hadleyhope fund

Hadley Hope Fund is a Federal Non-Profit 501(c)3 Tax Exempt Organization, governed by a Board of Directors in Southern Oregon. Two local children, Peyton & Kayla Hadley of Medford, Oregon are afflicted with the disease, for which this organization was formed in September 2008.

Our Mission

Fund ethical scientific research to accelerate therapies and a cure for Niemann-Pick Type C Disease (NP-C), known as "Childhood Alzheimer's".

By **January 1, 2011**, four prominent NP-C scientists expect to have a combination of FDA approved pharmaceutical drugs/ compounds that will significantly delay or slow the progression of NP-C disease.

How 1-1-11 Goal Will Be Achieved

- Through the love, prayers, and financial support of family, friends, and community.

- Four family organizations along with Hadley Hope have come together to support one common mission.

Reno, NV

DANA'S Angel's Research Trust

Greenwich, CT

Hide & Seek Foundation for LYSOSOMAL DISEASE RESEARCH

Long Beach, CA

Race for Adam Foundation — Learn about Niemann-Pick

Race for Adam Foundation — Allentown, PA

Four Key Researchers

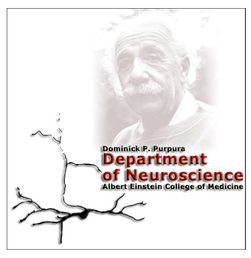
Washington University in St. Louis

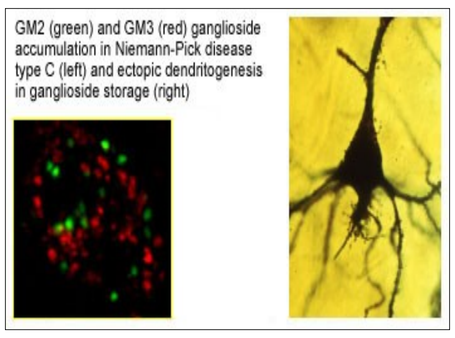
Daniel S. Ory, M.D.
Professor, Internal Medicine, School of Medicine, Division of Biology & Biomedical Sciences
Washington University in St. Louis

Cholesterol is an essential component of the plasma membrane in animal cells, regulating membrane fluidity and the formation of lipid microdomains. To perform these functions, the cellular distribution of membrane cholesterol must be maintained. Insight into these mechanisms has come from the study of genes that are mutated in the human Niemann-Pick type C (NPC) disease. Our studies have shown that NPC1 regulates sterol homeostasis through the generation of low-density lipoprotein (LDL) cholesterol-derived oxysterols. The goals of studies in the Ory lab are to understand the basic molecular mechanisms in regulation of cholesterol homeostasis, and the function of the NPC1 protein. First, our studies involve genetic screens in cultured cells to identify molecular machinery involved in intracellular cholesterol trafficking, which will then be studied in mouse models. In an interdisciplinary approach, we are using biophysical, cell biology, steroid chemistry and lipidomic methods to understand the mechanism through which oxysterols exert their homeostatic effects. These studies have led to identification of candidate cholesterol metabolites that are being examined as biomarkers for atherosclerosis and diabetes in human populations. Second, a major effort in the lab is to understand how NPC1 loss of function contributes to disease. The mechanism by which NPC1 loss of function contributes to neuronal cell death is being studied in a mouse knockout model. The latter studies have led to identification of novel approaches to slow the progression of neurodegeneration. Together, these studies may shed light on the pathogenesis of atherosclerotic vascular diseases, such as coronary artery disease, and provide new insight into the role of cholesterol in neurodegeneration.

Steven Walkley, D.V.M.
Professor, Albert Einstein College of Medicine

The research interests of my laboratory are concerned with analysis of pathogenic cascades and development of therapeutic strategies for genetic disorders of the endosomal-lysosomal system known as neuronal storage diseases. Disorders include Tay-Sachs, Hurler, Sanfilippo, Niemann-Pick, Batten, and other related conditions, all of which are characterized by insidious onset and progression of neurological dysfunction, including mental retardation, following an initial period of normal development. Our studies are focused on the link between the primary protein defect and the abnormal accumulation of substrate (gangliosides, glycosaminoglycans, and cholesterol) with subsequent induced changes in trafficking and signaling events within affected neurons. Therapeutic strategies include attempts to replace missing proteins through cell-mediated approaches (e.g., bone marrow transplantation) and to reduce storage pharmacologically with inhibitors of substrate synthesis, both of which have shown promise in specific types of storage disorders.





Frances M. Platt, PhD.
Department of Pharmacology,
University of Oxford

UNIVERSITY OF OXFORD

Dr. Fran Platt's research is currently focused in three main areas as it relates to NP-C & other storage disorders: 1)therapeutic strategies for treating storage diseases involving the brain, 2) mechanisms of pathogenisis in storage diseases, 3) glycosphingolipid functions and presentation within the immune system. She and her colleagues have pioneered a novel approach to treat these inherited metabolic diseases that has led directly to the development of an effective drug (Miglustat/Zavesca) for type 1 Gaucher Disease. This drug has now being approved for clinical use in Europe, Israel, and is awaiting approval in the U.S. Her most recent article as it relates to NP-C was published in October 2008, and a short summary follows:

Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium
The function of NPC1 is unknown, but when it is dysfunctional, sphingosine, glycosphingolipids, sphingomyelin and cholesterol accumulate. We have found that NPC1-mutant cells have a large reduction in the acidic compartment calcium store compared to wild-type cells. Chelating luminal endocytic calcium in normal cells with high-affinity Rhod-dextran induced an NPC disease cellular phenotype. In a drug-induced NPC disease cellular model, sphingosine storage in the acidic compartment led to calcium depletion in these organelles, which then resulted in cholesterol, sphingomyelin and glycosphingolipid storage in these compartments. Sphingosine storage is therefore an initiating factor in NPC1 disease pathogenesis that causes altered calcium homeostasis, leading to the secondary storage of sphingolipids and cholesterol. This unique calcium phenotype represents a new target for therapeutic intervention, as elevation of cytosolic calcium with curcumin normalized NPC1 disease cellular phenotypes and prolonged survival of the NPC1 mouse.

Yiannis Ioannou, PhD
Associate Professor, Genetics & Genomic Sciences, Mt. Sinai School of Medicine

Our lab is involved in a number of projects that center on the biology, function, and diseases of the endosomal/lysosomal system. In addition, we are developing methods to treat lysosomal diseases via enzyme and gene therapy approaches. Our overall objective is to identify and characterize the components of intracellular cholesterol and determine their function and interactions. Although the intercellular transport of cholesterol from the liver to pheripheral tissues has been intensively studied, little is known about its egress from the E/L system, its intracellular transport and the proteins involved in this process. The existence of such proteins is highlighted by the autosomal recessive disorder, NPC disease, which we are involved with in studying with other collaborators.

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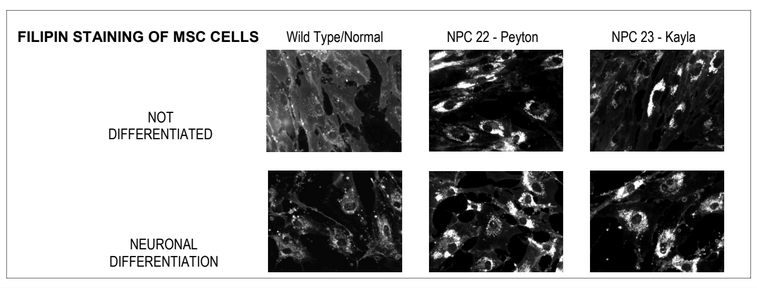
Only made possible through your generous donations.

JOHN PAUL II STEM CELL RESEARCH INSTITUTE with CELLULAR ENGINEERING TECHNOLOGIES 12/08
Iowa City, IA Directed by Dr. Allan Moy
Ad-MSC Project - Adipose derived mesenchymel stem cells (Ad-MSC's) were harvested from the fat cells of Niemann-Pick Type C patients (Peyton & Kayla) to test if they could be converted into neuroprogenitor cells. These cells have been successfully validated as cells that fully characterize the NP-C phenotype, which is the inability to transport cholesterol out of the cell. A secondary and more ultimate goal is to test these cells with compounds that could transport cholesterol, thereby correcting the defect. Two goals have been attained so far with this ongoing project. Scientists have been able to validate the expression of the NP-C Disease phenotype, and by applying the compound, Cyclodextrin, cholesterol is transported out of these cells. This is very exciting news, as it confirms the findings from both the Walkley and Dietschy labs (see s ref's.below) and we are hopeful with the progress being made. They have yet to differentiate these cells into neuronal progenitors. These Ad-MSC cells are currently being studied at The University of Alberta by Dr. Jean Vance and at the National Institutes of Health Chemical Genomics Center within their screening center.



JPII SRI
CET celleng-tech.com
UNIVERSITY OF ALBERTA
NCGC NIH Chemical Genomics Center

KING'S COLLEGE LONDON 1/09
Strand, London Directed by Dr. David Begley at request of Dr. Steven Walkley
Investigation into whether HPBCD crosses the Blood-Brain Barrier
A stunning finding in the last year at two independent labs has shown that the treatment of 2-hydroxypropyl-beta-cyclodextrin or HPBCD to NP-C deficient mice significantly increases their lifespan. Two imperative questions need to be answered as a result of these findings: 1.) Does HPBCD cross the BBB and 2.) If is does cross, what is the mechanism? Two secondary questions may also arise from this: If HPBCD doesn't cross the barrier, how is its beneficial effect in the NPC-/- mice mediated and if it does cross, can the ability of cyclodextrins to complex with and contain many other drugs be employed as a drug delivery system to treat a range of CNS diseases?

KING'S College LONDON

S C I E N T I F I C P A P E R S O N C Y C L O D E X T R I N

UT SOUTHWESTERN MEDICAL CENTER
EINSTEIN Albert Einstein College of Medicine

Reversal of defective lysosomal transport in NPC disease ameliorates liver dysfunction and neurodegeneration in the npc-/- mouse.
Benny Liu, Stephen D. Turley, Dennis K. Burns, Anna M. Miller, Joyce J. Repa, & John M. Dietschy

Departments of Internal Medicine, Pathology, & Physiology, University of Texas Southwestern Medical Center Dallas, TX 75390 Published December 4, 2008

Chronic Cyclodextrin Treatment of Murine Niemann-Pick Type C Disease Ameliorates Neuronal Cholesterol and Glycosppingolipid Storage and Disease Progression.
Cristin D. Davidson, Nafeeza F. Ali, Matthew C. Micsenyi, Gloria Stephney, Sophie Renault, Kostantin Dobrenis, Daniel S. Ory, Marie t. Vanier, Stephen U. Walkley

Albert Einstein College of Medicine, Washington University School of Medicine, Laennec Medical School & Lyon-1 University Published September 11, 2009