

# NEAG COMPREHENSIVE CANCER CENTER

# Dialogue

REMARKABLE CARE THROUGH RESEARCH AND EDUCATION



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## Introducing The “Carole and Ray Neag Comprehensive Cancer Center”

By **Christine Kaminski, BGS**, Administrator, Neag Comprehensive Cancer Program



Left to right: President Philip F. Austin, Carole Neag, Ray Neag, Carolyn D. Runowicz, MD, Peter J. Deckers, MD

A longtime UConn benefactor and his wife have donated \$10 million to the UConn Health Center in hopes of making its cancer program one of the nation's elite. Raymond and Carole Neag said their donation, the largest philanthropic donation in the Health Center's history, should allow the Cancer Center to recruit outstanding researchers and physicians and give state residents a cutting-edge cancer research and treatment center. "You've got the Dana Farber Cancer Institute in Boston and [Memorial] Sloan-Kettering Cancer Center in New York. If you live in Connecticut and you want a comprehensive, multi-faceted program, you have to go to one or the other. We thought it would be nice for Connecticut to have one, too," said Neag.

A Torrington native, Mr. Neag is a graduate of the University of Connecticut. He is the retired co-founder and Vice Chairman of Arrow International, Inc., a manufacturer of disposable critical care

and cardiac products. He has been a longtime UConn benefactor. In 1999, he donated \$23 million to UConn, the largest gift to a public university in New England at the time. The bulk of the gift, \$21 million, was earmarked for the University's School of Education, and \$2 million to the Health Center to establish a distinguished chair in vascular biology. The new gift is a sequel: Mr. Neag was inspired by the positive changes his previous donation brought to both campuses.

Dr. Carolyn D. Runowicz, director of the Neag Comprehensive Cancer Center, said the gift is a wonderful step toward making the cancer center one of the nation's elite. "This will help us recruit outstanding physicians and researchers," she said. The money will also be used to renovate labs and clinical space, buy new equipment and expand programs.

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# A Novel and Customized Vaccine Candidate for High Risk Ovarian Cancer

By **Zihai Li, M.D., Ph.D.**, Assistant Professor of Medicine, **John D. Nash, M.D.**, Associate Professor of Gynecology Oncology and **Carolyn D. Runowicz, M.D.**, Professor of Gynecology Oncology, Neag Comprehensive Cancer Center

Ovarian cancer, the fifth leading cause of cancer death, occurs with a lifetime incidence of approximately one in 58 women. It is estimated that approximately 23,300 new cases of ovarian cancer will be diagnosed this year in the United States, and will account for 13,900 deaths. Five-year survival for stage III and IV disease is less than 30%, despite introduction of the most effective combination chemotherapies (1). Although most patients have a good response to frontline therapy, the response is usually transient and most patients relapse with aggressive disease. Therefore, a treatment to prevent disease relapse is urgently needed. Unfortunately, no such treatment exists in the standard of care of this disease.

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We launched a study one year ago to harness the power of the immune system to attack ovarian cancer cells. Specifically targeted are patients with high-risk ovarian cancer (stage III and stage IV disease). The time we chose for immunological intervention is four to six weeks after conventional chemotherapy. It is our belief that immunotherapy might be effective during this time since a majority of patients, after standard chemotherapy, have a relatively low tumor burden and their overall immune system is uncompromised. Vaccination at this time may boost memory anti-tumor response to eradicate residual disease and prevent relapse.

Our vaccines are based on Heat Shock Proteins (HSPs) that are purified from the patients' own tumors. Over the years, our group has discovered, and other scientists have later confirmed, that HSPs can bind a wide array of antigenic peptides, which are unique to the given tumor. We can purify these intact HSP-peptide complexes from tumor cells. Studies have confirmed that immunization of animals with tumor-derived HSPs can generate protective immunity specific to the tumor where HSPs are obtained.

One of the HSPs is called gp96. Tumor-derived gp96 has been tested clinically in a variety of cancers including renal cell carcinoma, pancreatic cancer, melanoma and colorectal cancer, involving more than 500 patients worldwide (2). The vaccine is well tolerated and no unexpected toxicities were observed. Our study is the first clinical trial to test the feasibility and toxicity of HSP gp96 vaccine that is designed specifically for ovarian cancer in a "consolidation" setting. We will also study if the effect of gp96 vaccine is affected by co-injections of granulocyte-macrophage colony stimulating factor (GM-CSF) in this study.

Specifically, eligible patients with stage III or IV ovarian cancer will have their

tumor procured. These tumors have to be freshly frozen without fixative in the Human Trial Laboratory at the University of Connecticut Health Center. Thus, prospective patients must be referred to the Neag Comprehensive Cancer Center as soon as ovarian cancer is suspected. Gp96 vaccine will be purified from these tumors when patients fulfill additional eligibility criteria. All patients will receive standard chemotherapy, administered by the referring physicians. At the completion of the standard chemotherapy, the first 11 patients will receive injections of 25 µg HSP gp96, weekly for eight weeks at the Neag Comprehensive Cancer Center at the UConn Health Center. The second group of 11 patients will receive the same dose of gp96 plus GM-CSF 100 µg, weekly for eight weeks. Patients will be followed for toxicity and safety while receiving the vaccine and for disease-free survival. In addition, the function of the immune system will be analyzed by a variety of tests including study of cytotoxic T cell and natural killer cell, in response to this novel vaccine.

A total of 20 patients have signed consent and their tumors have been procured for the study. Five patients have completed the vaccination phase. So far, all patients have tolerated the vaccine well. The immunological efficacy is now being analyzed. Our ultimate goal is to determine the clinical and immune effects of HSP vaccines, and to pave the way for a large randomized trial in the future to establish the clinical efficacy of our approach for the treatment of high-risk ovarian cancers.

If you have a patient whom you would like to suggest for enrollment in this trial, please call Stephanie Simonich, BSN, at (860) 679-4535.

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# A Comprehensive Plan of Attack Against Colorectal Cancer

By **Chris Heinen, Ph.D**  
Assistant Professor of Medicine  
Neag Comprehensive Cancer Center

I am delighted to be joining the Carole and Ray Neag Comprehensive Cancer Center at a time of great possibility. In addition to receiving the generous donation from Ray and Carole Neag, the Cancer Center is committed to communication and cooperation between basic researchers and clinicians in order to translate new knowledge into patient care. This commitment was a principal reason I joined the cancer center. Not only will this intercommunication drive translational research, but also it will allow the basic researchers to pose better questions derived from issues clinicians face with their patients each day.

My major research focus has been on the molecular biology of colorectal cancer. As a graduate student I trained in the laboratory of Dr. Joanna Groden at the University of Cincinnati. Dr. Groden cloned the adenomatous polyposis coli (APC) tumor suppressor gene; the disease gene identified for familial adenomatous polyposis (FAP) (Grodin et al. 1991). Patients suffering from FAP develop hundreds to thousands of adenomatous polyps in their colon and rectum generally by the third decade of life. If left untreated, one of the adenomas invariably develops into carcinoma. We were interested in learning the function of the normal APC gene product and the pathways that were affected by APC mutation. My thesis work established that APC could regulate the G1/S cell-cycle transition through RB-dependent and independent pathways (Heinen et al. 2002).

As a postdoctoral fellow, I continued studying the molecular biology of colorectal cancer, focusing on the genes mutated in hereditary non-polyposis colon cancer (HNPCC). These genes are all members of the



mismatch repair (MMR) pathway. MMR corrects DNA mismatches and lesions that arise from polymerase errors, exposure to chemical mutagens and in heteroduplex sequences produced during homologous recombination. In addition, the MMR system is required for apoptotic and cell-cycle checkpoint responses to certain types of DNA damaging agents. The first human MMR gene hMSH2 was discovered by Dr. Richard Fishel (Fishel et al. 1993), in whose laboratory I performed my post-doctoral fellowship. In Dr. Fishel's laboratory at Thomas Jefferson University in Philadelphia, I studied the biochemistry of MMR proteins. Utilizing purified human proteins, I examined the effects of missense mutations of hMSH2 associated with HNPCC on normal hMSH2 biochemical functions, such as DNA binding and adenosine-nucleotide processing (Heinen et al. 2002). Although most of these mutants do not completely eliminate hMSH2 function, they result in an inefficient protein with ultimately impaired tumor protection abilities. My current research at the UConn Health Center examines the

consequences of these mutations on hMSH2 cellular functions, including DNA repair, apoptosis and cell-cycle checkpoint signaling. In addition, I will extend these studies to examine a series of cancer-associated mutations in another member of the MMR family hMSH6.

My research in the molecular causes of colorectal cancer will benefit enormously from the program in colorectal cancer established at the cancer center by Drs. Joel Levine and Daniel Rosenberg. Already utilizing the teamwork strategy, the clinicians and scientists involved in this program are currently categorizing information and developing research plans that will study some of the earliest identifiable lesions in the colon called aberrant crypt foci (ACF). Research of ACFs may result in exciting new therapies that could catch potential colorectal tumors in their initial stages. I am thrilled to be joining this exciting project as well as many others that will emerge from this comprehensive approach.

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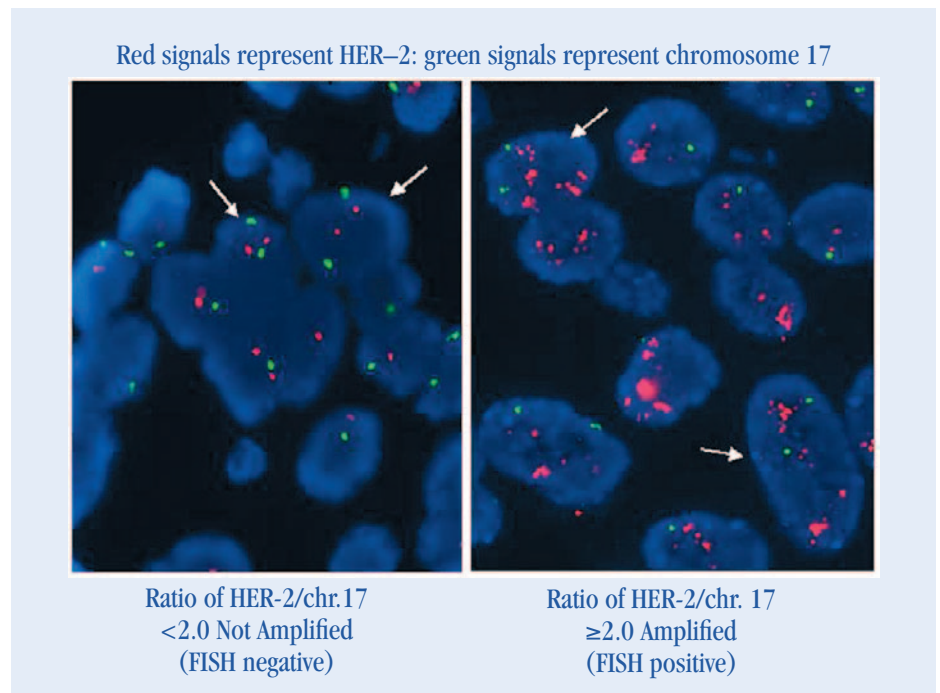
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# HER-2/neu Gene Amplification in Human Breast Cancer—What Does it Mean When IHC and FISH Do Not Agree?

By **Min Fang M.D., Ph.D.**  
Assistant Professor of Genetics and  
Developmental Biology; Director of  
Molecular Diagnostics, Human Genetics  
Laboratories

**H**uman epidermal growth factor receptor 2 (HER-2) gene located on chromosome 17, also known as c-erbB2 and neu, is an important biomarker for breast cancer. The gene codes for a 185 KD transmembrane cell surface receptor that is a member of the tyrosine kinase family. First identified in 1985, it was soon determined that this gene was amplified and overexpressed in certain breast carcinomas (20-30%) and that such overexpression was associated with shortened survival (1). Besides its prognostic value, HER-2 status provides important guidance for therapy. First and most importantly, it helps to determine potential response to Herceptin treatment (Trastuzumab®, a monoclonal antibody to abolish Her-2 protein). The average response rate among HER-2 amplifiers is 20% but close to zero among non-amplifiers. Secondly, it aids in the choice of other therapies. HER-2 amplifiers tend to be resistant to tamoxifen and sensitive to anthracycline-based regimen, and they do not respond to low/medium-dose chemotherapy as well as those non-amplifiers. Therefore, determination of HER-2 overexpression is important both for prognostic and pharmacogenetic purposes.

Assessment of HER-2 gene amplification/overexpression has become the standard of care in the U.S. and can be achieved at both the DNA and the protein level. Fluorescence in situ hybridization (FISH) employs fluorescently labeled DNA probes specific to the HER-2 gene to detect its amplification at the DNA level whereas immunohistochemistry (IHC) applies antibodies specific to the Her2 antigen to detect overexpression at the protein level. Results of FISH



are expressed as a ratio of HER-2 gene copy numbers over chromosome 17 copy numbers and interpreted as positive ( $\geq 2.0$ ) or negative ( $< 2.0$ ) for gene amplification. Results of IHC are expressed as 0, 1+, 2+, or 3+ and generally interpreted as positive (2+ and 3+) and negative (0 and 1+) according to the manufacturer's recommended criteria. Many pathologists would interpret the 2+ cases as negative. That is the current practice at UConn Health Center because the majority of 2+ cases are FISH negative. While comparisons of these two methods have been reported extensively (2), discordance remains in a portion of the breast cancer specimens even when technical and tissue variations are minimized. For example, samples with strong IHC staining show no gene amplification by HER-2/neu FISH (IHC 3+ / FISH negative) whereas specimens with weak or no

IHC staining show positive FISH result for HER-2 gene amplification (IHC 0~2 / FISH positive). Physicians are often left puzzling whether to treat such patients with Herceptin.

Clinical data obtained from our laboratory and others have led to the hypothesis that aneusomy 17 (changes in copy number of chromosome 17, where HER-2 resides) may account for the discordance between IHC and FISH results. A few recent publications support this hypothesis, especially with regard to polysomy 17.

A significant proportion (50~60%) of invasive breast carcinoma displays aneusomy 17, with approximately 35~50% polysomy 17 and 10~20% monosomy 17. Increased copy number of chromosome 17 even in the absence of HER-2 gene amplification (FISH negative) leads to increased copy number of

HER-2 gene, which may in turn result in enhanced Her2 protein expression and strong IHC staining (3+). Therefore, polysomy 17 theoretically explains the discordance between FISH negative and IHC positive cases. Data obtained from Memorial Sloan-Kettering Cancer Center in New York (total 561 cases) and Cedars-Sinai Medical Center in Los Angeles (total 690 cases) support this notion (3, 4). Both laboratories found that polysomy 17 rate was significantly higher in IHC 3+/FISH negative cases than in IHC 0~2+/FISH negative cases. Polysomy 17 rate did not appear to differ among IHC 0 to 2+ groups. These data suggested that polysomy 17 is an important factor in strong IHC staining without HER-2 gene amplification.

On the other hand, little data is available regarding the impact of monosomy 17 on IHC/FISH discordance. Only two cases of monosomy 17 were reported with regard to its association with discordance (FISH positive/IHC negative) (5). Mathematically, even

***“Most importantly, clinical outcome studies are essential to provide perspective for discordance between IHC and FISH results.”***

without increase in the copies of HER-2 gene, reduced copy number of chromosome 17 can result in higher ratio of HER-2/chromosome 17 and hence positive FISH result for HER-2 amplification. The clinical quality assurance program of our laboratory shows a 7.1% discordance rate between IHC and FISH. Among these, 20% were IHC 3+/FISH negative and 80% were IHC 1~2+/FISH positive. The average copy number of chromosome 17 were 2.4 for the former and 1.6 for the latter ( $p=0.001$ ), consistent with the hypothesis that reduced copy number of chromosome 17 (or monosomy 17) could, at least partly, account for discordance in the cases of HER-2 gene amplification by FISH but weak IHC staining. However, our data set is small, and sound conclusions await larger systematic studies.


More importantly, clinical outcome studies are essential to provide perspective for discordance between IHC and FISH results. Among all IHC/FISH discordant cases, how do patients respond to Herceptin monotherapy or combination therapy? With this subset of patients, are there any differences in biological behavior of the tumor, therapeutic response, and survival between the polysomy 17 and monosomy 17 groups? Based on current data, FISH is the most accurate and reproducible test with a better correlation with prognosis and response to therapy (6). Nevertheless, it is advisable based on existing evidence to consider the information of aneusomy 17 when interpreting FISH/IHC results, particularly in cases of discordance.

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# Is There a New Standard of Care in the Treatment of Early Stage Breast Cancer?

By **Agnes Smaradottir, M.D.**,  
Hematology Oncology Fellow and  
**Susan Tannenbaum, M.D.**, Assistant  
Professor of Medicine, Neag  
Comprehensive Cancer Center



*“A new class of anti-estrogen drugs for postmenopausal women has become available.”*

The treatment of early breast cancer has several components. The first is achieving local control with surgery, with or without radiation. The second is to reduce the risk of local and distant relapse. Although chemotherapy is important in helping to achieve this goal, in hormone sensitive breast cancers, hormonal manipulation is paramount in importance.

Tamoxifen (Nolvadex®) is an example of a drug class called selective estrogen receptor modulators (SERMs). They work by competing with estrogen for binding sites on cancer cells. Tamoxifen has been in clinical use for over thirty years and clearly reduces not only local and distant recurrences, but prolongs survival. It has been the standard of care for hormone sensitive breast cancer therapy for some time.

Its position as the drug of choice in this treatment is now being challenged. Recently, a new class of anti-estrogen drugs for *postmenopausal women* has become available. These are called aromatase inhibitors and they block estrogen synthesis from androgens. This occurs in the adrenal gland and fatty tissues in postmenopausal women. Aromatase inhibitors do not sup-

press estrogen synthesis in the ovaries adequately, hence their use is limited to postmenopausal women only.

Recently, three important prospective patient studies utilizing aromatase inhibitors as anti-hormone treatment of postmenopausal women with hormone sensitive cancer have been widely publicized. None of these studies has reached maturity but their results have brought into question which drug or drugs are best in these patients.

The first is the *Arimidex and Tamoxifen: Alone or in Combination (ATAC)* trial which compared tamoxifen to anastrozole (Arimidex®) for five years (1). Five years was chosen since studies with tamoxifen showed that five years of therapy was superior to two or 10 years. This trial continues to show a significant reduction in the number of breast cancer recurrences in women taking anastrozole.

The other two studies focused on treating women with early stage breast cancer with an aromatase inhibitor after treatment with tamoxifen. In the first study women who were treated with tamoxifen for five years received either the aromatase inhibitor letrozole (Femara®) for an additional five years or no further treatment (2). The other trial compared two groups of women; one that was switched to the aromatase inhibitor exemestane (Aromasin®) after two to three years of tamoxifen, compared to a tamoxifen only treated group for total of five years (3). The patients treated with aromatase inhibitors in these studies showed a significant reduction in the development of new breast cancers, local recurrences and distant metastatic disease. Based on this information the National Comprehensive Cancer Network (NCCN), a network of 19 nationally recognized cancer centers, has revised its guidelines to include the aromatase inhibitors as a treatment

option in postmenopausal women with estrogen sensitive early breast cancer (4).

Despite the positive outcomes seen in these trials favoring aromatase inhibitors, important issues need to be discussed with individual patients before choosing appropriate therapy. The aromatase inhibitors are a new class of drugs in which long term effects are not yet known. They are not associated with a risk of blood clots or uterine cancers as is tamoxifen, however aromatase inhibitors increase bone loss in this population of women already susceptible to osteoporosis.

In collaboration with Pamela Taxel, M.D. and the bone metabolism group, we are actively addressing some of these issues at the Health Center. A new study open to postmenopausal women with primary breast cancer who have completed five years of tamoxifen involves the short term effects of letrozole on bone markers and cardiovascular indices. For further information on this study, please contact Faryal Mirza at (860) 679-8139.

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# Low-density Lipoprotein (LDL)-mediated Targeting of Antitumor Agents to Estrogen-responsive Cancer Cells

By **Bruce White, Ph.D.**, Professor of Physiology and **Perry Smith**, Department of Cell Biology

In order to grow and proliferate, cancer cells must synthesize new cell membrane. Consequently, they display an increased demand for lipids, including cholesterol. Cancer cells often meet this demand through elevated expression of membrane proteins which can transfer cholesterol from the blood into the cancer cell. Indeed, this process can remove so much cholesterol from the blood that some cancer patients display abnormally low blood levels of cholesterol (hypcholesterolemia). A predominant protein involved in cholesterol transfer into the cell is the low density lipoprotein receptor (LDL receptor). LDL receptors bind to cholesterol-rich LDL particles that are outside the cell and deliver the LDL particles to the inside of the cell through the complex process of receptor-mediated endocytosis. This increased dependence on LDL receptor-mediated delivery of lipids provides a unique opportunity to attack breast cancer cells using one of the following two mutually-exclusive approaches: 1, targeted delivery of anti-tumor drugs or nucleic acids by complexing them with LDL particles; and 2, disruption of LDL receptor-mediated endocytosis. The first approach has been attempted previously in a small number of studies that have provided promising results [1]. Coupling drugs to LDL particles improved their specific delivery to rapidly growing cancer cells with fewer side-effects on healthy tissues, and LDL-mediated delivery bypasses the mechanisms for drug resistance. However, one problem with this approach is that a considerable degree of variability exists among different breast cancers in their ability to import LDL particles. Thus, not all patients would be expected to respond well to LDL-mediated drug therapy.

Current research has provided new insights into the process of receptor-mediated endocytosis and its regulation by estrogen. One major finding is

that of the role of “adaptor proteins”, which specifically interact with the LDL receptor and are absolutely required for efficient endocytosis of the LDL. We recently showed that the expression of one of these adaptor proteins, termed ezrin, and the LDL receptor itself, are regulated by estrogen [2, 3]. Thus, the ability of breast cancer cells to take up LDL cholesterol is dependent on the levels of both the LDL receptor and specific adaptor proteins, and these proteins may be regulated by estrogen, a hormone which promotes the progression of some breast cancers.

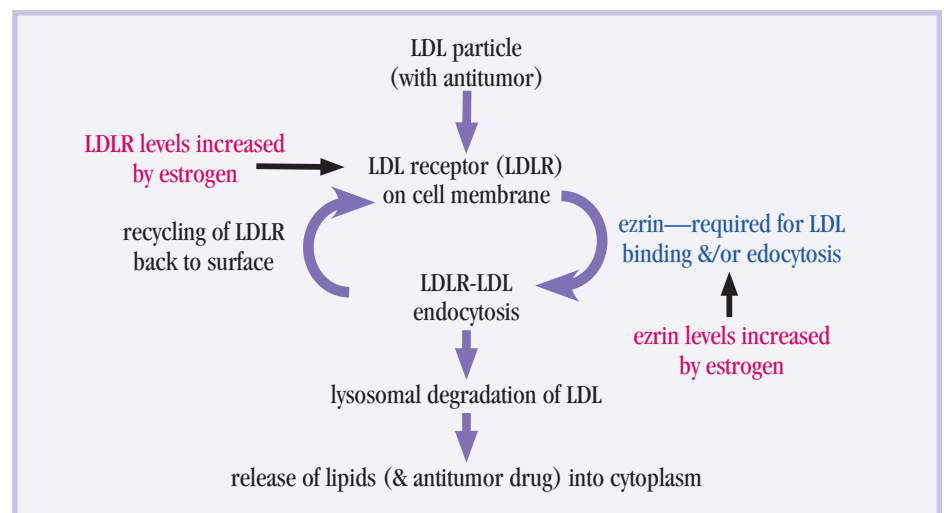
We have recently examined the expression of the LDL receptor in different breast cancers using a commercially-available breast cancer tissue array. We have found that most, but not all, samples of invasive breast carcinoma display high levels of LDL receptor expression. Thus, we are planning to develop a screening procedure for breast cancer cells obtained from patients who are undergoing core biopsy procedures because of suspected breast cancer. By focusing on the expression of the LDL receptor, and the identification of adaptor proteins in breast cancer and their regulation by estrogen, we hope to provide markers which will assist the physician in

predicting how well a particular breast cancer will respond to LDL-mediated targeting of anti-tumor drugs or nucleic acid.

As we examine the nature of LDL receptor adaptor proteins in breast cancer, we will gain a better understanding of a complex process, namely the transport of cholesterol into the cell, which ultimately supports the growth and proliferation of breast cancer cells. These studies will also provide potential targets for future therapies that aim to disrupt LDL receptor function in order to deprive cancer cells of cholesterol.

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## Announcements

### Neag Comprehensive Cancer Center Research Retreat

Members of the Neag Comprehensive Cancer Center will participate in a research retreat October 29-30, 2004. The two day program will highlight current UCHC basic, translational and applied cancer research, and promote expansion of this research by identifying new directions and collaborations. Future issues of the *Dialogue* will feature highlights from this conference.

#### Carolyn D. Runowicz, MD

*Carolyn D. Runowicz, M.D.*, Director of the Carole & Ray Neag Comprehensive Cancer Center, was appointed in June by President George W. Bush to serve as a member of the National Cancer Advisory Board. This board advises and consults with the Secretary of the Department of Health and Human Services and the Director of National Cancer Institute (NCI) with regard to NCI activities, including the review and recommendation of support grants and cooperative agreements. The board consists of 18 members including key representatives from health and science disciplines, as well as leaders in the fields of public policy and environmental carcinogenesis. Dr. Runowicz is also President-Elect of the American Cancer Society.

#### Kristen Zarfos, MD

*Kristen A. Zarfos, M.D.* was awarded the Leonard Tow Humanism In Medicine Award as part of the May 2004 School of Medicine commencement ceremony. This award is given to a student and faculty member who have consistently demonstrated compassion and empathy in the delivery of care to patients, and who have exhibited the highest standard of humanism in medicine.

Dr. Zarfos has received a number of awards for her work in recent years, particularly advocacy. She was a recipient of the Official Citation for Outstanding Dedication, Commitment, and Advocacy for the Women of CT from the State of Connecticut General Assembly. In February 1997, she was a guest speaker with First Lady Hillary Clinton at a White House Media Event on the subject "*The Impact of Outpatient Mastectomies on Women with Breast Cancer.*" She was also introduced and asked to stand by President William Clinton during a televised State of the Union address. In 2003, Dr. Zarfos was recognized by the Connecticut component of the Susan G. Komen Foundation with a public service award.

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### Carole and Ray Neag Comprehensive Cancer Center

She called the donation a beginning and said she hoped it would spur others to contribute.

The Neags' motivation is simple: to improve the lives of Connecticut families today and in years to come. "We have seen firsthand the advances that are occurring daily within the cancer center and understand the tremendous implications for those whose lives are affected by this disease" said Mr. Neag. At a dedication celebration held at the Health Center on Sunday, September 26, the Cancer Center was renamed "*The Carole and Ray Neag Comprehensive Cancer Center.*"

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### Vaccine Candidate...

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