

Cancer Lines

University of North Carolina School of Medicine & UNC Hospitals

Spring 2002



UNC Breast Cancer Program Strives to Translate Molecular Science to Better Clinical Care

Breast cancer is a complicated disease. Diagnosing, preventing and treating breast cancer requires a multidisciplinary program of scientists, clinicians and public health specialists looking at everything from the tiniest molecule to the environment. Much of their work is part of the Specialized Program of Research Excellence (SPORE) in Breast Cancer, one of eight such programs in the nation funded by the National Cancer Institute.

"The breast cancer SPORE integrates public health with clinical and molecular sciences to better investigate etiology, prevention and early detection in breast cancer," says Shelton Earp, Lineberger's director and the SPORE's principal investigator. "It also enables us to develop ways of reducing breast cancer mortality."

Projects within the SPORE fall into three categories: *gene discovery, clinical development and molecular epidemiology*. Earp continues. "Specialists from many disciplines work together to create a comprehensive picture of the disease, including biological, genetic, environmental, social and lifestyle factors."

Here's a look at a few of the many initiatives currently underway as part of the SPORE.

Several Lineberger researchers are looking at novel therapeutic combinations to create more effective treatments (*see related story, below*). "The idea is to take some commonly used drugs that are already available and known to be active in certain tumors and modify their efficacy," explains Bob Orlowski, assistant professor of medicine and Lineberger member.

Orlowski is collaborating with Al Baldwin, professor of biology and Center associate director, to investigate signal transduction pathways involved with apoptosis, or programmed cell death. "Our research is complementary because we're using similar models, but searching for different factors in tumor cell death," Baldwin explains. "Bob's lab is focused on the proteasome as a target, while mine is focused on NF-kB."

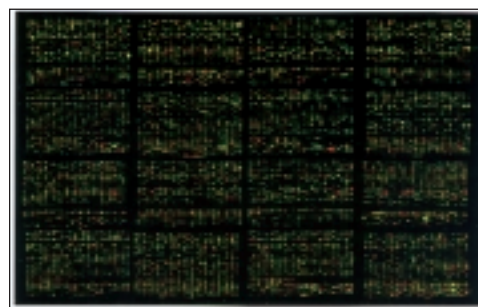
For example, consider drugs like doxorubicin, the active part of Doxil®. It's a very effective chemotherapy for breast cancer. But its performance may be enhanced by PS-341, a drug which blocks other tumor growth and survival pathways including those of the HER-2-NEU oncogene. The teams also are investigating PS-1145, an agent which deactivates NF-kB but doesn't inhibit the proteasome. "In collaboration with Al we are trying to determine if PS-1145 is more effective than PS-

341 in enhancing the killing of cancer cells by chemotherapy drugs," Orlowski notes.

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In the future, UNC SPORE researchers want to tailor treatment to fit each woman's breast cancer. Here's how it might work. A patient, such as Dorothy Joyner (above), and her physician, Dr. Lisa Carey, discuss the approach. Microarray technology creates a molecular profile of the woman's breast cancer (below). Using this profile, the multidisciplinary clinical team recommends the surgical, drug, and/or radiation treatment that works best for that kind of tumor.



Innovative Therapies & Drugs

A key element of the SPORE is clinical development — creating innovative ideas for therapies or drugs used in treating cancer.

New Drug Combinations May Be More Effective Against Some Cancers: Clinical Trial Now Open

"Recent advances in our understanding of both how tumor cells die and how they develop resistance to chemotherapy have opened the door for new combination treatments which may be more effective in treating cancer than existing therapies," according to Claire Dees and Robert Orlowski, assistant professors of medicine in the division of Hematology/Oncology.

Many tumor types today are treated with drugs called anthracyclines (such as doxorubicin or its liposomal form, Doxil®). This class of drugs has many effects on cancer cells. While it primarily kills or deactivates cancer cells, paradox-

ically, some of its action can actually help cancer cells survive. For instance, Doxil® is an active treatment for breast cancer and multiple myeloma tumors, despite the fact that it activates NF-kB, a protein that protects cancer cells from death.

If this tumor-protective mechanism can be counteracted by using an additional therapy, it may be possible to kill even more cancer cells, creating a more effective chemotherapy.

That's why Drs. Dees and Orlowski are undertaking a Phase 1 clinical trial evaluating a combination therapy in patients with solid tumors like breast and ovarian cancer and hematologic malignancies like lymphoma, myeloma, and leu-

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Director's Message



Dr. Shelton Earp

Should women have screening mammograms? Do they save lives? The value of screening mammography is once again under debate, renewed by an article published in the October 20, 2001 issue of

The Lancet, a British medical journal.

The article's Danish authors reviewed seven large randomized studies of screening mammography. They used standards to evaluate these studies—initiated between 1963 and 1982—and concluded that the data could be biased because of flaws in the study design. Not factored into their analysis is that technology and training for radiologists have considerably improved mammography in the years since these studies were completed.

Nonetheless, this group doubts that mammography affects overall death rates. In January the national Physician Data Query Screening and Prevention Editorial Board weighed in on the same side; their analysis of the prior studies also concluded that they did not prove that mammography saved lives. They recommended that the decision to

have a screening mammogram be a personal one, made by a woman and her physician.

However another group of experts, the Preventive Services Task Force, concluded that the best-designed studies do show a 20-30 percent reduction in death from breast cancer. The American Cancer Society, the Susan G. Komen Breast Cancer Foundation, and the National Alliance of Breast Cancer Organizations (NABCO) still advocate the benefits of mammography for women of appropriate age.

What's a woman to do (not to mention her confused physician)?

Breast cancer is a frightening disease, with over 180,000 women newly diagnosed each year. Yet, the good news is death rates from breast cancer are falling and the size of breast cancers being discovered each year in the U.S. is decreasing! I believe these two are related. Mammography coupled with physician or nurse breast exams is the best screening test currently available. But it is not perfect.

What are the drawbacks to mammography? Mammograms miss up to 10 percent of cancers. Mammograms also have a high rate of false positives—results that are reported as abnormal even when no cancer is present. False positives cause needless anxiety for a woman and often other tests to rule out cancer.

Mammograms detect more breast tumors at an earlier stage than any other screening test. Because many breast cancers are relatively slow growing, early detection should help us treat more cancers before they spread. Earlier detection also gives women more treatment options such as lumpectomy. Although we will miss some of the rapidly growing tumors and will do biopsies on a number of women without breast cancer, it is my feeling that the odds are definitely in favor of the woman over 50 who gets regular mammograms.

What we need to do is to develop better screening tests. Digital mammography might help. Here at the UNC Lineberger, Dr. Etta Pisano is leading a national study of 49,500 women to determine if digital mammography is better at detecting tumors than traditional x-ray mammography. Digital mammography allows radiologists to manipulate the breast image, much as you do with a digital camera. This improvement in imaging may reduce the need for repeat mammograms.

We also need to think about applying new and different technology to the breast cancer screening problem. And we need to have better therapy for the tumors mammography misses. Micro-arrays—the work of Dr. Chuck Perou described in the cover story on the SPORE—hold great promise, but until this new research is developed and refined further, mammograms are the best screening test available for women today. ●



UNC Lineberger is designated a comprehensive cancer center by the National Cancer Institute.

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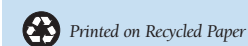
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New Drug Combinations

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kemia. The trial will combine Doxil with PS-341, a proteasome inhibitor that prevents NF-kB activation. The drug is being developed by Millennium Pharmaceuticals, Inc.

“By blocking this pathway with PS-341 there are fewer survival signals in cancer cells, and more of them should die than would be the case with Doxil alone,” Orlowski explains. “In the studies that have been done with PS-341 so far this doesn't seem to be accompanied by an increase in the death of normal cells, since proteasome inhibitors like PS-341 have a much greater effect on cancer cells.”

Targeting the proteasome itself (which is inhibited by PS-341) is a new way to enhance cancer therapy. The modulation of proteasome function appears to increase the sensitivity of cancer cells to some forms of chemotherapy already in use, apparently without significantly increasing toxicity. “These two factors together suggest that combinations like Doxil® and PS-341 have a lot of potential,” Orlowski concludes.

“This clinical trial is a dose-escalation trial in which groups of patients will receive increasing doses of PS-341 in combination with a standard dose of Doxil®. This will determine the side effects of the combination and the maximum safe dose



which can be given,” Dees explains. “We'll monitor patients for toxicity and response, as well as quality of life issues.” For more information please contact the UNC Lineberger Comprehensive Cancer Center Protocol Office (919-966-4432). ●

PS-341 Phase I Clinical trial group. Front (left to right): clinical research associate Henry Bell; study coordinator Melissa Hall. Back row (left to right): Dr. Claire Dees; Dr. Robert Orlowski; study coordinator Beth Hume; post-MD Fellow Dr. Anandhi Johri; Joy Ostroff, director of UNC LCC Protocol Office.

Scrapbook



Survivor Symposium. The Cancer Patient/Family Symposium “Cancer: Keys to Survivorship” was held last fall at the Friday Center. Thanks to sponsors UNC Healthcare, OrthoBiotech, Amgen, Alza Pharmaceuticals, GlaxoSmithKline, TAP Pharmaceuticals, Pharmacia Oncology and Zeta Tau Alpha.

Talks were given on what cancer survivors need to know about health insurance, skills for communicating with healthcare providers and rights as a cancer survivor. The luncheon speaker helped participants to bring more humor into their lives. Breakout sessions were held on nutrition, expressive arts, stress management and alternative therapies.

Symposium organizers pictured here (left to right): Amy Garner, Leukemia and Lymphoma Society, North Carolina chapter; Sharon Cush, program display chair; Nora Beidler, coordinator, Patient/Family Resource Center; Chuck Stone, keynote speaker and cancer survivor; Mary Cleary, Resource Center assistant; Dr. Shelton Earp, UNC Lineberger director.



UNC Lineberger Fellows and Joseph S. Pagano Fellows for Best Research Paper.

Lineberger Fellows are graduate students recognized for their outstanding research. Pagano Best Research Papers Fellows are postdoctoral fellows honored for superlative research papers. (Left to right) Dr. Elizabeth Wilson with Lineberger Fellow Bin He; Lineberger Fellow William Arthur with preceptor Dr. Keith Burrige; Pagano Fellow David Worthylake with preceptor Dr. John Sondek; and Lineberger Fellow Kent Rossman. Not pictured are Lineberger Fellow Deborah Marie John and preceptor Dr. Kevin Weeks and Pagano fellow Denis Guttridge and preceptor Dr. Al Baldwin.

The Lineberger Fellowships are made possible by Board of Visitors' member Mr. Shepard Ansley; Best Distributing Company; Board members Mr. and Mrs. Sanford Doxey, Jr.; Foundation for the Carolinas; Board member Ms. Rochelle T. Grubb; Ms. Elisabeth Lineberger Lyon; Board members Mr. and Mrs. Verner Stanley; and Mr. and Mrs. C.H. Trask. Joseph S. Pagano Awards are made possible by the Burroughs Wellcome Fund.



CCF Presentation. Carolina Cancer Focus, a UNC undergraduate group that raises funds for and awareness of cancer among UNC students presented an award to Dianne Shaw, CCF advisor, and a check for \$1800 to UNC Lineberger at the spring Board of Visitors meeting. Back row (left to right): Michael Abel; Dr. Shelton Earp, Center director; middle row: Robert Albright, CCF fund-raising chair; Arash Jaharian; UNC Provost Robert Shelton. Front row: Dianne Shaw, CCF advisor; Erica Simon, CCF president.



Golf Classic. The 5th Biennial Fountain Odom Golf Classic was held at the Carolina Golf and Country Club in Charlotte. Pictured (left to right): Dr. Shelley Earp, Lineberger director; Frank Sutherland; Norman Cohen; Senator Odom; and Randy Harris. Close to \$80,000 was raised for cancer research. The proceeds will be divided among UNC Lineberger the American Cancer Society and the Blumenthal Cancer Center in Charlotte.

New Endowment Established

The George Jefferson Cancer Education Endowment has been established by his wife, Eileen, to raise funds for educational opportunities (such as attendance at national conferences) for outpatient nurses of the cancer center. The Jefferson family decided to create this fund because of the dedication and care that UNC nurses provided to Mr. Jefferson while he was being treated for leukemia.

To make a contribution, please send tax-deductible contributions to UNC Lineberger Comprehensive Cancer Center CB# 7295, Chapel Hill, NC 27599-7295. Attention: George Jefferson Cancer Education Endowment.

Profile

Working between the worlds of hard science and medical science

Julian Rosenman is a star gazer. “My absolute passion is astronomy,” says the radiation oncologist. “When I retire, I want to be an astronomer — and I’ll work for cheap.”

Until then, however, Rosenman is a professor of radiation oncology at UNC, focusing on the treatment of lung and prostate cancers. “I’m part of a noisy minority that believes the treatment of cancer CAN be partly solved by technological developments.”

It’s a position that’s not exactly conventional. “All cells become resistant to chemical and biological treatments - it’s what they’ve been doing for a billion years. I think this is why we are having such a hard time developing biologic agents that are curative. But they haven’t seen much technology during this time. I go against the current,” he laughs, “and that’s a good place to be.”

Trained in physics, Rosenman didn’t grow up

wanting to be a doctor. Instead, he pursued the stars, earning a PhD in theoretical physics from the University of Texas at Austin. “I was into quantum mechanics and cosmology. Sadly, at graduation I

learned factories weren’t exactly hiring people with this skills set. So I decided on medical school — I had to do something.” Rosenman went to Southwestern Medical School in Dallas, Texas. He did his residency in radiation medicine at the Massachusetts General Hospital in Boston.

His physics background was a good fit for radiation oncology — “It is one of the most technical disciplines of medical science,” he says. He chose cancer because it was a challenging disease. Over the last several decades, he’s pioneered using imaging technology that allows physicians to target tumors correctly. “We can see tumors. And if we know where they are, we can eliminate them with radiation,” he explains.

Rosenman enjoys working between the worlds of hard science and medical science. In fact, it’s why he chose Chapel Hill. “UNC not only had a great medical center, but also a great physics department — so I had to come here. I accidentally walked into a computer laboratory where they were looking at these great 3D pictures created from medical CT scans. It was lust at first sight.” The experience prompted him to begin working on how one can use 3D images for guiding placement



of radiation beams. The result makes radiation treatment more effective and less damaging to healthy tissue.

In addition to the hard science, there’s clinical work with patients. “Not many hard science guys are good at healing, but I enjoy it. I work with patients who’re sick, and we have to make lifestyle choices, not necessarily logical ones,” he explains. “I think I’m pretty good at both. Hopefully my epitaph will say something like ‘He was able to live in both worlds and do each reasonably well.’” ●

Briefs

Genomics Used to Study Toxicological, Environmental Health Problems

UNC researchers were awarded a five-year, \$7 million-plus grant to use DNA microarray technology in studying environmental toxicology questions. The grant is part of a larger \$37 million effort that includes four other academic research organizations, the Toxicogenomics Research Consortium, which will use genomics to study toxicological and environmental health problems.

The UNC team is a collaboration between the School of Medicine’s Lineberger Comprehensive Cancer Center and the School of Public Health’s Center for Environmental Health and Susceptibility, and will focus on susceptibility factors in the genomic response to toxicants.

Dr. William K. Kaufmann, professor of pathology and laboratory medicine, is the principal investigator of the UNC team. The co-principal investigator is Dr. Charles Perou, assistant professor of genetics.

Every cellular injury results from alterations of gene expression and function. Specific toxicants produce specific alterations in gene expression that can be recognized by their pattern. Looking at 20,000 genes produces a very rich pattern. Using microarray techniques, the researchers hope to identify patterns of cellular response that predicts

which class of toxin causes injury. “Lots of things that people are exposed to in everyday life contain mixtures of toxins,” Kaufmann said.

These include things such as car exhaust, air pollution and contaminated water.

Other possible sources of carcinogenic toxins include cooked meat and cigarette smoke. The UNC researchers’ work could help determine which elements of these complex mixtures are dominating the cellular response, Kaufmann said.

UNC Lineberger/North Carolina Central University Partnership Grant Aimed at Reducing Minority Cancer Deaths, Increasing Minority Researchers

North Carolina Central University’s Julius L. Chambers Biomedical/Biotechnology Research Institute and the University of North Carolina at Chapel Hill’s Lineberger Comprehensive Cancer Center received a \$2.5-million five-year partnership grant from the National Cancer Institute to develop collaborative research focusing on reducing the excessive minority cancer rates and deaths in North Carolina and to increase the number of minority scientists engaged in cancer research.

The National Cancer Institute initiated the grants program as a means of developing a stronger national cancer program aimed at uniting NCI-designated cancer centers with research programs at minority-serving institutions. The overall objective is to understand the reasons behind the significant cancer disparities and impact on minority populations.

The partnership will feature both laboratory- and population-based initiatives. Already, a lab at NCCU has been established to conduct molecular studies. NCCU and UNC scientists will embark on a combined program aimed at population studies of the risk of prostate cancer in African-American men. Experts at both universities representing health education, epidemiology nutrition and genetics will be involved.

A major priority will be training NCCU students for careers in biotechnology, particularly in applied genetics and cancer research. The new lab will offer a setting for students to learn leading-edge techniques that will increase their marketability for biotechnology jobs.

“Both UNC-Chapel Hill and NCCU have strong commitments to serving the public,” said Carolina Chancellor James Moeser. “This new partnership examining disparities in cancer rates among minorities is the perfect example of how not only our two universities can gain from sharing resources — both monetary and intellectual — but also how the people of North Carolina and beyond can benefit. I’m very excited by this new collaboration and what it holds for the future of our two campuses.”

What Happens to Cancer Patients Once They’re Diagnosed?

Cancer experts at UNC schools of medicine and public health have been selected to participate in a new \$34 million national study measuring the quality of care cancer patients receive across the United States and how patients do following treatment.

“This project, which is being funded by the National Cancer Institute after a stiff nationwide

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Statewide Cancer Committee's Goal:

Reduce Cancer Incidence & Deaths in North Carolina

Reducing cancer incidence and mortality in North Carolina is the mission of the North Carolina Advisory Committee on Cancer Coordination and Control. The Committee, which was established by the General Assembly in 1993, is charged with recommending to the Secretary of Health and Human Services, a coordinated, comprehensive cancer control plan for the state of North Carolina. Dr. Joseph Pagano, Lineberger Professor of Cancer Research and Director Emeritus of the Lineberger Center, co-chairs the committee.

"We're working to improve prevention, detection and treatment of cancer, as well as enhancing access to quality treatment and support services," Pagano explains. "The key is to get as broad and deep an understanding of cancer in North Carolina as possible. Then we can develop comprehensive programs to serve various regions and populations in our state in the most effective way." Committee members include legislators, physicians, citizens, cancer survivors, public health officers and others.

The flagship project of the Committee is the North Carolina Cancer Control Plan, a five-year plan that's one of the best in the nation. "The U.S. Centers for Disease Control recognized the plan as a model for state-level initiatives," Pagano says. "We're proud of that."

The plan focuses on the early detection, prevention and treatment of cancer, including:

Colon cancer screening. Colorectal cancer affects more than 4,000 North Carolinians each year, with 1,700 dying from the disease. Routine screening via a Fecal Occult Blood Test (FOBT), a simple and effective early detection test that can be taken at home, or physician-performed tests, such as the flexible sigmoidoscopy or colonoscopy, can reduce mortality. Yet use of these tests remains quite low. In 1999, half or fewer of North Carolinians aged 50 years and up had ever gotten an FOBT and only about half of those used it. Fewer

still took advantage of the doctor-performed screenings. The Plan hopes to increase use by addressing economic, racial and other factors when promoting screening. The program will also work with physician practices to make it easier for them to offer in-office tests or refer patients to other sources.



Ribbon Cutting. (Left to right): Dr. Pagano, Lieutenant Governor Beverly Perdue and Senator Fountain Odom enjoy their part in the ribbon cutting ceremony to present the 2001-2006 North Carolina Cancer Control Plan.

Prostate cancer screening. The incidence of prostate cancer is especially high in black North Carolinians, and more black men die of the disease here than almost any other state. The Plan recommends educating men, especially high-risk men such as African-Americans or those with a family history, about their risk for disease and the possible options for chemoprevention, screening and treatment. Educating high-risk men is a key component. A pilot study targeting black men will focus on describing the disease, explaining risk, discussing screenings and reviewing treatment

options. If it's successful, the program will be expanded to determine the effect of improved knowledge, attitudes and screening practices on overall mortality and morbidity.

Tobacco use prevention. Tobacco use, particularly cigarette smoking, is alarmingly high among North Carolina's middle and high school students, compared to the rest of the nation. Studies show that almost 90 percent of adult smokers begin smoking as teens, making a clear case for teen-focused tobacco prevention programs. The Plan will tap into the Teen Empowerment Movement, which enables kids to become actively involved in creating, deploying and evaluating interventions to decrease the number of teens who start smoking. The program will help expand efforts in local schools and communities, and address racial and ethnic groups most affected by tobacco use. Another initiative addresses environmental tobacco smoke (ETS), which causes 1,500 deaths in North Carolina each year. The Plan focuses mainly on community level policies to reduce or prevent exposure in public places such as schools, restaurants and offices.

NC Central Cancer Registry. Another important component of the Plan is the NC Central Cancer Registry, which can help identify high- and low-risk populations, disparities in care and geographical and racial differences in occurrence. The registry helps researchers and public health officials to understand the dimensions of cancer in the state versus nationally. They can then use the data to target their research and activities to specific groups and regions in need. North Carolina has one of the best state cancer registries in the country.

"These initiatives all work together to provide an in-depth look at cancer in North Carolina," Pagano says. "This benefits researchers, public health officials and citizens alike." ●

clinical trials

For information about these and other clinical trials, call 919-966-4432 or visit the UNC LCCC website at <http://cancer.med.unc.edu> under "Patient Resources."

underway

Non Small Cell Lung Cancer IIIB or IV (CA163-011). This is a Phase II trial of a novel agent, BMS-247550, determining the efficacy and safety in patients who have previously failed one prior chemotherapy treatment using a platinum based chemotherapy agent. Patients are randomized to receive BMS-247550 as either a three-hour infusion every 21 days or as a one-hour infusion daily for five consecutive days (Day 1-5) every 21 days. PI, Mark Socinski, MD

Liver Cancer. Unresectable Hepatocellular Carcinoma-Liver Cancer (MTC-DOX-004). This is a Phase II trial which uses Magnetic Targeted Carriers (MTC). These carriers com-

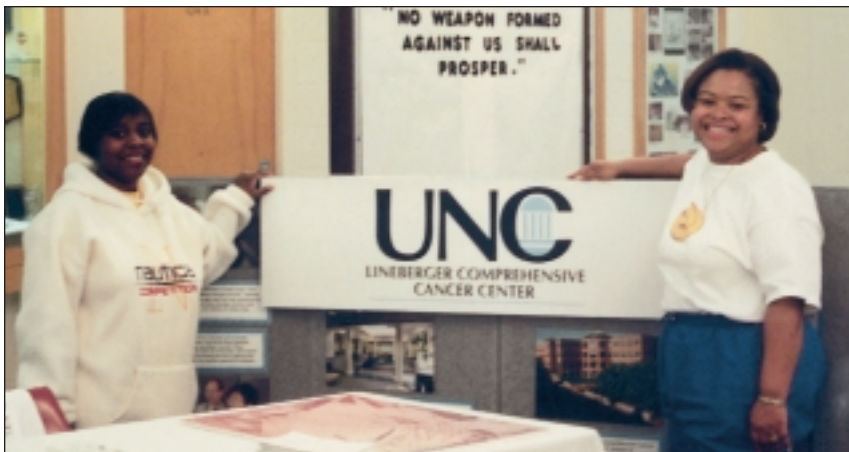
bine elemental iron and activated carbon that can absorb chemotherapy drugs like doxorubicin (DOX). The elemental iron component allows the complex to be targeted within a specific organ like the liver. The MTC-DOX is infused directly into the hepatic artery. During the infusion, an external magnet is placed indirectly over the tumor and used to draw the MTC-DOX out of the circulation and into the tumor. PI, Bert O'Neil, MD

Prostate Cancer. Hormone-Refractory Prostate Cancer (MOO-244). This is a Phase III multi-center trial evaluating the safety and efficacy of an oral novel agent as compared to placebo in the treatment of patients diagnosed

with non-metastatic, hormone-refractory prostate cancer. This is a daily oral medication. Patients are re-evaluated every 12 weeks. PI, James Mohler, MD

Locally Advanced Prostate Cancer (LCCC 0103). This is an investigator initiated trial evaluating the safety and efficacy of three chemotherapy agents; docetaxel, estramustine, and carboplatin administered orally and intravenously to patients prior to local therapy with radiation or surgery. This combination of drugs is repeated every 4 weeks for a total of 3 cycles. PI, Paul Godley, MD

Lineberger



NCCU Walk for the Cure. North Carolina Central University held its annual Walk for the Cure. UNC Lineberger's breast cancer program was one of the recipients. Over \$900 was raised. *Shown (left to right):* Melissa Stroud, UNC Lineberger program assistant and Sonya Scott, NCCU Walk organizer.



Coalition Visit. Members from the Prostate Cancer Coalition of North Carolina visited UNC Lineberger to learn about UNC's urologic cancer program. Physician talks, a presentation by Bob Anderson, Coalition director, lunch and a tour were all part of the day.



Pink Carolina.

(Left to right) Susan Rafte, Missy Julian-Fox and Dr. David Ollila worked to bring the Pink Ribbons Project to North Carolina. Showcasing nationally prominent dancers and local talent, Pink Carolina, a dance benefit this fall at Durham's

Carolina Theatre, raised more than \$70,000 in funding needed for breast cancer advocacy, education and research in North Carolina. UNC Lineberger is using the funds to raise awareness and provide free breast cancer screenings for low-income women in North Carolina through the NC Breast Cancer Screening Program. Pink Carolina proceeds are also used to support the center's Sentinel Lymph Node Program, which ensures state-of-the-art surgery as an option for women who need it but cannot afford it. Not pictured is Beth Seyda, who helped make the event possible.



Zeta Tau Alpha 5K.

Zeta Tau Alpha Sorority held its annual Franklin 5K. UNC Lineberger is one of the recipients of race proceeds. *(Left to right)* are: Jennifer Delk, 5K publicity chair; Anna Nisbet, sorority vice president and 5K party chair; and Dr. Shelley Earp, UNC Lineberger director.

Briefs

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competition, will involve UNC and five other U.S. medical centers as study sites," said Dr. Robert S. Sandler, co-director of UNC's Center for Gastrointestinal Biology and Disease and a member of the Lineberger Comprehensive Cancer Center. "We'll follow 1,000 newly diagnosed colon cancer patients for five years, and the others will follow more than 9,000 other patients with either lung or colon cancer."

Collaborating centers will collect identical information about what happens to patients and pool the data to make it more useful, he said. They also will pursue special projects of their own design. At the UNC site, researchers also will look specifically at "functional health literacy" — how people's literacy affects their health.

"Our hypothesis is that people who can't read and can't understand written information given to them by physicians or hospitals might not be able to negotiate the medical system and not do as well," Sandler said. UNC investigators also will collect blood samples and tumor tissue from

patients to learn if biological factors influence how patients fare, he said.

First results of the study are expected to appear in five years, Sandler said. "We'll learn quite a lot from this study, including whether being poor, living in rural areas or being a minority affects how patients do with either of these two important cancers," Sandler said. "Of special interest to us will be patients' survival and quality of life. We believe our pooled results eventually could improve both."

Growth Factor Receptor Signaling Critical to Intestinal Tumor Development

Scientists at UNC Lineberger and Vanderbilt University say they have uncovered a major clue to what causes and promotes development of intestinal tumors.

Working with laboratory mice, the researchers found that a molecule called epidermal growth factor receptor (Egfr) is necessary for most intestinal tumors to form. Their work also suggests that a drug or genetic manipulation that inhibits the receptor's chemical signaling machinery should help treat

advanced colorectal cancers in humans one day.

A report on the findings appeared in the January 29 edition of the *Proceedings of the National Academy of Sciences*. Authors include UNC doctoral student Reade B. Roberts and Dr. David W. Threadgill, assistant professor of genetics and Lineberger member and Dr. Robert J. Coffey, a cell biologist at Vanderbilt.

"The Egfr receptor is very important to all kinds of tissues and organs, but there hasn't been any genetic proof in whole animals that it could affect a major cancer like colon cancer," Roberts said. "We think this work represents proof because it relied on genetic experiments that were highly controlled compared with just injecting mice with drugs and hoping that they would affect the receptor."

"How well our results in mice wind up correlating with human treatment remains to be seen, but at this point we're excited about the possibilities."

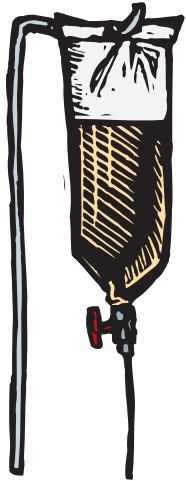
Several clinical trials of drugs that block Egfr signaling already have begun, Roberts said. Results from two previous mouse studies of compounds targeting the molecule have been contradictory, probably because the drugs used were not precise enough in their action. ●

Breast Cancer

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“These combinations would be very helpful, since a more specific drug that doesn’t act on other targets may have even fewer side effects,” he continues, “allowing these combinations to be more effective and better tolerated by patients.”

Another innovative therapy is being refined by Dr. Jon Serody, associate professor of medicine,



microbiology and immunology. Three years ago, he and a team of scientists and physicians developed a vaccine to treat breast cancer that had spread. The breast-cancer vaccine wasn’t a shot; instead it was an intravenous infusion of a patient’s genetically engineered protein in fragments linked to a group of the patients’ own immune cells called dendritic cells. It is intended to enhance the patient’s own immune response against their tumor.

Using results from this early trial in a small number of patients, the team is now refining the vaccine and hopes to begin a second trial in the next 12-18 months.

Still another innovation is a study involving neoadjuvant chemotherapy, or chemotherapy given before surgery. The traditional model has been surgery followed by either chemotherapy or radiation. Neoadjuvant therapy can shrink tumor size so that less surgery is needed. Dr. Lisa Carey, assistant professor of medicine, is leading this study called the *Correlation of Molecular Markers With Response to Neoadjuvant Chemotherapy*. Investigators hope that the results of this study will allow breast cancer patients to receive less, but more effective chemotherapy.

“We are looking at whether or not we can identify which cancer cells in a tumor are sensitive to certain types of chemotherapy. We do this by obtaining tissue samples before and after surgery to help determine which cancers respond to which chemos. We’re looking at several



tumor markers, including microarrays. If we can identify ahead of time which drugs a particular cancer is sensitive to, it will allow us to tailor the therapy to the individual patient in a way we cannot do now.”

Tumor Treatment & Gene Discovery

Molecular markers of breast cancer can be used for early diagnosis and treatment of the disease. Chuck Perou, assistant professor of genetics, uses DNA microarrays (see sidebar) to quickly analyze thousands of genes expressed in these breast tumors.

“By looking at overall breast cancer gene expression, we can determine which genes are produced in certain tumors, identify distinct subtypes and define new prognostic and predictive markers for breast cancer patient outcomes and responses to therapy.” Perou and his colleagues have identified biologically and clinically relevant breast tumor subtypes by assaying 150 human breast tumors using DNA microarrays containing at least 8000 different human genes.

“This database will be used to further refine our breast tumor classifications and to search for correlations between gene expression patterns and responses to chemotherapy.” In addition, Perou will perform microarrays on the 120 breast cancer patients participating in Dr. Carey’s neoadjuvant chemotherapy study.

“Instead of treating all breast tumors the same way, these findings will help us develop chemo- and radiation therapies based on the unique properties of specific tumor subtypes,” Perou explains.

“That will result in better patient care and outcomes.”

Environmental & Behavioral Factors

“About half of the lay public believes environmental factors cause breast cancer,” notes Marilie Gammon, associate professor of epidemiology. “The medical community is skeptical because no one has documented the association. At UNC, we have two of the largest population-based breast cancer studies; these will enable us to truly investi-

gate this issue.”

Gammon is the principal investigator for the Long Island Breast Cancer Study that looks at the impact of the environment on genes and cancer in 1,100 breast cancer patients. “We suspect the varying levels of breast cancer risk might have something to do with how individuals metabolize and respond to various environmental factors,” she says.

Another project, The Carolina Breast Cancer Study (CBCS), is helping identify environmental, behavioral and genetic factors that influence breast cancer development. Led by Bob Millikan, associate professor of epidemiology, it includes 2,314 cases and 2,024 controls. “Our study is one of the first to treat breast cancer not as a single entity, but to consider subtypes defined on the basis of genetic changes acquired in breast tissue as tumors develop. The particular patterns of mutations may help to uncover causes of breast cancer.”



The hope is that because tailored treatment works better than standard treatment, the patient returns to life with her family. Here Lillie Atwater is shown with her daughters Jo Atwater (left) and Donna Farrow (right) as she is being honored as Local Hero during the Drive for the Cure.

Data from the CBCS are being used for the Estrogen Receptor Alterations in Breast Cancer Development study led by Kathy Conway-Dorsey, research assistant professor of epidemiology. Estrogen plays an important role in the development of breast cancer, since most of main risk factors for breast cancer are related to hormonal or reproductive characteristics. Estrogen’s biological effects are mediated primarily through two estrogen receptors (ER) in the breast. “Our goal is to more clearly understand the role of both estrogen receptors in breast cancer, together with factors influencing estrogen exposure.”

These studies may lead to better diagnosis, prevention and treatment of breast cancer in the future, but they have near-term benefit, as well. “The most immediate impact of these studies will be to widen the scope of research into the causes of breast cancer,” Millikan notes.

Far-Reaching Impact

“Since 1992, when the SPORE was initially funded, the Lineberger Center has become one of the nation’s leading institutions for integrated breast cancer research,” Earp notes. “The opportunities and new ideas emerging from our SPORE, which mix behavioral, epidemiologic, molecular and clinical scientists—are truly remarkable. This intellectual melting pot will make a difference.” ●

Microarray Technology: How It Works

Though most cells in our bodies contain the same genes, not all of the genes are used in each cell. Some genes are turned on, or “expressed” when needed. Many genes are used to specify features unique to each type of cell.

Microarray technology now allows us to look at many genes at once and determine which are expressed in a particular cell type. DNA molecules representing many genes are placed in discrete spots on a microscope slide. This is called a microarray. Thousands of individual genes can be spotted on a single square

inch slide (see picture on front page)! RNA molecules that indicate which genes are being used in these cells are then “labeled” by attaching a fluorescent dye that allows us to see them under a microscope. The labeled RNA will stick to its own DNA gene spot on the microarray. After washing away all of the unstuck RNA, we can use the special microscopes to detect the stuck RNA. Since we know which gene each spot represents, and the RNA only sticks to the gene that encoded it, we can determine which genes are turned on in the

cells. UNC is using this powerful technology to learn which genes are turned on or off in diseased versus healthy human tissues. The genes that are expressed differently in the two tissues may be involved in causing the disease.

With this technology we can screen individuals for susceptibility to specific diseases based on their gene expression pattern. We will also be able to define people’s diseases to better classify treatment options for an individual patient and predict how s/he will respond.

A Wish Come True

Four-year-old Micaela Ward from Chadbourne, NC, was admitted to UNC Hospitals last April. During her stay, she was diagnosed with leukemia. At the same time back home, her dog was stolen out of her backyard. During a subsequent stay at UNC, she was visited by the volunteer pet therapist, Barb Hurlbutt, and her Great White Pyrenees dog named Bear. Micaela fell in love with Bear. Her physician, Dr. Stuart Gold, saw how Micaela bonded with Bear and decided to find Micaela a dog of her own.

He called breeders across the country and talked with Melanie Nadeau, a breeder in Farmington, Maine. Ms. Nadeau coincidentally had a three-year-old, therapeutically trained Great White Pyrenees being returned to her by a couple going into a nursing home. After talking with Dr. Gold, she decided to give the dog to Micaela. But, the dog was in Maine and the child was in Chadbourne.

Dr. Gold then called airlines, freight and truck-

ing companies, but to no avail. He then called a colleague at the Hole in the Wall Gang camp, a camp started by Paul Newman for children with life threatening illnesses, who then emailed Phi Kappa Tau fraternity, the fraternity of which Paul Newman is a member and chapters that work closely with the camp. Several chapters volunteered, and a dog relay was set. On December 21, the first of

the nine-man, five-car relay team set off. These young men were sacrificing their semester break to meet fraternity brothers they did not know to make the delivery possible.

At 3:30 on December 23, Micaela's dream came true. Melanie arrived. Strong bonds have developed between Melanie and the Ward family: Parents Vicki and Richard, Micaela, her older brother Charlton,

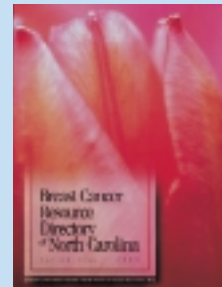
13; younger sister, Elizabeth, 20 months. Melanie goes around to each child's bed at night to check on them. She sleeps in Micaela's room, and if Micaela stirs during the night, Melanie will come and put her head on the bed to comfort Micaela.

A few weeks ago, Melanie the breeder, drove down from Maine to deliver two puppies to Dr. Gold and to visit with the Ward family.

Micaela, with her family's and Dr. Gold's care and Melanie's affection, is doing well. ●



Left to right: Micaela Ward; Matt McCuen, Phi Kappa Tau Fraternity member; Dr. Stuart Gold, Richard Ward (Micaela's father). In front: Melanie, the Great White Pyrenees.



Breast Cancer Resource Directory

The *Breast Cancer Resource Directory* is a joint project of the breast Cancer Coalition of North Carolina and UNC Lineberger Com-

prehensive Cancer Center. It is the first comprehensive local resource for women in North Carolina who need information about breast cancer diagnosis, treatment and support. The 264-page print directory is free of charge upon request at 800-514-4860. The online directory can be accessed at <http://bcresources.med.unc.edu/>.

The Resource Directory contains comprehensive, county-by-county listings of support groups, suppliers of breast cancer products, and hospitals and cancer centers. It provides information and resources about diagnosis and treatment decisions, managing side effects and post-treatment issues, clinical trials, genetics, complementary therapy and end-of-life issues. With every topic covered, there's always a list of phone numbers, Web sites, addresses and publications.

Major contributors and sponsors of the Directory include: the NC Triangle Affiliate of the Susan G. Komen Breast Cancer Foundation, U.S. Women's Open Wellness Fund (2001), Rex Healthcare Foundation, the Breast Cancer Fund, Breast Cancer Coalition of North Carolina, GlaxoSmithKline Oncology, American Cancer Society, Catawba Memorial Hospital, Comprehensive Cancer Center of Wake Forest University, Duke Comprehensive Cancer Center, Leo W. Jenkins Cancer Center, UNC Health Care, Genentech and Raleigh Community Hospital/ Duke Hematology/Oncology Clinic.

calendar of events

JUNE

5th Susan G. Komen Breast Cancer Foundation NC Triangle Race for the Cure. Raleigh, NC.

26-30th North Carolina Hunter Jumper Association Horse Show to benefit UNC Pediatric Hematology-Oncology. James B. Hunt Horse Complex, Raleigh, NC.

SEPTEMBER

13th Board of Visitors Meeting. Lineberger Cancer Center, Chapel Hill, NC.

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