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TITLE: Effects of Thyroid Hormone Metabolite Treatment for Postmenopausal Heart Repair

PRINCIPAL INVESTIGATOR: Carly S. Filgueira

CONTRACTING ORGANIZATION: Houston Methodist Research Institute

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Fort Detrick, Maryland 21702-5012

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

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14. ABSTRACT

During menopause circulating sex hormones decline as well as thyroid function. Estrogen reduction is correlated with reduced protection from cardiovascular diseases. Studies in pre-menopausal women show that hysterectomy, is associated with higher risk of cardiovascular disease. Similarly, a loss of thyroid hormone (TH) is also associated with reduced cardiac health in women. Research is needed to further understand the relationship between the loss of estrogen and thyroid hormone and cardiovascular disease. We hypothesize that TH (T3, 3,3′-T2) treatment will increase expression of GPR30 and reduce infarct area and fibrosis post-myocardial infarction (post-MI) in ovariectomized (OVX) female rats and that 3,3′-T2 will preferentially activate thyroid hormone receptor alpha proving more efficacious than T3 for heart repair. To test our hypothesis, we will 1) evaluate the role of THs (T3, 3,3′-T2) post-MI using euthyroid and hypothyroid female rats and compare efficacy of salvage treatment and 2) evaluate the role of THs (T3, 3,3′-T2) post-MI in OVX female rats with and without estrogen (E2) replacement therapy and compare efficacy of treatment. Major findings include that induction of hypothyroidism was found to decrease pulse rate (indicative of bradycardia) and result in symptoms similar to heart failure (reduced ejection fraction and fractional shortening).

15. SUBJECT TERMS

Cardiovascular disease, thyroid hormones, estrogens, 3,3'-diiodothyronine, postmenopause, myocardial infarction, heart repair, hypothyroidism, women's heart disease

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1. INTRODUCTION

Cardiovascular disease continues to be the leading cause of death for women in the United States, and women are diagnosed with heart failure later in life compared to men. A reduction of estrogen is correlated with reduced protection from cardiovascular diseases. Since sex differences exist in heart disease, sex-specific research for novel treatments and studies dealing with impacts of the endocrine system and menopause on cardiovascular health of women are essential. The subject of this research is to better understand the relationship between the loss of estrogen and thyroid hormone and cardiovascular disease. The purpose of this research is to determine if the lesser known thyroid metabolite 3,3'-diiodothyronine (3,3′-T2) can act as a therapeutic and offer a means to protect the cardiovascular health of women in the post-menopausal state. The scope of the proposed studies is to explore if thyroid hormones can activate protective factors against cardiac damage, a major problem for women.

2. KEYWORDS

Cardiovascular disease, thyroid hormones, estrogens, 3,3'-diiodothyronine, postmenopause, myocardial infarction, heart repair, hypothyroidism, women's heart disease

3. ACCOMPLISHMENTS

What were the major goals of the project?

Major Task 1 Prepare Institutional Animal Care and Use Committee (IACUC) protocol for animal purchase and in vivo studies. (Months 0-4)
Major task 1 was completed 100%.

Major Task 2 Treat euthyroid and hypothyroid female rats post-MI with THs (T3 and 3,3′-T2). (Months 3-12).
Major task 2 was completed 33%.

Major Task 3 Perform OVX and E2 replacement study. (Months 13-24).
Major task 3 was completed 0%.

What was accomplished under these goals?

Specific Aim 1. To evaluate the role of thyroid hormones (THs) (triiodothyronine (T3), 3,3'-diiodothyronine (3,3′-T2)) post-myocardial infarction (MI) using euthyroid and hypothyroid female rats and compare efficacy of salvage treatment (months 0-12).

Major Task 1 Prepare Institutional Animal Care and Use Committee (IACUC) protocol for animal purchase and in vivo studies. (Months 0-4)

The subtasks achieved were: 1) Initiate IACUC protocol and 2) Obtain DoD ACURO (Animal Care and Use Review Office) approval.

The IACUC protocol for this study entitled "Nuclear hormone receptor targeting in small animals" (ID IS00005507) was approved by the The Methodist Hospital Research Institute IACUC on 01/16/2020; IACUC approval expires 01/15/2023.

DoD ACURO approval was obtained as of 12/14/2021 for the use of rats and will remain so until modification, expiration or cancellation.

Major Task 2 Treat euthyroid and hypothyroid female rats post-MI with THs (T3 and 3,3′-T2). (Months 3-12)

The subtasks achieved were: 1) Subtask 1 Order (n=60) female Sprague Dawley rats (220–250 g) and allow them to acclimate. Record baseline animal weights/sizes and collect blood. Randomly sort into 6 groups. 2) Subtask 2 Induce hypothyroidism in the rats (n=30) using propylthiouracil (PTU). Confirm hypothyroid status by measuring T3 and thyroxine (T4) levels. Assess basal cardiac function with echocardiography. Acclimate rats to tail cuff for blood pressure readings. 3) Subtask 3 Induce MI in the rats (n=60) by ligation of the coronary artery. Confirm MI induction by color change and enlargement of the left atrium. Assess cardiac function post-MI.

Sprague Dawley rats (220–250 g) were ordered from Envigo and allowed to acclimate to the vivarium prior to handling. Baseline weights were recorded and blood collected prior to sorting into groups and administration of PTU. Half of the animals (n=30) remained euthyroid (normal thyroid functioning), while the other half received PTU in their drinking water (Figure 1A). Notably, the animals that received PTU showed significant weight loss starting on day 2. The euthyroid animals displayed a normal growth pattern across the study timeline (Figure 1A red circles). Clinical signs of PTU-induced hypothyroidism include a significant decrease in body weight compared to untreated rats as shown by Mishra *et al.*[1] and Kar *et al.*[2] Researchers have also noted decreased rectal temperature in hypothyroid rats compared to control rats.[3] This observation was confirmed in our studies as well (Figure 1B), where significance between groups increased over time (from **p<0.01 week 6 to ****p<0.0001 week 7).

While MI surgeries were performed in all animals (n=60), due to low body condition scoring the hypothyroid cohort was euthanized. The remaining euthyroid cohort was sorted into three treatment groups: 1) vehicle, 2) T3, or 3) 3,3’-T2 and body weights recorded daily post-MI (Figure 1C). No statistical differences in body temperature were observed for these three treatment groups post-MI (Figure 1D).

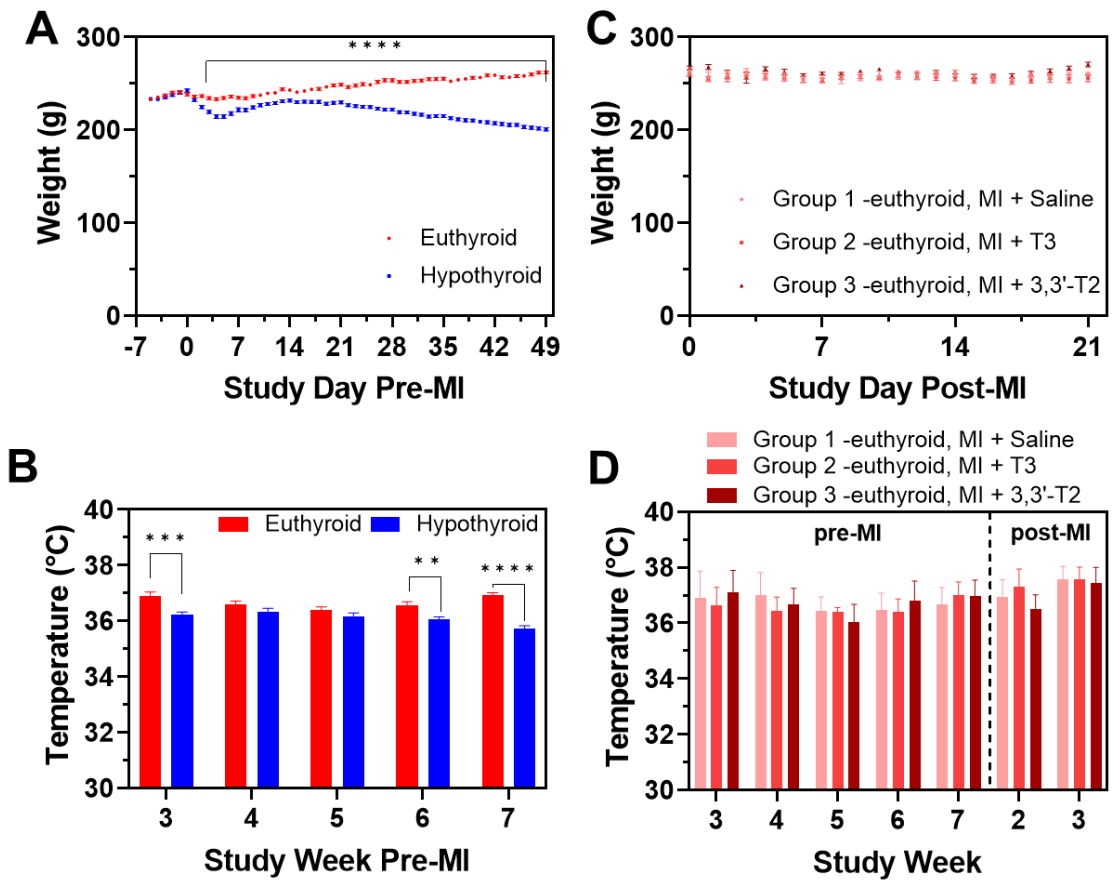

Figure 1. (A) Body weight versus study day for Euthyroid (red circles) and Hypothyroid (blue squares) rats (n=30/group), where the hypothyroid group received 1 mg/ml PTU in their drinking water starting on study day 0 (****p<0.0001). Unpaired T-test. Day 49 marks the day MI surgeries were performed. (B) Body weight vs. post-MI study day for Euthyroid rats sorted into group 1 (light red circles, n=6), group 2 (red squares, n=6), and group 3 (dark red triangle, n=5). (C) Temperature versus study week pre-MI for euthyroid (red) and hypothyroid (blue) rats (n=30/group, **p<0.01, ***p<0.001, ****p<0.0001). (D) Temperature versus study week post-MI for euthyroid rats sorted into group 1 (light red, n=6), group 2 (red, n=6), and group 3 (dark red, n=5).

By day 42 of PTU water induction the serum levels of total T3 and T4 were significantly decreased for rats receiving PTU indicative of hypothyroidism (Figure 2 A, B). Similarly, the TSH levels were significantly elevated for the PTU treated rats, also a sign of hypothyroidism (Figure 2 C). Reduced serum T3 and T4 levels and increased TSH have also been reported by others to demonstrate successful induction of hypothyroidism.[1,2]

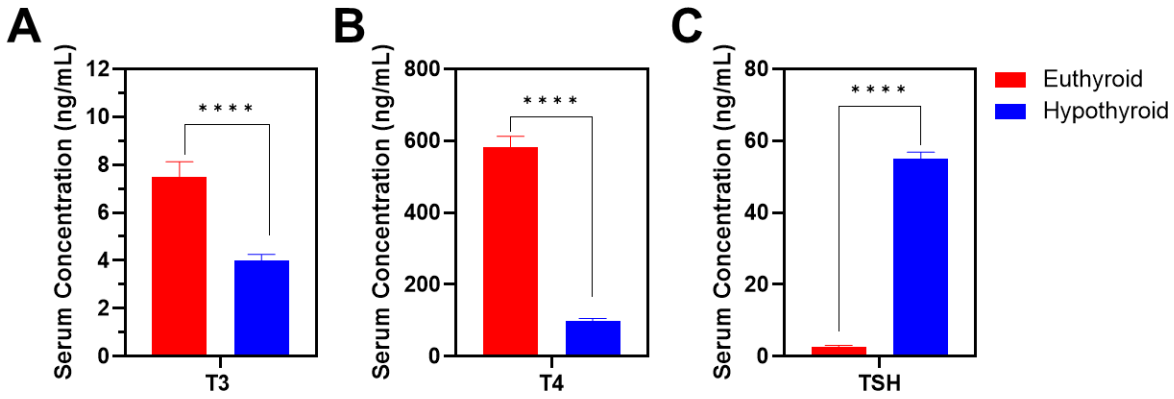

Figure 2. (A) Total T3, (B) Total T4, and (C) TSH from study day 42 for Euthyroid (red) and Hypothyroid (blue) rats, where the hypothyroid group received 1 mg/ml PTU in their drinking water (****p<0.0001). Data is plotted as average ± SEM.

Basal cardiac function with echocardiography was performed on a subset euthyroid and hypothyroid rats (n=6/group) on study day 42 prior to MI-induction (Fig. 3). While there is an observed decrease in the ejection fraction (Fig. 3B) and fractional shortening (Fig. 3C) for the hypothyroid group when compared to the euthyroid, there was no overall significance between these two groups. Untreated hypothyroidism has been shown to resemble the hallmarks of heart failure[1], such as reduced fractional shortening and ejection fraction via echocardiography.[4]

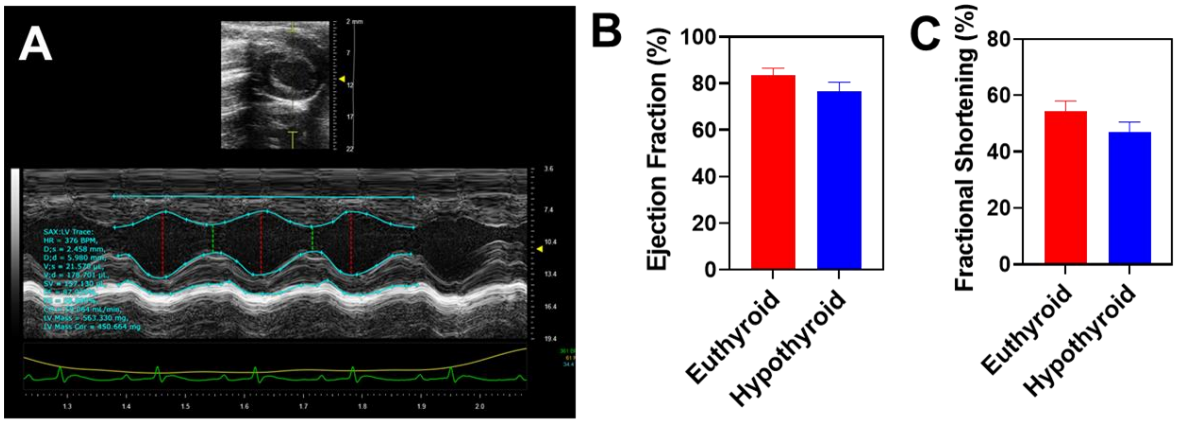

Figure 3. Basal cardiac functioning assessments performed on study day 44 for euthyroid (red, n=6) and hypothyroid (blue, n=6) rats where (A) top represents short axis view of the left ventricle and bottom represents corresponding M-mode waveform in a representative pre-MI animal, (B) ejection fraction, and (C) fractional shortening (average of 3 cardiac cycles).

Starting on study day 0, the rats were acclimated to the tail cuff for blood pressure (BP) readings by performing BP readings for 5 consecutive days. BP and pulse measurements were then obtained weekly throughout the course of the experiment. As hypothyroidism was induced, the significance between the euthyroid and hypothyroid animals for the average systolic blood

pressure increased (from $p<0.05$ day 0 to $p<0.01$ day 42) (Fig. 4A) as well as the significance in pulse data (from $p<0.05$ on day 7 to $p<0.01$ on day 28 to $p< 0.0001$ on days 35 and 42) (Fig. 4B). This can be attributed to the impaired systolic function in the left ventricle due to hypothyroidism.[6] Further, the decrease in pulse rate for the hypothyroid animals over time ($p<0.0001$ day 0 vs. days 7-42) is indicative of the onset and persistence of bradycardia.[5]

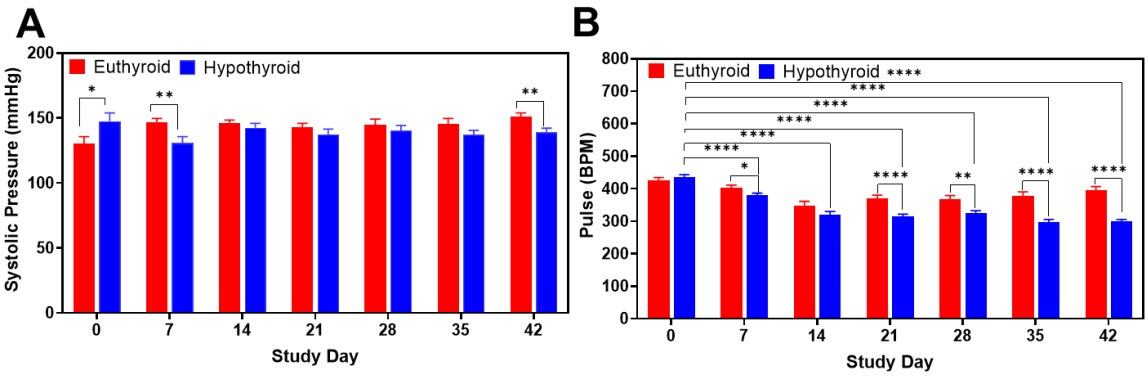

Figure 4. (A) Systolic BP and (B) Pulse data versus study day pre-MI for Euthyroid (red) and Hypothyroid (blue) rats (n=30/group), where the hypothyroid group received 1 mg/ml PTU in their drinking water (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001). Data is plotted as average ± SEM.

On day 49 MI surgeries were performed in all animals and the rats were sorted into treatment groups. Successful ligation was confirmed by visible blanching and cyanosis during the occlusion (Fig. 5). While MI surgeries were performed in all animals (n=60), due to low body condition scoring the hypothyroid cohort was euthanized. The remaining euthyroid cohort began treatment with either 1) vehicle, 2) T3, or 3) 3,3'-T2. Cardiac function post-MI assessments are ongoing. Initial comparisons with pre-MI euthyroid animals show an increase in the systolic diameter post-MI (green dashed line) (Fig. 6A versus Fig. 5A) as well as significant decreases in ejection fraction and fractional shortening (Fig. 6B,C) due to reduced cardiac output, indicative of a successful MI.

Figure 5. Rodent heart pre-ligation (left) and post-ligation (right) with blanching of the heart as a sign of successful artery ligation.

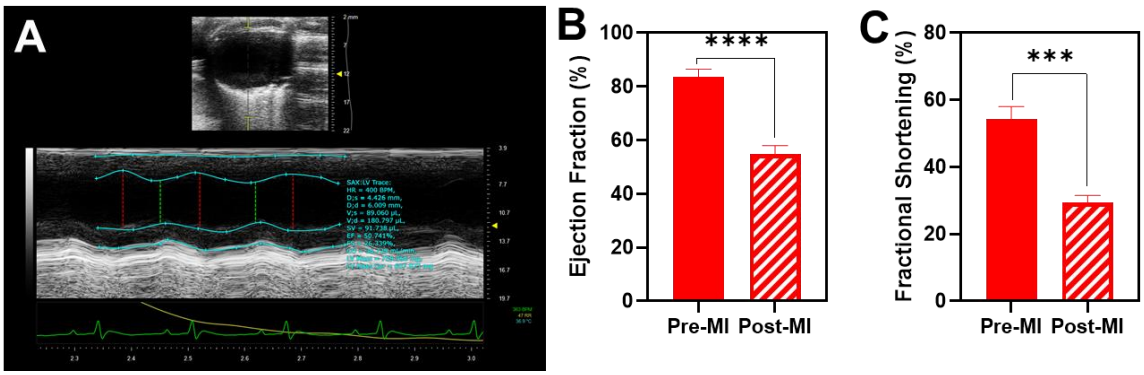

Figure 6. Cardiac functioning assessments performed 28 days post-MI for euthyroid rats where (A) top represents short axis view of the left ventricle and bottom represents corresponding M-mode waveform. (B) Ejection fraction (****p<0.0001) and (C) fractional shortening (***p<0.001) comparisons pre- (solid red, n=6) and post-MI (dashed red, n=6) (average of 3 cardiac cycles). Data is plotted as average ± SEM.

The subtasks not yet achieved were: 4) Treat with T3 and 3,3′-T2. Monitor weight, blood pressure, and perform blood draws for 12 weeks. 5) Perform detailed echocardiographic analysis, euthanasia, weigh hearts, thyroid, brain and measure tibia length. Divide left ventricle (LV) in half at the mid-heart level so half is frozen and half fixed. Fix thyroids. 6) Quantify cardiac injury markers (Troponin I, Troponin T, creatine kinase (CK), creatine kinase myocardial b fraction (CK-MB), and myoglobin). 7) Measure G protein-coupled receptor 30 (GPR30) expression. 8) Perform histology on the hearts and thyroids. Quantify myocyte size, degree of replacement fibrosis in the infarct and compensatory free-wall fibrosis. Perform immunohistochemical analysis to identify localization of GPR30 expression and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining to determine apoptosis. Assess thyroid morphology. 9) Measure thyroid stimulating hormone (TSH), T3, and T4 in plasma.

Specific Aim 2. To evaluate the role of THs (T3, 3,3′-T2) post-MI in ovariectomized (OVX) female rats with and without estrogen (E2) replacement therapy and compare efficacy of treatment (months 13-24).

Major Task 3 Perform OVX and E2 replacement study.

The subtasks not yet achieved were: 1) Order (n=60) female Sprague Dawley rats (220–250 g) and allow them to acclimate. Record baseline animal weights/sizes and collect blood. Randomly sort into 6 groups, 2) Induce OVX (n=60) and confirm by disappearance of regular estrus cycle and decreased E2 levels, 3) Induce hypothyroidism and MI in the rats (n=60) and confirm similarly to Aim 1, 4) Treat with T3, 3,3′-T2, and E2. Monitor weight, blood pressure, and perform blood draws for 12 weeks, 5) Perform detailed echocardiographic analysis, euthanasia, weigh hearts, thyroid, brain and measure tibia length. Divide LV in half at the mid-heart level so half is frozen and half fixed. Fix thyroids, 6) Quantify cardiac injury markers Troponin I, Troponin T, creatine kinase (CK), creatine kinase myocardial b fraction (CK-MB), and myoglobin, 7) Measure estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and the G protein-coupled estrogen receptor (GPR30) expression, 8) Perform histology on the hearts and

thyroids. Quantify myocyte size, degree of replacement fibrosis in the infarct and compensatory free-wall fibrosis. Perform immunohistochemical analysis to identify localization of GPR30 expression and TUNEL staining to determine apoptosis. Assess thyroid morphology, 9) Measure TSH, T3, and T4 in plasma, and 10) Statistical analyses, interpretations, report writing.

References.

1. Mishra, P., Paital, B., Jena, S. *et al.* Possible activation of NRF2 by Vitamin E/Curcumin against altered thyroid hormone induced oxidative stress via NFκB/AKT/mTOR/KEAP1 signalling in rat heart. *Sci. Rep.* 9, 7408 (2019). https://doi.org/10.1038/s41598-019-43320-5
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4. Hajje, G., Saliba, Y., Itani, T., Moubarak, M., Aftimos, G., Farès, N. Hypothyroidism and its rapid correction alter cardiac remodeling. PLoS One. 2014 Oct 15;9(10):e109753. doi: 10.1371/journal.pone.0109753. PMID: 25333636; PMCID: PMC4198123.
5. Kisso, B., Patel, A., Redetzke, R., Gerdes, AM. Effect of low thyroid function on cardiac structure and function in spontaneously hypertensive heart failure rats. J Card Fail. 2008 Mar;14(2):167-71. doi: 10.1016/j.cardfail.2007.10.018. PMID: 18325465; PMCID: PMC2292454.
6. Chen, Y.F., Redetzke, R.A., Said, S., Beyer, A.J., Gerdes, A.M. Changes in left ventricular function and remodeling after myocardial infarction in hypothyroid rats. Am J Physiol Heart Circ Physiol. 2010 Jan;298(1):H259-62. doi: 10.1152/ajpheart.00755.2009. Epub 2009 Nov 20. PMID: 19933415.

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?

A manuscript is in preparation.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Hypothyroidism effects many different physiological and metabolic pathways. When left untreated, this can progress into clinical signs that are similar to heart failure which can further confounded when a cardiac event occurs. Our major accomplishments were the observations of

difference in clinical signs between euthyroid and hypothyroid animals and the observation of significance in body weight reduction, body temperature, and serum levels of T3, T4, and TSH.

After induction for 7 weeks with PTU, hypothyroidism had pronounced effects on the physical condition of the animal pre- and post-MI. Importantly, the induction of hypothyroidism itself was found to display symptoms similar to heart failure. We found decreases in ejection fraction and fractional shortening for the hypothyroid group when compared to the euthyroid.

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

Nothing to report

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

There were delays in securing a rodent ventilator for surgery, but this has been resolved and the studies are ongoing. Further, the hypothyroid animals were euthanized earlier than expected due to low body condition scoring therefore our plan to resolve this is by repeating the study with an earlier timepoint for MI induction, which should allow for the study animals to survive the 5 week treatment course.

Changes that had a significant impact on expenditures

Nothing to report

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

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.

Eversole E, Carcamo-Bahena Y, Royal ALR, Fallon BC, Brero G, Bhimaraj A, Youker KA, Filgueira CS Developing a Hypothyroid Rat Model for Myocardial Infarction, HMRI Nanomedicine Department Symposium, Houston, TX, December 5, 2022. Poster Presentation.

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:	**Carly Filgueira**
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-3246-303X
Nearest person month worked:	1.7 CM
Contribution to Project:	Dr. Filgueira obtained IACUC and ACURO approval. Dr Filgueira led the project, coordinated all of the experiments, conducted the in vivo studies, and led the analysis.

Name:	**Keith Youker**
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-2535-7973

Nearest person month worked:	0.6
Contribution to Project:	Dr. Youker assisted with performing the echocardiograms.

Name:	**Arvind Bhimaraj**
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-3042-8027
Nearest person month worked:	0.2
Contribution to Project:	Dr. Bhimaraj provided his expertise in managing the animal conditions due to heart failure induction.

Name:	**Yareli Carcamo-Bahena**
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	0000-0001-9998-9696
Nearest person month worked:	1.7
Contribution to Project:	Ms. Carcamo assisted with conducting the in vivo experiments (i.e. obtaining animals weights, body temperatures and serum collection).

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, attached are the change to active support for Dr. Filgueira, Dr. Youker, and Dr. Bhimaraj.

What other organizations were involved as partners?

Not applicable

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

FILGUEIRA, CARLY S. (Principal Investigator)

Current Research Support

W81XWH2210007 (Filgueira) 12/1/2021 – 11/30/2023 1.8 calendar
DOD
Effects of Thyroid Hormone Metabolite Treatment for Postmenopausal Heart Repair
We propose to explore use of T3, the active form of TH, and its metabolite 3,3'-diiodothyronine (3,3′-T2) for post-myocardial infarction (MI) treatment in female rodents.
Specific Aims: 1) To evaluate the role of THs (T3, 3,3′-T2) post-MI using euthyroid and hypothyroid female rats and compare efficacy of salvage treatment. 2) To evaluate the role of THs (T3, 3,3′-T2) post-MI in OVX female rats with and without estrogen (E2) replacement therapy and compare efficacy of treatment.
Role: Principal Investigator
Point of Contact: Jodi Cardoza
Overlap: None

W81XWH2210002 (Filgueira) 1/1/2022 – 12/31/2023 1.2 calendar
DOD
A Spectroscopic Approach to Overcome the Barriers of Early Familial Hypercholesterolemia Diagnosis
Our goal at the end of the proposed project is to have developed a real-time, non-invasive cholesterol meter to improve early diagnosis of familial hypercholesterolemia and the implementation of diagnostic tools, including in the pediatric population.
Specific Aims: 1) To identify experimentally observable Raman vibrational modes for cholesterol detection. 2) To test sensitivity of cholesterol detection in serum and in tissue.
Role: Principal Investigator
Point of Contact: Michelle L. Cromwell
Overlap: None

Butler/**Filgueira** 9/1/2018-12/31/2022 0.24 calendar
Golfer's Against Cancer total
Nanoparticle Enhanced Radioimmunotherapy for Lung Cancer
Our goal is to intratumorally deliver gold nanoparticles and immunoadjuvants to significantly enhance radiotherapy and produce synergistic effects.
Our aims are to: 1) determine the dose dependent effects of irradiation coupled with gold nanoparticle treatment on lung cell tumor regression (measure tumor size, change in luminescence), 2) quantify the amount of gold nanoparticles required to achieve tumor regression, and 3) perform radiotherapy of the primary tumor in combination with immunoadjuvants (CD40 monoclonal antibody) to test for increased survival and immune-mediated regression of metastasis outside the radiation field, based on an abscopal effect.
Role: Co- Principal Investigator
Point of Contact: Tiffany Polk
Overlap: None

Butler/**Filgueira** 3/22/2019-12/31/2022 0.24 calendar
Golfer's Against Cancer total
Nanoparticle Induced Anti-tumor Immunity for Lung Cancer
Our goal is to improve cancer treatment and promote cancer immunity by inducing the abscopal effect in a more robust manner to generate a tumor-specific immune response using an antibody-gold nanoparticle construct.
Our aims are to: 1) develop an antibody-gold nanoparticle construct, 2) demonstrate with computed tomography (CT) imaging that our chemically modified nanoparticles distribute differently in the tumor environment than unmodified nanoparticles and monitor length of particle entrapment and clearance in a solid tumor, 3) determine the effects of treatment with irradiation and chemically modified nanoparticles (changes in tumor growth, immune activation, and prevalence of lung metatasis).

Role: Co- Principal Investigator
Point of Contact: Tiffany Polk
Overlap: None

(New)
Filgueira/Weiner 1/1/2022-12/31/2022 0.24 calendar
Houston Methodist Research Institute
Use of a Protaglandin Analog to Enhance Blood Flow and Tendon Regeneration in a Rabbit Model
Our goal is to show Remodulin can be administered locally in the knee to improve blood flow to the tendon and accelerate regeneration.
Specific Aims: 1) To optimize the 7T MR sequences for the patella tendon in a normal rabbit knee. 2) To induce tendon injury in rabbits and assess with contract enhanced 7T MR improvements due to repeated Remodulin administration.
Point of Contact
Overlap: None

(New)
B2TRI (**Filgueira**) 4/1/2022 – 9/30/2022 0.24 calendar
Houston Methodist Research Institute
Design of a Multi-Lumen Syringe and Catheter System
Our goal is to develop several prototypes of a multi-lumen syringe and catheter for multi-component *in situ* administration of gelatinous materials.
Specific Aims: 1) Design and fabricate multi-lumen syringe and catheter. 2) Test deployment in *in vivo* model. Point of Contact: Fernando Cabrera
Overlap: None

(New)
EnMed Capstone (Moskow, **Filgueira**) 9/1/2022 – 8/31/2024 0.12 calendar
Houston Methodist Research Institute
Design of an intra-articular injection system to aid in osteoarthritis diagnosis and management
This project supports the Graduate Capstone project of Joshua Moskow to be conducted under the mentorship of Dr. Filgueira. Goal of the project is to design and test a protype of an injection system.
Point of Contact:
Overlap: None

Previous Research Support

(Completed)
The Provost TMC Collaborator Fund (Hafner) 7/01/2021 – 6/30/2022 0.24 calendar
Rice University for Dr. Hafner, no funds for Dr. Filgueira. An
Optical Sensor for Lipophilic Biomarkers in Tissue
The major goal of this internal seed-funded project is to develop surface enhanced Raman scattering as a general platform for analysis of lipophilic biomarkers in tissue, with an emphasis on lipid chain saturation for intraoperative tumor margins.
Role: Co-Investigator
Overlap: None

YOUKER, KEITH (Co-Investigator)

Current Research Support

R01HL148338 (Cooke, Chen) 4/1/2020-3/31/2024 1.8 calendar months
NIH:NHLBI Direct costs
Reversal of Heart Failure: Role of Vascular Recovery
Our objective is to understand the recovery of the heart following heart failure by studying mechanisms of cell re-differentiation leading to increased vascularity. This phenomenon occurs in humans in response to the implantation of a Left Ventricular Assist Device as well as in our mouse model of non-ischemic heart failure. Specific Aims: 1) We will characterize the physiological, cellular, and molecular hallmarks of heart failure recovery in a unique mouse model. 2) Transcriptional profiling of disaggregated mouse hearts as well as human cardiac tissue obtained pre- and post-LVAD implantation will be combined with bioinformatics analyses to predict novel genes in heart failure recovery. 3) We will confirm the genetic determinants discovered in the first aim using gain- or loss-of-function studies in vitro and in vivo.
Role: Co-Investigator.
Point of Contact: Bishow B. Adhikari
No overlap with proposed study.

Industry Agreement (Youker) 3/4/2019-3/4/2022 0.9 calendar months
Cardiol Therapeutics total
Novel Pharmaceuticals in a Mouse Model of Heart Failure
Our objective is to develop and test nanoparticle delivery of therapeutics in our mouse model of heart failure. This is pre-clinical development only.
Role: Principal Investigator.
Point of Contact: Dr. Keith Youker
No overlap with proposed study.

PR210272 (Filgueira) 10/1/2021 – 9/30/2022 0.6 calendar months
DOD total
Effects of Thyroid Hormone Metabolite Treatment for Postmenopausal Heart Repair
We propose to explore use of T3, the active form of TH, and its metabolite 3,3'-diiodothyronine (3,3′-T2) for post-myocardial infarction (MI) treatment in female rodents.
Specific Aims: 1) To evaluate the role of THs (T3, 3,3′-T2) post-MI using euthyroid and hypothyroid female rats and compare efficacy of salvage treatment. 2) To evaluate the role of THs (T3, 3,3′-T2) post-MI in OVX female rats with and without estrogen (E2) replacement therapy and compare efficacy of treatment.
Role: co-Investigator
Point of Contact: Darrell L. Ellsworth, PhD
Overlap: None

(New)
RHL160552A (Gao) 4/1/2022 – 3/31/2026 2.4 calendar months
NIH/NHLBI Direct Costs/Year
Defining cellular mechanisms of chronic graft failure in transplanted hearts with single cell multi-omics
The main goals of this project are to develop novel single cell nanopore sequencing technology and bioinformatic tools to detect heterogeneous RNA splicing isoforms and polyA tailing polymorphism in single cells, and apply these methods to trace cell lineages and chimeric donor/host cell identifies to uncover the molecular mechanisms of chronic graft failure in heart transplantation patients.
Specific Aims: 1) we will develop novel technology to define a unifying cell lineage and cell fate roadmap for cardiac cells. 2) will dissect temporal changes of cellular components in transplanted hearts during CAH early onset. 3) is to trace cell lineages during CAH progression with time-series single cell multi-omics.
Role: co-Investigator

Point of Contact: Lisa Schwartz
Overlap: None

BHIMARAJ, ARVIND (Co-Investigator)

Current Research Support

R01HL148338-01A1 (Cooke) 07/15/2020 – 03/31/2024 0.6 calendar
NIH/NHLBI Direct Costs/Year
Reversal of Heart Failure: Role of Vascular Recovery
The major role of this project is to develop a better understanding of the biological mechanisms responsible for the endogenous recovery after heart failure in patients that receive a Left Ventricular Assist Device (LVAD) that may lead to a new therapeutic avenue.
Specific Aims: 1) We will characterize the physiological, cellular, and molecular hallmarks of heart failure recovery in a unique mouse model. 2) Transcriptional profiling of disaggregated mouse hearts as well as human cardiac tissue obtained pre- and post-LVAD implantation will be combined with bioinformatics analyses to predict novel genes in heart failure recovery. 3) We will confirm the genetic determinants discovered in the first aim using gain- or loss-of-function studies in vitro and in vivo.
Role: Collaborator
No overlap with the proposed study.

PR210272 (Filgueira) 10/1/2021 – 9/30/2022 0.24 calendar
DOD total
Effects of Thyroid Hormone Metabolite Treatment for Postmenopausal Heart Repair
We propose to explore use of T3, the active form of TH, and its metabolite 3,3'-diiodothyronine (3,3′-T2) for post-myocardial infarction (MI) treatment in female rodents.
Specific Aims: 1) To evaluate the role of THs (T3, 3,3′-T2) post-MI using euthyroid and hypothyroid female rats and compare efficacy of salvage treatment. 2) To evaluate the role of THs (T3, 3,3′-T2) post-MI in OVX female rats with and without estrogen (E2) replacement therapy and compare efficacy of treatment.
Role: co-Investigator
Point of Contact: Darrell L. Ellsworth, PhD
Overlap: None

(New)
RHL160552A (Gao) 4/1/2022 – 3/31/2026 0.36 calendar months
NIH/NHLBI Direct Costs/Year
Defining cellular mechanisms of chronic graft failure in transplanted hearts with single cell multi-omics
The main goals of this project are to develop novel single cell nanopore sequencing technology and bioinformatic tools to detect heterogeneous RNA splicing isoforms and polyA tailing polymorphism in single cells, and apply these methods to trace cell lineages and chimeric donor/host cell identifies to uncover the molecular mechanisms of chronic graft failure in heart transplantation patients.
Specific Aims: 1) we will develop novel technology to define a unifying cell lineage and cell fate roadmap for cardiac cells. 2) will dissect temporal changes of cellular components in transplanted hearts during CAH early onset. 3) is to trace cell lineages during CAH progression with time-series single cell multi-omics.
Role: co-Investigator
Point of Contact: Lisa Schwartz
Overlap: None

(New)
No grant number (Torre) 1/1/2004 – 12/30/2023 0.12 calendar month
Houston Methodist Hospital and the Methodist DeBakery Heart Center Annual total
E & J Campbell Fund for Cardiology Research
The foundation will support the work of cardiology research at the Methodist DeBakery Heart Center.
Role: co-Investigator
Point of Contact: Tiffany Polk
Overlap: None