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Project Title:	Growth Hormone Replacement Therapy in Veterans with Gulf War Illness and GH Deficiency
Principal Investigator Name:	Ricardo Jorge, MD
Contracting Organization:	Baylor College of Medicine, Houston, TX
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a feasibility trial of recombinant human growth hormone (rhGH) replacement therapy (using somatropin) in Veterans from Operations Desert Storm/Desert Shield with a history of Gulf War Illness (GWI) with adult growth hormone deficiency (AGHD). This study will assess the efficacy and safety of rhGH in this population, as well as treatment compliance. The primary hypothesis is that participants receiving rhGH for 6-months will show improvements in body composition (i.e., truncal fat mass reduction of 5.3% or greater) compared to placebo.

15. SUBJECT TERMS
Gulf War Illness, growth hormone replacement therapy, hormonal dysregulation

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1. **INTRODUCTION:**

There is a significant overlap between the symptoms of adult growth hormone deficiency (AGHD) and those of Gulf War Illness (GWI) such as fatigue, chronic pain, depression, anxiety, and cognitive dysfunction. AGHD is also associated with metabolic changes such as increased truncal fat mass, dyslipidemia, and increased cerebrovascular risk which can lead to neuroinflammation, neurodegeneration, and functional decline. Approximately 33% of veterans with a confirmed diagnosis of GWI test positive for AGHD. Growth hormone replacement therapy (GHRT) with recombinant human growth hormone (rhGH) reverses body composition and metabolic changes. Studies on civilians with AGHD caused by other conditions such as pituitary tumors suggest GHRT improves fatigue, chronic pain, mood disturbance, cognitive function, and improves quality of life (QoL). However, the effect of growth hormone replacement therapy in veterans with AGHD associated with GWI has not been studied.

This study is a placebo-controlled, double-blind, parallel-group randomized clinical trial (RCT) of recombinant human growth hormone (rhGH) replacement therapy (using somatropin) vs. placebo in Veterans from Operations Desert Storm/Desert Shield with a history of Gulf War Illness (GWI) and adult growth hormone deficiency (AGHD). This study will assess the efficacy and safety of rhGH in this population, as well as treatment compliance. The primary hypothesis is that participants receiving rhGH for 6-months will show improvements in body composition (i.e., truncal fat mass reduction of 5.3% or greater) compared to placebo.

2. **KEYWORDS:**

Endocrine measures; hormonal dysregulation; HPA axis; Gulf War Illness, recombinant human growth hormone (rhGH); growth hormone replacement therapy

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Major Task 1: Regulatory and Administrative Start-Up Tasks	Target Month	% Complete
- Coordinate CRADA	1-3	0%
- Pharmacy start-up	2-7	In Progress
Major Task 2: Coordinate Study Staff		
- Select members of DSMB	1-2	100%
- Develop and post job descriptions	1-2	100%
- Coordinate lab space, testing rooms, and calibrate DEXA	1-5	Pending
- Interview and hire study personnel / Train personnel	1-5	
Major Task 3: Recruitment		
- Create recruitment materials	1-3	100%
- Finalize recruitment strategy	1-3	100%
- Screen Participants	7-26	In Progress
Major Task 4: Data Collection		
- Identify potential GW candidates	7-25	In Progress
- Consent patients and collect data	8-26	0%

- **What was accomplished under these goals?**

  The objectives the past year included regulatory and administrative start-up tasks, coordination of study personnel across sites, recruitment, and data collection.

  - **Regulatory and Administrative Start-Up Tasks:**

    During the past year, the PIs at both sites were active in negotiating a CRADA between VA, Baylor, and Pfizer Pharmaceutical to obtain the study medication and placebo at no cost. Despite every effort, the CRADA between the study sites and Pfizer, an agreement could not be reached between the institutions. The inability to establish a CRADA left the team in a difficult predicament because placebo injector pens are currently unavailable on the market. Thus, the last quarter of the year was used to meet with stakeholders and redesign the study focused on completing the proposed trial promptly and with sufficient power to assess the non-futility of the trial. The initial study design was a two-arm (randomized placebo controlled) futility trial. The new protocol will assess futility in a single arm trial. The design was presented to the CDMRP science officer in July, and an amendment was submitted to the IRB at the end of the beginning of October. Upon approval from the IRB, the research team will submit the amendment to HRPO for review.

    The research team and pharmacists at both sites are in close contact. Since the medication would no longer be obtained through Pfizer, the team dedicated time to identify generic growth hormone manufacturers. Special consideration was given to cost and medication delivery system. Novo Nordisk's Norditropin was identified to replace Pfizer's growth hormone injection. Dr. Ricardo Jorge, PI in Houston, and the pharmacist at Michael E. DeBakey VA in Houston have been working with the local research service line to procure the medication at VA pricing.

  - **Coordination of Study Personnel:**

    During the past year, both sites have hired personnel. Personnel have completed the credentialing process and initiated protocol-specific training. The standardized operating procedures are being updated to reflect changes in the study design and fine-tuned based on the feedback of clinical research team.

  - **Recruitment**

    Since the last annual report, the research team obtained access to a list of patients from the Gulf War Registry enrolled in Houston and Seattle. At the time of this writing, 2,781 veteran medical records were screened. Of those, 540 met preliminary criteria and will be contacted upon study initiation.

    Additionally, the team submitted an amendment to the IRB in June 2023 adding patient lists from VA Informatics and Computing Infrastructure (VINCI) for recruitment purposes. The amendment was approved, and the lead site, Houston, initiated the application process to obtain access to the VINCI workspace in August 2023. Using patient lists from VINCI to identify potential candidates for the study is a significant advantage as the veteran's information is up to date and pre-filtered by preliminary inclusion criteria, unlike the Gulf War Registry patient list.

  - **Data Collection**

    Data collection has not begun, but every effort has been made to ensure once the new study design is approved, data collection can begin immediately.

- **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, the study intends to obtain HRPO approval, access VINCI lists for recruitment, procure the study medication, and launch the trial. Sites will contact the list of potential candidates identified during previous months and begin study enrollment/data collection.

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**

  As mentioned in previous section, a CRADA with Pfizer could not be established leaving the research team without an option to obtain a placebo for the study drug. The protocol was redesigned from a randomized, placebo-controlled futility trial to a single arm futility trial. Similar to the previous design, rejecting the null hypothesis would mean that the benefit is significantly smaller than anticipated, which would lead to the conclusion of futility. Given the time and budgetary constraints, a new power analysis was performed to adjust the number of participants for a single-arm trial. The following table shows the power under different μt for different sample sizes with alpha =0.10 as before. There is sufficient power to reject treatment with zero benefit or small to moderate benefit (e.g., μt≤2.05%) for sample sizes as small as 18. H0: μt ≥ 5.3% vs. HA: μt < 5.3%.

N enroll	N complete	True reduction μt							
		0%	1%	2.05%	2.5%	3%	4%	5.3%	6%
18	**15**	100	99.6	95.5	90	79.6	46.4	10	2.7
21	**17**	100	99.8	97.1	92.8	83.4	49.7	10	2.5
24	**20**	100	100	98.6	95.6	87.9	54.2	10	2.1
27	**22**	100	100	99.1	96.8	90.3	57	10	1.9
30	**25**	100	100	99.5	98.1	93	60.9	10	1.7
33	**27**	100	100	99.7	98.6	94.4	63.3	10	1.6
36	**30**	100	100	99.9	99.2	96	66.7	10	1.4

The change in design ensures completion of the study in a timely manner without modification of the budget, preserves the study's primary objective to assess the non-futility of a future, larger multicenter trial, and provides precise information about the feasibility and safety of the intervention.

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

  The changes to the design and reduction of the patients to be enrolled in the trial allow the team to overcome the challenges experienced to date.

- **Changes that had a significant impact on expenditures**

  The changes to the study design and reduction of sample size enable the team to pursue the trial without significant modification of the budget.

- **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

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.**
    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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Ricardo Jorge, MD
Project Role:	Principal Investigator (Houston)
Researcher Identifier	ORCID ID: 0000-0001-0001-6010-7297
Nearest person month worked:	4.0 CM
Contribution to Project:	Oversight of project, regulatory and administrative tasks including but not limited to CRADA negotiations, pharmacy start-up, procurement, study redesign, reports, and coordination of personnel at both sites.
Funding Support:	No change

Name:	Ruosha Li, PhD
Project Role:	Biostatistician
Researcher Identifier	ORCID ID:
Nearest person month worked:	0.6 M
Contribution to Project:	Redesign of study, power analysis calculations
Funding Support:	No change

Name:	Audri Villalon
Project Role:	Project Manager / Research Coordinator
Researcher Identifier:	ORCID ID: 0000-0001-5535-7558
Nearest person month worked:	5.0 M
Contribution to Project:	Assisted PI with regulatory and administrative tasks including amendments, reports, applications, personnel credentialing, and SOPs. Worked closely with database developers to update the case report forms and update the system following changes in study design.
Funding Support:	No support received during this quarter

Name:	Jose Manuel Garcia, MD
Project Role:	Co-Investigator (Seattle)
Researcher Identifier	ORCID ID:0000-0002-4245-1753
Nearest person month worked:	2.4 CM
Contribution to Project:	Oversight of regulatory and administrative tasks in Seattle, assisted with CRADA negotiations, pharmacy start-up, procurement, and coordination of personnel at Seattle VA.
Funding Support:	No change

Name:	Megan Herodes
Project Role:	Research Coordinator (Seattle)
Researcher Identifier	ORCID ID:0000-0002-9844-0375
Nearest person month worked:	5.0 CM
Contribution to Project:	Assist Dr. Garcia with submission of amendment and site initiation activities. Screened veteran medical records to identify potential candidates for the study.
Funding Support:	No change

Name:	Christopher Villanueva
Project Role:	Research Coordinator (Seattle)
Researcher Identifier	N/A
Nearest person month worked:	6.7 CM
Contribution to Project:	Completed institutional training, assisted with pre-screening and initiation activities at local site.
Funding Support:	No changes

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

  Yes, Dr. Garcia has new clinical trials and a pending NIH grant award. His current PCPS is attached.

- **What other organizations were involved as partners?**

Organization Name:	Seattle Institute for Biomedical and Clinical Research (SIBCR) / VA Puget Sound Healthcare System (VAPSHCS)
Location:	Seattle, WA
Contribution to Project:	As per the SOW, SIBCR manages external funding for researchers based at the VAPSHCS. Dr. Garcia serves as co-investigator and local site PI for this project.

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** N/A

9. **APPENDICES:**

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; daliza.crane@pfizer.com
Performance Period:	11/30/2016-07/01/2022
Funding Level:	
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:	
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:	
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:	

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:

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:

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:	
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:
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 (NCE)
Funding Level:
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:
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:
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
Supporting Agency:	Department of Defense/CDMRP, W81XWH1810461
Grant Officer:	Melanie Neagley, PhD; Melanie.a.Neagley.ctr@mail.mil
Performance Period:	9/1/2018-8/31/2024
Funding Level:	
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:	5/8/2019-4/30/2026
Funding Level:	
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:	

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:

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:

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:
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.

Title: **Towards precision medicine for cancer cachexia (PI: Harrison)**
Effort: 0.6 calendar months
Supporting Agency: Cancer Council Victoria via Monash University
Performance Period: 01/01/2018-12/31/2023
Funding Level:
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.

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:
Funding Level:
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:
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:	
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.

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:

Date: