAL

- All patients receive standard of care Keytruda®, plus pepinemab for first-line treatment
- 18 sites planned, USA
- Open-label, continuous monitoring
- Ph1b Safety: COMPLETE
  - Appeared to be well tolerated
  - RP2D: 20mg/kg pepi and 200mg pembro, Q3W
  - **Among 3 patients enrolled, 2 experienced complete response (CR)**
  - 1 confirmed CR, 1 unconfirmed CR (pending), 1 non-evaluable
- Ph2 Expansion: Accruing

KEYNOTE B84: pepinemab + Keytruda® for first-line treatment of recurrent or metastatic head and neck cancer



NCT04815720



# KEYNOTE-B84

## Case Studies, Phase 1b Safety Cohort

	Biopsy	Scans			Biomarkers	Adverse Events
	week 5	week 9	week 15	week 21		
<b>Case Study # 1: CR (confirmed)</b> <i>Oropharyngeal cancer</i> <i>Target lesions: metastatic lung lesions (Left 11mm, Right 15mm)</i>	NO malignancy	19% decrease, SD	100% decrease, CR	Confirmed, CR	PD-L1 CPS<20  HPV negative	<i>none of notable severity</i>
<b>Case Study # 2: CR (un-confirmed)</b> <i>Larynx cancer with direct invasion into thyroid and neck</i> <i>Target lesions: neck mass (37mm)</i>	NO malignancy	100% decrease, CR	Confirmatory Scan Pending	Scan Pending	PD-L1 CPS<1  HPV negative	<i>Grade 1 rash</i>
<b>Case Study # 3: Non-evaluable</b> <i>Cancer of the tongue</i> <i>Investigator Review: clinical progression withdrew from study at Week 6</i>	Tumor Present	Non-evaluable			PD-L1 CPS<20  HPV positive	Unrelated (SAE) attributed to a pre-existing co-morbidity (diabetes)



# KEYNOTE B-84

## Biomarkers

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- **PD-L1 low (CPS <20)**
  - historically low response rates to anti-PD-1/L1 antibodies administered as single agents. (1)
- **HPV-negative**
  - HPV-negative HNSCC have high levels of myeloid suppression (2) and tend to be more resistant to anti-PD-1/L1 antibodies.
  - **Preclinical data suggest that SEMA4D induces myeloid derived suppressor cells in HNSCC (3).**

### Biomarkers

#### Case Study # 1: CR (confirmed)

*Oropharyngeal cancer*  
*Target lesions: metastatic lung lesions*  
*(Left 11mm, Right 15mm)*

PD-L1  
**CPS<20**  
  
HPV  
**negative**

#### Case Study # 2: CR (un-confirmed)

*Larynx cancer with direct invasion into thyroid and neck*  
*Target lesions: neck mass (37mm)*

PD-L1  
**CPS<1**  
  
HPV  
**negative**

#### Case Study # 3: Non-evaluable

*Cancer of the tongue*  
*Investigator Review: clinical progression*  
*withdrew from study at Week 6*

PD-L1  
**CPS<20**  
  
HPV  
**positive**

1. Keynote-048, Lancet 2019, [http://dx.doi.org/10.1016/S0140-6736\(19\)32591-7](http://dx.doi.org/10.1016/S0140-6736(19)32591-7)
2. Cillo et al., 2020, Immunity, <https://doi.org/10.1016/j.immuni.2019.11.014>
3. Clavijo PE. 2019 CIR. DOI: 10.1158/2326-6066.CIR-18-0156

# PEPINEMAB FOR IMMUNO-ONCOLOGY SUMMARY & NEXT STEPS



## Mechanism of Action

Preclinical data suggest:  
Facilitate infiltration of T cells  
and dendritic cells

Reduce immunosuppression



## Safety and Tolerability

**Well tolerated**


Does not appear to enhance  
immune-related toxicities of  
partner drug



## Observed Clinical Activity

**Reprogram** immune infiltrate  
in TME

Potential to overcome immune  
resistance in  
PD-L1 negative/low tumors  
and ICI resistant/refractory tumors

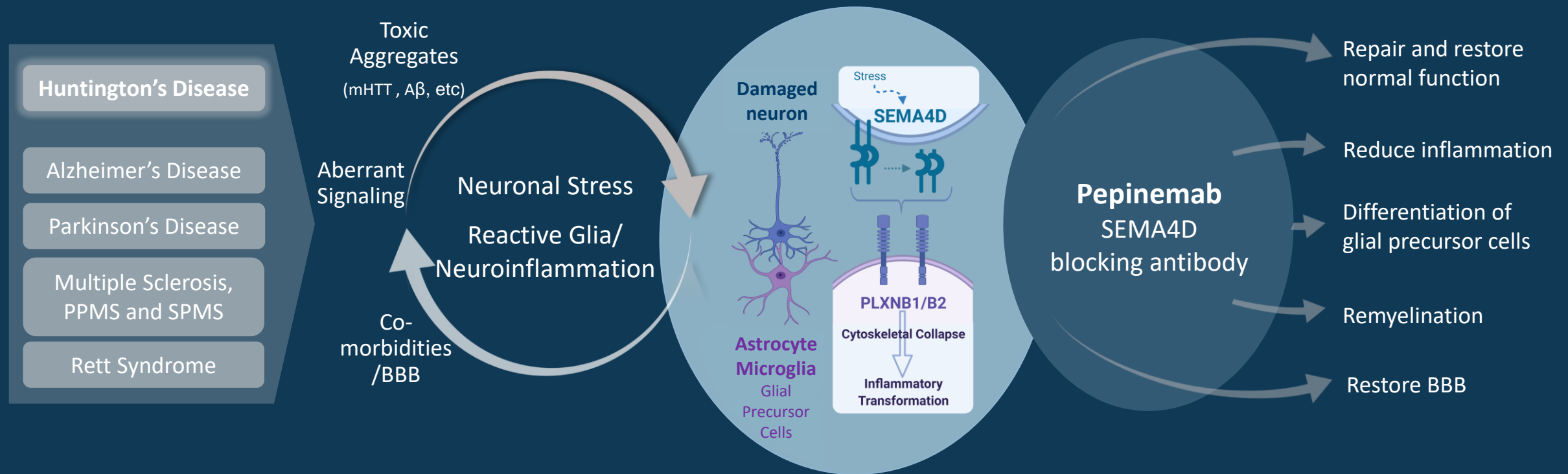
A large, dark blue-tinted microscopic image of brain tissue, showing various cellular structures and folds, serving as a background for the title text.

# Pepinemab Antibody for treatment of Neurodegenerative Disease

■ Unique Targets ■ Novel Mechanisms ■ New Medicines

# PROPOSED MECHANISM OF ACTION:

Preclinical and clinical evidence suggests pepinemab may reprogram underlying pathology in CNS diseases



# Preclinical Neurology Models

## SEMA4D antibody blockade improves disease phenotype

Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease

Amber L. Southwell<sup>a</sup>, Sonia Franciosi<sup>a</sup>, Erika B. Villanueva<sup>a</sup>, Yuanyun Xie<sup>a</sup>, Laurie A. Winter<sup>b</sup>, Janaki Veeraraghavan<sup>b</sup>, Alan Jonason<sup>b</sup>, Boguslaw Felczak<sup>a</sup>, Weining Zhang<sup>a</sup>, Vlad Kovalik<sup>a</sup>, Sabine Waltl<sup>a</sup>, George Hall<sup>a</sup>, Mahmoud A. Pouladi<sup>c,d</sup>, Ernest S. Smith<sup>b</sup>, William J. Bowers<sup>b</sup>, Maurice Zauderer<sup>b</sup>, Michael R. Hayden<sup>a,\*</sup>

2015 *Neurobiology of Disease*



SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease

Ernest S. Smith<sup>a</sup>, Alan Jonason<sup>a</sup>, Christine Reilly<sup>a</sup>, Janaki Veeraraghavan<sup>a</sup>, Terrence Fisher<sup>a</sup>, Michael Doherty<sup>a</sup>, Ekaterina Klimatcheva<sup>a</sup>, Crystal Mallow<sup>a</sup>, Chad Cornelius<sup>a</sup>, John E. Leonard<sup>a</sup>, Nicola Marchi<sup>b</sup>, Damir Janigro<sup>b</sup>, Azeb Tadesse Argaw<sup>c</sup>, Trinh Pham<sup>c</sup>, Jennifer Seils<sup>a</sup>, Holm Bussler<sup>a</sup>, Sebald Torno<sup>a</sup>, Renee Kirk<sup>a</sup>, Alan Howell<sup>a</sup>, Elizabeth E. Evans<sup>a</sup>, Mark Paris<sup>a</sup>, William J. Bowers<sup>a</sup>, Gareth John<sup>c</sup>, Maurice Zauderer<sup>a,\*</sup>

<sup>a</sup> Vaccinex, Inc., Rochester, NY 14620, USA

2014 *Neurobiology of Disease*





International Journal of  
*Molecular Sciences* 2021

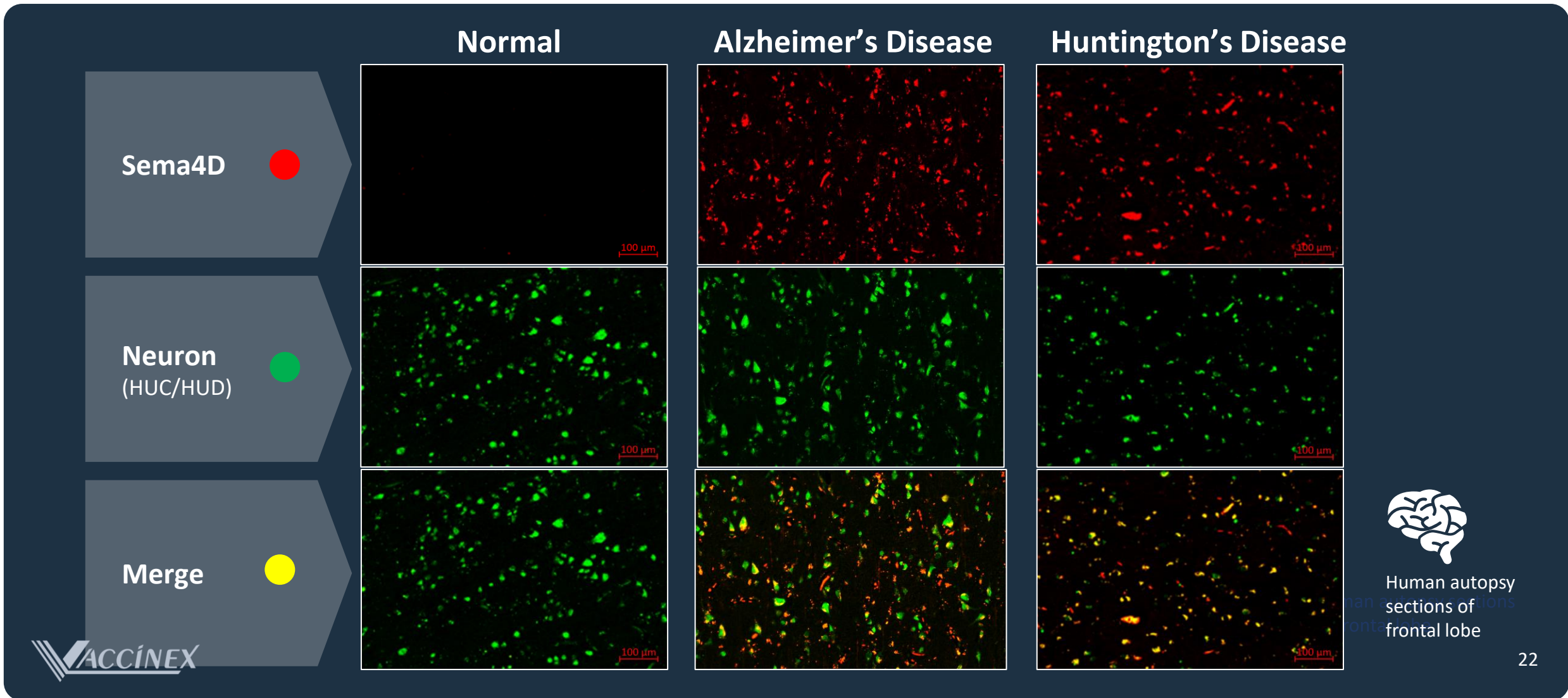


Article

### Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a Rett Syndrome Mouse Model

Yilin Mao<sup>1,2</sup>, Elizabeth E. Evans<sup>3</sup>, Vikas Mishra<sup>3</sup>, Leslie Balch<sup>3</sup>, Allison Eberhardt<sup>3</sup>, Maurice Zauderer<sup>3,t</sup> and Wendy A. Gold<sup>1,2,4,5,\*,†</sup>

# SEMA4D IS OBSERVED TO BE UPREGULATED IN NEURONS DURING UNDERLYING DISEASE PROGRESSION

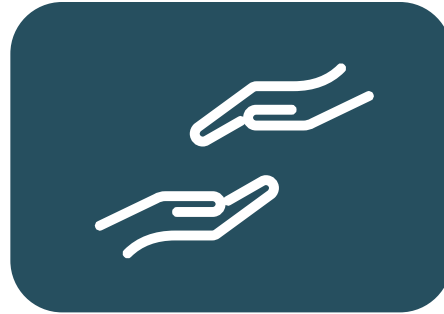


# HUNTINGTON'S DISEASE



## Genetic Disease

HD is caused by dominant mutation in a single gene.



## Unmet need

No approved treatments to alter the course of Huntington's Disease.

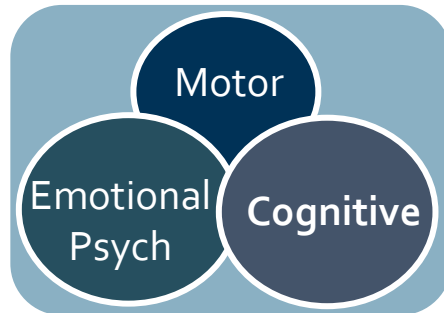


**~40,000 individuals**

with manifest disease in US

**>150,000 more**

at risk of inheriting mutation



## Symptoms

Cognitive impairment = most significant impact on daily life (FDA Voice of the Patient)

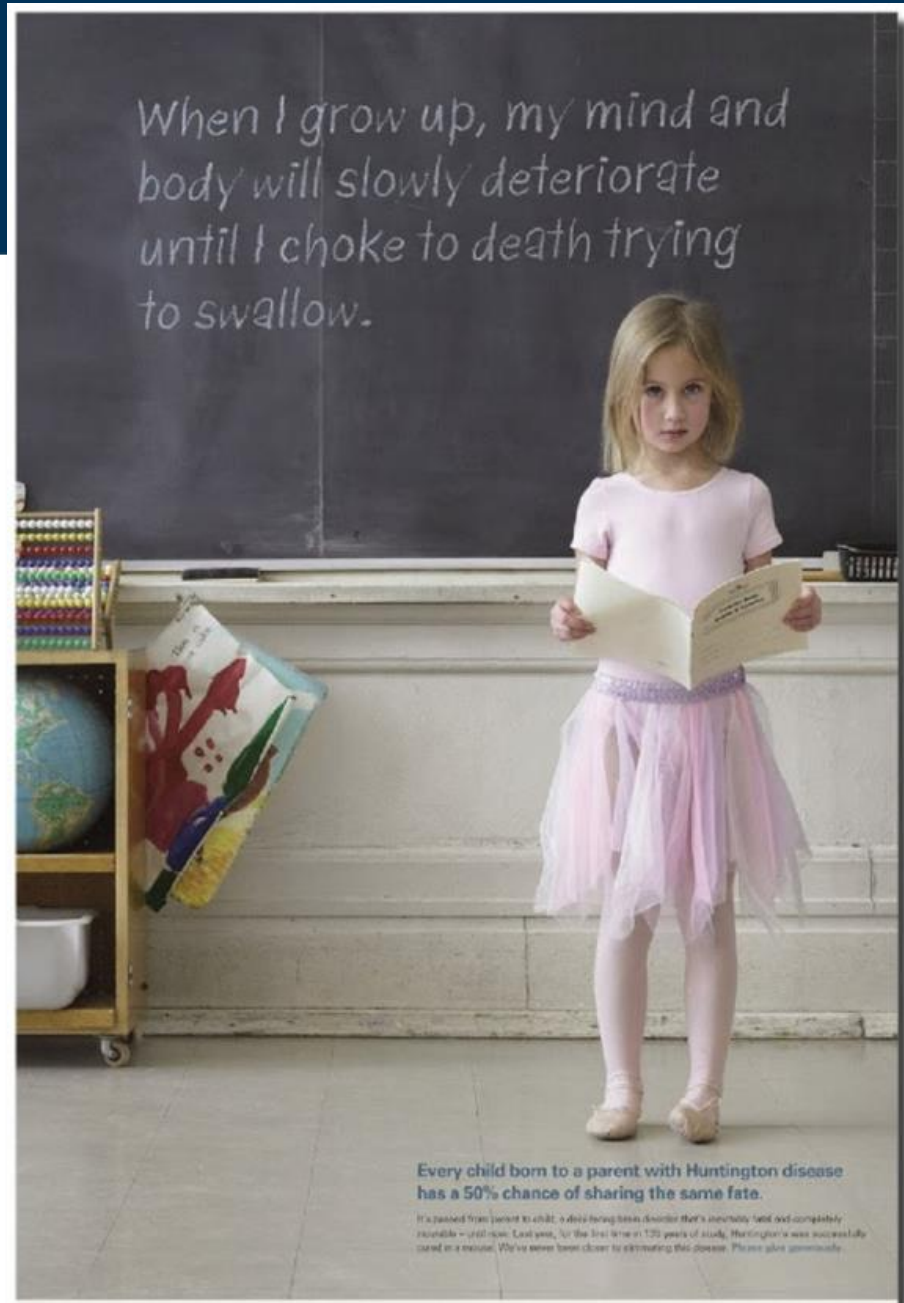


Photo credit: Huntington Society of Canada

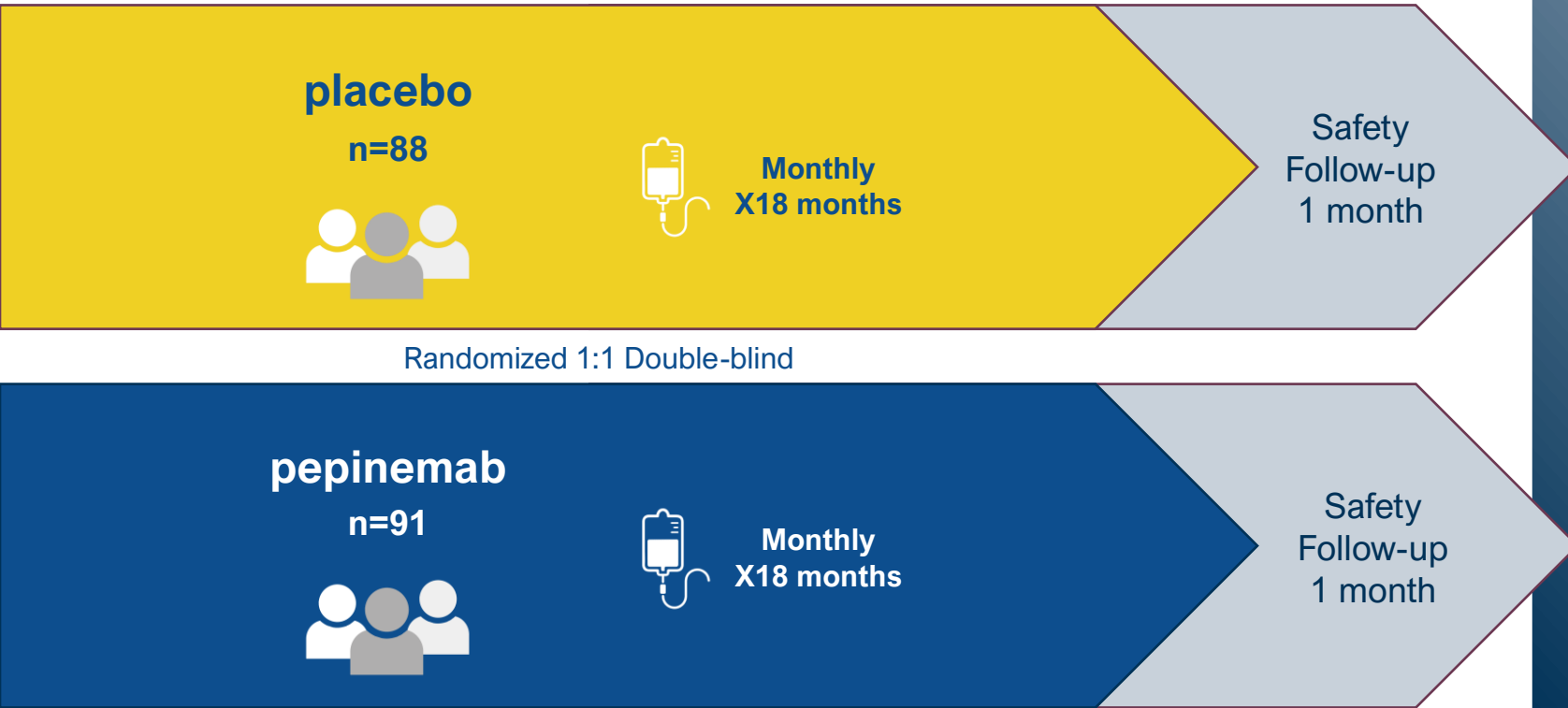
# HUNTINGTON'S DISEASE

## Abbreviated Clinical Trial Design\*



Orphan Disease and  
Fast Track Designations

### Early Manifest HD



### Data Analysis and Study Objectives

- Safety and tolerability**
- Primary Efficacy Outcomes (mITT)**
  - Cognitive Function
  - CGIC
- Key Exploratory and Biomarker Outcomes**
  - Brain Volume (vMRI)
  - Metabolic imaging (FDG-PET)
- Post-hoc Subgroup Analyses**

NCT02481674. \*Note 86 subjects with Late Prodromal HD were also included in study



# ABBREVIATED SAFETY AND BASELINE CHARACTERISTICS



mITT: Early Manifest HD

Pepinemab (PEPI)  
SEMA<sub>4</sub>D blocking  
antibody is well  
tolerated

Early Manifest HD	Placebo (n=88)	Pepinemab (n=91)
Discontinued Treatment Early	10	13
Had any SAE (*)	8	4
Had any Grade 3+ AE (*)	14	17
CAG repeat length	44.1	43.5
CAP score**	470	466
UHDRS-DCL at screening DCL-4, Unequivocal HD (>99% confident)	88 (100%)	91 (100%)
UHDRS-TFC at screening, n (%)		
11	33 (38%)	29 (32%)
12-13	55 (62%)	61 (68%)
MoCA score, mean (SE)	26.02 (2.04)	26.14 (2.30)
MoCA <26 subgroup	23.97 (0.94)	23.78 (1.07)
MoCA ≥26 subgroup	27.44 (1.21)	27.72 (1.34)

\*pre-COVID era;

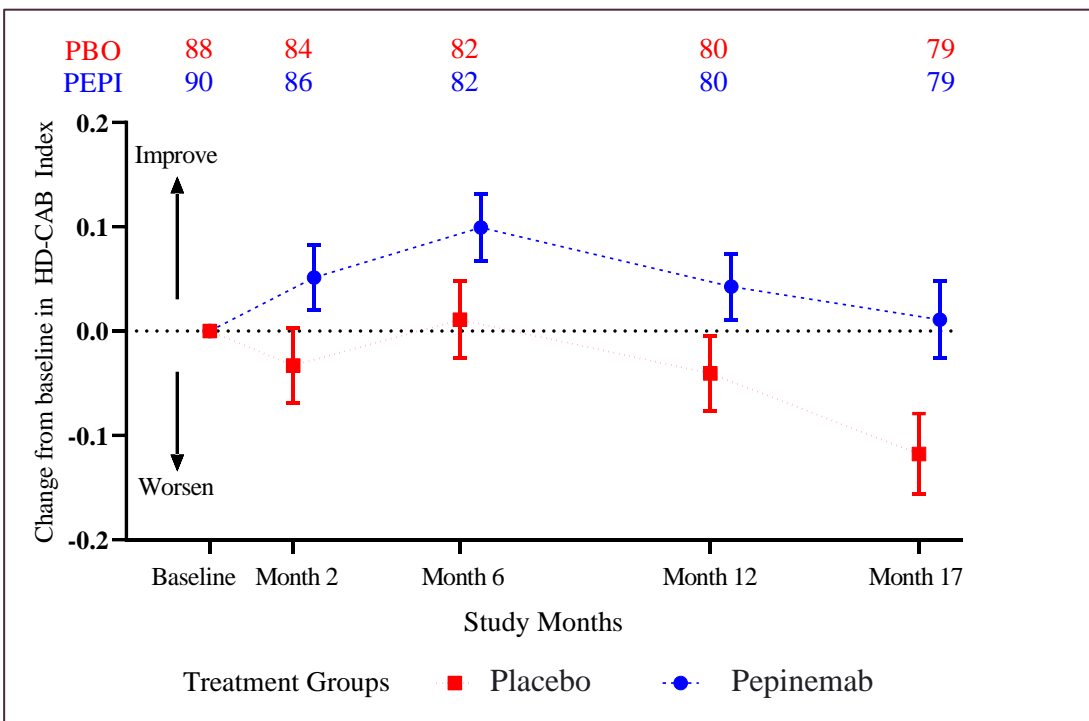
\*\*CAP score = age × (CAG repeat length – 33.66)

# COGNITIVE ASSESSMENT BATTERY (HD-CAB)

mITT Co-Primary and pre-specified Exploratory analysis, Early Manifest HD



## HD-CAB Composite Index of 6 Cognitive Assessments



## Two-item HD Cognitive Assessment: Pre-specified Co-Primary

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors Pepinemab	Critical value
<b>OTS:</b> -1.98 (-4.00, 0.05)	<b>0.028</b>	Yes	No [0.025]
<b>PTAP:</b> 1.43 (-0.37, 3.23)	<b>0.060</b>		

## HD-CAB Composite Index: Pre-specified Exploratory

LS Mean Difference Estimate (95% CI)	One-sided p-value	Favors Pepinemab	Critical value
0.13 (0.03, 0.23)	<b>0.007</b>	Yes	Yes [0.025]

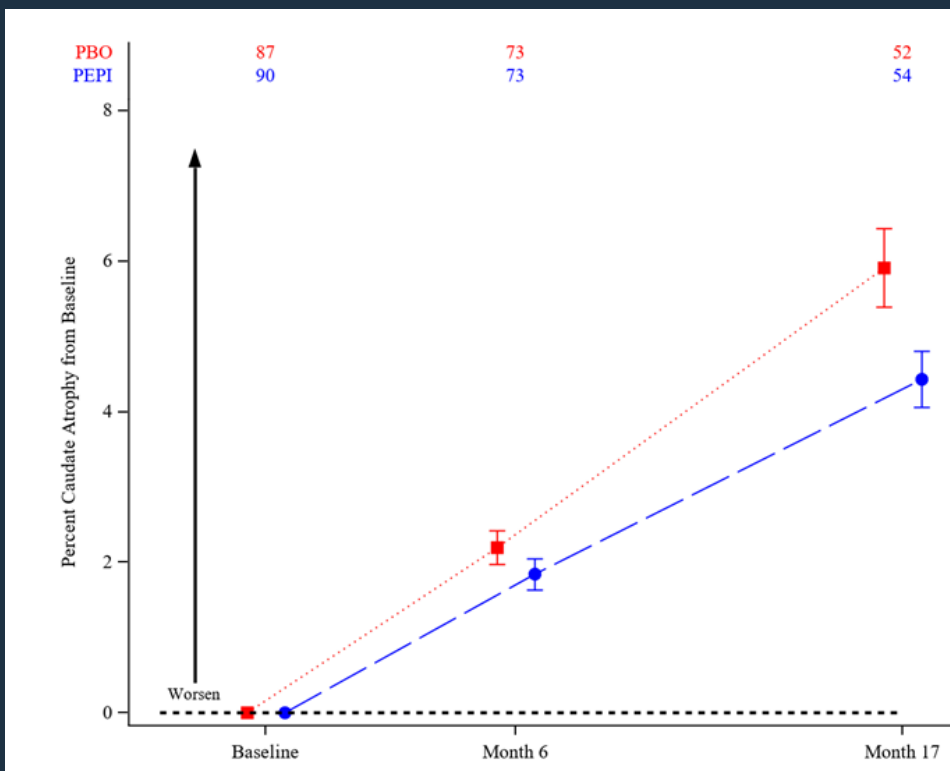
# PEPINEMAB APPEARS TO REDUCE BRAIN ATROPHY

Volumetric MRI– Boundary Shift Integral Analysis (BSI)

Pre-specified Exploratory Endpoint, Early Manifest cohort



## CBSI (caudate atrophy)

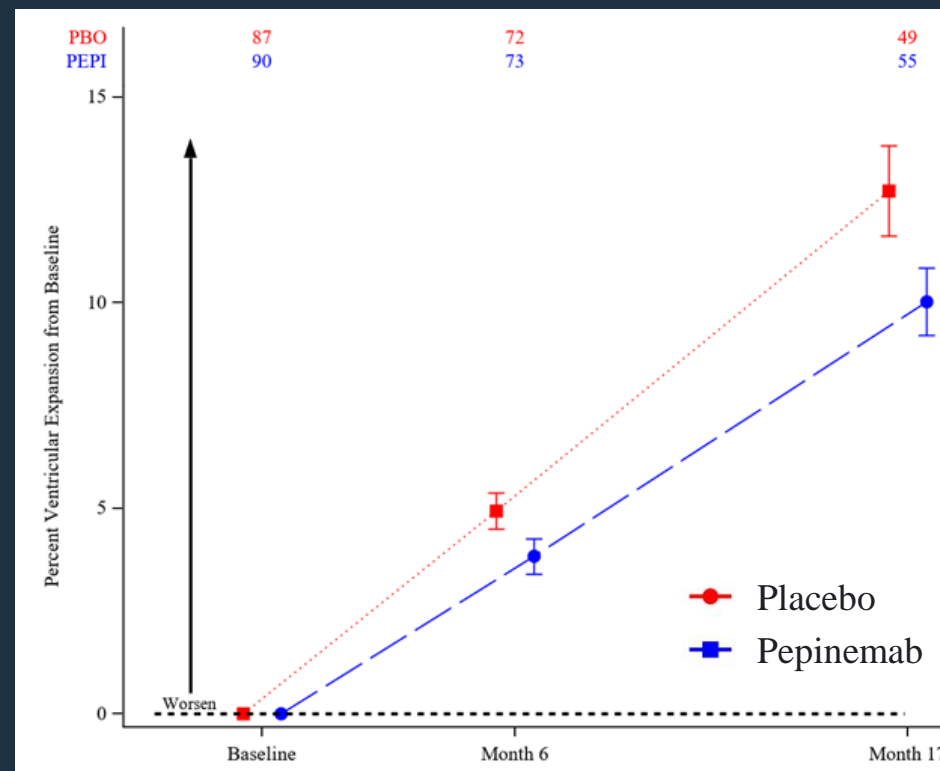


LS Mean Difference Estimate (95% CI):

CBSI: -1.54 (-2.79, -0.29);

**p = 0.017**

## VBSI (ventricular expansion)



VBSI: -2.47 (-5.04, 0.10);

**p = 0.060**

# FDG-PET CORRELATES WITH COGNITIVE FUNCTION

Pre-specified Exploratory Endpoint, Early Manifest cohort



1

FDG-PET measures brain metabolic activity.

2

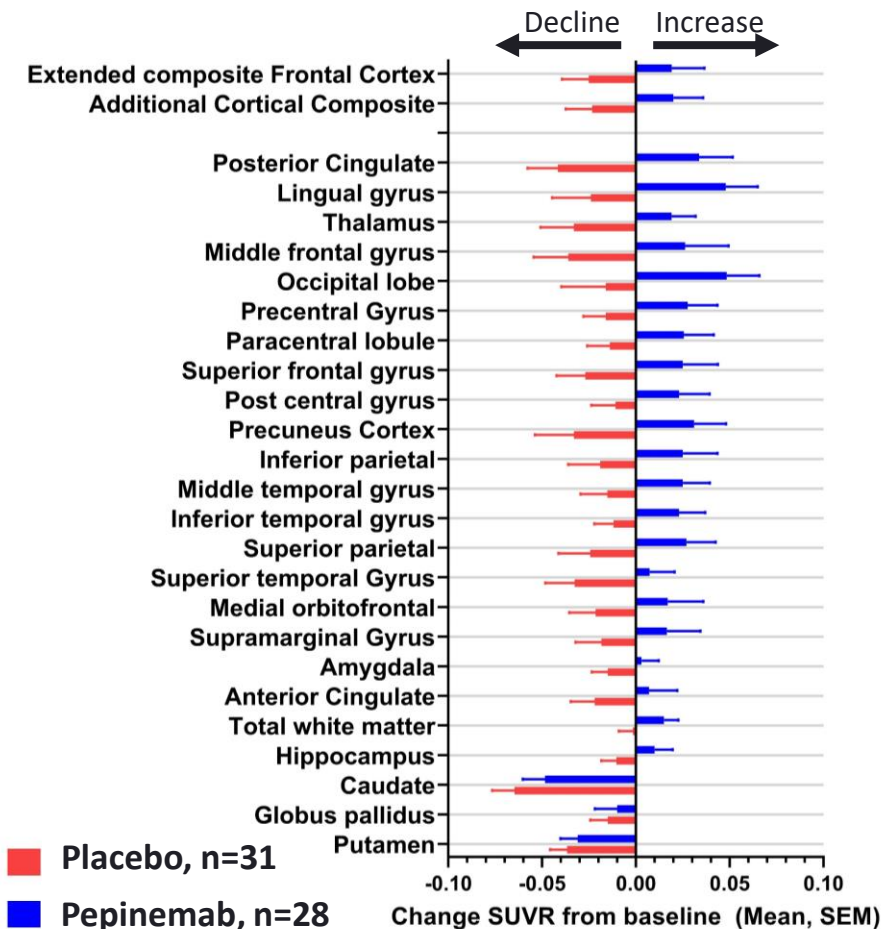
Decline in FDG-PET is reported to correlate with cognitive impairment in neurodegenerative diseases.



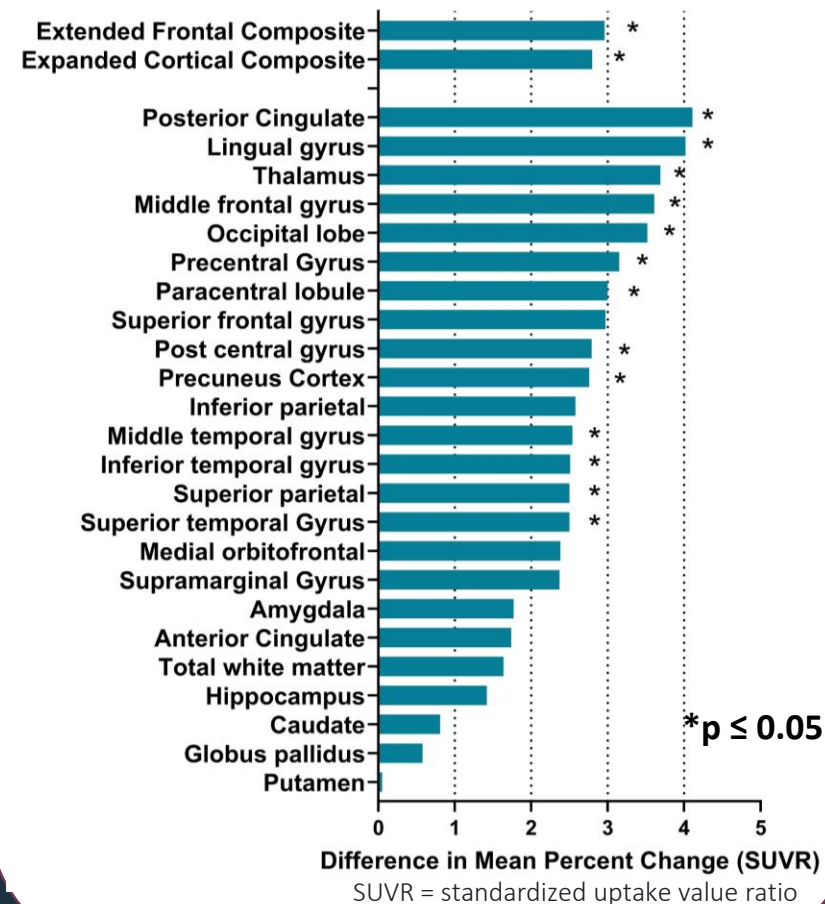
Pepinemab treatment appears to reverse loss of metabolic activity.



Change in FDG-PET at Month18



Difference (PEPI-PBO) at Month 18



# SIGNAL Phase 2 Trial



## Summary, Lessons Learned, Next Steps

Orphan Disease and Fast Track Designations



### Proposed Mechanism of Action

Preclinical data suggests reduced neuroinflammation and restoration of normal glia function

### Safety and Tolerability

**Well tolerated**  
Intravenous administration

### Clinical Activity

Prespecified primary endpoints were not significant  
Evidence suggests potential cognitive benefit (HD-CAB, Apathy, FDG-PET)  
Reduced brain atrophy observed  
Greatest benefit from treatment was detected in patients with signs of mildly advanced disease

### Target Engagement

Confirmed penetration into CNS at expected level  
Antigen-antibody complexes detected



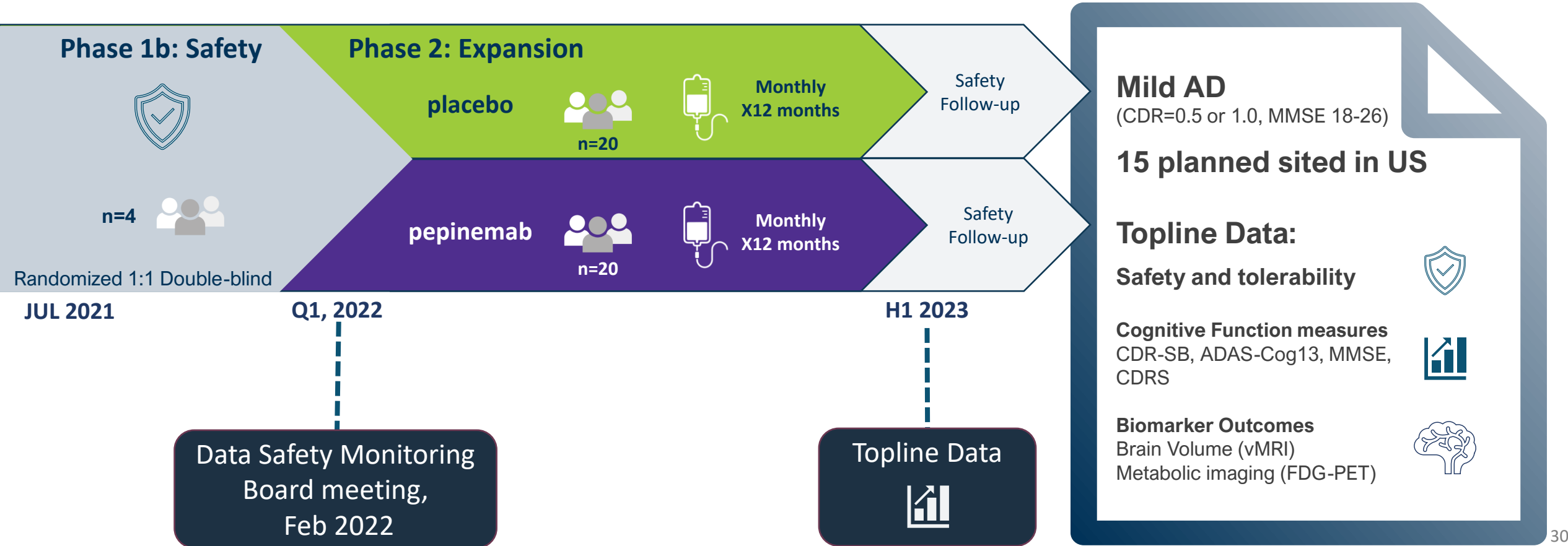
Continued clinical development in Huntington's Disease  
Initiated phase 1/2a trial in Alzheimer's Disease

# ALZHEIMER'S DISEASE

## Phase 1b/2 Trial Design



Funding by  Alzheimer's association  Alzheimer's Drug Discovery Foundation



# ACHIEVEMENTS AND MILESTONES

Publish Clinical Data for SIGNAL study in Huntington’s Disease	<b>2022</b>
Publish Preclinical Data in Rett Syndrome, an orphan disease	August, 2021
Publish Clinical Data for Pepinemab in Combination with Avelumab in NSCLC Clinical Cancer Research, <a href="https://clincancerres.aacrjournals.org/content/27/13/3505">https://clincancerres.aacrjournals.org/content/27/13/3505</a>	April, 2021
Enrollment of first patient for phase 2 study of Pepinemab in Combination with Keytruda® in front line Head & Neck Cancer <b>Expect interim data</b>	Q2 2021 <b>H2-2022</b>
Enrollment of first patient in Alzheimer’s disease phase 1b/2a study <b>Expect topline data from randomized, double-blind, placebo-controlled study</b>	Q2 2021 <b>H1 2023</b>

**Currently exploring pharma collaborations**



**INCORPORATED**  
2001



**HEADQUARTERS**  
Rochester, NY



**EMPLOYEES**  
39



**IPO NASDAQ VCNX**  
August 2018



**JANUARY 2022 CAPITAL RAISE**  
\$13.2 M



**CASH BALANCE\***  
\$13.8 M



**SHARES OUTSTANDING\***  
30.8 M



**ANALYSTS**  
BTIG (T.Shrader)

Vaccinex, Inc. (Nasdaq: VCNX) is a publicly traded clinical-stage biotechnology company engaged in the discovery and development of targeted biotherapeutics to treat serious diseases with unmet medical needs, including cancer and neurodegenerative diseases.

\*as of 30SEP2021



# Vaccinex Leadership Team

**Maurice Zauderer, Ph.D.**

**Founder, President and Chief Executive Officer.** Formerly, Professor at University of Rochester and at Columbia University.

**Scott E. Royer, CFA, MBA**

**Chief Financial Officer.** Formerly, Chief Financial Officer and Director of Finance of the Medical Films Group of Carestream Health, a medical and dental imaging company and an independent subsidiary of Onex Corporation, a Canadian publicly traded private equity investment firm. Mr. Royer earned an Executive MBA from Villanova University, and is a credentialed Chartered Financial Analyst (CFA)

**Ernest S. Smith, Ph.D.**

**Chief Scientific Officer and Senior Vice President, Research.** Dr. Smith received a Ph.D. in Immunology from the University of Rochester. Dr. Smith has held several leadership roles at Vaccinex since 2001 and holds several patents, including ActivMab<sup>®</sup> technology and Semaphorin 4D/pepinemab.

**Elizabeth E. Evans, Ph.D.**

**Chief Operating Officer and Senior Vice President, Discovery and Translational Medicine.** Dr. Evans received an M.S. in Immunology and a Ph.D. in Pathology from the University of Rochester. Dr. Evans has held several leadership roles at Vaccinex since 2001 and holds several patents on SEMA4D/pepinemab.

**John E. Leonard, Ph.D.**

**Senior Vice President, Development.** Formerly Vice President, Program Executive of Biogen Idec, Inc., a publicly traded biotechnology company. Dr. Leonard received a Ph.D. in Biochemistry from the University of California, Riverside

A large, dark blue background image with a microscopic, cellular appearance, showing various irregular shapes and textures in shades of blue and white, suggesting biological or medical research.

# Appendix

■ Unique Targets ■ Novel Mechanisms ■ New Medicines



# CONTACT US

**Maurice Zauderer, PhD**  
**President & CEO**  
[mzauderer@vaccinex.com](mailto:mzauderer@vaccinex.com)



**Elizabeth Evans, PhD**  
**COO**  
[eevans@vaccinex.com](mailto:eevans@vaccinex.com)



**Ernest Smith, PhD**  
**CSO**  
[esmith@vaccinex.com](mailto:esmith@vaccinex.com)

# Vaccinex Scientific Advisors - Neurology

## **Eric Siemers, MD**

President of Siemers Integration LLC. Distinguished medical fellow for Eli Lilly and Company's Alzheimer's Disease Global Development Team, founded and headed the Indiana University Movement Disorder Clinic. Served on the Board of Directors of the American Society of Experimental Neurotherapeutics, as founding member and Chair of the Alzheimer's Association Research Roundtable, and Steering Committee member for the Alzheimer's Disease Neuroimaging Initiative (ADNI).

## **Karl D. Kieburtz, MD, MPH**

President of Clintrex LLC, providing services regarding research and regulatory strategy for therapeutic development of interventions for brain disorders. Chair of the FDA Peripheral and Central Nervous System Drugs Advisory Committee and sits on the American Academy of Neurology (AAN) Clinical Research Subcommittee, the International Executive Committee of the Movement Disorders Society (MDS), the Board of Directors for the American Society for Experimental Neuro Therapeutics (ASENT), and the Council of the American Neurological Association (ANA), chair of the FDA Peripheral and Central Nervous System Drugs Advisory Committee.

## **Ira Shoulson, MD**

Dr. Shoulson is a long time leader in Huntington's disease research. From 2011 to July 2018, Dr Shoulson was Professor of Neurology, Pharmacology and Human Science and Director of the Program for Regulatory Science and Medicine (PRSM) at Georgetown University where he was principal investigator of the FDA-Georgetown University Collaborating Center of Excellence in Regulatory Science and Innovation. From 1990 to 2011, Dr Shoulson was the Louis C. Lasagna Professor of Experimental Therapeutics and Professor of Neurology, Pharmacology and Medicine at the University of Rochester School of Medicine & Dentistry in Rochester, New York. Dr. Shoulson is an elected member of the National Academy of Medicine of the National Academy of Sciences.

## **Ralf Reilmann, MD**

Founding Director and C.E.O. of the George-Huntington-Institute, Dept. of Radiology at the University of Muenster and the Dept. of Neurodegeneration and Hertie Institute for Clinical Brain Research at the University of Tuebingen.

# Vaccinex Scientific Advisors - HNSCC Clinical Advisory Board

**Barbara Burtness,  
MD**

Professor of Medicine (Medical Oncology) at Yale, leader of the Disease Aligned Research Team for the Head and Neck Cancers Program and Co-Leader of the Developmental Therapeutics Research Program at Yale Cancer Center. Chair of ECOG-ACRIN Head and Neck Therapeutics Committee, served on the NCCN and SITC Head and Neck Guidelines Committee, and the NCI Head and Neck Cancer Steering Committee. Co-chair of the NCI Clinical Trials Planning Meeting on TP53-Mutated Head and Neck Cancer and FDA Project 2025 for Head and Neck. Founding Director of the Yale Head and Neck Cancer SPORE and has led numerous clinical trials, including the international phase III trial which led to regulatory approval of immunotherapy in first-line treatment of head and neck cancer.

**Robert Haddad, MD**

Chief, Division of Head and Neck Oncology. McGraw Chair, Head and Neck Oncology, Dana-Farber Cancer Institute. Professor, Medicine, Harvard Medical School.

**Douglas Adkins, MD**

Professor, Department of Medicine, Oncology Division, Medical Oncology, Washington University School of Medicine in St. Louis. NCI Head and Neck Steering Committee and Metastatic and Recurrent Head & Neck Cancer Task Force

**Nabil Saba, MD**

Director of the Head and Neck Cancer Medical Oncology Program at Winship Cancer Institute of Emory University, Professor and Vice Chair for Quality and Safety in the Department of Hematology and Medical Oncology and holds a joint appointment as Professor in the Department of Otolaryngology at Emory University School of Medicine. Chair of the National Cancer Institute's task force for recurrent metastatic head and neck cancer and Chair of the Rare Tumors Task Force of the National Cancer Institute's Head and Neck Cancer Steering Committee. Member of the NRG Oncology and Eastern Cooperative Oncology Group (ECOG) Head and Neck Cancer Core Committees, the ASCO clinical guidelines committee, and the ASCO Head and Neck Guideline Advisory Group.

## Vaccinex Board of Directors

<b>Albert D. Friedberg</b>	Chairman, President and CEO of Friedberg Mercantile Group, a Toronto-based commodities and investment management firm he founded in 1971. He served as Chairman of the Toronto Futures Exchange from March 1985 to June 1988.
<b>Chrystyna M. Bedrij</b>	Co-Founder and Principal, Griffin Securities
<b>Jacob B. Frieberg</b>	Principal, The WTF Group.
<b>J. Jeffrey Goater</b>	CEO of Surface Oncology, Formerly, CFO of Voyager Therapeutics.
<b>Bala S. Manian, Ph.D.</b>	Founder (or co-founder) of Quantum Dot Corporation, SurroMed, Biometric Imaging, LumisysInc., Molecular Dynamics and ReaMetrix.
<b>Gerald E. Van Strydonck</b>	Formerly, Managing Partner at PricewaterhouseCoopers.
<b>Barbara Yanni</b>	Formerly, Vice President and Chief Licensing Officer at Merck & Co., Inc.
<b>Maurice Zauderer, Ph.D.</b>	Vaccinex Founder, President and Chief Executive Officer. Formerly, Professor at University of Rochester and at Columbia University.

# Vaccinex Selected References, Oncology

1. Shafique MR, Fisher TL, Evans EE, Leonard JEE, Pastore DRE, Mallow CL, Smith E, Mishra V, Schroder A, Chin KA, Beck JT, Baumgart MA, Govindan R, Gabriel NY, Spira AI, Seetharamu N, Lou Y, Mansfield AS, Sanborn RE, Goldman JW, Zauderer M. **A Phase Ib/2 Study of Pepinemab in Combination with Avelumab in Advanced Non–Small Cell Lung Cancer.** Clin Cancer Res 2021, doi: 10.1158/1078-0432.CCR-20-4792
2. Clavijo PE, Friedman J, Robbins Y, Moore EC, Smith ES, Zauderer M, Evans EE, Allen CT. **Semaphorin4D inhibition improves response to immune checkpoint blockade via attenuation of MDSC recruitment and function.** Cancer Immunol Res. 2019 Feb;7(2):282-291
3. Evans EE, Jonason AS Jr, Bussler H, Torno S, Veeraraghavan J, Reilly C, Doherty MA, Seils J, Winter LA, Mallow C, Kirk R, Howell A, Giralico S, Scrivens M, Klimatcheva K, Fisher TL, Bowers WJ, Paris M, Smith ES, Zauderer M. **Antibody blockade of semaphorin 4D promotes immune infiltration into tumor and enhances response to other immunomodulatory therapies.** Cancer Immunol Res. 2015 Jun;3(6): 689-701. <http://www.ncbi.nlm.nih.gov/pubmed/25614511>
4. Amita Patnaik, Glen J. Weiss, John E. Leonard, Drew Warren Rasco, Jasgit C. Sachdev, Terrence L. Fisher, Christine Reilly, Laurie A. Winter, Robert B. Parker, Danielle Mutz, Lisa Blaydorn, Anthony W. Tolcher, Maurice Zauderer and Ramesh K. Ramanathan. **Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of VX15/2503, a Humanized IgG4 anti-SEMA4D Antibody, in a First-In-Human Phase 1 Study of Patients with Advanced Solid Disease.** Clin Cancer Res. 2015 Oct 7. <http://clincancerres.aacrjournals.org/content/22/4/827.full.pdf+html>
5. Leonard JE, Fisher TL, Winter LA, Cornelius CA, Reilly C, Smith ES, Zauderer M. **Nonclinical Safety Evaluation of VX15/2503; a Humanized IgG4 Anti-SEMA4D Antibody.** Mol Cancer Ther. 2015 Feb 5 <http://www.ncbi.nlm.nih.gov/pubmed/25657333>
6. Fisher TL, Reilly CA, Winter LA, Pandina T, Jonason A, Scrivens M, Balch L, Bussler H, Torno S, Seils J, Mueller L, Huang H, Klimatcheva E, Howell A, Kirk R, Evans E, Paris M, Leonard JE, Smith ES, Zauderer M. **Generation and preclinical characterization of an antibody specific for SEMA4D.** Mabs. 2015 Oct 20. <http://www.tandfonline.com/doi/abs/10.1080/19420862.2015.1102813>
7. Fisher, T. L., J. Seils, C. Reilly, V. Litwin, L. Green, J. Salkowitz-Bokal, R. Walsh, S. Harville, J. E. Leonard, E. Smith, and M. Zauderer. 2016. **Saturation monitoring of VX15/2503, a novel semaphorin 4D-specific antibody, in clinical trials.** Cytometry B Clin. Cytom. 90: 199-208. <http://onlinelibrary.wiley.com/doi/10.1002/cyto.b.21338/abstract>

Schematics created with BioRender.com

# Vaccinex Selected References, Neurology

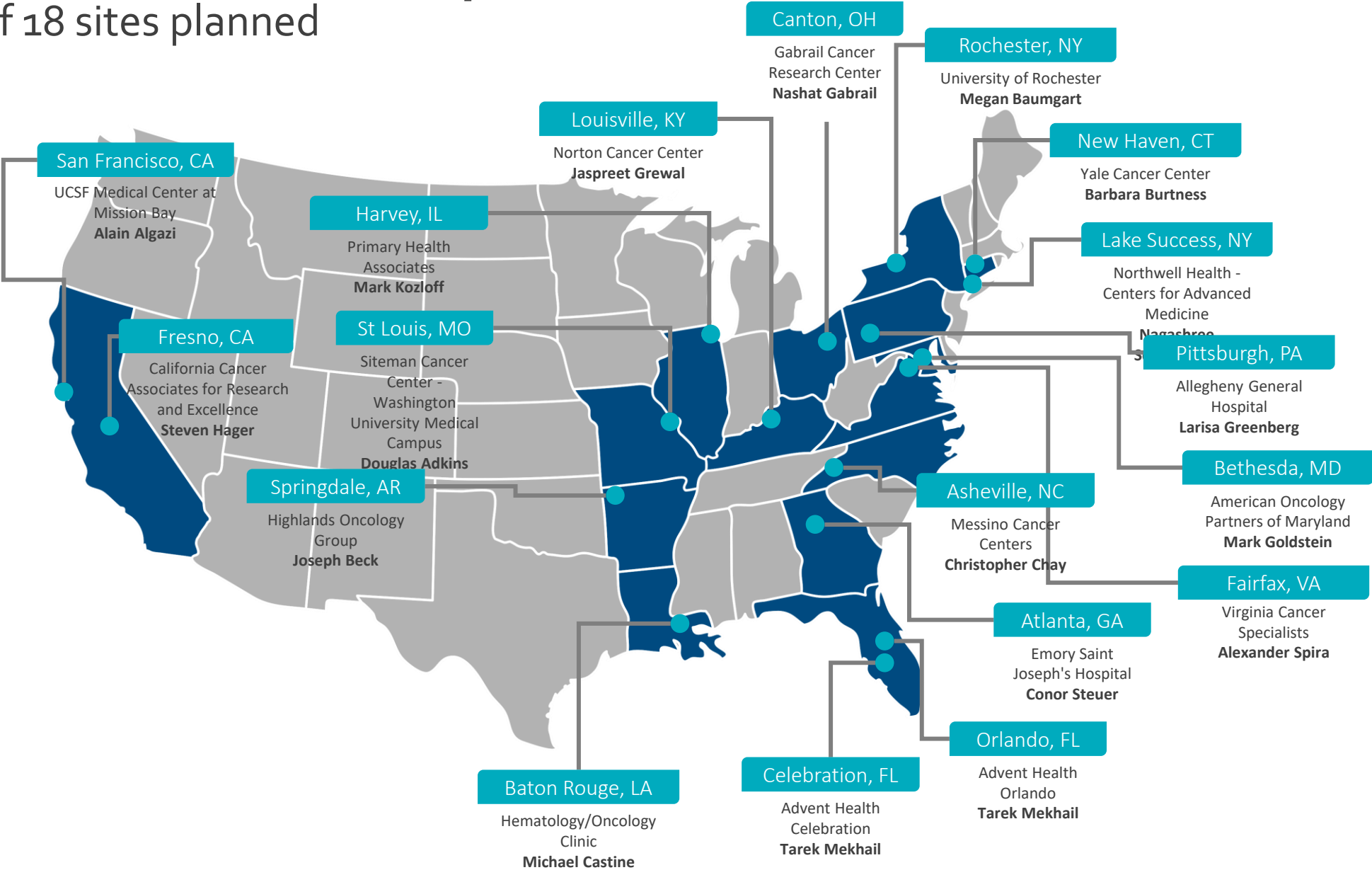
1. Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, Doherty M, Klimatcheva E, Mallow C, Cornelius C, Leonard JE, Marchi N, Janigro D, Argaw AT, Pham T, Seils J, Bussler H, Torno S, Kirk R, Howell A, Evans EE, Paris M, Bowers WJ, John G, Zauderer M. **SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease.** *Neurobiol Dis.* 2014 Oct 18;73C:254-268. doi: 10.1016/j.nbd.2014.10.008. <http://www.sciencedirect.com/science/article/pii/S0969996114003015>
2. Southwell AL, Franciosi S, Villanueva EB, Xie Y, Winter LA, Veeraraghavan J, Jonason A, Felczak B, Zhang W, Kovalik V, Waltl S, Hall G, Pouladi MA, Smith ES, Bowers WJ, Zauderer M, Hayden MR. **Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease.** *Neurobiol Dis.* 2015 Feb 3; 76:46–56. <http://www.sciencedirect.com/science/article/pii/S0969996115000145>
3. LaGanke, C., L. Samkoff, K. Edwards, L. Jung Henson, P. Repovic, S. Lynch, L. Stone, D. Mattson, A. Galluzzi, T. L. Fisher, C. Reilly, L. A. Winter, J. E. Leonard, and M. Zauderer. 2017. **Safety/tolerability of the anti-semaphorin 4D Antibody VX15/2503 in a randomized phase 1 trial.** *Neurol Neuroimmunol Neuroinflamm* 4: e367. <https://www.ncbi.nlm.nih.gov/pubmed/28642891>
4. Leonard JE, Fisher TL, Winter LA, Cornelius CA, Reilly C, Smith ES, Zauderer M. **Nonclinical Safety Evaluation of VX15/2503; a Humanized IgG4 Anti-SEMA4D Antibody.** *Mol Cancer Ther.* 2015 Feb 5 <http://www.ncbi.nlm.nih.gov/pubmed/25657333>
5. Zauderer M, Fisher TL, Mishra V, Leonard JE, Reader A, Mallow C, Balch L, Howell A, Smith ES, and Evans EE. **SEMA4D upregulation signals neuronal stress and triggers reactive transformation of astrocytes.** *In preparation*
6. Mao Y, Evans EE, Mishra V, Balch L, Eberhardt A, Zauderer M, Gold WA. **Anti-Semaphorin 4D Rescues Motor, Cognitive, and Respiratory Phenotypes in a Rett Syndrome Mouse Model.** *Int J Mol Sci.* 2021 Aug 31;22(17):9465. doi: 10.3390/ijms22179465. <https://www.mdpi.com/1422-0067/22/17/9465>
7. Feigin AS, Evans EE, Fisher TL, Leonard JE, Reader A, Wittes J, Oakes D, Smith ES, Zauderer M, and the Huntington Study Group SIGNAL investigators. **Safety and efficacy of pepinemab antibody blockade of SEMA4D in patients with early Huntington’s Disease: a randomized, placebo-controlled, multicenter, Phase 2 clinical trial (SIGNAL).** *In preparation*
8. Fisher TL, Reilly CA, Winter LA, Pandina T, Jonason A, Scrivens M, Balch L, Bussler H, Torno S, Seils J, Mueller L, Huang H, Klimatcheva E, Howell A, Kirk R, Evans E, Paris M, Leonard JE, Smith ES, Zauderer M. **Generation and preclinical characterization of an antibody specific for SEMA4D.** *Mabs.* 2015 Oct 20. <http://www.tandfonline.com/doi/abs/10.1080/19420862.2015.1102813>

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# KEYNOTE B84 Site Map

Total of 18 sites planned



# Signal-AD Site Map

