Our Appreciation

Dear Friends of The H Foundation:

On behalf of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, thank you for your longstanding support and partnership to advance cancer research at Northwestern for the benefit of people around the world.

For more than 15 years, hundreds of our Lurie Cancer Center members have benefited from generous funding from The H Foundation. Your giving has truly made a difference. Over time, you have helped to provide seed money for investigators’ preliminary research to obtain data needed for a grant from government agencies; to establish state-of-the-art facilities for conducting research or to purchase new equipment; and to support symposiums, conferences, and other educational programs. H Foundation funds continue to have a significant impact in so many ways.

It is my pleasure to share with you the following report featuring the faculty members who have received Basic Science Synergy Awards, Pilot Awards, Bridge Awards, and other support during 2016-2017. Your giving is far-reaching for our dedicated scientists who are working to translate interdisciplinary basic science and clinical research into personalized, patient-centered care.

The Lurie Cancer Center—one of 49 National Cancer Institute (NCI)-designated Comprehensive Cancer Centers in the nation—is committed to being a national leader in the battle to overcome cancer. We are a founding member of the National Comprehensive Cancer Network (NCCN), an alliance of 27 of the world’s leading cancer centers devoted to defining and advancing high-quality, high-value cancer care. We are the only member center in Illinois.

On behalf of all of us at the Lurie Cancer Center, thank you again for your exceptional philanthropic support and dedication. We are thankful to have The H Foundation as loyal partners in our efforts to study the causes and behavior of cancer and to develop more effective approaches for prevention, detection, and treatment.

Sincerely,

Leonidas C. Platanias, MD, PhD
Jesse, Sara, Andrew, Abigail, Benjamin and Elizabeth Lurie Professor of Oncology
Director, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
2016 H Foundation Awards – Outcomes Summary
The following projects were funded in 2016. We are delighted to share updates on each project’s purpose and outcomes.

H Foundation Multi-Principal Investigator Basic Science Synergy Awards
The goal of this award is to enable recipients to conduct collaborative, thematically-related studies that lay the foundation for the submission of a National Institutes of Health Program Project Grant application.

Robert Goldman, PhD, Chair and Stephen Walter Ranson Professor of Cell and Molecular Biology, Professor of Cell and Molecular Biology and Medicine-Pulmonary and Critical Care
Karen Ridge, PhD, Professor of Medicine-Pulmonary and Critical Care and Cell and Molecular Biology
Vladimir Gelfand, PhD, Leslie B. Arey Professor of Cell, Molecular, and Anatomical Sciences, Professor of Cell and Molecular Biology

*Vimentin intermediate filaments (IF) in EMT, invasion and metastasis*
Non–small cell lung cancer (NSCLC), the most common type of lung cancer, has a low rate of survival and a high rate of recurrence among patients with advanced disease. One reason is the current lack of treatments targeting the metastatic spread of NSCLC. One change that occurs when tumor cells transition to a more metastatic phenotype (referred to as “Epithelial-to-Mesenchymal Transition” or “EMT”) is an increase in a protein that makes up intracellular cytoskeletal filaments, called vimentin. Dr. Goldman, together with Drs. Ridge and Gelfand, are investigating how vimentin is required for NSCLC cells to invade healthy tissue and how disruption of the vimentin cytoskeletons can inhibit NSCLC cell migration to prevent metastatic spread. The insights gained through this research ultimately will lead to improved treatment options, and hence outcomes, for patients with non–small cell lung cancer.

Andrew Larson, PhD, Professor of Radiology
Riad Salem, MD, Professor of Radiology, Medicine-Hematology and Oncology, and Surgery-Organ Transplantation

*Yttrium-90 radioembolization: image-guided approaches to achieve superior treatment outcomes*
Radioembolization is a strategy in which tiny glass beads are used to selectively deliver radiation through the blood vessels that supply a liver tumor. Through collaborative efforts supported by the H Foundation Synergy Award, Dr. Larson has developed a battery of new imaging protocols that should permit early detection of treatment response. He has developed a new type of MRI and CT visible biodegradable bead for optimal dose planning prior to radioembolization procedures. Dr. Larson is also investigating new approaches using an additional infusion of therapeutics intended to target any remaining tumor tissues that are unresponsive to the administered radiation.

Additional investigators who received Basic Science Synergy Awards include:

Jindan Yu, MD, PhD, Professor of Medicine-Hematology and Oncology and Biochemistry and Molecular Genetics
Sarki Abdulkadir, MD, PhD, John T. Grayhack, MD, Professor of Urological Research, Professor of Urology and Pathology
Debabrata (Debu) Chakravarti, PhD, Professor of Obstetrics and Gynecology-Reproductive Science in Medicine and Pharmacology

*Integrating epigenomic and kinase signaling in castrate-resistant prostate cancer*
NCI Stimulus Award

This award is given to investigators who have submitted an application to the National Cancer Institute (NCI) and have received an outstanding score that just missed the payline for funding. These awards help to ensure that the momentum continues, thus allowing investigators to strengthen and resubmit a proposal that could ultimately lead to NCI funding.

C. Shad Thaxton, MD, PhD, Associate Professor of Urology

Exosomes as triggers of immune lustration in cancer

Exosomes are extremely small (nanometers in diameter) vesicles produced by cancer and immune cells that play a critical role in cancer development, progression, and resistance to treatment. Exosomes carry information in the form of lipids, nucleic acids, and proteins and enable communication between cancer cells, immune cells, and healthy cells. In cancer, exosome messages cause healthy cells to support cancer progression and aid in metastasis, and can disable immune cells that would otherwise destroy the tumor cells. In this project, Dr. Thaxton and Dr. Olga Volpert investigated the possibility that exosomes can contain anti-cancer “cargo,” which prevents tumor progression by activating immune cells. Gaining a better understanding for exosomes and their functions as anti-cancer delivery vehicles has the potential to lead to effective new treatments for cancer. Some work that this grant supported was recently published in Nature Communications.

Pilot Projects – Proteomics Center of Excellence Pilot Awards

Steven Kosak, PhD, Assistant Professor of Cell and Molecular Biology

Proteomic analysis of PML-localized translation during cellular transformation

One of the critical steps in a cell becoming cancerous is the mutation of genes and the subsequent harmful build-up of their proteins. Dr. Kosak’s project is focused on a novel mechanism that he and his laboratory have uncovered that integrates the degradation of aberrant messenger RNAs and the proteins they encode during a process they call ‘test translation’ at Promyelocytic Leukemia Bodies (known as PML bodies), which are a compartment within the cell’s nucleus. They have used a specialized technique—mass spectrometry—to identify all the types of molecular machinery that are found at PML bodies when a cell becomes cancerous. They anticipate their findings will lead to the identification of totally unique targets in the treatment of cancer.

Shi-Yuan Cheng, PhD, Professor of Neurology

Proteomic analysis of patient-derived glioma stem cell exosomes

Dr. Cheng’s project analyzes the composition of secreted membrane vesicles, called exosomes, which are released from tumor stem cells into the surrounding microenvironment in patients with the deadly brain cancer glioblastoma. The “cargo” in these exosomes varies between cell types, even within the same tumor, and can differentially modify the sounding cells in the microenvironment. Specifically, Dr. Cheng found that exosomes from radiation-resistant glioma stem cells increase the rate of tumor cell growth and enhance radiation resistance in tumor cells. Their large-scale analysis of proteins contained within these exosomes revealed cargo unique to these malignant cells that could help identify ways of interfering with cancer progression and acquisition of resistance to radiation.
Curt Horvath, PhD, Professor of Medicine-Hematology and Oncology; Microbiology-Immunology; and Weinberg College of Arts and Sciences

Histone profiling in interferon-treated cancer cells

Interferon is a signaling protein secreted by the cell to regulate the immune system during infection and anticancer immune therapies. Dr. Horvath’s project investigates the interferon-induced changes in the chemical groups (i.e. acetyl, methyl) attached to proteins called histones that package the cell’s DNA into chromatin. Chemical modifications on histone proteins can regulate the activation or repression of interferon target gene production and alter the functional consequences of these gene products. Identifying the chemical signatures at the chromatin/histone level advances our understanding of the mechanisms underlying interferon function in cancer and immunity and enables development of more targeted anticancer strategies and cancer immunotherapy.

Panagiotis Ntziachristos, PhD, Assistant Professor of Biochemistry and Molecular Genetics and Medicine-Hematology and Oncology

Targeting an oncogenic chromatin cross-talk in lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the most prevalent childhood cancer. ALL (both T- and B-cell derived) represents approximately 25% of cancer diagnoses among children younger than 15. T-cell acute lymphoblastic leukemia (T-ALL) is the most aggressive type of ALL, and the lack of a durable treatment option presents an urgent, unmet need. Using state-of-the-art proteomics approaches, with support from The H Foundation, Dr. Ntziachristos has discovered that a small number of proteins controlling splicing and DNA damage response are expressed at higher levels than normal in tumor cells and that this increase leads to resistance to chemotherapy. Dr. Ntziachristos hopes to uncover protein-based molecular mechanisms of aggressive leukemia and develop prognostic and therapeutic platforms for those patients. His innovation will be the development of a patentable platform for the prognosis of high-risk leukemia and for the creation of new therapies, irrespective of the genetic makeup of the patients.

Simone T. Sredni, MD, Research Associate Professor of Neurological Surgery

Targeting protein kinases to develop new therapies for aggressive pediatric tumors

Using state-of-the-art technology, Dr. Sredni has discovered a promising target to treat atypical teratoid/rhabdoid tumor (AT/RT), which are universally lethal brain tumors that mostly occurs in infants. Dr. Sredni and her colleagues found that these tumors’ growth and tendency to spread are regulated by a protein kinase called Polo-like kinase 4 (PLK4), which is increased in AT/RT. This is the first time that PLK4 has been described as a therapeutic target for brain tumors or in pediatric cancer. More importantly, they found that a drug that is in clinical trials for adult advanced, non-brain tumors seems to be effective against AT/RT cell models. The drug impairs tumor proliferation, survival, invasion, and migration while sparing normal cells, implying that it may be safe to be used in the pediatric population. With The H Foundation’s support, the group was able to perform studies of the proteins in these tumors’ cells before and after treated with this drug to further understand its mechanisms of action and effects.
Translational Bridge Awards

Established to foster the translation of basic science research into clinical advancements, the Translational Bridge Program’s awards provide funds for Lurie Cancer Center investigators to support postdoctoral fellows in their laboratories for one year. Under the co-mentorship of these investigators and a partnering clinician, bridge fellows will design and execute a translational project targeting a specific cancer type. The ultimate goal of the fellow’s work is to propel laboratory research into investigator-initiated clinical trials.

Hidayatullah Munshi, MD, Associate Professor of Medicine-Hematology and Oncology

BET inhibitors in pancreatic cancer

Pancreatic cancers are associated with specific marks on the DNA that affect expression of genes and proteins important for cancer progression. Dr. Munshi has previously shown that BET proteins, which are ‘readers’ of these specific marks, are increased in pancreatic tumors. With support from The H Foundation, Dr. Munshi has now evaluated the effects of blocking these BET proteins in mouse models of pancreatic cancer. The results show that BET inhibitors limit some of the earliest changes that happen during pancreatic cancer development. In addition, the results show that BET inhibitors limit the development of fibrosis (‘scar-like’ tissue) that is also commonly present in human pancreatic tumors and that can affect response to current therapies. Overall, his results suggest that BET inhibitors may have a role in the treatment of pancreatic cancer.

Karla Satchell, PhD, Professor of Microbiology-Immunology

A bacterial toxin that cleaves Ras

Dr. Satchell’s project examines the basic function and translation for cancer of the bacterial toxin effector domain Ras/Rap1 specific endopeptidase (RRSP). This project determined the mechanism by which this region of the bacterial toxin inactivates the tumor causing KRas protein. The objective of the study is to test whether this bacterial toxin domain can be repurposed to inhibit breast cancer in mice. Thus, providing proof-of-concept that RRSP can be used to reduce tumor growth. Simultaneously, this study will test if Ras is a druggable target in a living organism since this is the first known inhibitor that targets all forms of Ras.

Alexander Stegh, PhD, Assistant Professor of Neurology and Medicine

Spherical nucleic acids for the precision treatment of glioblastoma

Dr. Stegh’s laboratory aims to understand and to therapeutically harness the genetic underpinnings of glioblastoma, the most malignant form of brain cancer. This project is focused on a novel nanotechnological platform, termed Spherical Nucleic Acids (SNAs). SNAs are tiny balls of nucleic acids, which have the ability to reach brain tumor sites, and to reduce the expression of brain cancer-causing genes. Dr. Stegh and his colleagues will further optimize SNA chemistry for enhanced gene inactivation in brain tumors, and will develop novel treatment regimens, combining SNAs with chemo- and radiation therapy.
Derek Wainwright, PhD, Assistant Professor of Neurological Surgery, Medicine-Hematology and Oncology, and Microbiology-Immunology

**Targeting immunosuppressive IDO1 in brain cancer: Increasing efficacy through multi-modal approaches**

The Translational Bridge Award, generously provided by The H Foundation, facilitated the rapid and robust investigation of a novel immunotherapeutic approach in immunocompetent models of malignant brain cancer. The findings of Dr. Wainwright’s investigation are currently under full review in the journal, *Science Translational Medicine*. The work has provided the necessary underlying rationale for initiating a novel Phase I/II clinical trial that is proposing to test simultaneous IDO1 inhibition, targeted radiotherapy and PD-1 blockade in newly-diagnosed glioblastoma patients. This work would not have been possible in scope or impact without funding from The H Foundation, and Dr. Wainwright is deeply grateful for the Foundation’s support.

**Additional investigator who received a Translational Bridge Award:**

Irina Balyasnikova, PhD, Associate Professor of Neurological Surgery

**Brain/genetically engineered T-cells for glioblastoma immunotherapy**

**Program Supplemental Awards**

Program Supplemental Awards are awarded to each Basic Science Program for the purpose of nurturing collaborations and utilization of core facilities that provide state-of-the-art instrumentation and expertise to accelerate projects leading to translational outcomes. We are particularly interested in fostering intra-programmatic interactions for those programs that are trying to build these connections. More information about progress on each of these new awards will be provided in next year’s stewardship report.

Marie-Pier Tetreault, PhD, Assistant Professor of Medicine-Gastroenterology and Hepatology

**Regulation of the tumor microenvironment by epithelial STAT3 signaling in esophageal cancer**

Esophageal disorders are among the most common and the most deadly ailments in the United States and throughout the world. Esophageal cancer is the eight most common cause of cancer death worldwide. Our studies will examine how a specific factor, STAT3, controls inflammation in the cells that line the esophagus and also regulates the local environment around these cells. We anticipate that the results obtained through this research will lead to new approaches for the diagnosis and treatment of esophageal cancer.

Bin Zhang, MD, PhD, Associate Professor of Medicine-Hematology and Oncology and Microbiology-Immunology

**Overcoming melanoma immunotherapy resistance**

Recent approval of the several immunotherapies by the US Food and Drug Administration marks the validation of immunotherapy for advanced metastatic melanoma patients. However, the results in clinical practice remain mixed, and the therapeutic benefit has been limited to a fraction of patients. Dr. Zhang identified one particular type of ecto-enzymes, called CD73, that allows tumors to escape killing by the immune system. This pilot project will carry out a comprehensive analysis of the tumor cell and immune cell components that are regulated by CD73, thus searching for the resistance mechanisms underlying responsiveness to immunotherapy using clinically relevant mouse models of melanoma. Dr. Zhang hopes to rapidly translate this knowledge into novel combinatorial strategies for improving current immunotherapies.
Richard Carthew, PhD, Professor of Weinberg College of Arts and Sciences and Biochemistry and Molecular Genetics

**Role of CDK9-mediated biogenesis of microRNAs in acute myeloid leukemia**

The protein CDK9 is a molecular machine within cells that is one of the therapeutic targets for certain forms of acute myeloid leukemia. Although it is commonly thought that these CDK9 inhibitors modify epigenetic marks to affect the genomes of cancer cells, recent discoveries by Dr. Carthew and his group suggest that other molecular effectors might also be involved. H Foundation funds are being used to test the hypothesis that one of the reasons CDK9 inhibitors are effective against acute myeloid leukemia is that they repress processing of very small RNAs called microRNAs that are pro-oncogenic (promoting cancer). Dr. Carthew applied anti-CDK9 therapeutics to cell culture models of acute myeloid leukemia, and is performing next-generation sequencing of small RNAs from 40 different samples. This will determine if and how microRNA levels change after treatment.

Sui Huang, MD, PhD, Associate Professor of Cell and Molecular Biology (in collaboration with Julie Kim, PhD, Susy Y. Hung Research Professor, Associate Professor of Obstetrics and Gynecology-Reproductive Science in Medicine)

**Efficacy of metarrestin on ovarian cancer using patient derived xenograft models**

Drs. Huang and Kim’s project analyzes whether a novel anti-metastasis lead compound (metarrestin) would have efficacy against ovarian cancer growth and metastasis. Metarrestin inhibits ovarian cancer cell invasion in a tissue culture dish, and will now be tested against human tumors that have been explanted to mice (i.e., patient derived xenograft or PDX models). These experiments will determine whether metarrestin is effective against ovarian cancer in a physiologically relevant system.

Joshua N. Leonard, PhD, Associate Professor, Chemical and Biological Engineering; Robert R. McCormick School of Engineering and Applied Science

Milan Mrksich, PhD, Professor of McCormick School of Engineering/Cell and Molecular Biology

**Programmable cell-based therapies that sense and modulate the tumor microenvironment**

Engineered cell-based therapies represent a promising frontier in cancer immunotherapy. However, achieving clinical benefits in a broad range of cancers and patients will require new approaches for rendering tumors amenable to immune control. To meet this need, Drs. Leonard and Mrksich will develop synthetic biology technologies for constructing customized cell-based therapies that deliver therapeutic payloads specifically to tumors, improving both the safety and efficacy of cancer immunotherapy.

Additional investigators who received Program Supplemental Awards include:

Atique Ahmed, PhD, Assistant Professor of Neurological Surgery

**Investigating the role of calcium signaling networks promoting therapeutic resistant in brain cancer**

Vladimir Gelfand, PhD, Leslie B. Arey Professor of Cell, Molecular, and Anatomical Sciences, Professor of Cell and Molecular Biology

**Application of super-resolution microscopy for the analysis of vimentin intermediate filament dynamics during cell migration**

Stephen Miller, PhD, Judy Gugenheim Research Professor of Microbiology-Immunology, Professor of Microbiology-Immunology and Dermatology

**Identification of neoantigens and tumor infiltrating lymphocytes of urothelial carcinoma**
Christian Stehlik, PhD, John P. Gallagher Research Professor of Rheumatology, Professor of Medicine-Rheumatology

A novel pre-clinical mouse model for choriocarcinoma

Chyung-Ru Wang, PhD, Professor of Microbiology-Immunology

The role of RNA methylation in epigenetic regulation of T-cell fate and function

John Crispino, PhD, MBA, Robert I. Lurie, MD, and Lora S. Lurie Professor, Professor of Medicine-Hematology and Oncology and Biochemistry and Molecular Genetics

The Role of CHAF1B in normal and malignant hematopoiesis

Dileep Varma, PhD, Assistant Professor of Cell and Molecular Biology

Investigating the role of improper kinetochore microtubule attachments in myeloid leukemia

Xiaomin Bao, PhD, Assistant Professor of Weinberg College of Arts and Sciences and Dermatology

Characterizing SEC and KMT2D in squamous cell carcinoma progression

Navdeep Chandel, PhD, David W. Cugell, MD, Professor, Professor of Medicine-Pulmonary and Critical Care and Cell and Molecular Biology

Therapeutic targeting of SOD1 for lung cancer

Curt Horvath, PhD, Professor of Medicine-Hematology and Oncology; Microbiology-Immunology; and Weinberg College of Arts and Sciences

High throughput screen for interferon modulators in cancer

Thomas O’Halloran, PhD, Professor of Weinberg College of Arts and Sciences and Medicine-Endocrinology

Ming Zhao, PhD, Associate Professor of Medicine-Cardiology

New cancer research technology award

Other Support 2016-2017

The H Foundation Basic Science Symposium

Funds from The H Foundation were used for the Basic Science Symposium, held on Northwestern’s Chicago campus on April 21, 2017. The symposium centered on Cancer Metabolism. The keynote lecture, “The VHL Tumor Suppressor: Insights into Oxygen Sensing, Cancer Metabolism, and Drugging the Undruggable,” was given by William Kaelin, Jr, MD, from Harvard University. More than 180 guests attended the symposium.

Oncofertility Conference

The H Foundation funds also support the Oncofertility Conference, hosted by the Oncofertility Consortium at Northwestern University. In its 11th year, this annual conference was held on November 14–16, 2017, at Northwestern’s Prentice Women’s Hospital. The conference annually brings together more than 250 international leaders in this exciting field and provides cutting-edge research updates on fertility preservation for cancer patients.

Educational Enrichment Activities for Basic Science Programs

This past year, The H Foundation funds also furthered various programmatic activities including mini-symposia, lectures, and seminars that foster recurring collaborations and interactions among scientists. These collaborative groups enable faculty members in the basic sciences to come together and share their research.
Thank You for Your Commitment

Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University are deeply grateful for The H Foundation’s impactful partnership in funding and accelerating basic science research. Through your steadfast generosity, scientists within the Lurie Cancer Center can continue their scientific collaborations to develop innovative approaches to treat and prevent cancer.

If you would like more information regarding this report or the Lurie Cancer Center, please contact:

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