

Clinical Nutrition Research Unit at Strang Cancer Prevention Center

Start Date: 1980

Status: Ongoing

Source of NIH Support: NCI

Website: www.strang.org

Organization and Goals

The mission of our CNRU in its entirety remains that of advancing knowledge of nutrition in relation to cancer prevention and control. Strategies are being developed for reducing cancer prevalence in the population as a whole, particularly in individuals at high risk. The CNRU brings the latest technologies in molecular biology, molecular genetics, and other basic science disciplines to develop new concepts and methodologies that will enable clinical chemoprevention intervention trials to be designed, conducted, and evaluated in the most productive and economic fashion.

The interdisciplinary, interinstitutional organization of the CNRU makes optimal use of the expertise, technologies and resources of a large group of scientists and brings them together to accomplish this central mission. Since September 29, 2004, the CNRU has been organizationally located within the Strang Cancer Prevention Center, which is affiliated with Weill Medical College of Cornell University and New York Presbyterian Hospital. The CNRU involves close collaboration with Memorial Sloan-Kettering Cancer Center (MSKCC), Weill Medical College of Cornell University (WMC), The Rockefeller University (RU), and Westchester Medical Center-New York Medical College (WestMC).

Over a period of more than 2 decades, the research efforts of our CNRU have contributed new insights to the field of nutrition as a whole and, within the past decade, have focused exclusively on nutrition in relation to cancer prevention and control. The CNRU led to the first required courses in nutrition to be established for all medical students at Weill Medical College of Cornell University. The CNRU became the first collaborative research grant to be awarded to MSKCC-WMC-RU-Strang. As such it has been the primary mechanism for linking investigators in nutrition, for stimulating new research, for bringing investigators from other disciplines into nutrition, and for nurturing young scientists in the field of nutrition and cancer prevention. By sponsoring lectures, conferences, courses, and other scientific meetings, the CNRU has created a fertile ground for the growth of new ideas, concepts, and technologies. Scientists in our affiliated institutions come to us for project ideas and technologies with which to advance their research and to add a nutritional component to an existing line of inquiry.

A broad program is underway ranging from basic science studies to investigations in patients at high risk for cancer. The structure of the CNRU, with its core labs and pilot studies, greatly catalyzes advances in nutrition research. In this environment work can be accomplished more rapidly, more efficiently, and less expensively than if each investigator worked in isolation. New hypotheses can be tested rapidly; if not feasible, they can be quickly discarded, and, if promising, they can be pursued further with new grants and other resources. The CNRU is the magnet that brings the investigators together, facilitating communications, forging collaborations, and enhancing completion of research projects. In productivity and in organization, the whole is greater than the sum of the parts.

The New Investigator from the previous grant cycle (April 1, 2004 to March 31, 2005), Dr. Raghu Sinha, moved to Penn State Medical Center in Hershey, PA. With the guidance of our Internal Advisory and External Advisory Committees we decided to continue his financial support until the end of this grant year on March 31, 2005. Thus, he received a full 12 months of financial support. Starting April 1, 2005, another worthy candidate from our participating institutions, Dr. Petr Protiva, was selected from the solicitation of proposals. The goals of his project are summarized briefly below.

Core Laboratories

Administrative Core: Richard S. Rivlin, M.D., Program Director; *To be named*, Associate Program Director; Veronica Fortunato, MS, RD, MBA; Program Administrator; Linda M. Cotte, Program Secretary

External Advisory Group Members

David Kritchevsky, Ph.D., Wistar Institute, Philadelphia, PA, Chairman
Adrienne Bendich, Ph.D., SmithKline Beecham Consumer Healthcare, Parsippany, NJ
John Bogden, Ph.D., University of Medicine and Dentistry of New Jersey, NJ
Allan H. Conney Ph.D., Rutgers University College of Pharmacology, Piscataway, NJ
Krystyna Frenkel, Ph.D., New York University School of Medicine, New York, NY
F.X. Pi-Sunyer, M.D., M.P.H., St. Luke's-Roosevelt Hospital Center, New York, NY
I. Bernard Weinstein, M.D., Columbia University College of Physicians & Surgeons,
New York, NY
Chung S. Yang, Ph.D., Rutgers University College of Pharmacology, Piscataway, NJ

Internal Advisory Committee Members

Richard S. Rivlin, M.D., Strang Cancer Prevention Center and Weill Medical College of
Cornell University (Chairman)
Michael Bunk, Ph.D., Strang Cancer Prevention Center
Susanna Cunningham-Rundles, Ph.D., Weill Medical College of Cornell University
Lorraine Gudas, Ph.D., Weill Medical College of Cornell University
Peter Holt, M.D. Strang Cancer Prevention Center
Martin Lipkin M.D., Strang Cancer Prevention Center
Michael Osborne, M.D., Strang Cancer Prevention Center
John Pinto, Ph.D., Burke Rehabilitation Center – White Plains - affiliated with Cornell
University
Nitin Telang, Ph.D., Strang Cancer Prevention Center
Howard Thaler, Ph.D., Memorial Sloan-Kettering Cancer Center

Biostatistics Core: Howard Thaler, Ph.D., Director

Immunology Core Laboratory: Susanna Cunningham-Rundles, Ph.D., Director

Retinoids Analysis Core Laboratory: Lorraine Gudas, Ph.D., Director

Funded Research

Mechanism of Colon Cancer Inhibition by Polyisoprenylated Benzophenones from the Edible Fruit *Garcinia Xanthochymus*. Petr Protiva, M.D., Strang Cancer Prevention Center (CNRU New Investigator, April 1, 2005 – March 31, 2006). The purpose of this study is to

characterize the mechanism of anti-cancer action of three polyisoprenylated benzophenones from the Garcinia fruit and to conduct a cancer prevention study in a rodent model. During the first year of the study, we have been determining the intracellular pathway responsible for the apoptotic effect of these compounds in colon cancer cells. We are also analyzing possible effects of these compounds on the expression of genes and proteins involved in control of the cell cycle, histone modification and specific pathways of signal transduction. In the proposed second year of the study (April 1, 2006 – March 31, 2007), we will conduct animal cancer prevention studies using both genetic models of colon cancer and an azoxymethane-induced model. This study is expected to provide new insights on how edible plant-derived polyphenols can exert anti-tumor effects and thus suggest new approaches to cancer prevention and treatment.

Pilot and Feasibility Studies

A Novel Mouse Colon Cancer Model and Chemoprevention. Wei Dai, Ph.D., New York Medical College. This study aims to understand the relationship between deficiency in a cell cycle checkpoint gene and a putative chemopreventive compound using a newly developed animal model. The long term goal of this project is to elucidate the mechanism by which spindle checkpoint components and Wnt pathway components regulate cell proliferation and differentiation and to understand how deregulated processes result in genomic instability and development of colorectal cancer.

Selenium Supplementation Decreases Thyroid Cancer Growth in Humans through Up-regulation of Cell Cycle Arrest Genes. Thomas J. Fahey, III, M.D., Weill Medical Center of Cornell University. The goal of the proposed study is to determine whether the growth inhibitory effects of selenium that have been shown *in vitro* can be seen *in vivo*. We hypothesize that oral selenium supplementation in patients presenting with a thyroid nodule requiring treatment with partial or total thyroidectomy will retard neoplastic growth via the induction of cell-cycle arrest genes (GADD family) and selenoproteins.

Cellular Mediators of Resveratrol in Chemoprevention of Prostate Cancer. Tze-chen Hsieh, Ph.D., New York Medical College. This proposal, which is a competitive renewal of a 2004-2005 Pilot Study, aims to identify cellular mediators of a grape skin derived polyphenol, called resveratrol, with regard to its chemopreventive activities against prostate cancer (CaP). The studies described herein expand on my published observation that this dietary polyphenol significantly reduces growth of androgen-responsive (AD) and androgen-refractory (AI) CaP cells, and drastically lowers prostate specific antigen (PSA) expression. The substantial latency period associated with AD→AI transition in CaP makes this form of malignancy an attractive model for testing whether this specific agent confers chemoprotection in humans. As a requisite to fulfilling this long term objective, the investigator proposes to identify and characterize cellular targets of resveratrol using a novel approach, which he has named resveratrol-capture proteomics.

Circulating DNA from Food. David Thaler, Ph.D., The Rockefeller University. The study objective is to test the hypothesis that DNA from ingested food crosses anatomical barriers and might be detectable in circulating blood samples collected from normal human volunteers at The Rockefeller University Hospital. In this manner, the techniques of molecular biology will be utilized to provide accurate, quantitative, and specific measures of food intake. The specific aims are:

- To use quantitative PCR assays to obtain high-quality data from human blood samples of subjects recruited to the Rockefeller University Hospital under an approved protocol.
- To determine whether the DNA is associated with or has entered blood cells, or whether it is present in the serum fraction, if DNA originating from food tissue is identified in whole blood from volunteers undergoing a specific dietary regimen.
- To develop a QPCR assay system specific for the probiotics bacteria *Lactobacillus plantarum* strain that has been studied extensively by Dr. Susanna Cunningham-Rundles. Our first series of human experiments in the Rockefeller University Hospital will be carried out with a commercial yogurt formulation. Development of the assays for the *L. plantarum* probiotics will pave the way for future studies with this interesting strain.

Scientific Advances/Accomplishments

Well into the 4th year of our current 5 year cycle, we continue to make advances in a focused and dedicated grant program involving nutrition in relation to cancer prevention and control. The mission, impact, and unique features of the CNRU remain as previously, but with additional areas of investigation that address translational studies. Our program seeks to encourage basic studies involving molecular biology and clinical investigation with the expectation that novel information from the laboratory can be addressed in clinical trials and that clinical findings can be addressed mechanistically in the laboratory. Examples of our CNRU recent accomplishments include:

Novel cell lines have been developed for studies that utilize biological, biochemical, and molecular biology techniques for examining efficacy of chemopreventive agents.

- Mammary epithelial cells, isolated from the germline mutations of *Apc1638* and *Apc^{Min}* tumor suppressor gene mice, show increased risk for gastrointestinal carcinogenesis, exhibit increased susceptibility for transformation and are modifiable by select pharmacological and dietary agents.
- Lecithin: Retinol Acyl Transferase (LRAT) knockout mice have recently been generated via homologous recombination. These mice are currently being analyzed for retinol and retinyl ester content in various tissues, including liver, breast, lung, mammary gland, and prostate. To date findings have shown that the livers of these *LRAT^{-/-}* mice contain no retinyl esters. Thus, these mice are completely dependent on daily retinol intake in their diets for survival. These mice have also been placed on a vitamin A deficient diet; these mice are remarkably sensitive to vitamin A deficiency and develop signs of vitamin A deficiency within a few days to 2 weeks.

Novel mechanisms have been identified by which specific phytochemicals and nutrients affect growth of cancer cells.

- Resveratrol, a chemopreventive agent found in grapes, as well as carnesol, and ursolic acid suppress phorbol ester-mediated induction of inducible cyclooxygenase-2 in human mammary and oral epithelial cells; new cellular mediators of resveratrol are being identified.
- Indole-3-carbinol, a chemopreventive agent found in cruciferous plants, has an anti-proliferative effect on human breast cancer cells by altering the pattern of estradiol hydroxylation to a less mitogenic form.
- Diindolylmethane (DIM), a metabolite of indole-3-carbinol (I3C), is targeting the Akt signal transduction pathway, which may be a mechanism of its inhibition of prostate cancer cells.

- In human volunteers, selenized yeast increases blood glutathione (GSH) levels and decreases protein-bound GSH (bGSH), resulting in a decrease in oxidative stress. Concurrently, a small but significant decrease in prostate-specific antigen levels has been observed after 3 and 9 months of selenium consumption.
- Studies of nutrients, such as phytol, docosahexaenoic acid, and phytanic acid, have begun and have shown that these compounds, present in the diet, can influence retinol and retinoic acid metabolism in cultured normal human epithelial cells from the prostate, kidney, and lung. The results from these studies indicate that it may be possible to perturb endogenous retinoid functions by ingestion of high levels of various foods/and or nutrients in the diet.
- Based on the evaluation of expression of LRAT protein and mRNA in normal and malignant bladder tissue specimens from human patients, the effect of retinoids on *LRAT* expression in bladder cancer cell lines was also examined. An inverse correlation of LRAT mRNA and protein expression with increasing tumor stage was demonstrated, which suggests that loss of LRAT expression is associated with invasive bladder cancer.

Specific Accomplishments

Women's Health. A previous New Investigator established experimental models for human breast cancer, *in vitro* and *in vivo*. The effects of nutritional factors on gene expression in human breast cancer lines and the differential roles of N-3 and N-6 fatty acids upon carcinogenesis are being studied. Other studies are developing and validating intermediate biomarkers that can help identify individuals at increased risk for breast cancer and provide evidence on the effectiveness of nutritional interventions. This line of research should provide feasible, realistic, and effective strategies for using nutrition to help prevent breast cancer and its recurrence.

Colon cancer is also a major malignancy among women. Investigations at Strang documenting colon cancer prevention with calcium and vitamin D are of clinical significance for women. The previous development of a "stress diet" by CNRU investigators for animal models that resembles the Western Diet in being high in fat and phosphate, low in calcium and vitamin D, enables other CNRU investigators to identify those dietary factors most significant to cancer prevention in women. Studies by CNRU investigators are continuing at Strang and The Rockefeller University.

Thyroid cancer is another malignancy affecting women. Approximately 74 percent of newly diagnosed thyroid cancer patients in the U.S. are women. One of the current year pilot study award recipients is investigating whether the growth inhibitory effects of selenium that have been shown *in vitro* will retard neoplastic growth in human patients presenting with a thyroid nodule requiring treatment with partial or total thyroidectomy.

Angiogenesis is a well-recognized and essential step in the establishment, growth, and metastasis of malignant tumors. Growth of new vessels that enable tumor development depends on the balance between angiogenesis activators, inhibitors, and angiogenesis-modulating molecules such as copper. Copper is a required cofactor for multiple activators of angiogenesis such as: basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and angiogenin. Tetrathiomolybdate (TM) is a copper chelating agent that forms a stable tripartite complex with copper and protein. If given with food, it complexes food copper with food protein and prevents absorption of copper from the GI tract. A previous Phase I study in which varying doses of TM were administered to patients with late-stage (metastatic) advanced cancer, found

promising results that appeared limited by the length of time required to achieve copper deficiency. A subsequent study using higher dosing was successful in reducing the time to achieve copper depletion. Of the 40 patients treated in the combined phase I trials, 15 demonstrated stable disease \geq 90 days.

This previous work has led to a study in the CNRU Immunology Core Lab, which proposes to evaluate the effect of TM on circulating markers of angiogenesis to include bFGF, VEGF, VCAM-1, IL-8, thrombospondin, histidine rich glycoprotein, and circulating endothelial cells (resting and active) in patients with breast cancer at moderate to high risk of tumor recurrence.

Maitake mushroom “D-fraction” is an extract from the fruit body of *Grifola frondosa* that is widely used in Asia to treat breast cancer and other malignancies. Although little is known about its mechanism of action, Maitake D-fraction, beta 1,6-glucan with beta 1,3-branches, may activate the immune system to potentiate the cytotoxicity of natural killer cells and to activate macrophages. Previous basic scientific studies in the CNRU Immunology Core lab of Maitake mushroom “D-fraction” have led to a Phase I/II Study of Maitake “D-Fraction” in Breast Cancer Patients. Maitake is being given orally at four fixed doses in groups of six patients to allow us to study immune function at each dose. This Phase I/II trial of Maitake in breast cancer patients will allow for the development of dose-response relationships and correlative biological markers in breast cancer patients.

Minority Health. The CNRU program provides a multidisciplinary focus for studies on nutrition and cancer in a complex urban setting with access to a wide range of racially diverse patients of every socio-economic background, ensuring that the results obtained have general relevance. For the past several years, the CNRU Immunology Core Lab has been investigating nutritional and immunological aspects of AIDS, particularly in newborn children, a serious problem of women, African Americans, and Hispanics. The minority distribution in one of the recent studies was 50 percent male, 50 percent female, 8 percent White, 70 percent Black, 22 percent Hispanic, and 1 percent Asian. The studies listed above under Women’s Health also apply largely to minority health.

Drs. Pinto and Rivlin have been investigating prostate cancer prevention, a major health problem especially in African American males, utilizing allium derivatives from garlic. A major effort in the study of prostate cancer development in minority individuals has been initiated by collaboration with the Beaufort-Jasper-Hampton Community Health Services in rural South Carolina. We previously collaborated with this group in investigating dietary factors involved in the high prevalence of prostate cancer in African American males. We are currently initiating a study with a garlic supplement in this population in a double blind, placebo-controlled clinical trial. This clinical study is an outgrowth of the long term studies of Drs. Pinto and Rivlin on allium derivatives from garlic in cell-free systems and in specific animal models.

AIDS. Growth abnormalities are frequently observed in children with congenital HIV infection. The wasting syndrome is an AIDS defining condition in children and is a significant factor in both morbidity and mortality. While less is known about the long term consequences of chronic HIV infection in children, emerging data show that HIV+ children are showing increased susceptibility to tumors related to immune deficiency.

Chronically decreased growth velocity is often accompanied by gastrointestinal symptoms or symptoms of malabsorption that might indicate disturbances of the normal bacterial flora. Recent

studies have suggested that oral administration of probiotic lactobacilli may be therapeutic in accelerating reestablishment of normal flora in the G.I. tract in antibiotic associated diarrhea and might therefore be useful in the treatment of HIV-associated gastrointestinal enteropathy. The objective of this investigation has been to determine whether oral administration of the probiotic, *Lactobacillus plantarum*, 299v, LP299v, could improve nutrient status and promote growth in children congenitally exposed to HIV. In addition, the possible impact of *L. plantarum* 299v in modulating immune response is being evaluated.

In preliminary results, we observed that oral administration of *L. plantarum* 299v was effective in promoting a significant improvement in growth in 50 percent of children as indicated by change in weight or height or both. We also observed the ability of *L. plantarum* to colonize the intestinal tract of the HIV+ child and to elicit specific systemic immune response following oral supplementation. No child was colonized with *L. plantarum* prior to its oral administration and all children given active *L. plantarum* became colonized. There were no adverse side effects, and colonization was temporary and was not maintained in the absence of continued treatment. Interestingly, peripheral blood mononuclear cells from children with the most severely deficient cellular immune response to the T lymphocyte mitogen, phytohemagglutinin, PHA, and reduced CD4+ T cells, were able to respond vigorously to lactobacillus. Three children without prior response quickly developed a strong response. Thus, in the future gastrointestinal recolonization might be used to access the unique and powerful immune system of the gastrointestinal tract and may exert a restorative effect on immune response in children with HIV infection.

Health Promotion/Disease Prevention and Reduction in Healthcare Costs. A broad program is being undertaken ranging from basic science studies to investigations in patients at high risk for cancer. We seek to determine which dietary nutrients, alone and in combination with one another, hold promise for the prevention of human cancer, for improving immune function, and for reducing length of hospital stay once cancer has developed.

Nutritional interventions are expected to prevent or delay the onset of cancer, to retard metastases once cancer has appeared, and to minimize side effects of cancer treatment, thereby permitting safer and more effective therapy. A number of advances have already been made and many promising leads are currently being pursued that would certainly reduce healthcare costs.

Special emphasis has been placed upon the development and validation of intermediate biomarkers as clinically relevant endpoints, and then to utilize these specific molecular, metabolic, endocrine, and cellular biomarkers to evaluate efficacy of chemoprevention with specific dietary nutrients. The CNRU research programs on biomarkers are particularly relevant to prevention of breast, prostate, and colon cancer and may be useful to investigators in the field studying other cancer sites.

Basic Science and Clinical Investigation Interactions

1. Basic mechanistic studies on the cruciferous glucosinolate, indole-3-carbinol (I3C), conducted on the *in vitro* models of breast carcinogenesis have provided important leads to a clinical dose-ranging study. Current research directions focus on developing epithelial cell lines from clinical ductal breast carcinoma *in situ* and colon adenoma and are expected to provide new models for identifying molecular targets for clinical cancer chemoprevention.

2. Studies documenting that allium derivatives from garlic have inhibitory effects on cell lines of human prostate, colon, and breast cancer have led to the initiation of a clinical trial in the rural, impoverished, and medically underserved population of slave descendents in South Carolina.
3. The antitumorigenic effects of selenium are well documented, but the mechanism of action has yet to be elucidated. Previous *in vitro* studies conducted in the laboratory of Dr. Thomas J. Fahey, III, M.D., a CNRU pilot study award recipient in the current budget year, have shown that selenoproteins are down-regulated in thyroid tumors and that selenium causes growth inhibition via cell-cycle arrest in a thyroid cancer cell line. This work has led to a clinical trial designed to determine whether similar growth inhibitory effects of selenium can be seen *in vivo*, among patients at Weill Cornell Medical College/New York Presbyterian Hospital presenting with a thyroid nodule requiring treatment with partial or total thyroidectomy.
4. The advent of sensitive and high throughput detection methods for DNA based on real-time detection of products from the polymerase chain reaction (PCR) provides new tools to screen for DNA in the blood of humans. Basic molecular biology studies based on this technology performed at Rockefeller University have led to the initiation of a study at the Rockefeller University in New York City testing the hypothesis that DNA from ingested food crosses anatomical barriers and is detectable in circulating blood samples collected from normal human volunteers undergoing a specific dietary regimen. The demonstration that sequences from food can be found in human blood would be a novel finding. It could open the way to new studies, including the effects of genetic and environmental variables on the quantitative dimensions of uptake and fate, and the pharmacokinetics study of the informational content of food. Also, the measurement of the uptake of DNA from food may prove to be a new and sensitive biomarker for both food intake and/or intestinal permeability. Finally, the fate and consequence of DNA sequences that originate from food may be of both diagnostic and evolutionary interest.
5. Based on previous studies of all-trans retinoic acid and its metabolites, the levels of all-trans retinoic acid were examined in kidney cancer patients at various times following IV infusion of liposomal retinoic acid. The purpose of this collaborative study with oncologists in the Urological Oncology Division of Weill Medical College/Cornell Medical Center was to determine whether liposomal all-trans retinoic acid was superior to orally delivered all-trans retinoic acid in terms of its serum level and half-life in serum. The patients were treated with liposomal retinoic acid by IV infusion one time per week. At the end of the infusion and at various times thereafter, blood was drawn and serum was prepared and frozen at -70°C. Retinoids were then extracted from the serum and assayed. The pharmacokinetics of the liposomal all-trans retinoic acid delivery was analyzed in several patients and investigators were able to show that the all-trans retinoic acid is present at higher levels in the serum immediately after infusion as compared to all-trans retinoic acid given to patients orally in the prior studies that were performed in acute promyelocytic leukemia patients.

Professional/Public Nutrition Education Efforts

With the transfer of the CNRU to Strang, and the termination of the CNRU involvement in Public Information Activities at the Westchester Medical Center, we are in the process of reorganizing and redirecting our efforts. The program of lectures, cooking demonstrations, and outreach to health professionals, patients, and interested laypersons in the Westchester and Lower Hudson Valley areas has been curtailed. New plans are now being made for extensive

Public Information Activities organized and led by Strang with involvement of our colleagues at the collaborating institutions. Our current objective is to develop vigorous Public Information Activities on the potential of nutrition in cancer prevention and control for the benefit of health professionals, individuals at increased risk for developing cancer, individuals with cancer, and for the general public.

Website. A key element in our approach is the establishment of a website for the CNRU as a component of the overall Strang Cancer Prevention Center website. The CNRU comprises the key element of the Anne Fisher Nutrition Center, which Dr. Rivlin has directed since September 29, 2004. This website lists research in progress, information about CNRU lectures, applications for pilot studies and New Investigators, meetings and conferences sponsored by the CNRU, as well as discussions of new advances in nutrition research of practical benefit in cancer prevention.

Enrichment Program. The CNRU Enrichment Program has been strengthened by the high quality of the Special Nutrition Lecturers. Speakers from the CNRU faculty and staff review their progress at these monthly conferences. In addition, several prominent outside scientists are also invited to participate each year.

National Nutrition Month and National Cancer Prevention Month. In 2004, the Senate passed a resolution declaring February as National Cancer Prevention Month. After our initial experience it was apparent to us that February is not an ideal choice as it conflicts with National Heart Awareness Month and includes Valentine's Day, traditionally associated with the heart. We are now rethinking our planning for National Cancer Prevention Month and will bring a group of interested parties together, including NCI, the American Institute for Cancer Research, the Prevention Program of M.D. Anderson Medical Center in Houston, and other appropriate organizations and institutions that have expressed interest. National Nutrition Month each March is now well-established in the calendar, and we are undertaking a series of activities in coordination with the recently-established Nutrition Wellness Center at New York Presbyterian Hospital as noted below.

The Nutrition Wellness Center of New York Public Health (NYPH). Esther M. Trepal, M.S., R.D., Supervisor. The Nutrition Wellness Center, as part of the NYPH Department of Food and Nutrition, provides medical nutrition therapy in an ambulatory care setting. We provide up-to-date information from a behavioral perspective that fosters long term change and improved health outcomes. The patient population ranges from pediatric to geriatric. As a usual practice, the Center covers the gamut of medical conditions, including weight management, diabetes, cardiovascular disease, obstetrics, renal disease, GI complaints, and oncology but emphasizes cancer prevention and control.

The CNRU faculty participate as mentors in the medical student fellowship program sponsored by the American Society for Clinical Nutrition (ASCN). Stipends are provided for medical students to have a clinical and research experience at medical schools in the U.S. We have sponsored these fellows frequently. They have attended clinical rounds and conferences in nutrition, participated in the clinical activities noted above and performed research. During the current grant year we mentored an American student attending medical school in Dublin, Ireland. His research experience was with Drs. Thaler and Rivlin on detection of DNA from food in blood as a new molecular biology method of accurately determining food intake. Having a

reliable assessment of what people eat is central to any clinical research or epidemiological investigation on nutrition and cancer prevention.

Chairman of the Research Program and Advisory Committee. The Administrative Core plays a role at the national level in stimulating the field of nutrition and cancer prevention. In the current grant year the PI was appointed Chairman of the Research Program and Advisory Committee of the American Institute for Cancer Research (AICR). This Committee sets the national agenda and priorities for the entire competitive research grant programs of the AICR. The procedures, accountability, and standards of the AICR are entirely comparable to those of NIH. By sponsoring lectures, conferences, courses, and other scientific meetings, the CNRU has created a fertile ground for the growth of new ideas, concepts, and technologies.

International Conferences. Strang and UCLA organized an international conference on the role of garlic in health and disease, which took place on April 9 – 11, 2005. The conference was entitled “Significance of Garlic and its Constituents in Cancer and Cardiovascular Disease” and was held at Georgetown University, Washington, D.C. Investigators from around the world discussed basic and clinical aspects of garlic, emphasizing recent research on prevention of cancer and heart disease. Dr. Rivlin was conference co-chair and co-editor when the conference proceedings were submitted for publication as a supplement to a major peer-reviewed journal (Journal of Nutrition). Extensive press coverage was arranged to enable advances in this field to be made available to scientific audiences and to the general public. A number of interviews in the media, which were widely publicized, took place.

National and Local Conferences, Lectures, and Interviews by CNRU Staff. Members of the CNRU are often invited to speak to various professional and general audiences on nutrition and cancer prevention. The New York Presbyterian Hospital Department of Public Affairs has organized a series of lectures to community groups in Manhattan and frequently calls upon CNRU staff to participate. Dr. Rivlin spoke at two community group meetings during this grant year on nutrition and cancer prevention. CNRU staff members are also frequently interviewed by the media. An interview on nutrition and cancer prevention was given by Dr. Rivlin to BottomLine Health, a consumer publication that is widely distributed in the USA and resulted in front-page coverage in their publications. More recently, in December, 2005, Dr. Rivlin was interviewed by the national “Today” Show, NBC Channel 4 in New York to comment on vitamin D and cancer prevention and by MedStar, the medical television series, on meat in relation to nutrition and cancer prevention. In addition, the PI has lectured during this current grant year to a wide audience at the University of Colorado on “Fat, Obesity and Cancer Prevention”. He has been an advisor to Emory University on creating and submitting an application for a CNRU and continues to serve on the External Advisory Committee of the Harvard CNRU, stressing emphasis on nutrition and cancer prevention. At his 50th Reunion from Harvard College, in June, 2005, Dr. Rivlin spoke at a plenary session on “Keeping the Young-Old Healthy” through nutrition. The main message is that in one’s 70’s it is not too late to initiate appropriate prevention strategies for cancer and other chronic diseases. The presentations given at the Reunion are being prepared for submission for formal publication in a major peer-reviewed journal. The publication of these addresses on life expectancy, nutrition, lipids, and homocysteine metabolism in older, healthy adults should greatly increase the impact of the messages for a national and international audience. The AICR in Washington, D.C. organizes very well-attended national conferences for cancer survivors, an increasing population in the U.S.A. who are appropriately concerned with preventing recurrences of their cancers as well as development of new primary malignancies. Dr. Rivlin was a speaker at two of these

AICR conferences during the current grant year, one in Houston, Texas, and the other in Miami, Florida. Together with Dr. Cunningham-Rundles, Dr. Rivlin spoke at the parents meeting of the Brick Church School on nutrition and children's health. At their request, he wrote an article in the publication of the private schools association together with Michelle Loy, postdoctoral fellow, on nutrition and prevention of cancer in children. This article was an expansion of a scientific chapter for the Textbook of Nutrition in Pediatrics prepared earlier by Drs. Rivlin and Cunningham-Rundles, but with the focus here on non-scientific readership.

Some other recent examples of Public Information Activities from CNRU Faculty are listed below.

- Peter Holt, M.D.: Lecture to Medical Staff at St. Luke's-Roosevelt Hospital Center on "Colon Cancer", November, 2005.
- Peter Holt, M.D.: Appeared on Channel 7 ABC News in New York, interviewed regarding Vitamin D and Cancer Prevention, December, 2005.
- Susanna Cunningham-Rundles, Ph.D.: Weill Cornell Medical College Pediatric Grand Rounds: "Nutrition and Immune Response" New York, NY, June, 2005. Grand Rounds is intended to advance medical education for residents and fellows and to provide continuing education for faculty. This meeting is open to the general public.
- Susanna Cunningham-Rundles, Ph.D.: National Institutes of Health, National Cancer Institute, Immunonutrition Workshop: Enhancing Tumoricidal Cell Activity: "Are Botanical Glucans Effective in Enhancing Host Immune Response to Tumor?" Bethesda, M.D., March 2005. The workshop is intended to develop critical thinking on the role of nutrients in modulating immune response to protect against cancer development. The meeting was open to the NIH and the general public.
- Susanna Cunningham-Rundles, Ph.D.: National Institutes of Health, Institute of Medicine, Forum on Microbial Threats: "Role of Probiotics in Modulation of Immune Response". Washington D.C., March 2005.
The Institute of Medicine Board on Global Health and the Forum on Microbial Threats are charged with evaluation of present and future microbial threats and strategies to prevent or contain them for the US. This Forum was focused on the hypothesis that the host signaling pathways regulated by gut microbiota should be studied as these have a major impact on human metabolism and energy storage. The premise is that the evolutionary relationship between humans and their gut needs to be productively shifted to benefit modern humans with access to high calorie diets. The meeting was open to the NIH and the general public.
- Susanna Cunningham-Rundles, Ph.D.: International Life Sciences Institute Health and Environmental Sciences North America Annual Meeting: Session: Nutrition and Gut Physiology "Effect of Development and Aging on Mucosal Immune Response" New Orleans, LA, January, 2005. ILSI is organized to promote scientific programs aimed at public health throughout the world in areas of food safety, nutrition, and the environment. The meeting was open to the general public.
- Susanna Cunningham-Rundles, Ph.D.: International Life Sciences Institute Health and Environmental Sciences Europe: Workshop on Markers to Assess Impact of Nutrition on Immune Function in Man: "Markers of Immune Function" Vienna, Austria, June, 2004. This meeting was designed to discuss biomarkers that can be used to assess the impact of nutrition on human immune response. ILSI is organized to promote scientific programs aimed at public health throughout the world in areas of food safety, nutrition, and the environment. The meeting was open to the general public.

Education Activities/Accomplishments

Medical Student Education in Nutrition. The CNRU introduced the first required courses in nutrition for all year I and year II medical students at Weill Medical College of Cornell University. Nutrition is now firmly established in the Medical School curriculum. In the current curriculum at Weill Medical College, the effort is made to educate future physicians about the importance of nutrition in every medical specialty. As current director of the nutrition curriculum at Weill Medical College, Dr. Jonathan Waitman has attempted to steer the course in the following directions:

- Evidence-based-medicine: The crucial studies in nutrition are reviewed and critiqued during the course of the lectures. Any recommendations are based on the best evidence available. Too often in the past recommendations have been made that seemed logical and reasonable, but were not based on scientific data.
- Case-based-learning: Clinical scenarios are used as tools to keep classes interesting and clinically relevant.

In the first year of study, different types of malnutrition are covered, specifically, marasmus, kwashiorkor, specific vitamin and nutrient deficiencies, and obesity. During year two, nutritional management of specific diseases, including diabetes, hypertension, heart disease, and cancer is discussed. Additional lectures are: “Nutrition Support: Indications and Risks for Enteral and Parenteral Nutrition” and “Bariatric Surgery: Indications, Results and Risks.”

The CNRU offers research and clinical electives to third and fourth year medical students from Weill Medical College of Cornell University and also to students from other medical schools. Research electives are provided in the laboratories of the CNRU investigators and are basic, clinical and translational. Clinical electives are provided at the Comprehensive Weight Control Center (Dr. Aronne and Waitman), Nutrition Support Service for medical and surgical patients, including the Burn Center at New York Presbyterian Hospital (Drs. Bessey and Waitman), and the outpatient experience in nutrition and cancer prevention (Dr. Rivlin).

Students have shown a great deal of interest in nutrition. An examination is given to test knowledge and attitudes. Dr. Waitman was chosen by Weill Medical College of Cornell University as recipient of the Award for Teaching Excellence in June, 2005 “in recognition of outstanding contributions as an educator”.

During this grant year, Drs Rivlin and Cunningham-Rundles submitted an application to NIH for a R25 Training Grant in Nutrition and Cancer Prevention. We expect that this grant, if funded, will greatly enhance the existing education activities in the CNRU and its collaborating institutions.