BIOGRAPHICAL SKETCH

NAME: Shana McCormack

eRA COMMONS USER NAME: smccormack

POSITION TITLE: Assistant Professor of Pediatrics

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Harvard College, Cambridge MA	A.B.	1999	Biochemical Sciences
Harvard Medical School, Boston MA	M.D.	2005	Medicine
Massachusetts General Hospital, Boston MA	Resident	2005-2008	General Pediatrics
Massachusetts General Hospital, Boston MA	Chief Resident	2008-2009	General Pediatrics
Boston Children's Hospital, Boston MA	Clinical Fellow	2009-2012	Endocrinology
University of Pennsylvania	M.T.R.	2015	Translational Research

A. Personal Statement

I am a physician-scientist with a translational research program on the neuroendocrine systems that regulate energy balance in humans. I have two main areas of focus. First, I study individuals with metabolic disorders with characterized by risk for diabetes mellitus, including primary mitochondrial diseases, Friedreich's ataxia (FA), and lipodystrophy. Second, I study CNS disorders associated with excess weight gain, including brain-tumor related hypothalamic obesity syndrome and pseudotumor cerebri syndrome/idiopathic intracranial hypertension (IIH). Insights from these rare conditions can then be leveraged to better understand and treat common disorders of energy balance like type 2 diabetes mellitus and obesity.

As a fellow in pediatric endocrinology, with the support of a Kirschstein National Research Service Award, I investigated the role of disordered skeletal muscle bioenergetics in the pathogenesis of obesity-related insulin resistance in children, and its modification by exercise. As a junior investigator with the support of the Children's Hospital of Philadelphia's Division of Endocrinology and Diabetes K12 award, in collaboration with the University of Pennsylvania Center for Magnetic and Resonance and Optical Imaging, I adapted novel, non-invasive metabolic imaging techniques to measure skeletal muscle oxidative phosphorylation (OXPHOS) in human subjects with primary and secondary forms of mitochondrial impairment. Currently, with the support of an NIH/NIDDK K23 career development award, I am leveraging these imaging techniques to study the relationship between disordered glucose and lipid homeostasis and abnormal skeletal muscle OXPHOS capacity in individuals with primary mitochondrial disease as well as diet-induced obesity. These studies have formed the basis for ongoing interventional studies in mitochondrial disease and FA (low-glycemic index nutrition) and hypothalamic obesity syndrome (intranasal oxytocin). The latter trial is supported by a Doris Duke Clinical Scientist Development Award.

The support of the R03 award will catalyze the transition to independent investigation focused on mitochondrial metabolism by leveraging ongoing detailed phenotyping studies supported by the K23 award.

B. Positions and Honors

Positions and Employment:

2005-2008 Resident in Pediatrics, Massachusetts General Hospital for Children, Boston, MA
2008-2009 Chief Resident in Pediatrics, Massachusetts General Hospital for Children, Boston, MA
2009-2012 Clinical Fellow in Pediatric Endocrinology, Boston Children's Hospital, Boston, MA
2010-2012 Research Fellow in Pediatric Endocrinology, Massachusetts General Hospital, Boston, MA

2012-2014 Instructor in Pediatrics, Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
2014- Assistant Professor of Pediatrics, Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Honors:

1994 Research Science Institute participant, Massachusetts Institute of Technology, Cambridge MA
1996 Howard Hughes Medical Institute Undergraduate Research Fellowship, Case Western Reserve University School of Medicine, Cleveland OH
1996 – 1999 John Harvard, Harvard College, Elizabeth Cary Agassiz Scholarships, Harvard College, Cambridge MA
1999 Phi Beta Kappa Society, Harvard College, Cambridge MA
2002 – 2003 HHMI Medical Student Research Fellowship, Harvard Medical School, Boston MA
2002 – 2003 Health Sciences and Technology Society Albisetti Scholarship, Harvard Medical School, Boston MA and Massachusetts Institute of Technology, Cambridge MA
2005 MD Thesis, *Magna Cum Laude*, Harvard Medical School, Boston MA
2006 Family-Centered Care Award, Massachusetts General Hospital for Children, Boston MA
2008 Resident Teaching Award, Harvard Medical School, Boston MA
2010 Fellow Travel Award, Lawson Wilkins Pediatric Endocrine Society, Vancouver BC
2011 Outstanding Abstract and Travel Award Endocrine Society, Boston MA
2012 Travel Award for Young Investigators Pediatric Academic Society, Boston MA
2013 – 2015 University of Pennsylvania School of Medicine institute for Translational Medicine and Therapeutics (ITMAT) fellowship to support Master's in Translational Research
2016 American Society for Clinical Investigation Young Physician Scientist Award

Other Experiences and Professional Memberships:

2010- Pediatric Endocrine Society, Member
2010- Endocrine Society, Member
2012- Philadelphia Endocrine Society, Member
2013- Mitochondrial Medicine Society, Member
2013- United Mitochondrial Disease Foundation, Member
2014- NIH/NINDS Mitochondrial Disease Common Data Element Working Group on Endocrinology, Diabetes, GI, Nutrition, Chair
2015- Society for Inherited Metabolic Disorders, Member
2016- Mitochondrial Medicine Society, Preventive Care Screening Guidelines, Endocrinology Committee Chair

C. Contribution to Science

1. My research has focused on elucidating **the role of disordered mitochondrial bioenergetics in the pathogenesis of diabetes mellitus in humans**. Using non-invasive magnetic resonance spectroscopy techniques, we have shown evidence of impaired skeletal muscle oxidative phosphorylation in obese children and adolescents that may be ameliorable with exercise training. Disordered branched-chain amino acid metabolism and accumulation of ectopic lipid in muscle may also be manifestations of mitochondrial dysfunction in this population. In contrast, in a longitudinal study, healthy children demonstrated increased skeletal muscle oxidative phosphorylation during periods of rapid pubertal growth, which may reflect an effect of growth hormone on mitochondrial biogenesis. We have also adapted a novel creatine-based non-invasive imaging strategy to more deeply evaluate mitochondrial and phosphocreatine metabolism in humans, and validated this approach in individuals with primary mitochondrial diseases.

    a. **McCormack S**, McCarthy M, Harrington S, Farilla L, Hrovat M, Systrom D, Thomas B, Torriani M, McInnis K, Grinspoon S, Fleischman A. Effects of exercise and lifestyle modification on fitness, insulin resistance, skeletal muscle oxidative phosphorylation, and intramyocellular lipid content in obese children and adolescents. Pediatric Obesity, 2014;9(4):281-91. PMCID: PMC3808470.
    b. **McCormack S**, Shaham O, Deik A, Wang TJ, Gerszten R, Clish C, Mootha V, Grinspoon S, Fleischman A. Circulating branched-chain amino acid concentrations are associated with obesity

and future insulin resistance in children and adolescents. Pediatric Obesity, 2013;8(1):52-61. PMCID: PMC3519972.

c. Isaacs CA, Brigatti KW, Kucheruk O, Ratcliffe S, Sciascia T, **McCormack SE**, Willi SM, Lynch DR. Effects of genetic severity on glucose homeostasis in Friedereich Ataxia. Muscle Nerve, 2016 Apr 7. doi: 10.1002/mus.25136. PMCID: pending.

d. DeBrosse C, Nanga RPR, Wilson N, D'Aquilla K, Elliott M, Hariharan H, Yan F, Wade K, Nguyen S, Worsley D, Parris-Skeete C, McCormick E, Xiao R, Zolkipli-Cunningham Z, Fishbein L, Nathanson KL, Lynch DR, Stallings VA, Yudkoff M, Falk MJ, Reddy R, **McCormack SE**. Muscle oxidative phosphorylation quantitation using creatine chemical exchange saturation transfer (CrCEST) MRI in mitochondrial disorders. JCI Insight, accepted. PMCID: pending.

2. To delve more deeply into the mechanisms underlying the detailed observations in humans described above, I have studied the **effects of modulating mitochondrial and intermediary metabolism on glucose and lipid homeostasis in model systems**. We have explored the complex interactions between nutrient availability, intermediary metabolism, and the cellular response to metabolic stress in both *C. elegans* and tissue culture model systems. We have shown that there are characteristic, reproducible, tissue-specific changes in gene expression and intermediary metabolic flux that occur in response to specific genetic defects in the mitochondrial respiratory chain, and that these may be a viable target for therapeutic intervention.

    a. Zhang Z, Tsukikawa M, Peng M, Polyak E, Nakamaru-Ogiso E, Ostrovsky J, **McCormack S**, Place E, Clarke C, Reinter G, McCormick E, Rappaport E, Haas R, Baur J, Falk MJ. Respiratory chain disease causes tissue-specific dysregulation of the global transcriptome and nutrient-sensing signaling network. PLoS One, 2013, 24;8(7):e69282. doi: 10.1371/journal.pone.0069282. PMCID: PMC3722174.

    b. Schrier S, Rao M, **McCormack S**, Ostrovsky J, Clarke C, Preston J, Bennett MJ, Yudkoff M, Xiao, R, Falk MJ. In vivo metabolic flux profiling in *C. elegans* discriminates sites of mitochondrial dysfunction. Molecular Genetics and Metabolism, 2014, 111(3):331-41. PMCID: PMC3947636.

    c. **McCormack S**, Polyak E, Ostrovsky J, Dingley SD, Rao M, Kwon YJ, Xiao R, Zhang Z, Nakamaru-Osigo E, Falk MJ. Pharmacologic targeting of sirtuin and PPAR signaling improves longevity and mitochondrial physiology in respiratory chain complex I mutant *Caenorhabditis elegans*. Mitochondrion 2015, 22:45-59. PMCID: PMC4447550.

3. To identify the etiology of disordered bioenergetics in pediatric endocrine disease, I have studied the role of genetic variation. I have focused on identifying **genetic variation that underlies differences in body composition, energy expenditure, and the development of obesity and diabetes mellitus in children**. Innovative strategies to characterize growth and development in healthy children are also critical, and I have also created and validated new methodologies.

    a. **McCormack S**, Grant SFA. Allelic expression imbalance: tipping the scales to elucidate the function of type 2 diabetes associated loci. Diabetes, 2015, 64(4):1102-4. PMCID: 4876688.

    b. Roy SM, Chesi A, Mentch F, Xiao R, Chiavacci R, Mitchell JA, Kelly A, Hakonarson H, Grant SF, Zemel BS, **McCormack SE**. Body mass index (BMI) trajectories in infancy differ by population ancestry and may presage disparities in early childhood obesity. Journal of Clinical Endocrinology and Metabolism, 2015, Apr;100(4):1551-60. PMCID: PMC4399305.

    c. Roy S, Spivack J, Faith M, Chesi A, Mitchell J, Kelly A, Grant SFA, **McCormack SE**, Zemel B: Infant BMI or Weight-for-Length and Obesity Risk in Early Childhood. Pediatrics, 2016, 137(5): pii: e20153492. PMCID: PMC4845873.

    d. **McCormack SE**, Chesi A, Mitchell JA, Roy SM, Cousminer DL, Kalkwarf HJ, Lappe JM, Gilsanz V, Oberfield SE, Shepherd JA, Mahboubi S, Winer KK, Kelly A, Grant SF, Zemel BS. J Bone Miner Res. 2016, Jul 15: doi: 10.1002. PMCID: pending.

4. I have also produced **detailed clinical descriptions of a rare pediatric disorder of energy balance, pseudotumor cerebri syndrome (PTCS)**. We posit an effect of obesity-related abnormal mitochondrial metabolism on cerebrospinal fluid dynamics in both primary (obesity-related) and secondary PTCS. I have

also co-lead the development of a multi-site study to investigate the relationship between pubertal development and excess adiposity and PTCS.

a. Sheldon CA, Kwon YJ, Liu GT, **McCormack SE**. An Integrated Mechanism of Pediatric Pseudotumor Cerebri Syndrome: Evidence of Bioenergetic and Hormonal Regulation of Cerebrospinal Fluid Dynamics. Pediatric Research, 2015, 77(2): 282-9. PMCID: PMC4641240.
b. Paley GL, Sheldon CA, Burrows EK, Chilutti MR, Liu GT, **McCormack SE**: Overweight and obesity in pediatric secondary pseudotumor cerebri syndrome. Am J Ophthal, 2015, 159(2): 344-52. PMCID: PMC4643369.
c. Kwon YJ, Allen J, Liu GT, **McCormack SE**: Presumed pseudotumor cerebri syndrome after withdrawal of inhaled glucocorticoids. Pediatrics, 2016, 137(6): pii: e20152091. PMCID: PMC4894252.
d. Sheldon CA, Paley GL, Xiao R, Kesler A, Eyal O, Ko MW, Boisvert CJ, Avery RA, Salpietro V, Phillips PH, Heidary G, **McCormack SE***, Liu GT* (*denotes equal contribution). Pediatric idiopathic intracranial hypertension: age, sex and anthropometrics at diagnosis in a large, retrospective, multi-site cohort. Ophthalmology, 2016, *in press*. PMCID: pending.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/shana.mccormack.1/bibliography/42443072/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

Doris Duke CSDA McCormack (PI) 7/1/2016 – 6/30/2019
Intranasal oxytocin to reduce excess weight gain in children and adolescents with brain tumors and hypothalamic obesity syndrome.
This study is a randomized, double-blinded, placebo-controlled cross-over trial of intranasal oxytocin for pediatric hypothalamic obesity related to craniopharyngioma.

5K23DK102659-02 McCormack (PI) 7/1/2015 – 4/30/2018
Translational investigation of abnormal fat metabolism in mitochondrial disease.
The purpose of this study is to investigate the role of reductive glutamine metabolism in lipid and glucose homeostasis in primary mitochondrial disease, both *in vitro* and *in vivo*.

Pilot Project Grant Lynch (PI) 7/1/2015 – 6/30/2017
Penn Institute for Translational Medicine and Therapeutics Maturational Human Biology Grant
Temporal Evolution of Friedrich's Ataxia (FA). This grant provides additional support to perform OXPHOS assessments along with other biomarker measurements in individuals with FA.
Role: Co-I (no additional % effort)

Junior Investigator McCormack (PI) 7/1/2014 – 6/30/2017
Pilot and Feasibility Program, Children's Hospital of Philadelphia, Clinical and Translational Research Center
Glycemic index in mitochondrial disease. The purpose of this study is to identify the effect of low- versus high-glycemic index test meals on biochemical parameters in subjects with mitochondrial disease.
Role: PI (no additional % effort)

4R01 HD056465-09 Grant (PI) 7/1/2013 – 4/30/2018
This is a genome-wide association study for childhood obesity. This study provides critical infrastructure for my K23-suppported training in genetics.
Role: Other Significant Contributor (no % effort, subsumed by K23 training)

Completed Research Support

T32DK007699-29 Majzoub (PI) 7/1/2007-6/30/2011
Training in Pediatric Endocrinology at Children's Hospital Boston
Role: Trainee (7/1/2010 – 6/30/2011)

Research Fellows Award McCormack (PI) 7/1/12011-12/14/2011
Research Fellowship Award, Pediatric Endocrine Society
The goal of this project was to investigate the effects of exercise training on insulin resistance and mitochondrial function in overweight children and adolescents.
Role: PI

EFF Fellows Grant McCormack (PI) 6/1/2011-5/31/2012
Development Research Grant in Diabetes, Obesity, and Fat Cell Biology; Endocrine Fellows Foundation
The goal of this project was to measure cardiovascular fitness in overweight children and adolescents before and after an intensive in-home exercise training intervention.
Role: PI

F32 DK093206-01 McCormack (PI) 12/15/2011-6/30/2012
Ruth L. Kirschstein National Research Service Award
The goal of this project was to investigate the effects of exercise training on insulin resistance and mitochondrial function in overweight children and adolescents.
Role: PI

Pilot Project Grant McCormack (PI) 9/26/2013 – 1/1/2016
Children's Hospital of Philadelphia (CHOP) Metabolism, Nutrition and Development Research Affinity Group
Genetic variation associated with obesity-related premature adrenarche: clinical, biochemical, and transcriptional correlates. This grant provides support to perform additional laboratory assays (DHEA-S).
Role: PI (no additional % effort)

Pilot and Feasibility Grant Lazar (PI) 4/1/2014 – 3/30/2016
U Penn Diabetes Research Center
Metabolic imaging of mitochondrial function. The purpose of this study is to generate additional *in vivo* preliminary data on the novel magnetic resonance imaging technique to be used in human studies.
Role: Pilot and Feasibility Grant PI (no additional % effort)

Clinical Scholars Award McCormack (PI) 7/1/2014 – 6/30/2016
Pediatric Endocrine Society
Translational investigation of abnormal fat metabolism in mitochondrial disease. This study investigates the etiology of disordered lipid and glucose homeostasis in primary mitochondrial disease, both *in vitro* and *in vivo*.

5K12DK094723-02 Willi (PI) 9/16/2011 – 7/31/2016
Career Development Program in Pediatric Diabetes Research (K12) at CHOP
Translational investigation of abnormal fat metabolism in mitochondrial disease. This study investigates the etiology of disordered lipid and glucose homeostasis in primary mitochondrial disease, both *in vitro* and *in vivo*.
Role: Scholar (7/12/2012-6/30/2015)