JAMES & ESTHER KING
BIOMEDICAL RESEARCH PROGRAM

2005 ANNUAL REPORT

JANUARY – DECEMBER 2005

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February 1, 2006

The Honorable Jeb Bush, Governor
The Honorable Tom Lee, Senate President
The Honorable Allan Bense, House Speaker
Secretary M. Rony François, M.D., M.S.P.H., Ph.D., Florida Department of Health

Dear Governor Bush, President Lee, Speaker Bense, and Secretary François:

On behalf of the entire Advisory Council, I am pleased to present the 2005 James & Esther King Biomedical Research Program Annual Report. The report was prepared pursuant to section 215.5602, Florida Statutes, and provides the overall status of the Biomedical Research Program and its accomplishments to date.

I appreciate the opportunity to have served as chair for this critical program over the last three years. During this relatively short period of time, we have accomplished a great deal and are beginning to realize the potential far-reaching implications of our grantees' research. It's been a privilege to collaborate with my fellow advisory council affiliates and I'd like to recognize their service, as 2005 will be the last year on the council for several of our members.

Through the cumulative effect of our grantees' successes, we are gaining momentum. In the following pages, you will find evidence of the program's growing impact. The groundbreaking research of our grantees is being published in prominent peer-reviewed journals, presented to important organizations worldwide, and helping to secure additional funding from outside of Florida—from the National Institutes of Health and others.

This year built upon the regained impetus the program found in 2004 with legislative support that significantly stabilized and increased the levels of funding that we can make available to Florida's scientists. Because of these legislative victories, 2005 saw 16 additional research projects awarded in three categories.

Thanks to your assistance, Florida is clearly becoming better positioned to become a leader in biomedical research. We sincerely hope you are pleased with the details of our progress during 2005 and invite you to join us in looking ahead with optimism as the program continues to advance in its mission.

Sincerely,

Clyde B. McCoy, Ph.D.
Chair, Florida Biomedical Research Advisory Council

For questions or to request additional copies of this report, please contact Chuck Wells, Program Manager, in the Office of Public Health Research, (850) 245-4444 ext. 3933.

James & Esther King Biomedical Research Program

Annual Report

January–December 2005

Submitted to:

The Governor

The President of the Senate

The Speaker of the House of Representatives

The Secretary of the Department of Health

State of Florida

and

Florida Center for Universal Research to Eradicate Disease

by:

Biomedical Research Advisory Council

Clyde B. McCoy, Ph.D., Chair

February 1, 2006

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Executive Summary

The scientific discovery made possible by Florida's investment in the James & Esther King Biomedical Research Program can be likened to the rippling effect of a stone tossed into a quiet pool: the impact of each breakthrough can travel far in time and distance. Today, the important findings of our grantees are creating productive ripples—large and small—within the global research community. Their impacts become more significant and far reaching with each dollar invested, each hour spent in the lab, each paper presented, and most importantly, by each patient whose suffering is lessened.

Advances in the diagnosis, prevention, treatment, or cure of disease build on previous findings. Unfortunately, these advances typically are not instantaneously obvious or linear in nature—thus the necessity for ongoing research support. The passing of Senate Bills 2002 and 1278 in 2004 stabilized funding for the program and gave it a newfound security, which was renewed by the legislature and built upon in 2005. As a result, the program can provide increasingly significant levels of funding to Florida research institutions for the performance of high-quality and high-impact biomedical research and technology associated with tobacco-related diseases.

There are a number of signs that we're gaining momentum:

- In 2005, the program awarded $8 million in funding for 16 new projects rated as highly significant by panels of national experts.
- During 2005, grantees published at least 32 articles that presented their pioneering research in prominent, peer-reviewed journals and reported awards of more than two million dollars in additional funding.
- As of the end of 2005, grantees have published more than 140 journal articles and made over 200 presentations to important organizations worldwide.
- Grantees are leveraging the grants received from our program to secure more than $23 million to date in additional funding from outside of Florida—from the National Institutes of Health and other funding agencies.

During its May 2005 meeting, the Biomedical Research Advisory Council began a strategic planning process which is expected to culminate in 2006 with a five year roadmap for the program. In addition, to address ways to improve and responsibly monitor the use of grant funds, the James & Esther King Research Program made a number of enhancements to the program's administration in 2005.

A new electronic grant management system and improved processes were introduced to guide how research is conducted and how grant information and deliverables are managed. The program's Web site (www.floridabiomed.com) was improved to provide more information about all grantees that have been funded by the program. This Web site continues to be a dynamic resource that communicates current information about the program and serves as a portal for applicants, grantees, advisory council members, and program administrators.

Along with ongoing content updates to the Web site, significant efforts have been made to step up the marketing and promotion of the program to potential applicants—and more top researchers are being attracted.

The James & Esther King Biomedical Research Program is a vital contributor to the growing strength of Florida's biomedical research community. In the following pages, it is clear that the program's impact is getting us closer to treating, preventing, and even curing some of the most devastating diseases and causes of death in Florida, the United States, and beyond. With continued support of the program, our vision may only be a stone's throw away.

Program Vision, Mission, and Goals

The vision statement of the Biomedical Research Advisory Council (BRAC) reads: "The James & Esther King Biomedical Research Program will be the prime resource in the state for support of biomedical research and technology development and will be nationally recognized as an effective stimulus of new biomedical knowledge to improve the health of citizens and to encourage economic development." The statutory purpose 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 diseases including cancer, cardiovascular disease, stroke, and pulmonary disease.

The program's goals 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.

With the assistance of a team from the Collins Center for Public Policy, Inc., during a May 2005 retreat, the BRAC began a process for formulating a five year strategic plan for the Program. Members reviewed the Program's strengths and weaknesses and identified future opportunities and possible threats. This exercise led us to conclude that the Program had renewed strength because of recent legislative actions and had the potential to continue to be a flagship research program for the state. The BRAC went on to suggest specific metrics for assessing the impact of the Program in the future. This work has laid the foundation for additional Council business in 2006 to refine specific priorities, objectives, and action steps.

"The investment we make today in the James & Esther King Biomedical Research program will help lead to future scientific knowledge and treatments in order to reduce human suffering and the financial costs associated with the worst chronic diseases such as heart disease and stroke. Every dollar spent combating tobacco-related diseases today helps prevent death and disability tomorrow. Change tomorrow today!"

— Janet Connors, President, American Heart Association, Florida/ Puerto Rico Affiliate of the American Heart Association

2005 Grant Awards

"Tobacco is the leading cause of preventable death and it causes one-third of all cancers. By studying tobacco's harmful and deadly effects, scientists funded by the James & Esther King Biomedical Research Program are making discoveries that will save thousands of lives from cancer and other tobacco-related diseases."

—— Dr. Michael Kasper, Chairman and President of the American Cancer Society, Florida Division

GRANT PROGRAMS OFFERED

A Call for Grant Applications was announced December 15, 2004, for three types of grant programs: New Investigator Research grants, Small Business Technology Transfer grants, and Team Science Program grants.

New Investigator Research Grants

The intent of the New Investigator Research (NIR) grant is to foster development of new Florida-based investigators by helping them undertake independent research that promises to become competitive for national research funding. Projects are conducted over a three-year period under the mentorship of a senior investigator, and proposals must address an important biomedical or behavioral problem relevant to tobacco-related disease.

Small Business Technology Transfer Grant

The purpose of the one-year Small Business Technology Transfer (SBTT) grant is 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, such as the federal Small Business Technology Transfer Research (STTR) program.

Team Science Program Grant

The purpose of the Team Science Program (TSP) grant is to provide two years of support for broad-based, often multidisciplinary research programs with well-defined major objectives or themes addressing the prevention, diagnosis, treatment, or cure of tobacco-related disease that will result in an application at the national level to continue the research program over the long term.

TSP projects generally involve the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate the various aspects or components of the overall objective. TSP grants consist of at least three, but no more than five, interrelated yet individual research projects that are directed toward well-defined research program goals.

RESULTS OF THE 2005-2006 CALL FOR GRANT APPLICATIONS

As a result of the 2005-2006 Call for Grant Applications, 44 responses were received. The application review and award process was completed in June, and the Biomedical Research Advisory recommended funding 16 research grants beginning July 1, 2005.

Seventy percent of the applications submitted were for NIR grants, 16 percent for TSP grants, and 14 percent for SBTT grants. The overall proposal-to-award ratio was 36 percent.

2005-2006 Number of Grant Applications Received/Awarded			
Grant Mechanism	Applications Received	Applications Funded	Percent of Applications Awarded
NIR	31	11	35%
SBTT	6	2	33%
TSP	7	3	43%
Total	44	16	36%

"The James and Esther King Program allowed us to carry a research project to test for the use of a neurotensin agonist as a novel therapeutic agent for nicotine addiction. Additionally, we are studying the changes that take place in the brain after a single and repetitive nicotine exposure to help understand its neurobiologic basis. The results of using our novel neurotensin agonist, NT69L, in blocking nicotine self-administration in rats are very promising."

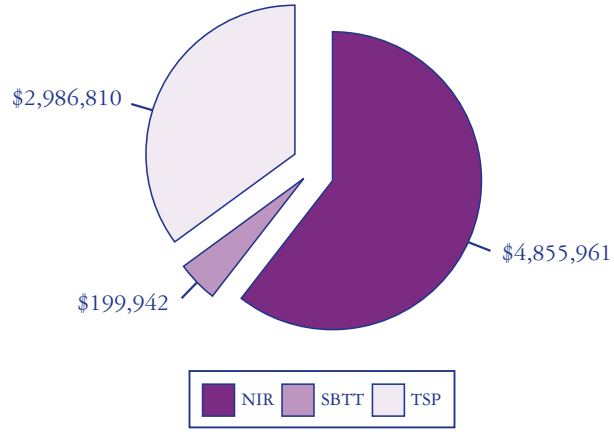
– Dr. Mona Boules, Research Associate, Mayo Clinic Jacksonville, 2004 NIR Grantee

Out of $20 million in applicant requests, the program awarded grants totaling $8,042,713 for 16 research projects. Sixty percent of this amount, or nearly $5 million, was designated for NIR grants for distribution over a three-year term. Approximately thirty-seven percent of the total funding awarded, almost $3 million, was for TSP grants for distribution over a two-year term, while the remaining two percent of funding was awarded for one-year SBTT grants.

"My grant will allow me the possibility to continue my research in lung cancer vaccines. More than 140,000 Americans will die this year from lung cancer in spite of all our existent technology. New modalities of therapy are urgently needed to fight this lethal disease. Our research is extremely essential for our state and our country, and thanks to this program it will be able to continue."

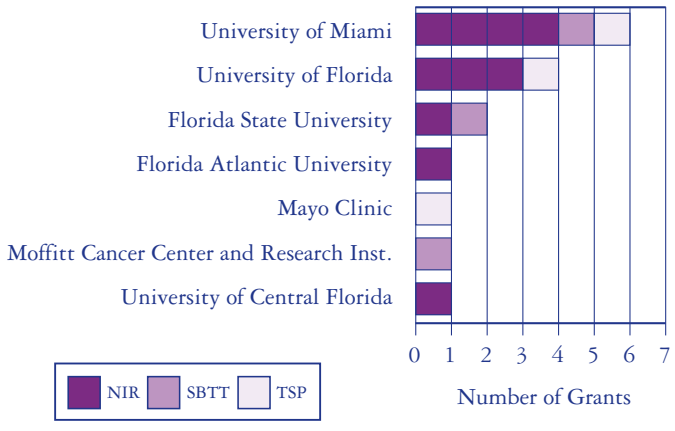
— Dr. Luis Raez, Assistant Professor of Clinical Medicine, University of Miami, 2005 NIR Grantee

2005-2006 Value of Grant Applications Awarded



The program awarded grants to researchers at seven Florida research institutions, with researchers at the University of Florida and the University of Miami accounting for 10 of the 16 awards, or 63 percent, distributed in 2005.

2004 Grants by Institution



GRANTS AWARDED IN 2005

The following is a list of the 16 research projects awarded grants for 2005, totaling $8,042,713. An abstract of each researcher's proposed project appears in Appendix A.

NEW INVESTIGATOR RESEARCH GRANTS

Karoline Briegel, Ph.D.

University of Miami,
Molecular Mechanisms of Breast Cancer and Development
$450,000

Christopher Cogle, M.D.

University of Florida
Defining the Hemangioblast Activity of the Hematopoietic Stem Cell in Lung Cancer Neovasculogenesis
$450,000

Noella Dietz, Ph.D.

University of Miami
The Effects of Eliminating an Anti-Tobacco Prevention Programs on Youth Smoking Behaviors
$380,067

Gregory Dudley, Ph.D.

Florida State University
Organic Synthesis and Methodology for Roseophilin, a Pharmacologically Active Natural Product
$450,000

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

University of Miami
Ischemic Axon Injury: Role of Neurotrophic Factors and Electrical Activity
$450,000

Ceylan Isgor, Ph.D.

Florida Atlantic University
Role of Cannabinoid Receptor 1 in Novelty-Seeking Phenotype & Treatment of Nicotine Dependence
$450,000

Alexander Ishov, Ph.D.

University of Florida
Tumor Suppression Function of Daxx in Tobacco Smoke Mediated c-met Dependent Breast Malignancy
$450,000

Luis Raez, M.D.

University of Miami
Immune Response Against Lung Cancer with gp-96 Fusion Proteins
$450,000

Charles Rosser, M.D.

University of Florida
Genomic Analysis of Voided Urine to Detect Bladder Cancer
$446,719

William Self, Ph.D.

University of Central Florida
Inhibition of Selenoprotein Synthesis by Arsenic Leading to Lung Cancer
$429,175

Erin Seigel, Ph.D.

Moffitt Cancer Center & Research Institute
Association of Smoking, HPV Infection and Aberrant Methylation in Cervical Cancer Carcinogenesis
$450,000

SMALL BUSINESS TECHNOLOGY TRANSFER GRANTS

Ching-Jen Chen, Ph.D.

Florida State University
Rapid Detection of Acute Myocardial Infarction
$99,942

Atwar Ganju-Krishan, Ph.D.

University of Miami
Dedicated Flow Cytometer for Monitoring of Body Cavity Fluids in Lung Cancer Patients
$100,000

TEAM SCIENCE PROGRAM GRANTS

John Copeland, Ph.D.

Mayo Clinic
Smoking and Renal Cell Carcinoma: An Integrative Approach to Improving Patient Outcome
$1,000,000

Richard Johnson, Ph.D.

University of Florida
Smoking as a Novel Risk Factor for Progression of Renal Disease
$997,286

Matthias Salathe, M.D.

University of Miami
Reactive Oxygen Species and Tobacco Smoke-Induced Airway Disease
$989,524

Program Impact

Simply put, tobacco-related diseases are killing Floridians. According to the 2005 Campaign for Tobacco-Free Kids, smoking kills more people than alcohol, AIDS, car crashes, illegal drugs, murders, and suicides combined[1]. This staggering statistic illustrates the magnitude of the challenge faced by the citizens of our state and our leaders.

The goals of the James & Esther King Biomedical Research Program are designed to meet this challenge head-on with a multi-pronged approach. While much work remains to be done, we are pleased to report substantial progress in 2005.

One goal of the program is to expand the foundation of biomedical knowledge relating to the prevention, diagnosis, treatment, and cure of diseases related to tobacco use. Substantiating the potential implications of program-sponsored research, a number of grantees have published and presented their groundbreaking findings.

Since the information for last year's report was collected, grantees have continued to demonstrate the impact of the program's research by documenting their work in at least 32 articles published in well-respected, peer-reviewed journals. Topics ranged from cigarette smoking in HIV patients to the neurobiologic basis of nicotine addiction. Many other articles are still pending or currently in preparation. Since the program began in 2001, grantees have published more than 140 articles in peer-reviewed journals. A list of grantee publications collected over the last year is provided in Appendix B of this report.

The program's researchers also are speaking their minds—presenting important research results gained from the program's funding to their peers in the United States and abroad at conferences and scientific sessions. In 2005, researchers discussed their findings at 65 meetings. To date, more than 200 presentations have been made as a direct result of the program's research findings.

Another goal of the program is to facilitate additional research funding for grantees from outside the state. Further evidencing the program's success, grantees have been successful in securing more than $23 million in additional funding for research that builds upon the work completed with the program's assistance. Thanks to the program's role in enabling researchers to gain outside funding, Florida is moving up the state ranks for NIH funding, being the 16th highest funded state in 2005, up from 19th just two years ago.

More information about current year rankings is available in Appendix C.

Through the three categories of grants and a diverse group of researchers and grantee institutions, a breadth of groundbreaking research has flourished since the program's inception. With each new study, scientists come closer to the end goals of reducing human suffering and eradicating tobacco-related deaths. Grantees in this program are adding significant new information to the body of knowledge that will eventually provide more effective treatments—and even cures—to many tobacco-related diseases. As demonstrated by the following profiles of only a few of the many Program grantees, it is clear that research funded by the James & Esther King Biomedical Research Program is making a difference.

Selected Grantee Profiles

2005 New Investigator Research Grantee - Luis Raez, M.D., University of Miami

Lung cancer has caused its fair share of devastation to Floridians. In 2004, the American Cancer Society estimated that 40,090 people would die of lung cancer in Florida alone, and 97,290 new cases would be diagnosed. University of Miami Medical School researcher Luis Raez, M.D., a 2005 New Investigator Research grantee, is giving lung cancer patients a new source of hope.

Four years ago, 19 non-small cell lung cancer patients who had not responded favorably to the traditional regimen of chemotherapy—radiation and surgery—agreed to participate in a phase one clinical trial of an experimental vaccine. Each patient participating in the clinical trial had advanced stages of lung cancer and prior treatment had failed to significantly reduce the presence of tumors. Patients entering the trial were expected to live less than one year, at best. Dr. Raez administered a B7 vaccine developed by Eckhard Podack, M.D., Ph.D., that sought to enlist the body's own natural defenses to attack lung cancer from within.

Dr. Raez believes the B7 vaccine can be administered to fight lung cancer in the same way the influenza vaccine facilitates the production of antigens to battle the flu. The B7 vaccine stimulates the immune system that destroys the vaccine but builds up a large army of fighters that go to the lung and attacks the deadly cancer cells in lung tissue, while leaving otherwise healthy cells intact. As a result, tumors are gradually reduced and stabilized, and patients may be spared the often-debilitating side effects associated with chemotherapy and radiation.

The vaccine showed impressive results: of the 19 patients who received the B7 vaccine three years ago, six are still living. One patient experienced a reduction in tumor size, while the vaccine stabilized tumor growth in the five other cases.

Based on the success of the B7 clinical trials, Dr. Podack and Dr. Raez developed a newer, stronger vaccine called GP 96, and it has worked well in laboratory experiments with mice. The primary objective of GP 96 is the same as B7: to reduce and/or stabilize tumor growth while potentially eradicating lung tumors altogether. For GP 96's true worth to be known, the next phase of research must entail phase one clinical trials with human subjects—an area where the Program's NIR grant will help Dr. Raez. The support of government-funded public health institutions is often the only means of raising the necessary funds for research, since the costs associated with such trials can be prohibitive.

Dr. Raez credits the crucial financial support provided by the James & Esther King Biomedical Research Program with not only allowing him to continue his own work, but also with maintaining a vibrant research community within academic institutions. To Floridians, the doctors' groundbreaking innovations will result in better, less invasive lung cancer treatment for nearly 100,000 new diagnoses annually. For Dr. Raez's patients, the initial success of B7 and the promise of GP96 means vast improvements in quality of life, better overall health, and—even in the deadliest of cancers—hope.

2005 Team Science Program Grantee - John Copland, Ph.D., Mayo Clinic

Team Science Project Investigators: (from left to right) Steven Ames, Ph.D.; Alexander Parker, Ph.D.; John A. Copland, Ph.D.; and Panos Anastasiadis, Ph.D.

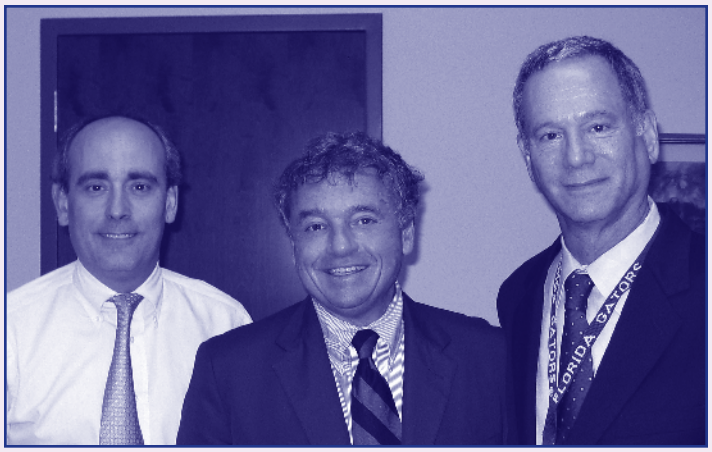
In 2005 alone, thousands of Americans—including about 740 Floridians—will succumb to some form of cancer of the kidney, and many more will receive the frightening news that they have the deadly disease, according to data from the National Cancer Institute. In many instances, cigarette smoke will be a prominent factor in how the disease developed, but no one knows exactly why.

A group of Mayo Clinic investigators in Jacksonville are looking to discover the mysterious correlation between smoking and kidney cancers so that more effective patient treatments can be developed, and they are moving forward thanks to support from the James & Esther King Biomedical Research Program.

With a $1 million grant from the Program, the Mayo group has launched a comprehensive, four-part program investigating a broad range of topics that cover the medical research spectrum: from studies at the molecular level to clinical research that will improve the quality of life for kidney cancer patients.

"This research funding has allowed us to form a multidisciplinary group to attack the complex, smoking-related disease of kidney cancer, for which there are very limited effective treatments," says John A. Copland, Ph.D., the senior investigator of the Mayo group, who is using genomic technologies to identify therapies targeting the genes involved. "Legislators and the governor have done an extraordinary service by promoting medical research that can impact the health of Floridians, the nation, and the world."

Though their ultimate research goals will take years to accomplish, the investigators say that the state funding is a critical first step. With state funding, they will be able to collect important data that demonstrates the potential benefits of their research. From there, they will be in a better position to obtain long-term support from NIH and other major funding agencies.



2004 Small Business Technology Transfer Grantee - Richard Melker, M.D., Ph.D., University of Florida

Dr. Richard Melker (right), with Co-Principal Investigators Dr. Bruce Goldberger (left) and Dr. Mark Gold (center)

Children who are exposed to environmental tobacco smoke (ETS) often are plagued with a variety of health problems. ETS increases the frequency and severity of ear infections, allergies, wheezing, upper respiratory tract infections, and pneumonia. It also has been linked to Sudden Infant Death Syndrome and is known to trigger more severe asthma attacks than those of children raised in non-smoking homes.

If pediatricians had a means to quantify the extent that ETS exacerbates asthma and other chronic conditions, medical professionals would be better able to advocate for children raised in smoking environments. Thankfully, with the support of the James & Esther King Biomedical Research Program, University of Florida researchers are one step closer to making the measurement of ETS' effects a reality.

Richard Melker, M.D., was inspired by the success of a landmine detector invented by the federal government's Department of Defense (DOD) as part of its "Dog's Nose Project," which replicated a dog's strong sense of smell to detect landmines. Dr. Melker collaborated with two fellow University of Florida researchers to develop a breathalyzer-like device to measure the presence of ETS in children with chronic respiratory conditions. A sensor capable of detecting cotinine, a by-product of tobacco, would provide a consistent and reliable measurement standard. He considered cotinine analysis nothing short of a "sixth vital sign" that, for children suffering from respiratory illnesses, had the potential to become as common as taking one's pulse, temperature, or blood pressure.

With the help of a private biomedical engineering firm, Convergent Engineering, Inc., the researchers developed a prototype cotinine breath detector capable of recognizing breath samples. A Small Business Technology Transfer grant from the James & Esther King Biomedical Research Program has been the lifeblood of the most critical phase of the physicians' research. They are now working to establish a blood-to-breath ratio by testing the device on both adult smokers and non-smokers, some with regular exposure to ETS and some without.

"Clinical trials are where the rubber meets the road in medical research and, given the success we've achieved thus far, we're anticipating even greater strides," Dr. Melker said. "The James & Esther King Biomedical Research Program understands the immense potential of applied research and technology transfer, resulting in practical and innovative medical advances that save lives."

2003 Small Business Technology Grantee - Shyam Mohapatra, Ph.D., University of South Florida

For many lung cancer researchers, the first grant is often the most important. Initial outside funding is not only essential for purchasing the necessary supplies, securing laboratory space, and hiring investigators; it also provides key third-party endorsement of the research's validity.

Shyam Mohapatra, Ph.D.—a 2003 Small Business Technology Transfer grantee developing novel lung cancer and asthma drugs—considers the support of the James & Esther King Program a "gateway," better enabling him to compete for other sources of funding. "You can really see this as a seed grant," Dr. Mohapatra explains, "because the King Program grant was the first that I'd received. It offered more than just financial support. It legitimized my work and sends the message to future granting organizations that it is important."

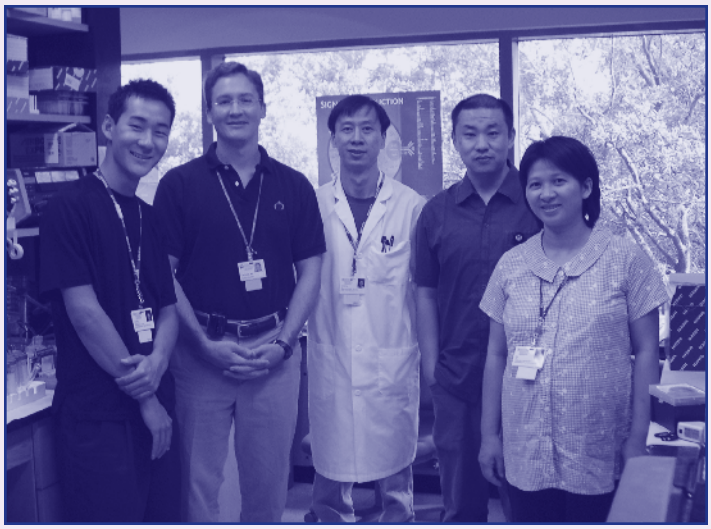
Dr. Mohapatra, of the University of South Florida Medical School, received the support of the James & Esther King Biomedical Research Program for research that could potentially lead to drugs that will not only combat lung cancer and asthma, but could also be used to treat such conditions preventatively.

Atrial natriuretic peptide (ANP) is a sodium-based hormone secreted by the heart and lungs that regulates the body's volume of blood flow in the body. ANP dilates constricted blood vessels to allow blood to flow more evenly. If a blood flow imbalance occurs, this hormone is secreted. Yet, Dr. Mohapatra, looking beyond ANP's cardiovascular function, wondered if ANP could also be used to dilate constricted bronchial tubes in asthma sufferers and control other such "inflammatory events" as tumor growth in the lungs.

Dr. Mohapatra extracted the specific segment of ANP responsible for controlling inflammation. He administered it intranasally to hundreds of mice with transfected lung cancer cells. In mice that received the ANP segment prior to the introduction of lung cancer cells, tumor size was very small—demonstrating that it was able to penetrate the master genes responsible for the rapid cell division increasing tumor size. In mice given the formulation after cancer cells were introduced, it eliminated 95 percent of tumors.

In being the first outside source of funding for this work, the James & Esther King Biomedical Program has helped the University of South Florida forge an innovative and award-winning partnership with TransGenex Nanobiotech, Inc., a potential developer of novel asthma and lung cancer drugs based on this research.

"The Small Business Technology Transfer grant has not only underwritten the successes we've seen so far, but has ushered in a great, and mutually beneficial, partnership between the public and private sectors," Mohapatra said. "With the help of the James & Esther King Biomedical Research Program, we're putting Florida at the center of a biotechnical renaissance that will someday save the lives of unnamed numbers of lung cancer and asthma suffers."



2001 New Investigator Research Grantee - Eric Haura, M.D., H. Lee Moffitt Cancer Center & Research Institute

Pictured are: (left to right) Arthur Edwards, Dr. Eric Haura, Dr. Jiannong Lie, Lanxi Song, and Bin Yu

Both chemotherapy and radiation affect healthy, dividing cells, such as those of the skin, hair, and certain organs of the digestive system. The attack on these cells, and the resulting damage that they must eventually repair, is the origin of the side effects most commonly associated with both forms of treatment.

Targeted therapy is based on the idea that a drug can attack only cancerous cells without damaging other tissue. These therapies act on the molecular level, altering cancer cells' inner growth and survival mechanisms —effectively turning them against themselves. The outcome? Tumor shrinkage with little to no side effects.

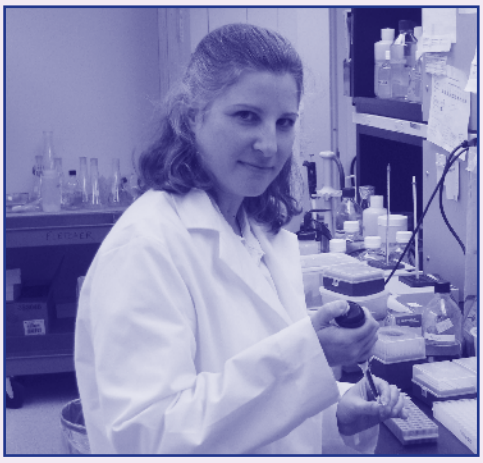
Eric Haura, M.D., a 2001 recipient of a three-year New Investigator Research grant, is working with STAT3 (signal transducers and activators of transcription), a protein belonging to a class called "transcription factors," to investigate the ways it promotes the growth of cancerous cells by allowing otherwise healthy cells to respond to inappropriate external signals to divide.

"STAT3 gives us a vantage point to better understand lung cancer cells' inner workings, allowing doctors to profile patients on the molecular level," Dr. Haura said. "By studying the biopsy of a tumor, we can look at the frequency of STAT activation and develop a targeted therapy to combat it."

With the support of the James & Esther King Biomedical Research Program, Dr. Haura set up an independent laboratory to devote his time and energy exclusively to his work on STAT3. His primary goal is to develop data that pharmaceutical companies can use to create novel drugs that will inhibit STAT3. While he has demonstrated the relationship between STAT3 and the regulatory functions it performs, his research also suggests that such drugs are likely to increase the effectiveness of chemotherapy. Regulating these survival proteins has been found to increase cancer cells' sensitivity to chemotherapy agents, invigorating its ability to eliminate them.

"Regardless of the circumstances, lung cancer patients deserve the best care and treatment possible," he said. "With the help of the King Biomedical Research Program, we're not only turning the tide on many of the misconceptions about lung cancer, but we're also able to maintain our focus on the ultimate goal—an eventual cure."

"With federal funding cut-offs at 15th percentile or lower, it is nearly impossible for young investigators to reach a point where they are competitive with established investigators. Consequently, many of my friends beginning their careers are now running out of their start-up funds before they receive their first federal grant. I have been able to continue because of the James & Esther King Program…When I was interviewing for positions, [this Program] definitely made an impact on my decision to accept an offer at the University of Miami."



— Dr. Terace Fletcher, Assistant Professor of Biochemistry and Molecular Biology, University of Miami, 2004 NIR Grantee

National Biomedical Research Funding and Funding Trends

Florida's James & Esther King Biomedical Research Program operates within a highly competitive environment for biomedical research funding from a variety of sources. The National Institutes of Health (NIH) is by far the largest federal source of biomedical research funding. Other significant federal sources include the Department of Defense and the National Science Foundation. In addition, private pharmaceutical and biotechnology companies fund 54 percent of general health research in the United States.[2]

Federal government support for biomedical research has increased substantially over the last few years. Total funding from federal, state, and local governments; private entities; and industry increased from $37.1 billion in 1994 to $94.3 billion in 2003. The National Institutes of Health nearly doubled its obligations (in 2003 dollars) from $13.4 billion in 1994 to $26.4 billion in 2003.

However, given current and projected national budget demands, the future trend of federal biomedical research funding is bleak. The American Association for the Advancement of Science (AAAS) projects[3] that NIH's 2005-2006 budget will not keep up with inflation. Growth in the budget has slowed from 3.2 percent in 2004 to 2 percent in 2005, and the budget is projected to fall even further to .5 percent in 2006. The percentage of NIH applicants who receive funding each year declined from 32 percent in 2001 to a projected rate of 21 percent for 2005—partly because of an increase in the number of qualified applicants and partly because of budget constraints—according to the AAAS.

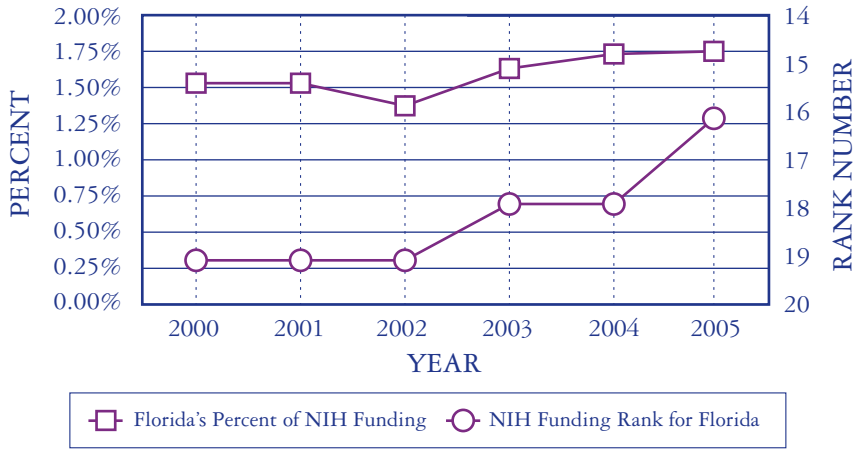
The graph on the following page provides a closer look at the trends in NIH funding for Florida institutions. Plotted against the left axis, the top line illustrates the slight increase in the percent of annual funding awarded to Florida research institutions from FY 2000 to 2005. The lower line shows how, during the same period, Florida

jumped from 19th to 16th place among the 50 states in relative share. In a national environment where many states are jockeying for an improved share of biomedical research dollars, this is a meaningful improvement. However, on a per-capita basis, Florida ranks 46th. Faced with the double challenge of belt-tightening at the federal level and the state's population influx, this program serves as a key countermeasure in attracting a greater share of NIH funding.

Appendix C lists total National Institutes of Health research awards for all states in fiscal years 2004 and 2005.

First, when faced with allocating a disappointingly low overall budget increase of 0.7% from 2005 to 2006 among each of its twenty-seven Institutes and Centers, NIH favored The National Cancer Institute, the National Institute on Neurological Disorders and Stroke, and the National Heart, Lung and Blood Institute with the second ($17M), third ($11M) and fourth ($10M) largest increases, respectively.[4] Given the tobacco-related cancer, stroke, and heart and pulmonary disease priority of the James & Esther King Biomedical Research Program, this is a solid indicator of high NIH receptivity for strong projects that build upon research sponsored by the Program.

NIH Funding Trend in Florida



An important consideration in improving Florida's position in the competition for federal funding is maintaining a close alignment with NIH research priorities. There are two pieces of evidence that clearly indicate that this program is nicely aligned with the direction of future federal biomedical research funding.

Second, across all institutes and led by NIH director Dr. Elias Zerhouni, NIH is pursuing a Roadmap for Medical Research that is focused on

" The American Lung Association of Florida has long recognized the need for funding vital research on the causes of and treatments for lung disease. Since 1999, we have been a proud member of the James & Esther King Biomedical Research Program Advisory Council. We are pleased to play a part in a program that funds valuable research aimed at finding better treatments for tobacco related diseases. The Program has helped Florida become more competitive in the field of biomedical sciences, attracting top-notch scientists and federal research dollars."

—Steven L. Scott, President, American Lung Association of Florida

three themes: cellular, molecular, and atomic level technologies; interdisciplinary collaboration; and research that will translate laboratory discoveries into clinical practice. As you will read elsewhere in this report, a large number of our current grants support work in these areas; these priorities can be expected to continue to guide future program planning and project selection.

This combination of disease-related and focus-oriented national funding priorities points to a high level of NIH receptivity for well-prepared Florida applicants.

In addition to federal research funding in Florida, national partner organizations including the American Heart Association, American Cancer Society and the American Lung Association fund critical biomedical research in areas similar to the James & Esther King Program. In 2005, the American Heart Association allocated $7,570,870 to Florida researchers.[5] The American Cancer Society funded $1,774,739 in Florida research[6], and the American Lung Association allocated $548,425 to fund lung research in Florida[7].

Finally, in order to capitalize on the full spectrum of investment dollars, Florida is committed to improving its own reputation as a nucleus for biomedical research. The state's recent effort to attract the private Scripps Research Institute is an example, along with investments for Centers of Excellence at a number of state institutions and funding for specific conditions such as Alzheimer's disease and spinal cord injuries.

By helping to attract and develop well-qualified biomedical researchers at Florida research institutions, each grant made with the state's investment in the James & Esther King Biomedical Research Program makes a difference in the economic vitality of our Florida communities. Once again, the analogy of the ripples from a stone dropped into a quiet pool applies, as the Program's impact becomes more significant and far reaching with each dollar invested, each lab technician hired, each follow-on grant won, each technology spun off, and each company formed.

A study conducted by the Leadership Board for applied Research and Public Service[8] found that Florida's fiscal year 2003-2004 university research expenditures impact the state's economy in many significant ways.

- Each research dollar spent in the state increases personal income by $5.43.
- University research results in an additional $218 million in tax revenues.
- University research expenditures in Florida generates 76,661 jobs.
- For every dollar spent on university research, Florida's Gross Regional Product increases by $10.89.

Program Operations

SUMMARY OF PROGRAM FUNDING HISTORY AND GOVERNMENT SUPPORT

The table below outlines the number of grant applications received and the number, type, and total value of grant awards extended for each of the six years the Program has been in existence.

Except for the three Small Business Technology Transfer (SBTT) grants awarded in September 2003, appropriations for fiscal years 2002-03 and 2003-04 were used for the second and third year funding of the 42 inaugural grants. From savings in program administration costs for fiscal year 2003–04, $150,000 was made available for the three SBTT awards; however, no funding was available for awarding any New Investigator Research (NIR) grants. Starting with fiscal year 2004-05, the Program was able to offer new grants on an annual basis.

This important change is attributed to legislative changes made in 2004 that created a more stable and sustainable funding base for the James & Esther King Biomedical Research Program. That year, Governor Jeb Bush and the Florida Legislature appropriated $6 million from alcoholic beverages and tobacco revenue for use by the Biomedical Research Program. Additional funding comes from the interest earned on a $150 million reserve within the Lawton Chiles Endowment Fund, a fund established with monies received from the tobacco industry through Florida's tobacco lawsuit settlement agreement.

This support gives the James & Esther King Biomedical Research Program the continued stability essential to the advancement of longer-term biomedical research projects, keeping research teams together, building research capacity, and training new scientists, which together will help Florida become a major global player in biomedical research and biotechnology.

	New Awards History									
	FY 2001-02		FY 2002-03		FY 2003-04		FY 2004-05		FY 2005-06	
Applicants	**189**		**No Call**		**55**		**57**		**44**	
Awards	No.	Million	No.	Million	No.	Million	No.	Million	No.	Million
IIR	28	9.08	n/a	–	n/a	n/a	n/a	n/a	n/a	n/a
NIR	14	7.37	n/a	–	0	0	13	5.62	11	4.85
SBTT	n/a	–	n/a	–	3	0.15	2	0.20	2	.20
TSP	n/a	–	n/a	–	n/a	n/a	3	2.91	3	2.99
Totals:	**42**	**$16.45**	**0**	**$ 0**	**3**	**$0.15**	**18**	**$8.73**	**16**	**$8.04**
* above numbers are rounded										

ADMINISTRATIVE COSTS

Five percent of the annual earnings on the Program's portion of the Lawton Chiles Endowment Fund is returned to the fund to build principal. Administrative costs are limited to 15 percent of the amount appropriated. As the data shown below clearly indicate, administrative costs have been held well below the legislative limit, freeing up more dollars for research project support.

Biomedical Research Program Actual Expenditures and Value of Grants Awarded ($ Million)					
Fiscal Year	Appropriation	New Grant Awards*	%	Administrative Expenses	%
FY 05-06	9.30	8.04	86%	n/a	–
FY 04-05**	9.40	8.73	93%	0.68	7%
FYs 01-04	17.64	16.45	93%	1.20	7%
Total	36.34	33.22	91%	1.88	7%

* Forty-two inaugural grants were awarded in fiscal year 2001. Appropriations through fiscal year 2003-04 were used to fulfill these grant obligations. Except for three one-year Small Business Technology Transfer grants, totalling $150,000 and funded from administrative expenses, no new grants were awarded until fiscal year 2004-05.

** Administrative expenses include $250,000 for the Center for Universal Research to Eradicate Disease pursuant to Section 561.121(1)(a)3, Florida Statutes.

PROGRAM ADMINISTRATION

The James & Esther King Biomedical Research Program is housed within the Florida Department of Health, Office of Public Health Research and a nine-member Biomedical Research Advisory Council (BRAC) provides recommendations and policy alternatives to the Program consistent with Chapter 20 and ss. 215.5601 and 215.5602, *Florida Statutes (see Appendix D)*. A program manager, along with the support of a sub-contracting partner, the Lytmos Group, LLC, provides program oversight and administration.

The program manager is responsible for:

- Working with the Advisory Council to develop Program policy, research grant programs and initiatives, evaluate Program effectiveness, and review long-term goals.
- Managing the budget to ensure appropriate use of trust fund monies.
- Procuring and managing any service contracts.
- Overseeing the award and payment process.
- Monitoring existing grants for progress and use of funds.

The Lytmos Group is currently in the second year of a three-year contract and provides consulting, business, and technology solutions for the grant-making industry. Their delivery of effective processes and innovative solutions helps biomedical research grant programs such as the James & Esther King Program improve grant program performance by reducing the burden of administrative functions and at the same introducing best-practice solutions. The selection of The Lytmos Group during a competitive procurement process was made based on the company's technical capabilities as well as the value offered in exchange for the cost.

Lytmos provides the following services in support of the James & Esther King Biomedical Research Program:

- Program Development: Funding cycle and call for grants preparation, development and refinement of Program policies and procedures and Program materials.
- Application Processing: Acceptance and processing of online applications, including administrative review for compliance with call requirements.
- Peer Review Management: Reviewer recruiting, panel & review assignments, and development of evaluation materials.
- Decision Support: Competition analysis and reporting, funding decision aides, and Biomedical Research Advisory Council support.
- Administrative and Programmatic Monitoring: Financial and progress report evaluations; site-visits; awardee compliance with human and animal use assurances; grantee support for project, budget, or key personnel changes; financial and scientific overlap monitoring; and continuation request processing.
- Program Evaluation and Improvements: Ongoing monitoring and implementation of process and performance enhancements.
- Technical Support: Web site development and maintenance, automated application processing grant management systems support, and grantee technical assistance.

THE GRANTING PROCESS

The level of programmatic impact ultimately delivered by a competitive grant program can be directly related to the effectiveness of the processes used to identify, attract, and support high potential projects and researchers. The James & Esther King Biomedical Research Program continues to seek ways to improve the Program's administrative processes by combining advances in technology designed to reduce overall administrative costs with development of strong granting policies and procedures that emulate the long-standing professional granting process conducted by the National Institutes of Health.

Each year, the granting process begins with guidance from the Advisory Council in preparing and issuing a Call for Grant Applications. Eligible institutions and other interested parties are notified in advance of upcoming opportunities, and applicants are allowed three months to submit an application for grant funding. When the application process has ended based on published Program deadlines, a two-tier evaluation process is used to evaluate proposals for administrative compliance and scientific merit. Experienced scientists with specific expertise in the application topics are recruited from outside the state of Florida to provide peer review of the applications—a process that examines both technical merit and compliance with the overall Program objectives. The Advisory Council makes funding recommendations to the Secretary of the Department of Health and, depending on available funds, awardees are announced.

"With the help of the King Biomedical Research Program, we're not only turning the tide on many of the misconceptions about lung cancer, but we're also able to maintain our focus on the ultimate goal —an eventual cure."

– Dr. Eric Haura, H. Lee Moffitt Cancer Center & Research Institute, 2001 NIR Grantee

Once grants are awarded, the Program staff provides technical support and monitors grantees' performance to ensure that funds are spent as approved by the Program.

The grant terms and conditions require grantees to provide the following reports:

- Quarterly financial reports for the term of the grant
- Annual narrative progress reports
- Final financial report
- Final narrative report

CALL FOR GRANT APPLICATIONS

In preparation for the upcoming 2006–2007 funding cycle, the Advisory Council recommended

that the NIR, SBTT, and TSP grant mechanisms offered in 2005 be repeated. A pre-announcement was broadcast in November to a list of more than 500 interested parties. The 2006–2007 Call for Grant Applications was released on Dec. 15, 2005, and posted on the James & Esther King Biomedical Research Program Web site at www.floridabiomed.com. The site offers visitors the capability of registering to receive Program notices, including the release of the call.

The call specifies a deadline date and time for the online submission of an application. A question-and-answer period allows applicants to submit written questions for clarification. These questions and answers will be published on the Program's Web site, and the open process will help guarantee that all applicants have access to the same information.

GRANT MANAGEMENT

Sound management of research funds sponsored by the James & Esther King Biomedical Research Program requires oversight by both the recipient institution and the sponsoring agency. The Program ensures integrity and accountability in its grant award and administrative processes by:

- Monitoring grants and grantee organizations through reviews of progress reports, financial reports, correspondence, site visits, and other mechanisms.
- Requiring the grantee to have adequate internal controls.
- Requiring the grantee to provide appropriate oversight of individual research projects.
- Requiring the grantee to justify all expenditures, all proposed changes in expenditures, and all proposed changes in key personnel.
- Providing technical assistance as needed.

Grantees and their institutions are accountable for properly administering

the sponsored activities in accordance with the applicable regulations and policies and award terms and conditions. The degree of scientific progress is a consideration in the decision to renew a multi-year project, and is assessed via annual grantee progress reports and site visits. The objective of both is to confirm that research progress is reasonable for the elapsed time and consistent with the work that was funded.

In their written progress reports, principal investigators describe the status of their work relative to the specific aims contained in their project proposal and share significant findings to date, as well as discuss plans for addressing unanticipated outcomes or project delays. This is an opportunity to report the generation of related published works and complementary funding.

Site visits, conducted once during the life of a grant, are intended to facilitate greater understanding about the research that is being conducted and ease dialogue regarding Program policies and administrative support in a non-critical, non-adversarial manner. The site visits are not viewed as investigations or audits; rather they are intended to be a positive learning experience for all involved and their success is dependent on the cooperation and candor of the institutional participants. Through this outreach effort, we hope to understand more about the research being conducted and the needs of the grantees that will allow us to enhance administrative oversight of sponsored research.

2004–2005 grantees were the first to be scheduled for site visits. Although the majority of site visits for the 2004–2005 grantees will be conducted in 2006, the University of Miami was the first institution to be visited. A three-person site review team conducted on-site reviews for four NIR grant recipients and one TSP grant recipient. Following the planned format for all institution site visits, institutional policies and controls and project records were examined; principal investigators conducted lab tours and made presentations on their research followed by a question-and-answer period in which the site visit team learned more about the research and experiments. Grantee mentors, project team members, and other university staff were in attendance at most presentations. The final segment of the site visit was reserved to share observations and findings with institutional officials and as many of the sponsored research investigators as time would allow. Overall, the experience was informative and educational for all involved. It succeeded in strengthening and humanizing the relationship between the university and Program staff and provided an opportunity to converse about the research underway, and exchange constructive feedback about the program.

PROGRAM ENHANCEMENTS

The operational focus for 2005 was on strengthening the Program's capabilities to manage and grow a competitively funded and professionally run grant program. This means ensuring that the Program is effective in attracting the right applicants, selecting the best projects through a peer-review process, and creating a fertile environment for grantee success while operating within the defined boundaries of the Program. The Program's concentration this year in making significant strides in achieving these objectives was to focus on promotion and marketing, process optimization, and testing new methods for assessing and supporting grantee scientific progress.

Program Promotion & Marketing

Raising awareness about the Program is a key factor in growing the number of potential applicants. Capitalizing on the design and logos created for the Program Web site www.floridabiomed.com, a new brochure and promotional posters were developed during 2005 for distribution and use at conferences and institutional visits.

Program staff increased exposure to the Program by attending several biomedical conferences in Florida to network and circulate with researchers and university administrators to discuss the Program. In 2005, James & Esther King Biomedical Research Program representatives attended the 4th Annual Engineers Week Town Hall meeting on Bioengineering and Medical Technology in Tallahassee, the 2nd Annual Florida Tech Transfer Conference in Orlando, and the Scripps/Oxford International Biotech Conference in Palm Beach. Outreach efforts such as these and visits to universities will continue to increase awareness of the Program.

Additionally, enhancements were made to the Program Web site to include brief profiles on all grantees and their sponsored research projects. Making this information easily accessible to Program stakeholders, potential collaborators, and prospective applicants promotes the importance of the Program and stimulates ideas for research topics.

Process Optimization

To prepare for administration complexities such as year-over-year competitions and increasing numbers of grantees, a concerted effort was placed on analyzing the existing grant management processes and practices. The objective was to streamline administrative processes for managing consistent and efficient treatment of grantees' requests and deliverables to allow more emphasis to be placed on accomplishing the goals of the Program.

One of the major enhancements introduced this year was the implementation of GrantEase™, a new extension of the Lytmos AEP® system that accepts and processes online applications and administers the review process. GrantEase gives grantees and Program administrators round-the-clock access to a virtual file of current and historical award information and related activities. It also advises grantees of due dates for reporting deliverables and serves as the mechanism for submitting progress and financial reports, human and animal assurance documents, and change requests and and approval routing. This product was customized and implemented by Lytmos specifically for use with the James & Esther King Biomedical Research Program by Lytmos at no cost to the Program.

"The James & Esther King Biomedical Research Program serves a pivotal role in my career. The program has provided me with resources needed for a career in academic medicine."

— Dr. Arzu Ilercil, Assistant Professor of Medicine, University of South Florida, 2004 NIR Grantee

This operational enhancement has already improved the ability of Program staff to respond quickly, appropriately, and effectively to grantee inquiries and requests. During 2006, the grantees will be surveyed to evaluate its utility in efficiently managing required administrative tasks.

Peer Review of Progress Reports

Performance management is currently a hot topic in the granting community. There has been considerable interest expressed at the national level in finding effective tools for managing and quantifying the impact and effectiveness of high-volume sponsored research programs. Typically, grantees are monitored for administrative compliance during the life of their grant, but programmatic monitoring is often left to program managers overseeing many grants involving a wide spectrum of technologies. In fulfilling their stewardship obligations, the challenge for program staff is especially great for multiple year awards, for which funding continuation decisions are often called. To address improving ways to responsibly monitor the use of grant funds, the James & Esther King Research Program piloted a new process improvement concept involving scientific peer reviews of interim grantee progress reports. All researchers were notified prior to submission that their research project might be chosen for this pilot. Eleven sponsored 2004–2005 research projects were selected for inclusion in the pilot, which involved arranging for three independent reviewers to evaluate and comment on the research progress to date. Evaluation reports were provided to the principal investigator and shared with Program staff.

At the conclusion of the pilot, the results were presented to the Biomedical Research Advisory Council. This included several important conclusions. First, the quality of the progress report appeared to be significantly higher than those previously received. Second, the peer reviews provided useful new information to be considered in making decisions about continuations for multi-year grants. Third, it appeared to hold promise as a grantee mentoring tool by serving as a constructive mechanism for arranging additional thought-provoking feedback from qualified independent reviewers. General feedback from participating principal investigators confirmed that careful consideration was given to the feedback and in several cases PIs adjusted their research studies accordingly.

As a result of the pilot's success, the Biomedical Research Advisory Council endorsed the recommendation to arrange for peer reviews of future grantee progress reports.

"Thanks to this grant, my work has attracted the attention of leading neurobiologists, who are now turning their attention to individual differences in nicotine addiction."

– Dr. Ceylan Isgor, Assistant Professor, Department of Biomedical Science, Florida Atlantic University, 2005 NIR Grantee

Appendix A. Abstracts of 2005 Grant Awards

NEW INVESTIGATOR RESEARCH GRANTS

BRIEGEL, Karoline (University of Miami)

Project Title: Molecular Mechanisms of Breast Cancer and Development

Project Summary: Smoking, as well as passive exposure to smoking, increases the risk of breast cancer in pre-menopausal women by greater than three to sevenfold. The majority of breast cancer cases result from the uncontrolled growth of cells that are part of the milk-secreting glands. These breast cells are prone to accumulate genetic mutations caused by environmental carcinogens (e.g., tobacco) over time, because they are rather long-lived. Another cancer-predisposing factor is that breast cells have a higher growth potential than most other cells in the human body. Full maturation of breast cells is achieved only by hormone induction during pregnancy and lactation periods.

A hallmark of breast cancer is that carcinogen-induced mutations activate genetic programs, which exploit the growth potential of breast cells by promoting cell growth and blocking cell maturation. Recent studies suggest that many of these genetic programs normally regulate similar processes during embryonic development. Despite the high incidence of mutational activation of embryonic genes in cancer, the role of these genetic programs in normal and cancerous breast development remain poorly understood.

One genetic program that is of key importance to both embryonic as well as cancer development is the Wnt signal transduction pathway. This signaling pathway activates growth-promoting genes, which are largely unknown. Dr. Briegel's previous work has identified a Wnt-regulated growth-promoting gene, Lbh, which is expressed at elevated levels in breast tumor cells in mice. Lbh controls gene expression and has been shown to be an important regulator of embryonic development. This research uses tissue culture model systems and transgenic mouse models to confirm that Lbh is a target of the Wnt signaling pathway in breast cells. Moreover, the potential role of Lbh in breast cancer and development will be determined in these model systems. As the Wnt pathway and Lbh have demonstrated cancer-causing potential, the results of Dr. Briegel's research will provide new insights into the development of breast cancer diagnostics and treatments.

COGLE, Christopher (University of Florida)

Project Title: Defining the Hemangioblast Activity of the Hematopoietic Stem Cell in Lung Cancer Neovasculogenesis

Project Summary: In the developing embryo, both blood cells and blood vessels are formed from a common cell called a hemangioblast. Dr. Cogle has shown that in adult mice, the blood stem cells act much like hemangioblasts in that they also contribute to new blood vessel development. Specifically, Dr. Cogle developed a new mouse model of lung cancer demonstrating that blood vessels within lung cancer are of bone marrow origin. In his research, Dr. Cogle employs a mouse model of lung cancer to determine how one marrow contributes to the growth of blood vessels that feed the tumor. His plan is to analyze these lung cancer blood vessels for evidence that they originated from bone marrow. If so, the blood stem cell may represent an excellent target to prevent the uncontrolled growth of lung cancer. He also will identify proteins that stimulate the blood stem cells to create blood vessels. Once identified, these proteins could be targeted. Blocking the ability of blood stem cells to generate cancer vessels would starve the tumor of nutrients and oxygen, thus stunting its growth and development.

Ultimately, this research will lead to bringing about new ways to cure lung cancer and improve quality of life by avoiding surgery, radiation, and chemotherapy.

DIETZ, Noella (University of Miami)

Project Title: The Effects of Eliminating an Anti-Tobacco Prevention Programs on Youth Smoking Behaviors

Project Summary: Since 1997, tobacco control efforts have been underway in a number of states; comprehensive state anti-tobacco programs have worked to prevent and decrease smoking among youths. Despite evidence demonstrating their effectiveness, severe budget cuts have led to the elimination of these youth-targeted programs. Furthermore, with the elimination of the prevention programs, the surveillance and evaluation mechanisms also were eradicated, thereby eliminating data needed to determine how the lack of programs is affecting youths.

As reported in the *Morbidity and Mortality Weekly Report* (MMWR), limited analyses of Minnesota youths—a state where youth prevention programs were cut—show program defunding had an effect on youth's awareness of the anti-tobacco campaign, and youth susceptibility to cigarette smoking increased. The primary objective of Dr. Dietz's work is to assess how the elimination of youth targeted programs has impacted tobacco use prevention outcomes in Florida and Minnesota, states that had effective youth prevention programs.

Because of limited knowledge of the effects that defunding prevention programs have on youth, the proposal will test four hypotheses and compare a number of measures related to youth's participation in anti-tobacco activities, smoking attitudes and beliefs and intentions and susceptibility to smoke, along with actual smoking behaviors. The study will test each outcome before, during, and after the campaign examined existed for both Florida and Minnesota. Furthermore, there is collected data of a national sample of youth who live in states that have never had an anti-tobacco program; these data currently are unanalyzed. This study also will compare these youth with a national sample of youths from states with no tobacco control programs. The study proposes to examine existing data from the pre-campaign baseline, existing data from the campaign, and collect new data from the post campaign.

DUDLEY, Gregory (Florida State University)

Project Title: Organic Synthesis and Methodology for Roseophilin, a Pharmacologically Active Natural Product

Project Summary: New treatments for cancer and other tobacco-related diseases come from myriad sources, with the drug discovery process of medicinal chemistry being one of the most successful and reliable. The strength of medicinal chemistry research derives from its systematic refinement of a lead compound into a powerful chemotherapy through painstaking optimization and testing.

Medicinal chemistry (biomedical research aimed at drug discovery and development) is an experimental science based on synthetic organic chemistry. New compounds may be chemically derived from the natural product, or they may be fully synthetic analogs prepared in the lab from bulk chemical ingredients. Either way, organic synthesis is the enabling technology for this type of biomedical research. Conversely, medicinal chemistry research is limited by confines in organic synthesis.

This research project focuses on advancing the state of the art in organic synthesis. The desire to develop new drugs based on complex natural products like roseophilin, which is potently toxic to a series of human cancer cell lines, drives this research. Several approaches for preparing the bridged multi-ring structure of roseophilin are under investigation, including novel ring-expansions and methods for incorporating key sub-structures within larger, pre-existing ring bridges. Devising new synthetic approaches to a molecule as challenging as roseophilin stimulates creativity and innovation. Several

new methods for organic synthesis also are proposed, with important applications for biomedical research within and beyond the current project.

Cancer chemotherapy is by its very nature a daunting task: The goal is to kill human cancer cells selectively in the presence of a much larger system of non-cancerous human cells. Toxic molecules of ever-increasing complexity are needed for precision targeting within a narrow chemotherapeutic window. Roseophilin is a particularly interesting target compound because of its intricate chemical structure and because its biochemical mechanism of action has not been linked to any known process. This hints at the possibility, pending further research, of a new approach to attacking cancer cells. Such research endeavors require efficient access to roseophilin and synthetic analogs, which would be made possible by successful realization of the ideas presented and explored within this research project.

GOLDBERG, Jeffrey (University of Miami)

Project Title: Ischemic Axon Injury: Role of Neurotrophic Factors and Electrical Activity

Project Summary: Both current and prior tobacco use is a major risk factor for stroke, likely contributing to more than 50 percent of strokes in the U.S. annually. However, it is not known why neurons in the central nervous system (CNS) die after these ischemic injuries. Even in cases where CNS neurons survive, they fail to regenerate their axons appropriately; thus deficits after stroke are frequently permanent.

Most stroke models study the effects of large scale global or focal ischemia and reperfusion, in which grey matter, where neuronal cell bodies are located, is subjected to the ischemic insult. Most strokes in humans, however, occur in CNS white matter, where neuronal axons are located, either exclusively or in part, but models of white matter ischemia are much less well studied. White matter ischemia leads to axon injury and then in most cases to retrograde cell death of CNS neurons. Thus, efforts must be directed toward modeling and studying white matter strokes directly.

Dr. Goldberg is examining the mechanisms of neuronal cell death using the rat retina and optic nerve in a novel model of white matter ischemia. He will use a laser-induced thrombosis model to induce a local ischemic lesion to the rat optic nerve. His experiment will, for the first time, examine the molecular basis for RGC death after ischemic axon injury. His goal is to discover new pathways to prevent neuronal death, then to see how these pathways interact with co-morbid disease (such as smoking) and ultimately to develop new treatments to maintain CNS neuronal survival after white matter stroke.

ISGOR, Ceylan (Florida Atlantic University)

Project Title: Role of Cannabinoid Receptor 1 in Novelty-Seeking Phenotype & Treatment of Nicotine Dependence

Project Summary: Smoking causes a number of diseases. Only 3 percent of smokers are able to quit each year by relying on willpower alone. However, most people do not continue to smoke out of choice, but because they are addicted to nicotine, an active compound in tobacco. Current treatments for smoking cessation are limited to nicotine replacement and antidepressant bupropion (Zyban, Wellbutrin). After all, nicotine patches may reduce smoking (tar, for instance)-related diseases but not nicotine-induced illness. With regard to bupropion, only 30 percent of people respond to this drug, which leaves the majority of people unaided in quitting smoking. Thus, it is important to search for alternative treatments of nicotine addiction.

Recent developments in neuroscience indicate that the personality trait of risk-taking may predetermine drug seeking and avoiding behavior. Specifically, this trait is

divided into high, low, and intermediate risk-takers in the population at-large. The person who falls into the category of a high risk-taker would be characterized by propensity to seek drugs such as nicotine, as well as a multitude of activities that puts self at risk. Such persons report a "thrill" in engaging such activities, and voluntarily choose them over others. It is very probable that neuropathology in drug addiction, specifically in nicotine dependence, is to some extent different in high risk-taking people than from low or intermediate risk-taking ones. Thus, the treatment should be different from one group to the other.

Current medicines for nicotine addiction are developed for the general population of smokers, and do not target differences in personality traits. This may be the reason for failures in treatment of nicotine addiction in some smokers. Furthermore, it is important to develop trait-specific medicine so that limited resources could be effectively used to stop smoking in particularly vulnerable people, such as adolescents. Adolescence is a period in development when the brain is still developing. Most recently, neuroscientists are finding out more about brain neuronal connectivity, which peaks during adolescence. Concurrently, this is also a time in human life when there are heightened sensation-seeking activities. Use of nicotine during this critical period may greatly put adolescents at risk for future emotional problems, such as depression.

In this study, Dr. Isgor proposes to test a hypothesis that nicotine induces distinct neurological changes in the novelty-seeking/risk-taking population during adolescence, and that this will result in differential response to therapeutic intervention. Using a rat model of novelty-induced locomotor response (i.e., novelty-seeking phenotype) resembling the human sensation-seeking behavior, animals will be classified into low, intermediate, and high responders to novelty. Behavioral response to nicotine exposure, as well as brain development and chemistry indices, will be compared between an antidepressant drug bupropion and cannabinoid receptor 1 antagonist treatments in HR-LR adolescents. We have obtained preliminary data in support of the hypothesis that cannabinoid system-targeting drugs may be better suited to aid smoking cessation in adolescents that seek nicotine as part of a novelty-seeking repertoire.

ISHOV, Alexander (University of Florida)

Project Title: Tumor Suppression Function of Daxx in Tobacco Smoke Mediated c-met Dependent Breast Malignancy.

Project Summary: Breast cancer is the leading cause of death in women, affecting more than 10 million women worldwide. North American women have a one-in-eight lifetime risk of developing breast cancer, and approximately one in three women with breast cancer will die of metastases. It is estimated in the US alone, 208,000 women will be diagnosed with breast cancer and 40,200 will die of this disease each year.

With the introduction of more effective treatments, mortality rates from breast cancer are declining and it may be treated as a chronic disease, particularly for hormone-sensitive tumors, which may be managed with sequential endocrine therapy. An active search is ongoing for new targets for breast cancer therapy and for new markers for early diagnosis.

Tyrosine kinase receptors (TKR) have been implicated in the development of multiple tumors, including breast malignancy. These proteins may be important therapeutic targets. One TKR group member, protein c-met, has established functions in tumor invasiveness and metastasis. C-met is over expressed in many types of tumors, including breast cancer and is associated with poor survival prognosis and increased metastasis rate. It was recently shown that high levels of expression of c-met is associated with invasive human breast cancer and is linked to metastasis. This high level of c-met has

been considered a possible indicator of earlier recurrence and shortened survival in breast cancer patients.

Investigators have recently observed that accumulation of c-met is repressed by a protein called Daxx. Moreover, Dr. Ishov found that Daxx is down regulated in several cancer cell lines, including breast carcinoma cell lines that overproduce c-met. He is hypothesizing that Daxx can inhibit activation of c-met. Hence, Daxx is a potential tumor suppressor and is an ideal target to study the physiological regulation of c-met in carcinogenesis, more specifically, in breast cancer progression.

Several studies have reported a link between tobacco smoke, including environmental tobacco smoke (ETS), and increased risk of breast cancer. Cigarette smoke condensate (CSC) contains free radicals and induces oxidative stress and DNA damage resulting in gene mutations. Down-regulation of Daxx or spontaneous mutation inactivating Daxx resulting from tobacco smoke exposure can release Daxx-mediated repression, leading to elevation of c-met gene expression. This event, in turn, can result in carcinogenic transformation of cells and, finally, in breast tumor progression. Dr. Ishov is testing the tumor suppression function of Daxx and studying the mechanisms of this suppression, including CSC-induced stress conditions. Understanding of these mechanisms will advance the knowledge of etiology of tobacco smoke-induced breast cancer. Eventually, Dr. Ishov hopes to find a way to regulate c-met protein production in order to block breast malignancy.

RAEZ, Luis (University of Miami)

Project Title: Immune Response Against Lung Cancer with gp-96 Fusion Proteins

Project Summary: The incidence of new lung cancer patients in the United States was 169,400 in 2002 and the number of deaths for lung cancer was 154,000. Lung cancer is the leading cause of death in the United States. Seventy percent of patients diagnosed with new lung cancers are in advanced stages or incurable since they are candidates only for palliative chemotherapy. Results of treatment with chemotherapy for this disease are poor. Large clinical studies with the best chemotherapy combinations available now have demonstrated responses (decreasing tumor size) in 15 percent to 35 percent of the patients; however, they can only place a patient in complete remission (total destruction of the tumor) in less than 10 percent of patients with a modest impact on survival. The average survival, even with chemotherapy, is still less than one year since diagnosis. Effective therapy requires innovative strategies that can improve the response rate and decrease chemotherapy toxicity such as the tumor vaccine approach proposed here.

Immunologic surveillance is believed to be one means by which cells undergoing malignant transformation are eliminated and controlled by a healthy person. Lung cancers, like other cancers, escape this surveillance and cannot be recognized by our immune system. Vaccines against tumors that have generated responses have been seen in melanoma and renal cell carcinoma. Unfortunately, there is not a vaccine effective against lung cancer yet. The tumor vaccine has the purpose to make the lung cancer tumor more immunogenic, allowing a proper immune response from the patient with the subsequent killing of the tumor without major side effects.

ROSSER, Charles (University of Florida)

Project Title: Genomic Analysis of Voided Urine to Detect Bladder Cancer

Project Summary: Bladder cancer is one of the most prevalent cancers worldwide. Furthermore, superficial bladder cancer has a high rate of recurrence, making it one of the biggest oncological burdens to the healthcare system. Patients with superficial tumors

require repeated routine cystoscopy examinations of the bladder to monitor tumor recurrence. The reason these patients have to undergo these painful procedures is due to the absence of accurate laboratory tests available to detect the presence of bladder cancer non-invasively. Consequently, the development of a urinalysis test to detect bladder cancer would be of tremendous benefit to both patients and healthcare systems.

The aim of Dr. Rosser's research is to create a test for detecting bladder cancer, which will facilitate the accurate detection of bladder cancer in naturally voided urine. He is first identifying the molecular profiles of bladder cancer cells from a large patient cohort. Bladder lining cells are being isolated from naturally voided urine samples collected from patients with cancer or non-cancer conditions. The genetic profile of these cells are being compared using microarray technology and the gene sets that best identify the tumor-bearing samples are being identified statistically. The products of these candidate genes are being used as biomarkers for validation assays in independent samples and the best discriminatory markers will be tested for potential in tumor-specific urinary tests. The project seeks insights that would enable improvements in the monitoring of bladder cancer by laboratory testing, and which, over the long-term, could lead to the development of routine cancer screening of the population.

SELF, William (University of Central Florida)

Project Title: Inhibition of Selenoprotein Synthesis by Arsenic Leading to Lung Cancer

Project Summary: Selenium is a required micronutrient in mammals. Selenium is required for the activity of several enzymes that act to prevent oxidative damage in cells. An increase in oxidative stress, caused by a decrease in the ability to produce selenoproteins, can result in damage to DNA, lipids and protein. DNA damage results in mutations that can ultimately lead to increased incidence of cancer. Thus, one's ability to produce active selenoproteins is tied directly to the occurrence of cancer in the organism as a whole. For this reason, selenium has been touted as an antioxidant that can reduce one's risk for many types of cancer by preventing oxidative stress.

Arsenic is known to cause lung cancer, however the molecular mechanisms behind arsenic-induced carcinogenesis are poorly understood. Many recent studies have determined that treating human cells with certain chemical forms of arsenic lead to an increase in oxidative stress and reactive oxygen species (ROS). The mechanism behind this increase is not understood. The consensus of many scientists studying the cancer-causing effects of arsenicals, however, is that these compounds cause an increase of ROS leading to mutations and subsequently increased rates of cancer.

A recent study in the *Journal of the American Medical Association* (December 2004) showed that the risk for lung cancer increased dramatically in smokers who had a higher intake of arsenic. This study also demonstrated that arsenic intake alone could lead to higher rates of lung cancer in non-smokers. Arsenic is found ubiquitously in the environment and most often as a contaminant in the water supply. Based on this strong association between increased rates of lung cancer and smoking, Dr. Self's study aims to test whether arsenical compounds can block selenoprotein synthesis in human lung cells. The study also aims to find nutritional sources of selenium that can bypass the effect(s) of arsenic on selenium metabolism. Thus, Dr. Self hopes to not only demonstrate why arsenic contributes to development of cancer, but also to identify a source of selenium that can be used as a nutritional supplement to reduce lung cancer rates, especially in smokers. Since many active smokers have trouble quitting, this may lead to a decreased rate or delayed onset of lung cancer in those who cannot fight their addiction to cigarettes.

SIEGEL, Erin (H. Lee Moffitt Cancer Center and Research Institute)

Project Title: Association of Smoking, HPV Infection and Aberrant Methylation in Cervical Cancer Carcinogenesis

Project Summary: Cervical cancer is a major public health issue among women world-wide, including women in the state of Florida. Over the past decade, researchers have identified that an infection of the cervix with Human Papillomavirus (HPV) will cause cervical cancer. However, most HPV infections are cleared by a woman's immune system and never cause any disease. Only a small number of HPV infections will cause changes to the cervical tissue that are detected by a Pap smear screen. It has been shown that smoking is a behavior that puts women with an HPV infection at a higher risk of cervical cancer compared to nonsmoking women that have an HPV infection. Women who smoke tend to have a harder time clearing the virus and have a greater risk of more advanced cervical disease. There are many ways that tobacco can cause damage to the cervix that would allow for the virus to remain active in the cervical cells. One proposed pathway of smoking damage is changing the control of gene expression and even turning important genes off. The expression of a gene is turned off when a methyl group is added to a specific DNA base, known as DNA methylation. There is little known about this pathway of gene silencing through DNA methylation among smokers as an HPV infection develops into cervical abnormalities that can lead to cancer of the cervix among women.

Dr. Siegel's goals for the project are to increase the understanding of the relationship between smoking and DNA methylation among women with cervical lesions or cancer and the possibility of using DNA methylation changes as a new test for women at risk of developing cervical cancer. The long-term goal of this research is to help develop a strong cervical cancer prevention message, encouraging women to quit smoking—especially when DNA methylation changes are found.

SMALL BUSINESS TECHNOLOGY TRANSFER GRANTS

CHEN, Ching-Jen (Florida State University)

Project Title: Rapid Detection of Acute Myocardial Infarction

Project Summary: Smoking is a major contributor to human loss worldwide. Nearly 40 percent of people who die from smoking die from heart and blood vessel disease. Tobacco use is accountable for a large proportion of heart attacks among younger cigarette smokers. This proposal is a joint collaboration between Florida State University and Nanomagnetics and Biotech Inc., a small business based in Tallahassee, to develop a rapid-testing device to identify at the point of care the levels of cardiac markers. Cardiac markers are used as one of the primary indicators to the existence and severity of a heart attack.

The device will be built on the technology that is being patented by Florida State University and has been licensed to Nanomagnetics and Biotech Inc. In this technology, magnetic nanoparticles are synthesized, then coated with suitable surfactant to functionalize them to capture the cardiac proteins in the blood serum. With the use of a magnet, these magnetic particles (after capturing the cardiac marker from the blood serum) will be isolated from the blood serum. An additional labeled protein that also is specific to the cardiac marker will be attached to form a sandwich complex. The second label is used to measure for the concentration of the cardiac protein in the blood sample.

At Florida State University, the second labels that have been tested include enzymes and flour cent labels. Using this technology, the time needed to perform the tests was reduced to a few minutes.

It has been recognized that specialized personnel may be needed to perform such tests with the technology developed. Dr. Chen proposed to utilize a commercial

glucometer to perform the test for heart attack. The developed technology will be utilized with a change in the second label. Instead of an enzyme or a florescent Dr. Chen proposes to use a glucose molecule. This introduction of the new label will make the utilization of rapid detectors available to every clinic and to the first responders. In addition to its speed, this technology will be relatively inexpensive in comparison to all products available in the market. The proposed platform technology can be used with minimum change to detect for infectious diseases, stroke markers, and a range of different applications.

GANJU-KRISHAN, Atwar (University of Miami)

Project Title: Dedicated Flow Cytometer for Monitoring of Body Cavity Fluids in Lung Cancer Patients

Project Summary: Lung cancer screening is primarily based on radiographic examination (chest X-rays) of the patients. Cytopathology of bronchial brushing and washing, bronchi alveolar lavage and of pleural fluid samples have been used for diagnostic purpose. As cytopathology is based on morphological examination of a small number of cells under a microscope, approximately one half of the body cavity fluid samples with malignant cells are not correctly diagnosed, thus resulting in a 50 percent rate of false negatives. Thus, there is an urgent need for improving detection of tumor cells in body cavity fluids by incorporating rapid analytical methods such as immunocytochemistry in combination with high-resolution flow cytometry. Using these highly quantitative and specific methodologies, a large number of cells in body cavity fluids can be rapidly screened and cellular markers of malignancy and cellular origin identified.

Although flow cytometry is extensively used for phenotypic analysis of leukemia, its use as a diagnostic tool for analysis of pleural fluids has been limited. The investigator's hypothesis is that a low-cost, high-resolution flow cytometer that rapidly measures nuclear volume versus DNA content along with the expression of specific markers can be developed for rapid screening of cells in body cavity fluids of patients suspected to have a malignancy. Specifically in patients suspected to have a smoking-related lung malignancy, this instrument could screen bronchial washings and pleural fluid samples to identify cells with aneuploid DNA content and for the expression of markers such as TTF, which is specific to cells of pulmonary origin. To be useful, this instrument will have to be low-cost, require very little technical expertise for operation and be capable of auto-analyzing the data. The investigator proposes to work with NPE Systems of Pembroke Pines to develop and test such a flow cytometer for screening of body cavity fluids. By correlating data obtained from this high resolution, low-cost, dedicated flow cytometer with conventional diagnostic cytopathology, the investigator may be able to improve detection of tumor cells in body cavity fluids of lung cancer patients.

TEAM SCIENCE PROGRAM GRANTS

COPLAND, John A. (Mayo Clinic)

Project Title: Smoking and Renal Cell Carcinoma: An Integrative Approach to Improving Patient Outcome

Project Summary: Renal cell carcinoma (RCC) is by far the most common form of cancer of the kidney. The number of people diagnosed each year with RCC, as well as those who eventually succumb to the disease, have been increasing steadily for more than three decades. Without question, RCC represents a human cancer that warrants close attention.

Despite its steady rise in the US population, RCC remains a cancer that is poorly understood. Studies conducted over the past two decades have established beyond a doubt that smoking cigarettes dramatically increases a person's risk of developing RCC. Unfortunately, there has been little effort to determine (1) exactly how smoking works within the body to increase the risk of RCC, (2) whether smoking is involved in helping a tumor

transition from one that remains confined to the kidney to one that spreads to the rest of the body, (3) whether drugs could be developed that would specifically target the alterations caused by smoking and (4) how smoking habits are affected by diagnosis and treatment for RCC.

In this application, Dr. Copland has assembled a team of experts from a variety of medical and research fields in order to address comprehensively some of the pressing issues with regard to RCC. He has laid out his intention to conduct four specific projects: one focused on examining how smoking increases the risk of developing RCC, one focused on determining which RCC patients will experience tumor spread beyond the kidneys and how to therapeutically target this process, one focused on determining new targets for drug development, and one that will identify the psychosocial needs of RCC patients.

JOHNSON, Richard J. (University of Florida)

Project Title: Smoking as a Novel Risk Factor for Progression of Renal Disease No. 2

Project Summary: Smoking tobacco is a well-known cause of lung and cardiac disease, and hundreds of studies have explored the underlying mechanisms. Often ignored has been an equally strong association of smoking tobacco with the development of kidney disease manifested by enhanced progression of kidney failure, protein in the urine (a sign of kidney damage), and even losing all kidney function, requiring hemodialysis.

There is an epidemic of kidney disease: over 660,000 individuals are projected to have end-stage kidney disease by the year 2010 and as many as 12 percent of Americans currently have depressed kidney function. The yearly medical cost in the United States for the care of end-stage kidney disease patients alone exceeds $12 billion annually. In the state of Florida, the money spent on the care of patients with end-stage kidney disease is equal to half the money spent on chronic obstructive pulmonary disease, even though only a quarter of the number of people are affected with kidney disease as are afflicted with obstructive pulmonary disease.

Smoking is known to cause transient increases in blood pressure and to damage the cells lining the blood vessel. Smoking leads to the absorption of oxidants which can chemically alter proteins, fats, and vitamins in the bloodstream with disastrous effects. Smoking can also cause inflammation. All of these are potential mechanisms by which smoking can lead to a worsening of kidney function.

The overall objective of the research is to evaluate all of the possible mechanisms by which smoking can accelerate worsening of kidney function. Remarkably, a study such as the one proposed has never been performed. Researchers will very accurately determine the level of kidney function in smokers and nonsmokers at the same time they are investigating all of the mechanisms of smoking that can worsen kidney function.

This research could identify new mechanisms underlying the progression of kidney disease itself, even in nonsmokers. This research will focus on investigating novel mechanisms leading to the progression of kidney disease that will lead to new interventions to prevent the progression of kidney disease and will have profound implications for the state of health for the people of Florida.

SALATHE, Matthias (University of Miami)

Project Title: Reactive Oxygen Species and Tobacco Smoke-Induced Airway Disease

Project Summary: Chronic bronchitis, the most common adverse effect of smoking occurring in up to 50 percent of all smokers, is a condition with productive cough due to increased phlegm production caused by an abnormally high production and reduced natural clearing of phlegm from the airways. Chronic bronchitis has detrimental effects

on lung health and is associated with an increased rate of being sick and, in some studies, an increased risk of death.

The long-term objective of this program is to understand how tobacco smoke leads to changes in the lungs of smokers that result in chronic bronchitis and why chronic bronchitis does not disappear in all ex-smokers. Understanding how tobacco smoke-induced changes occur and lead to chronic bronchitis will provide new ideas about how to treat chronic bronchitis in smokers and ex-smokers and perhaps how to prevent chronic bronchitis.

One important feature of tobacco smoke believed to contribute to the development of chronic bronchitis is the presence of reactive molecules that can oxidize components of the bronchi. These reactive molecules typically contain oxygen and are therefore called "reactive oxygen species" or ROS. ROS are not only contained in smoke itself but tobacco smoke can also induce an increased production of ROS by the airways themselves.

The three projects making up this program will examine how ROS, like those found in tobacco smoke and produced by the airway cells themselves, cause changes that are associated with chronic bronchitis. Thus, these projects may perhaps point to the reason why chronic bronchitis does not disappear in all ex-smokers.

All of the projects will use human bronchial lining cells that are obtained from organ donors whose lungs could not be transplanted and whose families consented to using the organs for research. These cells will be grown in a unique, specialized system that exposes the top of cells to sterile air, and the bottom to nutrients, thus resembling the bronchial lining and its functions in humans. Modern, highly sophisticated, microscopic imaging, state-of-the-art molecular genetics, and standard biochemical methods will be used to carry out the proposed research on these cells. These projects might be able to identify new therapeutic targets, thereby provide some relief from a significant social and financial burden on society caused by smoking.

"Young scientists often face an uphill battle when applying for research grants. Junior researchers only reach the level of 'independent investigator' through a body of peer-reviewed work, which is essential if you hope to receive any federal funding. The James & Esther King Foundation's support has allowed me to advance to the clinical trial phase and publish a paper in a prominent, peer-reviewed medical journal."

– Dr. Subhra Mohapatra, Research Assistant Professor, Department of Interdisciplinary Oncology , H. Lee Moffitt Cancer Center and Research Institute, 2004 NIR Grantee

Appendix B. Grantee Publications

The following list represents new publications based on funded research that were reported since October 2004 by all grantees, current and past, in peer-reviewed journals and books. This list does not include works submitted or in preparation. Publications are presented in alphabetic order by last name of the Principal Investigator.

Fredrickson P, **Boules M**, Lin S, Richelson E. Neurobiologic basis of nicotine addiction and psychostimulant abuse as a role for neurotensin. *Psychiatr Clin North Am*. 2005;28:737-751.

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Fritz SL, Chiu YP, Malcolm MP, Patterson TS, **Light KE**. Feasibility of electromyography-triggered neuromuscular stimulation as an adjunct to constraint-induced movement therapy. *Phys Ther*. 2005;85:428–442.

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Appendix C. National Institutes of Health 2000–2005 Funding by State

States are listed in order of total funding received in 2005.

	2005							2004	
State	2004 Population Estimate	Pop Rank	$ per capita	per capita rank	Funding 2005	Rank	% of total funding	Funding 2004	Rank
California	35,893,799	1	87.35	11	3,135,216,412	1	14.95%	3,029,549,006	1
Massachusetts	6,416,505	13	341.33	2	2,190,122,025	2	10.45%	2,126,924,348	2
New York	19,227,088	3	101.01	10	1,942,072,401	3	9.26%	1,904,319,575	3
Pennsylvania	12,406,292	6	113.76	7	1,411,362,641	4	6.73%	1,363,831,678	4
Texas	22,490,022	2	48.97	27	1,101,332,516	5	5.25%	1,102,854,885	5
Maryland	5,558,058	19	181.32	3	1,007,771,813	6	4.81%	1,006,930,873	6
North Carolina	8,541,221	11	105.69	9	902,740,214	7	4.31%	848,265,531	7
Washington	6,203,788	15	123.38	5	765,429,351	8	3.65%	751,818,346	8
Illinois	12,713,634	5	54.78	24	696,401,965	9	3.32%	657,567,989	9
Ohio	11,459,011	7	55.32	22	633,899,896	10	3.02%	590,131,573	10
Michigan	10,112,620	8	53.95	25	545,620,905	11	2.60%	514,728,532	11
Missouri	5,754,618	17	85.19	12	490,241,305	12	2.34%	475,214,844	12
Connecticut	3,503,604	29	128.24	4	449,285,014	13	2.14%	433,602,887	13
Tennessee	5,900,962	16	71.38	16	421,184,016	14	2.01%	397,114,662	14
Minnesota	5,100,958	21	78.75	13	401,700,381	15	1.92%	392,836,183	15
Florida	17,397,161	4	21.11	46	367,266,181	16	1.75%	349,140,295	18
Georgia	8,829,383	9	41.43	31	365,758,450	17	1.74%	365,914,396	17
Wisconsin	5,509,026	20	65.12	18	358,748,939	18	1.71%	373,078,807	16
Colorado	4,601,403	22	70.39	17	323,913,381	19	1.54%	314,413,693	19
Virginia	7,459,827	12	39.33	32	293,428,485	20	1.40%	264,391,789	20
Oregon	3,594,586	27	73.84	15	265,415,014	21	1.27%	256,024,062	21
New Jersey	8,698,879	10	29.60	40	257,504,198	22	1.23%	250,135,783	23
Alabama	4,530,182	23	55.15	23	249,850,414	23	1.19%	253,677,275	22
District of Columbia	553,523	50	367.79	1	203,579,268	24	0.97%	186,401,565	26
Indiana	6,237,569	14	32.39	36	202,007,526	25	0.96%	195,319,415	24
Iowa	2,954,451	30	63.16	20	186,597,985	26	0.89%	190,692,471	25
Louisiana	4,515,770	24	38.90	34	175,659,361	27	0.84%	150,694,964	28
Arizona	5,743,834	18	30.01	38	172,351,461	28	0.82%	156,445,984	27
Kentucky	4,145,922	26	39.15	33	162,320,263	29	0.77%	139,313,715	29
Utah	2,389,039	34	56.02	21	133,833,986	30	0.64%	127,111,596	31
Rhode Island	1,080,632	43	119.96	6	129,633,194	31	0.62%	129,554,156	30
South Carolina	4,198,068	25	29.73	39	124,809,575	32	0.60%	120,413,513	32
New Hampshire	1,299,500	41	75.09	14	97,582,429	33	0.47%	99,103,109	33
New Mexico	1,903,289	36	47.33	28	90,073,546	34	0.43%	90,986,772	34
Hawaii	1,262,840	42	63.76	19	80,513,845	35	0.38%	67,400,396	40
Kansas	2,735,502	33	27.79	41	76,014,728	36	0.36%	74,016,558	36
Nebraska	1,747,214	38	43.28	30	75,625,876	37	0.36%	73,496,561	37
Oklahoma	3,523,553	28	21.19	45	74,672,125	38	0.36%	84,554,337	35
Vermont	621,394	49	107.23	8	66,630,125	39	0.32%	68,228,642	39
Maine	1,317,253	40	50.50	26	66,526,259	40	0.32%	72,501,729	38
Arkansas	2,752,629	32	22.27	44	61,292,899	41	0.29%	55,236,091	41
Montana	926,865	44	44.12	29	40,893,222	42	0.20%	32,184,670	43
Mississippi	2,902,966	31	9.50	49	27,583,207	43	0.13%	32,510,919	42
Delaware	830,364	45	31.97	37	26,546,178	44	0.13%	29,080,909	44
Nevada	2,334,771	35	9.40	50	21,957,856	45	0.10%	20,587,637	45
North Dakota	634,366	48	32.67	35	20,727,876	46	0.10%	16,274,898	47
West Virginia	1,815,354	37	11.21	48	20,356,732	47	0.10%	18,894,683	46
South Dakota	770,883	46	23.74	42	18,299,537	48	0.09%	15,211,445	48
Alaska	655,435	47	23.57	43	15,446,156	49	0.07%	10,769,573	49
Idaho	1,393,262	39	8.28	51	11,539,956	50	0.06%	10,719,731	50
Wyoming	506,529	51	12.43	47	6,294,329	51	0.03%	8,126,436	51
TOTAL	293,655,404		71.40		20,965,635,417		100.00%	20,298,299,487	
Source:									
Population Estimates - http://quickfacts.census.gov/qfd/index.html (accessed 10/09/05)									
NIH Funding Data - http://grants1.nih.gov/grants/award/state/state.htm (2005 data accessed 10/20/05, 2004 data accessed 11/09/04, 2000-2003 data accessed 1/27/04)									

Appendix D. James & Esther King Biomedical Research Program

2004 Florida Statutes
215.5602—James & Esther King Biomedical Research Program

(1) There is established within the Department of Health the James & 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 & 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 & 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 nine 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 Governor shall appoint the remaining six members of the council, as follows:

1. Two members with expertise in the field of biomedical research
2. One member with expertise in the field of behavioral or social research
3. One member from a professional medical organization
4. One member from a research university in the state
5. One member representing the general population of the state

In making his or her appointments, the Governor 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 Governor's appointments shall be for a 3-year term and shall reflect the diversity of the state's population. A council member appointed by the Governor 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 Secretary of Health 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 Secretary of Health, 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 Secretary of Health, 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 Secretary of Health, 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.

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.

Endnotes

1 National Center for Tobacco-Free Kids, "Toll of Tobacco in the USA", 2005.

2 Moses, H., Dorsey, E.R.., Matheson, J.D., Their, S.O. Financial Anatomy of Biomedical Research. *JAMA*, September 21, 2005 (294, 111:1333).

3 American Association for the Advancement of Science (AAAS) R&D Funding Update on R&D in FY 2006 NIH Conference Appropriations, November 17, 2005. http://www.aaas.org/spp/rd/nih06c.htm.

4 *National Institutes of Health Summary of the FY 2006 President's Budget*, February 7, 2005

5 Mary Maynard, American Heart Association, Florida/Puerto Rico Affiliate, FY 2005, July 1, 2004 - June 30, 2005. Provided October 14, 2005.

6 Nina Entrekin, American Cancer Society, Florida Division, FY 2005, Sept 1, 2004 - August 31, 2005. Provided October 27, 2005.

7 Candy Holloway, American Lung Association of Florida, FY 2005, July 1, 2004 - June 30, 2005. Provided October 12, 2005.

8 Moses, H., Dorsey, E.R.., Matheson, J.D., Their, S.O. Financial Anatomy of Biomedical Research. *JAMA*, September 21, 2005 (294, 111:1333).

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