Inflammatory Bowel Diseases

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Research Goal 1

Establish objective basis for clinical diagnosis, detailed phenotype, and disease activity.

Research Goal 1 Objectives

- Develop a comprehensive genotypic profile.
- Define informative immunophenotypic profiles.
- Develop methodology and value for a microbiomic profile.

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Research Goal 1
Objectives (continued)

- Develop technology for effective anatomic and functional imaging of disease location and activity.

- Establish useful correlative and predictive biomarkers.

Research Goal 2

Develop an individualized approach to risk evaluation and management based on genetic susceptibility.

Research Goal 2 Objectives

- Complete identification of risk susceptibility genes among diverse patient populations.
- Determine the functional role of IBD associated gene variants in pathophysiologic pathways leading to IBD.
- Determine impact of environmental factors on disease associated genetic variants.

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Research Goal 2
Objectives (continued)

- Define genetic subset/phenotype – genotype correlations.
- Identify and assess relevant pharmacogenetic variations.
- Correlate genotype (disease susceptibility and pharmacogenetic) with response to therapy and incorporate genotypes into clinical trials.

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Research Goal 2
Objectives (continued)

- Use genotypic variations to define disease risk and to predict natural history and response to therapy.

Research Goal 3

Modulate the intestinal microbiome (IM) to prevent or control IBD.

Research Goal 3 Objectives

- Achieve a comprehensive molecular and functional delineation of the IM in all relevant niches across different individuals/ populations.

- Understand the factors that regulate the composition and functional characteristics of the IM including host factors (environmental, genetic, and mucosal function).

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Research Goal 3
Objectives (continued)

- Characterize the IM associated with IBD by location and disease activity.
- Develop experimental tools for understanding IM complexity and clinical methods for characterization and monitoring of the IM in patients.
- Develop experimental *in vivo* systems for pre-clinical studies of IM therapeutic modulation.

Research Goal 4

Effectively modulate the mucosal immune system to prevent or ameliorate IBD.

Research Goal 4 Objectives

- Define all relevant immune cell populations by their functional characteristics and differentiation pathways.
- Define the factors regulating innate and adaptive immunity, both genetic and environmental.
- Delineate innate and adaptive immune interaction with the microbiome.

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Research Goal 4
Objectives (continued)

- Identify relevant inflammatory mediators in effecting IBD injury and symptomatic manifestations of IBD and mechanisms regulating inflammatory processes.

- Characterize alterations in innate and adaptive immune function in IBD (including regulatory cell populations) especially related to microbiome.

Research Goal 5

Sustain the health of the mucosal surface.

Research Goal 5 Objectives

- Understand the functional biology of the epithelial compartment and identify alterations in IBD.

- Identify and characterize the stem cell compartment and develop the capacity to modulate lineage specification and maturation.

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Research Goal 5
Objectives (continued)

- Understand the structural and functional elements of the mucosal barrier (including the role of luminal flora and nutrients) and alterations associated with IBD.

- Define the systems biology of the intestinal mucosa including interactions among epithelial and *lamina propria* cell populations as well as integration with enteric nervous, endocrine and vascular elements.

Research Goal 6

Promote regeneration and repair of injury in IBD.

Research Goal 6 Objectives

- Understand normal reparative processes and characterize their alteration in IBD.
- Define the impact of the microbiome on tissue repair.
- Develop strategies to modulate repair processes to restore functional capacity.

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Research Goal 6
Objectives (continued)

- Identify mechanisms to reverse or remodel fibrotic response.

- Identify interventions that improve care of patients with surgically modified gut.

Research Goal 7

Provide effective tools for clinical evaluation and intervention.

Research Goal 7 Objectives

- Develop and validate technologies to evaluate disease status including biomarkers and non-invasive as well as novel endoscopic imaging methods.

- Develop innovative endoscopic and more physiologic surgical interventions.

- Develop effective and non-toxic mechanism-based pharmacologic therapies including manipulation of the microbiome.

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Research Goal 7
Objectives (continued)

- Develop tools for more efficient clinical development of investigational agents, including surrogate markers of response.

- Identify tools to more effectively identify pre-malignant mucosa and interventions to reduce cancer risk.

Research Goal 8

Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents.

Research Goal 8 Objectives

- Develop interventions that promote normal social interactions and mental health in all patients.
- Define the mechanisms that produce growth delay.
- Identify approaches that enable normal growth and development.

Major Challenges/Steps To Achieve Goals

- Basic mechanisms of IBD
- Translational research
- Clinical research and discovery

Major Challenges/Steps To Achieve Goals

Basic Mechanisms of IBD

- National and international collaborations for sample acquisition, analysis of genetic loci across diverse populations, and research on well-characterized patients followed on a longitudinal basis to define genotype-phenotype correlation

- Rapid, quantitative, high-throughput techniques to define individual members of complex microbial communities, robust bioinformatic tools, and metagenomic datasets with comprehensive data on provenance and host phenotype

- New computational tools, such as *in silico* techniques for modeling microbial populations and microbial-host interactions

- An intestinal microbiome project beginning with commissioning computational tools and pilot projects

- Techniques to isolate and sustain primary epithelial cell populations *in vitro* for research on these critical cells populations and their functional alteration in IBD.

Major Challenges/Steps To Achieve Goals

Translational Research

- Robust *in vitro* model systems (including primary cell and organ cultures) which recapitulate the complexity of intestinal mucosa and can be experimentally manipulated
- Better integration of basic and clinical research efforts for more effective translational progress
- Animal models with validated clinical relevance in which response to intervention is predictive of response in man
- Consortia of investigators across institutions to expedite research to understand the functional implications of gene variants associated with IBD

Major Challenges/Steps To Achieve Goals

Clinical Research and Discovery

- Objective and consistent criteria for diagnosis and substratification of patients
- Overcome barriers to therapeutic trials in pediatric populations
- Standards for clinical trials including end-points, incorporation of surrogate endpoints, phenotyping and DNA collection
- Strategies for enrolling patients in clinical trials
- Larger cadre of clinical investigators and clinical trial infrastructure to support an expanded national and international program of interventional clinical trials for IBD
- Greater public awareness and understanding of IBD through public educational programs
- Clinical summit of investigators, all stakeholding agencies, and industry