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Capturing tau kinetics in a clinical trial of ASO NI0752 in Alzheimer's

This Phase 1b clinical trial will evaluate safety, tolerability and dose of a novel compound aimed to reduce dementia-related tau production in individuals with Alzheimer's.

Background

Tau is a protein that primarily helps support nerve cell structure and helps to transport nutrients within brain cells. In Alzheimer's and other brain diseases, the shape of tau becomes modified or "misfolded" leading to the formation of clumps of tau known as "tangles" within the brain. Tau tangles have been shown to cause nerve cell damage and are linked to cell death. This is one of the hallmark features of these diseases.

The gene that provides instructions for making the tau protein is called microtubule associated protein tau, or MAPT. There are ongoing efforts to develop potential therapies to target the tau protein and/or the MAPT gene to impact the downstream disease-related tau changes.

In recent years, scientists have been testing a novel molecular biology technique which works to reduce abnormal tau levels in the brain. This technique uses molecules called antisense oligonucleotides (ASOs) which are created in the laboratory using small fragments of DNA that can target specific genes in cells. Using an ASO to target MAPT, the team can reduce MAPT gene production which leads to a subsequent reduction in the production of the tau protein ,

Research Plan

In initial studies led by Dr. Ross Paterson, a particular ASO called NI0752 which targets MAPT was found to be safe and tolerable in different animal model systems and can reduce the levels of the tau protein.

Dr. Paterson and colleagues will now lead an academic Phase 1b clinical trial to determine the effect this drug is having on the creation and synthesis of tau.

The researchers will recruit ten individuals, five of whom have sporadic Alzheimer's (the more common form Alzheimer's which has no clear genetic link), and five of whom have a rare inherited form of Alzheimer's called autosomal-dominant Alzheimer's disease (ADAD).

The primary measures will work to compare how tau production levels differ between those who received NI0725 and those who didn't. To measure tau production in these individuals, they will use a newly-developed state of the art technique called stable isotope labeling kinetics (SILK), which can "highlight" and measure changes in tau production in the blood and CSF. Protein changes in blood and CSF often indicate similar dementia-related changes in the brain. The secondary outcome of this study is to evaluate the safety and tolerability of NI0752.

Impact

The study results may give rise to information that will inform larger clinical trials for individuals with Alzheimer's or other tau related brain diseases. If successful, this study will identify a novel drug therapy method targeting tau.

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