Project Information

1I01CX001353-01A1

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DESCRIPTION DETAILS RESULTS HISTORY SUBPROJECTS SIMILAR PROJECTS NEARBY PROJECTS BETA LINKS NEWS AND MORE

Project Number: 1I01CX001353-01A1
Title: THE ROLE OF AXIN2+ STEM CELLS IN ULCER HEALING DURING COLITIS.

Contact PI / Project Leader: BARRETT, TERRENCE A.
Awardee Organization: VA MEDICAL CENTER - LEXINGTON, KY

Abstract Text:

DESCRIPTION (provided by applicant): A major cause of colon removal surgery in veterans with inflammatory bowel disease (IBD) is a failure of medically-induced mucosal healing. Mucosal healing is a reliable clinical marker of recovery after IBD therapy as it is associated with durable clinical remission. Despite the importance of mucosal repair, we continue to have a poor understanding of many of the cellular and molecular elements that mediate ulcer healing. The current proposal focuses on the role of colonic (epithelial) stem cells (CSC) in ulcer healing during colitis. Wnt/β-catenin signaling in stem cells promotes cell proliferation as well as self-renewal, both essential functions needed for ulcer healing and restitution of the mucosal barrier. A central tenant of this proposal is the hypothesis that Wnt/β-catenin signaling plays an integral role in mucosal repair in IBD and that steroids delay ulcer healing my impairing Wnt/β-catenin signaling. In mucosal ulceration, as seen in IBD, there is replacement of surface mucosa with granulation tissue that is re-epithelialized with new crypt structures. We suspect that active Wnt signaling is required for several steps through this sequence of events from stage 1) generation of an intestinal epithelial cell (IEC) monolayer, to stage 2) formation of epithelial invaginations, to stage 3) formation of crypt islands on ulcer surfaces and finally stage 4) regeneration of mature crypts (Fig 3). Biochemical data from our lab indicate Wnt/β-catenin signaling is increased during ulcer healing in colitis in mice and IBD patients. In studies to interrogate the role of Wnt signaling in ulcer healing, we discovered that IEC expressing mRNA for the Wnt target gene Axin2 expand in ulcer margins, on ulcer surfaces, and within newly-formed crypt structures in the middle of ulcers. Studies using a novel Axin2 reporter mouse model indicate that Axin2+ IEC are pluripotent and capable of growing colonoid structures in vitro from a single cell. Together the preliminary data suggest that Axin2+ IEC represent a novel ISC population that forms new crypt structures during ulcer healing. In Aim 1, Axin2lacZ/+ and Axin2 CreERT2/+; R26RmTmG/+ mice will be used to study ulcer-associated Axin2+ IEC localization and gene expression profiles of this new stem cell population, as well as perform lineage tracing during ulcer healing in DSS colitis. In Aim 2 we will examine ulcer healing in mice treated with steroids. New studies will utilize Axin2-specific expression of stabilized β-catenin to examine its role in ulcer healin during steroid therapy. Aim 3 studies will interrogate the role of Axin2+ IEC in human IBD and will analyze the mechanisms by which steroids impair ulcer healing. The goal of these studies will be to determine if untreated UC patients exhibit increased Axin2 expression, Wnt signaling and stem cell gene expression in areas of ulcer healing (Aim 3A) and determine whether steroid therapy reduces levels of Axin2 expression and stem cell activation in areas of delayed ulcer healing in a prospective trial of UC patients treated with steroids for a colitis flare (Aim 3B). Together the studies proposed will provide valuable insights into the molecular mechanisms that govern ulcer healing in colitis. The goal is to determine areas where therapeutic targets can be designed to safely accelerate ulcer healing and reverse the negative impact of steroids on mucosal repair in colitis.

Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: The incidence and prevalence of ulcerative colitis (UC) is higher among veterans than in the general population, and the prevalence of UC increased 2-fold to 3-fold among veterans between 1998 and 2009. Lifelong effects of this disease include expensive medical treatments, hospitalization, surgery, disability and increased risk of colon cancer. For many patients, oral steroids are the first-line treatment for UC. Although steroids are effective in reducing overt symptoms, studies have shown that approximately half of all patients are refractory to steroid treatment, with limited ulcer healing. We have identified a new type of intestinal stem cell that i involved in healing ulcers. The goal of this project is to identify which types of cells are involvd in ulcer healing, and to understand how the activity of those cells is regulated. Additionally, we propose to investigate how steroids influence stem cell activity and limit ulcer healing. Completion of this work will lead to new understanding of how to improve medical treatment of colitis and prevent surgery in veterans.

Project Terms:

Area; beta catenin; Biochemical; Cell Proliferation; cell type; Cells; Clinical Markers; clinical remission; Colitis; Colon; Colon Carcinoma; Data; design; disability; Disease; Elements; Epithelial; Epithelial Cells; Event; Excision; Exhibits; Failure; Flare; Gene Expression; Gene Targeting; General Population; Generations; Goals; Granulation Tissue; Healed; healing; Hospitalization; Human; improved; In Vitro; Incidence; Inflammatory Bowel Diseases; insight; Intestines; Island; Lasers; Lead; Mediating; Medical; Messenger RNA; Microscopy; Molecular; Molecular Profiling; monolayer; mouse model; Mucous Membrane; Mus; Natural regeneration; novel; Operative Surgical Procedures; Oral; Patients; Play; Population; Prevalence; prevent; prospective; public health relevance; Recovery; Refractory; repaired; Reporter; Risk; Role; self-renewal; Signal Transduction; Staging; stem; stem cell population; Stem cells; Steroid therapy; Steroids; Structure; Surface; Symptoms; therapeutic target; Ulcer; Ulcerative Colitis; Veterans; Work

ClinicalTrials.gov

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IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

Inositol in Preventing Colorectal Cancer in Patients With Colitis-Associated Dysplasia

This study has been terminated.

(The study was closed prematurely due to poor accrual.)

Sponsor:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:
NCT01111292

First received: April 24, 2010
Last updated: June 1, 2016
Last verified: June 2016
History of Changes

Purpose

This pilot, randomized phase I/II trial studies how well inositol works in preventing colorectal cancer in patients with abnormal cells (dysplasia) associated with inflammation of the colon (colitis). Patients with colitis-associated dysplasia may have an increased risk of developing colorectal cancer. Inositol is a vitamin-like substance that may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Condition	Intervention	Phase
Colon Carcinoma Dysplasia in Crohn Disease Low Grade Dysplasia in Ulcerative Colitis Rectal Carcinoma	Drug: Inositol Other: Placebo	Phase 1 Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double Blind (Participant, Investigator)
Primary Purpose: Prevention

Official Title: Myo-Inositol Chemoprevention in Colitis-Associated Dysplasia

Resource links provided by NLM:

Genetics Home Reference related topics: Crohn disease ulcerative colitis

Drug Information available for: Inositol

U.S. FDA Resources

Further study details as provided by National Cancer Institute (NCI):

Primary Outcome Measures:

- The Effect of Myo-inositol (Inositol) on P-β-catenin Staining in Areas of Low Grade Dysplasia in Subjects With Known Colitis-induced Low Grade Dysplasia. [Time Frame: Baseline to 90 days]

  The primary objective of this study will be to evaluate the effect of myo-inositol (inositol), administered for three months, on P-β-catenin staining in areas of low grade dysplasia or in areas of prior low grade dysplasia in subjects with known colitis-induced low grade dysplasia at baseline.

Enrollment: 5

Study Start Date: October 2010
Study Completion Date: September 2014
Primary Completion Date: September 2014 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Arm I (inositol) Beginning within 14 days after colonoscopy, patients receive inositol PO QD on days 1-14 and BID on days 15-90.	Drug: Inositol Given PO Other Name: myo-Inositol
Placebo Comparator: Arm II (placebo) Beginning within 14 days after colonoscopy, patients receive placebo PO QD on days 1-14 and BID on days 15-90.	Other: Placebo Given PO Other Name: PLCB

Detailed Description:

PRIMARY OBJECTIVES:

I. To evaluate the effect of myo-inositol (inositol), administered for 3 months, on phospho (P)-beta (B)-catenin staining in areas of low-grade dysplasia or in areas of prior low grade dysplasia in subjects with known colitis-induced low grade dysplasia at baseline.

SECONDARY OBJECTIVES:

I. To examine the effect of myo-inositol on regression of dysplasia. II. To examine the effect of inositol on p53 and Ki67 staining within remaining dysplasia.

III. To examine the effect of inositol on epithelial apoptosis (cleaved caspase-3) within dysplasia.

IV. To examine the effect of inositol on reductions in mucosal messenger ribonucleic acid (mRNA) levels of monocyte chemotactic protein 1 (MCP1), inducible nitric oxide synthase (iNOS), and cyclooxygenase (Cox)-2.

OUTLINE: Patients are randomized to 1 of 2 treatment arms.

ARM I: Beginning within 14 days after colonoscopy, patients receive inositol orally (PO) once daily (QD) on days 1-14 and twice daily (BID) on days 15-90.

ARM II: Beginning within 14 days after colonoscopy, patients receive placebo PO QD on days 1-14 and BID on days 15-90.

After completion of treatment, patients undergo biopsy and colonoscopy with or without mucosal resection.

After completion of study treatment, patients are followed up at 2 weeks.

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Participants must have ulcerative colitis or Crohn's disease with low grade dysplasia or polyploid dysplasia or have a history of dysplasia and increased positive beta-catenin levels confirmed by a consensus of the study pathologists (2 of 2, or 2 of 3)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Absolute neutrophil count (ANC) > 1,500/uL
- Platelets > 100,000/uL
- Total bilirubin within normal institutional limits
- Aspartate aminotransferase (AST)(serum glutamic oxaloacetic transaminase [SGOT]/alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT] =< 1.5 times upper limit of normal
- Creatinine within normal institutional limits
- International normalized ratio (INR) < 1.5
- Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from the time of baseline pregnancy test, throughout the duration of the study, and for 1 month following cessation of study drug; females must begin adequate contraception immediately following screening pregnancy test; should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately; if she is pregnant, she will be immediately withdrawn from the study and followed until the birth of the child
- Ability to understand and the willingness to sign a written informed consent document

Exclusion Criteria:

- Subjects with life-threatening medical conditions that would preclude study treatment intervention and colonoscopy
- Participants may not be receiving any other investigational agents
- History of allergic reactions to rice or compounds of similar chemical or biologic composition to myo-inositol (i.e., urticaria, dermatologic reaction)
- Use of medications known to elevate serum blood glucose; participants on steroids are still eligible, as they will be monitored weekly for fasting blood glucose
- Participants with dysplasia-associated lesion or mass (DALM), high-grade dysplasia or invasive colonic carcinoma are excluded
- Uncontrolled intercurrent illness including, but not limited to
  - Ongoing or active infection
  - Symptomatic congestive heart failure
  - Unstable angina pectoris
  - Cardiac arrhythmia
  - Chronic renal failure
  - Chronic renal insufficiency
  - Psychiatric illness or social situations that would limit compliance with study requirements
- Prior treatment with myo-inositol
- History of systemic chemotherapy within 18 months of screening
- Subjects taking valproic acid and/or lithium
- Diabetes mellitus
- History of total proctocolectomy
- Concomitant primary sclerosing cholangitis (PSC)
- Pregnant or lactating subjects are excluded

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01111292

Locations

United States, Illinois

Northwestern University
Chicago, Illinois, United States, 60611

University of Chicago Comprehensive Cancer Center
Chicago, Illinois, United States, 60637

United States, New York

Mount Sinai Medical Center
New York, New York, United States, 10029

Sponsors and Collaborators

National Cancer Institute (NCI)

Investigators

Principal Investigator: Seema Khan Northwestern University

More Information

Responsible Party: National Cancer Institute (NCI)
ClinicalTrials.gov Identifier: NCT01111292 History of Changes

Other Study ID Numbers: NCI-2011-01434
NCI-2011-01434 (Registry Identifier: CTRP (Clinical Trial Reporting Program))
CDR0000671302
NCI09-13-02 (Other Identifier: Northwestern University)
NWU09-13-02 (Other Identifier: DCP)
P30CA060553 (US NIH Grant/Contract Award Number)
N01CN35157 (US NIH Grant/Contract Award Number)
Study First Received: April 24, 2010
Results First Received: January 29, 2016
Last Updated: June 1, 2016

Additional relevant MeSH terms:

Carcinoma
Crohn Disease
Colitis
Colitis, Ulcerative
Hyperplasia
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Neoplasms
Inflammatory Bowel Diseases
Gastroenteritis
Gastrointestinal Diseases
Digestive System Diseases
Intestinal Diseases
Colonic Diseases
Pathologic Processes
Inositol
Vitamin B Complex
Vitamins
Micronutrients
Growth Substances
Physiological Effects of Drugs

ClinicalTrials.gov processed this record on April 21, 2017

Viewing Project

5T32CA080621-09 (T32) ApplID: 8117165			
Title	Training Program in Oncogenesis and Developmental Biology		
Institution	NORTHWESTERN UNIVERSITY AT CHICAGO, CHICAGO, IL		
Principal Investigator	CARTHEW, Richard	**NCI Program Director**	Sonia Jakowlew
Cancer Activity	Training	**Division**	CCT
Funded Amount	$263,409	**Project Dates**	04/06/2001 - 08/31/2013
Fiscal Year	2011	**Project Type**	Grant

Research Topics w/ Percent Relevance	Cancer Types w/ Percent Relevance
Cancer (100%)	N/A

Research Type

Resources and Infrastructure
Resources and Infrastructure Related to Etiology

Abstract

DESCRIPTION (provided by applicant): This application is a request for continued funding of T32 CA080621 at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, The Cancer Center is committed to promoting the highest caliber basic science and clinical science research. The Center has been supported by a support grant from the National Cancer Institute (NCI P30 CA60553) since 1993 and also has received support for SPORES in Prostate Cancer (P50 90386) and Breast Cancer (P50 CA89018). The Cancer Center is dedicated to preparing the next generation of research scientists through education and training programs. The Training Program in Oncogenesis and Developmental Biology has been preparing predoctoral and postdoctoral trainees to work at the interface of cancer biology and developmental biology through laboratory research, formal course work and participation in seminars, journal clubs and group meetings. Trainees learn how the gene networks controlling embryonic development play a central role in tumor formation and progression. In three and one half years, the Training Program in Oncogenesis and Developmental Biology has successfully trained five predoctoral students and six postdoctoral fellows, and five trainees are currently being supported (the sixth recently received her own funding). Of the eleven who completed the training program, seven have continued on in postdoctoral training and one accepted a senior scientist position in industry. Three students are still in the process of completing their Ph.D. training at Northwestern University. All trainees have remained in the field of cancer biology. Based on our expectation that we will continue to attract the same numbers of highly qualified candidates to Northwestern University, we request funding for two predoctoral students and four postdoctoral fellows per year for a period of five years in the current application. This will enable us to continue focused training in Oncogenesis and Developmental Biology.

Project Information

5R01DK095662-09

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DESCRIPTION DETAILS RESULTS HISTORY SUBPROJECTS SIMILAR PROJECTS NEARBY PROJECTS BETA LINKS NEWS AND MORE

Project Number: 5R01DK095662-09 **Former Number:** 2R01DK095662-06A1
Contact PI / Project Leader: BARRETT, TERRENCE A.
Title: REGULATION OF INTESTINAL STEM CELL ACTIVATION IN COLITIS
Awardee Organization: UNIVERSITY OF KENTUCKY

Abstract Text:

DESCRIPTION (provided by applicant): Induction of mucosal healing in inflammatory bowel disease (IBD) is associated with reduced hospitalizations and surgeries. Healing of the mucosal barrier requires control of the destructive inflammatory response as well as restitution of the epithelial barrier through enhanced proliferation and generation of new crypt structures. Although it is clear that induction of Wnt/B-catenin activation is a key factor in intestinal stem ell (ISC) and progenitor cell (PC) activation, there are few researchers that examine the regulation of B-catenin activation in colitis where mucosal healing and inflammation-induced dysplasia are major clinical concerns. Studies performed during the prior award period demonstrated that Akt phosphorylation of B-catenin increases in ISCs during colitis and colitis-induced cancer. The present proposal makes use of a novel genetic model for reducing PI3K signaling in colonic intestinal epithelial cells (IEC) during colitis. Data already produced in VilCre/pik3r1fl/fl mice given DSS colitis suggest that PI3K-mediated B-catenin activation plays a major role in wound healing. Acute and chronic forms of DSS colitis will be generated in VilCre/pik3r1fl/fl mice for in vivo studies in AIM 1 to examine the role of IEC class 1A PI3K in mucosal healing, B-catenin activation and ISC/PC gene expression (using novel enteroid cultures). Studies in AIM 2 utilize bone marrow chimera (BMC) mice to examine TNF-induced IEC B-catenin signaling in radioresistant epithelial populations in DSS colitis mice. AIM 3 studies examine the role of Nox1 in B-catenin activation using B6->Nox1-/- BMC DSS colitis mice. Together the studies propose that TNF-induced NOX1 stimulates PI3K-mediated B-catenin activation and ISC/PC gene expression to determine crypt responses in IBD. The underlying hypothesis is that inflammation-induced B-catenin signaling enhances epithelial regeneration and induces chronic architectural distortion by increasing ISC and progenitor cell expansion during colitis. The clinical relevance of these studies is great given that we hope to identify novel approaches to IBD therapy and chemoprevention.

Public Health Relevance Statement:

The proposal presented plans to examine how patients heal from ulcers (sores) in the bowel during colitis (ulcerative colitis and Crohn's disease). We find that in colitis, small protein molecules made by white blood cells cause stimulation of epithelial cells that line the colon. In this grant we will examine mechanisms that control how inflammation in colitis stimulates epithelial stem cells and increases their risk of turning into colon cancer.

NIH Spending Category:

Autoimmune Disease; Biotechnology; Cancer; Clinical Research; Colo-Rectal Cancer; Crohn's Disease; Digestive Diseases; Inflammatory Bowel Disease; Regenerative Medicine; Stem Cell Research; Stem Cell Research - Nonembryonic - Human; Stem Cell Research - Nonembryonic - Non-Human

Project Terms:

Acute; Attenuated; Award; base; Biopsy; Bone Marrow; carcinogenesis; Cell Culture Techniques; Cell Line; Chemoprevention; Chicago; Chimera organism; Chronic; Clinical; clinical predictors; clinical remission; Clinical Trials; clinically relevant; Colitis; colitis associated cancer; Colon; Colon Carcinoma; Colorectal Cancer; Crohn's disease; Data; Dysplasia; Enrollment; Epithelial; Epithelial Cells; Figs - dietary; Focal Infection; Gene Expression; Generations; Genes; Genetic Models; Goblet Cells; Grant; Healed; healing; Hospitalization; In Vitro; in vivo; Inflammation; Inflammatory Bowel Diseases; Inflammatory disease of the intestine; Inflammatory Response; Intestines; kinase inhibitor; Leukocytes; Malignant Neoplasms; Mediating; member; Modeling; Monoclonal Antibodies; Mucositis; Mus; Mutate; myoinositol; Natural regeneration; novel; novel strategies; Operative Surgical Procedures; Pathway interactions; Patients; Phosphorylation; Phosphotransferases; Play; Population; Proteins; Publishing; radioresistant; Reactive Oxygen Species; Regulation; repaired; Research Personnel; Residual state; response; Risk; Role; Sampling; Severities; Severity of illness; Signal Transduction; Sodium Dextran Sulfate; stem; Stem cells; Structure; Study models; Systemic infection; Testing; therapy outcome; Time; Tissues; TNFRSF1A gene; Tumor Necrosis Factor-alpha; Ulcer; Ulcerative Colitis; Universities; Wound Healing

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