

# APPENDIX 1:

## Summary List of Recommended Research Goals and Common Themes

The National Commission on Digestive Diseases recommends a series of research goals to guide the NIH and other entities in addressing scientific opportunities for digestive diseases research over the next 10 years. In addition, the Commission identified several common themes that, if addressed, would promote progress broadly across many areas of digestive diseases research. The Research Goals and Common Themes are numbered for ease of reference and are not listed in priority order.

### RESEARCH GOALS

#### Research on the Basic Biology of the Digestive System

- 1.1: Develop new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system for research and therapeutic applications.
- 1.2: Understand how particular cell and tissue niches are generated and maintained in the embryonic pancreas, liver, biliary tree, and digestive tract.
- 1.3: Exploit the advanced understanding of Wnt-APC- $\beta$ -catenin signaling in human epithelial function to develop new, effective treatment strategies for colorectal cancer.
- 1.4: Delineate specific signaling pathways, transcriptional regulation, and other interactions that mediate critical patterning events in gut endoderm, which generate and maintain its distinctive major derivatives (GI tract, liver, and pancreas).
- 1.5: Translate advances from laboratory research in gut development to identify disease mechanisms and therapeutic targets for diverse GI disorders (e.g., congenital disorders, cancer).
- 1.6: Define the physiologic basis for intestinal growth and adaptation and alterations with aging.
- 1.7: Define the physiologic basis of energy balance, appetite, and satiety and their roles in obesity.
- 1.8: Define the physiology of neuroimmune pathways involved in inflammation.
- 1.9: Develop a comprehensive profile of intestinal genes that regulate mammalian absorptive functions.
- 1.10: Identify critical pathways in murine and other *in vivo* models to develop targets for treatment of obesity and other disorders of nutrient absorption and metabolism.
- 1.11: Define pathways that regulate barrier function and transport function.
- 1.12: Define molecular pathways leading to differentiated absorptive and secretory functions.
- 1.13: Develop means to measure and manipulate epithelial function.
- 1.14: Define the basic cellular and molecular mechanisms responsible for neural activation, integration, and regulation in the ENS.
- 1.15: Understand the structure, function, and regulatory mechanisms responsible for motility in the GI tract.
- 1.16: Develop research tools to investigate the structure and functional organization of the ENS.

- 1.17: Characterize the neuromuscular phenotypes of human GI tissues.
- 1.18: Integrate cellular events in ENS with whole system physiology and translate findings to pathophysiologic conditions.
- 1.19: Translate knowledge of the ENS in digestive health and disease into diagnostics and therapies for human disease.
- 1.20: Determine the biologic activities of the microflora in healthy humans.
- 1.21: Determine the mechanisms of host-microbial interactions that are necessary to maintain health and contribute to pathological processes in disease.
- 1.22: Determine the role of epithelial cells in mucosal host defense and inflammation.
- 1.23: Understand the role of antigen-presenting cells in the mucosal immune system.
- 1.24: Understand trafficking of mucosal cells to various parts of the mucosal immune system.
- 1.25: Understand mucosal unresponsiveness (oral tolerance) and mucosal regulatory T cell development.
- 1.26: Understand the differentiation and function of mucosal lymphocytes and other immunologically active cells.
- 1.27: Develop mucosal vaccination strategies.
- 2.4: Understand the immune functions of the muscularis, integration between mucosal and muscle immune responses, and how inflammatory processes contribute to the pathogenesis and maintenance of functional GI and motility disorders.
- 2.5: Understand peripheral and central pain and sensory pathways and how these pathways are affected in functional GI and motility disorders.
- 2.6: Understand the noxious visceral signaling causing nausea and vomiting related to gastric neuro-electrical and/or motor dysfunction and the bi-directional brain-gut interactions.
- 2.7: Understand the role of the microflora in functional GI disorders and motility disorders.
- 2.8: Use information from studies of animal models and cellular physiology to understand the integrated function of the musculature and the intrinsic and extrinsic nervous systems.
- 2.9: Characterize the factors in diabetes that lead to the development of functional GI and motility diseases.
- 2.10: Determine how genotype contributes to or predisposes patients to the development of functional GI and motility disorders.
- 2.11: Determine the role of food in the development of functional GI and motility disorders.
- 2.12: Develop new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.
- 2.13: Evaluate therapeutic outcomes and the impact of doctor/patient interactions to determine effective treatments for functional GI and motility disorders.

### **Functional Gastrointestinal Disorders and Motility Disorders**

- 2.1: Understand the molecular and cellular events that yield normal motility, sensory behavior, and integration between motility and secretory activity in the GI tract and the pathophysiology of functional GI disorders and motility disorders.
- 2.2: Understand the development of the GI tract and brain-gut interactions and determine how the aging process and differences in sex and gender affect gut development and function and brain-gut interactions.
- 2.3: Understand the components and functional interactions of the peripheral (autonomic and enteric) and central nervous systems in normal physiology and in functional GI and motility disorders.

### **Infections of the Gastrointestinal Tract**

- 3.1: Elucidate the etiology, epidemiology, and pathogenesis and improve diagnostic tests for intestinal infections.
- 3.2: Improve the prevention and treatment of intestinal infections.
- 3.3: Understand and modulate the long-term intestinal and non-intestinal consequences of GI infection.

- 3.4:** Understand the human microflora and microbiome in health and disease and modulate them for beneficial effects.

### **Cancers of the Digestive System**

- 4.1:** Develop population-based strategies for screening and prevention of digestive cancers.
- 4.2:** Ascertain the importance, detection, and natural history of pre-malignant conditions progressing to digestive cancer.
- 4.3:** Evaluate health disparities in digestive cancer etiology, risk, treatment management, and outcomes.
- 4.4:** Improve outcomes in the care of digestive tract cancer patients.
- 4.5:** Develop biomarkers to detect neoplasia, target therapy, and evaluate therapeutic response in digestive cancers.
- 4.6:** Evaluate nutraceutical, probiotic, chemopreventive, and targeted therapies in digestive cancers.
- 4.7:** Understand the molecular and cellular mechanisms common to all digestive cancers.
- 4.8:** Determine the risk factors and pathogenesis of squamous carcinoma and adenocarcinoma of the esophagus and devise new methods for detection, diagnosis, treatment, and prevention of these diseases.
- 4.9:** Understand the molecular profiles of various types of gastric cancer to improve risk stratification, prevention, and treatment.
- 4.10:** Define the genetic and environmental factors contributing to pancreatic cancer and its precursor lesions and devise new methods for early detection, treatment, and prevention.
- 4.11:** Identify genetic and environmental risk factors for colon cancer and devise improved approaches for screening, early diagnosis, treatment, and prevention of colon cancer.
- 4.12:** Understand the etiology, natural history, prevention, and management of rare GI cancers.

### **Inflammatory Bowel Diseases**

- 5.1:** Establish an objective basis for determining clinical diagnosis, detailed phenotype, and disease activity in IBD.
- 5.2:** Develop an individualized approach to IBD risk evaluation and management based on genetic susceptibility.
- 5.3:** Modulate the intestinal microflora to prevent or control IBD.
- 5.4:** Effectively modulate the mucosal immune system to prevent or ameliorate IBD.
- 5.5:** Sustain the health of the mucosal surface.
- 5.6:** Promote regeneration and repair of injury in IBD.
- 5.7:** Provide effective tools for clinical evaluation and intervention in IBD.
- 5.8:** Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents.

### **Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation**

- 6.1:** Define mechanisms of intestinal growth and differentiation.
- 6.2:** Develop new strategies to treat short bowel syndrome and intestinal failure.
- 6.3:** Improve the success of intestinal transplantation.
- 6.4:** Understand and treat the metabolic and nutritional consequences of bariatric procedures and other surgical modifications of the gut.
- 6.5:** Optimize nutritional support of patients with GI disorders.

### **Diseases of the Oropharynx and Esophagus**

- 7.1:** Understand the neurobiology of oropharyngeal structure and function in health and disease.
- 7.2:** Understand the clinico-pathologic mechanisms leading to and/or associated with GERD and identify novel molecular, physiologic, and anatomic targets for more effective and rational treatment.

- 7.3:** Define the mechanisms responsible for esophageal injury and repair, with particular emphasis on the interactions among components of the esophageal wall.
- 7.4:** Understand the epidemiology, natural history, and outcomes of eosinophilic esophagitis and identify targets for more rational and effective therapy.
- 7.5:** Understand the etiopathogenesis of Barrett's esophagus, determine risk factors associated with its progression, and identify novel targets and/or therapies for chemoprevention and treatment.
- 7.6:** Understand the etiology and biology of esophageal neuromuscular function in health and disease and develop more effective treatments.

### **Diseases of the Stomach and Small Intestine**

- 8.1:** Understand mechanisms and improve treatment of *H. pylori* diseases.
- 8.2:** Reduce and prevent NSAID peptic diseases.
- 8.3:** Define the genetic, bacterial, and host factors that regulate epithelial and inflammatory cell responses to injury in gastric mucosa.
- 8.4:** Understand the basis of rare gastric cancers, develop effective measures for earlier and more accurate diagnosis, and develop effective treatment strategies.
- 8.5:** Determine the genetic, molecular, and integrated physiologic bases of intestinal water, nutrient, and electrolyte transport.
- 8.6:** Improve treatment, prevention, and diagnosis of malabsorptive and diarrheal diseases.
- 8.7:** Understand pathogenic mechanisms of celiac disease, autoimmune diseases, and allergic diseases of the digestive system.
- 8.8:** Improve screening, diagnosis, prevention, and treatment of celiac disease and of autoimmune and allergic disorders of the bowel. Characterize and define the mechanisms underlying the association of celiac disease with autoimmune and neurological diseases.
- 8.9:** Understand the pathogenesis of necrotizing enterocolitis and the unique susceptibility

of the premature infant, including genetic susceptibility, microflora, and immune/inflammatory processes.

- 8.10:** Develop novel predictive, therapeutic, and preventive approaches for necrotizing enterocolitis.
- 8.11:** Determine the genetic bases, mechanisms, natural history, and clinical phenotypes of eosinophilic gastrointestinal disorders and identify/develop novel therapeutic compounds.

### **Diseases of the Colon and Rectum**

- 9.1:** Establish mechanisms of colonic injury and repair to use as a basis for development of therapeutic interventions.
- 9.2:** Understand colonic mucosal absorption in health and disease.
- 9.3:** Determine the role of gut microflora in health and disease states of the colon.
- 9.4:** Establish the cause of diverticular disease and its complications, with modulation of disease.
- 9.5:** Understand mechanisms and develop tools for early diagnosis of colon ischemia and angioectasia.
- 9.6:** Improve management of anorectal disorders.
- 9.7:** Improve the understanding and management of fecal incontinence.
- 9.8:** Reduce the frequency and severity of radiation injury to the colon.
- 9.9:** Determine causes of appendicitis and modulate the course of the disease.

### **Diseases of the Pancreas**

- 10.1:** Determine the biologic factors involved in the pathogenesis of acute pancreatitis, with particular emphasis on the mechanisms of tissue necrosis and systemic complications.
- 10.2:** Understand the transition from acute to chronic pancreatic injury, particularly with respect to the role of alcohol.
- 10.3:** Understand genetic factors and their interactions with exogenous insults, with respect to pathogenesis, complications, and natural history of pancreatitis and other pancreatic disorders.

- 10.4:** Develop and validate therapeutic interventions for treatment and/or progression of pancreatitis and its complications.
- 10.5:** Understand the neurobiology of the pancreas with respect to mechanisms of pain and neurogenic inflammation.
- 10.6:** Define the epidemiology and clinical course of acute and chronic pancreatitis, including alcoholic pancreatitis, autoimmune pancreatitis, and cystic fibrosis, through population-based studies in adults and children.
- 10.7:** Develop more accurate and useful approaches to the diagnosis of chronic pancreatitis by functional, radiologic, endoscopic, or pathologic/cytologic means.
- 10.8:** Define the role of pathologic lesions, such as pancreatic intraepithelial neoplasms, and other factors that may correlate with the risk of malignant transformation in chronic pancreatitis and cystic neoplasms and map their morphologic and molecular progression.

### **Diseases of the Liver and Biliary System**

- 11.1:** 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.
- 11.2:** Understand the cellular mechanisms of liver injury, inflammation, repair, and fibrosis and develop effective means for monitoring and treating diseases caused by these processes.
- 11.3:** 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.
- 11.4:** 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 for diagnosis, treatment, and prevention of cholestatic liver disease and disorders of bilirubin metabolism.
- 11.5:** Develop safe and effective means to prevent and treat hepatitis C.
- 11.6:** Improve strategies for use of current therapies of hepatitis B and develop new, improved treatment regimens.
- 11.7:** Develop improved means to prevent and manage acute viral hepatitis.
- 11.8:** Define the causes of liver disease associated with HIV and develop means to prevent and treat liver disease in HIV-infected persons.
- 11.9:** Understand the basic mechanisms of injury and develop means to prevent and treat non-alcoholic and alcoholic fatty liver disease.
- 11.10:** Establish means to predict, prevent, diagnose, and treat hepatotoxicity due to drugs, herbal medications, and environmental toxicants.
- 11.11:** Determine the etiology, pathogenesis, and potential new targets for therapy of the three major forms of autoimmune liver disease: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC).
- 11.12:** 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, neonatal hemochromatosis, and mitochondrial hepatopathies in order to devise potential new targets for therapy.
- 11.13:** Evaluate and improve existing adult medical and surgical therapies for treatment of children with liver diseases.
- 11.14:** Elucidate the molecular pathways responsible for hereditary forms of liver disease, including 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.

- 11.15:** Refine current procedures in liver transplantation, including assessment of potential transplant recipients, immunosuppressive regimens, and management of donors and recipients for living donor transplantation, and improve management of recurrent liver diseases in transplanted patients.
- 11.16:** Identify ways to prevent or ameliorate the complications of portal hypertension and cirrhosis.
- 11.17:** Develop better means of prevention, management, and treatment of acute liver failure.
- 11.18:** Develop effective strategies for early detection and treatment of hepatocellular carcinoma and cholangiocarcinoma in high-risk groups.
- 11.19:** Develop better means to prevent and treat gallstones.

### **Bioengineering, Biotechnology, and Imaging**

- 12.1:** Define the optimal procedural approach for patients with digestive disorders amenable to endoscopic, image-guided, or minimal access surgery.
- 12.2:** Develop innovative technology for the diagnosis and treatment of luminal disease.
- 12.3:** Use tissue engineering and regenerative medicine approaches to develop innovative treatments for digestive diseases.
- 12.4:** Expand the application and integration of imaging and procedural technologies to deliver targeted interventions with minimal tissue injury to patients with digestive disorders.
- 12.5:** Develop high-fidelity interactive simulators of the digestive system.

## **COMMON THEMES**

**THEME 1: Increase the fundamental knowledge base for understanding health and digestive diseases.**

### **Strategies for Implementation:**

- 1.1:** Elucidate the molecular basis of biologic and pathologic processes in the digestive system.
- 1.2:** Define the genetic basis of digestive diseases.
- 1.3:** Understand the role of microbes in digestive health and disease.
- 1.4:** Harness research in immunology, inflammation, and transplantation to improve our understanding of the digestive system and its diseases.
- 1.5:** Discover the cellular and molecular basis of development, regeneration, and aging of the digestive system.
- 1.6:** Support the development and application of new research technologies for digestive diseases research.

**THEME 2: Translate fundamental new knowledge for the direct benefit of individuals.**

### **Strategies for Implementation:**

- 2.1:** Refine the phenotypes of patients with digestive diseases.
- 2.2:** Discover biomarkers and surrogate markers for digestive diseases.
- 2.3:** Define the natural history and risk factors for digestive diseases through epidemiologic research.
- 2.4:** Develop new, innovative technologies for clinical applications.
- 2.5:** Develop new means to prevent, cure, or treat digestive diseases through clinical trials.
- 2.6:** Bridge the gap between controlled clinical trials and dissemination of new knowledge into clinical practice.
- 2.7:** Support clinical research teams.

**THEME 3: Develop research resources and infrastructure.**

**Strategies for Implementation:**

- 3.1:** Increase the availability of specimens, data, and computational methods for research in digestive diseases.
- 3.2:** Create and make available new animal models for digestive diseases research.
- 3.3:** Support team research.

**THEME 4: Maintain a pipeline of research investigators for the future.**

**Strategies for Implementation:**

- 4.1:** Support research training, individual fellowship, and career development programs.

- 4.2:** Support mentorship.
- 4.3:** Maintain a substantially higher success rate for R01-equivalent grants for new investigators in digestive diseases than that of established investigators.
- 4.4:** Enhance career development educational workshops and conferences.
- 4.5:** Reduce the financial burden for new investigators.
- 4.6:** Assure a diverse workforce.
- 4.7:** Provide short-term training in digestive diseases research.
- 4.8:** Encourage entry of PhD scientists into translational and clinical research in digestive diseases.