Seed Grants for New Ideas in Cancer Research

2016 ANNUAL REPORT

UNC LINEBERGER

For UNC Lineberger physicians and scientists, seed grants not only yield early results, but also help develop the ideas that grow into large, federally funded projects aimed at transformative breakthroughs in patient care.

Over the past few decades, we have made remarkable progress towards finding a cure, but solving a problem as intractable as cancer will require a willingness to take on risks and the kind of big-picture thinking that fuels medical breakthroughs. The Seed Grant Program at UNC Lineberger Comprehensive Cancer Center gives talented researchers the opportunity to find answers to some of cancer's biggest challenges and develop promising new concepts for basic cancer research, clinical care, prevention, early detection and survivorship. An increasingly competitive funding environment has magnified the need for and impact of investments in this type of innovative research.

Funded by private support and state funds, seed grants have helped UNC become a top 10 institution for research funding.

A Catalyst for Great Ideas

The United States is a global leader in biomedical research, but our leadership depends on federal investment, primarily through the National Institutes of Health (NIH) and the National Cancer Institute (NCI). However, federal funding is in jeopardy. While the number of applicants for NCI grants has increased by 30 percent since 1998, the number of awards has remained the same. Fewer than one in seven researchers who apply for a research grant from the NCI will receive one—a historic low.

In making funding decisions, the NIH and NCI evaluate the significance of the research, approach and level of innovation. These criteria, coupled with the competitive award process, favor applicants who can show experience and preliminary data. Being able to discuss studies, data or experience pertinent to the application greatly improves the proposed project's likelihood of success, especially for young cancer investigators.

Seed grants give UNC Lineberger scientists an advantage in this competitive landscape. For the past 28 years, the program has maintained a steadfast focus on three guiding priorities:

- Accelerating cancer research by funding promising, novel ideas with no other source of funding;
- Providing venture capital to gather vital preliminary data to help secure major external funding for program implementation, human trials and further research; and
- Ensuring young, bright cancer researchers have the opportunity to establish a history of success, keeping them engaged and building a future in cancer research.

‘Like no other place in the world’
UNC Lineberger jumpstarts career of cancer researcher

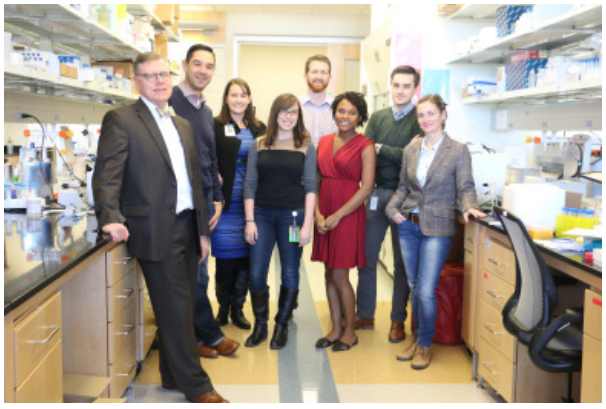
When Shawn Hingtgen, PhD, was finishing his postdoctoral training in Boston and considering where to start his career in cancer drug delivery research, the University of North Carolina at Chapel Hill stood out for its academic rigor, the strength of its faculty and its collaborative environment.

He and his wife were also drawn to Chapel Hill because they sought a community that was away from big city hustle and bustle and where their children could grow and play – and they liked the idea of not having to shovel snow. “I moved to UNC-Chapel Hill because the expertise and infrastructure matched what we needed like no other place in the world,” said Hingtgen, who is now a UNC Lineberger member and assistant professor in the UNC Eshelman School of Pharmacy. “It’s a place doing incredible research in a community that is fantastic for raising a family.”

Hingtgen is now working to advance a promising potential brain cancer treatment approach at UNC Lineberger. His team (pictured below) has shown they can turn skin cells into cancer-hunting stem cells that help destroy brain cancer tumors called glioblastomas. They advanced their approach to drug delivery in animal models, showing that their cancer-hunting stem cells home to brain cancer cells, and can dramatically increase survival. They have published their findings in two prominent journals, and Hingtgen and his team are now aggressively pursuing a first-in-human clinical trial for their approach.

“The key is that brain stem cells chase cancer, and we’re turning them loose on glioblastomas, a particularly deadly brain cancer tumor,” Hingtgen said.

It was a seed grant from UNC Lineberger that started it all. “Seed grants are the catalyst for innovation and discovery,” Hingtgen explained. “When you first start a lab, you are trying to find your way. You are testing different crazy ideas to see what works. The main obstacle is time. NIH and other government funding agencies are slow and won’t support this early stage work because it’s too risky. Seed grants fill this critical gap.”



Hingtgen received a University Cancer Research Fund seed grant after he arrived at UNC in March 2012. With that funding, Hingtgen and his team generated preliminary data that led to multiple awards: $1.2 million from the National Institutes of Health, $750,000 from the Eshelman Institute for Innovation, and $300,000 in state funding. Now, Hingtgen is actively pursuing a first-in-human clinical trial for testing the use of stem cells a means to deliver drugs to brain cancer tumors.

“We had this crazy idea of using skin cells as a new personalized therapy for cancer,” Hingtgen said. “A seed grant from UNC Lineberger jump-started everything for our group.” The cancer center’s cutting-edge facilities and technology help with all aspects of his research, he said, and collaborations with researchers across disciplines have been instrumental. “Cancer is not just one disease, and no one person will find a cure alone,” he said. “Having a strong team will give us a fighting chance.”

Hingtgen and his wife Anne now have a family of four. Their daughter Elliott is in first grade, and their son Bryson is in preschool. They love the outdoors. They spend their summers at the pool and the beach, and, though they don’t want to shovel snow, they do take trips to the mountains in the winter for snow sports. “We are really enjoying all North Carolina has to offer,” he said.

Private Support Fuels Progress

We are grateful to the many generous donors who share UNC Lineberger's commitment to investing in early stage research. Since the inception of the Seed Grant Program in 1986, donors have contributed more than $7 million and supported over 300 seed grants. UNC Lineberger currently has 42 permanently endowed, named seed grant funds:

Dr. and Mrs. Gerald Arney Fund for Liver Cancer Research
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Emily Bright Seed Grant Fund for New Ideas in Ovarian Cancer Research
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A concern for others drives a family's support of ovarian cancer research

When Susan Lambeth of Burlington was diagnosed with advanced ovarian cancer, she and her family were stunned. "Susan was very healthy, she took good care of herself, she held a black belt in taekwondo, and she just had her annual physical," said her husband Tom. "There was nothing to suggest she had ovarian cancer."

Ovarian cancer's symptoms are easy to miss – even in the doctor's office – and there are no reliably accurate screening tests. Consequently, only one in five ovarian cancers are diagnosed in the earliest, and most treatable, stage. Susan, true to her character, was determined to do her part to close the knowledge gap about ovarian cancer, even while she was in treatment. She spoke with women, as well as with medical students, to raise awareness about the disease, its symptoms and the need to act on them.

Sadly, 35 months after her diagnosis, Susan died from ovarian cancer in February 2009. She was 48.

During their discussions on how to best honor Susan's legacy, Tom, their sons, David and Steven, and Susan's parents and her siblings agreed that she would want to support ovarian cancer research and patient services at UNC Lineberger. Although Susan was not treated at UNC, her family had a deep connection to Carolina. Tom and Susan met at UNC while they were undergraduates, they and their sons graduated from UNC, and Tom and David earned law degrees from UNC.

The family established the Susan Hoke Lambeth Endowment Fund for New Ideas in Ovarian Cancer Research to support early stage investigations into the disease and its causes. Their intent is that the research will lead to better methods to detect ovarian cancer more accurately and earlier than are currently available.

They also provided funds for patient support services. Tom said Susan was disheartened by the financial burden cancer can place on a family and she wanted to address that issue. A consultation room in the Patient Family Resource Center named in Susan's memory is a fitting testament to her concern for others. "Susan saw the impact cancer treatments can have on a family," said Tom. "It is hard enough mentally, emotionally and physically to fight cancer. It is even worse if you have to worry about not being able to afford your medicine or the gasoline to drive to the doctors in Chapel Hill."

Tom is encouraged that both the state and federal governments are making investments in cancer research. As a public servant – he has served as a district court judge for the 15A Judicial Court in Alamance County since 2007 – he appreciates the important role the government plays in a community's well-being.

"I am extremely thrilled that the federal government made the commitment it has through the Cancer Moonshot Initiative, just as I was when our state government made the investment years ago in the University Cancer Research Fund to help Lineberger become a national leader in cancer care and research," said Tom. "However, we need the private sector, too. I hope people will be inspired to join and make a personal commitment to support cancer research, cancer detection and cancer prevention."

2015-2016 Seed Grant Awards

UNC Lineberger awards seed grants in three funding tiers across three research program areas:

- Clinical/Translational, which supports early-stage research that can translate basic science discovery into clinical applications
- Basic Science, which supports research to identify cancer-driving mechanisms in cells and potential drug targets
- Population Science, which supports innovative research in cancer prevention, early detection, health promotion, epidemiology and survivorship

AWARD RECIPIENTS

Emma H. Allott, PhD - $50,000
Molecular profiling of prostate cancer to understand mechanisms contributing to racial disparities (Population Science - Tier 1)

Laura Wells Bowers, PhD, RD - $50,000
Obesity-associated chemotherapy resistance in triple-negative breast cancer: the role of leptin-induced tumor-initiating cell enrichment (Clinical/ Translational - Tier 1)

Timothy Gershon, MD, PhD - $50,000
Developing KIF11 inhibition as a novel medulloblastoma therapy in mice (Basic Science/ Translational - Tier 1)

David Lalush, PhD - $50,000
Utility of PET/MR in surgical planning for breast cancer treated with neoadjuvant chemotherapy (Clincial/ Translational - Tier 1)

Zibo Li, PhD - $50,000
Development of 18F-PET probes to image the IDO pathway for immuno-oncology clinical research (Basic Science - Tier 1)

Stephen I. Park, MD - $50,000
Elucidating mechanisms of drug resistance to PI3K-inhibition in lymphoma (Clinical/ Translational - Tier 1)

Melanie Priestman, PhD - $50,000
Monitoring the Proteasome's catalytic signature in hematological malignancies (Basic Science - Tier 1)

Julian Rosenman, PhD - $50,000
Reconstruction of a 3D colonic image from colonoscopy video frames (Clinical/ Translational - Tier 1)

Jennifer Smith, PhD, MPH - $50,000
Validation of a novel low-cost colposcope to improve cervical cancer screening (Population Science - Tier 1)

Timothy Stuhlmiller, PhD - $50,000
High-throughput interrogation of the kinome and epigenome for adaptive bypass targeting and the discovery of synergistic combination therapies (Basic Science - Tier 1)

William A. Wood, MD, MPH - $50,000
Impact of geographic region, treating facility, and physician network characteristics on outcomes for patients with acute leukemia and multiple myeloma in North Carolina (Population Science - Tier 2)

Zhanhong Wu, PhD - $50,000
Detection of pancreatic cancer metastasis using PET agent targeting neurotensin receptor (Basic/ Translational - Tier 1)

Jing Zhang, PhD - $50,000
Identification of ZHX2 as a VHL substrate in ccRCC to promote tumorigenesis through regulation of NF-kB (Basic Science - Tier 1)

Award Abstracts

Clinical/Translational Recipients

Laura Wells Bowers, PhD, RD
Obesity-Associated Chemotherapy Resistance in Triple-Negative Breast Cancer: The Role of Leptin-Induced Tumor-Initiating Cell Enrichment

UNC Lineberger researchers are zeroing in on what they believe is a key link between obesity and drug resistance in people with triple-negative breast cancer, a highly aggressive breast cancer type.

Despite the evolution of targeted treatments that can be used in other cancers, triple negative breast cancer is still primarily treated with chemotherapy due to a lack of specific molecular targets that exist in these tumors. Drug resistance is likely a major contributor to poorer outcomes observed in obese patients with this breast cancer type. Consequently, greater understanding of the mechanisms that contribute to resistance is imperative to improving prognoses in this population. Obesity has been correlated with increased recurrence and lower survival rates in all breast cancer subtypes, including triple negative breast cancer. In addition, obese patients do not respond as well as women of a normal weight to cytotoxic chemotherapy.

Researchers have identified a key factor in the link between obesity and chemoresistance in triple negative breast cancer: The enrichment of tumor-initiating cells, which are cancer cells sometimes called “cancer stem cells” that are believed to be the cells that initiate and sustain cancer. UNC Lineberger researchers have demonstrated that obesity promotes tumor-initiating cell characteristics in pre-clinical models of triple-negative breast cancer, and these tumor-initiating cells are thought to be capable of evading the cytotoxic effects of chemotherapy.

In addition, studies from other labs have suggested that signaling of a hormone called leptin, which helps to tamper hunger when the body’s fat stores are elevated, is the primary mediator of obesity-induced tumor-initiating cell enrichment. Elevated serum leptin levels and breast tumor leptin receptor expression have been independently linked to a worse breast cancer prognosis.

UNC Linebeger researchers will test whether obesity-associated leptin signaling contributes to chemotherapy resistance in triple negative breast cancer by enriching tumor-initiating cells, and whether a reduction in leptin signaling improves chemotherapy response in a pre-clinical model of obesity and triple-negative breast cancer.

Timothy Gershon, MD, PhD
Developing KIF11 inhibition as a novel medulloblastoma therapy in mice

New treatment strategies are needed for medulloblastoma, the most common malignant brain tumor in children. Current therapy with radiation and chemotherapy, while often effective at treating the tumor, can cause unacceptable long-term brain injury. UNC Lineberger researchers have

developed a new formulation for a drug that they believe can be effective against this tumor type, and that can be used without disrupting brain function.

This new treatment takes advantage of a particular characteristic of medulloblastoma: that cells of this cancer type undergo a lot of division, which makes these cells susceptible to DNA damage. Because of this, researchers believe drugs designed to damage cells during cell division would be particularly effective against this brain cancer type. However, these agents are particularly toxic to the brain, and the clinically tolerable drugs that use this mechanism do not adequately penetrate the barrier between the blood stream and the brain.

UNC Lineberger researchers are investigating an alternative way to target cell division to kill brain cancer cells. This approach would inhibit kinesin, a type of protein important to cell division. Researchers say the mitotic kinesin KIF11 can be targeted without disrupting brain function.

Researchers have developed a formulation of a small-molecule KIF11 inhibitor SB743921 solubilized in polyethylene glycol, which crosses the blood brain barrier when injected in mice. In preliminary studies, they have found that a single dose of this new formulation causes mitotic arrest, DNA damage and apoptosis in medulloblastomas.

Researchers propose to develop a regimen of this novel formulation that is tolerated in mice and to test this regimen in transgenic mice that develop spontaneous medulloblastoma. The goal of these pilot studies is to determine whether this investigational formulation PEG-SB exerts a clinically relevant antitumor effect as a single agent. If so, researchers will plan future studies on how KIF11 inhibition may be integrated into conventional therapy, potentially allowing for reduced radiation and improved outcomes for patients with medulloblastoma.

David Lalush, PhD - $50,000
Utility of PET/MR in Surgical Planning for Breast Cancer Treated with Neoadjuvant Chemotherapy

For patients with operable breast cancer, attacking cancer with chemotherapy prior to surgery has increased the proportion of women who are candidates for breast-conserving surgery versus mastectomy with no increase in local recurrence rate. Pre-treatment chemotherapy has also been shown to improve the link between pathologic complete response and long-term outcomes. For physicians who are evaluating the success of pre-surgery chemotherapy in order to assess patients' surgical options, it is critical to utilize all available information in order to optimize efficacy and reduce the likelihood of local recurrence and the need for repeated surgical intervention.

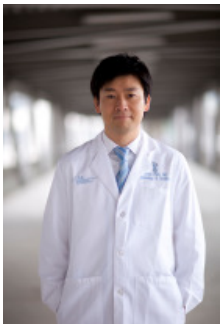
Both PET imaging and MRI have been used separately in the assessment of response to pre-treatment therapy; a logical next step is to evaluate the utility of simultaneous PET and MRI for assessment of treatment response, the impact on surgical planning, and the correlation with pathologic outcomes.

UNC Lineberger researchers plan to study how the use of simultaneous PET-MRI technology can contribute to surgical planning. This project will examine the ability of qualitative and quantitative measures derived from simultaneous 18F-FDG-PET and MRI to contribute to these decisions.
The project will enroll 25 subjects with operable breast cancer who will receive pre-treatment

chemotherapy followed by surgery. PET-MRI scans will be taken at before and after treatment, and evaluated for changes in standardized uptake values from PET as well as tumor size and perfusion functional measures from MRI. Post-surgery histology will be used to classify patients based on response to therapy.

Researchers plan to develop technology that would allow the PET-MRI scanner to enable clinical-equivalent breast MRI. They will also examine correlations between pre-treatment and post-treatment imaging metrics and response groupings of subjects based on surgery type, response to therapy, and residual tumor burden. And finally, they will develop an optimal quantitative metric combined from PET and MRI results, and assess its ability to classify patients based on surgical management and pathological outcomes.

Steven I. Park MD
Elucidating the Mechanisms of Resistance to PI3K Inhibition in Lymphoma

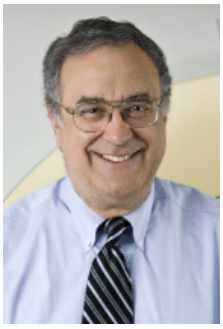


Despite the promise of novel targeted therapies in follicular lymphoma, the emergence of resistance presents a major obstacle to the sustained clinical benefit of these new treatments. UNC Lineberger researchers are seeking to further understand the mechanism of resistance in response to targeted therapy in this disease. They plan to look into the cellular machinery to see the mechanisms involved in resistance.

Specifically, they will analyze the genome, transcriptome, and kinome signatures before and after treatment to identify compensatory biological pathways responsible for resistance to targeted inhibition against the PI3K pathway using in vitro and in vivo lymphoma models. They will also characterize the mechanisms of innate as well as acquired drug resistance in tumor samples obtained from patients treated with idelalisib, a PI3Kδ inhibitor.

The successful outcome of this research will lead to rational design of highly potent drug combinations in follicular lymphoma to overcome drug resistance.

Julian G. Rosenman, MD, PhD
Reconstruction of a 3D colonic image from colonoscopy video frames



Screening colonoscopy now has a high enough detection rate of pre-cancerous lesions to have an impact on long-term survival for patients with colon cancer. Despite this success, colonoscopy video has some significant limitations. For example, video is not a good format for review, and it doesn't permit the physician to get a global view of the colon. As a result, it is almost impossible to determine which surface of the colon, if any, was not visualized or missed during the procedure. Finally, a visual comparison between serial colonoscopies or colonoscopy and CT scanning is not possible because video cannot be directly registered with another video or with a 3D image.

UNC Linebeger researchers believe the solution is to extract an accurate, fully interactive 3D image

of the colon from the thousands of video frames. Such an image would allow the clinician to see the entire colon at a glance as well as manipulate and analyze the image.

A UNC research team has recently succeeded in creating a 3D image for endoscopy of the human pharynx, and has proposed to extend and modify those same methods for use in colonoscopy. As a start, they will train a doctorate-level graduate student to learn the methodology from the pharynx team, and apply it to colonoscopy videos so as to prove its feasibility before beginning a full-scale project multi-year colonoscopy project.

Basic Science Recipients

Zibo Li, PhD
Development of 18F-PET probes to image the IDO pathway for immuno-oncology clinical research

Promising drugs have been recently approved by the U.S. Food and Drug Administration that work by unleashing the body's immune system against cancer. However, not every patient will respond to these expensive treatments, known as PD-1/PD-L1 pathway inhibitors, that sometimes must be administered across a patient's lifetime. In contrast to other drugs, whose use is contingent upon a companion diagnostic or biomarker, there are no reliable biomarkers for these immune-oncology drugs. Clearly, there is an urgent need to identify predictive biomarkers of response to these treatments.

UNC Lineberger researchers plan to develop a probe that's visible using position emmision tomography (PET) imaging. They plan to use this probe to mark tumors that contain a biomarker that they believe accurately indicates whether a patient is likely to respond to immunotherapy drugs.

Researchers are zeroing in on indoleamine2,3-dioxygenase (IDO1) as the potential biomarker for response to immunotherapy drugs. Upregulation of IDO1 significantly correlates with the number of various immune cells called T-cells in tumor tissues in melanoma and other cancers, suggesting that IDO expression is linked with effective and ineffective, or "exhausted," immune response in cancer.

PET imaging offers a means of non-invasively and reliably correlating real-time expression of this marker IDO1 in all tumor tissues with treatment outcome. UNC Lineberger researchers hypothesize that IDO-specific PET probes hold great potential to "mark" tumors bearing tumor-infiltrating immune cells, which is an absolute requirement for response to PD-1/PD-L1 pathway inhibitors. Clinically available PET tracers, 18F-fluorodeoxyglucose (FDG), and 18F-fluorothymidine, are nonspecific, whereas clinically available IDO PET tracers are 11C-based, and therefore short-lived and unavailable for widespread clinical use.

In this proposal, researchers aim to synthesize and evaluate novel 18F labeled PET agents with high IDO affinity and specificity, which could be used as a non-invasive predictive method to select patient to anti-PD-1 mAb-based therapies.

Melanie Priestman, PhD

Monitoring the Proteasome's Catalytic Signature in Hematological Malignancies

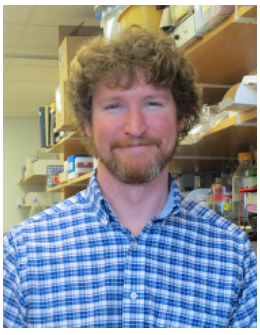
It is expected that more than 150,000 people will be diagnosed with any type of blood cancer this year, joining more than 1 million people living in the United States with these diseases. Although there has been significant progress in recent years in the treatment of hematological cancers with combination therapies, the five-year survival rates for non-Hodgkin lymphoma, leukemia and myeloma are still unacceptable at 69 percent, 57 percent, and 45 percent, respectively.

Within the last 10 years, the U.S. Food and Drug Administration has approved two new drugs carfilzomib and bortezomib, both proteasome inhibitors, for the treatment of multiple myeloma. In addition, these inhibitors are in clinical trials for treatment of leukemia, B-cell lymphoma, non-Hodgkin lymphoma and mantel cell lymphoma. Proteasome inhibitors have demonstrated utility for the treatment of blood cancers, yet there is a lack of a diagnostic that can tell in advance which patients will respond versus those that are intrinsically resistant or will acquired resistance during therapy. Development of tools that can be used to predict responses to proteasome inhibitors are critical.

UNC Lineberger researchers recently described a set of fluorescent proteasome peptides that will allow, for the first time, simultaneous monitoring of all three activities of the proteasome. Preliminary studies suggest that the ratios of these activities, defined here as the proteasome's "catalytic signature," are specific for each cell type and may be predictive of sensitivity to proteasome inhibitors. UNC Lineberger researchers will explore the feasibility of using these sensors to predict which subtypes of hematological malignancies are sensitive to proteasome inhibitors and which patients are resistant or will develop resistance to therapy.

Timothy J. Stuhlmiller, PhD

High-throughput interrogation of the kinome and epigenome for adaptive bypass targeting and the discovery of synergistic combination therapies



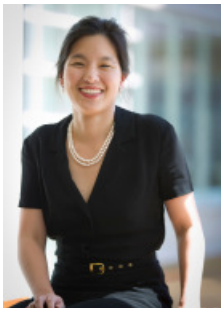
The discovery of the oncogenic drivers for many cancer types has fueled development of a vast array of small-molecule cancer drugs. However, these targeted therapies, which are designed to target specific molecules in cells that are malfunctioning in cancer, only benefit a subset of patients. Scientists know that cancer cells can find ways to work around these treatments through adaptive resistance. Tumors rewire their signaling networks to upregulate alternative, compensatory signals called kinases to bypass the effects of these drugs. Targeting these adaptive kinases can affect tumor cell growth, but researchers have found that selecting the right combination of drugs is a significant clinical challenge.

UNC Lineberger researchers have discovered a potential means of suppressing multiple pathways of resistance in cancer cells. Specifically, they found that targeting the epigenetic machinery – which is the way DNA is structured, and therefore, the way genes are turned on and off - involved in the upregulation of adaptive kinases could suppress multiple compensatory pathways at a transcriptional

level, generating a stable inhibition of growth. Researchers proposed developing a means of screening a high volume of drugs that they believe could work through this mechanism. They have proposed establishing a high-throughput cell viability screening platform of clinically-relevant kinase inhibitors and epigenetic enzyme-targeting small molecules for the discovery of synergistic combination therapies for cancer.

Researchers will draw upon a library of 160 compounds for this study. They will investigate how these investigational drugs impact compensatory kinase signaling and epigenetic regulatory networks. To do this, they will use two different lines of cancer cells that either have a mutated gene for PI3K, or that are normal. Screening these cell lines in parallel in the presence or absence of PI3K inhibitor will provide a comprehensive analysis of differential drug sensitivity imparted by this common genetic alteration. Establishing this platform will create a unique resource for therapeutic discovery at UNC that's applicable to virtually any cancer type. Identifying synergistic combination therapies provides a clear direction for extramural funding applications and presents preclinical rationale for clinical trial design.

Zhanhong Wu, PhD, and Jen Jen Yeh, MD
Detection of pancreatic cancer metastasis using PET agent targeting neurotensin receptor



Pancreatic cancer is one of the deadliest human malignancies, with an extremely poor five-year survival rate of 8 percent.

Although there has been some improvement in the strategies used to diagnose and treat pancreatic cancer, the prognosis for this disease is still poor due to a lack of efficient methods to detect pancreatic carcinoma. In addition, it is difficult to clearly differentiaite pancreatic cancer from benign pancreatic lesions, and the disease is very aggressive.

There is clearly a need to develop new diagnostic and therapeutic methods targeting both primary and metastatic pancreatic cancer.

Accumulating evidence suggests that cell surface receptors for neurotensin play key roles in pancreatic adenocarcinoma growth and survival. UNC Linebergers have done preliminary research that suggests that well-differentiated human pancreatic carcinomas have a high density of NTR-1 expression as compared with expression in normal human pancreas and in chronic pancreatitis, as well as in endocrine pancreatic tumors. Clearly, these NTR-1 receptors could potentially become important components of pancreatic cancer diagnosis and treatment.

UNC Lineberger researchers are planning to evaluate their lead NTR-1 targeted agent in detecting small pancreatic cancer metastasis. The success of this novel imaging approach could not only lead to novel imaging approach for the detection of pancreatic cancer metastasis, but also help them to better predict which patients and individual tumors are likely to respond to novel interventions targeting NTR-1 in the future.

Jing Zhang, PhD
Identification of ZHX2 as a VHL substrate in ccRCC to promote tumorigenesis through regulation of NF-kB

The most common form of kidney cancer, clear cell renal cell carcinoma, is resistant to a variety of cancer therapies and is highly lethal. A hallmark of this cancer is a mutation in the von Hippel Lindau tumor suppressor gene. In kidney cancer cases that lack functional copies of this gene, UNC Lineberger researchers have discovered a new biological mechanism that they believe helps to drive the disease. Their work could help better explain the role of this genetic defect in the disease, and could also provide a new target for future therapeutics.

Specifically, UNC Lineberger researchers have preliminary data showing that the protein ZHX2 helps to promote renal cancer cell oncogenic characteristics in von Hippel Lindau gene-deficient renal cancer by regulation of oncogenic NF-kB signaling genes, potentially through the interaction of another molecule called RelA/p65. They have hypothesized that the interaction of ZHX2 and this signaling pathway is critical to driving cancer in the absence of the von Hippel Lindau tumor suppressor.

With this grant, researchers are planning to characterize how the protein ZHX2 is normally regulated by the protein encoded for by the von Hippel Lindau gene, and determine the oncogenic significance of ZHX2 upregulation in VHL-deficient renal cancer with cancer cell lines, in human tumor tissue grated into laboratory models, and in patient tissue. They are also planning to find the functional significance of ZHX2-RelA/p65 signaling axis. And finally, they plan to implement integrated analyses of ChIP-Seq and gene expression to determine ZHX2-RelA/p65 genomic overlap and their potential inter-dependence.

Successful completion of this proposal would establish a critical mechanistic missing link between the loss of the von Hippel Lindau protein and hyperactivation of NF-kB signaling in renal cancer, and would provide significant new molecular insight into oncogenic mechanisms associated with this disease, as well as the potential targets for new therapies.

Population Science Recipients

Emma H. Allott, PhD
Molecular profiling of prostate cancer to understand mechanisms contributing to racial disparities

African Americans have the highest prostate cancer incidence in the United States, and a mortality rate that's more than double that of whites for this disease.

Socioeconomic status and health care access issues are known to contribute to this startling disparity in prostate cancer incidence and mortality, but these factors do not completely explain the racial

differences. And although there are biologic factors known to contribute to the problem in prostate cancer, they are not well understood.

UNC Lineberger researchers are planning to better understand how biologic factors contribute to racial disparities in prostate cancer using a multi-disciplinary research approach. Their project will integrate epidemiologic, clinical and tumor biomarker data, given that the mechanisms contributing to prostate cancer racial disparities span each of these research disciplines. For their study, they plan to draw upon the Health Registry/Cancer Survivorship Cohort, a large-scale study launched with support from the University Cancer Research Fund to gather information about patients with cancer and other diseases.

Researchers will examine patterns of gene expression in prostate cancer tumor samples gathered through the Health Registry/Cancer Survivorship Cohort, drawing upon UNC's particular strength in tumor profiling. To do this, researchers have identified 147 prostate cancer patients who underwent radical prostatectomy at UNC and participated in the Health Registry/Cancer Survivorship Cohort. They plan to use samples of prostate cancer tissue and healthy tissue from these patients to test whether they had a specific gene signature indicating activity of the androgen receptor, a receptor that's known to play a key role in prostate cancer development and progression. Using gene expression data drawn from these samples, they plan to investigate whether there are differences in androgen receptor activity between African American and white patients.

This work will establish the feasibility of building a molecular epidemiology prostate cancer cohort at UNC. In addition, researchers will investigate androgen receptor activity as a potential biologic pathway that could targeted alongside other treatments and interventions to help reduce racial disparities, and to improve prostate cancer-specific outcomes for all men.

Jennifer Smith, PhD, MPH - $50,000
Validation of a novel low-cost colposcope to improve cervical cancer screening

Invasive cervical cancer affects 500,000 women worldwide each year, resulting in more than 270,000 deaths, even though cervical cancer is highly preventable through early detection and treatment of precancerous lesions.

Current primary screening methods require confirmation of the presence of cancer through a procedure called a colposcopic evaluation. The evaluation is important to avoid overtreatment of clinically insignificant low-grade cervical lesions. However, conventional colposcopy relies on the availability of relatively expensive machines and highly trained colposcopists, creating bottlenecks in low-resource and remote regions of the United States and globally.

UNC Lineberger researchers have proposed to collect pilot data on the clinical validity of a newly developed trans-vaginal digital colposcope to improve cervical cancer screening programs in low-resource settings.

The new colposcope can be constructed using relatively low-cost materials, and collects high-quality digital images that can be easily transmitted for external colposcopic review.

The pilot project is designed to collect preliminary validation data on the clinical performance of this

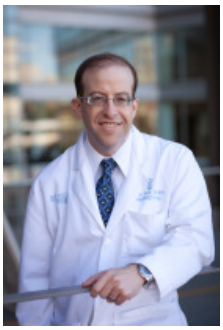
device. Researchers plan to assess the scope of Kenyan colposcopist readings of previously collected paired images obtained by the newly developed trans-vaginal digital coposcope and by a conventional colposcope for cases of different, known grades of histologically confirmed pathology. They also plan to assess the scope's clinical performance (sensitivity, specificity, positive predictive value, and negative predictive value) compared to conventional colposcopy for the detection of high-grade precancerous lesions (CIN2+) in a population of 200 high-risk women in Mombasa, Kenya.

The proposed pilot study will produce preliminary data for use in the development of a proposal for a large-scale validation study.

Aim 2: To assess TVDC clinical performance (sensitivity, specificity, positive predictive value, and negative predictive value) compared to conventional colposcopy for the detection of high-grade precancerous lesions (CIN2+) in a population of 200 high-risk women in Mombasa, Kenya.

The proposed pilot study will produce preliminary data for use in the development of an R01 proposal for a large validation study of the TVDC.

William A. Wood, MD, MPH
Impact of Geographic Region, Treating Facility, and Physician Network Characteristics on Outcomes for Patients with Acute Leukemia and Multiple Myeloma in North Carolina



For patients with blood cancer, disparities in mortality are seen along sociodemographic lines, but the underlying cause of these differences remains unclear. UNC Lineberger researchers are working to get to the bottom of why these disparities exist for patients with two types of blood cancer in North Carolina.

Recently, UNC Lineberger researchers found that survival for patients with acute myeloid leukemia in North Carolina varies according to region. Specifically, they found that patients who lived in three of nine Area Health Education Center regions had a higher risk of death even after researchers controlled for other socioeconomic variables. What was missing from their analysis was information about the health care providers caring for the patients.

Social network analysis is an innovative technique that can be employed to understand how providers work together to care for complex patients. UNC Lineberger researchers plan to leverage the UNC Lineberger Integrated Cancer Information and Surveillance System to characterize survival disparities for acute leukemia and multiple myeloma in North Carolina by geographic region and type of treating facility. They also plan to apply social network analysis methods to identify physician networks and explore how features of those networks affect outcomes.

This project will be the first in the nation to apply social network analysis to the study of disparities for any hematologic malignancy. Information from this study has the potential to establish social network analysis as an important methodology in disparities research and to improve outcomes for patients in North Carolina by informing statewide referral policies.

Seed Grant Award Process

The Seed Grant program is administered by senior cancer center leaders who review and critique applications. At least two peer scientific experts evaluate and score each proposal, a NIH-style study section evaluates the top-scoring proposals, and a scientific advisory board identifies top priorities for funding.

Seed grants are significant—and highly competitive—awards for our faculty researchers. Each year, we receive far more promising proposals than we are able to fund.

In 2015, with input from UNC Lineberger faculty and internal and external advisors, we revised the existing program to add two tiers of award that are larger in scope than those previously offered. The "regular" seed grants became Tier 1 Pilot Grants ($50,000); to these were added Tier 2 Stimulus Grants ($100,000-$200,000) and Tier 3 Multi-Project Grants (up to $400,000). We also added targeted request for applications to the mix, to stimulate proposals in new, high-priority areas.

With award recipients from a wide variety of departments and disciplines, the Seed Grant Program reflects one of UNC Lineberger's greatest strengths—multidisciplinary depth. UNC Lineberger is the largest research entity at the University of North Carolina, with approximately 300 scientists from 40 departments, including all five health affairs schools (medicine, public health, dentistry, nursing and pharmacy) as well as the College of Arts and Sciences. The Seed Grant Program encourages collaboration across campus as our faculty members work to combat cancer from all directions.

If you would like to learn more about the Seed Grant Program, please contact the UNC Lineberger Office of Development and Communications at lcccgiving@unc.edu or (919) 966-5905.

UNC Lineberger Comprehensive Cancer Center brings together some of the most exceptional physicians and scientists in the country to investigate and improve the prevention, early detection and treatment of cancer. One of only 47 NCI-designated comprehensive cancer centers in the nation, UNC Lineberger works to understand the causes of cancer at the genetic and environmental levels, conduct groundbreaking laboratory research and translate findings into pioneering and innovative clinical trials.

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