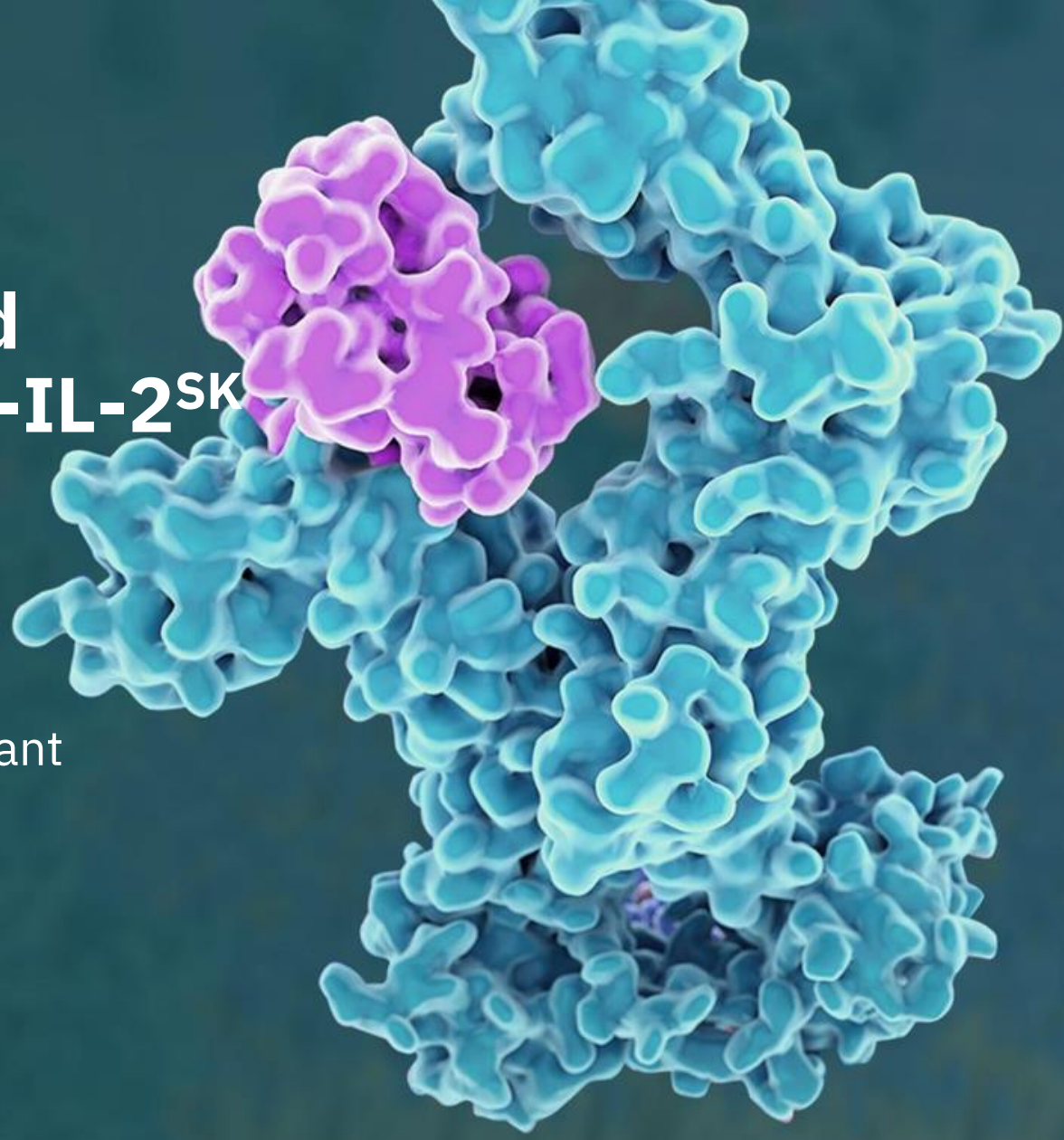
AACR 2025, 30th April

MDNA113: A tumor targeting and conditionally activated anti-PD1-IL-2^{SK} to enhance therapeutic index



Minh D. To, Qian Liu, Rosemina Merchant, Fahar Merchant and Aanchal Sharma

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MDNA113 is a Tumor Targeting & Conditionally Activated *Cis*-Binding Anti-PD1-IL-2^{SK} BiSKIT

IL-13 Superkine (IL-13^{SK})

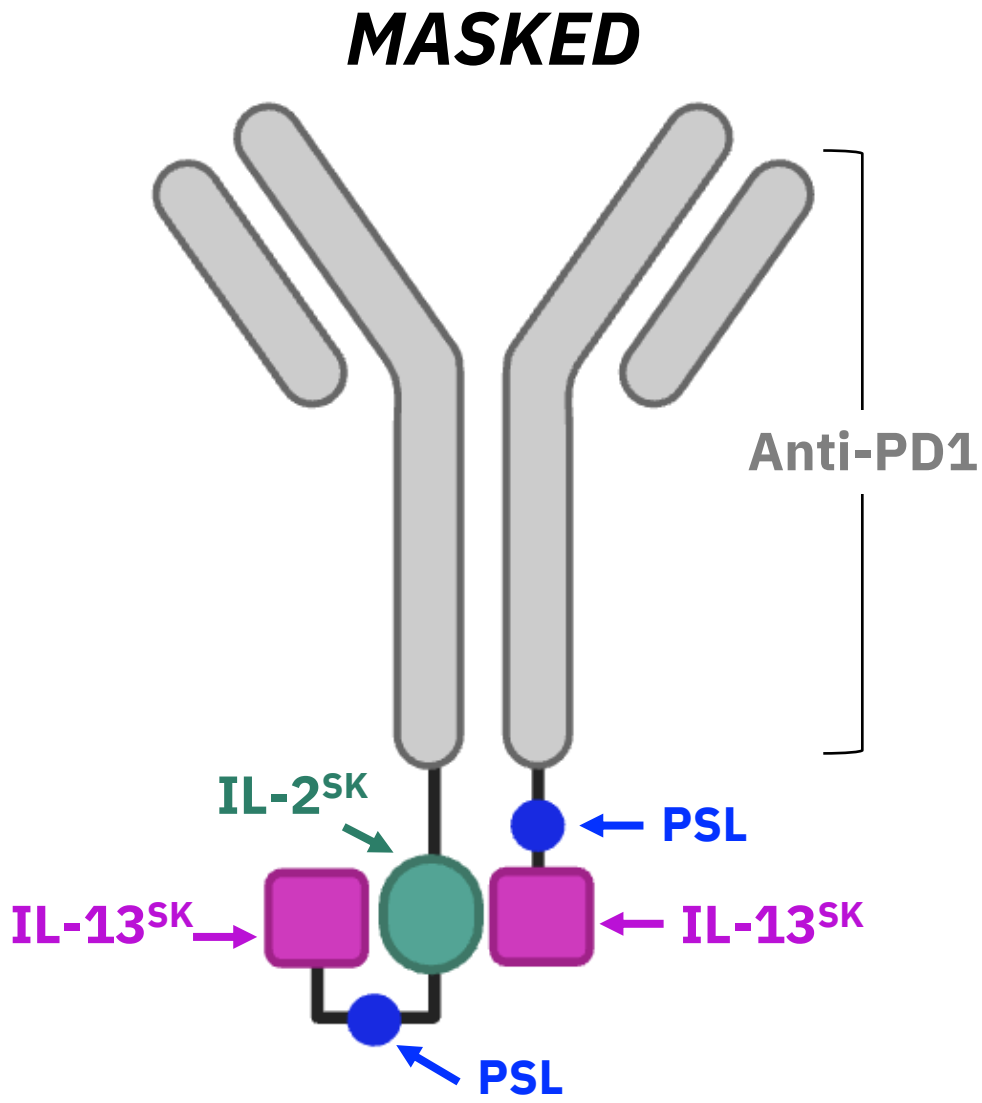
- **Tumor Targeting -** specific binding to decoy receptor **IL-13Rα2**, a tumor associated antigen (TAA)
- **Enhances Tolerability -** attenuates systemic immune stimulation by sterically hindering IL-2^{SK}

'β-enhanced not-α' IL-2 Superkine (IL-2^{SK})

- Preferential activation of immune effector cells (CD8^{+} T and NK cells)

Protease Sensitive Linker (PSL)

- Cleavage by matrix metalloproteases (MMPs) releases IL-13^{SK}, unmasking IL-2^{SK}



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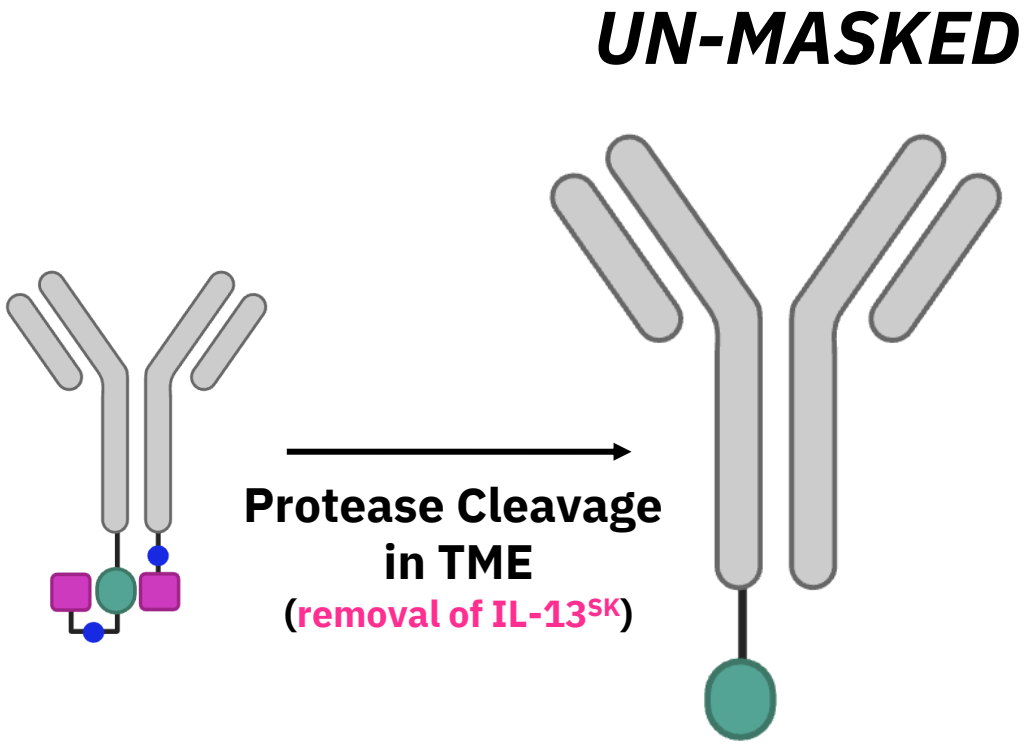
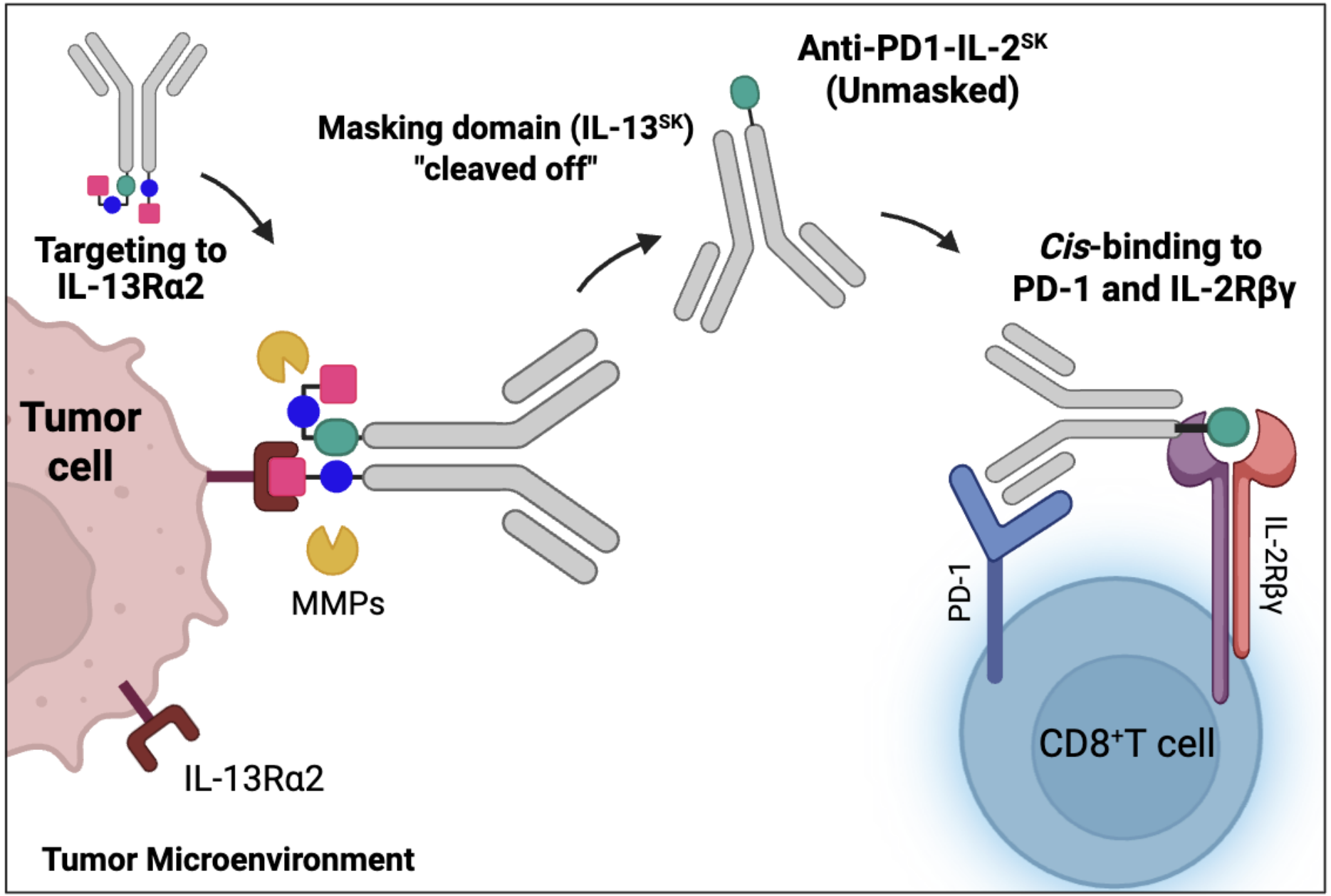


Unleashes immune effector activity within the TME

- *Cis*-binding to IL-2R and PD1 on CD8^{+} T cells
- Maximizes synergy between immune cell activation (by IL-2^{SK}) and immune checkpoint blockade (by anti-PD1)

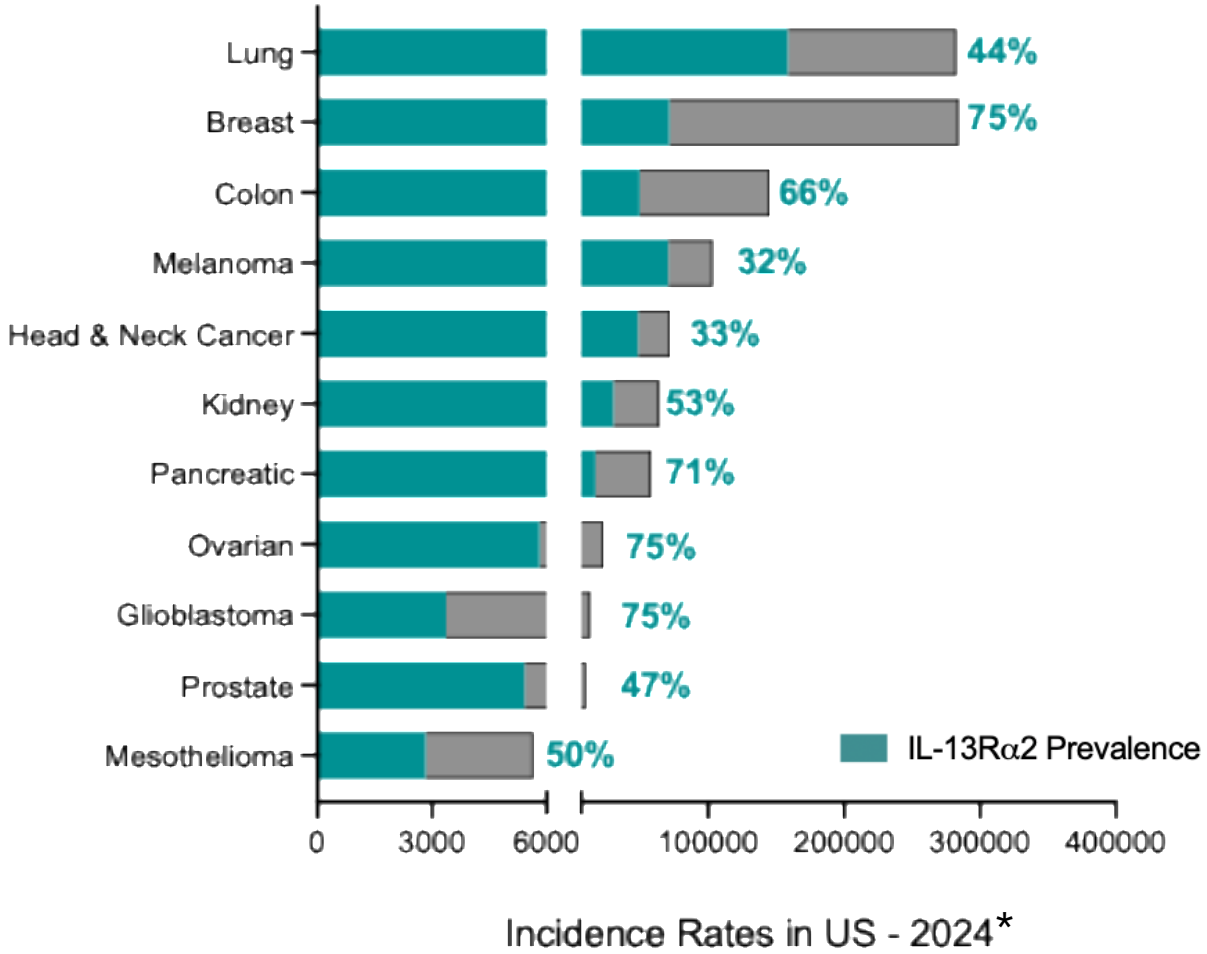
MDNA113: Mechanism of Action



IL-13Rα2: A Tumor Associated Antigen that Enables Targeted Immunotherapy

IL-13Rα2 expression is associated with unfavorable clinical outcomes in multiple cancers
(limited expression in normal tissues)

IL-13Rα2 Positive Cancers Annual World-Wide Incidence > 2M



PMID Nos.: 26208975, 11454721, 20179235, 22505647, 33917914, 36806727, 14695138 and OMCA database

*GlobalData source

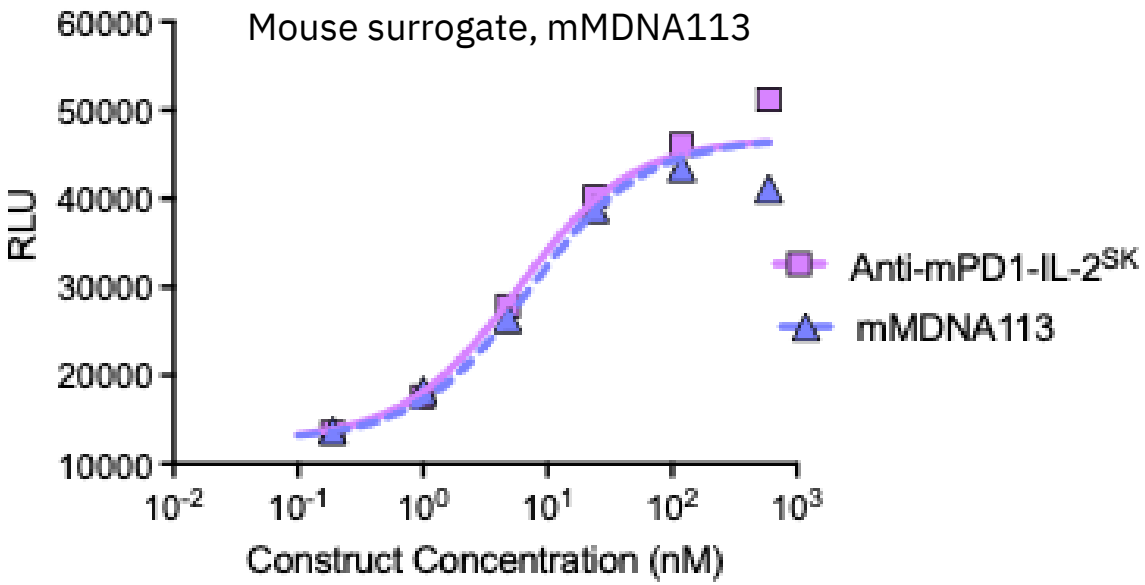
MDNA113 is Designed with a Unique Profile to Optimize Immuno-Oncology Efficacy & Safety

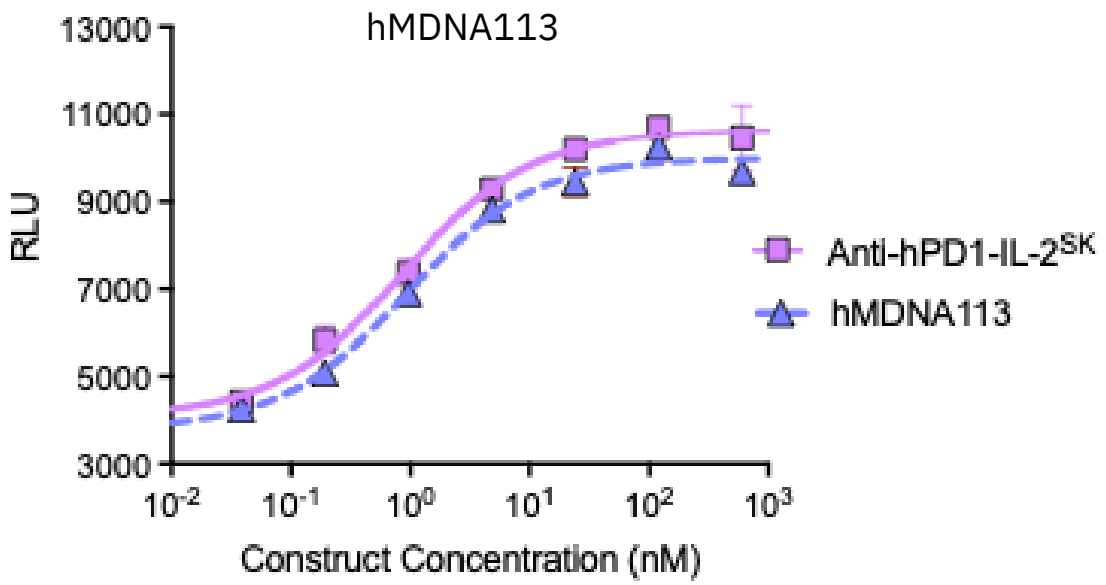
Differentiation of MDNA113 to other Bifunctional Anti-PD1-IL-2 Clinical Candidates

KEY FEATURES	Medicenna MDNA113	Other IL-2/anti-PD-1 candidates
β–enhanced and not-α IL-2^{SK} (clinically validated)	✓	✗
Tumor Specific Targeting (IL-13Rα2)	✓	✗
PD-1/PD-L1 Blockade (clinically validated)	✓	✓/✗
Cis-binding (IL-2R/PD-1) (Synergistic engagement potentiates immune activation)	✓	✓/✗
IL-2^{SK} attenuated in periphery	✓	✓/✗
IL-2^{SK} activated in TME	✓	✓/✗

MDNA113 Retains PD-1/PDL-1 Blockade but Exhibits Attenuated IL-2R Signaling

PD-1/PDL-1 Blockade is Maintained





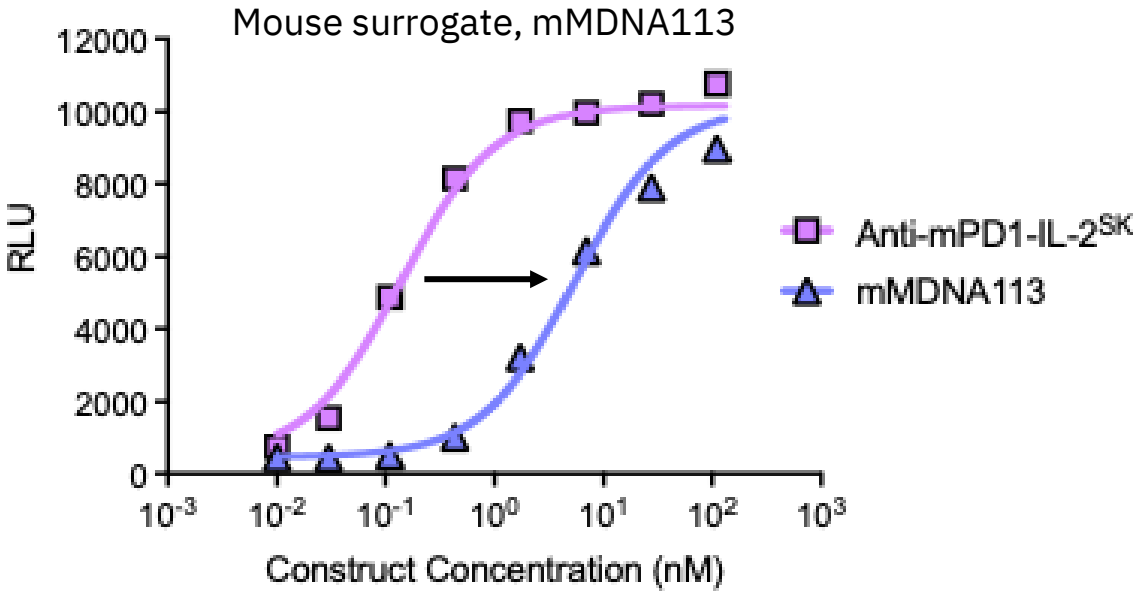
	EC_{50} (nM)
Anti-mPD1-IL-2^{SK} (No Mask)	8.8
mMDNA113 (Masked)	11.0

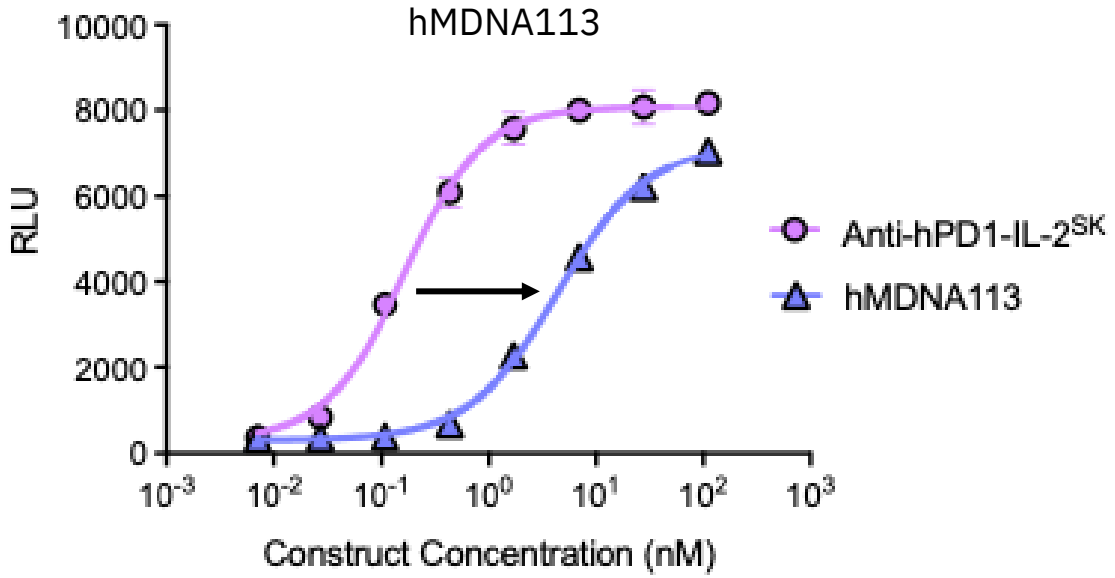
	EC_{50} (pM)
Anti-hPD1-IL-2^{SK} (No Mask)	878
mMDNA113 (Masked)	944

- PD-1/PD-L1 reporter assay: co-culture of PD-1 reporter cells and PD-L1 aAPC/CHO-K1 cells for 6 h followed by addition of luciferase substrate for luminescence
- Mouse and Human PD-1/PD-L1 reporter assays respectively from Promega

MDNA113 Retains PD-1/PDL-1 Blockade but Exhibits Attenuated IL-2R Signaling

IL-2R Agonism is Attenuated



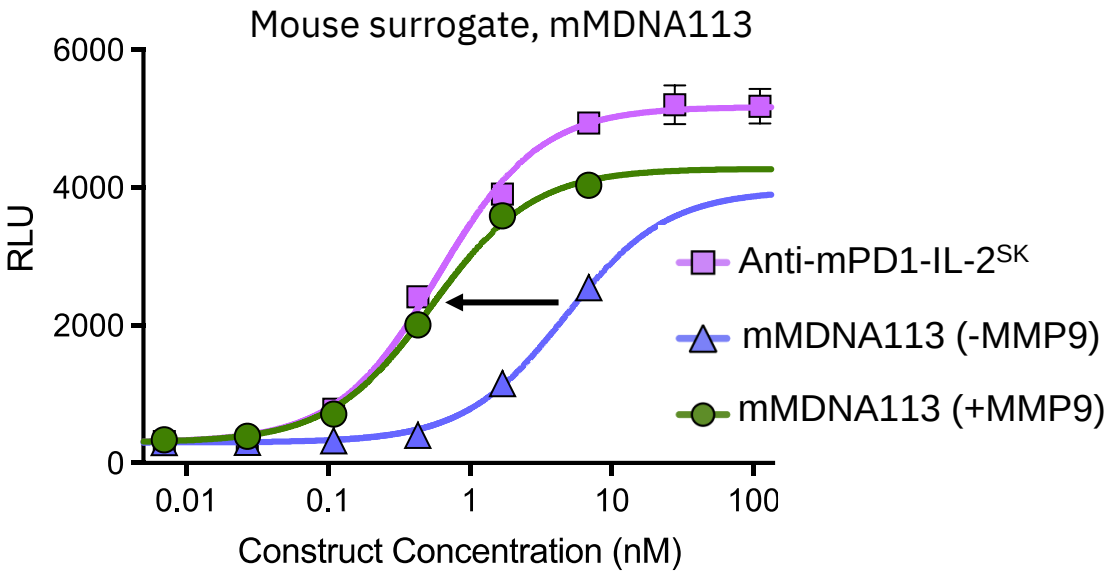


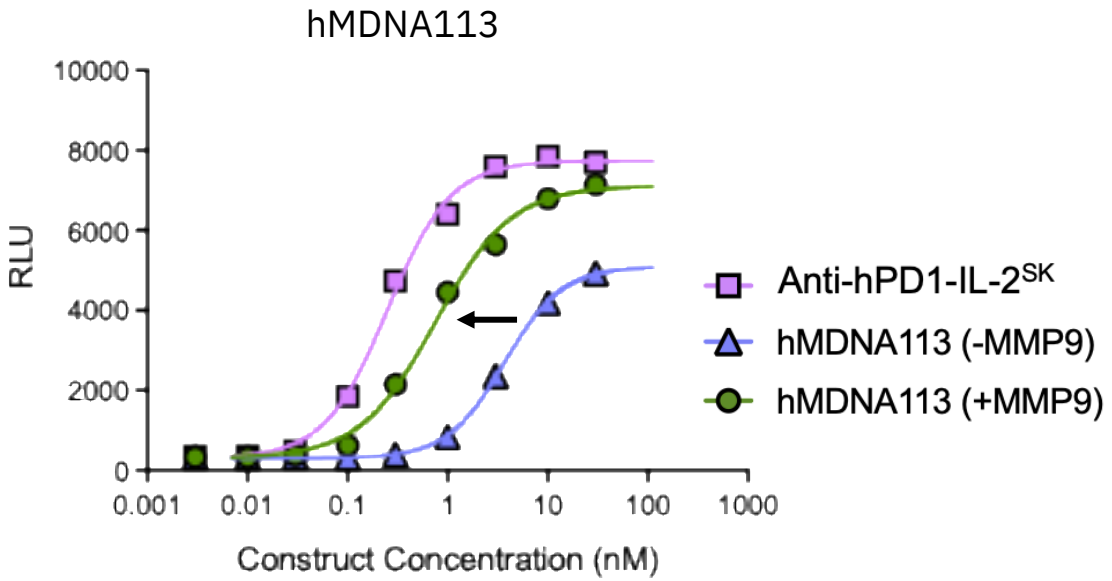
	EC_{50} (pM)	
Anti-mPD1-IL-2^{SK} (No Mask)	137	
mMDNA113 (Masked)	5313	↓ **38x**

	EC_{50} (pM)	
Anti-hPD1-IL-2^{SK} (No Mask)	164	
hMDNA113 (Masked)	4414	↓ **27x**

Jurkat IL-2Rβγ bioassay; cells lacking CD25 expression from Promega
RLU = relative luminescence unit
Cells were treated with increasing concentration of constructs for 6 h following which the plate was read for luminescence.

MMP9 Cleavage Releases IL-13^{SK} and Restores IL-2R Agonism





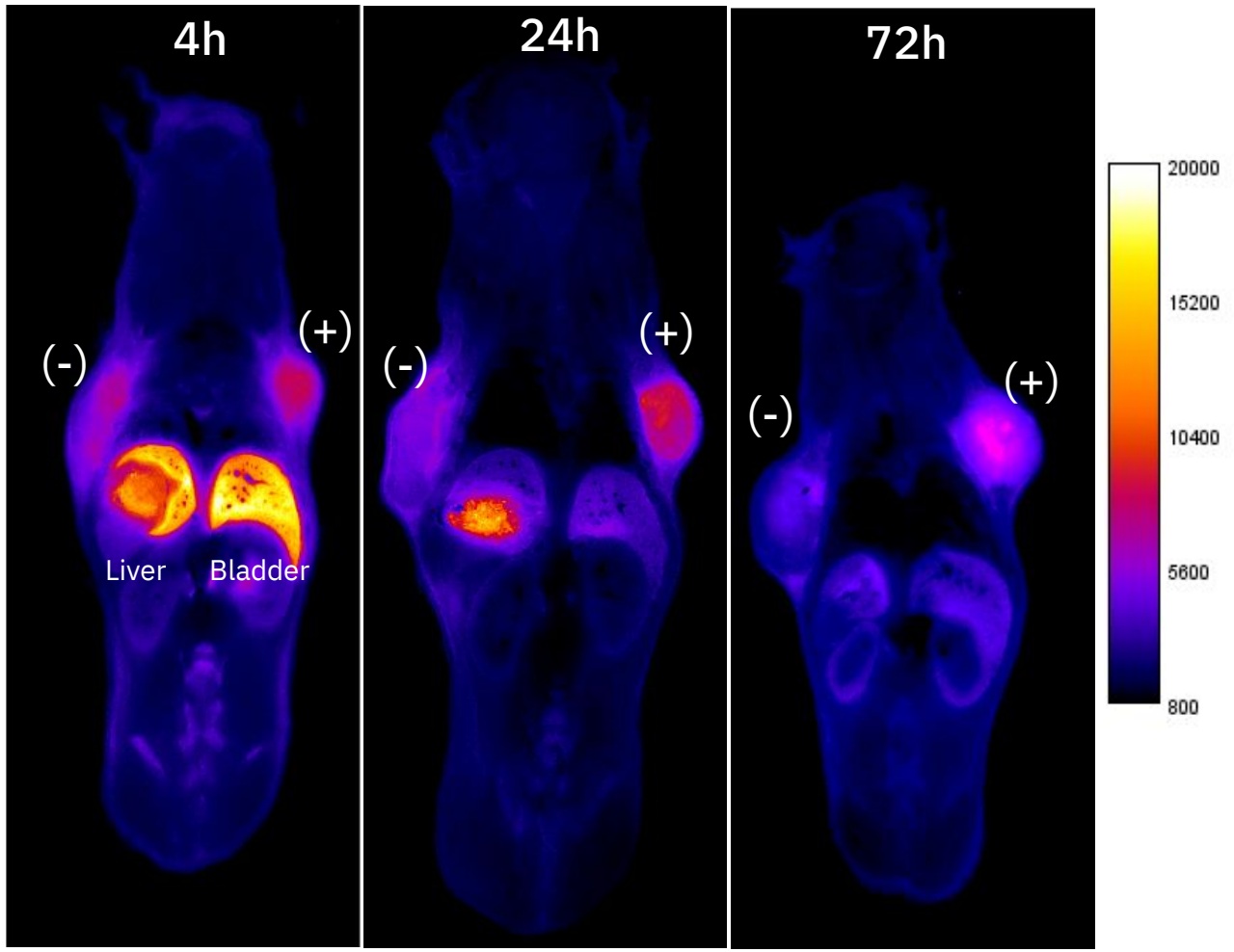
	EC_{50} (pM)
Anti-mPD1-IL-2^{SK} (No Mask)	597
mMDNA113 (-) MMP9	4477
mMDNA113 (+) MMP9	532

	EC_{50} (pM)
Anti-hPD1-IL-2^{SK} (No Mask)	251
hMDNA113 (-) MMP9	3694
hMDNA113 (+) MMP9	756

Jurkat IL-2Rβγ bioassay lacking CD25 expression RLU = relative luminescence unit
rMMP9 incubation at 5 µg/mL at 37°C for 1 h

Preferential Tumor Localization & Retention of MDNA113 in IL-13Rα2 Expressing Tumors

Biodistribution of Cy5-labeled hMDNA113 by Cryo Fluorescence Tomography*



(-) = IL-13Rα2 negative, (+) = IL-13Rα2 positive

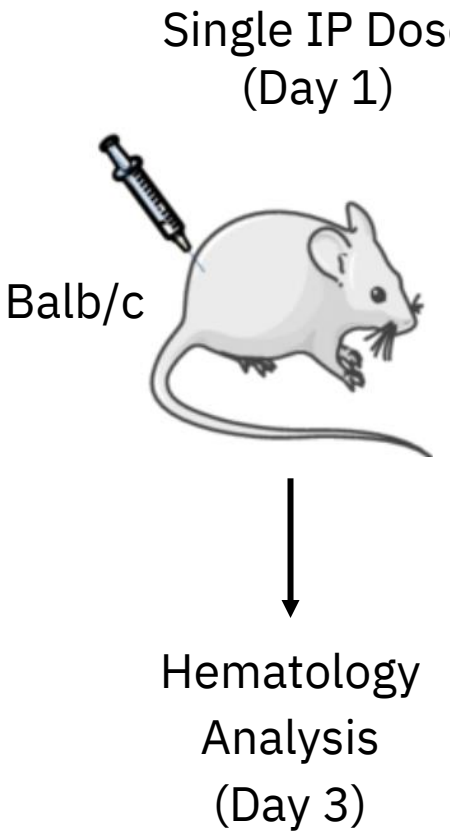
Observations:

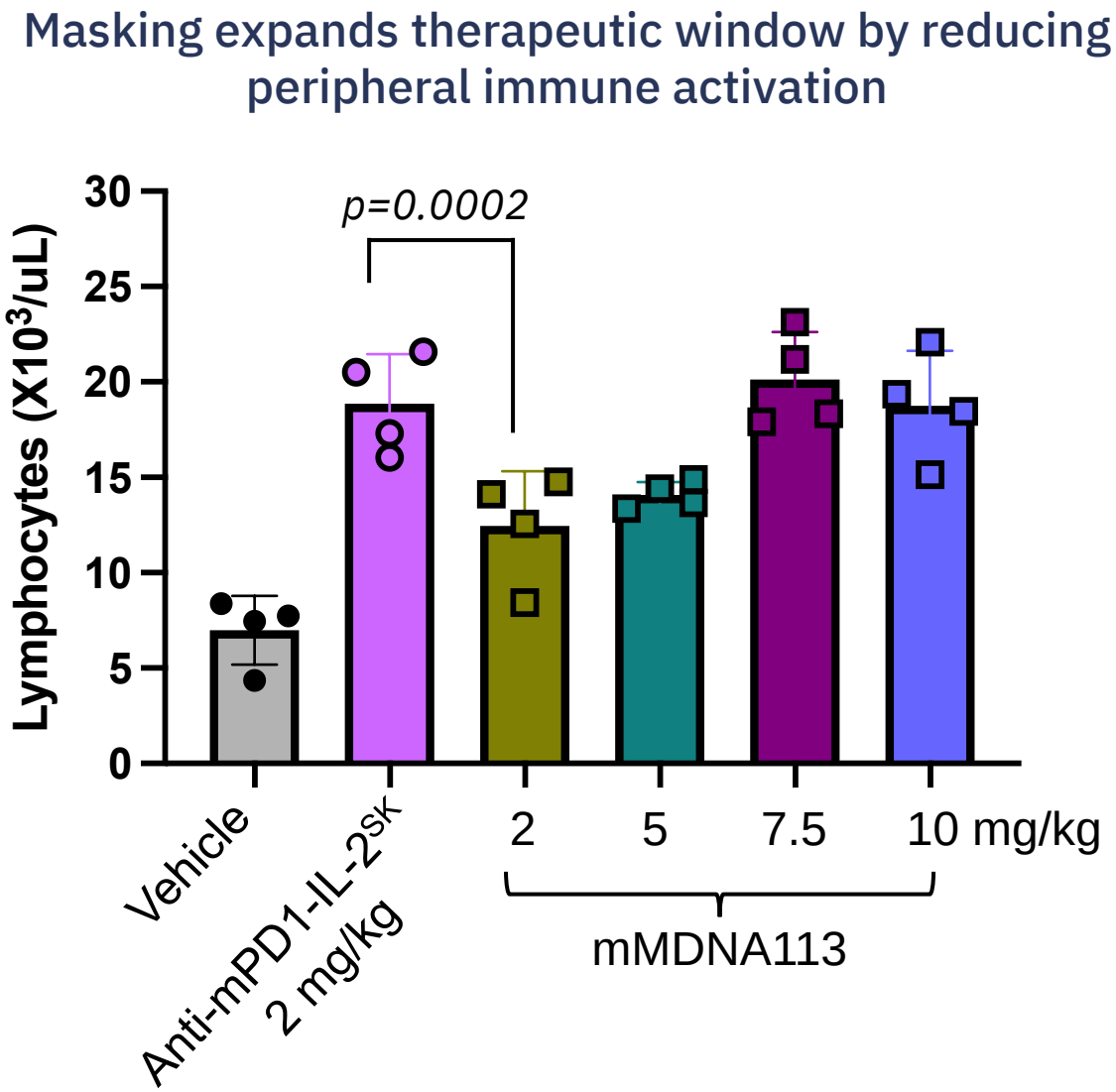
- Initial (4 h) high signal in tumors along with liver and bladder as well as kidneys and gallbladder (not shown)
- At 24 h, signal retained in tumors with reduced intensity in liver and kidney
- At 72 h, signal detected on in the IL-13Rα2$^{(+)}$ tumor

MC38 (IL-13Rα2 negative, left flank) and MC38/IL-13Rα2 (expressing human IL-13Rα2, right flank) tumors implanted in the same mice. Cy5 labeled hMDNA113 IV was administered when tumors reached ~ 150 mm^{3}. Whole animals were embedded for slicing dorsal-to-ventral along the horizontal plane. Images captured at 35 µm pixel resolution.

*EMIT Imaging

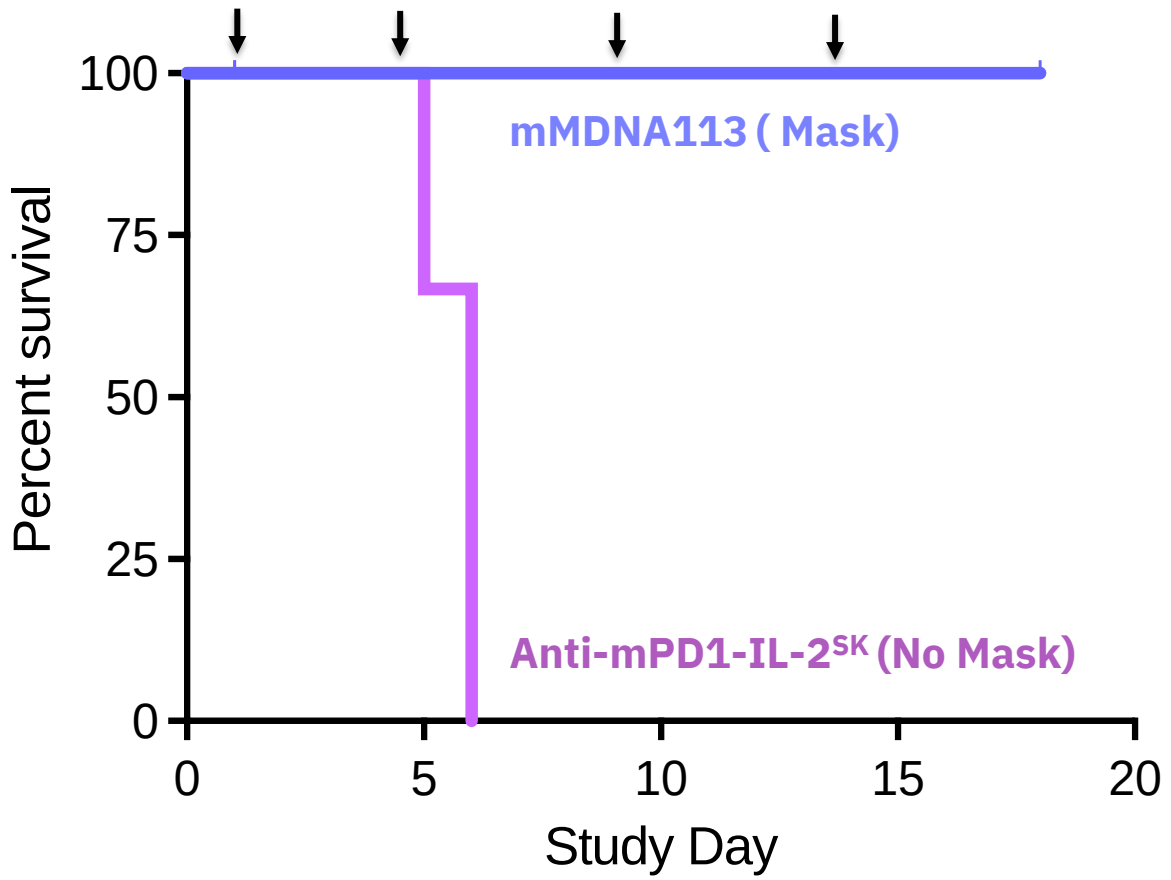
IL-13^{SK} Mask Attenuates IL-2^{SK} Induced Peripheral Lymphocyte Expansion in Mice





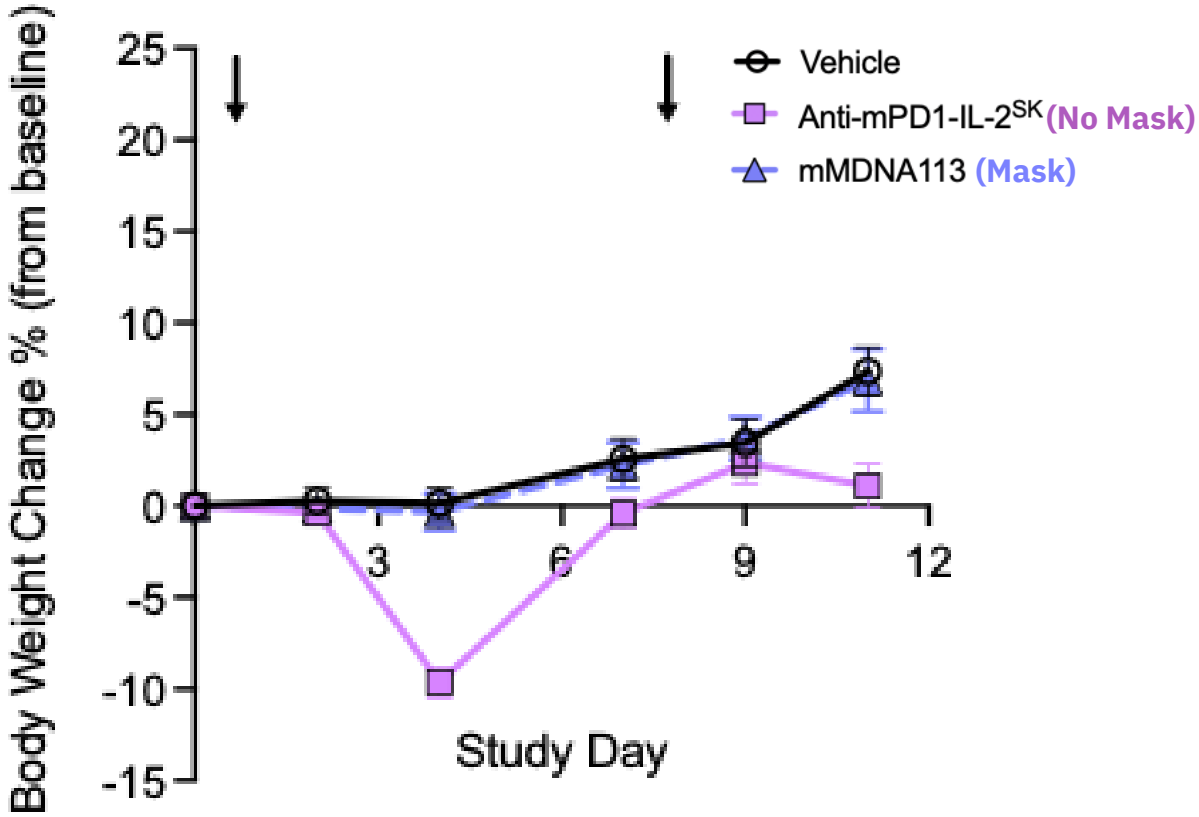
IL-13^{SK} Masking of IL-2^{SK} in MDNA113 Enhances Tolerability in Mice

mMDNA113 achieves 100% survival



C57Bl/6 mice were treated with equimolar doses of Anti-mPD1-IL-2^{SK} and mMDNA113 on a BIW schedule at 4 mg/kg. Arrows indicate dosing

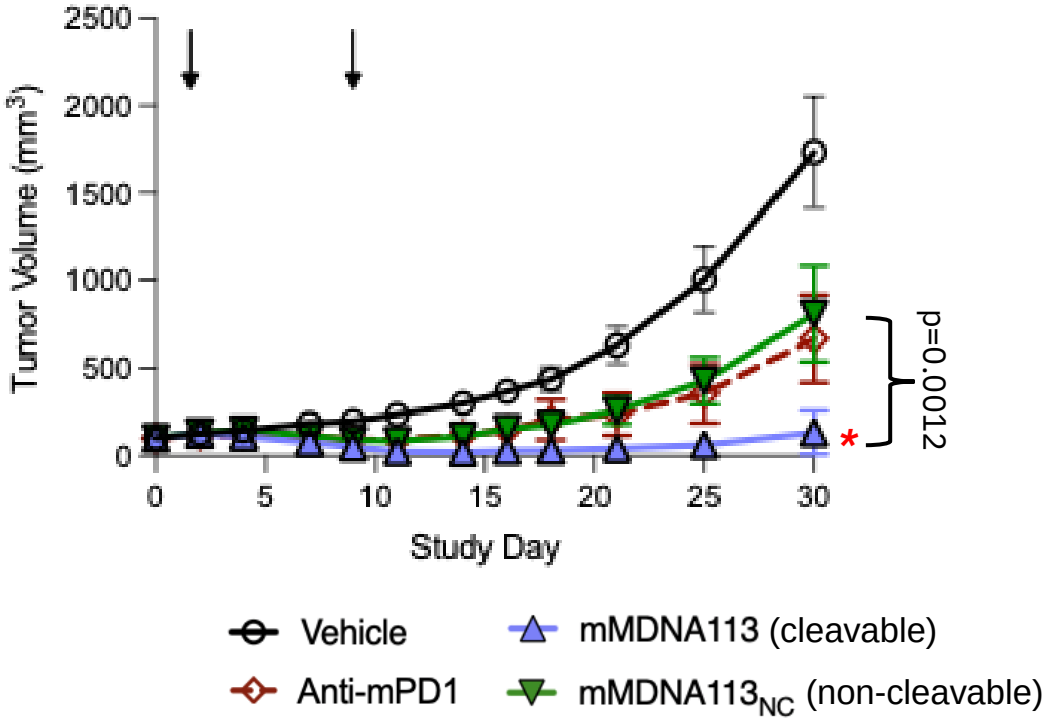
mMDNA113 shows **no** body weight loss



C57Bl/6 tumor bearing mice were treated with equimolar doses of Anti-mPD1-IL-2^{SK} and mMDNA113 QWx2 at 20 mg/kg. Arrows indicate dosing

MDNA113 Inhibits IL-13Rα2 Expressing MC38 Tumors & Promotes Memory Response Against Tumor Rechallenge

Anti-tumor activity maximized in IL-13Rα2 expressing tumors, including complete tumor regression

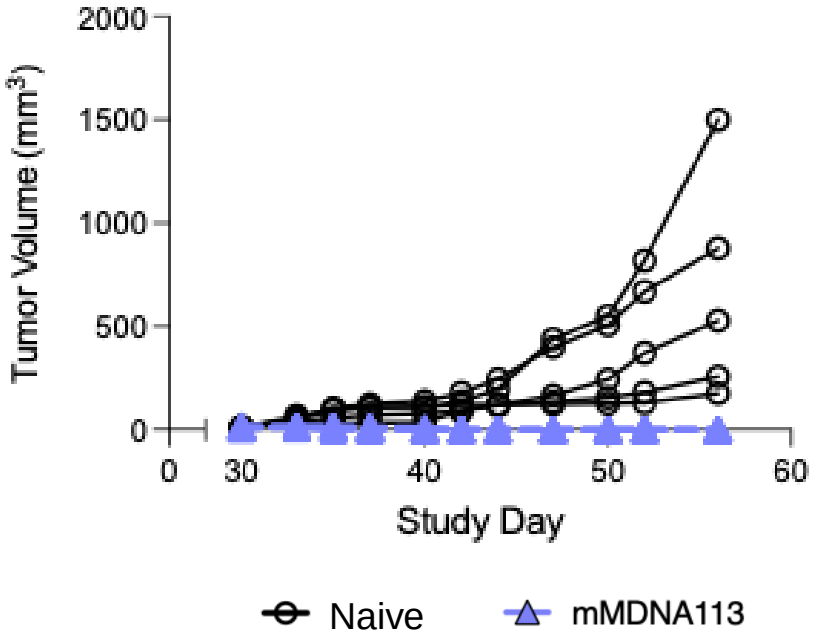


Complete responders rechallenged

(no further treatment)

6/8 CRs in mMDNA113 treatment group

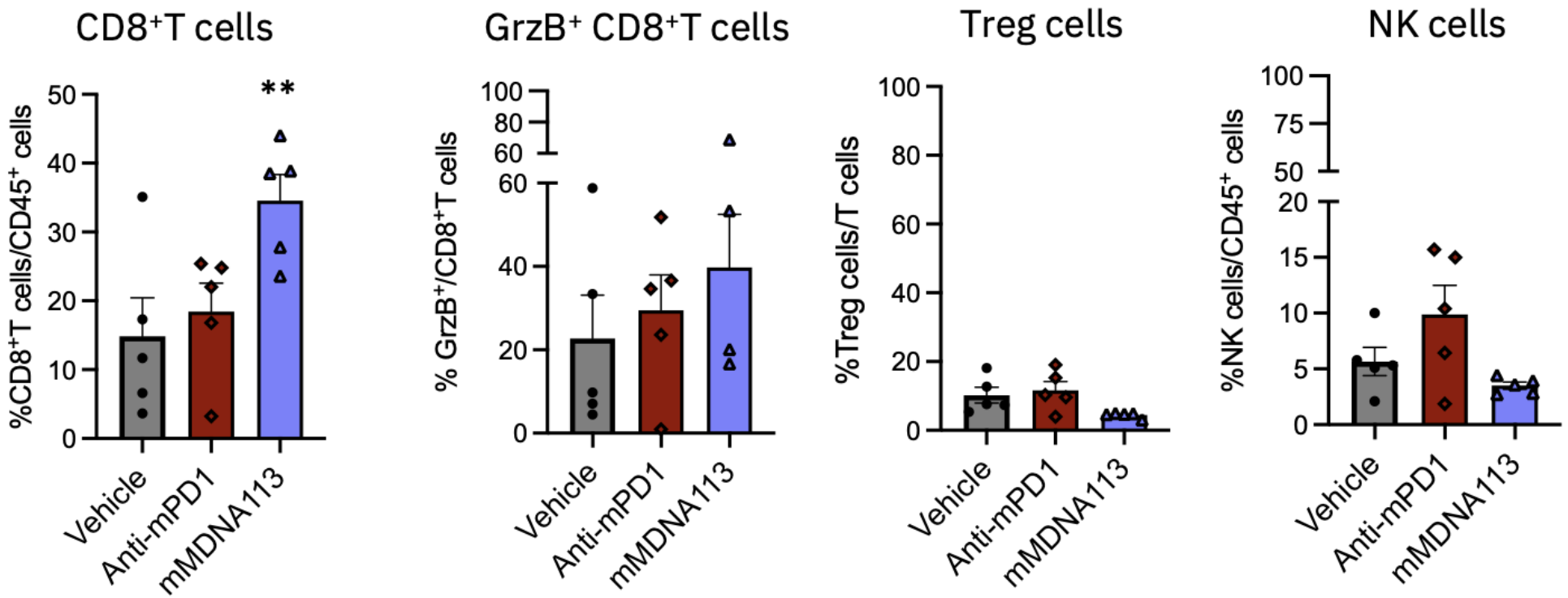
100% protection against tumor rechallenge



Avg tumor size at time of dosing: 100 mm^3.
Once weekly treatment at molar equivalent doses (1 mg/kg; IP).
Statistical analysis by one way ANOVA, Kruskal Wallis test.
Arrows indicate dosing

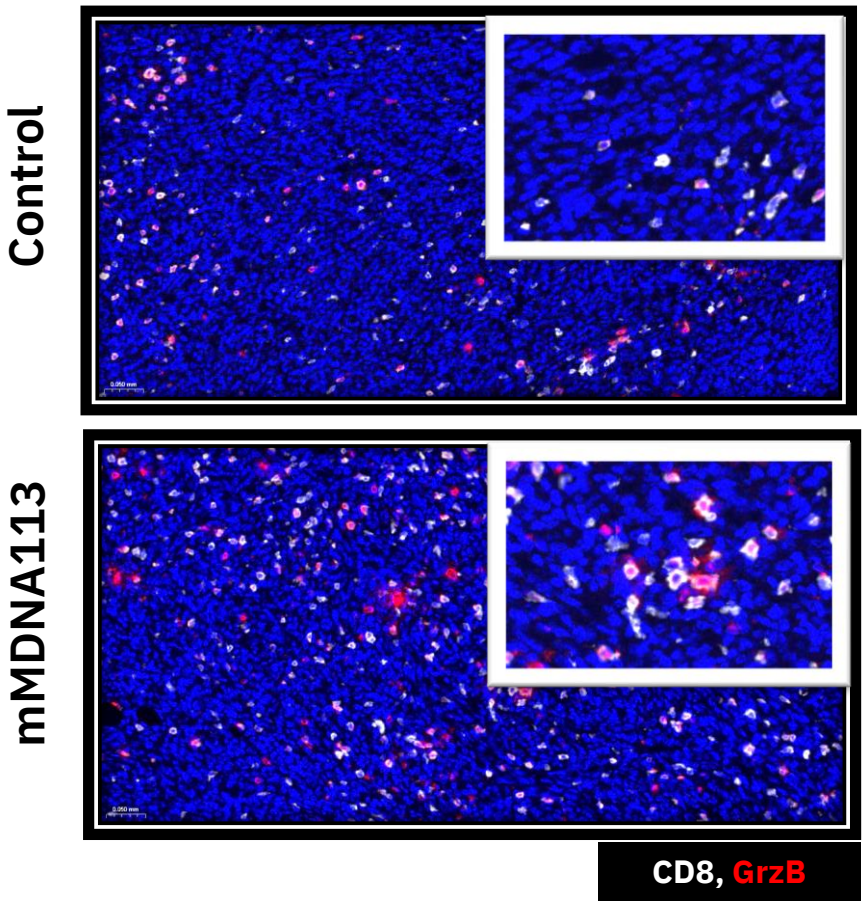
MDNA113 Enhances Infiltration of Functionally Active CD8⁺ T Cells in B16F10/IL-13Rα2 Melanoma Model

- No increase in Tregs and NK cells

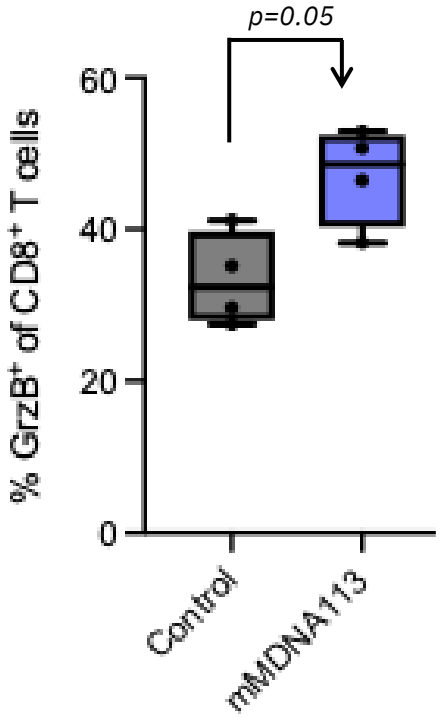


Avg tumor size at time of dosing: 150 mm^3, All dosed once weekly at molar equivalent dose (10 mg/kg; IP)
Samples were collected on Day 8 and processed for flow cytometry
Non-parametric t-test was used for statistical analysis; **p<0.05

MDNA113 Enhances Tumor Infiltration of Functionally Active CD8⁺ T Cells



4T1.2 Orthotopic Triple Negative Breast Tumor Model



Augmented immune effector function in tumors despite reduced lymphocyte expansion in systemic circulation

4T1.2 tumors in Balb/c mice were treated with equimolar dose (20 mg/kg) of Anti-mPD1-IL-2^{SK} or mMDNA113 and tumors were collected 3 days after for mIF analysis

Summary of MDNA113

Pre-clinical Highlights

- High specificity for tumors expressing IL-13Rα2
- Better tolerated than non-masked IL-2^{SK} with minimal peripheral activation *in vivo*
- Conditional activation in the TME
- *Cis*-binding preferentially activates CD8^{+} T cells for tumor cytotoxicity
- Generates immune memory response to protect against tumor rechallenge

Clinical Potential

- Tumor-restricted activation of IL-2^{SK} may enhance therapeutic window
- *Cis*-binding of checkpoint blockade with IL-2-driven T-cell activation boosts tumor cell killing
- Tumor targeting addresses limitations of current IL-2/PD-1 therapy
- Differentiated, first-in-class approach in a highly competitive immuno-oncology landscape
- Broad utility across ‘cold’ & aggressive solid tumors with IL-13Rα2 expression

Clinically validated **IL-2^{SK}** + Blockbuster **Anti-PD1** + Tumor Targeting **IL-13^{SK}** = **Improved Probability of Success MDNA113**

Thank you

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