

Report to the Community

“Without vigorous, farsighted and continuing encouragement of fundamental scientific research, we are in the position of eating our seed corn. We may fend off starvation for one more winter, but we have removed the last hope of surviving the following winter.”

—Carl Sagan



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Ohio Cancer Research Associates is an independent statewide, nonprofit organization dedicated to the cure and prevention of the many forms of cancer and the reduction of its debilitating effects through aggressive basic seed money research, cancer information and awareness. Ohio Cancer Research Associates is not affiliated with any other organization.

Over \$16 million has been spent on cancer awareness and seed money research projects. Of that amount, *over \$6.2 million in seed money* provided to researchers by Ohio Cancer Research Associates *has generated more than \$104.1 million in new money* from other sources to continue basic cancer research on projects initially funded.

Individual researchers have been funded at The Cleveland Clinic, Case Western Reserve University, MetroHealth Medical Center in Cleveland, The Ohio State University, Nationwide Children's Hospital in Columbus, Cincinnati Children's Hospital Medical Center, University of Cincinnati, University of Dayton, Ohio University, Wright State University, Hipple Cancer Research Center in Dayton, University of Toledo and Bowling Green State University.

Ohio Cancer Research Associates is recognized as a 501 (c) (3) organization. Donations are accordingly tax deductible.

(EIN 31-1038309)



Programs of Ohio Cancer Research Associates.

Seed Money Cancer Research

With the support of people all over Ohio, progressive and innovative ideas are given a chance to help in the fight. Ohio Cancer Research Associates' seed money projects often give a researcher the preliminary data needed to secure major funding from other sources.

Cancer Information

Cancer awareness and prevention information is disseminated to tens of thousands of persons throughout Ohio each year.

Ohio Cancer Research Associates Special Events are presented to raise funds for seed money cancer research and to increase awareness of the importance of early detection in saving lives. Radio and newspaper support reaches in excess of 1 million each year.

Public service announcements are being carried on cable and broadcast television reaching more than 5 million people annually.

Speakers are available to groups throughout the state such as Rotary Clubs, fraternal organizations, TV and radio talk shows, etc.

We provide information to callers regarding their experience with cancer. Staff informs callers of cancer information services such as (1-800-4CANCER) which answers questions concerning the disease.

Cancer Awareness

Staff and volunteers are committed to the public gaining knowledge of the many forms of cancer, the advancement of Ohio Cancer Research Associates, and its seed money cancer research projects.

Fitness Awareness

A dance program for children in grades 1-12 and adults stresses dance as an exercise for a prudent healthy lifestyle.

Symposiums

A limited amount of funds are available to provide scientific meetings. Recent symposiums were held at the Case Comprehensive Cancer Center and the Cincinnati Cancer Consortium.

Special Events

Ohio Cancer Research Associates Special Events are presented to raise funds for seed money cancer research and to increase awareness of the importance of early detection in saving lives.

A sampling of how the “seed money” concept works for Ohio researchers throughout the state.

I am happy to inform you that one of my papers is in print now in Molecular Microbiology. This paper has work that is primarily due to the opportunity provided to me by the OCRA grant. This work explains how DNA damage is recognized by the MutS protein. The human homologs of this protein, (MSH2 and in some cases MSH6) are mutated in colon cancers hence this work gives functional relevance to the mutations as we understand the protein more. Hopefully in future experiments I can utilize this in translational science.

Samir Acharya, Ph.D.
The Ohio State University

“As far as new funding for my program is concerned, I am in the 3rd year of NIH and American Cancer Society fundings which were made possible by the Ohio Cancer Research Associates funds. Total NIH and ACS funding comes to about \$940,000.”

Sohaib Kahn, Ph.D.
University of Cincinnati

“The RO1 grant from the National Institutes of Health and National Institute of Environmental Health Sciences is for a period of 4 years, beginning April 1, 1995 and will provide me with a total of \$395,859 in direct cost. This would not have been possible without the grant support I received from Ohio Cancer Research Associates, which enabled me to obtain sufficient preliminary data which served as the cornerstone for this NIH grant.”

Zalfa Abdel-Malek, Ph.D.
University of Cincinnati

“My group recently received national recognition for our publication in *Science* of the discovery of a new gene, the RII gene that is most important in causing colon cancer both in families with inherited colon cancer and also many individuals in the population at large.

“With your help my laboratory’s work on colon cancer genetics has been going great guns. Our most recent NIH grant...has been recommended for funding for 5 years at \$250,000 per year. Without the support of Ohio Cancer Research Associates this work would be dead in the water while we waited for a year or more for money from NIH to come through.”

Sandy Markowitz, M.D., Ph.D.
Case Western Reserve University

“I am writing to let you know that after being the recipient of an award from Ohio Cancer Research Associates for two years, I have been granted funds from the Case Cancer Center (\$30,000 for one year) and from the American Cancer Society (\$720,000 for four years). I am extremely grateful to your organization for giving my idea a chance during these crucial transition years when I was developing my research program, and I am proud that your choice to support me now results in more funding brought in Ohio.

Marie-Odile Parat, Pharm.D., Ph.D.
The Cleveland Clinic

“The seed money grant from Ohio Cancer Research Associates helped my lab receive major funding for four years (\$308,000) on a different project in lung molecular biology from the American Heart Association at the National level.”

Vrushank Davé Ph.D.
Case Western Reserve University

“I would like to let you know that I just received a Research Scholar Grant from The American Cancer Society for three years totalling \$840,000. The research funded by Ohio Cancer Research Associates contributed to my getting the ACS grant. Much of the preliminary data included in the ACS application resulted from the experiments proposed in my Ohio Cancer Research Associates grant proposal. I submitted a manuscript on Gfi-1/Miz-1 interaction to Proc Natl Acad Sci USA (PNAS) last year, which was supported in part by my Ohio Cancer Research Associates grant. This manuscript has just been accepted.

Fan Dong, M.D., Ph.D.
University of Toledo



SEED MONEY RESEARCH PROGRAM

Ohio Cancer Research Associates researchers are exploring innovative areas of cancer research in the genetic causes and preventions of cancer, skin cancer, stomach cancer, prostate cancer, colon cancer, liver cancer, kidney cancer, breast cancer, leukemia, vaccine studies, DNA studies, and new therapeutic strategies.

Projects are selected by a Scientific Review Committee with the help of out-of-state reviewers from across the country and the world.

The Scientific Review Committee is made up of doctors and scientists around the state. Committee Chairman Robert Brueggemeier, Ph.D., Dean of Pharmacology at The Ohio State University, is joined by these distinguished researchers and cancer experts in 2009:

Zalfa Abdel-Malek, Ph.D., University of Cincinnati
Ivana de la Serna, Ph.D., University of Toledo
Clark W. Distelhorst, M.D., Case Western Reserve University
Stanton L. Gerson, M.D., Case Western Reserve University
Pravin T. P. Kaumaya, Ph.D., The Ohio State University
Ruth Keri, Ph.D., Case Western Reserve University
Sohaib Khan, Ph.D., University of Cincinnati
Gustavo Leone, Ph.D., The Ohio State University
Monica Montano, Ph.D., Case Western Reserve University
Deborah Parris, Ph.D., The Ohio State University
Derek Raghavan, M.D., Ph.D., The Cleveland Clinic
Kenneth Rosenthal, Ph.D., NEOUCOM
Michael A. Vogelbaum, M.D., Ph.D., The Cleveland Clinic
Dawn Wooley, Ph.D., Wright State University
David Yohn, Ph.D., M.P.H., The Ohio State University (retired)

Following is a recap of past projects and a listing of currently funded projects with a brief description of each.



These researchers have had “seed money” projects funded by Ohio Cancer Research Associates.
Their area of cancer research is denoted in red.

These projects have generated over \$104.1 million in new research funds for Ohio.

BOWLING GREEN STATE UNIVERSITY

Doris J. Beck, Ph.D. **Molecular Genetics**
Vladimir Popik, Ph.D. **Breast Cancer**
Lakshmidivi Pulakat, Ph.D. **Breast Cancer**
William Scovell, Ph.D. **Molecular Genetics**

CASE WESTERN RESERVE UNIVERSITY

Rajesh Agarwal, Ph.D. **Prostate Cancer**
Nihal Ahmad, Ph.D. **Skin and Prostate Cancer**
Barbara Bedogni, Ph.D. **Skin Cancer**
Matthias Buck, Ph.D. **Molecular Genetics**
David Danielpour, Ph.D. **Prostate Cancer**
Clark W. Distelhorst, M.D. **Hormone Therapy**
Philip R. Garner, Ph.D. **Gene Mutation**
Antonio Gualberto, M.D. **Gene Mutation**
Zhongwu Guo, Ph.D. **Molecular Genetics**
Zhilin Hu, Ph.D. **Lung Cancer**
Hung-Ying Kao, Ph.D. **Leukemia**
Santosh Katiyar, Ph.D. **Skin Cancer**
Hua Lou, Ph.D. **Thyroid Cancer**
Patrick Ma, M.D. **Lung Cancer**
Sanford Markowitz, M.D., Ph.D. **Colon Cancer**
Monica Montano, Ph.D. **Breast Cancer**
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Scott Michael Welford, Ph.D. **Radiation Oncology**
Yanwu Yang, Ph.D. **Tumor Research**
Lan Zhou, M.D., Ph.D. **Leukemia**

NATIONWIDE CHILDREN’S HOSPITAL

Joan Durbin, M.D., Ph.D. **Rhabdomyosarcoma**
Natarajan Muthusamy, D.V.M., Ph.D. **Lymphoma**
Sue O’Dorisio, M.D., Ph.D. **Gastrointestinal**

CINCINNATI CHILDREN’S HOSPITAL

Robert Arceci, M.D., Ph.D. **Leukemia**
Takiko Daikoku, Ph.D. **Endometrial Cancer**
Vrushank Dave, Ph.D. **Lung Cancer**
Brian Andrew Gebelein, Ph.D. **Leukemia**
Raphael Hirsch, M.D. **Lymphoma**
Anil G. Jegga, D.V.M. **Molecular Genetics**
Tanya Kalin, Ph.D. **Gene Mutation**
Xinhua Lin, Ph.D. **Kidney Cancer**
Ruhikanta Meetei, Ph.D. **Genetic Research**
James Mulloy, Ph.D. **Leukemia**
Susan E. Waltz, Ph.D. **Skin Cancer**
Susanne Wells, Ph.D. **Cervical Cancer**

HIPPLE CANCER RESEARCH CENTER

Sten Jacobsen, M.D., Ph.D. **Leukemia**

METROHEALTH MEDICAL CENTER

Bruce Averbook, M.D., F.A.S.C. **Brain Cancer**
Aruna Basu, Ph.D. **Colon Cancer**
Subrata Haldar, Ph.D. **Skin Cancer**

OHIO UNIVERSITY

Elisar Barbar, Ph.D. **Tumor Research**
Monica Burdick, Ph.D. **Breast Cancer**

THE CLEVELAND CLINIC FOUNDATION

Munna Agarwal, Ph.D. **Gene Mutation**
Marina Antoch, Ph.D. **Cancer Therapy**
Sipra Banerjee, Ph.D. **Breast Cancer**
Christine Campbell, Ph.D. **Breast Cancer**
Tao Lu, Ph.D. **Colon Cancer**
Marie-Odile Parat, PHARM.D., Ph.D. **Molecular Genetics**
Nywana Sizemore, Ph.D. **Breast Cancer**
Michael Vogelbaum, M.D., Ph.D. **Brain Cancer**

THE OHIO STATE UNIVERSITY

Samir Acharya, Ph.D. **Colon Cancer**
Rami Aqeilan, Ph.D. **Tumor Cell Research**
Xue-Feng Bai, M.D., Ph.D. **Gene Mutation**
Robert Baiocchi, M.D. Ph.D. **Lymphoma**
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James W. DeWille, MPH, MS, Ph.D. **Breast Cancer**
Harold A. Fisk, Ph.D. **Molecular Genetics**
Darrell R. Galloway, Ph.D. **Skin Cancer**
Denis C. Guttridge, Ph.D. **Molecular Studies**
Tsonwin Hai, Ph.D. **Molecular Genetics**
Paul Kenneth Herman, Ph.D. **Molecular Genetics**
David H. Ives, Ph.D. **Molecular Genetics**
Sissy Jhiang, Ph.D. **Brain Cancer**
Lee F. Johnson, Ph.D. **Thyroid Cancer**
Laura A. Kresty, Ph.D. **Esophageal Cancer**
Michael D. Lairmore, D.V.M., Ph.D. **Lymphoma**
Mary MacVicar, R.N., Ph.D. **Breast Cancer**
Louis Malspeis, Ph.D. **Chemotherapy Delivery**
Louis Mansky, Ph.D. **Lymphoma**
George Milo, Ph.D. **Gene Mutation**
Stefan Niewiesk, D.V.M., Ph.D. **Leukemia**
Gregory Otterson, M.D. **Lung Cancer**

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Paivi Peltomaki, M.D., Ph.D. **Colon Cancer**
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Michael E. Weinstein, Ph.D. **Molecular Genetics**
Karl Werbovetz, Ph.D. **Chemotherapy**
Marshall Williams, Ph.D. **Colon Cancer**
Jian-Qui Wu, Ph.D. **Molecular Genetics**
Sung Yoon, Ph.D. **Molecular Genetics**
Pan Zheng, M.D. **Prostate Cancer**
Bruce Zwilling, Ph.D. **Gene Mutation**

Total research funded:
over \$6.2 million

Total research generated to date:
over \$104.1 million

UNIVERSITY OF CINCINNATI

Zalfa Abdel-Malek, Ph.D. **Skin Cancer**
David Askew, Ph.D. **Leukemia**
Michelle Craig Barton, Ph.D. **Breast Cancer**
Arthur Buckley, Ph.D. **Genetic Research**
Rodney DeKoter, Ph.D. **Leukemia**
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Sohaib A. Khan, Ph.D. **Breast Cancer**
Erik Knudsen, Ph.D. **Gene Mutation**
Andrew Lowy, M.D. **Stomach Cancer**
Shan Lu, Ph.D. **Prostate Cancer**
Shiuh Wen Luoh, M.D. **Prostate Cancer**
Mario Medvedovic, Ph.D. **Breast Cancer**
R. C. Samaratunga, Ph.D. **Radiation**
Yolanda Sanchez, Ph.D. **Gene Mutation**
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Ming You, M.D., Ph.D. **Lung Cancer**

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John J. Turchi, Ph.D. **Gene Mutation**
Yongie Xu, M.D., Ph.D. **Genetic Research**

Research Projects funded by Ohio Cancer Research Associates

July 2010 - June 2011

BARBARA BEDOGNI, PH.D.

(SKIN CANCER)

CASE WESTERN RESERVE UNIVERSITY

Dissecting the Role of the Notch Signaling Pathway in Melanoma Metastasis.

Melanoma is the deadliest form of skin cancer, accounting for only 4% of all skin cancer cases but for 80% of all skin cancer related deaths. The number of melanoma cases worldwide is increasing faster than that of any other type of cancer with an estimated doubling of melanoma incidence every 10-20 years.

While early detection of primary lesions is associated with a favorable prognosis, the 5-year survival rate of patients with metastasis is less than 10%. This is due to the aggressiveness of the tumor but also to the lack of effective therapies. This underscores the urgency of finding new molecules/pathways involved in the disease that can be effectively targeted for therapy. With this goal in mind, we have started to dissect the Notch signaling pathway. We previously showed that Notch signaling is elevated in melanoma and required for melanoma growth and survival. We now have new evidence strongly supporting a role of Notch1 in melanoma metastasis. Human melanoma cells lacking Notch1 expression and implanted orthotopically in mice do not metastasize to lungs whereas control cells expressing high levels of Notch1 form metastasis in 100% of animals. This phenomenon is in part due to Notch-dependent regulation of migration, through modulation of EMT (epithelial to mesenchymal transition) and invasion. We propose that Notch signaling is an essential mediator of melanoma metastasis via regulation of migration and invasion.

TAO LU, PH.D.

(COLON CANCER)

THE CLEVELAND CLINIC FOUNDATION

Study the Role of FBXL 11 Protein in Colitis Associated Cancer (CAC).

Colon cancer accounts for 10-13% of cancer at all sites. Colitis-associated cancer (CAC) ranks as one of the top 3 high-risk conditions, and is a common complication in patients suffering from chronic inflammatory bowel disease (IBD). Elevated NFkB activity has been widely observed in both IBD and CAC, and is believed to be a key link between IBD and CAC. Therefore, NFkB becomes an attractive therapeutic target for IBD-associated CAC. My research interest focuses on novel regulators of NFkB, and assessing their effect in cancer development with the ultimate goal of developing novel strategies for cancer diagnosis and therapy. Recently, using a novel validation based insertional mutagenesis (VBIM) technique established in our laboratory, we made an exciting observation and discovered the F-box and leucine-rich repeat protein 11 (FBXL11), a histone H3K36 demethylase, as a novel negative regulator of NFkB. This stimulating discovery has unveiled a previously unknown aspect of NFkB regulation, through post-translational methylation-demethylation modifications. This could lead to new strategies for prevention and treatment of cancer through regulation of NFkB. Based on this exciting observation, and utilizing the intestine-specific transgenic-FBXL11 mouse model established in our laboratory, the overall objectives of the current proposal are to further evaluate: 1) the role of FBXL11 in dextran sulfate sodium (DSS)-induced colitis; 2) the role of FBXL11 in DSS and azoxymethane (AOM) regimen-induced CAC cancer, and 3) delineate the molecular mechanisms. The results from these experiments will define the anti-inflammatory and anti-tumorigenic effect of FBXL11 in an IBD and CAC mouse model and further provide insights into the molecular mechanism underlying these effects. This may generate a solid basis for establishing FBXL11 as a diagnostic and therapeutic target for IBD and CAC.

RUHIKANTA MEETEI, PHD

(GENETIC RESEARCH)

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

Functional and Molecular Characterization of Two New Members of the Bloom Syndrome Complex

Bloom Syndrome (BS) is an autosomal recessive cancer-prone disorder caused by mutations in the BLM gene. BLM encodes a DNA helicase of the RECQ family, and associates with Topo III α , BLAP75/RMI1 (BLAP for BLM-associated polypeptide/RecQ-mediated genome instability) and BLAP18/RMI2. This complex can resolve the double Holliday junction (dHJ), a DNA intermediate generated during homologous recombination, to yield noncrossover recombinants exclusively. This attribute of the Bloom syndrome complex likely serves to prevent chromosomal aberrations and rearrangements. Here we propose to functionally characterize two newly isolated members of the BS complex termed, BLAP15 and BLAP120. We have obtained preliminary data to show that BLAP15 associates with the BS complex in both untreated and hydroxyurea (HU) treated complex while BLAP120 is enriched in the HU treated complex. Interestingly BLAP120 is known to bind to damaged DNA, indicating that BLAP120 might target BS complex at the DNA damaged site. Functional and molecular characterization of these two proteins will help us to better understand the Bloom syndrome (BS) -DNA repair pathway in the pathogenesis of cancer.

DAVID WALD, M.D, PHD

(LEUKEMIA)

CASE WESTERN RESERVE UNIVERSITY

Characterization of a Novel Pathway to Selectively Target AML Cells

Acute myeloid leukemia (AML) is one of the most common forms of leukemia in adults and despite advances in treatment the 5 year survival is less than 20-50% in adults and significantly lowers in the elderly. In fact, elderly patients frequently are not able to tolerate the current therapeutics leaving them with no satisfactory therapeutic options due to the high toxicity of existing agents. Agents that could more selectively target leukemic cells as opposed to normal cells offer the promise of reducing the toxicities inherent in the existing therapeutics. We have identified a nucleoside analogue as an AML therapeutic candidate that has a remarkable ability to preferentially enter AML cells. The aim of this proposal is to characterize the mechanisms through which this compound can preferentially enter AML cells using both biochemical and genetic approaches. The information gained from these studies would be valuable not only to further our understanding of a promising AML therapeutic candidate and nucleoside transport but more importantly it will provide valuable knowledge on a novel mechanism that could be exploited to preferentially target AML cells. Novel AML therapeutics and therapeutic strategies are greatly needed that lead to more tolerable toxicities especially for elderly patients that are often left without any satisfactory therapeutic options with the current agents.

SCOTT MICHAEL WELFORD, PH.D

(RADIATION ONCOLOGY)

CASE WESTERN RESERVE UNIVERSITY

The Impact of Tissue Hypoxia on Tumor Initiation

Tumor initiation is tightly controlled by well-established tumor suppressor pathways. The vast majority of oncogenic events never progress; only in extremely rare cases do aberrant cells manage to circumvent the action of cell cycle regulatory proteins and result in cancer development. In fact in most cases oncogene activation leads to cellular senescence, a tumor suppressor response characterized by an irreversible state of cell cycle arrest. Interestingly, this phenomenon has recently been found to depend on oxygen, such that high levels of oxygen promote senescence while low levels inhibit it. This is an intriguing finding because the oxygen content of the body varies over a large range, from approximately 110mm Hg in the lungs, to less than 8mm Hg in the bone marrow. Oxygen levels that are permissive for oncogene activation are well within the normal range of oxygen in various tissues, suggesting that oxygen may regulate the tolerance for oncogenic events in vivo. The goal of this project is to understand the contribution of tissue hypoxia to tumor initiation. Specifically, this project will assess the role of oxygen in regulating tumor initiation through inhibition of senescence due to oncogenic Akt signaling, particularly as it relates to the development of renal carcinoma. Renal cancer is frequently associated with inactivation of VHL, which is another senescence-inducing event. Thus the effects of oxygen in the context of combined Akt activation and loss of VHL will also be analyzed. Together, these studies will help uncover some of the critical factors involved in regulating tumor suppression that allow what should be innocuous mutations to develop into cancer.

January 2010 - June 2011

TAKIKO DAIKOKU, PH.D. (ENDOMETRIAL CANCER)
CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
Pten-Akt-Cox2 Signaling Axis in Endometrial Cancer

Endometrial cancer is the most common gynecological malignancy, with approximately 7,000 deaths each year in the United States. Underlying causes of endometrial cancer are not fully understood and treatment options for patients with advanced stage are limited.

Prostaglandins (PGs) are produced by cyclooxygenase-2 (COX-2) which is overexpressed in a number of solid tumors and this isoform is considered to play an important role in tumorigenesis. In fact, non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit the cyclooxygenase system, are effective in both cancer prevention and as an adjuvant therapy for the treatment of established tumors. Although endometrial cancers also express high levels of COX-2, its role in endometrial cancer remains unclear.

We have recently generated two highly efficient EMC mouse models that develop endometrial cancers with 100% penetrance within a short period with high expression of COX-2. These preliminary results are exciting and the basis of the present proposal.

The specific aim is to determine roles of COX-2 in endometrial cancer. We will use molecular, genetic and pharmacological approaches utilizing our novel EMC mouse models. The results are likely to provide information that would have clinical importance in preventing and treating endometrial cancer.

JIAN Z. WANG, PH.D. (PROSTATE CANCER)
THE OHIO STATE UNIVERSITY
Towards Optimal Radiation Therapy: Radiobiological Modeling of Prostate Cancer

Funded with the support of Sanford Goldston Memorial Research Fund

The therapeutic rationale in radiation therapy relies on the general principle that normal tissue cells have a better repair capability of radiation damage than tumor cells. A large component of sub-lethal radiation damage of a small dose (2 Gy) to normal tissues may be repaired within one day before the next dose. The current radiation therapy of 2-Gy daily fractionation is based on this philosophy. In prostate cancer, recent clinical studies have shown that prostate cancer cells may also possess a good repair capability, similar to normal tissue. Given enough time, prostate cancer cells may also repair a large portion of radiation damage. Therefore, the current treatment schedules delivering small 2-Gy fractions may not be optimal to treat this disease.

However, these initial findings have been under great debate. Many investigators published their comments and data analyses to challenge such a biological argument. More specifically, several important and clinically relevant effects have been ignored or not fully modeled in current studies of prostate cancer: (1) prostate brachytherapy has the advantage of conformal dose delivery to tumor; but the dose distribution inside the prostate is very inhomogeneous, and the dose coverage varies greatly from patient to patient. This dose heterogeneity has been ignored in current studies and instead, a point dose (i.e., uniform dose distribution) has been assumed in the published modeling studies; (2) the interpatient variation of radiation sensitivity and its impact on the model parameters remains unclear; (3) the debate about the onset time of tumor repopulation is ongoing; more comprehensive study with updated clinical data is necessary to reconfirm the earlier findings and estimate the RBE values. All of these effects may be significant enough to change the current understanding of prostate cancer response to radiation therapy and affect the selection of optimal radiation therapy regimens for prostate cancer patients.

In our pilot studies, we derived a new set of model parameters, which provide a consistent interpretation of most clinical data currently available for prostate cancer. These pilot studies become the foundation of our model describing prostate cancer radio-responsiveness. In the proposed study, we plan to compile and analyze the clinical and dosimetric data of over 300 prostate cancer patients, who were treated with brachytherapy in 2001-2003. We will also compile the available clinical data related to dose response, tumor repopulation, edema and RBE published in the literature. A comprehensive data analysis will be conducted to address these unsolved issues listed above. The ultimate goal is to provide a comprehensive and consistent modeling of prostate cancer, which can interpret the currently available clinical data, provide a reliable guide for future clinical trials, and optimize radiation therapy for prostate cancer patients.

YONGJIE XU, M.D., PH.D.

(GENETIC RESEARCH)

WIRGHT STATE UNIVERSITY

Phosphorylation Network of the DNA Replication Checkpoint in Fission Yeast

Funded with the support of Anderson Concrete

The human body is composed of hundreds of billions of cells and yet all cells derive from a single cell by rounds and rounds of cell division. Cell division is a highly coordinated process involving multiple steps. The critical step, however, is the DNA replication, a process to make an accurate copy of DNA, the genetic material, so that two daughter cells can have exactly the same copy of the DNA from the mother cell.

Since the human body is the product of millions of cell divisions, a tiny error in DNA replication (or mutation) during the early stage of human development can lead to a disaster in the end. Therefore, DNA has to replicate accurately once, and only once, per cell division, no more and no less. To ensure the accuracy of DNA replication, a surveillance mechanism called “replication checkpoint” has been evolved that can deal with various factors that block DNA replication. It is clear that defects in the replication checkpoint can lead to cancer. For example, the protein kinase CHK2 in the replication checkpoint is a well-known tumor suppressor.

Our long-term goal is to understand the molecular mechanism of the replication checkpoint and the short-term goal of this grant is to dissect the protein phosphorylation networks generated by two critical protein kinases in the replication checkpoint. Results from this study can have great implications to our understanding of how mutations generate during the development of cancer and how to improve cancer chemotherapies that interfere with DNA replication in tumor cells.

July 2008 - June 2010

MATTHIAS BUCK, PH.D.

(MOLECULAR GENETICS)

CASE WESTERN RESERVE UNIVERSITY

cMet/Eph Phosphorylation of Small GTPases and their Role in Cancer

Small GTPases are signaling proteins that exist in virtually all cells of the body. Their purpose is to receive incoming signals and then cause cells to develop, move, change shape, or rearrange their internal structures. Scientists' current understanding of how GTPases work is that they are active when they are bound to a small nucleotide molecule (GTP) having three phosphates and inactive when the GTP degrades to a molecule (GDP) having only two phosphates. This binding and the degradation of GTP are regulated by other molecules that are themselves controlled by the presence or absence of phosphate modifications.

The idea behind our research is that GTPases can be also regulated by the addition of phosphates to certain locations on the GTPase structure by itself, and not only by the number of phosphates on the nucleotide (GTP or GDP) that is already bound. This would result in a significant change in our understanding of how these molecules work. The idea is supported by our preliminary studies showing that adding phosphates to GTPases does change their activity.

Our current research involves adding phosphates to GTPases and studying how that changes the rate at which they function and the strength of interaction with their typical binding partners. We also aim to discover how the molecule is affected by studies of the GTPase proteins structure and dynamics. We will also examine the behavior of phosphorylated GTPases in cells.

Because GTPases are involved in many aspects of cell growth and motion, research has shown those cells can become cancerous when GTPases malfunction. The cells can multiply without stopping and become more capable of moving to other parts of the body (metastasis), forming cancerous tumors in other tissues. It has been speculated that phosphorylated GTPases function similarly to GTPases that are permanently modified by mutations in cancer. However, a phosphorylation would be reversible. That is why it is essential that scientists understand all the ways by which these molecules are regulated. Only then we can hope to design drugs to inhibit abnormal function of the GTPase proteins.

MONICA BURDICK, PH.D.

(BREAST CANCER)

OHIO UNIVERSITY

Identification of E-selection Ligands on Breast Cancer Cells

Funded with the support of the Logan County Cancer Society

The breast cancer five-year relative survival rate is 100% if detected in the primary tumor stage, largely due to improvements in early detection techniques and the success of modern surgical and chemotherapeutic strategies. However, treatment methods have been much less effective in combating those tumors that have spread to other organs, or metastasized.

Once the cancer has colonized distant sites such as the lungs or bones, the five-year survival rate drops precipitously to 20%. The difficulty in curing late-stage disease is hindered by the complexity of the metastatic process. Breast cancer spread to distant sites via the bloodstream occurs in a multi-step cascade that begins with malignant cells freeing themselves from the original breast tumor, traveling through the bloodstream, and concluding with the cancer cells attaching to endothelial cells lining the blood vessels, or vascular endothelium, of a secondary organ.

The vascular endothelium expresses a variety of adhesion molecules that can promote the attachment of metastasizing tumor cells in the bloodstream that express the proper counter-receptors to said endothelial adhesion molecules. One of these endothelial molecules, E-selectin, is continuously expressed by the on the endothelium of bone, a frequent site of breast cancer metastasis. Study of the E-selectin adhesion pathway in promoting breast cancer metastasis as a whole has been largely overlooked, despite clinical studies correlating this molecule and its counter-receptors with disease progression not only in breast cancer, but colon, prostate, and pancreatic cancers as well. In addition, recent studies have indicated that the main type of breast cancer cell found in metastases of bone are “cancer stem cells,” a particularly aggressive subpopulation of the whole tumor with an enhanced capability to form metastatic colonies. It is therefore hypothesized that breast cancer cells, particularly the cancer stem cells, express adhesion counter-receptors that bind E-selectin on bone endothelium. It is hoped that the identification of the molecules on tumor cells that bind to E-selectin will lead to new ways to diagnose and treat late-stage disease, ultimately leading to a cure for breast cancer.

IVANA de la SERNA, PH.D.
UNIVERSITY OF TOLEDO

(SKIN CANCER)

De-regulation of Chromatin Remodeling by BRAF (V600E) in Melanoma

Melanocytes are the cells that make melanin, the pigment that gives skin, hair and eyes their characteristic color. In melanoma, genetic changes occur that cause normal melanocytes to become cancerous by affecting their growth and survival. One very common mutation is in the BRAF gene. The BRAF gene encodes a protein that is important for transmitting extra-cellular signals about the environment into the cell in order to regulate gene expression. Having the BRAF mutation is not usually sufficient for a melanocyte to become a melanoma because benign nevi or moles often harbor this mutation but are not cancerous. Other changes must occur to allow the BRAF mutation to proceed to melanoma. These changes may involve the inappropriate regulation of gene expression.

The genetic material, DNA, is tightly packaged by its associations with histone and non-histone proteins to form chromatin. This packaging of DNA into chromatin allows large amounts of DNA to fit into the nucleus of a cell. For genes to be expressed, localized regions of DNA must be unwrapped so that the DNA can be processed. The SWI/SNF complex is composed of many components to form a large “machine” that can change the structure of chromatin in order to control which genes are expressed. Members of the SWI/SNF complex have been shown to play important roles in other types of cancer.

Based on our observation, our hypothesis is that SWI/ SNF function is altered by BRAF mutations to promote changes in gene expression that occur in melanoma. To test this hypothesis, we propose to determine how mutated BRAF can change the expression and activity of SWI/ SNF components.

BRIAN ANDREW GEBELEIN, PH.D.

(LEUKEMIA)

CINCINNATI CHILDREN’S HOSPITAL RESEARCH FOUNDATION

A New Tumor Suppression Pathway in Leukemia

Funded in part by Toyota Motor Manufacturing & Engineering North America, Inc.

In our blood, there are cells that are important for us to get energy and oxygen to our muscles and to fight infections. We require that new blood cells are formed everyday or we can get a number of diseases that make us sick.

Leukemia is a cancer of the blood that affects thousands of children and adults every year. Our long-term goal is to understand the causes of leukemia in the hope of finding better treatments for this disease. We currently know that leukemia is often caused by damaged blood cells that grow more than others and don’t perform their normal functions.

This proposal explores a new idea about how the damaged blood cells over grow. Surprisingly, our idea originated from experiments using an insect (the fruit-fly), revealing that this mechanism is ancient. In brief, we have found that two factors compete against each other in blood cells. If the wrong factor wins then the cells over grow and cancers form. The short-term goal of this proposal is to better understand these two factors and how they compete against each other. By doing these studies, we hope to provide new ways to treat human leukemia.

ANIL G. JEGGA, D.V.M.

(GENE MUTATION)

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

Functional Polymorphisms in p53 Response Elements

The p53 protein is a master regulator cancer suppressor protein and an important mediator controlling how our cells respond to toxic exposures. Following toxic exposure, p53 binds to specific sites on our DNA sequence called a p53 responsive element and brings about numerous, coordinated changes in the target genes.

Over half of human cancers result if this mechanism goes wrong. The errors can be in the p53 itself or its target genes. Since it is an important player in maintaining normal cell status and also in cancer, p53 and its target genes are highly sought-after drug targets for stopping cancer progression.

Although this pathway is of such importance, at this time very little is known as to what changes in the p53 target genes trigger it to become non-functional and eventually lead to cancer. Our long term goal here is to identify all such changes in our DNA which will prevent p53 to activate its target genes. The way p53 binds to its target genes are governed by several rules.

In this project, our main aim is to identify these rules and study the effects of breaking these rules. By understanding these rules and the consequences of breaking them (because of DNA mutations), we can, in the long run understand better as to what makes some of us more prone to cancer while why some are resistant. It also helps us to devise new ways to preventing or treating cancer.

SONG-TAO LIU, PH.D.

(GENE MUTATION)

UNIVERSITY OF TOLEDO

Regulation of the Mitotic Checkpoint by hMPS1 KINASE

Gain or loss of genetic materials (called aneuploidy) has been found in cells of over 80% of solid tumors. Aneuploidy may play significant roles in cancer initiation and progression.

It is our long-term goal to find out how aneuploidy happens in the first place, and once cells acquire aneuploidy how it further affects their evolution into malignant cancer cells. Cells do have intrinsic mechanisms to prevent aneuploidy, of which the mitotic checkpoint is one of them most important. Several mitotic checkpoint proteins have been identified and their alterations have been found in many cancer samples that are usually aneuploid.

This application focuses on studying the functioning mechanisms of one of these mitotic checkpoint proteins hMPS1. Our research will help elucidate the underlying mechanisms of the mitotic checkpoint signaling cascade and lead to a better understanding of tumor genesis arising from defective mitosis.

AMIT SINGH, PH.D.

(GENE MUTATION)

UNIVERSITY OF DAYTON

A Drosophila Model to Study the Role of the Notch Ligand Serrate (Jagged-1) in Growth and Cancer

Cancer is second leading cause of deaths in the United States. There are more than 100 different types of cancer. All cancers begin in cells, the body's basic unit of life. To understand cancer, it's helpful to know what happens when normal cells become cancer cells.

There are several genetic mechanisms responsible for uncontrolled growth phenotypes in different organs during cancer, Misregulation of Notch (N) signaling pathway, one of the highly conserved pathways, is responsible for several human cancers mainly affecting cell proliferation, cell survival and differentiation. An important member of N signaling pathway, Serrate (Ser, human homolog Jagged-1) is known to be involved in cell survival during organ development. Mutation in *Ser* leads to birth defects in heart, liver, kidney and also in breast cancer. However, the mechanism(s) by which *Ser/Jag-1* control growth remain unclear.

Here we propose to use the power of *Drosophila melanogaster* (a.k.a fruit fly) genetics, to study role of *Ser/Jag-1* in growth regulation during organ development. *Drosophila* is a well established model to study human diseases, as the genetic machinery is structurally and functionally similar from flies to humans. Here we will test the hypotheses that (1) *Ser* regulates growth by affecting tissue or organ size, control pathway and (2) *Ser* mutant cells gain unique survival characteristics and promote abnormal growth or cancer. Our aim is to identify other genes/partners collaborating or participating with *Ser* in growth function. These studies will help to elucidate the genetic circuitry involved in *Ser* mediated Notch pathway regulation of cell proliferation and differentiation during normal development and cancer.

NEVILLE TAM, PH.D.

UNIVERSITY OF CINCINNATI

Dietary Soy and Epigenetic Modulation in Androgen-Independent Prostrate Cancer

(PROSTATE CANCER)

Funded for one year by Larry and Rhonda Sheakley in honor of Rhonda's father, Dr. Sidney Goldstein

DNA methylation is a type of chemical modification of DNA that can be inherited and subsequently removed without changing the original DNA sequence. This process is associated with silencing the gene expression. If it happens in the wrong time or place (gene), it leads to perturbation of normal cellular functioning. If those abnormally methylated genes are for tumor suppression, tumors will be likely to develop.

The long term goal of our study is to understand how diet promotes the “healthy” DNA methylation patterns or even can rectify the “defective” DNA methylation status in established cancer cells. In this proposed study, we will evaluate the effectiveness of soy meal or individual soy-derived isoflavonoids/metabolites on reversing the “over”-methylated patterns of a DNA repair gene (MGMT) in prostate cancer cells.

It is our expectation that soy is able to “normalize” the MGMT methylation patterns and restore the DNA repair mechanism thereby suppressing tumor growth and behavior. We will testify this idea with animal and cell culture experiments. Our study will also determine whether soy metabolites are likely to be epigenetically active, and this information is extremely important to individuals who are deficient in soy metabolism, and have higher risk of prostate cancer. Regarding to MGMT (DNA repair gene), its epigenetic changes in methylation/ gene expression pattern by dietary soy products will be beneficial for individuals with genetic polymorphism of Mgmt leading to DNA repair deficiency and increased risk of prostate cancer.

HORST A. VON RECUM, PH.D.

CASE WESTERN RESERVE UNIVERSITY

Multiplexing Molecular Interactions to Improve Chemotherapeutic Delivery

(CHEMOTHERAPY)

Funded in honor of the late Robert Trombly

In our lab we propose to examine multiplying the effect of a unique molecular interaction (MI) to create a cancer drug delivery system that can be implanted at the tumor site for long-term, local drug release over time periods from months to years.

Our research team will examine polymers which contain pockets that can bind and release chemotherapy drugs. After the polymers are implanted by the doctor, small amounts of the chemotherapy drug will release out of the pockets and treat local tumors. Because these doses are locally high, but systemically low the side-effects of whole body chemotherapy would not be expected. One advantage these polymers offer is that while use of binding to single pockets results in a defined release rate, choosing drugs which bind to multiple pockets results in exponential increase in release rate from hours to weeks to months. This is particularly useful for slow-growing persistent tumors such as prostate cancer.

This proposal specifically will look at the extended release rate of drugs and polymer pellets, and then whether this drug release is able to kill tumor cells in a mouse model. Due to the extended delivery time possible through these interactions, devices developed herein will extend the therapeutic lifetime of drug delivery implants and remove the need for multiple implants or use of IV insertion drug pumps.

JIAN-QIU WU, PH.D.

THE OHIO STATE UNIVERSITY

Phosphorylation of the Anillin Mid1p by Polo Kinase During Cytokinesis

(MOLECULAR GENETICS)

Funded with the support of The John and Mary Alford Foundation

A significant gap exists in understanding the signaling pathways during cytokinesis, which divide cellular constituents into two new daughter cells and plays a crucial role in cell reproduction and cell differentiation. The long-term goal of our research is to investigate cytokinesis in yeast, in normal cells, as well as in cancer cells.

Our objective is to investigate the signaling pathway for the assembly of the contractile ring in fission yeast cytokinesis. The fission yeast has emerged as one of the leading model systems for the analysis of cytokinesis. Not only is it genetically tractable and favorable for microscopic analysis, but it also has the smallest fully sequenced eukaryotic genome and carries out cytokinesis much like animal cells. Contractile rings consisting of actin filaments, myosin-II motors, and more than 30 other proteins are essential for cytokinesis in both fission yeast and animal cells, including humans.

Our central hypothesis is that the contractile ring assembles progressively at the division site from a broad band of precursor nodes into a complex protein structure. The phosphorylation of the anillin Mid1p by the Polo kinase plays a crucial signaling role during the assembly. This hypothesis will be tested by investigating the identification of the phosphorylation site on Mid1p and investigating the role of Mid1p phosphorylation in Mid1p function in cytokinesis and exploring the roles of Polo1p kinase in Mid1p phosphorylation.

Discerning the assembly of the essential contractile-ring is an important step towards understanding cytokinesis. Uncontrolled and misoriented cell divisions are defining characteristics of cancer. The majority of proteins involved in cytokinesis are evolutionarily conserved. Thus, much of what we learned about the proteins in fission yeast cytokinesis is ultimately relevant and applicable to cancer and other human diseases.

JINSONG ZHANG, PH.D.
UNIVERSITY OF CINCINNATI

(LEUKEMIA)

Role of E Protein Inactivation in Leukemogenesis by AML1-ETO

Acute myeloid leukemia (AML) is a cancer that starts in cells that would normally develop into different types of blood cells. In 2007, more than 13,000 people were expected to be diagnosed and 9,000 deaths would occur from AML in the United States. The risk increases with age.

In children, about one in five leukemias is AML. An abnormal protein in blood cells called AML1-ETO is known to be the most frequent cause of acute myeloid leukemia. This abnormal protein is not present in normal blood cells. We have found that a group of key targets of AML1-ETO are cellular proteins known as E proteins. One of the key functions of E proteins is to protect healthy cells from becoming leukemias. Interaction of AML1-ETO with E proteins inactivates E proteins. As a result, this increases the odds of blood cells to develop leukemias.

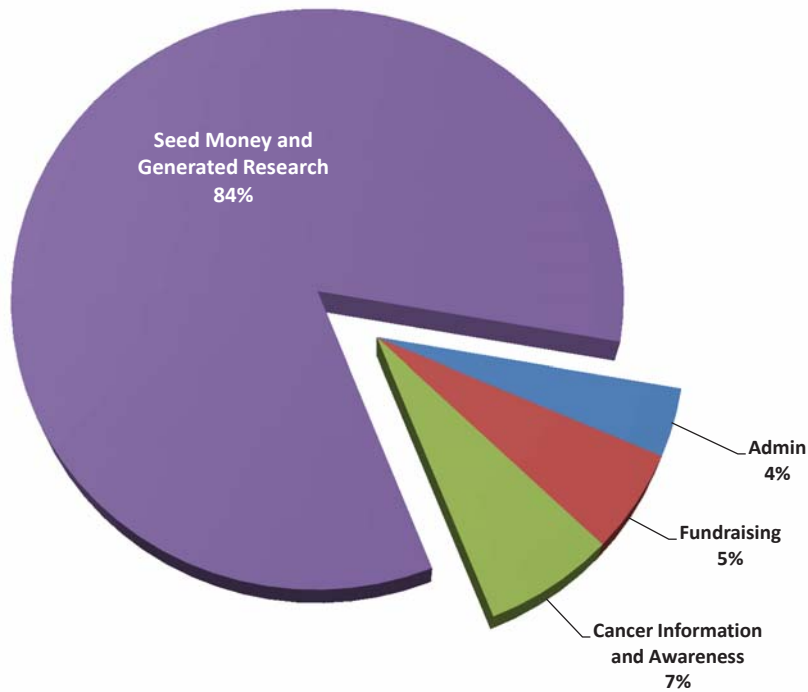
We will pursue two types of studies. We will develop strategies to allow reactivation of E protein function in leukemic cells. Then we will investigate how the inactivation of E protein function by AML1-ETO contributes to the leukemia development. These studies will help develop novel drugs that can be used to cure this common type of leukemias.



2009 FINANCIAL INFORMATION SUMMARY

The best investment!

84% of all resources allocated to cancer research for 2009.



I.	Generated research	\$ 3,633,161
II.	Seed money and generated research	\$ 414,398
III.	Cancer information and awareness	\$ 327,476
IV.	Fund raising and administrative	\$ 454,902

- Over \$6.2 million in seed money provided to researchers by Ohio Cancer Research Associates has generated more than \$104.1 million in new money from other sources to continue basic cancer research on projects initially funded.

