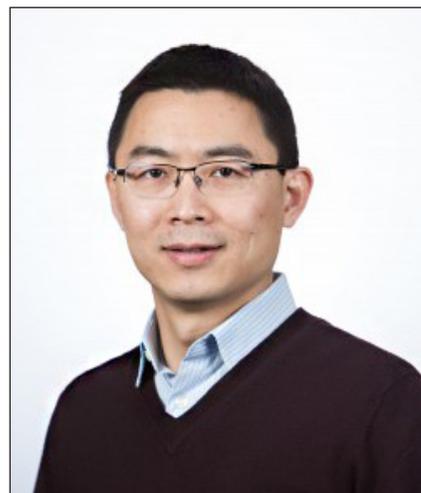




## Finding the Underlying Mechanisms of and Developing Treatment for Smith-Lemli-Opitz Syndrome

by Kate Forster

It is generally known that cholesterol plays an important role in maintaining the normal function of various cells in the body. What is not as well-known is the essential role it plays in the early development of the brain. In fact, 25% of the cholesterol in the human body is in the brain. The cholesterol that the brain uses is created by the body in a process called *cholesterol biosynthesis*, and when the body does not produce enough cholesterol, a number of serious health problems can result. Smith-Lemli-Opitz syndrome (SLOS) is an inherited disorder that affects a person's ability to make cholesterol, and those who have this disorder cannot make enough cholesterol to support normal brain development. As a consequence, SLOS can manifest in a broad range of characteristics, depending on the severity, including multiple congenital malformations, neurological defects, intellectual disability, and behavioral problems. Additionally, over 70% of children with SLOS display symptoms of autism spectrum disorder. It is estimated that approximately 1 in 20,000 babies are born with SLOS. However, the frequency of carriers of the genetic mutation was found to be 1 in 30 among Caucasians, suggesting that the disorder is most-likely underdiagnosed.



*Libin Xu studies the role of oxidized sterols (oxysterols) in the pathophysiology of Smith-Lemli-Opitz syndrome (SLOS), a cholesterol biosynthesis disorder that affects the development of the central nervous system.*

### The role of 7-DHC

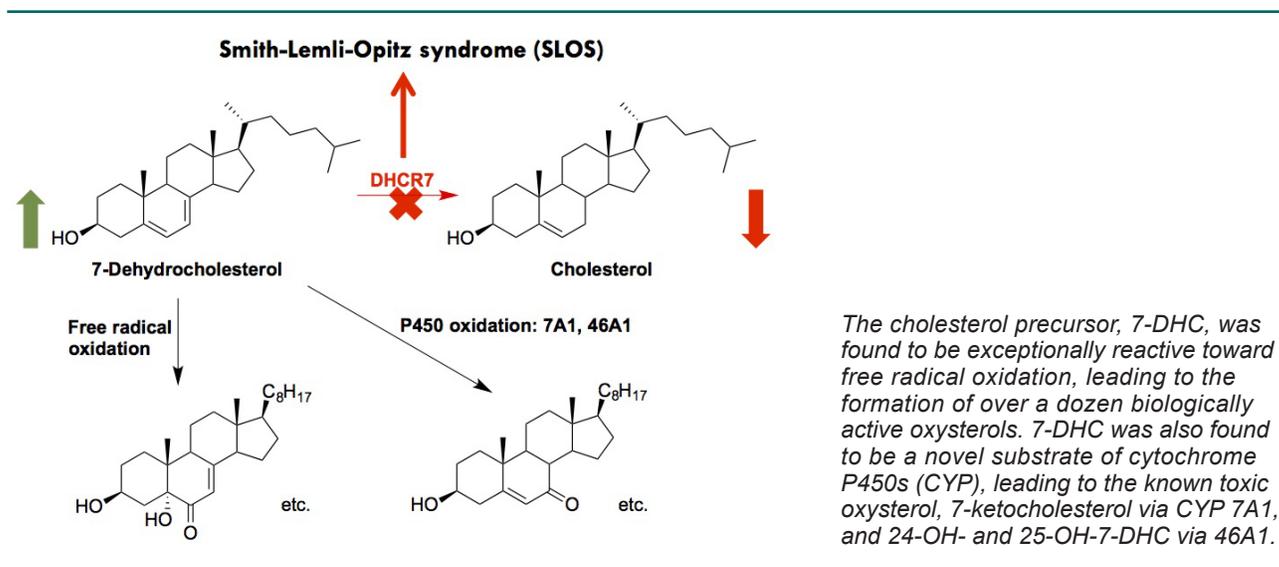
Because SLOS is caused by mutations in the gene encoding of an enzyme involved in cholesterol synthesis, most affected individuals have lower than normal cholesterol in their bodies. However, it is not just the lack of cholesterol that contributes to this disorder, it is also the increased levels of the cholesterol precursor, 7-dehydrocholesterol (7-DHC). Libin Xu, Ph.D., assistant professor of medicinal chemistry and CHDD research affiliate, hypothesizes that it is the oxysterols (oxidized forms of cholesterol) formed from 7-DHC that are the key causal agents in SLOS. Xu's research focuses on the specific function of these oxysterols and their contribution to the pathophysiology of SLOS. "My team and I want to show that it is the highly reactive, highly oxidizable precursor 7-DHC that leads to oxidative stress in SLOS," said Xu. "It is the body's cellular response to oxysterols, the oxidation products, that contributes to the pathophysiology of this disorder. For this project, we want to understand how the specific mechanisms related to 7-DHC-derived oxysterols are involved in the pathophysiology of this disease. We have identified over 15 oxysterols so far."

Xu's lab uses mass spectrometry to analyze different lipid and oxidative metabolites in the brain. "We find this method successful because it is sensitive and specific enough that it can target the different metabolites, and it allows us to study the particular oxidation products we are interested in as well as the related neurobiological activity," said Xu. "We can use some of this information to identify biomarkers of oxidative

stress that relates to SLOS.” Using these biomarkers, Xu hopes to ultimately develop a rapid and thorough diagnostic method using mass spectrometry.

Xu is using a genetically modified mouse model to study this disorder, and he is using the CHDD Genetics Core for gene expression analysis to complement the work he is doing in his lab as well as for help with bioinformatics and biostatistics. Plans also include the use of the CHDD Mouse Behavior Laboratory of the Animal Behavior Core to measure autism-related neurobehavioral and cognitive outcomes in the SLOS mouse model.

By understanding the role of 7-DHC-derived oxysterols in SLOS, Xu hopes to lay the groundwork for developing future therapies that inhibit the formation of these oxysterols and promote cholesterol synthesis in the brain. Conventional therapy for SLOS includes cholesterol supplementation, but the outcomes are inconsistent and controversial. Due to the blood-brain barrier, dietary cholesterol does not make it to the brain, which is why it is important to develop innovative therapies. Xu draws on his background in chemistry and that of the members of his lab to make the molecules that can cross the blood-brain barrier and to test the effectiveness of these molecules in cell and animal models of SLOS by monitoring the established biological markers.



## Broader implications

Xu expects his research will provide a better understanding of intellectual and developmental disabilities, particularly disorders of metabolism that affect brain function and development. In particular, he hopes his work has significant implications in the study of other diseases that are related to abnormal cholesterol biosynthesis or metabolism. “By studying SLOS, we want to learn how the oxidation of 7-DHC and disrupted cholesterol biosynthesis affects neurodevelopment and its subsequent effects on the metabolic profile of the whole neurological system,” said Xu. “By doing so, we want to lay the groundwork in developing therapies that inhibit the formation of these oxysterols and increase the synthesis of cholesterol in the brain. SLOS is the most common cholesterol biosynthesis disorder, and there are other disorders that come about during the early stages of cholesterol biosynthesis, so our research has broad implications. Understanding biosynthesis and metabolism of cholesterol is important in understanding a number of other neurological disorders.”

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

### CHDD Outlook

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