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Letter to the Editor

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Oral bacterium *Porphyromonas gingivalis*, an upstream driver of dementia

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Dear Editor:

Researches have been accumulating that oral microbiome can affect systemic diseases and cognitive functions beyond the oral cavity. Recently, there have been notable studies in this regard, and we would like to introduce them.

Cortexyme, Inc. (NASDAQ: CRTX), a biopharmaceutical company based in San Francisco, CA, has been conducting a phase 2/3 clinical trial evaluating the safety and efficacy of an investigational oral drug (atuzaginstat) that inhibits lysine gingipain from the bacterium *Porphyromonas gingivalis*. The gingipain protease is essential for the survival of the anaerobic asaccharolytic Gram-negative bacterium notorious for causing periodontal diseases. The results of the GAIN (GingipAIN Inhibitor for Treatment of Alzheimer's Disease) trial, based on emerging evidence that the oral pathogen can infect the brain and cause Alzheimer's disease, were first released at CTAD 2021 on November 11, 2021. Before the trial, there was a seminal study showing that the oral infection can cause Alzheimer's disease in a mouse model (Dominy et al, 2019). The GAIN trial, a double-blind and placebo-controlled study, was the first to provide the evidence involving human volunteers, which can be summarized as follows; first, the efficacy of atuzaginstat was not significant for all 643 participants after 48-week observation. Second, in 242 pre-specified cohorts with *P. gingivalis* infection, atuzaginstat was 50% more effective in slowing cognitive declines compared to placebo. Third, the reduction of *P. gingivalis* in the saliva is associated with the

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improvement of cognitive function.

The company's share plummeted 70% after the results were issued, as markets focus on the first finding of the above summary. However, we, as dental healthcare service providers, need to embrace the results with considerable significance in a positive way.

First, Cortexyme's results add more strength to the inflammatory hypothesis of Alzheimer's disease. Since the 1990s, the amyloid hypothesis has long been supported as the most plausible etiology of the disease (Hardy and Allsop, 1991). However, findings from the 2010s that showed that β-amyloid possesses antibacterial activity have been dismantling the basis of the hypothesis (Kumar et al, 2016; Gosztyla et al, 2018; de Oliveira et al, 2021). In other words, β-amyloid may not be the cause of the disease but the result of defensive responses to the brain-infiltrating microorganisms. Furthermore, new drug development based on the amyloid hypothesis has been unsuccessful so far. In the meantime, the inflammatory hypothesis has gained traction with the observations that brain blood barriers can weaken with aging (Hussain et al, 2021) and that, as ascertained by the Human Microbiome Project, no region of our body is free from microorganisms (Kinney et al, 2018; van de Guchte et al, 2018). Our entire body, including the brain, and microorganisms comprise a holobiont that needs continuous checks and balances between the host and the microbiome, which may lead to low-grade chronic inflammation.

Second, the GAIN trial seems to be the first to confirm the clinical significance of *P. gingivalis* among other pathogenic bacteria found during the emergence of the inflammatory hypothesis of Alzheimer's disease (Vigasova et al, 2021). Numerous studies have pointed out the relationship between oral health, periodontal disease, oral bacteria, and brain function (Carter et al, 2017; Choi et al, 2019; de Oliveira Araújo et al, 2021). More specifically, inflammation triggered in the oral cavity may spread to the whole body, including the brain. However, to shift from correlation to causality, a more elaborately designed clinical study is needed, which was conducted by Cortexyme, albeit partially.

Third, the trial seems to foretell that oral bacterial examination and appropriate oral care should be included in the healthcare program for patients with cognitive impairment in the future. The management of multifactorial disorders such as Alzheimer's disease needs multi-faceted approaches, rather than a single treatment, and among which oral bacterial management may be the most important. Indeed, Cortexyme pointed out the importance of proper sub-grouping of Alzheimer's patients with *P. gingivalis* burden for better efficacy of the drug. Those results can give patients hope that dental hygiene activities targeting oral pathogens can preserve and even improve cognitive function. Such hygiene activities can be easily implemented not only in dentistry, but also in everyday life. Above all, there is no concern about controversial side effects typically associated with drugs.

As health care providers in the dental community, we understand the differentiated significance of the study results because we may serve as gatekeepers for the management of patients with cognitive impairment. For example, when a

patient is diagnosed with dementia by a psychiatrist or neurologist, a subsequent examination for oral *P. gingivalis* may become essential to decide whether to include oral care in the treatment regime. We need to be prepared for this plausible and reasonable change.

Oral bacteria disseminate to the whole body through various channels that connect different systems, such as digestive tracts, blood vessels, and lymphatic vessels, thereby affecting systemic diseases including, but not limited to, cardiovascular disease and cancer (Willis and Gabaldón, 2020; Narengaowa et al, 2021). At last, we are uncovering the oral-gut-brain axis and recognizing that systemic health begins with oral healthcare. We envisage that Cortexyme's clinical study would catalyze the evolution of dental hygiene practices from physicochemical to biological and holobiont approaches.

Thank you.

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