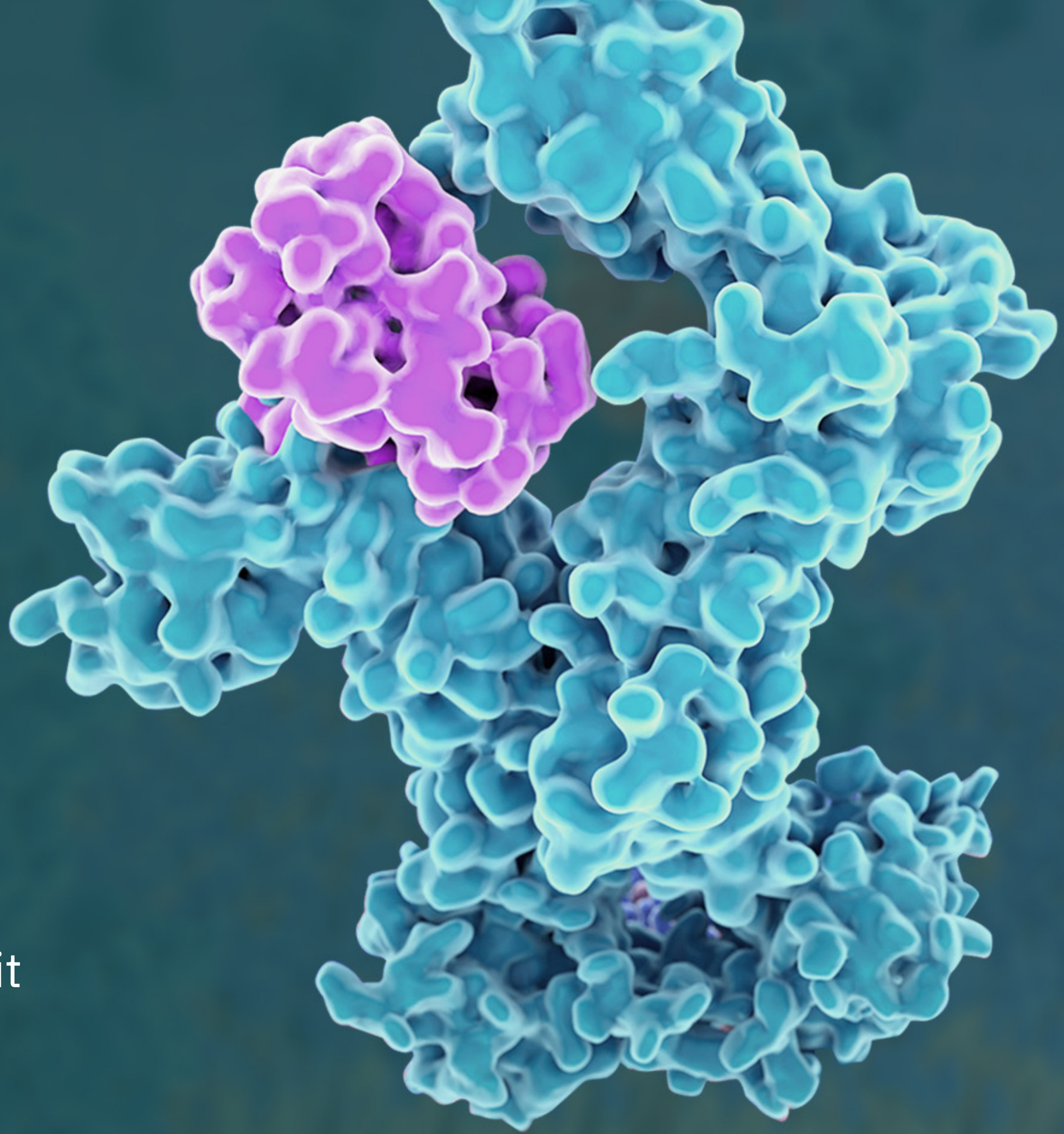
MARCH 25 2021

Designer Cytokines

Fahar Merchant, PhD
President & CEO

Cytokine-Based Cancer Immunotherapies Summit



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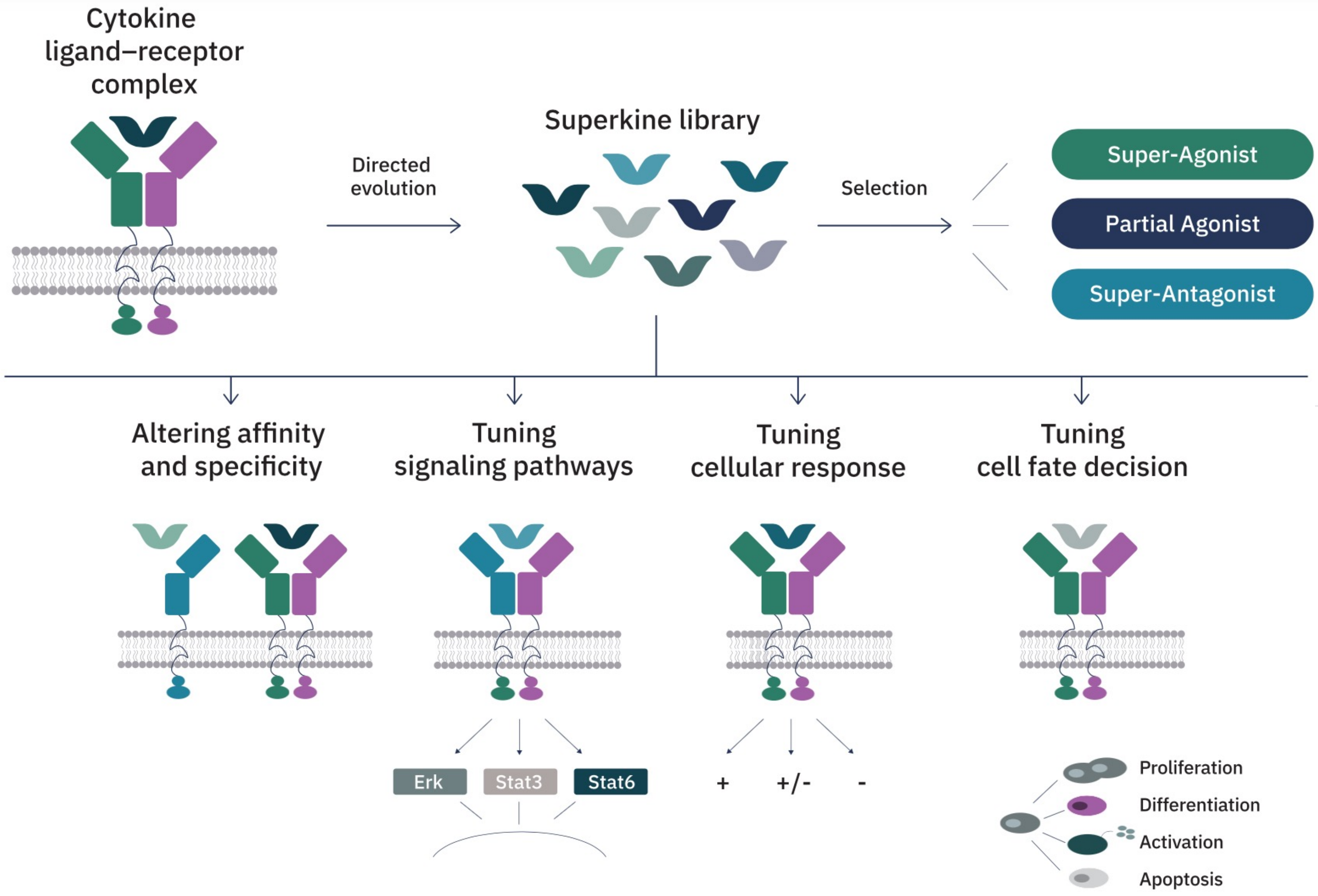
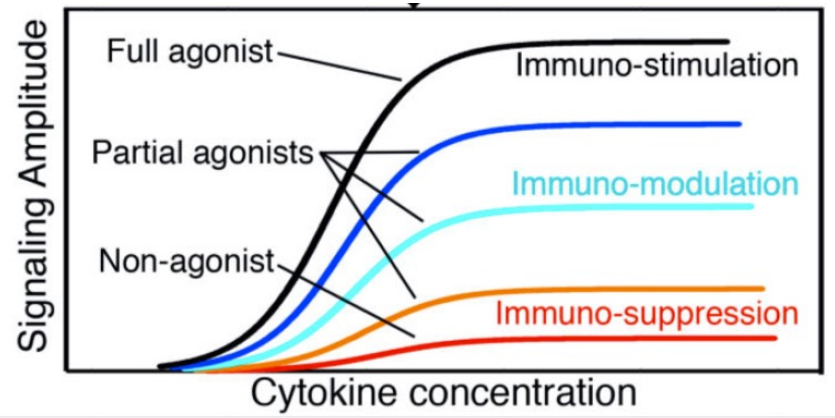
Synopsis

- Design of novel interleukin super-agonists, partial agonists and super-antagonists using directed evolution
- Utilize rational approaches to further design long-acting IL-2, IL-4 and IL-13 Superkines without masking functional activity
- Introduce next generation **Bi**-functional **S**uper**K**ine **I**mmuno**T**herapies (BiSKITs) for Cancer

Directed Evolution + Yeast Display = Tunable Superkines

Platform has generated extensive library of IL-2, IL-4, and IL-13 Superkines with unique properties





Medicenna's Superkine Platforms

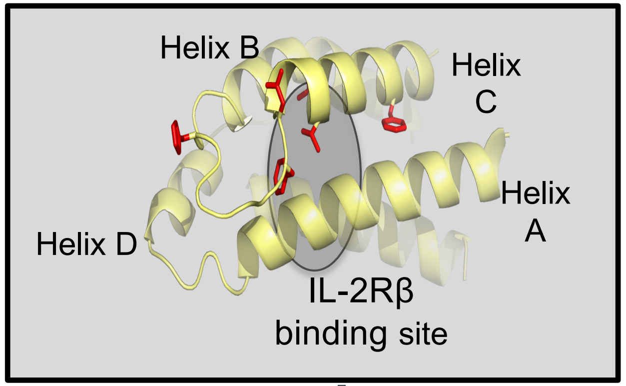
Superkines Fused to Pro- or Anti-apoptotic Payloads (Empowered Superkines™)

Long-Acting Interleukin Agonists or Antagonists (LAILA™)

Bi-Functional Superkine Immunotherapies (BiSKITs™)

Evolution of IL-2 Super-Agonists

MDNA109 is a First Generation Engineered Human IL-2 Showing Enhanced Agonist Activity



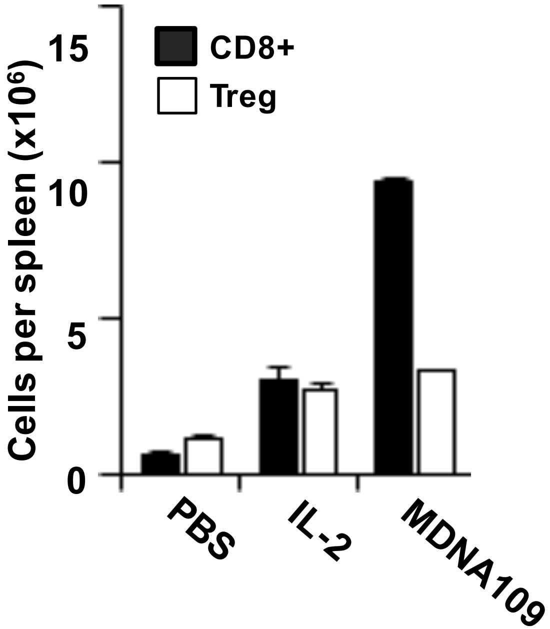
nature

Levin et. al, Nature, 2012

Enhanced Affinity for CD122 (IL-2Rβ)

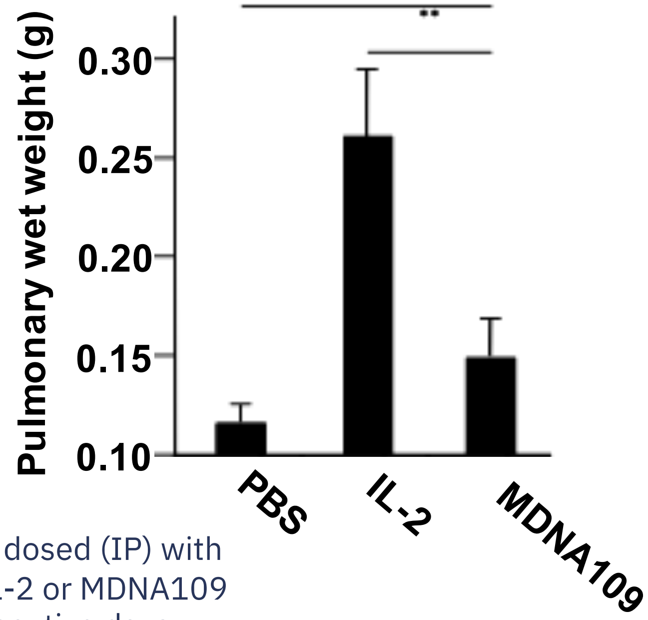
SPR data K_D (nM)	CD25	CD122
IL-2	6.6	280
MDNA109	6.6	1.4

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



Mice were dosed with 20 µg of IL-2 or MDNA109 (IP, for 5 days).

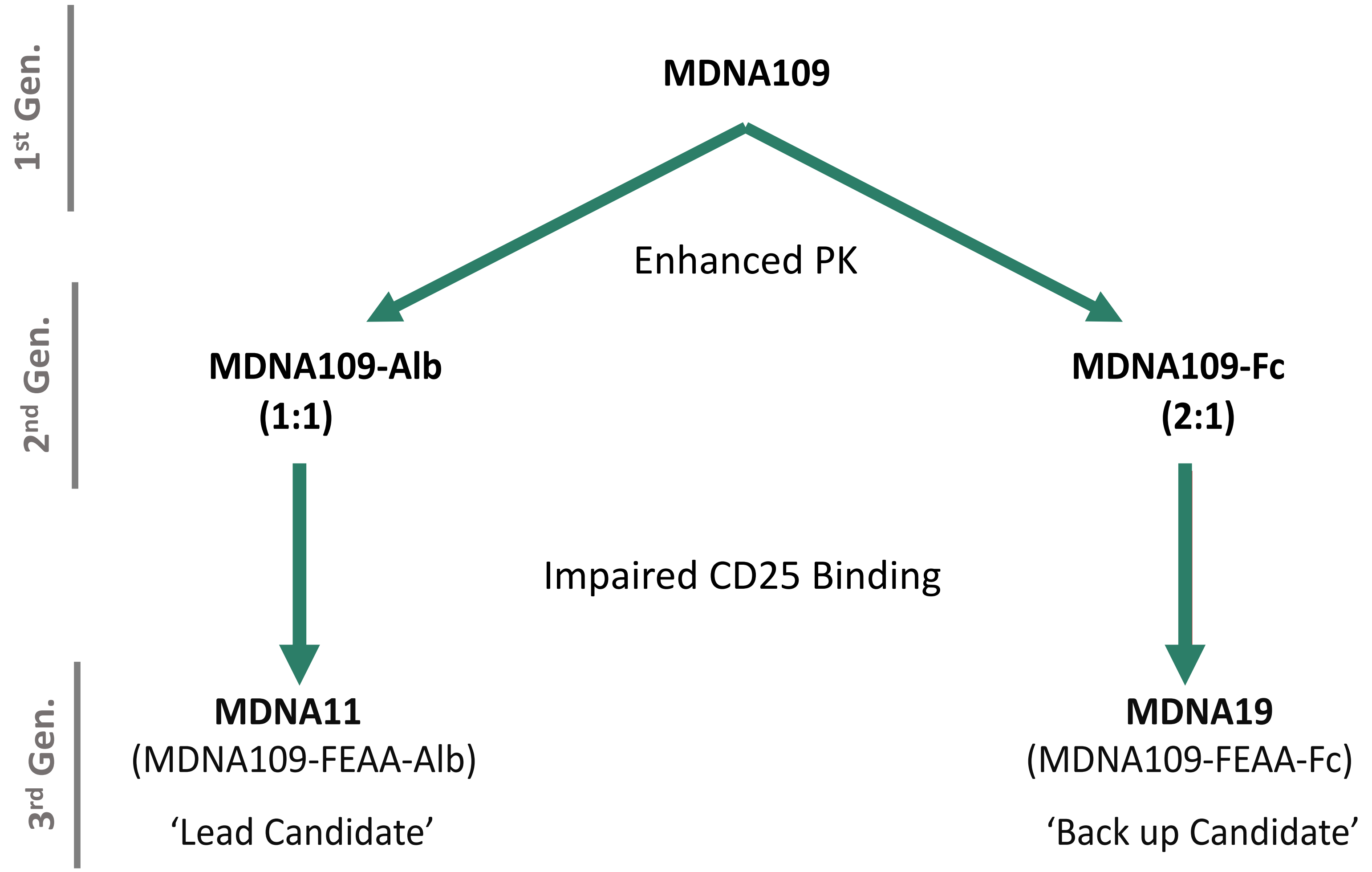
Reduced Adverse Side Effects in vivo



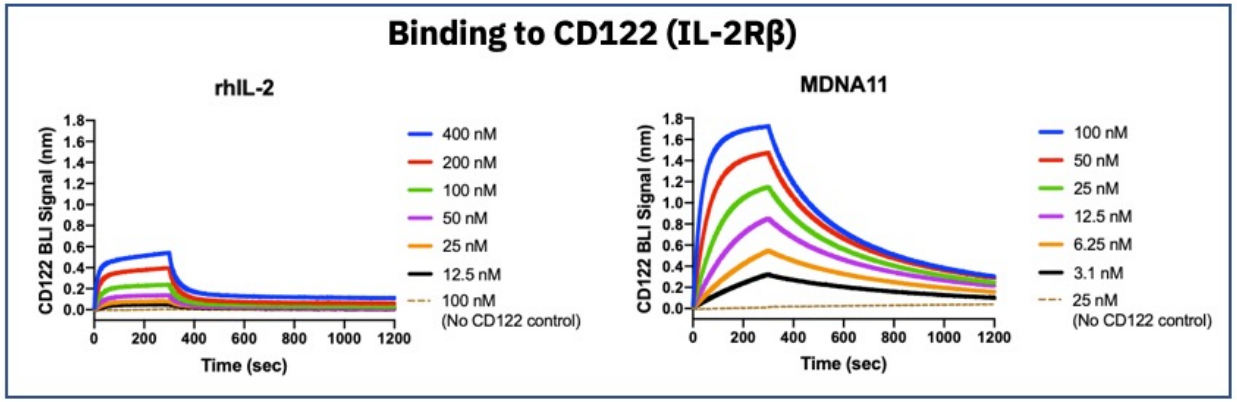
Mice were dosed (IP) with 20 µg of IL-2 or MDNA109 for 5 consecutive days. Analysis on Day 6.

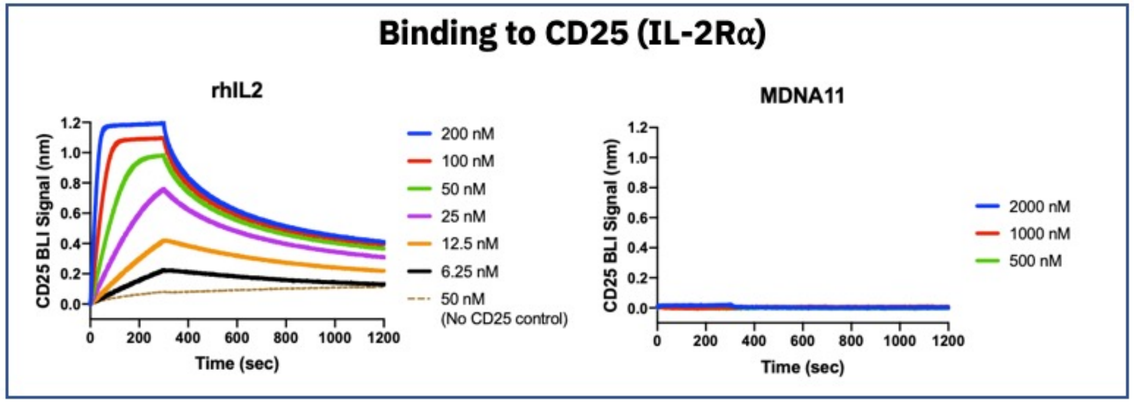
Transition to Long-Acting MDNA109 Superkines

MDNA109 family of ‘IL-2 Superkines’ have been engineered to improve PK characteristics and enhance selectivity to further improve therapeutic window



MDNA11 and MDNA19 are '*Beta-Only*' IL-2 Superkines





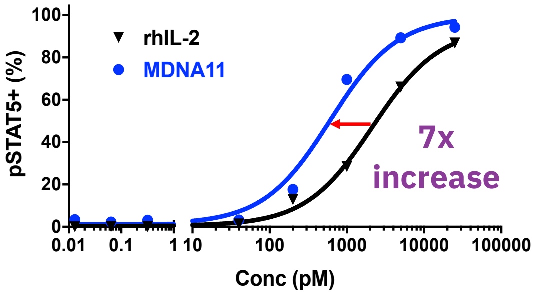
	K_D [CD25 (IL-2Rα)]	K_D [CD122 (IL-2Rβ)]
IL-2[a]	24 nM	210 nM
MDNA109 (*1st Gen.*)[a]	26 nM	1.8 nM
MDNA109-Fc (*2nd Gen.*)[b]	14 nM	2.7 nM
MDNA109-Alb (*2nd Gen.*)[a]	56 nM	3.5 nM
MDNA19 (*3rd Gen.*)[b]	**No binding**	**2.1 nM**
MDNA11 (*3rd Gen.*)[a]	**No binding**	**6.6 nM**

a. BLI/Octet; b. SPR data

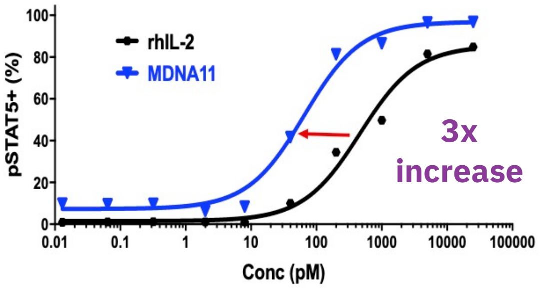
MDNA11 Preferentially Stimulates Immune Effector Cells But Not T_{regs}

P-STAT5 Signaling in Human PBMC

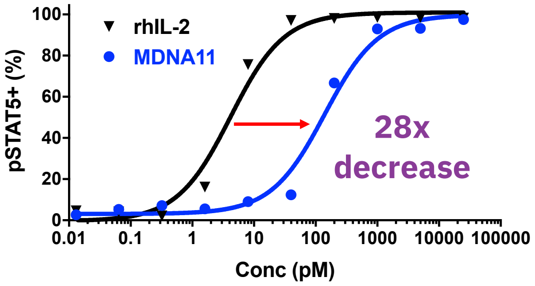
Naïve CD8 T-cells



NK Cells



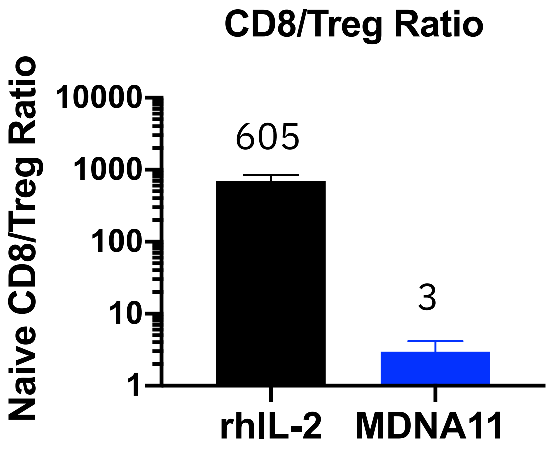
T_{REGS}

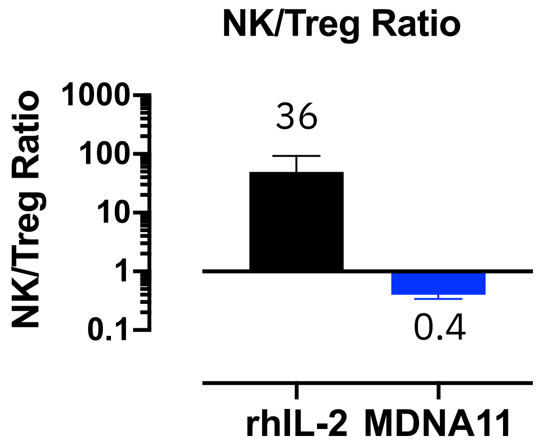


Protein	EC_{50} (pM)
rhIL2	3390
MDNA11	460

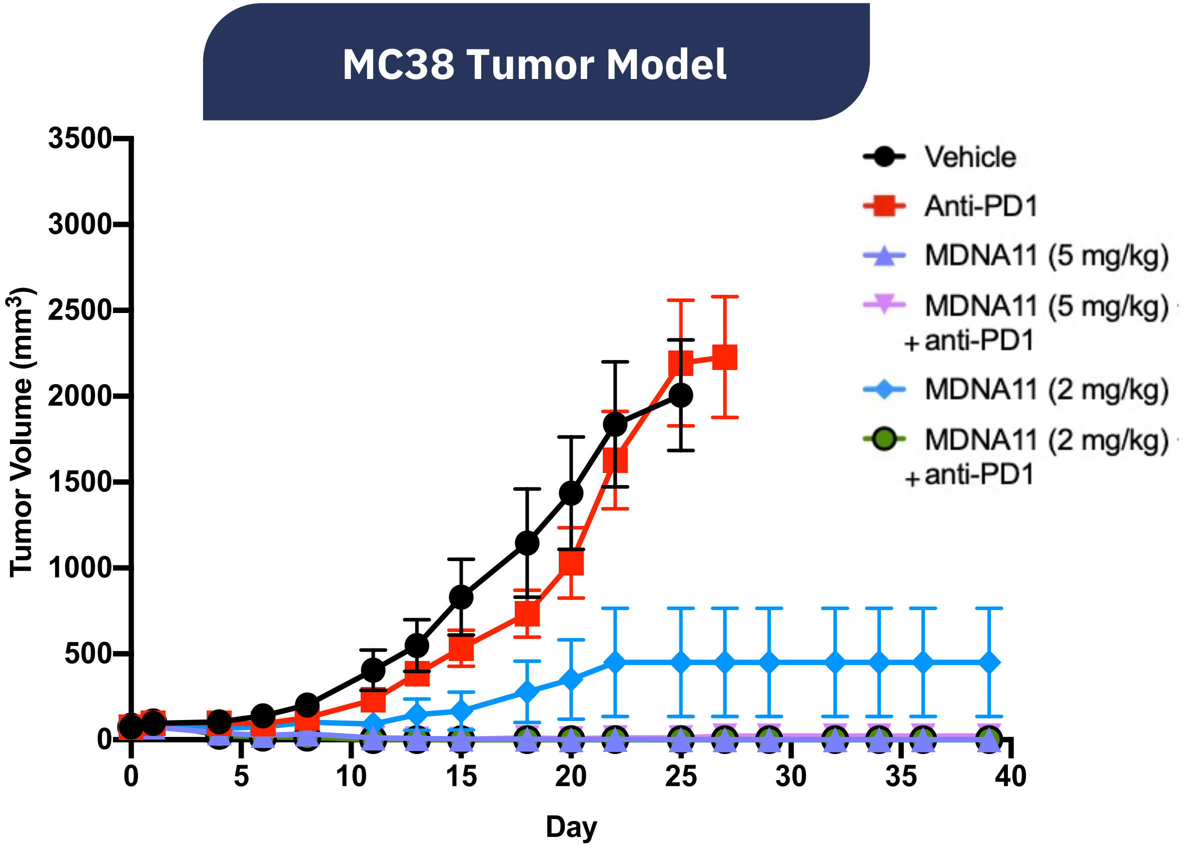
Protein	EC_{50} (pM)
rhIL2	200
MDNA11	69

Protein	EC_{50} (pM)
rhIL2	5.6
MDNA11	160



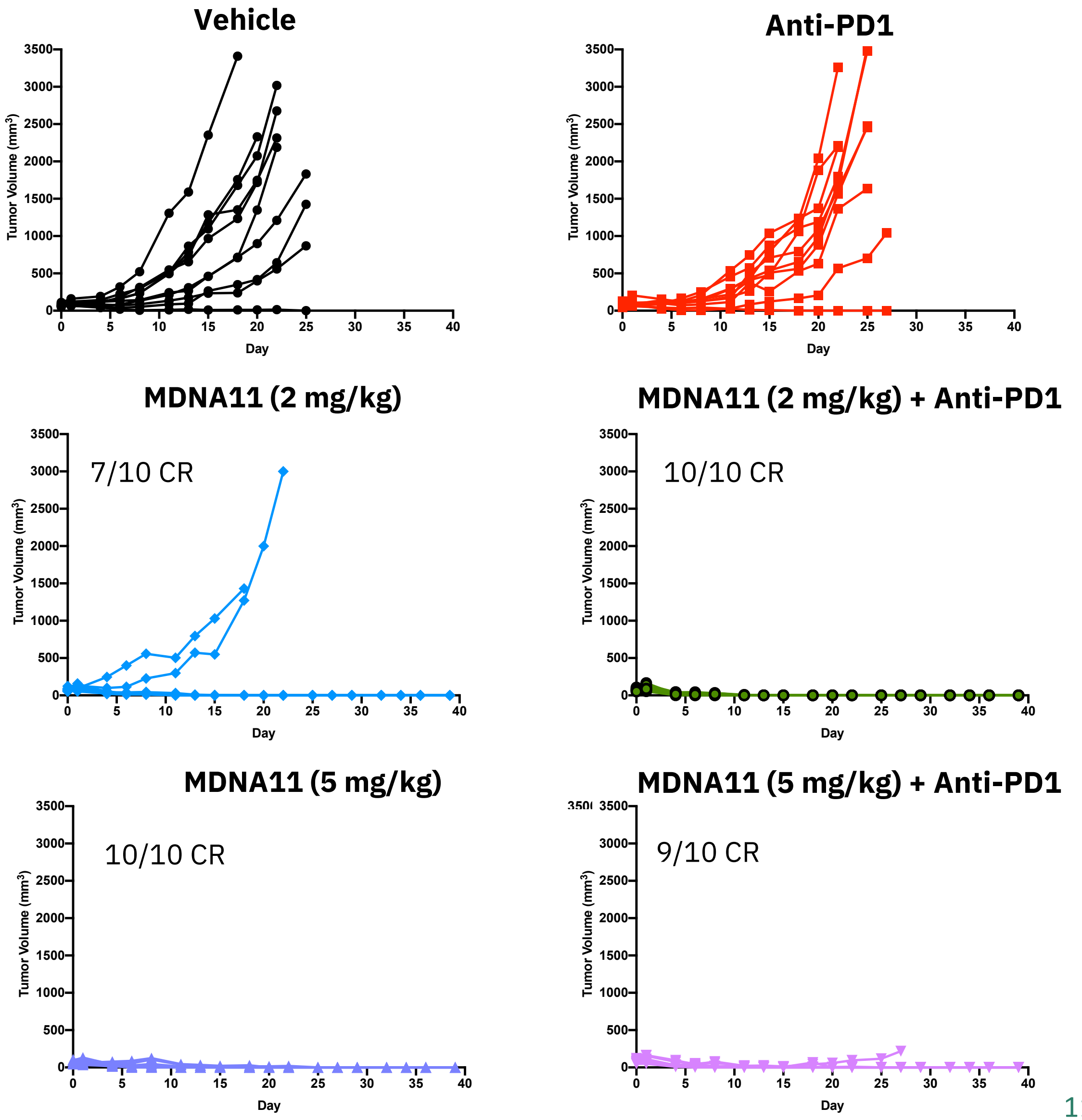


MDNA11 Alone or In Combination with Anti-PD1 Therapy Shows Potent Anti-Tumor Efficacy



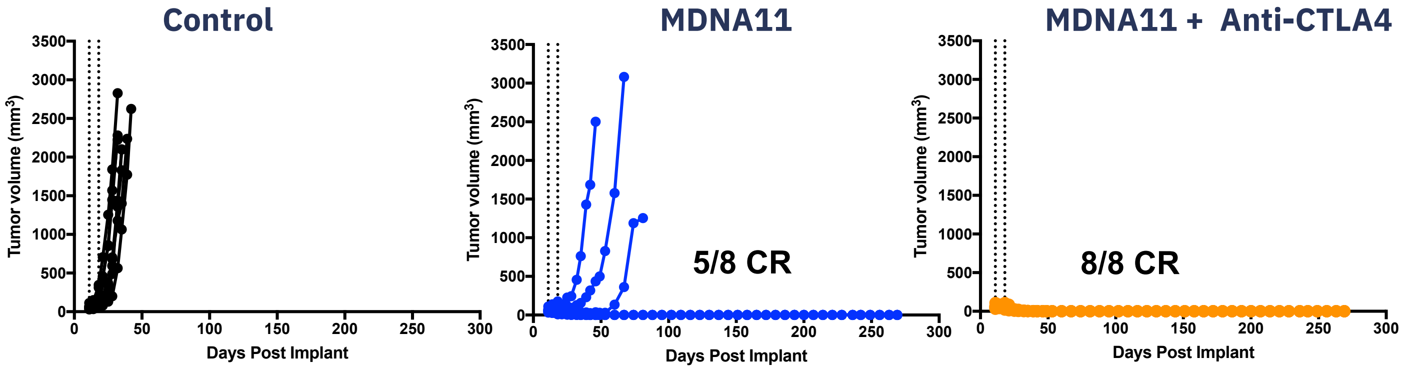
MDNA11: IP Q7Dx2
Anti-PD1 (RMP1-14; 10 mg/kg): IP BIWx3
Average size at initiation of dosing ~ 75 mm^3
Study in C57Bl/6 mice.

CR: Tumor volume = 0
Re-challenge study on-going



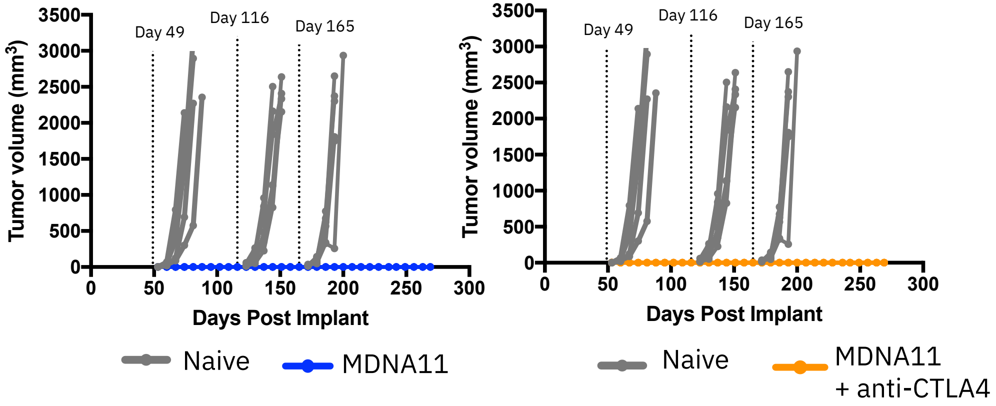
MDNA11 + Anti-CTLA4 Induces Tumor Clearance, Protects Against Re-Challenges & Promotes Antigen-Specific CD8 T-Cells

Primary Tumors (CT26 in Balb/c Mice)



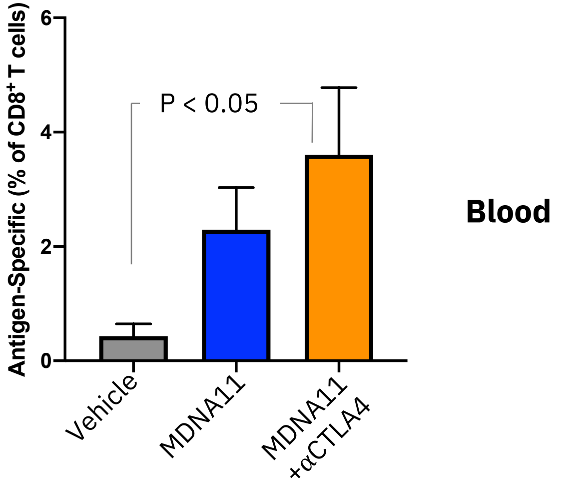
Re-challenges

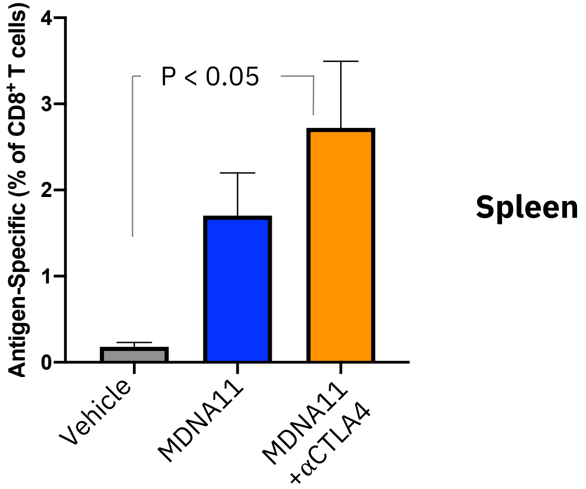
Mice re-challenged with CT26 tumor cells at different sites on their flanks



Antigen-specific CD8 T-cells on Day 270

(MDNA11 treatment on Day 11 & 18)



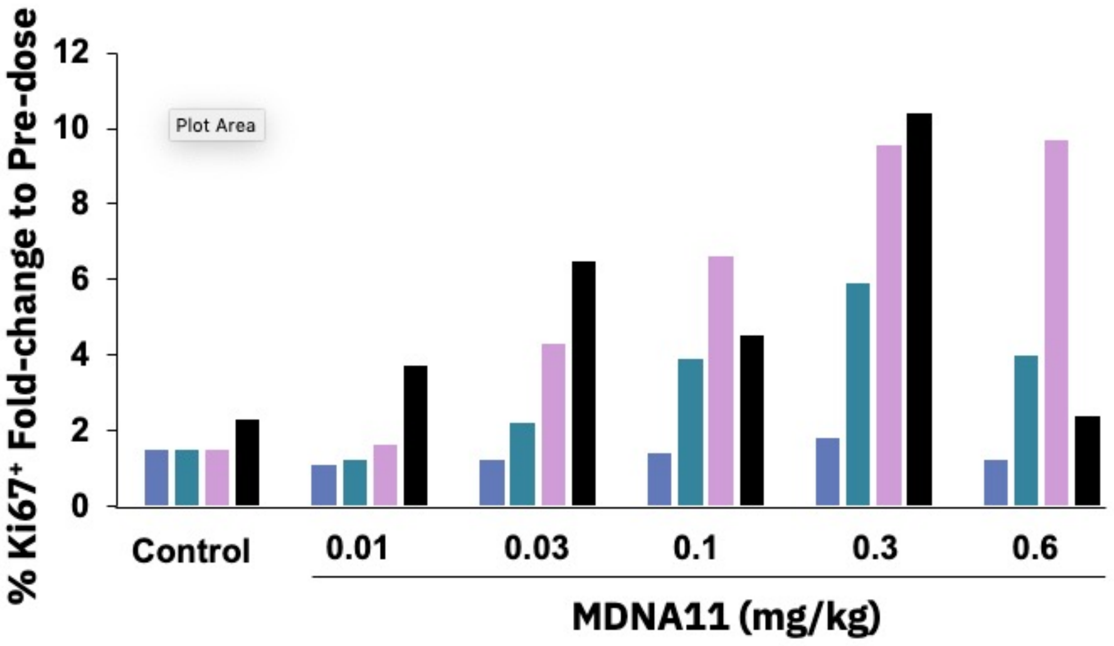


- Avg. tumor size in the treatment group at time of dosing: ~60 mm^3
- MDNA11 (5 mg/kg, IP, Q.W x 2wks); Anti-CTLA4 (9D9; 200 µg, IP, Q2W x 2wks)

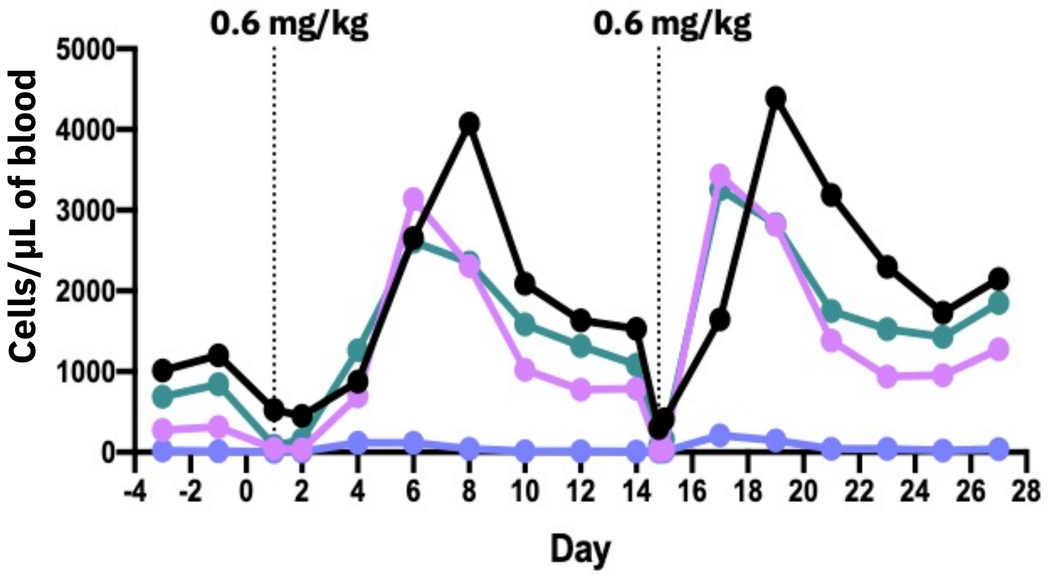
- Antigen-specific CD8T cells detected by anti-CD8 (KT15) and H-2Ld MuLV gp70 Tetramer
- All mice boosted with CT26 cells 5 days prior to analysis

MDNA11 Induces Durable & Sustained Proliferation & Expansion of Immune Effector Cells But Not T_{regs} in NHP

Peak Fold-change in Ki67 Expression



Kinetics of Immune Cell Expansion



Post first dose

T_{regs} | $CD4^{+}$ T Cell | $CD8^{+}$ T Cell | NK Cell

Bi-Functional Superkine Immunotherapies (BiSKITs™)

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Bi-Functional Superkine Immunotherapies (BiSKITs™)

Superkines Targeted with Antibodies (STAb Cancer™)

Interleukin-Thirteen Targeted Cancer Killing (iTTACK™)

Checkpoint Inhibitors Fused to Cytokines (CHECK Cancer™)

Interleukin Directed Bi-Specific T-Cell Engagers (iBITE™)

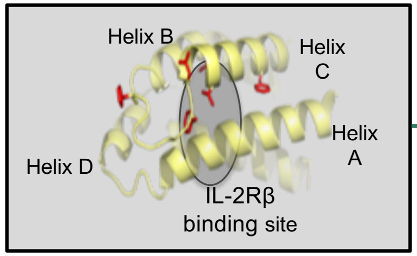
Dual Cytokines (DUCK Cancer™)

Superkines Targeted with Antibody (STAbTM) Enhances Accumulation in Tumors

nature COMMUNICATIONS

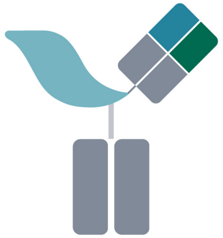
Sun et. al.,
Nat Comm, 2019

MDNA109



+FA

SumIL-2
(MDNA109FA)



αEGFR-SumIL-2
(αEGFR-MDNA109FA)

+FEAA

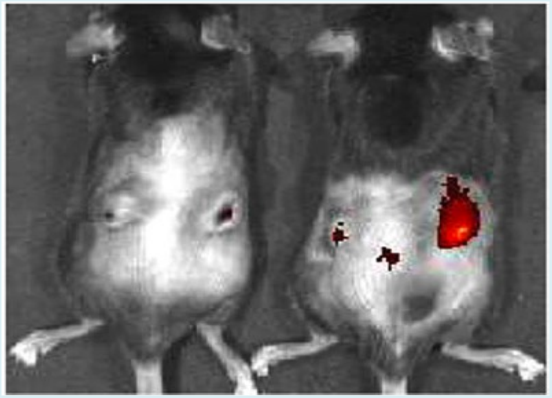
MDNA109FEAA

MDNA19
(MDNA109FEAA-Fc)

Medicenna
Therapeutics

Tumor Accumulation

Control αEGFR-MDNA109FA



Left tumor: MC38
Right tumor: MC38-EGFR5

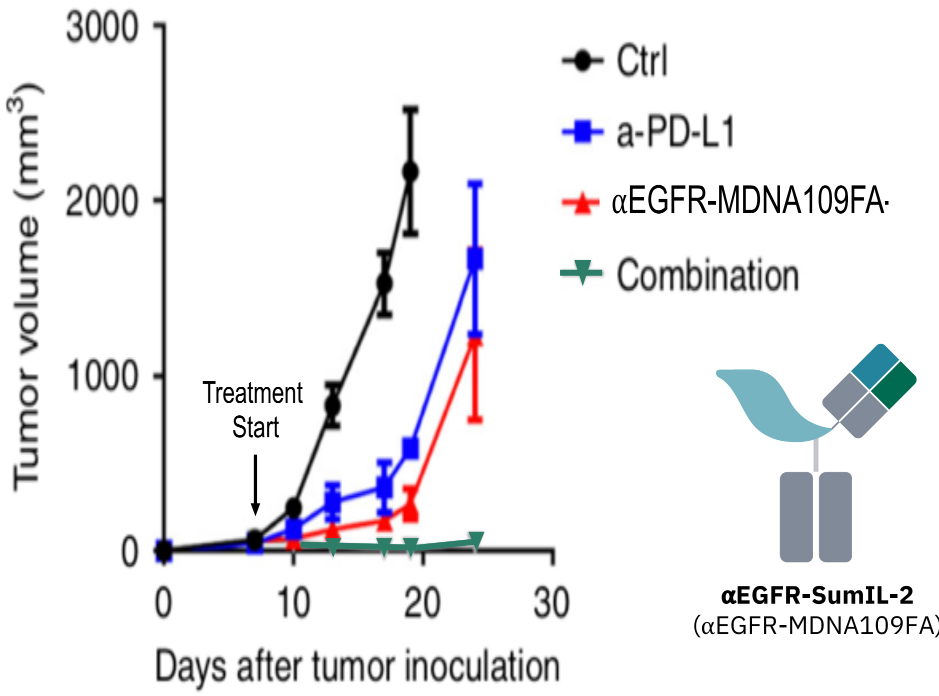
Fluorescence images of MC38 (left) and MC38-EGFR5 (right) tumor-bearing mice treated with a single dose of PBS or αEGFR-MDNA109FA (25 μg, IV)

Sun et al., Nature Communications, 2019

STAb™ Overcomes Checkpoint Resistance and 'Cold' Tumors

Overcoming Checkpoint Resistance

B16F10-EGFR5 Tumors

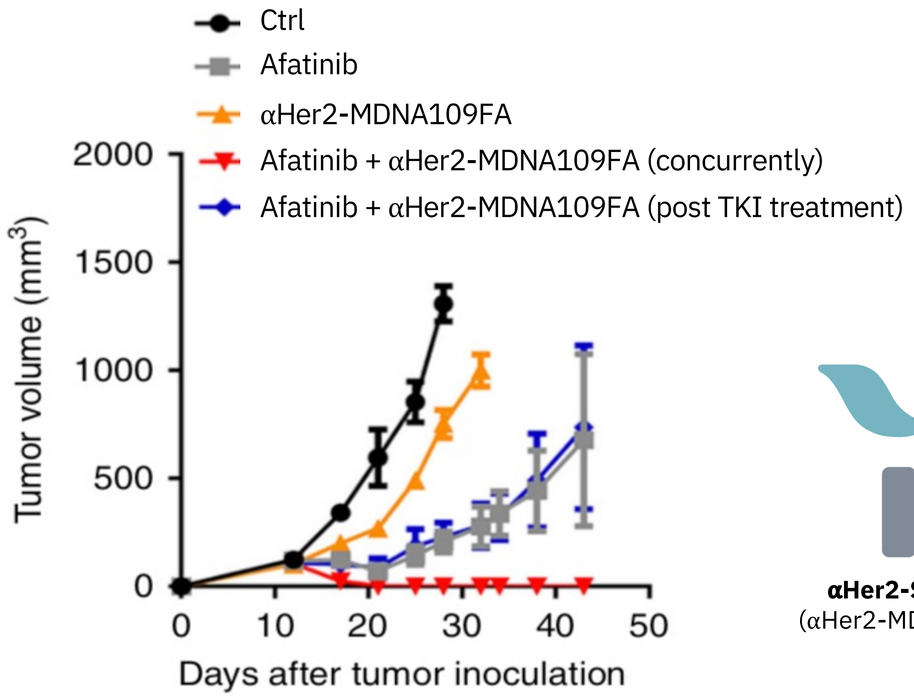


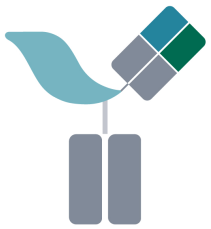
αEGFR-SumIL-2
(αEGFR-MDNA109FA)

IP treated with 25 µg of αEGFR-MDNA109FA-Fc
Intratumorally treated with 50 µg of anti-PD-L1 on days 8, 11, and 14.

Synergy with TKI to Tackle Immunological 'Cold' Tumors

TUBO Tumors (overexpress Her2)





αHer2-SumIL-2
(αHer2-MDNA109FA)

IP treated with 20 µg of anti-αHer2-MDNA109FA on either days 12, 15, and 18 or days 25, 28, and 31.
Orally with 1 mg of Afatinib on days 12 and 17.

Sun et al., Nature Communications, 2019

IL-13 BiSKITs

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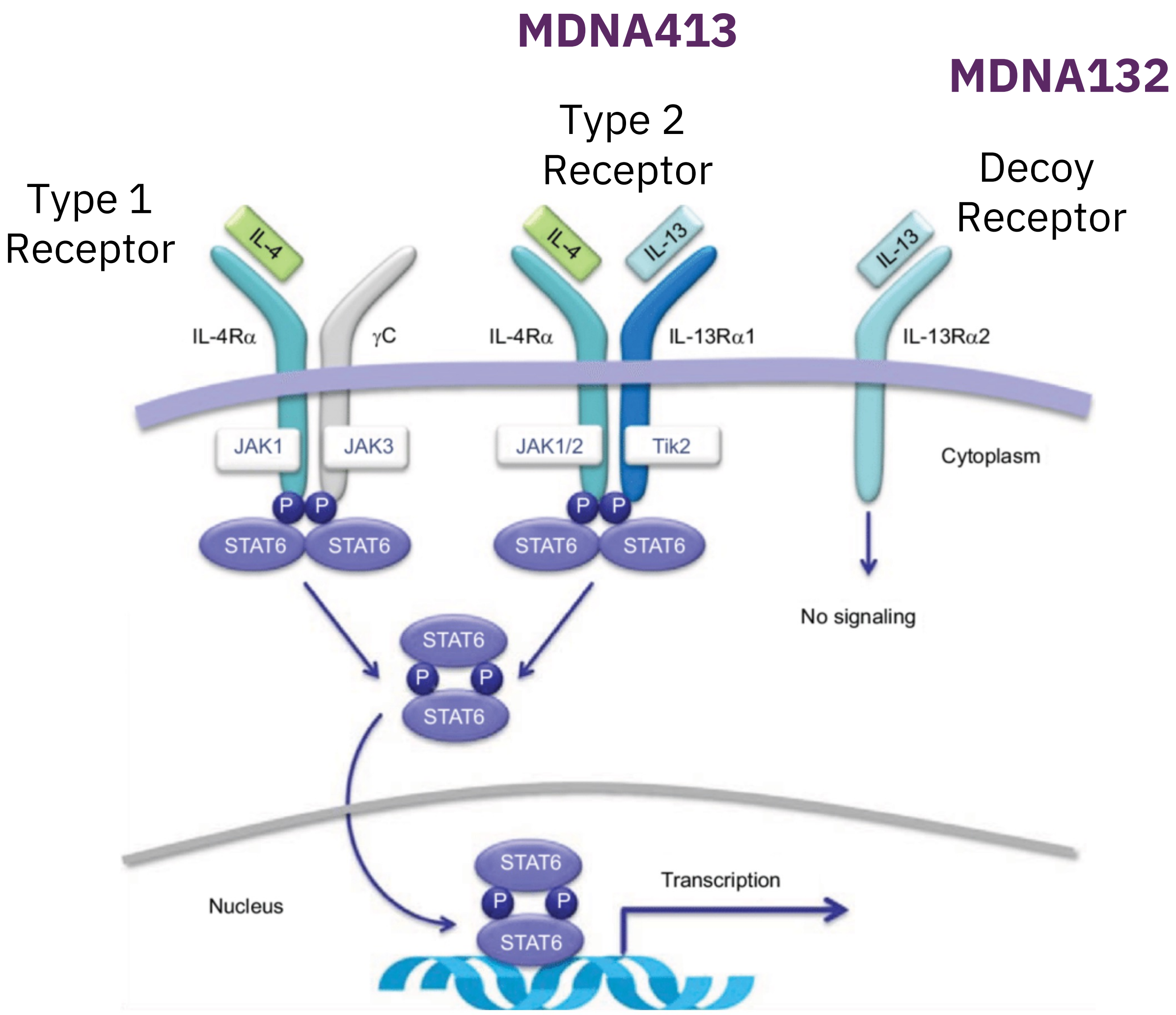
Role of IL-4 and IL-13 Receptors in Cancer



Awosika et al., 2018

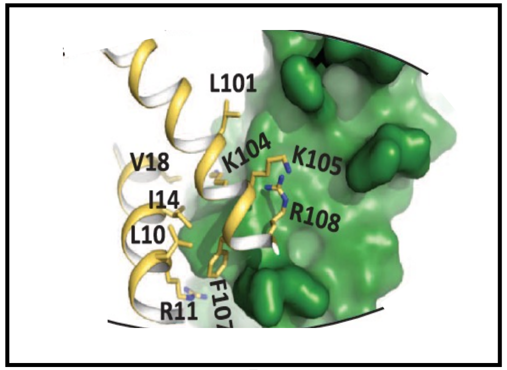
MDNA413 is a super-antagonist blocking IL-4 and IL-13 signaling via type 2 IL-4R to suppress MDSC and TAM

MDNA132 is a superkine that selectively targets decoy IL-13Rα2 that is overexpressed on solid tumors

MDNA132 is an Engineered Human IL-13 Targeting a Tumor Specific Antigen (IL-13Rα2)

Science Signaling

Moraga et. al, Science Signaling, 2015

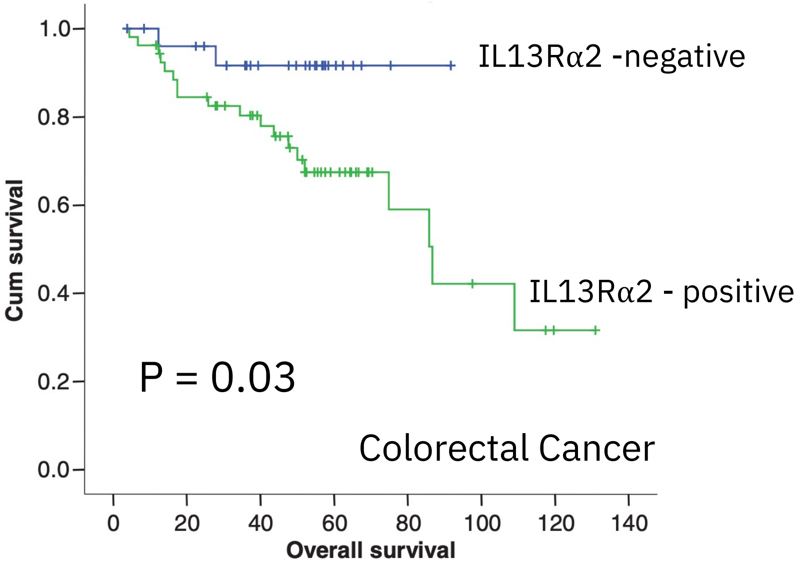


~4000 fold Selectivity for IL-13Rα2

SPR data K_D (nM)	IL-13Rα1	IL-13Rα2
IL-13	4.38	0.001
MDNA132	1600	0.0001

Tumors over-expressing IL-13Rα2
Bladder Cancer
Colorectal Cancer
Pancreatic Cancer
Triple Negative Breast Cancer
Glioblastoma
Lung Cancer
Head & Neck Cancer
Ovarian Cancer
Prostate Cancer
Mesothelioma

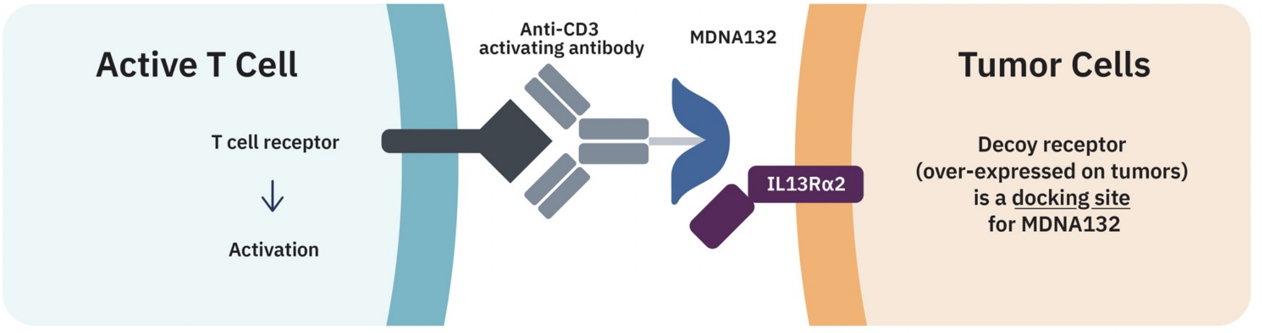
IL-13Rα2 Is Associated with Poor Survival



Barderas et al., Cancer Res, 2012

MDNA132: Localizing T-cell Engager and Checkpoint Inhibitor to Tumors

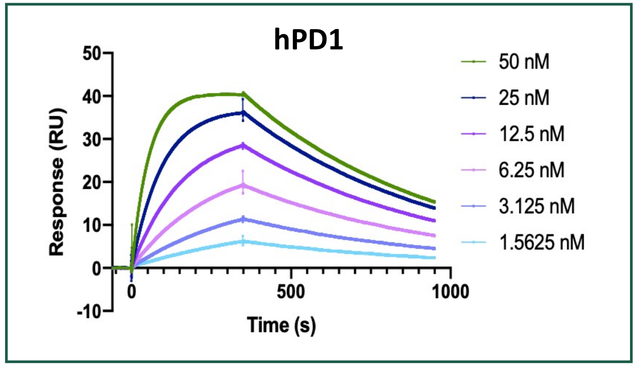
Anti-CD3-MDNA132 (iBITE™)

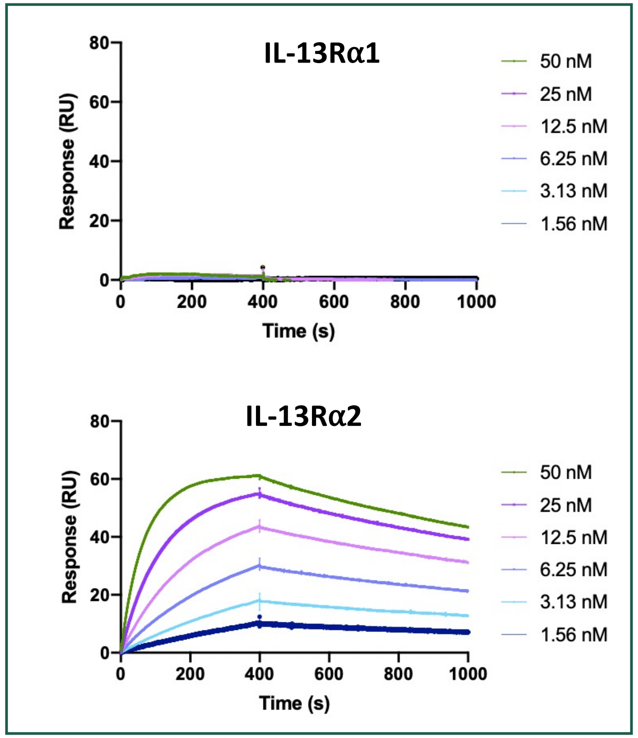


Increased T cell activity in the tumor microenvironment

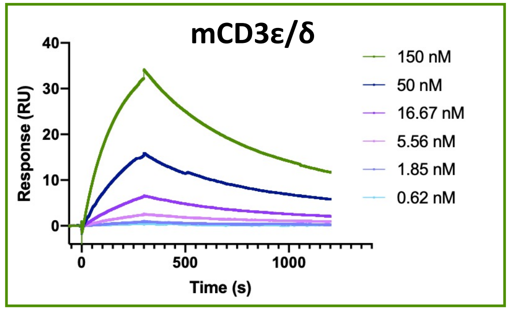
Increased targeting of anti-CD3 antibody to tumor cells

Anti-PD1-MDNA132 (iTTACK™)

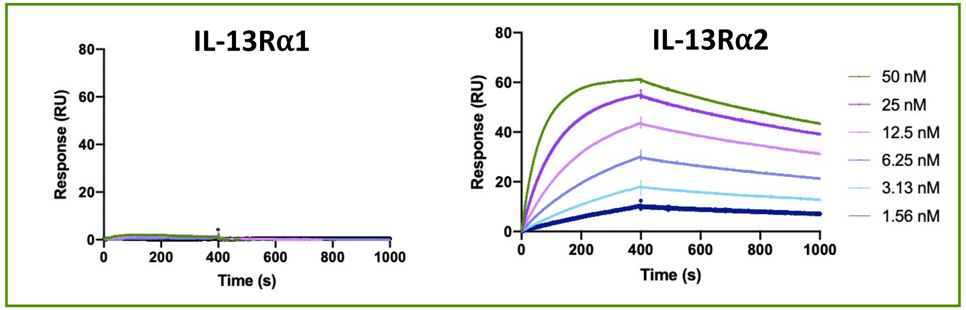




Binding to CD3 Epitope



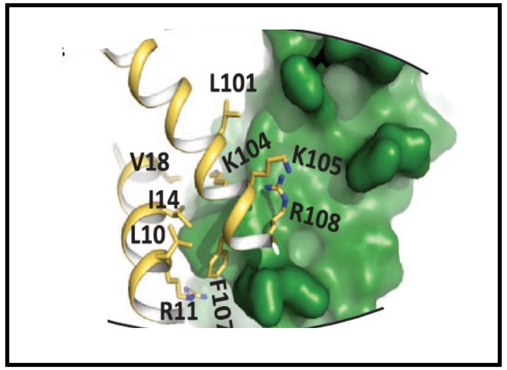
Selectivity for IL-13Rα2

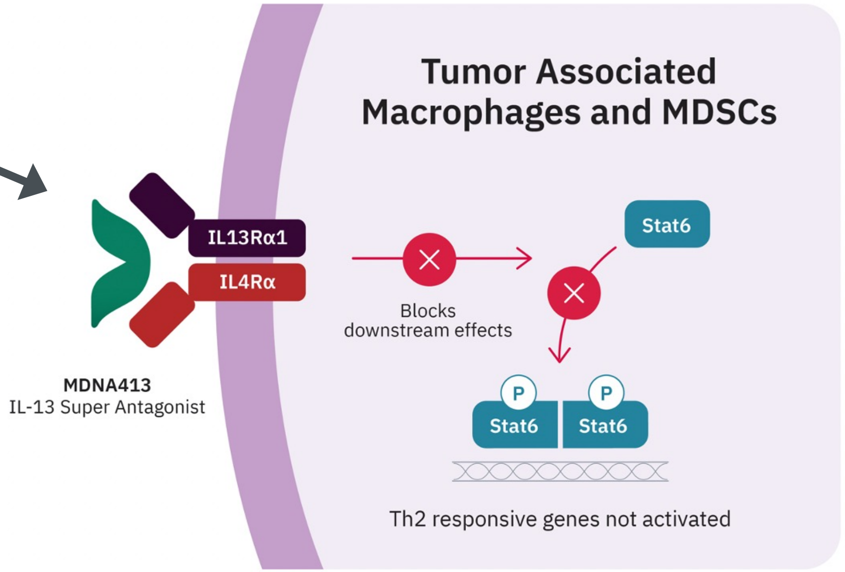


MDNA413 is an Engineered Human IL-13 with IL-4/IL-13 Antagonist Activity

Science Signaling

Moraga et. al, Science Signaling, 2015



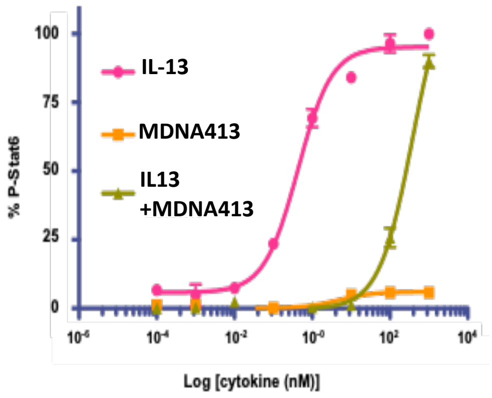


~20,000 fold Selectivity for IL-13Rα1

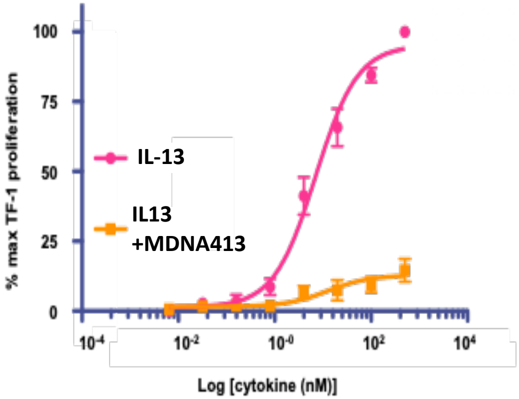
SPR data K_D (nM)	IL13Rα1	IL13Rα2
IL-13	4.38	0.001
MDNA413	0.084	0.391

Blockade of Downstream Signaling

Blockade of P-STAT6 Signaling



Inhibition of IL-13 Induced TF-1 Proliferation

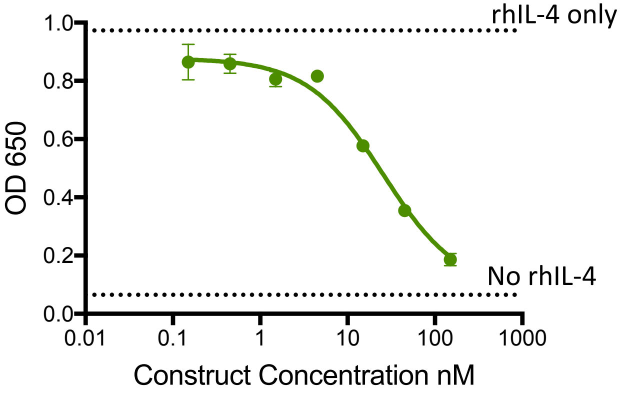


Lowered Immune Suppressing effects in the TME

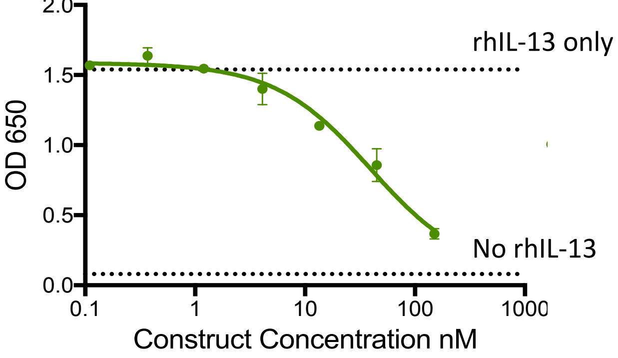
- Blocking pSTAT6 signaling
- Suppressing M2 polarization
- Preventing MDSCs suppression of T cells

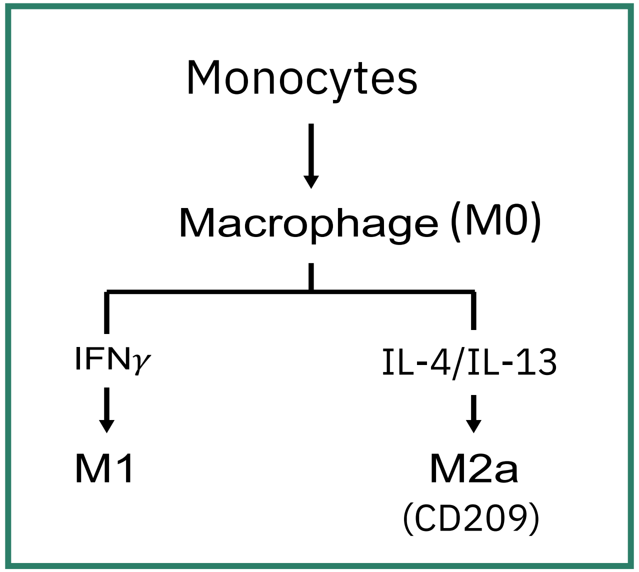
Long-Acting MDNA413 Inhibits IL-4 and IL-13 Induced Signaling and Function

Inhibition of IL-4 Signaling

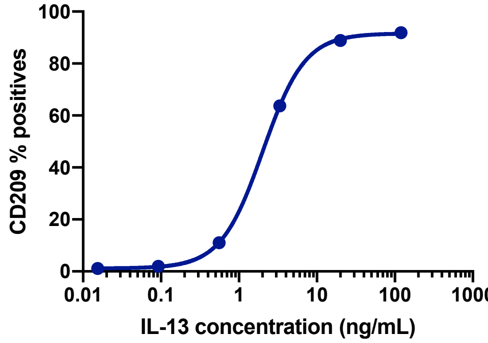


Inhibition of IL-13 Signaling

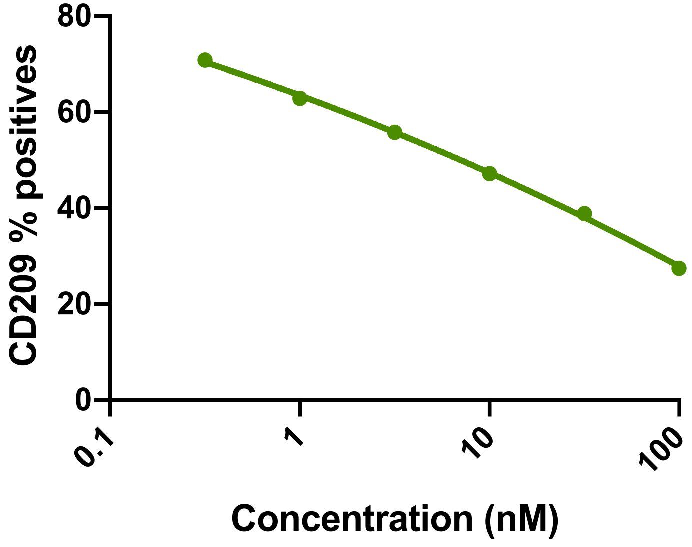




rhIL-13 Induced M2a Polarization



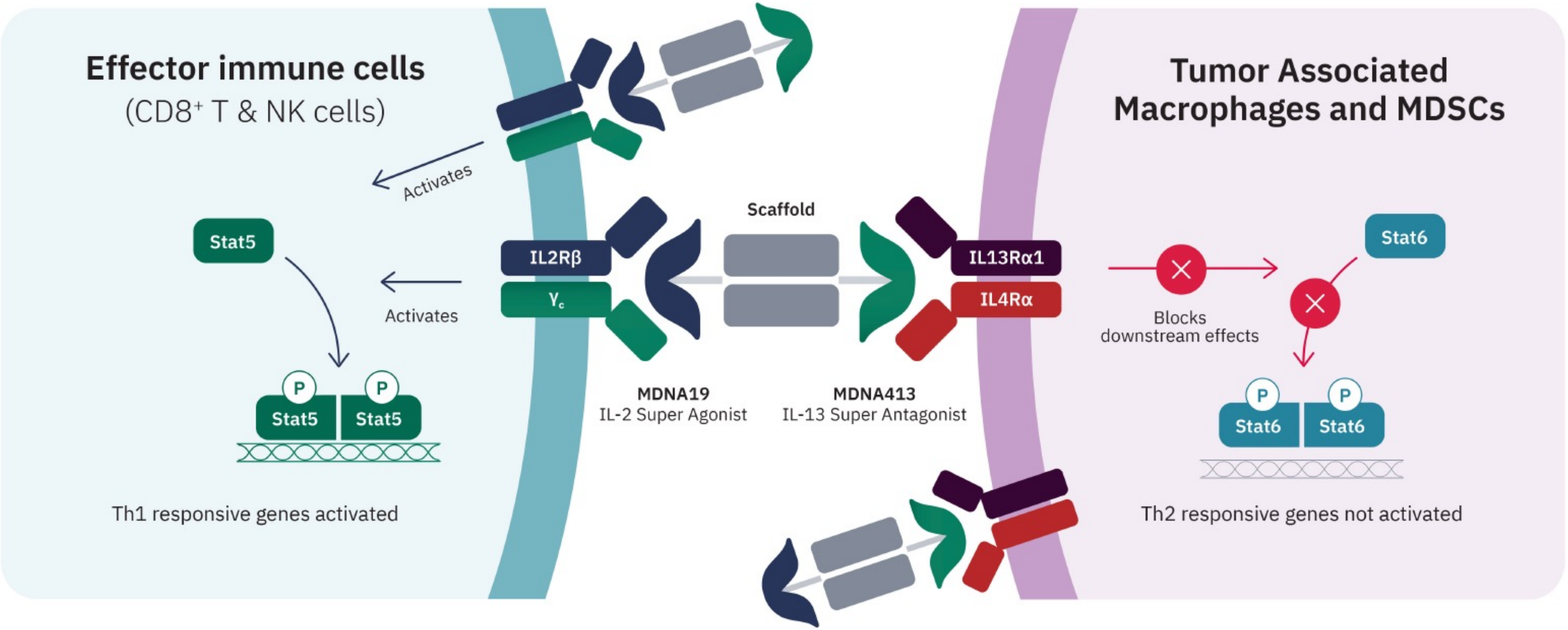
Inhibition of rhIL-13 Induced M2a Polarization by MDNA413



IC_{50} (nM)	Fc-MDNA413
IL-4 Signaling	26.4
IL-13 Signaling	39

Assay performed in HEK Blue IL-4/IL-13 reporter cells (From InvivoGen); Measurement of pSTAT6 signaling

Dual Cytokine (DUCK Cancer^{TM}): MDNA109FEAA-Fc-MDNA413 Mechanism of Action



Increased activation of CD8+ T & NK Cells to attack the tumor

Lowered Immune Suppressing effects in the TME

- Blocking pSTAT6 signaling
- Suppressing M2 polarization
- Preventing MDSCs suppression of T cells

Data to be presented at 2021 Annual AACR Conference

Designer Cytokines: Building Blocks of Medicenna's Superkine Pipeline

Levin et al., Nature (2012)
Moraga et al., Science Signaling (2015)
Junttila et al., Nature Chem Biol (2012)

Rafei et al, ASCO (2020)
Rafei et al., CICON (2019)
Mitra et al., Immunity (2015)

Sun et al., Nat Comm (2019)

Moraga et al., eLife (2017)

- Naked Interleukins (NAIL Cancer™)
- Long-Acting Interleukin Agonists or Antagonists (LAILAA™)
- Checkpoint Inhibitors Fused to Cytokines (CHECK Cancer™)
- Superkines Targeted with Antibodies (STAb Cancer™)
- Superkine-Cytokine Fusions
- Superkines Fused to Pro- or Anti-apoptotic Payloads (Empowered Superkines™)
- Dual Cytokines (DUCK Cancer™)
- Interleukin-13 Targeted Cytokine. (iTTACK™)
- Interleukin-13 Directed Bi-Specific T-Cell Engagers (iBITE™)
- Chimeric Antigen Cell Therapies and Oncolytic Viruses Armed with Superkines (CHAOS™)
- Tri-Functional Cytokines (TRICK Cancer™)

Sampson et al., ASCO (2020)

To et al., ENA 2020

Thank You!

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