Preclinical impact of pretreatment with CRS mitigation agents on pharmacodynamic response to TAK-500, a systemically delivered CCR2-targeted STING agonist iADC

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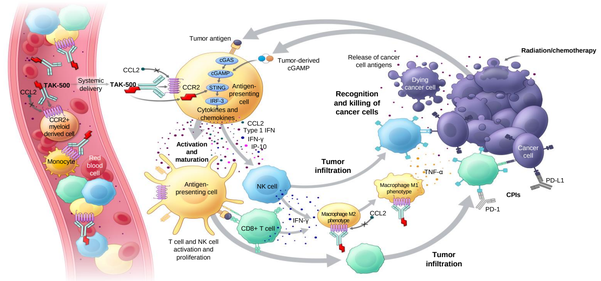
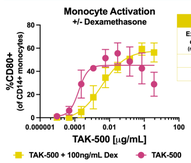
Background

- Stimulator of interferon genes (STING) agonist treatment promotes innate immune cell activation and subsequently mobilizes adaptive immune responses, supporting their clinical investigation as immunotherapies[1]
- TAK-500 is a first-in-class immunostimulatory antibody-drug conjugate (iADC) that selectively delivers the novel systemic STING agonist dazostinag (TAK-676) to CCR2-positive myeloid cells, resulting in enhanced immunity and antitumor efficacy in preclinical models[2,3]
- Historically, treatment with STING agonists has been associated with drug-mediated immunotoxicities and increasing evidence suggests that myeloid populations may be the primary mediators of cytokine release syndrome (CRS)
- Due to the unique mechanism of action of TAK-500, we evaluated the impact of pretreatment with agents used for mitigation of CRS, dexamethasone or tocilizumab, on the pharmacodynamic activity of TAK-500 and mTAK-500 murine surrogate in preclinical *ex vivo* and *in vitro* models

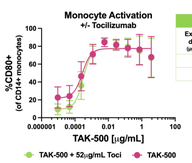


cGAMP, cyclic guanosine monophosphate adenosine monophosphate; cGAS, cyclic guanosine monophosphate adenosine monophosphate synthase; CPI, checkpoint inhibitor; IFN, interferon; IP-10, interferon gamma induced protein 10; IRF-3, interferon regulatory transcription factor 3; NK, natural killer; PD-L1, programmed cell death ligand; PD-1, programmed cell death protein 1; TNF, tumor necrosis factor.

TAK-500-driven monocyte activation is minimally impacted by dexamethasone or tocilizumab pretreatment *ex vivo*



Dexamethasone		
Ex vivo dose (ng/mL)	Clinical dose (mg)	TAK-500 EC_{50} ± SD (ng/mL)
0	-	0.15 ± 0.4
100	18	3.1 ± 14.8

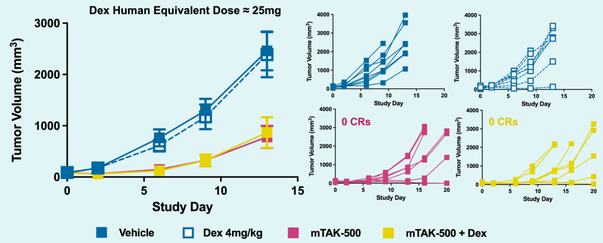


Tocilizumab		
Ex vivo dose (μg/mL)	Clinical dose (mg/kg)	TAK-500 EC_{50} ± SD (ng/mL)
0	-	0.28 ± 0.6
52	8	0.30 ± 1.2

Human PBMC (three donors) pre-treated with dexamethasone or tocilizumab at clinically relevant doses 1 hour prior to TAK-500 treatment *ex vivo* showed no significant differences in EC_{50} values for CD80 upregulation, as measured by flow cytometry, on total CD14+ monocytes with pre-treatment agents vs. TAK-500 alone. Toci, tocilizumab; EC_{50}, half maximal effective concentration; SD, standard deviation.

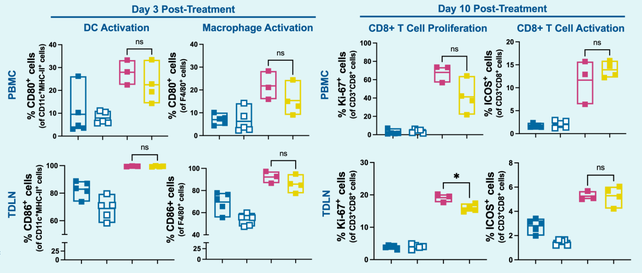
mTAK-500 treatment results in antitumor efficacy and activation of innate and adaptive immune responses in tumor-bearing mice, which are minimally impacted by pretreatment with CRS mitigation agents

Pretreatment with dexamethasone has no negative impact on mTAK-500-driven efficacy in MC38 tumor-bearing mice



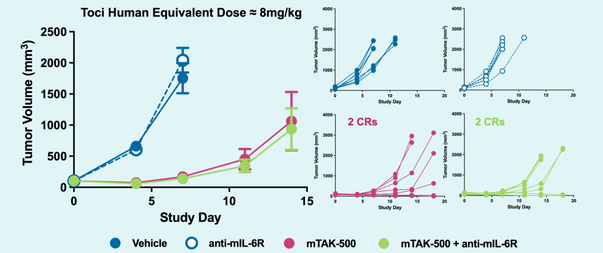
MC38 tumor-bearing mice were treated with dexamethasone (4mg/kg, IP) 1 hour prior to administration of a single efficacious dose of mTAK-500 (IV) on Day 0. For evaluation of immune responses, mice were euthanized on Day 3 and 10 post-treatment; peripheral blood mononuclear cells (PBMC), tumor-draining lymph node (TDLN), and tumor were harvested for analysis by flow cytometry. CR, complete response.

Pretreatment with dexamethasone has no negative impact on mTAK-500-driven innate immune or T cell activation *in vivo*



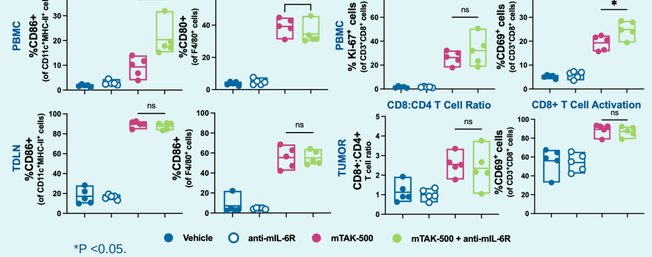
*P <0.05.

Pretreatment with anti-mIL-6R has no negative impact on mTAK-500-driven efficacy in MC38 tumor-bearing mice



MC38 tumor-bearing mice were treated with a murine surrogate for tocilizumab, anti-mIL-6R clone 15A7 (IP, 8mg/kg), 1 hour prior to administration of a single efficacious dose of mTAK-500 (IV) on Day 0. For evaluation of immune responses, mice were euthanized on Day 3 and 8 post-treatment; PBMC, TDLN, and tumor were harvested for analysis by flow cytometry.

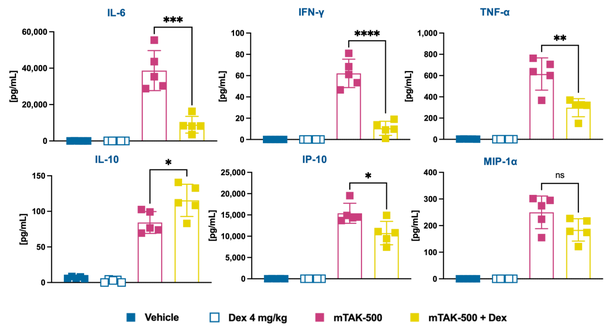
Pretreatment with anti-mIL-6R has no negative impact on mTAK-500-driven innate immune or T cell activation *in vivo*



*P <0.05.

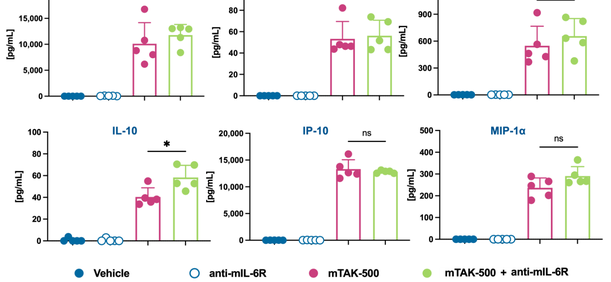
Key take away Pretreatment of mTAK-500 with dexamethasone or an anti-mIL-6R antibody has no negative impact on STING-mediated innate immune activation, mobilization of adaptive immune responses, or antitumor efficacy in MC38 tumor-bearing mice.

Pretreatment with dexamethasone results in suppression of mTAK-500-driven proinflammatory cytokine secretion *in vivo*



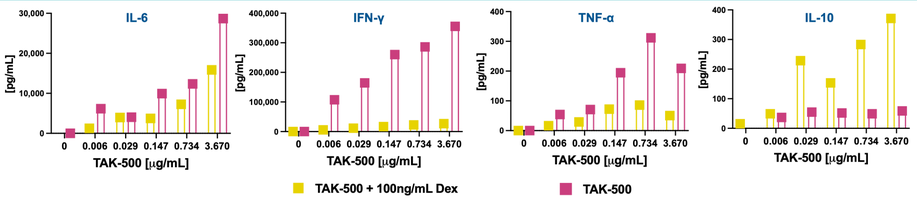
MC38 tumor-bearing mice were pretreated with dexamethasone (4mg/kg) followed by mTAK-500. Serum was collected 6 hours post-dosing and evaluated by MSD. Pretreatment with dexamethasone dampened TAK-500-driven proinflammatory cytokine secretion, which was consistent with ex vivo findings. *P <0.05; **P <0.01; ***P <0.001; ****P <0.0001.

Pretreatment with anti-mIL-6R results in less suppressive cytokine profiles compared to dexamethasone following mTAK-500 treatment *in vivo*



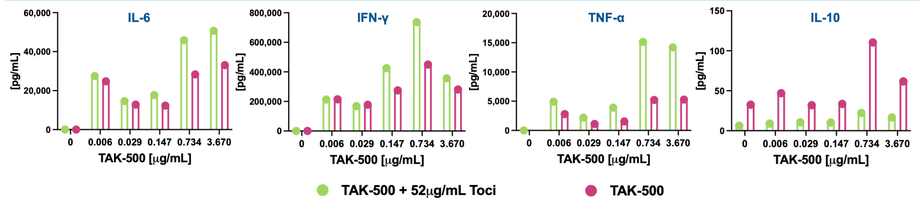
MC38 tumor-bearing mice were pretreated with anti-mIL-6R (8mg/kg) followed by mTAK-500. Serum was collected 6 hours post-dosing and evaluated by MSD. Pretreatment with anti-mIL-6R maintained a more proinflammatory mTAK-500-driven cytokine milieu, which was consistent with ex vivo findings.
*P <0.05.

Dexamethasone pretreatment limits TAK-500-driven secretion of proinflammatory cytokines and enhances secretion of anti-inflammatory IL-10 in human PBMC *ex vivo*



Supernatants from healthy human PBMC treated *ex vivo* (as described above) were evaluated by Meso Scale Discovery (MSD) multiplex assay and demonstrated dampened secretion of key CRS mediators, including IL-6, IFN-γ, TNF-α, and an increase in IL-10 with dexamethasone pretreatment compared to TAK-500 alone.

Tocilizumab pretreatment increases TAK-500-driven proinflammatory cytokines and suppresses secretion of anti-inflammatory IL-10 in human PBMC *ex vivo*



Supernatants from healthy human PBMC were evaluated by MSD and demonstrated enhanced secretion of IFN-γ and TNF-α, accumulation of soluble IL-6, and a decrease in IL-10 with tocilizumab pretreatment compared to TAK-500 alone, thereby maintaining a more proinflammatory milieu compared to dexamethasone.

Conclusions

- Here we demonstrate that pretreatment with dexamethasone successfully dampens pro-inflammatory cytokine release while maintaining (m)TAK-500-mediated immune cell activation and antitumor activity *ex vivo* and *in vivo*
- Compared to dexamethasone, pretreatment with IL-6R-blocking antibodies maintained a more proinflammatory cytokine milieu following (m)TAK-500 treatment *ex vivo* and *in vivo*
- Impact on IP-10 and MIP-1α secretion was less evident following pretreatment with either agent, which may suggest their important roles in mediating TAK-500-driven immune cell modulation and antitumor efficacy
- Clinically, these pretreatment strategies have been effective in mitigating immunotherapy-associated CRS with T cell therapies
- Our data suggest both agents may be viable pretreatment approaches to mitigate STING-induced immunotoxicities in patients, without negatively affecting immune cell modulation or antitumor efficacy despite altered cytokine profiles

References

1. Cunniff EC, et al. *Cancer Res Commun*. 2022;2(6):489–502
2. Diamond JR, et al. *Cancer Res.* 2022;82(Suppl 12):Abstract CT249
3. Appleman V, et al. *J ImmunoTher Cancer*. 2022;10(Suppl 2):Abstract 1153

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Disclosures

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