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Phase 1 Testing of a Muscarinic M1 PAM for Alzheimer’s Disease

Can a novel molecule that stimulates specific docking sites on the surface of nerve cells improve brain function?

Background
Nerve cells communicate using specific kinds of messenger molecules called “neurotransmitters.” Neurotransmitters bind to docking sites called “receptors” on the surface of nerve cells, activating these cells, which is inherent to how the brain functions. Individuals with Alzheimer’s disease often experience a specific loss of function in the “cholinergic” neurotransmitter system which is important for cell to cell communication and cognitive function.

In recent decades, a number of potentially therapeutic molecules have been developed to stimulate cholinergic neurotransmitter receptors on the surface of nerve cells, but their mechanisms of activation are not specific enough and can lead to unwanted side effects. Thus these molecules can only be given to individuals with Alzheimer’s disease in small amounts and are limited in their effectiveness.

Research Plan
Paul Newhouse, M.D. and colleagues have identified a novel molecule, called a “muscarinic M1 PAM,” that encourages activation of a specific type of cholinergic receptors on the surface of nerve cells, reducing unwanted side effects. In previous studies using animal models, the research team has shown that this molecule is well-tolerated and effectively targets brain regions important for cognitive function. For their current studies, the researchers will conduct their first human clinical trial in humans with this compound, or any compound of this class. They will administer increasing amounts of the muscarinic M1 PAM molecule to healthy volunteers to determine the most safe and effective dose. The team will measure the levels of the molecule in the blood to determine how it is absorbed, the length of time it stays in the blood, and how it is eliminated from the body. They will also examine the compound’s effect on memory and other brain functions.

Impact
These studies will provide critical information about the effects of this novel molecule and the optimal doses for use in future clinical trials. If successful, the results of this effort could advance this experimental drug, and other drugs in this class, as a potential therapeutics for preventing or treating Alzheimer’s disease.

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