Overview of the Digestive System

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Research Goal 1

Understand how particular cell/tissue niches are generated and maintained in embryonic pancreas, liver, biliary tree and digestive tract.

Research Goal 1 Objectives

- Apply diverse model systems to investigate aspects of gut development that are best approached through biochemical, genetic and developmental studies in *Drosophila*, chicken and zebrafish.

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Research Goal 1
Objectives (continued)

- Develop tools that permit accurately targeted genetic studies in the gut of various animal models, particularly a stable repertoire of transgenic animal that faithfully express Cre recombinase, green fluorescence protein or b-galactosidase reporter genes, or toxigenes, ideally in inducible forms.

Research Goal 2

Exploit the advanced understanding of Wnt-APC-ß-catenin signaling in human colorectal cancer to develop new and effective treatment strategies.

Research Goal 2 Objectives

- Identify small molecules that interfere with distal steps in the Wnt signaling pathway and can therefore be used to treat colorectal cancer rationally.

- Identify other signals that impinge on ß-catenin stability and activity in colorectal epithelial cells and might serve as alternative targets for pharmacologic therapy.

Research Goal 3

Delineate specific signaling pathways, transcriptional regulation, and interactions that mediate critical patterning events in gut endoderm that generate and maintain its distinctive major derivatives (gastrointestinal tract, liver, and pancreas).

Research Goal 3 Objectives

- Delineate the relative contributions of specific signaling pathways and transcriptional regulators in gut development and learn how the intersection between extraneous and cell-intrinsic signals drives development.

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Research Goal 3
Objectives (continued)

- Distinguish between factors whose functions are restricted to the developmental period from those that continue to influence critical activities in the adult organs.

Research Goal 4

Translate advances from laboratory research in gut development to identify disease mechanisms and therapeutic targets for diverse gastrointestinal disorders (congenital disorders, regenerative medicine, and cancer).

Research Goal 4 Objectives

- Recognize the specific molecular defects associated with particular congenital malformations and with tissue metaplasia and cancer, especially Barrett's esophagus, gastric intestinal metaplasia, intestine-type gastric cancer, pancreatic in situ neoplasia and adenocarcinoma, and non-infectious hepatic disorders.

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Research Goal 4
Objectives (continued)

- Integrate molecular databases (gene expression, chromatin-immunoprecipitation, cis-element analyses) with functional studies (siRNA, genetically engineered animal models) to identify new pathways and to better appreciate underlying regulatory circuits.

Research Goal 5

Define the physiologic basis for intestinal growth and adaptation.

Research Goal 5 Objectives

- Determine downstream mediators of growth factor signaling that affect enterocyte proliferation and apoptosis, including the neural pathways that regulate hormone action.

- Understand cross-talk and synergism among intestinotrophic peptides, growth factors, nutrients and other growth-promoting molecules using animal models.

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Research Goal 5
Objectives (continued)

- Characterize the molecular basis of stromal-epithelial interactions in gut injury and repair to identify potential therapeutic targets, using transgenic models, microarrays and proteomics.
- Demonstrate the efficacy of intestinotrophic mediators in clinical trials, including short bowel syndrome, inflammatory bowel disease, intestinal damage induced by cancer chemotherapy and ischemic injury.

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Research Goal 5
Objectives (continued)

- Develop novel methods of tissue engineering utilizing knowledge of the stem cell and its niche to create functional neomucosa.

Research Goal 6

Define the physiologic basis for obesity and satiety.

Research Goal 6 Objectives

- Integrate physiology with peptidomic/ proteomic/metabolomic and other technologies to identify adipokines that influence gut function, and determine how signals originating from the gut affect adipose tissue biology and metabolism.

- Understand the interactions between adipokines and the gut-brain axis.

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Research Goal 6
Objectives (continued)

- Understand the mechanisms by which bariatric surgery leads to changes in body mass.

- Develop therapeutic interventions to mimic the effects of bariatric surgery on body mass.

- Develop effective, peripherally active substances for control of food intake and body weight using gut hormone-based therapies to target appetite circuits.

Research Goal 6
Objectives (continued)

- Develop new tools to measure activity, nutrient intake, and energy balance.

- Find genetic risk alleles and discover new critical pathways.

Research Goal 7

Define the physiology of neuroimmune pathways involved in inflammation.

Research Goal 7 Objectives

- Develop multidisciplinary teams to address mechanisms responsible for neuroimmune protective and injurious states, including expertise in neuroanatomy/neurophysiology, immunology/ inflammation, trauma, nutrition, and gastroenterology.

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Research Goal 7 Objectives (continued)

- Understand the cause and effect relationships between inflammation and altered neural function and the functional implications of inflammation-induced changes in neural signaling.

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Research Goal 7
Objectives (continued)

- Understand the role of nutrition in animal models, including lipid-based diets, in neurally-mediated anti-inflammatory pathways.

- Use animal models of GI inflammatory conditions to manipulate neural signaling through pharmacological, electrical or nutritional interventions; identify mechanisms of response and effects on morbidity/mortality.

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Research Goal 7
Objectives (continued)

- Develop therapeutics (drugs or devices) and clinical trials based on neuroimmune pathways targeted to GI disease (e.g., IBD) and pathologies that have GI effects (e.g., shock, I/R injury).

Research Goal 8

Develop a comprehensive profile of intestinal genes that regulate mammalian absorptive functions.

Research Goal 8 Objectives

- Extend studies of candidate genes to examining selected absorptive and metabolic pathways (e.g., cholesterol, bile acid, micronutrients) from human populations using humanized knock-ins of informative polymorphisms.

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Research Goal 8
Objectives (continued)

- Develop targeted approaches to obesity, hyperlipidemia, and diabetes through testing candidate small molecule inhibitors of gene function using mouse and other models.

- Integrate advances in developmental biology to understand regional differentiation of intestinal absorptive function (e.g., ileal bile acid transporter, duodenal iron absorption) and possible plasticity.

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Research Goal 8
Objectives (continued)

- Develop selective siRNA and other tractable knockdown methodologies for widespread use in digestive/absorptive pathway interrogation.

- Understand the dialog between host and luminal bacteria and the signaling pathways involved.

Research Goal 9

Transition from basic mouse and other organismal models into testable pathways that target human obesity and other disorders of nutrient absorption and metabolism.

Alternate Research Goal 9

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

Research Goal 9 Objectives

- Design targeted therapeutics based on informative pathways that predict development of obesity, hyperlipidemia, and diabetes.

- Identify serum and tissue biomarkers that predict alterations in pathways identified above.

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Research Goal 9
Objectives (continued)

- Recognize the specific molecular defects associated with nutrient malabsorption (including obesity) and defective or inappropriately increased intestinal nutrient delivery.

- Define mechanisms by which metabolic pathways interface with immune function.

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Research Goal 9
Objectives (continued)

- Conduct trials of selected pre- and probiotics genetically selected to optimize luminal microbiome composition.

Research Goal 10

Define pathways mediating regulation of barrier function versus (and) transport function.

Research Goal 10 Objectives

- Examine the structure and function of proteins composing tight junctions, adherens junctions, and other elements mediating the epithelial barrier.

- Identify membrane transport proteins and intracellular chaperones of micronutrient and metal ion absorption (e.g. iron, calcium, magnesium).

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Research Goal 10 Objectives

- Expand use of non-mammalian models to studies of gut absorptive and secretory function (e.g. zebrafish, *C. elegans*, *Drosophila*).

Research Goal 11

Define molecular pathways leading to differentiated absorptive and secretory cell types.

Research Goal 11 Objectives

- Integrate information on the role of cellular and protein diversity in creating efficient absorptive and secretory function in healthy human and mouse tissues.

- Understand epithelial development and remodeling in response to injury, especially related to signals and pathways creating a balanced population of absorptive and secretory cells.

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Research Goal 11
Objectives (continued)

- Apply and develop mouse models that allow fine genetic mapping of qualitative trait loci related to complex traits and multi-factorial genetic disorders of absorption and secretion.

- Translate (Define) what the diversity of epithelial cell absorptive and secretory functions means at a proteomics level.

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Research Goal 11 Objectives (continued)

- Develop a proteome fingerprint of cell types important to gut absorptive and secretory functions (in mouse and man, with some pilot testing in non-mammalian models).

Research Goal 12

Develop means to measure and manipulate epithelial function.

Research Goal 12 Objectives

- Develop advanced mutant mouse models (tissue specific, knock-in, inducible mutations, humanized models, superior gene transfer methods for GI) to study human proteins that mediate or regulate nutrient and fluid absorption as well as secretion.

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Research Goal 12
Objectives (continued)

- Understand the molecular and functional adaptation of individual epithelial cells of the intestine to challenge (surgery, inflammatory, diabetes, obesity, or experimental manipulation).

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Research Goal 12
Objectives (continued)

- Develop conceptual basis, and technical approaches, for direct translation between human and animal studies of barrier, absorptive, and secretory processes in living tissues (e.g., imaging, molecular diagnostics and therapeutics).

- Foster interdisciplinary teams among clinical research, basic biomedical research, engineering, and computational fields.

Research Goal 13

Develop research tools to investigate the structure and functional organization of the ENS.

Research Goal 13 Objectives

- Investigate molecular and electrophysiological characteristics of various ENS cellular components as they may be targets for new developments to treat motility disorders.

- Develop tools to visualize the state of activity of relevant cells in live tissues, organs and systems.

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Research Goal 13 Objectives (continued)

- Characterize alterations in gut-based 5HT signaling system in IBS and motility disorders including genetic polymorphisms affecting receptors, transporters, and enzymes for serotonin pathways.

- Identify molecules and pathways that promote proliferation and differentiation of enteric neurons and/or molecules responsible for directing enteric axons to their targets.

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Research Goal 13 Objectives (continued)

- Define the molecular basis for chemo- and mechano-receptors in the gut to sense ingested nutrient environment and gain better understanding about interactions between nutrient and microbe sensing mechanisms in the gut.

Research Goal 14

Integrate cellular events in ENS with whole system physiology and translate findings to pathophysiological conditions.

Research Goal 14 Objectives

- Identify the distinct neural circuits involved in mediating different motility patterns, define the principal receptors, neurotransmitters and synaptic connections for each circuit, identify the “switch” responsible for changing one motility pattern to another and examine how mechanical stimulation, metabolic stress and inflammation can alter these circuits.

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Research Goal 14 Objectives (continued)

- Identify distinct brain circuits responsible for various gut functions and pain perception and characterize the signaling systems and receptors within these neural circuits using PET ligand imaging in rodents and humans with IBS and functional dyspepsia.

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Research Goal 14
Objectives (continued)

- Develop contemporary techniques for probing genetic and proteomic changes that occur with age. Establish the mechanism that maintains the integrity of the ENS and its capacity to respond to altered function or “plasticity” in adulthood and old age.

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Research Goal 14
Objectives (continued)

- Investigate the cellular and molecular mechanisms of neural and endocrine bi-directional communication between the gut and CNS for regulation of weight and metabolic function.

- Develop suitable animal models to mimic diseases of the ENS.

Research Goal 15

Transition from basic physiology and pathophysiology in cell and organ systems to human disorders associated with the ENS.

Alternate Research Goal 15

Elucidate the physiological and pathophysiological roles of ENS in digestive health and disease in humans.

Research Goal 15 Objectives

- Determine specific gene profiles that occur in tissues that suffer interstitial cells of Cajal or neuron loss or in tissues in the process of losing these elements and develop a molecular test to detect these pathological changes.

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Research Goal 15 Objectives (continued)

- Develop neural imaging techniques to correlate individual circuits identified with symptom production in IBS patients and establish correlation with distinct genotypes that include genome-wide search for polymorphism and haplotypes.

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Research Goal 15
Objectives (continued)

- Develop neuron replacement therapy to guide the growth of enteric axons to their targets as a therapy for neural degenerative disease of the ENS.

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Research Goal 15 Objectives (continued)

- Characterize the molecular, cellular and behavior mechanisms that link changes of stored body fat to adaptive adjustments of feeding behaviors by defining the diverse blood-borne and affective neural signals that transmit information regarding nutrient status and energy stores to the brain where it is integrated with cognitive, visual, olfactory and taste cues.

Research Goal 16

Determine the biologic activities of the microbiota in healthy humans.

Research Goal 16 Objectives

- Undertake a metagenomic analysis of the microbiota of healthy people and develop microarrays of these data to determine the extent of person-to-person or diet-related variation.

- Determine whether members of the major bacterial populations can transfer DNA to mammalian cells and test this hypothesis with in vitro and in vivo models.

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Research Goal 16
Objectives (continued)

- Develop a “humanized” mouse model of the microbiota in which germfree mice are colonized with the human microbiome.

- Obtain genome sequences of the gram positive anaerobic bacteria that account for over two-thirds of the colonic microbiota, but about which virtually nothing is known, for use in interpreting the metagenomic data and guiding biochemical studies of the activities of these bacteria.

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Research Goal 16
Objectives (continued)

- Take a census of the methanogenic archaea and sulfate reducing bacteria found in the colons of healthy people.

- Determine whether bacterial enzymes, toxins or hormone-like compounds affect intestinal epithelial and non-epithelial cells.

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Research Goal 16 Objectives (continued)

- Examine genome sequences from colonic bacteria to identify possible gene transfer events using advanced computational methods for detecting such events.

Research Goal 17

Define the role of the intestinal microflora in mucosal immune homeostasis and determine the links between the microbiota and disease.

Research Goal 17 Objectives

- Define the nature of the microbial microflora and use this information to understand why commensal organisms generally lead to protective and anti-inflammatory responses in normal individuals whereas pathogens lead to inflammation.

- Develop approaches to manipulating the commensal microflora subpopulations so they prevent or reverse infection and inflammation.

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Research Goal 17 Objectives (continued)

- Design probiotics and prebiotics for maintenance or restoration of a healthy microbiota.

- Determine whether the composition of the microbiota or microbial gene expression has a role in such conditions as inflammatory bowel disease, colon cancer or obesity.

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Research Goal 17
Objectives (continued)

- Determine the mechanism by which the normal intestinal microbiota provides resistance against infectious pathogen invasions.

- Define the properties of the microbiota that is associated with the maintenance and reparation of the epithelial barrier.

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Research Goal 17 Objectives (continued)

- Determine whether bacterial toxins or hormone-like compounds are involved in such diseases.

Research Goal 18

Determine the role of epithelial cells in mucosal host defense and inflammation.

Research Goal 18 Objectives

- Identify factors that regulate the expression of innate immune receptors (Toll-Like Receptors; TLR) in epithelial cells and the effect of stimulation of these receptors on epithelial barrier function, chemokine and cyokine production and antimicrobial peptide production.

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Research Goal 18
Objectives (continued)

- Elucidate the factors produced by epithelial cells including TSLP, IL-10 and TGFb that affect lamina propria DC function and/or T cell differentiation.

- Generate mouse models expressing epithelial cell-specific deletion of key genes involved in epithelial mucosal immune function and barrier function to define the function of these genes in epithelial cell roles in immune function.

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Research Goal 18 Objectives (continued)

- Characterize embryonic and adult stem cell differentiation into epithelial cells focusing on the attainment of properties that relate to epithelial immune function.

Research Goal 19

Understand the role of antigen-presenting cells in the mucosal immune system.

Research Goal 19 Objectives

- Define the factors that influence DC maturation and function that mediate T cell effector and regulatory functions within the mucosal environment.

- Elucidate the function of DC TLR signaling with respect to positive and negative DC responses.

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Research Goal 19 Objectives (continued)

- Generate mouse models characterized by DC dysfunction to study the role of DCs in mucosal host defense and inflammation.

Research Goal 20

Understand trafficking of mucosal cells to various parts of the mucosal immune system.

Research Goal 20 Objectives

- Elucidate the factors that control chemokine-chemokine receptor interactions or other cell-cell interactions that contribute to mucosal traffic patterns.

- Generate mice that lack key components of the gut homing apparatus and thus allow in-depth knowledge of gut homing mechanisms.

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Research Goal 20 Objectives (continued)

- Develop a systems approach to the study of lymphocyte and DC homing that integrates the many factors that affect this process.

Research Goal 21

Understand mucosal unresponsiveness (oral tolerance) and mucosal regulatory T cell development.

Research Goal 21 Objectives

- Explore the nature of the immunological milieu of the mucosa enhancing or retarding the development of regulatory T cells such as the synthesis of TGF-β, retinoic acid and IL-27.

- Elucidate the biology of regulatory T cells with relation to the function of foxp3 and other intra-cellular factors that control regulatory cell function.

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Research Goal 21 Objectives (continued)

- Develop gene therapy approaches to the enhancement of regulatory T cell function for the treatment of chronic inflammatory states.

Research Goal 22

Understand the pathogenesis of IBD.

Research Goal 22 Objectives

- Elucidate the function of major disease susceptibility genes such as CARD15 and IL-23R in the pathogenesis of experimental colitis and patients with Crohn’s disease.

- Determine the role of IL-12 and IL-23 in Crohn’s disease and IL-13 in ulcerative colitis.

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Research Goal 22
Objectives (continued)

- Evaluate the therapeutic efficacy of novel agents that affect the final common pathways of mucosal inflammation in inflammatory bowel disease.

- Establish the treatment of patients with Crohn's disease (or ulcerative colitis) with identified defects of the immune system with hematopoietic stem cells repleted with normal genes.

Research Goal 23

Develop mucosal vaccination strategies.

Research Goal 23 Objectives

- Elucidate epithelial or stromal cell factors and cytokines involved in elaboration of IgA B cells.

- Understand IgG responses in the mucosal immune system and the neonatal Fc transport system.

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Research Goal 23 Objectives (continued)

- Develop new adjuvants that target particular aspects of the mucosal immune response.

- Develop effective vaccines for the prevention of major epidemic viral infections including that due to HIV.

Major Challenges/Steps To Achieve Goals

- Animal models
- Germ-free animal facilities
- Intestinal cell lines
- Methods to characterize the microbiome
- Bioinformatics
- Translation of genetic findings into understanding of human disease

Major Challenges/Steps To Achieve Goals

Animal Models

- Targeted genetic studies for specific tissues and cell types
- Promoters/minigenes that drive tissue- or segment-specific gene expression
- Identification, characterization, and distribution of suitable mouse lines in a defined background, including conditional gain- and loss-of-function alleles
- Centralized animal repository of useful models
- Novel animal models of specific gastrointestinal, liver, and pancreatic disorders
- Equipment and chemical probes for parallel live tissue analyses in human endoscopy and mouse intestinal tract
- Interdisciplinary research between gastrointestinal researchers, chemists and biomedical engineers

Major Challenges/Steps To Achieve Goals

Germ-Free Animal Facilities

- Centralized germ-free facilities and/or microflora-defined mice for study under various conditions.

Intestinal Cell Lines

- Primary cells derived from humans and animal models with defined attributes for *in vitro* studies
- Cell lines related to the intestinal epithelial (and mesenchymal) stem cells and native intestinal epithelial cell and DC lines
- Innovative techniques for the long-term maintenance of cells in culture
- Central facilities to acquire and maintain these cells for distribution

Major Challenges/Steps To Achieve Goals

Methods To Characterize the Microbiome

- Tools to investigate and understand the composition of the normal intestinal microbiota
- Collaboration between experts in microbial physiology and bioinformatics
- Microarray technologies to allow direct sampling of community DNA and RNA
- Advanced bioinformatics approaches and computational approaches such as codon usage algorithms
- A curated database for 16S rDNA and metagenomic sequence data
- Microarrays that contain rDNA sequences from major human colonic species for rapid characterization of the species composition of the colonic population
- Microarrays that represent genes on mobile elements found in the major groups of colonic bacteria
- Noninvasive means of quantitating the amount of energy derived from colonic fermentation, the rate of intestinal cell turnover, and activity of the enteric nervous system

Major Challenges/Steps To Achieve Goals

Bioinformatics

- Novel genomics and proteomics approaches and bioinformatics databases.
- Computational biologists and bioinformatics infrastructure
- Interdisciplinary research between gastrointestinal researchers (including immunologists and bacteriologists) and computational biologists
- Mammalian models that provide systems biology resolution
- Centers for cell-type specific protein profiling and disease state profiling
- Proteome fingerprints of cell types in development, physiology, and immunology in mouse and humans
- National data and tissue banks for the application of modern genomic and proteomic technologies.

Major Challenges/Steps To Achieve Goals

Translation of Genetic Findings into Understanding of Human Disease

- Dialog between academia-industry to expand our understanding of digestive diseases in human populations
- Regional and national databases with appropriate serum, DNA, and tissue biobanking as crucial resources for the entire research community