

Reprogramming suppressive myeloid cells in tumor microenvironment with first-in-class Semaphorin 4D Mab enhances combination immunotherapy

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DEPARTMENT OF PEDIATRICS



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Disclosure Information

I will discuss the following investigational use in my presentation: pepinemab, nivolumab, ipilimumab, avelumab

Elizabeth E. Evans, Terrence L. Fisher, John E. Leonard, Crystal Mallow, Holm Bussler, Christine Reilly, Sebold Torno, Maria Scrivens, Alan Howell, Leslie Balch, Ernest S. Smith, Maurice Zauderer are Employees of Vaccinex, Inc.

Gregory B. Lesinski, is consultant for ProDa Biotech, LLC and receives research funding via a sponsored agreement through Emory University from Vaccinex, Inc., Merck, Inc., and Boehringer-Ingelheim, Inc.

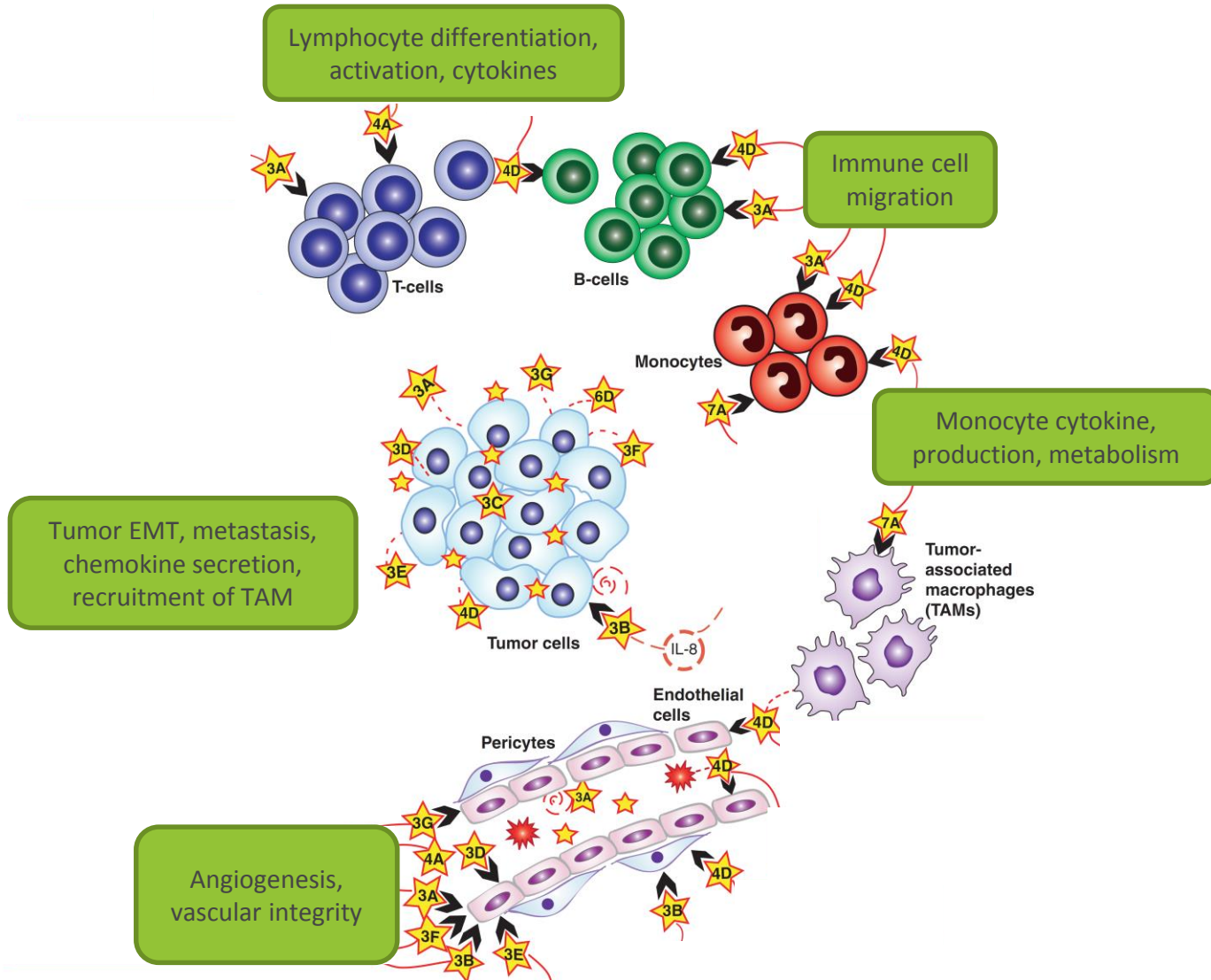
Christina Wu receives research funding via a sponsored agreement through Emory University from Vaccinex, Inc., Bristol Myers Squibb, Boston Biomedical Inc, Lycera, Seattle Genetics.

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Semaphorins are guidance cues in tumor microenvironment



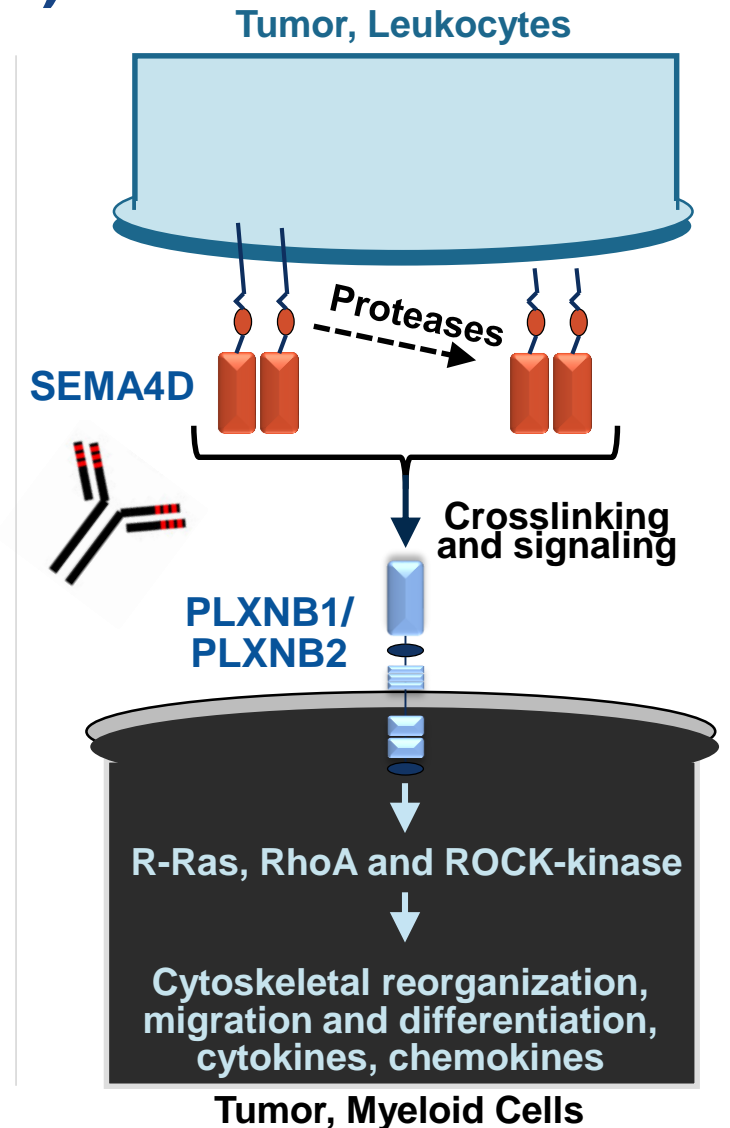
- Semaphorins are guidance molecules, directing cellular movement and differentiation
- Semaphorins and cognate receptors are overexpressed in many malignancies and some are associated with poor prognosis.
- **SEMA4D and its receptors are expressed on precursor cells, including immune cells, vasculature and tumor cells**
- **Many mesenchymal precursor cells are immunosuppressive within the TME**
 - MDSC, M2 TAM
 - Endothelial cells
 - Cancer associated fibroblasts
 - Tumor cells

Introduction to Semaphorin 4D (SEMA4D, CD100)

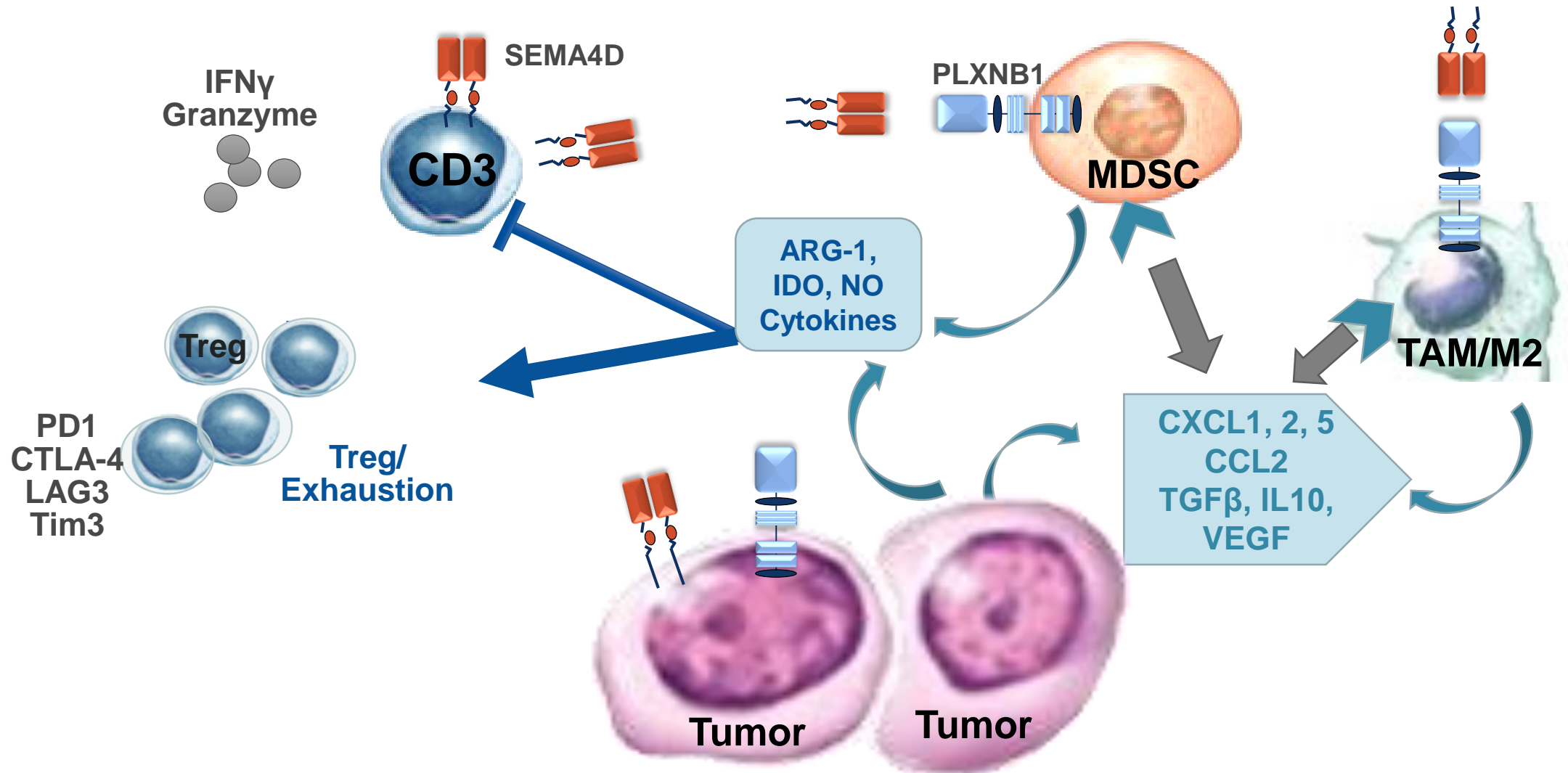
- SEMA4D is an extracellular signaling molecule that regulates the activity of inflammatory cells at sites of injury or cancer
- SEMA4D signals through PLXNB1 and PLXNB2 receptors to regulate (1) cell cytoskeleton (2) cytokine synthesis and secretion
- **In TME, SEMA4D inhibits migration and promotes 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 *in vivo* and do NOT generally affect immune responses in the periphery

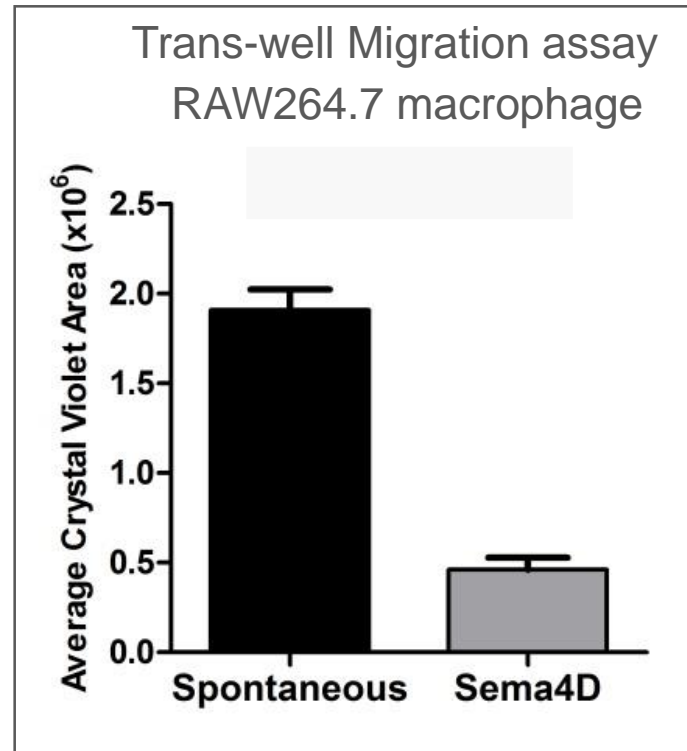
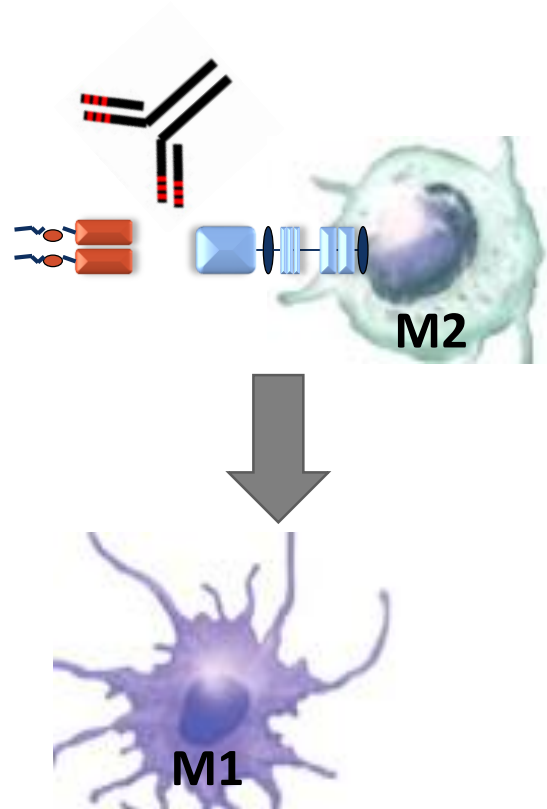


Mesenchymal cells and tumor cooperate to suppress T cell responses in the TME

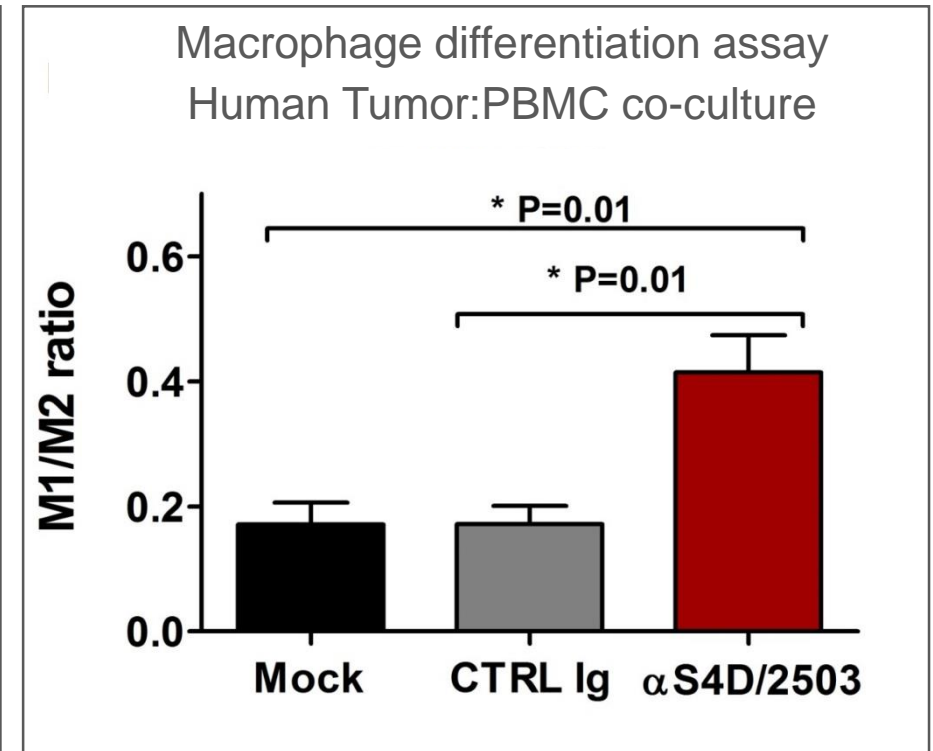


Anti-SEMA4D promotes differentiation of pro-inflammatory APC

SEMA4D inhibits migration of macrophage



Anti-SEMA4D shifts balance of M1/M2

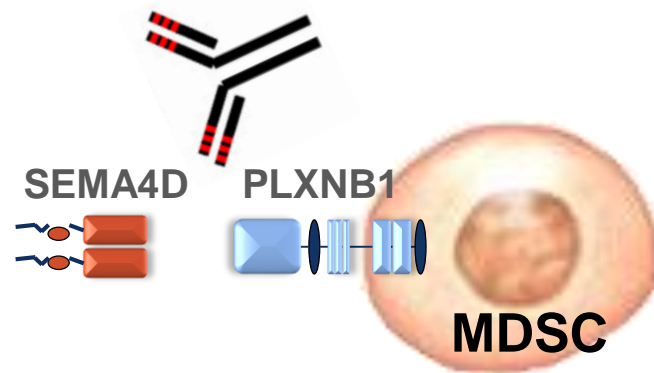


RPMI-8226 Multiple Myeloma tumor supe

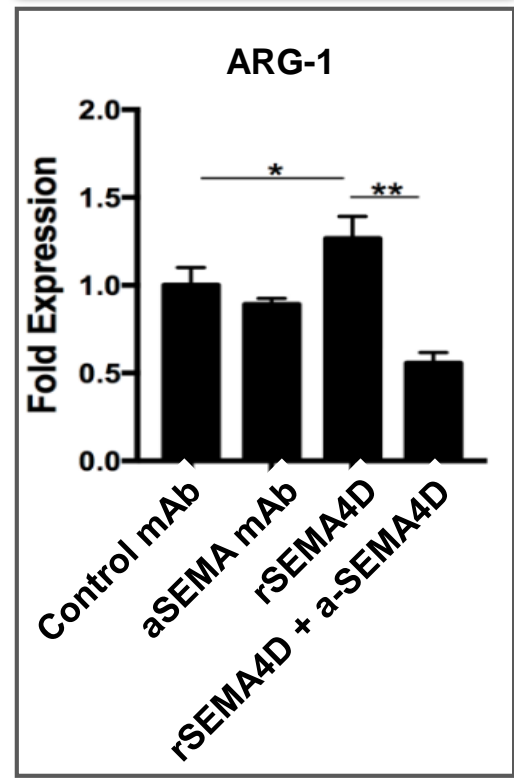
M1 = CD14-CD16+, M2 = CD14+CD16+

Anti-SEMA4D Ab reverses MDSC function and recruitment to TME

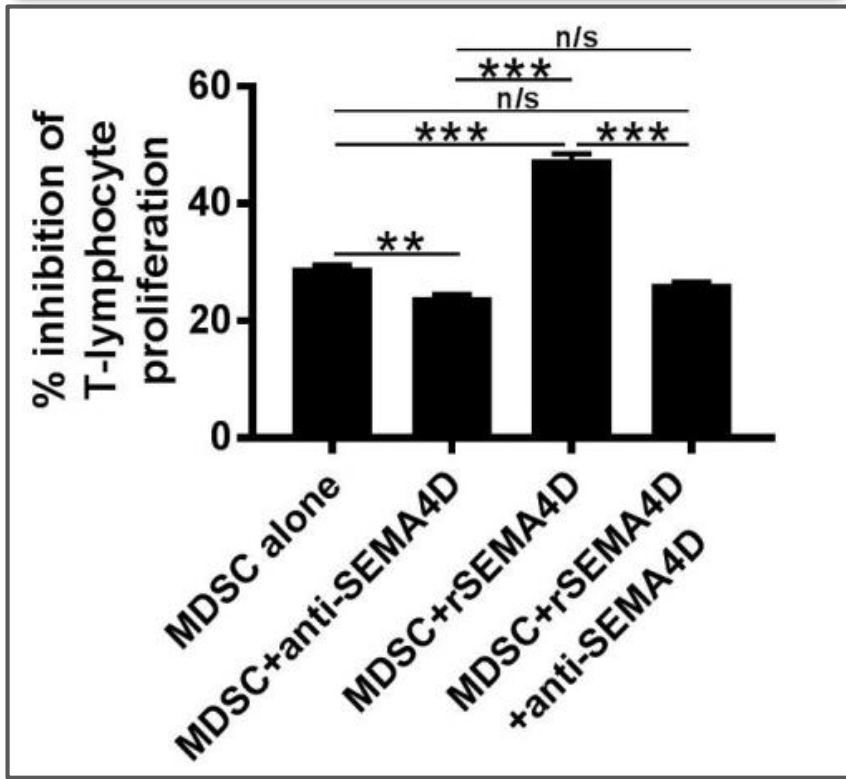
- SEMA4D promotes MDSC arginase production and suppression of T cell function
- Ab blockade reverses MDSC suppression of T cell proliferation and T cell activity.



Arginase Production



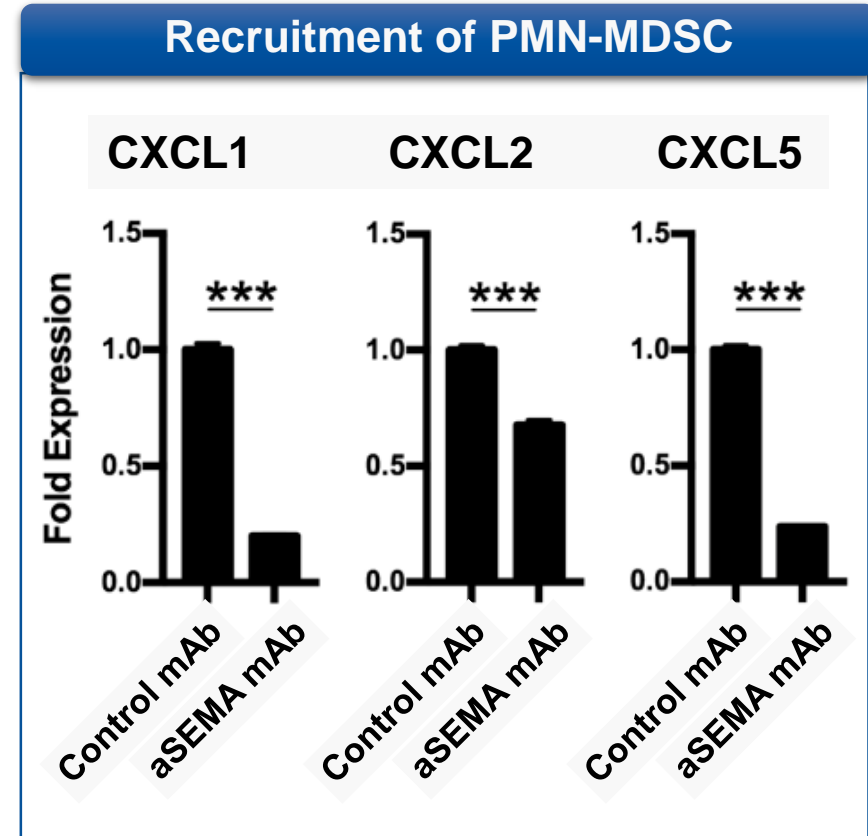
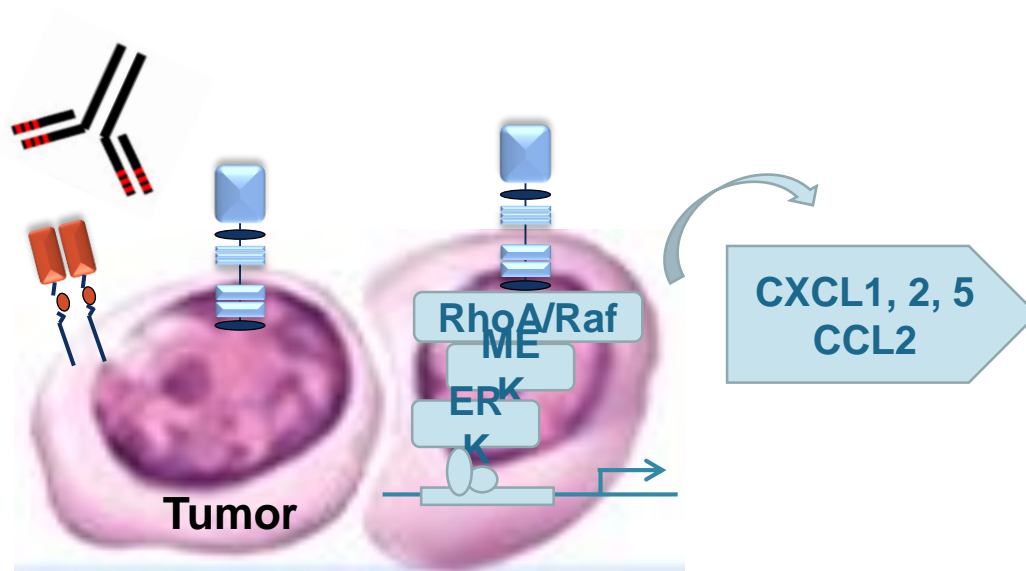
PMN-MDSC function



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

Anti-SEMA4D Ab reverses tumor recruitment of MDSC

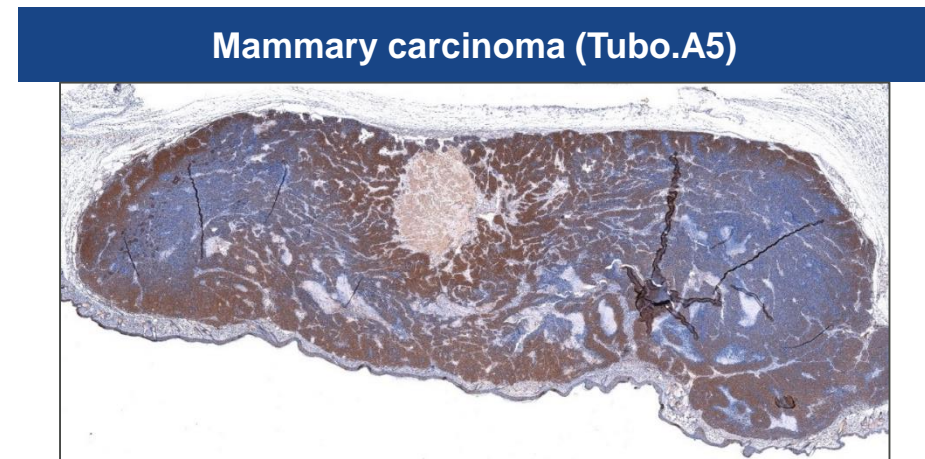
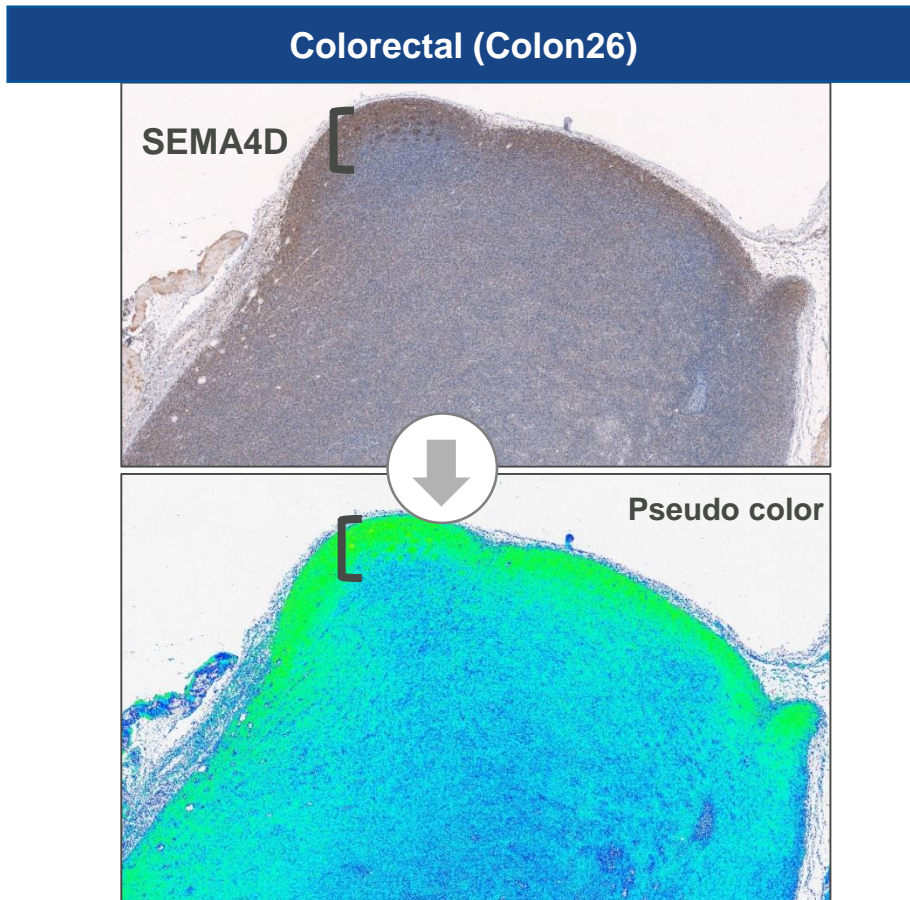
Ab blockade reduces secretion of chemokines that recruit MDSC



Chemokines measured in supe of *in vitro* MOC1 cells cultured with anti-SEMA4D

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

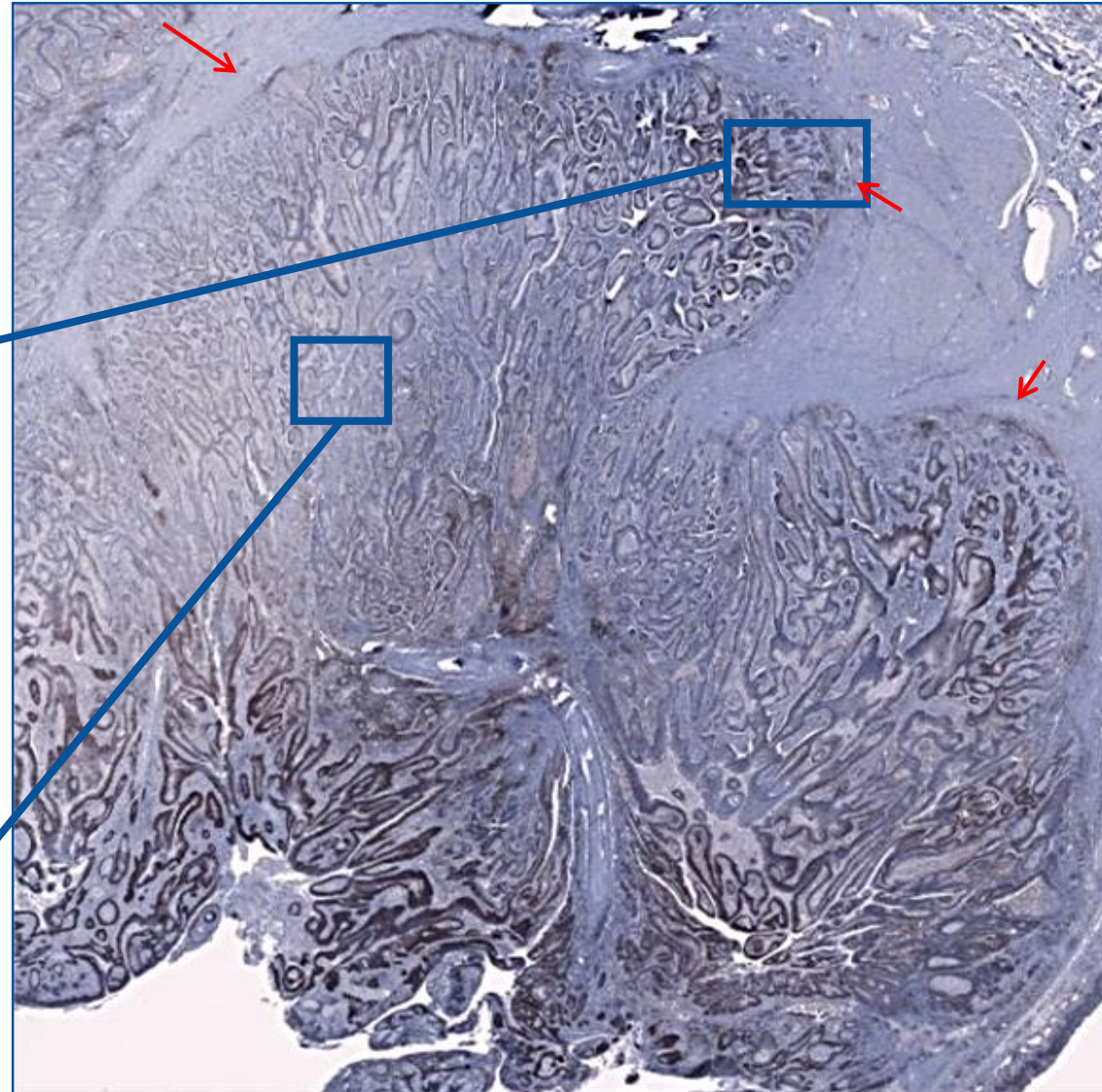
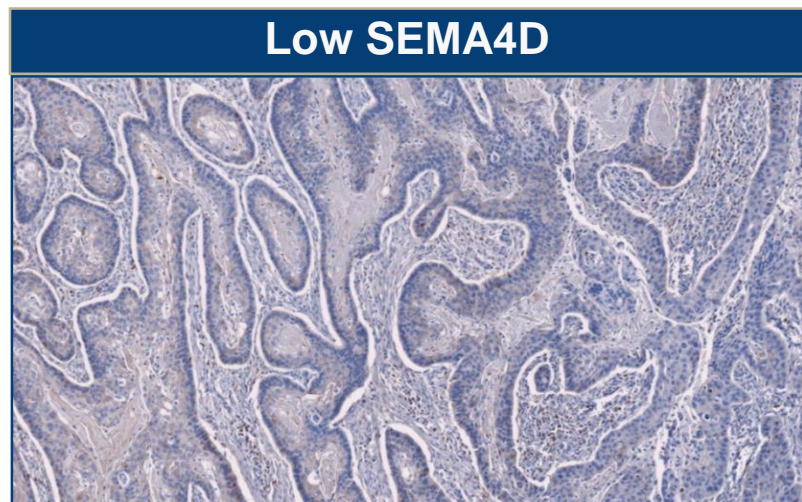
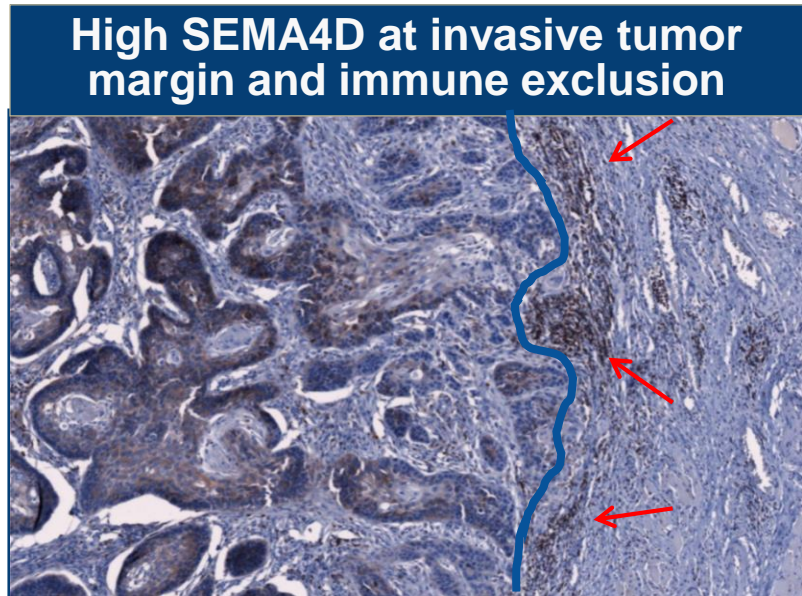
SEMA4D Expression Concentrated at Tumor Leading Edge in Murine Tumor Models



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

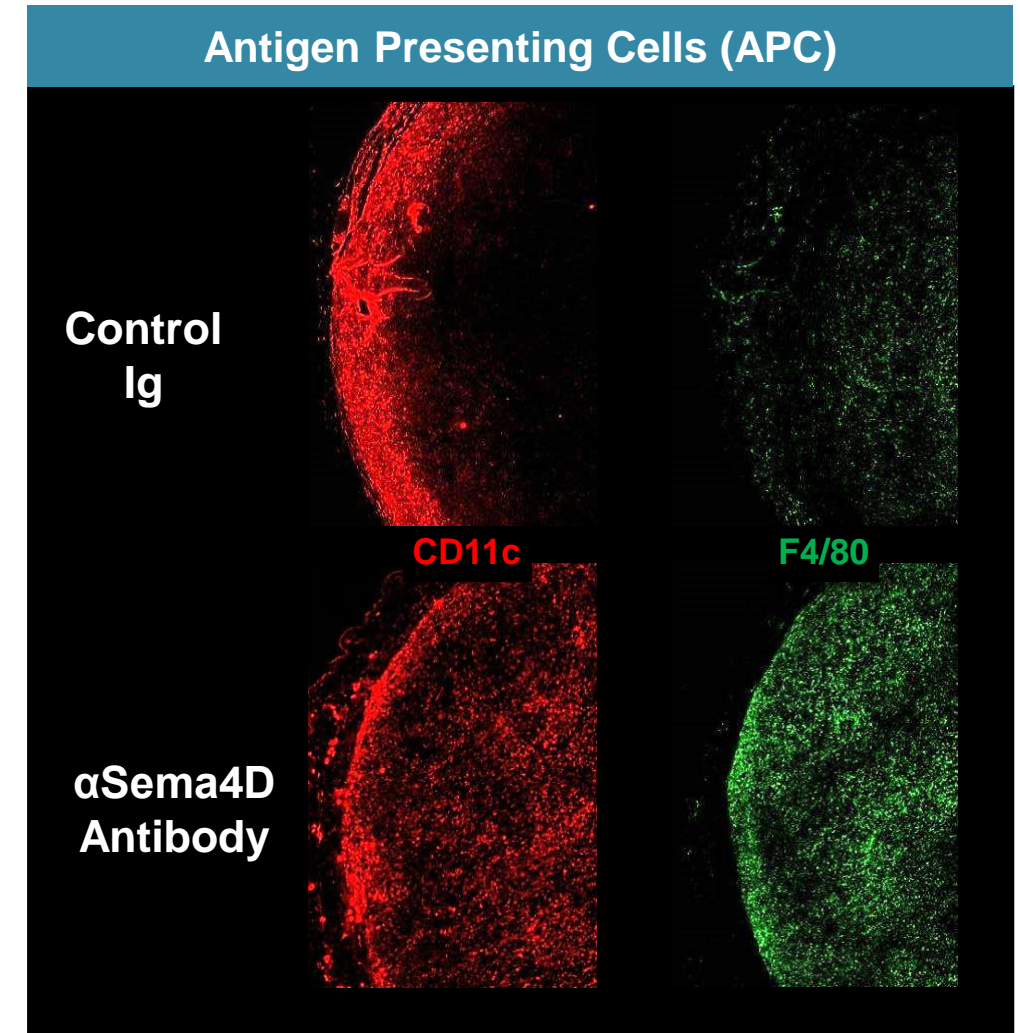
Immune cells are excluded where SEMA4D is concentrated at margins of human HNSCC of the Larynx



SEMA4D+
↑ TIL

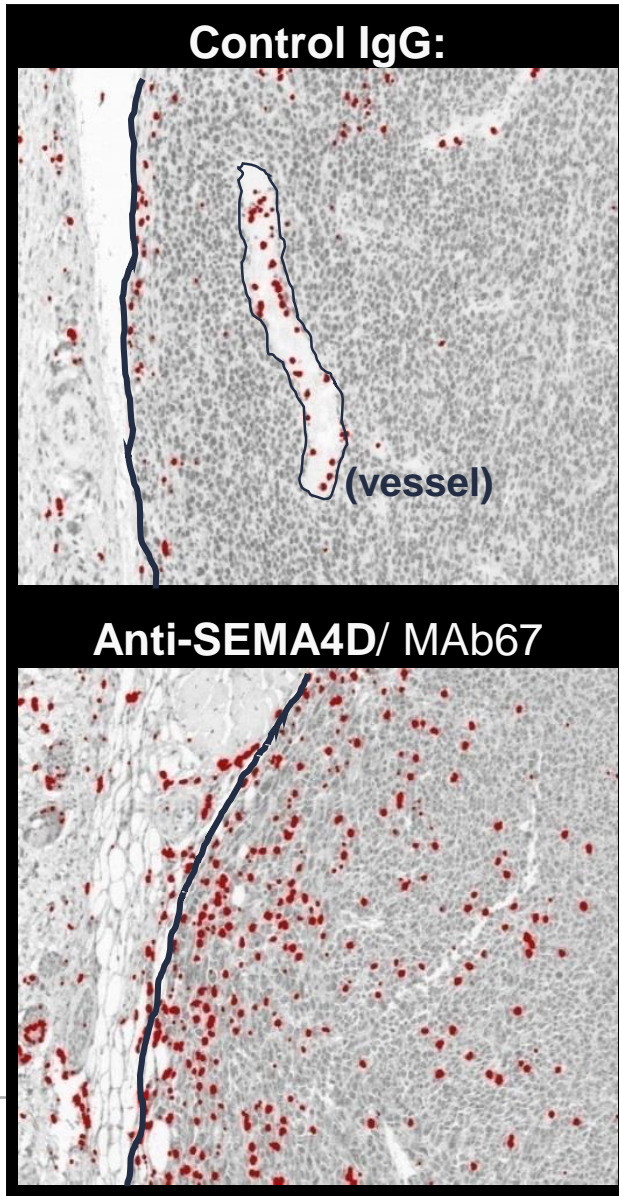
SEMA4D Controls Infiltration of Antigen Presenting Dendritic Cells into Tumor

- 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

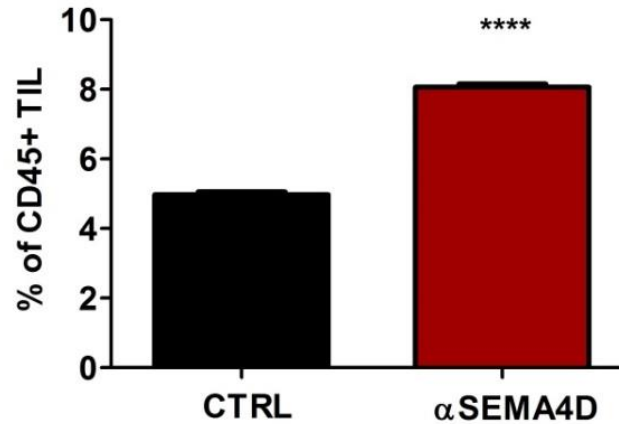


Anti-SEMA4D shifts balance of chemokines and suppressor cells to enhance anti-tumor T cell activity

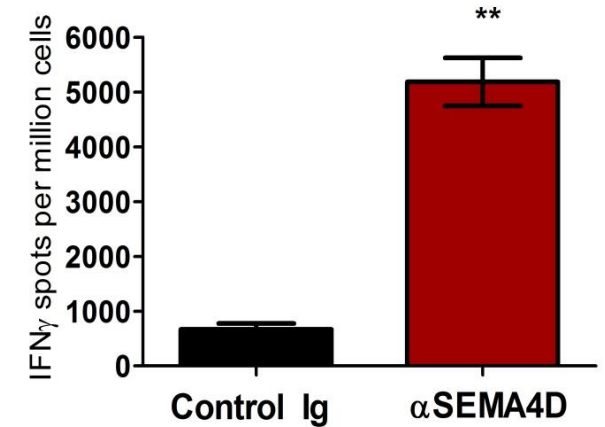
CD8+ CTL



T cell Infiltration:
% CD3+ CD8+ in TIL

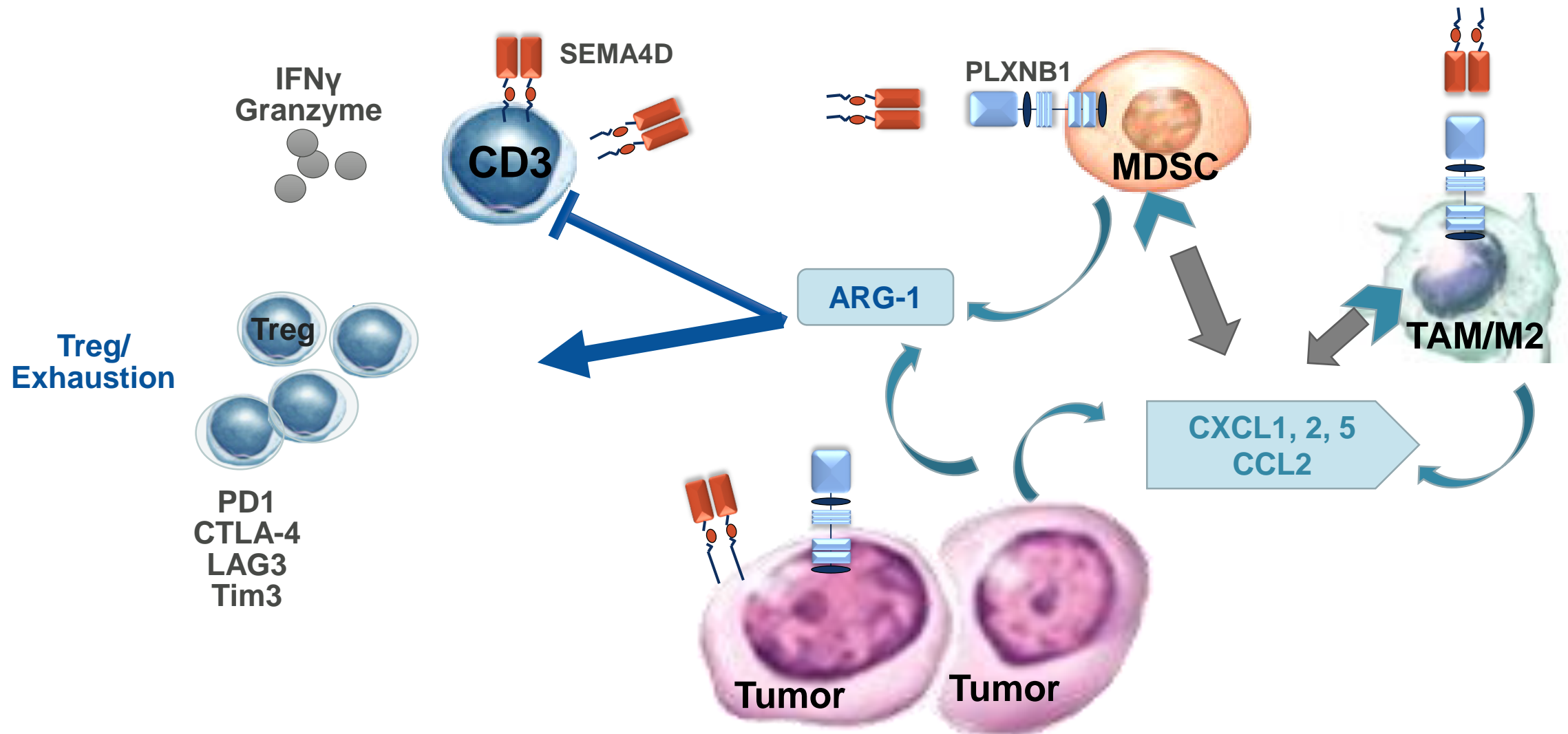


T cell Activity:
ELISPOT

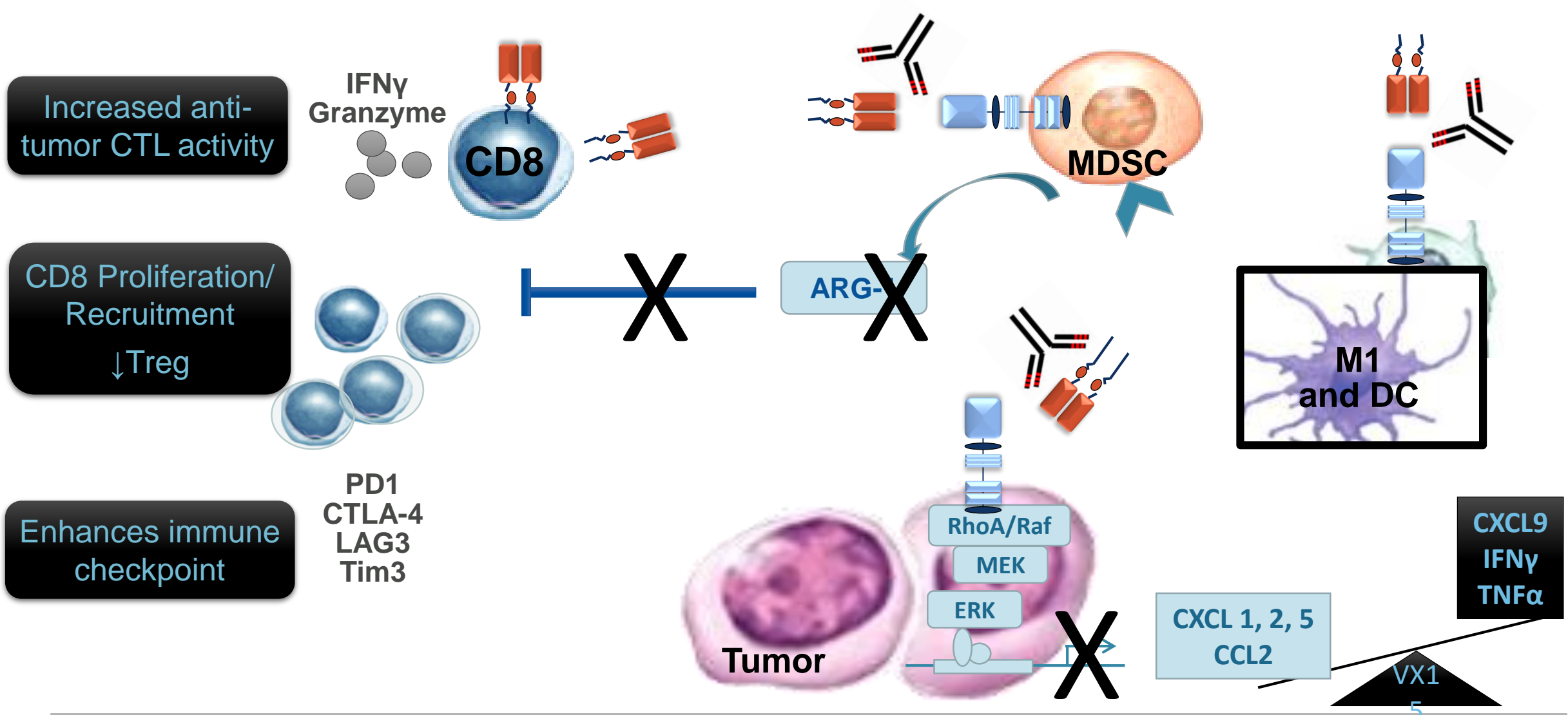


Also observed increase in Type 1 cytokines (IFN γ , TNF α) and chemokines that recruit T cells (CXCL9, CXCL10)

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



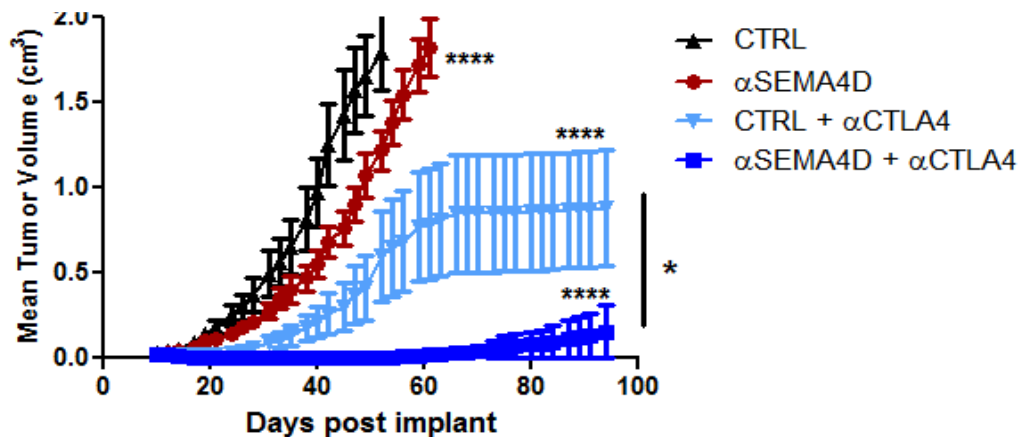
Anti-SEMA4D shifts the balance of mesenchymal suppression to promote T cell activity



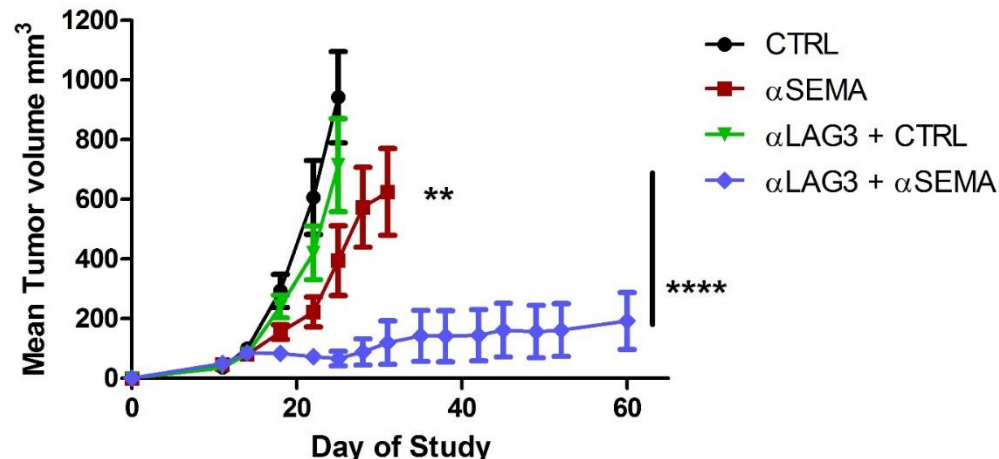
Anti-SEMA4D Antibody Enhances Activity of Immune Checkpoint Antibodies and HDAC inhibitor in Preclinical Syngeneic Models

anti-CTLA-4 Combination: MOC1 HNSCC

(Clint Allen, NIH)

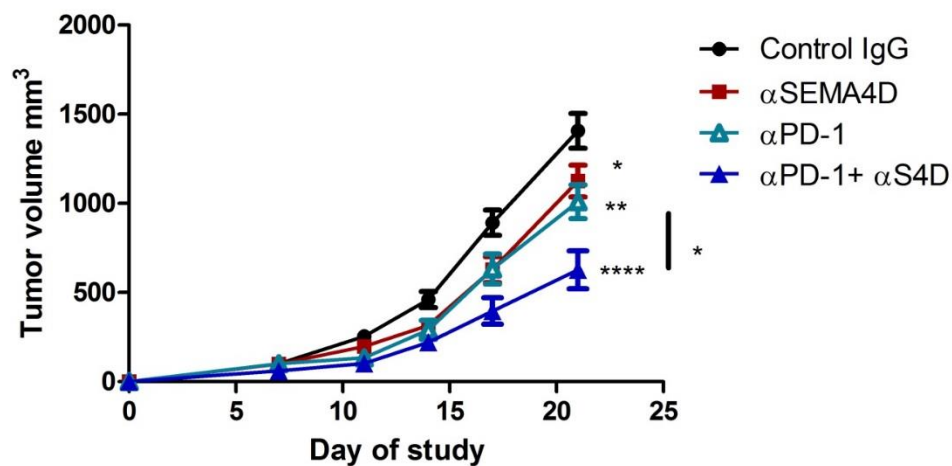


anti-LAG3 Combination: Colon26

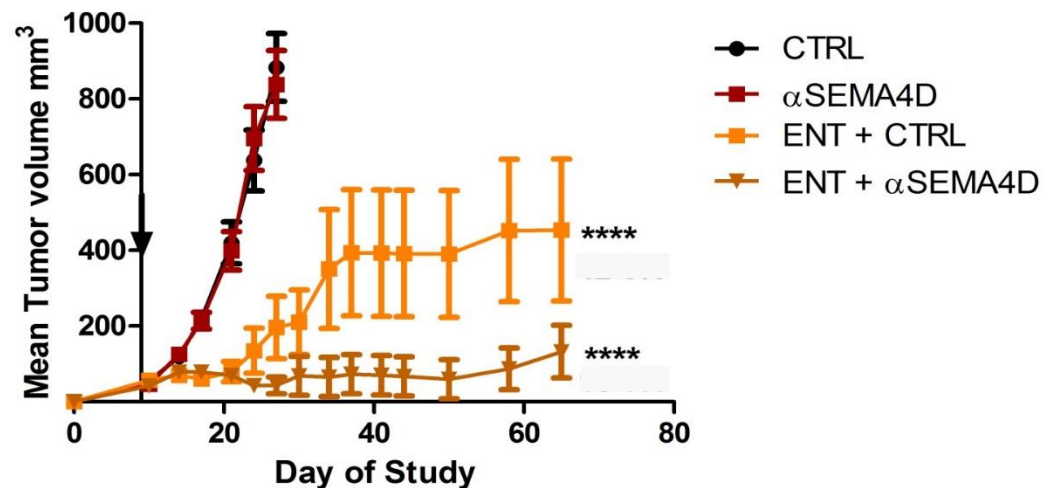


anti-PD-1 Combination: MC38

(Toni Ribas and Siwen Hu-Lieskovan, UCLA)



Entinostat Combination: Colon26
Treatment of established tumors



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

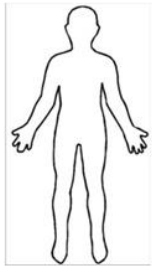
- **Pancreatic Ductal Adenocarcinoma**, resectable
- **Colorectal cancer**, MSS with resectable liver mets
- Phase 1 integrated biomarker trial, n=32
- IST: Christina Wu and Greg Lesinski, Emory
- **FPI MAY, 2018**

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

biomarkers
including
immune
infiltration in
tumor
biopsies

Neoadjuvant Trials Require Multidisciplinary Coordination

Medical Oncology Patient Consent



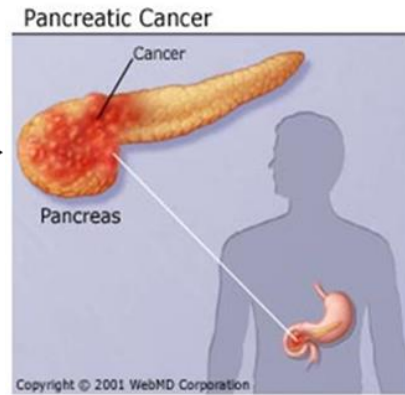
Baseline

Day 15

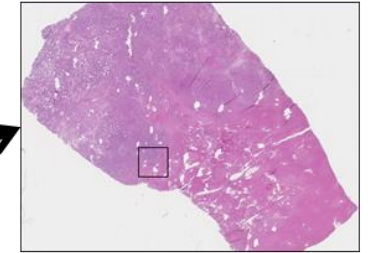
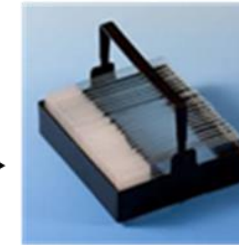
Day 29

Plasma Biomarkers

Surgical Oncology



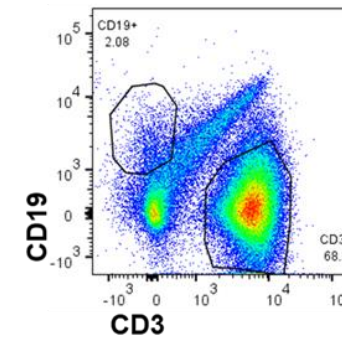
Pathology



IHC Analysis

Fresh Tissue

Flow Cytometry

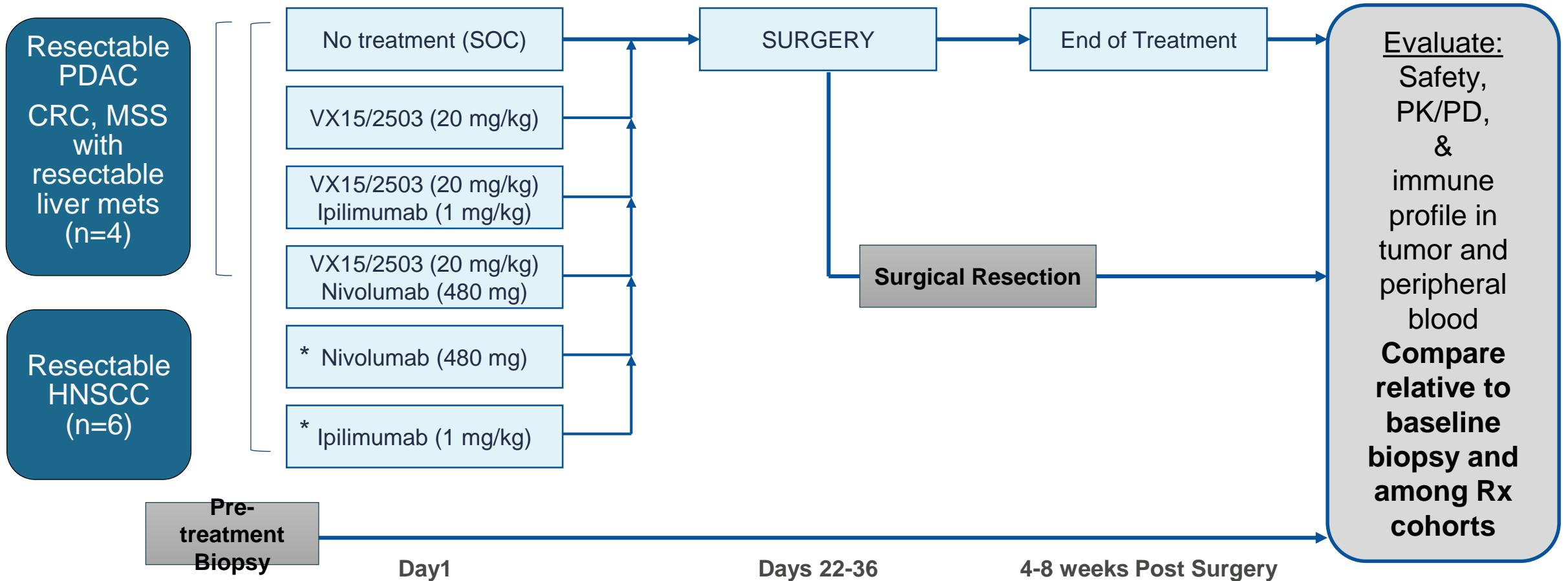


Buffy Coat

Lesinski Laboratory

Pepinemab (VX15/2503) Combo with Anti-PD-1 or with Anti-CTLA-4

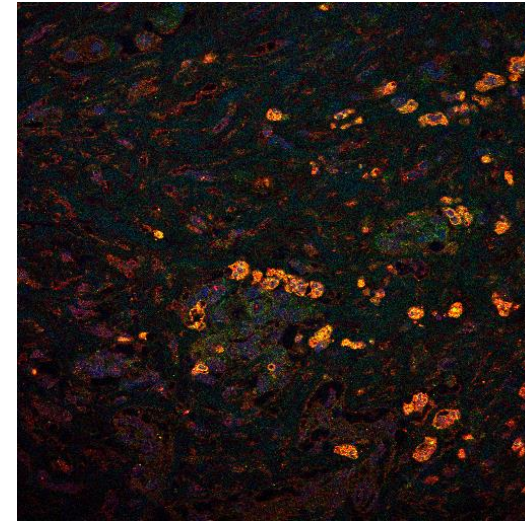
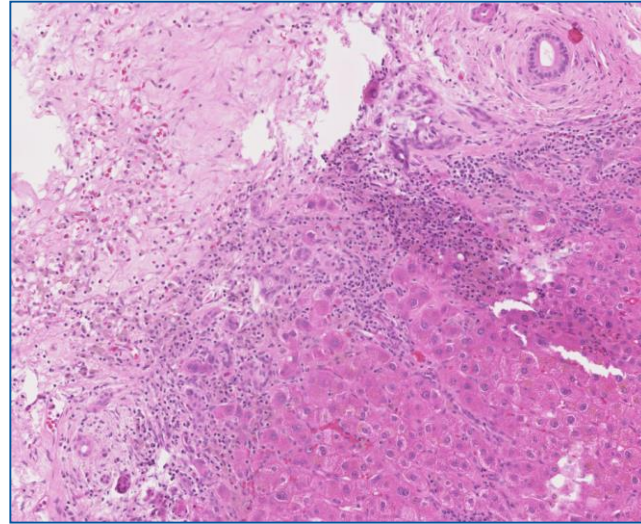
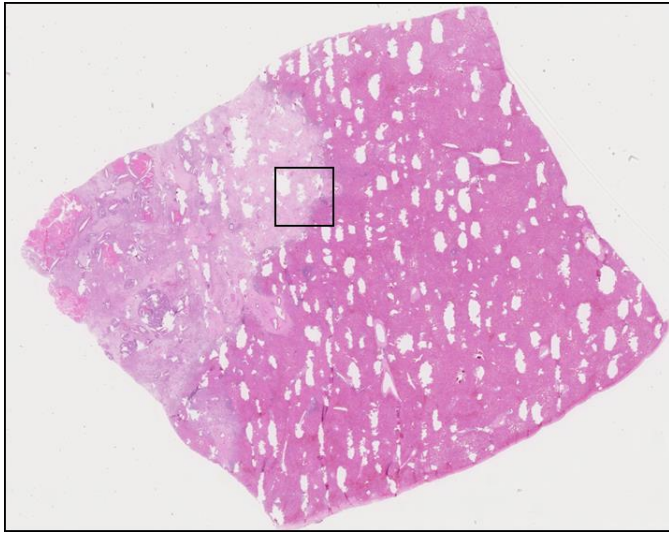
Colorectal Cancer with metastasis to liver, Pancreatic Cancer, *Head and Neck Squamous Cell Carcinoma. Integrated biomarker trials, Winship Cancer Institute (Lesinski and Wu, Steuer)



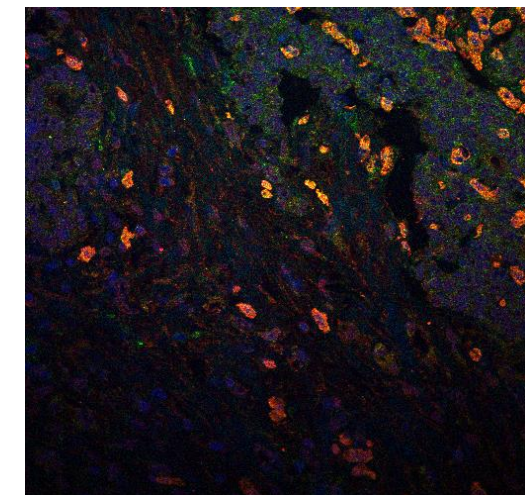
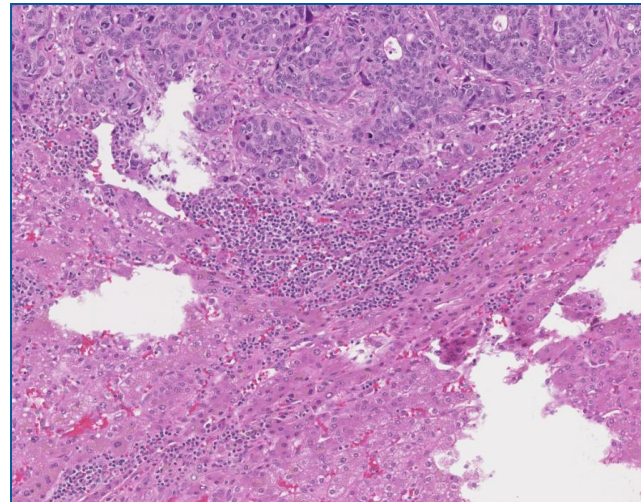
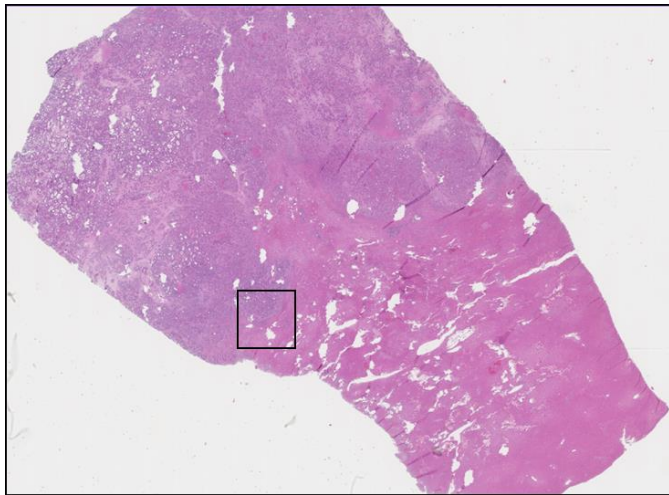
CRC and PDAC: NCT03373188 - RECRUITING

HNSCC: NCT03690986 – OPEN

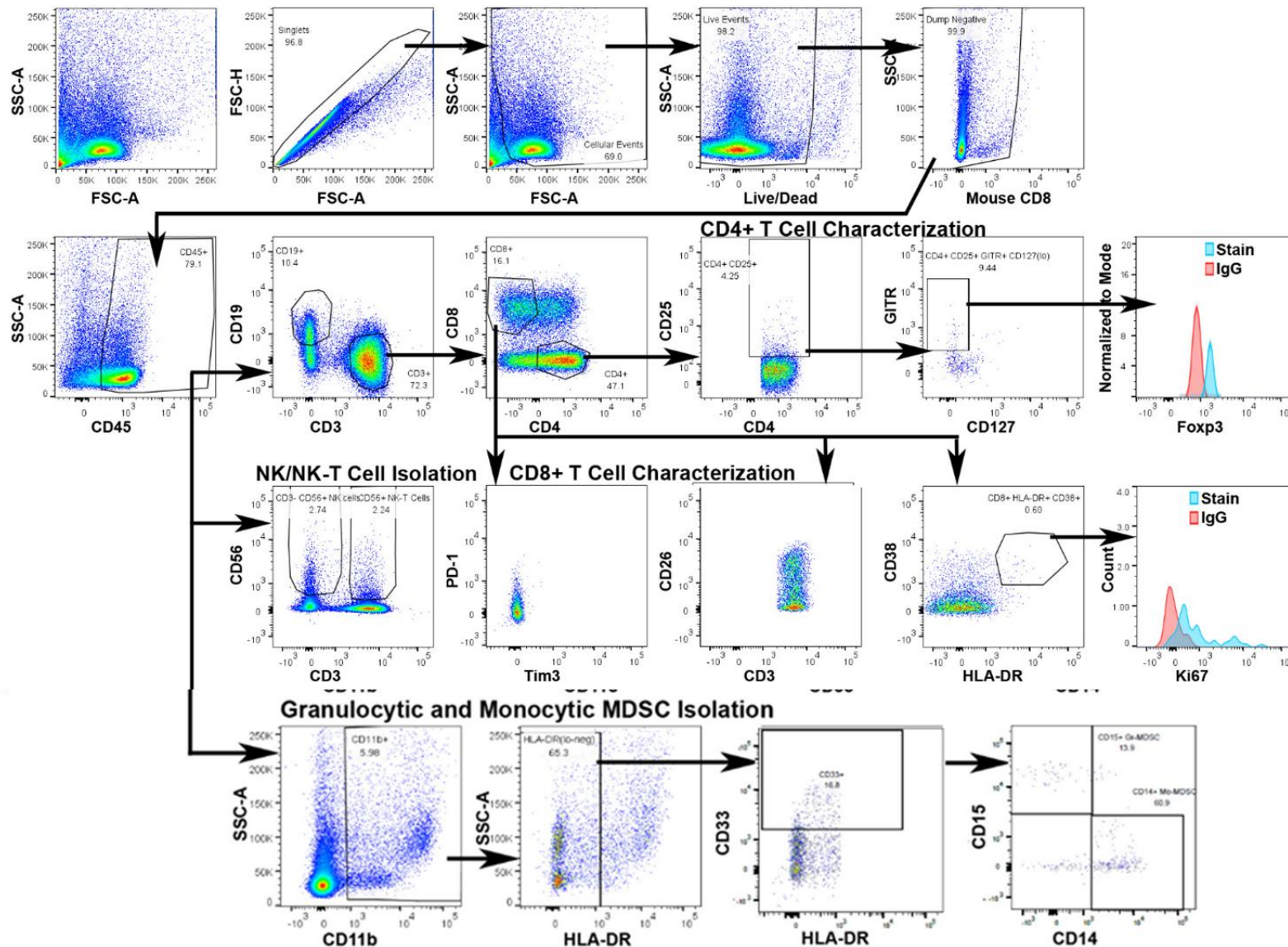
Preliminary Correlative Data from *NCT03373188*



20X
CD33
S100A
DAPI



Comprehensive Flow Cytometry Panel from *NCT03373188*



T lymphocyte Subsets
 NK/NKT Subsets
 M1/M2 Macrophage
 Markers
 MDSC Subsets
 Dendritic Cells
 Monocytes

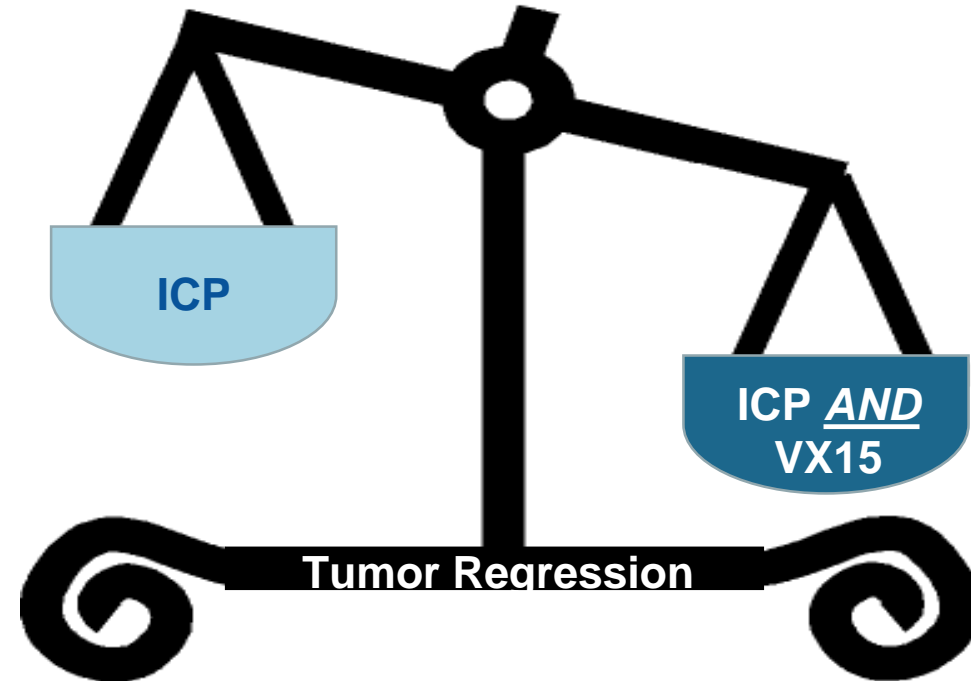


Brian Olson, Ph.D.

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

Immune Checkpoint (ICP):

- ↑ T_{effectors}
- ↑ Th1 cytokines: IFN γ , TNF α
- ↑ 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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- 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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Patients and their families

Poster #O20

