Functional GI Disorders and Motility Disorders

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Research Goal 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. Develop the means to repair or replace damaged cellular components.

Research Goal 1 Objectives

- Develop cell-specific markers for each cellular component involved in gut neuromuscular function and visceral sensation.

- Characterize differences in gene expression in specific cell populations in health and in disease.

- Develop biomarkers that can be used to assess the health and function of specific cellular components.

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Research Goal 1
Objectives (continued)

- Determine why interstitial cells of Cajal are lost in many motility disorders and how to restore this population of cells.

- Identify GI tract-specific stem cell populations and develop techniques to regenerate specific cell populations or tissues.

Research Goal 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.

Research Goal 2 Objectives

- Develop a comprehensive picture of how genetics and environmental factors affect development and maintenance of normal function of the GI tract and the brain-gut axis.

- Determine why women are disproportionately affected by functional GI and motility disorders.

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Research Goal 2
Objectives (continued)

- Determine how hormonal status affects the neuromuscular apparatus of the gastrointestinal tract and how it might predispose the gut to abnormal motility or abnormal sensation.

- Learn the mechanisms of fecal incontinence and develop means of prevention and treatment.

Research Goal 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.

Research Goal 3 Objectives

- Define the role of the vagal homeostatic system (e.g., vagal anti-nociception, vagal anti-inflammatory reflex).

- Determine the role of the sympathetic nervous system in regulating gut and sphincter function.

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Research Goal 3
Objectives (continued)

- Define how neural integration is accomplished in peripheral neurons and how GI sensation integrates with central pain pathways.

- Understand the degree to which cognitive and emotional processes participate in the generation and/or symptoms in chronic GI disorders.

Research Goal 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.

Research Goal 4 Objectives

- Define mucosal functions (immune, barrier, sensing/taste) and the role of inflammation.

- Determine the interactions of inflammatory, immune, and neural cells in diseases of the ENS and hypersensitivity.

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Research Goal 4
Objectives (continued)

- Characterize the inflammatory responses to various insults to the GI tract and develop the means to disrupt or reverse these responses.

- Characterize the effects of probiotics on mucosal-immune interactions.

- Determine the efficacy of antibiotics in prevention and treatment of post-infectious IBS.

Research Goal 5

Understand peripheral and central pain and sensory pathways and how these pathways are affected in functional GI and motility disorders.

Research Goal 5 Objectives

- Clarify enterochromaffin cell-afferent nerve terminal interactions. What are the mechanisms of afferent nerve activation and sensitization in the GI tract?

- Characterize the integration between visceral nociceptive pathways and motor pathways.

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Research Goal 5
Objectives (continued)

- Determine the mechanisms for gastrointestinal sensation and perception of sensation and how the gain of visceral sensory pathways increases in functional GI disorders.

- Develop new agents to reduce nociception and undesirable visceral sensation.

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Research Goal 5
Objectives (continued)

- Characterize the sites and mechanisms of central processing of inappropriate sensation in the GI tract in normal patients and patients with functional bowel disorders.

Research Goal 6

Understand the role of microflora in functional GI diseases and motility disorders.

Research Goal 6 Objectives

- Characterize the impact of the intestinal microflora on bidirectional brain-gut communication

- Characterize the effects of stress, diet and infections on gut microflora.

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Research Goal 6
Objectives (continued)

- Determine the relationship between a patient's genotype and the microbiome.
- Determine the impact of alterations in the content of the microflora on GI function and sensation.

Research Goal 7

Use information from studies of animal models and cellular physiology to understand the integrated function of the musculature and intrinsic and extrinsic nervous systems.

Research Goal 7 Objectives

- Develop conceptual and/or quantitative models to demonstrate how various pathophysiological inputs—such as stress, altered gut flora, or neuroendocrine dysfunction—might influence motor patterns, integration between motility and secretion and visceral sensation.

- Use animal models to determine the role of infection, metabolic disease, stress, and sex on GI phenotype, neural integration, afferent nerve sensitivity, neuroimmune responses, neuro-muscular transmission, pacemaking, and integration of information between the peripheral and central nervous systems.

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Research Goal 7
Objectives (continued)

- Use selective genetic models to determine the role of specific signaling pathways, neurotransmitter systems, and immune responses in normal and pathophysiological states.

- Use animal models to develop new biomarkers of gut health and function.

Research Goal 8

Determine how genotype contributes to or predisposes patients to the development of functional GI disorders and motility disorders.

Research Goal 8 Objectives

- Develop genetic epidemiological studies to discover common genetic factors that predispose patients to development of GI motility disorders or functional disorders.

- Develop and validate endophenotypes (intermediate hereditary characteristics between the disease and the genotype) as a means of clarifying links between the genotype and the complicated phenotypes of functional GI and motility disorders.

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Research Goal 8
Objectives (continued)

- Utilize validated endophenotypes to clarify classification and diagnosis of functional GI and motility disorders and to foster the development of animal models.

- Utilize a pharmacogenetic approach to predict which patients might respond to specific therapies.

Research Goal 9

Develop new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.

Research Goal 9 Objectives

- Develop and evaluate new therapeutic pharmaceutical agents for treatment of functional GI and motility disorders.
- Develop new devices or applications of novel stimulus regimes to target vagal nerve function.
- Develop new devices, surgical techniques or tissue replacement to enhance continence. →

Research Goal 9
Objectives (continued)

- Develop and validate standard measures for health outcomes research (e.g., primary treatment endpoints, health related quality of life, psychosocial assessment, health behaviors such as health care utilization and decreased daily function and costs).

- Standardize behavioral treatments making them generalizable to a broader population.

Evaluate therapeutic outcomes and the impact of doctor (provider)/ patient interactions to determine effective treatments for functional GI and motility disorders.

Research Goal 10

Develop new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.

Research Goal 10 Objectives

- Develop innovative ways to optimize health care delivery systems for GI disorders to enhance outcomes and reduce costs.

- Determine the elements of the health care provider-patient relationship, such as interview techniques, relationship centered care, emotion handling and placebo that will improve health care outcomes.

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Research Goal 10 Objectives (continued)

- Determine the effect of health care provider education and training to enhance the provider – patient relationship on clinical outcomes including patient satisfaction, adherence to treatment, improved symptoms, quality of life and health care costs.

- Conduct randomized, controlled trials of stress management and relaxation methods, hypnotherapy and cognitive behavioral therapy in pediatric and adult populations.

Major Challenges/Steps to Achieve the Goals

- Methods to study the diversity of GI cells
- Technologies to study the enteric nervous system
- Systems biology approaches
- Integrative biology approaches
- Standardized molecular definitions, biomarkers and clinical treatments
- Innovative transplantation techniques

Major Challenges/Steps to Achieve the Goals

Methods to Study the Diversity of GI Cells

- Innovative techniques to isolate and identify specific types of cells from healthy and diseased gut samples
- Use of state-of-the-art technologies such as genomic and proteomic analyses.
- New technologies to manipulate genetic expression of GI cell types while the cells are still in their native environment is required.
  - enhanced spatial and temporal targeting of transgenic methodologies
  - techniques to effectively turn on and off expression of specific genes in adult animals

Major Challenges/Steps to Achieve the Goals

Technologies to Study the Enteric Nervous System

- Techniques to discriminate between different classes of afferent nerve terminals and to clearly identify nociceptive nerve terminals in living tissues
- Dynamic imaging techniques to study the behavior of afferent nerve terminals in the *lamina propria* and muscularis
- Better recording methods to measure activity of the autonomic nervous system in conscious experimental animals and to correlate neural activity with motility
- Techniques to record from the central nervous system in conscious experimental animals (fMRI or PET) that correlate activity with peripheral neural activity and motility
- Methods to probe the links between disorders of GI function (e.g., constipation and diarrhea) and pain and discomfort in the gut

Major Challenges/Steps to Achieve the Goals

Systems Biology Approaches

- Models or a conceptual framework that unifies morphology and cell biology (anatomy, histology, histochemistry, molecular biology, and pathway analysis) with physiology (functions of cells, integration of cellular function in tissues and organs)
- Databases from gene and protein expression studies of specific GI cell types in normal and pathophysiological states
- Understand changes in gene and protein expression that are common to specific functional GI and motility disorders to identify biomarkers
- Dynamic imaging techniques to understand interactions between GI cells and how discrete cellular and sub-cellular defects in genetically-altered animal models contribute to function and dysfunction of tissues and organs

Major Challenges/Steps to Achieve the Goals

Integrative Biology Approaches

- Studies of how environmental factors and life experiences affect gut function
- Improved animal models to explore the cause-and-effect relationship between suspected pathological factors and the development of symptoms and disease.
- Complementary studies on human GI tissues and cells.
- Better techniques for monitoring GI function, autonomic function, and brain function in genetically-altered animals to increase efficiency for phenotyping animal models
- Genetic screens to identify defective GI motility, autonomic and CNS phenotypes and the inactivation of genes linked to defective motility phenotypes in animals
- Models to determine the functional effects of genetic variations in candidate genes that are reputed to alter motor and sensory functions and somatization manifesting in GI tract symptoms or diseases
- Techniques to evaluate GI motility in model organisms such as zebrafish or mice to screen genes that are linked to altered bowel function
- Testing human polymorphisms in vertebrate models

Major Challenges/Steps to Achieve the Goals

Standardized Molecular Definitions, Biomarkers, and Clinical Treatments

- Consensus clinical descriptions of functional GI disorders and motility disorders
- Multi-center patient registries and tissue/reagent banks
- Standardization of clinical assessments and treatments of functional GI disorders and motility disorders across patient populations and clinical research centers
- Standardization of techniques and methods of analysis of brain imaging, assays for mucosal cytokines and neuropeptides, and reporting of clinical outcomes in treatment trials
- Consortium approach to handle the large numbers of samples and controls that are required for proper studies.

Major Challenges/Steps to Achieve the Goals

Innovative Transplantation Techniques

- Better transplantation therapies possibly including solutions based on stem cell therapies and tissue-engineering
- More information about the stem cell populations in the GI tract and how to manipulate the phenotypes of stem cell derivatives
- Innovative techniques to create functional regions of GI organs by tissues engineering