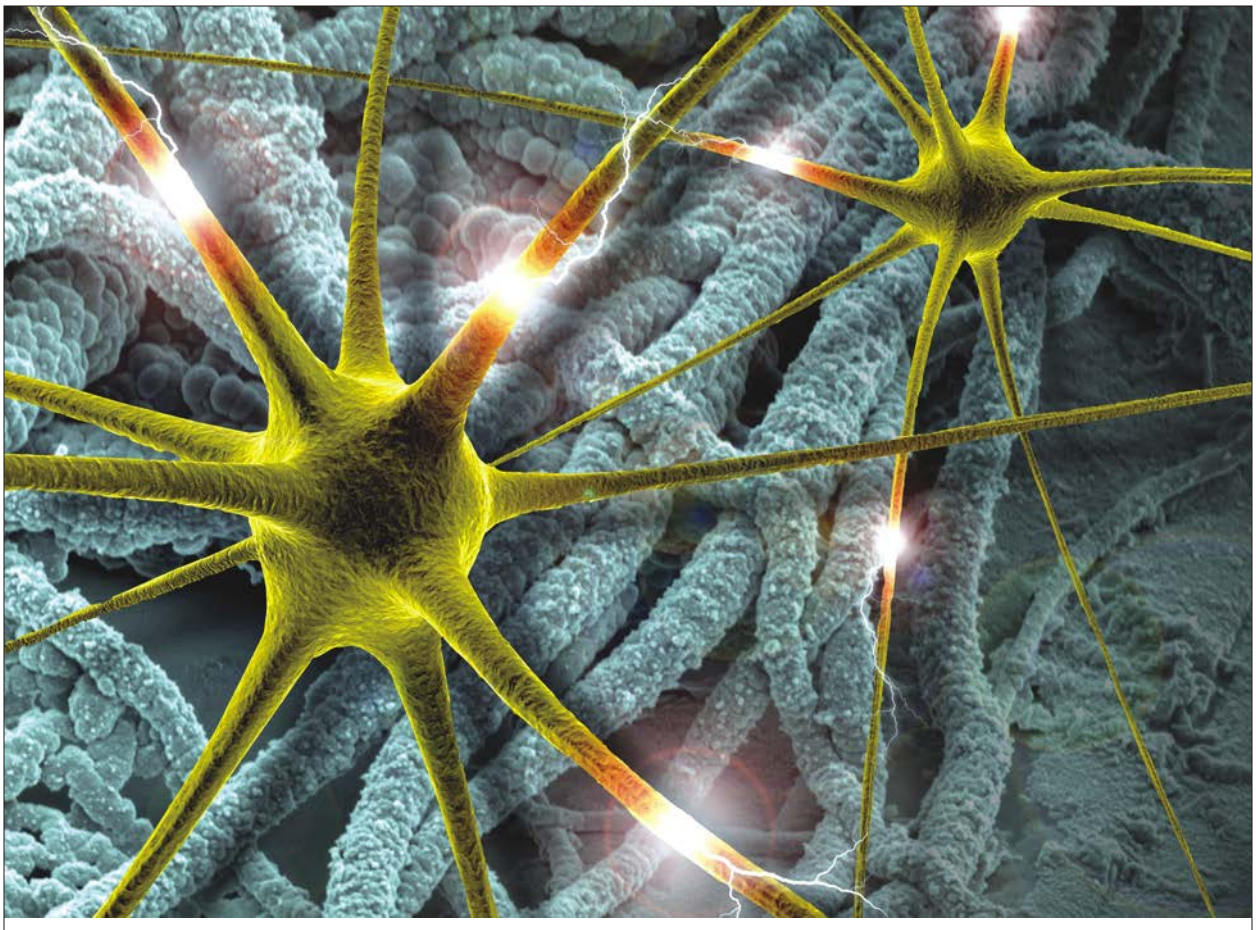

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Gene Therapy Prevents Memory Problems in Mice With Alzheimer's Disease

Scientists at the Gladstone Institute of Neurological Disease (GIND) in San Francisco have discovered a new strategy to prevent memory deficits in a mouse model of Alzheimer's disease (AD). Humans with AD and mice genetically engineered to simulate the disease have abnormally low levels of an enzyme called EphB2 in memory centers of the brain. Improving EphB2 levels in such mice by gene therapy completely fixed their memory problems.

The findings will be published in the Nov. 28 issue of the journal Nature.

In both humans and mice, learning and memory requires effective communication between brain cells called neurons. This communication involves the release of chemicals from neurons that stimulate cell surface receptors on other neurons. This important process, called neurotransmission, is impaired by amyloid proteins, which build up to abnormally high levels in brains of AD patients and are widely thought to cause the disease. But how exactly these poisonous proteins disrupt neurotransmission is unknown.

"EphB2 is a really cool molecule that acts as both a receptor and an enzyme," said Moustapha Cisse, PhD, lead author of the study. "We thought it might be involved in memory problems of AD because it is a master regulator of neurotransmission and its brain levels are decreased in the disease." To determine if low EphB2 levels actually contribute to the development of memory problems, the investigators used gene therapy to experimentally alter EphB2 levels in memory centers of mice. Reducing EphB2 levels in normal healthy mice disrupted neurotransmission and gave them memory problems similar to those seen in AD. This finding suggests that the reduced EphB2 levels in AD brains contribute to the memory problems that characterize this condition.

"What we were most curious about, of course, was whether normalizing EphB2 levels could fix memory problems caused by amyloid proteins," said Lennart Mucke, MD, director of the GIND and senior author of the study. "We were absolutely thrilled to discover that it did." Increasing EphB2 levels in neurons of mice engineered to produce high levels of human amyloid proteins in the brain prevented their neurotransmission deficits, memory problems and behavioral abnormalities. The scientists also discovered that amyloid proteins directly bind to EphB2 and cause its degradation, which helps explain why EphB2 levels are reduced in AD and related mouse models.

"Based on our results, we think that blocking amyloid proteins from binding to EphB2 and enhancing EphB2 levels or functions with drugs might be of benefit in AD.", Said Mucke. "We are excited about these possibilities and look forward to pursuing them in future studies." Also contributing to this study were Gladstone scientists Brian Halabisky, Julie Harris, Nino Devidze, Dena Dubal, Bin-Gui Sun, Anna Orr, Gregor Lotz, Daniel H. Kim, Patricia Hamto, Kaitlyn Ho, and Gui-Qiu Yu.

The study was supported by grants from the National Institutes of Health and a fellowship from the McBean Foundation.

Lennart Mucke's primary affiliation is with the Gladstone Institute of Neurological Disease, where he is Director/Senior Investigator and where his laboratory is located and his research is conducted. He is also the Joseph B. Martin Distinguished Professor of Neuroscience and Professor of Neurology at UCSF.