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2018 The Part the Cloud to RESCUE Brain Cell Degeneration in Alzheimer's Disease-
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Silent Allosteric Modulation of mGluR5 for Alzheimer's Disease

Can a drug block harmful functions of a brain cell protein without affecting its normal, healthy functions in people with Alzheimer's?

PI

- M.D. and Ph.D., Johns Hopkins University, 1986
- Director, Yale Alzheimer's Disease Research Center
- Director, Yale Memory Disorders Clinic
- Co-founded Yale Program in Cellular Neuroscience, Neurodegeneration, and Repair

STUDY

- CADRO category: Translational Research & Clinical Interventions
- Dr. Strittmatter has been awarded the Association's prestigious Zenith award in the past.

Background

One of the hallmarks of Alzheimer's is the accumulation of harmful beta-amyloid protein fragments in the brain. Beta-amyloid could attach to proteins on the surfaces of brain cells (called "receptors") and impair brain cell communication. Researchers have found that blocking one brain cell receptor, called mGluR5, can interrupt its interactions with beta-amyloid. This can reverse signs of Alzheimer's in some genetically engineered Alzheimer's-like mouse models—making the receptor an attractive drug target. However, the mGluR5 receptor is also central to healthy brain function. Blocking it entirely could have widespread, harmful effects in humans.

Dr. Stephen M. Strittmatter and colleagues have been searching for molecules that can block interactions between beta-amyloid and mGluR5, without affecting the receptor's normal function. The researchers call these molecules "silent allosteric modulators," or SAMs, as they are "silent" in regard to their impact on normal receptor function, but "allosteric" meaning they block other protein interactions. Dr. Strittmatter has studied SAMs in genetically-engineered Alzheimer's-like mouse models, and identified those that help improve memory.

Research Plan

Dr. Strittmatter has proposed to study one particularly promising mGluR5 SAM molecule in detail. Together with colleagues, he will develop an oral medication for testing purposes, with the SAM as the active ingredient. He will test different drug formulations in Alzheimer's-like mice, and study how the molecule is metabolized. Dr. Strittmatter will then seek FDA approval for a phase 1b clinical trial, where he will carefully monitor people with mild Alzheimer's-related cognitive impairment as they receive doses of the investigational drug.

Impact

Although early in the drug development process, the goal of this study is to develop an oral therapy that could slow, halt, or partially reverse Alzheimer's progression. If the mGluR5 SAM molecule proves therapeutic, results from this study could form a foundation for phase 2 clinical trials in people with Alzheimer's-related cognitive impairment.