

SpinOdyssey Grantees

Investigator	Institution	Donor Amount	Project Start	Project End
Douglas R. Hurst, PhD	University of Alabama, Birmingham	649,000	1-Jul-11	30-Jun-15
Pameeka S. Smith-Pearson, PhD	Duke University Medical Center	102,000	1-Oct-10	30-Sep-12
Brian D. Lehmann, PhD	Vanderbilt University Medical Center	150,000	1-Jul-10	30-Jun-13
Jenifer Prosperi, PhD	University of Chicago	102,000	1-Jul-10	30-Jun-12
Marc L. Mendillo, PhD	Whitehead Institute for Biomedical Research	138,000	1-Jul-09	30-Jun-12
Daniel K. Nomura, PhD	The Scripps Research Institute	113,701	1-Jul-09	14-Jul-10
Rachel Dusek, PhD	Stanford University	138,000	1-Sep-08	31-Aug-11
Traci R. Lyons, PhD	University of Colorado, Boulder	138,000	1-Sep-08	31-Aug-11
Joshua L. Andersen, PhD	Duke University Medical Center	138,000	1-Jul-08	30-Jun-11
Christopher T. Veldkamp, PhD	Medical College of Wisconsin	138,000	1-Jul-08	31-Aug-09
Meredith Crosby, PhD	Yale University	138,000	1-Jul-07	31-Jul-10
David DeNardo, PhD	University of California, San Francisco	138,000	1-Jul-07	30-Jun-10
Eric Smith, PhD	Fred Hutchinson Cancer Research Center	138,000	1-Jul-07	16-Oct-09

Investigator	Institution	Donor Amount	Project Start	Project End
Boris Wilson, PhD	Dana-Farber Cancer Institute	138,000	1-Jul-07	30-Nov-08
Michael H. Lam, PhD	Whitehead Institute for Biomedical Research	110,447	1-Jul-06	20-Mar-09
Victor R. Grann, MD, MPH	Columbia University	209,000	1-Jan-06	31-Dec-09
Kevin A. Janes, PhD	Harvard Medical School	138,000	1-Jul-05	30-Jun-08
Ryan B. Jensen, PhD	University of California, Davis	138,000	1-Jul-05	30-Jun-08
Dennis J. Slamon, MD, PhD	University of California, Los Angeles	300,000	1-Jul-04	30-Jun-10
Graham A. Colditz, MD	Washington University, St. Louis	300,000	1-Jul-03	30-Jun-09
Michael P. DiGiovanna, MD, PhD	Yale University	42,000	1-Jan-02	30-Jun-06
Leon O. Murphy, PhD	Harvard Medical School	96,000	1-Jul-00	30-Jun-03
David A. Wah, PhD	Massachusetts Institute of Technology	96,800	1-Jul-00	30-Jun-03
John J. Wysolmerski, MD	Yale University	375,000	1-Jan-00	31-Dec-02

DOUGLAS R. HURST, PHD
University of Alabama, Birmingham
Birmingham, Alabama

Composition of SIN3 Protein Complexes in Breast Cancer Metastasis

The five-year survival rate for people with breast cancer is nearly 100 percent when the disease is confined to the breast. However, this rate drops below 30 percent when the cancer has spread to other parts of the body. Understanding how to effectively treat patients with this advanced form of the disease is therefore vital to reducing breast cancer mortality and improving survival. Although there has been progress in researching breast cancer metastasis – breast cancer that has spread to other parts of the body – little is understood about the mechanism that drives metastasis. Basic research is necessary to understand the specific requirements of cancer cells for the process of metastasis. Once this process is understood and defined, researchers will be able to identify more effective treatments for preventing and treating breast cancer metastasis.

Douglas R. Hurst, PhD, of the University of Alabama, Birmingham, is conducting research into the interaction of cell proteins and DNA to learn how this interaction is associated with breast cancer metastasis. From July 1, 2011 through June 30, 2015, his work is being supported by a SpinOdyssey American Cancer Society grant of \$649,000. Dr. Hurst has identified a group of proteins called SIN3 that together regulate the genes that cause cancer metastasis. He hypothesized that interfering with the activity of this SIN3 protein group could interrupt the ability of cancer cells to metastasize.

Using laboratory animals to test his hypothesis, Dr. Hurst has discovered that altering the composition of the SIN3 protein group leads to suppression of 90 percent of cancer metastasis. In future research, Dr. Hurst hopes to learn what particular characteristic of the SIN3 proteins makes some cancers spread to other parts of the body and some remain confined to the breast. Once this is determined, it may be possible to develop pharmaceutical approaches to managing SIN3 to prevent breast cancer metastasis. This knowledge could enable doctors to know which breast cancer patients are most at risk for metastasis and adjust treatments accordingly.

Dr. Hurst stresses that it is not enough to look at only one protein, but a complex of proteins involved in cancer metastasis. “We need to learn how to tweak the right protein that regulates metastasis without altering other functions of the cell.” Dr. Hurst says. “We have to understand the whole protein complex in order to do this.”

Dr. Hurst says, “Having the necessary funding to get started is critical.” He goes on to state that the SpinOdyssey American Cancer Society grant allowed him to set up his laboratory, hire good people, and focus on his research.

Research does not translate immediately into new treatments, Dr. Hurst says. “It makes all the difference that SpinOdyssey and the American Cancer Society take chances and

fund projects that won't translate into new treatments in three years, but could make all the difference in ten years.”

He is currently assistant professor, Department of Pathology, School of Medicine.

PAMEEKA S. SMITH-PEARSON, PHD
Duke University Medical Center
Durham, North Carolina

The Role of Abl Kinases in Cancer and Metastasis

Most of the thousands of deaths from breast cancer that occur each year are the result of metastasis – cancer that has spread from the original breast tumor to other parts of the body. Metastasis occurs in several steps. First cancer cells detach themselves from the original or “primary” tumor. The cancer cells then escape through the surrounding tissue and into the blood stream where they travel to other parts of the body, enter distant organs or tissues, and form new cancers.

Pameeka Smith-Pearson, PhD, of Duke University Medical Center is interested in a cellular protein – part of cell’s genetic material – called Abl kinase that facilitates metastasis. Abl kinases regulate cell motility – the ability of a cell to move around – and cell adhesion – the ability of a cell to bind itself to another surface. She is working with the support of a SpinOdyssey American Cancer Society grant of \$102,000, which runs from October 1, 2010 to September 30, 2012, to study the role that Abl kinases play in cancer development.

Dr. Smith-Pearson has observed that cellular proteins in cancer metastasis alter the structure of the cell to form protrusions, called invadopodia, that enable cancer cells to detach themselves from a tumor in the breast, break through surrounding tissue, and travel to other organs. Abl kinases interact with other cell proteins that are crucial to the formation of invadopodia. Evidence suggests that the activity of the Abl kinase proteins is elevated in invasive breast, colorectal, and pancreatic cancers. Elevated levels of these and other proteins signal a poor prognosis for women with breast cancer.

In her research, Dr. Smith-Pearson is using a model of tumor metastasis to create images of the progression of tumor cells from their primary site to other organs to elucidate the role that Abl kinases play in promoting cancer metastasis. A better understanding of how these proteins function in the progression and spread of cancer will potentially lead to treatments that inhibit the activity of Abl kinases.

Of particular interest to Dr. Smith-Pearson is how a drug called Imatinib/Gleevec, which inhibits the activity of the Abl kinase protein, can be used along with chemotherapy following initial treatment for breast cancer to prevent breast cancer recurrence. Imatinib/Gleevec is currently FDA-approved for the treatment of some types of leukemia.

Dr. Smith-Pearson says that research into the activity of Abl kinases is leading to a broader understanding of other cell events associated with cancer. In the future, she hopes to focus her research on the cellular events that lead to treatment resistance in breast cancer patients. A certain group of women with particular types of breast cancer do not respond to drugs currently in use. Dr. Smith-Pearson would like to explore how Abl

kinase and other cell proteins interact in drug resistance and how new treatments based on these interactions can benefit women with these types of cancer.

In the current funding environment, Dr. Smith-Pearson says, finding support for basic research is difficult. She is grateful for the support of SpinOdyssey and the American Cancer Society. “The SpinOdyssey American Cancer Society grant has allowed me to focus my attention on research and to expand my research into new and promising areas.”

She is currently a post-doctoral associate in the Department of Pharmacology and Cancer Biology.

BRIAN D. LEHMANN, PHD
Vanderbilt University Medical Center
Nashville, Tennessee

p53 Signaling Axis and Triple Negative Breast Cancer

Breast cancer is diagnosed and treated based on the presence and absence of three genes that play a role in cancer growth and development: the estrogen receptor, the progesterone receptor, and human epidermal growth factor receptor 2. These genes damage the DNA of cells and signal them to grow and develop into cancer. Breast cancer that has these receptors – is “positive” for them – responds well to treatment with anti-estrogen drugs such as tamoxifen (for estrogen and progesterone receptors) or the drug Herceptin (for human epidermal growth factor receptor 2). About 15% of women with breast cancer have a form of the disease called triple negative breast cancer, a very aggressive cancer that lacks these three key molecules and is notoriously difficult to treat. Conventional treatments that work in women whose cancers are positive for the three receptors do not work for women whose cancers lack these three genes. Such women respond well to conventional treatments initially but are much more prone to relapse. There is a major need to better understand the molecular basis of triple negative breast cancer in order to develop effective treatments for this form of the disease.

Normal cells are “programmed” to grow, develop, and die. A gene called p53, which is mutated (damaged) in a majority of breast cancers, promotes the survival of cancer cells by “turning off” the cells programmed death so that the cells continue to grow and develop into cancer. The frequency of the mutation of this gene is significantly higher in women with triple-negative breast cancer.

Brian D. Lehmann, PhD, of Vanderbilt University Medical Center is focusing his research on triple negative breast cancer. With the support of a SpinOdyssey American Cancer Society grant of \$150,000, which provides funding through June 2013, he has identified six different types of triple-negative breast cancer. His research demonstrates that this type of breast cancer is not one disease but a collection of biologically different cancers. By characterizing each biological type, he hopes to be able to better match patients with existing chemotherapies or with new, targeted therapies. His study has the potential to move treatment in the direction of personalized medicine based on the genetic makeup of each patient’s disease.

Dr. Lehmann says that although it is still early, he anticipates that his research could provide the framework to provide patients with triple-negative breast cancer more effective treatments. He is continuing his research with the hope of translating his findings into patient care.

The results of Dr. Lehmann’s research have been published in articles in peer-reviewed scientific journals.

He is currently a visiting research fellow in the Biochemistry Department.

JENIFER R. PROSPERI, PHD
University Of Chicago
Chicago, Illinois

Impact of APC Loss in Mouse Models of Human Breast Cancer

Tumor suppressors are a class of genes that normally control cell growth and cell death. These genes limit the development of cancer in various ways that have not been fully defined. The tumor suppressor gene APC (adenomatous polyposis coli) has a normal role in breast development; however, loss of APC contributes to development of breast cancer. The APC gene can be “turned off” in about 50 percent of human breast cancers so that it ceases to fulfill its function as a cancer suppressor. Thus, characterizing the function of this gene under both normal and abnormal conditions could provide clues to how normal breast tissue is transformed into breast cancer.

The behavior of the APC gene and its relationship to breast cancer is the focus of the research of Jenifer R. Prospero, PhD. Working with the support of a SpinOdyssey American Cancer Society grant of \$102,000, Dr. Prospero is studying the behavior of the APC gene and how it interacts with other genes to facilitate development of breast cancer. The goals of her study are to characterize the impact of inactivation of the APC gene on the breast.

Dr. Prospero’s laboratory experiments with mice have confirmed that loss of the APC gene results in the formation of breast tumors. However, little is known about the process by which this occurs. Dr. Prospero’s research project, which began July 1, 2010, and will continue until June 30, 2012, is focused on testing her hypothesis, that it is the loss of APC in conjunction with the function of certain oncogenes – genes that are known to be linked to cancer -- that leads to the development of breast cancer. In her research, Dr. Prospero has developed systems, working with mouse models, which have enabled her to identify the mechanisms involved in breast tumor growth and development following APC loss. She hopes to demonstrate specific targets for treating breast cancer based on these mechanisms.

Dr. Prospero has shared the results of her research to date through publication of several articles in peer-reviewed scientific journals.

She is currently a post-doctoral scholar in the Department of Surgery.

MARC MENDILLO, PHD
Whitehead Institute for Biomedical Research
Cambridge, Massachusetts

The Role of HSF1 in Tumorigenesis

When a human cell is deprived of nutrients or oxygen, or exposed to external threats, it is said to undergo stress. The cell responds by going into survival mode and “turning on” the gene proteins that allow it to cope with the stress and survive. A specific protein, called human stress factor-1 (HSF1), regulates a whole network of genes involved in growth and development of cancer cells. This genetic network plays a vital role in allowing breast cancer cells not only to survive, but to grow and spread to other parts of the body. HSF1 is overexpressed, that is, the cell produces too much of it, in breast cancer cells, but not in normal breast cells. This overexpression of HSF1 is characteristic of many classes of breast cancer and is associated with poor survival.

Marc Mendillo, of the Whitehead Institute for Biomedical Research, is studying the role of HSF1 in breast cancer and how it enables the cancer to spread or “metastasize” to other parts of the body. Working under a SpinOdyssey American Cancer Society grant of \$138,000 since July 2009, Dr. Mendillo and his team revealed the whole network of genes that HSF1 controls in breast cancer. He has demonstrated how the network of genes that HSF1 controls enables efficient tumor formation.

In the area of breast cancer treatment, many of the key factors that determine whether or not a tumor will respond to chemotherapy are still not understood. Activation of HSF1, or the high expression of the gene network it regulates, could serve as an indicator of the extent to which normal breast tissue has been altered by the many abnormalities at work in a tumor. Dr. Mendillo has also used data on tumors from breast cancer patients followed for up to 25 years following diagnosis to show the relationship between different types of breast cancer treatments and breast cancer survival and how this is related to the activity of HSF1. Future directions for his studies are to show what drugs work best for which people with breast cancer, which could translate into more effective breast cancer treatments and improved survival.

Dr. Mendillo credits the SpinOdyssey American Cancer Society funding with giving him the freedom to completely focus on cancer research throughout the last several years. “The Society has a history of funding ground-breaking science,” Dr. Mendillo says, “and I am honored to be a part of it.”

Dr. Mendillo is currently preparing an article for publication to share results of his studies to date.

He is currently a post-doctoral fellow.

DANIEL K. NOMURA PHD
The Scripps Research Institute
La Jolla, California

Annotating Metabolic Pathways That Support Cancer Pathogenicity

A hallmark of cancer is the alteration of cell metabolism -- the chemical changes in living cells by which energy is provided for vital functioning. In cancer cells, there is a fundamental reprogramming of the cell function, or metabolism, that fuels tumor growth and aggressiveness. It has been recognized for nearly a century that cancer cell metabolism relies for nourishment on glucose, which these cells use in their growth and development. Cancer cells also use fatty acids, which they liberate from stored fat, to fuel their growth. These fatty acids give rise to molecules that send powerful genetic signals that can drive cancer to become more aggressive. Thus glucose and fatty acids together not only contribute to the growth of cancers, but they influence how fast-growing a cancer is and how it responds to treatment. All this has a direct effect on breast cancer survival and quality of life.

Daniel K. Nomura, PhD, of The Scripps Research Institute, La Jolla, California, is studying how cancer cells liberate and remodel fatty acids to nourish tumor growth and aggressiveness. An understanding of the nourishment process is critical to someday developing ways to control it and could lead to ways to treat cancer. Dr. Nomura is investigating the metabolic pathways that are upset or “perturbed” in cancer using an advanced strategy that allows him to assess globally the activity of genetic material in cancer cells.

Working with the support of a SpinOdyssey American Cancer Society grant of \$138,000, between July, 2009 and July, 2010, Dr. Nomura has identified an enzyme called MAGL (monocylglycerol lipase), a part of a cell’s genetic material, that is dramatically elevated in all aggressive cancers, including some forms of breast cancer. Dr. Nomura has successfully demonstrated that inhibiting the activity of MAGL reduces the fatty acid network that nourishes cancer cells, impairing the ability of cancer cells to grow.

Dr. Nomura hypothesizes that defining the role of MAGL may enable clinicians to use the enzyme in diagnosing breast cancer. Once the enzyme is characterized, it could be used to target treatment at cells where the enzyme’s activity signals the presence of cancer. He has shared the results of his research through publication in several peer-reviewed journals.

After completion of this SpinOdyssey American Cancer Society research project, Dr. Nomura continued this line of research under an NIH Pathway to Independence Award.

He is currently an assistant professor in the Department of Nutritional Sciences and Toxicology, University of California, Berkeley.

RACHEL L. DUSEK, PHD
Stanford University
Stanford, California

The Role of Perp in Mammary Gland Morphogenesis and Cancer

All living cells contain proteins – biochemical compounds that facilitate biological functions. A protein called Perp, which is found in cells lining many internal organs, is involved in the way cancer cells adhere to each other and in the ways in which these cells can be damaged. Researchers have observed that levels of Perp in the cells of breast tumors are lower than in normal cells. This suggests that loss of Perp is somehow associated with development of breast cancer and other types of cancer. Therefore, Perp may have the potential to prevent cancer from developing but also to slow progression of the disease. A greater understanding of Perp and the way it behaves in normal and cancerous tissue will provide insight into the cell mechanisms that contribute to cancer.

Rachel L. Dusek, PhD, of Stanford University has been working under a SpinOdyssey American Cancer Society grant of \$138,000 to study the role of Perp in breast cancer. She is focusing on defining how Perp functions in normal breast tissue as well as in the overall context of breast cancer. Of particular interest is how loss of Perp in the breast affects the way cells attaches themselves to each other and how Perp affects the structure and function of breast tissue. Dr. Dusek and her team have characterized Perp's location in breast cells and the protein's behavior. Their research has provided information on what genetic mechanisms go awry in cancer and how loss of the Perp protein can contribute to the formation of cancer.

Previous studies have shown that Perp has the ability to suppress skin cancer, and Dr. Dusek wants to know if Perp can also suppress breast cancer. The principal aims of Dr. Dusek's research are to look at the way the body produces Perp during normal breast development. She also seeks to define Perp's functional role in that process, and to determine more precisely how a deficiency of Perp may contribute to the development of breast cancer. Also of interest are what parts of the Perp protein affecting what functions and how Perp interacts with other proteins. Her ultimate goal is to relate findings back to human disease by evaluating human breast cancer samples and correlating their Perp levels with tumor grade and risk of cancer recurrence. An understanding of these interactions could ultimately lead to improvements in cancer diagnosis and treatment, and may enable clinicians to predict who is likely to develop breast cancer.

In tests on laboratory mice that are prone to breast cancer, Dr. Dusek determined that those that had Perp deficiencies had poorer survival, and, on average, their breast tumors formed more quickly than in mice with higher Perp levels. To examine the relevance of her findings in mice to human breast cancer, Dr. Dusek plans to analyze human breast cancer samples to determine how much Perp the samples contain and to assess where the gene is located in the cell structure. She hopes to relate this information to how breast cancer patients respond to treatment, to the stage of their disease, and to long-term

survival. Her research could point the way to using Perp to predict risk of recurrence and prognosis for long-term survival. For example, levels of Perp in human breast cancer might help to stage cancers (if loss of Perp correlates with more advanced disease for example) or to predict which cancers might respond most effectively to which treatments (if the presence or absence of Perp correlates with a positive response to a particular treatment) or to predict patient outcome (if the presence or absence of Perp is shown to correlate with cancer recurrence and long-term survival). Such information may make it possible to use Perp alone, or in conjunction with currently used markers, to guide health-care providers in selecting the most effective treatment options for a women with a particular type of breast cancer and to avoid subjecting patients to treatments that are not optimal. If tumors can be more accurately characterized in terms of their genetic makeup, treatments could be more effective, leading to increased life expectancy for women with breast cancer.

Dr. Dusek says that the funding from the SpinOdyssey American Cancer Society grant has been essential for her research. “Without it, I would not have been able to pursue this research. I am very grateful for the support.” Dr. Dusek shares the results of her research through publication of articles in peer-reviewed journals.

She is currently a post-doctoral scholar in the Department of Radiation Oncology.

TRACI R. LYONS, PHD
University of Colorado Denver
Aurora, Colorado

Mammary Gland Microenvironment in Breast Cancer Metastasis after Pregnancy

Women who give birth are at increased risk for developing breast cancer for five to ten years following delivery. These women generally have more aggressive cancers with poorer survival rates than women diagnosed while pregnant and women who have never been pregnant. An understanding of why women are more vulnerable to breast cancer following childbirth and why these cancers are more aggressive can lead to development of more effective treatments.

Traci Lyons, PhD, of the University of Colorado, has been studying how the breast changes following pregnancy and how these changes may predispose a woman to breast cancer. With the support of a SpinOdyssey American Cancer Society grant of \$138,000 Dr. Lyons has focused her research on a change that occurs in the breast following pregnancy in women who do not nurse and in women who have stopped nursing, a process, call postpartum mammary gland involution. This change appears to be the tumor-promoting event involved in pregnancy-associated breast cancer.

Dr. Lyons's has developed animal models for human postpartum breast cancer, which she is using to test her hypothesis that breast cancers arising in the involution period are more aggressive and more likely to metastasize. Using these animal models, she is comparing tumor cell proteins (part of a cell's genetic material) in breasts undergoing postpartum involution and non-involuting breasts in order to identify markers for postpartum breast cancer.

In the first year of her research, Dr. Lyons demonstrated that mammary gland involution is a tumor-promoting environment that exists in postpartum women and that cancer cells exposed to this environment are more likely to metastasize, or spread, to other parts of the body, leading to poorer survival rates. In the second year of her funding, Dr. Lyons identified two pro-tumor molecules, collagen and COX-2, that support tumor cell invasion of breast tissue and cancer metastasis. Together, these two molecules are involved in the development and spread of postpartum breast cancer. Dr. Lyon's research is advancing our understanding of breast cancer and is adding to the body of information that will ultimately lead to improved treatments and survival for women who develop breast cancer in the postpartum years.

Dr. Lyons has shared the results of her research through publications in the peer-reviewed journals, *American Journal of Pathology* and *Nature Medicine*.

She is currently a post-doctoral fellow in the School of Medicine, Division of Medical Oncology working in the breast cancer prevention lab.

JOSHUA L. ANDERSEN, PHD
Duke University
Durham, North Carolina

Caspase-2 Mediated Apoptosis

Normal cells, including those in the breast, are programmed by their genes to grow, develop, and die (cell death is called “apoptosis”). Cancer cells do not die but instead, continue to grow and develop, forming tumors. Chemotherapy is designed to kill cancer cells. A major obstacle in the treatment of breast cancer is that, over the course of the disease, breast tumor cells develop strategies for surviving and growing that make them resistant to chemotherapy. One strategy almost all breast cancer cells use is a to “reprogram” themselves to shut off the cellular pathways required for chemotherapy to be effective and to allow the cells to produce building blocks for new cells, which make the tumor grow.

Joshua L. Andersen, PhD, of Duke University in Durham, North Carolina, was awarded a SpinOdyssey American Cancer Society grant of \$138,000 to study how this reprogramming that breast cancer cells undergo enables them to grow and to become resistant to chemotherapy. Dr. Andersen also sought to demonstrate specific treatment strategies to be used in combination with common breast cancer treatments that could significantly improve the effect of chemotherapy on the breast tumor. The Society’s grant supported Dr. Andersen’s research from July, 2008 to July, 2011.

Dr. Andersen has explored the interaction of gene proteins and how they program a cancer cell to grow and develop. He has identified certain aspects of this genetic programming that can be suppressed to make cancer cells susceptible to existing chemotherapies. Application of his research in clinical practice has the potential to improve breast cancer treatments and long-term survival for people with breast cancer.

Dr. Andersen says that the reality of cancer research is that without funding sources like the SpinOdyssey and the American Cancer Society and its generous donors, work such as his simply does not happen; and most importantly, without innovative research, he says, we stand no chance of improving breast cancer treatment and life expectancy.

“I feel very fortunate and grateful to have received SpinOdyssey American Cancer Society funding,” Dr. Andersen says. “It enabled me to make progress on a disease that has impacted my family and so many others.” Dr. Andersen recently accepted a faculty position at Duke University where he will work toward carrying this research into the clinic where, he anticipates, it can have a positive impact on cancer treatment.

He is currently an assistant professor of medicine in the Medical Oncology Department.

CHRISTOPHER VELDKAMP, PHD
Medical College of Wisconsin
Milwaukee, Wisconsin

Novel Inhibition of Cancer Cell Metastasis Using an Engineered Chemokine

Breast cancer can be treated more successfully when it is confined to the breast rather than when it has spread (metastasized) to other parts of the body. Metastasis occurs when cancer cells break away from the breast tumor and develops new tumors in tissues outside the breast, such as bone marrow, liver, lungs, and lymph nodes where small cell proteins called chemokines, which are produced in these tissues, attract cancer cells away from the primary tumors. Chemokines accomplish this by activating a receptor on the cancer cell surface. When these chemokines signal each other, breast cancer cells migrate away from the breast tumor via the blood stream to bone marrow and other organs where they form these new tumors.

Working with the support of a \$138,000 SpinOdyssey American Cancer Society grant, Christopher Veldkamp of the Medical College of Wisconsin has been studying a way of inhibiting cancer cell metastasis by using an engineered chemokine. As the basis for his study, conducted from July, 2008 to June, 2011, he proposed a novel approach for preventing metastasis that takes advantage of the body's normal mechanism for halting cancer cell migration that occurs in response to chemokine signals. Dr. Veldkamp hypothesized that he could use the body's existing genetic system for stopping cancer cell migration to repress cancer metastasis through engineering a variant of the body's natural chemokines. He theorized that the engineered chemokine, by imitating the behavior of the natural chemokines, would disrupt the signals that trigger metastasis and stop cancer cell migration.

In his first year working under the SpinOdyssey American Society grant, Dr. Veldkamp successfully engineered a chemokine, called CXCL12₂, for use in testing his hypothesis. He then tested the CXCL12₂ on leukemia cells and observed that the engineered chemokine prevented leukemia cancer cells from migrating. With the successful engineering of CXCL12₂, Dr. Veldkamp began work on testing the chemokine on breast, prostate, and other cancers to see if it inhibited cancer cell migration in these cancers. Some technical difficulties have yet to be overcome, but Dr. Veldkamp continues to work in this area. He is testing CXCL12₂ in laboratory mice with cancer to determine if the engineered chemokine inhibits cancer metastasis.

Now that the mechanism by which cancer cells use chemokines to promote metastasis is understood, Dr. Veldkamp's long-term goal is to use this knowledge to develop new and more potent treatments to prevent metastasis in breast and other cancers. Dr. Veldkamp has published the results of his studies in peer-reviewed professional journals.

He is currently a visiting assistant professor in the Department of Biochemistry.

MEREDITH E. CROSBY, PHD
Yale University School of Medicine
New Haven, Connecticut

Hypoxia-Induced DNA Repair Pathway Regulation

Meredith E. Crosby, PhD, of Yale University, is engaged in an exciting area of cancer research related to how the body responds to or resists cancer treatment. Dr. Crosby is studying how the capacity of tumor cells to repair their DNA affects cancer growth. Her work has focused on the “microenvironment” of tumors – the framework of tissue and blood vessels that supports cancer cells – and how this microenvironment affects the ability of these cells to grow and reproduce.

One specific area that Dr. Crosby is studying is the way tumor cells behave when they are deprived of oxygen, a situation called hypoxia. Oxygen deprivation makes tumor cells able to survive toxic microenvironments, such as those caused by radiation and chemotherapy. Because of this ability to survive under adverse conditions, cancer cells are able to resist these treatments.

Dr. Crosby’s current work is focused on microRNA, one of the molecules contained in cells, which regulates bodily processes and is involved in the process by which cell hypoxia occurs.

A SpinOdyssey American Cancer Society grant in the amount of \$138,000 has permitted Dr. Crosby to pursue her research from July 1, 2007, to July 31, 2010, and to develop her research skills. She has established collaborative relationships with other scientists working in the same research area, Dr. Mircea Ivan of Indiana University School of Medicine and Dr. Adrian Harris of Cancer Research, UK. Dr. Crosby, together with these two researchers, published peer-reviewed articles on the subject of hypoxia in cancer development. In addition, she has taught a self-designed undergraduate seminar at Yale College Medical Institute, which was sponsored by the Howard Hughes Medical Institute. Based on her research work, Dr. Crosby was recently invited to serve as a peer reviewer for the journal *Clinical Cancer Research*, and she is under consideration for a grant from the National Institutes of Health.

Dr. Crosby’s research is directly related to the future of breast cancer treatment. A better understanding of the process by which cancer cells survive toxic conditions, such as an oxygen-depleted environment, could lead to more finely tuned treatments that will extend the life expectancy of women with breast cancer and potentially improve their quality of life.

She is currently a staff affiliate in the Department of Therapeutic Radiology.

DAVID G. DENARDO, PHD
University of California, San Francisco
San Francisco, California

The Role of Adaptive Immunity in Breast Cancer Progression

Leukocytes, a term that refers to a wide variety of human immune cells, are the body's defense against diseases of all sorts, including cancer. Historically, it was believed that leukocytes found in and around developing tumors represented an attempt by the body to eradicate cancer cells. However, increasing evidence indicates that some types of immune cells may contribute to the development of cancer.

David G. DeNardo, PhD, of the University of California, San Francisco, undertook a study to learn which immune system cells are involved in human breast cancer and to study how these cells function in the course of breast cancer development. Dr. DeNardo's goal was to characterize the mechanisms of breast cancer with the ultimate goal of applying this knowledge to development of new anticancer therapies. Dr. DeNardo's research project, conducted from July, 2007 to June, 2010, was supported by a SpinOdyssey American Cancer Society grant of \$138,000.

In his assessment of the role of immune cells during the development of breast cancer, Dr. DeNardo's first aim was to define the profile of the immune cells associated with human breast cancer. He examined more than 800 samples of premalignant and invasive breast cancer for all major types of immune cells and was able to successfully identify specific immune cells that predict recurrence-free survival as well as overall patient survival.

Dr. DeNardo's next step was to assess the functional role of the immune cells he had identified in the progression of breast cancer. Studying breast cancer in laboratory mice, Dr. DeNardo was able to demonstrate that a specific type of leukocyte, the CD4+T cell, manipulates other immune cells to promote invasive breast cancer and subsequent metastasis, or spread, of the cancer to the lungs. He also determined that depletion of CD4+T cells renders primary tumors less invasive and blocks pulmonary metastasis. This suggests that targeting certain populations of immune cells for further study of their roles in cancer development could lead to new anticancer treatments.

The results of Dr. DeNardo's study have been published in several peer-reviewed professional journals.

He is currently an assistant professor in the Department of Medicine, Oncology Division, Molecular Oncology Section, as well as the Department of Pathology and Immunology, Washington University in St. Louis.

ERIC E. SMITH, PHD
Fred Hutchinson Cancer Research Center
Seattle, Washington

Causes and Consequences of Adaptive Evolution in Dosage Compensation

Cell death, called “apoptosis,” is a normal process of human growth and development. As the body grows, cells die and are replaced by newer cells. In the average adult, up to 70 billion cells die each day.

Genes within cells regulate cell growth and “program” a cell to die on cue via a complex process of signals. Cancer cells, however, do not die. Instead, they undergo some sort of change in their genetic characteristics that causes them to miss their cues, continue to grow abnormally, and form tumors, such as breast cancer. Because these cancer cells have overcome their normal programmed cell death functions, they can grow uncontrollably. In order to understand how cancer cells manage to bypass cell death and survive and grow, it is necessary to first understand how cells die under natural conditions. This is fundamental to understanding how cancer develops.

Eric E. Smith, PhD, of the Fred Hutchinson Cancer Research Center was awarded a SpinOdyssey American Cancer Society grant of \$138,000 to pursue his study of a family of genes that are involved in controlling cell death. Dr. Smith is focusing on a gene called ApoL, which is known to be involved in a cellular process that kills invading infection cells, such as those that cause sleeping sickness and possibly other diseases. By understanding how these genes function to kill cells, Dr. Smith hopes to learn more about how certain cells avoid dying and go on to become cancer.

Dr. Smith has determined that the ApoL genes are active participants in programmed cell death; however, the conditions under which these genes cause cell death are not understood. The results of his research suggest that ApoL proteins interact with disease-causing proteins, perhaps as a means of triggering the death of invading disease cells as the body fights infections. Observing this programmed cell death in the context of infectious disease could lead to identification of the conditions under which cells commit programmed “suicide.” This knowledge would be directly transferable to understanding the failure of cancer cells to die. Dr. Smith hypothesizes that the ApoL proteins could be co-opted to trigger programmed cell death in cancer cells and could be useful for developing new cancer treatments in which only cancer cells and not healthy cells are killed.

Dr. Smith has shared results of his research through articles in peer-reviewed professional journals.

Currently Dr. Smith is a bioinformatics scientist at Illumina a publicly held biotechnology company.

BORIS WILSON, PHD
Dana-Farber Cancer Institute
Boston, Massachusetts

The Swi/Snf Tumor Suppressor in Stem Cell Self-Renewal and Pluripotency

While improvements in the diagnosis and treatment of breast cancer have led to increased survival, more aggressive and advanced types of breast cancer often respond poorly to current therapies and thus result in worse outcomes. Accumulating evidence suggests that treatments designed to block the activity of certain cell enzymes may prevent tumors from forming and also improve cancer survival.

Boris Wilson, PhD, of the Dana Farber Cancer Institute in Boston is evaluating the role of two of these enzymes, SNF5 and EZH2, and the way they interact with each other within the cell (these enzymes are part of a gene network called SWI/SNF). From July, 2007 to June, 2010, with the support of a SpinOdyssey American Cancer Society grant of \$138,000, Dr. Wilson undertook a study to better understand the role EZH2 and SNF5 in cell growth and development. He found that an imbalance of these two enzymes can spur tumors to form, and that shutting one of them down can make a tumor stop growing.

Using genetically engineered laboratory mice, Dr. Wilson observed behavior of SNF5 when the EZH2 enzyme was inactivated. He found that inactivating EZH2 blocked the SNF5 enzyme from developing tumors in mice. Based on these observations, he theorizes that EZH2 may be a basis for new treatments for breast and other cancers.

Dr. Wilson's research has led to an enhanced understanding of the molecular mechanisms that cause cancers to form, and has highlighted the potential of the EZH2 enzyme as a basis for new cancer treatments. Going forward, Dr. Wilson will continue to investigate the role enzymes play in developing cancer and how the insights gained can improve cancer treatments. He shares results of his research through publication of articles in peer-reviewed scientific journals.

Dr. Wilson says that SpinOdyssey American Cancer Society funding has had a major impact on his postdoctoral training. He says the support has enabled him to investigate questions pertinent to the understanding and treatment of cancer. This support has also provided him with the opportunity to attend global scientific meetings, present his research, and discuss his findings with leaders in the scientific community.

“The SpinOdyssey American Cancer Society funding facilitated a high level of research, mentoring, and training that would otherwise not be possible,” Dr. Wilson says. “It has also led to a deeper personal commitment to cancer research with an enhanced urgency to uncover effective ways to treat this disease.”

He is currently a research fellow in pediatrics.

MICHAEL H. LAM, PHD
Whitehead Institute for Biomedical Research
Cambridge, Massachusetts

The Potential Involvement of MicroRNAs in Repressing Oncogenic mRNAs

Research into human genetics has led to a growing body of knowledge of the role genes play in the development of many diseases, including cancer. When certain genes are activated or “turned on,” they cause a host of ailments. It follows then that learning how to control these genes could lead to therapies to treat, and even to prevent, these diseases from occurring.

MiRNAs are small gene molecules encoded in the DNA of all living things, plant and animal, that deactivates or interfere with the genes that cause a multitude of diseases, a process called “RNA interference.” Understanding how RNA interference functions could make it possible to develop treatments that turn off these genes.

Michael H. Lam, PhD, of the Massachusetts Institute of Technology is working with a team of researchers to develop new animal models related to MiRNAs and to determine ways in which these gene molecules can cause cancer. With the support of a SpinOdyssey American Cancer Society grant of \$110,447, he has succeeded in developing genetically engineered mice that lack a particular miRNA that is involved in the immune system. He has demonstrated that because of the removal of a single miRNA, the mice were unable to resist several disease-causing microbes and developed signs of early-stage leukemia. Dr. Lam continues to work with this particular miRNA to learn how it is able to play such a profound role in cancer prevention and immunity. An additional project focuses on another group of miRNA genes that likely function as tumor suppressors because of their ability to suppress the genes involved in cancer growth. The potential to block genetic messages that initiate disease has major implications for cancer control.

Dr. Lam has shared results of his research through publication of several articles in peer-reviewed journals.

Dr. Lam is currently senior research biology at Merck Laboratories.

VICTOR GRANN, MD, MPH
Columbia University
New York, New York

Decision Analysis of Population Screening for BRCA1/2 Mutations

About twelve percent of women in the United States – one in eight women – will develop breast cancer over the course of their lifetime. Five-to-10 percent of these cancers will occur in women who carry a mutation in the BRCA1 or BRCA2 gene, which puts them at a much higher risk of developing breast cancer than women without the mutation. Approximately 60 percent of women with these gene mutations develop breast cancer and often at an early age. BRCA1 and BRCA2 genes are tumor suppressor genes, that is, their function is to prevent breast and ovarian cancer. When these genes mutate, that is, are damaged, they no longer provide protection against these cancers.

Women who undergo genetic testing and test positive for BRCA1 or BRCA2 mutations may consider various options for reducing their risk of breast cancer. These options include prophylactic surgery (removal of healthy breasts or ovaries), chemoprevention (medicine that prevents breast cancer), and intensive surveillance. Currently, most women at high risk select surveillance, which includes yearly mammography beginning at around 30 years of age. A newer surveillance tool, Magnetic Resonance Imaging (MRI), is also available. Breast MRI is highly sensitive and has been shown to find 40 percent more cancers and at an earlier stage than mammography, ultrasound, or clinical breast examination.

Victor Grann, MD, MPH, of Columbia University, New York, undertook a study, with the aid of a SpinOdyssey American Cancer Society grant of \$209,000, to determine what options are the most effective for women with BRCA1 and BRCA2 mutations in order to assist them in the decision-making process. He also aimed to provide information to guide health policy makers in comparing MRI surveillance with other strategies for breast cancer prevention. In conducting his study, which was Society-funded from January of 2006 to December of 2008, he compared outcomes of MRI and mammography using a statistical method called decision analysis (a systematic approach that uses a variety of tools to evaluate all relevant information in the decision making process). His goal was to assess survival, quality-adjusted survival, and cost effectiveness of MRI and mammography and to develop a body of information that high-risk women and health policy makers could use in their decision-making.

Dr. Grann determined on the basis of his analysis that women who select chemoprevention or prophylactic surgery live longer and have better quality-adjusted survival than those who do not. He has completed the initial phase of his research project and has developed statistical methods to measure quality of life among women who test positive for breast cancer genetic mutations and those who do not. His article, "Breast Cancer-Related Preferences among Women With and Without BRCA Mutations," published in the peer-reviewed journal, *Breast Cancer Research and Treatment*, describes the results of

this SpinOdyssey American Cancer Society-funded research project.

He is currently a professor of clinical medicine with joint appointments at the Columbia University Medical Center, in the Department of Medicine, and the Herbert Irving Comprehensive Cancer Center.

KEVIN A. JANES, PHD
Harvard Medical School
Boston, Massachusetts

Cell Specification During Mammary Acinar Morphogenesis in Vitro

The answer to the question of how cancer develops likely lies in the genes that regulate the behavior of cells. What causes one cell to develop normally and another to turn into a cancer cell is the focus of intense scientific and medical research. Kevin A. Janes, PhD, of Harvard Medical School is approaching his research into breast cancer from a different angle. He wants to know what overall patterns prevail in the millions of cells that make up a breast tumor and how genetic programming that makes the cells behave in certain ways.

Dr. Janes was awarded a SpinOdyssey American Cancer society grant of \$138,000 to study cultured human acini cells *in vitro* – in the laboratory – to determine the roles genes play in cell development, how genes may cause cells to develop abnormally, and how this abnormal development may be related to various types of breast cancer. The breast is composed of grape-like clusters of hollow, spherical cells called acini. Breast cancer develops when these cells depart from their normal genetic programming and begin to grow abnormally in size and shape. An understanding of these processes is essential to an understanding of what happens when, instead of developing normally, normal breast cells develop into cancer.

Dr. Janes' laboratory at Harvard had already succeeded in growing cultures of human breast cells, and Dr. Janes used these cultures to extract genes from the cells and amplify them for closer study. His goal was to learn which genes are “turned off” and which are “turned on” as acini cells develop. He also wanted to know which genes contribute to normal development and which to abnormal development. His observations yielded some striking findings.

Working with cultured breast cells, Dr. Janes was able to identify several genes that, when disrupted, cause substantial changes in the structure of acini cells. When one of these genes, which Dr. Janes labeled *tghbr2*, is removed from a breast cell, acini become dramatically enlarged. These large cells, he observed, closely resemble an early stage of breast cancer called atypical ductal hyperplasia. Dr. Janes also identified two genes that cause cells to reproduce in structures that resemble a later stage of breast cancer called ductal carcinoma in situ or DCIS. Further research identified a clustering of cells that occurs in a specific type of DCIS called cribriform DCIS. Interestingly, some of these same genes are believed to function as tumor suppressors in other types of cancers, but in his study, he determined, conversely and for the first time, that these same genes are implicated in the formation of breast cancer.

Dr. Janes says that the support from the SpinOdyssey American Cancer Society' grant has been crucial to his research. At the time he proposed his study, his work was purely speculative, and he had no data to support his hypothesis. “It was a high-risk–high reward

type of project. All I had was an idea,” he says, “and SpinOdyssey and the Society took a chance on me.” He says that once he was awarded the grant, he was given complete flexibility as to what avenues of research to pursue and how to go about it. With the success of his research, he has now been able to obtain major funding. In 2009 he received the National Institutes of Health “New Innovator Award” in the amount of \$1.5 million grant and was selected as a 2009 Pew Scholar in the Biomedical Sciences by the Pew Charitable Trusts. The American Cancer Society provides ongoing support and recently awarded him a Research Scholar Grant to pursue additional aspects of his study.

Dr. Janes, whose doctorate is in biomedical engineering, stresses the importance of a multidisciplinary approach to cancer research. He says that researchers need to pay attention to what is happening in other fields, because sometimes the best inspiration comes from outside your own area. “Exposure to other disciplines can spark new ideas, new perspectives. You never know where the next idea is going to come from.”

Dr. Janes plans to continue this line of research into how changes or “perturbations” in the genes in breast cells relate to the development of various types of breast cancer. He is particularly interested in further study of the gene that appears to be related to cribriform DCIS.

Dr. Janes has shared the results of his research to date through publication in several peer-reviewed journals.

He is currently assistant professor in the Department of Biomedical Engineering at the University of Virginia School of Medicine with an appointment in the Cancer Center.

RYAN B. JENSEN, PHD
Yale University School of Medicine
New Haven, Connecticut

Delineating the Role of BRCA2 in Regulating Rad51-Mediated Recombination

BRCA1 and BRCA2 belong to a class of human genes known as tumor suppressors. Their role in human cancer is clear in that certain mutations in the gene are invariably linked to early development of breast cancer. Although most cancer is likely due to mutations in several genes, BRCA1 and BRCA2 are unique in that a mutation in either single gene leads to breast cancer. About 12 percent of women in the general population will develop breast cancer; however, among women with the BRCA1 or BRCA2 gene, 60 percent will develop breast cancer, most of them at an early age. Breast cancer in women with these two genes is often called familial or hereditary, because these women often have multiple family members who have been diagnosed with the disease. In addition, to breast cancer, BRCA2 mutations are also linked to pancreatic and prostate cancers.

Ryan B. Jensen, PhD, of Yale University School of Medicine, is devoting his research to a study of BRCA2 and how it interacts with DNA and cellular proteins. Working under a SpinOdyssey American Cancer Society grant of \$138,000 between July, 2005 and June, 2008, Dr. Jensen looked for ways in which BRCA2 could be isolated to permit more intensive study of the behavior and characteristics of the gene. Using a process called purification, he successfully isolated BRCA2 so that it is now possible to examine the ways in which the gene binds with other cellular material in the process of undergoing mutations. In accomplishing this, he has taken a huge step forward in understanding the function of BRCA2 and its role in DNA repair. A fuller understanding of BRCA2 in the cancer process may lead to improved therapies for breast cancer as well as provide insight into the origins of other cancers.

Dr. Jensen points out that in the 15 or so years since the BRCA2 gene was discovered, no one has been able to purify the gene and that doing so is vital to understanding its exact mechanism of action. "I decided that, although it was very challenging and time-consuming, it was necessary to purify the gene in order to understand how tumor mutations in BRCA2 disrupt its function," Dr. Jensen says. He hopes someday to be able to photograph the gene itself in order to better understand how it works and even guide development of drugs based on the structure of the gene.

Because BRCA2 is so inextricably linked to cancer, characterizing its function and structure could also reveal the molecular events that lead to sporadic (nonhereditary) breast cancer. Sporadic breast cancers are likely due to several gene mutations that are yet to be identified.

Dr. Jensen's further studies involve learning how BRCA2 interacts with other cellular proteins to bond to certain strands of DNA and to repair DNA that has been damaged. DNA damage in human cells is directly linked to cancer in terms of both the disease itself and as a side-effect of radiation and chemotherapy. Knowledge of the pathways human cellular machinery takes to repair DNA damage has the potential to improve clinical outcome, predict disease progression, and lead to more potent and successful cancer treatments.

When a woman undergoes genetic testing to determine if she carries the mutated BRCA2 gene, Dr. Jensen says, there is currently no way to foretell what her risk for breast cancer is. His goal is to enable genetic counselors and physicians to better manage a patient in whom one of the mutated BRCA2 genes turns up. "It is incredibly frustrating for a woman to undergo genetic testing and not to get any useful information out of it," Dr. Jensen says.

It took nearly four years for Dr. Jensen and his team to purify the BRCA2 protein and another year to characterize, or describe, it. He says that the donor supported funding he received from the American Cancer Society was crucial to keeping the project alive.

"It's rare nowadays to keep a research project alive for that long, not knowing if there will be success at the end," Jensen says. "Funding for biomedical research is at an all-time low, and I think it's very important that people understand that key discoveries take time and that we need to protect this time so that progress is made carefully and to the highest standard possible. The Society provided a funding bridge at a crucial time when projects are either moved forward or abandoned, and supported our research until we could get major funding from the National Institutes of Health and the National Cancer Institute."

Bridge funding is a really important contribution that the Society's grants make. I feel really indebted to the donors who thought my particular project was important enough to them to get it funded."

He has shared the results of his research via publication in peer-reviewed professional journals.

He is currently assistant professor of therapeutic radiology.

DENNIS J. SLAMON, MD, PHD
University of California, Los Angeles
Los Angeles, California

Her-2 Alteration in Human Breast Cancer: Delineation of Downstream Molecular Events and Identification of Additional Potential Therapeutic Targets

Using a repertoire of new technologies which are based on studying gene expression profiles associated with any particular genetic alteration, Dr. Slamon's lab studied the associated genes and pathways that are important in causing the more aggressive behavior of HER-2/neu positive tumors. By doing this type of analysis they hoped to identify additional or new targets downstream of HER-2/neu which might be approached therapeutically to further improve the gains seen with the drug Herceptin. A drug which is commonly used to treat women diagnosed with this form of metastatic disease and which targets a specific genetic alteration found in about 25 percent of breast cancer patients.

One important discovery that led to the development of Herceptin, Slamon said, was the realization that breast cancer is not just one disease, but many. "There is molecular diversity of human cancers that has largely gone unappreciated, and it's gone unappreciated because we've lumped things together," he said.

Slamon and his colleagues set out to find ways to target their treatments. They took breast cancer cells and mimicked what was happening in their patients, looking at genetic alterations in the genes that regulate growth. One of them was a gene called Her-2, human epidermal growth factor receptor No. 2.

They discovered that women who had the HER-2 alteration weren't doing as well because they had a more aggressive tumor. That made it a logical target. Slamon's group found that when they added an antibody to the receptor that the gene made when it mutated, the tumor growth rate dropped dramatically.

The process of identifying the target and validating it in the laboratory worked not just for breast cancer, but for other major malignancies, he said. The UCLA researchers developed models for several cancers, seeing which antibodies worked and which didn't.

"We were using the right therapy for the right patients, dramatically increasing the effectiveness and significantly decreasing the toxicity," Slamon said.

Within the next three to five years, he predicted a revolution in the way cancer is treated. "There are going to be more genetically identified driving alterations that we can target."*

Dr. Slamon has published his research in many peer-reviewed scientific journals.

He currently serves as director of Clinical/Translation Research, and as director of the Revlon/UCLA Women's Cancer Research Program at the Jonsson Comprehensive Cancer Center. He is a professor of medicine, chief of the Division of Hematology/Oncology and executive vice chair for research of UCLA's Department of Medicine. Additionally, he also serves as director of the medical advisory board for the National Colorectal Cancer Research Alliance.

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GRAHAM COLDITZ, MD
Washington University
St. Louis, Missouri

Breast Cancer Epidemiology and Prevention

Selected as an American Cancer Society Clinical Research Professor in 2003, Dr. Golditz is a renowned epidemiologist with a focused interest in prevention of chronic diseases like cancer. He is perhaps best known as the Principal Investigator of the Nurses' Health Study at the Brigham and Women's Hospital which followed more than 120,000 women to assess risk factors associated with chronic diseases. His most recent focus has been to utilize tissue samples from women in the study to search for markers which predict a future risk for breast cancer.

In recent years, his research has indicated that diet and lifestyle choices during adolescence can have significant impact on a woman's risk for cancer later in life. For example, his studies have suggested that exercise or alcohol consumption in young girls was associated with changes in risk for breast cancer as an adult. During the past year, Dr. Colditz has published results from more than 30 research studies covering colorectal, cervical, skin, and breast cancer and the impact of health disparities on cancer incidence and outcomes. For example, his work has shown that the association between the expression of the Vascular Epithelial Growth Factor Receptor (VEGFR) was not predictive of clinical outcome for women taking hormonal therapy but was associated with mortality in breast cancers arising from luminal tissues. From ongoing analysis of the Nurses' Study, a 2011 paper showed that the survival benefit of aspirin use in breast cancer was independent of COX2 expression, one of the targets of aspirin.

Currently a professor of medicine Dr. Golditz is slated to receive one of ACS' highest distinctions the Medal of Honor for Cancer Control.

MICHAEL P. DIGIOVANNA, MD, PHD
Yale University
New Haven, Connecticut

Targeting HER2 and ER in Breast Cancer

Cancer is caused by damage to the DNA of the genes that regulate cell growth and cell division. The two most important proteins involved in this damage (mutations) in breast cancer are human epidermal growth factor receptor 2 (HER2) and estrogen receptors (ER). These proteins signal cancer cells to grow and reproduce. Women diagnosed with breast cancer are tested to determine whether their cancer is receptor positive or receptor negative for these two proteins. This information determines which drugs will be most effective in treating their form of the disease.

Michael P. DiGiovanna, MD, PhD, of Yale University has been studying the effects of the drug treatments for breast cancer currently in use that inhibit the function of HER2 and estrogen receptors, Herceptin for HER2, and tamoxifen for estrogen receptors. Each of these drugs is effective in suppressing the activity of these proteins, thereby slowing the growth of tumors. Dr. DiGiovanna theorized that the two drugs in combination might be more effective than if used separately.

He was awarded a SpinOdyssey American Cancer Society grant of \$989,000, for the period from January, 2002 to December, 2005, to test his hypothesis. He tested the two drugs in combination both in laboratory cultures of human breast cancer cells and in laboratory mice with breast cancer. In tests of breast cancer cultures, Dr. Giovanna found that in cells that contain both estrogen receptors and HER2, either Herceptin or tamoxifen slowed the growth of these cancers. However, a combination of the two drugs stopped the cancer cells from growing. Although the combination of Herceptin and tamoxifen stopped the growth of the breast cancer cells, the cancer cells started growing again when the drugs were removed.

Dr. Giovanna studied what happens to the signals from HER2 and estrogen receptors inside the cancer cells to stop their growth when exposed to Herceptin and tamoxifen. Herceptin, he discovered, did not affect the amount of the HER2 protein in the tumor; instead, it inhibited the signals that the protein sends to cancer cells to make them grow. Similarly, tamoxifen inhibits the signals from estrogen receptors rather than reducing the number of receptors.

Dr. DiGiovanna next used the two drugs to treat laboratory mice with breast cancer. Just as he found in experiments with breast cancer cultures, the drugs used separately slowed the growth of cancer cells, and when combined, they stopped the cancers from growing. He went on to test Herceptin on breast cancer cells that do not over-produce HER2, a type of breast cancer that typically does not respond to the drug. As expected, Herceptin had no effect, but when combined with tamoxifen, it killed the cancer cells. This

combination of drugs is now being tested in clinical trials on human breast cancer patients.

Dr. DiGiovanna's work is advancing our understanding of the basic genetic mechanisms of the two most important cell proteins involved in breast cancer. His work will help in evaluation of the clinical trials of the combined drugs currently underway, with the ultimate goal of improving breast cancer treatment and survival.

Dr. DiGiovanna and his team of researchers have shared the results of their work through publication of articles in peer-reviewed journals.

He is currently associate professor of Medicine (Medical Oncology) and Pharmacology with joint appointments in the Comprehensive Cancer Center, the Yale Cancer Center, the departments of Biological and Biomedical Sciences, Internal Medicine and Pharmacology.

LEON O. MURPHY, PHD

Harvard Medical School
Boston, Massachusetts

Fos Phosphorylation and Cellular Transformation

Understanding how cells divide, move, and die is critical for the development of effective therapies for all forms of cancer. Cancer most often occurs when the normal controls on our cells are lost or broken. The focus of Dr. Murphy's work during his fellowship (2000-2003) in the laboratory of Dr. John Blenis was the transcription factor, c-Fos.

A transcription factor is a molecule which can turn a group of genes on or off inside of a normal cell or a cancer cell. From a number of years of study, scientists have learned that c-Fos is involved in a number of cellular processes like proliferation, differentiation to form different tissues, and in responses to cell damage. In addition, it has become apparent that c-Fos is often greatly increased in a wide range of tumors, and may play a specific role in bone cancer. At the root of the question was how does a single protein (c-Fos) known to be involved in cancer, participate in a number of very different processes in normal cells? Does its multifunctional nature contribute to its ability to induce cancer? How can diverse types of signals or damage to a cell result in very different outcomes including proliferation, differentiation or transformation?

During his fellowship, Dr. Murphy discovered that very subtle differences in how signals are transmitted from outside a cell to the nucleus can dramatically affect how c-Fos operates leading to differences in the biological response. Both short duration and longer duration signals from outside the cell can induce the same collection of proteins including c-Fos. However, if the signal is of short duration such as that produced by a pulse of epidermal growth factor, the c-Fos protein which is induced remains in cells for only a short time as it is metabolically unstable. In contrast, if a cell is stimulated with PDGF (platelet derived growth factor) resulting in a much longer duration signal for growth, the c-Fos which is induced is much more stable and remains in cells for hours rather than minutes. The longer lifespan for the c-Fos protein was due to the addition of phosphate groups to the protein which prevented its normal turnover. By increasing the stability of c-Fos, the amount of the protein accumulates to higher levels resulting in very different biological consequences – cancer versus normal differentiation to different types of cells. Based upon this understanding of a complex system of control, it may be possible to develop cancer drugs with only modest effects on the activity of c-fos which show major effects on the proliferation of tumor cells.

Dr. Murphy has shared the results of his research to date through publication of numerous articles in peer-reviewed scientific journals.

He is currently a research scientist at Novartis Institute for Biomedical Research in Cambridge, Massachusetts.

DAVID A. WAH, PHD
Massachusetts Institute of Technology
Cambridge, Massachusetts

Analysis of the Molecular Determinants in Protein Degradation

Normal cells are programmed by their genes to develop, perform their particular cellular functions, and die. Cancer occurs when this genetic programming goes awry. Breast cancer and other cancers are composed of cells in which the genetic programming is mixed up. Through some sort of disjointed interaction, genes send out the wrong signals, the cells grow abnormally, and they do not die. Instead, they become cancer. If the code for this faulty cell programming can be identified, the possibilities for cancer diagnosis and treatment – and possibly even prevention – could be enormous.

David A. Wah, PhD, of the Massachusetts Institute of Technology is interested in a type of genetic material, or protein, called a protease. Proteases not only recognize and destroy damaged genetic material in a cell, but they modulate the activity of key proteins involved in cell development and cell death. In order for proteases to do their job, they must select the right proteins in the cell and send the protein the right signal. If the protease destroys the wrong protein, the cell may be damaged. If the protease is not sufficiently active, the cell may not die. Either of these events can lead to the development of cancer.

Dr. Wah conducted research, with the support of a SpinOdyssey American Cancer Society grant of \$96,800, to define the interplay of proteases and cell proteins that leads to the development of cancer. He has successfully identified the mechanism by which a particular protease, called ClpXP, with the assistance of a smaller protein, called SspB, recognizes and manages specific cell proteins. This enhanced understanding of how these two proteases work together suggests ways in which their activity might be controlled. Such a detailed knowledge of cellular function at the molecular level lays the foundation for development of improved methods for recognizing and treating cancer.

He is currently Director of the X-ray Crystallography Core Facility, Public Health Research Institute Center, International Center for Public Health, New Jersey Medical School.

JOHN J. WYSOLMERSKI, MD
Yale University School of Medicine
New Haven, Connecticut

Role of PTHrP in Breast Cancer Metastases to Bone

Bone metastasis – the spread of cancer away from its original site and to the bones – is a common complication of breast cancer and contributes significantly to illness and death from the disease. Metastasis weakens bones and releases calcium into the bloodstream, contributing to the many disorders associated with high calcium levels. Bone metastasis is one of the most frequent causes of pain in people with cancer.

Working with the support of a \$375,000 SpinOdyssey American Cancer Society grant, from January, 2000 to December, 2002, Dr. John J. Wysolmerski of Yale University undertook a study to learn more about the process by which breast cancer cells metastasize to bone where they form tumors. A better understanding of this process could serve as the basis for new treatments and even lead to ways to prevent this painful complication.

Healthy bone is constantly being restructured and remodeled with new bone cells forming and old bone cells breaking down. The break-down of bone is handled by a group of specialized cells called osteoclasts. These osteoclasts moderate or manage bone breakdown, nibbling away at bone cells and digesting them. Breast cancer cells interfere with this normal process causing osteoclasts to reproduce and behave abnormally, forming bone tumors.

Dr. Wysolmerski's interest in the process of bone metastasis focused on the behavior of osteoclasts in bone metastasis. He was particularly concerned with a hormone called PTHrP (parathyroid hormone-related protein), which various studies suggest enables breast cancer cells to "home in" on bone and to over-stimulate osteoclast production and activity. The goal of his study was to test if this was true and to learn more about the behavior of this hormone's role in bone metastasis. Dr. Wysolmerski's central hypothesis was that the ability of breast cancer cells to cause bone metastases was related to their ability to stimulate the body's production of osteoclasts, which was related, in turn, to the cancer cells' production of PTHrP and another hormone-like protein called CSF-1.

Dr. Wysolmerski identified three specific steps for testing his hypothesis. First, he would grow and evaluate human breast tumors in the laboratory to examine their effect on osteoclasts and their secretion of PTHrP and CSF-1. Second, he would look at how PTHrP and CSF-1 affected the ability of breast cancer cells to make osteoclasts grow. Finally, using mouse models, he sought to explore if and how PTHrP in cancer cells influences how often bone metastasis occurs in breast cancer.

As a result of these experiments, Dr. Wysolmerski made an important discovery that has the potential to guide new breast cancer therapies. He learned that although over-

production of PTHrP in the mammary glands of mice appeared to lead to an increased number of mammary tumors, it did not lead to increased incidence of bone metastasis. These findings suggest that the production of PTHrP by breast cancer cells is not sufficient to produce bone metastases in mice. Furthermore, Dr. Wysolmerski theorizes that PTHrP produced in cancer cells is not likely to be involved in the homing in of these cells on bone. On the contrary, His work suggests that over-production of this hormone in breast cancer cells is a good sign. It signals improved results of treatment and increased life expectancy.

Dr. Wysolmerski has shared results of his research through publishing in several highly respected peer-reviewed journals.

He is currently a professor of medicine, Department of Internal Medicine, Endocrinology.