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Award Number: W81XWH-18-1-0206

TITLE: Defining alpha and beta-cell crosstalk for the treatment and prevention of diabetes

PRINCIPAL INVESTIGATOR: Dr. Bethany Cummings

CONTRACTING ORGANIZATION: Cornell University, Ithaca
ITHACA NY 14850-2820

REPORT DATE: July 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT
During this funding period we have bred up mice for study, have begun to enroll mice into study and generate samples for analysis in both aims 1 and 2. The primary finding to report at this time is our work in sham and VSG-operated MIPCre+ and MIPCre- mice that do not contain the floxed GLP-1R allele. These additional control groups demonstrate that the MIPCre allele does not alter our glucoregulatory findings after VSG in mice. In addition, as a complementary approach, we have developed a new single cell RNA-sequencing method for the study of islets. We have used this approach to study islets treated with and without a GLP-1 receptor agonist from healthy human donors. These data reveal that GLP-1 receptor signaling in human islets increases alpha cell expression of the prohormone convertase needed for GLP-1 production, demonstrating that our model of beta cell GLP-1R function has translational relevance in humans.

15. SUBJECT TERMS
Glucagon-like peptide-1, islet, bariatric surgery, alpha cell, vertical sleeve gastrectomy

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Table of Contents

1. INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic proportions world-wide. Therefore, this proposal addresses the FY17 PRMRP topic area of diabetes. Bariatric surgery, such as vertical sleeve gastrectomy (VSG), causes high rates of T2DM remission and produces remarkable changes in gut physiology. Therefore, VSG is an ideal model to understand how the gut regulates glucose homeostasis. The gut produces glucoregulatory hormones, such as glucagon-like peptide-1 (GLP-1). GLP-1 plays a critical role in islet function by potentiating glucose-stimulated insulin secretion (GSIS). The mechanisms by which GLP-1 potentiates GSIS are incompletely defined. VSG increases postprandial GLP-1 secretion and we find that increased β-cell GLP-1R signaling improves GSIS after VSG. This finding forms the foundation for our proposal to use our murine VSG model to advance our fundamental understanding of GLP-1 regulation of islet function. In the classic model of GLP-1 potentiation of GSIS, feeding stimulates secretion of gut-derived GLP-1 which acts as an endocrine hormone to signal through the beta-cell GLP-1R to potentiate GSIS. This model has been questioned because circulating levels of GLP-1 are low and GLP-1 is also produced by pancreatic alpha-cells. Proglucagon is expressed in the gut and alpha-cells and is cleaved to form either GLP-1 or glucagon depending on the prohormone convertase (PC) type present. It was thought that proglucagon processing is tissue-dependent; however, the PC required for GLP-1 production (PC1/3) is found in both the gut and alpha-cells. Our data show that increased beta-cell GLP-1R signaling increases alpha-cell PC1/3 and GLP-1 expression after VSG, revealing two novel premises in islet biology. **First**, our data point to a paracrine role for alpha-cell-derived GLP-1. **Second**, we have identified a novel role for the beta-cell GLP-1R as the regulator of a paracrine switch to increase alpha-cell GLP-1 production. Together, our data support a new model by which GLP-1 potentiates GSIS. Specifically, we hypothesize that β-cell GLP-1R signaling enhances α-cell PC1/3 and GLP-1 expression to amplify GLP-1-induced GSIS in a paracrine positive feedback loop.

2. KEYWORDS

Glucagon-like peptide-1, islet, bariatric surgery, alpha cell, vertical sleeve gastrectomy.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Research-Specific Tasks:

Specific Aim 1: Define the paracrine role of α-cell-derived GLP-1 in β-cell GLP-1R-mediated regulation of glucose homeostasis		
Major Task 1: Complete *in vivo* phase of aim 1	Target	Actual
Obtain local IACUC approval – to be completed prior to award receipt	0	0
ACURO Approval	0-4	0
Subtask 1: Generation of beta-cell GLP-1R knockout mice for study (will study an n of 10 per group – total of 60 mice needed)	4-8	Ongoing – 20% complete
Subtask 2: Feed mice high fat diet for 2 months prior to surgery	8-10	Ongoing – 10% complete
Subtask 4: Monitor mice *in vivo* and complete OGTT and IVGTT– includes measurement of body weight and food intake and ensuring that weight matched groups remain matched for body weight to the VSG groups throughout the in vivo phase.	10-11	Ongoing – 10% complete
Subtask 5: Euthanize mice and collect final fasting blood sample and islets	11-12	Ongoing – 10% complete

Milestone(s) Achieved: Completion of the *in vivo* phase of aim 1	12	
Major Task 2: Complete sample analysis for aim 1		
Subtask 1: Analyze fasting, OGTT and IVGTT samples	12-13	
Milestone(s) Achieved: Completion of aim 1 to determine if α-cell derived GLP-1 exerts paracrine actions within the islet.	13	
Specific Aim 2: Define the composition and function of the secretome released from the β-cell in response to β-cell GLP-1R signaling		
Major Task 1: Complete *in vivo* phase of aim 2		
Subtask 1: Breed up proglucagon Cre TdTomato mice	10-13	
Subtask 2: Isolate α- and β-cells	11-12	
Milestone(s) Achieved: Completion of the *in vivo* phase of aim 2	12	
Major Task 2: Complete sample analysis for aim 2		
Subtask 1: Metabolomic and proteomic analysis of β-cell derived media	12-16	
Subtask 2: Immunoblotting and qPCR analysis of α-cells	12-17	
Subtask 3: Preparation of a manuscript for publication to a peer reviewed journal	17-18	
Milestone(s) Achieved: Completion of aim 2 to define the function and composition of the β-cell GLP-1R induced secretome.	18	
Milestone(s) Achieved: Publication of the functional validation and composition of the β-cell GLP-1R induced secretome.	18	

What was accomplished under these goals?

Major Activities

We have been focusing our efforts on the completion of aim 1 and have begun generating samples for analysis in aim 2. We are breeding up beta cell GLP-1R wild-type and knockout mice for these studies and have started to enroll mice onto study. We experienced difficulties breeding our inducible beta cell-specific GLP-1R knockout mouse line which is why this portion of the study has taken longer than originally anticipated. Nevertheless, we have gotten 6 mice through study and have another 10 mice on high fat diet in preparation for surgery and study. Furthermore, our breeding program for this line is now performing at an adequate pace and we do not anticipate further issues in breeding.

In parallel we have completed study on additional control groups for this study. Specifically, we have studied sham and VSG-operated MIP-Cre mice (without the floxed *Glp-1r* gene) to control for MIP-Cre. This control was prompted by previous findings that MIPCreERT may cause growth hormone expression in islets and protect mice against hyperglycemia (Oropeza D, et al., Diabetes, 2015). This would have been expected to improve glucose regulation in $MIPCreERT^{+}$ compared with $MIPCreERT^{-}$ mice in our previous studies; however, the opposite was observed (Garibay, et al., Cell Reports, 2018). Furthermore, we did not detect a difference in islet growth hormone expression in our previous work (Garibay, et al., Cell Reports, 2018). Nevertheless, we have studied $MIPCreERT^{+}$ and $MIPCreERT^{-}$ mice without the floxed *Glp-1r* gene to control for any effect of MIPCreERT. We have completed study on an n=4-5 per group for this study and data from this study are presented below.

Using islets generated from the first cohort of mice studied in Aim 1, we have begun to generate samples for analysis in Sub-aim 2.1.

Specific Objectives

The objectives of this proposal are to test the following hypothesis by two specific aims:

Hypothesis: We hypothesize that β-cell GLP-1R signaling enhances α-cell PC1/3 and GLP-1 expression to amplify GLP-1-induced GSIS in a paracrine positive feedback loop. We propose two aims to test this hypothesis:

Specific Aim 1: Define the paracrine role of alpha-cell-derived GLP-1 in beta-cell GLP-1R regulation of islet function.

Specific Aim 2: Define the composition and function of the secretome released from the beta-cell in response to chronic and acute beta-cell GLP-1R signaling.

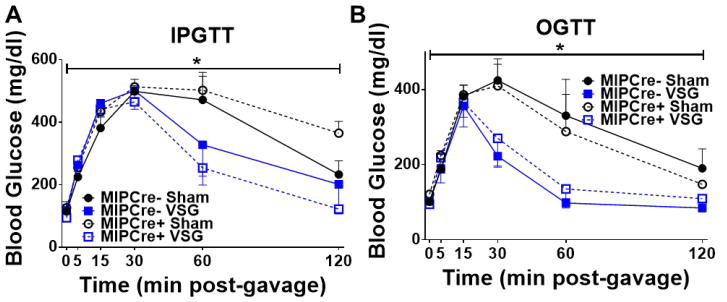

Figure 1. Blood glucose concentrations during an intraperitoneal glucose tolerance test (IPGTT) at 2 weeks after surgery (A) and an oral glucose tolerance test (OGTT) at 3 weeks after sham or VSG surgery (B) in mice with and without the MIPCreERT allele. Mice were maintained on HFD for 8 weeks before surgery. Two weeks before surgery mice were switched to HFD + tamoxifen for the rest of study. *P<0.05 sham vs VSG. n=4-5 per group.

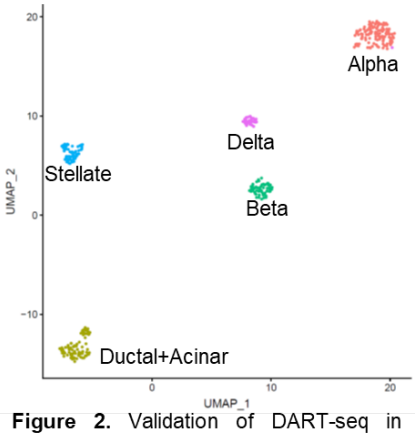

Figure 2. Validation of DART-seq in human islets. Unsupervised clustering of single cell transcriptomes by UMAP. Cell clusters were identified according to expression of known marker genes: insulin (beta), glucagon (alpha), somatostatin (delta), COL1A1 (stellate), KRT19 (ductal and acinar) .

Significant Results and Key Outcomes

Our primary results to report at this time are our findings in sham and VSG-operated MIPCreERT^{+} and MIPCreERT^{-} mice without the floxed *Glp-1r* gene. At two months of age male and female mice were placed on a 60% energy from fat high fat diet and were maintained on this diet for 6 weeks. Mice were then switched to a 60%en from fat HFD with tamoxifen (TD.06414, Teklad) for 2 weeks. Mice underwent sham or VSG surgery at 4 months of age and were continued on the same HFD supplemented with tamoxifen throughout study. Body weight and food intake were measured twice a week. Mice underwent an intraperitoneal glucose tolerance test (IPGTT; 2g/kg body weight dextrose given by IP injection) at 2 weeks and an oral glucose tolerance test (OGTT; 2g/kg body weight dextrose given by oral gavage) at 3 weeks after surgery. While data collection is ongoing, thus far we find that VSG tends to reduced body weight, food intake and adiposity compared with sham-operated control mice. We expect this finding to reach significance as we increase the number of mice studied. Body weight, food intake and adiposity do not differ between genotype (Cumulative Food Intake (g): MIPCre^{-} Sham = 61.0 ± 11.9, MIPCre^{-} VSG = 41.4 ± 4.1, MIPCre^{+} Sham = 46.8 ± 3.2, MIPCre^{+} VSG = 53.8 ± 7.2; Final Body Weight (g): MIPCre^{-} Sham = 23.7 ± 1.1, MIPCre^{-} VSG = 21.8 ± 2.2, MIPCre^{+} Sham = 24.1 ± 1.7, MIPCre^{+} VSG = 21.3 ± 2.2; Total White Adipose Mass (g): MIPCre^{-} Sham = 1.7 ± 0.1 , MIPCre^{-} VSG = 1.2 ± 0.2, MIPCre^{+} Sham = 1.6 ± 0.3, MIPCre^{+} VSG = 0.8 ± 0.3). VSG improves glucose tolerance compared to sham; however, glucose tolerance during the OGTT did not differ between genotype (**Fig 1A-B**, P<0.05)

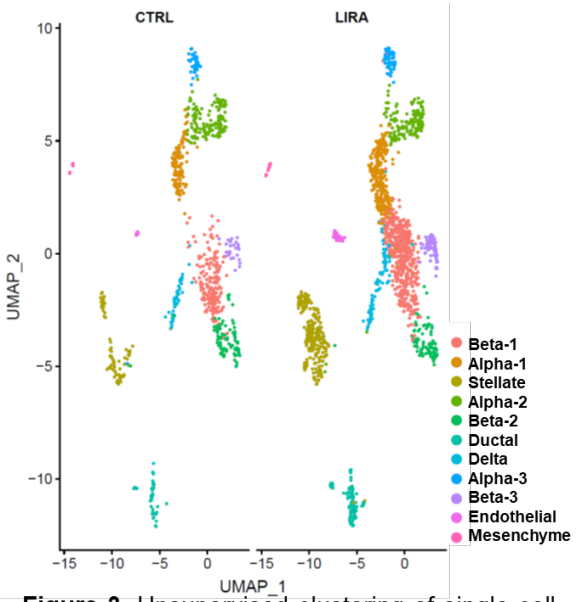

Figure 3. Unsupervised clustering of single cell transcriptomes by UMAP generated from non-diabetic human islets treated with saline (CTRL) or liraglutide (LIRA) (30nM for 12 hours) at 16.1 mM glucose. n=2 per group.

Other Achievements

As mentioned as an alternative approach in the original proposal, we are interested in applying single-cell RNA-sequencing to understand the mechanisms by which the beta cell

GLP-1R regulates alpha cell proglucagon processing. We have been working on applying a new highly sensitive single cell RNA-seq platform to the study of human islets, called DART-seq. DART-seq allows unbiased assessment of all cells within the sample, which is critical given the heterogeneity that exists within islet cell populations. Furthermore, to enhance sensitivity, DART-seq employs simultaneous measurement of the transcriptome as well as specific targeting of RNA molecules by using beads which carry a mix of poly-deoxythymidine (poly-dT) and specific probes in their tails (Saikia M, Nature Methods, 2019). We have adapted this technology to mouse pancreas and human islets. Furthermore, we have designed and tested DART-seq beads with a mix of poly-dT probes and *GCG*, *PCSK1* and *PCSK2*-specific probes in their tails and have validated their application to the study of human islets (**Figure 2**). Finally, we have used DART-seq to assess the effect of GLP-1R signaling on alpha cell *PCSK1* expression in human islets treated with saline or liraglutide (a GLP-1 receptor agonist) at 16.1 mM glucose for 12 hours. UMAP analysis identified 3 alpha cell clusters. Alpha-1 cells were proportionally expanded by liraglutide treatment and liraglutide treatment increased alpha-1 *PCSK1* transcript abundance compared with saline-treated islets (average log-fold change relative to control = 1.545, $P<0.05$) (**Figure 3**). These data demonstrate that enhanced islet GLP-1R signaling increases *PCSK1* expression in a sub-set of human alpha cells, suggesting that our model of beta cell GLP-1R function has translational relevance in humans.

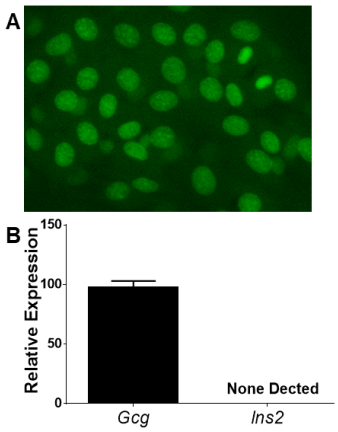

Figure 4. Primary isolated alpha cells in culture (A). Expression of *Gcg* and *Ins2* mRNA (relative to 18S rRNA) in isolated primary alpha cells. Expression normalized to sort negative cells (B). *n*=3.

Stated Goals Not Met

We are still working towards completing aims 1 and 2.

We have performed an initial in house validation of our primary alpha cell culture technique and have found that we can isolate pure alpha cells for culture (**Figure 4**), but that the number of mice required to produce these alpha cell numbers is limiting. We have been advised of a different alpha cell fluorescent reporter line that has better penetrance of the fluorescent allele and are in the process of procuring these mice. In the meantime, we have been using the alpha TC1-6 alpha cell line as an alternative strategy for aim 2.

What opportunities for training and professional development has the project provided?

This project has supported my graduate student's thesis work on the effect of beta cell GLP-1R signaling on alpha cell proglucagon processing and my postdoc's developing work on the application of DART-seq to the study of human islet biology. This training has encompassed, weekly individual meetings with me to go over project progress and development and review of the relevant literature. This has also provided opportunities for both my graduate student and postdoc to attend and present at the Boston Ithaca Islet Conference and for my graduate student to attend the American Diabetes Association Scientific Sessions.

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?

We plan to continue to enroll mice into study to complete aim 1 and continue to generate the samples needed to complete aim 2.

4. IMPACT

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

We are very excited about our DART-seq data that demonstrate that our newly defined beta cell GLP-1R pathway has application in human islet biology and are planning further experimentation to fully validate these data. Furthermore, the application of DART-seq to the study of islets represent an important improvement in technology in this arena.

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

We originally proposed performing the secretome studies in aim 2 on isolated beta cells. Upon further reflection, I think that studying the whole islet will be more informative and more physiologically relevant as this approach will retain the important cell-cell contacts that exist within the normal islet. Since we are manipulating GLP-1R expression at the level of the beta cell, this approach should still allow us to identify the beta cell-specific factor without biasing the data. Also, given the already complex nature of these studies, removing the beta cell FACS sorting step improves feasibility.

We originally proposed using mouse primary alpha cells. While we have successfully isolated primary alpha cells from mice (**Figure 4**), we have found that the alpha cell yields are quite low and will limit our progress with the proposed secretome studies in aim 1. Therefore, we are currently working with the alpha TC1-6 alpha cell line for these studies as an alternative. We are also working on generating a new mouse line with better penetrance of the florescent alpha cell marker to help increase our alpha cell yields in future studies.

We are also conducting an experiment to determine if conditioned media can go through a freeze-thaw cycle and retain efficacy to increase alpha cell *Pcsk1* expression. This experiment will help us figure out if we can bank conditioned media samples and then run them in bulk on alpha cells or if we need to study the conditioned media samples as they are generated. We would prefer to run conditioned media samples within the same experiment as this will help to reduce inter assay variation.

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

We experienced difficulties breeding our inducible beta cell-specific GLP-1R knockout mouse line which is why this portion of the study has taken longer than originally anticipated. We have resolved this issue, but anticipate needed to request and extension.

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.

We had originally proposed using an intravenous glucose tolerance test to assess glucose tolerance without enteral stimulation. We are interested in shifting this to the intraperitoneal glucose tolerance test since this test does not require placement of intravenous cannula and thus will decrease the risk of unwanted extra weight experienced due to the extra surgical stimulation.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS

Publications, conference papers, and presentations
Nothing to report.

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Bethany Cummings*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.36*
Contribution to Project:	*I have directed studies, overseen data management and analysis and supervised personnel.*
Funding Support:	
Name:	*Marlena Holter*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Performed surgery, cell culture studies, bred mice and performed in vivo testing. Maintains data records and contributes to data analysis.*
Funding Support:	
Name:	*Karolina Zaborska*
Project Role:	*Postdoctoral Fellow*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Contributed to breeding mice and assisted with in vivo testing.*
Funding Support:	

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

Ongoing Research Support:

(This project has completed)

5R21CA195002-02 (Cummings, PI)

Title: ***"Efficacy of Bariatric Surgery to Decrease the Risk of Colorectal Cancer in Mice"***

Time Commitment: 1.2 calendar months, 10% effort

Supporting Agency: NIH/NCI

Contracting/Grants Officer: Sarah M Lee, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760

Period of Performance: 04/01/16-03/31/19

Level of Funding: $370,838 (Project Total Cost)

Goal: To determine the efficacy of vertical sleeve gastrectomy surgery to decrease the risk of colorectal cancer development in mouse models and determine mechanisms by which vertical sleeve gastrectomy surgery interferes with protumorigenic environment for colorectal cancer.

Specific Aims: 1) Test the hypothesis that VSG interferes with an inflammatory protumorigenic environment for CRC through TGR5-mediated hydrophilic shifts in the circulating bile acid pool. 2) Test the hypothesis that VSG interferes with CRC tumorigenesis and metastasis in human CRC cells through TGR5-mediated hydrophilic shifts in the circulating bile acid pool.

Role: PI

Overlap: None

(This project has completed)

#N/A (Cummings, PI)

Title: ***"Efficacy of Dietary Blueberry Supplementation to Improve Glucose Homeostasis and Islet Morphology in Diet-Induced Obese Mice"***

Time Commitment: 0.6 calendar months, 5% effort

Supporting Agency: US Highbush Blueberry Council

Contracting/Grants Officer: Leslie Wada, 1847 Iron Point Rd, Suite 100, Folsom CA 95630

Period of Performance: 10/25/16-04/30/18

Level of Funding: $46,525 (Project Total Cost)

Goal: To confirm our previous findings on the effect of chronic blueberry consumption to preserve islet morphology and to translate these findings into milder prediabetic model such that the protective effects of blueberry consumption on the islet produce a corresponding improvement in glucose homeostasis.

Specific Aims: Test the efficacy of dietary blueberry supplementation to improve glucose regulation in obese insulin resistant mice.

Role: PI

Overlap: None

(New)

W81XWH-18-1-0206 (Cummings, PI)

Title: "***Defining Alpha and Beta-cell Crosstalk for the Treatment and Prevention of Diabetes"***

Time Commitment: 3% effort/year

Supporting agency: U.S. Army Medical Research Acquisition Activity

Contracting/Grants Officer: Christopher Baker, Fort Detrick – CDMRP, 1120 Fort Detrick, Frederick MD 21702

Period of Performance: 06/15/18-12/14/19

Level of Funding: $312,041 (Project Total Cost)

Goal: To characterize the proteins and metabolites secreted in response to beta cell GLP-1R signaling.

Specific Aims: Aim 1: Define the paracrine role of alpha-cell-derived GLP-1 in beta-cell GLP-1R regulation of islet function.

Aim 2: Define the composition and function of the secretome released from the beta-cell in response to chronic and acute beta-cell GLP-1R signaling.

Role: PI

Overlap: None

(New)

#N/A (Cummings, PI)

Title: ***"Harnessing the Alpha-Cell for Diabetes Treatment"***

Time Commitment: 15% effort/year

Supporting agency: The Hartwell Foundation

Contracting/Grants Officer: Heather Houser, 6000 Poplar Ave, Suite 250, Memphis, TN 38119

Period of Performance: 04/01/19-03/31/22

Level of Funding: $300,000 (Project Total Cost)

Goal: To define the mechanism by which beta cell GLP-1R signaling increases alpha cell PC1/3 expression.

Specific Aims: Aim 1: Identify the secreted factor(s) responsible for the effect of beta cell GLP-1R signaling to increase alpha cell PC1/3 expression. Aim 2: Identify and develop a pharmaceutical strategy for enhancing alpha cell PC1/3 expression for diabetes treatment.

Role: PI

Overlap: None

(New)

#N/A (Cummings, PI)

Title: ***"A New Single Cell RNA-sequencing Technique to Enable Targeting the Alpha Cell for Diabetes Treatment"***

Time Commitment: <0.1% effort/year

Supporting agency: Schwartz Research Fund Award

Contracting/Grants Officer: Yael Levitte, 122 Day Hall, Ithaca, NY 14853

Period of Performance: 01/14/19-01/13/20

Level of Funding: $15,000 (Project Total Cost)

Goal: To validate a new single cell RNA-sequencing technique to study glucagon-like peptide-1 receptor signaling in human islets.

Specific Aims: Aim 1: Determine the cell-specific transcriptome changes induced by β-cell GLP-1R signaling through application of a new high-sensitivity unbiased single-cell RNA-sequencing strategy in human islets.

Role: PI

Overlap: None

(New)

#N/A (Cummings, PI)

Title: ***"Efficacy of Dietary Resistant Starch to Improve Glucose Regulation"***

Time Commitment: 0%

Supporting agency: Ingredion

Contracting/Grants Officer: Maria Stewart, 10 Finderne Ave Suite C, Bridgewater NY, 08807

Period of Performance: 10/01/17-09/30/19

Level of Funding: $10,000 (Project Total Cost)

Goal: To investigate the effect of dietary resistant starch supplementation on GLP-1 secretion.

Specific Aims: Aim 1: Determine the requirement for TGR5 expressed in enteroendocrine cells in RS-induced improvements in glucose regulation.

Role: PI

Overlap: None

(New)

#N/A (Nishimura, Cummings, co-PIs)

Title: ***"Development of New Tools to Measure Neuronal Control of Vascular Function in Health and Disease"***

Time Commitment: <0.1% effort/year

Supporting agency: Cornell Neurotech Mong Fellowship Program

Contracting/Grants Officer: Chris Xu, 276 Clark Hall, Ithaca, NY 14853

Period of Performance: 08/01/18-07/30/19

Level of Funding: $53,165 (Project Total Cost)

Goal: To determine the effects of obesity, bariatric surgery and bile acid signaling on sympathetic neuronal regulation of vascular function.

Specific Aims: Aim 1: Determine the structure and function of sympathetic nerves within mesenteric PVAT and their modulation of vascular tone in health. Aim 2: Determine the role of sympathetic nerves in PVAT function in obesity and post-VSG.

Role: Co-PI

Overlap: None

(New)

#N/A (Cummings, PI)

Title: ***"Defining alpha cell PC1/3 expression regulation for type 2 diabetes"***

Time Commitment: <0.1% effort/year

Supporting agency: Cornell Center for Vertebrate Genomics Fellowship Program

Contracting/Grants Officer: John Schimenti, Department of Biomedical Sciences, Ithaca, NY 14853

Period of Performance: 12/01/18-11/30/20

Level of Funding: $15,000 (Project Total Cost)

Goal: This grant provides tuition support to my graduate student to perform pilot studies defining a new model describing the incretin action of glucagon-like peptide-1.

Specific Aims: Aim 1: Define the molecular triggers by which β-cell GLP-1R increases α-cell GLP-1 production in mice. Aim 2: Determine the translational relevance of transcriptomic changes induced by β-cell GLP-1R signaling in mice.

Role: Mentor

Overlap: None

(New)

#N/A (Cummings, PI)

Title: **"A New Single Cell RNA-Sequencing Technique for the Study of Islet GLP-1 Receptor Signaling"**
Time Commitment: <0.1% effort/year
Supporting agency: Integrated Islet Distribution Program Islet Award Initiative
Contracting/Grants Officer: James Cravens, 1500 East Duarte Rd, Duarte CA 91010
Period of Performance: 05/09/19-05/08/21
Level of Funding: $12,000 (Project Total Cost)
Goal: This award provides human islets for our pilot studies applying a new single cell RNA-sequencing technique to study the impact of a glucagon like peptide-1 receptor agonist on human islets.
Specific Aims: Aim 1: Apply a new single cell RNA-sequencing platform to the study of human islets.
Role: PI
Overlap: None

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

Award chart below.

PR172044: Defining alpha and beta-cell crosstalk for the treatment and prevention of diabetes

PI: Bethany Cummings, Cornell University, NY

Budget: Total Award Cost

Topic Area: Peer Reviewed Medical Research Program, Discovery Award

Mechanism: W81XWH-17-PRMRP-DA

Research Area(s): Diabetes

Award Status: 15 Jun 2018 – 14 Jun 2019

Study Goals:

To test the hypothesis that β-cell GLP-1R signaling enhances α-cell PC1/3 and GLP-1 expression to amplify GLP-1-induced GSIS in a paracrine positive feedback loop

Specific Aims:

Specific Aim 1: Define the paracrine role of alpha-cell-derived GLP-1 in beta-cell GLP-1R regulation of islet function.
Specific Aim 2: Define the composition and function of the secretome released from the beta-cell in response to chronic and acute beta-cell GLP-1R signaling.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: 6 new awards

Hartwell Individual Biomedical Research Award, “Harnessing the alpha cell for diabetes treatment” Role: PI
Schwartz Research Fund Award, “A new single cell RNA-sequencing technique to enable targeting the alpha cell for diabetes treatment” Role: PI
Cornell Neurotech Mong Fellowship Program, “Development of new tools to measure neuronal control of vascular function in health and disease”, Role: Co-PI
Ingredion, “Efficacy of dietary resistant starch to improve glucose regulation”, Role: PI
Cornell Center for Vertebrate Genomics Fellowship Program, “Defining alpha cell PC1/3 expression regulation for type 2 diabetes” Role: PI (Mentor)
Integrated Islet Distribution Program Islet Award Initiative, “A New Single Cell RNA-Sequencing Technique for the Study of Islet GLP-1 Receptor Signaling”, Role: PI

9. APPENDICES

None.