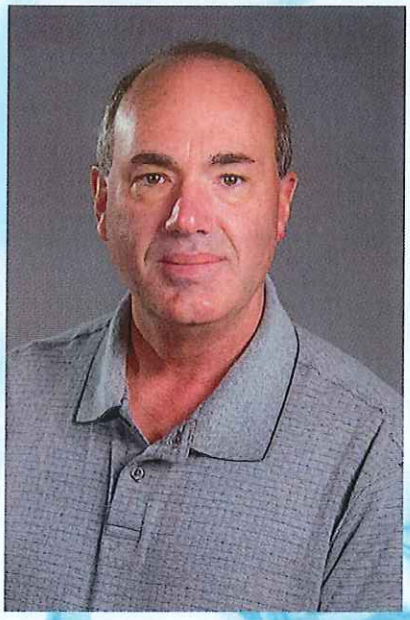
The Spectrum of Niemann-Pick C1 Gene Metabolic Disorders

William Sherman Garvar



Department of Biochemistry & Molecular Biology - University of New Mexico

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The Niemann-Pick C1 (NPC1) protein regulates the transport of cholesterol and fatty acids from late endosomes / lysosomes and has a central role in maintaining cellular, tissue, and whole-body lipid homeostasis. A large number of rare NPC1 gene mutations are responsible for NPC1 disease, a rare autosomal-recessive lipid-storage disorder characterized by lipid accumulation in all tissues and progressive neurodegeneration. In humans, one of the first genome wide-association studies (GWAS) for obesity identified the NPC1 gene as being associated with morbid-adult obesity, while subsequent transferability studies in other populations identified the NPC1 gene as also being associated with type 2 diabetes (independent of obesity). These results have been confirmed both in our local population and using NPC1 mouse models. We have recently reported the physiological mechanism responsible for these metabolic disorders as occurring through complex NPC1 gene x modifying gene and NPC1 gene x diet interactions. Finally, the NPC1 protein serves as the natural receptor for the Ebola virus (and other Filoviruses) used to gain entry into the cytosol for infection. In summary, this seminar will provide an overview of my studies describing initial mapping/cloning of the NPC1 gene, determining expression and cellular function of the encoded protein, identifying the present day therapy currently used to treat NPC1 disease, serving as director for the National / International NPC1 disease patient databases, and most recently our quest to determine the evolutionary origins of human NPC1 gene variants responsible for these metabolic disorders.