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# A Next Generation Bifunctional SuperKine for ImmunoTherapy (BiSKIT) Encompassing the Combined Therapeutic Potency of IL-2 Super-Agonist and Anti-PD1

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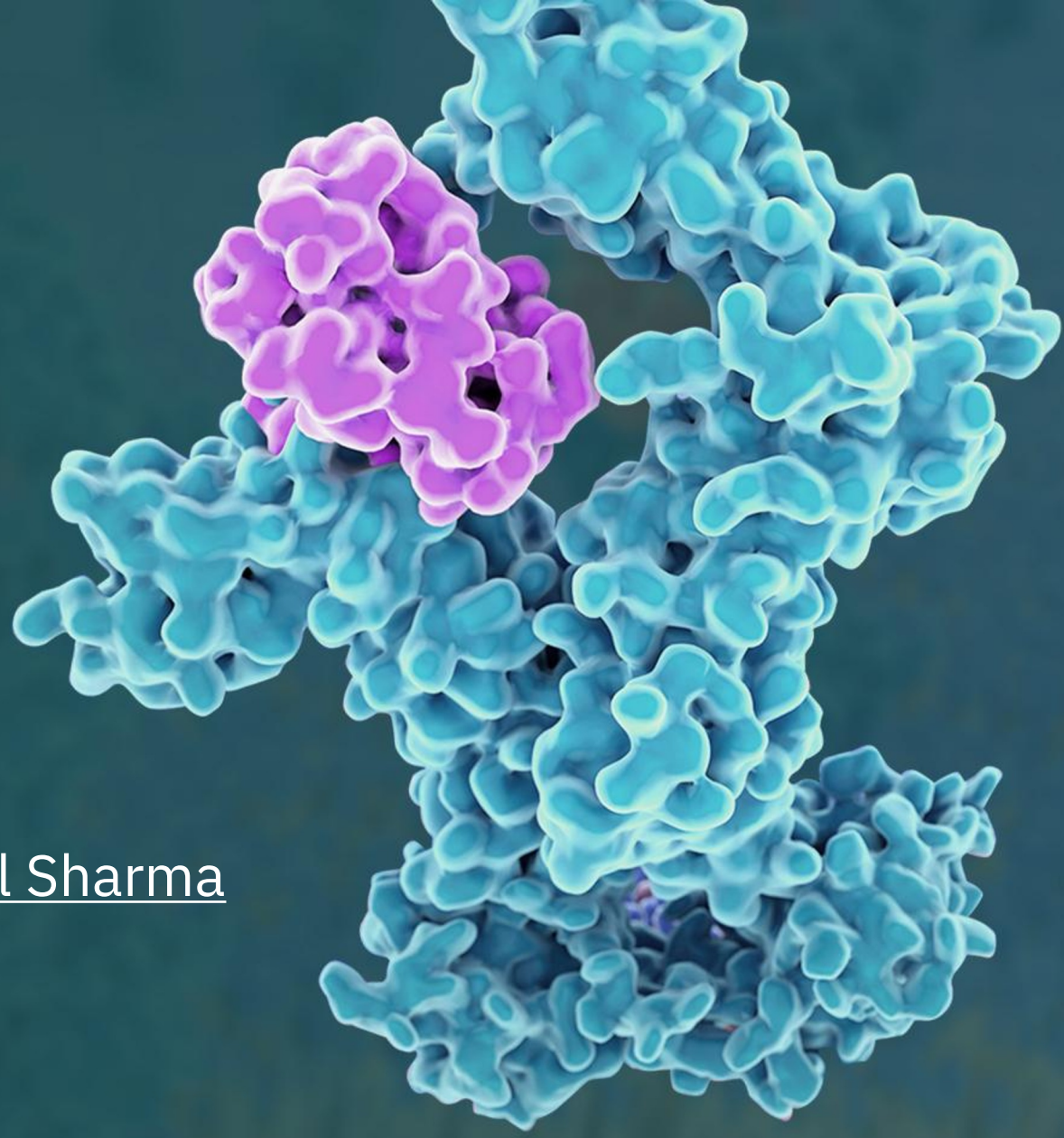

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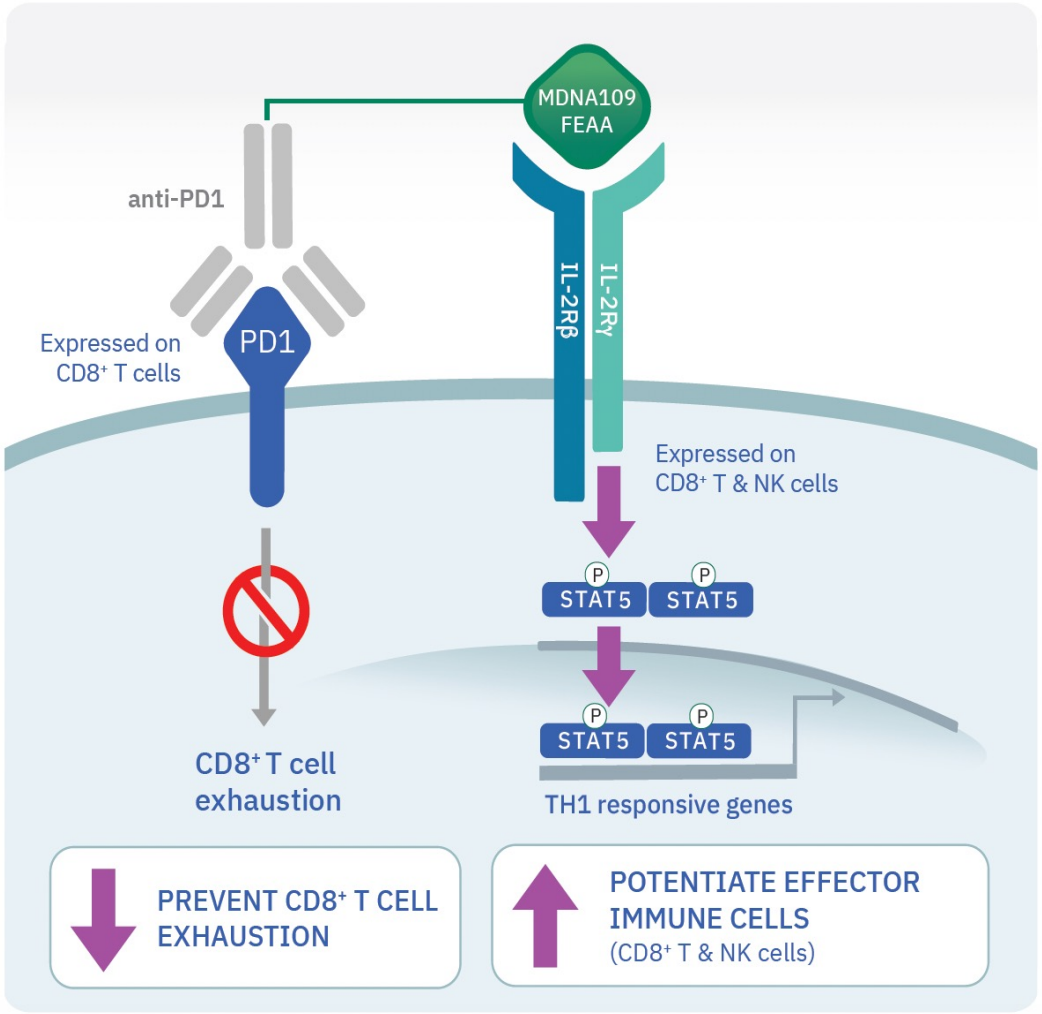
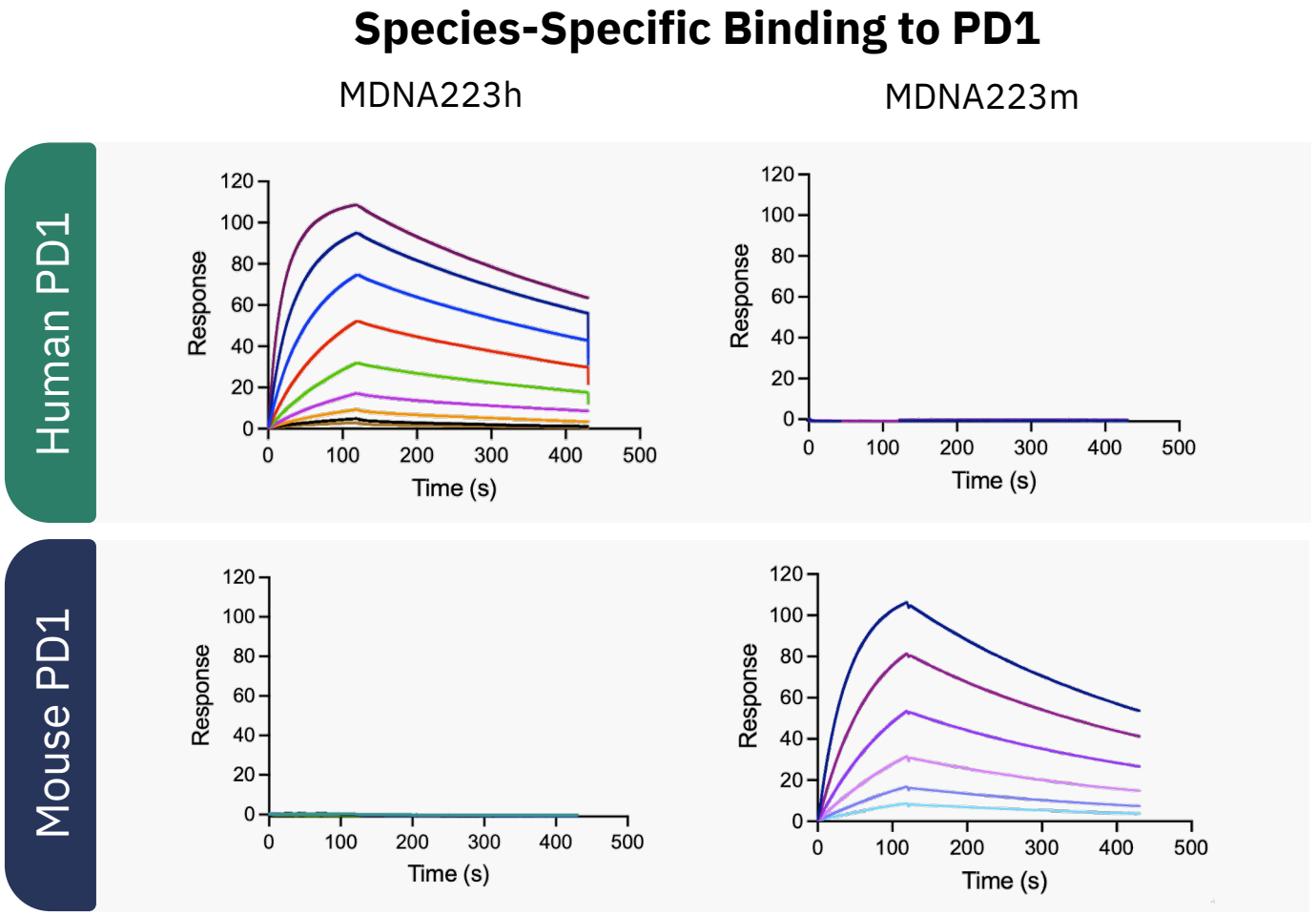
# Overview of Anti-PD1-MDNA109FEAA (MDNA223) for Cancer Immunotherapy




- MDNA223 is a novel Bifunctional SuperKines for ImmunoTherapy (BiSKIT) designed to:
  - facilitate cis-binding (i.e., on the same CD8+ T cell) to IL-2R and PD1
  - potentiate synergy between IL-2 agonism (CD8+ T cell activation) and PD1/PDL1 blockade (prevent CD8+ T cell exhaustion)
- MDNA109FEAA is a 'beta-only' IL-2 super-agonist with enhanced affinity for IL-2Rβ (CD122) and no binding to IL-2Rα (CD25) designed to:
  - preferentially activate immune effector cells (i.e., CD8+ T and NK cells) over Tregs
  - overcome toxicities associated with IL-2Rα engagement on non-immune cells (e.g., pulmonary endothelial cells)

# MDNA223 Maintains PD1 Binding

## Human (h) and mouse (m) anti-PD1 sequence used to generate MDNA223h/m

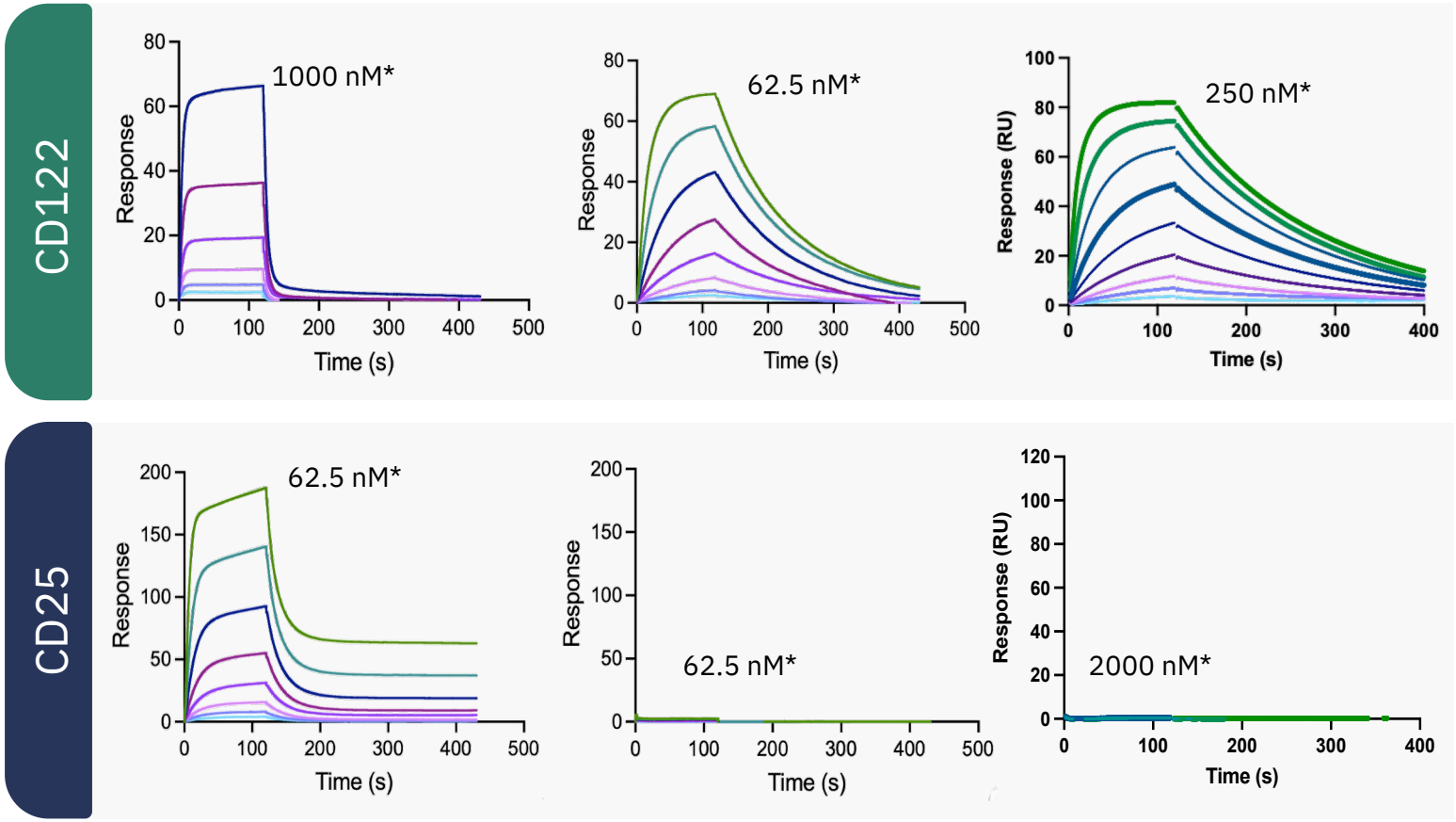



| Receptor Binding ($K_D$) | MDNA223h | MDNA223m |
|---|---|---|
| Human PD1 | 9.4 | No binding |
| Mouse PD1 | No binding | 102 |

SPR performed using immobilized PD1 and BiSKITs as flow analytes

# Enhanced IL-2 Receptor Selectivity

## Increase Affinity for IL-2Rβ and No Binding to IL-2Rα




| Receptor Binding ($K_D$) | IL2-Fc | MDNA223m | MDNA223h |
|---|---|---|---|
| IL-2Rβ (CD122) | 3540 | 11.3 | 16.1 |
| IL-2Rα (CD25) | 32 | No binding | No binding |

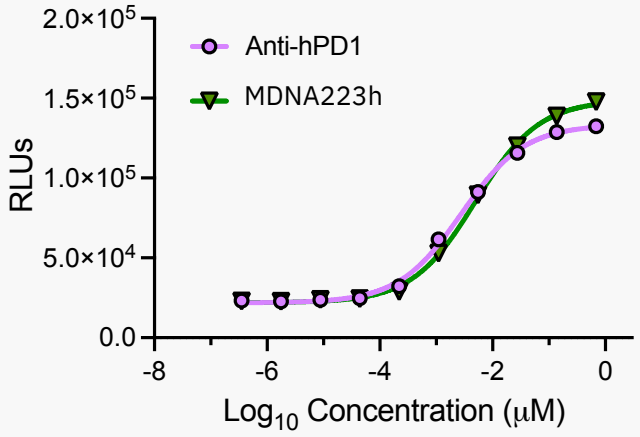
SPR studies using immobilized ligands and receptors as analytes *
Highest concentration of analytes tested

# MDNA223 Blocks PD1/PDL1 Interaction and Potentiates IL-2R Signaling

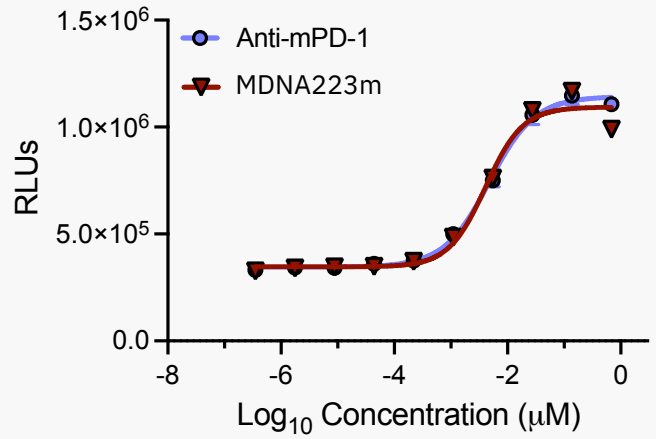
## Blockade of PD1/PDL1 Mediated Exhaustion

Bioassay (Promega) Measuring PD1/PDL1 Blockade

Human PD1/PDL1

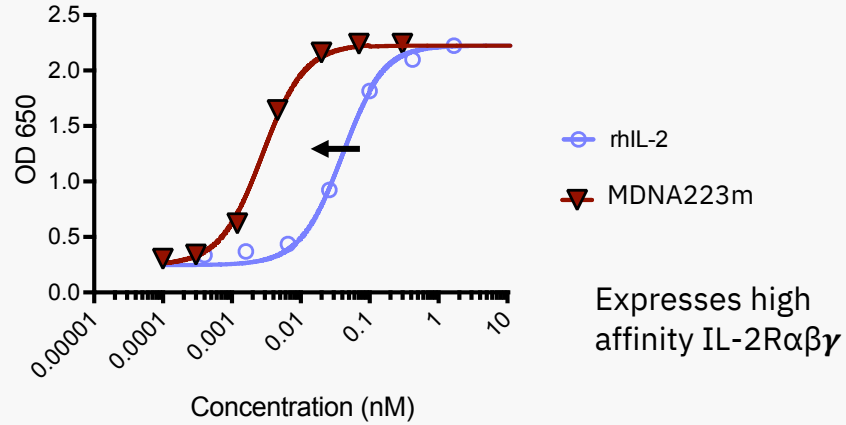



Mouse PD1/PDL1



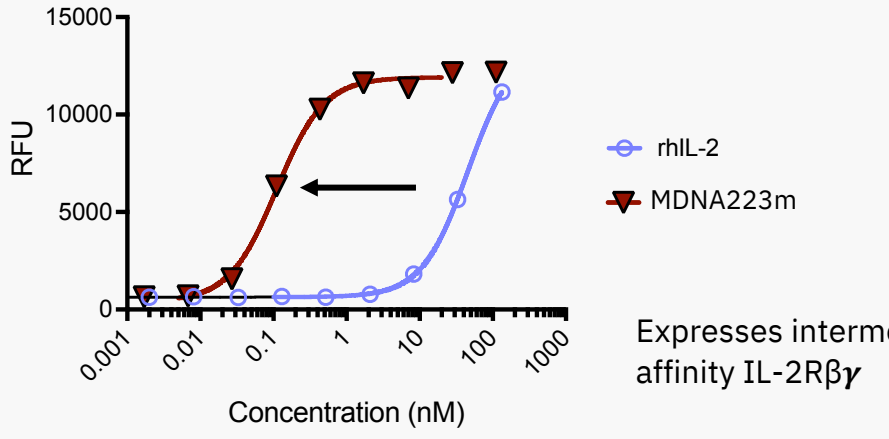

## Potentiate IL-2R Mediated pSTAT5 Signaling

HEK Blue IL-2




Expresses high affinity IL-2Rαβ$\gamma$

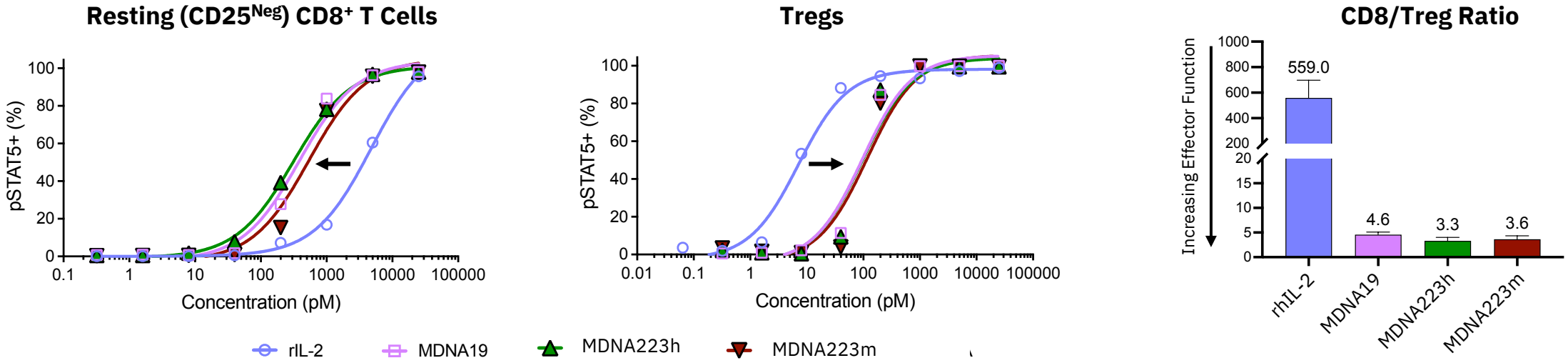
Jurkat IL-2Rβ$\gamma$




Expresses intermediate affinity IL-2Rβ$\gamma$

# Preferential Stimulation of CD8+ T Cells Over Tregs

## Enhanced stimulation of CD8+ T cells while reducing activity of immune suppressive Tregs




(representative dose-response plots of one PBMC donor)

| pSTAT5 $EC_{50}$ (pM) | rhIL-2 | MDNA109FEAA-Fc (MDNA19) | MDNA223h* | MDNA223m* |
|---|---|---|---|---|
| Resting CD8+ T cells | 2068 | 509 | 663 | 1108 |
| Tregs | 3.9 | 112 | 205 | 314 |

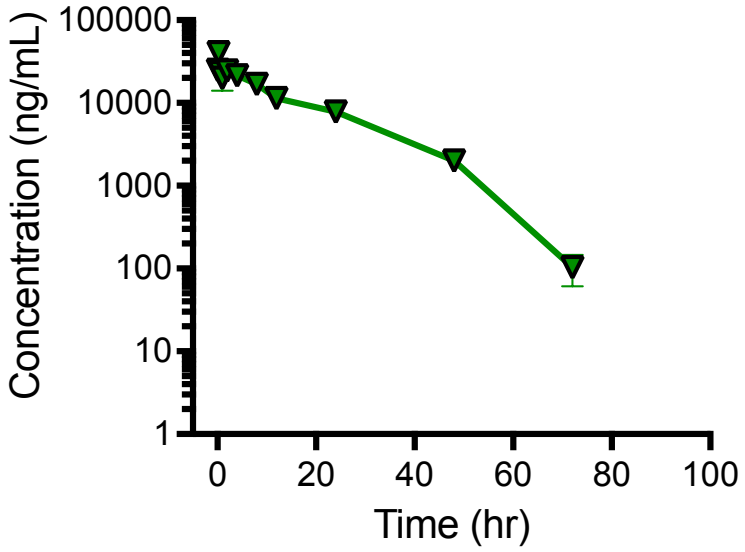
Average $EC_{50}$ of 3 unique PBMC donors
* h = human; m = mouse

PBMCs rested in complete media prior to stimulation for 15 min. Analysis by flow cytometry.

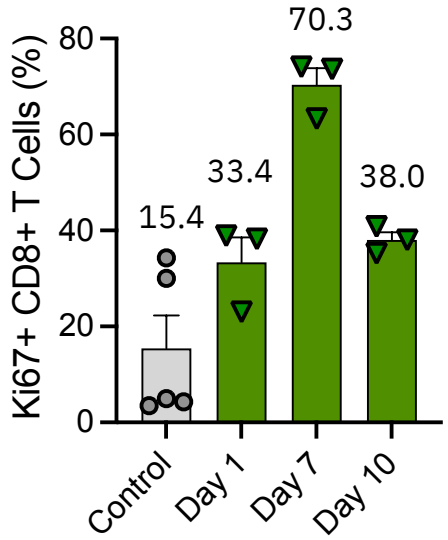
# MDNA223m Induces Prolonged PD Response

- Pharmacodynamic (PD) effects extend beyond duration of serum exposure (PK)
- Preferential expansion of circulating CD8+ T cells over Tregs

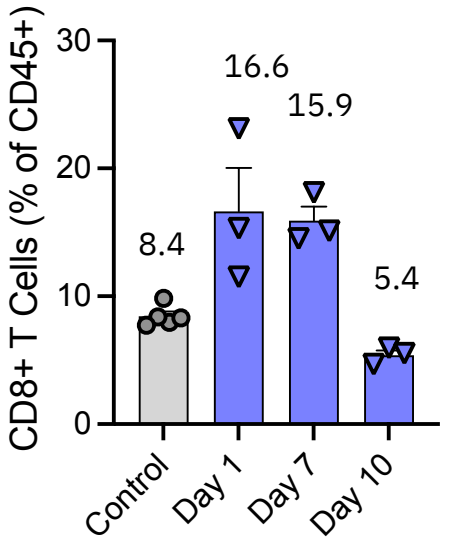
**PK Profile**



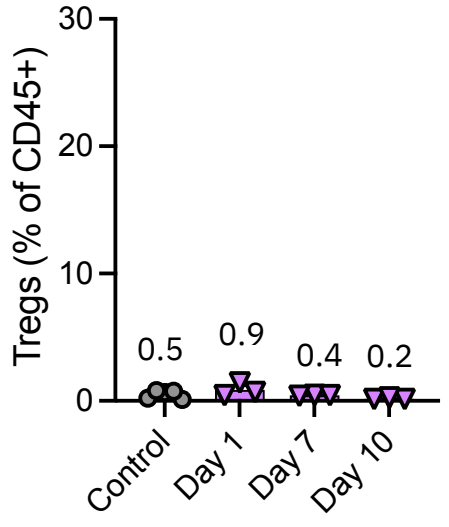

**CD8⁺ T Cell Proliferation (Ki67 Expression)**




**CD8⁺ T Cell Expansion (% of CD45⁺ Population)**




**Treg Cell Expansion (% of CD45⁺ Population)**

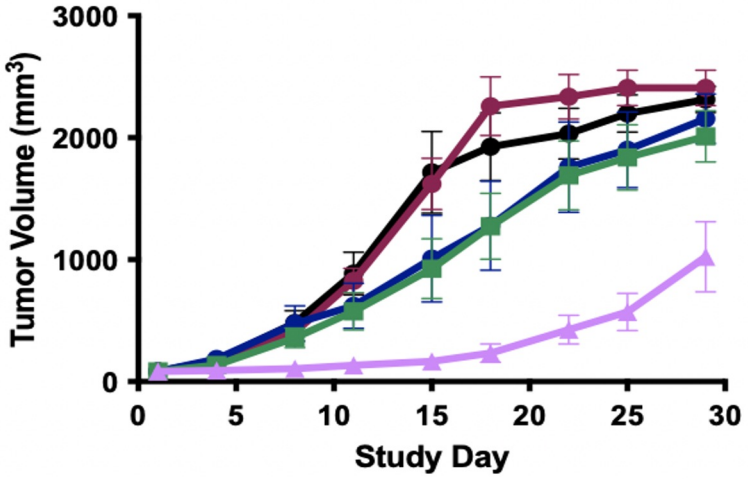



Mice (C57Bl/6) received single dose of MDNA223m (2 mg/kg) by intravenous injection on Day 0

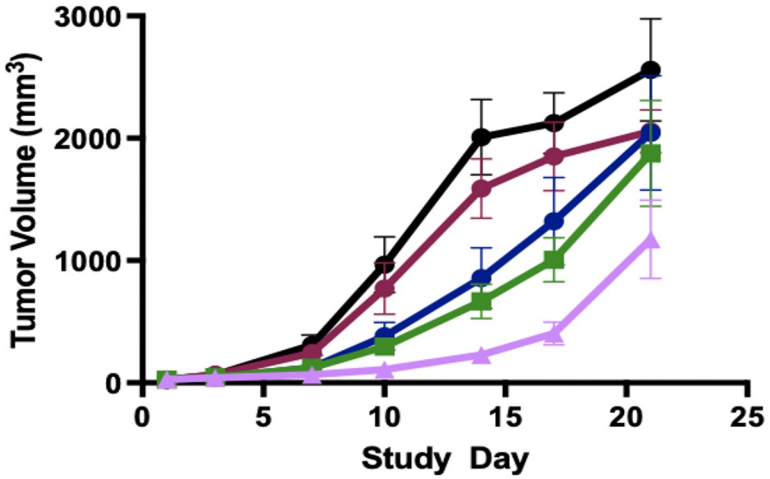
# MDNA223m Demonstrates Superior Efficacy in Tumor Models

## MDNA223m is more efficacious than co-administration of anti-mPD1 and MDNA19 (MDNA109FEAA-Fc)

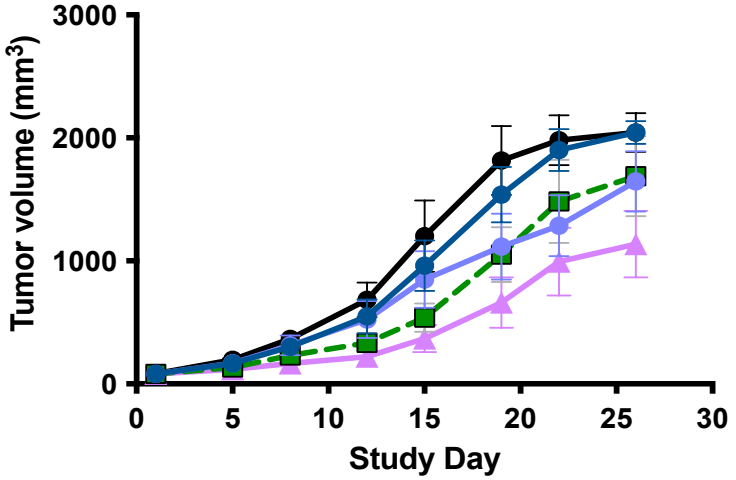
### CT26 Colon Tumor Model




### B16F10 Melanoma Model




### E0771 Breast Tumor Model




Vehicle
Anti-PD1 (1.8 mg/kg)
MDNA19 (1 mg/kg)
Anti-mPD1 (1.8 mg/kg) + MDNA19
MDNA223m (2 mg/kg)

Vehicle
Anti-mPD1 (10 mg/kg)
MDNA19 (1 mg/kg)
Anti-mPD1 (10 mg/kg) + MDNA19
MDNA223m (2 mg/kg)

Treatment with molar equivalent doses of anti-PD1 (150 Kda), MDNA19 (83 Kda) or MDNA223m (165 Kda).
IP treatment QWx2 (CT26 and E0771) and QWx3 (B16F10)
Avg tumor size at initiation of dosing: 127 $mm^3$ (CT26), 80 mm3 (E0771) or 30 $mm^3$ (B16F10)

# MDNA223m Provides Survival Benefit in Syngeneic Tumor Models

## CT26 Colon Tumor Model

| Treatment | % TGI* (Day 25) | Survival at Study End (%) |
|---|---|---|
| Vehicle | - | 10% |
| Anti-mPD1 + MDNA19 | 16.3% | 25% |
| MDNA223m | 74% | 100% |

## B16F10 Melanoma Model

| Treatment | % TGI* (Day 21) | Survival at Study End (%) |
|---|---|---|
| Vehicle | - | 0% |
| Anti-mPD1 + MDNA19 | 26.6% | 0% |
| MDNA223m | 54.1% | 43% |

*TGI = tumor growth inhibition

# Summary

- ***In vitro* Analysis of MDNA223 shows:**
  - MDNA223 exhibits enhanced binding affinity for CD122 and no binding to CD25
  - Potency on PD1/PDL1 blockade highly similar to control anti-PD1 antibody
  - Enhanced IL-2R selectivity resulting in preferential and enhanced stimulation of CD8+ T cells over Tregs in comparison of rhIL-2
- ***In vivo Analysis of BiSKIT MDNA223 shows:***
  - Prolonged PD response extending beyond duration of PK exposure, supporting a QW administration schedule
  - Superior tumor growth inhibition as a monotherapy over co-administration of anti-PD1 and MDNA19 in multiple syngeneic tumor models
- **These data demonstrate the therapeutic synergy of cis-binding facilitated by the BiSKIT platform and emphasize the versatility of superkines in developing next generation cancer immunotherapies**

# Thank you

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