Chapter 10
Pediatric Liver Disease

A1a. Characterize clinical syndrome, natural history, etiology, cofactors, and complications of pediatric NASH. The frequency of nonalcoholic fatty liver disease is increasing among children and adolescence. Among severely obese adolescents undergoing bariatric surgery, 83% had fatty liver disease and 20% had NASH (Xanthakos S. Clin Gastroenterol Hepatol 2006;4:226). In an autopsy series from the United States, 10% of children had fatty liver; rates increased with age (17% in 15-19 year olds) and were higher in Hispanic (12%) and Asian (10%) children than in whites (8.6%) or blacks (1.5%). Although cirrhosis was uncommon, 23% of children with fatty liver met diagnostic criteria for NASH (Schwimmer JB. Pediatrics 2006;118:1388). (2006 10%; Total 20%)

A1b. Develop definitions and diagnostic criteria for the major neonatal cholestatic syndromes. Investigators in the NIH-funded Biliary Atresia Research Consortium (BARC) and Cholestatic Liver Disease Consortium (CLiC) are in the process of developing and publishing clinical definitions and diagnostic criteria for the major neonatal cholestatic syndromes of children. (2006 0%; Total 10%)

A2. Develop systems to better characterize the frequency, medical burden, and epidemiology of pediatric liver disease. Epidemiology is a component of several NIH-supported studies, including the NASH Clinical Research Network, BARC, CLiC, the Pediatric Acute Liver Failure Study Group (PALFSG), the Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C (Peds-C) trial, and the SPLIT pediatric liver transplant registry. (2006 0%;Total 0%)

A3. Elucidate the major cause of idiopathic acute liver failure in children. The causes of acute liver failure (ALF) in children in the United States include acetaminophen overdose (14%), metabolic diseases (10%), autoimmunity (6%), and drug-induced liver injury (5%). In approximately half of cases the etiology is unknown (Squires RH. J Pediatr 2006;148:652). Testing for acetaminophen adducts in children with ALF of indeterminate cause suggests that 12% are due to unacknowledged or unrecognized acetaminophen-overdose (James LP. Pediatrics 2006;118:676). (2006 20%; Total 20%)

B1a. Define structural and functional development of the liver and biliary system. Factors that lead to differentiation of the liver are likely to be multiple, interrelated, and redundant. The Wnt/beta-catenin pathway has been found to be important in normal liver development in zebrafish and mice (Ober EA. Nature 2006;442:688; Tan X. Gastroenterology 2006;131:1561). Cell junction pathways are also important (Battle MA. PNAS 2006; 103:8419). Development of the liver from the embryonal foregut is mediated by fibroblast growth factor (FGF), which is produced by surrounding mesenchymal tissue and acts on endodermal epithelium. Recent studies have elucidated the intracellular pathways for FGF actions, which occur via MAP kinase pathways inducing differentiation of endoderm into hepatocytes, while the PI_3 kinase pathway leads to cell proliferation (Calmont A. Dev Cell 2006;11:339). The coordination of these signals is key to normal hepatogenesis. (2006 20%; Total 40%)

B1b. Evaluate long-term outcomes, complications, and tolerance-inducing regimens in children undergoing liver transplantation. New approaches to study of long-term outcomes and tolerance-inducing regimens in children are being pursued in the NIH-funded SPLIT registry. The long-term prognosis of children undergoing liver transplantation for hepatic malignancy is reasonably good, with 10-year survivals of 58% for HCC and 66% for hepatoblastoma (Austin MT. J Pediatr Surg 2006; 41:182). (2006 0%; Total 10%)

B2a. Delineate the molecular pathogenesis of at least 3 of the neonatal cholestatic syndromes. Using a variety of molecular approaches, Jagged1 (*JAG1*) mutations can be identified in 94% of children with Alagille syndrome, and a proportion of the remaining children have mutations in the gene encoding NOTCH2, the receptor for Jagged 1 (Warthen DM. Hum Mutat 2006;27:436; McDaniell R. Am J Hum Genet 2006; 79:169). Mutations in *VPS33B* have been linked to arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome, as well as other forms of intrahepatic cholestasis lacking extrahepatic features of the ARC syndrome (Bull LN. J Pediatr 2006; 148:269). (2006 20%; Total 20%)

B2b. Develop better animal models for neonatal cholestatic syndromes. Progressive familial intrahepatic cholestasis type 1 (PFIC-1) is linked to abnormalities of the *FIC1* gene, now referred to as *ATP8B1*. The function of this gene is not known, but a mouse *Atp8b1* knockout (-/-) model has been used to demonstrate the role of this gene in phospholipid membrane asymmetry, its deficiency leading to susceptibility of hepatocyte canalicular membranes to hydrophobic bile acid injury (Paulusma CC. Hepatology 2006;44:195). (2006 10%; Total 30%)

B3. Identify biomarkers for diagnosis, staging, and grading of neonatal cholestatic syndromes. NIH-funded CLiC investigators are developing study protocols to diagnose, stage, and grade cholestatic syndromes, and ancillary studies have now been funded that are directed at testing a novel customized re-sequencing gene chip and for use of proteomics technology to identify biomarkers for pediatric cholestasis. (2006 0%; Total 0%)

C1a. Conduct clinical trials to optimize medical and surgical management of biliary atresia. Enrollment has started in the NIH-funded randomized, placebo-controlled trial of corticosteroids after hepatoportoenterostomy in infants with biliary atresia (START). Recent retrospective analyses suggest that perioperative corticosteroids are beneficial (Escobar MA. J Pediatr Surg 2006; 41:99). (2006 0%; Total 10%)

C1b. Evaluate therapies for acute liver failure in children. A trial of N-acetyl-cysteine in children with acute liver failure has reached 50% of its planned enrollment and should be completed in two years. (2006 0%; Total 10%)

C2. Based upon molecular pathogenesis, identify small molecule therapies that might alleviate neonatal cholestatic syndromes. Targets for small molecule therapies include the nuclear hormone receptors that regulate bile acid and anion transport and secretion. *In vitro*, high-throughput screening of small molecules with possible use in neonatal cholestatic syndromes is encouraged through the

Roadmap trans-NIH RFA "Assay Development for High Throughput Molecular Screening" (RM-07-001). (2006 0%; Total 0%)

C3a. Define the etiology of biliary atresia. This goal is the major focus of the BARC network, which is enrolling patients and collecting clinical data, serum DNA, and liver and biliary tissue for investigation of the etiology of this disease. In a mouse model of biliary atresia (neonatal rotavirus infection), activated T cells were responsible for bile duct injury, suggesting either autoimmune reactions or T cell responses to virus-infected biliary epithelial cells might underlie the pathogenesis of biliary atresia (Mack CL. Hepatology 2006;44:1231). (2006 10%; Total 10%)

C3b. Develop gene, siRNA, cell transfer, or stem cell therapy for pediatric metabolic disease. Both NIH- and industry-funded research investigators are active in this area. (2006 0%; Total 0%)

Figure 12. Estimated Progress on Pediatric Liver Disease Research Goals, 2006 (Year 2)
[Cross-hatching indicates recent year's progress.]