

# **Smith-Lemli-Opitz Syndrome and Inborn Errors of Cholesterol Synthesis**

**Supported by:**

**Office of Rare Diseases, NIH, DHHS**

**National Institute of Child Health and Human Development, NIH,  
DHHS**

**Oregon Health & Science University**

**Grant awards: RO1 HL073980 03S1 ( RO1 supplement) recipient: Robert Steiner 263-MK-70568 DHHS NIH recipient: Robert Steiner -This meeting also received support from intramural research programs of National Institute of Child Health and Human Development and Office of Rare Diseases.**

**Edited by Louise S. Merkens, Ph.D., Christopher Wassif PhD., Jean-Baptiste Roulet PhD., Robert D. Steiner, MD, Forbes D. Porter, M.D, Ph.D., and Kristy Healy R.N. CCRC**

On June 28<sup>th</sup>-29<sup>th</sup> and 30<sup>th</sup> 2007, the National Institutes of Health, Office of rare Diseases, DHHS and the Smith-Lemli-Opitz/RSH Foundation held a scientific conference hosted by Dr. Robert Steiner from Oregon Health & Science University (OHSU) and Dr. Forbes D. (Denny) Porter from NIH/NICHD. One of the main goals of this meeting was to promote interaction between scientists with expertise in cholesterol homeostasis, brain cholesterol metabolism, embryonic development and oxysterol and neurosteroid biology with clinician–scientists studying and treating patients with inborn errors of cholesterol synthesis. We anticipate that these interactions will lead to collaborative projects that will ultimately improve our understanding and treatment of these genetic disorders.

Several of the scientists also participated in the Smith-Lemli-Opitz/RSH Foundation family session the morning of June 30<sup>th</sup> 2007. The families were invited to ask questions and express concerns to a panel of physicians, psychologists, dieticians and scientists currently working in the diagnosis and management of patients with Smith-Lemli-Opitz syndrome (SLOS). This important event offered parents the opportunity to discuss current research with experts in the field.

The keynote speaker for the conference was Dr. G. Stephen Tint, who, in 1992, first identified the cholesterol biosynthetic defect causing SLOS. The keynote speaker award is presented yearly as an honor to an individual with outstanding commitment in the field and is sponsored by the Smith-Lemli-Opitz Foundation Board. Dr. Tint's contributions and service to patients with Smith-Lemli-Opitz syndrome and to their families are recognized internationally and the sponsors of the conference were delighted that he was able to participate in this capacity.

SLOS is the most common among a group of disorders involving multiple malformations and mental retardation due to defects in cholesterol synthesis.

SLOS has an observed incidence of at least 1 in 30,000 but based on carrier rates; it is likely to be more common. The SLOS phenotype includes various congenital malformations, mental retardation and distinctive autistic-like behavior. This group of human syndromes provides a unique opportunity to study the role of cholesterol synthesis and homeostasis in health, development, and behavior. SLOS may also turn out to be a treatable form of mental retardation. Finally, learning more about cholesterol synthesis and metabolism by studying SLOS and related disorders will shed light on the more common disorders with hypercholesterolemia.

### **Sterols, development and the Hedgehog pathway**

Hedgehog (Hh) proteins are secreted signaling molecules that function in diverse patterning of the development of body parts during embryogenesis. Hh proteins can promote cell proliferation, prevent apoptosis and act as morphogens that specify cell responses depending on gradient tissue distribution.

As described by *Dr. Beachy*, newly synthesized Hh proteins undergo a series of posttranslational processing that involves covalent modification by cholesterol resulting in release of active signal with covalent cholesteryl adduct. Hh proteins are the only known proteins that are covalently modified by cholesterol. Even though 7-dehydrocholesterol may be substituted for cholesterol in the activation of Hh proteins, reduction of total sterols, especially during in utero development, could interfere with Hh protein signaling and function. In addition to its role in the biogenesis of the Hh protein, cholesterol has an important role in the response to the Hh protein signal. Cholesterol depletion limits the ability of cells to respond to the Hh protein.

In human CHILD syndrome and in bare patches (*Bpa*) mice, the mutation in sterol dehydrogenase involved in cholesterol biosynthesis results in defects in one or more developmental signaling pathways leading to male lethality as described by *Dr. Herman*. However, in vitro studies have shown that 7-dehydrocholesterol, desmosterol, 7 $\beta$ -hydroxyl cholesterol can substitute for cholesterol in processing domain-mediated transfer reactions. Some of the other proteins in the Hh pathway, PTCH1, have been found in mouse placenta. Affected placentas from another mutant mouse strain, *Nsdhl*<sup>*Bpa-8aH*</sup>, show decreased Hh signaling proteins. New mouse models are being developed to evaluate altered maternal cholesterol metabolism on the developing fetus.

### **Effects of changes in cholesterol synthesis and absorption**

Alterations in the cholesterol pathway affect not only the synthesis of cholesterol synthesized but also the synthesis of other products that branch off from the pathway. Evaluation of the effects of agents or genetic disorders that block or up-regulate enzymes in the cholesterol pathway provides insights of this complex system.

Mevalonate kinase is an enzyme early in the pathway. Mutations in this gene cause severe mevalonic aciduria (MA) and hyperimmunoglobulin D with periodic fever syndrome (HIDS). The homozygous MKD knock-out mice, developed in *Dr. Gibson's* lab, die as embryos implying a key role of this enzyme in mouse embryogenesis. The heterozygotes, however, survive and show immune dysfunction. This model provides an opportunity to understand the mechanism between altering the cholesterol pathway and immune function. Partial inactivation of mevalonate kinase may result in the depletion of the isoprene metabolites that are essential for prenylation of key proteins or the changes in lipid microdomains (rafts) of cell surface signaling proteins.

Lanosterol is a regulatory cornerstone in cholesterol biosynthesis. In the cholesterol pathway, it is the first sterol with the 4-ring structure characteristic of all sterol, steroids and bile acids. Itraconazole is an antifungal agent that inhibits CYP3A4 isoenzyme. As described by *Dr. Lütjohann*, clinical doses of this drug increase serum concentrations of lanosterol and dihydrolanosterol: lowering the LDL/HDL cholesterol ratio and potentially lowering liver degradation of 24S-hydroxycholesterol. Presenilins, endogenous proteins, also have effects on the lipid and protein composition of cellular membranes. Fibroblasts from presenilin double knock-out mice result in lowered lanosterol concentrations and up-regulation of cholesterol synthetic enzymes.

In SLOS, the last enzyme of the cholesterol pathway is inhibited resulting in high concentrations of 7-dehydrocholesterol and low concentrations of cholesterol. To slow down the synthesis of abnormal sterols, high cholesterol diets and high cholesterol diets with statin drugs (inhibitors of HMGCoA reductase) are being evaluated as potential treatments. It is important to evaluate their effects on the cholesterol synthesis pathway as well as on the absorption of dietary cholesterol. Complex techniques using stable isotopes and using gas chromatography (GC)-isotope ratio mass spectrometry (IRMS) by *Dr. Jones* are being used to study metabolism in children undergoing these treatments. Preliminary results show that high cholesterol diet with or without statins decreases the fractional cholesterol synthesis compared with very low cholesterol diet. In addition there is a trend of the high cholesterol with statins to decrease dietary cholesterol absorption compared to high cholesterol diet alone.

Any therapies for SLOS involving dietary cholesterol need to take into account the extent of cholesterol absorption from the intestines. There are many factors that have the potential to affect cholesterol absorption; these include genetic factors, biliary cholesterol secretion, and conversion of cholesterol to bile acids. In addition there are quantitative and qualitative differences in bile acids. Effects of bile acids were reviewed by *Dr. Heubi*. Some bile acids having no effect on cholesterol absorption, and others increasing cholesterol absorption. It has also been shown that cholesterol absorption is dependent upon luminal bile acids and micellar solubilization. In SLOS, urinary bile acids have been shown to be reduced compared to healthy children. Minimal information is available about luminal bile acid content in SLOS.

## Brain Sterol Metabolism

As cholesterol is not transported across the blood-brain barrier (BBB), cholesterol in the CNS is almost entirely from *de novo* synthesis. Under steady-state conditions, an equivalent amount of cholesterol must be eliminated from the brain, and oxysterols effectively perform as transport forms of cholesterol.

A novel route for the elimination of brain oxysterols was presented by *Dr. Meaney*. In addition to the well recognized passage of 24S-hydroxycholesterol across the BBB, there is also the passage of other oxysterols, most notably 27-hydroxycholesterol, from the circulation into the brain. 27-Hydroxycholesterol appears to traverse the lipophilic BBB along a concentration gradient from the relatively high concentration in circulation to the brain. This is coupled with highly efficient metabolism to more polar metabolites within the brain; C27-cholestenoic acids, which are rapidly eliminated from the brain. Cholesterol 27-hydroxylase activity is deficient in the disorder cerebrotendinous xanthomatosis (CTX). Derangements in the pathway described by Meaney may affect brain cholesterol balance in CTX and contribute to the cerebral pathophysiology.

The role of 27-hydroxylation was also described for another disorder, SLOS, by *Dr. Porter*. In addition to the accumulation of 7-dehydrocholesterol (7-DHC) and its metabolites, levels of a novel oxysterol identified in vivo, 27-hydroxy-7-dehydrocholesterol (27OH-7-DHC), demonstrated significant negative correlation to cholesterol levels in plasma from SLOS patients, suggesting a role for this oxysterol in cholesterol homeostasis. As hedgehog signaling is impaired by low cholesterol, increased 27OH-7-DHC may have detrimental effects during development by suppression of cholesterol levels. This hypothesis was tested by generating SLOS mice (*Dhcr7*<sup>-/-</sup>) expressing a *CYP27* transgene that have 2- and 20-fold increased levels of 27OH-7-DHC in plasma and brain, respectively. Consistent with the hypothesis that increased 27OH-7-DHC has detrimental effects during development, *Dhcr7*<sup>-/-</sup>:*CYP27g* embryos have a mutant phenotype that is more representative of severe human SLOS compared to littermate *Dhcr7*<sup>-/-</sup> embryos.

Cholesterol balance across the CNS and cholesterol turnover within the brain was reviewed by *Dr. Dietschy*. Cholesterol in the brain is present in two pools (1) cholesterol in the plasma membranes of glial cells and neurons and (2) cholesterol in the specialized membranes of myelin. Cholesterol turnover from these pools is normally low but may increase among glial cells and neurons during brain growth and neuron repair and remodeling. Internal recycling of cholesterol involves ligands such as apo E and A1, and one or more membrane transport proteins such as members of the low density lipoprotein receptor family.

In work presented by *Dr. Vance*, a population of lipoproteins secreted by glia, containing Apo E and cholesterol, stimulated axon growth of CNS neurons. In addition, neurons

were protected from apoptosis when apoE lipoproteins bound to the low density lipoprotein-receptor-related protein. Cholesterol turnover is known to be increased across the BBB for a number of neurodegenerative disorders, but alteration in sterol turnover within the brain that may in turn affect neuron and myelin integrity, has not been well studied. Niemann-Pick type C (NPC) disease is due to gene mutations in *NPC1* or *NPC2* that cause aberrant intracellular trafficking of cholesterol and result in accumulation of cholesterol in late endosomes/lysosomes. Other data showed that NPC1 deficiency in mouse neurons increased the cholesterol content of cell bodies but reduced cholesterol in distant axons. NPC1 protein is abundant in distal axons - in recycling endosomes in the pre-synaptic terminal. In addition to the role of NPC1 in cholesterol export from lysosomes, the findings suggest a neuron-specific role for NPC1 in the synaptic vesicle recycling pathway that may contribute to the severe neurological phenotype characteristic of NPC disease.

### **Prenatal and Postnatal Diagnosis of SLOS**

Accurate measure of incidence and early diagnosis of SLOS are important to establish the scope of this disorder. Diagnosis in utero is a prerequisite towards optimizing interventions to increase cholesterol transport to an affected fetus.

Methods of prenatal diagnosis of SLOS were discussed by *Dr. Roberson*. An SLOS risk screening algorithm based on the common maternal serum triple screen for Down syndrome (alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3)), was implemented at 15 prenatal screening programs. Diagnostic testing of amniotic fluid was offered to those with positive screens (risk  $\geq$  1:50). Of 1,079,301 pregnancies evaluated for risk, 3,083 were screen positive, and 5 pregnancies were ultimately diagnosed with SLOS. The prevalence of SLOS in second trimester pregnancies was 1:101,000. The pregnancies identified as high risk by screening that were not affected by SLOS were associated with high risk for other major fetal abnormalities.

A non-invasive method using maternal serum and urine to identify only those steroids produced in pregnancies with SLOS affected fetuses was also developed. The steroid ratios determined to be diagnostic were 7-dehydropregnanetriol/ pregnantriol (7-PT/PT), 8-dehydropregnanetriol/PT (8\_PT/PT), the sum of those two ((7+8)-PT/PT), and dehydroestriol/estriol (DHE3/E3). *Dr. Shackleton* evaluated those methods that he developed in a multi-center trial. Initial screening used the algorithm described above. This identified 737 pregnancies at risk for SLOS, of which 5 were positive for SLOS by amniotic fluid measurement and retroactively by urine and serum steroid ratio quantitation. It was determined that after the 15<sup>th</sup> week of gestation, either urine or serum steroid ratios are diagnostic, with urine a more definitive test.

*Dr. Krajewska-Walasek's* lab at the only health center in Poland where diagnosis of SLOS has been performed for the past 20 years has also implemented a new diagnostic procedure using urine. Maternal urinary steroids 7DHPT and 8DHE3 are being used for prenatal diagnosis in pregnancies suspected of SLOS. Using all methods of diagnosis,

SLOS has been identified by this institute in 71 patients and 20 prenatal cases over the past 20 years. The lab has identified 18 different DHCR7 mutations, with two (c.452>A and c.976C>T) accounting for 65.2 % of mutations. Population screening for these two mutations amongst 4,256 neonates indicated a carrier frequency of 2.4%, which would place the incidence of SLOS between 1:2300 and 1:3937, making it among the most common recessive genetic disorders in Poland. The actual incidence in Poland is currently under investigation using a population-based registry, monitoring 300,000 births/year in all Polish provinces.

The incidence of SLOS in the North American Caucasian population and in Central European populations has been calculated from carrier frequency of the common mutation and allele frequencies to be between 1:1,590 and 1:17,000. The observed prevalence and incidence are much lower. The discrepancy between expected and observed incidence can be explained in part by neonatal and infancy deaths of the most severely affected children, and under ascertainment of mild and atypical cases. According to *Dr. Nowaczyk*, recent observations put the estimate of SLOS prevalence at 16 weeks of gestation similar to that observed at birth (~1:60,000), suggesting that reduced fertility of carrier couples or fetal loss in the first trimester play a significant role in explaining the discrepancy. It is also possible that population screening for the most common mutation may not reflect true carrier rates.

### **Effect of SLOS on Embryonic Development and Placenta Transport of Cholesterol**

Maternal cholesterol, synthesis of cholesterol in the fetus and the transport of cholesterol during fetal development was discussed. These areas of research may lead to improved transport of cholesterol as a novel therapeutic intervention.

*Dr. Tint* has done extensive research to describe the differences in cholesterol synthesis and sterol accumulation in different organs of the developing mouse fetus. The SLOS knockout mouse, however, shows a phenotype different from human with SLOS. It is thought that, unlike humans, the extra-CNS tissues of the mouse receive maternal cholesterol for most of their fetal life. Thus, a better animal model is needed to learn more about the role of cholesterol transport and cholesterol synthesis in the fetus. A model of the pregnant rat that is treated with an inhibitor of 7-dehydrocholesterol  $\Delta^7$ -reductase may be more useful.

In addition to evaluating cholesterol synthesis in the brain, *Dr. Tint*, has identified the likely mechanism causing the relatively high concentrations of desmosterol in fetal brain. The promoter of the gene for 24-dehydrocholesterol reductase (the enzyme that converts desmosterol to cholesterol) responds to the regulatory protein REST as a transcriptional enhancer. Because the expression of REST is naturally reduced in brain compared to most other tissues, this results in a down-regulated state with reduced enzyme activity.

Another rodent model, hamster, has been studied by *Dr. Woollett*. An increase of cholesterol transport to the fetus has been demonstrated when the maternal cholesterol concentrations are elevated. In vitro studies of yolk sac and BeWo cells also demonstrated a relationship between “maternal” cholesterol concentrations and output of cholesterol to the “fetus”. The ability to manipulate the mass of maternal cholesterol that crosses to the fetus could improve fetal development and improved outcome in those with SLOS.

Maternal cholesterol is essential for hormonal and physical changes of pregnancy. *Dr. Muenke's* lab studied mother-infant pairs (9938) to assess whether low maternal serum cholesterol during pregnancy is associated adverse birth outcomes. They found an increase prevalence of preterm delivery and lower birth weights of term infants from mothers with low total cholesterol (<10<sup>th</sup> percentile). There was a trend toward microcephaly, but no increase of congenital anomalies. These results may be mediated by the decrease in substrate for hormonal and nutritional support of early pregnancy. Or perhaps the results are due to altered lipoproteins that have been shown to change pregnancy outcome in other studies. Whatever the reasons, the associations emphasize the importance of cholesterol for optimal fetal development.

### **Novel treatment of SLOS and related disorders**

The behavioral and learning problems in SLOS are likely due to a combination of neurodevelopmental deficits, and functional deficits as a result of abnormal sterol composition in the central nervous system. Although neurodevelopmental deficits may be permanent, functional deficits can potentially be treated. Since dietary cholesterol does not cross the blood-brain-barrier, various approaches are being considered to increase CNS cholesterol or to correct the biochemical disturbances that affect neurological function.

One approach to improve the biochemical abnormality in SLOS is gene therapy. *Dr. Watson* and colleagues are using the mouse models developed by *Dr. Porter's* group to evaluate the efficacy of adeno-associated viral (AAV) therapy in treating both peripheral organs and the central nervous system. Since cholesterol can be transferred between cells, a major question in these studies is whether product (i.e. cholesterol) cross-correction will occur between treated cells and untreated cells. *Dr. Watson* presented preliminary data showing that *DHCR7*-AAV vectors can be used to express *DHCR7* in mouse liver tissue, and that this therapy resulted in an improved serum dehydrocholesterol/cholesterol ratio. *Dr. Watson's* group has developed techniques for treatment of the central nervous system with AAV vectors in newborn mice. They will now apply these techniques to investigate the efficacy of gene therapy in SLOS mice. Since neurodevelopmental defects occur prior to birth, future studies will also investigate prenatal therapy.

7-dehydrocholesterol (7-DHC) accumulates in SLOS and 7-DHC can have detrimental effects. *Drs. Lloyd-Evans and Platt* have now clearly confirmed that a secondary defect

in intracellular cholesterol transport occurs in SLOS cells. This defect in intracellular transport is similar to what occurs in Niemann Pick Disease, type C (NPC) cells. Multiple experiments demonstrated other similarities between SLOS and NPC. These include defects in endosomal transport, deficient lysosomal calcium pools, and glycosphingolipid (GSL) accumulation. In SLOS the accumulation of GSLs increases with increased disease severity. Treatment of SLOS cells, *in vitro*, with an inhibitor of GSL biosynthesis decreased the abnormal accumulation of GSLs and reversed the defect in the intracellular transport of cholesterol. It is possible that this defect in intracellular cholesterol transport in SLOS exacerbates the cholesterol synthetic defect by decreasing the bioavailability of cholesterol. Thus, it is plausible that inhibition of GSL synthesis could increase cholesterol bioavailability, and thus be a novel therapeutic intervention for SLOS. Future studies in mouse models of SLOS are planned.

Although dietary cholesterol does not cross the blood-brain-barrier, anecdotal evidence suggests that behavior improves in SLOS patients on dietary cholesterol supplementation. In contrast to cholesterol, neuroactive steroids do cross the blood-brain-barrier and could potentially influence the SLOS behavioral phenotype. In NPC, it has been proposed that a deficiency of the neurosteroid allopregnanolone may be a contributing factor in the pathogenesis of this neurodegenerative disorder. Previous studies demonstrated that allopregnanolone therapy significantly increased the lifespan of NPC mice. *Dr. Ory* presented data on a series of studies addressing the mechanism of allopregnanolone therapy in the NPC mouse model. Although it was initially proposed that allopregnanolone worked through its interaction with GABA<sub>A</sub> receptors, *Dr. Ory's* work supports the idea that allopregnanolone may be activating PXR-dependent pathways. Furthermore, combinatorial therapy combining allopregnanolone with an LXR-agonist may provide additional benefit. Although these studies were focused on understanding NPC, they may provide some insight as to how disturbed neurosteroid synthesis may contribute to the pathology of SLOS, and how correction of a defect in neurosteroid synthesis could be of potential therapeutic benefit in SLOS.

### **Intracellular and membrane effects in SLOS: retina and fibroblasts:**

The genetic and phenotypic profiles of SLOS have been well described. New advances, however, are being made in characterizing the biochemical and cellular defects in this disorder using *in vitro* and *in vivo* models and human patient studies.

*Dr. Tulenko*, for example, compared human fibroblasts obtained from both patients and healthy controls, it has been shown that not only is the cellular membrane composition significantly altered in SLOS fibroblasts, but that these alterations have profound effects on the membrane electrophysiology, protein expression in the membrane, and downstream cellular signaling. In particular, the marked deficit of cholesterol and the increased accumulation of 7-dehydrocholesterol (7DHC) in the biological membrane alter membrane function that seems to suggest abnormal caveolar function. SLOS cells are transcriptionally deficient in the cholesterol binding, scaffolding and cellular signaling caveolar protein caveolin-1 (cav-1) which may be a direct result of the altered bilayer organization. One consequence of the cav-1 deficiency appears to be a reduction

in the BKCa protein, a protein that normally co-localizes with cav-1, which results in suppression of BKCa-mediated outward K<sup>+</sup> currents and globally-impaired membrane electrophysiology. Another consequence is structural defects due to disrupted actin distribution in response to decreased cav-1 levels.

In addition to this *in vitro* work, studies done with isolated whole retinas from rats treated with AY9944 (which produces an animal model that mimics key features of the human disease) have shown that hundreds of genes involved in multiple biochemical pathways are significantly affected. In addition, the levels of glycerophospholipid molecular species containing docosahexaenoic acid (DHA) in retinas from treated animals are markedly lower than in age-matched controls, and the treated retinas also contain oxidized lipids and oxidatively modified proteins. These studies, carried out by *Dr. Fliesler*, suggest that both global metabolic involvement beyond the initial defect in cholesterol biosynthesis as well as lipid and protein oxidation likely contribute to retinal dysfunction and pathogenesis in SLOS.

Complementing this work, human electroretinogram studies were performed in SLOS patients by *Dr. Elias*. All patients exhibited abnormal electroretinograms showing scotopic and photopic (rod and cone) aberrancy. Several of these patients also had abnormally formed optic nerves, retinal pigmentary deposits, early nuclear cataracts, and/or a reduction in visual acuity, supporting *in vivo* descriptions of retinal dysfunction. While many of the neurological symptoms of SLOS are still waiting for a treatment to be developed, there is some evidence that high cholesterol diets supplemented with antioxidants may improve some of the retinal abnormalities found in SLOS (in good agreement with parallel animal model studies performed in *Dr. Fliesler's* lab).

## **Conclusion**

The conference was universally felt by the participants to be a success. There was much camaraderie and scientific discourse at the conference and during breaks, meals, and receptions. It is our hope the interactions of the participants at the conference will initiate collaborative research and new insights to the scientific community at large. We will be conducting a survey one year after the conference to assess the status of new research that was initiated as a result of this collaboration.

Conference participants were the guests of The Portland Hilton & Executive Towers and the conference sessions were held at The Embassy Suites Hotel in Portland, Oregon.

We extend our up most thanks to Office of Rare Diseases, NIH, DHHS and National Institute of Child Health and Human Development, NIH, DHHS for their generous support for this conference.

The conference staff wishes to acknowledge the outstanding contributions of Christopher Wassif, without whom this conference would not have been possible. We also wish to thank Cindy Early and Cylia Amendolara in the OHSU Department of Pediatrics Business Office for their help with administrative details.

List of speakers:

G.S. Tint

VA Medical Center, East Orange, NJ

& UMDNJ-New Jersey Medical School, Newark, NJ.

Etiology of metabolic & physical abnormalities in SLOS/RSH or Was anyone really surprised when Dhcr7 knockout mice did not replicate the syndrome?

Peter Jones

The Richardson Centre for Functional Foods and Nutraceuticals, University of Manitoba, Winnipeg, Manitoba, Canada

Effects of dietary cholesterol and Simvastatin on cholesterol absorption and synthesis (CAS) in Smith-Lemli-Opitz syndrome (SLOS)

James Heubi

Cincinnati Children's Hospital Medical Center

Cincinnati, OH

The Impact of Bile Acid Composition on Cholesterol Absorption in Humans

Michael Gibson

Children's Hospital, University of Pittsburgh School of Medicine,

Pittsburgh, PA

Mechanisms of Inflammatory Disease in Murine Mevalonate Kinase (MvK) Deficiency

Laura Woollett

University of Cincinnati Medical School

Cincinnati, OH

Sources of Cholesterol for the SLOS Fetus and Embryo

Max Muenke

National Institutes of Health (NIH)

Bethesda, MD

Adverse Birth Outcome Among Mothers with Low Serum Cholesterol

Phil Beachy

Howard Hughes Medical Institute

Stanford, CA

Cholesterol and other Lipids in Hedgehog Signaling

Gail Herman

Columbus Children's Research Institute & The Ohio State University.

Columbus, OH

Cholesterol and the Placenta: Functional Studies Using Nsdhl Deficient Mice

Gordon Watson  
Heritable Disorders Branch, NICHD, NIH  
Bethesda MD  
Gene Therapy for SLOS: Preliminary Investigations

Steven Fliesler  
Saint Louis University School of Medicine  
Saint Louis, MO  
The Molecular and Metabolic Basis of SLOS: Thinking Beyond Sterols

Ellen Elias  
University of Colorado School of Medicine  
Denver, CO  
Retinal Studies of Patients with Smith-Lemli-Opitz Syndrome

John Dietschy  
UT Southwestern Medical Center  
Dallas, TX  
Cholesterol Balance across the CNS

Jean Vance  
University of Alberta,  
Edmonton, Alberta, Canada  
Cholesterol and Apo E in Neurons and Glial Cells

Dieter Lütjohann  
University of Bonn,  
Bonn, Germany  
Lanosterol, a Regulatory Cornerstone in Cholesterol Biosynthesis

Thomas Tulenko  
Thomas Jefferson University  
Philadelphia, PA  
Defective Caveolar Signaling in Smith-Lemli-Opitz Syndrome (SLOS)

Steven Tint  
VA Medical Center, East Orange, NJ  
& UMDNJ-New Jersey Medical School, Newark, NJ.  
Desmosterol is Elevated in the Fetal Brain because, unlike other Cholesterol Biosynthetic Genes, the DHCR24 Promoter Contains NRSE Sequences that Bind REST

Cedric Shackleton  
Children's Hospital Oakland Research Institute,  
Oakland, CA

Dehydrosteroid Measurements in Maternal Urine or Serum for the Prenatal Diagnosis of Smith-Lemli-Opitz Syndrome (SLOS)

Steven Meaney  
Karolinska University Hospital,  
Huddinge, Sweden  
Oxysterol Cross Talk at the Blood-Brain Barrier

Forbes D. Porter  
Heritable Disorders Branch NICHD, NIH, DHHS  
Bethesda, MD  
27-hydroxy-7-dehydrocholesterol is an Endogenous Teratogen in Smith-Lemli-Opitz Syndrome that Decreases Cholesterol Levels in Patients and Increases Phenotypic Severity in Mice

Daniel Ory  
Washington University School of Medicine,  
St. Louis, MO  
Mechanism of Neurosteroid Protection in a Mouse Model of Niemann-Pick

Emyr Lloyd-Evans  
University of Oxford  
Oxford, UK  
SLOS has Cellular Features of Niemann-Pick Disease Type C: Implications for SLOS Therapy

Christopher Wassif  
Heritable Disorders Branch NICHD, NIH, DHHS  
Bethesda, MD  
HEM Dysplasia and Mouse Ichthyosis are not due to Sterol  $\Delta 14$ -Reductase Deficiency