Washington University in St. Louis
Office of Technology Management

A BIOMARKER TO MONITOR CNS EFFICACY OF 2-HYDROXYPROPYL-B-CYCLODEXTRIN (HPBCD)

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T-012136

Background: Niemann-Pick type C1 (NPC1) disease is a rare neurological disorder characterized by cholesterol and lipid accumulation in the central nervous system. Individuals with the abnormal buildup of cholesterol and other lipids in the brain often suffer from cognitive and movement difficulties, and usually die in about 10-15 years after onset. There are no FDA-approved drugs or therapies for this disease, and a barrier to the drug/therapy development is the lack of outcome measures for clinical trials. 2-hydroxypropyl-β-cyclodextrin (HPBCD) is a promising drug candidate effective in slowing the progression of NPC1 disease in both animal models and clinical trials. The neuro-protective effect of HPBCD has been shown accompanied by reduction of CNS cholesterol storage. To better evaluate its therapeutic efficacy in clinical trials, scientists at Washington University in St. Louis have identified a pharmacodynamic biomarker to track efficacy of HPBCD treatment.

Technology Description: 24(S)-hydroxycholesterol [24(S)-HC] is a cholesterol metabolite exclusively made in the central nervous system and then released into the blood plasma. Conversion from cholesterol to 24(S)-HC represents the major pathway for cholesterol elimination from the brain. The concentrations of 24(S)-HC in plasma or cerebrospinal fluid (CSF) can therefore serve as a sensitive marker of altered cholesterol metabolism in the CNS. The team led by Dr. Ory developed a highly selective, sensitive, and high-throughput LC-MS/MS assay for quantification of 24(S)-HC in human plasma and CSF. This method has been successfully applied to explore 24(S)-HC as a pharmacodynamic biomarker in the clinical trial of HPBCD in NPC1 patients, and a significant increase of 24(S)-HC has been revealed both in plasma and CSF following intracerebroventricular administration of HPBCD.

Key Advantages:

• Enables outcome measures of HPBCD efficacy in clinical trials of NPC1

• A highly sensitive and robust LG-MS/MS method with reduced run time, increased throughput, and minimized nonspecific absorption issues for 24(S)-HC quantification

• Platform technology with potentials to be applied to other neurological diseases involving abnormal cholesterol storage, including Alzheimer's disease.

• Validated technology both in animal models and in clinical trials

Patent: Issued: 9,012,216

Publications: J Lipid Res. 2015 Jun;56(6):1222-33

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Dr. Ory is internationally recognized for his work on elucidating mechanisms underlying cholesterol homeostasis, and the translation of the findings to develop biomarkers for prevention and treatment of human diseases.