

AWARD NUMBER: W81XWH-15-1-0273

TITLE: The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

PRINCIPAL INVESTIGATOR: Andrea Burnett-Hartman, PhD, MPH

CONTRACTING ORGANIZATION: Kaiser Foundation Research Institute
Portland, OR 97227

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT The objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated colorectal polyps (SSPs). The project's specific aims are as follows: 1) Estimate the risk of colorectal cancer or advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia; and 2) Evaluate if the risk of incident colorectal cancer or advanced polyps varies according to methylation markers in SSPs. The following progress was made during year 1: Human Subjects approval was obtained from all institutions, SSPs with subsequent colorectal neoplasia and interval cancers were identified, the pathology review form and protocol were finalized, assays for 6 out of the 11 methylation markers were optimized, tissue blocks and clinical H&E slides were pulled for standard pathology review. Also, Dr. Burnett-Hartman participated in regular career development opportunities, including attending clinical research seminars, presenting at national and local research meetings, and connecting with new clinical partners at Kaiser Permanente Colorado. Dr. Burnett-Hartman also maintained regular meetings with mentors and collaborators at the Fred Hutchinson Cancer Research Center, the University of Washington, and Kaiser's Institute for Health Research.					
15. SUBJECT TERMS Colorectal Cancer, Colorectal Polyps, Sessile Serrated Polyps, Methylation					
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1. INTRODUCTION:

Recent research suggests that in addition to advanced conventional adenomas, some other polyp pathologies, such as sessile serrated polyps (SSPs), may be important precursors for colorectal cancer. Previously, SSPs were thought to have no malignant potential, but cross-sectional studies of molecular markers have linked SSPs to a subset of colorectal cancers characterized by a CpG Island methylator phenotype (CIMP) and methylation of key DNA repair genes, such as *MLH1* and *MGMT*. However, it is not clear which SSP features are associated with an increased risk of colorectal cancer. Thus, the primary objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with SSPs. We hypothesize that patients with SSPs that exhibit cytological dysplasia, *MLH1* or *MGMT* methylation, or patients that have CIMP-high SSPs will have an increased risk of incident colorectal cancer and metachronous advanced colorectal polyps compared to patients with SSPs that lack these characteristics. To test this hypothesis, we identified a cohort of patients who were diagnosed with SSPs at the University of Washington Medical Center during an index colonoscopy between 2003 and 2013. Within this cohort we will select 100 patients with SSPs who later developed colorectal cancer or advanced polyps and 200 patients with SSPs who did not develop colorectal cancer or advanced polyps after their SSP diagnosis. For these 300 study participants, we are in the process of conducting a standardized pathology review to assess the presence of cytological dysplasia in the index SSPs and molecular testing of index SSPs for CIMP and methylation of specific candidate genes. We will use logistic regression models to compare the risk of colorectal cancer and advanced colorectal polyps in those with each biomarker to those without each biomarker. We will also estimate the sensitivity and specificity of each biomarker to predict the risk of subsequent colorectal cancer or advanced polyps. Research findings from this study will improve effectiveness of colorectal cancer screening tests by informing the development of evidence-based guidelines for the surveillance of patients with SSPs.

2. KEYWORDS:

Colorectal cancer, colorectal polyps, molecular markers, DNA methylation, sessile serrated polyps, screening

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Below is a table displaying the major goals and milestones for this project in accordance with the approved scope of work. Target completion dates, actual completion dates, and percent complete are also listed. Dr. Burnett-Hartman completed all study start up activities in the first year of the award and has made progress towards accomplishing the primary study aims. She also participated in all planned career development activities during the first year of this award. Note, the table below shows goals and milestones for the entire project period, including goals and milestones that are planned for Years 2 and 3.

Table. Major Goals and Milestones

	Target Completion Date	Actual Completion Date	Percent Complete	Notes
Study Set up				
Update local IRB and obtain approval	11/1/15	10/23/2015	100%	IRB approval was obtained through UW, Fred Hutch and KPCO.
Complete IACUC/ HRPO/ACURO applications and obtain approvals	1/1/16	2/12/16	100%	

Complete study protocol for tissue pulling/sectioning and pathology review	12/1/15	9/1/15	100%	We completed the protocol/form quickly, so that we could include the form in our human subjects applications.
Specific Aim 1: Estimate the risk of incident colorectal cancer or metachronous advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia.				
Pulling clinical polyp tissue slides and tissue blocks on 300 patients	4/1/16		75%	We originally planned to pull all slides and blocks at once. However, Northwest Biotrust is working with Dr. Upton to pull batches as Dr. Upton reviews them.
Standard Pathology review of 300 patients	7/1/16		60%	Dr. Upton begun pathology review later than expected due to changes in her office space; she now expects to complete path review by 10/1/16.
Data cleaning of pathology data	9/1/17		0%	The new target date is 11/1/16, 1 month after completion of path review.
Complete data analysis of pathology data using STATA and summarize data in tables, figures, and graphs	2/1/17		0%	
Preparation, submission, and presentation of abstract on pathology data for national meeting	8/1/17		0%	
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	
Specific Aim 2: Evaluate whether the risk of incident colorectal cancer or advanced neoplasia varies according to certain methylation markers in SSPs, including the presence of CIMP, methylated <i>MLH1</i>, <i>MGMT</i> or <i>BMP3</i>.				
Tissue sectioning	9/1/16		0%	This activity is delayed, because path review needs to be complete before tissue sectioning; new target date is 11/1/16.

Polyp tissue DNA extraction and quantification for 300 samples	12/1/16		0%	
Methylite PCR Assay for 300 Samples, including quality control procedures (i.e. <i>ALU</i> control and 5% blind replication sample)	8/1/17		5%	Although testing of study samples has not begun, we have optimized the assay for 6 out of the 11 DNA methylation markers in preparation for testing study samples.
Data cleaning of CIMP and candidate gene methylation data	9/1/17		0%	
Complete data analysis of methylation data using STATA and summarize data in tables, figures, and graphs	12/1/17		0%	
Preparation and submission, and presentation of abstract for national meeting	5/1/18		0%	
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	
Additional Career Development Activities				
One-on-one meetings with mentors and collaborators	Throughout project period		N/A	Dr. Burnett-Hartman has had mentor meetings throughout Year 1 (see additional information under career development activities).
Attend and present at University of Washington Medical Center, Fred Hutchinson Cancer Research Center, and Kaiser Permanente clinical research seminars	Throughout project period		N/A	Dr. Burnett-Hartman has attended a presented at local clinical research seminars (See additional information under career development activities).
Attend the American Society for Clinical Oncology GI Symposium and workshops	3/1/17		0%	
Attend and present study findings at Digestive Disease Weeks (The annual meeting of the American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society of the Surgeons of the Alimentary Tract, and American Association for the Study of Liver Diseases)	7/1/18		0%	

What was accomplished under these goals?

As detailed in the table above, during year 1, we accomplished the following goals/objectives:

1. Institutional Review Board Human Subjects review and approval through the University of Washington, Fred Hutchinson Cancer Research Center, and Kaiser Permanente Colorado.
2. Completed IACUC/ HRPO/ACURO applications and obtain approvals
3. Developed the standard pathology review form (see attached appendix)
4. Selected the final list of methylation markers to analyze in our colorectal polyp samples
5. Began tissue slide and block pulling
6. Began standard pathology review
7. Optimized the methylation assay for 6 of the 11 DNA methylation markers for this project

The following goals/objectives, had planned completion dates during year 1. However, due to an unanticipated delay in beginning pathology review as a result of renovations in the study pathologist's work space, the following are currently behind schedule:

1. Completing pathology review
2. Completing tissue sections (needs to be done after pathology review is complete)

These activities will be completed in the first quarter of year 2, and the Grady Lab still plans to complete the methylation assays by the end of year 2, as originally planned.

What opportunities for training and professional development has the project provided?

1. **Training in clinical cancer research through seminars** – During Year 1 of this award, I attended multiple clinical research seminars, including: Translational Research in Oncology Seminars (quarterly through Kaiser Permanente), Center for Effectiveness and Safety Research Seminars (monthly through Kaiser Permanente), Genomics Workgroup Seminars (monthly through Kaiser Permanente), and Translational Research in Colorectal Cancer Seminars (monthly through the Fred Hutchinson Cancer Research Center).
2. **Meetings with mentorship team** – I have maintained a strong mentorship team and meet with one of more of my mentors via phone, video conference, or in-person on a weekly basis. In these meetings, we discuss ongoing projects, future grant applications, study design, and analyses methods. My mentors include Drs. Grady, Newcomb, and Zheng from the Fred Hutchinson Cancer Research Center, Dr. Inadomi from the University of Washington, and Dr. Feigelson from Kaiser Permanente Colorado's Institute for Health Research.
3. **Protected time for clinical research and developing new collaborations with clinical researchers** – As planned, I have maintained 30% protected time for this award and 60% time devoted to other successfully funded clinical research projects (see attached Research Support Document). Kaiser also provides institutional support to allow for future project development and grant proposal development. This year, I developed 3 new successfully funded pilot projects using institutional support, Cancer Research Network support, and PORTAL Colorectal Cancer Support. These pilot projects will provide preliminary data and feasibility assessments for future grant applications in clinical cancer research. I have also connected with new potential collaborators in clinical cancer research, including Dr. Mark Powis in Kaiser Gastroenterology and Dr. Alex Mentor in Kaiser Oncology.
4. **Attendance at national meetings** – In Year 1, I attended the following National Clinical Research Meetings: Center for Safety and Effectiveness Research (Denver, CO, October 2015), American Society of Preventive Oncology (Columbus, OH, March 2016) Health Care Systems Research Network (Atlanta, GA, April 2016).

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, my study team and I will accomplish the following major goals/objectives:

1. Complete the standard pathology review of index colorectal sessile serrated polyps
 2. Analyze the pathology review data to determine the association between nuclear dysplasia in sessile serrated polyps and colorectal cancer and advance colorectal polyp risk (Aim 1)
 3. Submit an abstract of our findings on nuclear dysplasia in sessile serrated polyps for presentation at a national clinical research meeting
 4. Complete tissue sectioning and DNA extraction on all sessile serrated polyps included in this project
 5. Complete DNA methylation assays on all polyp tissue DNA samples
 6. Continue to pursue career development activities, including: meetings with mentors, attending clinical research seminars, developing new clinical research proposals, and attending and presenting research findings at national clinical research meetings
4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report in this period, but future results may impact the DNA markers that are used in stool-based DNA testing for colorectal cancer screening.

What was the impact on society beyond science and technology?

Nothing to report in this period, but future results may inform the surveillance for colorectal cancer in patients with specific types of sessile serrated polyps and ultimately improve the effectiveness of colorectal cancer screening.

5. **CHANGES/PROBLEMS:**

Nothing to report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

We are in the process of collecting tissue biospecimens; future results from this project may inform colorectal cancer surveillance guidelines for patients with sessile serrated polyps, improve the effectiveness of colorectal cancer screening, and identify new DNA markers to include in stool-based DNA tests.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>Andrea Burnett-Hartman</i>
Project Role:	<i>Principle Investigator</i>
Researcher Identifier	ANDREABH
Nearest person month worked:	3.60
Contribution to Project:	<i>Dr. Burnett-Hartman is the PI of this project and is responsible for the overall scientific and administrative management for this project, including: compliance with human subjects policies, study design, protocol development, analysis, interpretation, and dissemination of research results.</i>
Funding Support:	No additional funding was provided

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, please see attached other support document for Dr. Burnett-Hartman and her mentor, Dr. Grady.

What other organizations were involved as partners?

We have two subcontracts under this award. Our partners are Fred Hutchinson Cancer Center and the University of Washington.

- **Organization 1 Name:** Fred Hutchinson Cancer Research Center
- **Location of Organization:** 1100 Fairview Ave. N., Seattle, WA 98109
- **Partner's contribution to the project:** Development and optimization of the methylation specific PCR assays that will be used to assess the polyp DNA is in progress. It is anticipated that the polyp tissue will be received in the next few months and that DNA extractions and methylation analysis will begin in the first or second quarter of year 2. Also, Dr. Grady is serving as a mentor to Dr. Burnett-Hartman under this award, and they meet regularly to discuss project progress and career development opportunities. Dr. Burnett-Hartman also attends Dr. Grady’s monthly seminars in Translational Research in Colorectal Cancer.
- **Financial support:** Year 1 total funds committed \$19,960; \$5,508 spent; \$14,456 remaining balance will be used in Year 2 for DNA extraction and methylation analysis.
- **In-kind support:** N/A
- **Facilities:** The Fred Hutchinson Cancer Research Center has state-of-the-art laboratories for conducting medical research. The labs encompass a total of 35,000 square feet and include, private lab space, common shared equipment rooms, shared resource space (for genotyping and other molecular work, pathology/histology, and specimen processing), and offices and conference

facilities for faculty and staff. The molecular testing for this project will be completed in the Grady Lab at the Fred Hutchinson Cancer Research Center.

- **Collaboration:** Dr. Burnett-Hartman has worked closely with Dr. William Grady on study design, selection of the relevant methylation markers, and assay development in Year 1. Dr. Grady also actively mentors Dr. Burnett-Hartman.
- **Personnel exchanges:** N/A

- **Organization 2 Name:** University of Washington
 - **Location of Organization:** 1959 NE Pacific St., Box 357470, Seattle, Washington
 - **Partner's contribution to the project:** Dr. Upton served as Co-Investigator on this project and worked on the pathology-related aspects of the project, including a standard pathology review for people with clinically diagnosed sessile serrated polyps.
 - **Financial support:** Year 1 total funds committed \$17,919; \$17,608.60 spent; \$310.40 remaining balance.
 - **In-kind support:** N/A
 - **Facilities:** For diagnostic and research purposes, the University of Washington's Department of Pathology stores and keeps inventory of H&E slides and associated formalin-fixed paraffin-embedded tumor blocks on patients who had biopsies and/or resections performed at the University of Washington Medical Center and Harborview Medical Center. Northwest Biotrust at the University of Washington has the infrastructure to efficiently pull H&E slides and tumor blocks for clinical and research purposes. This project uses Northwest Biotrust to pull relevant tissues slides and blocks; Dr. Upton, anatomic pathologists at the University of Washington reviews these slides and blocks in a designated office equipped with a high-powered digital microscope.
 - **Collaboration** Dr. Burnett-Hartman has worked closely with Dr. Melissa Upton to develop the pathology review form and is in the process of reviewing index H&E slides to confirm the sessile serrated polyp diagnosis and characterize nuclear dysplasia within the polyp tissue samples.
 - **Personnel exchanges** N/A

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES:

Appendix I: Pathology Review Form

Appendix II: Research Support for Dr. Burnett-Hartman

Appendix III: Research Support for Dr. Grady

APPENDIX I - STANDARD PATHOLOGY REVIEW FORM

Date of Pathologist Review ___ / ___ / ___	STUDY ID: _____
DATA ENTRY Date: ___ / ___ / ___ Initials: ____	DATA QC Date: ___ / ___ / ___ Initials: ____

	Comments:
Materials for Review:	
Slides (#)	Box #

10=polyp(s) NOS	16=villous adenoma	22=traditional serrated adenoma (TSA)	30=Carcinoma in situ
11=hp1=goblet cell hp	17=P-J polyp	23=mixed polyp HP/AD	40=Invasive CRC
12=hp2=microvesicular hp	18=juvenile/inflammatory polyp	24=mixed polyp SSP/AD	90=normal
13=adenoma NOS	19=other polyp	25=mixed polyp SSP/TSA	91=inconclusive (cannot tell if normal or lesional)
14=tubular adenoma	20=sessile serrated polyp	26=mixed polyp TSA/AD	93=benign
15=tubulovillous adenoma	21=indeterminate for HP vs SSP	27=prolapse polyp	99=other

Slide	Code (see above) & Confidence (0-100)		Comments	% Lesional	Tangential Orientation	Nuclear Dysplasia	Abnormal Crypts	
							#	%
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	___	___			<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		

APPENDIX II: EXISTING/PENDING/PREVIOUS SUPPORT – BURNETT-HARTMAN

BURNETT-HARTMAN, ANDREA

EXISTING SUPPORT (As of 08/17/2016)

R03 CA186215 (Burnett-Hartman) NCI	04/04/14 – 03/31/17 \$85,955	0.96 cal mos
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Using Medical Informatics to Follow-up a Colorectal Sessile Serrated Polyp Cohort

The primary objective of this proposal is to gather preliminary data to estimate the risk of colorectal cancer in a large cohort of patients with clinically diagnosed sessile serrated polyps.
Contracting Officer: Ester Young, National Cancer Institute, Office of Grants Administration, 9606 Medical Center Drive, Bethesda, MD 20892-9760

R01 CA 168338 (Newcomb) NIH/CA	04/22/13 – 3/31/17 \$68,140	1.20 cal mos
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A Cohort Study of Sessile Serrated Polyps and Subsequent Colorectal Neoplasia

Recent evidence implicates an additional group of polyps, sessile serrated polyps (SSPs), as important precursors to colorectal cancer. This project will investigate the clinical significance of SSPs in colorectal neoplasia, with the long-term goal of characterizing new high risk-groups to improve the effectiveness of colorectal cancer screening.

NIH U01CA163304 (Co-PIs: Feng/Barlow) NIH/NCI	09/20/11 – 08/31/16 \$24,329	0.60 cal mos
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PROSPR Statistical Coordinating Center (PSCC)

The goal of the PROSPR Statistical Coordinating Center (PPSCC) is to coordinate the research of PROSPR Research Centers (PRCs) to achieve PROSPR's mission of evaluating and improving the cancer screening process (recruitment, screening, diagnosis, and referral for treatment).
Contracting Officer: Tonya Parker, National Cancer Institute, Office of Grants Administration, BG 9609 RM 3E346, 9609 Medical Center Drive, West Tower, Rockville, MD 20805

ADM000369 Kaiser Permanente of Colorado	Ongoing N/A	0.60 cal mos
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Institutional Support- Institute for Health Research

The institutional funding provides salary support for investigators within the Institute for Health Research.
Contracting Officer: Kasier Foundation Health Plan of Colorado, 10350 E. Dakota Ave., Denver, CO 80231

RNG000511 (Feigelson) Kaiser Foundation Program Office Kaiser National Biobank	01/15/15 – 12/31/17 \$876,700	3.48 cal mos
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The KP National Biobank is a collaboration across all Kaiser regions nationally funded by Kaiser Permanente Program Office. The goal of the KP National Biobank is to collect blood samples from 500,000 adults KP members and utilize them, combined with survey data and medical information to create a state of the art resources for genetic and health services research.
Contracting Officer: Kaiser Permanente Program Office, 1800 Harrison St. 16th Floor, Oakland, CA 94612-3433

W81XWH-15-1-0273 (Burnett-Hartman) (This Award) 08/01/15 – 08/31/2018 3.60 cal mos
DOD/CDMRP \$490,546
The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

The primary objective of this career development award is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated polyps.

Contracting Officer: Elayne Seiler, Grants Specialist, USA MED Research MAT CMD, 1077 Patchel Street, BLDG 1077, Fort Detrick, MD 21702

U24CA171524 (Kushi) 09/25/15 – 8/31/2017 1.56 cal mos
NIH/NCI \$355,749
Cancer Research Network: a Research Resource within Health Care Delivery System

The goal of this grant is to take advantage of the HMO Research Network, a consortium of nonprofits HOMs, to study issues related to cancer prevention, detection and control.

Contracting Officer: Teresa Parker, Grants Management Officer, Office of Grants Administration, BG 9609
RM 3E346, 9609 Medical Center Drive, West Tower, Rockville, MD 20805

PENDING

R01 CA179906 (Newcomb) 04/01/15 – 03/31/20 0.90 cal mos
NIH/NCI \$23,516 effort to begin in 2017
Serrated Colorectal Cancer: An emerging Disease Subtype

The objective of this project is to characterize factors relating to the genetic predisposition, clinical presentation, and prognosis of serrated colorectal cancer.

Contract Officer: Pending

CDRN-1306-04681 (McGlynn) 06/01/16 - 05/31/17 0.42 cal mos
PCORI \$27,981
Pilot Feasibility study of Molecular Tumor Marker Testing in Colorectal Cancer Tissue Samples from PORTAL

In order to conduct research to characterize the molecular markers in colorectal tumors, researchers must be able to access clinical tissue blocks, isolated DNA from these tissue blocks, and successfully test this DNA for important tumor markers, such as BRAF mutation and CpG Island Methylator Phenotype (CIMP). In this pilot study, we will test the feasibility of conducting studies aimed at molecular characterization of colorectal cancers within the PORTAL CRC cohort.

Contracting Officer: Pending

PREVIOUS SUPPORT

KL2 TR000421 (Disis) 06/01/12 – 01/05/15 9.00 cal mos
NIH/NCATS \$109,650 (Subcont)
Institute of Translation Health Sciences (KL2)

This is a training award for Dr. Burnett-Hartman from the University of Washington's Institute of Translational Health Sciences.

Contracting Officer: Todd Wilson, National Center for Advancing Translational Sciences, BG 1DEM
RM 914, 6701 Democracy Boulevard, Bethesda, MD 20817

R01 CA097325 (Newcomb) 05/17/04 – 04/30/10 6.00 cal mos
NIH/NCI \$172,678
Colon Cancer Pathways: Hyperplastic Polyps & Adenomas

To investigate the relationship between risk factors, epigenetic characteristics and polyps, we propose to conduct a population based case-control study of hyperplastic polyps, adenomatous polyps, and normal controls. This study will provide the largest study of risk factors for hyperplastic polyps, their genetic characterization, and comparisons to adenomas and normals. The results of this study will have implications for understanding the biology and prevention of colorectal cancer.

Contracting Officer: Barbara Fisher, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd Floor, Rockville, MD 20850

R03 CA137752 (Newcomb) 08/01/09 – 07/31/12 3.00 cal mos
NIH/NCI \$50,000
Human Papillomavirus Association with Subsets of Colorectal Cancer

The overall goal of this project is to conduct a case-control study of localized colorectal cancer to determine the association between high-risk HPV infection and tumor and personal characteristics.

Contracting Officer: Amy Connolly, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850

R03 CA153323 (Newcomb) 08/01/10 – 07/31/13 3.00 cal mos
NIH/NCI \$48,500
GWAS Identified Colorectal Cancer SNPs and Colorectal Polyp Risk

This project, an ancillary study to R01 CA097325, seeks determine the risk of adenomas and hyperplastic polyps associated with 10 specific polymorphisms identified through GWAS, and the genes or regions of the genome that house these loci using a tagSNP approach.

Contracting Officer: Barbara Fisher, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850

OVERLAP

There is no scientific or budgetary overlap. If the Pending projects are funded, Dr. Burnett-Hartman anticipates reducing effort on the KP Institutional Support to effort to stay within 12.0 CM.

The study titled: **A Cohort Study of Sessile Serrated Polyps and Subsequent Colorectal Neoplasia**, will end on 3/31/2017 reducing her FTE (1.20 CM).

If additional reduction is necessary, Dr. Burnett-Hartman will reduce her FTE on other studies to stay within the NIH guidelines

APPENDIX III: EXISTING/PENDING/PREVIOUS SUPPORT – GRADY

GRADY, WILLIAM M.

ACTIVE

Institutional Funds (Grady) University of Washington Rodger C. Haggitt Endowed Chair in Gastroenterology Research Award Administrator: Roberta O. Fraese, Administrator, UW Department of Medicine, Division of Gastroenterology; rof@u.washington.edu.	02/01/07 - ongoing \$ variable	Effort: not required
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Donation (Grady) Mercer Island Rotary	09/01/14 - 08/31/16 \$3,000 (no-cost extension)	Effort: not required
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These funds support biomarker research in the Grady lab.
Award Administrator: Nural Booth, norgun@fredhutch.org.

Restricted donation (Grady) Cottrell T	09/01/14 - 10/31/16 \$59,193 (no-cost extension)	Effort: not required
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These funds support research in the Grady lab.
Award Administrator: Angela Bush, Manager, Benefactor Relations; abush@fhcrc.org.

Institutional Support (Grady) FHCRC / Listwin Family Foundation	05/01/13 - 04/30/17 \$153,070 no-cost extension	Effort: not required
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Early Detection of Colon Cancer Research

These funds support biomarker research in the Grady lab.

Award Administrator: Angela Bush, Manager, Benefactor Relations; abush@fhcrc.org.

5U01CA182940-03 (Luebeck, Hur, Inadomi, Wang) NIH NCI	09/17/13 - 08/31/18 \$518,170	0.6 cal mos
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Esophageal Cancer from Cells to Population: A Multi-scale Approach

The goal of the proposed research is to reduce the burden of esophageal adenocarcinoma (EAC) by optimizing surveillance of patients with Barrett's esophagus (BE) using cutting-edge Optical Coherence Tomography (OCT) imaging and advanced epigenetic profiling of neoplastic tissues in combination with standard endoscopic screening. To accomplish this goal we will establish a multidisciplinary collaboration between epidemiologists, geneticists, clinicians, and computational and mathematical modelers to develop a multi-scale modeling framework that synthesizes and integrates data generated at different scales and sources to provide a coherent and informative picture of the natural history of EAC.

2P30CA015704-40 (Gilliland) NIH NCI	01/01/97 - 12/31/19 \$3,162,851	1.08 ca mos
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Cancer Center Support Grant

The Fred Hutchinson/University of Washington Cancer Consortium (Consortium) brings together more than 450 members with research interests in basic, clinical, and public health sciences related to cancer. The goal of the Consortium is the elimination of cancer through more effective prevention, diagnostics, and treatment, deriving from fundamental insights into the biology of the disease. The extensive

interdisciplinary collaboration among the partner institutions in the cancer research disciplines of basic, clinical, and public health sciences affords new opportunities to reduce suffering and mortality from cancer. The Consortium faculty are organized into 16 productive research programs with the emphasis on the Public Health (Biostatistics, Epidemiology, Prevention), Clinical (Transplantation Biology, Clinical Transplantation, Human Immunogenetics, Immunology, Infectious Disease), Fundamental Sciences (Basic, Human Biology), and programs that impact all three disciplines (Breast, Prostate, Gynecologic, Genetics, Imaging, and Genetic Instability). Dr. Grady serves as head of the Gastroenterology Program. Grants Management Specialist: Gerard B. McCann; mccannge@mail.nih.gov.

1R01CA194663-01 (Grady) 04/14/15 - 03/31/19 1.2 cal mos
NIH NCI \$241,048

(PQC1) Accelerated Biological Aging and Colon Polyp to Cancer Progression

Specific aims: 1.) To determine if the biological age of the normal colon mucosa predicts the presence of advanced colon adenomas or adenocarcinomas; 2.) To determine if age-related DNA methylation is increased in biologically older colons and correlates with the presence of advanced adenomas or CRC; 3.) To determine if tumorigenic effects of age related senescence mediate the increased risk of polyp→CRC transformation.

Grants Management Specialist: Samantha Ann Farrell; farrellsa@mail.nih.gov.

1R01CA189184-01A1 (Li, Ulrich) 05/01/15 - 04/30/20 0.19 cal mos
NIH NCI \$744,585

Discovery and Verification of Novel Biomarkers of Colorectal Cancer Recurrence

This study is specifically designed to meet the overarching goal of discovery and verification of novel blood-based biomarkers predictive of recurrence among CRC patients, through achieving the following specific aims: 1.) Discovery and verification of novel biomarkers predictive of recurrence among CRC patients; and 2.) Discovery and verification of novel biomarkers useful for the early detection of CRC recurrence.

Grants Management Specialist: Bryann E. Benton, National Cancer Institute, BG 9609 Rm 2W514, 9609 Medical Center Dr., Rockville, MD 20850, bentonb@mail.nih.gov, 240-276-5863.

CA140616 (Burnett-Hartman) 08/01/15 - 07/31/18 0.24 cal mos
DoD/CDMRP (Prime: Kaiser Permanente of Colorado) \$11,341 (subaward - Grady)

The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

The primary objective of this career development award is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated polyps.

Sponsored Programs Administrator : Judy Hayes, CRA. , Kaiser Permanente. Judy.R.Hayes@kp.org

5P30CA015704-40 (Gilliland) 01/01/97 - 12/31/19
NIH NCI \$3,162,851

Pilot Project (Grady, Grim) 12/15/15- 12/14/16 0.12 cal mos
(concurrent) \$75,000

Development of Intestinal Organoids Culture Systems to Study the Pathogenesis of Colorectal Cancer

Specific aims: Aim 1.) Establish colon organoid cultures from primary mouse and human colon epithelium; Aim 2.) Perform genome editing using CRISPR/Cas9 on immortalized human colon epithelial cells to introduce CRC relevant gene mutations; Aim 3.) Use CRISPR/Cas9 genome editing in colon organoid cultures to introduce CRC relevant gene mutations into primary colon cells.

Grants Management Specialist: Gerard B. McCann; mccannge@mail.nih.gov.

DeGregorio Family Foundation (Grady) 03/01/16 - 02/28/18 0.12 calendar
DeGregorio Family Foundation \$81,000

Epigenetic Drift in Barrett's Esophagus as a Novel Risk Marker for Esophageal Adenocarcinoma

This study will determine whether recently identified epigenetic "biological clock" biomarkers can be used to more precisely 'date' the age of BE tissue and refine current EAC risk estimates based on multiscale modeling, which can improve our understanding of the pathogenesis of EAC and ability to detect EAC at an early stage. Specific Aim: To determine if tissue age progresses differentially between normal and BE tissue using established markers of age-related epigenetic drift and to determine if the "biological age" of BE (expressed as effective BE dwell time) can be used as a risk marker for progression to EAC.

Grant Administrator: Lynn DeGregorio, lynn@degregorio.org

2U01CA152756-06 (Grady, Markowitz) 05/13/2016- 03/31/2021 1.2 cal mos
NIH NCI \$792,202

Biomarkers for Reducing Mortality of Cancers of the Colon and Esophagus

The goal of this EDRN renewal proposal is the discovery and validation of i) biomarkers of increased risk of gastrointestinal cancers, and ii) biomarkers for the early detection of gastrointestinal malignancies. We particularly target cancers of the colon, that are the second leading cause of cancer deaths in the U.S., and adenocarcinomas of the esophagus, that are the fastest increasing cause of cancer deaths, with a 7-fold increased incidence over the last 3 decades, and with a 90% lethality rate.

Grant Administrator, John Poundardjian, Case Gastrointestinal Cancers SPORE, and Cancer Research Laboratory, hxp125@case.edu

STTR- Team Grant 07/01/2016-06/30/2017 0.24 cal mos
FHCRC/various \$176,000

Development of Simultaneous Multiple Interaction T-cell Engaging (SMITE) Antibodies for the Treatment of Colorectal Cancer

We propose to develop novel BiTE derivatives that will activate T-cell signaling to overcome this resistance

mechanism, enhancing the potency of BiTE antibodies, and to apply these to the treatment of CRC.

Raquel Sanchez, Division Administrator, STTR , rsanchez@fredhutch.org

PENDING

1U01CA204809-01 (Luebeck, Grady, Inadomi) 04/01/17 - 03/31/22 1.2 cal mos
NIH NCI \$757,431

Multiscale Study of Tissue Aging, Field Cancerization, and Colorectal Screening

The goals of the proposed research are to: 1.) Determine epigenetic signatures of tissue aging and field-cancerization and their impact on the risk of developing colorectal neoplasia, 2.) Use the normal and (pre)neoplastic tissue characterizations from Aim 1 and population level data to inform a multiscale model of polyp formation and progression to CRC and 3.) Optimize population screening for CRC prevention through targeting of high-risk individuals.

1R21CA209203-01 (McTiernan) 04/01/2017-03/31/2019 0.6 cal mos
NIH \$150,000

Exercise Effects in Men & Women on Colon DNA Methylation

This project will investigate the effects of physical activity on colon DNA methylation in genes related to colon cancer. Excessive DNA methylation is thought to be a risk factor for colon cancer, and no previous study has tested the effect of exercise on DNA methylation in the colon. The project includes 202 initially sedentary men and women who have already completed the trial from which colon samples will be used. Specific aim: to investigate the effects of a 12-month exercise program on sigmoid colon DNA methylation of 4 candidate genes that have been related to colon cancer risk: *EVL*, *MGMT*, *p14*, and *ESR1*.

R21 CA205993-01A1 (Shibata) 03/01/2017-02/28/2019 0.24 cal mos
USC subaward \$151,200 (Grady subaward)

Stem Cell Mutation Burdens and Numbers Explain Cancer Risks in the Human Intestine

Dr. Grady and appropriate staff will grow sufficient numbers of organoids derived from human intestines to supply this R21 effort. Needed are 63 organoids consisting of 6 organoids from each of 7 individuals at three sites (small intestine, proximal colon, and distal colon). The organoids will be shipped frozen to Dr. Shibata. Dr. Grady will provide clinical data relevant to the organoid cultures sent to Dr. Shibata.

R01 (Bowen) 04/01/2017-03/31/2021
NIH \$82,748 (Grady subaward)

CRC Screening in Diverse Families

Dr. Grady will review all materials and data collection instruments to be appropriate and relevant for families with a case of colorectal cancer, both high and low risk families. He will review in particular the intervention protocols for clinical relevance and appropriateness, and will provide expertise in genetic and genomic risk and patient advice. He will assist with all queries from families at high risk for CRC in the study.

5U54 (Chak, Grady, Markowitz) 04/01/2017-03/31/22 0.84 cal mos
NIH/NCI (CWRU prime) \$144,805 (subaward - Grady)

Genetic Determinants of Barrett's Esophagus and Esophageal Adenocarcinoma

Prospectively collected Surveillance Epidemiology and End Results (SEER) data indicate that the incidence of esophageal adenocarcinoma (EAC) has increased more than 5-fold in the past three decades. Over 10,000 cases are now diagnosed annually. The prognosis for patients with EAC is poor with less than 20% of patients surviving beyond 5 years. In the proposed studies, we will identify and evaluate detection biomarkers for Barretts esophagus, a precancerous condition for EAC. The detection biomarkers can be used in non-invasive assays for detecting people who have Barretts esophagus. These people can then be placed in surveillance programs in order to prevent them from getting EAC.

OVERLAP

None

COMPLETED (WITHIN THE PAST 5 YEARS)

5U01CA152756-05 (Grady, Markowitz) 08/25/10 - 06/30/16 **** 1.8 calendar

NIH NCI	\$6,000 (no-cost extension)	(concurrent)
3U01CA152756-05S1	\$142,300	

Identify and Validate Novel Epigenetic Molecular Markers for Colorectal Neoplasm

We propose to create a Research Team to lead an EDNRN Biomarker Developmental Lab to discover novel methylated genes using cutting-edge and complementary approaches, HumanMethylation27 DNA Analysis Beadchip (Illumina Infinium platform), and deep sequencing of captured NaHSO3 treated DNA (Agilent and Solexa). The specific aims are: 1.) To develop and validate epigenetic signatures of colon adenomas and early stage non-metastatic colon cancers; 2.) To perform a comprehensive epigenomic characterization of colorectal cancer molecular subtypes (stages I-III, n=1536); 3.) To identify and characterize biologically relevant novel methylation targets in colorectal cancer.

5U54CA163060-05 (Chak, Grady, Markowitz, Shaheen)	
NIH NCI	09/26/11 - 08/31/16

CWRU (prime)	\$707,866
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Genetic Determinants of Barrett’s Esophagus and Esophageal Adenocarcinoma

The overall objectives of this BETRNet Translational Research Center (TRC-F) are: 1.) to conduct a rigorous, integrated spectrum of transdisciplinary human research in Barrett’s esophagus (BE) and esophageal adenocarcinoma (EAC); 2.) to increase the biological understanding of key observations made by our clinical researchers (familial aggregation of BE and EAC, restitution of squamous mucosa after ablation); 3.) to translate knowledge derived from genetic and physiologic research to solving clinical dilemmas in detection, prognosis, and therapy of BE in order to prevent EAC and improve the outcomes of EAC; 4.) to foster a transdisciplinary and translational research culture and to effectively expand and enhance scientific research focused on BE and EAC; 5.) to evaluate research and transdisciplinary programs and to continuously improve research, productivity and enhance translational implementation.

Sub-project i.d. # 5418 (Grady, PL)	\$75,470 (subaward)	1.2 calendar **
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Project 2: The Biology and Translation of Epigenetic Alterations in Barrett’s Esophagus
(concurrent)

Specific Aims: 1.) To characterize the genome wide methylation status of BE, BE+LGD, BE+HGD, and EAC and to correlate the methylation status with clinicopathological features of the patients; 2.) To determine the methylome of familial vs. sporadic BE and EAC cases and determine if familial cases differ from sporadic cases based on the methylation status of the BE and EAC; 3.) To determine whether methylated genes can be used as detection molecular markers for the identification of people with BE using Cytosponge esophageal brushings; 4.) To determine if methylated genes can be used for the prediction of recurrent BE in Barretts esophagus patients after Radiofrequency Ablation (RFA).

5U01CA163304-04 (Barlow, Thornquist)	09/19/11 - 08/31/16	effort: 3.8% (0.46 calendar)
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NIH NCI	\$918,341	effort: not measurable after 1/31/15
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PROSPR Statistical Coordinating Center (PSCC)

The goal of the PROSPR Statistical Coordinating Center (PSCC) is to coordinate the research of PROSPR Research Centers (PRCs) to achieve PROSPR’s mission of evaluating and improving the cancer screening process (recruitment, screening, diagnosis, and referral for treatment).

Grants Management Specialist: Renee Carruthers; carruthersr@mail.nih.gov.

5U54CA143682-05 (Davies)	09/30/09 - 08/31/14	effort: 5% (0.6 calendar)
NIH NCI / ASU		

A Center for the Convergence of Physical Science and Cancer Biology

Core 2 – Materials Core (Grady)

\$69,476 (FHCRC subaward)

A center for studying physical characteristics of cancer cells, including nuclear and cytoplasmic membrane elasticity using single cell computed tomography, and chromatin structure using atomic force measurements, will be developed to gain new understandings of the physical properties of cells that may be used to therapeutic or diagnostic advantage.

5P01CA077852-15 (Monnat)

07/01/09 - 06/30/14

effort: 2.5% (0.3 calendar)

NIH NCI

Human RecQ Helicases in Biology and Oncology

Project 5: Human Tumor Analysis (Grady)

\$29,639

The goal of this project is to assess the role of RecQ helicases in colon cancer. The specific aims are: 1.) To determine the frequency of loss of expression and epigenetic inactivation of Rec Q helicases in two of the most common epithelial cancers that occur in the US: colorectal cancer and breast cancer; 2.) To determine the role of WRN, BLM, and RECQL4 inactivation and RECQ helicase interacting proteins in modifying the effect of chemotherapy on colorectal cancers (CRC); 3.) To determine the role of WRN, BLM, and RECQL4 inactivation and RECQ helicase interacting proteins in modulating the effect of chemotherapy on breast cancers (BrCA).

5P30CA015704-38 (Corey)

01/01/09 - 12/31/14

NIH NCI

\$6,651,621

Cancer Center Support Grant

Pilot Project (Grady)

04/01/11 - 12/31/12

effort: 2% (0.24 calendar) *

\$9,991 (no-cost extension)

Novel Forward Genetic Screen for Functional Colon Cancer Genes: Development of Analysis Techniques

The studies in this project employ an innovative forward genetic screen using the Sleeping Beauty (SB) transposon mouse model to identify novel genes that cooperate with TGFBR2 inactivation to affect CRC formation. This novel mouse model system uses the cre-lox system to direct mutagenesis events to the tissue of interest (e.g. colon) and thus limits confounding events caused by tumors arising in unrelated tissues. In order to identify the novel genes that arise in this system, we will establish a new method for integration site analysis using next generation sequencing (Illumina HiSeq 2000 System, Genomics Shared Resource). The Specific Aim of this proposal is as follows: To develop a high throughput method for identifying novel genes that cooperate with TGF- β signaling inactivation to effect CRC formation in the SB Transposon mouse model, which is a forward genetic screen.

5U24CA074794-14 (Newcomb)

09/22/08 - 08/31/12

NIH NCI

effort: 5% (0.6 calendar)

\$988,842

The Colon Cancer Family Registry: Seattle

The Colon Cancer Family Registry - Seattle (CCFR -S), a center within the multinational six-site Colon CFR consortium, is a population-based resource for studies of the genetics and genetic epidemiology of colorectal cancer. Activities for this period (Phase III) will include: expanding accrual of the cohort, conducting follow-up with existing cohort members, continued biospecimen collection and processing, and provision of data and samples to CCFR-approved research projects.

5R01CA115513-05 (Grady)

01/01/07 - 06/30/12

calendar)

effort: 18.75% (2.25

NIH NCI

\$196,854 (no-cost extension)

TGF-Beta Signaling and Colon Cancer

This research will address how *TGFBR2* and its inactivation paradoxically affect central biological behaviors of cancer, cell proliferation and apoptosis, and will elucidate the signaling pathways and downstream proteins that regulate these events in both *in vitro* and *in vivo* systems. The specific aims are: 1.) To determine the effect of TGF- β signaling pathway inactivation in the setting of Apc mutation and Wnt signaling activation on intestinal cancer formation; 2.) To determine if TGF- β signaling pathway inactivation cooperates with Kras2 mutation and Ras-Raf pathway activation in intestinal cancer formation; 3.) To determine the *in vivo* consequences of TGFBR2 inactivation on colon cancer initiation and progression using novel mouse models of intestinal cancer that genetically recapitulate human colon cancer, Apc1638N;LSL-Kras2G12D;Tgfbr2IEKO, and Apc1638N;LSL-Trp53R172H;Tgfbr2IEKO mice.

CRA (Grady) 07/01/08 - 06/30/12 effort: 2% (0.24 calendar)
Takeda Pharmaceuticals North America, Inc \$56,004 (no-cost extension)

Epigenetic Alterations in Barrett's Epithelium and Esophageal Adenocarcinoma

The specific aims of this grant are: 1.) To identify novel methylated loci involved in the initiation and progression of Barrett's esophagus through the use of genome-wide methylation studies using "methylation" arrays; and 2.) To identify a panel of methylated genes that discriminates BE, BE+HGD, and EAC and to determine the potential of these genes to be used as predictive biomarkers for BE progression.