

The Negative Checkpoint Regulator VISTA in Cancer and Tolerance

Isabelle Le Mercier, PhD
Randolph Noelle Lab



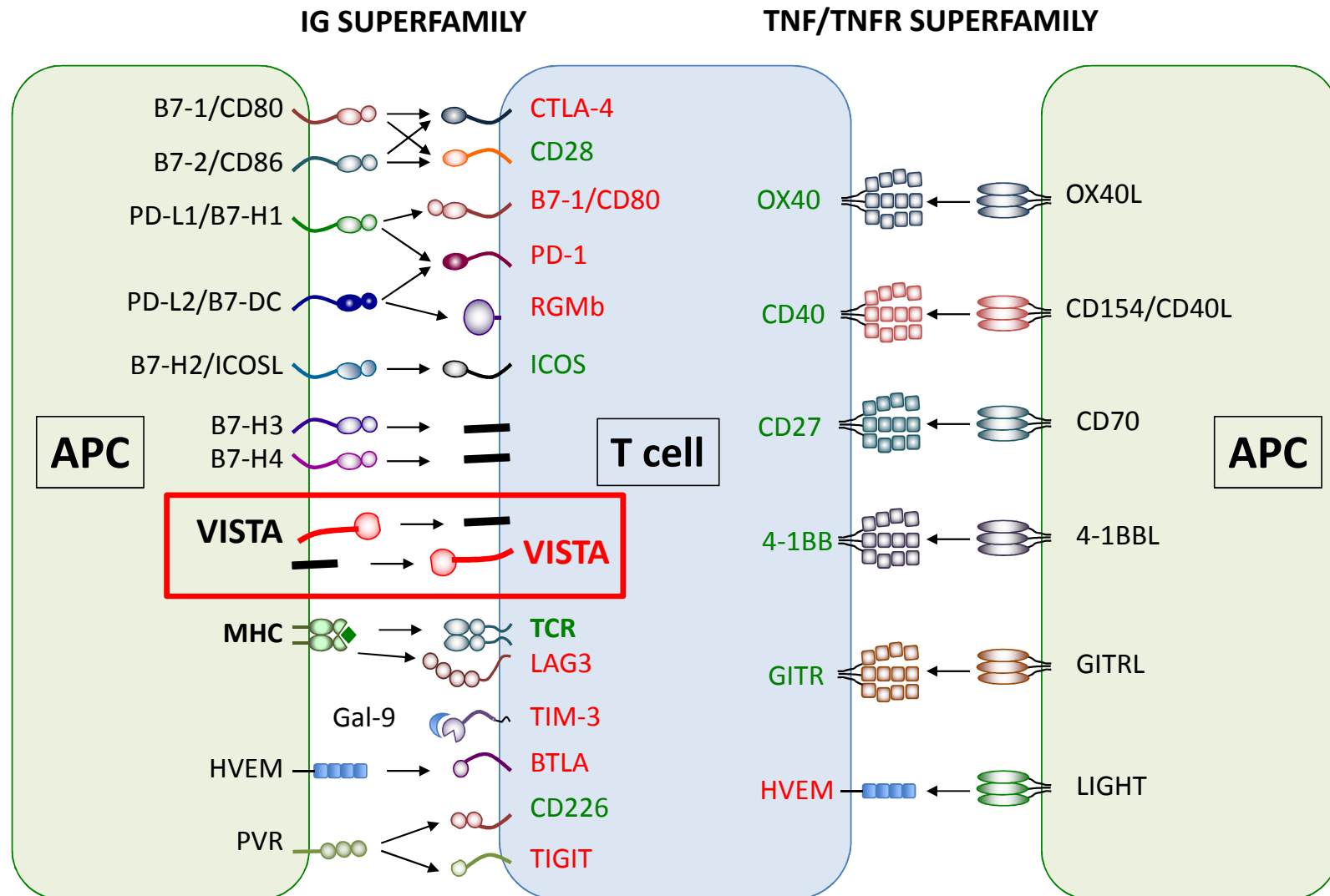
Presenter Disclosure Information

Isabelle Le Mercier

The following relationships exist related to this presentation:

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What are the Immune Checkpoints ?



VISTA (PD-1H, DD1a)

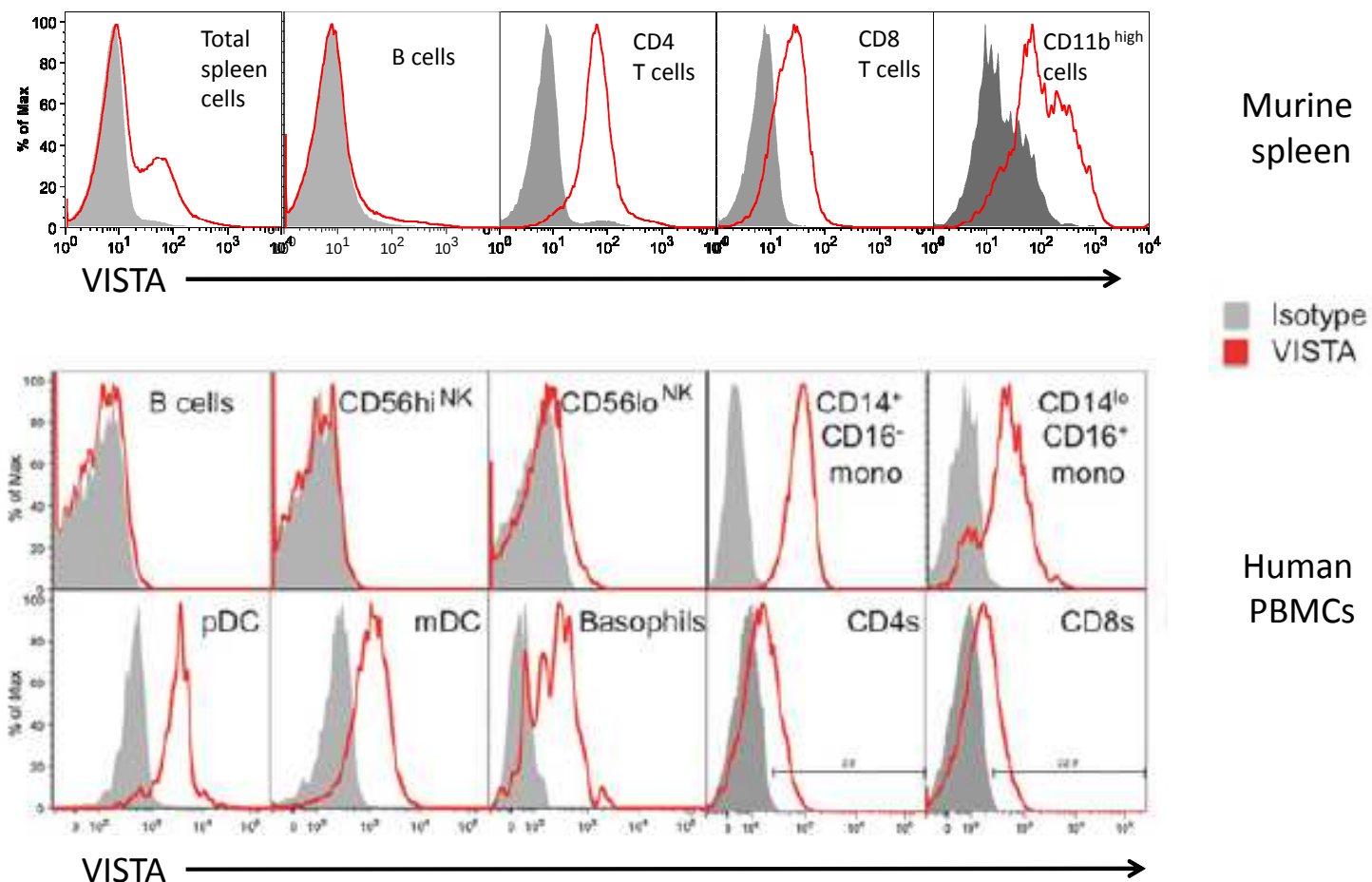
V-region of **I**mmunoglobulin containing **S**uppressor of **T** cell **A**ctivation

Negative Checkpoint Regulator

- Membrane protein of the Ig SF
- 92 Aa cytoplasmic domain
- Homologous to PD-L1 (ligand) or PD-1 (receptor)
- Hematopoietically-restricted *
 - VISTA is expressed on:
 - Myeloid cells
 - T cells
 - In the TME on MDSCs, human TILs
- Controls inflammation through the suppression of T cell and myeloid cell mediated activities
- It is likely both a ligand *and* a receptor

VISTA Biology

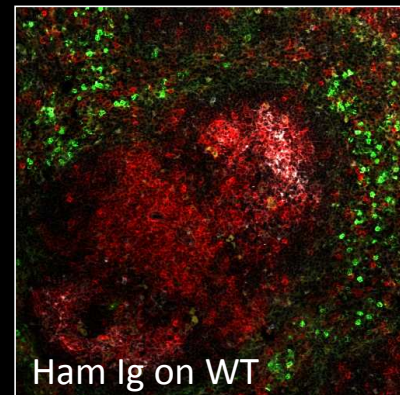
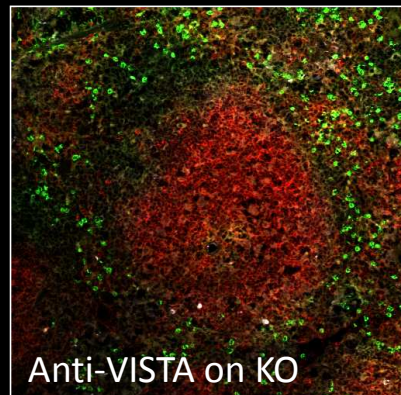
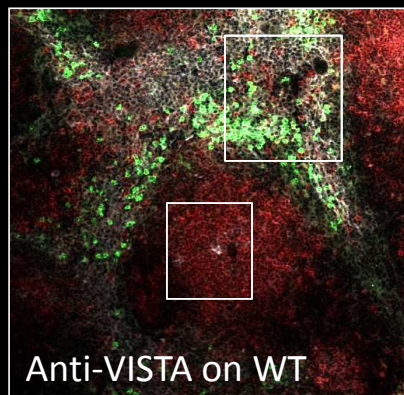
VISTA is expressed on T cells and myeloid cells



Li Wang et al. J Exp Med 2011

Louise Lines et al. Cancer Res. 2014

VISTA is expressed on T cells and myeloid cells

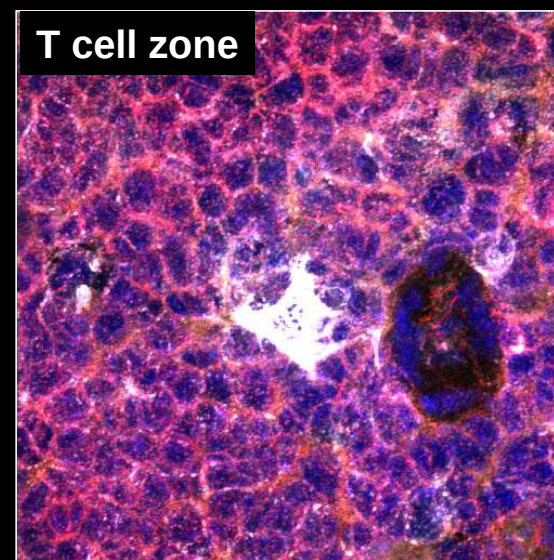
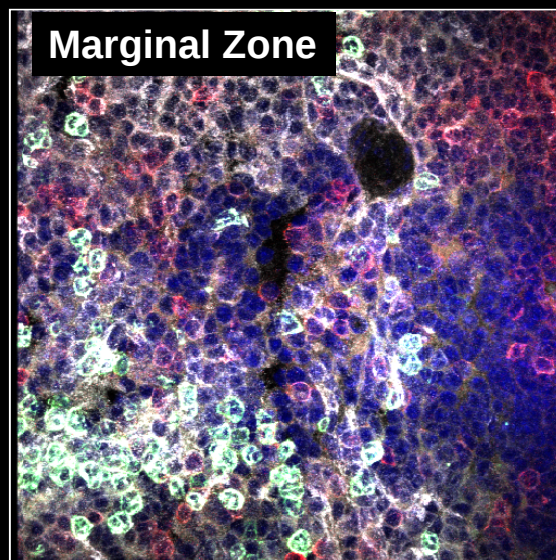


SPLEEN

CD11b

CD3

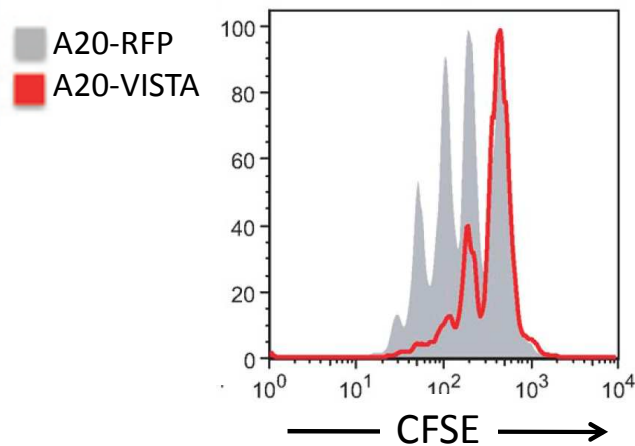
VISTA



Over expression of VISTA on APCs inhibits T cell activation

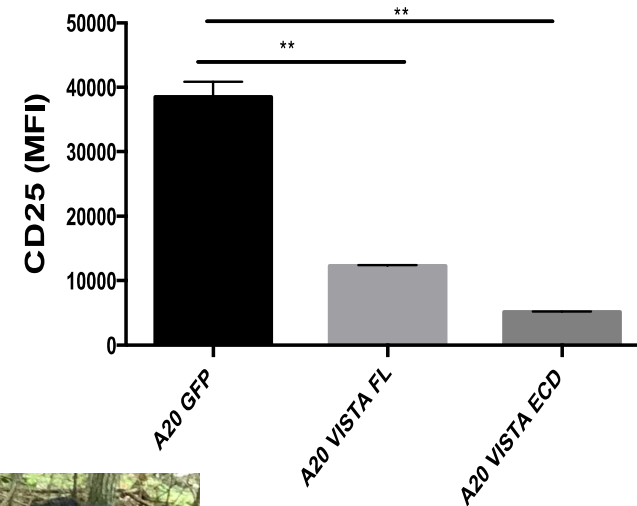
A20 B cell line + OVA peptide + OVA specific (DO11) TCR T_H T cells

VISTA on APCs inhibits T cell proliferation



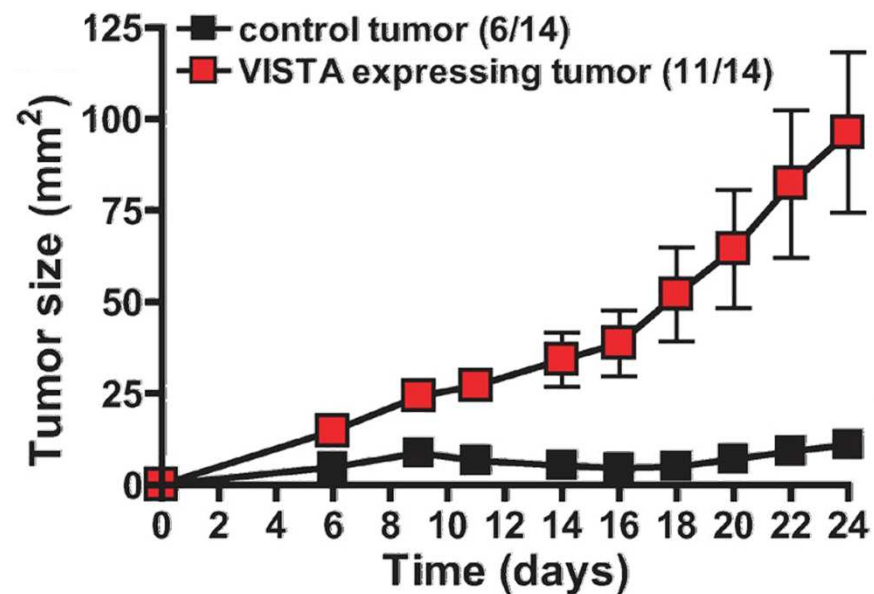
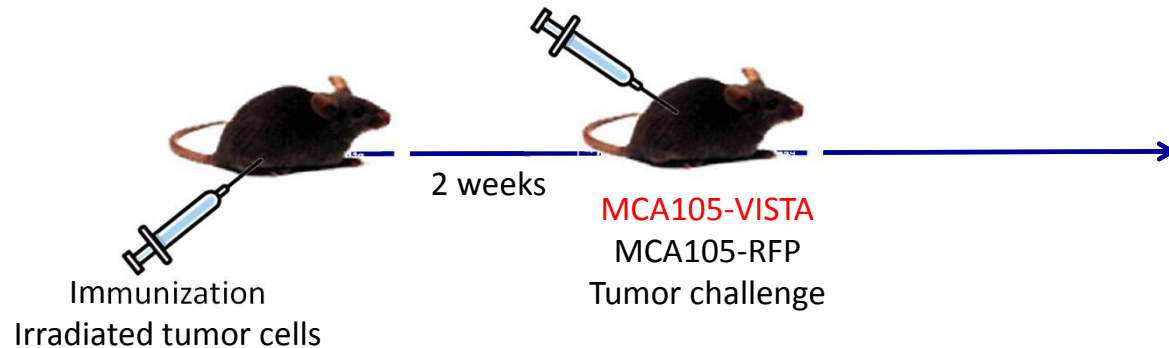
Li Wang et al. J Exp Med 2011

VISTA on APCs inhibits activation markers upregulation



Jiannan Li

Over expression of VISTA on tumor cell prevents antitumor immunity

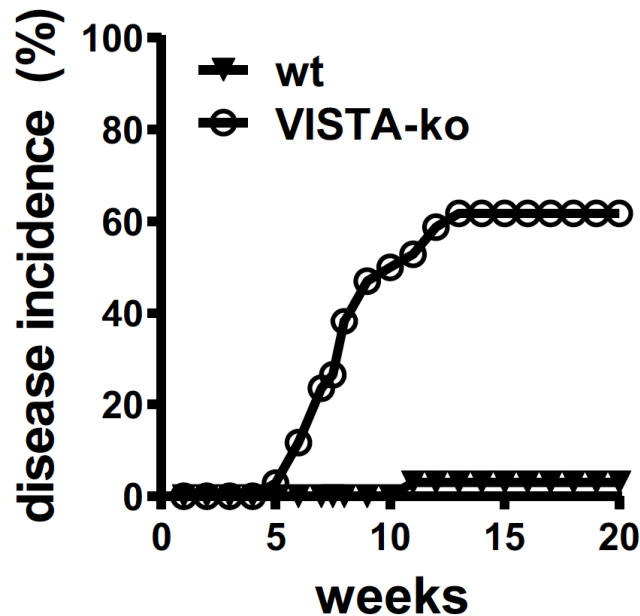


Activated T cell and myeloid cell phenotype in VISTA deficient mice

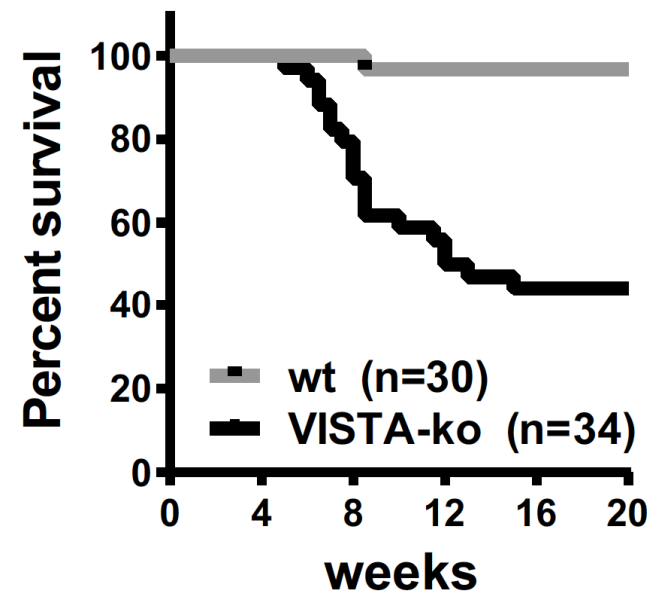
- **Mild splenomegaly/lymphadenopathy in aged mice**
- **Increased in myeloid populations**
- **Gradual accumulation of spontaneously activated T cells (CD44⁺ CD62L low)**
- **Enhanced T-cell responsiveness**
- **Increased infiltration in specific organs**
- **No systemic or organ specific autoimmune disease**

VISTA deficiency exacerbates EAE, model of MS

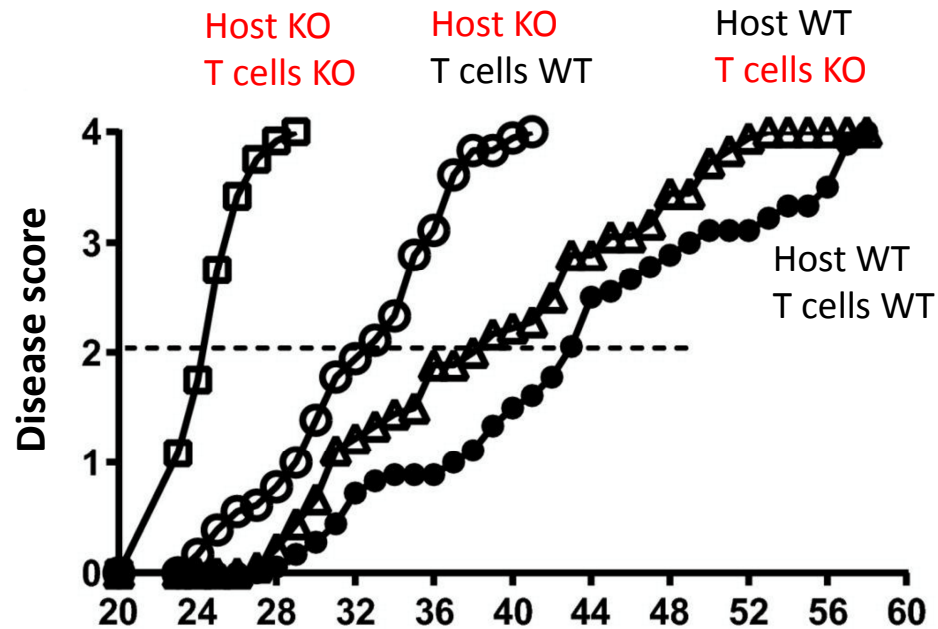
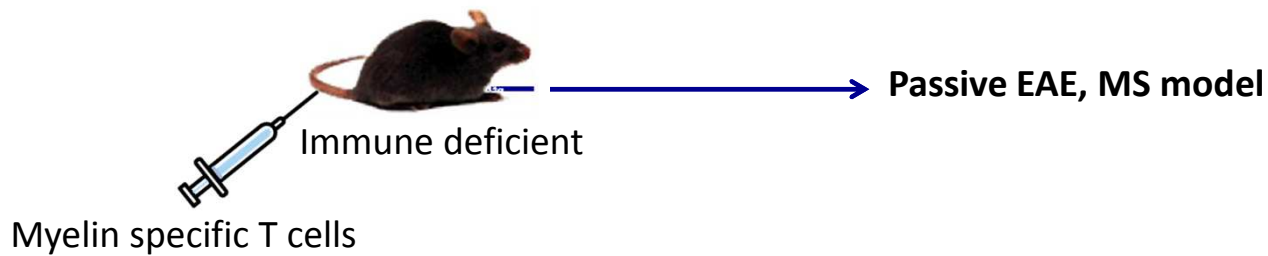
Myelin specific (2D2) TCR Tg **WT**
- No disease



Myelin specific (2D2) TCR Tg x **VISTA KO**
- Spontaneous EAE disease (MS model)
- Ascending paralysis
- Reduced survival

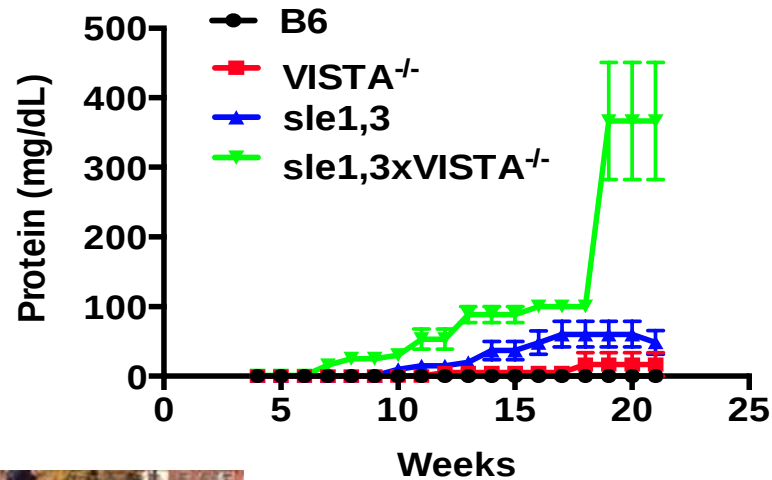


VISTA deficiency on the host exacerbates passive EAE

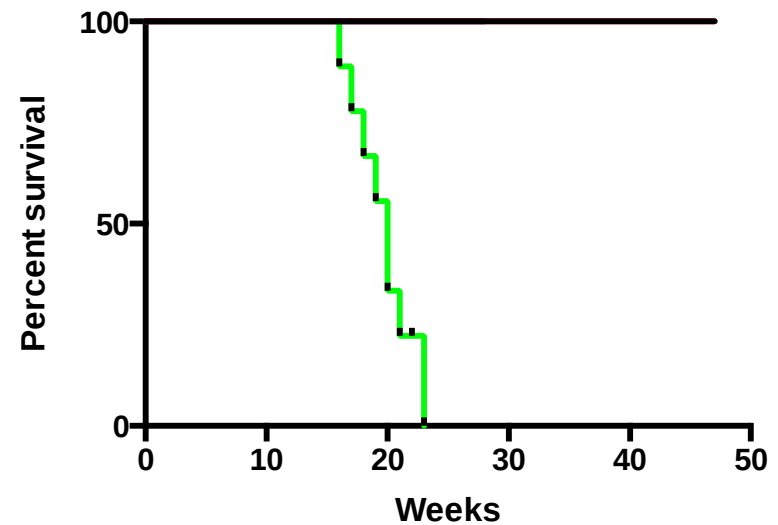


VISTA deficiency in SLE prone mice exacerbates disease

Sle1/Sle3 **WT**
- Late incidence lupus

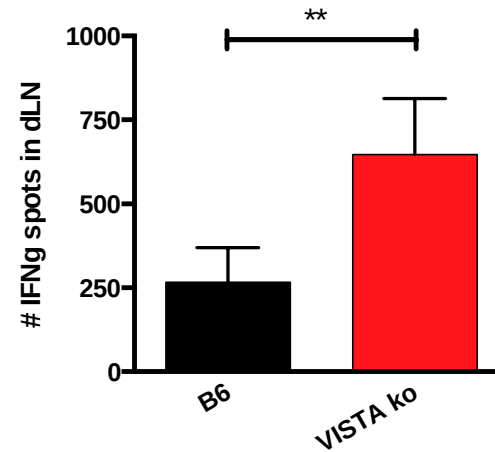
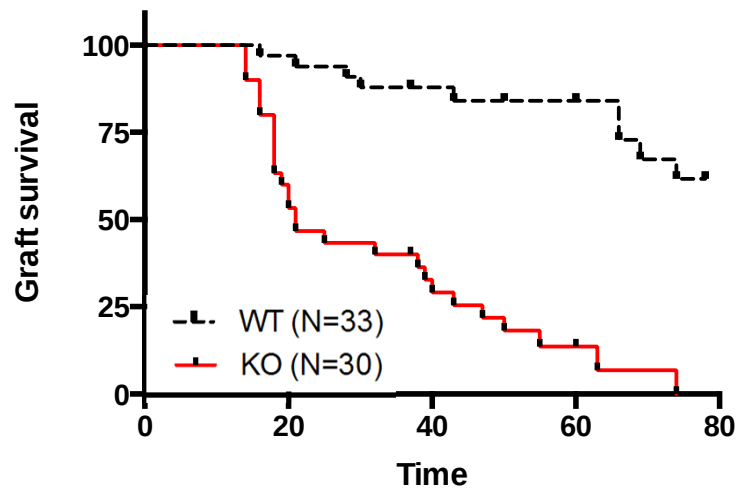
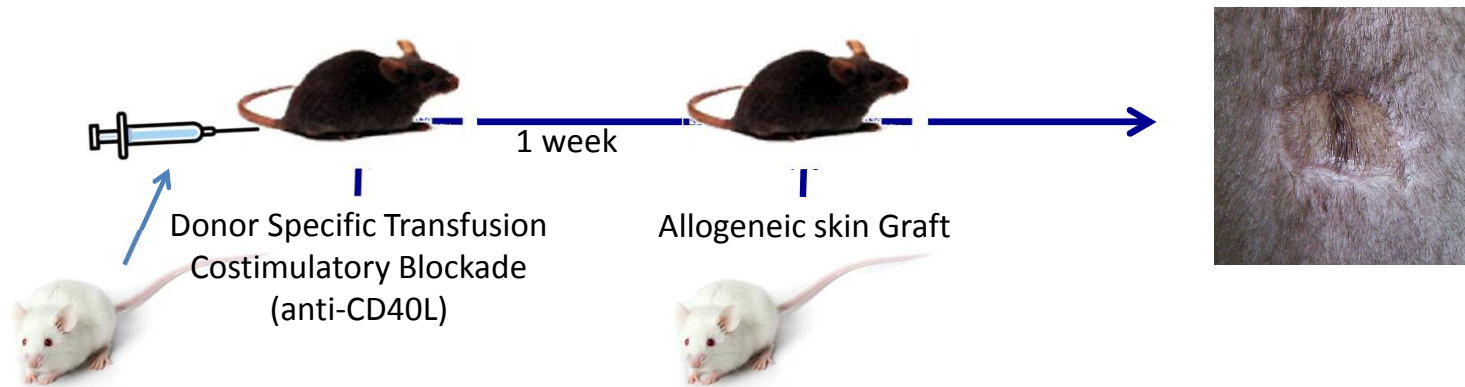


Sle1/Sle3 x **VISTA KO**
- Early incidence lupus (starts 7 weeks)
- Reduced survival (< 20 weeks)



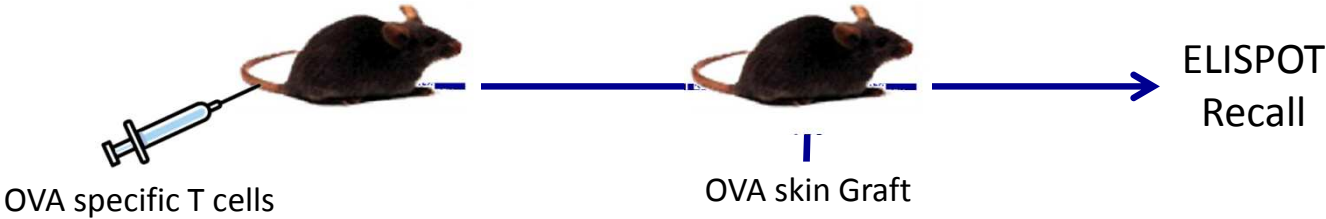
Sabrina Ceeraz Delong

VISTA deficiency prevents allograft tolerance

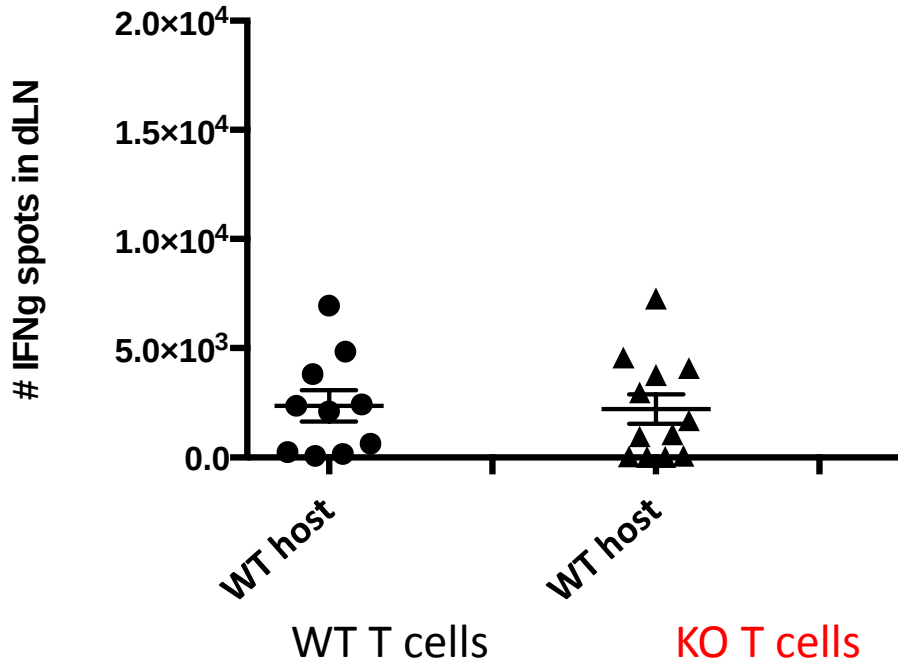


No defect in graft specific T cell deletion and Treg conversion / suppressive function

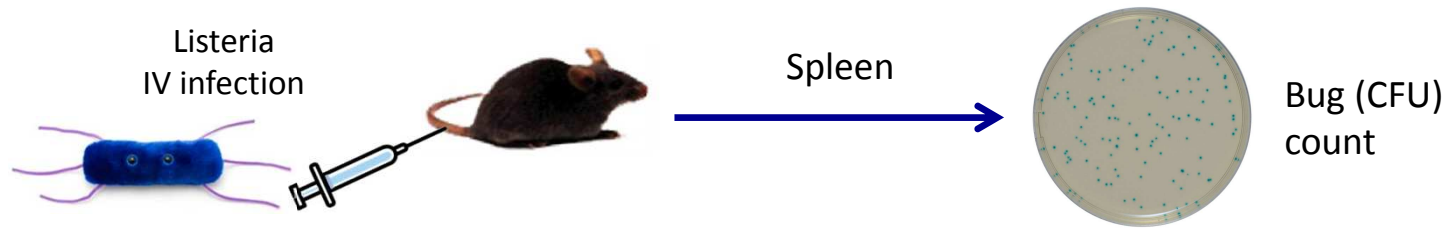
Loss of VISTA from the host is responsible for enhanced graft T cell response



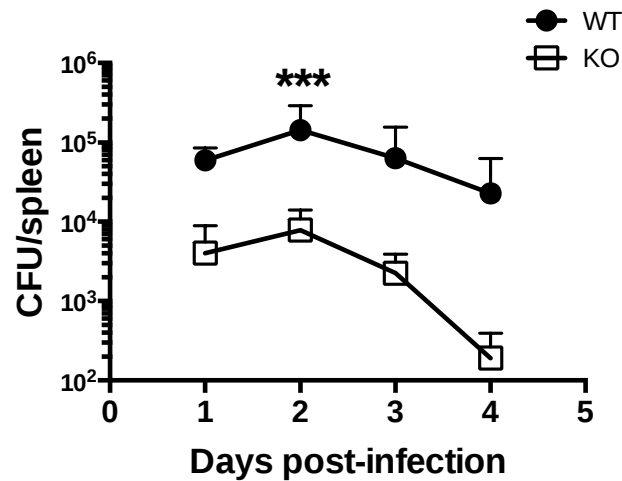
Host T cell	WT host	VISTA KO host
WT T cell		
VISTA KO T cell		



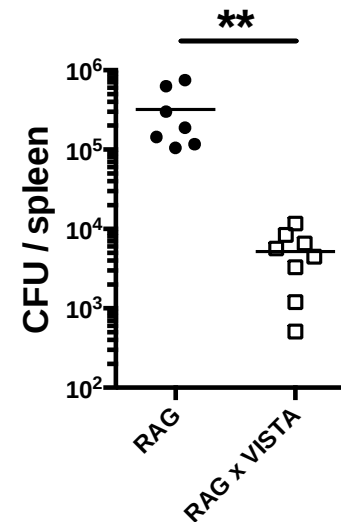
VISTA intrinsically regulates innate immunity



Early infection control
in VISTA KO



Control in T cell deficient
RAG KO x VISTA KO



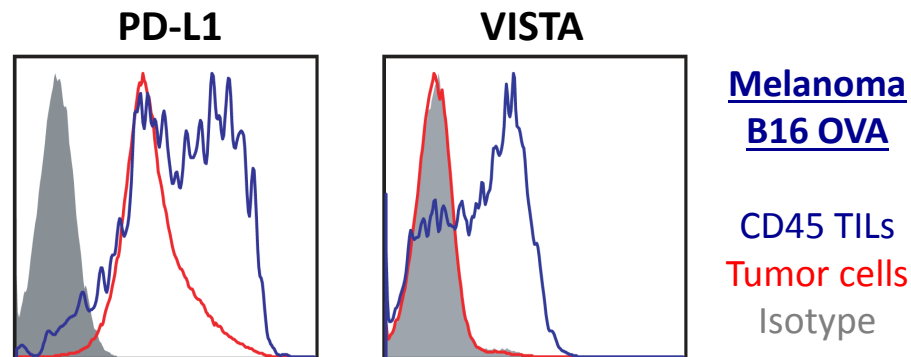
Louise Lines

VISTA negatively regulates T cells and myeloid cells activities

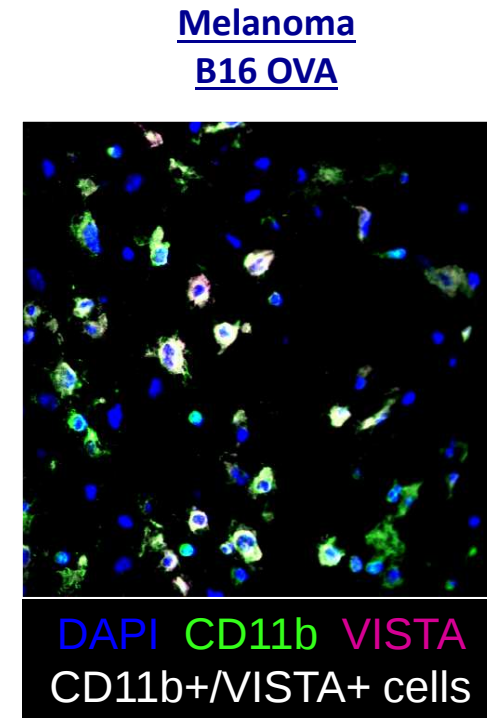
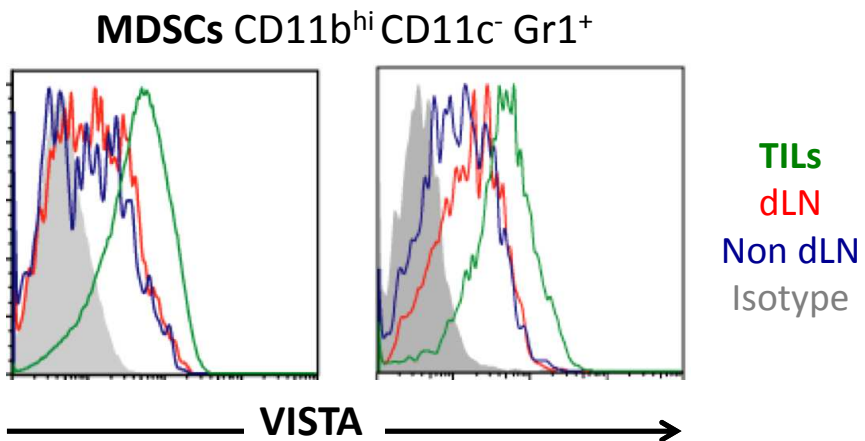
- **Negatively regulates T cell responses**
 - acts as a ligand expressed on APCs (host)
- **Negatively regulates innate immunity**
 - acts as a receptor
- **Prevents autoimmunity in various susceptible models**
- **Is critical for tolerance induction**

VISTA in Cancer

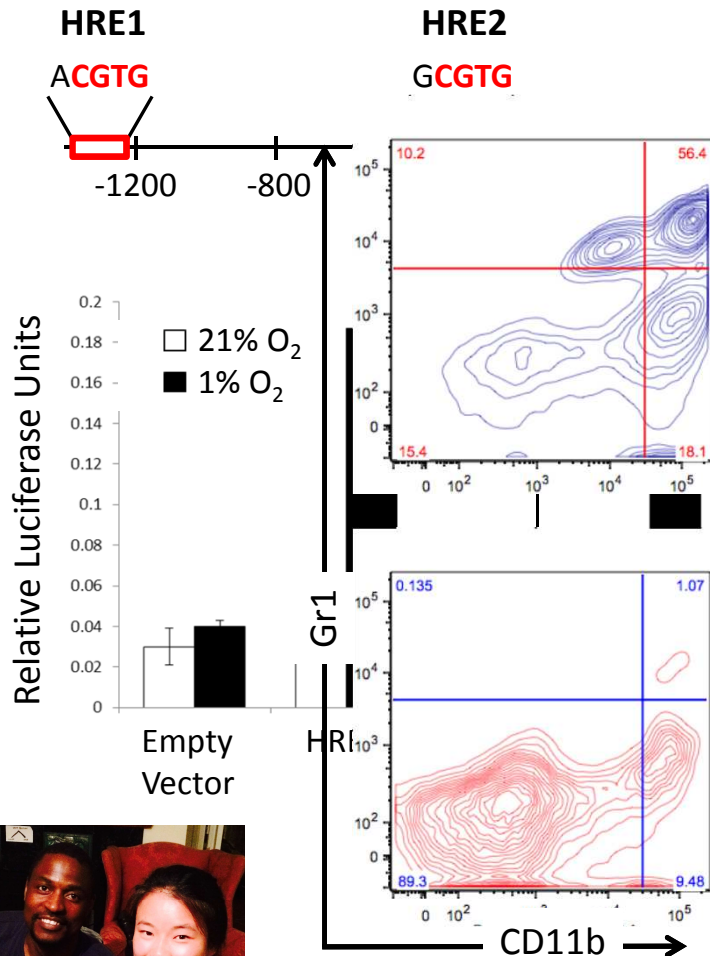
VISTA is highly expressed in tumor infiltrating MDSCs



Bladder carcinoma MB49 Melanoma B16 OVA



Hypoxia upregulates VISTA expression in the TME

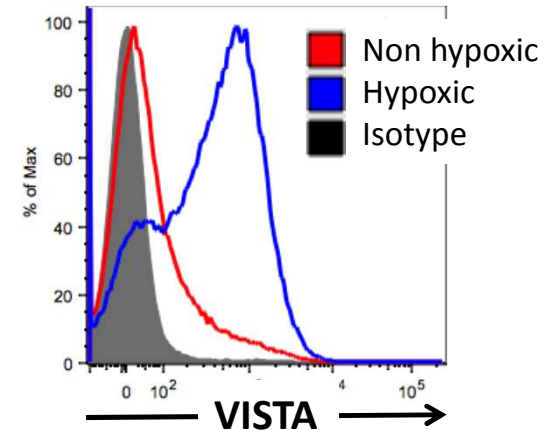
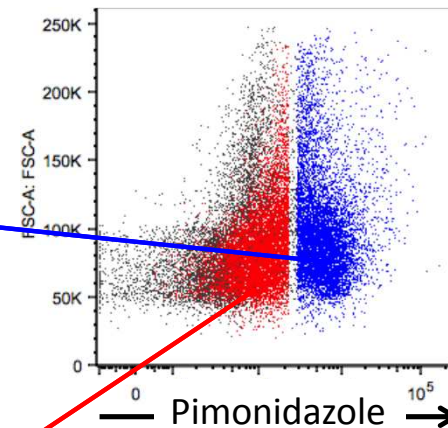


TA

Mut-HRE2

Bladder carcinoma MB49

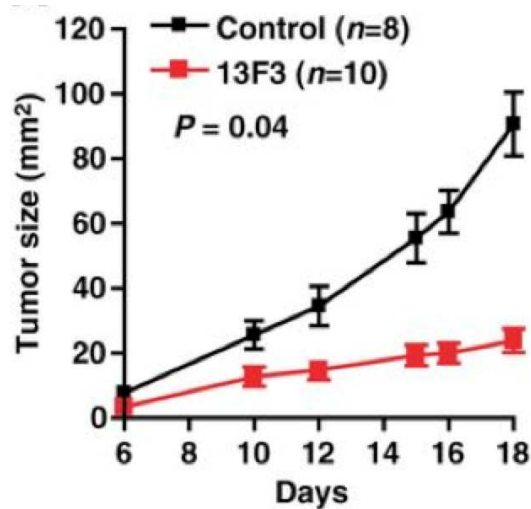
CD45 TILs



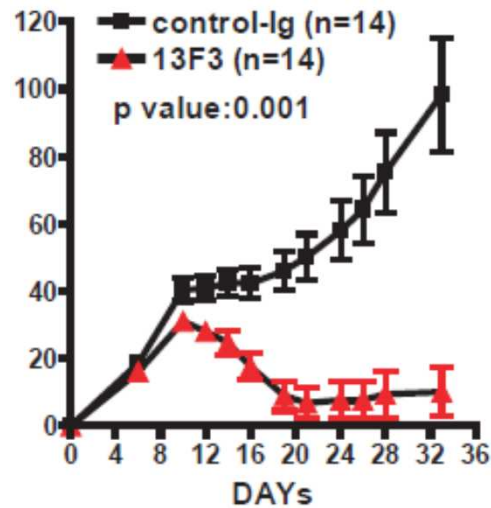
Jie Deng
Rodwell Mabaera

Anti-VISTA monotherapy controls tumor growth in multiple models

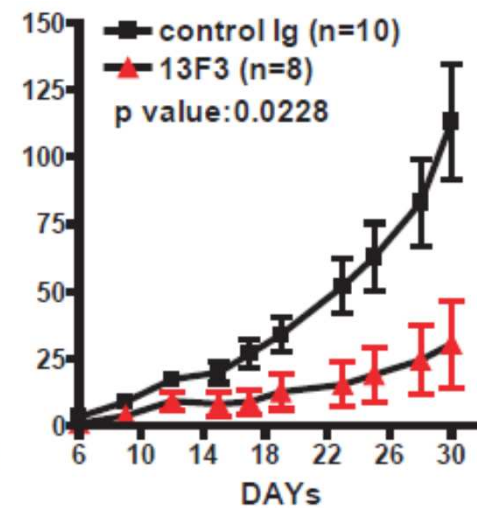
Melanoma
B16-OVA



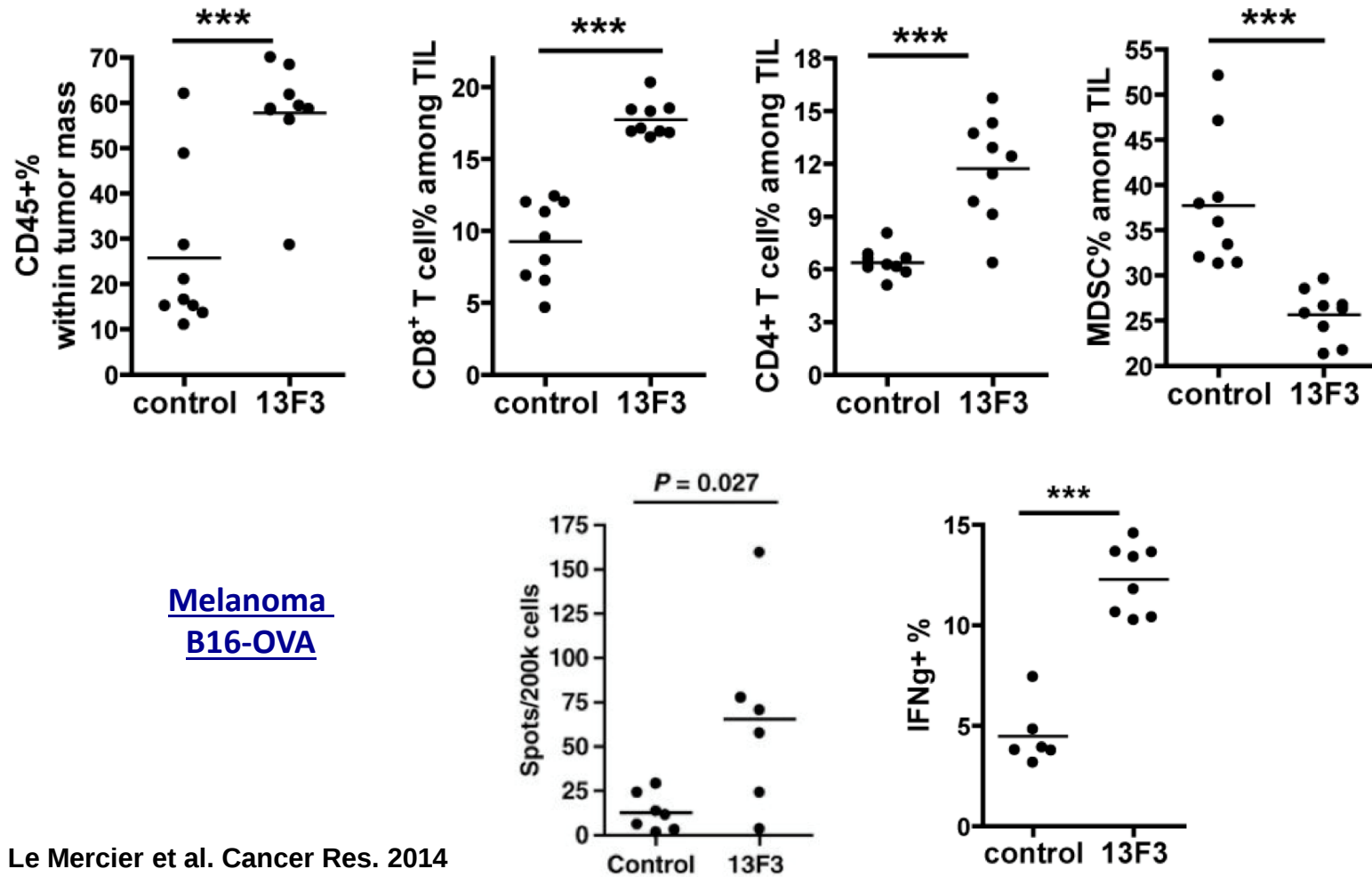
Bladder carcinoma
MB49



Fibrosarcoma
MCA105



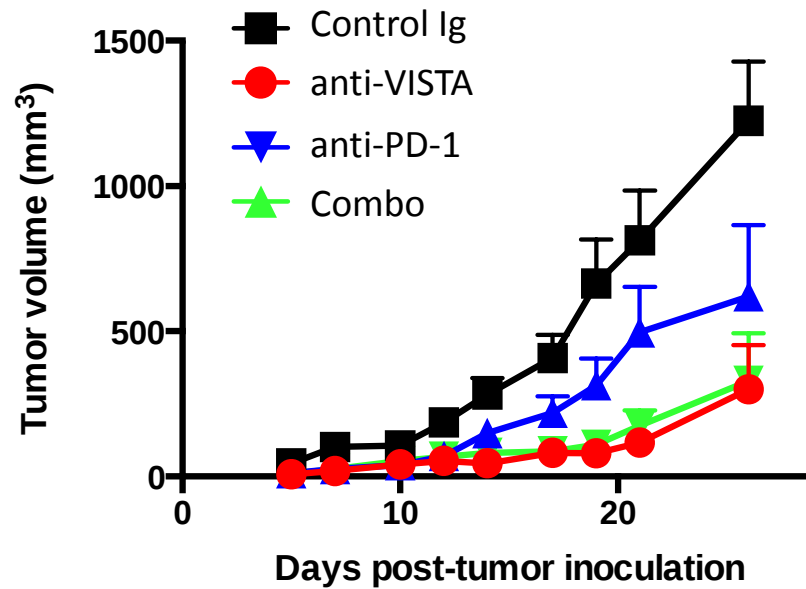
Anti-VISTA mediated changes in TME and antitumor immune responses



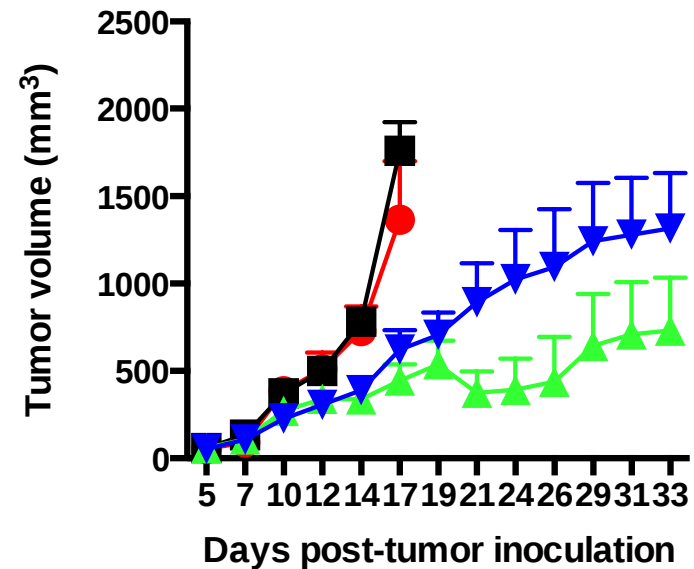
Anti-VISTA synergizes with anti-PD-1 to control tumor growth

CT26
Colon Carcinoma

Early intervention (2-3 mm)



Late intervention (5-6 mm)



Combo : 50% CR

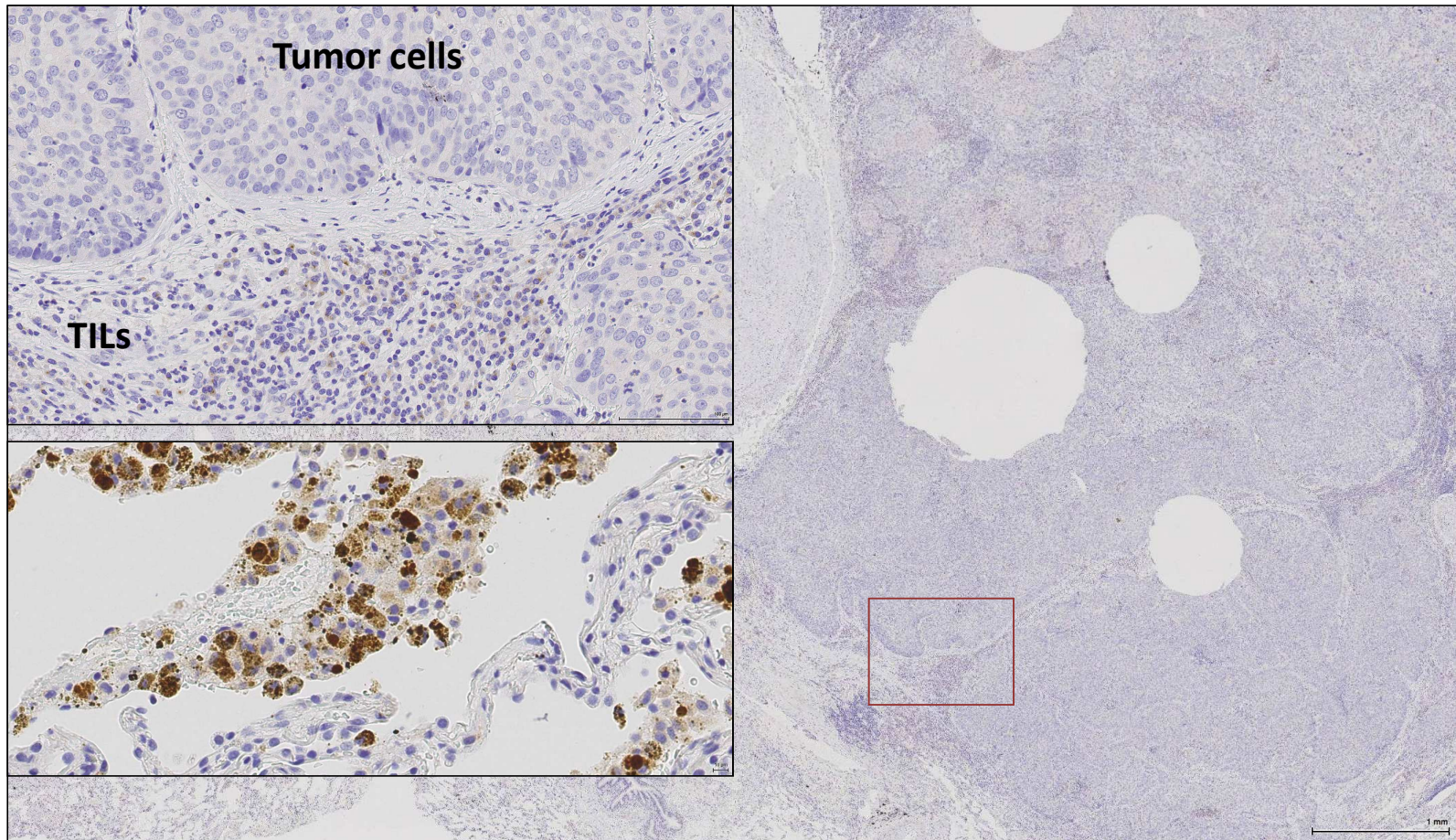
Other groups 0%

Louise Lines

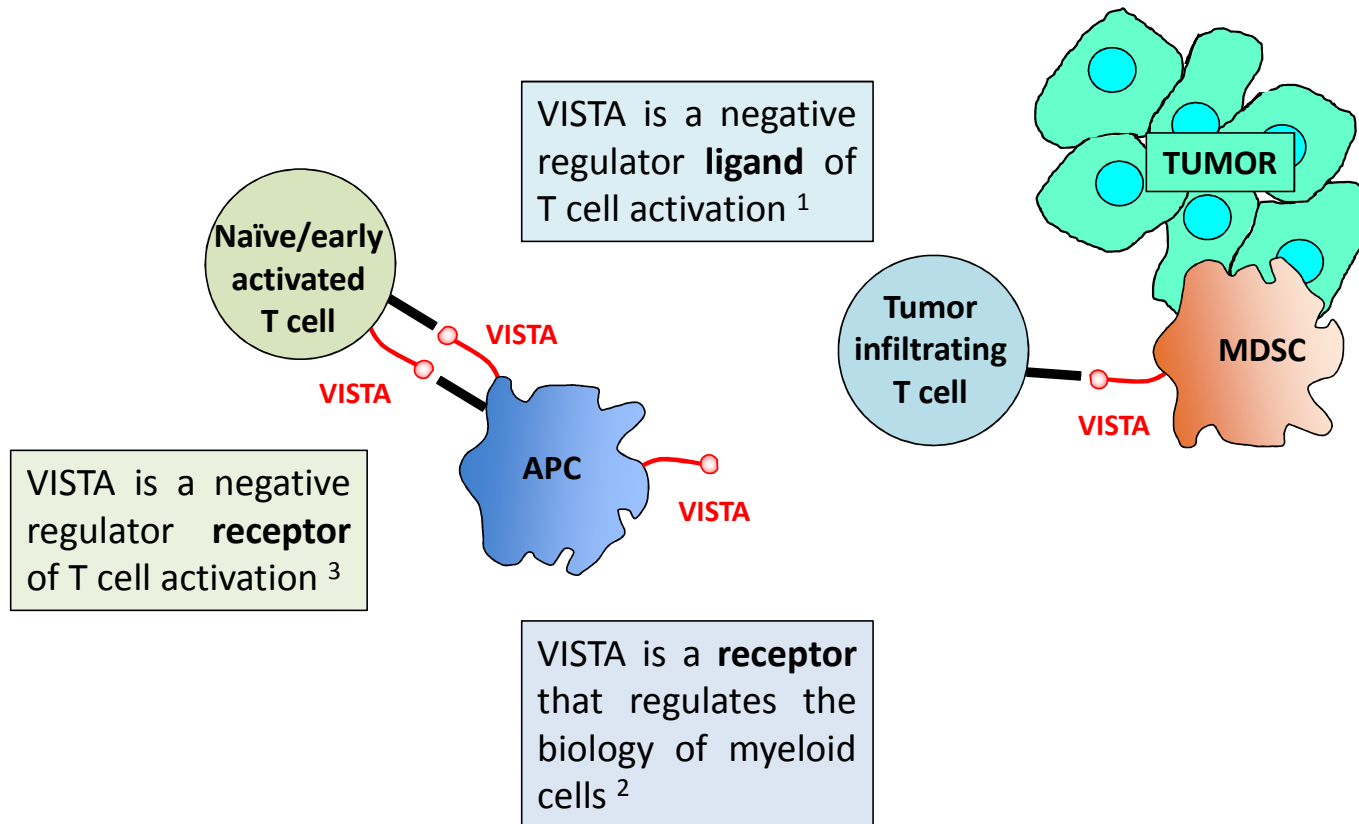
Anti-VISTA mediated changes in cancer immunity

- **VISTA is highly expressed in the TME:**
 - **Expression on MDSCs**
 - **Transcriptionally regulated by hypoxia**
- **Anti-VISTA mediated myeloid changes:**
 - **Decrease in MDSCs**
 - **Increase in macrophages and activated DCs**
- **Anti-VISTA mediated lymphoid changes:**
 - **Increase in T cells infiltration and recall responses**
- **Anti-VISTA synergizes with anti-PD-1 Therapy**

VISTA is a potential target in lung cancer



VISTA regulation of immunity



1. Wang (J Exp Med 2011), Wang (PNAS 2014), Le Mercier (Cancer Res 2014); Lines (Cancer Immunol 2014);
2. Bharaj (PLOS One 2014) and unpublished data
3. Flies (J Clin Invest 2014), Flies (J Immunol 2015), Flies (J Immunol 2011)



Geisel School of Medicine at Dartmouth



Janssen

Pharmaceutical Companies
of Johnson & Johnson



ImmuNext



Randolph Noelle Team

Rodwell Mabaera, M.D. Ph.D.

Louise Lines, Ph.D.

Sabrina Ceeraz Delong, Ph.D

Anna Kuta, Ph.D.

Elizabeth Nowak, Ph.D.

Tommy Broughton

Jie Deng

Yuchi Lee

Jiannan Li

Aurelien Sarde

Petra Sergent

Rheumatology

Christopher Burns , M.D.



Catherine Carriere



Anh Huong

