Opportunities for Nutrition Doctoral Students at the UNC Nutrition Research Institute

UNC NRI, 500 Laureate Way, Kannapolis NC 28081 (704-250-5006)

exploring nutritional individuality • www.uncnri.org

UNC Nutrition Research Institute Exploring a New Field

Several faculty members in the Department of Nutrition are looking to accept and mentor a new doctoral student next year. This is an exceptional opportunity to work at the cutting edge of science in an amazing new facility.

The UNC Nutrition Research Institute (NRI), established in 2008, located in Kannapolis, NC and part of the University of North Carolina at Chapel Hill, is leading the development of "individualized nutrition" – understanding why people's metabolism and nutrition requirements differ from one another by providing sound science supporting the understanding of genetic, epigenetic and other mechanisms that cause individual variations in metabolism.

The UNC System General Administration has located research programs from seven Universities on a new 350-acre campus in Kannapolis, NC (2 hours from Chapel Hill and 30 minutes from Charlotte). The NRI is Chapel Hill's component of this science campus.

Mission: "The NRI's mission is to become the world leader in defining optimal nutrition requirements. By using the most up-to-date research knowledge and technologies, the NRI will contribute significantly to the discovery of the health benefits of nutrition, and will apply this knowledge to define and implement optimal nutrition based on individual biological characteristics."

The Department of Nutrition is holding an open house for prospective doctoral students on November 21, 2014 (with a welcome dinner on the evening of November 20th) in Chapel Hill.

For students **wishing to visit the UNC NRI** as well – you will need to arrive before 11 AM at Charlotte Airport (CLT) on November 20, 2014. We will pick you up at the airport, give you a chance to see campus, and drive you to Chapel Hill in time to make the welcome dinner. If you are driving yourself, we will begin with lunch at the NRI in Kannapolis at 12 Noon on November 20th. Come to Dr. Zeisel's office at 2218 UNC NRI.

So that we can plan transportation, you must **make a reservation** with us if you plan to visit the UNC NRI – email steven_zeisel@unc.edu before November 11, 2014.

Research at the NRI Creating a Healthier Tomorrow

The NRI studies nutritional individuality using new "omic" methods such as nutrigenomics, epigenetics and metabolomics. Nutrigenomics is the study of the interaction between genes and nutrition, and how together they affect human health. Epigenetics is the study of chemical marks on genes that turn them on or off, and are often affected by nutrition in early life. Metabolomics is the simultaneous measurement of thousands of molecules — in blood, urine or tissues — that are generated as a result of an individual's

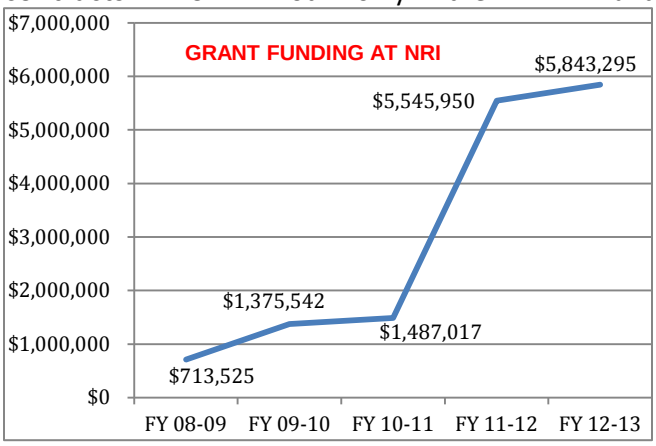
metabolism.

Because most traditional approaches to nutrition only consider the "average person," there is a lot of unexplained "noise" in experimental data. This noise occurs because we mix responders with non-responders in nutrition studies. If we could better understand why people have different nutrient requirements (e.g. identify responders from non-responders), we could replace a one-size-fits-all nutritional approach with one that considers individual differences in people's metabolism.

The NRI is equipped with state-of-the-art research laboratories, a whole room calorimeter (capable of measuring calories burned to within 75kCal/d), a fully-equipped metabolic kitchen, an outpatient clinical examination suite, a behavioral testing suite equipped with sophisticated instrumentation for the study of brain function, mass spectrometers and state-of-the-art genetics equipment.

Funded Research at the NRI

Since its inception in 2008, NRI scientists have been awarded **$26,214,349** in grants and contracts from not only the NIH and

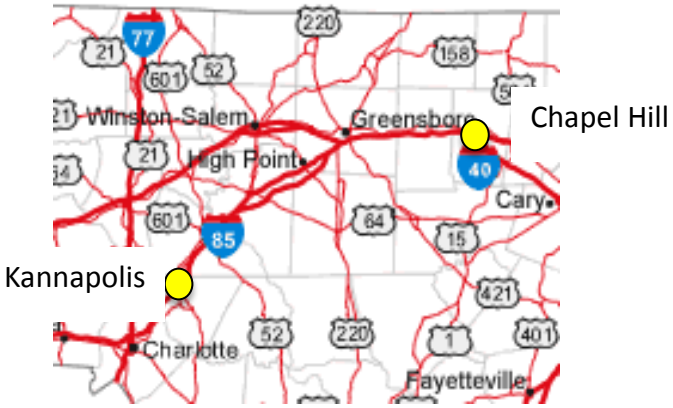


USDA, but also from other prestigious sources (e.g. The Bill & Melinda Gates Foundation), and industry partners with interests in nutrition. The international recognition of NRI researchers in the field is demonstrated by the international awards they receive, the presence of NRI faculty members in national and international review panels (e.g. NIH, MRC, BBSRC, etc.), by their presence as journal reviewers and as members of journal editorial boards, and by their presence at national and international conferences as invited speakers.

NRI researchers possess the broad range of expertise necessary for successfully competing for funding in the era of systems biology: metabolomics, transcriptomics, genomics, epigenomics, behavior and cognition, energy metabolism, gut metabolism, brain development, epidemiological and intervention research (including international locations such as the South African Republic, The Gambia, and Romania). This expertise is complemented by collaborations with other universities with a local presence (e.g. NC State, Appalachian, NCCU), and by collaborations within the main UNC CH campus and with universities around the world.

What is it like to be a student at Kannapolis?

Students take the same courses and meet the same requirements as do nutrition students working with faculty members in Chapel Hill. Students live and work in Kannapolis and attend required classes using high-speed videoconferencing equipment. The Department of Nutrition offers all of its classes in this way. Some students chose to live in Chapel Hill during some part of their first year to take specific classes from other departments that are not offered by videoconference. After the first year students are expected to spend their time in labs in Kannapolis.



The drive to Chapel Hill is almost all on major highways, with little traffic, and takes about 2 hours. Kannapolis is a small town that is friendly, safe. Parking is free and housing prices are lower than in Chapel Hill. The public high school is nationally recognized for its science programs. Next door, Concord has NASCAR, great restaurants, a world-class discount mall and amusement parks. The nightlife, professional sports arenas, and museums of Charlotte are about a 30 minute drive away by highway.

The Following Faculty Members in Nutrition are looking for Doctoral Students to Work at the NRI

Please email them directly to discuss the opportunity.

These faculty members are ready to accept and mentor a new doctoral student and will provide funding for stipend and in-state tuition for at least 4 years and will cover research expenses associated with the thesis project. ALL RESEARCH WOULD BE DONE AT THE KANNAPOLIS LOCATION – NOT IN CHAPEL HILL.

Brian Bennett, Ph.D.
Assistant Professor of Genetics and Nutrition
brian_bennett@med.unc.edu

Dr. Bennett studies the role of the human diet, genes and nutrition as they relate to heart disease. He explores genetic components of chronic metabolic diseases, such as cardiovascular disease and obesity, through integrative genetic studies, also called "systems genetics." He examines genetic variants, gene expression levels, metabolite levels and dietary components, and determines how these interact to increase susceptibility to cardiovascular disease. In particular he is focused on how diet affects gene expression in studies on a particular metabolite (TMAO), which appears to change with diet, and is predictive of cardiovascular disease in humans.

<u>Potential thesis project areas for a new doctoral student:</u>

1. Our overarching research question is: "How does our underlying genetic architecture interact with diet to increase susceptibility to atherosclerosis and metabolic diseases?" These studies use a systems approach where we combine "omic" scale data such as RNA expression and metabolite profiling to identify novel gene/diet interactions. These studies would be a combination of traditional laboratory work with computational approaches (bioinformatics). Our current pathway of interest involves the metabolite TMAO and the gene Fmo3.
2. My laboratory also validates our genetic "hits." A potential thesis project is to determine how natural variation in the mRNA levels of the gene Desmin lead to increased atherosclerosis? Using knockout mice and cells in culture a student would identify the mechanism by which the candidate gene, Desmin, affects atherosclerosis.

Folami Ideraabdullah, Ph.D.
Assistant Professor of Genetics and Nutrition
folami@email.unc.edu

Dr. Ideraabdullah's research seeks to identify and characterize genetic sources of epigenetic response to environment. Her research investigates DNA sequence differences that confer susceptibility or resistance to epigenetic change caused by environmental factors such as diet/nutrition and toxicant exposure. Furthermore, her research aims to understand how these gene-environment interactions contribute to heritable diseases. A growing list of environmental factors are implicated in perturbing epigenetic programs however individuals in both human and animal models vary in response to these exposures. These important studies will help elucidate mechanisms responsible for these differences.

<u>Potential thesis project areas for a new doctoral student:</u>

1. Why are some loci more susceptible to epigenetic changes induced by deficiency/over-supplementation of methyl donor nutrients? Several studies show epigenetic changes associated with deficiency of methyl donor nutrients such as folate and choline. However, it remains unclear why some loci are altered while others remain unaffected. The doctoral student would alter methyl donor nutrient levels using reproductive mouse models and a combination of locus specific and genomic analysis to identify sequences that are

susceptible to epigenetic change and potential trans acting factors responsible.

2. What is the role of nutrient metabolism in modulating epigenetic effects of toxicants? Epigenetic defects due to toxicant exposure vary between individuals. To determine the role of methyl donor nutrient metabolism, the doctoral student would characterize epigenetic changes induced by toxicant exposure in *ex vivo* (cell culture) and *in vivo* mouse models defective in methyl donor nutrient metabolism.

Venkata Saroja Voruganti, Ph.D.
Assistant Professor of Nutrition
Saroja@unc.edu

Dr. Voruganti's research interests are directed towards understanding how genetic and environmental factors influence hyperuricemia (gout) and associated diseases such as diabetes and cardiorenal disease using a combination of genetic, metabolomic, statistical and bioinformatic approaches. Specifically, her interests focus on the influence of gene variants on serum uric acid levels; the effect of high-protein and high-fructose diets on serum uric acid levels and gene expression of molecules related to hyperuricemia and cardiorenal disease; and the influence of genotype by environment (alcohol intake, smoking, diabetes and hypertension status) interactions on the regulation of serum uric acid levels.

<u>Potential thesis project areas for a new doctoral student:</u>

1. Why and how does genetic variation in uric acid transporters affect renal function? Several polymorphisms in uric acid transporters (SLC2A9, SLC22A12, ABCG2, etc) have been associated with altered renal function phenotypes. The doctoral student would analyze datasets from populations such as Mexican Americans, and American Indians using statistical, bioinformatic and molecular methods to understand the functionality of these polymorphisms and the mechanism by which they affect renal function.
2. Why do obese children have high serum uric acid levels? We found specific polymorphisms in uric acid transporter, SLC2A9, to be associated with high serum uric acid levels in children. Is the mechanism related to their co-morbidities of obesity or maternal complications during pregnancy? The doctoral student would work on a pediatric dataset using statistical and bioinformatic methods and follow up with molecular assays to identify and confirm the functionality of variants associated with serum uric acid levels.

Natalia Krupenko, Ph.D.
Assistant Professor of Nutrition
natalia_krupenko@unc.edu

Dr. Krupenko's laboratory investigates the molecular mechanisms by which an essential nutrient, folate, and folate-related methylation pathways maintain the normal functions of an organism, and how disruptions of folate metabolism lead to development of diseases. Dr. Krupenko has recently discovered a novel function of a folate-binding methyltransferase GNMT in the regulation of cellular proliferation. This function is associated with the nuclear translocation of this cytosolic protein and regulation of transcription. Dr. Krupenko's group studies genetic variations in GNMT and their effects on cellular homeostasis and human health. This lab is also interested in the cross talk between folate metabolism and sphingolipid pathways as a mediator of folate stress. This knowledge will allow development of more rational general nutritional recommendations as well as individually tailored, personalized dietary recommendations that will improve human health.

<u>Potential thesis project areas for a new doctoral student:</u>

1. Why tumors down-regulate GNMT, and why the GNMT knockout mice develop hepatocellular carcinomas? These questions will be addressed by studying cell culture and animal *GNMT* knockout and knock-in models. The doctoral student will study SNPs in the *GNMT* gene and will use the biochemical and molecular biology methods to evaluate their effects on the protein structure and activity, as well as cell biology methods to determine

the effect on cellular function. Metabolomic and proteomic approaches as well as mRNA profiling will be used to identify the GNMT interacting targets and relevant pathways.

Sergey A. Krupenko, Ph.D.
Professor, Nutrition
sergey_krupenko@unc.edu

Sergey Krupenko studies the role of folate metabolism in cellular homeostasis and cancer disease. Dr. Krupenko has discovered that the major folate enzyme, ALDH1L1 possesses properties of a type 2 tumor suppressor and is silenced in tumors. This finding raises the question of whether ALDH1L1 is a marker of malignant transformation. Studies in the Krupenko lab also demonstrated that the dietary folate regulates cellular migration and invasion, and affects cancer metastasis. The researchers found that the main players in metastasis mechanisms responding to nutritional folate status are actin and actin depolymerizing factor cofilin.

Potential thesis project areas for a new doctoral student:

1. The project will address the question of why ALDH1L1 is so abundant in normal tissues but silenced in malignant tumors. The doctoral student will study the cellular function of this enzyme and its transformation-inhibiting properties using chemical models of carcinogenesis and Aldh1l1 knockout mice, recently generated in the Krupenko lab. Intriguingly, ALDH1L1 has been recently established as a pan-astrocyte marker, underscoring the role of folate in glia. Therefore, another part of the mouse knockout project will study the role of the enzyme and folate metabolism in the central nervous system.

2. How does dietary folate affect tumor metastasis and what are molecular mechanisms engaged in this process? This question becomes especially important in light of recent controversies regarding the role of folate in cancer disease. The project will focus on the folate-dependent regulation of cellular migration and metastasis through the control of actin dynamics. The overarching goal is to provide better dietary recommendations to cancer patients with regard to folate supplementation.

3. A project is also available to explore the role of a novel folate enzyme ALDH1L2 (the mitochondrial isoform of ALDH1L1) recently discovered by the Krupenko lab. Using Aldh1l1 and Aldh1l2 knockout mice, interested students will study mitochondrial folate metabolism, and its interplay with the overall folate function in the regulation of cellular homeostasis.

Steven Zeisel, M.D., Ph.D.
Professor of Nutrition and Pediatrics
steven_zeisel@unc.edu

Dr. Zeisel is developing the emerging science of nutrigenomics. Dr. Zeisel discovered that people require choline, which is important for liver, muscle and brain function, and he has demonstrated that the requirement for this nutrient is influenced by genetic variation. Mouse studies in the Zeisel lab showed that choline - found in foods like eggs, beef liver, wheat germ and spinach - has a critical role in a mother's diet during pregnancy and is essential for the formation of nerve cells in the developing infant brain and retina.

Potential thesis project areas for a new doctoral student:

1. Why does deletion of the gene *Bhmt* in the mouse result in the development of liver cancer? There are common polymorphisms in this gene of choline metabolism in humans, and these people might be at risk for cancer. The doctoral student would work with the knockout mice and cells in culture and use molecular biological, "omic", immunohistochemical, and biochemical methods to discover the underlying molecular mechanisms responsible for cancer in these mice.
2. Why do men with a polymorphism in the gene *CHDH* have abnormal sperm motility and can

this be treated? Almost 10% of men have a polymorphism in this gene of choline metabolism, and they have sperm in which mitochondria do not make enough ATP to support normal motility. Mice in which this gene has been deleted have the same problem, and get better when treated with betaine. The doctoral student would work with humans, knockout mice and cells in culture and use molecular biological, "omic", immunohistochemical, and biochemical methods to discover the underlying molecular mechanisms responsible for mitochondrial dysfunction in these mice.

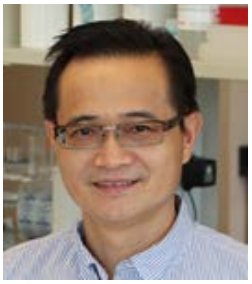
The Intellectual Environment for Doctoral Students Who Work at the NRI is excellent.

The UNC Nutrition Research Institute provides an intellectually stimulating environment for students. Other faculty members at the NRI, but who are not taking on new students this year include:

Carol Cheatham, Ph.D.
Assistant Professor of Psychology

Dr. Cheatham's research focuses on differences in cognitive and social development and how these may be related to diet, genetic variation and metabolism. Specifically, she is interested in the development of memory and attention as they are the basis for learning, and therefore school readiness. For example, her research asks if supplementation of children's diets with omega-3 fatty acids has an effect on memory function, and whether genetic variation in the mother or infants alters responses to diet. In another study, Dr. Cheatham examines older adults with mild memory impairment and determines whether dietary intervention can moderate these deficits. Many different methods and tools are used in the Cheatham lab to assess abilities, including assessment of evoked response potentials as well as more classical methods for the psychological assessment of brain function.

Wenhong Cao, M.D.
Associate Research Professor of Nutrition

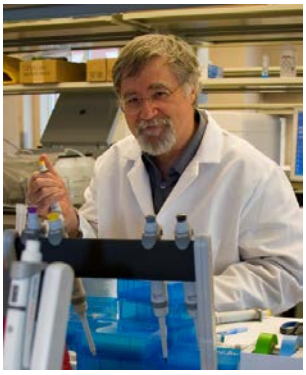


Dr. Cao finds new and more effective ways to prevent and treat obesity and diabetes and their associated cardiovascular disorders by investigating mechanisms underlying insulin resistance. Insulin resistance is a precursor or key component of many modern health problems such as obesity, metabolic syndrome, type II diabetes, cardiovascular disorders, non-alcoholic fatty liver, some cancers and aging. His lab studies hepatic gluconeogenesis, hepatic lipogenesis, production of new mitochondria, autophagy-dependent removal of aged or damaged mitochondria, and insulin receptor isoforms using various molecular, cellular and animal models in studies.

Karen Corbin, R.D., Ph.D.
Research Assistant Professor of Nutrition

Dr. Corbin studies the role of nutritional and genetic variation in obesity, fatty liver and metabolic syndrome. She recently identified a pattern of gene polymorphisms that predict which people will develop fatty liver when they become obese. Currently, Dr. Corbin is using a mouse model to understand the linkage between one-carbon metabolism and regulation of energy expenditure. Dr. Corbin is a trained dietitian, and is involved with several of the human studies ongoing at the NRI.

Martin Kohlmeier, M.D.
Research Professor of Nutrition



Dr. Kohlmeier's research program examines the effects of genetic variation on dietary requirements. He is developing tools with which physicians can translate genetic test information into dietary recommendations for their patients. He also is filling a significant void in nutrition education for

students in medical schools throughout the United States and the world. The Kohlmeier team has developed a web-based curriculum, "Nutrition in Medicine" that is used by more than 5000 medical students each year. Physicians also want and need continuing education about nutrition, and the NRI now offers an online course, "Nutrition Education for Practicing Physicians", also developed by Dr. Kohlmeier and his team.

Phillip May, Ph.D.
Research Professor of Nutrition

The May research team is investigating the prevalence of Fetal Alcohol Spectrum Disorders (FASD) in North Carolina, New Mexico and South Africa funded by a pair of multi-million dollar grants awarded this year by the National Institute of Health's National Institute on Alcohol Abuse and Alcoholism. An estimated 20 percent of the South African population, and a significant portion of pregnancies in America, are affected by mothers drinking alcohol during pregnancy. Children with FASD exhibit symptoms such as poor coordination, speech and language delays, poor memory and hyperactivity. As part of the study, Dr. May and his team hope to identify why some pregnancies are vulnerable to alcohol and others are not. They hope to identify effective methods for early intervention in children to minimize their disabilities and to identify alcohol use in the prenatal period.

Mihai Niculescu, M.D., Ph.D.
Assistant Professor of Nutrition

Dr. Niculescu studies how maternal obesity influences children's health and development. He specializes in the study of epigenetics and nutrition, which helps to explain how diet sets the "switches" that control gene expression. Specifically, he focuses on the impacts of maternal obesity and omega-3 fatty acids upon fetal and postnatal brain development. His work shows that maternal diet during pregnancy can alter epigenetic marks on genes, thereby changing fetal brain development

In addition, on the Kannapolis campus, NC State University, Appalachian State University, NC Central University, UNC Charlotte and NC A&T University maintain active research programs.

For more info, see our web site:
http://www.uncnri.org

and see:
www.ncresearchcampus.net/explore-ncrc