

News

Free Radical Scavenger Protects Heart from Adriamycin Toxicity

A potent chemotherapy that is highly effective in treating the most common form of childhood leukemia can significantly harm the heart, but findings from a multi-center study led by Dana-Farber Cancer Institute researchers suggest that adding an experimental drug to the therapy can reduce or prevent the damage.

If longer-term studies confirm the results, it would be the first strategy proven to reduce the heart problems that some acute lymphoblastic leukemia (ALL) survivors develop years after being treated with doxorubicin (Adriamycin). The study appears in the July 8 issue of the *New England Journal of Medicine*.

"These findings demonstrate that it is possible to decrease some of the chemotherapy's toxic effects on the heart," explains Stephen E. Sallan, M.D., senior author of the paper and chief of staff at Dana-Farber.

The use of doxorubicin in children with ALL makes it a highly curable disease, but because the chemotherapy kills heart muscle cells as a side effect, survivors can experience an improperly beating left ventricle, congestive heart failure, or arrhythmias that can cause sudden death. One study estimated that, even 25 years after they were treated, their risk of dying from heart disease is more than eight times normal.

More than 200 children under 18 who had newly diagnosed ALL that was considered high-risk—more life threatening than average—between 1996 and 2000 were invited to participate in the multi-center study. One group (101 participants) was treated with doxorubicin alone—the standard therapy. The other (105 participants) received doxorubicin and dexrazoxane (Zinecard), an experimental drug manufactured by Pfizer, Inc. that has shown to be cardioprotective in adults receiving chemotherapy.

Studies have shown that doxorubicin injures the heart muscle when it is metabolized. As the body breaks down the drug, "free radicals"—chemicals that are toxic to heart cells—are produced. Dexrazoxane, conversely, is a "free radical scavenger" that mops up the harmful substances and reduces the muscle damage.

For a preliminary assessment, the scientists compared blood levels of troponin T, a protein that is elevated when the heart had been injured. This test can detect heart damage before it can be seen with echocardiograms.

Fifty percent of the children in the doxorubicin-alone group had elevated troponin T, compared with 21 percent of those who also received dexrazoxane. Extremely elevated troponin levels—indicating more severe heart

muscle injury—occurred in 32 percent of the doxorubicin-only patients, but in just 10 percent of those who received the protective drug.

Importantly, the study also found that adding the dexrazoxane did not reduce the doxorubicin's ability to cure the children.

"This isn't a perfect solution but it is promising," cautioned Sallan, who is also a pediatric oncologist at Dana-Farber and a professor of pediatrics at Harvard Medical School. "We reduced the incidence of heart damage from 50 percent to about 25 percent with dexrazoxane, but there is some damage." Lead author of the report is Steven E. Lipshultz, M.D., Chairman of the Department of Pediatrics, University of Miami School of Medicine and Chief of Staff of the Holtz Children's Hospital.

The research was supported in part by the National Institutes of Health, Pharmacia-Upjohn, and Roche Diagnostics.

Radiolabeled J591 Antibody Delivers Lethal Hit to Advanced Prostate Cancers in a Phase I Trial

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Researchers at NewYork-Presbyterian Hospital/Weill Cornell Medical Center have released final findings of a Phase I trial of an investigational drug, radiolabeled J591, in patients with advanced prostate cancer. J591 is a de-immunized monoclonal antibody therapeutic that was developed at Weill Cornell Medical College. In this trial, published in the July 1 issue of *Journal of Clinical Oncology*, the antibody delivered radiation directly to prostate cancer sites. The treatment was well tolerated and demonstrated anti-tumor activity.

As a result of these promising findings, a Phase II protocol designed to evaluate anti-tumor activity of radiolabeled J591 has been accepted by the Food and Drug Administration and is expected to begin patient entry later this year. This multi-center trial will be led by NewYork-Presbyterian/Weill Cornell along with NewYork-Presbyterian/Columbia and Memorial Sloan-Kettering Cancer Center.

J591 works by targeting a molecule called prostate specific membrane antigen (PSMA), a protein located on the surface of all prostate cancer cells. PSMA expression is minimal in normal prostate tissue and is greatly increased in prostate cancer. In this trial, J591 was labeled with—or carried—a radioactive isotope. The goal of this targeted therapeutic approach is to use J591 to selectively deliver radiation to the tumor cells, thereby minimizing exposure of radiation to normal cells.

Prostate cancer is the third most common cause of cancer deaths in men. Once cancer cells escape the prostate, the current standard of care is hormonal treatment. Hormonal therapy causes side effects—including hot flashes, sweats, weight gain, muscle wasting, thinning of the bone, fatigue, weakness, and anemia. Furthermore, hormonal therapy is palliative and not curative; all patients ultimately become refractory to its effects.

"Early results with J591 suggest that it is a promising new approach that could fill a substantial, unmet medical need," said lead study investigator Neil H. Bander, M.D., the Bernard and Josephine Chaus Professor of Urologic Oncology at Weill Cornell Medical College, and Director of Urologic Oncology and Attending Urologist at NewYork-Presbyterian/Weill Cornell. "We are encouraged to continue studies to assess the optimal dose, schedule, and duration of therapy so that the role of this targeted compound in the treatment of prostate cancer can be determined."

STUDY FINDINGS

The published clinical trial evaluated the effects of the radioisotope ⁹⁰Y (Yttrium) attached to J591. The study included 29 patients whose prostate cancer had spread throughout the body and whose disease was progressing despite both hormonal treatment and, in almost 40% of cases,



Stephen E. Sallan, M.D.



Steven E. Lipshultz, M.D.

chemotherapy. In this Phase I study, the dose of isotope attached to J591 was progressively increased in groups of patients in order to determine the maximum tolerated dose. The radiolabeled antibody was found to be well tolerated by the patients; blood tests revealed an expected drop in platelet and white blood cell counts that spontaneously returned to or near normal. The maximum tolerated dose of the radiolabeled antibody was determined in this clinical trial.

Although this was a Phase I trial, designed primarily to define dose and toxicity rather than anti-tumor response, J591 demonstrated anti-tumor activity. Radiolabeled J591 reduced prostate specific antigen (PSA) levels by as much as 85% and measurable tumor lesions by 90% for periods of up to and beyond eight months. PSA is a protein produced by prostate cells that can be detected in the blood. In prostate cancer patients, changes in PSA levels generally reflect whether a prostate cancer is worsening or improving. Several previous clinical trial publications have indicated that treatment-related PSA declines of greater than 50% correlate with improved survival.

In addition to Dr. Bander, collaborating authors on the study included Drs. Matthew I. Milowsky (first author), David M. Nanus, Lale Kostakoglu, Shankar Vallabhajosula, and Stanley J. Goldsmith—all of NewYork-Presbyterian/Weill Cornell.

The study was funded by the NIH General Clinical Research Center Program; the Cancer Research Institute; the David H. Koch Foundation; the Peter Sacerdote Foundation; the Robert H. McCooney Memorial Cancer Research Fund; BZL Biologics, Inc.; and Millennium Pharmaceuticals, Inc.

About Prostate Cancer

According to the National Cancer Institute, there are approximately 1.7 million men living in the U.S. with a diagnosis of prostate cancer. To this number, approximately 230,000 new cases of prostate cancer will be diagnosed, and 29,900 men will die of the disease this year in the United States. The five-year survival rate of men with prostate cancer is 89%, with this percentage jumping to 100% if the cancer is found before it metastasizes (spreads to another area of the body). Today, there is a tremendous, unmet medical need for treating the disease, particularly for end-stage or hormone-refractory prostate cancer. Early detection is important, and the American Cancer Society recommends that men over the age of 50 have a PSA blood test every year. Coupled with a digital rectal exam (DRE), the PSA is a very useful test for determining which men need further evaluation.

ABOUT J591 DEVELOPMENT PLANS

The monoclonal antibody J591 was developed in the laboratory of Dr. Neil Bander at Weill Cornell Medical College and licensed to BZL Biologics, Inc. Dr. Bander serves as a consultant to BZL Biologics, Inc. In April 2001, Millennium Pharmaceuticals, Inc. (NASDAQ: MLNM) entered into an agreement with BZL Biologics, L.L.C., for the joint development and commercialization of antibody-based therapeutics targeting PSMA, including both chemotherapeutic agent conjugated and radiolabeled products. These products include MLN2704 and J591RL. Millennium currently has exclusive development and worldwide marketing rights to these products.

Oral BMS-354825 Rescues Gleevec-Resistant CML

For more information contact: Kim Irwin; Director, Media Relations; UCLA's Jonsson Cancer Center; Tel.: 310.206.2805

An experimental therapy that may battle resistance to the drug Gleevec in patients with chronic myeloid leukemia (CML) has shown promising results in a study at UCLA's Jonsson Cancer center, increasing survival in animal models and perhaps paving the way for a second generation targeted therapy.

The results of the study appear in the July 16, 2004 issue of the peer-reviewed journal *Science*, published by the American Association for the Advancement of Science, the world's largest general scientific organization.



Neil Shah, M.D., Ph.D.



Charles Sawyer, M.D.

Early phase human studies of the experimental therapy, taken in pill form like Gleevec, already are underway at the Jonsson Cancer Center in patients who have developed a resistance to Gleevec.

About 15 to 20 percent of CML patients who take Gleevec become resistant to the drug and suffer a relapse, leaving them with few effective treatment options, said Dr. Neil Shah, an oncologist and researcher, an assistant professor of hematology/oncology and the study's first author. In patients with resistant disease, secondary mutations in the gene linked to CML allow the cancer to evade therapy. It is those mutations that are targeted by the new compound, BMS-354825, being developed by Bristol-Myers Squibb.

"Learning from what happens when a drug fails in some patients can lead to a new treatment paradigm," Shah said. "In the future, we may be combining therapies that can, amongst them, override all the resistance mechanisms that allow cancer to evade individual therapies. In the future, cancer may be treated similarly to HIV, with a cocktail of drugs."

Gleevec targets a mutant cancer-causing protein linked to CML, which each year strikes more than 10,000 adults worldwide. Specifically, Gleevec is a tyrosine kinase inhibitor, one of a new class of drugs that can interfere with cell signaling pathways implicated in tumor development. Much of the pioneering work done to link the gene and its mutant protein to CML was performed at UCLA's Jonsson Cancer Center.

In some patients, secondary mutations in the CML-linked gene arise that prevent Gleevec from binding to its intended target. These mutations, because they then operate unchecked, cause the leukemia to recur.

Dr. Charles Sawyers, a professor of hematology/oncology, an investigator with the Howard Hughes Medical Institute and the senior author of the study, said this work could represent a major advance for the patients who suffer a relapse on Gleevec.

"Gleevec remains a spectacular step forward in the application of targeted therapy to CML specifically, and serves as a model for how to do this more generally in cancer," Sawyers said. "However, some CML patients develop resistance to Gleevec after several years of therapy. Structural modeling studies predicted that other inhibitors that bind to the target protein differently from Gleevec should work against these mutants. This paper reports the effectiveness of such an inhibitor in Gleevec resistant cells in tissue culture and in mice."

Shah and Sawyers are hopeful that the experimental inhibitor will prove effective in human patients as well. Future studies may eventually pair Gleevec with this new inhibitor, if it proves to be safe and effective in clinical trials.

"We hope this represents another viable treatment option for patients with this disease," Shah said. "There may now be hope beyond Gleevec should their disease relapse."

Shah said the drug also may be useful for treating other diseases that respond to Gleevec initially, such as gastrointestinal stromal tumors.

The research, conducted at UCLA's Jonsson Cancer Center, was funded in part by the Howard Hughes Medical Institute and the Leukemia and Lymphoma Society of America.

Simon Powell Moving to Head Radiation Oncology at Washington University

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Simon Powell, M.D., Ph.D., a cancer physician-scientist from Massachusetts General Hospital and Harvard University, has been appointed head of the Department of Radiation Oncology at Washington University School of Medicine in St. Louis.

"Simon is a talented research scientist who has done much to uncover the molecular mechanisms that allow normal tissues and cancer cells to repair their DNA after exposure to ionizing radiation," says Larry J. Shapiro, M.D., dean of the School of Medicine and executive vice chancellor for medical affairs. "He possesses the leadership skills and vision to move our Department of Radiation Oncology forward in a continued effort to achieve excellence in all of its missions."

Powell is a leader in research into BRCA1 and BRCA2, two genes that can sharply increase a woman's risk of developing breast cancer. Among other accomplishments, Powell developed new tests that let doctors interpret formerly ambiguous results from tests for the risk-enhancing forms of BRCA1 and BRCA2.

Powell, who is originally from England, was head of the breast cancer service and clinical director of the Gillette Women's Cancer Center Program at Massachusetts General, which is affiliated with Harvard Medical School. He earned both his medical degree and doctorate in cell and molecular radiation biology at the University of London. Powell trained at the Royal Marsden Hospital and the Institute of Cancer Research in England before coming to the United States in 1991 as a clinical oncology fellow at Harvard.

Powell also will become a professor in the Department of Radiation Oncology. As department head, he succeeds Carlos A. Perez, M.D., who led the department since it was founded in September 2001.

"Replacing a colleague like Carlos Perez was not easy, but I think in Simon we are incredibly fortunate to have someone with solid leadership capability and outstanding clinical and research skills," says Timothy J. Eberlein, M.D., the Spencer T. and Ann W. Olin professor and director of the Alvin J. Siteman Cancer Center.

Powell currently is principal investigator or co-principal investigator for six federal research grants and has served on various committees for the National Institutes of Health, including site visit committees that have reviewed major cancer-related grants at the University of Pennsylvania, the University of North Carolina and M.D. Anderson Cancer Center in Houston. He was associate editor of the *International Journal of Cancer* for eight years and currently serves on the editorial boards of the journals *Radiation Research* and *Cancer Biology and Therapy*.

Powell says his goals include creation of a center for molecular targeted radiotherapy that will work to "combine the latest biology with the best technology."

"We plan to encourage this attitude in the teaching of residents, the recruitment of new faculty and the development of clinical trials within the Siteman Cancer Center," he says. "The opportunity clearly exists to make Washington University's Department of Radiation Oncology the premier radiation oncology department in the country."

The department employs more than 200 faculty and staff at Washington University and is composed of four divisions. The

clinical division provides treatment for patients and conducts clinical trials; the cancer biology division studies the effects and interactions of radiation, heat and cytotoxic agents on cells; the physics division explores the physics of radiation oncology, plans treatment, and researches and develops new treatment equipment; and the administration and information systems division maintains computer services and information systems.

Department member Joseph L. Roti Roti, Ph.D., professor of biochemistry and molecular biophysics and of cell biology and physiology, notes that radiation oncology includes a unique mixture of applied medical research, basic biological research and physics research. These three areas focus on different aspects of one question: how best to use radiation to destroy tumor cells while minimizing damage to regular tissues.

"Radiation damages DNA, and how well cells can repair that damage is one of the main determinants of how well they survive after radiation treatments," says Roti Roti. "Simon has a solid record of achievements in DNA repair research, and that experience is going to be essential to improving our ability to make it tougher for tumor cells to recover while reducing damage to normal tissues."

Powell assumes his duties as department head and professor at Washington University on October 1.

"Simon is committed to the best possible patient care, to providing superb training and education, to continuing the development of the scientific basis of radiation oncology and to translating new discoveries into meaningful clinical advances," says Shapiro.

New Clues to Target Duo of Chemokines in Breast Cancer Stromal Microenvironment

In the first comprehensive survey of gene activity in each cell type composing normal and malignant breast tissue, scientists at Dana-Farber Cancer Institute have identified genes in non-cancerous supporting cells that can spur the growth of breast cancer cells.

The findings suggest that aiming chemotherapy at both cancer cells and their genetically normal cellular "microenvironment" might improve the success of breast cancer treatment.

In the July 20 issue of *Cancer Cell*, the researchers report that genes in these "stromal" cells were overactive in specimens taken from women with ductal carcinoma in situ (DCIS)—an early, precancerous condition—and in full-blown "invasive" cancer.

"By finding factors released by surrounding stromal cells that support the growth of the tumor and targeting these components with cancer drugs, it might be more effective than targeting the tumor cells alone," says Kornelia Polyak, M.D., Ph.D., of Dana-Farber and the study's senior author. This suggestion is based on basic research findings and physicians are not directing therapy at stromal cells currently—except for antiangiogenic drugs that target the blood vessels that surround and nourish tumors.

The scientists singled out two such genes as potential targets for therapy. The genes, CXCL12 and CXCL14, contain the genetic code for proteins called chemokines that can prompt cancer progression.

Chemotherapy is designed to kill malignant cells in tumors that develop from the lining, or epithelium, of the breast's milk ducts. But under prolonged assault by chemotherapy agents, these cancerous epithelial cells often undergo genetic mutation that makes them resistant to the drugs that previously were killing them. Resistance to drugs is the bane of successful treatment for breast cancer.

The researchers led by Polyak studied the gene activity in all types of cells known to be or suspected of being involved in normal breast development and breast cancer. They found that the epithelial cells of the ducts' lining had many mutations in genes and damage to chromosomes—the hallmarks of cancer.

In the cells of the stroma—including fibroblasts, myofibroblasts, leukocytes, and myoepithelial cells—genes were intact and the cells weren't cancerous. Yet their abnormally high activity levels indicated they were sending signals causing epithelial cells to grow abnormally and burrow through



Simon Powell, Ph.D.



Kornelia Polyak, M.D., Ph.D.

barriers that are meant to contain cancer, explained Polyak, who is also an assistant professor of medicine at Harvard Medical School.

By sampling tissue taken surgically from normal breasts and in early and late stages of breast cancer, the researchers traced changes in gene structure and activity in the different cell types.

Until now, most research has focused on the epithelial cells inside the milk ducts. Breast cancer begins with abnormal growth of epithelial cells due to

genetic damage, and in many cases the cancer remains confined harmlessly within the ducts for years or decades. Some, but not all DCIS lesions penetrate and escape from the “basement membrane” that separates the ducts from the stromal tissue. When this happens, DCIS has progressed to full-fledged “invasive” breast cancer that can spread widely and become life threatening.

One potential benefit of the new gene survey could be a way to detect a gene activity “signature” in DCIS cells to predict how likely they are to progress to invasive cancer. Such a test, not available now, might save some women from needlessly aggressive treatment.

Before they could study gene activity in breast cells and make a “profile” of each gene, the researchers first needed to make very pure samples of each of six cell types in the breast tissue specimens. (These were taken from women without cancer undergoing breast reduction surgery, and from women with DCIS or invasive breast cancer.)

Next they used a powerful laboratory tool, called SAGE (serial analysis of gene expression) to measure the amount of activity of each gene in the different cell types. These activity profiles changed depending on whether the cells were from a normal specimen or were from DCIS or invasive cancer.

From the genes’ activity in tissues of different types, the scientists were able to deduce which ones were involved in the beginning or progression of cancer. Some of the genes were previously unknown. In other instances, the genes were known but their involvement in breast cancer hadn’t been recognized.

For example, the Polyak team found in the cancer samples the two abnormally active genes that make chemokines, molecular messengers implicated in cancer. Polyak said work is in progress to determine whether blocking the overactive chemokine genes might be an effective therapy.

Mina Bissell, Ph.D., a noted breast cancer scientist at the Lawrence Berkeley Laboratory in California, is the author of a commentary accompanying the article in *Cancer Cell*. She termed it “an important proof-of-principle study” for still more comprehensive efforts to profile the genes involved in breast cancer progression.

Noting the cast of supporting molecular players that is now being implicated, Bissell quipped, “It is time to accept that treating cancer will also take a village!”

The paper’s first author is Minna Allinen, Ph.D., of Dana-Farber.

The study was funded in part by the National Institutes of Health.

Carlo Croce Moving to Ohio State University

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Ohio State University has recruited world-renowned physician-researcher Carlo M. Croce to direct OSU’s nationally recognized Human

Cancer Genetics Program, which was initiated and built by another world-renowned cancer researcher, Dr. Albert de la Chapelle.

Croce will chair the Department of Molecular Virology, Immunology, and Medical Genetics. In addition, the university has plans to create an Institute of Genetics and Dr. Croce will be instrumental in that process. His appointment takes effect Oct. 1, 2004.

Croce, a member of the National Academy of Sciences, studies the molecular changes in genes that lead to cancer. He is particularly interested in the early changes of malignancy and how they might serve as targets for new treatment and preventive agents. He has also discovered a number of cancer-related genes, including BCL2, ALL1, TCL1, FHIT and LZTS1.

“Carlo Croce is a brilliant researcher whose work has revealed the variety of mutated genes—oncogenes—that are involved in leukemias, lymphomas and other cancers,” says Dr. Michael A. Caligiuri, director of The Ohio State University Comprehensive Cancer Center. “His findings greatly expanded our understanding of cancer and the process of programmed cell death,” Caligiuri says, “and his work has provided important tools for patient management.”

Croce is presently director of the Kimmel Cancer Institute/Kimmel Cancer Center at Jefferson Medical College, Thomas Jefferson University, in Philadelphia. He was drawn to Ohio State by the OSU cancer program’s efforts to facilitate collaborations between physician-scientists and laboratory scientists to improve patient care, by the directorship of the planned Institute of Genetics and by the opportunity to direct OSU’s Human Cancer Genetics Program.

The Human Cancer Genetics Program (HCGP) was started in 1997 by de la Chapelle, the Leonard and Charlotte Immke Professor of Cancer Genetics, who also is a member of the National Academy of Sciences.

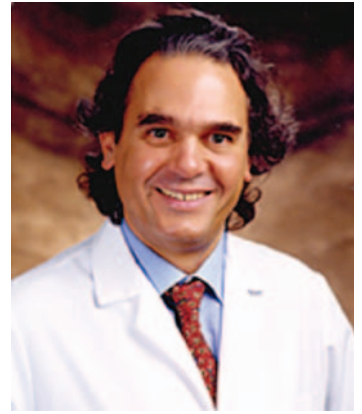
The HCGP has since grown to include 16 faculty members, 150 full-time staff and up to 50 students. Faculty conduct both clinical and basic research. Basic research projects focus on how genes are activated and inactivated, how cell-growth signals are transmitted and regulated within cells, and how cells interact with the immune system. Clinical research focuses on discovering genes linked to cancer and mutations that predispose people to cancer.

“This recruitment is an excellent manifestation of OSU’s continuing to strive upward,” de la Chapelle says. “Dr. Croce’s arrival signals the initiation of the second and crucial phase in Ohio State’s development of national and international excellence in cancer genetics.”

De la Chapelle will remain at OSU and continue his research, working closely with Croce. He will become the second OSU Cancer Scholar, enabling him to further expand his research program.

Croce also will succeed Dr. Caroline C. Whitacre as chair of the Department of Molecular Virology, Immunology and Medical Genetics. Whitacre will continue to focus, with expanded responsibilities, on her two other critical leadership roles as vice dean of research in the College of Medicine and Public Health, and associate vice president for research in the Office of Health Sciences. She also will maintain her successful research program on immunological aspects of multiple sclerosis. Whitacre’s leadership over the past few years has played a key role in the significant increases in research funding and productivity in the medical center.

Croce’s standing in the cancer-research community is readily shown by the awards he has been given. “Carlo has received almost every significant award for cancer research one can earn,” says Dr. David E. Schuller, executive director of the OSU Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. “They include two Outstanding Investigator awards from the National Cancer Institute, the Rosenthal Award from the American Association for Cancer Research, the John Scott Award, the Pasarow Foundation Cancer Award, the GM Cancer Research Foundation Charles S. Mott Prize and many others.”



Carlo M. Croce, M.D.

In 2003 Croce became a member of the Accademia Nazionale delle Scienze, detta dei XL, the Italian National Academy of Science. Currently, Croce is principal investigator on four federal research grants and has more than 650 published research papers.

Croce has also served as an external adviser to the OSU cancer program since 1988, providing him an intimate view of the program's growth.

"I strongly believe that the OSU cancer program is developing into one of the nation's foremost leaders in cancer research," Croce says. "My strength in cancer-gene discovery complements the strengths at the OSU Comprehensive Cancer Center. Together, we will work to develop novel and successful approaches to cancer prevention, diagnosis, monitoring and treatment based on gene-target discovery, verification and rational drug development."

The benefits of Croce's arrival at the OSU medical center extend far beyond the cancer program.

"Dr. Croce's recruitment adds to our already strong programs in microbiology, molecular virology, immunology and medical genetics, as well as in human cancer genetics," says Dr. Fred Sanfilippo, senior vice president and executive dean for health sciences at Ohio State, dean of Ohio State's College of Medicine and Public Health, and CEO of OSU Medical Center.

"We have recruited stellar investigators in these areas during the past few years, and with Carlo's added leadership these teams of researchers, educators and clinicians will provide even greater benefits to patients, students and the scientific world."

Croce's appointment is part of the university's ongoing effort to build a world-class faculty, says Ohio State University President Karen A. Holbrook. "His work is legendary, and to attract a scientist who is as world-renowned as Dr. Croce speaks volumes for the strength of the programs already here at Ohio State. His research will catalyze new partnerships and relationships across the scientific community, and I join others in expressing great enthusiasm for this very important addition to our faculty."

A native of Milan, Italy, Croce earned his medical degree, *summa cum laude*, in 1969 from the School of Medicine, University of Rome. He began his career in the United States the following year as an associate scientist at the Wistar Institute of Biology and Anatomy in Philadelphia. In 1980, he was named Wistar Professor of Genetics at the University of Pennsylvania and associate director of the Wistar Institute, titles he held until 1988.

From 1988-91, he was director of the Fels Institute for Cancer Research and Molecular Biology at Temple University School of Medicine in Philadelphia. In 1991, he was named director of the Kimmel Cancer Center.

"The recruitment of Carlo advances the cancer program's expansion plan, as well as supports our strategic plan," Schuller says. "That plan includes selective investment in experimental therapeutics, chemoprevention and human cancer genetics research. Carlo will contribute to all three, and we are fortunate to have him join our team."

"Clearly, Carlo is one of the top cancer scientists in the world today," Caligiuri says. "His genetic discoveries have often caused us to stop in our tracks and start thinking differently. We are excited and pleased to welcome him to the OSU cancer program."

Cancer Drug Development and Translational Research are High Priorities of Special Workshop

For more information contact: Duke Medical Center News; dukemednews@contact.duke.edu

A summit of prominent cancer researchers from academia, industry and the Food and Drug Administration (FDA) is gathering in Baltimore for an interactive workshop July 13 and 14 in an effort to accelerate the testing and approval of promising cancer drugs, a process that now takes an estimated 15 years from drug discovery to patient use. Cancer consumer groups are participating in the workshop.

The two-day collaborative workshop is providing training, instruction and immediate feedback for early-career scientists on how they can most efficiently develop and validate new anti-cancer drugs to diagnose, treat and prevent various cancers.

"Some of the very best scientists don't necessarily have the tools or the training to develop their drugs and move them through the approval pipeline," said H. Kim Lyerly, M.D., director of the Duke Comprehensive Cancer Center, chairman and sponsor of the two-day workshop.

"Decisions about how to proceed with testing a particular drug have often occurred in a vacuum, without input from the FDA," he said. "We're removing barriers to constructive dialogues by linking academics, early-stage drug developers and the FDA in a creative way to talk about new strategies for accelerating drug discovery."

The workshop, "Accelerating Anticancer Agent Development and Validation," is providing an opportunity for seasoned cancer researchers from industry, academia, government and consumer groups to share their knowledge of drug development with 50 early-career cancer scientists from the U.S. and abroad. Each scientist is bringing an agent or strategy with promising early-stage clinical data. Senior scientists are mentoring them as they design strategic plans for fully developing and validating their anti-cancer agents.

Participants are refining and amending their strategic plans with the guidance of three mentors each—a representative from the FDA, a biostatistician and an academic or industrial clinical investigator. Scientists from the FDA, the National Cancer Institute (NCI), industry and academic institutions such as the Duke Clinical Research Institute are providing critical knowledge about design and conduct of clinical trials.

"We'll be discussing the nuts and bolts of how to take great ideas and deliver effective and safe products to society quickly," said Lyerly. "Our goal is to make the system work better, to make it more open and understandable to scientists who are trying to navigate their way through unknown territory."

Dozens of new anticancer agents are discovered each year, but many of them fall short of reaching patients because of the painstaking process of drug testing and development. Scientists are trained to study the biologic basis of cancer or to treat patients, but they generally have not been trained to conduct multi-phase clinical trials or to negotiate the regulatory processes that lead to drug approval, said Lyerly.

The workshop's primary goal is to encourage what is called "translational research"—transforming scientific discoveries made in the laboratory into viable treatments for patients, said Richard Pazdur, M.D. director, Division of Oncology Drug Products at the FDA. Pazdur said the sessions will provide insights into ways to facilitate and expedite drugs through the regulatory process.

Developing new drugs has been seen as a purely industrial enterprise in the past, but this scenario is changing, Lyerly said. Societal pressure is building to rapidly bring new drugs to patients—even for rare cancers—an endeavor that may not seem like good business. Academic investigators can take the lead in developing drugs for these so called "orphan" diseases, he said. In addition, Lyerly said the strategies for battling cancer have changed, so must the methods of developing these strategies.

"For the past few decades, most cancer drugs have been DNA poisons that kill the genetic machinery of the cancer cell and other healthy cells in their wake," he said. "The newer anti-cancer agents tend to much more targeted: we attempt to block or activate a very specific pathway inside



H. Kim Lyerly, M.D.



Richard Pazdur, M.D.

cancer cells that is critical to its growth or death. Drugs that target these pathways validate themselves as effective anti-cancer agents, but they also illuminate the pathway's molecular role in the formation of cancer."

In this manner, the development of new drugs is also contributing to the understanding of how cancer forms, grows and dies, said Lyerly.

The gathering of scientists from academia, industry, consumer groups and the government provides an opportunity for each sector to share its unique experience and expertise with others who may benefit from that knowledge base, added Lyerly.

Participants in the workshop include the Duke Comprehensive Cancer Center, Duke Clinical Research Institute, FDA, NCI, American Association for Cancer Research, American Society of Clinical Oncology, National Institutes of Health, and Friends of Cancer Research.

Gleevec Target Abl Important for Normal Immune Activation of T Cells

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Leukemia patients who take the anti-cancer drug imatinib mesylate (brand-name Gleevec) are at increased risk for developing suppressed immune systems, and researchers at the Duke Comprehensive Cancer Center have discovered a mechanism that likely explains why.

Their findings, reported in the July 2004 issue of the journal *Current Biology*, may also lead to newer drugs that target cancer cells for destruction without targeting important immune system cells.

Their discovery explains the role of a critical protein in the body called ABL. When mutated, ABL is overly active and gives rise to an excess of defective blood cells that become chronic myeloid leukemia. Imatinib mesylate inhibits ABL's activity in leukemia cells and, without enough ABL, the cancer cells die.

In normal white blood cells, however, the function of the ABL family of proteins—c-ABL and the related Arg—was unknown until now. The Duke team discovered that ABL proteins activate the production of infection-fighting cells called "T-cells." Specifically, they showed that ABL proteins are key communicators in the chain of events that leads to T-cell activation and, thus, infection control.

While imatinib mesylate targets and inhibits the activity of ABL proteins in cancer cells, it also turns off ABL function in normal cells. When ABL is inactivated by imatinib mesylate, the researchers found that T-cells could no longer mount a robust activation response. Their findings support the observation that patients can become immuno-suppressed if they receive too much of the drug.

"Gleevec, which has been highly successful at obliterating leukemia cells, also inhibits T-cells, the basis of the body's defense against infection," said Ann Marie Pendergast, Ph.D., principal investigator and professor of molecular cancer biology at Duke. "This study demonstrates the vulnerability of the immune system to Gleevec-like drugs and gives a graphic illustration of why it is important to understand the normal function of drug targets."

Scientists have known since 1986 that ABL plays a key role in causing chronic myeloid leukemia. With this disease, ABL becomes fused to another protein called BCR in a genetic rearrangement that causes the ABL protein to lose a crucial "off" switch. The defective BCR-ABL protein is always turned on, continually stimulating bone marrow stem cells to make more and more white blood cells. Over time, the buildup of defective white blood cells develops into leukemia.

At the doses given to patients, imatinib mesylate shows very low toxicity. However, in isolated cases, some patients have experienced bouts of shingles and other symptoms of a lowered immune response.

"The reason we haven't seen more side effects with Gleevec is that leukemia cells are exquisitely sensitive to the drug so it can be given in doses low enough not to cause noticeable harm to normal cells in most instances," said Pendergast.

To demonstrate ABL's role in T-cell response, Pendergast and Duke colleagues Patricia Zipfel, Ph.D., Weiguo Zhang, Ph.D., and Marisol Quiroz studied mice in which one copy of the ABL gene and both copies of the Arg gene had been deleted. In these mice, T-cell activation was reduced dramatically compared to normal mice.

The researchers then treated T-cells isolated from the spleens of normal mice with imatinib mesylate and tested their ability to respond to T-cell stimulation. Again, the response was drastically reduced.

These effects were caused by a cascade of events in which ABL and Arg convey signals from molecules on the cell surface to activator molecules ZAP70 and LAT inside the cell. These proteins, in turn, set into motion a host of activities that ultimately lead to T-cell proliferation and activation.

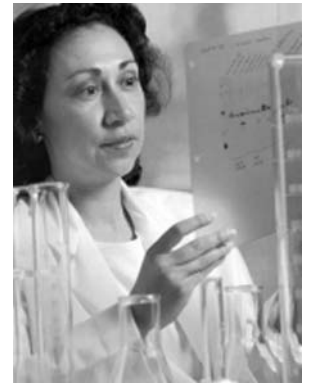
The findings support a larger picture of the role of ABL that is emerging from the work of Pendergast and other researchers. The protein appears to be a crucial switch for a number of processes that involve coordination between events happening on the cell surface, recruitment of a large number of proteins and reorganization of cells' inner scaffold, the "cytoskeleton."

"When an antigen-presenting cell stimulates a T-cell, we see rapid movement of a large number of molecules that congregate just below the cell membrane," Pendergast said. "We suspect ABL plays an even larger role in the chain of events that lead to T-cell activation and are working on identifying additional roles for ABL."

The reason such studies are important, said Pendergast, is that in some cases patients have developed resistance to Gleevec, leading investigators to look for the "next-generation Gleevec."

"The success of Gleevec has spurred a race for the next great protein kinase inhibitor," said Pendergast. "It's important that we know what ABL is doing in normal cells because the new generation of protein kinase inhibitors are much more potent than Gleevec and have greater potential for toxicity."

The research was funded by the National Institutes of Health.



Ann Marie Pendergast, Ph.D.

Perturbing and Detecting Phospho-Protein Networks in Single Leukemia Cells

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People diagnosed with acute myelogenous leukemia usually receive the most commonly effective chemotherapy as a first line of attack, but it doesn't work for everyone. Faced with these resistant cancers, doctors move on to the next most effective treatment or perhaps a drug still in development. This process is time-consuming and can cost patients years of damaging therapy with no remission.

Speeding up this lengthy process is one goal of research by Garry Nolan, Ph.D., associate professor of microbiology and immunology at the Stanford University School of Medicine. He reports a new technique for getting AML



Garry Nolan, Ph.D.

patients on the right drug the first time in the July 23 issue of *Cell*.

Although all people with AML have a cancer of the same type of white blood cells, those cells behave very differently from person to person. By watching those behaviors, Nolan said doctors could quickly identify patients who need stronger treatment or less common chemotherapy drugs.

AML is the most common form of leukemia, with about 10,500 new cases diagnosed each year. The cancerous white blood cells divide out of control and

drown out the other types of cells normally present in the blood. People with the disease tend to bruise easily because their blood doesn't contain enough platelets to clot, and they have a shortage of red blood cells, causing fatigue.

Nolan equates his technique to figuring out which people in a room are more aggressive, noting that you can't always tell at first glance. "But if I go around and kick everybody in the shin, I can see their response and learn something about that person," he said.

Exposing cancer cells to different molecules is like kicking them in the shin, and Nolan's technique is the snapshot that reveals how the cell behaved. Those cells that simply look surprised are fairly normal and will probably respond well to drugs; those that glower need special treatment.

The cellular expressions Nolan watches are message-carrying pathways that translate a signal in the environment into action in the cell's nucleus. In all cells, a carefully orchestrated network of molecules passes messages between the cell's surface and the nucleus. Molecules that relay those messages follow a strict order in healthy cells, always handing the note—in this case, a phosphate atom—to the next molecule in line.

In cancerous cells, those highly regulated note-passing brigades grow independent. Molecules hand notes to the wrong counterpart, and sometimes write a note of their own and pass it along. A signal at the cell's surface saying "stop dividing" may get handed to a neighboring pathway where it becomes a signal to divide rapidly—a hallmark of cancer cells—or may get destroyed altogether.

These disturbances aren't visible just by looking at a tumor sample. Nolan got his first glimpse inside the cell's machinery using a technique developed by postdoctoral scholar Omar Perez, Ph.D. He harnessed a decades-old device called flow cytometry to act as a hidden security camera monitoring the note-passing molecules. The data is a snapshot of which molecules have a phosphate note in hand and which don't in response to normal signals that a cell would encounter.

Postdoctoral scholar and first author on the paper Jonathan Irish, Ph.D., applied Perez' technique to samples from healthy people, people with AML who responded to chemotherapy and people whose AML did not respond to the initial chemotherapy attempt. He monitored six of the molecular handoffs to see which differed when the cells were exposed to five different signals they would normally encounter in the body.

What he found was striking. Doctors usually treat a cancer as a single, uniform entity. When they take a sample to determine how far the cancer has progressed, the entire cancer gets graded on a scale of 1 to 4, with 4 being the most severe. But Nolan and Irish found that many different populations can exist within a cancer at any point in time. Some of these populations are farther along in their cancerous path than others and were passing a greater number of notes to the wrong counterpart.

A major difference between people who did and did not respond to chemotherapy was the way in which their cells responded to environmental signals. The cells that handed messages down the wrong set of pathways were able to avert the normal cell-death signals triggered by chemotherapy.

Learning to recognize the pathways most commonly disrupted in aggressive cancers could help researchers predict which patients won't respond to standard chemotherapy. Doctors could immediately propose that the person consider less common therapies.

"This is the first time we've been able to look at cancer signaling messages in a population of individual cells to distinguish treatment options," Nolan said. What's surprising is that the equipment was around for decades before Perez and then Irish honed the new technique. Nolan said flow cytometry machines are widely available to doctors treating AML and other cancers, making the technique practical and helpful to doctors.

In follow-up experiments Nolan hopes to correlate the patterns in the note-passing network to how well the patients responded to different forms of chemotherapy and how long their remission lasted. Armed with that information, doctors can help patients get the best treatment for their disease sooner.

Inhibitor of Apoptosis (IAP) Rescues Migration Defect in Rac-Deficient Flies

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By studying fruit fly ovaries, Johns Hopkins scientists have discovered that a protein known to block cell death also has the completely independent role of enabling normal cell movement.

The discovery creates an unexpected new path to follow in the effort to understand the biochemical steps behind cells' movement, a critical aspect of embryonic development and the spread of cancer. The work is described in the July 9 issue of *Cell*.

By studying fruit flies engineered to make extra use of random genes, the Hopkins team discovered that a protein called "inhibitor of apoptosis-1" (or IAP) can restore the tightly choreographed cellular movement that naturally occurs in fruit fly ovaries as egg cells mature.

"This discovery was completely unexpected," says Denise Montell, Ph.D., professor of biological chemistry in Johns Hopkins' Institute for Basic Biomedical Sciences. "Based on what was known about this protein's function in blocking cell death, there would have been no way to predict its involvement in cell migration."

Instead, graduate student and now postdoctoral fellow Erika Geisbrecht and Montell relied on "forward genetics," an approach in which the scientists alter the expression of random genes, look for a specific effect in the resulting flies and then figure out which gene was affected.

In Geisbrecht's experiments, a small number of cells in the fruit fly ovaries had a dysfunctional protein called Rac, which caused those cells not to move properly and the flies to be sterile. Geisbrecht then randomly increased production of other genes in the cells and looked for flies whose fertility was restored, an obvious sign that their cellular choreography had returned to normal.

"The idea is simple—if the cell migration problem improved, the overexpressed gene must have fixed or compensated for the lack of functional Rac," says Montell.

The fruit fly ovary consists of about 100 egg chambers, each made of 16 cells—15 "nurse" cells and one oocyte, which becomes the egg—surrounded by a layer of several hundred epithelial cells. At a certain point in development of the egg, a single small cluster of these epithelial



Denise J. Montell, Ph.D.

cells normally detaches from the others and moves from the edge of the egg chamber to the center, sliding between nurse cells and coming to rest at the edge of the oocyte.

In egg chambers whose cells were missing Rac's function, the epithelial cluster rarely made it even halfway to the oocyte. Returning a working Rac protein to these cells allowed about half of the epithelial clusters to complete their journey, as did overexpression of IAP and overexpression of proteins called actin and profilin, two components of cells' internal skeletons, the researchers found.

Once IAP had been identified as the "rescuing" protein, Geisbrecht determined that IAP's effects on cell migration stem not from its previously known role in preventing cell death, but from its ability to bind to and block enzymes called caspases that chew up a variety of proteins. By doing so, IAP prevents the destruction of a whole host of other proteins.

Montell says she'll be trying to identify the "downstream" proteins that may be more directly responsible for restoring fertility in flies with dysfunctional Rac. Two initial candidates are actin and profilin, she says, and other components of cells' internal skeletons will be on the short list, too, since cells have to take apart and rebuild their skeletons in order to move.

"If these obvious choices don't pan out, we'll go back to a forward genetic screen," says Montell. "Then we can let the animal tell us what is happening."

As always, Montell and her colleagues will use genetic tricks so they can change the genes in a limited number of cells in the ovary. Doing so allows them to study genes whose functions, if altered in the entire animal, wouldn't let the insect fully develop. The use of these so-called mosaic flies is crucial for studying cell migration, since migration gets all the cells of a developing embryo where they need to be to form a normal, viable insect.

Authors on the study are Geisbrecht and Montell. The work was funded by the National Institute of General Medical Sciences, part of the National Institutes of Health.

Francis Crick, 1916-2004

Francis Harry Compton Crick, co-discoverer of the double helical genetic blueprint of life known commonly as DNA, died July 28, 2004. He was 88 years old and a resident of La Jolla, Calif.

For his work, Crick—a distinguished research professor and former president of the Salk Institute for Biological Studies—was awarded the Nobel Prize in Physiology or Medicine in 1962, along with his colleagues James D. Watson and Maurice Wilkins.

The impact of their discovery is recognized by many as one of the most significant of the 20th century and affects practically every scientific discipline in the life sciences.

"Francis Crick will be remembered as one of the most brilliant and influential scientists of all time," said Richard A. Murphy, the Salk Institute's president and chief executive officer. "He will be missed as a gentleman, a role model, and a person who has contributed so much to our understanding of biology and the health of mankind. For those of us privileged to know him at Salk, he will also be remembered as a dear friend."

"We were honored to have him with us for so many years and will miss him tremendously."



Francis Crick

To those who knew him best, it was Crick's insatiable curiosity about life and the creativity of his mind that set up him apart from others. In recent years, he put these qualities to work in an attempt to find the neural correlate of consciousness, a problem he defined as the search for the link between the mind and the brain. Although he was a pathfinder in this young field, he knew that it would take

younger minds than his to one day untangle the myriad mysteries of the human brain.

When asked what he hoped his future contributions would be, he said, "To excite younger people to study the problem of consciousness."

Said Christof Koch, a professor of neuroscience at the California Institute of Technology and one of Crick's collaborators: "Francis delighted in playing the important role of devil's advocate for several generations of young researchers."

Born in Northampton, England, on June 8, 1916, Francis Crick showed an early curiosity for all things—but for science in particular. The young Crick attended Northampton Grammar School and later the Mill Hill School in North London, where he received a basic education in chemistry, physics and mathematics.

To help answer his many questions, his parents—Harry Crick and Annie Elizabeth Wilkins—bought their young son a Children's Encyclopedia that covered a vast range of topics, from history and music to science. But the subjects that intrigued him the most centered on things like the nature of the galaxy, chemistry and how things were made of atoms.

Later, Crick would study physics at University College in London, where he received a bachelor of science degree in 1937. He began studying for his Ph.D., but this work was interrupted by the outbreak of war in 1939. During World War II, he worked as a scientist for the British Admiralty, helping to design magnetic and acoustic mines.

When the war ended, however, Crick found himself less interested in physics and somewhat vague about what he wanted to do with his future.

"I still didn't know much about anything so I could go into whatever I wanted," Dr. Crick recalled in 1997 during an honors seminar lecture at Rutgers University.

"I used what I call the 'Gossip Test' to decide what I wanted to do," he said. "The gossip test is simply that whatever you find yourself gossiping about is what you're really interested in. I had found that my two main interests which I discussed the most were what today would be called molecular biology, what I referred to as the borderline between living and the nonliving, and the workings of the brain."

In 1947, Crick left the Admiralty and turned to studies in biological research at the Strangeways Laboratory in Cambridge, supported by a studentship from the Medical Research Council and some financial help from his family. At that time, Crick knew little biology and practically no organic chemistry or crystallography; however, he soon went beyond the fundamentals in each of these areas.

In 1949, Crick joined the Medical Research Council Unit as a laboratory scientist in the Cavendish Laboratory at Cambridge University. During the next few years Crick, working with colleagues at the lab, worked out the general theory of x-ray diffraction by a helix.

A critical influence in Crick's career was his friendship, beginning in 1951, with James Watson, then a brash, young American on a postdoctoral fellowship in genetics. The duo immediately struck up an intense collaboration, based on a conviction that DNA, not proteins, was the critical factor for passing on genetic information from generation to generation.

"It was obvious that I knew more about x-rays and structures than Jim did and he had more background in biological things which I'd only toughly taught myself," he said. "So you might have guessed that I did the structural part and he did the more biological aspect."

"That really wasn't true. For example, Watson discovered exactly how the base pairs went together, which is structural. He made that discovery."

Their work led in 1953 to the proposal of the double-helical structure for DNA and the replication scheme. Crick and Watson subsequently suggested a general theory for the structure of small viruses. Later, in research with Sydney Brenner, professor of genetic medicine at the University of Cambridge, Crick developed ideas about protein synthesis ("the adaptor hypothesis") and the genetic code.

By 1966, sensing that the foundation for molecular biology was adequately set, Crick turned his attention to embryology. Then, in 1976, he joined the Salk Institute for a sabbatical year from the Medical Research Council. The following year, after 30 years and 87 scientific papers, he

decided to make a permanent switch to the Salk, where he pursued his interests in understanding the brain and the nature of consciousness.

In the epilogue of his book "What Mad Pursuit: A Personal View of Scientific Discovery," Crick says that the brain sciences today are reminiscent of the state of molecular biology and embryology in the 1920s and 1930's.

"The brain sciences still have a very long way to go," he writes. "But the fascination of the subject and the importance of the answers will inevitably carry it forward. It is essential to understand our brains in some details if we are to assess correctly our place in this vast and complicated universe we see all around us."

Aside from more than 130 published papers in his life, Crick also wrote several books including "Molecules and Men" (1966), "Life Itself" (1981), and "The Astonishing Hypothesis, The Scientific Search for the Soul" (1994).

In addition to the Nobel Prize, his honors included the Lasker Award, the Award of Merit from the Gairdner Foundation, and the Prix Charles Leopold Meyer of the French Academy of Sciences. He was a member of the U.S. National Academy of Sciences, the Royal Society, the French Academy of Sciences and the Irish Academy.

Crick is survived by his wife, artist Odile Speed; two daughters by his marriage, Gabrielle A. Crick and Jacqueline M-T Nichols, both residing in England; a son by a previous marriage, Michael F.C. Crick of Seattle, and four grandchildren. Crick's first wife is Ruth Doreen Dodd. They were divorced in 1947.