

Dr. Robin Clugston

" Alcoholism is a recurring public health problem in our society and is associated with a significant disease burden. The main organ affected by alcohol is the liver, with effects ranging from excess fat accumulation to fibrosis, and ultimately liver failure. The applicant has been a Postdoctoral Research Scientist in the laboratory of Dr. William S. Blaner since October 2009, who is an accomplished researcher in the field of vitamin A biology with 35 years of experience. Vitamin A is an essential micronutrient with an important role in many biological processes. This K99/R00 application focuses on the pathogenesis of alcoholic liver disease (ALD) and the importance of vitamin A in this process, leading to a better understanding of how ALD develops and the potential to improve treatment strategies to mitigate the toxic effects of alcohol on the liver. A detailed career development plan designed to prepare the applicant for an independent academic research career is provided, as well as a 5-year research plan addressing the importance of the liver's vitamin A status in the development and progression of ALD. During the K99 phase of this program the applicant will be mentored by Dr. Blaner, in the Department of Medicine's Division of Preventive Medicine and Nutrition, at Columbia University in New York City. Career development activities planned during the K99 phase include strengthening the applicant's experience in several areas, including: discipline-specific conceptual knowledge, research skills, leadership and laboratory management, effective communication, and mentoring young scientists. These career development activities will take advantage of the exceptional research environment and resources at Columbia University, and will be facilitated by the guidance of an Advisory Committee, chaired by Dr. Blaner and including Drs. Henry Ginsberg, Robert Schwabe, and Jaime Rubin of Columbia University, and Dr. Arthur Cederbaum of Mount Sinai Medical Center, New York City. The research focus of this application lies at the intersection between alcohol's effect on vitamin A in the liver, and the pathogenesis of ALD. We believe alcohol has an underappreciated effect on the actions of vitamin A in maintaining hepatic health and preventing hepatic disease. Accordingly, our central hypothesis states that long-term alcohol consumption impairs the action of vitamin A in the liver, contributing to the development of ALD. We propose a combination of complimentary in vitro and in vivo mouse studies designed to test the following hypotheses and provide a mechanistic understanding of the interactions between alcohol and vitamin A in the development of ALD. Our first hypothesis focuses on the initiation of ALD, and states that: alcohol disrupts the actions of vitamin A within hepatocytes, contributing to fat accumulation and the development of alcoholic fatty liver disease. Our second hypothesis focuses on the progression of ALD, and states that: alcohol disrupts the vitamin A status of hepatic stellate cells, contributing to their activation and the development of hepatic fibrosis. Taken together, these studies will provide novel insight into the role that altered hepatic vitamin A homeostasis has on the initiation and progression of ALD."