

University of Washington Nutrition Obesity Research Center

Start Date: 1985

Status: Ongoing

Funding Agency: NIDDK

Website: <http://depts.washington.edu/uwcnru/>

Organization and Goals

The overall theme of the research supported by the NORC at the University of Washington continues to relate to the role of nutrition in the etiology, prevention, and management of chronic disease states. Several areas of research strength and focus have been delineated and refined during the past several years. They currently include:

- Body weight regulation and obesity
- Diabetes
- Lipids and atherosclerosis
- Cancer and other areas of interest

There currently are 80 Affiliate Investigators that constitute the Research Base of the NORC. The Affiliate Investigators receive their research funding from a variety of federal and non-federal sources, predominantly the NIH. Because of the number and variety of investigators, nutrition research at the University of Washington uses multiple means to address problems relating to these chronic disease states, including state-of-the-art basic molecular, genetic, and cell biological techniques; clinical investigation; animal experimentation; and epidemiological and intervention trials. These various approaches are used in a complementary fashion to provide a broad-based and in depth approach to the role of nutrition in chronic diseases. The NORC has facilitated interaction and collaboration among investigators using these different experimental disciplines to address questions of mutual interest.

Core Laboratories

Administrative and Enrichment Core: Alan Chait, M.D., NORC Director; Michael W. Schwartz, M.D., NORC Associate Director; Edward W. Lipkin, M.D., Ph.D., Associate Director, Enrichment Component

Animal Studies Core: Michael W. Schwartz, M.D., Director; Renee LeBoeuf, Ph.D., Co-Director; Greg Morton, Ph.D., Associate Director

Analytic Core: Mark Wener, M.D., Director; Andrew Hoofnagle, M.D., Ph.D., Associate Director

Human Studies Core: Johanna Lampe, Ph.D., R.D., Associate Director; D. Scott Weigle, M.D., Associate Director

External Advisors: The External Advisors who have contributed include:

- Wilfred Y. Fujimoto, M.D., Professor Emeritus of Medicine, University of Washington
- Daniel Porte, Jr., M.D., University of California, San Diego
- Jerrold Olefsky, M.D., University of California, San Diego
- Ira Goldberg, M.D., Columbia University
- Stephen C. Woods, Ph.D., University of Cincinnati

Pilot and Feasibility Studies, 2009–2010

Savitha Subramanian, M.D., Assistant Professor, Department of Medicine

Adipose Tissue Inflammation in Obesity-Associated Insulin Resistance

Obesity is characterized by adipose tissue inflammation, which contributes to insulin resistance, type 2 diabetes, and other metabolic disorders. The main goals of this proposal are: 1. To determine the time sequence of macrophage infiltration, macrophage activation in adipose tissue, and systemic inflammation during the development of diet-induced obesity and insulin resistance, and 2. To establish the role of T-lymphocytes in macrophage accumulation and activation that occurs in obesity. To study these aims, Dr. Subramanian will perform a time course study by placing C57BL/6J mice on a high-fat, high-carbohydrate diet for varying lengths of time and studying macrophage accumulation and activation and the role of T-cells in adipose tissue in diet-induced obesity.

Tomas Vaisar, Ph.D., Research Assistant Professor, Department of Medicine

Effects of Omega-3 Polyunsaturated Fatty Acid Diet Supplementation on HDL and its Biological Activity

Multiple mechanisms likely contribute to the cardioprotective effects of omega-3 polyunsaturated fatty acids (PUFA), including reduction of arrhythmias, effects on hemostatic systems, improvement in endothelial function, lowering of post-prandial triglyceride levels, and, importantly, inhibitory effects on atherosclerosis and inflammation. The main hypothesis of this project is that omega-3 PUFA, through their lipid metabolism altering and/or antiinflammatory effects, may modulate protein composition of high-density lipoprotein (HDL), thereby modulating biological processes. To address these questions Dr. Vaisar is quantifying changes in the HDL proteome in a clinical study of omega-3 PUFA supplementation, and testing HDL biological activity in an endothelial cell model of inflammation.

Carole L. Wilson, Ph.D., Research Assistant Professor, Department of Pathology

Macrophage ADAM17-mediated Proteolysis in Diet-induced Obesity

One of the hallmarks of obesity is a chronic low-grade inflammation in visceral adipose tissue. Recruitment of circulating monocytes in response to inflammatory stimuli can be rapidly controlled by proteolytic cleavage of cell-surface adhesion receptors and adipokines, a process known as ectodomain “shedding.” ADAM17, a transmembrane metalloproteinase, is the prototypical sheddase of macrophages and cleaves a number of inflammatory proteins, including tumor necrosis factor (TNF) and its receptors. To test the hypothesis that ADAM17 regulates the recruitment and inflammatory state of adipose tissue macrophages, with subsequent downstream effects on adipocyte function, a model of diet-induced obesity is being used to assess macrophage accumulation and activation in fat depots of mice with either hematopoietic or myeloid-selective deletion of ADAM17.

Funding Derived from Previous Pilot and Feasibility Studies

Andrew Hoofnagle, M.D., Ph.D., Assistant Professor, Laboratory Medicine: Increased Oxidative Stress as a Biomarker for Rapid Progression of Atherosclerosis in SLE (PI of subcontract with the University of California, San Francisco), NIH/NIAID R01 (pending), 12/01/10-11/30/15.

Gregory Morton, Ph.D., Research Assistant Professor, Medicine: Neuroendocrine Control of Glucose Metabolism, NIH/NIDDK 1R01DK089056-01A1 (pending), 04/01/11-03/31/16; Effect of Hypothalamic Leptin Action on Glucose Metabolism, American Heart Association Scientist Development Grant, 07/01/08-06/30/12; Normalization of Blood Glucose Levels in Uncontrolled Diabetes Without Insulin; Perkins-Coie for Discovery Award, 05/01/10-04/30/11.

Paul E.M. Phillips, Ph.D., Research Assistant Professor, Psychiatry & Behavioral Sciences: Spatiotemporal Dynamics of Striatal Dopamine Release in Reinforcement Learning, NIH/NIDA 1R01DA027858-01, 09/30/09-05/31/14 (awarded).

Scientific Advances/Accomplishments

Synopsis of Accomplishments, Including How the Center Has Fostered Clinical Investigations and/or Translational Research

With respect to its major mission, i.e., facilitating nutrition research, the NORC has been successful in fostering many new collaborations, which would likely not have occurred had the NORC not been in existence. Many of the junior investigators who have received NORC support through the mechanisms of the Pilot and Feasibility Program and the New Investigator Award, have been successful in using data generated as a result of these awards to compete successfully for peer-reviewed funding. The research efforts of many of its Affiliate Investigators have been aided considerably by the services offered by the Cores, which have adapted and developed to accommodate the needs of individual investigators. The Human Studies Core has been expanded in response to increasing and changing needs of Affiliate Investigators performing patient-oriented research.

Several prestigious programs and awards that interface directly with the NORC have been acquired, thereby further facilitating nutrition research, education, and clinical practice at the University of Washington. In particular, the acquisition of an award from the Murdoch Charitable Trust has enabled purchase of state-of-the-art equipment that has enabled considerable expansion of the Animal Studies Core. The receipt of a Mouse Metabolic Phenotyping Center (MMPC) from the NIDDK (Dr. LeBoeuf, Director, Dr. Schwartz, Co-Director) provides access to several new services that were not previously available to NORC Affiliate Investigators. There also has been increased institutional commitment with the recent establishment of a Center of Excellence in Diabetes and Obesity, which is housed at the new South Lake Union campus. This research building also houses the NORC Animal Studies Core.

Thus, numerous accomplishments at multiple levels have been achieved since the inception of the NORC at the University of Washington. We believe that many of these are directly or indirectly related to the presence, visibility and viability of our NORC.

Examples of Research Accomplishments Within Each Area of Research Focus

The three major areas of research focus are body weight regulation and obesity, carbohydrate metabolism and diabetes, and lipids and atherosclerosis. There is considerable overlap among these three areas of research, such that it is sometimes difficult to decide in which area the major accomplishments should be reported. (Authors whose names appear in bold print are Affiliate Investigators or Key Staff Members of the NORC.)

Body Weight Regulation and Obesity

Advances include:

- Dissociation of the cost and benefit encoding of future rewards by mesolimbic dopamine. Gan JO, Walton ME, **Phillips PEM**: Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. *Nature Neuroscience* 13:25–27, 2010. PMID: PMC2800310
- Demonstration that Hindbrain leptin receptor stimulation enhances the anorexic response to cholecystokinin. Williams DL, **Baskin DG**, **Schwartz MW**: Hindbrain leptin receptor stimulation enhances the anorexic response to cholecystokinin. *Am J Physiol Regul Integr Comp Physiol* 297:R1238–1246, 2009. Epub 2009 Sep 2. PMID: PMC2777775 [Available on 2010/11/1]
- Evidence that intestinal glucagon-like peptide-1 plays a physiological role in satiety.
- Williams DL, **Baskin DG**, **Schwartz MW**: Evidence that intestinal glucagon-like peptide-1 plays a physiological role in satiety. *Endocrinology* 150:1680–1687, 2009. PMID: PMC2659282 Observation that atypical protein kinase C activity in the hypothalamus is required for lipopolysaccharide-mediated sickness responses. Thaler JP, Choi SJ, Sajan MP, **Ogimoto K**, Nguyen HT, Matsen M, Benoit SC, **Wisse BE**, Farese RV, **Schwartz MW**: Atypical protein kinase C activity in the hypothalamus is required for lipopolysaccharide-mediated sickness responses. *Endocrinology* 150:5362–5372, 2009. Oct 9 [Epub ahead of print]. PMID: PMC2795721 [Available on 2010/12/1]
- Receptors for TNF-alpha play a protective role against obesity and alter adipose tissue macrophage status. Pamir NE, **McMillen TS**, Kaiyala K, **Schwartz MW**, **Leboeuf R**: Receptors for tumor necrosis factor-alpha play a protective role against obesity and alter adipose tissue macrophage status. *Endocrinology* 150:4124–4134, 2009. Epub 2009 May 28. PMID: PMC2736076

Carbohydrate Metabolism and Diabetes

Accomplishments in this area include:

- Evidence that hypothalamic leptin signaling regulates hepatic insulin sensitivity via a neurocircuit involving the vagus nerve. 1) German J, **Kim F**, Schwartz GJ, Havel PJ, Rhodes CJ, **Schwartz MW**, **Morton GJ**: Hypothalamic leptin signaling regulates hepatic insulin sensitivity via a neurocircuit involving the vagus nerve. *Endocrinology* 150:4502–4511, 2009. PMID: PMC2754686 [Available on 2010/10/1]. 2) German JP, **Wisse BE**, Thaler JP, Oh-I S, Sarruf DA, **Ogimoto K**, Kaiyala KJ, Fischer JD, Matsen ME, Taborsky GJ Jr,

Schwartz MW, Morton GJ: Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. *Diabetes* 59:1626–1634, 2010. PMID: PMC2889761 [Available on 2011/7/1]

- Demonstration of an association between preeclampsia and the development of diabetes. **Carr DB, Newton KM, Utzschneider KM,** Tong J, Gerchman F, **Kahn SE,** Easterling TR, Heckbert SR: Preeclampsia and risk of developing subsequent diabetes. *Hypertens Pregnancy* 28:435–447, 2009. PMC Journal – In Process
- Use of data from the cardiovascular health study to demonstrate the association between lifestyle risk factors and new-onset diabetes mellitus in older adults. **Mozaffarian D,** Kamineni A, Carnethon M, Djousse L, Mukamal KJ, **Siscovick D:** Lifestyle risk factors and new-onset diabetes mellitus in older adults: The cardiovascular health study. *Arch Intern Med* 169:798–807, 2009. PMID: PMC2828342 [Available on 2010/4/27]
- Observation that hyperinsulinemia precedes adipose tissue macrophage accumulation during the development of obesity in LDLR^{-/-} mice. 1) **Subramanian S,** Goodspeed L, Wang SA, Omer M, **O'Brien KD, Chait A:** Time course of inflammation and insulin resistance in diet-induced obesity. Abstract # P542, 2010 Scientific Sessions of Atherosclerosis, Thrombosis and Vascular Biology, April 8–10, San Francisco, California. 2) **Subramanian S,** Goodspeed L, Wang SA, Omer M, **O'Brien KD, Chait A:** Hyperinsulinemia precedes adipose tissue macrophage accumulation during the development of obesity in LDLR^{-/-} mice. American Diabetes Association, accepted for presentation, June 2010.
- Discussion of the role of HDL lipids in insulin resistance. **Hoofnagle AN, Vaisar T,** Mitra P, **Chait A:** HDL lipids and insulin resistance. *Curr Diab Rep* 10:78–86, 2010. PMC Journal – In Process

Lipids, Inflammation, and Atherosclerosis

Recent research accomplishments in the area of lipids and atherosclerosis include:

- Demonstration of the association between endogenous red blood cell membrane fatty acids and sudden cardiac arrest. **Lemaitre RN,** King IB, Sotoodehnia N, **Knopp RH,** Mozaffarian D, McKnight B, Rea TD, Rice K, Friedlander Y, Lumley TS, Raghunathan TE, Copass MK, **Siscovick DS:** Endogenous red blood cell membrane fatty acids and sudden cardiac arrest. *Metabolism* 59:1029–1034, 2010. PMID: PMC2882498 [Available on 2011/7/1]
- Observation that dietary long-chain n-3 polyunsaturated fatty acids and fish intake are associated with biomarkers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis. **He K,** Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, Steffen L, **Siscovick D,** Tsai M, Herrington D: Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol* 103:1238–1243, 2009. PMID: PMC2697819
- Demonstration that exchanging carbohydrate or protein for fat improves lipid-related cardiovascular risk profile in overweight men and women. **Kratz M, Weigle DS,** Breen PA, Meeuws KE, Burden VR, Callahan HS, Matthys CC, Purnell JQ: Exchanging carbohydrate or protein for fat improves lipid-related cardiovascular risk profile in overweight men and

women when consumed ad libitum. *J Invest Med* 58:711–719, 2010. PMC Journal – In Process.

- Comparison of the effects of moderate vs. low fat diet on insulin sensitivity and endothelial function in metabolic syndrome. **Paramsothy P**, Thirumalai A, **Dowdy A**, **Fish B**, **Knopp RH**: Effects of moderate vs. low fat diet on insulin sensitivity and endothelial function in metabolic syndrome. Presented as poster at American College of Cardiology, Atlanta, GA, March 2010.
- Description of the use of mass spectrometry-based proteomics to explore the assembly, structure, and function of lipoproteins. **Hoofnagle AN**, **Heinecke JW**: Lipoproteomics: Using mass spectrometry-based proteomics to explore the assembly, structure, and function of lipoproteins. *J Lipid Res* 50:1967–1975, 2009. PMC Journal – In Process
- Observation that mice lacking hepatic lipase are lean and protected against diet-induced obesity and hepatic steatosis. Chiu HK, Qian K, **Ogimoto K**, **Morton GJ**, **Wisse BE**, Agrawal N, McDonald TO, **Schwartz MW**, **Dichek HL**. Mice lacking hepatic lipase are lean and protected against diet-induced obesity and hepatic steatosis. *Endocrinology* 151:993–1001, 2010. PMID: PMC2840680 [Available on 2011/3/1]

Perusal of the list of authors in these publications demonstrates the considerable degree of collaboration that takes place among NORC Affiliate Investigators. Moreover, this list provides evidence for the diversity of studies that spans the spectrum from bench to bedside and includes basic research, clinical studies, and population-based investigations.

Other Areas of Research Interest

Several other general areas of research are supported by the Cores of the NORC, including nutrition and aging, women's health, nutrition and cancer, and nutrition and HIV infection.

Education Activities/Accomplishments

Enrichment Program. This program consists of NORC-sponsored research seminars, an annual NORC retreat, and coordination of University-wide, nutrition-related lectures. The objective of this program is to foster exchange of ideas and facilitate interdisciplinary individual exchange and research collaboration. A Web page is available and includes a calendar of events and links to nutrition-related sites.

Awards. Major support was acquired in the recent past through the receipt of a large and prestigious award from the Murdock Charitable Trust Fund to support state-of-the-art equipment for a burgeoning area of research by Affiliate Investigators. A grant from the Seattle Foundation provided funding for the ultrasound equipment to be used for vascular research, as part of the Human Studies Core. In addition, the NORC has benefited recently from receipt of American Recovery and Reinvestment Act funding that enabled the Animal Studies Core to acquire state-of-the-art calorimetry equipment that essentially doubles the capacity of animals that can be studied at one time. It allows NORC Affiliate Investigators to perform pair-feeding studies, allows body weight to be recorded remotely, features running wheels, and has an advanced software package to analyze data more easily.

The University of Washington also recently established the Diabetes and Obesity Center of Excellence, directed by Dr. Michael Schwartz, who is the Associate Director of this NORC and Co-Director of the Mouse Metabolic Phenotyping Center (MMPC) and the NORC Animal Studies Core. This Center has brought together approximately 20 investigators, the majority of whom are NORC Affiliate Investigators, and all of whom have a research interest in diabetes, obesity, inflammation, and lipid metabolism. The Center is housed in a brand new building at the University of Washington's South Lake Union Campus. The NORC Animal Studies Core is housed in this Center's space. This has resulted in increased usage and exposure of this Core.

Examples of Basic Science and Clinical Interactions

The University of Washington has many centers, each with unique objectives, services, and goals. While the NORC offers specialized services not provided by other centers at the University of Washington, by careful integration of complementary facilities offered by other centers, we are able to provide NORC Affiliate Investigators with cost-effective and directed access to many more cores, facilities, and tests than is possible within the confines of the NORC budget itself. Thus, NORC Affiliate Investigators have access to considerably more core services than are funded directly through the NORC grant.

During the present funding period, we have been working closely with the directors of several such centers, such that we are able to offer NORC Affiliate Investigators "one-stop-shopping" access to the core facilities of other NIH-funded centers in addition to the NORC, with no budgetary overlap. The four centers with which we interact formally are:

- Mouse Metabolic Phenotyping Center
- Center for Ecogenetics and Environmental Health
- Diabetes Endocrinology Research Center
- Clinical and Translational Science Award (CTSA, formerly General Clinical Research Center, GCRC)

Several interactions between basic science and clinical investigation have resulted from the presence of the NORC. In particular, several groups of investigators are collaborating in studying many aspects of appetite and body weight regulation and obesity, with a particular focus on the metabolic syndrome. Another central theme is the role of inflammation in obesity, diabetes, and atherosclerosis. There also is a strong interface between basic science in atherosclerosis research and clinical studies focusing on preventing atherosclerosis and on regulating plasma lipids and lipoproteins; these studies include the role of dietary components.

In addition, there is a long history of considerable and extensive interaction between the NORC and the CTSA (formerly the GCRC) at the University of Washington. The NORC Director (Dr. Chait) was a previous Clinical Associate Physician of the GCRC and has had GCRC research projects for many years. The past NORC Associate Director (Dr. Fujimoto) previously was the Associate Director of our CTSA/GCRC and Chair of its Scientific Advisory Committee. Dr. Weigle, Associate Director of the Human Studies Core, also is an Associate Director of the GCRC component of the CTSA. Many Affiliate Investigators of the NORC also have CTSA/GCRC protocols. Conversely, many CTSA/GCRC members are also Affiliate Investigators of the NORC and take active advantage of the NORC Core facilities (e.g., the

Analytic Core). The strong interfacing between our NORC and the CTSA/GCRC is documented by many joint publications.

Our CTSA/GCRC recently built a vector laboratory to be used for cell and gene therapy. The Genetics Component of the Animal Studies Core of the NORC currently is focusing on small animal models. Increased interaction between this NORC Core and the CTSA/GCRC vector laboratory will provide new opportunities for increasing the interface between basic and clinical science.

During the past few years, there has been increasing interaction with the University of Washington's Center for Ecogenetics and Environmental Health (CEEH) funded by the NIH. This interaction benefits NORC Affiliate Investigators by providing them access to the CEEH Core, and benefits CEEH Investigators by providing them access to Nutritional Science and to NORC Cores.

From its inception, the Pilot and Feasibility Program has continued to attract a large number of applications annually from individuals with diverse backgrounds from multiple departments and schools at the University of Washington. Many Pilot and Feasibility and New Investigator awardees over the years have gone on to receive peer reviewed funding and have continued careers in nutritional research, and several have taken on leadership roles at this University and elsewhere in the United States.