

Conditionally Active Antibodies for Immuno-oncology

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Engineered Selectivity to Extend the Reach of Immuno-oncology Agents



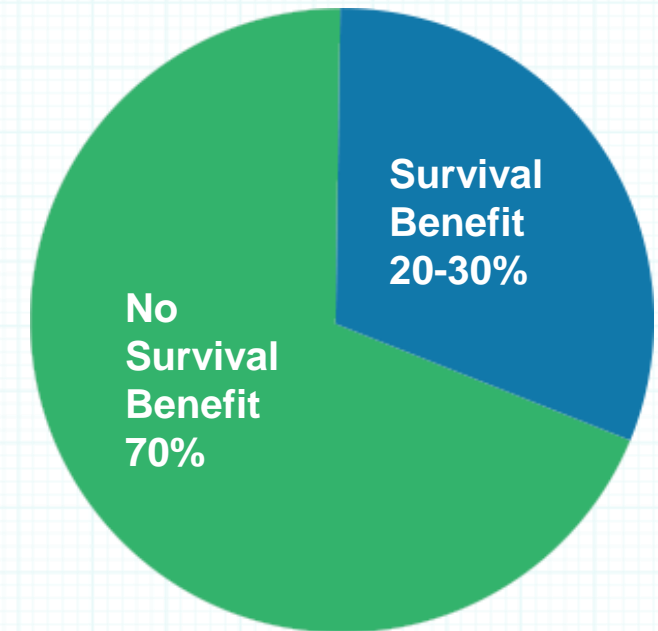
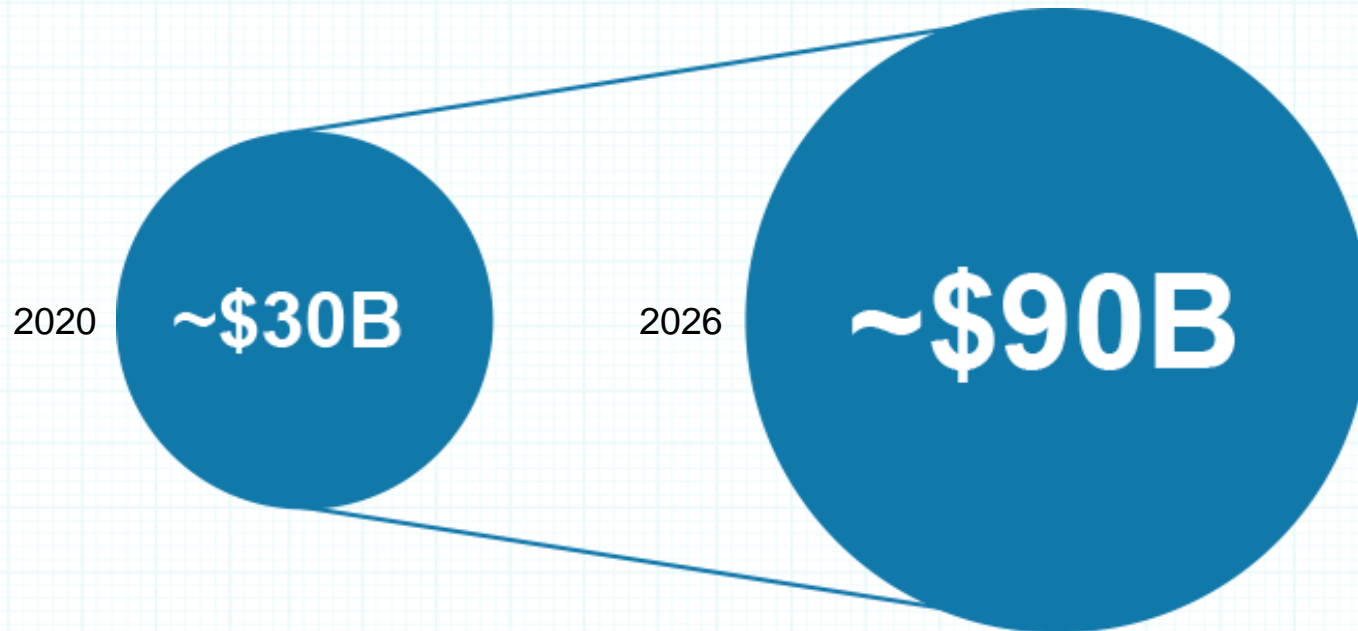
Innovative Pipeline of IO Drugs with Broad Commercial Potential

Program (Target)	Indication	Discovery	IND-enabling	Phase 1 / 2 Clinical
SNS-101 (VISTA)	Solid Tumors			
SNS-102 (VSIG4)	Solid Tumors			
SNS-103 (ENTPDase1/CD39)	Solid Tumors			

The Modern-Day Challenge in Immuno-Oncology

The PD-1/PD-L1 market is big and growing fast¹

PD-1/PD-L1 monotherapy does not benefit 70% of patients²



Lack of Selectivity is a Major Obstacle to CI Innovation

Industry Problem	Sensei's Solution
<p>Conventional antibodies target immune checkpoints that are highly expressed in normal tissues, resulting in:</p> <ul style="list-style-type: none">Dose-limiting toxicities due to on-target/off-tumor actionPharmacological sink effect requires higher and more frequent dosingSuboptimal activity due to poor PK and dose-limiting toxicities	<p>Conditionally active antibodies are selectively targeted to the tumor microenvironment, potentially providing:</p> <ul style="list-style-type: none">Little or no toxicity due to selective on-target/on-tumor actionLower and less frequent doses by avoiding normal tissue bindingPowerful activity selectively focused on the tumor microenvironment

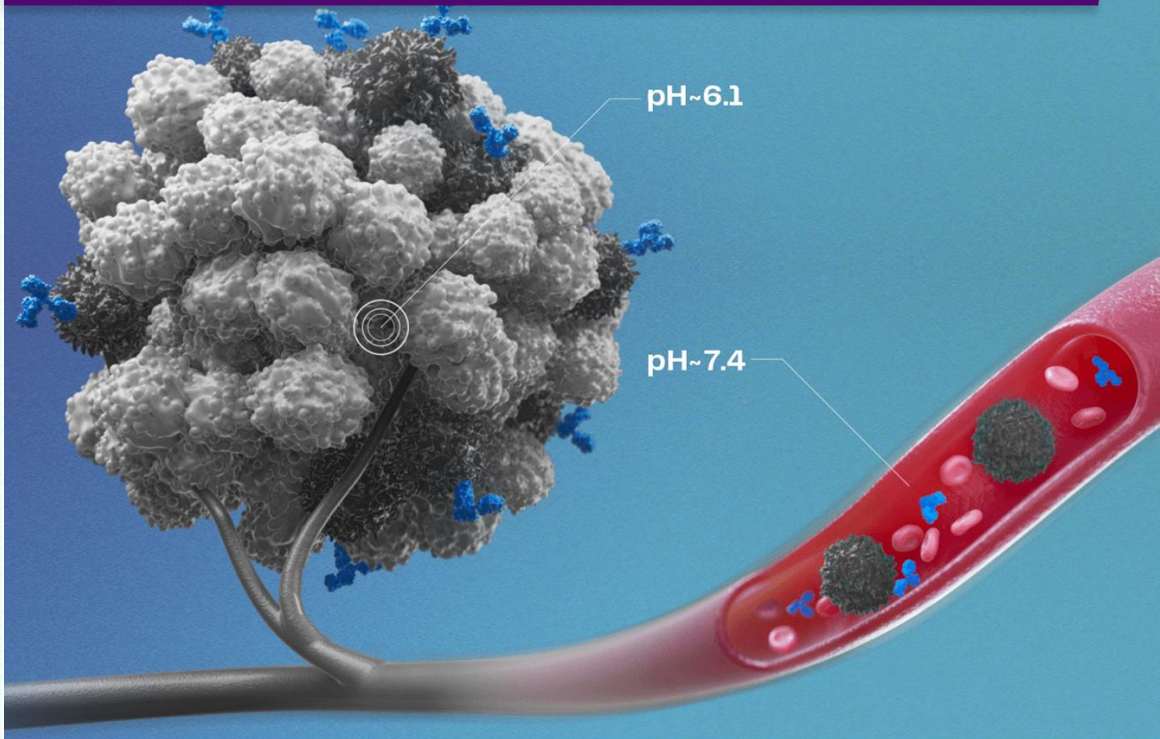
Only one new checkpoint inhibitor has been approved since the original CTLA-4 and PD-1/PD-L1 group



pH-sensitive Antibodies Have Potential to Selectively Bind Their Targets in the Low-pH Tumor Microenvironment

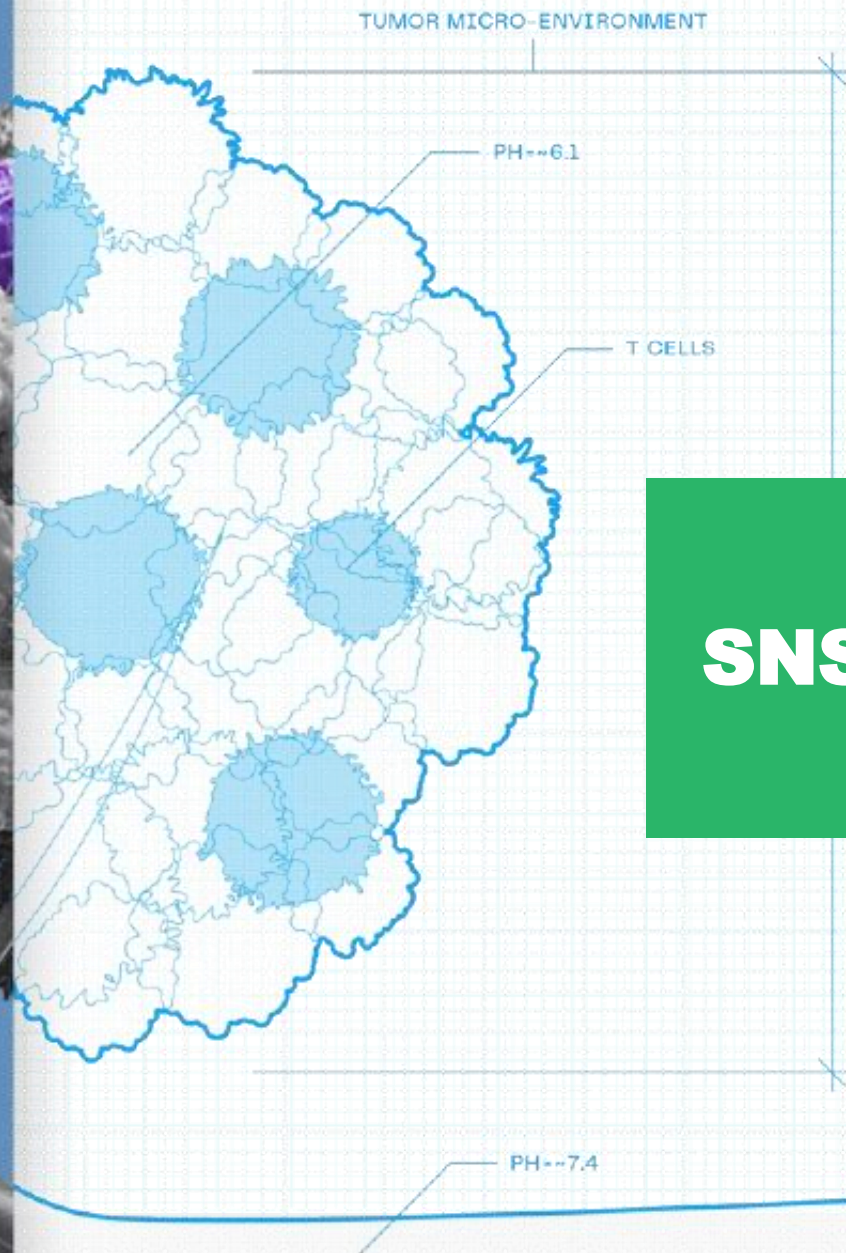
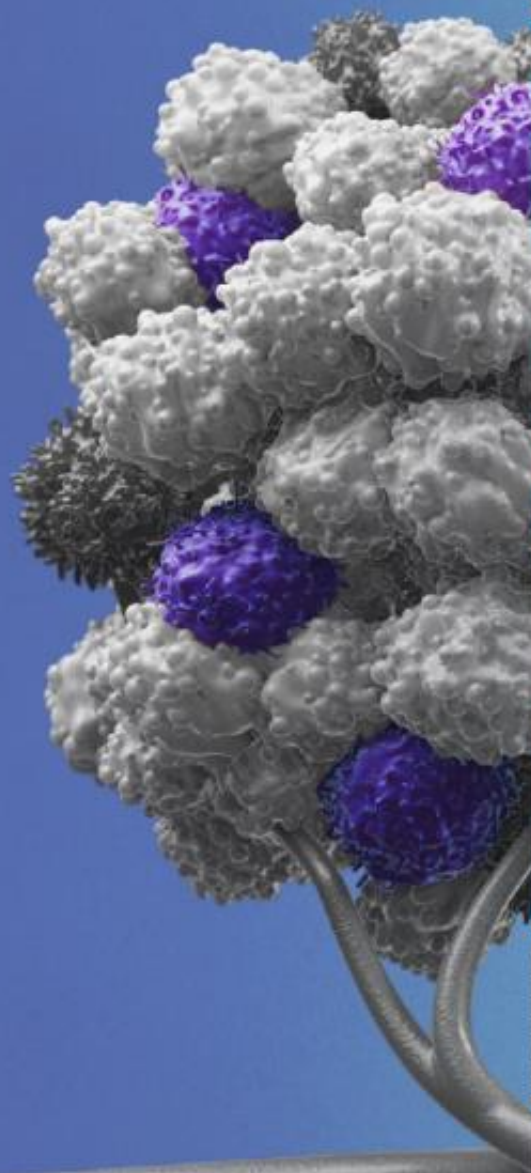
TMAb Platform

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



Sensei's technology identifies pH-sensitive antibodies designed to bind only at the tumor

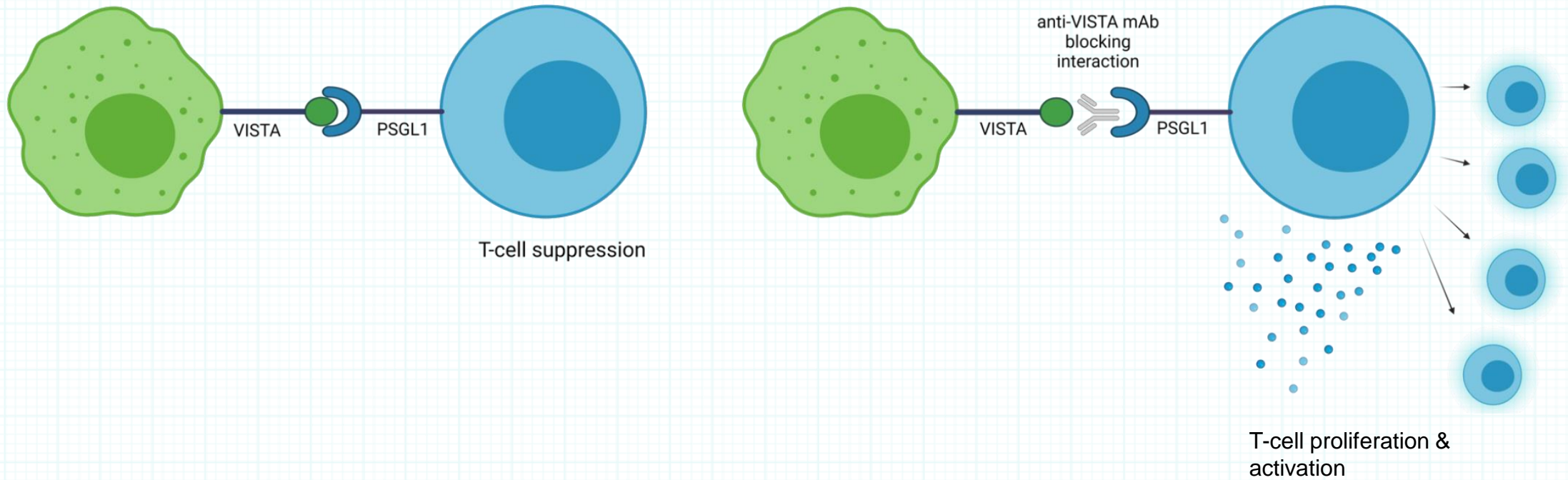
- Exploits the tumor microenvironment using pH-selective properties
- Intended to alleviate undesirable properties:
 - Dose-limiting toxicities due to on-target/off-tumor binding
 - Higher and more frequent dosing due to poor pharmacokinetics (Target-mediated Drug Disposition (TMDD))
- Bolsters specific activities
- Goal is to unlock previously undruggable immune targets



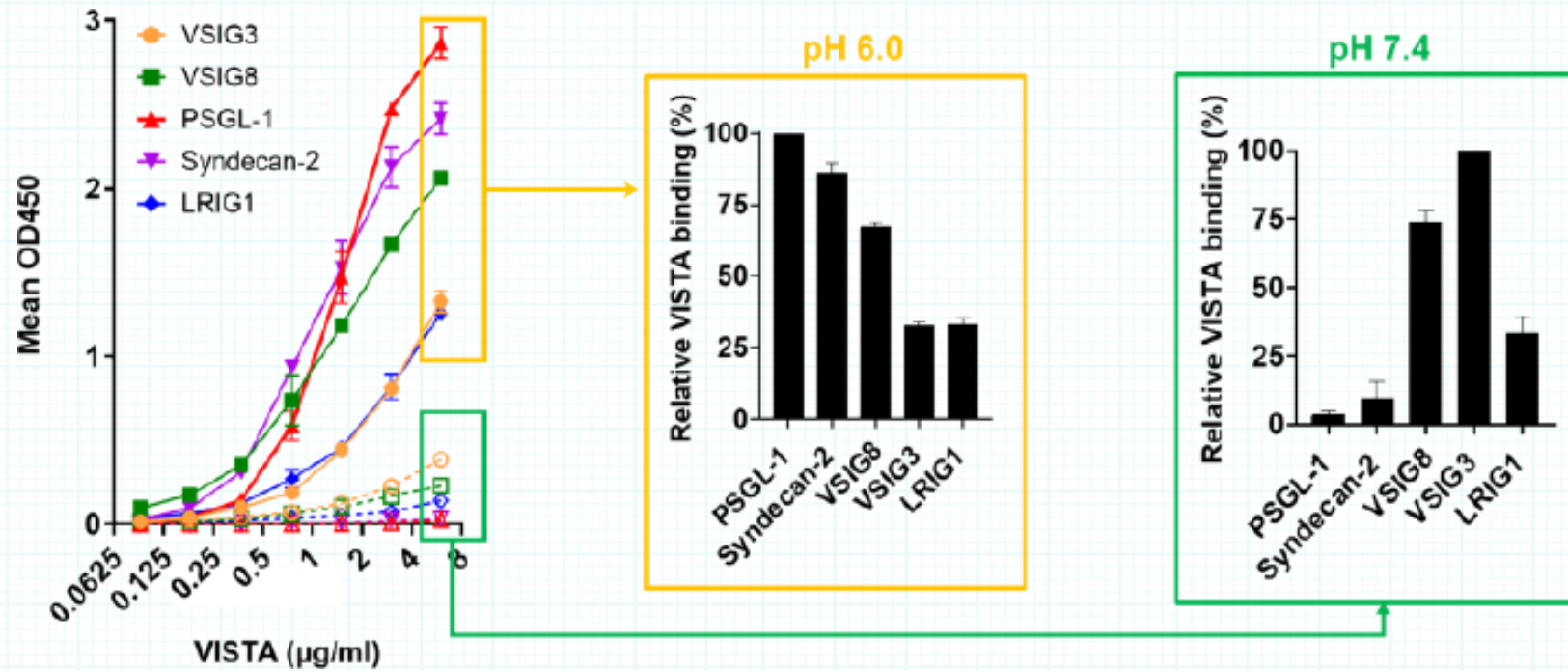
SNS-101

VISTA: A Potent T cell Checkpoint Extensively Expressed on Myeloid Cells¹

VISTA is a B7 family member that suppresses T cell function



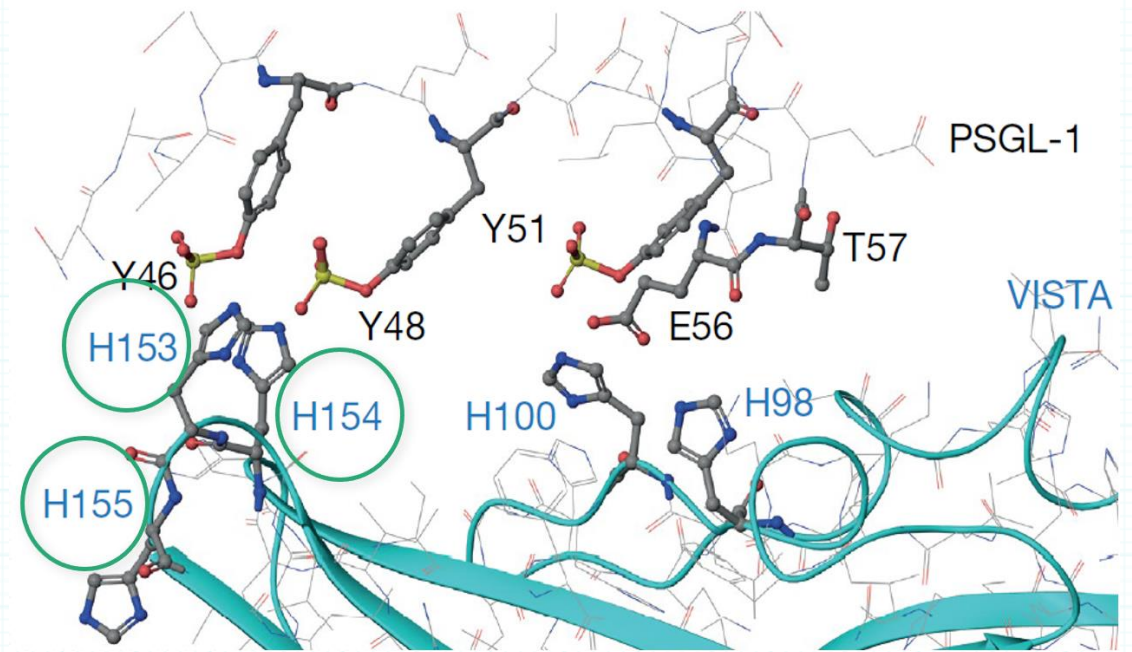
The VISTA:PSGL-1 Interaction is Selective for low pH



VISTA Checkpoint is Activated at the Low pH of the Tumor Microenvironment

VISTA extracellular domain is uniquely rich in histidines¹

Protonated VISTA histidines are required for
PSGL-1 binding¹



SNS-101: Selectively Targeting VISTA with a pH-sensitive Antibody

Key features


- Selectivity for Active VISTA^{pH6} over VISTA^{pH7.4}
- Designed to block VISTA's interaction with PSGL-1 and all other T-cell receptors at pH 6.0
- IgG1 format
- Active Fc

	pH 6.0	pH 7.4
Monovalent Affinity (K _D) [nM]	0.218	132 (~No binding)

Development milestones

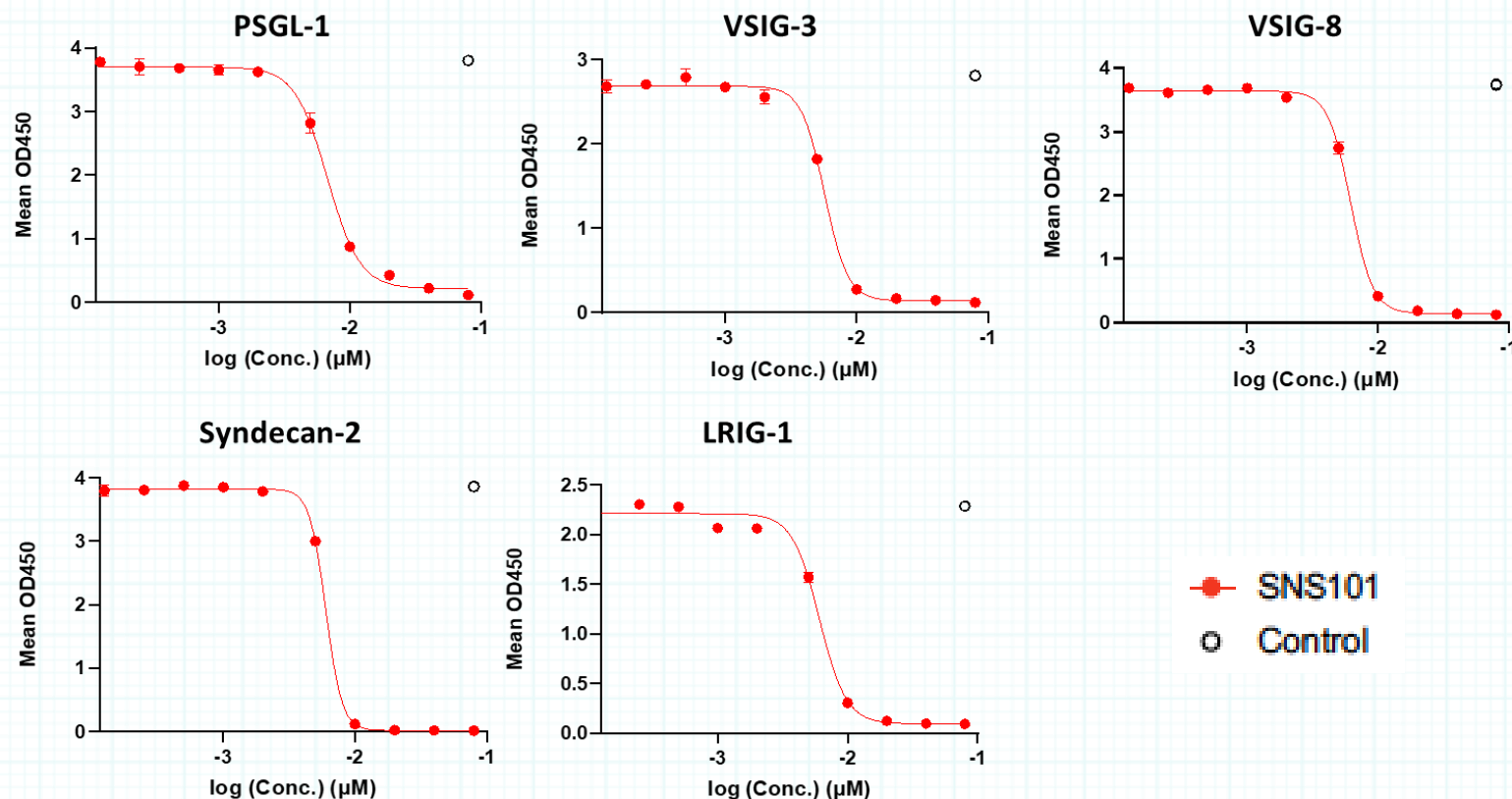
- Preclinical PK, safety and efficacy data presented at conferences throughout 2022
- IND submission planned for 1H23

SNS-101 Is a Fully Differentiated Anti-VISTA Antibody

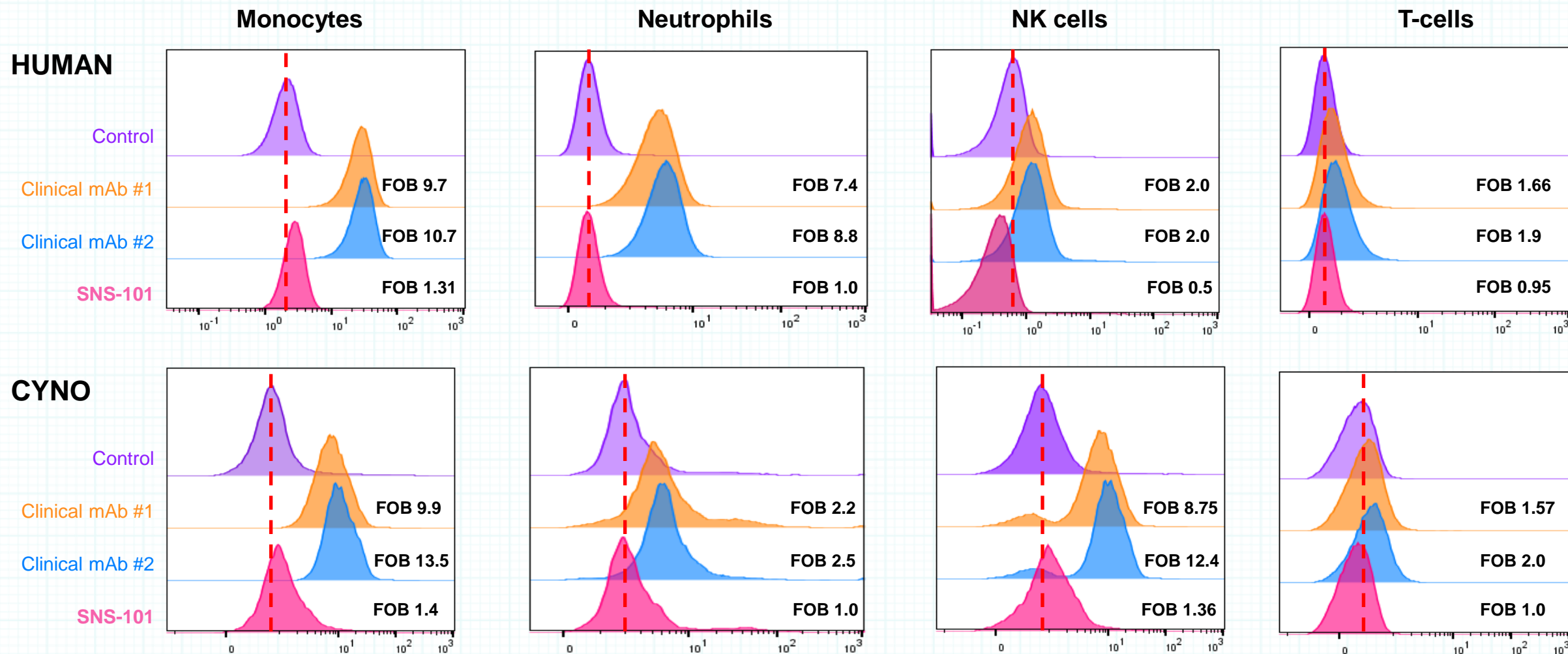
	SNS-101 	CI-8993; JNJ-61610588 (J&J/Curis)	K01401-020; W0180 (Pierre Fabre)	HMBD-002 (Hummingbird)	KVA12.1 (Kineta)	VISTA.18 (BMS)	(PMC-309) Pharm Abcine
Inhibit PSGL-1 Binding	✓	✓	✓	✗	✓	✓	✓
pH Sensitive Binding	✓	✗	✗	✗	✗	✓	✗
Fc Active	✓ (IgG1)	✓ (IgG1)	N/A	✗	✓ (IgG1)	✗ (IgG4)	✓ (IgG1)
Stage	Preclinical	Phase 1	Phase 1	Phase 1	Preclinical	Preclinical	Preclinical

SNS-101 Strongly Inhibits the VISTA:PSGL-1 Interaction And All Other Potential Binding Partners at pH 6.0 in *In Vitro* Assay

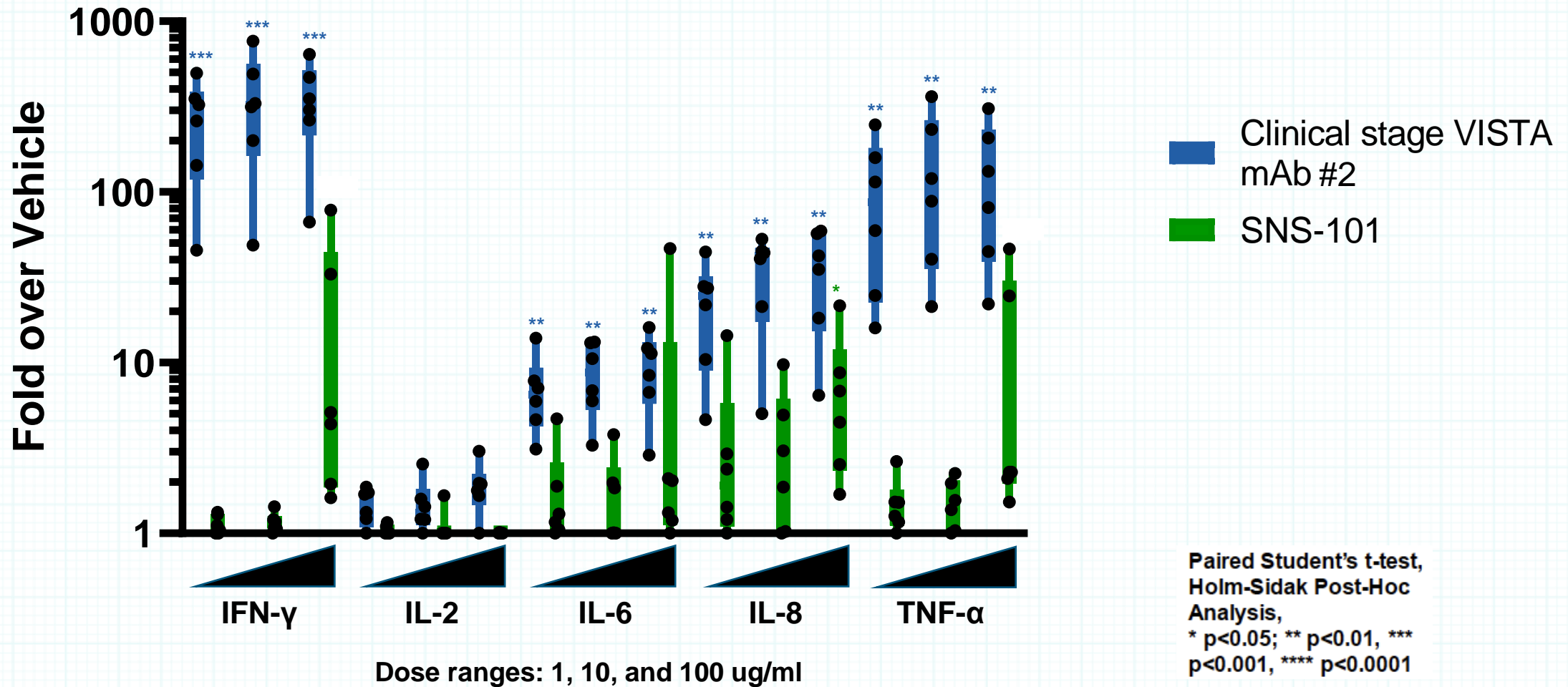
Receptor	IC50 [nM]
PSGL-1	7
VSIG3	6
VSIG8	6
Syndecan-2	6
LRIG1	6



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

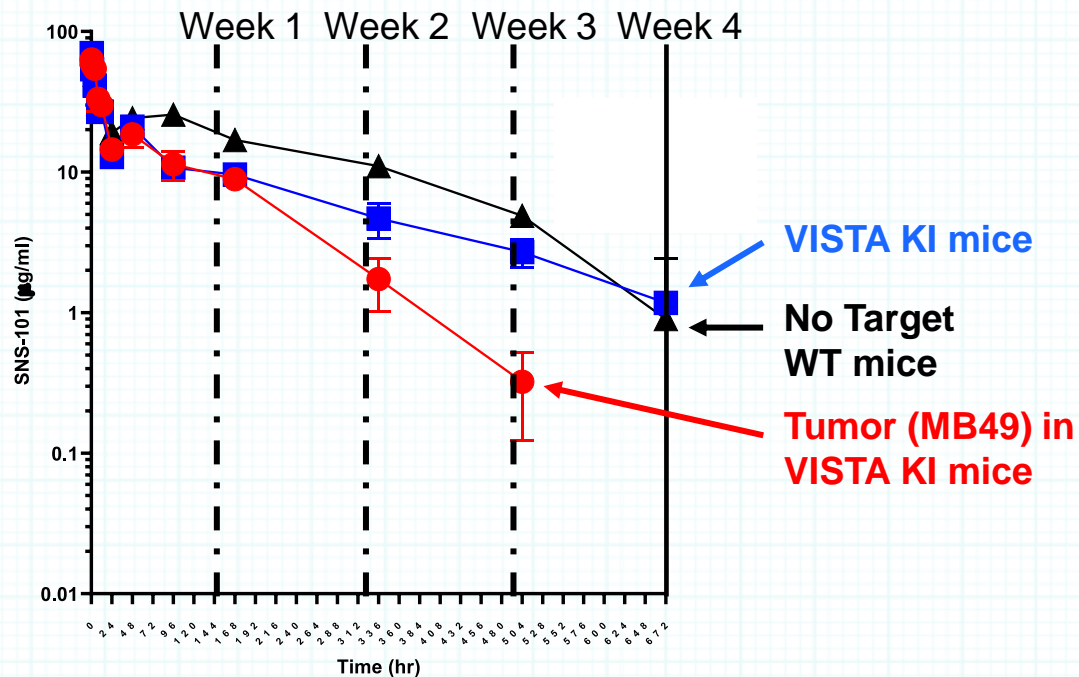


SNS-101 Induced Substantially Lower Cytokine Release in Whole-blood Assay at Neutral pH Compared to pH-independent VISTA Antibody



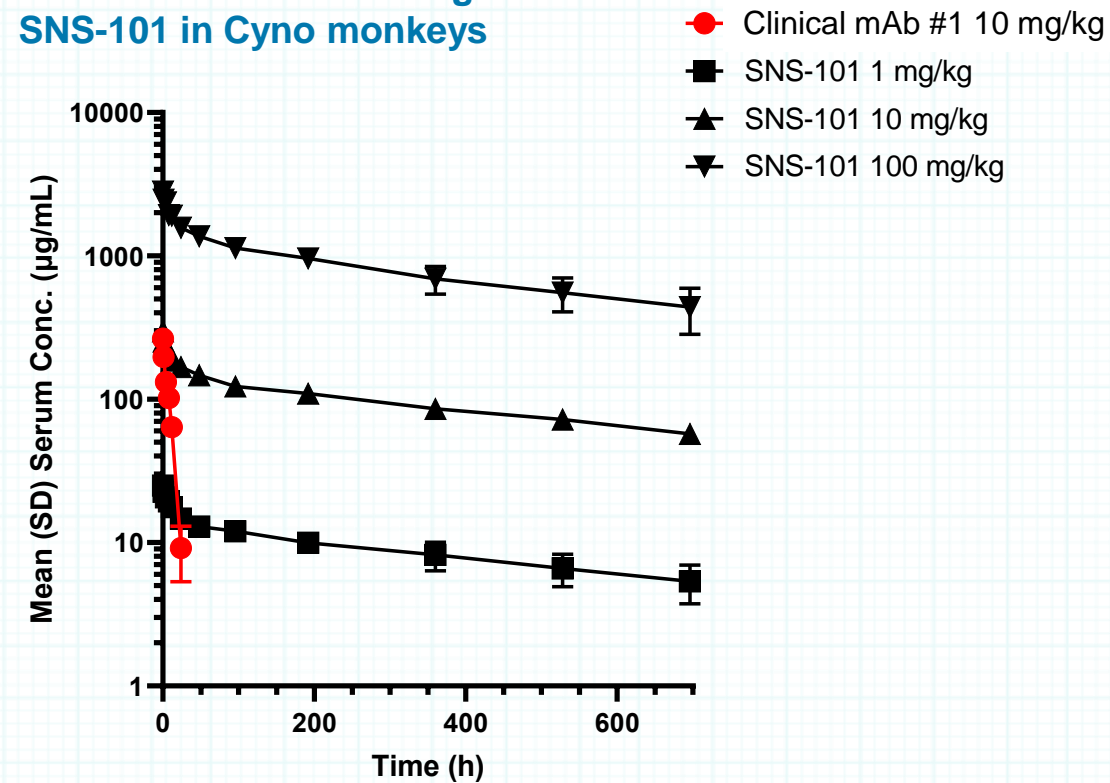
SNS-101 Has Displayed a Favorable Single-dose PK Profile in Preclinical Studies - *No Significant TMDD in Human VISTA KI Mice or Cyno Monkeys*

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



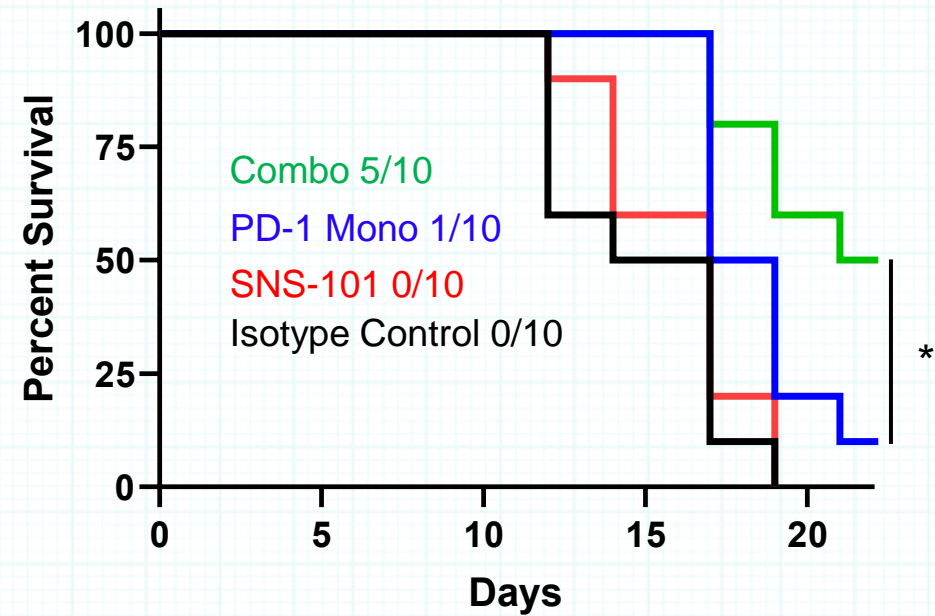
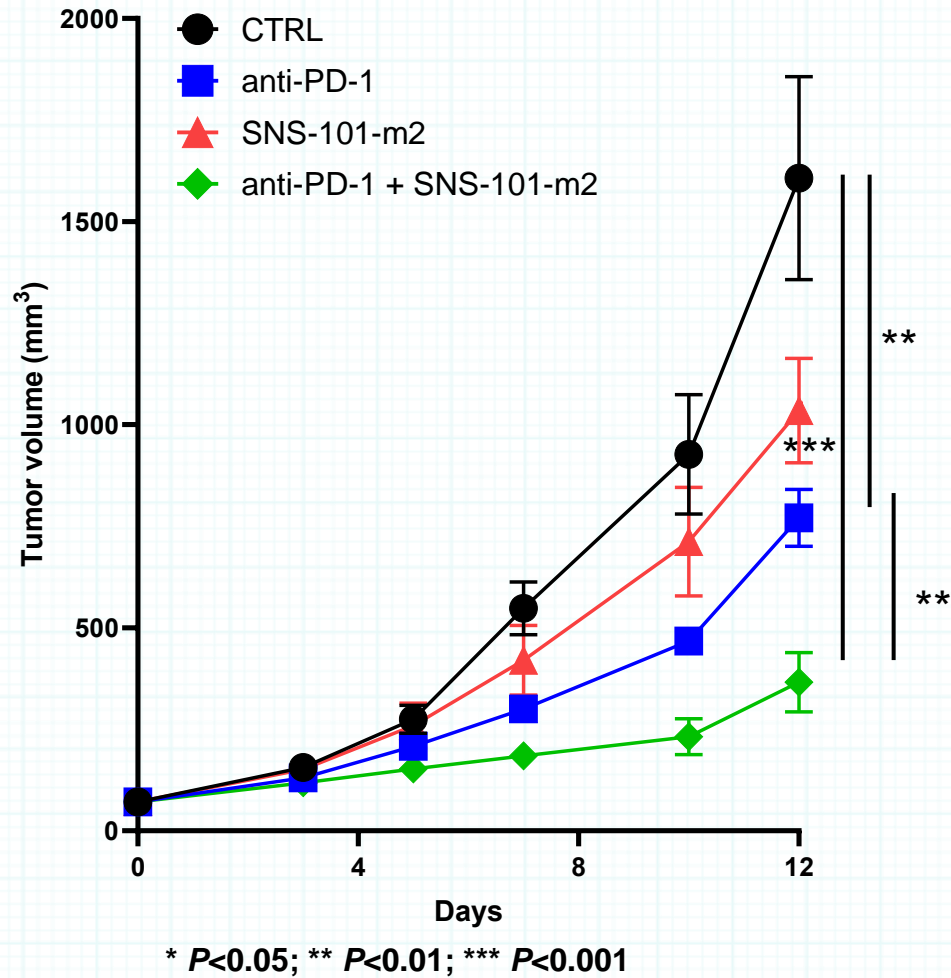
Demonstrated a long mean residence time in the blood, indicating a lack of significant target-mediated drug disposition (TMDD) and clearance in non-malignant tissues

Pharmacokinetics of Single Dose SNS-101 in Cyno monkeys

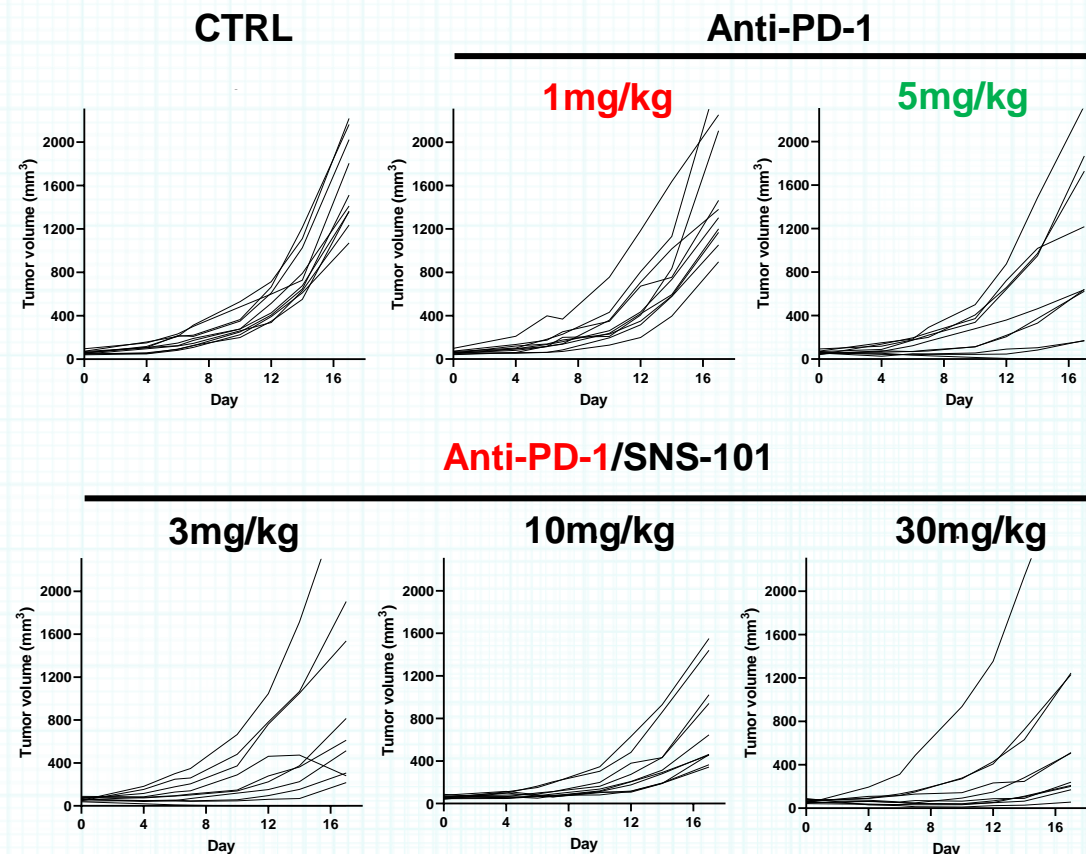
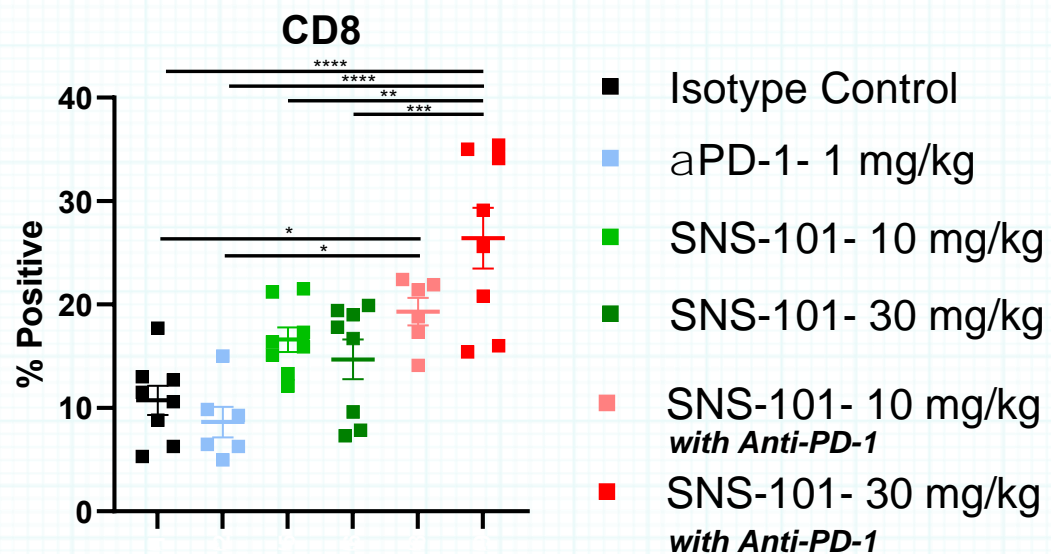


SNS-101 displays linear elimination kinetics unlike a pH-independent anti-VISTA mAb, which demonstrates TMDD and rapid clearance

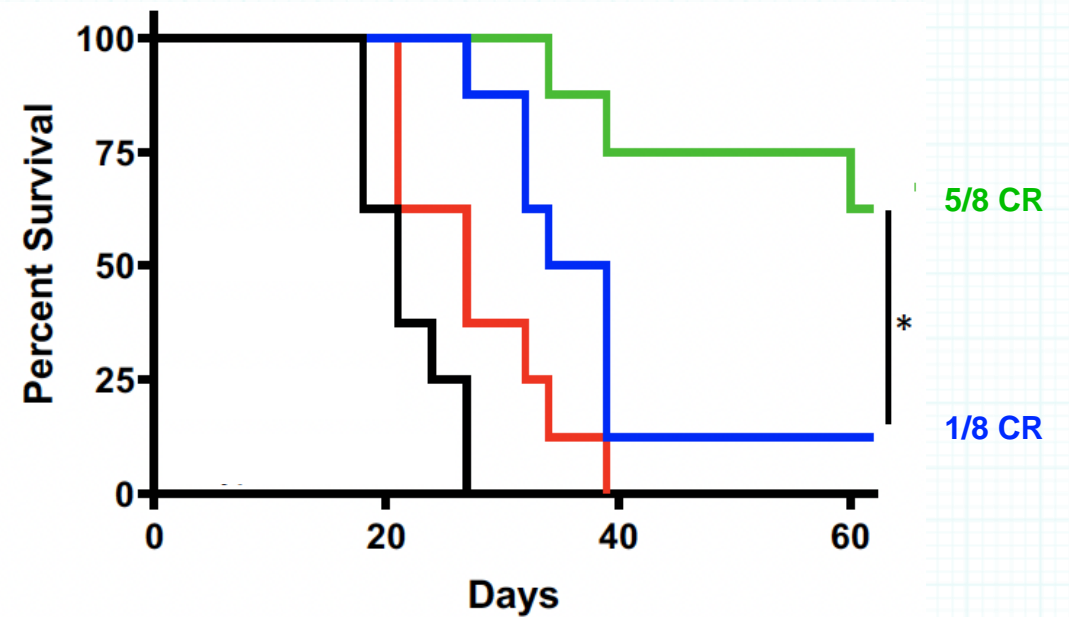
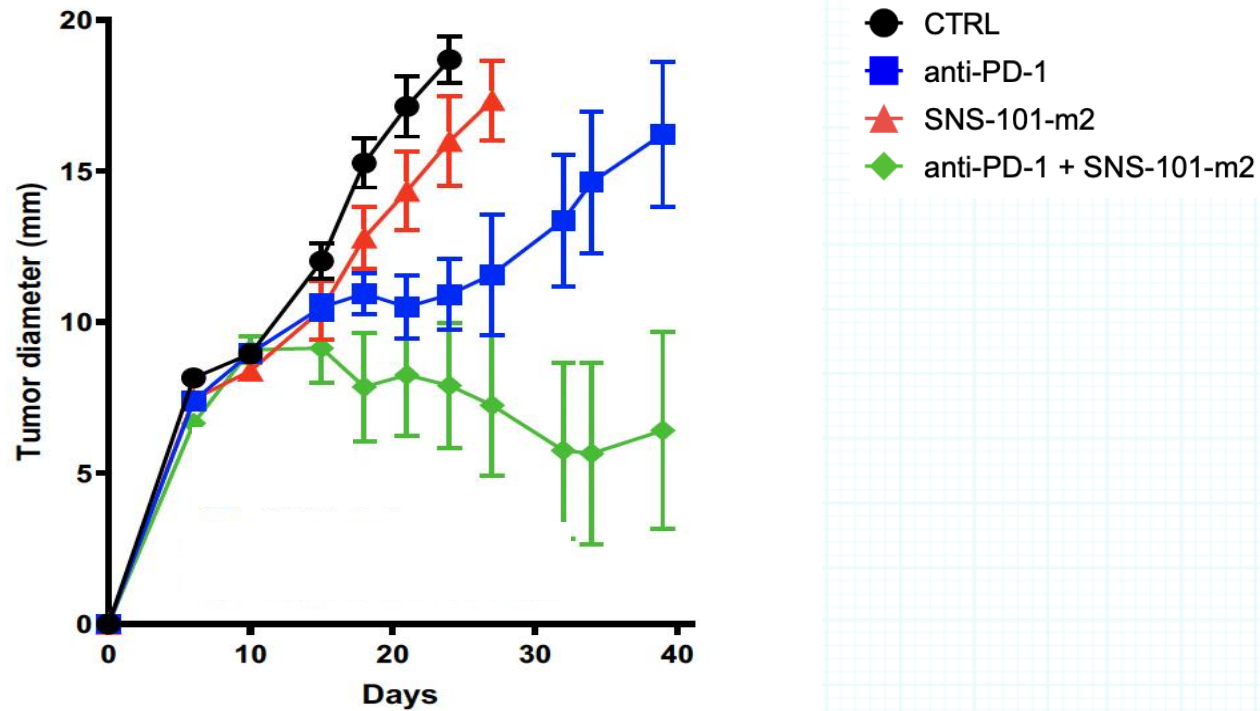
SNS-101 Demonstrated Strong Combinatorial Activity with Anti-PD-1 in MC38 Model in Human VISTA Knock-in Mice



SNS-101 Demonstrated Increased CD8 T-cells in Combination With Anti-PD-1 in MC38 Tumors *In Vivo*

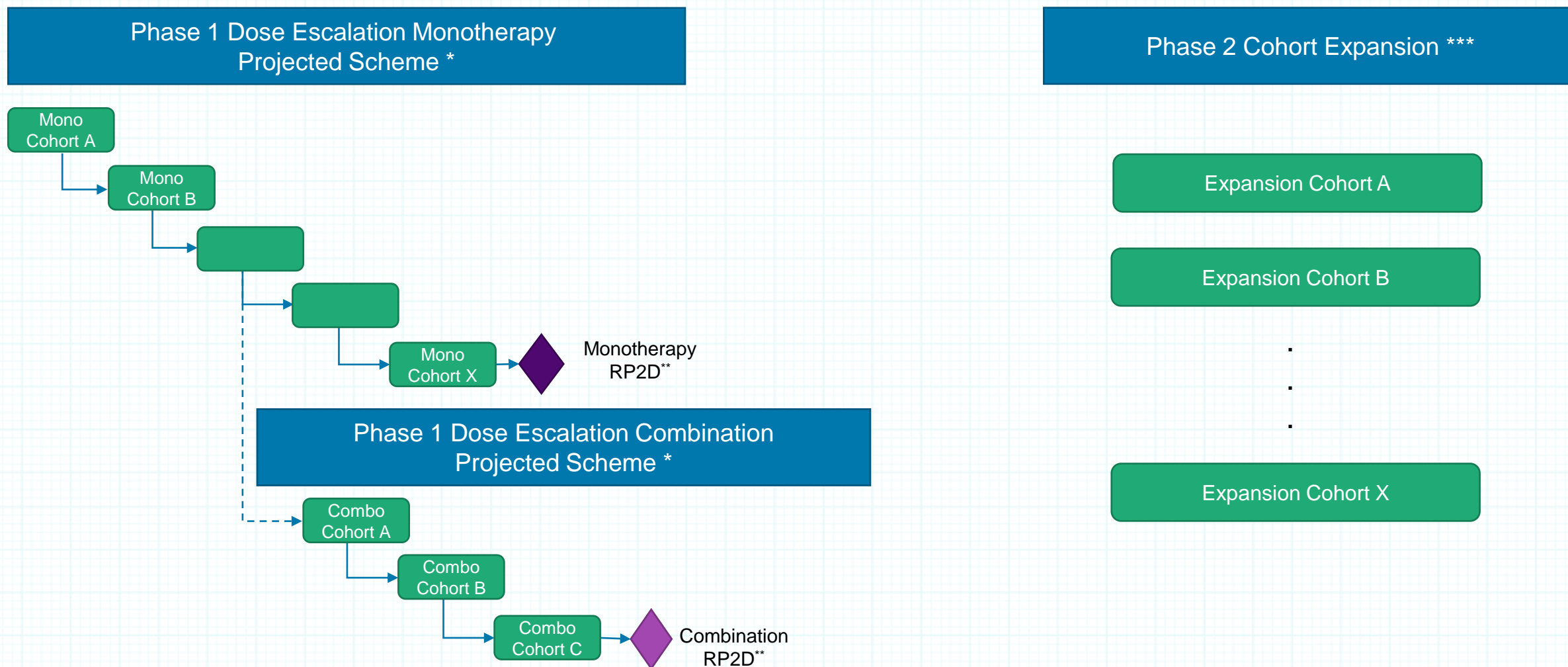


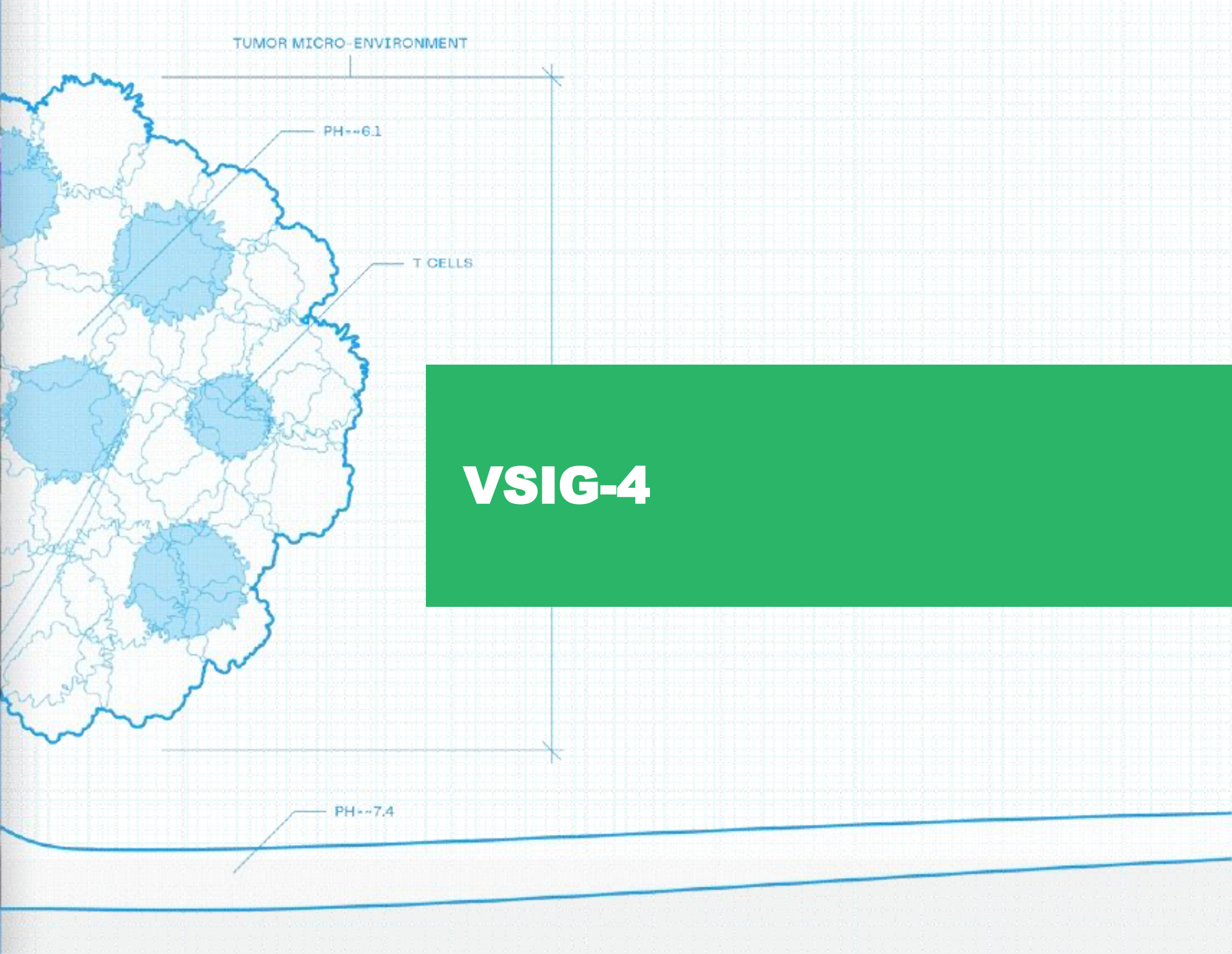
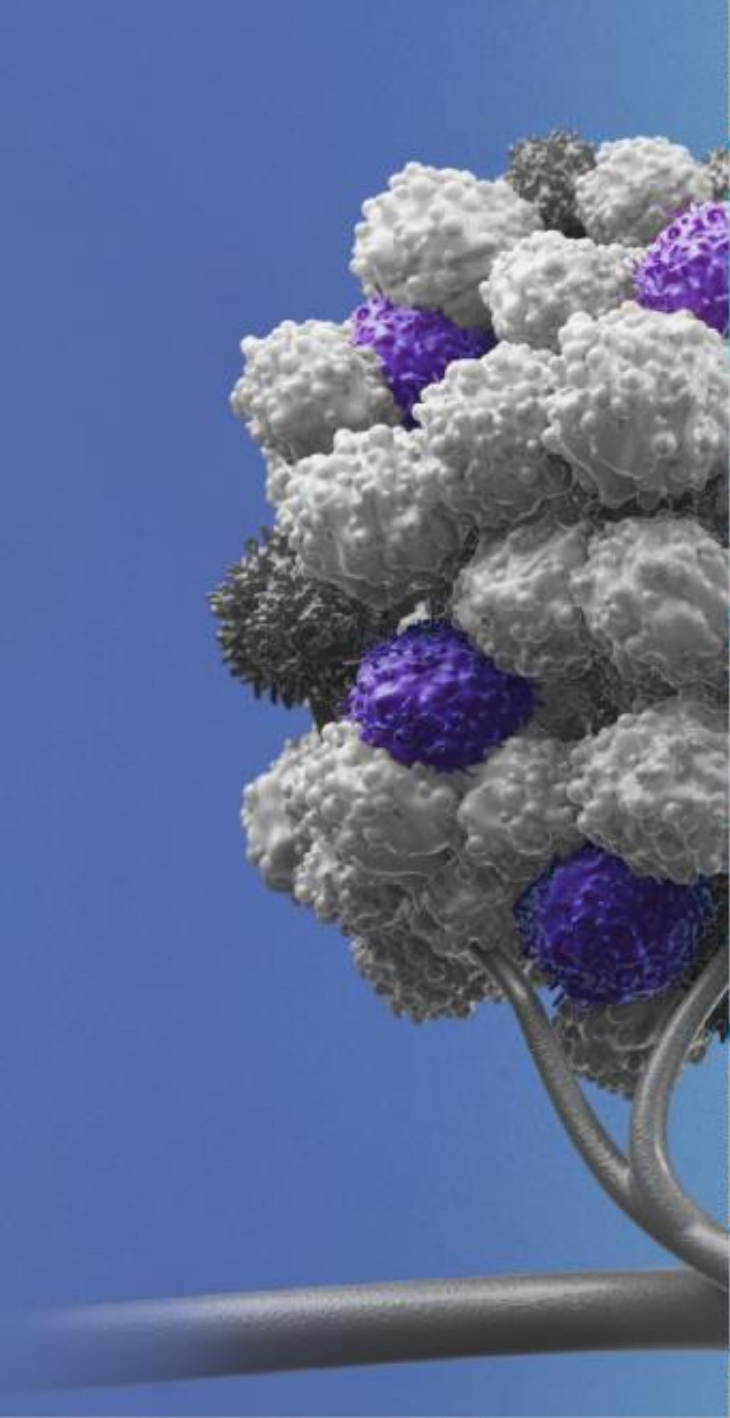
SNS-101 Re-sensitized Anti-PD-1 Insensitive Sarcomas Tumors in 1956 Model in Human VISTA Knock-in Mice



* p<0.05

Preliminary SNS-101 Phase 1/2 Study Schematic

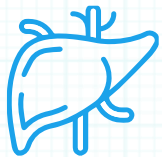
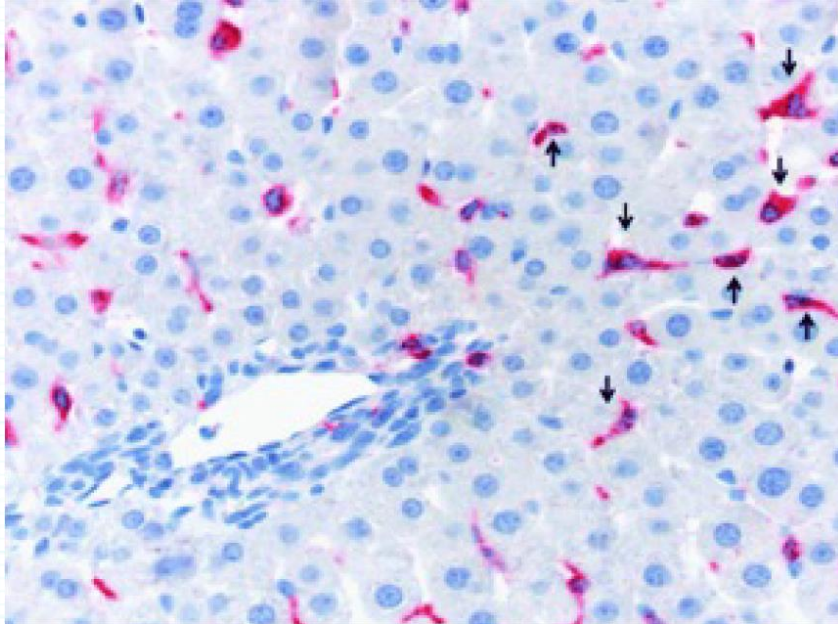




VSIG-4

VSIG4 is an Immunosuppressive Receptor Expressed On- and Off-tumor

Tissue macrophages (Kupffer cells) in liver

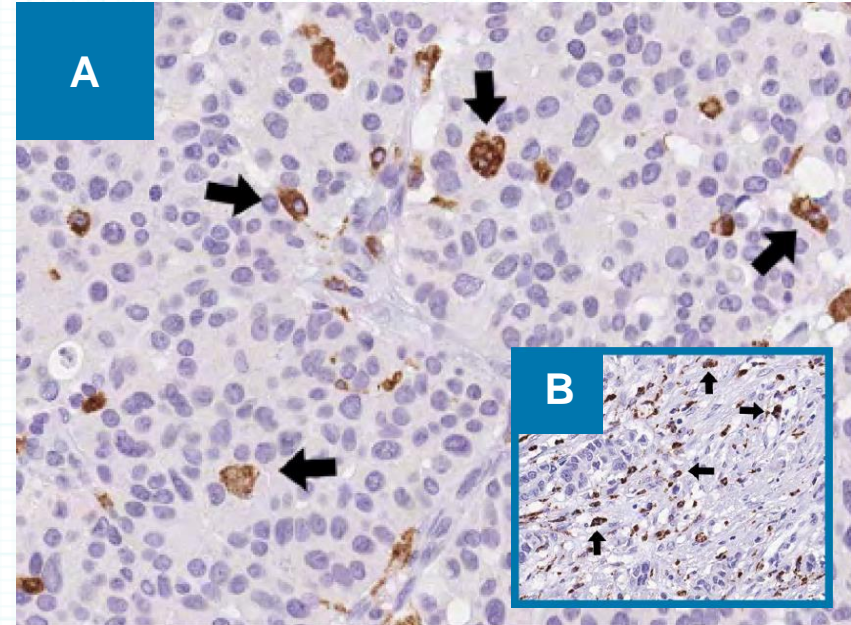


In the liver, VSIG-4 ...

Is expressed on Kupffer cells

Appears to drive significant target-mediated drug disposition (TMDD) and clearance

Tumor-associated macrophages in tumor and stroma (inset)



In the tumor microenvironment, VSIG-4 ...

Correlates with immunosuppressive "M2" macrophage infiltration

Inhibits T cell activation

Promotes tumor growth based on data from a syngeneic Lewis lung carcinoma model in knockout mice

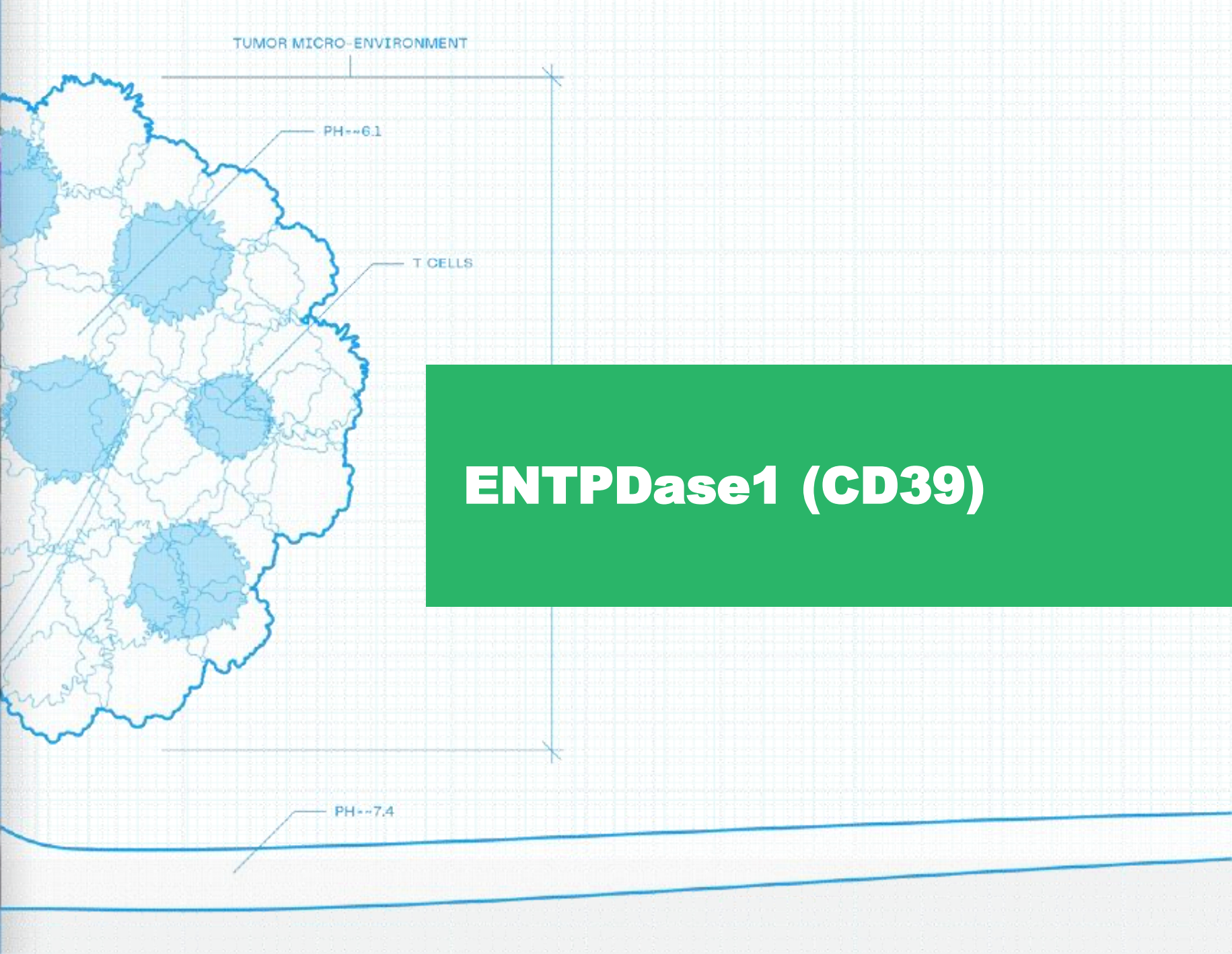
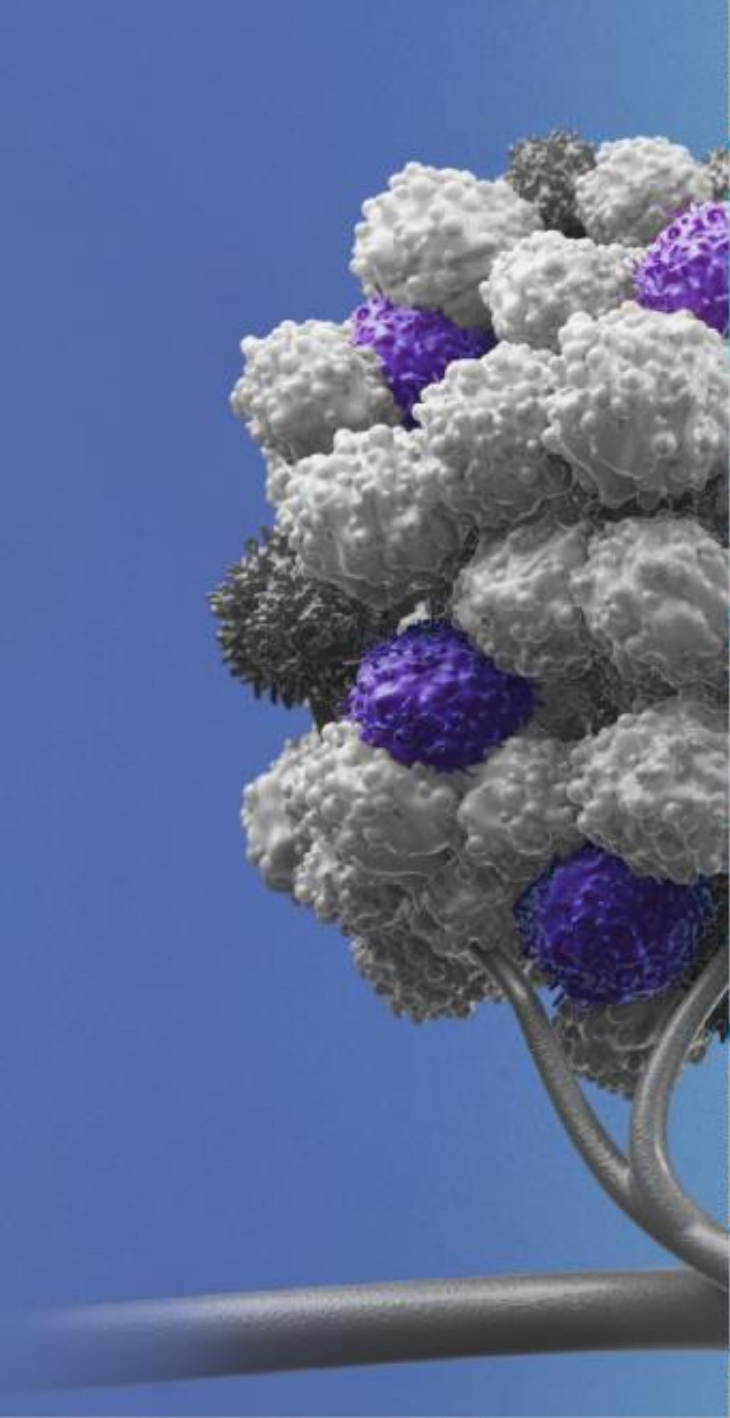
Sensei Has Identified pH-sensitive VSIG4 Antibodies

- As of August 2022, Sensei has:
 - Identified 8 parental antibodies for further optimization;
 - Identified novel VSIG4 receptors on primary T-cells by Hi-Res proteomics, which are currently in verification stage;
 - Identified pH-sensitive antibodies highlighting the potential breadth of the TMAb platform
- Plan to select product candidate in 2023

pH-Sensitive VSIG4 Parental Antibodies Selected for Further Optimization

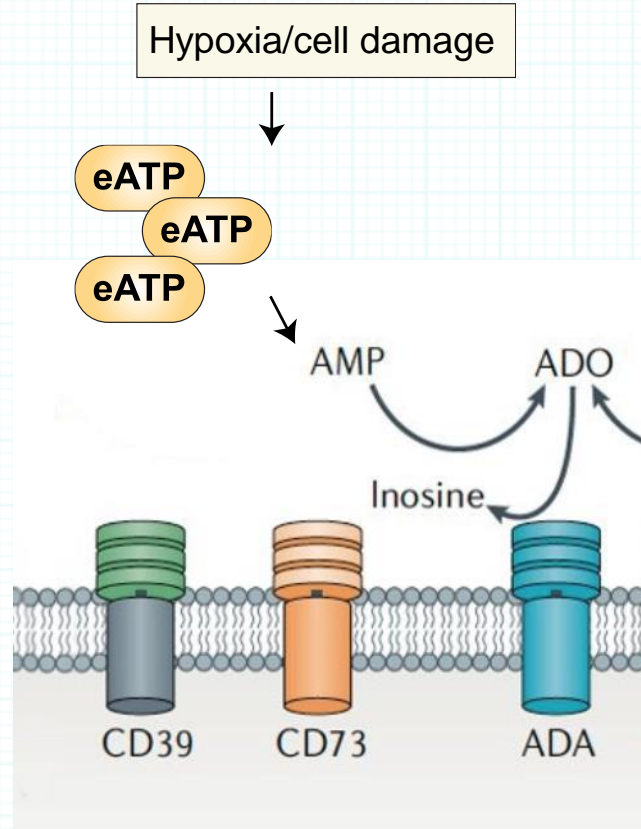
Antibody Reference #	Ratio of pH Selectivity (6.0 vs 7.4)	Blockage of Immobilized VSIG4-T-cell Inhibition	Blockage of Cellular VSIG4-T-cell Inhibition
1	1	+	+
2	7	+	+
3	1	+	+
4	3	+	+
5	3	+/-	+
6	25	+	+
7	1	+	+
8	2	-	+

* Ratio assessed by flow cytometry on VSIG4 overexpressing cells

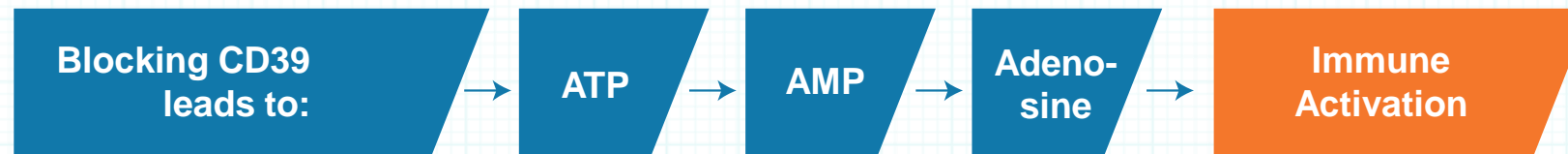


ENTPDase1 (CD39)

ENTPDase1 (CD39) is the Rate Limiting Enzyme in the Production of Immunosuppressive Adenosine



- Primary function is conversion of extracellular ATP / ADP to adenosine, which exerts immunosuppressive properties through binding to A2a/A2b receptors
- Expressed on various immune cells in both tumors and normal tissues
- Development of a TMAb antibody has potential for improved safety and PK profile compared to competitor CD39 mAbs
- First set of parental antibodies received September 2022



Expected Program Milestones



SNS-101 (anti-VISTA)

- 1H 2023: Multi-dose Non-Human Primate (NHP) PK & Toxicology data
- 1H 2023: IND filing



SNS-102 (anti-VSIG4)

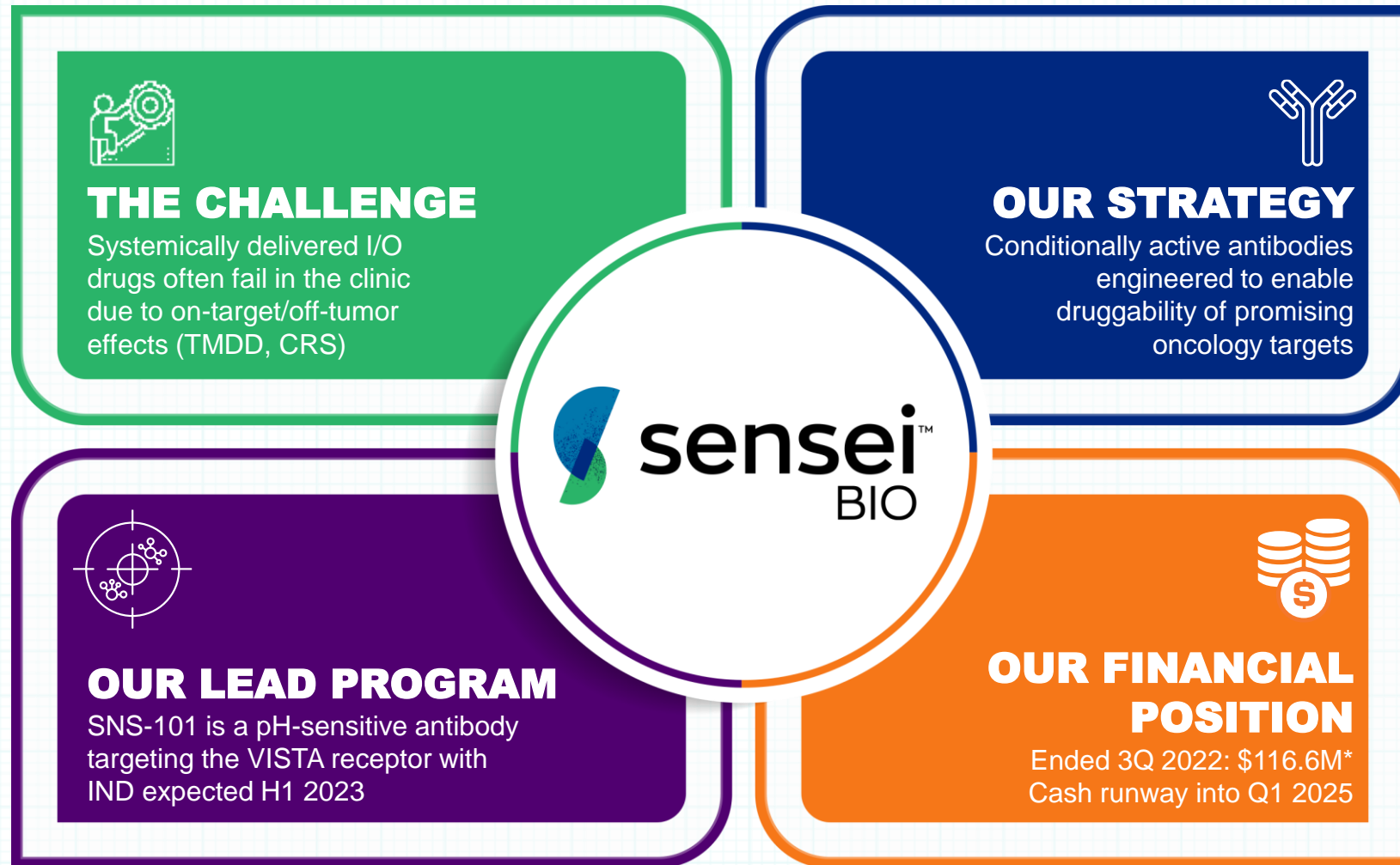
- 2023: Select product candidate



SNS-103 (anti-ENTPDase1/CD39)

- 2023: Select product candidate

Engineered Selectivity to Extend the Reach of Immuno-oncology Agents



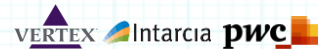
Proven Team With Deep Experience



John Celebi, MBA
President and CEO



Erin Colgan
Chief Financial Officer



Robert Pierce, M.D.
Chief R&D Officer



Patrick Gallagher
Chief Business Officer



Elisabeth Colunio
VP, Human Resources

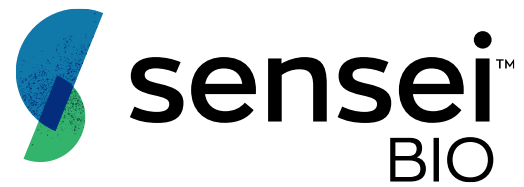


Edward van der Horst, Ph.D.
SVP, TMAb Antibodies



Christopher Gerry, J.D.
VP, General Counsel





HQ: 451 D St, Unit 710 , Boston, MA 02210 / **MD:** 1405 Research Blvd, Suite 125, Rockville, MD 20850

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Appendix

References for Slide 23

1. Zheng F, Devoogdt N, Sparkes A, Morias Y, Abels C, Stijlemans B, Lahoutte T, Muyldermans S, De Baetselier P, Schoonooghe S, Beschin A, Raes G. Monitoring liver macrophages using nanobodies targeting Vsig4: concanavalin A induced acute hepatitis as paradigm. *Immunobiology*. 2015 Feb;220(2):200-9. doi: 10.1016/j.imbio.2014.09.018. Epub 2014 Oct 2. PMID: 25440182.
2. Reviewed in Zang X, Allison JP. To be or not to be B7. *J Clin Invest*. 2006 Oct;116(10):2590-3. doi: 10.1172/JCI30103. PMID: 17016555; PMCID: PMC1578606.
3. Helmy KY, Katschke KJ Jr, Gorgani NN, Kljavin NM, Elliott JM, Diehl L, Scales SJ, Ghilardi N, van Lookeren Campagne M. CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens. *Cell*. 2006 Mar 10;124(5):915-27. doi: 10.1016/j.cell.2005.12.039. PMID: 16530040.
4. Voillet V, Berger TR, McKenna KM, Paulson KG, Tan WH, Smythe KS, Hunter DS, Valente WJ, Weaver S, Campbell JS, Kim TS, Byrd DR, Bielas JH, Pierce RH, Chapuis AG, Gottardo R, Rongvaux A. An In Vivo Model of Human Macrophages in Metastatic Melanoma. *J Immunol*. 2022 Aug 1;209(3):606-620. doi: 10.4049/jimmunol.2101109. Epub 2022 Jul 11. PMID: 35817516; PMCID: PMC9377377.
5. Reviewed in Small AG, Al-Baghdadi M, Quach A, Hii C, Ferrante A. Complement receptor immunoglobulin: a control point in infection and immunity, inflammation and cancer. *Swiss Med Wkly*. 2016 Apr 5;146:w14301. doi: 10.4414/smw.2016.14301. PMID: 27045607.
6. Liu G, Fu Y, Yosri M, Chen Y, Sun P, Xu J, Zhang M, Sun D, Strickland AB, Mackey ZB, Shi M. CRIg plays an essential role in intravascular clearance of bloodborne parasites by interacting with complement. *Proc Natl Acad Sci U S A*. 2019 Nov 26;116(48):24214-24220. doi: 10.1073/pnas.1913443116. Epub 2019 Nov 13. PMID: 31723045; PMCID: PMC6883839.
7. Vogt L, Schmitz N, Kurrer MO, Bauer M, Hinton HI, Behnke S, Gatto D, Sebbel P, Beerli RR, Sonderegger I, Kopf M, Saudan P, Bachmann MF. VSIG4, a B7 family-related protein, is a negative regulator of T cell activation. *J Clin Invest*. 2006 Oct;116(10):2817-26. doi: 10.1172/JCI25673. PMID: 17016562; PMCID: PMC1578631.
8. Liao Y, Guo S, Chen Y, Cao D, Xu H, Yang C, Fei L, Ni B, Ruan Z. VSIG4 expression on macrophages facilitates lung cancer development. *Lab Invest*. 2014 Jul;94(7):706-15. doi: 10.1038/labinvest.2014.73. Epub 2014 May 26. PMID: 24862966.