University of California - Los Angeles
Clinical Nutrition Research Unit
Start Date: 1985
Status: Ongoing
Source of NIH Support: NCI

Organization and Goals

The UCLA Clinical Nutrition Research Unit (CNRU) was established in 1985 and is funded by the National Cancer Institute (NCI). Its goals are to:

- Encourage, develop, and support multidisciplinary research in nutrition and cancer prevention that would not otherwise exist through the provision of expert technology, services, and leadership which identifies and fosters new research opportunities among investigators from different departments and institutions;
- Strengthen the training environment for medical students, graduate students, housestaff, practicing physicians, and allied health personnel in clinical nutrition, especially as applied to cancer and nutrition; and
- Enhance the utilization of nutrition for the prevention of cancer through nutrition education of practicing physicians, allied health personnel, and the general public.

Core Laboratories

Administrative and Planning Core: David Heber, M.D., Ph.D., Director and V.L.W. Go, M.D., Associate Director

External Advisory Board Members

David Alberts, M.D., Ph.D., Professor and Director, Leon Levey Cancer Center, University of Arizona, Tucson, Arizona

Bruce Ames, Ph.D., Professor of Biochemistry and Molecular Biology, University of California at Berkeley, Berkeley, CA

Wayne Bidlack, Ph.D., Dean, College of Agriculture, California State Polytechnic University, Pomona, CA

Frank Meyskens, M.D., Director, Comprehensive Cancer Center, University of California at Irvine, Irvine, CA

Malcolm Pike, Ph.D., Professor of Preventive Medicine, University of Southern California, Los Angeles, CA

Nutritional Biomarker Core: Susanne Henning, Ph.D., R.D., Director and V.L.W. Go, M.D., Co-director

Energetics Core: Zhaoping Li, M.D., Ph.D., Director

Gene-nutrient Interaction Core: Diane M. Harris, Ph.D., Director and A.J. Lusis, Ph.D., Co-director

Molecular Oncology Core: Phillip Koeffler, M.D., Director and Carl Miller, Ph.D., Co-director

Stable Isotope Core: W.N. Paul Lee, M.D., Director and Laszlo Boros, Ph.D., Co-director

Statistical Coordinating Unit Core: R.M. Elashoff, Ph.D., Director

Pilot and Feasibility Studies

Kurt Hong, M.D., is the New Investigator Awardee for the current year. He was previously a postdoctoral fellow through the Clinical Nutrition and Obesity Training Grant at the Center for Human Nutrition, was accepted into the prestigious Combined Ph.D. Specialized Training in Advanced Research (STAR) Program, and is currently completing coursework for his Ph.D. in molecular biology. He plans to study the regulation of chemokines in adipocytes and its effect on adipocyte differentiation and metabolism.

Dr. Hong's research involves studying the adipocytokine profile in obese patients with Metabolic Syndrome, and his pilot feasibility proposal, "Dietary Fat and Prostate Cancer Metastatic Potential: Role of NF-kappa B and CXCL12/CXCR4 axis in Regulating Progression to Androgen Independence," was funded for the current year. The specific aims of this project are to examine whether transition from androgen-dependent to androgen-independent metastatic disease during prostate cancer progression is correlated to expression of CXCR4 and associated with downstream activation of NF-kappaB, and to evaluate if dietary intervention using a low-fat diet will inhibit the progression of prostate cancer to a hormonal refractory state, with associated molecular changes leading to increased metastatic potential involving CXCR4 expression.

In addition to Dr. Hong's Pilot and Feasibility (P/F) study, two other P/F studies were funded for the current year:

- **Oliver Hankinson, Ph.D., "Inhibition of Invasive/Metastatic Potential of Human Breast and Ovary Cancer Cells by Phytochemicals."** This application has as its working hypothesis the idea that cancer chemoprotective effects of phytochemicals in general are mediated in part via down-regulation of the G-protein coupled receptor, CXCR4, in malignant breast cancer cells and in an ovary cancer cell line. The specific aims of this proposal are: 1) to ascertain whether genistein down-regulates the hypoxic induction of CXCR4 in malignant breast and ovarian cancer cell lines (CXCR4 is known to be inducible by hypoxia in breast and ovary cancer cell lines); 2) to ascertain whether genistein inhibits the chemotactic response of breast and ovary cancer cells to CXCL12, in the presence of hypoxia, and also investigate its effect in combination with 3,3'-diindolylmethane (DIM); 3) to investigate whether the phytochemicals, resveratrol, sulforophane, 2-phenylisothiocyanite, ellagic acid, (-)-epigallocatechin-3-gallate, and lycopene down-regulate CXCR4 in the breast and ovary cancer cells; and 4) to investigate if any of the compounds in aim 3 that down-regulate CXCR4 also do so in the presence of hypoxia, and whether they inhibit the chemotactic response to CSCL12 by using approaches described in aims 1 and 2.
- **Qing-Yi Lu, Ph.D., "Green Tea for Lung Cancer Chemoprevention."** Chemoprevention using phytochemicals has been considered an important preventive strategy to reduce the incidence of cancer. Most lung chemoprevention trials have produced either neutral or harmful primary endpoint results, whether in the primary, secondary, or tertiary settings. Numerous studies have reported that green tea as a dietary

source exhibits anti-tumor activities at many organ sites, including lung. Preliminary data from Dr. Lu's lab show that green tea extract inhibited lung adenocarcinoma A549 cell proliferation. Using proteomics technique, more than a dozen proteins have been identified which are expressed differentially in response to green tea exposure in A549 cells. The purpose of this study is to explore the mechanism of green tea in lung cancer prevention through understanding of the regulation of protein expression by GTE. This project has the following aims: 1) to confirm the altered formation/modification of proteins in response to green tea exposure in lung adenocarcinoma A459 cells and 2) to validate the protein expression with quantitative real-time PCR analysis. The results of this study may lead to the identification of new proteins as targets as well as intermediate markers for chemoprevention using green tea.

Funding Derived from Previous P/F Studies

BANGEO. Dr. David Heber and Gloria Mao, Ph.D., received funding for a supplement to the CNRU under the Bio-Active Nutrient Gene Expression Omnibus (BANGEO) funding mechanism. This is an add-on to the pilot project to investigate the potential for a "Western-style" diet to increase the incidence of prostatic intra-epithelial neoplasia (PIN) and/or prostate cancer in these prostate-specific RXRα null mice.

The specific aims that apply to the BANGEO project are to:

- Determine whether the New Western Diet (NWD) compared to control diet will increase the frequency of PIN in RXRα null mice;
- Determine whether the NWD compared to control diet will induce prostate cancer in RXRα null mice;
- Evaluate the level of adenoma and carcinoma development in colon of mice fed the NWD compared to the control diet;
- Examine gene expression in prostate tissues by microarray analyses under the different genetic, dietary, and exposure time conditions; and
- Examine gene expression in colon tissues by microarray analyses under the different dietary conditions.

AGA Student Research Fellowship Award. High-school student Alex Berger was funded to study a Chinese herb in pancreatic cancer under the mentorship of Vay Liang Go, M.D. and Diane Harris, Ph.D. The overall goal of the proposal is to evaluate *Scutellaria baicalensis* for its chemopreventive properties in *in vitro* and *in vivo* models of pancreatic cancer. An extract of *Scutellaria* will be compared to the isolated compounds baicalin and its agycone baicalein. The aims of study are: 1) to evaluate the *in vitro* inhibitory activity of pure baicalin and baicalein in comparison to whole *Scutellaria* extract on the proliferation of pancreatic cancer cells; and 2) to evaluate the bioavailability of baicalin from the whole *Scutellaria baicalensis* extract vs. pure baicalin in normal C57Bl/6 mice. Wild-type B6 mice will be administered a supplement of *Scutellaria* or pure baicalin, and plasma will be obtained at various time points from 0–8 hours after dosing for assay of flavonoid content.

AICR. A similar proposal was submitted to the American Institute for Cancer Research Grant Program by Dr. Harris. In this study, the overall goal of the proposal is to evaluate *Scutellaris baicalensis* for its ability

to inhibit lipoxygenase activity, leading to chemoprevention, in both *in vitro* and *in vivo* models of pancreatic cancer. *Scutellaris baicalensis* will be compared to the isolated compounds baicalin and/or its aglycone baicalein as well as other flavonoids. These studies will also provide a paradigm for evaluation of other natural LOX inhibitors from plant sources in PaCa.

Jonsson Comprehensive Cancer Center Foundation Board Initiative – Chronic Inflammation and GI Malignancy. Dr. Harris also submitted a local grant to look at modulation of the lipoxygenase pathways *in vitro* and *in vivo*. It is hoped that what results from these studies will provide further evidence of the importance of the lipoxygenase pathways in colon and pancreatic cancer development, and provide justification for use of pharmacological and naturally derived lipoxygenase inhibitors in cancer adjuvant therapy or prevention.

Scientific Advances/Accomplishments

Since its competitive renewal in 2002, the CNRU has further developed its capabilities and successfully conducted research, as evidenced in peer-reviewed grants and publications in the areas of phytochemicals and cancer prevention, metabolomics, nutrigenetics, nutrigenomics, and energy balance in cancer. The CNRU's main accomplishments include:

- Significant advances in the understanding of the mechanisms of action of phytochemicals at a cellular and subcellular level beyond antioxidation. Our studies have included xenograft and transgenic animal models of cancer, human pharmacokinetic, and unique studies of the metabolism of phytochemicals by gut bacteria setting the stage for human intervention trials. In fact, for pomegranate extract, preliminary studies and marker studies were so successful that a multicenter clinical trial to confirm the observation of a 50-percent decrease in the rise of prostate-specific antigen (PSA) levels in advanced cancer has been initiated with the support of the Prostate Cancer Foundation.
- Research findings on the effects of phytochemicals from fruits and vegetables on the multistep process of carcinogenesis. We have found that metabolites of phytochemicals may also have potent anticancer activity.
- Experiments in which omega-3 fatty acids were shown to reduce the rate of growth of LAPC-4 Xenograft prostate tumors through effects on proliferation and apoptosis without any effect on cyclo-oxygenase 2 expression. These studies explored varying ratios of omega-6/omega-3 fatty acids relevant to the human dietary intake and what is possible in intervention trials.
- The first study of lycopene supplementation in transgenic adenocarcinoma mouse prostate (TRAMP) mice after weaning. The data are still being analyzed with independent pathological reviews of slides obtained from prostate glands at sacrifice.
- The appointment of Dr. Hong as the CNRU's new investigator. Dr. Hong is currently studying chemokines such as CXCR-4 and their role in the development of androgen-independent prostate cancer.
- Continued support of a component project within a program project to investigate chemoprevention of superficial bladder cancer by green tea extract.
- The fostering of the NIH-funded Nutrition and Obesity Training Grant with research opportunities for young trainees that overlap in the areas of energy balance and cancer.
- The affiliation of the blood sampling and preparation area and the research kitchen of the UCLA Center for Human Nutrition with the NIH-funded General Clinical Research

Center. This has facilitated future trials of nutrition and cancer prevention through the newly configured Energetics Core.

- The development of metabolomic methodology with Paul Lee, M.D. This has resulted in publications and new grant applications through the work of the Stable Isotope Core.
- The development of Multidimensional Profiling to assess patterns of phytochemicals in foods and in botanical extracts through the work of the Statistical Coordinating Unit and the expanded Nutritional Biomarker and Phytochemistry Core.

In the past year, the UCLA CNRU has established itself as a center with new capabilities in the study of Phytochemicals and Cancer Prevention through publications from newly recruited participating scientists and due in large part to the resources now provided by the Mark Hughes Laboratory for Cellular and Molecular Nutrition for the LCMSMS and GCMS analysis of phytochemicals in foods and biological fluids. The CNRU expertise in obesity research has been focused on the new NCI research initiative on Energy Balance and Cancer through the activities of the Energetics Core. The initiative of the CNRU in gene-nutrient interaction had been further advanced with the recruitment of Simin Liu, M.D., Ph.D., to the Center for Human Nutrition and the development of a planned Center for Human Nutrigenomics in collaboration with the School of Public Health Dept. of Epidemiology's program in Nutrition and Genomics. The CNRU will provide the facilities for controlled feeding studies and has obtained new equipment for studies of gene expression within the Gene-nutrient Interaction Core of the CNRU. The Stable Isotope Core has developed expertise in metabolomics relevant to cancer prevention. The Statistical Coordinating Unit has continued to provide leadership in national clinical trials while developing innovative statistical methods for many of the modern technologies related to cellular and molecular nutrition.

Nutritional Biomarker and Phytochemistry Core

The UCLA CNRU Nutritional Biomarker Core Laboratory continues to enhance research in nutrition and cancer prevention through standardized high quality measurements of lipids, carotenoids, hormones, micronutrients, and selected phytochemicals derived from plant-based foods to assess the impact of dietary patterns and dietary interventions on the absorption, metabolism, action, and excretion of active constituents with cancer preventive potential. The laboratory is certified by the CDC Lipid Standardization Program, by the NIST/NCI Micronutrient Measurement Quality Assurance Program, and by the Vitamin D External Quality Assessment Scheme (DEQAS). In addition to optimizing established methods, the laboratory is expanded to use additional methods to determine oxidative damage and the regulation of SH-containing redox-sensitive compounds such as glutathione and cysteine. We established the comet assay which is able to determine single and double strand breaks in mononuclear lymphocytes. We are currently also establishing an immunohistochemical method to determine tissue oxidative DNA damage (8-hydroxydeoxyguanosine – 8OhdG)) and an ELISA method to measure small amounts of 8OhdG in cell culture medium. These new methods in turn have led to new grant applications, collaborations, and funding, which would not otherwise have been possible. Furthermore, this established laboratory resource has provided a scientific center within the UCLA Center for Human Nutrition, attracting new investigators to the CNRU. Some of the projects utilizing this core include controlled metabolic feeding studies which utilize the special dietary and metabolic resources of the two NIH-funded GCRCs associated with the CNRU, while others are conducted as part of ongoing NCI-funded population-based nutritional

epidemiology studies or clinical intervention trials. We are starting a new collaboration with Larry Kolonel, M.D., Ph.D., from the Hawaii Cancer Center. As a result of our new laboratory facilities equipped with LCMSMS and GCMS and newly recruited natural products chemists under the direction of Navindra Seeram, Ph.D., we have made significant advances in the understanding of the mechanisms of action of phytochemicals at a cellular and subcellular level in animals and in humans. With these additional facilities, we have expanded our Nutritional Biomarker Core to include phytochemistry and changed the name to the Nutritional Biomarker and Phytochemistry Core. This core interacts closely with the Statistical Coordinating Unit Core and the Energetics Core.

Energetics Core

The Dietary Assessment and Intervention Core was renamed the Energetics Core last year. Along with the dietary intervention, assessment, and body composition measurement that we previously conducted, we added exercise fitness testing. We continued to provide our expertise to researchers from other departments and schools, and, additionally, have extended our collaborations to investigators from other institutions such as USC, UC Irvine, and Northern California Cancer Center.

We made several other changes this past year. We expanded our "at risk" study populations to include adolescent girls. We incorporated clinical studies designed to uncover nutrigenomic associations. We broadened our research on postmenopausal women and proposed a multi-ethnic controlled feeding study of obesity among African American, Latina, and white women.

With the expansion of the Core to include exercise physiology studies and nutrigenomics, we continued to include nutritional assessment on a population-level in conjunction with biomarker measurement. Nutritional research in relationship to weight-loss studies and in relationship to dietary intervention has continued to be a strong component of our center. The Core Director is Dr. Zhaoping Li, who shares with Dr. David Heber the responsibility for supervising the research fellows and the clinical research area.

The Energetics Core provided needed services to investigators for a variety of clinical and community-based studies. The Core provided services described below in the ongoing and proposed research sections. In summary, these services included:

- clinical and population-based intervention research with development of diet and exercise interventions designed to increase fitness and promote healthy body compositions among adolescent girls and postmenopausal women, two at-risk populations for breast cancer;
- analysis of determinants of obesity, including genetic polymorphisms, in relationship to pre- and post-menopausal breast cancer risk;
- assistance with development of community-based cooking intervention among African-American women at risk for breast cancer; and
- conduct of clinical trial on effects of protein supplementation on weight-loss.

Additionally, we are proposing a clinical trial designed to promote weight-loss among postmenopausal obese women and dietary assessment combined with biomarker measurement in relationship to DNA methylation and lung cancer risk.

Gene-nutrient Interaction Core
The Gene-nutrient Interaction Core has been divided into two thematic programs: nutrigenetics and nutrigenomics, in both humans and model systems. The nutrigenetics program is conducted with genetically modified mice and in human molecular epidemiological studies. The Core utilizes the mouse breeding and housing facilities of the Department of Laboratory and Animal Medicine. The nutrigenomics program benefits from the capabilities of the Gene-nutrient Interaction Core Laboratories (that include the Dennis A. Tito Gene-nutrient Interaction Laboratory) dedicated to high throughput genomic analysis as well as facilities for cell culture studies and molecular biologic analyses. Dr. Harris is the Core Director and is responsible for the utilization of the core by researchers in nutrition and cancer prevention. Dr. Harris also serves on the National CNRU Basic Biology Committee. The laboratory has a close working relationship with the Department of Genetics and A.J. Lusis, Ph.D., the Co-director of this Core, is a professor in the Department of Genetics.

Dr. Lusis is conducting mouse cross-breeding and human genetic mapping studies with a focus on chronic diseases, including cancer, through his involvement with the CNRU. He is using transgenic mouse models and mouse breeding technology to study gene-nutrient interaction in cancer. He previously identified a model of hepatoma in mice with a germline mutation leading to overexpression of thioredoxin. The CNRU Gene-nutrient Interaction Laboratory is characterizing this tumor model further. Dr. Lusis has also used the core to develop congenic mouse strains that isolate important loci on a common genetic background. Examples developed with assistance from the core are: 1) a congenic strain carrying a locus leading to hyperlipidemia and strikingly enhanced atherosclerosis susceptibility; 2) a set of congenics that span a region of multiple loci contributing to obesity and insulin resistance; and 3) ongoing work to develop sets of congenic strains that span the genome.

This laboratory has already enhanced the interdisciplinary collaboration among CNRU scientists, and will increase the emphasis on gene-nutrient interaction studies relevant to cancer prevention. The research focus of the Core has included using mouse models of cancer to study mechanisms of cancer. The Core funds support for one technician who is primarily in charge of the genotyping service. In addition, a full-time mouse technician is funded through other sources but oversees the breeding colonies and conduct of experimental protocols.

Molecular Oncology Core
H. Philip Koeffler, M.D., provided Core activities with other investigators that delved into the interaction of nutrition with molecular and cellular biology. In addition, a clinical trial of a vitamin D analog in preleukemia was done, and some basic science augmented the clinical study.

Areas that were featured this past year include vitamin D compounds and their role in limiting cancer growth, their interaction with other compounds to limit cancer growth, and their anti-microbial activities. We helped examine additional nuclear hormone receptor ligands such as a novel PPAR ligand. We did several studies examining the anti-cancer effects of herbal compounds and purified reagents from the herbal compounds. We also helped with studies of compounds that affect the histone-deacytelase (HDAC). HDACs silence genes, including tumor suppressor genes in cancer. We are aiding in the examination of HDAC inhibitors and their anti-cancer activity. In addition, in collaboration with a number of principal investigators, we are

helping with studies of a variety of miscellaneous agents that appear to have anti-cancer activity, such as HIV proteasome inhibitors and several interesting monoclonal antibodies.

Stable Isotope Core Laboratory - Metabolomics

Significant advances have been made in the understanding of tracer metabolomics results and their implications in biological sciences. The first important theoretical development is in making the distinction between metabolite profiling (metabonomics) and metabolic profiling (tracer-based metabolomics). These are different not so much in the analytical technique used but in the nature of the information they provide. Thus, the analytical tools that are applicable to metabonomics are those of distribution analysis such as principal component analysis (PCA) and other clustering techniques. By contrast, the analytical tools for tracer-based metabolomics are those of linear programming and optimization analysis. The implications of such distinction are great because metabolomics provides correlative information, and tracer-based metabolomics provides predictive information on the phenotypic changes. From such analysis of phenotypic changes in cell proliferation, differentiation, and apoptosis, we conclude that genetic endowment results in a large set of possible phenotypes, and metabolic environment selects the phenotype that is observed.

Statistical Coordinating Unit

The Statistical Coordinating Unit (SCU) of the CNRU has continued to support nutrition and cancer prevention research in the CNRU over the past year. The SCU worked with a number of investigators during the past year to formulate new grant proposals for peer review by State and Federal funding agencies. This past year at least seven major proposals received such assistance from the SCU, including a complex U-54 application involving multiple collaborators and a clinical trial for pomegranate juice's effects on prostate cancer funded by the Prostate Cancer Foundation. Core personnel reviewed protocols, aided in study design, and composed specific statistical analysis sections for manuscripts and grant applications for CNRU investigators aiding in the publication of nutrition and cancer prevention research at UCLA.

In addition, the Biostatistics Core has developed specific analyses for microarray gene expression in green tea and developed new statistical methodology for these specific studies. The Core is investigating statistical analyses for complex mixtures in supplements and foods specifically carrying out the mathematical analysis of our new Multidimensional Profiling (MDP) capability, which uses LCMSMS or GCMSMS data to define complex matrix profiles of foods and supplements extracted from foods. In addition, this Core has developed novel methods to handle missing data problems, such as in time to event studies where a nonparametric data model is used and where the mechanism of missing is not missing at random.

Power computation was conducted for linkage analysis using observed phenotype data. This expertise will be critical for planned studies of gene-nutrient interaction. Data management and analysis were conducted for several of the studies already discussed. This expert assistance makes it possible for the CNRU to maximize the information obtained from nutritional intervention studies. For example, analysis of different diets and repeated measures analysis of macronutrient data was used in the analysis of the studies of nutrition intervention in breast and prostate cancer patients. The Statistical Coordinating Unit has been involved in the review and mentoring of all young investigators carrying out P/F studies within the CNRU. In addition, in

response to data collected by some of these investigators, new methods were developed to carry out data analysis.

Specific Accomplishments

Phytochemicals and Cancer Prevention. Dr. Seeram has been involved in the publication of four peer-reviewed articles resulting directly from the laboratory technical expertise for measuring phytochemicals. Dr. Seeram is being supported with institutional funds to augment the activities of the Biomarker Core. Studies on pomegranate ellagitannins in prostate cancer, funded by the pilot program with Allan Pantuck, M.D., resulted in findings of significant inhibition of PSA increases in advanced prostate cancer, which are being examined in a multicenter trial funded by the Prostate Cancer Foundation. Research on tea polyphenols was also advanced by this lab, resulting in publications and NIH-funded research being completed by Dr. Henning. Her research has localized green tea polyphenols in the human prostate and studied the pharmacokinetics of catechins and their antioxidant activity as the result of the ingestion of green tea, black tea or a green tea extract dietary supplement (Polyphenon E) that is being used in NCI-funded clinical trials.

Of note, Robert Schiestl, Ph.D., in the School of Public Health was funded to study lycopene and DNA Repair with institutional funds supplementing the CNRU. He is studying Ataxia Telangiectasia (AT) which is a hereditary human disorder resulting in a wide variety of clinical manifestations, including progressive neurodegeneration, immunodeficiency, and high incidence of lymphoid tumors. Cells from patients with AT show genetic instability, hypersensitivity to radiation, and a continuous state of oxidative stress. Oxidative stress and genetic instability, including DNA deletions, are involved in carcinogenesis. Atm-deficient mice are known to have an increased frequency of DNA deletions. After confirming this, these CNRU researchers found that Atm-deficient mice had significantly increased levels of 8-OH deoxyguanosine, an indication of oxidative DNA damage. Dietary supplementation with lycopene is being investigated in this study to determine whether 8-OH deoxyguanosine levels and the frequency of DNA deletions in Atm-deficient mice will be decreased. Genetic instability and oxidative stress is a theme being pursued as well in collaboration with Dr. Schiestl in studies of advanced prostate cancer. In separate studies, Dr. Henning found that citrus flavonoids stimulate base excision repair of DNA in cells exposed to iron-induced oxidative stress.

Energy Balance and Cancer. The Dietary Assessment, Intervention, and Body Composition Core was renamed the Energetics Core last year by the CNRU Executive Committee as a result of the new emphasis on energy balance and cancer and the research opportunities that this focus presents. Equipment for breath-by-breath oxygen analysis during exercise, along with our existing nutrient assessment, DEXA, and Nutrition Intervention capabilities have been brought together under the new Energetics Core and are being supplemented with recently obtained contributions to purchase a Bod Pod and strength testing equipment (Keiser equipment). This effort has involved our former New Investigator Awardee, Catherine Carpenter, Ph.D., and has attracted new collaborations with investigators from the School of Public Health (Antronette Yancey, M.D.) in energetics-based research initiatives. Dr. Carpenter has completed her research funded by the Breast Cancer Research Program of the State of California to examine the impact of leptin polymorphisms on postmenopausal breast cancer survivors, and she has recently

submitted a research grant application to extend her research findings. She has also initiated a collaborative study with Karen Duvall, M.D., in the Department of Family Medicine, in which postmenopausal women will undergo a combined exercise and diet intervention and changes in breast ductal fluid physiology will be examined.

Gene-nutrient Interaction in Cancer: Nutrigenetics and Nutrigenomics. The development of the Dennis A. Tito Gene-nutrient Interaction Laboratory and the complete renovation of contiguous space for cell culture and molecular biology studies has provided the research environment for the housing and fostering of new young faculty in the Center for Human Nutrition. There are now seven junior faculty (2 M.D.s and 5 Ph.D.s) appointed in the Division of Clinical Nutrition of the Department of Medicine, in addition to the many junior faculty in other departments at UCLA affiliated campuses and at USC.

Dr. Hong is the first STAR participant from the Nutrition Division of the Department of Medicine. This highly competitive program has an outstanding track record of developing new independently funded physician scientists. He was selected as the CNRU New Investigator Awardee this year. He is pursuing research on chemokines and cancer within the CNRU. Chemokines or chemotactic cytokines are known to be important in the directional migration or chemotaxis of leucocytes in conditions of homeostasis and in inflammatory or immunological responses. However, the role of chemokines is extending beyond their involvement in mediating leucocyte trafficking with an increasing body of evidence suggesting these proteins are intimately involved in many stages of tumor development and progression. Chemokine ligand:receptor CXCL12:CXCR4 complex is one particularly important chemokine axis recently shown to be involved in the determination of progression and metastasis of prostate cancer. While CXCR4 expression has been associated with aggressive tumor phenotype, its regulation during disease transition, particularly from androgen dependence to independence, is poorly understood. His work will concentrate on this issue.

The genetics laboratory is currently functioning with two high throughput genotypers and facilities to support high-throughput genomics. Research publications involving collaborations of Dr. Lu and Dr. Zhang have been completed in the past year consistent with the mission of this core. Importantly, the recruitment of Dr. Liu from Harvard Medical School to the Dept. of Epidemiology in the School of Public Health has stimulated the development through the CNRU of a Center for Human Nutrigenomics within the Center for Human Nutrition, in which the space and facilities of the Gene-nutrient Interaction Core and the Energetics Core will be interacting to provide the capability for controlled feeding studies of individuals with different genotypes and phenotypes relevant to cancer prevention. Dr. Liu has been provided with both office and laboratory space within the Center for Human Nutrition and we believe this collaboration will lead to exciting new research in nutrition and cancer prevention.

The Administrative Core has also reorganized its resources as suggested in the last review of the CNRU to increase administrative and scientific oversight of the Core activities. The specific scientific and educational achievements of the CNRU are listed below, but the coordination of this multicampus program has served to establish the Center for Human Nutrition as a base for innovative research in nutrition and cancer which would not have otherwise occurred since the competitive renewal of the CNRU in 2002.

Enrichment Program. As the primary visible focus for cancer and nutrition research at UCLA, a major mission of the UCLA CNRU is to enhance the level of research on the role of nutrition in cancer prevention. This is accomplished through research meetings with investigators, small working groups, and through scientific symposia. In addition, talks are given by CNRU key investigators to groups of trainees in Public Health, Experimental Pathology, and Medicine, on topics that serve to highlight the major areas of nutrition and cancer research at UCLA. In addition, the CNRU reaches out to investigators in the UCLA Jonsson Comprehensive Cancer Center and its Division of Cancer Control and Prevention to support wide ranging research initiatives in many areas of nutrition and cancer prevention by providing expertise and core resources to investigators. The first step in this process is often arrangements for a research seminar presentation.

A number of visiting professors conducted seminars at UCLA relevant to nutrition and cancer prevention. The following talks were given between March 2005 and the present:

- March 6, 2005, David Kritchevsky, Ph.D., The Wistar Institute, Philadelphia, PA
- April 27, 2005, Ong Choon Nam, M.D., Professor of the Medical Faculty, National University of Singapore, "The Role of Dietary Phytochemicals in Cancer Chemoprevention"
- April 29, 2005, Shiuan Chen, City of Hope, Duarte, CA, "Natural Aromatase Inhibitors and Breast Cancer Prevention"
- May 20, 2005, William Evans, Ph.D., Director of the Nutrition, Metabolism, and Exercise Laboratory in the Donald Reynolds Department of Geriatrics at the University of Arkansas for Medical Sciences, Little Rock, AR, "Macronutrient Intake and Exercise: Effects on Body Weight and Insulin Action"
- June 3, 2005, Katherine Pratt, JD, Professor of Law, Loyola Law School, Los Angeles, CA, "Normative Justifications for Food Excise Taxes"
- July 22, 2005, Jiankang Liu, Ph.D., Nutritional Genomics Center, Children's Hospital Oakland Research Institute, Oakland, CA, "Reducing Mitochondrial Decay With Mitochondrial Nutrients in Aging and Age-related Neurodegenerative Diseases"
- August 19, 2005, Philippe Thuillier, Ph.D., Assistant Professor, Cancer Research Center, Oregon Health Sciences University, Portland, OR, "Role of PPARs and Ligands in Mouse Skin Cancer Prevention"
- October 27, 2005, Michael Aviram, M.D., Lipid Research Laboratory, Technion Faculty of Medicine, Rambam Medical Center, Haifa, Israel, "Red Wine and Pomegranate Juice Polyphenolic Antioxidants Increases Serum HDL-associated Paraoxonoase Activity and Attenuates Atherosclerosis Development"
- February 23, 2006, Raul Bastarrachea, M.D., Auxology and Metabolism Working Group, Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX, "Gene Discovery For Obesity And Type 2 Diabetes: An Overview"
- February 27, 2006, John Foreyt, Ph.D., Director, Behavioral Medicine Research Center, Baylor College of Medicine, Houston, TX, "Behavioral Methods in Energetics-based Intervention"

Educational Program

School of Medicine. In 1996, a faculty-student retreat evaluated the existing curriculum. After deciding where improvements might be made, a task force looked for the best aspects of medical curricula across the nation. Using these as a starting point, a new curricular structure was developed incorporating principles selected as "best practices" in medical education. We implemented this new curriculum in our third and fourth years in 2000 and 2001. Next, under the direction of the Medical Education Committee and with the assistance of our educational experts as well as special funding from the Dean's Office, over 100 faculty and students re-planned the curriculum for the first two years. After several presentations of the details at faculty meetings, many discussions with department chairs, and extensive modifications, the Faculty Executive Committee approved the implementation, and gave a final go-ahead to start the new curriculum for years 1 and 2 in August 2003.

The block-based curriculum has been designed to increase integration of normal human biology with disease processes and clinical skills from the first week onward. Basic science is taught in the context that it will eventually be used clinically, and unplanned redundancy is minimized. Nutrition is addressed across the curriculum in all four years, and the prominence of nutrition in the new curriculum is indicated by the bold lettering in the table below. The CNRU leadership is involved in assessing content of these parts of the curriculum and works closely with the committees developing the new curriculum.

The following blocks are to be taught in sequential order, i.e., one course at a time.

Year 1

1. Foundations – pathologic processes, genetics, molecular and cellular, immunology and critical appraisal
2. Cardiovascular, Renal, Respiratory – anatomy, physiology, histopathology, **Endocrinology,** biochemisty, genetics, clinical assessment
3. **GI, Endocrine & Reproductive** – Anatomy, histopathology, biochemistry, **nutrition**
4. Neurologic, Musculoskeletal, Psychiatric- Anatomy, histopathology, neurobiology, neurology, imaging, psycho-pharmacology, pathophysiology, and clinical assessment

Year 2

5. Foundations – Pharmacology, microbiology, infectious diseases, cancer, hematology
6. **GI, Endocrine & Reproductive Medicine – reproductive health, prevention, including nutrition**
7. Cardiovascular, Renal and Respiratory – Pathology and pathophysiology; **pharmaceuticals and other treatments; prevention**

- Instruction is driven by cases explored in small groups, laboratories, conferences, clinical skills workshops, and independent study settings accompanied by 10 hours of lecture a week.
- Contact time is limited to 24 hours a week to allow time for independent study and electives.

- All but one of the thematic blocks is taught in two "passes." There is planned redundancy as well as progressive depth and expectations of competency. Most blocks are eight weeks in length.
- Curricular threads are woven into the fabric of each block, and include:
    - Doctoring principles and clinical skills
    - Anatomy, histopathology, and embryology
    - Genetics and genomics
    - Population medicine, informatics, and clinical reasoning
    - Pharmacology
- Special issues are addressed across the curriculum in all four years:
    - Gender-specific health
    - Geriatrics
    - Integrative medicine
    - Cultural components of health and disease
    - Cancer prevention and survivorship
    - Nutrition
    - Professionalism
- Curricular themes are woven into the fabric of each course, and include:
    - Doctoring principles and clinical skills
    - Anatomy, histopathology, and embryology
    - Genetics and genomics
    - Population medicine, informatics, and clinical reasoning
    - Pharmacology
- Progress through this curriculum is evaluated on a pass/fail basis. Regular assessments during each block allow students to track their understanding and adjust study practices or emphasis as indicated.

College of Letters and Sciences. An undergraduate upper division course entitled "Physiology of Nutrition"—first taught in the winter quarter of 1994 by Dr. Heber in the Department of Physiological Sciences—has grown rapidly. Each year, the enrollment is approximately 225 undergraduate students with about 50 percent declared pre-medical students. This department intends to integrate nutrition into its overall program and will support graduate students in nutritional science research working in CNRU laboratories. It is hoped that this will grow as a focus for graduate work in nutritional sciences at UCLA. It is also an activity with high visibility among undergraduates and may lead to the development of more nutrition curriculum at UCLA. The curriculum has been updated annually and now includes extensive contents on nutrition and cancer prevention, as well as phytochemicals and antioxidant mechanisms.

The Center for Educational Development and Research. Established in 1992 with initial support from the Whittier Foundation, the Center for Educational Development and Research (ED&R) provides educational consultation to the school on curriculum design, performance evaluation, faculty development, instructional technology, and program evaluation research. ED&R interacts with the CNRU through the monthly Nutrition Education Committee meetings. Of note, the UCLA CNRU provided the ED&R with its first peer-reviewed funding support through the NCI R-25 grant for nutrition and cancer education. Since then, a second R-25 was funded through NCI on cancer prevention, and a recent R-25 and K-30 Academic Award were

submitted through the support of the CNRU. LuAnn Wilkerson, Ed.D., the founder of the ED&R, has assumed its directorship. ED&R staff and faculty members continue to play central roles in the coordination, evaluation, and continuous quality improvement of the medical student curriculum by: 1) stimulating creative discussion of the purpose and methods of medical education at UCLA; 2) providing educational expertise for the design and implementation of innovative educational programs; 3) assisting faculty, residents, and students to develop and enhance their skills as teachers; 4) designing and overseeing the use of information technologies for teaching and learning; 5) coordinating the interdisciplinary components of the curriculum; 6) collaborating with faculty members to conduct research that will yield a better understanding of the process and outcomes of medical education; and 7) collecting, analyzing, and reporting student evaluations of courses, clerkships, and faculty members.

School of Public Health. Dr. Antronette Yancey, associate professor of Health Services and Dr.P.H. Program Director in the Department of Community Health Sciences, heads the Physical Activity Promotion and Obesity Prevention & Control (PAP-OPC) Collaborative. She teaches a Seminar in Obesity, Physical Activity, and Nutrition, a course in which Dr. Heber has also lectured. There are currently active nutrition programs in the Department of Epidemiology, Department of Biostatistics, Department of Environmental Sciences, and the Department of Community Health Sciences. A doctoral program in public health, awarding the Dr.P.H. and M.P.H. degrees, is currently active. Nutrition-related coursework in the School of Public Health includes courses in maternal and child nutrition and health-related behavior change.

Zuo-Feng Zhang, M.D., Ph.D., in the Department of Epidemiology teaches a course entitled "Cancer Epidemiology," which is an introduction to basic concepts of cancer and molecular and genetic epidemiology. The course includes a review of current epidemiologic research in cancer in recent medical and epidemiological literature. The syllabus includes a lecture on genetic susceptibility to cancer and a lecture on nutrition and cancer.