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

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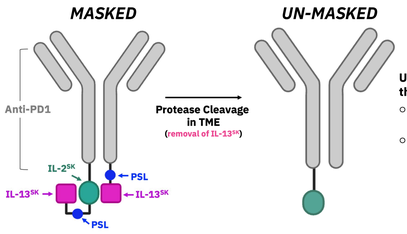
#7330

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

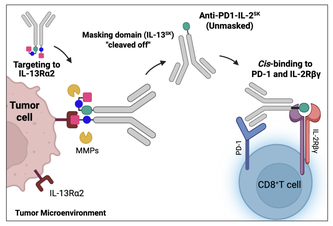
- **IL-13 Superkine (IL-13^{SK})**
  - **Tumor Targeting -** specific binding to decoy receptor **IL-13Rα2**, a tumor associated antigen (TAA)
  - **Enhances Tolerability -** attenuates systemic immune stimulation by sterically hindering IL-2^{SK}
- **'β-enhanced not-α' IL-2 Superkine (IL-2^{SK})**
  - 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}



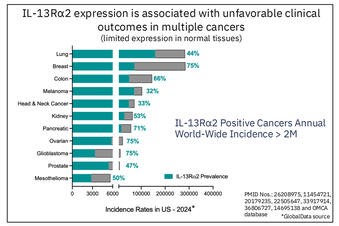
Unleashes immune effector activity within the TME

- *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



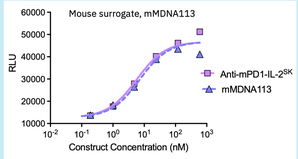
MDNA113 is Designed with a Unique Profile to Optimize Immuno-Oncology Efficacy & Safety

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

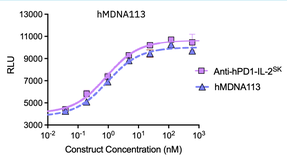
KEY FEATURES	Medicenna MDNA113	Other IL-2/anti-PD-1 candidates
β-enhanced and not-α IL-2^{SK} (clinically validated)	✓	✗
Tumor Specific Targeting (IL-13Rα2)	✓	✗
PD-1/PD-L1 Blockade (clinically validated)	✓	✓✗
Cis-binding (IL-2R/PD-1) (Synergistic engagement potentiates immune activation)	✓	✓✗
IL-2^{SK}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

MDNA113 Retains PD-1/PDL-1 Blockade but Exhibits Attenuated IL-2R Signaling that is Restored upon MMP9 Cleavage

PD-1/PDL-1 Blockade is Maintained

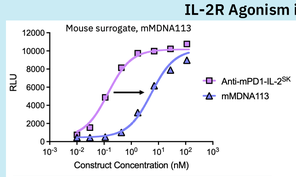


	EC_{50} (nM)
Anti-mPD1-IL-2^{SK} (No Mask)	8.8
mMDNA113 (Masked)	11.0

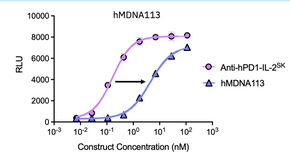


	EC_{50} (pM)
Anti-hPD1-IL-2^{SK} (No Mask)	878
mMDNA113 (Masked)	944

IL-2R Agonism is Attenuated

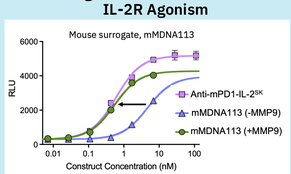


	EC_{50} (pM)	
Anti-mPD1-IL-2^{SK} (No Mask)	137	↓38x
mMDNA113 (Masked)	5313	

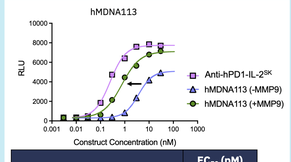


	EC_{50} (pM)	
Anti-hPD1-IL-2^{SK} (No Mask)	164	↓27x
hMDNA113 (Masked)	4414	

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



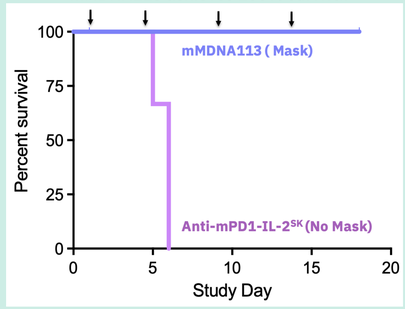
	EC_{50} (pM)
Anti-mPD1-IL-2^{SK} (No Mask)	597
mMDNA113 (-) MMP9	4477
mMDNA113 (+) MMP9	532



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

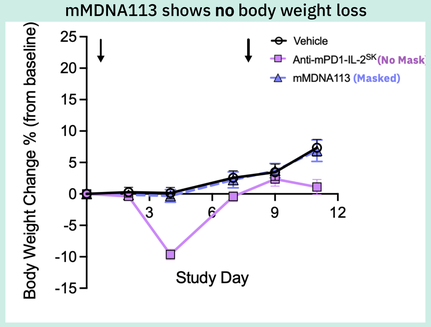
IL-13^{SK} Masking of IL-2^{SK} in MDNA113 Enhances Tolerability & Attenuates IL-2^{SK} Induced Peripheral Lymphocyte Expansion in Mice

mMDNA113 achieves 100% survival



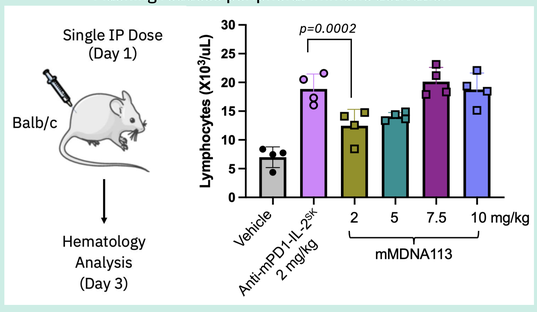
C57Bl/6 mice were treated with equimolar doses of Anti-mPD1-IL-2^{SK} and mMDNA113 on a BIW schedule at 4 mg/kg. Arrows indicate dosing

mMDNA113 shows **no** body weight loss



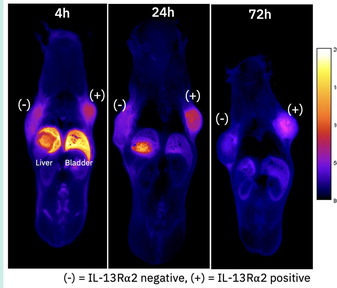
C57Bl/6 tumor bearing mice were treated with equimolar doses of Anti-mPD1-IL-2^{SK} and mMDNA113 QWx2 at 20 mg/kg. Arrows indicate dosing

Masking reduces peripheral immune activation



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

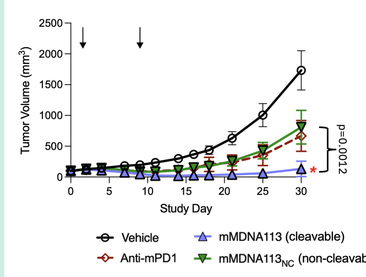
Observations:

- 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

**EMIT Imaging*

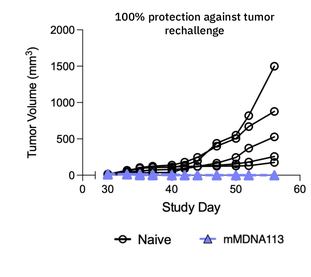
MC38 (IL-13Rα2 negative, left flank) and MC38/IL-13Rα2 (expressing human IL-13Rα2, right flank) tumors implanted in the same mice. Cy5 labeled hMDNA113 IV was administered when tumors reached ~ 150 mm^3. Whole animals were embedded for slicing dorsal-to-ventral along the horizontal plane. Images captured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

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*

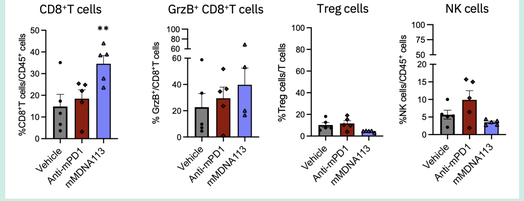
Mice rechallenged with MC38-IL-13Rα2 without any additional treatment



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

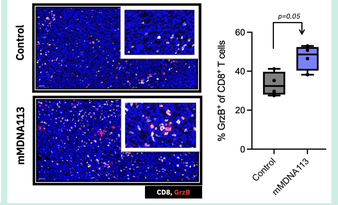
MDNA113 Enhances Infiltration of Functionally Active CD8$^+$ T Cells Over NK cells & Tregs in Different Tumor Models

B16F10/IL-13Rα2 Model



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

4T1.2 Triple Negative Breast Tumor Model



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**