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

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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.

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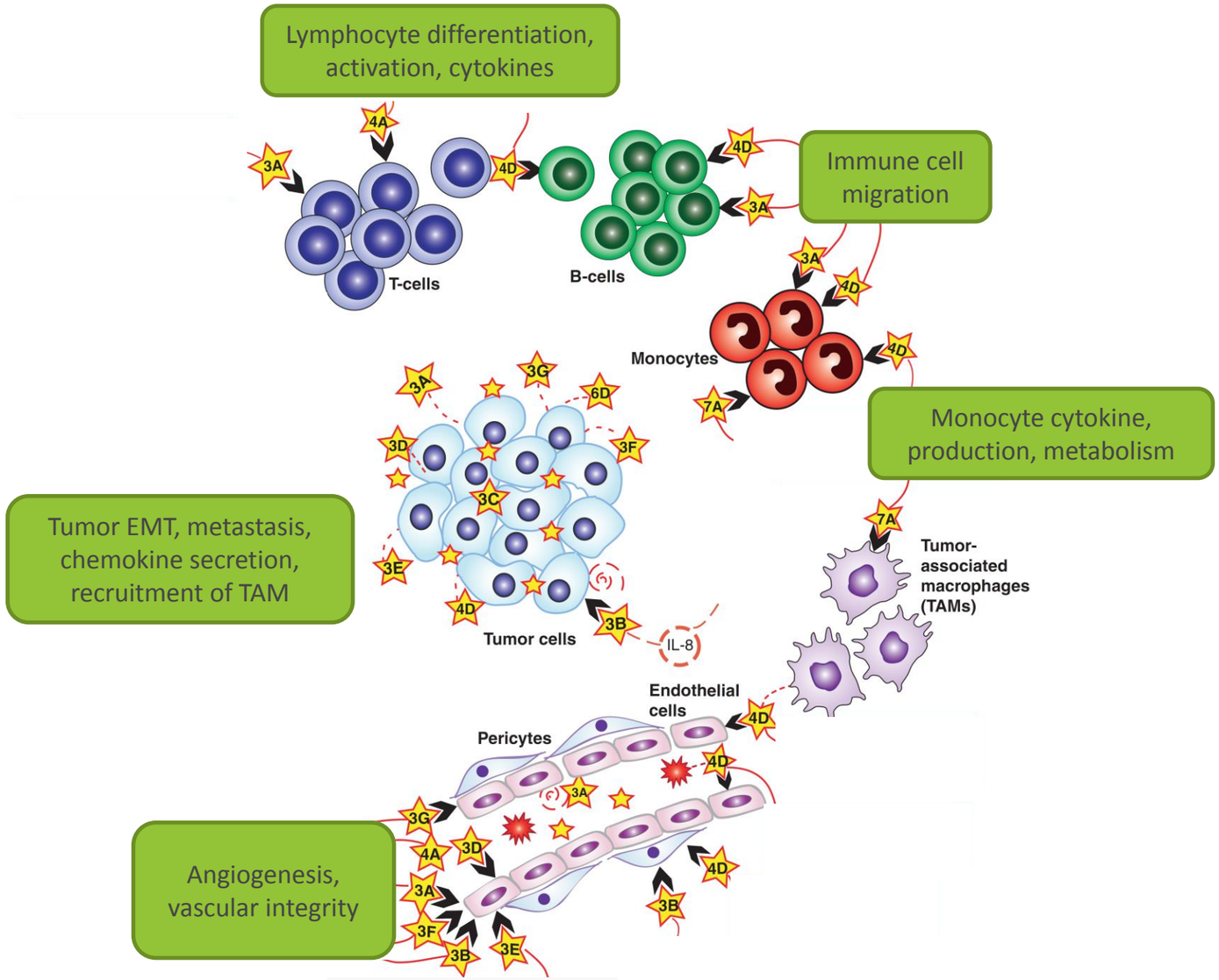
Semaphorins are guidance cues in tumor microenvironment



Adapted from Neufeld et al, Drug Resistance Updates 2016

- 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.

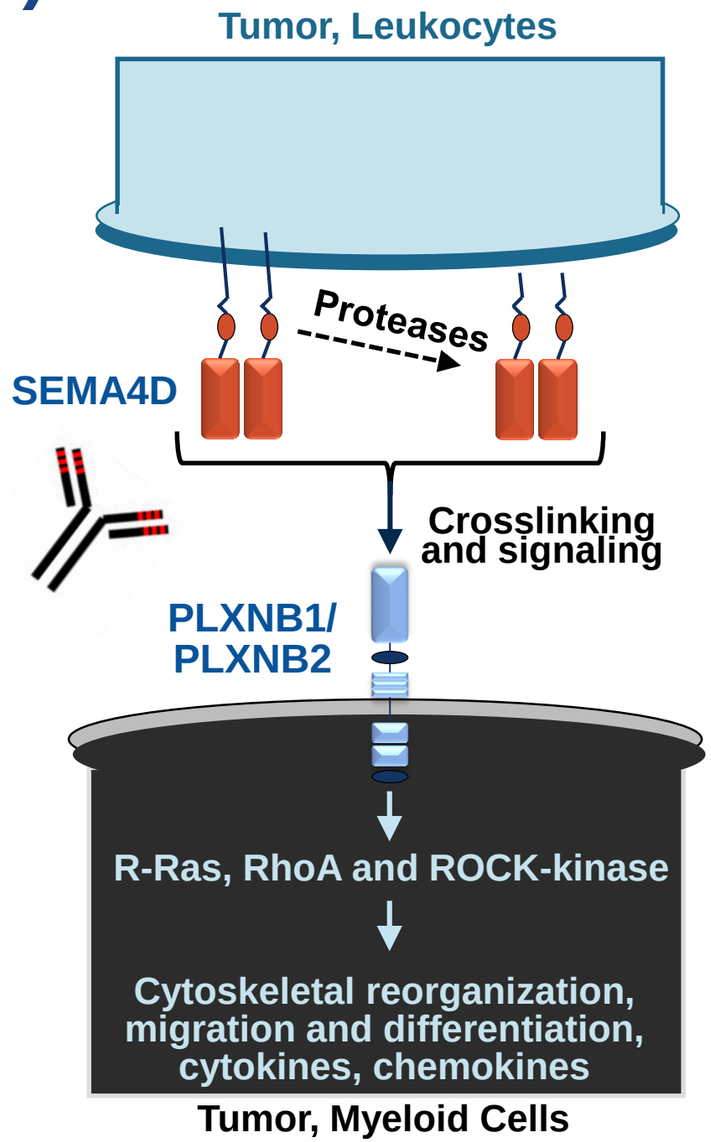
- **SEMA4D and its receptors are expressed on precursor cells, including immune cells, vasculature and tumor cells**
- **Many mesenchymal precursor cells are immunosuppressive within the TME**
  - **MDSC, M2 TAM**
  - **Endothelial cells**
  - **Cancer associated fibroblasts**
  - **Tumor cells**

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.**

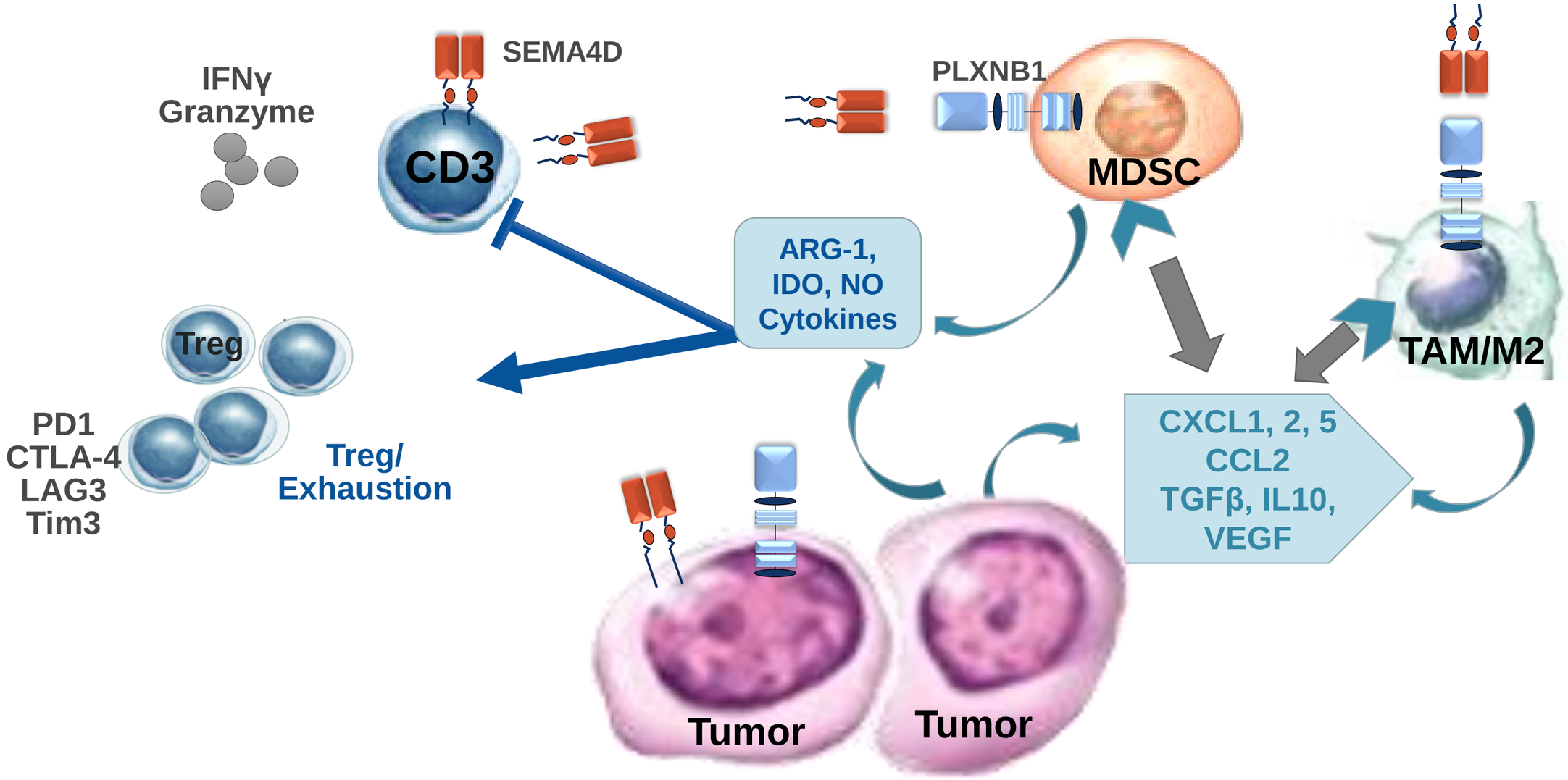
Anti-SEMA4D antibody blocks binding to its receptor and signaling activity

- **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 i*n vivo* and do NOT generally affect immune responses in the periphery

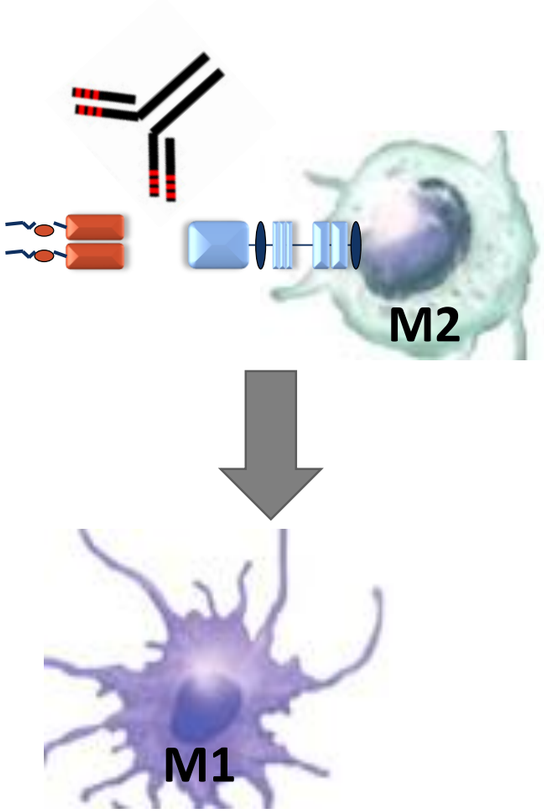


Evans EE et al. Cancer Immunol Res. 2015
Fisher et al. Mabs 2015
Leonard et al. Mol Cancer Ther 2015

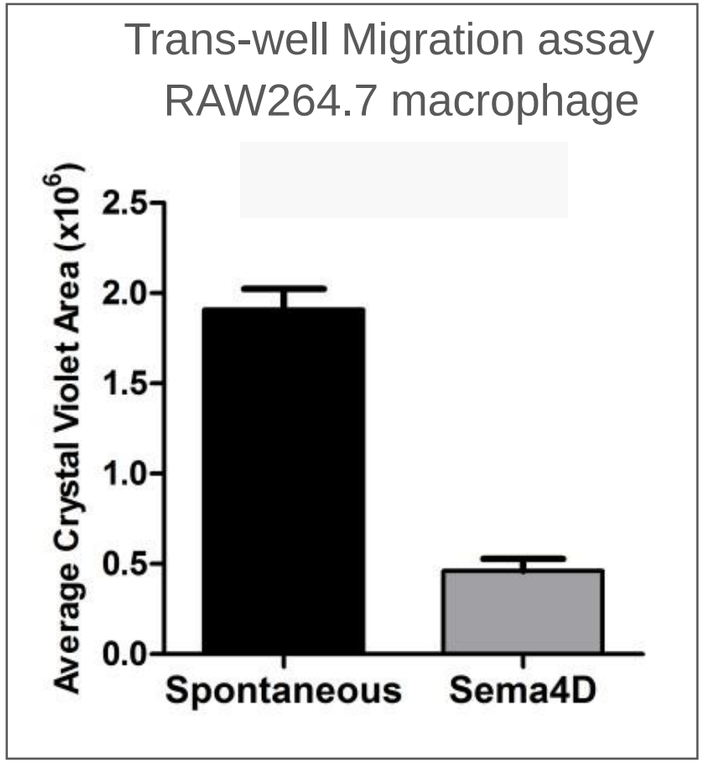
Mesenchymal cells and tumor cooperate to suppress T cell responses in the TME



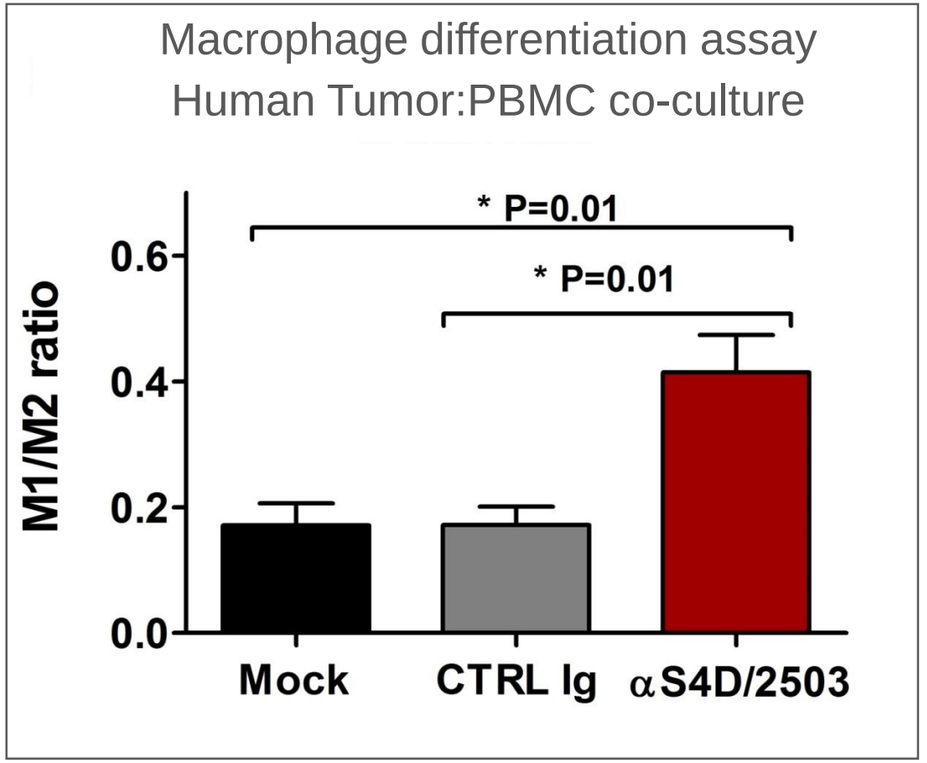
Anti-SEMA4D promotes differentiation of pro-inflammatory APC



SEMA4D inhibits migration of macrophage



Anti-SEMA4D shifts balance of M1/M2

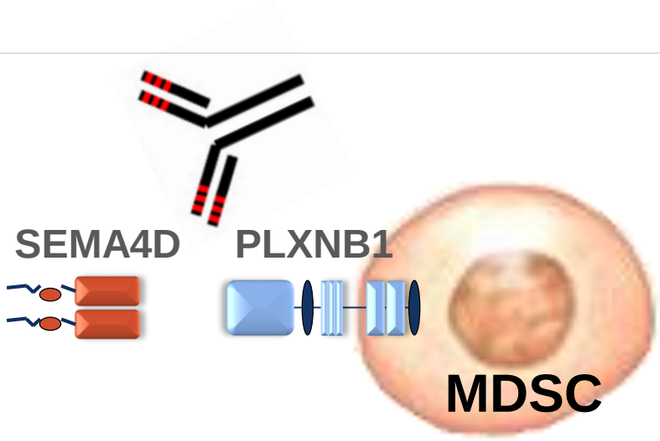


RPMI-8226 Multiple Myeloma tumor supe

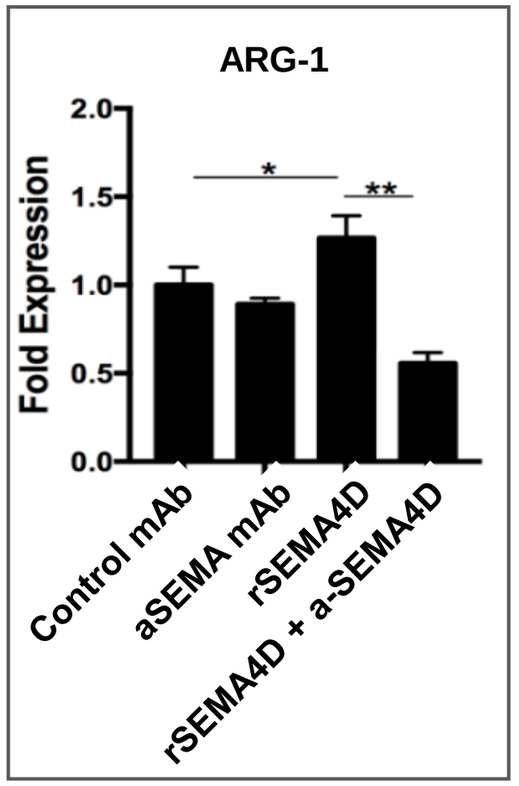
M1 = CD14-CD16+, M2 = CD14+CD16+

Anti-SEMA4D Ab reverses MDSC function and recruitment to TME

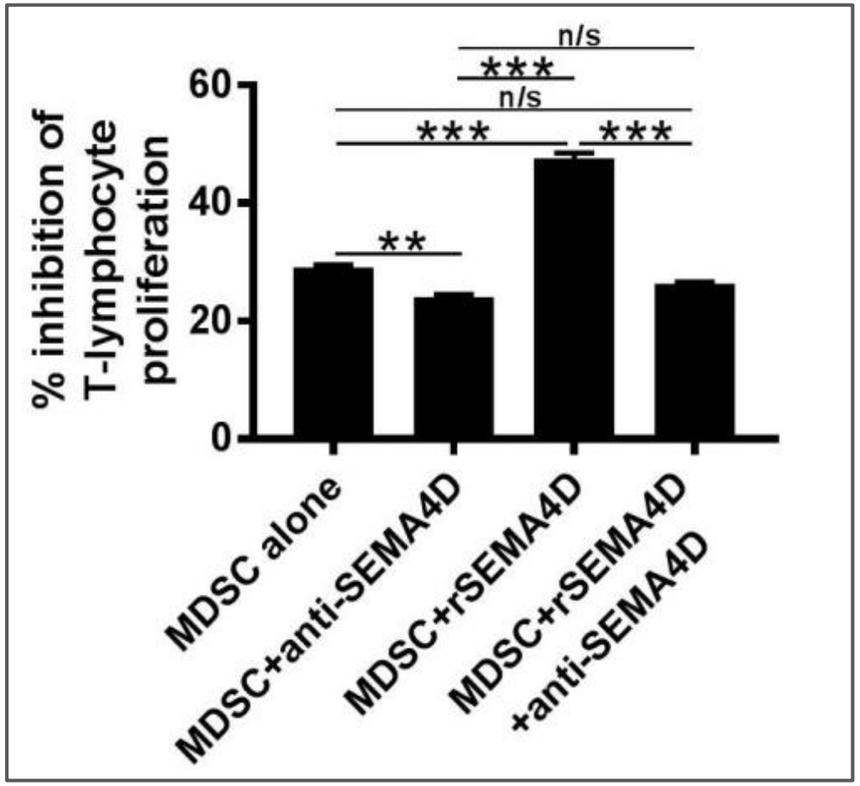
- **SEMA4D promotes MDSC arginase production and suppression of T cell function**
- **Ab blockade reverses MDSC suppression of T cell proliferation and T cell activity.**



Arginase Production



PMN-MDSC function



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

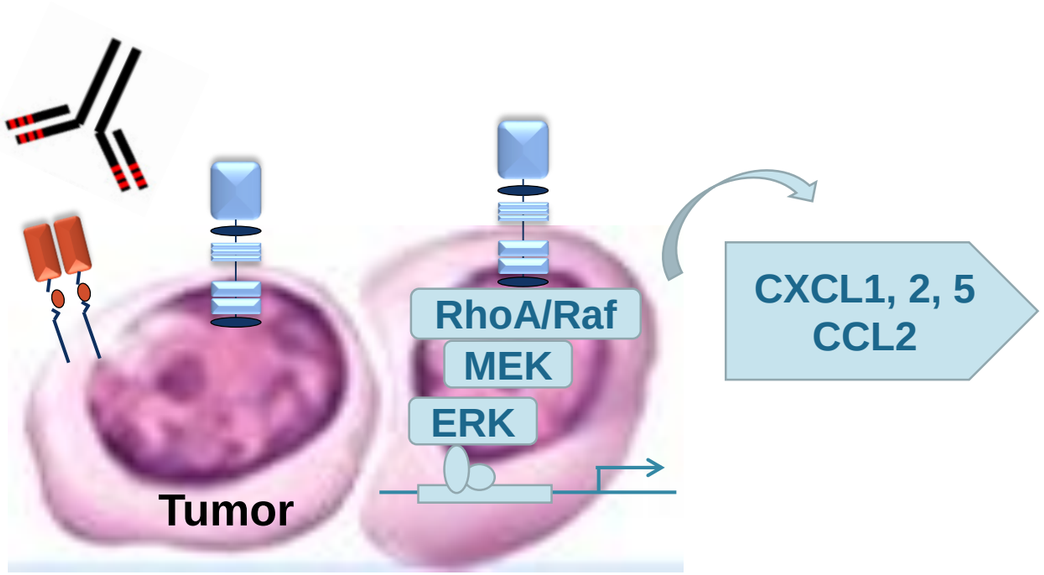
Similar results observed in gMDSC isolated from mice treated *in vivo* with anti-SEMA4D

Clavijo, Allen et al., manuscript in preparation

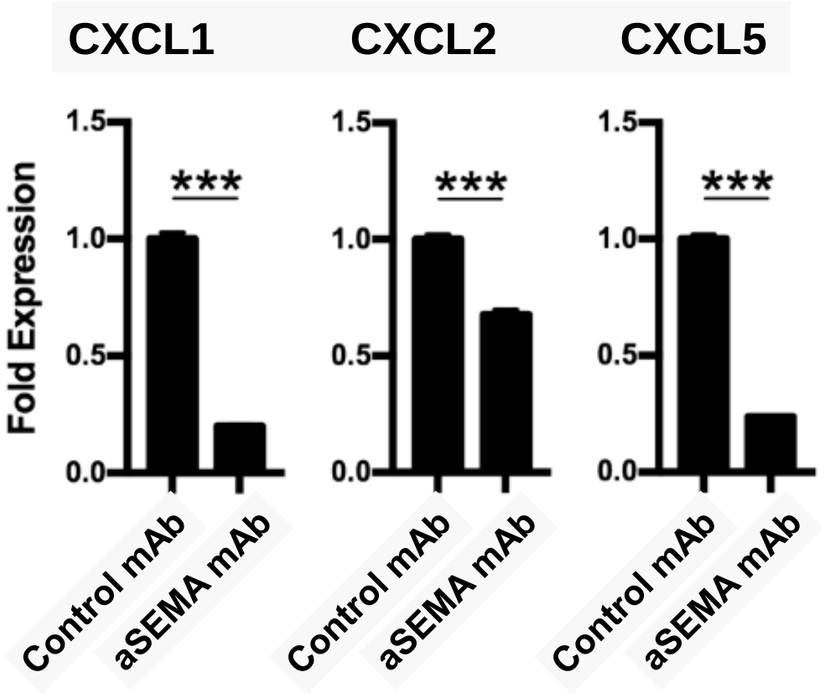
DO NOT POST

Anti-SEMA4D Ab reverses tumor recruitment of MDSC

Ab blockade reduces secretion of chemokines that recruit MDSC



Recruitment of PMN-MDSC



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

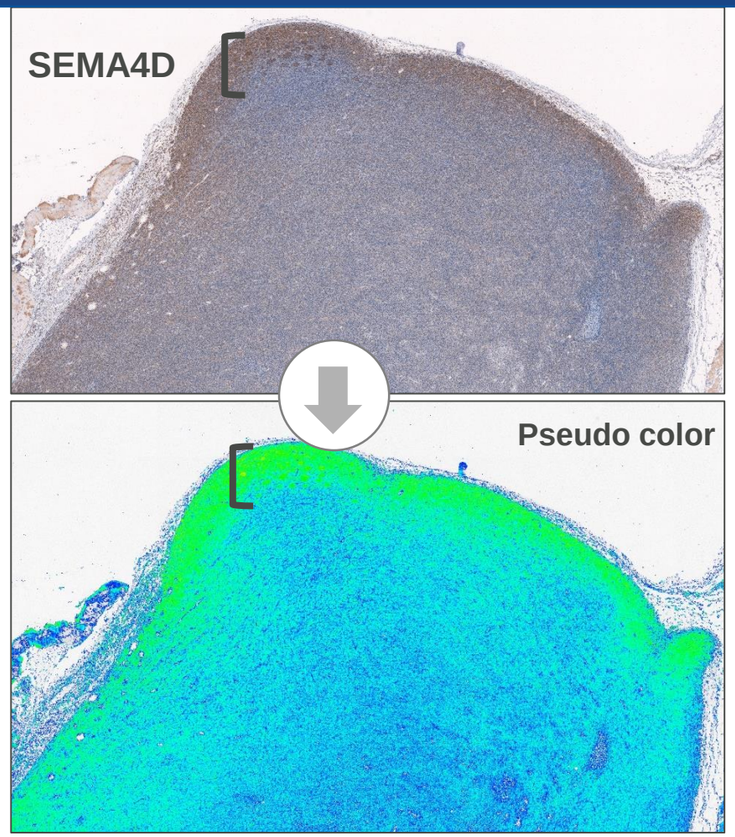
Similar results observed in tumor cells isolated from mice treated *in vivo* with anti-SEMA4D

Clavijo, Allen et al., manuscript in preparation

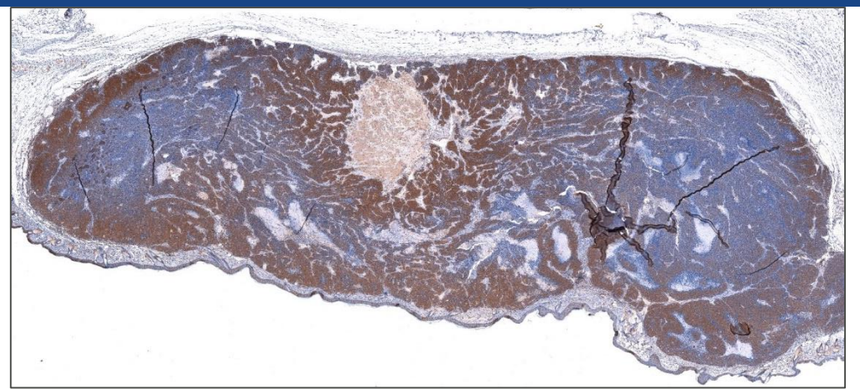
DO NOT POST

SEMA4D Expression Concentrated at Tumor Leading Edge in Murine Tumor Models

Colorectal (Colon26)



Mammary carcinoma (Tubo.A5)



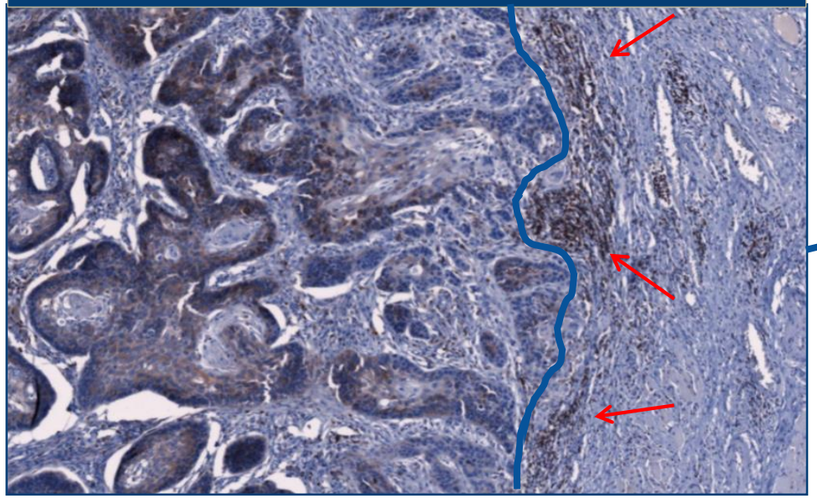
SEMA4D at the invasive margin of the tumor forms a barrier that restricts the infiltration of anti-tumor immune cells

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

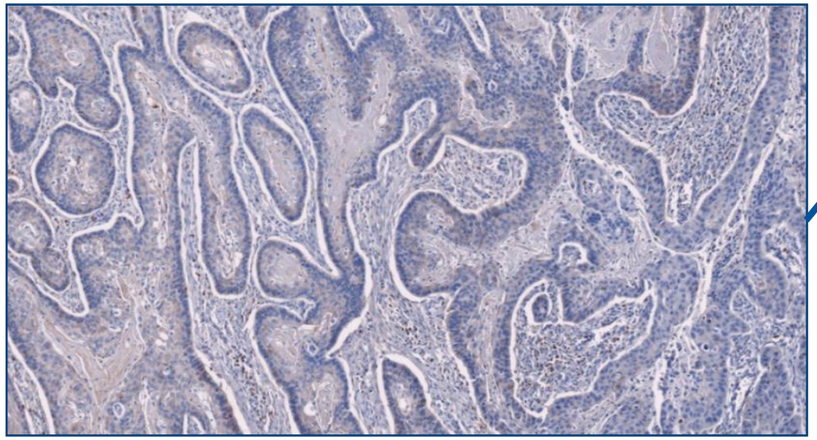
Evans EE et al. Cancer Immunol Res. 2015

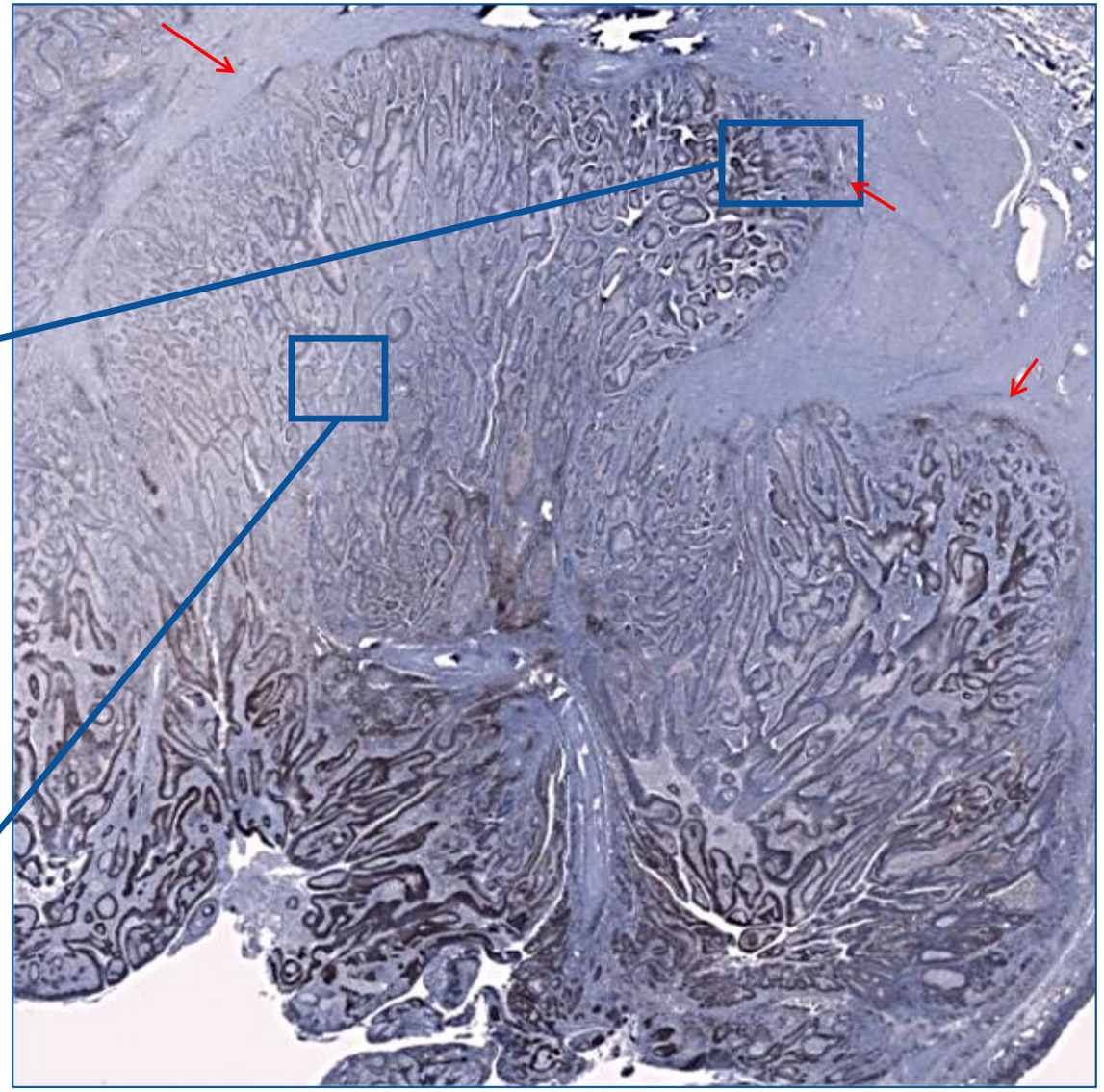
Immune cells are excluded where SEMA4D is concentrated at margins of human HNSCC of the Larynx

High SEMA4D at invasive tumor margin and immune exclusion



Low SEMA4D

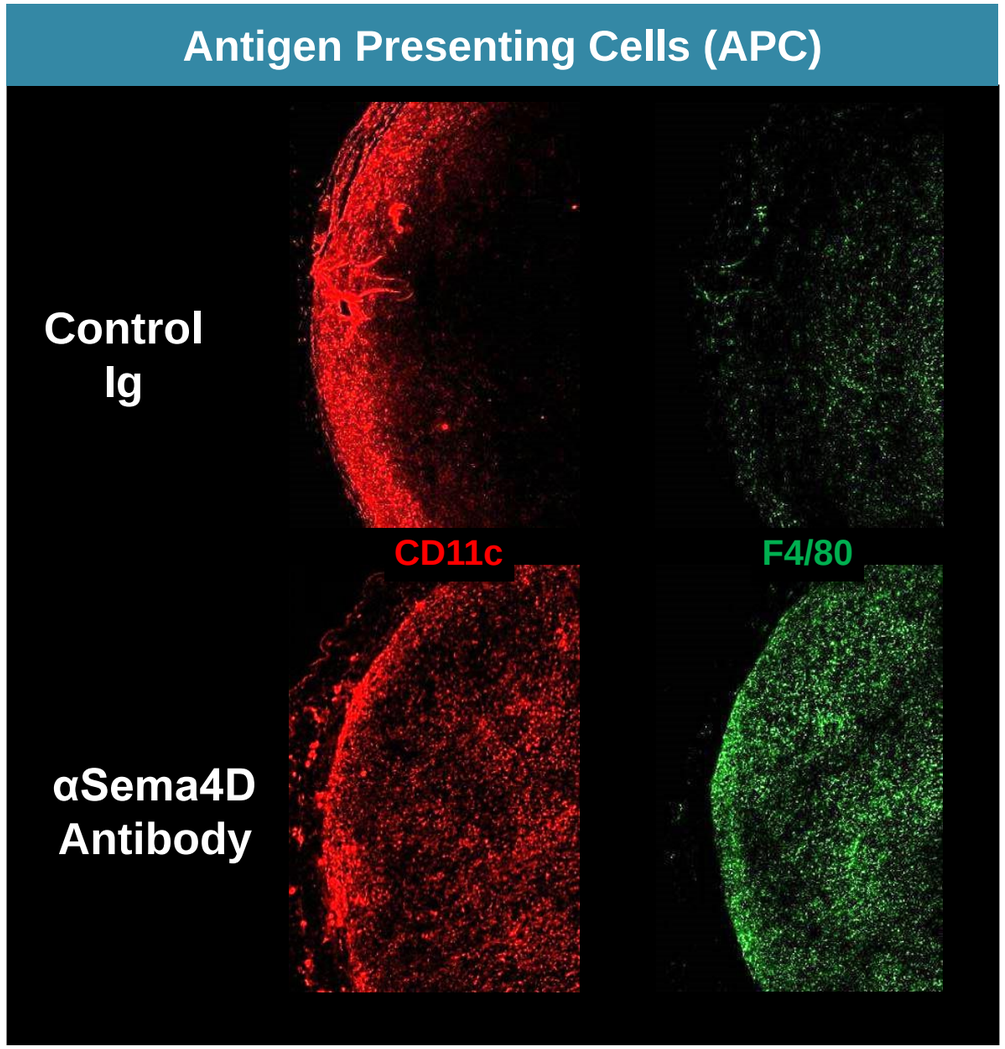




SEMA4D+
↑ TIL

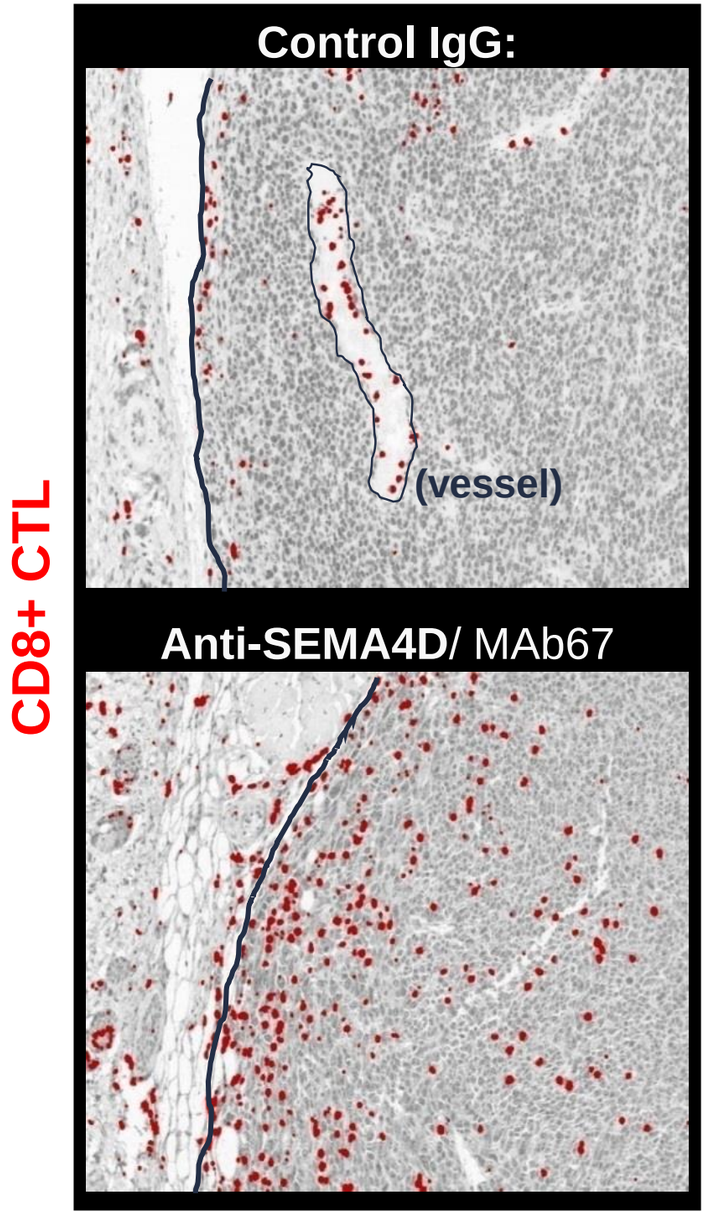
SEMA4D Controls Infiltration of Antigen Presenting Dendritic Cells into Tumor

- **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

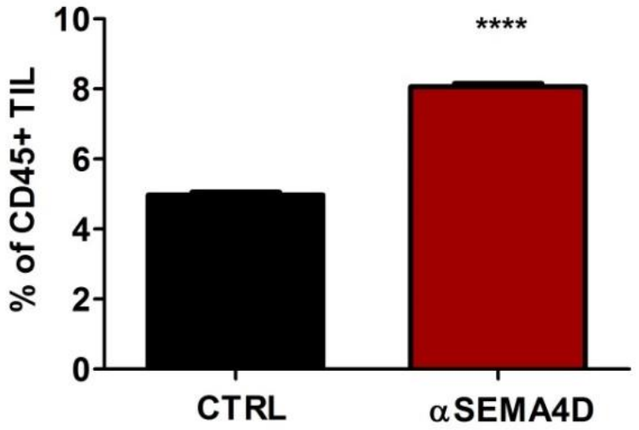


Evans EE et al. Cancer Immunol Research 2015;3(6): 689-701

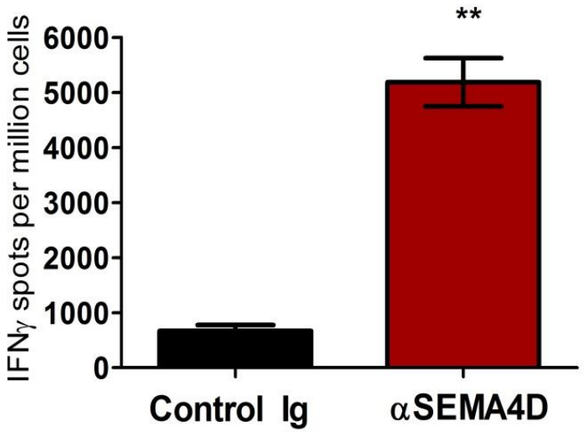
Anti-SEMA4D shifts balance of chemokines and suppressor cells to enhance anti-tumor T cell activity



T cell Infiltration: % CD3+ CD8+ in TIL



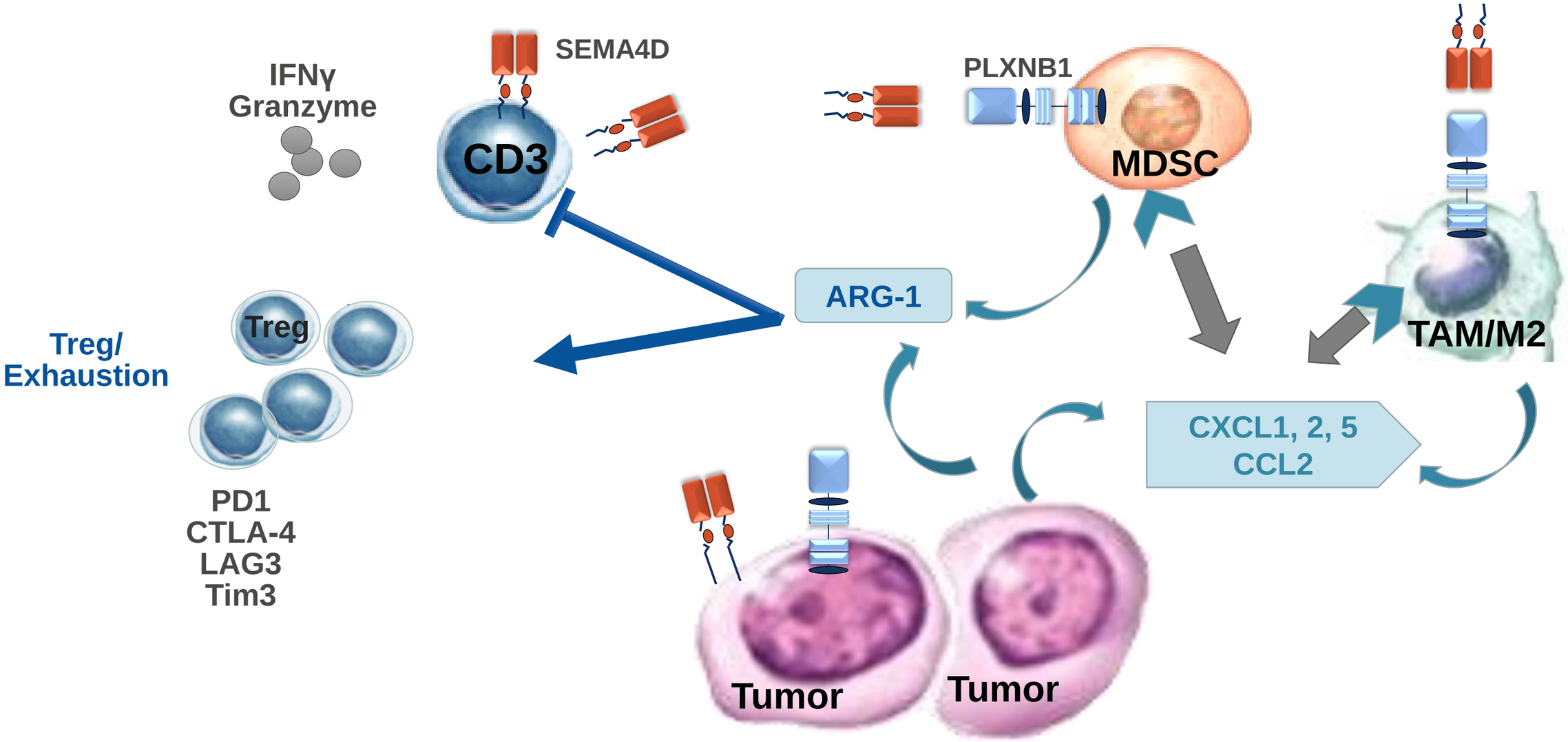
T cell Activity: ELISPOT



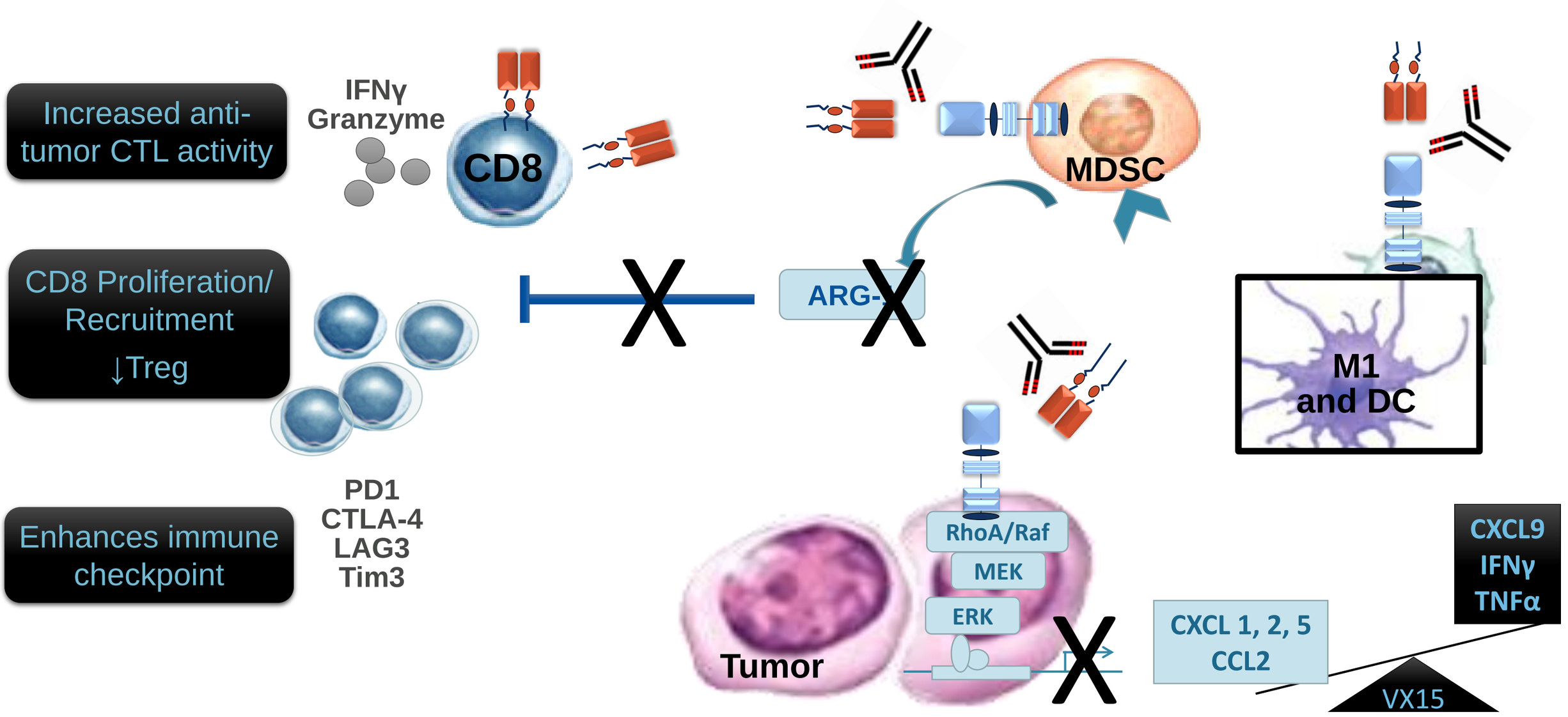
Also observed increase in Type 1 cytokines (IFNg, TNFa) and chemokines that recruit T cells (CXCL9, CXCL10)

Evans EE et al. Cancer Immunol Res. 2015

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



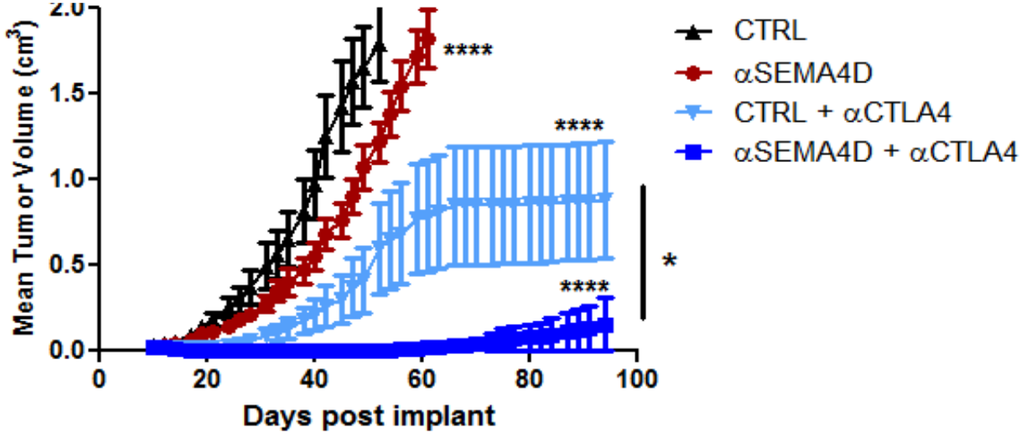
Anti-SEMA4D shifts the balance of mesenchymal suppression to promote T cell activity



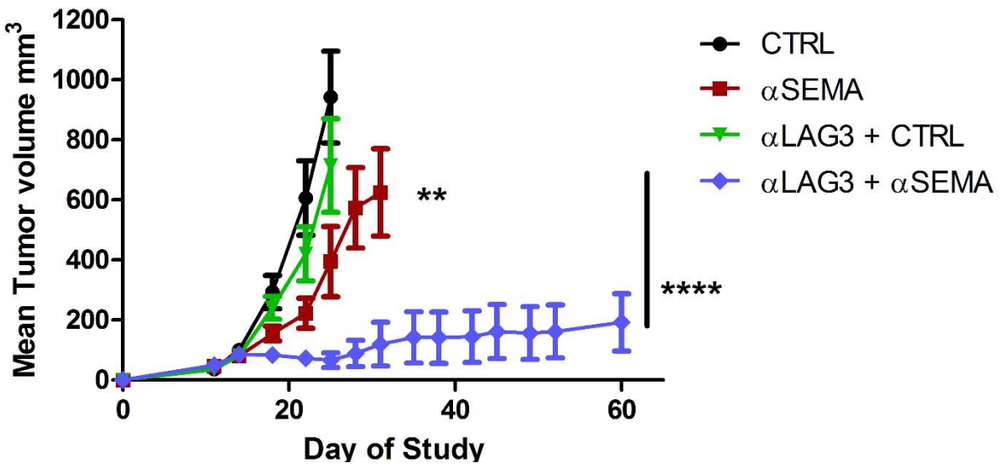
Anti-SEMA4D Antibody Enhances Activity of Immune Checkpoint Antibodies and HDAC inhibitor in Preclinical Syngeneic Models

anti-CTLA-4 Combination: MOC1 HNSCC

(Clint Allen, NIH)

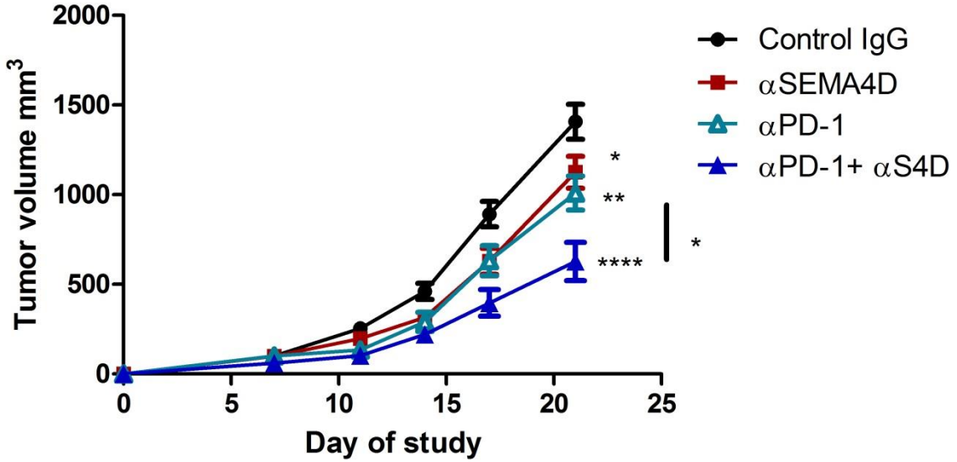


anti-LAG3 Combination: Colon26

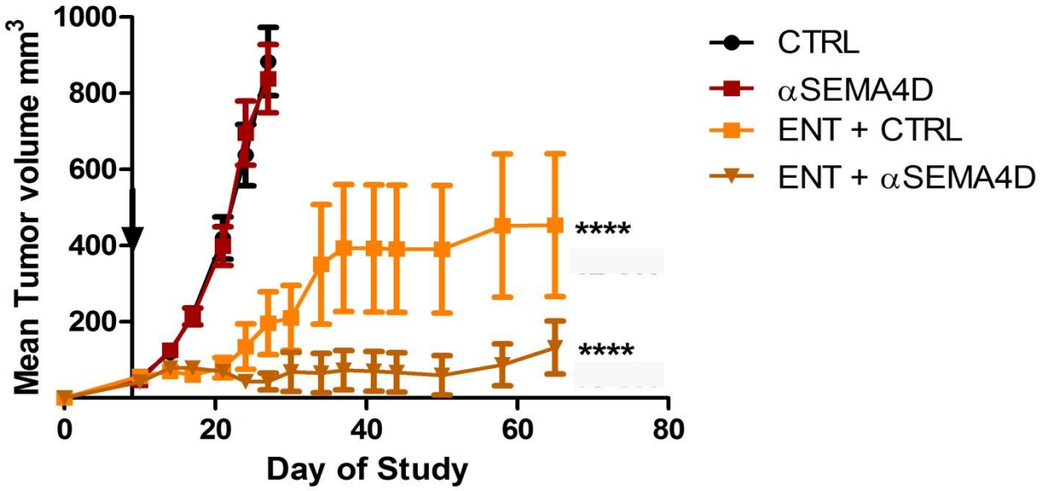


anti-PD-1 Combination: MC38

(Toni Ribas and Siwen Hu-Lieskovan, UCLA)



Entinostat Combination: Colon26
Treatment of established 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**

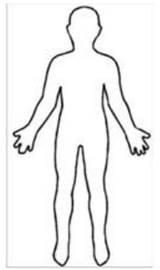
Evaluate: Safety, PK/PD, clinical activity (ORR, DoR, PFS) **&…**

biomarkers including immune infiltration in tumor biopsies

Neoadjuvant Trials Require Multidisciplinary Coordination

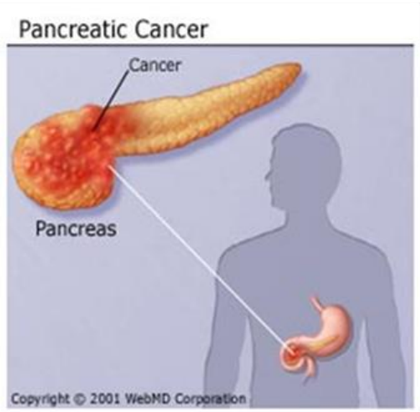
Medical Oncology

Patient Consent

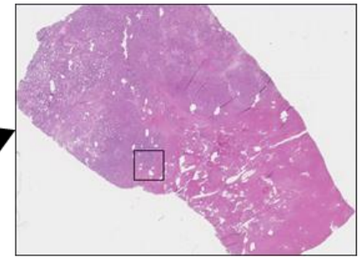


Baseline **Day 15** **Day 29**

Surgical Oncology



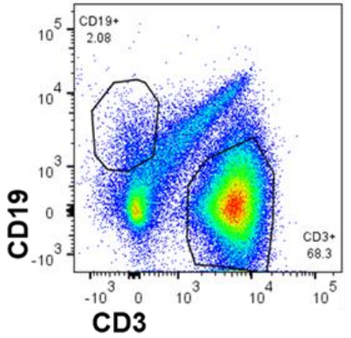
Pathology



IHC Analysis

Fresh Tissue

Flow Cytometry



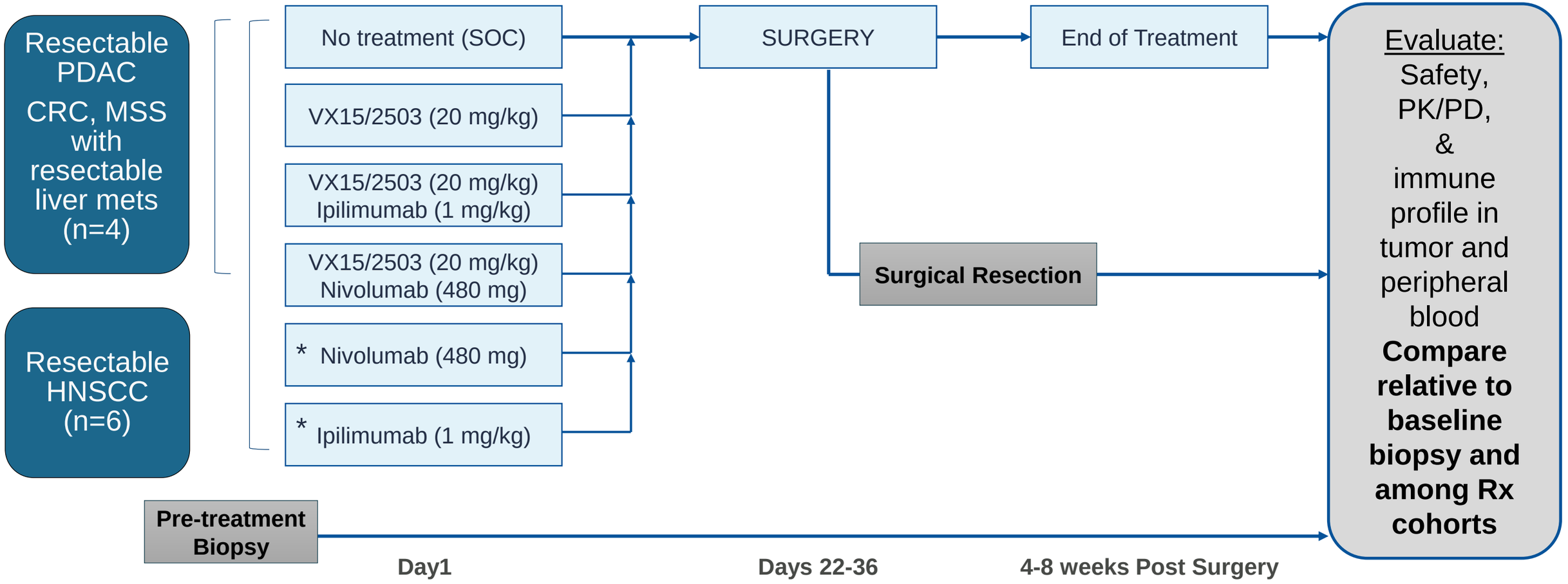
Plasma Biomarkers

Buffy Coat

Lesinski Laboratory

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

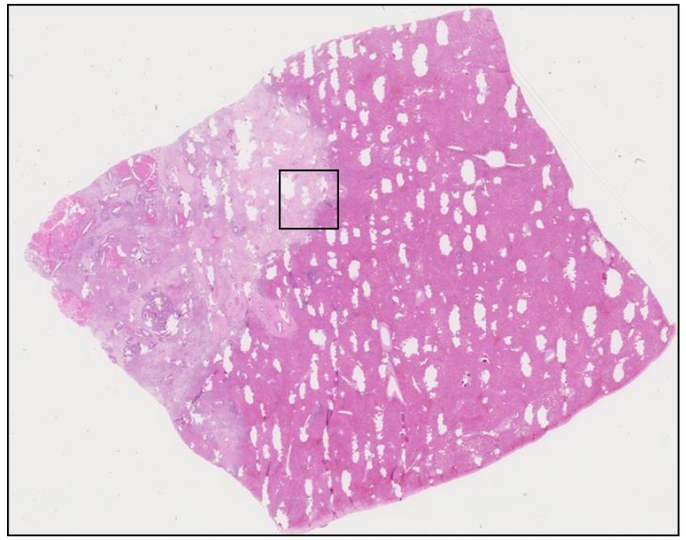
Colorectal Cancer with metastasis to liver, Pancreatic Cancer, *Head and Neck Squamous Cell Carcinoma. Integrated biomarker trials, Winship Cancer Institute (Lesinski and Wu, Steuer)

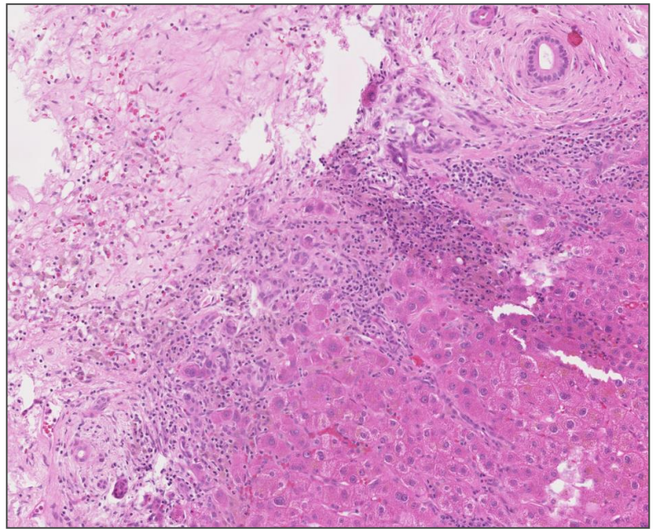


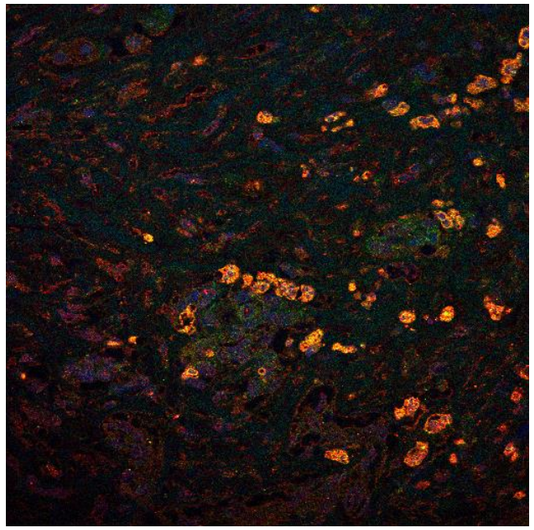
CRC and PDAC: NCT03373188 - RECRUITING

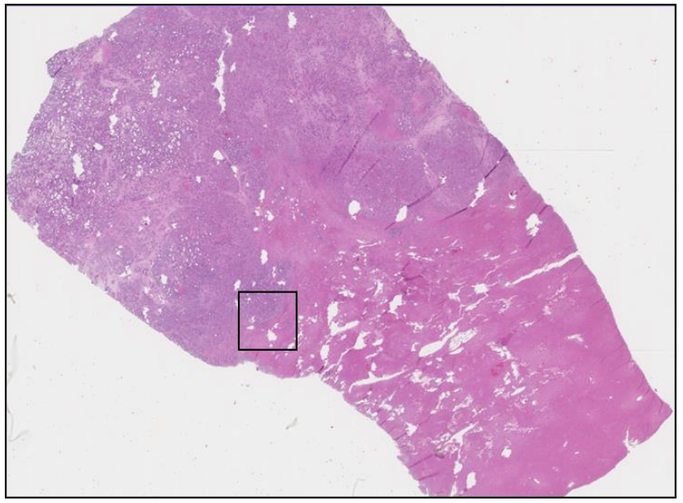
HNSCC: NCT03690986 – OPEN

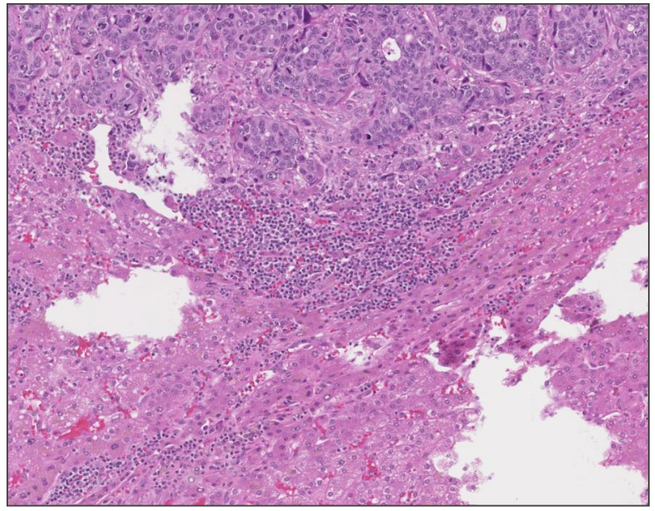
Preliminary Correlative Data from *NCT03373188*

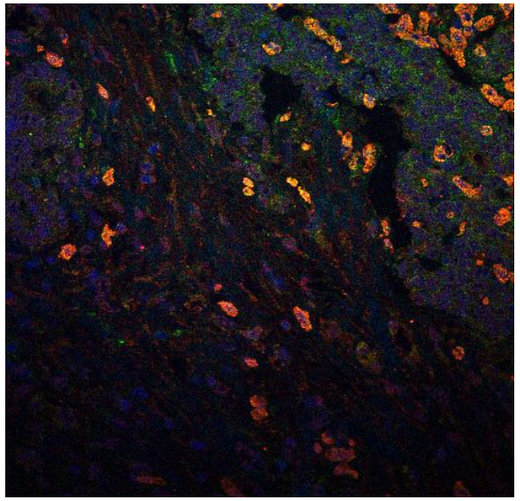












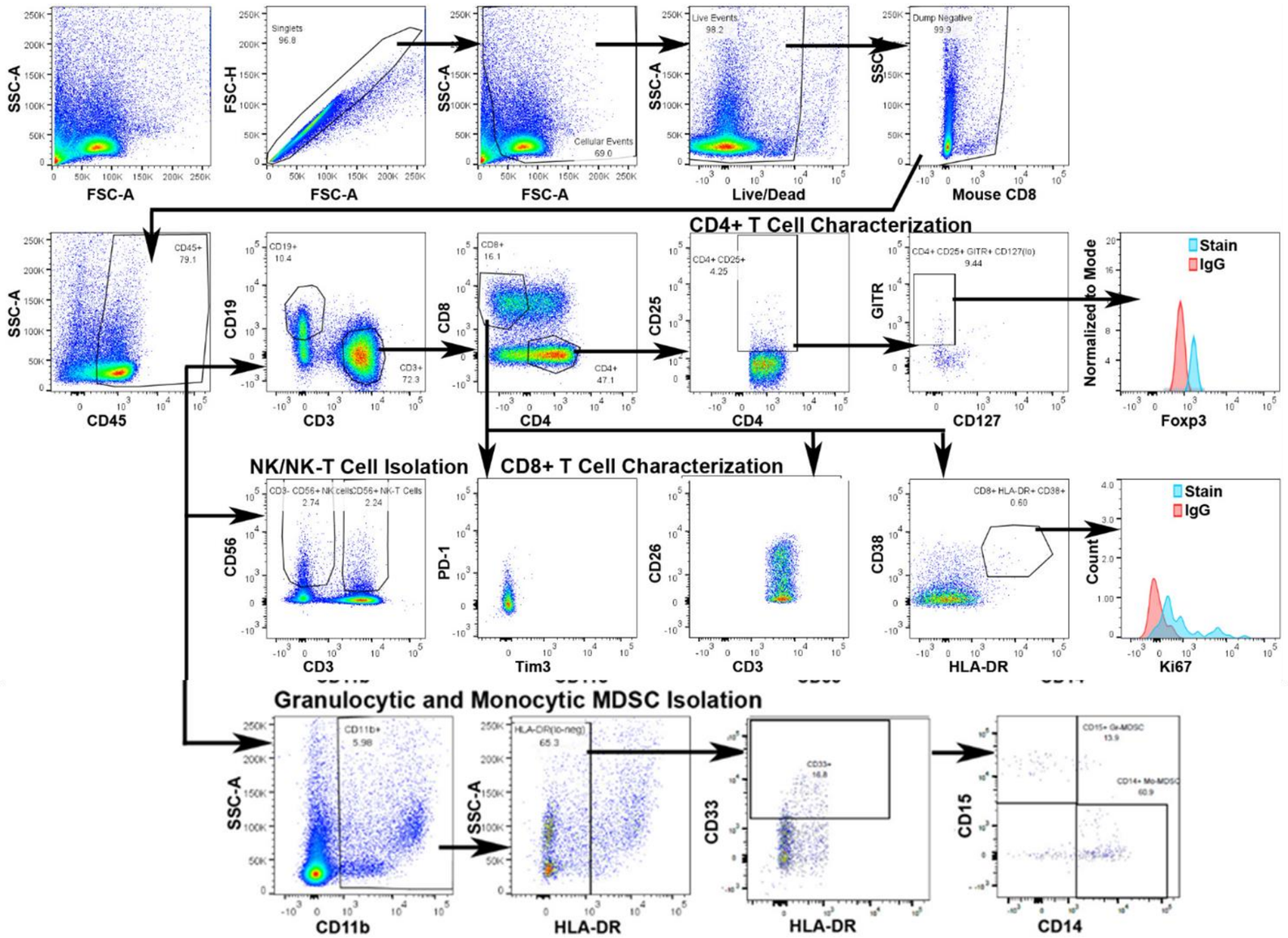
20X

CD33

S100A

DAPI

Comprehensive Flow Cytometry Panel from *NCT03373188*

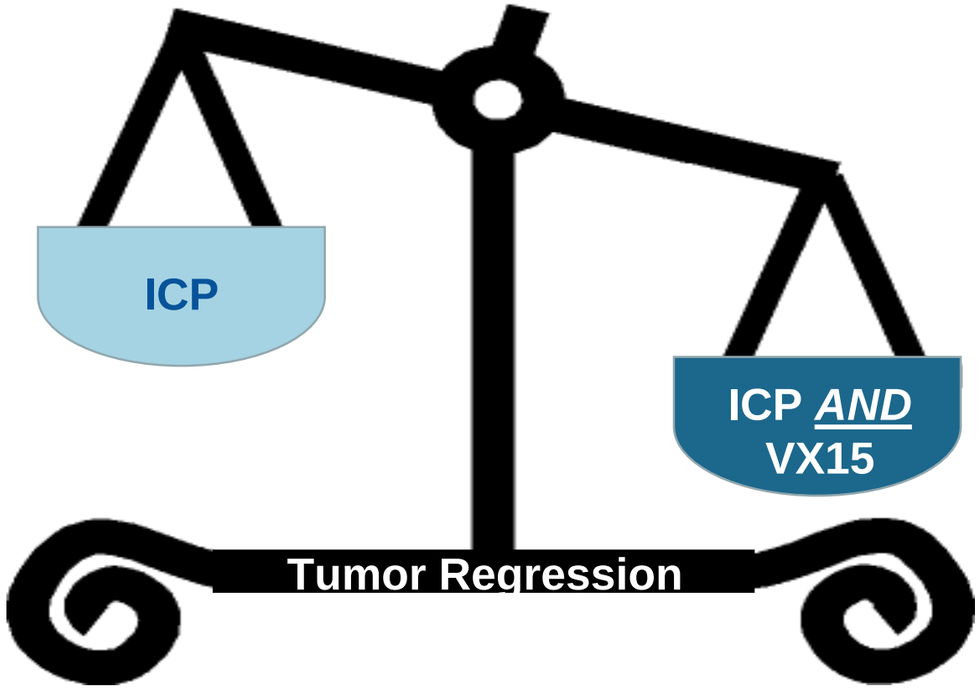


- T lymphocyte Subsets
- NK/NKT Subsets
- M1/M2 Macrophage Markers
- MDSC Subsets
- Dendritic Cells
- Monocytes

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: 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.

Acknowledgements

Vaccinex, Research:

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

EMD Serono

Winship Cancer Institute of Emory University Gregory Lesinski, Christina Wu, Brian Olson, Conor Steuer, Michael Lowe, Ragini Kudchadkar, Bassel El-Rayes, Shishir Maithel, Juan Sarmiento, Mihir Patel, Nabil Saba, Yue Xue, Alyssa Krasinskas, Matthew Farren, Brandon Ware

UCLA Siwen Hu-Lieskovan & Toni Ribas

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

NIH/NIDCD, Head and Neck Surgery Branch. Paúl Clavijo & Clint Allen

University of Rochester Cancer Center Ellen Giampoli & Jerome JeanGilles

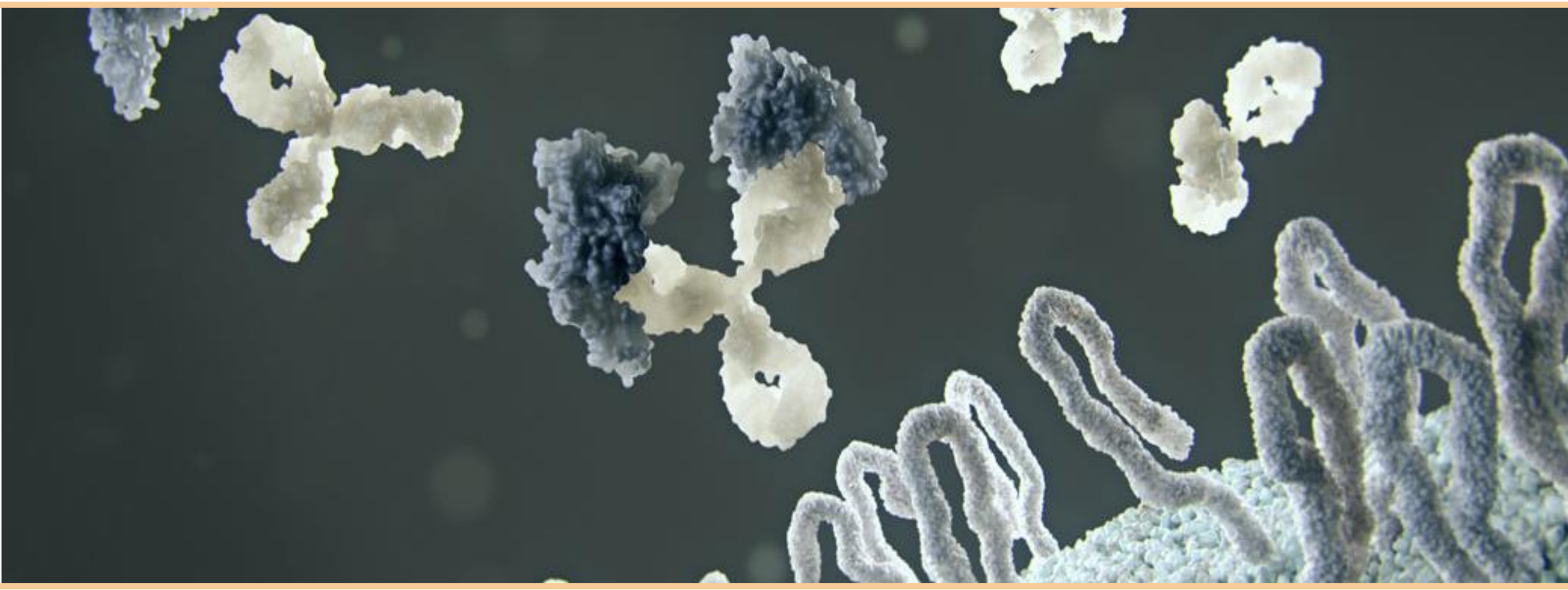
Charles River Discovery Services

South Texas Accelerated Research Therapeutics (START) Center for Cancer Care. PI: Amita Patnaik, MD

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

Patients and their families

Poster #O20

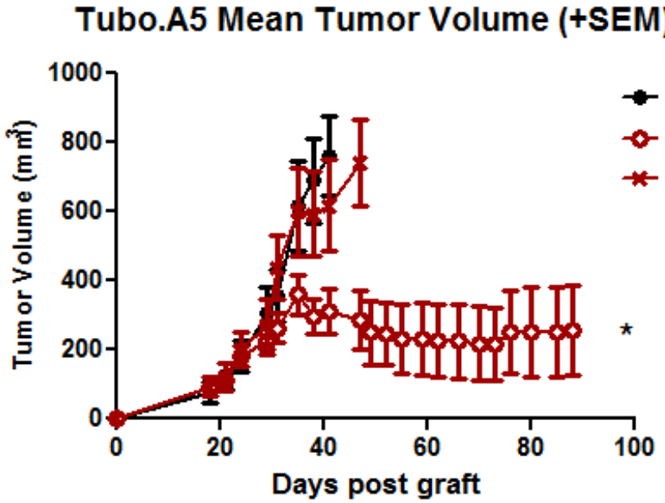


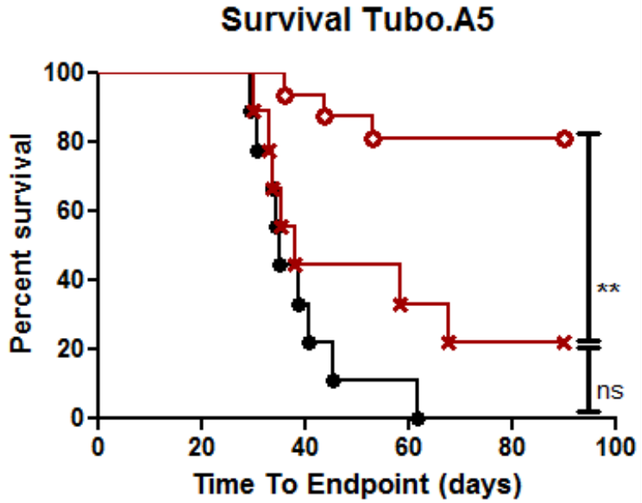
extras

Minimum effective dose and PD marker: Nonclinical

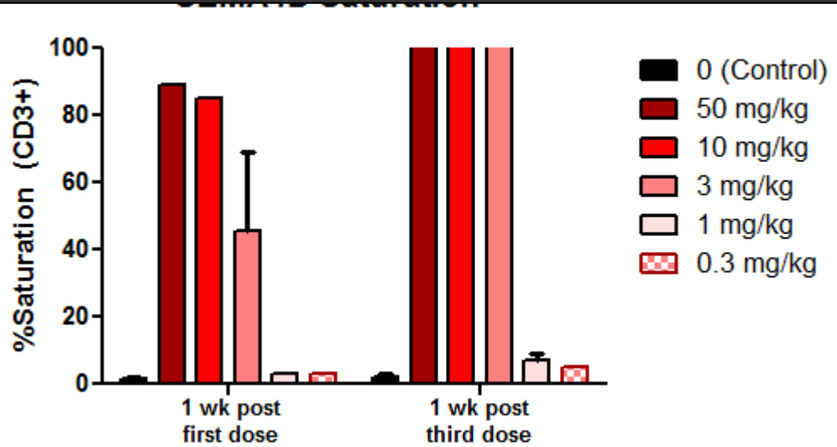
- Minimal effective dose was determined in several preclinical models to be ≥3 mg/kg.
- PD assay was developed to measure drug saturation of cellular

Minimal Effective Dose in Preclinical Oncology Models

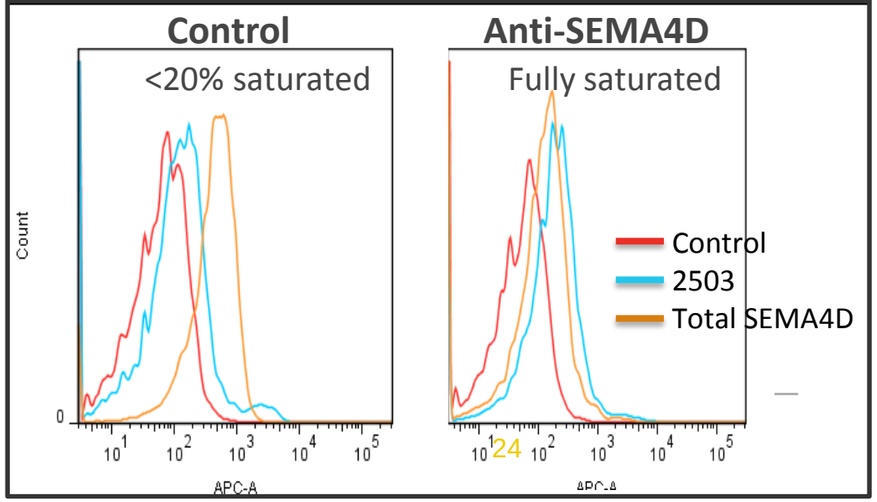




SEMA4D is saturated in BLOOD



SEMA4D is saturated in TUMOR



Single Agent pepinemab (VX15/2503) was well tolerated in Phase 1 trial

Phase 1

- Phase I, two-center, non randomized, open-label, **multiple-dose, dose-escalation in patients with advanced solid tumors**
- Standard 3 + 3 Dose Escalation
- Dose levels: 0.3, 1, 3, 6, 9, 15 and 20 mg/kg weekly

Safety and Tolerability

- 460 doses administered to 42 patients
- Weekly pepinemab (VX15/2503) infusions **well tolerated** up to 20 mg/kg (highest dose tested)
  - One DLT (grade 3 GGT elevation at 15 mg/kg) was reported in a pancreatic cancer patient with concomitant liver metastasis.
  - The most frequent treatment-related AE's were grade 1/2 nausea (14.3%) and fatigue (11.9%).

Disease control

- Nineteen patients (45.2%) exhibited stable disease for ≥8 weeks.
- Of these, 6 patients (14.3%) had stable disease for ≥16 weeks, and
- **3 patients had stable disease for 48-55 weeks, and one patient experienced PR**.

Patnaik et al. Clin Can Res 2015

CLASSICAL-Lung: pepinemab (VX15/2503) Combo with avelumab (anti-PD-L1)

Non-Small Cell Lung Cancer (NSCLC): IO naïve and IO refractory

Phase 1b/2 Combination Trial

VX15/2503 (pepinemab) in combination with avelumab (Anti-PD-L1)

NSCLC immunotherapy naïve	**DOSE ESCALATION PHASE** To determine the recommended Phase 2 dose of VX15 (pepinemab) in combination with avelumab, 10 mg/kg, Q2W in groups of 3-6 patients	**EXPANSION PHASE** Patients will be stratified but unselected for PD-L1; pre- and post-treatment biopsies mandatory
NSCLC Progressed following immunotherapy	*28-days for each escalation phase* ***COMPLETE***	*Up to 28 patients at recommended dose*

Co-funded by: MERCK

- Study to enroll up to ~62 subjects with advanced NSCLC
- Treatment of up to 6 subjects (3 + 3 design) in each of three VX15/2503 (pepinemab) dose levels (5, 10 and 20 mg/kg)
- A fixed standard dose of avelumab will be employed

Trial to evaluate Safety, PK/PD, clinical activity (ORR, DoR, PFS) and biomarkers including immune infiltration in tumors

NCT03268057 - RECRUITING

VINO: Pepinemab (VX15/2503) Combination with nivolumab or ipilimumab

Melanoma – failed any aPD-1/PD-L1

Phase 1 Combination Trial

VX15/2503 (pepinemab) Combination with nivolumab (Anti-PD-1) or ipilimumab (Anti-CTLA-4)

DOSE ESCALATION PHASE
VX15 (pepinemab) dose will be escalated from 10 to 20 mg/kg, Q4W, with nivolumab 480 mg Q4W

or

up to 20 mg/kg VX15 (pepinemab) Q3W with ipilimumab 3 mg/kg Q3W x4
in groups of 3-6 patients

EXPANSION PHASE

18 patients/cohort
pre- and post-treatment biopsies mandatory

VX15/2503 (pepinemab) + nivolumab

VX15/2503 (pepinemab) + ipilimumab

Collaboration with Antoni Ribas group at UCLA and with BMS providing nivolumab and ipilimumab

- Randomized Phase 1 study to enroll up to 60 patients with advanced (stage III or IV) melanoma who have progressed on anti-PD1/L1 based checkpoint inhibitors

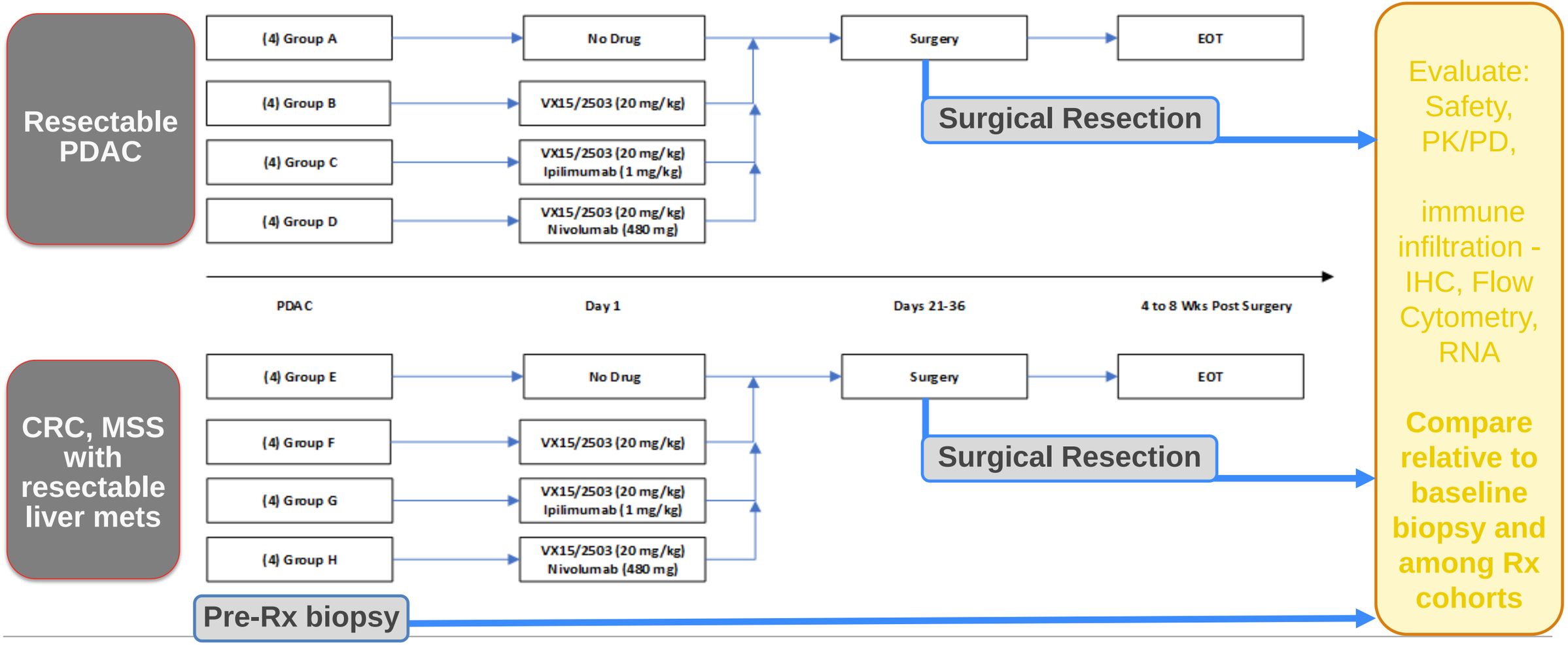
Trial to evaluate Safety, PK/PD, clinical activity (ORR, DoR, PFS) and biomarkers including immune infiltration in tumors

NCT03425461 - RECRUITING

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

Colorectal Cancer with metastasis to liver & Pancreatic Cancer

Integrated biomarker trial, Winship Cancer Institute of Emory University (Wu & Lesinski)



NCT03373188 - RECRUITING

A *Sleeping Beauty* forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis

NATURE GENETICS VOLUME 47 | NUMBER 6 | JUNE 2015

Branden S Moriarity[1–3], George M Otto[1–4], Eric P Rahrmann[1–4], Susan K Rathe[3], Natalie K Wolf[3,4], Madison T Weg[3,4], Luke A Manlove[4], Rebecca S LaRue[3,5], Nuri A Temiz[3], Sam D Molyneux[6], Kwangmin Choi[7], Kevin J Holly[4], Aaron L Sarver[3], Milcah C Scott[3,8], Colleen L Forster[9], Jaime F Modiano[3,8,10], Chand Khanna[11], Stephen M Hewitt[12], Rama Khokha[6], Yi Yang[13], Richard Gorlick[14,15], Michael A Dyer[16] & David A Largaespada[1–4]

Osteosarcomas are sarcomas of the bone, derived from osteoblasts or their precursors, with a high propensity to metastasize. Osteosarcoma is associated with massive genomic instability, making it problematic to identify driver genes using human tumors or prototypical mouse models, many of which involve loss of *Trp53* function. To identify the genes driving osteosarcoma development and metastasis, we performed a *Sleeping Beauty* (SB) transposon-based forward genetic screen in mice with and without somatic loss of *Trp53*. Common insertion site (CIS) analysis of 119 primary tumors and 134 metastatic nodules identified 232 sites associated with osteosarcoma development and 43 sites associated with metastasis, respectively. Analysis of CIS-associated genes identified numerous known and new osteosarcoma-associated genes enriched in the ErbB, PI3K-AKT-mTOR and MAPK signaling pathways. Lastly, we identified several oncogenes involved in axon guidance, including *Sema4d* and *Sema6d*, which we functionally validated as oncogenes in human osteosarcoma.

Suppression of bone formation by osteoclastic expression of semaphorin 4D

NATURE MEDICINE VOLUME 17 | NUMBER 11 | NOVEMBER 2011

Takako Negishi-Koga[1–3], Masahiro Shinohara[1,3], Noriko Komatsu[1,3], Haruhiko Bito[4], Tatsuhiko Kodama[5], Roland H Friedel[6] & Hiroshi Takayanagi[1–3,7]

Most of the currently available drugs for osteoporosis inhibit osteoclastic bone resorption; only a few drugs promote osteoblastic bone formation. It is thus becoming increasingly necessary to identify the factors that regulate bone formation. We found that osteoclasts express semaphorin 4D (Sema4D), previously shown to be an axon guidance molecule, which potently inhibits bone formation. The binding of Sema4D to its receptor Plexin-B1 on osteoblasts resulted in the activation of the small GTPase RhoA, which inhibits bone formation by suppressing insulin-like growth factor-1 (IGF-1) signaling and by modulating osteoblast motility. *Sema4d*$^{-/-}$ mice, *Plxnb1*$^{-/-}$ mice and mice expressing a dominant-negative RhoA specifically in osteoblasts showed an osteosclerotic phenotype due to augmented bone formation. Notably, Sema4D-specific antibody treatment markedly prevented bone loss in a model of postmenopausal osteoporosis. Thus, Sema4D has emerged as a new therapeutic target for the discovery and development of bone-increasing drugs.

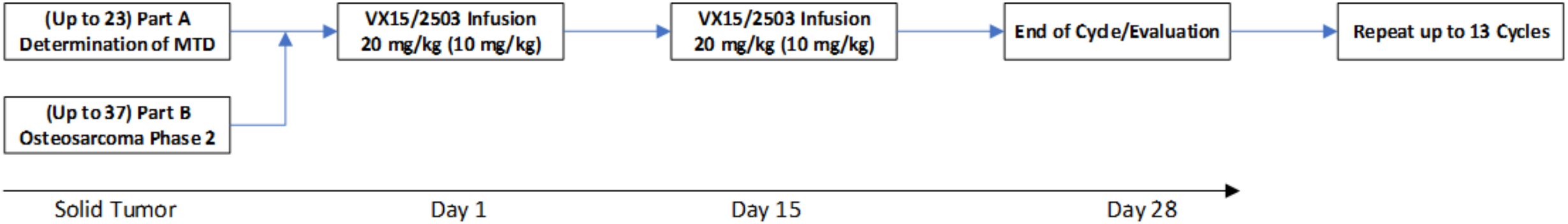
Rationale for targeting SEMA4D in Osteosarcoma

- SEMA4D has been identified as a proto-oncogene in osteosarcoma
- SEMA4D plays a role in bone homeostasis
- Anti-SEMA4D is immunomodulatory within tumor microenvironment

- **Children's Oncology Group and the NCI are sponsoring a trial to evaluate pepinemab (VX15/2503) in pediatric cancer and osteosarcoma.**
- NCT03320330: RECRUITING
  - FPI: FEB 2018

Pepinemab (VX15/2503) in Pediatric cancers and Osteosarcoma

A Phase 1/2 Trial of VX15/2503 in Children, Adolescents, or Young Adults With Recurrent or Relapsed Solid Tumors

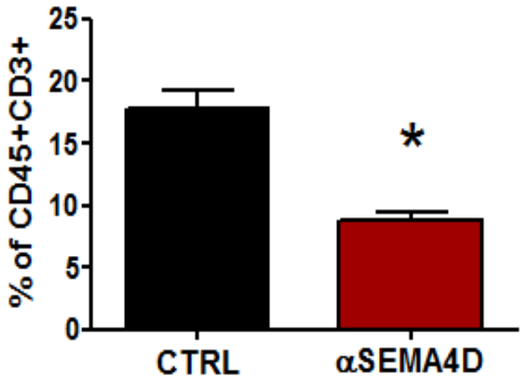


- PRIMARY OBJECTIVES:
  - I. To estimate the MTD and/or RP2D of VX15/2503 to children with recurrent or refractory solid tumors. (Part A)
  - II. To define toxicities and III. PK. (Parts A-B)
  - IV. To preliminarily define the antitumor activity of VX15/2503 for the treatment of relapsed or refractory osteosarcoma. (Part B)
- SECONDARY OBJECTIVES: PD & immunogenicity of VX15/2503 in pediatric patients

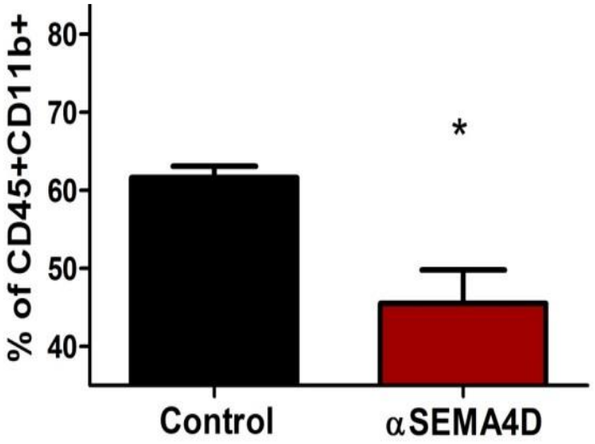
NCT03320330: RECRUITING

Anti-SEMA4D reduces suppressor cells in TME

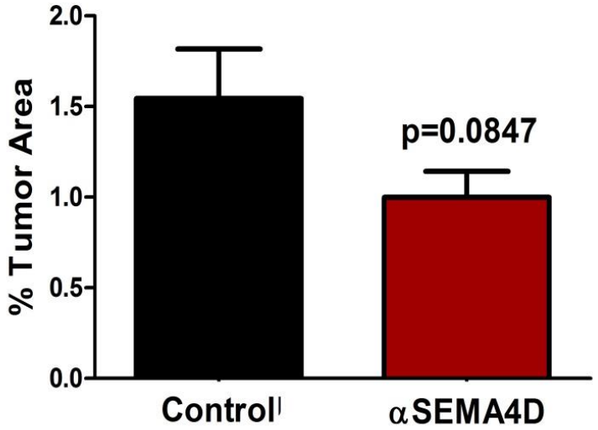
Treg in Tumor (CD4+CD25+)



MDSC in Tumor ($CD11b^{+}Gr1^{lo}$)



M2 TAM (CD206+)

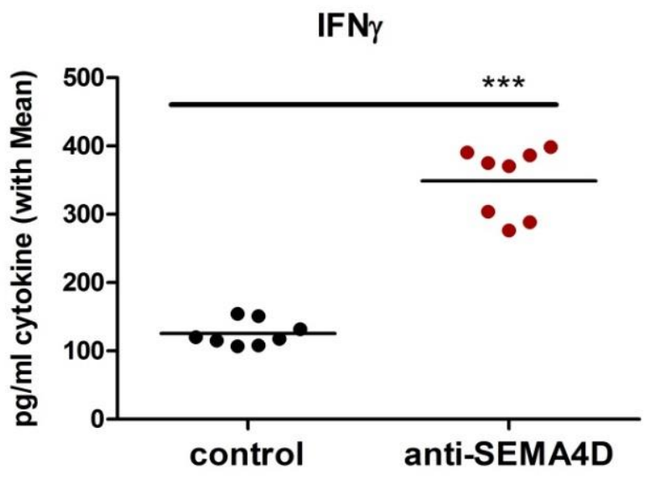


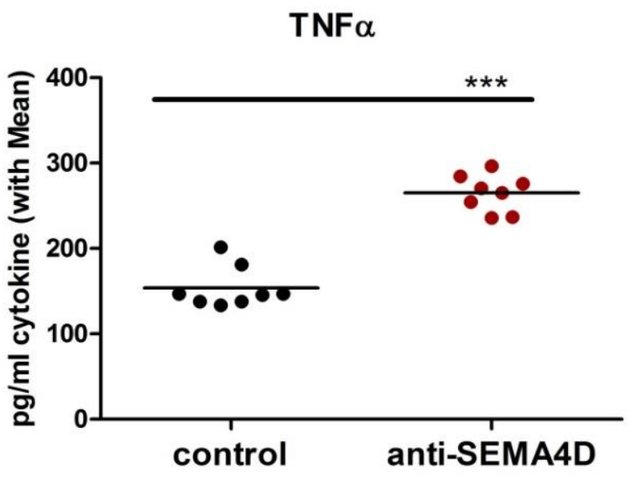
Also observed reduction in chemokines that recruit and polarize these cells

(CCL2, CXCL1, CXCL5)

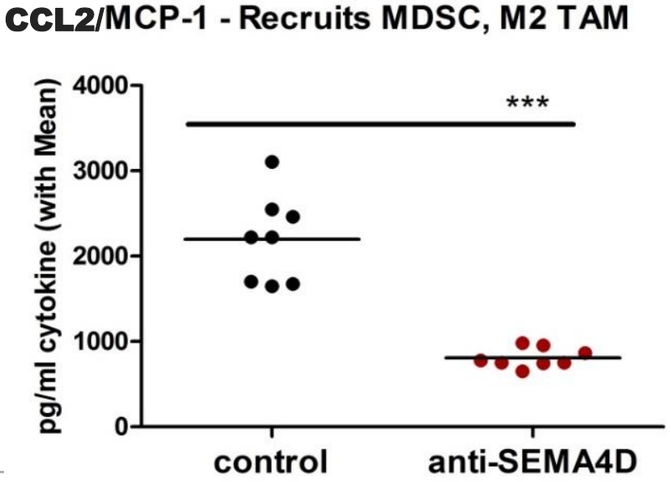
Anti-SEMA4D treatment shifts the balance of cytokines and chemokines in the tumor microenvironment

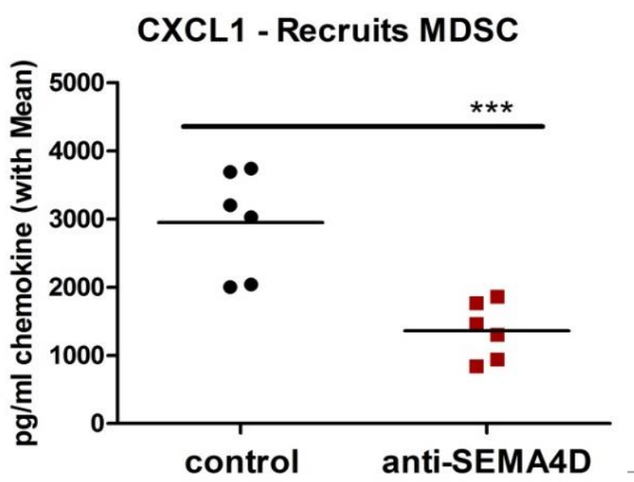
Tumoricidal Factors

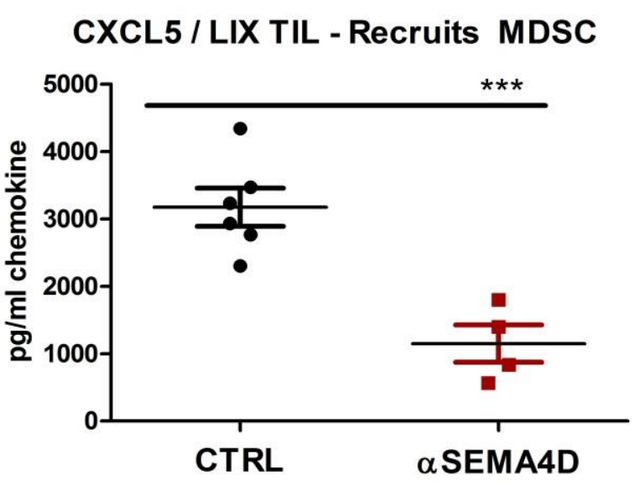




Immunosuppressive Factors



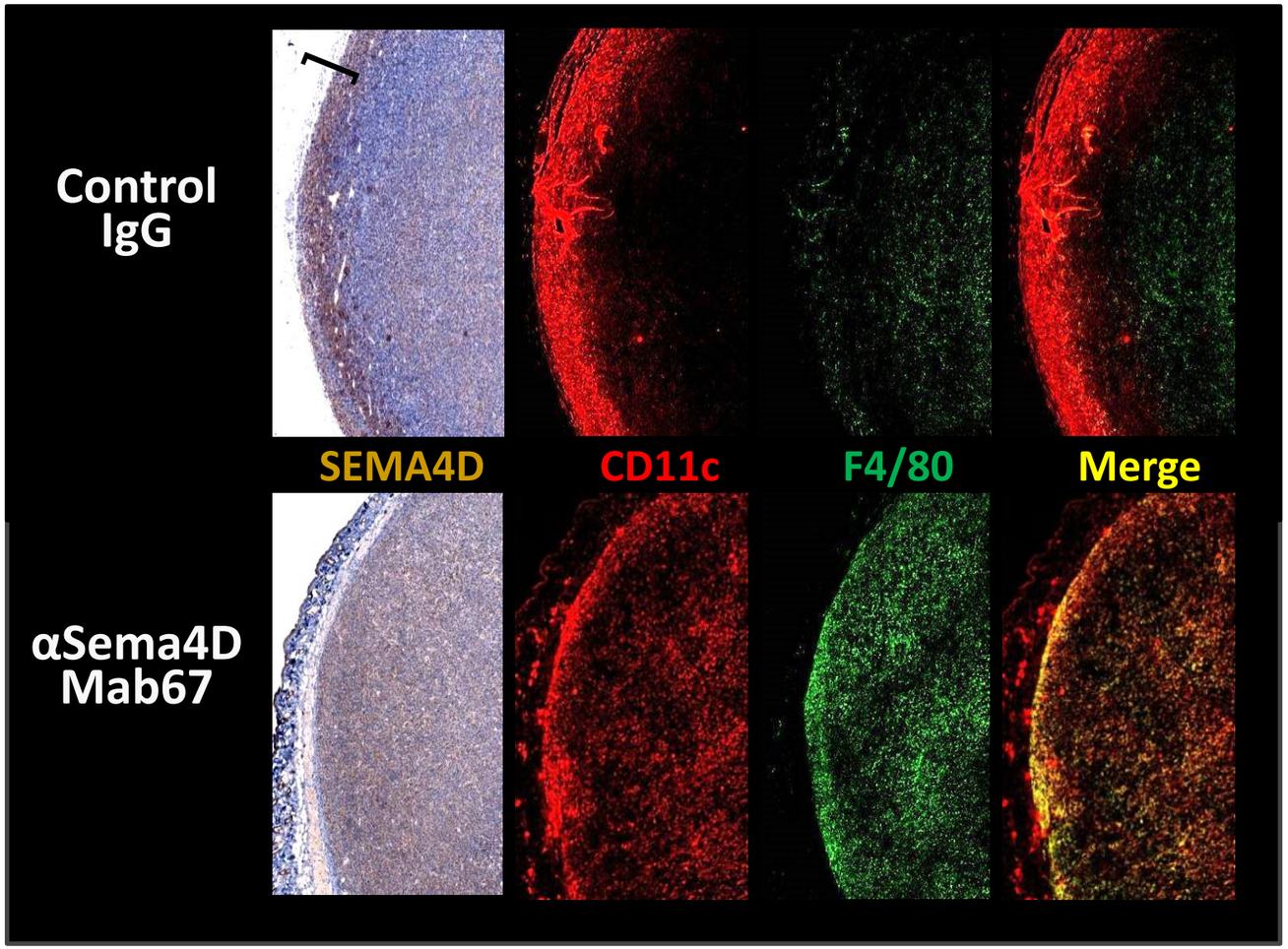


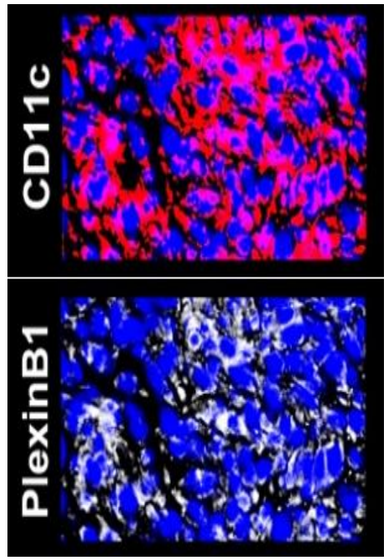


SEMA4D Regulates Organization of PLXNB1+ APC in Tumor Microenvironment of Preclinical Models

- Dendritic cells (DC) express receptor PLXNB1.
- Binding to SEMA4D restricts penetration of DC into Colon26 tumor.

Antibody blockade of SEMA4D enhances migration and differentiation of pro-inflammatory APC within TME.





Evans EE et al. Cancer Immunol Res. 2015

Also observed reduction in cells and chemokines that recruit and polarize MDSC, M2 TAM, Treg

Vaccinex Product Pipeline

Research/Preclinical	Phase 1	Phase 2	Phase 3
SEMA4D Antibody Platform			
VX15 (pepinemab) Huntington's Disease (Orphan Disease and Fast Track Designation)		SIGNAL	
VX15 (pepinemab) Non-Small Cell Lung Cancer		CLASSICAL – Lung	
VX15 (pepinemab) Melanoma, Osteosarcoma			
ActivMAb Antibody Platform			
VX5 Anti-CXCL13 for Autoimmune Diseases			
Partnered Anti-CD20 Antibody			
BVX20 Multiple Sclerosis		Biocon	

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