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TITLE: Define the Twist-ATX-LPAR1 Signaling Axis in Promoting Obesity-Associated Triple-Negative Breast Cancer

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14. ABSTRACT

Breast cancer remains the second leading cause of cancer-related death in women worldwide. Triple negative breast cancer (TNBC) carries a poorer prognosis, given its higher genomic instability, tendency toward early metastasis, and lack of effective targeted therapies. Obesity is a risk factor for TNBC so understanding the link between TNBC and obesity is crucial to the development of novel prevention and treatment strategies. TNBC activates the epithelial-mesenchymal transition (EMT) program and a key EMT inducer, the transcription factor Twist is highly expressed in TNBC. Autotaxin (ATX) and LPAR1 were dramatically increased in Twist-overexpressing breast cancer and adipose cells. Encoded by the ENPP2 gene, ATX is a secreted enzyme that produces most of the extracellular lysophosphatidic acid (LPA), which signals through its receptors (LPAR1-6) to mediate a wide range of inflammatory processes including wound healing, fibrosis and metastasis. Adipose is an important source for the synthesis and secretion of ATX, so ATX level/activity are increased during obesity associated adipose tissue expansion. Accordingly, we propose that Twist activation intensifies the ATX-LPAR1 signaling to promote the development and progression of obesity-associated TNBC. We are testing this hypothesis using genetic and pharmacological approaches in cell and animal models of breast cancer.

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1. Introduction

Triple-negative breast cancer (TNBC) has the poorest prognosis among breast cancer subtypes, which results from its high genomic instability, tendency toward early and recurrent metastases, and lack of effective targeted therapies. Standard surgery with adjuvant chemotherapy and radiotherapy offers limited efficacy once the tumor cells begin to metastasize. Epidemiological evidence strongly identifies TNBC and obesity as co-morbid conditions; women with overweight/obesity are at a significantly higher risk of developing TNBC. The obesity rate has been increasing rapidly in the U.S. population over recent decades, posing another daunting threat to TNBC prevention and treatment. This study aims to elucidate the mechanistic linkage between TNBC and obesity for the development of novel targeted therapies. Specifically we found that a transcription factor called TWIST that is increased in both breast tumor cells and in breast adipose tissue increases the expression of genes encoding Autotaxin, an enzyme that generates a bioactive lipid called lysophosphatidic acid (LPA) and a particular LPA selective G protein coupled receptor LPAR1. This supports our hypothesis that Twist activation during inflammatory breast cancer development and progression exacerbates development of obesity associated TNBC. We propose studies to test this hypothesis using cell and animal models.

2. Keywords

ATX: Autotaxin

LPA: Lysophosphatidic acid

LPAR1: Lysophosphatidic acid receptor 1

RUNX1: Runt Related Transcription Factor 1

TNBC: Triple negative breast cancer

3. Accomplishments

3.1. Major goals and accomplishments

We hypothesize that Twist activation intensifies pro-inflammatory ATX-LPAR1 signaling to promote the development and progression of obesity-associated triple negative breast cancer (TNBC). The overall objective of this proposal is to delineate the function and regulation of Twist, and to explore the therapeutic potential of targeting Twist-ATX-LPAR1 axis in TNBC and obesity. Accordingly, we have defined three Major Tasks: 1 Characterize the function of Twist in regulating ATX and LPAR1 expression; 2 Delineate the role of Twist-ATX-LPAR1 axis during TNBC cell-adipocyte crosstalk; 3 Define the Twist-ATX-LPAR1 signaling axis in promoting obesity-associated TNBC *in vivo*.

As we continued to characterize the transcriptional regulation of ENPP2, the gene that encodes ATX, we obtained initial evidence suggesting that ENPP2 transcription can be co-regulated by Twist and another transcription factor RUNX1. **This is an important finding and highly relevant to the major goal of the project, which is to target the Twist-ATX-LPAR1 axis for the treatment of obesity-associated TNBC, as co-targeting of RUNX1 may more efficiently disrupt the signaling cascade and result in better therapeutic outcomes.** Our findings are summarized below.

First, we successfully cloned the ENPP2 promoter and its proximal enhancer and generated a luciferase reporter construct (Figure 1). By performing dual-luciferase assay, we found that transfection of Twist only induced moderate change of luciferase activity (Figure 2), which is in contrast to our microarray data showing that Twist overexpression dramatically increased the mRNA level of ENPP2. We performed RNA-Seq analysis of T47D-Twist stable cell line and confirmed the significant upregulation of ENPP2 mRNA upon Twist overexpression (Figure 3). **To resolve the discrepancy, we decided to look further into transcriptional regulation of ENPP2.** We hypothesized that there are additional layers of transcriptional regulation of ENPP2, as Twist may regulate ENPP2 expression indirectly by cooperating with other transcription factors or transactivate intermediate molecules to indirectly regulate ENPP2 transcription.

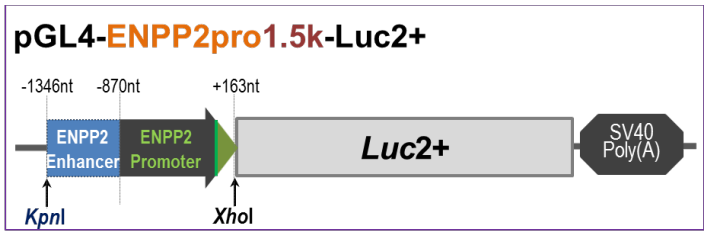

Figure 1 *Schematic representation of ENPP2 promoter/enhancer luciferase construct.*

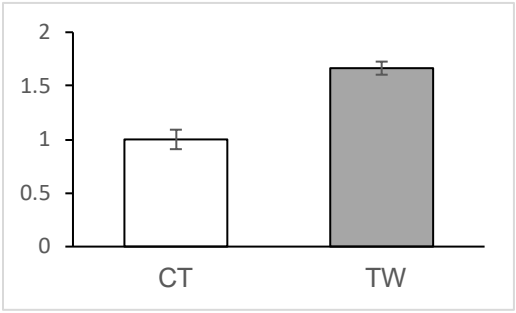

Figure 2 *An ENPP2 promoter/enhancer luciferase construct was co-expressed with (TW) or without Twist (CT) in HEK293 cells. Cells were treated with 2mM TSA for 12 hours before luciferase activities were measured.*

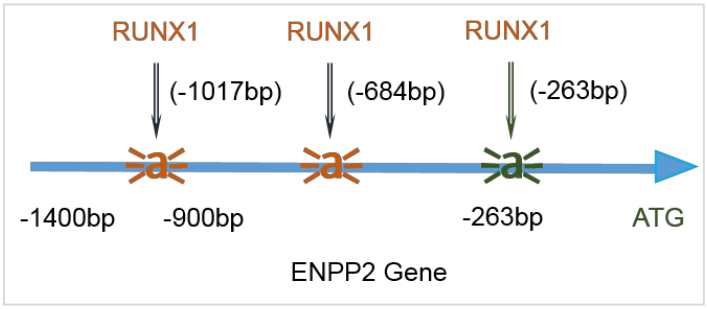

Figure 4 *Schematic representation of potential RUNX1 binding sites on ENPP2 gene promoter/enhancer.*

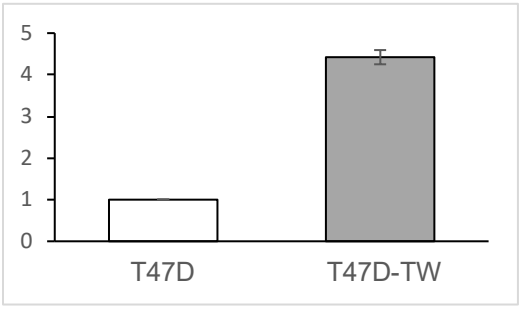

Figure 3 *RNA-Seq results showing that the mRNA level of ENPP2 was significantly increased in T47D cells stably expressing Twist.*

Next, we searched the promoter/enhancer sequence of ENPP2 gene for binding motifs of other families of transcription factors. Indeed, we identified RUNX1 responsive elements, suggesting potential binding of RUNX1 (Figure 4). We then performed luciferase assay to find that co-transfection of Twist and RUNX1 further enhanced luciferase activity, in comparison to transcription in response to expression of either construct alone (Figure 5).

Deregulation of RUNX1 has been associated with various malignancies, including breast cancer. Consistently, we found that RUNX1 is highly expressed in TNBC cell lines compared to luminal counterparts (Figure 6). Furthermore, we performed both exogenous and endogenous co-immunoprecipitation and found that Twist interacts with RUNX1 (Figure 7). It remains to be found whether and how Twist-RUNX1 interaction can affect their binding of ENPP2 promoter/enhancer. **Together, these results indicate that RUNX1 may play a role in Twist-mediated ENPP2 transcription.**

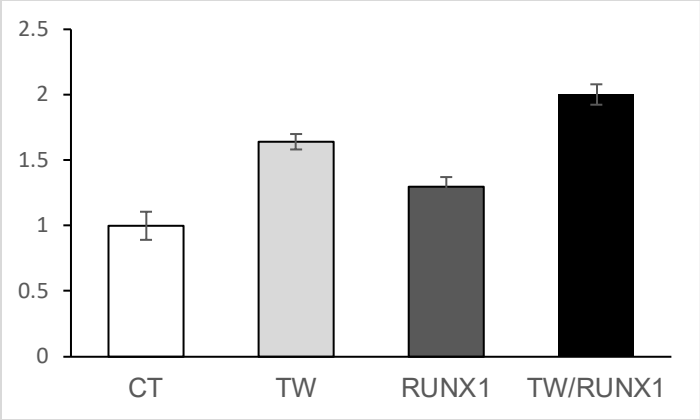

Figure 5 *An ENPP2 promoter/enhancer luciferase construct was co-expressed with (1) Twist, (2) RUNX1 or (3) Twist and RUNX1 in HEK293 cells. Cells were treated with 2mM TSA for 12 hours before luciferase activities were measured.*

According to the original Statement of Work, mouse models will be used to test the *in vivo* function of the Twist-ATX-LPAR1 axis. These animal experiments have been pending as we continue to collect and comprehensively analyze *in vitro* data about transcriptional regulation of ENPP2. We plan to start the *in vivo* experiment only for testing the mechanisms we verified *in vitro*. **This is an ethical requirement for the use of animals in research. We also note that some of our key findings could not have been anticipated at the outset of the project. Consistent with good scientific practice we continue adjust our focus and research strategies based on the progress we have made, while ensuring that the work remains consistent with the major objective of the original proposal.**

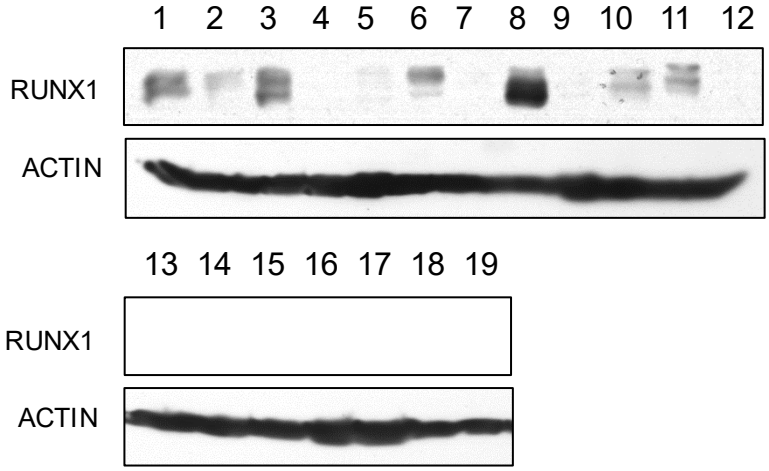

Figure 6 *Western blot analysis of RUNX1 expression in multiple breast cancer cell lines. 1 MCF10A; 2 HMLE; 3 MDA-MB-231; 4 MDA-MB-157; 5 BT549; 6 Hs578T; 7 SUM1315; 8 SUM149; 9 SUM159; 10 MDA-MB-468; 11 BT20; 12 HCC1937; 13 MCF7; 14 T47D; 15 ZR75; 16 MDA-MB-361; 17 SKBR3; 18 BT483; 19 HCC1428.*

In addition to the abovementioned results, we evaluated Twist expression in 130 TNBC patients (**relevant to Major Task 3, Subtask 3c**). Based on chi-square test performed by Dr. Chen,

the biostatistician included in this project, there is no significant difference in the 5-year survival between patients with high vs. low expression of Twist. However, we did find that Twist expression in a different set of human primary TNBC specimens is positively correlated with tumor recurrence (Figure 8). Unfortunately we failed to generate ideal IHC results using our di-acetylated Twist antibody. This is possibly due to hindered/limited epitope recognition during tissue staining, as we do not have technical issues on performing IHC.

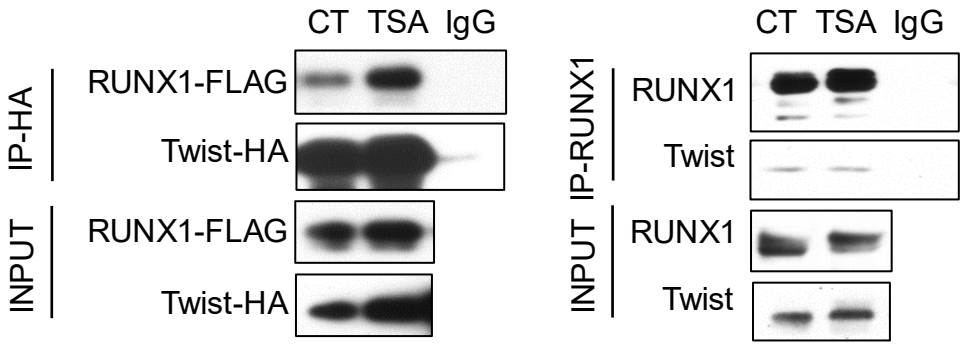

Figure 7 *Left panel: HEK293 cells were co-transfected with Flag-tagged RUNX1 and HA-tagged Twist. Cells were treated with 2mM TSA or solvent control for 12 hours before being harvested. Twist protein was immunoprecipitated with HA and Flag-RUNX1 was examined by Western blot. Right panel: Hs578T cells were treated with TSA or solvent control as described above, and Twist-RUNX1 interaction was examined by co-immunoprecipitation followed by Western blot.*

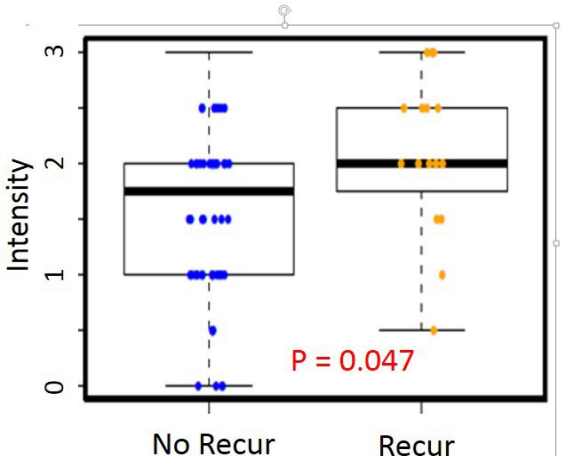

Figure 8 *IHC was performed on Twist expression in 75 cases of TNBC samples with blinded scoring. Each tissue core was assigned an intensity score: negative (0), weak (1), moderate (2), and strong (3). Data were traced forward in time for 5 years to identify patients with recurrence. Box-and-whisker plot shows different expression levels. P-value was obtained from Wilcoxon signed rank test.*

3.2. Opportunities for professional development

A. Grant review/study section service
NIH peer review (Dr. Morris)

03/27/2018 at CSR

Meeting 2018/05 ZRG1-BST-X-50 SRO: Craig Giroux

08/21/2018 at NIEHS

Meeting 2019/01 EHS-P SRO: Linda Bass

11/16/2018 at NHLBI

Meeting 2019/01 ZHL1-CSR-H-F3 SRO: YingYing Li-Smerin

03/27/2019 at NHLBI

Meeting 2019/05 ZHL1-CSR-H-M3 SRO: YingYing Li-Smerin

B. Journal reviewing/editorial Board service

Dr. Morris

Associate Editor: Molecular Pharmacology
Editorial Board: Journal of Lipid Research
Ad hoc peer review for several commercial and societal journals.

Dr. Lin

Scientific reviewer of multiple journals

3.3. Dissemination of research results

A. Presentations (Dr. Morris)

Regulation of atherosclerosis by lysophosphatidic acid and autotaxin. Department of Biochemistry, Virginia Commonwealth University, November 10 2019

Effects of diet and hyperlipidemia on circulating levels and distribution of lysophosphatidic acid. Keystone Conference on Lipidomics, Steramboat Springs, CO March 31-April 5, 2019

B. Publications of relevance to the project

1: Yang L, Kraemer M, Fang XF, Angel PM, Drake RR, Morris AJ, Smyth SS. LPA receptor 4 deficiency attenuates experimental atherosclerosis. J Lipid Res. 2019 May;60(5):972-980. doi: 10.1194/jlr.M091066. Epub 2019 Feb 22. PubMed PMID: 30796085; PubMed Central PMCID: PMC6495174.

2: Brandon JA, Kraemer M, Vandra J, Halder S, Ubele M, Morris AJ, Smyth SS. Adipose-derived autotaxin regulates inflammation and steatosis associated with diet-induced obesity. PLoS One. 2019 Feb 7;14(2):e0208099. doi: 10.1371/journal.pone.0208099. eCollection 2019. PubMed PMID: 30730895; PubMed Central PMCID: PMC6366870.

3: Jafari N, Drury J, Morris AJ, Onono FO, Stevens PD, Gao T, Liu J, Wang C, Lee EY, Weiss HL, Evers BM, Zaytseva YY. De Novo Fatty Acid Synthesis-Driven Sphingolipid Metabolism Promotes Metastatic Potential of Colorectal Cancer. Mol Cancer Res. 2019 Jan;17(1):140-152. doi: 10.1158/1541-7786.MCR-18-0199. Epub 2018 Aug 28. PubMed PMID: 30154249; PubMed Central PMCID: PMC6318071.

4: D'Souza K, Nzirorera C, Cowie AM, Varghese GP, Trivedi P, Eichmann TO, Biswas D, Touaibia M, Morris AJ, Aidinis V, Kane DA, Pulinilkunnil T, Kienesberger PC. Autotaxin-LPA signaling contributes to obesity-induced insulin resistance in muscle and impairs mitochondrial metabolism. J Lipid Res. 2018 Oct;59(10):1805-1817. doi: 10.1194/jlr.M082008. Epub 2018 Aug 2. PubMed PMID: 30072447; PubMed Central PMCID: PMC6168304.

5: Liu J, Duan Z, Guo W, Zeng L, Wu Y, Chen Y, Wang Y, Lin Y, Zhang Q, He Y, Deng J, Stewart RL, Wang C, Lin PC, Ghaffari S, Evers BM, Liu S, Zhou MM, Zhou BP, Shi J, Targeting

the BRD4/FOXO3a/CDK6 axis Sensitizes AKT Inhibition in Luminal Breast Cancer, Nature Communications (2018) 9(1), 5200.

3.4. Future plans

We will continue to address the goals of the funded proposal. We plan to design experiments including RNA-Sequencing, co-immunoprecipitation, Chromatin-immunoprecipitation, luciferase assay and functional assays to comprehensively characterize the Twist-ATX-LPAR1 axis. Particularly, we will focus on the role of RUNX1 on Twist-mediated transcription of ENPP2 (the gene that encodes ATX) in both TNBC cells and adipocytes. We will also continue to develop new ATX inhibitors, analytical methods and animal models to provide orthogonal experimental approaches to those described in the proposal.

4. Impact

TNBC is the most aggressive breast cancer subtype. TNBC is aggressive metastatic and more likely to recur than other breast cancer subtypes. TMBC does not respond to receptor targeted therapies. Currently TNBC is treated by surgery with adjuvant chemo or radiation therapy. Obesity is a risk factor for TNBC and a poor prognostic factor. The major impact of the research we are conducting is that it will identify a mechanism linking obesity to the development and progression of TNBC. The pathways we propose to study may then be targets for pharmacological intervention in TNBC.

5. Changes/Problems

As we found that Twist only moderately enhances transcription of ENPP2, which is in contrast to our RNA-Seq and microarray results, we plan to resolve the discrepancy and examine additional factor, i.e. RUNX1, in Twist-mediated ENPP2 transcription. We have gathered initial evidence of function of RUNX1 and will perform additional experiments to prove our hypothesis that co-targeting of Twist-BRD4 and RUNX1 can more efficiently disrupt the signaling axis and inhibit the development of obesity-associated TNBC. Accordingly, we have requested and were approved for a one-year No-Cost-Extension for this project to continue our study.

6. Products

ENPP2 promoter reporter constructs.

7. Participants and collaborating organizations

Andrew Morris (no change)

Guogen Mao (added to clone and study ENPP2 promoter)

Yiwei Lin (no change)

Other Support

Morris, Andrew J.

ACTIVE

5R01HL120507 Smyth, Morris (MPIs)	04/01/15 – 03/31/20	1.0 Cal Mnths

NIH/NHLBI
Lipid Phosphate Phosphatase 3 as a Novel Atherosclerosis Suppressor
The goal of this study is to use pre-clinical models to identify the mechanisms involved in protective effects of lipid phosphate phosphatase 3 against cardiovascular disease with a focus on foam cell formation in atherosclerosis.
Role: PI(MPI), OVERLAP: None

W81XWH-16-1-0067 Morris (PI) 04/15/16 – 04/14/20 0.7 Cal Mnths DOD/ USAMRAA
Define the Twist-ATX-LPAR1 signaling axis in promoting obesity-associated triple negative breast cancer
The goal of this project is to test the hypothesis that transcriptional regulation of autotaxin and lysophosphatidic acid receptors by twist is important for obesity associated risk and progression of triple negative breast cancer.
Role, PI, OVERLAP: None

BX001984-04 Smyth (PI) 10/01/10 – 12/31/19 1.0 Cal Mnth
VA BLR&D Merit Review
Adipose autotaxin: a novel link between obesity and cardiovascular disease
The goal of this project is to test the hypothesis that adipocytes are a source of the enzyme autotaxin, which promotes cardiovascular disease in obese mouse models.
Role Co-I, OVERLAP: None

I01CX001550 Morris, Smyth (MPI) 01/01/17 – 12/31/20 3.0 Cal Mnths
VA BLR&D Merit Review
Lysophosphatidic acid and cardiovascular disease risk
The goal of this project is to test the hypothesis that association of the bioactive lipid lysophosphatidic acid with atherogenic lipoproteins is a determinant of cardiovascular disease risk.
Role PI (MPI) OVERLAP: None

5P30ES026529 (Shi) 05/01/17 – 03/31/22 0.6 Cal Mnth
NIH/NIEHS (direct cost for the core)
Center for Appalachian Research in Environmental Sciences – Analytical Services Core
The overall goal of this application is to support an integrated core center to increase the efficiency and impact of environmental disease research at the University of Kentucky.
Role: Analytical Core Director, OVERLAP: None

5P42ES007380-21 Hennig (PI) 04/07/97 – 03/31/20 0.7 Cal Mnth
NIH/NIEHS (direct cost for the core)
Nutrition and Superfund Chemical Toxicity – Research Support Core B
The goal of this center is to explore the paradigm that healthy nutrition and exercise can reduce Superfund chemical toxicity through research projects and core service support.
Role: Analytical Core DirectorOVERLAP: None

5P42ES007380-21 Hennig (PI) 04/07/97 – 03/31/20 0.48 Cal Mnths
NIH/NIEHS
Nutrition and Superfund Chemical Toxicity
The goal of this study is to identify mechanisms by which environmental pollutants impair vascular endothelial cell function to promote cardiovascular disease.
Role: Co-PI, OVERLAP: None

5P20GM103527 Cassis (PI) 09/08/08 – 07/31/23 0.6 Cal Mnths
NIH/NIGMS (direct cost for the core)
Center of Research in Obesity and Cardiovascular Disease – Analytical Core
The Center aims to identify mechanisms linking the epidemic of obesity to the high incidence of cardiovascular disease in the obese population and to develop promising junior project investigators.
Role, Analytical Core Director, Mentor, OVERLAP: None

1P20GM121327 St Clair (PI) 03/01/17 – 12/31/21 0.6 Cal Mnths
NIH/NIGMS
University of Kentucky Center for Cancer and Metabolism
This award supports a program of training and infrastructure to enable the career development of early stage independent investigators working in the area of cancer and metabolism. I am a mentor for two of these investigators.
Role: Mentor, OVERLAP: None

5R01HL123358 Zhou (PI) 08/01/15 – 05/31/19 0.35 Cal Mnths
NIH/NHLBI
A Novel Mechanism for ART-Associated Dyslipidemia and Atherosclerosis
The goal is to investigate a novel mechanism linking antiretroviral (ARV) drugs with dyslipidemia and cardiovascular disease.
Role, Co-I, OVERLAP: None

R56 AI135021 Korotkova (PI) 08/6/18 – 07/31/19 .6 Cal Mnths
NIH
Biogenesis and Function of Lancefield Group A Carbohydrate Expressed by Streptococcus Pyogenes The goal of this study is to delineate biochemical steps and enzymes involved in the synthesis of this bacterial cell wall component.
Role: Co-I, OVERLAP: None

5R01ES023470 Zhou (PI) 09/26/13 – 06/30/19 0.0 Cal Mnths during NCE NIH/
NIEHS (NCE)
Endocrine Disruptor Mediated Activation of PXR Causes Dyslipidemia
The goal is to investigate a novel mechanism linking endocrine disrupting chemical exposure and hyperlipidemia.
Role: Co-I, OVERLAP: None

5R01DK107646 Kern (PI) 09/21/15 – 07/31/19 0.0 Cal Mnths
NIH/NIDDK
Cold Induced Changes in Human Subcutaneous White Adipose
The goal of this study is to define the mechanisms and physiological consequences of cold-induced “browning” of while adipose tissue. I will make measurements of lipids and related metabolites for this project.
Role: Co-I, OVERLAP: None

5K01CA197073 Onono (PI) 07/01/15-06/30/20 0.0 Cal Mnths
NIH/NCI
Intestinal phosphatidylcholine exposure and breast cancer risk

This is a mentored career development award that will enable the recipient to become an independent investigator working on mechanisms that link obesity and cancer risk. I am the primary mentor.
Role: Mentor, OVERLAP: None

No ID Kraemer (PI) 07/1/18 – 06/30/20 0 Cal Mnths
American Heart Association
Regulation and Function of Lipoprotein Associated Bioactive Lysophospholipid Mediators of Atherosclerosis
This is a post doctoral fellowship application to support research training for the applicant.
Role: Co-I, OVERLAP: None
1IS1BX004791-01(Morris, PI) 04/01/19-03/31/20 0 Cal Mnths
VA, CSR&D
ShEEP Request For Gas Chromatograph Mass Spectrometer
This application requests funds for purchase of an integrated gas chromatograph mass spectrometer system which will be used to support research in areas that include cardiovascular disease, thrombosis, muscle weakness and intestinal inflammation
Role: PI OVERLAP:none

PENDING

R01 CA234026 Zaytseva (PI) 07/01/19-06/30/24 0.6 Cal Mnths
NIH
The role of Fatty Acid Synthase in regulation of cancer cells survival and metastasis in colorectal cancer
The goal of this study is to test the hypothesis that de novo fatty acid synthesis promotes cancer cell survival and metastasis through effects on sphingophospholipid metabolism.
Role: Co-I, OVERLAP: None

U2C ES030858 Morris (PI) 08/01/19-07/31/24 7.14 Cal Mnths
NIEHS
University of Kentucky Targeted Environmental Analysis Laboratory (UK-TEAL)
The goal of this application is to support a targeted analysis laboratory component of the NIEHS Human Health Exposure Analysis Resource which will enable large scale studies to investigate the relationships between exposure to environmental stressors and human health. The Laboratory comprises an administrative core, a targeted analysis core and a developmental core.
Role: Director, Core Leader. OVERLAP: None

No ID Unrine (PI) 10/01/19-09/30/22 .15 Cal Mnths
EPA
Treatment and management of biosolids and soils to minimize mobility of poly- and perfluoroalkyl substances (PFAS)
The goal of this application is to study mechanisms determining the mobility of per and poly fluorinated substances in soil. These are persistent environmental pollutants that associate with human disease risk factors and are particularly relevant to populations in Kentucky. I will make measurements of these chemicals.
Role: Co-I OVERLAP: None

R01DE028916 Korotkova (PI) 07/01/19-06/30/24 .35 Cal Mnths
NIH
Biosynthesis, structure and function of cell wall in Streptococcus mutans
The goal of this application is to identify enzymes and pathways involved in the synthesis of the cell wall of this pathogenic bacterium. I will conduct studies using high resolution mass spectrometry to determine the structure of intermediates and end products in these pathways.
Role: Co-I OVERLAP: None

5P42ES007380 Hennig (PI) 12/01/19-11/30/24 1 Cal Mnths
NIH/NIEHS
Nutrition and Superfund Chemical Toxicity
The overarching goal of this Center is to investigate the distribution, remediation and adverse health effects of superfund environmental chemical pollutants with a particular focus on the roles of diet and exercise as healthy interventions to mitigate these effects. I am involved in a component project that seeks to identify mechanisms by which environmental pollutants impair vascular endothelial cell function to promote cardiovascular disease. I am also the director of the Biomonitoring and Environmental Analyticla Chemistry Core component.
Role: Co-PI, Core Director, OVERLAP: None

Lin, Yiwei

Active

W81XWH-16-1-0066 Lin (PI) 04/15/16 – 04/14/20
DOD/USAMRAA
Define the Twist-ATX-LPAR1 signaling axis in promoting obesity-associated triple negative breast cancer
The goal of this project is to test the hypothesis that transcriptional regulation of autotaxin and lysophosphatidic acid receptors by twist is important for obesity associated risk and progression of triple negative breast cancer.
Role, PI, OVERLAP: None

8. Special reporting requirements

N/A

9. Appendices

N/A