Abstract 1573P

Decoy-resistant IL-18 combination with Bi-specific T cell engager enhances anti-tumor efficacy

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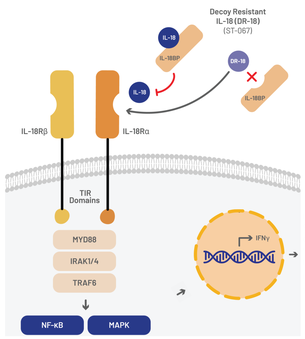
Introduction

- Interleukin-18 (IL-18) is a proinflammatory cytokine modulating both innate and adaptive immune responses [1].
- IL-18 signaling enhances activity and function of multiple T cell mediated therapies including CAR T cells, TCR-T, and gamma delta T cells [2-4]
- Wild-type recombinant IL-18 has shown limited anti-tumor efficacy in preclinical models and clinical trials, due to upregulation of IL-18 binding protein (IL-18BP).
- **Simcha Therapeutics is developing ST-067, a Decoy-Resistant IL-18 (DR-18), engineered to be resistant to IL-18BP, for use as a universal T-cell enhancer to combine with multiple therapeutic modalities including checkpoint inhibitors, cell therapy and T cell engagers (TCE) [5].**



DR-18 avoids endogenous negative regulator IL-18BP to activate an IFN-γ based immune activation program

- ST-067 is currently being investigated in multiple clinical trials, including post-allo-HCT in R/R AML patients (NCT06492707) and post-CD19 CAR T (NCTNCT07098364).

Aims

1. Evaluate the potential of DR-18 to enhance bispecific T cell engagers as clinical combinations for treating solid and liquid cancers
2. Assess the durability of DR-18 mediated tumor regression and the ability of DR-18 to induce immunological memory after re-challenge

DR-18 enhances TRP1 BiTE tumor growth inhibition in syngeneic melanoma model

Tumor Model: B16-F10 s.c. injection

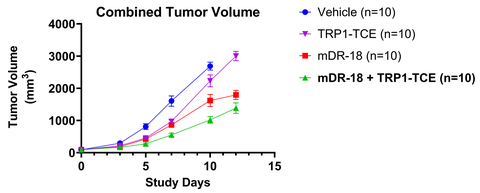
C57BL/6

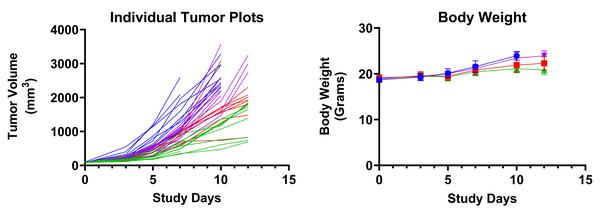
12ug mTRP1 BiTE x 3 doses i.p,. Q3D

D0

0.32mpk mDR-18 x 5 doses i.p. BIW

Measurements:
- Tumor Growth Inhibition
- Body Weight Loss





Mice removed from study once tumor volume exceeded 2000 mm³ or body weight loss exceeded 20% of D0 baseline.

DR-18 combines with gresonitamab to enhance survival in humanized CRC model

Tumor Model: huCLDN18.2 – MC38 s.c. injection

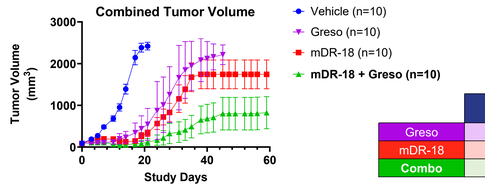
C57BL/6 huCD3e

0.5 mpk gresonitamab x 5 doses i.p. BIW

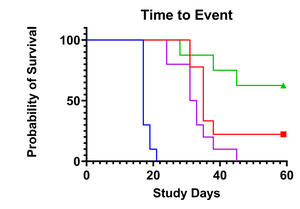
D0

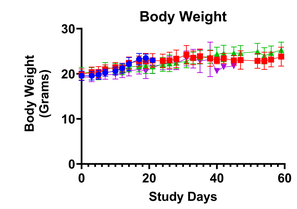
0.32mpk mDR-18 x 5 doses BIW

Measurements:
- Tumor Growth Inhibition
- Survival
- Body Weight Loss



	Complete Tumor Regressions (0mm³)
Greso	0
mDR-18	2
Combo	5





Event defined as tumor volume exceeding 2000 mm³ or body weight loss exceeded 20% of D0 baseline and mark removal from study.

DR-18 enhances blinatumomab tumor growth inhibition in humanized B-ALL model

Tumor Model: huCD19 – A20 s.c. injection

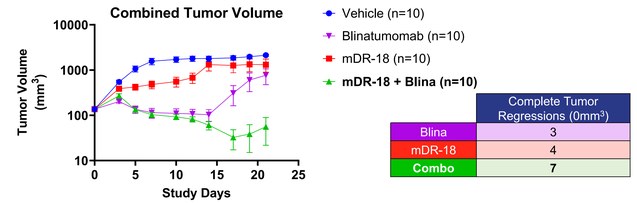
C57BL/6 huCD3e

0.05 mpk blinatumomab x 10 doses i.p. QD

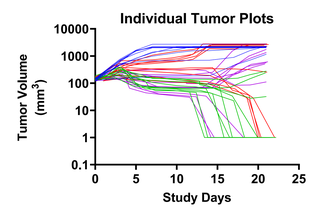
D0

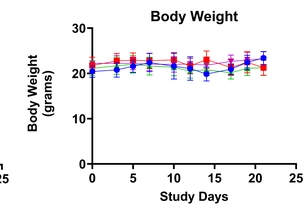
0.32mpk mDR-18 x 5 doses i.p. BIW

Measurements:
- Tumor Growth Inhibition
- Body Weight Loss



	Complete Tumor Regressions (0mm³)
Blina	3
mDR-18	4
Combo	7





Mice removed from study once tumor volume exceeded 2000 mm³ or body weight loss exceeded 20% of D0 baseline.

DR-18 induces immunological memory to inhibit tumor growth upon rechallenge

Tumor Model: A20

BALB/c

D0: SC tumor injection in Left Flank

0.32mpk mDR-18 x 5 doses BIW

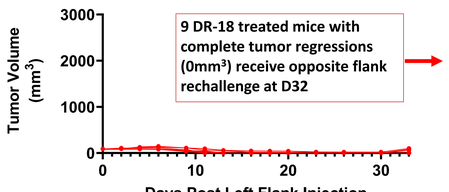
D32: SC tumor injection in Right Flank

No additional treatment with DR-18

1) DR-18 Left Flank CR Rechallenge Cohort
2) Naïve BALB/c Initial Challenge Control

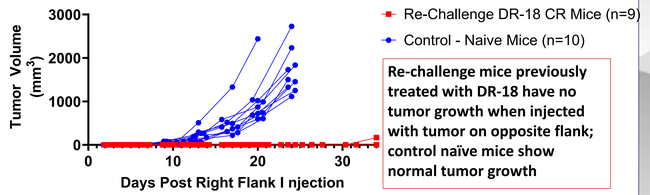
Measurements
- Tumor Growth Inhibition

Initial A20 Left Flank Tumor Volume



9 DR-18 treated mice with complete tumor regressions (0mm³) receive opposite flank rechallenge at D32

A20 Right Flank Tumor Volume



Re-challenge mice previously treated with DR-18 have no tumor growth when injected with tumor on opposite flank; control naïve mice show normal tumor growth

Mice removed from study once tumor volume exceeds 3000 mm³ or body weight loss exceeds 20% of D0 baseline.

Conclusions

- Addition of DR-18 to T cell engagers in preclinical models enhanced tumor growth inhibition with no observed body weight loss
- Clinical synergy seen in both solid and heme tumor models
- DR-18-mediated complete regressions are durable to rechallenge, suggesting mechanism of action includes induction of immune memory
- Findings strengthen rationale for ST-067 to be used as a clinical combination with BiTEs to enhance clinical response in solid and heme malignancies

Disclosures

- J.N.L and H.U. – Simcha employees and equity holders
- AR – Simcha equity holder, Board of Directors, and Scientific Advisory Board
- Study sponsored by Simcha Therapeutics

References 1) Dinarello CA et al. 2013 *Front Immunol,*4:289 2) Li YR et al. 2025 T*rends Cancer,*S2305-8033(25))00151-7 3)Drakes DJ et al. 2020 *Cancer Immunol Res,* 8(6):743-755 3) Hull CM et al. 2024 *Mol Ther,* 32(7):2373-2392 5) Zhou T et al. 2020 *Nature*, *583(7817):609-614*

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