March 7, 2023

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 07, 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)*

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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 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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Source: Tonix Pharmaceuticals Holding Corp.