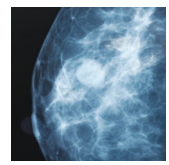
bankheadcoley

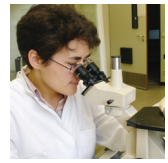
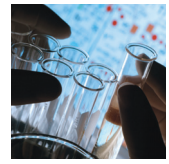
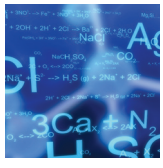
Florida Biomedical Research Program

2007 Annual Report

Building the Foundation






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

William G. "Bill" Bankhead, Jr. and David Coley Cancer Research Program
Annual Report
January – December 2007

Submitted to

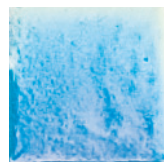
The Governor
The President of the Senate
The Speaker of the House of Representatives

and

The Florida Center for Universal Research to Eradicate Disease

By
The State Surgeon General
State of Florida

December 15, 2007

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Executive Summary

Florida faces an extraordinary healthcare burden associated with cancer. Compared to national averages, Floridians experience higher death rates from the ten most common forms of cancer. To ease this burden in the coming years, the Governor and the Legislature created the William G. "Bill" Bankhead, Jr. and David Coley Cancer Research Program to advance progress toward cures for cancer through peer-reviewed, competitive research projects.

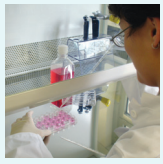
The Program's challenge during 2006 was planning and managing its first and second annual funding cycles within one fiscal year. The first competition funded 32 projects starting in January 2007. The second round of funding began in February 2007, when 36 Florida researchers submitted applications. The Biomedical Research Advisory Council met in May 2007 to consider the independent peer review results of these proposals. They formed their recommendations for awards based on the goals provided in section 381.922, *Florida Statutes,* with a focus on scientific merit. The State Surgeon General offered Program awards on June 1, 2007, and 22 Florida investigators launched cancer research projects in 2007. This brought the total number of peer-reviewed, competitively awarded research grants to 54. Due to the print deadline for the 2006 Annual Report, this report covers all 54 projects.

Collectively, these projects aim to expand cancer research capacity in the state, to increase participation in Florida clinical trials networks, and to reduce the impact of cancer on disparate groups. Some of these grants are providing state-of-the-art research instruments for cancer research. Others are maintaining funding for Florida investigators whose cancer projects were highly rated in national competitions yet not selected for federal funding due to budget constraints. Program grants are helping collaborative teams of scientists and clinical investigators in Florida prepare to compete more successfully for very large, multi-year national cancer research awards. At a time when competition for federal research funding has grown intense, many awards are helping new cancer investigators establish a home for their research at Florida institutions.

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. It has also implemented financial controls. The Biomedical Research Advisory Council has followed best practices in scientific peer review and avoided conflicts-of-interest in recommending Program awards.

In less than one year's time, Bankhead-Coley awardees have documented their research findings in 23 publications in major scientific journals. They have given 40 presentations regarding their progress and have attracted more than $9,900,000 in additional funding related to Program-sponsored research. Because contributions to the body of knowledge are the measuring rod for success within the research community, these early results represent a success story for the State of Florida.

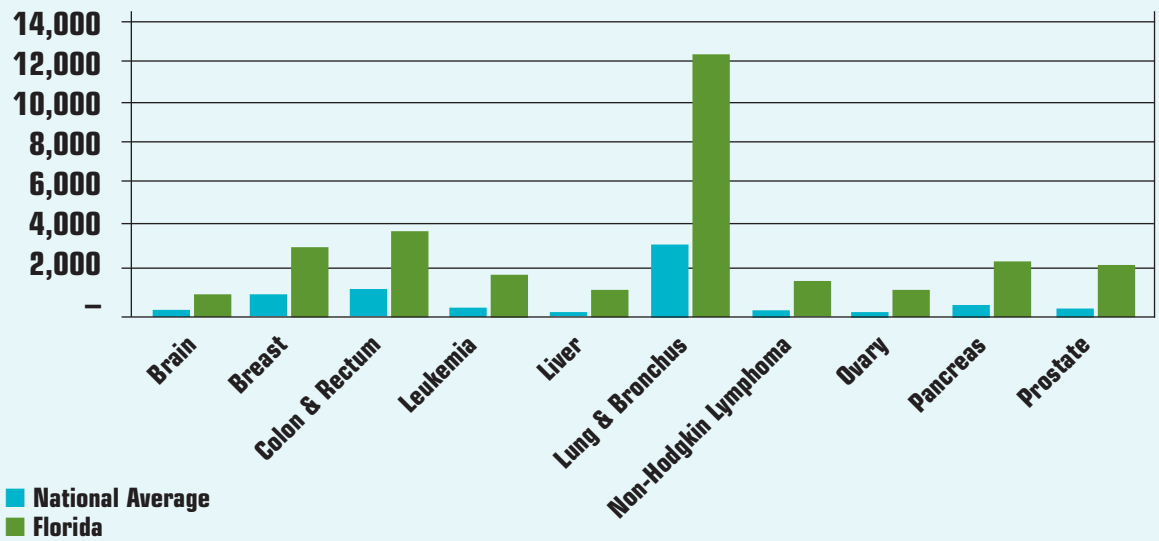
The Program faces ambitious goals. To meet them, it offers vital funding to new and experienced cancer researchers throughout our state with the most promising projects. As the Program follows an "Open to all, fund the best" policy, it continues to build the foundation for accelerating progress toward cancer cures in Florida.



Florida's Cancer Burden

Florida ranks second in the nation in cancer incidence and mortality.[1] The American Cancer Society (ACS) estimates 106,000 cancer diagnoses and more than 40,000 cancer deaths among Floridians in 2007.[2] This represents an estimated increase of 7,000 diagnoses compared with last year. Figure 1 illustrates the fact that Floridians experience higher death rates from the ten most common forms of cancer than the national average.[3] The proportion of Florida's population considered at high-risk for cancer (35 percent) further contributes to Florida's cancer burden.[4]

Figure 1: 2007 Florida Cancer Deaths by Type, Compared to National Averages



For our minorities, cancer incidence and mortality rates are particularly high. Minorities comprise one-fourth of Florida's total population and one-third of the population younger than 40.[5] Florida's nonwhite population experiences a 10 percent higher rate of cancer mortality than the white population.[6] Death rates from prostate, stomach, and cervical cancers among African Americans are more than twice those in whites.[7]

For our rural citizens, cancer mortality rates are higher than for their urban counterparts. (Forty-nine percent of Florida's counties are rural.) Of the 17 counties with the highest cancer mortality rates in Florida, 13 are rural counties.[8]

For our low-income population, lack of health insurance and other barriers prevent many from receiving optimal health care. People in the highest-income bracket are 10 times more likely to obtain needed medical care than low-income citizens. This hinders early diagnosis and treatment—the key to effective cancer therapies.[9]

For our seniors, the risk of developing cancer increases with age. More than 29 percent of our current population consists of adults 55 years of age and older, making it the state with the largest proportion of older adults.[10] About 77 percent of all cancers are diagnosed in persons 55 and older, according to the Florida Division of the American Cancer Society. This increases demands on our state healthcare system.

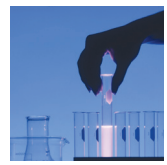
For our young — those under age 18, who comprise 23 percent of Florida's Population,[11] cancer is the second leading cause of death, behind accidents. Leukemia, brain and nervous system cancers, and soft tissue sarcomas are a few of the cancer types affecting our children.[12]

For our men, the likelihood of developing cancer during one's lifetime is approximately one in two. Among men, cancers of the prostate, lung, colon, and rectum account for about 54 percent of all newly diagnosed cancers nationally. Estimates are that 15,710 Florida men will receive a diagnosis of prostate cancer and 2,180 will die of this disease in 2007.[13]

For our women, the likelihood of developing cancer is approximately one in three. For women, breast, lung, and colorectal cancer account for 52 percent of estimated new cases.[14] Projections are that 11,710 Florida women will receive a diagnosis of breast cancer and 2,700 will die of this disease in 2007.[15]

For all "Sunshine State" residents, of particular concern is melanoma, the most serious and potentially deadly form of skin cancer. Florida has the second-highest melanoma rate in the U.S.,[16] and this disease affects not only adult Caucasians, but everyone—children, African Americans, and Hispanics. Despite its frequency, melanoma is highly curable when detected and treated early.

What is Florida doing about this cancer burden? As described throughout the rest of this report, the Bankhead-Coley Cancer Research Program represents the state's focused effort to accelerate leading-edge cancer research in Florida. By design, it challenges scientists and clinicians throughout Florida to come forward with innovative proposals and provides vital support for those with the greatest promise to prevent, treat, and cure cancer. (See the Program Goals and Progress Toward Goals sections for specific Program strategies and progress.) As a result, new investigators are choosing cancer research as a lifetime focus for their labs, established investigators are developing new collaborations, and efforts are renewed to improve the health of the people of Florida.

Program Goals

In June 2006, the Florida Governor and Legislature created the William G. "Bill" Bankhead, Jr. and David Coley Cancer Research Program and appropriated for cancer research $9 million annually for five years through 2010.

The Program represents Florida's commitment to join with groups like the Florida Dialogue on Cancer and the American Cancer Society to reduce the state's cancer incidence and mortality rates. The Biomedical Research Advisory Council (the Council) advises the Office of Public Health Research and the Florida State Surgeon General on 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 Program's purpose is to advance progress toward cures for cancer through grants awarded in a peer-reviewed, competitive process, operating within the following guidelines:

- To extend equal opportunity and access to funding to all qualified investigators throughout the state
- To fund the most worthwhile projects as determined by a scientifically rigorous, unbiased review process
- To emphasize productive collaborations among institutions, investigators, and community practitioners

The Legislature linked the goals of the Program to those already established for the Florida Cancer Council in section (s.) 381.921, *Florida Statute (F.S.)* – Florida Cancer Council Mission and Duties (included in Appendix A).

Specific Program goals include:

- Expand cancer research capacity
- Improve research and treatment through greater participation in clinical trials
- Increase efforts to reduce the impact of cancer on disparate groups
- Give priority to collaborative research efforts including those that advance the finding of cures

Members of the Council meet several times yearly to determine the best course for pursuing these goals. Based on areas of greatest Program need in its first two years, the Council agreed on the following strategies.

2006 Program Priorities:

1. **Fill existing gaps in access to specialized equipment critical to conducting leading edge cancer research.** Most researcher-supported funding does not allow the purchase of expensive equipment. The Council recognizes that shared access to specialized instruments fosters collaborative cancer-related research and increases the likelihood of competing successfully for larger national grants and contracts. In addition, the availability of a larger network of state-of-the-art instruments helps attract scientists to Florida institutions.

   The Program offered the **Shared Instrument Grant (SIG)** to address justified infrastructure needs of investigators across the state. Applications for SIG support were limited to two per institution and required compelling evidence that multiple cancer research teams would benefit from the instruments for more than convenience. Awardees have agreed to provide ongoing maintenance and support at no expense to the Program. For up to five years, SIG recipients will report the value of additional grants and publications produced by cancer research using the acquired equipment.

2. **Provide short-term funding for promising cancer investigators in Florida who face increasing competition for federal funding.** Recent data show that in 2006 there was only a nine percent chance of obtaining funding from National Institutes of Health (NIH) on the first try.[17] Without continual funding, Florida investigators face major challenges in retaining key laboratory personnel and maintaining research momentum. Their research often stalls until their proposal revisions are evaluated many months later during the next round of federal funding.

To address this need, the Council recommended offering the **Bridge Grant**. This award targets Florida investigators whose cancer research proposals have been highly rated in national peer-review processes during the previous 12 months and not selected for federal funding. The Program requires grantees to continue aggressive efforts to secure federal funding.

2007 Program Priorities:

1. **Continue to offer short-term funding for promising Florida cancer investigators whose projects narrowly miss receiving federal awards.** Based on the high quality of projects submitted in 2006 and the positive response of Florida's research community to the approach, the Program again offered the **Bridge Grant** mechanism.

2. **Help Florida's new cancer investigators successfully launch an independent research career.** According to data published by the NIH,[18] the average age of new investigators at their first major award reached 41.7 years in 2006, up from age 34 in 1970. Relying mainly on start-up funds offered by institutions to equip a laboratory, these new scientists need additional funds in order to obtain the preliminary data and produce the manuscripts normally required to obtain federal funding. This places tremendous financial pressure on Florida institutions when competing with prestigious research institutes around the nation to attract the best and brightest talent.

   The Council selected the **New Investigator Research (NIR) Grant** to offer vital support for cancer research projects of Florida investigators who met two conditions. First, they must have held full-time faculty (or equivalent) positions for less than five years. Second, they must not have served as a principal investigator on a major research project. NIR recipients work on high-potential projects spanning a period of up to three years and receive mentoring from an experienced investigator. While all cancer-related applications were accepted, the Program expressed a special interest in receiving proposals that addressed two key areas: efforts to improve research and/or treatment through greater participation in clinical trial networks, and efforts to reduce the impact of cancer on disparate groups.

3. **Develop a fact-based understanding of the reasons Florida's rate of patient participation in cancer clinical trials is among the lowest in the nation.** Researchers nationwide who are conducting clinical trials continue to report challenges in reaching their recruitment goals (especially for disparate groups). A number of studies have suggested reasons for this phenomenon.[19] However, clinical trials are a critical resource for the discovery of new prevention, diagnostic, and treatment methods for cancer. With a better understanding of the impact on patient participation of Florida's unique demographics, cancer prevalence, existing resources, and research collaborations, it should be possible to develop more effective intervention strategies.

   The Program offered a **Special Emphasis Project (SEP) Grant** mechanism to study the reasons contributing to Florida's very low cancer patient participation in clinical trials. Rather than repeating earlier national surveys, applicants were required to propose methodologies to capture Florida patient and provider perspectives as well as those of disparate populations in the state. The Program emphasized a preference for projects involving inter-institutional collaboration.

4. **Accelerate the development of one or more NCI Specialized Programs of Research Excellence (SPOREs) in Florida.** Of 59 multi-million dollar, multi-year, organ-specific cancer SPOREs sponsored by the NCI,[20] none are currently based in Florida. SPOREs must involve translational research (converting basic research to a clinical application). They also must involve partnerships among investigators conducting basic and applied research. The SPORE mechanism clearly matches Program goals. To be competitive for this federal support and bring the health benefits of this interdisciplinary approach to Florida, it is necessary to increase the number of productive, collaborative relationships among laboratory and clinical scientists.

   The Program devised a **SPORE Planning Grant** with the objective of assembling and preparing strong interdisciplinary teams of Florida investigators to compete successfully for SPORE grants. The Program allowed one SPORE Planning Grant application per institution. Awardees must begin developing the required SPORE infrastructure components immediately and submit an NCI SPORE application at least six months before the end of the grant. Program investments in SPORE Planning Grants should help the sponsored teams secure federal awards of up to $2.5 million per year for up to five years.

Progress Toward Goals

During 2007, the Bankhead-Coley Cancer Research Program began building a foundation to accelerate progress in Florida toward preventing and curing cancer through grant awards.

The first 32 projects sponsored by the Bankhead-Coley Program began in January 2007. Later in 2007, another 22 Florida investigators launched cancer research projects under state sponsorship. New and experienced investigators at nine public and private research institutions in Florida direct these 54 competitively awarded research grants.

To illustrate how these grants fit with Program goals, each of the following sections introduces specific cancer research projects and the teams of talented Florida investigators who lead them.

Goal: Expanding Research Capacity

The Program has considered both short- and long-term views in building the state's capacity for cancer research. An important way to increase both immediate and long-term capacity is to improve access to state-of-the-art research instruments.

During 2007, seven Shared Instrument Grants provided new or upgraded state-of-the-art research instruments at five different campuses in the state. In each case, the planned use for cancer-related research is anticipated to demand at least 75 percent of the available capacity of the equipment. These awards are supporting the work of 21 different externally-funded cancer projects that, together, involve more than 250 senior investigators, post-doctoral fellows, graduate and undergraduate students, and laboratory personnel. Recipient institutions committed to provide more than $2 million in matching funds to cover all set up, operating and maintenance expenses for the new instruments, significantly leveraging the state's investment in this vital research infrastructure.

Leaders of two of the SIG projects, Dr. Meeks and Dr. Shibata, explain the impact of receiving the new equipment and the research made possible by the investment.

- Dr. Sanford Meeks and his staff at M.D. Anderson Cancer Center sought the Calypso® 4D Localization System for its ability to use radio frequency technology to track the motion of a tumor during therapy. Wireless, electromagnetic markers (smaller than a grain of rice) called Beacon® transponders are implanted on or near the tumor. The instrument then detects any movement of the target, up to sub-millimeter shifts from the prescribed location. Using this new system, a radiation therapist can monitor tumor location at a rate of 10 times per second, and shut off the beam and reposition a patient if necessary. The patient receives on-target radiation, and healthy tissue exposure to radiation is minimal.

Equipment purchased with Shared Instrument Grants:

- **Genotyping and Gene Expression Instrument** to scan whole genomes, profile gene expression, and detect changes in tumor tissues
- **Mass Spectrometer for Proteomics** to selectively identify the molecular basis for cancer
- **Calpso® 4D Localization System** to more closely guide radiation treatment for lung, prostate, breast, and spinal tumors
- **Two Fluorescence Activated Cell Sorters** to study individual live cells in large numbers and analyze characteristics of individual cells
- **Confocal Microscope** to record images of structural features of cancer cells, tumors, and the tumor environment
- **BioBank -80°C Automated Storage System** to better preserve biological function and properties of biological samples during long-term storage

- Dr. Yoshima Shibata at Florida Atlantic University bought a Fluorescence Activated Cell Sorter (FACS) to isolate and compare cancer and normal cells by marking particular surface proteins found only in cancer with a fluorescent antibody. The FACS draws the cells into a fine tube, examines them one at a time, and places the cancer cells with fluorescence in one test tube, normal cells in another. In five minutes, a FACS can separate more than 20 million cells into 99 percent pure populations. According to Dr. Shibata, "No other instrument can be substituted for FACS—it is essential for generating good data that can compete and receive strong project grants. It's common knowledge that [national] funding agencies do not accept studies using poorly purified cell populations."

> "To push a grant over to a nationally fundable level, you have to work one to two years to show your ideas are on the right track. If you don't have funding, how can you gather preliminary data for a submission and build your case?"
>
> – Dr. Jiandong Chen
> H. Lee Moffitt Cancer Center & Research Institute
> 2006 Bridge Grant

Also during 2007, Bridge Grants enhanced the competitiveness of 34 of Florida's cancer investigators by providing more time to collect data, answer relevant reviewer questions, and publish results. This investment in building the state research capacity is already producing a number of important benefits:

Obtaining additional external funding. More than one-third of the 2006 and 2007 Bridge Grant investigators had received federal grant awards by October 2007. This means that Florida investigators have received additional federal funds to support their cancer research, and also means that unused state funds are being returned to the Program for future use. Eleven surrendered Bridge Grant awards, representing a total Program investment of approximately $896,000, obtained federal support totaling $8.1 million.

Stimulating further cancer research, the translation of that research to human treatment, and a strengthened biomedical research structure. Dr. Theodore Lampidis, University of Miami, has used his Bridge Grant to maintain momentum in translating his research into human treatment. Three Florida clinicians are planning clinical trials based on his work to investigate tumor treatment for prostate cancer, genital/urinary cancers, and retinoblastoma (cancer of the eye) within the next year.

Attracting biotech companies. Biotech companies often locate near successful research groups. Dr. Lori Hazlehurst, Bridge Grant recipient at the H. Lee Moffitt Cancer Center & Research Institute, reports that her team frequently collaborates with small companies in the course of their research. A Bridge Grant has also helped Dr. Anuradha Godavarty at Florida International University avoid an interruption in the design and development of a hand-held imaging device for breast cancer diagnostics, a project with significant commercial potential.

Building continuity and stability in the state's research teams and mentoring relationships. This is a critical component for the foundation of Florida's biomedical research infrastructure. Dr. Derek Radisky, Bridge Grant recipient at Mayo Clinic-Jacksonville, explained: "Without grant support, a researcher's lab may have to close, resulting in loss of good researchers, their labs, and support staff. These breaks in funding not only have immediate implications for halting research progress, but also limit a state's ability to draw future funding."

As another step toward increasing longer-term research capacity in the state, in July 2007 the Program offered 10 NIR Grants that gave promising new scientists working at four different institutions the opportunity to lead their first major projects as independent investigators. During the first six months of their grant, these awards made it possible for them to hire their first laboratory personnel, successfully navigate the approval process for working with human and animal subjects, and begin collecting preliminary data. It will be at least another year before their work will yield enough findings to allow them to submit manuscripts to peer-reviewed journals and make presentations at scientific conferences. It may be two years or more before they will be successful in competing for federal funding. The Program has required each principal investigator to seek guidance from at least one official mentor. For the life of the grant, this individual serves as a sounding board for ideas, shares timesaving lab techniques, and offers advice about publishing research findings and seeking other sources of funding.

"My mentors have taught me how to write a grant proposal and develop methods, protocols, and a patient-oriented approach. They are helping me establish a good track record and obtain valuable data with this funding, which will be a vast help for my next grant application."

– Dr. Mia Liza Lustria
Florida State University
2007 New Investigator
Research Grant

Exploring the Biological Basis of Esophageal Cancer

George Sarosi, M.D.
University of Florida, 2006 Bridge Grant

According to Dr. George Sarosi, "Esophageal cancer is one of the most deadly human cancers, with only a 10 percent cure rate; it is the sixth leading cause of cancer deaths. The incidence of esophageal cancer has increased by 300 percent over the last 30 years, faster than all other gastrointestinal cancers. Additionally, there has been a change in the type of esophageal cancer, with more diagnoses of a denocarcinoma (malignant tumors in gland tissue). Investigators believe that Barrett's esophagus (BE), a cancerous condition caused by chronic heartburn, may cause the vast majority of adenocarcinomas. People with BE have a 100 to 200 times greater risk of developing esophageal cancer than others."

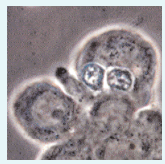
Why the increase in cancer, if today's medicines are more effective than ever at preventing acid from getting into the esophagus? Approximately half of people on antacids or proton pump inhibitors still have reflux. The decrease in stomach acids caused by these medications may create another problem. The elimination of an acid pH in the stomach may make bile salts more soluble, which means they dissolve and cover a greater area when reflux into the esophagus occurs.

Why may bile salts cause a problem in the esophagus? In the colon and small intestine, bile salts make intestinal cells grow. However, they may transform the lining of the esophagus from its normal skin-like state to intestinal cell types. This change in the cell types may ultimately lead to cancer. Dr. Sarosi questions treatments for heartburn, asking if eliminating reflux through other medicines or surgery may be a more effective treatment for BE in the long run. He believes the first step to an answer lies in isolating the role of bile salts in the esophagus.

What keeps Dr. Sarosi focused and passionate about his research? "This form of cancer is fairly common, and it tends to strike middle-aged men during the most productive time of their lives. As a physician, I see this as becoming more of a public health problem all the time. As a scientist, this research raises fascinating questions. As a surgeon, a medical procedure is potentially one of the long-term solutions to this problem. The current treatment for esophageal cancer is to remove the esophagus. It would be nice to protect people in a way that would have less of an impact on their lives."

Dr. Sarosi explained the value of the Bankhead-Coley Bridge Grant to investigators and the state of Florida. "It's incredibly helpful! It was very important for me personally. Support from the Bankhead-Coley Program gave me a year to expand the team, conduct research, and generate the preliminary data needed for other grant submissions. It also gave the team the time to resubmit another grant [application] without losing research momentum and continuity. Once you lose funding, it's difficult to re-submit."

According to Dr. Sarosi, "The Bridge Grants give Florida researchers a competitive advantage in procuring NIH funding. In the era of tough federal funding, researchers have to submit applications repeatedly to be funded. My colleagues in other states are quite impressed by this program. The Bridge Grant allows a researcher to keep going and generate the data requested for a resubmission. It is a clever strategy to help gain more research funding for the state, and the cancer focus of the Bankhead-Coley Program is really important. I'm quite grateful that it's helped me get over this first hurdle of procuring additional funding and allowed me to transition from a mentored position to a more independent research position." The state is investing one year of funds, with a high likelihood of receiving three years of additional federal funding and a strengthened cancer research team in return.



Goal: Increasing Participation in Clinical Trials

Clinical trials are scientific research studies that evaluate the effectiveness of drugs or treatment strategies. Cancer clinical trials offer cancer patients a unique opportunity to participate in ground-breaking research and utilize medications under development that could improve treatment results and/or reduce pain and suffering. If a new approach is effective, study participants are among the first to benefit.

The advantages of trial participation are numerous.

- Participants can play a more active role in their own health care and gain access to new treatments before they are widely available.
- Participants receive expert health care at leading medical facilities during the trial. The clinical trial team includes leading physicians in the field of cancer research and other healthcare professionals who check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed.
- Clinical trials advance medical research.
- The entire State benefits when individuals choose clinical trials. As more people participate in clinical trials, costs are reduced and pharmaceutical companies are more likely to sponsor trials in Florida, which ultimately directs more investigators and grant funds to Florida. A high number of participants are necessary to produce valid and generalizable results.

Despite these benefits, studies of recruitment for national NCI-sponsored trials show the overall recruitment rate to be less than two percent of all newly diagnosed cancer patients, with the elderly, racial and ethnic minorities, and the medically underserved even less likely to participate.[21] Studies reported in the *Journal of Clinical Oncology* show that physicians are less likely to offer clinical trials to older individuals and minorities.[22] Further, certain regions have significantly lower accrual to clinical trials than nationwide figures. *Florida has one of the lowest rates of accrual per number of incident cancer cases, ranking in the bottom nine states.*[23]

During 2007 the Program developed the SEP Grant to identify specific factors that contribute to Florida's extremely low participation rates and to investigate policies, interventions, and incentives that may increase enrollment. Investigations require the capturing of both patient and provider perspectives as well as those of disparate populations.

While past studies have been isolated to one clinic or cancer type, the two SEP Research Projects are comprehensive and include analyses of statewide data on participation rates, surveys of cancer patients, and surveys of healthcare providers and investigators. Further studies will examine the development of an educational and clinical trial information system designed to improve services and increase physician referrals to clinical trials.

Both SEP projects will culminate in reports to the Council of strategies and recommendations for strengthening this fundamental component of Florida's cancer research infrastructure.

Understanding Barriers to Participation in Cancer Cinical Trials

Margaret Byrne, Ph.D.
University of Miami, 2007 Special Emphasis Project Grant

Special Emphasis Project recipient, Dr. Margaret Byrne, recently explained the background and need for her research: "Florida has extremely low participation rates in clinical trials. In 2002, Florida ranked in the bottom nine states in patient participation in clinical trials. This Bankhead-Coley Grant allows us to focus on a statewide project to study barriers and facilitators to participation. This is important because cancer clinical trials are the best way to improve treatment and patient care and reduce the mortality and suffering associated with cancer. Many people have misconceptions about clinical trials — erroneously believing some patients receive placebo or 'fake' treatments. This is not true. Actually, patients often receive better care overall when they are involved in a clinical trial as compared to when they are not. We have seen this in breast cancer. Unfortunately, when there are not enough people willing to enroll in clinical trials, it slows down research and raises costs tremendously. Slow progress on clinical trials testing means new research advances cannot be translated into improved therapies."

"…cancer clinical trials are the best way to improve treatment and patient care and reduce the mortality and suffering associated with cancer."

This research includes a statewide effort with three related, but distinct studies:

1. Statewide examination of participation rates and demographics at the county level. The team will be able to determine, among other things: where participation is lowest; how participation is related to levels of income, education, age distributions, rural/urban setting, availability of cancer centers, and what populations are least represented.
2. Comprehensive patient survey of 1,200 patients that reflects the diversity of Florida's population and includes people with breast, prostate, lung, and colorectal cancer. The survey focus is on cancer patients' beliefs, attitudes, barriers to participation, and factors that could enhance participation in cancer clinical trials.
3. Cancer healthcare provider and investigator surveys to assess attitudes toward clinical trials, perceptions of patients' willingness to participate, and barriers and facilitators faced by providers in identifying and referring patients to trials. Dr. Byrne will collaborate with both the Florida Society of Clinical Oncology (FLASCO) and the University of Miami Sylvester Clinical Trials Network to identify participants in this survey.

The Bankhead-Coley grant allows Dr. Byrne to focus her research efforts on the people of Florida rather than nationally as would be expected with federal funds. After the initial research, important knowledge will be available on how participation rates vary by location in Florida, by racial/ethnic background, and by neighborhood characteristics. These results will guide recommendations for improving rates of participation in cancer clinical trials and facilitate sound patient decisions regarding clinical trials.

Goal: Reducing Cancer Impact on Disparate Groups

Florida's rural, minority, elderly, and populations with low-income and education levels have higher incidences of cancer mortality than the rest of the population. The challenge of resolving these differences is especially acute in our state, where these groups represent significant portions of the population.

While research findings from the vast majority of projects funded by the Program will be applicable to broad categories of cancer victims, including members of disparate groups, the Program gave careful consideration in 2007 to supporting research aimed at improving healthcare access for Florida's underserved population.

The "Call for Grant Applications for Biomedical and Behavioral Research Grants, Fiscal Year 2007-2008," (the Call) is the published document announcing requests for grant applications. In the Call, the Program specifically encouraged research proposals targeting the impact of cancer on disparate groups with the following language:

> *"While all cancer-related applications are welcome, the Program has a special interest in receiving biomedical or behavioral research proposals addressing a) efforts to improve research and/or treatment through greater participation in clinical trial networks, and b) efforts to reduce the impact of cancer on disparate groups." (New Investigator Research (NIR) Grants, p. 9)*

and

> *"They must propose methodologies for capturing and integrating both patient and provider perspectives, including those of disparate and underserved groups (such as ethnic and rural populations and women), and develop a set of recommendations for concrete interventions to overcome barriers to participation." (Special Emphasis Project: Identification of Barriers to Participation of Florida Cancer Patients in Clinical Trials, pp. 21-22)*

Two mechanisms that support this goal include Special Emphasis Project Grants and New Investigator Research Grants. The Council funded two Special Emphasis Projects in order to double the chances for meaningful outcomes that could help the Program support effective strategies in the future for reducing the impact of cancer on disparate groups.

One New Investigator Research project ranked among the highest in scientific merit based on peer review also addresses these issues – that of Dr. Mia Liza Lustria, who proposed studying a means for improving access for women in rural areas to regular screenings for breast cancer. The collaboration she has arranged for this project is extensive, incorporating clinicians, oncologists, the Tallahassee Memorial Cancer Center, and university investigators.

Bridging Breast Cancer Screening Needs Among Rural Floridians

Mia Liza A. Lustria, Ph.D.
Florida State University, 2007 New Investigator Research Grant

Dr. Mia Liza A. Lustria, in conjunction with the Tallahassee Memorial Cancer Center and a team of investigators at Florida State University, is using her Bankhead-Coley award to develop an automated system for more effectively reminding clinicians and patients of the need for regular mammography screenings.

The need for such a system in rural Florida is crucial. Dr. Lustria says, "Nationally, mammography screenings have helped stabilize breast cancer incidence and mortality, yet one million Florida women over age 40 have never had a mammogram. Women of lower socio-economic status who live in rural areas and are less educated are two times more likely to be diagnosed at an advanced stage of breast cancer and to develop larger tumors than their urban counterparts. Compared to urban women, rural women experience longer delays in recognizing symptoms and in seeking medical help. Both patient-perceived barriers to treatment and lack of physician reminders have hindered the use of regular mammography screening in these women." The goal of the system, termed *STEER* (System for Tracking, Empowering, Equipping, and Reminding), is to provide an automated, patient-tailored reminder system for clinicians, who can then contact patients for scheduling. Developing such a system is a "huge undertaking" according to Lustria and involves the following steps:

1. Needs Assessment: The team plans to interview 1,000 rural, low-income, less educated women asking them to identify their information needs and barriers to care. This could include financial, childcare, and/or transportation issues. For some patients, the closest mammography center is anywhere from 20 to 50 miles from their homes. The team also plans to conduct focus groups with breast cancer patients as well as health practitioners in the area to determine their needs and challenges to accessing care.
2. Resource Directory: This step includes compiling a list of local and national resources and support programs, such as transportation and childcare, currently available to disadvantaged women. The team will be working closely with community groups and the NCI's Cancer Information Service in this step of the project.
3. Development and Testing of the System: The research team will develop and test an automated reminder system designed to generate tailored reminders that would include a list of resources patients could use to address their identified needs. For example, a patient may have identified transportation as a problem; the reminder prompts her to schedule a mammogram then lists transportation options.
4. Research Study: A randomized, controlled trial in two counties will help monitor the impact of the STEER system on physician and patient adherence to breast cancer screening guidelines and should provide insight as to why at-risk patients miss appointments.

In addition to agreeing with the Bankhead-Coley Program goal to "reduce the impact of cancer on disparate groups," Dr. Lustria places a high priority on developing a system that will be comprehensive and sustainable in rural settings. "We are using this grant to provide pilot data for a longer-term and more comprehensive trial that could measure more adequately the cost effectiveness and cost benefits of such a system and its sustainability, especially in clinics serving vulnerable populations."

Dr. Lustria believes the NIR grant is a tremendous opportunity for new investigators to build credibility. She finds personal motivation for the project as well. Her mother-in-law, a mother of eight, died of breast cancer. Dr. Lustria believes that, like many women targeted by the STEER project, she could have survived longer if only she had knowledge of and access to resources.

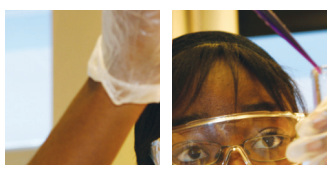
Goal: Fostering Collaborative Research

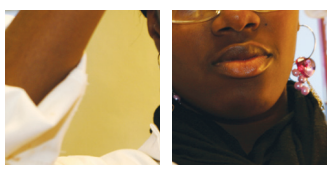
The Program's award of two SPORE Planning Grants in July 2007 promotes interdisciplinary research and translating basic research findings from the laboratory to a clinical setting. By targeting melanoma and lymphoma, these two project teams are capitalizing on the research and treatment strengths and real patient needs in Florida.

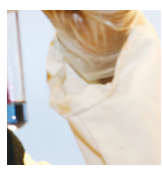
- Exposure to the sun's ultraviolet (UV) rays is commonly cited as the most important environmental factor involved in the development of skin cancer. With their Bankhead-Coley SPORE Planning Grant, co-investigators Dr. Vernon Sondak and Dr. James Mulé have begun assembling a strong team of interdisciplinary investigators who aim to bring an NCI SPORE Grant in melanoma to Florida. They are uniting physicians experienced in patient-oriented melanoma research with basic and population scientists, and extending existing collaborations at the H. Lee Moffitt Cancer Center & Research Institute and the University of South Florida as well as establishing new collaborations between physicians and scientists throughout Florida.

- "Viruses are considered the second most important cause of malignant disease in humans and are highly associated with aggressive lymphomas, including Adult T-cell Leukemia/Lymphoma, non-Hodgkin's lymphoma, and Hodgkin lymphoma," explained Dr. William Harrington, Bankhead-Coley SPORE Planning Grant recipient. "South Florida is endemic for these pathogens due to its close proximity to the Caribbean and large population of chronically immuno-compromised patients, including organ transplant recipients and AIDS cases. The incidence of non-Hodgkin's lymphoma is increased nearly 200-fold in HIV-positive patients, and Jackson Memorial Health Center cares for the largest number of viral-associated (HIV) lymphomas in the country. The University of Miami and the Jackson Memorial Health Center are the ideal sites for combining both clinical and basic research from which to develop a multi-investigator program focused on viral lymphomas." This SPORE Team is using their grant to reduce the incidence and mortality of this cancer, and to improve the quality of life for its survivors.

If one or both of these projects are successful in winning an NCI SPORE grant within the next three years, the state's commitment of $2 million will be returned many times over, and the research will allow far-reaching collaborations with other NCI/NIH programs, and public-private partnerships with industry and non-profit organizations, patient advocates, and international groups.





Tackling Melanoma in the Sunshine State: Florida Researchers Unite

Vernon Sondak, M.D. *(left)* and James J. Mulé, Ph.D. *(above)*
H. Lee Moffitt Cancer Center & Research Institute
2007 SPORE Planning Grant

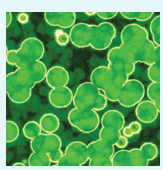
"Melanoma, the most serious and potentially deadly form of skin cancer, is a major cause of cancer-related death in Florida. In fact, Florida has the second-highest melanoma rate in the U.S. We are seeing melanoma not only affecting Caucasian adults, but also children, African Americans, and Hispanics. This is an enormous problem for the state. Last year we saw more than 1,700 new patients in our Cutaneous Oncology Clinic, and melanoma was the #1 diagnosis. Melanoma and other skin cancers are now the second most common reason people come to Moffitt Cancer Center for treatment," explained Dr. Vernon Sondak. "Despite its frequency, though, when detected before it has spread, melanoma is highly curable."

According to Dr. Sondak, his team's SPORE planning grant has several components aimed at identifying tumors with good prognoses and those with bad prognoses that may benefit from aggressive early therapy. "Understanding why some melanomas spread when other seemingly similar tumors do not is one question we'd like to answer. It is important to find patients with early melanoma that is aggressive. Because most doctors have completely removed and disposed of melanomas before patients come to a cancer center like Moffitt, we are reaching out to clinicians around the state to gain access to the original melanoma lesion. We want to learn how to predict which melanomas are metastatic and which ones are not. Which patients need treatment at a cancer center versus a dermatologist's care? We need a diverse group of patients — a broad range of ethnic groups and skin types — to understand these issues, and Florida provides that."

A second component of the research spearheaded by Dr. James Mulé involves learning to harness the immune system to treat widespread melanomas. This project involves the development of dendritic cell vaccine immunotherapy, a complex but potentially effective treatment for metastatic melanoma. Only a few specialized centers in the U.S. offer this treatment. The Bankhead-Coley grant provides the means to develop collaborations with immunologists at the University of Florida and the University of Miami to assist in conducting and monitoring trials investigating this type of therapy. The actual clinical trial is supported by a grant from the V Foundation, which sponsors innovative cancer research.

In addition to the two main projects, the SPORE Planning Grant includes funds to support junior investigators starting new melanoma research projects at any participating Florida institution; pilot studies on the influences of age or race/ethnicity on melanoma; career development awards for additional training in melanoma research; and tumor procurement core facilities. The grant builds the infrastructure and collaboration necessary to conduct statewide melanoma research that, according to Dr. Sondak, "markedly increases the chance of bringing a collaborative melanoma SPORE grant to the state of Florida. Our team's goal is to use this research as the basis for submission of an NCI proposal within six months of completion of this grant; potentially bringing over $8 million in federal funds to the state."

This research grant unites investigators across disciplines and institutions. Extended and new collaborations are occurring between the H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, University of Miami, University of Florida Jacksonville and Gainesville, and other physicians throughout Florida who will participate in a new Florida Melanoma Consortium. This extensive network enables research that "no single institution or researcher could do before," commented Dr. Sondak. "New partnerships are being forged as hospitals partner with each other and dermatologists work with us in tumor procurement. The teamwork is unprecedented and involves collaboration between surgeons, oncologists, immunologists, epidemiologists, pathologists, and molecular biologists. The H. Lee Moffitt Cancer Center & Research Institute thinks so highly of this effort that they exceeded the minimum in matching funds and are contributing more than $500,000 in support."



Award History

The 2006 Annual Report for the Bankhead-Coley Program went to press in early December 2006, just as the Program awarded projects beginning in January 2007. Consequently, this report provides details regarding the outcome of the first round of funding as well as the awards made for projects that began in July 2007.

Results for the 2006-2007 Call for Grant Applications

The value and term of the **Bridge Grant** is the amount requested in the qualifying federal proposal (up to $200,000) for a period of one year, or until funding begins for the resubmitted federal proposal (whichever is less); new investigators were eligible for up to two years of funding, if needed, for a maximum award of $400,000. **Shared Instrument Grants** offered were up to $500,000 for one year.

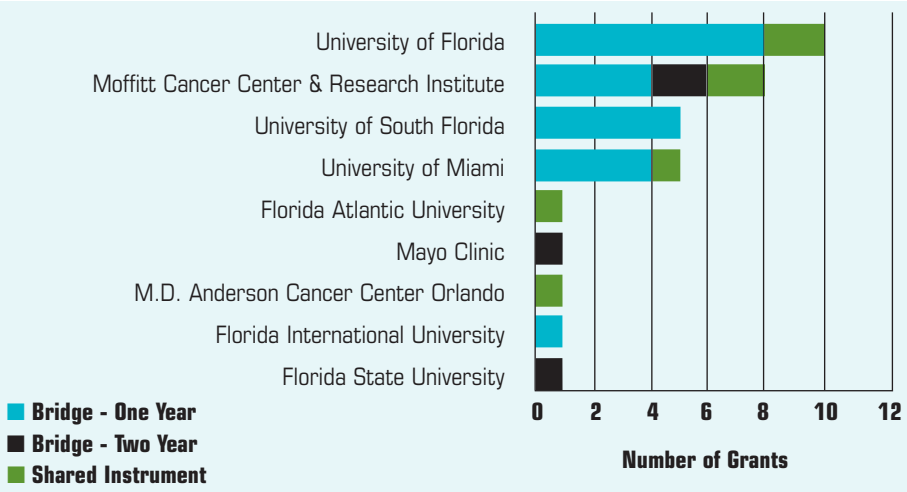
Table 1: 2006-2007 Grant Applications Received/Awarded

Grant Mechanism	Applications Received	Applications Awarded	Percent of Applications Awarded	Awarded Funding Amounts
Bridge Grant - One Year	31	23	74%	$ 3,795,782
Bridge Grant - Two Year	5	3	60%	$ 946,000
Shared Instrument Grant	11	7	64%	$ 3,358,214
Total	**47**	**33**	**70%**	**$ 8,099,996**

The Program awarded 33 grants totaling $8,099,996 and 32 projects began January 1, 2007. (One awardee relinquished a Bridge Grant before drawing any funds due to receipt of a federal grant.) The funding decisions that led to these awards represented an overall proposal-to-award ratio of 70 percent. Table 1 provides a breakdown of requests and awards across the grant mechanisms.

Of the 2006 awards, 47 percent of grant funds were for one-year Bridge Grants and 12 percent of grant funds were for new investigators for two-year Bridge Grants. The remaining 41 percent of the available funding was dedicated to seven one-year SIGs. These funds are restricted to the purchase of the equipment; in exchange, recipient institutions committed more then $2 million in matching funds to provide the operational expenses to operate and sustain this equipment.

Figure 2: Number of 2006-2007 Grants Awarded by Institution



Public and private research institutes throughout Florida are benefiting from these awards. The Program awarded grants to nine Florida research institutions, as shown in Figure 2. Five institutions are beneficiaries of funds to acquire or upgrade key equipment that multiple investigation teams are quickly putting to use for cancer research.

Refer to Appendix B for the fiscal year (FY) 2006-2007 grantee information including principal investigator, institution, award amount, project title, and abbreviated abstract.

Results for the 2007-2008 Call for Grant Applications

In the second round of funding, the maximum value and term of **Bridge Grant** awards are the same for investigators at all experience levels. The Program offered each award for the amount requested in the qualifying federal proposal (up to $200,000) for up to one year, or until funding begins for the resubmitted federal proposal (whichever is less).

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 are for up to three years for a maximum award of $1,000,000. The Program limited applications to one per institution and required recipient institutions to provide a minimum 25 percent match.

Awards for the **Special Emphasis Project** are up to $500,000 for a period of up to two years.

In response to the FY 2007-2008 Call, the Program received 36 proposals requesting a total of $14,139,551. More than half of all the applications were for Bridge Grants, and one-third sought New Investigator Research Grants. As anticipated, the Program received only a small number of applications for the SPORE Planning Grant and the Special Emphasis Project Grant due to 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 2007, and the Council recommended funding 25 research grants totaling $8,523,209. This action resulted in an overall proposal-to-award ratio of 69 percent. Table 2 provides a breakdown of requests and awards across the grant mechanisms.

Table 2: 2007-2008 Grant Applications Received/Awarded

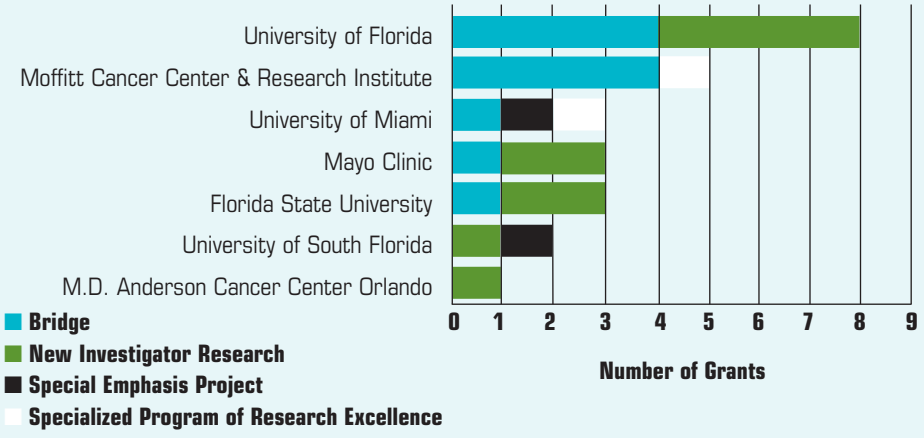
Grant Mechanism	Applications Received	Applications Awarded	Percent of Applications Awarded	Awarded Funding Amounts
Bridge Grant	19	11	58%	$ 2,069,638
New Investigator Research	12	10	83%	$ 3,558,030
Special Emphasis Project	2	2	100%	$ 895,542
Specialized Program of Research Excellence	3	2	67%	$ 1,999,999
Total	**36**	**25**	**69%**	**$ 8,523,209**

Of the 2007 awards, 42 percent of grant funds were allocated to support 10 new cancer investigators. Another 24 percent were dedicated to Bridge Grants for 11 investigators with promising and unfunded cancer projects, and 23 percent were split between two new collaborative research teams planning to pursue NCI SPORE funding. The remaining 11 percent were awarded to two Special Emphasis Projects.

As illustrated in Figure 3, seven Florida research institutions received awards in the second competition based on the scientific merit of the proposals received.

Refer to Appendix B for the FY 2007-2008 grantee information including principal investigator, institution, award amount, project title, and abbreviated abstract.

Figure 3: Number of 2007-2008 Grants Awarded by Institution



Program Operations

Administrative Costs

The Program by statute can use up to 10 percent of the appropriated funds for administrative expenses. Despite the challenge of administering both a full inaugural funding cycle and all pre-award activities supporting the second year of Program operations during one fiscal year (2006-2007), administrative costs stayed below the allocation. (See Table 3)

Table 3: Program Expenditures ($ Million)

Fiscal Year	Appropriation	Grants Awarded	Percent	Administrative Expenses[a]	Percent
FY 07-08	9.00	8.15	91%	n/a	n/a
FY 06-07	9.00	8.10	90%	0.82	9%
Total	**18.00**	**16.25**			

[a] This number excludes indirect costs, which are provided by the Department of Health.

Note: Money that is obligated but not disbursed by the end of the fiscal year is carried forward to pay out multi-year grants in future years.

Program Administration

The Office of Public Health Research, within the Department of Health, is responsible for administering the Program. Based on the continuing quality of services provided, the Office of Public Health Research renewed the contract with Lytmos Group, LLC, for an additional three-year period, through June 2010, subject to the availability of funds.

Lytmos provides consulting, business, and technology solutions for the grant-making industry. Their delivery of effective processes and innovative solutions helps biomedical research grant programs such as the Bankhead-Coley Cancer Research Program and the James & Esther King Biomedical Research Program improve grant program performance by reducing the burden of administrative functions and introducing best-practice solutions.

Jointly, the Office of Public Health Research and Lytmos are responsible for:

- Program Development—Funding cycle and call for grant applications preparation, researching grant programs and initiatives, development and refinement of Program policies and procedures, and creation of Program materials
- Application Processing—Acceptance and processing of online applications, administrative review of applications for compliance with all requirements
- Peer Review Process Management—Reviewer recruiting, panel and review assignments, and development of evaluation materials
- Funding Decision Support—Competition analysis and reporting, funding decision aids, and direct Council support
- Administrative and Programmatic Monitoring of all Grants—Financial and progress report evaluations, site visits, compliance with human and animal use assurances; direct grantee support, financial and scientific overlap monitoring, and continuation request processing
- Budget and Finance—Managing the budget, direct grantee payments, and procuring and managing award contracts
- Program Evaluation and Improvements—Ongoing monitoring and implementation of process and performance enhancements, strategic planning, working with the Council to compare the Program against benchmarks, reviewing and updating long-term goals
- Technical Support—Automated application processing, grant management systems support, and grantee technical assistance, and website development and maintenance (www.floridabiomed.com)

Granting Process and Grant Management

The FY 2007-2008 grant process began with guidance from the Council in August and September 2006 that was incorporated into the "Call for Grant Applications FY 2007-2008" released in December 2006. The Program publicized the availability of funding to nearly 700 individuals in Florida via e-mail in November and December 2006 and posted information about available grants on the Program website at www.floridabiomed.com.

The Program collected written questions from applicants and published answers on the Program website for the benefit of all candidates. Applicants completed online applications tailored for each grant mechanism by the due date of February 23, 2007.

The Program began its project selection process by subjecting each application to an independent peer review. The reviewers were nationally prominent individuals from universities, government agencies, and industry whose expertise match the application's topic. To avoid conflicts-of-interest, none of the reviewers was associated with any Florida-based public or private entity working in the life sciences. Reviewers agreed to respect the confidentiality of new, unpublished research contained in applications they examined. Each reviewer was required to declare any recognized conflict-of-interest during the assessment period, and program staff adjusted review assignments as needed. The reviewers judged proposals using an evaluation questionnaire that was published on the Program web site, www.floridabiomed.com, prior to the competition due date.

For all applications except those seeking Bridge Grant funding, the Program relied on a numeric indicator of scientific merit as rated by Program peer reviewers. This metric consisted of the average reviewer rating for each proposal (using a scale similar to the one used by the NIH in its peer review process), excluding the highest and lowest scores. For Bridge Grant applications, the Program relied entirely on the federal peer review scores (normalized across agencies) as the indicator of scientific merit. To satisfy additional programmatic interests, three independent peer reviewers examined Bridge Grant applications to rate the relationship of the proposed research to cancer, the feasibility of the work proposed for the Program grant period, and the appropriateness of the budget.

At the May 2007 Council meeting, Lytmos presented scientific merit scores and data while concealing the identity of the investigator and institution in order to avoid conflicts-of-interest of both Council members and Department staff. The Council considered overall Program objectives and fundable ranges for each grant mechanism to establish award priorities. Council members then provided funding recommendations to the State Surgeon General, who made the final award determinations. Program staff conducted a final check of eligibility requirements before completion of the granting process and, once approved, announced new awards on June 1, 2007.

Award processing activities consisted of finalizing budgets, establishing contracts specifying the award terms and conditions, obtaining human subject and animal study approvals from official organizations, and updating other support information.

During 2007, the Program ensured integrity and accountability in its grant award and administrative processes by:

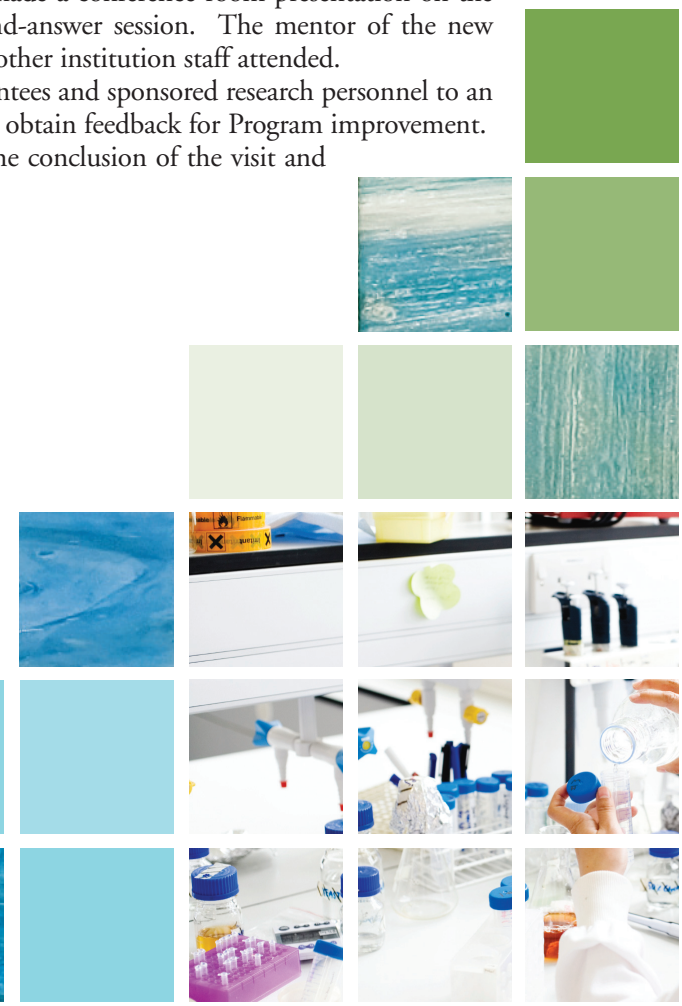
- Requiring periodic financial reports and monitoring spending patterns
- Requiring justification of expenditures and proposed changes to budgets, key personnel, and research protocols
- Requiring annual narrative progress reports
- Conducting grantee site visits
- Providing technical assistance as needed

With the understanding that research by its very nature is unpredictable, the Program maintained high expectations of its grantees to complete the planned project aims. Grant managers required principal investigators to provide a "Research Milestone Chart" for multi-year grants as a tool to communicate research plans and progress. Maintained for the life of the project, this chart shares the planned, high-level schedule for each project aim and includes major milestones. The rationale for this tool is that effective project planning by the principal investigator is essential to project success.

In written progress reports submitted by the first round of grantees in October 2007, investigators described the status of their work relative to their specific aims and shared significant findings. They also presented plans for addressing unanticipated outcomes or project delays and reported project-related published works, patents, and complementary funding. Program staff evaluated each progress report and provided feedback to the grantees, including required follow-up activities. The Program processed requests for continuations of multi-year projects and no-cost extensions of one-year awards in November and December 2007.

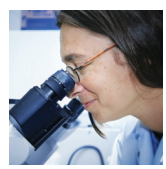
Program representatives make every attempt to conduct site visits once during the life of all multi-year grants, allowing Program staff to meet the investigators and sponsored research personnel, see and hear more about project progress, and ensure that proper institutional controls are in place to support the state's investment. One site visit took place in August 2007 for a 2006 two-year Bridge Grant at the Mayo Clinic in Jacksonville (other site visits are scheduled). This visit followed the Program's prescribed format:

- The site visit team examined institutional policies and controls and audited expenditures charged to the project.
- The principal investigator led a lab tour and made a conference room presentation on the sponsored research, followed by a question-and-answer session. The mentor of the new investigator, other project team members, and other institution staff attended.
- The site team invited current and potential grantees and sponsored research personnel to an open session to discuss Program guidelines and obtain feedback for Program improvement.
- The site team shared preliminary findings at the conclusion of the visit and followed up with a written site visit report.



Furthering the Program's Purpose

The Biomedical Research Advisory Council is concerned that full implementation of s. 381.921, F.S., is not currently possible through the Bankhead-Coley Cancer Research Program under s. 381.922, F.S. In order to achieve the desired outcomes, additional funding may need to be directed to the Florida Cancer Council to competitively procure goods and services.

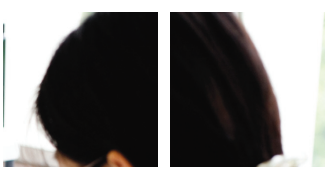


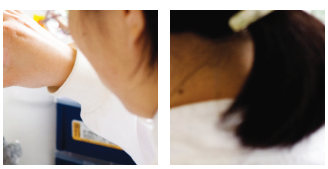
The Bankhead-Coley Cancer Research Program incorporates the goals of the Florida Cancer Council (FCC) by reference in s. 381.922(2)(a), *F.S.* The FCC was created in 2004 as a result of the efforts of the Florida Dialogue on Cancer (FDOC). The FCC has never received funding.

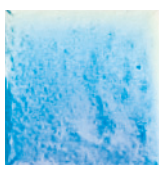
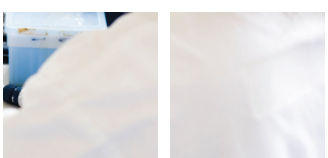
The Florida Division of the American Cancer Society sponsors the FDOC.[24] The FDOC promoted the idea of a formal entity under the Department of Health that would fund cancer research, including clinical trials, recognizing that Florida's high cancer burden made it incumbent upon the state to take a leadership role.

In creating the FCC, the vision of the FDOC was to secure $500 million from the Florida Legislature over a five-year period to accomplish the goals established in s. 381.921, *F.S.* After failing to obtain funding for the FCC in 2004 and 2005, the FDOC was successful in getting 2006 legislation sponsored that created the Bankhead-Coley Cancer Research Program, more modestly funded at $9 million per year and with a limited scope of awarding grants to investigators through a competitive peer-reviewed process. Program oversight was awarded to the Biomedical Research Advisory Council instead of the FCC.

While the Biomedical Research Advisory Council embraces the three broad goals of the FCC, it is apparent that the highly specific ministerial duties of the FCC cannot be implemented fully with the modest funding and limited scope of the Bankhead-Coley Cancer Research Program.





Biomedical Research Advisory Council

Section 215.5602, *F.S.*, charges the Council 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 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 an advisory 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 Florida/Puerto Rico 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 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
  - One from a cancer program approved by the American College of Surgeons
- Two members appointed by the Speaker of the Florida House of Representatives
  - One from a professional medical organization
  - 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 Department of Health, relying primarily upon the outcome of an independent scientific peer review process.

When Florida lawmakers added responsibility for the Bankhead-Coley Cancer Research Program to the Council in May 2006, they also added two seats reserved for professionals with clinical cancer research experience. In July 2006, Senate President Ken Pruitt named **Daniel Morris, M.D.**, a practicing clinical oncologist at Naples Medical Center, to the Council. In April 2007, **Randal Henderson, M.D.**, a past president of the Florida Society of Clinical Oncology (FLASCO), was appointed to the Council by House of Representatives Speaker Marco Rubio.

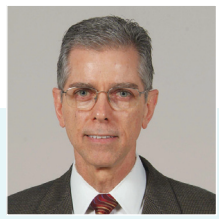
Another notable change to Council membership during 2007 was a rotation in the designated representative of the American Lung Association. Effective July 1, after seven years of distinguished service as an integral contributor to the work of the Council, **Edward Block, M.D.**, yielded his seat to **Veena Antony, M.D.**

Veena Antony, M.D.
Chief of Pulmonary, Critical Care
and Sleep Medicine
Professor, College of Medicine
University of Florida
Seat: American Lung Association
Appointed: July 1, 2007

Edward R. Block, M.D.
Distinguished Professor and Chair
Department of Medicine
University of Florida
Seat: American Lung Association
Appointed: July 1, 2000
Relinquished: June 30, 2007

Richard J. Bookman, Ph.D.
Executive Dean for Research & Research
Training, Miller School of Medicine
and Vice Provost for Research
University of Miami
Seat: Advisory Council Chair
and American Heart Association
Appointed: July 1, 2000

Nikolaus Gravenstein, Ph.D.
Professor and Chair
Department of Anesthesiology
University of Florida
Seat: Biomedical Research
Appointed: February 27, 2006



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: April 20, 2007

Myra Hurt, Ph.D.
Associate Dean, Research & Graduate
Programs, Professor Department of
Biomedical Sciences
College of Medicine
Florida State University
Seat: Research University
Appointed: February 27, 2006

Albert Latimer, B.B.A.
Vice President
External Affairs
Enterprise Florida, Inc.
Seat: General Public
Appointed: February 27, 2006

Daniel Morris, M.D.
Medical Physician
Medical Oncology and Hematology
Naples Medical Center
Seat: Senate-Cancer Program (ACoS)
Appointed: July 17, 2006

Sigurd Normann, M.D., Ph.D.
Professor
Pathology, Immunology and
Laboratory Medicine
University of Florida
Seat: American Cancer Society
Appointed: July 1, 2000

Penny Ralston, Ph.D.
Dean and Professor
College of Human Sciences
Florida State University
Seat: Senate-Behavioral/Social Research
Appointed: July 17, 2006

Mary Lou Sole, R.N., Ph.D., CCNS, FAAN
Professor, College of Nursing
University of Central Florida
Seat: House-Professional Medical Organization
Appointed: April 19, 2007

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: February 27, 2006

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.

1Note.—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: Abbreviated Abstracts of Grant Awards

The following list represents 2006 and

ABDELRAHIM, Maen

2007 NIR
M.D. Anderson Cancer Center
$209,520

Inhibition of Pancreatic Cancer Growth and Metastasis by NSAIDs and Derivatives

Considered by many to be one of the deadliest malignancies, pancreatic cancer is associated with a death to incidence ratio of approximately 0.99. The major cause of death from pancreatic cancer is due to metastases, which are extremely resistant to conventional therapies. Due to local invasion and/or metastasis, only 15-20 percent of pancreatic cancer patients qualify for surgical intervention, and chemotherapeutic options are limited. Researchers at M. D. Anderson Cancer Center Orlando's Cancer Research Institute are studying the process by which pancreatic cancer cells manipulate the tumor environment, recruit nutrients, and metastasize. For the first time, research has identified a structural class of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit pancreatic cancer cell growth. The proposed research will identify the most potent NSAID analogs as lead compounds for development of new treatment options.

BAI, Wenlong

2006 Bridge
University of South Florida
$200,000

Molecular Mechanism Underlying the Resistance of Ovarian Cancers to Vitamin D

Although 1,25-dihydroxycholecalciferol (1,25VD), an active form of Vitamin D, has been shown to suppress the cell growth of many human cancers, clinical trials with a synthetic form of Vitamin D for human cancers were met with limited success. This proposal examines the mechanism underlying alteration of the growth suppression by 1,25VD during ovarian tumorigenesis that causes resistance of frankly malignant ovarian cancer to the hormone. The study may lead to the development of a novel strategy to overcome the Vitamin D resistance, allowing more ovarian cancer patients to benefit from the 1,25VD-based therapeutic treatment. The study of PAK4 may reveal a novel oncogenic pathway that contributes to ovarian epithelial tumorigensis.

BLANCK, George

2006 Bridge
University of South Florida
$179,071

Negative Regulation of the MHC Class II Promoters

The bridge funding will be used to further our understanding of why the MHC class II genes are not expressed in cells with a mutated Rb tumor suppressor gene, especially bladder carcinoma cells. The focus will be on determining conclusively whether a protein named YY1 represses the MHC class II gene under more natural conditions. This research, which will support a more extensive application to the NIH, would be designed to determine the exact molecular mechanism of YY1-mediated repression of the MHC class II gene. This in turn will lead to proposals for therapeutic elimination of YY1 and re-expression of the MHC class II gene in patients' cancers, thus facilitating the eradication of the cancer by the patient's T-cells. Thus, the bridge funding is expected to lead to the development of novel treatments for numerous different types of cancers that develop due to Rb-mutations, including lung, breast, and bladder cancers.

BROWN, Kevin

2006 Bridge
University of Florida
$52,500

ATM in Breast Cancer Suppression

The ATM protein is a critical molecule in maintaining normal, healthy DNA by activating a series of appropriate cellular responses following DNA damage. The importance of the ATM protein is underscored by the fact that children born without functional ATM develop a cancer-prone disorder termed Ataxia-Telangiectasia (A-T), leading to heightened rates of breast cancer occurrence. The reason for this defect was unknown until our group found that the ATM gene is efficiently turned off in invasive breast cancer and other tumor types by a process termed epigenetic silencing. The aims of this research focus on developing a mouse line with conditional deletion of the ATM gene in mammary epithelium in order to make the study of various tumor types more practical and to determine when during breast cancer progression in humans ATM is targeted for epigenetic silencing by analyzing tumor samples from breast cancer patients.

BYRNE, Margaret

2007 SEP
University of Miami
$395,542

Understanding Disparities and Barriers to Participation in Cancer Clinical Trials Among Floridians: A Health Behavior Population-Based Approach

Florida has one of the lowest rates of participation in clinical cancer trials in the country. However, since the root causes of low participation is unknown, policy solutions and interventions to increase participation rates have not been developed. This project is a comprehensive study of barriers and facilitators to participation in cancer clinical research trials in the state of Florida and will include: 1) a state-wide examination of participation rates in cancer clinical trials; 2) surveys of cancer patients throughout the state, focusing on patients' beliefs, attitudes, and perceived barriers; and 3) surveys of healthcare providers and researchers who conduct research on cancer and/or care for cancer patients to assess attitudes toward clinical trials, perceptions of patients' willingness to participate, and barriers and facilitators faced by providers in identifying and referring patients to trials. At the conclusion of the study, important knowledge will be available on how participation rates and factors affecting participation rates, vary by location in Florida, by individuals' racial/ethnic background, and by neighborhood characteristics of cancer patients. These results will guide recommendations for improving rates of participation in Florida cancer clinical trials.

CHELLAPPAN, Srikumar

2006 Bridge
H. Lee Moffitt Cancer Center
& Research Institute
$200,000

Nicotinic Receptor Signaling Pathways in NSCLC

Tobacco smoke contains many cancer-causing agents, many of which are derivatives of nicotine. The first set of experiments proposed here will identify the signaling pathways by which nicotine induces the proliferation of non-small lung carcinoma cells. The second set of experiments will assess the molecular mechanisms by which nicotine prevents the lung cancer cells from dying, with special emphasis on two molecules, XIAP and surviving. The third set of experiments seek to understand the role of signaling molecules like Src and Raf-1 in the process of new blood vessel growth in tumors; the research team will also assess the relative contribution of other molecules like Akt and cell cycle proteins. Further, these experiments will also help elucidate whether exposure to nicotine alone, independent of other carcinogens present in tobacco smoke, affects lung cancer.

CHEN, Jiandong

2006 Bridge
H. Lee Moffitt Cancer Center
& Research Institute
$199,898

Function and Regulation of SirT1 in Cancer

Recent work has shown that the SirT1 gene controls the activities of several human genes that normally promote cell death, including several tumor suppressor genes. The research team plans to investigate further whether abnormal SirT1 production in human tumor cells leads to resistance to cell death induced by chemotherapy drugs and whether suppressing SirT1 activity can improve the therapeutic effects of cancer drugs. Another goal is to determine whether SirT1 activity is closely linked to the overall malignant status of the tumor cell by a signaling mechanism called phosphorylation. Discovery of new signaling mechanisms may lead to development of drugs that modify SirT1 activity and improve response to cancer chemotherapy.

CHENG, Jin

2007 Bridge
H. Lee Moffitt Cancer Center
& Research Institute
$200,000

AKT1 Function and Carcinogenesis

AKT1 is a cancer-causing gene, which plays a pivotal role in human oncogenesis. However, the molecular mechanism of AKT1 in human oncogenesis remains elusive. The team has recently identified a specific AKT1-associated protein, TZP, which is an uncharacterized nuclear protein. The team hypothesizes that AKT1/MST1/TZP cascade plays an important role in the control of cell survival, proliferation, and transformation induced by AKT1. The broad, long-term objective of this project is to elucidate the normal cellular function of the AKT1 protein and determine the importance of perturbations of the AKT1 pathway in human carcinogenesis. The specific aims include: defining the role of the AKT1-associated protein TZP in AKT1 signaling; examining the effects of AKT1 phosphorylation of MST1 on MST1/WW45/LATS function; and defining the MST1 regulation of TZP and TZP/FOXO3a complex as well as the effect of AKT1 on MST1/TZP/FOXO3a cascade.

COPLAND, John

2007 Bridge
Mayo Clinic
$200,000

Combinatorial Therapy for Anaplastic Thyroid Carcinoma

The long-term goal of this effort is to identify and characterize the molecular mechanisms underlying the cause and progression of human anaplastic thyroid carcinoma (ATC), with the goal to develop effective molecular-targeted therapies. ATC is one of the most aggressive and deadliest known cancers with no effective treatment options. The team has identified a combination of drugs: paclitaxel (Taxol) and a novel peroxisome proliferator activated receptor gamma (PPARg) agonist (RS5444) that act together to block cell proliferation and induce programmed cell death (apoptosis) in human ATC cells. The purpose of this research is to better understand the signaling pathways used by RS5444 to inhibit tumor growth of ATC cells. This study will determine whether the tumor suppressor, RhoB, blocks tumor growth of human ATC cells and tumors by re-expressing RhoB in ATC cells. The project will also examine global gene expression to identify new molecular markers (proteins) of response to combinatorial therapy. This will become important in a clinical trial to assess early on, whether RS5444 and Taxol are working or not.

GABRILOVICH, Dmitry

2006 Bridge
H. Lee Moffitt Cancer Center
& Research Institute
$180,887

Notch Signaling in Chemotherapy of Multiple Myeloma

Multiple myeloma (MM) is a hematological malignancy that results from a proliferation of clonal plasma cells, which accumulate preferentially in the bone marrow. MM is a treatable but rarely curable disease with a median survival of three to six years and a 10-year survival of three percent. Recently it became increasingly clear that the bone marrow environment and specifically bone marrow stroma play a major role in survival of multiple myeloma and its resistance to chemotherapy. The research team has recently discovered that receptor/transcriptional regulator Notch is one of the major factors responsible for protection of myeloma cells from drug-induced apoptosis. Preliminary experiments demonstrated that inhibition of Notch signaling with gamma-secretase inhibitors kills MM cells without affecting normal bone marrow cells and substantially enhances the effect of chemotherapy. Here, the team's intent is to investigate the mechanisms and clinical significance of these novel findings as well as potential approaches to use this new information in treatment of MM.

GANJU-KRISHAN, Awtar

2006 Bridge
University of Miami
$105,000

Nuclear Marker Expression in Human Breast Tumors

The incidence of Ductal Carcinoma in situ (DCIS), a pre-malignant and localized abnormal cell growth in breast, has increased. Not all DCIS develop into invasive breast cancer. However, for the lack of clear-cut distinction between those at low or high risk of developing invasive breast cancer, all patients with DCIS undergo surgery followed by radiation therapy. The team has developed a high-resolution flow cytometer, which can rapidly measure the nuclear volume, DNA content, and expression of hormone receptors simultaneously. Data will be analyzed to see if a correlation exists between grade of the DCIS as determined by the pathologist using conventional methods and expression of markers determined by this team. The hope is that this may allow pathologists on our team to refine the grading system for breast tumors and ultimately predict which of the patients may not need aggressive therapy.

GILBERT, David

2007 Bridge
Florida State University
$200,000

Genome Plasticity during ES Cell Differentiation to Neural Lineages

The long-term goal of this project is to understand the relationship of DNA replication to chromosome structure and function and how misregulation of replication leads to cancer. The research team is studying the progression of mouse embryonic stem cells as they mature into committed neural precursor cells. Recent evidence suggests that cancer cells may be stem cells that cannot lose certain properties of their "stemness", keeping them from progressing to normal adult cells. This abnormal behavior may be a result of errors in the way the cell's DNA is packaged into chromatin. Chromatin is a complex of DNA and proteins that wrap them into chromosomes. For DNA replication to occur, segments of the chromosome are unfolded. The sequence, method and timing in which segments of DNA are unwrapped, replicated and re-packaged changes as embryonic stem cells turn into their intended cell type. Understanding how this process is controlled may yield important information about cancer. Dr. Gilbert hopes to find clues as to how chromatin packaging can affect the very character of cells and their fate as normal or cancerous entities. If successful, this information could lead to new ways to detect and treat cancer.

GODAVARTY, Anuradha

2006 Bridge
University of Miami
$52,500

Hand-Held Optical Probe for Fluorescence Imaging of Breast Cancer

X-ray mammography is used as the primary screening test for breast cancer. However, the conventional x-ray mammography technique is limited by: its harmful x-ray radiation; lack of sensitivity and specificity for early stage cancer or dense breasts; and patient discomfort due to the compression of the breast tissue. Near-infrared (NIR) optical imaging using external fluorescence contrast agents is an emerging non-invasive modality that can become an important tool in the diagnosis of early-stage breast cancer and prognosis of the disease. The current research proposes to design and develop a hand-held based optical probe using a unique measurement approach that images large tissue volumes with no compression and rapid imaging rates. The future goal is to develop a hand-held based optical imager by integrating the novel hand-held optical probe to an NIR sensitive and rapid data-acquiring detector; such that high-resolution diagnostic and prognostic breast cancer imaging can be obtained at an earlier stage of the disease.

GUNJAN, Akash

2007 NIR
Florida State University
$375,000

Regulation of Histone Protein Levels by Tumor Suppressor Chk2 and Its Impact on Genomic Stability

Cancer is the second leading cause of death in America; 50 percent of all men and a third of all women will develop cancer at some point. It is believed that damage to DNA and other factors that cause genomic instability contribute to cancer formation. DNA is wrapped around positively charged histone proteins to form filaments called chromosomes. Histones help package the DNA to fit it inside the nucleus of each cell and thus regulate processes such as gene expression that require access to the genetic information contained within the DNA. Due to their positive charge, histones can potentially "stick" non-specifically to the negatively charged DNA and adversely affect processes that require access to DNA. The team is investigating whether the tumor suppressor Chk2 and the highly related kinase Chk1, as well as their known upstream and downstream factors, are playing a role in regulating histone levels. These studies may discover novel mechanisms by which histone/chromatin metabolism and Chk2 prevent genomic instability and cancer.

HARRINGTON, William

2007 SPORE
University of Miami
$999,999

Pathogenesis and Therapy of Viral Lymphomas

Viruses are considered the second most important cause of malignant disease in humans and are highly associated with aggressive lymphomas including Adult T-cell Leukemia/Lymphoma (ATLL) (HTLV-I), non-Hodgkin's (NHL), and Hodgkin lymphoma (EBV). South Florida is endemic for these pathogens due to its close proximity to the Caribbean and large population of chronically immuno-compromised patients such as organ transplant recipients and AIDS cases. This makes UM/JMH the ideal site for combining clinical and basic research from which to develop a multi-investigator program focused on viral lymphomas. Projects include 1) a clinical trial for ATLL, focusing on the transcription factors associated with resistance to interferon (IFN-alpha) based therapy, 2) the development of novel prognostic models for HIV-associated large cell lymphoma using analysis of RNA from paraffin-embedded specimens, 3) determining the mechanisms whereby oncogenic viruses such as EBV escape innate immune surveillance, and 4) a fusion protein that combines a clinically efficacious anti-B cell CD-20 with a ligand that has been shown to recruit cytotoxic NK cells in breast cancer. These studies are promoting collaborative efforts in anticipation of submission of an NCI SPORE application.

HAZLEHURST, Lori

2006 Bridge-Two Year
H. Lee Moffitt Cancer Center
& Research Institute
$400,000

Role of Bim in Mediating CAM-DR in Hematopoietic Tumors

It is well accepted that initial chemotherapy of chronic myelogenous leukemia and acute myeloid leukemia results in rapid clearing of detectable disease in the peripheral blood. However, elimination of disease in the bone marrow is a more arduous task, suggesting that de-novo drug resistance of leukemia cells associated with the bone marrow microenvironment may contribute to Minimal Residual Disease (MRD) following chemotherapy. Based on recent findings, the team has hypothesized that adhesion of leukemia cells via beta1 integrins in the bone marrow microenvironment contribute to the failure of conventional chemotherapy to eliminate minimal residual disease and thereby increases the incidence of disease relapse. The teams research goals are: to determine the causal role of Bim in mediating the drug resistant phenotype in adherent leukemia cells; utilize pharmacological inhibitors of beta1 integrin mediated signaling to test for increased Bim expression and drug sensitivity in the bone marrow microenvironment and in the molecular pathway whereby Bim is degraded.

HELLER, Richard

2006 Bridge
University of South Florida
$200,000

Therapeutic Potential of IL-15 Plasmid Delivery to Tumors Using Electroporation

Metastatic melanoma is a devastating disease due to the lack of an effective treatment. The survival for patients with advanced melanoma is very poor. Systemic infusions of recombinant cytokines have been evaluated in melanoma but can be toxic because of the high doses needed, and in most cases, they are not very effective. One way to attenuate the toxicity is to replace the high-dose systemic treatments with local gene therapy. The major focus of this study is the use of electrically mediated nonviral gene delivery for immunotherapy of solid tumors using the cytokine IL-15. The study is designed to obtain a more complete characterization of this delivery approach and an understanding of how the expression pattern impacts regression.

HU, Jennifer

2006 SIG
University of Miami
$493,580

Illumina Beadstation: High-Throughput Genotyping and Gene Expression Shared Instrumentation

This grant will fund the purchase of the Illumina BeadStation 500GX to support four multidisciplinary research programs within the Sylvester Comprehensive Cancer Center at the University of Miami (UM) Miller School of Medicine—Biobehavioral Oncology and Cancer Control, Hormone-Regulated Cancers, Tumor Immunology, and Viral Oncology. The Sylvester Cancer Center serves as the hub for cancer-related research, diagnosis, and as a treatment center that handles more than 1,400 inpatient admissions annually. It is important to be able to identify many of the genetic variations across the genome that may contribute to cancer risk. Current research emphasis has been placed on "personalized medicine" with the utilization of inherited genetic factors and expression profiling. Now, there is a gene expression core facility at UM to support researchers at the medical school. With the advancement of high-throughput technology, such as the Illumina's BeadArray technology, it will become feasible to perform whole genome scan and targeted genetic variations studies, gene expression profiling, and changes in tumor tissues in a larger number of samples with adequate statistical power.

HUANG, Suming

2007 NIR
University of Florida
$375,000

The Mechanisms of TAL1/SCL-Induced Leukemogenesis

Leukemia is a severe, malignant blood disease. Activation of the TAL1/SCL gene, a transcription factor required for normal blood cell development, has been frequently associated with a specific form of leukemia called T-cell acute lymphoblastic leukemia (T-ALL). The function of TAL1 in blood cell development is modulated by its binding partners, called co-regulators. Two TAL1 interacting proteins contain specific enzymatic activities that add or remove a methyl group to a group of specific DNA interacting proteins termed histones, which have been shown to have an important function in regulating chromatin structure and gene expression. This study investigates how these histone-modifying enzymes regulate TAL1-directed gene expression. Furthermore, this study will explore how the TAL1-associated histone-modifying enzymes alter TAL1 function in blood cell growth and differentiation and whether inappropriate TAL1-co-regulators' interactions influence leukemia development.

KATO, Yoichi

2006 Bridge-Two Year
Florida State University
$146,000

The Mechanism of Notch Signaling Pathway in Radial Glial Development

Exploring the mechanisms that control cell fate during development can yield important insights into the mechanisms of cancer formation and potentially yield new targets for therapy. Radial glia cells function as guiding cells for newborn neurons to reach their final destination and as a source of neural stem cells during brain development. Recently, radial glia cells have been indicated as candidate cancer stem cells of ependymoma, a type of brain cancer. The team's data have shown that radial glia cell formation is regulated by Notch signaling, but this Notch signal is carried into the nucleus by both an unknown intracellular pathway and the well-characterized classical Notch pathway. This unknown pathway is called a Su (H)-independent Notch signaling pathway. However, the mechanism of this pathway is poorly understood. As such, the research plan is to identify missing components that are involved in a Su (H)-independent pathway and characterize their functions.

HUGHES, Jeffrey

2006 Bridge
University of Florida
$200,000

Multifaceted Non-Viral Cancer Gene Therapy

Migrating brain tumor cells are highly proliferative, creating a high-nutrient demand. New blood vessels are formed around these lesions in order to supply the needed nutrients. This research will take advantage of this property to create a nonviral gene therapy that is safe and effective in treating the malignant tumors. Gene therapy consists of delivering a gene to a cell that instructs the cell to make a protein that will kill the tumor or kill the tumor endothelium or both. The gene that is delivered to the tumor cells will restrict only those endothelial cells that are dividing (creating new blood vessels) to read the gene. A recognition molecule coats the surface of the particle that is recognized only by the tumor endothelium and nowhere else. Once the gene is delivered to the tumor endothelial cells, the cells pump the cell-killing protein into the tumor cells directly in contact with the blood vessel wall. Treatment would ensue following surgical resection of the primary tumor or after a combination of surgery plus radiation.

KOOMEN, John

2006 SIG
H. Lee Moffitt Cancer Center
& Research Institute
$427,961

Acquisition of Hybrid Quadrupole Ion Trap Mass Spectrometer for Proteomics

This grant will provide funds for a liquid chromatography coupled to mass spectrometry (LC-MS) system featuring a hybrid triple quadrupole ion trap mass spectrometer (4000 QTrap, Applied Biosystems). This mass spectrometer combines the functions of triple quadrupole mass spectrometers, which set the standard for monitoring specific molecules in complex mixtures, and ion trap instruments, which are powerful tandem mass spectrometry (MS/MS) tools for peptide sequence analysis. Thus, the QTrap is used for specific molecular monitoring and targeting, yet still provides peptide sequence verification using MS/MS. As such, this LC-MS system can validate candidate biomarkers for diagnosis, prognosis, and chemo prediction; it can also selectively identify the events that form the molecular basis of cancer by targeting peptides with particular types of post-translational modifications based on their fragmentation signatures. Unknown phosphopeptides can be detected, enabling the analysis of signaling pathways, distinguishing relevant downstream events, and possibly defined novel drug targets.

ISHOV, Alexander

2007 Bridge
University of Florida
$200,000

Function of Daxx in Mitosis that Determines Paclitaxel Sensitivity in Breast Cancer

Taxanes are among the most powerful drugs for breast cancer treatment; however, a large number of patients are resistant to this therapy for unknown reasons. It is essential to develop prognostic tools and predictive markers to differentiate patient population for appropriate chemotherapy selection. This research aims to evaluate the function of a protein called Daxx as a predictive marker for taxane response and is based on our observation that sensitivity to paclitaxel treatment correlates with the level of Daxx. The central hypothesis is that Daxx deficiency can determine resistance to paclitaxel-induced mitotic catastrophe in breast cancer patients by reversibly blocking cells in prometaphase upon treatment. Identification of Daxx as a novel mitotic checkpoint protein that determines resistance for taxanes will aid in proper selection of breast cancer patients to receive this therapy and add to understanding of mechanisms that connect cell division, genome instability, and breast cancer progression.

KUSMARTSEV, Sergei

2007 NIR
University of Florida
$375,000

Role of VEGFR1+CD11b+ Myeloid Cells in Tumor-Induced Immune Suppression

Renal cell carcinoma (RCC) accounts for more than 12,000 deaths in the United States annually. These studies assess the association of specific circulating immunosuppressive cell populations with certain stages of cancer disease and metastatic process. The major goal of this research is to establish whether targeting of VEGFR1 can reverse immune suppression and improve the effect of cancer immune therapy. The first part of this study focuses on analysis of the VEGFR1-positive myeloid cells present in tumor host, and may show its association with certain stages of cancer disease. The second part of this study includes several series of experiments to better understand the molecular mechanisms of tumor-induced immune suppression mediated by these cells. The third part of this study will test whether targeting of VEGF-VEFR1 axis in tumor-bearing mice could enhance the therapeutic effect of a cancer vaccine directed against murine renal cell carcinoma. Information obtained in this research will be extremely useful for the design of future clinical trials using both anti-angiogenic and immunotherapeutic approaches for treatment of patients with renal cell carcinoma.

LAMPIDIS, Theodore

2006 Bridge
University of Miami
$200,000

Anti-Tumor Activity of Sugar Analogs via Blocking Glycolysis versus Glycosylation

Standard cancer chemotherapy attacks all fast-dividing cells. This is why slow-growing tumor cells are the most difficult to cure. Since they survive standard chemotherapy, slow-growing cancer cells can give rise to more rapidly dividing cells that eventually become resistant to all drugs. In most, if not all, solid tumors there are pockets of slow-growing cells that reside in areas that receive little or no oxygen (hypoxic). Under hypoxia, cancer cells burn (or metabolize) sugar inefficiently and therefore need to take up much more of it to survive than normal cells in the body that are well-oxygenated. Thus, if tumor cells are fed false sugars such as 2-deoxyglucose (2-DG), their only energy source is cut off, and they literally starve to death. The FDA has recently approved a Phase I clinical trial using 2-DG in combination with a standard chemotherapeutic, taxotere, in patients suffering from various types of solid tumors. By combining these two approaches, we hope to raise the clinical efficacy of chemotherapy.

LAW, Brian

2007 Bridge
University of Florida
$200,000

A Novel Class of Anticancer Agents Targeting Cyclin-Dependent Kinases

Knowledge of how breast cancer cells proliferate uncontrollably is increasing rapidly. In particular, protein enzymes called Cyclin-dependent kinases are known to become hyper-activated in breast cancers. Preventing the production of these proteins using genetic approaches prevents breast cancer induced by the Her2/neu oncogene, activated in about 30 percent of human breast cancers. Numerous pharmaceutical companies have developed Cyclin-dependent kinase inhibitors. The problem with these agents is that they are likely to inhibit many other types of kinases resulting in unanticipated toxic side-effects. In addition, these drugs block only some of the actions of Cyclin-dependent kinases, but leave other actions of these proteins unaffected. We have recently identified a new class of Cyclin-dependent kinase inhibitors. These inhibitors block all of the actions of Cyclin-dependent kinases. In addition, they are highly specific for Cyclin-dependent kinases and are therefore expected to exhibit fewer and less severe side effects. This research explores how these drugs function to inhibit the growth of breast cancer cells.

LIPSHULTZ, Steven

2007 Bridge
University of Miami
$200,000

Genetic Mechanisms of Anthracycline Cardiotoxicity in Pediatric Cancer Survivors

Anthracycline chemotherapy has been used in more than 50 percent of patients with childhood cancer and has helped contribute to 5-year survival rates of more than 77 percent. This therapeutic success is tempered by the well-recognized and clinically significant late cardiotoxicity. In this grant, we will extend the understanding of anthracycline-based cardiotoxicity through the study of mitochondrial DNA mutations (mtDNA) and genetic mutations of the hemochromatosis genes (HFE) as potential causes/mechanisms of the increased cardiovascular risk in survivors of childhood acute lymphoblast leukemia (ALL). This research will also examine whether dexrazoxane, which has been seen to protect the heart, acts through a reduction in the frequency of mtDNA mutations. Targeting patients at risk for developing cardiovascular disease for clinical intervention will result in a decreased toxicity. Further, identifying patients at a lower risk for cardiovascular complication may permit increased doses in therapy, thereby increasing overall survivorship.

LO, Chun-Min,

2006 Bridge
University of South Florida
$52,500

c-Met Mediated Ovarian Cancer Cell Motility

Ovarian cancer is the most lethal of the gynecologic cancers with 50 percent of women dying within five years. Despite the improvements in detecting and treating the primary ovarian tumor, current therapies against metastasis are still limited. Dysregulated HGF/c-Met signaling of cell migration has been suggested to contribute to tumor invasion and metastasis. The goal of the proposed research is to investigate the efficacy of a c-Met specific ATP-competitive small-molecule SU-11274 to decrease high-activated c-Met human ovarian carcinoma cell growth, scattering, and transendothelial invasion. The project will be facilitated by the use of electric cell-substrate impedance sensing (ECIS), a novel cell-based biosensor that monitors morphological changes of cells. The possible toxicity of SU-11274 will also be evaluated in normal HOSE cells. Lastly, the study will explore the possibility of using the ECIS system to analyze potential drugs for their abilities to suppress metastasis, particularly at the level of transendothelial invasion.

LOKESHWAR, Balakrishna

2006 Bridge
University of Miami
$198,426

Anti-tumor and c Hemopreventive Activity of the Ecuadorian Plant Extract BIRM

The goal of the present proposal is to investigate the preclinical efficacy of a formulation from an indigenous plant product found in the Andes called BIRM (Biological Immune Response Modifier, Life Root-Ecuadorian oral solution; BIRM Inc., Quito, Ecuador). In Ecuador and Columbia, local clinicians and pharmacies dispense BIRM for AIDS and cancer. Our laboratory has shown that BIRM is effective in killing prostate cancer cells. Since prostate cancer develops and progresses in several distinct stages, it is necessary to evaluate the efficacy of a therapeutic at every stage of the disease. This team proposes to test this natural product on prevention and cure of prostate cancer in TRAMP (transgenic mouse model) mice. The team will also work to identify the mechanism by which BIRM is able to stop tumor cells from proliferation, accelerating their death and degradation of androgen receptor, the main culprit in androgen unresponsive growth of the cancer.

LOSSOS, Izidore

2006 Bridge
University of Miami
$200,000

Prognostic Models in Diffuse Large B-Cell Lymphoma

Marked biological and clinical heterogeneity characterize diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin's lymphoma. The standard treatment has evolved to include the rituximab, an anti-CD20 antibody with CHOP (R-CHOP). Initial studies suggest that addition of rituximab changes the predictive power of specific molecular biomarkers. There is an urgent need to establish reliable biomarker-based prognostic models for DLBCL patients treated with R-CHOP, potentially forming the basis for risk-adjusted therapies. This project is based on a new methodology of RNA extraction from formalin-fixed, paraffin-embedded tissues (developed in the research team's laboratory), which allows reliable measurement of gene expression by either real-time PCR or oligo-microarrays. This methodology will be used to identify a list of genes whose expression correlates with survival of DLBCL patients treated with R-CHOP. Identification of the genes-proteins involved could also lead to recognition of new molecular therapeutic targets.

LUSTRIA, Mia Liza

2007 NIR
Florida State University
$348,510

Participatory Design & Evaluation of STEER: a Clinic-Based Tool to Help Health Providers Support Breast Cancer Care Needs in Rural Florida

While the development of highly targeted therapies and increased use of mammography screening and adjuvant therapy services have contributed to the overall decline of breast cancer deaths, these benefits have not been equitable for rural, low socio-economic status and non-white women. This is particularly telling in Florida. The aims of this research are to: (1) use participatory approaches to design a clinic-based tool to help build rural health providers' capacity to improve screening rates and access to breast cancer care resources; and (2) evaluate the system's usability, sustainability, and perceived benefits in a rural health clinic setting, as well as its effects on increasing physicians' breast cancer screening referrals and rural patients' adherence to breast cancer screening and treatment referrals. The proposed system, STEER (System for Tracking, Empowering, Equipping, and Reminding), will: send regular alerts to physicians to provide timely referrals in accordance with breast cancer screening guidelines; generate screening reminders that will include information and recommended actions tailored to patients' specific needs; provide a tool to collect information from at-risk patients and enable better tracking of patients throughout the cancer care continuum; and provide a tool to help monitor physician and patient adherence to breast cancer screening guidelines.

MAY, W. Stratford

2006 Bridge
University of Florida
$200,000

The Role of PKR in a Novel IL-3 Signal Transduction Pathway

Recently the research team's laboratory has discovered a novel protein that regulates cell growth and protein synthesis by activating the dsRNA-dependent protein kinase, PKR. The team named this new protein PKR activator X, or RAX. The evidence indicates that a diverse range of cellular stresses, such as growth factor deprivation, treatment with inflammatory molecules or chemotherapy agents, and viral infection initiate RAX-dependent PKR activation to shut down protein synthesis and induce cell death. Furthermore, reduced levels of RAX protein promote inappropriate cell growth. Taken together, these findings suggest that RAX may be critical for preventing cancer, maintaining the correct composition of bone marrow cells, and initiating the response to infection from foreign agents. The current research emphasis is to determine both the molecular mechanism by which RAX activates PKR and the physiologic function of RAX in the context of a whole animal using "knockout" mice.

MEEKS, Sanford

2006 SIG
M.D. Anderson Cancer Center
$437,000

Calypso 4D Localization System for Real-Time Tumor Tracking

Knowledge of the location of a tumor is critical during external-beam radiation therapy to optimize therapy and minimize complications. Targets such as the prostate, focal liver tumors and lung tumors move with respect to traditional positioning methods that use the skin or skeleton as references. This motion can be up to 2 cm and can compromise the ability to deliver a curative dose of radiation. The Calypso® 4D Localization System is an innovative target localization platform based on detection of wireless electromagnetic markers, called Beacon® transponders. The tiny Beacon transponders, are implanted in or near the treatment site. Any misalignment of the treatment target can be detected by Calypso Medical's proprietary algorithm. M. D. Anderson Orlando researchers will use the Calypso system for translational research on interfaces, targeting, and real-time dosimetry, and will conduct clinical trials using the Calypso system for the treatment of lung tumors, prostate cancer, breast cancer, and spinal tumors. Additionally, researchers from the Optical Diagnostics and Applications Laboratory at the University of Central Florida will use the system for validation of their virtual reality models that predict tumor motion.

MOFFITT, Karen

2007 SEP
University of South Florida
$500,000

Florida Cancer Clinical Trial Physician/Patient Information and Education Program

The Florida Cancer Clinical Trial Information Service was launched in 2004 to provide a centralized platform from which patients, advocates, and healthcare providers would have increased access to Florida's cancer clinical trials. The result was www.FloridaCancerTrials.com, a website that houses a complete, verified list of Florida's open cancer trials along with functionality that allows patients and healthcare professionals to match to open trials through a single questionnaire. The FCT also provides a toll-free number that allows patients, advocates, and healthcare professionals to search for trial matches or basic cancer clinical trial information over the phone (available in English and Spanish). The purpose of this research is to expand the suite of offerings to develop a clinician-centric solution for identifying clinical trial matches, prescreening patients, and tracking enrollments. The project encompasses four major aims, including an analysis of current practices for each site to identify gaps and bottlenecks, development of an educational and clinical trial information system designed to improve practices, an analysis of patient and provider data related to the systems implementation and utility, and an analysis of differences across clinical trial sites to inform program scalability and generalizability.

MOHAPATRA, Shyam

2006 Bridge
University of South Florida
$181,250

Nanoparticle-Mediated Targeting of Natriuretic Peptide Pathway for Lung Cancers

Lung cancer is the leading cause of cancer death for both men and women. More people die of lung cancer than of colon, breast, and prostate cancers combined. Herein, we propose to develop a targeted integrative gene expression and regulation (TIGER) technology for treatment of lung cancer using a novel anti-tumor agent, natriuretic peptide KP73-102, through a chitosan-based nanoparticle gene delivery system. The proposed TIGER system will be mediated by adenoassociated virus Rep protein or Sleeping Beauty transposon. KP73-102 by TIGER technology will minimize its toxicity. The team will first test the TIGER system on cells *in vitro* and then will further investigate the potential of KP73-102 for treatment of lung cancer in a murine model. We believe that KP73-102 nanoparticle therapy may offer a safe and effective treatment of patients with lung cancer and other adenocarcinomas in the future.

QIU, Yi

2007 NIR
University of Florida
$375,000

The Functional Analysis of Histone Deacetylase 1 (HDAC1) and HDAC2 and Their Role in Hematopoiesis and Leukemogenesis

Histone deacetylases (HDACs) are a group of enzymes that can modify histone and non-histone proteins. Acetylation or deacetylation often changes the function of proteins in the cell. Histone deacetylase inhibitiors (HDACi) are a group of very promising anti-cancer drugs. Clinical trials have indicated that structurally different HDAC inhibitors are well tolerated and exhibit activity against a variety of human malignancies. However, most of the HDAC inhibitors do not exhibit specificity on various HDAC isoforms. HDAC1 and HDAC2 are very similar enzymes and both have been shown to be important for cell survival and cell proliferation, two important characteristics for cancer development. Misregulation of GATA-1 is linked to hematologic diseases including leukemia. The team will investigate how HDAC1 is acetylated in the GATA-1 complex, how HDAC1 acetylation changes the activity of the GATA-1 protein complex, and how HDAC1 acetylation affects HDAC2 activity. Understanding these mechanisms could lead to the development of new HDAC inhibitors for the treatment of leukemia and other cancers.

RADISKY, Derek

2006 Bridge-Two Year
Mayo Clinic
$400,000

Mechanisms of MMP-Induced Malignancy in Breast Cells

The structure and form of the body is defined by dense networks of proteins known as the extracellular matrix. At early stages of cancer development, the growth of tumors is constrained by the extracellular matrix. Cancers become much more dangerous when they begin to synthesize matrix metalloproteinases (MMPs), specialized enzymes that break down the extracellular matrix, as this allows the tumors to metastasize, spreading throughout the body. This research team has recently identified specific pathways induced by MMPs in tumors that stimulate invasion and metastasis. In this project, specific experiments are designed to elucidate these pathways so as to reveal potential points of therapeutic intervention. The experiments will investigate how MMPs act upon cells to induce the production of reactive oxygen species and also to determine how the reactive oxygen species stimulate aggressive cellular behaviors. Identifying the points of convergence between MMPs and reactive oxygen species will lead to novel and much more effective therapies that target metastasis, the most dangerous aspect of tumor behavior.

RADISKY, Evette

2007 NIR
Mayo Clinic
$375,000

Structural and Mechanistic Studies of Mesotrypsin, an Oncogenic Inhibitor-Resistant Serine Protease

Proteases are proteins that digest other proteins; they fulfill many important biological roles, but misregulated proteases can promote tumor initiation, growth, and metastasis. The protease mesotrypsin promotes malignancy in culture models of human breast cancer, suggesting that this enzyme may provide a novel target for development of cancer therapeutics. Naturally-occurring protein protease inhibitors serve as a promising starting point for the development of new drugs targeting oncogenic proteases; however, mesotrypsin is unusually resistant to these inhibitors, having a unique ability to digest and inactivate them. The aims of this project are (1) to determine the protein structures of mesotrypsin bound to protein protease inhibitors and to identify the structural changes that take place upon binding using X-ray crystallography; (2) to determine the physical criteria by which mesotrypsin selects protein targets for degradation, both in test tubes and in live cancer cells; and (3) to determine how the structure of mesotrypsin promotes degradation of protein protease inhibitors using enzyme kinetic approaches.

RENNE, Rolf

2006 Bridge
University of Florida
$200,000

KSHV-Encoded MicroRNAs

Kaposi's sarcoma-associated herpes virus (KSHV), a virally induced cancer, is the causative agent of Kaposi's sarcoma (KS) and lymphoproliferative diseases such as primary effusion lymphomas and a subset of Multicentric Castleman's disease. KS, predominantly observed in patients with compromised immune systems, primarily afflicts the skin but in aggressive cases also affects internal organs. MicroRNAs (miRNAs), a new class of gene expression regulators, are small nonprotein-coding regulatory RNA molecules that bind to messenger RNAs and as a result decrease or stop protein production. Increased levels of miRNAs targeting tumor suppressor genes have been identified in breast, colon, lung, and prostate cancer. The focus of this research will be to investigate under which conditions miRNAs are expressed in KSHV–infected lymphoma cells. These experiments will provide the basis for translational studies in which the team will probe for miRNA expression in tumor samples of patients suffering from various KSHV-related malignancies.

SAROSI, George

2006 Bridge
University of Florida
$105,000

Bile-Induced Growth in Barrett's Esophagus

Esophageal cancer remains one of the most deadly human cancers with only a 15 percent cancer cure rate. Since 1974, the incidence of esophageal cancer has increased sixfold, a rate faster than that of all other gastrointestinal cancers. Moreover, there has been a change in the type of esophageal cancer, with less squamous cell carcinoma, and more adenocarcinoma, currently being diagnosed. Barrett's esophagus (BE) is a cancerous condition caused by chronic heartburn and the vast majority of esophageal adenocarcinomas are thought to arise from BE. Intriguingly, clinical studies show that patients with BE have significantly higher levels of bile salts along with acid in the refluxed material than patients without BE. Prior research has shown that both bile salts and acid exposure make Barrett's cells proliferate and activate molecules called mitogen activated protein kinases (MAPK) in other cancer cell types, suggesting that reflux of bile salts may act as a cancer promoter in BE and esophageal cancer. This bridge grant examines the mechanisms by which bile salts act as cancer promoters in BE and esophageal cancer.

SHIBATA, David

2006 Bridge
H. Lee Moffitt Cancer Center
& Research Institute
$131,250

Mechanisms of HPP1-Mediated Tumor Suppression

The state of Florida has the second highest number of annual colorectal cancer cases and deaths of any state in the country. HPP1 is a novel gene that appears to belong to a group of genes known as tumor suppressors that function to halt cancer progression. The loss of expression of HPP1 has been found to occur in a number of different cancer types including those arising from the colon, rectum, stomach, pancreas, esophagus, and lung. Significantly, alterations of the HPP1 DNA can be detected in the blood and stools of patients with colorectal cancer. Despite this growing interest in HPP1 as a cancer gene and its role as a biomarker, very little is known about its biologic function. The team will determine whether STAT1 is required for HPP1-associated tumor suppression, and will also identify putative protein interactors of HPP1. Findings will substantiate further investigation of HPP1 as an important colorectal biomarker that may prove useful for early detection, diagnosis, and determining prognosis in patients with colorectal cancer.

SHIBATA, Yoshimi

2006 SIG
Florida Atlantic University
$500,000

High-Speed Cell Isolation by FACS in FAU Cancer Research

The Cancer Research Program at Florida Atlantic University received a fluorescence activated cell-sorter (FACS) to support their funded research and to permit rapid completion of pilot programs with high probability of federal support. The FACS machine will be used to research the role of COX2 enzymes in the ability of macrophages to suppress cancers, the effect on T-lymphocytes of high levels of CCL-2 (a chemotactic peptide for macrophages and T-cells that is associated with increased survival in breast cancer patients), and the activation of androgen receptors in prostate cancer cells. A FACS is also essential to develop pilot data on ways to non-invasively target common fatal brain tumors, teach patients' immune cells to destroy their tumors, and identify leukemia at early (and most treatable) stages. In 5 minutes, a FACS will separate over 20 million cells into pure populations. The addition of FACS to the FAU campus supports the development of stronger interdisciplinary teams and boosts the prospects of establishing strong, extramurally funded program project grants. Finally, the FACS encourages stronger research collaborations with the highly trained oncologists in the community.

SIEMANN, Dietmar

2006 Bridge
University of Florida
$200,000

Combining Anti-Angiogenesis Strategies and Radiotherapy

Aggressive growth of cancer and the ability of cancer cells to spread (metastasize) to other organs in the body are both critically influenced by the state of the tumor vasculature (the blood vessel network that supports the growth of the cancer). There has been a great deal of interest in developing new anticancer drugs that target the tumor blood vessel network to amplify the anti-tumor effects of radiation. This proposal will perform preclinical studies designed to develop treatment approaches that will maximize the anticancer effects of vascular targeting therapies. Questions that will be addressed include whether tumors that have very extensive blood vessel networks will be more susceptible to vascular targeting therapies, determining how a tumor is able to grow its own blood vessels, whether the cells that make up the blood vessels in a tumor can be targeted using a virus that is not capable of growing but can infect the cells of the tumor blood vessels, and the use of several vascular targeting therapies in combination in order to maximize the anti-tumor activity.

STORZ, Peter

2007 NIR
Mayo Clinic
$375,000

The Role of the FOXO3a Transcription Factor in Breast Cancer

Breast cancer is the second leading cause of cancer-related death in women. In order to develop effective therapies that stop breast cancer growth and spreading via the blood and lymphatic system, the respective underlying biological and molecular events must be investigated. A transcription factor named FOXO3a is upregulated in invasive ductal tumors. The overall hypothesis guiding the research is that FOXO3a promotes normal breast cell transformation, breast tumor growth, metastasis, and thus the malign phenotype. We will analyze the role of FOXO3a in the regulation of genes that allow the degradation of extracellular matrix, an important step in tumor progression and metastasis. The long-term objectives of this project are to determine if FOXO3a expression or activity could serve as a biomarker for the malign potential of breast tumors. The identification of a transcription factor such as FOXO3a as a regulator of genes that is involved in tumor formation would be of great benefit for the development of assays that allow pharmacological screening for drugs that inhibit its activity.

SONDAK, Vernon

2007 SPORE
H. Lee Moffitt Cancer Center
& Research Institute
$1,000,000

Melanoma SPORE Planning Grant

Melanoma, the most serious and potentially deadly form of skin cancer, is a major problem in Florida, which has the second-highest melanoma rate in the U.S. This project will unite physicians experienced in patient-oriented melanoma research with basic and population scientists, and will extend existing collaborations at the Moffitt Cancer Center and the University of South Florida (USF) as well as establish new collaborations between physicians and scientists at Moffitt/USF with those throughout the state of Florida. In order to achieve this goal, this grant supports two collaborative translational melanoma treatment research projects; pilot studies on the influences of age and race/ethnicity on melanoma; career development awards for additional training in melanoma research; establishing an organizational structure promoting cross-fertilization between basic and applied scientists, and fostering collaborations between researchers in Tampa and physicians and scientists throughout the state; meetings of collaborators and advisors; and tumor procurement core facilities to support the scientific goals of the Pre-SPORE. The result will be an organizational structure and research collaborations that markedly increase the chance of bringing a melanoma NCI SPORE grant to the State of Florida.

SUGRUE, Stephen

2006 SIG
University of Florida
$499,693

Leica TCS SPR5 AOBS Confocal Microscope with Tandem Scanner

University of Florida Shands Cancer Center (UFSCC) researchers are using a confocal microscope for the recording of high-resolution images that show the structural features of cancer cells both in the plane of the image and perpendicular to the image, tumors, and the tumor microenvironment. The Leica TCS SP5 AOBS confocal microscope with tandem scanner was selected because it allows acquisition of both slow high-resolution imaging and fast dynamic quantitative measurements. The instrument has the following major options: 1) FRET/FRAP/FLIP capabilities, and 2) full environmental incubation systems for the study of live cell populations. The projects described in the grant are representative of the broad base of the UFSCC research that spans the College of Medicine, College of Liberal Arts and Science, Engineering, and IFAS. The projects cover areas ranging from the study of the transport of zinc within cancer cells, therapeutically targeting the blood vessels that feed tumors, exploring the role of focal adhesion kinase (FAK) in breast cancer progression, investigate the newly discovered relationship of the cancer-related protein Daxx to cell division, and employ innovative nanotechnologies to explore important molecular events in the cancer cell.

SRIVASTAVA, Arun

2006 SIG
University of Florida
$499,980

Fluorescence-Activated Cell Sorter

Fluorescence-Activated Cell Sorting (FACS) is an essential technology for basic and clinical research where individual live cells must be studied in large numbers, particularly when the source material is a mixture of cells, such as patient tissue samples, research animal tissues, or mixed cell cultures. In addition to powerful analytical capabilities, "cell sorters" are specialized flow cytometers, machines that can analyze characteristics of individual cells within a tissue one cell at a time, that have the additional ability of separating desired cell types with similar characteristics (thus enriching them) at very high speed. In addition to allowing the ability to enrich various populations of cells, the cell sorter can be used to study the activity of single cells in a test tube or an animal model. The sorter is capable of isolating single cells, allowing for the ability to treat them with various drugs, or to remove them and inject them into animals. Such experiments allow researchers to test the efficacy of newer drugs and to clearly define what specific cell types are capable of forming tumors. A number of investigators at the University of Florida Shands Cancer Center (UFSCC) will use the FACS to support ongoing cancer research as well as yield wide and long-lasting benefits for the biomedical community.

TAN, Weihong

2006 Bridge
University of Florida
$157,500

Enrichment and Detection of Exfoliated Cancer Cells Using Aptamer/Nanoparticles

One of the most important aspects of cancer treatment is the early and accurate diagnosis of the disease. A diagnosis based on the molecular fingerprints of the disease would be far more effective for not only the diagnosis of the cancer but also for its treatment. This research addresses the generation of molecular probes for the identification of cancer cells and the sensitive detection of exfoliated tumor cells. Recently, the team developed a novel cell-based aptamer selection strategy (cell-SELEX) to produce a group of aptamers for the specific recognition of individual cells without prior knowledge of the biomarkers on the cells. The cell-SELEX uses whole cells as targets to select aptamers that can distinguish target from control cells. Effective molecular probes will be developed for small cell lung cancer (SCLC) using cell-SELEX. Once completed, this research will not only show that cell-based aptamer selection can be widely applicable to various types of diseased cells, but also convincingly demonstrate the advantages of using cell-SELEX to generate aptamers for effective cancer studies and early cancer diagnosis.

TAN, Weihong

2007 Bridge
University of Florida
$200,000

Molecular Analysis of Liver Cancer Using Aptamers

Liver cancer is one of the most deadly and common malignancies in the United States and the world. Liver cancer development usually takes a long time, which provides a window of opportunity for early detection and therapy. Early diagnosis leads to greatly improved survival rates. Therefore, one of the major issues in improving cancer survival rates is the accurate and early diagnosis of the disease. DNA miroarray and proteomics have been used for identification of molecular fingerprints. However, liver-cancer specific markers are still elusive. The objective of this research is to identify liver-specific tumor markers using a novel cell-based aptamer selection strategy (cell-SELEX). Through a series selection process, the team will be able to identify a group of aptamers that are highly specific for liver cancer cells. If successful, this study will provide much needed molecular tools for early liver cancer diagnosis, targeted therapy, and biomarkers for basic and clinical studies of liver cancer.

TERADA, Naohiro

2006 Bridge
University of Florida
$200,000

Myelodysplastic Syndrome, Dnmt3 and Azacitidine

Myelodysplastic syndrome (MDS) is the most common hematological disease among the elderly, and often transforms into acute leukemia. Presently, MDS treatment has focused on the use of azacitidine, which delays clonal evolution to acute leukemia, improves blood counts, and lengthens patient survival. However, how the drug works remains unsolved. Azacitidine becomes incorporated into genomic DNA, and forms adducts with DNA methyltransferase (Dnmt). This covalent and irreversible binding of the enzyme to drug-substituted DNA is believed to be the principal cause for cytotoxicity. This research initially focuses on the hypothesis that Dnmt3 expression facilitates azacitidine susceptibility in hematopoietic cells. It is possible that DNA hypermethylation caused by aberrant Dnmt3 expression will disturb normal hematopoiesis, thus becoming a predisposition to myelodysplasia and subsequent malignancies. These studies are expected to lead the way in developing novel therapeutic strategies for MDS treatment and in gaining meaningful insight into the etiology of the disease.

WEIGEL-VAN AKEN, Kirsten

2007 NIR
University of Florida
$375,000

Parvovirus B19-Based Vectors for Gene Therapy of Breast Cancer Bone Metastases

Breast cancer patients die from metastases to vital organs such as bone. This research will develop a targeting system that takes advantage of the high HER2 expression on metastatic breast cancer cells and exploits the bone marrow tropism of the human parvovirus B19 combined with a novel viral co-receptor function-inducing feature. Parvovirus B19 enters the human body through the upper respiratory track and 'travels' to the bone marrow space where it is able to replicate exclusively in erythroid progenitor cells. The team has identified the adhesion receptor a5b1 integrin, as a co-receptor for parvovirus B19 internalization and demonstrated that a5b1 integrin is recruited as viral co-receptor only after its functional activation. The parvovirus B19 vectors combine three features to ensure specificity for bone metastatic breast cancer cells: (1) enrichment in the bone marrow compartment based on the bone marrow's natural inclination toward parvovirus B19; (2) replacement of the erythroid-specific P antigen binding site by a HER2 binding epitope inserted into the viral capsid; (3) activation of the b1 integrin viral co-receptor for virus entry into target cells, and induction of re-entry of targeted cells into the cell cycle to enhance their susceptibility to the parvovirus B19 vector-mediated expression of a cell death-inducing gene product.

WIDMER, Charles

2007 Bridge
University of Florida
$162,000

Androgen-Mediated Reversal of Muscle Wasting

Prostate cancer is the most common cancer affecting men in the United States. This achievement is dependent on the development of effective therapies that allow maintenance of the quality of life for the patient. Current management approaches include the use of hormone therapy to cease testosterone production or block testosterone receptor sites to effectively block the actions of testosterone and slow or halt the growth of prostate cancer. However, these approaches are not specific to the prostate and affect all tissues that depend on testosterone for maintenance, including muscle and bone. A new category of hormone therapy that appears promising for treatment of prostate cancer is the use of new novel non-steroidal selective androgen receptor modulators (SARMs). One goal of this research is the evaluation of the response of different muscles to SARMs that may be specific for muscle and bone maintenance but minimally support prostate growth. The second goal of our research is to investigate one potential cellular mechanism that is responsible for many of the effects of testosterone and testosterone-like compounds on muscle. Understanding these mechanisms is an important advancement towards the ability to develop compounds that would specifically target muscle, but exclude activation of the prostate.

YEATMAN, Timothy

2006 SIG
H. Lee Moffitt Cancer Center
& Research Institute
$500,000

Proposal for the Acquisition of a BioBank -80°C Automated Storage System

This grant will fund the purchase of a Thermo Electron BioBank -80° C Automated Sample Management System. The BioBank is an ultra-low temperature automated freezer system designed to safely store biological samples at -80° C for future use in cancer-related research initiatives. The key to the BioBank's storage capabilities is the robust robotics technology that allows for selective retrieval of samples of interest, while leaving unneeded samples in a safely undisturbed, ultra-low temperature state. Temperature fluxuations from opening the freezer door are avoided, preventing repeated thermal fluctuations that directly affect the integrity and quality of these samples. The Moffitt Cancer Center is delivering new technologies to cancer patients throughout Florida with an initiative entitled Total Cancer Care (TCC). Tissue and blood samples from cancer patients around the state will be stored at Moffitt's central Bio-repository. Moffitt investigators can then use these samples to investigate the genetic profiles, or "fingerprints," of these tumors. New clinical trials can then be developed to test the efficacy of specific drugs. The data will also be used to analyze treatment patterns, identify variables in cancer practice, and develop evidence-based guidelines for cancer diagnosis, treatment, and prevention.

ZHANG, Mary

2007 NIR
University of South Florida
$375,000

HDAC6 deacetylation of cortactin in EGF-induced breast cancer cell migration

Breast cancer is the leading cancer in most countries in terms of incidence rate and ranks second in cancer mortality. Tumor metastasis is the principal cause of death for most breast cancer patients. Cell migration plays an important role in tumor metastasis. Identification of key molecules in the migration process will therefore lead to the identification of not only prognosticators in the progress of the disease but also therapeutic targets. Recently, we discovered that cortactin, a key regulator of cell migration and a prominent Src substrate, is a novel substrate for histone deacetylase 6 (HDAC6). Moreover, the majority of cortactin was deacetylated in breast cancer specimens whereas the acetylated forms predominate in normal breast tissues. Consistent with our novel finding that HDAC6 is the enzyme that deacetylates cortactin, the level of HDAC6 is higher in breast cancer specimens than that of normal breast tissue, implying that HDAC6 and deacetylated form of cortactin are associated with tumorigenesis and possible metastasis in breast cancer. Therefore, the hypothesis is that PI3K/PKCzeta signaling cascade up-regulates HDAC6 activity, down-regulates the acetylation level of cortactin and promotes cortactin tyrosine phosphorylation by Src and leads to its translocation from the cytoplasmic to membrane ruffle/lamellipodia, the migratory front, which, in turn, enhances cell migration.

Appendix C. Grantee Publications

The following list represents new publications in peer-reviewed journals and books 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.

Bridge Grants

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Appendix D. Related Awards Reported by Grantees

Chen, J. (2006 Bridge), "Function and Regulation of SirT1 in Cancer," National Institute of Health, $850,000.

Ganju-Krishan, A. (2006 Bridge), "Tumor cells in Body Cavity Fluids," Women's Cancer Association, $50,000.

Godavarty, A. (2006 Bridge), "Hand-held Optical Probe for Fluorescence Imaging of Breast Cancer," National Cancer Institute, $196,644.

Gilbert, D. (2007 Bridge), "Genome Plasticity during ES Cell Differentiation to Neural Lineages," National Institute of Health, $1,819,319.

Hazlehurst, L. (2006 Bridge – Two Year), "Role of Bim in mediating CAM-DR in hematopoietic tumors," National Institute of Health, $278,730.

Hu, J. (2006 SIG), "Molecular Epidemiology and Prevention of Breast Cancer," National Cancer Institute, $257,216.

Hu, J. (2006 SIG), "Molecular Genetics of Colon Cancer in Blacks and Whites," National Cancer Institute, $181,169.

Ishov, A. (2007 Bridge), "Function of Daxx in Mitosis that determines Paclitaxel Sensitivity in Breast Cancer," National Institute of Health, $1,000,000.

Koomen, J. (2006 SIG), "Optimization of Phosphotyrosine Proteomics for Examination of Signaling Networks in Lung Cancer," Department of Defense, $30,000.

Koomen, J. (2006 SIG), "Interrogation of WNT Pathway Directed Apoptosis in Human Colon Cancer," Department of Defense, $200,000.

Lampidis, T. (2006 Bridge), "Anti-Tumor Activity of Sugar Analogs via Blocking Glycolysis vs Glycosylation," National Institute of Health, $1,250,000.

Lo, C. (2006 Bridge), "c-Met Mediated Ovarian Cancer Cell Motility," National Institute of Health, $145,000.

Lokeshwar, B. (2006 Bridge), "Antitumor and Chemopreventive Activity of the Ecuadorian Plant Extract BIRM," National Institute of Health, $302,940.

Lossos, I. (2006 Bridge), "Prognostic Models in Diffuse Large B-cell Lymphoma," National Cancer Institute, $1,187,331.

Radisky, D. (2006 Bridge – Two Year), "Mechanisms of MMP-induced Malignancy in Breast Cells," National Institute of Health, $1,434,500.

Radisky, D. (2006 NIR), "Experimental Models RFA, Engineered Culture Model of Breast Fibrogenesis," Susan G. Komen Foundation, $300,000.

Widmer, C. (2007 Bridge), "Androgen-Mediated Reversal of Muscle Wasting," National Institute of Health, $438,000.

Endnotes

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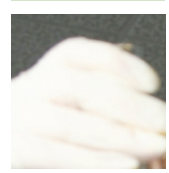
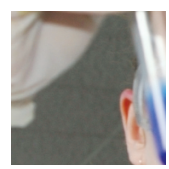
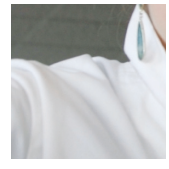

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