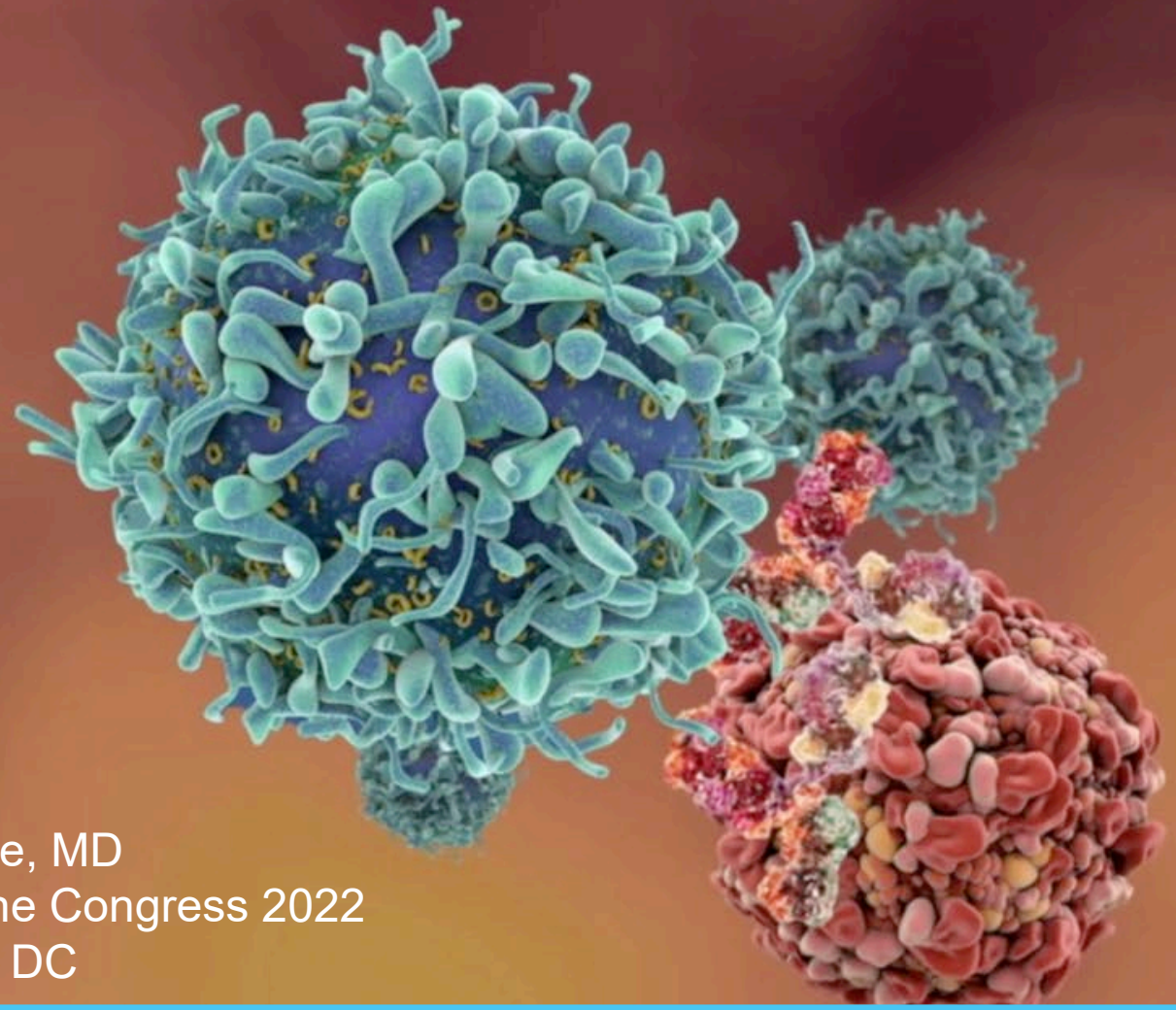

Robert Pierce, MD
World Vaccine Congress 2022
Washington, DC

SNS-101, A Unique Tumor-selective Anti-VISTA Monoclonal Antibody with a Novel Mechanism of Action

SENSEI BIOTHERAPEUTICS

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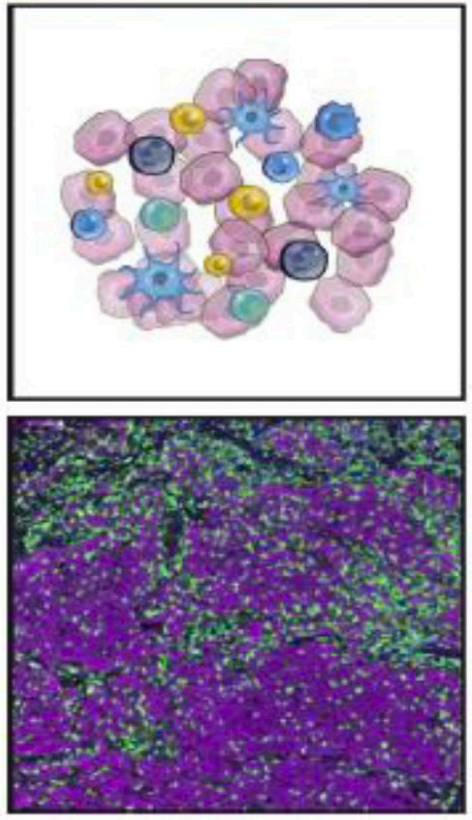
The Therapeutic Problem: PD-1/PD-L1 Non-Response

Anti-PD-1 or PD-L1 Treatment →

More Likely to Respond

T-cells Inside Tumor

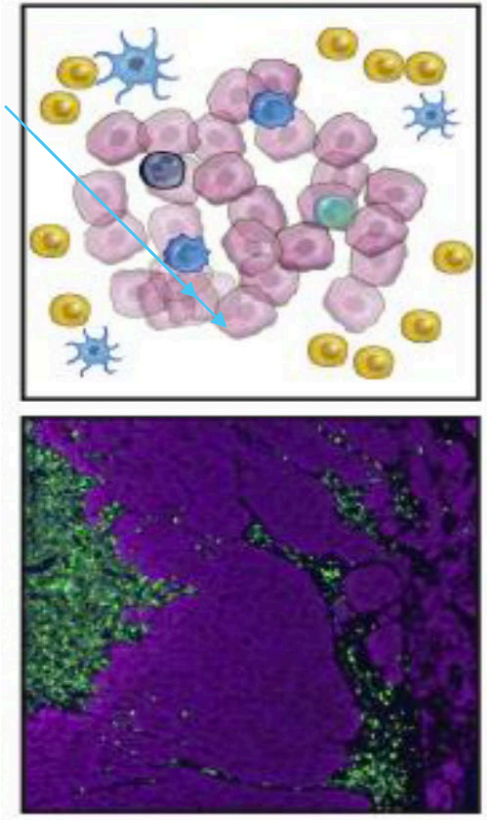
Hot (inflamed) tumor



Less Likely to Respond

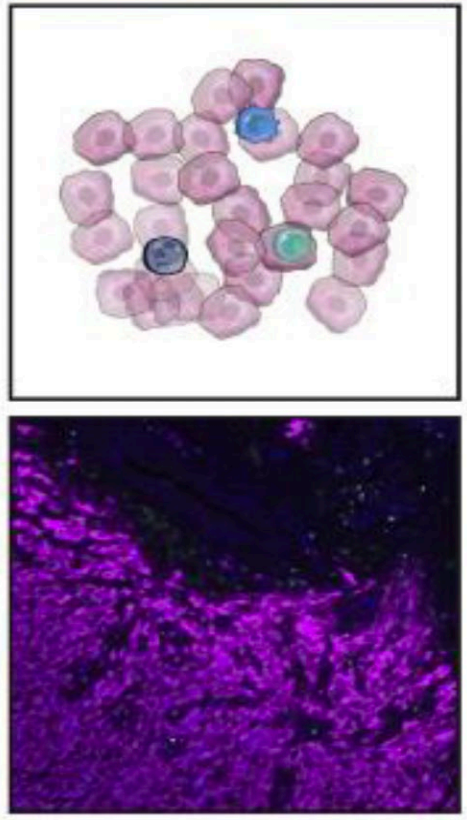
T-cells Outside Tumor

Cold (excluded) tumor



T-cells Absent

Cold (ignored) tumor



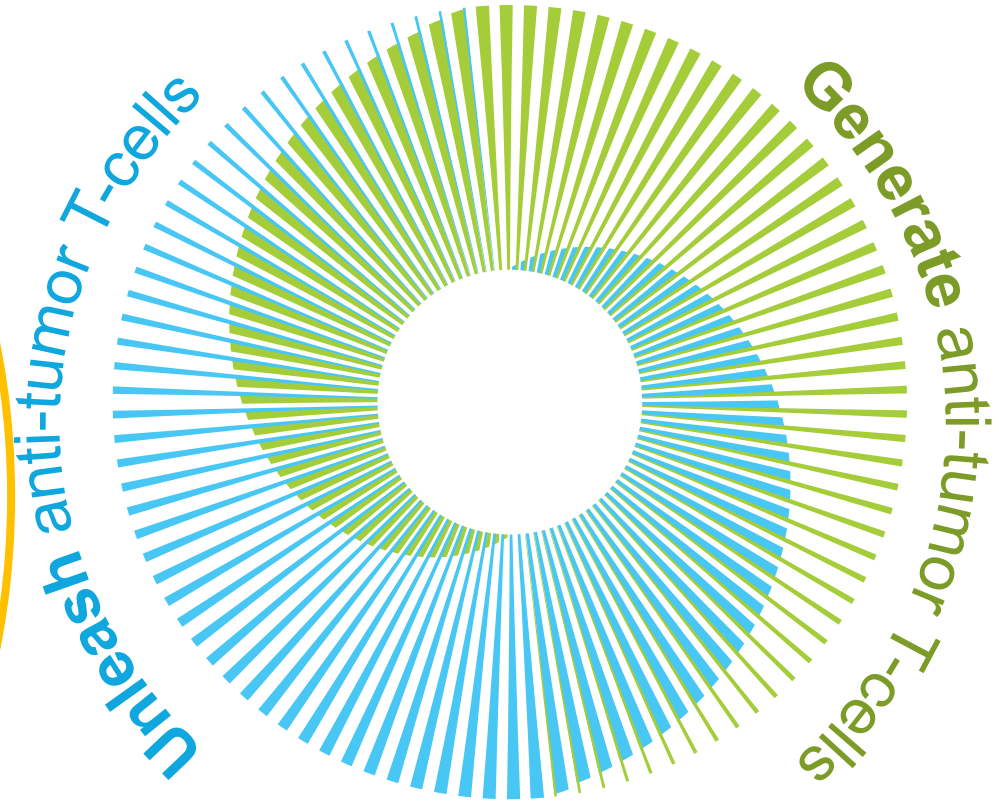
Green = T-cells
Purple = tumor

Adapted from Van der Woulde-LL, et al, Trends in Cancer, 2017

Two Platforms to Unleash Anti-Cancer T-cell Activity

TMAb™ (Tumor Microenvironment Activated Biologics) Platform

- Next-generation tumor activated mAbs
- Binding only in the low-pH tumor microenvironment
- Target checkpoints and/or other immune pathways
- Enable improved PK/PD and toxicity profiles



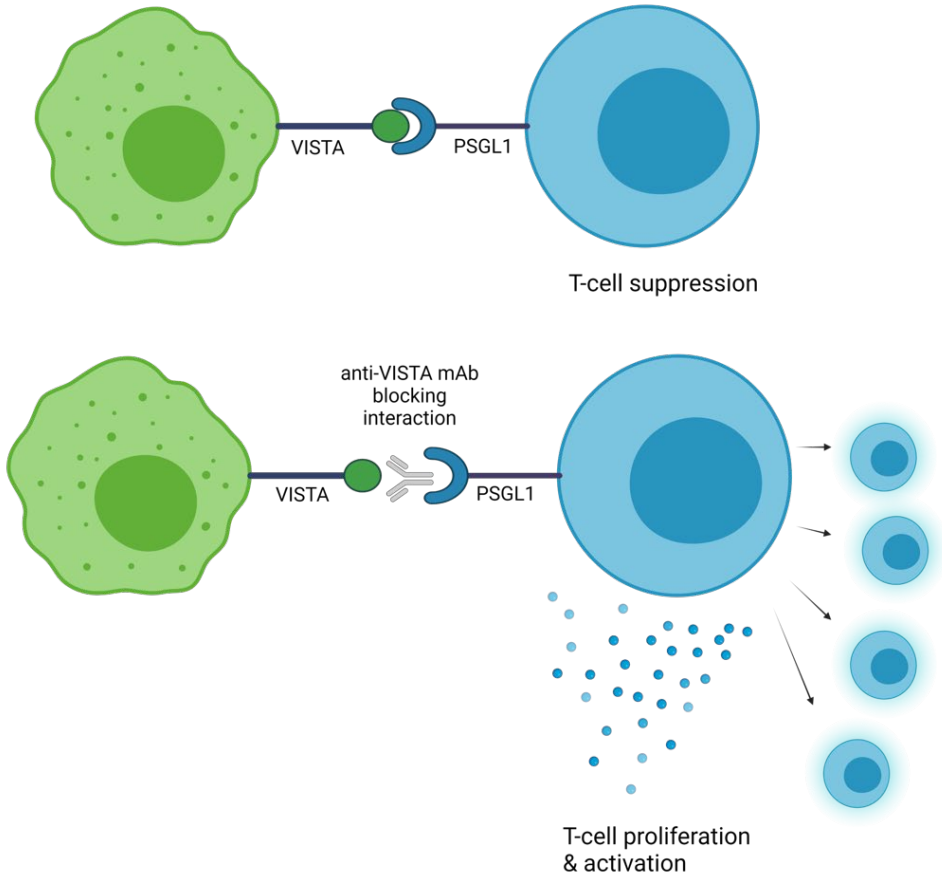
ImmunoPhage™ Platform

- Powerfully self-adjuvanted nanoparticle vaccine can drive B cell and T cell responses
- Multi-antigen vaccine enables personalized approach from “off-the-shelf” components
- Targets APCs
- Enhanced through addition of immunostimulatory nanobodies & cytokines

VISTA: A Promising but Difficult Target on Myeloid Cells

- VISTA (aka B7-H5; PD-1H) is B7 family ligand with homology to PD-L1
- VISTA suppresses T cell activation[1]
- Expressed on myeloid cells including macrophages and neutrophils; NK cells and T-regs[2]
- Inhibition of VISTA may “convert” myeloid cells to a proinflammatory/immune activating state
- Excellent therapeutic combinability with CTLA-4 or PD-1/PD-L1 ICIs, especially in cold tumors[3]
- Identity of critical VISTA binding partner/receptor remains subject of debate.

VISTA is a Negative Regulator of T cell Function

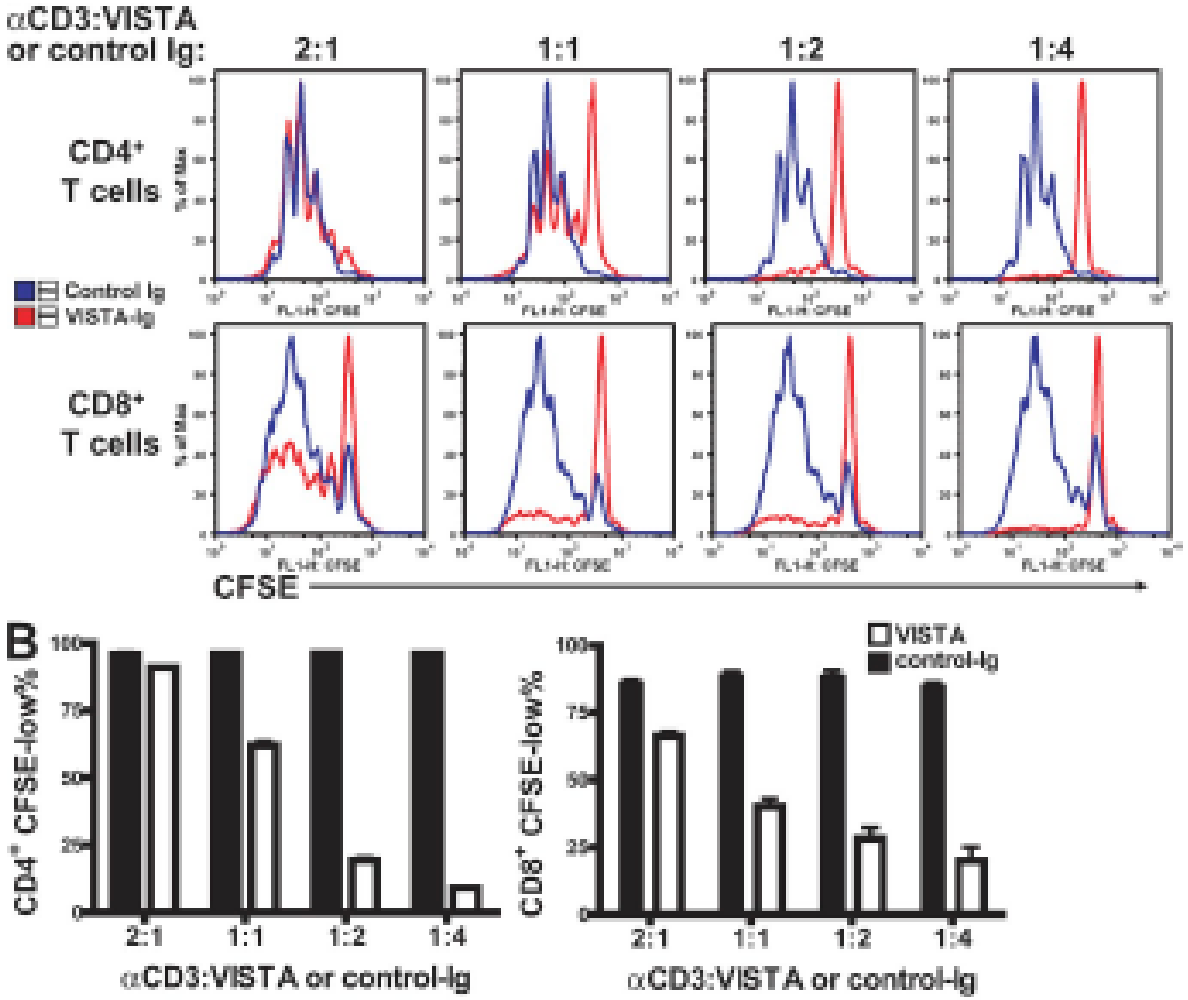


1 Wang et al, *JEM*, 2011
2 Lines et al. *Cancer research* vol. 74,7 (2014)
3 Gao et al. *Nature medicine* vol. 23,5 (2017)

VISTA Negatively Regulates CD4 and CD8 T Cell Responses

VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses

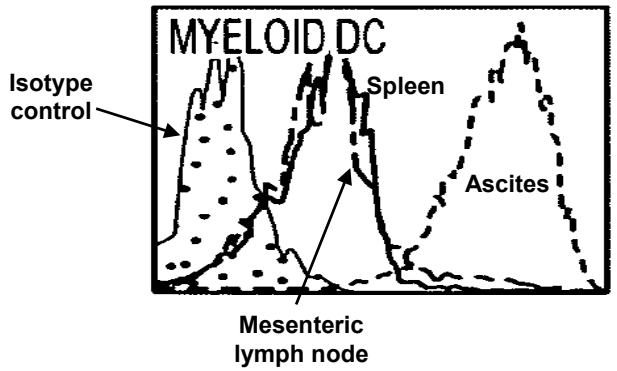
Li Wang,[1] Rotem Rubinstein,[4,5] Janet L. Lines,[1] Anna Wasiuk,[1] Cory Ahonen,[1] Yanxia Guo,[1] Li-Fan Lu,[1] David Gondek,[1] Yan Wang,[1] Roy A. Fava,[3] Andras Fiser,[4,5] Steve Almo,[5] and Randolph J. Noelle[1,2]



Wang_L, et al, *JEM,* 2011

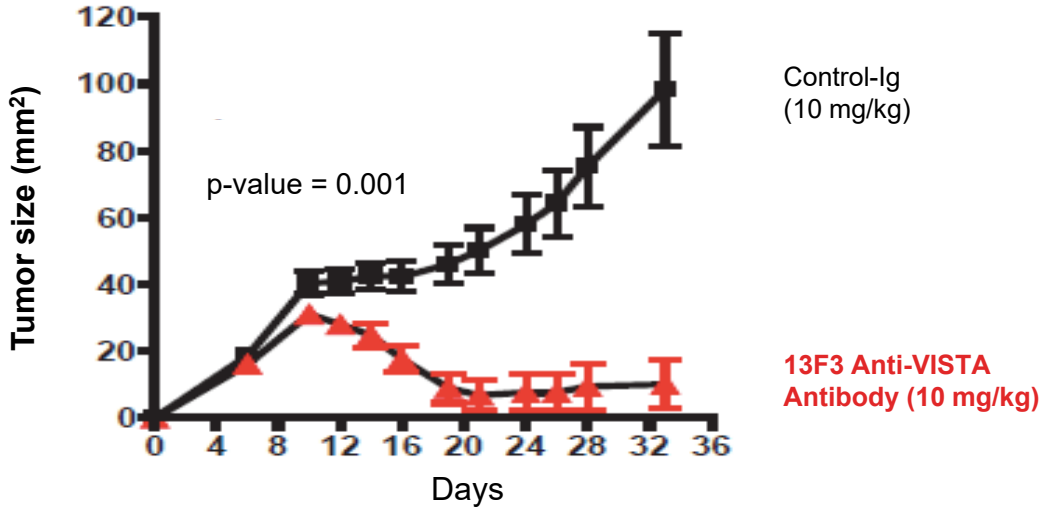
Anti-VISTA mAb Treatment Leads to Tumor Growth Inhibition in Multiple Syngeneic Mouse Tumor Models

VISTA Expression on Myeloid Cells in Tumor-Bearing Mice

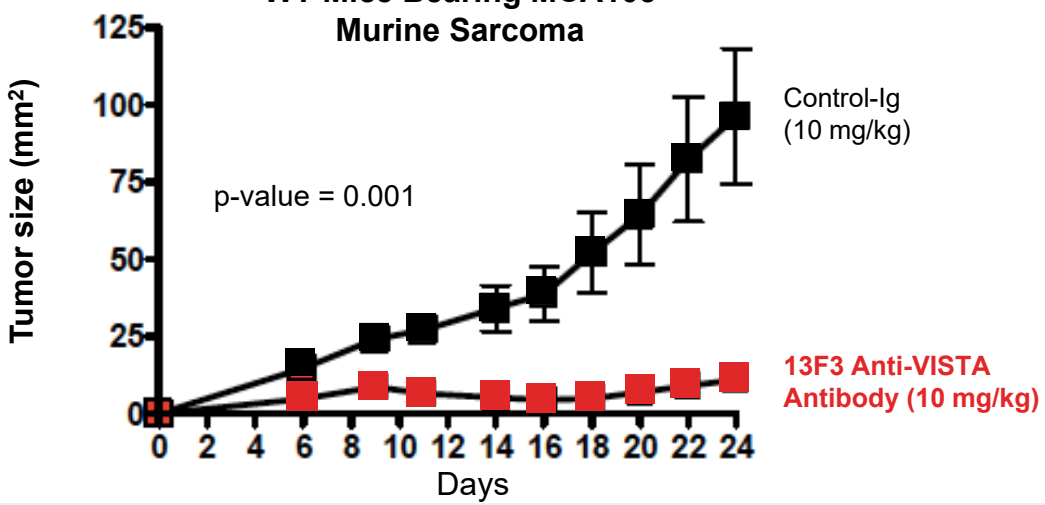


- An anti-murine VISTA antibody (13F3) was administered to WT mice bearing tumors
- Myeloid cells from these mice were assessed and found to have high levels of VISTA expression

WT Mice Bearing MB49 Murine Bladder Carcinoma



WT Mice Bearing MCA105 Murine Sarcoma

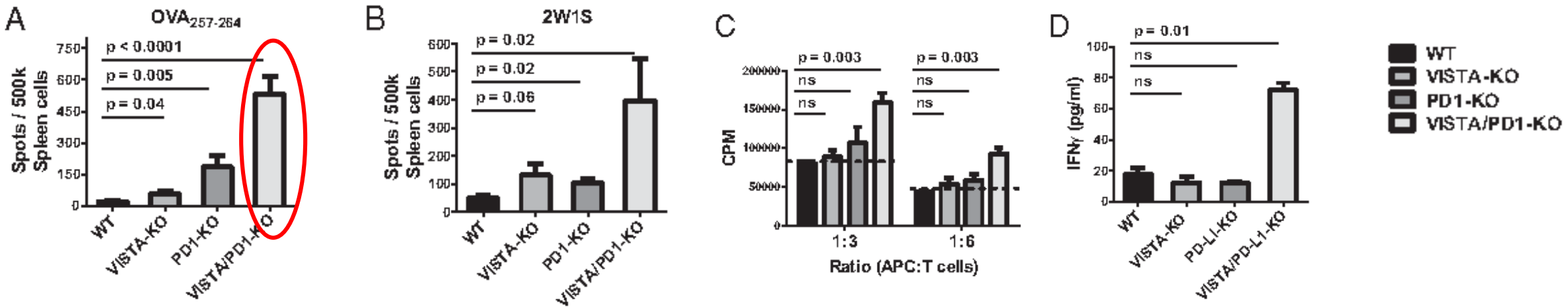


Noelle et. al., US 2013/0177557

PD-1/VISTA Double Knock-out Mice Have Increased Antigen-specific T cell Responses

Immune-checkpoint proteins VISTA and PD-1 nonredundantly regulate murine T-cell responses

Jun Liu[a,b], Ying Yuan[a,1], Wenna Chen[a], Juan Putra[c], Arief A. Suriawinata[c], Austin D. Schenk[d], Halli E. Miller[a], Indira Guleria[e], Richard J. Barth[d], Yina H. Huang[c], and Li Wang[a,2]



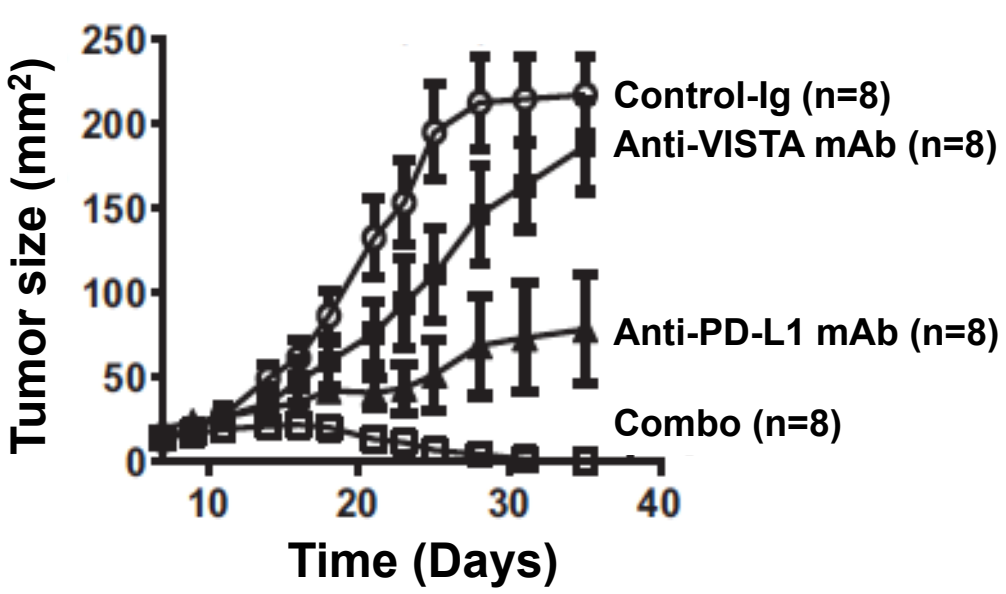
Liu J. et al. PNAS 2015

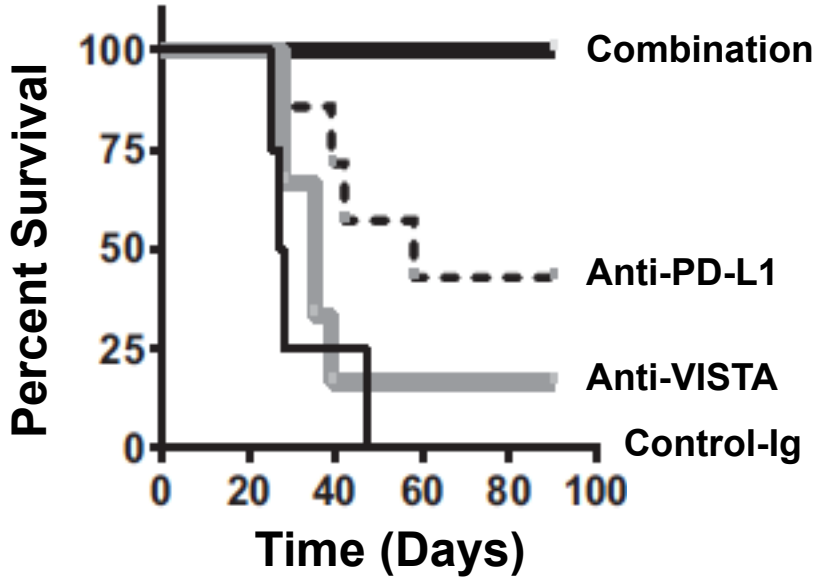
Combination of VISTA Inhibition and PD-1 Blockade Yields Synergistic Anti-tumor Responses

Immune-checkpoint proteins VISTA and PD-1 nonredundantly regulate murine T-cell responses

Jun Liu[a,b], Ying Yuan[a,1], Wenna Chen[a], Juan Putra[c], Arief A. Suriawinata[c], Austin D. Schenk[d], Halli E. Miller[a], Indira Guleria[e], Richard J. Barth[d], Yina H. Huang[c], and Li Wang[a,2]

Mice Bearing CT26 Tumors

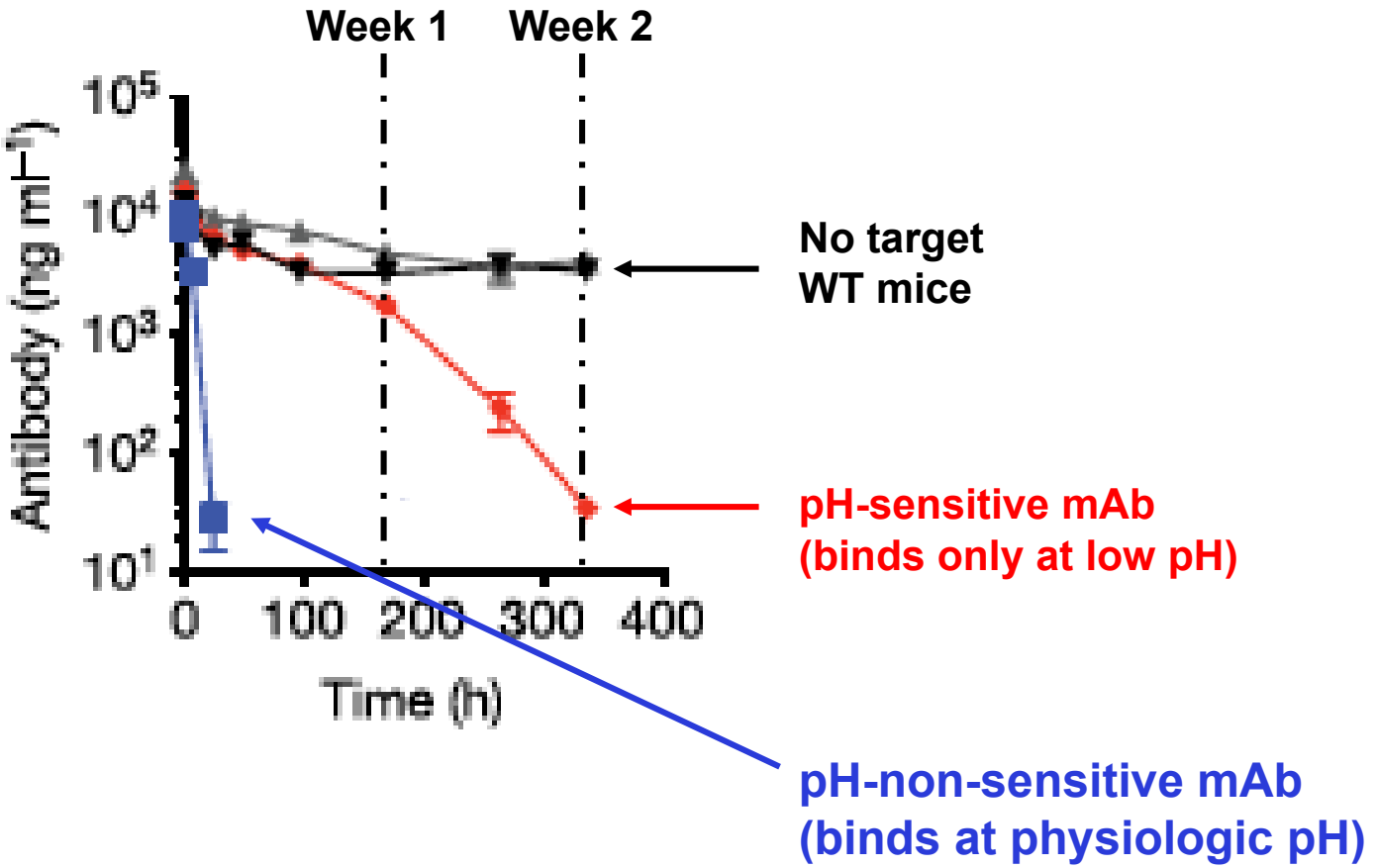




Liu J. et al. PNAS 2015

Anti-VISTA mAb Binding on Myeloid Cells in Blood Results in Significant Target-mediated Drug Disposition (TMDD)

Mouse Pharmacokinetics of Anti-VISTA Antibodies (BMS) at 5 mg/kg

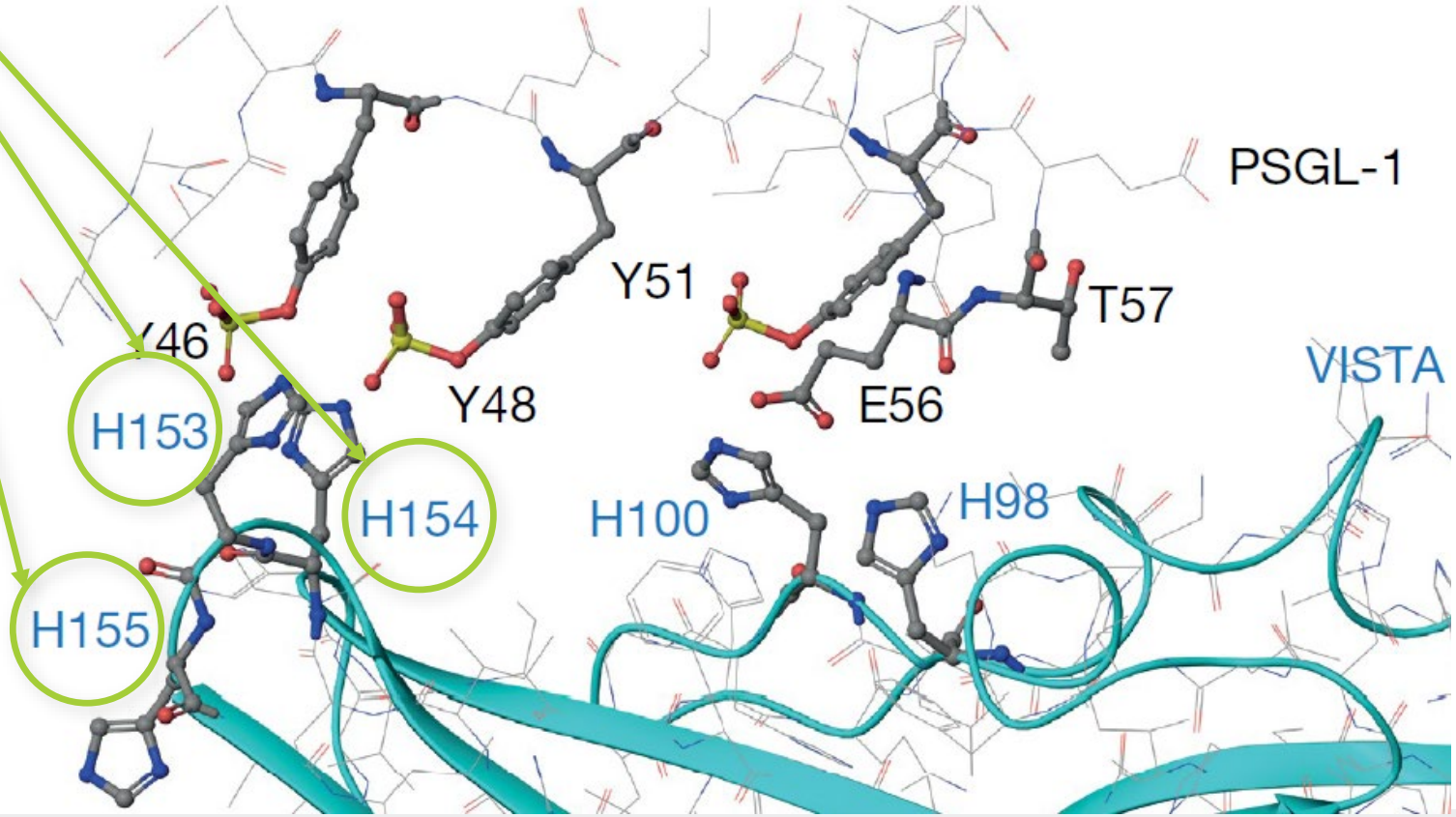


- Antibodies binding VISTA^{+} cells (e.g. monocytes) at physiological pH are eliminated from circulation through targeted-mediated drug disposition (TMDD)
- An antibody binding at pH 6 will accumulate in the TME resulting in an improved PK and safety profile

Johnston et al, Nature, 2019

VISTA Binding to PSGL-1 is pH-dependent Due to a Unique Histidine-rich Extracellular Binding Domain

Antibodies that block protonated VISTA histidines interrupt PSGL-1 binding[1]

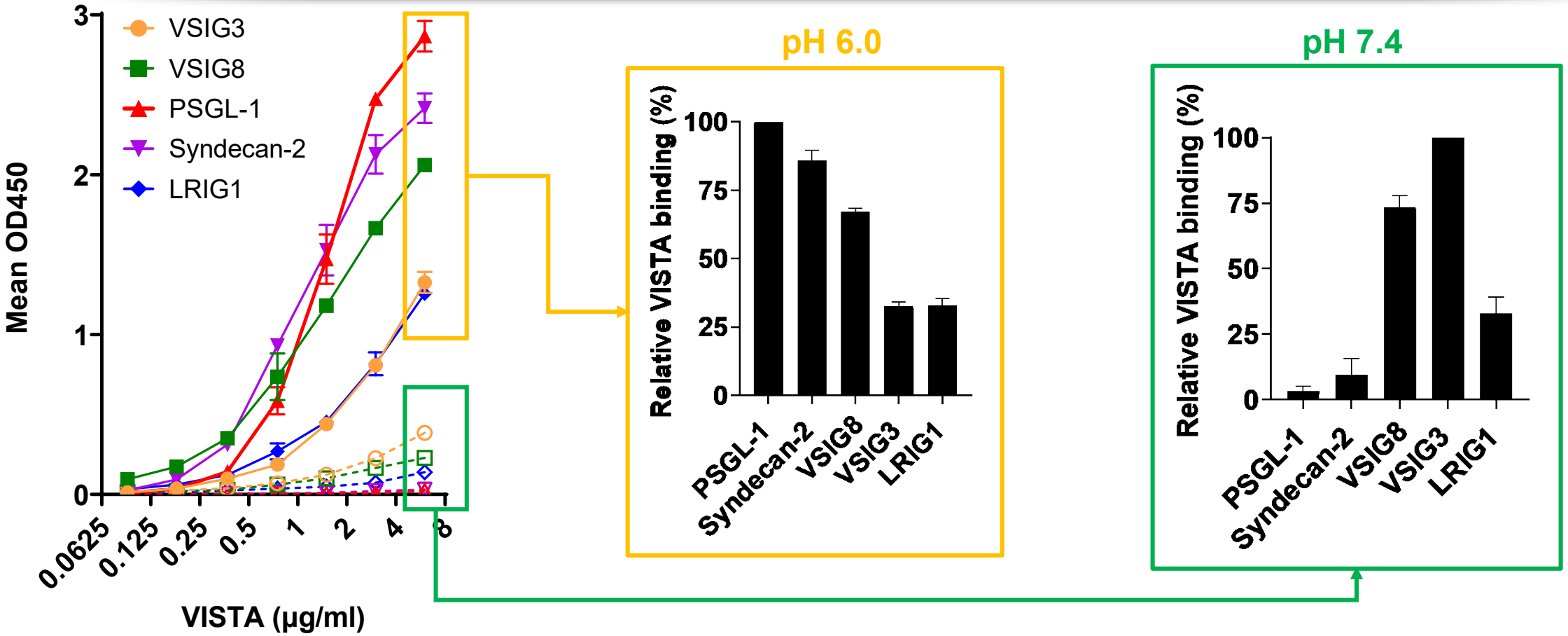


VISTA's extracellular domain is uniquely rich in histidines[1]

Histidines are protonated at low pH enabling VISTA to distinguish the active (acidic pH) and inactive (neutral pH) PSGL-1 binding interface

1. Johnston et al., Nature 2019

Strongest Interaction between Candidate VISTA Binding Partners is VISTA/PSGL-1 at Low pH

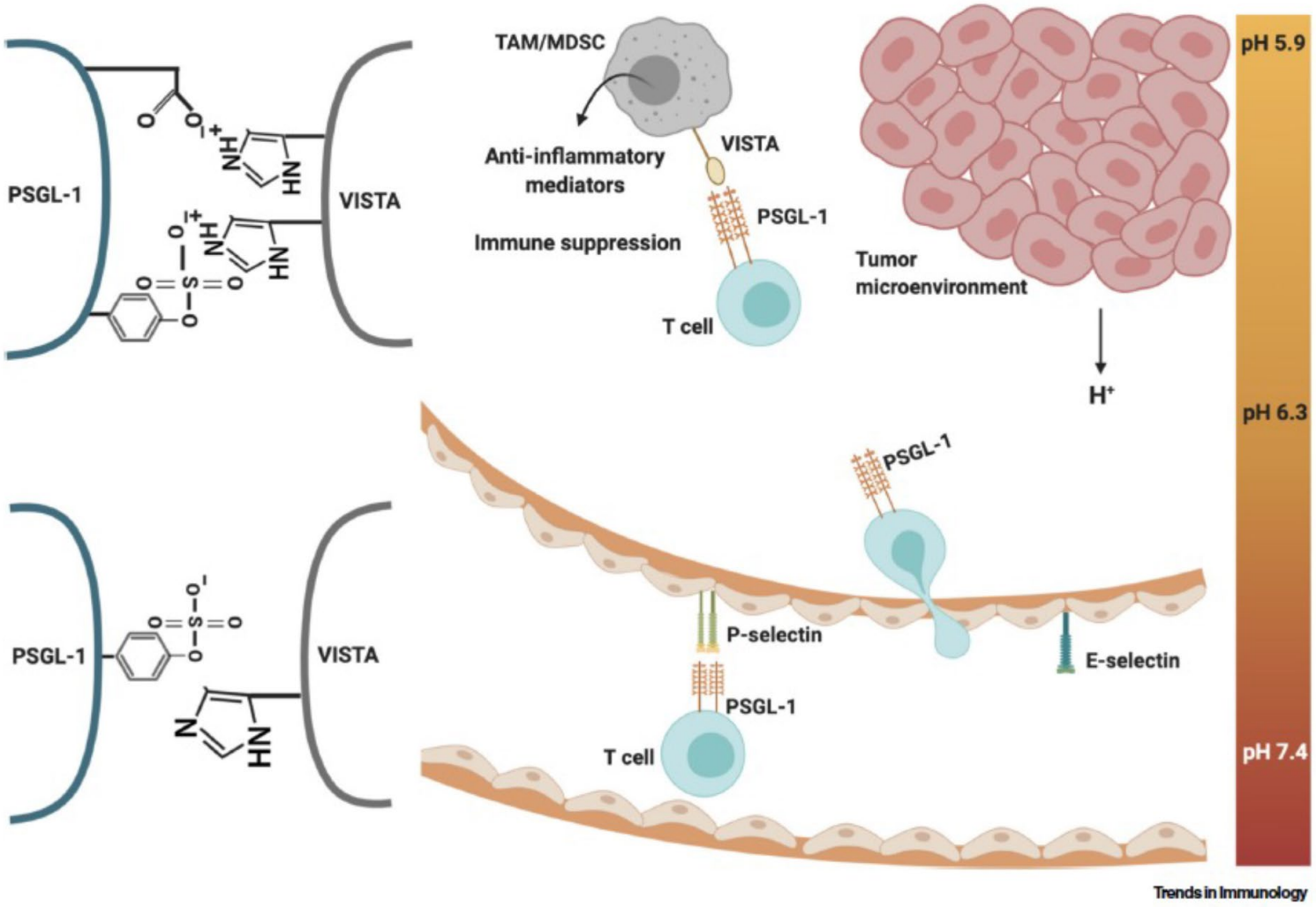


- **VISTA binds specifically to PSGL-1 and Syndecan-2 in a pH-dependent manner**
- VSIG-3, VSIG-8 and LRIG-1 interactions are very weak (pH 7.4)
  - The VSIG-3 interaction (pH 7.4) is 1/7 the affinity of PSGL-1 (pH 6.0)

Active “Protonated” VISTA Binds the T cell Checkpoint PSGL-1 in the Tumor Microenvironment

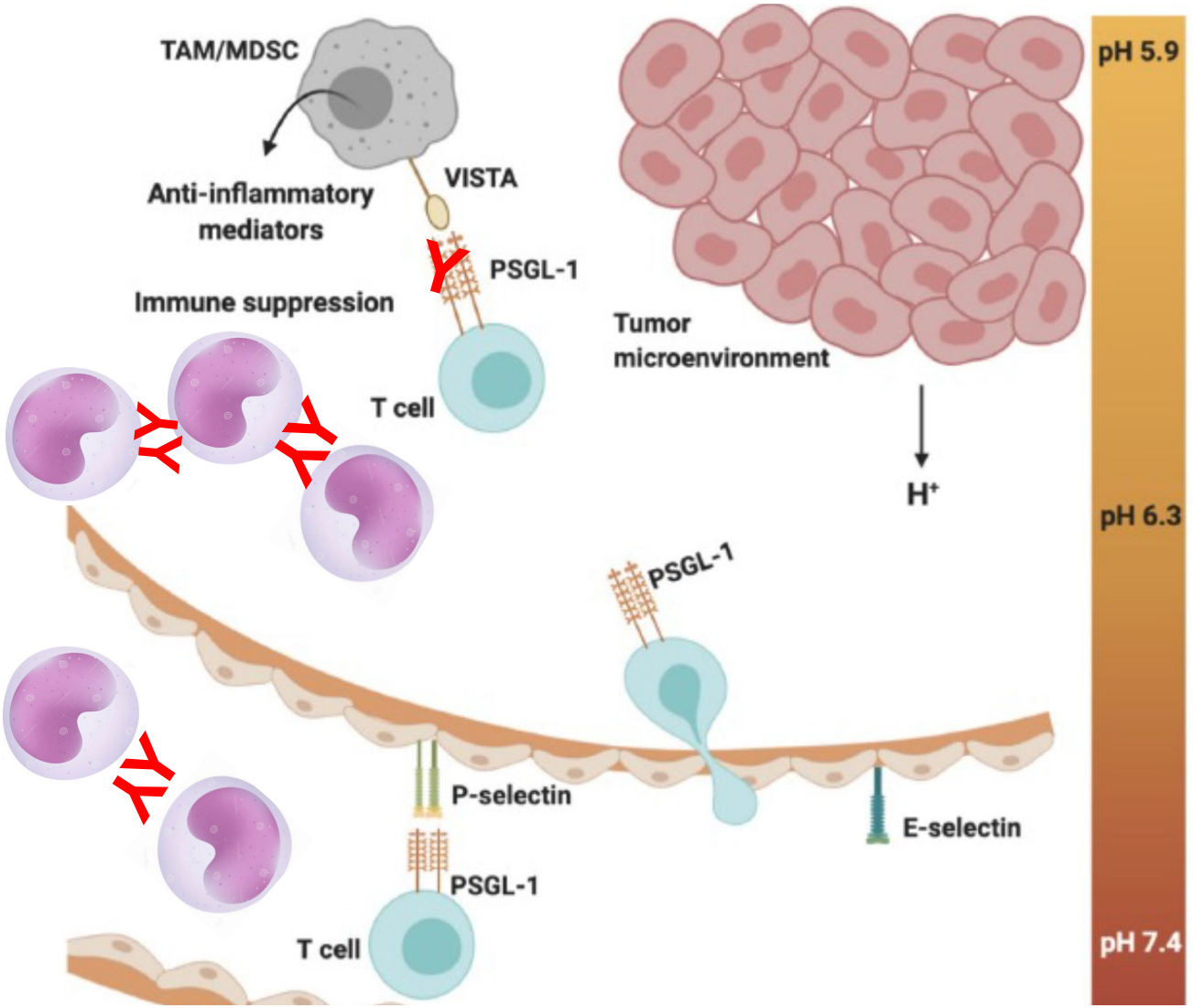
“Active”
VISTA Protonated

“Inactive”
VISTA
Unprotonated



Adapted from Yuan-L, Trends Immunol, 2021 Mar;42(3):209-227

pH-dependent mAb Binding to VISTA May Mitigate On-Target/Off-tumor Reactivity



	Low pH-selective Binder	pH Non-selective Binder
Tumor	• Blocks VISTA/PSGL-1 checkpoint • IgG1 Fc ➔ myeloid activation	• Blocks VISTA/PSGL-1 checkpoint • Active Fc ➔ myeloid activation • TMDD ➔ low tumor drug exposure
Blood	• No significant VISTA binding • No significant TMDD • No significant myeloid activation • Decreased risk of CRS	• Binds VISTA on myeloid cells in blood ➔ TMDD • Potential for myeloid activation AND CRS

Adapted from Yuan-L, Trends Immunol, 2021 Mar;42(3):209-227

Critical Design Features for SNS-101

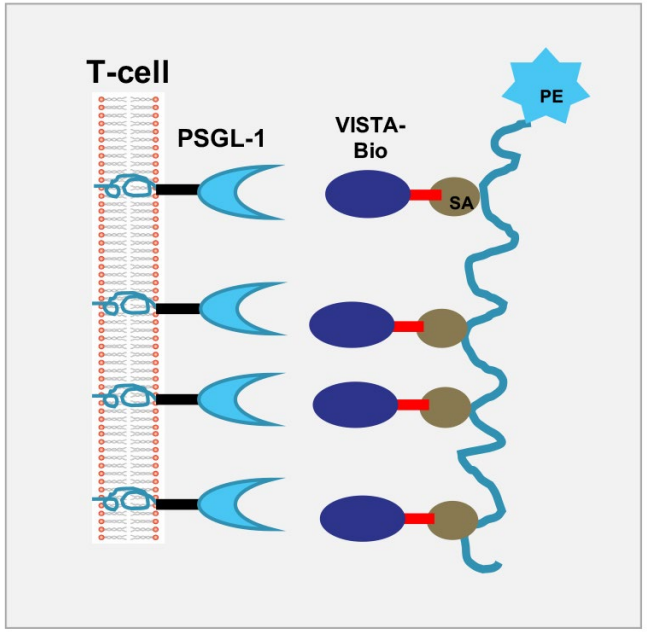
1. Block the critical checkpoint (pH-dependent binding of VISTA to PSGL-1 on T cells)

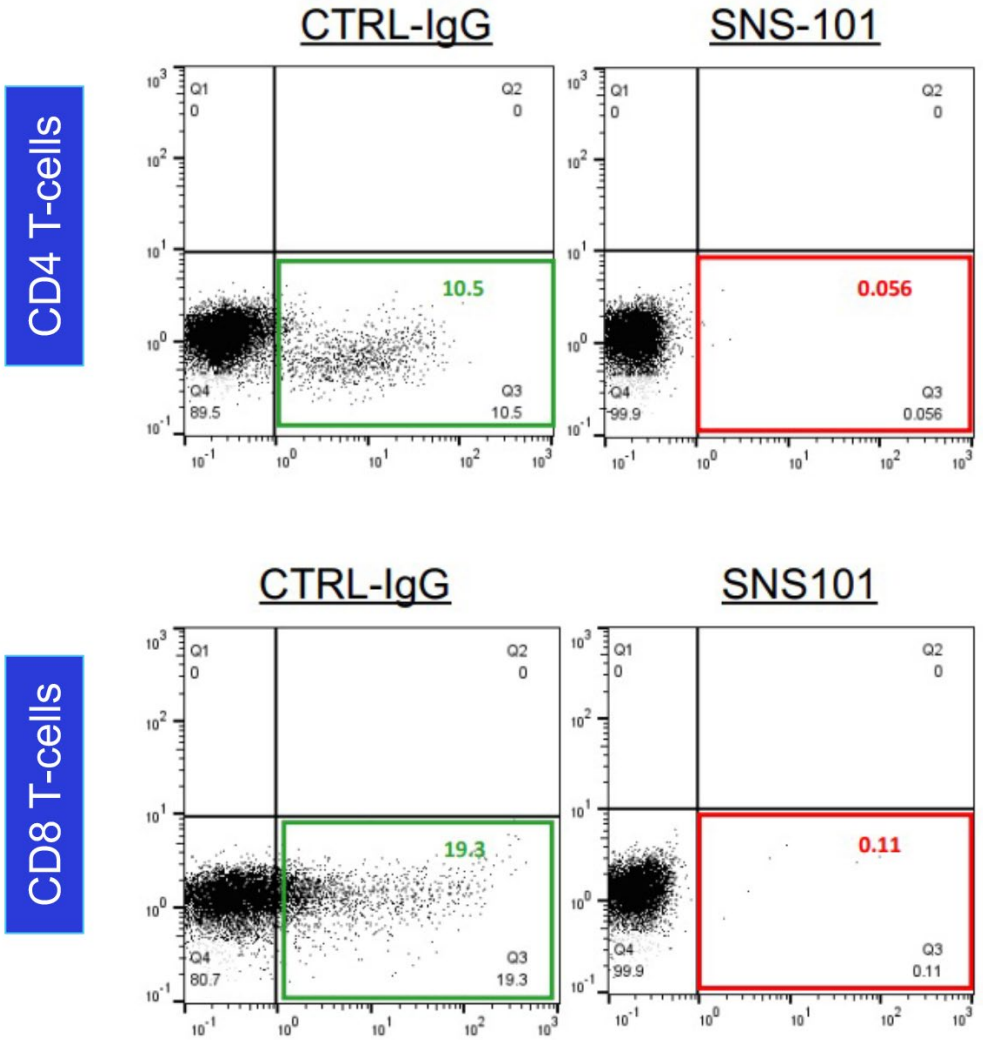
2. Selectively bind “active”/protonated VISTA at low pH to avoid:
   - target mediated drug disposition (TMDD)
   - on-target/off-tumor side effects

3. Utilize an Fc-competent IgG (e.g. IgG1) backbone to engage and activate FcɣR on tumor-infiltrating myeloid cells

SNS-101 Inhibits VISTA/PSGL-1 Interaction

PSGL-1: VISTA Interaction on Primary T-cells at pH 6.0

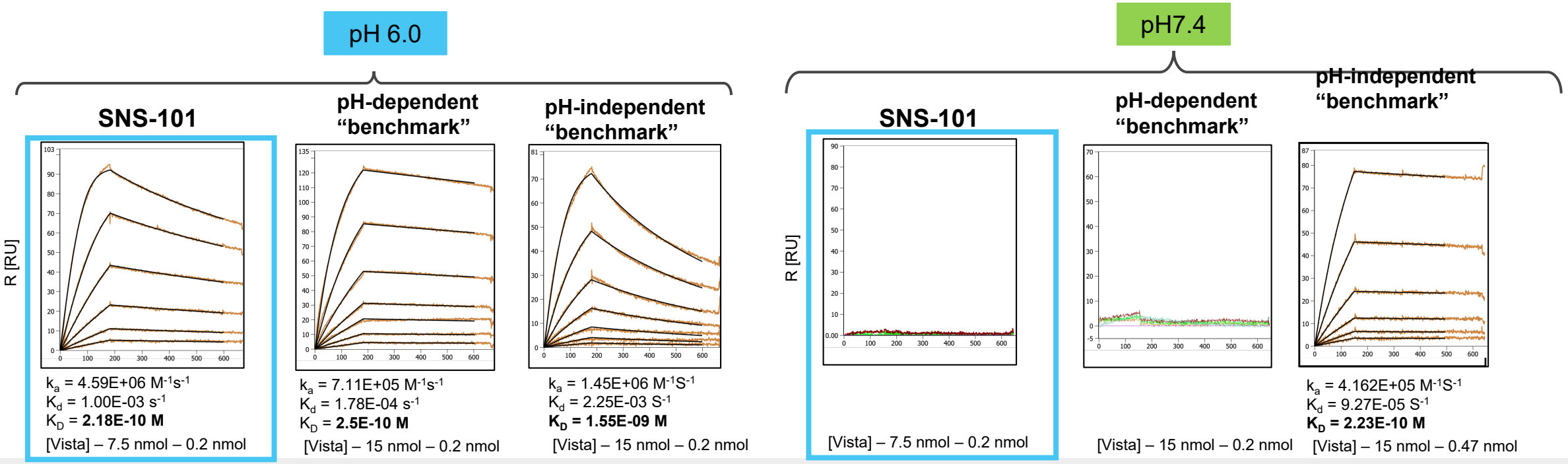




SNS-101 Has >600-Fold Selectivity for VISTA^{pH6}

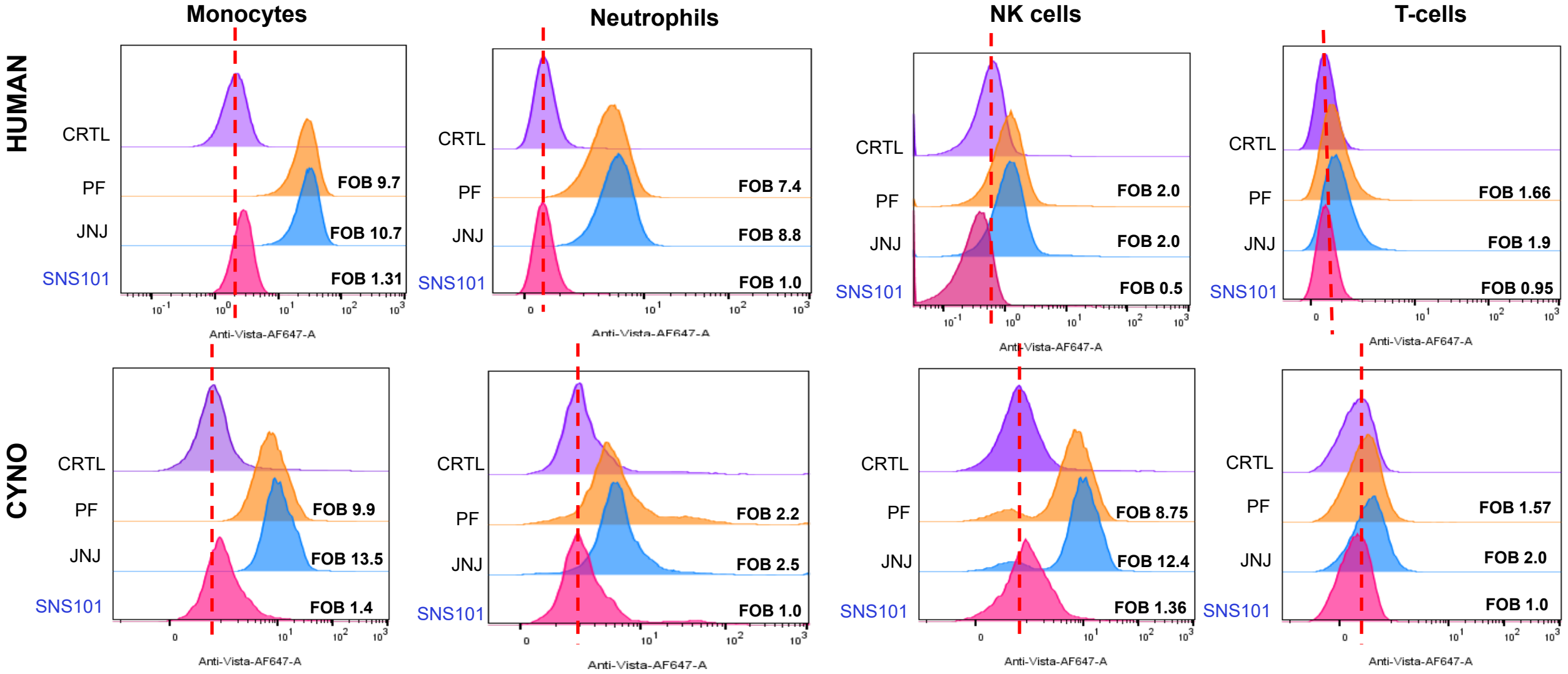
- **>600-fold selectivity for VISTA at pH 6.0**
- **Subnanomolar binding at low pH**
- **No significant binding observed at physiological pH (7.4)**

	pH 6.0	pH 7.4
Monovalent Affinity (K_D) [nmol]	0.218	132 (~No binding)



SITC 2021: Poster titled: Antagonistic pH-selective VISTA antibody SNS-101 potentiates anti-PD-1/PD-L1-induced anti-tumor immunity

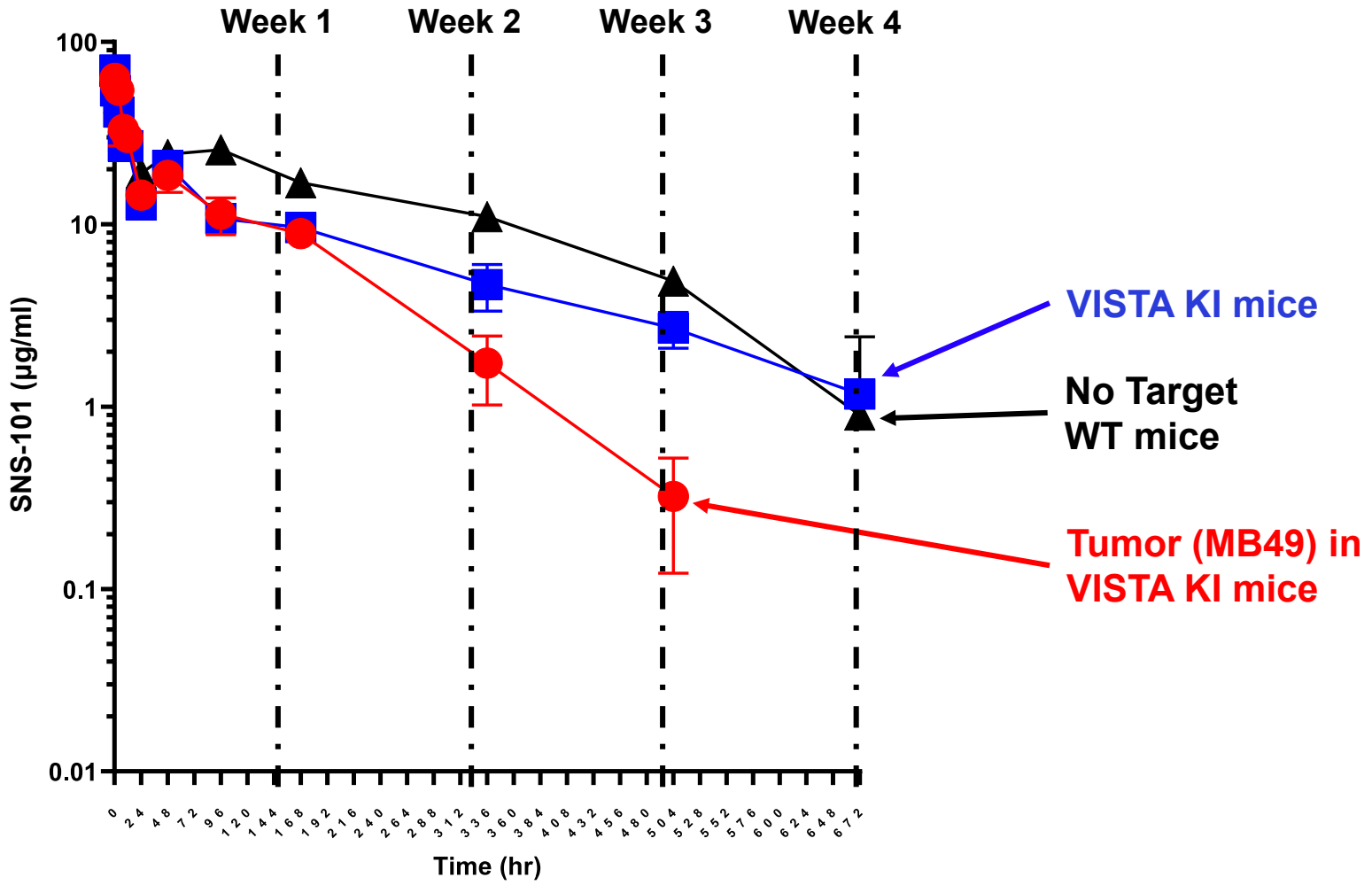
No Significant Binding of SNS-101 to Monocytes, Neutrophils, NK Cells and T-cells in Whole blood at Physiological pH



SNS-101 Displays Favorable PK Profile

No significant TMDD in human VISTA KI mice

Pharmacokinetics of Single Dose 5 mg/kg SNS-101 in VISTA Knock-in Mice

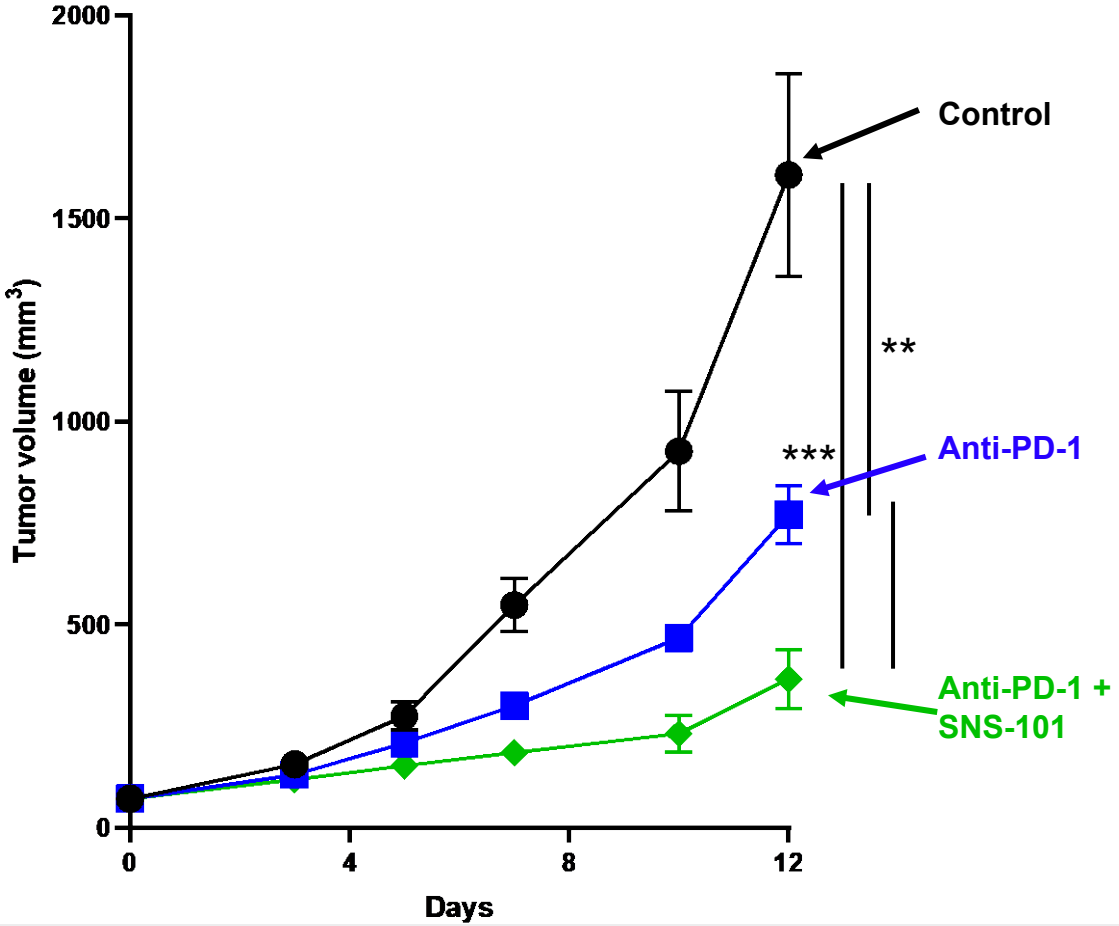


- Tumor bearing mice have a favorable PK profile
- Non-tumor bearing mice demonstrate no TMDD

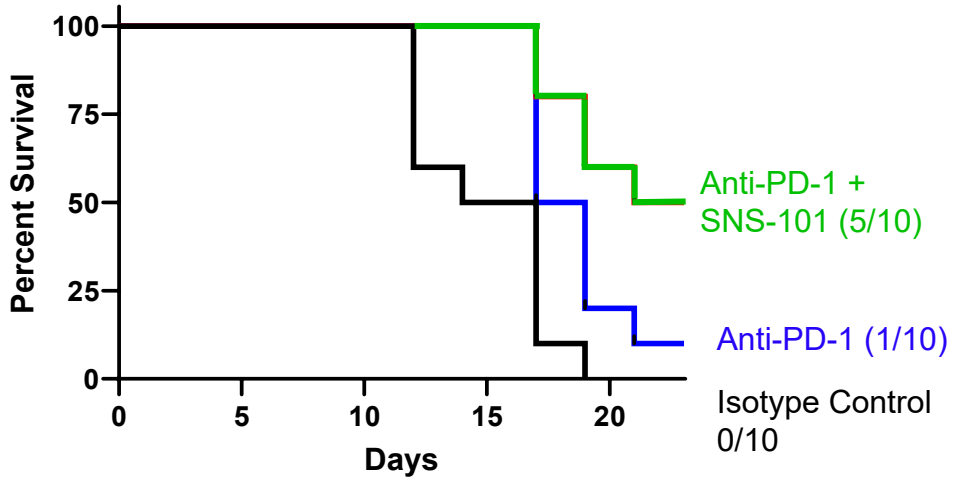
MC38 Syngeneic Tumor Model in huVISTA Knock-in Mice Confirms Combinatorial Activity of SNS-101

SNS-101* in Combination with Anti-mouse PD-1

Tumor Growth Inhibition



Survival



**SNS-101 was grafted on to a mouse IgG2a framework to decrease anti-drug antibody production*

Preclinical Development Summary

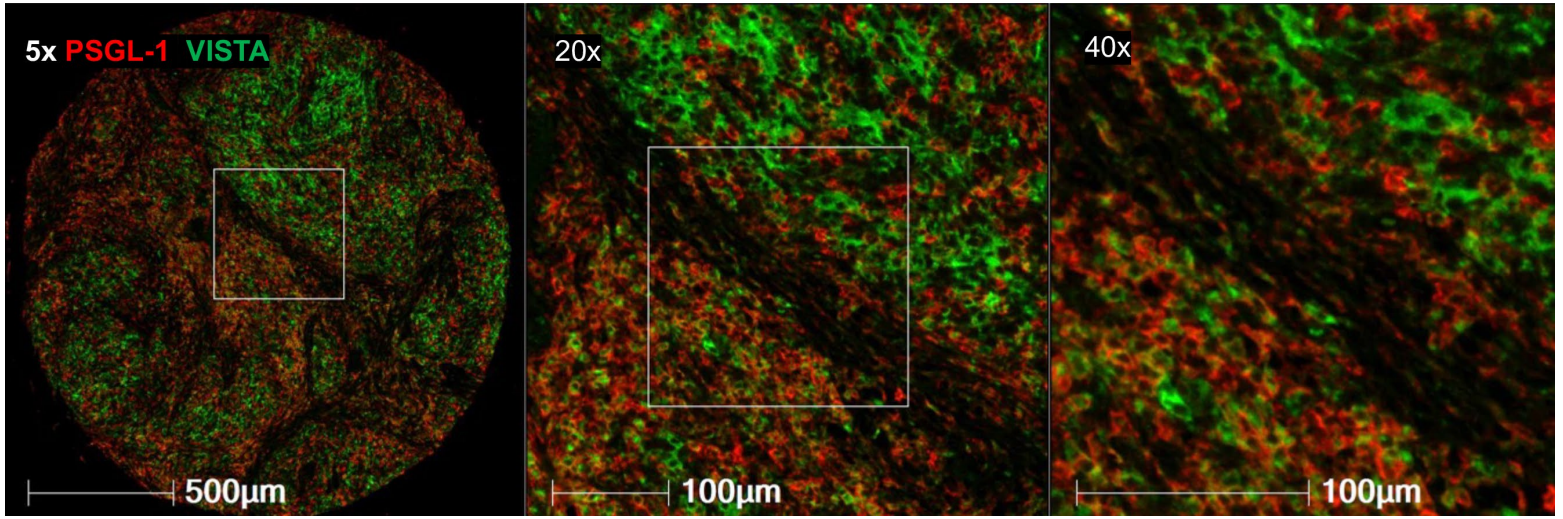
- **Manufacturing of SNS-101 is ongoing**
  - No “developability” issues to date
  - Cell line has demonstrated great productivity/quality (~ 9 grams/liter and low % aggregates)

- **IND-enabling studies have been initiated**
  - Single-dose mouse and non-human primate PK
  - Optimized preclinical efficacy models in huVISTA-KI mice
  - GLP multi-dose PK and toxicology studies contracted
  - In vitro and In vivo CRS risk assessment models

- **Translational Medicine studies are underway to support FIH clinical trial in 2023**
  - Generate SNS-101 responder hypothesis ➔ rationalize early development plan/focus on high probability of success indications

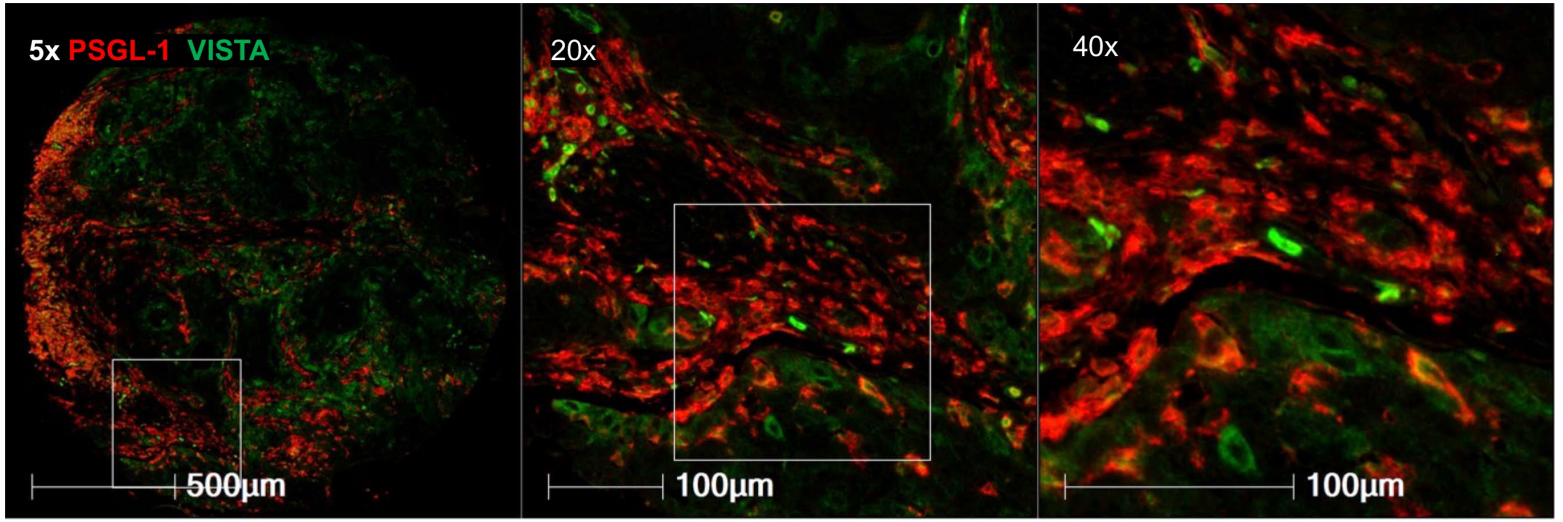
Preliminary PSGL-1/VISTA Proximity Assay on HNSCC Tumor Samples

High Proximity



H&N (HN483a)
Core C6,R7

Low Proximity

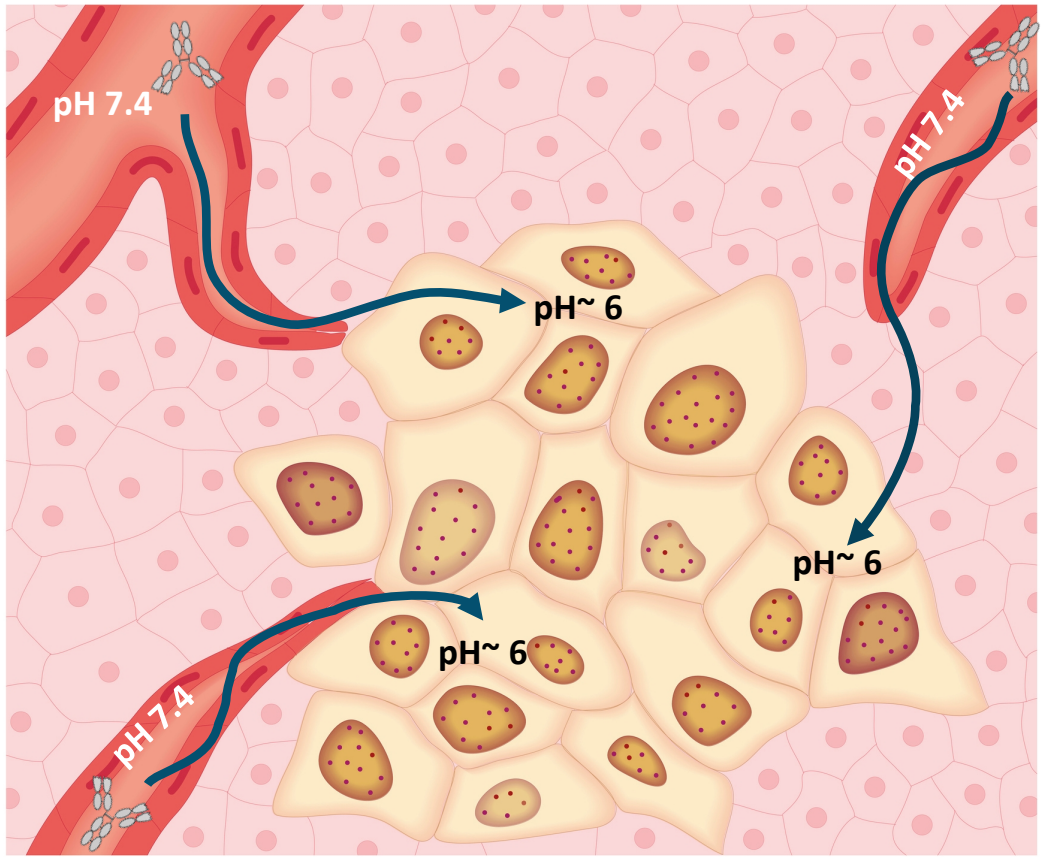


H&N (HN483a)
Core C5,R4

Beyond VISTA:

Tumor Microenvironment Activated Biologics (TMAbs)

The tumor microenvironment of pH ~6 is lower than physiological pH of 7.4



Sensei's technology identifies antibodies that selectively bind in the distinct biochemical milieu of the tumor, for example, sub-physiologic pH

- Antibodies that bind at physiological pH may encounter a "sink"
  - Prevents effective binding at the tumor and may lead to toxicity
- TMAb antibodies bypass tissue compartments other than the low-pH tumor microenvironment
- Goal is to unlock previously undruggable immune targets through potential for improved safety and clinical activity profile

Acknowledgements

Sensei Biotherapeutics

TMAb

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