

Harnessing Hope to Treat Rare Disease in Children

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New research from Victoria University of Wellington has provided insight into the effectiveness of a potential drug to treat a rare, fatal disease in children.

Sometimes referred to as childhood Alzheimer's, Niemann-Pick Type C (NPC) disease is a genetic disorder characterised by an inability of the body to transport cholesterol and other fatty substances (lipids) inside cells in the brain and liver. Lipids consequently accumulate in the liver, spleen and brain.

The disease causes quick and progressive mental and physical deterioration with typical loss of life prior to adolescence. Though rare, an estimated 500 children currently suffer from NPC disease worldwide.

An international team, led by Dr Andrew Munkacsi from Victoria's School of Biological Sciences and Dr Stephen Sturley at Columbia University Medical Center, investigated the therapeutic efficacy of Vorinostat—a drug approved to treat cancer—to treat NPC disease.

"As no cure exists, finding drug therapy is crucial," explains Dr Munkacsi. "Given that it takes more time to develop a new drug than the average lifespan of an NPC patient, identifying an existing drug treatment is the goal."

"Vorinostat is currently in a clinical trial for NPC disease. This clinical trial was approved without some therapeutic efficacy testing because the drug was already approved to treat cutaneous T-cell lymphoma and potential drugs to treat NPC disease are in very high demand."

In 2011, Drs Munkacsi and Sturley published a paper that identified the potential of Vorinostat to treat NPC disease. The study involved experiments using yeast as a model of NPC disease and then translating these experiments to cultures of human cells.

A new paper, published online last month in *The Journal of Biological Chemistry*, builds upon the 2011 study.

It found Vorinostat has the ability to correct multiple pathophysiological defects in the liver of an animal model that closely mimics human patients. The accumulation of lipids in liver cells was reduced and liver health was improved.

"By measuring the expression of approximately 14,000 genes in the liver, we were able to determine that Vorinostat normalised expression of key genes in the biosynthesis and transport of cholesterol in the liver," says Victoria University Master's graduate Natalie Hammond, a co-author on the new paper.

"It's an exciting result that shows the potential of Vorinostat to treat NPC disease in the clinical trial", says Dr Munkacsi.

"While it helped reduce lipids in the liver, it is unable to cross the blood-brain barrier and so may not address the build-up of lipids in the brain."

Other contributing authors to the paper were from Callaghan Innovation in Lower Hutt, Tottori University in Japan and various research institutions in the United States (Mount Sinai School of Medicine, Washington University School of Medicine, Giesel School of Medicine at Dartmouth and University of Texas Southwestern Medical Center).

The study was primarily supported by the National Niemann-Pick Disease Foundation, the Ara Parseghian Medical Research Foundation and Dana's Angels Research Trust.

"These parent-patient funded foundations are critical to investigations in rare diseases like NPC disease," says Dr Munkacsi.