Poster 1026

mTFF2-MSA (mTNX-1700*) Suppresses Tumor Growth and Increases Survival in an Anti-PD-1 Treated MC38 Colorectal Cancer Model by Targeting MDSCs

Bruce L. Daugherty[1], Rebecca J. Boohaker[2], Rebecca Johnstone[2], Karr Stinson[2], Jin Qian[3], Timothy C. Wang[3], Seth Lederman[1]

[1]Tonix Pharmaceuticals, Inc., 26 Main Street, Suite 101, Chatham, NJ 07928; [2]Southern Research, 2000 9th Ave S, Birmingham, AL 35205; [3]Division of Digestive and Liver Diseases, Irving Cancer Research Center, Columbia University Medical Center, New York, NY 10032

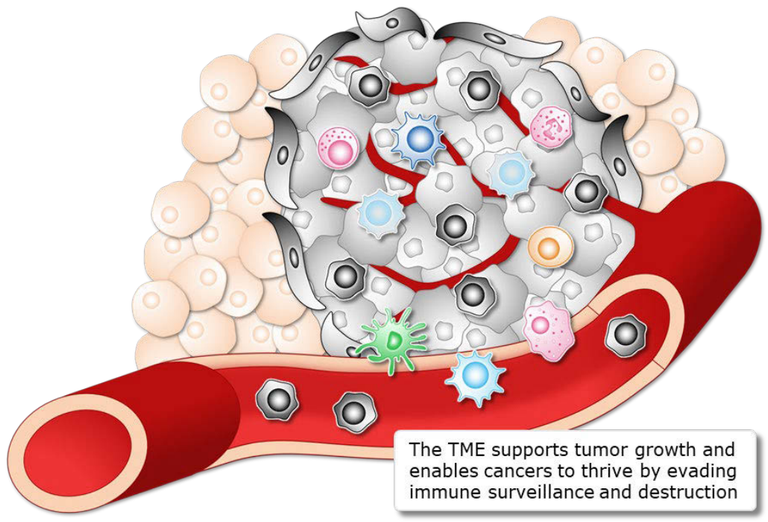
*TNX-1700 is an investigational new biologic and has not been approved for any indication

Abstract

Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment are a potential therapeutic target in immune checkpoint cancer therapy, but improved survival has yet to be shown targeting MDSCs. It has previously been demonstrated that trefoil factor family 2 (TFF2), a secreted anti-inflammatory peptide, can partially suppress MDSC expansion and partially activate tumor immunity through agonism of the CXCR4 receptor[1-3]. We investigated whether a novel recombinant fusion protein, designated murine TNX-1700, which contains murine TFF2 fused to murine serum albumin (mTFF2-MSA), can improve survival in an anti-PD-1 treated syngeneic mouse model of colorectal cancer (CRC). The fusion protein was designed with the goal of increasing half-life and reducing dose frequency. We developed a model using MC38 CRC cells grafted subcutaneously into C57BL/6 mice. Mice subsequently received either mTFF2-MSA, anti-PD-1 antibody (clone 29F.1A12), or both, and tumor volume, and survival were measured. Flow cytometry was performed to examine treatment-induced effects on immune profiles. Administration of mTFF2-MSA suppressed tumor growth (TGI 50%), while the combination of mTFF2-MSA and anti-PD-1 antibody had an additive effect and suppressed tumor growth dramatically (TGI 87%). Mice receiving both mTFF2-MSA, and anti-PD-1 exhibited a survival rate of 90% after 50 days, while vehicle and single mTFF2-MSA therapy were 30% and 60%, respectively. The percentage of exhausted CD8+ T cells was markedly reduced in the draining lymph node by the combination treatment, as measured by flow cytometry using antibodies against LAG3, TIM3, and PD-1. mTFF2-MSA in combination with checkpoint inhibition via anti-PD-1 antibody is additive in an advanced syngeneic mouse model of colorectal cancer.

Introduction

Tumors Create a Toxic, Immunosuppressive Microenvironment (TME)



Key

- *Healthy cell*
- *Malignant cell*
- *Myeloid-derived suppressor cell (MDSC)*
- *Cancer-associated fibroblast*
- *Exhausted CD8 T cell*
- *Cytotoxic CD8 T cell*
- *CD4 T cell*
- *Dendritic cell (DC)*
- *B cell*
- *Natural Killer (NK) cell*
- *Macrophage*
- *Neutrophil*

- Tumors are surrounded by endothelial and stroma cells, and invading immune cells, both innate and adaptive[4,5]
- Complex regulatory network supports tumor growth, enabling cancers to thrive by evading immune surveillance and destruction[5,6]
- The TME sabotages tumor-killing cytotoxic CD8 T cells[1]
- Myeloid-derived suppressor cells (MDSCs) interfere with anticancer immunity[5,6]

MDSCs are a Major Therapeutic Target

- Levels of MDSCs tend to correlate with tumor stage, patient survival, and metastatic burden and may predict poor response to certain cancer treatments[7]
- MDSCs represent a central mechanism of immunosuppression in cancer; targeting these cells could significantly improve our ability to fight cancer[8,9]
- **Therapeutic Strategies Include[9]:**
  - Promoting differentiation of MDSCs to a non-immunosuppressive cell type
  - Blocking MDSC immunosuppressive functions
  - Inhibiting MDSC expansion
  - Eliminating MDSCs

Results

Fig. 1: mTFF2-MSA is a Novel Fusion Protein

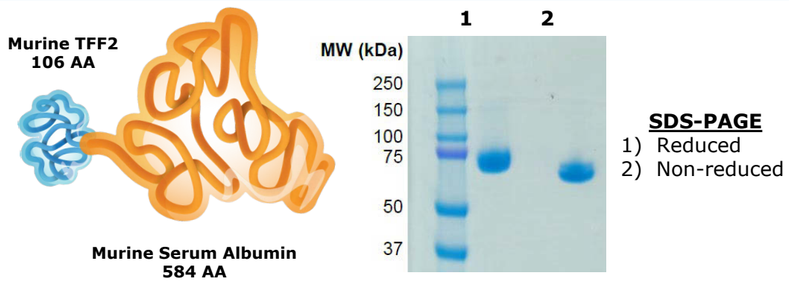


Fig. 2: Schematic of Syngeneic MC38 CRC Tumor Model

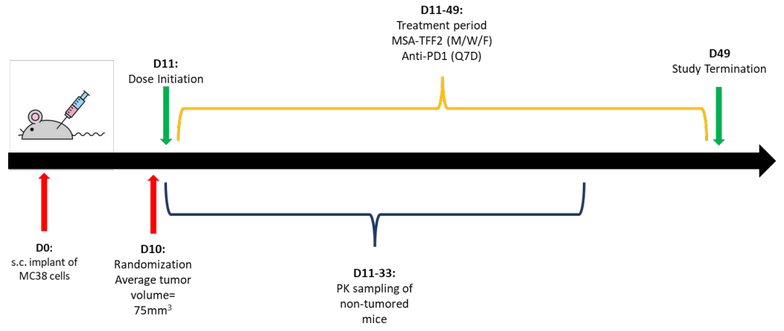


Fig. 3: Pharmacokinetic Analysis of mTFF2-MSA in Mice

- Dose: 40 mg/kg i.p.
- N = 3/group
- Murine TFF2 ELISA on mouse serum

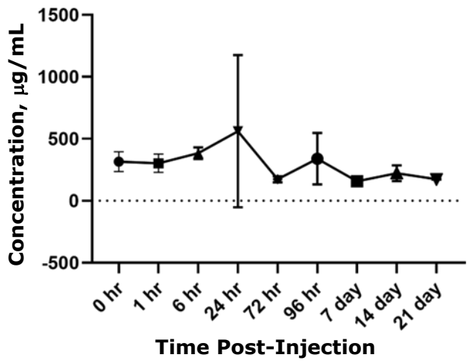


Fig. 4: Inhibition of Tumor Growth in the MC38 CRC Model

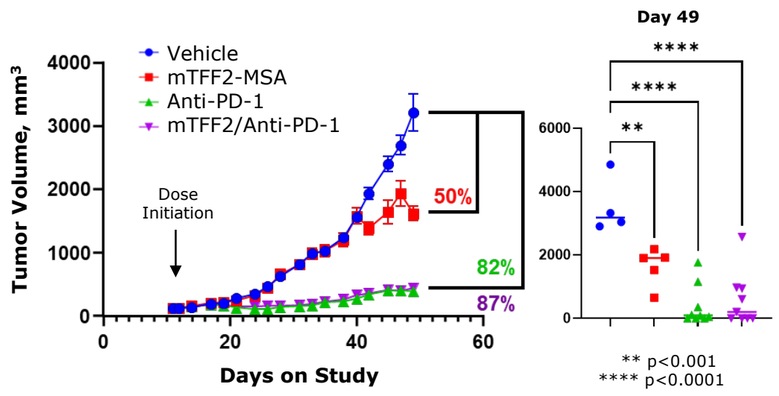
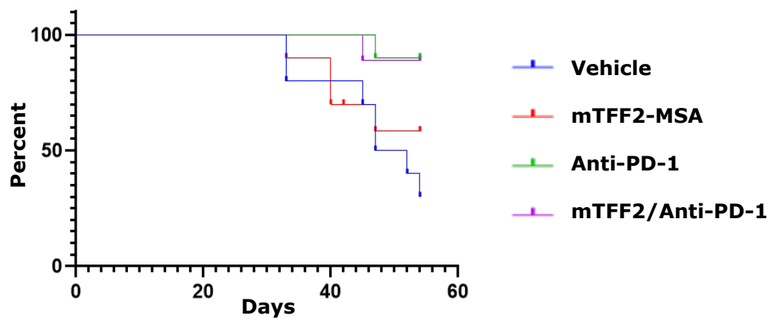


Fig. 5: Probability of Survival in the MC38 CRC Model



Hazard Ratio (Mantel-Haenszel)	Vehicle/mTFF2-MSA	Vehicle/Anti-PD-1	Vehicle/Combo
Ratio	2.57	5.46	5.08
95% CI	0.74 – 8.92	1.50 – 19.88	1.36 – 18.95

Fig. 6: Inhibition of Tumor Growth in the CT26.wt CRC Model

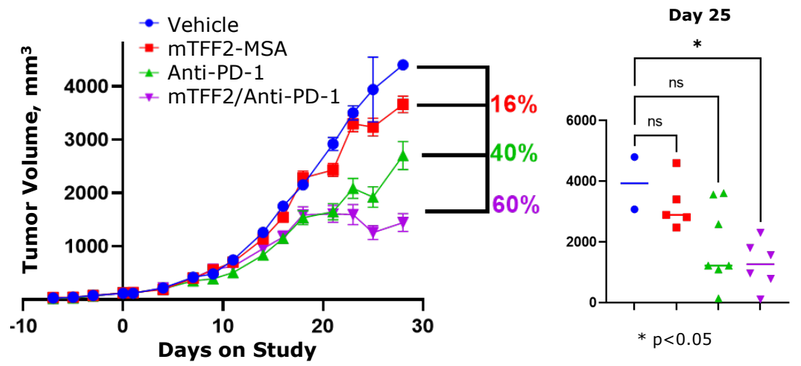
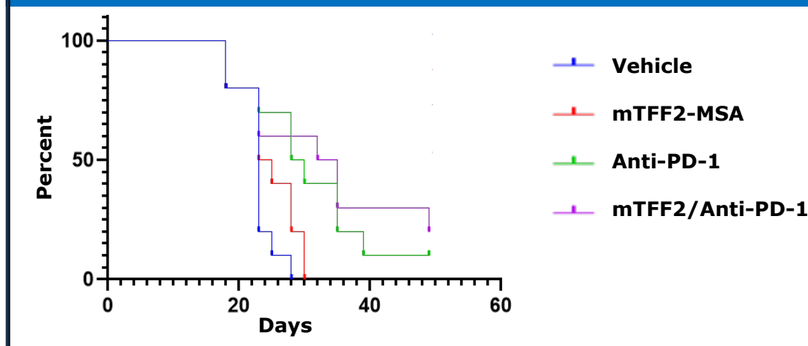


Fig. 7: Probability of Survival in the CT26.wt CRC Model



Hazard Ratio (Mantel-Haenszel)	Vehicle/mTFF2-MSA	Vehicle/Anti-PD-1	Vehicle/Combo
Ratio	2.57	5.46	5.08
95% CI	0.74 – 8.92	1.50 – 19.88	1.36 – 18.95

Conclusions

- mTFF2-MSA (mTNX-1700) is a novel fusion protein and exhibits an extended half-life *in vivo* in mice.
- In the MC38 mouse model of colorectal cancer, mTFF2-MSA alone inhibited tumor growth by 50%, and is additive with anti-PD-1 by inhibiting tumor growth by 87%.
- In the MC38 model, survival was 90% in the combination treated group after 50 days, with 40% exhibiting a complete response, while 20% survived in the untreated group.
- In the CT26.wt mouse model of colorectal cancer, mTFF2-MSA alone inhibited tumor growth by 16%, and is additive with anti-PD-1 by inhibiting tumor growth by 60%.
- In the CT26.wt model, survival was 60% in the combination treated group after 30 days, while 0% survived in the untreated group.
- TNX-1700 is a novel mechanism for suppressing MDSCs and has the potential to synergize with other immuno-oncology drugs.

References

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