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Working Group: #9 Colon and Rectum

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Chair

Working Group Members

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Overarching Goals

I. Establish mechanisms of colon injury & repair with development of therapeutic interventions

II. Develop understanding of colonic mucosal absorption in health and disease

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

IV. Establish cause of diverticular disease & its complications with modulation of disease

V. Promote understanding of mechanisms and early diagnosis of colonic ischemia and angioectasia

VI. Improve management of anorectal disorders

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

VIII. Determine causes of appendicitis & modulate course of disease

Goal I: Establish mechanisms of colon injury & repair with development of therapeutic interventions - ST

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

2. Determine the major signaling pathways involved in *trefoil factor 3 (*TFF3)/growth-mediated epithelial cell migration and restitution (including the specific receptors) and determine whether TFF3 peptide protects established colonic injury or prevents the induction of epithelial cell destruction.

Yellow font = priority objective

Goal I: Establish mechanisms of colon injury & repair with development of therapeutic interventions - IT

1. Identify the molecular basis of the cell-specific expression of TFF3 and other growth factors
2. Determine whether or not one or more of the different TFFs/growth factors can attenuate established colitis in a T- or B-cell dependent model of chronic colitis.
3. Determine whether the enteric bacteria /macrophage /TLR axis can be exploited to treat chronic colitis in T-cell dependent models of chronic disease.
4. Define the molecular determinants used by the monocytes/macrophages to migrate into the colon to help in colonic mucosal repair.

Goal I: Establish mechanisms of colon injury & repair with development of therapeutic interventions - LT

1. 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.

2. Develop strategies for mimicking the enteric antigen/Toll-like receptor interactions to promote gut healing.

Goal II: Develop understanding of colonic mucosal absorption in health and disease - ST

1. Initiate comprehensive survey of known Na+, Cl-, SCFA, and ammonia transporter expression in human colon with comparison to murine models with evaluation of segmental alterations in transporter expression on varied defined fiber and protein diets.

2. Establish complementary cultured colonocyte and native tissue preparations that allow correlation of transport with levels of expression of Na+ transporters and key scaffolding proteins to eludicate the basis for redundancy of transporter isoform expression and the functional activity of transporters within specific membrane domains.

Goal II: Develop understanding of colonic mucosal absorption in health and disease - IT

1. Develop a comprehensive understanding of the regulation of Na+ absorptive and Cl- secretory pathways during disease, and identify targets for potential therapy of diarrheal disorders and non-immunosuppressive approaches to enhance repair.

   - Examine injury and repair responses of transporter knockout mice in standard models of ischemic and inflammatory colitis.
   - Develop functional imaging techniques that define dynamics of transporter surface expression and local pH microdomains *in vivo*.

Goal II: Develop understanding of colonic mucosal absorption in health and disease - LT

1. 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 goal of development individualized strategy for patients with chronic constipation or diarrhea.
2. Develop and test small molecule inhibitors of Cl- transport and agents that enhance Na+ absorptive pathways in the diarrheal and reparative response to ischemia and inflammation-associated colonic disease
3. Develop comprehensive understanding of the effect of diet-derived luminal fermentation products on colonic absorption.

Goal III: Determine the role of gut microflora in health and disease states of colon - ST

1. Organize a multidisciplinary NIH topic conference with researchers from microbiology, GI, pediatrics, and related fields to develop strategies to elucidate the intestinal microflora in health and disease.

2. Establish and validate functional parameters (biomarkers) of the microflora such as redox potential, volatile fatty acid profile, or other microbial metabolites that can serve as surrogate biomarkers for the entire human flora irrespective of bacterial speciation.

3. Establish rapid throughput, chip-based technology to compare major components of the microflora in health and disease.

Goal III: Determine the role of gut microflora in health and disease states of colon - IT

1. 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.

2. Compare bacterial flora in obese and lean humans using molecular fingerprint assays and sequence analysis of cloned 16 S ribosomal DNA.

3. Compare colonic microflora before and after antibiotics in patients with and without colonization by *C. difficile*, and from these data develop a rational approach to reconstitute the microflora.

Goal III: Determine the role of gut microflora in health and disease states of colon - LT

1. Organize randomized, double-blind, controlled trials (RCTs) to manipulate the colonic microflora in obesity as a possible adjunct therapy.

2. Organize RCTs of bacteriotherapy to prevent *C. difficile* colonization and to treat chronic and recurrent infection.

Goal IV: Establish cause of diverticular disease & its complications with modulation of disease - ST

1. Identify risk factors for DD including genetics and life style and association with complications (specifically diverticulitis and bleeding).

2. Study the factors involved in the pathogenesis of DD, including altered colonic wall expression of matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMP), reduced numbers of colonic interstitial cells of Cajal and glial cells, increased levels of pro-inflammatory mediators, and heightened visceral sensitivity.

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Goal IV: Establish cause of diverticular disease & its complications with modulation of disease - IT

1. 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.

2. 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 reoperation without adversely affecting mortality as compared with a two-stage procedure.

Goal IV: Establish cause of diverticular disease & its complications with modulation of disease - LT

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

2. Determine why some people with diverticulosis develop symptoms and others do not.

3. Determine whether reversal of altered colonic wall matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMP) expression and other pathophysiologic abnormalities can lead to a reduced risk of complications in patients with diverticulosis.

Goal V: Promote understanding of mechanisms and early diagnosis of colonic ischemia and angioectasia

1. Devise a means of diagnosing CI early (i.e., before infarction ensues) and differentiation from other disorders by developing biomarkers for this disease process.
2. 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.
3. Understand why colonic ischemia is associated with IBS.
4. Determine why angioectasia develop and the potential mechanisms for altered vasculature and blood flow.

Goal VI: Improve management of anorectal disorders

1. Understand the epidemiology, cost, & QOL impact of fecal incontinence, anal fistulas in patients with and without inflammatory bowel disease, and hemorrhoids.
2. Develop educational tools for providers and the public to raise awareness of impact of fecal incontinence and treatment options, anal abscess, anal fistula and hemorrhoids with particular focus on accurate diagnosis and initial treatment.
3. Understand risk factors and preventive strategies for fecal incontinence with appropriate modification: natural history & impact of obstetrical sphincter injury, medical and neurological conditions, and pelvic surgery and the role of surgical repair of sphincter defects.

Goal VI: Improve management of anorectal disorders

4. Initiate studies comparing outcome and cost of treatment alternatives for mild fecal incontinence and incontinence associated with sphincter defect and intact sphincter muscles, neurological injury, childhood and aging

5. Develop a better understanding of risk factors and mechanisms of development of perianal fistulas in patients with and without IBD.

6. Initiate long-term collaborative studies of effectiveness (outcome and cost) of medical vs. surgical therapy for anal fistulas patients with and without Crohn's disease.

Goal VI: Improve management of anorectal disorders

7. Improve understanding of the risk factors for symptomatic hemorrhoids including during pregnancy with long term studies of effectiveness (outcome and cost) of medical management, office procedures, stapled hemorrhoidectomy, traditional hemorrhoidectomy and pain control following these procedures.
8. 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.
9. Develop effective public and professional educational material about prevention and treatment of fecal incontinence, anal fistulas and hemorrhoids.
10. Identify effective preventive strategies for symptomatic hemorrhoids particularly in high-risk conditions such as pregnancy, IBD.

Goal VII: Reduce the radiation injury to the colon

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

2. Determine prognostic factors (genetic, co-morbidities) important in the development of chronic radiation injury.

3. Determine efficacy of agents in prevention of radiation injury via multi-center trials with collaboration between gastroenterology, oncology, and radiation oncology.

Goal VIII: Determine causes of appendicitis & modulate course of disease

1. Study the effect of dietary factors especially fiber content, prebiotics, probiotics, bowel function (constipation) on the incidence of appendicitis especially in children.

2. Evaluate the role of immune-mediated response in the histopathology and clinical course of appendicitis.

3. Identify high risk patients from immune standpoint with modifications of responses.

4. Study the effect of dietary modification, prebiotics and probiotics on gastrointestinal microflora and the incidence of appendicitis.

Major Challenges/Steps To Achieve Research Goals

Colonic Mucosal Injury and Repair

1. Identify other gut-specific growth factors capable of promoting colonocyte restitution and repair.
2. Initiate collaborations with protein chemists and the biotech/pharmaceutical communities to produce sufficient quantities of the different TFFs/growth factors to test in chronic preclinical studies as well as human studies.
3. Develop TLR agonists that mimic the protective effect of enteric bacteria.

Major Challenges/Steps To Achieve Research Goals

Colonic Mucosal Absorption and Colon Vasculature

4. Comprehensive tissue bank of normal and diseased human colonic specimens defined with respect to anatomic segment and clinical data.

5. Development of database capabilities and clinical consortia for randomized clinical trials with standardized endpoints.

6. Development of systems-based approach to study of colonic transport using limited number of 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 Research Goals

Role of Gut Microflora (Challenges)

7. The microflora adherent to the mucosa, the so-called biofilm, more relevant to health and disease than the microflora in feces - necessitates use of mucosal biopsies from colonoscopy vs. the traditional reliance on stool specimens.

8. Sensitive molecular techniques such as PCR or chip assays do not reliably distinguish between dead or non-viable organisms, or organisms that are ingested and simply passing through the gut vs. those that are viable and capable of growth.

Major Challenges/Steps To Achieve Research Goals

Role of Gut Microflora (Challenges)

9. The total metabolic activity ("metabolome") of the microflora is summation of thousands of species and, in theory, could provide a less complex, quantitative approach to the microflora. Lack sophisticated technology to assess metabolome of the colonic flora *in vivo* except for measurement of colonic gases and metabolites such as SCFA.
10. NIH in collaboration with industry needs to support large-scale approach to the human colonic biome, as with Human Genome Project to provide a basic catalogue of constituents of stable microbial flora in all humans and a description of variable flora that differ among humans. Allow development of sensitive chip assays to apply to human-based studies of IBD, antibiotic therapy, etc. Update: see Road Map.

Major Challenges/Steps To Achieve Research Goals

Role of Gut Microflora

11. Development of metabolomic techniques to study the human or animal microflora *in vivo* using non-invasive techniques such as breath tests as with current breath tests. Use of radioactive precursors of bacterial end-products like ammonia or hydrogen would allow assays for microbial metabolism in health and disease.

12. Given the expected complexity and diversity of the microflora, development of sophisticated databases will be required, as well as sophisticated software to retrieve and analyze the information for individual laboratories, as is currently available for the human genome.

Major Challenges/Steps To Achieve Research Goals

Diverticular Disease

13. Diverticulosis is common in Western countries but infrequent in underdeveloped countries, and studies comparing different populations will be needed to understand the risk factors.

14. Clearly defining symptomatic diverticular disease and distinguishing symptomatic diverticular disease from irritable bowel syndrome is difficult but necessary.

15. In long-term treatment trials, differences in diet among participants will need to be controlled.

16. Prevention trials will require long-term (multi-year) follow-up to detect significant differences in outcomes.

17. There is no animal model for human diverticular disease.

Major Challenges/Steps To Achieve Research Goals

Anorectal Disorders

18. Frequency of the disorders and interface of patients with multiple providers makes development of effective system of data collection difficult.
19. Anal disorders frequently occur concomitantly making evaluation of treatment outcomes complicated. No clear criteria for distinguishing acute and chronic fissures on examination.
20. Frequent misdiagnosis of etiology of symptoms.
21. Particularly for incontinence, reluctance of patients to discuss their symptoms and reluctance of providers to inquire about these symptoms.

Major Challenges/Steps To Achieve Research Goals

Radiation Colitis

22. Elderly population with multiple medical problems limiting clinical studies.

23. Few viable animal models.

Appendicitis

24. Pediatric population with acute self-limited disorder would be difficult to develop a network in which to study.
25. Dietary histories difficult to obtain especially in children and more difficult to control.