

DEPARTMENT OF INTERNAL MEDICINE - DIV OF ENDOCRINOLOGY
COLLEGE OF MEDICINE

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE WOMEN

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PROJECT TITLE: Defenses Against, And Biological Effects Of Xenosterols On The Mammalian Body

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Project Description

Biological Effects of Xenosterols On The Mammalian Body The normal human diet consists not only of cholesterol, but also xenosterols, such as plant sterols, but the mammalian body uses a number of different mechanisms to protect itself against the entry and effect of dietary xenosterols. One of these mechanisms was identified by us when we elucidated the gene defect causing the human disorder of sitosterolemia. Our current research now focuses on how xenosterols affect mammalian metabolism, ranging from their effects on adipose tissue, arterial wall and platelet development. This research uses animal models, as well as clinical studies. These studies have involved humans genetic mapping, and positional cloning, clinical studies aimed at defining the physiological defects, as well as development of knockout and transgenic mouse models to identify the underlying mechanisms. In addition, we also identified a commonly used rat model, SHR, that also has defects in xenosterol trafficking and have created a congenic rat model to study the pathophysiology. We have created mouse models that lack Abcg8, as well as Abcg5, we have developed special diets to restrict or control xenosterol intakes and made congenic rats that carry a mutant Abcg5 allele on the SD background and a wild-type Abcg5 allele on the SHR background (the SHR has a natural mutation in the Abcg5 gene).

In particular work in the lab involves the following projects:

1. The impact of loss of either the Bloch pathway (via Dhcr24), or the Kandustch-Russell pathway (Dhcr7) on embryonic development, and uses conditional and global knockout mice for these genes,
2. the pathways used but the mammalian body to remove sterols, in addition to

that regulated by ABCG5/ABCG8, using knockout mice that impact sterol trafficking (such as NPC1l1, MDR1a/b etc.)

3. developing a mouse model to recapitulate the pathophysiology of cerebrotendinous xanthomatosis (CTX) where the gene defect is CYP27A1, but mice with this gene defect remain normal. We hypothesize that altering other bile-acid genes may lead to pathology and newer models are being investigated, and

4. in some rare humans, a genetic defect in STAP1 leads to hypercholesterolemia and we have obtained a mouse that has Stap1 knocked out to investigate the mechanism of how this small protein leads to hyperlipidemia.