

General Research Description

Research Interests:

Molecular mechanisms and genetics of non-alcoholic fatty liver disorders

Department: Internal Medicine, Division of Hepatology

Research Description:

Non-Alcoholic Fatty Liver Disease (NAFLD) is now the leading cause of abnormal liver function tests in the United States and developed countries. It is associated with the metabolic syndrome and is a growing problem due to the epidemic of obesity. Unfortunately, the molecular mechanisms and genetics of this common hepatic disorder remain poorly understood. Our laboratory focuses on delineating the molecular mechanisms of injury in murine models of NAFLD. In addition, we are utilizing Quantitative Trait Loci (QTL) Analysis in order to identify the genetic mechanisms that may be important for disease development and progression.

Molecular Mechanisms of Fatty Liver Disorders

My laboratory has developed and utilized several nutritional murine models to study the mechanisms responsible for the development of fatty liver disease. Methionine-choline deficient (MCD) and high-fat high-caloric (HFHC) diets are utilized in order to characterize the signaling pathways that are important for hepatic injury and fibrosis. The unfolded protein response (UPR), endoplasmic reticulum (ER) stress, oxidative stress and fibrogenesis pathways that are activated in these nutritional models of fatty liver disease are being investigated. In addition, genetic and pharmacologic approaches to prevent disease progression are being investigated. Several inbred strains and transgenic mice are used to identify the cellular genes that are important in this pathophysiologic process.

Hepatic Bile Salt Metabolism and Gene Regulation

For the past several years, the laboratory of the PI has performed physiologic studies in hepatobiliary lipid secretion. We have previously cloned the mouse liver canalicular bile salt transporter (Abcb11) and developed transgenic mice which over-express this gene in the liver. The phenotype of this mouse includes altered susceptibility to the development of fatty liver disorders, an increased propensity to develop gallstones, obesity, and alterations of hepatic and systemic lipid metabolism. In addition, gene regulation by bile salts in the FXR-SHP and G-protein signaling pathways are being actively investigated. Polymorphisms of ABCB11 are also being examined in translational human studies.

Quantitative Trait Loci (QTL) Analysis of Fatty Liver Genes

For the past several years, the laboratory has focused on identifying inbred strains of mice with differing susceptibility to develop fatty liver disorders. We have exploited these differences of disease susceptibility in order to perform QTL analysis to identify loci that are important for the development and progression of fatty liver disorders. Ongoing studies will utilize standard genetic techniques for QTL analysis to identify the genetic loci, fine map the loci and identify the actual genes that are responsible for NAFLD.

Description of MSSRP or RTP projects

Student projects can focus on any of the 3 areas of investigation in the laboratory. It is anticipated that investigations into the unfolded protein response using nutritional models of fatty liver disease will continue to be a very important area of investigation, both at the present and in the future. In addition, the regulation of hepatic and systemic genes and regulation of physiologic processes by bile salts and FXR ligands provides an active area of research. Finally, NAFLD is a highly prevalent disease and the genetic mechanisms responsible for disease development and progression remain very poorly understood. Thus, QTL analysis, and confirmatory techniques to demonstrate the importance of the identified QTL, will remain an area of active investigation in the future.

Reason for My Interest in Serving as a Mentor:

I am currently the Director of the Medical Student Summer Research Program (MSSRP) and Research Thesis Program (RTP). Since coming to Northwestern University, I have run an active laboratory investigating the molecular and genetic mechanisms of hepatic injury in fatty liver disorders. I have supervised the training of several medical and post-doctoral students, and research fellows, including several who are currently junior faculty members in the Department of Medicine at Northwestern University and other institutions. I have a strong interest in training young investigators, both individuals who have had prior experience and those who wish to have an initial exposure to basic scientific investigation.

Prior Trainees:

1994-1996	Zakko, Wisam MD, Research fellow
1998-2000	Veendamali Subramanian PhD, Post-doctoral researcher
2000-2003	Igolnikov, Alexander MD, Resident/Fellow/Postdoc
2002-2004	Nei, Wenxian PhD, Post-doctoral researcher
2002-2004	Koppe, Sean MD, Resident researcher
2002-2004	Wang, Andy MD, Resident researcher
2003-2005	Iyer, Kishore MD, Sabbatical
2003-2005	Henkel, Anne MD, Resident researcher
2002-2005	Rinella, Mary MD, Fellow researcher/Junior Faculty
2004-2005	Chang, Lee Jah, Medical Student
2004-2005	Shapiro, David MD, Resident researcher
2005-2006	Radnekar, Amol, Medical Student
2005-2006	Chang, Lee Arng, Medical Student
2007-present	M. Shadab Siddiqui, MD, Resident researcher
2007-present	M. Bilal Siddiqui, Undergraduate student

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Green, Richard M.	POSITION TITLE Associate Professor of Medicine		
eRA COMMONS USER NAME RGREEN2			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Duke University, Durham, NC Duke University, Durham, NC	B.A. M.D.	1982 1986	Economics Medicine

A. Positions and Honors.

1986-1989 Intern and Resident, Internal Medicine, Northwestern University-McGaw Medical Center, Chicago, IL

1989-1990 Chief Medicine Resident, Northwestern Memorial Hospital, Northwestern University, Chicago, IL

1990-1991 Clinical Fellow, Division of Gastroenterology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

1991-1993 Research Fellow, Divisions of Gastroenterology and Genetics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

1993-1997 Instructor in Medicine, Harvard Medical School, Boston, MA

1994-1997 Associate Physician, Division of Gastroenterology, Brigham & Women's Hospital, Boston, MA

1997-2000 Assistant Professor of Medicine, University of Illinois at Chicago, Chicago, IL

1997-2000 Attending Physician, Division of Digestive and Liver Diseases, University of Illinois at Chicago and Westside VAMC, Chicago, IL

2000-2004 Chief, Division of Gastroenterology and Hepatology, Lakeside VAMC; and Attending Physician, Division of Gastroenterology and Hepatology, Northwestern Memorial Hospital, Chicago, IL

2000-present Associate Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

2002-present Chief, Division of Hepatology, Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital, Chicago, IL

Other Experiences and Professional Memberships

1987-Present Diplomate, National Board of Medical Examiners

1989-Present Diplomate, American Board of Internal Medicine

1993-Present Diplomate, American Board of Internal Medicine -Gastroenterology

1996-Present Member AASLD, AAAS, AGA, APS

2001-2006 Associate Editor, *Hepatology*

2005-2007 Vice Chair, Liver and Biliary Section, American Gastroenterology Association

2007-present Chair, Liver and Biliary Section, American Gastroenterology Association

Honors

1982 Graduation with Distinction, Duke University, Summa Cum Laude, Phi Beta Kappa

1992 American Gastroenterological Association Senior Fellow Research Award

1992 Glaxo Research Institute Fellow's Award

1993 American Liver Foundation Postdoctoral Research Fellowship

1993 Glaxo Institute of Digestive Health Basic Research Award

Selected peer-reviewed publications (in chronological order)

Green RM, Stiles GI. Chronic caffeine ingestion sensitizes the A₁ adenosine receptor-adenylate cyclase system in rat cerebral cortex. *J Clin Invest* 77:222, 1986.

Burk S, Landau S, **Green RM**, Tseng C, Nattakom T, Canchis W, Yang L, Kaiserlian D, Gespach C, Balk S, Blumberg R. Rat cluster of differentiation molecule: Expression on the surface of intestinal epithelial cells and hepatocytes. *Gastroenterology* 106:1143, 1994.

Green RM, Whiting JM, Rosenbluth AB, Gollan JL. Interleukin-6 inhibits hepatocytes taurocholate uptake and sodium-potassium-adenosinetriphosphate activity. *Am J Physiol* 267: (Gastrointest. Liver Physiol. 30):G1094-G1100, 1994.

Craig RM, Coy D, **Green RM**, Meersman R, Rubin H, Janssen I. Hepatotoxicity related to total parenteral nutrition: comparison of low-lipid and lipid-supplemented solutions. *J Crit Care* 1994; 9(2):1111-3.

Whiting JF, **Green RM**, Rosenbluth AB, Gollan JL. Tumor necrosis factor- α decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. *Hepatology* 22:1273-1278, 1995.

Cohen DE, **Green RM**. Cloning and characterization of a cDNA encoding the specific phosphatidylcholine transfer protein from bovine liver. *Gene* 163:327, 1995.

Blumberg RS, Koss T, Story CM, Barisani D, Polischuck J, Lipin A, Pablo L, **Green RM**, Simister NE. An MHC class1-related Fc receptor for IgG on rat hepatocytes. *J Clin Invest* 95:2397, 1995.

Green RM, Crawford JM. Hepatocellular cholestasis: Pathobiology and histologic outcomes. *Sem Liv Dis* 15:372-389, 1995.

Zakko WF, **Green RM**, Gollan JL, Berg CL. Hepatic regeneration is associated with preservation of microsomal glucuronidation. *Hepatology* 24:1250-1255, 1996.

Green RM, Beier D, Gollan JL. Regulation of hepatocytes bile salt transporters by endotoxin and inflammatory cytokines in rodents. *Gastroenterology* 111:193-198, 1996.

Green RM, Gollan JG. Effects of endotoxin and cytokines on hepatocellular bile salt transporters. Falk Symposium No. 93, Bile Acids in Hepatobiliary Diseases: Basic Research and Clinical Application. Kluwer Academic Publishers, p. 112-117, 1997.

Green RM, Lipin A, Meier-Abt P, Hagenbuch B, Gollan JG, Beier DR. Regulation of hepatocyte bile salt transporters during hepatic regeneration. *Am J. Physiol* 273(Gastrointest. Liver Physiol. 36): G621-G627, 1997.

Green RM, Ananthanarayanan M, Suchy FJ, Beier DB. Genetic mapping of the Na-taurocholate cotransporting polypeptide to mouse chromosome 12. *Mamm Genome* 9:598, 1998.

Zakko WF, Berg CL, Gollan JL, **Green RM**. Hepatocellular expression of glucose-6-phosphatase is unaltered during hepatic regeneration. *Am J. Physiol* 275 (Gastrointest. Liver Physiol) G717-722, 1998.

Brady KP, Dushkin H, Fornzler D, Koike T, Magner F, Her H, Gullans S, Segre GV, **Green RM**, Beier DR. A novel putative transporter maps to the osteosclerosis (OC) mutation and is not expressed and in the OC mutant mouse. *Genomics* 15; 56 (3):254-261, 1999.

Green RM, Lo K, Sterritt C, Beier DR. Cloning and functional expression of a mouse liver organic cation transporter. *Hepatology* 29 (5):1556-1562, 1999.

Matkowskyj KA, Marrero JA, Carroll RE, Daniilovich AV, **Green RM**, Benya RV. Azoxymethane-induced fulminant hepatic failure in C57BL/6J mice: Characterization of a new animal model. *Am J Physiol* (Gastrointest. Liver Physiol) 277:G455-G462, 1999.

Cohen DE, **Green RM**, Wu MK, Beier DR. Cloning, tissue-specific expression, gene structure and chromosomal localization of human phosphatidylcholine transfer protein. *Biochim. Biophys. Acta.* 1999; 1447:265-270.

Green RM, Hoda F, Ward KL. Molecular cloning and characterization of the murine bile salt export pump. *Gene.* 2000; 241(1): 117-123.

Sinclair CJ, Chi KD, Subramanian V, Ward KL, **Green RM**. Functional Expression of a High-Affinity Mammalian Hepatic Choline/Organic Cation Transporter. *J. Lipid Res.* 2000 41: 1841-1848.

Zucker SD, Qin X, Rouster SD, Yu F, **Green RM**, Keshavan P, Feinberg J, Sherman KE. Mechanism of indinavir-induced hyperbilirubinemia. *Proc Natl Acad Sci U S A* 2001; 98(22):12671-6.

Green RM. NASH-hepatic metabolism and not simply the metabolic syndrome. *Hepatology.* 2003; 38(1):14-7.

- Hoda F, **Green RM**. Hepatic Canalicular Membrane Transport of Bile Salt in C57L/J and AKR/J Mice: Implications for Cholesterol Gallstone Formation. *J Membr Biol*. 2003;196(1):9-14.
- Dyck PA, Hoda F, Osmer ES, **Green RM**. Microarray Analysis of Hepatic Gene Expression in Gallstone Susceptible and Resistant Mice. *Mamm Genome*. 2003;14(9):601-10.
- Rinella ME, **Green RM**. The methionine-choline deficient dietary model of steatohepatitis does not exhibit insulin resistance. *J Hepatol*. 2004;40(1):47-51.
- Figge A, Lammert F, Paigen B, Henkel A, Matern S, Korstanje R, Schneider BL, Chen F, Stoltenberg E, Spatz K, Hoda F, Cohen DE, **Green RM**. Hepatic over-expression of murine Abcb11 increases hepatobiliary lipid secretion and reduces hepatic steatosis. *J Biol Chem*. 2004;279(4):2790-9.
- Sahai A, Malladi P, Melin-Aldana H, **Green RM**, Whittington PF. Upregulation of Osteopontin Expression is Involved in the Development of Nonalcoholic Steatohepatitis in a Dietary Murine Model. *Am J Physiol Gastrointest Liver Physiol* 2004; 287: G264-273.
- Koppe S, Sahai A, Malladi P, Whittington P, **Green RM**. Pentoxifylline attenuates steatohepatitis induced by the methionine-choline deficient (MCD) diet. *J Hepatol*. 2004;41: 592-598.
- Sahai A, Malladi P, Pan X, Paul R, Melin-Aldana H, **Green RM**, Whittington PF. Obese and Diabetic db/db Mice Develop Marked Liver Fibrosis in a Model of Nonalcoholic Steatohepatitis: Role of Short-Form Leptin Receptors and Osteopontin. *Am J Physiol Gastrointest Liver Physiol*. 2004; 287:G1035-G1043.
- Nie W, Sweetser S, Rinella M, **Green RM**. Transcriptional Regulation of Murine Slc22a1 (Oct1) by Peroxisome-proliferator agonist receptor (PPAR)-alpha and -gamma. *Am J Physiol Gastrointest Liver Physiol*; 2005; 288: G207-G212.
- Sundaram SS, Whittington PF, **Green RM**. Steatohepatitis develops rapidly in transgenic mice over-expressing Abcb11 fed a methionine-choline deficient diet. *Am J Physiol Gastrointest Liver Physiol*. 2005 Jan; 288 (2) G1321-27.
- Henkel, A, Zhixin W, Cohen D, **Green, RM**. Mice over-expressing hepatic Abcb11 rapidly develop cholesterol gallstones. *Mammalian Genome*; 2005;16(12):903-8.
- Igolnikov, A, **Green, RM**. Mice heterozygous for the Mdr2 gene demonstrate decreased PEMT activity and diminished steatohepatitis on the MCD diet. *J Hepatology*; 2006;44(3):586-92.
- Rangnekar, AS, Lammert, F, **Green, RM**, Identification of nonalcoholic steatohepatitis quantitative trait loci (QTLs) using silico mapping analysis. *Liver Int*. 2006;26 (8):1000-5.