

Conditionally Active CD28xVISTA Bi-specific Antibodies for Myeloid- driven Tumor-specific T-cell Co-stimulation

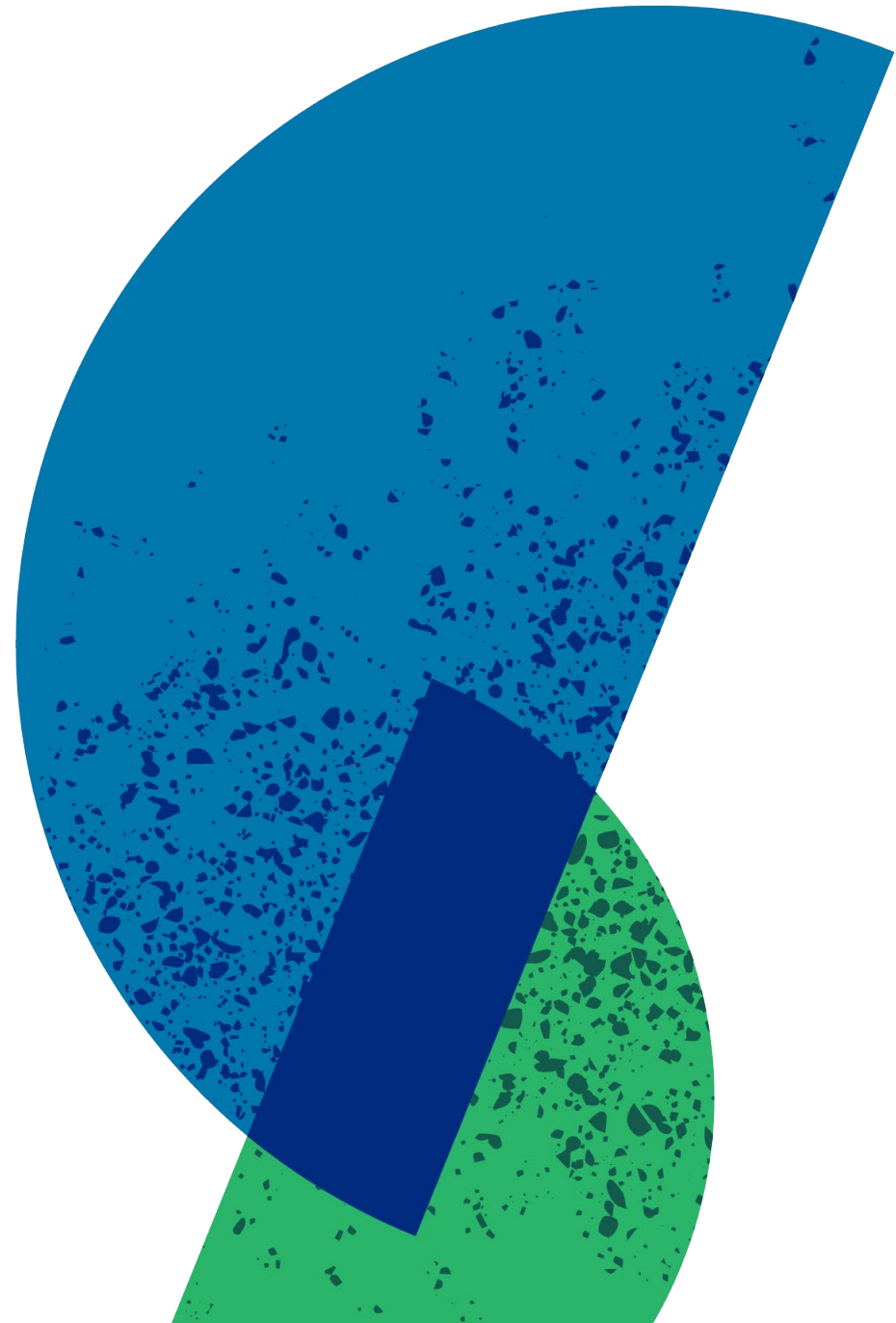
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Biologics Discovery & Early Development

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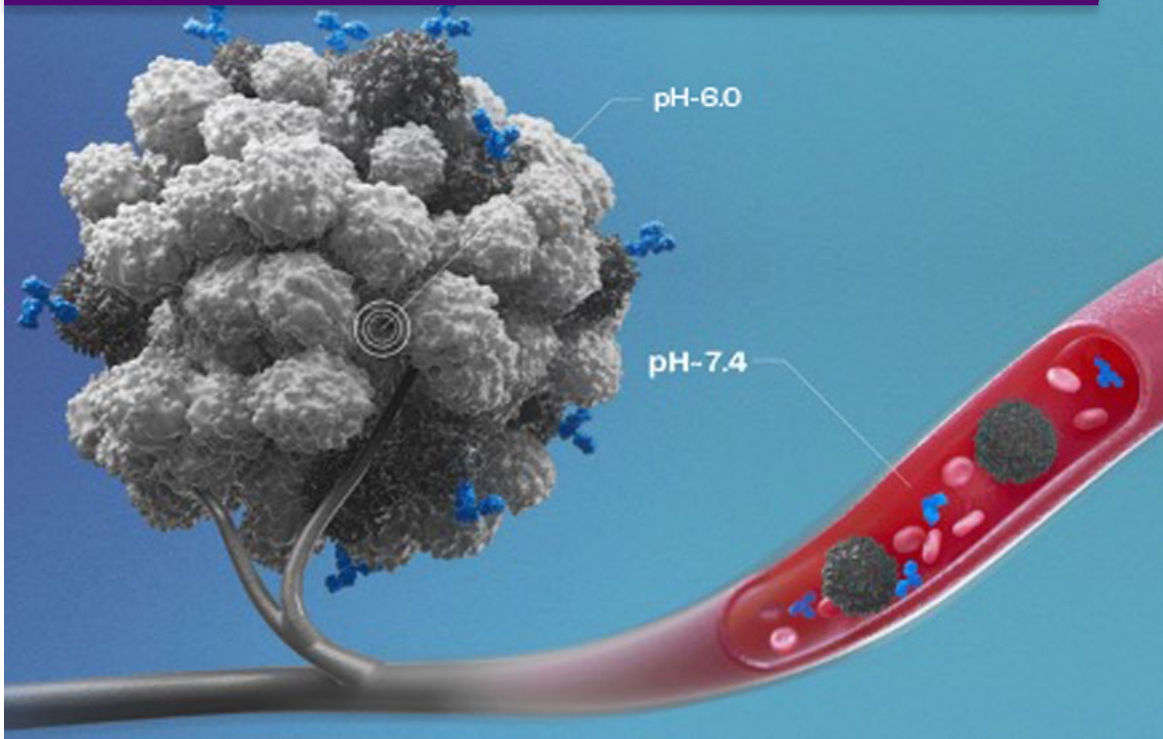
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The TMAb Platform: Antibodies That Selectively Bind to Targets in the Low-pH Tumor Microenvironment

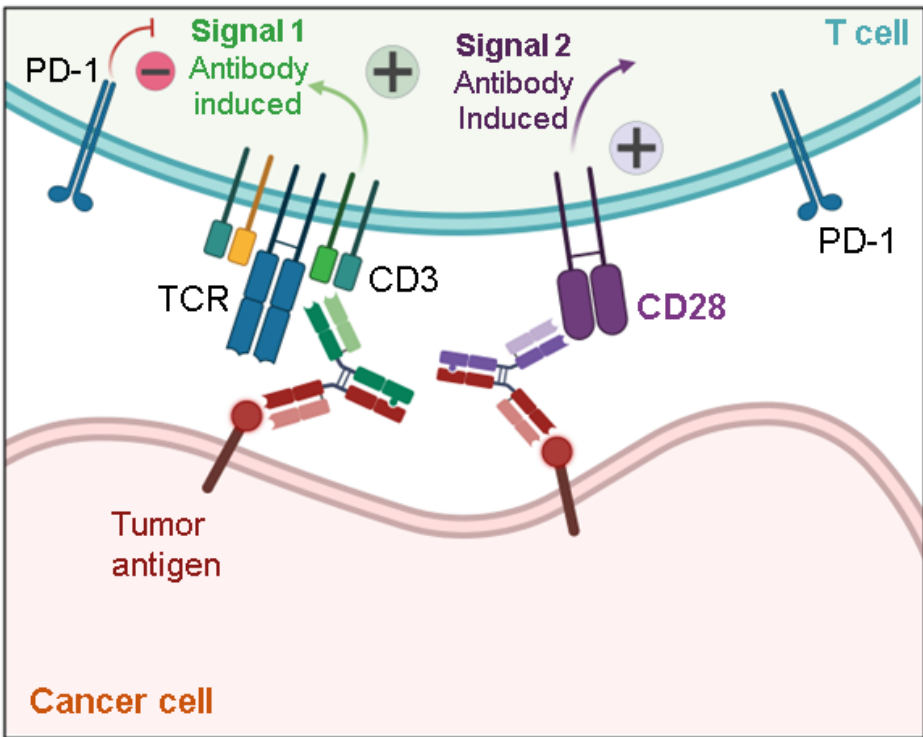
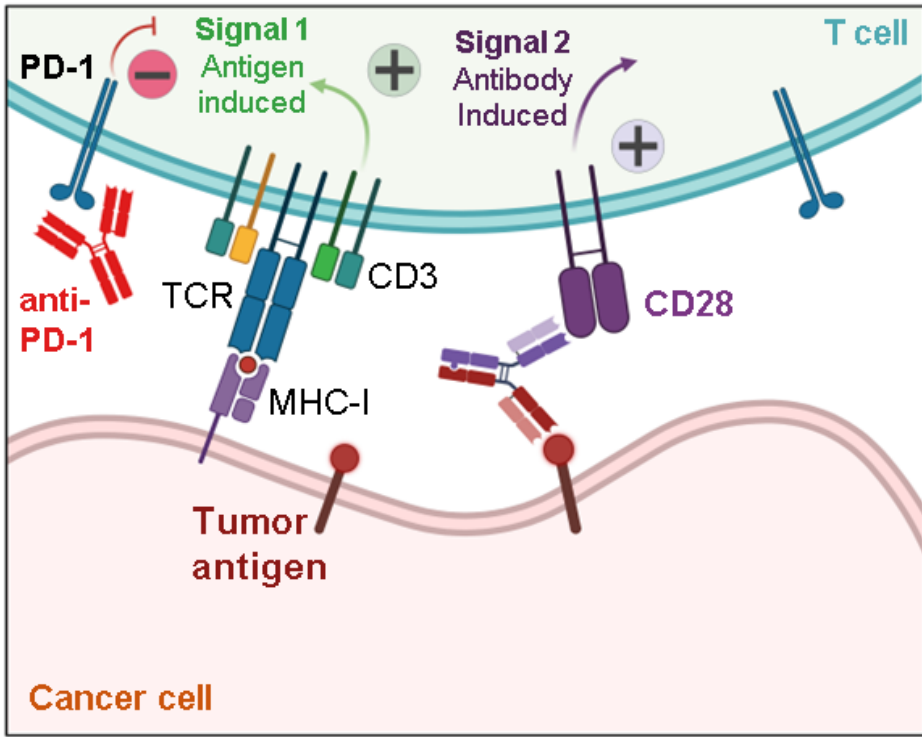
The tumor microenvironment of pH ~6 is lower than physiological pH of 7.4



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

- Exploits the tumor microenvironment using pH-selective properties
- Intended to alleviate undesirable PK/PD properties:
 - Dose-limiting toxicities due to on-target/off-tumor binding
 - Higher and more frequent dosing due to poor pharmacokinetics
- Bolsters specific activities
- Unlocks previously undruggable immune targets

Conventional CD28xTAA T-cell Co-stimulation Approach Requires Specific and Targetable Tumor Associated Antigens (TAAs)



Current CD28-targeted mAb Programs

Table 1 | Industry-sponsored CD28-targeted antibodies in clinical or preclinical development for cancer therapy^a

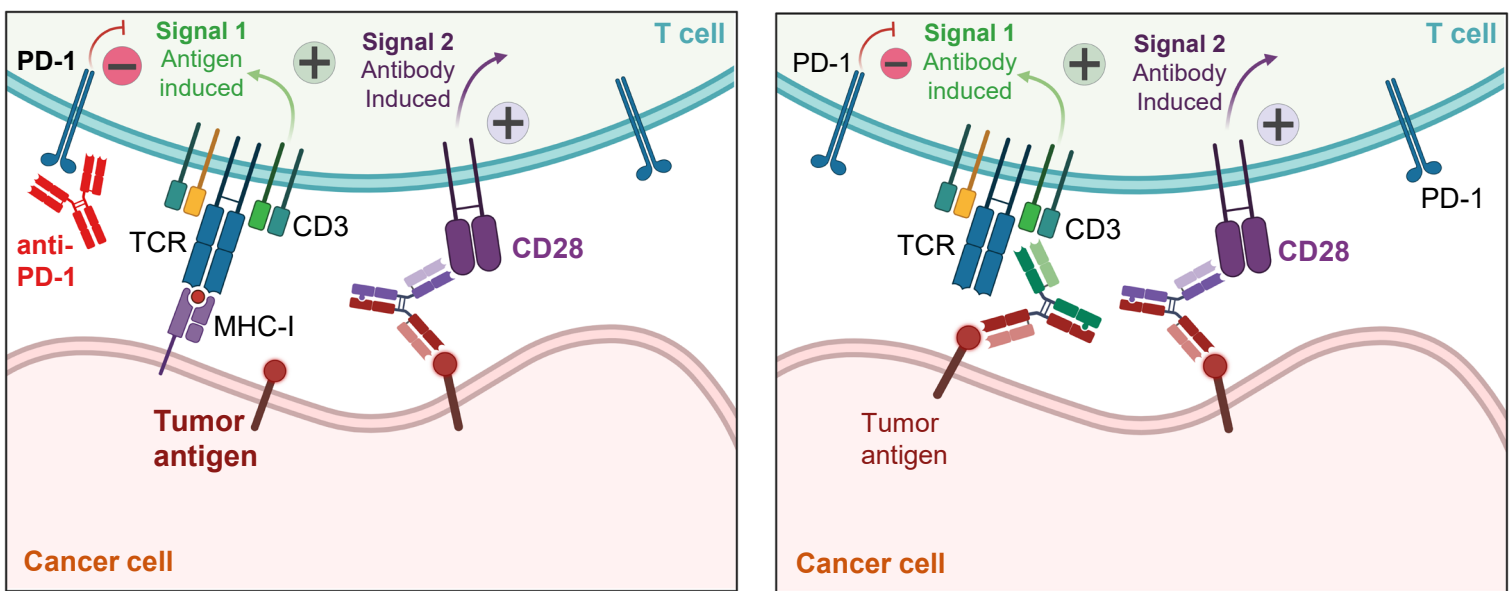
Company	Candidate	Target×CD28	Furthest stage of development	ClinicalTrials.gov trial number	Indication
Bispecific antibodies					
Janssen	JNJ-87189401	PSMA×CD28	Phase I	NCT06095089	Prostate cancer
	JNJ-87801493	CD20×CD28	Phase I	NCT06139406	B cell malignancies
Janux	JANX009	PD-L1×CD28	Preclinical	–	TBD
Light Chain Biosciences/ Novimmune	NI-3201	PD-L1×CD28	Preclinical	–	TBD
LamKap Bio Group	NILK-3301	CEA×CD28	Preclinical	–	TBD
	NILK-3801	GPC3×CD28	Preclinical	–	TBD
Regeneron	REGN5678	PSMA×CD28	Phase I–II	NCT03972657, NCT05125016	Prostate cancer
	REGN7075	EGFR×CD28	Phase I–II	NCT04626635 ¹⁷²	EGFR ⁺ solid tumours
	REGN5668	MUC16×CD28	Phase I–II	NCT04590326	Ovarian cancer
	REGN5837	CD22×CD28	Phase I	NCT05685173	DLBCL
Roche	RG6333 (RO7443904)	CD19×CD28	Phase I	NCT05219513	NHL
Xencor	XmAb808	B7H3×CD28	Phase I	NCT05585034	Solid tumours, prostate cancer
Trispecific antibodies					
CytoCares	CC312	CD19×CD3×CD28	Phase I	NCT06037018	B cell malignancies
Sanofi	SAR443216	HER2×CD3×CD28	Phase I (discontinued)	NCT05013554	Advanced solid tumours
	SAR442257	CD38×CD3×CD28	Phase I (discontinued)	NCT04401020	Haematological malignancies
Tetraspecific antibodies					
Opko/Modex	MDX2001	TAA×TAA×CD3×CD28	Phase I–II	NCT06239194	Solid tumours
	MDX2003	TAA×TAA×CD3×CD28	Preclinical	–	B cell malignancies
Others					
Alpine	Davoceticept (ALPN-202) ^b	PD-L1×CD28/ CTLA4+PD-L1 ICB	Phase I (discontinued)	NCT04186637, NCT04920383	Solid tumours
Five Prime/Amgen	FPT155	CD28	Phase I (discontinued)	NCT04074759	Solid tumours
TeGenero	TGN1412	CD28	Phase I (discontinued)	–	Healthy volunteers

DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; NHL, non-Hodgkin lymphoma; TAA, tumour-associated antigen; TBD, to be determined. ^aAs of 27 May 2024.

^bCD80 ectodomain binds both CD28 and CTLA4.

Sensei's CD28xVISTA Bispecific MOA Bypasses TAA Requirement

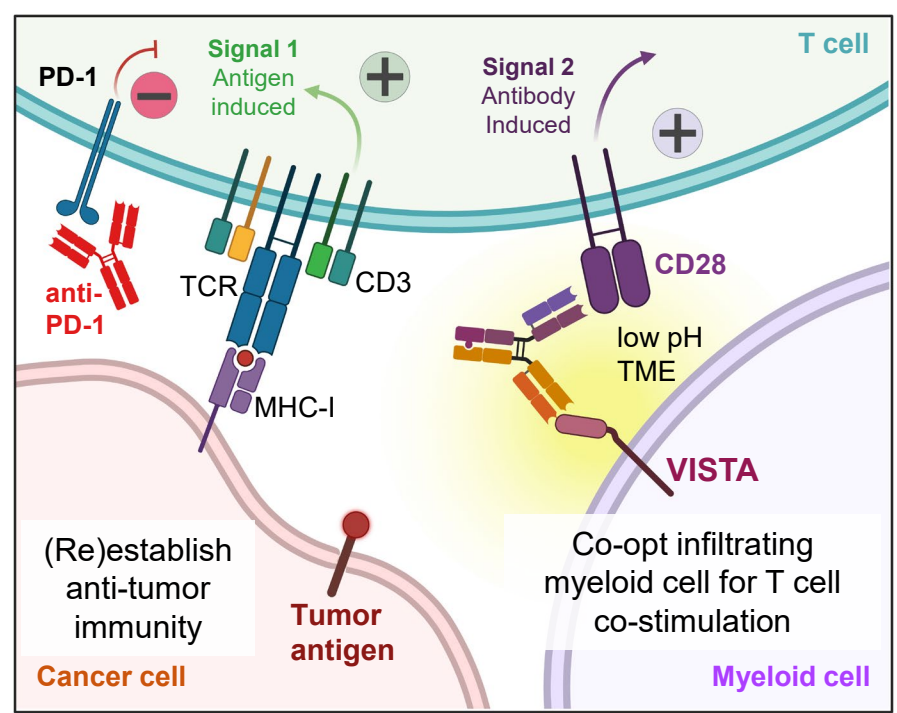
Conventional CD28xTAA co-stimulation approach



cis

- Requires specific and targetable tumor associated antigens (TAAs)

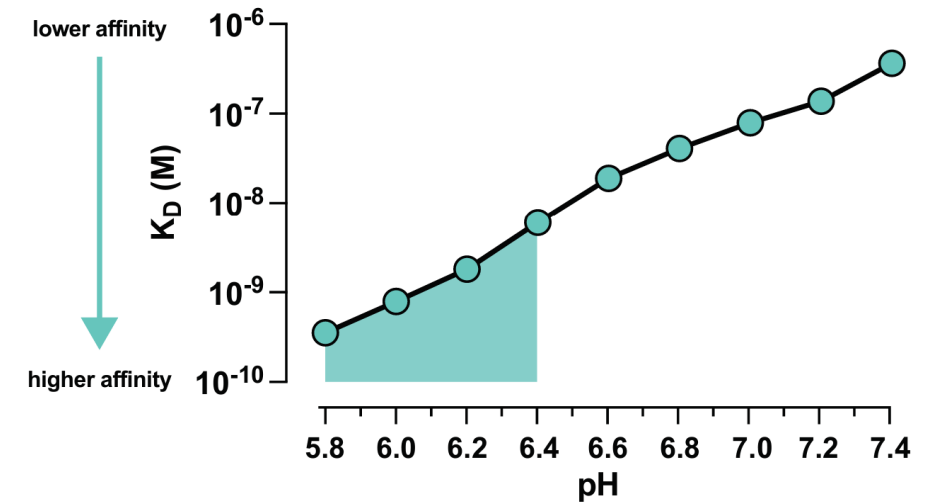
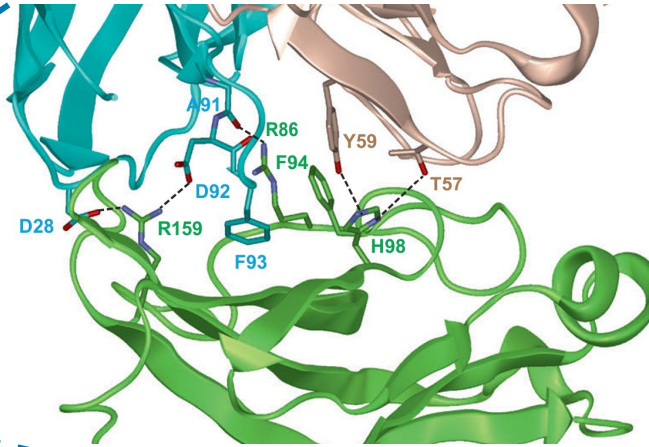
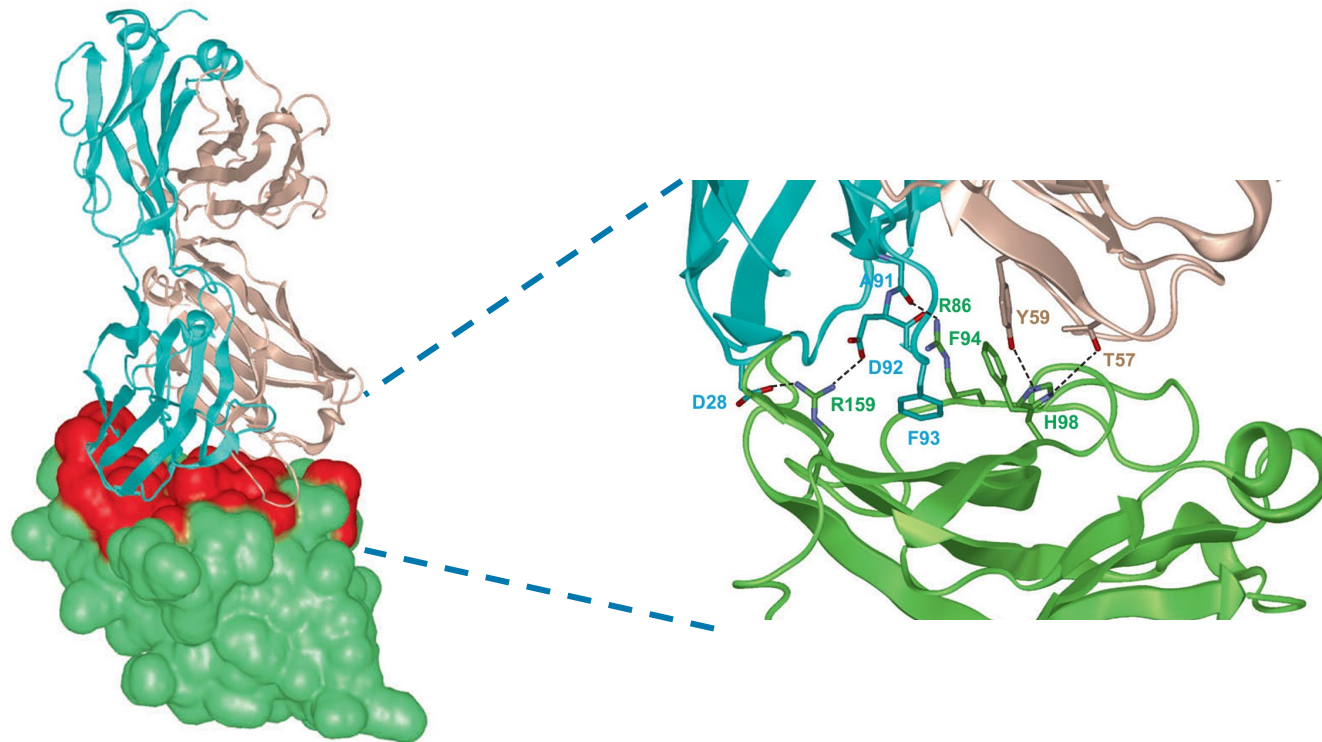
Sensei's tumor-targeted agonist approach



trans

- pH-selective VISTA binding ensures potency in TME with minimal risk of systemic CRS

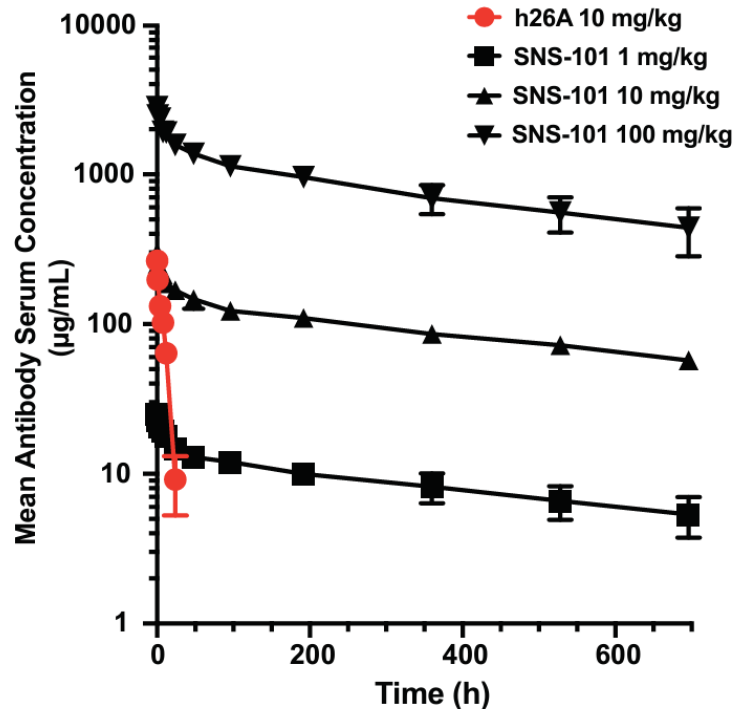
Sensei's pH-selective VISTA Binding Fab



(Thisted *et al.*, *Nat Commun* 15, 2917 (2024))

- Anti-VISTA Fab discovery by pH-selective selection strategies of a yeast-based display library
- Protonation of key His-residues in epitope/paratope interface at low pH responsible for pH-selective binding

pH-selective VISTA Binding Fab Ensures No TMDD and Rapid Tumor Accumulation

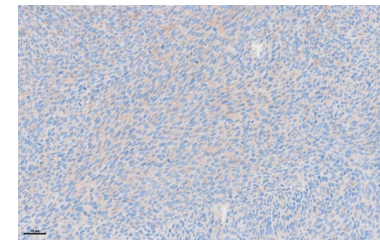


(Thisted *et al.*, *Nat Commun* 15, 2917 (2024))

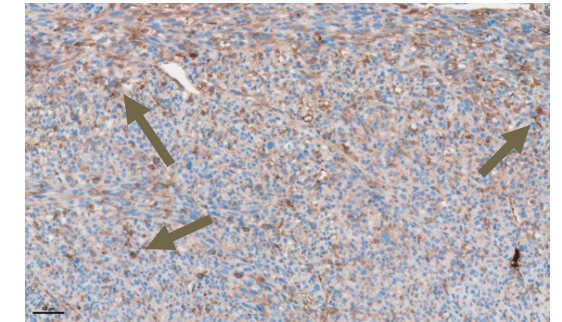
- VISTA⁺ myeloid cells are abundant outside tumor; pH-selective binding abrogates TMDD
- VISTA binding at low pH leads to efficient tumor accumulation

Tumor (Acidic pH)

SNS-101 rapidly accumulates in the tumor



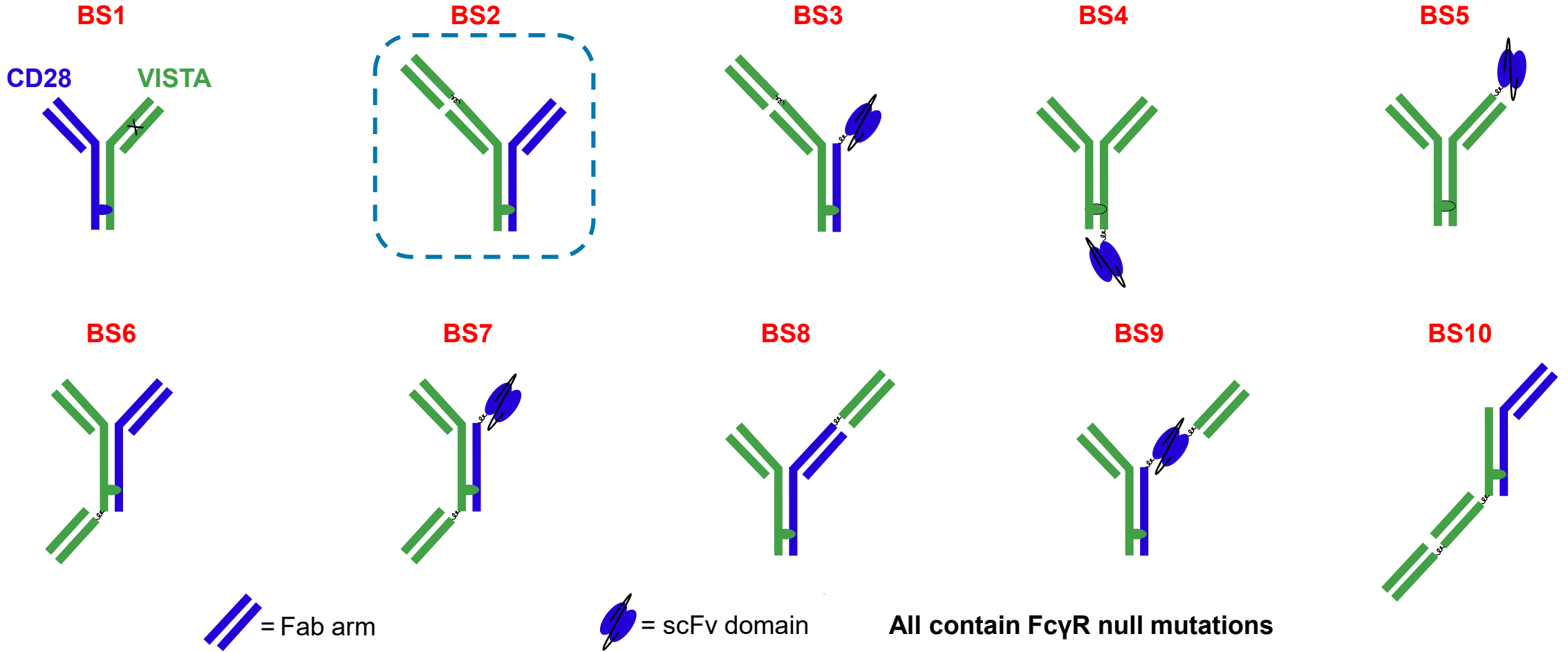
Isotype control
6h post-dosing



SNS-101
6h post-dosing

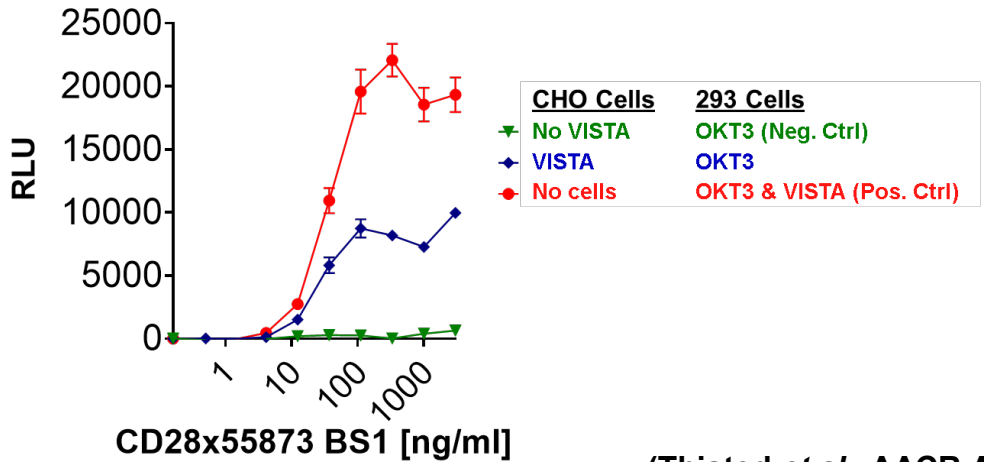
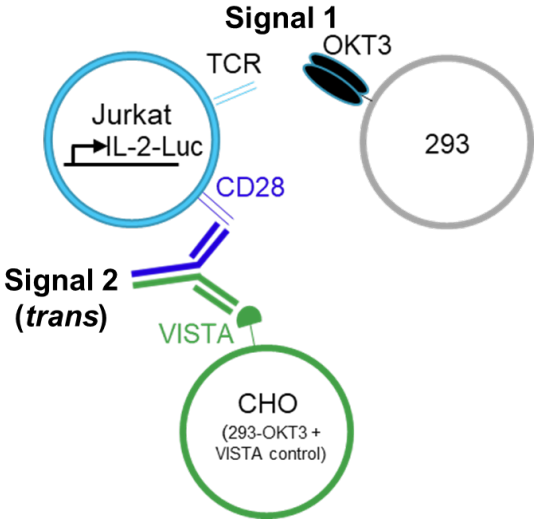
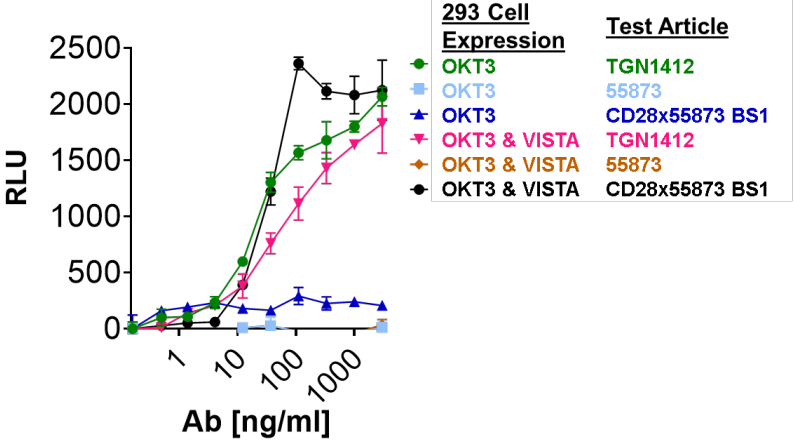
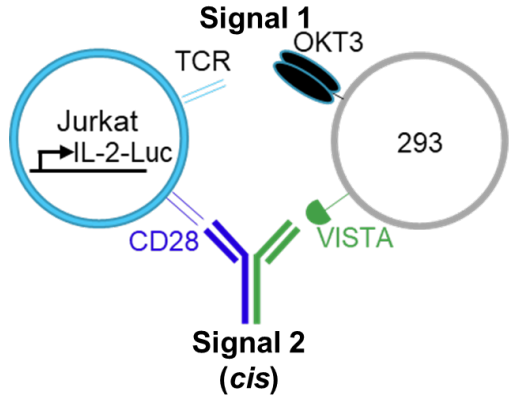
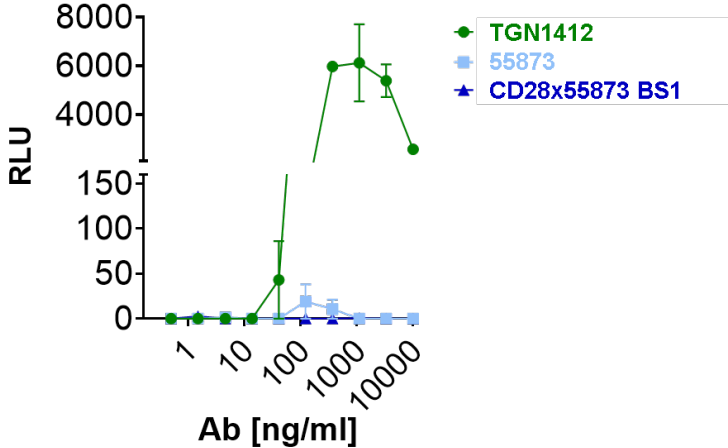
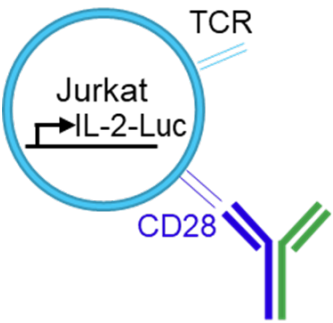
Blue = tumor
Brown = SNS-101

CD28xVISTA Bispecifics Exhibit Favorable Properties



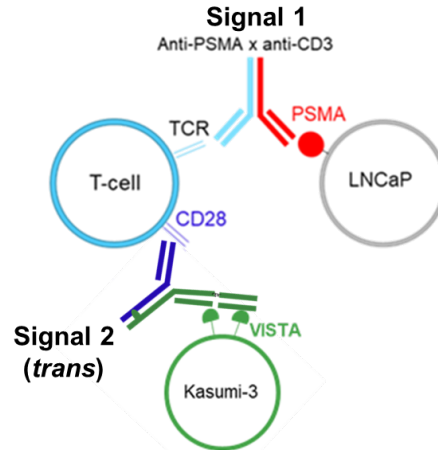
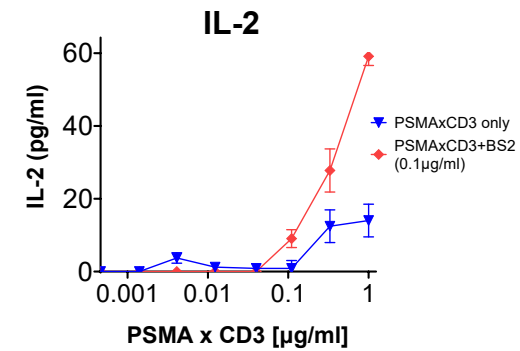
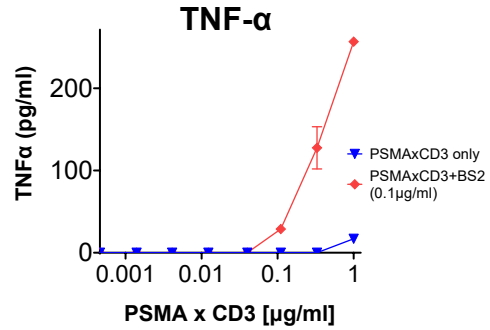
- High transient expression levels, monomeric purity, and thermal stability comparable to starting mAb's
- Efficient (but variable) simultaneous target engagement (ELISA, SPR, cell binding assays)

CD28xVISTA bsAb Induces IL-2–luciferase Reporter Expression in *cis* and in *trans*

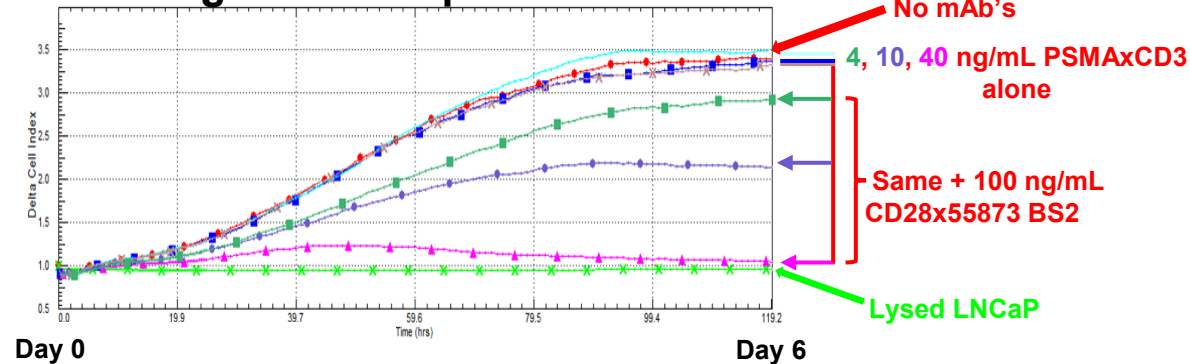


CD28xVISTA mAb Potentiates a PSMAxCD3 Bispecific T-cell Engager

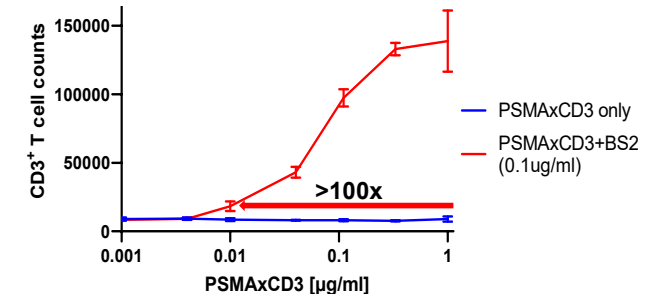
Cytokine release (Day 1)



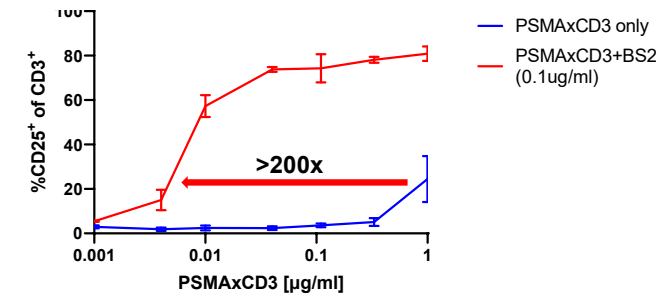
T-cell killing of LNCaP prostate cancer cells



T-cell proliferation (Day 6)



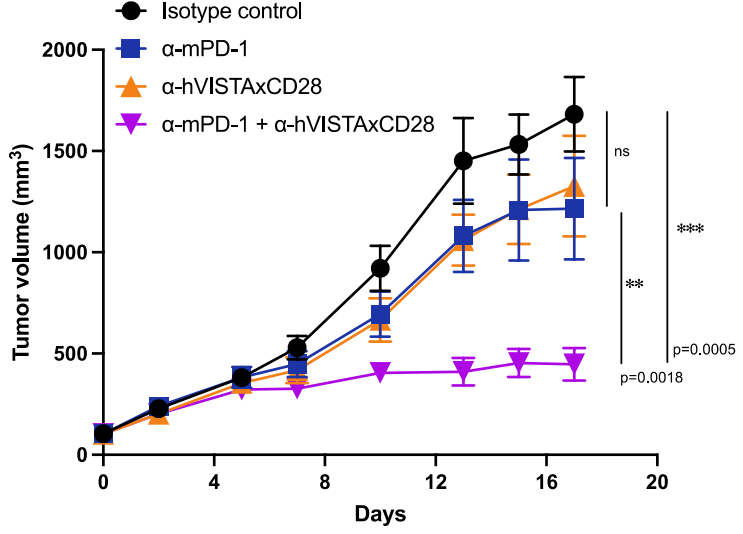
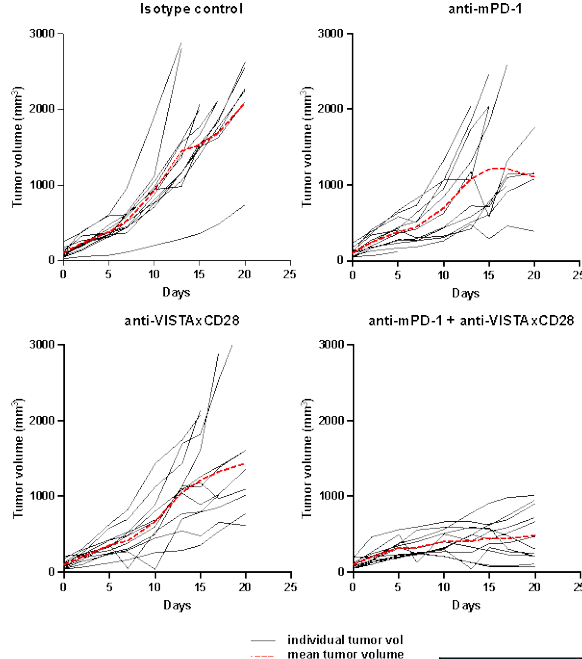
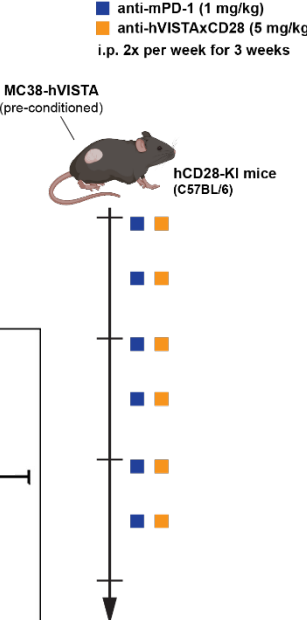
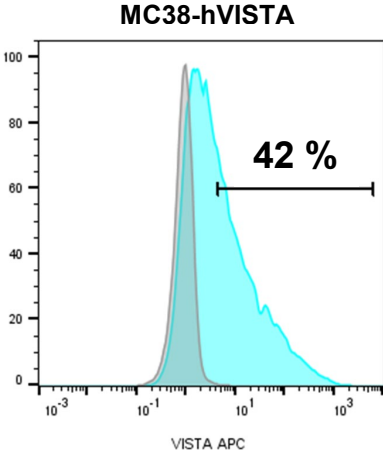
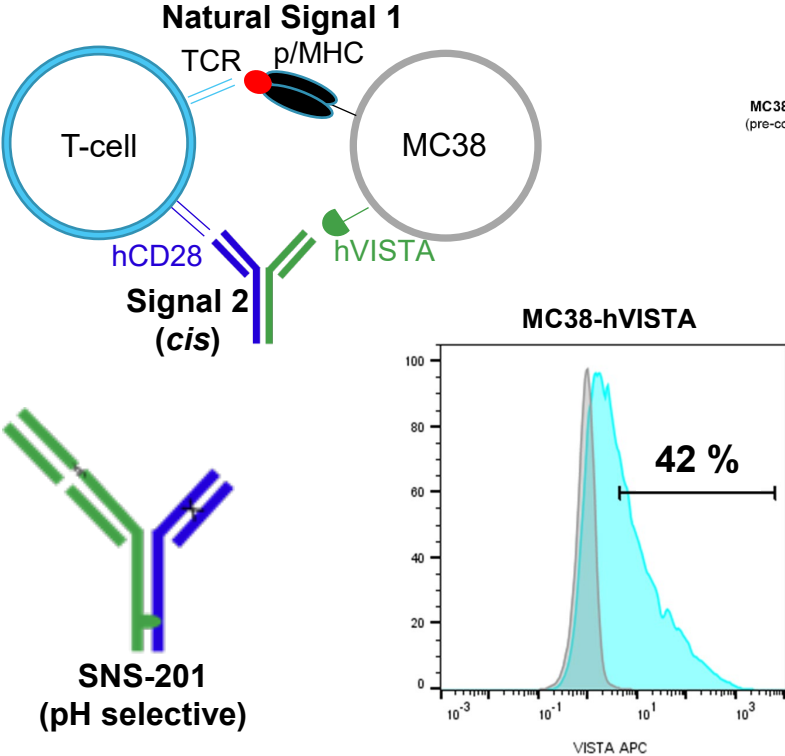
T-cell activation (Day 6)



Signal 1
Signal 1 + Signal 2 (*trans*)

- CD28xVISTA BS2 potentiates LNCaP killing by a PSMAxCD3 bispecific mAb in *trans*
- Enhances T-cell activation, proliferation and cytokine release
- No effect in the absence of Signal 1: *no super-agonistic properties*

CD28xVISTA bsAb SNS-201: Inhibition of MC38-hVISTA Tumor Growth in hCD28 KI Mice in Combination with anti-PD-1



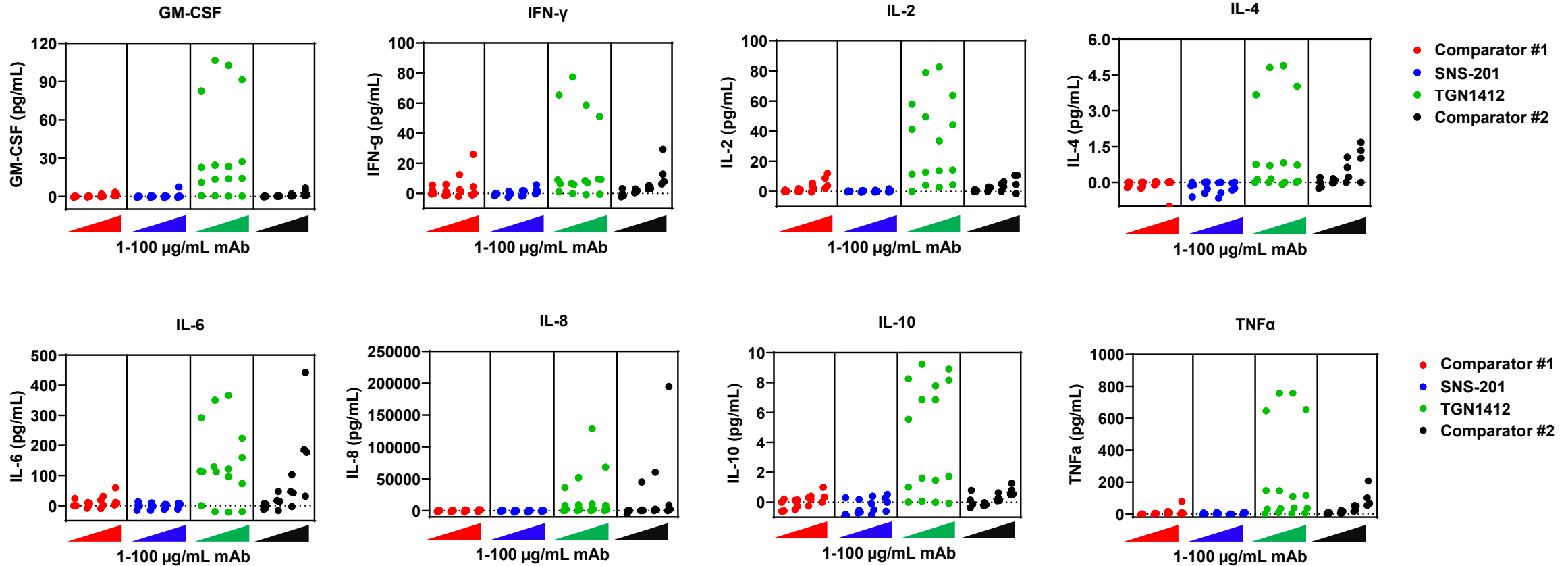
- CD28xVISTA BS2 antibody (SNS-201 with pH-selective VISTA engagement) induces significant tumor growth inhibition in combination with anti-mPD-1
- Efficient tumor control despite highly heterogeneous tumor cell population

Group	Treatment	TGI at D17 (%)
1	Isotype Control	0.0
2	anti-mPD-1 1 mg/kg	27.4
3	anti-VISTAxCD28 5 mg/kg	28.0
4	anti-mPD-1 1 mg/kg + anti-VISTAxCD28 5 mg/kg	73.4

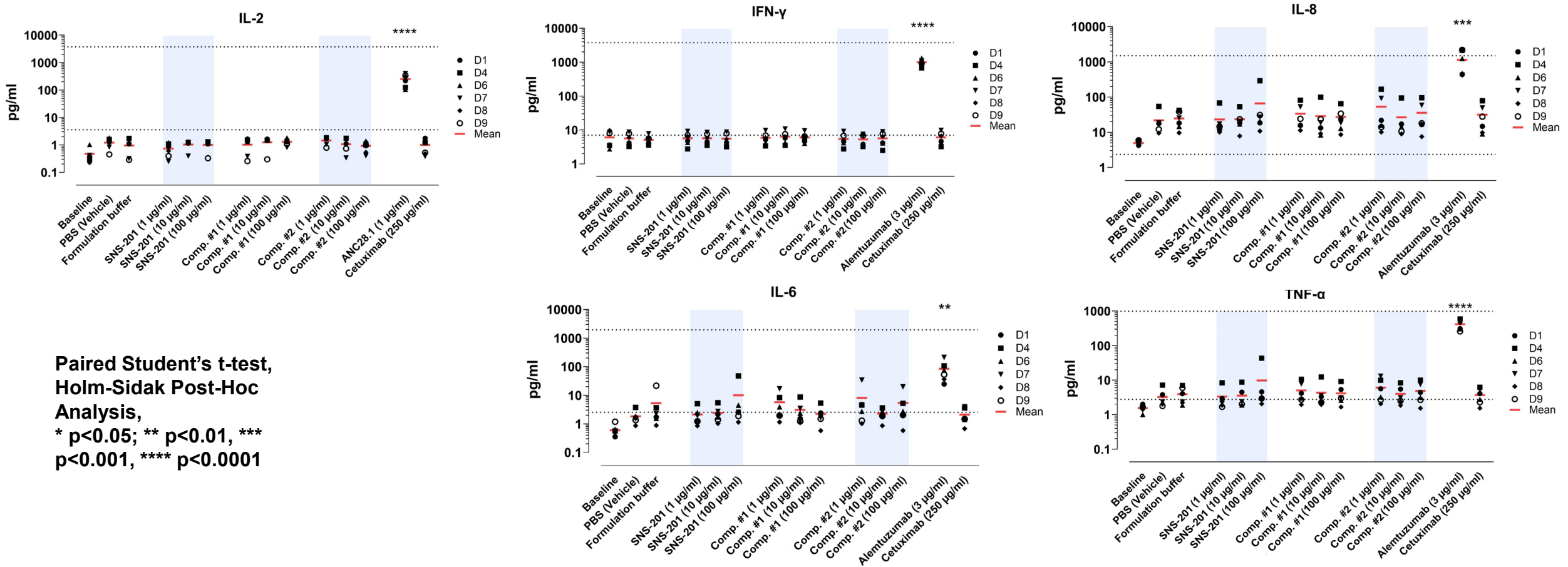
TGI = Tumor growth inhibition



SNS-201 Does Not Induce Significant Cytokine Release in HUVEC:PBMC Co-culture Assays



SNS-201 Does Not Induce Significant Cytokine Release in Sensitive *ex vivo* Whole Blood ID.Flow Assays



Paired Student's t-test,
Holm-Sidak Post-Hoc
Analysis,
* p<0.05; ** p<0.01, ***
p<0.001, **** p<0.0001

- *Ex vivo* assay with fresh whole blood in constant circulation to mimic human blood circulation (ID.Flow)
- No significant response compared to negative Control up to 100 µg/mL

Conclusion

A conditionally active CD28xVISTA bsAb was developed as a TME-specific CD28 agonist

- SNS-201 potentiates LNCaP cancer cell killing by a CD3xPSMA T-cell engager *in vitro*
- SNS-201 shows effective TGI inhibition of MC38-hVISTA tumors in hCD28 KI mice in combination with anti-PD-1 (natural Signal 1)
- SNS-201 displays a good safety profile with no “super-agonistic” properties and no induction of cytokine release in physiological relevant assays
- PK profile in hCD28 KI mice is favorable
- SNS-201 has good developability properties

SNS-201 bsAb could complement PD-1/PD-L1 inhibitors or enhance bispecific T-cell engagers' selectivity and efficacy by targeting dual/orthogonal antigens on tumor and myeloid cells

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- **Vikas Saxena**
- **F. Donelson Smith**