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2001 Program
Investigator Initiated (2-year project)

Project Title: Regulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase

Project Summary: The number 1 killer in the State of Florida is vascular disease. The risk for vascular disease increases exponentially when an individual has multiple risk factors such as smoking together with hypertension and elevated serum cholesterol levels. The primary objectives of this project were to determine the molecular mechanisms by which the hormones, insulin and thyroid hormone regulate the expression of the key enzyme of cholesterol biosynthesis and the impact of these hormones on resistance to dietary cholesterol.

Project Successes: In experimental animals deficient in either insulin or thyroid hormone, the addition of cholesterol to the diet caused two- to three-fold elevations in serum cholesterol levels. In normal, hormone-sufficient animals, very little (if any) increase in serum cholesterol was observed in response to the addition of the same amount of cholesterol to the diet. These normal animals had much higher rates of hepatic cholesterol synthesis than the hormone deficient animals. This shows that high rates of hepatic cholesterol synthesis confer resistance to dietary cholesterol.

Selected publications from BRP funded research in Peer Reviewed Journals:

Ness GC, Gertz KR, Holland RC. Regulation of hepatic lanosterol 14 α demethylase gene expression by dietary cholesterol and cholesterol-lowering agents. *Arch Biochem Biophys.* 2001;395:233-238.

Ness GC. Cholesterol homeostasis in sterols and oxysterols: Chemistry, Biology and Pathobiology. In: Fliesler S, ed. *Recent Research Developments in Biochemistry Series, Research Signposts*; 2003;1-14.

Ness GC. Physiological and pharmacological regulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase. In: Pape M, ed. *Current Medicinal Chemistry – Immunology, Endocrine and Metabolic Agents.* 2003;3:219-227.

Ness GC. Defects in cholesterol biosynthesis. In: Daum G, ed. *Topics in Current Genetics, Lipid Metabolism and Membrane Biogenesis Series.* 2004;6:169-182.

Ness GC, Gertz KR. Increased sensitivity to dietary cholesterol in diabetic and hypothyroid rats associated with low levels of hepatic HMG-CoA reductase expression. *Exp Biol Med.* 2004;229:407-411.

Ness GC, Gertz KR. Hepatic HMG-CoA reductase expression and resistance to dietary cholesterol. *Exp Biol Med.* 2004;229:412-416.

Osborne AR, Pollock VV, Lagor, **Ness GC.** Identification of insulin responsive regions in the HMG-CoA reductase promoter. *Biochem Biophys Res Commun.* 2004;318:814-818.

Selected presentations from BRP funded research:

Ness GC, Holland RC, Gertz KR. *Genetic variation in level of hepatic HMG-CoA reductase expression and extent of feedback regulation in inbred rat strains: relation to susceptibility to dietary cholesterol*. XIV International Symposium on Drugs Affecting Lipid Metabolism; 2001. pp 49.

Ness GC, Gertz KR. Increased sensitivity to dietary cholesterol in diabetic and hypothyroid rats. *FASEB J*. 2002;16:A909.

Ness GC. *Translational and transcriptional regulation of hepatic HMG-CoA reductase*. Symposium on Inborn Errors of Cholesterol Synthesis, NIH; November, 2002.

Ness GC, Osborne AR, Pollock VV. Identification of an insulin response element in the HMG-CoA reductase promoter. *FASEB J*. 2003;17: A1020.

New grants based in part on BRP-funded work:

Merck

Title: Compensatory responses to ezetimibe

Project period: 09/22/04 to 09/21/05

Award amount: \$24,464