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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)
Dr. Jose Garcia
E-Mail: jg77@uw.edu

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Seattle Institute of Biomedical and Clinical Research
1660 S Columbian Way #151F
Seattle, WA 98108-1532

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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 August 31, 2023, we have enrolled 60 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 we have now completed study recruitment under a no cost extension already granted.

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

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TABLE OF CONTENTS

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: 4-60)

- *Milestone Achieved: Recruitment and evaluation completed for study 1* (Percentage of completion: 100%; RECRUITMENT COMPLETED: 2/10/2023; EVALUATIONS COMPLETED: 9/01/2023.

Patients screened	Patients Eligible	Patients Enrolled
3,006	114	60 (one lost to FU)

Major Task 5: Measure LBM and muscle performance (Months: 4-66)

- *Milestone Achieved: Measures of LBM and muscle performance obtained* (Percentage of

Median (STD)	**Baseline (*n = 59*)**	**3moFU (*n* = 57)**	**6moFU (*n = 54*)**
ALM (kg)	25.12 (4.01)	24.33 (4.01)	24.8 (3.88)
Mean HGS (kg)	42.0 (7.96)	39.5 (8.74)	38.5(7.61)
6MWT (m)	523.34 (102.36)	508.59 (108.75)	478.88 (120.56)
SCP (W)	377.89 (112.26)	366.30 (100.94)	369.05 (118.34)

Major Task 6: Measure Mitochondrial Function (Months: 4-66)

- *Milestone Achieved: Measures of mitochondrial function obtained* (Percentage of completion: 77.5%)

Median (STD)	**Baseline (*n = 49*)**	**6moFU (*n = 44*)**
Basal respiration (OCR)	47.9 (49.66)	43.86 (41.71)
ATP-linked respiration (OCR)	321.81 (325.22)	263.97 (303.91)
Maximal respiration (OCR)	320.57 (391.72)	268.29(428.05
Non-mitochondrial respiration (OCR)	42.9 (42.86)	37.15 (37.14)

Major Task 7: Measure Fatigue and HR-QOL Scores (Months: 4-66)

- *Milestone Achieved: Measures of Fatigue and HR-QOL scores obtained* (Percentage of completion: 95.0 %)

Median (STD)	**Baseline (*n* =59)**	**3moFU (*n* = 57)**	**6moFU (*n* = 55)**
FACIT-F (QOL)	115 (23.91)	111.0 (22.25)	107 (26)
QLQ-C30 (%) (fatigue score percentile)	22.0 (22.0)	33.3 (23.62)	33.33 (25.84)

Major Task 8: Explore the predictive value of the baseline measurements (Months: 6-66)

- *Milestone Achieved: Recruitment and evaluation completed for study 2* (Percentage of completion: 100%)

Major Task 9: Data analysis manuscript preparation and dissemination of results (Months: 66-72)

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

What was accomplished under these goals?

As of August 31, 2023, we have enrolled 60 research participants in the study and have completed recruitment.

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 be completing study testing of enrolled study participants and proceed with data analysis, and manuscript writing.

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 in 2021 and the no-cost extension granted in 2022, we have been able to complete study recruitment as of August 31, 2023. The additional one-year cost extension granted through August 31, 2024 will enable data analysis and manuscript preparation.

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

N/A

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 cost extension granted in 2021 helped ensure that the project has sufficient funds to meet all objectives by the end of the recently extended project period. The no-cost extensions in 2022 and 2023 enabled us to complete recruitment/enrollment and will allow us to proceed with sample processing/assaying, data analysis and manuscript preparation.

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].
8. Frailty. University of Washington/ VA GRECC Geriatric Fellowship Lecture Series, Seattle, WA, October 2021.
9. "Effects of Androgen Deprivation Therapy on Body Composition, inflammation and Physical Function". Weight Matters Seminar Series, Puget Sound VA HCS, Seattle, WA, January 2022.
10. "The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients" Fred Hutchinson Cancer Research Center/Univ. of Washington Prostate Group Joint Lab Meeting, Seattle, WA, January 2022.
11. "A systems-based approach to cancer treatment related impairments: Cancer cachexia" Cancer Rehabilitation VA-ECHO Program. March 30, 2022. [National Webinar]
12. Use of biomarkers to assess treatment effect in cancer cachexia. Society for Sarcopenia Cachexia and Wasting Annual Meeting. Lisbon, Portugal. June 2022.

- **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:	Haiming Liu, PhD
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0003-3142-3690
Nearest person month worked:	9 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:	Lauren Paulsen
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.2 CM
Contribution to Project:	No changes.

Name:	Branda Levchak
Project Role:	Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2.2 CM
Contribution to Project:	Patient recruitment/study procedures

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. Dr. Garcia's reflects a new clinical trial:

C3651003, Pfizer Pharmaceuticals
07/27/2023 – present
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of Ponsegromab in Patients with Cancer, Cachexia, and Elevated Concentrations of GDF-15, Followed by an Optional Open-Label Treatment Period
Role: Site PI

There is also a new pending project on both Dr. Garcia's and Dr. Dash's PCPS that we expect to be funded in the next year

R01CA279220, NIH/NCI
09/01/2023-08/31/2028
SArcopenia in men with Prostate Cancer undergoing ADT (SAP-ADT)
Role: PI (Garcia); Co-Investigator (Dash)

SIBCR has submitted a prior approval request to DoD to lower Dr. Garcia's committed effort on this project to 5% during the final no-cost extension (NCE) period, 9/1/2023-8/31/2024. Dr. Garcia's PCPS reflects this reduction. Dr. Dash's PCPS reflects similar reduction to 2% during the same period, which UW has requested approval for from SIBCR.

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

N/A

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, 2024

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:

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].
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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].
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12. Use of biomarkers to assess treatment effect in cancer cachexia. Society for Sarcopenia Cachexia and Wasting Annual Meeting. Lisbon, Portugal. June 2022.

Patents: None.

Funding Obtained: In 2021, Dr. Lindsey Anderson (PI) applied for and received a $38,583 pilot grant titled "Metabolomics approach to characterize the effects of androgen deprivation therapy on skeletal muscle in prostate cancer patients" (June 2021-February 2022) from the UW Center for Translational Muscle Research, funded by the National Institutes of Health (NIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases, P30AR074990. Dr. Anderson's Co-PI is Dr. Atreya Dash and Dr. Garcia is a Co-Investigator. There is no overlap between the CTMR pilot grant and W81XWH-17-PCRP-IA. The CTMR funding supported effort for a research assistant to perform muscle ultrasound and supports metabolomics analysis of blood and muscle specimens by the UW CTMR core.

PREVIOUS/CURRENT/PENDING SUPPORT
GARCIA, JOSE, MD, PhD,

PREVIOUS (past 5 years)

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

Title:	**Genetic Approaches to Aging Training Grant (PI: Rabinovitch)**
Effort:	0.1 calendar months
Role:	Co-Investigator/Mentor
Supporting Agency:	NIH/NIBIB, T32AG000057
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.

Title:	**Examining SSRI- Induced Disruption of Pubertal Growth Spurt (PI: Calarge)**
Effort:	0.6 calendar months
Role:	Co-Investigator
Supporting Agency:	NIH/NICHD, R21HD097776
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. 2) Establish the persistence of fluoxetine-induced disruption of GH function in peripubertal youth. 3) Examine the causal relation between fluoxetine-induced disruption in GH function and longitudinal growth in peripubertal youth.

Title:	**Intramuscular Mechanisms of Cancer Cachexia (PI: Li)**
Effort:	1.2 calendar months
Role:	Co-Investigator
Supporting Agency:	NIH/NIMS, R01AR067319
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.

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
Role: Co-Investigator
Supporting Agency: NIH/NIBIB, R01CA206476
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.

Title: **Long-acting ghrelin for cancer cachexia (PI: Soliman)**
Effort: 1.2 calendar months
Role: Co-Investigator
Supporting Agency: NIH/NCI, R44CA174094
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).

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.

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, Inc.,C3651010
Performance Period:	10/2021-09/2022
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

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; kirsten.duncan@pfizer.com
Performance Period:	11/2020-06/2022
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.

Title:	**Metabolomics approach to characterize the effects of androgen deprivation therapy on skeletal muscle in prostate cancer patients (PIs: Anderson and Dash)**
Effort:	0 calendar months
Role:	Co-Investigator
Supporting Agency:	NIH/ UW Center for Translational Muscle Research Pilot Grant, P30AR074990
Grant Officer:	Emily Carifi, emily.carifi@nih.gov
Performance Period:	06/2021-02/2022

Funding Level:	total costs
Project Goals/Aims:	To establish the role of androgen-dependent molecular pathways leading to androgen deprivation therapy (ADT)-induced sarcopenia in men with prostate cancer assessed by targeted metabolomics perturbations in skeletal muscle and plasma which will be associated with sarcopenia.

Title:	**Metabolic and Quality of Life Effects of Growth Hormone Treatment in Patients with Mild Traumatic Brain Injury and AGHD (PI: Garcia)**
Effort:	0.1 calendar months
Role:	PI
Supporting Agency:	Pfizer Pharmaceuticals, W1210860
Grant Officer:	Carol Grant, carol.grant@pfizer.com
Performance Period:	11/2016-07/2022
Funding Level:	(NCE) total costs
Project Goals/Aims:	The goal of this project is to explore the role of GH replacement in veterans with mild TBI and AGHD.

CURRENT

Title:	**The Role of Ghrelin and the GHSR-1a receptor in Sarcopenic Obesity (PI: Garcia)**
Effort:	2.4 calendar months
Supporting Agency:	Department of Veterans Affairs, I01BX002807
Grant Officer:	Kimberlee Potter, PhD; Kimberlee.Potter@va.gov
Performance Period:	10/1/2019-9/30/2023
Funding Level:	Total 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.

Title:	**Neurobehavior, Neuropathology, and Risk Factors in Alzheimer's Disease (MPI: Peskind, Kraemer)**
Effort:	0.1 calendar months
Role:	Co-Investigator/Mentor
Supporting Agency:	NIH/NIA, T32AG052354
Grant Officer:	Dallas Anderson, PhD; andersda@nia.nih.gov
Performance Period:	5/1/2022-4/30/2027
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.

Title:	**The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients (PI: Garcia)**
Effort:	0.6 calendar months (requested reduction)
Supporting Agency:	Department of Defense/CDMRP, W81XWH1810461
Grant Officer:	Melanie Neagley, PhD; Melanie.a.Neagley.ctr@mail.mil
Performance Period:	9/1/2018-8/31/2023
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. 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). 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.

Title:	**Improving Patient-Important Outcomes with Testosterone Replacement in Hypogonadal Men with a Prior History of Cancer (MPI: Garcia, Basaria)**
Effort:	1.4 calendar months
Supporting Agency:	NIH/NCI, R01CA239208
Grant Officer:	Ashley Smith, PhD; smithas@mail.nih.gov
Performance Period:	5/8/2019-4/30/2025
Funding Level:	Total 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.

Title:	**Improving cancer-related fatigue, sexual dysfunction and quality of life in older men with cancer and androgen deficiency (MPI: Garcia, Basaria, DelFabbro)**
Effort:	1.4 calendar months
Supporting Agency:	NIH/NIA, R01AG061558
Grant Officer:	Sergei Romashkan, MD, PhD; romashks@nia.nih.gov
Performance Period:	8/1/2019-4/30/2025
Funding Level:	Total 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.

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; o.lawson@accelsiors.com
Performance Period:	5/13/2021-12/31/2024
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 compare efficacy of a new long acting GH formulation to placebo and to daily GH in patients with AGHD.

Title:	**GH replacement therapy in Veterans with mTBI and AGHD (PIs: Garcia and Jorge)**
Effort:	0.92 calendar
Supporting Agency:	VA Cooperative Studies Program, CSP #2018
Performance Period:	03/01/2021-09/30/2028
Funding Level:	total costs
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.
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

Title:	**Growth Hormone Replacement Therapy in Veterans with Gulf War Illness and GH Deficiency (PI: Jorge)**
Effort:	1.82 calendar months
Supporting Agency:	Department of Defense/CDMRP, W81XWH2110450 (Subaward #7000001651)
Performance Period:	10/01/2021-09/29/2024
Funding Level:	Total Costs (subaward)
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.

Title: **A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults with Growth Hormone Deficiency (Site PI: Garcia)**
Effort: 0.1 calendar months
Supporting Agency: Ascendis Pharma Endocrinology Division A/S, TCH-306-EXT
Grant Officer: Olu Lawson, Clinical Trial Manager; o.lawson@accelsiors.com
Performance Period: 5/20/2022-02/28/2025
Funding Level: Dependent on enrollment
Project Goals/Aims: To assess the long-term safety of once-weekly lonapegsomatropin in adults with growth hormone deficiency (GHD/AGHD) who participated in trial TCH-306.

Title: **Summer Research Program**
Effort: 0.1 calendar months
Supporting Agency: Department of Veterans Affairs
Performance Period: 05/01/2022-04/30/2025
Funding Level: Total Costs
Project Goals/Aims: This project enhances the diversity of the biomedical, behavioral, clinical, health services and rehabilitative research workforce by providing research experiences and related opportunities that can enrich the pool of individuals from diverse backgrounds, including nationally underrepresented groups, veterans, and disabled individuals who will be available to compete for future research opportunities in the mission areas of importance to the VA.

Title: **A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of Ponsegromab in Patients with Cancer, Cachexia, and Elevated Concentrations of GDF-15, Followed by an Optional Open-Label Treatment Period (Site PI: Garcia)**
Effort: 0.1 calendar months
Supporting Agency: Pfizer Pharmaceuticals, C3651003
Grant Officer: Shrinidhi Balu, shrinidhi.balu@pfizer.com
Performance Period: 07/27/2023-Present
Funding Level: Dependent on enrollment
Project Goals/Aims: Patients with advanced cancer and elevated concentrations of GDF-15 frequently develop cachexia which impacts their quality of life and survival. Inhibiting the activity of GDF-15 in such patients may help reverse cachexia and improve their quality of life. This study will evaluate the efficacy, safety and tolerability of ponsegromab, an inhibitor of GDF-15, compared to placebo, in patients with cancer, cachexia, and elevated concentrations of GDF-15.

PENDING

Title: **SArcopenia in men with Prostate Cancer undergoing ADT (SAP-ADT) (MPI: Garcia, Gharib)**
Effort: 1.8 calendar months
Supporting Agency: NIH/NCI, R01CA279220
Performance Period: 09/01/2023-08/31/2028
Funding Level: Total Costs
Project Goals: In men with prostate cancer undergoing hormonal treatment (known as “ADT”), loss of muscle mass and function – “sarcopenia” – is one of the most prevalent and debilitating symptoms with a profound negative effect on quality of life, and

without any known effective treatment. To set the foundation for the development of these much-needed treatments in the future, we are proposing a clinical trial where men with prostate cancer starting ADT will be followed for one year with the goals of establishing how best to measure and predict sarcopenia, as well as delineating skeletal muscle mechanisms leading to this complication, including the role of the mitochondria. The data generated will provide essential information on tools to measure sarcopenia that are clinically meaningful to patients, shed light on new biological targets for this condition, and identify markers of sarcopenia that can lead to early diagnosis and guide the selection of patients and outcomes for future clinical trials.

Specific Aims: 1) Establish the effects of ADT on different outcome measures assessing sarcopenia in PCa patients and ascertain their clinical meaningfulness; we also will characterize the lived experiences of these men regarding impact on QOL. 2) Identify and prioritize the molecular pathways mediating the effects of ADT on physical function and muscle strength and mass using a comprehensive multi-omics approach. 3) Determine the role of baseline biomarker levels as predictors of physical function and muscle strength and mass. 4) Perform mechanistic studies in muscle tissue to define the role of mitochondrial dysfunction in ADT-induced sarcopenia.

Title: **Quantitative Magnetic Resonance Evaluation of Mechanisms of Cancer Cachexia (PI: Lee)**
Effort: 0.3 calendar months
Supporting Agency: NIH, TBC
Performance Period: 07/01/2023-06/30/2028
Funding Level: Subaward Total Costs
Project Goals/Aims: Dr. Garcia will oversee the measurements of key mediators of muscle wasting in cancer by PCR, and of inflammatory markers in samples from 56 animals. His lab will also perform immunohistochemistry staining for key markers; measure selected protein levels to confirm the PCR results and determine muscle cross sectional area differences between groups. These will provide insight into the underlying molecular mechanisms mediating changes in skeletal muscle and help develop MR biomarkers of cancer cachexia using the KPC mouse model.

Title: **Physiological Changes Underlying the Weight Loss Plateau in Humans (PI: Schur)**
Effort: 0.9 calendar months
Supporting Agency: NIH, TBC
Performance Period: 07/01/2023-06/30/2028
Funding Level: Subaward Total Costs
Project Goals/Aims: Dr. Garcia will be responsible for the supervision and performance of the adipose tissue seahorse assay for the VA portion of the study. He will also lead the adipose tissue biology aspects of the grant and will co-lead, along with Dr. Marcinek, its metabolism and energetics portions in muscle. He will share responsibilities with the rest of the team on data review, scientific publications and presentations of the research.

Title: **Towards precision medicine for cancer cachexia (PI: Harrison)**
Effort: 0.1 calendar months
Supporting Agency: Cancer Council Victoria via Monash University

Performance Period:	Pending, 2023-2024
Funding Level:	Subaward Total Costs
Project Goals/Aims:	Cachexia is a life-threatening wasting syndrome lacking effective treatment, which occurs in many cancer patients. We hypothesize that the intractable nature of this condition arises because each cancer type, and potentially every cancer patient, has a characteristic signature of tumour-induced factors (tumourkines) that contribute to the initiation and progression of cachexia. Aim 1; Characterize key tumourkine "signatures" that are associated with weight loss and mortality in cancer patients. Aim 2: Utilize our unique model system to examine how the most common tumourkine signatures in cancer patients induce the multi-organ pathology of cachexia. Aim 3: Deconstruct pro-cachectic signatures to identify which tumourkines are best targeted to slow/reverse wasting in cancer patients. Dr. Garcia will measure tumourkine levels in cancer cachexia patients and identify 'signatures' associated with specific cachectic phenotypes.

OVERLAP

There is no scientific or budgetary overlap amongst current or pending projects. If all pending applications are funded, the percent effort on funded projects will be adjusted to maintain sponsored support at or below 12 calendar months.

The following statements assure:

I certify that the current and pending support provided here is current, accurate, and complete;

I agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award;

I have been made aware of these disclosure requirements as required under Section 223(a)(1) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021 (https://www.govinfo.gov/content/pkg/PLAW-116publ283/pdf/PLAW-116publ283.pdf).

I am aware that false, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties (218 USC 1001).

Signature: DocuSigned by: Jose Garcia 6AEB84FAA15549C...

Date: Aug 25, 2023

PREVIOUS/CURRENT/PENDING SUPPORT
ATREYA DASH, MD

PREVIOUS (past 5 years)

Title: *Metabolomics approach to characterize the effects of androgen deprivation therapy on skeletal muscle in prostate cancer patients*
Grant Number: P30AR074990
Time Commitment: 0 calendar months
Supporting Agency: NIH/ UW Center for Translational Muscle Research Pilot Grant (PI: Anderson)
Grants Officer: Emily Carifi, emily.carifi@nih.gov
Period of Performance: 06/2021-02/2022
Level of Funding:
Goals/Aims: To establish the role of androgen-dependent molecular pathways leading to androgen deprivation therapy (ADT)-induced sarcopenia in men with prostate cancer assessed by targeted metabolomics perturbations in skeletal muscle and plasma which will be associated with sarcopenia.
Role: Co-PI
Overlap: None

CURRENT

Title: *The role of mitochondria in ADT-induced sarcopenia in prostate cancer patients*
Grant Number: W81XWH1810461
Time Commitment: 0.24 calendar months
Supporting Agency: Department of Defense/SIBCR (PI: Garcia)
Grants Officer: Pamela Allen, pamela@sibcr.org
Period of Performance: 09/01/2019-08/31/2024 (NCE)
Level of Funding:
Goals/Aims: 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.
Role: Consortium PI
Overlap: None

Title: *Prostate cancer Active Surveillance Study (PASS) Cohort: Infrastructure Support for Cancer Research*
Grant Number: U01CA224255
Time Commitment: 0.17 calendar months
Supporting Agency: NIH/Fred Hutchinson Cancer Center (PI: Lin)
Grants Officer: Remy Loges, rloges@fredhutch.org
Period of Performance: 09/20/1019-08/31/2024
Level of Funding: (subaward)
Goals/Aims: Site will continue to follow participants according to the Canary Prostate Active Surveillance Study (PASS) Protocol.
Role: Consortium PI
Overlap: None

PENDING

Title: *Sarcopenia in men with Prostate Cancer undergoing ADT (SAP-ADT)*
Grant Number: R01CA279220
Time Commitment: 1.2 calendar months
Supporting Agency: NIH/NCI
Grants Officer: TBD

Period of Performance: 09/01/2023-08/31/2028
Level of Funding:
Goals/Aims: In men with prostate cancer undergoing hormonal treatment (known as "ADT"), loss of muscle mass and function – "sarcopenia" – is one of the most prevalent and debilitating symptoms with a profound negative effect on quality of life, and without any known effective treatment. To set the foundation for the development of these much-needed treatments in the future, we are proposing a clinical trial where men with prostate cancer starting ADT will be followed for one year with the goals of establishing how best to measure and predict sarcopenia, as well as delineating skeletal muscle mechanisms leading to this complication, including the role of the mitochondria. The data generated will provide essential information on tools to measure sarcopenia that are clinically meaningful to patients, shed light on new biological targets for this condition, and identify markers of sarcopenia that can lead to early diagnosis and guide the selection of patients and outcomes for future clinical trials.
Role: Co-I
Overlap: None

The following statements assure:

I certify that the current and pending support provided here is current, accurate, and complete;

I agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award;

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I am aware that false, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties (218 USC 1001).

Signature:

Date: Atreya Dash 360468 Digitally signed by Atreya Dash 360468 Date: 2023.08.25 09:37:40 -07'00'