Abstract 1721

TAC-001, a Toll-Like Receptor (TLR9) Agonist Antibody Conjugate Targeting B cells, Promotes Anti-Tumor Immunity and Favorable Safety Profile Following Systemic Administration in Preclinical Models

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CONFIDENTIAL

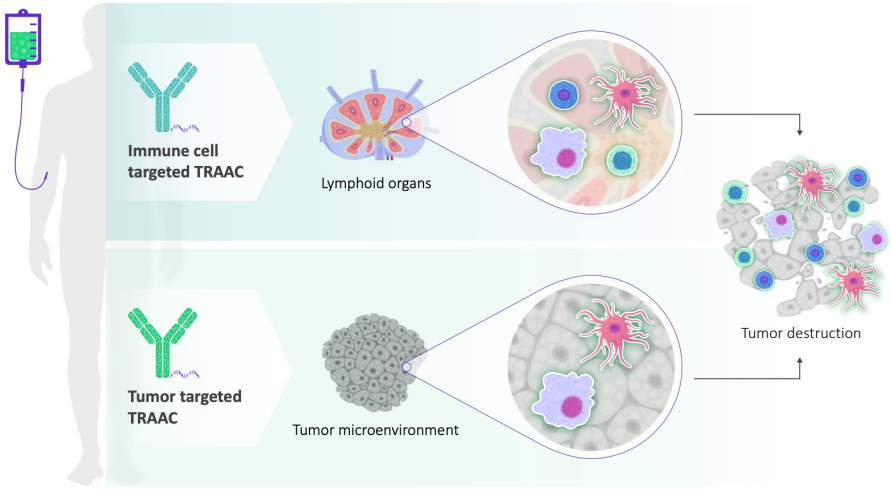
Introduction

- Novel therapies engaging both innate and adaptive immune response may produce more robust and durable anti-cancer immunity [1].
- Activation of toll-like receptor 9 (TLR9) by unmethylated CpG oligonucleotides (ODNs) promotes innate inflammatory responses and the induction of adaptive immunity [2]. Several CpG-ODNs have demonstrated clinical benefit in melanoma patients by intra-tumoral injection [3].
- We developed a novel Toll-like Receptor Agonist Antibody Conjugate (TRAAC) platform to deliver a potent TLR9 agonist (T-CpG) for targeted immune activation via systemic administration.
- Recent studies have described the presence and the potential role of B cells in the response to checkpoint inhibitors in multiple solid tumor types.
- We developed CD22 TRAAC, comprised of T-CpG conjugated to an anti-CD22 antibody, a receptor restricted to B cells.
- CD22 TRAAC was evaluated *in vitro* and in tumor models, demonstrating robust immune modulation and potent single agent anti-tumor activity in pre-clinical settings.
- TAC-001 is a CD22 TRAAC and is being developed for solid tumor malignancies.

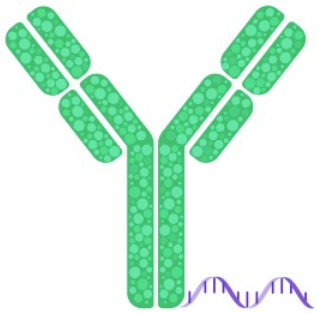
References
1. Kobold., Innate and adaptive immunity combined for cancer treatment. *PNAS* 2019, 116 (4) 1087-1088.
2. Dowling et al., Toll-like receptors: the swiss army knife of immunity and vaccine development. *Clin. Transl. Immunology*. 2016 5(5), e85–10.
3. Hamid et al., Intratumoral Immunotherapy—Update 2019. *The Oncol*. 2019; 25:343–359.

TAC-001 is a CD22 TRAAC, a Toll-like Receptor Agonist Antibody Conjugate, intended for systemic delivery of T-CpG, a potent TLR9 agonist

TRAAC platform



TAC-001



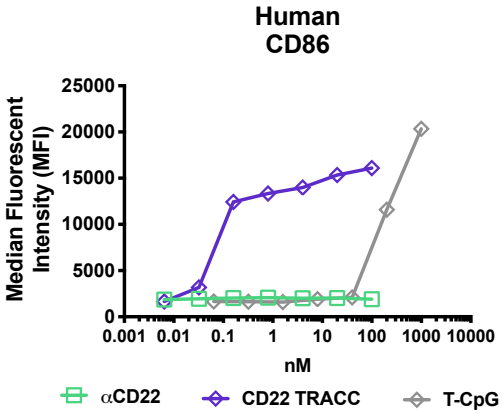
Antibody: anti-CD22
- Targets B cells expressing CD22
- Cross-reactivity towards human and cynomolgus monkey
- Efficient internalization

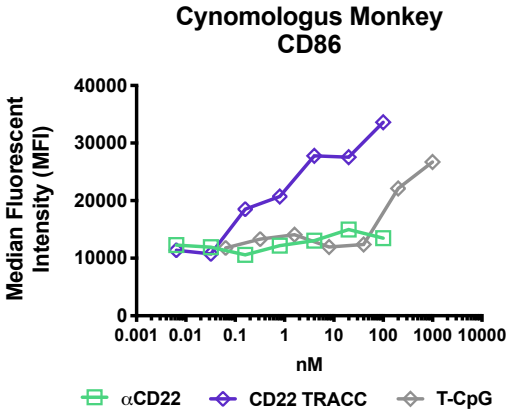
Conjugation: Site-specific

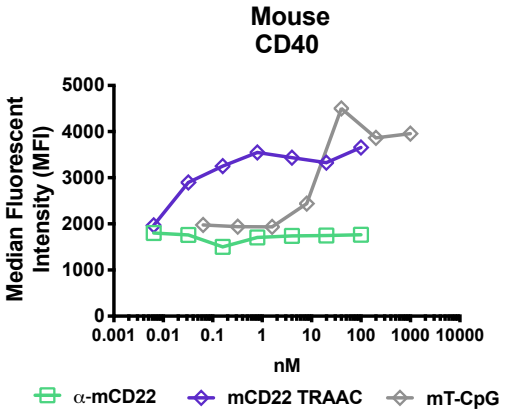
Immune Activator: T-CpG
- Potent TLR9 agonist
- Linear, monomeric, and non-aggregated
- Sequence optimized for potency and stability
- Innovative design enables efficient site-specific conjugation

TALLAC THERAPEUTICS

T-CpG is a potent TLR9 agonist across species



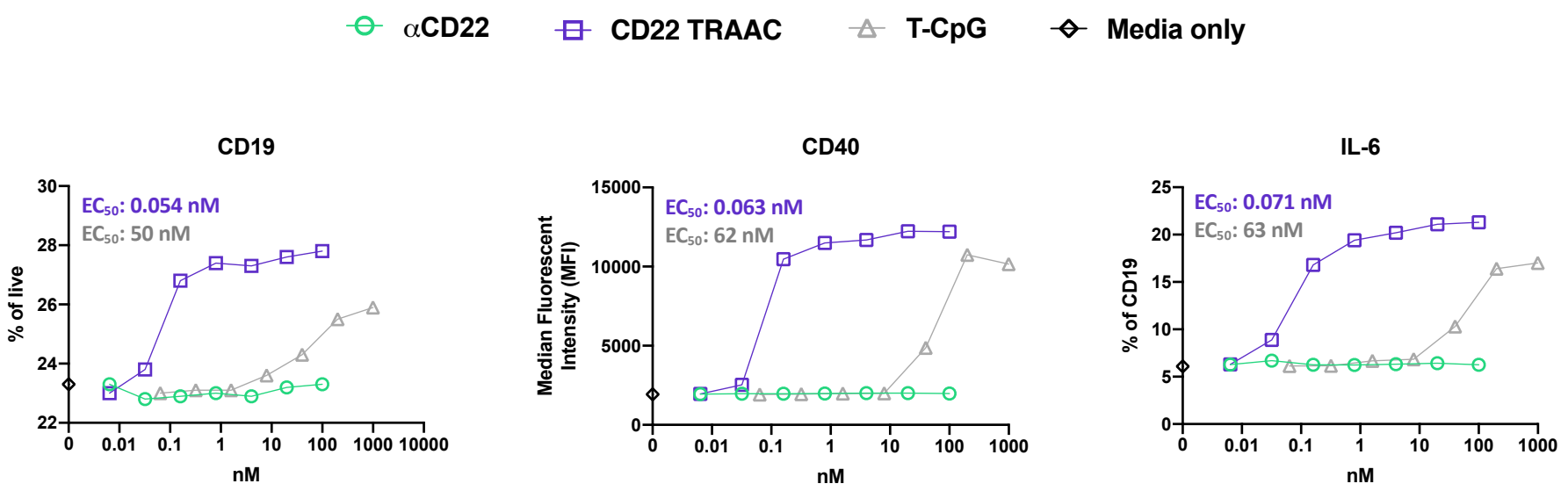




Human, cynomolgus PBMCs, and mouse splenocytes were stimulated with anti-CD22, CD22 TRAAC, or T-CpG for 48hrs and expression of activating receptors were assayed by flow cytometry. Murine CD22 TRAAC comprised of mouse reactive α-CD22 antibody (mCD22) and mouse reactive T-CpG (mT-CpG).

TALLAC THERAPEUTICS

Targeted delivery by CD22 TRAAC leads to superior TLR9 activation in B cells



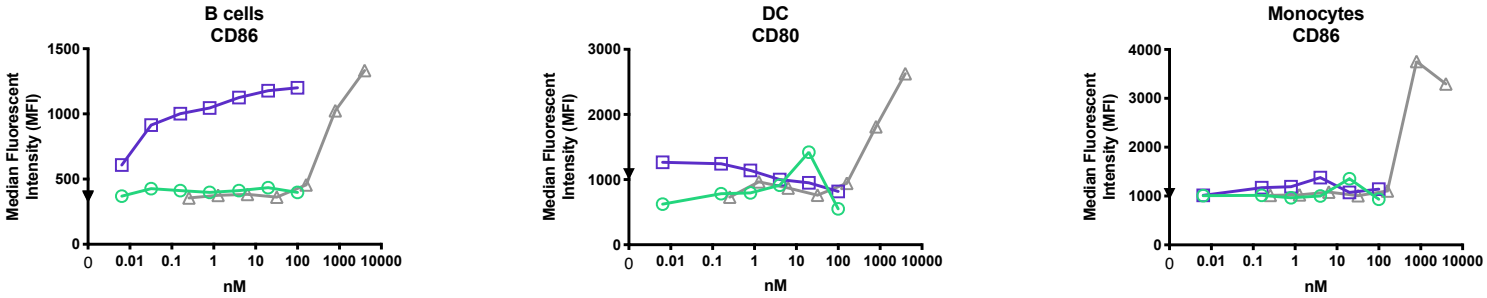
Human PBMCs were stimulated for 48hrs in the presence of anti-CD22, CD22 TRAAC, or T-CpG . Surface marker expression and cytokine were assayed by flow cytometry.

TALLAC THERAPEUTICS

CD22 TRAAC demonstrates specific activation of B cells and T-CpG broadly activates TLR9 expressing cells

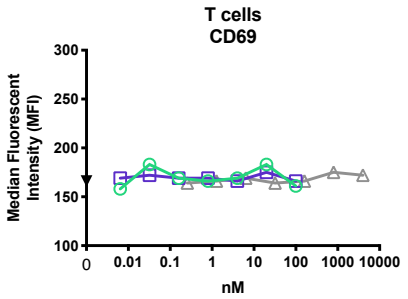
αCD22 CD22 TRAAC T-CPG media only

TLR9 positive cells



Cell type	TLR9 activation
(p)DC	✓
B cell	✓
monocytes	✓

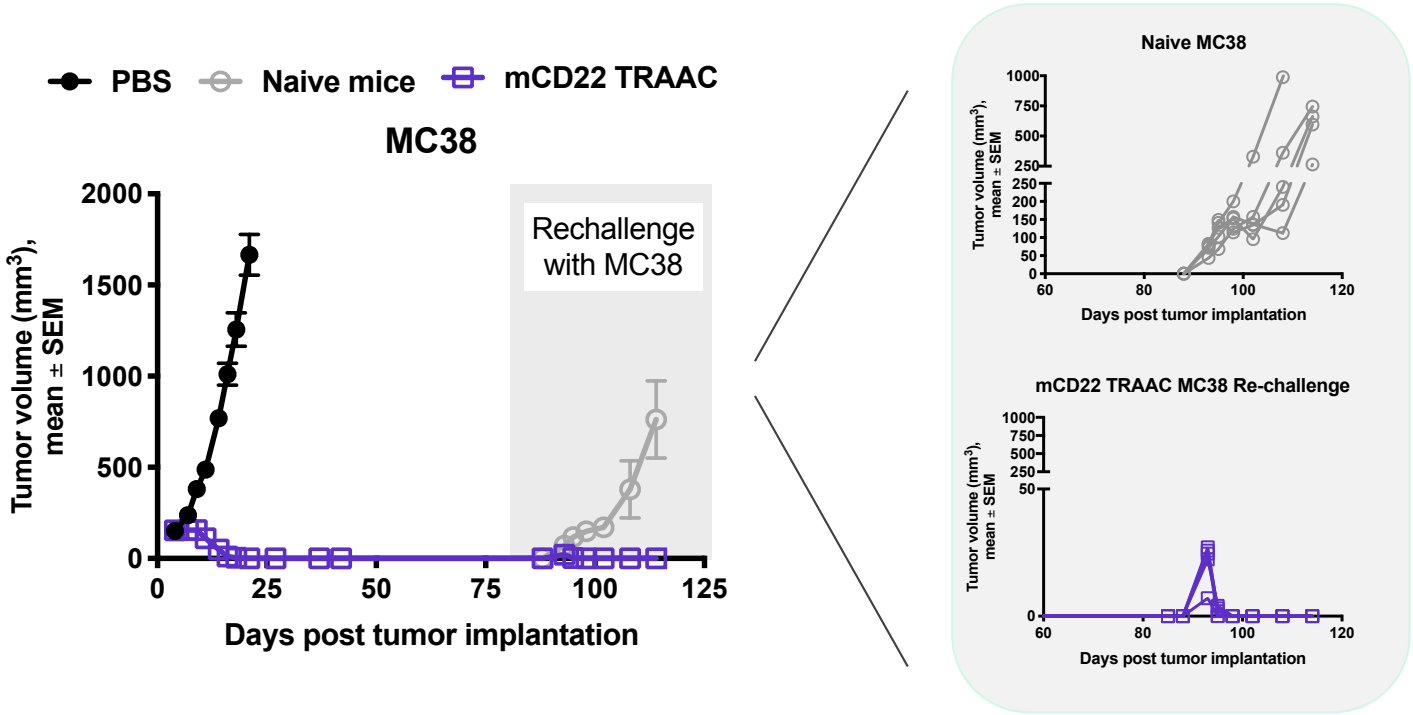
TLR9 negative cells



Human PBMCs were stimulated for 18hrs in the presence of anti-CD22, CD22 TRAAC, or T-CpG . Surface marker expression was assayed by flow cytometry.

TALLAC THERAPEUTICS

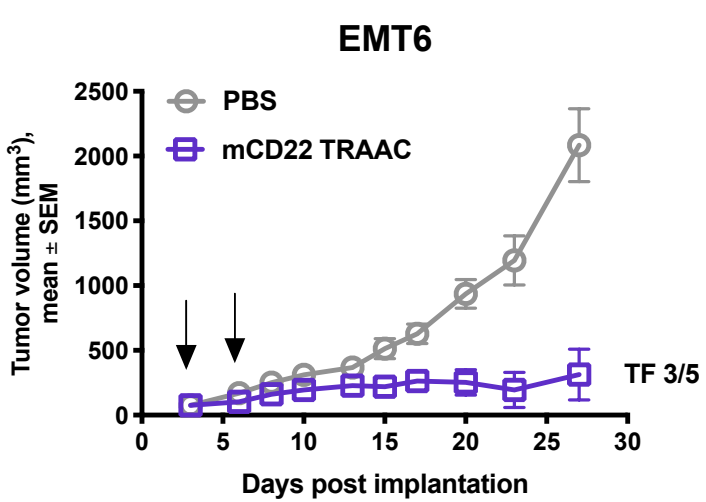
mCD22 TRAAC demonstrates robust single agent activity and memory response in tumor model

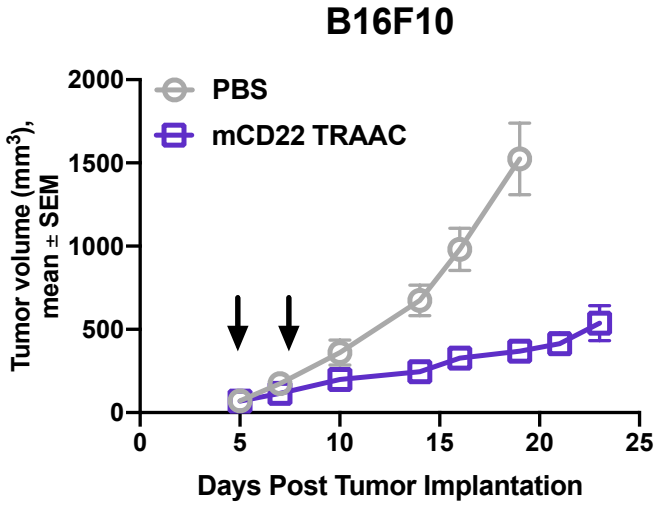


Tumor eradicated mice from MC38 tumor-bearing mice following 10mg/kg 2q3d systemic treatment with CD22 TRAAC were re-challenged 60-70 days post-initial tumor clearance. mCD22 TRAAC is mouse reactive CD22 antibody conjugated to mouse reactive T-CpG. Naïve age-matched mice were used as control for tumor growth.

TALLAC THERAPEUTICS

mCD22 TRAAC exhibits potent single agent activity in CPI refractory tumor models

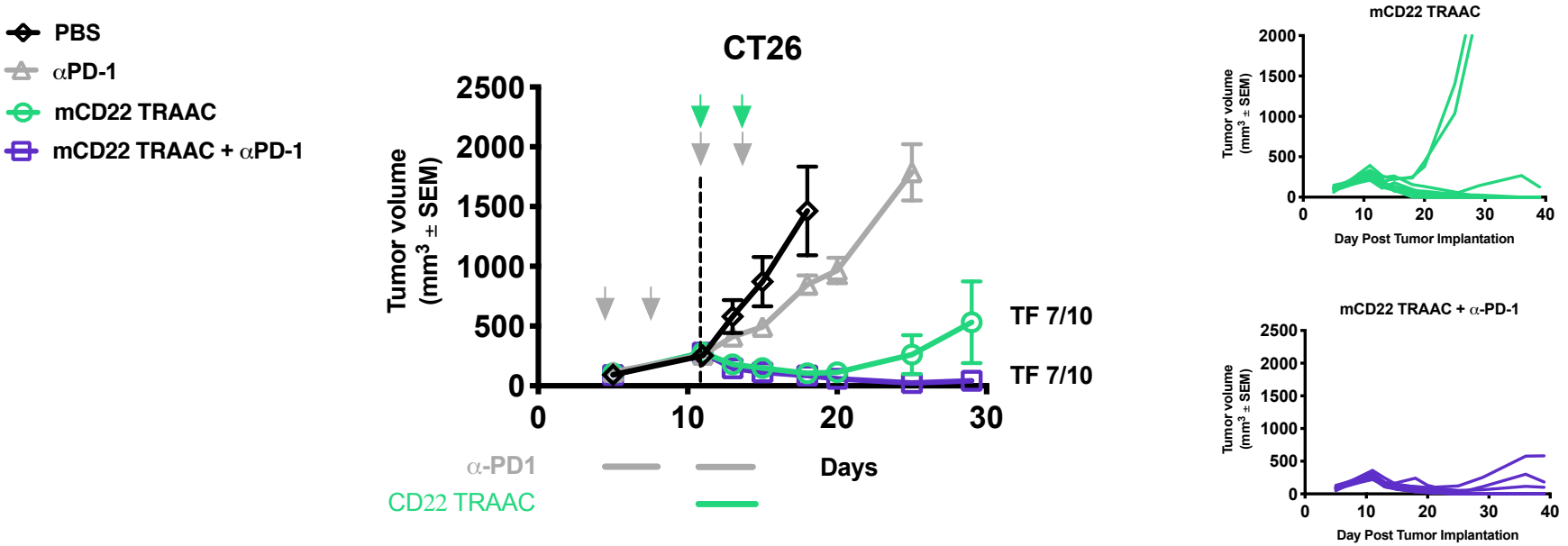




Mice bearing (A) EMT6 and (B) B16F10 were treated intraperitoneally with PBS or mCD22 TRAAC at 10 mg/kg and 30 mg/kg, respectively. Arrows indicate doses administered. TF, tumor free.

TALLAC THERAPEUTICS

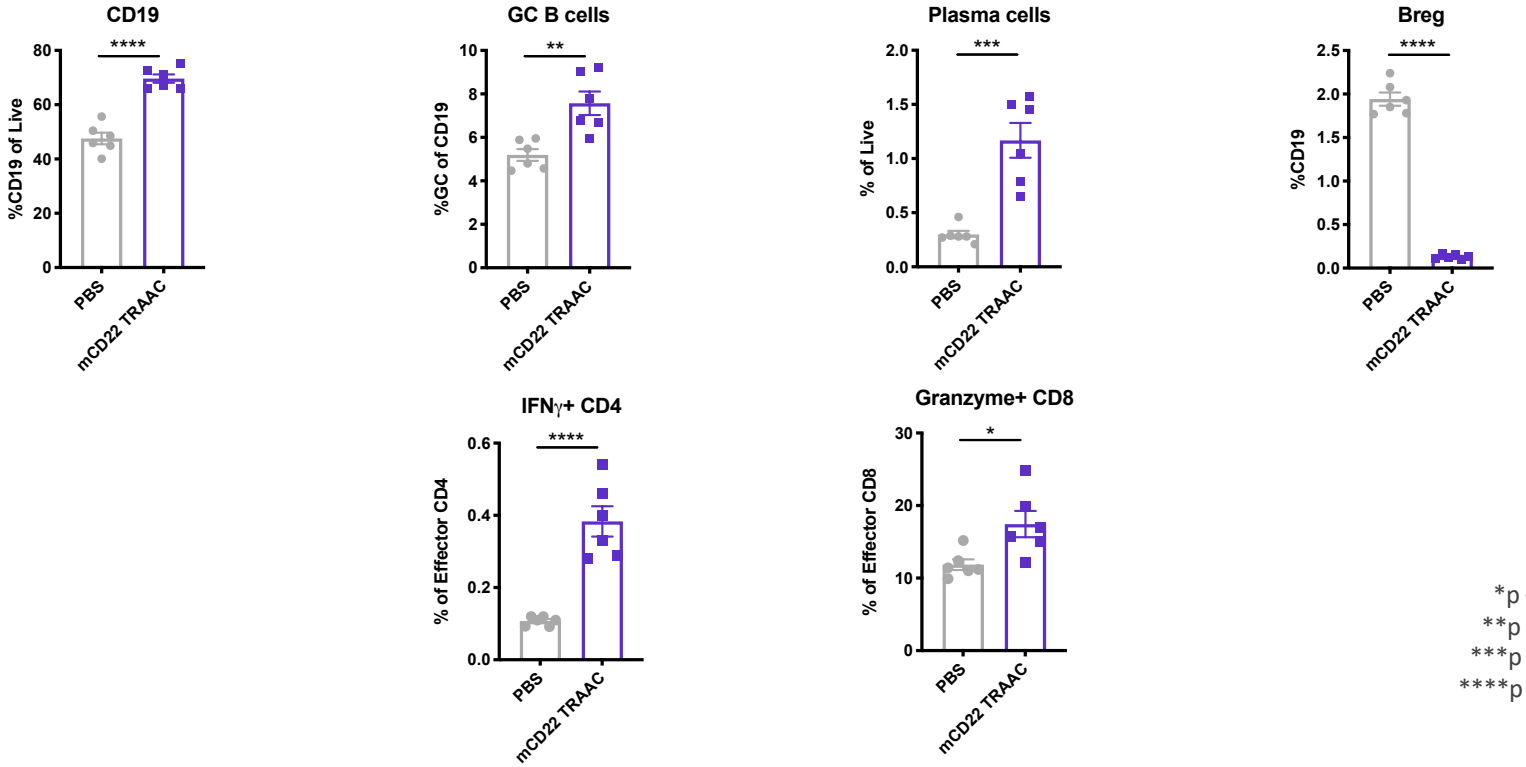
mCD22 TRAAC exhibits potent single agent activity in CT26 PD-1 resistant model



Mice bearing CT26 were dosed intraperitoneally with anti-PD-1 twice, three days apart at 10mg/kg. Mice resistant to two doses of anti-PD-1 treatment on day 11 were randomized and treated with PBS, anti-PD-1, mCD22 TRAAC or combination of anti-PD-1 and mCD22 TRAAC. Arrows indicate doses administered. TF, tumor free.

TALLAC THERAPEUTICS

mCD22 TRAAC stimulates induction of functional B and T cells in the spleen

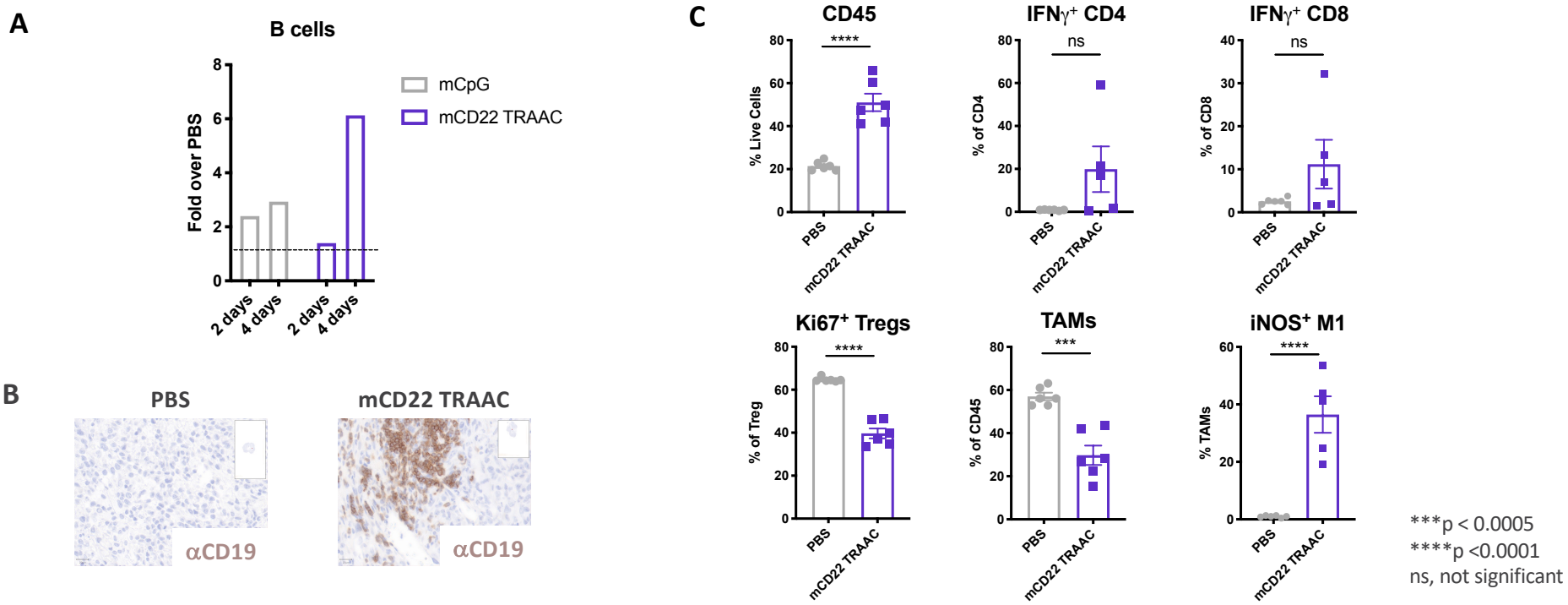


*p <0.05
**p < 0.005
***p < 0.0005
****p <0.0001

Mice bearing CT26 were dosed intraperitoneally with PBS and mCD22 TRAAC twice, 3 days apart at 10 mg/kg. Spleens were harvested two days post last dose. Cell surface expression were analyzed by flow cytometry to identify cellular subsets. P-values were calculated using two-tailed unpaired t-test.

TALLAC THERAPEUTICS

mCD22 TRAAC increases B cell infiltration and engenders a pro-inflammatory tumor microenvironment

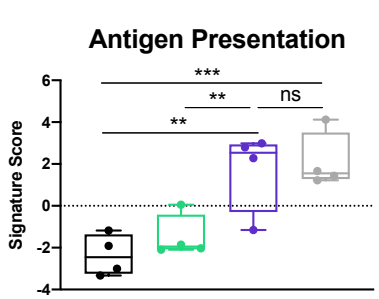


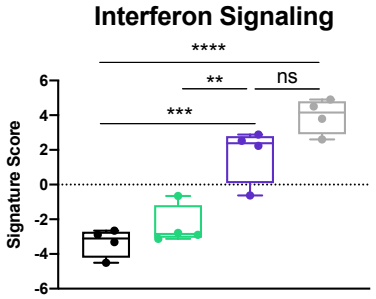
Mice bearing EMT6 were dosed intraperitoneally with PBS or mCD22 TRAAC once at 10 mg/kg. Tumors were harvested two and four days (A) or 11 days (B) post dose. B cells in the tumor were assessed by flow cytometry (A) and immunohistochemistry (B). Mice bearing CT26 (C) were dosed intraperitoneally twice, three days apart with PBS and mCD22 TRAAC at 10 mg/kg. Tumors were harvested two days post last dose and assessed by flow cytometry. P-values were calculated using two-tailed unpaired t-test.

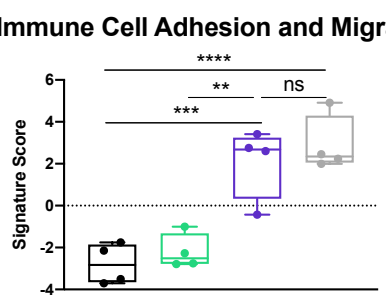
TALLAC THERAPEUTICS

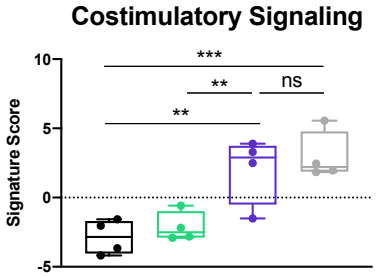
Systemic administration of mCD22 TRAAC triggers rapid innate and adaptive immune signatures similarly to intra-tumoral injection of T-CpG within tumor microenvironment

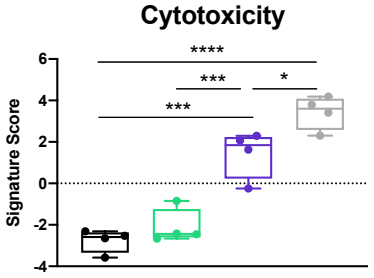
PBS
α-mCD22
mCD22 TRAAC
mT-CpG

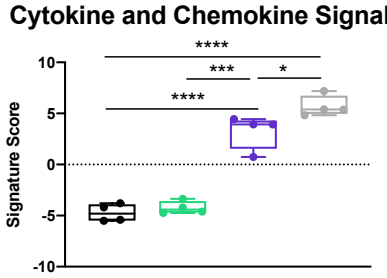












*p <0.05
**p < 0.005
***p < 0.0005
****p <0.0001
ns, not significant

Mice bearing CT26 were dosed intraperitoneally with PBS, anti-mCD22 and mCD22 TRAAC intraperitoneally at 10 mg/kg. Mouse mT-CpG was injected intratumorally at 50ug/mouse. Tumors were harvested 8hrs post-dose for NanoString analysis. Raw data was normalized and visualized using nSolver software by NanoString. P-values were calculated using two-way ANOVA with Tukey's correction for multiple comparison.

TALLAC THERAPEUTICS

Summary

- CD22 TRAAC triggers B cell activation with 1000-fold increased potency relative to free T-CpG *in vitro*.
- mCD22 TRAAC demonstrates robust, curative and durable single agent anti-tumor activity in CPI resistant and refractory tumor models.
- Systemic administration of mCD22 TRAAC engages both innate and adaptive immunity by increasing tumor B cell infiltration, T cell effector functions and modulation in suppressive myeloid cells within the tumor microenvironment.
- Systemic administration of mCD22 TRAAC shows similar NanoString defined immune signatures as intra-tumoral injection of mT-CpG.
- TAC-001 is in preclinical development for patients with solid tumor malignancies.