# Cortexyme announces publication of foundational data for groundbreaking approach to treating Alzheimer's disease in Science Advances

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-- Seminal peer-reviewed paper details discovery of bacterial pathogen in brains of Alzheimer's patients and evidence of disease causation

-- Therapeutic path using small molecule bacterial protease inhibitors identified for disease-modification, with Phase 2/3 testing beginning in 2019

Cortexyme, Inc., the privately held, clinical-stage pharmaceutical company developing therapeutics to alter the course of Alzheimer's disease (AD) and other degenerative disorders, today announced publication of a foundational paper supporting its approach in Science Advances, a top-ranked multidisciplinary journal published by the American Association for the Advancement of Science (AAAS). In the paper, an international team of researchers led by Cortexyme co-founders Stephen Dominy, M.D. and Casey Lynch detail the role of a common bacterium, Porphyromonas gingivalis (Pg), in driving Alzheimer's disease pathology and demonstrate the potential for small molecule inhibitors to block the pathogen.

"Infectious agents have been implicated in the development and progression of Alzheimer's disease before, but the evidence of causation hasn't been convincing," said Stephen Dominy, M.D., Cortexyme co-founder, chief scientific officer, and lead author on the paper. "Now, for the first time, we have solid evidence connecting the intracellular, Gram-negative pathogen, Pg, and Alzheimer's pathogenesis while also demonstrating the potential for a class of small molecule therapies to change the trajectory of disease."

The Science Advances publication details how researchers identified Pg, the keystone pathogen in chronic periodontal disease, in the brains of patients with AD. In mouse models, oral Pg infection led to brain colonization and increased production of amyloid beta (Aβ), a component of the amyloid plaques commonly associated with Alzheimer's.

In addition to Pg itself, the study team also detected the organism's toxic proteases, or gingipains, in the neurons of patients with AD. The team correlated the gingipain levels with pathology related to two markers: tau, a protein needed for normal neuronal function, and ubiquitin, a small protein tag that marks damaged proteins for degradation and is found in tau tangles and Aβ plaques. The gingipains were found to be neurotoxic in vivo and in vitro, exerting detrimental effects on tau.

Seeking to block Pg-driven neurotoxicity, Cortexyme set out to design a series of small molecule therapies targeting Pg gingipains. In preclinical experiments detailed in the paper, the researchers demonstrated that inhibition by COR388, the most promising compound in the series and the subject of Cortexyme's ongoing clinical development program, reduced the bacterial load of an established Pg brain infection, blocked Aβ42 production, reduced neuroinflammation, and protected neurons in the hippocampus, the part of the brain that mediates memory and frequently atrophies early in the development of AD.

"Despite significant funding and the best efforts of academic, industry, and advocacy communities, clinical progress against Alzheimer's has been frustratingly slow," said Casey Lynch, Cortexyme's co-founder, chief executive officer, and an author on the Science Advances paper. "The Science Advances publication sheds light on an unexpected driver of Alzheimer's pathology – the bacterium commonly associated with chronic gum disease – and details the promising therapeutic approach Cortexyme is taking to address it with COR388."

In October 2018, Cortexyme announced encouraging results from its Phase 1b clinical trial of COR388 at the 11th Clinical Trials in Alzheimer's Disease Conference. Investigators reported the compound was safe and well tolerated in healthy older volunteers and Alzheimer's patients when given at a range of doses for up to 28 days. COR388 was detectable in the cerebral spinal fluid (CSF) along with fragmented DNA from the bacterium that COR388 targets. Additionally, while the study was not powered for significance, COR388 showed positive trends across several cognitive tests in patients suffering from AD. Cortexyme plans to initiate a large Phase 2/3 clinical trial of COR388 in mild to moderate AD in 2019.

Read the Science Advances paper in full here:

http://advances.sciencemag.org/content/5/1/eaau3333

About Cortexyme

Cortexyme is a privately held, clinical-stage pharmaceutical company developing therapeutics to alter the course of Alzheimer's and other degenerative disorders. Cortexyme is targeting a specific, infectious pathogen tied to neurodegeneration and chronic inflammation in humans and animal models. The company's lead compound, COR388, is entering Phase 2/3 development; additional proprietary small molecules are moving forward in preclinical development. Cortexyme's investors include Sequoia Capital, Vulcan Capital, Verily Life Sciences, EPIQ Capital Group, RSL Investments, Lamond Family, Pfizer, Takeda Ventures, Breakout Ventures, Dolby Family Ventures, and Breakout Labs among others. For more information on Cortexyme, visit www.cortexyme.com.