

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

REPORT DATE: August 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE Aug 2018		2. REPORT TYPE Annual		3. DATES COVERED 1 Aug 2017 - 31 July 2018	
4. TITLE AND SUBTITLE The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-1-0273	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Andrea Burnett-Hartman Email: Andrea.N.Burnett-Hartman@kp.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Kaiser Foundation Research Institute 1800 Harrison St. 16 th Floor Oakland, CA 94612-3429				8. PERFORMING ORGANIZATION REPORT	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
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 years 1-2: 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 methylation markers were optimized, tissue slide and block pulling and the standard pathology reviews were completed, data cleaning of the pathology review data was finished and analyses of the pathology data was completed, tissue sectioning and DNA extraction was completed on all samples, molecular marker methylation testing was conducted on all samples, and data cleaning of molecular marker methylation testing was 90% completed. Also, Dr. Burnett-Hartman participated in regular career development opportunities, including attending clinical research seminars, presenting at national and local research meetings, and continued to connect with new clinical partners at Kaiser Permanente Colorado and the University of 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					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES 24	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)
			Unclassified	2 4	

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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 identified 265 patients with either an incident colorectal cancer diagnosis or a follow-up colonoscopy at least 6 months after the index colonoscopy at which we assessed the presence or absence of colorectal neoplasia. For these 265 study participants, we were able to locate clinical tissue blocks from the index colonoscopy of on 248 individuals. A standardized pathology review was completed on all biopsies from the index colonoscopy to confirm the SSP diagnosis, assess the presence of cytological dysplasia in the index SSPs, and assess the presence of other types of polyps or colorectal cancer at index colonoscopy.

We excluded 34 individuals who the study pathologist determined did not have an SSP at index colonoscopy and 8 people that had a synchronous or prior colorectal cancer. Thus, 206 individuals (14 with SSPs harboring nuclear dysplasia and 192 with SSPs without nuclear dysplasia) were included in our analyses of the association between index SSP nuclear dysplasia and subsequent colorectal neoplasia. We conducted a standard pathology review of biopsies and pathology reports from subsequent colonoscopies on these 206 individuals and determined that: 14 had incident colorectal cancer diagnoses, 112 had subsequent SSP or conventional adenomas, and 90 had no subsequent colorectal polyps or cancer. We used logistic regression to estimate Odds Ratios (ORs) and 95% confidence intervals (Cis) comparing the risk of colorectal cancer and other colorectal neoplasia between individuals harboring SSP with nuclear dysplasia to those with SSP without nuclear dysplasia.

There was no association between the presence of nuclear dysplasia in SSPs and colorectal cancer risk (OR = 1.06; CI: 0.13 -8.74), nor was there an association between nuclear dysplasia and risk of subsequent SSP or conventional adenomas (OR = 1.41; CI: 0.45-4.49). This suggests that nuclear dysplasia in SSPs may not be a good predictor of colorectal cancer risk for individuals with SSPs that have been removed at endoscopy.

For our second aim, we are assessing if molecular testing of index SSPs for CIMP and methylation of specific candidate genes can help predict which individuals with SSPs removed at endoscopy are at the highest risk for subsequent colorectal cancer or other colorectal neoplasia. 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 has continued to make progress towards accomplishing the primary study aims in Year 3. She also participated in all planned career development activities during the first 3 years of this award. Note, the table below shows goals and milestones for the entire project period, including goals and milestones that are planned for the no-cost extension period of this project.

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	2/1/17	100%	We originally planned to pull all slides and blocks at once. However, Northwest Biotrust worked with Dr. Upton to pull batches as Dr. Upton reviews them.
Standard Pathology review of 300 patients	7/1/16	4/1/17	100%	Dr. Upton begun pathology review later than expected due to changes in her office space; she has now completed path review.
Data cleaning of pathology data	9/1/16	6/1/17	100%	

Complete data analysis of pathology data using STATA and summarize data in tables, figures, and graphs	2/1/17	12/1/17	100%	Completion of pathology review was delayed due to changes in the pathologist work space and schedule; analysis of path review data expected 10/1/17; Dr. Burnett-Hartman will summarize pathology results with molecular marker test results once the molecular marker analyses are complete.
Preparation, submission, and presentation of abstract on pathology data for national meeting	8/1/17		0%	Dr. Burnett-Hartman now plans to submit an abstract that includes both the pathology and molecular marker test results; new target date is 1/1/19, following completion of the molecular marker analyses.
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	Dr. Burnett-Hartman now plans to prepare a manuscript that includes both the pathology and molecular marker test results; new target date is 7/1/19.
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	12/1/18	100%	This activity was delayed, because path review needed to be complete before tissue sectioning, but this is now complete.
Polyp tissue DNA extraction and quantification for 300 samples	12/1/16	3/1/18	100%	Samples are being extracted as sectioning is complete for each batch; new target date 11/1/17
Methylite PCR Assay for 300 Samples, including quality control procedures (i.e. <i>ALU</i> control and 5% blind replication sample)	8/1/17	5/31/18	100%	Testing is now complete and included 296 unique samples.

Data cleaning of CIMP and candidate gene methylation data	9/1/17		80%	New expected completion date is 9/15/18
Complete data analysis of methylation data using STATA and summarize data in tables, figures, and graphs	12/1/17		0%	New target date is 12/1/18
Preparation and submission, and presentation of abstract for national meeting	5/1/18		0%	Dr. Burnett-Hartman now plans to submit an abstract that includes both the pathology and molecular marker test results; new target date is 1/1/19, following completion of the molecular marker analyses.
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	Dr. Burnett-Hartman now plans to prepare a manuscript that includes both the pathology and molecular marker test results; new target date is 7/1/19.
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 2 (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 and presented at clinical research meetings (See additional information under career development activities).
Attend the American Society for Clinical Oncology GI Symposium and workshops	3/1/17	2/1/18	100%	The ASCO GI meeting was January 2018; Dr. Burnett-Hartman attended this meeting and presented finding from her research.
Attend and present study findings at Digestive Disease Week (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	6/15/18	100%	The DDW was June 2018, Dr. Burnett-Hartman attended this meeting and presented finding from her research; Dr. Burnett-Hartman will attend 1 more national meeting

				during the NCE period and present results from this study by 7/31/19
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What was accomplished under these goals?

As detailed in the table above, during years 1-3, 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. Optimized the methylation assay for DNA methylation markers
6. Completed tissue slide and block pulling
7. Completed standard pathology review
8. Completed data cleaning for path review data and analysis of path review data
9. Completed DNA tissue sectioning and DNA extraction
10. Completed molecular marker DNA methylation assays and began cleaning the molecular marker data

The following goals/objectives, had planned completion dates during year 3. However, due to an unanticipated delay in beginning pathology review as a result of renovations in the study pathologist's work space and changed work schedules for histopathology, the project's subsequent steps were behind. The following project objectives are currently behind schedule:

1. Completing cleaning and analysis of polyp molecular marker data
2. Submission of, and presenting an abstract of results from this project, at a national meeting
3. Completion of the manuscript summarizing studying findings

These activities will be completed during the NCE period of this project.

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

1. **Training in clinical cancer research through seminars** – During Years 1-3 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 or 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 over 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. I also collaborated on 5 new successfully funded grant applications or contracts during years 1-3 of this award. These include an NIH-funded project on Lynch Syndrome and a Garfield foundation-funded project on precision medicine, and 2 NIH-funded projects on cancer screening, and 1 collaborative project with NIH to build a national

cohort aimed at studying cancer prevention. I also worked on 2 additional grant applications, 1 of which was not funded; the other builds on and expands the work completed under this application, and it will be submitted to National Cancer Institute in November 2018. I have maintained connections with new potential collaborators in clinical cancer research, including Dr. Mark Powis in Kaiser Gastroenterology and Dr. Alex Mentor in Kaiser Oncology, and Dr. Scott Kono in Kaiser Oncology. I made new collaborations with clinical researchers at the University of Colorado, in year 3, including: Dr. Adriaan Van Bokhoven, a pathologist, and Dr. Greg Austin, a gastroenterologist. I also continue to serve on the KP Colorado Colorectal Cancer Quality Council.

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), and Health Care Systems Research Network (Atlanta, GA, April 2016). In Year 2, I attended and presented at: The American Association for Cancer Research Colorectal Cancer Symposium (Tampa, FL, September 2016), American Society for Preventive Oncology (Seattle, WA, March 2017), and Health Care Systems Research Network (San Diego, CA, March 2017). In Year 3, I attended and presented at: The ASCO Gastrointestinal Cancer Symposium (San Francisco, CA, January 2018) and Digestive Disease Week (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) (Washington DC, June 2018).

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 analysis of the molecular marker data to determine the association between molecular DNA methylation markers in sessile serrated polyps and colorectal cancer and advance colorectal polyp risk (Aim 2)
2. Submit an abstract of our findings for presentation at a national clinical research meeting
3. Develop a manuscript summarizing the results of Aims 1 and 2
4. 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 cleaning and analyzing data on molecular marker DNA methylation tests; 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:	Andrea Burnett-Hartman
Project Role:	Principle Investigator
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, her mentor, Dr. Grady, and study pathologist, Dr. Upton.

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 used to assess the polyp DNA was conducted at Fred Hutch, as was the DNA and methylation analyses that were completed in Year 3. 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:** Years 1-3 total funds committed \$100,378; \$100,378 spent; \$0 balance remaining.
- **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 was completed under the direction of the Grady Lab at the Fred Hutchinson Cancer Research Center.
- **Collaboration:** Dr. Burnett-Hartman worked closely with Dr. William Grady on study design, selection of the relevant methylation markers, and assay development in Years 1 and 2 and completion of methylation testing in Year 3. 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:** Years 1-3 total funds committed \$53,757; \$53,757 spent; \$0 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 used Northwest Biotrust to pull relevant tissues slides and blocks; Dr. Upton, anatomic pathologists at the University of Washington reviewed these slides and blocks in a designated office equipped with a high-powered digital microscope.
- **Collaboration** Dr. Burnett-Hartman worked closely with Dr. Melissa Upton to develop the pathology review form and Dr. Upton used that form to review index H&E slides to confirm the sessile serrated polyp diagnosis and characterize nuclear dysplasia within the polyp tissue samples. She also reviewed biopsies and pathology report data from subsequent endoscopies.
- **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 IV: Research Support for Dr. Upton

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

Slide	Code (see above) & Confidence (0-100)		Comments	% Lesional	Tangential Orientation	Nuclear Dysplasia	Abnormal Crypts	
							#	%
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		
	____	____			☐ Yes ☐ No	☐ Yes-LGD ☐ Yes-HGD ☐ No		

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

BURNETT-HARTMAN, ANDREA N.

EXISTING SUPPORT (As of 08/29/2018)

R01 CA 168338 (Newcomb) 04/22/13 – 3/31/19 0.60 calendar
NIH/CA

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.

Contracting Officer: Ester Young, National Cancer Institute, Office of Grants Administration, BG 9609
9609 Medical Center Drive, Rockville, MD 20892-9760

RNG000511 (Feigelson) 01/15/17 – 12/31/18 2.76 calendar
Kaiser Foundation Program Office
Kaiser National Biobank

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

(This Award)
W81XWH-15-1-0273 (Burnett-Hartman) 08/01/15 – 08/31/19 (NCE) 2.40 calendar
DOD/CDMRP

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

R01 CA179906 (Newcomb) 05/01/15 – 04/30/2020 0.12 calendar
NIH/NCI

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: National Cancer Institute, Office of Grants Administration, BG 9609
9609 Medical Center Drive, Rockville, MD 20892-9760

CDRN-1306-04681 (McGlynn) 10/01/16 – 3/30/19 0.42 calendar
PCORI

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: Scott Solomon, Director of Contracts Management and Administration, 1828 L Street NW, Suite 900, Washington, DC 20036

RNG209101 (McGlynn) 2/15/17 – 12/31/18 1.80 calendar
Garfield Memorial Foundation

Kaiser Permanente Medicine Assessment and Response

The primary objectives of this project are to identify attitudes, barriers, and facilitators to returning research-derived genomic information among KP members and enable the development of robust, stakeholder-informed return of research-derived genomic testing results policies and procedures.

Contracting Officer: Edward Thomas, Director, Garfield Memorial Fund, One Kaiser Plaza, Oakland, CA 94612

RO1 CA 211723 (Rahm) 8/1/17 – 7/31/22 0.60 calendar
NIH/NCI

Implementing Universal Lynch Syndrome Screening across Multiple HealthCare Systems: Identifying Strategies to Facilitate and Maintain Programs in Different Organizational Contexts

This project seeks to identify strategies that are important to implementing and sustaining Universal Lynch Syndrome screening programs in different healthcare systems and moves health systems towards implementing tailored prevention strategies.

Contracting Officer: Justin Birken, Grants Management Specialist, 9609 Medical Center Drive, West Tower 2nd floor, Rockville, MD 20850

U24 CA 221936 (Li) 4/15/18 – 3/31/23 0.90 calendar
NIH/NIC

Coordinating Center for Population-based to Optimize Cancer Screening (PROSPR) (U24)

The goal of the PROSPR Coordinating Center (PCC) 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: Dianna N. Bailey, Grants Management Specialist, Grants Management Specialist, 9609 Medical Center Drive, West Tower 2nd floor, Rockville, MD 20850

UM1 CA 221939 (Ritzwoller/Doubeni) 4/15/18 – 3/31/23 2.40 calendar
NIH/NCI

Center for Research to Optimize Precision Lung Cancer Screening in Diverse Populations
PROSPR II Lung

The long-term goal of this multi-site center grant is to identify critical gaps in the lung cancer screening process and to design innovative, multilevel interventions to reduce lung cancer mortality, particularly among underserved populations.

Contracting Officer: Dianna N. Bailey, Grants Management Specialist, Grants Management Specialist, 9609 Medical Center Drive, West Tower 2nd floor, Rockville, MD 20850

PENDING

None

PREVIOUS SUPPORT

U24CA171524 (Kushi) 09/25/15 – 8/31/18 (NCE) 1.44 calendar
NIH/NCI

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

NIH U01CA163304 (Co-PIs: Feng/Barlow) 09/20/11 – 08/31/17 0.10 calendar
NIH/NCI

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

R03 CA186215 (Burnett-Hartman) 04/04/14 – 03/31/17 0.96 calendar
NCI

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

KL2 TR000421 (Disis) 06/01/12 – 01/05/15 9.00 calendar
NIH/NCATS

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 calendar
NIH/NCI

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 calendar

NIH/NCI

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 calendar

NIH/NCI

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

None

APPENDIX III: EXISTING/PENDING/PREVIOUS SUPPORT – GRADY

GRADY, WILLIAM M.

EXISTING SUPPORT

Institutional Funds (Grady) required	02/01/07 - ongoing	Effort: not
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University of Washington
Rodger C. Haggitt Endowed Chair in Gastroenterology Research

\$ variable

Donation (Grady) required	09/01/14 - 08/31/19	Effort: not
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Mercer Island Rotary

These funds support biomarker research in the Grady lab.
Award Administrator: Nural Booth, norgun@fredhutch.org.

Restricted donation (Grady) required	09/01/14 - 10/31/19	Effort: not
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Cottrell T	\$83,997 (no-cost extension)
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These funds support research in the Grady lab.
Award Administrator: Angela Bush, abush@fredhutch.org.

Institutional Support (Grady) required	05/01/13 - 04/30/19	Effort: not
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FHCRC / Listwin Family Foundation

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.

Institutional Support (Grady) required	07/01/14 - 06/30/19	Effort: not
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FHCRC

ColoCare Study

The objectives of this study are to identify factors that determine both short-term and long-term survival in a prospective cohort of colorectal cancer patients.

Award Administrator: Doug Lowe, MS, MBA, Division Fiscal Administrator, Clinical Research Division;
dlowe@fredhutch.org.

2P30CA015704-40 (Gilliland)	01/01/97 - 12/31/19	1.2 CM
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NIH NCI

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.

5P30CA015704-40 (Gilliland)
Pilot Project (Grady, Grim)

01/01/97 - 12/31/19
12/15/15- 12/14/17

0.12 CM

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.

1R01CA194663-01 (Grady)
NIH NCI

04/14/15 - 03/31/19

1.2 CM

(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; samanthal.farrell@mail.nih.gov.

1R01CA189184-01A1 (Li, Ulrich)
NIH NCI

05/01/15 - 04/30/20

0.19 CM

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.

CA140616 (Burnett-Hartman)
DoD/CDMRP (Prime: Kaiser Permanente of Colorado)

08/01/15 - 07/31/18

0.24 CM

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

DeGregorio Family Foundation (Grady)
DeGregorio Family Foundation

03/01/16 - 02/28/18

0.12 CM

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.

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

2U01CA152756 (Grady, Markowitz)
NIH NCI (EDRN prime)

05/13/2016- 03/31/21

1.2 CM

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.

Suzanne Morris, Department Administrator, Case Gastrointestinal Cancers SPORE, 216-368-1976, sxm1068@case.edu

STTR – Program Infrastructure Grant
FHCRC/various

07/01/16-06/30/19

0.12 CM

STTR CRC Team Grant

We propose to generate and characterize CRC PDX tumors that can then be used in studies of novel therapeutics and studies of the molecular and cell biology of CRC.

Award Administrator: Rachel Galbraith, Program Administrator, Solid Tumor TransRes, 206-667-5183, rgalbrai@fredhutch.org

R21 CA209203 (McTiernan)
CM
NIH

04/01/17 – 03/31/19

0.6

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.

Award administrator: Sarah M. Lee, Grants Management specialist, 240-276-6280, SARAH.LEE@nih.gov

5U54CA163060 (Chak, Grady, Markowitz)
NCI (CWRU prime)

04/01/17-03/31/22

1.2 CM NIH/

Genetic Determinants of Barrett’s Esophagus and Esophageal Adenocarcinoma

In the proposed studies, we will identify and evaluate detection biomarkers for Barrett’s esophagus, a precancerous condition for EAC. The detection biomarkers can be used in non-invasive assays for detecting people who have Barrett’s esophagus. These people can then be placed in surveillance programs in order to prevent them from getting EAC.

Award Administrator: Alicia DePlatchett, Department Administrator, alicia.deplatchett@case.edu.

PQ6R01R01CA220004 (Grady)
NIH/University of Wisconsin

09/21/17-08/31/22

1.2 CM

Radiogenomics of colorectal polyps to assess benign proliferative vs. premalignant states.

This project will have the potential to identify factors that affect the progression of polyps to CRC and will provide insight into different mechanisms of clonal evolution of colon adenomas and their role in malignant transformation. Program Official: Matthew Young, 240-276-9790, youngma@mail.nih.gov

PENDING

U01CA238717 (Luebeck, Grady, Hullar, Inadomi)

04/01/19-03/31/24

1.2 CM

NIH/NCI

The impact of microbiome and methylome on colorectal tissue aging and cancer

This proposal seeks to develop a quantitative and predictive systems biology for colorectal cancer (CRC) and its precursors (polyps) to identify specific components in host-microbiome-methylome ecologies in colorectal tissues that segregate high- from low-risk individuals for polyp formation and influence the molecular pathogenesis of colorectal cancer.

Program Official: Shannon Hughes, 240-276-6224, shannon.hughes@nih.gov

R01CA238911 (Grady)

04/01/19-03/31/24

1.2 CM

NIH/NCI

Epigenetic pre-malignant fields in the colon and risk of colorectal polyps and cancer in Lynch syndrome

This study will use a unique bank of Lynch Syndrome (LS) colon samples and primary colon organoid lines to conduct innovative studies assessing mechanisms affecting colorectal cancer variance in LS.

Program Official: Okano, Paul, 240-276-6250, [http://po8k@nih.gov](mailto:po8k@nih.gov)

OVERLAP

None

APPENDIX IV: EXISTING/PENDING/PREVIOUS SUPPORT – UPTON

UPTON, MELISSA P.

EXISTING SUPPORT

W81XWH-15-1-0273 (Burnett-Hartman)

08/01/15 –07/31/18

0.24 calendar

DOD/CDMRP

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

PENDING: None

PREVIOUS SUPPORT

FFPE Validation of a Survival Gene Signature in HPV-Negative Oral Cavity Cancer

12/1/14 – 12/31/17

0.60 calendar

NIH/NCI (1 R01 CA177736-01A1) Chen, Chu, PI

Project Description: Oral cancer is a substantial global health burden, with an estimated 529,000 new cases and 292,000 deaths occurred in 2012. The results of this study have the potential to create, for the first time, a rapid, reliable, and cost-effective formalin-fixed, paraffin-embedded tumor based assay to improve the prediction of survival of human papillomavirus-negative oral cavity cancer patients and help physicians and patients to make timely, personalized treatment choices.

Role: Co-Investigator

Sponsor Contact: Chu Chen, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, cchen@fhcrc.org.

Needle biopsy preservation and preparation for rapid 3D pathology of pancreas

8/14/2014 – 8/31/16

0.36 calendar NIH

(1 R21 CA186791-01) Seibel, Eric PI

Project Description: The goal of this project is to reduce the time for biopsy tissue preparation to less than half the standard time in a pathology lab. Furthermore the 3D architecture of the tissue will be preserved for the first opto-mechanical measures of biopsy intactness. The diagnostic value of the needle biopsy specimens after automated preparation will be determined by experienced pathologists. The ability to visualize 3D morphology within tissue biopsies will also allow the pathologists to better compare ex vivo diagnosis with new in vivo 3D imaging technologies, such as confocal, optical coherence tomography, and photoacoustic imaging. This project is expected to lead to a transformation in pathology from 2D to 3D, and in the ability to provide less invasive, low-cost and rapid cancer diagnosis, directly affecting several millions of US citizens per year.

Role: Co-Investigator

Sponsor Contact: Eric Seibel, PhD., Human Photonics Laboratory, University of Washington, Box 352600, Seattle, WA 98195, eseibel@uw.edu.

Esophageal Cancer from Cells to Population: A Multiscale Approach

9/1/2013 – 6/30/2016

0.48 calendar

NCI/FHCRC (Sub-award# 0000813441) Inadomi, John

Project Description: 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 endoscopic imaging and advanced epigenetic profiling of neoplastic tissues in combination with standard endoscopic techniques

Role: Co-Investigator

Sponsor Contact: John Inadomi, PhD., Division of Gastroenterology, University of Washington, Box 356424, Seattle, WA 98195, jinadomi@medicine.washington.edu.

Colon Cancer Biomarkers

8/16/2010 – 6/30/2015

0.12 calendar

FHCRC (Sub-award# 0000748868) Lampe, Paul, PI

Project Description: Affinity based strategies to fast track development of colon cancer biomarkers. The proposed research involves the discovery of early detection and diagnostic biomarkers of colon cancer using high density antibody microarrays as part of the Early Detection Research Network.

Role: Co-Investigator

Sponsor Contact: Paul Lampe PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, plampe@fhcrc.org.

GI Service Center

7/1/2012 –

1.20 calendar

6/30/2015 University of Washington

Project Description: Dr. Upton serves as the GI Pathology Medical Director.

Integrated Genomic Approach for Therapeutic Target Selection in Oral Cancer

1/1/2014 – 12/31/2014

0.12 calendar

FHCRC (Sub-award#0000764374) Mendez, Eduardo, PI

Project Description: The aims for the proposed study are to validate the usefulness of markers by testing the respective markers for invasive cancer, metastasis, and survival of OSCC patients for their predictive abilities for clinical outcomes of OSCC using previously collected but not yet tested tissue samples and data and new samples and data to be collected in year 1 of the proposed study.

Role: Co-Investigator

Sponsor Contact: Eduardo Mendez PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:D5-390, PO Box 19024, Seattle, WA 98109-1024, edmendez@uw.edu.

A New Integrated Endoscope System

7/1/2011 – 6/30/2014

0.34 calendar NIH

(5 R01 EB 07636-04) Lin, Lih-yuan, PI

Project Description: The objective of this project is to develop and validate a new generation of scanning fiber-optic endoscopes and molecular contrast agents for improving early detection of cancer in luminal organs.

Role: Co-Investigator

Sponsor Contact: Lih-yuan Lin, PhD., M414 EE1 Bldg., 185 Stevens Way, University of Washington, Seattle, WA, 98195-2500, lylin@uw.edu.

Complete 3D Imaging of Needle Biopsy to Diagnose Pancreatic Cancer

3/15/2012 – 2/28/2014

0.24 calendar NSF

(CBE-1212540) Seibel, Eric PI

Project Description: An exploratory project is designed to improve the minimally-invasive diagnostic ability of needle biopsy for pancreatic cancer. To accomplish this, a systems approach begins with thin-needle core biopsy specimens acquired from ex vivo tissues from mouse models of pancreatic cancer and resected human tissue. The visualization of the 3D images with H&E staining and selected immunofluorescence biomarkers will be used to determine the presence of neoplasia and cancer invasion. This OPTM diagnosis by a pathologist will be compared to matching the needle aspirate (FNA) in a blinded study against the gold standard of tissue-slice pathology.

Role: Co-Investigator

Sponsor Contact: Eric Seibel, PhD., Human Photonics Laboratory, University of Washington, Box 352600, Seattle, WA 98195, eseibel@uw.edu.

Oral Cancer: Molecular Profiles and Clinical Outcomes

9/1/2009 – 8/31/2012

0.60 calendar

NIH (2R01 CA95419) Chen, Chu, PI

Project Description: The purpose of this competing renewal is to validate various biomarkers that we have previously found to be associated with tumor characteristics and clinical outcomes of oral squamous cell carcinomas in our previous R01 application

Role: Co-Investigator

Sponsor Contact: Chu Chen, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, cchen@fhcrc.org.

(5R01 CA115513) Grady, William, PI

Project Description: The major goals of this project are to identify and validate microcytometer-based methylation specific PCR molecular markers assays for assessing the prognosis of colorectal cancer. My role is to assess tissue specimens of colonic and intestinal neoplasms and to provide accurate TNM staging data for use in the interpretation of the molecular marker assay results.

Role: Co-Investigator

Sponsor Contact: William Grady, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., PO Box 19024, Seattle, WA 98109-1024, wgrady@fhcrc.org.

OVERLAP: None