

Award Number: W81XWH-18-1-0152

TITLE: Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients

PRINCIPAL INVESTIGATOR: David Weinberg, M.D.

CONTRACTING ORGANIZATION:

The Research Institute of Fox Chase Cancer Center
333 Cottman Avenue, Philadelphia, PA 19111

REPORT DATE: OCTOBER 2019

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; Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188		
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) OCTOBER 2019		2. REPORT TYPE Annual		3. DATES COVERED 15 SEP 2018 - 14 SEP 2019	
4. TITLE AND SUBTITLE Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-18-1-0152		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) David Weinberg, M.D. E-Mail: David.Weinberg@fcc.edu			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Research Institute of Fox Chase Cancer Center 333 Cottman Avenue Philadelphia, Pennsylvania 19111 E-Mail: osr@fcc.edu			8. PERFORMING ORGANIZATION REPORT NUMBER		
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 Colorectal cancer is the 4 th most common cancer in the United States. To date, no tenable chemoprevention agents have been identified for widespread use to minimize the burden of this common cancer. Previously the study team has produced preclinical as well as early clinical data in support of a novel agent class, GUCY2C agonists, as a potential chemopreventive agent. The current trial will randomize two types of patients: those with previous colorectal adenomas, as well as those with documented colorectal cancer awaiting resection. Participants of either type will receive either placebo or linaclotide 0.870mg (an FDA approved GUCY2C agonist) for 7 days. At the conclusion of drug/placebo exposure adenoma participants will undergo colonoscopy and colorectal cancer participants will undergo surgery with standardized collection of normal and abnormal tissue. Assays for a series of biomarker assays relevant to GUCY2C signaling will be collected. We hypothesize that recipients of active agent will have differential modulation of pathways relevant to colorectal carcinogenesis. Assuming benefit as well as tolerability is demonstrated, results from this study should set the stage for larger scale, longer term chemoprevention for colorectal cancer.					
15. SUBJECT TERMS chemoprevention; colorectal cancer; guanylyl cyclase C, linaclotide; GUCY2C					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			UU
Unclassified	Unlimited	Unclassified			19b. TELEPHONE NUMBER <i>Include area code</i>

Table of Contents

1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	7
8. Special Reporting Requirements	8
9. Appendices	8

Principal Investigator: David Weinberg, M.D.

Institution: Institute for Cancer Research

Grant Number: W81XWH-18-1-0152

INTRODUCTION:

Colorectal cancer is the 4th most common cancer in the United States. To date, no tenable chemoprevention agents have been identified for widespread use to minimize the burden of this common cancer. Previously the study team has produced preclinical as well as early clinical data in support of a novel agent class, GUCY2C agonists, as a potential chemopreventive agent. The current trial will randomize two types of patients: those with previous colorectal adenomas, as well as those with documented colorectal cancer awaiting resection. Participants of either type will receive either placebo or linaclotide 0.870mg (an FDA approved GUCY2C agonist) for 7 days. At the conclusion of drug/placebo exposure adenoma participants will undergo colonoscopy and colorectal cancer participants will undergo surgery with standardized collection of normal and abnormal tissue. Assays for a series of biomarker assays relevant to GUCY2C signaling will be collected. We hypothesize that recipients of active agent will have differential modulation of pathways relevant to colorectal carcinogenesis. Assuming benefit as well as tolerability is demonstrated, results from this study should set the stage for larger scale, longer term chemoprevention for colorectal cancer.

KEYWORDS: chemoprevention; colorectal cancer; guanylyl cyclase C, linaclotide; GUCY2C

ACCOMPLISHMENTS:

What were the major goals of the project?

- Major Task 1. Clinical trial of oral linaclotide in patients with colorectal adenomas and carcinomas (Months 1-30).
- Major Task 2: Oral linaclotide re-establishes GUCY2C signaling in adenomas and carcinomas (Months 6-36).
- Major Task 3: Oral linaclotide reconstitutes guanylin expression in adenomas and carcinomas (Months 6-36).
- Major Task 4: Oral linaclotide will repair mutant APC- β -catenin signaling in adenomas and carcinomas (Months 6-36).
- Major Task 5: Linaclotide reverses epithelial dysfunction (Months 6-36).

What was accomplished under these goals?

- Finalize study protocol;
- Submit study protocol for approval by HRPO. Fox Chase Cancer Center component under review.
- Received CIRB approval for study protocol at Thomas Jefferson University
- Finalized the Pharmacy Manual for the study.
- Held Site Initiation Visit (SIV) at Thomas Jefferson University February 22, 2019.
- Study protocol revised according to feedback from SIV (v3.2), submitted and received IRB approval
- Completed the database creation to support data collection and entry for the three participating sites.
- Drug delivery by Ironwood to Thomas Jefferson University and Fox Chase Cancer Center
- Received final approval for final data/sample sharing agreements between Thomas Jefferson University and Fox Chase Cancer Center.

- Received final approvals to initiate patient recruitment at Thomas Jefferson University and Fox Chase Cancer Center.
- Specific Objectives
 - Obtain central approval of study protocol and final data/sample sharing agreement to permit study initiation in third quarter of 2019.
 - Received final local approval for final data/sample sharing agreements between Thomas Jefferson University and Fox Chase Cancer Center that permit initiation of patient enrollment in October, 2019.
- Key Outcomes
 - Study protocol was finalized;
 - Study protocol was submitted to Thomas Jefferson University IRB for approval for conduct at Jefferson and Fox Chase Cancer Center.
 - Study protocol was approved by IRB at Thomas Jefferson University for both Thomas Jefferson University and Fox Chase Cancer Center.
 - SIV for study initiation at Thomas Jefferson University and Fox Chase Cancer Center was held.
 - All legal agreements (data/sample sharing agreements) between Thomas Jefferson University and Fox Chase Cancer Center were completed to enable initiating patient enrollment in October 2019.

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

Nothing to report

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?

- Conduct “mini” site initiation visit (“refresher” SIV) for Thomas Jefferson University on October 17, 2019.
- Begin enrolling subjects at Thomas Jefferson University and Fox Chase Cancer Center immediately after the mini-SIV on October 17, 2019.
- Conduct a Site Initiation visit between VA Puget Sound and Thomas Jefferson University and Fox Chase Cancer Center once data/sample sharing agreements have been completed.
- Begin molecular analyses of samples to establish whether oral linaclotide:
 - Restores the GUCY2C signaling axis in tumors;
 - Reconstitutes guanylin expression in tumors;
 - Repairs mutant APC-beta-catenin signaling in tumors;
 - Reverses epithelial dysfunction in tumors.

IMPACT:

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

What was the impact on society beyond science and technology?

Nothing to report

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Fox Chase Cancer Center awaits HRPO approval. Once complete, we will begin to enroll.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

PRODUCTS:

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

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**What individuals have worked on the project?**

Name:	David Weinberg, M.D.
Project Role:	PD/PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-2107-7651
Nearest person month worked:	1
Contribution to Project:	<i>Dr Weinberg is responsible either directly or in a supervisory role to ensure that all study related activities at Fox Chase are successfully completed.</i>
Funding Support:	

Name:	Harry Cooper, M.D.
Project Role:	Pathologist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Dr Cooper, as detailed in the study protocol, is responsible for pathology evaluation of relevant tissue samples collected during the trial.</i>
Funding Support:	

Name:	Eric Ross, Ph.D.
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Dr. Ross has supervised production of the study database and will provide ongoing biostatistical support during the trial.</i>

Funding Support:	
------------------	--

Name:	Sara McCarney
Project Role:	Clinical Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	<i>Ms. McCarney has participated in submission of all regulatory materials for the trial and will contribute to participant identification and retention as enrollment begins.</i>
Funding Support:	

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

Please see attached updated Other Support for key personnel. Changes are marked with a line in the right hand margin.

What other organizations were involved as partners?

Nothing to report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report

QUAD CHARTS: Nothing to report

APPENDICES: Please see attached Award Chart.

Other Support**Weinberg, David S.**CURRENT

W81XWH-18-1-0152 (PI: Weinberg)	9/15/2018 - 9/14/2022	10.0%
DOD	\$84,706	1.20 calendar

Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients
This Translational Team Science project is linked to the prime organization, Thomas Jefferson University. The overall goal is to develop a prevention strategy for colorectal cancer by exploiting the role of GUCY2C signaling in inhibiting colorectal epithelial malignant transformation.
Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

COMPLETED

HHSN26100014
FujiFilm Project

OVERLAP

None

Other Support

Cooper, Harry S.

CURRENT

R01 CA183301 (PI: Clapper)	9/1/2015 - 8/31/2020	5.0%
NIH	Salary only	0.60 calendar

Targeted Chemoprevention of Flat and Polypoid Colitis-associated Dysplasias

The major goals of this project are: 1a) Use genetically defined mice to evaluate the ability of mutant beta catenin or loss of function of p53 to drive the formation of polypoid and flat colitis-associated dysplasias, respectively, by comparing the morphological subtypes; 1b) To determine if induction of inflammation triggers activation of p53 and degradation of beta catenin in colon carcinoma cell lines with defined mutations in p53 and beta-catenin; 2) To assess the chemopreventive activity of CP31398 (p53 reactivation) and/or ICG-001 (inhibition of beta catenin-mediated TCF signaling) on colitis-associated neoplasia in WT Tcf4 luciferase reporter mice; and 3) To characterize the proliferative vs. apoptotic capacity of human flat and polypoid colitis-associated dysplasias.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

HHSN26100003 (PI: Clapper)	7/25/2018 - 7/24/2021	5.0%
NIH	Salary only	0.60 calendar

A Novel Non-COX Inhibitory Sulindac Derivative for Colorectal Cancer Chemoprevention with Selective PDE-10 and Wnt/ β -Catenin Inhibitory Activity (Task Order 3)

The major goals of this task order are to: 1) Determine an optimal, nontoxic dose of orally administered MCI-030 in APC+/Min-FCCC mice, in the presence and absence of DSS; and 2) Evaluate the efficacy of MCI-030 against colorectal adenomas and colorectal dysplasias / cancers.

Procuring Contracting/Grants Officer: Christy Hunter, 8490 Progress Dr., Rm 4035, Fredrick MD 21701, 301-624-8788

W81XWH-18-1-0152 (PI: Weinberg)	9/15/2018 - 9/14/2022	10.0%
DOD	Salary only (yrs1-3)	1.20 calendar

Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients

This Translational Team Science project is linked to the prime organization, Thomas Jefferson University. The overall goal is to develop a prevention strategy for colorectal cancer by exploiting the role of GUCY2C signaling in inhibiting colorectal epithelial malignant transformation.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

R21 CA216825 (PI: Wiest)	12/15/2017 - 11/30/2019	5.0%
NIH	Partial Salary	0.60 calendar

Rpl22-Like1 as a Novel Prognostic Marker in Colorectal Cancer

The major goals of this projects are to: 1) Assess the association between Like1 induction and survival in colorectal cancer; and 2) Elucidate the molecular basis for Like1 induction.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

OVERLAP

None

Other Support

Ross, Eric A.

CURRENT

W81XWH-19-1-0766 (PI: Abbosh)	9/1/2019 - 8/31/2022	3.0%
DOD	Salary only	0.36 calendar

Immunologic and Microbial Correlates and Mechanisms of Complete Response to Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer
 The major goals of this project are: 1) To dissect CD8+ effector T cell activation and exhaustion states associated with pCR; and 2) To define microbial ecosystems in bladder cancer and their association with chemoresponse.
 Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

P30 CA006927 (PI: Fisher)	8/12/2016 - 7/31/2021	70.0%
NIH	Partial Salary	8.40 calendar

Comprehensive Cancer Center Program at Fox Chase
 The major goal of this Cancer Center Support Grant is to provide partial salary support for professional personnel, including senior and program leadership, administration, planning and evaluation, and developmental funds, as well as support for 5 established peer-reviewed Research Programs, 12 Shared Research Resources and 2 Support Elements.
 Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

1552416 (PI: Bangasser, Temple Univ.)	3/15/2016 - 2/28/2021	2.0%
NSF	\$1,236 (No Salary)	0.24 calendar

CAREER: Interactions between Stress and Attention Circuits: Investigating Corticotropin Releasing Factor Modulation of the Basal Forebrain
 This project is a subcontract to Temple University. Fox Chase Cancer Center will be responsible for coordinating and supervising bioinformatics activities to make sure that the research team has ready access to high quality support.
 Procuring Contracting/Grants Officer: Sherri Gibbs, Temple, 1852 N. 10th St., Phila., PA 19122, 215-707-3106

U54 CA221705 (PI: Ma, G., Temple)	9/19/2018 - 8/31/2023	10.0%
NIH	Salary only	1.20 calendar

Temple University Fox Chase Cancer Center/Hunter College Regional Comprehensive Cancer Health Disparity Partnership
 This project is a subcontract to Temple University. The goals of this Partnership are to: a) develop a strong and sustainable collaborative cancer health equity research infrastructure, b) support the development of outstanding URM students and ESIs who are committed to careers in cancer research, and c) collaboratively engage the community in enhancing quality and feasibility of these efforts.
 Procuring Contracting/Grants Officer: Angie Calicat, TASB, 2450 W. Hunting Park Ave., Phila., PA 19129, 215-707-9227

W81XWH-18-1-0152 (PI: Weinberg)	9/15/2018 - 9/14/2022	8.3%
DOD	Salary only	1.00 calendar

Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients
 This Translational Team Science project is linked to the prime organization, Thomas Jefferson University. The overall goal is to develop a prevention strategy for colorectal cancer by exploiting the role of GUCY2C signaling

in inhibiting colorectal epithelial malignant transformation.

Procuring Contracting/Grants Officer: Danielle Reckley, USAMRAA, 830 Chandler St., Fort Detrick, MD 21702, 301-619-1139

R21 CA216825 (PI: Wiest)

12/15/2017 - 11/30/2019

5.0%

NIH

Partial Salary

0.60 calendar

Rpl22-Like1 as a Novel Prognostic Marker in Colorectal Cancer

The major goals of this projects are to: 1) Assess the association between Like1 induction and survival in colorectal cancer; and 2) Elucidate the molecular basis for Like1 induction.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

OVERLAP

None

CA170223P1: Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients

Weinberg, David



PI: David Weinberg, M.D., Institute for Cancer Research, PA

Budget: \$548,342

Topic Area: PRCRP

Mechanism: Translational Team Science Award

Research Area(s): 0805 - Targeted Therapies

Award Status: 9/15/2018 – 9/14/2022

Study Goals:

- Major Task 1. Clinical trial of oral linaclotide in patients with colorectal adenomas and carcinomas (Months 1-30).
- Major Task 2: Oral linaclotide re-establishes GUCY2C signaling in adenomas and carcinomas (Months 6-36).
- Major Task 3: Oral linaclotide reconstitutes guanylin expression in adenomas and carcinomas (Months 6-36).
- Major Task 4: Oral linaclotide will repair mutant APC- β -catenin signaling in adenomas and carcinomas (Months 6-36).
- Major Task 5: Linaclotide reverses epithelial dysfunction (Months 6-36).

Specific Aims:

Primary

To determine whether, compared to placebo, linaclotide administered as a single oral daily dose x 7 days, induces a PD effect on cGMP levels, based on biopsy samples of adenomas or resected colorectal adenocarcinomas.

Secondary

- (1) To compare Ki-67, guanylin levels and GUCY2C expression in adenomas and cancers versus normal tissue after exposure to linaclotide or placebo.
- (2) To confirm the safety and tolerability of linaclotide in sporadic adenoma and cancer patients.

Translational

To assess the pharmacodynamic effect of linaclotide on pathway-specific biomarkers relevant to GUCY2C signaling (i.e. VASP phosphorylation), markers of mutant APC- β -catenin signaling (β -catenin levels, β -catenin nuclear localization, axin levels, c-Myc levels, guanylin levels, PCNA expression), based on adenoma/cancer and normal mucosa biopsy samples obtained by endoscopy following linaclotide or placebo exposure.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date