Sangamo Therapeutics Logo

Sangamo Therapeutics Announces Nature Medicine Publication Detailing the Activity of Disease Allele-Selective Zinc Finger Proteins in Preclinical Models of Huntington's Disease

July 1, 2019

BRISBANE, Calif.--(BUSINESS WIRE)--Jul. 1, 2019-- Sangamo Therapeutics, Inc. (Nasdaq: SGMO), a genomic medicine company, today announced the publication of a manuscript describing the activity of allele-selective zinc finger protein transcription-factors (ZFP-TFs) in preclinical models of Huntington's disease (HD). The data were published online on July 1 and will appear in the July 2019 issue of *Nature Medicine*.

The publication describes research by Sangamo and collaborators at the CHDI Foundation, in which ZFP-TFs were engineered to selectively target the mutant form of the huntingtin gene *(HTT)* and repress its transcription, selectively lowering production of the mutant Huntingtin protein (mHTT). Preclinical data from HD patient-derived fibroblasts and neurons demonstrated that a single administration of ZFP-TFs resulted in the selective repression of over 99% of HD-causing *HTT* disease alleles over a wide dose range, while preserving the expression of at least 86% of healthy wild-type *HTT* alleles.

Huntington's disease is a progressive, fatal, neurodegenerative disorder caused by a dominant mutation involving the expansion of a CAG trinucleotide repeat in exon 1 of the *HTT* gene. Fully penetrant disease alleles of mutant *HTT* have more than 39 CAG repeats, but most HD patients have one healthy wild-type copy of *HTT* with less than 22 CAG repeats. Led by first author Bryan Zeitler, PhD, Sangamo scientists engineered ZFP-TFs capable of preferentially binding longer CAG repeat arrays on the disease allele while avoiding the shorter repeat array on the healthy allele. These ZFP-TFs exhibited disease-allele selectivity and also demonstrated a high level of specificity for the mutant *HTT* repeat as compared to other CAG-containing genes in the human genome.

"Ever since the mutation that causes Huntington's Disease was identified in 1993, the ultimate goal for HD research has been to develop a therapy that could directly target the mutant CAG repeat while avoiding the wild-type form given its important role in many cellular functions," said Gillian Bates, PhD, Professor of Molecular Neuroscience, Queen Square Institute of Neurology, UCL, London, who played a key role in the international effort to clone the *HTT* gene and disease causing mutation and is not involved in the study. "Sangamo's ZFP-TF approach is particularly compelling because it represents a potentially universal allele-selective treatment that could possibly require a one-time administration. If successfully translated into the clinic, this could be transformative for patients and their families."

Data from preclinical *in vivo* studies using different HD mouse models demonstrated improvements in a range of molecular, histopathological, electrophysiological, and other functional endpoints following treatment with Sangamo's ZFP-TFs. In neurons cultured from the zQ175 mouse model (~188 CAG repeats) of HD, recombinant AAV delivery of ZFP-TFs to primary neurons resulted in reduction of mutant *HTT* mRNA and HTT protein by more than 98% with no reduction of wild-type HTT. *In vivo*, toxic aggregates of the mutant HTT protein were reduced by greater than 99%. Moreover, the well-characterized zQ175 electrophysiological deficits in the brain were fully reversed following ZFP treatment. Functional restoration of neuronal biomarkers was also demonstrated by several measures, including the use of PET imaging ligands in living mice. This outcome has the potential to be translated for use as an efficacy marker in clinical trials. The results were confirmed and extended in an additional mouse model of HD, in which treatment with ZFP-TFs led to the repression of mutant HTT protein and significant improvement in motor function.

Finally, extensive *in vivo* tolerability assessments showed no evidence of a neuroinflammatory response or changes in behavior or locomotor function in mice treated with ZFP-TFs out to 15 months of age. This suggests that the long-term striatal expression of ZFP-TFs is generally well-tolerated in mice.

"These studies present the first direct demonstration of disease allele-selective transcriptional repression at the mutated Huntingtin gene locus. While several *HTT*-lowering therapies are advancing into the clinic, they all rely on indirect approaches that do not directly target the mutation. Moreover, these strategies either lower both mutant and normal *HTT* or employ allele-targeting that is limited to a subgroup of patients, in some cases requiring multiple intrathecal injections over a patient's lifetime," said Adrian Woolfson, M.D., Ph.D., Sangamo's Executive Vice President of Research and Development. "Sangamo's engineered ZFP-TFs demonstrated a combination of high selectivity, genome-wide specificity, and long-term tolerability that we believe establishes a new benchmark for engineered transcription factors. Overall, these data provide compelling preclinical evidence for the potential viability of Sangamo's ZFP-TF gene regulation platform as a novel disease modifying therapeutic approach for the treatment of Huntington's disease."

About Huntington's Disease

Huntington's disease (HD) is an inherited neurodegenerative disease that typically presents in adults aged between 30 and 50. HD is caused by a mutation in one of the alleles of the huntingtin gene (*HTT*), leaving only one functional or healthy copy of *HTT* in the cell. The mutated *HTT* produces the mutant HTT protein, leading to profound neuronal loss and progressive deterioration of motor, psychiatric, and cognitive abilities. There are currently no disease-modifying therapies available for HD.

About Sangamo's Gene Regulation Platform

Sangamo's zinc finger protein transcription factor (ZFP-TF) gene regulation technology is designed to either selectively repress (down-regulate) or activate (up-regulate) the expression of a specific gene or gene allele following a single administration. This technology enables targeting of a broad range of diseases requiring regulation of endogenous gene expression and differs from other approaches such as gene therapy or zinc finger nuclease-mediated (ZFN) genome editing, which are designed to replace or correct a missing or mutated gene or DNA sequence.

Sangamo is developing ZFP-TFs as a novel therapeutic approach for diseases of the central nervous system (CNS). Sangamo has a collaboration with Pfizer, deploying the ZFP-TF gene regulation approach to repress the expression of the mutated C9ORF72 gene allele linked to genetic forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Sangamo is also developing ZFP-TFs to down-regulate the expression of tau, a protein associated with Alzheimer's disease and other tauopathies.

Takeda Pharmaceutical Company Limited is working with Sangamo on further engineered ZFP-TFs designed to selectively target the mutant *HTT* gene and repress its transcription. Takeda intends to evaluate this potential clinical candidate for the treatment of HD in potential preclinical

Investigational New Drug (IND)-enabling studies.

About Sangamo Therapeutics, Inc.

Sangamo Therapeutics is committed to translating ground-breaking science into genomic medicines with the potential to transform patients' lives using gene therapy, *ex vivo* gene-edited cell therapy, *in vivo* genome editing and gene regulation. For more information about Sangamo, visit www.sangamo.com

Forward-Looking Statements

This press release contains forward-looking statements based on Sangamo's current expectations. These forward-looking statements include, without limitation, statements relating to the therapeutic potential of Sangamo's ZFP-TF gene regulation platform for the treatment of CNS diseases, including the potential of Sangamo's ZFP-TF gene regulation platform as a novel disease modifying therapeutic approach for the treatment of HD; the potential for Sangamo's ZFP-TF approach to represent an allele-selective treatment that could possibly require a one-time administration; the potential for HD mouse model preclinical data to translate into the clinic; the potential for preclinical studies to be IND-enabling; and other statements that are not historical fact. These statements are not guarantees of future performance and are subject to certain risks, uncertainties and assumptions that are difficult to predict. Factors that could cause actual results to differ include, but are not limited to, risks and uncertainties related to: early preclinical data, including the risk that the early preclinical data may not warrant regulatory approvals to conduct any human clinical trials, and may not be representative of the results of any such human clinical trials; whether ZFP-TFs will produce any beneficial therapeutic effect in humans; Sangamo's reliance on Takeda, its other partners and other third-parties to further develop its technology; Sangamo's ability to develop commercially viable products; and the potential for technological developments by Sangamo's competitors that will obviate Sangamo's ZFP-TF technology. These risks and uncertainties are described more fully in Sangamo's Quarterly Report on Form 10-Q for the quarter ended March 31, 2019 as filed with the Securities and Exchange Commission. Forward-looking statements contained in this press release are made as of this date, and Sangamo undertakes no duty to update such information except as required under applicable law.

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