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Working Group: *#5*
Inflammatory Bowel Diseases

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Working Group Members

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OVERALL GOALS

- Identify individuals at risk for IBD and intervene to prevent onset or progression of disease

- Provide safe and definitive treatment for patients with clinically manifest IBD

GOAL I. – Establish objective basis for clinical diagnosis, detailed phenotype & disease activity

- Develop a comprehensive genotypic profile
- Define informative immunophenotypic profiles
- Develop methodology and value for a microbiomic profile
- Develop technology for effective anatomic and functional imaging of disease location and activity
- Establish useful correlative and predictive biomarkers

GOAL II. – Develop an individualized approach to risk evaluation & management based on genetic susceptibility

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

GOAL III– Modulate the intestinal microbiome (IM) to prevent or control IBD

- Achieve a comprehensive molecular & functional delineation of IM in all relevant niches across different individuals/populations
- Understand the factors that regulate the composition and functional characteristics of IM including host factors (environmental, genetic, & mucosal function)
- Characterize IM associated with IBD by location and disease activity
- Develop both experimental tools for understanding IM complexity & clinical methods for characterization & monitoring
- Develop experimental in vivo systems for pre-clinical studies of IM therapeutic modulation.

GOAL IV – Effectively modulate the mucosal immune system to prevent or ameliorate IBD

- Define all relevant immune cell populations by their functional characteristics and differentiation pathway
- Define the factors regulating innate and adaptive immunity - both genetic and environmental
- Delineate innate and adaptive immune interaction with microbiome
- Identify all relevant inflammatory mediators in effecting IBD injury and symptomatic manifestations of IBD and mechanisms regulating inflammatory processes
- Characterize all alterations in innate and adaptive immune function in IBD (including regulatory cell populations) especially related to microbiome

GOAL V– Sustain the health of the mucosal surface

- Achieve a comprehensive understanding of the functional biology of the epithelial compartment and identify alterations in IBD
- Identify and characterize the stem cell compartment and develop capacity it modulate lineage specification and maturation
- Understand the structural and functional elements of mucosal barrier (including the role of luminal flora and nutrients) and alterations associated with IBD
- Define the systems biology of the intestinal mucosa including interaction among epithelial and lamina propria cell populations as well as integration with enteric nervous, endocrine and vascular elements

GOAL VI – Promote regeneration and repair of injury in IBD

- Achieve a comprehensive understanding of normal reparative processes and characterize their alteration in IBD
- Define impact of the microbiome on tissue repair
- Develop strategies to modulate it to restore functional capacity
- Identify mechanisms to reverse or remodel fibrotic response
- Identify interventions that improve care of patients with surgically modified gut

GOAL VII – Provide effective tools for clinical evaluation and intervention

- Develop & 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
- Develop the tools for more efficient clinical development of investigational agents e.g. surrogate markers of response
- Identify tools to more effectively identify pre-malignant mucosa and interventions to reduce cancer risk

GOAL VIII– Ameliorate or prevent adverse effects of IBD on growth & development in children & adolescents

- 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 & development

Major Challenges/Steps To Achieve Goals

1. Need for standards in clinical trials including end-points, incorporation of surrogate endpoints, phenotyping & DNA collection

2. Need for standardization of techniques of sample acquisition

3. Need for rapid quantitative high throughput techniques to define individual members of complex microbial communities and robust bioinformatic tools

4. Need for metagenomic datasets with comprehensive data on provenance and host phenotype.

5. Magnitude of the datasets and need for new computational tools to effectively mine, including *in silico* techniques for modeling microbial populations & microbial-host populations

Major Challenges/Steps To Achieve Goals

6. Need for national and international scale in both genomic and clinical studies.

7. Need for public and governmental understanding; and need for appropriate educational strategies.

8. Need for clinically relevant studies in animal models and translational research to enable rapid progress from *in vitro* and animal model studies to patients.

9. Need for better integration of basic and clinical research efforts to ensure more effective translational progress

10. Need for definitive criteria for diagnosis and stratification

Major Challenges/Steps To Achieve Goals

11. Difficulty in patient recruitment and limited cadre of clinical investigators as well as limited clinical trial infrastructure.

12. Particular difficulty in enrolling pediatric patients & industry concern about risks of trials in pediatric population

13. Need for more robust *in vitro* (including primary cultures) and *in vivo* models with validated relevance to human disease

Some Initial Steps To Achieve Goals

- Form consortia of functional genomic, clinical & translational investigators
- Initiate an intestinal microbiome project beginning with commissioning computational tools & pilot projects
- Form a clinical summit convening investigators, all stakeholding agencies and industry
- Target methodologic development