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

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Fort Detrick, Maryland 21702-5012

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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
David Weinberg, M.D.

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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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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			USAMRDC
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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)?

- Patient enrollment was slowed by COVID and multiple levels: patient hesitation to seek care (a real but shrinking subset of patients), difficulties with staffing clinical research teams and challenges scheduling procedures as patients from all backgrounds began to seek pent up care as COVID receded (the flip side of the first related COVID barrier).

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

- Key Outcomes
  - To date, 21 participants have been randomized, received agent/placebo, and 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.
  - Initiated 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.

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?

Fox Chase Cancer Center will complete the data analysis following the completion of the lab assays at Thomas Jefferson University as noted in no-cost extension request.

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

There has been a delay in the lab assays. Upon receipt of the lab assays we will complete the data analysis.

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:	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 Snell
Project Role:	Clinical Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Ms. Snell was a new addition to the team. She has proved essential to facilitate patient identification and enrollment.*
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 Supports for Drs. Weinberg and Ross. 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

4100094422 (PI: Zeigler-Johnson) 7/1/2021 - 9/30/2024 5.0%
PA DHS No Salary 0.60 calendar
Cancer Screening Comes to You
This major goal of this application is to provide access to health screening and public education on chronic disease prevention and management through screening and cancer education.
Procuring Contracting/Grants Officer: Sherry Shaffer, 625 Forster St., Rm 525, Harrisburg, PA 17120, 717-214-1328

Year (YYYY)	Person Months (##.##)
3. 2024	0.60 calendar

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

Year (YYYY)	Person Months (##.##)
5. 2024	1.50 calendar
6. 2025	1.50 calendar
7. 2026	1.50 calendar
8. 2027	1.50 calendar

W81XWH-18-1-0152 (PI: Weinberg) 9/15/2018 - 9/14/2024 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

Year (YYYY)	Person Months (##.##)
4. 2024 (NCE)	1.20 calendar

UG1 CA242635 (PI: Bailey, Univ. of WI) 8/1/2021 – 7/31/2024 5%
NIH 0.60 calendar The MW
Cancer Prevention Clinical Trials Network
This project is a subcontract to the University of Wisconsin. Dr. Weinberg is a Study Co-Chair. Fox Chase Cancer Center will be responsible for accruing patients and the related treatment.
Procuring Contracting/Grants Officer: Catherine Shults, 21 North Park Street, Madison, WI, 53715, 608-262-6999

Year (YYYY)	Person Months (##.##)
3. 2024	0.60 calendar

OVERLAP
None

Other Support

Ross, Eric A.

CURRENT

P50 DE030707 (PI: Burtness, Yale Univ.) 9/22/2020 - 6/30/2025 7.5%
NIH Salary only 0.90 calendar
Yale Head and Neck Cancer SPORE: Overcoming Treatment Resistance in Head and Neck Cancer
This project is a subcontract to Yale University. Fox Chase Cancer Center will participate on this SPORE as a primary site. Investigators at FCCC will co-Lead Project 2, entitled, "Synthetic Lethal Therapy in TP53 Mutated Head and Neck Cancer." Fox Chase Cancer Center investigators will also support the Biostatistics and Bioinformatics Core, Biospecimen Core and the Career Enhancement Program.
Procuring Contracting/Grants Officer: Makawa Kourouma, OSP, 25 Science Park, 34d Floor, 150 Munson St., New Haven, CT 06520, 203-432-3380

Year (YYYY)	Person Months (##.##)
4. 2024	0.90 calendar
5. 2025	0.90 calendar

P30 CA006927 (PI: Chernoff) 8/12/2016 - 7/31/2024 (NCE) 30.0%
NIH No Salary 3.60 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 4 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

Year (YYYY)	Person Months (##.##)
55. 2024 (NCE)	3.60 calendar

W81XWH-18-1-0152 (PI: Weinberg) 9/15/2018 - 9/14/2024 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.) 9/19/2023 - 8/31/2028 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. This project is a subcontract to Temple University. Fox Chase Cancer Center will play a key role in the implementation of the U54 Partnership and be involved in the following components: Administrative Core, Research Education Core, Biostatistics and Bioinformatics Core, Community Outreach Core, Genomics Testing Project and Pilot Breast Cancer Study.
Procuring Contracting/Grants Officer: Angie Calicat, TASB, 2450 W. Hunting Park Ave., Phila., PA 19129, 215-707-9227

R01 CA173453 (PI: El-Deiry, Brown Univ.) 5/1/2019 - 4/30/2024 5.0%
NIH Partial Salary 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

Year (YYYY)	Person Months (##.##)
5. 2024	0.60 calendar

N/A (PI: El-Deiry, Brown Univ.) 1/1/2020 - 12/31/2023 (NCE) 8.0%
WAF Partial Salary 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

Year (YYYY)	Person Months (##.##)
3. 2023 (NCE)	0.96 calendar

R01 CA259188 (PI: Yang, Y.) 4/6/2021 - 3/31/2026 NA
NIH Salary only calendar
Investigating the IL-1R Pathway in Anaplastic Large Cell Lymphoma for Targeted Therapy
The major goals of this project are to: 1) Elucidate the molecular functions of the IL-1R pathway in ALK- and BIA ALCL; 2) Determine how the IL-1R pathway is primed and regulated, and how it cooperates with recurrent genetic lesions in ALK- and BIA ALCL; and 3) Assess the therapeutic potential of targeting the IL-1R pathway to provide novel intervention strategies in ALK- and BIA ALCL.
Procuring Contracting/Grants Officer: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850, 240-276-6280

Year (YYYY)	Person Months (##.##)
3. 2024	0.00 calendar
4. 2025	0.00 calendar
5. 2026	0.24 calendar

R01 CA251674 (PI: Yang, Y.) 6/1/2021 - 5/31/2026 NA
NIH Salary only calendar
Analysis and Therapeutic Targeting of the Linear-Ubiquitination Pathway in Hodgkin Lymphoma
The major goals of this project are to: 1) Delineate the molecular functions of the LUBAC-A20 axis in supporting HRS cell survival; 2) Evaluate how linear-ubiquitin-dependent signaling regulates the molecular circuitry that drives tumor immune escape of HL; and 3) Assess the therapeutic potential of targeting LUBAC to provide novel intervention strategies for both targeted and immune therapies in HL.
Procuring Contracting/Grants Officer: Mike Steenstra, 9609 Medical Center Dr., Rockville MD 20850, 240-276-7651

Year (YYYY)	Person Months (##.##)
3. 2024	0.00 calendar
4. 2025	0.00 calendar
5. 2026	0.60 calendar

U01 CA260369 (PI: Abbosh) 8/1/2021 - 7/31/2026 5.0%
NIH Salary only 0.60 calendar
Optimization of Urinary DNA Deep Sequencing Tests to Enhance Clinical Staging of Bladder Cancer Patients

The major goals of this project are: 1) To identify the optimal urine compartment and sequencing method for UTeRD; 2) To establish the optimal urine preservation protocol for UTeRD; and 3) To determine the test performance of optimized UTeRD (O-UTeRD).
Procuring Contracting/Grants Officer: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850, 240-276-6280

Year (YYYY)	Person Months (##.##)
3. 2024	0.60 calendar
4. 2025	0.60 calendar
5. 2026	0.60 calendar

75N91023F00003 (PI: Testa) 5/3/2023 - 5/2/2026 NA
NIH Salary only calendar
Sulforaphane for the Prevention of Malignant Mesothelioma (Task Order)
The major goal of this Task Order is to assess the ability of SRN and Avmacol to inhibit the formation of asbestos-associated Malignant Mesothelioma
Procuring Contracting/Grants Officer: Erin Dwyer, 9609 Medical Center Dr., MSC 0805, Rockville, MD 20850, 301-624-8764

Year (YYYY)	Person Months (##.##)
1. 2024	0.00 calendar
2. 2025	0.00 calendar
3. 2026	0.54 calendar

U54 CA272686 (PI: Clapper) 9/1/2022 - 8/31/2027 10.0%
NIH Salary only 1.20 calendar
Cancer Prevention-Interception Targeted Agent Discovery Program at Fox Chase Cancer Center
The major goals of this project are: 1) To use the existing resources of the FCCC RAP and public databases, engineered cell lines and archived biosamples from high-risk subjects to validate the critical function of candidate molecular pathways/targets in the transition from precancer to early cancer, and confirm their utility for precision prevention/early interception; 2) To identify agents that modulate the lead targets and inhibit tumor initiation and/or progression using customized in vitro screening assays and cell lines from high-risk subjects, followed by prioritization and selection of the optimal target and agents; 3) To perform pilot efficacy studies in clinically-relevant mouse models that recapitulate the cancer continuum (precancer to cancer) to assess the on-target effects of lead agents and evaluate potential toxicities at doses efficacious for tumor inhibition; and 4) To collaborate with other CAP-IT Centers and the NCI through the Data and Resource Coordination Center to foster productivity and integration, and share data and resources across the CAP-IT Network.
Procuring Contracting/Grants Officer: Rebecca Brightful, 8490 Progress Dr., Rm. 4083, Frederick, MD 21701, 301-631-3011

Year (YYYY)	Person Months (##.##)
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar
5. 2027	1.20 calendar

R21 CA277402 (PI: Astsaturov/Olszanski) 7/1/2023 - 6/30/2025 5.0%
NIH Salary only 0.60 calendar
A Phase I Proof-of-Concept Study of CBL0137 Combined with Ipilimumab and Nivolumab Therapy in Locally Advanced or Metastatic Melanoma (MPI)
The major goals of this project are: 1) To conduct a proof-of-concept clinical trial to examine the feasibility of CBL0137+ICB (nivolumab and ipilimumab) in melanoma; and 2) To elucidate the biological effects of CBL0137+ICB against melanoma.
Procuring Contracting/Grants Officer: Michael McGraw, 9609 Medical Center Dr., Rockville, MD 20850, 240-276-5197

Year (YYYY)	Person Months (##.##)
1. 2024	0.60 calendar
2. 2025	0.60 calendar

UG3 HL170034 (PI: Fang/Ma, Temple Univ./Hu, Harvard) 8/15/2023 - 7/31/2025 3.0%
NIH Salary only 0.36 calendar
Asian American Community Cohort and Equity Study (ACCESS) (Multi-PI)
The major goals of this project are to: 1) Leverage existing networks and resources to establish an administrative and scientific infrastructure for ACCESS involving clinical/community partnerships to support the implementation of cohort activities including participant recruitment and retention strategies; 2) Work collaboratively with the Coordinating Center (CC) and other Clinical/Community Field Centers (CCFCs) to finalize protocols for data collection procedures and build a secure data repository in accordance with the goals of the overall cohort program; and 3) Conduct a collaborative pilot study to assess the feasibility of using a novel image-assisted mobile application for dietary assessment across the 3 subgroups involving 5% of study participants.
Procuring Contracting/Grants Officer: Julie A Delgado, NHLBI, 301-435-0833

Year (YYYY)	Person Months (##.##)
1. 2024	0.60 calendar
2. 2025	1.20 calendar

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 – 9/14/2024

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