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TITLE: The Role of Mitochondria in ADT-Induced Sarcopenia in Prostate Cancer Patients

PRINCIPAL INVESTIGATOR: Dr. Jose M Garcia, MD, PhD

CONTRACTING ORGANIZATION: Seattle Institute for Biomedical and Clinical Research

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6. AUTHOR(S)
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None

14. ABSTRACT

Prostate cancer (PCa) is the most common cancer among men. Androgen deprivation therapy (ADT) is the standard treatment for advanced and metastatic PCa and nearly 400,000 men remain on androgen deprivation therapy (ADT) for advanced PCa in the U.S. Unfortunately, ADT also induces a decrease in muscle mass and function, known as sarcopenia, a condition that leads to decreased endurance, increased fatigue, falls, poor health-related quality of life (HR-QOL) and increased mortality. The mechanisms underlying the development of ADT-induced sarcopenia are incompletely understood and remain a significant barrier to the development of therapies for this condition. Mitochondria play an essential role in generating the adenosine triphosphate (ATP) needed for muscle contraction and abnormalities in mitochondria function have been reported in animal models of sarcopenia. The extent to which mitochondrial dysfunction mediates ADT-induced sarcopenia and muscle dysfunction is not known.

The *overall goal* of this proposal is to establish the role of mitochondrial dysfunction on ADT-induced sarcopenia in patients with PCa. Our *hypothesis* is that ADT in men with PCa will induce mitochondrial dysfunction leading to sarcopenia. To test this hypothesis, we will carry out a pilot study of men with PCa undergoing ADT (n=60).

As of September 15, 2021, we have enrolled 34 research participants in the study. Research participant recruitment and performance of study visits were impacted beginning in March 2020 due to the COVID-19 epidemic but have now resumed and are proceeding normally under a cost extension granted recently.

15. SUBJECT TERMS					
Mitochondrial dysfunction, prostate cancer, androgen deprivation, sarcopenia					
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1. INTRODUCTION:

Prostate cancer (PCa) is the most common cancer among men. Androgen deprivation therapy (ADT) is the standard treatment for advanced and metastatic PCa. Unfortunately, ADT also induces a decrease in muscle mass and function, known as sarcopenia, a condition that leads to decreased endurance, increased fatigue, falls, poor health-related quality of life (HR-QOL) and increased mortality. The mechanisms underlying the development of ADT-induced sarcopenia are incompletely understood and remain a significant barrier to the development of therapies for this condition. Mitochondria play an essential role in generating muscle contraction but the extent to which mitochondrial dysfunction mediates ADT-induced sarcopenia and muscle dysfunction is not known. The overall goal of this proposal is to establish the role of mitochondrial dysfunction on ADT-induced sarcopenia in patients with PCa. Our hypothesis is that ADT in men with PCa will induce mitochondrial dysfunction leading to sarcopenia.

2. KEYWORDS:

Prostate cancer, androgen deprivation, sarcopenia, mitochondria

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Obtain regulatory approvals for Study 1 (Months 1-3)

- *Milestone Achieved: Regulatory approvals obtained* (COMPLETED: 4/26/2018)

Major Task 2: Coordinate Study Staff for Clinical Trials (Months 1-3)

- *Milestone Achieved: Research staff trained* (COMPLETED: 12/1/2018)

Major Task 3: Equipment certification/calibration and data transfer plan (Months 1-3)

- *Milestone Achieved: Equipment certification/calibration and data transfer plan established* (COMPLETED: 11/30/2018)

Major Task 4: Participant Recruitment, Participant Evaluation for trial 1 (Months: 4-30)

- *Milestone Achieved: Recruitment and evaluation completed for study 1* (Percentage of completion: 56.7%)

Patients screened	Patients Eligible	Patients Enrolled
2533	67	34 (one lost to FU)

Major Task 5: Measure LBM and muscle performance (Months: 4-30)

- *Milestone Achieved: Measures of LBM and muscle performance obtained* (Percentage of completion: 44.4%)

Median (STD)	**Baseline (*n* = *32*)**	**3moFU (*n* = 27)**	**6moFU (*n* = *21*)**
ALM (kg)	25.63 (4.52)	24.46 (6.30)	23.66 (5.13)
Mean HGS (kg)	43.5 (8.95)	40.0 (8.32)	38(7.34)
6MWT (m)	523.34 (121.48)	508.60 (102.89)	474.15 (116.96)
SCP (W)	417.24 (130.56)	396.65 (115.67)	316.30 (117.72)

Major Task 6: Measure Mitochondrial Function (Months: 4-30)

- *Milestone Achieved: Measures of mitochondrial function obtained* (Percentage of completion: 35.8%)

Median (STD)	**Baseline (*n* = *25*)**	**6moFU (*n* = *18*)**
Basal respiration (OCR)	46.9 (35.71)	26.72 (33.75)
ATP-linked respiration (OCR)	207.69 (274.52)	229.27 (243.82)
Maximal respiration (OCR)	212.85 (327.08)	211.51(396.38)
Non-mitochondrial respiration (OCR)	42.6 (27.62)	16.63 (17.87)

Major Task 7: Measure Fatigue and HR-QOL Scores (Months: 4-30)

- *Milestone Achieved: Measures of Fatigue and HR-QOL scores obtained* (Percentage of completion: 42.2%)

Median (STD)	**Baseline (*n* = 30)**	**3moFU (*n* = 27)**	**6moFU (*n* = 19)**
FACIT-F (QOL)	111.5 (26.40)	103.0 (22.63)	100.5 (34.57)
QLQ-C30 (%) (fatigue score percentile)	33.0 (26.06)	44.3 (22.56)	50.0 (27.58)

Major Task 8: Explore the predictive value of the baseline measurements (Months: 6-30)

- *Milestone Achieved: Recruitment and evaluation completed for study 2* (Percentage of completion: 0%)

Major Task 9: Data analysis manuscript preparation and dissemination of results (Months: 30-36)

- *Milestone Achieved: Report results from data analyses* (Percentage of completion 0%)

What was accomplished under these goals?

Much of our focus for this reporting period has been directed towards research participant recruitment and performing study visits for subsequent enrollees. The Research Coordinator has been actively screening potential participants from the VA Puget Sound Health Care System (VAPSHCS) Urology clinic every week.

We have also been actively recruiting from the University of Washington Medical Center (UWMC). Our second research coordinator is actively overseeing recruitment activities at UWMC.

As of this reporting period, we have enrolled 34 participants.

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?

During the next reporting period, we will continue recruitment activities at UWMC and the VAPSHCS Urology clinics. With the recruitment efforts of the primary Research Coordinator in the Urology clinic at VAPSHCS in Seattle and a second research coordinator to oversee recruitment activities at UWMC, we anticipate that having two open recruitment sites will continue to increase our recruitment numbers and thus aid in accomplishing our end goal of enrolling 60 participants in the study. Study testing of enrolled participants will also continue through the next reporting period.

4. 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.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Due to delays related to the COVID pandemic, our recruitment was temporarily delayed. With the cost extension granted recently, we are on track to complete recruitment over the next year.

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

Due to the COVID-19 pandemic, recruitment was slower than originally anticipated but research activities are currently increasing. Recruiting subjects at VAPSHCS and UWMC with Urology clinics open every single weekday will allow for continued recruitment and boost our enrollment numbers. Our currently enrolled subjects are provided with our contact information to allow them to contact us with any study related questions or concerns they may have. Participants are also contacted a few weeks prior to their next scheduled study visit to allow them to plan ahead. As stated above, the cost extension provided recently will be very instrumental in allowing to complete recruitment over the next year.

Changes that had a significant impact on expenditures

Personnel costs and PPE supply costs continued during the pandemic with decreased recruitment rate and patient-related costs. The recently granted cost extension will ensure that the project has sufficient funds to meet all objectives in the coming year.

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

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

1. Measuring physical function and body composition in older patients with cancer. Geriatrics Grand Rounds, September 2020 (online Seminar due to COVID).
2. Frailty. University of Washington Geriatric Healthcare Series, Seattle, WA, October 2020.
3. "Current clinical trials in cancer cachexia and cancer-related fatigue at PSVAHCS" VAPSHCS Oncology section monthly meeting. Given via Zoom due to COVID. December 2020.
4. Novel Insights on Body Composition and Physical Function in Patients with Cancer Cachexia. 3rd Cachexia Conference. September 2020, [Originally scheduled to take place in Montreal, Canada, online conference due to COVID].
5. Ghrelin in Cancer Cachexia and Aging-Related Sarcopenia. 2021 Padua Days on Muscle & Mobility Medicine (PDM3). May, 2021. Padova, Italy. [Online conference due to COVID].
6. Cancer Cachexia – A Complex Problem: Pathophysiology. Multinational Association of Supportive Care in Cancer Annual Meeting, June 2021. [Online conference due to COVID].
7. Clinically Relevant Outcomes of Physical Function and Muscle Strength. Multinational Association of Supportive Care in Cancer Annual Meeting, June 2021. [Online conference due to COVID].

- **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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Jose M Garcia, MD, PhD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-4245-1753
Nearest person month worked:	1.2 CM
Contribution to Project:	No changes.
Name:	Atreya Dash, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-2634-5539
Nearest person month worked:	0.41 CM
Contribution to Project:	No changes.
Name:	Michelle Garrison, PhD MPH
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-6603-7696
Nearest person month worked:	0.95 CM
Contribution to Project:	No changes.
Name:	Gary Miranda, LPN
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.8 CM
Contribution to Project:	No changes
Name:	Kora Krumm
Project Role:	Research Technician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	6.7 CM
Contribution to Project:	No changes.

Name:	Lauren Paulsen
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.9 CM
Contribution to Project:	No changes.
Name:	Haiming Liu, PhD
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0003-3142-3690
Nearest person month worked:	12 CM
Contribution to Project:	No changes.

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

See the attached, updated Previous/Current/Pending Support (PCPS) documents from Dr. Garcia and Dr. Dash. Two industry-funded clinical trials with Dr. Garcia as the PI began during the reporting period. These clinical trials have no scientific, budgetary effort overlap with this grant. They are:

C3651009, Pfizer
11/19/2020 - present
A Phase 1b, 12-Week, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Following Repeated Subcutaneous Administrations of PF-06946860 in Patients with Cancer and Cachexia
This study is an early phase registration clinical trial study of a new drug modulating GDF-15
Role: Principal Investigator

TCH-306, Ascendis
05/13/2021 – present
foresiGHt: A multicenter, randomized,parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency
Clinical trial of a long-acting GH in patients with GH deficiency
Role: Principal Investigator

In addition, two of Dr. Garcia's previously active projects ended during the reporting period:

T32AG000057 (PI: Rabinovitch, UW)
NIH/NIBIB
5/1/2013-4/30/2021
Genetic Approaches to Aging Training Grant
This training program provides support for eight postdoctoral and eight predoctoral trainees in studies of the biology of aging

R21HD097776 (PI – Calarge, Baylor)
NIH/NICHD
01/01/2019 – 12/31/2020
Examining SSRI-Induced Disruption of Pubertal Growth Spurt
This study aimed to establish the relationship between SSRI use and pubertal growth

What other organizations were involved as partners?

Organization Name: University of Washington
Location of Organization: (if foreign location list country): Seattle, WA, United States
Partner's contribution to the project: Facilities (recruitment site)

Organization Name: UW (Harborview Medical Center)
Location of Organization: (if foreign location list country): Seattle, WA, United States
Partner's contribution to the project: Facilities (recruitment site)

8. SPECIAL REPORTING REQUIREMENTS

See attached Award Chart

9. APPENDICES:

PCPS documents for Dr. Jose Garcia (PD/PI) and Dr. Atreya Dash (Co-Investigator/Consortium PI) are provided on the following pages.

PC170059: The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients

PI: Dr. Jose Garcia, MD, PhD, SIBCR

Budget: $1,072,012 **Topic Area:** Prostate Cancer **Mechanism:** W81XWH-17-PCRP-IA

Research Area: 0300 **Award Status:** September 1, 2018 – August 31, 2022

Study Goals: To establish the role of mitochondrial dysfunction on ADT-induced sarcopenia in patients with PCa

Specific Aims:

To determine the extent to which ADT induces changes in:

1) Lean body mass (LBM) and muscle performance
2) Mitochondrial function measured both in-vivo and ex-vivo
3) Fatigue and Health-related-quality of life (HR-QOL) scores

Key Accomplishments:

Publications: None.
Patents: None.
Funding Obtained: None.

PREVIOUS / CURRENT / PENDING SUPPORT

Garcia, Jose, PhD, MD

CURRENT

Title:	**Mechanisms of action of ghrelin in muscle and adipose tissue in cancer-related cachexia (PI: Garcia)**
Effort:	2.4 calendar months
Supporting Agency:	Department of Veterans Affairs
Grant Officer:	Kimberlee Potter, PhD; Kimberlee.Potter@va.gov
Performance Period:	10/1/2015-9/30/2025
Funding Level:	Annual Direct Costs
Project Goals:	The goal of this project is to characterize the mechanisms leading to muscle and fat preservation by ghrelin in the setting of cancer-related cachexia
Specific Aims:	1) Characterize the mechanisms mediating the effects of ghrelin in skeletal muscle in the setting of sarcopenic obesity. 2) Determine the mechanisms mediating the effects of ghrelin on adiposity and adipocyte function in sarcopenic obesity. 3) Establish the extent to which GHSR-1a mediate the effects of ghrelin in sarcopenic obesity.
Overlap:	No overlap

Title:	**Neurobehavior, Neuropathology, and Risk Factors in Alzheimer's Disease (PI: Peskind, Kraemer)**
Effort:	0.1 calendar months
Supporting Agency:	T32AG052354, NIH/NIA
Grant Officer:	Dallas Anderson, PhD; andersda@nia.nih.gov
Performance Period:	5/1/2016-4/30/2022
Funding Level:	Total Costs
Project Goals:	The objective of our research training program is to provide interdisciplinary training for basic science, clinical, and translational researchers so that they will be able to advance clinical hypotheses about the etiology, pathophysiology, and treatment of AD and related disorders.
Specific Aims:	Our training program is the only formal program at the University of Washington focused on training investigators to carry out basic, clinical, and translational research in AD and related neurodegenerative dementing disorders.
Overlap:	No overlap

Title:	**Metabolic and QOL effects of GH in mTBI (PI: Garcia)**
Effort:	0.1 calendar months
Supporting Agency:	Pfizer
Grant Officer:	Daliza Crane; 484-865-5988; daliza.crane@pfizer.com
Performance Period:	11/30/2016-07/01/2022
Funding Level:	Total Costs
Project Goals:	The goal of this project is to explore the role of GH replacement in veterans with mild TBI and AGHD.
Specific Aims:	Determine the effects of GH replacement in patients with AGHD due to TBI
Overlap:	No overlap

Title:	**The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients (PI: Garcia)**
Effort:	1.2 calendar months
Supporting Agency:	Department of Defense/CDMRP
Grant Officer:	Melanie Neagley, PhD; Melanie.a.Neagley.ctr@mail.mil
Performance Period:	9/1/2018-8/31/2022
Funding Level:	Total Costs
Project Goals:	This project will study the role of mitochondria in prostate cancer patients undergoing ADT.
Specific Aims:	The specific aims of this proposal are to determine the extent to which ADT induces changes in: 1) Lean body mass (LBM) measured by X-ray densitometry (DEXA), and muscle performance measured by handgrip strength, actigraphy, stair climbing power, 6-minute walk test, and VO2 peak. These assessments will be performed before starting ADT, and repeated 3 and 6 months after starting ADT. 2) Mitochondrial function assessed in-vivo by magnetic resonance spectroscopy and optical spectroscopy (31P MRS/OS) and ex-vivo in muscle biopsy specimens by measuring different aspects of mitochondrial metabolism and function including biomarkers of mitochondrial content and oxidative phosphorylation, mitochondrial respiration, mitochondrial biogenesis, mitophagy and production of reactive oxygen species (ROS). 31P MRS/OS will be performed at baseline and repeated 3 and 6 months after starting ADT. Vastus lateralis muscle biopsies will be performed at baseline and repeated 6 months after starting ADT. 3) Fatigue and HR-QOL scores as measured by well-validated questionnaires: Functional Assessment of Cancer Therapy–Prostate (FACT-P), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) and Expanded Prostate Cancer Index Composite (EPIC) Assessment. These assessments will be performed before starting ADT, and repeated 3 and 6 months after starting ADT.
Overlap:	No overlap

Title:	**Improving Patient-Important Outcomes with Testosterone Replacement in Hypogonadal Men with a Prior History of Cancer (PI: Garcia)**
Effort:	1.8 calendar months
Supporting Agency:	R01CA239208, NIH/NCI
Grant Officer:	Ashley Smith, PhD; (240) 276-6714; smithas@mail.nih.gov
Performance Period:	5/8/2019-4/30/2024
Funding Level:	Annual Direct Costs
Project Goals:	This project will study the efficacy of testosterone replacement on cancer-related fatigue in male cancer survivors who report fatigue and have testosterone deficiency.
Specific Aims:	1) To compare the efficacy of weekly testosterone injections versus placebo on our primary outcome, fatigue, in cancer survivors with testosterone deficiency. 2) To compare the effects of weekly testosterone injections on sexual function (sexual activity score, sexual desire, erectile function), well-being, mood and QOL. 3) To determine whether testosterone administration improves body composition, muscle strength and physical activity more than placebo.
Overlap:	No overlap

Title:	**Improving cancer-related fatigue, sexual dysfunction and quality of life in older men with cancer and androgen deficiency (MPI: Garcia)**
Effort:	1.8 calendar months
Supporting Agency:	R01AG061558, NIH/NIA
Grant Officer:	Sergei Romashkan, MD, PhD; (301) 435-3047; romashks@nia.nih.gov
Performance Period:	8/1/2019-4/30/2024
Funding Level:	Annual Direct Costs
Project Goals:	This project will study the effects of testosterone in elderly men with androgen deficiency and cancer.
Specific Aims:	1) To compare the efficacy of weekly testosterone injections versus placebo on our primary outcome, fatigue, in men with cancer and testosterone deficiency. 2) To compare the effects of weekly testosterone injections on sexual function (sexual activity score, sexual desire, erectile function), QOL (including mood, well-being and loss of productivity) and burden on the caregivers. 3) To compare the efficacy of testosterone administration versus placebo on body composition, muscle strength and physical function.
Overlap:	No overlap

Title:	**A Phase 1b, 12-Week, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Following Repeated Subcutaneous Administrations of PfF06946860 in Patients with Non-Small Cell Lung Cancer and Cachexia (Site PI: Garcia)**
Effort:	0.1 calendar months
Supporting Agency:	Pfizer, Inc, C3651009
Grant Officer:	Kirsten Duncan, PharmD; 425.941.9359; kirsten.duncan@pfizer.com
Performance Period:	11/19/2020-Present
Funding Level:	Dependent on enrollment
Project Goals:	This project will study the safety and tolerability of the novel agent PF06946860 in NSCLC suffering from cachexia.
Specific Aims:	The specific aims for the study include to assess the safety, tolerability, pharmacokinetic and pharmacodynamics of repeated doses of this novel agent in patients with cachexia due to NSCLC. This multicenter, regulatory study will set the basis for future studies in cachexia.
Overlap:	No overlap

Title:	foresiGHt: A multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency **(Site PI: Garcia)**
Effort:	0.1 calendar months
Supporting Agency:	Ascendis Pharma Endocrinology Division A/S, TCH-306
Grant Officer:	Olu Lawson, Clinical Trial Manager 281-849-7884 o.lawson@accelsiors.com
Performance Period:	5/13/2021-Present
Funding Level:	Dependent on enrollment
Project Goals:	To compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency

Specific Aims:	1) To compare safety; and 2) to comapre efficacy of a new long acting GH formulation to placebo and to daily GH in patients with AGHD.
Overlap:	No overlap

Title:	**GH replacement therapy in Veterans with mTBI and AGHD (PIs: Garcia and Jorge)**
Effort:	1.2 calendar
Supporting Agency:	VA Cooperative Studies Program
Performance Period:	10/01/2020-09/30/2024
Funding Level:	Annual direct costs approximately
Project Goals:	This is large multicenter study that will be examine the efficacy of rhGH to improve quality of life (QoL) among Veterans with mild TBI and GH deficiency. This trial has been recently approved by the CSP with an estimated start of recruitment in the fall of 2021.
Specific Aims:	When compared with placebo, GHRT will have a beneficial effect on: 1) QoL; 2) Body composition (specifically reduction of fat content and visceral fat); 3) Fatigue; 4) Chronic Pain; 4) Depression; 5) Cognitive functioning (specifically attention, memory and executive functioning
Overlap:	No overlap

PENDING

Title:	**Growth Hormone Replacement Therapy in Veterans with Gulf War Illness and GH Deficiency (PI: Jorge)**
Effort:	1.0 calendar months
Supporting Agency:	Department of Defense/CDMRP
Performance Period:	10/2021-09/2024
Funding Level:	Direct Costs requested
Project Goals:	This project is a multicenter, VA, randomized clinical trial of GH vs placebo in Veterans with Gulf War Illness and AGHD
Specific Aims:	To establish the safety and efficacy of GH replacement in individuals with AGHD and GWI.
Overlap:	No overlap.

Title:	**A 6-Week, Randomized, Doubleblind, Sponsor-Open Study to Assess the Effect of Repeated Subcutaneous Administration of PF-06946860 on Appetite in Participants with Advanced Cancer and Anorexia, Followed by an 18-Week Open-Label Treatment Period (Site PI: Garcia)**
Effort:	0.1 calendar months
Supporting Agency:	Pfizer, C3651010
Performance Period:	TBC
Funding Level:	Dependent on enrollment
Project Goals:	To Assess the Effect of Repeated Subcutaneous Administration of PF-06946860 on Appetite in Participants with Advanced Cancer and Anorexia,
Specific Aims:	To Assess the Effect of the GDF-15 antibody PF-06946860 on Appetite in Participants with Advanced Cancer and Anorexia, Followed by an 18-Week Open-Label Treatment Period
Overlap:	No overlap.

PREVIOUS

Title:	**Genetic Approaches to Aging Training Grant (PI: Rabinovitch)**
Effort:	0.1 calendar months
Supporting Agency:	T32AG000057, NIH/NIBIB
Grant Officer:	Max Guo, PhD; max.guo@nih.gov
Performance Period:	5/1/2013-4/30/2021
Funding Level:	Annual Direct Costs
Project Goals:	This training program provides support for 8 postdoctoral and 8 predoctoral trainees in studies of the biology of aging.
Specific Aims:	The goal of our program is to train new independent investigators who will utilize molecular and genetic techniques to investigate the biology of aging.
Overlap:	No overlap

Title:	**Examining SSRI- Induced Disruption of Pubertal Growth Spurt (PI: Calarge)**
Effort:	0.6 calendar months
Supporting Agency:	R21HD097776, NIH/NICHD
Grant Officer:	Zhaoxia Ren, MD, PhD; zren@mail.nih.gov
Performance Period:	1/1/2019-12/31/2020
Funding Level:	Total Costs
Project Goals:	This project will study the effect of SSRI exposure on growth in children.
Specific Aims:	1) Compare the effect of fluoxetine and sertraline on markers of GH function in peripubertal youth. We hypothesize that, compared to sertraline, fluoxetine will be associated with a reduction in serum IGF-1 and IGFBP-3 concentration, between pre-treatment and 8 weeks after treatment onset, in Tanner stage 2-4 youth. 2) Establish the persistence of fluoxetine-induced disruption of GH function in peripubertal youth. Fluoxetine-induced disruption in GH activity, as reflected by IGF-1 and IGFBP-3 serum concentration, is expected to persist six months after treatment onset. 3) Examine the causal relation between fluoxetine-induced disruption in GH function and longitudinal growth in peripubertal youth. Reduction in IGF-1 and IGFBP-3 by 8 weeks in fluoxetine-treated Tanner stage 2-4 youth will mediate reduction in their longitudinal growth at 6 months.
Overlap:	No overlap

Title:	**Intramuscular Mechanisms of Cancer Cachexia (PI: Li)**
Effort:	1.2 calendar months
Supporting Agency:	NIH/NIMS
Grant Officer:	Rebecca Liddell Huppi, PhD; liddellr@exchange.nih.gov
Performance Period:	10/1/2015-7/31/2020
Funding Level:	Annual Direct Costs
Project Goals:	The goal for this study is to determine novel intramuscular mechanisms contributing to muscle wasting in cancer cachexia.
Specific Aims:	1) To determine whether UBR2 is a key E3 ubiquitin ligase responsible for cancer-induced muscle wasting. 2) To determine whether site-specific acetylation of C/EBPβ mediates cancer-induced UBR2 upregulation. 3) To determine the signaling mechanism that mediates cancer-induced acetylation of C/EBPβ.
Overlap:	No overlap

Title:	**Novel Pharmacologic Risk factors for Common Non-AIDS defining Cancers in Individuals with Well-controlled HIV Infection (PI: Chiao)**
Effort:	0.6 calendar months
Supporting Agency:	R01CA206476, NIH/NIBIB
Grant Officer:	Rebecca Liddell Huppi, PhD; liddellr@exchange.nih.gov
Performance Period:	6/10/2016-5/31/2020
Funding Level:	Total Costs
Project Goals:	The goal for this study is to find drugs that can modify the risk of cancer in HIV-infected patients.
Specific Aims:	1) a) To measure the effect of the duration of specific classes of cART medications on the risk of each of the 8 NADCs of interest in a cohort of veterans with well-controlled HIV, adjusting for known risk factors for each type of cancer, and b) to assess the extent of cancer risk that is mediated by metabolic disorders. 2) a) To measure the effect of duration of specific classes of common medications used to treat metabolic disorders known to impact cancer risk, utilized by HIV-infected individuals (e.g., statins, metformin, beta-blockers and ACE-Inhibitors) on the risk of developing the 8 NADCs of interest in a cohort of veterans with well-controlled HIV-infection; and b) to assess the extent that the observed cancer risk association from these common metabolic disorder- related medication is primarily mediated through their impacts on metabolic disorder control.
Overlap:	No overlap

Title:	**Long-acting ghrelin for cancer cachexia (PI: Soliman)**
Effort:	1.2 calendar months
Supporting Agency:	R44CA174094, NIH/NCI
Grant Officer:	Patricia A. Weber, PhD; weberpa@mail.nih.gov
Performance Period:	7/1/2017-3/31/2020
Funding Level:	Annual Direct Costs
Project Goals:	This project will study the effects of a novel long acting ghrelin on different murine models of cancer- related anorexia and cachexia.
Specific Aims:	Methods for cGMP production of the long-acting ghrelin will be put in place. We will perform IND-enabling GLP toxicity and immunogenicity studies using the cGMP material. These studies are needed prior to beginning human trials. Once fully developed, this long- acting ghrelin derivative would provide a patient-friendly cachexia therapy that would significantly improve the prognosis and quality of life in patients with cancer and also in patients with other chronic disorders such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD).
Overlap:	No overlap

Title:	**Validation of Macimorelin as a Test for Adult Growth Hormone Deficiency (PI: Garcia)**
Effort:	0.6 calendar months
Supporting Agency:	Aeterna Zentaris, Inc
Grant Officer:	Jill Steeley; jill.steeley@ergomedplc.com
Performance Period:	2/8/2016-9/30/2019
Funding Level:	Annual Direct Costs

Project Goals:	The goal for this study is to determine the role of macimorelin as a diagnostic test for adult growth hormone deficiency.
Specific Aims:	Validate the use of macimorelin as a test for AGHD diagnosis.
Overlap:	No overlap.

Title:	**NAFLD: Mechanisms and treatments. (PI:Timchenko)**
Effort:	0.6 calendar months
Supporting Agency:	R01DK102597, NIH/NCI
Grant Officer:	Basil Eldadah, MD, PhD; eldadahb@mail.nih.gov
Performance Period:	7/1/2015-12/21/2016
Funding Level:	Total Costs
Project Goals:	The goal for this study is to determine the mechanisms involved in the development of NAFLD.
Specific Aims:	The specific aims for this project included to characterize novel mechanisms mediating MAFLD in animal models and in liver samples from humans.
Overlap:	No overlap.

Title:	**The Role of Immune Homeostasis in Protection from Cancer Cachexia (PI: Davies)**
Effort:	0.3 calendar months
Supporting Agency:	R01CA185349, NIH/NCI
Grant Officer:	Barbara A. Spalholz, PhD; bs62d@nih.gov
Performance Period:	7/1/2015-8/31/2016
Funding Level:	Total Costs
Project Goals:	The goal for this study is to determine the role of subsets of lymphocytes in the pathogenesis of cachexia.
Specific Aims:	The specific aims for this project included to test the potential role for immune dysregulation caused by the tumor in patients with cancer induced cachexia.
Overlap:	No overlap.

Current and Pending Support

NAME OF INDIVIDUAL: Atreya Dash (Co-Investigator)
ACTIVE

Title of Project: ***The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients*** Funding Source: W81XWH1810461 (PI: Garcia, SIBCR), DOD Role: Co-Investigator *Grant/Science Officer: Melanie Neagley, PhD; Melanie.a.Neagley.ctr@mail.mil* This project will study the role of mitochondria in prostate cancer patients undergoing ADT. Overlap: There is no financial, effort or scientific overlap between this project and the current proposal	Dates of Approved/Proposed Project: 09/01/2019 - 08/31/2022 Total Direct Costs:	

NAME OF INDIVIDUAL: Atreya Dash (Sub-Investigator)
PREVIOUS

Title of Project: ***Canary Prostate Cancer Surveillance Study*** Funding Source: Canary Foundation *Scientific Program Manager: Heidi Auman – heudu@canaryfoundation.org* This is a multi-center, prospective active surveillance study with selective intervention in patients with previously untreated, clinically localized prostate cancer at diagnosis. Primary objective is to discover and confirm biomarkers that predict aggressive disease as defined by pre-specified histological, PSA, clinical criteria, or outcomes based on these variables. Secondary objectives are to determine the proportion of patients on active surveillance who progress based on the above criteria and determine the clinical predictors of disease progression. Overlap: There is no financial, effort or scientific overlap between this project and the current proposal.	Dates of Approved/Proposed Project: 01/15/2009 - 05/31/2018 Annual Direct Costs:	

Current and Pending Support

NAME OF INDIVIDUAL: Atreya Dash (Sub-Investigator)
PREVIOUS

Title of Project: ***Open versus Robotic Assisted Radical Cystectomy: a Randomized Trial.*** Funding Source: NIH R01CA155388 (PI: Parekh, University of Texas Health Sciences Center San Antonio), NIH/NCI Role: Investigator *Program Official: Paul Doria-Rose - doriarop@mail.nih.gov* This grant supported a multi-institutional randomized control trial to compare robotic-assisted radical cystectomy against traditional open surgery in the treatment of invasive bladder cancer. Overlap: There is no financial, effort or scientific overlap between this project and the current proposal.	Dates of Approved/Proposed Project: 07/2011 – 11/2017 While I was at UC Irvine 2011-13.	
Title of Project: ***Genomic Health VA Prostate Study*** Funding Source: Genomic Health, Inc. *Grant Manager: Megan Rothney - mrothney@genomichealth.com* Improving Risk Stratification Among Veterans with Newly Diagnosed, Clinically Low-risk Prostate Cancer Using the 17-gene Genomic Prostate Score™ Assay. To compare treatment patterns before and after introduction of the GPS assay to determine if the 17-gene GPS result assists in standardizing treatment of prostate cancer across six Veteran Affairs Medical Centers Overlap: There is no financial, effort or scientific overlap between this project and the current proposal.	Dates of Approved/Proposed Project: 06/10/2014 - 12/31/2016 Annual Direct Costs:	