Diseases of the Stomach and Small Intestine

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Research Goal 1

Understand mechanisms and improve treatment of *H. Pylori* acid-peptic diseases.

Research Goal 1 Objectives

- Profile the microbial, molecular, cellular, and epidemiological features of *H. pylori*-induced gastric carcinogenesis and PUD to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.
- Define the relationship between *H. pylori* and GERD complications and assess prolonged proton-pump inhibitor use.
- Develop noninvasive technologies to screen for *H. pylori*-induced premalignant lesions.
- Develop prevention strategies based on mechanisms of *H. pylori*/host interactions that lead to premalignant/malignant lesions and evaluate their effectiveness in at-risk populations.

Research Goal 2

Reduce and prevent NSAID peptic diseases.

Research Goal 2 Objectives

- Define pathogenic mechanisms that regulate NSAID-induced injury.
- Develop population-based screening and pharmacogenomic approaches for identification of individuals at risk for NSAID-induced peptic ulcer disease as a basis for subsequent intervention.
- Educate patients and physicians regarding risk factors, and improve adherence to appropriate strategies for decreasing NSAID-associated GI complications.

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Research Goal 2
Objectives (continued)

- Determine long term risks of chronic NSAID usage and proton pump inhibitor therapy, including the risk of neoplasm.

- Design anti-inflammatory agents of comparable or higher efficacy to traditional NSAIDs, but which lack traditional GI side effects and cardiovascular toxicity.

Research Goal 3

Define the genetic, bacterial, and host factors that regulate epithelial and inflammatory cell responses to injury in gastric mucosa.

Research Goal 3 Objectives

- Elucidate genetic, bacterial, and host factors that regulate or affect gastric mucosa response to pathogens and stress
- Understand mechanisms of mucosal cytoprotection and wound healing.
- Develop novel therapies that promote mucosal cytoprotection and wound healing.

Research Goal 4

Understand the basis of gastric cancers, develop effective measures for earlier and more accurate diagnosis, and develop effective treatment strategies.

Research Goal 4 Objectives

- Perform population-based evaluation of adjuvant and palliative therapy.
- Develop new treatment modalities that target the genetic basis of gastric cancer.
- Identify, develop, and validate genetic, biochemical, and biological markers that will help uncover host-environment interactions in gastric carcinogenesis.

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Research Goal 4
Objectives (continued)

- Develop more sensitive methods for detecting gastrinomas and metastases.

- Develop a reliable mouse model of gastrinoma that will mimic features of ZES, specifically duodenal tumors.

Research Goal 5

Determine the genetic, molecular, and integrated physiological bases of intestinal water, nutrient, and electrolyte transport.

Research Goal 5 Objectives

- Identify and characterize proteins involved in intestinal transport function, e.g. fatty acid transport proteins and transport proteins in the basolateral membrane of sodium absorptive cells involved in moving amino acids, sodium, chloride, or heavy metals into blood as well as signaling molecules and accessory proteins that regulate the activity, expression, trafficking, membrane abundance, and degradation of these transport proteins.

- Understand the processes that allow coordination of motility, absorption, and secretion in intact animal intestine and in human intestine. Determine how changes in sodium absorptive and chloride secretory processes are integrated with changes in tight junctions.

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Research Goal 5
Objectives (continued)

- Determine the proteome of intestinal sodium absorptive cell and chloride secretory cell, including the subcellular proteome of brush border and basolateral membrane under normal conditions and in diarrhea and malabsorption.

- Characterize the effects of knocking out enteroendocrine cells on the development of the gut and on integrative aspects of absorptive, secretory and digestive functions of the intestine. Determine how maldigestive states affect normal gut development and differentiation of the genes involved in nutrient digestion and transport.

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Research Goal 5
Objectives (continued)

- Identify bacteria that are present in small intestine and colon of normal humans and the changes that occur in bacterial overgrowth, Crohn's disease, microscopic colitis, eosinophilic enteritis, celiac disease, other malabsorptive disease, lactase deficiency and obesity.

- Determine the contribution of paracellular transport of luminal materials to intestinal disease, characterize how tight junctions limit specific molecule movement, and understand the integration of cellular and paracellular movement and regulation of movement.

Research Goal 6

Improve treatment, prevention, and diagnosis of malabsorptive and diarrheal diseases.

Research Goal 6 Objectives

- Determine the causes of chronic diarrheal diseases in 40 percent of patients in which no specific cause is identified (some will be due to polymorphisms and/or mutations in intestinal transporters). Determine the epidemiology of acute diarrhea in the elderly, including mortality.

- Develop preventative measures to limit the incidence of acute diarrheal diseases. Evaluate the role of non-hydrolyzable starch based ORS in treatment of acute diarrhea in adults and children in developing countries and the U.S.

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Research Goal 6
Objectives (continued)

- Develop clinically useful imaging and diagnostic techniques to examine digestive processes and abnormalities in diarrheal and malabsorptive diseases.

- Test new anti-chloride-secretory and pro-sodium absorptive drugs in animal models of acute diarrheal diseases. Conduct clinical trials for acute diarrhea.

- Develop gene therapy targeting intestinal epithelial cells and pharmacologic agents capable of blocking or augmenting pathways that control intestinal gene expression as part of future treatment strategies for chronic diarrheal and malabsorptive/maldigestive diseases.

Research Goal 7

Understand pathogenic mechanisms of celiac disease and related autoimmune diseases.

Research Goal 7 Objectives

- Define the early innate events and the interplay between innate and adaptive immunity in celiac disease pathogenesis.
- Elucidate the events leading to transglutaminase activation and define its role in celiac disease pathophysiology both as an autoantigen and as a modifier of toxic gluten peptides.
- Define mechanisms and events that link the generation of large gluten peptides and the ultimate development of pathogenic T cell populations.

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Research Goal 7
Objectives (continued)

- Define the role of antibodies and immune complexes in celiac disease.
- Define patterns in intestinal microbiome relevant to celiac disease and autoimmune/allergic disorders of the bowel.
- Define signaling pathway (e.g. protease, MLCK, enteric toxins, cytokines) that are involved in the regulation of intestinal permeability under physiological and pathophysiological conditions.
- Distinguish between the effects of IL-23 and IL-12 in the pathogenesis of chronic inflammation.

Research Goal 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.

Research Goal 8 Objectives

- Develop a more complete understanding of the pathogenesis of celiac disease, including the role of immune, epithelial, microbiological, environmental, and host factors as well as its relationship to other autoimmune diseases.

- Identify novel biomarkers, including additional genetic risk factors, to predict the development of autoimmune disease in high risk patients and to determine severity of illness and response to treatment.

Research Goal 8
Objectives (continued)

- Identify environmental triggers of celiac disease.
- Identify new, non-invasive methods to diagnose celiac disease.
- Develop non-dietary methods to treat celiac disease.

Research Goal 8
Objectives (continued)

- Establish the safety/efficacy and benefits of therapeutic interventions that improve intestinal barrier function in patients with autoimmune diseases and identify the autoimmune pathologies (GI and non-GI) that may benefit from such interventions.

Research Goal 9

Understand the pathogenesis of NEC and the unique susceptibility of the preterm infant, including genetic susceptibility, microbiome, and immune/inflammatory processes.

Research Goal 9 Objectives

- Develop models of immature gut relevant to the development of NEC.
- Investigate the development of intestinal host defense mechanisms and the intestinal immune system relevant to NEC.
- Define normal patterns of bacterial colonization in the healthy preterm infant relevant to NEC.

Research Goal 9
Objectives (continued)

- Understand the role appropriate bacterial balance plays in intestinal development.

- Identify mechanisms responsible for probiotic effects on acute gut injury in preterm infants.

Research Goal 10

Develop novel predictive, therapeutic, and preventative approaches for NEC.

Research Goal 10 Objectives

- Complete phase I and phase II trials in U.S. of promising therapeutic interventions to assess tolerability and dosing strategy in pre-term infants including PAF acetylhydrolase, probiotics and factors found in human milk.

- Develop other novel therapies or preventive measures based on discoveries made in understanding NEC pathophysiology and causes.

Research Goal 10
Objectives (continued)

- Investigate the mechanisms behind and possible interventions to prevent the poor neurodevelopmental outcome of infants with NEC.

- Investigate the role of clinical practices in the development of NEC – i.e. H2 blockers, opioids, indomethacin, umbilical catheters, treatment of patent ductus arteriosus, and feeding patterns.

- Develop programs to encourage breast milk feeding of preterm infants.

Research Goal 11

Determine the genetic bases, mechanisms, natural history, clinical phenotypes of EGIDS and identify/develop novel therapeutic compounds.

Research Goal 11 Objectives

- Define the genetic bases, epidemiology and natural history of EGIDS.
- Define clinical phenotypes of EGIDS (e.g. allergic, non-allergic, or autoimmune) and develop novel animal models and reagents to study eosinophilic gastrointestinal inflammation.
- Define cellular and molecular pathways that regulate eosinophil-dependent tissue remodeling.

Research Goal 11 Objectives (continued)

- Identify and develop novel agents for treatment of EGIDS such as anti-IL-5 antibody, anti-CCR3 receptor antibody, and imatimib.

Major Challenges/Steps To Achieve Goals

- **Animal models**
- **Clinical research collaboration**
- **Central research resources**
- **Physician communication and education**
- **Innovative technologies**
- **Drug development**

Major Challenges/Steps To Achieve Goals

Animal Models

- Experimental models that replicate human disease include *H. pylori*-induced gastric cancer and ZES, intestinal transport, malabsorption, and maldigestion, celiac disease, autoimmune and allergic diseases of the bowel, and NEC

- Animal models to study infection, morphologic interpretation of lesions, imaging technology, basic cellular processes such as endocytosis, migration, and ion transport in intestine and drug testing

- Related resources:
  - Improved organ cultures,
  - organotypic culture technologies, and
  - *H. pylori* strain repositories

Major Challenges/Steps To Achieve Goals

Clinical Research Collaboration

- Multicenter, systems biology-based consortia or networks of health care professionals to share materials and information and increase statistical power
    - Interdisciplinary, population-based, endoscopic, multi-institutional studies to identify *H. pylori*-infected populations at greatest risk for gastric cancer, and to determine the prevalence and natural history of premalignant lesions.
    - Multicenter networks to coordinate research and management of a range of diseases that include rare gastric tumors, ZES, dyspepsia, chronic diarrheal and malabsorptive diseases, NEC, celiac disease, and eosinophilic gastroenteritis
- Small conferences for clinical and scientific interactions that could spark innovative approaches

Major Challenges/Steps To Achieve Goals

Central Research Resources

- Centralized resources, such as databases, patient registries, and biosample repositories
- Databases with an emphasis on enrollment of minority gastric cancer patients and a specimen and tissue banks
- Large-scale biology approaches to identify protein-protein interactions, pH and calcium homeostasis during digestion and in diarrheal diseases in sodium absorptive, chloride secretory and enteric endocrine cells
- Repositories of clinical data and samples from celiac disease or eosinophilic gastroenteritis patients
- Repository for autoimmune patient samples or databases on families with high incidence of autoimmune diseases

Major Challenges/Steps To Achieve Goals

Physician Communication and Education

- Small conferences to promote interactions between adult and pediatric clinicians to define the natural history of these diseases
- Programs to determine cause of poor adherence to guidelines, make appropriate recommendations, develop mechanisms to disseminate recommendations, assess whether recommendations are being followed, and assess alterations in outcomes (quality of care) for acid-peptic diseases
- Educational campaign to increase awareness of celiac disease among health care professionals

Major Challenges/Steps To Achieve Goals

Innovative Technologies

- Experimental tools and models to study intestinal epithelial physiology and diseases, including diarrhea, malabsorption, development, inflammation, and pediatric disorders
- Infrastructure to develop proteomics approaches to study of GI disease
- Methods to target epithelial cells/GI tissues with siRNA or expression vectors or integrative models of gut absorptive and digestion function in humans
- Communication between basic scientists developing the technology for evaluation of microbial ecology and clinical scientists who are able to bring these technologies to the patient
- Genomic and proteomic techniques to identify biomarkers using human intestinal samples

Major Challenges/Steps To Achieve Goals

Drug Development

- Collaboration between academia and the pharmaceutical and biotechnology industries.
- High-throughput screening of anti-diarrheal drugs that inhibit chloride secretion and/or stimulate sodium absorption
- Collaboration with industry to develop specific microbes (probiotics) or microbial products that stabilize the intestinal mucosal immune system and mutual funding of multicenter trials for therapies in NEC