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GABAeron Presents Promising Preclinical Data on Stem Cell–Based Therapy for Alzheimer's Disease
Human interneuron progenitors derived from induced pluripotent stem cells (iPSCs) can be successfully transplanted and integrate into mouse brains, mature, and reverse signs of hippocampal network dysfunction associated with Alzheimer's disease, GABAeron scientists reported at ISSCR/JSRM.

SAN FRANCISCO, Calif. – GABAeron, Inc. today presented promising preclinical data on their first-in-class, iPSC-based cell therapy product for Alzheimer's disease at the International Society for Stem Cell Research (ISSCR) and Japanese Society for Regenerative Medicine (JSRM) international meeting "Stem Cells: From Basic Science to Clinical Translation." The data, the first to be publicly shared since the company was founded in 2017, highlight the potential of transplanted, human iPSC-derived interneuron progenitors in treating Alzheimer's disease as well as other neurological disorders with interneuron deficit or loss.

GABAeron scientists successfully differentiated GABAergic interneuron progenitors from human iPSCs, and showed that — when transplanted into the brains of an Alzheimer's disease mouse model carrying the major genetic risk factor apolipoprotein E4 (*APOE4*) — the cells could mature, integrate into the hippocampus, and reverse signs of the hippocampal network dysfunction associated with Alzheimer's disease.

"We are incredibly excited by these data, which show the safety and efficacy of our novel iPSC-based approach in an Alzheimer's disease mouse model," said Robert W. Mahley, MD, PhD, chief executive officer and chief scientific officer of GABAeron. "Based on these results, we plan to continue our work to develop a cell replacement therapy to treat patients with *APOE4*-positive Alzheimer's disease."

Over the course of his career, Mahley — president emeritus of the Gladstone Institutes and professor of pathology and medicine at the University of California, San Francisco — has illuminated the importance and molecular details of the protein APOE. The gene for *APOE* comes in several versions and we now know that people with the *APOE4* version of the gene have an increased risk of Alzheimer's disease and an earlier age of disease onset compared to people with the more common *APOE3* version. Strikingly, *APOE4* is associated with 60–75% of all Alzheimer's disease cases.

GABAeron scientific co-founder Yadong Huang, MD, PhD, director of the Center for Translational Advancement at the Gladstone Institutes, San Francisco, discovered one important reason for the

association between *APOE4* and Alzheimer's disease. *APOE4*, his lab demonstrated, leads to the impairment and loss of hippocampal GABAergic interneurons — cells critical for maintaining normal hippocampal activity, required for normal learning and memory, and damaged or lost in Alzheimer's disease brains.

"GABAeron was founded on the premise that if we can replace those interneurons via cell-based therapy, we can restore normal hippocampal activity and thus slow or reverse many of the memory and cognitive impairments associated with Alzheimer's disease," said Huang. "If this approach works, it will be a single treatment with long-lasting impact for Alzheimer's patients."

In the new study, researchers led by Wen-Chin (Danny) Huang, PhD, and Iris Avellano, developed a novel effective method of coaxing human iPSCs carrying the *APOE3* gene to differentiate into GABAergic interneuron progenitors. The resulting cells showed high viability, purity, and robust functionality with more than 90% committed to the correct developmental lineage.

A team led by Wan-Ying Hsieh, PhD, transplanted these interneuron progenitors into the hippocampus of 10-month-old mice carrying the human *APOE4* gene; the interneuron progenitors showed robust survival and matured into functional GABAergic interneurons. At 7 months post-transplantation, more than half of the surviving cells had migrated out of the local area, populated the hippocampal subregions, and established connections with other existing neurons throughout the hippocampus.

"These exciting data reveal the high quality of human iPSC-derived interneuron progenitors generated at GABAeron and highlight the feasibility of their long-term survival and integration into mouse brains," said Hsieh. "Importantly, there was no tumor formation from the transplanted cells in over a hundred mice."

They next carried out electrophysiological recordings to study hippocampal network activity in the mice. As expected, the *APOE4* mice had deficits in hippocampal activity that can underlie the memory impairments associated with Alzheimer's disease. Specifically, the mice had fewer sharp-wave ripples and their associated slow gamma power in the hippocampus — both of which are critical for memory formation and retrieval. When each mouse was transplanted with approximately 120,000 iPSC-derived human interneuron progenitors carrying *APOE3*, these measurements of hippocampal activity both improved to the levels seen in healthy mice 7 months later.

"These results as a whole represent a critical step toward a potential interneuron-based therapy for *APOE4*-related Alzheimer's disease," said Qin Xu, PhD, senior director at GABAeron. "This builds up a solid foundation for our further work with clinical-grade human iPSCs."

GABAeron scientists are now adapting their culture techniques for the mass production of clinical-grade human iPSC-derived GABAergic interneuron progenitors. They are also working to identify the molecular characteristics of the mature GABAergic interneurons, which become successfully integrated into the hippocampus in the Alzheimer's disease mouse model.

"With this critical milestone reached, GABAeron will move forward, with great confidence, toward IND-enabling studies and future trials with clinical-grade human iPSC-derived interneuron progenitors for treating *APOE4*-related Alzheimer's disease," said Sheng Ding, PhD, scientific co-founder of GABAeron and a serial entrepreneur who co-founded two leading public companies, Fate Therapeutics (FATE) and Tenaya Therapeutics (TNYA). "We also plan to explore the usefulness of such a cell-based therapy for other neurological diseases with interneuron deficits or loss."

The ISSCR/JSRM international meeting "Stem Cells: From Basic Science to Clinical Translation" runs from October 27–29, 2021 and is being held virtually this year.

About GABAeron

GABAeron, Inc. is a biopharmaceutical company founded in 2017, based on pioneer work initiated at the Gladstone Institutes, to build on the promise of combining precision medicine, regenerative medicine, and pharmaceutical intervention. The company is exploring a new first-in-class IND candidate to replace or restore neurons injured or lost in the brains of patients suffering from neurodegenerative and neurodevelopmental disorders.

For more information about GABAeron, please visit www.GABAeron.com or contact Sylvia Richmond, sylvia.richmond@gabaeron.com.