MMPC
National Mouse Metabolic Phenotyping Center

University of Massachusetts
UMASS Medical School

UMass MMPC

19th Annual National MMPC Meeting
Cincinnati Zoo & Botanical Garden
October 29th, 2019

Welcome to the National Mouse Metabolic Phenotyping Center at UMass!

The National Mouse Metabolic Phenotyping Center (MMPC) at UMass is a National Institutes of Health-sponsored resource (NIH Grant 5U2C-DK093000) that provides an array of sophisticated research tools to the global scientific community for the purpose of investigating mouse models of human diseases with particular focus on diabetes, obesity, and diabetic complications. The mission of the UMass MMPC is to advance medical and biological research by offering comprehensive, standardized, and high-quality experimental testing services to the academic and industry scientists. The UMass MMPC is composed of multidisciplinary group of investigators and leading scientists with state-of-the-art technologies at the UMass Medical School and consists of six complementary Phenotyping Cores. The collective goal of our research program is to find a cure for diabetes and improve human health.

Dr. Jason K. Kim, Director

Metabolism Core performs elegant, physiological, and non-invasive metabolic experiments to assess insulin sensitivity hyperinsulinemic-euglycemic clamp & GTT/ITT), glucose/lipid/protein metabolism using labeled metabolites, body composition using ^{1}H-MRS, energy balance (food/water intake, energy expenditure, physical activity) at varying temperature and light/dark cycle using TSE Metabolic Cage System with Environmental Chamber, and exercise capacity using treadmill in mice. The Core also conducts comprehensive drug trial studies for PK/PD, efficacy, and toxicity analysis with academic and pharmaceutical institutions.

Analytical Core utilizes Luminex, Cobas Clinical Chemistry Analyzer, and molecular experiments to perform a high-throughput, multiplexed analysis of serum/tissue/urine levels of hormones, cytokines, chemokines, electrolytes, and metabolites, liver/kidney/thyroid function panels, and metabolic/inflammatory signaling pathways. Samples can be directly sent to the Core or obtained from mice by the Core.

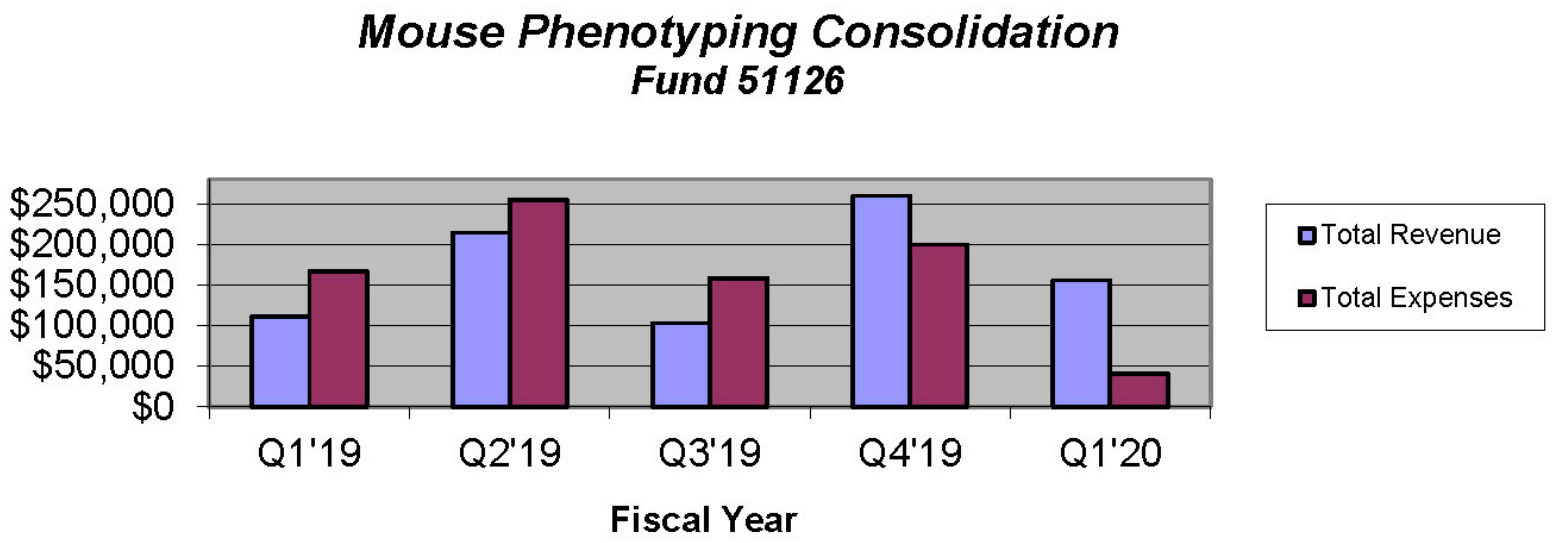
Islet Core conducts sophisticated *in vivo*, *ex vivo*, and *in vitro* analysis of insulin secretion, islet function/structure, and pancreatic function using hyperglycemic clamp, perifusion, and molecular experiments in mice. The Core also performs histological and morphological analysis with islet isolation.

Cardiovascular Core applies state-of-the-art high-frequency and high-resolution digital imaging platform with color Doppler mode (VisualSonics Vevo2100) to perform 2-D and M-mode echocardiography to non-invasively assess cardiac function and structure in mice. The Core also measures ECG/blood pressure and vascular/endothelial function, and conducts elegant micro-surgery procedures to generate mouse models of cardiovascular and peripheral vascular diseases.

Microbiome Core provides expert knowledge and metagenomics 16S rRNA NextGen sequencing tools for state-of-the-art analysis of gut microbiota to investigate their role in altered energy balance and metabolism in mice. The Core also offers Fecal Microbiota Transplant (FMT) and antibiotic treatment procedures to facilitate alterations in gut microbiota population.

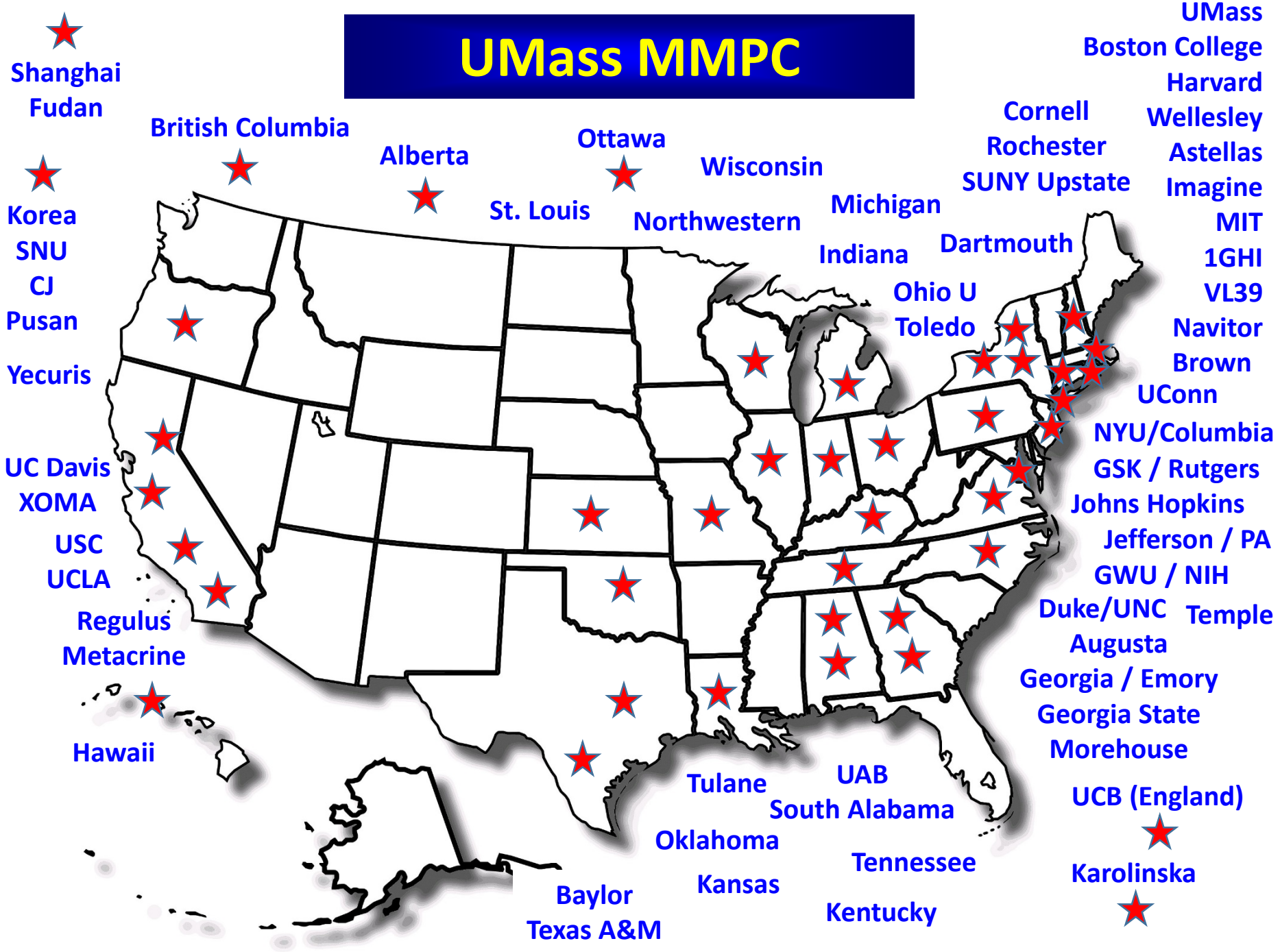
The Humanized Mouse Cell Transplantation and Assessment Core offers unique “humanized” mice engrafted with functional human cells/tissues to conduct clinically relevant *in vivo* experiments of human cells, tissues, and immune system. The Core also provides expert and standardized techniques to assess *in vivo* function of transplanted human islets and stem cell-derived beta-cells in immunodeficient mice.

UMass MMPC in Year 8



Beginning Fund Balance	***-$19,069***					***-$91,230***
	Q1'19	**Q2'19**	**Q3'19**	**Q4'19**	**FY'19 YTD**	**Q1'20**
Revenue	$1,151	$73,412	$16,253	$122,432	**$213,248**	$155,902
5U2C Grant	$110,090	$141,050	$86,942	$137,394	**$475,476**	$0
Total Revenue	$111,241	$214,462	$103,195	$259,826	**$688,724**	$155,902
Expenses	$56,901	$114,015	$71,027	$62,534	**$304,478**	$41,084
5U2C Grant	$110,090	$141,050	$86,942	$137,394	**$475,476**	$0
Total Expenses	$166,991	$255,065	$157,969	$199,929	**$779,954**	$41,084
Net Balance	-$55,750	-$40,603	-$54,774	$59,898	**-$91,230**	$114,818
					Current Fund Balance	***$23,589***

UMass MMPC


Shanghai
Fudan
Korea
SNU
CJ
Pusan
Yecuris
British Columbia
Alberta
St. Louis
Ottawa
Wisconsin
Northwestern
Michigan
Indiana
Ohio U
Toledo
Cornell
Rochester
SUNY Upstate
Dartmouth
UMass
Boston College
Harvard
Wellesley
Astellas
Imagine
MIT
1GHI
VL39
Navitor
Brown
UConn
NYU/Columbia
GSK / Rutgers
Johns Hopkins
Jefferson / PA
GWU / NIH
Duke/UNC
Temple
Augusta
Georgia / Emory
Georgia State
Morehouse
UCB (England)
Karolinska
UC Davis
XOMA
USC
UCLA
Regulus
Metacrine
Hawaii
Tulane
UAB
South Alabama
Oklahoma
Tennessee
Kansas
Kentucky
Baylor
Texas A&M

Drug Trial Study

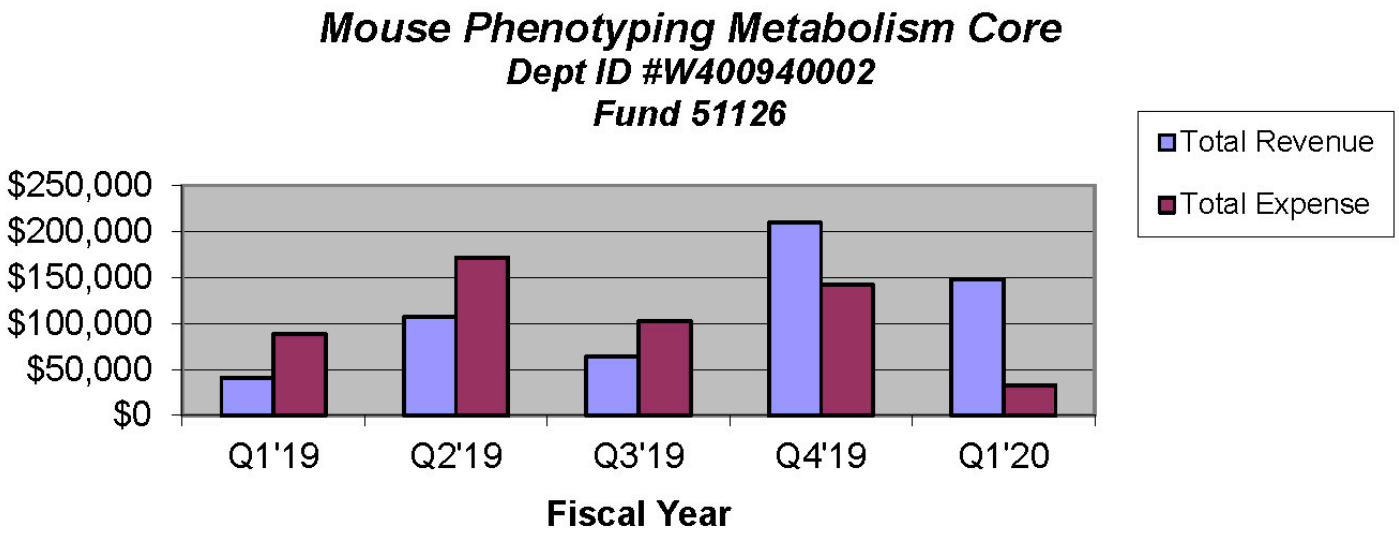
Metabolism Core

Research Staff
Lauren Tauer, M.S.

Director, Charles River Laboratories

Core Director
Randall Friedline, Ph.D.

Metabolism Core



FY20 CUSTOMER REVENUE

Molecular Medicine	0.9%
Gene Therapy	7.3%
Infectious Disease	5.8%
MCCB	1.4%
GlaxoSmithKline LLC	43.9%
G. Washington Univ.	14.0%
New York University	11.8%
Harvard	8.9%
Other External (3)	6.1%

Microbiome Core

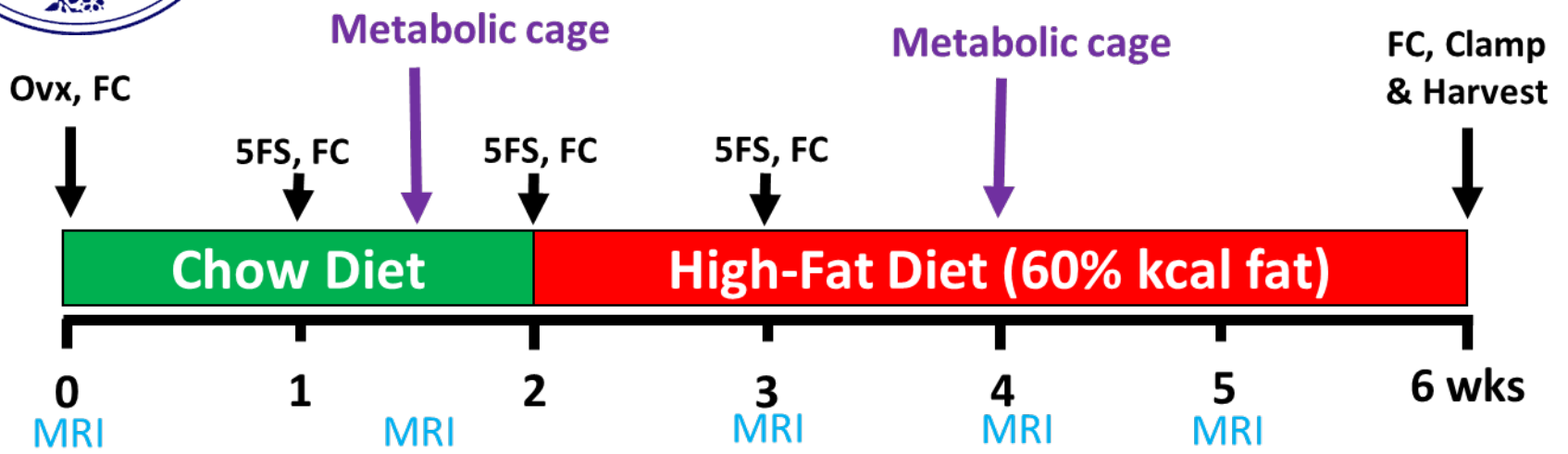
Director: Beth A. McCormick, PhD

The Microbiome Core offers:

- Consultation service for the design and implementation of gut microbiome studies
- Sample preparation and quality control tests
- Metagenomic 16S rRNA NextGen sequencing methodologies
- Post-sequencing consultation for data analysis, interpretation, upload, and presentation
- Fecal Microbiota Transplant (FMT) procedure to selectively alter gut microbiota in mice
- Chronic and acute antibiotic treatment to induce altered gut microbiota in mice

MMMRP Brings Together Wellesley College with Metabolism Core & Microbiome Core of UMass MMPC

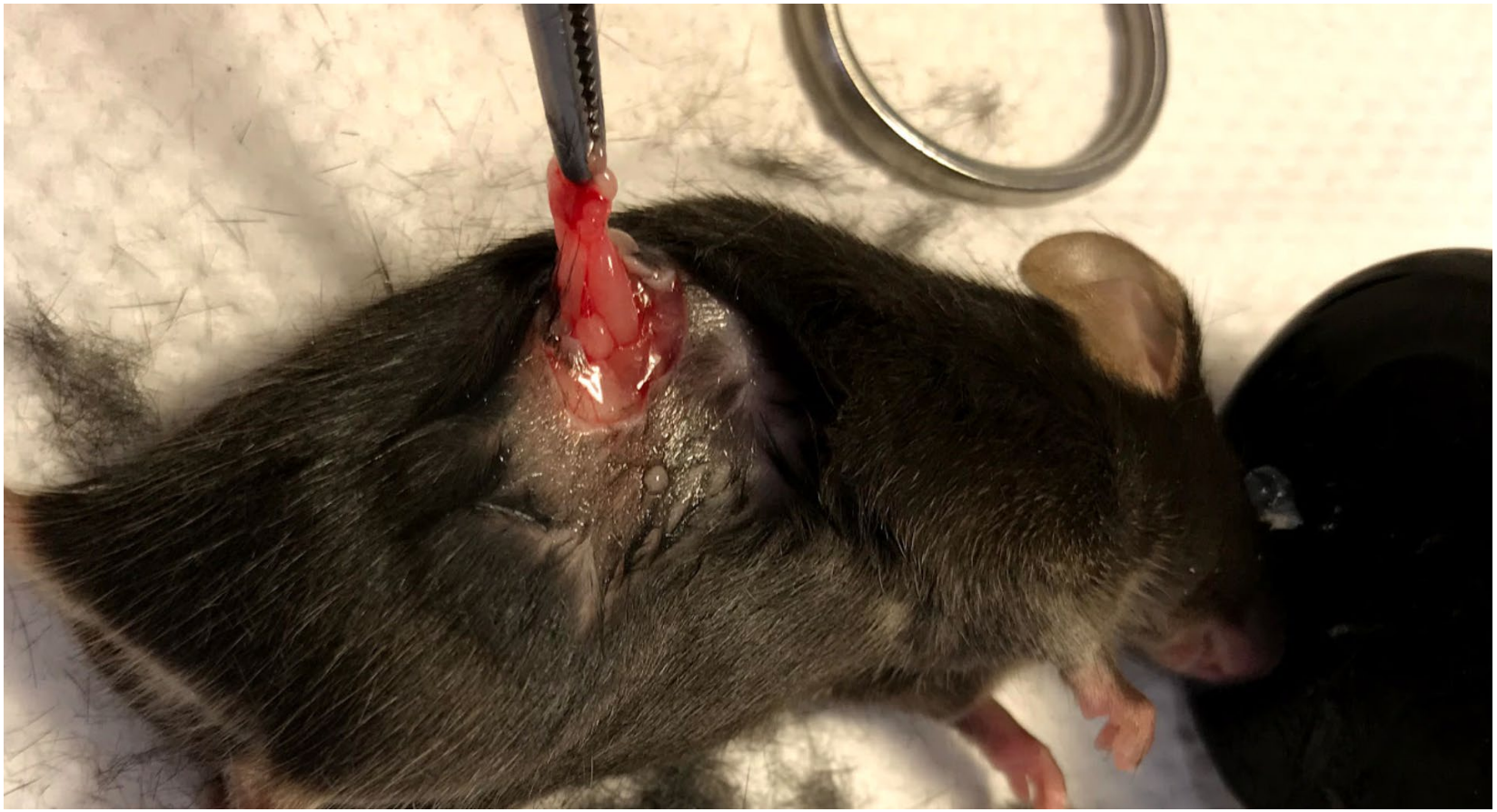
MMMRP Service Using Metabolism & Microbiome Core



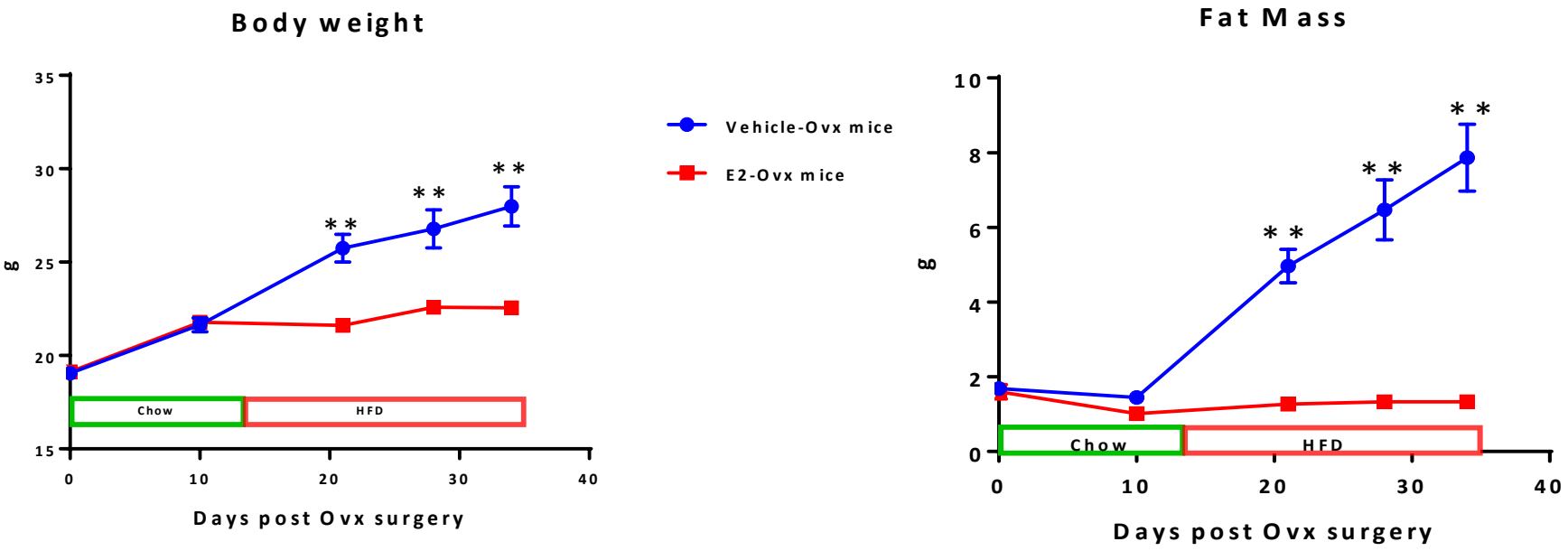
- Ovx: Ovariectomy and impalnt capsules
- 5FS: 5-hr fasting glucose
- Clamp: Hyperinsulinemic-euglycemic clamp
- MRI : Body composition (g; using 1H-MRS)
- FC: Fecal samples

- ❑ Vehicle-treated Female Mice (n=6)
- ❑ E2-treated Female Mice (n=6)

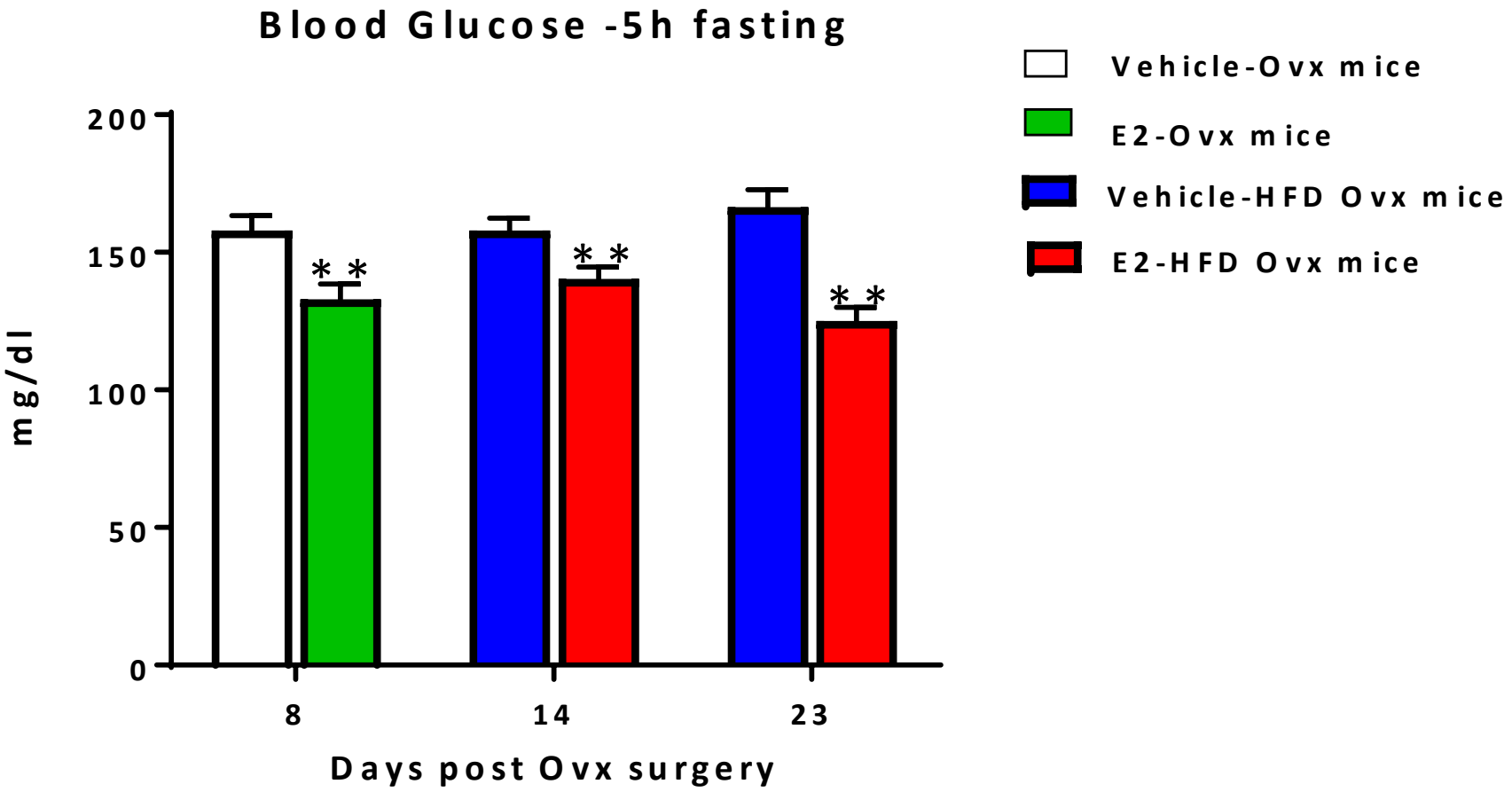
Ovariectomy Procedure for Studies Using Female Mice



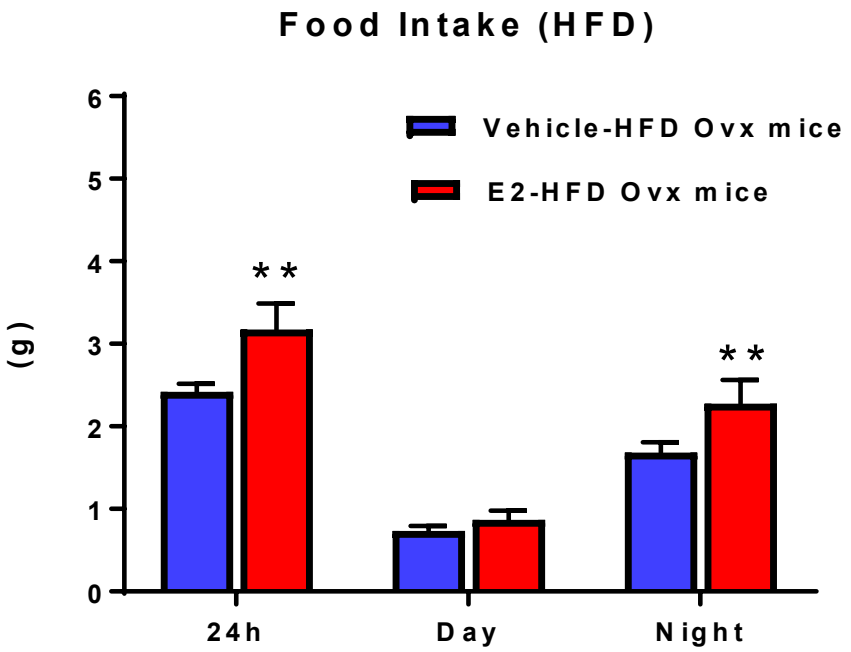
Ovariectomized Female Mice Become Obese on HFD, But Diet-Induced Obesity is Prevented with Estrogen Replacement

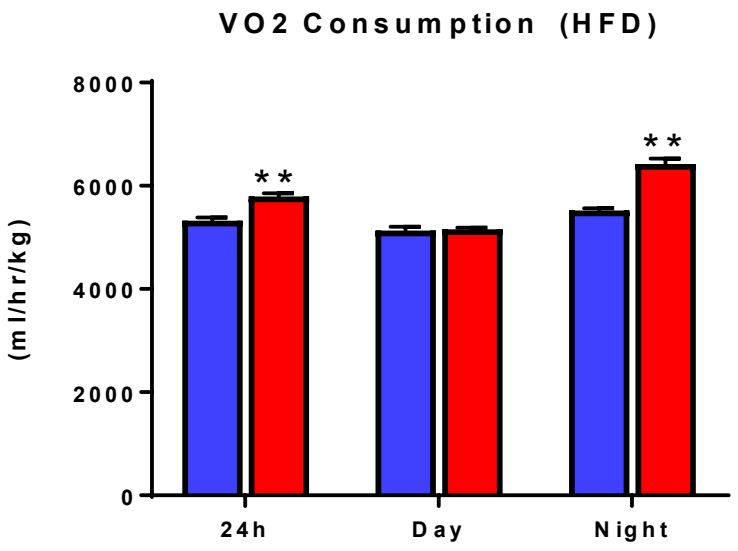


Estrogen Replacement Lowers Blood Glucose Levels in Ovariectomized Female Mice on Chow and HFD

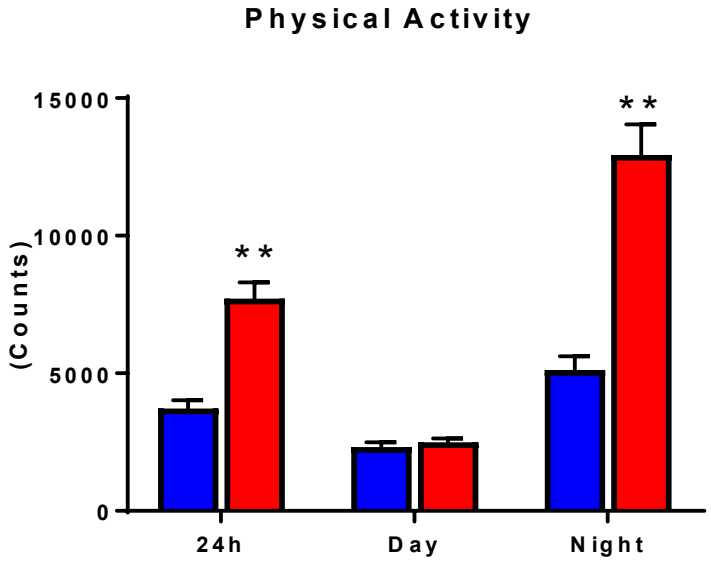


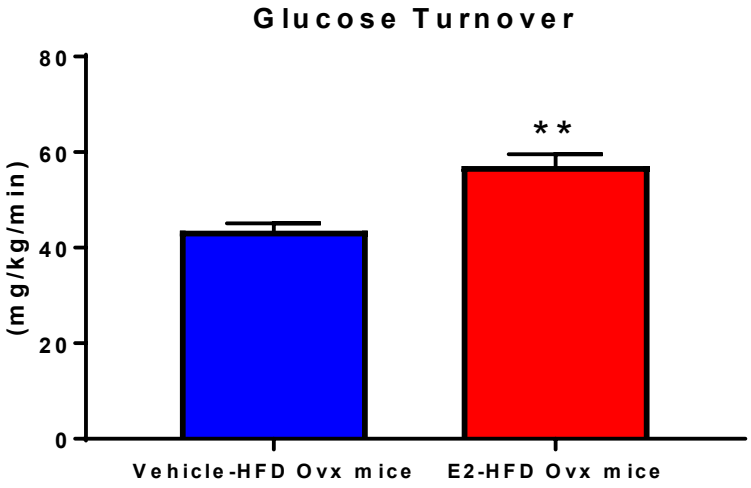
Estrogen Replacement Increases Food Intake and Energy Expenditure in Ovariectomized Female Mice on HFD



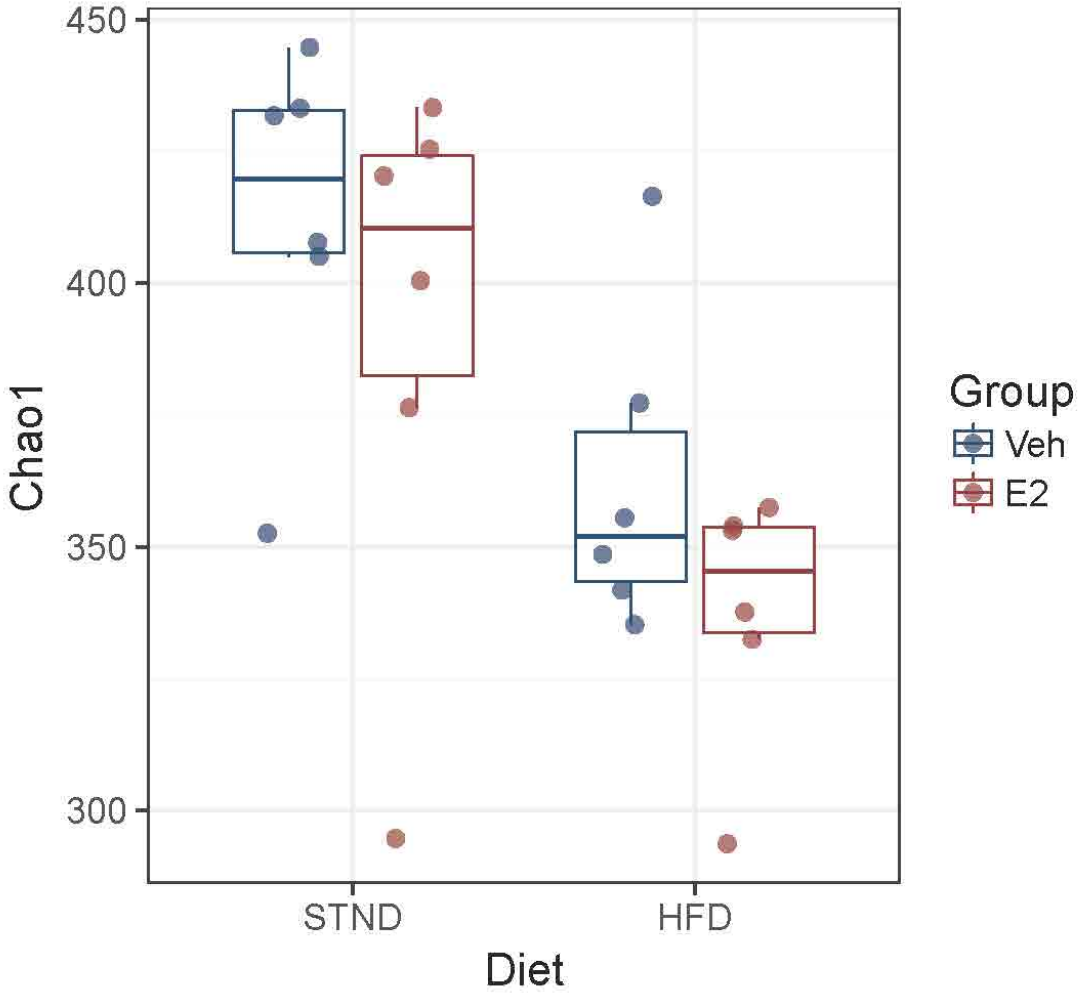


Estrogen Replacement Increases Physical Activity and Insulin Sensitivity in Ovariectomized Female Mice

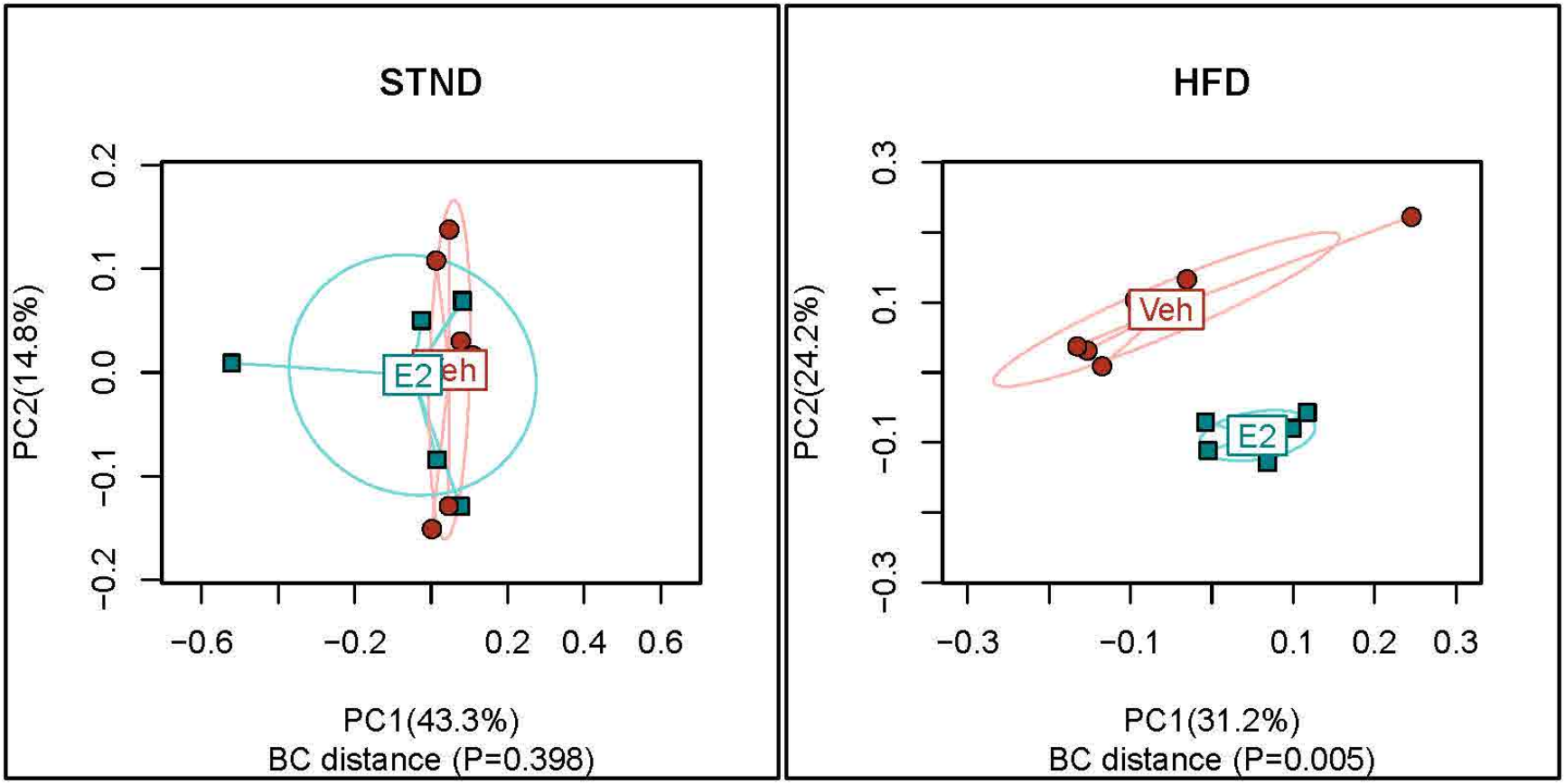




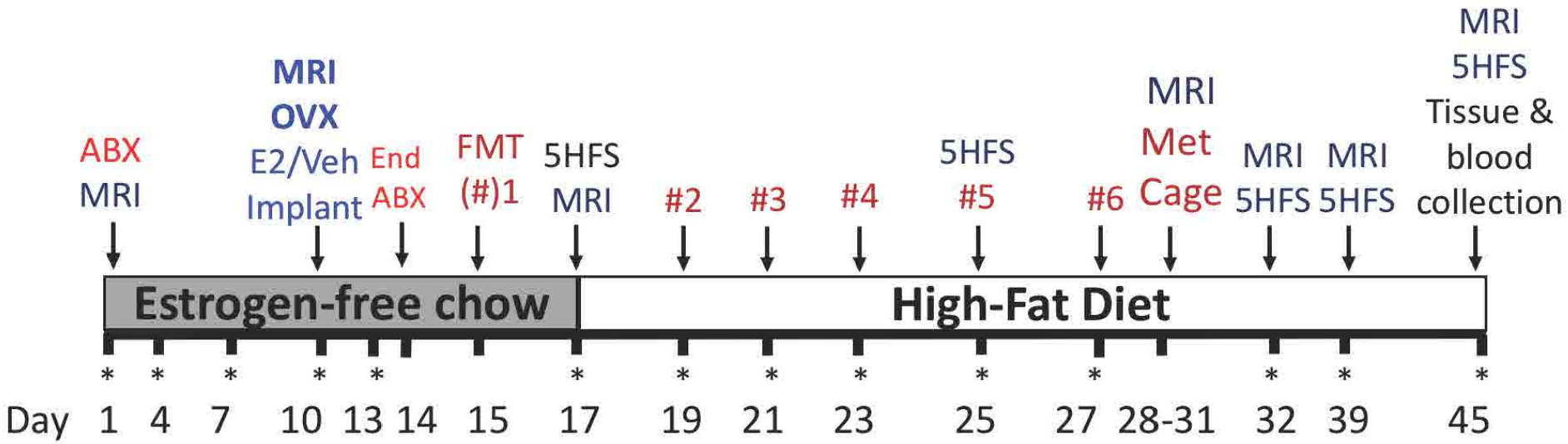
Alpha Diversity of Gut Microbiome is Affected by Different Diets But Not By Estrogen Treatment



Beta Diversity of Gut Microbiome is Significantly Affected by Estrogen Treatment in HFD-Fed Female Mice



Metabolic Effects of Fecal Microbiota Transplantation & Akkermansia in HFD-Fed Ovariectomized Female Mice



TREATMENT GROUPS (n=4 /group)

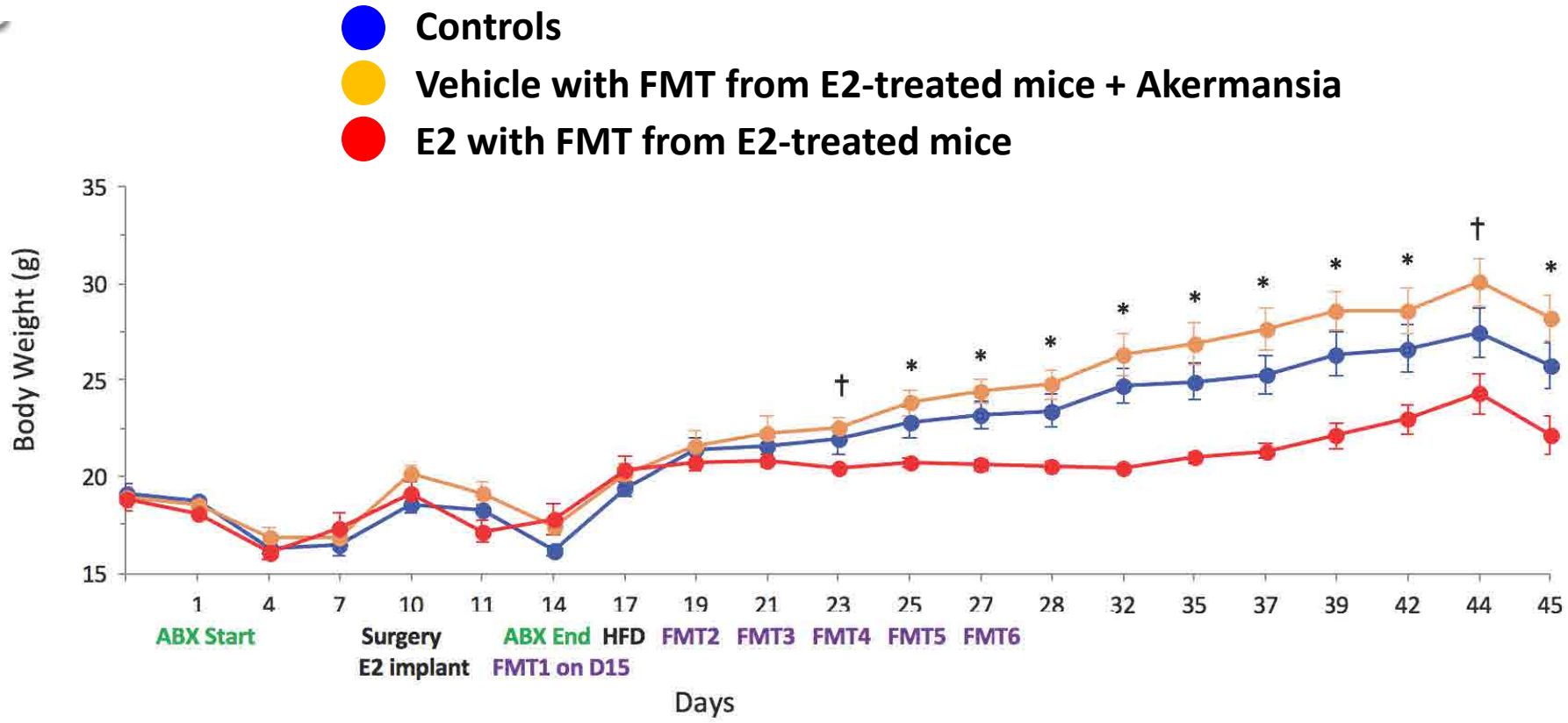
1. **VV** (Veh mice getting Veh-FMT)
2. **VA** (Veh mice getting E2-FMT with Akkermansia
3. **EE** (E2 mice getting E2-FMT)

TIMELINE ABBREVIATIONS

- **OVX**: Ovariectomy & implant capsules (E2 or Veh)
- **5HFS**: 5-hr fasting blood glucose.
- **ABX**: AVNM cocktail in drinking water for 14 days
- **FMT**: Fecal microbiota transplant
- *: Fecal samples collection days
- MRI: Body composition
- Every 4 days, body weight was also be measured.

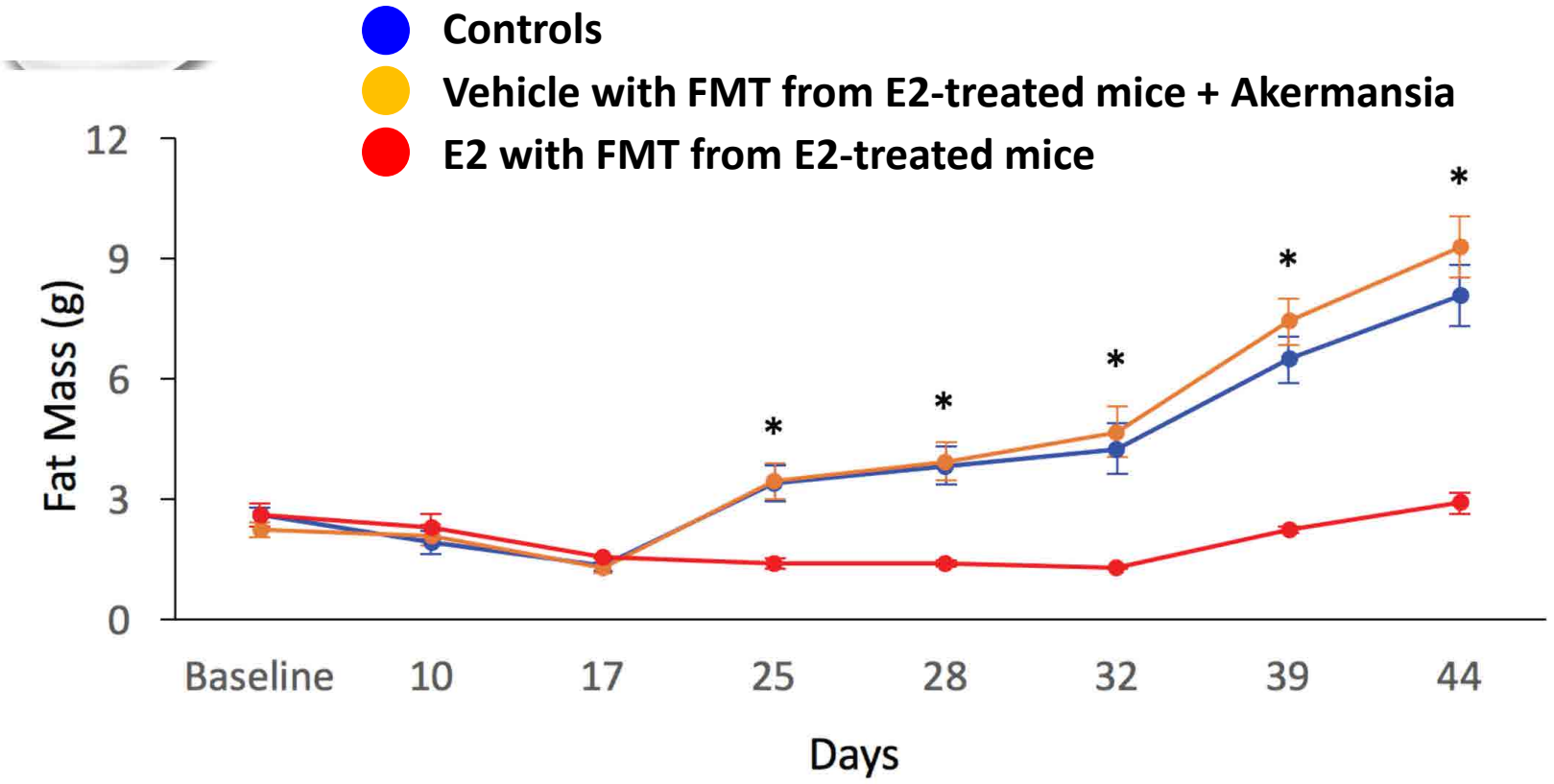
Vehicle Mice Receiving FMT from E2-Treated Mice + Akkermansia Are Not Protected from Diet-Induced Obesity

Body Weights (g)



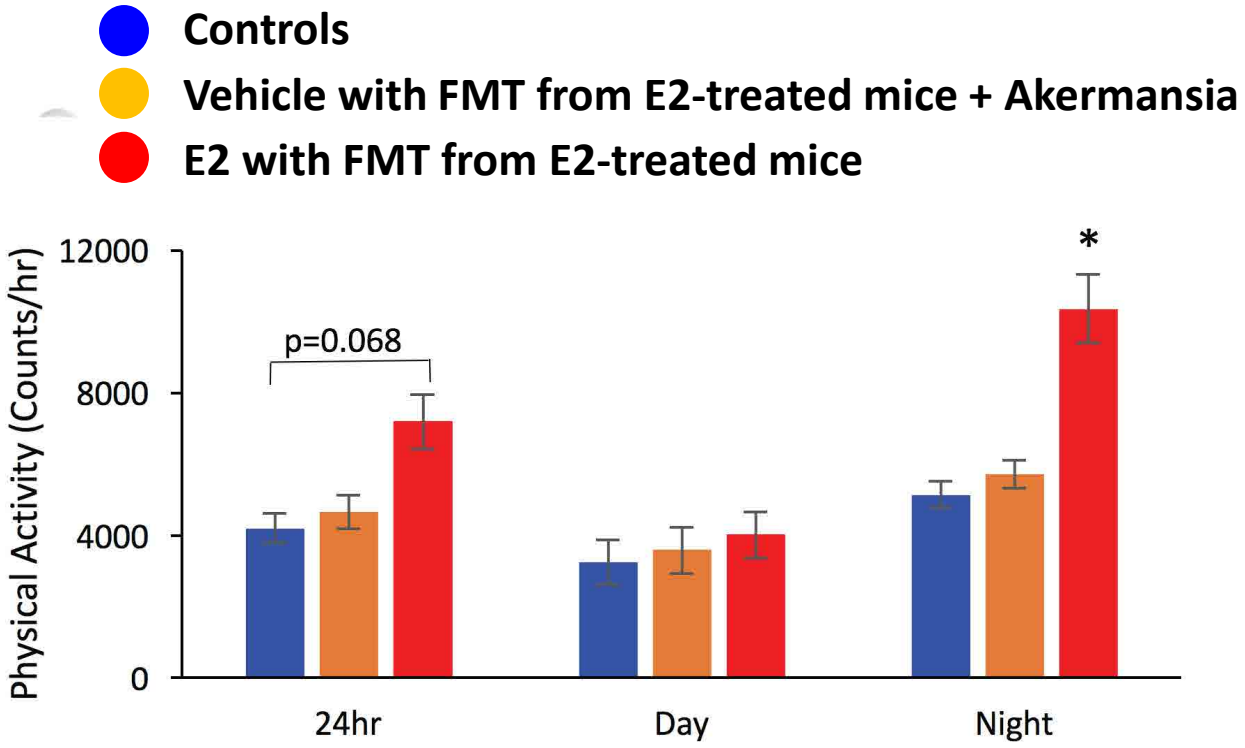
Vehicle Mice Receiving FMT from E2-Treated Mice + Akkermansia Are Not Protected from Diet-Induced Obesity

Fat Mass (g)



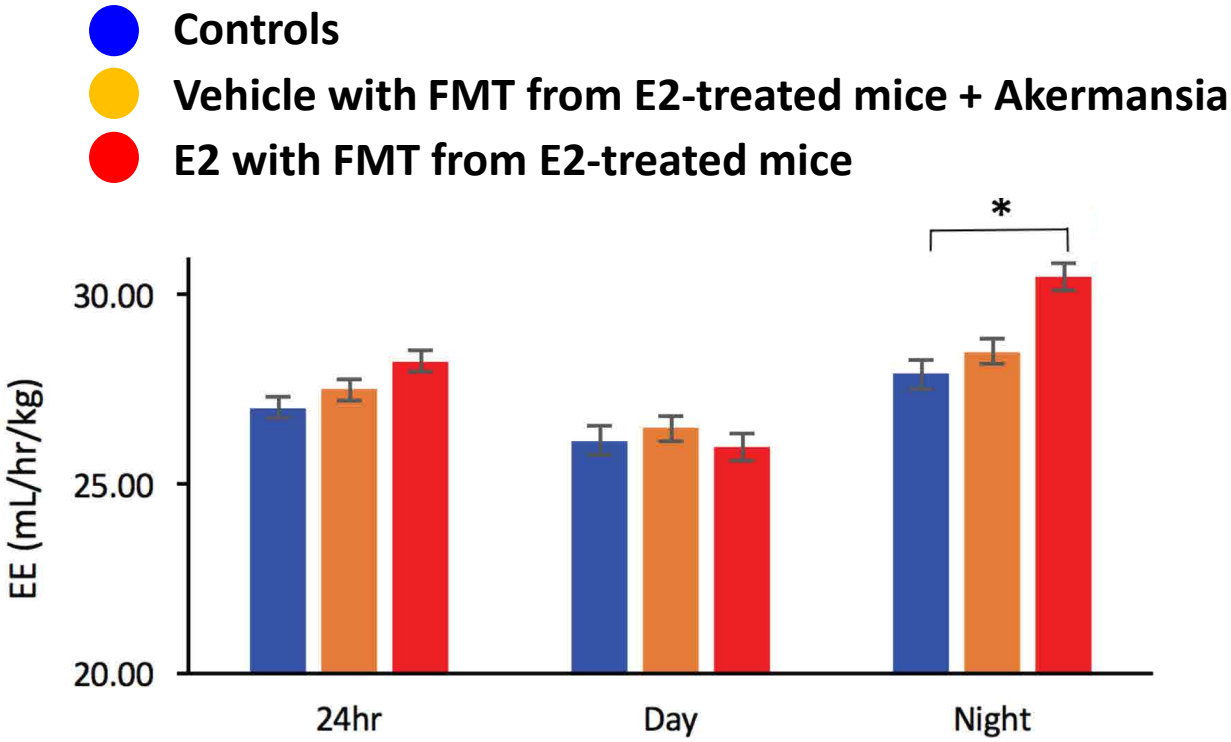
Activity is Increased in E2 Mice But Not in Vehicle Mice Receiving FMT from E2-Treated Mice + Akkermansia

Physical Activity



Increased Energy Expenditure in E2 Mice But Not in Vehicle Mice Receiving FMT from E2-Treated Mice + Akkermansia

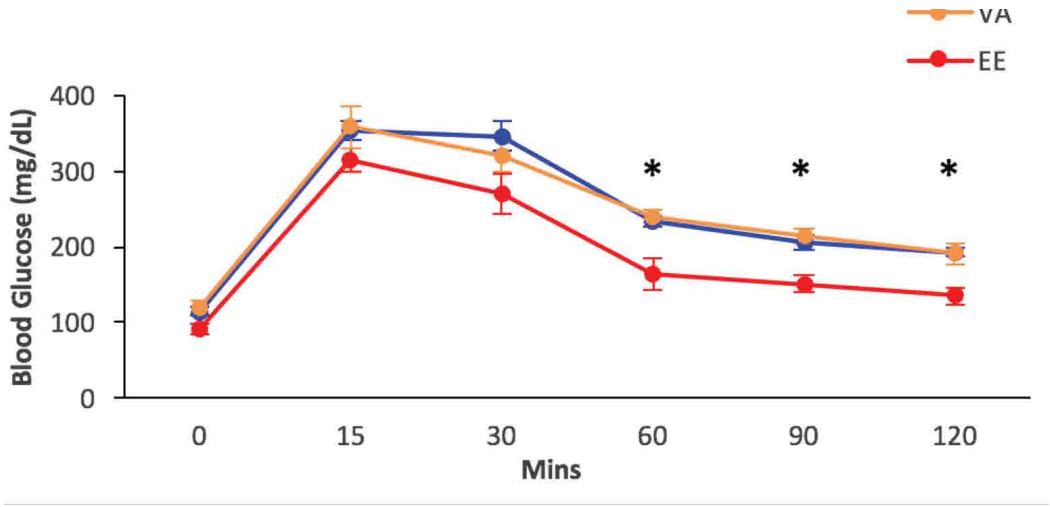
Energy Expenditure

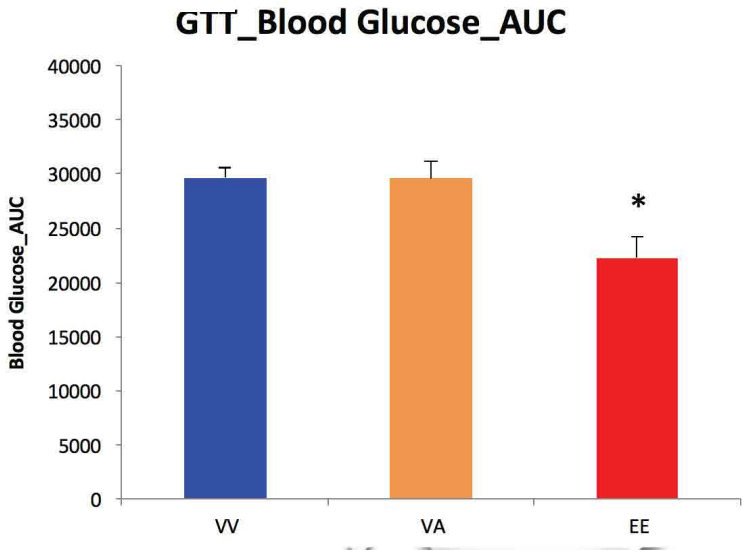


Vehicle Mice Receiving FMT from E2-Treated Mice + Akkermansia Remained Insulin Resistant After HFD

Glucose Tolerance Tests

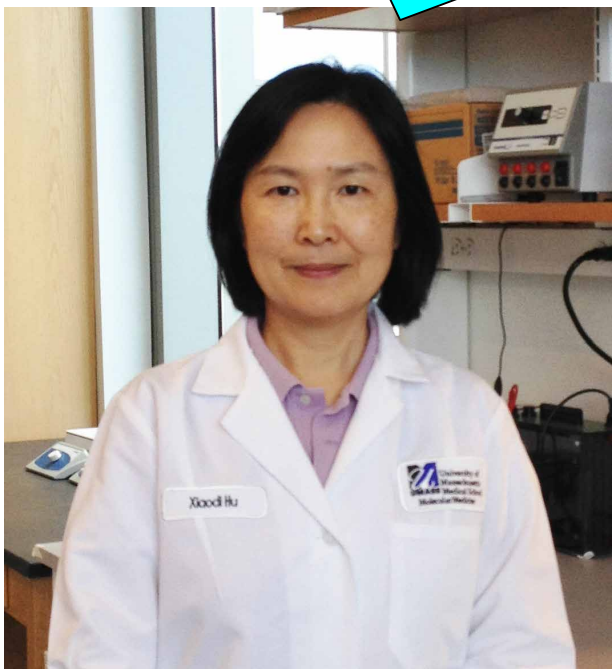
- Controls
- Vehicle with FMT from E2-treated mice + Akermansia
- E2 with FMT from E2-treated mice





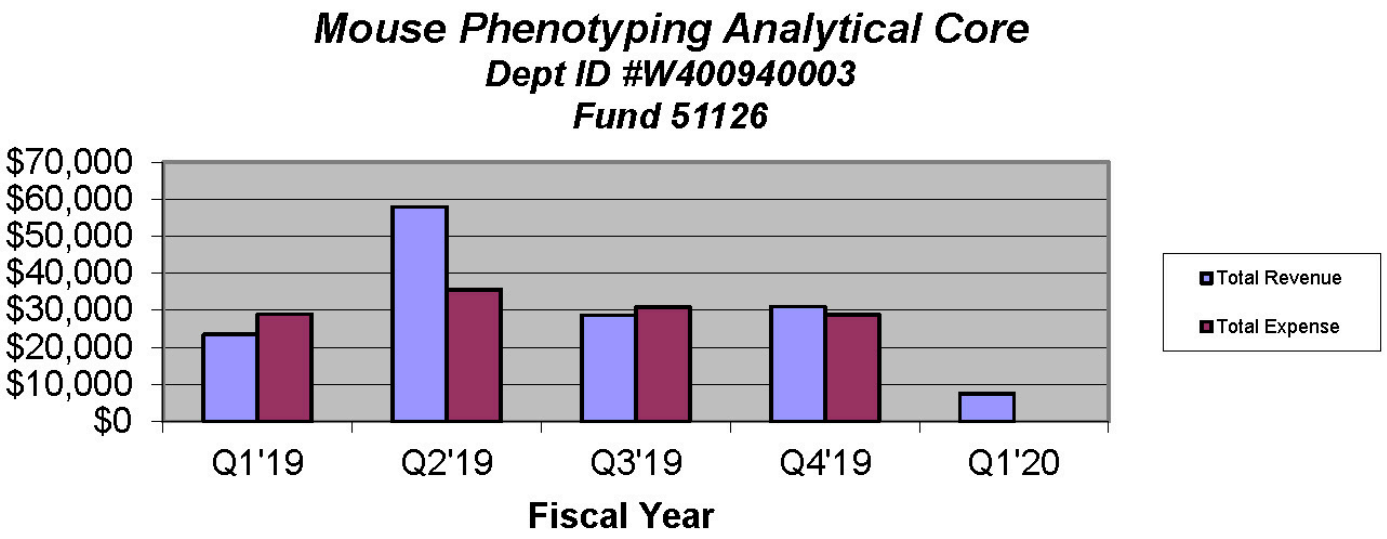
Analytical Core

Core Director
Xiaodi Hu, M.S.



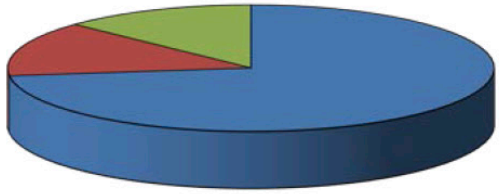
Research Staff
Duy Tran, B.S.

Analytical Core



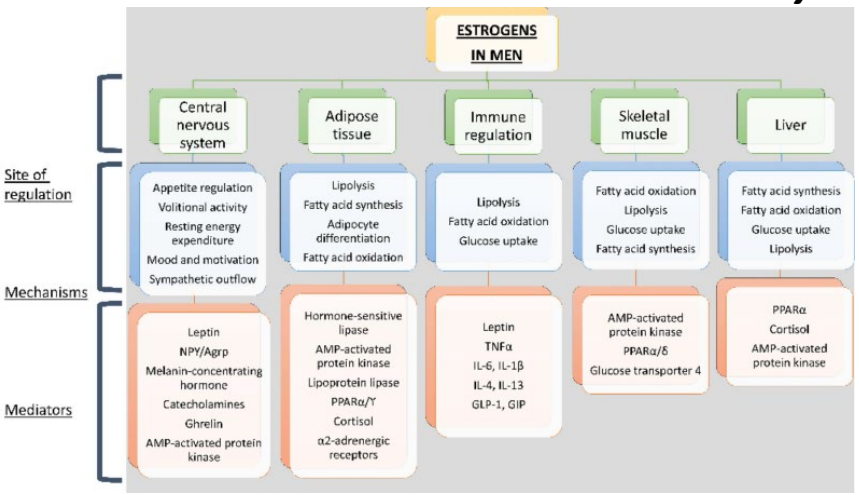
FY20 CUSTOMER REVENUE

Diabetes	73.0%
Harvard University	14.1%
University of Tennessee	12.9%



Analytical Core

Sex Steroid Imbalances in obesity



Rubinow, KB. 2017. *Adv Exp Med Biol.* 1043:285.

How can the Analytical Core help?

Draw upon our extensive experience and knowledge to work with dependable suppliers to identify and review available ELISA assays

Process samples and return data in a timely manner

Provided ID	Matrix	Estradiol (pg/ml)	Progesterone (ng/ml)	Testosterone (ng/ml)
1	plasma	3.3	4.4	0.38
2	plasma	2.6	15.1	0.73
3	plasma	2.3	12.2	0.96
4	plasma	2.8	6.3	0.26
5	plasma	2.4	8.6	0.66
6	plasma	0.7	4.2	0.19
7	plasma	1.0	5.2	0.11
8	plasma	3.3	4.1	0.19
9	plasma	0.9	3.3	0.15
10	plasma	0.3	16.2	0.43
11	plasma	2.0	5.6	0.26
12	plasma	1.2	3.3	0.15
13	plasma	2.0	2.2	0.12
14	plasma	3.6	4.6	8.0
15	plasma	3.4	16.9	0.51
16	plasma	6.5	8.5	0.33
17	plasma	1.4	6.0	3.60
18	plasma	3.0	15.9	0.84
19	plasma	0.1	16.5	1.32
20	plasma	1.2	10.5	0.88

Analytical Core Working with Metabolism Core

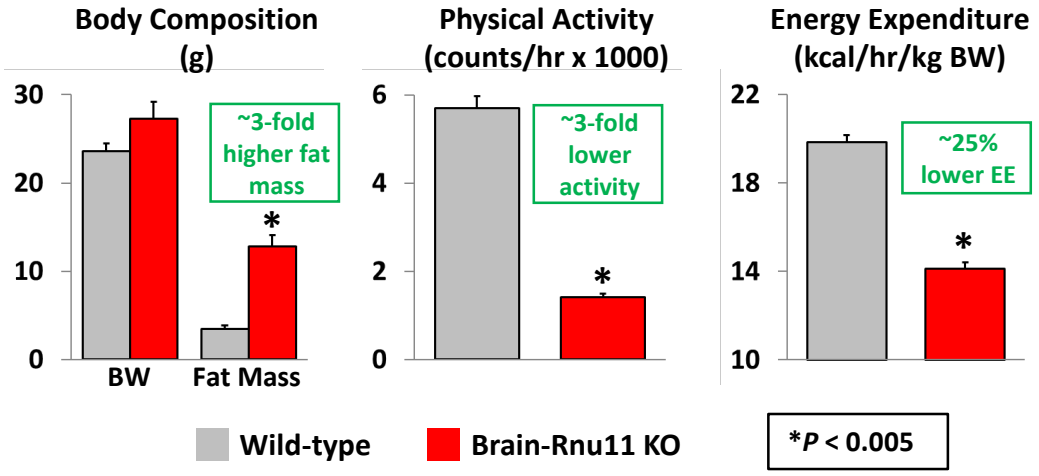
Obesity – not just a lifestyle choice….

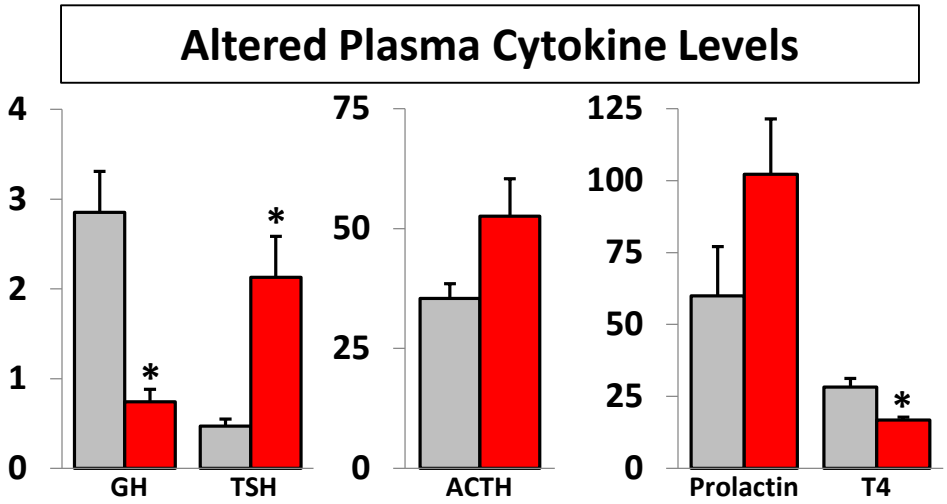
Tanzeel Ur Rehman/ Cover Asia Press

Prader-Willi Syndrome - most common known genetic cause of morbid obesity in children. Characterized by:

- infantile hypotonia
- hypogonadism and hypogenitalism
- growth hormone deficiencies
- ***hyperphagia leading to early childhood obesity***.

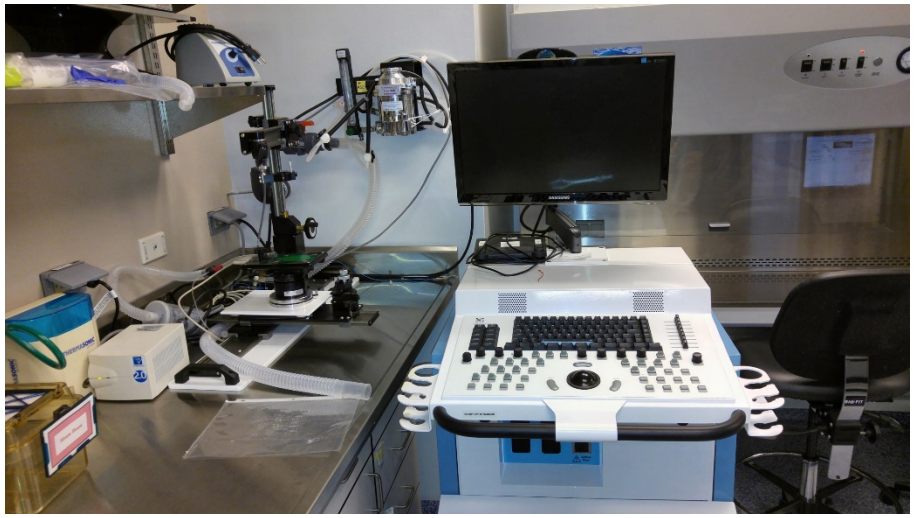
UMass MMPC assisted a junior faculty at UConn in characterizing a new brain-specific Rnu11 KO mice using Analytical & Metabolism Core





Cardiovascular Core

Core Director
Tim Fitzgibbons, M.D., Ph.D.

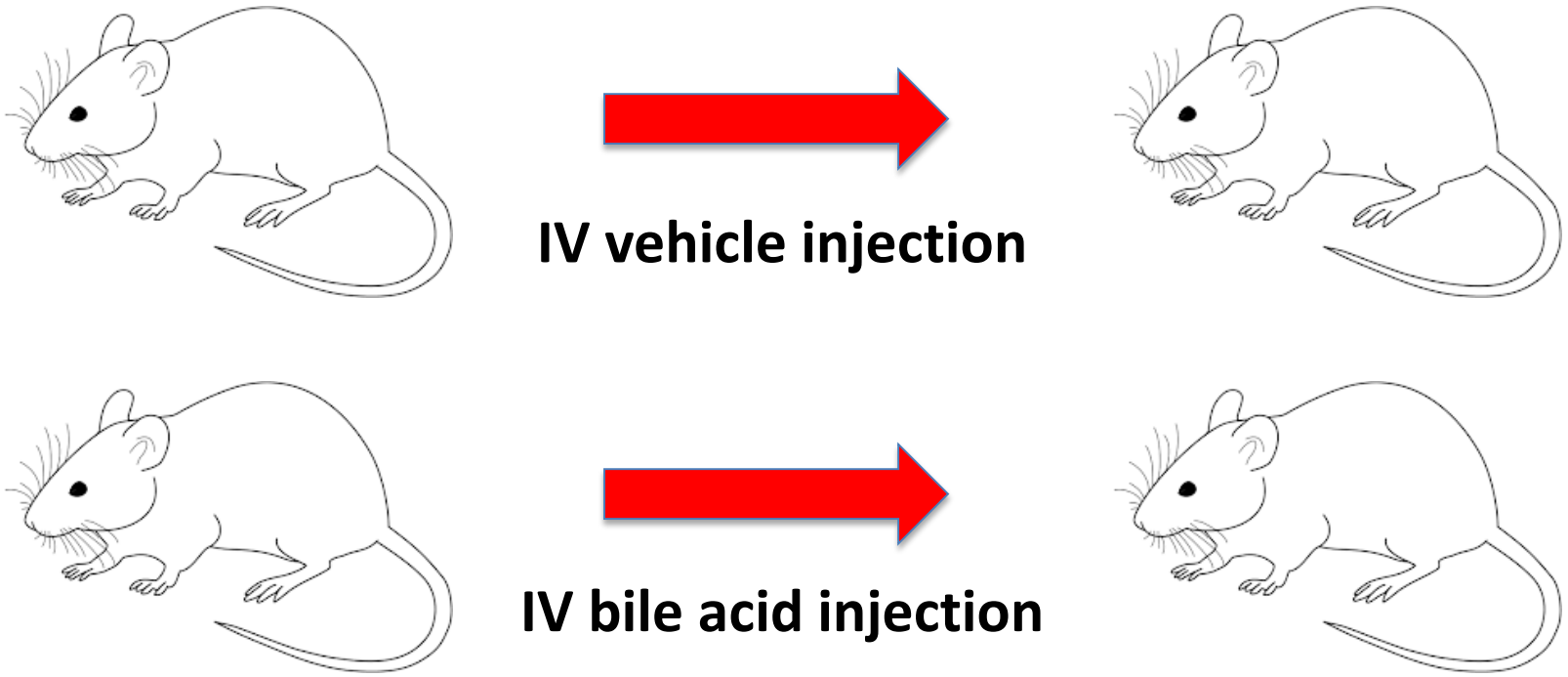


In Utero Measurement of Fetal Heart Rate

- Congenital heart disease and maternal metabolic disorders are common causes of fetal morbidity
- Cholestasis of pregnancy - Maternal cholestasis causes an increase in plasma bile acids that is associated with decreased fetal HR and poor outcomes.

Do Bile Acids Affect Fetal Heart Rate?

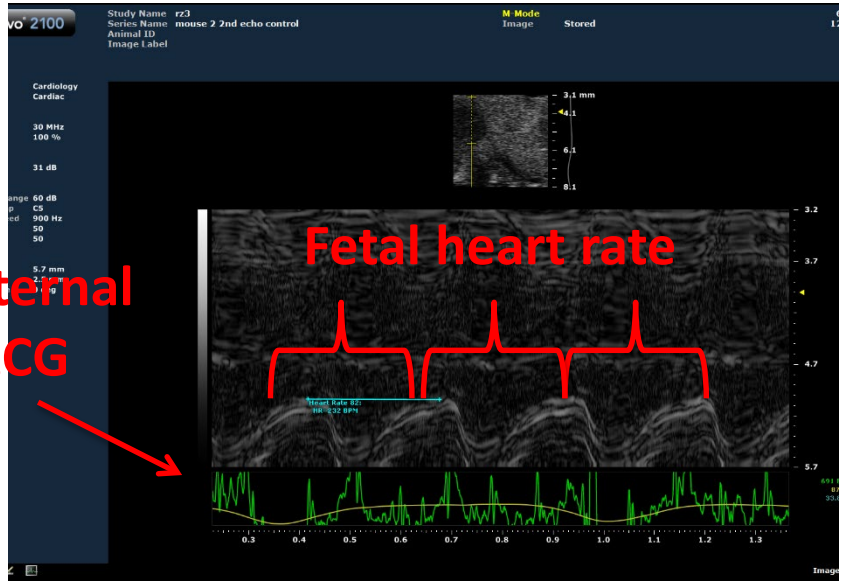
Embryonic Day E18.5 in Pregnant C57BL/6J Mice



✓ Fetal HR using ultrasound & simultaneous maternal HR using ECG

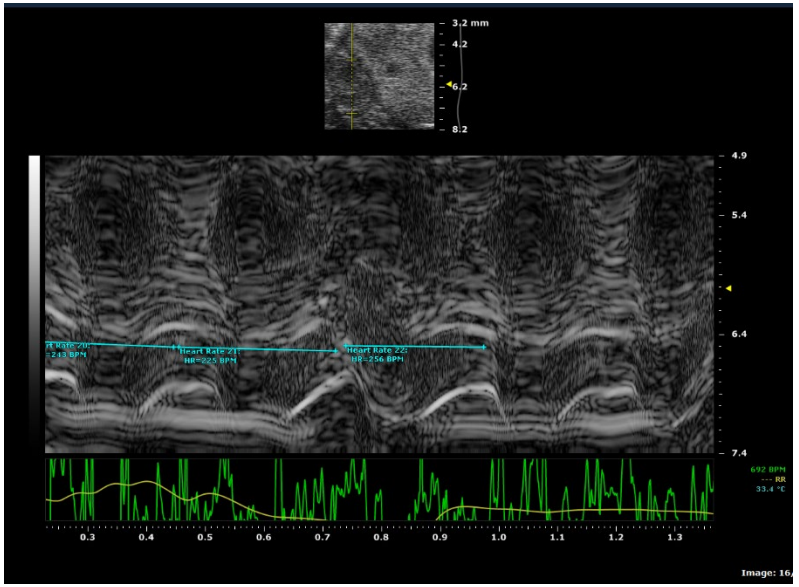
Controls (Vehicle-Treated Mice)

Baseline



Maternal HR 707 bpm
Fetal HR 233 bpm

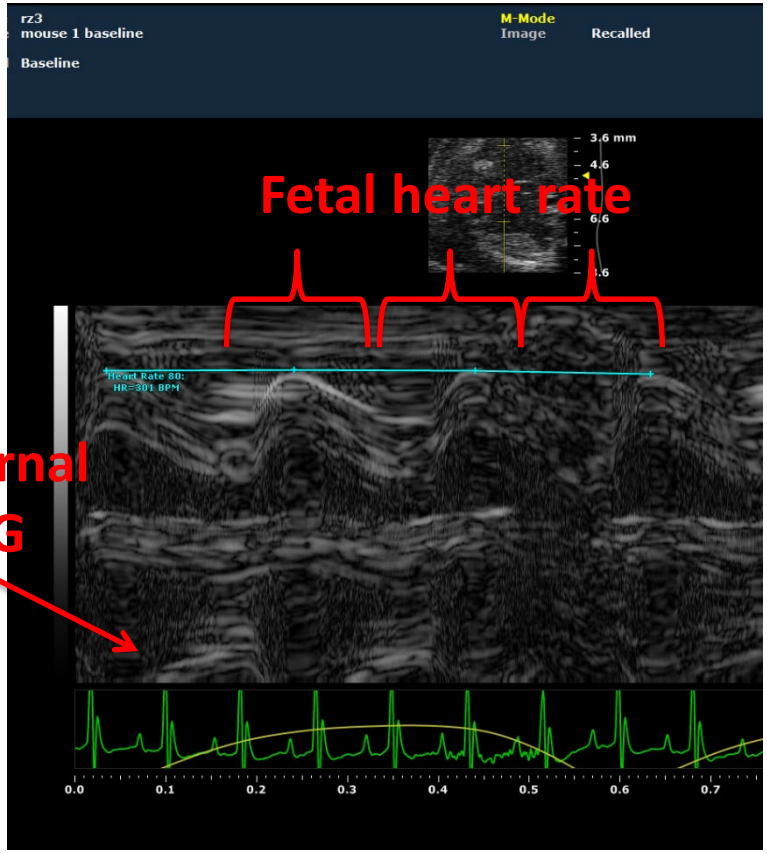
30-min Post-injection



Maternal HR 694 bpm
Fetal HR 233 bpm

Bile Acids-Treated Mice

Baseline

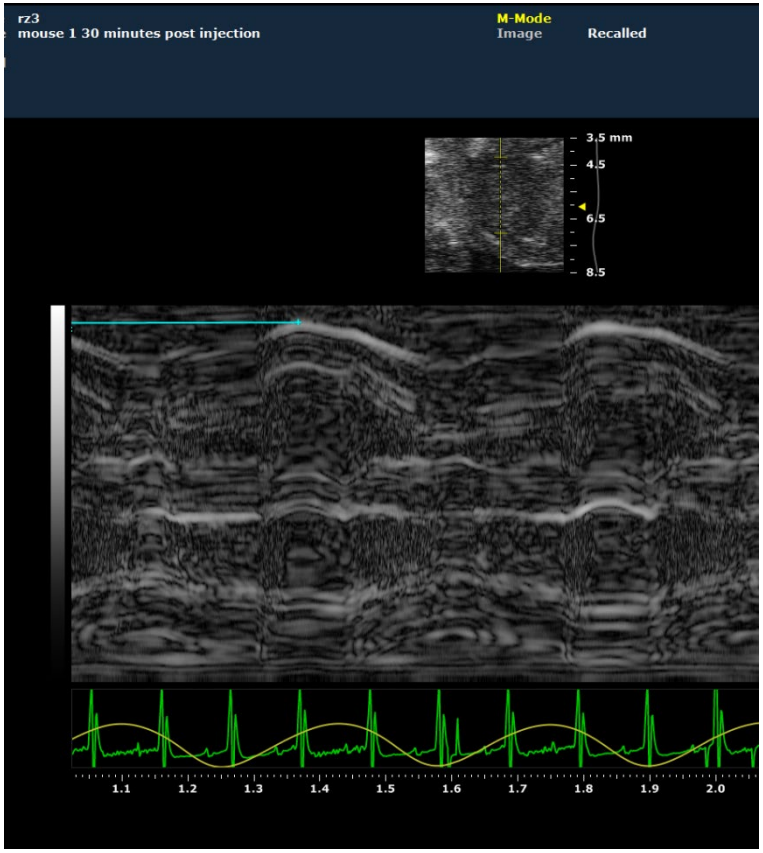


Maternal ECG

Maternal HR 707 bpm

Fetal HR 232 bpm

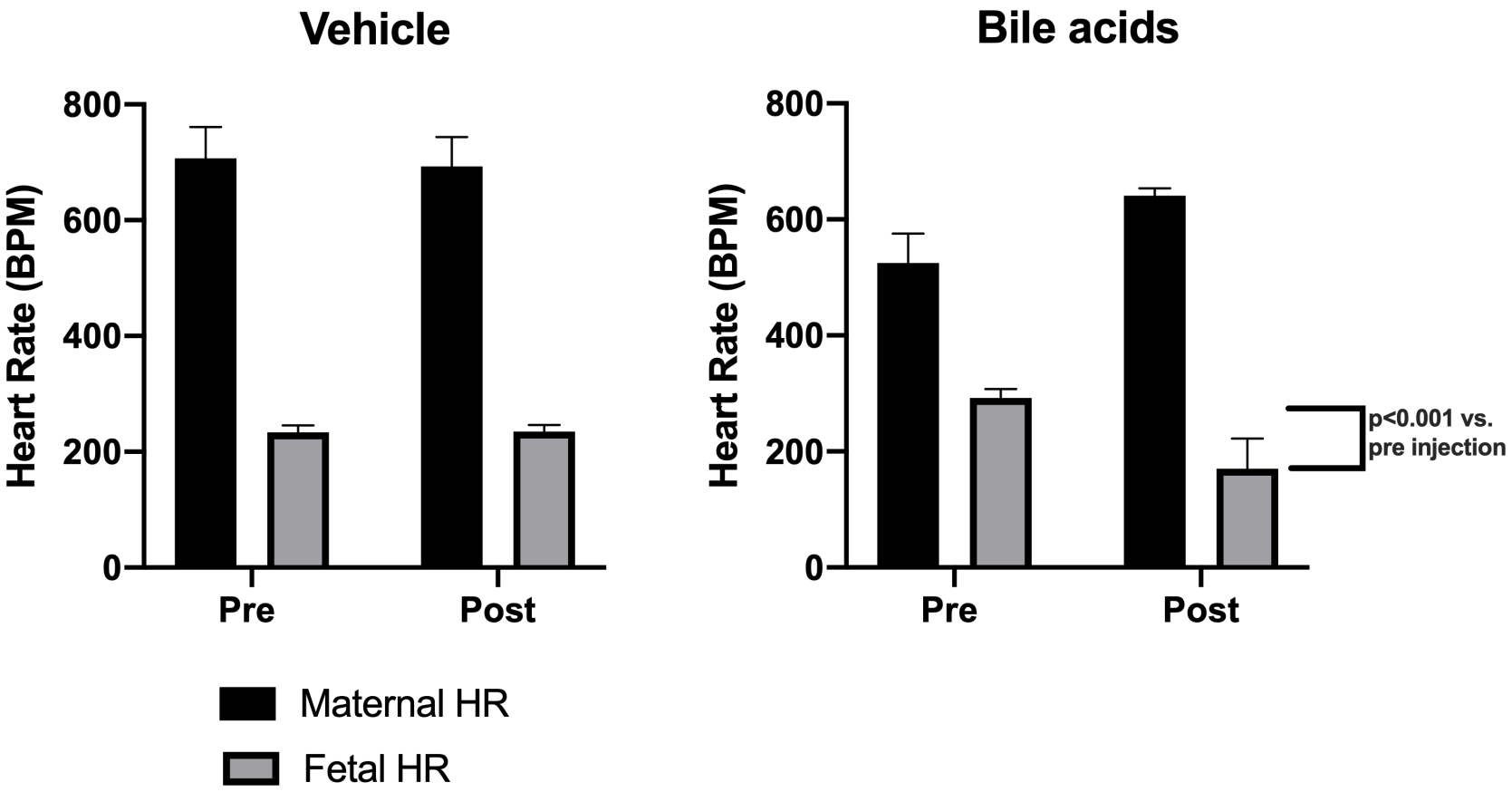
30-min Post-injection



Maternal HR 627 bpm

Fetal HR 153 bpm

Bile Acids Reduce Fetal Heart Rate But Not Maternal Heart Rate



R Zhuge unpublished

UMass MMPC from 2011 ~ 2019

UMass MMPC Functions	Project Year 1	Project Year 2	Project Year 3	Project Year 4	Project Year 6	Project Year 7	Project Year 8
Users of Metabolism Core (# local / # outside)	7 (4 / 3)	11 (3 / 8)	16 (6 / 10)	29 (9 / 20)	47 (10 / 37)	33 (8 / 25)	36 (15 / 21)
Services of Metabolism Core (# local / # outside)	72 (60 / 12)	57 (13 / 44)	63 (23 / 40)	139 (39 / 100)	233 (40 / 192)	317 (33 / 284)	312 (102 / 210)
Users of Analytical & Functional Core (# local / # outside)	5 (5 / 0)	10 (5 / 5)	12 (5 / 7)	20 (4 / 16)	30 (18 / 12)	34 (7 / 27)	27 (11 / 16)
Services of Analytical & Functional Core (# local / # outside)	16 (16 / 0)	27 (15 / 12)	27 (12 / 15)	152 (46 / 106)	205 (125 / 80)	189 (36 / 153)	147 (83 / 64)
Publications citing MMPC: With center co-authorship	5	11	8	6	13	12	14
Total Publications citing MMPC: No center co-authorship	0	0	0	2	2	3	5
Program Income	$160,221	$148,476	$168,136	$656,313	$807,025	$438,812	$415,188

Providing Support for NIH Grant Applications

Investigator	Institution	Department
Ann Marie Schmidt, MD	New York University	Endocrinology & Diabetes
Basak Icli, PhD	Harvard Medical School	Cardiovascular Biology
David Hui, PhD	University of Cincinnati	Pathology
John Kopchick, PhD	Ohio University	Biomedical Sciences
John Ussher, PhD	University of Alberta	Pharmacology
Ming Xu, PhD	University of Connecticut	Genetics
Noemi Polgar, PhD	University of Hawaii	Biochemistry & Physiology
Ricardo Gazinelli, PhD	UMass Medical School	Infectious Disease
Richard Lee, MD	Harvard Medical School	Cardiovascular Medicine
Ta Yuan Chang, PhD	Dartmouth College	Biochemistry & Cell Biology
Ahmed Lawan, PhD	Yale University	Pharmacology
Andrea Zsombok, PhD	Tulane University	Physiology & Medicine
Andrew Wolfe, PhD	Johns Hopkins University	Pediatrics & Physiology
Beiyan Zhou, PhD	University of Connecticut	Immunology
Emily Sims, MD	Indiana University	Pediatric Endocrinology
Fawaz Haj, PhD	UC Davis	Nutrition
Henry Ruiz, PhD	New York University	Endocrinology
Jianguo Wu, PhD	University of Connecticut	Physiology & Neurobiology
Michael Stitzel, PhD	JAX-Connecticut	Genomic Medicine
Vishwajeet Puri, PhD	Ohio University	Biomedical Sciences

UMass MMPC Training

Investigator	Institution	Core
Weikang Cai	Harvard Medical School	Metabolism
Francois Moreau	Harvard Medical School	Metabolism
William King	LSU-Pennington Biomedical Center	Metabolism
Kathryn Pergola	LSU-Pennington Biomedical Center	Metabolism
Il-Young Kim	Gachon University, South Korea	Metabolism
Jiwoon Jang	Gachon University, South Korea	Metabolism
Sanghee Park	Gachon University, South Korea	Metabolism
Yeongnim Kim	Gachon University, South Korea	Metabolism
Stephen Vatner	Rutgers University	Metabolism
Ruexin Wang	Rutgers University	Metabolism
Kalpana Acharya	Wellesley College	Metabolism
Seung Ham	Navitor Pharmaceuticals, Cambridge	Metabolism
Tony Kang	Navitor Pharmaceuticals, Cambridge	Metabolism

UMass MMPC Training

University of Massachusetts Medical School

MMPC National Mouse Metabolic Phenotyping Center

Informed Consent Form for Training at the UMass MMPC

Health Risks and Animal Research

Working with laboratory animals carries some health risks, especially for individuals with a history of allergies. Working with nonhuman primates carries a risk of exposure to tuberculosis. It is recommended that all participants be up to date with their tetanus vaccination and those working with nonhuman primates have a test for TB within one year. We encourage everyone to seek the advice of a physician to determine if they are healthy enough to work with animals.

Dr. Jason K. Kim

Training Program Director

The Training Program Director has informed me of the potential risks of working with animals including but not limited to serious and potentially fatal allergic reactions, animal inflicted bite and scratch wounds, possible exposure to injectable anesthetics or anesthetic gases, and other conditions listed below by the program director:

I understand the risks and the recommendations for participating investigator. I also understand that no photography or video recording is allowed in the facility. I will comply to these policies as well as standard laboratory policies during my participation in the training program.

Affiliated Institution Pennington Biomedical Research Center

Principal Investigator John P. Kirwan, PhD

Signature _____ **Date** 9/25/2019

Participating Trainee Kathryn Pergola

Signature _____ **Date** 9/25/2019

This form must be completed by the Principal Investigator of the Affiliated Institution and the Participating Trainee as part of the IACUC protocol review for all trainees who do not work at the University of Massachusetts or its hospitals and signed by the trainee at least one week prior to the start of direct work with animals.

UMass MMPC Seminar Series

National MMPC Seminar Series

Franck Mauvais-Jarvis, MD, PhD

Director, Tulane Diabetes Research Program
Professor of Medicine, Section of Endocrinology
Price-Goldsmith Professor of Nutrition Research
Tulane University Health Sciences Center

"Bi-directional Modulation of Insulin Secretion by Testosterone in Males and Females"

Friday
November 9, 2018
12:00 pm

Hosted by: Dr. Jason Kim

Albert Sherman Center
9th Floor, AS9-2072
Conference Room

National MMPC Seminar Series

Chang-Hwa Song, Ph.D.

Deputy Dean for Research Affair
Professor of Microbiology and Department Head of Medical Science, College of Medicine
Deputy Head, BK21-CNU Biomedical Convergence Program
Chungnam National University, South Korea

"Endoplasmic reticulum stress regulates the innate immunity against mycobacteria"

Tuesday
June 12, 2018
12:00 pm

Hosted by: Dr. Jason Kim

Albert Sherman Center
6th Floor, AS6-2072
Conference Room

MMPC
National Mouse Metabolic Phenotyping Center

NIH
National Institute of Diabetes and Digestive and Kidney Diseases

Working to Cure Diabetes