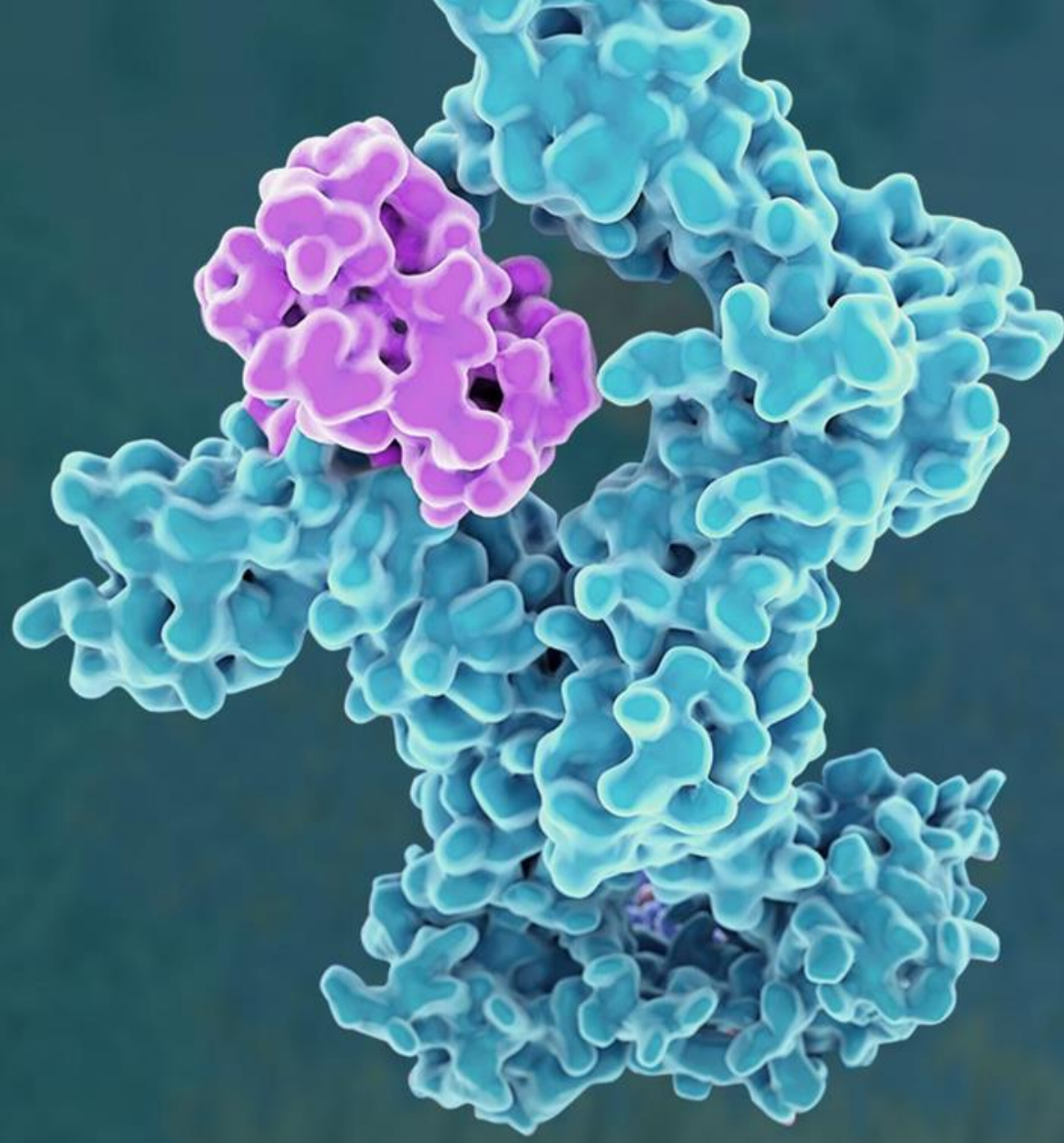
Sept 7, 2024

MDNA113, an IL-13Rα2 Tumor Targeting and Conditionally Activatable anti-PD1-IL-2^{SK} BiSKIT Shows Enhanced Safety and Potent Therapeutic Efficacy



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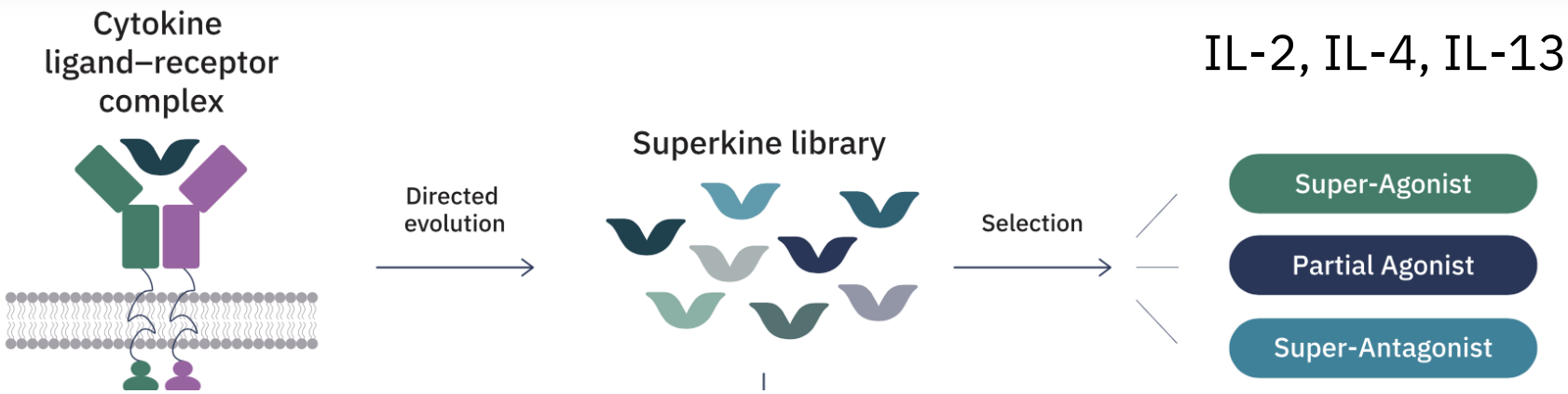
The Promise of IL-2 Therapy 2024

Directed Evolution Platform Generated Unique Library of Superkines



IL-2 Superkines

Super-Agonists

MDNA11
(Albumin-fused 'β-enhanced not-α' IL-2^{SK})

Ph1/2 ABILITY Study

MDNA113
(Bifunctional IL-2^{SK})

- Tumor targeting
- Activatable

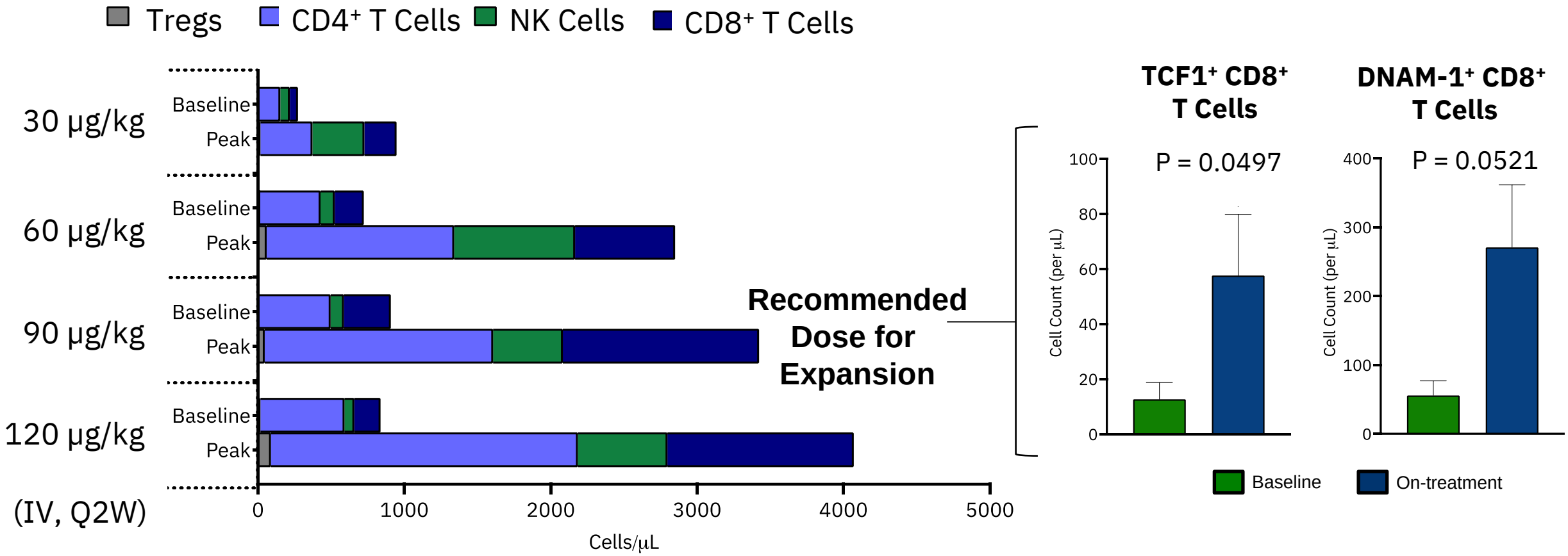
Oncology

Super-Antagonists

MDNA209

Autoimmune Disease

MDNA11 Activates Effector Immune Cells & Demonstrates Single Agent Efficacy



Single Agent Activity in CPI Resistant Patients (N = 14)

- 1 Complete Response (melanoma)
- 3 Partial Responses (melanoma, small bowel cancer, PDAC)
- 3 Durable (> 6 months) Stable Disease

MDNA113 is a Tumor-Targeting Protease-Activatable Anti-PD1-IL-2^{SK}

Design to Widen Therapeutic Index:

- Reduces risk of systemic toxicity
- Maximizes therapeutic activity at the tumor site

THERAPEUTIC 'BiSKIT' CORE

- **Anti-PD1-IL-2^{SK}** is a potent activator of immune effector function
- ***cis-binding*** to IL-2R and PD1 maximizes synergy between immune activation and immune checkpoint blockade

TUMOR TARGETING + MASKING DOMAIN

- **IL-13^{SK}** has high selectivity for IL-13Rα2, a tumor associated antigen
- Targets and retains MDNA113 within the TME
- Sterically attenuates activity of IL-2^{SK}

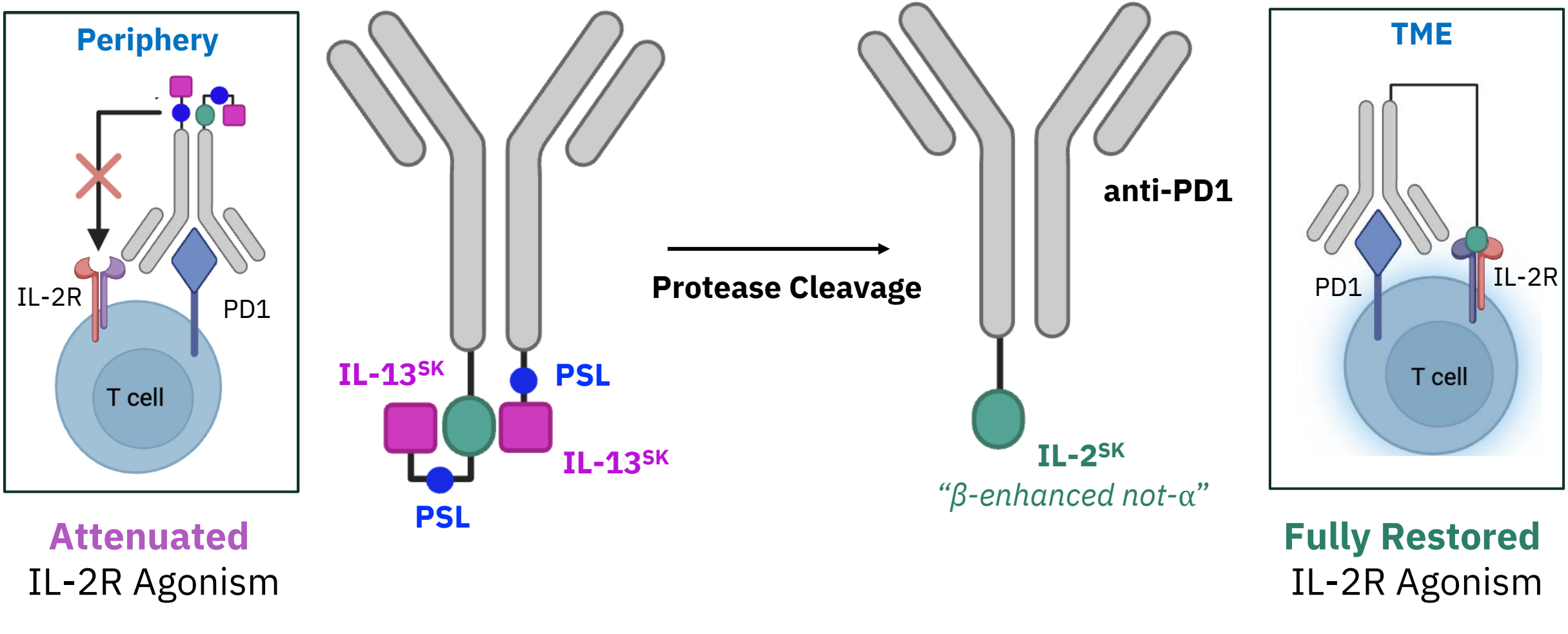
Protease Sensitive Linker (PSL)

Cleavage within TME

Restores IL-2^{SK} Activity at Tumor Site

BiSKIT: Bifunctional SuperKine for ImmunoTherapy

MoA of MDNA113

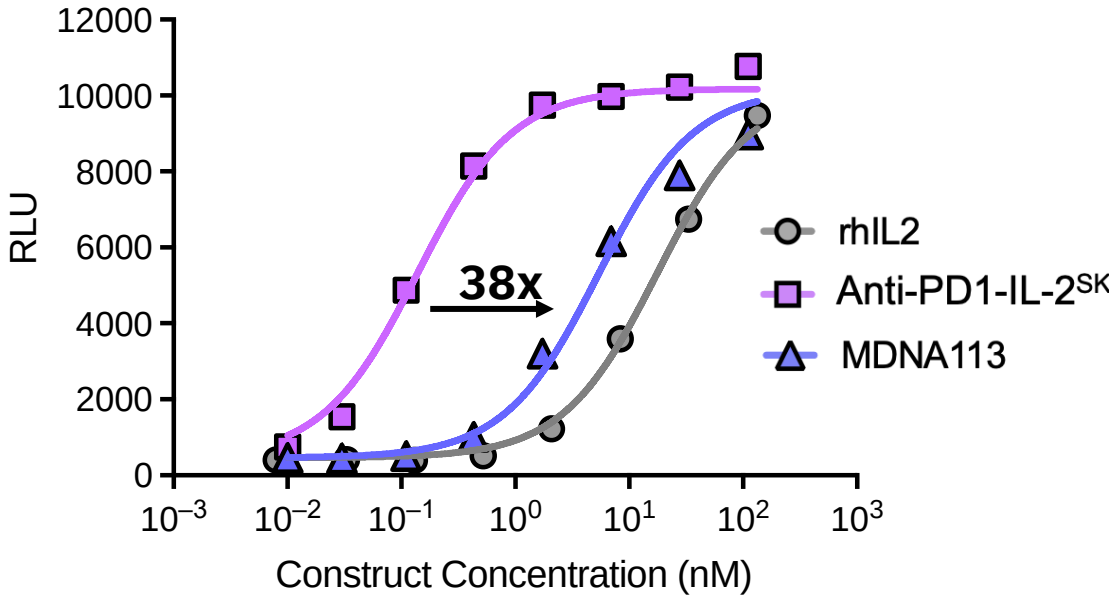


Attenuated
IL-2R Agonism

Fully Restored
IL-2R Agonism

Attenuated IL-2R Signaling with No Impact on PD1/PDL-1 Blockade

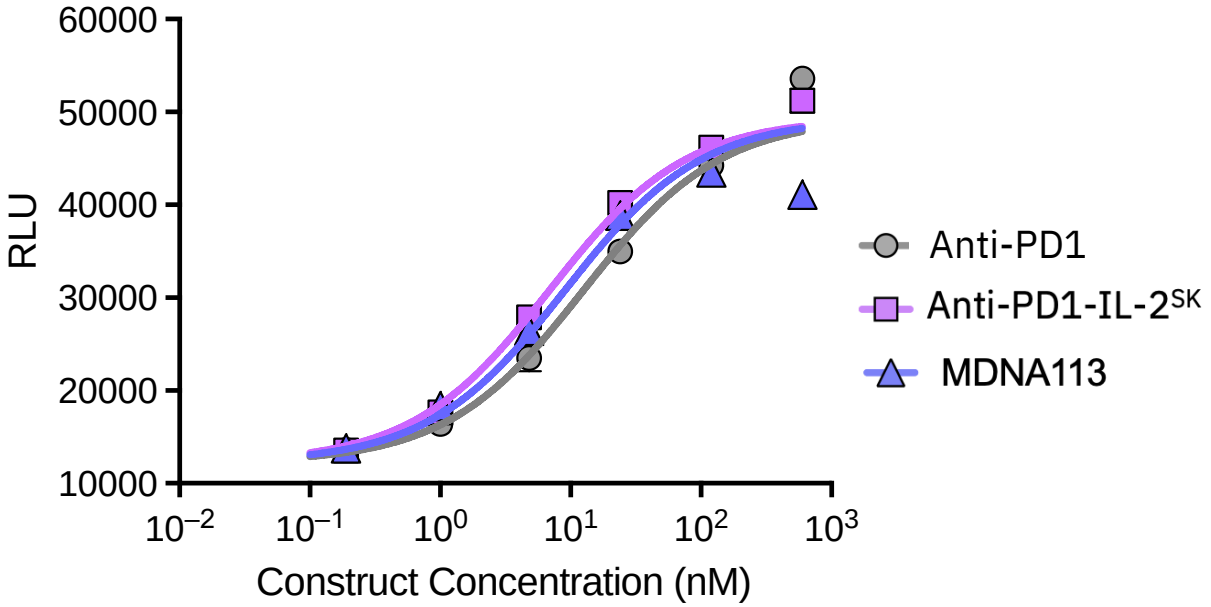
IL-2R Agonism is Attenuated



	EC_{50} (pM)
rhIL-2	17,260
Anti-PD1-IL-2^{SK}	137
MDNA113	5,313

Jurkat IL-2Rβγ bioassay lacking CD25 expression
RLU = relative luminescence unit

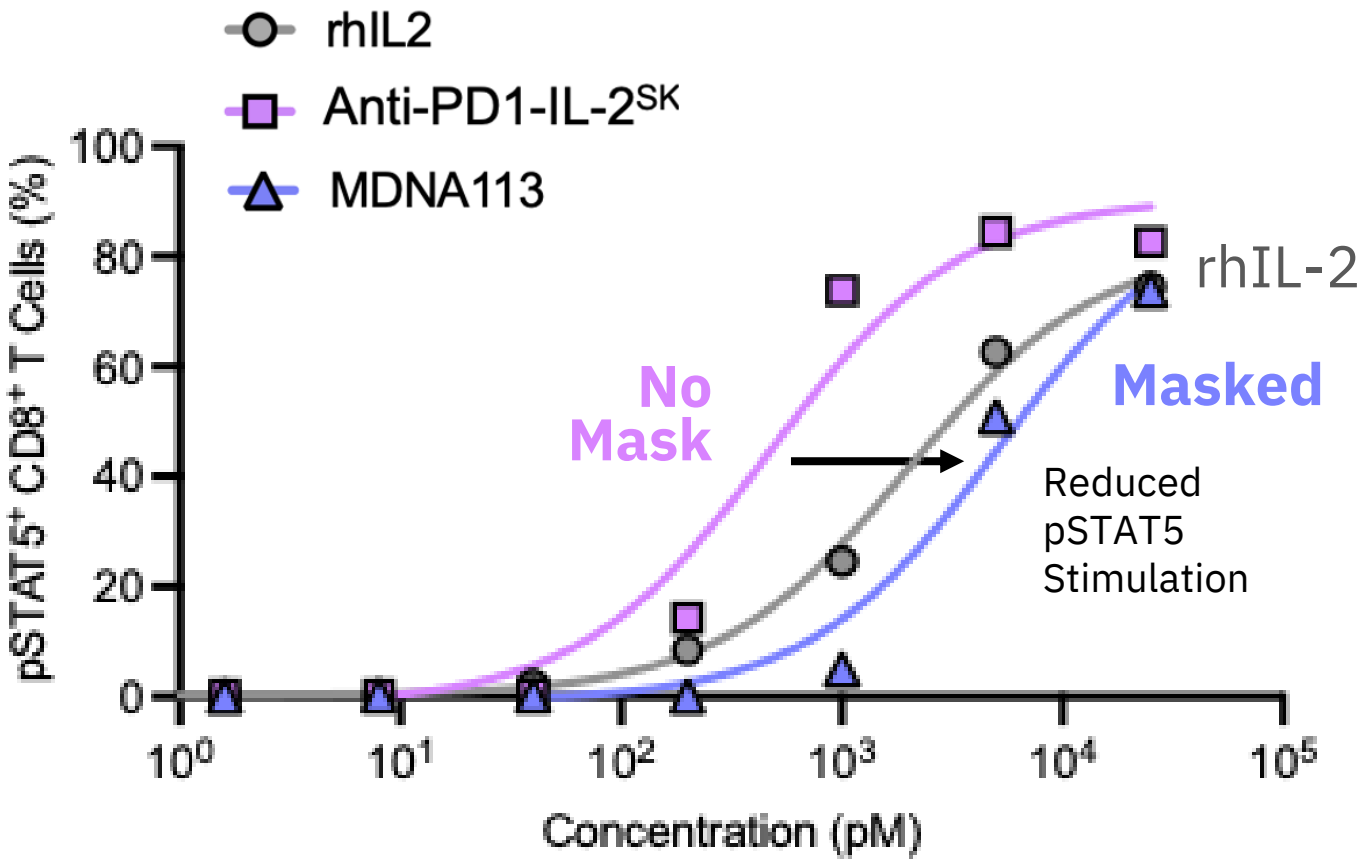
PD-1/PDL-1 Blockade is Maintained



	EC_{50} (nM)
Anti-mPD1	15.5
Anti-PD1-IL-2^{SK}	8.8
MDNA113	11.0

PD-1 reporter assay: co-culture of PD-1 reporter cells and PD-L1 aAPC/CHO-K1 cells.

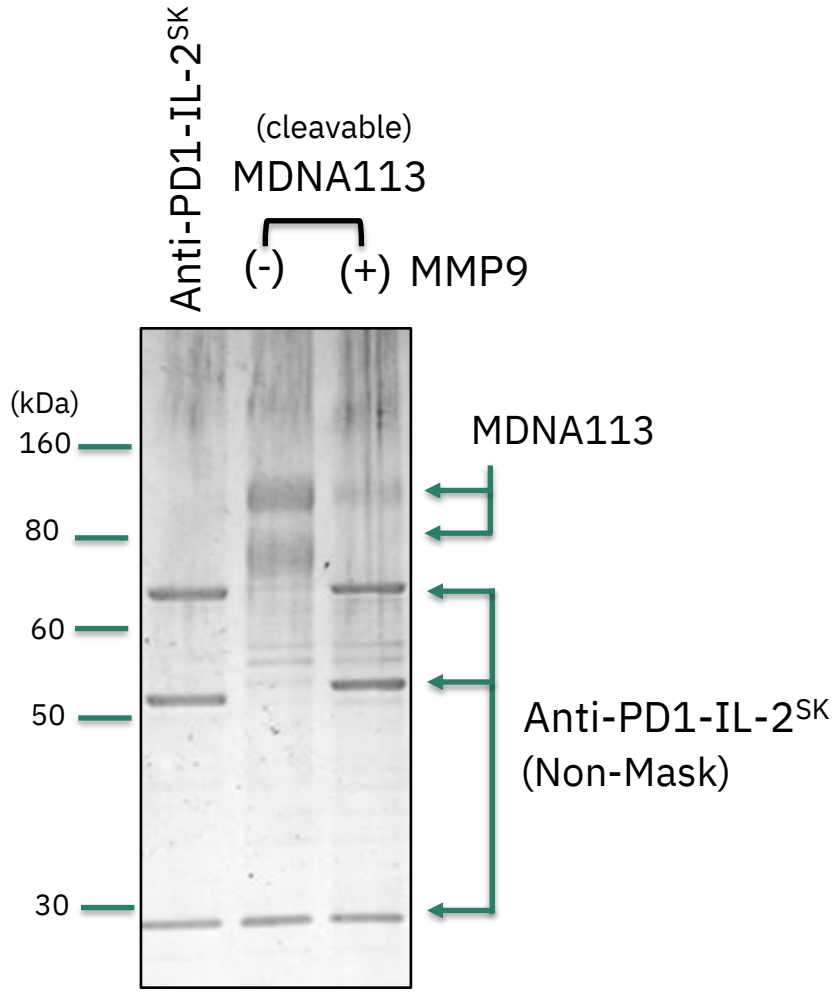
Attenuated pSTAT5 Signaling in Human CD8+ T Cells

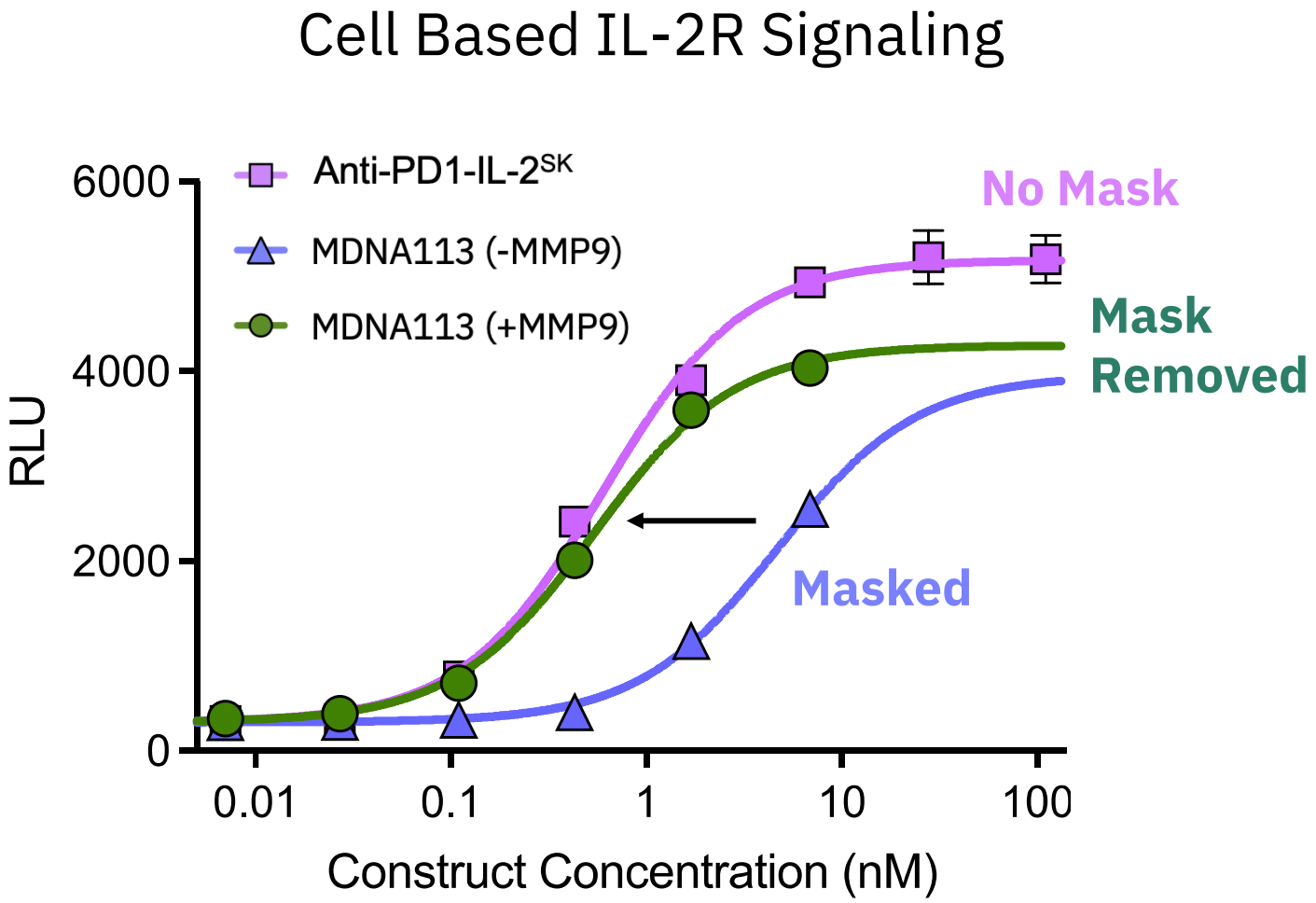


EC_{50} (pM)	$CD8^+$ T Cell
rhIL-2	2113
Anti-PD1-IL-2^{SK}	512.8
MDNA113	3, 674.3

Human PBMCs rested in complete media prior to stimulation for 15 min. Analysis by flow cytometry.
Average of 3 healthy PBMC donors

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





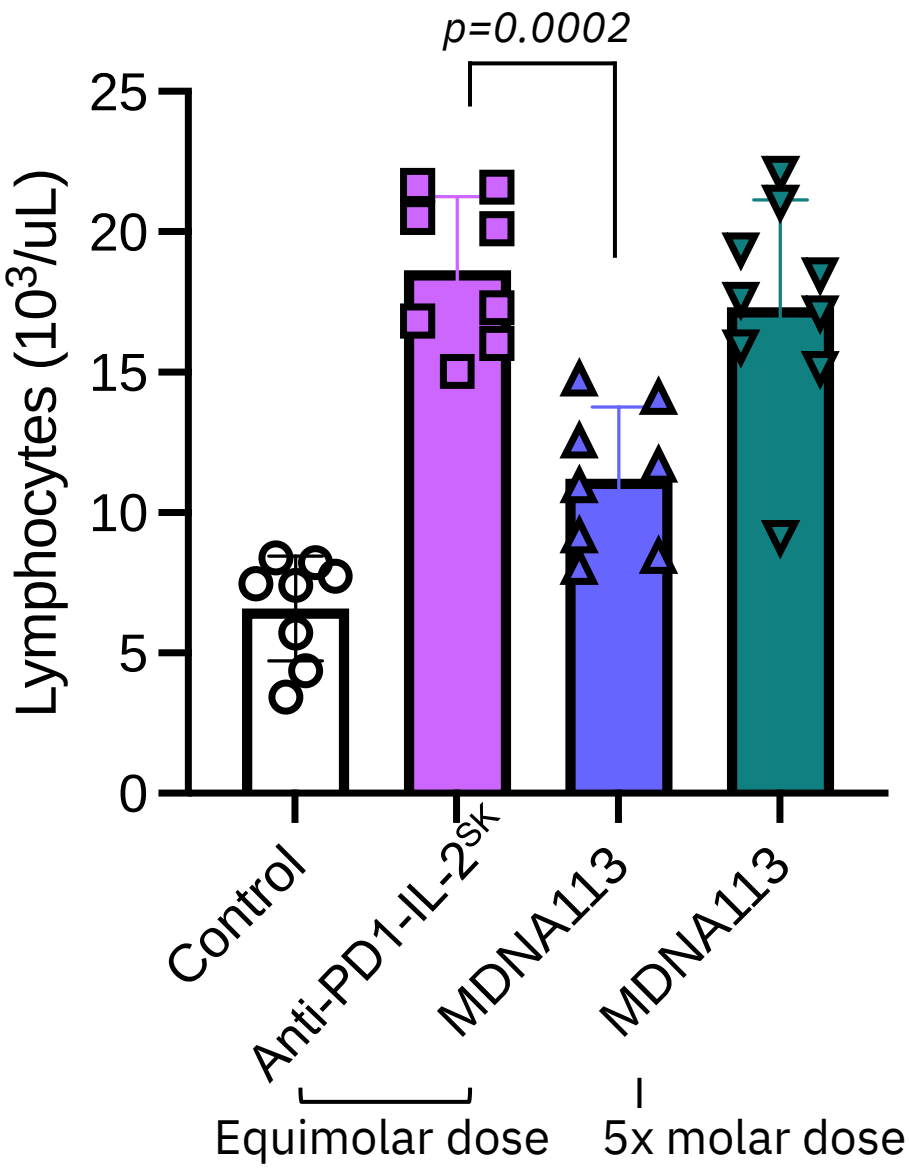
rMMP9 incubation at 5 µg/mL at 37°C for 1 h

Jurkat IL-2Rβγ bioassay lacking CD25 expression
RLU = relative luminescence unit

Partially Attenuated Peripheral Lymphocyte Expansion in Mice

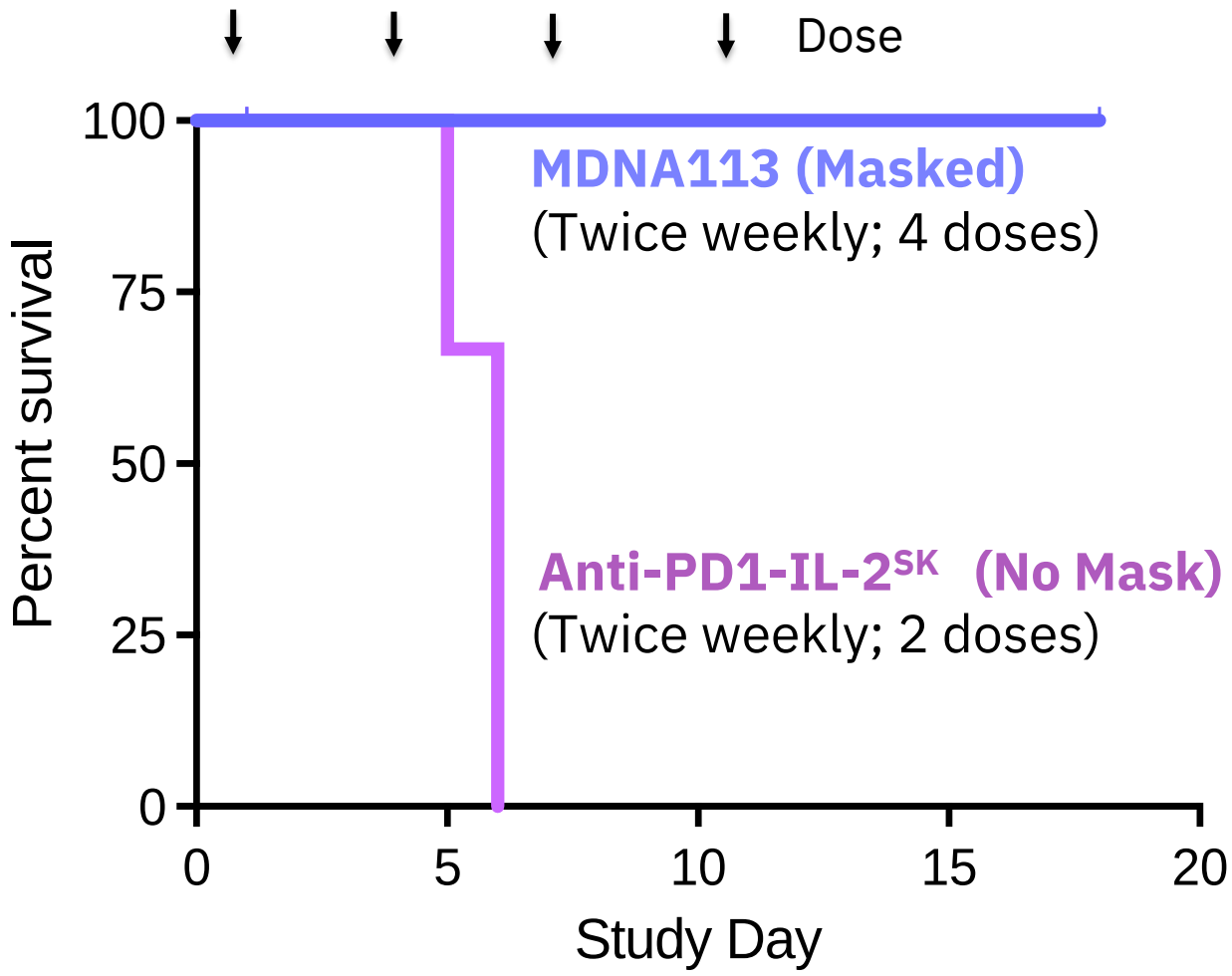
Single IP Dose
(Day 1)

Hematology
Analysis
(Day 3)



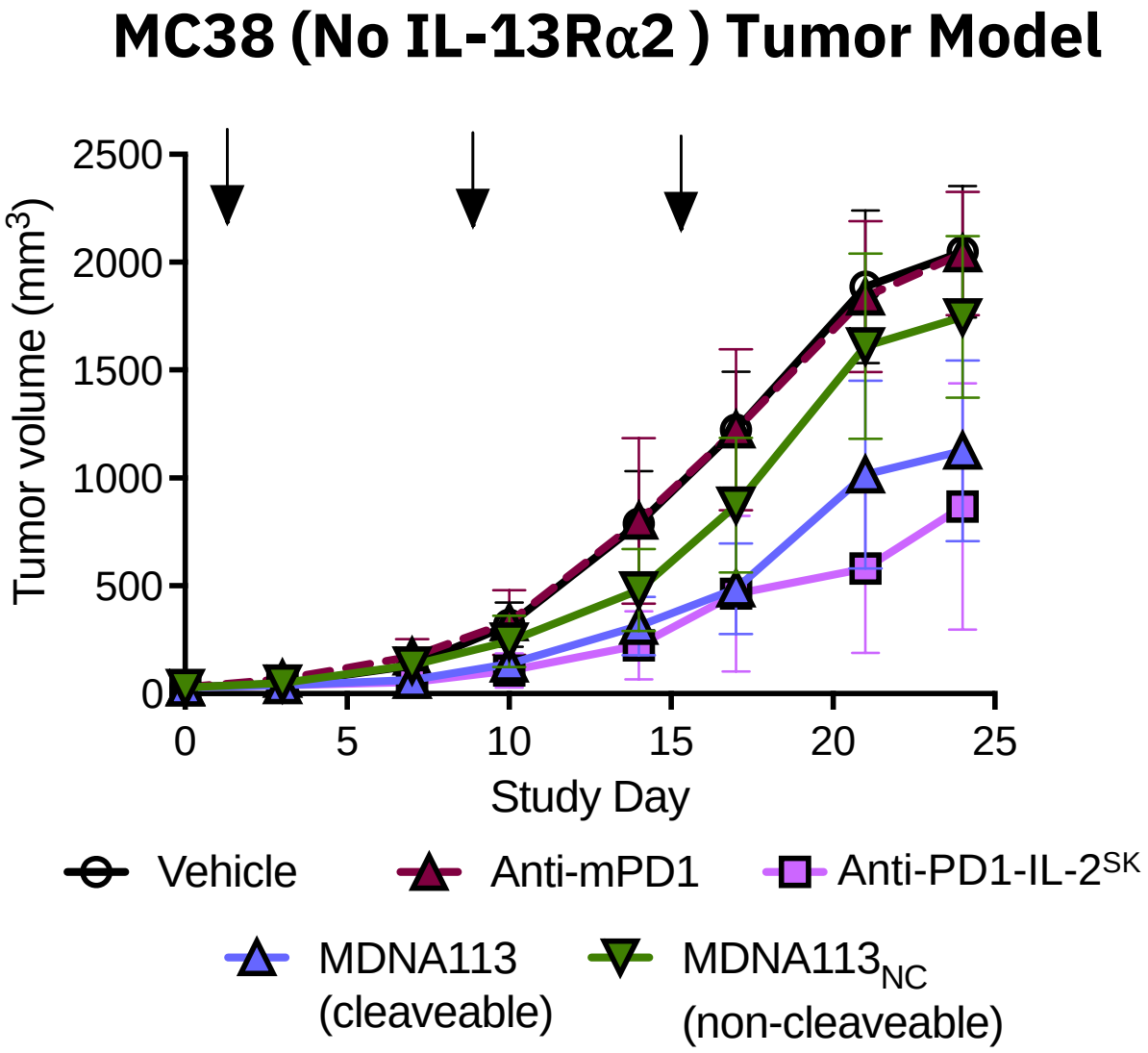
Partial attenuation compensated by increased dose

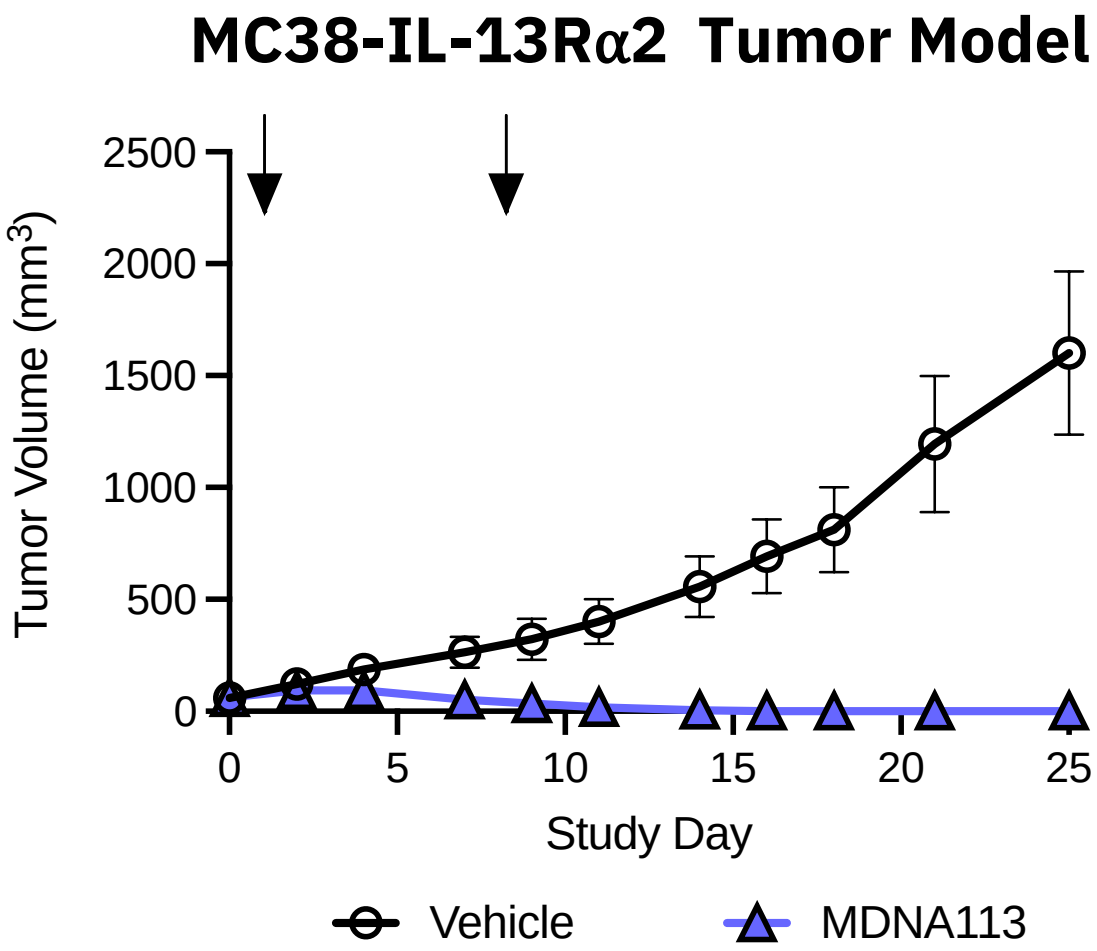
Attenuated IL-2R Agonism Increases *In Vivo* Tolerability



C57Bl/6 mice were treated with equimolar doses of Anti-PD1-IL-2^{SK} and MDNA113 on a twice weekly schedule at 4 mg/kg

MDNA113 Inhibits MC38 Tumor Growth in Mice



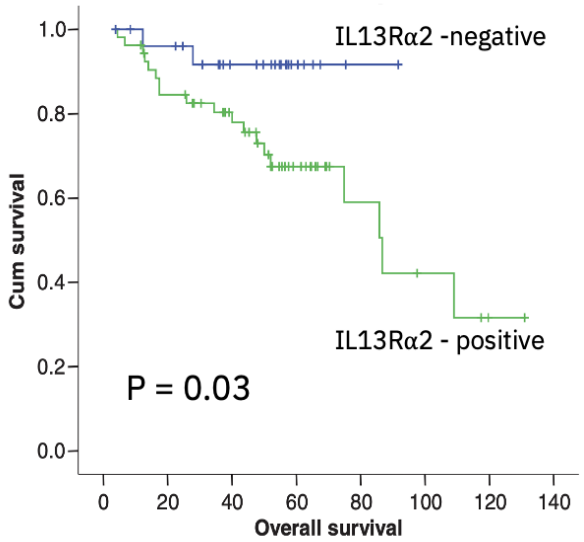


All dosed once weekly at molar equivalent dose (20 mg/kg; IP)

IL-13Rα2 is Expressed in a Broad Range of Tumors

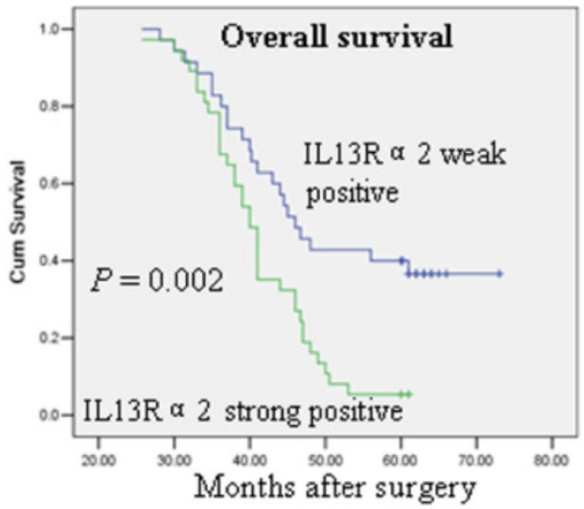
Liver Cancer 82% Hou et al., J Cancer Res & Clinical Oncol (2009)	**Breast Cancer** 75% Papageorgis et al., Br Cancer Res (2015)	**Glioblastoma** 75% Joshi et al., Cancer Res (2000)
Pancreatic Cancer 71% Shimamura et al. Clin Cancer Res (2010)	**Colon Cancer** 66% Barderas et al., Cancer Res (2012)	**Kidney Cancer** 53% Kang et al., J Per Med (2021)
Prostate Cancer 47% Nagai et al., Cancer Reports (2023)	**Lung Cancer** 44% Xie et al., Oncotarget (2015)	**Head & Neck Cancer** 33% Kawakami et al., Clin Cancer Res (2003)
Ovarian Cancer 75% Kioi et al., Cancer (2006)	**Mesothelioma** 50% Oncomine Cancer MicroArray (OMCA Database)	**Melanoma** 32% Beardi et al., Clin Cancer Res (2013)

High IL-13Rα2 is Associated with Poor Clinical Outcome



Colon Cancer

Barderas et al., Cancer Res, 2012

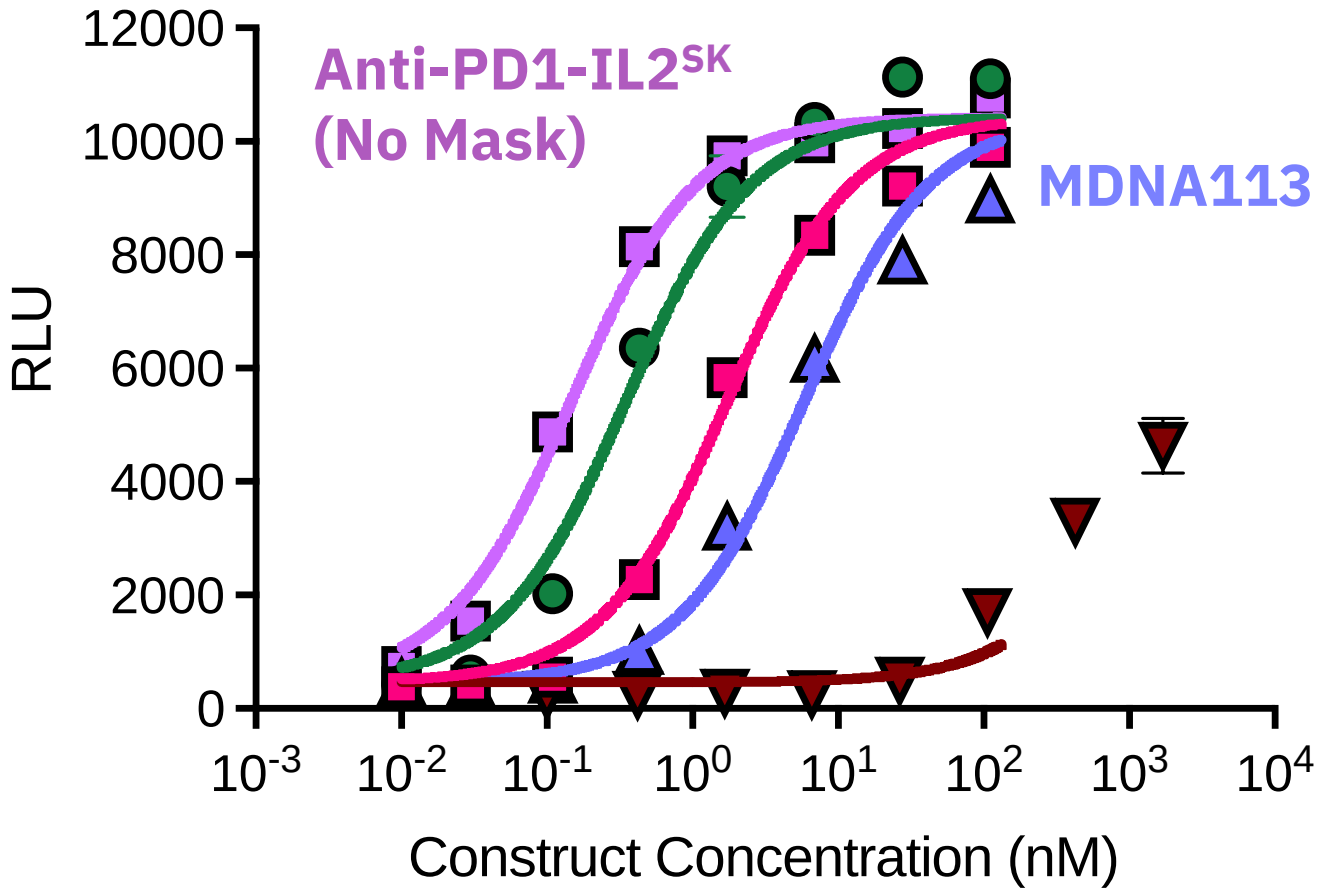


Lung Cancer

Xie et. al. Oncotarget, 2015

Versatility of the IL-13^{SK} Masking Platform

Different Variants of Masked Anti-PD1-IL-2^{SK} With Differential Masking Effects



Summary

- MDNA113 integrates tumor targeting and conditionally activatable features to mitigate risk of systemic toxicity and maximize therapeutic activity at tumor site

- Unique features of MDNA113:
  - Attenuated IL-2R agonism that is fully restored upon proteolytic activation in TME
  - Enhanced tolerability and potent therapeutic activity that is particularly effective against IL-13Rα2 expressing tumors

- Versatility of the IL-13^{SK} tumor-targeting and proteolytic activatable platform provides opportunities for a broad range of therapeutic modalities

Thank you

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