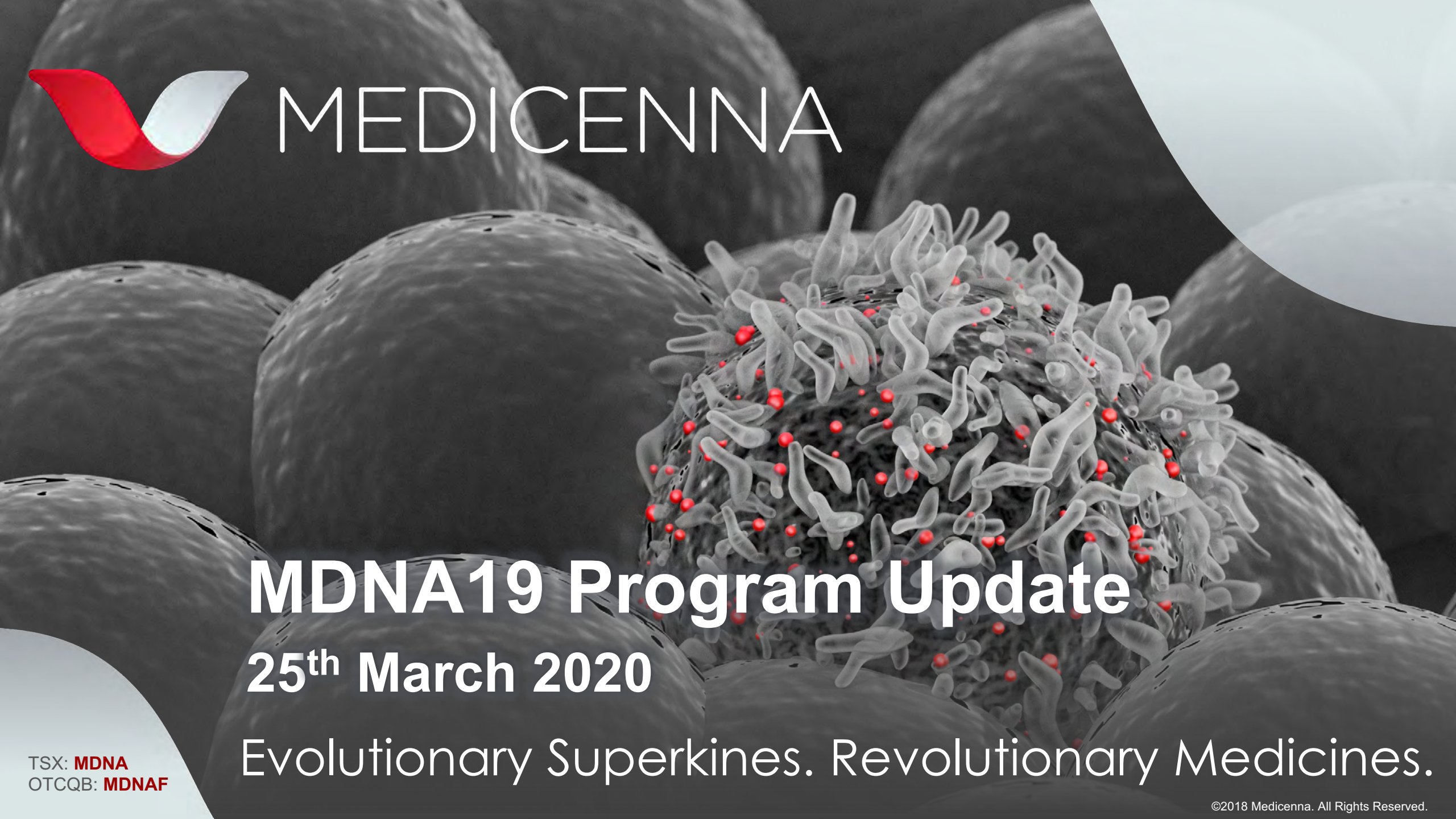


MDNA19 Program Update

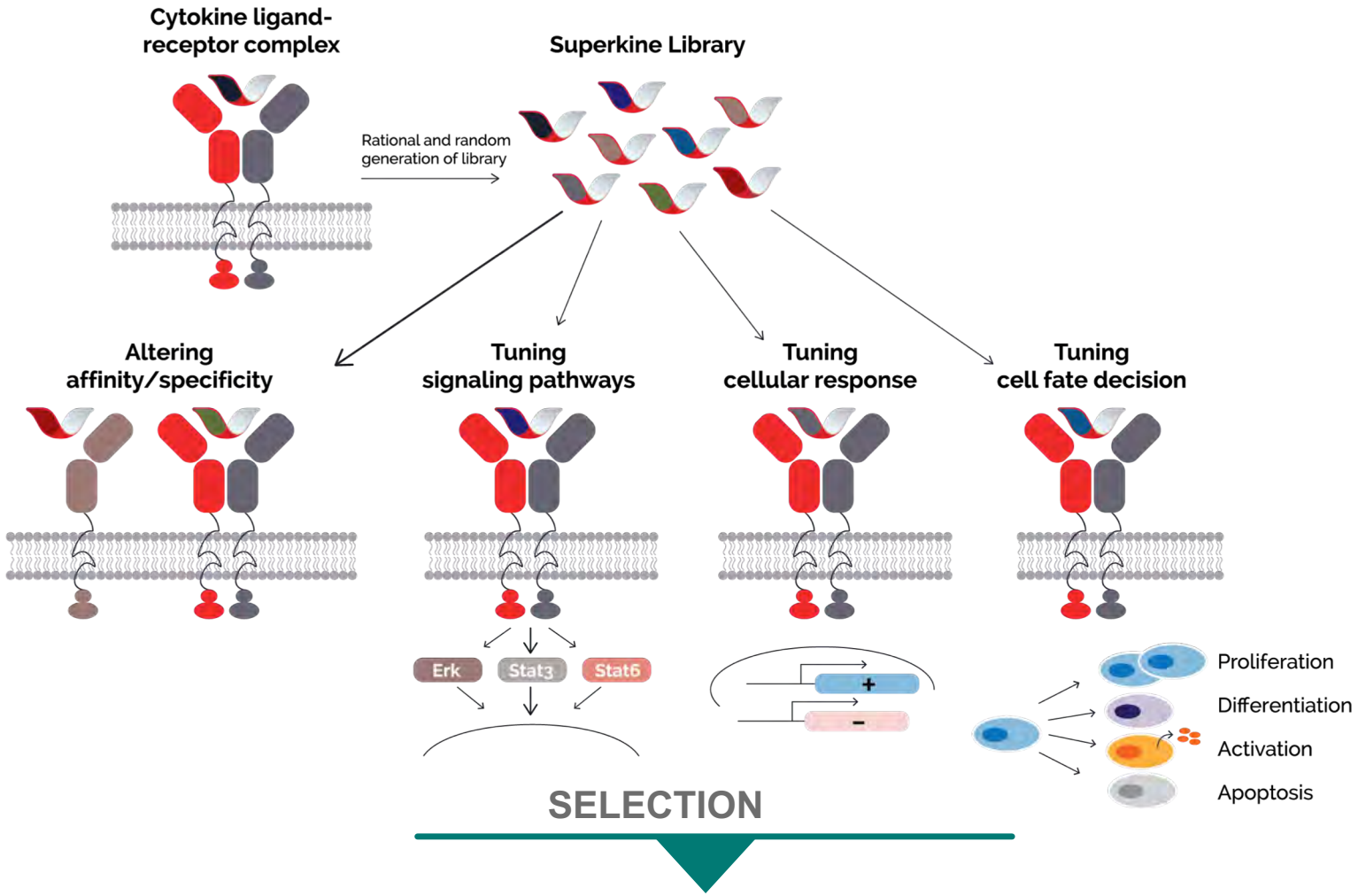
25th March 2020

Evolutionary Superkines. Revolutionary Medicines.

TSX: **MDNA**
OTCQB: **MDNAF**

DIRECTED EVOLUTION + YEAST DISPLAY = TUNABLE SUPERKINES

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



Super-agonist or super-antagonist

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Introduction to the MDNA109 Platform

Super Agonist for Cancer Immunotherapy

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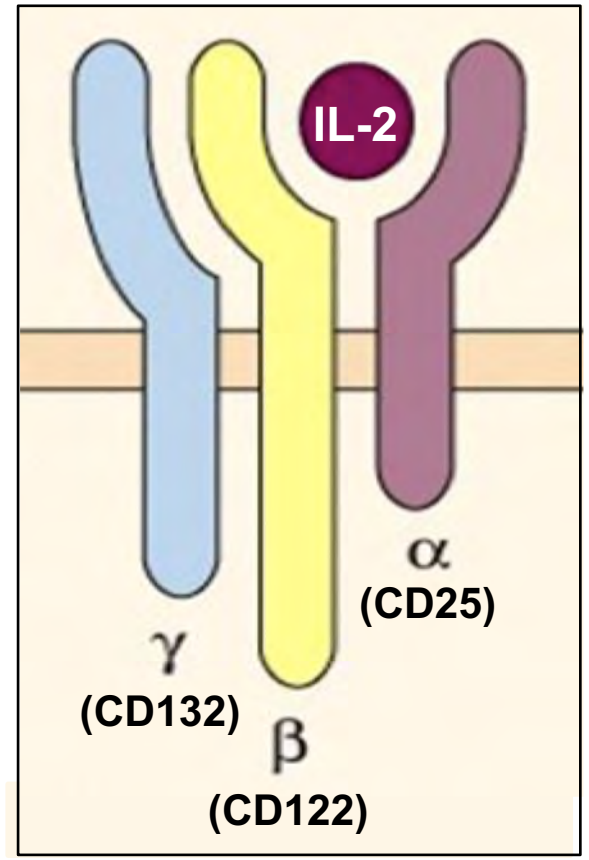
RATIONALE FOR AN IL-2 SUPERKINE AGONIST i.e., MDNA109

Proleukin (hIL-2): first targeted immunotherapy

High-affinity receptor



Has very high affinity for IL-2

- Proleukin preferentially stimulates the high-affinity receptor, causing:
  - Activation of $T_{regs,}$ which serves to abrogate anti-tumor responses due to its immuno-suppressive capacity
  - Extreme toxicity – hard to complete a full course of therapy; treatment is usually in Intensive Care Unit
- Requires three daily administration for 2 cycles[1]

[1]1 cycle = 14 doses max. administered q.8.h.

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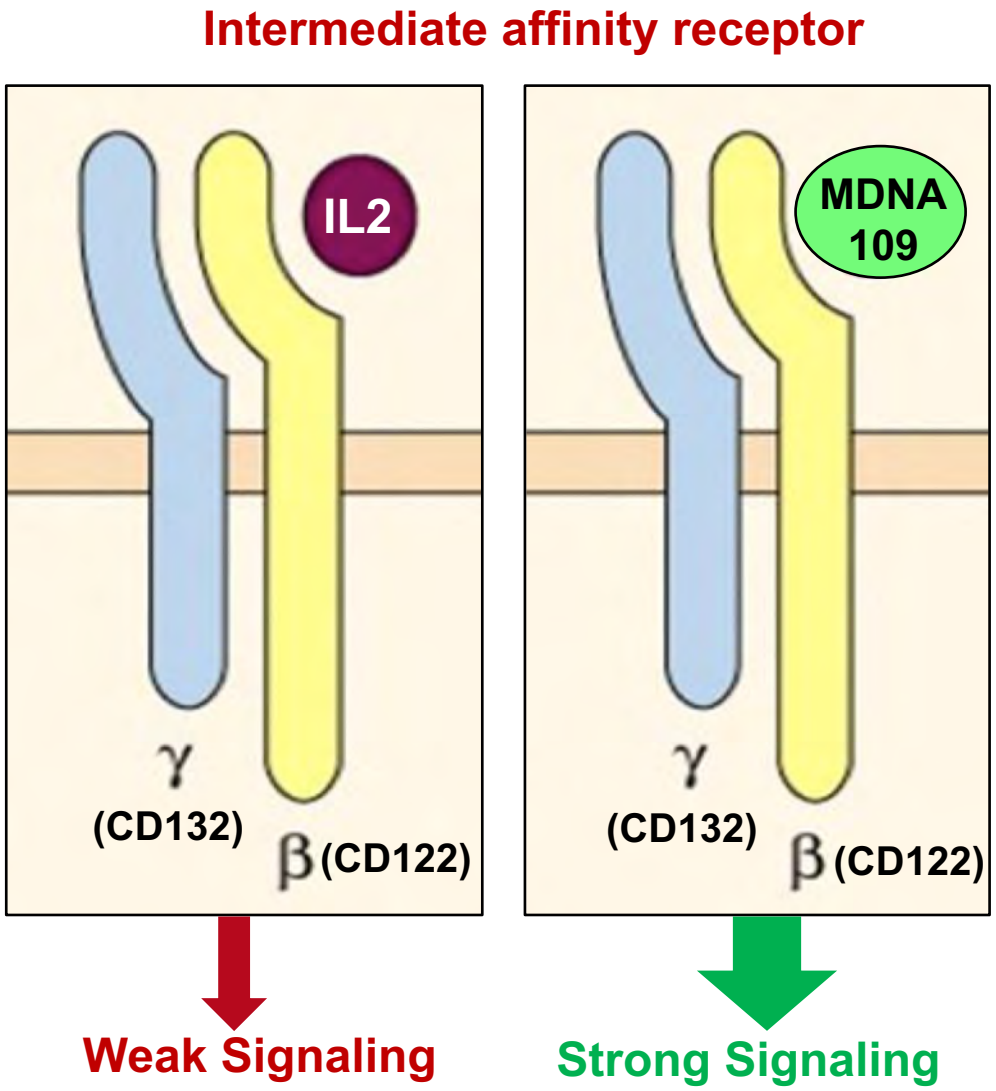
RATIONALE FOR AN IL-2 SUPERKINE AGONIST i.e., MDNA109 (contd.)

Stimulation of Intermediate Affinity Receptor Required for Anti-Tumor Effect



- In contrast to Proleukin, MDNA109 induces a strong signal via the intermediate affinity receptor, causing:
  - Preferential activation of effector T-cells that attack tumor cells (naïve T-cells, NK cells, and CD8 T-cells) mediating an anti-tumor effect
  - An increase in the therapeutic activity without the underlying toxicity

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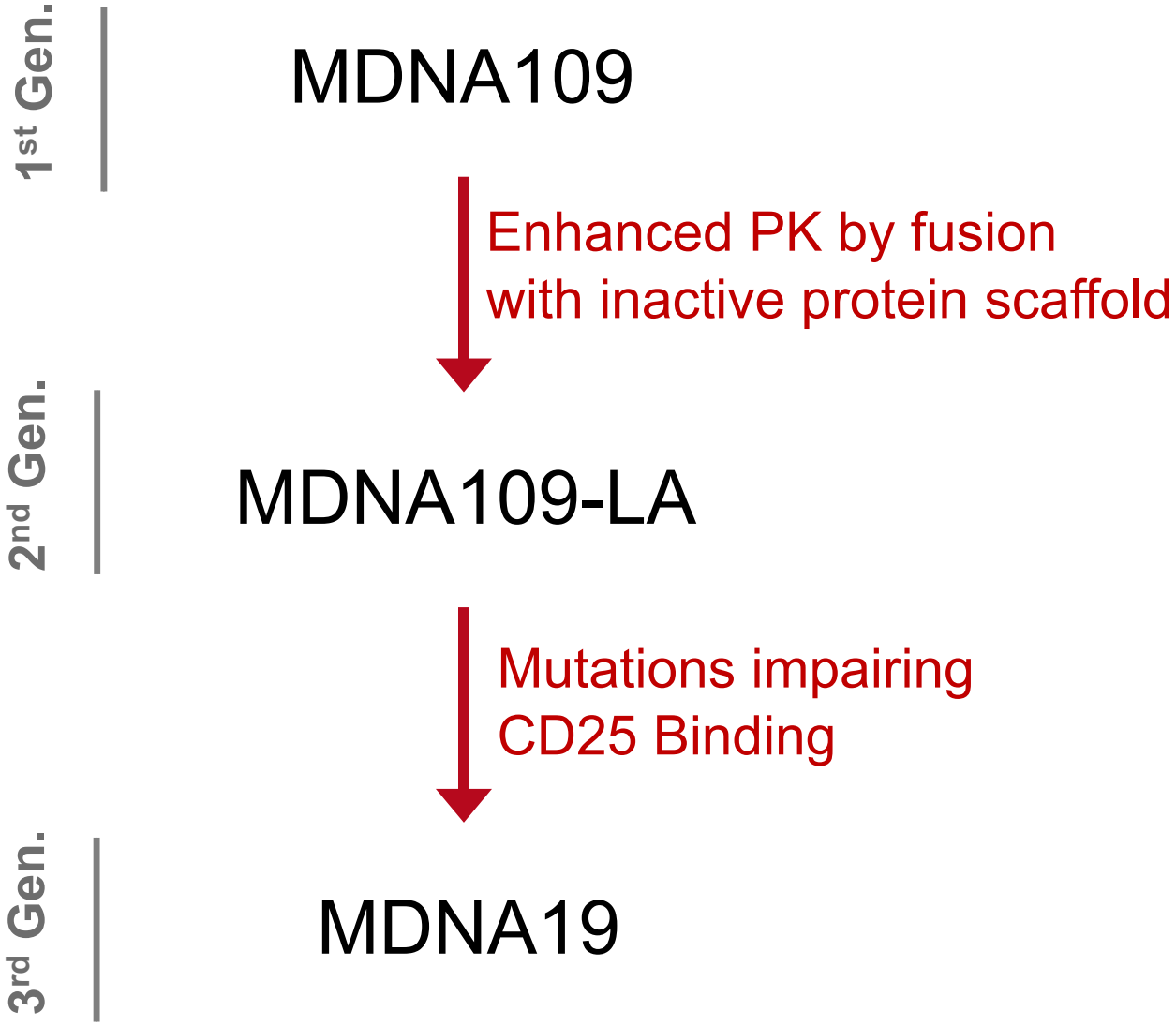
NEXT STEP: FURTHER ENGINEERING TO REDUCE CD25 BINDING TO IMPROVE RECEPTOR SELECTIVITY



LA = long acting

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IN SILICO ASSESSMENT SHOWING LOW IMMUNOGENICITY RISK OF MDNA109 CONSTRUCTS

Construct	DRB1 Score
Proleukin	310
MDNA109 (Addition of core mutations)	213
MDNA109-LA (Addition of core mutations + protein scaffold)	296
MDNA109 with CD25-binding mutations	473
MDNA19 (MDNA109-LA + CD25-binding mutations)	**555**
Human Therapeutic Antibodies	150-850
Humanized Therapeutic Antibodies	800-1300
Chimeric Therapeutic Antibodies	1300 > 2200
Chicken ovalbumin (positive control)	4404

- EpiScreen™ platform analysis indicated that MDNA19 shows low risk of immunogenicity; with DRB1 score below the range of human therapeutic antibodies.

Immunogenicity Assessment using the EpiScreen™ in silico T-cell epitope screening platform to predict whether peptides derived from a given protein of interest bind to the HLA class II histocompatibility antigen, DRB1 beta chain.

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BINDING AFFINITY OF VARIOUS IL-2-BASED COMPOUNDS TOWARDS IL-2 RECEPTOR SUBUNITS

	K_D [CD25 (IL-2Rα)]	K_D [CD122 (IL-2Rβ)]
IL-2	25 nM	586 nM
IL2-LA	26 nM	135 nM
NKTR-214 (1-PEG)[1]	190 nM	1770 nM
THOR-707[2]	No binding	> IL-2
Neo-2/15[3]	No binding	11.2 nM
MDNA109	52 nM	8 nM
MDNA109-LA	14 nM	2.7 nM
MDNA19	**No binding**	**2.1 nM**

1. Charych et al., PLOS ONE (2017)
2. Milla et al., SITC (2018)
3. Silva et al., Nature (2019)

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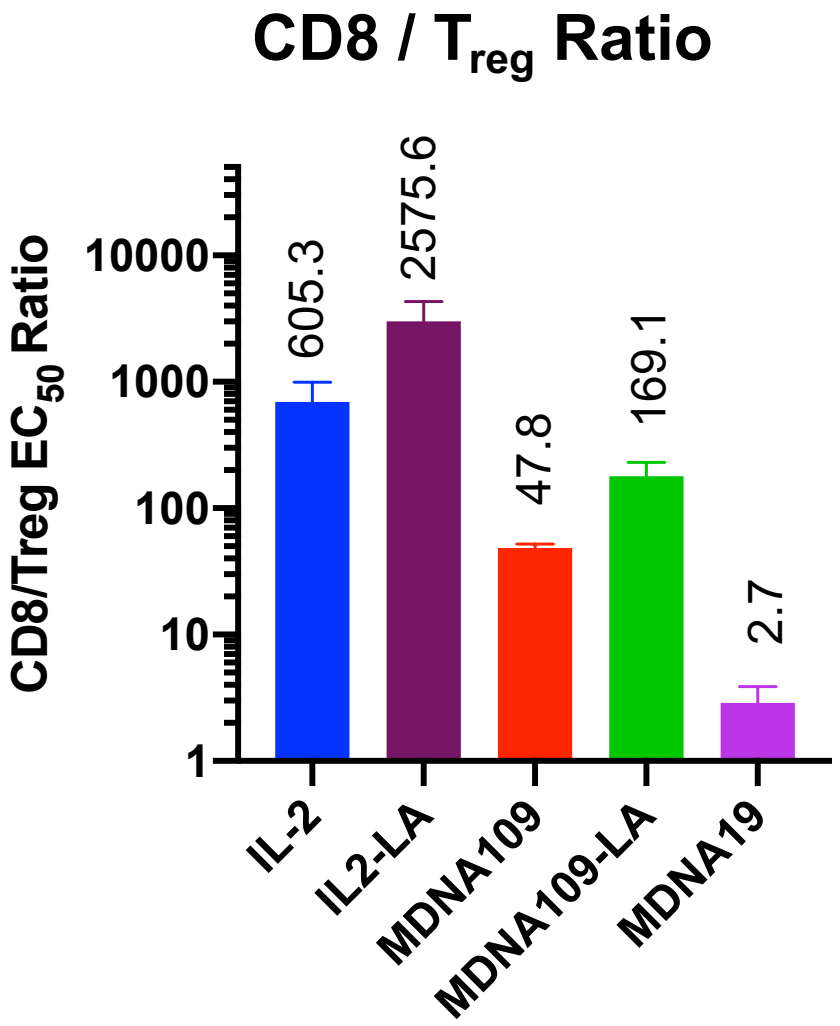
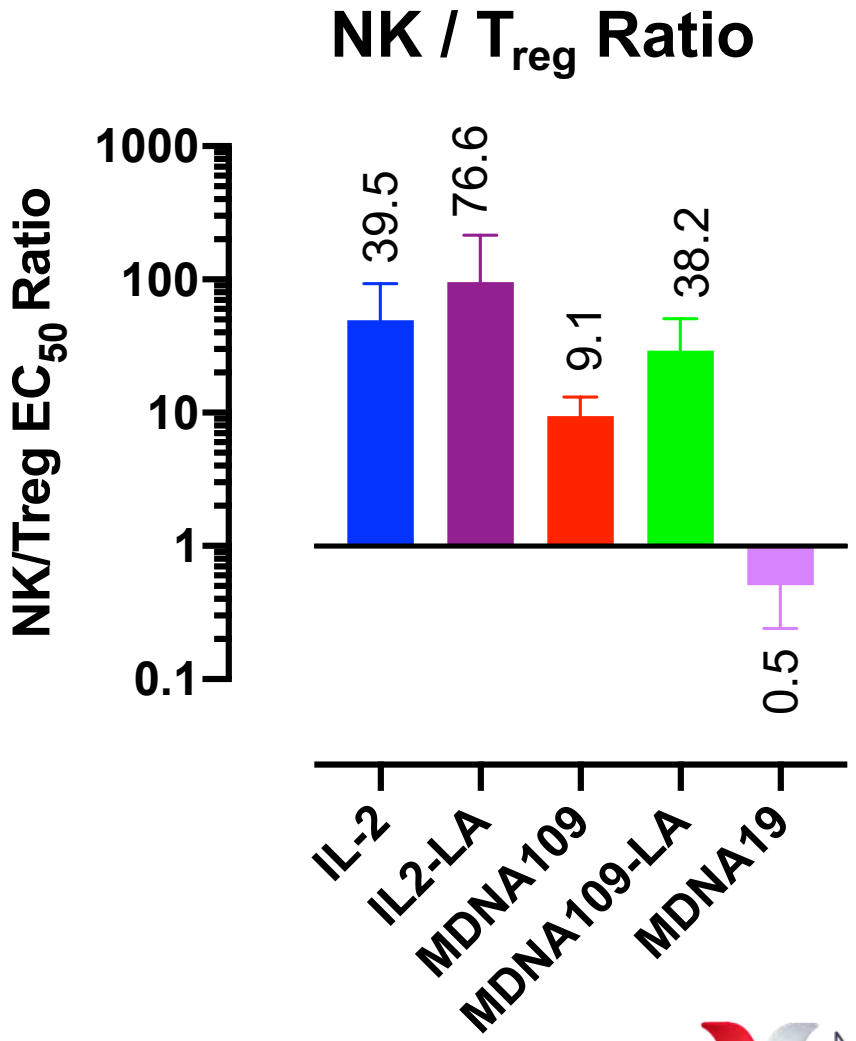
MDNA19 - SUPERIOR AT STIMULATING EFFECTOR AND NK CELLS IN HUMAN PBMC STUDY





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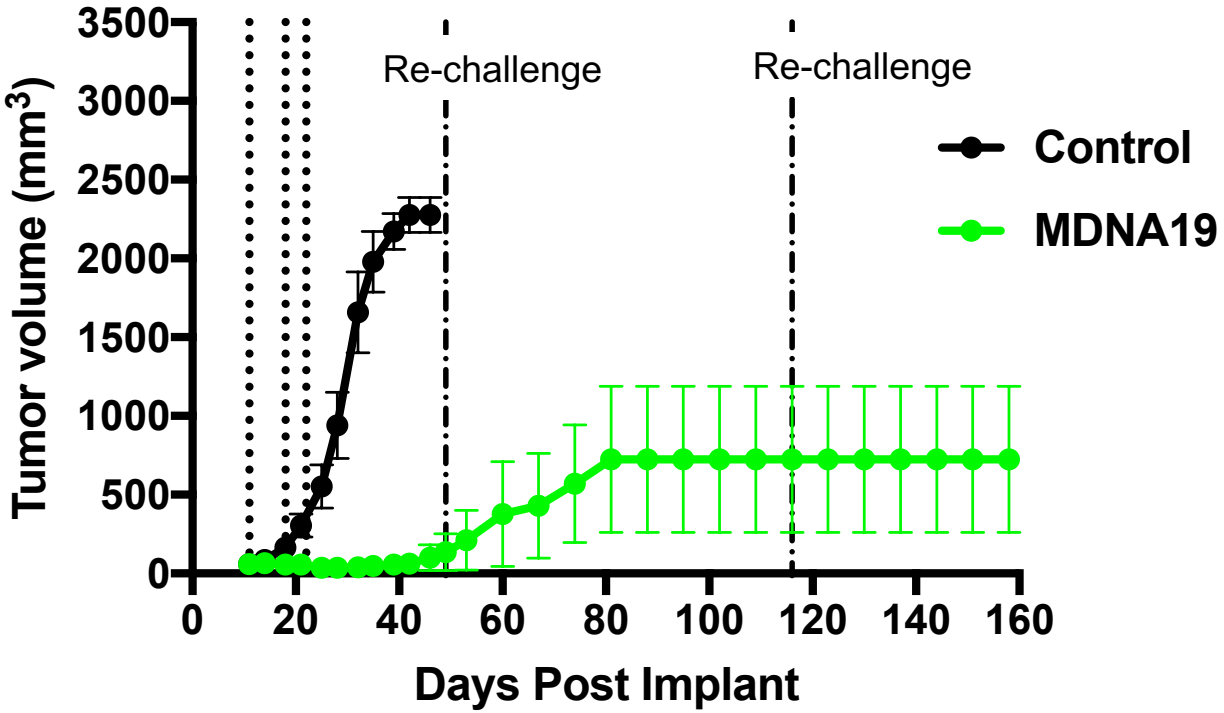
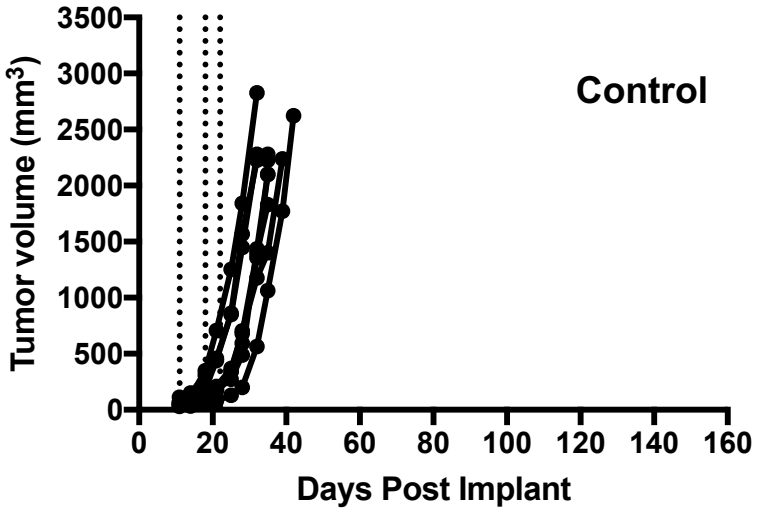
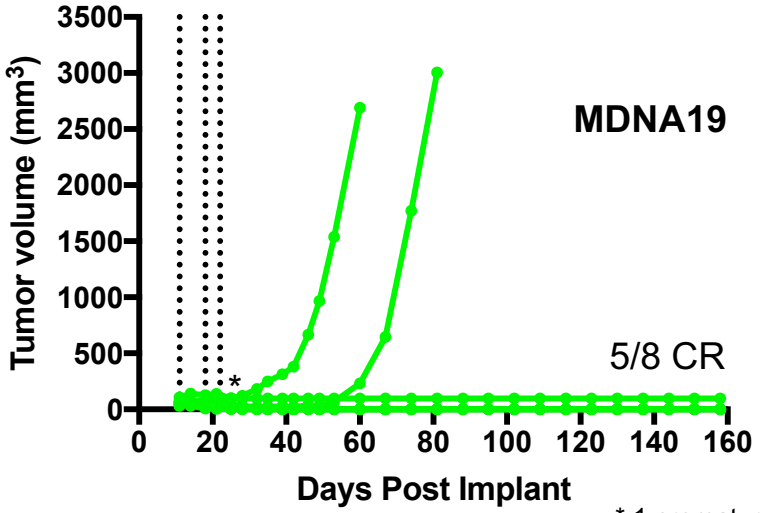
MDNA19 MONOTHERAPY POTENTLY INHIBITS TUMOR GROWTH IN CT26 MODEL







Female BALB/c mice were implanted with 2 x 10^6 CT26 cells subcutaneously in the right flank (study day 0) and allowed to grow for 11 days prior to the initiation of dosing.
Avg. tumor size in the treatment group at time of dosing: ~60 mm^3
MDNA19 (5 mg/kg, IP, Q.W x 2wks).

* 1 premature death

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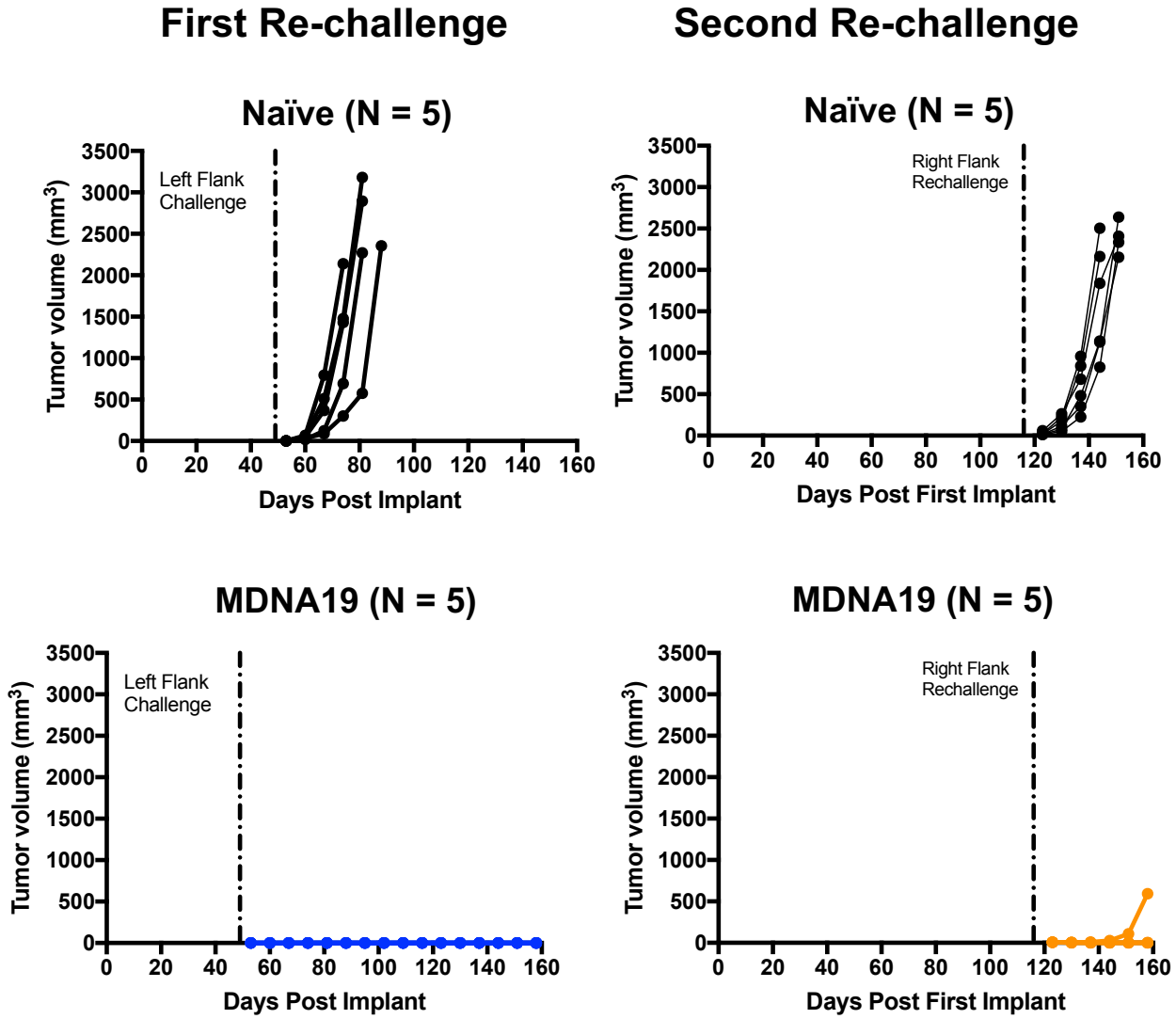
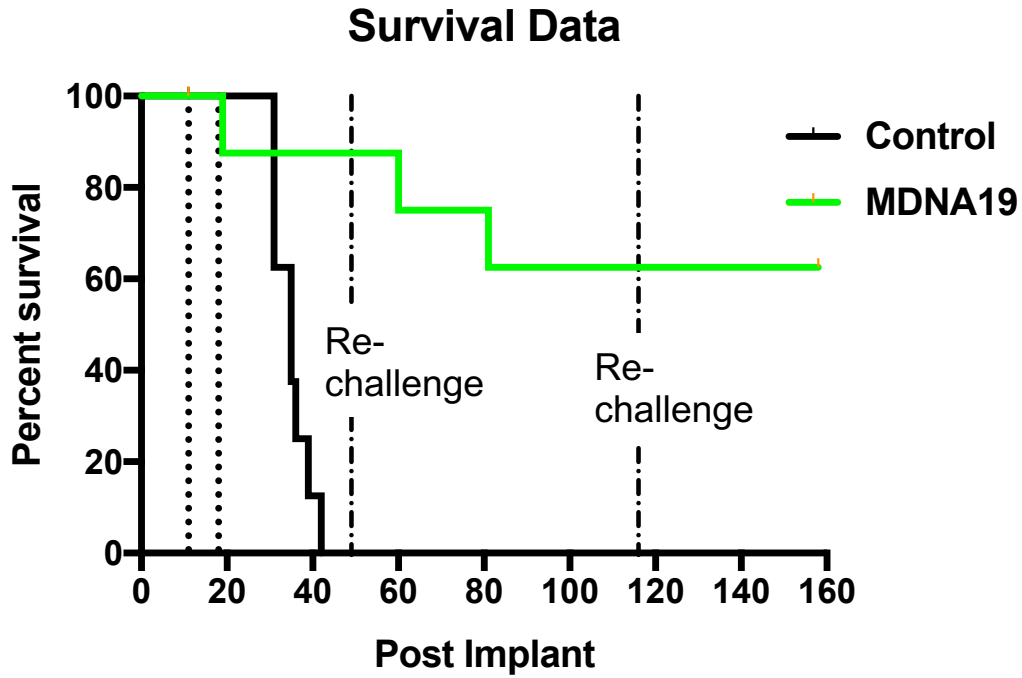
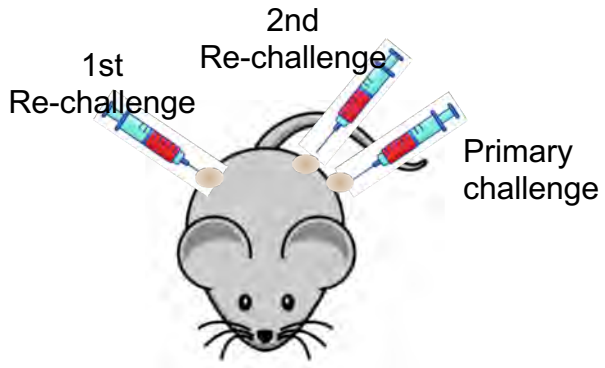
MDNA19 MONOTHERAPY INDUCEDS A MEMORY RESPONSE & SIGNIFICANTLY IMPROVES SURVIVAL IN CT26 TUMOR MODEL







Mice were implanted with 2 x 10^6 CT26 cells subcutaneously in re-challenge experiments

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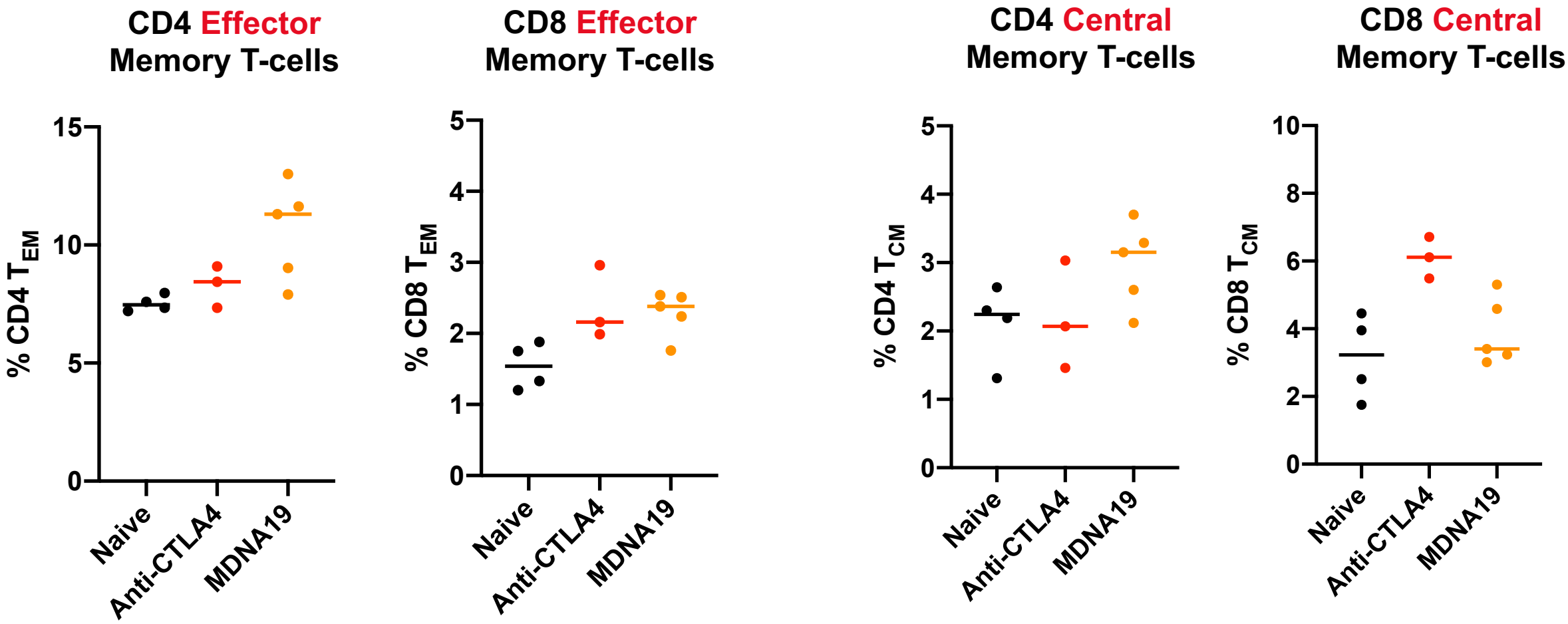
MDNA19 INCREASES MEMORY T-CELLS CORRELATING WITH RESISTANCE TO CT26 RE-CHALLENGE



Peripheral blood was isolated from MDNA19 treatment group to evaluate whether the mice developed effector memory T-cell responses

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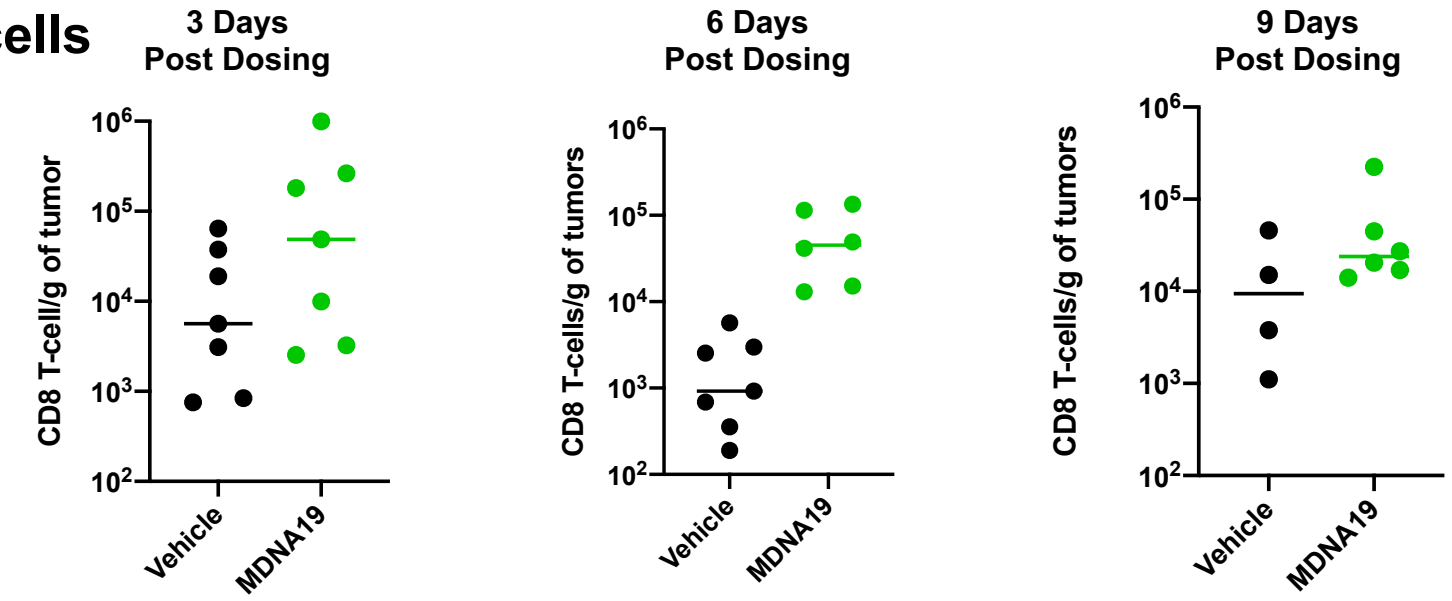
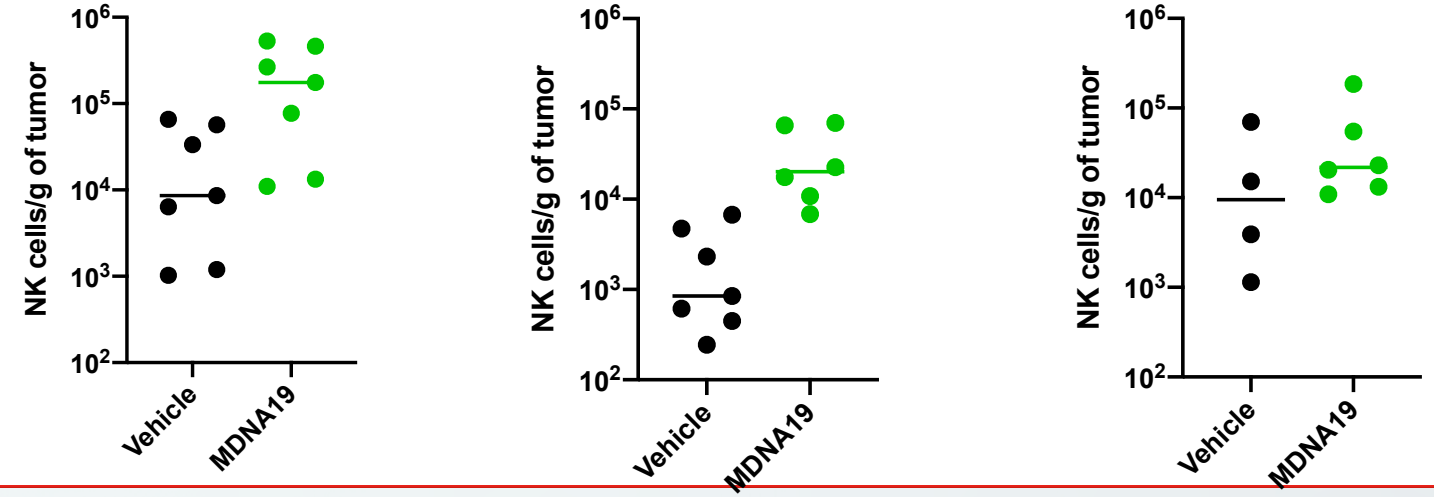
MDNA19 INDUCES TUMOR INFILTRATING CD8+ T & NK CELLS IN B16F10 MELANOMA MODEL

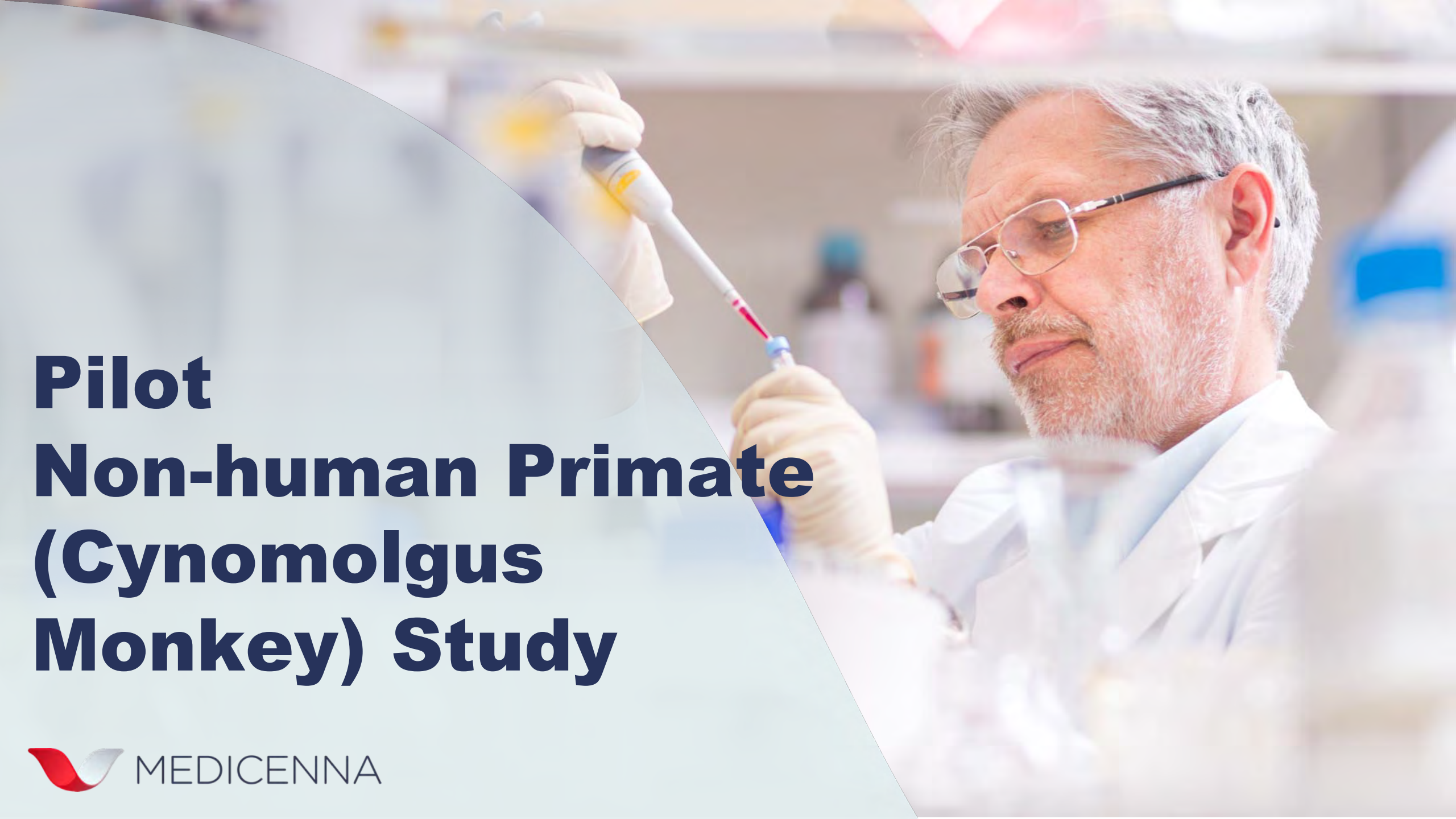
CD8+ T cells



NK cells



Pilot Non-human Primate (Cynomolgus Monkey) Study



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STUDY DESIGN TO EVALUATE SAFETY, PK AND PD PROFILE OF MDNA19

- Adult cynomolgus monkeys (age: 8-12 years) received 2 doses of MDNA19 by slow IV bolus 14-day apart and monitored for total of 28 days.
  - Dose: 0.01, 0.03, 0.1, 0.3, and 0.6 mg/kg
  - One male monkey per group
  - One monkey also received single dose of 0.3 mg/kg MDNA19 and total of 21 days monitoring

- Study measurements included (1) Clinical observations, (2) Clinical chemistry, (3) Hematology, (4) Immune-profiling with Ki67 analysis of peripheral blood, (5) organ weights and macroscopic pathology

- Sample collection also for (1) PK , (2) ADA and (3) cytokines/chemokines.

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Immune Parameter Assessment in Pilot NHP Study

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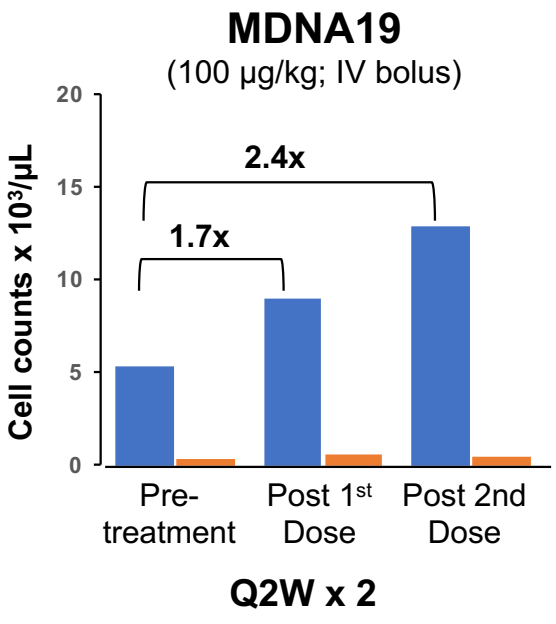
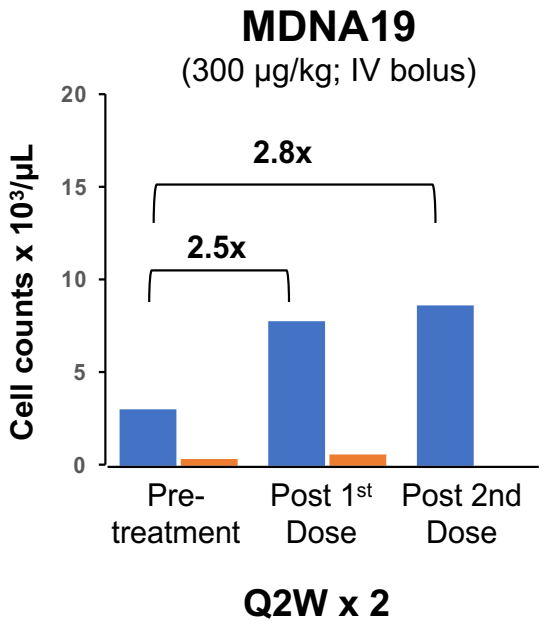
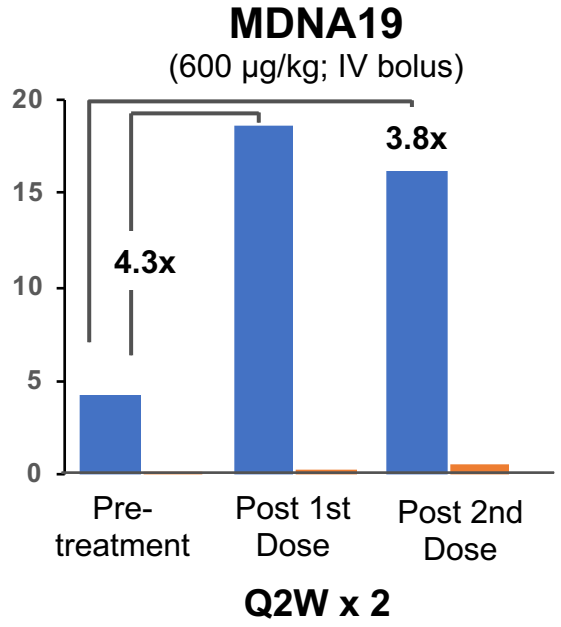
MDNA19 INDUCES EXPANSION OF LYMPHOCYTES, BUT NOT EOSINOPHILS

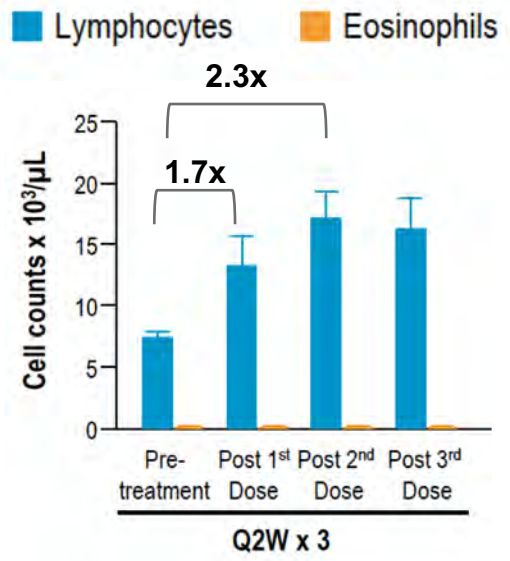
- Fold increase in lymphocytes compared to pre-treatment.
  - No expansion of eosinophils, responsible for VLS.







THOR-707
(100 mcg/kg)

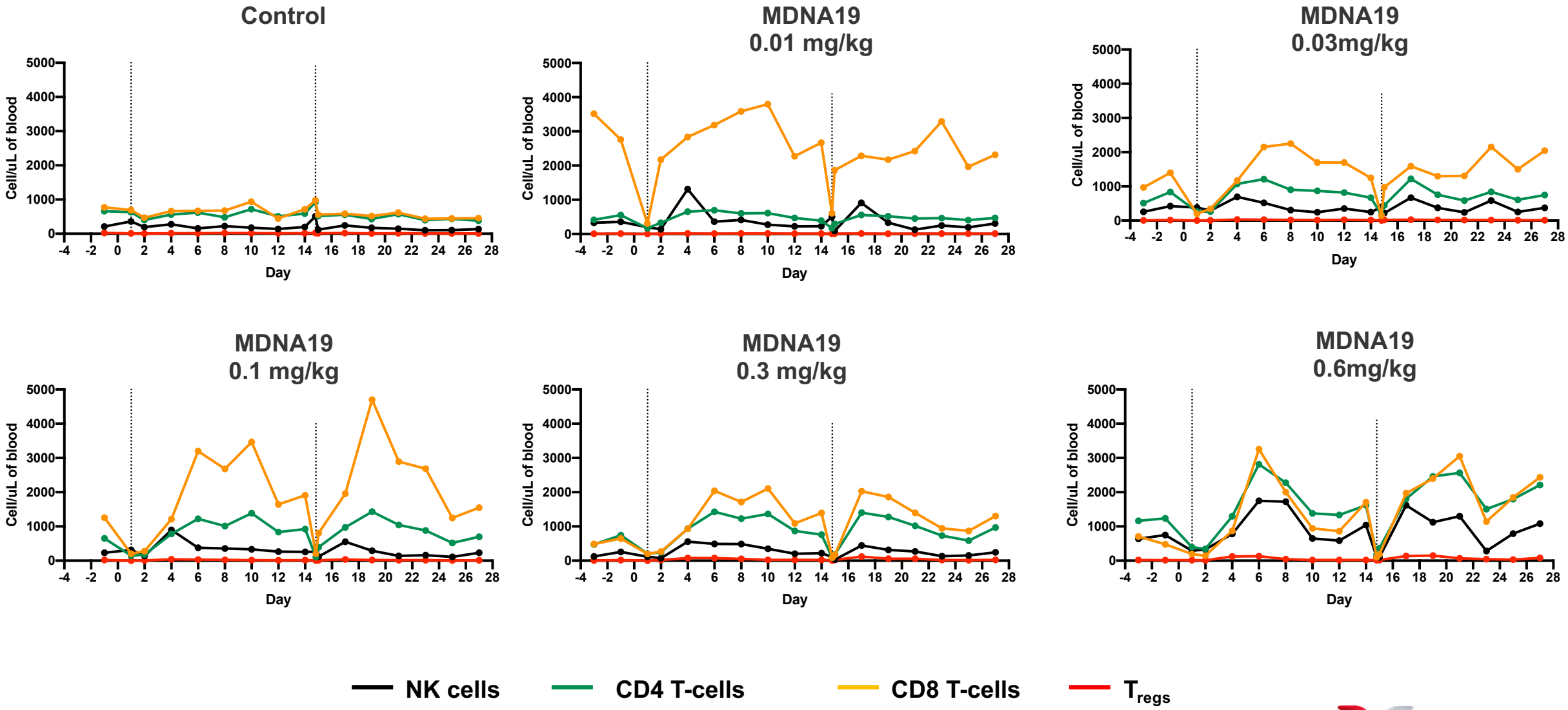


(Milla et al., ASCO 2019)

Lymphocytes
Eosinophils

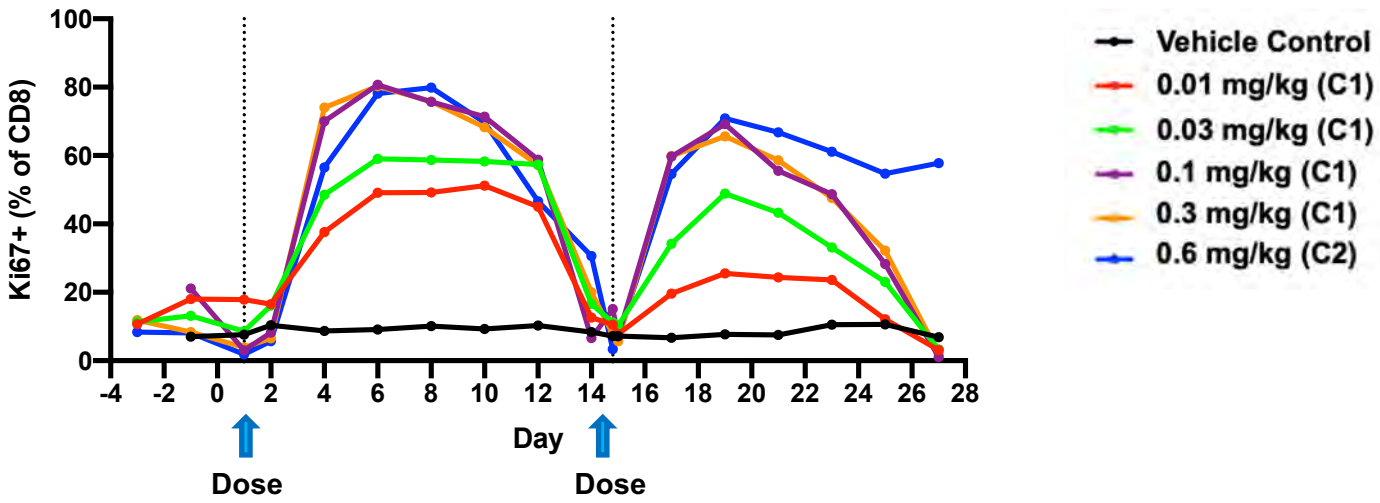
N = 1 per dose

MDNA19 INDUCES EXPANSION OF NK, CD4 & CD8 T-CELLS BUT NOT T_{REGS}

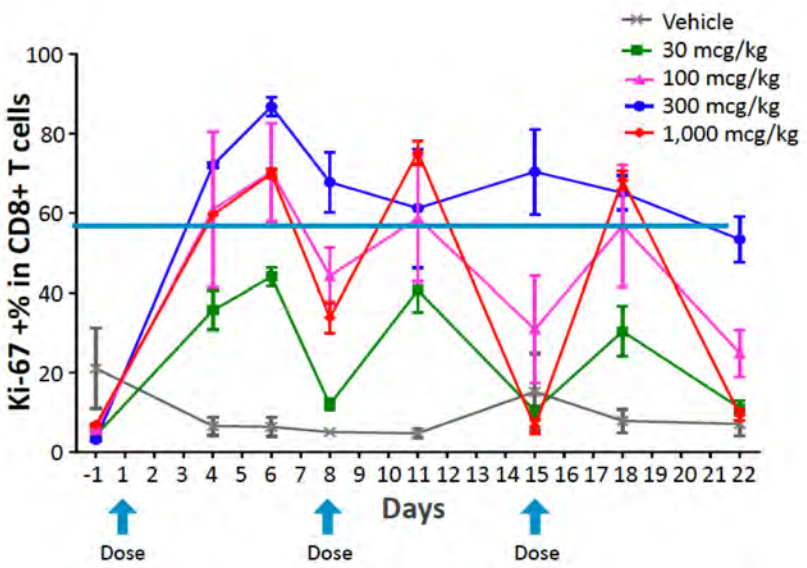


MDNA19 INDUCES DURABLE & DOSE-DEPENDENT Ki67 EXPRESSION IN CD8+ T-CELLS

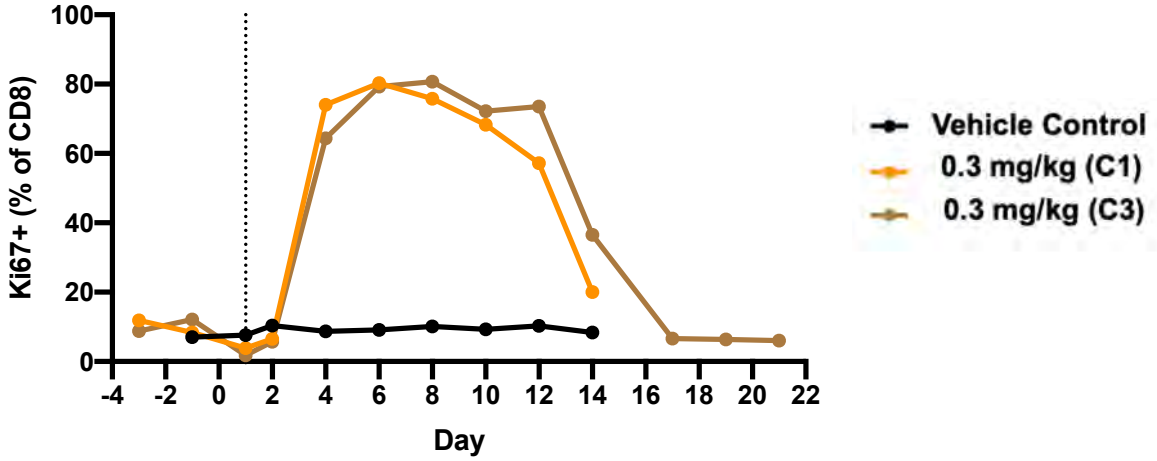
Repeat Dose of MDNA19 (Q2W x 2)



THOR-707 – Dosed 7 days apart



Single Dose of MDNA19



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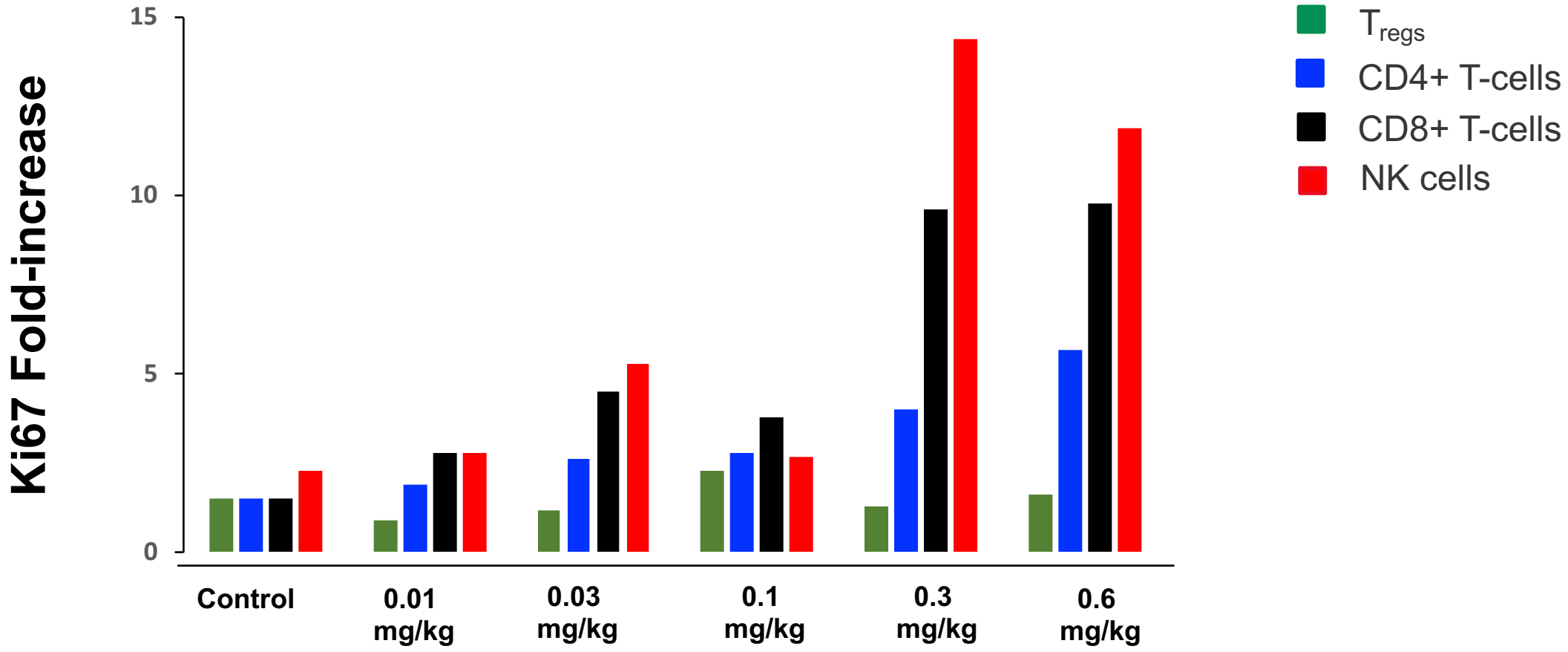
MDNA19 INDUCED PROLIFERATION OF CD4, CD8 & NK CELLS WITH LITTLE EFFECTS ON T_{REGS}



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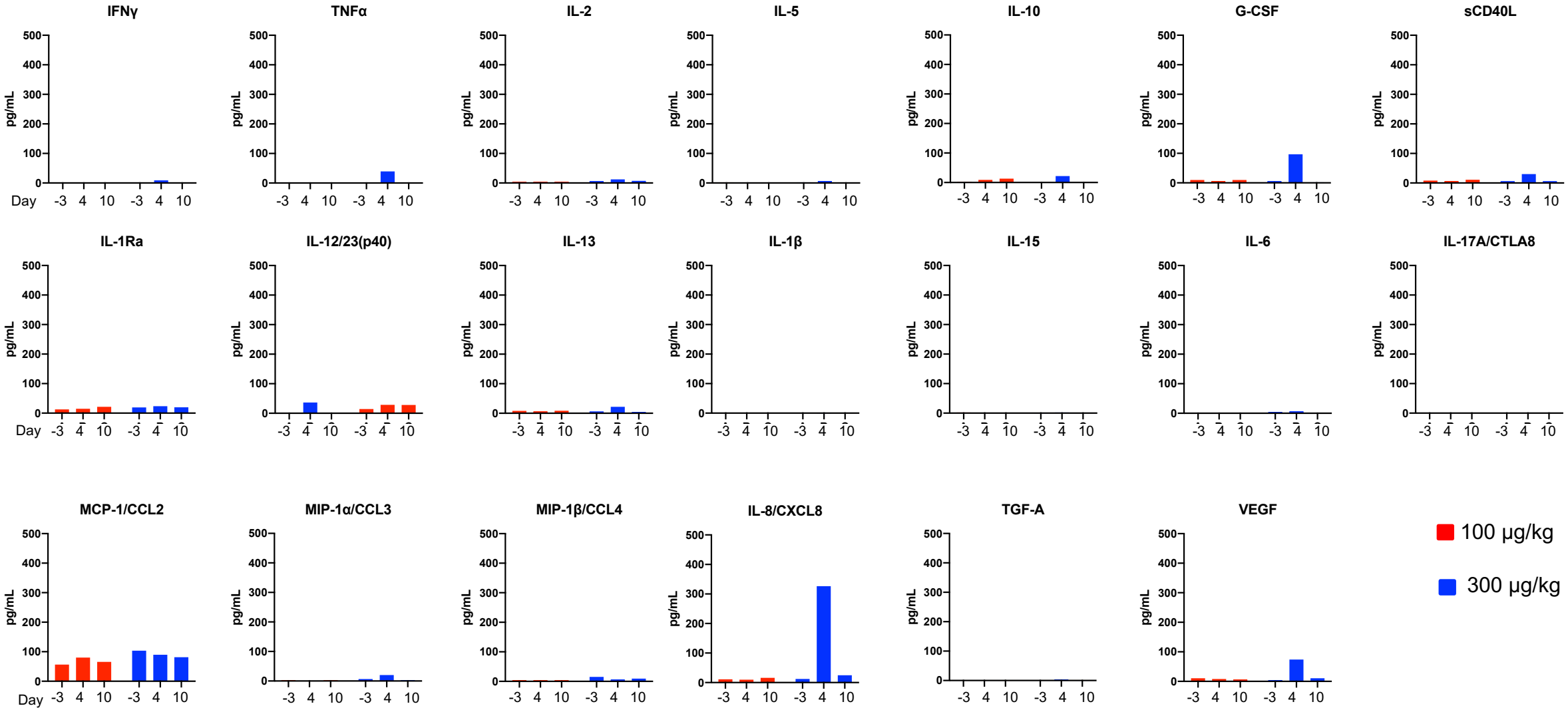
MDNA19 DOES NOT INDUCE CYTOKINE STORM



Plasma samples were analyzed on the Luminex Platform. Time-point: Day -3 Pre-dose, and Day 4 and Day 10 Post-dose.

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Clinical Observations

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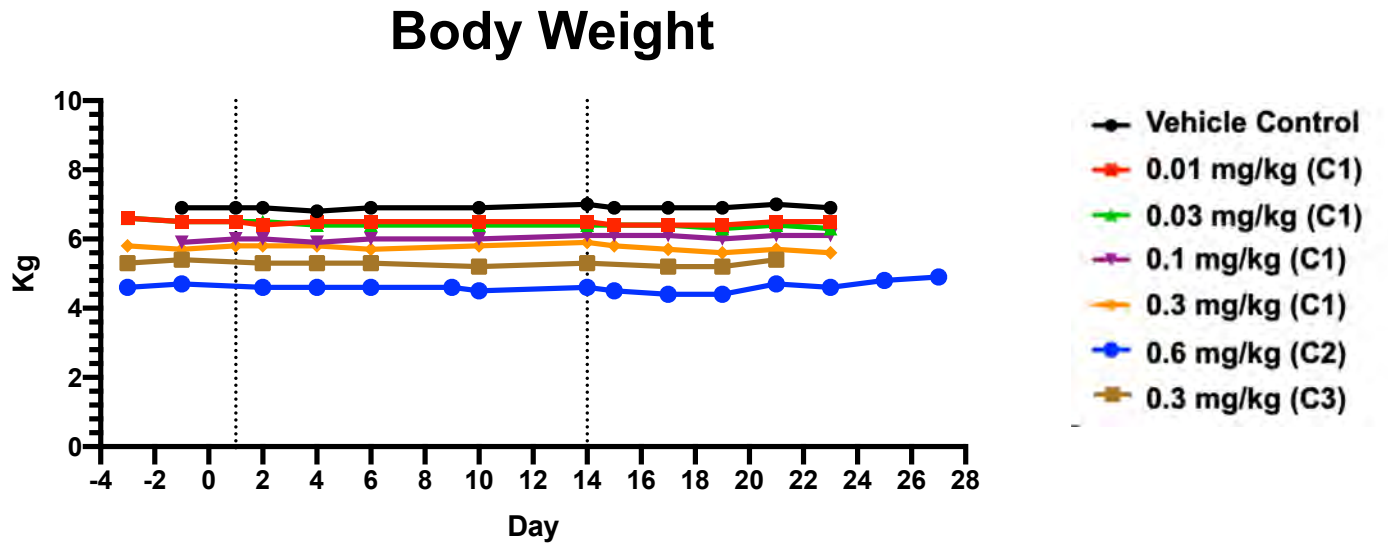
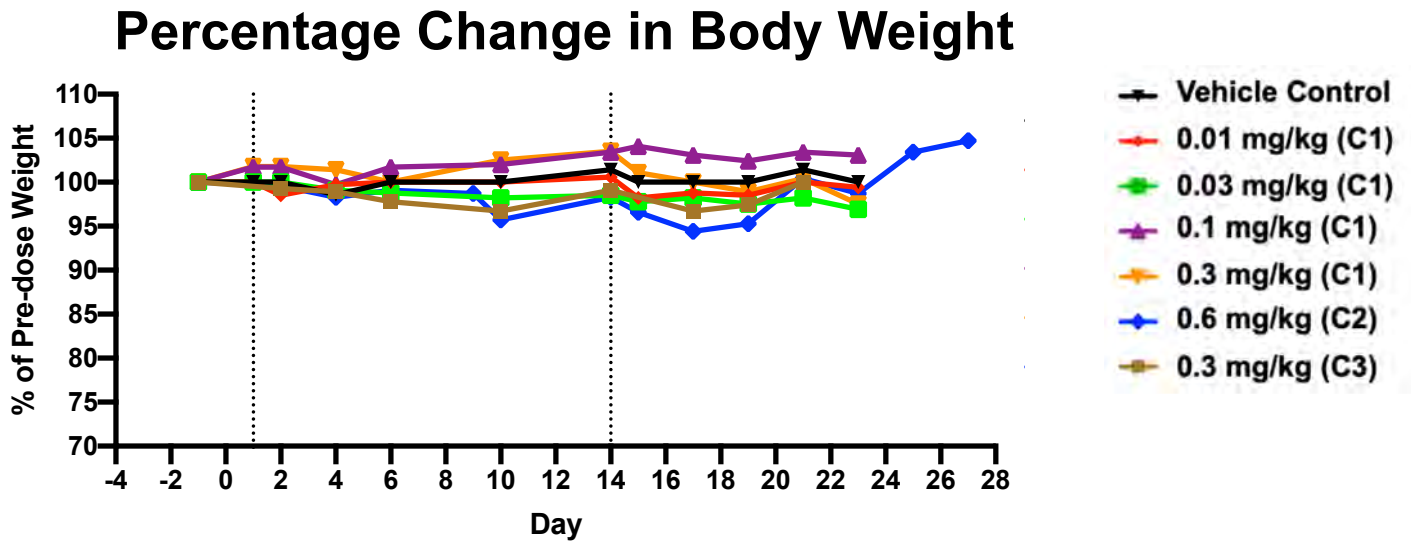
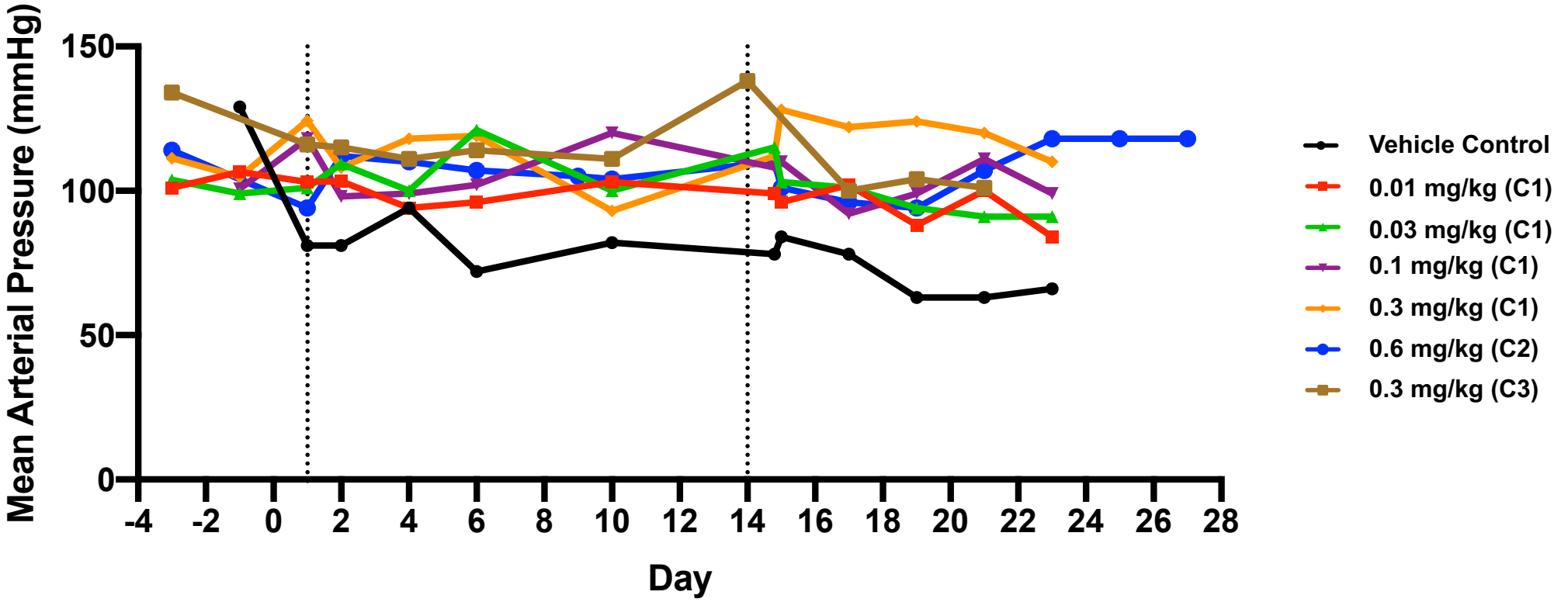
MINIMAL EFFECT OF MDNA19 ON BODY WEIGHT





NO EFFECT OF MDNA19 ON BLOOD PRESSURE
(NO SIGN OF VASCULAR LEAK SYNDROME)



Mean arterial blood pressure = (systolic blood pressure – diastolic blood pressure)/3 + diastolic blood pressure (mmHg)

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PK IN NHP and Mice

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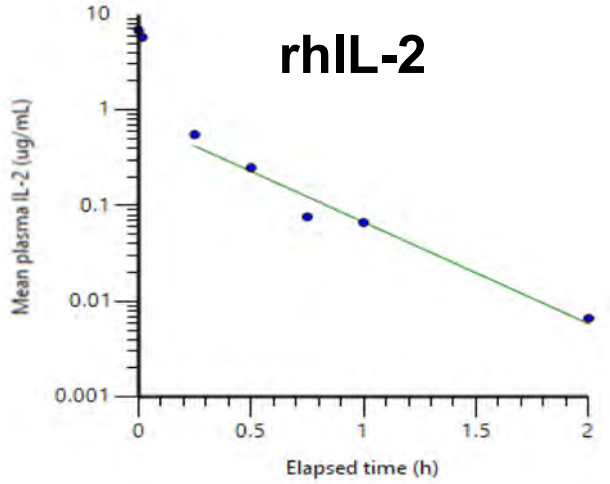
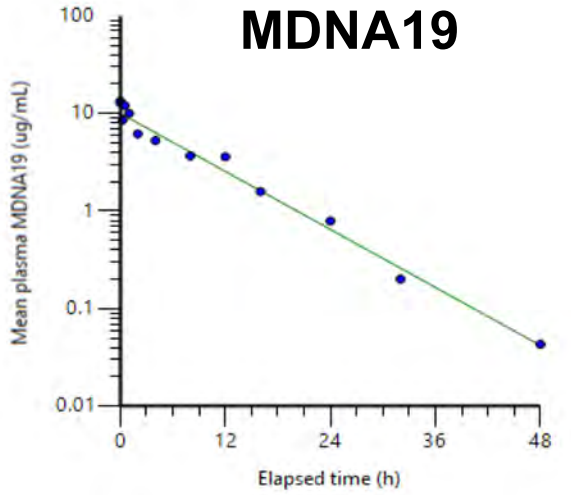
COMPARISON OF PK PROFILES OF LONG-ACTING IL-2 IN MICE

	NKTR-214 1-PEG	THOR-707	rhIL-2	MDNA109	MDNA19
Dose (mg/kg)	0.8[b]	0.3	1	1	**1**
Half-Life[a] (hr)	10.8	13.3	0.28	0.43	**6.08**
Cmax (µg/mL)	0.13	n/a	5.77	6.66	**12.96**
AUC[a] (µg.hr/mL)	5.81	45.6	1.07	1.06	**89.32**





a. Mouse PK after single IV dose.
b. Initial dose of NKTR-214 (6-PEG)
NKTR-214 data: Charych et al., PLoS ONE (2017)

Studies of rhIL-2, MDNA109, MDNA10 conducted head to head with NKTR-214, THOR-707, or Aldesleukin

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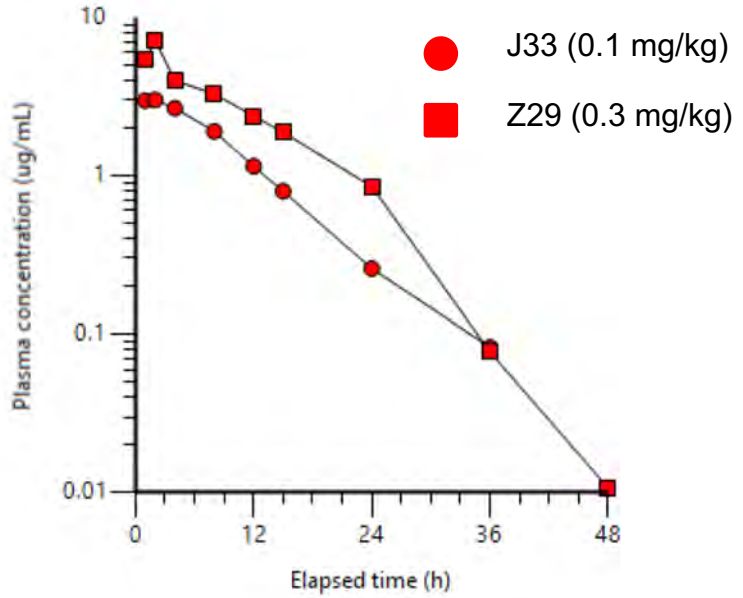
COMPARISON OF MDNA19 AND THOR-707 PK IN NHP

	MDNA19		THOR-707[a]	
Dose (mg/kg)	0.1	0.3	0.1	0.3
Half-life (hr)	6.2	8.8	7.88	11.0
AUC (µg.hr/mL)	37.3	78.1	46.3	76.1
C_{max} (µg/mL)	3.0	7.1	3.2	



a. Milla et al., SITC (2018) & Joseph et al., AACR (2019)

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SUMMARY OF PILOT NHP STUDY

- No unusual safety findings observed with repeat dosing (Q2W x 2) of MDNA19 at 0.01 – 0.6 mg/kg.

- Treatment with MDNA19:
  - Induced WBC & lymphocyte expansions with limited effects on eosinophils, (normally linked to VLS).
  - Induced durable expression of Ki67 in $CD4^+$ and $CD8^+$ T-cells with corresponding increase in cell numbers
  - Displayed limited effects on T_{regs}.
  - Did not cause systemic induction of pro-inflammatory cytokines (i.e., no cytokine storm).
- Exhibited extended half-life compared to rIL2

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Thank You!