UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): November 8, 2024

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: **(862) 904-8182**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

Tonix Pharmaceuticals Holding Corp. (the "Company") updated its TNX-1700 product candidate presentation, which it intends to place on its website and which may contain nonpublic information. A copy of the product presentation is filed as Exhibit 99.01 and hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.01 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

The Company announced data from a manuscript posted on BioRXIV, which has not been peer-reviewed, titled "*A CXCR4 partial agonist improves immunotherapy by targeting polymorphonuclear myeloid-derived suppressor cells and cancer-driven granulopoiesis.*" The manuscript reports on studies with murine TNX-1700 (mTNX-1700), a soluble fusion protein of murine TFF2 and mouse serum albumin, conducted in collaboration with scientists from Columbia University. The data show that mTNX-1700 synergized with anti-PD-1 monoclonal antibody treatment to induce gastric cancer tumor regression or eradication, inhibited distant metastases, and prolonged survival in several animal models, suggesting that mTNX-1700 treatment targets a suppressor subtype of polymorphonuclear leukocytes, and facilitates the action of anti-PD1 treatment to stimulate a CD8+ T cell anti-cancer immune response.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	**Description**
99.01	TNX-1700 Product Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: November 8, 2024

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Cautionary Note on Forward-Looking Statements

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate" and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the "SEC") on April 1, 2024, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

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[1]human trefoil family factor 2 – human serum albumin fusion protein
[2]myeloid-derived suppressor cells
[3]azoxymethane/dextran sodium sulfate
[4]murine TFF-2 – murine serum albumin fusion protein

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TNX-1700 (hTFF2-HSA) Fusion Protein

Tumor Microenvironment, MDSCs

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TNX-1700*: Gastric and Colorectal Cancers
Recombinant Trefoil Factor 2 (hTFF2) Fusion Protein

Potential New Cancer Treatment
- mTNX-1700 (mTFF2) has effects on cancer by altering the tumor micro-environment
- Mechanism of action: suppresses myeloid-derived suppressor cells and activates anti-cancer CD8+ T cells
- Potential synergy with anti-PD-1 or anti-PD-L1 monoclonal antibodies (mAbs)

Preclinical Evidence for Inhibiting Growth of Cancer Cells
- Data showed that mTFF2-CTP augmented the efficacy of mAb anti-PD-1 therapy. Anti-PD-1 in combination with mTFF2-CTP showed greater anti-tumor activity in PD-L1-overexpressing mice

Licensed from Columbia University
- Developing in partnership under sponsored research agreement

Patents Filed

Market Entry: Immuno-oncology, combination therapy with PD1 blockers for gastric and colorectal cancer

Status: Preclinical

Next Steps: Animal studies ongoing

Differentiator: No product yet identified consistently augments PD1 effects on cold tumors

*TNX-1700 is in the pre-IND stage of development and has not been approved for any indication.

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Colorectal Cancer (CRC) is Common and Lethal

- ~150,000 new cases each year in the US
- ~53,000 expected to die
- 3rd most leading cause of cancer death in women
- 2nd most in men
- Steady increase in incidence in men/women under age 50 at a rate of 2.1%/yr since 1992
- 86% symptomatic at diagnosis, associated with more advanced disease and poorer outcomes
- Financial burden ~ $17B (2018)

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TNX-1700 (hTFF2-HSA): A Potential Treatment for Gastric and Colorectal Cancers

Pre-IND Candidate

Targeting a Condition with Significant Unmet Need

Targeted as a treatment for cancer

- Particularly for gastric and colorectal cancer
- Mechanism of Action (MOA) is different from checkpoint inhibitors
- Potential synergy with anti-PD-1 or anti-PD-L1 monoclonal antibodies

Patents and patent applications directed to recombinant TFF2 (rTFF2)

- Issued patent licensed from Columbia University

Inventor: Dr. Timothy Wang, MD

- Chief, Division of Digestive and Liver Diseases at Columbia University and Cancer Research Center and Silberberg Professor of Medicine
- Investigated the molecular mechanisms of gastrointestinal carcinogenesis for decades
- Leadership roles in gastroenterology and cancer biology fields

Pre-clinical evidence for inhibiting growth of cancer cells

- Several studies have shown rTFF2 to be active in the treatment of cancer[1-2]

[1]Dubeykovskaya Z, et al. Nat Commun. 2016 7:1-11
[2]Dubeykovskaya ZA, et al, Cancer Gene Ther. 2019 26(1-2):48-57

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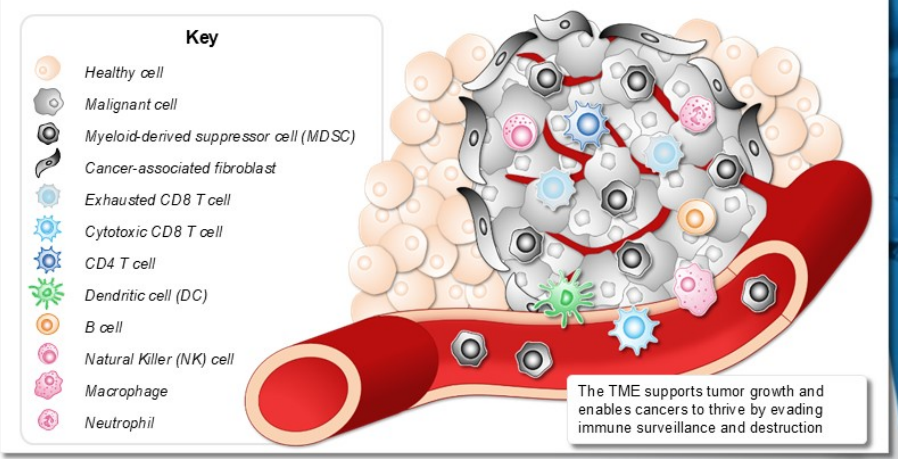
Cancers Create Toxic, Immunosuppressive Tumor Microenvironments (TME)

- Tumors are surrounded by endothelial and stroma cells, and invading immune cells, both innate and adaptive[1,2]
- Complex regulatory network supports tumor growth, enabling cancers to thrive by evading immune surveillance and destruction[2-3]
- The TME sabotages tumor-killing cytotoxic CD8 T cells[1]
- Myeloid-derived suppressor cells (MDSCs) interfere with anticancer immunity[2,3]

Tumors Create a Toxic, Immunosuppressive Microenvironment[1-3]



[1]Belli C, et al. *Cancer Treat Rev.* 2018;65:22-32.
[2]Roma-Rodriguez C, et al. *Int J Mol Sci.* 2019;20(4):840.
[3]Tsai M, et al. *ISRN Biochem.* 2014:351959.

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MDSCs Are a Major Treatment Target

- Levels of MDSCs tend to correlate with tumor stage, patient survival, and metastatic burden and may predict poor response to certain cancer treatments[1]
- MDSCs represent a central mechanism of immunosuppression in cancer; targeting these cells could significantly improve our ability to fight cancer[2,3]
- Therapeutic strategies include[3]:
  - Promoting the differentiation of MDSCs to a non-immunosuppressive cell type
  - Blocking MDSC immunosuppressive functions
  - Inhibiting MDSC expansion
  - Eliminating MDSCs

[1]Condamine T, et al. *Annu Rev Med*. 2015;66:97-110.
[2]Tuccito A, et al. *Virchows Arch*. 2019;474(4):407-420.
[3]Gabrilovitch DI, et al. *Nat Rev Immunol*. 2009;9(3):162-174.

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Trefoil Family Factor 2 (rTFF2) and Cancer Biology

- **TFF2 is a small secreted protein**
  - Encoded by the TFF2 gene in humans
  - Expressed in gastrointestinal mucosa where it functions to protect and repair mucosa
  - TFF2 is also expressed at low levels in splenic memory T cells
  - Upregulated in chronic inflammation
  - Activates the chemokine receptor CXCR4 in cancer cells
    - Blocked by AMD3100 (CXCR4 antagonist) or anti-CXCR4 mAb
- **TFF2 is epigenetically silenced in gastric cancer**
  - Postulated to protect against cancer development through multiple mechanisms
  - Has effects on cancer cells and tumor microenvironment, including marked suppression of MDSCs
  - Knockout of the TFF2 gene leads to faster tumor growth, while overexpression of TFF2 in T cells suppresses tumor growth in a manner dependent on CD8+ T cells.

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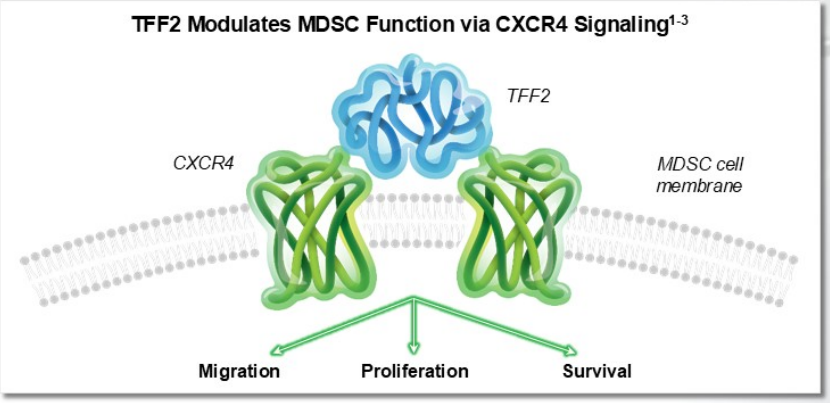
TFF2 Signals Through CXCR4

- Importantly, TFF2 activates CXCR4 and may therefore modulate immune and tumorigenic responses, specifically by reducing the expansion or migration of immunosuppressive MDSCs[1-3]
- TFF2 upregulates ApoE fifty-fold in myeloid progenitor cells; ApoE has been shown to suppress MDSCs[4]



[1]Dubeykovskaya Z, et al. *J Biol Chem.* 2009;284(6):3650-3662.
[2]Balkwill F. *Semin Cancer Biol.* 2004;14(3):171-179.
[3]Teixidó J, et al. *Int J Biochem Cell Biol.* 2018;95:121-131.
[4]Tavazoie MF et al, *Cell* 2018; 172:825-840.

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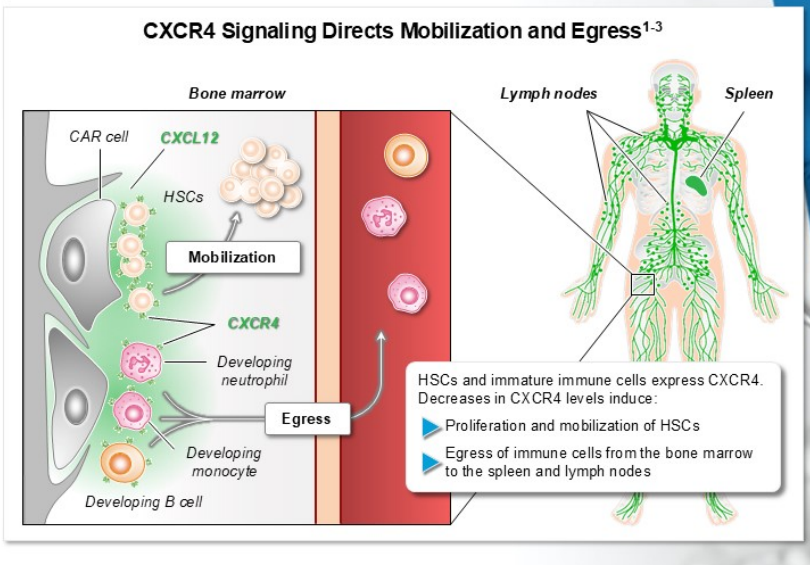
Chemokines Direct Immune Cell Production and Migration

- Immune cells constantly migrate from the blood into and out of lymphoid organs, processes known as homing and egress[1,2]
- Homing and egress are regulated by chemokines[1,2]
- CXCL12-CXCR4 is a crucial chemokine signaling axis that regulates[1-3]:
  - Proliferation and mobilization of hemopoietic stem cells (HSCs)
  - Retention of developing immune cells within the bone marrow



[1]Griffith JW, et al. Annu Rev Immunol. 2014;32:659-702.
[2]Schultz O, et al. Annu Rev Immunol. 2014;34:203-242.
[3]Balkwill F. Semin Cancer Biol. 2004;14(3):171-179.

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Chemoprevention Studies
Murine AOM/DSS Model, mTFF2-MSA

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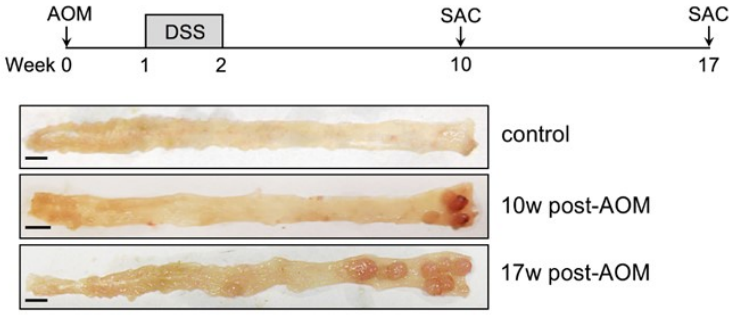
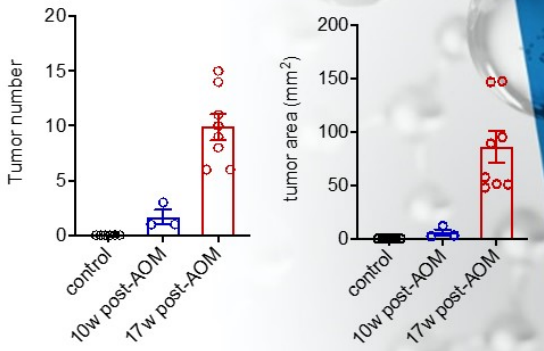
AOM/DSS Induces Colorectal Cancer in a Mouse Model

- The azoxymethane/dextran sodium sulfate (AOM/DSS) model is the most commonly used model of chemically-induced colon carcinogenesis
- Tumors display similar pathological and genetic features as human CRC
- AOM (carcinogen), DSS (inflammatory agent)





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Kim W, et al. *AACR*. 2020 (Poster # 6640)

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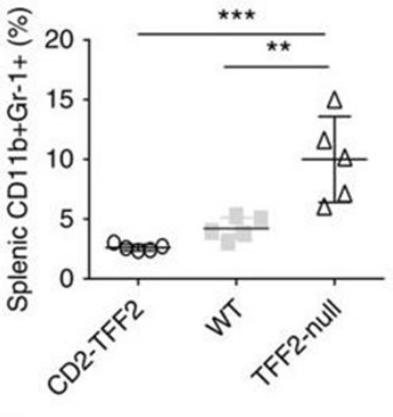
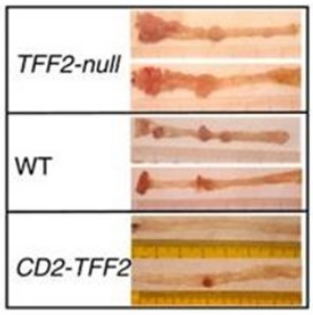
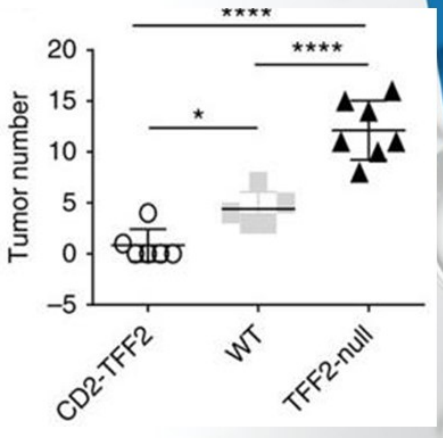
Transgenic Overexpression of mTFF2 Reduces Tumorigenesis *via* Suppression of MDSCs



MDSC number



Colon appearance



Tumor burden

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Dubeykovskaya Z, et al. *Nat Commun.* 2016 7:1-11

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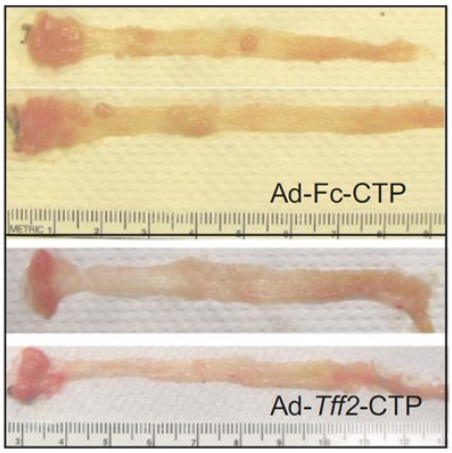
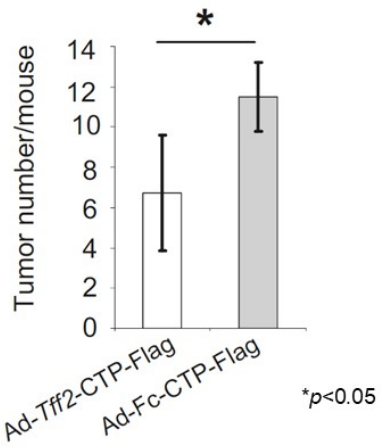
Adenoviral Delivery of mTFF2-CTP-Flag Reduces Tumorigenesis *via* Suppression of MDSCs

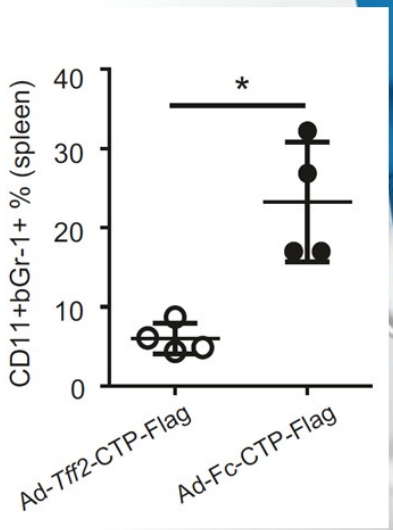


Colon appearance



*p<0.05

Tumor burden



MDSC number

Dubeykovskaya et al, *Cancer Gene Ther* 26:48-57 (2019)

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*p<0.05

TNX-1700 Structure
Domains, CXCR4 Interaction

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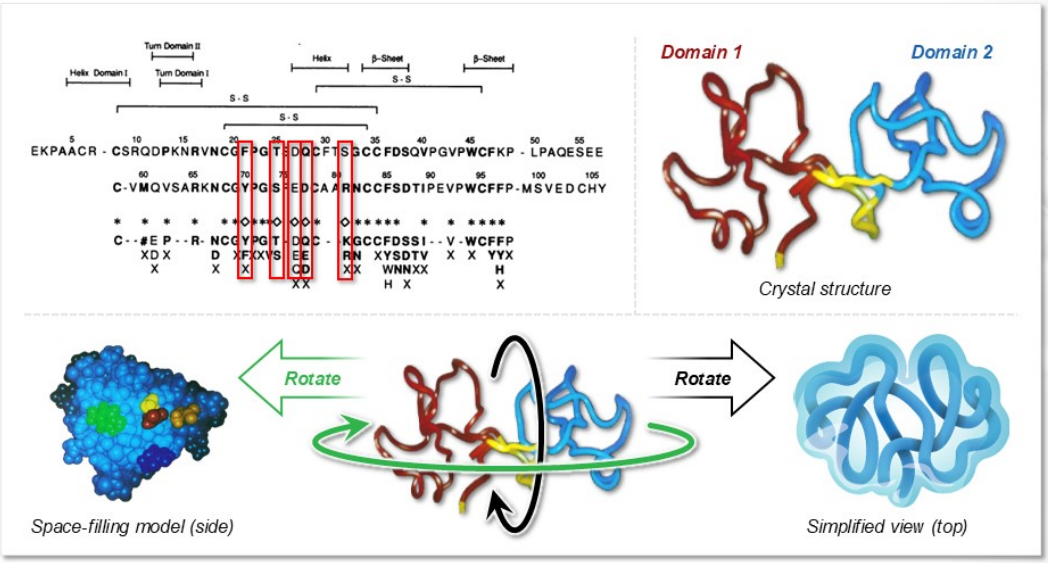
TFF2 Contains 2 Trefoil Domains, Each Containing 5 Conserved Residues



Carr M, et al. *Biochemistry*, 1994 91:2206-2210

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Carr et., PNAS (1994)

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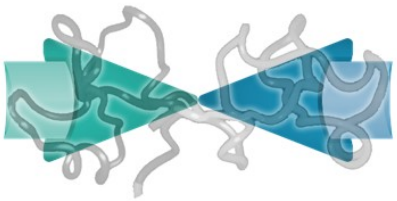
Chimeric rTFF2 Domain (D) Swaps



Wild type = **DI/II**

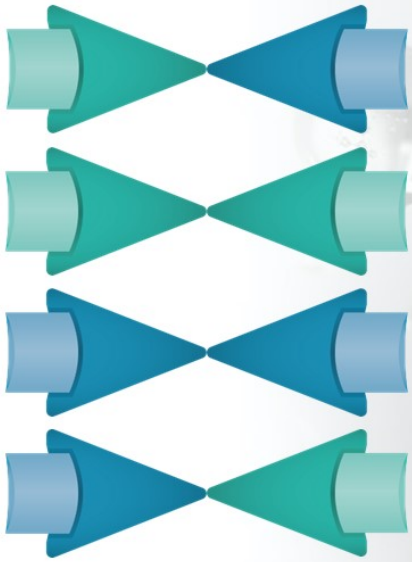
Key

TFF2 Domains (D)	TFF2 Ligand Binding Domains (LBD)
DI	*LBDI*
DII	*LBDII*

DI/I

DII/II

DII/I



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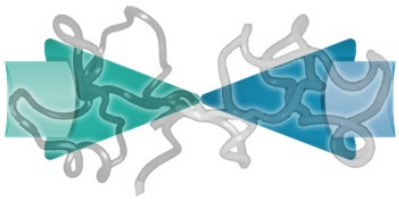
Chimeric rTFF2 Ligand Binding Domain (LBD) Swaps



Wild type = **LBDI/II**

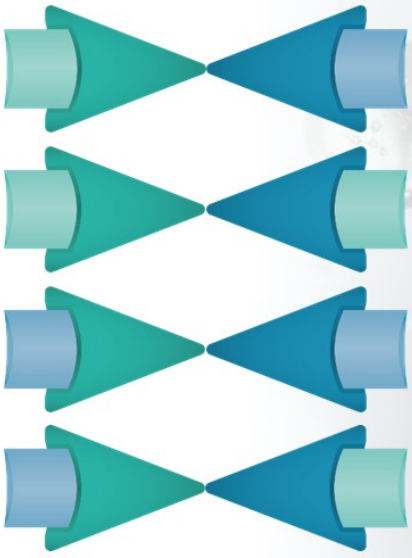
Key

TFF2 Domains (D)	TFF2 Ligand Binding Domains (LBD)
DI	*LBDI*
DII	*LBDII*

LBDI/I

LBDII/II

LBDII/I



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TNX-1700 Protein Design
Albumin Fusion Proteins, Pharmacokinetics

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Strategies for Half-Life Extension: Albumin Fusion

- **Albumin**
  - Most abundant plasma protein
  - Involved in transport of nutrients in the body
  - Interaction with cellular receptors Gp18, Gp30, and Gp60, which regulate transcytosis/endocytosis of albumin across the endothelial cell surface
  - High circulatory half-life of ~ 19 days mediated mainly due to neonatal Fc (FcRn)-mediated recycling
- **Marketed albumin fusions and conjugates**
  - Levemir
  - Eperzan/Tanzeum
  - Victoza
  - Abraxane

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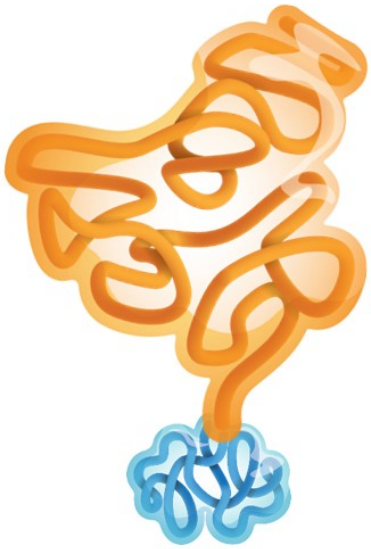
hTFF2-HSA Fusion Protein

Human Serum Albumin



hTFF2

Predicted Mw ~ 78,000 daltons

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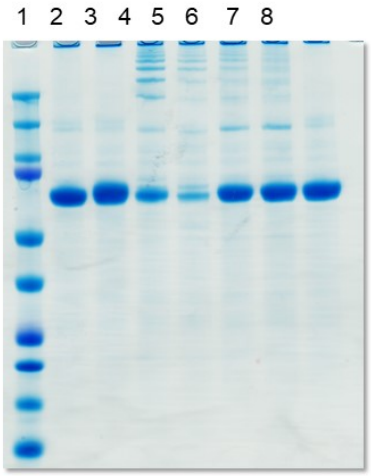
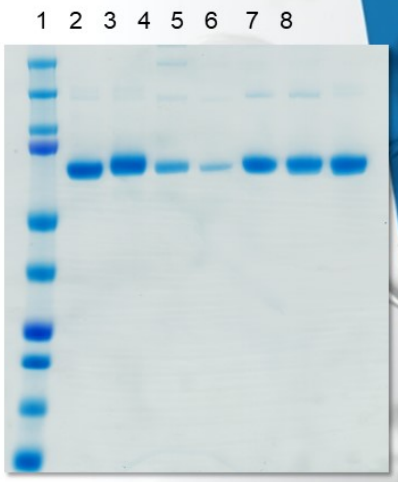
SDS-PAGE of hTF2-HSA Fusion Proteins

Lane 1: Marker
Lane 2: TFF2-HSA [WT]
Lane 3: TFF2-HSA [DI/I]
Lane 4: TFF2-HSA [DII/I]
Lane 5: TFF2-HSA [DII/II]
Lane 6: TFF2-HSA [LBDI/I]
Lane 7: TFF2-HSA [LBDII/I]
Lane 8: TFF2-HSA [LBDII/II]



Clarified Harvest



AlbuPure Elution

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Therapeutic Studies

Synergy with PD-1 Blockade

Colorectal Cancer (CRC)

MC38 and CT26.wt Subcutaneous and CT26-Luc Orthotopic Syngeneic Murine Models

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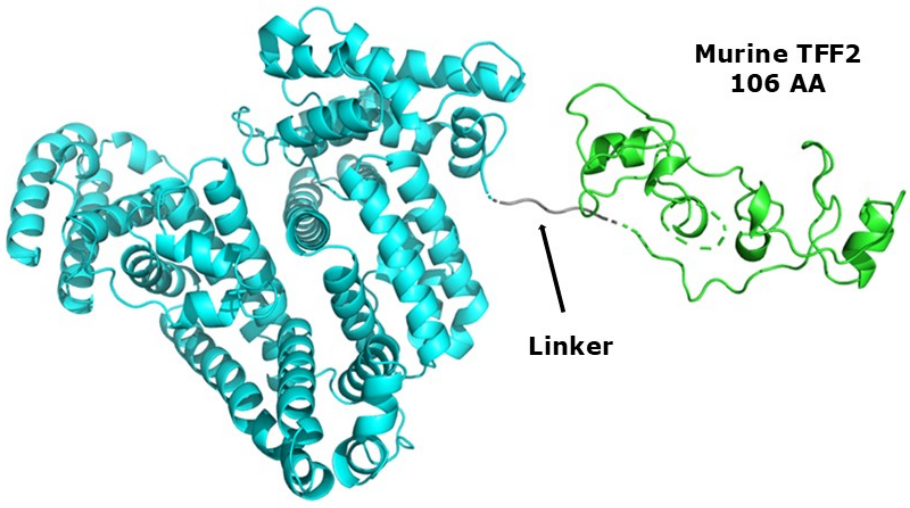
Murine TFF2-MSA Fusion Protein used for Murine Syngeneic Cancer Models



*artistic representation

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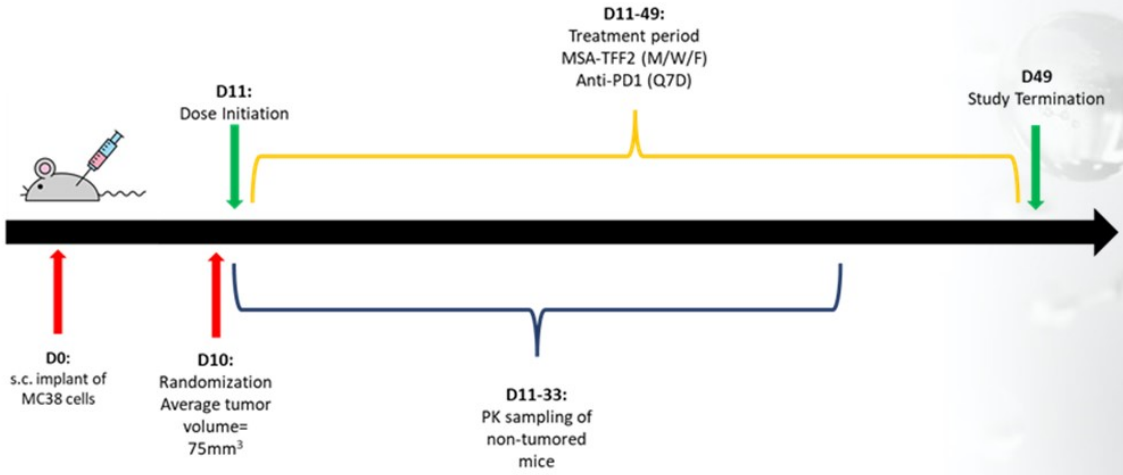
Schematic of Syngeneic MC38 CRC Tumor Model



Daugherty et al., AACR Poster. 2023. MDSC-targeted TFF2-MSA suppresses tumor growth and increases survival in anti-PD-1 treated MC38 and CT26.wt murine colorectal cancer models. https://bit.ly/45XbGK9

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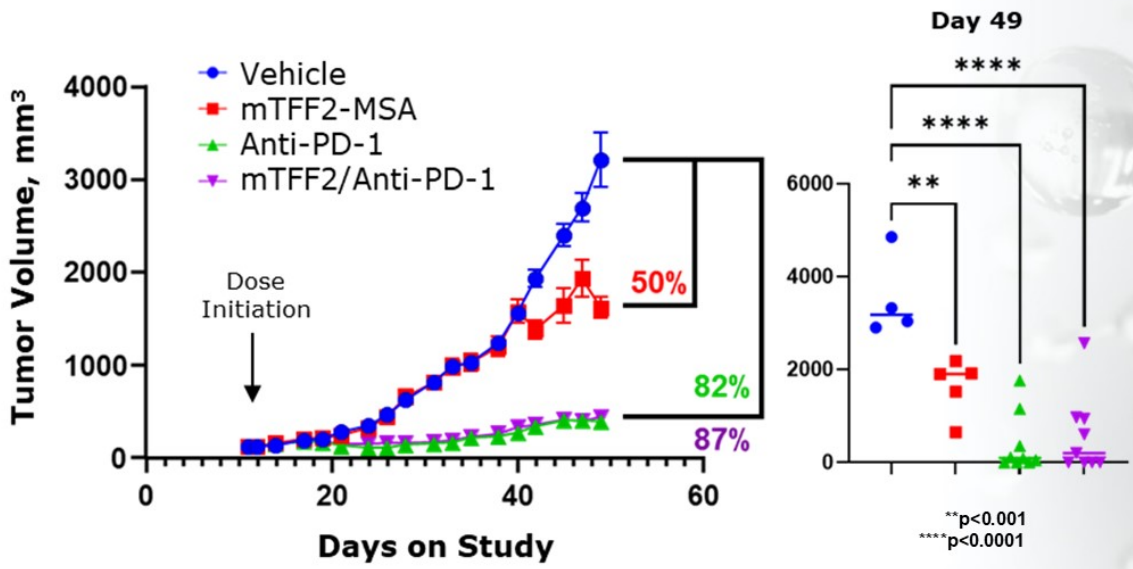
Inhibition of Tumor Growth in the MC38 CRC Model



Daugherty, *op. cit*

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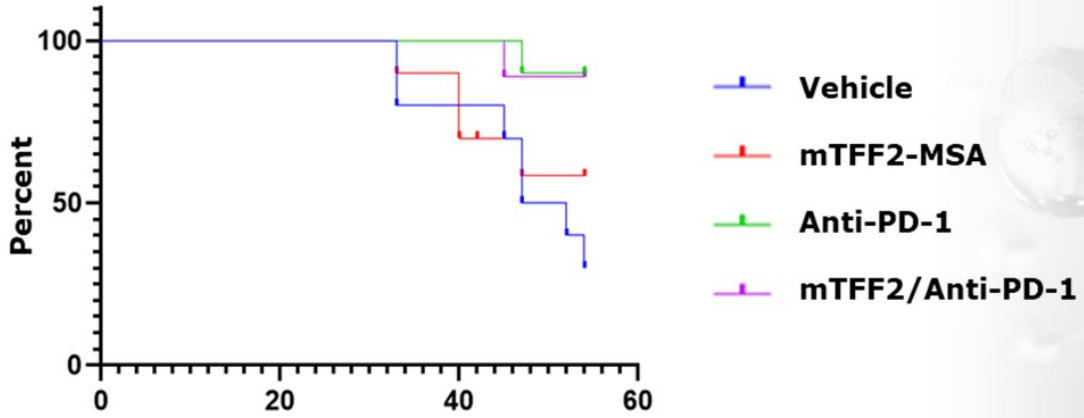
Probability of Survival in the MC38 CRC Model



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

Daugherty, *op. cit*

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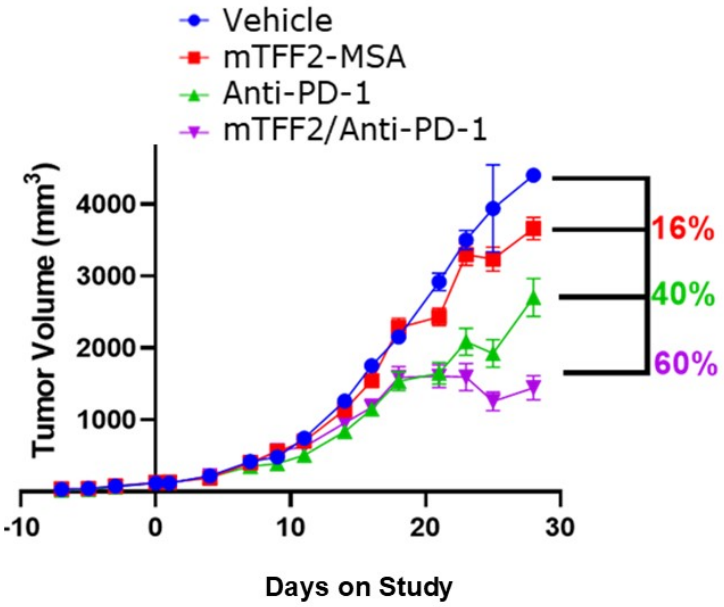
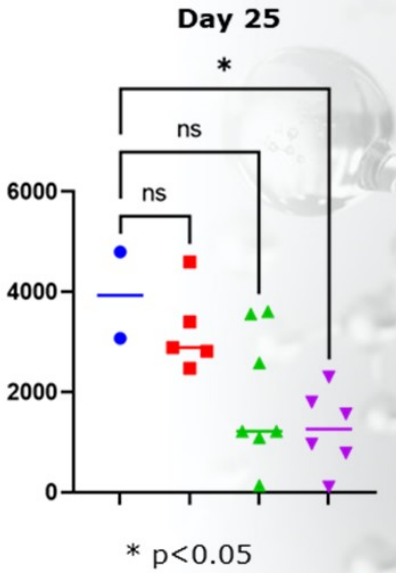
Inhibition of Tumor Growth in the CT26.wt CRC Model





Daugherty, *op. cit*

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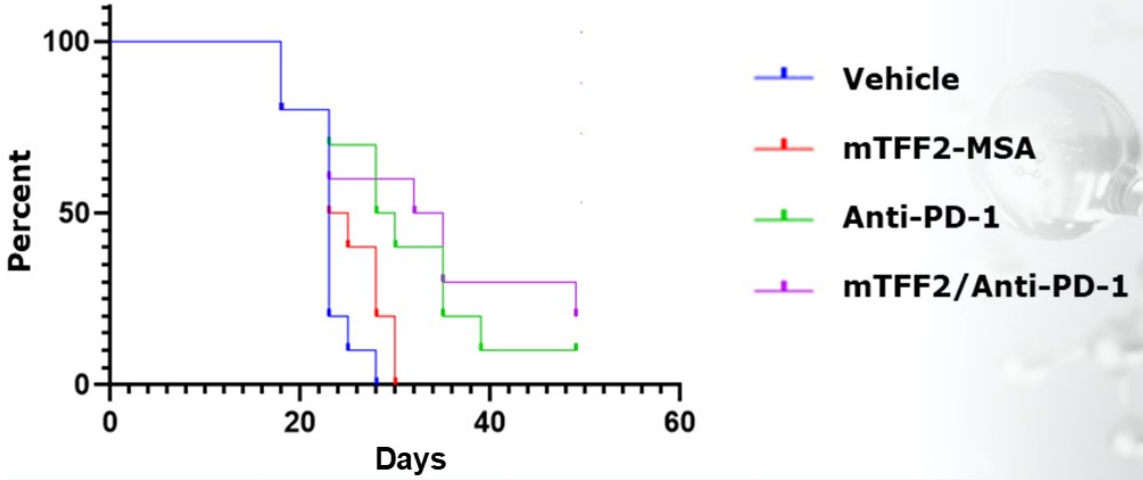
Probability of Survival in the CT26.wt CRC Model



Hazard Ratio (Mantel-Haenszel)	Vehicle/mTFF2-MSA	Vehicle/Anti-PD-1	Vehicle/Combo
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Daugherty, *op. cit*

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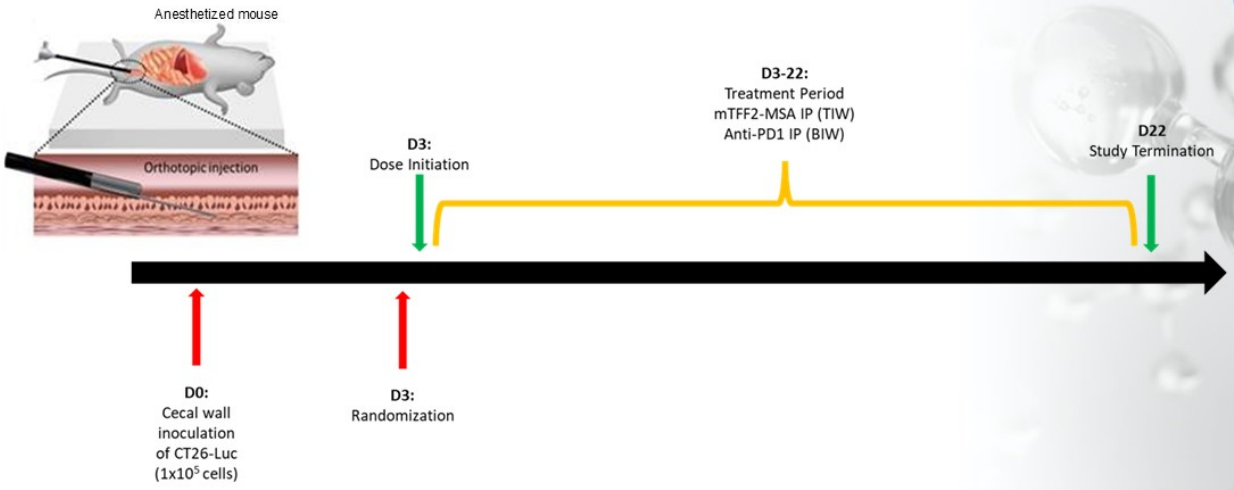
Schematic of the CT26-Luc Orthotopic Tumor Model



Daugherty et al., SITC Poster. 2023. mTFF2-MSA (mTNX-1700) suppresses tumor growth and increases survival in anti-PD-1 treated CT26.wt subcutaneous and CT26-Luciferase orthotopic syngeneic colorectal cancer models by targeting MDSCs; https://jitc.bmj.com/content/11/Suppl_1/A1499

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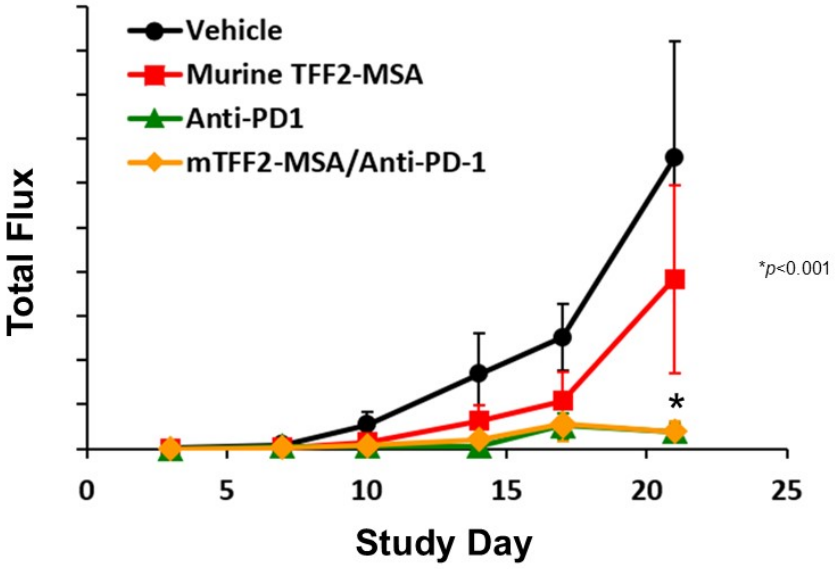
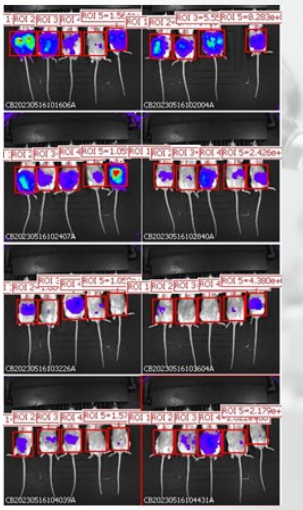
Inhibition of Tumor Growth in the CT26-Luc Orthotopic Tumor Model



*p<0.001



Daugherty, *op. cit*

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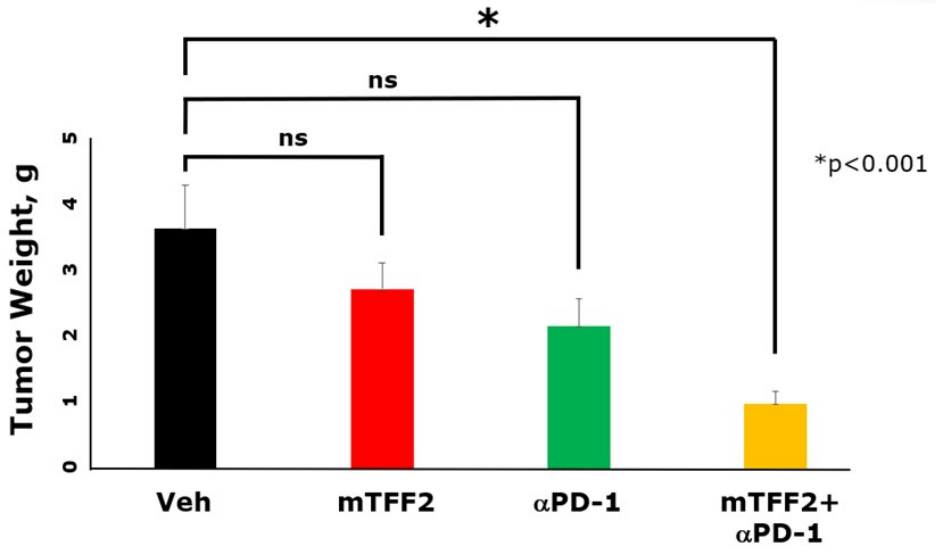
Tumor Weight on Day 22 in the CT26-Luc Orthotopic Model



*p<0.001

Daugherty, *op. cit*

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Therapeutic Studies

Synergy with PD-1 Blockade

Gastric Cancer

ACKP Murine Model

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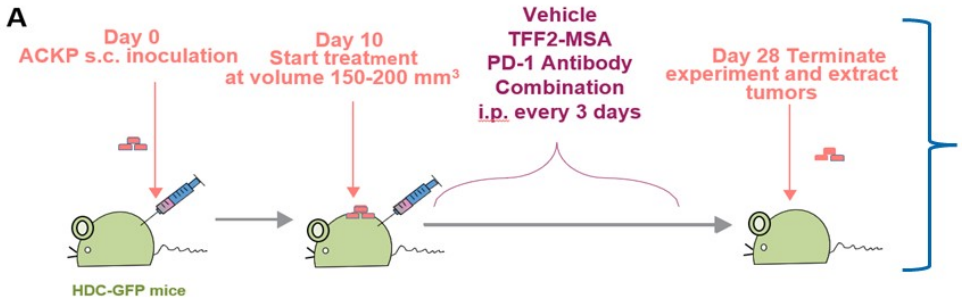
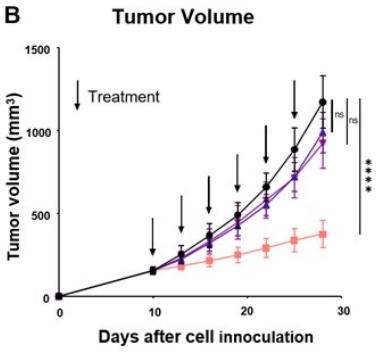
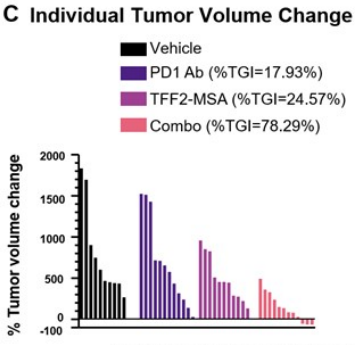
mTNX-1700 (mTFF2-MSA) Showed Synergy with anti-PD1 Antibody in Inhibition of *s.c.* ACKP Xenograft Growth



Schematic representation of treatment





B. Tumor growth curve of s.c. implanted ACKP tumors in response to anti-PD1 antibody, mTFF2-MSA or their combination.

C. Tumor volume change relative to the initial volume of each tumor. Each bar represents one tumor. Positive or negative value represents volume increase or decrease respectively. $P < 0.0001$.

Qian et al., A CXCR4 partial agonist improves immunotherapy by targeting polymorphonuclear myeloid-derived suppressor cells and cancer-driven granulopoiesis; https://www.biorxiv.org/content/10.1101/2024.10.09.617228v1

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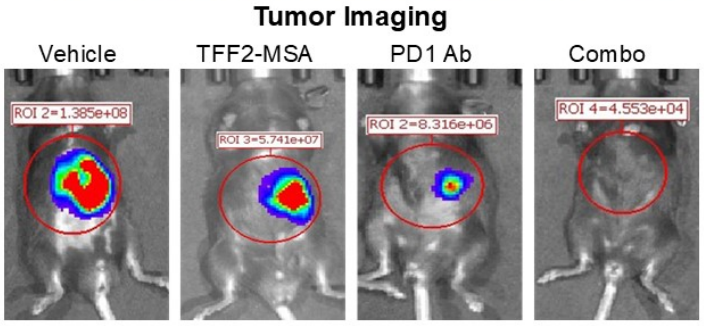
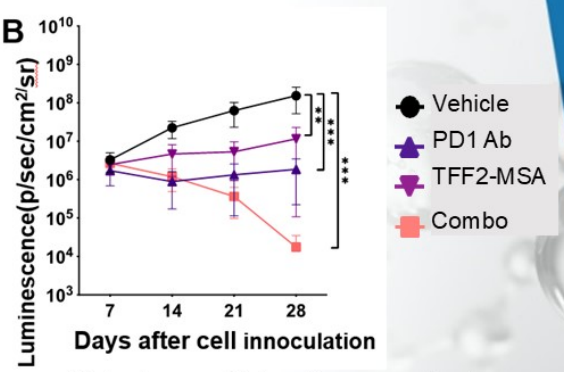
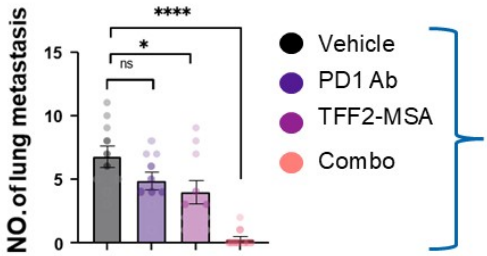
mTNX-1700 Showed Synergy w/ anti-PD1 Antibody in Inhibition of Orthotopic ACKP Xenograft Growth & Spontaneous Lung Metastasis



Representative bioluminescence images showing orthotopically injected ACKP tumors in response to different treatments



Bioluminescent intensity curves showing changes of orthotopic tumors



Number of lung micrometastasis in mice from different treatment groups

Qian, *op. cit*

* P < 0.05, **** P < 0.0001

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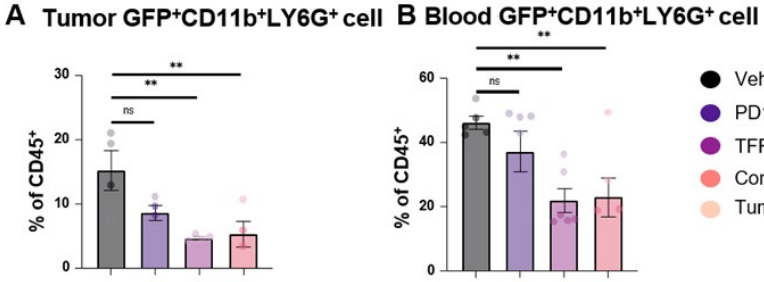
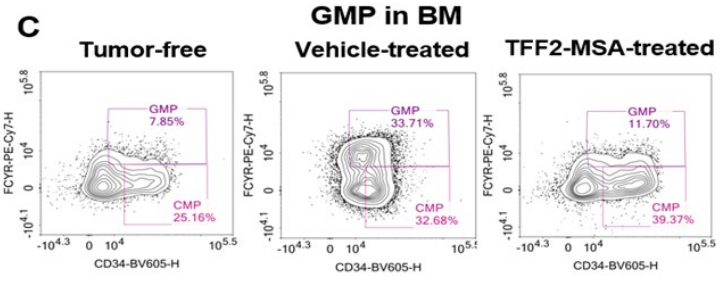
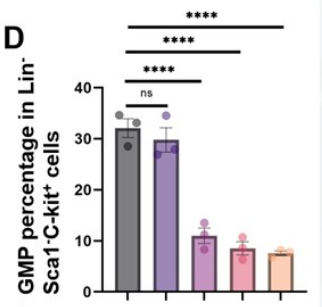
mTNX-1700 Reduced MDSC Accumulation in the Tumor and Biogenesis in the Bone Marrow



A. HDC-GFP⁺CD11b⁺LY6G⁺cell percentage among CD45⁺ cells in TME.

B. HDC-GFP⁺CD11b⁺LY6G⁺cell percentage among CD45⁺ cells in blood.





D. GMP percentage in Lin⁻Sca1⁻C-kit⁺ cells within the BM. Data are presented as means ± SEM. One-way ANOVA.
** P < 0.01
**** P < 0.0001.

C. Representative flow cytometry plots showing ACKP tumor-bearing mice has increased granulocyte-monocyte progenitor (GMP) percentage in the bone marrow (BM) than tumor-free mice, while TFF2-MSA reduces GMP to a level similar to tumor-free mice.

Qian, *op. cit*

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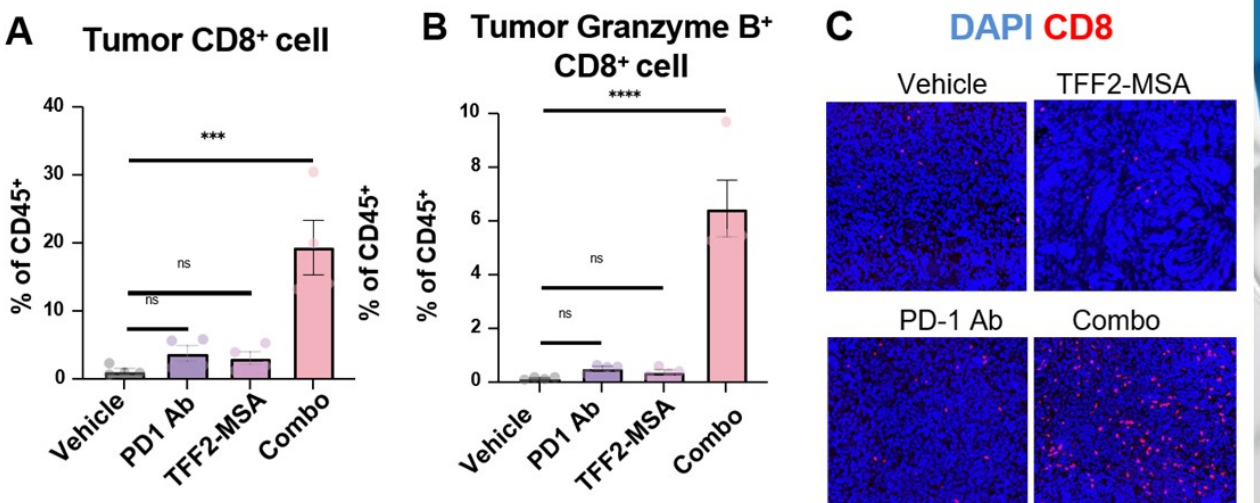
mTNX-1700/Anti-PD1 Ab Combination Increased Tumor-Infiltrating CD8⁺ T cell Associated with a Better Effector Phenotype



A. CD8⁺ t cell percentage among CD45⁺ cells in TME. **B.** Granzyme B⁺CD8⁺ t cell percentage among CD45⁺ cells in TME. **C.** Representative immunofluorescent images showing CD8⁺ T cell infiltration into the TME. Scale bars: 100μm. Data are presented as means ± SEM. One-way ANOVA. *** P < 0.001, **** P < 0.0001.

Qian, *op. cit*

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Summary

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Conclusions

- TFF2 is a naturally occurring anti-inflammatory peptide that is a key part of the inflammatory reflex.
- TFF2 is a partial agonist for CXCR4, upregulates ApoE and suppresses the proliferation and expansion of myeloid progenitors, thus reducing MDSCs.
- Overexpression of TFF2, either through transgenic or adenoviral expression, reduces the development of colorectal cancer (CRC) following AOM/DSS treatment.
- mTFF2-MSA (mTNX-1700) peptide synergizes with PD1 blockade therapy to reduce tumor size and increase survival in CRC syngeneic subcutaneous and orthotopic mouse models.
- mTNX-1700 synergizes with anti-PD1 blockade to increase survival and eradicate gastric cancer (GC) in advanced orthotopic and metastatic models.
- mTNX-1700 reduces the production of MDSC and promotes a T-cell rich microenvironment, inducing a 50-fold increase in intratumor CD8+ T cells.

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Product Development

- Progress
  - Expression of TNX-1700 (hTFF2-HSA fusion protein)
- Next Steps
  - Plan to meet with the FDA to seek guidance on program development
  - GLP toxicology Study
  - Scale-up production of GMP TNX-1700 for GLP toxicology and human clinical trials
  - File the Investigational New Drug (IND) application in the US
  - Phase 1 – Evaluate safety and pharmacokinetics
  - Phase 2 – Study effects on tumors in anti-PD1 treated patients

UpToDate, Sept 2020

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THANK YOU
APPENDIX

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AACR Presentations

Presentation #1

Title: MDSC-targeted TFF2-MSA suppresses tumor growth and increases survival in anti-PD-1 treated MC38 and CT26.wt murine colorectal cancer models

Authors: Bruce L. Daugherty[1], Rebecca J. Boohaker[2], Rebecca Johnstone[2], Karr Stinson[2], Jin Qian[3], Timothy C. Wang[3], Seth Lederman[1]
Tonix Pharmaceuticals, Inc., 26 Main Street, Suite 101, Chatham, NJ 07928
Southern Research, 2000 9th Ave S, Birmingham, AL 35205
Division of Digestive and Liver Diseases, Irving Cancer Research Center, Columbia University Medical Center, New York, NY 10032, USA

Topic: Oncolytic Viruses, Anticancer Vaccines, and Other Immunomodulatory Therapies
Location: Orange County Convention Center, Orlando, Fla.
Section: 24, #704
Date: Sunday, April 16, 2023
Time: 1:30 p.m. – 5:00 p.m. ET
Abstract: Click here

Presentation #2

Title: MDSC-targeted TFF2-MSA synergizes with PD-1 blockade therapy in diffuse-type gastric cancer

Authors: Jin Qian[1], Sandra Ryeom[1], Bruce Daugherty[2], Seth Lederman[2], Timothy C. Wang[2].
Division of Digestive and Liver Diseases, Irving Cancer Research Center, Columbia University Medical Center, New York, NY 10032, USA
Tonix Pharmaceuticals, Inc., 26 Main Street, Suite 101, Chatham, NJ 07928

Title: Combination Immunotherapies 1
Location: Orange County Convention Center, Orlando, Fla.
Section: 21, #5088
Date: Tuesday, April 18, 2023
Time: 1:30 p.m. – 5:00 p.m. ET
Abstract: Click here

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AACR Presentations

Presentation #3

Title: A CXCR4 partial agonist TFF2-MSA improves anti-PD-1 immunotherapy in advanced gastric cancer by selectively targeting PMN-MDSC

Authors: Jin Qian[1], Chenkai Ma[2], Quin T. Waterbury[1], Christine S. Moon[1], Xiaofei Zhi[1], Feijing Wu[1], Ruhong Tu[1], Biyun Zheng[1], Hiroki Kobayashi[1], Leah B. Zamechek[1], Ryan H. Moy[1], Arnold Han[1], Bruce Daugherty[3], Seth Lederman[3], Timothy C. Wang[1]
[1]Irving Cancer Research Center, Columbia University Irving Medical Center, New York, NY,[2]Integrated Diagnostic, Human Health, Health and Biosecurity, CSIRO, Westmead, Australia,[3]Tonix Pharmaceuticals, Inc., Chatham, NJ

Topic: Immune Targets and Therapies
Location: San Diego Convention Center, San Diego, CA.
Session: MS.IM01.02
Date: Monday, April 8, 2024
Time: 3:20 p.m. – 3:35 p.m. PT
Abstract: Click Here

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TONIX PHARMACEUTICALS

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Appendix

Qian et al., AACR 2023 Abstract #5088

Daugherty et al., AACR 2023 Abstract #704

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