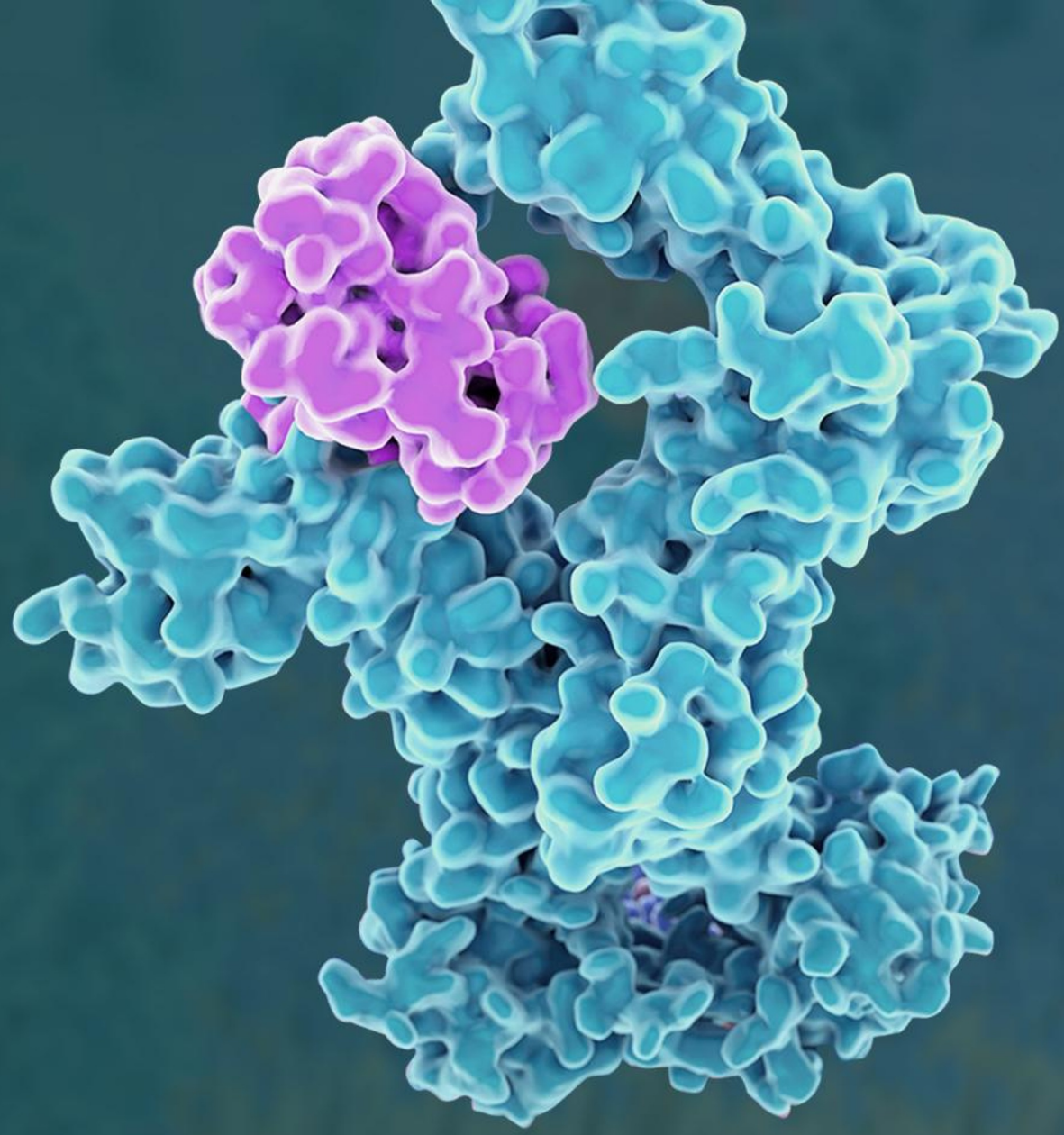
Sept 17, 2022

IL-2 Superkines Engineered with Tunable Selectivity for IL-2Rα, β and γ Chains Enabling Pro-and Anti-Immune Functions

Fahar Merchant
Medicenna Therapeutics

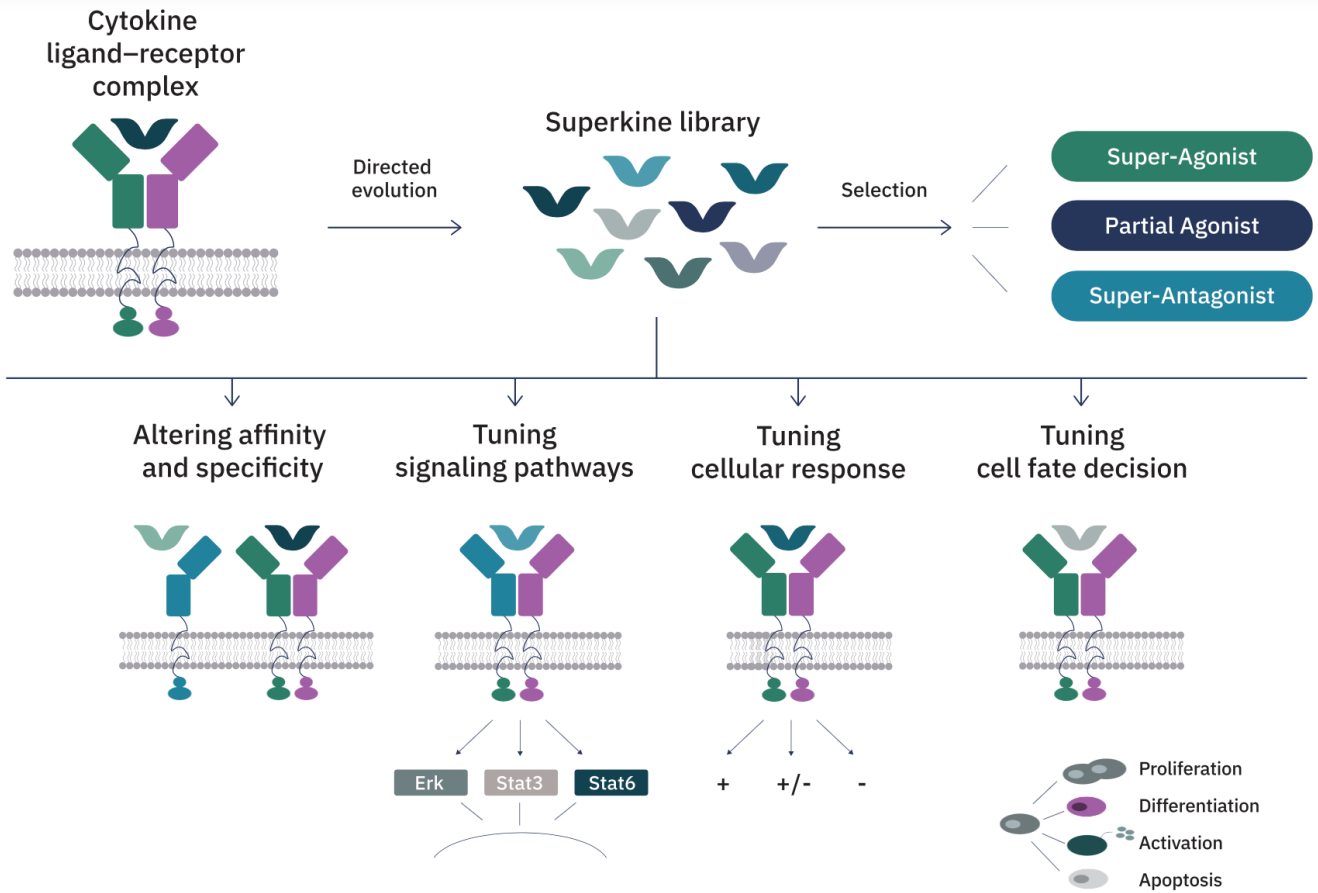


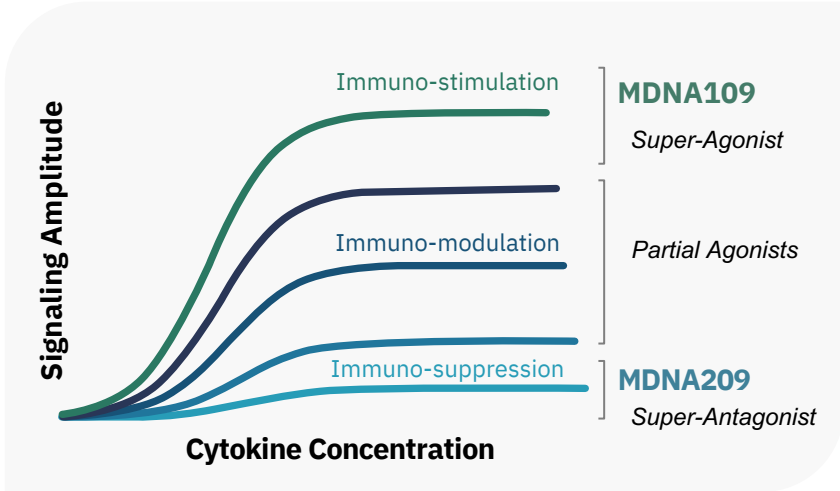
MEDICENNA

The Promise of IL-2 Therapy (Paris, France)

Directed Evolution + Yeast Display = Tunable Superkines

- Platform has generated a library of Superkines with diverse immune modulating capabilities



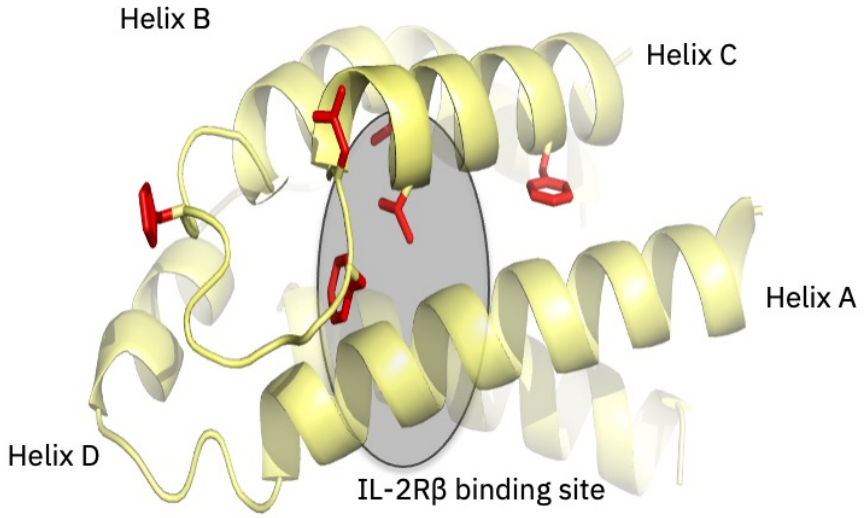


MDNA109 is a First-Generation IL-2 Superkine

LETTER

nature

Exploiting a natural conformational switch to engineer an interleukin–2 'superkine'



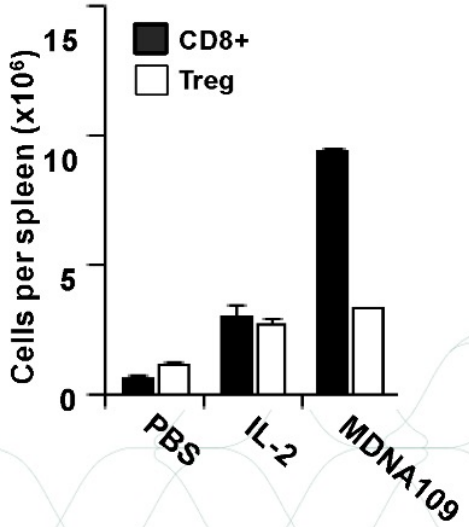
Core Mutations: L80F, R81D, L85V, I86V, I92F

Levin et. al, Nature, 2012 484(7395): 529–533.

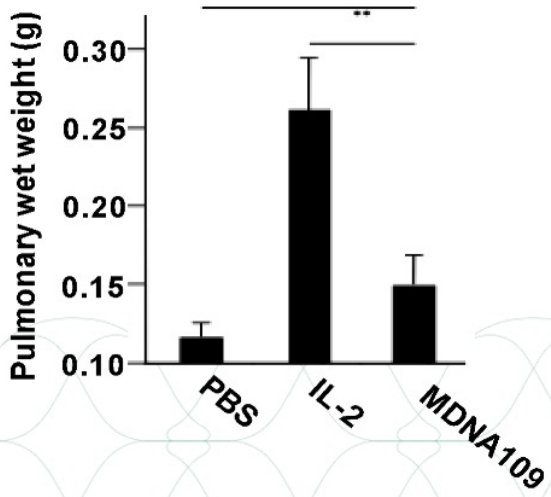
Enhanced Affinity for CD122 (IL-2Rβ); Retains binding to CD25 (IL-2Rα)

SPR data K_D (nM)	CD122 (IL-2Rβ)	CD25 (IL-2Rα)
IL-2	280	6.6
MDNA109	1.4	6.6

Selective Expansion of CD8⁺ T-cells over T_{regs}



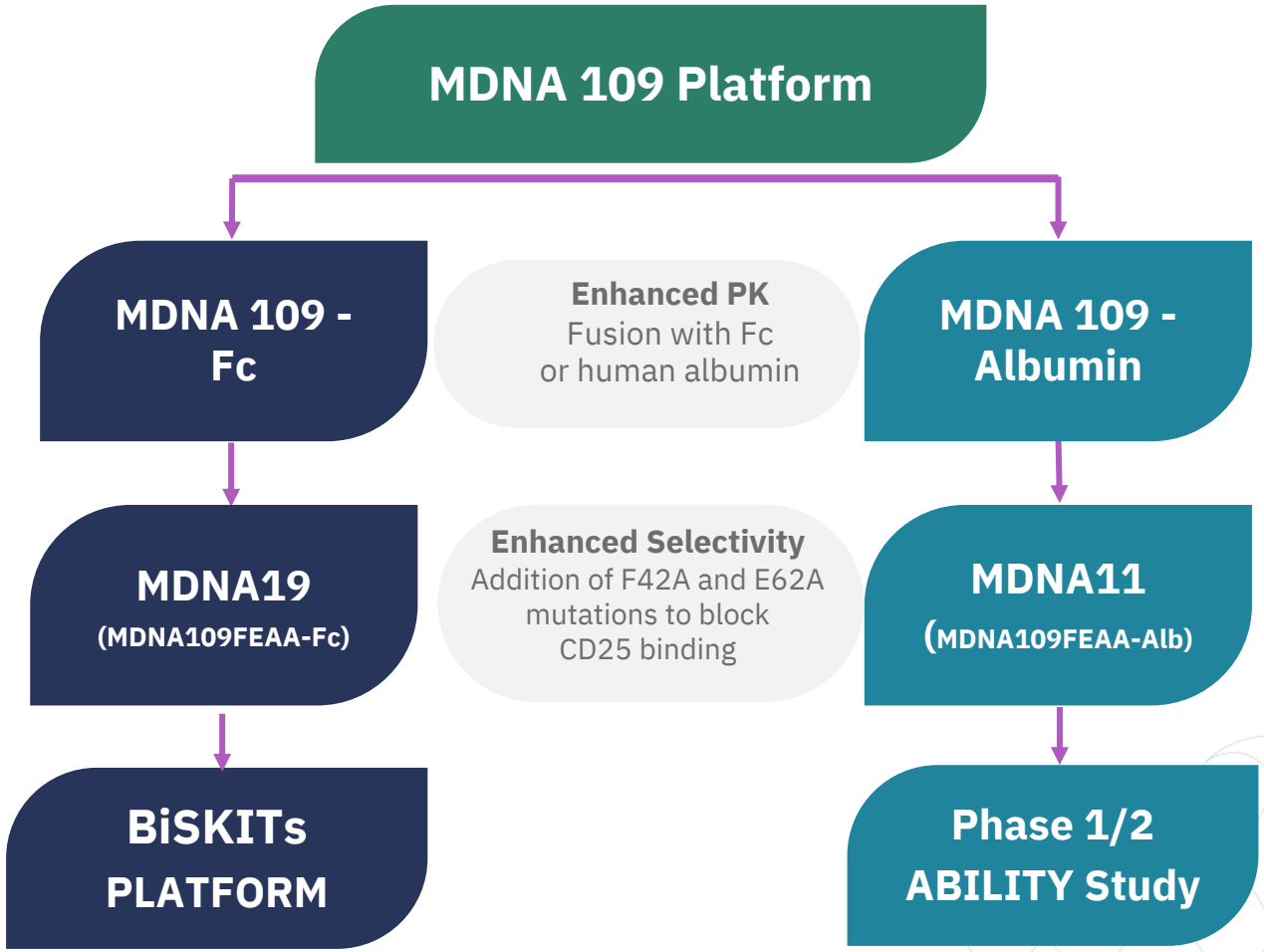
Reduced Adverse Side Effects



Mice were dosed with 20 µg of IL-2 or MDNA109 (IP, for 5 days).
Data shown above based on analysis performed on day 6

Engineering MDNA109 to Extend PK & Enhance Selectivity

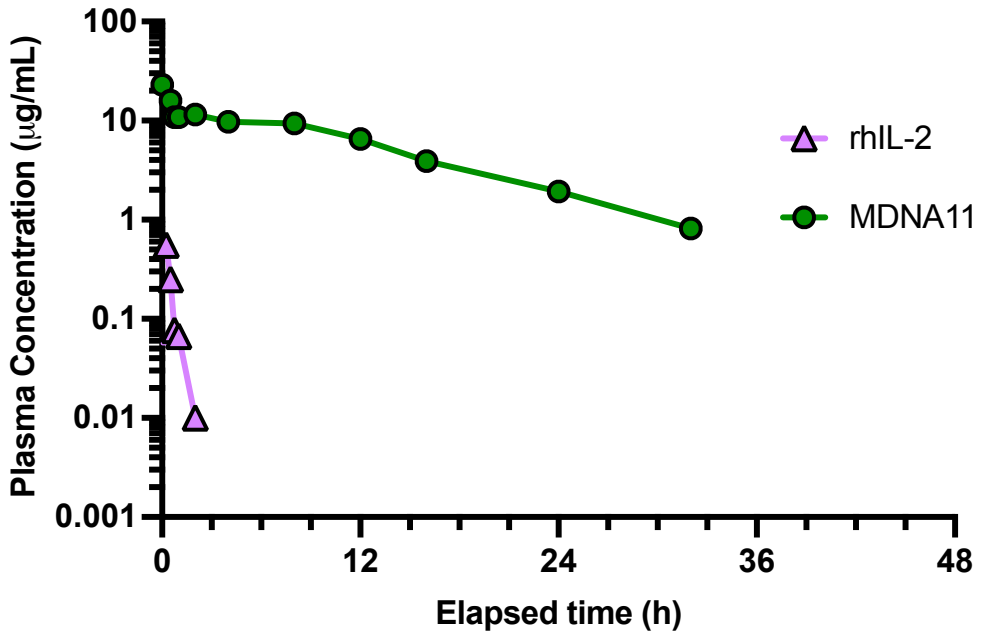
- Enhanced IL-2Rβ Binding and Abolish IL-2Rα Binding



	Affinity for IL-2Rβ K_D(nM)	Affinity for IL-2Rα K_D(nM)
rhIL-2	280	6.6
MDNA109	14	6.6
MDNA11	6.6	No binding

MDNA11: Fusion to Albumin Extends Half Life and Bioavailability

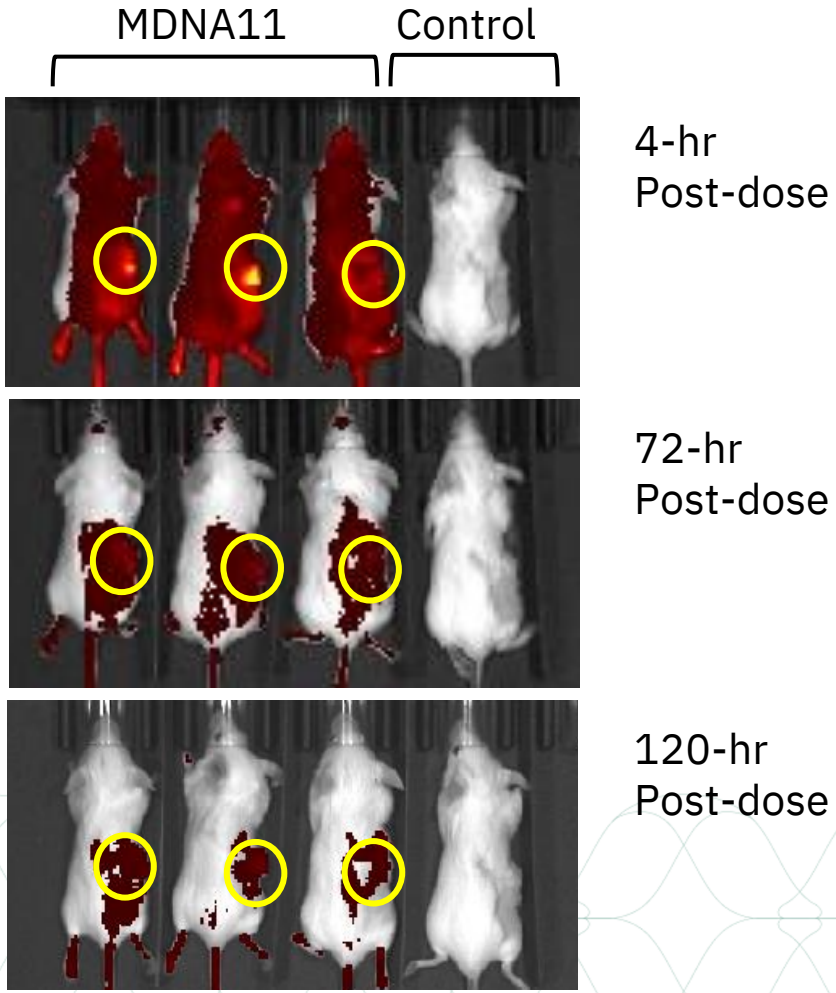
Improves PK Profile in Mice



	C_{max} (µg/mL)	AUC (µg.hr/mL)	T_{half} (hr)
rhIL-2	5.77	1.07	0.28
MDNA11	23.02	182.3	6.83

Naive C57Bl/6 mice IV dosed at 1 mg/kg IV

Durable Accumulation in CT26 Tumor Bearing Mice



MDNA11 labelled with VivoTag800
IV dose: 1 mg/kg
Tumor size: 150-200 mm^3

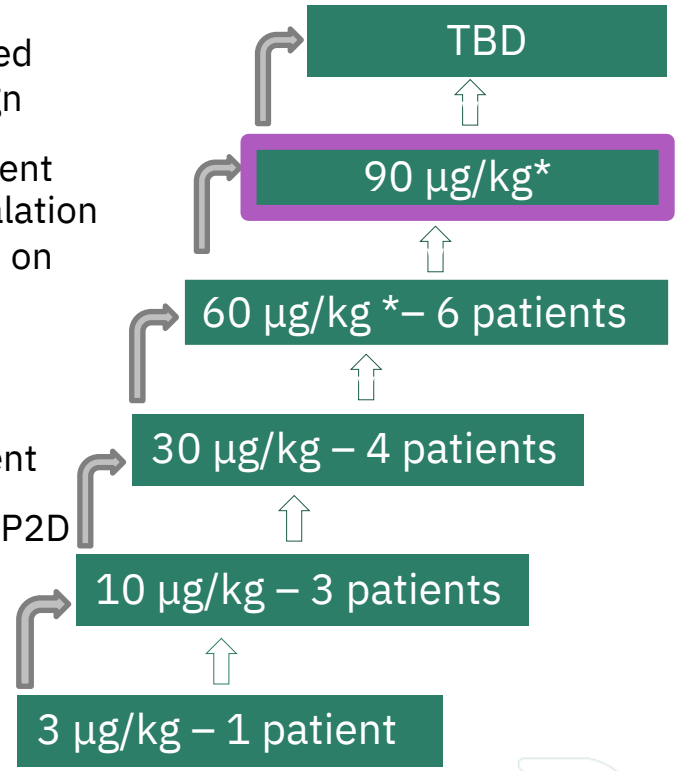
Phase 1/2 ABILITY Study Schema: Enrolling DL5

Basket, Accelerated Sequential Dose Escalation and Expansion Study of MDNA11 +/- Pembrolizumab

MDNA11
Monotherapy Dose Escalation

N ~ 20: Select tumors

- Modified, accelerated 3+3 design
- Intra-patient dose escalation permitted on sponsor approval
- DLT assessment
- Identify RP2D



MDNA11
Monotherapy Dose Expansion

N~ 40
(Melanoma, up to N = 20)

MDNA11 administered alone at RP2D via IV infusion Q2W or Q3W

Signals of anti-tumor activity

MDNA11 + Keytruda
Dose Expansion

N~ 40
(Melanoma, up to N = 20)

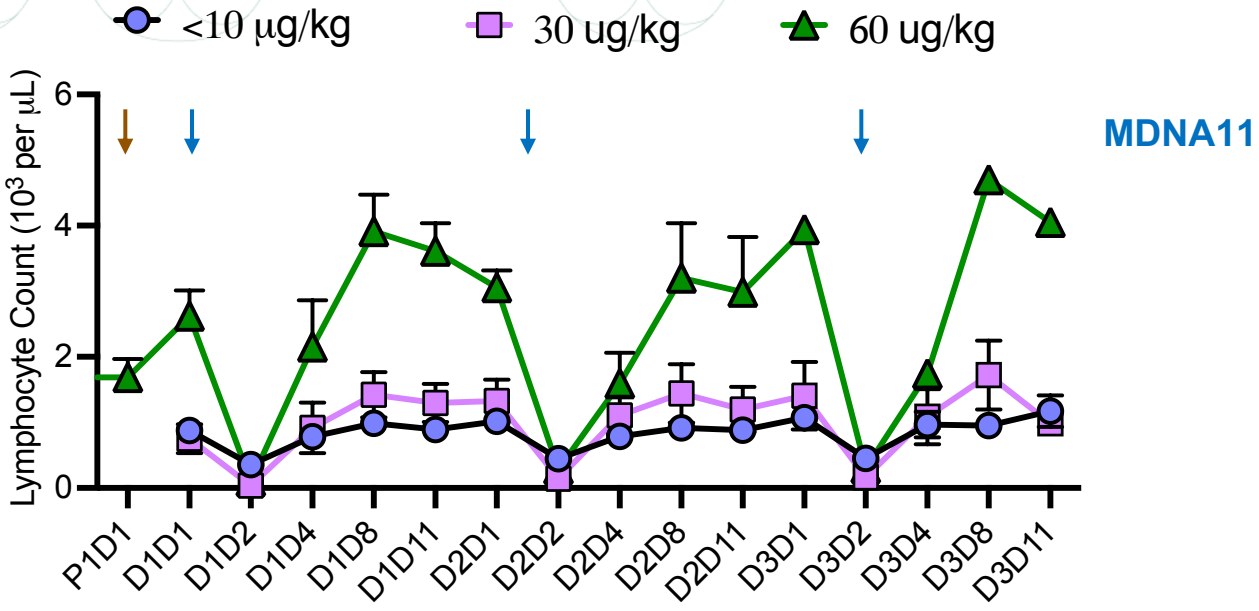
Safety run-in (21 days)

MDNA11 administered at RP2D in combination with CPI via IV infusion Q3W (planned)

Signals of anti-tumor activity

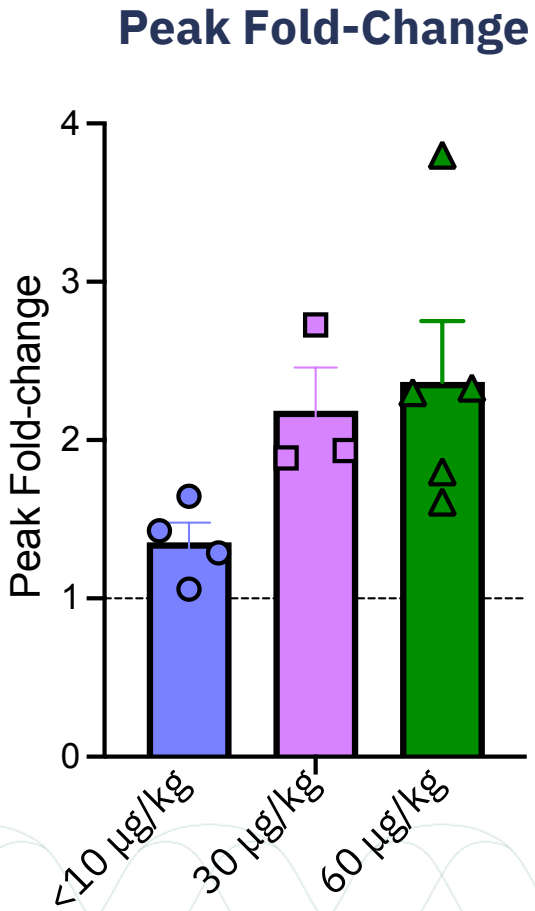
*Step-up dosing utilized: two priming doses of 30 µg/kg given before the indicated target dose

MDNA11 Induces Dose Dependent Increase in Lymphocyte Count



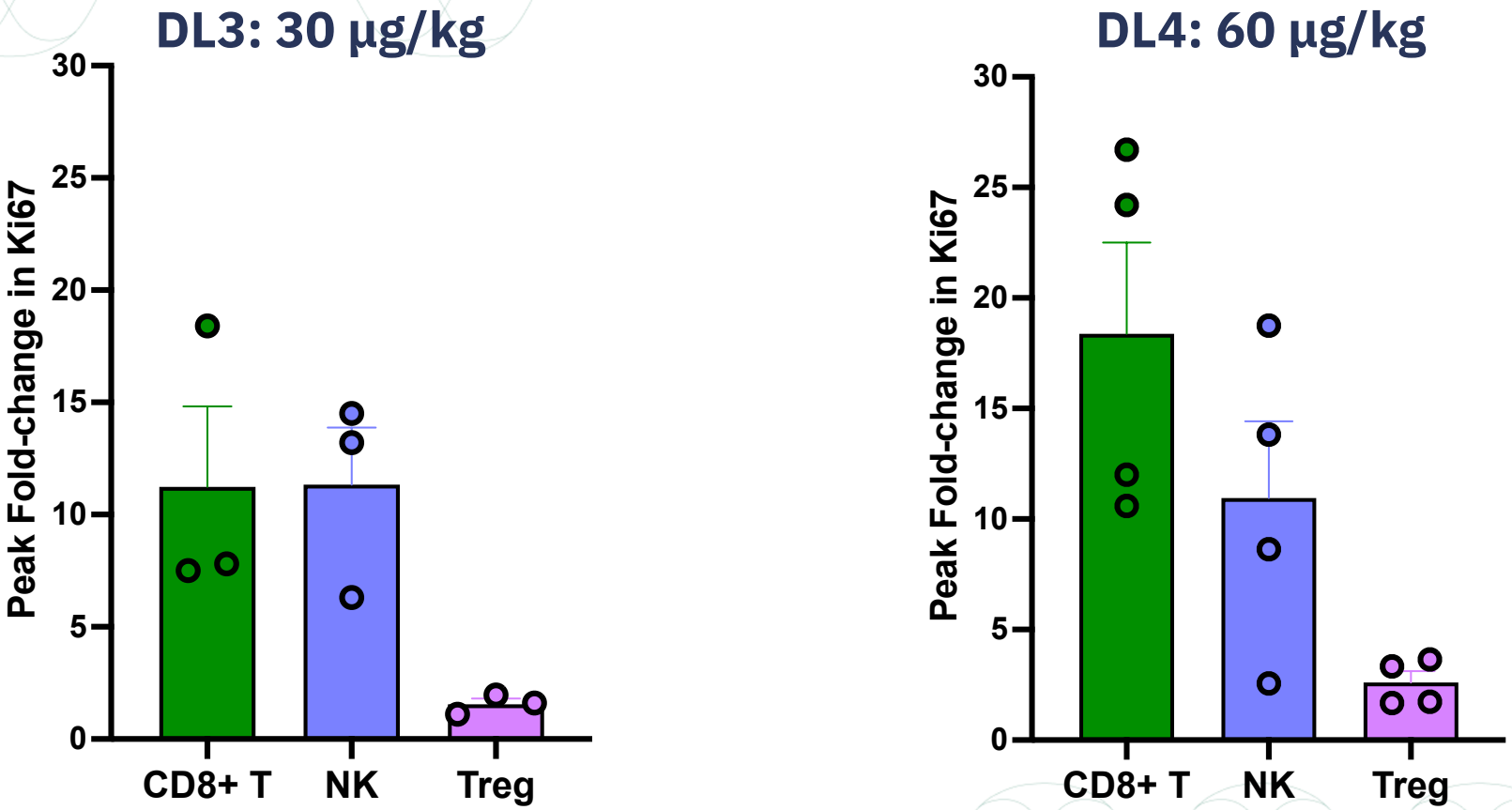
	Average AUC (day.10^3 cells/µL) (Average of Dose 1 & 2)
< 10 µg/kg	3
30 µg/kg	4.8
60 µg/kg	12.2

DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to target dose (60 µg/kg Q2W)
AUC measured as area between minimum lymphocyte count values



Peak fold-change relative to baseline
For < 10 µg/kg and 30 µg/kg, peak data for Dose 3
For 60 µg/kg, peak data for Target Dose 1

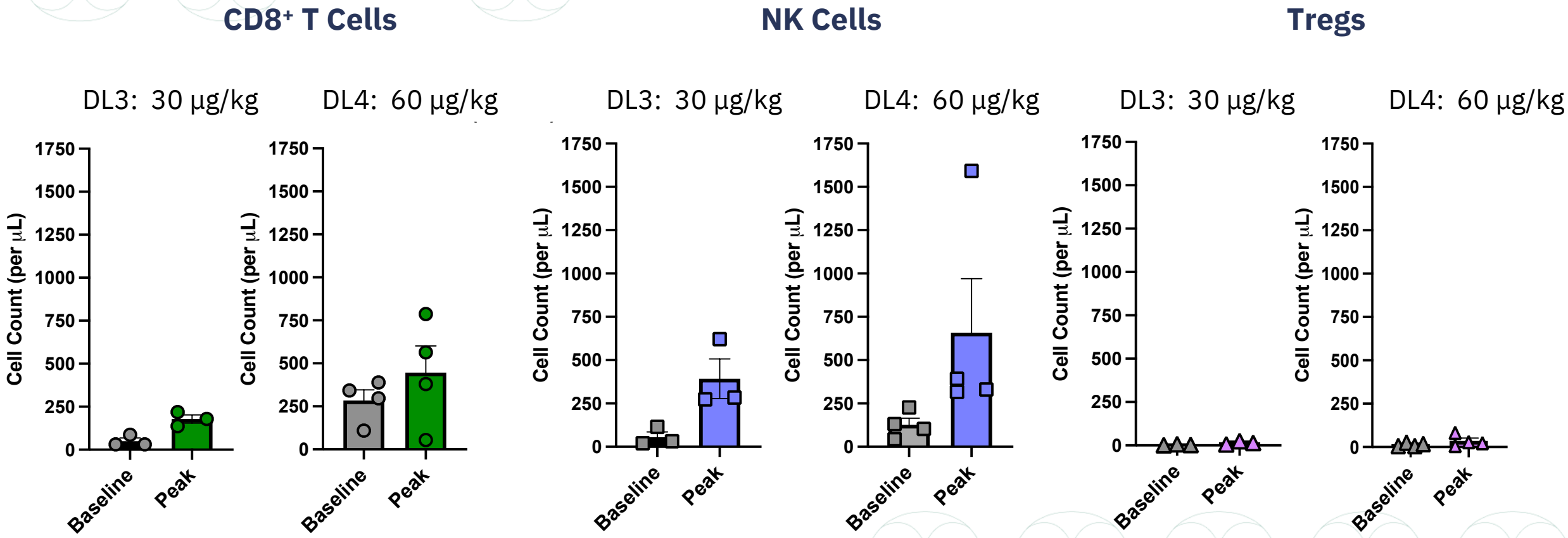
MDNA11 Preferentially Stimulates CD8+ T & NK Cell Proliferation (Ki67)



Peak fold-change relative to respective baseline (D1D1 for DL3; P1D1 for DL4)
DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W)
DL3 data based on 3rd dose cycle

MDNA11 Preferentially Expands CD8+ T and NK Cells Over Tregs

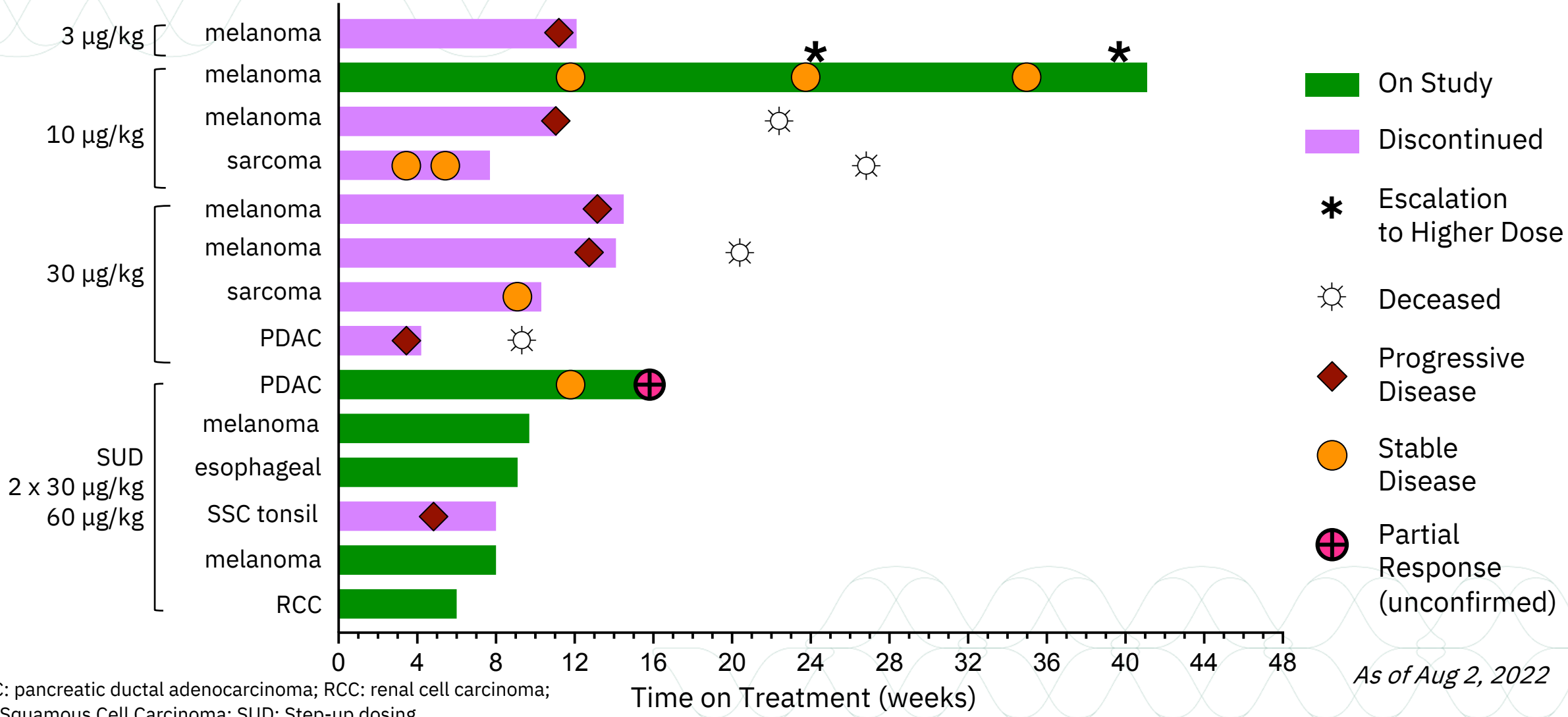
- Increase in number of CD8+ T and NK cells with minimal change in Treg counts



DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W).
DL3 data based on 3rd dose cycle; DL4 data based on 1st dose

Duration of Treatment and Summary of Treatment Response

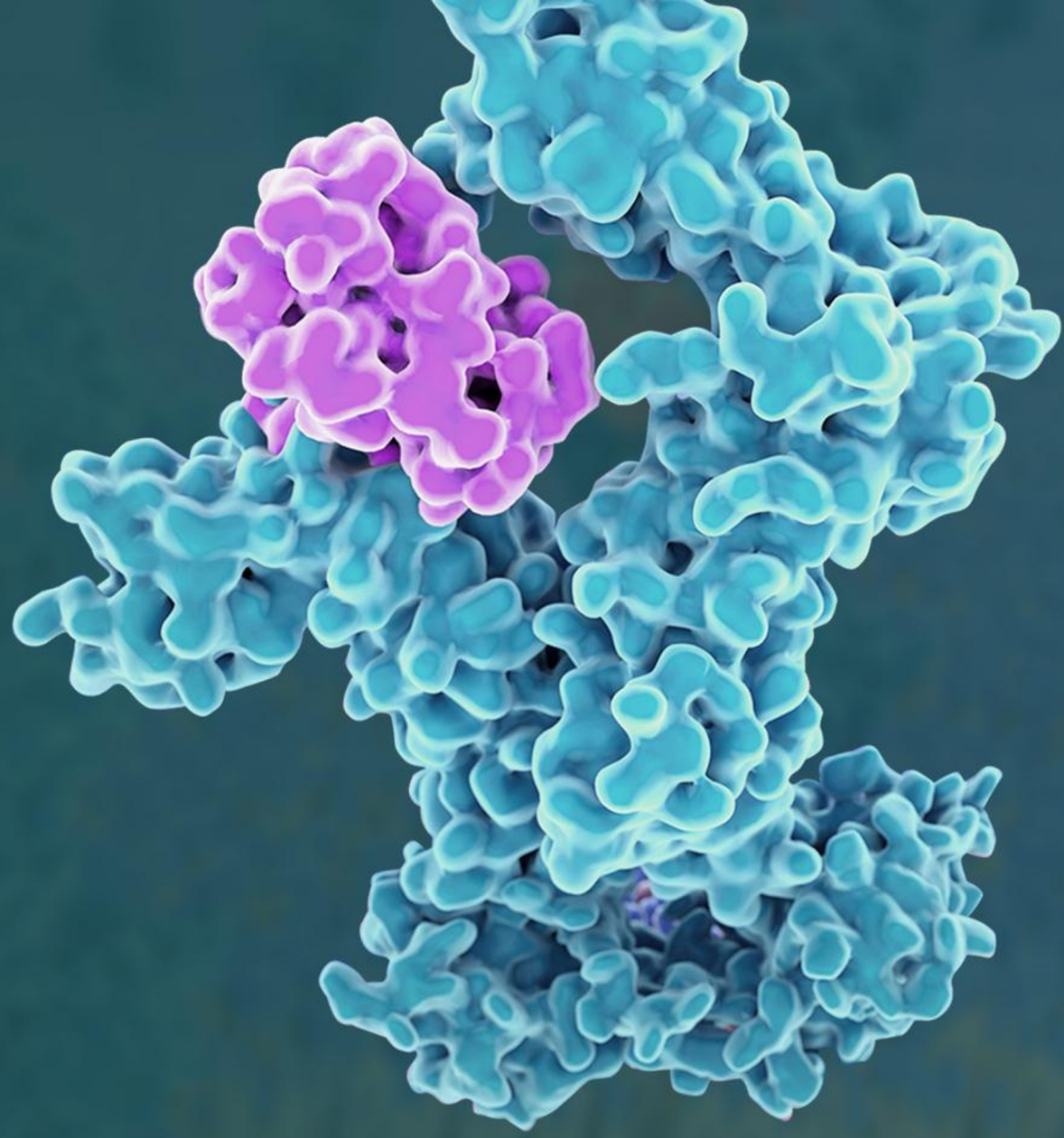
- Of the 10 evaluable patients, 3 show stable disease (SD) and 1 shows partial response (PR; unconfirmed)



As of Aug 2, 2022

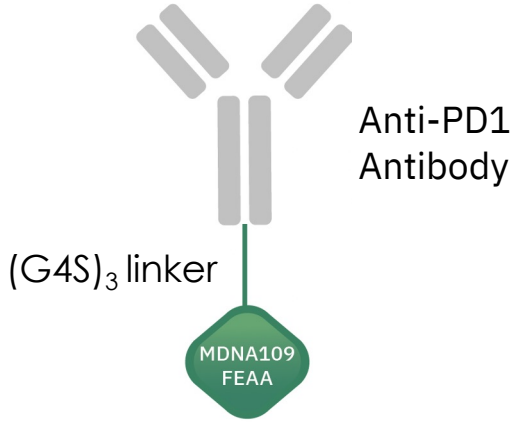
PDAC: pancreatic ductal adenocarcinoma; RCC: renal cell carcinoma;
SSC: Squamous Cell Carcinoma; SUD: Step-up dosing

Bifunctional **S**uper**K**ines for **I**mmuno**T**herapy (BiSKIT)

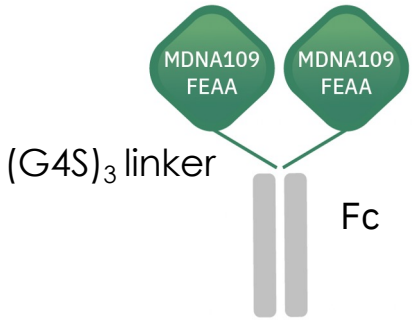


Overview of Anti-PD1-MDNA109FEAA (MDNA223) and Proposed MOA

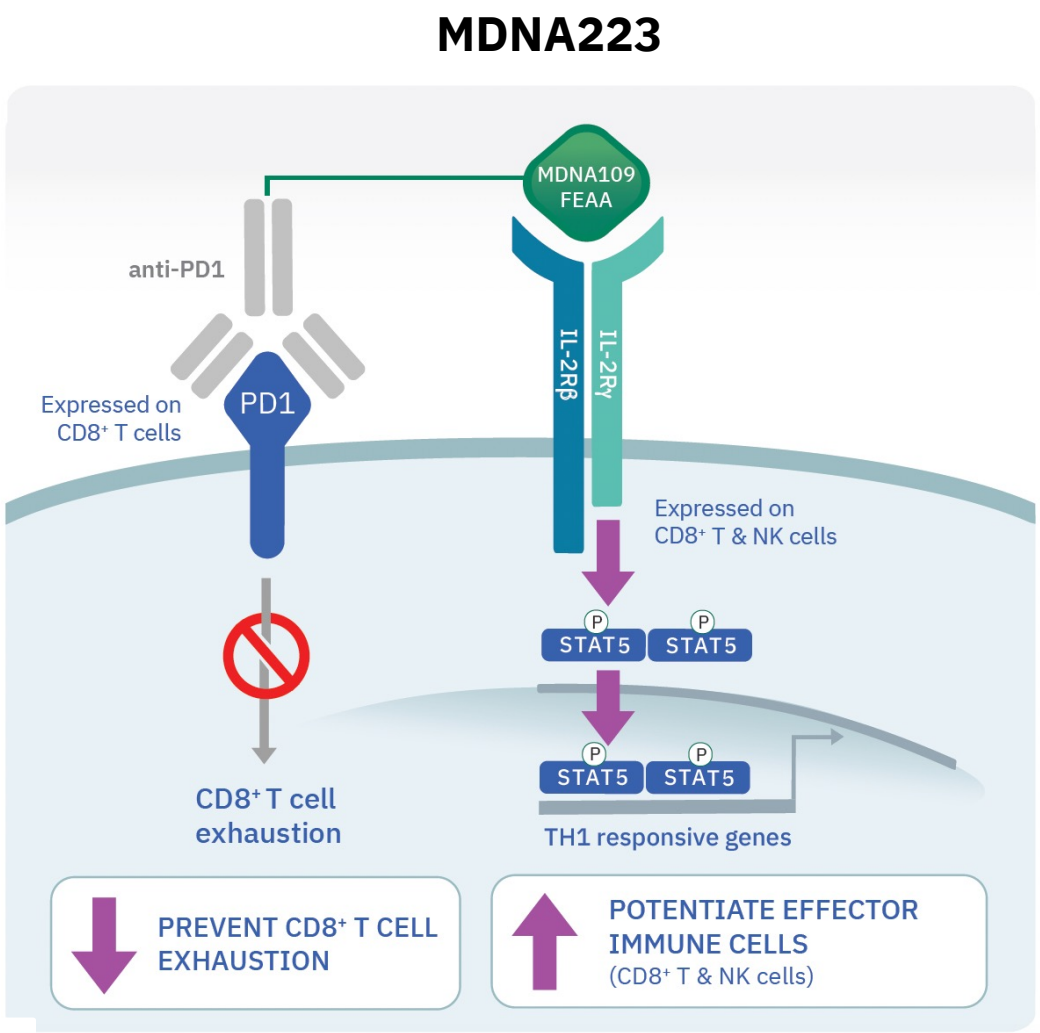
MDNA223 (Anti-PD1-MDNA109FEAA)



MDNA19 (MDNA109FEAA-Fc)



cis-Binding to IL-2R and PD1 on Same CD8⁺ T Cell



Synchronized

IL-2R Activation
+
PD1 Blockade

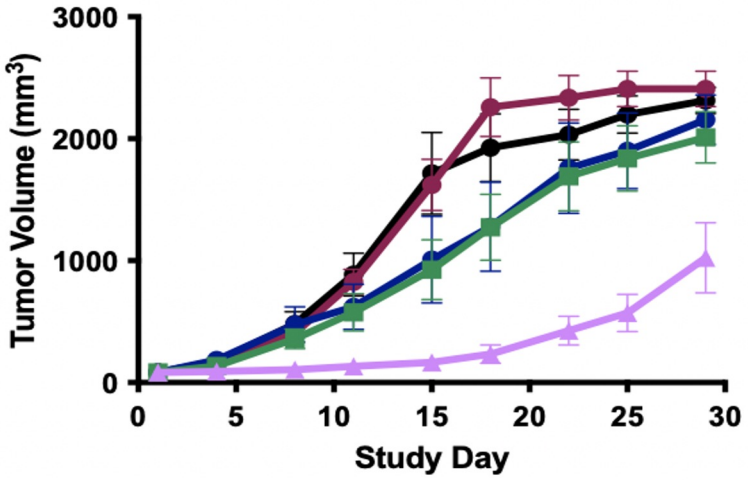
↓

Superior Therapeutic Efficacy

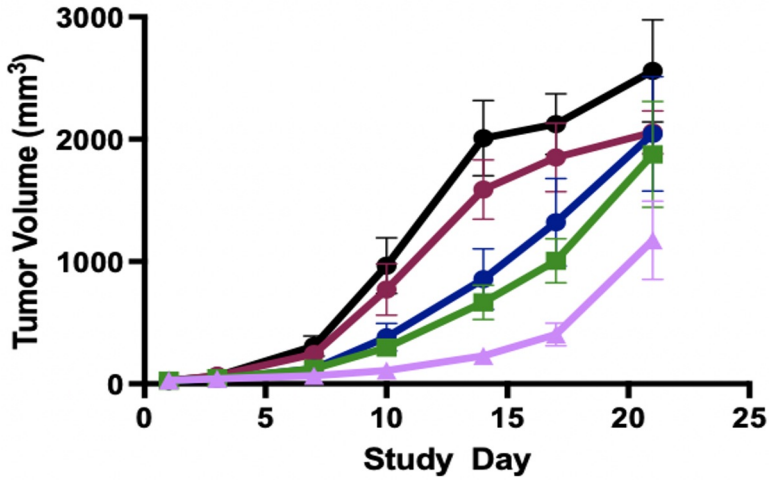
MDNA223m Demonstrates Superior Efficacy in Multiple Tumor Models

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

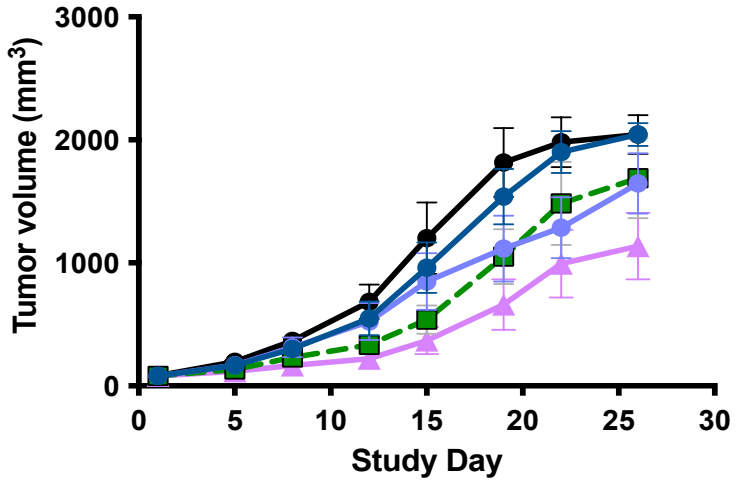
CT26 Colon Tumor Model



B16F10 Melanoma Model



E0771 Breast Tumor Model

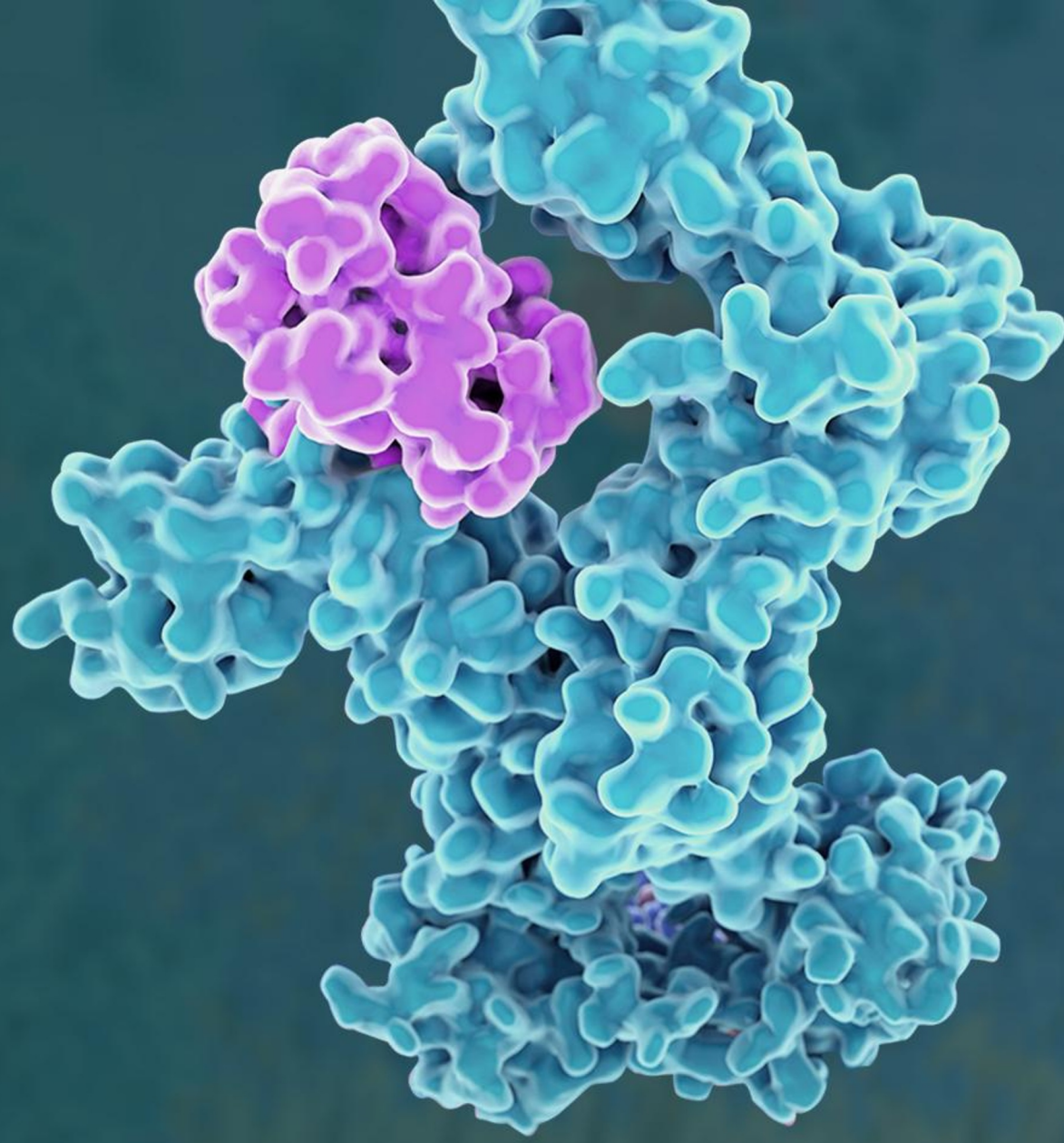


Vehicle
Anti-mPD1 (1.8 mg/kg)
MDNA19 (1 mg/kg)
Anti-mPD1 (1.8 mg/kg) + MDNA19
MDNA223m (2 mg/kg)

Vehicle
Anti-PD1 (10 mg/kg)
MDNA19 (1 mg/kg)
Anti-PD1 (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)

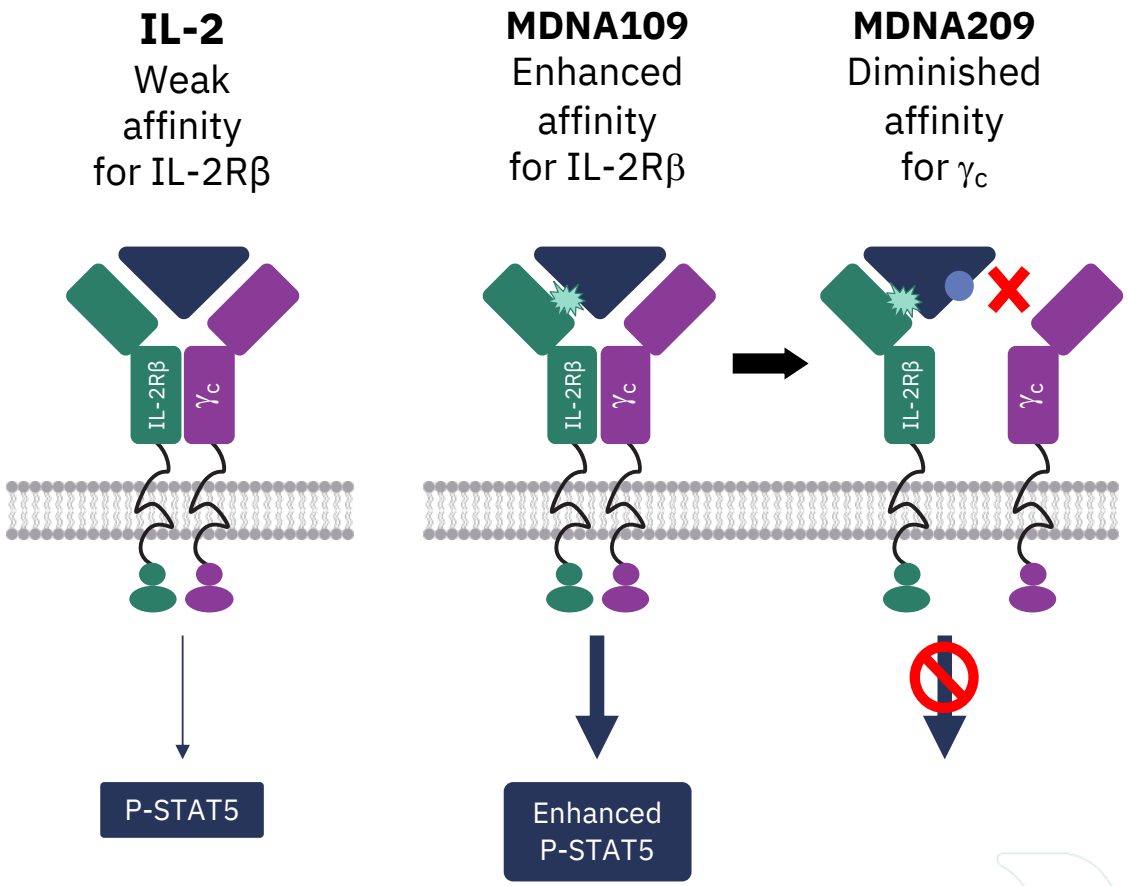
MDNA209:
IL-2 Super-Antagonist

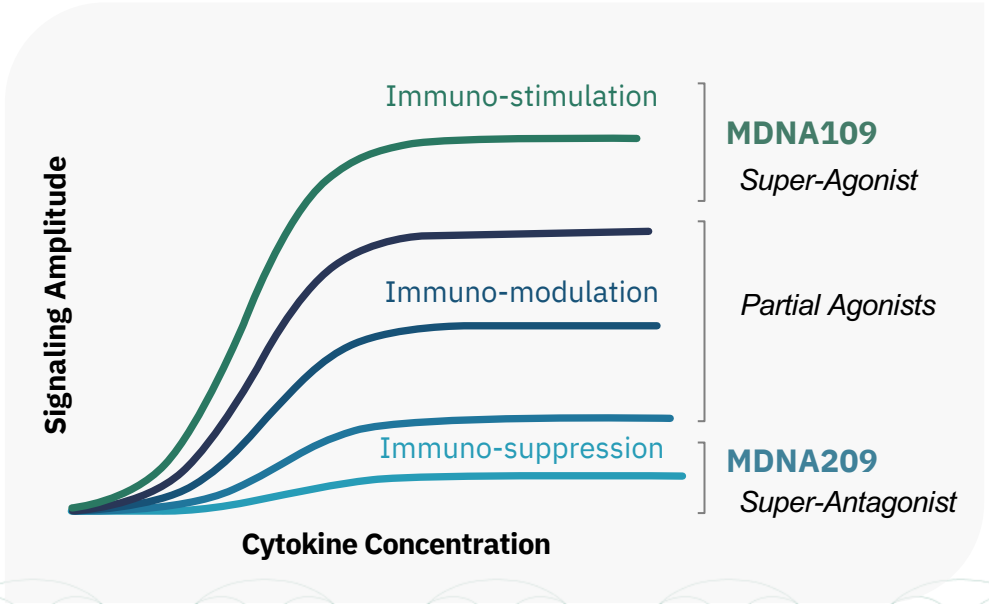


MDNA209: An IL-2/IL-15 Antagonist with a Unique MOA

Dominant-negative Inhibitor of IL-2R Signaling

- Binds IL-2Rβ with high affinity and blocks engagement of γ_c to suppress downstream signaling





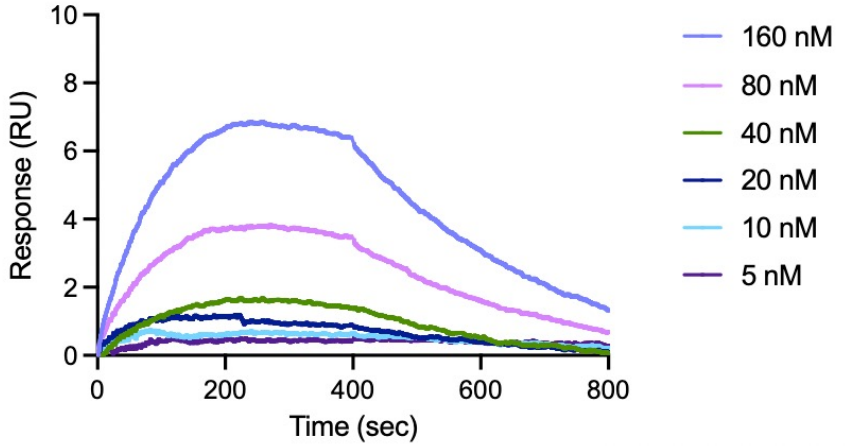
MDNA209 Blocks Formation of Functional IL-2R βγc Complex

Individual Receptor Subunit Binding

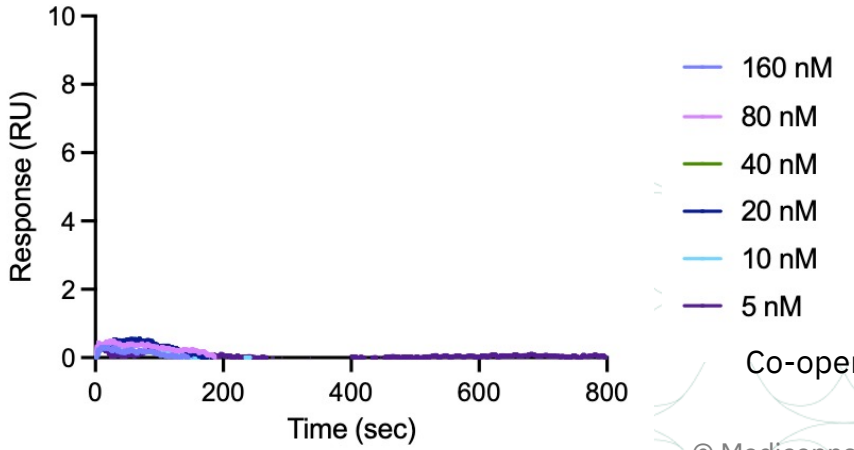
	Affinity for IL-2Rβ K_D(nM)	Affinity for IL-2Rα K_D(nM)
IL2-Fc	135	26
MDNA109-Fc	2.7	14
MDNA209-Fc	3.9	39.1

Affinity measured using SPR

High Affinity of γ_c to Dimeric MDNA109-Fc/IL-2Rβ Complex



No Binding of γ_c to Dimeric MDNA209-Fc/IL-2Rβ Complex



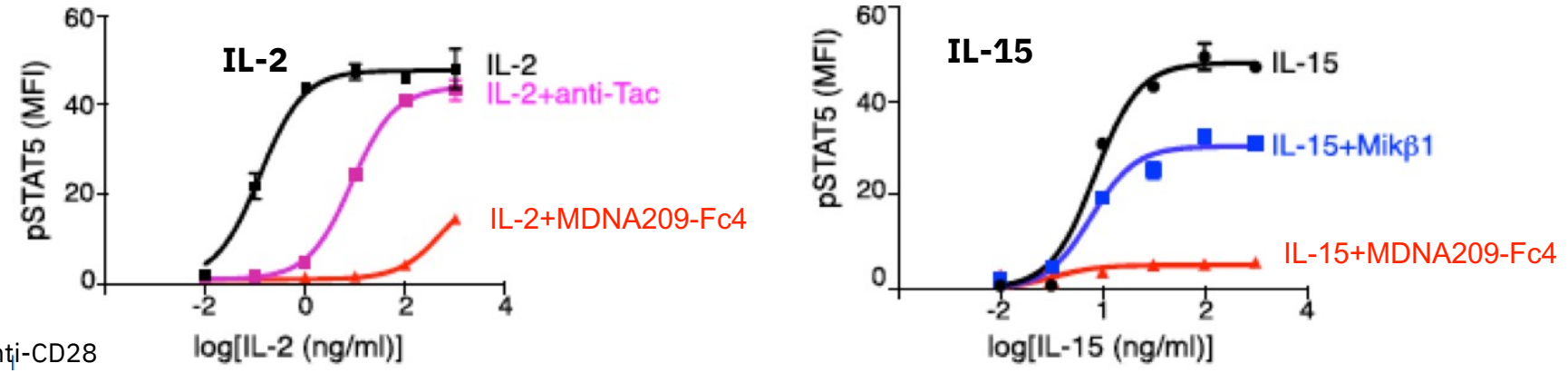
Co-operative binding by SPR

MDNA209 Blocks IL-2/IL-15 Mediated Signaling and Proliferation

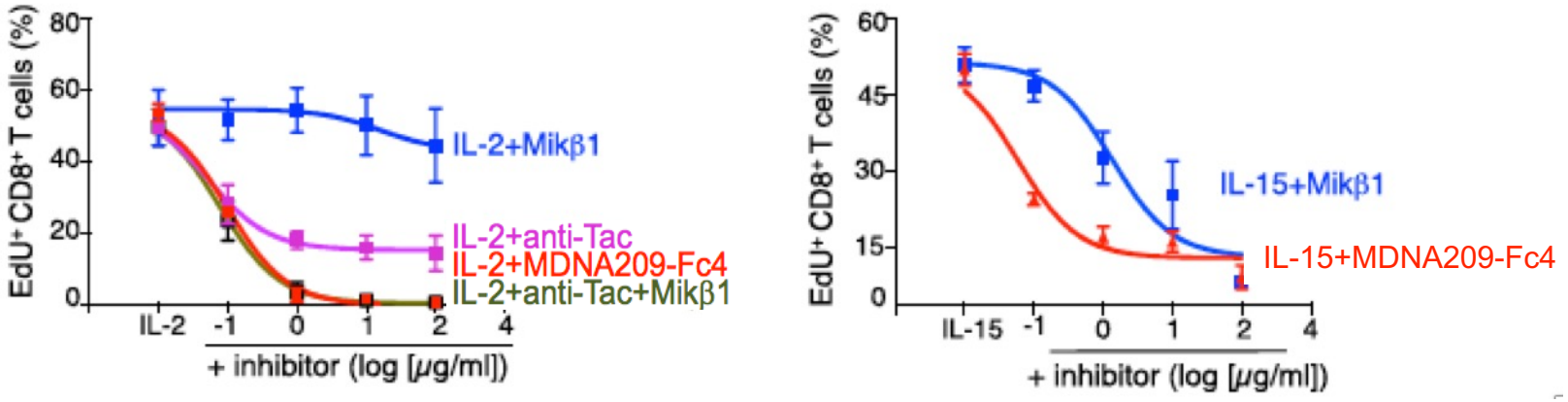
- MDNA209-Fc4 Inhibits IL-2 and IL-15 Induced Signaling & Function More Potently than anti-Tac (anti-IL2Rα) and Mikb1 (anti-IL2Rβ) Blocking Antibodies

Signaling

Human CD8+ T cells
pre-activated with anti-CD3 + anti-CD28

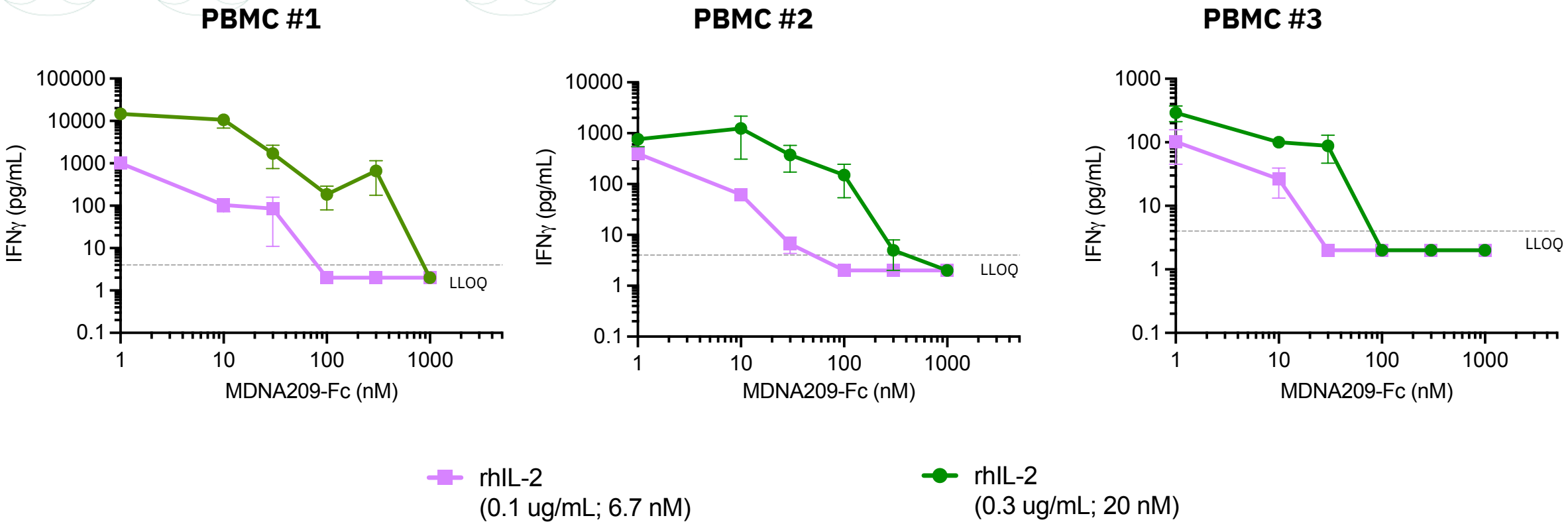


Proliferation



Mitra S, *et al.*, Immunity. 2015 May 19;42(5):826-38

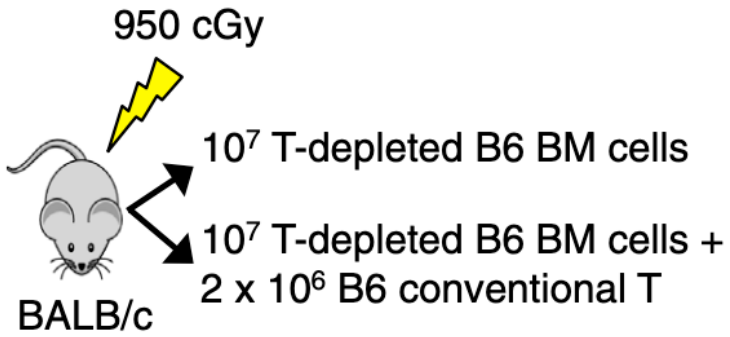
Blockade of IL-2 Induced IFNγ Secretion by MDNA209-Fc

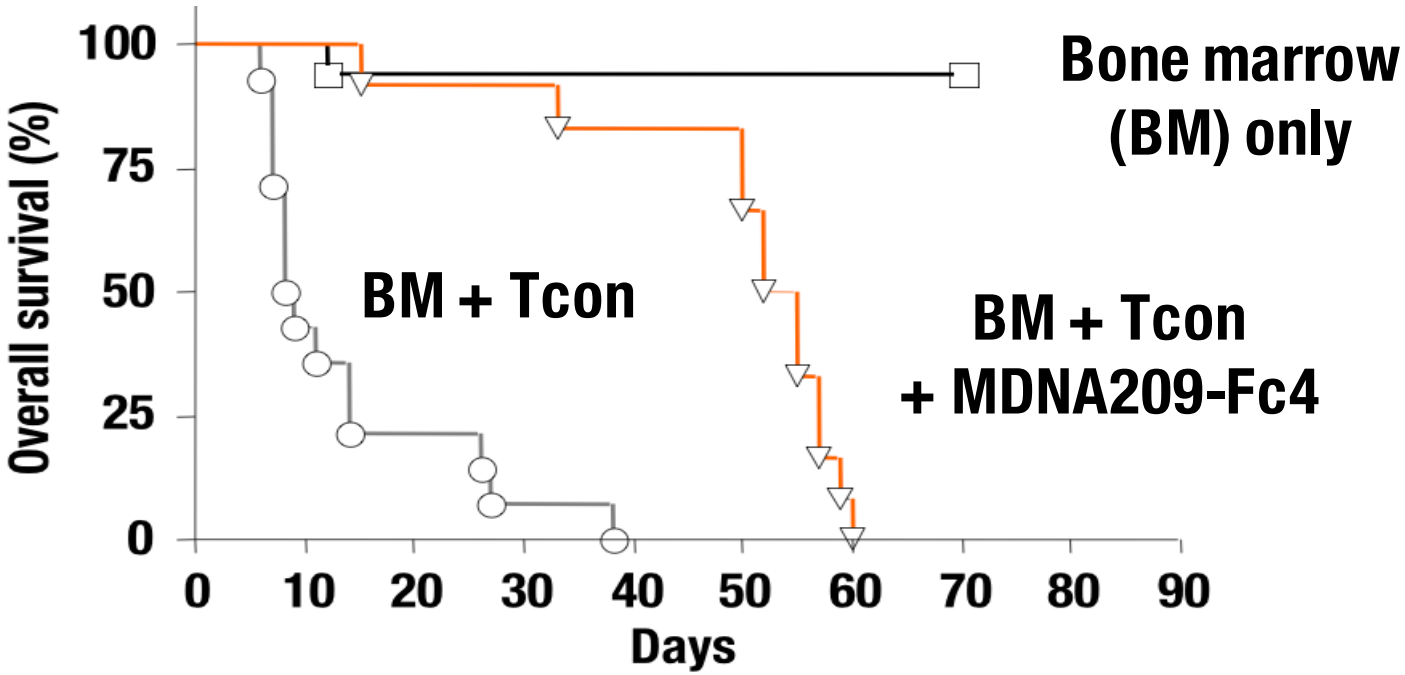


PBMC treated with increasing concentration of MDNA209-Fc in presence of indicated rhIL-2 concentration for 48 hours
IFNγ quantify by ELISA
Values below Lower Limit of Quantification (LLOQ) plotted as 0.5 x LLOQ
Values above Upper Limit of Quantification (ULLOQ) plotted as 2 x LLOQ

Long-Acting MDNA209 Demonstrates In Vivo Efficacy in GVHD Model

Allogeneic Model with BALB/c Host and C57Bl/6 Donor





GVHD: Graft Vs. Host Disease;
Mitra S, *et al.*, Immunity. 2015 May 19;42(5):826-38

10-day treatment with MDNA209-Fc4 (100 µg twice per day by IP injection)

MDNA209's Differentiated MOA Offers Opportunity

IL-2-Targeting Competitive Class

Agonists of Regulatory T-cells

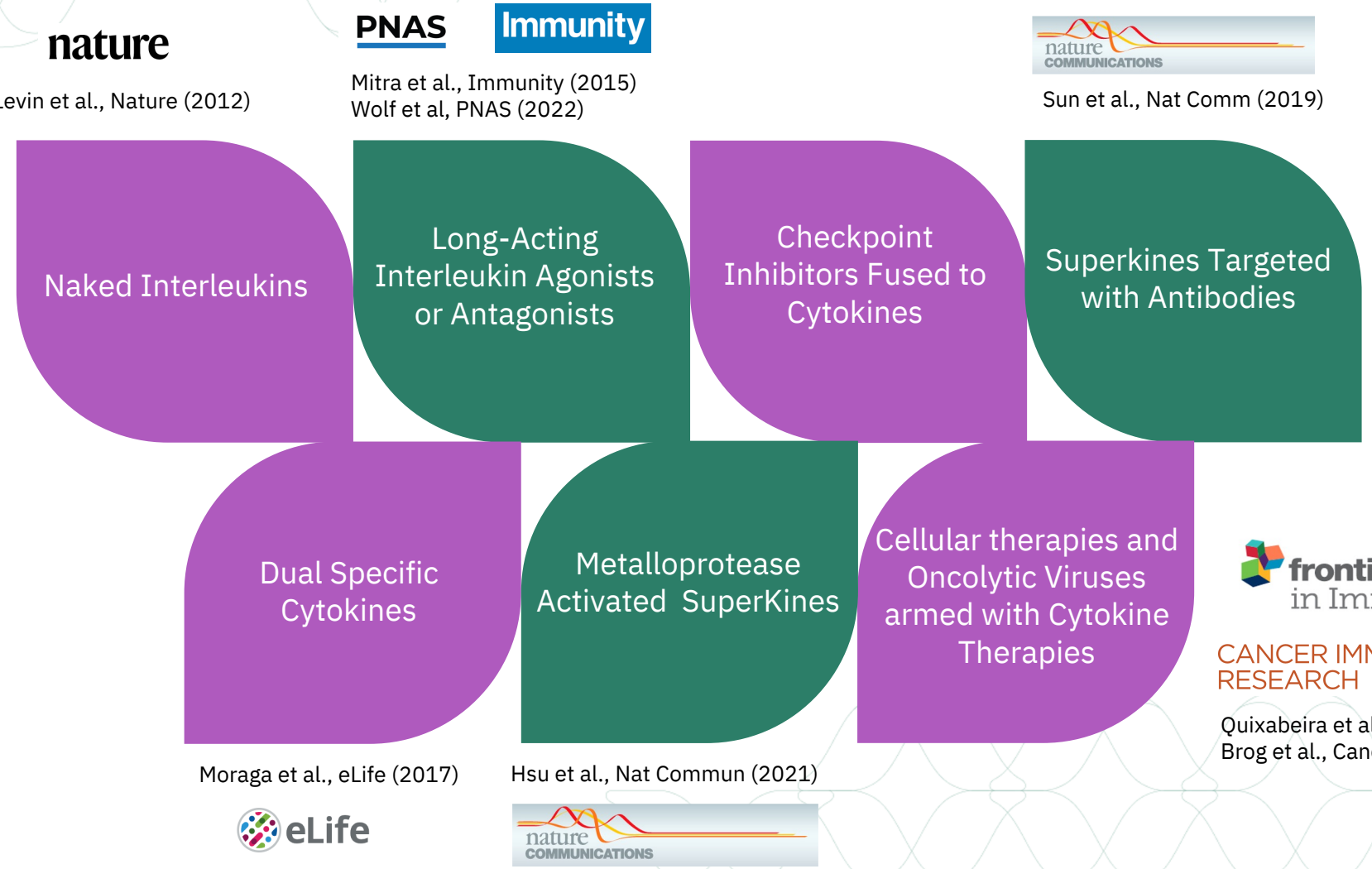
- ✗ Indirect targeting of effector immune cells
- ✗ Dependent on regulatory T-cells *not always present during acute autoimmunity*
- ✗ Do not *directly* reduce the destructive activity of self-reactive T or NK cells

MDNA209

Antagonist of Effector Cells

- ✓ *Directly* targets disease-driving effector immune cells
  - Blocks $CD4^+$ and $CD8^+$ T cells and NK cells
- ✓ Opportunity for broad use in autoimmune indications with minimal T-reg involvement

IL-2 Superkines Independently Validated Across Diverse Treatment Modalities



Thank You