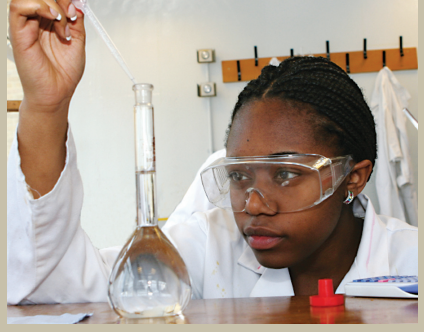
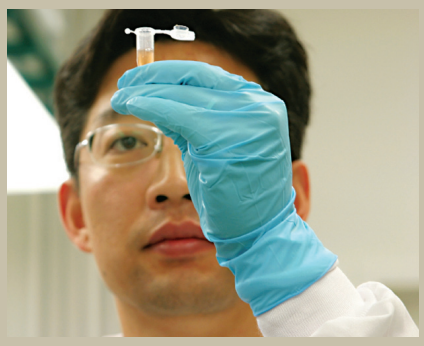
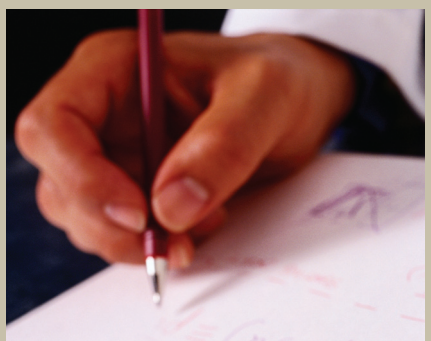






JAMES & ESTHER KING
BIOMEDICAL RESEARCH PROGRAM

# Tobacco-Related Diseases: Making a Difference

## 2007 Annual Report

February 1, 2008

The Honorable Charlie Crist, Governor
The Honorable Ken Pruitt, Senate President
The Honorable Marco Rubio, House Speaker
Surgeon General Ana M. Viamonte Ros, M.D., M.P.H., Florida Department of Health

Dear Governor Crist, President Pruitt, Speaker Rubio, and Surgeon General Viamonte Ros:

On behalf of the Biomedical Research Advisory Council, I am pleased to present the 2007 James and Esther King Biomedical Research Program Annual Report.

In keeping with section 215.5602, *Florida Statutes*, this report accounts for the use of $9 million invested by the state during this year and documents the most immediately tangible grantee accomplishments–new publications and additional related research funding.

Our report also describes the careful peer review and grants management processes we have put in place to ensure good stewardship of the funds entrusted and provides a briefing on Florida's most recent share of federal funding for biomedical research.

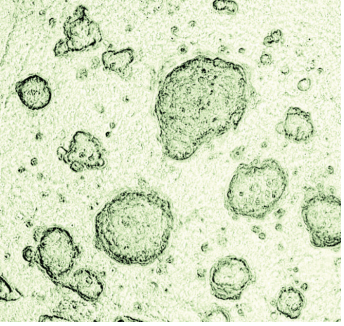
In this year's report we highlight the scientific accomplishments of our sponsored researchers from the perspective of the tobacco-related behaviors and diseases that are the focus of their work. Making significant advances in preventing, diagnosing, treating, and curing tobacco-related diseases is a long-term undertaking. While it is important to maintain realistic expectations for the pace at which measurable progress can be made, we are proud to feature some outstanding Florida researchers, particularly the rising generation of young investigators, who are producing notable scientific discoveries and promising new treatments for many diseases with this critical funding.

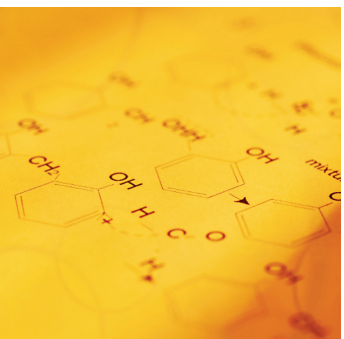
These are challenging financial times, and we know you have had to make many hard decisions that call for sacrifices in worthwhile programs. Ongoing investments in and support for biomedical research helps to lay the foundation for a better Florida – for a healthier population and for economic development.

Using the resources you have provided for this purpose, we gratefully remain committed to devoting our best efforts to building and operating a model biomedical research program in the state of Florida.

Sincerely,

Richard J. Bookman, Ph.D.
Chair, Florida Biomedical Research Advisory Council





*The report does not necessarily reflect the opinions of the Florida Department of Health or its staff, and any recommendations contained within are those of the Program's Advisory Council.*

*For more information or to request additional copies of this report, please contact Florida Biomedical Research Programs in the Office of Public Health Research, (850) 245-4585. To download a copy of this and prior years' reports, go to www.floridabiomed.com.*

# James and Esther King Biomedical Research Program

## Annual Report
## January–December 2007

Submitted to
The Governor
The President of the Senate
The Speaker of the House of Representatives
The State Surgeon General

and

The Florida Center for Universal Research to Eradicate Disease

by

Biomedical Research Advisory Council
Dr. Richard Bookman, Chair

February 1, 2008

**Tobacco use remains the leading actual cause of death in the United States.**

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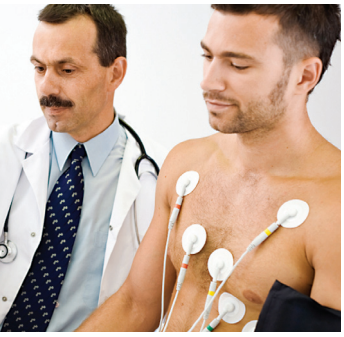
# Executive Summary



Ten years after Florida led the nation in negotiating its $11.3 billion settlement with the tobacco industry, the state is still faced with more than $6 billion per year in ongoing healthcare costs related to tobacco use. According to the National Institutes of Health, tobacco use is a major public health hazard with harmful effects to every organ in the body. It remains the leading preventable cause of death nationwide. The James & Esther King Biomedical Research Program represents Florida's challenge to all qualified researchers in the state to accelerate progress toward the prevention, diagnosis, treatment, and cure of tobacco-related disease.

The Program held its sixth annual grant competition in 2007, receiving 55 proposals from Florida researchers at 12 different institutions. The Biomedical Research Advisory Council considered the independent peer review results of these proposals and formed their recommendations for awards based on the goals provided in section 215.5602, *Florida Statutes*, with a focus on scientific merit. The State Surgeon General offered 24 Program awards and on July 1, 2007, investigators launched research projects at 10 different Florida institutions. This brought the total number of peer-reviewed, competitively awarded research grants to 120 since 2001.

The portfolio of active grants is diverse. A number of projects seek to prevent tobacco-related disease by focusing on smoking behavior. Many others target the effects of tobacco use—cancer, cardiovascular disease, stroke, and pulmonary disease. Some of these grants are maintaining funding for Florida investigators whose tobacco-related projects were highly rated in national competitions yet not selected for federal funding due to budget constraints. Others are helping collaborative research teams compete more successfully for larger, multi-year national awards. At a time when competition for federal research funding has intensified, many awards are helping new investigators establish their tobacco-related research at Florida institutions.

In the last year, James & Esther King awardees have documented their research findings in 57 publications in major scientific journals. They have given 105 presentations regarding their progress and have attracted more than $14,000,000 in external funding. Sponsored projects provided focused research opportunities for 97 pre-doctoral or post-doctoral students around the state on a nearly full-time basis. Earlier Program investments in partnerships between academic researchers and small businesses continued to pay off, as four commercial projects thrived with more than $2 million in further external funding.

To ensure accountability for the use of public funds, Program staff monitored scientific progress against the research aims of all active grants and conducted site visits to 21 grantees. The Program renewed 25 of 26 multi-year grants based on performance; one was conditionally renewed. Thirteen awardees requested no-cost extensions, and the Program granted ten based on the merits of each case. Eighteen projects concluded during 2007. The Office of Public Health Research collected unspent funds from these grantees and returned them to the Biomedical Research Trust Fund.

The Program faces ambitious goals. To meet them, it offers vital funding to new and experienced researchers throughout Florida with the most promising projects. It is making a difference in the fight against the effects of tobacco use in Florida by accelerating progress in preventing, diagnosing, treating, and curing tobacco-related diseases.

# Program Vision and Goals

August 2007 marked the 10-year anniversary of Florida's legal settlement with tobacco companies and the establishment of the Lawton Chiles Endowment Fund, a struggle spearheaded by former Governor Chiles. The settlement came after Florida's leadership in the tobacco litigation arena: Florida was one of the first five states to enter into a settlement with a tobacco company in 1996, and a Florida citizen was the first individual to win a lawsuit against Big Tobacco later the same year. The culmination of the tobacco settlements included the establishment of the Florida Biomedical Research Program in 1999, now known as the James & Esther King Biomedical Research Program. With this proactive measure to fight the devastating impact of tobacco use and to advance the health of its citizens, the Legislature endorsed biomedical and behavioral research for the prevention, diagnosis, treatment, and cure of tobacco-related diseases.

The long-term Program goals are as critical to the health and welfare of Florida's citizens as ever. Despite advertising restrictions, Big Tobacco still spends $1 billion yearly in Florida, more than in any other state,[1] by sponsoring sports events, advertising in local convenience stores and magazines, and through discreet advertising in movies. Approximately three million adults and 143,000 (15 percent) high school students in Florida smoke, and seven percent use smokeless tobacco.[2] The resulting annual costs to Floridians are devastating–29,000 deaths from tobacco-related causes and an average of $6.3 billion in healthcare costs.[3]

Florida law[4] outlines five long-term goals to support research related to tobacco use in the state:

1. Improve the health of Floridians by researching better prevention, diagnoses, treatments, and cures for cancer, cardiovascular disease, stroke, and pulmonary disease.
2. Expand the foundation of biomedical knowledge relating to the prevention, diagnosis, treatment, and cure of diseases related to tobacco use including cancer, cardiovascular disease, stroke, and pulmonary disease.
3. Improve the quality of the state's academic health centers by bringing the advances of biomedical research into the training of physicians and other healthcare providers.
4. Increase the state's per capita funding for research by undertaking new initiatives in public health and biomedical research that will attract additional funding from outside the state.
5. Stimulate economic activity in the state in areas related to biomedical research including the research and production of pharmaceuticals, biotechnology, and medical devices.

In order to enhance the state's research capacity and competitive edge for national funding, the philosophy driving award decisions is to "make the Program open to all; fund the best."[5] As a result, the Program awards grants to qualified investigators throughout the state based on scientific merit as determined by an independent, competitive peer review process. Current research covers a variety of tobacco-related diseases, spans the spectrum of science from basic research to clinical application, and offers opportunities for qualified investigators at all experience levels.

**The Program awards grants to qualified investigators throughout the state based on scientific merit as determined by an independent, competitive peer review process.**

# Program Impact

**Forty-eight percent of Program grants are applied or translational, meaning the research goes beyond a molecular level and involves the study of animal models or human tissue.**

In the "Florida Life Sciences Roadmap" published in June 2007,[6] the Milken Institute warns "To stay competitive, the [life sciences] sector must depend increasingly on technological and scientific advances. Yet these advances likely will take place elsewhere unless the state takes immediate steps to bolster its small but growing research infrastructure, and attract and support the necessary human capital: researchers, engineers, and skilled technicians. ...Florida's life sciences industry is skewed toward health-care services and delivery, which exploit but rarely generate innovation. Furthermore, they fail to provide value sufficient to give the state a competitive edge."

During 2007, with its competitive research grants, the Program contributed to the economy, research capacity, and progress of biomedical research in Florida.

## Stimulating Economic Activity

- The Program has awarded more than $50 million since 2001. This translates into a total economic value of $544 million for the communities surrounding Tampa, Orlando, Gainesville, Miami, Jacksonville, and Tallahassee.[7]
- Grantees reported 29 related awards from other sources totaling more than $14 million during the period of October 2006 – October 2007, bringing the total since Program inception to more than $47 million. Follow-on grants typically lag Program awards by up to five years.
- To date, sponsored research projects have produced at least four invention disclosures and 34 patent filings, many of which are already forming the basis for early commercial partnerships

A 2005 Small Business Technology Transfer (SBTT) Grant led by Dr. Atwar Ganju-Krishan at the University of Miami produced a new high-resolution flow analyzer for the detection of tumor cells. He describes the role of the Program grant in its development: "The SBTT grant provided the right initiative as it allowed us to work with a Florida company (NPE Systems of Pembroke Pines) to modify an instrument for use in cancer research. The instrument (Quanta Flow analyzer) made by NPE is sold worldwide by Beckman Coulter. We are proud of this being a U.S. product developed with the support of NIH and the Florida Department of Health."

Mr. Ernie Thomas, one of the industrial collaborators on this project and Executive Vice President of NPE, highlighted the economic benefits of this partnership: "NPE Systems has entered into a multi-year/multi-million dollar research and development arrangement with Beckman Coulter. This arrangement has produced three exciting products to the market in the last 2 years. These award-winning instruments are manufactured in South Florida by CMSI [Contract Manufacturing Solutions, Inc.] CMSI was founded to produce these instruments and is ISO 13485 compliant. Between NPE Systems and CMSI there have been over 30 jobs created. Many of these are good paying engineering, scientific, management, and assembly functions. There are also further benefits to the south Florida economy due to the use of custom machining, metal fabrication, and optical component companies here in Florida. The SBTT grant that helped develop these products has created a long-term and significant benefit to humanity and the Florida economy."

## Growing Research Capacity

Research capacity is the volume of directed resources available to conduct research in a specific area of interest–in this case tobacco-related disease. Capacity can be increased and retained and can include personnel and equipment.

- Fourteen new investigators received funding to help establish independent careers in tobacco-related research in 2007, bringing the total number supported by the Program since 2001 to 64.

- Ninety-seven pre-doctoral or post-doctoral students were employed on 68 active projects during 2007. These individuals spent an average of 80 percent of their time on Program-sponsored research.
- Seven Florida researchers received bridge funding offered for the first time in fiscal year (FY) 2007-2008 in response to decreased availability of funds at the federal level.

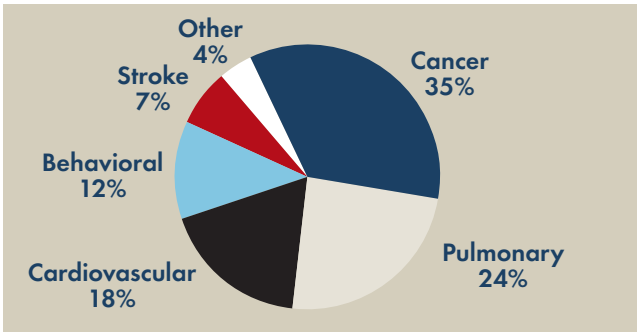
## Expanding the Foundation of Biomedical Knowledge

- Publications in respected peer-reviewed journals and presentations to colleagues at major scientific gatherings are two common measures for the dissemination of new discoveries. To be accepted in these venues, articles and presentations must demonstrate sound science and represent a new contribution to the body of knowledge. This is the goal of grant funding: to increase knowledge through research and publication so that shared learning can eventually lead to cures. Between October 2006 and October 2007, Florida researchers documented significant discoveries from Program-sponsored research in at least 58 peer-reviewed journal articles.
- During the same period, awardees gave 105 presentations at national scientific or professional meetings to report their research and findings based on Program grants.

## Improving Healthcare for Floridians

Florida's Supreme Court firmly reinforced the value of a biomedical research program dedicated to tobacco-related research. In July 2006, medical evidence connecting tobacco use to a wide range of serious illnesses led the Court to rule "that smoking cigarettes causes aortic aneurysm, bladder cancer, cerebro-vascular disease, cervical cancer, chronic obstructive pulmonary disease, coronary heart disease, esophageal cancer, kidney cancer, laryngeal cancer, lung cancer (specifically, adenocarcinoma, large cell carcinoma, small cell carcinoma, and squamous cell carcinoma), complications of pregnancy, oral cavity/tongue cancer, pancreatic cancer, peripheral vascular disease, pharyngeal cancer, and stomach cancer" and "that nicotine in cigarettes is addictive."[8] A growing body of scientific evidence points to other diseases related to tobacco use. While the Program entertains research proposals addressing any illness with a strong association to tobacco, the majority of awards focus on cancer, pulmonary disease, cardiovascular disease, and stroke, in addition to smoking behavior and addiction. Figures 1 and 2 categorize all Program grants awarded since 2001 according to their disease or behavioral emphasis and healthcare perspectives.

**Figure 1**
**Topics Addressed by Program Grants, 2001-2007***



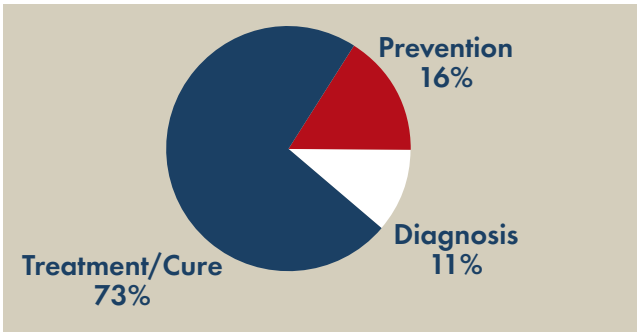




**Figure 2**
**Targeted Healthcare Gains of Program Grants, 2001-2007***

**Data compiled according to project classification. If more than one category applies, both are included.*

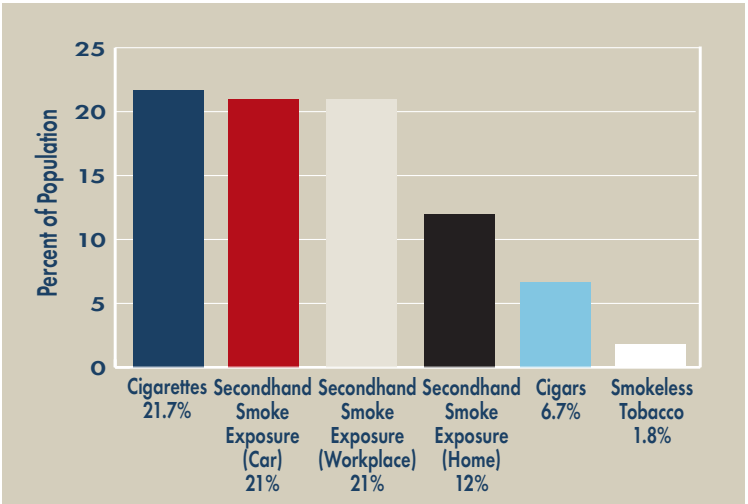
The following sections provide snapshots of progress made possible through the Program in changing smoking behavior and improving our ability to prevent, diagnose, treat, and cure cardiovascular disease, stroke, cancer, and pulmonary disease. One representative project is profiled in each section to highlight the commitment of the investigative team, the importance of their discoveries, and the future implications of their research.

# The Dynamics of Tobacco Prevention and Cessation

Nearly half of all current smokers in Florida have stopped smoking for one day or longer in the past year in an attempt to quit smoking. Self-reporting by current smokers shows that 44 percent plan to stop within the next 30 days, and 57 percent plan to quit in the next six months. However, in the U.S., fewer than five percent succeed in quitting.[9] Even though there are a number of interventions that increase tobacco cessation, only a small proportion of tobacco users ever try them.

Figure 3 reflects Florida adult tobacco use by type in 2006 based on a Florida Department of Health survey.[10] Secondhand smoke, also called environmental tobacco smoke, includes smoke exhaled by a smoker as well as smoke coming from the end of a lighted cigarette, pipe, or cigar. The percentage of children exposed to secondhand smoke is even higher than adult exposure shown in the figure: 50 to 67 percent of children younger than five years of age live in homes with at least one adult smoker.[11]

**Figure 3**
**Florida's 2006**
**Adult Tobacco Use and Exposure**




## Making a Difference

As a primary strategy for preventing tobacco-related diseases, the Program sponsors research that focuses on understanding and overcoming tobacco-related addictions.

Several researchers are working on the neurobiology of addiction. Dr. Paul Kenny, 2007 New Investigator Research Grant recipient at The Scripps Research Institute, has made a number of advances in recent months on the mechanism of nicotine addiction. He has identified a central role for N-methyl-D-aspartic acid (NMDA) in the neurologically rewarding properties of nicotine and the corresponding brain areas involved. He is investigating whether novel inhibitors of NMDA receptors can help people stop using tobacco.

Dr. David Lee, 2006 Team Science Program recipient at University of Miami, is studying the relationship between smoking behavior and cancer prevalence to understand where anti-smoking programs and treatments are most needed. His team found a higher risk among Caucasian Floridians relative to other parts of the United States. They also learned that communities with higher-than-expected rates of tobacco-associated cancers also tend to have higher levels of poverty. Additional findings suggest that patients with select cancers treated at cancer specialty centers with high surgical case volumes have better survival rates. He hopes this information may help guide tobacco education and public health policy in Florida.

The following grant profile features the work of Dr. Ceylan Isgor in examining the relationship between individual neurological differences and responses to smoking cessation treatments.

# Tailoring Smoking Cessation Treatments to Individual Differences

Ceylan Isgor, Ph.D.

Florida Atlantic University

## 2005 New Investigator Research Grant

Times have changed, and so has public perception of tobacco use. Every year, the percentage of U.S. adults who smoke cigarettes continues to decline, and more adults have quit successfully than ever before. For teens, smoking rates have also been diminishing steadily since 1997. Today's smokers benefit from a larger number of treatment methods, ranging from education and counseling to nicotine replacement therapy in the form of patches, gum, and lozenges. Many ex-smokers have also benefited from Zyban - an anti-depressant shown to alleviate nicotine withdrawal symptoms - since it became available by prescription in 1998.

Yet, many smokers still find themselves unable to stop smoking completely, with each quit attempt eventually resulting in relapse. Dr. Ceylan Isgor believes that the "one size fits all" approach to current smoking cessation techniques does not address the specific, individual ways in which certain smokers become addicted to nicotine. "Individual differences in nicotine addiction play a major role in smoking cessation," Dr. Isgor explains. "My research found that when a person begins smoking plays a decisive role in how nicotine affects individual brain chemistry and level of addiction."

A 2005 New Investigator Research Grant recipient at Florida Atlantic University, Dr. Isgor has discovered that smokers who begin in their teens often have the most difficult time quitting completely. For many years, the importance of adolescence as a developmental phase was often overlooked, and "previous research focused on early childhood and adulthood, and adolescence was considered developmentally stagnant," she explains. "But we now know that major neurological development takes place during the teen years." At a time when neuronal connectivity is occurring at a rapid pace, "many addictive behaviors also tend to emerge," meaning that for teens who take up smoking, the physiological effects of nicotine – and the resulting addiction – may be even more pronounced.

Drawing upon recent advances in neuroscience, Dr. Isgor is studying how the personality trait of risk-taking may predetermine drug seeking and avoidance behavior. Individuals demonstrating a high-risk tolerance will voluntarily seek out novel sensory experiences, which may be partly determined by neurological factors. Previous drug addiction research has found that those who seek greater sensory stimulation also tend to develop a heightened neurological sensitivity to certain drugs. This makes them especially vulnerable to becoming addicted.

To understand how an individual's risk-taking profile influenced subsequent addiction to nicotine, Dr. Isgor classified three groups of adolescent rats into low, intermediate, and high risk-taking profiles. Her criterion was the extent to which they moved around and explored their environment, with rats in the high-risk tolerance category demonstrating the greatest degree of motor activity. The rats were placed in behavioral sensitization boxes and given self-administered doses of nicotine. "High responders were given repeated doses of nicotine, and then put through repeated periods of withdrawal. Next, we challenged them with lower doses of nicotine, and again noticed increased motor activity, indicating craving." Put differently, rats in the high-risk tolerance category were willing to work harder to get another dose of nicotine.

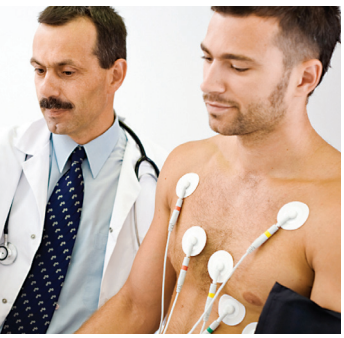
"The goal of my work is to develop a trait-specific treatment targeting the specific neurotransmitters affected by nicotine." For many smokers, nicotine replacement and Zyban are effective in offsetting many of the initial effects of withdrawal and craving. However, they do not address the underlying neurological cues triggering addiction. "The relapse rate for Zyban is around 80 percent, but if we can introduce a drug that prevents the effects of nicotine altogether, relapse should be greatly reduced." Dr. Isgor has been studying a new drug that essentially works as a CB-1 receptor antagonist. It blocks nicotine's affect on the brain by shutting down the receptors responsible for addiction. "The CB-1 receptor targeting drug is unique because it can adapt to changing neurological conditions in the brain, providing consistent protection from addiction."

CB-1 receptor antagonists are currently in clinical trials, which Dr. Isgor says wouldn't be possible without the support of the James & Esther King Biomedical Research Program. "Thanks to this grant, my work has attracted the attention of leading neurobiologists, who are now turning their attention to individual differences in nicotine addiction," she said. She credits the James & Esther King Program for contributing to one of the most innovative avenues in current neuroscience research.

**"At a time when competition for resources is at an all-time high, I'm able to contribute to a body of work that has the potential to help many more smokers successfully quit smoking."**

# Cardiovascular Disease

## Fighting Florida's #1 Killer



According to the Centers for Disease Control, cardiovascular disease (CVD) is the leading cause of death in Florida and among all Americans.[12] In 2005, cardiovascular disease accounted for 35 percent of all Florida deaths and cost approximately $17 billion in the state's hospital charges.[13] Within the United States:

- One in three Americans has one or more types of CVD.[14]
- By retirement age, 65 percent of Americans will have some form of CVD.[15]
- CVD causes one out of every five smoking-related deaths.[16]
- The estimated direct healthcare and indirect costs of CVD in the U.S. for 2007 is $431.8 billion.[17]

### The Tobacco Connection

Cigarette smoking accelerates CVD and is one of nine risk factors identified for heart disease in national and international studies.[18] Tobacco is the number one preventable cause of heart disease.[19] According to a report on involuntary smoking by the U.S. Surgeon General, second-hand smoke has immediate adverse effects upon the cardiovascular system and causes coronary heart disease. Due to the high concentrations of toxic chemicals, breathing tobacco smoke for even a short time can interfere with normal functioning of the heart, blood, and vascular systems in ways that increase the risk of a heart attack. Even brief exposure to environmental tobacco smoke causes blood platelets to become stickier, damages the lining of blood vessels, and reduces heart rate variability, potentially increasing the risk of a heart attack.[20]

### Making a Difference

According to 2006 New Investigator Research Grant recipient, Dr. Roberto Vazquez-Padron from University of Miami, "Cigarette smoking increases the rate of vascular diseases, including the pace at which blood vessels become blocked." Dr. Vazquez-Padron's research focuses on an enzyme activated by nicotine called protein kinase B. He is studying whether blocking its action can help prevent the proliferation of cells in the arterial wall of smokers.

Recent data indicate that smoking increases susceptibility to irregular heart beats in patients with diseases such as heart failure. Dr. Eric Bennett from University of South Florida received 2007 Bridge Grant funding to strengthen his well-received RO1 submission to the National Institutes of Health (NIH). Program money will fund studies that investigate how the number of sugar molecules on an ion channel (pores which control the voltage of a cell) affects the excitability of heart muscle. He will study two types of potassium channels (Ito and IKS) that play important roles in the electrical signals of the heart.

Two investigators from Dr. Keith Webster's 2007 Team Science Program Grant at the University of Miami made parallel observations that nicotine accelerates atherosclerosis ("hardening of the arteries") in the kidney and blood vessels. These investigators are currently studying how nicotine promotes the growth of plaque on the vessel walls and whether this can be "cured" by introducing a subset of specialized adult stem cells derived from bone marrow.

The following profile provides a more detailed look into the research of Dr. Teng Ma, who is working to develop vascular grafts for heart bypass surgery.

# Using Biotechnology to Grow Vascular Grafts for Coronary Bypass Patients

**Teng Ma, Ph.D.**

**Florida State University**

## 2004 New Investigator Research Grant

"Many families have someone with heart disease–it affects millions–but relatively few people have approached the problems associated with it from an engineering perspective," pointed out Dr. Teng Ma, who has degrees in biomedical and chemical engineering. He is now working as one of a six-member biomedical engineering team in collaboration with a cardiologist to solve a problem for heart bypass patients.

Surgeons perform bypass grafting, the mainstay treatment for heart disease, on over 200,000 people yearly. Current practice for coronary bypass grafting is to use the patient's own blood vessels. Unfortunately, these small blood vessels (less than 6 mm) can accumulate plaque, and tissue grows in the graft until, eventually, the whole tube is clogged again. After several years, a high percentage of patients have to undergo repeat bypass surgery to replace a clogged graft. This increases both the risk for patients and the cost of treatment. Using a patient's own vessels is also problematic because the need for smaller blood vessel bypasses occurs more often in patients with systemic vascular disease or older patients, who may not be able to supply healthy vessels or withstand additional surgeries. Although angioplasty is an option, stents are often only a short-term solution, as they often become clogged too. Companies have manufactured synthetic grafts that have been used in other locations, but none have shown success for coronary artery bypass.

Dr. Ma aims to fully restore the functions of diseased or injured vessels by replacing the small blocked areas with grafts made from human cells grown *in vitro* (in a laboratory apparatus). He believes such grafts will meet the high demands of the heart and remain strong, elastic, and unclogged.

There are still many challenges ahead to fully realizing his goal, including finding new materials that support cell growth and function as well as developing new culturing technologies and strategies. Some of the questions the team must resolve include what is the best technology to enable cells to grow *in vitro*? How does one encourage cell growth, but not at a cancerous rate? What techniques cause the cells to form a functional tube? Other challenges include developing a method that produces usable cells with the ability to sustain high pressure and remain open for a long time. Additionally, it is difficult to find an adequate source of cells. Dr. Ma is currently using adult human stem cells from bone marrow. Once this research team has successfully produced a graft, developing clinical tests is the next step towards bringing patients improved grafts.

Despite the obstacles, the research team made the important discovery that these cells grow better in low-oxygen conditions. This is a key finding that may be important for other discoveries involving cell growth. Based on work completed with this grant, Dr. Ma received a patent in October 2006 for a three-dimensional culture system for growing human tissue in a particular shape. A strong commercial interest has resulted from this team's work.

Other research institutions have recognized the contributions of this team with additional grants. Dr. Ma received a grant of $824,000 from the Department of Defense on bone tissue regeneration using the techniques he developed with this grant. In addition, Dr. Feng Zhao, a post-doctoral researcher working on the project, received a $162,000 grant as a result of her work on this project. She credits the Program for helping launch her own independent research career. "The James & Esther King Biomedical Research Program provided me a unique opportunity to work in the field of Cardiovascular Tissue Engineering, allowing me to build up knowledge and experience with bioreactor design and vascular biology. The valuable background and accumulated preliminary data, in turn, helped me to propose an approach for a biomimetic blood vessel to fill a crucial need for functional small-diameter conduits. I am now funded by the Flight Attendant Medical Research Institute (FAMRI) as Principal Investigator." On the funds invested by Florida in Dr. Ma's project, there has already been a return of 200% in external funding.

**"The King grant provided the funds to build up the lab and allowed us to test new ideas and accumulate knowledge that has proven to further the development of human grafts. This may have a long-term impact on future treatments for heart disease."**

# Stroke

## On the Road to New Treatments

Stroke is the fourth leading cause of death in Florida[21] and the third largest cause of death in the U.S.[22] Stroke is more prevalent among certain groups within the state; for example, a person's chance of having a stroke more than doubles for each decade of life after age 55.[23] With more than 29 percent of Florida's current population at age 55 and older,[24] the risk of stroke incidence is heightened. African Americans, who comprise 16 percent of the state's population, have almost twice the risk of first-ever stroke compared with Caucasians.[25] In 2005, gross hospital charges associated with stroke in Florida were approximately $1.9 billion.[26]

### The Tobacco Connection

Cigarette smoking is the number one preventable risk factor for stroke. According to the American Heart Association, the nicotine and carbon monoxide in tobacco smoke reduce the amount of oxygen in the blood. They also damage blood vessel walls, making clots more likely to form.[27]

Smoking particularly increases stroke risk among women. According to Dr. Ami Raval, a 2007 New Investigator Research Grant recipient, "Circulating estrogen provides a natural protection against stroke injury in women. However, nicotine addiction reduces circulating estrogen levels and negates estrogen's neuroprotective qualities. The result is increased risk of stroke and cardiovascular disorders in female smokers. This is particularly troubling because there is a rise in female smoking incidence, and quitting smoking is more difficult for females than for men."

Heavy smokers (more than 40 cigarettes a day) have twice the risk of stroke than light smokers (less than 10 cigarettes a day). Stroke risks decrease significantly after cessation of cigarette smoking and are at the level of nonsmokers after five years.[28]

### Making a Difference

Dr. Christof Grewer, a 2004 New Investigator Research Grant recipient at University of Miami, described his new findings regarding smoking-related stroke. His research aims to understand the cellular processes that lead to uncontrolled GABA (Gamma-Amino-Butyric Acid) release and nerve cell death during stroke. GABA is associated with some of stroke's harmful side effects. He has chosen to focus on transport proteins that take GABA back into the cell. Dr. Grewer discovered that during stroke, these transport proteins travel in the opposite direction. Besides learning how these transport proteins fail, he has also discovered how to block this mechanism. Future studies will determine if this approach can treat the adverse effects of stroke and improve recovery.

Dr. Alison Willing, 2007 Bridge Grant recipient at University of South Florida, reports that administering certain white blood cells from human umbilical cord blood (HUCB) improves stroke recovery. One of the biggest changes her team observed in the stroked brain after administering HUCB was a reduction in "multiple indicators" of inflammation. The T-cell population in the spleen also returned to normal after HUCB injection. T-cells play an important role in establishing and maximizing the capabilities of the immune system. This research team hypothesized that HUCB cells' ability to induce stroke recovery was critically dependent on the changes these cells caused in the spleen. Dr. Willing is using an animal model to explore the relationship between changes in the spleen and behavioral and anatomical recovery from stroke. This research team hopes to gain understanding of the whole body immune response in the development of brain damage after stroke and learn how HUCB aids stroke recovery.

Dr. Bingren Hu, 2007 Bridge Grant recipient at University of Miami, studies the toxic protein compounds generated by tobacco smoking. His team recently found large quantities of these proteins in organelles, specialized parts of the cell that perform unique functions for the cell. These organelles fail to function after stroke, and tobacco use aggravates the stroke severity and function failure of multiple cellular organelles. His research aims to understand the molecular mechanisms underlying this functional failure and to explore treatment measures that rescue damaged, vital organelles after stroke.

The following profile of Dr. Jeffrey Goldberg offers a closer look into another example of how the Program is helping to develop new treatments for stroke victims.

# Developing a Model and Treatment for Optic Nerve Stroke


## Jeffrey Goldberg, M.D., Ph.D

### University of Miami
### 2005 New Investigator Research Grant


Most of us have seen or know someone who lives with permanent stroke damage. Both current and prior tobacco use is a major risk factor for stroke, likely contributing to more than 50 percent of strokes in the U.S. annually. Dr. Jeffrey Goldberg sees dozens of patients yearly who have suffered strokes of the optic nerve. "We have so little to offer them. Despite much research in the area of stroke, therapies have not translated into effective treatments. There is not a lot we can provide. In the case of optic nerve stroke, their vision is permanently damaged, 20/200 or worse–partial or total blindness."

Dr. Goldberg explained why most stroke victims experience permanent damage. "After strokes, most neurons (cells that receive and transmit nerve impulses) in the central nervous system die. We do not know why the neurons in the brain, spinal cord, and eye die and fail to regenerate when other parts of our body can repair themselves after injury. Even when these neurons survive, they fail to repair their axons (threadlike extensions) appropriately; the injuries after stroke, then, are frequently permanent." The damage stroke causes to them produces devastating results. "We know that tobacco is a big risk factor for this kind of stroke."

Better models to mimic human disease are needed. Most stroke models study the effects of stroke in grey matter of the central nervous system (CNS). However, many strokes, including optic nerve strokes, occur in CNS white matter.

Dr. Goldberg developed a new model for studying how stroke affects these neurons in white matter. His animal model mimics human stroke of the optic nerve. Next he plans to research the mechanisms responsible for stroke damage and treatments for them. He then plans to translate the treatment back to humans. More accurate modeling in animals may lead to more plausible human treatments than currently exist. He has chosen the optic nerve because it contains the only easily accessible white matter. (White matter in the brain is located under grey matter and cannot be accessed without also damaging grey matter.)

Several aspects of this research make it groundbreaking. The combined contributions of his mentor, Dr. W. Dalton Dietrich, and collaborating investigator, Dr. Brant Watson, have enabled some research "firsts." These scientists are the first to study white matter stroke in the optic nerve. The method uses light generated from a YAG laser to cause clots in the blood vessels feeding the optic nerve. The elegance of the model lies in its reproducibility and selectiveness that enables sound data collection throughout the experiments. Also for the first time, this research combines the creation of a model in a living organism with an examination of how specific survival signals keep neurons alive after injury.

The innovations described above have produced results that promise even more progress. Dr. Goldberg explained: "We have shown that neurons injured by white-matter stroke are not responsive to survival signals. We understand now that we need to give them survival signals, but we also need to cue the neurons to enhance their responsiveness to those signals. We may be on the path to new therapies."

In addition to these research advances and the opportunity to work on treatments for his patients, Dr. Goldberg enumerated the Program's benefits. "The Program has allowed me the resources to develop this project, and has captured my interests in tobacco-related stroke research. My post-doctoral students are now pursuing this research area as well. The King Program provided enough stable funding to get this novel research off the ground. I now have two years' worth of data and am currently preparing an NIH grant [application]. As the work continues, we hope to develop therapeutic approaches that we can patent, which also produces economic benefits for Florida."

**"The Program has allowed me the resources to develop this project and has captured my interests in tobacco-related stroke research. My future direction is set for my lab. My post-doctoral students are now pursuing this research area as well. As the work continues, we hope to develop therapeutic approaches that we can patent, which also produces economic benefits for Florida."**

# Cancer

## Moving Toward Patient Therapies

In recent years, cancer killed one in every four Floridians.[29] The American Cancer Society estimates for 2007 include 106,000 cancer diagnoses and more than 40,000 cancer deaths among Floridians.[30] This is an increase of approximately 7,000 diagnoses compared with last year.

### The Tobacco Connection

More than forty years ago, the U.S. Congress passed legislation requiring the Surgeon General's warning on cigarette packs. Since that time, research has shown that tobacco use is responsible for cancers in every organ system and is responsible for 90 percent of all lung cancer cases.[31] Of all the cancer deaths in Florida during 2002, approximately 65 percent were attributable to cigarette use.[32]

Research has also established cancer risks for people breathing environmental tobacco smoke. Current reports are that cigarette smoke contains more than 4,000 chemical compounds. More than 40 of these are carcinogenic (cancer-causing), including nickel, lead, benzene, hydrazine, chromium, and urethane. Sidestream smoke, which goes straight into the air from burning tobacco, actually has higher amounts of some harmful compounds than the mainstream smoke breathed in by the smoker.[33] Secondhand smoke has been designated as a known human carcinogen by the U.S. Environmental Protection Agency, National Toxicology Program, and the International Agency for Research on Cancer (IARC). The National Institute for Occupational Safety and Health has concluded that secondhand smoke is an occupational carcinogen as well. Nonsmokers who breathe environmental tobacco smoke at home or at work increase their risk of developing lung cancer by 20-30 percent.[34]

### Making a Difference

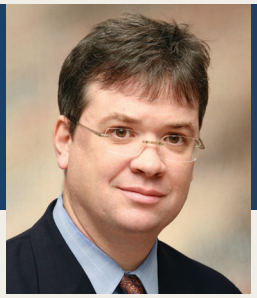
Researcher Dr. Gregory B. Dudley, 2005 New Investigator Research Grant recipient at Florida State University, explains his work. "Cancer chemotherapy is by its very nature a daunting task. The goal is to attack cancerous cells selectively in the presence of a much larger system of non-cancerous human cells. Organic synthesis (the construction of organic molecules using chemical processes), is an enabling technology for overcoming such challenges in biomedical research. Our research project focuses on advancing the state-of-the-art in this field."

In breast cancer research, Dr. Karoline Briegel, 2005 New Investigator Research Grant recipient at University of Miami, along with her team may have discovered a new marker for basal-subtype breast cancer. The LBH (limb-bud and heart) gene promotes cell division during embryonic development and may cause the cellular changes that are prerequisite to spread of cancer cells. Clinicians may be able to use this information to determine the best treatment plan for a patient with this aggressive form of cancer. Dr. Briegel explains her work with breast cancer: "Without the New Investigator Research Grant from the King Program, we would not have been able to venture into a relatively new area of breast cancer research that led to the discovery of a promising new biomarker for particularly mutagenic forms of breast cancer."

Dr. Christopher Cogle, 2005 New Investigator Research Grant recipient at University of Florida, has researched new ways to interfere with blood vessels in lung tumors. He is currently negotiating with a company to provide a product for a planned Phase I clinical trial.

Dr. Roman Manetsch, 2007 New Investigator Research Grant recipient at University of South Florida, is researching new anti-cancer drugs and explains: "Submission of a highly competitive grant application to the National Institutes of Health is challenging for a young investigator. For such an application, fundamental and solid experimental data is an absolute necessity. The James and Esther King Biomedical Research Program has allowed me to continue with ongoing research. I am now better positioned to submit future grant applications. Additionally, I think that the interactions between the new investigators and their mentors facilitated by the Program are key to the development of a new investigator."

A profile of Dr. Stephen Grobmyer's work to diagnose and treat cancer using nanoparticles and an innovative imaging system follows.



# Using Nanoparticles for High-Resolution Imaging of Cancer

Stephen Grobmyer, M.D.

University of Florida
2006 New Investigator Research Grant

Keys to fighting cancer successfully include making an early diagnosis and effectively targeting cancer cells instead of healthy ones during treatment. With this in mind, Dr. Stephen Grobmyer, surgical oncologist, is leading a multidisciplinary team to develop high-tech methods for early detection and improved treatment of tobacco-related cancer. Since his days as an undergraduate student at Rice University, Dr. Grobmyer has believed that nanotechnology holds the promise for increasing a physician's skill to both treat and diagnose cancer. Nanotechnology is the design and engineering of nano-objects or nanoparticles less than 500 nanometers in size. One nanometer is one billionth of a meter. To put that scale into context, the comparative size of a nanometer to a meter is the same as that of a marble to the size of the earth.[35] The smallest cellular life forms are around 200 nanometers in length. Cancer nanotechnology research examines the interaction of nanoscale devices with cells and molecules specifically related to cancer diagnosis and therapy.

Nanotechnology is allowing Dr. Grobmyer to make progress towards his goal as an oncologist: to develop clinically relevant, novel approaches to cancer diagnosis and treatment. "As a physician, I recognize that while some effective treatments exist, our success in using them is limited to our ability to diagnose cancer effectively. The potential of nanotechnology lies in the ability to engineer vehicles with therapeutic properties that because of their small size can deeply penetrate tumors with a high-level of specificity," Dr. Grobmyer explained. He added that the National Cancer Institute recognizes that nanotechnology offers an "unprecedented" opportunity to make significant breakthroughs in cancer diagnosis and treatment.

The University of Florida offers a unique environment that is ideal for this type of synergistic research. With collaborators from the Department of Surgery, Department of Biomedical Engineering, and the Particle Engineering Research Center, this multidisciplinary team is already producing great progress. They are designing and developing new nanoscale contrast agents (particles) for use in locating and treating cancer. The biomedical group has been studying a new imaging technology that uses pulsed light and ultrasound to generate images called photoacoustic tomography. This technique creates high-resolution images without the use of radiation. "We hope to use photoacoustic tomography in conjunction with existing cancer imaging methods to improve imaging accuracy. Further, we are planning to use these contrast agents to simultaneously diagnose and treat cancer."

Other related projects include the use of photo-thermal therapy, which allows drug delivery directly targeted to a tumor. Once the particle reaches a tumor, they plan to use near infrared light to activate it. Its toxic effects then are limited to the tumor, and surrounding tissue remains unaffected by the treatment.

"We are developing a better understanding of nanobiology, which is increasingly important. We are able to look at how man-made nanostructures interact with tumors and normal cells. As we look at the interactions of cancer cells versus normal cells, we are asking why they are different. Do we have different mechanisms in operation, or are the mechanisms similar and just occurring at different rates?" To answer these questions, the team is conducting applied research in a mouse model of human cancer.

"The King Program is entirely responsible for this unique collaboration that has produced a common team vision, more grant proposals in pursuit of federal funding, and a number of new, related projects stimulated through group discussions. Without the grant, we were struggling to get ideas off the ground and were moving at a very slow pace. Last year we came a long way in a short amount of time. Now other departments are much more active in helping us move this forward. We have now filed a patent application, allowing for even more momentum. We hope to see a full clinical application of our technology along with additional imaging and treatment techniques developed here in Florida. Most important, we believe the people of Florida will see unique health benefits."

**"Without the grant, we were struggling to get ideas off the ground and were moving at a very slow pace. Last year we came a long way in a short amount of time. We have now filed a patent application, allowing for even more momentum."**

# Pulmonary Disease

## Pioneering New Treatment Strategies

Nationwide, lung cancer is the number one cancer killer of both men and women.[36] About six out of 10 people with lung cancer die within one year of being diagnosed; another two will die within two years.[37] Lung and bronchus cancers are the most frequently diagnosed of all cancer types. The 2007 estimated number of new lung and bronchus cancer cases in Florida is 17,490, with an estimated 12,360 cancer deaths from these diseases.[38]

### The Tobacco Connection

Tobacco use and pulmonary disease are directly linked:

- Tobacco use is responsible for about 90 percent of all lung cancer cases and more than 90 percent of all chronic obstructive pulmonary disease (COPD) deaths.[39]
- The U.S. Surgeon General has included pneumonia in the list of diseases caused by smoking.[40]
- Even among smokers who have quit smoking, chronic lung disease accounts for 50 percent of smoking-related conditions.[41]

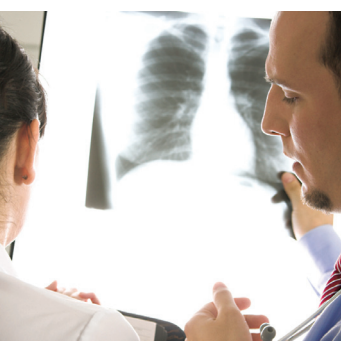
The chemicals in secondhand smoke can quickly damage the airway linings. Even brief exposure can result in upper airway changes in healthy persons, creating such lung-related problems as bronchitis and pneumonia.

### Making a Difference

One pulmonary research project led by Dr. Paul Davenport, 2006 Team Science Program at University of Florida, has discovered several ways that nicotine interacts with the respiratory system through sensory gating, or the ability to detect its presence. His team has found that nicotine inhibits the cough response by an action in the brainstem. Nicotine also disrupts sleep patterns, increasing sleep time but making it more fragmented at the same time. The mechanism for this may be due to dysfunction of the autonomic nervous system, which regulates unconscious body functions including temperature, blood pressure, and heart rate. This mechanism may also explain cardiovascular disease later in life.

Dr. S. Marina Casalino-Matsuda, 2007 New Investigator Research Grant recipient at University of Miami, explains her work in pulmonary research and Program benefits. "Research supported by Program funds will help to enhance the understanding of the causes of tobacco-related pathologies. Our goal is to clarify how cigarette smoke reacts with the airway to change the type of mucus produced by the lung. This Program is important because it will help reduce not only the morbidity and mortality of tobacco-induced diseases but also the human and economic cost of tobacco use."

The research of Dr. Alan Fields and his team in smoking-related lung cancer is a productive project highlighted in the following section.



# Pioneering Novel Techniques for Lung Cancer Detection and Treatment

## Alan Fields, Ph.D.

### Mayo Clinic
### 2006 Team Science Program

According to Dr. Alan Fields, only 15 percent of lung cancer patients are alive five years after diagnosis, making it one of today's deadliest diseases. With this in mind, and with the varied background of team members and the collaboration made possible by the King grant, the team made important basic scientific discoveries about how lung cancer develops and spreads. Next, they translated this information into new diagnostic markers and cancer staging techniques. They are now ready to start a Phase I clinical trial to gather dosage and tolerance data, which may lead to a new therapy developed from their basic science discoveries. The following list captures team discoveries in terms of causation, cancer cell movement, diagnosis, and treatment:

1. Identification of two mutations, caused by smoking, that are responsible for more than 70 percent of lung cancers. These mutations activate an enzyme called protein kinase C iota (PKC iota), which was identified as a new oncogene, a gene that can cause cells to become cancerous. Dr. Fields summarized the magnitude of their conclusion: *"If you disrupt the PKC iota gene, cancer cells can't grow tumors."*
2. Discovery that PKC iota enables cancer cells to move. This is critical information because cell mobility is what makes cancer cells so deadly. If their movement is halted, the cancer is much more treatable. The PKC iota oncogene is also activated in other types of cancers so this information has implications for more than lung cancer treatment.
3. Discovery that a major gene involved in tumor metastasis called matrix metalloproteinase (MMP), which is regulated by cells surrounding lung tumors, is tied to PKC iota through Rac1b, a protein that stimulates the growth and movement of cancer cells. Dr. Derek Radisky, team member, has led this aspect of the research.
4. Recognition that PKC iota levels are often elevated in early stage tumors; higher levels of PKC iota indicate more aggressive cancers and a worse prognosis. According to Dr. Fields, "Levels of PKC iota predict how likely a patient will respond to standard therapy and can help guide the choice of therapeutics."
5. Identification of two other genes activated simultaneously with PKC iota that are required for cancer cell growth. Dr. E. Aubrey Thompson, team member, is exploring whether these genes can help identify patients at high risk for relapse and can predict how likely the cancer is to spread through the body.
6. Identification of a drug, aurothiomalate or ATM, that blocks PKC iota signaling and inhibits tumor growth, especially in tumors with elevated PKC iota levels. Results have led to approval of a Phase 1 clinical trial to establish appropriate dosage levels of ATM for treatment of lung cancer.
7. New diagnostic technologies, endoscopic ultrasound and endobronchial ultrasound, previously developed by team member Dr. Michael Wallace, have rapidly become the gold standard in lung cancer staging. Adding ultrasound to staging procedures allows imaging and biopsy of the vast number of chest lymph nodes without opening the chest. The team has combined the molecular information obtained by the basic researchers with this new clinical technique to improve diagnosis and cancer staging. In addition to traditional tumor pathology, measuring levels of PKC iota, MMP, and Rac1b may allow clinicians to more accurately detect and stage lung tumors. Accurate cancer assessment is important because it determines which treatments a patient receives. These latest technologies indicate that some lung cancers may be mis-staged because of the difficulty in detecting metastases in chest lymph nodes. Tumors too small to be seen by pathology may now be detected with more sensitive genetic markers.

"We could not have developed this level of interaction among our investigators without the King Program. The collaboration between basic science, translational research, and clinical study has made our progress possible. We are expanding the foundation of biomedical knowledge and developing a way to bring these advances to physicians. A new lung cancer staging procedure is now standard practice at the Mayo Clinic, bringing the most current advances in medicine into the training of new physicians. In addition, a new therapy is being tested for treatment of lung cancer, which if effective, will impact how lung cancer patients are treated. We hope that our work will also result in an increase in the federal support for biomedical research in the state through the award of collaborative grant applications that are being submitted for funding as a result of this grant."

**"We could not have developed this level of interaction among our investigators without the King Program. The collaboration between basic science, translational research, and clinical study has made our progress possible. We are expanding the foundation of biomedical knowledge and developing a way to bring these advances to physicians. A new lung cancer staging procedure is now standard practice at the Mayo Clinic, bringing the most current advances in medicine into the training of new physicians."**

# 2007 Grant Awards

## Grant Mechanisms Offered

The Program released the *"Call for Grant Applications for Biomedical and Behavioral Research Grants, Fiscal Year 2007-2008,"* (the Call) on December 15, 2006, for three types of grants that began July 1, 2007: Bridge Grants, New Investigator Research Grants, and Team Science Program Grants. The Call is the published document announcing requests for grant applications.

### Bridge Grants

In 2006 there was only a nine percent chance of obtaining funding from NIH on the first try.[42] 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 Biomedical Research Advisory Council recommended offering the Bridge Grant. This award targets Florida investigators whose tobacco-related research proposals have been highly rated in national peer review processes during the previous 12 months and not selected for federal funding due to budget constraints. The Program offered a maximum of $200,000 for up to 12 months, with a requirement for timely resubmission of a federal proposal.

### New Investigator Research (NIR) Grants

According to the NIH, the average age of investigators at their first major award reached 41.7 years in 2006, up from age 34 in 1970.[43] Relying mainly on start-up funds offered by the institution to equip a laboratory, these new scientists need additional funds to obtain the preliminary data and produce the manuscripts normally required to gain 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 new talent.

The Council selected the New Investigator Research Grant to offer essential support for new Florida-based 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. Annual awards were for up to $125,000 each, with up to two yearly renewals extended for a total maximum award of $375,000.

### Team Science Program (TSP) Grants

For the fourth consecutive year, the Program offered a Team Science Program Grant to provide support for broad-based, often multi-disciplinary research programs with well-defined major objectives or themes addressing the prevention, diagnosis, treatment, or cure of tobacco-related diseases. TSP projects are expected to lead to multiple applications for additional funding at the national level to continue the research program over the long-term. These projects generally involve the organized efforts of relatively large groups, with team members conducting research projects designed to investigate the various aspects or components of the overall objective. TSP grants consist of at least three, but no more than five, interrelated yet individual research projects directed toward well-defined research program goals. Annual awards are for up to $500,000, with one renewal available for a total maximum award of $1 million.

# Results of the 2007-2008 Call for Grant Applications

In response to the FY 2007-2008 Call, the Program received 55 research proposals. Sixty-seven percent of the applications submitted were for NIR grants, 22 percent for Bridge grants, and 11 percent for TSP grants. Requests for funding totaled $21,381,843. The Department completed the application review and award process in June 2007, and the Council recommended funding 24 research grants totaling $8,746,999 beginning July 1, 2007. This action resulted in an overall proposal-to-award ratio of 44 percent. Table 1 provides a breakdown of requests and awards across the grant mechanisms.

Of the 2007 awards, 59 percent of grant funds were for three-year New Investigator Research grants, and 18 percent of grant funds were for one-year Bridge grants, while the remaining 23 percent funded two-year Team Science Program grants. In all cases of multi-year eligibility, continued funding is conditional upon acceptable grantee performance as well as the availability of funds.

Public and private research institutes throughout Florida are benefiting from these awards. The Program awarded grants to ten Florida research institutions, as shown in Figure 4. Eight of these institutions are beneficiaries of funds to support one or more new investigators, illustrating the broad distribution of new talent establishing independent research careers across the state.

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

**Table 1**
**2007-2008 Grant Applications Received/Awarded**

| Grant Mechanism | Applications Received | Applications Awarded | Percent of Applications Awarded | Awarded Funding Amounts |
|---|---|---|---|---|
| Bridge Grant | 12 | 8 | 67% | $ 1,584,257 |
| New Investigator Research | 37 | 14 | 38% | $ 5,166,610 |
| Team Science Program | 6 | 2 | 33% | $ 1,999,132 |
| **Total** | **55** | **24** | **44%** | **$8,749,999** |

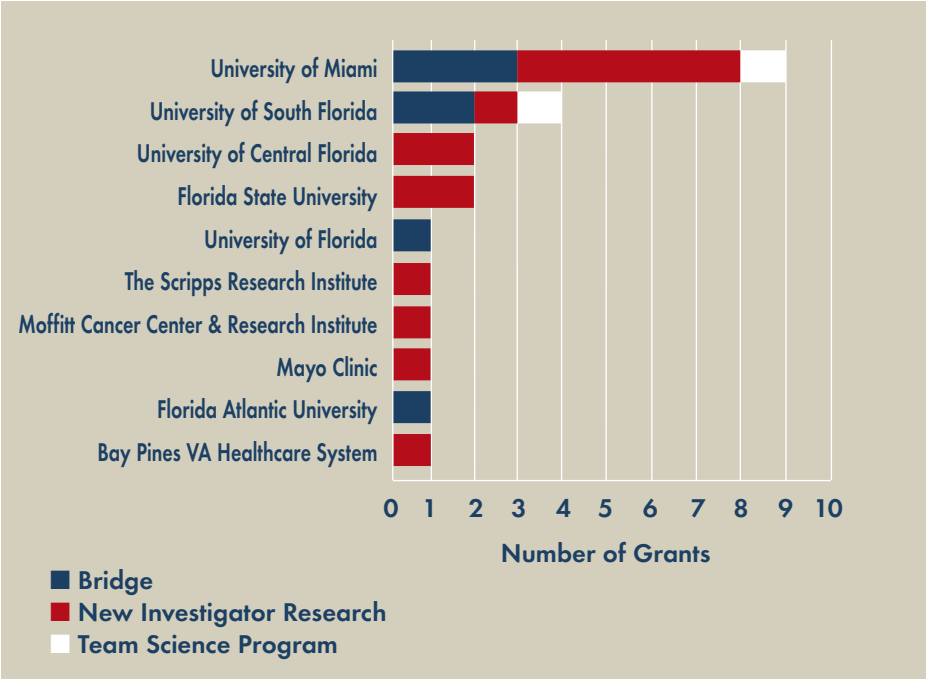
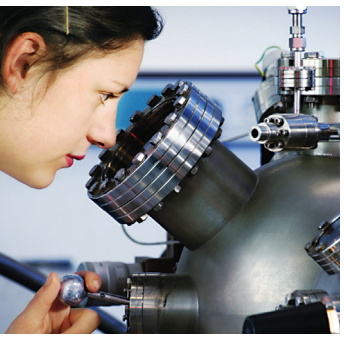



**Figure 4**
**Number of 2007-2008 Grants Awarded by Institution**

# National Biomedical Research Funding and Funding Trends



To better understand the current and future state of national funding, it is helpful to begin by looking back over the last decade.

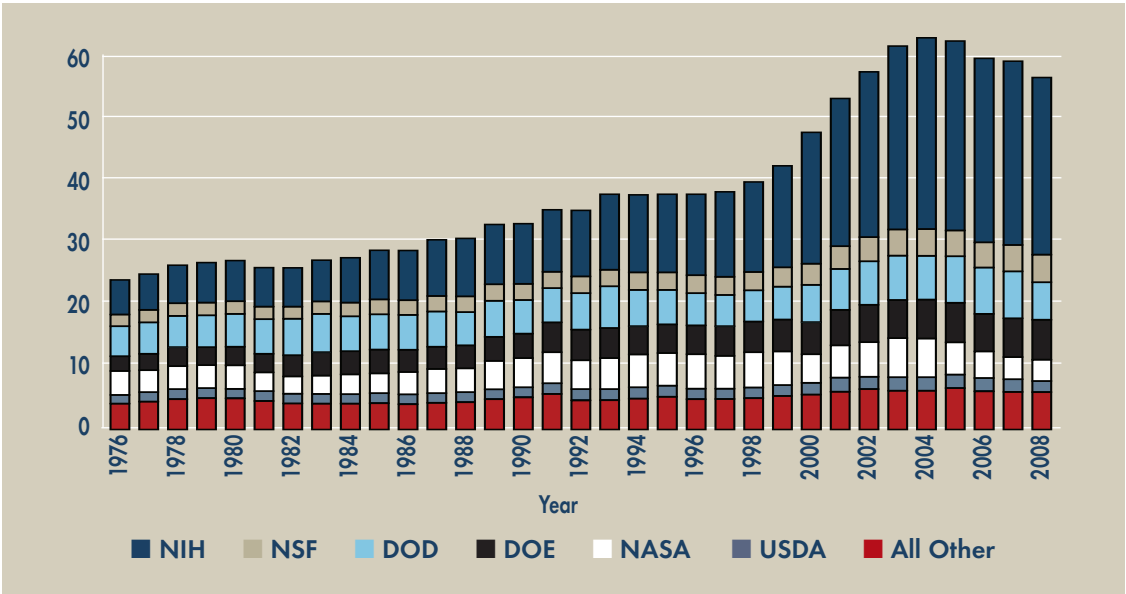
Between 1998 and 2003, the NIH budget effectively doubled to roughly $27 billion per year (see Figure 5). This increase led to rapid growth in the nation's biomedical research capacity. A 2001 survey by the Biotechnology Industry Organization found that 41 of the 50 states had "engaged in some kind of effort to lure the biosciences."[44] In 2005, the National Science Foundation (NSF) published data showing the largest reported increase ever (11 percent) in research space at research-performing colleges and universities between FY 2001 and FY 2003. More than half of this space was for research in the biological or medical sciences.[45]

However, after a modest gain in 2004, the total annual budget of NIH has remained essentially flat. Further complicating matters, the agency reported a reduction in its purchasing power from 2004 to 2007 of nearly 13 percent as the cost of conducting biomedical research continued to increase at a rate higher than inflation.[46]

Meanwhile, scientists who received an unprecedented number of grants during the high growth period have been seeking competitive renewals after three to five years. To compensate for lower funding success rates, they are submitting more proposals to keep their labs open. In addition, as they construct and equip their new facilities and hire and train additional faculty members, research institutions are submitting even more federal grant applications.

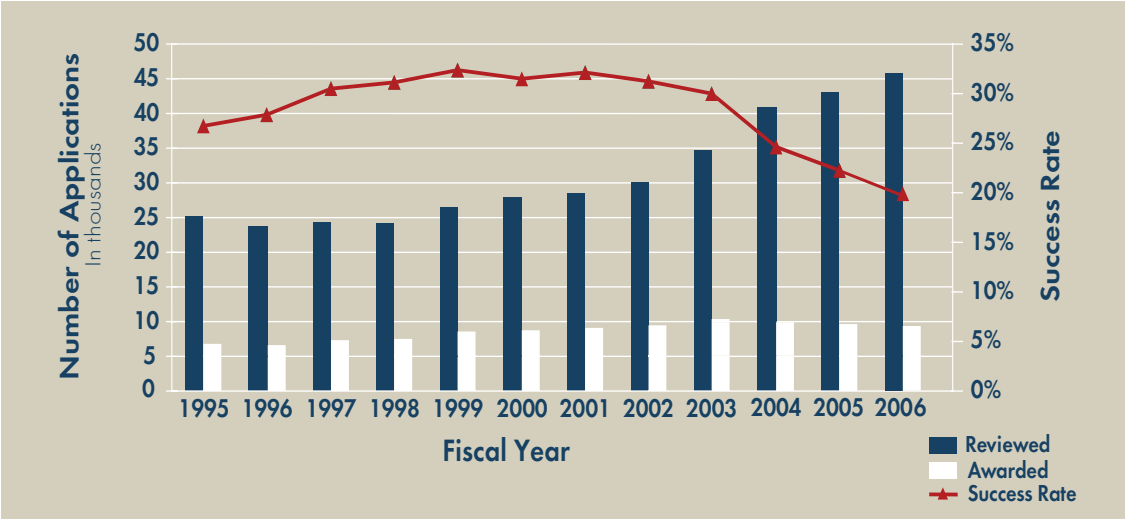
Beginning in 2003, the number of research proposals received by NIH has increased sharply. In April 2007, the Center for Scientific Review within NIH reported an 80 percent increase during the last five years.[47] Figure 6 shows the trend in the number of applications

**Figure 5**
**Trends in Reseearch by Federal Agency**
*Fiscal years 1976-2008, in billions of constant FY 2007 dollars.*




*Source: AAAS analyses of R&D in annual AAAS R&D reports. FY 2008 figures are President's request. 2007 figures are latest AAAS estimates of research in 2007 appropriations. Research includes basic research and applied research. 1976-1984 figures are NSF data on obligation in the Federal Funds survey. March '07 revised©2007 AAAS.*

**Figure 6**
**Trend in Funding from National Institutes of Health**
*Facts and Figures on National Institutes of Health Extramural Programs, May 2007*




undergoing peer review (roughly half are screened out before the review process), along with the chances of a research proposal being selected for funding at its first submission.

These trends are unlikely to change in the near future. In May 2007, John Marburger, Science Advisor to the President and Director of the Office of Science and Technology Policy, told the American Association for the Advancement of Science Policy Forum, "It is clear that the doubling [of the budget] has had a profound impact on the nation's biomedical research enterprise. The response . . . has been an abrupt increase in research capacity, financed not only by the direct federal investment, but by state governments and private sector sponsors eager to leverage this investment, not least to enhance competitiveness for additional federal funds. We now have an enlarged biomedical R&D labor pool – a new generation of researchers – who are populating new expanded research facilities and writing federal grant proposals in competition with the previous still-productive generation of their faculty advisors. And they are training yet another generation of new researchers who hope to follow the same pattern. I cannot see how such an expansion can be sustained by the same business model that led to its creation. The new researchers will either find new ways to fund their work, or they will leave the field and seek jobs in other sectors of the economy."[48]

Florida researchers at 50 organizations classified as domestic higher education, research institutes, independent hospitals, and industry received new awards from NIH totaling $337 million during FY 2006. As of October, NIH awards to the state's investigators had reached nearly $340 million during FY 2007. For the second year in a row, this level of funding places Florida 18th among the 50 states in total percent of NIH funding and 45th on a per capita basis (see Appendix B).

# Program Operations

## Summary of Program Funding History

Funding for the Program in FY 2007-2008 included $3.9 million in interest earned on the $150 million reserve within the Lawton Chiles Endowment Fund and $6 million from the state's annual appropriations.

The following table outlines the number of grant applications received and the number, type, and total value of grant awards extended for each of the seven years the Program has been in existence. There have been 120 grants awarded since inception, representing over $50 million in research funding. The Program awarded 42 inaugural grants in FY 2001. Appropriations through FY 2003-04 were used to fulfill multi-year continuation awards to these grantees, where appropriate. Except for three one-year Small Business Technology Transfer Grants totaling $150,000 and funded from administrative expenses, no new grants were awarded until FY 2004-2005.

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

## Administrative Costs

Florida law limits administrative costs to 15 percent of the total appropriation. As the data shown in Table 3 below indicate, Program staff has held administrative costs well below the legislative limit, freeing up more dollars for research project support.

**Table 2**
**Program Award History**
*below numbers are rounded*

| | FY 2001-02 | | FY 2002-03 | | FY 2003-04 | | FY 2004-05 | | FY 2005-06 | | FY 2006-07 | | FY 2007-08 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Applicants** | 189 | | No Call | | 55 | | 57 | | 44 | | 51 | | 55 | |
| **Awards** | **No.** | **Million** | **No.** | **Million** | **No.** | **Million** | **No.** | **Million** | **No.** | **Million** | **No.** | **Million** | **No.** | **Million** |
| IIR | 28 | 9.08 | | | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| NIR | 14 | 7.37 | | | 0 | 0 | 13 | 5.62 | 11 | 4.85 | 12 | 5.05 | 14 | 5.17 |
| SBTT | n/a | n/a | | | 3 | 0.15 | 2 | 0.20 | 2 | 0.20 | 2 | 0.19 | n/a | n/a |
| TSP | n/a | n/a | | | n/a | n/a | 3 | 2.91 | 3 | 2.99 | 3 | 2.85 | 2 | 2.0 |
| Bridge | n/a | n/a | | | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 8 | 1.58 |
| **Total** | **42** | **$16.45** | **0** | **$ 0** | **3** | **$0.15** | **18** | **$8.73** | **16** | **$8.04** | **17** | **$8.09** | **24** | **$8.75** |

| Fiscal Year | Appropriation | Grant Awards | Percent | Administrative Expenses[a] | Percent |
|---|---|---|---|---|---|
| FY 07-08 | 9.90 | 8.75 | 85% | n/a | n/a |
| FY 06-07 | 9.50 | 8.09 | 85% | 0.88 | 9% |
| FY 05-06 | 9.37 | 8.04 | 86% | 0.67 | 7% |
| FY 04-05[b] | 9.40 | 8.73 | 93% | 0.68 | 7% |
| FY 01-04 | 17.64 | 16.45 | 93% | 0.87 | 5% |
| **Total** | **55.81** | **50.06** | **89% (avg)** | **3.10** | **7% (avg)** |

**Table 3**
**Program Expenditures ($ Million)**

[a] This number excludes indirect costs, which are provided by the Department of Health.
[b] Beginning with FY 2004-2005 administrative expenses include $250,000 for the Center for Universal Research to Eradicate Disease pursuant to s. 215.5602 (12.) *F.S.*

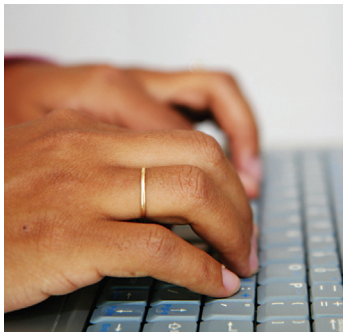
# Program Administration

The Office of Public Health Research, within the Department of Health, is responsible for administering the Program. Based on the continuing quality of service 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 James & Esther King Biomedical Research Program and the Bankhead-Coley Cancer 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 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, directing 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, and reviewing and updating long-term goals
- Technical Support – Automated application processing, grant management systems support, grantee technical assistance, and website development and maintenance (www.floridabiomed.com)



## The Granting Process

The FY 2007-2008 grant process began with guidance from the Council in August and September 2006 that was incorporated into the FY 2007-2008 Call 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 tobacco illnesses, the feasibility of the work proposed for the Program grant period, and the appropriateness of the budget.

At the May 2007 Advisory Council meeting, Lytmos presented scientific merit scores and data in a manner that concealed the identity of the investigator and institution in order to avoid conflicts-of-interest of both the Council members and the 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 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.

## Grant Management

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

- Requiring periodic financial reports and monitoring grantee 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 held 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 introducing this tool is that effective project planning by the principal investigator is essential project success.

### Progress Reports

In written progress reports provided in April 2007, principal investigators described the status of their work relative to the specific aims and shared significant findings to date. They also presented plans for addressing unanticipated outcomes or project delays and reported project-related published works, patents, and complementary funding. Sets of three subject matter experts from outside Florida reviewed each of these reports for reasonableness, and in many cases offered helpful suggestions. Each principal investigator received a copy of his/her peer review evaluation and had an opportunity to respond to reviewer comments.

## Site Visits

Program representatives make every attempt to conduct site visits once during the life of a multi-year grant, 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. During 2007, Program staff conducted site visits to 21 grantees at Florida State University, University of Miami, Florida Atlantic University, University of Florida, and Mayo Clinic.

- The site visit team examined institutional policies and controls and audited expenditures charged to the project.
- The principal investigator lead 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 other past, 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.

## Grant Completions and Continuations

Eighteen projects concluded during 2007. The Office of Public Health Research collected unspent funds from these grantees and returned them to the Biomedical Research Trust Fund.

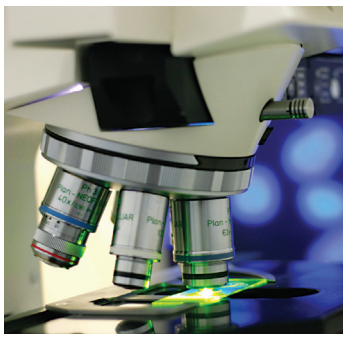
Program policy requires multi-year awardees to submit formal requests to renew their grants on an annual basis. Continuation funding is contingent upon evidence of acceptable progress towards the project aims and research milestones, including the narrative progress report and associated peer review, principal investigator response, the "Research Milestone Chart," and site visit information.

After reviewing all available information in May 2007, the grant manager recommended continuation, conditional continuation, or grant termination for each award.

Based on evidence of satisfactory progress, the Program granted requests in June for the next year funding for the remaining 26 multi-year grants. However, this process led to a Program decision to continue one grant with conditions. The principal investigator was required to submit a "get well" plan at the beginning of the next year of funding in July, with an interim progress report due in November. Unacceptable progress at that time would be cause for termination of the award.

## No-Cost Extensions

Seventeen sponsored research projects were scheduled to end on June 30, 2007. The investigators for 13 of these projects requested "no-cost extensions," or additional time to complete the planned research using funds already disbursed by the Program that remained unspent. These requests were accompanied by justification for needing the extension, amount of additional time needed, an estimate of the amount of funds that would remain at the end of the grant, and the amount of funds needed for the extension period. Using the satisfactory progress of the project to date and the reasonableness of the research plan for the extension period as the determinant, the Program approved 10 of these requests. Having remaining funds at the end of the grant is not enough justification to approve a "no-cost extension." The remaining awards concluded according to the original end date, and the Office of Public Health Research initiated collection of any unspent funds. Unspent funds were returned to the Biomedical Research Trust Fund and are available for future use by the Program.



**Veena Antony, M.D.**
Chief of Pulmonary, Critical Care and Sleep Medicine
Professor of Medicine, Molecular Genetics, and Microbiology
Vice Chair for Research
Department 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
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 and 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*

# Biomedical Research

Section 215.5602, *F.S.*, charges the Council with awarding grants for cancer research through the King Program (included in Appendix C). 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 Bankhead-Coley Cancer Research Program.

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 Speaker Marco Rubio.



James and Esther King

# Advisory Council

Another notable change to Council membership during 2007 was a rotation in the designated representative of the American Lung Association. Effective July 1, 2007, 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.**

## 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

**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 Emeritus 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. Abbreviated Abstracts of 2007 Grant Awards

The following list represents Program grants that began research in 2007. The grants are listed in alphabetical order by Principal Investigator name. Full lay abstracts are posted on the Program web site, www.floridabiomed.com.

**BENNETT, Eric**

2007 Bridge
University of South Florida
$200,000

## Role of Non-peptide Domains in Sodium Channel Function

Heart diseases such as heart failure, ischemia, and cardiac arrhythmias lead to a loss of quality of life and potentially to death. Cardiac arrhythmias cause the death of hundreds of thousands of individuals annually. Heart disease is exacerbated by tobacco use. Recent reports indicate that the risk of deadly cardiac arrhythmias increases in smokers suffering from heart failure. The long-term objective of this research is to understand better how cardiac rhythms are controlled and how these rhythms tend to become irregular during heart disease. The contraction of the heart is regulated by the elaborate conduction of electrical signals, called action potentials, throughout the cells of the heart. The action potential is produced by the orchestrated functions of transmembrane proteins, called ion channels. Any change in ion channel function can alter the action potential and lead to changes in conduction across the heart, thereby impacting cardiac function. Cardiac ion channels have large and variable amounts of sugars attached to the channel protein, and these sugars can alter how the channel works. The question to be answered is whether the amounts and types of sugars that contribute to cardiac ion channel function are also remodeled such that the cardiac action potential and thereby cardiac conduction is altered. Sugar-dependent changes in cardiac conduction will be studied by measuring electrocardiograms in mice that do not express an enzyme that normally adds sialic acids (a sugar residue) to proteins, including ion channels. The team will investigate whether and how sugars alter neonatal and adult action potentials as well as study how sugars impact cardiac potassium currents and channels. Understanding how cardiac rhythm is controlled and modulated is necessary in order to develop feasible methods for preventing the onset of deadly cardiac arrhythmias.

**BOLANOS, Carlos**

2007 NIR
Florida State University
$357,767

## Long-term Neurobiological Effects of Nicotine Exposure during Adolescence in Male Rats

Tobacco dependence through cigarette smoking is the leading preventable cause of death in the world, killing nearly 4 million people annually. Over 30 percent of the U.S. population aged 12 and over (approximately 71.5 million Americans) report past month use of a tobacco product. Nearly all of current adult smokers began their habit during their juvenile or teenage years, and almost all current smokers report becoming daily smokers by the age of 20. In addition, 30-60 percent of cigarette smokers have a lifetime prevalence of major neuropsychiatric disorders, and smokers have about four-times greater risk of mood disorders and depression than non-smokers. Though many studies have focused on identifying social and psychological risk factors underlying teen's susceptibility to smoking, very little is known about the biological mechanisms and the long-term neurobiological effects of nicotine exposure during the adolescent years. Therefore, the major experimental goal of this research is to characterize the long-term behavioral and biochemical changes induced by nicotine exposure during adolescence using animal models. In addition, this study will identify genes regulated by nicotine exposure during this developmental period that may influence future sensitivity to drugs and enhanced vulnerability to psychiatric disorders later in life. This will be accomplished by determining changes in behavioral sensitivity to nicotine, cocaine and morphine, natural rewards, and alterations in behavioral reactions to anxiety- and stress-induced environments in adult rodents. Moreover, gene transfer therapy will be used to more directly assess the functional role played by the identified genes in mediating pathological behavior. The results from these experiments will contribute to better understanding of how biochemical and behavioral mechanisms interact to mediate nicotine-induced vulnerability to disorders of mood and motivation and increase susceptibility to other drugs of abuse.

**CASALINO-MATSUDA, S. Marina**

2007 NIR
University of Miami
$375,000

## Role of Monocyte Chemotactic Protein -1/CCR2 on Oxidative Stress-Induced Mucous Phenotype

Cigarette smoke is the major risk factor of chronic bronchitis, chronic obstructive pulmonary disease (COPD), and other respiratory diseases that represent a significant health care problem. This research aims to understand how cigarette smoke induces these pathologies in order to delineate new strategies aimed at improving the current therapies, especially for COPD, a severe condition characterized by progressive, irreversible airflow limitation and excessive mucus secretion. In particular, efforts are focused at trying to identify the mechanisms responsible for two important features of this disease: increased mucus production and changes in the cells that produce mucus (known as goblet cells). To accomplish this, the team will use a model of airway in which airway cells are grown in the laboratory with one side directly exposed to the air and the other to a solution of nutrients. This type of cell culture, known as air liquid interface, resembles the cells that line the inside of human airways. These cells will be exposed to some of the components of the cigarette smoke called reactive oxygen species or ROS. The hypotheses is that ROS induce a series of "unfortunate events" that result in excessive mucus production. To test this hypothesis, the cells will be exposed to ROS, measuring the production of some mucus components, and learning about the cascade of events that leads to mucus excess by blocking the different steps of this pathway. The overall goal of this project is to advance the understanding of how cigarette smoke can lead to smoking-related respiratory diseases. The exploration of these mechanisms will provide important new information that might open the possibility for new therapeutic interventions.

**CHAN, Sic**

2007 NIR
University of Central Florida
$375,000

## Nicotine Disrupts Adult Hippocampal Neurogenesis

Nicotine, the neuroactive compound responsible for tobacco addiction, has recently been shown to reduce adult hippocampal neurogenesis. The hippocampus is a brain structure that plays a critical role in learning and memory processes and is a site of neuronal degeneration in Alzheimer's disease, stroke, and epilepsy. Neurogenesis is the process that involves the proliferation, migration, and differentiation of progenitors into neurons. Adult hippocampal neurogenesis decreases during aging, an alteration that could conceivably account for deficits in hippocampus-mediated brain functions and for the declining ability of the nervous system to recover from injury and disease with advancing age. Several lines of evidence also suggest that impairments in neurogenesis may be involved in the pathophysiology of stroke, Alzheimer's, and Parkinson's disease. Because nicotine-induced inhibition of neurogenesis can adversely impact the brain to respond to functional demands and injury, concerns have been raised for the potentially serious consequences of tobacco addiction and nicotine abuse. The goal of this research is to investigate how chronic nicotine treatment blocks the molecular CREB response and whether restoring CREB activity or the expression of downstream genes can reverse nicotine-induced inhibition of neurogenesis. These studies will provide insights into the molecular basis of nicotine-induced inhibition of neurogenesis and support strategies for enhancing CREB function as a means to preserve neurogenesis in habitual smokers and chronic nicotine users.

## Role of cRaf-1/ERK Pathway on Cotinine Neurotoxicity

**ECHEVERRIA-MORAN, Valentina**

There is growing evidence that tobacco exerts toxic effects in the human brain, although the mechanisms are poorly understood. Cigarette smoke is a complex mixture of more than 4,700 chemical compounds including oxidants that stress the brain. Primary and secondary smoke is one of many potential early events promoting the development of neurodegenerative disorders for which everyone is at risk. In fact, the toxin cotinine, produced from nicotine in the body, decreases the survival of brain cells and impairs human cognitive abilities. All of the preliminary data investigating the causes of neurodegeneration for almost a decade, shows that the abnormal activity of proteins involved in memory are altered in the brain. These factors, which are activated by oxidants and other toxins, are a common theme and are also affected in stroke, epilepsy, and Alzheimer's disease. This research will use cellular and animal models to study the involvement of these factors in cotinine's effect on learning and memory and the use of potential therapies to balance the activity of these factors in the brains of people exposed to tobacco during pregnancy or adolescence.

2007 NIR
Bay Pines VA Healthcare System
$375,000

## Mechanisms of Oxidant-Induced Chronic Bronchitis

**FORTEZA, Rosanna**

Chronic bronchitis is a debilitating disease characterized by chronic cough and frequent respiratory infections that result in frequent hospitalizations and poor quality of life. The most common cause of chronic bronchitis is exposure to cigarette smoke. Gases in tobacco smoke have been shown to have substances called reactive oxygen species that damage the lung epithelium and can result in chronic bronchitis in individuals exposed to cigarette smoke. In this research, cells obtained from lung donors suffering from chronic bronchitis will be used in combination with state-of-the-art techniques to understand why mucous hypersecretion occurs and what can be done to prevent the disease or the progression of the disease in individuals that have been exposed to cigarette smoke. The long-term goal of this research is to understand the cellular and molecular mechanisms that lead to the structural changes associated with chronic bronchitis. This project focuses on oxidative stress-induced epidermal growth factor receptor (EGFR) activation and mucus hypersecretion.

2007 Bridge
University of Miami
$200,000

## Anxiety-Based Smoking Treatment

**GEREND, Mary**

Smokers with anxiety vulnerabilities represent a common, but understudied, segment of the smoking population who are at heightened risk for continued nicotine dependence and its associated morbidity and mortality. Although researchers have attempted to understand the utility of integrating cognitive-behavioral treatment of depression into standard cessation protocols, very little research has directly targeted anxiety vulnerability factors in smoking cessation. This research aims to fill this gap in the existing literature by developing a novel, cognitive-behavioral approach to smoking cessation treatment for smokers with elevated levels of anxiety sensitivity. In the first phase of the project, a specialized protocol will be developed for the treatment of nicotine dependence. This Anxiety-based Smoking Treatment (AST) will integrate interoceptive exposure, cognitive restructuring, and psychoeducation exercises developed for anxiety prevention and treatment programs with standard smoking cessation strategies and nicotine replacement therapy. Initially, a small sample of smokers with elevated levels of anxiety sensitivity will complete the protocol, which will be modified and refined based upon feedback from participants and clinicians. In the second phase, 60 smokers with elevated levels of anxiety sensitivity will be assigned to either: (1) standard smoking cessation treatment and nicotine replacement therapy (ST) or, (2) AST, which integrates ST plus cognitive-behavioral exercises aimed at reducing anxiety-related symptoms. The results of this project will significantly increase knowledge about the role of anxiety-related vulnerability processes in relapse to smoking. By employing cognitive and behavioral strategies to reduce anxiety-related vulnerability, it may be possible to promote effective smoking cessation among an at-risk group of smokers with elevated levels of anxiety sensitivity.

2007 NIR
Florida State University
$375,000

## Irreparable Ribosomal Damage after Focal Brain Ischemia (Stroke)

**HU, Bingren**

Stroke (or focal brain ischemia) is a serious clinical problem. On average, every 45 seconds someone in the United States has a stroke, totaling more than 700,000 incidents each year. A substantial number of these stroke incidents can be associated with tobacco use as well as increasing stroke severity and the incidence of stroke death by two- to threefold. The molecular mechanisms of stroke-induced neuronal damage are still poorly understood, and there are few effective clinical treatments available for stroke patients. Therefore, study of molecular mechanisms of stroke is essential to understand how tobacco use increases stroke incidence and how to develop new therapeutics for treatment of this devastating tobacco-related disease. Tobacco smoking generates numerous reactive intermediates that interact with proteins to form toxic protein adducts in our body. These protein adducts are highly toxic in neurons. We have recently found large quantities of toxic proteins in the proteasomes, and on mitochondrial and endoplasmic reticulum membranes. Deposition of toxic proteins in these vital organelles leads to functional failure of these organelles after focal brain ischemia (stroke). Tobacco use is likely to increase incidence of stroke and stroke severity by aggravating the functional failure of multiple cellular organelles. The objective of this project is to investigate molecular mechanisms underlying the functional failure of vital cellular organelles and to explore treatment measures that rescue damaged vital organelles after stroke. Studies strongly suggest that toxic deposition of abnormal proteins in vital cellular machinery is a consequence of malfunction of protein quality control systems. This research employs state-of-the-art molecular gene transfection technologies to rescue the failure of protein quality control systems in neurons after stroke, providing a new avenue for treatment of stroke.

2007 Bridge
University of Miami
$200,000

## KENNY, Paul

2007 NIR
The Scripps Research Institute Florida
$375,000

### Mechanisms of Nicotine Reinforcement in Rats: An RNA Interference Approach

Nicotine is the active ingredient in tobacco smoke most likely responsible for the addictive properties of tobacco and the persistence of the harmful tobacco habit in human smokers. This research aims to investigate the mechanisms by which nicotine acts in the brain to produce its addictive properties. Nicotine activates proteins in the brain termed *nicotinic acetylcholine receptors* (nAChRs) that are located in brain reward pathways or "pleasure centers." In this project, the expression of different nAChR subunits likely to regulate the addictive actions of nicotine will be decreased in a specific region of the rat brain that has been widely implicated in regulating the pleasurable/addictive properties of nicotine. To "knock down" targeted nAChR subunits, a virus will be injected (lentivirus) into this region of the rat brain that can infect brain cells in this area, and make a molecule called a short interfering RNA (siRNA) inside the brain cells. We can design this siRNA such that it binds to specific (RNA) targets within the infected brain cells. Upon binding to their targets, siRNAs activate machinery within the cell to destroy the target to which it has bound, by a process termed RNA interference. So, by targeting siRNAs to individual nAChR subunits, we can knock down the expression of these nAChR subunits in brain cells important for the development of nicotine addiction. The plan is to examine the effects of knocking down discrete nAChR subunits in rat brain on the ability of nicotine to produce its pleasurable effects and on the desire to consume nicotine, compared with control rats with intact nAChRs. It is predicted that, if nAChR subunits that regulate the actions of nicotine are knocked down, the excitatory effects of nicotine on brain pleasure centers will be decreased, as will the amount of nicotine that rats will consume.

## LINCOLN, Joy

2007 NIR
University of Miami
$375,000

### Molecular Regulation of Heart Valve Development and Disease

Epidemiological studies have identified tobacco use as a clinical risk factor for increasing the incidence of cardiovascular disease including calcification of heart valve leaflets. Despite the clinical relevance, the fundamental mechanisms that lead to calcification of valve structures are not known. Human studies are beginning to provide evidence that developmental pathways important in valvulogenesis also contribute to adult valve disease. Following birth, valve interstitial cells (VICs) and ECM (extracellular matrix) become highly organized within the valve structures to facilitate and maintain normal valve function. Diseased or malfunctioning adult valves are associated with alterations in ECM homeostasis and VIC distribution. During chondrogenesis (the process in which cartilage is formed), Sox9 regulates expression of cartilage genes, a regulatory pathway that appears to be conserved in cartilage-like cells during valve development. However, in developing bone, Sox9 expression is reduced with increased expression of bone matrix proteins, suggesting that Sox9 function plays a pivotal role in maintaining chondrogenesis and repressing bone formation in tissues that must remain cartilaginous. Calcified valves display alterations in Sox9 expression and ectopically express bone matrix proteins, suggesting that aberrations in Sox9 function may lead to alterations in ECM homeostasis and valve disease. The molecular mechanisms of Sox9 required for ECM homeostasis in normal embryonic and adult valves are not clear and may be important in calcified valve disease. The overall hypothesis is: Sox9 is required to maintain ECM homeostasis in normal embryonic and adult valves by directly regulating expression of cartilage-associated genes and inhibiting expression of bone-related genes, thus preventing pathological calcification. These studies will examine the molecular mechanisms of Sox9 for ECM homeostasis during valve development, maintenance, and disease using *in vitro* and *in vivo* systems of pathological valve calcification.

## LITOSCH, Irene

2007 Bridge
University of Miami
$200,000

### Regulation of Phospholipase C-beta by Receptor Signaling

Smoking is a major risk factor contributing to cardiovascular disease, including hypertension and stroke. The major component in tobacco, nicotine, is implicated in the mechanism leading to hypertension. Both direct and indirect effects of nicotine on vascular smooth muscle tone have been identified, but mechanisms remain incompletely understood. Vascular smooth muscle tone is regulated by Gq-linked G protein-coupled receptors (GPCR) signaling through phospholipase C-beta. Aberrant GPCR-PLC-b signaling induces cellular changes that lead to the development of cardiovascular disease, including the development of hypertension. Chronic nicotine administration increases the expression levels of the PLC-b1 isoform, implicating this specific isoform in adaptation to nicotine. This laboratory has identified the phospholipid, phosphatidic acid (PA), as a novel modulator of GPCR-PLC-b1 signaling, potentially mediating cross-talk between PLC-b1 and multiple receptor-regulated pathways. PA stimulation is PLC-b1 isoform dependent, PA specific, and synergistic with alpha-q stimulation. PA regulates PLC-b1 binding to membranes and sensitivity to inhibition by protein kinase C (PKC). A PA binding region has been identified within the PLC-b1 C-terminus through a mutagenesis approach. This study will test the hypothesis that PA binding to this region is required for GPCR regulation of PLC-b1 activity *in vitro* and in cells. The hypothesis that dimerization constitutes part of the mechanism for PA regulation of GPCR-PLC-b1 signaling will be tested. Model systems of increasing complexity ranging from purified proteins to cells will be used. These studies will delineate a novel regulatory pathway, identify interactions with signaling networks, determine the requirement for PLC-b1 dimerization in the regulation of GPCR signaling, and identify new therapeutic targets.

## MANETSCH, Roman

2007 NIR
University of South Florida
$375,000

### Bcl-XL-Templated Assembly of Compounds Modulating Bcl-XL-Protein Interactions

In the last decade, certain biological molecules in cells have been identified to be accountable for the development of cancer if they bind to other biological molecules. One family of these biological molecules represents the proteins of the Bcl-2 family. These proteins directly relate to many cancers such as B-cells lymphomas, prostate cancers, colorectal adenocarcinomas, breast cancers, and lung cancers. The main goal of this research is to develop anticancer drugs that induce apoptosis of cancer cells. The team will develop a novel and efficient drug discovery method, which will significantly improve the discovery process of these novel anticancer drug molecules targeting the proteins of the Bcl-2 family. In traditional drug discovery applications, a large number of different compounds are first prepared, then in a subsequent step are tested for biological activity. The decline in the rate of submission and introduction of new drug candidates over the last 10 years is alarming and provokes questions about the effectiveness of the existing approaches to drug discovery. Researchers presume that compounds, which are screened for inhibitory activity, have to be stable "finished" products before they encounter their actual biological target. In this research, a drug discovery methodology will be developed that shows potential to create a shortcut in drug discovery efforts. This methodology will combine preparation and testing of collections of compounds in the very same step. The hypothesis is that in the presence of the target biomolecule, reactive fragments are directly assembled to bigger compounds, which bind very strongly to the target biomolecule. Thus, even fragments, which only modestly bind to a biological target's individual binding pocket, can ultimately provide compounds with strong binding properties when coupled in the correct way. The approach to find drug molecules has enormous potential not only for the discovery of new anticancer drugs but also to influence biological and medical sciences in general.

## Engineered Nanoparticles for Biomarker Detection and Targeted Drug Delivery to Cancers

**MOHAPATRA, Shyam**

Smoking is the number one cause of lung cancer in the United States, but it also increases the risk of other cancers. The risk of getting cancer is now one in two for men and one in three for women over their lifetimes. The National Cancer Institute (NCI) says that each year in this country there are a million cancer surgeries, 750,000 radiation treatment visits, and 50 million cancer-related trips to the doctor. The NCI estimates that the total cost of cancer in this country is $171.6 billion per year. Early detection, early treatment, and continuous monitoring of the disease will go a long way towards eliminating cancer. Recent advances in technology, and especially in nanotechnology, are providing novel approaches for disease detection and drug delivery, which could revolutionize cancer treatment. Prof. Mohapatra's laboratory, in collaboration with the College of Engineering, has developed nanoscale fabrication methods for making novel biomedical devices. An example of this new engineering is the microfluidic gold-nanowire electrode system, which was successfully used to detect cholesterol and cortisol levels in the blood. In the area of cancer research, the Mohapatra lab has produced nanoparticles made from a derivative of crustacean shells (chitosan), which are harmless to humans but able to carry potent anticancer drugs directly to the tumor. This discovery is expected to rapidly advance the development of new anticancer treatments. The application of nanotechnology to medicine and particularly cancer has led to the creation of a team of scientists dedicated to harnessing its unique potential for early diagnosis and effective treatment. The Team Science Program concentrates on three main projects: Application of the microfluidic gold nanowire system to early cancer detection; Investigation of nanoparticle RNA interference for treatment of lung cancer; and Nanoparticle-based targeting of drugs for treatment of prostate cancer.

2007 TSP
University of South Florida
$999,132

## Matrix Metalloproteinase-induced Lung Fibrosis and Malignancy

**RADISKY, Derek**

The structure and form of the body is defined by networks of proteins known as the extracellular matrix (ECM). Organ development and wound healing require remodeling of the ECM, which is accomplished in part by matrix metalloproteinases (MMPs). Sustained expression of MMPs in the lung is associated with lung fibrosis and lung cancer. Because of the critical role of MMPs in fibrosis and cancer progression, considerable research effort has focused on inhibiting MMPs as a therapeutic strategy for treating lung cancer and other cancers. However, because MMPs also function in many normal physiological processes such as wound healing and development of new blood vessels, most drug trials evaluating MMP inhibitors have found them to be more detrimental than beneficial. What is needed is a better understanding of the tumor-specific activities of MMPs so that more effective therapeutics can be designed to target these tumor-specific pathways. It has previously been found that MMPs can stimulate the development and multiplication of myofibroblasts, the principal cellular mediators of lung fibrosis, as well as the fact that expression of a single MMP is sufficient to induce early characteristics of lung fibrosis. Experiments will determine how this MMP stimulates lung fibrosis and potentiates lung cancer. The objective of this research is to identify MMP-dependent, fibrosis/tumor-specific processes and to develop animal models for evaluating potential therapeutic interventions in these processes. This work is innovative because it investigates wholly unexplored pathways by which a key element of the pathological microenvironment facilitates fibrosis development and tumor progression. This work is significant because elucidation of these pathways will provide key insight into mechanisms of lung fibrosis and cancer and will enable the development of new therapies for lung cancer targeting these pathways.

2007 NIR
Mayo Clinic
$375,000

## Inhibitory Effect of Nicotine on Estrogen-induced Natural Hippocampal Neuroprotection Against Ischemia

**RAVAL, Ami**

Millions of smokers in the U.S. are disabled as a result of stroke. Stroke blocks blood supply to the brain, and neurons in the close vicinity of the vascular blockage may die quickly from oxygen and glucose deprivation. This condition is known as cerebral ischemia. Cerebral ischemia causes delayed degeneration of hippocampal CA1 neurons. The hippocampal CA1 is the most vulnerable region of the brain against global cerebral ischemia. It has been observed that females suffer less post-ischemic damage compared to their male counterparts in their pre-menopausal life owing to circulating levels of estrogen in their body. During the past century, the average life span of women has increased dramatically from 50 years to more than 80 years, yet the age of menopause has remained essentially fixed at 51 years. Hence, a greater proportion and a greater total number of women will spend over 30 years of their lives in the hypo-estrogenic postmenopausal state, which is accompanied with rapid increase in stroke incidences. This suggests greater need for hormone replacement. Importantly, smoking accompanied with hormone replacement therapy elevates adverse effects of smoking in women, and the beneficial effect of estrogen on neurons is lost. Nicotine, tobacco's third main component, is believed to be the primary reason that people consume tobacco products. Nicotine addiction modulates estrogen metabolism, reduces circulating estrogen levels, disturbs normal periodicity of menstrual cycle, and ultimately leads to early onset of menopause in females. Therefore the hypothesis is that chronic nicotine exposure inhibits natural CA1 neuroprotection conferred by estrogen against ischemia. This study intends to increase the understanding of the changes that take place in the hippocampal neurons of females due to nicotine addiction as result of smoking.

2007 NIR
University of Miami
$375,000

## Nanocolumn-Supported Nanoparticle Array for Early Detection of Lung Cancer Biomarkers

**SU, Ming**

The early detection and screening of lung cancers are believed to be the most effective approaches (other than to quit smoking) to enhance the lung cancer survival rate. Although irreplaceable in obtaining spatial distributions of cancer, most of the current diagnostic techniques such as x-ray scans, computer tomography, and bronchoscopy have low sensitivities and cannot detect small cancers. Traditional molecular biology techniques such as polymerase chain reaction depend upon extensive analyses in a comprehensive laboratory and cannot be widely deployed for routine screening due to the high cost. On the other hand, the highly sensitive and integrated devices that can detect cancer biomarkers at a very early stage have been the targets of much research. Ideally, such a device should be able to detect multiple, low-concentration, genetic biomarkers within a small volume of sample both economically and efficiently. Recent progress in nanotechnology shows great promise in achieving this goal. The team has developed a method to make well-controlled glass microcolumn arrays by combining fiber drawing and chemical etching. The column arrays are used as a platform to make surface plasmon resonance sensors for the early detection of genetic lung cancer biomarkers. The sensitivity is greatly enhanced as the result of structural uniformity; the signal-to-noise ratio is improved due to the large array size; the specificity will be improved by the detection of multiple biomarkers; and the single basepair mismatch can be detected using stringency washing or electrical field-induced dehybridization. Furthermore, an integrated device that consists of DNA microarray and microfluidic channels is going to be fabricated for the low-cost, label-free, and real-time biomarker sensing. The development of such a biosensing system reflects the state of Florida's commitment to improve the lives of its citizens, benefit the state's economy, and solidify its role in the technological community.

2007 NIR
University of Central Florida
$375,000

## TAKENAKA, Norito

2007 NIR
University of Miami
$328,841

### Chiral Organic Cations as Catalysts for Enantioselective Synthesis

Medicinal chemistry (biomedical research aimed at drug discovery and development) is one of the most successful and reliable paradigms to provide new treatments for cancer and other tobacco-related diseases. Its strength derives from the systematic refinement of a lead compound into a true drug via multiple steps of testing and synthesizing analogs. The advent of efficient organic synthetic methods has shortened the timelines for this drug discovery process. However, in order to cope with the continual needs for efficacious new drugs, it invariably comes down to the ability to make the absolutely "correct" molecule in a timely and cost-effective manner. Hence, medicinal chemistry research is restricted by limitations in organic synthesis. Asymmetric organic synthesis is dedicated to the preparation of handed (chiral or not superimposable on its mirror image) compounds with defined three-dimensional molecular structure (stereochemistry). The importance of stereochemistry in chemical interaction is probably best appreciated in the context of drug-receptor interactions because most biological targets are chiral entities. Hence, there is enormous pressure to devise viable and practical methods for preparing chiral compounds in pure form. Indeed, nine of the top 10 pharmaceutical drugs have chiral active ingredients, seven of which are in a single-hand form. Of course, methods based on chiral catalysts rather than on stoichiometric chiral reagents can be advantageous from the standpoints of efficiency and economy. This research focuses on discovery and development of efficient catalytic synthetic methods for the preparation of organic molecules in a single-hand form, which is critical to successful development of efficacious new therapeutics. Such methods allow therapeutics to become accessible in a highly pure form, at a low cost, and without toxic byproducts, and thus can significantly reduce the amount of time between the initial discovery and availability to patients from all economic segments of society.

## WEBSTER, Keith

2007 TSP
University of Miami
$1,000,000

### Cellular Therapeutics and Mechanisms of Vascular Dysfunction in Heart and Kidney Disease

This research focuses on the mechanisms of blood vessel growth, injury, and repair that underlie coronary artery disease, ischemic heart disease, and chronic kidney disease. The overriding theme is that defects in blood vessel repair accumulate during aging, and this results in the atherosclerotic lesions (hardening of the arteries) that cause both myocardial and renal ischemia (lack of blood supply) and ultimately organ failure. The process of atherosclerosis is accelerated by the multiple risk factors that are associated with these diseases including tobacco use. The combined goals of this research program are both mechanistic (cause of disease) and therapeutic (treatment). It will be determined how nicotine promotes the growth of plaque on the vessel walls and whether this can be "cured" by introducing a subset of specialized stem cells derived from the bone marrow. Attempts to determine whether aging and other cardiovascular disease risk factors cause defects in a specialized fraction of human bone marrow-derived stem cells that are essential for blood vessel growth and repair will be made. Two investigators recently made the novel discoveries that human blood vessel smooth muscle cells and kidney mesangial cells both bind nicotine directly (mesangial cells are specialized smooth muscle cells that surround the vessel walls within the kidney). These investigators will attempt to determine how nicotine adversely modulates the function of their target cells within the vessel walls. Investigators from this program also made two discoveries that could change the direction of this field. The first is identification of an abundant fraction of cells within the bone marrow of young animals that may be able to slow or prevent atherosclerosis. The second is identification of a defective growth factor gene expression in a subset of bone marrow-derived stem cells from aged animals. If the same defects are present in humans, it may be possible to correct them and significantly improve stem cell therapy for patients after heart attack.

## WILLING, Alison

2007 Bridge
University of
South Florida
$200,000

### Splenic Mechanisms of Cord Blood Induced Brain Repair

Heart disease and stroke are the first and third leading cause of death and disability in the United States. Smoking has been implicated in approximately one in five deaths from cardio- or cerebro-vascular disease in this country while the death rate from stroke in Florida is the fifth highest in the nation. Clearly, tobacco places a significant burden on our healthcare system from these diseases alone. Studies have shown that intravenously (iv) administering the mononuclear fraction from human umbilical cord blood (HUCB) enhances stroke recovery, with one of the biggest changes being a reduction in multiple indicators of inflammation. In addition, observations showed changes in the T-cell population of the spleen after stroke; it returned to normal after HUCB transplantation. The hypothesis is that the HUCB cells' ability to induce stroke recovery was critically dependent on the changes these cells induce in the spleen. This research project will explore the relationship between changes in pro- and anti- inflammatory cytokines in the spleen and behavioral and anatomical recovery from stroke. Aim one examines this issue in animals in which the spleen has been removed and treated with or without iv HUCB cells. Behavior is measured as well as infarct volume (brain damage), astrocytes, and microglia response to the stroke and cytokine production in spleen and brain. Aim two determines which HUCB subpopulation alters spleen function using fluorescent-activated cell sorting (FACS) to isolate the individual HUCB subpopulations. These studies may increase understanding of the critical role of the whole body immune response in the development of brain damage after stroke and the mechanisms underlying the recovery from stroke induced by HUCB cell transplantation. The team may also identify other potential targets for development of stroke treatments that may extend the physician's arsenal in the battle against this devastating disease.

## WU, Jang-Yen

2007 Bridge
Florida Atlantic University
$184,280

### Regulation of GABA Biosynthesis in the Brain

The communication between neurons is mediated through neurotransmitters (NT). There are two types of NT dependent on their effect on the neurons. The excitatory NT stimulates neurons, whereas the inhibitory NT suppresses neurons. For the brain to function properly, it needs to maintain a precise balance between excitation and inhibition. The most abundant excitatory and inhibitory NT are glutamate and gamma-aminobutyric acid (GABA), respectively. Excessive stimulation by glutamate is believed to be the underlying mechanism for many neurological diseases including stroke-induced brain injury. This research is designed to understand how the brain maintains its proper function through the study of GABA synthesis in the brain. GABA is synthesized from glutamate by an enzyme called glutamate decarboxylase (GAD). GAD converts glutamate to GABA, and hence plays a crucial role in determining the overall state of excitation in the brain. This study is designed to further investigate the phosphorylation of GAD under normal and pathological conditions such as stroke. Specifically, this study identifies the phosphorylation sites in GAD and elucidates the function of GAD phosphorylation under physiological and stroke conditions. Compared to glutamate, GABA has received relatively little attention in the area of therapeutic intervention for stroke-induced brain damage. However, many of the drugs that enhance GABA function have been shown to have beneficial effects in animal models of stroke. These drugs have already been used clinically for other conditions, e.g., anxiety and seizures, with few side effects. Thus, drugs that can increase GABA function may be attractive candidates for further development as potential therapeutic agents for stroke. Information gained from this research will enable the team to develop a therapeutic strategy to maintain the proper level of brain excitation and prevent brain injury due to excessive excitation by glutamate as in the condition of stroke.

## Mechanisms of Smoking-related Retinal Degeneration

**ZHUKOV, Tatyana**

Tobacco smoke is composed of about 4,000 active compounds, most of them toxic on either acute or long-term exposure. Although it has been widely recognized that cigarette smoking is highly irritating to the eyes of smokers as well as nonsmokers by passive exposure (secondhand smoking), the long-term effects of smoking on vision have largely been neglected or overlooked. Comparative studies on smokers and nonsmokers have found that smoking directly accelerates the progress of macular degeneration, a retinal degenerative disease that causes severe visual impairment and blindness. Macular degeneration is a leading cause of blindness in the Western world. Unfortunately, currently there is no effective treatment for macular degeneration. The effect of smoking on the retina can be long-term, and even past smokers have a higher chance of developing macular degeneration. It is thought that the toxins in tobacco smoke affect eye tissues mainly through oxidative mechanisms; however, the details about how smoking causes and accelerates retinal degeneration are unclear. The research in this laboratory focuses on the molecular mechanisms of retinal degeneration using fruit flies as a model system. Similar to humans, fruit flies are diurnal, and they rely on color vision to navigate. More importantly, flies can easily be manipulated genetically, and there are many genetic tools available publicly through the fly community (www.flybase.org). It has recently been discovered that a neural protective factor called NMNAT protects the retina from degeneration under intense sunlight exposure. This research will study the process of smoking-related retinal degeneration by examining the dose- and time-dependent effect of oxidative damage on the eye and therefore establish a causal link between the toxic compounds in tobacco smoke and retinal degeneration. This study will help to understand the complex process of smoking-related retinal degeneration and reveal potential drug targets.

2007 NIR
H. Lee Moffitt Cancer Center & Research Institute
$355,002

## Gender-based Prognosis in Lung Cancer

**ZHAI, R. Grace**

The lung cancer death rate in women has doubled over the past 25 years. This cancer is projected to kill approximately 73,020 U.S. women–more than breast and ovarian cancer combined. Although several lines of evidence suggest that women may be more susceptible to tobacco-induced lung cancer than men, definitive results related to disparity in lung cancer survival are lacking. The indication in Dr. Zhukov's previous study of the association between actively functioning estrogen receptor pathways and impaired DNA repair mechanisms that may underlie a more malignant behavior of female lung tumors and lead to a worse prognosis in female patients required further research for confirmation in a much larger sample of patients. There are two major objectives in this research project. The first is to demonstrate gender-based lung cancer survival by analysis of the data that are available through the Florida Cancer Data System. The second is to validate if biomarkers characterizing estrogen receptors' status and DNA damage/repair signaling pathways are indicative of differential prognosis and if they may be used as a markers of the effectiveness of therapy. Potentially this study may lead to novel estrogen receptor-specific drug development and intervention in the treatment of early stages of lung cancer to improve female patients' survival.

2007 NIR
University of Miami
$375,000

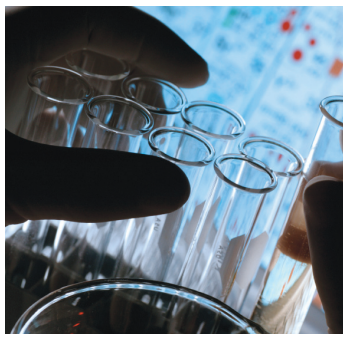
# Appendix B. National Institutes of Health, Funding by State

**2006-2007 Funding by State**[49]

Listed below are the 30 states that received the most NIH funds in 2007.

| | 2007 | | | | | | | 2006 | |
|---|---|---|---|---|---|---|---|---|---|
| State | 2006 Population Estimate | Pop Rank | $ Per Capita | Per Capita Rank | Funding 2007 | Rank | % of Total Funding | Funding 2006 | Rank |
| California | 36,457,549 | 1 | 86.78 | 11 | 3,163,763,094 | 1 | 15.07% | 3,048,138,519 | 1 |
| Massachusetts | 6,437,193 | 13 | 347.35 | 1 | 2,235,939,038 | 2 | 10.65% | 2,149,369,222 | 2 |
| New York | 19,306,183 | 3 | 100.25 | 10 | 1,935,399,273 | 3 | 9.22% | 1,846,780,769 | 3 |
| Pennsylvania | 12,440,621 | 6 | 112.33 | 7 | 1,397,422,734 | 4 | 6.65% | 1,333,388,400 | 4 |
| Texas | 23,507,783 | 2 | 46.09 | 28 | 1,083,464,922 | 5 | 5.16% | 1,041,045,029 | 5 |
| Maryland | 5,615,727 | 19 | 173.89 | 3 | 976,541,042 | 6 | 4.65% | 964,957,683 | 6 |
| North Carolina | 8,856,505 | 10 | 105.11 | 9 | 930,882,958 | 7 | 4.43% | 905,135,143 | 7 |
| Washington | 6,395,798 | 14 | 122.85 | 6 | 785,736,150 | 8 | 3.74% | 803,033,656 | 8 |
| Illinois | 12,831,970 | 5 | 56.39 | 20 | 723,645,370 | 9 | 3.45% | 678,357,778 | 9 |
| Ohio | 11,478,006 | 7 | 54.74 | 22 | 628,293,858 | 10 | 2.99% | 613,183,796 | 10 |
| Michigan | 10,095,643 | 8 | 54.77 | 21 | 552,932,019 | 11 | 2.63% | 535,678,937 | 11 |
| Missouri | 5,842,713 | 18 | 80.97 | 13 | 473,057,974 | 12 | 2.25% | 460,424,407 | 12 |
| Connecticut | 3,504,809 | 29 | 133.79 | 5 | 468,893,912 | 13 | 2.23% | 438,035,882 | 13 |
| Minnesota | 5,167,101 | 21 | 85.84 | 12 | 443,523,672 | 14 | 2.11% | 391,328,715 | 15 |
| Tennessee | 6,038,803 | 17 | 72.00 | 15 | 434,819,317 | 15 | 2.07% | 405,745,744 | 14 |
| Wisconsin | 5,556,506 | 20 | 66.66 | 17 | 370,395,477 | 16 | 1.76% | 360,689,308 | 16 |
| Georgia | 9,363,941 | 9 | 39.05 | 30 | 365,703,745 | 17 | 1.74% | 352,122,831 | 17 |
| **Florida** | **18,089,888** | **4** | **18.78** | **45** | **339,754,376** | **18** | **1.62%** | **331,128,265** | **18** |
| Colorado | 4,753,377 | 22 | 66.54 | 18 | 316,292,851 | 19 | 1.51% | 294,328,406 | 19 |
| Oregon | 3,700,758 | 27 | 74.90 | 14 | 277,168,923 | 20 | 1.32% | 262,452,372 | 20 |
| Virginia | 7,642,884 | 12 | 35.49 | 32 | 271,243,779 | 21 | 1.29% | 249,983,605 | 21 |
| New Jersey | 8,724,560 | 11 | 28.74 | 39 | 250,701,373 | 22 | 1.19% | 230,533,886 | 23 |
| Alabama | 4,599,060 | 23 | 50.79 | 26 | 233,576,930 | 23 | 1.11% | 33,747,040 | 22 |
| Indiana | 6,313,520 | 15 | 32.94 | 35 | 207,951,807 | 24 | 0.99% | 203,163,367 | 24 |
| District of Columbia | 581,530 | 50 | 336.59 | 2 | 195,737,381 | 25 | 0.93% | 177,058,601 | 26 |
| Iowa | 2,982,085 | 30 | 65.27 | 19 | 194,631,513 | 26 | 0.93% | 184,434,413 | 25 |
| Arizona | 6,166,318 | 16 | 27.71 | 40 | 170,898,328 | 27 | 0.81% | 159,420,033 | 27 |
| Rhode Island | 1,067,610 | 43 | 134.35 | 4 | 143,434,997 | 28 | 0.68% | 128,449,419 | 31 |
| Kentucky | 4,206,074 | 26 | 33.18 | 34 | 139,578,376 | 29 | 0.66% | 139,887,962 | 29 |
| Louisiana | 4,287,768 | 25 | 31.98 | 36 | 137,123,345 | 30 | 0.65% | 159,339,837 | 28 |

# Appendix C. Section 215.5602, *Florida Statutes* - James and Esther King Biomedical Research Program



1) There is established within the Department of Health the James and Esther King Biomedical Research Program funded by the proceeds of the Lawton Chiles Endowment Fund pursuant to s. 215.5601. The purpose of the James and Esther King Biomedical Research Program is to provide an annual and perpetual source of funding in order to support research initiatives that address the health care problems of Floridians in the areas of tobacco-related cancer, cardiovascular disease, stroke, and pulmonary disease. The long-term goals of the program are to:
   (a) Improve the health of Floridians by researching better prevention, diagnoses, treatments, and cures for cancer, cardiovascular disease, stroke, and pulmonary disease.
   (b) Expand the foundation of biomedical knowledge relating to the prevention, diagnosis, treatment, and cure of diseases related to tobacco use, including cancer, cardiovascular disease, stroke, and pulmonary disease.
   (c) Improve the quality of the state's academic health centers by bringing the advances of biomedical research into the training of physicians and other health care providers.
   (d) Increase the state's per capita funding for research by undertaking new initiatives in public health and biomedical research that will attract additional funding from outside the state.
   (e) Stimulate economic activity in the state in areas related to biomedical research, such as the research and production of pharmaceuticals, biotechnology, and medical devices.

(2) Funds appropriated for the James and Esther King Biomedical Research Program shall be used exclusively for the award of grants and fellowships as established in this section; for research relating to the prevention, diagnosis, treatment, and cure of diseases related to tobacco use, including cancer, cardiovascular disease, stroke, and pulmonary disease; and for expenses incurred in the administration of this section. Priority shall be granted to research designed to prevent or cure disease.

(3) There is created within the Department of Health the Biomedical Research Advisory Council.
   (a) The council shall consist of 11 members, including: the chief executive officer of the Florida Division of the American Cancer Society, or a designee; the chief executive officer of the Florida/Puerto Rico Affiliate of the American Heart Association, or a designee; and the chief executive officer of the American Lung Association of Florida, or a designee. The remaining 8 members of the council shall be appointed as follows:
      1. The Governor shall appoint four members, two members with expertise in the field of biomedical research, one member from a research university in the state, and one member representing the general population of the state.
      2. The President of the Senate shall appoint two members, one member with expertise in the field of behavioral or social research and one representative from a cancer program approved by the American College of Surgeons.
      3. The Speaker of the House of Representatives shall appoint two members, one member from a professional medical organization and one representative from a cancer program approved by the American College of Surgeons.

      In making these appointments, the Governor, the President of the Senate, and the Speaker of the House of Representatives shall select primarily, but not exclusively, Floridians with biomedical and lay expertise in the general areas of cancer, cardiovascular disease, stroke, and pulmonary disease. The appointments shall be for a 3-year term and shall reflect the diversity of the state's population. An appointed member may not serve more than two consecutive terms.
   (b) The council shall adopt internal organizational procedures as necessary for its efficient organization.
   (c) The department shall provide such staff, information, and other assistance as is reasonably necessary to assist the council in carrying out its responsibilities.
   (d) Members of the council shall serve without compensation, but may receive reimbursement as provided in s. 112.061 for travel and other necessary expenses incurred in the performance of their official duties.

(4) The council shall advise the [1]State Surgeon General as to the direction and scope of the biomedical research program. The responsibilities of the council may include, but are not limited to:
   (a) Providing advice on program priorities and emphases.
   (b) Providing advice on the overall program budget.
   (c) Participating in periodic program evaluation.
   (d) Assisting in the development of guidelines to ensure fairness, neutrality, and adherence to the principles of merit and quality in the conduct of the program.
   (e) Assisting in the development of appropriate linkages to nonacademic entities, such as voluntary organizations, health care delivery institutions, industry, government agencies, and public officials.

(f) Developing criteria and standards for the award of research grants.
(g) Developing administrative procedures relating to solicitation, review, and award of research grants and fellowships, to ensure an impartial, high-quality peer review system.
(h) Developing and supervising research peer review panels.
(i) Reviewing reports of peer review panels and making recommendations for research grants and fellowships.
(j) Developing and providing oversight regarding mechanisms for the dissemination of research results.

(5) (a) Applications for biomedical research funding under the program may be submitted from any university or established research institute in the state. All qualified investigators in the state, regardless of institution affiliation, shall have equal access and opportunity to compete for the research funding.
(b) Grants and fellowships shall be awarded by the [1]State Surgeon General, after consultation with the 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. Predoctoral and postdoctoral research fellowships.

(6) 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 scientific priority score. The priority scores shall be forwarded to the council and must be considered in determining which proposals shall be recommended for funding.

(7) 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 conflict 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 shall be subject to the provisions of chapter 119, s. 286.011, and s. 24, Art. I of the State Constitution.

(8) The department may contract on a competitive-bid basis with an appropriate entity to administer the program. Administrative expenses may not exceed 15 percent of the total funds available to the program in any given year.

(9) The department, after consultation with the council, may adopt rules as necessary to implement this section.

(10) The council shall submit an annual progress report on the state of biomedical research in this state to the Florida Center for Universal Research to Eradicate Disease and to the Governor, the [1]State Surgeon General, the President of the Senate, and the Speaker of the House of Representatives by February 1. The report must include:
(a) A list of research projects supported by grants or fellowships awarded under the program.
(b) A list of recipients of program grants or fellowships.
(c) A list of publications in peer reviewed journals involving research supported by grants or fellowships awarded under the program.
(d) The total amount of biomedical research funding currently flowing into the state.
(e) New grants for biomedical research which were funded based on research supported by grants or fellowships awarded under the program.
(f) Progress in the prevention, diagnosis, treatment, and cure of diseases related to tobacco use, including cancer, cardiovascular disease, stroke, and pulmonary disease.

(11) The council shall award grants for cancer research through the William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program created in s. 381.922.

(12) Beginning in fiscal year 2006-2007, the sum of $6 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 James and Esther King Biomedical Research Program pursuant to this section. From these funds up to $250,000 shall be available for the operating costs of the Florida Center for Universal Research to Eradicate Disease.

(13) 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.

(14) The Legislature shall review the performance, the outcomes, and the financial management of the James and Esther King Biomedical 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.

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

**History.**—s. 2, ch. 99-167; s. 4, ch. 2000-159; s. 2, ch. 2000-255; s. 5, ch. 2000-367; s. 4, ch. 2001-73; s. 1, ch. 2003-414; s. 8, ch. 2004-2; s. 3, ch. 2006-182.

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

# Appendix D. Related Awards Reported by Grantees

The following list represents $7,151,448 in additional single and multi-year research awards reported since October 2006 by current and past grantees that are based directly on research findings from projects funded by the James & Esther King Biomedical Research Program. Grants are presented in alphabetic order by last name of the principal investigator, with the award year and grant type listed in parentheses.

**Braith R.** (2001 IIR), "Skeletal Effects of Teriparatide," University of Florida, $41,000

**Cogle C.** (2005 NIR), "Targeting Leukemia Hemangioblast Activity," Luekemia Lymphoma Society, $600,000

**Crary M.** (2001 IIR), "Muscle Composition and Swallow Function following Radiation Therapy for Head and Neck Cancer: A Dose Response Study," American Cancer Society, $828,000

**Dietz N.** (2005 NIR), "A Pilot Study Examining a Relationship-Based Smoking Cessation Program for Women," Florida American Cancer Society, $43,320

**Dietz N.** (2005 NIR), "A Pilot Study Identifying Survivorship Needs through Community Partners," Lance Armstrong Foundation, $27,500

**Fletcher T.** (2004 NIR), "Grant-in-Aid-The Role of a Telomere Binding Protein in Vascular Remodeling Following Injury," American Heart Association, $264,000

**Ganju-Krishan A.** (2005 SBTT), "Tumor Cells in Body Cavity Fluids," Women's Cancer Association, $50,000

**Grobmyer S.** (2006 NIR), "Faculty Career Development Award," University of Florida Department of Surgery, $25,000

**Hackam A.** (2007 Bridge), "WNT Signaling and Neuroprotection in the Retina," National Eye Institute, $1,720,000

**Kobetz E.** (2006 TSP), "Testing the Acceptability of the Founeier Self Sampler among Haitian Women: A Pilot Study," University of Miami Sylvester Comprehensive Cancer Center and University of Miami Institute for Women's Health, $100,000

**Ma T.** (2004 NIR), "Bone Tissue Regeneration from Human Mesenchymal Stem Cells," U.S. Army, $824,212

**Ma T.** (2004 NIR), "Small Diameter Blood Vessel Regeneration by Biomimetic Engineering," Flight Attendant Medical Research Institute, $162,000.

**Magelby K.** (2001 IIR), "Engineered Bio-molecular Nano-deviced Systems," Electronic Biosciences, $290,000

**Magelby K.** (2001 IIR), "Mechanism of Ion Channel Activity, National Institute of Health/NIAMD, $330,000

**Mann G.** (2001 IIR), "Muscle Preservation and Swallow Function following Radiotherapy," American Cancer Society, $828,000

**Mitra K.** (2003 IIR), "Tissue Imaging and Irradiation Using 1552 nm Ultrashort Pulse Laser," Raydiance, Inc., $300,000

**Salathe M.** (2005 TSP), "Mucociliary Function in Chronic Bronchitis," National Institute of Health, $1,530,000

**Vazquez-Padron R.** (2006 NIR), "Diabetes, Stem Cells and Vascular Restenosis," Stanley J. Glaser Foundation, $25,000

Since October 2006, current and past grantees reported $6,985,291 in awards that are indirectly based on research findings from projects funded by this Program. However, the James & Esther King award enhanced their competitiveness in earning this additional funding. Grants are presented in alphabetical order by last name of the principal investigator, with the King award year and type listed in parentheses.

**Ames, S.** (2001 NIR), "Brief Integrative Alcohol Interventions for Adolescents," National Institute on Alcohol Abuse and Alcoholism, $3,195,386

**Anastasiadis P.** (2005 TSP), "Cadherins and Catenins as Biomarkers of Pediatric and Adult Gliomas," Accelerate Brain Cancer Cure, $125,000

**Carraway K.** (2001 IIR), "Function of Muc4 in Mammary Epithelia and Tumors," National Institute of Health, $1,146,760

**Luesch H.** (2006 NIR), "Algal Diversity in the Florida Keys and Dry Tortugas for Drug Discovery," Florida Institute of Oceanography, $10,000

**Melker R.** (2004 SBTT), "A Breath-based Medication Adherence Monitoring System for HIV/AIDS Therapies," National Institute for Mental Health, $100,000

**McCarty C.** (2003 SBTT), "Social and Cultural Context of Racial Inequalities in Health," National Science Foundation, $347,430

**McCarty C.** (2003 SBTT), "Social Network Analysis of the Collaborative Interaction of Scientists in Academic and Non-academic Settings," National Science Foundation, $355,993

**McCarty C.** (2003 SBTT), "Quantifying Scientific Impact: Cross-Disciplinary Trends and Attitudes," University of Florida Opportunity Grant, $52,000

**Self W.** (2005 NIR), "Mechanism of SOD Mimetic Activity of Vacancy-Engineered Ceria Nanoparticles," National Institute of Health, $552,722

**Self W.** (2005 NIR), "NIRT: Engineered Therapeutic Nanoparticles as Catalytic Antioxidants," National Science Foundation, $1,000,000

**Self W.** (2005 NIR), "Surface Chemistry in Metal Oxide Nanoparticle Cytotoxicity," National Science Foundation, $100,000

# Appendix E. Grantee Publications

The following list represents new publications in peer-reviewed journals and books since October 2006 based on funded research from Program grantees. 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.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**Dudley GB**, Engel DA, Ghiviriga I, Lam H, Poon KWC, Singletary JA. Synthesis of dihydro-epi-deoxyarteannuin B. *Org Lett.* Jul 19, 2007;9(15):2839-42.

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# Endnotes


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