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The insightful work of these dedicated investigators is characterized by scientific excellence, translational value, and lasting impact. The members of the selection committee are confident that they will continue to be major contributors in the field of cancer research for years to come.

Stephen Goff, PhD, chairman of the Paul Marks Prize search committee

The prize winners are:

Scott A. Armstrong, MD, PhD, 44, of Dana-Farber Cancer Institute and Children's Hospital Boston, whose notable achievements in the fields of cancer stem cell research and genomics have led to landmark findings that point to potential new therapies for leukemia.

[Kornelia Polyak, MD, PhD](#), 44, of Dana-Farber Cancer Institute, who is being recognized for her pioneering genomic discoveries in normal and cancerous breast tissue and for her efforts to translate those findings into improved diagnostic and therapeutic approaches.

[Victor E. Velculescu, MD, PhD](#), 41, of Johns Hopkins Kimmel Cancer Center, whose creation and application of novel technologies to detect genomic alterations in cancer and to develop personalized biomarkers has elucidated key features underlying this disease and led to opportunities for individualized approaches to cancer care.

"It is important to encourage this new generation of talented scientists because they have a unique opportunity to help influence the future of cancer research and treatment," said [Craig B. Thompson, MD](#), President and CEO of Memorial Sloan Kettering. "This year's winners have clearly taken full advantage of that opportunity early in their careers with outstanding records of clinically relevant research that has yielded a better understanding of the genetic underpinnings of tumor formation and development."

The winners were selected by a committee made up of prominent members of the cancer research community and chaired by Stephen Goff, PhD, a Howard Hughes Medical Institute (HHMI) investigator at Columbia University College of Physicians and Surgeons. "The insightful work of these dedicated investigators is characterized by scientific excellence, translational value, and lasting impact," he said. "The members of the selection committee are confident that they will continue to be major contributors in the field of cancer research for years to come."

Including this year's winners, a total of \$850,000 has been awarded to 18 promising young scientists since 2001, when the prize was created to honor the many contributions made by distinguished scientist, teacher, and leader Paul A. Marks, MD, President Emeritus of Memorial Sloan Kettering, during

the 19 years he led the Center.

## Scott A. Armstrong

Dr. Armstrong is a pediatric oncologist at Dana-Farber Cancer Institute and Children's Hospital Boston, where his research program is at the interface of cancer genetics, stem cell biology, and cancer modeling. His scientific focus on the genetic abnormalities that are common in childhood [leukemias](#) complements his clinical expertise in treating children with these cancers.

Dr. Armstrong uses genome-wide technologies to characterize the molecular pathways responsible for leukemia development. Early in his career, he and his colleagues identified a unique expression signature in leukemias that have a specific broken chromosome, or rearrangement, in the mixed lineage leukemia (MLL) gene - a common trait of a lethal blood cancer called acute lymphoblastic leukemia (ALL) that strikes infants in their first year of life.



Scott A. Armstrong, MD, PhD

He then showed that the receptor tyrosine kinase FLT3 is highly expressed and often mutated in MLL leukemias, identifying FLT3 as a potential therapeutic target in ALL. An ongoing international clinical trial is evaluating FLT3 inhibitor therapy in children with relapsed leukemia.

In another study, Dr. Armstrong and his team were the first to isolate rare leukemia stem cells in a mouse model of leukemia. They found that leukemia stem cells - which survive through endless self-renewal and are resistant to typical cancer treatments - are largely different from normal stem cells, but acquire stem-cell-like properties. This research has led to the search for pathways that are specifically required in leukemia stem cells but not normal stem cells.

Recently, Dr. Armstrong showed that one such pathway, the Wnt/beta-catenin pathway, is necessary for survival of leukemia stem cells, but not normal stem cells, suggesting that drugs designed to target and block this pathway may eradicate leukemia stem cells and prevent the growth, development, and recurrence of AML.

Dr. Armstrong's research is now trying to understand which epigenetic pathways are required for maintaining the stem-cell-like features of cancer - discoveries that may lead to the development of additional therapeutic molecules to target and inhibit enzymes that control gene expression in those pathways. His recent work demonstrated that inactivation of the histone methyltransferase DOT1L is a potential therapeutic approach in leukemia.

"The most exciting part of our findings is that we now have a small molecule that can inhibit this enzyme, and early studies have shown it to have a very specific antitumor effect against leukemias that have an MLL rearrangement," said Dr. Armstrong.

"Scott Armstrong is an extremely talented individual whose research program has helped define new directions for the field of leukemia genetics and yielded numerous important observations," said HHMI investigator Tyler Jacks, PhD, Director of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology and a previous Paul Marks Prize winner, who nominated Dr. Armstrong for the award. "He is a prime example of a physician-scientist who is committed to carrying out cutting-edge research and translating new insights into improved diagnosis and treatment of disease."

Dr. Armstrong obtained his MD and PhD degrees from the University of Texas Southwestern Medical School in 1996. He completed an internship and residency at Children's Hospital Boston, and a clinical fellowship in pediatric hematology and oncology at Dana-Farber. Dr. Armstrong joined the staff of Dana-Farber, Children's Hospital Boston, and Harvard Medical School in 2001. In 2008, he was appointed Director of Translational Research in Pediatric Cancer and Blood Disease, a joint venture between Dana-Farber and Children's Hospital Boston. He has also served as co-Director of the Cancer Program at the Harvard Stem Cell Institute since 2009.

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## Kornelia Polyak

Dr. Polyak is Associate Professor of Medicine at Dana-Farber, where her research is dedicated to the molecular analysis of human [breast cancer](#) and the translation of those findings into clinical practice. Her studies have focused on analyzing all the cell types that compose a tumor, identifying the genetic differences between normal and cancerous breast tissue, and defining the role of stem cells in the development of breast cancer.

Dr. Polyak has been at the forefront of optimizing and employing cutting-edge gene-analysis technologies such as serial analysis of gene expression (SAGE), which has played an important role in her study of ductal carcinoma in-situ (DCIS, a localized, early-stage breast cancer). Because DCIS tissue samples tend to be small, she and her colleagues scaled down the SAGE method in order to enhance their ability to analyze very small numbers of breast tumor cells. Her lab was one of the first to publish the comprehensive gene expression and genetic profiles of all major cell types from DCIS, invasive breast cancers, and normal breast tissue.



Kornelia Polyak, MD, PhD

Dr. Polyak's team subsequently studied multiple cell types within a breast tumor and its microenvironment (the benign cells surrounding the tumor) and found that gene expression was altered by epigenetic changes that were absent in normal breast tissue. They also found that altered gene function in the tumor's microenvironment can induce proliferation and increase aggression in breast cancer cells.

In later work Dr. Polyak found that when DCIS becomes invasive, the cause lies not in the tumor cells themselves but in abnormalities in the tumor's microenvironment that cause the walls of the milk duct to deteriorate, enabling tumor cells to escape. These findings may lead to screening tests to determine whether DCIS is likely to spread based on abnormalities in the ducts' lining, and also set the stage for new treatments.

In addition, Dr. Polyak is known for her studies characterizing the differences among stem cells in normal breast tissue and defining their role in tumor development. She led a study that identified two genetically diverse populations of cancer cells that are responsible for breast tumor progression and recurrence, suggesting that all the cancer cells would need to be eliminated for effective treatment, not just the cancer stem cells, which was the prevailing view at the time. She and her team are currently trying to understand why tumors are heterogeneous and whether changes in diversity before and after treatment could be predictive of clinical outcome.

"Kornelia Polyak is a superb example of someone who can bring the best of basic science to translational medicine," commented Edward J. Benz, Jr., MD, President and CEO of Dana-Farber, who nominated Dr. Polyak for the prize. "She is an innovator and has made seminal contributions to cancer research by exploring novel areas and applying creative approaches to find clinically relevant clues."

A self-described "fan of Darwin and evolution," Dr. Polyak sums up her work: "We need to bear in mind that tumor progression is an evolutionary process. In order to understand what is driving this evolution and how to stop it we must study the tumor as a whole ecosystem, including its microenvironment. We can use what we learn about a tumor's diversity, its evolving cell populations, and the molecular changes that occur during its growth to eventually develop better ways of treating cancer."

Dr. Polyak received her MD degree from Albert Szent-Györgyi Medical University and her PhD from [Weill Cornell Graduate School of Medical Sciences](#). She completed a research fellowship in oncology at Johns Hopkins Oncology Center and became an independent researcher at Dana-Farber in 1998.

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## Victor E. Velculescu

Dr. Velculescu is Professor of Oncology and co-Director of the Cancer Biology Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. He is internationally known for developing a series of novel genomic technologies and applying these cutting-edge tools to make seminal discoveries that have important implications for the basic understanding and clinical management of cancer.

It became clear to him early on that examining the underlying genetic changes that frequently occur in cancer was critical to obtaining a better understanding of the disease. In order to simplify this daunting task, Dr. Velculescu developed a method called serial analysis of gene expression (SAGE) to simultaneously study thousands of genes, measure their expression, and quickly identify the expression differences between normal cells and cancer cells. He and his colleagues are responsible for a number of critical findings as a result of this approach, including the first systematic analyses of gene expression in a number of cancers and the identification of a novel set of genes uniquely expressed in cancer that serve as targets for therapy.



Victor E. Velculescu, MD, PhD

Dr. Velculescu is also responsible for developing methods to analyze the cancer genome, including high-throughput sequencing approaches and a variation on SAGE called Digital Karyotyping, which is used to identify genetic alterations that may be useful for therapeutic or diagnostic intervention. While SAGE was useful for looking at the activity of genes, Digital Karyotyping was designed to detect copy number changes, including genetic amplifications and deletions that frequently occur in cancer cells. Under Dr. Velculescu's direction, these genomic approaches were used to identify alterations in the *PIK3CA* gene, which has proven to be one of the most frequently mutated genes ever identified in cancer, including colon, breast, brain, and other tumors. A number of clinical trials currently under way are evaluating whether mutations in *PIK3CA* can help identify patients who are more likely to respond to targeted therapies against this enzyme or its signaling pathway.

Dr. Velculescu's creation of a next-generation sequencing method to develop personalized biomarkers offers the most significant clinical potential among his research accomplishments. The technology, called personalized analysis of rearranged ends (PARE), is designed to identify genetic alterations, or rearrangements, specific to a patient's cancer DNA. Researchers are studying the ability of PARE-based biomarker blood tests to spot cancers that may be missed by conventional imaging methods like CT scans and to detect the presence of cancer cells in surgical margins or lymph nodes removed during surgery.

"This technology is poised to become an important tool in the use of genetic information for the personalized management of patients," said Dr. Velculescu. "Our long-term goal is to refine these genomic approaches beyond the research environment and use them to help people with cancer."

"Victor Velculescu is one of a handful of individuals who have developed groundbreaking genomic approaches and applied them to make important clinical problems," said HHMI investigator Bert Vogelstein, MD, Director of the Ludwig Center for Cancer Genetics and Therapeutics at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, who nominated Dr. Velculescu for the prize. "His extraordinary record illustrates his courage to tackle projects of huge proportions aimed at understanding and treating human disease."

Dr. Velculescu obtained his MD and PhD degrees in 1999 from Johns Hopkins University, where he also completed his postdoctoral fellowship in oncology. He became Assistant Professor of Oncology in 2002, Associate Professor of Oncology in 2006, and Professor of Oncology in 2011. He is also Director of Cancer Genetics at the Ludwig Center for Cancer Genetics and Therapeutics at the Sidney Kimmel Comprehensive Cancer Center.

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