

*Diseases of the Colon
and Rectum*

Chair: Joanne A. P. Wilson, MD

Vice Chair: Nancy J. Norton

Research Goal 1

Establish mechanisms of colon injury and repair with development of therapeutic interventions.

Research Goal 1

Objectives

- Identify the specific interactions (receptors/ligands) between enteric microbiota and Toll-like receptors (TLRs) that promote macrophage-dependent proliferation of progenitor cells and determine which mediators released by macrophages are required for epithelial cell proliferation.

Research Goal 1

Objectives (continued)

- Determine the bioavailability, safety, and efficacy of orally-administered trefoil factors (TFFs) and other epithelial cell growth factors in models of mucosal injury and inflammation.
- Develop strategies for mimicking the enteric antigen/Toll-like receptor interactions to promote gut healing.

Research Goal 1

Objectives (continued)

- Identify other gut-specific growth factors capable of promoting colonocyte restitution and repair.
- Develop TLR agonists that mimic the protective effect of enteric bacteria.

Research Goal 2

Understand colonic mucosal absorption in health and disease.

Research Goal 2

Objectives

- Survey known sodium, chloride, short chain fatty acid and ammonia transporter expression in human colon with comparison to murine models and evaluate segmental alterations in transporter expression on varied defined fiber and protein diets.

Research Goal 2

Objectives (continued)

- Understand the regulation of sodium absorptive and chloride secretory pathways during disease, and identify targets for potential therapy of diarrheal disorders and non-immunosuppressive approaches to enhance repair.

Research Goal 2

Objectives (continued)

- Screen pediatric and adult U.S. populations for altered transporter complex expression and/or gene mutations in congenital and acquired constipation and diarrheal disorders with the goal of developing individualized strategies for patients with chronic constipation or diarrhea.

Research Goal 3

Determine the role of gut microflora in health and disease states of the colon.

Research Goal 3

Objectives

- Establish tissue banks of mucosal biopsies to allow large-scale, chip-based comparison of adherent bacteria to the surface epithelium (biofilm) to bacteria in the normal flora in feces.
- Compare bacterial flora in obese and lean humans using molecular fingerprint assays and sequence analysis of cloned 16S ribosomal DNA.

Research Goal 3

Objectives (continued)

- Compare colonic microflora before and after antibiotics in patients with and without colonization by *C. difficile*, and use these data to develop a rational approach to reconstitute the microflora.
- Conduct randomized, double-blind, controlled trials to manipulate the colonic microflora in obesity as a possible adjunct therapy.

Research Goal 4

Establish the cause of diverticular disease and its complications with modulation of disease.

Research Goal 4

Objectives

- Identify risk factors for diverticular disease including genetics and life style and association with complications (specifically diverticulitis and bleeding).
- Determine whether treatment with non-absorbable antibiotics, mesalamine, probiotic agents, prebiotic agents or other agents reduces the risk of recurrent diverticulitis and is cost effective.

Research Goal 4

Objectives (continued)

- Determine indications for surgery and the optimal surgical approach to complicated diverticular disease and establish whether a one-stage surgical procedure reduces the rates of postoperative peritonitis and emergency re-operation without adversely affecting mortality as compared with a two-stage procedure.

Research Goal 4

Objectives (continued)

- Determine whether changes in lifestyle, especially diet, reduce the prevalence of diverticulosis and its complications (i.e., specifically, avoidance of specific dietary factors such as seeds and popcorn), and reduce the risk of diverticulitis.

Research Goal 5

Understand mechanisms and early diagnosis of colonic ischemia and angioectasia.

Research Goal 5

Objectives

- Devise a means of diagnosing colonic ischemia early (i.e., before infarction ensues) and differentiation from other disorders by developing biomarkers for this disease process.
- Determine the underlying, proximate cause of colonic ischemia, especially with regard to the behavior of colonic arteriolar and venular microvasculature and the relationship of the bowel vasculature to serotonergic agents.

Research Goal 6

Improve management of anorectal disorders.

Research Goal 6

Objectives

- Understand risk factors and preventive strategies for anal disorders including anal fistulas, hemorrhoids and fecal incontinence with appropriate modification: natural history and impact of obstetrical sphincter injury, medical and neurological conditions, and pelvic surgery and the role of surgical repair of sphincter defects.

Research Goal 6

Objectives (continued)

- Develop evidence-based treatment algorithms for prevention, diagnosis, and treatment of fecal incontinence and perianal fistulas (cryptoglandular and Crohn's) and for treatment of hemorrhoids.

Research Goal 6

Objectives (continued)

- Develop educational tools for providers and the public to raise awareness of the impact of fecal incontinence and treatment options, anal abscess, anal fistula and hemorrhoids with particular focus on accurate diagnosis, initial treatment and prevention.

Research Goal 7

Reduce the frequency and severity of radiation injury to the colon.

Research Goal 7

Objectives

- Develop evidence-based algorithms for prevention and treatment of radiation proctitis.

Research Goal 8

Determine causes of appendicitis and modulate the course of the disease.

Research Goal 8

Objectives

- Study the effect of dietary factors especially fiber content, prebiotics, probiotics, bowel function (constipation) on the incidence of appendicitis especially in children.
- Develop diagnostic tests, identify biomarkers
- Develop antibiotic Rx

Major Challenges/Steps To Achieve Goals

- Collaboration with industry
- Research resources
- Research tools for the microbiome
- Clinical research
- Animal models

Major Challenges/Steps To Achieve Goals

Collaboration With Industry

- Collaboration with protein chemists and the biotechnology and pharmaceutical industries to provide sufficient quantities of TFFs and other growth factors for testing in chronic preclinical studies and clinical intervention trials in human patients

Major Challenges/Steps To Achieve Goals

Research Resources

- Centralized resources for sharing of biological samples and patient data
- A comprehensive tissue bank to collect, store, and disseminate normal and diseased human colonic specimens defined with respect to anatomic segment and clinical data
- Database capabilities and clinical consortia for randomized clinical trials with standardized endpoints
- A systems-based approach to the study of colonic transport using defined cultured cell and transgenic mouse models and comprehensive expertise in cell biology, structural biology, transepithelial transport, nutrition, imaging, and computational modeling

Major Challenges/Steps To Achieve Goals

Research Tools for the Microbiome

- Use of mucosal biopsies from colonoscopy rather than the traditional reliance on stool specimens
- New technology development for measurement of the metabolome of the colonic flora
- Metabolomic techniques to study the human or animal microflora *in vivo* using non-invasive methods such as breath analysis
- Robust databases and software tools to analyze large amounts of data from multiple laboratories

Major Challenges/Steps To Achieve Goals

Clinical Research

- Clinical research studies comparing different populations to define the risk factors for diverticular disease and to distinguish symptomatic diverticular disease from irritable bowel syndrome
- Methods to control differences in diet among participants in trials for diverticular disease
- Central resources for diseases that are difficult to study in a single center with limited access to patients, such as radiation colitis
- Clear criteria for distinguishing acute and chronic fissures on examination and better means to diagnose the etiology of symptoms
- Methods to overcome the reluctance of patients to discuss their symptoms and the reluctance of providers to inquire about these symptoms
- Innovative approaches to research collaboration on appendicitis.
- New methods to obtain accurate dietary histories in patients, including children

Major Challenges/Steps To Achieve Goals

Animal Models

- Novel animal models for conditions such as diverticular disease and radiation colitis