



Oppenheimer Fall Healthcare Life Sciences and MedTech Summit

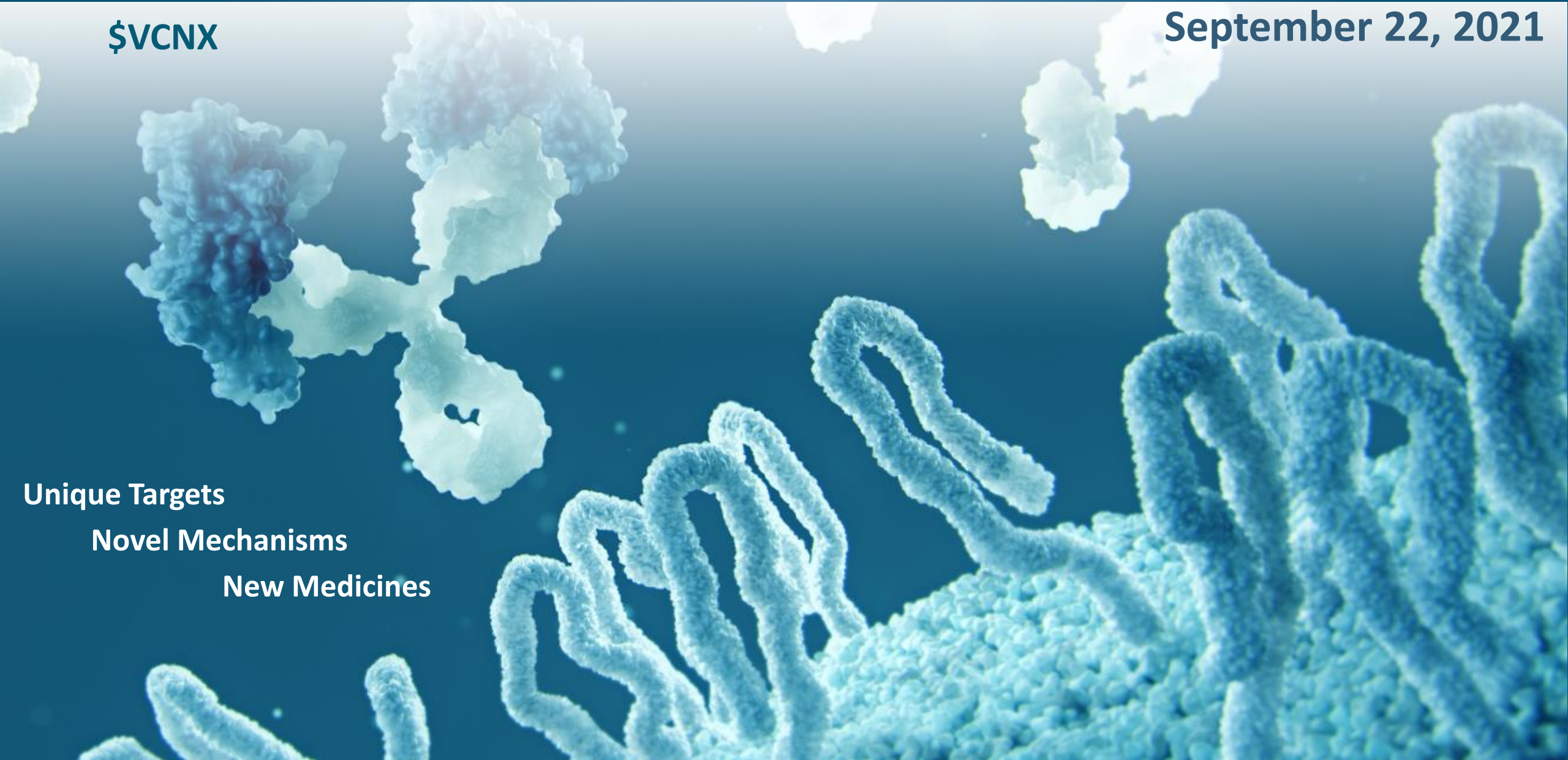
\$VCNX

September 22, 2021

Unique Targets

Novel Mechanisms

New Medicines



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, 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 its 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 Form 10-K for year end December 31, 2021 and subsequent filings with the SEC.

Novel antibody therapeutics target unmet needs

- ✓ **Novel Mechanistic Approach**
Lead product: Pepinemab
Humanized IgG4 monoclonal antibody, first in class
Blocks a unique target, Semaphorin 4D (SEMA4D)
- ✓ **Clinical Proof of Concept**
- ✓ **Advanced clinical programs with near term opportunities for monetization by partnering**

- ✓ **Proprietary Drug Discovery Platform**



SEMA4D pathways are activated in immune and central nervous systems in response to stress/disease

Neurodegenerative Disease

- Targets underlying disease pathology, a trigger of neuroinflammation
- Ability to repair and restore normal functions
- Broad application
- Phase 3-ready asset in Huntington's Disease

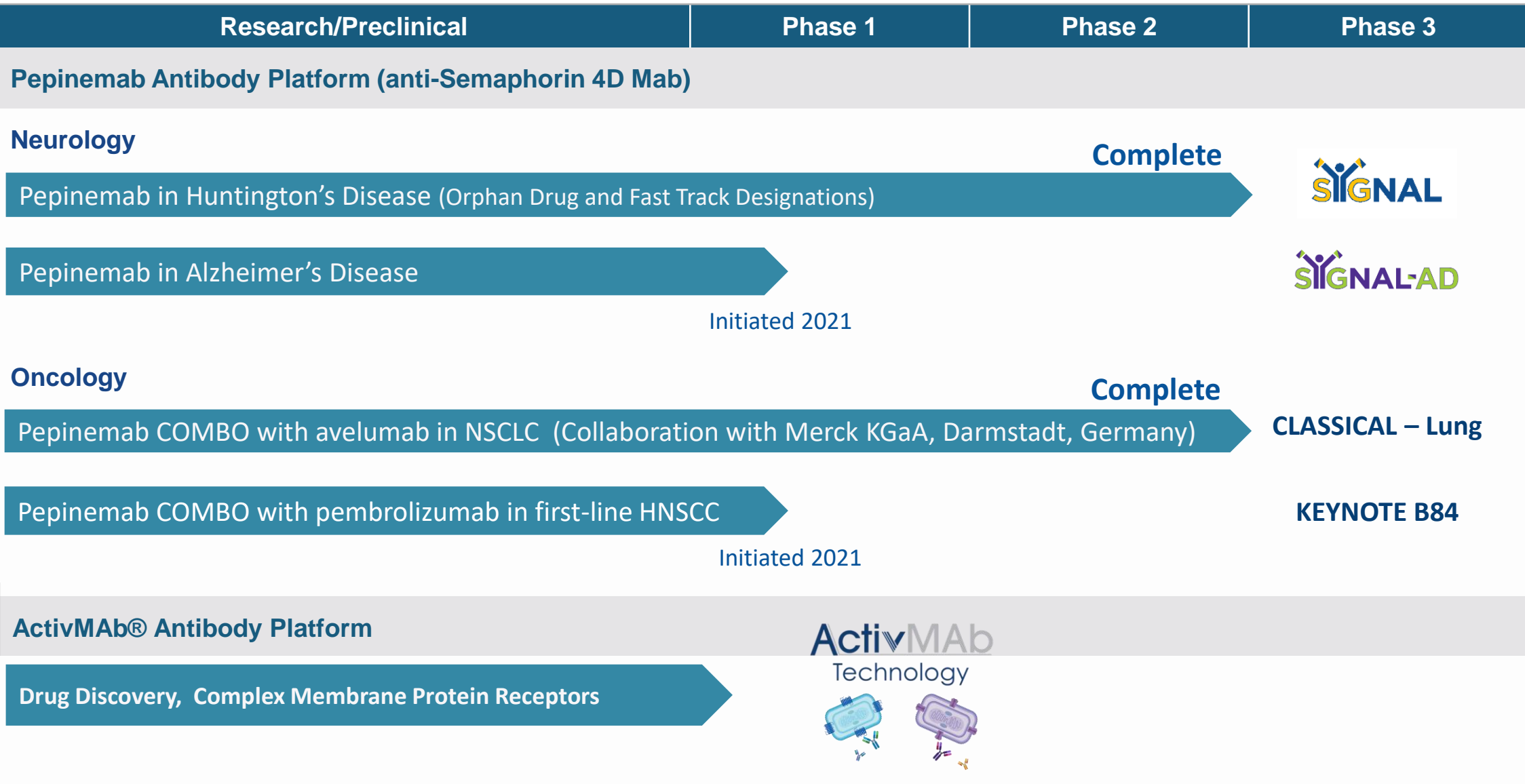


Cancer Immunotherapy

- Overcomes resistance to existing immunotherapies
- Complements immune checkpoint therapies without added toxicity
- Ongoing Phase 1/2 trial in head and neck cancer, partnered with Merck



Clinical Pipeline



All studies Sponsored by:



Additional Funding &/or Support by:





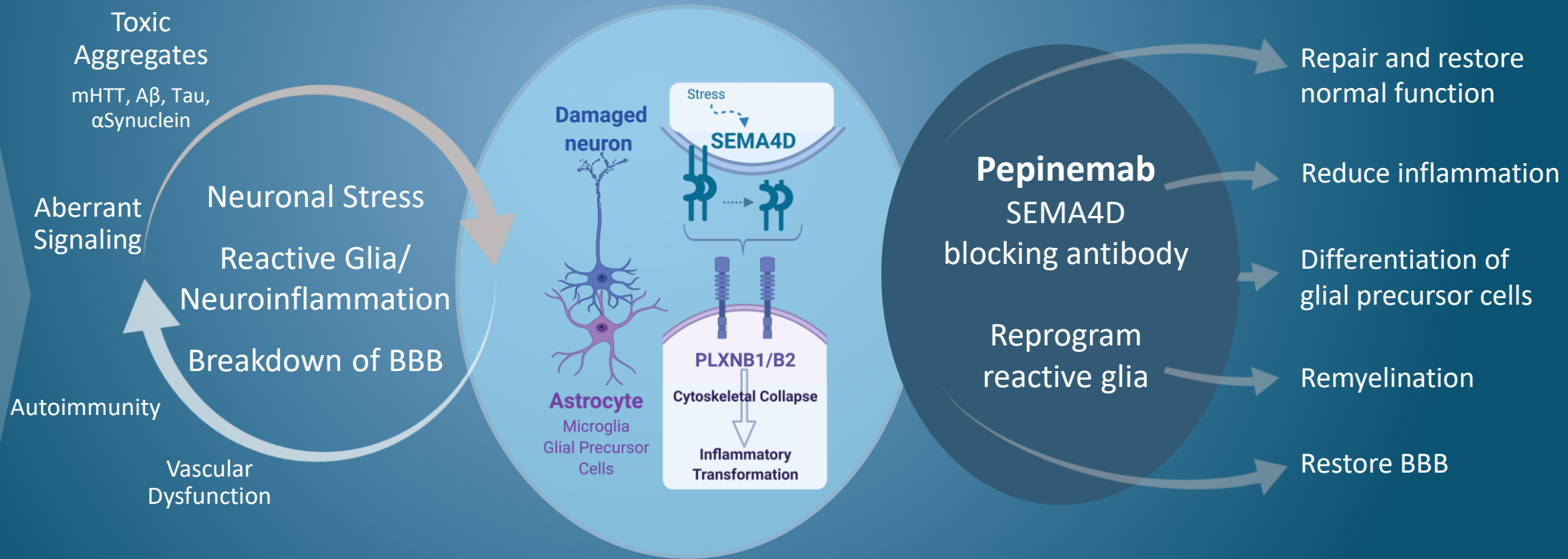
Pepinemab Antibody for treatment of Neurodegenerative Disease

Science in the Service
of Medicine



Pepinemab reprograms underlying pathology in CNS disease

- Huntington's Disease
- Alzheimer's Disease
- Parkinson's Disease
- Rett Syndrome
- Multiple Sclerosis, PPMS
- Co-morbidities



SEMA4D antibody blockade improves disease phenotype in preclinical models

TARGET: SEMA4D is upregulated on damaged neurons SEMA4D binding to Plexin receptors on glial cells to triggers transformation to reactive inflammatory state and loss of normal support functions

Chronic activation contributes to and exacerbates neurodegeneration

DRUG: Pepinemab is a humanized IgG4 Mab that blocks the binding of SEMA4D to its receptors

- Repair and restore normal glial functions
- Reduce neuroinflammation

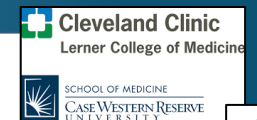
Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease



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

2015 Neurobiology of Disease

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



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

2014 Neurobiology of Disease

^a Vaccinex, Inc., Rochester, NY 14620, USA

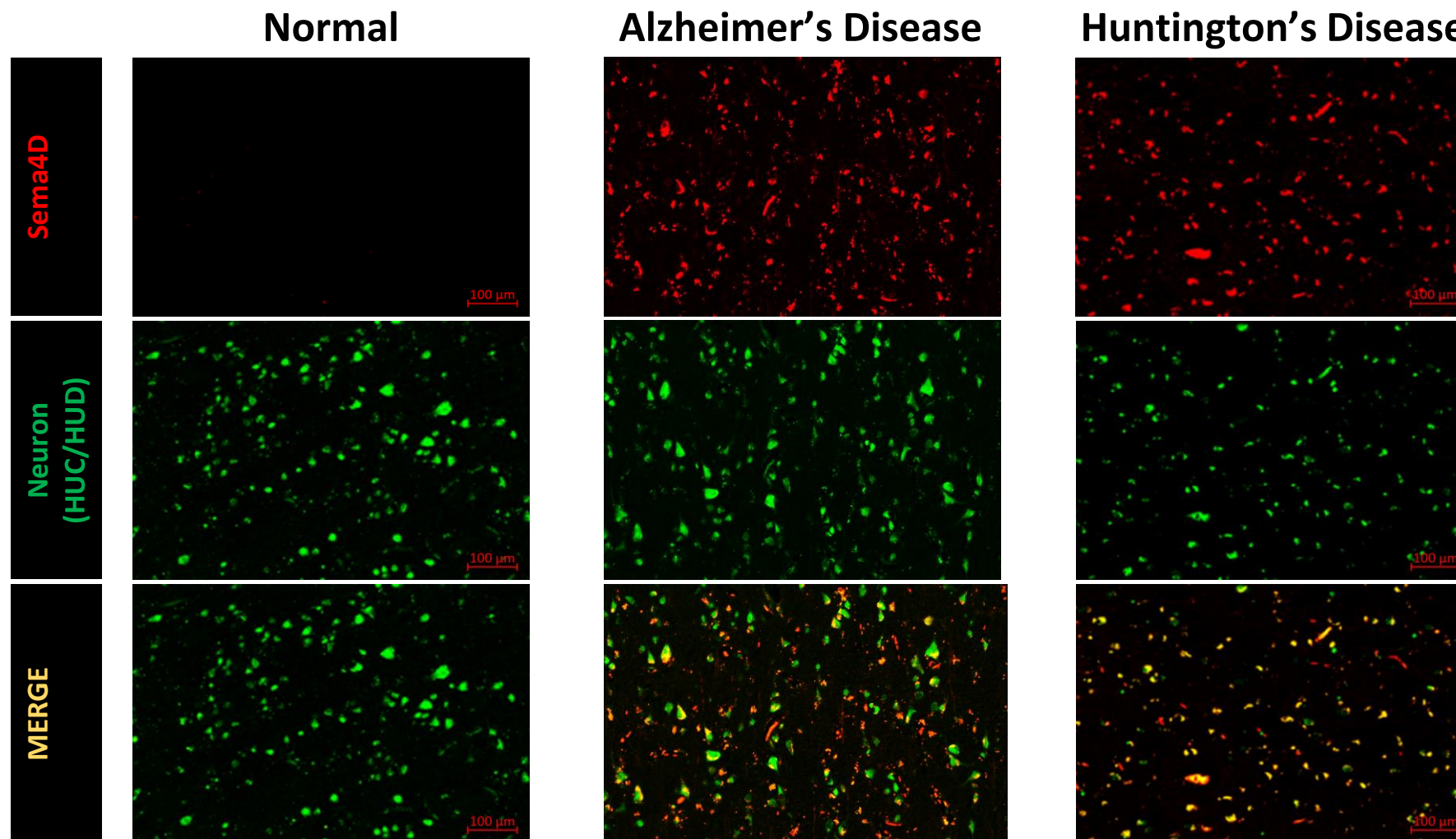


Article

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

Yilin Mao^{1,2}, Elizabeth E. Evans³, Vikas Mishra³, Leslie Balch³, Allison Eberhardt³, Maurice Zauderer^{3,†} and Wendy A. Gold^{1,2,4,5,*}

SEMA4D is upregulated in neurons during underlying disease progression



Human autopsy sections of frontal lobe

Huntington's Disease - slowly progressive, fatal neurodegenerative 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.

Orphan Disease

Estimated patient population in major markets is ~80,000 individuals with manifest disease and >5X more are at risk of having inherited the HD mutation.

Neuronal degeneration, neuroinflammation, and severe **atrophy** is observed in multiple brain regions affecting **cognition**, emotion, and motor function.



Voice of the Patient Huntington's Disease

“Perspectives on most significant symptoms

In a polling question..., participants were asked to identify up to three symptoms that had the most significant impact on daily life. **Cognitive impairment (such as difficulty concentrating and difficulty completing tasks) received the highest number of responses,** followed by depression and anxiety, and unsteady gait/trouble with walking.”

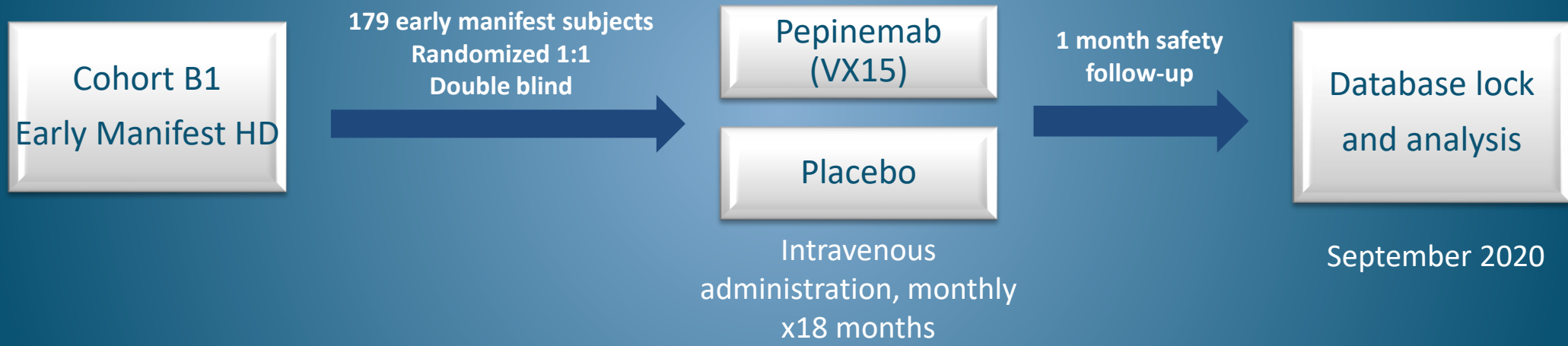
“[My daughter, who once wanted to be an engineer] cannot even focus to read a newspaper today. Today she can't even write a grocery list, handle a monetary transaction, or help her son with homework.”



Clinical Trial Design – Group B1, Early Manifest HD



Orphan Disease and Fast Track designations



Study Objectives

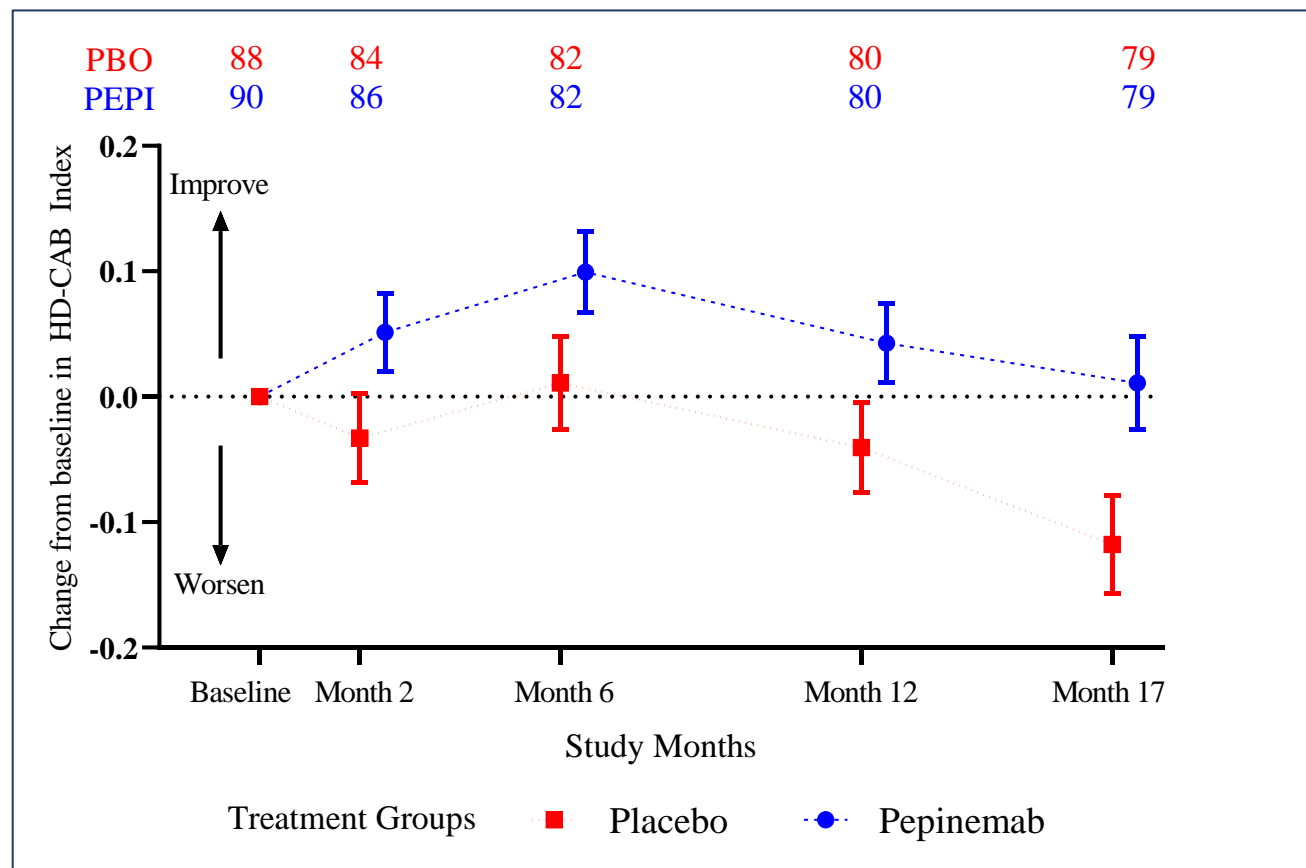
- Safety and tolerability
- Cognitive Function and Clinical global impression of change (CGIC)
- Brain imaging measures

Cognitive Assessment Battery (HD-CAB) Prespecified exploratory analysis – Early Manifest HD



HD-CAB Composite Index of 6 Cognitive Assessments

Early manifest HD



HD-CAB Composite Index:

| One-sided p-value | Favors PEPI | Critical value |
|-------------------|-------------|----------------|
| 0.007 | Yes | Yes [0.025] |

Co-primary endpoints:

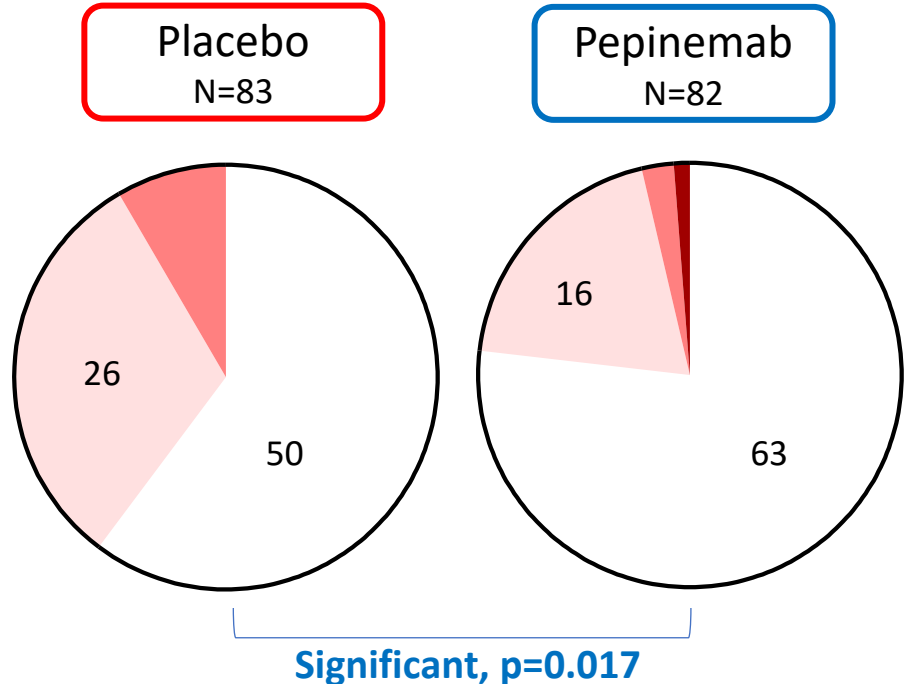
| One-sided p-value | Favors PEPI | Critical value |
|-------------------|-------------|----------------|
| OTS: 0.028 | Yes | No [0.025] |
| PTAP: 0.06 | | [0.0125] |

Apathy: a manifestation of cognitive impairment



Several HD studies suggest that among behavioral measures apathy severity correlates best with disease progression and correlates with cognition

“The majority of participants stressed that psychiatric problems were the most significant manifestation of **cognitive impairment**. This included excessive anger, **apathy or lack of emotion**, irritability, aggression, physical violence ... “
-Voice of the patient



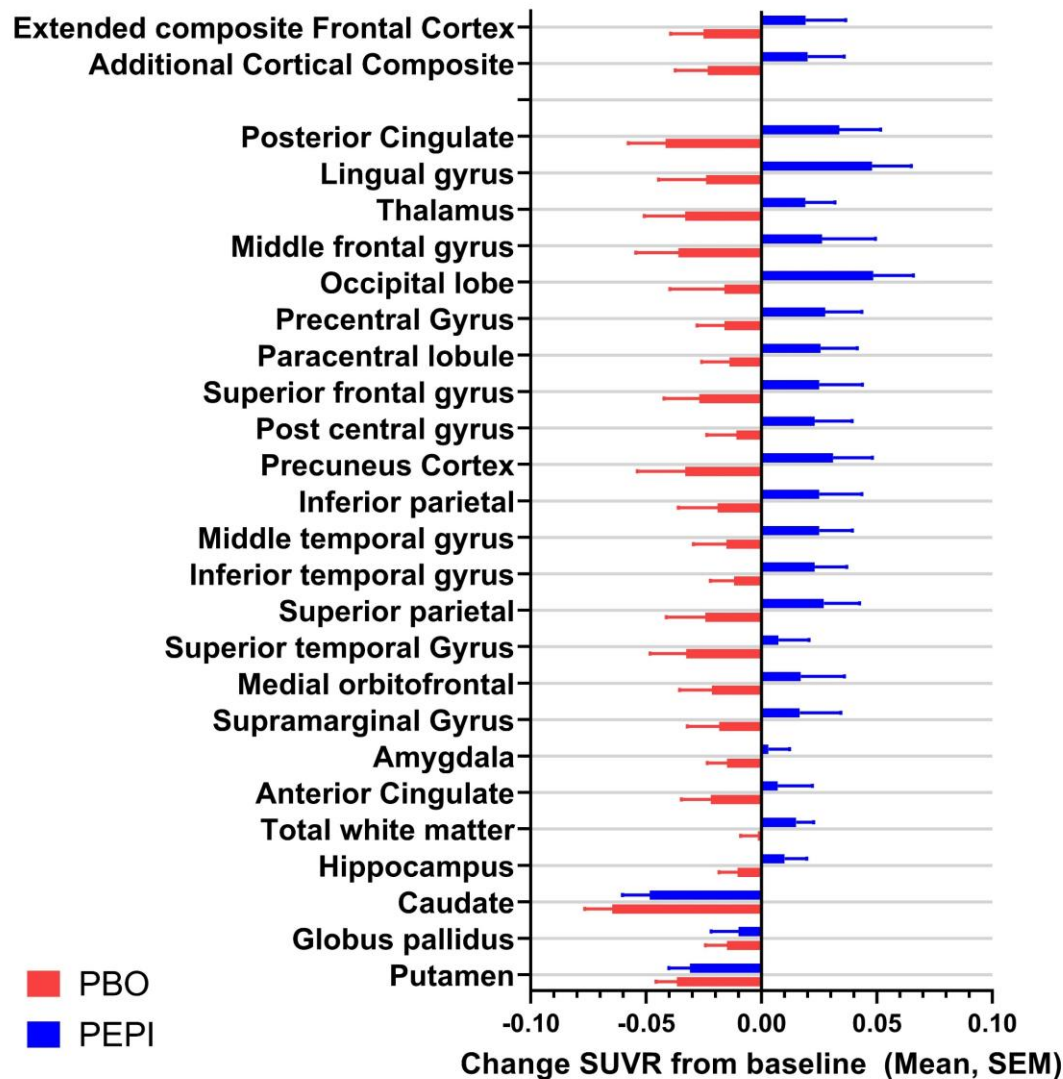
Apathy Severity Scale, 18 months

- Absent
- Slight, questionable, mild
- Moderate
- Severe

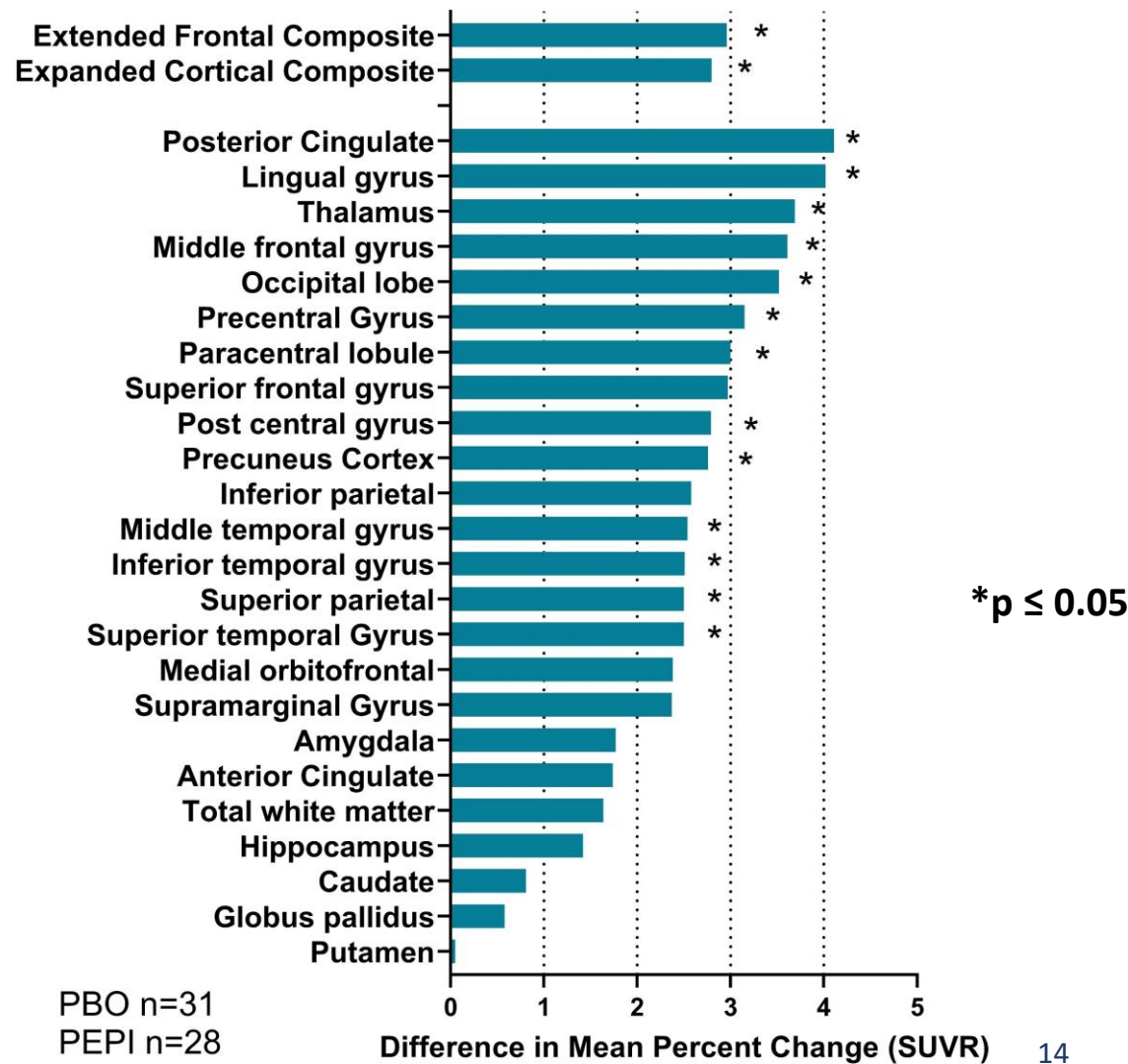
FDG-PET correlates with Cognitive function



**FDG-PET Change SUVR
Early Manifest at visit 18**



**FDG-PET Difference in % Change SUVR (PEPI-PBO)
Early Manifest at Visit18**

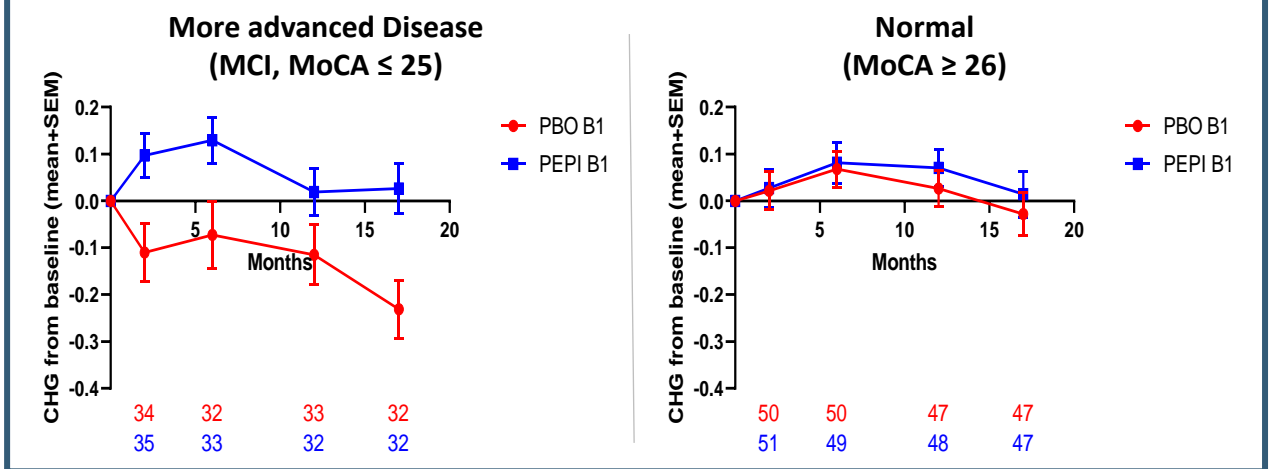


Lessons learned from Phase 2 HD trial

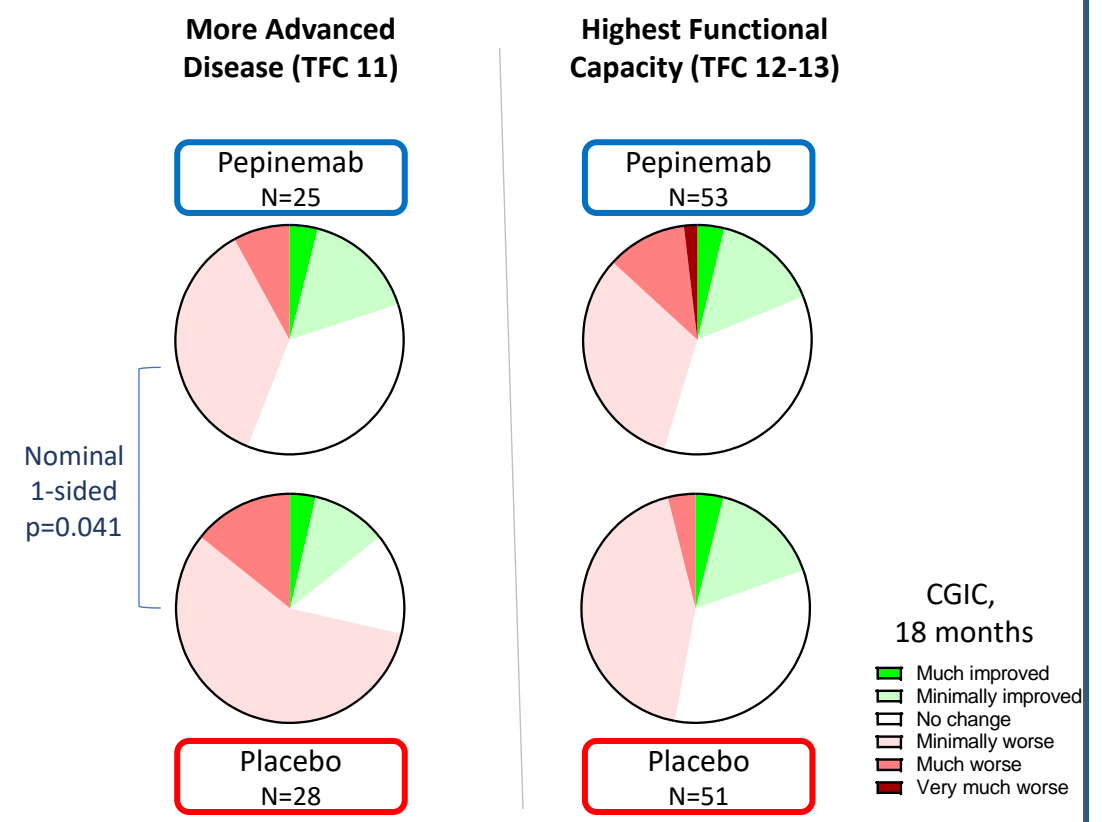


1. Multiple assessments support cognitive benefit
2. Signs of efficacy were more readily detected in patients with slightly more advanced disease at time of enrollment

HD-CAB effect is observed in patients with mild cognitive impairment at baseline



CGIC effect is observed in patients with lower baseline Total Functional Capacity



SIGNAL Phase 2 trial: Summary, Lessons learned, Next steps



Orphan Disease and Fast Track designations



Mechanism of Action

- Reduce neuroinflammation and restore normal glia function



Safety and Tolerability

- **Well tolerated**
- Intravenous administration



Clinical Efficacy

- Improved cognition: HD-CAB, Apathy, FDG-PET
- Treatment effects detected in patients with slightly more advanced disease
- Reduced brain atrophy

Target engagement

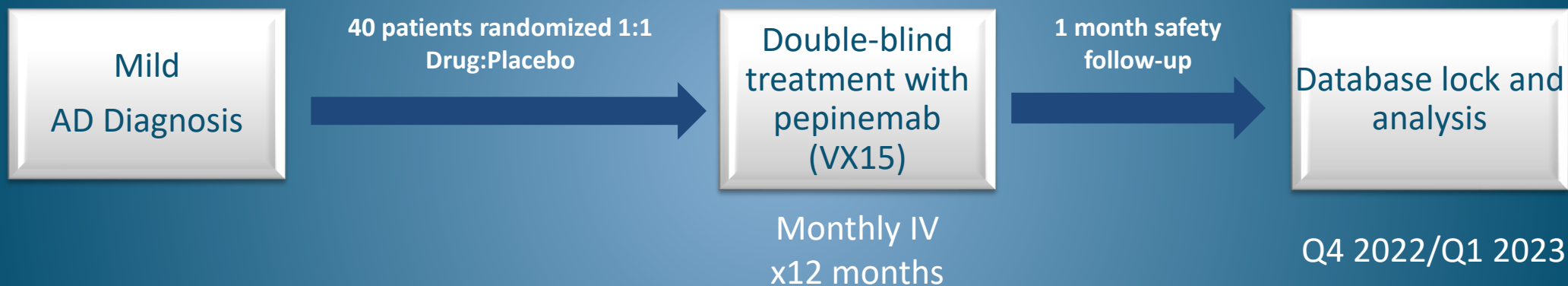
- Confirmed penetration into CNS at expected level
- Antigen-antibody complexes detected

Phase 3-ready asset for HD

Broad application – targets common pathology in neurodegeneration

Initiated phase 1/2 trial in AD

Clinical Trial Design Alzheimer's Disease



Study Objectives

- Safety and tolerability
- Cognitive Function measures, CDR-SB, ADAS-Cog13
- Brain imaging measures, FDG-PET

Funding by



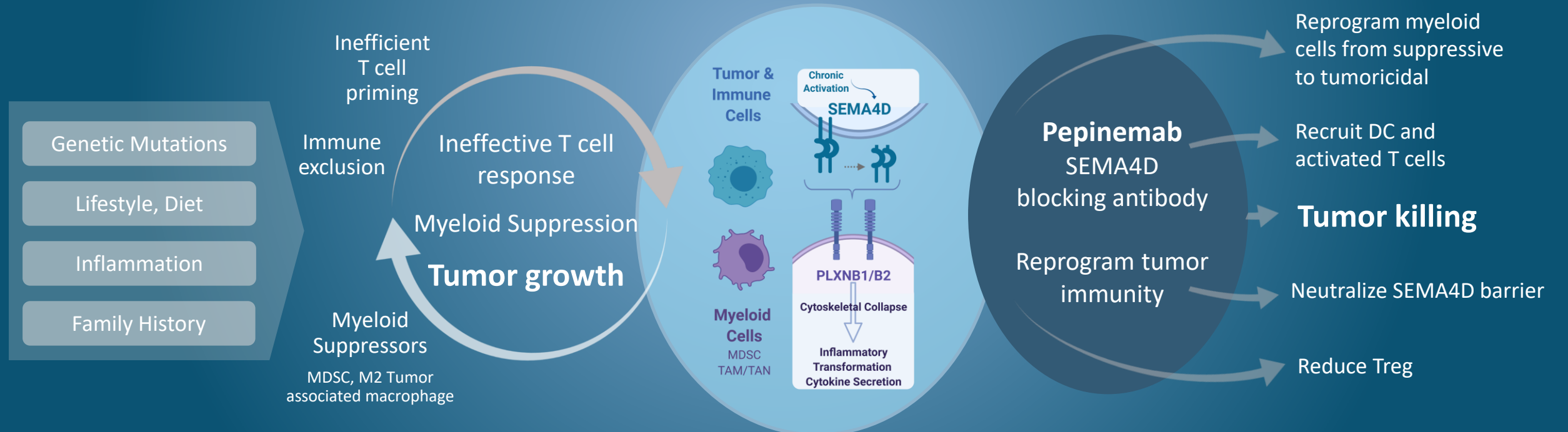


Pepinemab Antibody Cancer Immunotherapy

Science in the Service
of Medicine



Pepinemab reprograms underlying pathology in Cancer



Why does immune response fail in tumors?

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

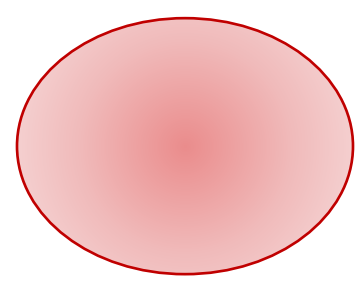
Paul E. Clavijo¹, Jay Friedman¹, Yvette Robbins¹, Ellen C. Moore¹, Ernest Smith², Maurice Zauderer², Elizabeth E. Evans², and Clint T. Allen^{1,3}



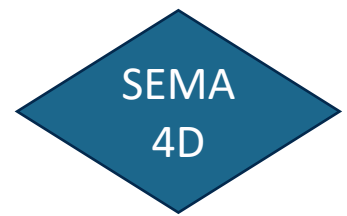
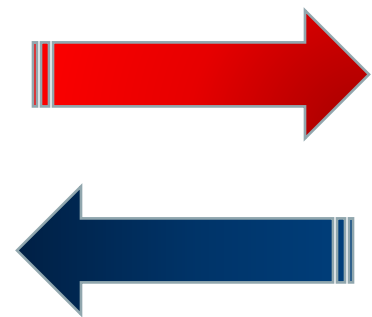
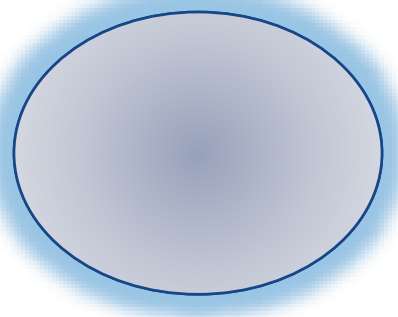
1. T cell exhaustion:
PD-L1, CTLA-4, etc
Treg

2. Myeloid cell exhaustion:
MDSC, M2 Tumor
associated macrophage

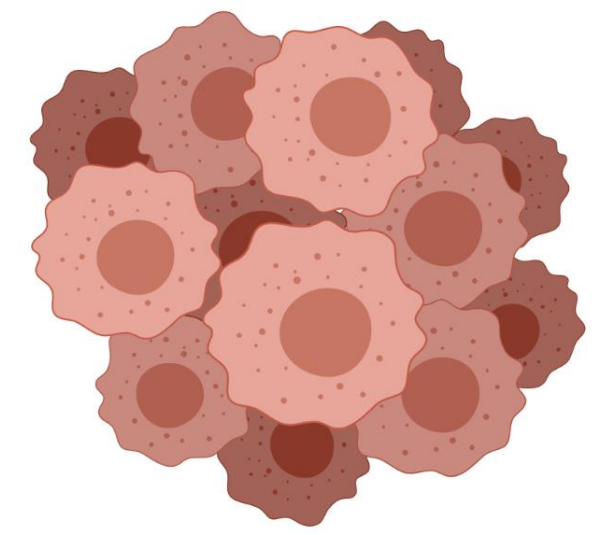
“Killer” T cells



Suppressor cells



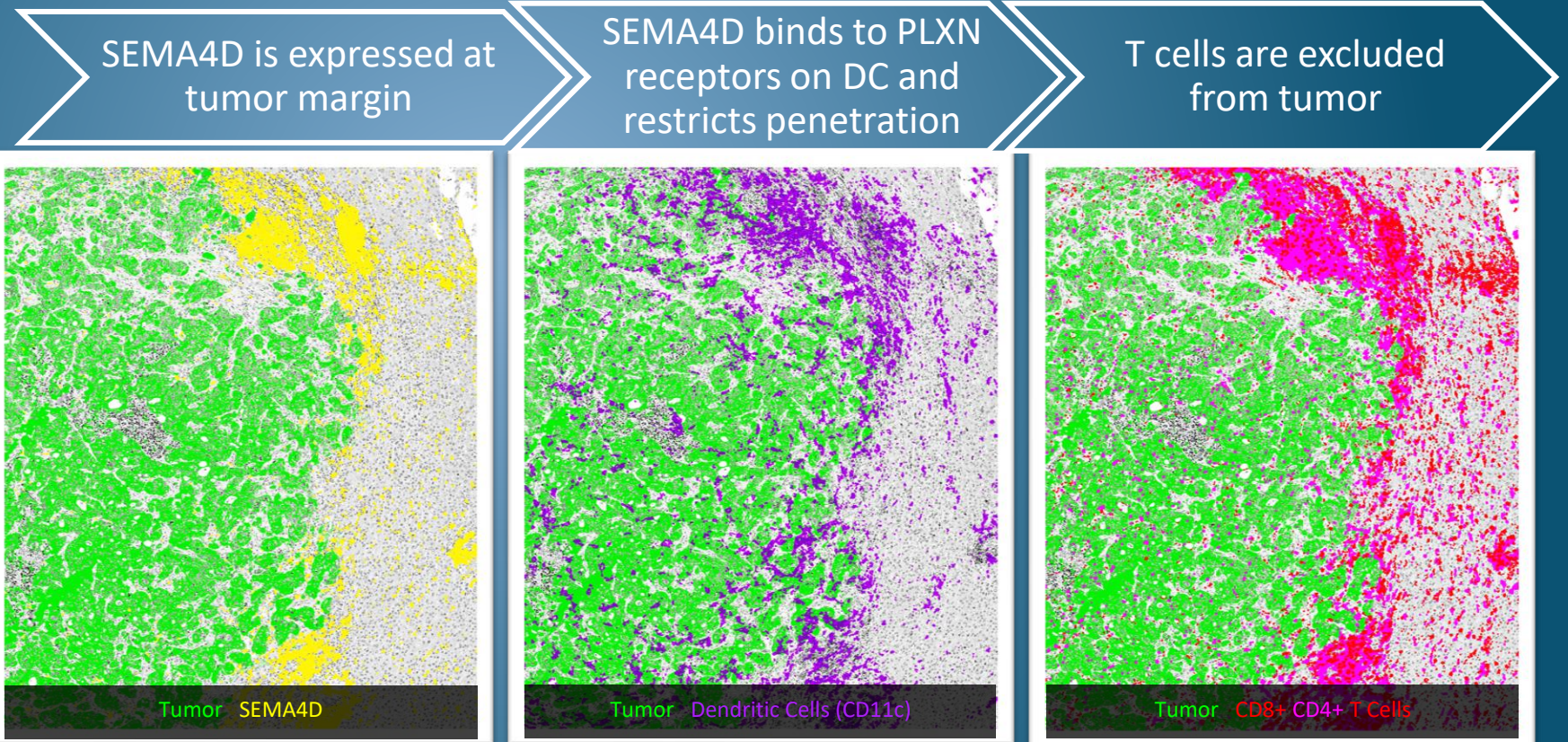
Tumor



Why does natural immune response fail in cancer?

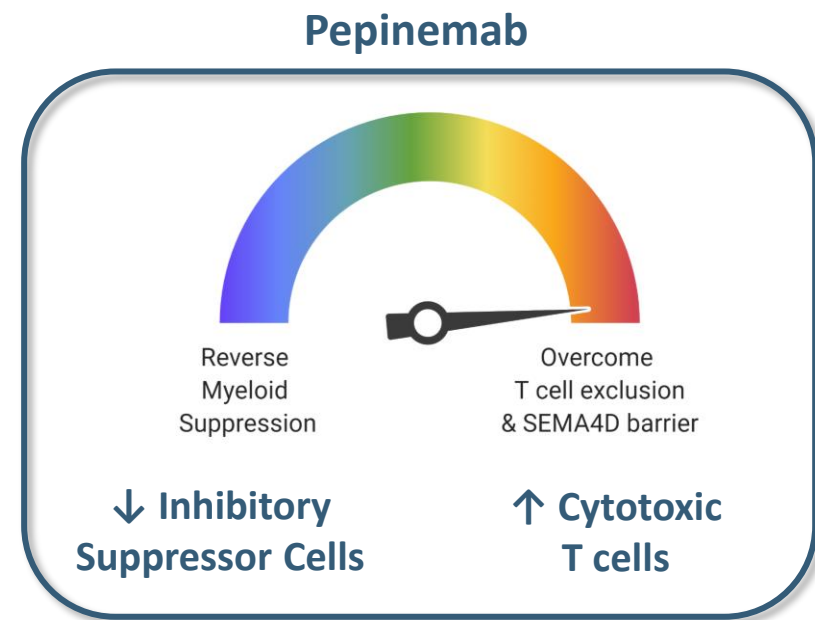
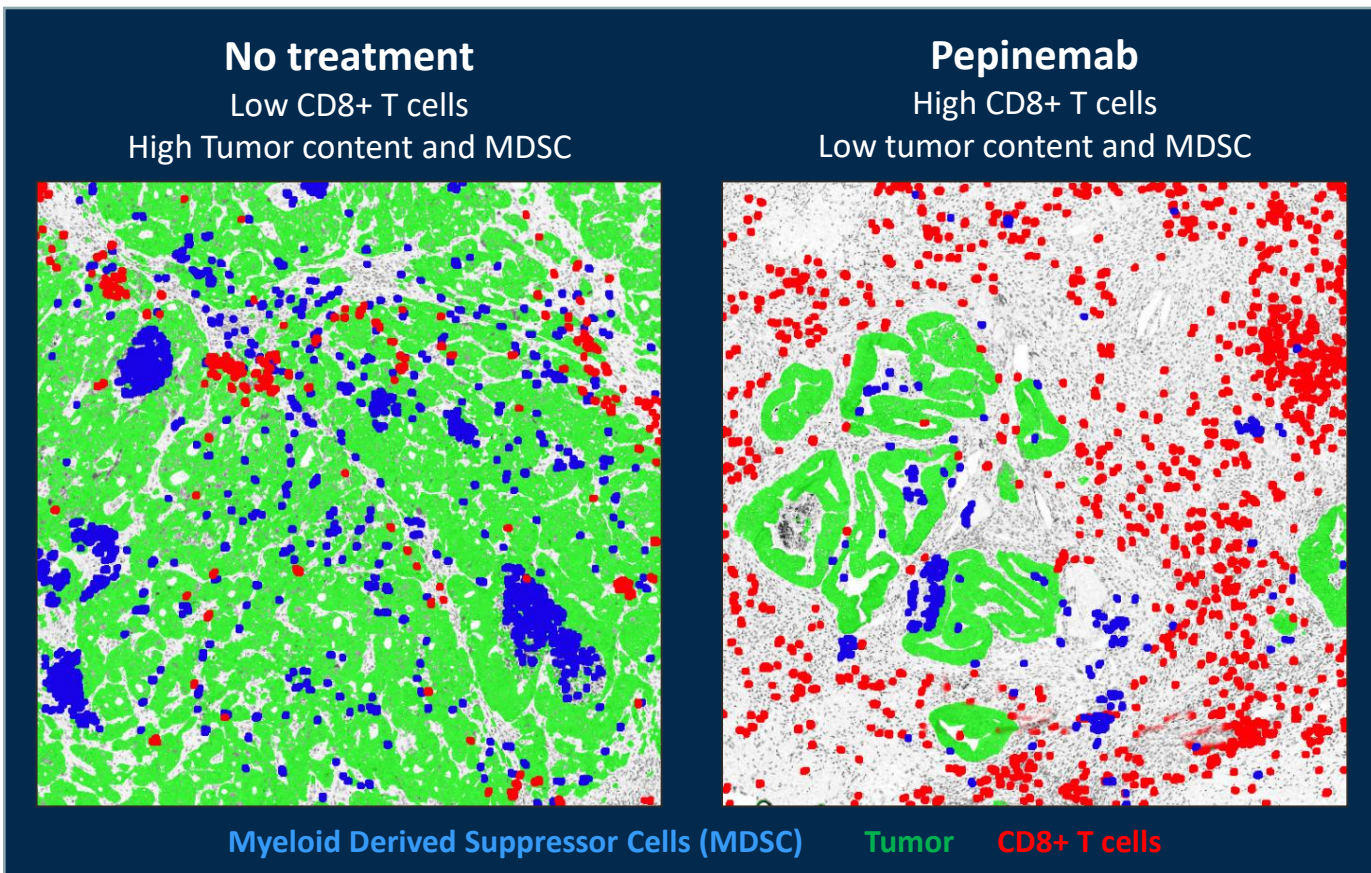
3. Immune Exclusion:

Activated T cell and Dendritic cells can't get in



Pro-inflammatory cells are excluded from the metastatic CRC 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.

Clinical POC - Pepinemab increases cytotoxic T cells while reducing inhibitory suppressor cells



Biopsies from patients with metastatic MSS Colorectal Cancer

Patients received neoadjuvant chemotherapy before immunotherapy and surgery
Winship Cancer Institute, Emory University – neoadjuvant/"window of opportunity" study

Pepinemab has a unique Mechanism of Action that complements Immune Checkpoint Therapy

Combination therapy to overcome multiple immune resistance mechanisms

Pepinemab

Facilitates T cell infiltration
Reduces immune suppression

+

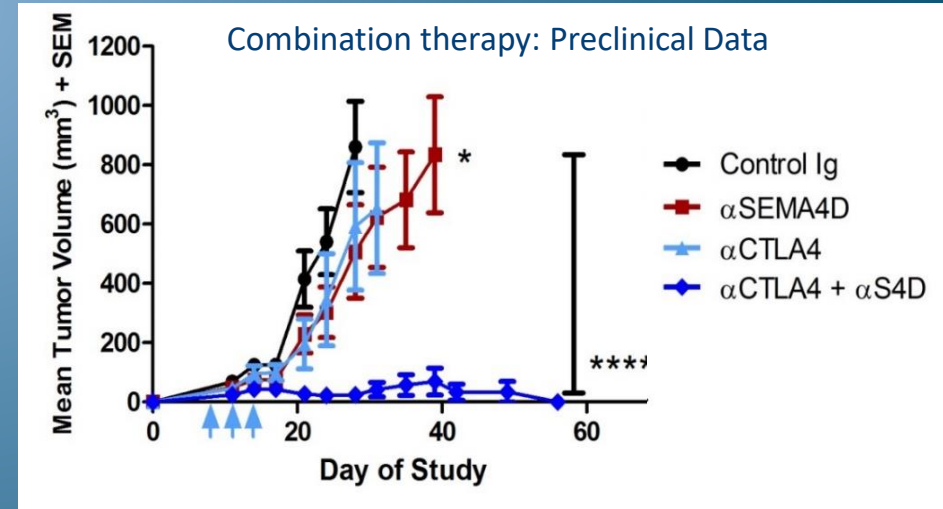
Immune Checkpoint Inhibitors
Sustain T cell activity

Research Article

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

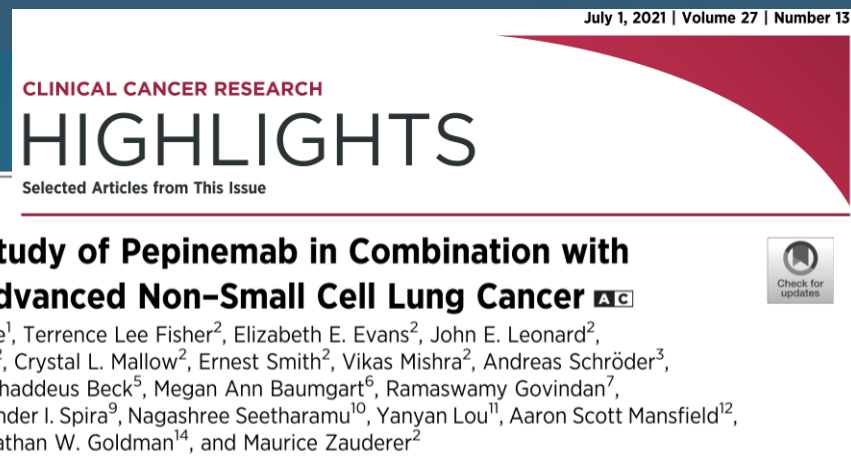
Elizabeth E. Evans, Alan S. Jonason Jr, Holm Bussler, Sebold Torno, Janaki Veeraraghavan, Christine Reilly, Michael A. Doherty, Jennifer Seils, Laurie A. Winter, Crystal Mallow, Renee Kirk, Alan Howell, Susan Giralico, Maria Scrivens, Katya Klimatcheva, Terrence L. Fisher, William J. Bowers, Mark Paris,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

Cancer Immunology Research

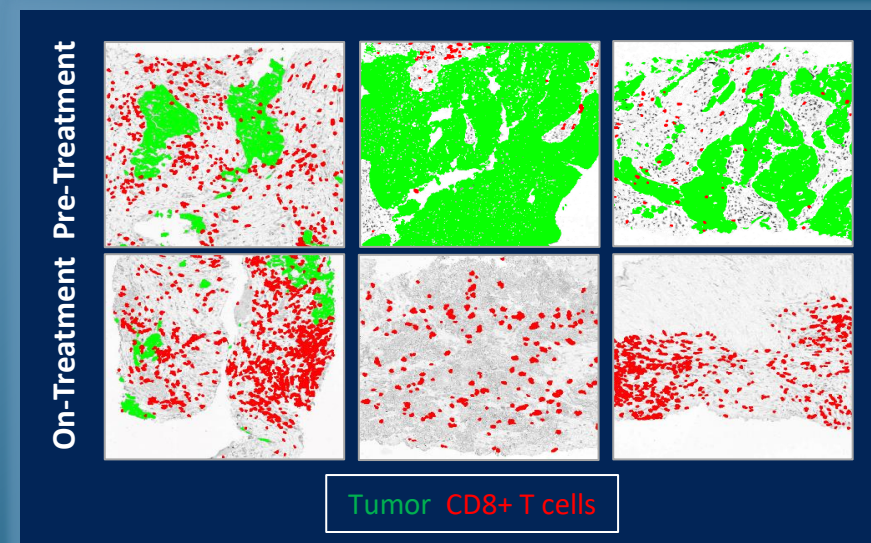


Pepinemab complements other immune-activating therapies - anti-PD1/L1, anti-CTLA-4, anti-LAG3, anti-TGF-β, DC vaccine, etc

Phase 1b/2 CLASSICAL-Lung Highlights

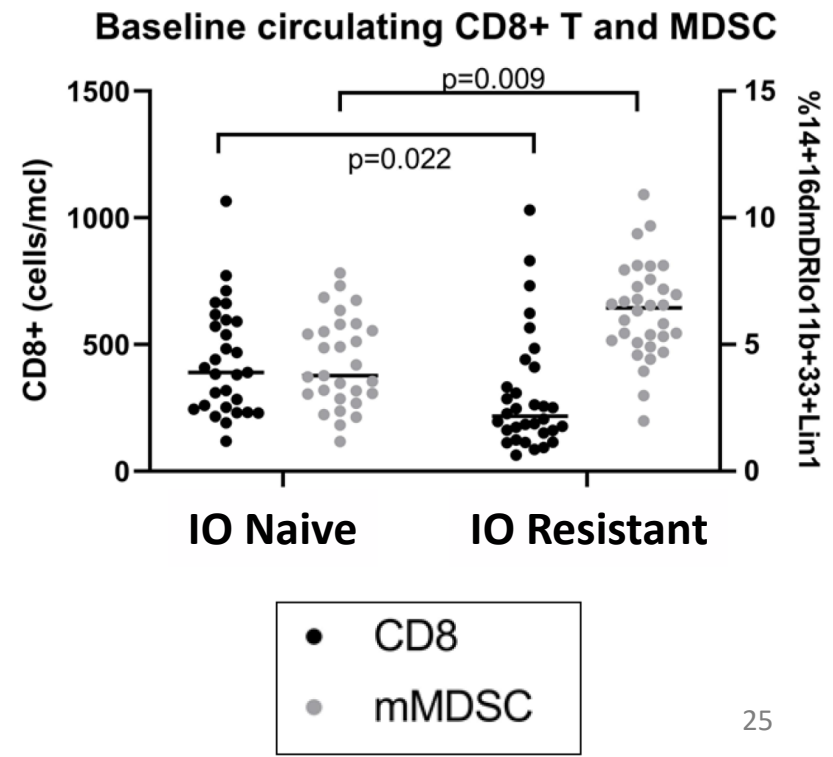
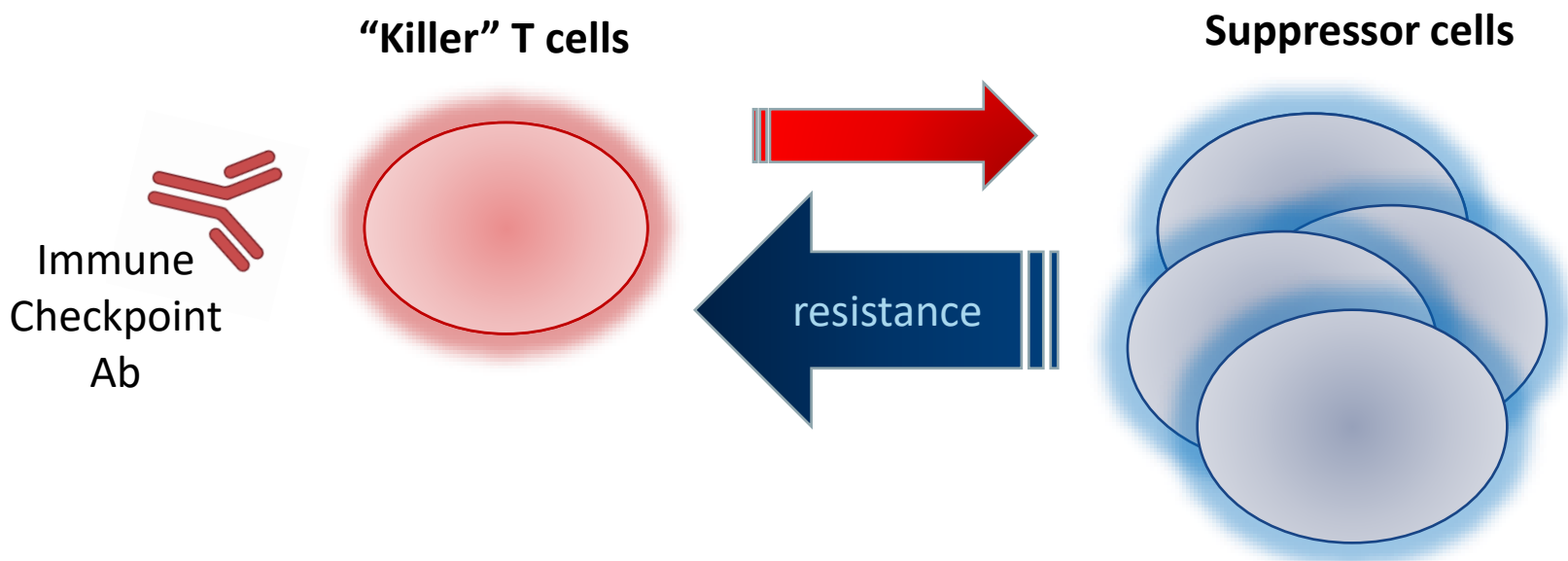


1. Well tolerated. Pepinemab does not enhance immune-related toxicities of partner drug.
2. **Unmet Need:** Antitumor activity in PD-L1 low or PD-L1 negative tumors
 - **Reported single agent anti-PDx:** ORR ~10-15%
 - **Combination with pepinemab:** ORR 25-33%
3. **Unmet Need:** Antitumor activity in tumors that were resistant/refractory to prior therapy with single-agent checkpoint inhibitors
4. Increased penetration of cytotoxic T cells following treatment



Lessons learned: CLASSICAL-Lung

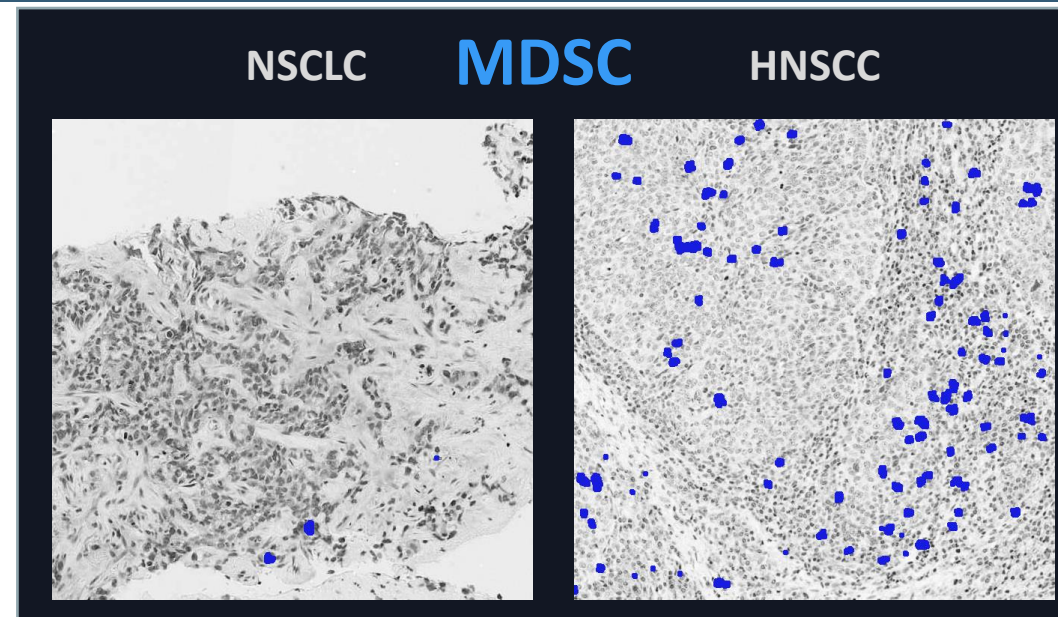
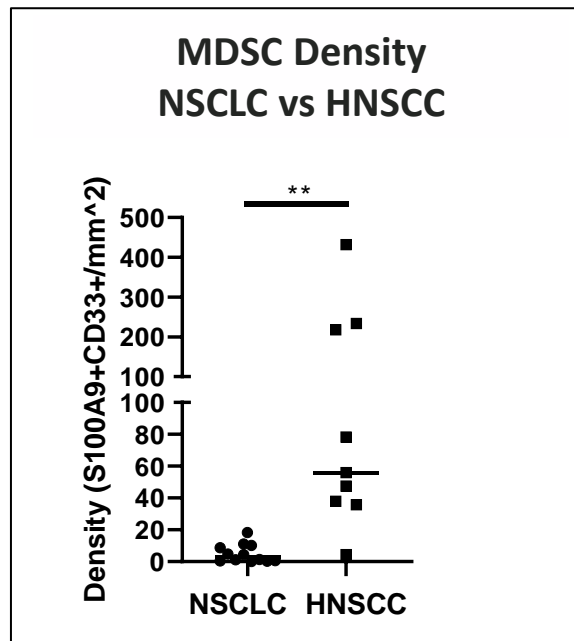
1. Pepi is well tolerated
2. Pepi overcomes resistance factors
3. Accumulation of myeloid suppressors drives resistant/refractory tumors



Lessons learned: Next steps

4. Head and Neck cancer (HNSCC) have high levels of MDSC, relative to lung cancer (NSCLC)

- SEMA4D is strongly expressed in HNSCC & induces high levels of myeloid derived suppressor cells (MDSC)
- Low response rate to immune checkpoint therapy in HNSCC
- **Hypothesis:** Inhibiting MDSC with pepinemab will enhance response to pembrolizumab in HNSCC



NSCLC: pre-treatment biopsies from CLASSICAL-Lung

HNSCC: pre-treatment and no treatment biopsies from HNSCC integrated biomarker trial (collaboration at Emory University)

Keynote B84 for front line treatment in R/M Head & Neck Cancer patients Combination Immunotherapy with KEYTRUDA®

Phase 1b
Safety Run-in

Phase 2
Efficacy
(up to 65)

20 mg/kg Pepinemab
+200 mg Pembrolizumab
~50% CPS < 20
~50% CPS ≥ 20

Sponsored by:


Drug provided by:
Merck, MSD



Study Objectives

- Safety, tolerability, RP2D (Phase 1b) and Objective Response Rate (Phase 2)
- Secondary objectives include further evaluation of activity (PFS, OS, DOR), biomarkers within TME
- Data anticipated mid-2022

Pepinemab for Immuno-Oncology



Mechanism of Action: Facilitate infiltration of T cells and dendritic cells
Reduce immunosuppression



Safety and tolerability: Well tolerated
Does not enhance immune-related toxicities of partner drug



Clinical Efficacy (POC): Appears to increase frequency and duration of objective responses
Durable responses in some patients with PDx-resistant/refractory disease
Apparent 2-3X increase in ORR in patients with PD-L1 negative/low tumors compared to single agent checkpoint inhibitor

Initiated Phase 2 trial in HNSCC

Broad application in solid tumors – enhances activity of immunotherapies

Current Achievements and Milestones

| | |
|---|----------------------------|
| Final Clinical Data for SIGNAL Cohort B study in Huntington’s Disease | Q3 2021 |
| Publish Clinical Data for SIGNAL study in Huntington’s Disease | 2021 |
| 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, https://clincancerres.aacrjournals.org/content/27/13/3505 | April, 2021 |
| Enrollment of first patient for phase 2 study of Pepinemab in Combination with Keytruda® in front line Head & Neck Cancer Expect interim data mid-2022 | Q2 2021 Mid-2022 |
| Enrollment of first patient in Alzheimer’s disease phase 1b/2a study Expect data from blinded placebo-control study | Q2 2021 Q1 2023 |

Currently exploring pharma collaboration in HD and AD



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.

| VCNX (NASDAQ) | |
|-----------------------------|-------------------|
| Incorporated | 2001 |
| Headquarters | Rochester, NY |
| Employees | 39 |
| IPO | August 2018 |
| February 2021 Capital Raise | \$32 M |
| Cash balance* | \$22.4M |
| Shares Outstanding* | 30.8M |
| Analysts | BTIG (T. Shrader) |

Contact us



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Vaccinex Selected References, Oncology

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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
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