AACR honors eminent researchers

EurekAlert

ORLANDO, Fla. ? The American Association for Cancer Research will recognize leading cancer researchers whose work has significantly contributed to progress in the fight against cancer at the AACR 102nd Annual Meeting 2011. Each recipient will present an educational lecture at the meeting, which will be held April 2-6 at the Orange County Convention Center.

"We are honoring an exceptional group of scientists who have made major, historic contributions to the field," said Margaret Foti, Ph.D., M.D. (h.c.), chief executive officer of the AACR. "Their efforts in basic cancer research, clinical research, epidemiology, therapeutics and prevention have moved the bar forward and helped an incalculable number of people. These awards honor their contributions, and encourage ongoing research."

The honorees are:

Helen M. Blau, Ph.D., will be awarded the Seventh Annual AACR-Irving Weinstein Foundation Distinguished Lectureship. She is the Donald E. and Delia B. Baxter professor and director of the Baxter Laboratory for Stem Cell Biology in the microbiology and immunology department, at the Stanford Institute for Stem Cell Biology and Regenerative Medicine at the Stanford University School of Medicine.

"It is a very great honor to deliver the Irving Weinstein Foundation Distinguished Lecture for 2011," said Blau. "The control of cellular differentiation is a key problem in regenerative medicine and cancer biology. I have found that cell fate is far more flexible than we thought ? an idea that is reflected in numerous therapeutic strategies that are currently being pursued worldwide. One of the things I have learned in science is that pushing the envelope and challenging dogma, while risky, can often be worth it. This award provides welcome validation to me and importantly encouragement to young scientists to pursue high risk, high gain science."

Blau is world renowned for the broad impact of her research on our understanding of maintenance of the differentiated state, cellular reprogramming, regulation of cell fate, as well as skeletal muscle regeneration and stem cell biology. In particular, she is recognized for her unique approach to science, which capitalizes on the continuous development of new research tools to challenge current scientific dogma. In the 1980s, when it was generally accepted that cell differentiation was a 'terminal' state, Blau showed by cell fusion that a cell's differentiated state is not fixed, but instead is reversible and plastic. Her work in this area has demonstrated that cellular phenotypes result from the particular balance of regulators present at any given time and may be readily altered. She provided surprising evidence that stable differentiated states are maintained by dynamic mechanisms. This concept has been a recurrent underlying theme in most of Blau's work, and has recently re-

emerged in her studies of regeneration, reprogramming towards pluripotency and stem cell biology. The clinical significance of this concept of plasticity is clear in the area of regenerative medicine. Novel treatments will come from altering cell fate and reprogramming cells by altering the expression of intracellular factors.

In recent groundbreaking research, Blau proved that terminally differentiated mammalian cells could be induced to dedifferentiate, as they do during the remarkable regenerative process that occurs in newts. When the brakes on cell cycle are temporarily removed ? by inactivating two tumor suppressors ? the cells go one step back, so they can divide and reproduce while they remain relatively differentiated. This transient controlled inhibition of tumor suppressor activity leads to propagation of cells of known identity and function, constituting a novel approach to modeling diseases in culture and regenerating damaged tissues in the body.

Another major focus of the Blau laboratory is that the approach to regenerating skeletal muscle tissue damaged due to disease, injury or aging involves capitalizing on the stem cells present in muscle. Her contributions to this goal include developing strategies to isolate adult stem cells from mouse skeletal muscle tissue and propagate these cells using bioengineered microenvironments that mimic tissue properties. Finally, she has generated a mouse model of Duchenne Muscular Dystrophy that mimics the human disease, explaining its etiology and allowing a test of therapeutic strategies. Blau is now translating this work into humans and is confident that clinical trials that take advantage of her recent findings to treat skeletal muscle wasting in Duchenne Muscular Dystrophy patients is in the near future.

The AACR-Irving Weinstein Foundation Distinguished Lectureship was established in 2004 to acknowledge an individual whose outstanding innovations in science and whose position as a thought leader have the potential to inspire creative thinking and new directions in cancer research. Blau's lecture, "(Re)-evolutionary Regenerative Medicine," will take place at 5:30 p.m. ET on Saturday, April 2 in room W320 of the Orange County Convention Center.

Nathanael Gray, Ph.D., associate professor of biological chemistry and molecular pharmacology at the Dana-Farber Cancer Institute and Harvard Medical School, is the recipient of the 31st Annual AACR Award for Outstanding Achievement in Cancer Research for his work using synthetic chemistry and functional small molecule discovery to modulate biological pathways important in cancer.

"It's a great honor to accept this award on behalf of my laboratory and my numerous collaborators," said Gray. "We are faced with a great challenge of trying to translate the exponential increase in our understanding of basic cancer mechanisms into new therapeutic options for patients. On the academic side we need to go beyond ending our studies with conclusions that simply implicate a particular target or pathway as being critical for a certain tumor to actually demonstrating the therapeutic relevance of newly proposed targets using experimental drugs. If this can be done more accurately and efficiently, the private sector can focus on developing new drugs against those targets that are most likely to lead to responses in patients."

Gray's lab develops small molecules that can selectively target signaling proteins that become deregulated in cancer. He is currently trying to develop new methods to modulate kinase activity. Gray recently discovered the first allosteric non-ATP competitive inhibitors of the Bcr-Abl, the causative oncogene in Chronic Myelogenous Leukemia (CML). Currently, his lab is seeking to design allosteric Bcr-Abl kinase inhibitors that, in combination with the clinical stage ATP-competitive inhibitors, can target all the clinically observed Bcr-abl kinase mutants.

A second major breakthrough has been the discovery of irreversible inhibitors of a drug resistant form of the epidermal growth factor receptor tyrosine kinase (EGFR). In addition, he has developed novel inhibitors of the fibroblast growth factor receptor tyrosine kinase (FGFR), the mitotic spindle checkpoint kinase (Mps1), ephrin receptor tyrosine kinases and the mammalian target of rapamycin (mTor). Gray's work on kinase inhibitors focuses on optimizing the potency, selectivity and pharmacological properties of the inhibitors he discovers to the point that they become generally useful as research tools or as potential drug candidates.

Gray received his doctorate in chemistry from the University of California at Berkeley in 1999. Through the generous contribution of an anonymous donor, the AACR established this award in 1979 to give recognition to a young investigator on the basis of meritorious achievement in cancer research. Gray's lecture, "Pharmacological Validation of Kinase Targets," will take place at 4 p.m. ET on Tuesday, April 5 in room W415A of the Orange County Convention Center.

Philip C. Hanawalt, Ph.D., the Morris Herzstein professor of biology at Stanford University and a pioneer in the field of DNA repair, will receive the Fifth Annual AACR Princess Takamatsu Memorial Lectureship for international collaboration.

"I am deeply honored on behalf of my many worthy students and research associates from over 30 different countries to accept this prestigious recognition. The award is particularly important to me because of my great admiration for the lifetime dedication of Princess Takamatsu to the support of international cooperation in research on the causes of cancer and its eradication," said Hanawalt.

In 1963, Hanawalt and his student, David Pettijohn, first reported DNA repair replication in Escherichia coli. That seminal observation, along with cotemporaneous findings from the groups of Richard Setlow and Paul Howard-Flanders, constituted the discovery of the excision repair of damaged DNA, launching a new biological field that continues to grow and provide remarkable insights into the etiology of cancer, aging and human hereditary disease.

Hanawalt's group went on to discover intragenomic heterogeneity of DNA repair ? demonstrating that repair does not occur uniformly throughout the genome. Expressed genes, in particular the transcribed strands of expressed genes, were more efficiently repaired than were silent genes and non-transcribed strands. Novel methods were developed to document and characterize this pathway of transcription-coupled DNA repair in bacteria, yeast and mammalian cells.

His current research focuses on effects of particular DNA lesions and unusual DNA structures on transcription and repair, including studies on the responses to oxidative DNA damage in cells from victims of the hereditary DNA repair deficiency disorders, xeroderma pigmentosum, Cockayne syndrome and UV-sensitive syndrome.

In addition to his groundbreaking research, and his training of a remarkable number of students from all over the world, Hanawalt has propelled the field by organizing numerous meetings, including the first international conference on DNA repair in 1974.

The AACR Princess Takamatsu Memorial Lecture is presented to a scientist whose novel and significant work has had or may have a far-reaching impact on the detection, diagnosis, treatment or prevention of cancer, and who embodies the dedication of the Princess to multinational collaborations. Hanawalt's lecture, "Transcription, DNA Repair and Cancer," will take place at 3:30 p.m. ET on Monday, April 4 in room 415B/C of the Orange County Convention Center.

Jean-Pierre Issa, M.D., will be awarded the 35th Annual AACR Richard and Hinda Rosenthal Memorial Award in recognition for his far reaching contributions to the field of epigenetics and its clinical applications in leukemia therapy. An American Cancer Society clinical research professor and chief of the section of translational research in the department of leukemia, Issa is also co-director of the Center for Cancer Epigenetics in the Institute of Basic Science Research at The University of Texas MD Anderson Cancer Center, Houston, Texas.

"It is wonderful to be recognized by my peers in the most prestigious cancer research organization in the world, and very humbling to join the list of previous winners of the AACR Richard and Hinda Rosenthal Memorial Award," he said. "Translational research is now a buzzword, but the AACR recognized its importance early on, at a time when it was neither prestigious nor adequately funded. It has been amazing to watch the progress in this field over the past 10 years, and I am lucky and proud to have been part of it. This award also legitimizes the work of many scientists who have taken the field of cancer epigenetics from a fringe hypothesis 20 years ago to the forefront of cancer research. Any contribution I have made must be seen in the context of this remarkable group of scientists."

Issa was involved in pivotal studies that established epigenetic changes as alternates to genetic changes in tumor-suppressor gene inactivation: He was the first to describe the effects of aging on abnormal DNA hypermethylation and gene silencing; his laboratory described the CpG Island Methylator Phenotype and he played a pivotal role in the development of hypomethylation based epigenetic therapy.

Issa took an active role in moving this information to the clinic. Results of his Phase I biologic study showed that decitabine was most active as a hypomethylating drug at low doses. This observation led to a series of new clinical trials with decitabine, showing activity in various leukemias. Further studies showed responses to the drug were preceded by epigenetic modulation, and that gene expression induction

correlated with response, thus closing the loop on these proof-of-principle studies for epigenetic therapy.

Issa has published over 250 papers that have garnered more than 16,000 citations. He is a key member of the AACR/Stand Up To Cancer Epigenetics Dream Team.

This award is designed to provide incentive to young investigators relatively early in their careers. It was established in 1977 by the AACR and the Rosenthal Foundation to recognize research that has made, or promises to make, a notable contribution to improved clinical care in the field of cancer. Issa's lecture, "Epigenetic Therapy," will take place at 10:30 a.m. ET on Wednesday, April 6 in room W320 of the Orange County Convention Center.

Guillermina Lozano, Ph.D., chair and professor in the department of genetics at The University of Texas MD Anderson Cancer Center, is the recipient of the Sixth Annual AACR-Minorities in Cancer Research Jane Cooke Wright Lectureship. Lozano, an internationally recognized scientist and leader in understanding the regulation of the p53 tumor suppressor pathway, is committed to promoting the careers of minority investigators in cancer research and has recruited an outstanding group of investigators at MD Anderson.

"I am honored to receive this award for my commitment to fostering the careers of minorities in cancer research," Lozano said.

In a landmark study, Lozano was the first to identify p53 as a transcriptional activator and showed that the common p53 mutants failed to activate transcription. She made the groundbreaking observation that embryonic lethality afforded by germ-line inactivation of Mdm2 was rescued by coincident deletion of germ-line p53, ushering in the modern era of p53 biology by genetically demonstrating the critical role Mdm2 plays in restraining untoward p53 activity.

Using a mouse model with a p53 missense mutation that distinguishes cell cycle arrest from apoptotic pathways, Lozano demonstrated that p53 arrest of cell cycle and maintenance of chromosomal stability are as important as apoptosis in preventing tumorigenesis. This seminal work established the dual role of p53 as gatekeeper and caretaker.

Additionally, she collaborates with clinical investigators to translate her findings to develop more effective cancer therapeutic regimens. By incorporating both K-ras and p53 missense mutations, she worked with oncologists to develop an improved mouse model that more closely simulates human metastatic lung adenocarcinoma than previous models.

Since 1988, Lozano has directed a productive and independent research program with continuous funding from the National Cancer Institute (NCI). In addition, she has published 135 peer-reviewed and review articles in prestigious journals. She received her doctorate from Rutgers University and completed post-graduate work at Princeton University. Earlier this year, Lozano was elected a fellow in the American Association for the Advancement of Science for her distinguished

contributions to the field of cancer genetics and molecular biology. She also won the 2010 MD Anderson Faculty Achievement Award for Basic Research.

The AACR-Minorities in Cancer Research Jane Cooke Wright Lectureship was established in 2006 to give recognition to an outstanding scientist who has made meritorious contributions to the field of cancer research and who has, through leadership or by example, furthered the advancement of minority investigators in cancer research. Lozano's lecture, "The p53/MDM2 Axis in Tumor Development and Response to Therapy," will take place at 4:15 p.m. ET on Sunday, April 3 in the Orange County Convention Center's West Hall F5.

Carol L. Prives, Ph.D., the Da Costa professor of biology at Columbia University, will be awarded the 14th Annual AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship for her exceptional contributions to our understanding of the regulation and function of p53 as a major tumor suppressor.

"The AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship is doubly meaningful to me," said Prives. "First, it honors the dedication of the past and present members of my group to elucidating the mechanisms underlying cancer through basic research. Second, in the larger arena, it recognizes the fact that women have played incredibly important roles in cancer research."

Prives was among the first to make the critical discovery that p53 is a sequence specific DNA binding protein that functions as a transcription factor. This laid the groundwork for unraveling how p53 works. Her work has also illuminated our understanding of p53 as a tumor suppressor, since she showed that many of the mutant p53 proteins that are frequently found expressed in cancers are dysfunctional as transcription factors. Her findings revealed processes by which wild-type p53 regulates expression of genes that mediate cell cycle and cell death and conversely how tumor-derived mutant forms of p53 may facilitate tumor cell morphology and growth.

Prives contributed significantly to the knowledge of how p53 is regulated. Her research revealed how stress, such as DNA damage, might signal to stabilize p53 by promoting the phosphorylation of p53, which inhibits its interaction with the ubiquitin ligase (MDM2) that normally targets p53 for degradation. She has characterized the structure and functions of both p53 and Mdm2 proteins and how they are regulated by both covalent and non-covalent modifiers.

Prives received her Bachelor of Science and doctorate degree from McGill University. She has served on both extramural and intramural National Institutes of Health (NIH) review panels and has chaired both the Experimental Virology and Cancer Molecular Pathobiology NIH study sections. She sits on numerous science advisory boards and senior panels, serves on the editorial boards of Cell, Genes & Development and other journals. She is a senior editor for the AACR journal Molecular Cancer Research, a member of the AACR Nominating Committee, and served on the AACR Board of Directors (2004 to 2007). She became an American Cancer Society research professor in 1998, and was elected to the American Academy of Arts and Sciences, the Institute of Medicine and the National Academy

of Sciences. Last year, she received the NCI Rosalind E. Franklin Award for Women in Science. She has published more than 200 research articles.

The AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship was established in 1998 in honor of renowned virologist and discoverer of the Friend virus, Dr. Charlotte Friend, for her pioneering research on viruses, cell differentiation, and cancer. The lectureship recognizes an outstanding scientist who has made meritorious contributions to the field of cancer research and who has, through leadership or by example, furthered the advancement of women in science. Prives' lecture, "Lessons Learned from Studying the p53 Tumor Suppressor," is scheduled for presentation at 5:30 p.m. ET on Saturday, April 2 in room W415D of the Orange County Convention Center.

Ching-Hon Pui, M.D., chair of the department of oncology; co-leader of the Hematological Malignancies Program; Fahad Nassar Al-Rashid Chair of Leukemia Research; and an American Cancer Society professor at St. Jude Children's Research Hospital, will be awarded the 16th Annual AACR Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research.

"I am humbled by this great honor, which I accept on behalf of my mentors and colleagues with whom I have worked throughout my career to advance understanding and treatment of childhood leukemia," said Pui. "Despite our progress, cancer remains the leading cause of death by disease in U.S. children, reminding us there is still much work to be done. Our vision is a future in which treatments are not only more effective, but less toxic, and our patients not only survive, but thrive. I thank the AACR for this award and St. Jude for making my work possible."

Pui has been at the forefront of leukemia research for the past three decades. His efforts have facilitated numerous studies in leukemia cell biology and have driven progress in leukemia treatment.

His work led to the discontinuation of end-of-therapy testicular biopsy and the successful omission of prophylactic cranial irradiation in all patients, once regarded as a standard treatment for childhood leukemias, thus sparing patients from the devastating side effects. By rapidly translating advances in cytogenetic, molecular genetics, pharmacodynamic and pharmacogenetic research into clinical trials, Pui and his team have been able to help boost the cure rate for childhood acute lymphoblastic leukemia (ALL) to 90 percent and acute myeloid leukemia to 70 percent.

More recently, his treatment approach resulted in an exceptionally high cure rate, approaching 90 percent in older adolescents with ALL. Pui's team pioneered the use of pharmacogenetics to individualize chemotherapy, and used genome-wide analyses to accurately classify leukemias; to identify cooperative mutations and molecular targets for therapy; to optimize use of existing drugs; and to disclose host genes associated with the development of leukemia. His organizational and leadership skills were instrumental in establishing the International Childhood ALL Working Group in 1995.

The AACR Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research is presented to a scientist who has made outstanding achievements in clinical cancer research. Pui's lecture, "Toward the Cure of Childhood Acute Lymphoblastic Leukemia," is scheduled for 4 p.m. on April 5 in room W320 of the Orange County Convention Center.

John T. Schiller, Ph.D., head of the Neoplastic Disease Section in the Laboratory of Cellular Oncology at the NCI, is the recipient of the 20th Annual AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention. The award is given in recognition of his longstanding achievements in human papillomavirus (HPV) research; development of the virus-like particle (VLP) prophylactic HPV vaccine (FDA-approved in 2006); leadership in discussions concerning global public health issues related to HPV vaccination; and efforts to facilitate technology-transfer to HPV vaccine manufacturers in developing countries.

"I am very pleased to receive this award on behalf of the current and former members of my laboratory, particularly Drs. Lowy and Kirnbauer, and also on behalf of the many colleagues in the field of HPV biology and epidemiology who provided the critical conceptual underpinnings for the development and testing of vaccines against cancer-associated HPVs," said Schiller. "It represents a gratifying acknowledgement by the AACR and the ACS of the significance our collective work for cancer prevention efforts worldwide."

Schiller made the two key discoveries underpinning the current VLP vaccine: that the L1 major structural protein of papillomaviruses could self-assemble into non-infectious VLPs, and that VLPs could induce high-titer neutralizing antibodies. He went on to develop a practical HPV vaccine, proved it effective in animals, developed the serological assays critical for vaccine development and characterization, identified the vaccine's salient immune responses, and demonstrated its safety and immunogenicity in humans.

Schiller, along with Lowy and Kirnbauer, is an inventor on government-owned patents covering these discoveries, now licensed to Merck and GlaxoSmithKline, who are developing HPV VLP vaccines commercially. Merck and GlaxoSmithKline vaccines were recently approved in more than 100 countries. These vaccines are expected to have a profound impact on morbidity and mortality associated with cervical and other HPV-associated cancer.

Schiller currently leads the efforts to develop second-generation vaccines and HPV microbicides to improve international public health. He is a thought leader in promoting discussion of global public health issues related to HPV vaccine implementation and has served as an advisor to the World Health Organization and the Gates Foundation on these issues. He is also a major facilitator of technology transfer to vaccine manufacturers in developing countries. Schiller is working closely with companies in India to produce the current-generation vaccine and to bring to clinical trials low cost second-generation prophylactic HPV vaccines.

The AACR-American Cancer Society Award for Research Excellence in Cancer

Epidemiology and Prevention was established in 1992 to honor outstanding research accomplishments in the fields of cancer epidemiology, biomarkers and prevention. Schiller's lecture, "Why Prophylactic HPV Vaccines Work So Well," will take place at 3 p.m.ET Tuesday, April 5 in room W415D of the Orange County Convention Center.

Gregory L. Verdine, Ph.D., Erving professor of chemistry in the departments of stem cell and regenerative biology and of chemistry and chemical biology at Harvard University, will receive the 5th Annual AACR Award for Outstanding Achievement in Chemistry in Cancer Research. From his work elucidating the molecular mechanism of the antitumor drug mitomycin C, to his studies on DNA methylation, DNA repair and peptide-based agents to target intracellular protein-protein interactions, Verdine has made pioneering, creative and significant contributions to both the basic science of cancer and toward treatment of the disease.

"Cancer is a molecular disease as much as a genetic disease, because the genetic manifestations of cancer result directly from changes in the chemical structure of the genome," said Verdine. "Treatment of the disease has increasingly focused on creating chemical agents that exploit the unique molecular landscape of tumors. Thus the science of cancer and of chemistry are fundamentally connected, and this award has been created to recognize and foster work at the intersection between the two worlds. We are thrilled that our contributions and those of our collaborators aimed at understanding the molecular origins of cancer and at discovering powerful new agents for its treatment, have been chosen for recognition in this very special way."

Verdine elucidated the catalytic mechanism of DNA methylation by DNA methyltransferases and developed the chemistry by which to produce complexes of these enzymes bound in a suicidally inactivated complex with their substrates. This chemistry paved the way for the X-ray structure determination of DNA methyltransferases bound to DNA.

He has provided the most comprehensive description available to date for how DNA repair proteins locate and excise mutagenic damaged nucleobases in DNA. Verdine isolated the enzyme responsible for base-excision repair of 8-oxoguanine (oxoG) in DNA. His crystallogra¬phic structure of the human enzyme, hOGG1, bound to DNA provided the first view of how this important endogenous mutagen is recognized and excised. Using a disulfide crosslinking technology developed in his lab, Verdine has revealed for the first time how these proteins wrench undamaged DNA while searching for lesions, how encounter with a lesion triggers ejection of the damage from the DNA duplex, and how the chemistry of repair proceeds.

Verdine has achieved success in tackling one of the most vexing problems in cancer drug discovery, the difficulty of targeting transcription factors and other proteins that engage in intracellular protein-protein interactions. He developed the α-helix peptide "stapling" system that has provided the first new class of cell-permeable molecules that can target intracellular proteins previously believed to be "undruggable."

Verdine earned his Bachelor of Science degree in 1982 from St. Joseph's University, his doctorate in 1986 from Columbia University, and did postdoctoral work at MIT and Harvard Medical School in 1986-1987. He joined the department of chemistry at Harvard University in 1988 and the department of stem cell and regenerative biology in 2009. Together with Stanley J. Korsmeyer, Verdine co-founded the Harvard/Dana-Farber Program in Cancer Chemical Biology and was named its first director. He also serves as the director of the Dana-Farber Chemical Biology Initiative. Verdine founded Gloucester Pharmaceuticals and advised the company through the successful clinical development of romidepsin for cutaneous T-cell lymphoma, FDA approval of the drug, and merger of the company with Cellgene.

The AACR and its Chemistry in Cancer Research Working Group established the Award for Outstanding Achievement in Chemistry in Cancer Research in 2007 to recognize the importance of chemistry to advancements in cancer research. The award is given for outstanding, novel and significant chemistry research, which has led to important contributions to the fields of basic cancer research; translational cancer research; cancer diagnosis; the prevention of cancer; or the treatment of patients with cancer. Verdine's lecture, "Chemical Biology Approaches to Problems in Cancer," is scheduled for 3 p.m. ET on Tuesday, April 5 in room W415A of the Orange County Convention Center.

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