Tenaya Therapeutics Publishes Preclinical Data in Science Translational Medicine Detailing Discovery of HDAC6 Inhibitor for Treatment of Heart Failure

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Tenaya's Precision Medicine Platform Used to Identify HDAC6 Target Using Phenotypic Screening and Machine Learning Algorithms

Tenaya's HDAC6 Inhibitor TN-301 Advancing to the Clinic for HFpEF, with IND Filing on Track for 2H 2022

SOUTH SAN FRANCISCO, Calif., July 06, 2022 (GLOBE NEWSWIRE) -- Tenaya Therapeutics, Inc. (NASDAQ: TNYA), a biotechnology company with a mission to discover, develop and deliver curative therapies that address the underlying causes of heart disease, announced the publication of preclinical research in the July 6 issue of *Science Translational Medicine*. The article, titled "Phenotypic screening with deep learning identifies HDAC6 inhibitors as cardioprotective in a BAG3 mouse model of dilated cardiomyopathy," describes the discovery of histone deacetylase 6 (HDAC6) as a promising therapeutic target. These insights led to the development of the company's lead small molecule candidate, TN-301, a highly selective HDAC6 inhibitor initially being developed for the potential treatment of heart failure with preserved ejection fraction (HFpEF).

"While cardiovascular diseases remain the leading cause of death worldwide, innovation in therapeutic discovery has suffered from the challenge of identifying targets with validation in human tissue that can address underlying mechanisms of heart disease. The success of our approach using disease models based on human cells plus machine learning algorithms to discover promising new therapeutic targets for heart diseases provides reason to believe that this methodology may be broadly applicable to accelerating target and drug discovery of other disease-modifying therapies," said Timothy Hoey, Ph.D., Chief Scientific Officer of Tenaya Therapeutics. "Research presented in this paper highlight the exquisite target selectivity and cardioprotective qualities of our HDAC6 inhibitors. We look forward to advancing TN-301, the first product candidate in our pipeline to be discovered and validated using this approach, into clinical studies."

Key Research Findings
The publication in *Science Translational Medicine* details Tenaya's distinct Precision Medicine platform approach of applying phenotypic screening and deep learning to human induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) disease models. Tenaya developed and validated a BAG3 knock-down human iPSC-CM model of dilated cardiomyopathy (DCM), a genetic cardiomyopathy that can lead to enlargement of the heart and heart failure in humans, for target identification and screening of novel cardiovascular disease candidates. In the BAG3-deficient human iPSC-CM models, HDAC6 inhibition was shown to protect against damage of the sarcomere, one of the basic building blocks of heart muscle present in all cardiomyocyte cells. Tenaya then developed a series of novel HDAC6 inhibitors through medicinal chemistry efforts that includes TYA-018 and TN-301, which are structurally and functionally similar. TYA-018 is used in Tenaya's preclinical *in vitro* and *in vivo* studies of HDAC6 inhibition, while TN-301 is being advanced into clinical studies.

To further validate the potential of HDAC6 inhibition, Tenaya translated its initial *in vitro* findings to a BAG3 cardiomyocyte knockout mouse model of DCM. BAG3 loss-of-function mutations have been linked to DCM and, in preclinical animal models, result in a steady loss of heart function leading to death from heart failure that simulates the progressive decline observed in human disease, providing a relevant model by which to study the results of targeted intervention.

When evaluated in a BAG3 knock-out mouse model of DCM, HDAC6 inhibition with TYA-018:

- Demonstrated exquisitely selective enzyme inhibition, with greater than 2500-fold preference for HDAC6 over other members of the HDAC family
- Reduced sarcomeric damage, improved heart dilation, and conferred protection of left ventricular function from rapidly progressive decline.
- Enhanced cardiac energetics, mitochondrial membrane potential and reserve respiratory capacity, which contribute to maintaining improved heart function.

Studying the mechanism of action of HDAC6 inhibition in these *in vitro* and in *vivo* DCM models provided additional insights that subsequently led to the discovery that HDAC6 inhibition may be highly effective in the setting of HFpEF with a multi-model mechanism of action. Based on extensive preclinical evaluation, Tenaya will seek to initially develop TN-301 for the potential treatment of HFpEF. Tenaya is on track to submit an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) in the second half of 2022.

About TN-301 and HFpEF
TN-301 is a highly specific small molecule HDAC6 inhibitor initially being developed for the potential treatment of HFpEF. HFpEF accounts for approximately 50% of all heart failures, yet there are few proven treatment options. This disease involves systemic inflammation, left ventricular hypertrophy, fibrosis, and diastolic dysfunction resulting in high morbidity and mortality in affected individuals. In preclinical studies, TN-301 has been shown to have a multi-modal mechanism of action and to reverse many of the signs and symptoms of HFpEF in multiple relevant models, with evidence of reduced inflammation and fibrosis, overall improvement in metabolism, and improvements in left ventricular function and diastolic filling and pressures. Tenaya plans to submit an IND application to study TN-301 in human clinical studies to the FDA in the second half of 2022.

About Tenaya's Precision Medicine Platform
Tenaya's Precision Medicine platform uses human iPSC-CMs as proprietary disease models combined with analysis of human genetics and the use of

machine learning algorithms for the identification of new targets, validation of known targets, and high-throughput screening for drug discovery. This platform is intended to overcome the shortcomings of traditional drug development efforts that rely more heavily on insights from animal models to identify targets and to develop therapies intended for human heart disease. This platform has potentially broad utility for the identification of targets and therapies in a modality-agnostic manner — including gene therapy, small molecules, and biologics — for both genetic and non-genetic forms of heart disease.

About Tenaya Therapeutics
Tenaya Therapeutics is a biotechnology company committed to a bold mission: to discover, develop and deliver curative therapies that address the underlying drivers of heart disease. Founded by leading cardiovascular scientists from Gladstone Institutes and the University of Texas Southwestern Medical Center, Tenaya is developing therapies for rare genetic cardiovascular disorders, as well as for more prevalent heart conditions, through three distinct but interrelated product platforms: Gene Therapy, Cellular Regeneration and Precision Medicine. For more information, visit www.tenayatherapeutics.com.

Forward Looking Statements
This press release contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this press release that are not purely historical are forward-looking statements. Words such as “look forward,” “believe,” “will,” “potential” and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, Tenaya’s clinical development plans for TN-301; the therapeutic potential of TN-301 as a treatment for HFpEF; expectations regarding the timing of the IND filing for TN-301 and the broad potential of Tenaya’s precision medicine platform for the identification of targets and therapies. The forward-looking statements contained herein are based upon Tenaya’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. These forward-looking statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, including but not limited to: the timing, scope and likelihood of regulatory filings and approvals; the timing, progress and results of clinical studies for TN-301; the potential for any clinical trial results to differ from preclinical, interim, preliminary, topline or expected results; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early stage company; Tenaya’s ability to develop, initiate or complete preclinical studies and clinical trials, and obtain approvals, for any of its product candidates; Tenaya’s ability to raise any additional funding it will need to continue to pursue its business and product development plans; negative impacts of the COVID-19 pandemic on Tenaya’s manufacturing and operations, including preclinical studies and planned clinical trials; Tenaya’s reliance on third parties; Tenaya’s commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which Tenaya operates; Tenaya’s ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled “Risk Factors” in documents that Tenaya files from time to time with the Securities and Exchange Commission. These forward-looking statements are made as of the date of this press release, and Tenaya assumes no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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