CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

CASE COMPREHENSIVE CANCER CENTER

SUMMARY OF HIGHLIGHTS AND ACTIVITIES 2000-2009

Stanton L. Gerson, M.D.
Director
Stanton.Gerson@case.edu
(216) 844-8562

Anne M. Duli, M.P.A.
Associate Director for Research
Administration and Finance
Anne.Duli@case.edu
(216) 844-8797

Website: http://cancer.case.edu
Email: cancer@case.edu

Case Comprehensive Cancer Center

Summary of Highlights and Activities 2000-2009

Table of Contents

The Case Comprehensive Cancer Center (Case CCC) is a reorganization of the NCI-designated Comprehensive Cancer Center originally approved as a Clinical Cancer Research Center in 1987 and designated as Comprehensive in 1998. In 2004, the institutional and membership base from the founding partnership between Ireland Cancer Center of University Hospitals and Case Western Reserve University was expanded to include Cleveland Clinic. The Case CCC integrates the cancer research activities of the largest biomedical research and health care institutions in Ohio — Case Western Reserve University, University Hospitals Case Medical Center and Cleveland Clinic — under a single leadership structure.

The Case CCC is an evolving, innovative center emphasizing the translation of discovery into patient-based research and clinical trials for the treatment of cancer. As a consortium cancer center, it is a powerful example of the potential generated by complementary institutions coming together for the benefit of research and discovery, patient treatments, and community impact. Its research programs extend to Case Western Reserve University affiliates: MetroHealth Medical Center and Louis Stokes Veterans Affairs Hospital, as well as to the community medical centers operated by University Hospitals and Cleveland Clinic. Together, these institutions and their network affiliates see more than 22,000 new cancer cases a year, over 40% of all cancer cases in the state of Ohio. Case CCC programs extend throughout northern Ohio offering residents access to innovative clinical trials, cancer risk reduction and epidemiology programs, and educational and community outreach, as well as long term follow-up of cancer survivor efforts.

<u>Highlights:</u>

- Our highly regarded Cancer Genetics Program has made discoveries into cancer-causing genes and genetic changes in colon cancer, gastric cancer, gliomas, prostate cancer, Barrett's esophagus and Myelodysplastic syndrome. These discoveries have resulted in the identification of loss of vimentin expression in the majority of colon cancers, leading to an approved new DNA-based screening test for colon cancer that is now being compared to colonoscopy for the general population.
- Our Developmental Therapeutics Program continues to be a site for Phase I drug development with NCI-CTEP, generating novel study design and establishing efficacy of new agents linked to biologic correlates. Many of the agents under study, especially those targeting DNA repair, were developed in Case CCC laboratories.
- Our new program, Cancer Imaging, is one of the few in the country that applies very high quality cellular and clinical imaging applications to cancer research for tumor detection, tumor metabolism, tumor drug localization, and nano tumor drug delivery.
- Our Aging-Cancer Research Program links biologic and genetic processes of aging and cancer risk with psychosocial assessments of comorbidities and survivorship, and includes studies of obesity and cancer, and cancer energetics. These efforts have been funded by the P20 in cancer and aging and the Transdisciplinary Research on Energetics and Cancer (TREC) Center, one of four NCI-funded initiatives nationwide.
- Our Cancer Prevention, Control and Population Research Program has identified new genetic cancer risks, noted shortfalls in the use of cancer screening tests such as colonoscopy, and conducted survivorship research to improve the outcome and quality of life for cancer survivors.
- Highly interactive transdisciplinary research efforts are ongoing in colon cancer, brain tumors, breast cancer, stem cells, melanoma and lung cancer.
- Scientific Highlights:
    - Anti-cancer agent dose de-escalation design by **Afshin Dowlati, M.D.**

- EGF-R drug-resistance mutations identified by **Patrick Ma, M.D.** in lung cancer patients.
- Evidence by **Sanford Markowitz, M.D., Ph.D.** that malfunction of the gene known as 15-PGHD may lead to metastasis and is a drugable target.
- Xenotropic murine leukemia virus-related virus (XMRV) identified as a viral infectious agent in the stroma of prostate cancer patients predisposing to tumor initiation and progression by **Robert Silverman Ph.D.** and **Eric Klein, M.D.**
- Identification of Base Excision Repair as a target for inhibitors in drug combinations, and introduction of methoxyamine as a first in class agent in clinical trials by **Drs. Lili Liu**, **Stanton Gerson** and **Yanming Wang**.

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Major Scientific Accomplishments and Publications 2000-2009

(Organized by Theme)

Role of Environment (Tumor Environment and External)

Chen WD, Eshleman JR, Aminoshariae MR, Ma AH, Veloso N, **Markowitz S, Sedwick WD, Veigl ML**. Cytotoxicity and mutagenicity of frameshift-inducing agent ICR191 in mismatch repair-deficient colon cancer cells. J Natl Cancer Inst 92:480-485, 2000.

- **Drs. Sanford Markowitz, David Sedwick, and Martina Veigl** found that frame shift-inducing mutations can selectively induce mutations in mismatch repair-deficient genes versus mismatch repair-proficient cells. This study suggests that environmental exposures may therefore favor development of cancers with the microsatellite instability in tissues like the gut. This group also reported that frame shift-inducing chemotherapy agents could preferentially kill mismatch repair-deficient cancer cells and, thus, represent a prototype of novel therapeutic compounds.

Patocs A, Zhang L, Xu Y, Weber F, Caldes T, Mutter G, Platzer P, **Eng C**. LBreast-cancer stromal cells with TP53 mutations and nodal metastases. N Engl J Med 357:2543-2551, 2007.

- **Dr. Charis Eng** examined the role of epithelial and stromal genomic TP53 alterations in hereditary and sporadic breast cancer. She found that stroma-specific loss of heterozygosity or allelic imbalance is associated with somatic TP53 mutations and regional lymph-node metastases in sporadic breast cancer but not in hereditary breast cancer. This work expands the emerging arena of tumor microenvironment and the role it plays in clinical outcomes.

Yun J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, **Willson JK***, **Markowitz S**, Zhou S, Diaz LA Jr, Velculescu V, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. Science 325:1555-1559, 2009. PMCID: PMC2820374

- **Dr. Sanford Markowitz and James Willson*** extended studies into the mechanism of KRAS in colon cancer. This work showed that glucose deprivation increases the activity of the KRAS oncogene in colon cancer. This study provides further evidence for the role of environmental conditions, such as diet, that select for genetic mutations that promote tumor progression.

New Methodology

Nadeau JH, Balling R, Barsh G, Beier D, Brown SD, Bucan M, Camper S, Carlson G, Copeland N, Eppig J, Fletcher C, Frankel WN, Ganten D, Goldowitz D, Goodnow C, Guenet JL, Hicks G, de Angelis MH, Jackson I, Jacob HJ, Jenkins N, Johnson D, Justice M, Kay S, Kingsley D, Lehrach H, Magnuson TR, Meisler M, Poustka A, Rinchik EM, Rossant J, Russell LB, Schimenti J, Shiroishi T, Skarnes WC, Soriano P, Stanford W, Takahashi JS, Wurst W, Zimmer A. Sequence interpretation. Functional annotation of mouse genome sequences. Science 291:1251-1255, 2001.

- **Dr. Joseph Nadeau**, as part of the International Mouse Mutagenesis Consortium, was first author in a paper that proposed goals and outlined plans for annotating the mouse genome and compiling data on mouse mutations over the next 10 years. The Consortium found that in addition to the challenges of identifying new assays to probe biological functions, more efficient and reliable methods were needed for archiving, managing, analyzing, displaying, and disseminating the complex phenotype data sets resulting from mutagenesis programs.

Zhang X, Guo C, Chen Y, Shulha HP, Schnetz MP, **Laframboise T**, Bartels CF, **Markowitz S**, Weng Z, **Scacheri PC**, **Wang Z**. Epitope tagging of endogenous proteins for genome-wide ChIP-chip studies. Nat Methods 5:163-165, 2008. PMCID: PMC2435063

- **Drs. Thomas LaFramboise, Sanford Markowitz, Peter Scacheri and Zhenghe Wang** reported the development of a major new method for using gene knock-in technology to introduce epitope tags into the endogenous genomic locus of any gene. This method provides the ability to analyze protein-protein interactions or protein-chromatin interactions across the genome, including newly discovered genes for which high quality antibodies do not exist.

Prevention, Control, and Screening

Goodwin MA, **Zyzanski SJ**, Zronek S, Ruhe M, Weyer SM, Konrad N, Esola D, **Stange KC**. A clinical trial of tailored office systems for preventive service delivery. The Study to Enhance Prevention by Understanding Practice (STEP-UP). Am J Prev Med 21:20-28, 2001.

- **Drs. Stephen Zyzanski and Kurt Stange** published findings from a clinical trial involving 79 community family practices and more than 10,000 patients. This STEP-UP trial showed the effectiveness of a practice-tailored strategy for increasing rates of cancer preventive services.

Chak A, Ochs-Balcom H, **Falk G***, Grady WM, Kinnard M, **Willis JE**, **Elston R**, **Eng C**. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. Cancer Epidemiol Biomarkers Prev 15:1668-1673, 2006.

- **Drs. Amitabh Chak, Gary Falk*, Joseph Willis, Robert Elston and Charis Eng** led a prospective population assessment that found that there is a greater rate of familial Barrett's esophagitis in patients with benign and malignant esophageal disorders, with a higher percentage than previously reported. This indicates that relatives of patients with esophageal cancer and Barrett's esophagitis should receive prospective screening in order to identify and treat malignant esophageal disorders potentially at an earlier stage.

Cooper GS, Payes JD. Receipt of colorectal testing prior to colorectal carcinoma diagnosis. Cancer 103:696-701, 2005.

Cooper GS, Doug Kou TD. Underuse of colorectal cancer screening in a cohort of medicare beneficiaries. Cancer 112:293-299, 2008.

- **Dr. Gregory Cooper** found that African-Americans were less likely to receive screening colonoscopies for colorectal cancer detection, and found that less than 30% of individuals diagnosed with colon cancer had a recommended screening test prior to the diagnosis. Additional studies using large database analysis of 153,469 Medicare beneficiaries to assess screening for colon cancer showed that screening remains low. Together, these studies demonstrate the need to improve and publicize the advantages of colonoscopy to screen for colon cancer, particularly in African-Americans.

Itzkowitz S, Brand R, Jandorf L, Durkee K, Millholland J, Rabeneck L, Schroy PC 3rd, Sontag S, Johnson D, **Markowitz S**, Paszat L, Berger BM. A simplified, noninvasive stool DNA test for colorectal cancer detection. Am J Gastroenterol 103:2862-2870, 2008.

- **Dr. Sanford Markowitz** and collaborators at Exact Sciences continued to report development and improvement of their novel method for early detection of colon cancer based on detection of abnormally methylated DNAs in patient feces. The group reported enhancing the sensitivity of this assay for detecting curable early stage colon cancers to 84%, and demonstrated a similar sensitivity for also detecting premalignant advanced colon adenomas. In March 2008, the American Cancer Society endorsed fecal DNA

screening as an accepted method for early detection of colon cancer, and in August 2008 Laboratory Corporation of America introduced the first commercially available fecal DNA test colon cancer screening (ColoSure™), basing the test on licensed technology from the Markowitz laboratory.

New and Developing Treatments

Zielske SP, **Gerson SL**. Cytokines, including stem cell factor alone, enhance lentiviral transduction in nondividing human LTCIC and NOD/SCID repopulating cells. Mol Ther 7:325-333, 2003.

Zielske SP, Reese JS, Lingas KT, Donze JR, **Gerson SL**. *In vivo* selection of MGMT(P140K) lentivirus-transduced human NOD/SCID repopulating cells without pretransplant irradiation conditioning. J Clin Invest 112:1561-1570, 2003. PMCID: PMC259124

- In a series of studies involving mutant MGMT drug resistant gene transfer into hematopoietic stem cells, **Dr. Stanton Gerson** characterized optimal conditions for lentiviral gene transfer into human CD34 cells and the ability to select for these cells *in vivo* after drug treatment. These studies form the basis of an ongoing clinical trial to test the feasibility of using mutant MGMT drug resistant gene transfer to enhance clinical transplantation of hematopoietic progenitor cells into people.

Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, Stevens C, Barker JN, Gale RP, **Lazarus HM**, Marks DI, van Rood JJ, Scaradavou A, Horowitz MM. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 351:2265-2275, 2004.

- **Drs. Mary Laughlin and Hillard Lazarus** published the results of a multi-center trial of adults transplanted with UCB for hematologic malignancies. They found there were no differences in outcome between patients with one HLA mismatch and those with two HLA mismatches after cord blood transplantation. Their data indicated that HLA-mismatched cord blood should be considered for adult hematopoietic stem cell grafts in the absence of an HLA-matched donor.

Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, Racevskis J, Dewald GW, Ketterling RP, Bennett JM, Rowe JM, **Lazarus HM**, Tallman MS. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 361:1249-1259, 2009.

- **Dr. Hillard Lazarus** in a clinical trial that will have a direct impact on patient care, found that in young adults with AML, intensifying induction therapy with a high daily dose of daunorubicin improved the rate of complete remission and the duration of overall survival, as compared with the standard dose. (ClinicalTrials.gov number, NCT00049517) 2009 Massachusetts Medical Society.

Cell Signaling and Cellular Mechanisms

Lu T, Burdelya LG, Swiatkowski SM, Boiko AD, **Howe PH**, **Stark GR**, **Gudkov AV***. Secreted transforming growth factor beta 2 activates NF-kappaB, blocks apoptosis, and is essential for the survival of some tumor cells. Proc Natl Acad Sci USA 101:7112-7117, 2004. PMCID: PMC406474

- **Drs. Philip Howe, George Stark and Andrei Gudkov*** revealed a novel role for both the active and latent forms of TGF-beta in cancer. These two forms of the cytokine secreted by many different tumors have the novel function of activating the transcription factor NF-kappaB, which is constitutively active in most tumors and has an important pro-survival function. Latent TGF-beta does not activate SMADs, but does activate NF-kappaB. These dual functions of TGF-beta may help to explain the seemingly conflicting

data that this cytokine is important to inactivate TGF-beta -dependent SMAD signaling early in tumorigenesis, but to retain TGF-beta secretion late in this process.

Ramesh S, Qi XJ, Wildey GM, Robinson J, Molkentin J, **Letterio J**, **Howe PH**. TGFbeta-mediated BIM expression and apoptosis are regulated through SMAD3-dependent expression of the MAPK phosphatase MKP2. EMBO Rep 9:990-997, 2008. PMCID: PMC2572119

- **Drs. John Letterio and Philip Howe** demonstrated that transforming growth factor-beta (TGFbeta)-mediated BIM expression and apoptosis are regulated through SMAD3-dependent expression of the MAPK phosphatase. Their results provide further evidence of the importance of TGF-beta and SMAD3 signaling, as well as mitochondrion-mediated events, in cell survival.

Ma PC, Tretiakova MS, Mackinnon AC, Ramnath N, Johnson C, Dietrich S, Seiwert T, Christensen JG, Jagadeeswaran R, Krausz T, Vokes EE, Husain AN, Salgia R. Expression and mutational analysis of MET in human solid cancers. Genes Chromosomes Cancer 47:1025-1037, 2008. PMCID: PMC2583960

- **Dr. Patrick Ma** has shown that MET is often overexpressed and mutated in human solid tumors, including lung cancer. This suggests that MET and MET mutants seen in human cancers would be attractive targets for drug screening.

Shen J, Yu WM, Brotto M, Scherman JA, Guo C, Stoddard C, Nosek TM, Valdivia HH, **Qu CK**. Deficiency of MIP/MTMR14 phosphatase induces a muscle disorder by disrupting Ca(2+) homeostasis. Nat Cell Biol 11:769-776, 2009. PMCID: PMC2693472

- **Dr. Cheng-Kui Qu** identified and characterized the novel phosphatase MIP, which is essential for normal hematopoietic stem cell function and leukemia stem cell development. While this work is important to stem cell development, he also found that this phosphatase has an important role in muscle performance. This work expands the knowledge of cell-signaling networks and opens a new area of investigation.

Li C, Yu S, Nakamura F, Yin S, Xu J, Petrolla AA, **Singh N**, **Tartakoff A**, Abbott DW, **Xin W**, **Sy MS**. Binding of pro-prion to filamin A disrupts cytoskeleton and correlates with poor prognosis in pancreatic cancer. J Clin Invest 119:2725-2736, 2009. PMCID: PMC2735930

- **Drs. Neena Singh, Alan Tartakoff, Wei Xin and Man-Sun Sy** found that binding of pro-prion to filamin A disrupts cytoskeleton and correlates with poor prognosis in pancreatic cancer. This work showed that PrP expression in tumors correlated with a marked decrease in patient survival, making it an attractive target for therapeutic intervention in human PDAC.

Miao H, Li DQ, Mukherjee A, Guo H, Petty A, Cutter J, **Basilion JP**, Sedor J, Wu J, **Danielpour D, Sloan AE**, Cohen ML, **Wang B**. EphA2 mediates ligand-dependent inhibition and ligand-independent promotion of cell migration and invasion via a reciprocal regulatory loop with Akt. Cancer Cell 16:9-20, 2009. PMCID: PMC2860958

- **Drs. James Basilion, David Danielpour, Andrew Sloan, and Bing-Cheng Wang** studied the role of EphA2 kinase signaling in prostate cancer and demonstrated that there are opposing roles of EphA2 in regulating cell migration and invasion. While activation of EphA2 with its ligand ephrin-A1 inhibited chemotactic migration of glioma and prostate cancer cells, EphA2 overexpression promoted migration in a ligand-independent manner. This work explains the paradox that was previously observed in investigations into these proteins.

Jiang Y, Dunbar A, Gondek LP, Mohan S, Rataul M, O'Keefe C, **Sekeres M**, Sauntharajah Y, **Maciejewski JP**. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. Blood 113:1315-1325, 2009. PMCID: PMC2637194

Jankowska AM, Szpurka H, Tiu RV, Makishima H, Afable M, Huh J, O'Keefe CL, Ganetzky R, McDevitt MA, **Maciejewski JP**. Loss of heterozygosity 4q24 and TET2 mutations associated with myelodysplastic/myeloproliferative neoplasms. Blood 113:6403-6410, 2009. PMCID: PMC2710933

Makishima H, Cazzolli H, Szpurka H, Dunbar A, Tiu R, Huh J, Muramatsu H, O'Keefe C, **Hsi E**, Paquette RL, Kojima S, List AF, **Sekeres MA**, McDevitt MA, **Maciejewski JP**. Mutations of E3 ubiquitin ligase Cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. J Clin Oncol 27:6109-6116, 2009.

- **Drs. Jaroslaw Maciejewski, Mikkael Sekeres and Eric Hsi** published a series of work elucidating the genetic changes associated with the transition from myelodysplastic syndrome to acute leukemia. Their work provided further evidence of the roles of p53 and TET2 in cancer progression. Work investigating DNA methylation demonstrated that E3 ubiquitin ligase FZD9 is a tumor suppressor, suggesting these proteins may be potential therapeutic targets.

Dong B, Kim S, Hong S, Das Gupta J, Malathi K, **Klein EA**, Ganem D, Derisi JL, Chow SA, **Silverman RH**. From the Cover: an infectious retrovirus susceptible to an IFN antiviral pathway from human prostate tumors. Proc Natl Acad Sci USA 104:1655-1660, 2007. PMCID: PMC1776164

Hong S, **Klein EA**, Das Gupta J, Hanke K, Weight CJ, Nguyen C, Gaughan C, Kim KA, Bannert N, Kirchhoff F, Munch J, **Silverman RH**. Fibrils of prostatic acid phosphatase fragments boost infections by XMRV, a human retrovirus associated with prostate cancer. J Virol 83:6995-7003, 2009. PMCID: PMC2704761

Lombardi VC, Ruscetti FW, Das Gupta J, Pfost MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, **Silverman RH**, Mikovits JA. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. Science 326:585-589, 2009.

- **Drs. Eric Klein and Robert Silverman** reported identification of an undescribed gammaretrovirus genome, xenotropic murine leukemia virus-related virus (XMRV), in prostate cancer tissue from patients homozygous for a reduced activity variant of the antiviral enzyme RNase L, and have begun studies elucidating the mechanism of the virus. Additional studies are aimed at using the virus as a screening tool for patients with prostate cancer. These studies will lead to a test for exposure, identification of high risk males, development of anti-infectious and anti-inflammatory trials, and studies of the basic biology of viral associated prostate cancer.

Yan M, Rerko RM, Platzer P, **Dawson D**, **Willis J**, Tong M, Lawrence E, Lutterbaugh J, Lu S, **Willson JK***, **Luo G**, Hensold J, Tai HH, Wilson K, **Markowitz SD**. 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-{beta}-induced suppressor of human gastrointestinal cancers. Proc Natl Acad Sci USA 101:17468-17473, 2004.

- **Drs. Dawn Dawson, Joseph Willis, James Willson*, Guangbin Luo and Sanford Markowitz** reported the discovery of a human “celebrex like” gene, 15-Prostaglandin Dehydrogenase, that they demonstrated is a COX-2 oncogene antagonist that has colon cancer tumor suppressor activity. It is a major effector of the TGF-beta tumor suppressor pathway, and is inactivated in colon cancers when this pathway is lost. This work provides further data supporting targeting of PDGH with therapeutic drugs.

Personalized Medicine

Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker JS, Zhang Z, Croshaw R, **Willis J**, **Dawson D**, Shipitsin M, **Willson JK***, Sukumar S, Polyak K, Park BH, Pethiyagoda CL, Pant PV, Ballinger DG, Sparks AB, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, **Markowitz SD**, Parmigiani G, Kinzler KW, Velculescu VE, Vogelstein B. The genomic landscapes of human breast and colorectal cancers. Science 318:1108-1113, 2007.

- **Drs. Joseph Willis, Dawn Dawson, James Willson*, and Sanford Markowitz** found the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly mutated genes and a much larger number of genes mutated at a low frequency. This work increases our understanding that numerous pathways contribute to cancer with dominant genes and pathways serving as tumorigenesis triggers. These results have implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.

Leidner RS, **Fu P**, Clifford B, Hamdan A, Jin C, Eisenberg R, Bogon TJ, Skokan M, Franklin WA, Cappuzzo F, Hirsch FR, Varella-Garcia M, **Halmos B**. Genetic abnormalities of the EGFR pathway in Africa American patients with non-small cell lung cancer. J Clin Oncol 27:5620-5626, 2009.

- **Drs. Rom Leidner and Pingfu Fu** presented work demonstrating ethnicity plays a significant role in the response of individuals to EGFR-targeting agents in non-small-cell lung cancer, finding that African American patients with NSCLC are significantly less likely than white patients to harbor activating mutations of EGFR, which suggests EGFR tyrosine kinase inhibitors are unlikely to yield major remissions in this population. Their findings underscore the need for consideration of these ethnic differences in the design of future trials of agents that target the EGFR pathway.

Aging and Cancer

Rose JH, **O'Toole EE**, **Koroukian S, Berger NA**. Geriatric oncology and primary care: promoting partnerships in practice and research. J Am Geriatr Soc 57 Supp 2:S235-238, 2009.

- **Drs. Julia Rose, Elizabeth O'Toole, Siran Koroukian and Nathan Berger** were involved in the publication of an entire supplement focused on geriatric oncology and primary care. This supplement focused on the main themes of the Aging-Cancer Research Program in the area of clinical management of the older cancer patient including prevention and screening, intensity of care with co-morbidities, survivorship, communication, as well as emphasizing and promoting partnerships in practice and research.

Rose JH, Kypriotakis G, **Bowman KF**, Einstadter D, **O'Toole EE**, Mechekano R, Dawson NV. Patterns of adaptation in patients living long term with advanced cancer. Cancer 115:4298-4310, 2009.

- **Drs. Julia Rose, Karen Bowman and Elizabeth O'Toole** examined the role of psychospiritual adaptation in longer term survivors with advanced cancer. The work focuses on an often overlooked area of patients who are living longer with late-stage cancer, including anxiety, depression, and spiritual well-being. This work helps to identify the potential subgroups of survivors who are at greatest risk for poor outcomes.

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Major Scientific Accomplishments and Publications 2000-2009

(Chronological Order)

Chen WD, Eshleman JR, Aminoshariae MR, Ma AH, Veloso N, **Markowitz S, Sedwick WD, Veigl ML**. Cytotoxicity and mutagenicity of frameshift-inducing agent ICR191 in mismatch repair-deficient colon cancer cells. J Natl Cancer Inst 92:480-485, 2000.

- **Drs. Sanford Markowitz, David Sedwick, and Martina Veigl** found that frame shift-inducing mutations can selectively induce mutations in mismatch repair-deficient genes versus mismatch repair-proficient cells. This study suggests that environmental exposures may therefore favor development of cancers with the microsatellite instability in tissues like the gut. This group also reported that frame shift-inducing chemotherapy agents could preferentially kill mismatch repair-deficient cancer cells and, thus, represent a prototype of novel therapeutic compounds.

Nadeau JH, Balling R, Barsh G, Beier D, Brown SD, Bucan M, Camper S, Carlson G, Copeland N, Eppig J, Fletcher C, Frankel WN, Ganten D, Goldowitz D, Goodnow C, Guenet JL, Hicks G, de Angelis MH, Jackson I, Jacob HJ, Jenkins N, Johnson D, Justice M, Kay S, Kingsley D, Lehrach H, Magnuson TR, Meisler M, Poustka A, Rinchik EM, Rossant J, Russell LB, Schimenti J, Shiroishi T, Skarnes WC, Soriano P, Stanford W, Takahashi JS, Wurst W, Zimmer A. Sequence interpretation. Functional annotation of mouse genome sequences. Science 291:1251-1255, 2001.

- **Dr. Joseph Nadeau**, as part of the International Mouse Mutagenesis Consortium, was first author in a paper that proposed goals and outlined plans for annotating the mouse genome and compiling data on mouse mutations over the next 10 years. The Consortium found that in addition to the challenges of identifying new assays to probe biological functions, more efficient and reliable methods were needed for archiving, managing, analyzing, displaying, and disseminating the complex phenotype data sets resulting from mutagenesis programs.

Goodwin MA, **Zyzanski SJ**, Zronek S, Ruhe M, Weyer SM, Konrad N, Esola D, **Stange KC**. A clinical trial of tailored office systems for preventive service delivery. The Study to Enhance Prevention by Understanding Practice (STEP-UP). Am J Prev Med 21:20-28, 2001.

- **Drs. Stephen Zyzanski and Kurt Stange** published findings from a clinical trial involving 79 community family practices and more than 10,000 patients. This STEP-UP trial showed the effectiveness of a practice-tailored strategy for increasing rates of cancer preventive services.

Zielske SP, **Gerson SL**. Cytokines, including stem cell factor alone, enhance lentiviral transduction in nondividing human LTCIC and NOD/SCID repopulating cells. Mol Ther 7:325-333, 2003.

Zielske SP, Reese JS, Lingas KT, Donze JR, **Gerson SL**. *In vivo* selection of MGMT(P140K) lentivirus-transduced human NOD/SCID repopulating cells without pretransplant irradiation conditioning. J Clin Invest 112:1561-1570, 2003. PMCID: PMC259124

- In a series of studies involving mutant MGMT drug resistant gene transfer into hematopoietic stem cells, **Dr. Stanton Gerson** characterized optimal conditions for lentiviral gene transfer into human CD34 cells and the ability to select for these cells *in vivo* after drug treatment. These studies form the basis of an ongoing clinical trial to test the feasibility of using mutant MGMT drug resistant gene transfer to enhance clinical transplantation of hematopoietic progenitor cells into people.

Lu T, Burdelya LG, Swiatkowski SM, Boiko AD, **Howe PH**, **Stark GR**, **Gudkov AV***. Secreted transforming growth factor beta 2 activates NF-kappaB, blocks apoptosis, and is essential for

the survival of some tumor cells. Proc Natl Acad Sci USA 101:7112-7117, 2004. PMCID: PMC406474

- **Drs. Philip Howe, George Stark and Andrei Gudkov*** revealed a novel role for both the active and latent forms of TGF-beta in cancer. These two forms of the cytokine secreted by many different tumors have the novel function of activating the transcription factor NF-kappaB, which is constitutively active in most tumors and has an important pro-survival function. Latent TGF-beta does not activate SMADs, but does activate NF-kappaB. These dual functions of TGF-beta may help to explain the seemingly conflicting data that this cytokine is important to inactivate TGF-beta -dependent SMAD signaling early in tumorigenesis, but to retain TGF-beta secretion late in this process.

Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, Stevens C, Barker JN, Gale RP, **Lazarus HM**, Marks DI, van Rood JJ, Scaradavou A, Horowitz MM. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 351:2265-2275, 2004.

- **Drs. Mary Laughlin and Hillard Lazarus** published the results of a multi-center trial of adults transplanted with UCB for hematologic malignancies. They found there were no differences in outcome between patients with one HLA mismatch and those with two HLA mismatches after cord blood transplantation. Their data indicated that HLA-mismatched cord blood should be considered for adult hematopoietic stem cell grafts in the absence of an HLA-matched donor.

Yan M, Rerko RM, Platzer P, **Dawson D**, **Willis J**, Tong M, Lawrence E, Lutterbaugh J, Lu S, **Willson JK***, **Luo G**, Hensold J, Tai HH, Wilson K, **Markowitz SD**. 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-{beta}-induced suppressor of human gastrointestinal cancers. Proc Natl Acad Sci USA 101:17468-17473, 2004.

- **Drs. Dawn Dawson, Joseph Willis, James Willson*, Guangbin Luo and Sanford Markowitz** reported the discovery of a human “celebrex like” gene, 15-Prostaglandin Dehydrogenase, that they demonstrated is a COX-2 oncogene antagonist that has colon cancer tumor suppressor activity. It is a major effector of the TGF-beta tumor suppressor pathway, and is inactivated in colon cancers when this pathway is lost. This work provides further data supporting targeting of PDGH with therapeutic drugs.

Cooper GS, Payes JD. Receipt of colorectal testing prior to colorectal carcinoma diagnosis. Cancer 103:696-701, 2005.

Cooper GS, Doug Kou TD. Underuse of colorectal cancer screening in a cohort of medicare beneficiaries. Cancer 112:293-299, 2008.

- **Dr. Gregory Cooper** found that African-Americans were less likely to receive screening colonoscopies for colorectal cancer detection, and found that less than 30% of individuals diagnosed with colon cancer had a recommended screening test prior to the diagnosis. Additional studies using large database analysis of 153,469 Medicare beneficiaries to assess screening for colon cancer showed that screening remains low. Together, these studies demonstrate the need to improve and publicize the advantages of colonoscopy to screen for colon cancer, particularly in African-Americans.

Chak A, Ochs-Balcom H, **Falk G***, Grady WM, Kinnard M, **Willis JE**, **Elston R**, **Eng C**. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. Cancer Epidemiol Biomarkers Prev 15:1668-1673, 2006.

- **Drs. Amitabh Chak, Gary Falk*, Joseph Willis, Robert Elston and Charis Eng** led a prospective population assessment that found that there is a greater rate of familial

Barrett's esophagitis in patients with benign and malignant esophageal disorders, with a higher percentage than previously reported. This indicates that relatives of patients with esophageal cancer and Barrett's esophagitis should receive prospective screening in order to identify and treat malignant esophageal disorders potentially at an earlier stage.

Dong B, Kim S, Hong S, Das Gupta J, Malathi K, **Klein EA**, Ganem D, Derisi JL, Chow SA, **Silverman RH**. From the Cover: an infectious retrovirus susceptible to an IFN antiviral pathway from human prostate tumors. Proc Natl Acad Sci USA 104:1655-1660, 2007. PMCID: PMC1776164

Hong S, **Klein EA**, Das Gupta J, Hanke K, Weight CJ, Nguyen C, Gaughan C, Kim KA, Bannert N, Kirchhoff F, Munch J, **Silverman RH**. Fibrils of prostatic acid phosphatase fragments boost infections by XMRV, a human retrovirus associated with prostate cancer. J Virol 83:6995-7003, 2009. PMCID: PMC2704761

Lombardi VC, Ruscetti FW, Das Gupta J, Pfost MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, **Silverman RH**, Mikovits JA. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. Science 326:585-589, 2009.

- **Drs. Eric Klein and Robert Silverman** reported identification of an undescribed gammaretrovirus genome, xenotropic murine leukemia virus-related virus (XMRV), in prostate cancer tissue from patients homozygous for a reduced activity variant of the antiviral enzyme RNase L, and have begun studies elucidating the mechanism of the virus. Additional studies are aimed at using the virus as a screening tool for patients with prostate cancer. These studies will lead to a test for exposure, identification of high risk males, development of anti-infectious and anti-inflammatory trials, and studies of the basic biology of viral associated prostate cancer.

Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker JS, Zhang Z, Croshaw R, **Willis J**, **Dawson D**, Shipitsin M, **Willson JK***, Sukumar S, Polyak K, Park BH, Pethiyagoda CL, Pant PV, Ballinger DG, Sparks AB, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, **Markowitz SD**, Parmigiani G, Kinzler KW, Velculescu VE, Vogelstein B. The genomic landscapes of human breast and colorectal cancers. Science 318:1108-1113, 2007.

- **Drs. Joseph Willis, Dawn Dawson, James Willson*, and Sanford Markowitz** found the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly mutated genes and a much larger number of genes mutated at a low frequency. This work increases our understanding that numerous pathways contribute to cancer with dominant genes and pathways serving as tumorigenesis triggers. These results have implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.

Patocs A, Zhang L, Xu Y, Weber F, Caldes T, Mutter G, Platzer P, **Eng C**. LBreast-cancer stromal cells with TP53 mutations and nodal metastases. N Engl J Med 357:2543-2551, 2007.

- **Dr. Charis Eng** examined the role of epithelial and stromal genomic TP53 alterations in hereditary and sporadic breast cancer. She found that stroma-specific loss of heterozygosity or allelic imbalance is associated with somatic TP53 mutations and regional lymph-node metastases in sporadic breast cancer but not in hereditary breast cancer. This work expands the emerging arena of tumor microenvironment and the role it plays in clinical outcomes.

Zhang X, Guo C, Chen Y, Shulha HP, Schnetz MP, **Laframboise T**, Bartels CF, **Markowitz S**, Weng Z, **Scacheri PC**, **Wang Z**. Epitope tagging of endogenous proteins for genome-wide ChIP-chip studies. Nat Methods 5:163-165, 2008. PMCID: PMC2435063

- **Drs. Thomas LaFramboise, Sanford Markowitz, Peter Scacheri and Zhenghe Wang** reported the development of a major new method for using gene knock-in technology to introduce epitope tags into the endogenous genomic locus of any gene. This method provides the ability to analyze protein-protein interactions or protein-chromatin interactions across the genome, including newly discovered genes for which high quality antibodies do not exist.

Ramesh S, Qi XJ, Wildey GM, Robinson J, Molkentin J, **Letterio J**, **Howe PH**. TGFbeta-mediated BIM expression and apoptosis are regulated through SMAD3-dependent expression of the MAPK phosphatase MKP2. EMBO Rep 9:990-997, 2008. PMCID: PMC2572119

- **Drs. John Letterio and Philip Howe** demonstrated that transforming growth factor-beta (TGFbeta)-mediated BIM expression and apoptosis are regulated through SMAD3-dependent expression of the MAPK phosphatase. Their results provide further evidence of the importance of TGF-beta and SMAD3 signaling, as well as mitochondrion-mediated events, in cell survival.

Itzkowitz S, Brand R, Jandorf L, Durkee K, Millholland J, Rabeneck L, Schroy PC 3rd, Sontag S, Johnson D, **Markowitz S**, Paszat L, Berger BM. A simplified, noninvasive stool DNA test for colorectal cancer detection. Am J Gastroenterol 103:2862-2870, 2008.

- **Dr. Sanford Markowitz** and collaborators at Exact Sciences continued to report development and improvement of their novel method for early detection of colon cancer based on detection of abnormally methylated DNAs in patient feces. The group reported enhancing the sensitivity of this assay for detecting curable early stage colon cancers to 84%, and demonstrated a similar sensitivity for also detecting premalignant advanced colon adenomas. In March 2008, the American Cancer Society endorsed fecal DNA screening as an accepted method for early detection of colon cancer, and in August 2008 Laboratory Corporation of America introduced the first commercially available fecal DNA test colon cancer screening (ColoSure™), basing the test on licensed technology from the Markowitz laboratory.

Ma PC, Tretiakova MS, Mackinnon AC, Ramnath N, Johnson C, Dietrich S, Seiwert T, Christensen JG, Jagadeeswaran R, Krausz T, Vokes EE, Husain AN, Salgia R. Expression and mutational analysis of MET in human solid cancers. Genes Chromosomes Cancer 47:1025-1037, 2008. PMCID: PMC2583960

- **Dr. Patrick Ma** has shown that MET is often overexpressed and mutated in human solid tumors, including lung cancer. This suggests that MET and MET mutants seen in human cancers would be attractive targets for drug screening.

Jiang Y, Dunbar A, Gondek LP, Mohan S, Rataul M, O'Keefe C, **Sekeres M**, Saunthararajah Y, **Maciejewski JP**. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. Blood 113:1315-1325, 2009. PMCID: PMC2637194

Jankowska AM, Szpurka H, Tiu RV, Makishima H, Afable M, Huh J, O'Keefe CL, Ganetzky R, McDevitt MA, **Maciejewski JP**. Loss of heterozygosity 4q24 and TET2 mutations associated with myelodysplastic/myeloproliferative neoplasms. Blood 113:6403-6410, 2009. PMCID: PMC2710933

Makishima H, Cazzolli H, Szpurka H, Dunbar A, Tiu R, Huh J, Muramatsu H, O'Keefe C, **Hsi E**, Paquette RL, Kojima S, List AF, **Sekeres MA**, McDevitt MA, **Maciejewski JP**. Mutations of E3 ubiquitin ligase Cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. J Clin Oncol 27:6109-6116, 2009.

- **Drs. Jaroslaw Maciejewski, Mikkael Sekeres and Eric Hsi** published a series of work elucidating the genetic changes associated with the transition from myelodysplastic syndrome to acute leukemia. Their work provided further evidence of the roles of p53 and TET2 in cancer progression. Work investigating DNA methylation demonstrated that E3 ubiquitin ligase FZD9 is a tumor suppressor, suggesting these proteins may be potential therapeutic targets.

Shen J, Yu WM, Brotto M, Scherman JA, Guo C, Stoddard C, Nosek TM, Valdivia HH, **Qu CK**. Deficiency of MIP/MTMR14 phosphatase induces a muscle disorder by disrupting Ca(2+) homeostasis. Nat Cell Biol 11:769-776, 2009. PMCID: PMC2693472

- **Dr. Cheng-Kui Qu** identified and characterized the novel phosphatase MIP, which is essential for normal hematopoietic stem cell function and leukemia stem cell development. While this work is important to stem cell development, he also found that this phosphatase has an important role in muscle performance. This work expands the knowledge of cell-signaling networks and opens a new area of investigation.

Miao H, Li DQ, Mukherjee A, Guo H, Petty A, Cutter J, **Basilion JP**, Sedor J, Wu J, **Danielpour D, Sloan AE**, Cohen ML, **Wang B**. EphA2 mediates ligand-dependent inhibition and ligand-independent promotion of cell migration and invasion via a reciprocal regulatory loop with Akt. Cancer Cell 16:9-20, 2009. PMCID: PMC2860958

- **Drs. James Basilion, David Danielpour, Andrew Sloan, and Bing-Cheng Wang** studied the role of EphA2 kinase signaling in prostate cancer and demonstrated that there are opposing roles of EphA2 in regulating cell migration and invasion. While activation of EphA2 with its ligand ephrin-A1 inhibited chemotactic migration of glioma and prostate cancer cells, EphA2 overexpression promoted migration in a ligand-independent manner. This work explains the paradox that was previously observed in investigations into these proteins.

Rose JH, Kypriotakis G, **Bowman KF**, Einstadter D, **O'Toole EE**, Mechekano R, Dawson NV. Patterns of adaptation in patients living long term with advanced cancer. Cancer 115:4298-4310, 2009.

- **Drs. Julia Rose, Karen Bowman and Elizabeth O'Toole** examined the role of psychospiritual adaptation in longer term survivors with advanced cancer. The work focuses on an often overlooked area of patients who are living longer with late-stage cancer, including anxiety, depression, and spiritual well-being. This work helps to identify the potential subgroups of survivors who are at greatest risk for poor outcomes.

Yun J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, **Willson JK***, **Markowitz S**, Zhou S, Diaz LA Jr, Velculescu V, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. Science 325:1555-1559, 2009. PMCID: PMC2820374

- **Dr. Sanford Markowitz and James Willson*** extended studies into the mechanism of KRAS in colon cancer. This work showed that glucose deprivation increases the activity of the KRAS oncogene in colon cancer. This study provides further evidence for the role of environmental conditions, such as diet, that select for genetic mutations that promote tumor progression.

Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, Racevskis J, Dewald GW, Ketterling RP, Bennett JM, Rowe JM, **Lazarus HM**, Tallman MS. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 361:1249-1259, 2009.

- **Dr. Hillard Lazarus** in a clinical trial that will have a direct impact on patient care, found that in young adults with AML, intensifying induction therapy with a high daily dose of daunorubicin improved the rate of complete remission and the duration of overall survival, as compared with the standard dose. (ClinicalTrials.gov number, NCT00049517) 2009 Massachusetts Medical Society.

Li C, Yu S, Nakamura F, Yin S, Xu J, Petrolla AA, **Singh N**, **Tartakoff A**, Abbott DW, **Xin W**, **Sy MS**. Binding of pro-prion to filamin A disrupts cytoskeleton and correlates with poor prognosis in pancreatic cancer. J Clin Invest 119:2725-2736, 2009. PMCID: PMC2735930

- **Drs. Neena Singh, Alan Tartakoff, Wei Xin and Man-Sun Sy** found that binding of pro-prion to filamin A disrupts cytoskeleton and correlates with poor prognosis in pancreatic cancer. This work showed that PrP expression in tumors correlated with a marked decrease in patient survival, making it an attractive target for therapeutic intervention in human PDAC.

Leidner RS, **Fu P**, Clifford B, Hamdan A, Jin C, Eisenberg R, Bogon TJ, Skokan M, Franklin WA, Cappuzzo F, Hirsch FR, Varella-Garcia M, **Halmos B**. Genetic abnormalities of the EGFR pathway in Africa American patients with non-small cell lung cancer. J Clin Oncol 27:5620-5626, 2009.

- **Drs. Rom Leidner and Pingfu Fu** presented work demonstrating ethnicity plays a significant role in the response of individuals to EGFR-targeting agents in non-small-cell lung cancer, finding that African American patients with NSCLC are significantly less likely than white patients to harbor activating mutations of EGFR, which suggests EGFR tyrosine kinase inhibitors are unlikely to yield major remissions in this population. Their findings underscore the need for consideration of these ethnic differences in the design of future trials of agents that target the EGFR pathway.

Rose JH, **O'Toole EE**, **Koroukian S, Berger NA**. Geriatric oncology and primary care: promoting partnerships in practice and research. J Am Geriatr Soc 57 Supp 2:S235-238, 2009.

- **Drs. Julia Rose, Elizabeth O'Toole, Siran Koroukian and Nathan Berger** were involved in the publication of an entire supplement focused on geriatric oncology and primary care. This supplement focused on the main themes of the Aging-Cancer Research Program in the area of clinical management of the older cancer patient including prevention and screening, intensity of care with co-morbidities, survivorship, communication, as well as emphasizing and promoting partnerships in practice and research.

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Significant Collaborations

CTEP

More than 15 center investigators are involved in the drug development effort that brings new agents through preclinical and clinical development often with laboratory correlates. The Case CCC Developmental Therapeutics Program members collaborate with NCI and other cancer centers to develop novel new treatments, design clinical trial interventions, and carry out and accrue patients to new therapeutic trials. This group has provided sentinel observations on methoxyamine and benzylguanine to inhibit DNA repair, rebeccamycon analogue for DNA damage, antiangiogenic agents now in phase III clinical trials for medulary thyroid carcinoma, new targeted therapeutics inhibiting EGFR receptor kinases and akt and met kinases.

The Case CCC participates in the following CTEP initiatives:

- Blood and Marrow Clinical Trials Network (BMT CTN)
- Eastern Cooperative Oncology Group (ECOG)
- Gynecologic Oncology Group (GOG)
- Adult Brain Tumor Consortium (ABTC)
- Southwest Oncology Group (SWOG)
- Cancer and Leukemia Group B (CALGB)
- Radiation Therapy Oncology Group (RTOG)
- Children's Oncology Group (COG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- Organ Dysfunction Studies

CTEP High Impact Publications

Dowlati A, Robertson K, **Cooney M**, Petros WP, Stratford M, Jesberger J, Rafie N, **Overmoyer B***, Makkar V, Stambler B, Taylor A, Waas J, **Lewin J***, **McCrae KR**, and **Remick SC***. A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin A4 phosphate on a single-dose intravenous schedule in patients with advanced cancer. *Cancer Res* 62:3408-16, 2002.

Cooper BW, Veal GJ, **Radivoyevitch T**, Tilby MJ, **Meyerson H**, **Lazarus HM**, **Koc ON***, Creger RJ, Pearson G, Nowell GM, Gosky D, Ingalls ST, **Hoppel CL**, **Gerson SL**. A phase I and pharmacodynamic study of fludarabine, carboplatin, and topotecan in patients with relapsed, refractory, or high-risk acute leukemia. *Clin Cancer Res* 10:6830-9, 2004. (PI: BW Cooper, R21 CA815000).

Dowlati A, Robertson K, **Radivoyevitch T**, Waas J, Ziats N, Hartman P, Abdul-Karim F, Wassman J, Jesberger J, Lewin J, **McCrae K**, Ivy P, and **Remick SC**. Novel phase I dose de-escalation design trial to determine the biological modulatory dose of the anti-angiogenic agent SU5416. *Clin Cancer Res* 11:7938-44, 2005. (NCI# T99-0095).

Motzer RJ, **Rini BI**, **Bukowski RM**, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, and Michaelson MD. Sunitinib in patients with metastatic renal carcinoma. *JAMA* 295:2516-24, 2006.

Fu P, **Dowlati A**, **Schluchter M**. Comparison of power between randomized discontinuation design and upfront randomization design on progression-free survival. *J Clin Oncol* 27(25):4135-41, 2009.

Colorectal Cancer

Dr. Sanford Markowitz has assembled a set of collaborators who coordinate efforts in colon cancer genetics, development of gene-based tests for colon cancer and evaluation of genetic changes involved in metastasis. Key discoveries include the role of mismatch repair in colon cancer, the role of 15 PGDH in colon cancer progression, the existence of silenced vimentum only in colon cancers, and recent work evaluating genes critical to Barrett's esophagitis.

Colorectal Cancer High Impact Publications

Bardelli A, Parsons W, Silliman N, Ptak J, Szabo S, Saha S, **Markowitz S**, **Willson JK***, Parmigiani G, Kinzler K, Vogelstein B, Velculescu V. Mutational analysis of the tyrosine kinome in colorectal cancers. *Science* 300:949, 2003.

Samuels Y, **Wang Z**, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, **Willson JK***, **Markowitz S**, Kinzler K, Vogelstein B, Velculescu V. High frequency of mutations of PIK3CA gene in human cancer. *Science* 304:554, 2004.

Wang Z, Shen D, Parsons DW, Bardelli A, Sager J, Szabo S, Ptak J, Silliman N, Peters BA, Van Der Heijden MS, Parmigiani G, Yan H, Wang TL, Riggins G, Powell SM, **Willson JK***, **Markowitz S**, Kinzler KW, Vogelstein B, Velculescu VE. Mutational analysis of the tyrosine phosphatome in colorectal cancers. *Science* 304:1164-1166, 2004.

Parsons DW, Wang TL, Samuels Y, Bardelli A, Cummins JM, DeLong L, Silliman N, Ptak J, Szabo S, **Willson JK***, **Markowitz S**, Kinzler KW, Vogelstein B, Lengauer C, Velculescu VE. Colorectal cancer: mutations in a signalling pathway. *Nature* 436:792, 2005.

Sjöblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber T, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, **Markowitz SD**, **Willis J**, **Dawson D**, **Willson JK***, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The consensus coding sequences of human breast and colorectal cancers. *Science* 314:268, 2006.

Wood LD, Parsons D, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky V, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker J, Zhang Z, Croshaw R, **Willis J**, **Dawson D**, Shipitsin M, **Willson JK***, Sukumar S, Polyak K, Park BH, Pethiyagoda C, Pant P, Ballinger D, Sparks A, Hartigan J, Smith DR, Suh E, Papadopoulos N, Buckhaults P, **Markowitz SD**, Parmigiani G, Kinzler K, Velculescu VE, Vogelstein B. The genomic landscapes of human breast and colorectal cancers. *Science* 318:1108-1113, 2007.

Chng WJ, Loeb L, Bielas JH, Strauss B, Sjoblom T, Jones S, Wood LD, Parsons D, Lin J, Barber T, Mandelker D, Leary R, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, **Markowitz SD**, **Willis J**, **Dawson D**, **Willson JK***, Gazdar A, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman K, Papadopoulos N, Vogelstein B, Kinzler K, Velculescu V. Limits to the human cancer genome project? *Science* 315:762b-766b, 2007.

Xenotropic Murine Leukemia Virus-related Virus (XMRV)

Drs. Robert Silverman and **Eric Klein** were part of the team of researchers from the Cleveland Clinic and the University of California that discovered xenotropic murine leukemia virus-related virus, commonly referred to as XMRV, in cancerous prostate tissue in 2006.

Based upon their previous work with RNase L, which showed that RNase L has an anti-viral role and that mutations in RNase L are found in prostate cancer, they examined if XMRV is present in RNase L mutation positive prostate cancer. Using DNA microarray and PCR, they found that there is a strong association between the presence of the virus and having two copies of mutant RNase L. These findings were the first documented cases of human infection with this family of viruses, and represent a previously unexplored area of research that has the potential to lead to improved methods for diagnosis and treatment of prostate cancer.

XMRV High Impact Publications

Kim S, Kim N, Dong B, Boren D, Lee SA, Das Gupta J, Gaughan C, **Klein EA**, Lee C, **Silverman RH**, Chow SA. Integration site preference of xenotropic murine leukemia virus-related virus, a new human retrovirus associated with prostate cancer. *J Virol* 82:9964-9977, 2008.

Hong S, **Klein EA**, Das Gupta J, Hanke K, Weight CJ, Nguyen C, Gaughan C, Kim KA, Bannert N, Kirchhoff F, Munch J, **Silverman RH**. Fibrils of prostatic acid phosphatase fragments boost infections by XMRV, a human retrovirus associated with prostate cancer. *J Virol* 83:6995-7003, 2009.

Dong B, **Silverman RH**. Androgen stimulates transcription and replication of XMRV (Xenotropic Murine Leukemia Virus-Related Virus). *J Virol* 84(3):1648-51, 2010.

GLIOGENE Study

Drs. Jill Barnholtz-Sloan (local PI), **Gene Barnett** (co-I) and **Andrew Sloan** are collaborators on the GLIOGENE study, an international collaboration to map genes for brain tumors. It is conducted by an international consortium of familial brain tumor researchers in the United States, the United Kingdom, Sweden, Denmark and Israel. It is the largest study ever to be conducted on familial gliomas, or primary brain tumors.

GLIOGENE High Impact Publications

Malmer B, Adatto P, Armstrong G, **Barnholtz-Sloan J**, Bernstein JL, Claus E, Davis F, Houlston R, Il'yasova D, Jenkins R, Johansen C, Lai R, Lau C, McCarthy B, Nielsen H, Olson SH, Sadetzki S, Shete S, Wiklund F, Wrensch M, Yang P, Bondy M. GLIOGENE an International Consortium to Understand Familial Glioma. *Cancer Epidemiol Biomarkers* Prev 16(9):1730-4, 2007.

Davis FG, Malmer BS, Aldape K, **Barnholtz-Sloan JS**, Bondy ML, Brännström T, Bruner JM, Burger PC, Collins VP, Inskip PD, Kruchko C, McCarthy BJ, McLendon RE, Sadetzki S, Tihan T, Wrensch MR, Buffler PA. Issues of diagnostic review in brain tumor studies: from the Brain Tumor Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 17(3):484-9, 2008.

Bondy ML, Scheurer ME, Malmer B, **Barnholtz-Sloan JS**, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, Sadetzki S, Schlehofer B, Tihan T, Wiemels JL, Wrensch M, Buffler PA; Brain Tumor Epidemiology Consortium. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. *Cancer* 113(7 Suppl):1953-1968, 2008.

McKean-Cowdin R, **Barnholtz-Sloan J**, Inskip PD, Ruder AM, Butler M, Rajaraman P, Razavi P, Patoka J, Wiencke JK, Bondy ML, Wrensch M. Associations between polymorphisms in DNA repair genes and glioblastoma. *Cancer Epidemiol Biomarkers Prev* 18(4):1118-26, 2009.

Stem Cell Center

The National Center for Regenerative Medicine (NCRM) acts as an umbrella organization for the Center for Stem Cell and Regenerative Medicine (CSCRM), directed by Dr. Stanton Gerson, PI, and Clinical Tissue Engineering Center (CTEC). The NCRM is comprised of three principal non-profit institutions: Case Western Reserve University, University Hospitals of Cleveland, and Cleveland Clinic. The broad-based excellence of its partner institutions provides the NCRM a comprehensive approach including basic and clinical research, biomedical and tissue engineering, and the development and administration of the new therapies to patients with cancer, heart, blood, bone, and nervous system disease. The Stem Cell Center became a viable, fundable center based on the established stem cell research record of the Case CCC Stem Cell and Hematologic Malignancies Program, as well as the infusion of Cleveland Clinic researchers into the Cancer Center.

Cancer Center members are currently involved in the following areas of research through CSCRM:

- **Dr. Stanton Gerson**- stem cell gene transfer, drug selection, transdifferentiation
- **Dr. Mary Laughlin**- UCB for hematopoietic and vascular regeneration, transplantation
- **Dr. Dr. Hillard Lazarus**- clinical MSC and HSC transplantation
- **Dr. Maria Parat***- endothelial cell migration and angiogenesis in breast cancer
- **Dr. Cheng-Kui Qu**- signaling mechanisms of hematopoietic cell processes
- **Dr. Jeremy Rich**- glioma stem cell and brain tumor malignancy, signal transduction pathways in brain tumors, and small molecule inhibitors and brain cancer treatments
- **Dr. Nywana Sizemore***- gene expression, oncogenesis, and apoptosis in cancer
- **Dr. Andrew Sloan**- treatment modalities for gliomas as well as outcome measurements of various therapies
- **Dr. Sree Sreenath**- signal transduction in cancer and inflammation
- **Dr. William Tse***- lymphoma, leukemia, and multiple myeloma
- **Dr. Martina Veigl**- mutagenesis by chemotherapeutic agents
- **Dr. Yu-Chung Yang**- cytokine signal transduction

The Case CCC also collaborates with the Clinical Tissue Engineering Center (CTEC), a partner of CSCRM, which was created in 2005 through a $4 million award from the State of Ohio as a Wright Center of Innovation. CTEC is a multi-disciplinary center devoted to developing new drugs, devices, and therapeutic strategies in tissue engineering and is comprised of 60 clinicians from Case Western Reserve University, Cleveland Clinic, University Hospitals of Cleveland, NASA Glenn Research Center, and Ohio Supercomputer. The CTEC is led by **Drs. George Muschler**, Director, and **Arnold Caplan**, Co-Director. **Drs. Paul DiCorleto**, **Stan Gerson**, and **Kevin Cooper** are on the CTEC Internal Advisory Board.

Leukemogenesis

Dr. Jaroslaw Maciejewski and collaborators have focused on mechanisms of DNA damage accumulation in myelodysplastic syndrome (MDS) and its overlap syndromes. This work has also defined signal transduction aberrations involved in subsequent malignant progression, with a particular focus on myeloid malignancies. Overall the important clinical findings from this group suggest that reduced degradation of activated tyrosine kinases promotes leukemia.

Leukemogenesis High Impact Publications

Jankowska AM, Szpurka H, Tiu RV, Makishima H, Afable M, Huh J, O'Keefe CL, Ganetzky R, McDevitt MA, **Maciejewski JP**. Loss of heterozygosity 4q24 and TET2 mutations associated with myelodysplastic/myeloproliferative neoplasms. *Blood* 113:6403-6410, 2009.

Jasek M, Gondek LP, Bejanyan N, Tiu R, Huh J, Theil KS, O'Keefe C, McDevitt MA, **Maciejewski JP**. TP53 mutations in myeloid malignancies are either homozygous or hemizygous due to copy number-neutral loss of heterozygosity or deletion of 17p. *Leukemia* 24(1):216-9, 2010.

Jiang Y, Dunbar A, Gondek LP, Mohan S, Rataul M, O'Keefe C, **Sekeres M**, Saunthararajah Y, **Maciejewski JP**. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. *Blood* 113:1315-1325, 2009.

Makishima H, Cazzolli H, Szpurka H, Dunbar A, Tiu R, Huh J, Muramatsu H, O'Keefe C, **Hsi E**, Paquette RL, Kojima S, List AF, **Sekeres MA**, McDevitt MA, **Maciejewski JP**. Mutations of E3 ubiquitin ligase Cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. *J Clin Oncol* 27(36):6109-16, 2009.

Sekeres MA, Maciejewski JP, Giagounidis AA, Wride K, Knight R, Raza A, List AF. Relationship of treatment-related cytopenias and response to lenalidomide in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol* 26:5943-5949, 2008.

Transdisciplinary Research on Energetics and Cancer (TREC)

Led by **Dr. Nathan Berger**, the TREC initiative is a five-year scientific research effort aimed at reducing cancer linked with obesity, poor diet, and low levels of physical activity. Finding answers to complex questions about obesity and cancer requires a transdisciplinary research approach where scientists from diverse fields come together to integrate knowledge across disciplines.

This $54 million initiative that began in the fall of 2005 is funded by the NCI. Scientists at the NCI, four research centers (Case Comprehensive Cancer Center, Cleveland, OH (**Nathan Berger, M.D.**); Fred Hutchinson Cancer Research Center, Seattle, Washington (Anne McTiernan, M.D., Ph.D.); University of Minnesota, Minneapolis, Minnesota (Robert Jeffery, Ph.D.); University of Southern California, Los Angeles, California (Michael Goran, Ph.D.) collaborate on the TREC initiative.

TREC High Impact Publications

Barber TD, McManus K, Yuen KW, Reis M, Parmigiani G, Shen D, Barrett I, Nouhi Y, Spencer F, **Markowitz S**, Velculescu VE, Kinzler KW, Vogelstein B, Lengauer C, Hieter P.

Chromatid cohesion defects may underlie chromosome instability in human colorectal cancers. *Proc Natl Acad Sci USA* 105:3443-3448, 2008.

Hill-Baskin AE, Markiewski MM, Buchner DA, Shao H, DeSantis D, Hsiao G, Subramaniam S, **Berger NA**, Croniger C, Lambris JD, **Nadeau JH**. Diet-induced hepatocellular carcinoma in genetically predisposed mice. *Hum Mol Genet.* Aug 15;18(16):2975-88, 2009.

Myung SJ, Rerko RM, Yan M, Platzer P, Guda K, Dotson A, Lawrence E, Dannenberg AJ, Lovgren AK, Luo G, Pretlow TP, Newman RA, Willis J, Dawson D, Markowitz SD. 15-Hydroxyprostaglandin dehydrogenase is an in vivo suppressor of colon tumorigenesis. *Proc Natl Acad Sci USA* 103:12098-12102, 2006.

Yan M, Myung SJ, Fink SP, Lawrence E, Lutterbaugh J, Yang P, Zhou X, Liu D, Rerko RM, **Willis J, Dawson D,** Tai HH, **Barnholtz-Sloan JS**, Newman RA, Bertagnolli MM, **Markowitz SD.** 15-Hydroxyprostaglandin dehydrogenase inactivation as a mechanism of resistance to celecoxib chemoprevention of colon tumors. *Proc Natl Acad Sci USA* 106(23):9409-13, 2009.

Yun J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, **Willson JK***, **Markowitz S,** Zhou S, Diaz LA, Jr., Velculescu V, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science* 325:1555-1559, 2009.

Cancer Genome Atlas

Drs. Andrew Sloan and Jill Barnholtz-Sloan are co-PIs of the Cancer Genome Atlas (TCGA) project. This national initiative is a comprehensive and coordinated three-year effort, funded by the NCI and National Human Genome Research Institute (NHGRI), to accelerate our understanding of the molecular basis of cancer through the application of genomic analysis technologies, including large-scale genome sequencing. Specifically, ovarian cancer, lung cancer and glioblastoma have been prioritized for the pilot phase of this project.

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Significant Clinical Trials

These trials were directed by Case CCC members and the center is the lead institution.

1) *Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia* (*N Engl J Med* 351(22):2265-75, 2004)

   This group compared the outcomes of the transplantation of hematopoietic stem cells from unrelated donors in adults with leukemia who had received cord blood that was mismatched for one HLA antigen (34 patients) or two antigens (116 patients), bone marrow that had one HLA mismatch (83 patients), and HLA-matched bone marrow (367 patients). Hematopoietic recovery was slower with transplantation of mismatched bone marrow and cord blood than with matched marrow transplantations. Acute graft-versus-host disease (GVHD) was more likely to occur after mismatched marrow transplantation, and chronic GVHD was more likely to occur after cord-blood transplantation. The rates of treatment-related mortality, treatment failure, and overall mortality were lowest among patients who received matched marrow transplants. Patients who received mismatched bone marrow transplants and those who received mismatched cord-blood transplants had similar rates overall mortality. HLA-mismatched cord blood should be considered an acceptable source of hematopoietic stem-cell grafts for adults in the absence of an HLA-matched adult donor. As a result of this study use of umbilical cord blood for transplantation in adults became more common.

   Mary Laughlin, Mary Eapen, Pablo Rubinstein, John Wagner, Mei-Jei Zhang, Richard Champlin, Cladd Stevens, Juliet Barker, Robert Gale, **Hillard Lazarus**, David Marks, Jon van Rood, Andromachi Scaradavou, and Mary M. Horowitz.

2) *Cardiovascular safety profile of combretastatin a4 phosphate in a single-dose phase I study in patients with advanced cancer* (*Clin Cancer Res* 10:96-100, 2004)

   Combretastatin A4 phosphate (CA4P) was given to 25 patients in a Phase I study with advanced solid tumors. A patient with anaplastic thyroid cancer had a complete response and is alive 30 months after treatment. After CA4P administration, there were significant increases in QTc interval at the 4-h time points [30.8 ms ($P < 0.0001$),] and HR [15.1 bpm ($P < 0.001$)]. Two patients had ECG changes consistent with an acute coronary syndrome within 24-h of CA4P infusion. CA4P prolongs the QTc interval. This agent has potential cardiovascular toxicity but is useful in medullary Thyroid carcinoma. As a result of this trial, a phase 2 and now international Phase 3 trial in medullary thyroid carcinoma is underway.

   Matthew Cooney, **Tomas Radivoyevitch**, **Beth Overmoyer***, **Nathan Levitan**, Kelly Robertson, Sandra Levine, Kathleen DeCaro, Carol Buchter, Anne Taylor, Bruce Stambler, and **Scot Remick***.

3) *Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab--an Eastern Cooperative Oncology Group Study* (*Clin Cancer Res* 14:1407-1412, 2008.)

   E4599 was a phase II/phase III trial, in which 878 patients with advanced non-small cell lung cancer were randomized to carboplatin + paclitaxel (PC arm) or PC + bevacizumab (BPC

arm). Survival and progression-free survival were superior on the BPC arm. Patients with low baseline ICAM had a higher response rate (32% versus 14%; P = 0.02), better overall survival (P = 0.00005), and better 1-year survival (65% versus 25%) than those with high ICAM, respectively, regardless of treatment arm. Patients with high VEGF levels were more likely to respond to BPC compared with PC. This study was used to support FDA approval of bevacizumab in lung cancer.

Afshin Dowlati, Robert Gray, Alan Sandler, Joan Schiller, and David Johnson.

4) *Phase I study of sunitinib plus bevacizumab in advanced solid tumors* (*Clin Cancer Res* 15(19):6277-83, 2009)

Bevacizumab is an antibody against vascular endothelial growth factor; sunitinib is an inhibitor of vascular endothelial growth factor and related receptors. The safety of sunitinib plus bevacizumab was assessed in this phase I trial. Thirty-eight patients were enrolled. Seven patients had a confirmed partial response (18%; 95% confidence interval, 8-34%). Nineteen of the 32 patients with a postbaseline scan (59%) had at least some reduction in overall tumor burden (median, 32%; range, 3-73%). Antitumor activity was observed across multiple solid tumors. Based on this study 2 phase 2 clinical trials have been approved for melanoma and renal cell carcinoma.

Brian Rini, **Jorge Garcia**, **Matthew Cooney**, **Paul Elson**, Allison Tyler, Kristi Beatty, Joseph Bokar, **Tarek Mekhail**, **Ronald Bukowski**, **G. Thomas Budd**, **Pierre Triozzi**, **Ernest Borden**, Percy Ivy, Helen Chen, **Afshin Dowlati**, and **Robert Dreicer.**

4) *Comparison of power between randomized discontinuation design and upfront randomization design on progression-free survival.* (*J Clin Oncol* 27(25):4135-41, 2009)

These authors evaluated the sample size and power of studies with small patient cohorts to identify methods that enhance the information derived from Phase I and II studies to improve overall prediction of therapeutic efficacy and optimization of treatment schedules.

Pingfu Fu, **Afshin Dowlati** and **Mark Schluchter.**

5) *High-dose carmustine, etoposide, cisplatin, autologous stem cell transplant with or without involved-field radiotherapy for relapsed/refractory lymphoma: an effective regimen with low morbidity and mortality*. (*Biol Blood Marrow Transplant* 11:13-22, 2005)

This group described an effective chemotherapy regimen for patients with advanced and refractor lymphoma, providing a high degree of curative therapy to such patients in conjunction with autologous stem cell transplantation.

Punit Wadhwa, **Pingfu Fu**, **Omer Koc*, Brenda Cooper,** Robert Fox, Richard J. Creger, David Bajor, Teja Bedi, **Mary Laughlin,** Jennifer Payne, **Stanton Gerson,** and **Hillard Lazarus.**

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Community Outreach Highlights

With 3.9 million people throughout northeast Ohio, a region with a higher than average cancer mortality rate, the Case Comprehensive Cancer Center supports cancer prevention efforts throughout Ohio with an active outreach program.

Outreach coordinators work with community organizations and governmental institutions to educate the underserved populations of greater Cleveland through classes, health fairs and screening efforts and partner with taskforces, coalitions and committees throughout the city and county including: Minority Health Alliance, Colon Cancer Coalition, Susan G. Komen for the Cure, Cleveland Medical Association, Cuyahoga County Food Policy Coalition, Cleveland Office of Minority Health and Ohio Partners for Cancer Control, to name a few.

Highlights

- **Project Safe Conduct,** a collaboration between Case CCC and the Hospice of the Western Reserve, integrates palliative care across the lifespan for people with cancer. Considered a model by the National Coalition for Cancer Survivorship, it won a 2002 Circle of Life Award from the American Hospital Association as well as the National Hospice and Palliative Care Organization Award of Excellence in education.

- **Project T.E.M.P.L.E.** (Teaching, Educating, Mentoring, Preventing, Learning, and Empowering) targets underserved African-American women in greater Cleveland. Using culturally-sensitive, small group classes the program educates them in breast health and breast cancer screening, and assists them in overcoming barriers with the assistance of a health advocate. More than 2,200 women have been reached since the program's inception in 2004.

- **Beauticians and Barbershops Program**, a local program through the Taussig Cancer Institute, involves community sites in cancer prevention activities.

- A partnership of Public Health Television (PHTV) and Case CCC focused on Latino and African American populations with video-based campaigns to encourage screening, increase participation in clinical trials among low income minorities, and increase the cultural competency of physicians. Two of the programs in particular received recognition: the **Urban Cancer Project** was recognized as a national model at the 2003 annual legislative conference of the Congressional Black Caucus, and the news series **Wisdom from Within,** designed by PHTV and the Case CCC to educate the community about the purpose and necessity of cancer screening programs, especially for minorities, was awarded an Emmy. The program was based on the input of focus groups comprised of residents of the Cuyahoga Metropolitan Housing Authority.

- The Case CCC and the NCI-funded CIS made efforts to reach underserved rural areas in northeast Ohio. The northern Ohio Partnership Program Coordinator (PPC) for the CIS worked in partnership with the Tri-County Breast Cancer Coalition, Geneva Memorial Hospital, Ireland Cancer Center, Hospice of the Western Reserve, American Cancer Society, and area health professionals to create programs to increase breast cancer screening among underserved in three rural counties in northeast Ohio. The PPC also partnered with the Northeast Ohio Affiliate of the Susan G. Komen Breast Cancer Foundation to develop a comprehensive breast cancer community profile for the 15 county region.

- In September 2009, Dr. Derek Raghavan participated in the President's Cancer Panel on America's "Demographic and Cultural Transformation: Implications for the Cancer Enterprise." Dr. Raghavan, Immediate Past Co-Chair of the Health Disparities Advisory Group of the American Society of Clinical Oncology, presented the disparities programs from Cleveland Clinic, Case CCC and ASCO.

- **Church-based Programs.** Many outreach programs have partnered with local churches to reach the community through their congregations. These programs include:

    - The **Body and Soul** program, introduced to Cleveland Baptist churches in 2006 by Ireland Cancer Center. Church leaders are trained on how to incorporate the principles of this NCI-developed, evidence-based program into the daily lives of parishioners and the weekly activities of the church.

    - Establishment of resource centers at area churches, a collaboration of the Taussig Cancer Institute with the Cleveland African-American Pastors Association to reach underserved populations. These resource centers include a computer with full internet access and shortcuts to American Cancer Society, NCI, and Taussig Cancer Institute, and literature on screening, risk reduction, and nutrition as well as information for caregivers.

    - **Churches and Hospitals Against Cancer**, a program including the Case CCC, Cleveland Medical Association and local churches, will begin in April 2010.

CASE COMPREHENSIVE CANCER CENTER
CASE WESTERN RESERVE UNIVERSITY

Member Awards and Special Positions

SENIOR LEADERS AND PROGRAM LEADERS

Stanton L. Gerson, M.D.

- 2003 Parent Committee, NCI IRG Program Projects Grants Subcommittee A
- 2004-present Board of Trustees, American Cancer Society
- 2005 NCI Cancer Center Directors Working Group Steering Committee
- 2005 NCI Early Detection Subcommittee
- 2006-2010 Association of American Cancer Institutes (AACI) Board of Directors
  - 2006 National Program Chair
  - 2010 National Program Chair
- 2006-present Ohio Partners for Cancer Control Executive Board
- 2007 Mt. Sinai Foundation, Cleveland, Maurice Salzman Award for Distinguished Service with the Case Comprehensive Cancer Center
- 2007-2011 Cancer Centers and Site Visit Chair, NCI IRG Subcommittee A
- 2008 Heroes of Hope Award, American Cancer Society
- 2009-present National Program Chair, American Society of Gene Therapy

Neal J. Meropol, M.D.

- 2003-present Chair, Eastern Cooperative Oncology Group (ECOG) Developmental Therapeutics Committee
- 2006-present Chair, NCI Colon Cancer Task Force
- 2010 Chair-Elect, ASCO Cancer Research Committee

George Stark, Ph.D.

- **2002-present Member, Institute of Medicine of the National Academy of Sciences**

Derek Raghavan, M.D., Ph.D.

- 1998-2000 Chair, ASCO Cancer Communications Committee
- 2000-2005 Cancer Centers Support Review Committee, NCI
- 2002-2006 Member, Clinical Trials and Awards Advisory Committee, Cancer Research, UK
- 2003 Chair, NCI Special Emphasis Panel ZCA1 GRB-H, Integrating Aging and Cancer
- 2003 Member, NCI Special Emphasis Panel ZCA1 SRRB-Y, Loan Repayment Program
- 2003 Chair, NCI Special Emphasis Panel ZCA1 GRB-H, Integrating Aging and Cancer
- 2004 Member, External Advisory Board, American College of Surgeons Oncology Group
- 2005 External Scientific Advisor – Eastern Cooperative Oncology Group (ECOG) Genitourinary Committee
- 2006-present Member, Deutsche Krebshilfe (German Cancer Aid) Funding Program – International Scientific Review Panel
- 2007-2011 Member, NCI Clinical Oncology Study Section
- 2007 Fellow, American Association for the Advancement of Science
- 2007-2009 Chair, ASCO Disparities of Care Task Force
- 2008-present Co-Chair, ASCO Health Disparities Advisory Group
- 2009 Appointed Member, International Scientific Advisory Board for Deutsche Krebshilfe (German Cancer Aid)

(Former members BOLD*)

Clark W. Distelhorst, M.D.

- 2009 American Cancer Society Hero of Hope Research Medal of Honor for the State of Ohio

Kurt C. Stange, M.D., Ph.D.

- **1999-present Member, Institute of Medicine of the National Academy of Sciences**
- 2007 Named an American Cancer Society Clinical Research Professor

Sanford D. Markowitz, M.D., Ph.D.

- Co-chair, GI Correlative Sciences Committee for the CALGB
- 1998-2010 Investigator, Howard Hughes Medical Institute
- 2008 Hero of Hope Research Medal, American Cancer Society, Ohio Division

Nancy L. Oleinick, Ph.D.

- 1999-2002 NCI Cancer Manpower and Training Subcommittee (IRG-F) Chair
- NCI-D Parent Committee
- Member, RTB study section

Hillard M. Lazarus, M.D.

- 1986-2003 Chairman, Blood & Marrow Transplantation Committee, ECOG
- 1992- present Co-Chair, Lymphoma Committee, Center for International Blood and Marrow Transplantation Research
- 1993-2001 Co-Chairman, Acute Leukemia Subcommittee of the Research and Publications Committee, National Marrow Donor Program
- 2002-2006 Chair, Publications Committee, BMT CTN
- 2007- present Chair, Clinical Trials Advisory Committee, Resource for Clinical Investigations in Blood and Marrow Transplantation, CIBMTR
- 2007 American Cancer Society Research Award “The Standing Tall Tribute” (Lifetime Achievement)

Ernest C. Borden, M.D.

- 2000- 2007 Chairman, SWOG Sarcoma Committee

James P. Basilion, Ph.D.

- Treasurer, Society For Molecular Imaging
- Center Director, National Foundation for Cancer Research Center for Molecular imaging at Case

Jeffrey L. Duerk, Ph.D.

- 2008 President, International Society for Magnetic Resonance in Medicine

Gregory S. Cooper, M.D.

- 2005 John Peter Minton Hero of Hope Research Medal of Honor from the American Cancer Society, Ohio Division

Nathan A. Berger, M.D.

- NCI Program Project Site Visit Committees
  - 1991-present Member
  - 1994-present Chair

(Former members BOLD*)

- Member and Chair, Scientific Review Subcommittee D for Clinical Research Studies
  - 1997-2001 Member
  - 2001-2002 Chair
- 2000-2003 State of Ohio Biomedical Research & Technology Transfer Commission
- 2001 American Cancer Society, Cancer Care Hall of Fame Research Award
- 2002 Chair, NCI/ NCCAM Special Emphasis Review Panel
- 2004 Academy of Medicine of Cleveland/ Northern Ohio Medical Association, John H. Budd Distinguished Membership Award
- 2005-2008 Member, NCI Special Emphasis Review Panel, Minority Institutions-Cancer Center Partnerships
- 2006 Member, NCI Review Committee Loan Repayment Program
- 2008-2009 Member, NCI Review Committee Loan Repayment Program
- 2009 Member, ARRA NCI P30 Biomedical Research Core Centers Review Committee

Julia H. Rose, Ph.D.

- 1999-2004 Elected Council and Board Member, National Association of Geriatric Education Centers
- 2005 Appointed Member, Gerontological Society of America (GSA) Leadership Committee for Research, Education and Policy

GENERAL MEMBERSHIP

David J. Adelstein, M.D.

- Co-Chairman, Previously Untreated, Locally Advanced Head and Neck Cancer Task Force, NCI Head and Neck Cancer Steering Committee
- American Society of Clinical Oncology
  - 2000-2001 Chairman, Head and Neck Cancer Program Committee
- Southwest Oncology Group (SWOG)
  - 1989-2007 Head and Neck Committee
  - Subcommittee Chair: Chemoradiation

Anjali S. Advani, M.D.

- 2002-present Member, Southwest Oncology Group (SWOG) Leukemia Committee
- 2004 Co-Chair, American Society of Hematology Session, Acute Lymphocytic Leukemia Treatment
- 2010 American Society of Clinical Oncology Educational Session Speaker, Acute Lymphocytic Leukemia

James M. Anderson, M.D., Ph.D.

- Co-Chair, Working Group 1 for the development of the ISO Standard on Biological Evaluation of Medical Devices, ISO 10993, International Standards Organization
- 1990-present Chairman, ISO 10993-1 Committee, Biological Response Evaluation of Medical Devices under a Risk Management Program
- 2003-2004 President, Controlled Release Society
- Founding Member, Society for Biomaterials and the Controlled Release Society
- 2005 Elsevier Biomaterials Gold Medal Award
- 2006 Chugai Mentoring Award, American Society for Investigative Pathology
- 2008 Elected Member, Association of American Physicians

- 2006 Honoris Causa (Honorary Doctorate of Philosophy Degree),University of Geneva, Switzerland

Gene H. Barnett, M.D.

- Former State Representative, Joint Council of State Neurosurgical Societies
  - Served as Chairman of its Northwest Quadrant
  - Executive Committee of the Section on Tumors (Formerly)
  - Board of Directors of the Joint Section of Stereotactic and Functional Neurosurgery (Formerly)
  - Board of Directors of the American Association of Neurological Surgeons (Formerly)

Jill S. Barnholtz-Sloan, Ph.D.

- Vice President (U.S.) for the Brain Tumor Epidemiology Consortium
- 2009-present Invited Member, The Cancer Genome Atlas (TCGA) Glioblastoma Working Group
- 2009 Chair, Low Grade Glioma Comparison Working Group, TCGA Annual Meeting
- 2010-present Invited Member, Cancer Genome Atlas Low Grade Glioma Working Group

Brian J. Bowell, M.D.

- Chairman, Board of Trustees of the Ohio Hematopoietic Stem Cell Transplant Consortium, for more than ten years

Elaine A. Borawski, Ph.D.

- National Board Member, American Academy of Health Behavior

Arnold I. Caplan, Ph.D.

- 2007 Genezyme Life-Time Achievement Award, International Cartilage Repair Society

Mark R. Chance, Ph.D.

- 2001-2003 Chair, Biomedical Technology Centers Directors' Organization, National Center for Research Resources

Kenneth R. Cooke, M.D.

- 2001 Translational Research Award, Leukemia and Lymphoma Society
- 2005 Scholar in Clinical Research Award, Leukemia and Lymphoma Society
- 2005 Clinical Scientist Award in Translational Research, Burroughs Wellcome Fund
- 2008 Board of Directors, American Society of Blood and Marrow Transplantation; Director of Laboratory Science
- 2008-2011 Appointed Member, ASH Scientific Committee on Transplantation Biology
- 2008 Elected member, American Society of Clinical Investigation

Kevin D. Cooper, M.D.

- 2009 Marion B. Sulzberger, MD, Memorial Award and Lectureship, American Academy of Dermatology

Pamela B. Davis, M.D., Ph.D.

- 2001-2006 Board of Scientific Counselors, National Heart Blood and Lung Institute (NHLBI), NIH

Gary T. Deimling, Ph.D.

- 2002 Outstanding Researcher in the State of Ohio, Ohio Research Council on Aging
- 2004 Outstanding Contribution to the Field of Cancer Survivorship Research, Office of Cancer Survivorship, NIH
- 2006 Trish Greene Quality of Life Award, American Cancer Society

Paul E. DiCorleto, Ph.D.

- 1999-present Advisory Panel on Research, Association of American Medical Colleges
- 2001-2002 President, North American Vascular Biology Organization

Robert Dreicer, M.D.

- Co-Chair of NCI Bladder Cancer Task Force
- Chair, Bladder Subcommittee, Eastern Cooperative Oncology Group (ECOG)
- Fellow, American College of Physicians
- 2005 Chair, Department of Defense Prostate Cancer Research Program Integration Panel
- 2008 Chair, ASCO GU Symposium Steering Committee

Charis Eng, MD, Ph.D.

- 2000-2008 Member, National Comprehensive Cancer Network Guidelines Panel for Breast Cancer Genetics
- 2005-2008 Board of Directors, American Society of Human Genetics
- 2006 John Peter Minton, MD, PhD Hero of Hope Medal of Honor, American Cancer Society
- 2007-2011 Board of Scientific Directors of National Human Genome Research Institute, NIH
- 2008-2009 Panel Member, American Thyroid Association Guidelines for Medullary Thyroid Cancer
- 2009-present Clinical Research Professorship, American Cancer Society
- 2009-present Secretary's Advisory Committee for Genetics, Health and Society, Department of Health and Human Services (DHHS)

Robert L. Fairchild, Ph.D.

- American Heart Association, Ohio Valley-S. East Res.
  - 1998-2000 Consort Co-Chair, Rev. Committee #4
  - 2001-2002 Chair
- 2001-2004 Member, SAT Study Section, National Institute of Allergy and Infectious Diseases (NIAID)
- 2004-2005 Member, TTT Study Section, NIAID
- 2008-2010 Member, TTT Study Section, NIAID
- 2010-2012 Chair, NIAID (NIH) Member TTT Study Section
- 2004-present Immune Tolerance Network, Network Steering Committee
- 2005-2009 Councilor, American Society for Transplantation Board of Directors
- *Journal of Immunology*

(Former members BOLD*)

  - 1999-2001 Associate Editor
  - 2001-2005 Section Editor
- *Transplantation*
  - 2003-present Associate Editor
- *American Journal of Transplantation*
  - 2003-2005 Associate (Section) Editor
  - 2005-present Deputy Editor

Gary W. Falk, M.D.

- 2000 Chairman, Special Emphasis Panel ZDK1 GBR-7 (J2S), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- 2003 Chairman, Special Emphasis Panel ZDK1 GRB-D 01(J2S)
- 1998-2009 Governing Board, American Society for Gastrointestinal Endoscopy
- 2001-2008 Executive Committee, American Society for Gastrointestinal Endoscopy

Timothy D. Gilligan, M.D.

- 2005-present Vice-Chair, Genitourinary Tumor Marker Panel, American Society of Clinic Oncology
- 2006 Chair, Prostate Cancer Clinical Health Science and Epidemiology grant review panel, Congressionally Directed Medical Research Program, U.S. Department of Defense
- 2008-present Member, NCI PDQ Adult Treatment Editorial Board

George I. Gorodeski, M.D.

- 2002-present Chair, Special Emphasis Panel, Division of Biologic Basis of Disease, Center for Scientific Review, NIH

Edward M. Greenfield, Ph.D.

- 2005-2006 Chairman, Infection and Inflammation Topic Committee, Orthopaedic Research Society (ORS)

John R. Haaga, M.D.

- 1994-present American Roentgen Ray Society (ARRS) Executive Council, Scientific Exhibits Committee Chairman

Clifford V. Harding, M.D., Ph.D.

- 1999-2001 Chair, Allergy, Immunology & Transplantation Research Committee (AITRC) Study Section, NIH

Eva F. Kahana, Ph.D.

- Outstanding Journal Special Issue Award for significant contribution to scholarship in applied communication theory, research, and practice, Applied Communication Division, National Communication Association
- 2000-2001 Chair, American Sociological Association, Section on Aging and the Life Course
- 2000-2001 Chair, Section on Sociology of Aging and the Life Course, American Sociological Association
- 2004 Outstanding Gerontological Educator in the State of Ohio, OAGE
- 2005 Holocaust Survivor of Achievement, featured in 60th Anniversary of the Holocaust Commemorative Issue for the State of Ohio

- 2006 Fellow, Association for Gerontology in Higher Education
- 2007 Scholar Award, American Psychosomatic Society
- 2009 Chair-Elect, Fellowship Committee, Gerontological Society of America (GSA)

Jonathan Karn, Ph.D.

- 2005-2007 Chairman, AIDS Molecular and Cellular Biology Study Section (AMCB), Center for Scientific Review, NIH
- 2008-present Director, Case Center for AIDS Research
- 2009 Avant Garde Award for Innovative HIV/AIDS Research, National Institute on Drug Abuse

Tamila L. Kindwall-Keller, D.O.

- 2006 Vice President, Oncology Subcommittee for American College of Osteopathic Internists (ACOI)

Timothy Kinsella, MD*

- 1997-2001 Member, Board of Scientific Counselors of the NCI, Subcommittee A
- 2008-present Board of Directors, National Cancer Advisory Board

Keith McCrae, M.D.

- 2003-present Chair, Scientific Subcommittee on kinin-kallikrein, ISTH
- 2003-present ASH Scientific Subcommittee on Clinical and Laboratory Medicine

Robert H. Miller, Ph.D.

- Founding member and the research coordinator, Myelin Repair Foundation
- 2005 Director, Cleveland Brain Tumor Consortium

Joseph H. Nadeau, Ph.D.

- 2009 Fellow, American Association for the Advancement of Science in the Section of Biological Sciences

Brian P. Rubin, M.D., Ph.D.

- 2002-2008 Secretary, International Society of Bone and Soft Tissue Pathology
- 2005-2008 Board Member, Connective Tissue Oncology Society
- 2009-present Senior Associate Editor, *Laboratory Investigation*

Roy L. Silverstein, M.D.

- Editor in Chief, *The Hematologist*
- Executive Committee for American Society of Hematology (ASH)
    - 2005-2008 Chair, ASH Government Affairs Committee
- 2009 Russell Ross Memorial Lecture in Vascular Biology, American Heart Association Annual Meeting

Mark A. Smith, Ph.D.

- 1998-present International Society for Neurochemistry
    - 1998-2005 Travel Grant Committee
    - 199-2001 Program Committee
    - 2002-2003 Program Chair

(Former members BOLD*)

- 2000 Jordi Folch-Pi Award, American Society for Neurochemistry
- 2002 Hermann-Esterbauer Award, HNE Society
- 2006-present Editor in Chief, *Journal of Alzheimer's Disease*
- 2007-present Deputy Chief Editor Reviews, *Journal of Neurochemistry*
- 2008 Denham Harman Research Award, American Aging Association
- 2008 Fellow, Royal College of Pathologists
- 2008-2010 Member, NIH, Neural Oxidative Metabolism and Death (NOMD)
- 2008-present Executive Director, American Aging Association
- 2008-present Scientific Advisory Board, Medivation Inc., San Francisco
- 2009-present Science Translational Medicine, Science Advisory Board

Ronald M. Sobecks, M.D.

- Diplomat, American Board of Hematology
- Diplomat, American Board of Oncology
- Diplomat, American Board of Internal Medicine

Kingman P. Strohl, M.D.

- 2004, 2006 NIH Committee Chair, Special Emphasis Panel

John W. Sweetenham, M.D.

- Chairman, Clinical Trials Advisory Panel, Leukemia & Lymphoma Research, Great Britain
- Member, Data Safety Monitoring Board, National Cancer Institute of Canada Clinical Trials Group

Aloen L. Townsend, Ph.D.

- 2006-2008 Secretary/Treasurer, Behavioral and Social Sciences Section, Gerontological Society of America

Pierre L. Triozzi, M.D.

- 2005 Chairperson, NCI Special Emphasis Panel, Experimental Therapeutics 1

Vivian E. von Gruenigen, M.D.*

- 2005-present Board Member, Gynecologic Cancer Foundation
- 2008-present Director, Cancer Survivor Courses, Gynecologic Cancer Foundation
- 2009 Appointed to the Gynecologic Oncology Group (GOG) Uterine Corpus Committee

Steven E. Waggoner, M.D.

- Board of Directors of Gynecologic Oncology Group (GOG)
  - Chair, Ancillary Data Committee
- Member, GOG Human Subjects Review Committee
- Member, GOG Phase 1 Chemotherapy Working Group