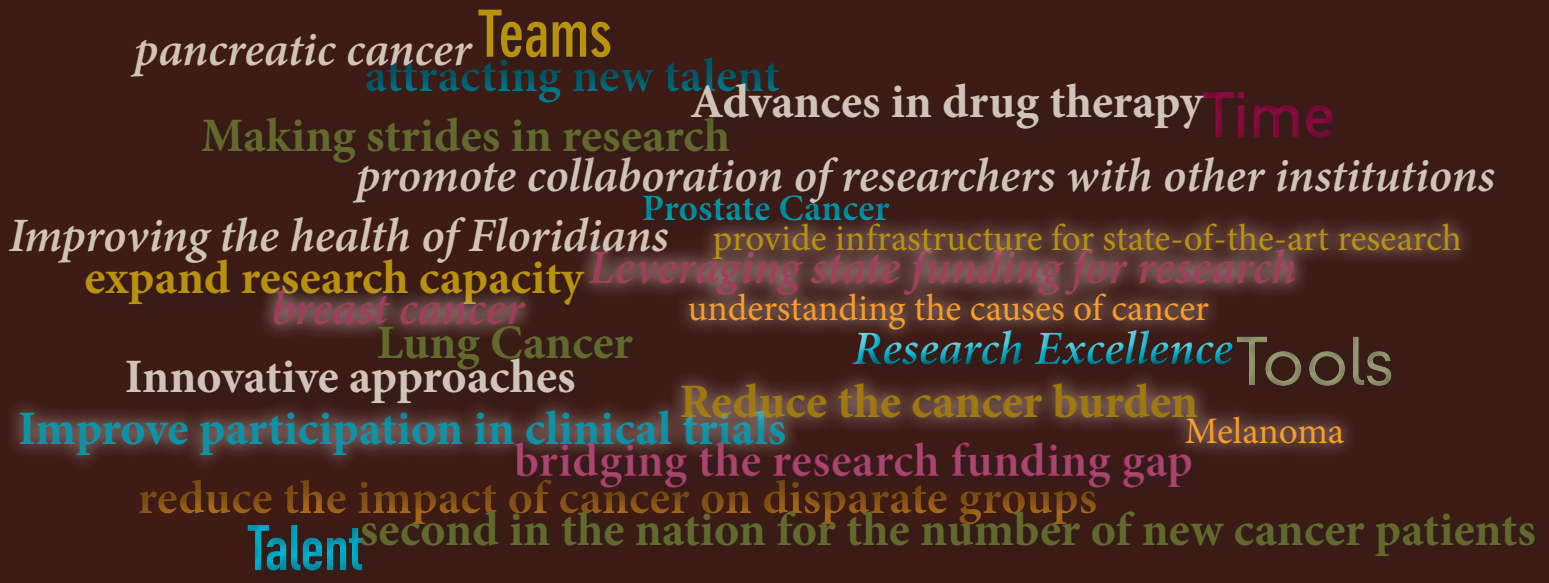
bankheadcoley
Florida Biomedical Research Program



IMPROVING THE ENVIRONMENT FOR SUCCESS

2008 ANNUAL REPORT

The Bankhead-Coley Cancer Research Program

As established in section (s.) 381.922, ***Florida Statutes,*** the purpose of the Bankhead-Coley Cancer Research Program is to advance progress towards cures for cancer by awarding research grants using a peer-reviewed, competitive process.

Specifically, the Program seeks to:

- Expand research capacity in the state
- Improve participation in clinical trials
- Reduce the impact of cancer on disparate groups
- Foster collaborations among institutions, researchers, and community practitioners

For more information about the Program, visit www.floridabiomed.com or contact the Florida Department of Health Office of Public Health Research, (850) 245-4585. Additional print copies of this report are available upon request.

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William G. "Bill" Bankhead Jr. and David Coley Cancer Research Program

Annual Report

January – December 2008

Submitted to

The Governor
The President of the Senate
The Speaker of the House of Representatives

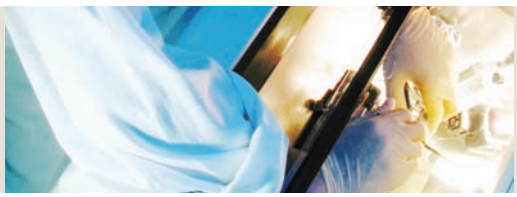
and

The Florida Center for Universal Research to Eradicate Disease

by

The State Surgeon General
State of Florida

December 15, 2008



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Executive Summary

Despite having the second-highest numbers of new cancer diagnoses and cancer deaths in the nation, Florida has among the fewest nationally recognized cancer research and treatment centers. This gap has serious healthcare implications for Florida's cancer patients who would benefit from state-of-the-art treatment but cannot travel the distance required to obtain it. It also represents lost economic opportunity for our state, considering the sizeable federal funding and highly skilled jobs associated with major cancer centers. Two full years after making its first awards, the Bankhead-Coley Cancer Research Program is already proving to be an effective strategy to help remedy this gap.

By the end of 2008, Florida's total investment of $27 million in the Program to date has already helped Bankhead-Coley grantees attract an additional $29 million in funding to the state, based on the high quality of their cancer research. As evidence of the national and international importance of their findings, the total number of articles published in peer-reviewed journals based on Bankhead-Coley research more than doubled in 2008 to 54, and since the National Cancer Institute has endorsed the peer review and funding decision processes used to select Bankhead-Coley awards, these grants are accelerating the ability of at least three emerging cancer centers in Florida to achieve formal national recognition.

Other highlights of how Bankhead-Coley grants are improving key elements of Florida's cancer research environment at nine public and private institutions across the state, as of the end of 2008:

Talent: 20 investigators are leading their first independent research projects and Program grants are supporting 62 graduate and postdoctoral students and laboratory personnel

Tools: at least 64 cancer researchers are using the seven state-of-the-art instruments purchased with Program grants during 2007

Teamwork: 60 scientists and clinicians on four teams are conducting projects that link basic and clinical research for lymphoma, skin, prostate, and colorectal cancers

Time: 49 cancer researchers have been able to continue their work between federal grant applications in an increasingly competitive national climate

More than reporting just the numbers, the Program Accomplishments section of this report describes how the promising findings of many of these projects offer hope for new cancer treatments and cures.

To ensure accountability for the use of public funds, the Office of Public Health Research has put processes in place to track, monitor, and report scientific progress against the research aims of these grants. The Biomedical Research Advisory Council (Council) has followed best practices in scientific peer review and avoided conflicts-of-interest in recommending Program awards.

Since the Program's inception, the Council has carefully narrowed the grant types offered to target what its members have identified as the most pressing needs among Florida's cancer research community. Still, the 27 new grants awarded in July of this year represented less than half of the funds requested. While recognizing the many difficult sacrifices being made in the state budget during the current and coming fiscal years, the Council strongly recommends that funding for the Bankhead-Coley Cancer Research Program be maintained at the current level.

Florida's Cancer Care Gap

While cancer is a global health concern, Florida faces a major cancer burden, which includes significant health and cost consequences. The gap between the needs of current and future cancer patients in this state and the resources and capacity to meet them is large.

As evidenced in Table 1 below, Florida ranks second in the nation for the number of new cancer patients as well as the number of cancer deaths, yet we have among the fewest Cancer Centers recognized by the National Cancer Institute (NCI), and only one of the 62 NCI Specialized Programs of Research Excellence (SPOREs).

Table 1:
Cancer Cases, Number of NCI Cancer Centers, and Specialized Programs of Research Excellence

	Estimated New Cancer Cases in 2007[1]	Estimated Cancer Deaths in 2007[2]	Number of NCI Cancer Centers[3]	Number of NCI SPOREs[4]
California	151,250	54,890	10	7
Florida	**106,560**	**40,430**	**2**	**1**
New York	100,960	35,270	6	11
North Carolina	38,210	16,880	3	22
Tennessee	28,440	12,920	2	3

In 2008, the H. Lee Moffitt Cancer Center & Research Institute (Moffitt Cancer Center) in Tampa, and the Mayo Clinic in Jacksonville, were the only NCI-designated Comprehensive Cancer Centers in Florida.[5] In addition, the Moffitt Cancer Center received Florida's first NCI SPORE grant in September 2008.

By continuing to appropriate funds for the Bankhead-Coley Cancer Research Program, the Governor and Florida legislature are providing a vital accelerator to closing the critical gap between the health needs of Floridians and our cancer research and treatment infrastructure.

Why NCI Cancer Centers Matter

"The NCI-designated Cancer Centers are a major source of discovery of the nature of cancer and of the development of more effective approaches to cancer prevention, diagnosis, and therapy. They also deliver medical advances to patients and their families, educate healthcare professionals and the public, and reach out to underserved populations. They are characterized by strong organizational capabilities; institutional commitment; and trans-disciplinary, cancer-focused science; experienced scientific and administrative leadership, and state-of-the-art cancer research and patient care facilities."[6]

The NCI offers Cancer Center Support Grants of up to $1 million per year to qualified institutions. The size of these competitive awards depends on the amount of the institution's peer-reviewed, cancer-related funding, with $4 million per year set as the minimum research base for eligibility.

When an institution earns the NCI designation as a Cancer Center, it is better able to:

- Recruit talented scientists
- Improve cancer patient treatment (quality, quantity, and location)
- Promote collaboration of researchers with other institutions
- Increase the number of local clinical trials
- Reduce cancer risk, incidence, morbidity, and mortality (prevention studies)
- Expand treatment to underserved populations
- Promote collaboration with industry (develop new medical devices, drugs, and diagnostic tests)
- Boost the regional economy (more grant money, more industry and biotechnology, more high-paying jobs)

Why NCI SPOREs Matter

NCI SPOREs "promote interdisciplinary research and move basic research findings from the laboratory to clinical settings, involving both cancer patients and populations at risk of cancer. The outcome of interdisciplinary research is a bidirectional approach to translational research, moving laboratory discoveries to clinical settings or clinical observations to the laboratory environment. Laboratory and clinical scientists share the common goal of bringing novel ideas to clinical care settings that have the potential to reduce cancer incidence and mortality as well as improve survival and the quality of life."[7]

Rather than being organized around an institution, each SPORE focuses on a single organ-specific cancer or a highly related group of human cancer types such as gastrointestinal cancer. All SPORES involve collaborations between scientists and clinicians who form a multidisciplinary team of experts. The NCI provides SPOREs with significant grants (up to $12.5 million over five years). Having the SPORE designation makes the cancer center and the state a destination for those afflicted with that particular cancer.

How This Program Is Helping Florida Establish More NCI Cancer Centers and SPOREs

Bankhead-Coley Program grants count toward the cancer research base required of NCI Cancer Centers. In 2007, the Florida Department of Health sought and received NCI recognition of the Bankhead-Coley Cancer Research Program (Program) and the James & Esther King Biomedical Research Program as having approved peer review and funding systems. This means Florida institutions can now use grants awarded by these state-funded, competitive programs in meeting the $4 million research-funding threshold required to become an NCI Cancer Center.

As of 2008, the following Florida institutions are actively pursuing the NCI Cancer Center designation:

- MD Anderson Cancer Center Orlando
- University of Florida (UF) Shands Cancer Center
- University of Miami (UM) Sylvester Comprehensive Cancer Center

Bankhead-Coley Program grants are jumpstarting Florida teams competing for NCI SPORE Grants. Through the Program's SPORE Planning Grants, four collaborative teams of researchers have launched new research projects during the last two years. These teams are developing SPORE capabilities focused on lymphoma, skin, prostate, and colon cancer. With the help of this preparatory work, these teams will be better prepared to compete successfully for the NCI SPORE grants in 2009 and 2010.

The new NCI SPORE Grant at the Moffitt Cancer Center will provide $10 million in federal funding over five years for lung cancer research. The importance of Bankhead-Coley grants (as well as a grant from the James & Esther King Biomedical Research Program) in helping bring this major award to Florida is evident:

Jiandong Chen, Ph.D. (2006 Bankhead-Coley Bridge Grant recipient). Dr. Chen's Bridge Grant allowed him to develop a better understanding of the roll of SirT1 molecules in cells, and this knowledge is now being expanded to test their role in lung tumors.

Jin Cheng, M.D., Ph.D. (2007 Bankhead-Coley Bridge Grant recipient). Data produced by Dr. Cheng with his Bridge Grant work on AKT1 function went into the SPORE grant application.

Dmitry Gabrilovich, M.D., Ph.D. (2006 Bankhead-Coley Bridge Grant recipient). Although his Bankhead-Coley Bridge Grant work was not directly related to the SPORE grant subject, Dr. Gabrilovich maintains that all the research in his lab is intertwined. "The Bankhead-Coley grant helped us to develop the foundation and mechanisms of the role of the immune system. This led to new hypotheses and new preliminary data that helped lead to this SPORE grant."

Douglas Cress, Ph.D. (2008 Bankhead-Coley Bridge Grant recipient). Many of the people in Dr. Cress's lab work on more than one project, and their work on the Bankhead-Coley grant regarding E2F relates to their work on the SPORE grant.

Mark Alexandrow, Ph.D. (2006 James & Esther King New Investigator Research Grant recipient). The information Dr. Alexandrow obtained with his King grant helped lay the foundation for understanding Mcm proteins. This experience led to an invitation to be named Principal Investigator (PI) on a clinical trial for the SPORE, testing a chemopreventive drug for lung cancer that uses the Mcm proteins as biomarkers. Normally junior faculty is not considered to be qualified to serve as a PI on a SPORE Grant; however, NCI staff commented very favorably on his King funding when deciding in favor of his participation in this SPORE Grant.

Program Accomplishments

Highlights

A total of 85 Bankhead-Coley investigators have led cancer research efforts in projects ranging from understanding the causes of cancer to discovering new natural compounds for drug development to finding novel ways to make current treatments more effective. Later sections of this report describe the quality of the research enabled by the Program in Florida, while the quantitative indicators of productive research such as publications, patents, presentations, and additional external funding are included in the following table.

Florida's investment in Bankhead-Coley grants is also generating significant benefits for the state's economy. According to a 2005 report from the Florida Board of Governors, a study by the Leadership Board for Applied Research and Public Service showed that every dollar invested by the state in research at Florida's higher education institutions produces an increase in Gross Regional Product of nearly $11, after adjustments to reflect net present value.

Table 2:
Bankhead-Coley Program Performance Indicators

Performance Indicator	Total for 2008	Total
Number of publications in peer-reviewed journals (2008 publications listed in Appendix B)	31	54
Number of presentations at professional meetings	45	87
Number of patents filed or applied for	1	2
Dollars of additional external funding (2008 external funding listed in Appendix C)	$19.3M	$28.8M

Improving the Environment for Success

Charged with the goals of advancing progress towards cures for cancer and reducing Florida's cancer burden, the Biomedical Research Advisory Council (Council) has recommended multiple strategies for investing Bankhead-Coley Program resources. These strategies fall into four foundational elements essential to improving the research environment and knowledge base that will advance cancer research in Florida:

More Talent

To attract new research talent to the state, the Program provides grants for new researchers. These grantees have less than five years of full-time faculty experience. A mentor works closely with the grantee to provide guidance for research and grant applications. The goal of funding new researchers is to speed up their progress and improve the quality of their federal applications for longer-term funding.

More Tools

To provide the infrastructure for state-of-the-art research in Florida, the Program provides grants for large-scale equipment to conduct research. Having this equipment expands the state's research capacity and increases the likelihood of future funding.

$10.89

The projected contribution to Florida's economy for every dollar awarded in Bankhead-Coley grants.[8]

More Teamwork

Building collaboration among Florida's cancer researchers increases the sharing of knowledge and discoveries, allows teams to conduct complex research projects, and makes it possible to develop and submit more competitive applications for federal funding. The Program offers grants that promote the formation of multidisciplinary teams, which can continue working long after the end of their Bankhead-Coley grant.

More Time

To reduce human suffering from cancer and to help underserved Floridians find quality care, the Program offers grants to bridge the gap between federal grant funding cycles. Such time allows researchers to collect more data for their next grant submission. More importantly, this time is spent researching the why's and how's of cancer, which in turn fuels the development and testing of new cancer treatments.

Dr. Dietmar Siemann
University of Florida
2006 and 2008
Bridge Grant Recipient

"This Program is absolutely a selling point for keeping faculty and attracting new faculty. Florida has really done a good thing by doing this."

On the following pages, we present many compelling stories of how these grants are improving the research environment throughout the state and accelerating the development of cures for Floridians suffering from cancer.

More Talent: Providing Essential Support to New and Future Investigators

According to the National Science Foundation (NSF), global competition for scientific talent is intensifying such that the United States may not be able to rely on the international scientific labor market to fill unmet skill needs.[9] A crucial part of growing Florida's capabilities and reputation in the biomedical sciences is training, recruiting, and keeping talented researchers in Florida.

Bankhead-Coley New Investigator Research Grants are helping new Florida faculty members and staff scientists establish independent cancer research careers. Under the guidance of senior Florida researchers, these grantees are leading their first large projects. As they establish their own laboratories and pursue research, they are providing opportunities for many more Florida undergraduate, graduate, post-doctoral students and laboratory personnel to participate in high-quality cancer-related research.

Funding

New Investigator Research Grant recipients are using their multi-year awards to cover a portion of their salaries, hire lab personnel, and purchase small equipment and supplies as they pursue specific research judged to have high scientific merit by external peer reviewers. With dramatic increases in competition for federal funding over the past decade, Bankhead-Coley grants are vital to helping these scientists pay for the expenses involved in accumulating preliminary data and demonstrating their ability to lead productive research.

According to University of Miami's Dr. Balakrishna Lokeshwar, a 2006 Bridge Grant recipient who is investigating a plant-derived extract to treat prostate cancer, "To retain research talent is a national problem; researchers need small grants here and there during funding gaps. That is exactly what Bankhead-Coley is doing, and that is an excellent thing—actually, the best thing a Program can do. Researchers in other states are envious of me."

20

The number of new Florida researchers that have received three years of Program funding since 2006.

Wen Lieu
University of Miami
2008 New Investigator Research Grant Recipient

"The Bankhead-Coley Program gives new investigators great opportunities to establish their study populations, collect preliminary data for future larger scale studies, and to obtain funding from NCI and NIH . . ."

Mentoring

Mentoring new researchers is a crucial aspect of helping develop new scientific talent. Today's researchers require a wide range of skills—not only in the technical aspects of their specific area of research, but also in managing projects and personnel, building collaborations, communicating results, and writing grant proposals. Not all of these skills come naturally. For this reason, the Bankhead-Coley Program requires all New Investigator Research Grant recipients to cultivate a relationship with a senior Florida researcher actively working in a related field. This mentor is accountable to the Program for advising the researcher and regularly reviewing progress during the course of the project.

The project leader, or principal investigator, is not the only beneficiary of mentoring. Nearly every project provides students and laboratory personnel with experience in high-potential cancer-related research, thereby adding to Florida's research talent.

62

The number of Florida graduate and post-doctoral students and laboratory personnel that were supported by Program grants in 2008.

Examples of New Talent

During 2008, Dr. Yulia Nefedova, a trainee of Dr. Dmitry Gabrilovich on a project funded by his 2006 Bankhead-Coley Bridge Grant, won her first major federal grant, helping her become an independent full-time faculty member at the Moffitt Cancer Center.

Dr. Sergei Kusmartsev, a 2007 New Investigator Research Grant recipient at the University of Florida is a good example of the new talent supported by Bankhead-Coley funding. Dr. Kusmartsev is working to help patients with renal cell carcinoma, which does not respond well to chemotherapy. Treatment is complicated because the tumor suppresses the immune system. He sought to establish whether a substance secreted by the tumors is attracting specialized cells that suppress the body's beneficial immune response against the tumor. He recently published a high-impact paper in the *Journal of Immunology*, showing that renal cell carcinoma tumors in mice can induce these specialized cells (***Journal of Immunology***, 2008, 181(1):346-53). His findings are important enough that he and his collaborators are already planning to start a clinical trial for combination treatment of patients with metastatic renal cancer.

Two other new investigators, Dr. Maen Abdelrahim of MD Anderson Cancer Center Orlando, and Dr. Evette Radisky, Mayo Clinic, offer their Bankhead-Coley Program research stories on pages 11 and 13. Both contribute a fresh perspective, new discoveries, and great enthusiasm for the Bankhead-Coley Program.

Omar Zeidan
MD Anderson Cancer Center Orlando
2008 New Investigator Research Grant Recipient

"As a young investigator, the Bankhead-Coley Cancer Research Program grant has provided a much needed boost to my scientific career that is not readily available elsewhere. I believe the data from this grant-supported project will provide a strong basis on which I plan to apply for NIH grants in the near future."

Innovative Approaches to Halting Pancreatic Cancer Tumor Growth

Maen Abdelrahim, Ph.D.

MD Anderson Cancer Center Orlando
2007 New Investigator Research Grant

Considered by many to be one of the deadliest malignancies, pancreatic cancer patients have an average survival time of six months; 99 percent of diagnosed patients will die of the disease. According to the NCI, an estimated 1,800 Floridians will die of pancreatic cancer in 2008, and the numbers increase yearly. Only one drug is available today – gemcitabine.

Dr. Abdelrahim hopes to change these statistics with a new treatment. His lab is studying ways to stop pancreatic cancer cell growth using non-steroidal, anti-inflammatory agents that resemble ibuprofen. His initial data are significant, generating interest from patients and pharmaceutical companies alike.

Early in his research, Dr. Abdelrahim studied proteins with unique 3-D structures called specificity proteins (Sp's). He observed that Sp's are growth factors for cancer, contributing to its survival and spread. While numerous Sp's exist, previous research has focused on Sp1 and Sp3 as the key players. His team is the first to discover and publish that another Sp protein, Sp4, is just as important in cancer growth and metastasis as Sp1 and Sp3. Why is this a critical finding? Treatment strategies aimed only at Sp1 or Sp3 will be less effective without considering Sp4's role as well.

With a pharmacy background, Dr. Abdelrahim began looking for a drug to target all three "bad" Sp's. At the same time, the drug's action needed to have a minimal effect on the functions of the good members of the Sp protein family.

Based on data connecting painkillers to a decrease in some cancers, the team selected tolfenamic acid for study and administered it in combination with radiation therapy to animals. The results were very positive. Tolfenamic acid appears to support apoptosis–programmed cell death–in several pancreatic cancer cell lines without hindering normal cell function. In his experiments, tumor size decreased dramatically after one month, and tumors became more susceptible to radiation. In control animals receiving radiation alone, tumor size decreased by 50 percent. In animals receiving the drug in combination with radiation, tumor size decreased by more than 87 percent (See Figure 1). Dr. Abdelrahim is very excited at data that demonstrates such an increased sensitivity to radiation. His recent findings show that prostate, gastric, colon, thyroid, and brain cancers may be responsive to this therapy as well.

Tolfenamic acid enhances the sensitivity of pancreatic tumors to radiation therapy. Pancreatic tumor cells were injected into four groups of mice, and then each group was treated, as follows: 1) corn oil (Control); 2) radiation (Rad); 3) daily tolfenamic acid (Tol); 4) combination of tolfenamic acid + radiation for 4 weeks (Tol + Rad).

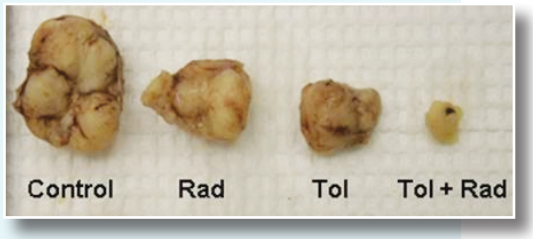


Figure 1:
Effect of Tolfenamic Acid on Tumors Receiving Radiation

Because tolfenamic acid has been approved for more than 15 years to treat migraines with minimal side effects, the team hopes to initiate FDA approval for clinical trials in 2-3 months. Dr. Abdelrahim now holds a patent on this drug for pancreatic cancer use. His future plans include determining how tolfenamic acid works and conducting clinical studies to test toxicity and identify the largest safe dose. In addition, the team will test the drug alone and in combination with different radiation doses to see if it can increase the response to radiation. Their goal is to reduce the amount of radiation needed in order to lessen its harmful side effects.

State and national pharmaceutical companies have shown an interest in this work. Dr. Abdelrahim has received calls from patients anxious to participate in his study. "Patients need hope, new drugs. This is a new approach, not just a chemotherapy with horrible side effects. This drug is just the first on the list of potential new therapies I want to explore."

Targeting Cancer—Investigating Enzymes

Evette Radisky, Ph.D.

Mayo Clinic, Jacksonville
2008 New Investigator Research Grant

The Radisky lab is working on a piece of the cancer puzzle having to do with the enzymes involved in digestion and blood clotting called serine proteases. "I started looking at the involvement of serine proteases in breast and prostate cancer to see if they were good targets for drug development. I started with mesotrypsin—a digestive enzyme normally produced by the pancreas and secreted into the digestive system. The more invasive and aggressive the cancer cells, the more they produce mesotrypsin."

Based on this evidence, Dr. Radisky believes mesotrypsin is a key player in cancer. Her team is designing drugs as inhibitors to disrupt it and block cancer progression. She explained that the body makes natural inhibitors for other enzymes, but mesotrypsin responds to them in a unique and unusual way.

"[The natural inhibitors] serve no barrier whatsoever to mesotrypsin; it chews them up as if they were its favorite food. I'm really motivated to figure out what is unique about mesotrypsin that enables it to digest these inhibitors and what role it may play in facilitating cancer progression. Once we figure out the pieces of the puzzle, we may be able to come up with something to block it."

"Within the first year of our grant, we reported a crystal structure of mesotrypsin bound to an inhibitor called BPTI in the *Journal of Biological Chemistry*. The crystal structure we solved gave us some really useful insights into what is different about mesotrypsin."

Dr. Radisky explains how, without Bankhead-Coley Program support, such progress and applications for national grants would be difficult if not impossible. "The burden of proof—the amount of data that is required to show feasibility and viability for a project—has grown immensely with the tightness of funding at the NIH right now. . . . Receiving funding from the state of Florida has kept my lab alive—it's been essential, and given me hope that we can hang in and continue to work towards enough results that I will be able to garner an R01 NIH [major federal] grant before the completion of my Bankhead-Coley grant. Without that, it would really be a challenge. Since coming to Florida and becoming aware of this Program and the James & Esther King Program as well, I've been telling colleagues in other places about all of our opportunities. They are impressed. I am certainly getting the word out that Florida is a good place to be and a good place to come for new investigators. The Program is a huge calling-card for Florida."

Dr. Alan Fields, Dr. Radisky's mentor, provides guidance in lab management and experience with clinical trials. Dr. Radisky, in turn, provides biomedical research training for her staff and maintains ongoing collaborations with structural biologists at University of Florida and Brookhaven National Laboratories in Upton, NY.

More Tools: Providing State-of-the-Art Instruments and Equipment

One definition of a tool is an instrument or piece of equipment that provides an advantage in accomplishing a task or that enables the accomplishment of a task not otherwise possible.[10] Today's scientific tools not only allow more science to be done in less time, they also enable the accomplishment of tasks that were impossible yesterday, revolutionizing research and the nature of lab work.

During 2007, five Florida institutions purchased and installed seven state-of-the-art research instruments with Bankhead-Coley Shared Instrument Grants. The Program's investment totaled $3.4 million and recipient institutions contributed matching funds of $2 million to cover all set up, operating, and maintenance expenses for the new instruments, thus significantly leveraging the state's investment in this vital research infrastructure. Each of these tools required an investment that could only be justified on a shared-use basis, meaning that multiple teams and individual researchers were already planning to use the instruments, even before they were purchased. After only one year's use, these tools can already be credited with bringing in $6.4 million in new national or private grant awards (excluding state awards) to Florida researchers.

64

The number of researchers at five Florida institutions that have used seven new major pieces of equipment for cancer-related research purchased with Program grants.

Examples of Benefits

- The Bankhead-Coley Program grant made possible the purchase of an Illumina BeadStation, a tool for genetic analysis, at the University of Miami. Nine teams from the Sylvester Comprehensive Cancer Center currently use the BeadStation, and this number is expected to double rapidly with the release of ten Sylvester Pilot Grants for BeadStation users. In addition to benefitting existing cancer center members, the instrument is a key component in recruiting cancer researchers and expanding Florida's research capacity as well. It has enabled Dr. Jennifer Hu to study genetic variations and sequences to investigate how they impact cancer risk. Dr. Hu, in collaboration with Drs. Joseph Lucci and Edward Jimenez, is also testing an anti-viral drug to kill human papillomavirus (HPV)-infected cells. (HPV is the primary culprit in cervical cancer.)

- Researchers at Florida Atlantic University were significantly hampered by the lack of access to a fluorescence activated cell-sorter (FACS). This instrument can isolate over 20 million specific cells with high accuracy into 100 percent pure populations in five minutes. Use of a FACS is the accepted standard for this work, and without it, research results are often not publishable. The closest instrument of this type required a two-hour round trip. Because their fragile samples are typically stored on ice, transporting samples led to temperature changes and jarring that often destroyed sample integrity. A Bankhead-Coley Shared Instrument Grant solved this problem by enabling researchers at Florida Atlantic University to purchase a FACS.

- Conventional laboratory freezers are large boxes where several researchers store their precious biological samples. With several people opening and closing the doors and placing and removing samples on the shelves, it is easy for samples to be lost. The Moffitt Cancer Center used a Bankhead-Coley Shared Instrument Grant to purchase a Thermo Scientific BioBank -80°C Automated Sample Management System. The BioBank is an ultra-low temperature freezer that has built-in robotic retrieval and is about the size of two large freezers side-by-side. Researchers who store their samples there never have to open the freezer and risk thawing precious samples. When they need a specific sample, the robotic device retrieves it. Utilizing the BioBank, the Total Cancer Care (TCC) initiative at Moffitt Cancer Center has created a state-of-the-art bio-repository of tissue and blood samples from hospitals throughout Florida that do not have basic research capabilities.

On the next page, Dr. Stephen Sugrue, University of Florida, describes the improved capabilities now available in his department at the Shands Cancer Center, where 75 percent of his staff use a confocal microscope purchased with a Bankhead-Coley Shared Instrument Grant.

The Confocal Microscope: Window into a New World for Researchers

Stephen Sugrue, Ph.D.

University of Florida
2006 Shared Instrument Grant

With a confocal microscope (scope) acquired through a Bankhead-Coley Shared Instrument Grant, staff at University of Florida's Shands Cancer Center can observe high-speed, dynamic processes within cancer cells—a possibility that was unheard of a short time ago.

"Ten years ago, we assembled a series of images, frozen in time and space, and tried to imagine the dynamics of the cancer cell. This scope allows us to track molecular movements in real time," explained Dr. Sugrue.

Researchers use the scope to conduct live experiments, make real-time observations, record data, and capture high-resolution images that show the structural features of cancer cells, tumors, and the tumor microenvironment.

Dr. Sugrue is passionate about the importance of gaining this understanding: "Just knowing something is broken or that a drug is effective isn't enough. In order to make giant strides, we need to get as much information as possible about how a drug works or a cancer thrives at a molecular level."

For example, if a cancer therapy stops working or begins producing harmful side effects, scientists need to know why. The scope helps them pin down the exact molecular interactions that allow a particular drug to be effective.

"We once thought molecules were in a rigid structure, but using this kind of scope, we know now that their structure is much more like a cloud: the structure is dynamic. Entities are coming and going all the time and having short interactions-picking up speed and going again; it's much more like a Times Square model than something static like a bike rack. . . . These dynamics are telling us another dimension of the story. In a cancer cell, the molecular dynamics are different than in a normal cell. It would be impossible without such a scope to even predict this at all. Being able to look at the dynamics in a living cell is an incredibly new dimension in cell biology research."

Although harder to quantify, an additional benefit of shared equipment is additional collaboration. This microscope has become a focal point to launch a number of interesting collaborative efforts. Dr. Alexander Ishov, an expert in its use, is frequently sought by other researchers for technical advice. Intrigued by others' research, he has assisted many scientists with their research. This instrument is typically booked 70 percent of the daytime workweek and frequently used for overnight and multiple daytime studies.

From attracting talent to procuring new funding to building collaborations, the scope plays a key role in research at the University of Florida. Dr. Sugrue noted that potential recruits frequently ask about the availability of a scope. For investigators obtaining grant renewals or new funding, the scope is critical to data collection—a key part of a winning proposal. A number of researchers use the equipment—23 last year alone—on a wide variety of cancer-related projects. Researchers share in operational costs to encourage responsible and efficient use. According to Dr. Sugrue, "There's just not enough time in the day for everyone to use it if we don't encourage efficiency."

More Teamwork: Enabling Collaborations

While work collaborations are nearly always beneficial to scientific discovery, it is particularly so in cancer research. Many projects require such a wide range of expertise that a diverse group effort is the only way to produce significant results. Additionally, many findings are often highly transferrable across cancer types. "There is an enormous amount of overlap among cancers. The same characters, the same players are involved in different cancer types, although the subtleties of the story may be different. We are amazed at the similarities." Dr. Stephen Sugrue, University of Florida.

The early progress of the Program's four SPORE Planning Grant awardees shows that this strategy is already stimulating more collaborative cancer research in Florida. These teams are already developing new approaches to prevention, early detection, diagnosis, and treatment of cancer.

60

The number of researchers on four sponsored collaborative teams that are fast-tracking research in lymphoma, skin, prostate, and colorectal cancers.

Collaboration Within Teams

Dr. Johannes Vieweg, a 2008 SPORE Planning Grant recipient from the University of Florida, has assembled a strong team of interdisciplinary researchers in a prostate SPORE Planning Grant. This grant unites more than two dozen researchers from the University of Florida, Moffitt Cancer Center, and the North Florida Veteran's Health System. The team's comprehensive approach allows for a thorough examination of prostate cancer factors including population-based studies, the impact of aging, and genetics. Other members of this diverse team will use this information as the basis for developing and testing new patient treatments. To avoid duplication of effort and facilitate rapid progress, three core facilities provide support for all the projects (biostatistics and epidemiology; biospecimens; and clinical trials). The exchange of data within the group will allow the team to make progress that would be impossible on an individual level.

Dr. Vernon Sondak at Moffitt Cancer Center, leader of a 2007 melanoma SPORE Planning Grant, describes his team's collaboration as unprecedented in Florida melanoma research. The team encompasses surgeons, oncologists, immunologists, epidemiologists, pathologists, and molecular biologists. Dermatologists and hospitals are cooperating to supply tumor samples. Further, the grant established the Florida Melanoma Consortium for coordinating statewide research efforts and includes Moffitt Cancer Center, University of South Florida, University of Miami, University of Florida Jacksonville and Gainesville, and other physicians throughout Florida.

$787,000

The contribution committed by Florida institutions to match the state's investment in SPORE Planning Grants.

Collaboration Among Teams

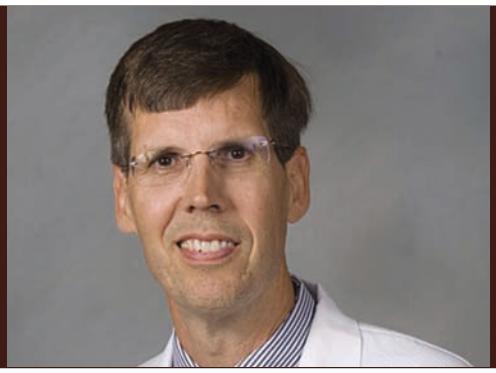
Not only are these two teams building their own synergies for these specific forms of cancer, but they are also partnering with each other and UF Shands Cancer Center to develop and test new immunotherapy approaches – cancer vaccines – that may benefit both studies.

"Overall, the combined Moffitt-Shands-UF program offers much more firepower to make an impact on cancer in the state of Florida and beyond than what we had before," Vieweg says. "There is a natural synergy here that makes our programs better."

Dr. James Mule, researcher at Moffitt Cancer Center and a member of Dr. Sondak's SPORE planning team, adds "This partnership allows us to formalize a real connection, a real bond, through shared video conferences, shared meetings, and by learning more about the researchers at each site."

In the following profile, Dr. Timothy Yeatman describes the growing teamwork and long-term academic relationships that are possible through his the SPORE Planning Grant.

Molecular Signatures for Colon Cancer



Timothy Yeatman, M.D.

H. Lee Moffitt Cancer Center & Research Institute
2008 SPORE Planning Grant

Dr. Timothy Yeatman and the SPORE Planning Grant Team at Moffitt Cancer Center are addressing colorectal cancer, which represents a large volume of cancer cases each year and a substantial number of cancer-related deaths. This team represents a wide range of disciplines and backgrounds, including experts in medicine, biochemistry, molecular biology, genetics, biostatistics, bioinformatics, computer science, and mathematics.

The context for their approach is an initiative in personalized medicine at Moffitt Cancer Center called "Total Cancer Care," which is an information repository containing both RNA-based, genome-wide gene expression data, as well as DNA sequencing data on thousands of patients that will ultimately be used to match the right drugs to the right patients. A Total Cancer Care consortium of eight participating Florida hospitals will supply tissue samples for gene-based trial matching. The Team plans to leverage this unique resource along with the data collected through their SPORE Planning Grant to become extremely competitive in the NCI SPORE application process.

A portfolio of relevant, collaborative projects is a necessary ingredient of an NCI SPORE application. Within the focus of primary and metastatic colorectal cancer, Dr. Yeatman outlined three specific projects being performed with this grant:

Improving Existing Therapies. Biomarkers are proteins or genes that the body uses as "signal flags" for specific chemical pathways and can be used to guide the development of more effective cancer therapies. Dr. Yeatman is collaborating with Dr. Deepak Agarwal from the Department of Interdisciplinary Oncology at the University of South Florida to use biomarkers to better understand a particular molecular pathway in colon cancer. The biomarkers give them feedback about whether or not a drug is working on a particular pathway. Then they can focus on that pathway as a possible therapeutic avenue.

Developing New Therapies. MicroRNA molecules are one of the newest therapies being tested against cancer. MicroRNA molecules act as master switches to turn on or off genes which may promote the growth of colon cancer. This project links together basic science researcher Dr. Jin Cheng, from the Molecular Oncology Program at the Moffitt Cancer Center, with a colorectal surgeon, Dr. David Shibata from the Surgery and Oncology department. Dr. Cheng explains, "We are trying to understand which microRNAs control gene expression in colon cancer and therefore, which microRNAs would make good targets for this type of drug therapy."

Preventing Colorectal Cancer. This project tests vitamin E as a cancer preventive agent. It appears that this common vitamin can induce some cancer cells to commit suicide, providing a simple, inexpensive way to prevent cancers before they even start. This project teams up colorectal surgeon Dr. Mokenge Malafa from the Moffitt Cancer Center with Dr. Said Sebti, Director of Drug Discovery at Moffitt Cancer Center.

Other aspects of this Planning Grant that will enhance the team's ability to gain an NCI SPORE:

- The projects bring together teams of translational and basic physician-scientists and basic researchers with a wealth of experience in the clinical management of this disease and substantial funding track records with the NCI in gastrointestinal cancer.
- The projects collaborate with the Total Care Center to find the right drugs for the right patients through a process called "gene-based trial matching."
- The three projects are tied together by three "core facilities." Each of these cores is an independent unit of experts providing services in state-of-the-art techniques to help researchers work faster, more efficiently, and without having to hire and train additional personnel for each of their separate labs.

Dr. Yeatman explained the critical role of the Bankhead-Coley Program: "This Program is extremely important because it develops a new opportunity that otherwise wouldn't exist for us to get the right Teams together. We start working together and develop relationships that go on–it is not something that is short-term. We also have the opportunity to create the preliminary data to be competitive on a national level with others applying for NCI SPORE dollars. This program will energize and facilitate that process, truncating the timeline substantially so that we can be competitive for the gastrointestinal SPORE grant within the three-year timeline and have a better probability of success."

More Time:
Sustaining Momentum for Proven Researchers

Research is a long-term process that leads to improved treatment for people many years down the road. It can take up to 12 years for a new anti-cancer agent to reach the Food and Drug Administration, and, even then, only 5 percent to 10 percent are ever approved for use.[11] For example, the widely used cancer drug now known as Taxol®, discovered at Florida State University in 1962, took 30 years for approval as an ovarian cancer treatment and two more years for approved use in breast cancer.[12]

In addition to drug development, time to understand the how, why, and what of cancer is crucial for designing better medicines and predicting how they will treat or prevent a disease. This information is also necessary to attract support from pharmaceutical firms or the NIH, the largest source of grant funding for biomedical research.

42

The average age in 2008 of investigators receiving their first major grant from the National Institutes of Health.[14]

Time for Obtaining Needed Funding

In 2008, public universities in Florida joined other state agencies in making tough decisions in budget cuts. In doing so, they sacrificed many biomedical research positions. More researchers have become almost entirely dependent on non-university funds, such as from the NIH and private foundations. However, with the flattening of the NIH budget since 2004, increasing national competition has squeezed the proportion of winning applications; in 2007, only 18.7 percent of all applications for new NIH grants were successful.[13] Consequently, obtaining NIH funding typically requires re-submitting improved versions of the same proposal multiple times over many months or even years. In the meantime, researchers need to generate more convincing preliminary data. In other words, they have to work just as hard as before, but now their lab may be running short of funds. Without funding, many face leaving the institution and perhaps the state, thus depriving Florida of valuable scientific talent.

Bankhead-Coley Bridge Grants serve as a lifeline for Florida researchers whose federal proposals are unfunded in spite of receiving a very good scientific merit score in national peer-reviewed competitions. Bridge Grants allow investigators to continue collecting data while improving the scientific merits of their applications. They can keep their talented people, their laboratory space and equipment, and maintain project momentum. All of these factors are crucial for continued success, and allow many to make the cut during the next rounds of federal funding. In this way, the Bankhead-Coley Program helps retain talented scientists and builds Florida's research capacity.

Examples of Impact:

- Dr. Dietmar Siemann, University of Florida, describes some of the Program's benefits: "Not having an interruption in the work makes an unbelievable difference: I kept pushing the work forward during this period. The stronger the preliminary findings, the easier it is to convince my colleagues at the NIH that I am on the right track. . . . At the end of my 2006 Bankhead-Coley Grant, our lab received funding from the NIH; it's brought $1.2 million in research funding to the state. The Bankhead-Coley [Program] certainly helped me get that second five years of funding." **After a 2006 Bridge Grant award of $200,000, Dr. Siemann received a $1.2 million NIH grant in 2007.**
- Although NIH reviewers liked the application submitted in 2006 by Dr. Balakrishna Lokeshwar, University of Miami, they wanted more data and clarification. "The Bridge Grant helped me to make a significant improvement in the scientific and technical value of the project. . . . It was more than just receiving the money. It . . . deepened our sense of purpose and conviction that we should do this." **After a 2006 Bridge Grant award of $198,000, Dr. Lokeshwar's project received a $1.2 million grant in 2007.**
- "Bridge funding is critical for maintaining project productivity in an era of tight national research funding. Providing this opportunity will be beneficial in the long run for the State of Florida in the prestige of its research institutions and the amount of indirect benefits–new biotech companies, patents developed within the State of Florida, and indirect income from subsequent grants." Derek Radisky, Mayo Clinic. **After a 2006 Bridge Grant award of $200,000, Dr. Radisky received a $1.4 million NIH grant after one year.**

Florida's seasoned researchers must hire talented people as well and train them in scientific techniques. Once researchers invest months or years training their team members, they do not want to lose them because federal grant funding decreased. Dr. Amy Wright, Florida Atlantic University, relates her Bankhead-Coley Program story in the following profile. She has kept staff and project momentum through her Bridge Grant and recently received a federal grant award.

Tapping the Sea for New Antitumor Agents

Amy Wright, Ph.D.

Florida Atlantic University
2008 Bridge Grant

Dr. Amy Wright and her research team at Harbor Branch Oceanographic Institute (HBOI), Florida Atlantic University, are exploring deep-water marine habitats and organisms to discover natural marine products that will contribute to the treatment of pancreatic cancer. According to Dr. Wright, compounds found in plants have inspired 78 percent of the drugs approved for use against cancer.

"The compounds are rich and varied off Florida's extensive coastlines, and we're close to the Caribbean as well. In the 1950's, compounds in a sponge found off Elliot Key inspired synthetic chemists in the development of several compounds that are currently used for the treatment of herpes, pancreatic cancer, and non-Hodgkin's lymphoma. More recent discoveries at HBOI include a sponge-derived compound that selectively blocks cancer cells from dividing, and a compound from a sponge collected near Ft. Pierce inhibits the growth of pancreatic cancer cell lines." Her team has found compounds to block cancer cells at mitosis (cell division), block tumor cell migration, and restore cancer cells to normal cell growth.

Three steps the team uses to discover usable compounds include the following:

- Collect and extract: Researchers collect sponges, soft corals, and marine invertebrates and then use ethyl alcohol to extract compounds. The team uses specially equipped Johnson-Sea-Link submersibles, which include a robotic arm and suction device, to retrieve samples. Once retrieved, specimens are kept alive using a "Biobox," insulating them from rapid temperature changes. Dr. Wright has made over 100 dives at depths up to 3,000 feet to guide the collection of unusual marine organisms.

- Test: The team tests the ability of organism extracts to block the growth of five pancreatic cancer cell lines. They also test for compounds that will affect two molecular targets thought to be important in pancreatic cancer. Blocking these targets can either stop pancreatic cell growth or make the tumor more sensitive to the normal cell death process.

- Analyze: If an extract is effective in inhibiting cancer growth in the cell lines or inhibiting the molecular targets, a chemist purifies and defines the structure of the active compound, and the team investigates how the extracted compound is working.

A biomedical technology firm has recognized the potential of the research and shown interest in moving the central compound forward.

The unique challenges of bringing a compound from the sea through to drug development take a combination of leadership and support, which seem to have converged here.

"It takes a champion—the support of people with foresight and vision who will not let go regardless of the obstacles—to see a promising new compound from discovery to clinical stages to new therapeutic treatments," explained Dr. Wright.

When her first five-year grant from NIH came up for renewal, she was surprised and disheartened when her request for another round of funding was denied. In most years, this team would have received a renewal; however, with increasing competition for funding, the threshold for winning follow-on grants has been raised significantly.[16]

Rather than having to dramatically scale back her research efforts and staff, the Bankhead-Coley Bridge Grant allowed Dr. Wright and her team to continue making progress. The team has addressed NIH peer reviewer concerns, kept project momentum, and gained data for another application submission.

With the time gained from the Bankhead-Coley grant and the team's continued effort, Dr. Wright received notification of an NIH award in August of 2008 for $.3 million and relinquished her Bankhead-Coley award. This promising work can now continue with no lost momentum on the road to developing new treatments.

2008 Grant Awards

Grant Mechanisms Offered

The Bankhead-Coley Program released the "Call for Grant Applications: Medical, Biological, Behavioral, and Social Scientific Research and Development, Fiscal Year 2008-2009," (the Call) on December 10, 2007. Four types of grants, to begin July 1, 2008, were offered: Bridge Grants, Clinical Research Planning Grants (CRP), New Investigator Research (NIR) Grants, and Specialized Program of Research Excellence (SPORE) Planning Grants. The Call is the published document announcing requests for grant applications.

49

The number of Florida cancer researchers who have been able to continue their work between federal grant applications with Program support.

Bridge Grants

Purpose: To provide interim support for promising cancer-related research projects that have been highly rated by national panels of scientific peer reviewers in recent federal competitions but were not funded due to budgetary constraints. Researchers use the Bridge period to collect preliminary data and to improve their applications based on feedback from the Program's scientific peer reviewers. As a result, subsequent applications are more likely to win funding in the next round of federal competitions.

Amount and Duration: The Bridge Grant maximum is $200,000 for a period of one year, with a requirement for timely resubmission of an improved federal proposal.

Clinical Research Planning Grants

Purpose: The intent of this grant mechanism is to increase the likelihood of success in research projects involving clinical investigations (clinical trials) of new drugs, biologics, and devices intended for licensure by the Food and Drug Administration, and behavioral studies.

Amount and Duration: The Clinical Research Planning Grant maximum is $100,000 for a period of one year, with the requirement for timely submission of a follow-on full-scale national clinical trial/live human subject research grant or a follow-on Bankhead-Coley New Investigator Research Grant.

New Investigator Research Grants

Purpose: To foster development of new investigators so that they can undertake independent research that will be competitive for national research funding. New investigators are those who have been full-time faculty for less than five years and have not received a large ($100,000 or greater) federal grant. A senior researcher serves as a mentor, and projects must address an important cancer biomedical or behavioral problem.

Amount and Duration: The maximum annual award for New Investigator Research Grants is $125,000 per year, not to exceed $375,000 over three years.

SPORE Planning Grants

Purpose: To assemble and prepare strong interdisciplinary teams of Florida researchers to plan and compete successfully for NCI SPORE grants. Teams collect preliminary data and conduct and translate basic research findings from the laboratory to a clinical setting.

Amount and Duration: SPORE Planning Grants provide up to three years of support with a maximum award of $1,000,000. The Program limited applications to one per institution and required recipient institutions to provide a minimum of 25 percent in matching funds.

Results for the 2008-2009 Call for Grant Applications

In response to the fiscal year (FY) 2008-2009 Call, the Program received 57 proposals requesting a total of $15,944,473. Half of all the applications were for Bridge Grants, 44 percent sought New Investigator Research Grants, three percent applied for the Clinical Research Planning Grants, and three percent applied for SPORE Planning Grants. As anticipated, the Program received only a small number of applications for the SPORE Planning Grant due to the one per institution limit, the magnitude of the work, and the high degree of collaboration and interdisciplinary research involved. The Program completed the application review and award process in June 2008, and the Council recommended funding 27 research grants totaling $8,100,000 to begin July 1, 2008. This action resulted in an overall award-to-proposal ratio of 47 percent, compared to success rates of fewer than 20 percent for NIH. Table 3 summarizes applications received and awarded.

Table 3:
2008-2009 Grant Applications Received/Awarded

Grant Mechanism	Applications Received	Applications Awarded	Percent of Applications Awarded	Awarded Funding Amounts
Bridge Grant	28	15	54%	$ 2,448,608
New Investigator Research Grant	25	10	40%	$ 3,705,584
Clinical Research Planning Grant	2	0	0%	————
SPORE Planning Grant	2	2	100%	$ 1,945,808
Total	**57**	**27**	**47%**	**$ 8,100,000**

Of the 2008 awards, 45 percent of grant funds were allocated for New Investigator Research Grants, and 30 percent were for Bridge Grants. The remaining 24 percent of the available funding was dedicated to two SPORE Planning Grants.

Public and private research institutes throughout Florida are benefiting from these awards. The Program awarded grants to eight Florida research institutions (see Figure 2). Cancer topics addressed by the 2008 awards are diverse, with the majority focusing on breast cancer and prostate cancer as shown in Figure 3.

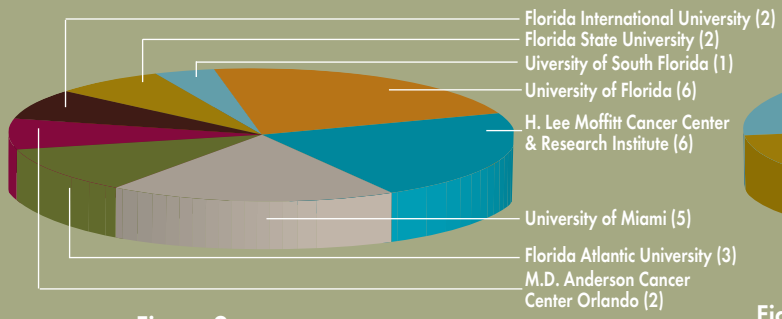


Figure 2:
2008 Grants Awarded by Institution

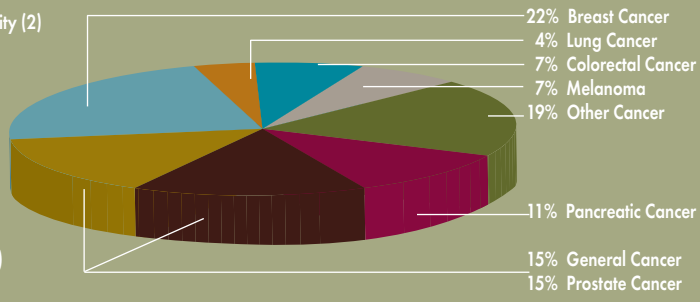


Figure 3:
2008 Grants by Cancer Type
Refer to Appendix D for the FY 2008-2009 grantee information including principal investigator, institution, award amount, project title, and abbreviated abstract.

Program Operations

Program funding for FY 2008-2009 consisted of $9 million from the state's annual appropriations. The Program has awarded 85 grants since inception, representing $24.75 million in research funding. The following table outlines the number of grant applications received and the number, type, and total value of grant awards extended for each of the Program's three years.

Grant money that is obligated but not disbursed by the end of the fiscal year is carried forward to pay out multi-year grants in subsequent years.

Table 4:
Program Award History

	Award History					
	FY 2006-07		FY 2007-08		FY 2008-09	
Applicants	**47**		**35**		**57**	
Awards	No.	Million	No.	Million	No.	Million
Bridge	23	3.8	11	2.0	15	2.5
Bridge (2 year)	3	0.9	n/a	n/a	n/a	n/a
NIR	n/a	n/a	10	3.6	10	3.7
SEP	n/a	n/a	2	0.9	n/a	n/a
SIG	7	3.4	n/a	n/a	n/a	n/a
SPORE	n/a	n/a	2	2.0	2	1.9
Total	**33**	**$8.10**	**25**	**$8.50**	**27**	**$8.10**

Program Administrative Costs

The Program by statute can use up to ten percent of the appropriated funds for administrative expenses. As shown in Table 5 below, Program staff has held administrative costs below this statuatory limit, freeing up more dollars for direct use and project support.

Table 5:
Program Expenditures (Million)
*Percent difference equals monies returned to the Biomedical Research Trust Fund.

Fiscal Year	Appropriation	Grant Expenses	Percent	Administrative Expenses	Percent*
FY 08-09	9.00	8.10	90%	n/a	n/a
FY 07-08	9.00	8.15	91%	0.73	8%
FY 07-07	9.00	8.10	90%	0.82	9%
Total	**$27.00**	**$24.35**	**90% (avg)**	**$1.55**	**8.6% (avg)**

Program Management

The Office of Public Health Research, within the Department of Health manages the Bankhead-Coley Cancer Research Program. In addition to the support from the Biomedical Research Advisory Council, the Department of Health relies on the assistance of a contracting partner, Lytmos Group, Inc., to assist in program oversight and administration.

Jointly, the Office of Public Health Research and the Lytmos team fulfill a number of behind-the-scenes responsibilities, providing a seamless interface to support applicants, grantees, and the Council. See Table 6 for key activities that support Program operations.

Table 6:
Program Administration

Program Area	Activities
Program Planning and Development	• Plan and implement Program logistics and funding cycles • Prepare and release the Call for Grant Applications • Develop and refine Program policies and procedures and Program materials
Application Processing	• Prepare for, accept, and process online applications and provide technical assistance • Complete an administrative review of applications, checking compliance with all requirements
Scientific Peer Review Management	• Develop evaluation materials • Recruit, assign, and manage peer reviewers for scientific reviews of applications and progress reports • Maintain confidentiality agreements and monitor peer reviewer conflicts of interest • Monitor peer reviewer performance to ensure quality reviews
Decision Support	• Analyze and report competition statistics and data • Provide funding decision aids • Provide Biomedical Research Advisory Council support
Applicant and Grantee Support	• Provide ongoing Program and technical support from application through project work to grant completion
Administrative and Programmatic Monitoring	• Evaluate financial reports and budget changes; monitor grants for financial and scientific concerns • Review scientific and technical progress, conduct independent progress assessments, conduct site visits, and process project protocol change requests • Ensure compliance with human and animal use regulations • Process continuation and no-cost extension requests
Program Evaluation and Improvements	• Monitor and implement process and technology improvements • Work with the Biomedical Research Advisory Council to compare the Program against benchmarks, review and update long-term goals, and assist with strategic planning
Technical Support	• Provide automated application processing, grant management systems support, and website development and maintenance (www.floridabiomed.com)

How Grants are Awarded

The Program follows an annual cycle for soliciting applications and making awards, as illustrated in Figure 4. In evaluating proposals, the Program draws on the expertise of more than one hundred independent subject matter experts from outside Florida. These scientific peer reviewers evaluate grant applications that match their specific expertise, rating scientific and technical merit and fit with programmatic goals. Unlike other peer review processes in which reviewers consult with each other, these peer reviews are performed independently, with scores compiled. To ensure the validity of this approach, the Program sought and received recognition from the National Cancer Institute as having an approved scientific peer review process.

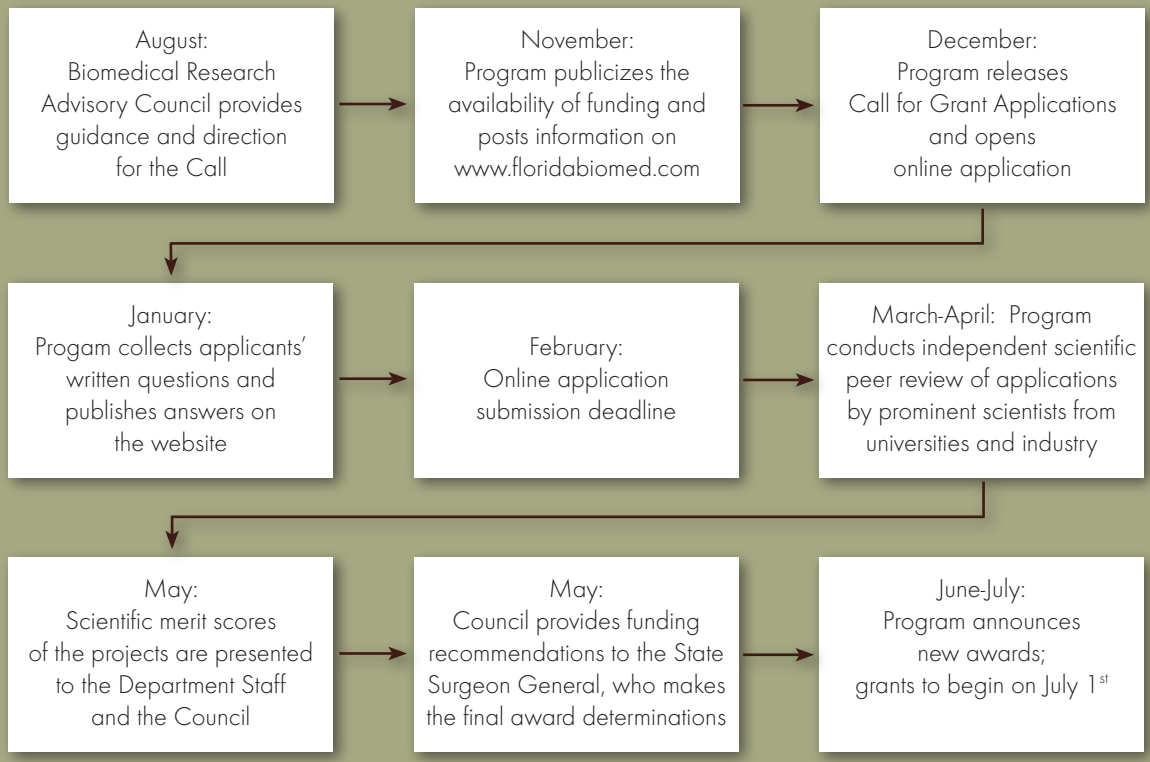


Figure 4:
The Annual Funding Cycle

In making funding recommendations, the Biomedical Research Advisory Council considers a number of factors about each application without knowing the names of the researchers, their institutions, or proposal titles in order to avoid conflicts-of-interest. They consider the peer review scores for scientific merit, cancer relatedness, and degree of collaboration, along with categories of research to develop a funding plan across all grant types, within budget constraints.

After awards are announced, the Program obtains signed contracts, final budgets, and human subject and animal study approvals from grantees.

How Grants are Managed

The Program uses tools and processes to ensure financial and research accountability, to support grantees, and to maintain compliance with Award terms and conditions, as illustrated in Table 7. Reporting requirements are intended to ensure progress rather than add administrative burden.

Annual renewal of multi-year grants is dependent on satisfactory performance.

Table 7:
Grant Management Processes and Tools

	Process or Tool	Value
Internal Controls	Signed terms and conditions (contract) with schedule of deliverables	• Defines expectations
	Grant Administration Manual	• Provides instructions for grantees
	Web-based system	• Provides grantees with convenient report submission • Serves as central data center • Provides efficient review of project deliverables
Financial Management	Regular review of budgets, financial reports, and expenditure changes	• Satisfies Program accountability
	Analysis of spending patterns	• Identifies potential accounting problems or project delays
Performance Management	Project work plans and research milestone charts	• Provides measurement framework
	Scientific peer review of annual progress reports for multi-year grants	• Obtains informed progress assessment • Provides additional mentoring to grantees
	Periodic site visits	• Validates project progress • Checks institutional controls • Solicits stakeholder feedback • Promotes the Program to increase future applicant pools

Feedback from stakeholders–including potential applicants, principal investigators, sponsored research office officials, and technology transfer offices, among many others–is highly valued and reflects the Program's emphasis on making continuous improvement.

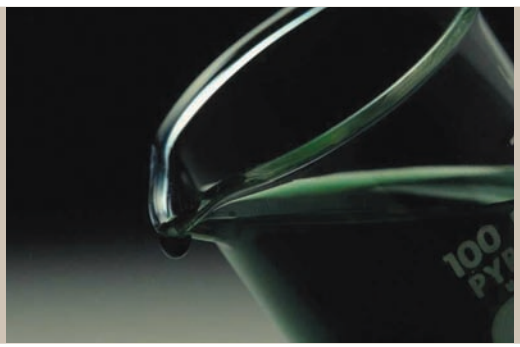
Recommendations to Further the Program's Purpose

According to s. 381.922(2)(a), *F.S.*, the Program is scheduled to expire January 1, 2011. Based on the Program goals, benefits, and accomplishments provided in this Annual Report, the Biomedical Research Advisory Council strongly recommends the renewal of the Bankhead-Coley Cancer Research Program.

Furthermore, the Council recommends maintaining the current limit of administrative expenses at ten percent to allow the Department of Health to continue providing necessary support and oversight in ensuring that the State of Florida receives a high return on its investment in this Program.

Biomedical Research Advisory Council

Section 381.922, *F.S.*, charges the Program with awarding grants for cancer research through the Bankhead-Coley Program (included in Appendix A). The Council meets this directive by advising the Office of Public Health Research at the Department of Health and the Florida State Surgeon General for the direction and scope of the Program and assists in the development of guidelines to ensure fairness, neutrality, and adherence to the principles of merit and quality in the conduct of the Program. The Council also functions in the same role for the James & Esther King Biomedical Research Program.



The Eleven Delegates to the Biomedical Research Advisory Council:

- One representative of the Florida Division of the American Cancer Society
- One representative of the Greater Southeast Affiliate of the American Heart Association
- One representative of the American Lung Association of Florida
- Four members appointed by the Governor, two with expertise in biomedical research
- One member from a Florida research university
- One representing the Florida general population
- Two members appointed by the President of the Florida Senate: One with expertise in behavioral or social research and one from a cancer program approved by the American College of Surgeons (ACoS)
- Two members appointed by the Speaker of the Florida House of Representatives: One from a professional medical organization and one from a cancer program approved by the American College of Surgeons

Among the significant contributions of the Council is the determination of specific grant mechanisms and eligibility requirements to achieve the statutory goals of the Program. The Council follows strict measures to avoid conflict-of-interest in making funding recommendations to the State Surgeon General, relying primarily upon the outcome of an independent scientific peer review process.

(above, pictured from left to right)

Nikolaus Gravenstein, M.D. Professor, Department of Anesthesiology, University of Florida. Seat: Biomedical Research. Appointed: 02/27/06

Veena Antony, M.D. Chief of Pulmonary, Critical Care and Sleep Medicine, Professor , College of Medicine, University of Florida. Seat: American Lung Association. Appointed: 0 7/01/07

Sigurd Normann, M.D., Ph.D. Professor, College of Medicine, Department of Pathology, Immunology and Laboratory Medicine, University of Florida. Seat: American Cancer Society. Appointed: 07/01/00

Herbert Weissbach, Ph.D. Distinguished Research Professor and Director, Center for Molecular, Biology and Biotechnology, Department of Biological Sciences, Florida Atlantic University. Seat: Advisory Council Vice-Chair and Biomedical Research. Appointed: 02/27/06

Albert Latimer, B.B.A. Senior Vice President, External Affairs, Enterprise Florida, Inc. Seat: General Public. Appointed: 02/27/06

Penny Ralston, Ph.D. Dean Emeritus and Professor, College of Human Sciences, Florida State University. Seat: Senate-Behavioral/ Social Research. Appointed: 07/17/06

Randal Henderson, M.D. Associate Medical Director of Proton Therapy Institute, Professor/Medical Director, Department of Radiation Oncology, University of Florida. Seat: House – Cancer Program (ACoS). Appointed: 04/20/07

Richard J. Bookman, Ph.D. Executive Dean for Research & Research Training and Vice Provost for Research, Miller School of Medicine, University of Miami. Seat: Advisory Council Chair and American Heart Association. Appointed: 07/01/00

not pictured:
Myra Hurt, Ph.D. Associate Dean, Research and Graduate Programs Professor, Department of Biomedical Sciences , College of Medicine, Florida State University. Seat: Research University. Appointed: 02/27/06

Daniel Morris, M.D. Medical Physician, Medical Oncology and Hematology, Naples Medical Center. Seat: Senate-Cancer Program (ACoS). Appointed: 07/17/06

Mary Lou Sole, R.N., Ph.D., CCNS, FAAN Professor, College of Nursing, University of Central Florida. Seat: House – Professional Medical Organization. Appointed: 04/19/07

Appendix A. Section 381.922, *Florida Statutes* – William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program

(1) The William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program, which may be otherwise cited as the "Bankhead-Coley Program," is created within the Department of Health. The purpose of the Program shall be to advance progress towards cures for cancer through grants awarded through a peer-reviewed, competitive process.

(2) The Program shall provide grants for cancer research to further the search for cures for cancer.

(a) Emphasis shall be given to the goals enumerated in s. 381.921, as those goals support the advancement of such cures.

(b) Preference may be given to grant proposals that foster collaborations among institutions, investigators, and community practitioners; as such, proposals support the advancement of cures through basic or applied research, including clinical trials involving cancer patients and related networks. (3)(a) Applications for funding for cancer research may be submitted by any university or established research institute in the state. All qualified investigators in the state, regardless of institutional affiliation, shall have equal access and opportunity to compete for the research funding. Collaborative proposals, including those that advance the Program's goals enumerated in subsection (2), may be given preference. Grants shall be awarded by the [1]State Surgeon General, after consultation with the Biomedical Research Advisory Council, on the basis of scientific merit, as determined by an open, competitive peer review process that ensures objectivity, consistency, and high quality. The following types of applications shall be considered for funding:

1. Investigator-initiated research grants.
2. Institutional research grants.
3. Collaborative research grants, including those that advance the finding of cures through basic or applied research.

(b) In order to ensure that all proposals for research funding are appropriate and are evaluated fairly on the basis of scientific merit, the [1]State Surgeon General, in consultation with the council, shall appoint a peer review panel of independent, scientifically qualified individuals to review the scientific content of each proposal and establish its priority score. The priority scores shall be forwarded to the council and must be considered in determining which proposals shall be recommended for funding.

(c) The council and the peer review panel shall establish and follow rigorous guidelines for ethical conduct and adhere to a strict policy with regard to conflicts of interest. A member of the council or panel may not participate in any discussion or decision with respect to a research proposal by any firm, entity, or agency with which the member is associated as a member of the governing body or as an employee or with which the member has entered into a contractual arrangement. Meetings of the council and the peer review panels are subject to chapter 119, s. 286.011, and s. 24, Art. I of the State Constitution.

(4) By December 15 of each year, the Department of Health shall submit to the Governor, the President of the Senate, and the Speaker of the House of Representatives a report indicating progress towards the Program's mission and making recommendations that further its purpose.

(5) Beginning in fiscal year 2006-2007, the sum of $9 million is appropriated annually from recurring funds in the General Revenue Fund to the Biomedical Research Trust Fund within the Department of Health for purposes of the William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program and shall be distributed pursuant to this section to provide grants to investigators seeking cures for cancer, with emphasis given to the goals enumerated in s. 381.921. From the total funds appropriated, an amount of up to 10 percent may be used for administrative expenses.

(6) By June 1, 2009, the Division of Statutory Revision of the Office of Legislative Services shall certify to the President of the Senate and the Speaker of the House of Representatives the language and statutory citation of this section, which is scheduled to expire January 1, 2011.

(7) The Legislature shall review the performance, the outcomes, and the financial management of the William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program during the 2010 Regular Session of the Legislature and shall determine the most appropriate funding source and means of funding the Program based on its review.

(8) This section expires January 1, 2011, unless reviewed and reenacted by the Legislature before that date.

History.–s. 8, ch. 2006-182.

[1]Note.–Chapter 2007-40 redesignated the Secretary of Health as the State Surgeon General.

Section 381.921, *Florida Statutes* – Florida Cancer Council Mission and Duties

The council, which shall work in concert with the Florida Center for Universal Research to Eradicate Disease to ensure that the goals of the center are advanced, shall endeavor to dramatically improve cancer research and treatment in this state through:

(1) Efforts to significantly expand cancer research capacity in the state by:

(a) Identifying ways to attract new research talent and attendant national grant-producing researchers to cancer research facilities in this state;

(b) Implementing a peer-reviewed, competitive process to identify and fund the best proposals to expand cancer research institutes in this state;

(c) Funding through available resources for those proposals that demonstrate the greatest opportunity to attract federal research grants and private financial support;

(d) Encouraging the employment of bioinformatics in order to create a cancer informatics infrastructure that enhances information and resource exchange and integration through researchers working in diverse disciplines, to facilitate the full spectrum of cancer investigations;

(e) Facilitating the technical coordination, business development, and support of intellectual property as it relates to the advancement of cancer research; and

(f) Aiding in other multidisciplinary research-support activities as they inure to the advancement of cancer research.

(2) Efforts to improve both research and treatment through greater participation in clinical trials networks by:

(a) Identifying ways to increase adult enrollment in cancer clinical trials;

(b) Supporting public and private professional education programs designed to increase the awareness and knowledge about cancer clinical trials;

(c) Providing tools to cancer patients and community-based oncologists to aid in the identification of cancer clinical trials available in the state; and

(d) Creating opportunities for the state's academic cancer centers to collaborate with community-based oncologists in cancer clinical trials networks.

(3) Efforts to reduce the impact of cancer on disparate groups by:

(a) Identifying those cancers that disproportionately impact certain demographic groups; and

(b) Building collaborations designed to reduce health disparities as they relate to cancer.

History.–s. 11, ch. 2004-2; s. 7, ch. 2006-182.

Appendix B. Grantee Publications

The following list represents new publications in peer-reviewed journals and books since October, 2007 based on funded research that current Program grantees have reported. This list does not include works submitted or in preparation. Publications are presented in alphabetic order by last name of the principal investigator, shown in **bold** type.

Dasgupta P, Rizwani W, Pillai S, Kinkade R, Kovacs K, Rastogi S, Banerjee S, Carless M, Kim E, Haura E, Coppola D, **Chellappan S**. Nicotine induces cell proliferation, invasion and epithelial-mesenchymal transition in a variety of human cell lines. *International Journal of Cancer*, 2008;124(1):36-45.

Yang H, Kong W, He L, Zhao JJ, O'Donnell JD, Wang J, Wenham RM, Coppola D, Kruk PA, Nicosia SV, **Cheng JQ**. MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. *Cancer Res*. 2008;68:425-33.

Dickey CA, Koren J, Zhang YJ, Xu YF, Jinwal UK, Bimbaum MJ, Monks B, Sun M, **Cheng JQ**, Patterson C, Bailey RM, Dunmore J, Soresh S, Leon C, Morgan D, Petrucelli L. Akt and CHIP coregulate tau degradation through coordinated interactions. *Proc Natl Acad Sci USA*. 2008;105(9):3622-7.

Cheng GZ, Park S, Shu S, He L, Kong W, Zhang W, Yuan Z, Wang LH, **Cheng JQ**. Advances of AKT pathway in huma oncogenesis and as a target for anti-cancer drug discovery. *Curr Cancer Drug Targets*. 2008;8(1):2-6.

Cheng JQ. Editorial "Targeting the AKT pathway for cancer intervention." *Curr Cancer Drug Targets*. 2008;8:1.

Wang J, Cheng JQ. A simple method for profiling of microRNAs expression. *Methods Mol Biol*. 2007;414:183-190.

Takahashi Y, Copploa D, Matsushita N, Cualing HD, Sun M, Sato Y, Liang C, Jung JU, **Cheng JQ**, **Mulé J**, Pledger WJ, Wang HG. Bif-1/Endophilin B1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. *Nat Cell Biol*. 2007;9(10):1142-51.

Lee H, Kim D, Dan HC, Cao C, Nicosia SV, Golemis EA, Liu W, Coppola D, Brem S, Testa JR, **Cheng JQ**. Identification and characterization of putative tumor suppressor NGB, a GTP-binding protein that interacts with the neurofibromatosis 2 protein. *Mol Cell Biol*. 2007;27(6):2103-19.

MF, Boulware D, Pinilla-Ibarz J, **Hazlehurst LA**. Stat3 contributes to resistance towards BCR-ABL inhibitors in bone marrow microenvironment model of drug resistance. *Molecular Cancer Therapeutics*. 2008;7(10):3169-75.

Huang S, Li X, Yusufzai TM, Qiu Y, Felsenfeld G. USF1 recruits histone modification complexes and is critical for maintenance of a chromatin barrier. *Mol Cell Biol*. 2007;27(22):7991-8002.

Takemoto CM, Lee YN, Jegga AG, Zablocki D, Brandal S, Shahlaee A, **Huang S**, Ye Y, Gowrisankar S, Huynh J, McDevitt MA. Mast cell transcriptional networks. *Blood Cells Mol Dis*. 2008;41(1):82-90.

Kiyota T, Kato A, and **Kato Y**. Ets-1 Regulates Radial Glia Formation During Vertebrate Embryogenesis. *Organogenesis*. 2007;3; 93-101.

Kiyota T, Kato A, Altmann CR, and **Kato Y**. The POU homeobox protein Oct-1 regulates radial glia formation downstream of Notch signaling. *Dev Biol*. 2008;315(2):579-592.

Kusmartsev S, Eruslanov E, Kubler H, S Sakai Y, Su Z, Rosser C, Dahm P, Siemann D, Vieweg J. Oxidative stress up-regulates expression of VEGFR1 in myeloid cells: link to tumor-induced immune suppression in renal cell carcinoma. *J Immunol.* 2008;181(1):346-53.

Koike N, Pilon-Thomas S, **Mulé JJ**. Nonmyeloablative chemotherapy followed by T-cell adoptive transfer and dendritic cell-based vaccination results in rejection of established melanoma. *J Immunother.* 2008;31(4):402-12.

Matsushita N, **Pilon-Thomas SA**, Martin LM, Riker AI. Comparative methodologies of regulatory T cell depletion in a murine melanoma model. *J Immunol Methods* 2008;333(1-2):167-79.

Radisky DC, and LaBarge MA. Epithelial-Mesenchymal Transition and the Stem Cell Phenotype. *Cell Stem Cell.* 2008;2(6):511-512.

Nelson, CM, Khauv D, Bissell, MJ, and **Radisky DC**. Change in cell shape is required for matrix metalloproteinase-induced epithelial-mesenchymal transition of mammary epithelial cells. *J Cell Biochem.* 2008;105(1):25-33.

Frederick LA, Matthews JA, Jamieson L, Justilien V, Thompson EA, **Radisky, DC**, Fields AP. Matrix metalloproteinase-10 is a critical effector of protein kinase Ciota Par6alpha-mediated lung cancer *Oncogene.* 2008;27(35):4841-53.

Przybylo JA, **Radisky DC**. Matrix metalloproteinase-induced fibrosis and malignancy in breast and lung. *Proc Am Thorac Soc.* 2008;5(3):316-22.

Orlichenko LS, **Radisky DC**. Matrix metalloproteinases stimulate epithelial mesenchymal transition during tumor development. *Clin Exp Metastasis.* 2008;25(6):593 600.

Radisky DC. Leading the charge. *Nat Cell Biol.* 2007; 9(12):1341-2.

Salameh MA, Soares AS, Hockla A, **Radisky ES**. Structural basis for accelerated cleavage of bovine pancreatic trypsin inhibitor (BPTI) by human mesotrypsin. *J Biol Chem.* 2008;283(7):4115-4123.

Tsuji S, Yamashita M, Nishiyama A, Shinorata T, Li Z, Myrvik QN, Hoffman DR, Henriksen RA, **Shibata Y**. Differential structure and activity between human mouse intelectin-1: human intelectin-1 is a disulfide-linked trimer, whereas mouse homologue is a monomer. *Glycobiology.* 2007;17(10):1045-1051.

Yamashita M, Shinohara T, Tsuji S, Myrvik QN, Nishiyama A, Henriksen RA, **Shibata Y**. Catalytically inactive cyclooxygenase 2 (COX-2) and absence of PGE2 biosynthesis in murine peritoneal macrophages following in vivo phagocytosis of heat-killed *Mycobacterium bovis* BCG. *J Immunol.* 2007;179(10):7072-7078.

Nishiyama A, Shinohara T, Tsuji S, Yamashita M, Henriksen RA, Myrvik QN, **Shibata Y**. Depletion of cellular cholesterol enhances macrophage MAPK activation by chitin microparticles but not by heat-killed Mycobacterium bovis BCG. *Am J Physiol Cell Physiol.* 2008;295:341-349.

Lopatiuk-Torpak O, Langen KM, Meeks SL, Kupelian PA, Maryanski MJ, and **Zeidan OA**. Performance evaluation of an improved gel dosimeter system for 3D dose verification of static and dynamic phantom deliveries. *Med Phys.* 2008;35(9):3847-59.

Zhang Y, Zhang M, Yong S, Li X, Olashaw N, Kruk P, Cheng JQ, Bai W, Chen J, Nicosia S, **Zhang X**. Deacetylation of cortaction by SIRT1 promotes cell migration. *Oncogene.* Epub Oct. 13.

Appendix C. Related Awards Reported by Grantees

Chellappan, S. (2006 Bridge), "Role of beta arresin1 and Src in nAChR signaling and lung cancer," National Cancer Institute, $1,730,032.

Hazlehurst, L. (2006 Bridge), "Targeting Stat3 in the bone marrow microenvironment in CML," Leukemia Lymphoma Society, $600,000.

Hazlehurst, L. (2006 Bridge), "Beta 1 integrin inhibitory peptides: Novel agents for the treatment of MM," Multiple Myeloma, $200,000.

Lokeshwar, B. (2006 Bridge), "Antitumor and chemopreventive properties of the Ecuadorian Plant Extract BIRM," National Institutes of Health, $1,192,884.

Moffitt, K. (2007 SEP), "Health Information Technology Special Congressional Initiative Florida Cancer Clinical Trials Project," Health and Human Services, $521,370.

Qiu, Y. (2006 Bridge), "Transcriptional regulation of TAL1/SCL in normal and malignant hematopoiesis," National Institutes of Health, $1,250,000.

Radisky, D. (2006 Bridge), "Investigation of relationship between cell structure and malignancy," National Cancer Institute, $95,000.

Shibata, Y. (2006 SIG), "Interfering with CCL2 and CCR2 to limit tumor growth," National Institutes of Health, $220,000.

Siemann, D. (2006 Bridge), "Combining Anti-Angiogenesis Strategies and Radiotherapy," National Cancer Institute, $1,252,430.

Teplitski, M. (2006 SIG), "Pilot study: Salmonella genes involved in colonization of oysters," Florida Sea Grant, $5,000.

Wright, A. (2006 SIG), "Post harvest treatment of live oysters and investigation of therapeutic potential of biological controls," USDA, $372,096.

Wright, A. (2008 Bridge), "Discovery of Novel Antitumor Agents Effective Against Pancreatic Cancer," National Institutes of Health, $339,179.

Yamamoto, J. (2006 SIG), "Protective CMI mechanisms of a dual-subtype FIV vaccine," National Institutes of Health, $1,887,125.

Appendix D. Abbreviated Abstracts of 2008 Grant Awards

The following is a list of grants awarded by the Program in 2008.

Detection of Melanoma by Canine Olfactory Receptors

ABAFFY, Tatjana

2008 Bridge
University of Miami
$162,000

Melanoma is the most serious form of skin cancer. It has an aggressive course, and successful treatment requires early diagnosis. Current diagnosis is based on the results of biopsy analysis using a more than 100-year old method. Distinguishing between benign pigmented lesions and early melanomas can be difficult. The central hypothesis is that melanoma tissue contains unique volatile compounds that can be recognized by olfactory receptors. We are identifying volatile melanoma biomarkers and olfactory receptors that detect these biomarkers. The major innovation of this grant is to lay the foundation for the clinical diagnosis of melanoma based on volatile by-products of altered metabolism. Identification of the specific olfactory receptors that recognize melanoma biomarkers will enable future work–a biosensor for early detection of melanoma. Our long-term objective is the development of a safe and non-invasive diagnostic tool. The profile that emanates from cancerous tissue forms an odor signature that is different from control tissue. In order to find a differential pattern, profiling melanoma volatiles is being done by gas chromatography and mass spectrometry. To identify "smell" receptors that respond to melanoma biomarkers, we are using two assays: electrophysiological assay for functional receptor expression and a gene expression microarray analysis.

Dynamic Eukaryotic Replication Machines

BLOOM, Linda

2008 Bridge
University of Florida
$200,000

The genome is replicated prior to every cell division. DNA damage encountered during replication can cause point mutations and genetic rearrangements both of which can lead to cell transformation and cancer. Cells have a surveillance mechanism to monitor levels of DNA damage during replication and halt the process when damage is severe. One component of this checkpoint system is a complex of five proteins, four of which are also found in the clamp loader, a component required for synthesizing DNA. The mechanism of action of the replication clamp loader is reasonably well established, but the mechanism of the checkpoint complex is less understood. Studies show that the extra subunit difference alters the substrate specificity (molecules upon which the enzymes act) of the checkpoint complex. The major goal of this grant is to compare the biochemical activities of the replication and checkpoint complexes to determine how substitution of a single subunit can alter the function. Specifically, our aims are to compare 1) the DNA-binding activities and 2) the clamp-binding activities of the replication and checkpoint clamp loaders. Our approach is to use fluorescence-based assays with purified proteins to measure these dynamic interactions directly in solution and in real time. One hypothesis is that the checkpoint complex functions as a clamp unloader to help stop replication. Many types of cancer and syndromes predisposing individuals to cancer result directly from defects in cell cycle checkpoint responses. The goal of this research is to increase our understanding of the biochemical basis for a checkpoint response that functions during DNA replication and contribute to the knowledge base required to develop effective therapeutic strategies against cancer.

The Role of T Box Transcription Factor 2 (TBX2): A Novel Therapeutic Target in Breast Cancer

BRIEGEL, Karoline

2008 Bridge
University of Miami
$104,945

These studies aim to elucidate the molecular mechanisms underlying tumor development in familial breast cancer. T-box transcription factor 2 (TBX2), a protein that normally regulates fetal development, is present in abnormally high amounts in breast tumors of patients with a family history of breast cancer. Hereditary breast cancer is characterized by mutations in the breast cancer susceptibility genes BRCA1/2, early onset, and poor clinical outcome. At present, very little is known about the molecular mechanisms that lead to breast cancer development in these patients. Published research as well as our own work strongly suggest that reactivation of TBX2 in BRCA1/2-mutant breast cells may facilitate breast tumorigenesis (production of tumors). For example: 1) TBX2 possesses characteristic features of an oncoprotein (cancer-causing protein), 2) TBX2 has the potential to induce cellular changes in primary breast tumor cells that are prerequisite to cancer metastasis, 3) Reactivation of TBX2 may endow cancer cells with an increased resistance against chemotherapy. In this grant we are testing the hypothesis that TBX2 overexpression and familial BRCA1/2 gene mutations have a cooperative effect on promoting breast cancer development. The goal of Aim1 is to analyze the consequences of abnormal TBX2 expression on tumorigenesis of BRCA1-associated breast cancers in a mouse model that harbors both genetic events. This model will help to determine tumor incidences as well as the molecular events downstream of TBX2 function. The purpose of Aim 2 is to assess the role of TBX2 in tumor progression of BRCA1-associated breast cancers in a cell culture model. Specifically, we are examining if abnormal activation of TBX2 makes these cancer cells more resistant to chemotherapy. A better understanding of these mechanisms will be pivotal for the future development of preventive and more specific therapies for difficult-to-treat forms of breast cancer.

Identification and Characterization of MicroRNAs Involving Breast Cancer Metastasis

CHENG, Jin

2008 Bridge
H. Lee Moffitt Cancer Center & Research Institute
$100,000

Tumor metastasis is the most common cause of mortality in breast cancer patients. Understanding the molecular basis of breast cancer metastasis can provide the critical information needed to generate targeted therapies that have a distinct mechanism of action separate from the conventional chemotherapeutics. A number of protein-coding genes have been shown to play an important role in different steps of metastasis. However, the role of micro ribonucleic acids (microRNAs or miRNAs), a class of small RNAs (22 nucleotides long) that regulate numerous genes, in breast cancer metastasis is currently unknown. We have recently identified that a dozen miRNAs were deregulated in Transforming Growth Factor beta (TGF-beta)-mediated breast cell migration and invasion as well as in highly metastatic breast cancer cell lines. Micro-RNAs like miR-155 and miR-214 were significantly elevated in TGFbeta-treated cells and metastatic cell lines. Knockdown of miR-155 and miR-214 decreased cell migration and invasion. Previous studies show frequent deregulation of miRNAs in breast cancer. Each miRNA negatively regulates hundreds of genes; therefore, miRNAs could play a significant role in breast cancer metastasis and serve as important therapeutic targets for blocking this process. To test this hypothesis, we are: 1) Identifying the miRNAs involving metastasis in human primary breast tumor and 2) Applying knockdown of microRNAs systems to identify target genes of miR-214. This will be followed by an evaluation of the impact of miR-214 target gene PTEN on miR-induced cell migration and invasion.

CRESS, Doug

2008 Bridge
H. Lee Moffitt Cancer Center & Research Institute
$200,000

Basic Mechanisms of E2F Regulation in Cancer Therapeutics

A recent NIH Think Tank workshop put forth four specific recommendations "to accelerate progress in cancer research." One of these recommendations is to "Support further identification of molecular targets for enhancing programmed cell death in response to DNA damage, particularly by investigating p53-independent pathways of DNA damage response . . . and by investigating strategies . . . to amplify cell death signals." In lay terms, this recommendation means that cancer researchers need to focus on improving what we already know works. We know that radiation and chemotherapy work, but we also know that cancer cells find ways to avoid dying during radiation and chemotherapy. Thus, it is very important for us to find new drugs that will block these unwanted survival pathways–at least temporarily–so that standard cancer treatments can be effective. Our research has focused on a transcription factor–a part of the system that controls the transfer (or transcription) of genetic information from DNA to RNA. Over the past five years, we have used our basic understanding of the E2F family of transcription factors to develop a new drug (HLM006474) that we expect will help standard cancer therapies work much better and may even have activity on its own. This work focuses on a further characterization of HLM006474 in preclinical studies. It is our goal to better understand how the drug works to kill cancer cells while sparing normal cells, to predict which lung cancers are most sensitive to the drug (based on the mutation they have), and to test if the drug works in human cancer cells grown in mice. The outcome of these studies will enhance our ability to gain long-term support for development of this novel class of cancer drug.

FANG, Jia

2008 NIR
H. Lee Moffitt Cancer Center & Research Institute
$375,000

Role of Novel Methyl-H3K9 Binding Protein MPP8 in Transcription Silencing and Tumorigenesis

Epigenetic modifications, including DNA methylation and histone modifications, occur within a larger context of chromatin and influence a variety of cellular processes from regulation of gene transcription to proper chromosome segregation. Altered epigenetic regulation could result in aberrant gene function or a gene expression pattern that could lead to carcinogenesis. As one of the best-studied epigenetic modifications, histone H3K9 methylation is catalyzed by several histone methyltransferases and has been linked to transcription regulation of heterochromatic and euchromatic genes. To further dissect the function of this modification, we have identified and characterized a novel methyl H3K9 binding protein, MPP8. Our preliminary data argue for a model by which MPP8 is a key regulator in methyl-H3K9 mediated euchromatic gene silencing and in turn plays an important role in tumorigenesis by epigenetically silencing tumor suppressor genes. To extend our studies, we are using a combination of approaches to further characterize H3K9 methylation, recognition, and transcription regulation cooperated by histone methyltransferases and MPP8. We are also determining the role of MPP8 in the repression of tumor suppressor genes and in breast cancer metastasis. Since the overall disruption of the epigenetic landscape is the most common feature of all human tumors, advances in our understanding of the functional significance has a major impact on issues related to human cancer.

GODAVARTY, Anuradha

2008 Bridge
Florida International University
$108,000

Diagnostic Mammography Using a Real Time Co-Registering Novel Hand-Held Optical Imager

Optical imaging is emerging as a non-invasive and non-ionizing imaging modality towards breast cancer diagnosis. Most of the currently available optical imaging systems are either bulky and/or not adaptable for different tissue shapes and volumes. Recently, hand-held based optical imagers have been developed, although none to date can contour to different tissue curvatures, nor register their precise location on the breast tissue during real-time imaging. Hence, the objective of our work is to implement an automated co-registration scheme in a novel hand-held optical probe, such that real-time, 3-D optical imaging towards tomography studies is feasible. Our major aims are to: 1) Implement a 3-D motion tracker for real-time tracking of the exact position and orientation of the hand-held probe during imaging studies and 2) Perform 3-D co-registered tracking on different tissue phantom geometries. The rationale of the work is that the hand-held imaging concept, although common in ultrasound and nuclear imaging, will be unique in its co-registering capabilities for real-time, 3-D optical imaging using non-ionizing light. Specifically, the target of the research is to positively impact early diagnosis in high-risk, younger women with dense breasts (upon using external contrast agents) and improve the survival rate of women affected by breast cancer (1 in 8 in the United States). The long-term goal of our work is to implement the novel hand-held optical imager as a routine breast imaging tool (at various stages of the disease) in cancer centers nationwide, complimenting the existing and widely used x-ray and nuclear techniques. Ultimately, we want to allow a cost-effective and a more affordable health care alternative for women of any age group and geographical background.

IRAGAVARAPU-CHARYULU, Vijaya

2008 Bridge
Florida Atlantic University
$81,000

Use of Selective PGD2 Receptor Antagonists to Reduce MMP- Secretion and Decrease Metastasis in a Breast Cancer Model

Chronic inflammation contributes towards the development of tumors, their growth, and metastasis. Tumors will not grow unless a blood supply is established by production of angiogenic molecules such as vascular endothelial growth factor (VEGF). Metastasis is dependent on degradation of extracellular matrix, a process mediated by zinc-dependent proteases, matrix metalloproteinases (MMPs). [A protease is the digestive enzyme needed to digest proteins.] Elevated levels of both these types of molecules (VEGF and MMP-9) have been associated with aggressive breast cancer. Using a breast cancer mouse model (DA-3), we reported elevated levels of angiogenic molecules, VEGF, CXCL2, and MMP-9. These molecules are produced by both DA-3 tumor cells and inflammatory T lymphocytes of tumor-bearing mice. Functions of inflammatory T cells and macrophages are altered in tumor-bearing hosts resulting in tumor growth. We have shown that tumor-infiltrating inflammatory cells aid tumors by: a) secreting angiogenic molecules VEGF and CXCL2 and b) enabling metastasis by secreting MMP-9. High MMP-9 and VEGF levels are associated with expression of inducible cyclooxygenase (COX-2). COX-2, catalyzing formation of prostaglandin E2 (PGE2) and inflammatory prostaglandin D2 (PGD2), is expressed by macrophages and tumor cells. Elevated levels of COX-2 and PGD2 may affect cancer growth and metastasis. PGD2 mediates its effects through DP1 and CRTH2 receptors, expressed by T cells. Thus, we hypothesize that blocking of PGD2 receptors to inhibit inflammation will decrease VEGF and MMP-9 production leading to suppressed tumor growth and metastasis. To test this, we are administering CRTH2 and DP1 antagonists, ramatroban and BWA868C (selective blockers of PGD2 receptors) to mice orally followed by these analyses: 1) Assays for VEGF by ELISA (a biochemical technique used mainly in immunology to detect the presence of an antibody or an antigen in a sample), 2) MMP-9 levels by zymography (a simple, sensitive, quantifiable, and functional approach for the analysis of proteolytic [digestion of proteins] activity in cell and tissue extracts), 3) Measurement of tumor size. The aim of these studies is the identification of new selective molecular targets for breast cancer and new treatment options.

RNA Silencing of Oral Cancer

JAKYMIW, Andrew

RNA interference (RNAi) is a cellular process that is revolutionizing scientific research, and there is considerable excitement about using RNAi for therapy. [RNAi creates the opportunity to silence the production of disease-causing proteins.] Despite the growing number of reports demonstrating the many exciting therapeutic aspects of RNAi, little has been studied regarding the application of RNAi in the treatment of oral cancer. Therefore, it is the immediate goal of this grant to address this concern by bringing RNAi-based treatments to oral medicine. A major advantage is that the mouth is readily accessible to manipulation and may be especially suitable for RNAi-based treatments. The research involves the characterization of RNAi function in oral cancer cells, and optimization of drug and viral gene delivery techniques. Furthermore, several potential cancer-promoting genes will be targeted and suppressed using RNAi, after which the feasibility of using RNAi-based drug and gene therapy approaches to treat a mouse model that mimics a human oral cancer will be determined. The long-term research goal of this grant is to exploit this novel technology and develop it into an effective therapy for oral cancer. By harnessing RNAi for oral medicine, it will allow both scientists and clinicians to silence diseases of the oral cavity. Results from these studies may have a broader impact applicable to treatment of other diseases using RNAi-based therapies.

2008 NIR
University of Florida
$375,000

SHIP and Immunoregulatory Cell Function

KERR, William

Doctors transplant bone marrow (BM) from a normal, healthy donor into a cancer patient for two reasons. It provides a tumor-free graft to replenish the blood cells damaged by chemotherapy and radiation. In addition, the BM graft also contains immune cells from the donor that attack tumor cells in the patient's body. Unfortunately, despite the best efforts to genetically match patients with donors, there is still sufficient difference between them that a war results between their immune systems. The patient's immune cells try to kill the incoming BM graft, while the immune cells from the donor attack vital organs. This immune war is the leading cause of treatment-related death in allogeneic BM transplantation. In addition, some patients succumb to infectious complications caused by the immunosuppressive drugs they receive to prevent this immune war. Thus, although allogeneic BM transplants can cure, they can also kill. We have identified a gene, SHIP, that when turned off reduces immune wars between patients and donors and thus allows improved survival after the BM transplant. There are two types of cells that can prevent or limit these immune wars after BM transplant. When the SHIP gene is turned off, the activity of these "peacekeeper" cells is increased. The goal of this grant is to determine whether one or both of the "peacekeepers" are required to prevent these immune wars. Therefore, we have developed mice in which the SHIP gene is turned off in one or the other peacekeeper cells. We will perform allogeneic BM transplants with both of these mice to determine whether increases in one peacekeeper or the other are able to protect mice from life-threatening immune wars. These studies will aid our understanding of how we might use such peacekeepers to prevent BM transplant-related deaths in cancer.

2008 Bridge
H. Lee Moffitt Cancer Center & Research Institute
$200,000

Prediction Models of Complex DNA Repair Pathways in Prostate Cancer Risk

LIU, Wen

Prostate cancer is the most common cancer and the second leading cause of cancer death in American men. Despite rapid advances in cancer research, the cause of prostate cancer remains largely unknown. Critical questions to predict a man's risk for prostate cancer remain unanswered. To improve strategies for prostate cancer prevention, our long-term objectives are: (i) to develop and validate prediction models of DNA repair genes in prostate cancer risk; (ii) to identify high-risk populations by validated prediction models of gene-gene and gene-environment interactions; and (iii) to reduce prostate cancer risk in genetically susceptible (sub) populations through screening and targeted intervention. The Specific Aims are: 1) To test the hypothesis that genetic variations of DNA-repair genes contribute to prostate cancer risk, 2) To test the hypothesis that gene-environment interactions play critical roles in prostate cancer risk and, 3) To investigate whether genetic variations impede DNA-repair function, elevate DNA damage, and contribute to prostate cancer susceptibility. Multiple DNA repair pathways are critical in maintaining genome integrity. Therefore, a comprehensive evaluation of mutations in DNA repair genes is crucial. The outcome of this research will advance our knowledge in building prediction models of prostate cancer susceptibility and identify prevention targets that can be translated into healthy behavior promotion to reduce prostate cancer risk.

2008 NIR
University of Miami
$375,000

Mechanisms of Bladder Cancer Progression

LOKESHWAR, Vinata

Bladder cancer (BCa) is the costliest cancer to treat due to the heterogeneity in tumor progression and frequent recurrence. Two accurate molecular markers for BCA that stimulate BCA growth, invasion, and angiogenesis include HYAL1 hyaluronidase and hyaluronic acid (HA), a glycosaminoglycan. We hypothesize that HA and HYAL1 inhibitors cripple BCa growth and metastasis, and that HYAL1 expression is transcriptionally regulated. The two inhibitors we are working with include HYAL1 inhibitor, sulfated-HA (sHA), and HA synthesis inhibitor, 4-methylumbelliferone (4-MU). They inhibit BCa growth by inducing cell cycle arrest and apoptosis, respectively. They are non-toxic and have antitumor activity. To examine the mechanism of sHA and 4-MU action, we are evaluating their effects on membrane proximal signaling events induced by the cell surface HA-HA receptor interaction in BCa cells. We will also test the effect of sHA, 4-MU, HA and HA-oligosaccharides on normal bladder cells. We will perform cDNA microarray and microRNA analyses to examine the global changes in gene expression induced by sHA or 4-MU in BCa cells (Aim 1). The regulation of HYAL1 expression is unknown. We identified HYAL1 promoter and showed that DNA methylation regulates HYAL1 expression in BCa. To identify any enhancer/repressor elements that regulate HYAL1 expression, we will analyze up to 5-kb sequence up stream of the HYAL1 transcription start site by cloning and reporter assays in BCa and normal urothelial cells. EMSA and ChIP assays will be performed to identify the possible regulators of HYAL1 transcription in the far up stream region. We will also characterize any demethylase activity in BCa and normal urothelial cells that might be involved in regulating HYAL1 promoter methylation (Aim 2). This study should reveal how HYAL1 and HA inhibitors control BCa through intracellular signaling and the potential of these inhibitors as BCa treatments. Analysis of how HYAL1 expression is regulated in BCa may suggest ways to control it.

2008 Bridge
University of Miami
$199,633

LU, Michael

2008 Bridge
Florida Atlantic University
$135,000

PAK6 Activation in Advanced Prostate Cancer

Tumor metastasis is the major cause of treatment failure for cancer patients. This grant aims at studying a novel signal pathway that regulates prostate cancer metastasis. Most current treatment modalities such as surgery, radiation, hormonal therapy, and chemotherapy have limited effect in treating metastatic tumors. Novel targets aiming at blocking tumor metastasis are urgently needed for future development of new therapeutic treatment. In steroid hormone-dependent human cancers, hormones are known to promote metastasis of prostate, breast, and ovarian cancers. We recently identified a novel molecular regulator, a protein kinase enzyme named PAK6, as a dominant factor in controlling androgen-regulated tumor metastasis in prostate cancer cells. This grant is designed to fully delineate the molecular process of how androgen influences the development of advanced metastatic prostate cancer. We are using state-of-the-art proteomic technology, including chromatography and mass spectrometer, to identify cellular components that interact directly with PAK6 in this signal pathway. Once we identify the candidate interacting partners, we will subject each of them to a stringent authentication process to prove that the interactions are physiologically genuine. Bona fide interacting partners will then be identified and their roles in regulating androgen-stimulated prostate cancer metastasis will be defined. We firmly believe that the results obtained from this project will open a new avenue to define various new targets pivotal to the future development of clinical modalities for the intervention of prostate cancer metastasis. Given the urgency in the need for new drug targets, immediate application of our research results will undoubtedly benefit the drug discovery effort. The ultimate goal is to deliver valid, therapeutic targets for prostate cancer treatment.

MANETSCH, Roman

2008 NIR
University of South Florida
$375,000

Chemical Tools for Proteomic Profiling

Proteomics is a relatively novel technique that allows the investigation and study of all the proteins in a cell. Most of the time, proteomics is heavily dependent on analytical techniques such as gel electrophoresis or mass spectrometry. Although these analytical techniques are considered classical for chemical and biochemical studies, recent advances have actually made studies of the entire cell content possible. We aim at developing chemical tools that will allow us to study and quantify the biochemical processes in a complex mixture, such as can be found inside a cell. Our approach is based on the synthesis of small molecules, which can be attached to certain proteins upon irradiation of UV light. The small molecules we will synthesize are closely related to adenosine, one of the major components in a cell. It has been shown that cancer cells quite often express different types or different levels of proteins, which then cause cancer. We think that our molecules will enable us to determine and quantify the extent of aberrant proteins. This method has tremendous potential in the development of methods for the early diagnosis of cancer, for the assessment of the severity of cancer, for the identification of new targets for the development of novel anticancer drugs, and for the evaluation of the selectivity of these newly developed drugs.

MCGORON, Anthony

2008 Bridge
Florida International University
$200,000

Image Guided Intervention for Breast Cancer: Combined Hyperthermia and Chemotherapy with Reduced Cardiotoxicity

Many current chemotherapy agents cause non-target tissue toxicity that complicates long-term treatment planning. Therefore, new, highly effective targeted drugs with low toxicity are needed. Actively targeted chemotherapy to solid tumors using cancer-specific cell receptors has the potential to greatly improve drug delivery and reduce unintended toxicity. Hyperthermia in combination with chemotherapy improves cell killing, but the heating is generally global, affecting surrounding normal tissue as well. To effectively utilize the advantages of targeted chemotherapy and hyperthermia for cancer therapy, the development of a new drug, which combines a chemotherapy agent and a light absorbing dye, is the grant's goal. In addition to facilitating local heating, the optical dye will also serve as the contrast agent for imaging. The drug will further be modified to enhance its targeting to cancer cells. The objective is the preclinical development of targeted therapeutics, specifically to develop a methodology of improved cancer treatment by combining a novel therapy and imaging function in the same drug and testing the compound in vitro and in vivo. This grant describes a drug/therapy that will be targeted to cancer cell receptors and employs a modified and improved classical chemotherapy drug, doxorubicin (DOX), which is enhanced by local specific tissue heating following optical identification. The heating will be accomplished by illuminating the optical dye component of the drug, indocyanine green (ICG), at the tissue site. The first hypothesis is that newly developed DOX-peptide-conjugates will be as effective as DOX alone in killing DOX-sensitive cancer cells and improve drug toxicity to DOX-resistant cancer cells, but with less cardiotoxicity. The second hypothesis of this grant is that local cellular heating with a light absorbing dye combined with actively targeted chemotherapy will improve cancer cell killing more than heating or chemotherapy alone.

ROUX, Kyle

2008 NIR
University of Florida
$375,000

Targeting A-type Lamins as a Cancer Therapy

We are targeting lamin A in order to inhibit cancer progression. Our overall hypothesis is that mechanisms of cell senescence (biological processes of an organism approaching an advanced age) observed in patients with Hutchinson-Gilford progeria syndrome (HGPS) can be harnessed to treat various forms of cancer. Mutations in the gene encoding A-type lamins (lamins A/C) lead to HGPS, a disease resembling premature aging. The most common of these mutations inhibits complete processing of prelamin A; however, other mutations alter the surface of the lamin molecule at a discrete site. In this grant, we are using multiple experimental approaches that capitalize on both types of mutations to create anti-cancer therapies. Furthermore, we are investigating the mechanism(s) behind lamin A-dependent progeria to identify new targets for an anti-cancer treatment. We envision a future therapy in which a transient induction of A-type lamin-dependent cell senescence and death would arrest the growth of, and ultimately lead to the destruction of, rapidly dividing cancer cells.

Enhancing Radiation Therapy: Vascular Targeting Agents

SIEMANN, Dietmar

Cancer growth and its ability to spread are critically dependent on its supportive blood vessel network. Consequently, there has been a great deal of interest in cancer research in developing new anticancer agents that are designed to specifically damage and destroy the tumor vasculature. For the past 10 years, our laboratory has been involved in evaluating such so-called vascular disrupting agents (VDAs) using a variety of mouse and human tumor cells grown in tissue culture or mice. We have shown that these agents have the ability not only to severely damage tumors when used on their own but also to markedly increase the antitumor effects of chemotherapy or radiation therapy when used in combination with these traditional anticancer treatments. Based on preclinical studies such as our own, several of the lead VDAs have now entered clinical evaluations in cancer patients. Early indications from those trials are very encouraging, but the patient studies have also raised several questions. For example, it has become increasingly clear that further information regarding the optimization of dose scheduling and drug delivery is needed. The goal of our studies is to use human kidney cancer models grown in mice to examine several VDA treatment scheduling and dosing strategies in order to determine how to maximize VDA antitumor activity. Our preliminary findings indicate that such an approach is not only feasible but can be highly effective. These current preclinical investigations are allowing us to develop a rational choice of treatment schedules that will provide guidelines/suggestions for future clinical VDA initiatives in cancer.

2008 Bridge
University of Florida
$200,000

SHP-2 and c-Src in Pancreatic Cancer Cell Biology, Tumorigenesis, and Metastasis

SUMMY, Justin

Pancreatic cancer is one of the deadliest human malignancies, with fewer than five percent of patients surviving five years after diagnosis. The reasons for the poor prognosis include a lack of obvious symptoms, rapid progression and metastasis, and resistance to conventional chemotherapeutic agents and radiation treatments. There is a great need for the development of improved pancreatic cancer therapies, and a comprehensive understanding of pancreatic cancer biology is crucial to this process. Therapeutic targets are necessary for the promotion of cellular events that are crucial for the development and progression of pancreatic tumors and/or metastases. Some of these events include cell division, cell migration, invasion into surrounding tissues, and acquisition of resistance to cell death. We have determined that the proteins c-Src and SHP-2 are ideal and complementary therapeutic candidates for pancreatic cancer, as they are both strongly expressed in pancreatic cancer and both have been demonstrated, in other systems, to promote many of the cellular events described above. We are examining the regulation and function of these proteins in human pancreatic cancer cells grown in culture, banked human pancreatic cancer samples, and a mouse model of the human disease. We are using multiple techniques to inhibit the function of these proteins, individually and in combination, in order to evaluate their therapeutic potential in a pre-clinical model of human pancreatic cancer.

2008 NIR
M. D. Anderson Cancer Center Orlando
$346,298

Role of RNA polymerase II in Genome Maintenance

TORNALETTI, Silva

Tumorigenesis is a complex, multistage process in which normal cells are transformed into cancer cells. Intensive research efforts have increased our understanding of carcinogenesis, and have identified a genetic basis for the multi-step process of tumor development. Tumors grow through a process of expansion driven by changes in the way normal cells regulate their growth. When these genetic changes occur in critical genes, such as proto-oncogenes and tumor suppressor genes, they result in abnormal control of cell division and cell death, leading to tumor development. These genetic changes often occur at common regions or "hotspots," which are particularly susceptible to chromosome breakage. Emerging evidence indicates that these hot spots frequently localize to DNA sequences that can assume unusual DNA structures and correlate them with tumor development. However, the molecular mechanisms underlying the genetic instability associated with these structures are poorly understood. In this grant, we are exploring the mechanisms and the factors involved in resolving those DNA structures that have been implicated in carcinogenesis. The results from this research will have significant implications not only for mechanisms of carcinogenesis, but also for the development of novel modes of cancer chemotherapy.

2008 NIR
University of Florida
$375,000

Developing a Translational Prostate Cancer Research Program

VIEWEG, Johannes

The University of Florida (UF) and H. Lee Moffitt Cancer Center (Moffitt) have made a major commitment to unify their efforts and provide the considerable resources necessary to establish, promote, and support translational research in prostate cancer. In this grant, a multidisciplinary team of investigators will collaborate in the development of a comprehensive prostate cancer program through the integration of basic, applied, and clinical research. This program will unite researchers from UF, Moffitt, and the North Florida Veteran's Health System to translate the knowledge gained from basic science discoveries into clinical applications for treatment, prediction of disease progression, and treatment response. Our consortium seeks to create an exceptional environment that allows creative investigators to move ideas rapidly from the laboratory to the bedside. The goal of this grant is to assemble an interdisciplinary team and to create a prostate cancer-focused research environment to compete successfully for an NCI Prostate Cancer Specialized Program of Research Excellence grant application within a 2-year horizon. Successful development of such a program would represent the first and critical step towards developing an integrated translational prostate cancer research model in the State of Florida; one that will be poised to develop and implement the biomedical breakthroughs of the 21st century.

2008 SPORE
University of Florida
$972,404

WEBER, Jeffrey

2008 Bridge
H. Lee Moffitt Cancer Center & Research Institute
$196,362

PD-1 Abrogation and Immunity in Melanoma

We plan to treat ten patients with stage IV distant melanoma in a clinical trial; we will give increasing doses of an antibody against a molecule on immune T cells, called Programmed Death-1 (PD-1). PD-1 is found on the surface of immune T cells that have been activated or turned on. It causes immune cells to decrease their function. Decreasing the function of PD-1 on immune T cells by the use of antibodies in animals that have tumors has resulted in increased immunity to those tumors but also caused a reaction against normal tissues called auto-immunity. Early testing of an anti-PD-1 antibody in animals as well as with human immune T cells in the test tube has shown that decreasing the function of PD-1 results in shrinkage of tumors in mice and causes the rapid growth of potent tumor-killing immune T cells. Ten patients with widespread stage IV melanoma that have the blood type HLA A0201 will receive increasing amounts of the anti-PD-1 antibody with a vaccine to measure the side effects of the combination and find out how well tolerated it is. We also wish to find out how long the injected anti-PD-1 antibody can be detected in the blood and how it affects the immune system with particular attention to the development of increased immunity against the body's own normal tissues. Anti-PD-1 antibody will be given every two weeks, six times with a vaccine. In this trial, we will ask whether anti-PD-1 antibody will have the same effects predicted from the mouse experiments such as increased growth of immune anti-tumor T cells. We will also find out if the presence of certain variants of the gene for PD-1 found in the population can predict whether increased immune reactions against normal tissues will occur in patients in the group receiving the anti-PD-1 antibody with vaccine. We will also examine the variants that seem promising to be able to predict the effects of the PD-1 antibody at that dose on the immune system.

WRIGHT, Amy

2008 Bridge
Florida Atlantic University
$200,000

Discovery of Novel Antitumor Agents Effective Against Pancreatic Cancer

The overall objective of this grant is to discover marine natural products that will contribute to the development of novel therapeutic agents for the treatment of pancreatic cancer. Although eleventh in occurrence, pancreatic cancer is the fourth cause of cancer death in the U.S., with over 33,000 deaths predicted for 2008. Less than 5 percent of patients diagnosed with pancreatic cancer survive five years post diagnosis. Natural products have proven to be useful in the development of cancer therapeutics, with over 78 percent of the drugs approved for use against cancer being either natural products themselves or compounds based upon natural products. Examples include: the Vinca alkaloids, Taxol, irinotecan, topotecan, and doxorubicin. Gemcitabine, the treatment of choice for pancreatic cancer, is a simple analog of a sponge-derived nucleoside. The research group at Harbor Branch Oceanographic has pioneered the discovery of agents useful in the treatment of cancer from organisms living in deep-water habitats. They have contributed significantly to the discovery and development of marine natural product drug candidates including discodermolide, dictyostatin, ecteinascidin 743, and leiodermatolide. In the current grant, we will continue our research program aimed at the discovery and development of new natural products with potential in the treatment of pancreatic cancer. The various components of this research include: 1) Screening of the HBOI collection of marine extracts against a panel of pancreatic tumor cell lines and in assays targeting aberrant signaling associated with pancreatic cancer, 2) Bioassay-guided fractionation, spectroscopic identification, and pharmacological studies on the purified natural products, with the final goal of identifying lead structures for development as cancer therapeutics. The compounds discovered will also have utility in other cancers where similar changes in signaling and cell cycle control are in play.

YEATMAN, Timothy

2008 SPORE
H. Lee Moffitt Cancer Center & Research Institute
$973,404

Molecular Signatures for Colon Cancer

Colorectal cancers represent a large volume of cancer cases each year and a substantial number of cancer-related deaths. This pre-SPORE planning grant is intended to assemble a strong team of collaborative investigators from multiple disciplines to address translational issues pertinent to this common disease. Specific Team projects include: understanding a particular molecular pathway in colon cancer better as a potential target for drug therapy; understanding a potentially new area of therapy called microRNA; and examination of Vitamin E as a cancer preventive agent. At Moffitt Cancer Center, we have recently developed a new initiative in personalized medicine called "Total Cancer Care" (TCC) that we plan to fully leverage when applying for an NCI-funded GI SPORE grant within 3 years of submitting this grant. The TCC initiative is enabling the development of a large biorepository and an associated prospective clinical and molecular database. This unique information repository will contain both RNA-based, genome-wide gene expression data, as well as DNA sequencing data on thousands of patients that will ultimately be used to match the right drugs for the right patients.

YU, Hong-Guo

2008 NIR
Florida State University
$375,000

Chromosome Mechanics in DNA Double-Strand Break Repair

The long-term goal of this grant is to elucidate the molecular mechanisms responsible for regulating the dynamic progression of changes in higher-order chromosome structure that are necessary to safeguard genomic integrity. A landmark of biomedical research is the completion of sequencing the human genome, but we do not yet understand how DNA is packaged into a higher-order chromosome structure inside the living cell. Chromosome organization is achieved by the action of a class of conserved and essential protein factors, including the protein complexes condensin and cohesin. Our preliminary studies of condensin and cohesin function have led us to the identification of a practical approach to characterizing chromosome higher-order structure formation and its function in DNA break repair at the point of their occurrence in a living cell. One hallmark of cancer cells is genomic instability arising from errors during the repair of chromosome lesions. Our approaches have broad applications for investigation of the in vivo cellular and biochemical activities of factors required for chromosome structural dynamics and functions. This research will provide insights into the genetic and molecular mechanisms of chromosome lesion repair in a model eukaryote and will have implications for our understanding of some of the factors contributing to genomic instability and tumor formation.

Evaluation of a Novel 3-D Polymer Gel Dosimetry System for Proton Radiotherapy

ZEIDAN, Omar

As proton therapy becomes a prevalent radiotherapy modality, it is critical to ensure that optimized radiation dose distributions as modeled by treatment planning systems are, in fact, accurately delivered to cancer patients. The ability to provide accurate 3-D proton dosimetry proton information as outlined in this grant will provide physicians with the confidence to tailor the proton dose even closer to the tumor volume, hence decreasing the risk of complications from proton radiation therapy. In addition, these tighter dose distributions may allow dose escalation to the tumor volume, hence increasing the probability of cancer control. Therefore, the overall aim of this project is to improve the accuracy and confidence in proton radiotherapy (PRT) deliveries. In order to achieve this goal, we are implementing a novel proton-sensitive polymer gel with our currently well-characterized 3-D optical tomography dosimetry system for successful verification of all areas of proton beam deliveries and more specifically for patient-related QA. Specific research aims include: Aim 1: Characterizing the new proton-sensitive gel system for proton beam dosimetry, Aim 2: Assessing the overall gel system dosimetric accuracy for QA of clinical proton beam deliveries, Aim 3: Evaluating the capability of the gel dosimeter system for estimating and quantifying various sources of uncertainties in PRT.

2008 NIR
M. D. Anderson Cancer Center Orlando
$359,286

RecQ Family of DNA Helicases in Human DNA Mismatch Repair

ZHANG, Yanbin

The long-term objective of this grant is to understand the molecular mechanism of human mismatch repair (MMR) and its impact on human health. MMR is extremely important to maintain genome stability, whose defects directly lead to hereditary non-polyposis colon cancer and sporadic cancers. To find a cure for these deadly diseases, many fundamental questions about this repair pathway need to be answered. One such question is which DNA helicase(s) participates in MMR in humans. Given the fact that members of the RecQ family of DNA helicases interacts with MMR proteins, it is hypothesized that RecQ helicases are directly involved in human MMR by increasing repair efficiency. To test this hypothesis, we will first determine the involvement of all five RecQ helicases in MMR in the precisely defined in vitro reconstituted MMR system. Second, we will dissect the physical and functional interactions between RecQ helicases and MMR proteins and their involvement in MMR. Third, we will test the involvement of RecQ helicases in MMR through helicase-deficient cell lines and stable siRNA knockdown of the candidate helicases and measurement of microsatellite instability that is the established biomarker for loss of mismatch repair in tumor cells. These research studies should provide important insights into the development of novel diagnostic markers and the design of effective strategies against cancers resulting from MMR deficiency.

2008 NIR
University of Miami
$375,000

Activation of the ERK/RSK MAPK Pathway by KSHV

ZHU, Fanziu

Tumor viruses account for about 15 percent of human cancers. Kaposi's Sarcoma Associated Herpesvirus (KSHV) is such a tumor virus; it causes Kaposi's Sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. It is well documented that KS development requires recurrent episodes of lytic KSHV replication, so blocking viral replication could prevent or cure KSHV-related human cancers. One way to inhibit KSHV replication is to disrupt cellular signaling, which viruses rely on for their replication. A common cellular signaling pathway called extracellular signal regulated kinase (ERK) MAPK is activated by KSHV and plays a pivotal role in KSHV lytic replication, but the mechanism and the viral factor responsible are unknown. We recently found that a KSHV protein called ORF45 interacts with cellular kinases called RSK1 and RSK2 and strongly stimulate their enzyme activities. RSKs are direct substrates and functional mediators of ERK. Activation of RSK by ORF45 requires ERK. RSK and ERK are activated with similar kinetics during KSHV infection. We further showed that ORF45 contributes significantly to the sustained ERK activation during KSHV replication. Importantly, depletion of RSK or inhibition of RSK activity with an inhibitor specific to it strongly suppresses KSHV lytic replication, suggesting that ERK/RSK signaling can be a useful target for anti-KSHV intervention. In this grant, we will characterize the mechanism of ERK/RSK activation and its role in viral lytic replication and pathogenesis. Results from this research may lead to a novel therapeutic approach to KSHV-related human cancers.

2008 Bridge
Florida State University
$161,668

Endnotes

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5 While M.D. Anderson Cancer Center in Houston, TX, and Burnham Institute in Torrey Pines, CA, hold NCI Cancer Center designations, these do not extend to the Florida campuses of these institutions.

6 http://cancercenters.cancer.gov/about/index.html, accessed 9/8/2008.

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