KARIN GRUNEBAUM
cancer research foundation

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From the Chair

Dear Friends of the Karin Grunebaum Cancer Research Foundation:

The period between my last annual letter to you and this one encompasses one of the most turbulent years in recent world history – from the summer of 2008 to the summer of 2009. During this period global recessions, major banking failures and devastated net values flooded the headlines and unnerved people worldwide. In spite of this perceived financial apocalypse, I am very pleased to report that during this period the Foundation received funding which amounted to over 15% of the value of our previous endowment.

This was also a major transition year for the Foundation's esteemed Board of Trustees. We sadly bid farewell to Drs. Andrew Warshaw and Thomas Michel, whose personal circumstances required them to leave their positions as a Foundation Trustee. But, we are delighted to welcome Dr. Frank Hsu and Dr. David Golan as new members of the Board of Trustees.

In spite of this perceived financial apocalypse, I am very pleased to report that during this period the Foundation received funding which amounted to over 15% of the value of our previous endowment.

Dr. Hsu is a former Karin Grunebaum Cancer Research Fellow (1986) and is currently Senior Medical Director at Genzyme Oncology – a leading biotechnology firm working on advanced cancer-related medications and treatments. Dr. Hsu's medical specialty is in oncology and hematology, and he is the third former Fellow to serve as a Trustee, along with Dr. Michael Droller (1966) and Dr. Michael Gimbrone (1967). Dr. Hsu will also be the first member of the pharmacology industry to be on the Board.

Dr. Golan is currently Dean of Graduate Education at Harvard Medical School, and his appointment to the Board of Trustees continues the Foundation's tradition extending over 40 years of having a Dean of Harvard Medical School serving on the Board. Dr. Golan's medical specialty is in pharmacology and hematology, and he also serves as a Professor of Medicine and Molecular Pharmacology at Harvard Medical School as well as being an attending physician both at Brigham & Women's Hospital and at the Dana Farber Cancer Institute.

Cancer research is not only the Foundation's middle name, but also the sole purpose for our existence. Thus, we are always gratified when the significant cancer research work done by our Fellows is recognized by others. This year Dr. Christine Iacobuzio-Donahue (Karin Grunebaum Fellow 1996) was awarded the 2009 Ramzi Cotran Young Investigator Award by the United States and Canadian Academy of Pathology (USCAP) for her pioneering work in pancreatic

(continued on page 3)

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Meet the New Trustees

David E. Golan M.D., Ph.D., Harvard Medical School Dean for Graduate Education and Special Advisor for Global Programs;Professor of Biological Chemistry and Molecular Pharmacology; Professor of Medicine; Physician, Brigham and Womens Hospital and Dana-Farber Cancer Institute;

Dr. David E. Golan became the first Dean for Graduate Education at Harvard Medical School in November 2008. He is a professor in the HMS Department of Biological Chemistry and Molecular Pharmacology, where his laboratory applies biophysical and cell-imaging methodologies to the study of membrane-targeted proteins in blood cells and in the vascular endothelium. He also is Professor of Medicine at HMS and a physician in the Department of Medicine at Brigham and Women's Hospital, where he sees patients as a practicing hematologist and clinician-teacher.

After earning his AB summa cum laude in chemistry at Harvard College, Dr. Golan received his PhD in molecular biophysics and biochemistry and his MD degree from Yale University, followed by clinical training in internal medicine and in hematology at BWH. For many years, he designed and taught the Pharmacology course for first-year medical students at HMS, and is the principal author of the best-selling textbook *Principles of Pharmacology.*

In addition to many awards and honors for his discoveries in red blood cell biophysics and cellular imaging, including an NIH MERIT Award, he received the Robert J. Glaser Distinguished Teacher Award from the Association of American Medical Colleges in 2005. He is an Associate Director of the Leder Human Biology and Translational Medicine graduate program, and is a founding Scholar of the Academy at Harvard Medical School.

In his role as Dean for Graduate Education, Dr. Golan works closely with the Dean of the Faculty of Medicine, the Dean for Education, and the Dean for Medical Education, to create a new educational environment at HMS that brings together graduate students, medical students, trainees, and faculty in shared education and research activities throughout the broad spectrum of biomedical investigation at Harvard. He will direct the newly formed Program in Graduate Education, which will bring together leaders of graduate education across Harvard, including graduate program directors, chairs of basic science departments on the Quadrangle, hospital-based scientists, graduate curriculum fellows, and other leading educators in our community. Under his leadership, the HMS Program in Graduate Education will coordinate activities and develop new programs across the University to enhance graduate students' engagement in all aspects of biomedical discovery.

As Dean for Graduate Education, Dr. Golan will continue to direct the Harvard Catalyst Research Education Program. In this role, he will continue to coordinate the design, development, implementation, and oversight of the master's degree programs at HMS.

Dr. Golan also will serve as Special Advisor to the Dean on global programs at HMS, together with his appointment as Dean for Graduate Education. In this role, he will work with HMS and Harvard University in strategizing and designing the School's global education programs and research partnerships.

Frank J. Hsu, M.D. is a Senior Medical Director of Clinical Research at Genzyme Corporation. Dr. Hsu is a former Grunebaum fellow. While a medical student at Harvard in 1986, Dr. Hsu received a fellowship grant to support his early research career in cancer immunology. He subsequently continued to develop a career in oncology, first in academics and then in the biopharmaceutical field.

Dr. Hsu received his undergraduate degree from Stanford University and his medical degree from Harvard Medical School as part of the Heath, Science and Technology (Harvard-MIT) program. His residency training in Internal Medicine was at the University of California, San Francisco. He then spent six years as a clinical and research fellow in Oncology at Stanford University. Dr. Hsu joined the faculty of Yale University in 1996 and served as an Assistant Professor of Medicine in the Section of Oncology and as co-Director/ Director of the Immunology Research Program of the Yale Cancer Center until 2003. He was a recipient of several grant and awards including the James S. McDonnell Fellow Award for Molecular Medicine in Cancer Research and was a translational research fellow of the Leukemia and Lymphoma Society.

Dr. Hsu's research focused on non-Hodgkin's lymphomas, Hodgkin's disease and multiple myeloma. His work has involved both basic immunology and translational work in the development of anti-cancer antibody and vaccine approaches for the treatment of B cell malignancies. While in academics, his research concentrated on the development and clinical application of idiotype vaccine therapies for B cell non-Hodgkin's lymphomas, and his work led to the first clinical trial of an anti-cancer vaccine based on antigen-pulsed dendritic cells. The results of these early clinical studies provided the basis for further development of these vaccine approaches in lymphoma and prostate cancer. He has published extensively in this area of research and has been an invited lecturer to both professional and lay audiences.

Dr. Hsu has been with Genzyme since leaving academics and has continued to pursue the clinical development of novel anti-cancer therapeutics. At Genzyme, Dr. Hsu is responsible for clinical research and development of both early and late stage small molecule and antibody therapeutics for use in hematopoietic stem cell transplantation and for the treatment of both hematologic and solid cancers.

From the Chair *(continued from page one)*

cancer research. Other Fellows who have also achieved prominence in the field of cancer research and medical education are featured on the Foundation's website (www.grunebaumfoundation.org) under "Focus on Research."

But, the Foundation's recognized success in funding such significant cancer research can only continue with your support. We have no way of continuing to fund this critical research except through your generous donations. Our Trustees serve as unpaid volunteers; we have no employees; and our expenses are minimal. Therefore, almost every penny you contribute goes directly to funding advanced cancer research. Please either mail your tax deductible donation to: Karin Grunebaum Cancer Research Foundation, 85 Sherman Street, #8, Cambridge, MA 02140 or use our on-line donation capability at www.grunebaumfoundation.org.

Thank you for your generosity.

Please feel free to contact me at any time if you have any questions about the Foundation.

Sincerely,

Steven Wallach
Chairperson
(561) 750-7366;
e-mail: steven.wallach@grunebaumfoundation.org.

Dr. Iacobuzio-Donahue wins Ramzi Cotran Prize for Her Pancreatic Cancer Research

Congratulations to Dr. Christine Iacobuzio-Donahue (Karin Grunebaum Fellow '96), winner of the 2009 Ramzi Cotran Young Investigator Award. This award was presented to Dr. Iacobuzio-Donahue at the 98th Meeting of the United States and Canadian Academy of Pathology (USCAP) in Boston, MA. The award recognizes a body of work by a scientist under the age of 45 which has contributed significantly to the diagnosis and understanding of human disease. Dr. Iacobuzio-Donahue was awarded this prestigious award specifically for her pancreatic cancer research, including her discoveries into why some pancreatic cancers metastasize. She is currently an Associate Professor of Pathology and Oncology at The Johns Hopkins University School of Medicine.

The award is being presented by Dr. Michael Gimbrone (Karin Grunebaum Fellow '67), the Elsie T. Friedman Professor of Pathology at Harvard Medical School and a Trustee of the Karin Grunebaum Cancer Research Foundation.

Dr. Michael Gimbrone and Dr. Christine Iacobuzio-Donahue

Your Support is Vital to our Mission

The Karin Grunebaum Cancer Research Foundation and the support we are able to give to the dedicated cancer researchers is solely dependent on donations from you.

To further demonstrate our dedication, we keep our overhead funding at **1%** – meaning that **99%** of your contribution will go directly to research.

Your tax-deductible contribution will directly help fund the cancer research effort, since almost 99% of our income is spent on supporting the researchers. Our Officers and Trustees are all unpaid volunteers, and the Foundation has no paid employees.

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Harvard Medical School

Wenyi Wei, Ph.D., Assistant Professor
Department of Pathology, Beth Israel Deaconess Medical Center
Harvard Medical School

Description of the Proposed research project

Defective cell cycle regulation leads to genomic instability and ultimately, cancer development. Two related, multiunit E3 ubiquitin ligase enzymes, Anaphase Promoting Complex (APC) and Skp1-Cullin1-F-box complex (SCF) are thought to be the major driving forces governing cell cycle progression. I have previously discovered that Fbw7 regulates the degradation of c-Jun, a member of the AP-1 family of transcription factors, in a GSK-3 phosphorylation-dependent manner, and is responsible for the rapid clearance of c-Jun in the early G1 phase (Wei et al., Cancer Cell 2005). In addition to turnover of c-Jun, Fbw7 is also involved in the degradation of c-Myc, cyclin E and Notch protein. Interestingly, most of the Fbw7 targets require GSK3-phosphorylation on their CPD (central phosphorylation domain) for efficient recognition by Fbw7. In addition, the conserved collinear degron sequence within these known Fbw7 substrates resembles each other, indicating that the presence of the CPD sequence could be used for a "candidate-based" approach to search for Fbw7 novel substrates. Using the ProSite Motif scan program, we screened the entire human proteome to generate a list of candidate proteins containing the "TPxLSP" degron sequence. We also compared putative degrons in different species to address whether this motif is conserved throughout evolution, adding stringency to the screen. We found that the KLF4 protein contained an almost identical CPD domain as c-Jun and c-Myc. Using the Scansite program, we also found that there are putative GSK3 phosphorylation sites within this CPD.

KLF4 belongs to the family of Kruppel-like transcription factors, whose functions have been implicated in regulation of tissue-specific development. KLF4 overexpression promotes malignant transformation through downregulation of the Cdk inhibitor p21. Elevated KLF4 overexpression is frequently seen in many types of cancers while the molecular mechanisms remain unclear. Recent studies also demonstrated a critical role of KLF4 in the regulation of differentiation of hematopoetic stem cells into T lymphocytes and monocytes. The important function of KLF4 in regulation of stem cell differentiation is further illustrated by the recent demonstration that in combination of c-Myc, Sox2 and Oct4, KLF4 could promote the transition of various differentiated human cells into induced pluripotent stem (iPS) cells. Interestingly, loss of Fbw7 is frequently found in T cell acute leukemia (T-ALL), a disease caused by the blockage of proper differentiation from progenitor cells to mature T cells. Thus we would like to test the hypothesis whether Fbw7 can also degrade KLF4 in a GSK3- dependent manner. As a result, loss of Fbw7 causes accumulation of the KLF4 transcription factor, which subsequently blocks proper differentiation process, leading to the development of leukemia. In support of my hypothesis, we found that downregulation of Fbw7 by RNAi resulted in a dramatic increase in the steady state level of KLF4 in both asynchronized and synchronized (late G1 or S phase-arrested) Hela cells. Moreover, steady state KLF4 levels are elevated in Fbw7-/- HCT116 cells, indicating a role of Fbw7 in regulation of KLF4 expression. Furthermore, I found that KLF4 interacts with Fbw7 in an in vivo co-immunoprecipitation assay, and overexpression of Fbw7 together with the modifying enzyme GSK-3 results in accelerated destruction of KLF4. In order to further determine whether Fbw7 regulates KLF4 in a GSK3-dependent manner, as well as to better understand the tumor suppressor function of Fbw7, I propose the following research plan:

Specific Aim 1. To determine whether Fbw7 regulates KLF4 degradation in a GSK-3 dependent manner. We will identify the key phosphorylation sites within the KLF4 degron sequence, phosphorylation of which by GSK-3 is required for proper interaction with Fbw7. We also propose to further illustrate that loss of Fbw7 results in a longer half-life of endogenous KLF4 protein, which contributes to the elevation of KLF4 expression, while overexpression of Fbw7 and GSK3 results in a shorter half-life of KLF4 that correlates with the rapid disappearance of KLF4. More importantly, utilizing both in vitro and in vivo ubiqutination assays, we propose to gather experimental evidence to support the notion that Fbw7 could promote the ubiquitination of KLF4 in a GSK3-dependent manner.

Specific Aim 2. To determine whether elevated KLF4 expression plays a critical role in development of T-ALL after loss of the Fbw7 tumor suppressor. Loss of Fbw7 is frequently observed in T-ALL cells. First, we would like to examine whether disruption of the GSK3/Fbw7 pathway results in elevated KLF4 expression in these cells. This could be due to the loss of Fbw7, or the inactivation of GSK3 due to loss of the PTEN tumor suppressor. If so, we would like to further investigate whether overexpression of Fbw7 or PTEN in these cells leads to downregulation of KLF4, which provides a causal relationship for KLF4 overexpression. Furthermore, we would like to further investigate whether knock down of endogenous KLF4 expression in these cells will trigger differentiation of these tumor cells into mature T cells. Loss of Fbw7 in T cell-lineage of mice results in T cell leukemia. As a future research goal, we would like to further demonstrate whether additional depletion of KLF4 will block Fbw7 loss-induced leukemia development.

Dirk Bausch M.D., Research Fellow
Massachusetts General Hospital, Department of Surgery

PLECTIN-1 IS A BIOMARKER OF MALIGNANT PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Intraductal papillary mucinous neoplasms (IPMN) are cystic tumors of the pancreas that progress from benign adenoma to malignant invasive carcinoma through borderline malignancy. Over the past decades, IPMNs have been identified with increasing frequency and now account for up to 20% of pancreatic surgeries in large referral centers[1, 2]. Surgery is usually recommended for IPMNs arising in the main pancreatic duct due to their high risk of malignancy. IPMNs arising in the branch ducts have a much lower risk of malignancy resulting in less clear treatment strategies[3]. The risk of malignancy in IPMNs is usually stratified by clinical symptoms, cross-sectional abdominal imaging and endoscopic ultrasound with fine needle aspiration biopsies for cytology and cyst fluid analysis. Current international consensus management guidelines recommend following asymptomatic patients with small branch duct IPMNs regularly[4]. However, the predictive value of these guidelines to correctly distinguish benign from malignant cystic tumors is low: Up to 85% of surgically treated patients have no malignant IPMN while some small and asymptomatic branch duct IPMNs are malignant[5].

Improved detection of malignancy using novel biomarkers in cyst fluid analysis and imaging may improve diagnostic accuracy. One such promising novel biomarker is Plectin-1 (Plec-1). Plec-1 was initially identified in a screen for unique markers of pancreatic ductal adenocarcinoma[6] and found to be highly specific and sensitive for early and invasive pancreatic cancer (Bausch et al., manuscript in preparation). Based on these findings, we evaluated whether Plec-1 is also a potential biomarker for malignant IPMN and whether cyst fluid analysis for Plec-1 allows the discrimination of malignant from benign cysts.

Using immunohistochemistry, we were able to identify Plec-1 in 26 of 31 of malignant IPMNs. Eight of 10 of the carcinoma in situ samples expressed Plec-1 and 18 of 21 invasive carcinomas were Plec-1 positive. In contrast to malignant IPMNs, only 1 of 6 benign IPMN was Plec-1 positive. The specificity of Plec-1 in discriminating malignant and benign IPMN was therefore 83% and its sensitivity, 84%. Sensitivity for in situ carcinoma was 80% and for invasive carcinoma, 86% (Figure 1). Twelve of the 31 malignant IPMN evaluated had metastases to lymph nodes. All twelve lymph node metastases stained for Plec-1. To determine whether Plec-1 is also specifically identifiable in malignant IPMN cyst fluids, Plec-1 immunoprecipitation of cyst fluids from benign and malignant IPMN was performed. Plec-1 was found in 4 of 4 cyst fluids from malignant IPMN. In contrast, cyst fluid from all 3 benign IPMN contained no detectable Plec-1.

Overall, we found that Plec-1 is a sensitive and specific biomarker for the early detection of malignant IPMN. Plec-1 expression analysis offers improved specificity over current methods of detecting malignancy in IPMN. Furthermore, Plec-1 expression analysis can easily be incorporated into routine clinical cyst fluid analyses where it may contribute substantially to improving diagnostic accuracy for the detection of malignancy arising in IPMN.

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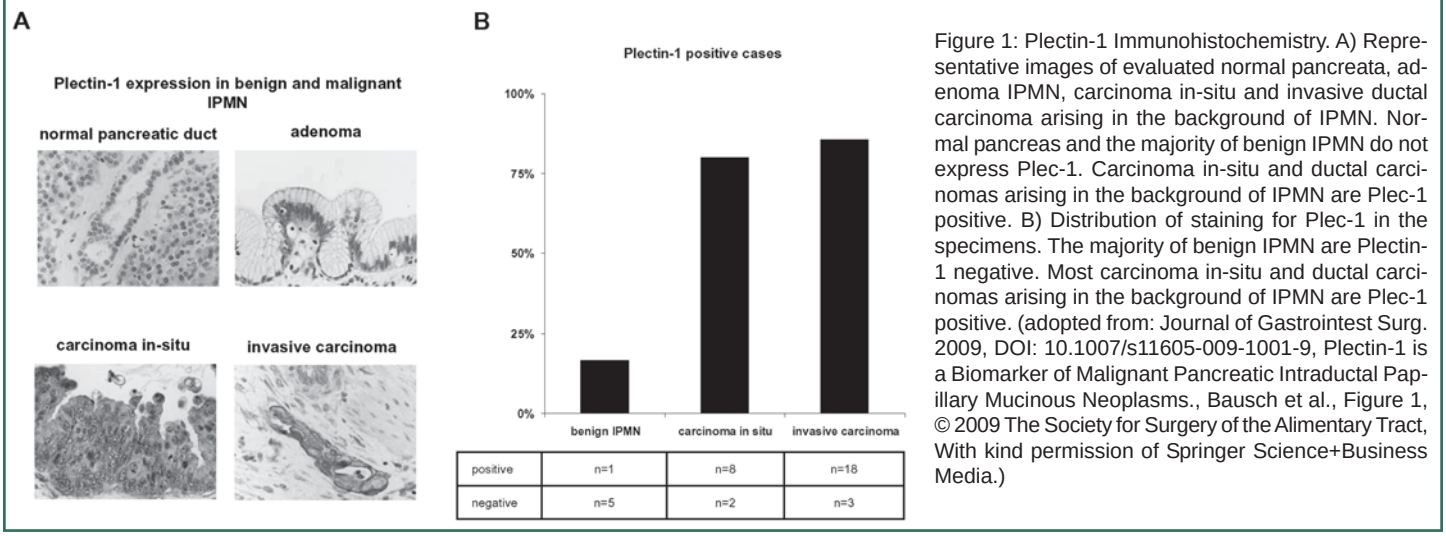

Figure 1: Plectin-1 Immunohistochemistry. A) Representative images of evaluated normal pancreata, adenoma IPMN, carcinoma in-situ and invasive ductal carcinoma arising in the background of IPMN. Normal pancreas and the majority of benign IPMN do not express Plec-1. Carcinoma in-situ and ductal carcinomas arising in the background of IPMN are Plec-1 positive. B) Distribution of staining for Plec-1 in the specimens. The majority of benign IPMN are Plectin-1 negative. Most carcinoma in-situ and ductal carcinomas arising in the background of IPMN are Plec-1 positive. (adopted from: Journal of Gastrointest Surg. 2009, DOI: 10.1007/s11605-009-1001-9, Plectin-1 is a Biomarker of Malignant Pancreatic Intraductal Papillary Mucinous Neoplasms., Bausch et al., Figure 1, © 2009 The Society for Surgery of the Alimentary Tract, With kind permission of Springer Science+Business Media.)

Boston University Medical School

Yan Dai, Ph.D., Assistant Professor
Cancer Research Center, Department of Medicine

SIRT1 IN PROSTATE CANCER DEVELOPMENT AND PROGRESSION

Prostate cancer is the most common form of cancer and the second leading cause of cancer death in men in the United States. Prostate cancer begins as an androgen-dependent tumor that typically undergoes clinical regression in response to pharmacological and surgical strategies, which reduce testosterone levels. However, patients invariably develop untreatable, androgen-independent tumors within 18 months. The mortality is mainly due to the progression of localized primary prostate cancer to advanced prostate cancer, which becomes androgen independent and metastasizes to multiple organs. The complex mechanism of refractory prostate cancer development and metastasis are largely unknown. The available treatments and surgical options have proven to be inadequate in controlling the mortality and morbidity of prostate cancer. It is therefore necessary to intensify our efforts to better understand this disease and develop novel approaches for its prevention and treatment.

Our laboratory's research interest is studying the mechanism and cell signaling of prostate cancer development and progression. One of our studies focuses on the role of NAD dependent histone deacetylase (Sirtuins) in the androgen-independent tumors development and prostate cancer metastasis.

SIRT1 is a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase (class III HDAC), which has been reported to play an important role in a variety of physiological processes such as aging, metabolism, neurogenesis and cell survival, due to its ability to deacetylate both histone and numerous non-histone substrates. Recent studies have shown that there are multiple connections between SIRT1 and the pathways involved in tumor initiation and progression, which suggest a crucial role of SIRT1 in the pathophysiology of cancer development.

We recently have identified SIRT1 is a novel corepressor of androgen receptor (AR). We have found that SIRT1 is required for androgen antagonist mediated transcription suppression. The Androgen Receptor (AR) is central to the initiation and growth of prostate cancer, and aberrant, androgen-independent AR signaling is postulated to be an important mechanism of progression to hormone-refractory growth. The transcriptional activity of AR is modulated by its co-regulators. Mutations in or altered expression of AR co-regulators contributes to the progression of prostate cancer. Our finding of SIRT1 regulating AR dependent transcription suggests an important role of SIRT1 in the hormone-refractory prostate cancer development.

In addition, we have recently found that SIRT1 silencing affects prostate cancer cell adhesion and migration. We found that SIRT1 is a key protein in the regulation of E-cadherin expression and in the E-cadherin mediated prostate cancer cell adhesion and migration. In normal prostate tissue, secretory epithelial cells express high levels of E-cadherin. A reduction or a loss of E-cadherin was significantly correlated with a lower survival rate in patients with carcinoma of the prostate, thus indicating that disruption of the cell-cell adhesion complex leads to subsequent prostate cancer progression. Our data has clearly shown that SIRT1 knockdown specifically increases prostate cancer cell adhesion and reduces cell motility of prostate cancer cells. SIRT1 is overexpressed in prostate cancer cells and cancer tissues when compared to normal prostate cells and tissues, and SIRT1 overexpression is correlated with prostate cancer Gleason score. In addition we show that SIRT1 knockdown upregulates E-cadherin protein levels and increases E-cadherin adhesion junction localization. These new findings suggest that overexpression of SIRT1 in prostate cancer may play an important and physiological role in the cells-cell adhesion, migration and prostate cancer progression. Currently we are testing our hypothesis that over-expression of SIRT1 regulates prostate cancer cell adhesion and migration and that SIRT1 may thereby play an important role in prostate cancer cell progression.

"Our current research projects include:

- SIRTt1 in androgen-dependent transcriptional regulation. The goal of this study is to understand the mechanism and signaling changes in refractory prostate cancer development.
- SIRT1 in the regulation of cell-cell adhesion migration. The goal of this study is to determine the role and molecular mechanism that SIRT1 regulate prostate cancer cell migration and metastasis. We will investigate the effects of SIRT1 on prostate cancer metastasis by using orthotopic prostate cancer mice model.
- Development of SIRT1 modulators for the treatment of prostate cancers.

Our studies will contribute to the understanding of the mechanisms underlying the refractory prostate cancer development and prostate cancer metastasis,
We sincerely hope that the information derived from our studies will ultimately provide a therapy which significantly affects the field of prostate cancer therapy.

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