OrthoCARs: Engineered human IL-2/IL-2Rb orthogonal pairs selectively enhance CAR T cell antitumor efficacy

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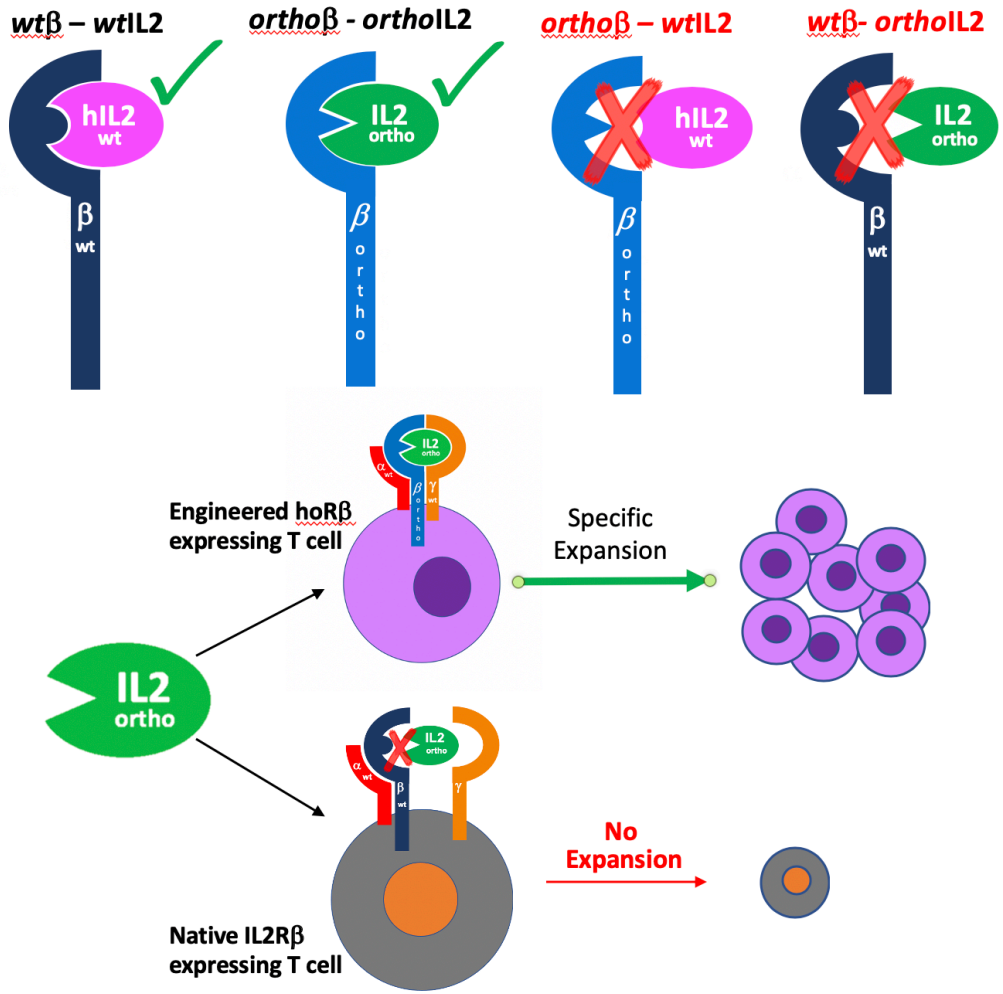
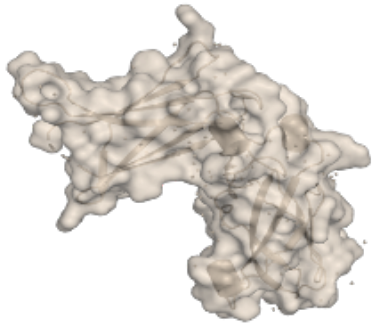
Disclosures

- Employee: Synthekine, Inc.

Orthogonal IL-2 Program Selectively Activates CAR-Ts *In Vivo*





hoRβ

Human orthogonal IL-2Rβ uniquely expressed on CAR-T

STK-009

Orthogonal IL-2 Ligand

Incorporated into:

SYNCAR-001

- Lentiviral vector
- CD19 CAR
- Ortho receptor (hoRβ)
- Bicistronic expression via T2A cleavage peptide

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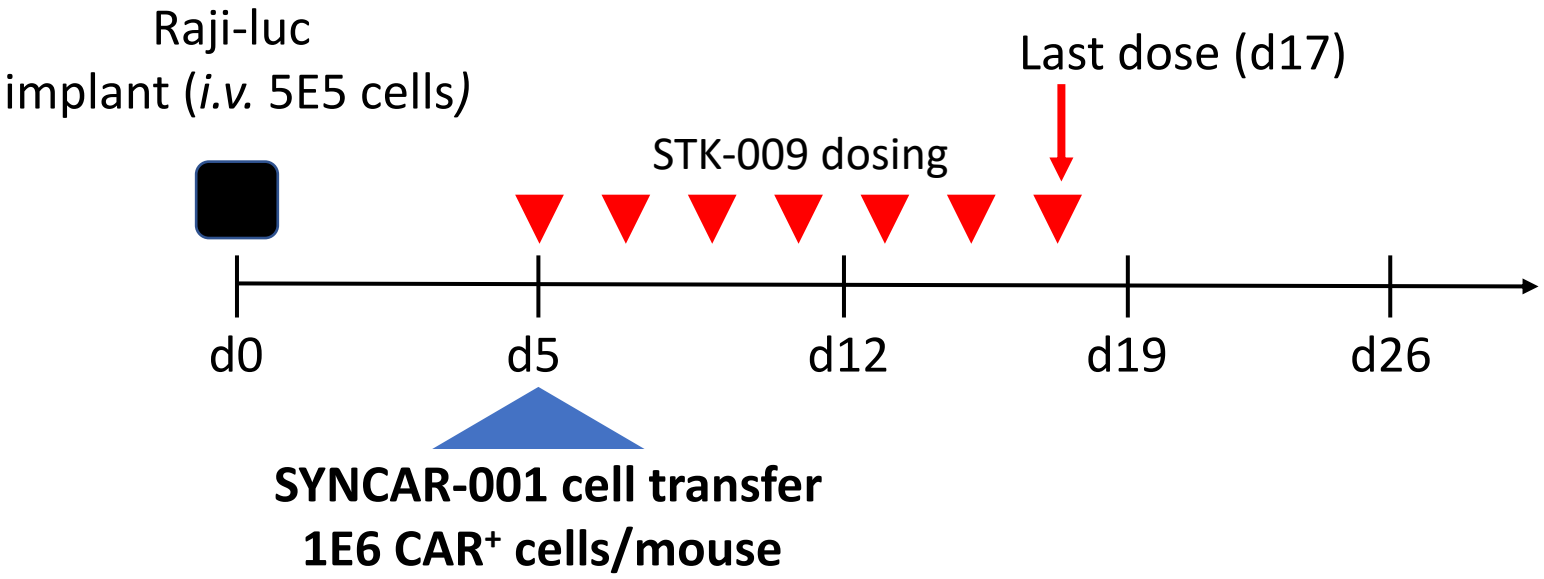
Efficacy of STK-009 and SYNCAR-001 In a Disseminated Raji NSG Model

Study Design



Treatment Groups

Cells	Treatment	Mice
-	PBS	8
SYNCAR-001	-	8
SYNCAR-001	STK-009 1ug (q.o.d.)	8

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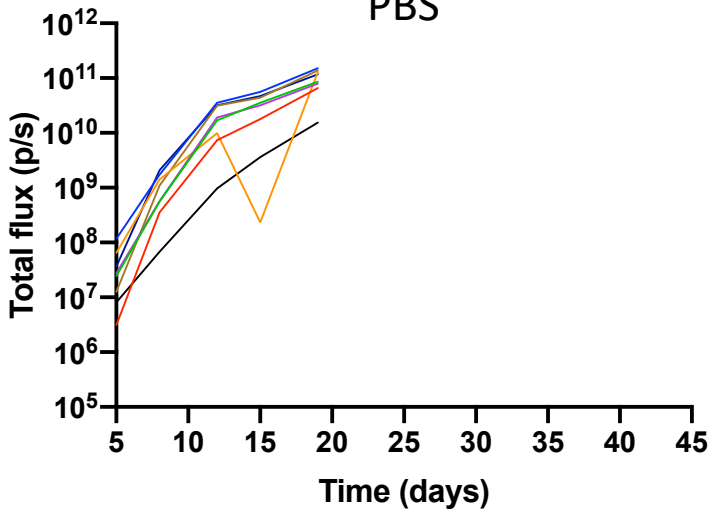
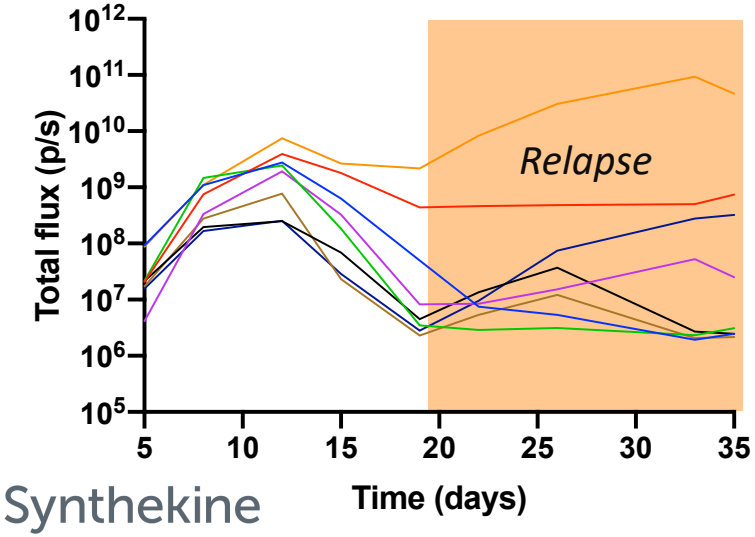
STK-009 Drives Complete Responses Even With a Sub-Efficacious CAR Dose

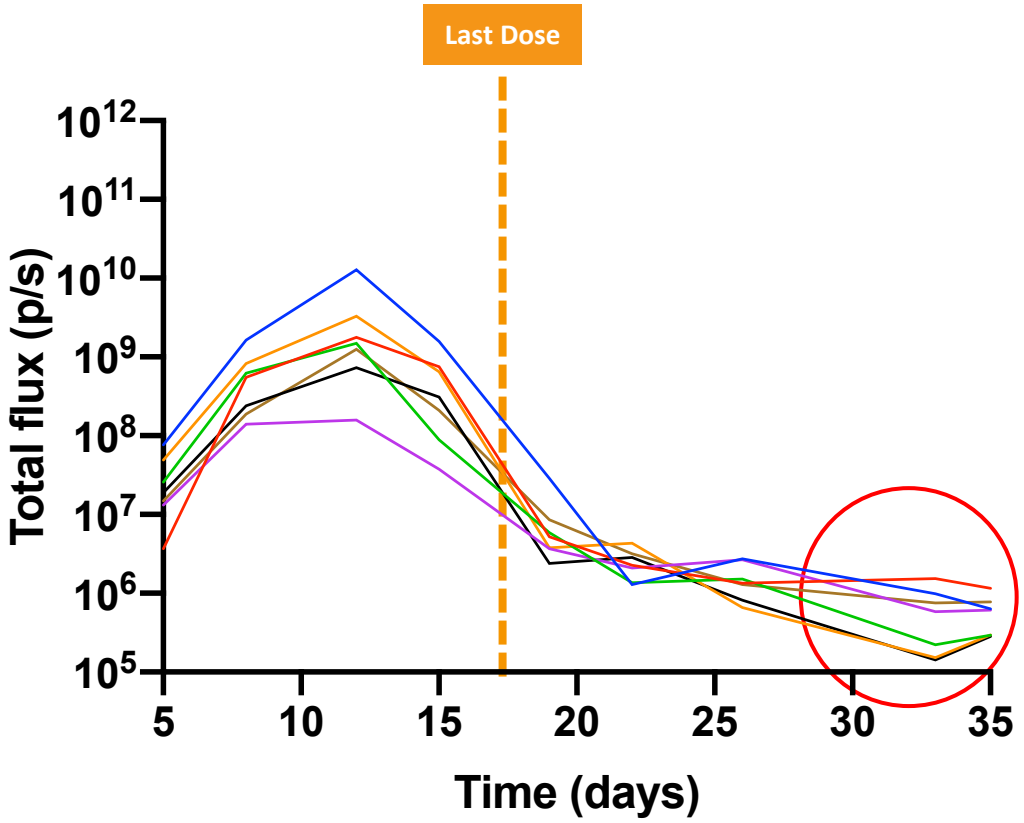
PBS



SYNCAR-001 + PBS



SYNCAR-001 + STK-009 (1 µg)



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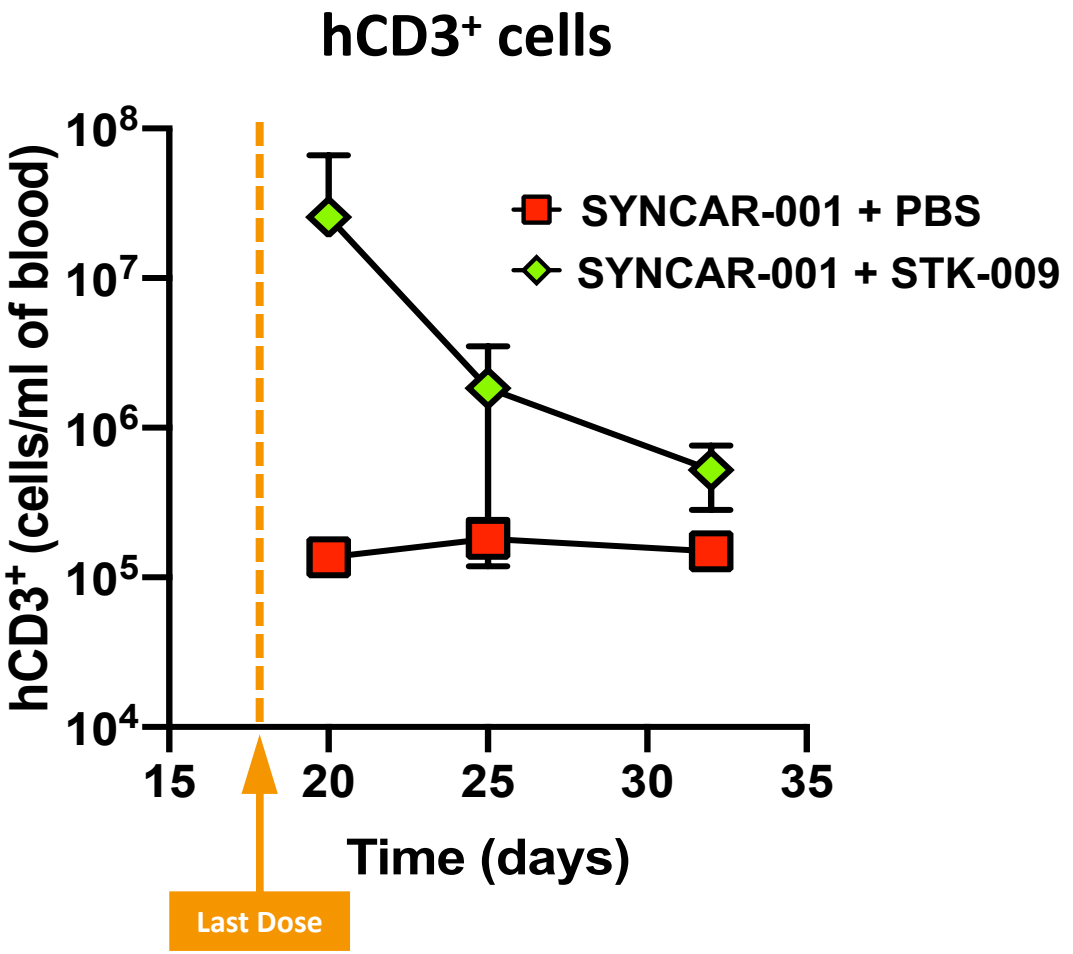
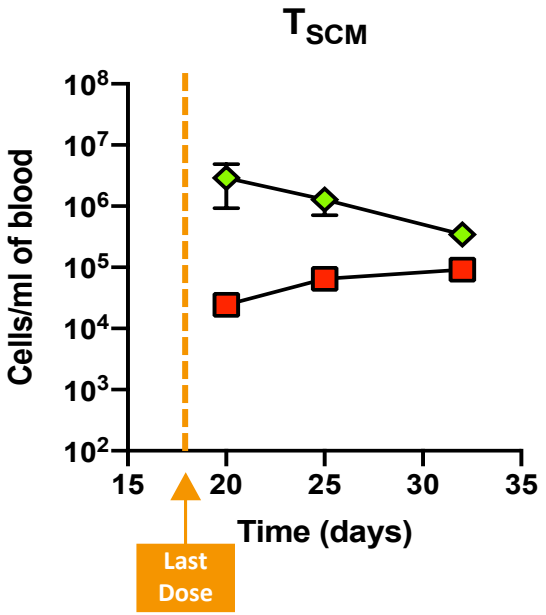
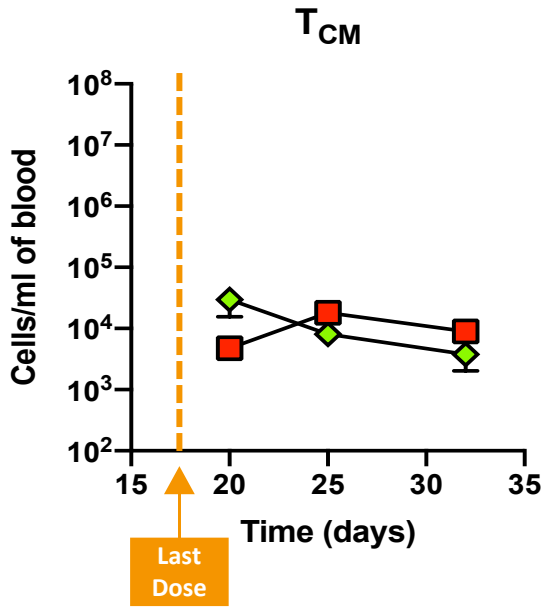
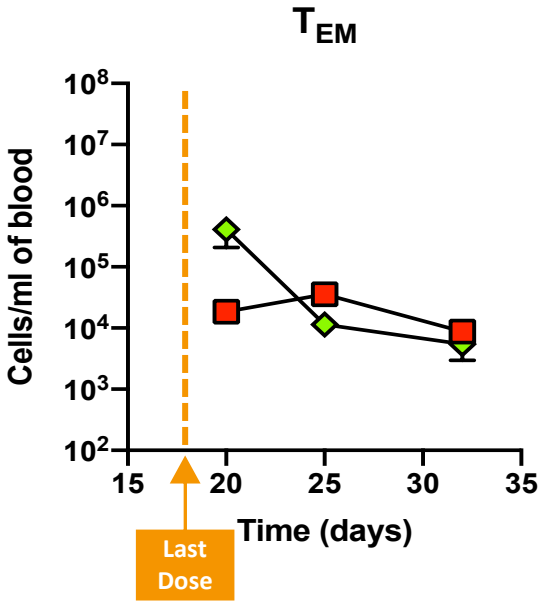
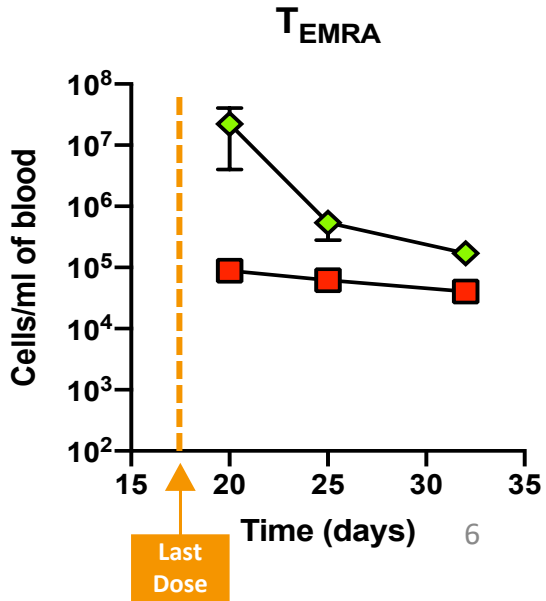
STK-009 Treatment Increases CAR-T Levels With Elevated Long Lived Memory T_{SCM} Populations











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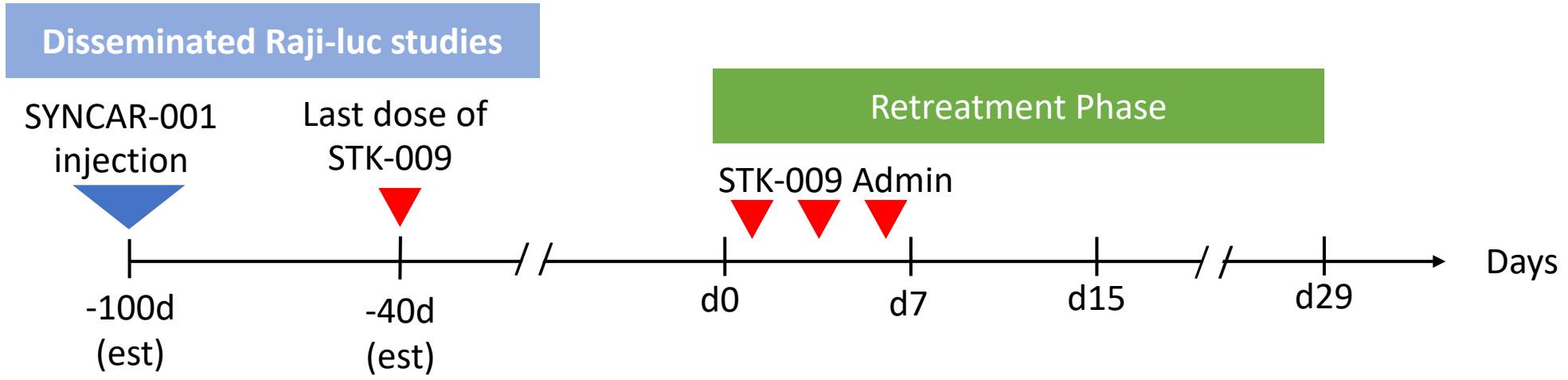
Study to Address Whether Retreatment of Mice with "Resting" SYNCAR-001 Cells with STK-009 Increases T Cell Levels

Study Design



Treatment Groups

Group	Treatment	Mice
1	PBS	4
2	STK-009 1 µg q.o.d., s.c.	5
3	STK-009 10 µg q.o.d.,s.c.	5

All mice clear of tumor burden (IVIS)

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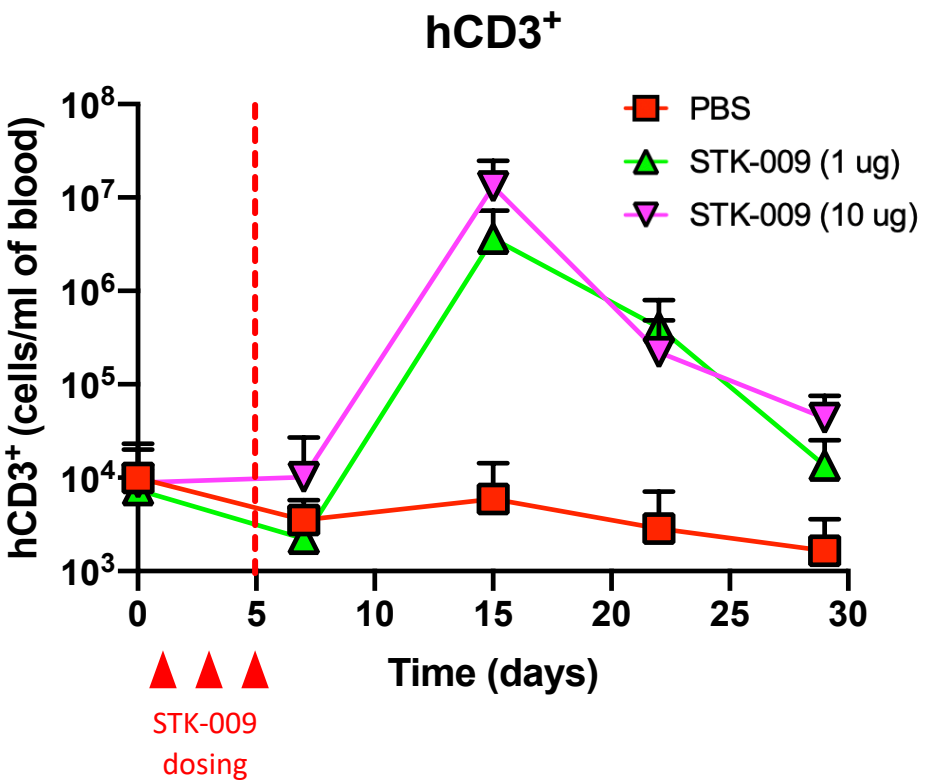
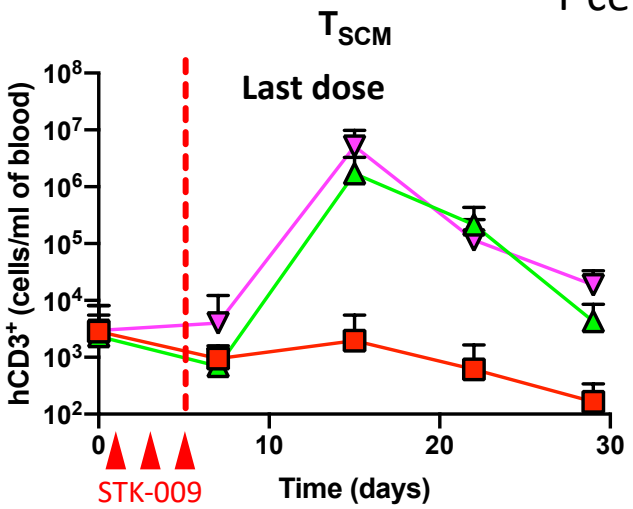
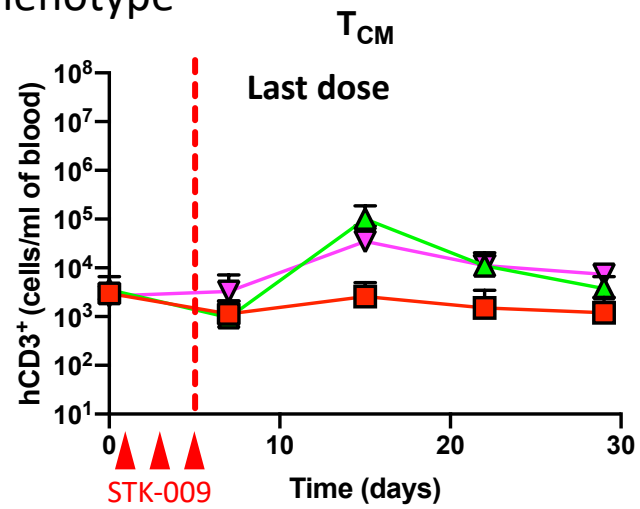
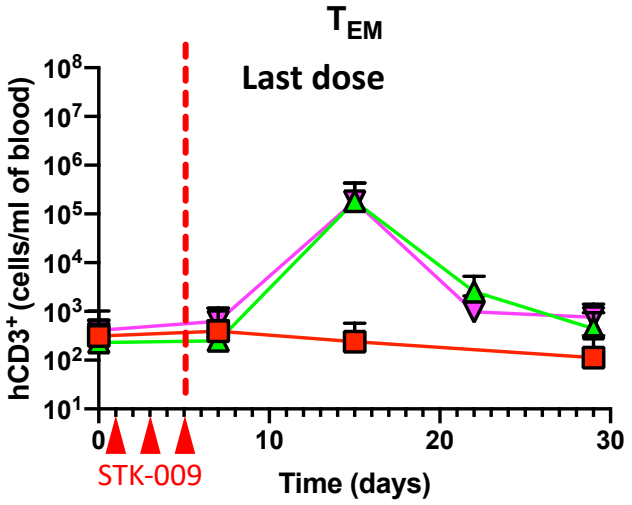
STK-009 Induces Re-expansion of CAR-T Cells Following Complete Response And 40+ day Drug Holiday

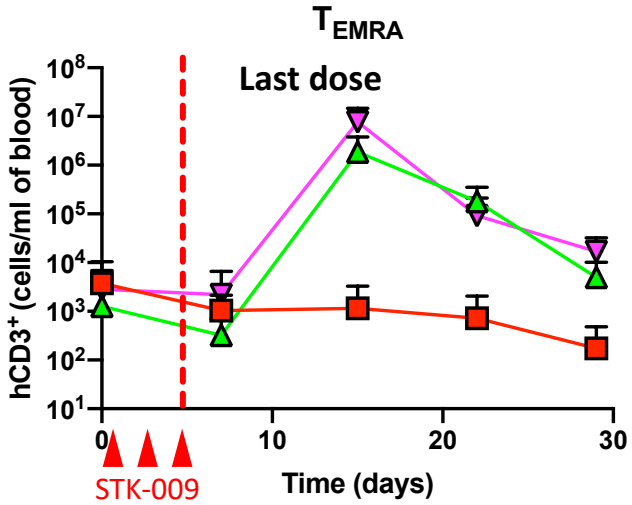


T-cell phenotype









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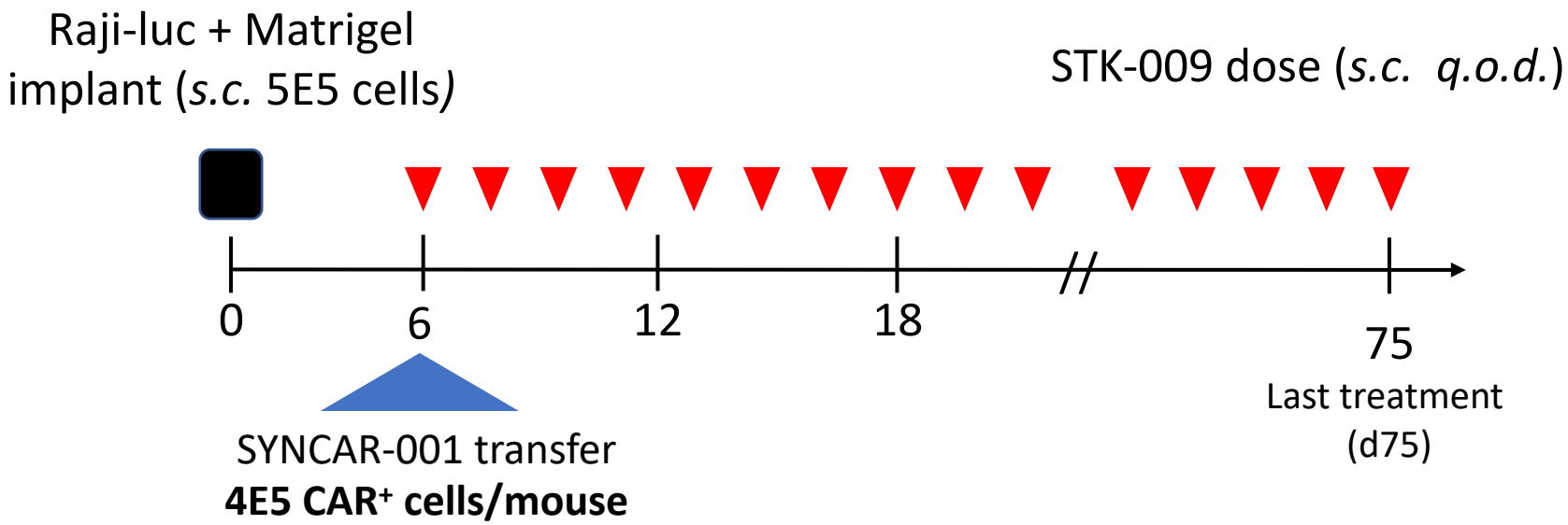
Efficacy of STK-009 and SYNCAR-001 in a **Subcutaneous** Raji NSG Model

Study Design



Treatment Groups

Group	CAR T Cells	Treatment	Mice
1	-	PBS	8
2	SYNCAR-001	-	8
3	SYNCAR-001	STK-009 10ug (q.o.d.)	8
4	SYNCAR-001	STK-009 1ug (q.o.d.) -> 10 ug on Day 50 (q.o.d)	8

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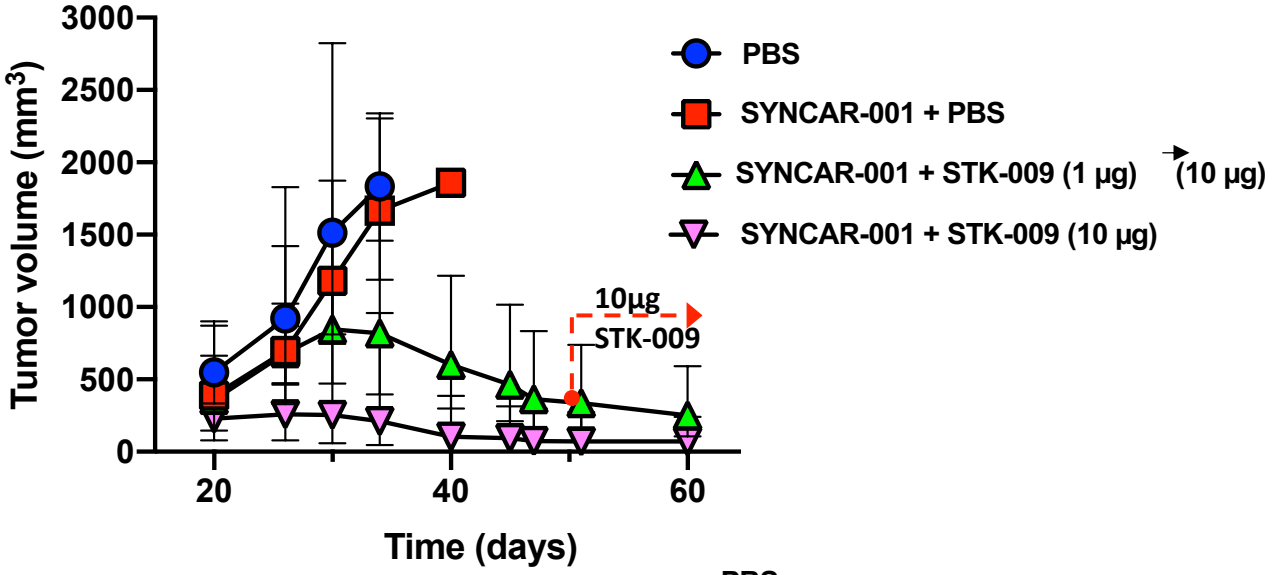
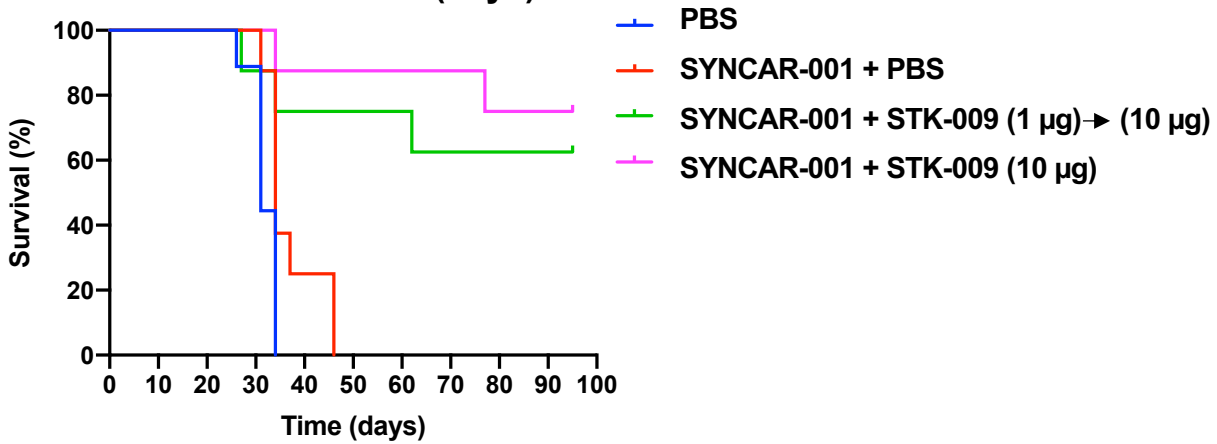
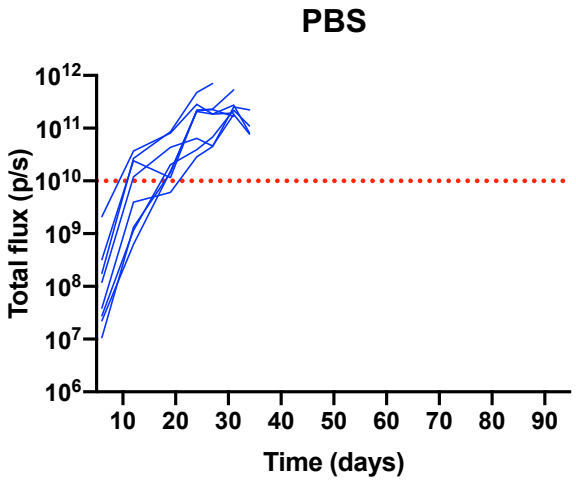
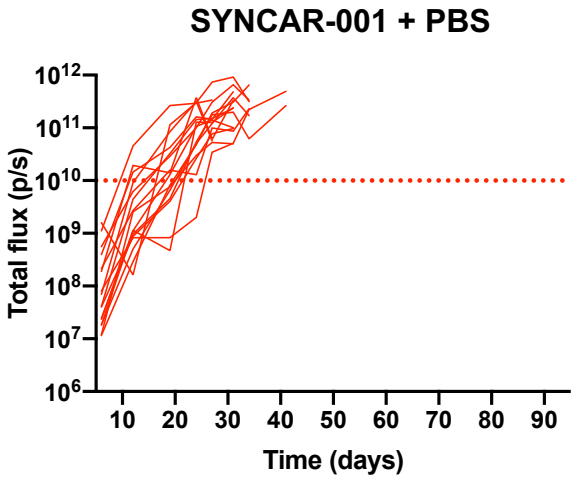
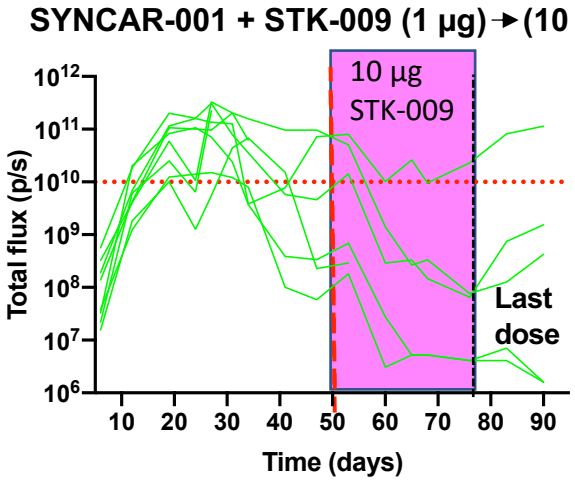
STK-009 Delivers Complete Responses With a Non-Efficacious Dose of CARs

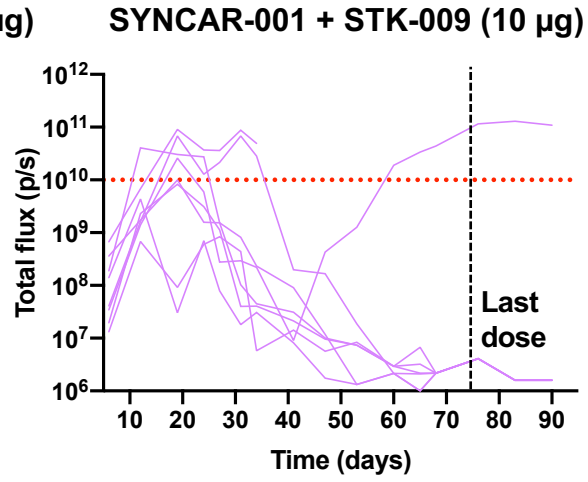












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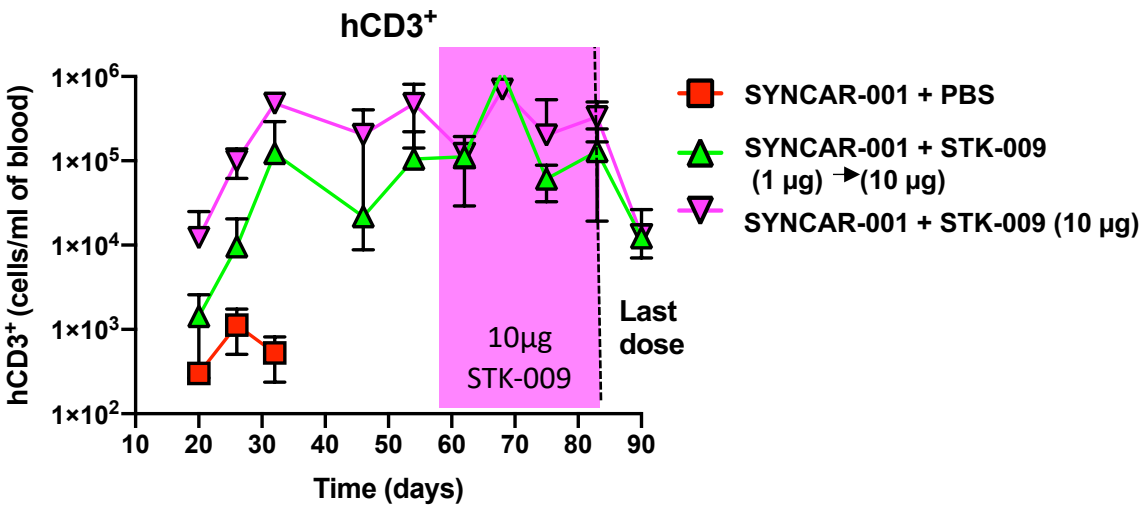
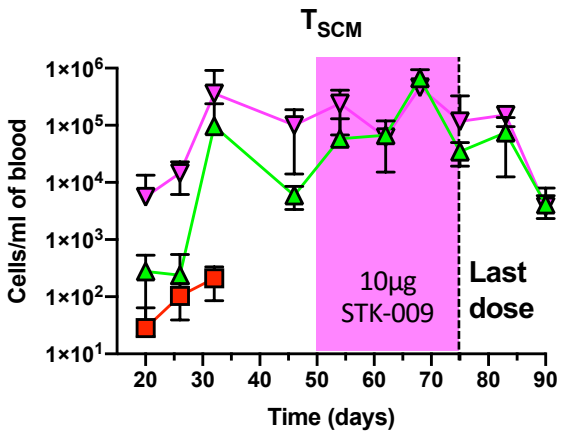
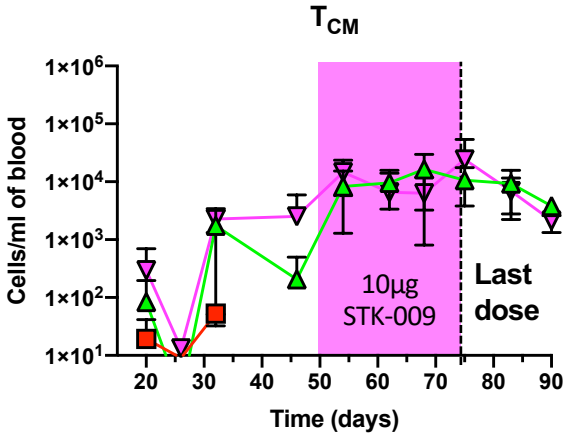
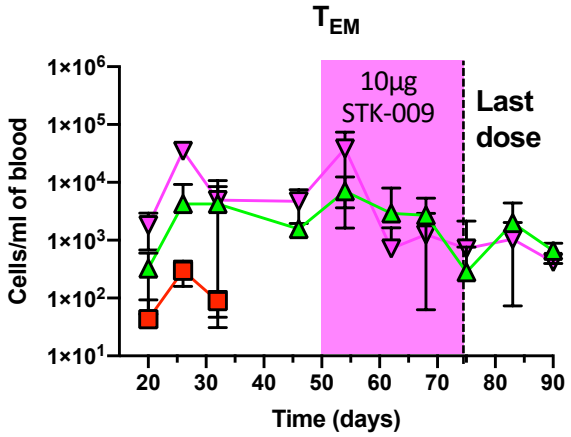
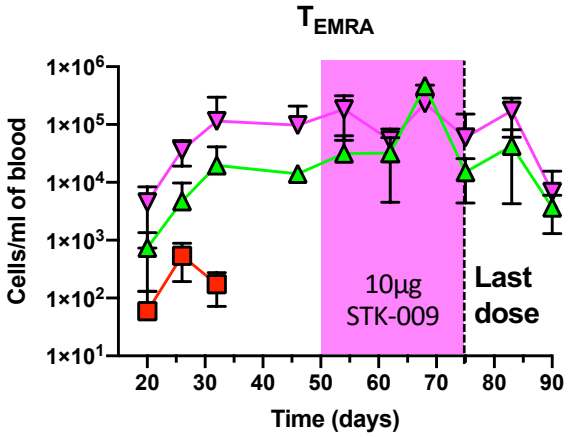
STK-009 Significantly Increases Peripheral T Cell Numbers and All T Cell Memory Subtypes Including T_{SCM} Cells











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STK-009 non-GLP tolerability and toxicology study in non-human primates

Study design

Group	Test Material	Dose Frequency	Dose Level (mg/kg)		
			Day 1	Day5	Day 10
1	Proleukin (control)	single dose	0.037	-	-
2	STK-009	q5d	0.06	0.06	0.06
3	STK-009	q5d	0.12	0.12	0.12
4	STK-009	q5d	0.02	0.12	-
5	STK-009	q5d	0.06	0.25	-

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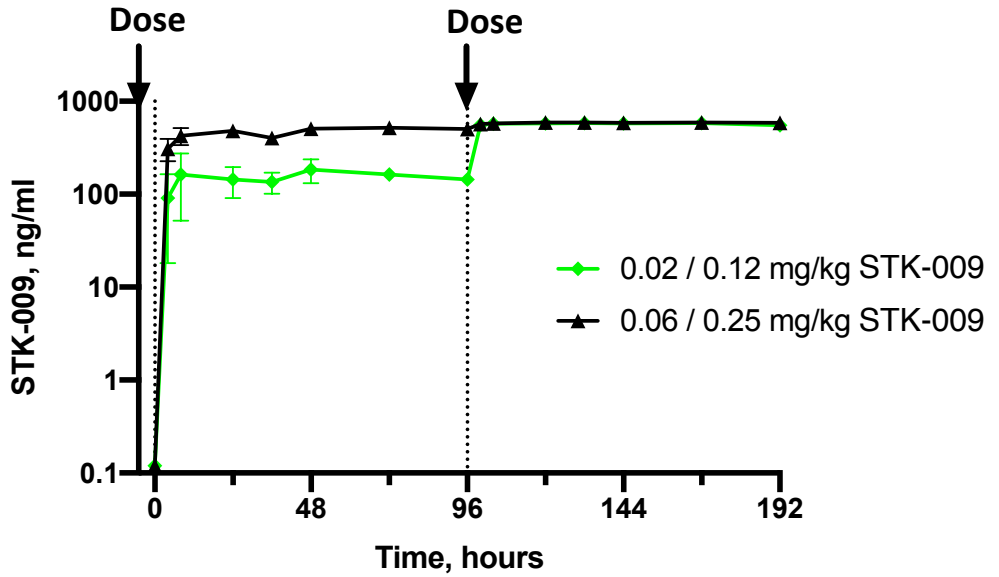
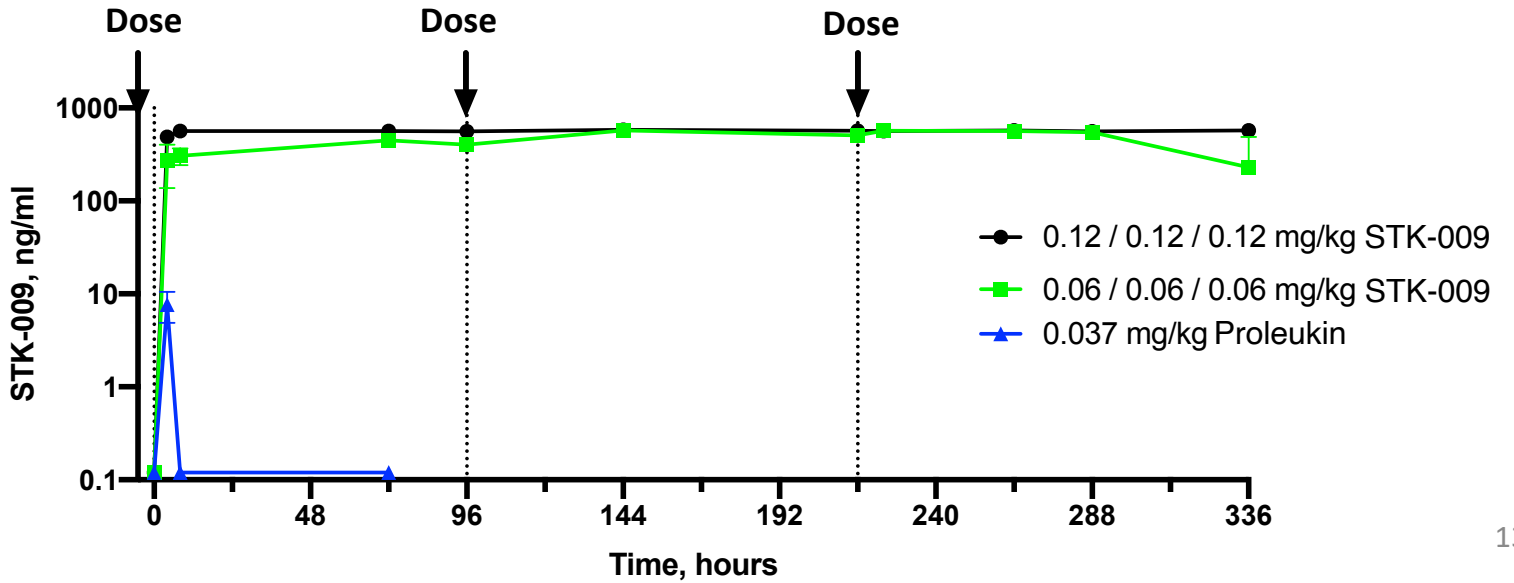
STK-009 has a favorable PK profile in cynomolgus monkeys

STK-009 exposure was very stable with minimal clearance between doses.

In the absence of an hoRβ expressing cell, STK-009 does not undergo target mediated clearance.





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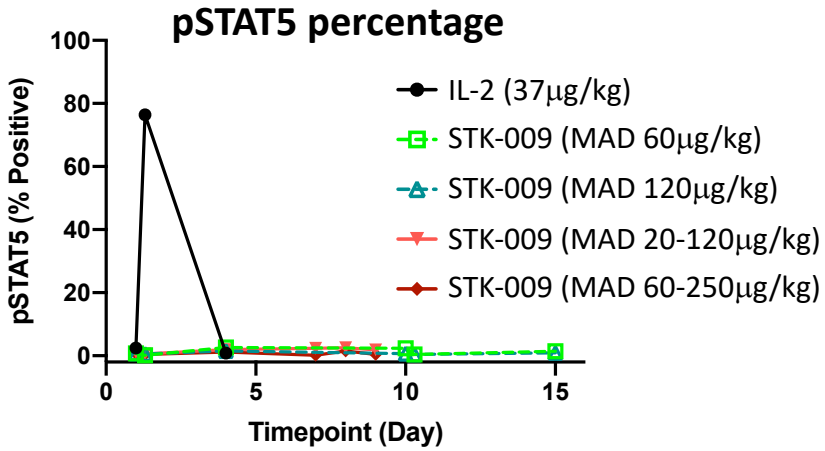
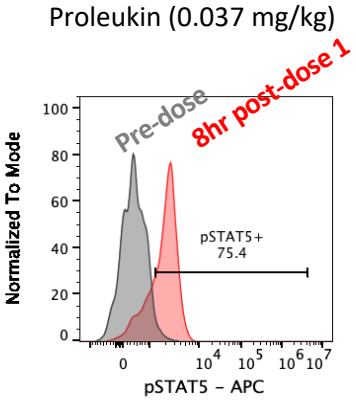
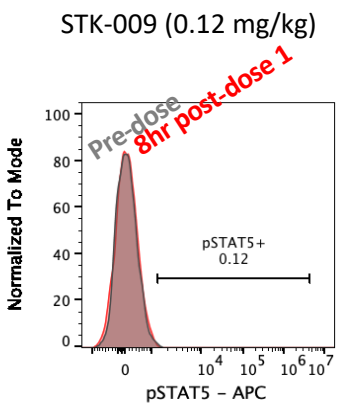
STK-009 avoids any T cell or NK cell activation in cynomolgus monkeys

STK-009 has negligible effects on cells that express WT IL-2 receptors and are responsive to WT IL-2 (Proleukin)

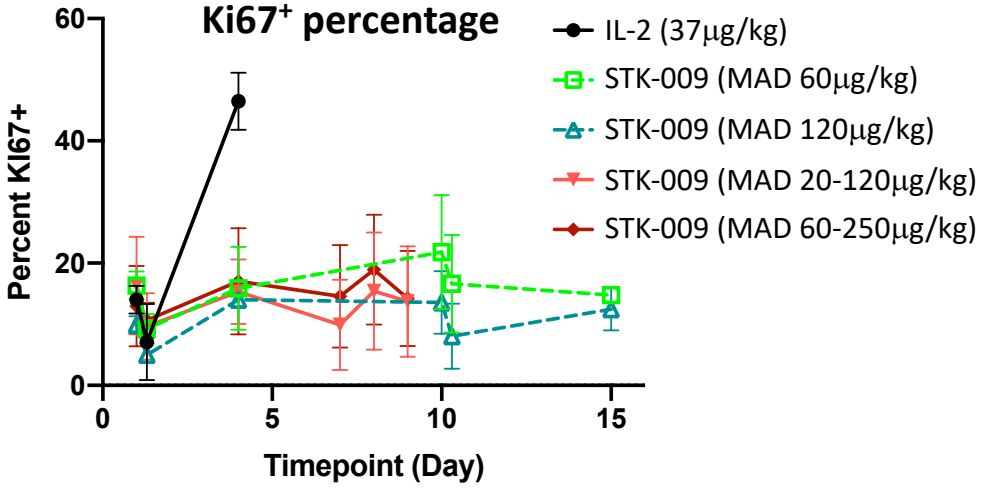
CD4⁺ CD25⁺ T cells

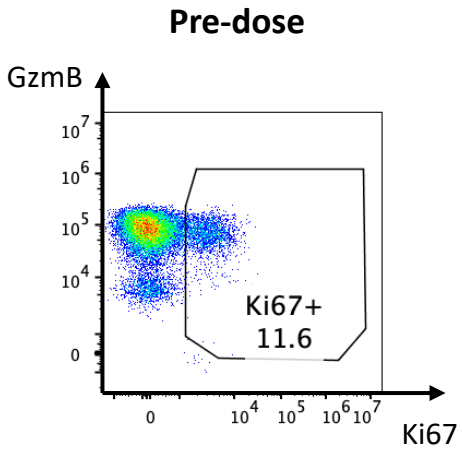


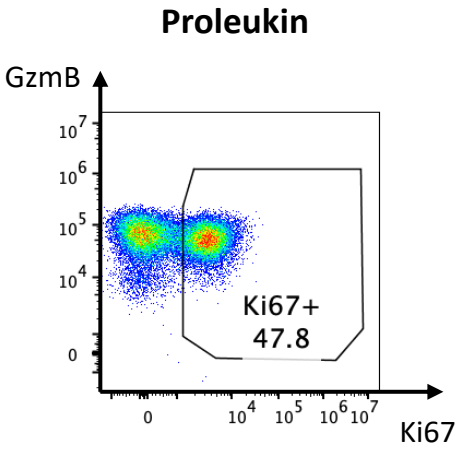


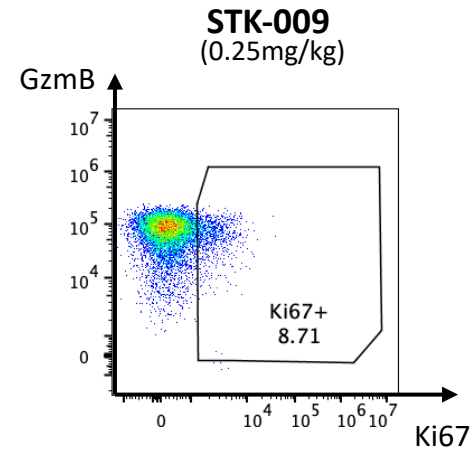


NK cells









Conclusions

- **STK-009/SYNCAR-001 platform drives improved efficacy**
  - STK-009 rescues ineffective doses of SYNCAR-001 in subcutaneous and disseminated Raji models
- **STK-009 dramatically increases SYNCAR-001 cell counts**
  - **3-6 log** effect depending on donor and tumor model
- **SYNCAR-001 can be expanded at will by STK-009 dosing**
  - Resting SYNCAR-001 cells in tumor burden free mice can be expanded by STK-009 after a 40 day drug holiday
- **SYNCAR-001 cells contract in the absence of tumor burden and STK-009 dosing**
  - Enables ability for STK-009 dosing regimens to dictate increased or decreased SYNCAR-001 cell numbers
- **STK-009/SYNCAR-001 cell platform expands both T^{scm} and T^{eff} SYNCAR-001 T cells**
  - STK-009 increases desired populations for anti-tumor efficacy and long term surveillance
- **STK-009 is well tolerated and does not induce biological effects at the explored doses in non-human primates**
  - STK-009 is highly specific for hoRb expressing cells
- **Therefore, the STK-009/SYNCAR platform has the potential to overcome clinically relevant hurdles in cell therapy**