Award Number: W81XWH-18-1-0152

TITLE: Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients

PRINCIPAL INVESTIGATOR: David Weinberg, M.D.

CONTRACTING ORGANIZATION:

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REPORT DATE: OCTOBER 2020

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3 DATES COVERED
OCTOBER 2020	Annual	15SEPT2019 - 14SEPT2020

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)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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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 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.

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			USAMRMC
Unclassified	Unlimited	Unclassified	13	13	19b. TELEPHONE NUMBER *Include area code)*

Table of Contents

Principal Investigator: David Weinberg, M.D.
Institution: Institute for Cancer Research
Grant Number: W81XWH-18-1-0152

INTRODUCTION:

In 2020, there will be an estimated 104,610 new cases of colon cancer and 43,340 cases of rectal cancer diagnosed in the US. The relative survival rate for CRC is 64% at 5 years following diagnosis and 58% at 10 years. The most important predictor of CRC survival is stage at diagnosis. For common cancers, CRC is one of the most preventable through the identification and removal of colorectal adenomas. Unfortunately, no tenable chemoprevention agents have been identified for widespread use to minimize the burden of this common cancer or reduce the need for widespread screening efforts.

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 randomizes 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 undergo colonoscopy and colorectal cancer participants undergo surgery with standardized collection of normal and abnormal tissue. Mucosal samples are collected for a series of biomarker assays relevant to GUCY2C signaling. 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 (since last annual report)?

- Study protocol finalized
- HRPO approval obtained
- FCCC IRB approval obtained. CIRB approval for study protocol at Thomas Jefferson University
- 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

- Data/sample sharing agreements between Thomas Jefferson University and Fox Chase Cancer Center completed.
- Received final approvals to initiate patient recruitment at Thomas Jefferson University and Fox Chase Cancer Center.
- Enrollment commenced at FCCC

- Specific Objectives
  - Initiate screening, enrollment and execution of study related activities for participants.

- Key Outcomes
  - To date, 4 participants have been randomized, received agent/placebo, submitted to collection of endoscopic biopsy specimens (all in the adenoma arm).
  - Study specimens uneventfully obtained, processed, stored shipped to Jefferson for study specific assays.

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?

- 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.
- Aggressive efforts to “make up for lost time” due to inevitable clinical research slowdowns related to COVID epidemic

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

At its height, the COVID epidemic reduced elective surgical procedures and colonoscopies very substantially. Further, patient related concerns about additional infection risk due to study participation severely limited patient interest and participation. At FCCC, clinical volumes are slowly returning to normal (about 90%). We are hopeful that interest/participation in clinical research projects like this one will rebound and remain robust.

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:	*Dr Weinberg is responsible either directly or in a supervisory role to ensure that all study related activities at Fox Chase are successfully completed.*
Funding Support:	

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

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

Name:	Sara McCarney
Project Role:	Clinical Coordinator

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Ms. McCarney is well versed in all regulatory materials for the trial and contributes to participant identification, enrollment and retention as enrollment begins.*
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.

Remaining salary support from clinical activities.

CURRENT

UG1 CA189828 (PI: O'Dwyer, ECOG-ACRIN) 10/1/2019 - 7/31/2027 12.5%
NIH 1.50 calendar EA2185 -
Comparing the Clinical Impact of Pancreatic Surveillance Programs
This project is a subcontract to the ECOG-ACRIN Medical Research Foundation.
Procuring Contracting/Grants Officer: Christina Chink, 1818 Market St., Ste 3000, Phila., PA 19103, 215-789-3638

W81XWH-18-1-0152 (PI: Weinberg) 9/15/2018 - 9/14/2022 10.0%
DOD 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

OVERLAP

None

Other Support

Cooper, Harry S.

Remaining salary support from clinical activities.

CURRENT

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/ß-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 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

R01 CA183301 (PI: Clapper) 9/1/2015 - 8/31/2021 5.0%
NIH Salary only 0.60 calendar
Targeted Chemoprevention of Flat and Polypoid Colitis-associated Dysplasias
This grant is in a one year extension.
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

OVERLAP

None

COMPLETED

R21 CA216825

Other Support

Ross, Eric A.

Remaining salary support from institutional sources.

CURRENT

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

U54 CA221705 (PI: Ma, Temple Univ.) 9/19/2018 - 8/31/2023 10.0%
NIH Salary only 1.20 calendar
1/2 TUFCCC/HC 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-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

R01 CA173453 (PI: El-Deiry, Brown Univ.) 4/1/2019 - 3/31/2024 5.0%
NIH Salary only 0.60 calendar
ONC201/TIC10 Anti-tumor Effect Through Regulation of the TRAIL Pathway
This project is a subcontract to Brown University. Fox Chase Cancer Center will provide general expertise in immunology and specific expertise with NK cell activation pathways. They will provide additional expertise with both mouse models and assessment of immune correlatives in patient tumors and blood samples, as well as expertise in biostatistics and data analysis.
Procuring Contracting/Grants Officer: Daniel St. John, OSP, Box 1929, Providence RI 02912, 401-863-3004

(PI: El-Deiry, Brown Univ.) 1/1/2020 - 12/31/2022 8.0%
WAF 0.96 calendar ONC212 as Novel Therapy for Pancreatic Cancer
This project is a subcontract to Brown University. Fox Chase Cancer Center will provide biostatistical study design, conduct statistical analyses related to the evaluation of study data, participate in monitoring of the clinical trial, and collaborate with project investigators on publications and presentations related to research

accomplishments.
Procuring Contracting/Grants Officer: Daniel St. John, OSR, Box 1929, Providence, RI 02912, 401-863-3004

P30 CA006927 (PI: Fisher) 8/12/2016 - 7/31/2021 58.2%
NIH Partial Salary 6.98 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: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850, 240-276-6280

OVERLAP

None

COMPLETED

1552416
R21CA216825

CA170223P1: Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients

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