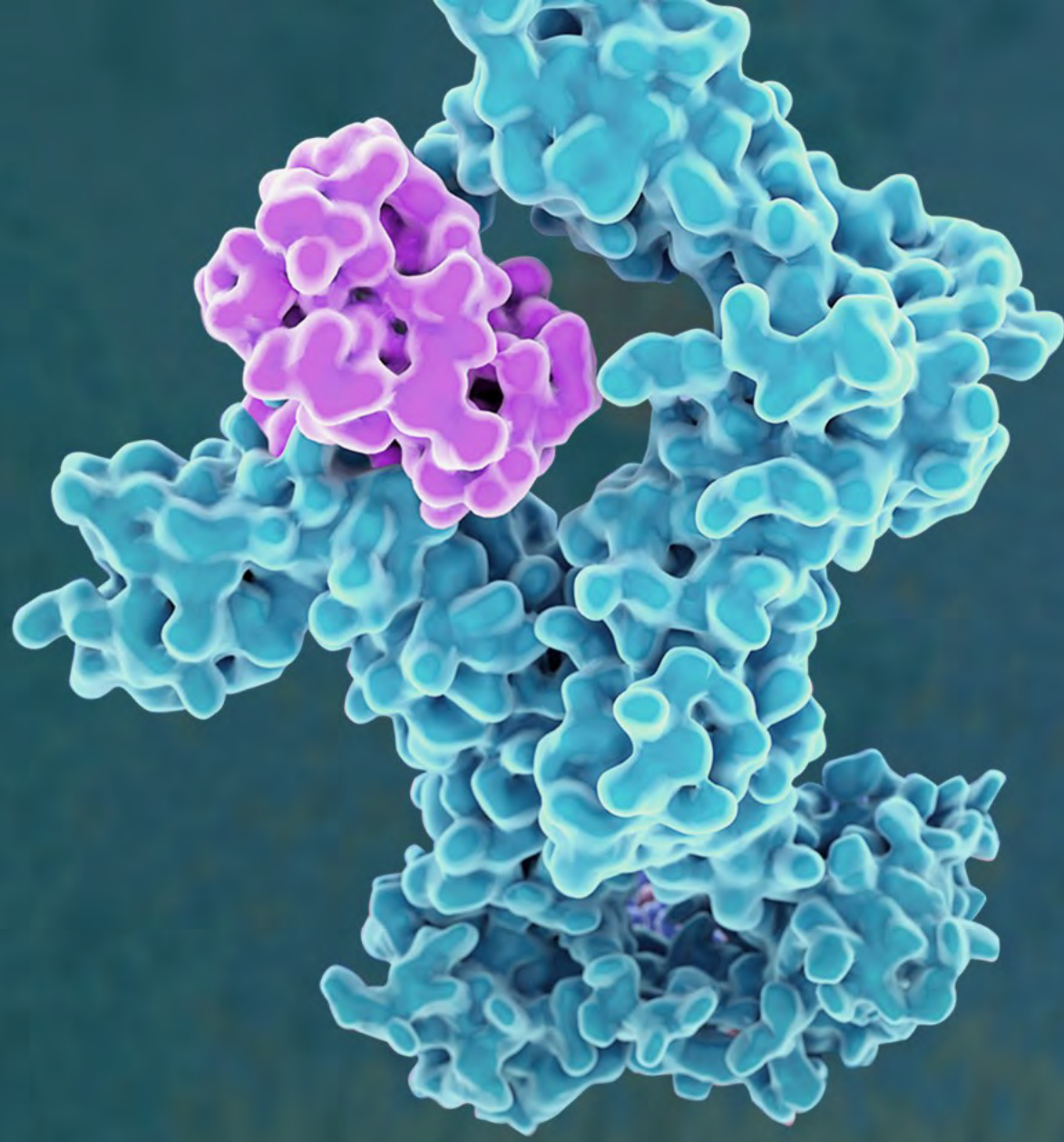
Next-Gen Cytokine
Therapeutics Summit

Designer Superkines: Modulating Immune Cells of Choice



Fahar Merchant, Ph.D
President and CEO

MEDICENNA

Forward Looking Statements

Certain statements in this presentation are “forward-looking statements. Any statements that express or involve discussions with respect to predictions, expectations, beliefs, plans, projections, objectives, assumptions or future events or performance (often, but not always using words or phrases such as “expect”, “seek”, “endeavour”, “anticipate”, “plan”, “estimate”, “believe”, “intend”, or stating that certain actions, events or results may, could, would, might or will occur or be taken, or achieved) are not statements of historical fact and may be “forward-looking statements”.

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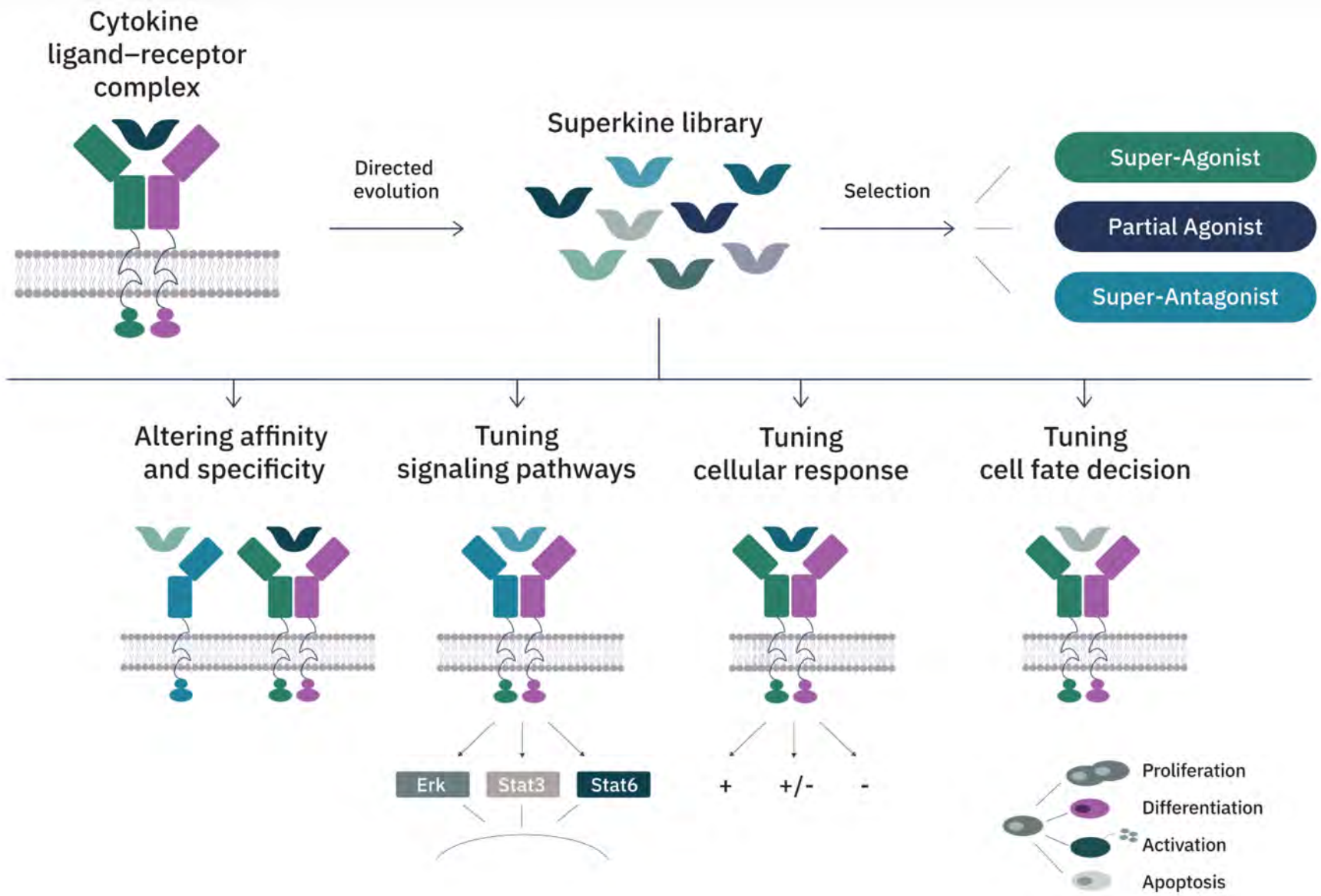
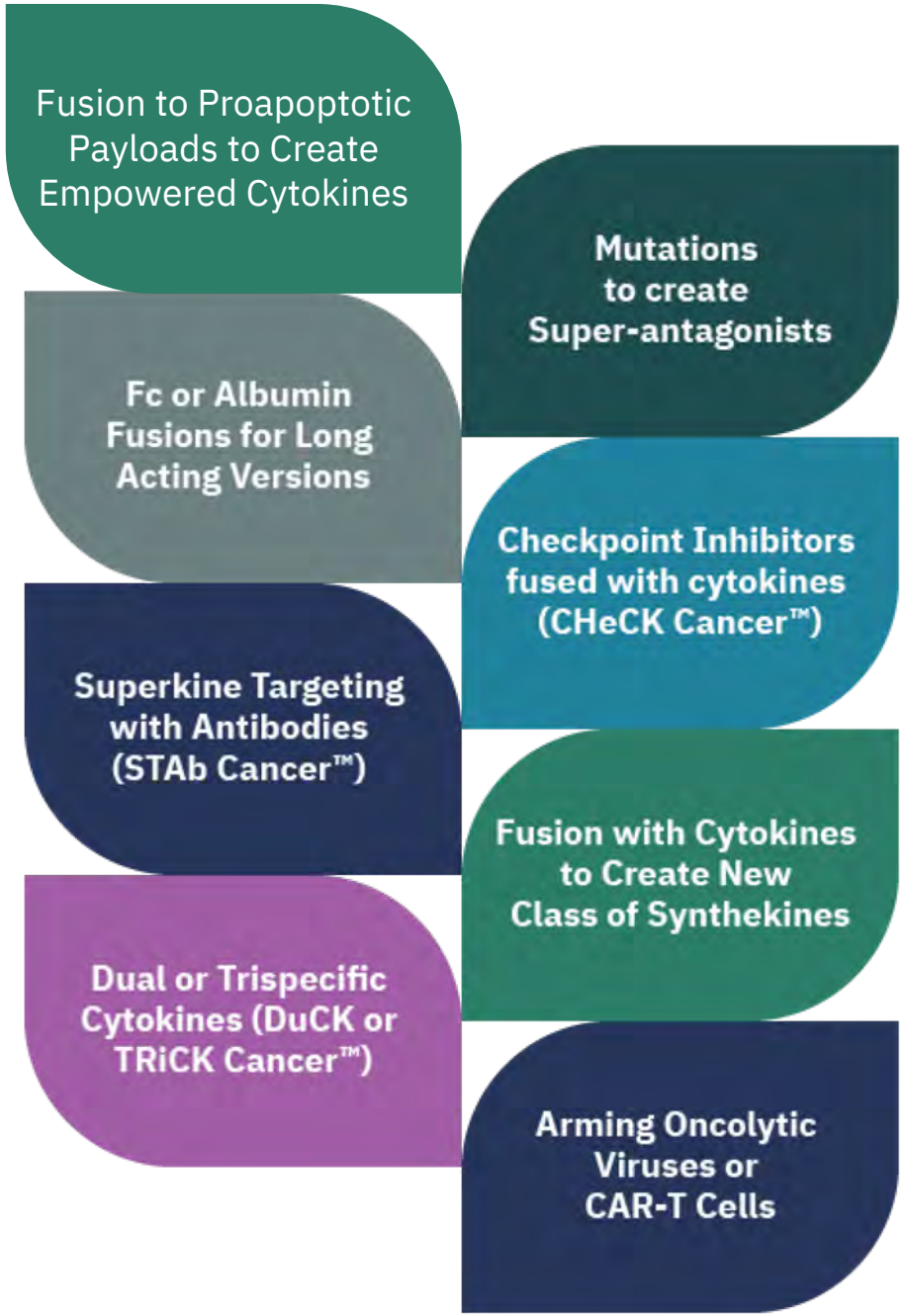
A Fine Balance: Directed Evolution to Create Superkines



Designer Superkines

Ease of Pipeline Expansion

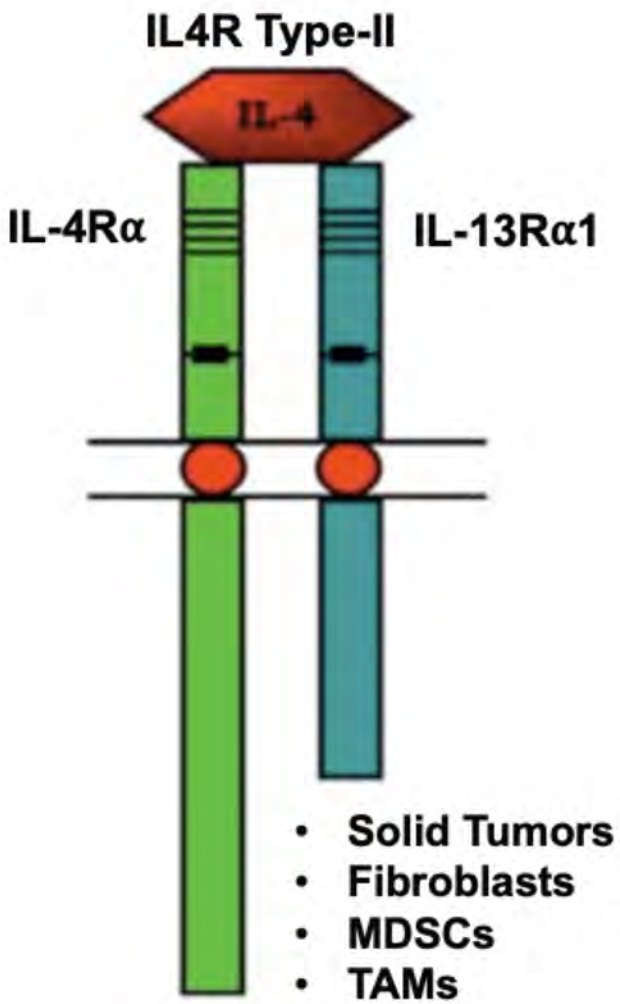
- **Relies on Simple and Reliable Manufacturing Platform**
- **Rapid In Vitro Screening of Large Libraries**
- **Allows Bespoke Therapeutic Design**



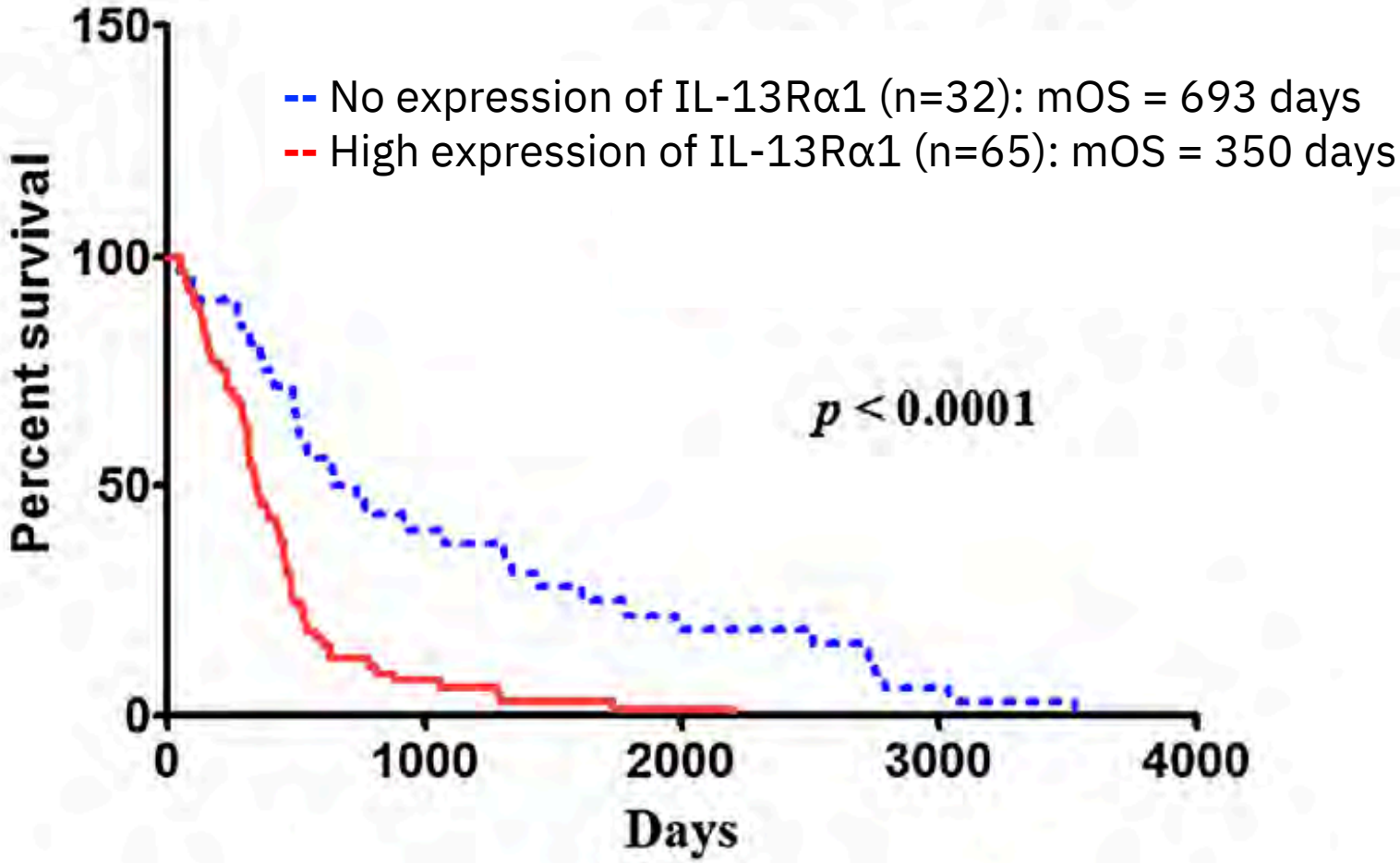
MDNA55

A Powerful Molecular Trojan Horse Targeting Glioblastoma

Type 2 IL4R Expression Predicts Poor Survival in GBM

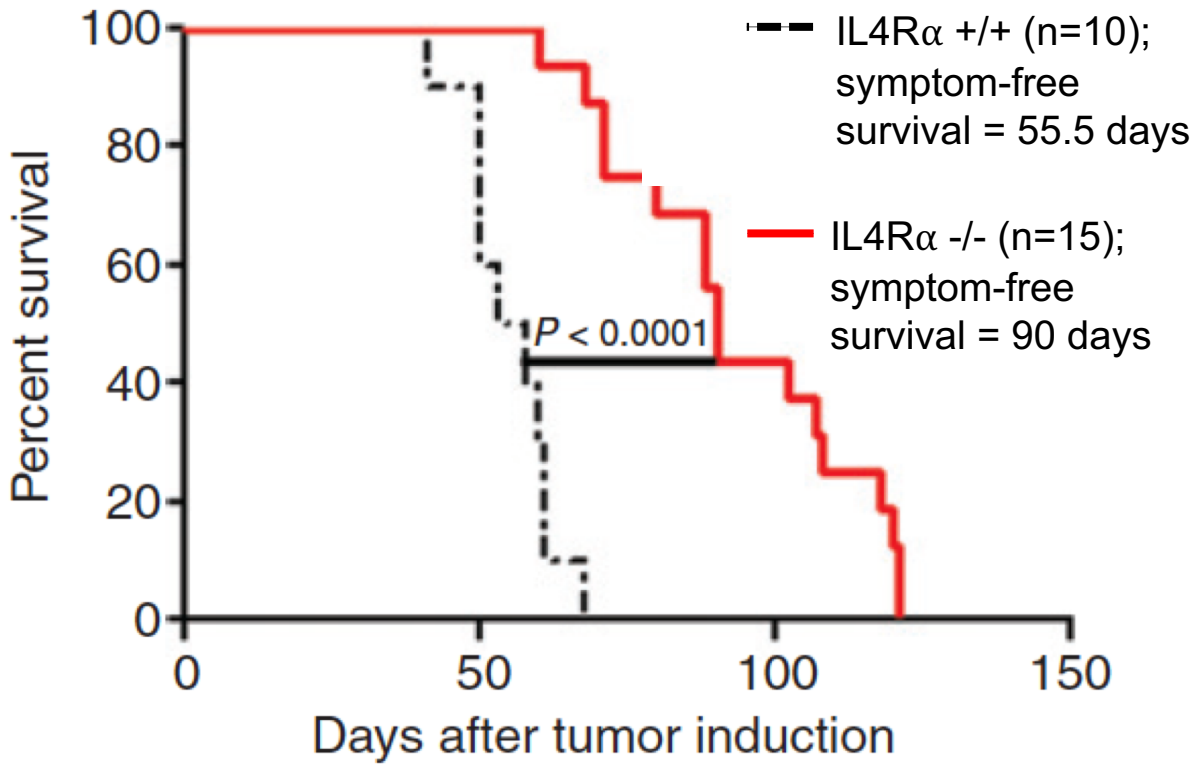


Survival in Subjects with GBM - TCGA



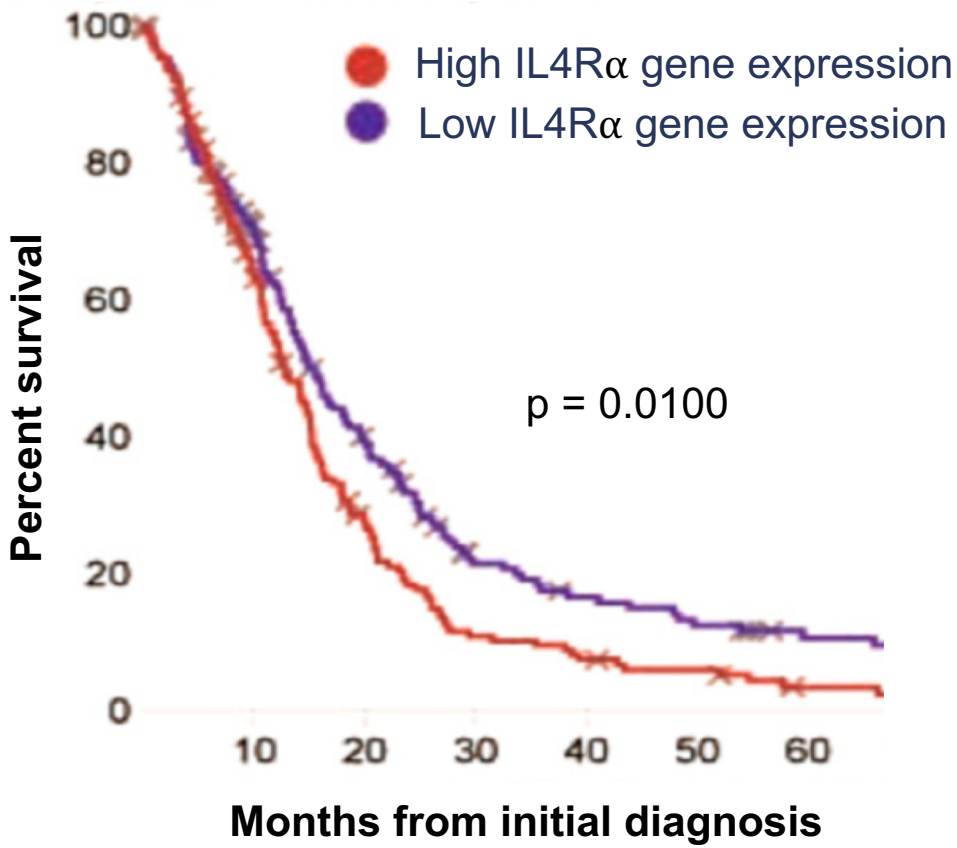
High IL4Rα Expression Predicts Poor Survival in GBM

Survival in BALB/c Glioma Mouse Model



Kohanbash G et al. Cancer Res 2013;73:6413-6423

Survival in GBM Patients - TCGA



Data Derived from TCGA GBM Database (https://tcga-data.nci.nih. gov/tcga/)

D'Alessandro G, et al. Cancers (Basel). 2019

MDNA55: A Targeted Immunotherapy for GBM

MDNA55

Targets the IL4R, which is expressed in brain tumors and in the tumor microenvironment (TME), but not the healthy brain

Highly Selective

Avoids off-target toxicity

Disrupts the TME

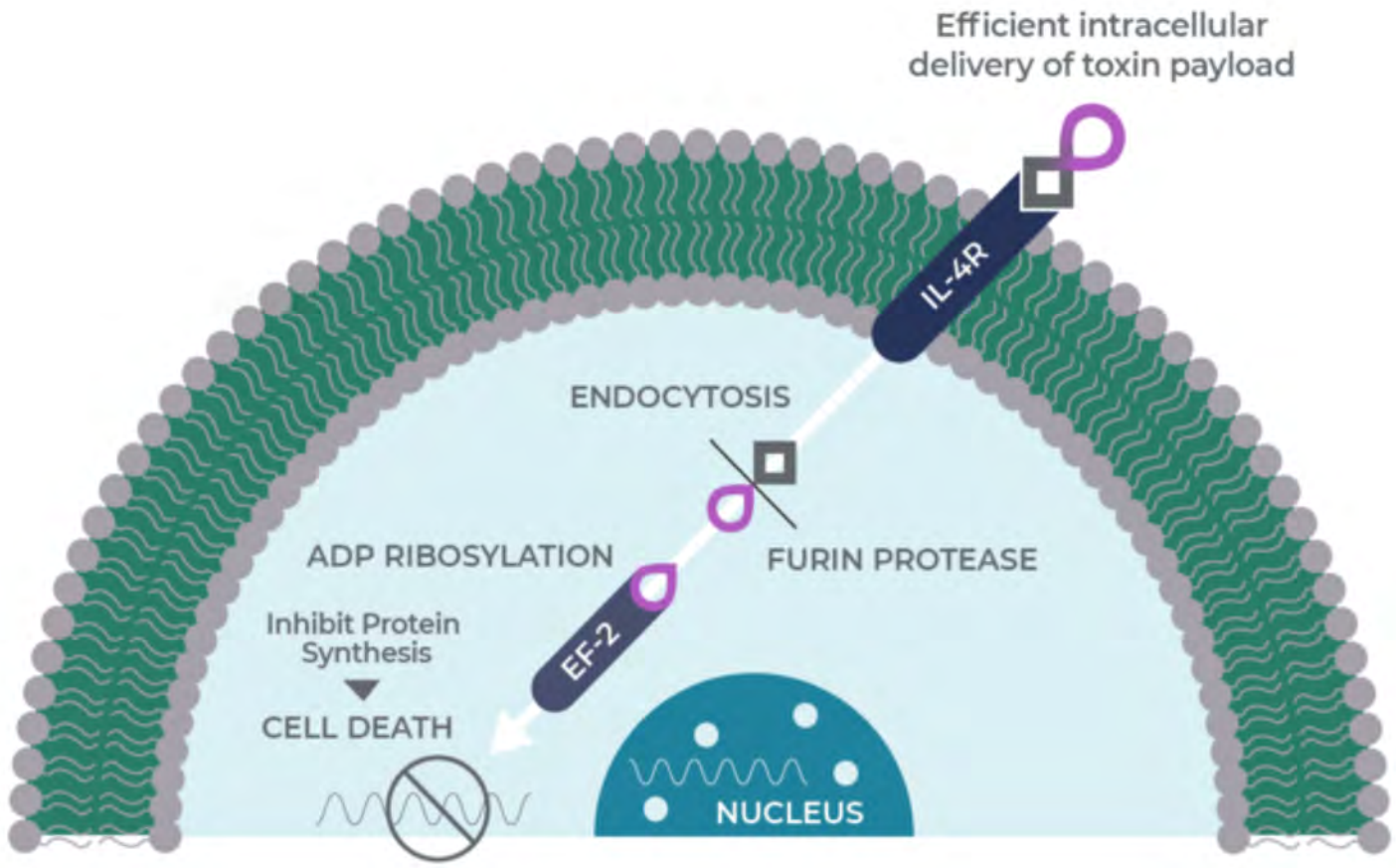
By targeting IL4R positive cells found throughout the TME, MDNA55 unblinds the tumor to the body's immune system

Sustained Immune Memory Response

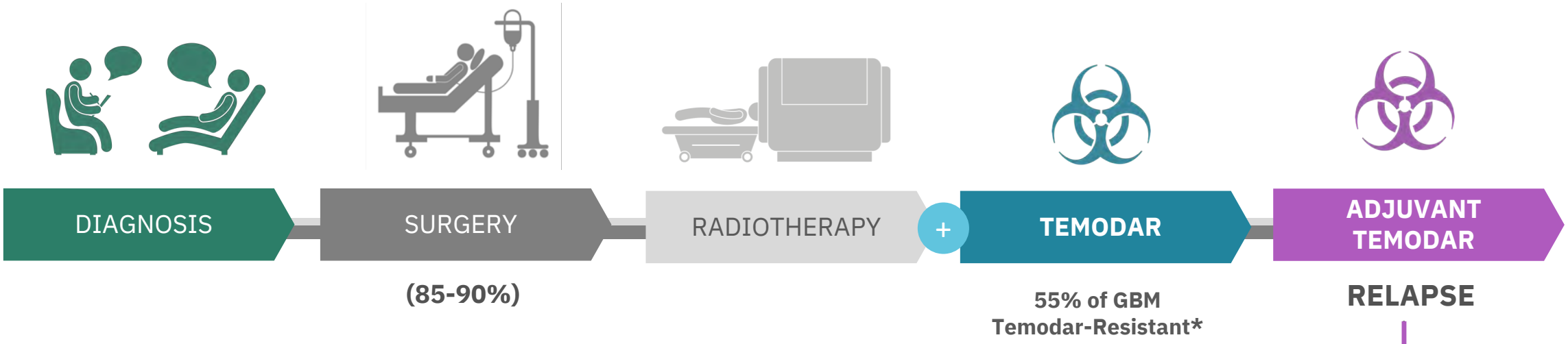
Anti-tumor immunity is initiated and remains active after MDNA55 is cleared

Targeting Domain
Circularly Permuted Interleukin-4 (cpIL-4)

Lethal Payload
Catalytic domain of *Pseudomonas* Exotoxin A (FDA approved Moxetumomab pasudotox)



Current Treatment Strategies for GBM are Ineffective

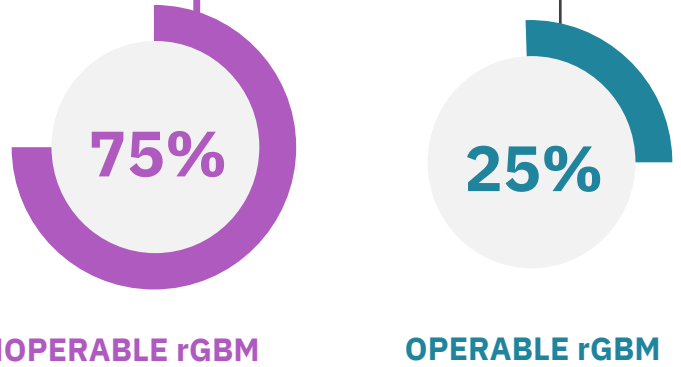


Glioblastoma (GBM) & IL4 Receptor

- Uniformly fatal – virtually all tumors will recur
- New treatment strategies are needed
- IL4 receptor (IL4R) is overexpressed in GBM cells and the tumor microenvironment making it a promising target for GBM treatments

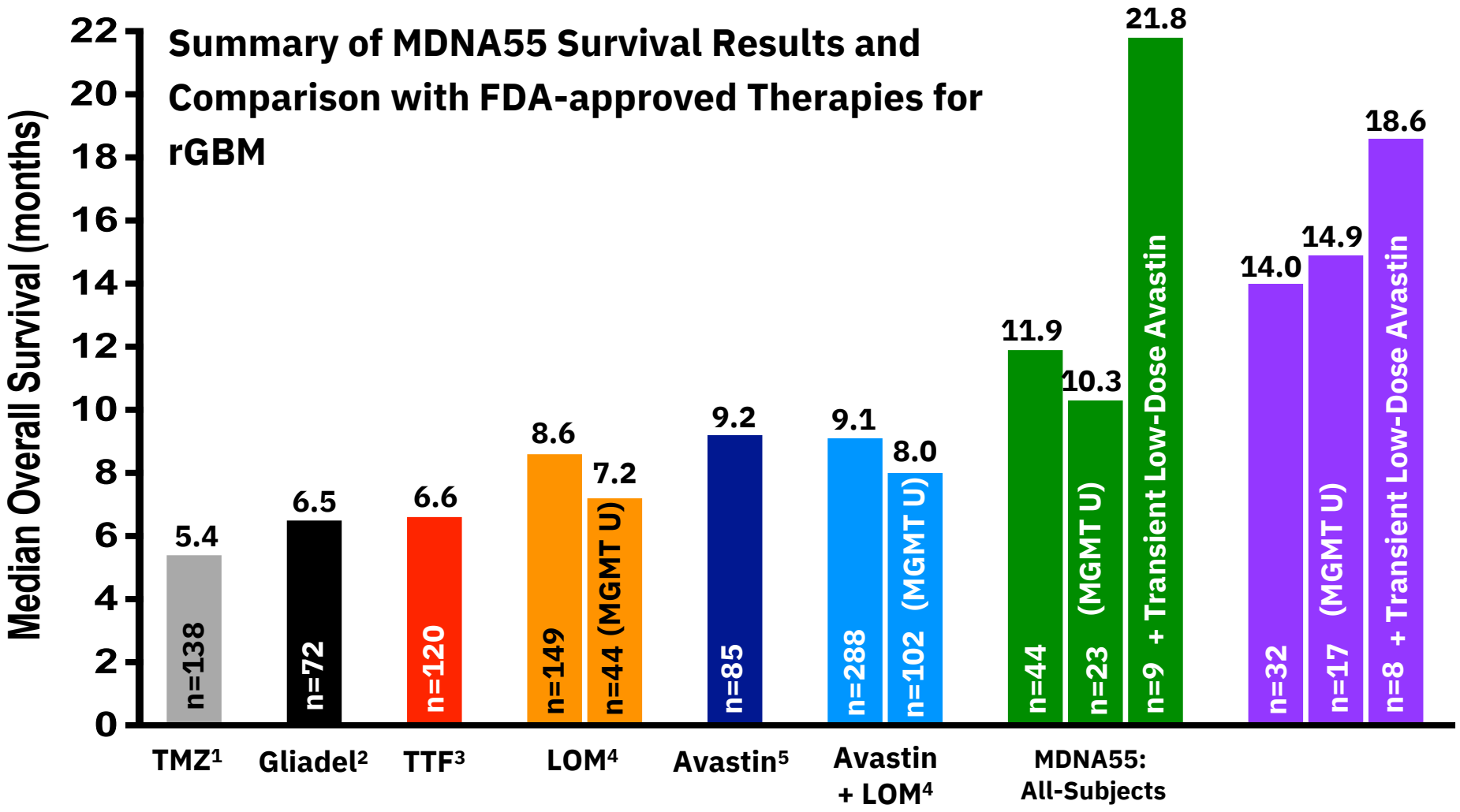
MDNA55 Treatment

Direct infusion into tumor *via convection enhanced delivery (CED)*



* Expression of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) is responsible for resistance to Temodar used in GBM treatment.

Encouraging Survival Rates Compared to Approved Therapies



TTF = Tumor Treating Fields;

LOM = Lomustine;

MGMT U = MGMT unmethylated promoter

Refences:

1=Brada et al., 2001;

2=Gliadel FDA Label 2018;

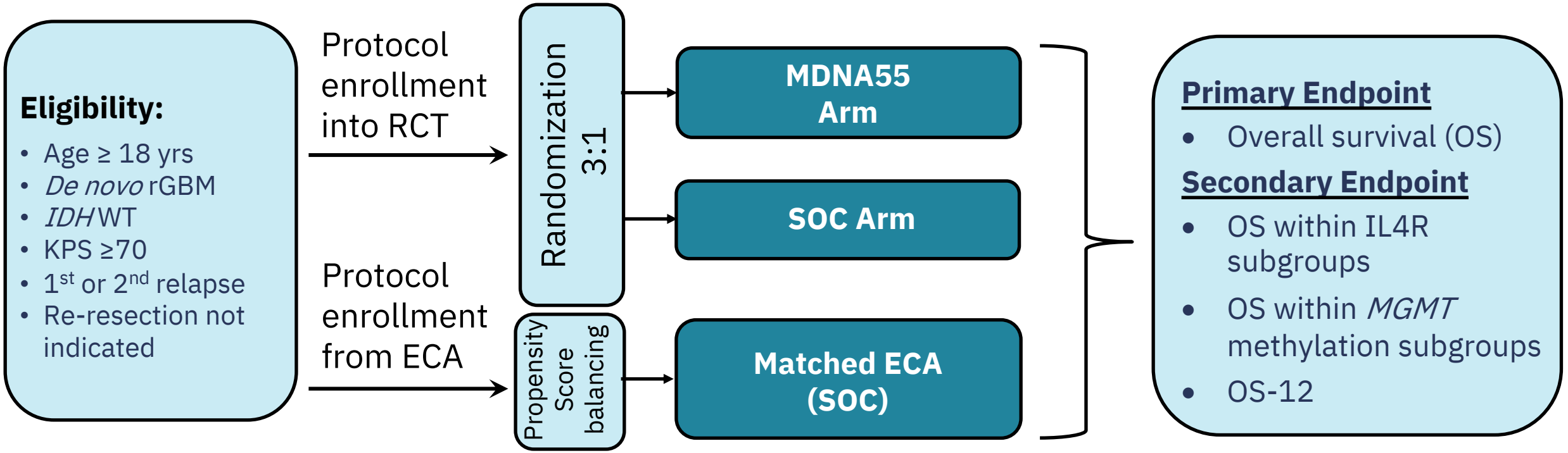
3=Stupp et al., 2012;

4=Wick et al., 2017;

5=Friedman et al., 2009

Planned Phase 3 Trial

Pioneered a Hybrid Design Using External Control



Future Opportunity: 1 Million IL4R Cancers Annually

>2000 Patient Biopsies Analyzed Consistently Show IL4R Over-Expression

Glioblastoma 76%	Bladder 73%	Breast 82%	Colorectal 89%	Head and Neck 75%
	NSCLC 79%	Mesothelioma 96%	Ovarian 60%	Pancreatic 60%

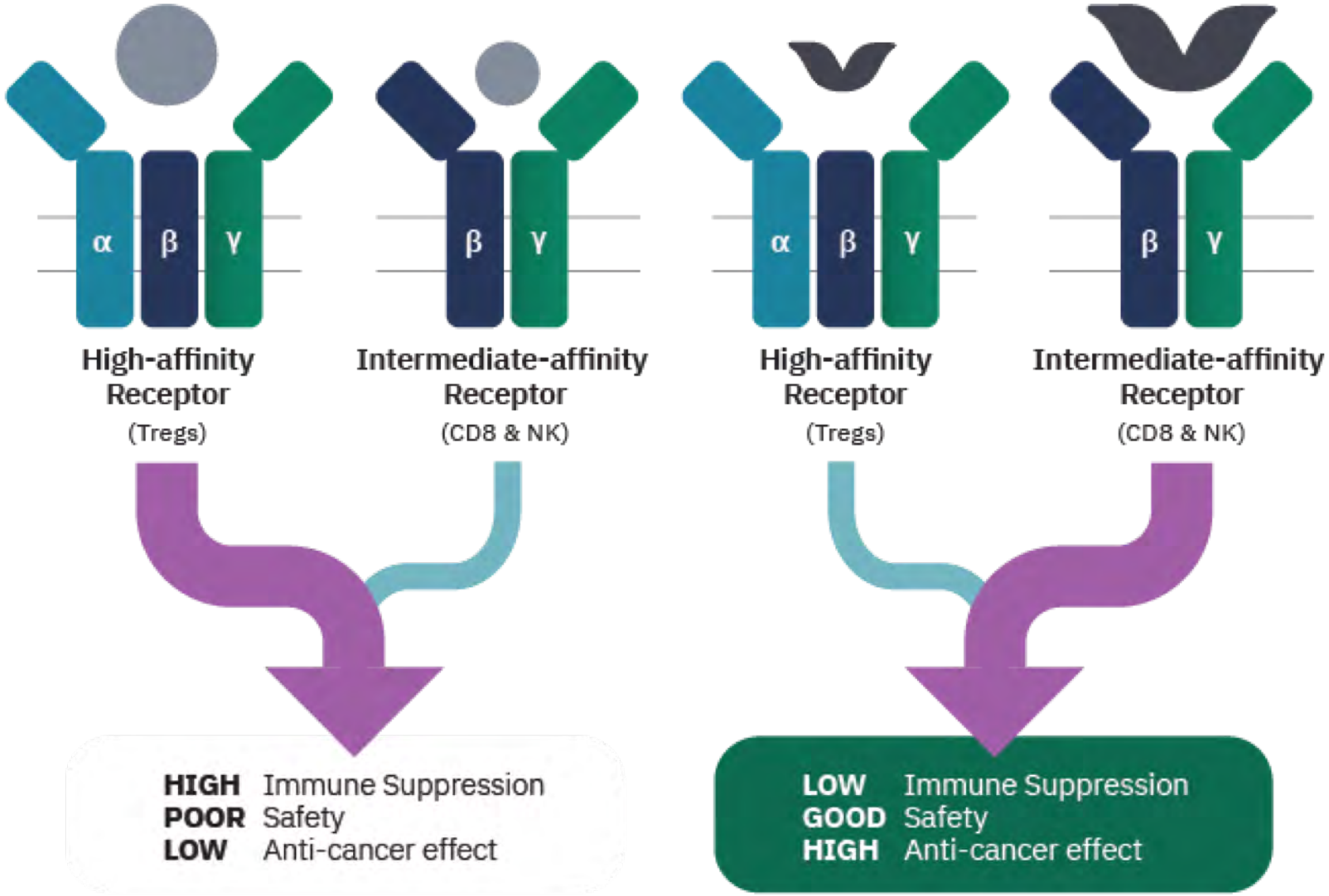
MDNA11

IL-2 Super Agonist for Cancer Immunotherapy

Targeting IL-2 Receptor Subunits in Cancer Therapy

IL-2

MDNA109

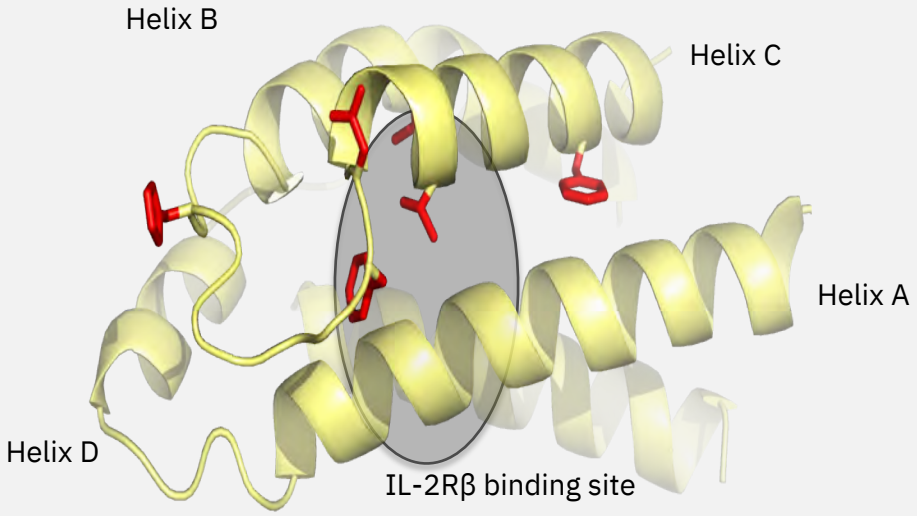


Superkines: First-Generation IL-2 Variants

LETTER

nature

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

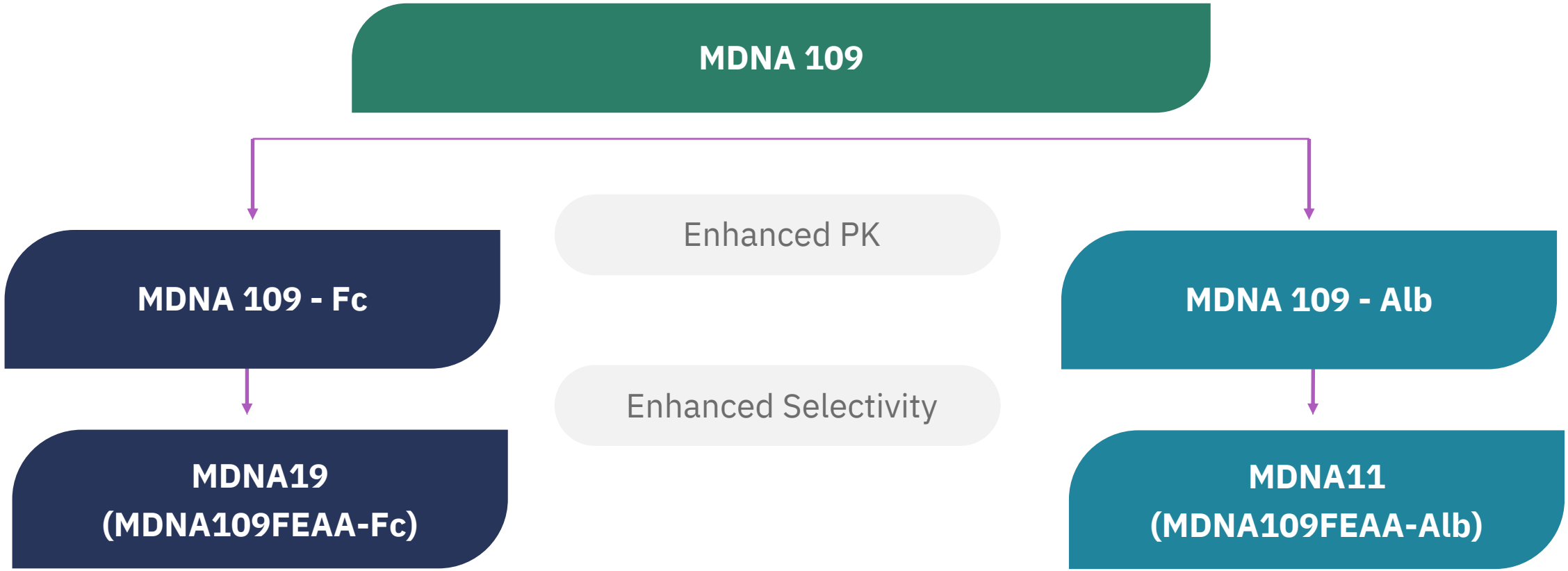


Levin, Bates, and Ring et. al, Nature, 2012

Medicenna's MDNA109 platform produced first generation IL-2 variants with 200-fold higher affinity for CD122 (IL-2Rβ), which is key for the activation of immune cells responsible for cancer killing (CD8+ T cells, naïve T cells, NK cells), yet similar affinity to CD25

	Similar affinity to CD25	200X increased affinity to CD122
SPR data (nM)	CD25	CD122
IL-2	6.6	28
MDNA109	**6.6**	**1.4**

MDNA11: Next-Generation IL-2 Superkine

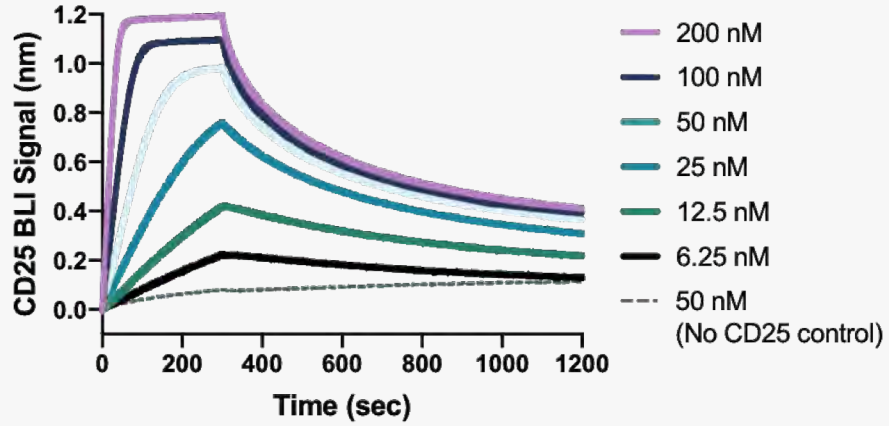


MDNA11 is a ***potentially best-in-class next-generation IL-2 superkine*** with superior CD122 binding without CD25 affinity, thereby preferentially stimulating cancer killing effector T cells and NK cells when compared to competing IL-2 programs.

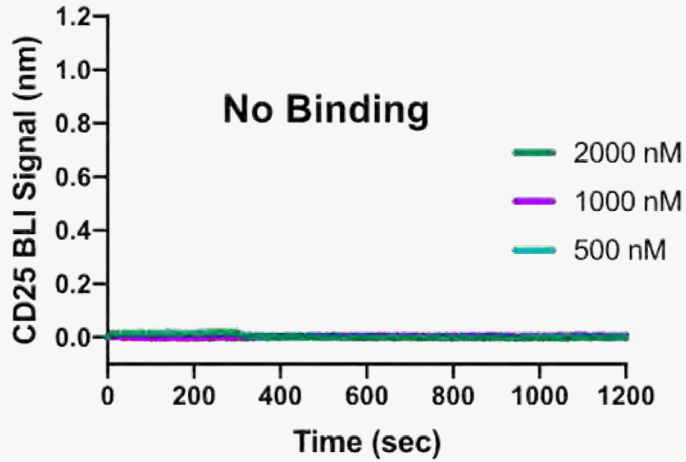
MDNA11

No CD25 Binding and Enhanced Affinity and Selectivity for CD122 Compared to rhIL-2

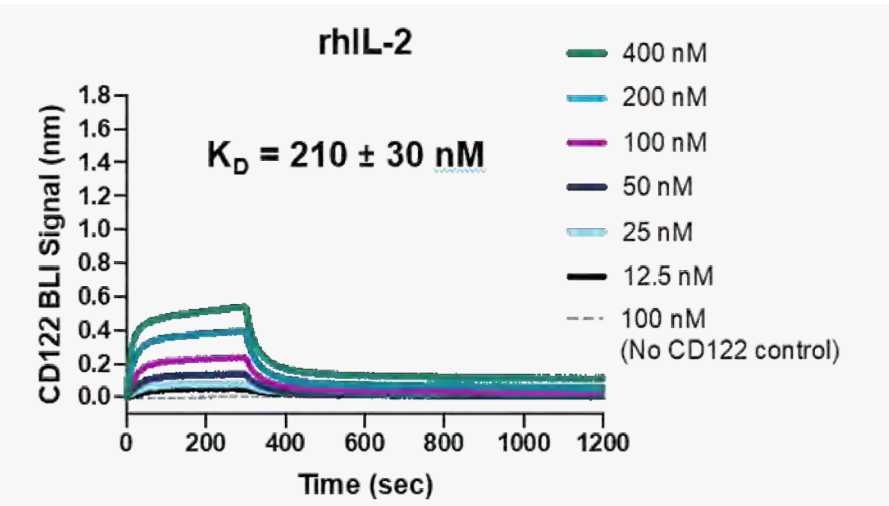
rhIL-2 – CD25 Binding



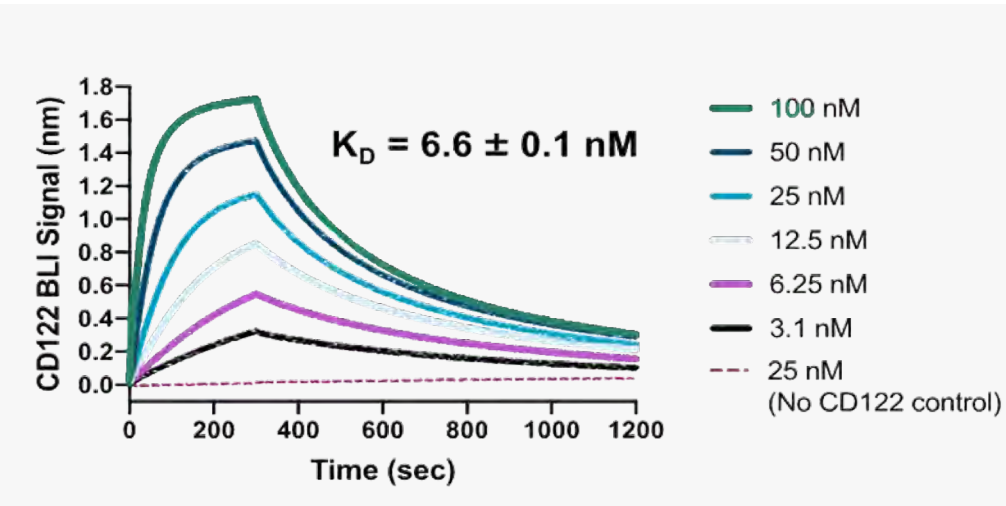
MDNA11 – CD25 Binding



rhIL-2 – CD122 Binding



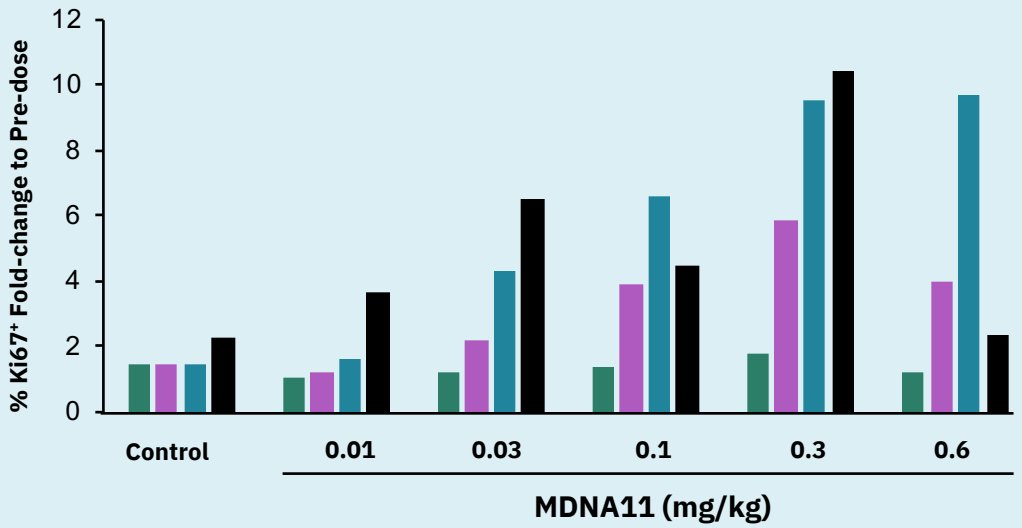
MDNA11 – CD122 Binding



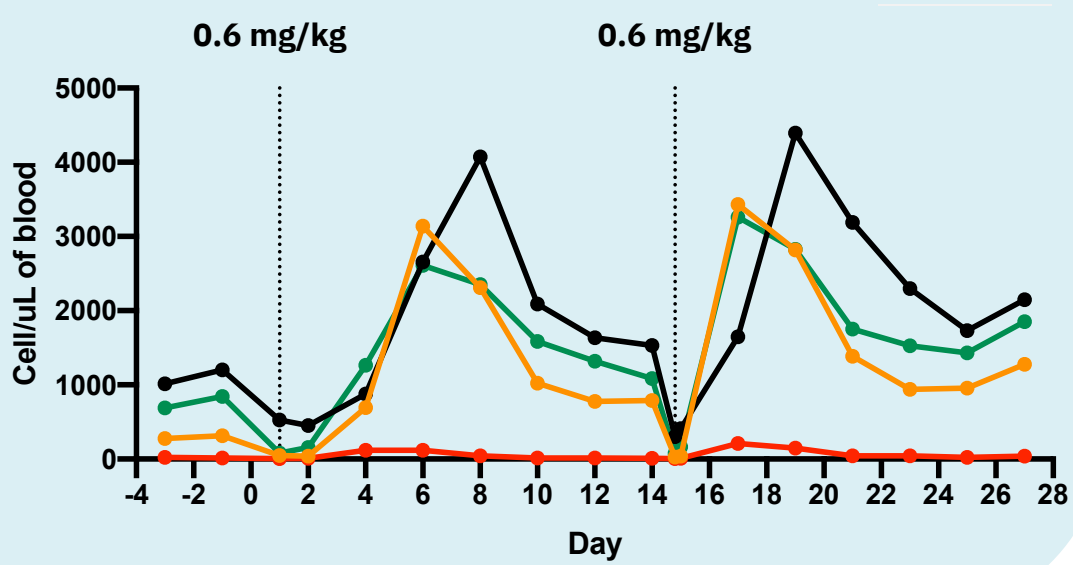
Proliferation & Expansion of Immune Cells but Not Tregs

MDNA11 induced up to 10-fold expansion in cancer-fighting immune cells (CD4+ T, CD8+ T, and NK Cells) in non-human primate study without: (a) Treg expansion, (b) generating anti-drug antibodies, (c) causing hypotension associated with vascular leak syndrome, (d) cytokine storms, or (e) other undesirable immune mediated side effects.

Percent Ki67⁺ Cell Fold Change



Immune Cell Counts



Tregs CD4⁺ T Cell CD8⁺ T Cell NK Cell

MDNA209

An IL-2/IL-15 Super-Antagonist

Repurposed MDNA109

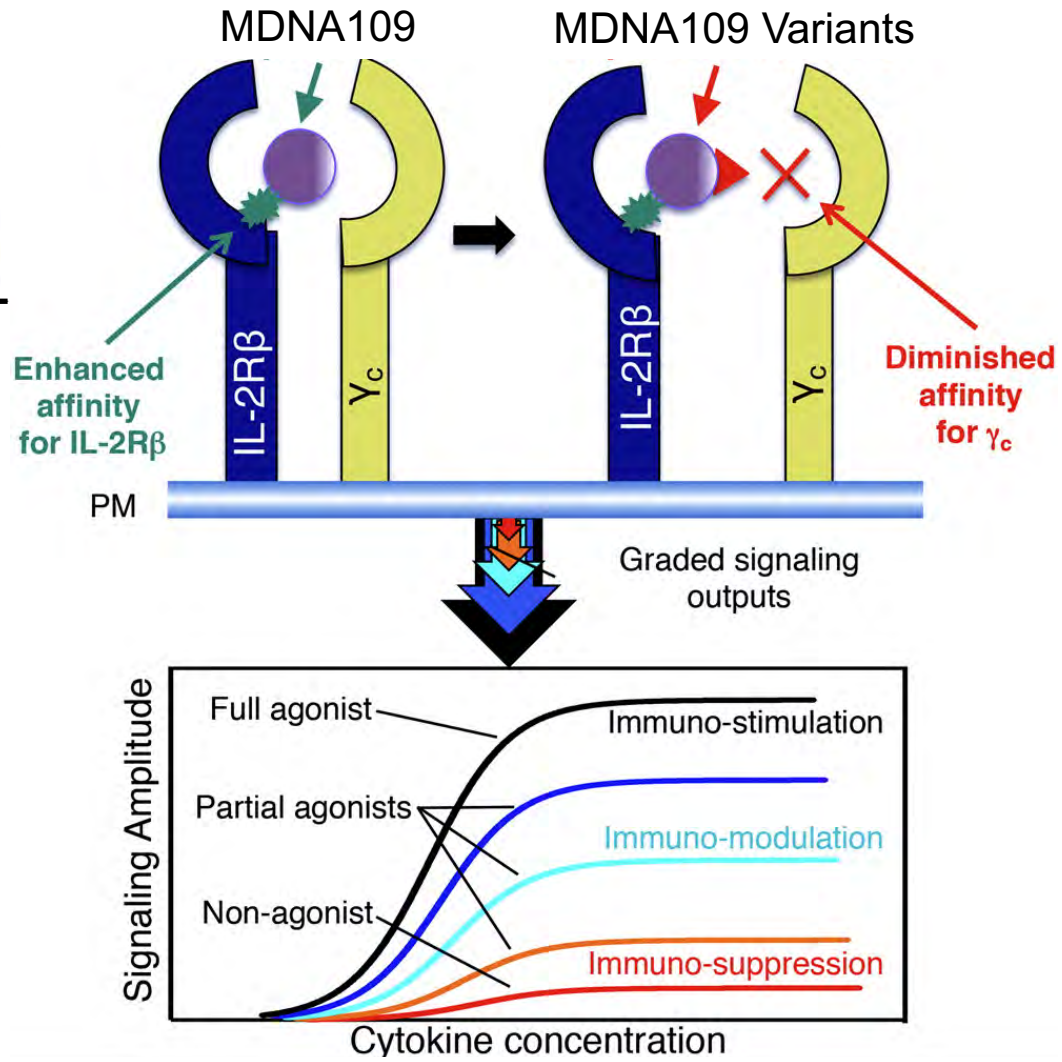
IL-2 Agonist with Graded Signaling Amplitude

Cell PRESS **Immunity**

Interleukin-2 Activity Can Be Fine Tuned with Engineered Receptor Signaling Clamps

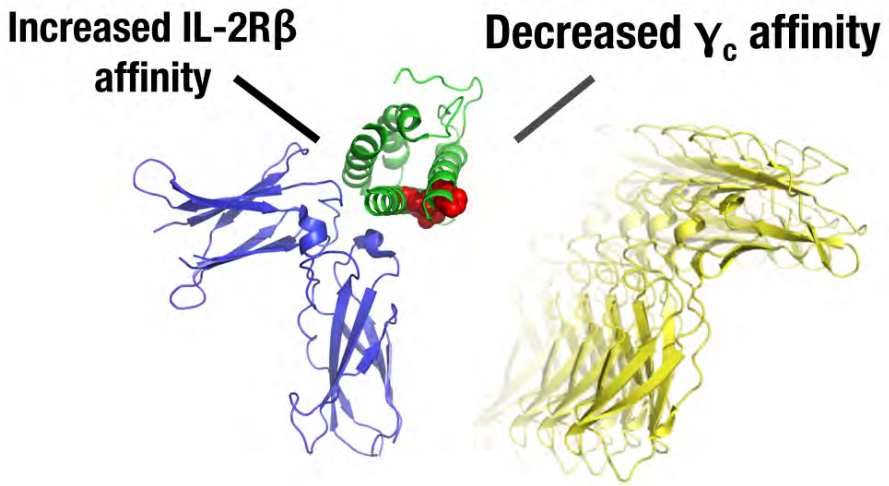
- Partial IL-2 agonists with enhanced binding to IL-2Rβ (CD122) but attenuated γ_c (CD132) interaction.
- Yields a spectrum of altered signaling amplitudes and biologic effects.

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



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

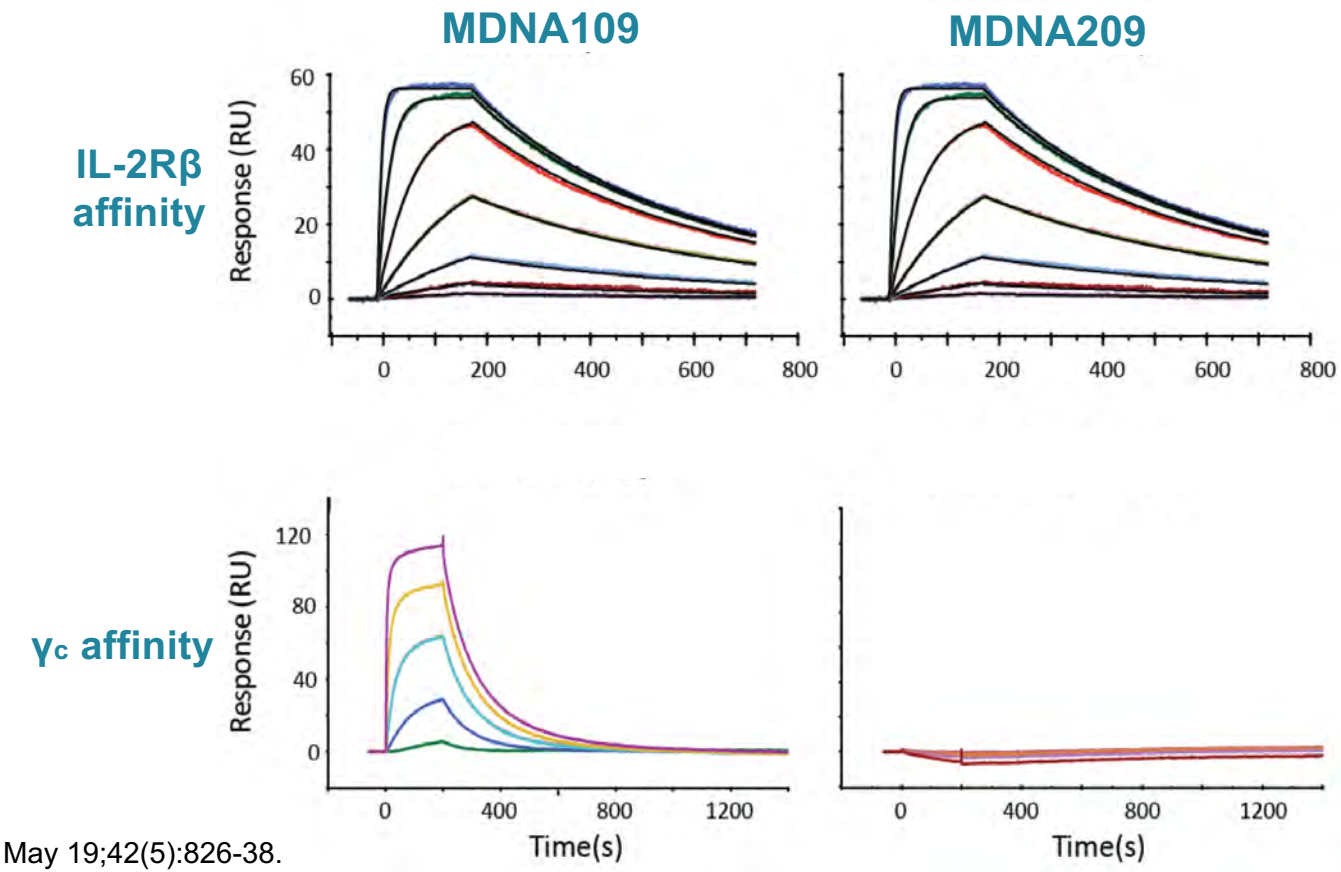
MDNA209 Design: Based on the MDNA109 scaffold



IL-2R Signalling blockade

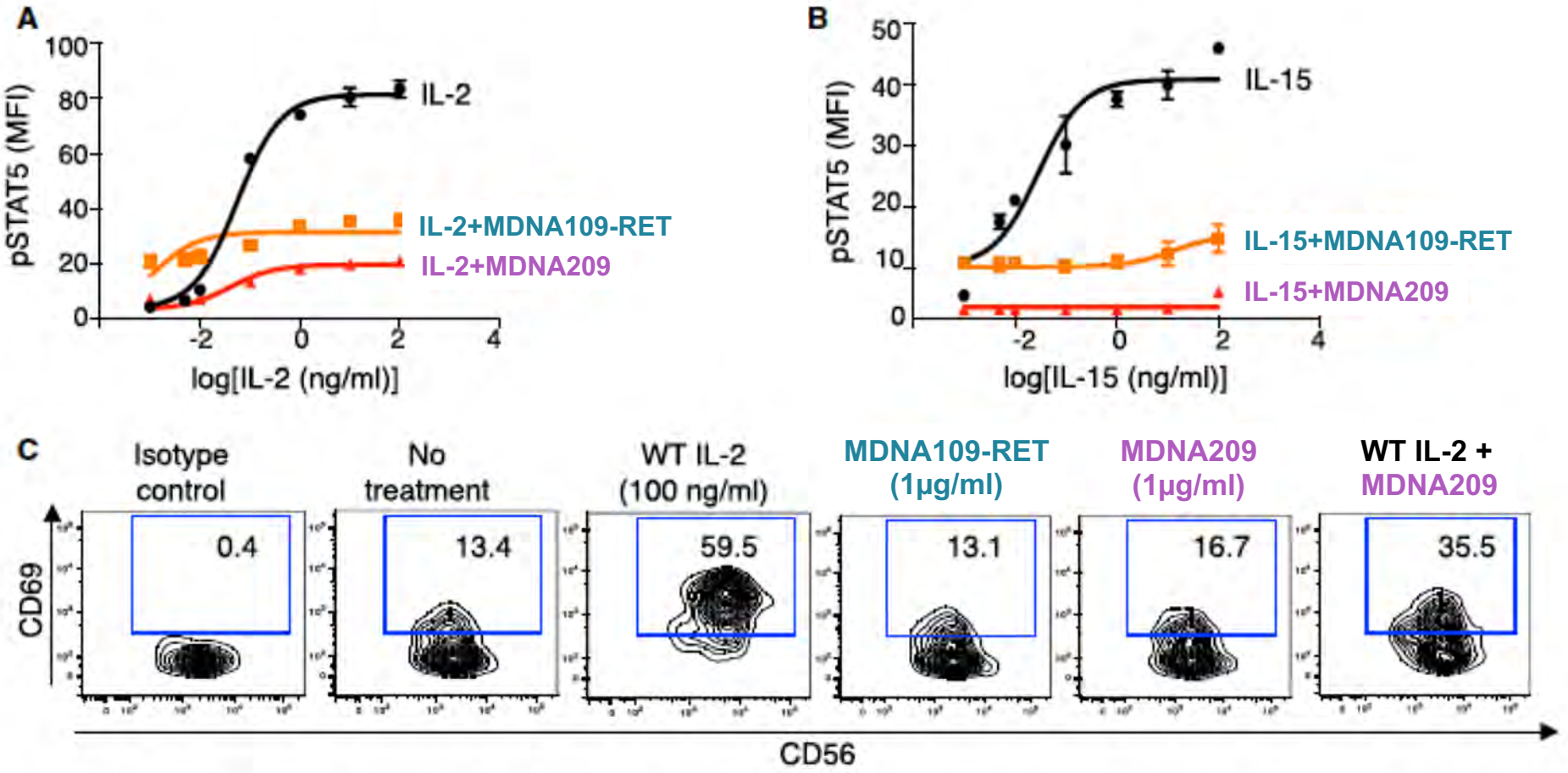
Mitra S, *et al.*, Immunity. 2015 May 19;42(5):826-38

MDNA209 Receptor binding properties: High affinity for IL-2Rβ but no binding to γc



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

MDNA209 Potently Inhibits IL-2 and IL-15 Signaling



Figures A and B: Pre-activated human CD8+ T cells incubated with IL-2 or IL-15 in the absence or presence of 1 µg/ml of MDNA109-RET or MDNA209

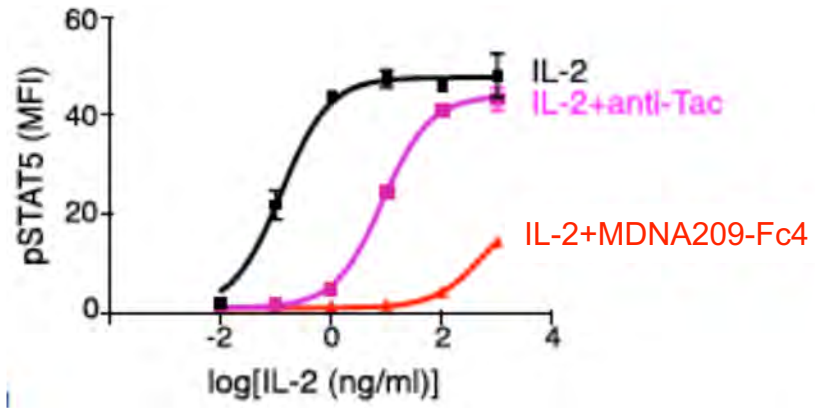
Figure C: MDNA209 blocks IL-2-induced NK cell activation and cytotoxicity

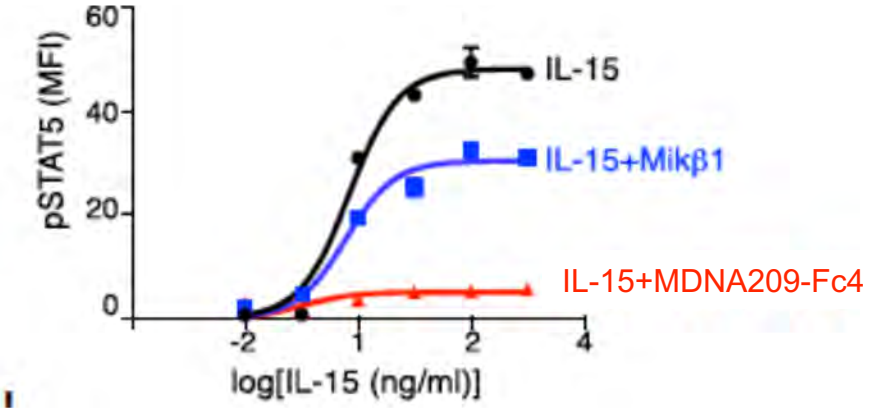
Mitra S, *et al.*, Immunity. 2015 May 19;42(5):826-38

MDNA209-Fc4: Long Acting MDNA209

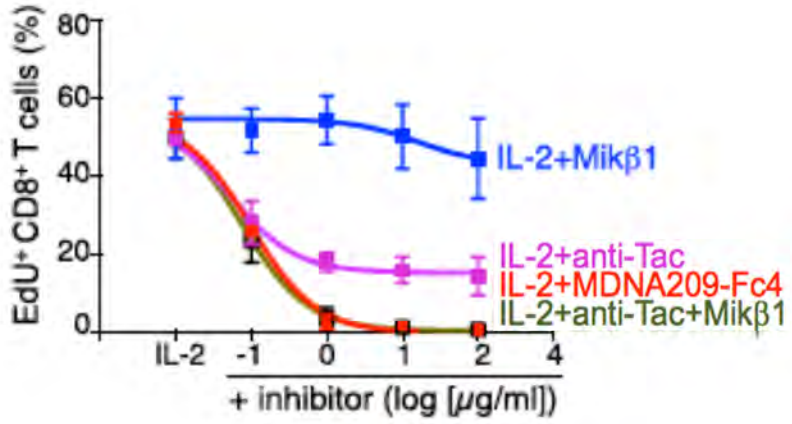
MDNA209 Fused to Fc Domain of hIgG4 Demonstrates Superior Activity on Human CD8⁺ T Cells

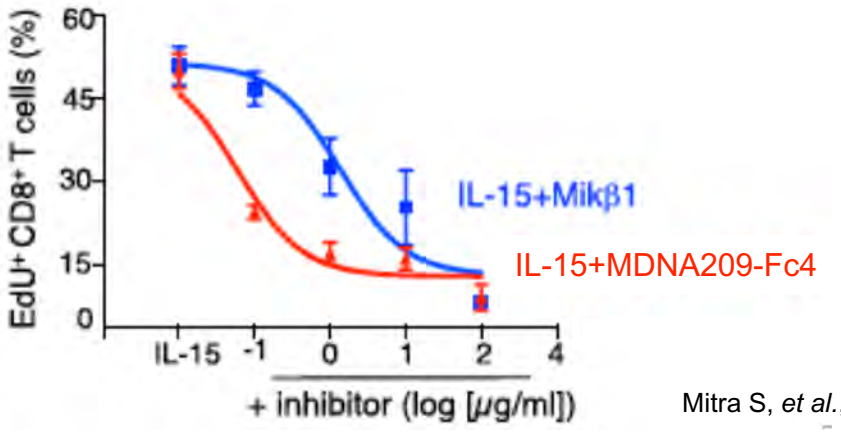
MDNA209-Fc4 more potently blocks IL-2-induced and IL-15-induced signaling than anti-Tac (anti-CD25) or Mikb1 (anti-CD122) mAbs





MDNA209-Fc4 more potently inhibits IL-2-induced or IL-15-induced proliferation than anti-CD25 or anti-CD122 mAbs

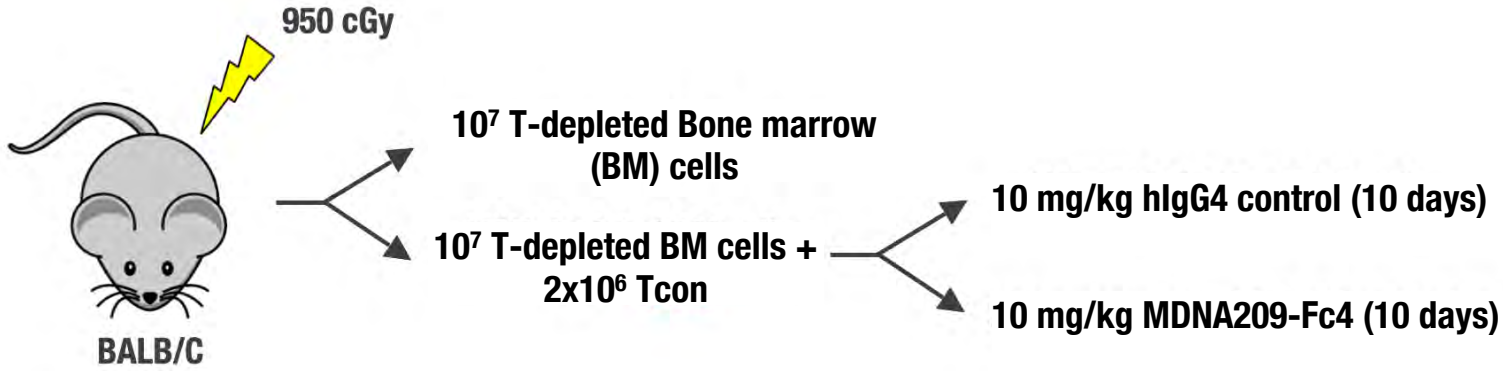


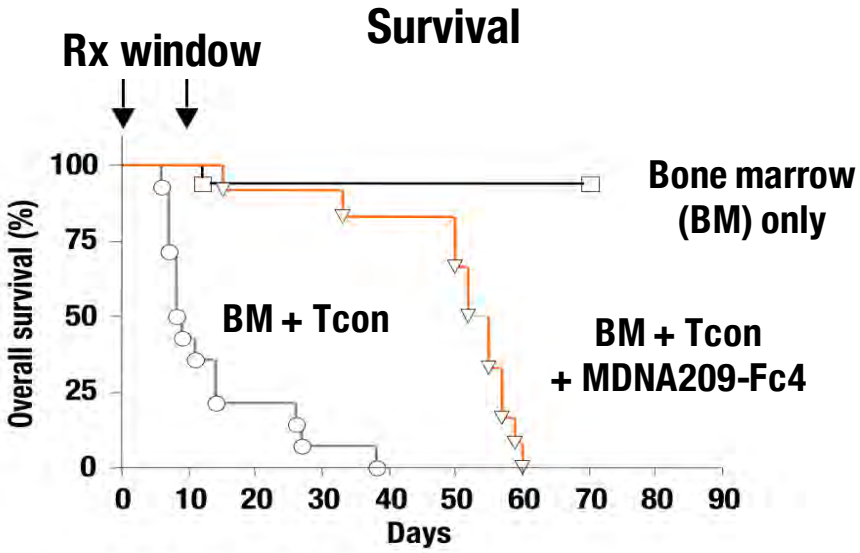


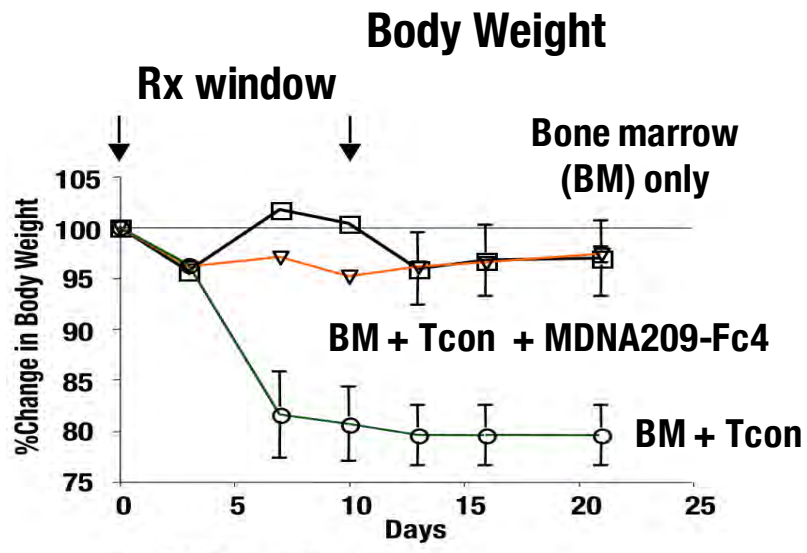
Mitra S, *et al.*, Immunity. 2015 May 19;42(5):826-38

MDNA209-Fc4 is Efficacious in a Graft Versus Host Disease Model

Short Duration of Treatment Has Long-Lasting Therapeutic Effect





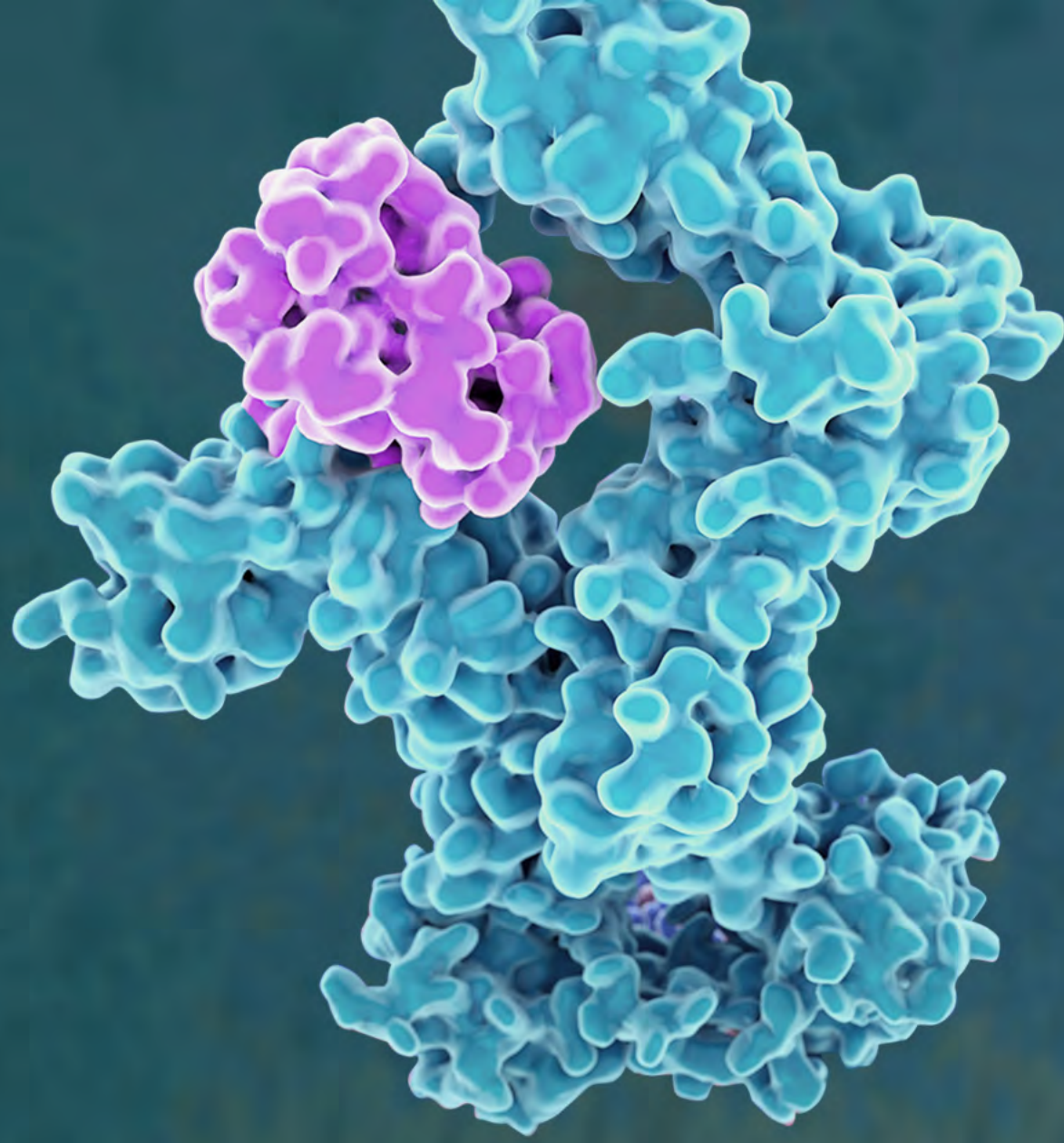


- 10 day treatment with MDNA209-Fc4 provides >5-fold extension of median survival
- GVHD efficacy is key *in vivo* POC of MDNA209-Fc4

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

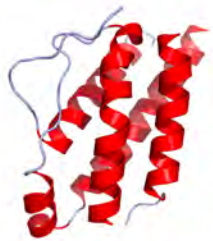
Superkines Targeted with Antibodies: STAb Cancer™

A next-generation tumor-targeting IL-2 preferentially promotes tumor-infiltrating CD8+ T-cell response and effective tumor control



Sun et al., Nat Commun. 2019 Aug28;10(1):3874.

MDNA109 Platform Fusions Used By Sun et al. (Nat Comm., 2019)

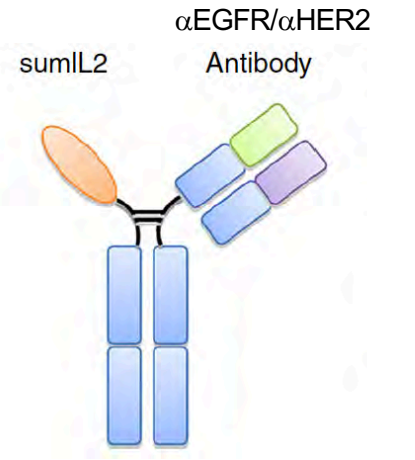


IL-2

5 additional mutations

Sun et. al., Nat Comm, 2019

sumIL-2 (MDNA109FA)

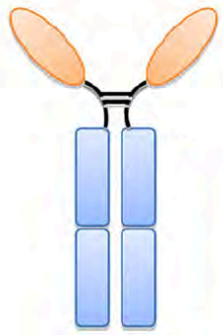


Erb/HER2-sumIL2
aka Erb/HER2-MDNA109FA

MDNA109

+FEAA

Medicenna Therapeutics

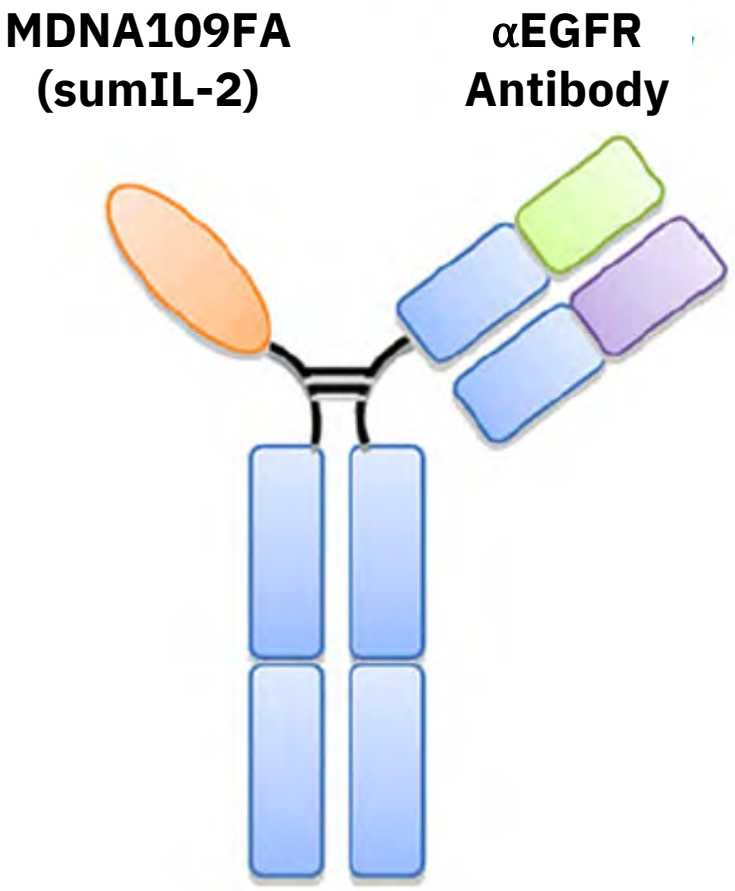


MDNA19
(MDNA109FEAA-Fc)

NOTE: sumIL2 = MDNA109-FA

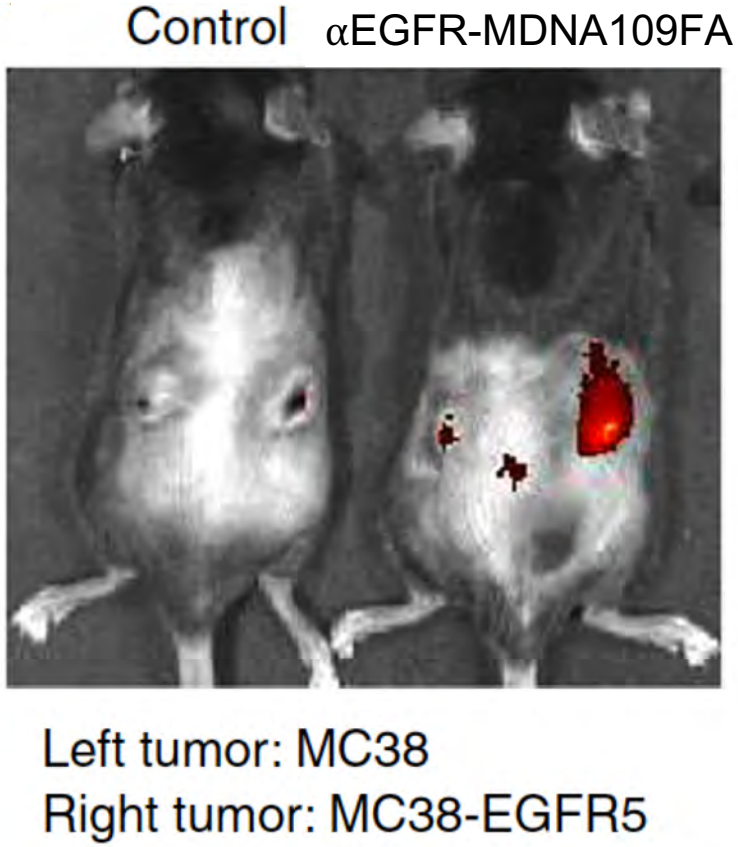
IL-2 Superkine Targeted With Antibody (STAb™)

Tumor Accumulation Enhances Therapeutic & Memory Response



Sun et al., Nature Communications 2019

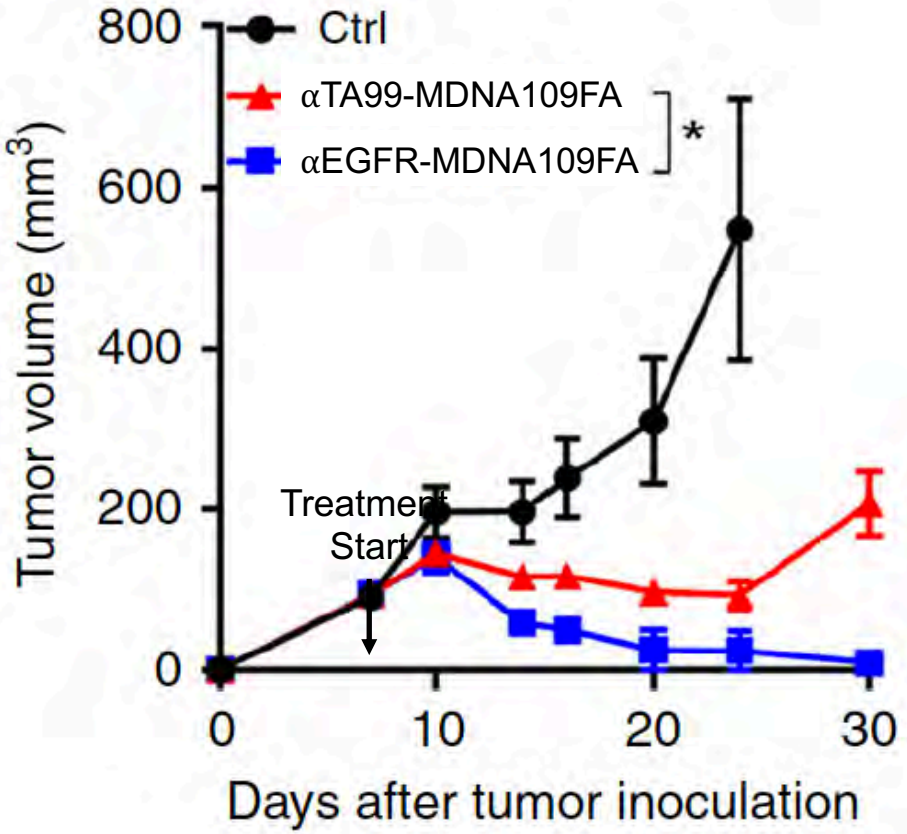
Increased accumulation in EGFR-overexpressing Tumors



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)

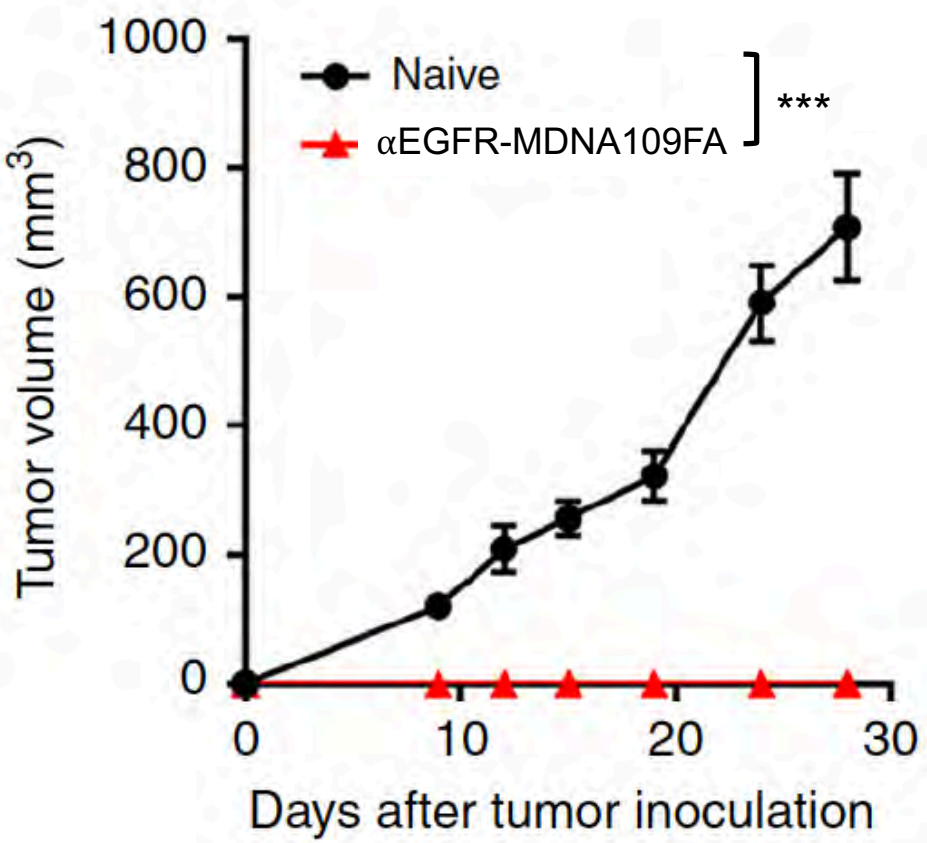
Accumulation at Tumor Site Enhances Therapeutic & Memory Response

MC38-EGFR5 Primary Treatment



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.

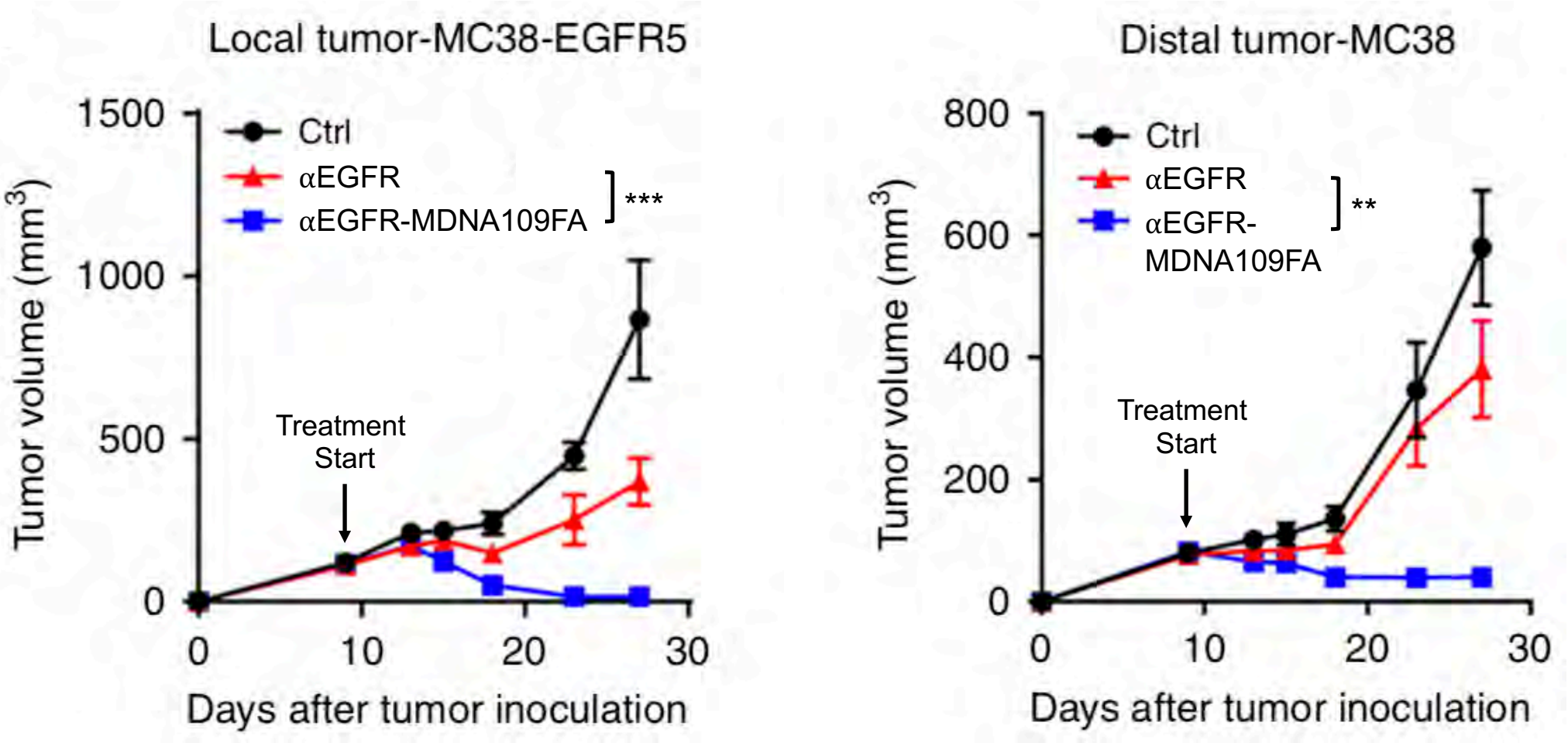
MC38-EGFR5 Re-challenge



C57BL/6 mice or mice with tumor clearance by αEGFR-MDNA109FA (n = 5/group) were rechallenged 3 months later with 3 × 10^6 of MC38-EGFR5 (SQ), and the growth of the tumor was measured and compared twice a week

Sun et al., Nature Communications 2019

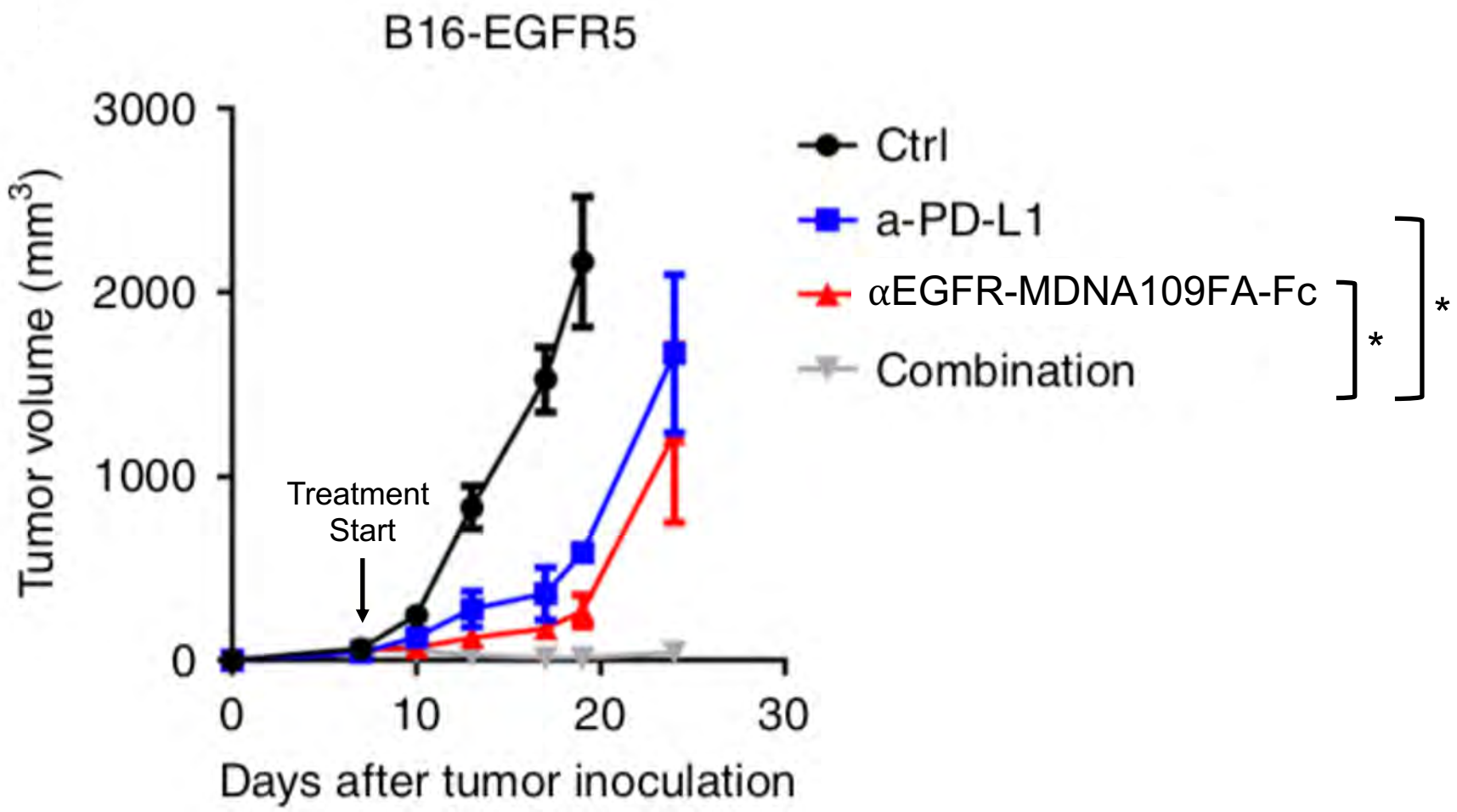
STAb™ Activated Cytotoxic T Lymphocytes Can Control Distal Tumors



C57BL/6 mice (n = 5 group) were injected SQ with 5 × 10^5 MC38 (left flank) and MC38-EGFR5 (right flank) cells. MC38-EGFR5 tumor was intratumorally treated with 10 μg Cetuximab (αEGFR) or 10 μg αEGFR-MDNA109FA on days 9, 12, and 15. The volume of both tumors was measured twice a week. **P < 0.01, ***P < 0.001

Sun et al., Nature Communications 2019

STAb™ Therapy Overcomes Checkpoint Blockade Resistance



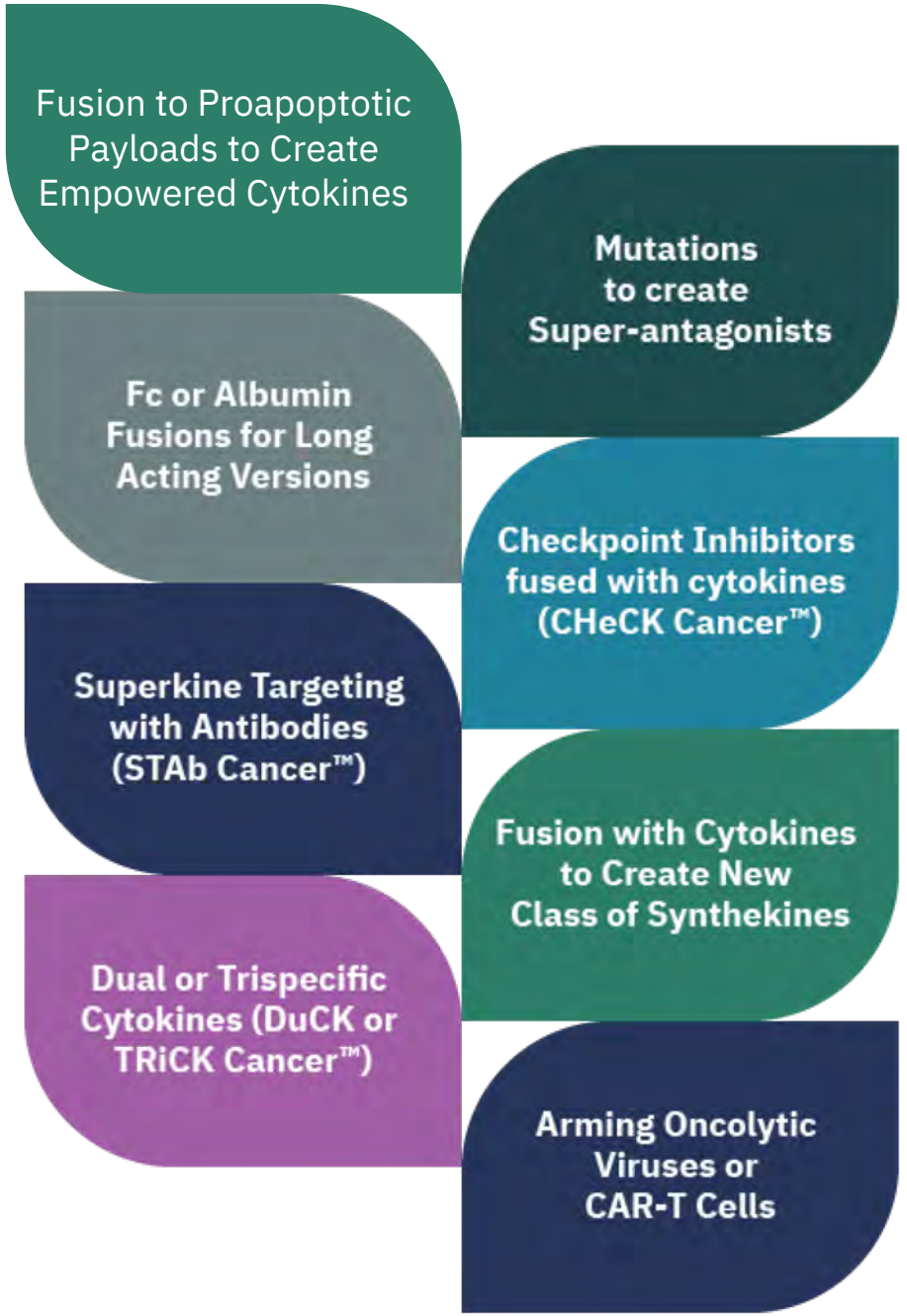
C57BL/6 mice (n = 5/group) were injected SQ with 5 × 10^5 of B16F10-EGFR5 cells and IP treated with 25 µg of αEGFR-MDNA109FA-Fc or/and intratumorally treated with 50 µg of anti-PD-L1 on days 8, 11, and 14. *P < 0.05

Sun et al., Nature Communications 2019

Designer Superkines

Ease of Pipeline Expansion

- **Relies on Simple and Reliable Manufacturing Platform**
- **Rapid In Vitro Screening of Large Libraries**
- **Allows Bespoke Therapeutic Design**



Thank you

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