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(From left) Paul Marks Prize winners Scott Armstrong, Kornelia Polyak, and Victor Velculescu

## Summary

Memorial Sloan Kettering Cancer Center feted three gifted young investigators for their insightful contributions to cancer research in a public symposium on December 1, 2011.

Memorial Sloan Kettering Cancer Center feted three gifted young investigators for their insightful contributions to cancer research in a public symposium held at the Center on December 1, 2011. The investigators received the [Paul Marks Prize for Cancer Research](#), a biennial award honoring promising

scientists under the age of 46.

“It is important to encourage this new generation of outstanding researchers early in their careers because they have a unique opportunity to help influence the future of cancer care,” says [Craig B. Thompson](#), President and CEO of Memorial Sloan Kettering. “Their clinically relevant work has provided a better understanding of the genetic underpinnings of tumor formation and development.”

The 2011 recipients of the Paul Marks Prize are Scott A. Armstrong, 44, of Dana-Farber Cancer Institute and Children’s Hospital Boston; [Kornelia Polyak](#), 44, of Dana-Farber Cancer Institute; and [Victor E. Velculescu](#), 41, of Johns Hopkins Kimmel Cancer Center.

## Scott A. Armstrong

A pediatric oncologist, Dr. Armstrong uses genome-wide technologies to characterize the genetic abnormalities and molecular pathways responsible for leukemia development. His landmark findings have pointed to potential new therapies for leukemia.

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 that strikes infants in their first year of life.

He then showed that the protein FLT3 is highly expressed and often mutated in MLL — a finding that has spurred an international clinical trial to evaluate FLT3 inhibitor therapy in children with relapsed leukemia.

Dr. Armstrong and his team were the first to isolate rare leukemia stem cells — which survive through endless self-renewal and are resistant to standard treatments — in a mouse model of leukemia. This research led him to search for altered pathways in leukemia stem cells. One study he led suggested that drugs designed to target and block one such pathway — the Wnt/beta-catenin pathway — may eradicate leukemia stem cells and prevent the growth, development, and recurrence of acute myelogenous leukemia.

He also demonstrated that inactivation of the enzyme DOT1L is a possible therapeutic approach for 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 specific anti-tumor effect against leukemias that have an MLL rearrangement,” says Dr. Armstrong.

“Scott is an extremely talented physician-scientist whose cutting-edge translational research program has helped define new directions for the field of leukemia genetics and has yielded numerous important observations,” says Howard Hughes Medical Institute (HHMI) investigator Tyler Jacks, Director of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology and a previous Paul Marks Prize winner, who was among those who nominated Dr. Armstrong for the award.

Dr. Armstrong obtained his MD and PhD degrees from the University of Texas Southwestern Medical School. He completed an internship and residency at Children’s Hospital Boston and a clinical fellowship at Dana-Farber.

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## Kornelia Polyak

Dr. Polyak has been at the forefront of optimizing cutting-edge gene-analysis technologies to analyze normal and cancerous breast tissue. She is recognized for her efforts to translate her pioneering genomic discoveries into improved diagnostic and therapeutic approaches for [breast cancer](#).

She and her colleagues scaled down an approach called serial analysis of gene expression (SAGE) to enhance their ability to study very small tissue samples of ductal carcinoma in situ (DCIS), a localized, early-stage breast cancer. Her lab was one of the first to publish the comprehensive genetic profiles of all major cell types from DCIS, invasive breast cancers, and normal breast tissue.

Dr. Polyak and her team studied multiple cell types within a breast tumor and the benign cells surrounding it — called the microenvironment — and found that gene expression was altered by epigenetic changes that were absent in normal breast tissue. Later, she demonstrated that abnormalities in a tumor’s microenvironment can cause the walls of the milk duct to deteriorate, enable tumor cells to escape, and lead to invasive cancer. These findings may result in screening tests to determine whether DCIS is likely to spread based on alterations in the ducts’ lining and set the stage for new treatments.

Her lab also identified genetically diverse populations of cancer cells that are responsible for breast tumor progression and recurrence, suggesting that all cancer cells would need to be eliminated for effective treatment, not just cancer stem cells. She and her team are now investigating why tumors are heterogeneous and whether changes in diversity before and after treatment could be predictive of clinical outcome.

"Kornelia is an innovator and has made seminal contributions to cancer research by exploring novel areas and applying creative approaches to find clinically relevant clues," comments Edward J. Benz, Jr., President and CEO of Dana-Farber, who nominated Dr. Polyak for the prize.

Calling herself a "fan of Darwin and evolution," Dr. Polyak explains that "by studying a tumor as a whole ecosystem, including its microenvironment, we can use what we learn about its diversity, evolving cell populations, and molecular changes that occur during its growth to develop better ways of treating cancer."

Dr. Polyak received her MD degree from Albert Szent-Györgyi Medical University in Hungary and her PhD degree from [Weill Cornell Graduate School of Medical Sciences](#). She completed a research fellowship in oncology at Johns Hopkins Kimmel Cancer Center.

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## Victor E. Velculescu

Dr. Velculescu is known for developing a series of novel genomic technologies and applying them to make seminal discoveries that have implications for the basic understanding and clinical management of cancer.

Working with his mentor Kenneth W. Kinzler, Dr. Velculescu created the SAGE method to simultaneously study thousands of genes, measure their activity, and quickly identify the expression differences between normal cells and cancer cells. Dr. Velculescu and his colleagues are responsible for a number of critical findings made using 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.

Drs. Velculescu, Kinzler, and their colleagues have also developed other types of methods to analyze the cancer genome, including digital karyotyping, which is used to identify genetic alterations that frequently occur in cancer cells and may be useful for therapeutic or diagnostic intervention. These approaches were employed to identify alterations in the *PIK3CA* gene, which has proven to be one of the most frequently mutated genes ever identified in cancer. A number of clinical trials 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 and his colleagues have also implemented a next-generation sequencing method called personalized analysis of rearranged ends (PARE) to identify genetic rearrangements specific to an individual patient's cancer. "This technology is poised to become an important tool in the use of genetic information for the personalized management of patients," he explains. 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.

"Victor is one of a handful of individuals who have developed groundbreaking genomic approaches and applied them to help understand and treat human disease," says HHMI investigator Bert Vogelstein, 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.

Dr. Velculescu obtained his MD and PhD degrees from Johns Hopkins University, where he also completed his postdoctoral fellowship in oncology.

"The exceptional work of these dedicated investigators is characterized by scientific excellence, translational value, and lasting impact," says Stephen Goff, an HHMI investigator at Columbia University College of Physicians and Surgeons, who chaired the selection committee.

Each of the winners received \$50,000 and spoke about their innovative work at the December 1 symposium. Memorial Sloan Kettering has awarded a total of \$850,000 to 18 scientists since 2001, when the prize was created to honor the many contributions made by distinguished scientist and teacher Paul A. Marks, President Emeritus of Memorial Sloan Kettering, during the 19 years he led the Center.

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