

Progressline

Twice-monthly news for staff at the Comprehensive Cancer Center –
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RESEARCHERS TO LAUNCH GRANT-FUNDED STUDY OF GENE PROMOTERS IN CANCER

A team of scientists at Ohio State University Medical Center will use a four-year, \$720,000 Research Scholar Grant from the American Cancer Society (ACS) to study how aberrant gene activity may lead to cancer.

Principal investigator Ramana Davuluri, PhD, an assistant professor in the Department of Molecular Virology, Immunology and Medical Genetics, where he works in the area of Human Cancer Genetics, says basic science discoveries over the past several decades have shown cancer to be a complex disease involving a mix of molecular and cellular processes.



Ramana Davuluri, PhD

Although advances have been made in understanding differences between normal and cancer cells, Davuluri says scientists are still challenged to achieve optimum diagnoses and treatments that can come about only through a better understanding of how cancer arises.

“We have learned that cancers arise from the gradual accumulation of genetic and epigenetic changes in specific cells,” says Davuluri, a member of the Molecular Biology and Cancer Genetics Program at Ohio State’s Comprehensive Cancer Center. Epigenetic changes are alterations in gene function that occur without a change in the genetic sequence of a cell’s DNA.

This study, he explains, will focus on gene promoters, or sections of DNA that generally determine the activity or inactivity of specific genes – in particular their ability to produce proteins, a primary gene function.

“Recent annotations of the human genome suggest that up to 70 percent of protein-coding genes make one or more alternative forms,” Davuluri says. His team’s gene promoter databases indicate that at least 26 percent of human genes have two or more non-overlapping tandem promoters.

“Notably,” he says, “we have found that the incidence of multiple promoters among cancer genes is much higher than the proportion among the remainder of genes in our database.” He says more and more evidence links aberrant use of multiple promoters with cancer formation.

“Several oncogenes and tumor-suppressor genes are already known to have multiple promoters; moreover, we know that the aberrant use of one promoter over another in some of these genes is directly linked to cancerous cell growth,” Davuluri says.

Consequently, his team hypothesizes that alternative promoters in a gene are improperly used – either activated or silenced – in cancer formation.

With their new ACS grant, Davuluri and colleagues will combine computational, statistical and high-throughput approaches to better characterize alternative promoters of human genes in cancer cells. This should reveal new biomarkers that can be targeted with new drugs tailored to correct the aberrant gene activity.

Davuluri compares the improper gene promoter activity to deficient light switches.

“We know that cancer is caused by genes being turned on or off at the wrong times, but recent research has shown that most genes actually have more than one switch, or promoter, controlling them,” Davuluri says. “To fix the problem, you first must figure out which switch is broken. Our research is based on the same principle, but applied to genes instead of light bulbs. Once we identify the switch that is malfunctioning in a particular cancer-causing gene, we are in a better position to figure out ways to fix it.”

SCIENTIST NAMED V FOUNDATION SCHOLAR

Laura Rush, DVM, PhD, a scientist at Ohio State University Medical Center, has been named a V Foundation Scholar and will receive \$100,000 for a two-year study of biological events leading to hematologic malignancies.

Dedicated to the memory of North Carolina State basketball coach Jim Valvano, The V Foundation for Cancer Research awards millions of dollars in grants each year to promising young researchers who are working on innovative approaches to fighting cancer. It has supported cancer research at Ohio State for many years, awarding grants to 15 scientists since 1996.

Rush, a member of the Molecular Biology and Cancer Genetics Program at Ohio State’s Comprehensive Cancer Center, will use her grant to study a transgenic mouse model that may help clarify the role of a methyltransferase gene called *DNMT3b* in disrupting normal DNA methylation and triggering the development of leukemia and lymphoma.



Laura Rush, DVM, PhD, will receive \$100,000 from The V Foundation for Cancer Research to further her studies of the biological basis of human leukemia and lymphoma.

DNA methylation is a chemical process through which cells deregulate, or turn off, some unneeded genes. Properly regulated methylation is important for normal cell development, but aberrant methylation apparently contributes to cancer by silencing tumor-suppressor genes that would normally prevent the improper cell division that characterizes this disease.

Rush, an assistant professor in the College of Veterinary Medicine’s Department of Veterinary Biosciences, says abnormal DNA methylation is present in almost every type

of human cancer, including leukemia and lymphoma. She adds that aberrant DNA methylation in gene promoters (controlling regions of the gene) can take place early in carcinogenesis, or cancer formation.

“Mechanisms leading to disruption of normal DNA methylation patterns are unknown, but one possibility is overexpression of one of the DNA methyltransferase enzymes,” she says, noting that several laboratories have reported higher levels of DNA methyltransferase enzymes in cells of hematopoietic (blood) tumors compared with normal tissues.

“We hypothesize that overexpression of *DNMT3b*, a methyltransferase gene, in hematopoietic cells of transgenic mice will cause promoter methylation of genes similar to human disease and lead to leukemia and lymphoma,” she says.

Rush believes genetic analysis of these mice will help scientists identify genes that drive malignant transformation of hematopoietic cells. “This will increase our understanding of the pathogenesis of leukemia and lymphoma,” she says.

STUDY: STRESS HORMONES MAY PLAY ROLE IN SPEEDING SPREAD AND GROWTH OF CANCER

Research at Ohio State University Medical Center suggests that hormones produced during periods of stress may increase the aggressiveness of cancer.

The study, reported in the journal *Cancer Research*, showed that an increase in norepinephrin, a stress hormone, can stimulate tumor cells to produce two compounds that can break down tissue around the tumor cells and allow them to more easily move into the bloodstream. From there they can metastasize, or travel to other locations in the body to form additional tumors.

The research also suggests the same hormone can stimulate the tumor cells to release another compound that can aid in the growth of new blood vessels that feed cancer cells, hastening the growth of the tumor.



Ronald Glaser, PhD, a scientist at Ohio State’s Comprehensive Cancer Center, led research showing that hormones produced during stress may increase cancer aggressiveness.

“This opens an entirely new way of looking at stress and cancer that’s different from current interpretations,” says Ronald Glaser, PhD, a member of the Viral

Oncogenesis and Cancer Control programs at Ohio State's Comprehensive Cancer Center. Glaser is also a professor of Molecular Virology, Immunology and Medical Genetics, and he directs the Institute for Behavioral Medicine Research at Ohio State.

Glaser and Eric Yang, PhD, a research scientist in the same institute, focused on the role of these three compounds. Two of them, both matrix metalloproteinases - MMP-2 and MMP-9 - play a role in breaking down the scaffolding that cells attach to in order to maintain their shape. The third compound, vascular endothelial growth factor (VEGF), is important in the growth of new blood vessels into tumor cells.

Earlier work by researcher Anil Sood at the University of Texas M.D. Anderson Cancer Center had shown that the same stress hormones can stimulate ovarian tumor cells to produce these three compounds. The key to that discovery was that the two stress hormones – epinephrine and norepinephrine – would bind to molecules on the surface of ovarian cancer cells, called adrenergic receptors, and stimulate the release of MMP-2, MMP-9 and VEGF, which might then foster cancer growth.

The Ohio State team wanted to see if the same occurred with other cancer cells.

They turned to cell lines Glaser had developed in the late 1980s to study nasopharyngeal carcinoma (NPC), an incurable head and neck cancer that occurs most frequently among people of Chinese descent.

They treated Glaser's cell line with norepinephrine, and, as predicted, the cells all produced MMP-2, MMP-9 and VEGF. This showed that the receptors for this hormone were present on cells in Glaser's cell line, but the scientists realized that this might have been just a laboratory aberration in the tissue cultures.

"We needed to see how relevant this finding was to what happened with actual tumors," Glaser says. When he asked colleagues to look for similar receptors in a variety of NPC tumor samples, they found them in all types.

"From this we can say that there is a likelihood that all NPC tumors will have these receptors as well," he says.

"MMP-2 and MMP-9 contribute to the aggressiveness of these tumors," Yang says. "It isn't clear exactly how they are operating, but they may work with VEGF to facilitate blood vessel growth in new tumors so they can grow."

The target adrenergic receptors for these hormones are well-known to clinicians dealing with high-blood-pressure patients. Typically, such patients are given a class of drugs known as beta-blockers that lower blood pressure levels.

Glaser and Yang wanted to see how these same drugs affected these tumor cells. They added propranolol, a beta-blocker, to the tumor cells and then exposed them to both

norepinephrine and epinephrine. With the drug present, the levels of MMP-2, MMP-9 and VEGF didn't increase.

"This suggests a new approach to possibly fight some cancers – the prescribing of beta-blocker-type drugs that would block these receptors and perhaps slow the progression of the disease," Glaser says. "Using this approach may not cure this cancer, but perhaps we could slow down its growth, making the tumor more sensitive to anticancer therapy, and therefore extending the patient's lifespan and improving quality of life."

BIOMEDICAL RESEARCH TOWER WILL HELP ADVANCE CANCER RESEARCH

Hundreds of people attended a Nov. 3 grand opening celebration for Ohio State University Medical Center's new Biomedical Research Tower (BRT), a symbol of the institution's commitment to research that will benefit personalized health care.

The BRT, under construction since 2003 on West 12th Avenue, will open its doors in December to researchers pursuing discoveries that will dramatically advance patient care in many medical disciplines, including cancer.

The celebration featured remarks from Mary Woolley, a nationally recognized advocate for science and president of Research!America, a nonprofit alliance working to elevate health research among the nation's priorities.



OSU Medical Center's Biomedical Research Tower

The new tower has 10 stories and 264,000 square feet of dedicated research space that is designed in open-lab

layouts to promote interdisciplinary interaction among research teams.

“This structure will allow for productive interactions among faculty, students and postdoctoral researchers. It’s a very powerful model,” says Caroline Whitacre, PhD, vice dean and associate vice president for Health Sciences Research at the Medical Center, and a member of the Immunology Program at Ohio State’s Comprehensive Cancer Center (OSUCCC).

“This design allows for faster progression of research,” Whitacre adds. “We’re constantly looking to progress faster, publish faster and be more successful at securing external grant funding. This will only help that process along.”

OSUCCC investigators will occupy more than 50,000 square feet of research space in the BRT when it opens, and plans call for moving into an additional 48,000 square feet of space within the next few years.

Further, the OSUCCC is in the planning stages for moving several shared resource facilities into the BRT over the next two to three months, including Nucleic Acid, Proteomics, Microarray, Small Animal Imaging, Analytical Cytometry and Transgenic Animal.

“The opening of the Medical Center’s BRT signals a new chapter in biomedical research for cancer and several other disciplines at Ohio State,” says OSUCCC Director Michael Caligiuri, MD, a Distinguished University Scholar who also directs the Division of Hematology and Oncology in the Department of Internal Medicine. “This building underscores our commitment to innovative studies that identify biological mechanisms of disease and thus help us tailor treatment to individual needs – the hallmark of personalized health care.”

PART OF TISSUE PROCUREMENT SHARED RESOURCE NOW HOUSED AT POLARIS

A portion of Ohio State’s Comprehensive Cancer Center’s (OSUCCC) Tissue Procurement Shared Resource (TPSR) operations, including administrative staff and management, moved to the Polaris Innovation Centre in late September.

Included in the move were the Human Tissue Resource Network (HTRN) management and administration, the Cancer and Leukemia Group B Pathology Coordinating Office, the HTRN Specialty Labs, the Pathology Core Facility, and OSUCCC and Cooperative Human Tissue Network (CHTN) staff.

The TPSR and CHTN distribution component, virtual microscopy technology, were slated to move to Polaris in

early November. The HTRN biorepository will move there in mid to late November. The OSUCCC and CHTN Tissue Procurement agents will remain in the Gross Room of Surgical Pathology in Doan Hall.



Scott Jewell, PhD

“The new Polaris space will ensure that OSU Medical Center is among the top academic entities in the United States to have a state-of-the-art facility for human biospecimen resources that serve the cancer research community,” says TPSR principal investigator Scott Jewell, PhD. In addition to the Children’s Hospital Biopathology Center, the OSU College of Medicine and Children’s Research Institute have one of the largest and most extensive banks of clinical trial research biospecimens in the country.

The Polaris Innovation Centre, housed in the former Borden Foods Corporation research and development building off Polaris Parkway, will provide 10,000 square feet of new space for the TPSR. Jewell says it supplies much-needed office, laboratory and biorepository space for consolidating all of the HTRN services, plus better working conditions and improved efficiency.

RECENT HONORS



John Byrd, MD, of the Experimental Therapeutics Program in Ohio State’s Comprehensive Cancer Center, is one of five researchers selected to receive the Leukemia & Lymphoma Society’s Stohman Scholar Award for outstanding contributions in blood cancer research. The award is given to scientists in their fifth year of research as funded Society Scholars – investigators who have demonstrated an ability to conduct original research in leukemia, lymphoma or myeloma. Byrd, who also directs the Hematologic Malignancy Program in the Department of

Internal Medicine's Division of Hematology and Oncology, has focused his research on targeted therapies for patients with chronic lymphocytic leukemia (CLL). He has received several grants from the Society, including a five-year, \$6.25 million Specialized Center of Research (SCOR) grant to develop new therapies and improve current treatments for CLL patients. Byrd, the D. Warren Brown Professor of Leukemia Research at Ohio State, is principal investigator for the SCOR grant, which will fund four research projects and three clinical trials.



Michael Caligiuri, MD, director of Ohio State's Comprehensive Cancer Center, co-chaired the Biologic Research and Tissue Sample/Collection Breakout Group at the Nov. 11 joint implementation meeting of the LIVESTRONG™ Young Adult Alliance (or LSYAA, part of the Lance Armstrong Foundation) and the Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG). Caligiuri, who also directs the Division of Hematology and Oncology at Ohio State and holds the John L. Marakas Nationwide Insurance Enterprise Foundation Chair in Cancer Research, was invited to help lead the breakout group following his role as co-chair of the PRG, which was conducted in 2005-06 by the National Cancer Institute and the Lance Armstrong Foundation. The PRG addressed the cancer research and care needs of the adolescent and young adult age group (15 to 39 years old) and made recommendations for a national agenda to improve cancer prevention, detection, treatment and outcomes among these patients. The PRG, which involved more than 100 experts from diverse disciplines in research, cancer control, and the advocacy and survivor communities, culminated in a report titled "Closing the Gap: Care Imperatives for Adolescents and Young Adults with Cancer." The Research and Tissue Sample/Collection Breakout Group that Caligiuri is co-chairing will focus on recommendations from the PRG report regarding life stage and developmental characteristics, creating assessment tools, grant coding and procedures for increasing the number of annotated specimens. This will mark the first time in the history of PRGs that the implementation phase is a collaboration between public and private entities.



Michael Grever, MD, co-leader of the Experimental Therapeutics Program in Ohio State's Comprehensive Cancer Center, was named a Legacy Laureate by the University of Pittsburgh during Homecoming 2006 festivities on Oct. 19. Launched in 2000, the Legacy Laureate program recognizes Pitt alumni who have excelled professionally and personally, and who exemplify the best in leadership qualities for the good of their professions, communities and the world. Grever, one of only four alumni to win the award in 2006, earned his undergraduate degree in chemistry at Pitt in 1967 and his medical degree from that university in 1971. At Ohio State, he is professor and chair of the Department of Internal Medicine and holds the Charles A. Doan Chair in Medicine. The Legacy Laureate Program honored him as a medical scientist who is internationally recognized for his contributions to drug discovery and development – particularly for his role in developing chemotherapeutic agents to treat patients with chronic lymphocytic leukemia.



Electra Paskett, PhD, MsPH, associate director for population sciences at Ohio State's Comprehensive Cancer Center (OSUCCC) and co-leader of the OSUCCC's Cancer Control Program, was elected president-elect for the American Society of Preventive Oncology (ASPO). ASPO advocates cancer prevention and research through communication with other oncology groups, forming advisory groups and serving as a worldwide cancer prevention source. Prior to this election, Paskett was an at-large executive committee member for ASPO. She will serve two years as president-elect and then become president for two years.



David Schuller, MD, senior executive director of Ohio State's James Cancer Hospital and Solove Research Institute, has been appointed co-chair of the National Cancer Institute (NCI) Head and Neck Scientific Steering Committee, a new NCI initiative to coordinate clinical cancer research throughout all of the cooperative groups nationally. Schuller, who also holds the John W. Wolfe Chair in Cancer Research at Ohio State, says the Head and Neck Scientific Steering Committee is the third committee created under this initiative. In a letter to Schuller, James Doroshow, MD, director of the NCI's Division of Cancer Treatment and Diagnosis, states that he believes there is "enormous potential to enhance the ability to do state-of-the-art correlative science in the context of clinical trials that could be conducted jointly by head and neck (cancer) investigators nationwide."



Allan Yates, MD, PhD, of the Molecular Biology and Cancer Genetics Program at Ohio State's Comprehensive Cancer Center, was elected chair-elect of the steering committee for the Group on Graduate Research, Education, and Training (GREAT Group) at its annual meeting held Oct. 6-9 in Tucson, Ariz. Yates is a professor of Pathology and associate dean for Graduate Education in the College of Medicine. Established in 1996 by the Association of American Medical Colleges (AAMC), the GREAT Group promotes quality PhD and postdoctoral education in biomedical science by coordinating the exchange of information and ideas among faculty and administrative leaders of biomedical PhD, MD-PhD and postdoctoral programs. The Group functions as a national forum to help these programs achieve their goal of educating biomedical researchers. Yates has been a member of the Group since 2001 and was elected to the steering committee in 2004. He will serve as chair-elect until October 2007, when he will assume the position of chair for one year. In that capacity, he will interact with other groups of the AAMC and be responsible for organizing the GREAT Group's annual meeting to be held

in 2008. At Ohio State, Yates' research has been devoted to studying the role of glycolipids in the biology of human brain tumors and nerve regeneration. He has authored or co-authored 175 publications in scientific journals and book chapters, and he has edited three science books.

RSVP FOR OSU RECEPTION HELD AT ASH MEETING

Anyone attending the 48th annual meeting of the American Society of Hematology (ASH) in Orlando, Fla., is invited to The OSU Scarlet and Gray Reception, which will be held as part of the proceedings on Friday, Dec. 8, from 6:30-8 p.m. in second floor salons 3 and 4 of the Rosen Plaza Hotel, 9700 International Drive. The reception will be sponsored by Ohio State's Comprehensive Cancer Center. If you would like to attend the reception, RSVP with Nancy Jones at 293-3688 or nancy.jones@osumc.edu. Also, If you have any posters or oral presentations accepted for ASH, please notify Nancy.Jones@osumc.edu by Wednesday, Nov. 22. If you have any current collaboration posters, those can be displayed as well. Direct any questions to Jones or to Fannie Beasley at 513-636-1330.

PEDIATRIC ONCOLOGY RETREAT SET FOR DEC. 1

The Pediatric Oncology Program at Ohio State's Comprehensive Cancer Center will hold its second program retreat at the Roberts/Holiday Inn Convention Center in Wilmington, Ohio, on Friday, Dec. 1. Please register by Nov. 22 using the form sent to you via e-mail on Nov. 9. After printing and filling out the registration form, please fax it to Fannie Beasley at (513) 636-1330. The retreat will enable program members to learn more about the OSUCCC's structure, organization and mission, its other scientific programs, its cores, and ongoing research within the Pediatric Oncology Program. Other retreat goals are to expand hypothesis-focused work groups and collaborations, and to develop a new centerpiece joint initiative. Several members of the OSUCCC's Experimental Therapeutics Program will attend to present examples of innovative clinical trials using the OSUCCC cores.

(If you have a news item for Progressline, call 293-6825, fax 293-3666 or e-mail robert.hecker@osumc.edu.)