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): March 7, 2023

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.

On March 7, 2023, Tonix Pharmaceuticals Holding Corp. (the "Company") announced that preclinical results of the Company's preclinical product candidate, mTNX-1700 (recombinant murine TFF2-murine serum albumin, or MSA, fusion protein) were presented in a poster at the Keystone Symposia, "Cancer Immunotherapy: Mechanisms of Response Versus Resistance" (the "Poster"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. The Poster, which may contain nonpublic information, is filed as Exhibit 99.02 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 and 99.02 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.

On March 7, 2023, the Company announced that preclinical results of mTNX-1700 were presented in a poster entitled*TFF2-MSA Suppresses Tumor Growth and Increases Survival in an anti-PD-1 Treated MC38 Colorectal Cancer Model by Targeting MDSCs* , which includes data from preclinical studies which evaluated the ability of mTNX-1700 to treat colorectal cancer as monotherapy or in combination with anti-PD-1 in mouse models. TNX-1700 targets myeloid-derived suppressor cells ("MDSCs") which interfere with the immune response to cancer by suppressing the CD8+ T cell response and creating a toxic tumor microenvironment. The data show that mTNX-1700 and anti-PD-1 monotherapy each were able to evoke anti-tumor immunity in the MC38 model of colorectal cancer, and that mTNX-1700 augmented the anti-tumor efficacy of anti-PD-1 therapy in two different colorectal cancer models. The Company is developing TNX-1700 (recombinant human TFF2-human serum albumin or HSA) for the treatment of colon and gastric cancers.

The Company believes that data from these preclinical studies demonstrate that mTNX-1700 treatment augmented the response of two different models of colorectal tumors, and that mTNX-1700 inhibits the MDSCs which contribute to the toxic element of the tumor microenvironment. Together these findings support the idea that whether a tumor is anti-PD1 non-responsive or responsive may relate to the tumor microenvironment rather than the tumor itself.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d) **Exhibit No.**	**Description.**
99.01	Press release of the Company, dated March 7, 2023
99.02	TFF2-MSA Suppresses Tumor Growth and Increases Survival in an anti-PD-1 Treated MC38 Colorectal Cancer Model by Targeting MDSCs
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: March 7, 2023

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

Exhibit 99.01

Tonix Pharmaceuticals Announces Results from a Preclinical Study of Murine TNX-1700 Presented in a Poster at the Keystone Symposia, "Cancer Immunotherapy: Mechanisms of Response Versus Resistance"

Murine TNX-1700 (mTNX-1700) Enhances Anti-Tumor Activity of PD-1 Blockade in Mouse Models of Colorectal Cancer

TNX-1700 is in Development as Monotherapy and in Combination with Anti-PD-1 Checkpoint Inhibitor Therapy for Colorectal and Gastric Cancers

In Animal Models of Colorectal Cancer, mTNX-1700 Treatment Leads to the Activation of Cancer-Killing $CD8^+$ T Cells and Limits Immune Evasion by Cancer Cells

CHATHAM, N.J., March 7, 2023 (GLOBE NEWSWIRE) -- Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced that preclinical results of mTNX-1700 (recombinant murine TFF2-murine serum albumin, or MSA, fusion protein) were presented in a poster at the Keystone Symposia, "Cancer Immunotherapy: Mechanisms of Response Versus Resistance" on March 6, 2023, at the Fairmont Banff Springs Conference Center in Banff, Alberta, Canada. The poster can be found on the Scientific Presentations page of Tonix's website.

The poster, titled "*TFF2-MSA Suppresses Tumor Growth and Increases Survival in an anti-PD-1 Treated MC38 Colorectal Cancer Model by Targeting MDSCs*" includes data from preclinical studies which evaluated the ability of mTNX-1700 to treat colorectal cancer as monotherapy or in combination with anti-PD-1 in mouse models. TNX-1700 targets myeloid-derived suppressor cells (MDSCs) which interfere with the immune response to cancer by suppressing the $CD8^+$ T cell response and creating a toxic tumor microenvironment. The data show that mTNX-1700 and anti-PD-1 monotherapy each were able to evoke anti-tumor immunity in the MC38 model of colorectal cancer, and that mTNX-1700 augmented the anti-tumor efficacy of anti-PD-1 therapy in two different colorectal cancer models. Tonix is developing TNX-1700 (recombinant human TFF2-human serum albumin or HSA) for the treatment of colon and gastric cancers.

"Anti-PD-1 treatment has revolutionized the treatment of other cancers and is known as immuno-oncology," said Seth Lederman, M.D., Chief Executive Officer of Tonix. "Colorectal cancer is notoriously unresponsive to anti-PD-1 treatment. Much research has been focused on trying to turn anti-PD-1 unresponsive tumors into anti-PD-1 responsive tumors."

Bruce Daugherty, Ph.D., Executive Vice President, Research of Tonix, the presenter and lead author of the study added, "we believe that the data from these preclinical studies demonstrate that mTNX-1700 treatment augmented the response of two different models of colorectal tumors. In addition, it was shown that mTNX-1700 inhibits the MDSCs which contribute to the toxic element of the tumor microenvironment. Together these findings support the idea that whether a tumor is anti-PD1 non-responsive or responsive may relate to the tumor microenvironment rather than the tumor itself. We are excited to start additional work to learn if TNX-1700 therapy modifies the toxic tumor microenvironment in humans and will make colorectal cancer responsive to anti-PD-1 therapy."

About Trefoil Factor 2 (TFF2)

Human TFF2 is a secreted protein, encoded by the TFF2 gene in humans, that is expressed in gastrointestinal mucosa where it functions to protect and repair mucosa. TFF2 is also expressed at low levels in splenic immune cells and is now appreciated to have intravascular roles in the spleen and in the tumor microenvironment. In gastric cancer, TFF2 is epigenetically silenced, and TFF2 is suggested to be protective against cancer development through several mechanisms. Tonix is developing TNX-1700 (rTFF2-HSA) for the treatment of gastric and colon cancers under a license from Columbia University. Columbia was granted patent claims, which, excluding possible patent term extensions, is expected to provide U.S. market exclusivity until April 2, 2033[1,2]. The inventor at Columbia is Dr. Timothy Wang, who is an expert in the molecular mechanisms of carcinogenesis whose research has focused on the carcinogenic role of inflammation in modulating stem cell functions. Dr. Wang demonstrated that knocking out the mTFF2 gene in mice leads to faster tumor growth and that overexpression of TFF2 markedly suppresses tumor growth by curtailing the homing, differentiation, and expansion of MDSCs to allow activation of cancer-killing $CD8^+$ T cells[3]. He went on to show that a novel engineered form of recombinant murine TFF2 (mTFF2-CTP) had an extended half-life *in vivo* and was able to suppress MDSCs and tumor growth in an animal model of colorectal cancer. Later, he showed in gastric cancer models that suppressing MDSCs using chemotherapy enhances the effectiveness of anti-PD1 therapy and significantly reduces tumor growth.[4] Dr. Wang proposed the concept of employing rTFF2 in combination with other therapies in cancer prevention and early treatment. Dr. Wang presented data at the American Association for Cancer Research (AACR) conference as a collaboration between Tonix and Columbia University in 2020[5] that includes data from a preclinical study which investigated the role of PD-L1 in colorectal tumorigenesis and evaluated the utility of targeting myeloid-derived suppressor cells (MDSCs) in combination with PD-1 blockade in mouse models of colorectal cancer. The data show that anti-PD-1 monotherapy was unable to evoke anti-tumor immunity in this model of colorectal cancer, but mTFF2-CTP augmented the efficacy of anti-PD-1 therapy. Anti-PD-1 in combination with TFF2-CTP showed greater anti-tumor activity in PD-L1-overexpressing mice.

[1] *Tonix Pharmaceuticals Announces Licensing Agreement with Columbia University for the Development of Recombinant Trefoil Family Factor 2 (rTFF2), or TNX-1700, for the Treatment of Gastric and Pancreatic Cancers :: Tonix Pharmaceuticals Holding Corp. (TNXP)*

[2] *The U.S. Patent and Trademark Office issued U.S. Patent No. 11,167,010 on November 9, 2021.*

[3] *Dubeykovskaya ZA et al, Nat Commun 2016*

[4] *Kim W et al, Gastroenterology 2021*

[5] *Tonix Pharmaceuticals Announces Results from Preclinical Study of TNX-1700 Presented in a Poster at AACR Virtual Annual Meeting 2020 :: Tonix Pharmaceuticals Holding Corp. (TNXP)*

Tonix Pharmaceuticals Holding Corp. *

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing therapeutics to treat and prevent human disease and alleviate suffering. Tonix's portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia with a new Phase 3 study launched in the second quarter of 2022 and interim data expected in

the second quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Tonix initiated a Phase 2 study in Long COVID in the third quarter of 2022. TNX-1300 (cocaine esterase) is a biologic designed to treat cocaine intoxication and has been granted Breakthrough Therapy designation

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by the FDA. A Phase 2 study of TNX-1300 is expected to be initiated in the second quarter of 2023. TNX-1900 (intranasal potentiated oxytocin), a small molecule in development for chronic migraine, is being studied in a potential pivotal Phase 2 study that initiated enrollment in the first quarter of 2023 and for which interim data is expected in the fourth quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets) is a once-daily formulation of tianeptine being developed as a potential treatment for major depressive disorder (MDD) with a Phase 2 study expected to be initiated in the first quarter of 2023. Tonix's rare disease portfolio includes TNX-2900 (intranasal potentiated oxytocin) for the treatment of Prader-Willi syndrome. TNX-2900 has been granted Orphan Drug designation by the FDA. Tonix's immunology portfolio includes biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft and xenograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the second quarter of 2023. Tonix's infectious disease pipeline includes a vaccine in development to prevent smallpox and monkeypox, TNX-801; a next-generation vaccine to prevent COVID-19, TNX-1850; a platform to make fully human monoclonal antibodies to treat COVID-19, TNX-3600; humanized anti-SARS-CoV-2 monoclonal antibodies, TNX-3800; and a class of broad-spectrum small molecule oral antivirals, TNX-3900. TNX-801, Tonix's vaccine in development to prevent smallpox and monkeypox, also serves as the live virus vaccine platform or recombinant pox vaccine (RPV) platform for other infectious diseases. A Phase 1 study of TNX-801 is expected to be initiated in the second half of 2023.

**All of Tonix's product candidates are investigational new drugs or biologics and have not been approved for any indication.*

This press release and further information about Tonix can be found at www.tonixpharma.com.

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of 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," "expect," 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, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; 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. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission (the "SEC") on March 14, 2022, and periodic 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. The information set forth herein speaks only as of the date thereof.

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

Poster 1026

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

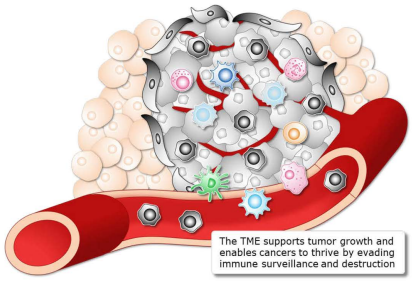
*TNX-1700 is an investigational new biologic and has not been approved for any indication

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

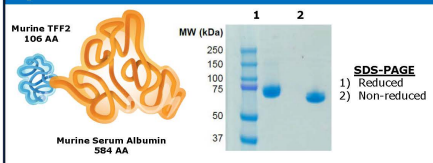


Fig. 2: Schematic of Syngeneic MC38 CRC Tumor Model

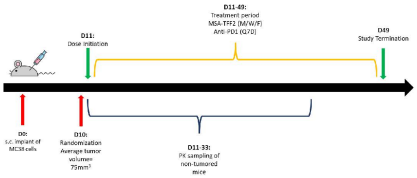


Fig. 3: Pharmacokinetic Analysis of mTFF2-MSA in Mice

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

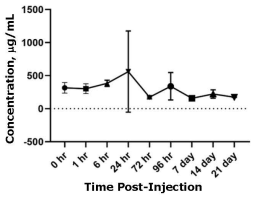


Fig. 4: Inhibition of Tumor Growth in the MC38 CRC Model

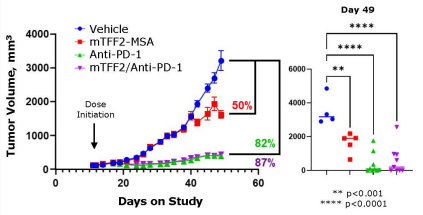
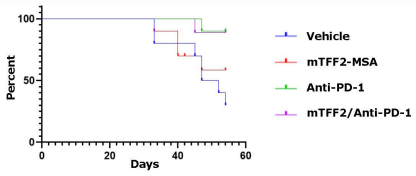


Fig. 5: Probability of Survival in the MC38 CRC Model



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

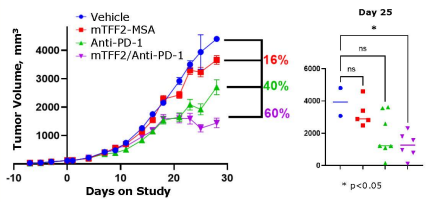
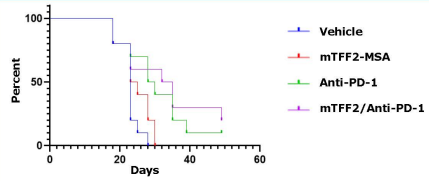


Fig. 7: Probability of Survival in the CT26.wt CRC Model



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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