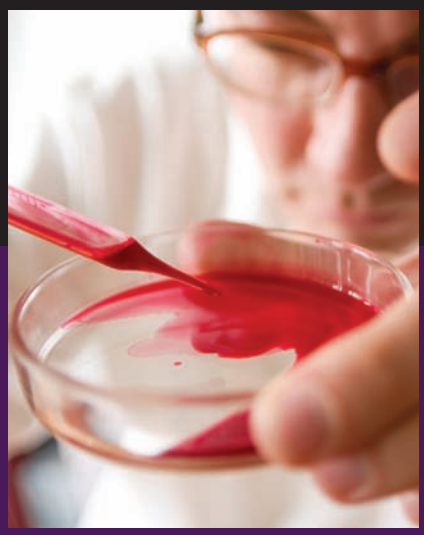
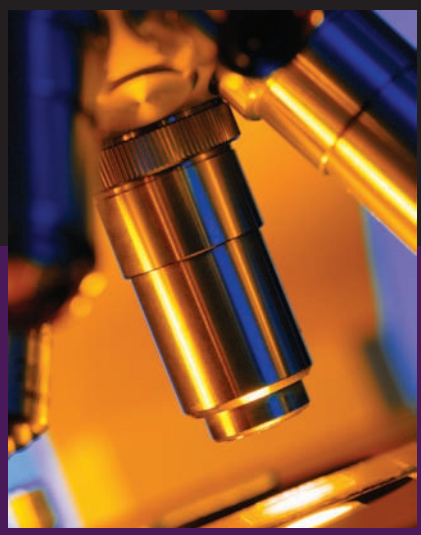
JAMES & ESTHER KING BIOMEDICAL RESEARCH PROGRAM

Delivering on a Promise

Annual Report 2008





The James & Esther King Biomedical Research Program

The five long-term goals of the Program are to:

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.

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.

The Honorable Charlie Crist, Governor
The Honorable Jeff Atwater, Senate President
The Honorable Ray Sansom, House Speaker
Ana M. Viamonte Ros, M.D., M.P.H., State Surgeon General, Florida Department of Health

Dear Governor Crist, President Atwater, Speaker Sansom, and State Surgeon General Viamonte Ros:

When Florida's lawmakers created this program in 1999, they had hope for the future of biomedical research in our State, and a vision of excellence in a competitive, peer-reviewed grant program that would support the most promising science, statewide. They put forth the challenge of achieving five ambitious long-term goals. Over the years, they and you have protected funding for the James & Esther King program at approximately $9 million a year, trusting that Florida's citizens would be rewarded with much greater returns.

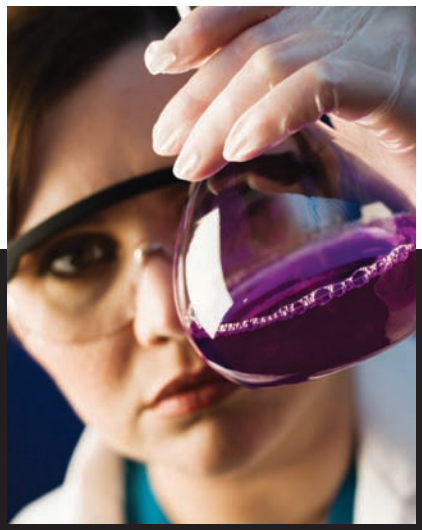
The Biomedical Research Advisory Council and the Department of Health have been careful stewards of this program, targeting grants to meet the greatest needs and to produce science with high potential for both additional external funding and social benefit. The good news is that, by 2008, it is becoming clear that the original vision for this program is becoming a reality.

Besides providing an accounting of program operations and statistics, this report attempts to convey the larger picture of program accomplishments against our broad statutory goals and offers a glimpse into the many individual success stories that these grants represent. Florida's steady investment in this program is producing outstanding work for the benefit of the health of Floridians, building the research capacity of our universities and research institutes, enhancing our State's reputation in biomedical research, and stimulating our economy.

We understand this is a difficult financial time and know that you are making many hard choices to protect our State's financial health. Based on its proven value to the State of Florida, we urge you to continue support for the James & Esther King Biomedical Research Program at the current level until we can afford to invest more.

Sincerely,

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



James and Esther King Biomedical Research Program

Annual Report
January–December 2008

Submitted to

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

and

The Florida Center for Universal Research to Eradicate Disease

by

Dr. Richard Bookman, Chair
Biomedical Research Advisory Council

February 1, 2009

Delivering on a Promise

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Executive Summary

Beginning with the first appropriation of funds in 2001 for what is now known as the James & Esther King Biomedical Research Program (Program), the State of Florida began investing in the long-term promise of accelerated progress toward preventing, diagnosing, treating, and curing tobacco-related disease. Seven years and $58 million later, the Program is delivering on that promise.

By 2008, research produced by Program grantees has already brought an additional $90.4 million in funding to Florida. This figure will continue to climb in the next few years as sponsored research still underway matures. The findings from these grants are producing an accelerating number of publications – impressive not only in number, but also in quality; as the data show, many are attracting wide readership. Of nearly 650 invited presentations, more than half have been delivered in national forums, and another quarter have been in international settings.

Rather than funding bricks and mortar, these grants have been building Florida's human biomedical research capacity. More than 170 scientists at 15 different institutions throughout the state have led projects, aided by hundreds more graduate and post-doctoral students and laboratory personnel. Nearly 50 project leaders have been physician scientists, hastening the progress of research to clinical applications. More than half of the funds have been devoted to projects led by new Florida investigators, as tightened competition for national funding has made it increasingly difficult for early-career scientists to gain a foothold.

Program-sponsored research has resulted in the formation of at least five thriving new Florida businesses and led to more business partnerships and spillovers from university research to private-sector research and development.

The Program's strategy to bring improved healthcare from the point of discovery to the patient in the clinic has been to attack the problem from many angles. Grants have focused on a broad range of tobacco-related diseases as well as nicotine addiction. They have commissioned individual scientists and teams of investigators at all experience levels to pursue basic science, translational research, and clinical studies. Independently judged by national experts in annual statewide competitions, each of these projects represents high potential research.

By 2008, funding for the National Institutes of Health has fallen to 13 percent below the 2004 level in inflation-adjusted dollars at a time when healthcare spending is rising at its highest rate in history. Florida is the fourth most populous state in the nation, yet the per capita share of the National Institutes of Health funding is only 42 percent of the national average. The King Program is playing a vital role in helping Florida improve this standing.

Of 65 grant proposals seeking more than $24 million in 2008 from the King Program, 23 received awards. Ten Florida institutions were beneficiaries of these new grants.

This report provides a brief program history, summarizes the outcome of grantmaking activity in 2008, and accounts for the use of Program funds. It also explains how the Biomedical Research Advisory Council and the Department of Health select and manage the portfolio of grants. Most importantly, it offers insight into the many ways in which the Program and its Florida grantees are rising to the challenge presented by the King Program's five ambitious long-term goals.

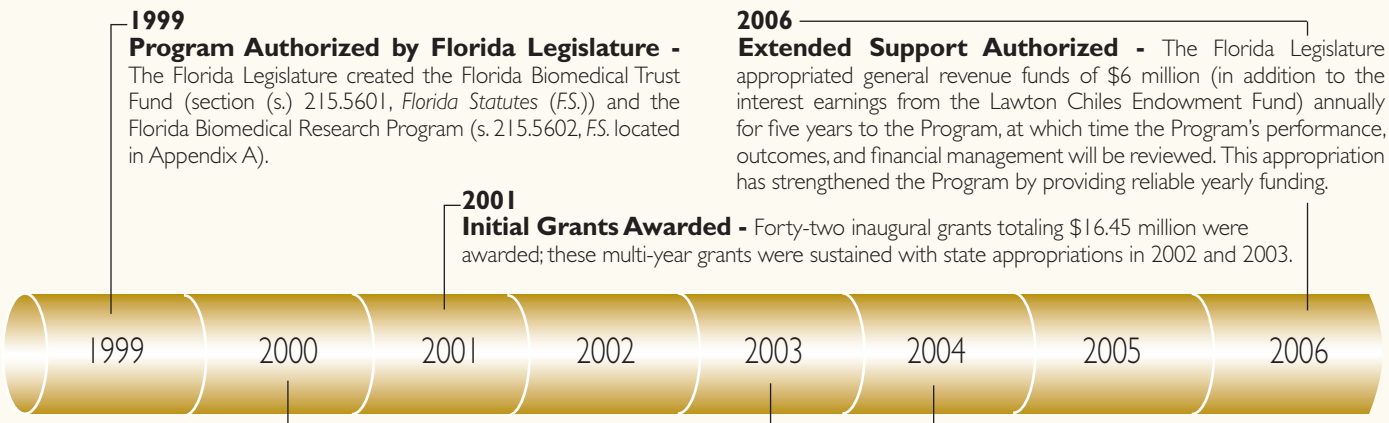
Background

Every year, smoking kills more people in Florida than alcohol, AIDS, car crashes, illegal drugs, murders, and suicides combined and thousands more die from other tobacco-related causes such as fires caused by smoking and smokeless tobacco use.[1]

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 that same year. The James and Esther King Biomedical Research Program represents a proactive measure by the State of Florida to fight the devastating impact of tobacco use and to advance the health of its citizens.

The Program offers competitive grants to researchers throughout Florida to fulfill its goals. Awards are based on scientific merit, as determined by independent peer review involving experts located outside the State. The Florida Department of Health manages the Program in conjunction with the Florida Biomedical Research Advisory Council (Advisory Council) and Lytmos Group, Inc.

The following timeline summarizes key milestones in the life of the Program:



1999
Program Authorized by Florida Legislature - The Florida Legislature created the Florida Biomedical Trust Fund (section (s.) 215.5601, *Florida Statutes* (*F.S.*)) and the Florida Biomedical Research Program (s. 215.5602, *F.S.* located in Appendix A).

2000
Funds Authorized for Initial Grants - Investment earnings from a $150 million portion of the Lawton Chiles Endowment Fund were marked exclusively for funding research initiatives into the prevention, diagnosis, treatment, and cure of tobacco-related diseases such as cancer, cardiovascular disease, stroke, and pulmonary disease.

2001
Initial Grants Awarded - Forty-two inaugural grants totaling $16.45 million were awarded; these multi-year grants were sustained with state appropriations in 2002 and 2003.

2003
Funding Limited to Existing Grants - The Legislature appropriated money for continuing years of existing grants only, which threatened the Program with a loss of credibility in the scientific community. Three grants totaling $150,000 were made based on money allotted for Program administrative costs.

2004
Stable Funding Base Created - The Florida Legislature allowed annual appropriation balances from the Biomedical Research Trust Fund to be expended over a period of up to three years. This decision protected the completion of grant awards, allowed for the continuity of multi-year research, and created a more stable and sustainable funding base.

2006
Extended Support Authorized - The Florida Legislature appropriated general revenue funds of $6 million (in addition to the interest earnings from the Lawton Chiles Endowment Fund) annually for five years to the Program, at which time the Program's performance, outcomes, and financial management will be reviewed. This appropriation has strengthened the Program by providing reliable yearly funding.

Based on the goals of advancing progress towards cures for tobacco-related diseases, the Advisory Council has carefully selected the grant types offered since the first Call for Grant Applications in 2001. Their decisions have been based on the most pressing needs of Florida's research community and the most effective strategies for achieving Program goals. Table 1 provides a brief description and history of the grant mechanisms offered.

Table 1 - Grant Mechanisms Offered

Grant Type	Purpose	Maximum Amount & Duration
Bridge Grant Offered in 2007, 2008	To provide interim support for promising tobacco-related research projects that have been highly rated by national panels of scientific peer reviewers in recent federal competitions but not funded due to budgetary constraints. Researchers use the Bridge period to collect preliminary data and improve their national applications based on peer review feedback. At the conclusion of the Bridge Grant, researchers must submit a new/revised application to the funding agency that denied funding on the first submission.	$200,000 for one year
Investigator Initiated Research Grant (IIR) Offered in 2001	To assist established investigators to initiate research that can attract funding from national sources. The IIR Grant is similar to the National Institutes of Health (NIH) "R-01" grant, which provides support for health-related research and development for the conduct of a specific research project that is hypothesis driven, fully developed, scientifically rigorous with promising preliminary studies or supporting data.	$400,000 for 25 months
New Investigator Research Grant (NIR) Offered in 2001, 2004-2008	To foster development of new investigators so that they can undertake independent research that will be competitive for national research funding. New investigators are those who have been full-time faculty for less than five years and have not received a large ($100,000 or more) peer-reviewed national grant. A senior researcher serves as a mentor.	Ranged from $375,000 to $450,000 for three years
Small Business Technology Transfer Grants (SBTT) Offered in 2003-2006, 2008	To help biomedical researchers at Florida universities or research institutions collaborate with Florida-based small businesses to initiate private sector commercialization of technology. The objective is to establish the technical/scientific merit and feasibility of the proposed research and development efforts so that the project may become competitive for further industry investment or national-level development funding.	Ranged from $50,000 to $100,000 for one year
Team Science Program Grants (TSP) Offered in 2004-2008	To provide support for broad-based, often multidisciplinary research programs with well-defined major objectives or themes. The Program expects Team Science grants to lead to multiple applications for additional funding at the national level in order to continue the research program over the long-term. TSP grants consist of at least three, but no more than five, interrelated yet individual research projects directed toward well-defined research goals.	$1,000,000 for two years The Program limits applications to one per institution and requires recipient institutions to provide a minimum of 25 percent in matching funds.

Improve the Health of Floridians

Improve the health of Floridians by researching better prevention, diagnoses, treatments, and cures for cancer, cardiovascular disease, stroke, and pulmonary disease.

Challenges

- Approximately 21 percent of adults smoke; 15 percent of high school students in Florida smoke, and 10 percent use smokeless tobacco. The number of kids exposed to secondhand smoke at home in Florida is 692,000.[2]
- Annual healthcare costs in Florida directly caused by smoking are $6.32 billion, a resident cost of $585 per household.[3]
- Florida ranks 46th in the nation in state cigarette tax ($0.34 per pack compared to the national average of $1.18),[4] missing out on a proven incentive to reduce smoking.
- It is universally difficult to recruit and retain patients in clinical trials, and to ensure that participating patients adhere to the treatment protocols.

Overall Program Impact

The Program's strategy to bring improved healthcare from the point of discovery to the patient in the clinic has been to attack the problem from many angles.

Funding Clinical Studies

Many Program grantees are far along in the process of bringing new diagnostics, treatments, and devices to use by live patients. Floridians have already tested new strategies and experienced both improved healthcare and health based on the products of Program grants. A number have contributed to surveys that increase our understanding of the nature of Florida's costly tobacco problem and addictive behaviors in general. Highlights include:

- Twenty-three clinical studies have been conducted in Florida involving more than 2000 human research subjects.
- Five survey studies involving more than 200,000 human study subjects have been completed in Florida.
- Twenty patents have been filed by Program grantees that involve a clinical improvement towards better prevention, diagnoses, treatments, and cures.

Support for Different Stages of Research

While clinical studies are extremely important, basic science is the foundation of all new discoveries and treatments for diseases. Basic science builds on the understanding of how things operate at the molecular/cellular level. Results from basic research often lead to useful intermediate applications (translational research) involving testing in animals or human tissue. Such studies, may in turn, enable progress for human use and testing in clinical studies. By design, the Program funds a broad spectrum of research options in order to bring advances and discoveries all the way from the test tube to the patient.

Program grants cover a wide range of research types, from basic inquiry into the dynamics of disease at a cellular level to clinical (human) testing of new drugs (see Figure 1).

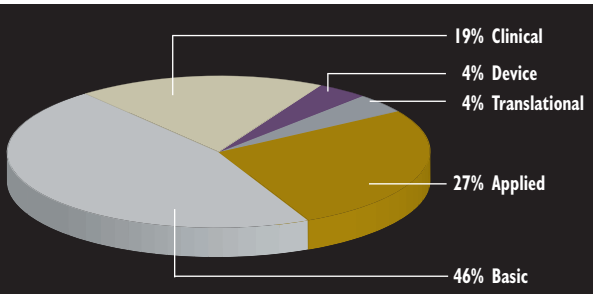


Figure 1 - Grants by Research Stages

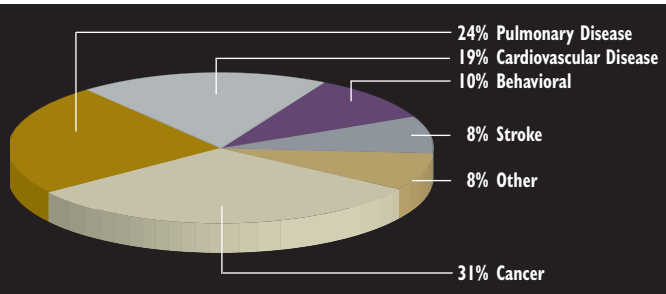


Figure 2 – Breakdown of King Funding by Topic Area

Projects also include behaviorial research as well as business partnerships aimed at commercialization.

Attention to Primary Tobacco-Related Diseases

While the Program considers any illness with a strong association to tobacco, the majority of award funds focused on the disease areas of pulmonary disease, cancer, and cardiovascular disease. In addition, smoking behavior and the dynamics of addiction are funded as shown in Figure 2.

Support for New and Seasoned Investigators, Individuals and Teams

New investigators comprise 58 percent of the grant funding to date; the remaining 42 percent of funds sponsored grants for experienced investigators. Researchers encompass physicians, surgical oncologists, medical school professors, cancer center researchers, basic research scientists, social scientists, physical therapists, synthetic chemists, and biomedical engineers to name a few. A multidisciplinary approach is necessary to discover, synthesize, and test new treatments successfully.

Strong Emphasis on Disease Treatment and Cure

While the Program funds work involving prevention, diagnosis, and treatment and cure, the prevention and diagnosis categories are usually a smaller portion than treatment and cure. Prevention usually involves behavioral research and supports investigators seeking to inhibit the onset of disease. Until we understand a disease, it is difficult to develop methods of prevention. Diagnosis usually involves devices or instruments for improved, earlier disease detection. Treatment and cure is a broad category that encompasses work from basic science to clinical trials. These two are combined because it can be difficult to determine if a disease has been cured.

"People cannot foresee the future well enough to predict what's going to develop from basic research. If we only did applied research, we would still be making better spears."

- Dr. George Smoot, Berkeley National Laboratory

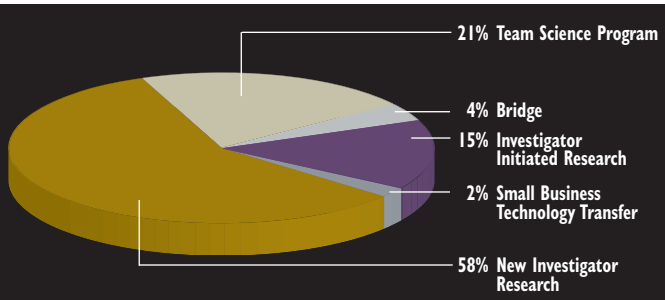


Figure 3 - Funding by Grant Mechanism

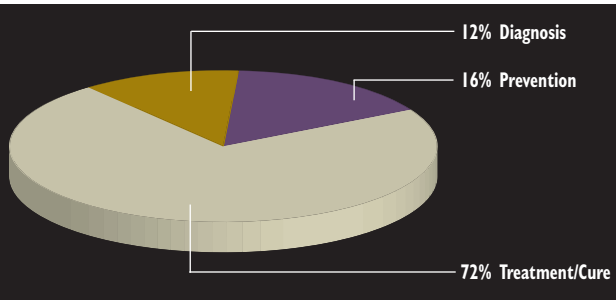


Figure 4 - Grants by Research Goals

The following examples demonstrate new methods, techniques, and information touching the lives of Floridians with support from the Program.

Dr. Rosanna Forteza, 2001 Investigator-Initiated Research and 2007 Bridge Grant recipient, University of Miami, has spent 18 years studying chronic bronchitis and airway inflammation. Cigarette smoke causes greatly increased phlegm production, which can lead to chronic bronchitis. Dr. Forteza's group identified a way to stop mucus overproduction, a major symptom of smoking-induced chronic bronchitis. She is currently developing an inhaler for human use that could work for asthmatics as well. Dr. Forteza explains that both findings will mean better treatment strategies for patients, fewer emergencies for them, and thus lower healthcare costs. University of California Davis, Cleveland Clinic, University of North Carolina, and Oxford University, England, are a few of the institutions drawing on the expertise of the Forteza team with invitations for training, lectures, and collaborations.

"The James and Esther King grants were key to my chronic bronchitis study. Without them, I wouldn't have been able to generate preliminary data or hire people to work."

Dr. Johathan Li, 2006 Small Business Technology Transfer Grant recipient, University of Florida (UF), is testing a new method of calculating radiation dose in lung cancer using magnetic resonance imaging (MRI). This technology, developed by former Program grantee, James Dempsey, allows for real time, simultaneous MRI imaging and radiation delivery. Because the lung moves more than any other organ, it has been difficult to know if tumors actually receive the right dose. MRI images obtained during radiation delivery tell clinicians where the dose is actually going. Of 70 Florida patients tested by Dr. Li, measurements have proven accurate except in patients with emphysema, which required the additional assignment of density to the emphysemic lung.

"This grant support is important because it could lead to significantly improved outcomes for lung cancer patients," explained Russell Donda, CEO of ViewRay, the small business collaborating with Dr. Li to develop the technology.

Dr. Kathy E. Light, 2001 Investigator Initiated Research Grant recipient, University of Florida, received a King grant to study movement therapy for stroke patients to help improve motor function. Her work led to an important clinical trial known as the EXCITE study (Extremity Constraint Induced Therapy Evaluation). According to a 2006 article in the Journal of the American Medical Association, this trial has opened new avenues for clinical care, stroke recovery, rehabilitation and research, which is extremely significant for stroke survivors who hope to recover from brain injury.[5] Her findings have since been tested all over the world and have shown that the therapy continues to help stroke patients improve, even two years after their stroke. In 2008, an article in an Australia journal reported: The EXCITE trial has renewed the hope for stroke survivors and moved the research of stroke rehabilitation into the area of evidence based treatments.[6] Dr. Light continues to be funded by NIH for her work on Constraint-Induced Therapy.

Dr. David Lee and Co-Project Director, **Dr. Lora Fleming**, 2006 Team Science Program Grant recipients, University of Miami, study the relationship between smoking behavior and cancer prevalence. Their data provides a foundational guide for tobacco education and public health policy in Florida by demonstrating:

- contributing factors for cigarette smoking among Florida's youth
- tobacco-associated cancer clusters in Florida and the communities in greatest need for interventions
- an association between socioeconomic status and late stage breast cancer
- an association between socioeconomic status, community smoking rates, and esophageal cancer clusters in Florida

"The Biomedical Research Program funding is enabling us to generate many new and interesting research ideas, as well as interventions to reduce the risk of tobacco-related diseases. Since Florida is a low tobacco tax State and therefore a high tobacco use State, I hope that these research findings will call attention to this important Florida public health issue."

New Survivorship Strategy Improves Health for Head and Neck Cancer Patients

Today more patients are surviving head and neck cancer after treatment at UF than five years ago. More patients are swallowing and eating after radiation and managing the searing effects on their throats without resorting to stomach tube feeding. More patients are avoiding pneumonia because they can swallow properly using their throats and thus prevent food or liquid slipping down an airway.

What has made the difference? In 2001, Dr. Michael Crary and Dr. Giselle Mann started work on a King grant to study a patient intervention that would help head and neck cancer patients keep swallowing in the days and weeks following their radiation treatments.

Giselle Mann, Ph.D. & Michael Crary, Ph.D.
2001 Investigator Initiated Research Grant
University of Florida

Dr. Mann explained: "Many patients were not coming for help with their difficulties in swallowing until three months following medical treatment for head/neck cancer. By then, they were in extreme distress. Some could not swallow their saliva."

Although the cancer in these patients was under control, they were not successful in terms of quality of life and survival. Chemo-radiotherapy can cause swelling, inflammation, and nerve damage, making swallowing extremely painful. Without intervention, some people stop swallowing, relying on feeding tubes instead. Their swallowing mechanisms become even weaker with disuse.

"We decided to start their intervention and education earlier in the process. Patients were not aware of any preventive strategies they could use to maintain their ability to eat throughout treatment and into survivorship. We developed a set of simple swallowing exercises to keep their muscles active and strong and started treatment at tumor diagnosis."

"The King grant was the catalyst launching this work. It gave us specific data from our facility to support our theory that we could keep this mechanism active and relieve suffering. We found that the intervention made a difference in lean muscle mass at six weeks and that the intervention could maintain itself at six months. The exercises enabled patients to keep swallowing their food. . . . I have dozens of patients' stories."

"This grant allowed our medical physicians, radiation oncologists, and ear/throat/nose surgeons to see the data and understand that we need to change the way we intervene with these patients…Now at our facility, patients are referred at tumor diagnosis for at least an initial assessment by the swallowing team."

"We believe that as healthcare staff, we need to be more active earlier. What started as a small project with a select group of head/neck patients has moved to a rehabilitative strategy to effect the treatment of all cancer patients who are coming for cancer treatment at our center."

"In addition to helping head/neck patients, what the King grant has begun at UF is a change in the model of care. Although it sounds like common sense, early patient intervention is not something that is routinely done in any cancer center across America."

Undoubtedly, this work has the potential to affect the standard of care nationwide. Already the Crary/Mann King grant has led directly to a follow-up treatment-dose response grant from the American Cancer Society for approximately $800,000. This four-year study will help refine their treatment package and is currently underway (the team has recruited more than half of the 130 necessary patients).

Additionally, this team received an internal grant from UF to assess how to alter cancer services to an earlier intervention and prevention rehabilitation model. This research involves a wide range of healthcare fields such as physical therapy, nutrition therapy, psychology, and speech/language pathology.

The team will continue to incorporate the benefits of a multidisciplinary focus in future research. For example, the team is currently training physicians, nutritionists, and dentists in the public health aspects of this research and would like to test the approach in other centers and extend it to other cancer types to reduce suffering and morbidity.

The Crary/Mann team is not only affecting patient care at UF but is also having an impact worldwide through publications in highly respected academic journals and presentations at national and international conferences.

Expand the Foundation of Biomedical Knowledge

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.

Challenges

The research community considers publications in peer-reviewed journals and presentations the most important measure of research success. Obstacles to disseminating results include:

- New approaches do not always work, and adjustments are part of the scientific process. While proving a theory wrong can represent research success, it is much less common for a journal to accept papers describing these outcomes.
- It is a long, difficult, and sometimes costly process to get papers published in peer-reviewed journals. The process usually requires multiple submissions, is time-consuming, and may require a payment to the journal.

Overall Program Impact

Generating High Impact Publications

Since 2001, Program grantees have published at least 310 peer-reviewed journal articles and book chapters as shown in Figure 5. Appendix B contains the list of publications reported since October 2007 by current and past grantees.

Grantees are required to acknowledge support from the James & Esther King Biomedical Research Program in all publications, adding to the reputation of the Program and Florida's commitment to supporting excellent research.

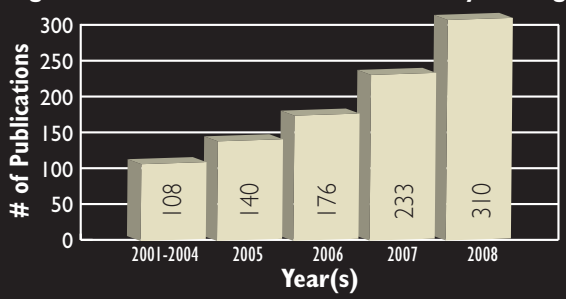
One indication of the quality of publications is the impact factor of the journal. This factor is a measure of how frequently a journal publication is cited by other authors in the scientific literature. A lower impact factor means the articles are not referenced as frequently, or the area is likely highly specialized. For example, the *Magnetic Resonance Quarterly* is considered a highly specialized journal with a lower impact factor due in part to the number of people working in this field. Conversely, publishing in a high-impact factor journal, such as the *Journal of the American Medical Association*, means there are a high number of professionals reading the journal on a regular basis. As imperfect as impact factors are, they have become a standard by which many universities compare their faculty's scientific research.

According to rating categories provided by Journal Citation Reports, 62 percent of the top 1500 journals are considered highly specialized/good. The other 38 percent are considered outstanding/exceptional due to the number of people utilizing and referencing such journals.[7] (See Figure 6.)

King grantees have been successful in getting their results published in highly meritorious journals. In fact, almost half of the 2007-2008 King publications fell into the top 38 percent of ranked journals. Three Program publications ranked in the top three percent of rated journals (See Figure 7).

These numbers mean that King Program research results are being widely disseminated in important journals, are considered to have high impact, and are likely influencing the work of other researchers. As researchers publish findings, they expand the knowledge base for developing better methods of diagnosis, prevention, and treatments for tobacco-related disease.

Figure 5 – Cumulative Publication History of Program Grantees



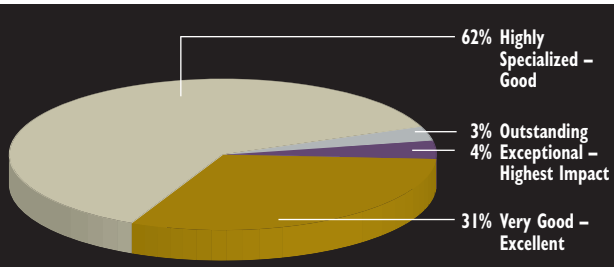


Figure 6 - The Top 1500 Journals Categorized by Impact Factor

Delivering Scientific Presentations

Giving scientific seminars, presentations, and workshops are highly effective ways for researchers to spread their newest findings and to compare results with other scientists. Researchers rely on attending meetings – both highly specialized and more general – to keep current on what is happening in their field and in the scientific community as a whole.

The number of presentations reported by Program grantees on their research has grown each year and has reached a cumulative total of 646.

- 140 were regional and local meetings
- 359 were at national meetings
- 147 were presented at international meetings and universities abroad

Many grantees are invited not only to present their science, but also to chair a scientific session on their field of research. The added prestige that goes with these invitations shows that Program grantees are having a significant impact in their respective fields of science. Figure 8 shows the cumulative history of presentations each year by current and past King grantees.

"Other accomplishments are not those generally reported in scientific journals but are related to . . . learning about grantsmanship. I have learned about management and administration, something that I did not learn as a graduate student or junior faculty member and had never performed as a clinician: things like how to hire the appropriate laboratory staff, coordinating multiple staff members in different roles, payroll decisions and budgeting. Also, dealing with multiple . . . oversight agencies and reporting requirements . . . I am not making these points glibly. Without this new investigator award I would not have acquired these skills that are, to my mind, easily as important as designing and performing experiments."

- Dr. Mark Bishop
2004 New Investigator Research Grant
University of Florida

Providing Mentoring to New Investigators

To date, the Program has funded 80 new investigators, 16 of those in 2008 (by definition, a new investigator has held a full-time faculty position for less than five years and has not served as a principal investigator on a major research project). New investigators face a significant challenge in establishing their credibility in the scientific community. This typically begins with making presentations and getting papers accepted in respected journals that attract attention. Until this happens, it is extremely difficult to compete successfully for national funding.

In addition to the opportunity for first time funding, the Program requires new investigators to recruit a senior researcher to serve as a mentor. Besides fulfilling a research advisory role, mentors review data, manuscripts, and grant proposals; identify appropriate journals, conferences, and funding agencies; and help grantees navigate the submission and revision process.

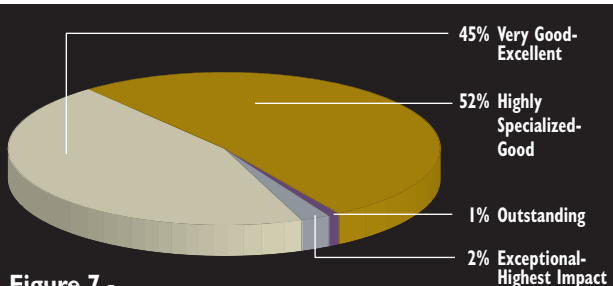
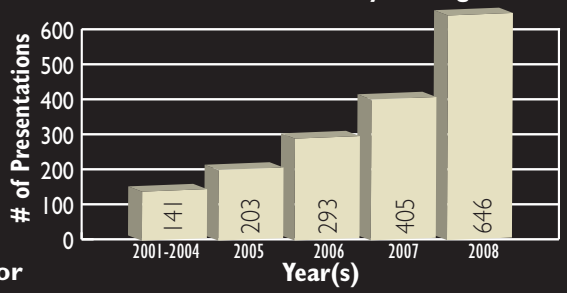


Figure 7 -
The 2007-2008 King Publications Categorized by Impact Factor

Figure 8 – Cumulative Presentation History of Program Grantees



Selected from a number of Program grantees making unique additions to research, the following examples demonstrate the depth and breadth of the contributions grantees are making to the body of biomedical knowledge.

Dr. Mark McLean, 2004 Team Science Program Grant recipient, University of South Florida, has demonstrated how regulation of cholesterol takes place and the role of nicotine and hormones in the process. In addition to expanding the body of knowledge, the grant resulted in a number of ongoing benefits.

"The TSP linked us [together] and provided greater interactions and scientific insights. NIH prefers project experience with multiple principal investigators; the more we can show collaboration, the better chances we have of getting funding. In addition . . . the Program enabled me to generate the preliminary data needed to obtain an NIH grant. . . . The TSP has brought in $5 million in additional research support, yielded 16 publications, and resulted in the training of medical students and interns, post-doctoral students, and graduate students—all still in Florida."

Dr. Ewa Wojcikiewicz, 2006 New Investigator Research Grant recipient, University of Miami, used her King grant to build an atomic force microscope to study how and why lesions form on the lining of blood vessels. Smokers have 200 percent more of these deposits than nonsmokers, and her goal is to design drugs to block lesion formation. This microscope is a sophisticated imaging tool that measures the force or strength of the interaction between cells. In her study, it is helping explain when and how cells bind to the blood vessel wall and start to build up. Dr. Wojcikiewicz's expertise with the instrument has led to other tobacco-related collaborations including a breast cancer project, numerous publications, and international presentations. She authored the chapter on atomic force microscopy in *The Wiley Encyclopedia of Medical Devices and Instrumentation.*

Dr. Grace Zhai, 2007 New Investigator Research Grant recipient, University of Miami, studies damage to the retina caused by tobacco smoke. Smoking accelerates macular degeneration, a leading cause of blindness. When Zhai relocated to Florida (due in part to the King Program), she established a new type of lab in South Florida.

"This new lab . . . creates a research environment stimulating other studies using the drosophila [fruit fly] such as genetics, tissue and organ formation, cancer research, and immune response studies. I'm now helping set up the labs of colleagues. King reviewers suggested I study the function of a protein [that protects neurons]. I am now studying how genes regulate it and how to boost production of it. Studying the protective capacity of neurons has enormous potential. I published these results in the journal, Nature, in April 2008. Now people are thinking differently about how we should look at neurons and what we can do to strengthen them."

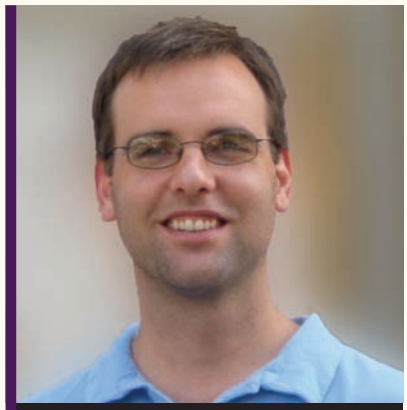
Dr. Roman Manetsch, 2007 New Investigator Research Grant recipient, University of South Florida, is developing a more cost-effective process to identify small molecules displaying anti-cancer activity. This new process reduces the workload and increases the rate of discovery of inhibitory compounds. He also synthesized several molecules that disable a protein necessary to most cancers. These findings were published in one of the world's most prestigious chemistry journals, the *Journal of the American Chemical Society* (September 2008). His work has resulted in two patent filings. Dr. Manetsch credits his biomedical contributions to the mentoring he received in his King grant.

"Mentoring is a crucial component of my grant and helped me gain invaluable training in the field of computational chemistry. My mentor, Dr. Wayne Guida, is one of the world's leaders in the field."

Developing Cutting-Edge Tools for Drug Development

Tremendous technological advances in the drug discovery and development processes offer hope for exciting new medicines. However, promising drugs from natural sources still have to be made or modified. Making new treatments for cancer and other tobacco-related diseases is the work of synthetic organic chemistry and Dr. Gregory Dudley's lab.

According to Dr. Dudley, the National Institutes of Health has identified biosciences' number one obstacle to be organic synthesis of compounds. Why is organic synthesis an obstacle? Most, if not all new cancer therapies are derived from substances found in nature. Biomedical researchers scour the globe in search of the next great drug, but nature is more likely to provide tantalizing clues than concrete solutions. It is up to the synthetic chemists to follow up on the leads that nature provides by making biologically active compounds in the lab. The Program has enabled Dr. Dudley's lab to overcome important obstacles in chemical synthesis, so that cancer-fighting chemicals can one day be made more affordably and reliably, avoiding the destruction of delicate organisms and habitats.



Gregory Dudley, Ph.D.
2005 New Investigator Research Grant
Florida State University

"Natural products are a great starting point for drug discovery, but they are rarely the final solution. We have to optimize and refine natural products to suit our purposes, which requires a thorough knowledge of organic synthesis."

"The challenge in synthesis is to provide on demand the desired molecular structures. In our lab, we take the approach of making a larger-than-needed structure, which we then chip down to make a smaller, more complex structure. For example, it's a lot easier to carve Mt. Rushmore from a mountain that's already there than to build it from scratch."

Part of the chipping process in this analogy is breaking a particular basic chemical structure called carbon-carbon (C-C) bonds.

"Breaking C-C bonds was a limitation for us, so we developed a new reaction for breaking them. We've published papers, tested our techniques in many molecules, and actually have become experts in this area. We can now make unique contributions because of this skill. Having this tool in our toolbox gives us a valuable starting point for making other cancer drugs."

For example, a very important compound for cancer research, palmerolide, was recently discovered at the South Pole. It is extremely toxic against melanoma and does not appear to harm other cells. "We can probably make it in ways other labs can't because of our C-C cleavage reaction."

Dr. Dudley attributes his current research direction and new funding to the Program. "The James & Esther King Program allowed me to get a foothold and establish my research." Dr. Dudley has quickly transferred his knowledge into mentoring students—31 so far.

"Currently, I have 13 in my lab, and I've trained nine undergraduates, three graduate students, and six post-doctoral students as well." Students trained by Dr. Dudley have gone on to work for drug companies, universities, or are completing graduate work in organic synthesis.

The work has certainly gone in a good direction for this lab. Dr. Dudley has two patent applications and two invention disclosures. Additionally, they just received their first prestigious federal grant from the National Science Foundation (NSF) for $0.3 million, and they have another proposal submitted to the NIH.

"The King Program is flexible, which is good for young investigators. Once we got started, the work took unexpected turns. The Program helped me revise my aims and budget and move forward. I think I will be able to do more now than I could have with [my] original plans. They allowed my lab to see just where this work could take us."

Improve the Quality of Florida's Academic Health Centers

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

Challenges

- The environments in which academic scientists and healthcare providers work, including physicians, are typically very different, and do not normally provide natural interaction: they work in separate areas, read different literature, and attend different conferences.
- Community physicians have little or no formal training in conducting research.
- Even if a community physician wants to participate in research projects, heavy patient schedules are often prohibitive.

Overall Program Impact

Supporting Physician-Scientists in Research

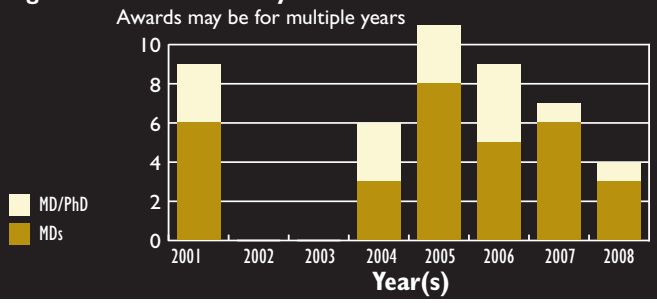
Since 2001, the Program has funded 31 principal investigators with M.D. degrees and 16 with M.D. and Ph.D. degrees out of at total of 173 funded principal investigators. (See Figure 9). Usually these researchers are physicians who have pursued additional training in any of a number of scientific disciplines, including basic laboratory research techniques, translational studies using experimental animals, and planning and conducting human clinical trials. Due to their focus on patient care, these researchers bring a unique approach to science because most researchers and their institutions are primarily focused on laboratory (basic) research. Many have extensive patient contact, which allows them to see where medical care needs innovation and which patients it would benefit most. The Program grants provide them with "protected time," away from the clinic, to do research and to train and mentor other young physician scientists.

As illustrated in Figure 10, physician scientists have participated in every award type offered by the Program. However, most have been participants on collaborative teams, and many have relied on Program support to begin an independent research career.

"If it wasn't for a grant from the Program, I would not have been able to invent new therapies for treating cancer. The King grant empowered me with protected research time and covered my laboratory's expenses as we unlocked the secrets of how bone marrow contributes to blood vessels in cancer. From this discovery, we have created new treatment regimens for patients suffering from cancer. In the end, my cancer patients benefit, and Florida's biotechnology industry benefits."

- Dr. Christopher Cogle
2005 New Investigator Research Grant
University of Florida

Figure 9 - Number of Physician Scientists Awarded Grants



Teaching Medical Students and Healthcare Providers

Program grantees include many scientists (Ph.D.) and physicians (M.D. or M.D./Ph.D.) who spend a lot of time giving back to their institutions by teaching the next generation of students. They pass on their extensive knowledge by giving lectures, mentoring students, teaching clinical skills and helping plan what subject matter is covered in coursework and in clinics. They do this for many kinds of students and many different types of health care providers. The following is a list of the many forms of teaching reported by King grantees.

Fellowship programs to train medical doctors (interns, residents, and fellows)
- Clinical research mentorship
- Diagnosis and treatment of diseases
- Introductory courses in research methods

Post-Doctoral Fellows
- Research supervision
- Mentoring to foster independent researchers

Graduate & Undergraduate students
- Guiding research projects
- Teaching: Neurosciences, Developmental Biology, Pharmacology, Cell Biology, Genetics, etc.
- Medical Scientist Training Program (This program encourages and supports the training of outstanding students who desire to pursue careers in both biomedical research and academic medicine).

Medical school students
- Basic medical knowledge
- Clinical skills; physical exam skills

Nursing programs and advancement programs for nurse practitioners
- Patient care improvements
- Treating side effects of medication
- Basic and applied science lectures

Curriculum Committee for teaching graduate and medical training

Public awareness through popular media, including newspapers, T.V. and radio
- Cancer information, research, diagnosis, therapy, end of life, and life-death issues
- Patient education and cancer prevention
- Youth education on drug addiction and medical topics like breast cancer, lung cancer and smoking prevention/ cessation

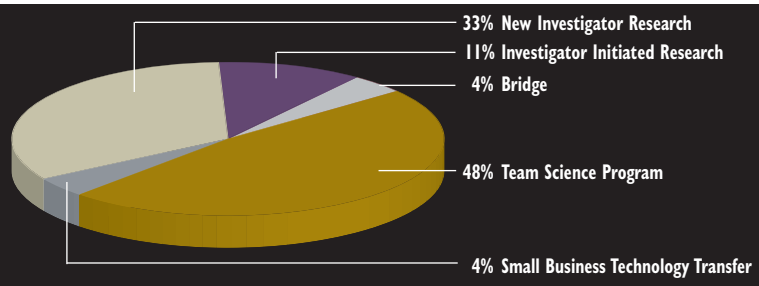


Figure 10 - Types of Grants Awarded to Physician Scientists

In addition to the composite picture of training by King grantees, the following examples show how cutting-edge medical advances are reaching Florida's physicians and healthcare providers.

Dr. Mark Bishop, 2004 New Investigator Research Grant recipient, University of Florida, is a physical therapist who studies the connection between tobacco use and self-perceived physical function and balance in older adults. He published some of the findings from his King project in the *Journal of Rehabilitation Research & Development.* In addition, he has drawn on this work to provide insight for a broad range of healthcare providers, making presentations to:

- The American Physical Therapy Association (2004, 2007, 2008)
- The American Geriatric Society (2008)
- The International Conference on Aging, Disability, and Independence (2008)

Dr. Bishop is continuing his research and training colleagues in the physical therapy field today with the help of a grant from the Brooks Rehabilitation Research Center based on his King Program Research.

Dr. Stephen Grobmyer, 2006 New Investigator Research Grant recipient, University of Florida and a surgical oncologist at Shands Cancer Center, leads a multidisciplinary team from Surgery, Biomedical Engineering, and the Particle Research Center working to develop a nanoparticle for early detection and improved treatment of tobacco-related cancer. Dr. Grobmyer has published and presented his findings to physicians and researchers, obtained two additional grants from the University of Florida and the American Cancer Society, and has begun a collaboration with another physician scientist, Brad Fletcher M.D., Ph.D., from the University of Florida's Pharmacology Department, to study nanoparticle treatment of tumors.

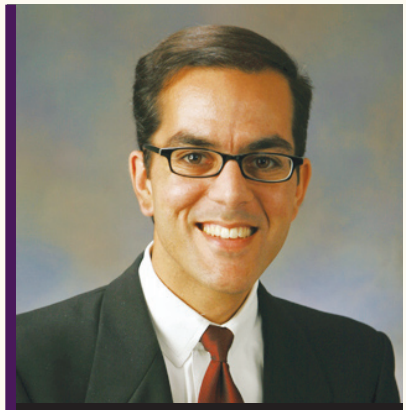
"The Program is entirely responsible for this unique collaboration that has produced a common team vision . . . and a number of new, related projects stimulated through group discussions. Without the grant, we were struggling to get ideas off the ground . . . We have now filed a patent application. We 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."

Dr. Alan Fields, **Dr. Michael Wallace**, **Dr. E. Aubrey Thompson**, and **Dr. Derek Radisky** of Mayo Clinic College of Medicine received a 2006 Team Science Program Grant focused on lung cancer. Dr. Wallace, Director of Research for the Department of Medicine, developed a minimally invasive technique to detect lung cancer and clinically tested the method using this grant. The results showed nearly perfect detection of lymph nodes with metastatic lung cancer. In 2008, his findings were published in the *Journal of the American Medical Association (JAMA)*.[8] Publication in the *JAMA*, the most circulated medical journal worldwide, means that approximately 300,000 physicians and 18,000 medical students will be exposed to this advancement.[9] Physicians at all three Mayo Clinic sites are now being trained in this technique. Additional team discoveries have resulted in 11 publications and 14 national and international presentations.

Dr. Fields, the Project Director on the grant, reports: *"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 therapeutic agent has been identified that is being tested in clinical trials for treatment of lung cancer, which, if effective, will impact how lung cancer patients are treated."*

Training the Next Generation of Physician Scientists

Despite recent gains in diagnosing and treating cancer, disease recurrence remains a formidable challenge. Many patients may achieve a remission in their disease, but relapse and spread often occurs, leading to death. In order to truly eradicate cancer, a better understanding of what makes cancers tick and development of more novel strategies are desperately needed. One particularly intriguing explanation is that cancers coerce the body into supporting its growth with vital blood vessels.



Christopher Cogle, M.D.
2005 New Investigator Research Grant
University of Florida

Dr. Christopher R. Cogle's group discovered that bone marrow cells are tricked into assisting a variety of smoking-related cancers such as lung cancer, melanoma, pancreatic cancer, and lymphomas by secreting substances that promote blood vessel growth in the tumors. With his King grant, he discovered the mechanism cancer cells use is dependent on the chemical messenger, stromal cell derived factor 1 (SDF-1). Moreover, he discovered that by blocking SDF-1, blood vessel production in tumors was diminished, resulting in a slower cancer growth. Dr. Cogle has filed a patent to administer anti-SDF-1 in the treatment of cancer and has begun discussions with the FDA.

As a result, the Leukemia & Lymphoma Society awarded Dr. Cogle $600,000 to study this potential new therapy in blood cancers. Likewise, the University of Florida awarded him $96,000 to study cancer resistance in microenvironments where cell regeneration is taking place. Dr. Cogle is also Co-Investigator on two grants from the NIH totaling $1.6 million.

Now, Dr. Cogle is creating his own spin-off company. His group is exploring whether they can deliver the new therapy via an inhaler, so patients will breathe in the medicine, and it can seep into the lung tissues, where it is most needed. He is working with an international firm in Japan to scale up production for possible use in a clinical trial of anti-SDF-1 antibody. Dr. Cogle states that his work is *"tapping the global biomedical market and connecting it to Florida's economy by attracting and hiring bright and productive scientists from worldwide locations to Florida."*

Dr. Cogle firmly believes, as a physician, there is fulfillment in helping patients one at a time; but as a scientist, his research discoveries may help several thousands of patients. For that reason, he is passionate about educating physicians-in-training regarding the potential of research and its importance in medicine. Balancing clinical expertise and research expertise is difficult. Dr. Cogle mentors several physicians-in-training each year to show them how to be successful future physician-scientists.

In the short three years since he received his King grant, Dr. Cogle:

- Conceived, developed, and directed three annual hematology/oncology wet lab programs, which have become a signature training event at the University of Florida, and two annual University of Florida Myelodysplastic Syndromes Seminars
- Received an appointment as member of the Florida Medical Association's Council on Medical Education & Science
- Directed a graduate course in Advanced Stem Cell Biology and mentored fourteen physicians-in-training and six graduate and undergraduate students (last two years)

"The King grant allowed me to have twice as many mentees as I might have had otherwise and gave me the protected time to allow meaningful interactions with trainees. I could fully mentor trainees, allowing them sufficient training to co-author papers and to decide on their medical and scientific specialties. The King grant has been crucial for me to show my mentees the excitement of having a fulfilling professional life as both a physician and a researcher."

Increase Florida's Per Capita Funding for Research

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.

Challenges

- Between 1998 and 2004, Florida fell from 18th to 33rd in the nation in per capita federal research and development funding, according to a 2008 report by the Milken Institute.[10]
- From 2000 to 2006, Florida's population grew by 13.6 percent, more than twice the national average of 6.4 percent[11] making it difficult to increase per capita research funding at the same rate.
- The annual budget of the NIH, the largest source of federal funds for biomedical research, has leveled off since 2003.[12]
- The number of researchers nationwide submitting federal applications has grown, increasing competition for limited funding. In 2007, the NIH reported that one in ten researchers received funding on their first submission. The national average age of researchers receiving their first major grants has risen to 42 from 34, 38 years ago.[13]

Overall Program Impact

Attracting Additional Funding

The Program's success in obtaining additional funding is due to careful consideration of strategies that focus on:

- Selecting and funding the most promising projects in the state
- Helping new investigators accelerate their entry into the national funding stream and training promising young scientists
- Bridging funding gaps for projects scoring high on initial submissions that have great potential to win an award in a subsequent application
- Building new collaborations with potential for large-scale federal funding and providing training opportunities for young scientists
- Stimulating academic-industry partnerships on early-stage projects with commercial potential

Funding Results

67 grantees have reported146 related additional external awards totaling $90.4 million since the Program's inception in 2001.

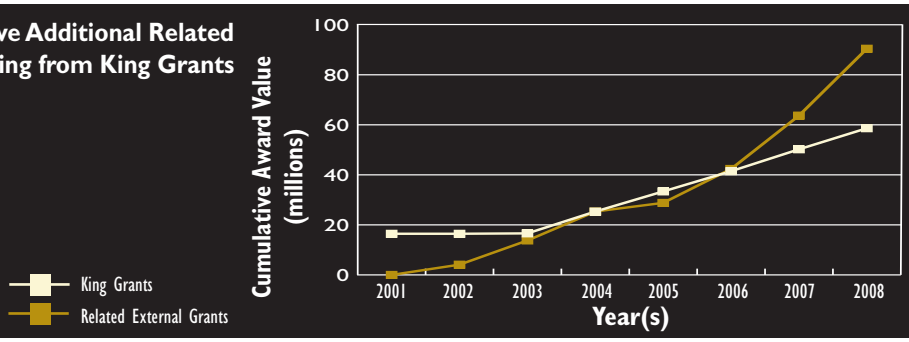
68 percent of all completed King Program grants have reported receiving related external funding, with an average total of $647,636 per grantee.

74 percent of completed New Investigator Research Grants have reported receiving related external funding, with an average total of $577,269 per grantee.

$44.6 million in additional funding was reported by grantees for the past year alone.

Figure 11 illustrates the state's investment in Program grants compared to additional related funding earned by grantees.

Figure 11 – Cumulative Additional Related Funding Stemming from King Grants



Several points are notable:

- The Program dedicates a significant portion of its funding to new investigators; these researchers typically face the greatest challenge in obtaining competitive national funding.
- The data shows an overall lag of two to three years between Program award and significant additional funding, during which time researchers accumulate important data, present findings, and publish their results.
- Sustained state funding for the Program since 2004 began paying dividends by 2006, when cumulative external funding exceeded Florida's total investment; this differential has continued to grow significantly through 2008.

Building Research Capacity

In addition to funding new investigators, the Program provides training opportunities for graduate and post-doctoral students. Since 2004, 137 graduate students and post-doctoral students have worked on grant projects receiving training in new procedures, techniques, and research methods. Such exposure offers students a taste for research in general and often stimulates interest in a particular research topic.

Bridging Gaps in National Funding

With increased competition for federal funding, a significant number of high-quality research projects proposed by Florida investigators are barely missing the funding cutoff. The Program offers Bridge grants to help many of these researchers (typically highly experienced) hold on to their laboratory staff, continue collecting data for time-sensitive studies, and strengthen and resubmit their federal grant applications. From an initial investment in July 2007 of $1.5 million in Bridge grant funds, grantees won an additional $4.7 million in federal funding by July 2008, just one year later.

Supporting Large Collaborative Projects

The Program recognizes that the team approach to science can often generate answers and breakthroughs where a single-minded approach cannot. Thus, between the years 2004-2008, the Program has funded 13 Team Science Program grants with more than $12.5 million total at six different Florida institutions. Including the principal investigator on each TSP, these projects funded 43 investigators studying at least five different scientific areas in tobacco-related diseases as shown in Figure 12.

Thirteen TSP grants have involved at least 198 scientific personnel, from the principal investigator to the post-doctoral fellows, graduate students, and lab technologists.

Although it is still early, these projects have already brought over $12.8 million in additional grant funding to the state, with much more expected in future years. The Program expects TSP grants to foster the kind of collaboration that enables researchers to win the largest NIH grants, known as Program Project Grants. These grants represent synergistic research programs designed to achieve results not attainable by investigators working independently, and single awards may run as high as $12 million.[14]

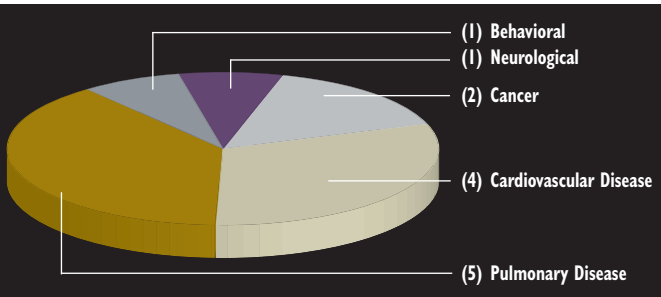


Figure 12 - Team Science Program Grants by Topic Area Addressed

Among many success stories in this category, the following examples show how the Program is helping Florida's investigators attract additional funding from outside Florida.

Dr. Eric Haura, 2001 New Investigator Research Grant recipient, H. Lee Moffitt Cancer Center & Research Institute (Moffitt), began his independent research career in lung cancer with the help of the Program. His work centers on errors in molecular signaling pathways that can cause fundamental changes at a protein or DNA level resulting in lung cancer. Dr. Haura has gone on to win seven follow-on grants from the NIH, the U.S. Army, the American Society of Clinical Oncology, and Bristol Myers Squibb.

"The King grant was huge for me. It gave me time to develop preliminary data and expertise to compete at the national level."

King funding: $400,000. Total additional funding: $5,800,000.

Dr. Mark Alexandrow, 2006 New Investigator Research Grant recipient, H. Lee Moffitt Cancer Center & Research Institute, studies the causes of lung cancer growth. He made groundbreaking discoveries about proteins that alter cell signals and cause out-of-control cancer growth. In 2008, Dr. Alexandrow's preliminary data helped Moffitt win a prestigious five year, $12.5 million Specialized Program of Research Excellence (SPORE) Grant for lung cancer research from the National Cancer Institute (NCI). Dr. Alexandrow is a principal investigator on one of the projects.

"It is not common for junior faculty to be team members on SPORE grants; however, the NCI commented very favorably on my King funding when approving my project, and me as co-principal investigator, as part of this larger award."

King funding: $427,500. Total additional funding: $1,544,750.

Dr. Karl Magleby, 2001 Investigator Initiated Research Grant recipient, University of Miami, focuses his research on understanding the key proteins involved in regulating blood pressure. (Smoking raises blood pressure, and it increases the risk of cardiovascular diseases.) Since 2003, he has been continuously funded with four additional related grants from the NIH, the Muscular Dystrophy Association, and Electronic Biosciences. His latest award from the NIH will support his research through 2013.

"These grants were awarded based on my original King grant work and the research progress that started with that grant. It takes a long time to develop new ideas to the point of NIH funding, which the Program made possible."

King funding: $203,390. Total additional funding: $4,000,000.

Dr. Kendall Morris, 2001 Investigator Initiated Research Grant recipient, University of South Florida, investigates neurons in the brain during low-oxygen episodes. A better understanding of this physiology can lead to improved treatments for diseases such as Sudden Infant Death Syndrome (SIDS) and sleep apnea, both of which are tobacco-related. Perinatal tobacco exposure is the single greatest risk factor for SIDS. Dr. Morris and his colleagues have since received three NIH grants related to this work.

"The King grant allowed us to study formerly unknown properties of a poorly understood area of respiratory and cardiovascular control, while significantly augmenting the infrastructure of our laboratory for future similar studies."

King funding: $190,800. Total additional funding: $6,200,000.

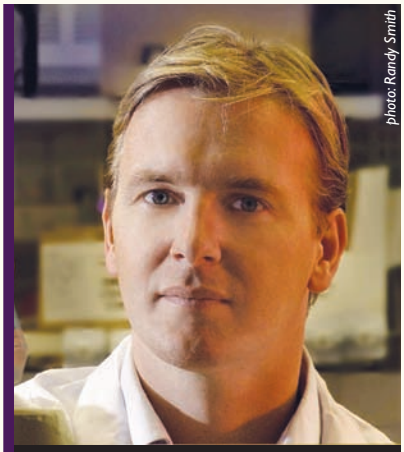
Understanding Nicotine Addiction in the Brain

In an era of tight funding when new investigators struggle repeatedly to get their first federal grant, Dr. Paul Kenny's lab just received their fourth federal grant in the past 18 months. The most recent related grant is a five-year, $2.1 million grant from the National Institute on Drug Abuse.

Prior to 2007, Dr. Kenny had no federal grants and qualified for a New Investigator Research Grant through the Program.

"Two of the federal grants I received are related to the work that's ongoing in the Program. There's no way those two applications would have been funded without the expertise and techniques we developed as part of the King Grant."

"One of the grants is very related to the Program-funded project, the other is fairly distal, but we use the same techniques that the Program led us to develop. I'm incredibly grateful to the Program."



Paul Kenny, Ph.D.
2007 New Investigator Research Grant
The Scripps Research Institute

Dr. Kenny's work focuses on the neurobiology of addiction. "What do addictive drugs do to the brain to make an individual a compulsive drug user? Nicotine is my primary focus as I study why smokers persist in a habit that can give rise to such devastating health problems. We're looking at which sites and regions in the brain are important for nicotine addiction and how nicotine acts in those sites."

Dr. Kenny is using a multidisciplinary approach to determine which locations in the brain are affected by nicotine and the molecular pathways through which nicotine and other addictive drugs may act. This information can be used to design better drugs to control the actions of nicotine, thus helping people break the smoking habit.

"Since coming to Florida, I've established gene transfer work in the lab. It is a really powerful approach. I had never done it before, but the King Program took a chance on me being able to do it. It has worked wonderfully. We have the [gene transfer] technique really well established. We have gotten good data using the technique, which is essential for competitive NIH grants. The King grant has also allowed us to establish a number of new procedures, including intracranial brain surgical procedures, primary tissue culture from the brain, and a number of immunochemistry techniques."

"So the grant's really been a catalyst for the type of work we're doing. Without it, I'm certain we wouldn't have made the type of progress we have."

Dr. Kenny explained one of his areas of exploration in a new field of biology working with very small pieces of genetic material called microRNAs. Unlike other RNAs, these microRNAs do not make new proteins, but instead regulate the synthesis of other proteins. Dr. Kenny's lab has found that microRNAs are disrupted in the brains of addicts, and is investigating the role that they may play in addiction.

Dr. Kenny noted the progress enabled by his mentor, Dr. Pat Griffin. "He suggests routes to explore, and I get his insight and expertise on a regular basis. He points me in new directions I would not have considered myself, and it has been a real help. Pat's input is always valuable and insightful."

Dr. Paul Kenny was recently selected as a "World Changer" —a high-impact leader who is making a difference in Florida and beyond—by *Florida Trend* magazine. Dr. Kenny was praised for his research to understand the mechanisms of addiction and lessen its burden. He was also recognized for the number of young investigator awards he's won.

Stimulate Economic Activity in Florida

Stimulate economic activity in the state in areas related to biomedical research including the research and production of pharmaceuticals, biotechnology, and medical devices.

Challenges

- The skills required to develop new tools and techniques are not the same as those needed to successfully commercialize them.
- There are few natural links between academic researchers and private industry.
- Successful commercialization of new technology is labor intensive, requiring time to develop, test, and modify—making it an expensive process.

Overall Program Impact

Encouraging Commercial Partnerships

To specifically encourage business partnerships leading to commercialization of technology, the Program has awarded $933,988 for 11 SBTT grants since 2003. Five of the eight completed SBTT grants have been successful in moving technology into the commercial marketplace:

- Five active, thriving new companies
- $11.84 million in additional funding
- At least 45 new Florida jobs, including research and development, engineering, scientific management, and assembly

Other Program-sponsored research has also resulted in the formation of new businesses, business partnerships, spillovers from university research to private-sector research and development, and stimulated private investment in Florida companies.

"Florida lags the nation in technology, information, and life-science jobs. The 'high-paying jobs deficiency' exposes a weakness in Florida's position in an otherwise healthy economy and may dampen the state's long-term growth prospects. Jobs in the sciences are rapidly growing on a national level. This sector is proven to create high-paying, high-value-added jobs in major U.S. metropolitan areas. The sector's contribution goes beyond simply improving the state's job quality, however. Its reliance on R&D, an educated work force and high capital investment can transform the state's technology base and aid long-term economic development. Breakthrough developments stemming from this sector translate into treatments and cures that are capable of reaching out to a global platform."

- Excerpt from the Milken Institute report, "Economic Benefits of Proposed University of Central Florida College of Medicine," March 12, 2006

Creation of Intellectual Property

Intellectual property is critical because of the vital role patents and inventions play in the growth of today's knowledge-based economy. Since 2001, King grants have produced:

- 31 patents filed
- 3 patents issued
- 16 patents/inventions planned or disclosed

Many of these are forming the basis for early commercial partnerships with life science entrepreneurs from around the world. For example, Dr. Shyam Mohapatra, University of South Florida, published a significant paper in *Cancer Research*, a prestigious journal. As a result, his research was reviewed and selected by LeadDiscovery, a United Kingdom firm that helps companies optimize drug discovery and product pipelines. The company highlighted his findings as a new major target for cancers.

Dr. Terace Fletcher, 2004 New Investigator Research Grant recipient, University of Miami, investigates gene instability caused by tobacco products. She credits the Program for her move to Florida and for a new grant award.

"The Program is a lifesaver for young investigators. I turned down a larger start-up package to come to Florida for this grant program…The funding climate has steadily been getting worse for basic researchers. The funding mechanism is a great way to recruit talented investigators to Florida and keep them active while many of their colleagues in other universities drop out."

She attributes her recent three-year grant award from the American Heart Association for $200,000 to the data and experience from her King Grant.

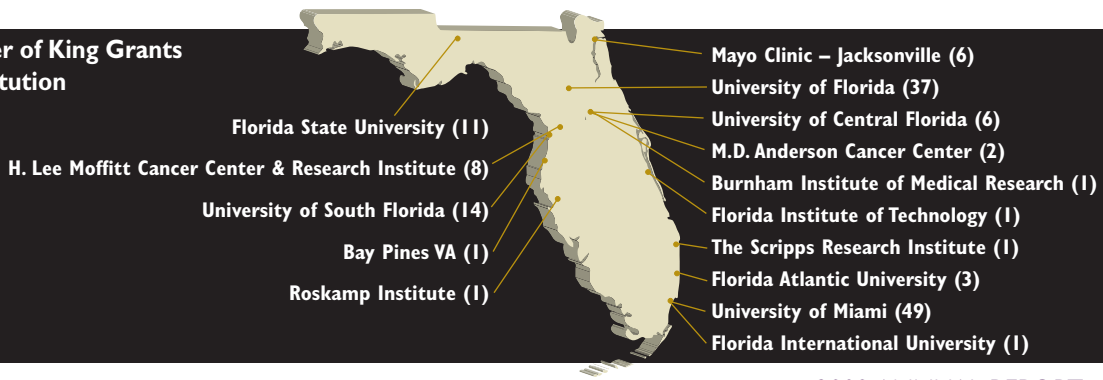
More High-Paying Jobs

An analysis of Program-funded projects shows that approximately 69 percent of grant budgets were allocated to personnel salaries. The Program has provided employment and partial or full salary support for many scientists, post-doctoral and graduate students, laboratory staff, and health care providers throughout the state (see Figure 13). As these grants have produced $87 million in additional funding, the number of high-paying jobs has multiplied.

A study on the economic impact of research throughout Florida's higher education institutions reported that for every dollar invested by the state, an increase in Gross Regional Product of $10.89 results.[15] This statistic is a measurement of the amount of economic stimulus flowing from the investment in terms of number of jobs created, number of people employed, dollars of economic sales, and generation of taxes that stimulate local and regional economies.

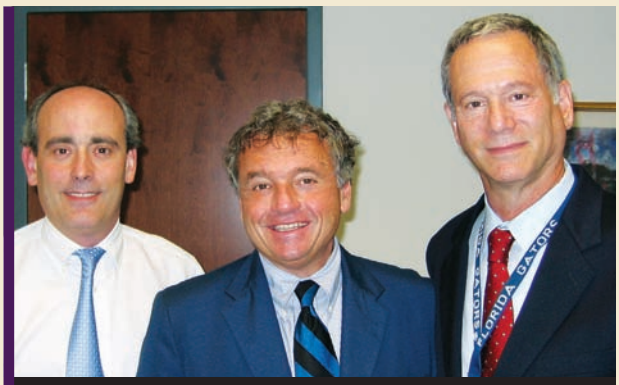
The following profiles illustrate two cases out of many in which the Program grants are helping to stimulate the Florida economy.

Figure 13 – Number of King Grants by Institution



New Instruments for Breath Analysis

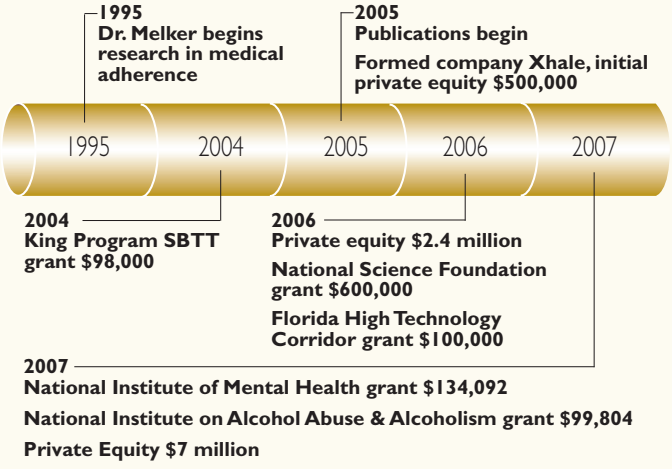
Dr. Richard Melker's project focus was to study detection of environmental tobacco smoke in the breath of children. Inspired by a U.S. Department of Defense project to develop a device that replicates a dog's strong sense of smell to detect landmines, Dr. Melker's team, including Drs. Mark Gold and Bruce Goldberger, researched a device to detect cotinine, a by-product of tobacco, in children with chronic respiratory conditions. Cotinine was difficult to detect, and the Melker team began to ask: Can we detect other things – like medication – in breath?



Richard Melker, Ph.D. (right)
with his team, Drs. Mark Gold and Bruce Goldberger
2004 Small Business Technology Transfer Grant
University of Florida

The following startling evidence from the National Council on Patient Information and Education set their research focus: only 50 percent of all patients in clinical trials ever take the medication being tested, and only 50 percent of patients take their medications as prescribed. If the team could monitor drug adherence through breath analysis, their research could improve the quality of data generated during clinical trials and halt unnecessary disease progression. (Inadequate or bad data in clinical trials means there will likely be undesirable side effects once the drug is released, which could later require a recall.)

The team developed a system consisting of a tagged medication that, once ingested, can be measured by blowing into the disposable portion of a testing device, which records and transmits information to a physician or caregiver. The testing device can also remind the patient to take their medications at the appropriate time.



The addition of the compound to tag the medicine, called a taggant, does not change how the active ingredient of the drug works, or how it is absorbed, metabolized, or excreted. Further, it does not affect the manufacture of the drug.

Based on the initial research and seed funding from the Program and funds from the University of Florida Opportunity Fund, the Melker team started Xhale, Inc. in 2005. Since that time, the Melker team has raised $10 million in private equity and has received a Florida High Technology Corridor grant, one National Science Foundation grant, and two NIH Small Business Innovation Research grants. They have met strong success in developing devices that sample exhaled breath and analyze the breath sample for a particular target substance. Based on what they have learned from these successes, they believe they can now develop a device to detect cotinine and they will be researching cotinine detection again soon.

Four years after the conclusion of the King grant, Xhale consists of 15 employees and has 20 patents pending that exploit the use of exhaled breath as a novel method for diagnosing, detecting, and measuring various compounds. The applications are broad, ranging from detecting patient compliance in taking medication to the use of illicit substances. Product lines under development include:

- SMART™ Breath-based Medication Adherence Monitor- Measures drug compliance of patients including those enrolled in clinical trials and disease management programs.
- SMART™ Drugs - Consist of re-engineered formulations of existing pharmaceuticals (generic and patented), and when used with the company's SMART Monitors will "self-report" patient adherence, metabolism in the body, and drug concentration in the blood.
- Breath-Based Diagnostic Devices (over-the-counter) - Analyze breath for glucose concentration as an alternative to finger stick devices for patients with diabetes.
- Anesthesia Monitoring - Monitors and maintains set blood levels of IV-anesthetic agents based on exhaled breath in intensive care, operating room, and outpatient settings.

According to Dr. Melker, "If not for the King grant and [the University of Florida], we never would have been able to get to the point we are now - we are probably one of a handful of researchers in the world who fully understand how to handle condensed breath samples for analysis."

Improving Cancer Detection and Classification

Imagine waiting seven days to find out test results for cancer. Or worse, imagine receiving a misdiagnosis and later discovering cancer.

Dr. Awtar Ganju-Krishan used his King grant funds to address these two common problems with results that have improved cancer diagnosis. For patients experiencing accumulation of fluid in body cavities such as those surrounding the lung or in the belly, doctors send a fluid sample for examination by a pathologist to rule out presence of malignant cells. Using traditional methods, the pathologist examines the sample under a microscope. Given the high volume of samples (37,000 a year in a typical hospital), turnaround time is traditionally a week. A false negative result (meaning cancer exists but is not detected in the fluid) is common. Up to 50 percent of samples fall into this category due to the small number of malignant cells present and the difficulty in differentiating between a tumor and a normal cell.

Awtar Ganju-Krishan, Ph.D.
2005 Small Business Technology Transfer Grant
University of Miami

Dr. Krishan, in conjunction with NPE Systems, Inc., of Pembroke Pines, Florida, developed and tested a laser flow cytometer for cell analysis. The American Cancer Society (Florida Division) and National Aeronautics and Space Administration (NASA) supported this work. With support from the King Program through a Small Business Technology Transfer grant, Dr. Krishan's team modified this basic prototype into a functional unit, adding optical capabilities and a laser to measure cell size and to detect tumor cells in body cavity fluids. As tumor cells have normally larger nuclear size and DNA content, this rapid analytical method can distinguish between normal and tumor cells in body cavity fluids. The use of this instrument could decrease the number of false negatives by 2/3 in body cavity fluids (*Diagnostic Cytopathol*. 34: 528-54, 2006).

These techniques combined with detection of specific diagnostic markers can not only find malignant cells but also suggest their possible origin from other primary sites. The procedure involves staining of the cells from body cavity fluids with an antibody that has been labeled with a fluorescent tag. When the antibody finds a cancer cell, it binds very tightly to it. The instrument uses a laser beam to excite the fluorescent tag. The color of the florescent tag is an indicator of cancer type. The instrument can detect lung, breast, and ovarian cancers, to name a few.

Based on the work he completed in this grant, Dr. Krishan received a Bridge Grant from the Bankhead-Coley Cancer Research Program and a Women's Cancer Association grant to test the modifications using 200 patient samples. Based on positive results, Dr. Krishan's modifications have resulted in:

- A drop in the false negative rate from 42 percent to 14 percent, which means that the instrument is more accurately detecting the presence of cancer than previous methods
- Shortened time for analysis: It's now possible to determine malignancy and identify tumor location in less than a couple of hours
- Instrument certification by the Centers for Disease Control and the Federal Drug Administration
- An advanced and modified version of this instrument sold worldwide by the Beckman Coulter Corporation, a biomedical lab equipment supplier
- Publication of three papers regarding instrument modifications, pending publication of instrument testing results, and another pending grant application
- A private grant and University seed funds of $60,000 for instrument research and development
- Creation of 30 jobs in South Florida by NPE Systems, Inc., and its subcontractor CMSI (Contract Manufacturing Solutions, Inc.) for instrument manufacture. Production has also stimulated local work in optics, metal fabrication, and custom machining as well.

Dr. Krishan, who reviews grants for the NIH Small Business Innovation Research Program, insists there is no other grant type as profitable for the State as ones that promote research leading to commercialization. "What started in Florida is now sold all over the world. …The technology—the commercialization—stays in Florida."

Results of the 2008-2009 Call for Grant Applications

The Program released the *"Call for Grant Applications: Medical, Biological, Behavioral, and Social Scientific Research and Development Fiscal Year for 2008-2009,"* (the Call) on December 15, 2007. Four types of grants began on July 1, 2008: Bridge Grants, New Investigator Research Grants, Small Business Technology Transfer Grants and Team Science Program Grants. The Call is the published document announcing requests for grant applications.

In response to the fiscal year (FY) 2008-2009 Call, the Program received 65 research proposals requesting a total of $24,861,134. Figure 14 provides the breakdown of applications by grant mechanism.

The Program completed the application review and award process in June 2008, and the Council recommended funding 23 research grants totaling $8.4 million, with projects beginning July 1, 2008. This action resulted in an overall proposal-to-award ratio of 35 percent. Table 2 provides a breakdown of requests and awards across the grant mechanisms.

Public and private research institutes throughout Florida are benefiting from these awards. The Program awarded grants to ten Florida research institutions as illustrated in Figure 15. Seven 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.

Figure 16 shows the funds award by grant mechanism. The majority of grant funds were for three-year New Investigator Research Grants followed by two-year Team Science Program Grants.

Grant Mechanism	Applications Received	Applications Awarded	% of Applications Awarded
Bridge Grant	9	3	33%
New Investigator Research	42	16	38%
Team Science Program	9	2	22%
Small Business Technology Transfer	5	2	40%
Total	**65**	**23**	**35%**

Table 2 - 2008-2009 Grant Applications Received/Awarded

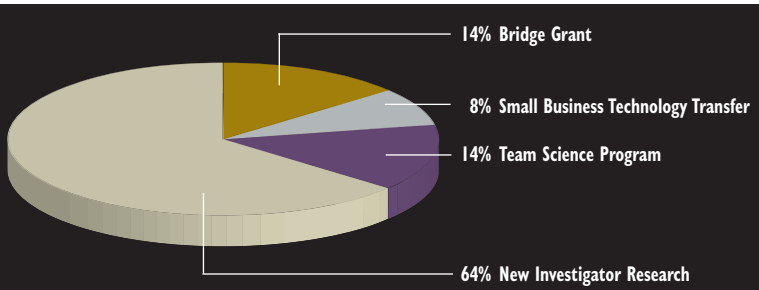


Figure 14 – 2008-2009 Applications Submitted by Grant Mechanism

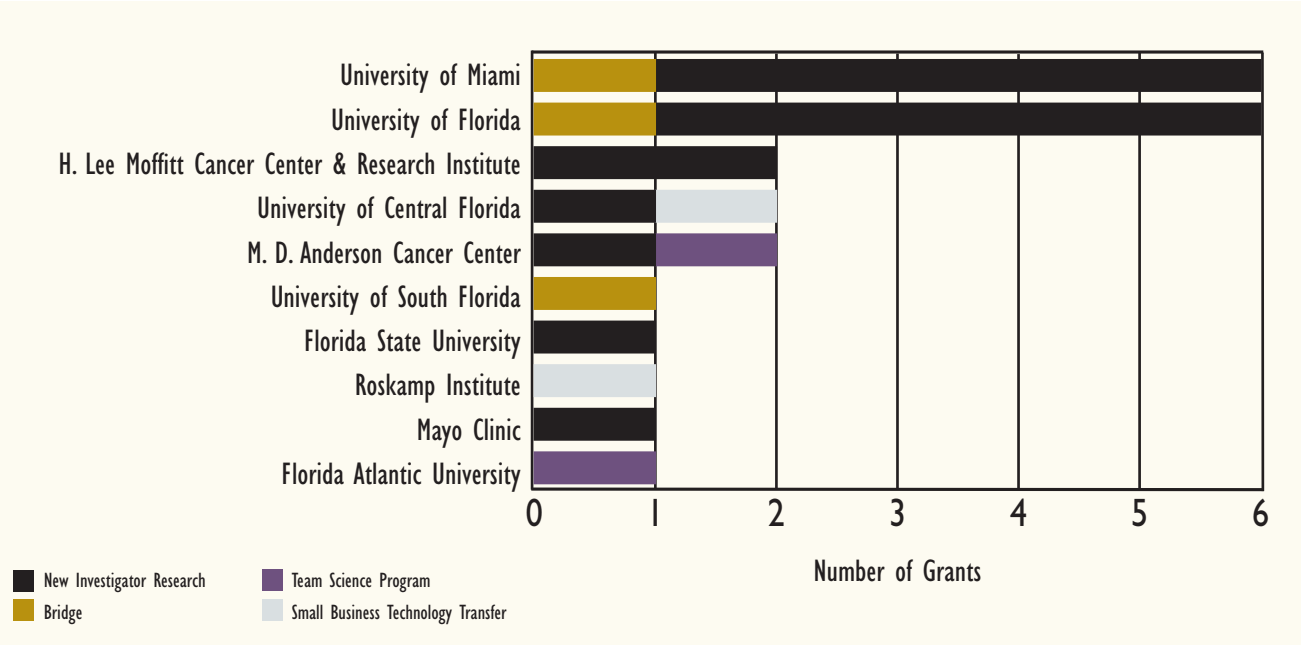


Figure 15 - Number of 2008-2009 Grants Awarded by Institution

Refer to Appendix E for the FY 2008-2009 grantee information including principal investigator, institution, award amount, project title, and abbreviated lay person abstract.

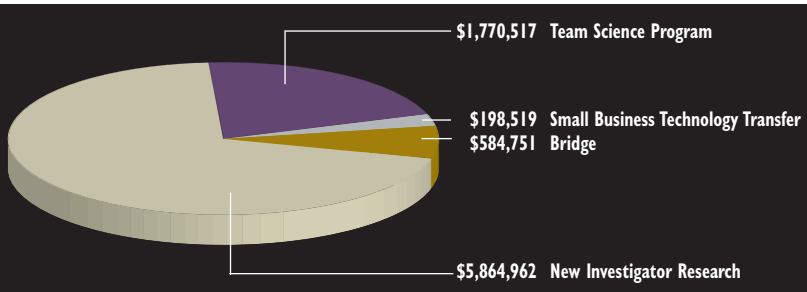


Figure 16 – 2008-2009 Funds Awarded by Grant Mechanism

National Biomedical Research Funding Trends

Over 3,000 research institutions, and tens of thousands of researchers and personnel, depend on external funding from the NIH and other national funding mechanisms to support their scientific work. While the NIH budget doubled between 1998 and 2003, between 2004 and 2006 funding only grew by two percent each year. With current funding levels at 13 percent below 2004 levels (in inflation-adjusted dollars),[16] reductions in funding and limitations on the types of projects that will be selected for funding have made a significant impact on the ability to advance research at a time when healthcare spending is rising at its highest rate in history.

Healthcare spending, which rose at a rate of 6.9 percent in 2007, makes up 16 percent of our economy or approximately $7,000 per person per year.[17]

As evidenced in Figure 17, investment in health research and development has dereased while total health costs continue to rise.

While on average the government invested $44.00[18] per year per capita for research at the NIH, Florida researchers were able to only capture an average of $18.36 for each resident.[19]

Federal budget restraints have clearly had an impact on the competition for federal research dollars and consequently on the way researchers work, laboratories operate, and universities hire.

"The King award was critical to my early success as a young investigator; it would have been more difficult to get my research program up and running without it. Since this award, many other grants on similar and other projects have been funded."

Dr. William Self
2005 New Investigator Research Grant
University of Central Florida

- In 2002 when federal funding levels were on the rise, one in five researchers received federal funding. Today, only one in ten research proposals receive funding.
- The average age of a first grant recipient is over 42 (up from age 34 in 1970); a deterrent for young people considering scientific research as a career.[20]
- Investigators are abandoning innovative, high-risk studies which may be less likely to get funding.

Meanwhile, scientists who received an unprecedented number of grants during the high growth period have been seeking competitive renewals after three to five years of funding. To compensate for lower funding success rates, they are submitting more proposals or having to look elsewhere for funds to keep their laboratories going. Currently state government comprises only seven percent of all national funding sources, making the Program vitally important in helping to grow and maintain the total pool of health research funding available to researchers in the state of Florida.

Florida researchers at 50 organizations classified as domestic higher education, research institutes, independent hospitals, and industry received new awards from the NIH totaling

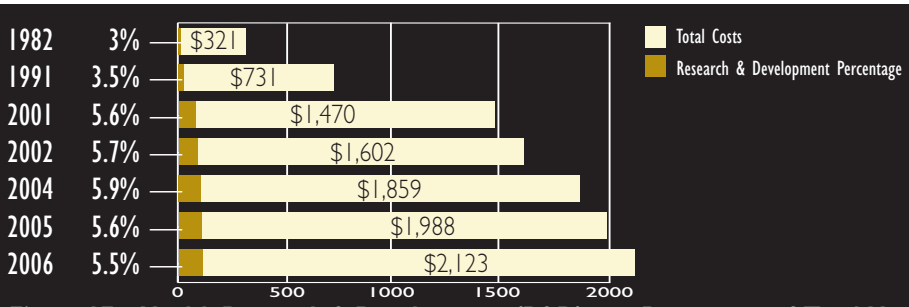


Figure 17 – Health Research & Development (R&D) as a Percentage of Total Health Costs (in billions) [17]

$340 million during FY 2007. As of October, the NIH awards to the state's investigators had reached nearly $336 million during FY 2008. For the third year in a row, this level of funding places Florida 18th among the 50 states in total percent of the NIH funding, while Florida is 4th in population (see Appendix E).

The competition for research funds is further heightened by flat line investments across all sectors, revealing stagnation in every area except for industry (see Figure 18).

In the 2008 State Technology and Science Index Report by the Milken Institute, Florida has dropped in ranking from 29th in 2002 to 37th in 2008 on the composite state technology and science index. This report ranks the 50 states in terms of their technology and science assets and their ability to leverage those resources to achieve economic growth. The index uses 77 indicators in five categories to measure how well a state will perform in a knowledge-based economy.

"Long-term NIH commitments to dedicated research interests are our strongest foundational basis towards significant progress towards the cure of tobacco-related diseases. Funding provided by the Program is absolutely critical towards successful development of new research projects so that they can be competitive for long-term NIH funding. I owe special appreciation to the James & Esther King Program for providing the stimulus necessary to compete and win NIH funding for my project, which is aimed at developing more effective anti-cancer drugs."

Dr. Thomas Harris
2001 New Investigator Research Grant
University of Miami

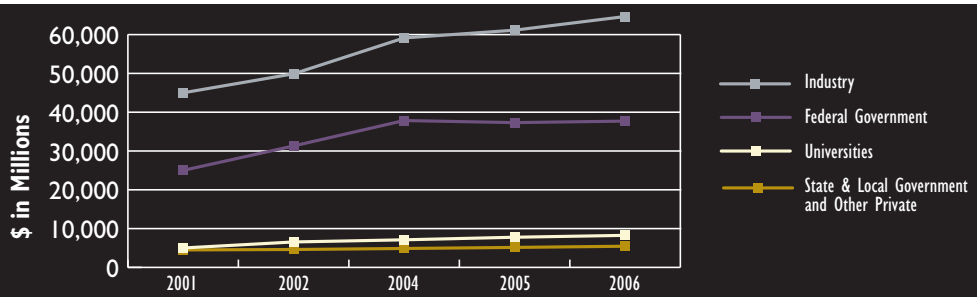


Figure 18 – U.S. Investment in Health R&D[17]

Program Operations

Summary of Program Funding History

Funding for the Program in FY 2008-2009 included $4.84 million in interest earned on the $150 million reserve within the Lawton Chiles Endowment Fund and $6 million from the state's annual appropriations. However, only $9.9 million was available for grants and administrative expenses.

There have been 143 grants awarded since Program inception, representing over $58 million in research funding.

Table 3 below outlines the number of grant applications received and the number, type, and total value of grant awards since 2004.

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.

	FY 2004-05		FY 2005-06		FY 2006-07		FY 2007-08		FY 2008-09	
Applicants	57		44		51		55		65	
Awards	**No.**	**Million**	**No.**	**Million**	**No.**	**Million**	**No.**	**Million**	**No.**	**Million**
Bridge	n/a	n/a	n/a	n/a	n/a	n/a	8	1.58	3	0.58
NIR	13	5.62	11	4.85	12	5.05	14	5.17	16	5.86
SBTT	2	0.20	2	0.20	2	0.19	n/a	n/a	2	0.20
TSP	3	2.91	3	2.99	3	2.85	2	2.00	2	1.77
Total	**18**	**$8.73**	**16**	**$8.04**	**17**	**$8.09**	**24**	**$8.75**	**23**	**$8.41**

Table 3 - Program Award History (numbers are rounded)

Program Administrative Costs

Florida law limits administrative costs to 15 percent of the total appropriation. As the data shown in Table 4 below indicates, Program staff has held administrative costs below the statutory limit, freeing up more dollars for direct research project support.

Program Management

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

Fiscal Year	Appropriation	Grant Awards	Percent	Administrative Expenses	Percent*
FY 08-09	9.90	8.41	84%		
FY 07-08	9.90	8.75	88%	1.13	11%
FY 06-07	9.50	8.09	85%	0.88	9%
FY 05-06	9.37	8.04	86%	0.80	9%
FY 04-05	9.40	8.73	93%	0.68	7%
FY 01-04	17.64	16.45	93%	0.87	5%
Total	**65.71**	**58.47**	**88.8% (avg)**	**4.09**	**7.3% (avg)**

Table 4 - Program Expenditures ($ Million)
*Percent difference equals monies returned to the trust fund

Ensuring Smooth Program Operations

Jointly, the Office of Public Health Research and the Lytmos team fulfill a number of behind-the-scenes responsibilities, providing a seamless interface to support applicants, grantees, and the Council. See Table 5 for key activities that support Program operations.

Table 5 - Program Administration

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

How Grants are Awarded

The Program follows an annual cycle for soliciting applications and making awards, as illustrated in Figure 19 below. In evaluating proposals, the Program draws on the expertise of more than one hundred independent subject matter experts from outside Florida. These scientific peer reviewers evaluate grant applications that match their specific expertise, rating scientific and technical merit and fit with programmatic goals. Unlike other peer review processes in which reviewers consult with each other, these peer reviews are performed independently, with scores compiled after completion. To ensure the validity of this approach, the Program sought and received recognition from the National Cancer Institute as having an approved scientific peer review process.

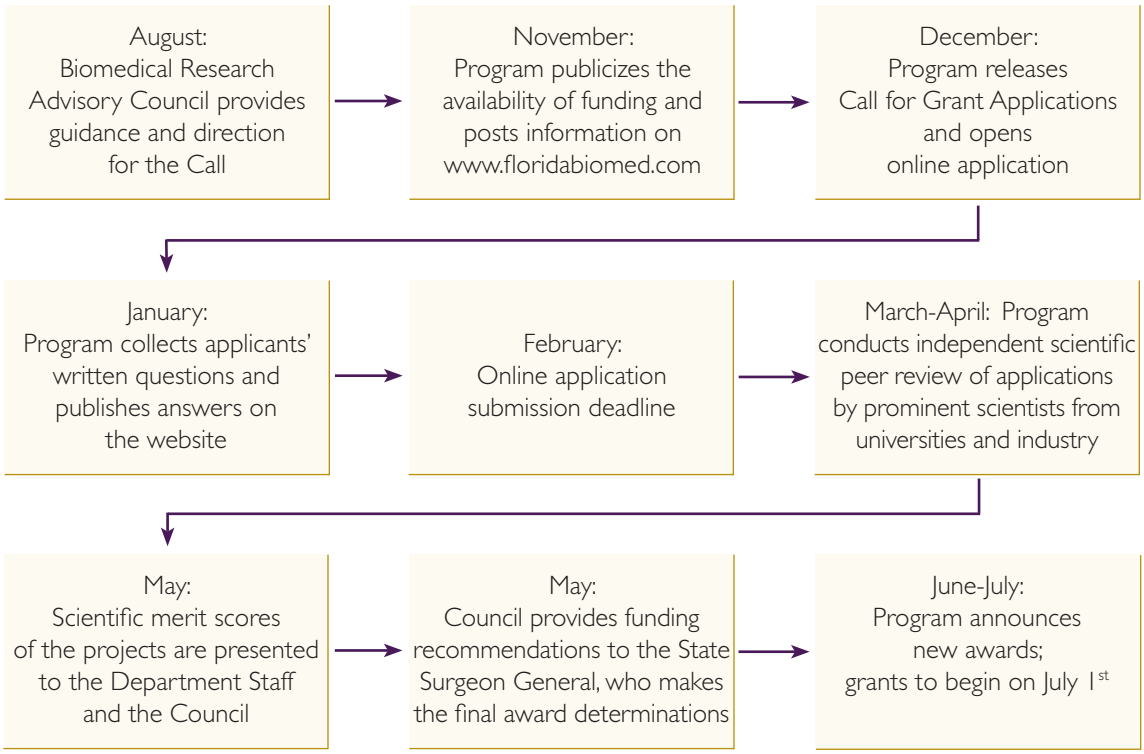


Figure 19 - The Annual Funding Cycle

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

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

How Grants are Managed

The Program uses tools and processes to ensure financial and research accountability, to support grantees, and to maintain compliance with Award terms and conditions, as illustrated in Table 6. Reporting requirements are intended to ensure progress rather than add administrative burden.

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

Table 6 - Grant Management Processes and Tools

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

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

Recommendation for Policy Change

According to s. 381.922(2)(a)(6), *F.S.*, the Program is scheduled to expire January 1, 2011. Based on the Program goals, benefits, and accomplishments evidenced in this Annual Report, the Biomedical Research Advisory Council fully recommends the renewal of the James and Esther King Biomedical Research Program.

Biomedical Research Advisory Council

The Eleven Delegates to the Biomedical Research Advisory Council:

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

Section 215.5602, *F.S.*, charges the Program with awarding grants for tobacco-related research through the King Program (included in Appendix A). The Council meets this directive by advising the Office of Public Health Research at the Department of Health and the Florida State Surgeon General for the direction and scope of the Program and assists in the development of guidelines to ensure fairness, neutrality, and adherence to the principles of merit and quality in the conduct of the Program. The Council also functions in the same role for the 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 State Surgeon General, relying primarily upon the outcome of an independent scientific peer review process.

(above, pictured from left to right)

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

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

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

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

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

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

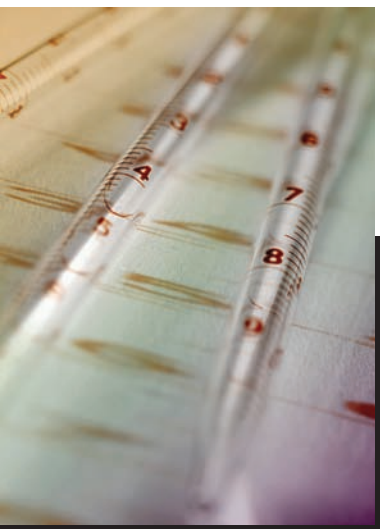
Randal Henderson, M.D. Associate Medical Director of Proton Therapy Institute, Professor/Medical Director, Department of Radiation Oncology, University of Florida. Seat: House – Cancer Program (ACoS). Appointed: 04/20/07

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

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

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

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



Appendix A: *Florida Statutes*

Section 215.5602, 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 B: Grantee Publications

The following list represents new publications in peer-reviewed journals and books reported since October 2007 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.

Campos MA, Alazemi S, Zhang G, Sandhaus RA, Wanner A. Influenza Vaccination in Subjects With Alpha1-Antitrypsin Deficiency. *Chest.* 2008 Jan;133(1):49-55.

Mendes ES, Horvath G, **Campos MA**, Wanner A. Rapid Corticosteroid Effect on Beta(2)-Adrenergic Airway and Airway Vascular Reactivity in Patients with mild Asthma. *J Allergy Clin Immunol.* 2008 Mar;121(3):700-4.

Wanner A, **Campos MA**, Mendes E. Airway Blood Flow Reactivity in Smokers. *Pulm Pharmacol Ther.* 2007;20(2):126-9.

LaGorio L, **Carnaby-Mann GD**, **Crary MA**. Cross system effects of dysphagia treatment on dysphonia: a case report. *Cases J.* 2008 Jul 30;1(1):67.

Monzon ME, Manzanares D, Schmid N, **Casalino-Matsuda SM**, Forteza RM. Hyaluronidase Expression and Activity is Regulated by Pro-Inflammatory Cytokines in Human Airway Epithelial Cells. *Am J Respir Cell Mol Biol.* 2008 Sep;39(3):289-95.

Casalino-Matsuda SM, Monzon ME, Day AJ, and **Forteza RM**. Hyaluronan Fragments and CD44 Mediate Oxidative Stress-Induced MUC5B Up-Regulation on Human Airway Epithelium. *Am J Respir Cell Mol Biol.* 2008 Aug 28 [Epub].

Monzon ME, Manzanares D, Schmid N, **Casalino-Matsuda SM**, **Forteza RM**. Hyaluronidase Expression and Activity is Regulated by Pro-inflammatory Cytokines in Human Airway Epithelial Cells. *Am J Respir Cell Mol Biol.* 2008 Sep;39(3):289-95.

Chen M, **Chen LM**, Lin CY, Chai KX. The epidermal growth factor receptor (EGFR) is proteolytically modified by the matripatase-prostasin serine protease cascade in cultured epithelial cells. *Biochem Biophys Acta.* 2008 May;1783(5):896-903.

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Crary MA, **Mann GD**. Chapter "Rehabilitation after Treatment for Head Neck Cancer" in *Cancer: Principles and Practice of Oncology*. 7th Eds Lippincott Williams & Wilkins Philadelphia PA. 2005.

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Tummatorn J, **Dudley GB**. Ring-opening / fragmentation of dihydropyrones for the synthesis of homopropargyl alcohols. *J Am Chem Soc.* 2008 Apr 16;130(15):5050-1.

Engel DA, Lopez SS, **Dudley GB**. Lewis acid-catalyzed Meyer–Schuster reactions: methodology for the olefination of aldehydes and ketones. *Tetrahedron Lett.* 2008, 64:6988-6996.

Tummatorn J, Albiniak PA, **Dudley GB**. Synthesis of benzyl esters using 2-benzyloxy-1-methylpyridinium triflate. *J Org Chem*. 2007 Nov 9;72(23):8962-4.

Albiniak PA, **Dudley GB**. Thermally generated phenylcarbenium ions: acid-free and self-quenching Friedel–Crafts reactions. *Tetrahedron Lett.* 2007, 48;8097–8100.

Albiniak PA, Amisial SM, **Dudley GB**, Hernandez JP, House SE, Matthews ME, Nwoye EO, Reilly MK, Tlais SF. Stable oxypyridinium triflate (OPT) salts for the synthesis of halobenzyl ethers. *Synth Commun*. 2008;38:656-665.

Yang J, **Dudley GB**. Conjugate addition of organocopper reagents in dichloromethane to unsaturated esters. *Tetrahedron Lett.* 2007, 48;7887–7889.

Kozytska MV, **Dudley GB**. On the intramolecular pyrone Diels-Alder approach to basiliolide B. *Tetrahedron Lett*. 2008;49:2899-2901.

Dudley GB. Engel DA, Ghiviriga I, Lam H, Poon KWC, Singletary JA. Synthesis of dihydro-*epi*deoxyarteannuin B. *Org Lett*. 2007 Jul 19;9(15):2839-42.

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Liang J, Wang J, Azfer A, Song W, Tromp G, Kolattukudy PE, **Fu M**. A novel CCCH-Zinc finger protein family regulates proinflammatory activation of macrophages. *J Biol Chem*. 2008 Mar 7;283(10):6337-46.

Liang J, Song W, Tromp G, Kolattukudy PE, and **Fu M**. Genome-wide survey and expression profiling of CCCH-zinc finger family reveals a functional module in macrophage activation. *PLoS One*. 2008 Aug 6;3(8):e2880.

Gutierrez JC, Hurley J, Housri N, Perez EA, Byrne MM, Koniaris LG. Are Many Community Hospitals Under-Treating Breast Cancer? Lessons from 24,834 Patients. *Ann Surg*. 2008 Aug;248(2):154-62.

Keshwani MM, **Harris TK**. Kinetic Mechanism of Fully Activated S6K1 Protein Kinase. *J Biol Chem*. 2008 May 2;283(18):11972-80.

Keshwani MM, Ross DB, Ragan TJ, **Harris TK**. Baculovirus-mediated Expression, Purification, and Characterization of a Fully Activated Catalytic Kinase Domain of the 70 kDa 40S Ribosomal Protein S6 Kinase-1 Alphall Isoform (S6K1alphall). *Protein Expr Purif*. 2008 Mar;58(1):32-41.

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Appendix C: Related Awards Reported by Grantees

The following list represents $31.6 million in additional single and multi-year research awards reported since October 2007 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.

Alexandrow, M.[21] (2006, NIR), "Chemoprevention Trial of Enzastaurin for Metastatic and Dysplastic Lung Lesions in Prior Smokers," National Cancer Institute, Sep 15, 2008 – Aug 31, 2012, $1,544,750.

Bishop, M. (2004, NIR), "Psychosocial Factors Influence on Response to Falls Intervention Program in Older Adults," Brooks Rehabilitation Research Center, Jul 2, 2008 – Jul 1, 2009, $39,944.

Bolanos, C. (2007, NIR), "Ontogeny of Physical versus Emotional Stress and Reward Pathways," National Institute on Drug Abuse, May 1, 2008 – Apr 30, 2010, $373,733.

Bolser, D. (2001, IIR), "Regulation of the Cough Reflex," National Institute of Health, May 1, 2003 – Apr 30, 2008, $900,000.

Bolser, D. (2001, IIR), "Neurogenesis of Cough," National Institute of Health, Sep 15, 2008 – Jun 30, 2011, $1,662,730.

Chai, K. (2006, NIR), "Novel Regulators of EGFR Signaling in Breast Cancer," Susan G. Komen for the Cure, Jul 15, 2007 – Jul 14, 2010, $300,000.

Cogle, C. (2005, NIR), "Defining Cancer Resistance in Regenerating Microenvironments," May 1, 2008 – Apr 30, 2009, University of Florida, $85,561.

Cousins, S. (2001, IIR), "Aging and Vasculogenisis in Macular Degeneration," National Institute of Health, May 1, 2004 – Apr 30, 2008, $600,000.

Davenport, P. (2006, TSP), "Central Neural Gating of Pharyngeal Mechanically Elicited Cortical Evoked Potentials (CEP): An Evaluation of Swallow Neural Integration in Parkinson's Disease (PD)," American Parkinson Disease Association, Jul 1, 2008 – Jun 30, 2009, $50,000.

Dudley, G. (2005, NIR), "New Fragmentation Reactions and Strategies for Chemical Synthesis," National Science Foundation, Jul 1, 2008 – Jun 30, 2009, $378,000.

Ferreira, G. (2001, IIR), "5-Aminolevulinate Synthase and Heme Biosynthesis," National Institute of Health, Feb 15, 2004 – Jan 31, 2008, $603,967.

Forteza, R. (2007, Bridge), "Mechanisms of Oxidant-Induced Chronic Bronchitis," National Institute of Health, Jul 1, 2008 – Jun 30, 2013, $1,530,000.

Ganju-Krishan, A. (2005, SBTT), "Flow Cytometry Development," NPE Systems, Inc., Jun 1, 2008 – Dec 31, 2008, $36,000.

Ganju-Krishan, A. (2005, SBTT), "Electronic Volume of Stem Cells in HPCA Blood," Department of Pathology Seed Funds, University of Miami, Jun 1, 2008 – Dec 31, 2008, $12,000.

Ganju-Krishan, A. (2005, SBTT), "Tumor Stem Cells in Body Cavity Fluids," Department of Pathology Seed Funds, University of Miami, Jun 1, 2008 – May 30, 2009, $12,000.

Grobmyer, S. (2006, NIR), "Use of Novel GSS Nanoparticles for Image Mediated in Vivo Photothermal Therapy," American Cancer Society, Jan 1, 2008 – Dec 31, 2008, $22,500.

Haura, E.[21] (2001, NIR), "Stat 3 in EGFR Driven Non-Small Cell Lung Cancer," National Cancer Institute, Mar 1, 2007 – Jan 31, 2012, $1,582,067.

Haura, E. (2001, NIR), "Antitumor Mechanisms of SRC Inhibitors in Lung Cancer," National Cancer Institute, Jun 2007 – Apr 2012, $1,265,083.

Haura, E. (2001, NIR), "ACRA in Lung Cancer: Targeting EGFR and SRC," American Society of Clinical Oncology, Jul 1, 2007 – Jun 30, 2010, $150,000.

Haura, E.[21] (2001, NIR), "Role of Beta-arrestin-1 and SRC in nAChR Signaling and Lung Cancer," National Cancer Institute, Apr 17, 2008 – Jan 31, 2013, $1,730,032.

Haura, E. (2001, NIR), "Targeting EGFR and SRC Tyrosine Kinase Signaling in Lung Cancer," American Society of Clinical Oncology, Jul 1, 2007 – Jun 30, 2010, $450,000.

Haura, E. (2001, NIR), "Phase I Dasatinib Erlotinib in Recurrent NSCLC," Bristol Myers Squibb Company, Feb 13, 2007 – Feb 12, 2009, $104,817.

Haura, E. (2001, NIR), "Antitumor Mechanisms of SRC Inhibitors in Lung Cancer," National Cancer Institute, Sep 15, 2008 – Aug 31, 2009, $309,924.

Haura, E. (2001, NIR), "Antitumor Mechanisms of SRC Inhibitors in Lung Cancer," National Cancer Institute, Sep 15, 2008 – Aug 31, 2012, $2,000,000[21]

Haura, E. (2001, NIR), "Phosoproteomic Strategies to Evaluate Tyrosine Kinase Signaling Pathways in Cancer," US Army, Jul 1, 2008 – Aug 25, 2009, $191,411.

Hayward, L. (2006, TSP), "Genetic Mechanisms Underlying the Development of Hypertension Following Prenatal Nicotine Exposure," University of Florida Opportunity Fund, May 1, 2008 – Sep 30, 2009, $83,000.

Ishov, A. (2005, NIR), "Function of Daxx in Mitosis tat Determines Paclitaxel Sensitivity in Breast Cancer," National Cancer Institute, Sep 25, 2007 – Jul 31, 2012, $378,250.

Jaimes, E. (2007, TSP), "Effects of Nicotine on the Progression of Glomerular Injury," Flight Attendant Medical Research Institute, Jul 1, 2008 – Jun 30, 2011, $300,000.

Kenny, P. (2007 NIR), "Role of MicroRNAs in the Mechanisms of Drug Dependence," National Institute on Drug Abuse, Sep 15, 2008 – Jun 30, 2013, $2,100,000.

Leeuwenburgh, C. (2006, TSP), "Claude D. Pepper Older Americans Independence Center (OAIC)," National Institute of Aging, Oct 1, 2006 – Jun 30, 2011, $1,200,000.

Li, H. (2001, NIR), "Structure and Function Studies on RNA Splicing Endonuclease," National Science Foundation, Jul, 15, 2005 – Jul 30, 2010, $660,000.

Li, J. (2004, NIR), "Laminn-8 and Laminin-10 in Squamous Cell Carcinomas," National Cancer Institute, Sep 1, 2005 – Aug 30, 2009, $700,082.

Magleby, K. (2001, IIR), "Mechanisms of ION Channel Activity," National Institute of Health, Sep 1, 2008 – Aug 31, 2013, $1,683,000.

Melker, R. (2004, SBTT), "Detection of Ethanol in Human Breath: Mini-GC Use and Exhaled Breath Condensate," National Institute on Alcohol Abuse and Alcholism, Sep 20, 2007 – Mar 31, 2009, $134,092.

Mohapatra, S. (2003, SBTT), "Chitosan IFNgamma-pDNA Nanosphere Therapy and Immunopathology of Allergic Asthma," National Heart, Lung, and Blood Institute, Sep 1, 2003 – Aug 31, 2009, $1,160.000.

Mohapatra, S. (2003, SBTT), "Association between ANP and NPRA Gene Polymorphisms and Severity of Atopy and Asthma," Apr 1, 2008 – Mar 31, 2010, National Institute of Health, $199,360.

Morris, K. (2001, IIR), "Neurogenesis of Cough," National Heart, Lung and Blood Institute, Sep 15, 2008 – May 31, 2011, $734,642.

Ness, G. (2004, TSP), "Feedback and Hormonal Regulation of Hepatic HMG-CoA Reductase," National Institute of Health, Apr 1, 2008 – Mar 31, 2011, $840,509.

Podack, E. (2005, NIR), "HSP GP96 Fusion Vaccine for Cytotoxicity Against NSCLC," Alliance for Cancer Gene Therapy, Oct 1, 2006 – Jun 24, 2011, $1,000,000.

Rieger, M. (2005, NIR), "Regulation and Function of Transcription Factor Lbh in Breast Cancer," Department of Defense, Jul 1, 2008 – Jun 30, 2011, $97,007.

Segal, M. (2006, TSP), "Ancillary Functional Studies for the CCTRN," National Heart, Lung, and Blood Institute, Sep 30, 2007 – Jul 31, 2012, $2,748,679.

Smith, L. (2006, NIR), "HTS to Identify Chemical Probes of the Apelin Receptor Signaling Pathway," National Institute of Health, Sep 30, 2007 – Aug 31, 2009, $216,350.

Su, Y. (2004, TSP), "eNOS-actin Interaction and Oxygen in Lung Endothelium," National Heart, Lung, and Blood Institute, Jul 10, 2008 – Jun 30, 2013, $1,575,000.

Su, Y. (2004, TSP), "Calpain Mediates VEGF-induced Collagen Synthesis in Pulmonary Vascular Cells," American Heart Association, Jul 1, 2008 – Jun 30, 2010, $165,000.

Su, Y. (2004, TSP), "Nitric Oxide and Side-Stream Tobacco Smoke Modification of Calpains in Airway Epithelial Repair," Flight Attendant Medical Research Institute, Jul 1, 2008 – Jun 30, 2011, $300,000.

Wang Y. (2004, NIR), "Investigate the Negative Regulation of Cyclin-Dependent Kinase," American Cancer Society, Jan 1, 2008 - Dec 31, 2011, $707,000.

Since October 2007, current and past grantees reported $9.5 million in awards that are based indirectly 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.

Briegel, K. (2005, NIR), "Role of Transcription Factor TBX2 in Breast Cancer," Flight Attendant Medical Research Institute, Jul 1, 2008 – Jun 30, 2011, $325,000.

Briegel, K. (2005, NIR), "The Role of TBX2 – a Novel Therapeutic Target – in Breast Cancer," Florida Department of Health, Jul 1, 2008 – Jun 30, 2009, $104,945.

Cogle, C. (2005, NIR), "Short Course of G-CSF as Immunomodulatory Therapy for Type 1 Diabetes Mellitus," National Institute of Health, Apr 20, 2008 – Mar 31, 2010, $396,048.

Dudley, G. (2005, NIR), "Organic Reagents for Current and Future Markets," Florida State University Research Foundation, Jan 1, 2008 – Dec 31, 2008, $46,400.

Echeverria-Moran, V. (2007, NIR), "Molecular Mechanisms Underlying the Neuroprotective Actions of Cotinine," Alzheimer's Association, Sep 1, 2008 – Aug 31, 2010, $50,000.

Echeverria-Moran, V. (2007, NIR), "Cotinine as a therapeutic agent against AD," Johnnie Byrd Alzheimer Center, Apr 1, 2008 – Mar 31, 2009, $50,000.

Elliot, S. (2001, NIR), "ECM Regulation by Estrogen in ARMD," National Eye Institute, Jul 1, 2003 – Jun 30, 2007, $1,200,000.

Goldberg, J. (2005, NIR), "Magnetic Nanoparticles for Trophic Stimulation and Axon Regeneration," National Institute of Neurological Disorders and Stroke, Jun 1, 2007 – May 31, 2011, $1,204,876.

Goldberg, J. (2005, NIR), "Developmental Control of Axon Regeneration in RGCs," National Eye Institute, Feb 1, 2007 – Jan 31, 2010, $390,393.

Goldberg, J. (2005, NIR), "Intrinsic Molecular Control of Axon Regeneration in RGCs," National Eye Institute, Sep 1, 2005 – Aug 31, 2008, $446,553.

Kenny, P. (2007 NIR), "Role of Noncoding RNAs in Schizophrenia," National Institute on Mental Health, Jul 1, 2008 – Feb 28, 2013, $2,147,625.

Li, J. (2004, NIR), "Evaluation of Wound Healing in a Pig Wound Model," Department of Defense/US Army, Feb 22, 2008 – Feb 21, 2009, $42,457.

Li, J. (2004, NIR), "Comprehensive and Alternative Medicine in Preventing Radiotherapy-Induced Adverse Skin Reactions," Department of Defense, Sep 1, 2008 – Aug 31, 2009, $75,000.

Li, J. (2004, NIR), "Use of Recombinant Human Lactoferrin (rhLF) for Wounds by Stimulating Cell Growth," National Institute of Health, Aug 2, 2008 – Aug 1, 2009, $100,000.

Lincoln, J. (2007, NIR), "Molecular Regulation of Heart Valve Development and Function," National Institute of Health, Aug 1, 2008 – May 31, 2013, $1,900,000.

Luesch, H. (2006, NIR), "Activation of the Cancer Preventive Nrf2-ARE Pathway by Seaweed," National Institute of Health, Jul 8, 2008 – Jun 30, 2010, $357,447.

Luesch, H. (2006, NIR), "Pilot-Scale Libraries of Marine Cyanobacterial Natural Products," National Institute of General Medical Sciences, Sep 15, 2008 – Jul 31, 2011, $1,000,000.

Raval, A. (2007, NIR), "Organotypic Slice Cultures to Model Neurogenesis and Neuronal Survival in HIV-1 Infection," University of Miami Development Center for AIDS Research, Jun 1, 2008 – May 31, 2009, $31,500.

Rollison, D. (2006, NIR), "Nested Case-Control Study of JC Virus Infection and Incident Colorectal Cancer," National Cancer Institute, Sep 1, 2006 – Jul 31, 2009, $905,138.

Self, W. (2005, NIR), "Catalytic Properties of Nanoceira," National Institute on Aging, Mar 1, 2008 – Feb 28, 2012, $1,047,960.

Appendix D: Abbreviated Abstracts of 2008 Grant Awards

The following is a list of grants awarded in 2008. The grants are listed in alphabetical order by Principal Investigator name.

BREW, Keith — TSP
Florida Atlantic University
$820,800

A Rat Model of Individual Differences in Neuro-Immune Responses to Nicotine and Stress

Human beings differ in their vulnerability for smoking addiction. This grant uses a rat model of individual differences in nicotine craving, the novelty-seeking phenotype (characteristic), where rats are categorized as showing high reactivity (HRs) or low reactivity (LRs) to novelty based on their free exploration of a novel environment. Project 1 showed regulation of this phenotype with two chronic stress regimens: chronic, variable physical stress (CVP) and social stress (CVS). A phenotype shift is observed with the chronic, variable physical stress promoting high reactivity-like vulnerability to nicotine in low reactivity rats. The chronic, variable social stress inhibited the pre-existing vulnerability in high reactivity rats. Project 1 investigates switch in neural activational patterns underlying this phenotype shift. Project 2 showed that the immune system of high reactivity rats is vulnerable to nicotine-induced overproduction of the pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-a). This indicates induction of a "disease state" in the HRs with nicotine. Project 2 investigates the cytokine profiles of different subpopulations of the immune cells in both groups of animals with nicotine. Project 3 elaborated on molecular modulators of increased TNF-a production in high reactivity animals. Project 3 employs TACE inhibitors and TIMP 3 mutants to reverse nicotine effects in high reactivity animals.

DOGARIU, Aristide — SBTT
University of Central Florida
$98,519

Real Time Monitoring of Blood Coaguability for Thrombolytic Therapy

Smoking and chronic obstructive pulmonary disease have been linked to pathologic blood clotting causing acute coronary syndromes, venous thromboembolism, and stroke. Timely restoration of blood flow via thrombolytic therapy in intensive care units (ICU) is effective in salvaging the affected tissue. Similarly, anticoagulants are routinely used to prevent blood clotting during a wide range of procedures. To ensure that patients receive the correct dose of anticoagulant or thrombolytic agent, clinicians must accurately assess their coagulability status before, during, and after the procedure. Current ICU or operating room (OR) blood clotting tests do not allow for real-time blood coagulability monitoring. The grant aims to develop a near-patient instrument for ICU/OR use, capable of real-time, continuous coagulation monitoring without the use of reagents. The instrument is based on a novel optical method, Low-Coherence Dynamic Light Scattering, with proven capabilities of investigating viscoelastic properties of whole blood. The instrument is capable of real-time, in-vivo measurements using an optical fiber probe that could be simply inserted into a peripheral vein or through a cannulated vessel. If introduced in clinical practice, the optical real-time blood coagulability-monitoring instrument could eliminate unnecessary operational delays while facilitating decision-making on initiation and maintenance of thrombolytic or anticoagulant therapies.

DIAZ, Francisca — NIR
University of Miami
$372,455

Neuronal Adaptations to Defects in Mitochondrial Respiration

The focus of this grant is metabolic adaptations that promote neuronal survival in a mouse model created by the investigator (COX10 conditional knockout). We observed that in this mouse model, neurons survived for a relatively long time in the absence of mitochondrial respiration. Our hypothesis is that there are metabolic adaptations to maintain neuronal survival to avoid an energetic crisis during the absence of cellular respiration, and the main adaptive response is an upregulation of the glycolytic pathway. The following aims are being used to test this hypothesis: 1) define the spatio-temporal pattern of the respiratory defect and correlate it with the presence of apoptotic markers and mitochondrial proliferation in the affected neurons at different ages after onset of the defect. 2) determine neuronal adaptive metabolic responses to the lack of mitochondrial respiration by studying changes in activity and changes in gene and protein expression with emphasis in the glycolytic and survival pathways. The belief is that some of the mechanisms of neuronal survival in mitochondrial respiration defects are similar to those operating in the absence of oxygen (hypoxia). Therefore, understanding of endogenous adaptive strategies to compensate for mitochondrial respiration defects will create a window for therapeutic intervention for the prevention and treatment of tobacco-related diseases (stroke/ischemia) and other neurodegenerative diseases.

EICHLER, Duane — Bridge
University of South Florida
$199,800

Regulation of the Endothelial Citrulline-Nitric Oxide Cycle

Impairment of vascular wall (endothelial cell) function has been suggested to be an early, causative event in smoking, diabetes, and hypertension leading to atherosclerosis. In this grant, the cellular mechanisms will be investigated by which physiologic and pathogenic stimuli affect vascular wall health through the regulation of a critical enzyme named argininosuccinate synthase (AS). Based on our evidence that insulin regulates vascular wall health, in part, through a modification process of AS, the first aim of this grant explores the mechanisms and biological significance of this insulin-mediated modification as it relates to vascular wall function. The research will also explore the mechanisms that impair the action of insulin in mediating this type of regulation by examining alterations under inflammatory pathogenic conditions. The second aim is based on our work demonstrating that components of the gene encoding AS in the vascular wall also produce an alternative small protein we named Argininosuccinate Synthase Regulatory Protein (ARP). The mechanism by which ARP represses the synthesis of AS in the vascular wall in response to pathogenic stimuli are being examined. In the third specific aim, the molecular mechanisms underlying cardiovascular actions of insulin on AS production utilizing an animal model that is known to demonstrate vascular wall (endothelial) dysfunction will be examined. Overall, the belief is that examination of this critical enzyme is essential to understanding vascular wall function and will potentially distinguish new therapeutic strategies for the treatment of diabetes, hypertension, and smoking-related cardiovascular disease.

DIEZ-SAMPEDRO, Ana — NIR
University of Miami
$372,791

Investigation of SGLT3 and Its Effect on the Activity of the Intestine

Cessation of smoking is often accompanied by constipation, which may be defined as a lack of peristalsis and intestinal motility, and patients often resort to self-medication by resumption of smoking. The enteric nervous system (ENS) includes two networks of neurons called plexuses, located within the walls of the intestine. These neurons contain receptors for nicotine, the addictive component of tobacco. Many of these neurons control the smooth muscles of the gastrointestinal tract, regulating peristalsis and clearing of intestinal contents. Recently, research showed that a newly identified protein known as SGLT3 that binds sugars is co-localized with nicotine receptors in the intestinal plexuses. The preliminary data suggest that sugars that bind and activate SGLT3 cause intestinal contraction in isolated intestine, and that intestinal contraction is damped when SGLT3 is blocked. This grant will be used to investigate the activity of SGLT3, how it affects the function of intestinal neurons, and how activators and inhibitors of SGLT3 affect nicotine-induced intestinal contractions. A full understanding of the function of SGLT3 and its role in intestinal motility may lead to effective treatments for the constipation that often accompanies cessation of smoking, thus leading to increased success in quitting.

FU, Mingui — NIR
University of Central Florida
$375,000

Role of MCPIP1 in Nicotine-Induced Repression of Macrophage Inflammation

Cigarette smoking is an established risk factor for cardiovascular disease, lung cancer, chronic obstructive pulmonary disease, respiratory infections, and the leading cause of avoidable mortality in industrialized countries. Its effects are largely due to cigarette smoke-induced impairment of the immune system. Nicotine is a major immunosuppressive component in cigarette smoke. However, how nicotine impairs the immune system is not clear. Previously it has been found that a novel protein MCPIP1 can suppress macrophage inflammation through targeting an important signal pathway NF-kB signaling in macrophages. The preliminary studies suggest that MCPIP1 may be an important mediator in nicotine-induced repression of macrophage inflammation. One of the long-term goals is to identify molecular signals mediated by cigarette smoke action on macrophage inflammation and study their contribution to human diseases such as atherosclerosis. In this grant, MCPIP1 knockout mice will be used as a tool to further define the mediator role of MCPIP1 in nicotine-induced repression of macrophage inflammation. A series of in vitro experiments to define how MCPIP1 inhibits NF-kB activation and how nicotine induces MCPIP1 transcription will also be carried out. Understanding the molecular mechanisms involved in the inflammatory processes in tobacco/nicotine-treated macrophages is essential for development of novel drug therapies against tobacco-related inflammatory diseases.

HONG, Sukwon
NIR
University of Florida
$374,765

Catalytic Enantioselective Synthesis of Anti-Cancer Natural Products

Is it possible to develop a drug that can cure a cancer without any side effects? Many chemotherapeutic agents are effective at killing cancerous cells that are rapidly dividing. However, those anti-cancer drugs in general also act on non-cancerous cells causing many serious side effects. Discovery of better chemotherapeutic agents is limited by our ability to make diverse candidate molecules used in biological testing. Organic synthesis is the foundation for the drug development process because systematic variation of the structure of promising lead compounds is a key to finding more potent and less toxic medicine. Biological systems are three-dimensional objects so a subtle difference in the three-dimensional structure of the drug can cause unexpected outcomes as witnessed by the thalidomide tragedy. Controlling three-dimensional structure of the complex molecule (asymmetric synthesis) is highly necessary to access a pool of new candidate molecules that are currently unavailable. This research project is aimed at developing new catalysts that allow us to efficiently create challenging three-dimensional structures often found in naturally occurring anti-cancer agents. Highly concise and flexible syntheses of anti-cancer natural products will be developed using new methodology. This research will not only pave the way to analog compounds to those important targets but also advance the synthetic chemist's toolbox to access more sophisticated chemotherapeutic agents.

JIANG, Zhihua
NIR
University of Florida
$374,997

Mechanisms of MCP-1/CCR2 Axis-Regulated Vein Graft Neointimal Hyperplasia

Vein bypass surgery remains the only option for a large set of patients suffering from occlusive arterial disease. However, nearly 50 percent of the vein grafts fail within two years, and the risk of graft occlusion for tobacco users is 3.1-fold that of non-tobacco users. Vein grafts occlude largely as the result of neointimal hyperplasia (NIH). Recent studies have established a stimulatory role for the CC chemokine monocyte chemoattractant protein (MCP) -1 and its receptor CCR2 in this process. The deleterious impact of the MCP-1/CCR2 axis on vein graft performance is more pronounced in tobacco users due to the elevated levels of serum MCP-1 in this population. Emerging evidence suggests that MCP-1/CCR2 promote vein graft NIH via monocyte independent mechanisms. However, neither have the exact cellular producers and functional performers been identified, nor has the impact of the MCP-1/CCR2 axis on neointimal cell biologies been defined. While the existing data suggest that MCP-1/CCR2 intrinsic to the graft wall promotes NIH, direct evidence remains lacking. Therefore, the grant's research goals are to define the impact of MCP-1 and CCR2 signaling both intrinsic and extrinsic to the graft wall on NIH during vein graft adaptations. Genetic and molecular approaches will be employed in these studies. Completion of this research will lead to the identification of therapeutic targets and lay the foundation for the development of effective therapeutic strategies.

JOHNSON, Kevin
NIR
University of Florida
$375,000

Validation of Coronary Calcium Scoring Using Dual Energy CT

Smoking is a known contributor and risk factor for coronary artery disease (CAD), the leading cause of death in the United States. One early diagnostic test used in the diagnosis of CAD is the quantification of coronary calcium. This test has repeatedly been shown to be a strong indicator of CAD and a predictor of future CAD development. The current protocol used for coronary calcium quantification and assessment of the coronary arteries for stenotic disease requires two separate CT scans, the first without contrast media and the latter with contrast media. A new technology known as dual energy CT allows the separation of a single scan into a contrast image and a virtual non-contrast image. If this technique could be employed to quantify coronary calcium from a CT angiography scan, significant improvements in examination time and radiation dose to the patient would be attained. The hypothesis is that dual energy CT will allow accurate quantification of coronary calcium and CT angiography examination of the coronary arteries in a single scan. This hypothesis is being tested first using a heart phantom with calcified lesions of known size and then in a patient population. Then the plan is to compare calcium scores from the conventional method with the dual energy CT technique.

JUDGE, Andrew
NIR
University of Florida
$373,122

Cytokine-Induced Muscle Atrophy Following Exercise Claudication

While there are a number of risk factors for the development of Peripheral Arterial Disease (PAD), cigarette smoking is the risk factor most correlated with the onset and progression of PAD. In addition, smoking increases the development of intermittent claudication (or intermittent, activity-induced, leg pain), which is the symptomatic form of PAD, by as much as 8-to 10-fold. This activity-induced pain is a result of muscle ischemia, which has previously shown to cause muscle damage and debilitation in PAD patients. The long-term goal is to prevent this debilitation by further elucidating the mechanisms causing the damage and debilitation to skeletal muscle and to develop countermeasures. This work will determine if muscle ischemia, associated with PAD, increases the production of cytokines and leads to muscle weakness, atrophy, and dysfunction. This is based on findings from other chronic diseases, such as cancer, chronic heart failure (CHF), sepsis, and AIDS, in which high levels of cytokines have been shown to trigger skeletal muscle breakdown, leading to atrophy, weakness, fatigue, exercise intolerance, and deterioration of the patient prognosis. Incidentally, cigarette smoking also increases the expression of cytokines, which could further amplify these affects. By understanding these processes, specific countermeasures will be able to be tested to prevent the debilitation.

KROTOVA, Karina
NIR
University of Florida
$375,000

Involvement of Arginase in the Response of Endothelial Cells to Hypoxia

Cigarette smoking is a major cause of chronic obstructive pulmonary disease (COPD) which is characterized by poor gas exchange in the lungs. This inadequate pulmonary ventilation is associated with cellular hypoxia, a reduced availability of oxygen for cellular functions. Lung endothelial cells release nitric oxide (NO), which acts to dilate blood vessels and maintain normal blood pressure in the pulmonary circulation. Hypoxia induces a decrease in NO production. NO production is regulated by a variety of mechanisms, one of which is the availability of L-arginine, the substrate for NO production by endothelial nitric oxide synthase (NOS). L-arginine is also metabolized by intracellular arginases. Sharing a common substrate, arginase and NOS compete for L-arginine. The exposure of cultured endothelial cells to hypoxia activates arginase, and we suggest that this upregulation of arginase activity leads to a decrease in NO production. The objective of this grant is to study the effects of hypoxia on arginase activity and, in turn, NO production in endothelial cells and to investigate possible mechanisms for the action of hypoxia on arginase activity. Elucidation of the role arginase plays in the regulation of NO production and the subsequent development of endothelial cell dysfunction under hypoxic conditions would be a new step in our understanding of endothelial physiology with implications for tobacco-related disease such as COPD.

KUPELIAN, Patrick
TSP
M.D. Anderson Cancer Center
$949,717

Incorporating 3-D Lung Dynamics into Lung Radiotherapy for Non-Small Cell Lung Cancer

Smoking accounts for 87 percent of all lung cancer deaths. With an annual incidence of more than 160,000 cases, smoking-induced lung cancer represents our greatest oncologic challenge. Non-Small Cell Lung Cancers (NSCLC) account for approximately 75-80 percent of all lung carcinoma cases. In clinical radiology, it has been hypothesized that the local failure (the inability to ablate localized tumors) of radiotherapy may be a cause for subsequent development of metastases, the spread of cancer to distant parts of the body. One of the key sources of this local failure is related to the motion of the lung tumor and its surrounding tissues during breathing. Since tobacco inhalation also leads to tissue damages, which co-occur with NSCLC, this conjunction of disease states leads to variations in these motions. This TSP is supported by three subprojects with an integrated focus in the development of model-guided radiation therapy including: 1) Study of smoking-induced tissue damages inside the lung and the tracheobronchial tree (Project 2). 2) Prediction of tumor motion and its surrounding tissues (Project 1) during radiation therapy of individual patients. For the first time, oncologists will be able to see and quantify radiation doses depositing in the process of radiotherapy. 3) Understand the process of metastases formation as it relates to lung radiotherapy and work towards improving the radiation treatment effectiveness (Project 3) based on data from Subproject 1.

LI, Yiwen
NIR
University of Miami
$375,000

Age-Related Macular Degeneration: Experimental Model and Neuroprotection

The long-term goal of this research is to understand Age-related Macular Degeneration (AMD) and find ways to save and restore vision for AMD patients. AMD is the leading cause of irreversible vision loss in people over 65 years of age in developed countries. A well-established risk factor for AMD is tobacco smoking. AMD affects cone photoreceptors in the macula, the center of the retina critical for fine and color vision. Patients with AMD lose their central vision due to the death of cones. Currently there is no treatment for cone degeneration. Advances in research on cone degeneration are slow, partially because of the lack of well-characterized experimental models. This not only limits our understanding of cone degeneration, but also hinders the development of new treatments. There is an urgent need for cone degeneration models. Several findings from my recent studies could help to change the situation. It has been found that cone degeneration in a specific line of transgenic rat could serve as a good model. It also has been found that during cone degeneration, cones first lose outer segments (OS), the light-receiving devices of cone cells. When treated with neurotrophic factors, cones that lost OS could be stimulated to regenerate OS. This demonstrates that in early stages, cone degeneration is reversible. In this grant, the research goal is to characterize the cone degeneration in transgenic rat to establish a model for basic and preclinical studies. An additional research purpose is to study cone OS regeneration by two neurotrophic factors.

LIU, Zhao-Jun
NIR
University of Miami
$375,000

Role of Notch Signaling in Endothelial Differentiation of Bone Marrow Stem Cells

Smoking has been implicated as a major risk factor in various vascular diseases. Smoke accelerates and contributes to vascular diseases by inducing endothelial cell injury and dysfunction. Endothelial progenitor cells (EPCs) have a role in ongoing endothelial repair. EPCs in adults originate from bone marrow stem cells (BMSCs) and can be released into peripheral blood (circulating EPCs). Circulating EPCs are able to be recruited to remote lesions, with the influence of chemoattractant signals, and differentiate in situ into mature endothelial cells to form new blood vessels. Infusion of ex vivo expanded EPCs augments neovascularization of tissue after ischemia and contributes to reendothelialization after endothelial injury. Transplanted EPCs formed capillaries among preserved skeletal myocytes in the ischemic hindlimb of athymic nude rats in vivo. Thus, transplantation of EPCs may become a useful strategy to modulate postnatal neovascularization. However, we know little about the molecular mechanism(s) that modulates differentiation of BMSCs specifically toward an endothelial cell fate. We hypothesize that Notch signaling plays an integral role in controlling endothelial cell lineage differentiation. Therefore, gaining insight into this regulation will enable us to generate abundant EPCs and better use such cells for the development of therapeutic application toward a variety of cigarette smoke-related vascular diseases.

MARTYNYUK, Anatoly
Bridge
University of Florida
$184,951

Balanced, Polyvalent Antiglutamatergic Action as a Novel Approach to Efficacious and Safe Neuroprotection

Tobacco consumption, both active and passive, is an important risk factor for stroke. The pathophysiology of stroke is a complex process with overactivated glutamate signaling as one of the primary events that initiates numerous and diverse intracellular processes leading to cell death. For this reason, the glutamatergic system has been a promising target for potential neuroprotective therapy. However, glutamate is a major excitatory neurotransmitter that plays a critical role in normal brain physiology. Therefore, it is not surprising that many previous highly selective and potent glutamate receptor antagonists failed clinical trials, primarily because of side effects they produced. This study tests the novel concept that antiglutamatergic agents with polyvalent actions and moderate potency have the potential to overcome these limitations by producing efficacious neuroprotection and still enabling a level of balanced glutamate receptor activity required for physiological brain functions and thus avoiding significant side effects. During investigation of the mechanisms whereby high concentrations of the aromatic amino acid phenylalanine (Phe) affect the brain in phenylketonuria (PKU) patients, we found that this aromatic amino acid depresses the glutamate system in a way that may form a basis for the development of such drugs. This grant aims at investigating neuroprotective effects of the aromatic amino acid derivative, 3, 5-dibromo-D-tyrosine. It may become a novel, much-needed drug, or a prototype of drugs, not only against stroke, but also against a variety of other pathologies involving similar etiology, such as epilepsy, Alzheimer, and Parkinson.

PARIS, Daniel
SBTT
Roskamp Institute
$100,000

Treatment of Lung Adenocarcinoma and Metastasis by Anti-angiogenic Fragments of Abeta

Lung cancer incidence has been increasing in the last few decades, particularly in females due to rising ratio of female to male smokers. Research indicates that the factor with the greatest impact on risk of lung cancer is long-term exposure to inhaled carcinogens due to exposure to tobacco smoke. In the U.S., smoking is estimated to be responsible for 87 percent of lung cancer cases and accounts for one-third of all cancer deaths annually. Since tumor growth, transformation, and spread are dependent on angiogenesis (growth of new blood vessels from preexisting blood vessels), blocking angiogenesis is considered an attractive therapeutic strategy for treatment. It has previously been identified that a naturally occurring peptide called beta-amyloid (Abeta) can block the growth of human lung tumor transplanted into mice by stopping angiogenesis. It was then determined that a shorter fragment has the same efficacy as the full-length peptide at blocking angiogenesis. The goal now is to determine the mechanisms underlying this action and to investigate the molecular mechanisms responsible for the anti-angiogenic activity of Abeta-derived peptides. In this grant, it will examine if the smaller fragments of Abeta can stop the growth of lung tumors in mice models. It will also investigate different methods of delivery of these peptides to fully elucidate their therapeutic potential as a novel therapeutic for the treatment of lung cancer.

PEREZ-PINZON, Miguel
Bridge
University of Miami
$200,000

Ischemic Preconditioning: Mechanisms of Neuroprotection

Multivariable assessment of stroke risk factors has identified cigarette smoking as a potent risk factor for ischemic stroke. Although the most effective preventive measures are never to smoke, quitting smoking is difficult. Thus, it is very important to define therapies that are efficacious against ischemic stroke in humans with non-preventable and preventable (smoking) risk factors. Interestingly, the phenomenon of ischemic preconditioning has emerged as a potential therapy and was demonstrated to provide prophylactic protection in animal stroke models. [A prophylactic is a medication or a treatment designed and used to prevent a disease from occurring.] The most direct and significant application of understanding the mechanism of ischemic preconditioning is therapeutic access to this protective state in patients with high probability for a stroke, such as those that smoke or passive smokers. In this context, a recent study from our laboratory demonstrated that the chemical resveratrol can emulate ischemic preconditioning neuroprotection against cerebral ischemia. Resveratrol, a phytoalexin found in red wine, is currently the focus of intense research both in the cardiovascular biology and in neurological sciences. We recently showed that a brief resveratrol pretreatment conferred neuroprotection against cerebral ischemia. Based on our findings, it has been proposed that resveratrol could be used as a prophylactic preconditioning agent. The translational value of resveratrol is supported by the fact that there are currently at least five clinical trials on resveratrol as an anti-carcinogenic compound. The main goals of the grant are to define the common signaling pathways activated by resveratrol and ischemic preconditioning (IPC) that promote ischemic tolerance.

PRABHAKAR, Rajeev
NIR
University of Miami
$272,245

Effect of Nicotine on Amyloidosis and Oxidative Stress in Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of senile plaques and neurofibrillary tangles in the brain. The major component of these plaques is 42 amino acid residues containing amyloid beta (Ab) peptide. There is a direct association between cigarette smoking and AD, and recently it was demonstrated that current smokers are at roughly double the risk of developing AD as those who have never smoked. The potential therapeutic strategies for AD include blocking the generation and aggregation of Ab peptides, inhibiting the cytotoxic effects, and disruption of preformed fibrils. However, recent efforts in this direction are hindered by the lack of atomic level understanding of biochemical processes occurring in AD. Due to inherent complexities, this understanding cannot be achieved by experiments alone. A radically different approach to realize this goal through the development and application of a comprehensive theoretical and computational strategy involving molecular dynamics (MD), quantum mechanics (QM), hybrid quantum mechanics/molecular mechanics (QM/MM), bioinformatics, and X-ray spectroscopic (X-ray photoelectron [XPS] and X-ray absorption [XAS]) techniques, has been designed. In these studies, roles of Methionine35, nicotine, and metal ions (Cu, Zn, and Fe) will be elucidated. The outcome of these studies will advance the efforts to develop effective therapeutic strategies for treating AD.

RADISKY, Evette
NIR
Mayo Clinic Cancer Center
$375,000

Development of Highly Selective MMP-10 Inhibitors for Lung Cancer Therapy

Lung cancer is the leading cause of cancer mortality in Florida and elsewhere in the U.S. Extremely poor survival rates associated with this deadly disease highlight a need for new and improved treatment strategies. Matrix metalloproteinase-10 (MMP-10) is an enzyme produced by lung tumors that promotes tumor invasion and metastasis; inhibitors of MMP-10 may be useful as drugs for lung cancer therapy. However, currently available inhibitors target a broad spectrum of MMPs (including some with beneficial functions) and cause problematic side effects. This research has proposed a new approach to the development of highly selective MMP-10 inhibitors for lung cancer therapy through modification of a human protein, the tissue inhibitor of metalloproteinases-1 (TIMP-1). We are creating a library of modified TIMP-1 proteins displayed on the surface of cells, and plan to select from this library the TIMPs with greatest potency and selectivity for inhibiting MMP-10. Another avenue being studied is the molecular structures of MMP-10 and TIMP-1 to discover how they interact; this information will lead to further optimization of TIMPs as drugs to target MMP-10. Finally, the plan is to test TIMP-1 and improved TIMPs for the ability to prevent or slow the growth or metastasis of human lung tumors implanted into mice. These studies will enable evaluation of MMP-10 inhibition as a therapeutic strategy for treating lung cancer, and of modified TIMPs as a new class of drugs for lung cancer therapy.

TAKAHASHI, Yoshinori
NIR
H. Lee Moffitt Cancer Center & Research Institute
$361,795

Functional Role of Bif-1 in the Regulation of Autophagy and Lung Tumorigenesis

Non-small cell lung cancer (NSCLC) accounts for nearly 80 percent of lung cancer cases. The incidence of NSCLC is strongly correlated with smoking and exposure to tobacco products. Although numerous efforts have improved the treatment of NSCLC, the five-year survival rate remains quite low at approximately 15 percent. Thus, identifying better targets for drug development to treat and cure lung cancer patients is urgently required. Autophagy is a process for the degradation of intracellular components within membrane-enclosed structures. This process prevents cells from accumulating oncogenic stresses, such as unfolded proteins and damaged organelles. Moreover, the induction of autophagy can promote cell death even in apoptosis-impaired cells, suggesting that the activation of autophagy could be a new strategy for the treatment of cancer. Bif-1 is a member of the endophilin protein family that is involved in intracellular membrane dynamics. Loss of this protein inhibits autophagy induction and enhances spontaneous cancer incidence. This highlights Bif-1 not only as a regulator of autophagy, but also as a tumor suppressor. This grant aims to elucidate the molecular mechanism underlying Bif-1-mediated autophagy and to investigate the potential benefit of inducing autophagy as treatment for tobacco-induced lung cancer. The knowledge obtained through this grant may lead to the development of new drugs with the goal of improving the survival of lung cancer patients.

SHELLENBERGER, Thomas
NIR
M.D. Anderson Cancer Center
$372,600

Protease Inhibition of Invasion in Head and Neck Cancer

Cancers of the head and neck arise from the mouth, throat, and voice box. These cancers pose grave consequences for patients who suffer the loss of speech and swallowing and often form while patients are succumbing to their disease. A better understanding of the ways in which these cancers grow and spread can result in new strategies and improved treatment for these patients. We have identified a key characteristic of cancers of the head and neck that portends their aggressive behavior. These studies at the laboratory bench, in experimental animals, and in patients treated for cancers of the head and neck show that the loss of an important regulator of normal cells can result in cancer cells capable of destruction. This grant will determine why that key regulator is lost, how those changes are orchestrated, and how the consequences are manifested in patients. The knowledge gained from this research will shed new light on the way cancers destroy and spread in patients as well as lead to more effective weapons in our arsenal in the fight against cancers of the head and neck.

ZHU, Lei
NIR
Florida State University
$375,000

Development of Sensitive Fluorescent Probes for Physiological Zn2+ Over Large Dynamic Ranges

The research goals of this grant are to develop fluorescent probes for imaging biological zinc ions with both high sensitivity and large dynamic ranges. Zinc is known to play many important roles in human physiology. Tobacco smoking has been found to alter the activities of zinc-containing enzymes such as superoxide dismutase, which is linked to degenerative diseases. Development of prevention and treatment for such diseases has been hampered due to poor understanding of the physiological functions of zinc. This deficiency in knowledge is due to a lack of tools to determine the distribution of zinc in biological systems. Our strategy is to develop fluorescent probes for zinc with both high sensitivity and large dynamic ranges. Success of this project will provide tools for gaining understanding of the physiological functions of zinc thus aiding the prevention and treatment of related diseases. Built upon a molecular system established in our laboratory, there are four Specific Aims for developing molecular probes targeting zinc under physiological conditions: 1) Preparation of probes to achieve sub-nanomolar sensitivity of zinc detection while maintaining a large dynamic range. 2) Optimization of the fluorescence and coordination properties of the probes for achieving suitable sensitivity and high selectivity. 3) Development of probes for zinc detection in deep tissues. 4) Application of our probes in biological imaging using fluorescence microscopy.

SIMMONS, Vani
NIR
H. Lee Moffitt Cancer Center & Research Institute
$365,192

Secondary Smoking Prevention for College Students: Testing an Experiential, Web-based Intervention

The young adult years (ages 18-24) have the highest prevalence of smoking, and nearly one-third of college students report being current smokers. Cigarette smoking among college students has been identified as a critical public health problem. Although research has progressed in the development of tobacco prevention programs for adolescents and smoking cessation treatments for adults, little attention has been paid to the period of young adulthood. Fourteen million students enter college each year, and college represents an important transitional period in which young adults typically either quit or become nicotine-dependent adults. College represents a unique window of opportunity for smoking interventions. Given the alarming lack of smoking cessation interventions for college students and underutilization of the limited available resources, the development of novel smoking cessation approaches is clearly warranted. Toward this end, it is believed that the rapidly growing interest, access, and use of the World Wide Web can serve as a powerful vehicle for delivering an intervention to a large number of college smokers. The current study will adapt a previously efficacious intervention into a novel, web-delivered intervention to greatly increase its reach. The goal of this grant is to conduct an initial randomized study testing the efficacy of an experiential, theory-based intervention designed to reach college student smokers and administered via the web.

Appendix E: National Institutes of Health

Funding by State

2007-2008 Funding by State[22]

Listed below are the 30 states that received the most NIH funds in 2008.

State	2007 Population Estimate	2008						2007	
		Pop Rank	$ Per Capita	Per Capita Rank	Funding 2008	Rank	% of Total Funding	Funding 2007	Rank
California	36,553,215	1	80.39	11	2,938,508,186	1	14.87%	3,163,763,094	1
Massachusetts	6,449,755	14	327.43	1	2,111,812,799	2	10.69%	2,235,939,038	2
New York	19,297,729	3	91.82	10	1,771,900,981	3	8.97%	1,935,399,273	3
Pennsylvania	12,432,792	6	102.49	8	1,274,230,035	4	6.45%	1,397,422,734	4
Texas	23,904,380	2	42.81	27	1,023,375,828	5	5.18%	1,083,464,922	5
North Carolina	9,061,032	10	98.16	9	889,419,114	6	4.50%	930,882,958	7
Maryland	5,618,344	19	158.23	3	888,964,062	7	4.50%	976,541,042	6
Washington	6,468,424	13	112.12	6	725,240,867	8	3.67%	785,736,150	8
Illinois	12,852,548	5	53.33	21	685,420,000	9	3.47%	723,645,370	9
Ohio	11,466,917	7	53.28	22	610,996,488	10	3.09%	628,293,858	10
Michigan	10,071,822	8	53.98	20	543,721,827	11	2.75%	552,932,019	11
Missouri	5,878,415	18	77.73	13	456,915,120	12	2.31%	473,057,974	12
Connecticut	3,502,309	29	128.48	4	449,973,891	13	2.28%	468,893,912	13
Minnesota	5,197,621	21	79.97	12	415,677,994	14	2.10%	443,523,672	14
Tennessee	6,156,719	17	66.76	15	411,002,632	15	2.08%	434,819,317	15
Georgia	9,544,750	9	37.73	30	360,080,361	16	1.82%	365,703,745	17
Wisconsin	5,601,640	20	64.19	16	359,593,817	17	1.82%	370,395,477	16
Florida	**18,251,243**	**4**	**18.39**	**44**	**335,667,853**	**18**	**1.70%**	**339,754,376**	**18**
Colorado	4,861,515	22	63.79	18	310,124,207	19	1.57%	316,292,851	19
Virginia	7,712,091	12	36.39	31	280,606,867	20	1.42%	271,243,779	21
Oregon	3,747,455	27	70.28	14	263,364,393	21	1.33%	277,168,923	20
Alabama	4,627,851	23	46.43	25	214,851,967	22	1.09%	233,576,930	23
New Jersey	8,685,920	11	24.38	40	211,790,607	23	1.07%	250,701,373	22
Indiana	6,345,289	15	31.12	36	197,473,261	24	1.00%	207,951,807	24
Iowa	2,988,046	30	63.92	17	190,965,267	25	0.97%	194,631,513	26
District of Columbia	588,292	50	313.06	2	184,172,694	26	0.93%	195,737,381	25
Arizona	6,338,755	16	24.34	41	154,288,102	27	0.78%	170,898,328	27
Kentucky	4,241,474	26	33.14	34	140,562,367	28	0.71%	139,578,376	29
Rhode Island	1,057,832	43	128.10	5	135,505,800	29	0.69%	143,434,997	28
Utah	2,645,330	34	49.35	24	130,557,859	30	0.66%	132,537,079	31

Endnotes

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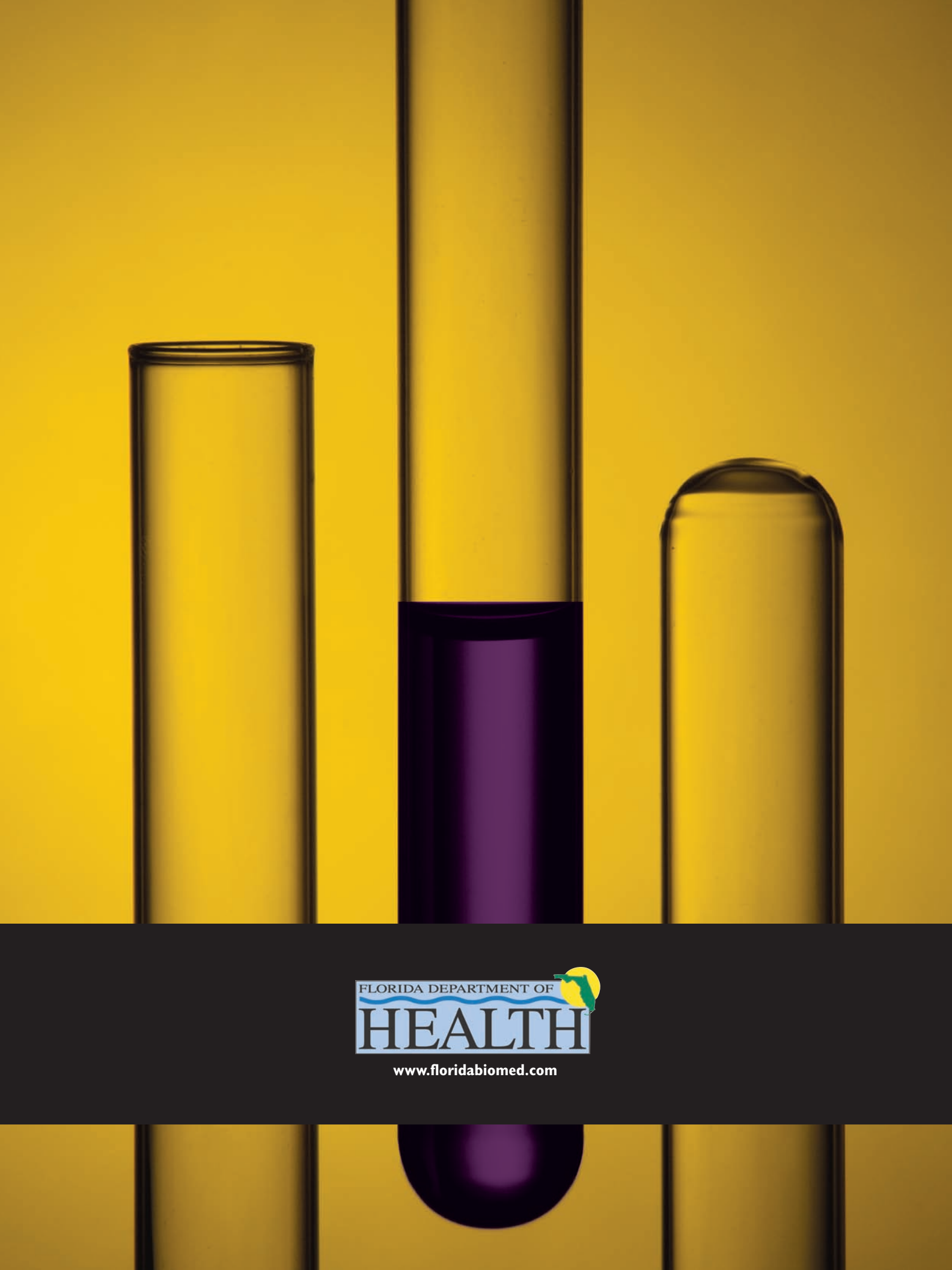

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