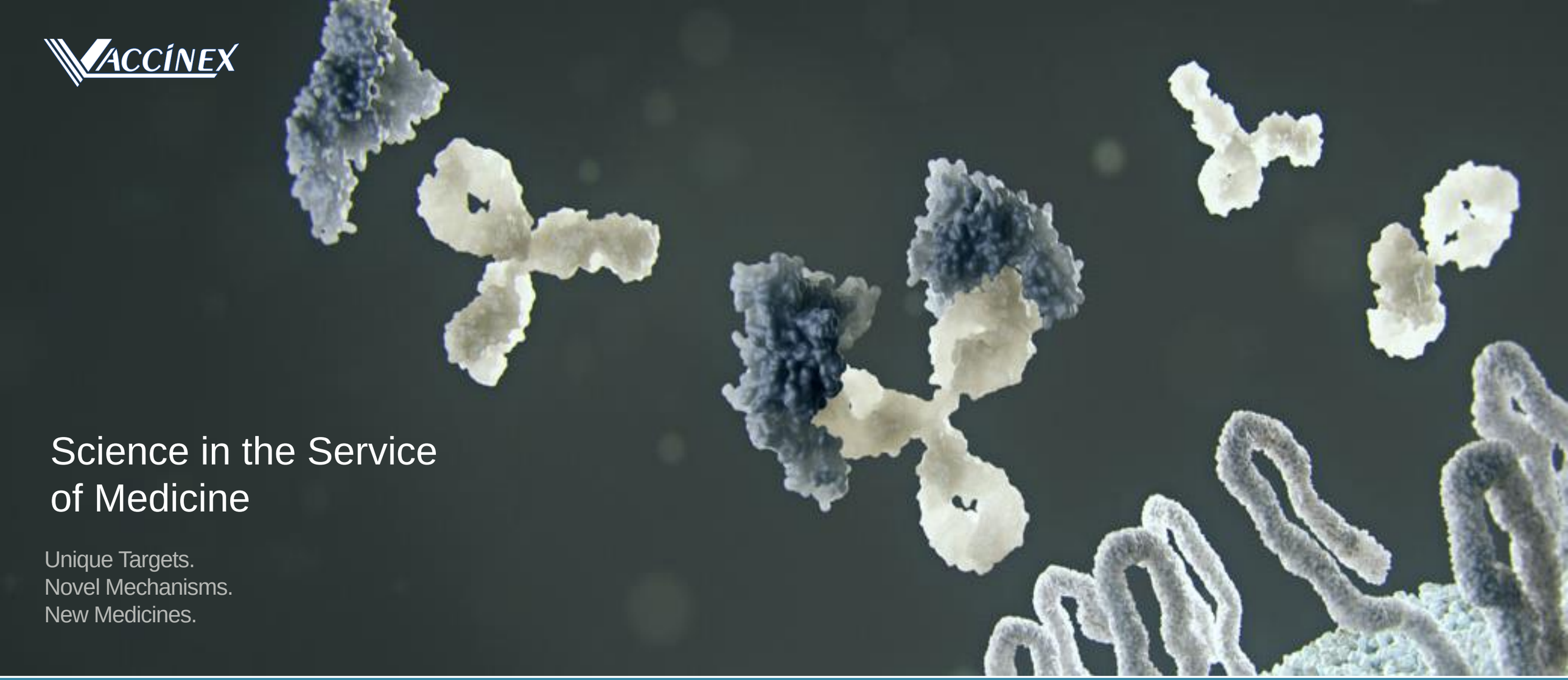

Reprogramming myeloid cells in TME with first-in-class Semaphorin 4D Mab enhances combination immunotherapy

Elizabeth Evans, VP Preclinical Research

Disclosure Information

Fourth CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, 2018

Elizabeth Evans

I have the following financial relationships to disclose:

Employee of: Vaccinex, Inc

- and -

I will discuss the following investigational use in my presentation: pepinemab

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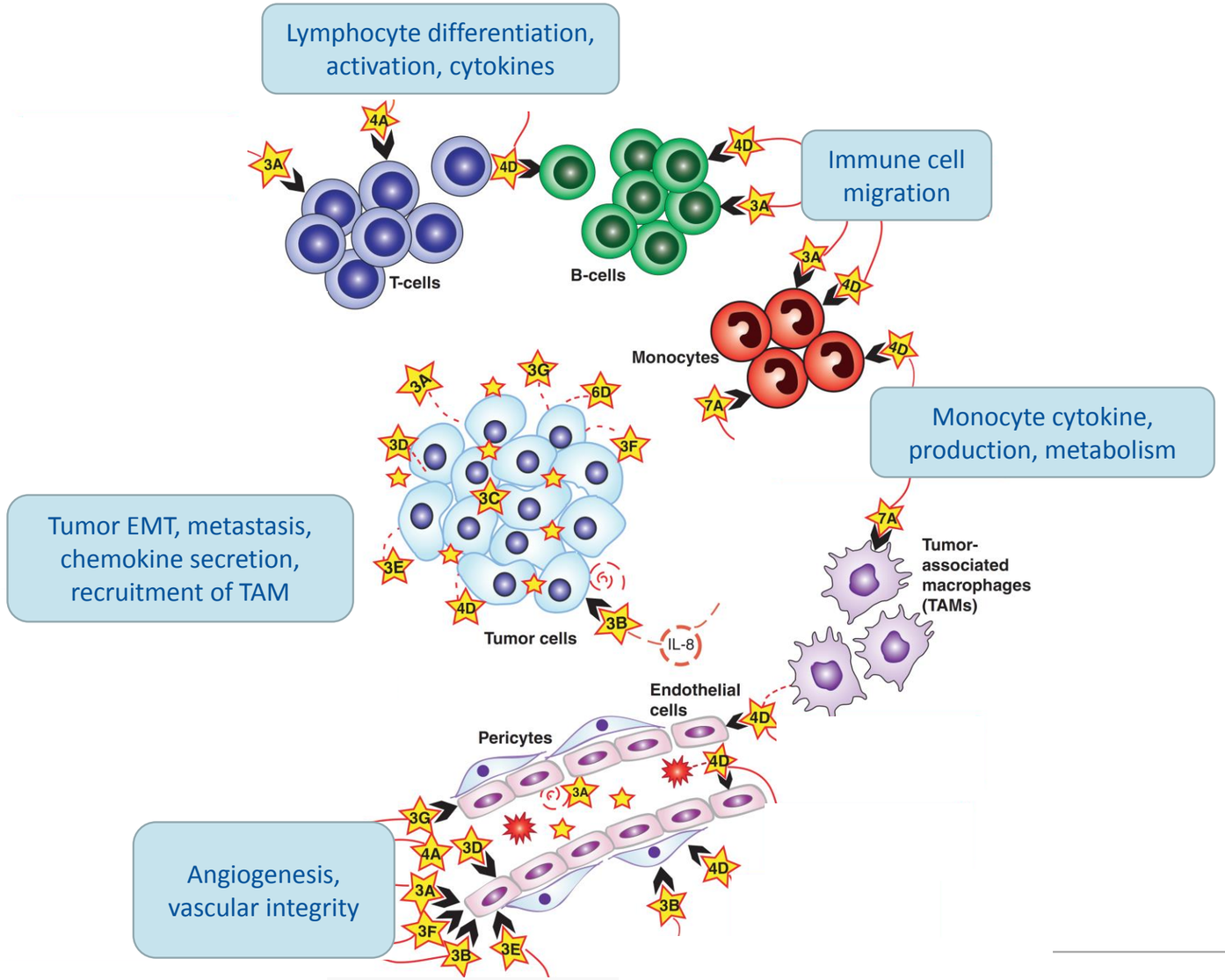
Semaphorins are guidance cues in tumor microenvironment



- Semaphorins are guidance molecules, directing cellular movement and differentiation
- Semaphorins and cognate receptors are overexpressed in many malignancies and some are associated with poor prognosis.

- **SEMA4D and its receptors are expressed on precursor cells, including immune cells, vasculature and tumor cells**
- **Many mesenchymal precursor cells are immunosuppressive within the TME**
  - **MDSC, M2 TAM**
  - **Endothelial cells**
  - **Cancer associated fibroblasts**
  - **Tumor cells**

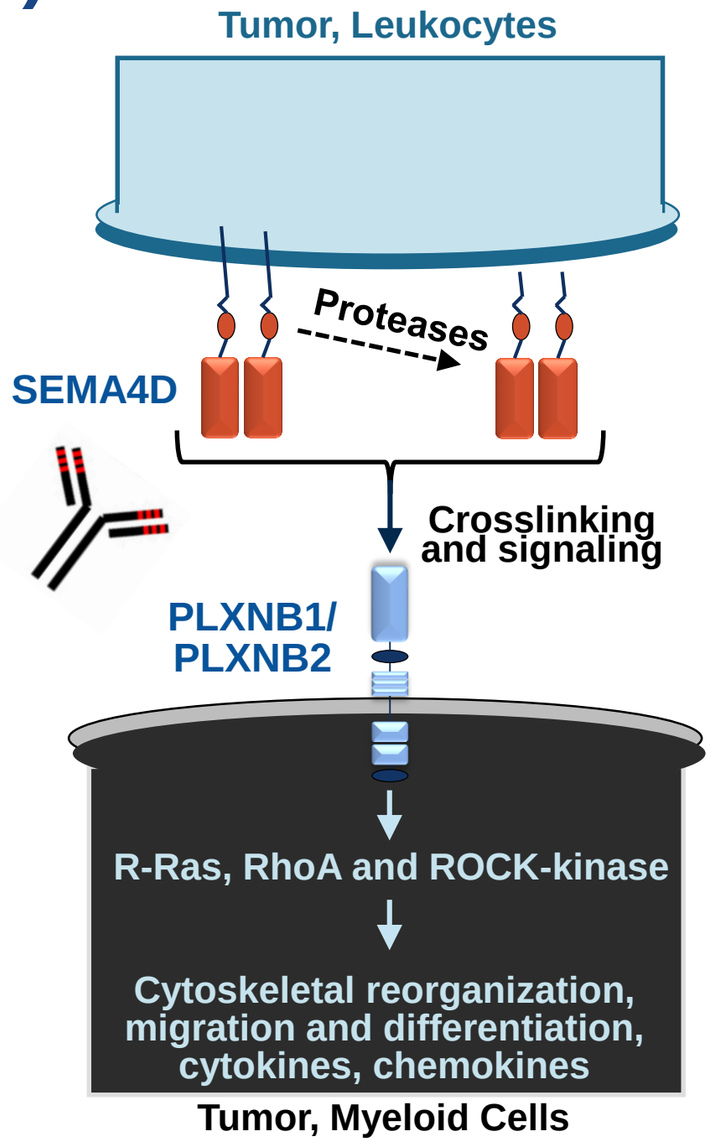
Adapted from Neufeld et al, Drug Resistance Updates 2016

Introduction to Semaphorin 4D (SEMA4D, CD100)

- SEMA4D is an extracellular signaling molecule that regulates the activity of inflammatory cells at sites of injury or cancer
- SEMA4D signals through PLXNB1 and PLXNB2 receptors to regulate (1) cell cytoskeleton (2) cytokine synthesis and secretion
- **In TME, SEMA4D inhibits migration and promotes immunosuppressive functions of PLXNB1+ myeloid cells.**

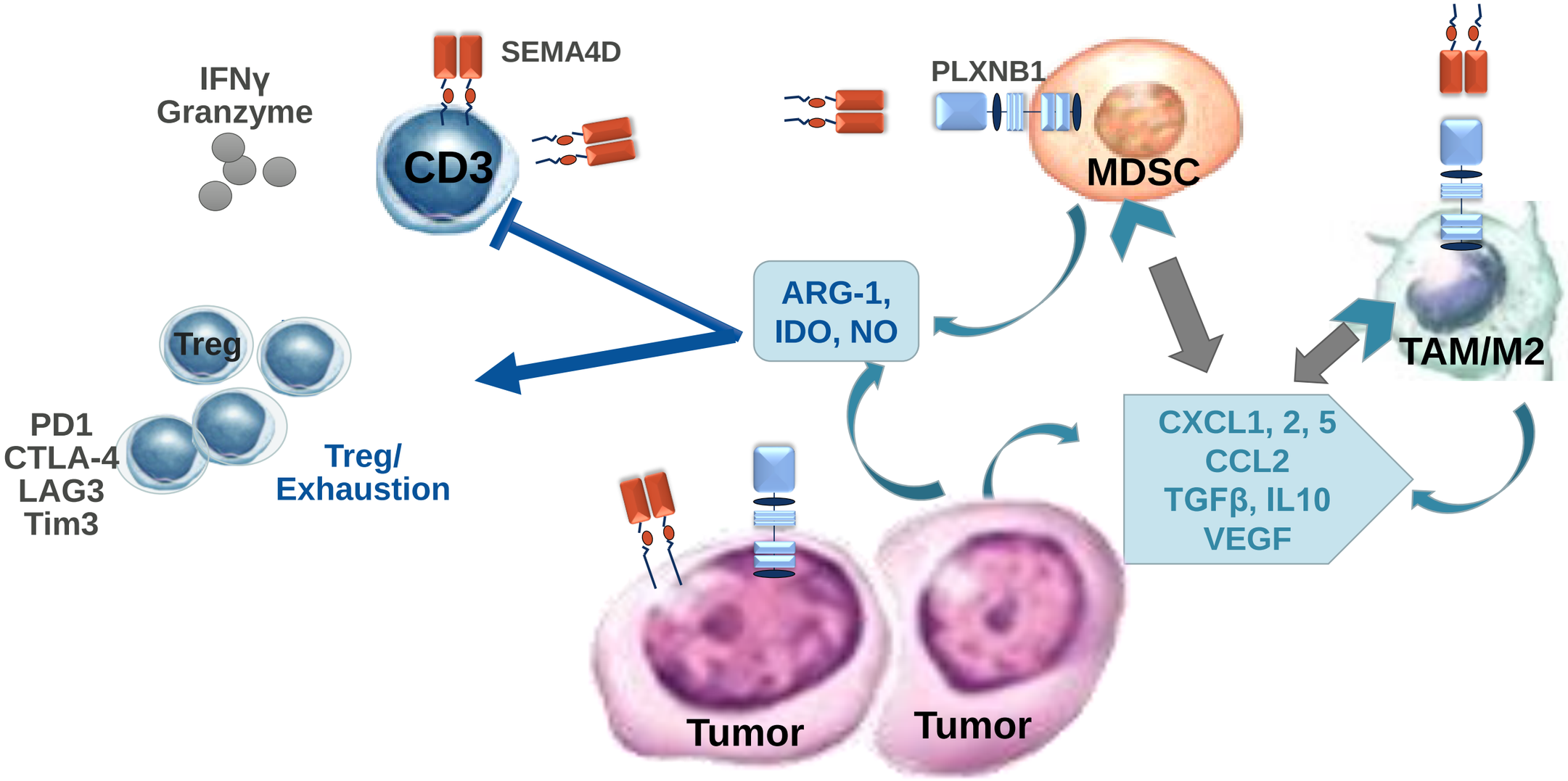
Anti-SEMA4D antibody blocks binding to its receptor and signaling activity

- **Promotes infiltration of potent APC and T cells**
- **Inhibits differentiation/function of MDSC, M2 TAM and Treg**
  - Pepinemab (VX15/2503): humanized IgG4 with hinge modification
  - MAb67: mouse IgG1, cross reacts with mouse and human SEMA4D
    - MAbs do NOT deplete immune cells i*n vivo* and do NOT generally affect immune responses in the periphery

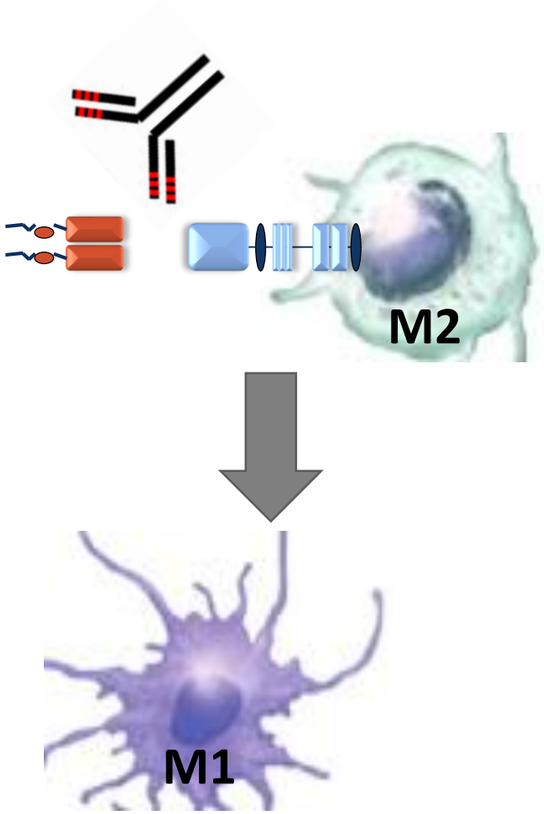


Evans EE et al. Cancer Immunol Res. 2015
Fisher et al. Mabs 2015
Leonard et al. Mol Cancer Ther 2015

Mesenchymal cells and tumor cooperate to suppress T cell responses in the TME

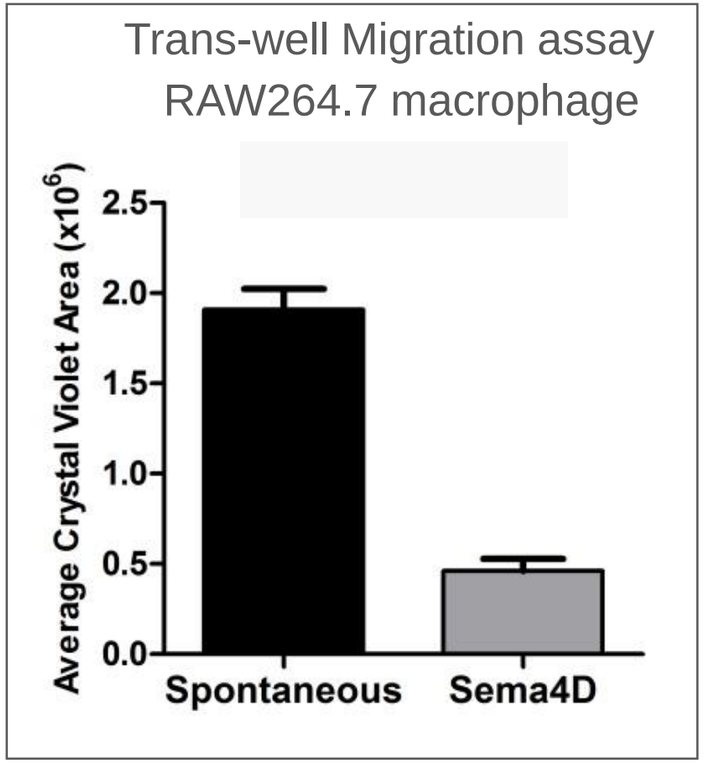


Anti-SEMA4D promotes migration and differentiation of pro-inflammatory APC



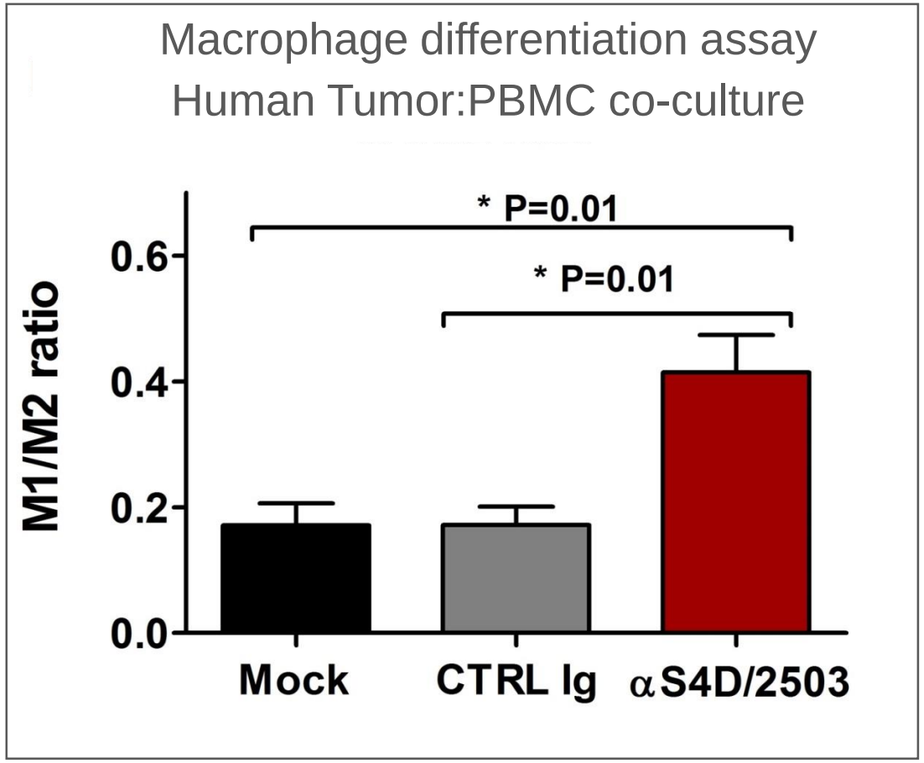
SEMA4D inhibits migration of macrophage

Trans-well Migration assay
RAW264.7 macrophage



Anti-SEMA4D shifts balance of M1/M2

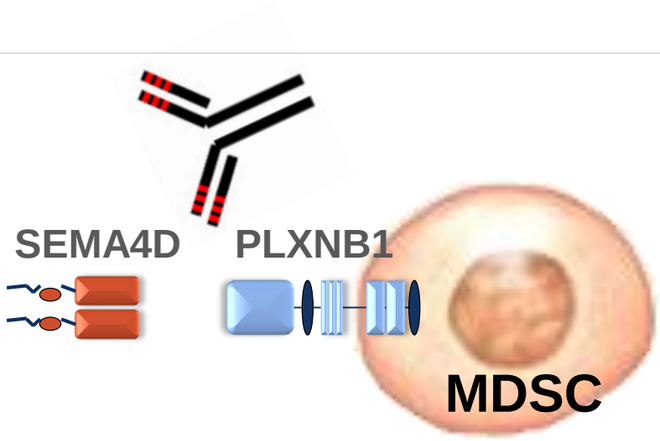
Macrophage differentiation assay
Human Tumor:PBMC co-culture

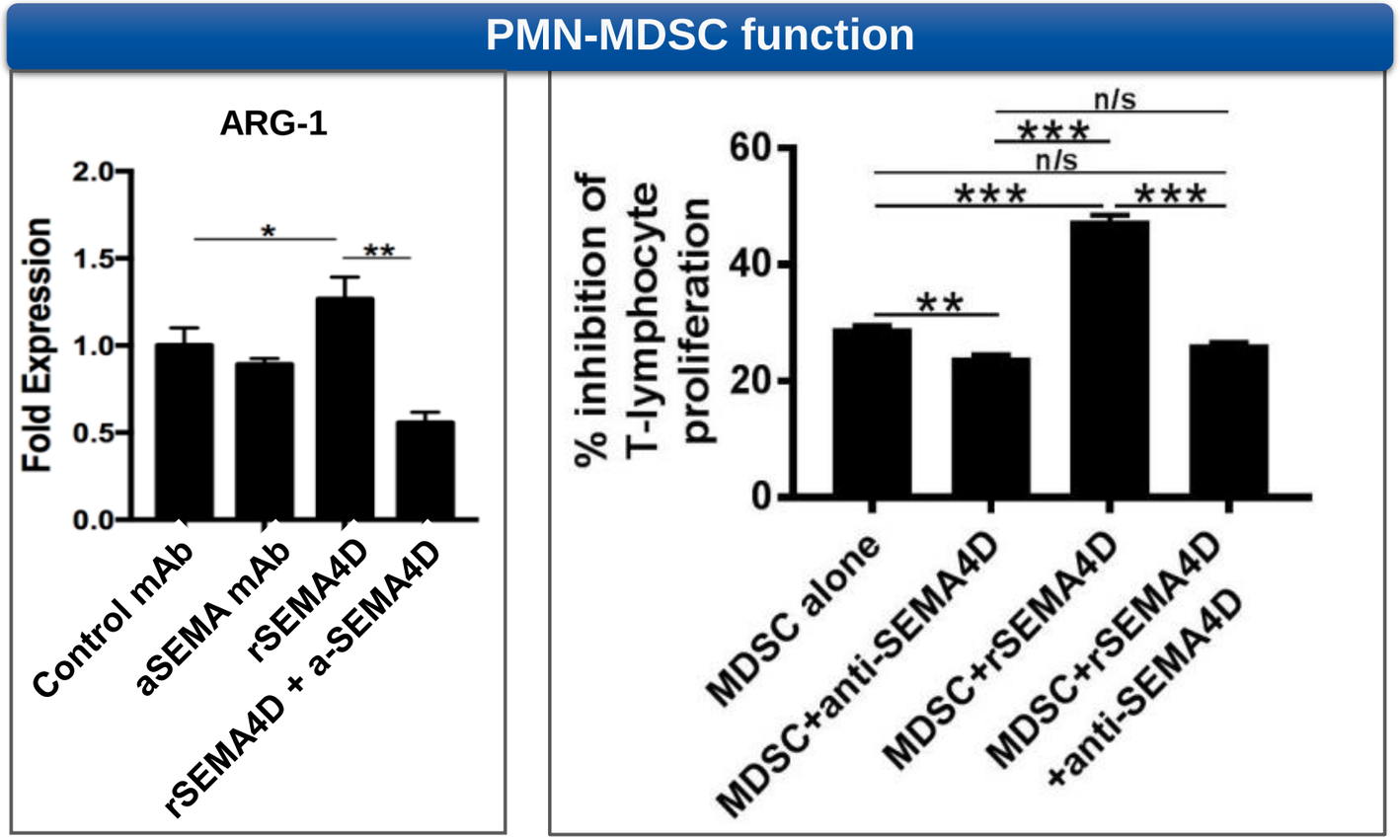


RPMI-8226 Multiple Myeloma tumor supe
M1 = CD14-CD16+, M2 = CD14+CD16+

Anti-SEMA4D Ab reverses MDSC function and recruitment to TME

- **SEMA4D promotes MDSC arginase production and suppression of T cell function**
- **Ab blockade reverses MDSC suppression of T cell proliferation and T cell activity.**





gMDSC isolated from MOC1 tumors and treated *in vitro* with rSEMA and Ab

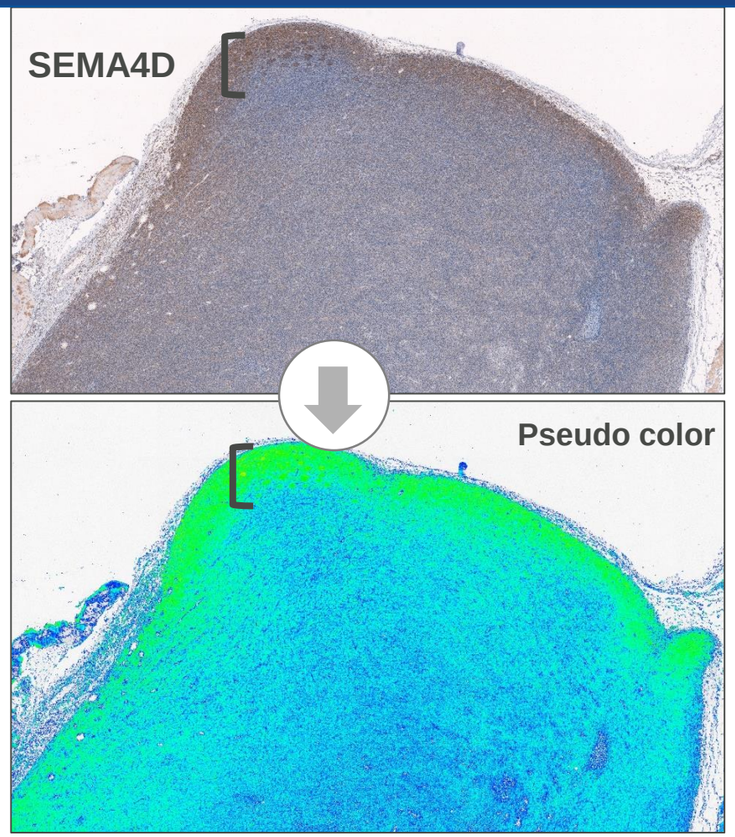
Similar results observed in gMDSC isolated from mice treated *in vivo* with anti-SEMA4D

Clavijo, Allen et al., manuscript in preparation

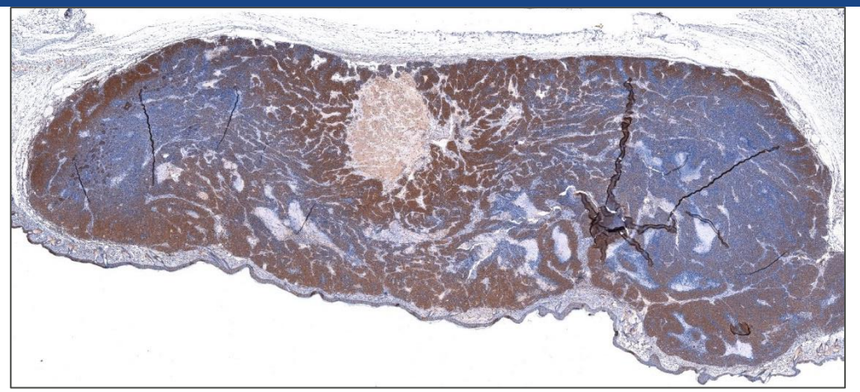
DO NOT POST

SEMA4D Expression Concentrated at Tumor Leading Edge in Murine Tumor Models

Colorectal (Colon26)



Mammary carcinoma (Tubo.A5)



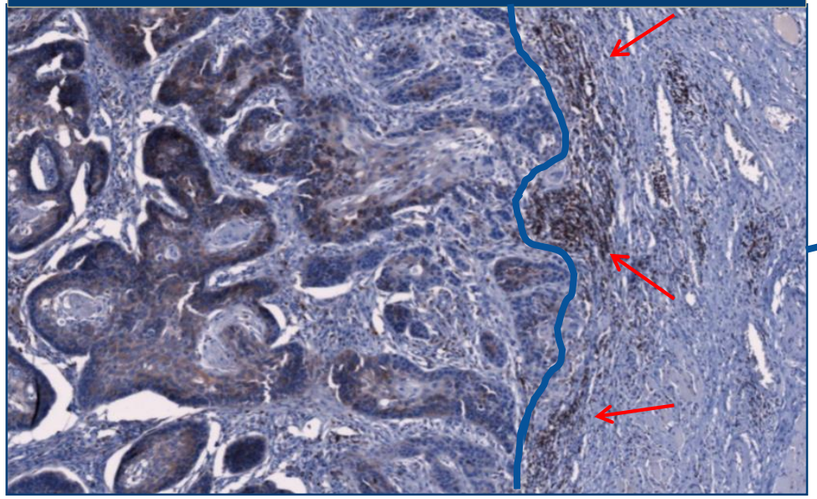
SEMA4D at the invasive margin of the tumor forms a barrier that restricts the infiltration of anti-tumor immune cells

Blocking antibodies against SEMA4D neutralize this barrier and “open the gates” of the tumor to the immune system

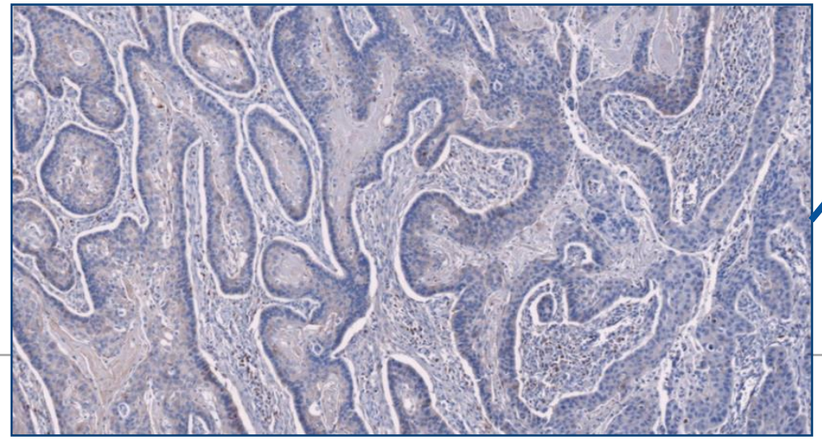
Evans EE et al. Cancer Immunol Res. 2015

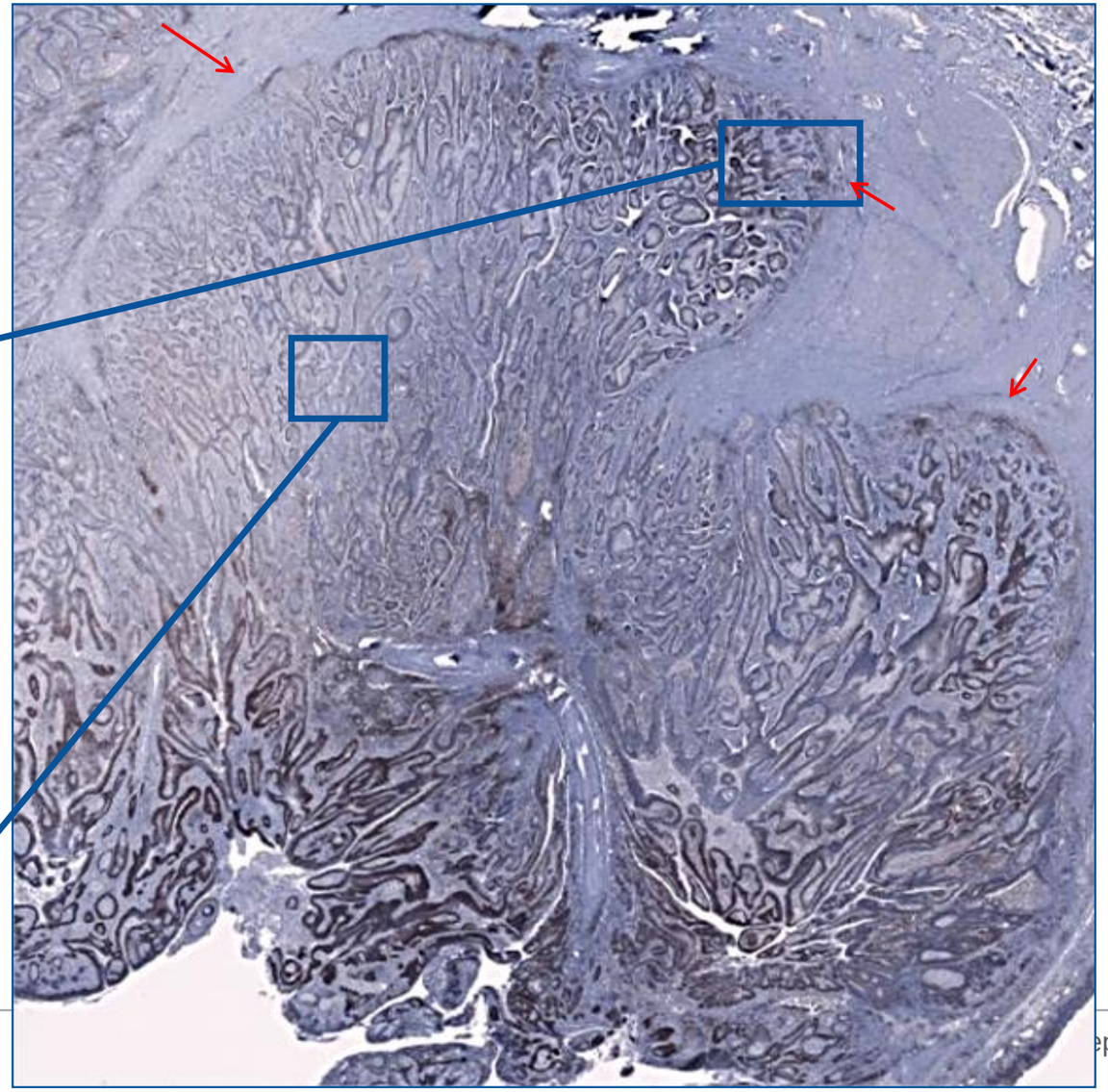
Immune cells are excluded where SEMA4D is concentrated at margins of human HNSCC of the Larynx

High SEMA4D at invasive tumor margin and immune exclusion



Low SEMA4D

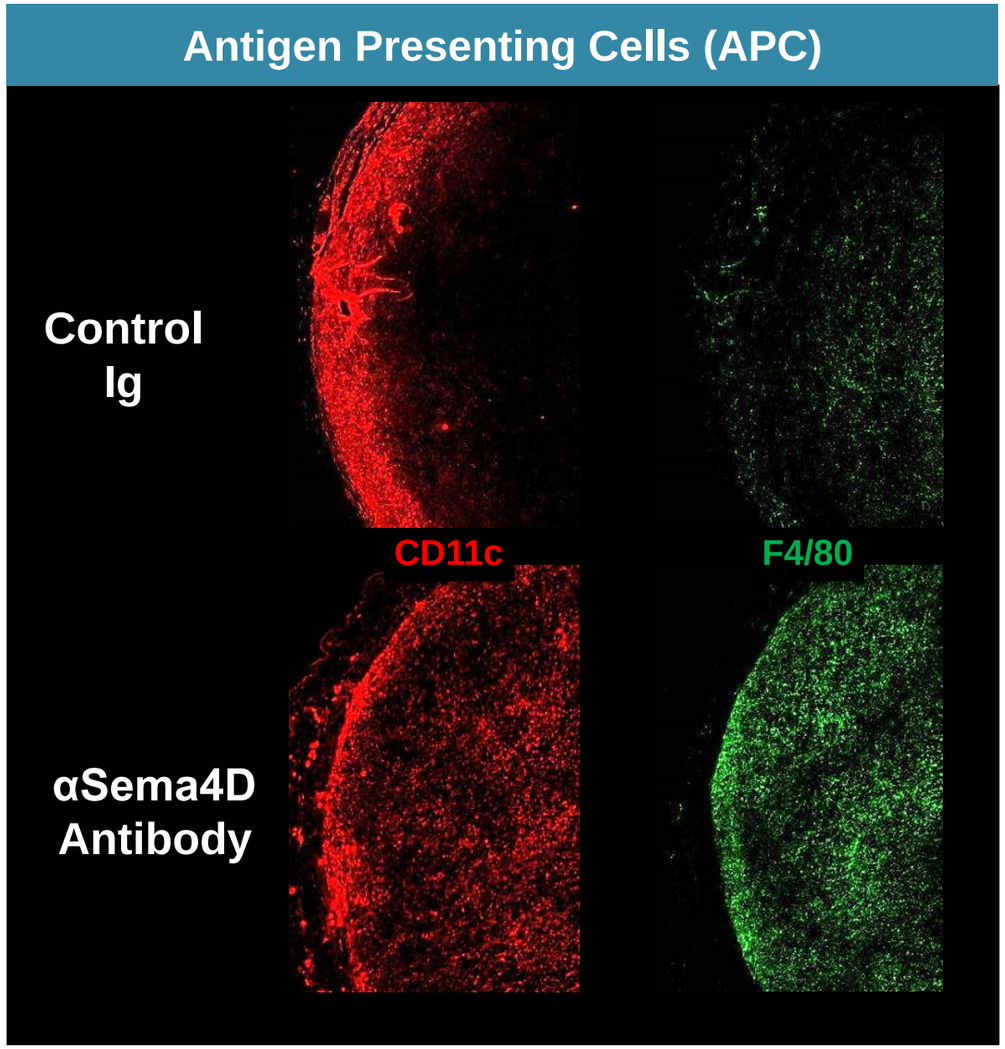




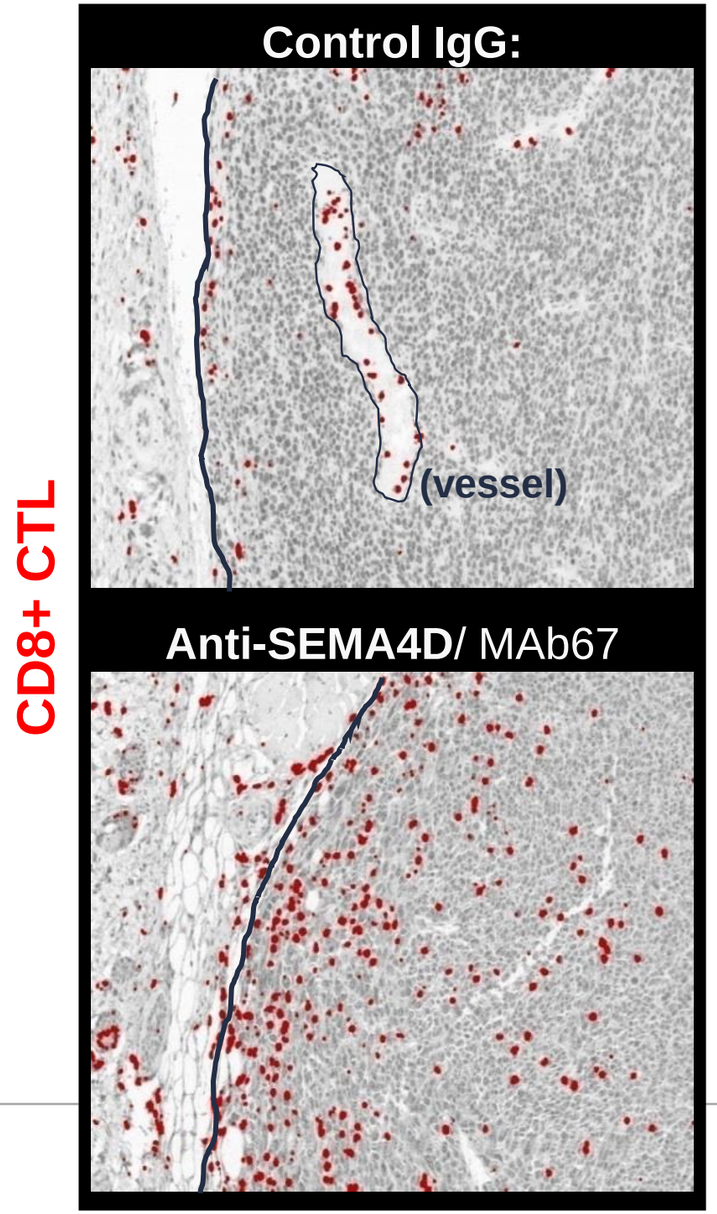
SEMA4D+
↑ TIL

SEMA4D Controls Infiltration of Antigen Presenting Dendritic Cells into Tumor

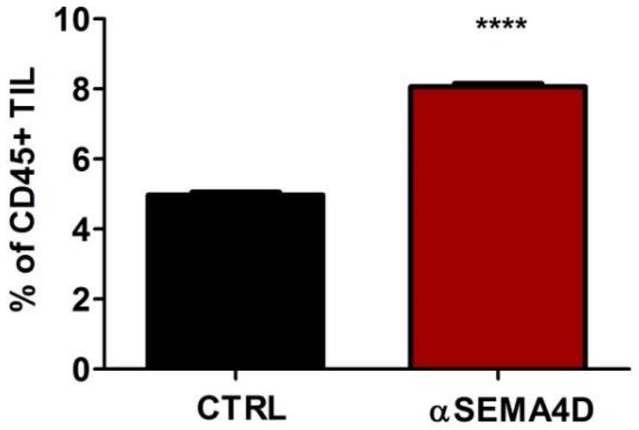
- **Dendritic cells (DC) express receptor PLXNB1.**
- **Binding to SEMA4D restricts penetration of DC into tumor.**
- **Antibody blockade of SEMA4D enhances migration and differentiation of DC within tumor**
  - Reduction in suppressive myeloid cells, such as CD206+ M2 TAM and MDSC, and associated chemokines and
  - Increase in pro-inflammatory APC, with associated chemokines/cytokines



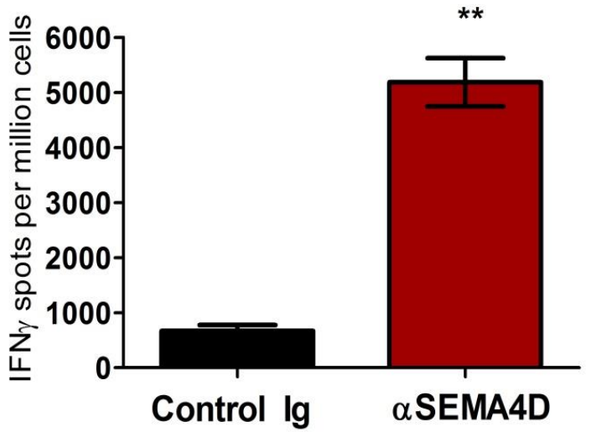
Anti-SEMA4D shifts balance of chemokines and suppressor cells to enhance anti-tumor T cell activity



T cell Infiltration: % CD3+ CD8+ in TIL



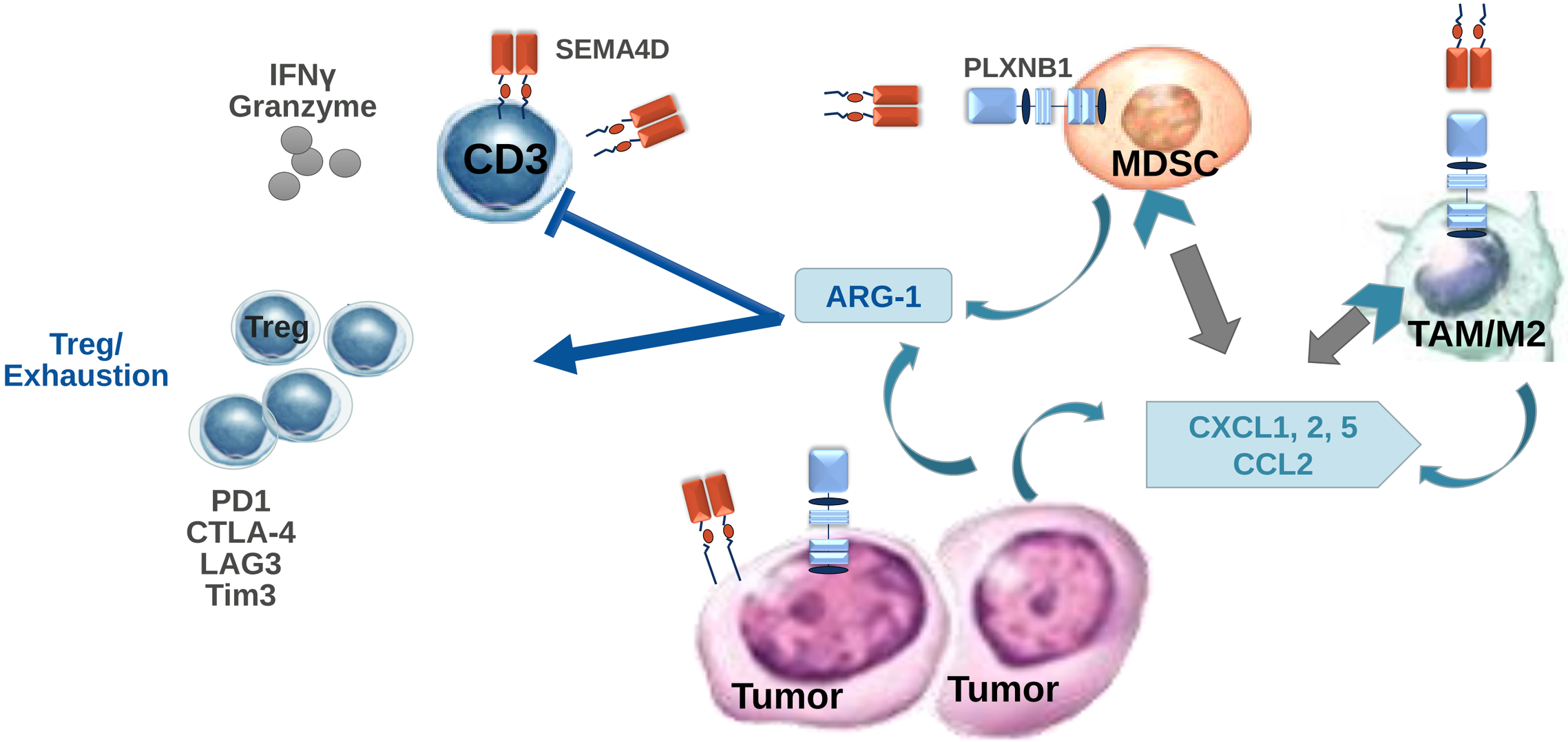
T cell Activity: ELISPOT



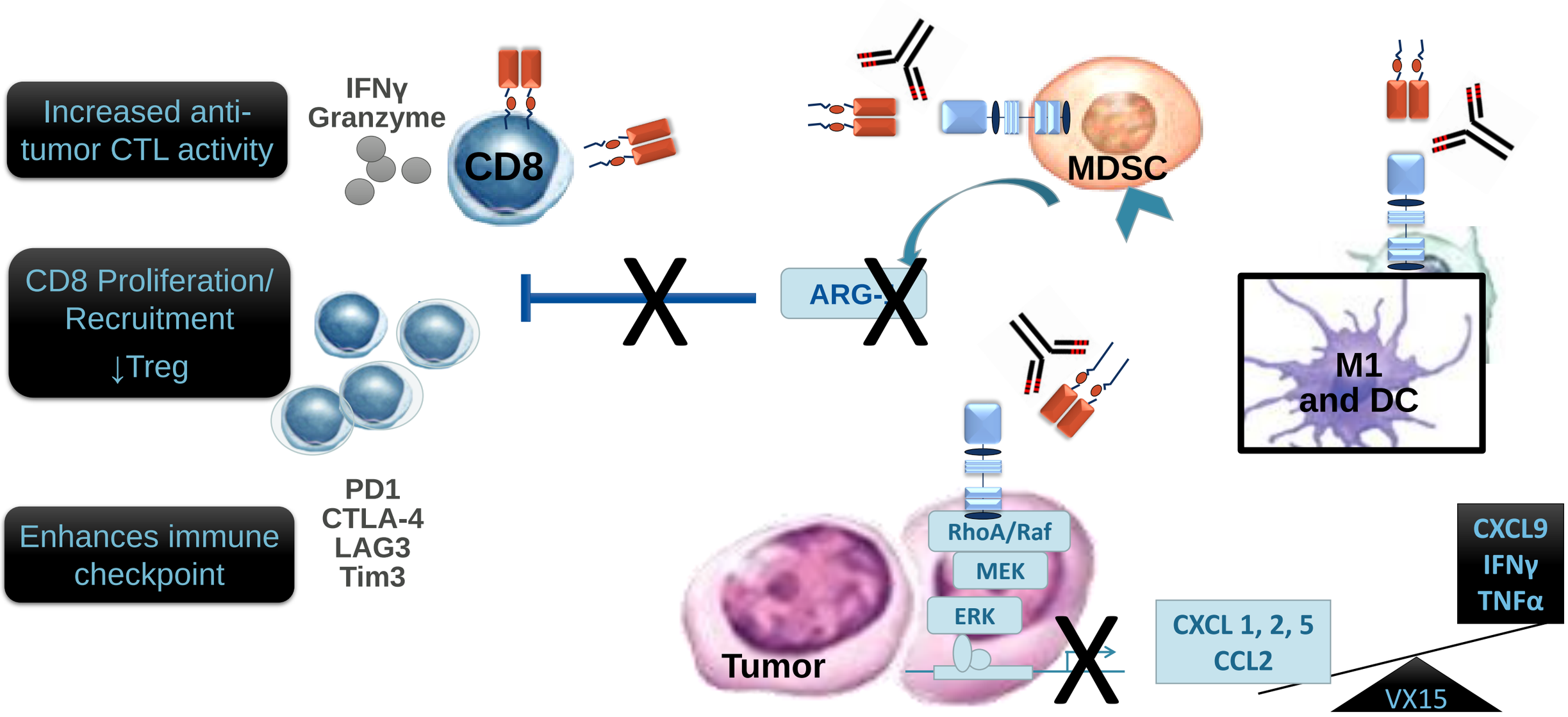
Also observed increase in Type 1 cytokines (IFNg, TNFa) and chemokines that recruit T cells (CXCL9, CXCL10)

Evans EE et al. Cancer Immunol Res. 2015

Mesenchymal cells and tumor cooperate to suppress T cell responses in the TME



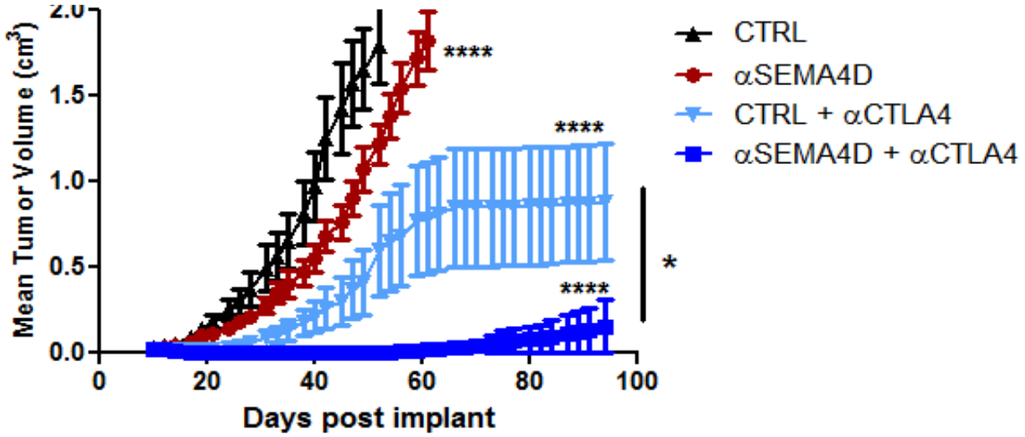
Anti-SEMA4D shifts the balance of mesenchymal suppression to promote T cell activity



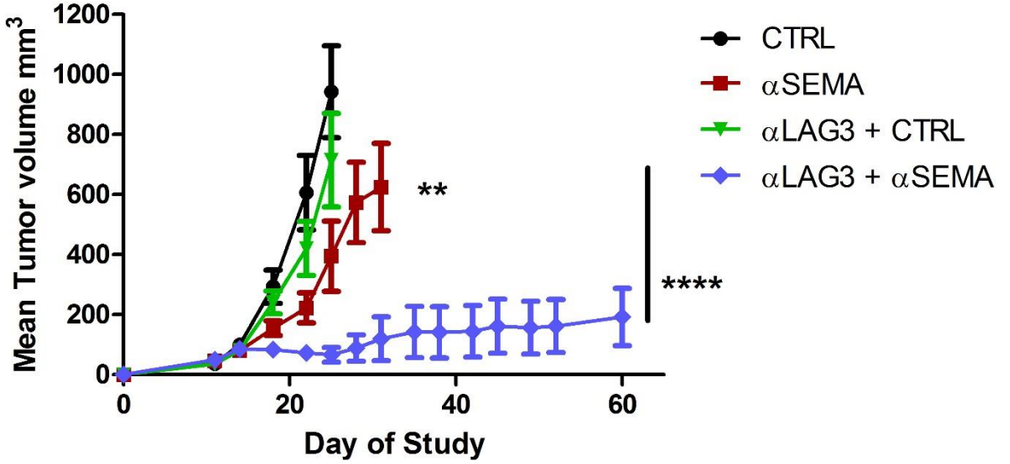
Anti-SEMA4D Antibody Enhances Activity of Immune Checkpoint Antibodies and HDAC inhibitor in Preclinical Syngeneic Models

anti-CTLA-4 Combination: MOC1 HNSCC

(Clint Allen, NIH)

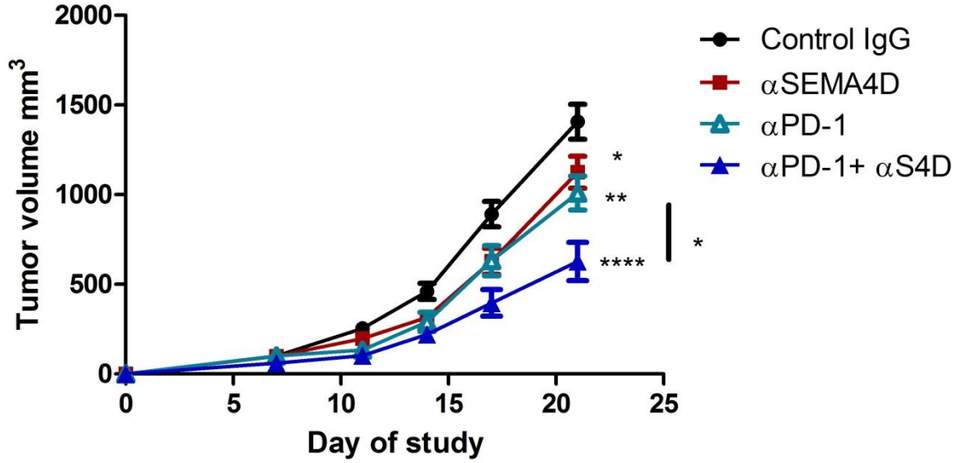


anti-LAG3 Combination: Colon26



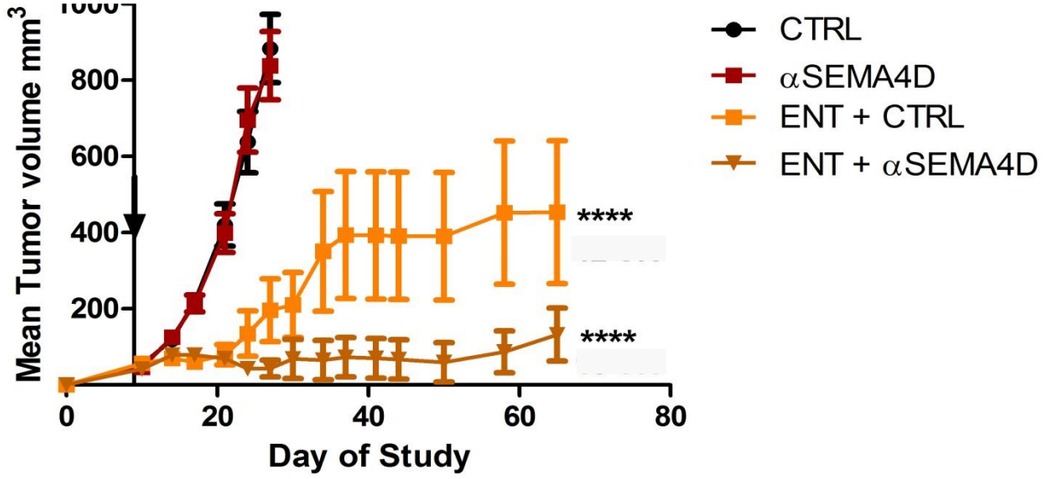
anti-PD-1 Combination: MC38

(Toni Ribas and Siwen Hu-Lieskovan, UCLA)

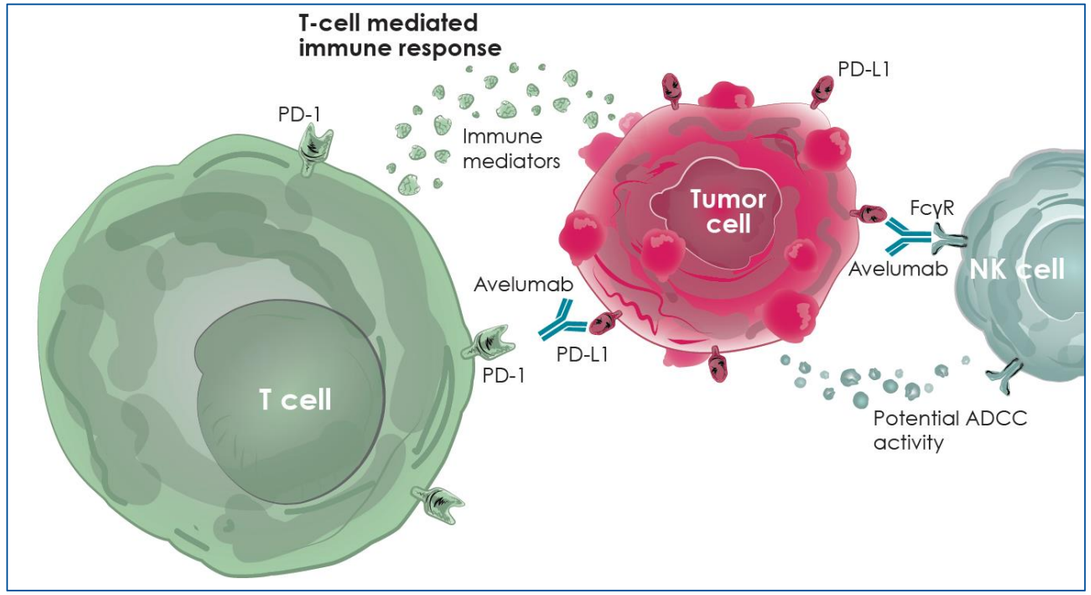


Entinostat Combination: Colon26

Treatment of established tumor



Avelumab in NSCLC : room to improve with combination therapy



Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial

James L Gulley, Arun Rajan, David R Spigel, Nicholas Iannotti, Jason Chandler, Deborah J L Wong, Joseph Leach, W Jeff Edenfield, Ding Wang, Hans Juergen Grote, Anja von Heydebreck, Kevin Chin, Jean-Marie Cuillerot, Karen Kelly

Summary

Background Avelumab, a human Ig-G1 monoclonal antibody targeting PD-L1 and approved in the USA for the treatment of metastatic Merkel cell carcinoma, has shown antitumour activity and an acceptable safety profile in patients with advanced solid tumours in a dose-escalation phase 1a trial. In this dose-expansion cohort of that trial, we assess avelumab treatment in a cohort of patients with advanced, platinum-treated non-small-cell lung cancer (NSCLC).

Lancet Oncol 2017; 18: 599–610
Published Online
March 31, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30240-1

	Patients (n=184)
Complete response	1 (1%)
Partial response	21 (11%)
Stable disease	70 (38%)
Progressive disease	69 (38%)
Non-evaluable*	23 (13%)
Objective responses	22 (12%; 8–18)
Disease control	92 (50%)
Progression-free survival	
Progression-free survival, weeks	11·6 (8·4–13·7)
Progression-free survival at 24 weeks	26% (20–33)
Progression-free survival at 48 weeks	18% (12–26)
Overall survival	
Overall survival, months	8·4 (7·3–10·6)
Overall survival at 12 months	36% (26–46)

Data are n (%) or n (%; 95% CI), % (95% CI), or median (95% CI). Response rates are based on confirmed responses. *Patients with missing or no assessable information included 19 patients without post-baseline tumour assessments (12 patients died within 6 weeks, one patient had an unevaluable post-baseline target lesion, four patients withdrew consent, and two patients discontinued because of disease progression) and four patients with stable disease who did not meet minimum duration requirement and for whom no further tumour assessments were available during follow-up.

Table 3: Clinical activity of avelumab

Phase 1/2 Immune Combination Trials of Checkpoint Blockade with pepinemab (VX15/2503)

CLASSICAL-Lung: pepinemab (VX15/2503) combination with avelumab

- **NSCLC**, immunotherapy naïve, n=40
- Expanded to include immunotherapy refractory, n=20
- Collaboration with EMD Serono, Merck KGaA
- Vaccinex IND
- **FPI OCT, 2017**

VINO: pepinemab (VX15/2503) combination with nivolumab or ipilimumab

- **Melanoma**, immunotherapy refractory, n=60
- IST: Siwen Hu-Lieskovan and Tony Ribas, UCLA
- **FPI JUL, 2018**

"window of opportunity" biomarker trial: pepinemab (VX15/2503) combination with nivolumab or ipilimumab

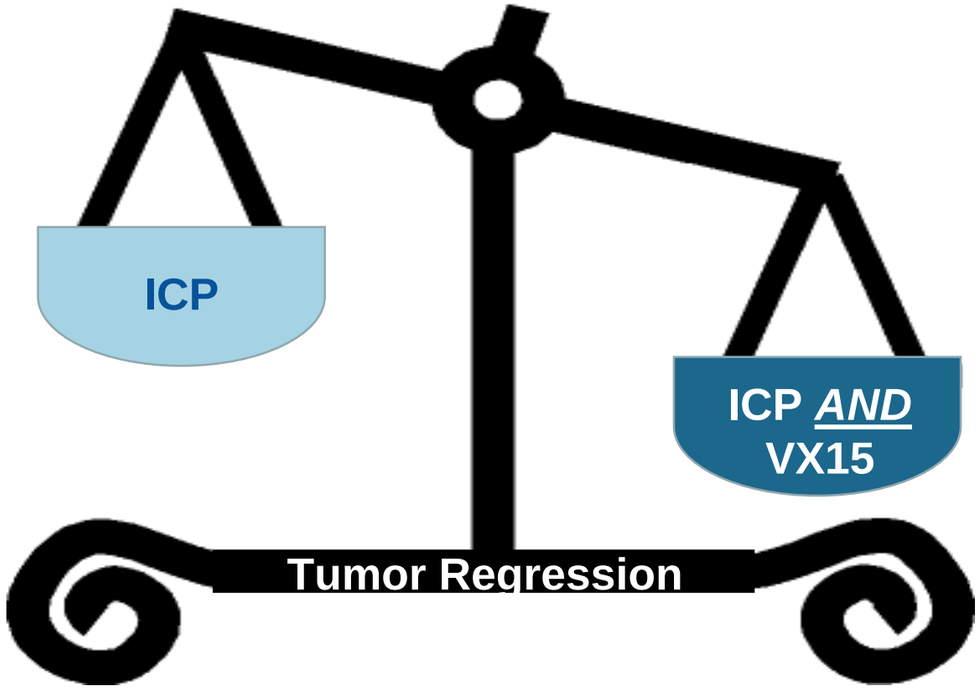
- **Pancreatic Ductal Adenocarcinoma**, resectable
- **Colorectal cancer**, MSS with resectable liver mets
- Phase 1 integrated biomarker trial, n=32
- IST: Christina Wu and Greg Lesinski, Emory
- **FPI MAY, 2018**

Evaluate: Safety, PK/PD, clinical activity (ORR, DoR, PFS) **&…**

biomarkers including immune infiltration in tumor biopsies

Anti-SEMA4D Shifts the Immune Balance to Enhance Activity of Immune Checkpoint Inhibitors and Other Immunotherapies

Immune Checkpoint (ICP):
- ↑ $T_{effectors}$
- ↑ Th1 cytokines: IFNg, TNFa
- ↑ CXCL9, CXCL10



Combination with anti-SEMA4D *enhances* effects of ICP and *adds* benefits of reversing myeloid suppression:
- ↓ M2 TAM
- ↓ MDSC
- ↓ $T_{regulatory}$
- ↓ Chemokines that recruit M2 and polarize Treg: CCL2, CXCL1, CXCL5, IL-10

- The unique mechanism of action, facilitating penetration of activated immune cells, enhances activity of immunotherapy, including immune checkpoint inhibition.
- Pepinemab (VX15/2503) was well-tolerated with a favorable safety profile in two Phase I clinical trials; Phase1/2b combination trials with immune checkpoint inhibitors have been initiated.

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- Alisha Reader
- Robert Parker
- Jason Condon
- William Bigham
- Noelle Feldbauer
- Cindy Dawson

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- John Parker, VP
- Liz Evans, VP
- Ernest Smith, CSO
- Maurice Zauderer, CEO
- Raymond Watkins, COO
- Scott Royer, CFO

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Virginia G. Piper Cancer Centear at Scottsdale Healthcare/Tgen. PI: Ramesh K. Ramanathan, MD

EMD Serono

Emory University, Winship Cancer Center Gregory Lesinski, Christina Wu

UCLA Siwen Hu-Lieskovan & Toni Ribas

University of Minnesota Division of Pediatric Hematology/Oncology Brenda Weigel, Emily Greengard

Patients and their families

eevans@vaccinex.com