Diseases of the Liver and Biliary System

Chair: Bruce R. Bacon, MD
Vice Chair: Maurice Cerulli, MD

Research Goal 1

Molecular and Cell Biology of the Liver and Biliary System

(Action Plan Chapter 1)

Define the molecules, processes, and pathways that underlie normal liver cell function, which can then be applied to understanding the cellular and molecular basis of disease processes.

Research Goal 1 Objectives

- Define how molecules are transported across membranes and to specific sites in the liver cell (cell trafficking). (Chapter 1: A3, C1)

- Fully understand the signaling mechanisms that control the activity of liver cells (signal transduction) and how these signaling mechanisms interact. (Chapter 1: A1)

Research Goal 1
Objectives (continued)

- Elucidate the steps of regulation of cholesterol and lipid synthesis, transport and excretion. (Chapter 1: A2)

Research Goal 1
Objectives (continued)

- Develop a comprehensive knowledge base of the normal liver proteome, comprising an analysis of the proteins in the hepatocytes, their amino acid sequences, carbohydrate and lipid modifications, secondary and tertiary structure, interactions and functions. A better knowledge of the normal liver proteome would advance all components of knowledge about the liver and its functioning. (Chapter 1: C3)

Research Goal 2

Liver Cell Injury, Inflammation, Fibrosis, and Repair

(Action Plan Chapter 2)

Understand the cellular mechanisms of liver injury, inflammation, repair, and fibrosis and develop effective means for monitoring and treating diseases caused by these processes.

Research Goal 2 Objectives

- Delineate the steps in the process of hepatocyte apoptosis. (Chapter 2: A2)

- Understand how liver cells produce and respond to inflammatory mediators and cytotoxic signaling mechanisms. (Chapter 2: A1, B1)

Research Goal 2
Objectives (continued)

- Develop better small animal models for liver cell injury, inflammation, repair and fibrosis. (Chapter 2: C1)

- Develop non-invasive means of assessing liver injury and fibrosis. (Chapter 2: A3)

Research Goal 2
Objectives (continued)

- Translate findings about cell injury, inflammation, repair and fibrosis to clinical diseases: identify small molecules that might alter these processes and form basis for translational research. (Chapter 2: B3, C2a, C3)

Research Goal 3

Developmental Biology and Regeneration of the Liver

(Action Plan Chapter 3)

Define the molecular and cellular mechanisms underlying liver development and regeneration in health and disease and apply these findings to developing improved therapies for liver disease.

Research Goal 3 Objectives

- Define the cellular and molecular events that underlie liver development and what processes are shared with liver regeneration. (Chapter 3: A1b, B3).

Research Goal 3
Objectives (continued)

- Identify and characterize the stem cells of the liver and how to use such cells in gene transfer and transplant studies to allow for correction of abnormal genes that lead to inherited diseases such as hemophilia, porphyria, alpha-1-antitrypsin deficiency, Crigler Najjar syndrome and other devastating diseases that might be corrected by liver gene transfer. (Chapter 3: A1a, C3).

Research Goal 3
Objectives (continued)

- Improve gene transfer techniques, gene transfer vectors, and means of homing and supporting cells to the liver (Chapter 3: B1, C1).

Research Goal 4

Bile, Bilirubin, and Cholestasis

(Action Plan Chapter 4)

Delineate the normal pathways of uptake, metabolism, and secretion of bile salts, bilirubin, and other biliary lipids and solutes; characterize the alterations in these pathways that participate in the pathogenesis of liver diseases; and develop means of diagnosis, treatment and prevention of cholestatic liver disease and disorders of bilirubin metabolism.

Research Goal 4 Objectives

- Fully define the normal physiology and regulation of bile formation, including cholesterol synthesis and catabolism. (Chapter 4: B2a, B2b)

- Understand the pathophysiology of acquired forms of cholestatic liver disease, what disturbed processes account for the retention of bile, and how to alleviate the consequences of bile retention. (Chapter 4: A2, C1, C2)

Overarching Research Goal

Viral Hepatitis

(Action Plan Chapter 5)

Develop practical, safe, and effective means of prevention, treatment, and control of the five forms of viral hepatitis.

Research Goal 5

Viral Hepatitis

(Action Plan Chapter 5)

Develop safe and effective means to prevent and treat hepatitis C.

Research Goal 5 Objectives

- Develop a vaccine or specific means of prevention of hepatitis C. (Chapter 5: C3a)

- Develop safer and more effective means of treating chronic hepatitis C that can be applied to all categories of patients. (Chapter 5: B2a, B1b, C2a, C2b)

Research Goal 5 Objectives (continued)

- Better understand the structure and replication cycle of the hepatitis C virus to help develop new therapeutic targets and better small molecular therapies for this disease. (Chapter 5: A3, B1, B3)

- Better understand the host and HCV interactions that determine viral clearance versus persistence.

Research Goal 6

Viral Hepatitis

(Action Plan Chapter 5)

Improve strategies for use of current therapies of hepatitis B and develop new, improved treatment regimens.

Research Goal 6 Objectives

- Develop a better understanding of the pathogenesis of hepatitis B in all its forms (acute, chronic, active, inactive). (Chapter 5: B1a, B2b, B3b)

- Better define the optimal means of treatment of chronic hepatitis B. (Chapter 5: B2a, B2b, C1, C3)

- Conduct clinical trials to compare multi-modality therapies for hepatitis B. (Chapter 5: C1b)

Research Goal 7

Viral Hepatitis

(Action Plan Chapter 5)

Develop improved means of prevention and management of acute viral hepatitis.

Research Goal 8

HIV Infection and the Liver

(Action Plan Chapter 6)

Define the causes of liver disease associated with HIV and develop means to prevent and treat liver disease in HIV-infected persons.

Research Goal 8 Objectives

- Define the prevalence and incidence of liver disease in HIV-infected persons and identify the causes of liver disease, their means of diagnosis, prognosis and management. (Chapter 6: B1a, B2a, B2b, B3, C3b)

- Identify the optimal approach to therapy of HCV in HIV coinfected individuals and apply new agents active against HCV as soon as possible to this important cohort of patients. (Chapter 6: A1b, A2, C1b)

Research Goal 9

Fatty Liver Disease

(Liver Action Plan Chapter 7)

Understand the basic mechanisms of injury and develop means of prevention and treatment of nonalcoholic and alcoholic fatty liver disease.

Research Goal 9 Objectives

- Identify the underlying pathogenesis of nonalcoholic fatty liver disease. (Chapter 7: A3, B2a)

- Elucidate the basic mechanisms of pathogenesis of alcoholic liver disease. (Chapter 7: B1a, B2a)

Research Goal 9
Objectives (continued)

- Develop noninvasive means to distinguish steatosis and steatohepatitis. (Chapter 7: B2b)

- Identify and test safe and effective means of treatment of both forms of fatty liver disease. (Chapter 7: B1b, B3a, B3b, C1a, C1b)

Research Goal 10

Drug-Induced Liver Disease

(Action Plan Chapter 8)

Establish means to predict, prevent, diagnose and treat hepatotoxicity due to drugs, herbal medications, and environmental toxicants.

Research Goal 10 Objectives

- Develop reliable animal models or laboratory systems to study different forms of drug-induced liver injury. (Chapter 8: A3a, B3b)
- Elucidate the genetic basis of drug and toxicant induced liver injury. (Chapter 8: C1)
- Develop standardized methods to accurately diagnose drug-induced liver toxicity. (Chapter 8: A1)

Research Goal 10 Objectives (continued)

- Develop predictive tests for risk of drug induced liver injury that may allow for prevention of serious liver disease. (Chapter 8: C2b, C3)

- Develop effective means of treating drug-induced liver injury. (Chapter 8: C2a)

Research Goal 11

Autoimmune Diseases

(Liver Action Plan Chapter 9)

Determine the etiology, pathogenesis and potential new targets for therapy of the three major forms of autoimmune liver disease: autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis.

Research Goal 11 Objectives

- Develop robust animal models to study mechanisms of liver injury associated with autoimmunity and conduct preclinical studies of novel treatments. (Chapter 9: B3b)

Research Goal 11 Objectives (continued)

- Define the genetic risk alleles for each of the three major forms of autoimmune liver disease, followed by identification of physiological pathways associated with these alleles that may contribute to understanding the pathogenesis or reveal new opportunities for therapy. (Chapter 9: B3)

Research Goal 11 Objectives (continued)

- Identify novel biomarkers and define surrogate endpoints to assist in diagnosis, assessment of disease activity, predict natural history or response to different treatments. (Chapter 9: C2)

- Conduct natural history studies in childhood onset autoimmune liver diseases to refine phenotype definitions, identify genetic risk alleles, and search for potential environmental triggers. (Chapter 9: A2)

Research Goal 12

Pediatric Liver Diseases

(Action Plan Chapter 10)

Determine the molecular and genetic pathways responsible for the major forms of inherited and early onset severe liver diseases of childhood, including biliary atresia, neonatal hepatitis, progressive familial intrahepatic cholestasis, Alagille syndrome, alpha-1-antitrypsin deficiency, and mitochondrial hepatopathies in order to devise potential new targets for therapy.

Research Goal 12 Objectives

- Define the etiology and pathogenesis of biliary atresia and identify new pathways for development of potential therapies. (Chapter 10: C3)

- Optimize current approaches to medical and surgical therapy of biliary atresia. (Chapter 10: C1)

Research Goal 12 Objectives (continued)

- For familial childhood liver diseases, determine their genetic basis including primary alleles and modifying alleles, which will permit development of standardized genetic tests and identification of potential pathways for development of translational therapies. (Chapter 10: A1, B2a, C2)

Research Goal 13

Pediatric Liver Diseases

(Action Plan Chapter 10)

Evaluate and improve existing adult medical and surgical therapies for treatment of children with liver diseases.

Research Goal 13 Objectives

- Conduct clinical studies to validate use of medical regimens and liver transplantation for treatment of liver diseases in children. (Chapter 10: B1b)

- Identify biomarkers and surrogate markers for assessment of children with chronic liver diseases. (Chapter 10: A1a, B3)

Research Goal 14

Genetic Liver Disease
(Action Plan Chapter 11)

Elucidate the molecular pathways responsible for liver disease associated with the currently recognized hereditary forms of liver disease, which include hereditary hemochromatosis, Wilson disease, the porphyrias, cystic fibrosis, polycystic liver disease, and congenital hepatic fibrosis; use knowledge of these pathways to devise novel approaches to treatment.

Research Goal 14 Objectives

- For each of the genetic liver diseases, define the primary genes and modifying genes and their molecular pathways that lead to disease. (Chapter 11: A1a, A3, B2a, B3, C2a)

- Accelerate translational research to identify new target pathways for treatment, including development of animal models for pre-clinical testing. (Chapter 11: C2b)

Research Goal 14 Objectives (continued)

- For diseases having no target for drug treatment or alternative approaches to treatment, develop approaches to gene therapy to correct the underlying defect. (Chapter 11: C3b)

- Develop clinically applicable noninvasive tests to accurately measure metabolic consequences of these diseases, such as iron or copper overload. (Chapter 11: C1, C3a)

Research Goal 15

Liver Transplantation

(Liver Action Plan Chapter 12)

Refine current procedures in liver transplantation, including assessment of potential transplant recipients, immunosuppressive regimens, management of donors and recipients for living related donor transplantation, and improve management of recurrent liver diseases in transplanted patients.

Research Goal 15 Objectives

- Further refine MELD and PELD systems to optimize allocation of livers for transplantation. (Chapter 12: A1)

- Identify biomarkers for adequate immunosuppression, for active rejection, and for immune tolerance. (Chapter 12: A2, C2b)

Research Goal 15 Objectives (continued)

- Develop approaches to improve long-term tolerance for allografts in order to minimize the need for immunosuppressive drugs. (Chapter 12: C2a, C1a)

- Improve treatment for recurrence of underlying liver diseases, such as viral hepatitis, in transplant recipients. (Chapter 12: B2b, C3)

Research Goal 16

Complications of Liver Disease

(Action Plan Chapter 13)

Identify ways to prevent or ameliorate the complications of portal hypertension and cirrhosis.

Research Goal 16 Objectives

- Define in detail the pathophysiologic mechanisms that cause portal hypertension. (Chapter 13: A3a)

- Identify small molecular targets for interventions to reduce portal hypertension. (Chapter 13: B3a)

Research Goal 16 Objectives (continued)

- Develop reliable, non-or minimally-invasive methods to measure portal pressure and screen for esophageal varices. (Chapter 13: B3b, C3b)

- Better characterize the cause of increased susceptibility to bacterial infections in cirrhosis and how to manage these infections. (Chapter 13: A3b, B1)

Research Goal 17

Complications of Liver Disease

(Action Plan Chapter 13)

Develop better means of prevention, management and treatment of acute liver failure.

Research Goal 17 Objectives

- Identify the cause(s) of idiopathic acute liver failure. (Chapter 10: A3)
- Develop biomarkers that more accurately reflect hepatic regeneration and reserve in acute liver failure. (Chapter 13: C2a)
- Develop non-specific, hepatoprotective therapies that improve survival or allow time for liver transplantation in acute liver failure. (Chapter 13: A1b, B2a)

Research Goal 17 Objectives (continued)

- Develop and evaluate bioartificial liver support devices that improve survival in acute liver failure or allow for temporary support until a liver becomes available for transplantation. (Chapter 13: C3)

Research Goal 18

Liver Cancer

(Liver Action Plan Chapter 14)

Develop effective strategies for early detection and treatment of HCC and cholangiocarcinoma in high risk groups.

Research Goal 18 Objectives

- Identify new biomarkers for early detection of primary liver cancers, particularly HCC and cholangiocarcinoma. (Chapter 14: A2; Chapter 15 C2b)

- Develop new imaging techniques that detect primary liver cancers in the setting of underlying chronic liver disease. (Chapter 14: A3)

Research Goal 18 Objectives (continued)

- Identify the cellular and molecular pathways leading to primary liver cancer in order to identify potential new targets for therapy. (Chapter 14: A2b, C2, C3)

- Identify strategies to prevent HCC and cholangiocarcinoma in high risk populations. (Chapter 14: C1; Chapter 15: C1)

Research Goal 19

Gallbladder and Biliary Disease

(Action Plan Chapter 15)

Develop better means to prevent and treat gallstones.

Research Goal 19 Objectives

- Determine the genetic basis for increased risk and protection from gallstone disease. (Chapter 15: A1, C2a)

- Define better the pathophysiologic basis of gallstone formation, including the role of bacterial factors. (Chapter 15: B2)

Research Goal 19 Objectives (continued)

- Identify biomarkers for gallstone formation. (Chapter 15: B3)

- Design approaches to prevent gallstone formation in high risk groups. (Chapter 15: C3)

Major Challenges/Steps To Achieve Goals

- Basic mechanisms of liver disease
- Translational research
- Clinical research

Major Challenges/Steps To Achieve Goals

Basic Mechanisms of Liver Disease

- Multidisciplinary and inter-disciplinary collaborations between investigators interested in liver diseases and basic scientists in disciplines in areas such as immunology, genetics, virology, oncology, molecular and cell biology and other disciplines

- Resources for collaborative studies such as gene, liver and serum repositories of samples from well defined patients

Translational Research

- New, robust models of liver diseases for understanding these diseases and preclinical testing of novel therapies

Major Challenges/Steps To Achieve Goals

Clinical Research

- Standard criteria for case definition
- Precision in disease assessment by liver biopsy
- Biomarkers and surrogate markers, particularly for indolent diseases
- Pipeline of potential new therapeutic interventions that might emerge from basic and translational research.
- Multicenter clinical trials because of low disease prevalence
- In partnership with FDA, best practices for clinical trial design
- Public-private partnerships with the pharmaceutical industry to generate interest in development of drugs to treat uncommon diseases