

Claudia Adams Barr Program in Innovative Basic Cancer Research
Dana-Farber Cancer Institute

BARR PROGRAM IMPACT STATEMENTS

1. Computational Analysis of Gene Expression: Shirley Liu, PhD, created complex statistical tools that are having enormous impact on the work of scientists around the world. These tools, which she makes available to other scientists, enable descriptions of the precise manner in which gene expression is regulated in several cancers, especially breast and prostate, and could eventually help lead to exciting new methods for normalizing abnormal cell growth. *Key impact areas: breast and prostate cancers; personalized medicine*

- The Human Genome Project and genomics technology in general have provided the important tools needed to uncover and then treat the genetic abnormalities that cause cancer. But the fact that there are three billion units of DNA in the genome and an unknown number of ways that their functions are controlled means that research on the genetics of cancer produces an unmanageably large amount of data. Awarded Barr funding in 2005, Shirley (Xiaole) Liu, PhD, conducted groundbreaking research to provide a way to manage that inundation of data. Application of her tools to the genetics of breast and prostate cancer has uncovered new pathways toward cancer development that can be targeted by novel and effective therapies.

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He HH, Meyer CA, Shin H, Bailey ST, Wei G, Wang Q, Zhang Y, Xu K, Ni M, Lupien M, Mieczkowski P, Lieb JD, Zhao K, Brown M, Liu XS. Nucleosome dynamics define transcriptional enhancers. Nat Genet. 2010 Apr;42(4):343-7.

2. Controlling Cancer Growth: William Sellers, MD, and his colleagues identified genetic abnormalities in proteins that control cell growth in cancers. These major discoveries led directly to the development of targeted drugs used by patients worldwide for the treatment of multiple cancers, including lung cancer, leukemia, and melanoma. This work has become the model for personalized medicine in cancer treatment and is widely credited for helping transform the approach that pharmaceutical companies use for drug development. *Key impact areas: colon, leukemia, lung, melanoma, and prostate cancers; new drug development; personalized medicine*

- The Kinome Project, with initial Barr Program funding in 1997, discovered mutations in a family of genes called “kinases” that prevent cell growth stimulators from being turned off, resulting in cancer cells that replicate uncontrollably. This discovery enabled the development of drugs that specifically target these kinases and successfully eliminate

or slow the growth of cancer cells. An example of widely-used drugs that resulted from insights gained in part from the Kinome Project includes Iressa and Tarceva for lung cancer. Promising new treatments for metastatic melanoma have also been based on this work. The targeted use of these drugs in patients whose cancers demonstrate particular genetic abnormalities resulted directly from the Kinome Project's foundational discoveries and has become the model for personalized medicine in cancer treatment.

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3. Controlling Growth of Breast Cancer: Peter Sicinski, MD, PhD, discovered that the proteins that control cell division, called Cell Cycle Control proteins, behave abnormally in breast cancer. This discovery could lead to groundbreaking treatments in breast cancer and is being heavily invested in by drug companies and other research organizations. *Key impact areas: breast cancer; new drug development*

- Understanding the basic molecular controls of cell growth is essential to understanding the development of cancer, which is the uncontrolled growth of cells in the human body. Dr. Sicinski discovered that abnormal activity of one of these controls causes cancer in mammary glands in mouse models. The results of his studies, funded by the Barr Program in 1998, are being used by drug and research organizations as the basis of their work to discover new drugs targeting breast cancers.

Yu Q, Geng Y, Sicinski P. Specific protection against breast cancers by cyclin D1 ablation. *Nature*. 2001 Jun 28;411(6841):1017-21.

Yu Q, Sicinska E, Geng Y, Ahnström M, Zagozdzon A, Kong Y, Gardner H, Kiyokawa H, Harris LN, Stål O, Sicinski P. Requirement for CDK4 kinase function in breast cancer. *Cancer Cell*. 2006 Jan;9(1):23-32.

4. Enabling Immune Systems to Fight Cancers: Shannon Turley, PhD, is determining the fundamental reasons why human immune systems do not reject cancers and has discovered a new class of cells that can suppress immune responses against cancer. Dr. Turley's discoveries are focusing on some of the toughest cancers to treat, such as pancreatic, and will lead to new therapies that can help the immune system to reject these cancers. *Key impact areas: pancreatic and prostate cancers; vaccines*

- Cancers can be thought of as "foreign" tissues. Unlike other foreign tissues, however, cancers are not efficiently rejected by the immune system. Determining why this happens could lead to methods of enhancing immune rejection of cancers. Dr. Shannon Turley, with Barr funding awarded in 2008, is using mouse models to understand how cancers such as pancreatic are able to suppress immune rejection. This growing understanding of

the process is enabling development of new treatments, such as the prostate cancer vaccine Provenge, that enhance the immune system's ability to reject cancers.

Lee JW, Epardaud M, Sun J, Becker JE, Cheng AC, Yonekura AR, Heath JK, Turley SJ. Peripheral antigen display by lymph node stroma promotes T cell tolerance to intestinal self. *Nat Immunol.* 2007 Feb;8(2):181-90.

Epardaud M, Elpek KG, Rubinstein MP, Yonekura AR, Bellemare-Pelletier A, Bronson R, Hamerman JA, Goldrath AW, Turley SJ. Interleukin-15/interleukin-15R alpha complexes promote destruction of established tumors by reviving tumor-resident CD8+ T cells. *Cancer Res.* 2008 Apr 15;68(8):2972-83.

Fletcher AL, Lukacs-Kornek V, Reynoso ED, Pinner SE, Bellemare-Pelletier A, Curry MS, Collier AR, Boyd RL, Turley SJ. Lymph node fibroblastic reticular cells directly present peripheral tissue antigen under steady-state and inflammatory conditions. *J Exp Med.* 2010 Apr 12;207(4):689-97.

5. Linkages Between Cancer and Obesity: Bruce Spiegelman, PhD, is one of the world leaders in understanding the molecular basis for obesity. His research is explaining why obesity is such a major risk factor for human cancers. Determining the link between obesity and these cancers could be important to inhibiting cancer development in both obese and non-obese people. *Key impact area: new drug development*

- Obesity has been estimated to contribute to the development of 10% to 15% of human cancers. Dr. Bruce Spiegelman's work, supported by the Barr Program in 2005, has demonstrated that obesity causes many body-wide alterations in metabolism, hormone levels, and inflammation, and that these abnormalities may affect the development and progression of cancers. Understanding how obesity leads to these disruptions will provide new insights into the development of cancers in general and will lead to new therapeutic interventions.

Mueller E, Smith M, Sarraf P, Kroll T, Aiyer A, Kaufman DS, Oh W, Demetri G, Figg WD, Zhou XP, Eng C, Spiegelman BM, Kantoff PW. Effects of ligand activation of peroxisome proliferator-activated receptor gamma in human prostate cancer. *Proc Natl Acad Sci U S A.* 2000 Sep 26;97(20):10990-5.

Girnun GD, Smith WM, Drori S, Sarraf P, Mueller E, Eng C, Nambiar P, Rosenberg DW, Bronson RT, Edelmann W, Kucherlapati R, Gonzalez FJ, Spiegelman BM. APC-dependent suppression of colon carcinogenesis by PPARgamma. *Proc Natl Acad Sci U S A.* 2002 Oct 15;99(21):13771-6.

Kulke MH, Demetri GD, Sharpless NE, Ryan DP, Shivdasani R, Clark JS, Spiegelman BM, Kim H, Mayer RJ, Fuchs CS. A phase II study of troglitazone, an activator of the

PPARgamma receptor, in patients with chemotherapy-resistant metastatic colorectal cancer. *Cancer J*. 2002 Sep-Oct;8(5):395-9.

Burstein HJ, Demetri GD, Mueller E, Sarraf P, Spiegelman BM, Winer EP. Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. *Breast Cancer Res Treat*. 2003 Jun;79(3):391-7.

Girnun GD, Chen L, Silvaggi J, Drapkin R, Chirieac LR, Padera RF, Upadhyay R, Vafai SB, Weissleder R, Mahmood U, Naseri E, Buckley S, Li D, Force J, McNamara K, Demetri G, Spiegelman BM, Wong KK. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. *Clin Cancer Res*. 2008 Oct 15;14(20):6478-86.

Kajimura S, Seale P, Kubota K, Lunsford E, Frangioni JV, Gygi SP, Spiegelman BM. Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. *Nature*. 2009 Aug 27;460(7259):1154-8.

Gupta RK, Arany Z, Seale P, Mepani RJ, Ye L, Conroe HM, Roby YA, Kulaga H, Reed RR, Spiegelman BM. Transcriptional control of preadipocyte determination by Zfp423. *Nature*. 2010 Mar 25;464(7288):619-23.

Choi JH, Banks AS, Estall JL, Kajimura S, Boström P, Laznik D, Ruas JL, Chalmers MJ, Kamenecka TM, Blüher M, Griffin PR, Spiegelman BM. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. *Nature*. 2010 Jul 22;466(7305):451-6.

6. Mapping Genes to Control Breast Cancer: Myles Brown, MD, discovered the way estrogen works in normal tissues and breast cancers, resulting in the first genome-wide map of all genes that estrogen controls. His research is leading to new drugs specifically targeting this pathway in breast cancer. *Key impact areas: breast cancer; personalized medicine*

- The steroid hormones estrogen and testosterone play critically important pathological roles in breast and prostate cancers. Dr. Brown's map of the genes controlled by these hormones, achieved with Barr funding in 2002, is now being used to match specific drugs for specific cancers. Explaining at a molecular level how drugs like Tamoxifen work is the first step to furthering drug development and developing more specific and effective drugs. This work is expected to lead to new drugs and treatments for cancers that target the estrogen and testosterone pathways.

Carroll JS, Liu XS, Brodsky AS, Li W, Meyer CA, Szary AJ, Eeckhoute J, Shao W, Hestermann EV, Geistlinger TR, Fox EA, Silver PA, Brown M. Chromosome-wide mapping of estrogen receptor binding reveals long-range regulation requiring the forkhead protein FoxA1. *Cell*. 2005 Jul 15;122(1):33-43.

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Wang Q, Li W, Zhang Y, Yuan X, Xu K, Yu J, Chen Z, Beroukhim R, Wang H, Lupien M, Wu T, Regan MM, Meyer CA, Carroll JS, Manrai AK, Jänne OA, Balk SP, Mehra R, Han B, Chinnaiyan AM, Rubin MA, True L, Fiorentino M, Fiore C, Loda M, Kantoff PW, Liu XS, Brown M. Androgen receptor regulates a distinct transcription program in androgen-independent prostate cancer. *Cell.* 2009 Jul 23;138(2):245-56.

7. Molecular Classification of Cancers: Todd Golub, MD, discovered unique molecular characteristics of cancers, completely changing the way oncologists treat their patients by enabling them to target treatments toward those who are most likely to benefit. This breakthrough led, for example, to a commonly-used test that tells physicians which of the 30–40 percent of early-stage breast cancer patients should receive chemotherapy, sparing the rest from unnecessary treatment. *Key impact areas: breast cancer and lymphoma; personalized medicine*

- We now know that not all tumors are alike, and that treatment strategies need to be based on the unique molecular characteristics of each cancer – not just the organs where tumors originate. Funded by the Barr Program in 1996, Todd Golub, MD, achieved early molecular classification of tumors, leading directly to customized treatments now used by oncologists around the world with significantly better outcomes for patients. For example, gene expression is now used routinely to help determine those breast cancer patients who are most likely to relapse after surgery and therefore need additional treatment. This Barr research is also serving as the foundation for how many other diseases will be routinely treated as well.

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G, Daidone MG, Roayaie S, Schwartz M, Thung S, Salvesen HB, Gabriel S, Mazzaferro V, Bruix J, Friedman SL, Kumada H, Llovet JM, Golub TR. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med*. 2008 Nov 6;359(19):1995-2004

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8. Molecular Control of Cancer Pain: Qiufu Ma, PhD. created a new biological understanding of pain syndromes in cancer patients. This discovery could lead to new drugs that would improve both quality of life and treatment outcomes by enabling the continuation of specific therapies that might otherwise have been stopped due to painful side effects. *Key impact area: new drug development*

- Managing the pain that cancer patients experience as a result of their disease and from the side effects of treatments is an area in which little progress has been made. Few effective medicines are available for the neuropathic pain commonly experienced by cancer patients, and more than 45% of cancer patients in the United States suffer from various forms of untreatable pain. With Barr support in 2007, Qiufu Ma, PhD, revolutionized the understanding of this problem by identifying the underlying genes expressed in neurons critical for pain perception. Eventually, this will enable drug companies to develop novel therapeutic targets for pain treatment.

Chen CL, Broom DC, Liu Y, de Nooij JC, Li Z, Cen C, Samad OA, Jessell TM, Woolf CJ, Ma Q. Runx1 determines nociceptive sensory neuron phenotype and is required for thermal and neuropathic pain. *Neuron*. 2006 Feb 2;49(3):365-77.

Xu Y, Lopes C, Qian Y, Liu Y, Cheng L, Goulding M, Turner EE, Lima D, Ma Q. Tlx1 and Tlx3 coordinate specification of dorsal horn pain-modulatory peptidergic neurons. *J Neurosci*. 2008 Apr 9;28(15):4037-46.

Samad OA, Liu Y, Yang FC, Kramer I, Arber S, Ma Q. Characterization of two Runx1-dependent nociceptor differentiation programs necessary for inflammatory versus neuropathic pain. *Mol Pain*. 2010 Jul 30;6:45.

9. New Treatment for Neuroblastoma in Children: Rani George, MD, PhD, discovered a new mutation in neuroblastoma, the most common solid tumor in children. It is a cancer with poor prognosis that is very difficult to treat. Dr. George is now testing drugs that have already proven successful in treating other cancers that have this same mutation, with the exciting potential to translate these therapies into treatments for children with neuroblastoma. *Key impact areas: neuroblastoma; new drug use; pediatric; personalized medicine*

- Neuroblastoma has historically been a very difficult cancer to treat in children, and, although chemotherapy and stem cell transplants have improved survival, relapse is common and nearly almost always fatal. With Barr support in 2007, Rani George, MD, PhD, discovered that a significant number of neuroblastoma tumors contain a mutation in the gene *ALK*. Several successful drugs already exist to treat other types of cancer that demonstrate these same *ALK* mutations, and Dr. George and her team have initiated clinical trials that could result in new treatments that will improve survival for children with neuroblastoma.

George RE, Sanda T, Hanna M, Fröhling S, Luther W 2nd, Zhang J, Ahn Y, Zhou W, London WB, McGrady P, Xue L, Zozulya S, Gregor VE, Webb TR, Gray NS, Gilliland DG, Diller L, Greulich H, Morris SW, Meyerson M, Look AT. Activating mutations in *ALK* provide a therapeutic target in neuroblastoma. *Nature*. 2008 Oct 16;455(7215):975-8.

10. New Understanding of Lung Cancer: Matthew Meyerson, MD, PhD, and his colleagues discovered specific mutations that led to the successful use of new drugs and increased survival for 10–20 percent of lung cancer patients worldwide. Previously, these patients' cancers were largely untreatable. *Key impact areas: lung cancer; new drug development; personalized medicine*

- Lung cancer claims more lives than any other cancer, and is extremely difficult to treat. The Barr Program provided the initial funding in 2002 to Dr. Matthew Meyerson, who discovered genetic abnormalities in certain lung cancer tumors. This discovery defined the patients who benefit from two drugs, Iressa and Tarceva, which have proven effective in treating the 10% to 20% of lung cancer patients whose tumors contain the specific mutations that were discovered from this Barr research. Today, these drugs are being used successfully with lung cancer patients across the world whose cancers were previously untreatable.

Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004 Jun 4;304(5676):1497-50

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M. Characterizing the cancer genome in lung adenocarcinoma. *Nature*. 2007 Dec 6;450(7171):893-8

11. New Uses for Existing Cancer Drugs: Kim Stegmaier, MD, developed a novel approach to discovering how drugs currently used for one cancer might be highly effective for other cancers in completely unanticipated ways. This research led to the discovery that the drug Gefitinib, initially only used for treating lung cancer, might be effective for acute leukemias. The discovery also led directly to a promising new clinical trial at DFCI. *Key impact areas: leukemia and sarcoma; new drug use*

- Dr. Stegmaier's laboratory focuses on pediatric and other malignancies not well addressed by industry. In order to overcome the limitations to traditional screening, Dr. Stegmaier and her colleagues received Barr Program funding in 2006 to develop a molecular genetic approach to screening, in which a gene expression signature serves as a surrogate for different biological states. This technology has led to the discovery that Gefitinib, initially used to treat lung cancer, was also effective in acute leukemias – a completely unexpected finding that led to a clinic trial for patient with AML. Ongoing drug screens for the pediatric tumors Ewing's sarcoma and neuroblastoma have also resulted from this research.

Stegmaier K, Wong JS, Ross KN, Chow KT, Peck D, Wright RD, Lessnick SL, Kung AL, Golub TR. Signature-based small molecule screening identifies cytosine arabinoside as an EWS/FLI modulator in Ewing sarcoma. *PLoS Med*. 2007 Apr;4(4):e122

Hahn CK, Ross KN, Warrington IM, Mazitschek R, Kanegai CM, Wright RD, Kung AL, Golub TR, Stegmaier K. Expression-based screening identifies the combination of histone deacetylase inhibitors and retinoids for neuroblastoma differentiation. *Proc Natl Acad Sci U S A*. 2008 Jul 15;105(28):9751-6

DuBois SG, Krailo MD, Lessnick SL, Smith R, Chen Z, Marina N, Grier HE, Stegmaier K; Children's Oncology Group. Phase II study of intermediate-dose cytarabine in patients with relapsed or refractory Ewing sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2009 Mar;52(3):324-7.

Corsello SM, Roti G, Ross KN, Chow KT, Galinsky I, DeAngelo DJ, Stone RM, Kung AL, Golub TR, Stegmaier K. Identification of AML1-ETO modulators by chemical genomics. *Blood*. 2009 Jun 11;113(24):6193-205.

12. Overcoming Drug-Resistant Cancers: Michael Eck, MD, PhD, and Nathanael Gray, PhD, used Barr funding to invent new compounds that block the growth of some drug-resistant tumors. These compounds are now under development by major drug companies, and may be the next “super drugs” to treat several of the most resistant cancers, including lung and colon. *Key impact areas: colon and lung cancer, sarcoma; new drug development*

- One of the difficult problems facing cancer physicians is the ability of tumors to become resistant to therapies that are initially effective. A most promising area of cancer therapeutics is using chemistry for basic research to design and create new classes of compounds that bind to and inhibit the growth of cancer cells that have become drug-resistant. In 2006, Michael Eck, MD, PhD, and Nathanael Gray, PhD, received Barr funding to uncover structural characteristics of cancer cells and to develop compounds that attach themselves to these structures in a way that inhibits their growth. This work is leading to the development of new drugs that are effective against resistant cancers. Pharmaceutical companies are now rushing to develop new drugs based on the work initially funded by the Barr Program and to schedule these drugs for clinical trials. These could provide exciting treatment options for some of the most difficult cancers, including lung and colon.

Zhou W, Ercan D, Chen L, Yun CH, Li D, Capelletti M, Cortot AB, Chirieac L, Iacob RE, Padera R, Engen JR, Wong KK, Eck MJ, Gray NS, Jänne PA. Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature*. 2009 Dec 24;462(7276):1070-4

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13. Telomerase in Cancer Cells: William Hahn, MD, PhD, is conducting exciting new work focused on understanding the role that telomerase, an enzyme required for normal chromosome function, has in promoting the survival of cancer cells. This work provides entirely new ways of attacking nearly all types of cancers. *Key impact areas: new drug development*

- All normal cells are programmed to divide a certain number of times and then either die or simply stop dividing. This happens because structures at the end of chromosomes, called telomeres, get smaller with every division; when they get short enough, cells cannot divide. Cancer cells bypass this control and divide indefinitely by activating an enzyme called telomerase that rebuilds the telomeres after every division. Supported by the Barr Program in 2004, William Hahn, MD, PhD, was instrumental in identifying the role telomerase plays in cancer, and his research has led to the development of potential anti-cancer therapies that work by blocking telomerase and therefore preventing cancer cells from dividing indefinitely.

Masutomi K, Yu EY, Khurts S, Ben-Porath I, Currier JL, Metz GB, Brooks MW, Kaneko S, Murakami S, DeCaprio JA, Weinberg RA, Stewart SA, Hahn WC. Telomerase maintains telomere structure in normal human cells. *Cell*. 2003 Jul 25;114(2):241-53.

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14. Triggering Death of Cancer Cells: Loren Walensky, MD, PhD, developed a novel method for creating compounds that block the effects of formerly “untargetable” proteins in cancers, triggering the death of these cancer cells. This method has already led to the development of potential new drugs for lymphoma and several other cancers. Additional clinical trials are planned that could result in other new treatments. *Key impact areas: lymphoma new drug development*

- All living cells contain “executioner proteins” that help control the growth of normal cells. Cancer cells find a way to prevent activation of these proteins, enabling them to replicate uncontrollably. The 2008 Barr research project of Loren Walensky, MD, PhD, generated novel agents that bind to these proteins in cancer cells, reactivating their “executioner” function and triggering cell death. By integrating chemistry, biology and cancer medicine, this work has the potential to create groundbreaking new therapies for multiple types of cancer, many of which were previously untreatable.

Gavathiotis E, Suzuki M, Davis ML, Pitter K, Bird GH, Katz SG, Tu HC, Kim H, Cheng EH, Tjandra N, Walensky LD. BAX activation is initiated at a novel interaction site. *Nature.* 2008 Oct 23;455(7216):1076-81.

Stewart ML, Fire E, Keating AE, Walensky LD. The MCL-1 BH3 helix is an exclusive MCL-1 inhibitor and apoptosis sensitizer. *Nat Chem Biol.* 2010 Aug;6(8):595-601.

15. Uncovering Cancer Causing Molecules: Jean J. Zhao, PhD, and her colleagues developed a breakthrough technology that can tell when genetic abnormalities will likely lead to human cancers. This technology is currently being used in clinical trials for multiple cancers, including breast and colon, and could result in new and exciting ways to limit cell growth in cancers with these abnormalities. *Key impact areas: breast, colon, and prostate cancers; new drug development, personalized medicine*

- Cancer cells replicate uncontrollably when genetic abnormalities in a specific type of protein prevent cell growth stimulators from being turned off. Dr. Jean Zhao’s technology activates any hidden potential these proteins may possess to cause cancer and has already been used to find abnormal proteins that may cause breast cancer. This novel Barr Program project, funded in 2004, represents the first attempt to systematically reveal proteins with cancer-causing potential in certain cells and has already led to activity by several drug companies on treatments to block the effects of a new molecular target in breast cancer called PIK3CA.

Zhao JJ, Gjoerup OV, Subramanian RR, Cheng Y, Chen W, Roberts TM, Hahn WC. Human mammary epithelial cell transformation through the activation of phosphatidylinositol 3-kinase. *Cancer Cell*. 2003 May;3(5):483-95.

Zhao JJ, Liu Z, Wang L, Shin E, Loda MF, Roberts TM. The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells. *Proc Natl Acad Sci U S A*. 2005 Dec 20;102(51):18443-8.

Jia S, Liu Z, Zhang S, Liu P, Zhang L, Lee SH, Zhang J, Signoretti S, Loda M, Roberts TM, Zhao JJ. Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. *Nature*. 2008 Aug 7;454(7205):776-9.

16. Use of Vaccines to Control Cancer: Glenn Dranoff, MD, discovered regulatory pathways in the immune system that have enabled the development of new vaccines for multiple types of cancer. His work is a crucial part of the bright future for immune therapies to fight cancer including vaccines and immune stimulators for many cancers including melanomas. *Key impact areas: melanoma, ovarian, and prostate cancer; vaccines*

- An important area of cancer research asks why humans don't reject tumors in their own bodies. Funded by the Barr Program in 1998, Glenn Dranoff, MD, discovered complex regulatory pathways in the human immune system that cancers exploit in order to escape destruction. Reversal of these effects can lead to the development of vaccines against cancer, a recent example of which is Provenge for prostate cancer. This Barr research has also enabled the development of multiple other vaccines and immune modulators for melanoma, ovarian cancer, and prostate cancer that are now in advanced clinical trials across the world. If these trials are successful, an exciting and entirely new option for treating certain types of cancer will become available.

Soiffer R, Lynch T, Mihm M, Jung K, Rhuda C, Schmollinger JC, Hodi FS, Liebster L, Lam P, Mentzer S, Singer S, Tanabe KK, Cosimi AB, Duda R, Sober A, Bhan A, Daley J, Neuberg D, Parry G, Rokovich J, Richards L, Drayer J, Berns A, Clift S, Cohen LK, Mulligan RC, Dranoff G. Vaccination with irradiated autologous melanoma cells engineered to secrete human granulocyte-macrophage colony-stimulating factor generates potent antitumor immunity in patients with metastatic melanoma. *Proc Natl Acad Sci U S A*. 1998 Oct 27;95(22):13141-6.

Hodi FS, Mihm MC, Soiffer RJ, Haluska FG, Butler M, Seiden MV, Davis T, Henry-Spires R, MacRae S, Willman A, Padera R, Jaklitsch MT, Shankar S, Chen TC, Korman A, Allison JP, Dranoff G. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci U S A*. 2003 Apr 15;100(8):4712-7.

Hodi FS, Butler M, Oble DA, Seiden MV, Haluska FG, Kruse A, Macrae S, Nelson M, Canning C, Lowy I, Korman A, Lantz D, Russell S, Jaklitsch MT, Ramaiya N, Chen TC,

Neuberg D, Allison JP, Mihm MC, Dranoff G. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. *Proc Natl Acad Sci U S A.* 2008 Feb 26;105(8):3005-10.