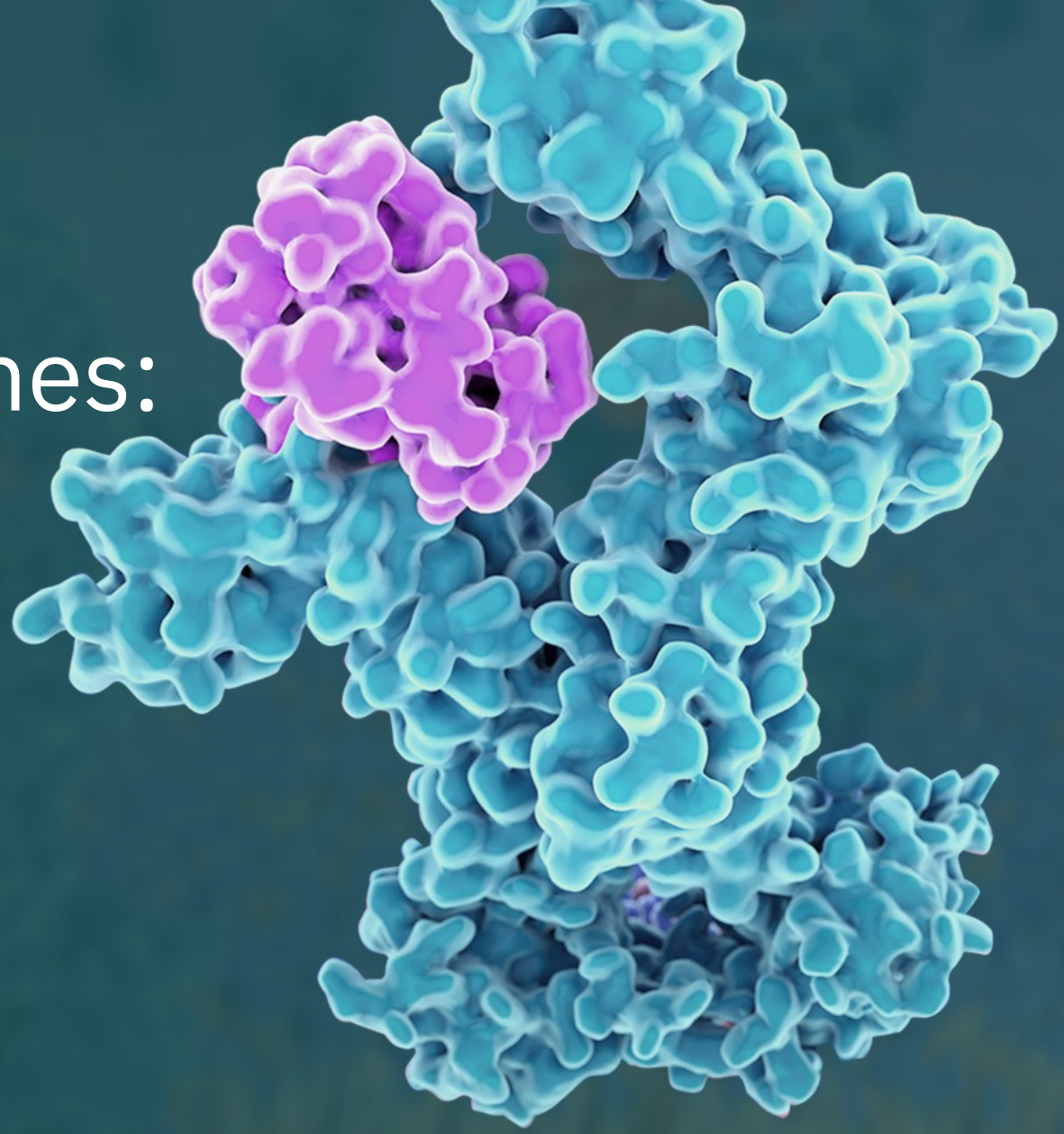
SEPTEMBER 22, 2021

Evolutionary IL-2 Superkines: *Past, Present and Future*

Next-Gen Cytokine Therapeutics Summit

Fahar Merchant, Ph.D
President and CEO



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The PAST: Proleukin®

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Validated with Durable Responses: Severe Toxicities Limit Use

High Unmet Need for Better IL-2 Immunotherapies

Proleukin

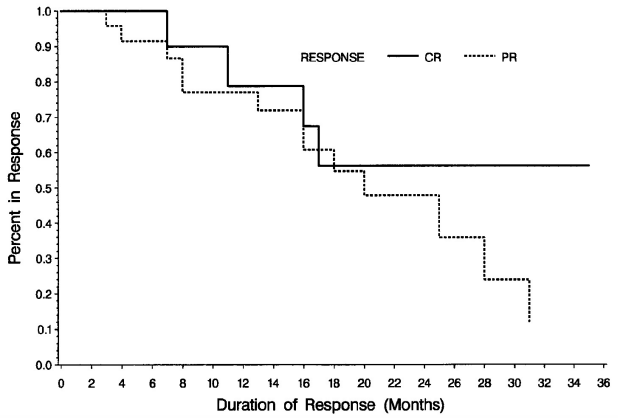
Lack of Selectivity and stimulation of CD25

- Patients often unable to receive a full course of therapy
- Patients must be treated in ICU
- Stimulation of pro-tumoral Tregs

Poor pharmacokinetic profile

- Short $t_{1/2}$
- 600,000 or 720,000 IU/kg IV Q 8 hours for up to 14 doses

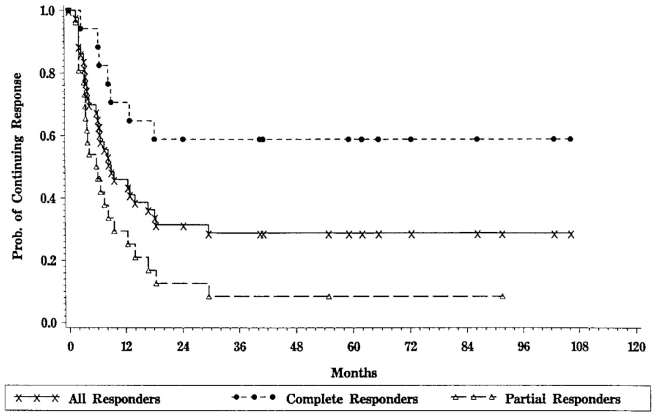
Metastatic Renal Carcinoma



- ORR = 14% (90% CI 10-19%)
- CR Rate = 5% (12/255)
- PR Rate = 9%
- Severe acute toxicities observed

Fyfe et al. (J Clin Oncol, 1995)

Metastatic Melanoma



- ORR = 16% (90% CI 12-21%)
- CR Rate = 6% (17/270)
- PR Rate = 10% (26/270)
- Severe acute toxicities observed

Atkins et al. (J Clin Oncol, 1999)

The PRESENT: Superkines

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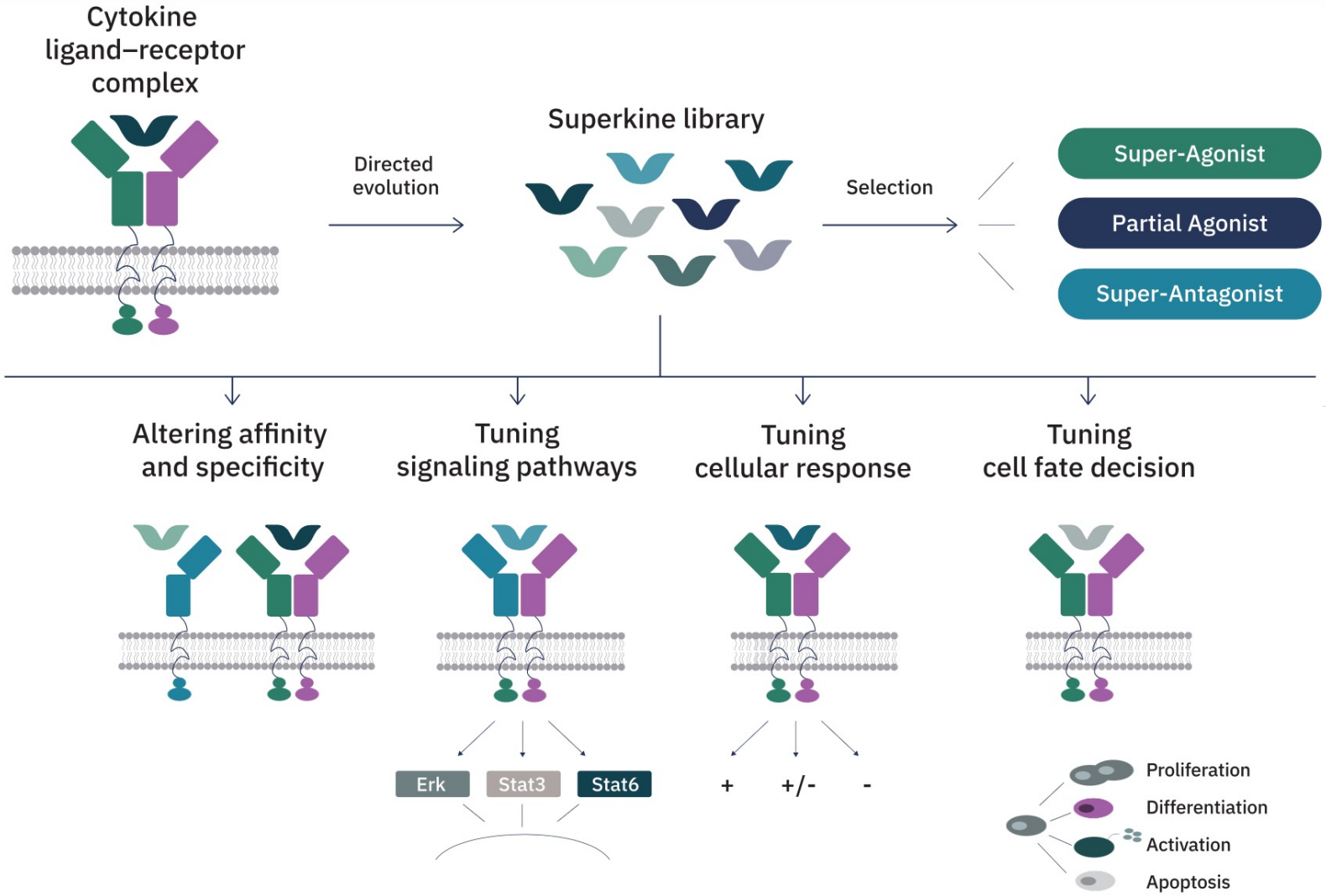
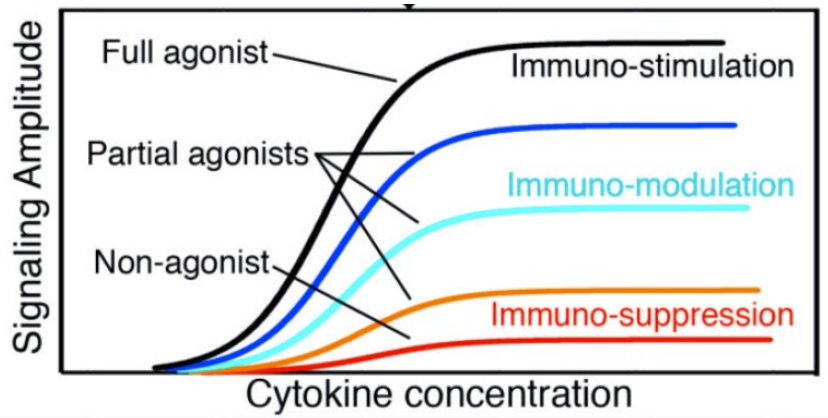
Directed Evolution + Yeast Display = Tunable Superkines

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

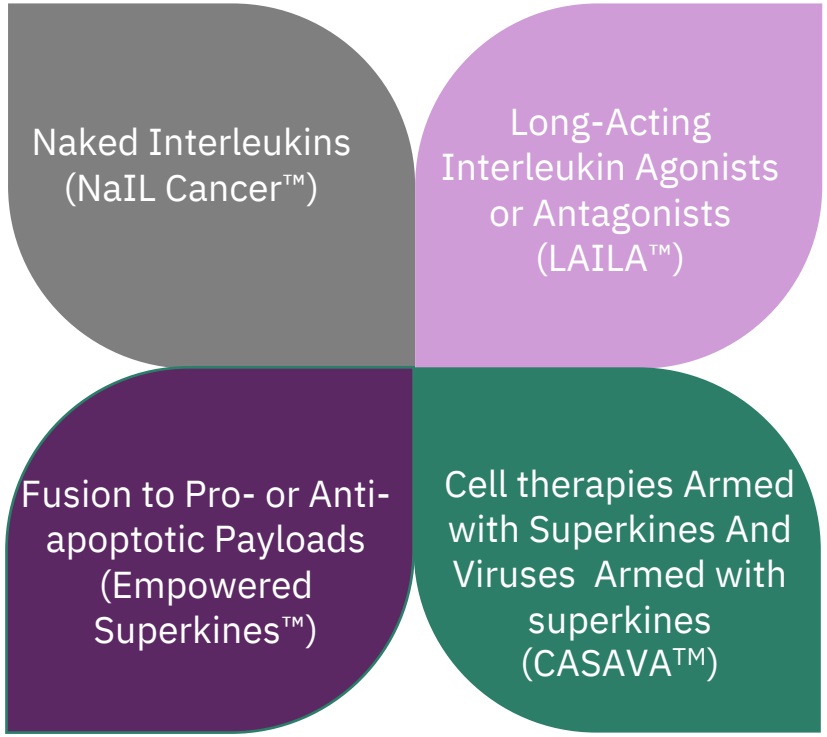




Basis of Versatile Superkine Platform

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

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

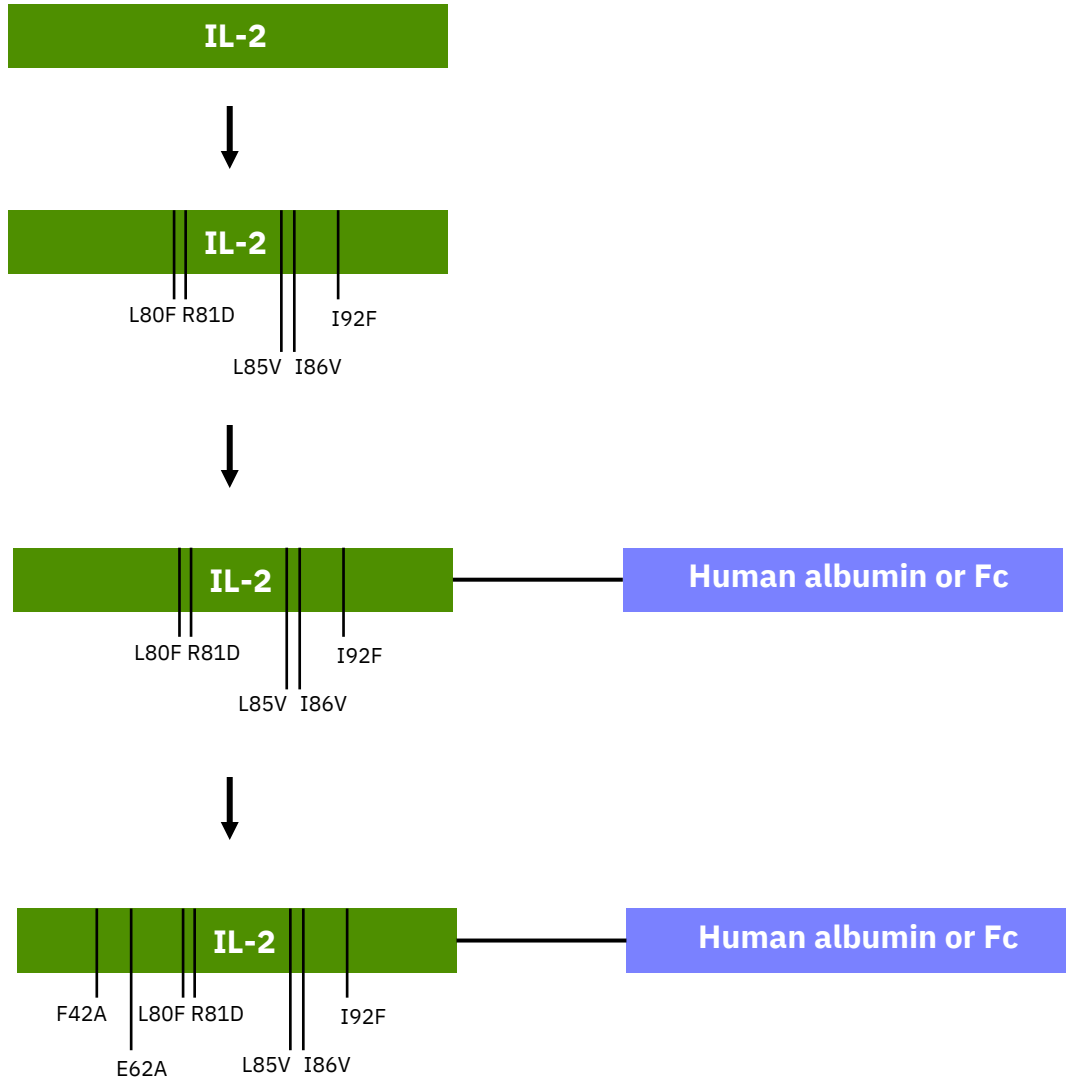


Sampson et al., ASCO (2020)
Ellingson et al, Clin Cancer Res (2021)

Quixabeira et al., Front Immunol (2021) [1]

[1] Work conducted independently of Medicenna at the University of Helsinki

Evolution of IL-2 Superkines: The MDNA109 Platform



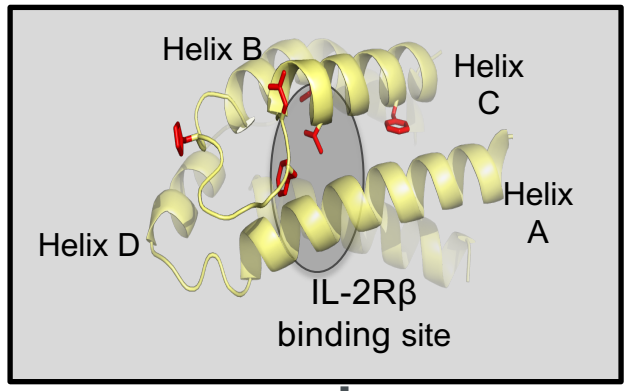
Preferential activation of Tregs

Preferential activation of CD8 T and NK cells

Extension of in vivo half-life (overcome need for frequent administration)

Limit activation of Tregs while maintaining high potency on CD8 T and NK cells

MDNA109: A First-Generation IL-2 Super-agonist Without CD25 Dependency



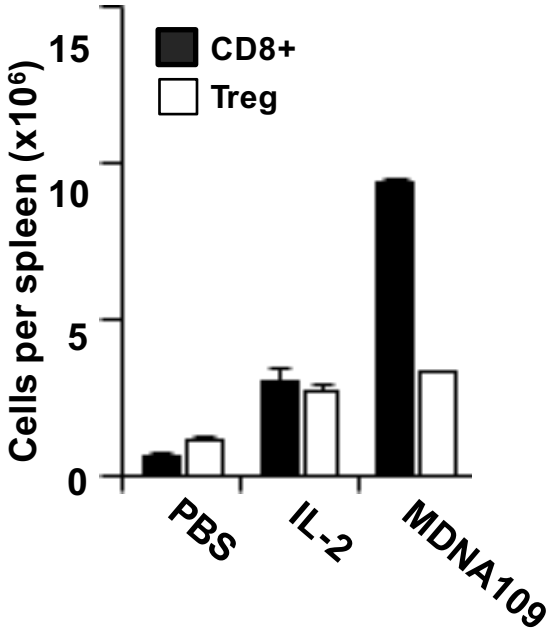
nature

Levin et al., Nature 2012

Enhanced Affinity for CD122 (IL-2Rβ)

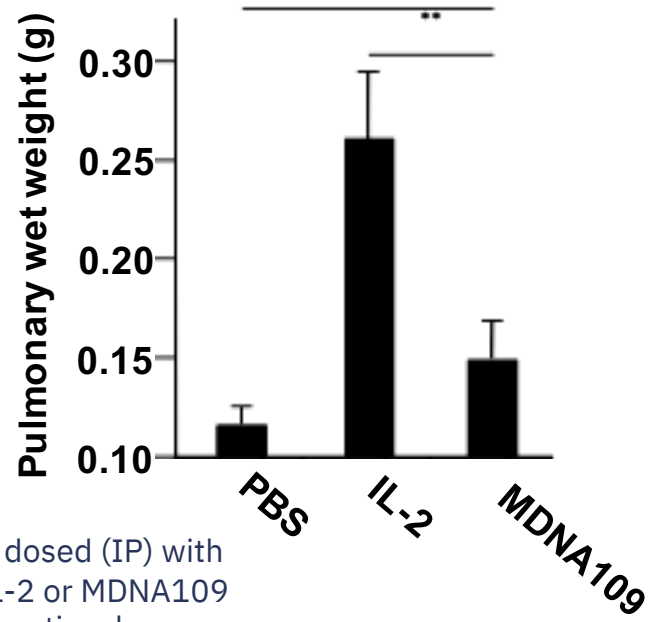
SPR data K_D (nM)	CD25	CD122
IL-2	6.6	280
MDNA109	6.6	1.4

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



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

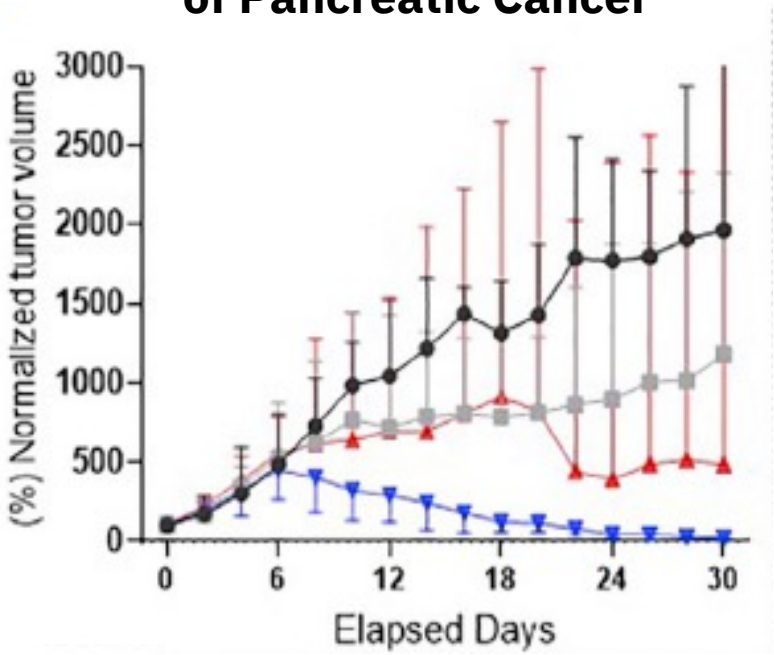
Reduced Adverse Side Effects in vivo



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

MDNA109 Armed Virus Induces Potent Anti-Tumor Transcriptomic Program in TILs*

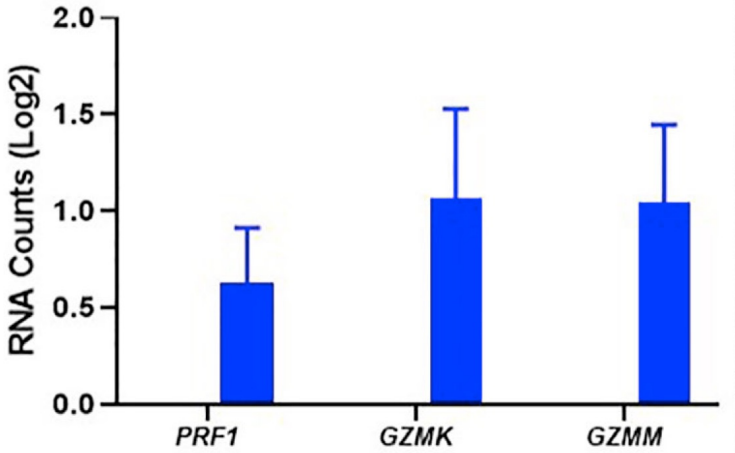
Hamster Model of Pancreatic Cancer



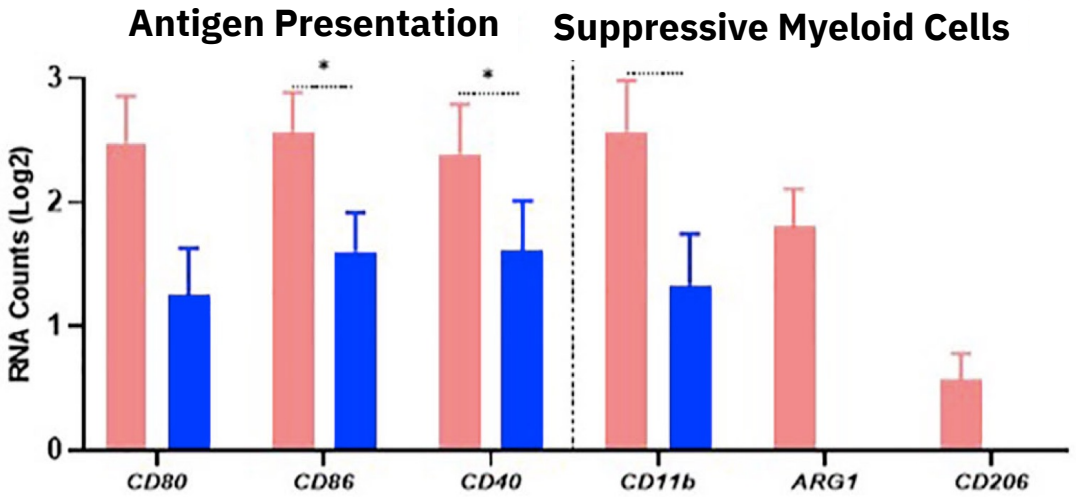
- Mock
- Unarmed Virus
- Virus – WT IL-2
- Virus – MDNA109

Hamster pancreatic tumor model
IT treatment on Days 1, 4, 8, 13, 18, 23, 28

Enhanced Cytotoxic Activity



Repression of Immune Suppression Genes

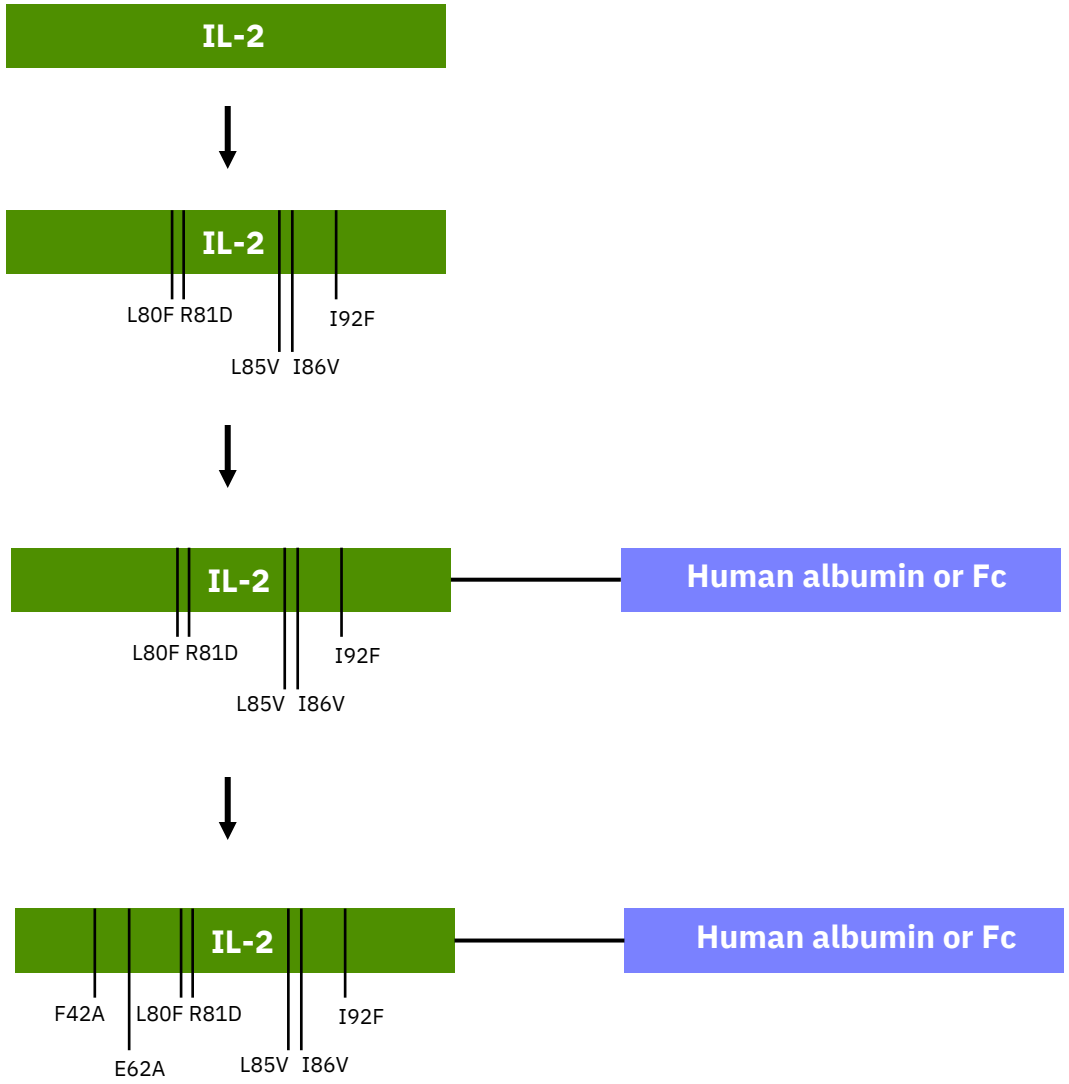


* P < 0.05

Quixabeira et al., Frontiers in Immunology 2021

Work conducted independently of Medicenna at the University of Helsinki

Evolution of MDNA109 Superkine



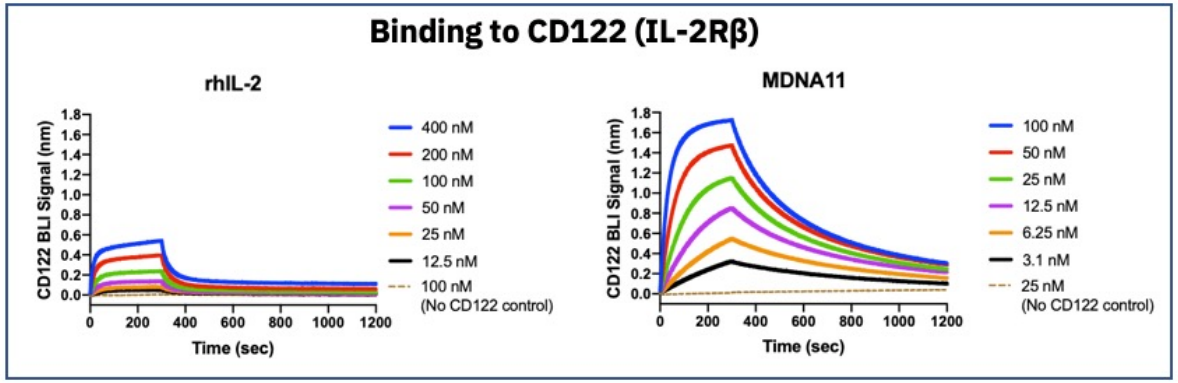
Preferential activation of Tregs

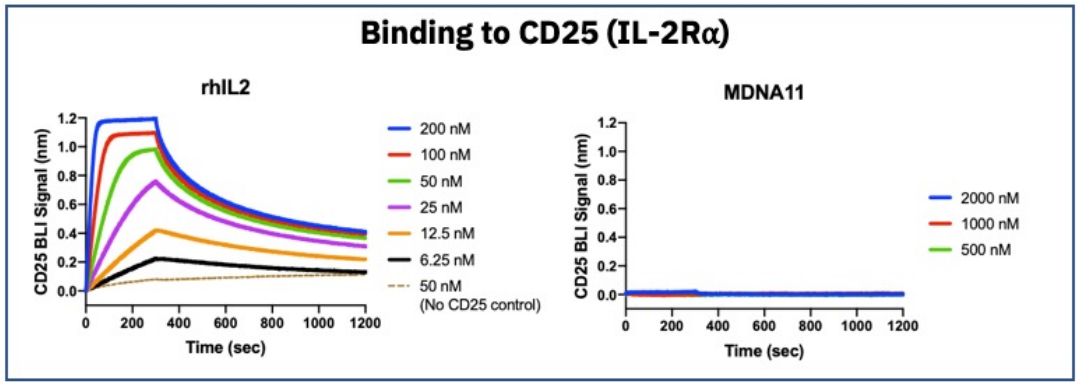
Preferential activation of CD8 T and NK cells

Extension of in vivo half-life (overcome need for frequent administration)

Limit activation of Tregs while maintaining high potency on CD8 T and NK cells

Receptor Selectivity of MDNA109 Superkine Platform





	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**

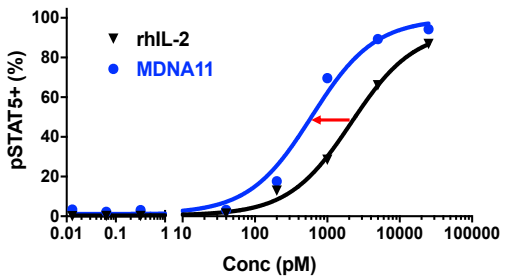
a. BLI/Octet; b. SPR data

Rafei et al., ASCO 2020
Merchant et al, ENA 2020

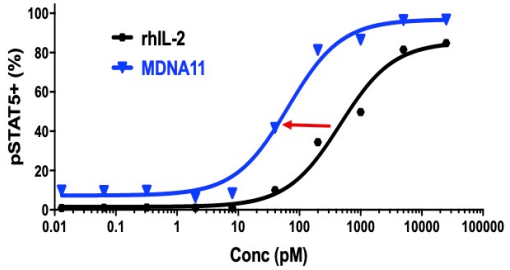
MDNA11 & MDNA19 Preferentially Stimulate Immune Effector Cells Over T_{regs}

STAT5 signaling in PBMCs from healthy donors

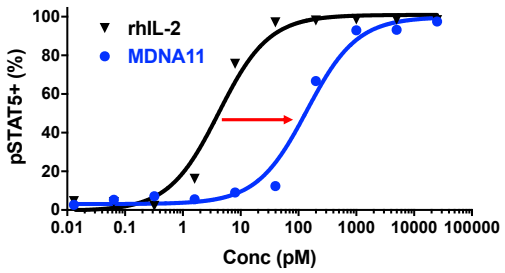
Naïve CD8 T-cells



NK Cells



T_{regs}

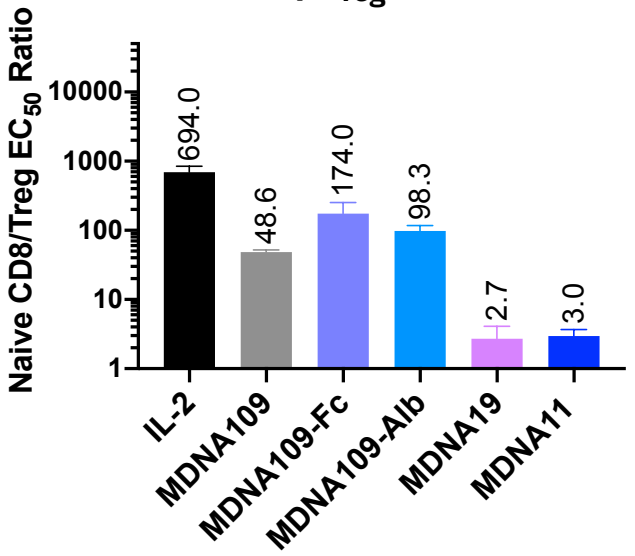


Protein	EC_{50} (nM)
rhIL2 (N = 4)	3.39
MDNA19 (N = 7)	0.37
MDNA11 (N = 3)	0.46

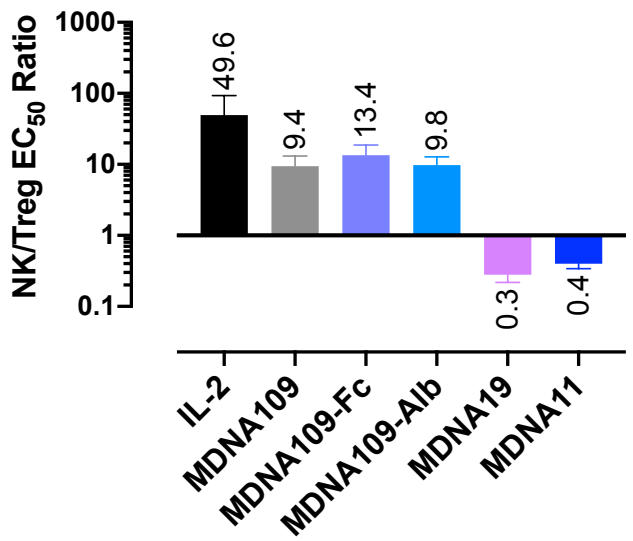
Protein	EC_{50} (nM)
rhIL2 (N = 4)	0.2
MDNA19 (N = 7)	0.071
MDNA11 (N = 3)	0.069

Protein	EC_{50} (nM)
rhIL2 (N = 4)	0.0056
MDNA19 (N = 7)	0.135
MDNA11 (N = 3)	0.160

CD8/T_{reg} Ratio

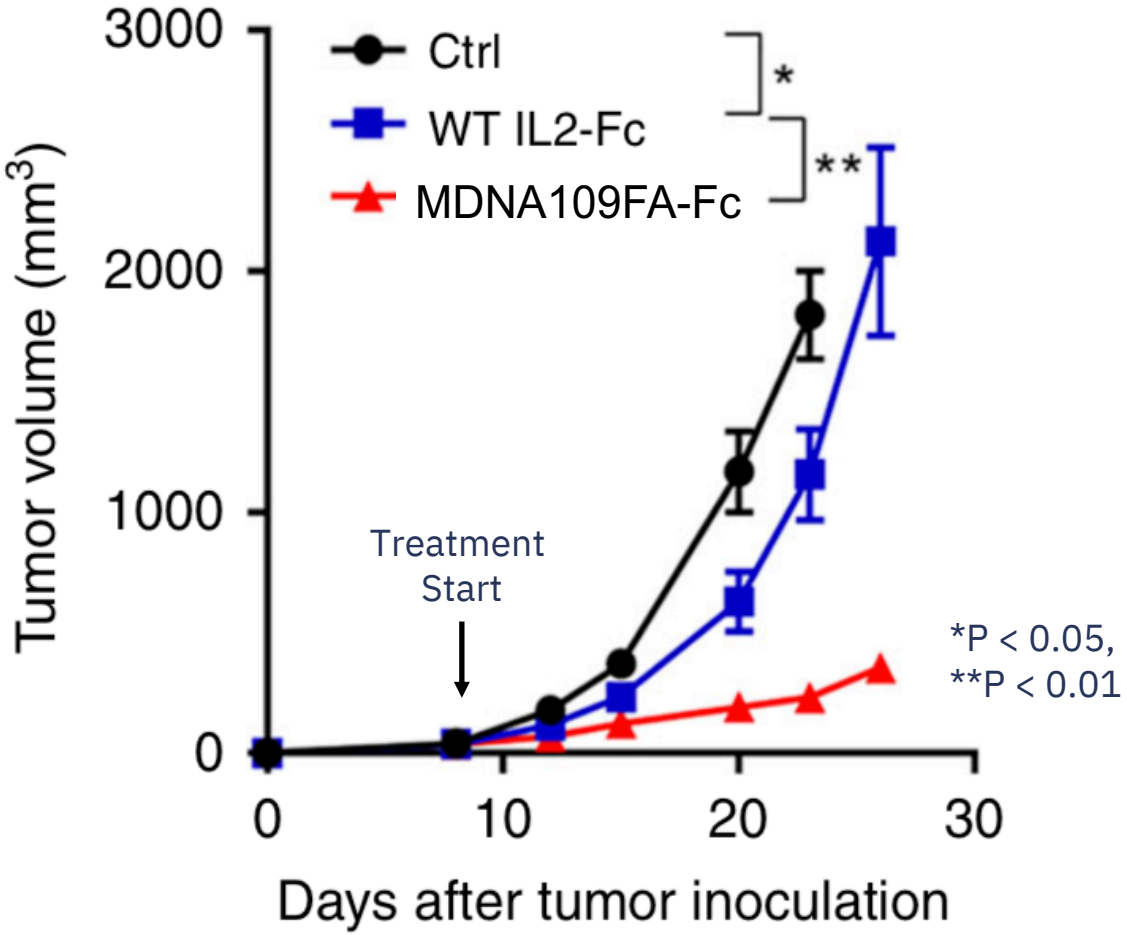


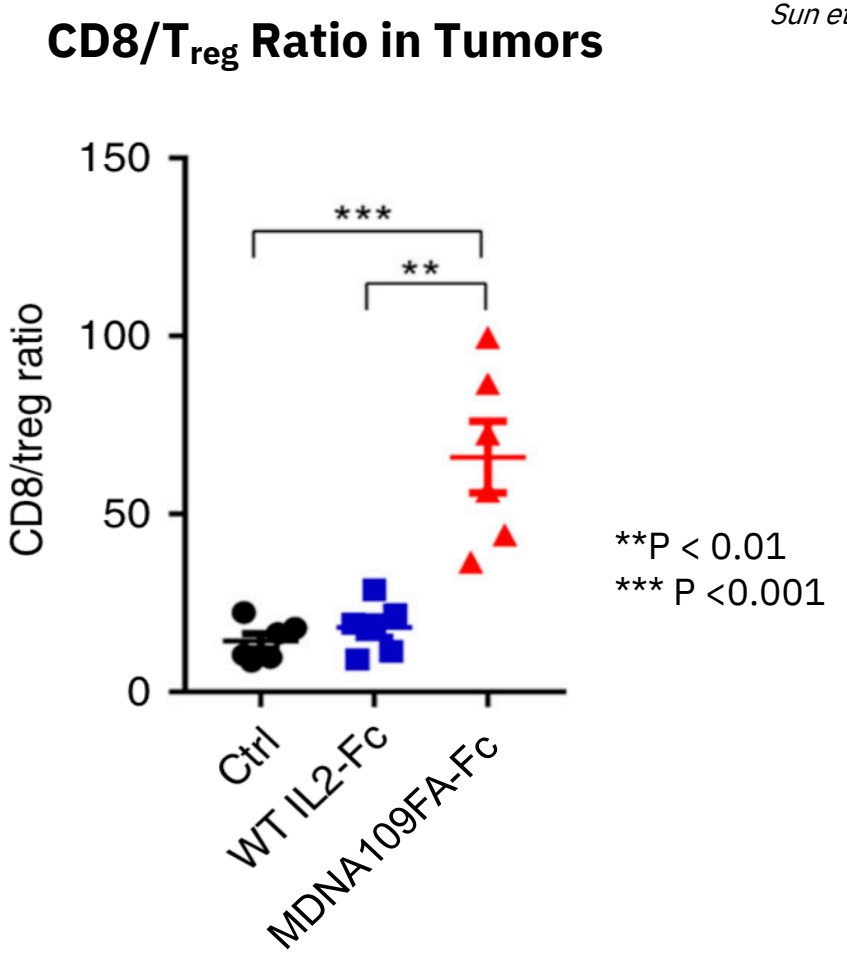
NK/T_{reg} Ratio



Merchant et al, ENA 2020

MDNA109FA-Fc Exhibits Superior Anti-Tumor Efficacy in B16F10 Tumor Model





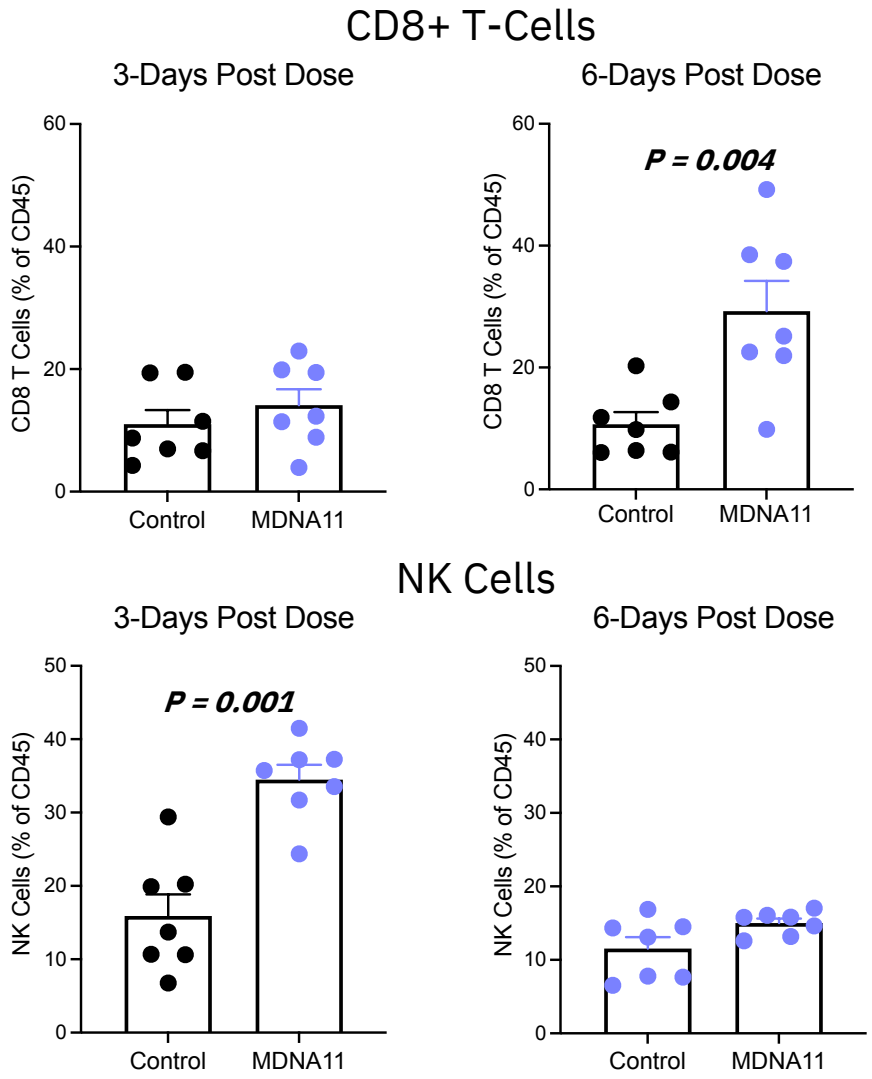
nature COMMUNICATIONS

Sun et al., Nat Comm., 2019

C57BL/6 mice (n = 5/group) were injected SQ with 5×10^5 B16F10 and treated IT with 5 µg of WT IL2-Fc or MDNA109FA-Fc on days 9, 12 & 15.

Work Conducted independently of Medicenna at the Chinese Academy of Sciences & University of Texas Southwestern Medical Center

MDNA11 Induces Preferential Tumor Infiltration of Effector Immune Cells



	CD8/Treg Ratio	
	Control	**MDNA11**
3 Days Post Dose	2.7	5.5
6 Days Post Dose	3.9	16.9

	NK/Treg Ratio	
	Control	**MDNA11**
3 Days Post Dose	3.8	15.9
6 Days Post Dose	4.8	8.4

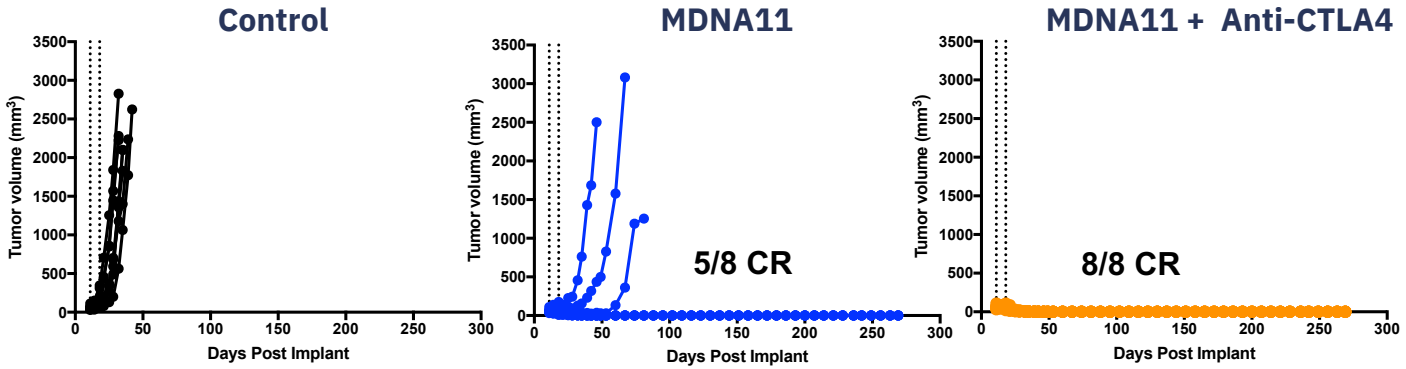
B16F10 Tumor Model

Tumor bearing mice treated with a single dose of MDNA11 (5 mg/kg; IP)

MDNA11 + Anti-CTLA4 Induces Tumor Clearance, Protects Against Re-Challenges

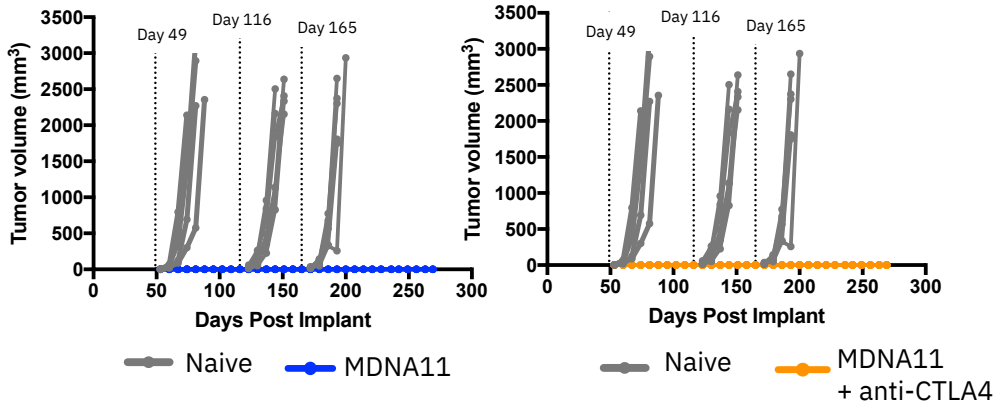
Promotes Antigen-Specific CD8 T-Cells in a CT26 Tumor Model

Primary Tumors (CT26 in Balb/c Mice)



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

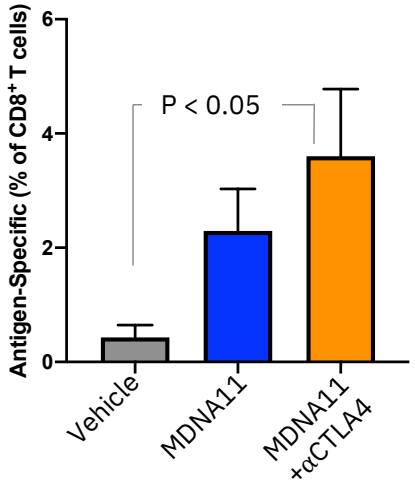
Re-challenges



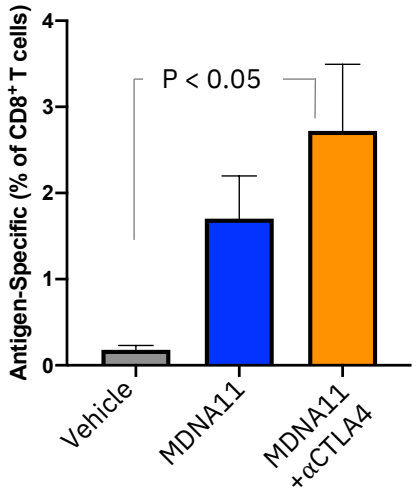
- Avg. tumor size in the treatment group at time of dosing: ~60 mm^3
- MDNA11 (5 mg/kg, IP, Q.W x 2wks); Anti-CTLA4 (9D9; 200 µg, IP, Q2W x 2wks)

To et al., ENA 2020

Antigen-specific CD8 T-cells on Day 270
(MDNA11 treatment on Day 11 & 18)



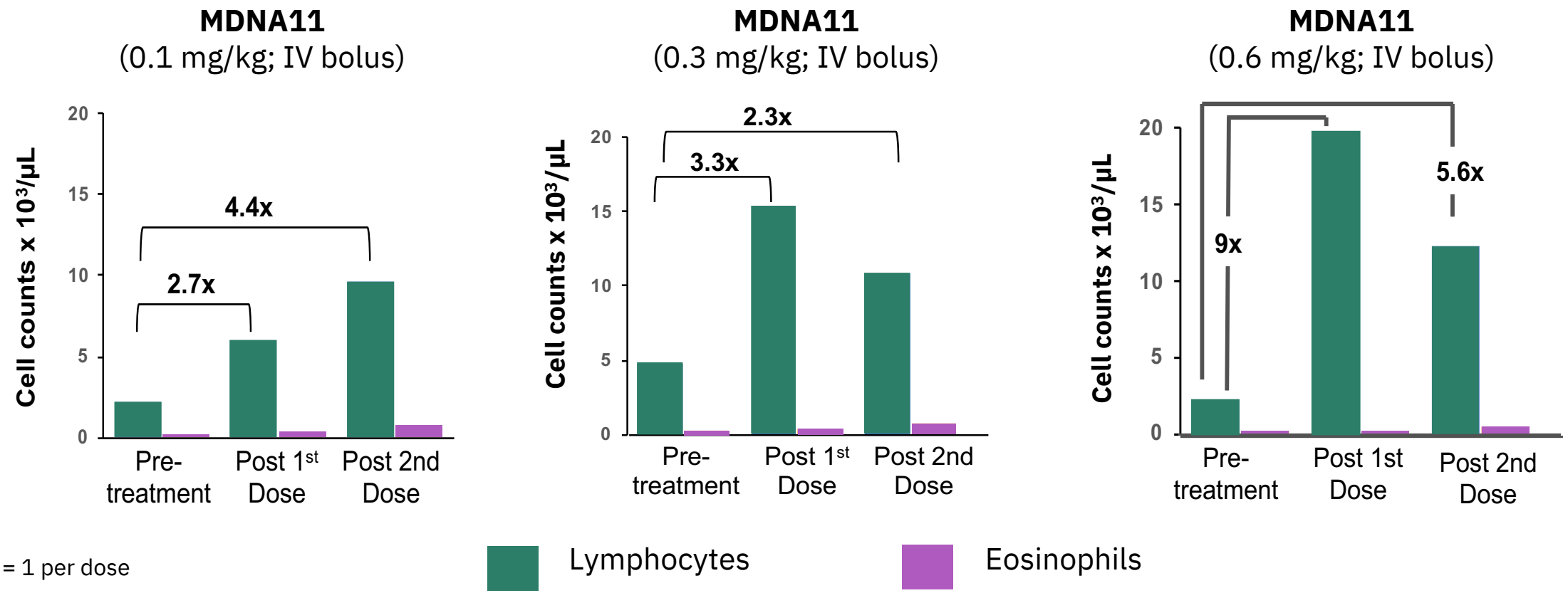
Blood



Spleen

- 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 Expands Lymphocytes Without Boosting Eosinophils in NHP



N = 1 per dose

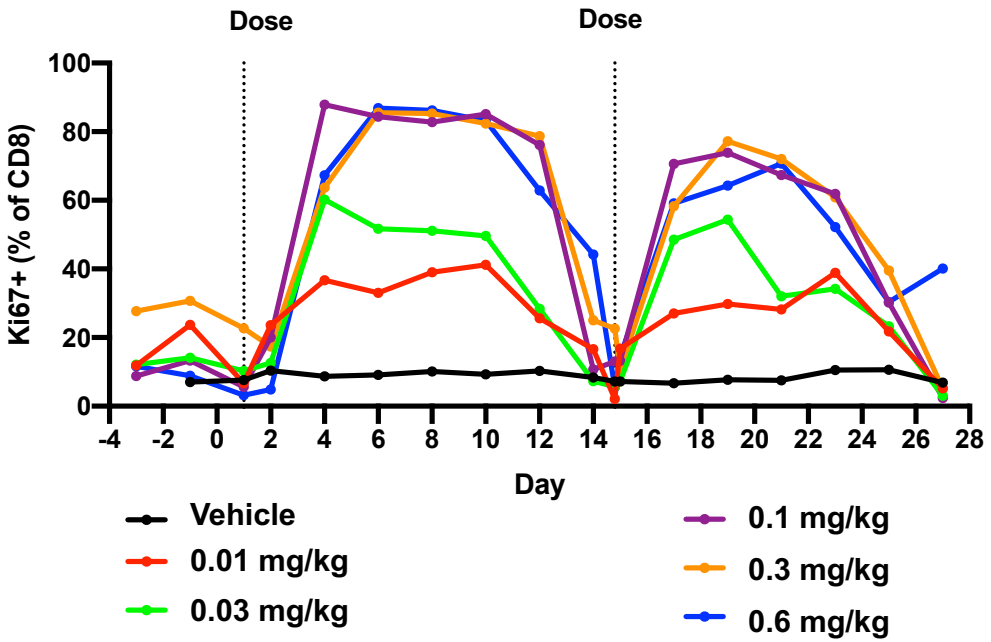
- Up to 9-fold increase in lymphocytes compared to pre-treatment.
- No expansion of eosinophils, potentially associated with VLS
- No evidence of Pulmonary Edema and no VLS observed
- No hypotension and no evidence of cytokine release syndrome nor ADA

To et al., ENA 2020

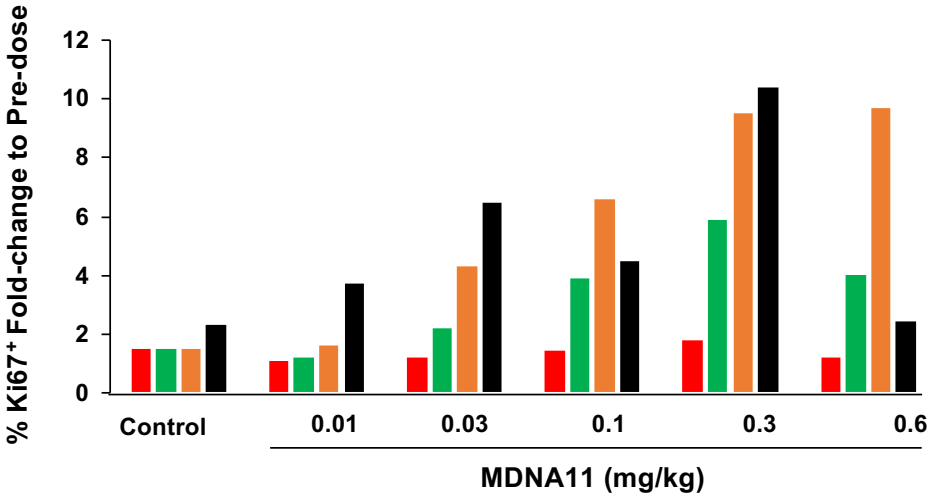
MDNA11 Induces Effector Immune Cells But Not Tregs in NHP

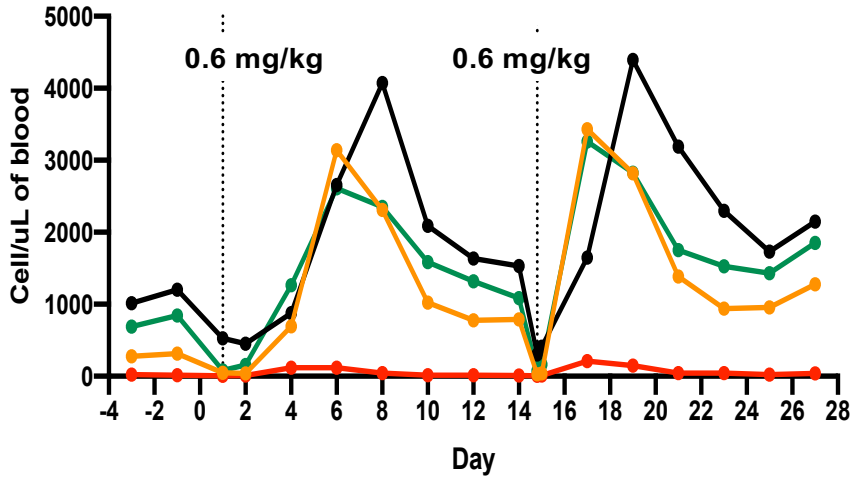
Durable Proliferation and Expansion

CD8 T Cell Proliferation (Ki67 Expression)



Preferential Proliferation & Expansion of CD4 T, CD8 T and NK cells





To et al., ENA 2020

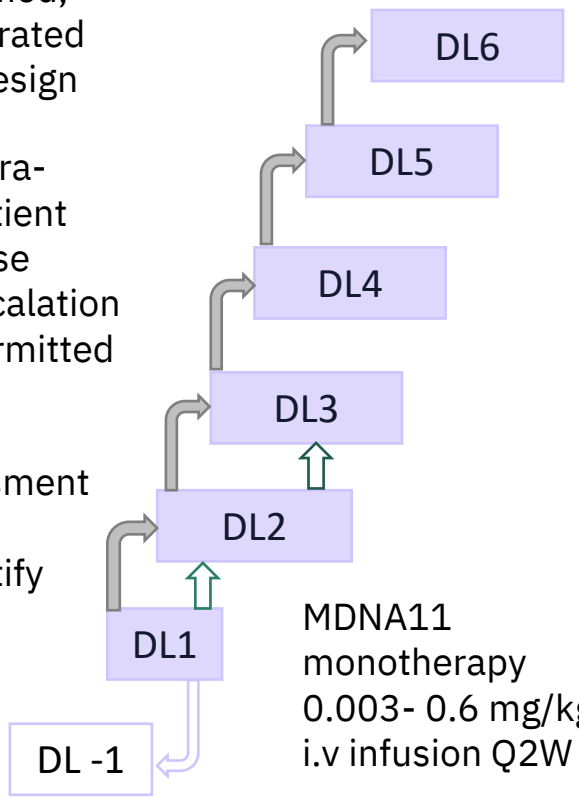
MDNA11-01: ABILITY Phase 1/2 Study in Progress

Basket, accelerated sequential dose escalation and expansion study of MDNA11

MDNA11 Monotherapy Dose Escalation

N~ 20: Select tumors

- Modified, accelerated 3+3 Design
- Intra-patient dose escalation permitted
- DLTs assessment
- Identify RP2D



MDNA11 monotherapy 0.003- 0.6 mg/kg, i.v infusion Q2W

MDNA11 Monotherapy Dose Expansion

N~ 30: Melanoma, RCC and other select tumors (1:1:1)

MDNA11 administered alone at RP2D via i.v infusion Q2W

Signals of anti-tumor activity

MDNA11 + CPI Dose Expansion

N~ 30: Melanoma, RCC and other select tumors (1:1:1)

Safety run-in (21 days)

MDNA11 administered at RP2D in combination with CPI via i.v. infusion Q3W (planned)

Signals of anti-tumor activity

Endpoints:

- ORR (RECIST 1.1)
- DCR
- DoR
- TTR
- Clinical Benefit Rate (CBR) (CR + PR + SD 12 weeks)
- Survival Eps (TTE Analysis): PFS/OS

Treatment: until PD/unacceptable toxicity/withdrawal of consent

The FUTURE

Bifunctional SuperKine ImmunoTherapies

BiSKITs™

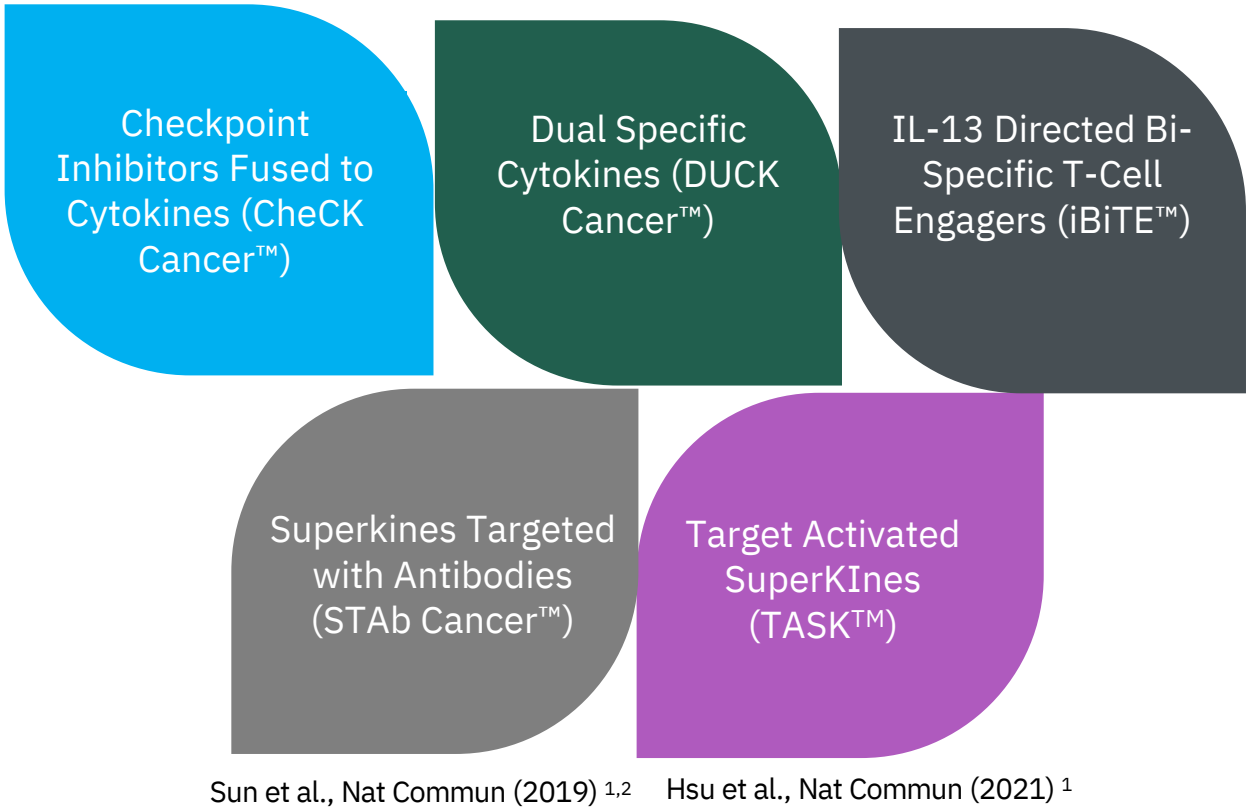
MEDICENNA

Potential of Medicenna's BiSKITs™ Platform

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)

Merchant et al., ENA 2020
Merchant & To, AACR (2021)

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)



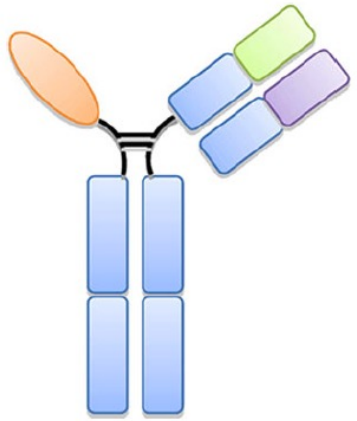
Sun et al., Nat Commun (2019) [1,2]

Hsu et al., Nat Commun (2021) [1]

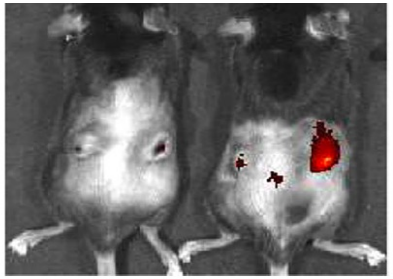
Work conducted independently of Medicenna at: [1]the Chinese Academy of Sciences; [2]University of Texas Southwestern Medical Center

MDNA109 STAB™ : Tumor Accumulation Enhances Response*

MDNA109FA (sumIL-2) **αEGFR Antibody**

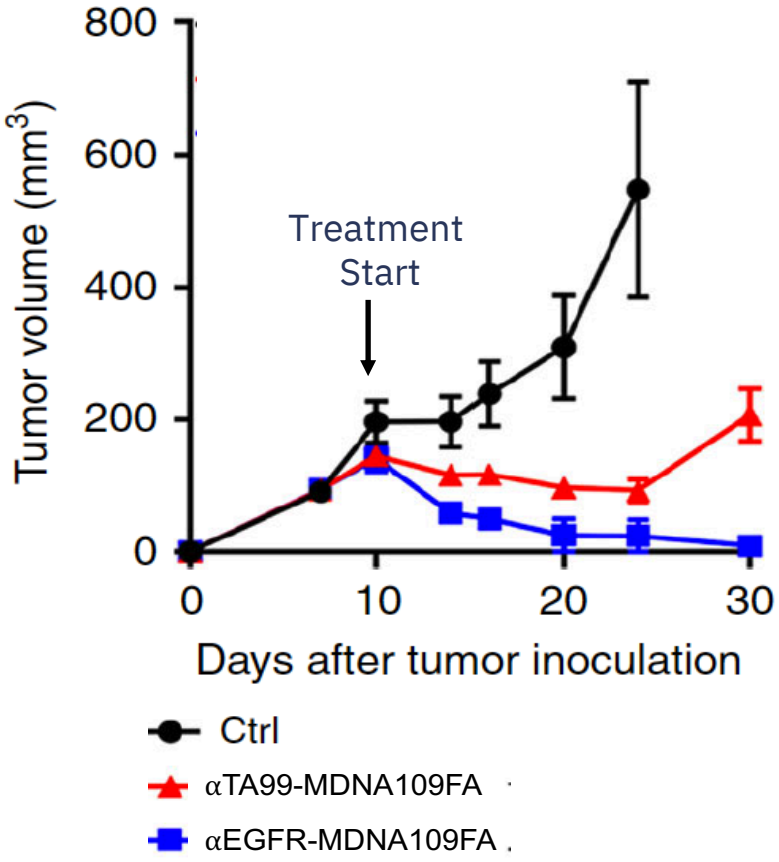


Control αEGFR-MDNA109FA



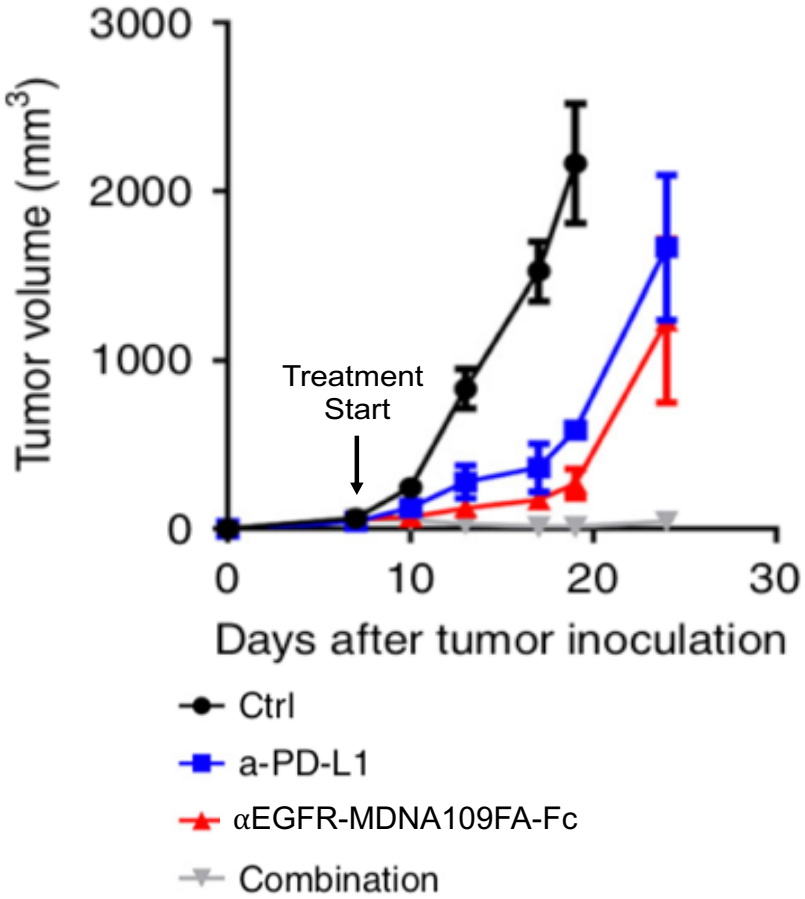
Left tumor: MC38
Right tumor: MC38-EGFR5

MC38-EGFR5



C57BL/6 mice were (n = 5/group) injected subcutaneously with 5 × 10^5 of MC38-EGFR5 cells, and then i.v. treated on days 7 and 10 with PBS, 25 μg of αEGFR-MDNA109FA or 25 μg αTA99-MDNA109FA.

B16F10-EGFR5



C57BL/6 mice (n = 5/group) were injected SQ with 5 × 10^5 of B16F10-EGFR5 cells and IP treated with 25 μg of αEGFR-MDNA109FA-Fc or/and intratumorally treated with 50 μg of anti-PD-L1 on days 8, 11, and 14

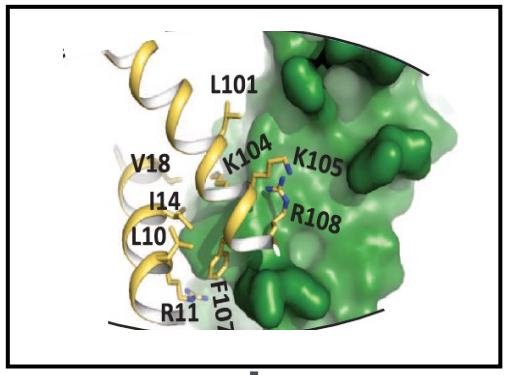
Sun et al., Nat Comm., 2019

*Work Conducted independently of Medicenna at the Chinese Academy of Sciences & University of Texas Southwestern Medical Center

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

Science Signaling

Moraga et al., Science Signaling, 2015

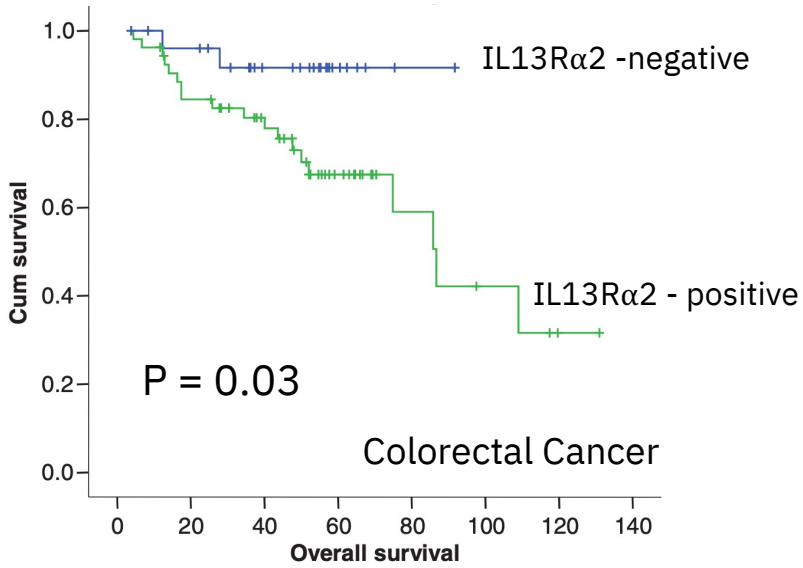


~4000 fold Selectivity for IL-13Rα2

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

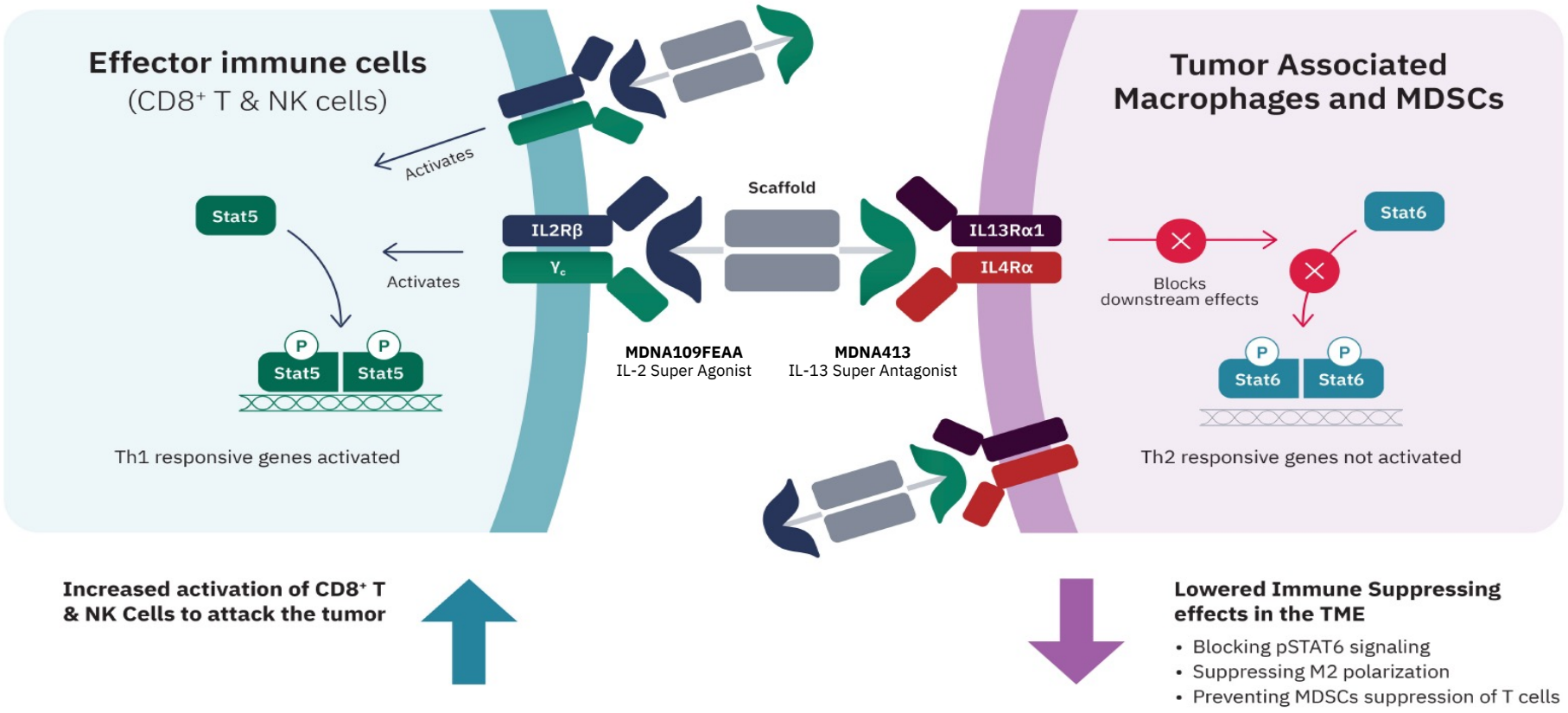
IL-13Rα2 Is Associated with Poor Survival



Barderas et al., Cancer Res, 2012

MDNA19-413 is a Bi-functional Superkine

Targeting immunologic ‘cold tumors’ by modulation of TME

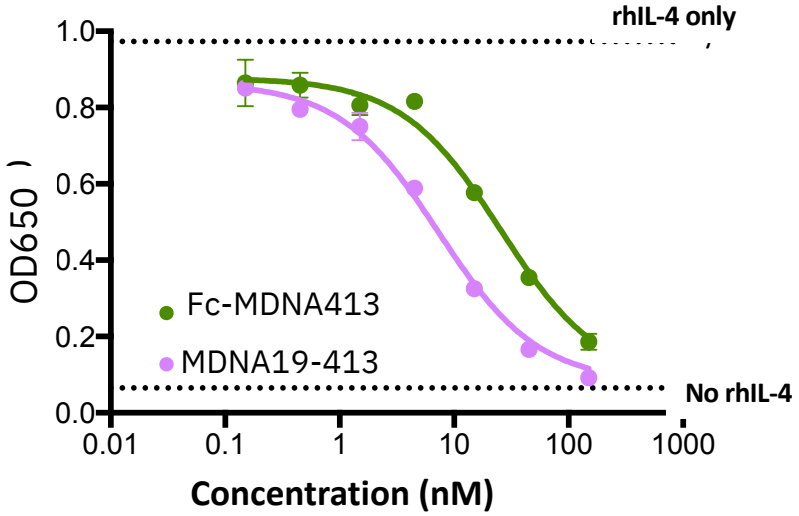


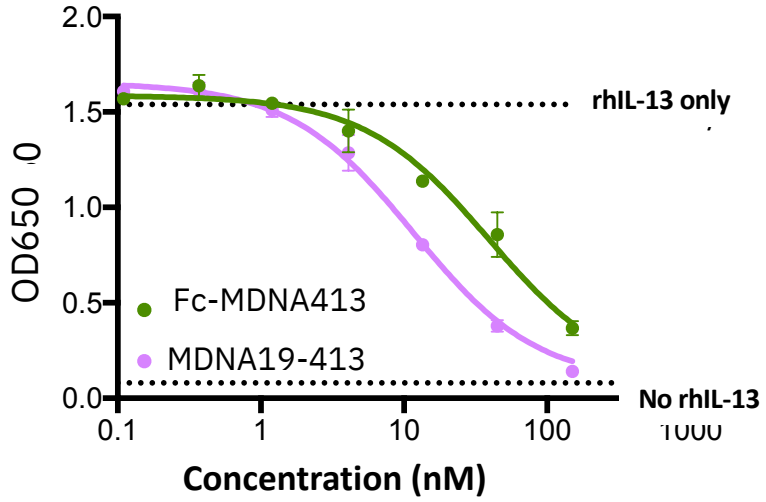
‘Cold’ tumors are not responsive to immunotherapies because of a Th2 (pro-tumoral) microenvironment:

- Low CD8⁺ & NK cell counts; high T_{reg} counts
- High number of immune-suppressive myeloid cells (TAM & MDSC)
- TAMs & MDSCs overexpress the Type II IL-4 receptor

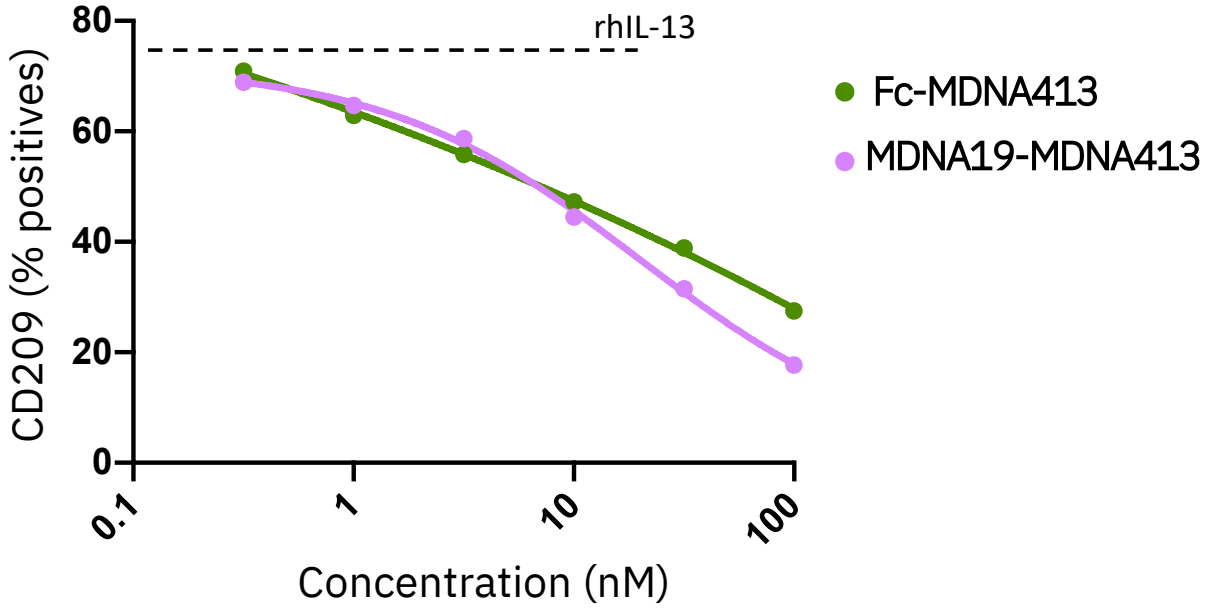
MDNA19-413 Inhibits IL-4 & IL-13 Induced Signaling & M2a Polarization

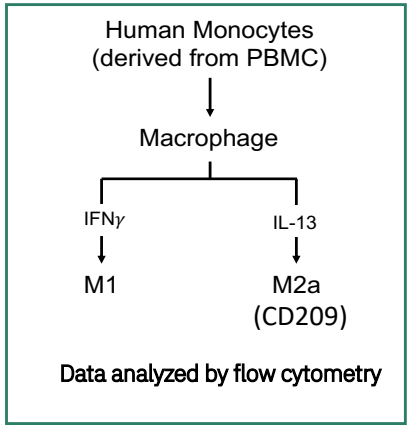
Inhibition of IL-4 and IL-13 Induced Signaling





Inhibition of IL-13 Induced M2a Polarization





HEK Blue IL-4/IL-13 reporter cells (InvivoGen);
Measurement of pSTAT6 activity

Merchant & To, AACR 2021

Potential of Medicenna's Versatile Superkine Pipeline

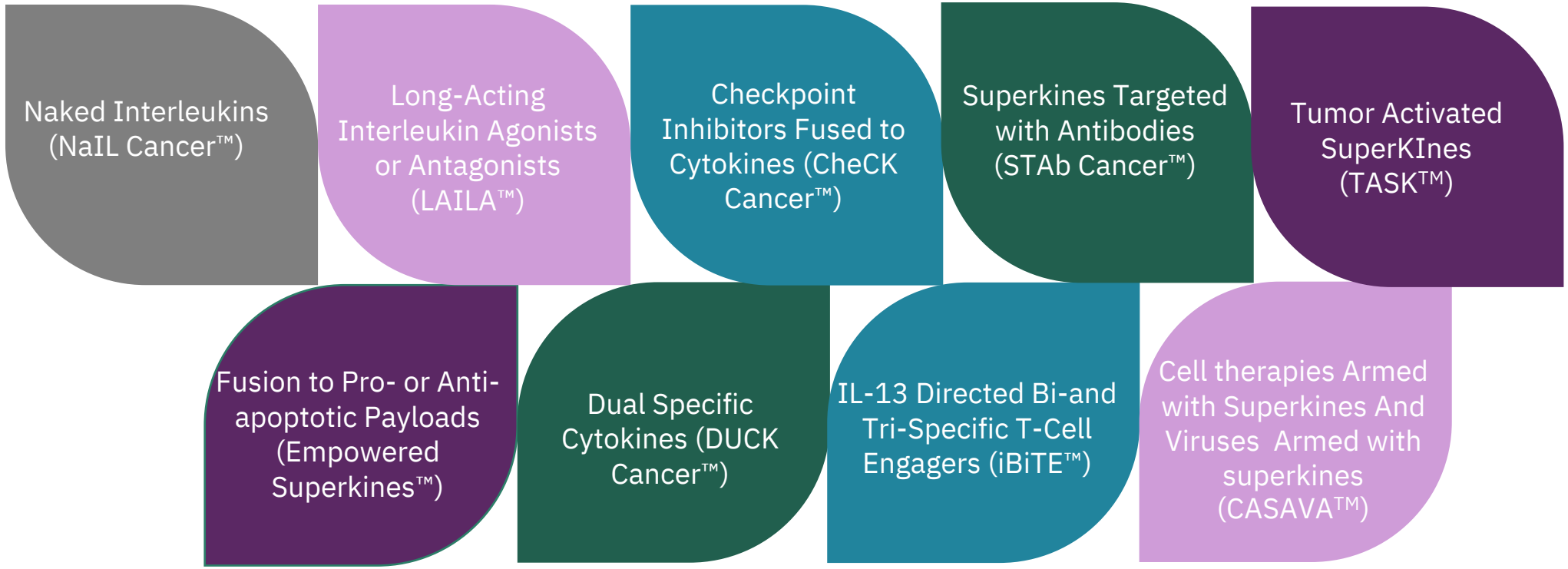
Levin et al., Nature (2012)
Moraga et al., Science Signaling (2015)
Junttila et al., Nature Chem Biol (2012)

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

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)

Sun et al., Nat Commun (2019) [1,2]

Hsu et al., Nat Commun (2021)[2]



Sampson et al., ASCO (2020)
Ellingson et al, Clin Cancer Res (2021)

Merchant et al., ENA 2020
Merchant & To, AACR (2021)

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)

Quixabeira et al., Front Immunol (2021)[3]

Work conducted independently of Medicenna at: [1]the Chinese Academy of Sciences, [2]University of Texas Southwestern Medical Center; [3]University of Helsinki

Thank You!

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President and CEO
fmerchant@medicenna.com

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