# JAMES & ESTHER KING BIOMEDICAL RESEARCH PROGRAM

## Annual Report 2010

February 1, 2011

## The James & Esther King Biomedical Research Program

The purpose of the King Program is to provide grants for research initiatives that address diseases related to tobacco use.

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

1) Improve the health of Floridians by researching better prevention, diagnoses, treatments, and cures for tobacco-related 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.

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

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

Pictured on the cover from left to right:

First Photo: (From left to right, front row) Principal Investigator Joy Lincoln, Laboratory members Harriet Hammond, Ge Tao, and Damien Barnette. (From left to right, back row) Laboratory members Jacqueline Peacock, Margaret Benny Klimek, and Agata Levay, 2007 NIR, University of Miami. Second Photo: Nithya Bagavatula, Laboratory member on Claudia Rodrigues' grant, 2009 NIR, University of Miami. Third Photo: (From left to right) Kemal Kaya and Saumya Roy, laboratory members on Igor Alabugin's grant, 2009 TTCP, Florida State University

The Honorable Rick Scott, Governor
The Honorable Mike Haridopolos, Senate President
The Honorable Dean Cannon, House Speaker
Dr. Claes Wahlestedt, Chair, Florida Center for Universal Research to Eradicate Disease
Deputy Secretary Kimberly Berfield, Florida Department of Health

Dear Governor Scott, President Haridopolos, Speaker Cannon, Dr. Wahlestedt, and Deputy Secretary Berfield:

Every year, the use of tobacco kills more people in Florida than alcohol, AIDS, car crashes, illegal drugs, murders, and suicides combined. For more than a decade, the James & Esther King Biomedical Research Program has represented a proactive measure by the State of Florida to fight the devastating effects of tobacco by developing more effective methods of preventing, diagnosing, and treating diseases related to its use. Using competitively awarded King grants, the biomedical research community throughout the State has produced a wealth of important discoveries, many of which have already found their way into clinical practice.

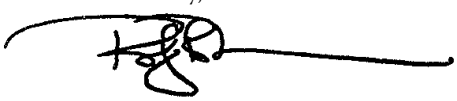
During this same time, the King Program has also proven to be an integral component of Florida's larger investment in growing our technology-based economy in the biosciences in two important ways. First, our grants are awarded based on scientific merit as determined by scientific peer review, regardless of the applicant's institution. As a result, King grants are providing Florida research institutions across the state with vital resources to hire and retain scientists and laboratory personnel, to obtain necessary supplies, and to purchase much-needed state-of-the-art instruments. Secondly, the Program significantly leverages the state's investment in biomedical research, since on average, King grantees have tripled the amount of their Program awards within three years by acquiring additional funding from outside Florida.

On behalf of the entire Biomedical Research Advisory Council, I am pleased to present this 2010 annual report, in which King Program accomplishments, the year's operations, and our plans for the near- and long-term future are described in greater detail. I encourage you to give special attention to the Strategic Planning section of the report, in which we present our funding priorities for the future and offer recommendations for furthering the purpose of the Program.

Within the context of this plan, the Program is currently soliciting applications for 2011 grants. Central to our grant selection is Council members' serious concern that Florida's researchers will see dramatically heightened competition for federal grants in the coming year due to the end of federal Recovery Act funds.

We are grateful for the confidence in this program that led to its reenactment in 2010. Understanding the difficult financial choices you continue to face in the current economic environment, we urge you to support this competitive, peer-reviewed research program as a funding priority – not only to save lives of Floridians, but also to create and sustain high-paying jobs and a skilled biomedical research workforce in the State of Florida.

Sincerely,



Dr. Richard J. Bookman
Chair, Florida Biomedical Research Advisory Council

# James & Esther King Biomedical Research Program

## Annual Report
## January–December 2010

**Submitted to**

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

**and**

**The Florida Center for Universal Research to Eradicate Disease**

**by**

**Dr. Richard Bookman, Chair**
**Biomedical Research Advisory Council**

**February 1, 2011**

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"The state of Florida is in the midst of a once-in-a-generation reinvention of its economy. The level of time, money, and community involvement that have been invested in making Florida a major player in biomedical research has been unprecedented, and has helped establish our leadership in this arena. We have a great deal of momentum right now in terms of recruiting companies and faculty, developing new academic curricula, generating new focus areas of research, and creating translational research programs that will bring the benefits of this research directly to the citizens of Florida. Perhaps most important, Florida is now a serious player in the biomedical research sector. The James & Esther King Program is a critical component of this recent growth. Without it, all the momentum we have gained in the past decade would be lost and our ability to compete on the national level – for dollars, for talent, and as visionaries – would be compromised."

**Philip Arlen, 2009 Technology Transfer/Commercialization Partnership grantee, Patricia and David Schwartz Senior Research Scientist and Assistant Professor, M. D. Anderson Cancer Center**

# EXECUTIVE SUMMARY

For the James & Esther King Biomedical Research Program (the King Program), a major highlight of 2010 was the re-enactment of the King Program in the regular Legislative session after last year's favorable review of Program performance by Senate professional staff.

Forty-two new grants awarded in 2010 are detailed in this report. The portfolio of active King Program grants grew to 121, a 42 percent increase in the 18 months since June 2009. This number includes the final outcome of the 2009 Call for Technology Transfer applications, which was not available at press time for the 2009 report. Florida lawmakers made this growth possible with a substantial increase in annual funding, beginning in 2009 due to an increase in the tax on cigarettes and tobacco products.

The King Program continues to produce valuable insights into more effective prevention and treatment of diseases related to tobacco use. Throughout this report there are a number of grant profiles as evidence, along with summary metrics on publications and presentations demonstrating the productivity and scientific significance of work funded by King Program grants.

Notable accomplishments for 2010 include:

- Grants are leveraging their King Program research, bringing federal dollars to Florida for the study of pulmonary and cardiovascular disease, stroke, cancer, and nicotine addiction. Additional funding earned by King grantees exceeded $160 million as of October 2010, 97 percent of which was from outside Florida.
- The Biomedical Research Advisory Council (Advisory Council) and staff reached out to key stakeholders in order to better understand research needs and respond with suitable grant types. Working with a team of university-based technology transfer directors, the King Program refined a long-standing grant type and introduced a complementary new one. Partnering with the Florida Department of Health (Department) Office of Minority Health, Florida Center for Universal Research to Eradicate Disease (FL CURED), and BioFlorida, the King Program drew upon the outcome of an invitational summit to begin defining a statewide health disparities research agenda. This agenda can be supported with future King grants because tobacco use disproportionately affects minorities and people of low socioeconomic status.

## Strategic priorities for the next three to five years

1) Target the training of new scientists and support successful ongoing research efforts
2) Provide equipment and resources to support research discovery and emerging technologies
3) Increase investment in clinical, translational, and health disparities research
4) Accelerate technology transfer
5) Improve key processes

The Advisory Council and staff continued strategic planning exercises begun in late 2009, identifying five strategic priorities for the next three to five years. The King Program is proceeding to implement these priorities with its preparations for 2011 awards. Factored into the set of grant types offered is a strong concern that Florida's biomedical research community will face sharply increased competition for federal funding as American Recovery and Reinvestment Act funds are depleted.

- The Department continues to ensure accountability to the citizens of Florida for the use of public funds with disciplined processes for tracking, monitoring, and reporting scientific progress and compliance with award terms and conditions. In order to remain responsive to the needs of Florida's research community, feedback is solicited in surveys of applicants and grantees. Surveys have led to a number of changes in Program operations such as an improved question and answer process before the application deadline, more website information regarding competition results, attaching instructions to each Call for Application, and decreasing reporting requirements for minor grant changes.

- The King Program successfully managed an annual competition for grants that produced 2.5 times the number of applications customarily received. Staff completed application processing, peer review, and award announcements according to the normal funding schedule.

- Consistent with its statutory responsibilities, in this report the Advisory Council makes the following primary recommendations to advance the King Program's mission:

  - Advocate for stable state funding with adequate allowance for administrative expenses;

  - Obtain an exemption from Florida open meeting law for the scientific peer review of grant proposals to align with best practices and enable frank reviewer communication regarding scoring variations; and

  - Obtain authority to extend the maximum carry-forward period for grant funds from three years to five years to enable longer grant projects.

The balance of this report aggregates the impact of King Program grants in building Florida's capacity for the research of diseases related to tobacco use, in developing and sustaining a skilled scientific workforce, and in bolstering the state's technology-based economy. It details the King Program's accomplishments against each of its statutory goals, providing snapshots of progress made possible by individual grants. Finally, it relays the sentiments of King Program grantees across the state, who voice their gratitude and emphasis on the value of these grants in pursuing their research careers in Florida, giving Floridians first access to their important discoveries in improving the prevention, diagnosis, treatment, and cure of diseases related to tobacco use.

## Program at a Glance

The King Program offers competitive tobacco-related research grants to Florida institutions based on scientific merit.

**How funded:** $20 million from the proceeds of the state cigarette and tobacco product surcharges plus a portion of interest earnings from the Lawton Chiles Endowment Fund, established with monies received from Florida's legal settlement with the tobacco industry.

**Who manages:** Florida Department of Health and 11-member advisory council

| | |
|---|---|
| First awards made | June 2001 |
| Total no. of awards made | 234 |
| Total no. of Florida research institutions supported | 20 |
| Total value of awards | $98.55 million |
| Additional funding leveraged as of October 2010 | $163.7 million |
| No. of publications generated | 648 |
| No. of invited presentations at scientific meetings | 1,104 |
| No. of jobs supported by Program grants | Estimated at 1,100[1] |

# BACKGROUND

Of the five most common causes of death in Florida reported by the Centers for Disease Control (CDC), the first four are diseases related to tobacco use: heart disease, cancer, stroke, and chronic lower respiratory disease (e.g., lung disease).[2]

## Tobacco's Disease Burden

Smoking is considered the world's leading cause of preventable death.[3] Evidence of its harmful health effects include:

- More than 582,000 Floridians currently suffer from tobacco-associated health problems such as cancer, heart, and lung diseases.
- More than 12,000 Floridians will die this year from smoking-related cancers.[4]
- For every person who dies from smoking, 20 more suffer from at least one serious tobacco-related illness.[5]
- Secondhand smoke is now related to deaths from heart disease, cancer, lung infections, and asthma.[6]
- Infants and young children are especially vulnerable, and smoking during pregnancy causes premature birth, low-birth weights, and sudden infant death syndrome.[7]

Smoking makes health outcomes worse for many, if not all, diseases, and the negative impacts are not isolated to only smokers.

### Program Created to Further Disease Research Related to Tobacco Use in Florida

Ten years ago, Florida made a commitment to address the challenges of diseases related to tobacco use. When the state received settlement funds in 1997, Florida dedicated a portion to support biomedical disease research related to tobacco use, setting the money aside in the Lawton Chiles Endowment Fund. In 1999, the Legislature established the Florida Biomedical Research Program to provide perpetual funding to support research addressing Florida's health issues in tobacco-related cancer, cardiovascular disease, stroke, and pulmonary disease, as well as in behavioral research targeting prevention of disease stemming from tobacco use. The Program was renamed the James & Esther King Biomedical Research Program (King Program) in 2003. Appendix A contains a copy of the King Program's enabling legislation, Section (s.) 215.5602 *Florida Statutes* (F.S.)

### Legislature Reaffirms Commitment to King Program

In its sunset review of the King Program in 2009 and 2010, Senate staff examined the Program's performance, outcomes, and financial management, recommending re-enactment due to the Program's achievement of goals and tangible and intangible benefits to the state.[8] During the 2010 Regular Session, the Legislature renewed the King Program's enabling legislation and appropriated $20 million from the state tobacco surcharge, as well as $2.2 million from the Lawton Chiles Endowment Fund.

## Competitive Awards Based on Scientific Merit

The underlying principles for awarding King Program grants are to open the competition to all researchers regardless of institutional affiliation and to fund the best science. Researchers throughout Florida submit applications in response to a Call for Applications and compete for funding based upon merit. Each application is evaluated for scientific merit and tobacco-relatedness in a peer review process involving experts from outside Florida. Scores are then rank ordered and presented to the Biomedical Research Advisory Council (Advisory Council) for funding recommendations in a manner that blinds Advisory Council members to applicant identities, thus avoiding conflicts of interest.

The King Program's peer review and funding decision processes have earned special National Cancer Institute (NCI) recognition for Program grants. Since 2007, Florida institutions have been able to count cancer-related King Program grants in the research portfolio required to earn NCI Cancer Center designation. This designation matters because it qualifies the institution for multi-year, multi-million dollar funding from the NCI and enhances the institution's ability to offer state-of-the-art patient treatments. See "Program Operations" for more information about the King Program's peer review process.

## Strict Oversight Required to Ensure Accountability

During 2010, the Florida Department of Health (Department) with support of contracting partner, Lytmos Group, Inc., managed a King Program portfolio of 121 active grants, each comprising a contract for research services. The Department uses business processes that comply with the Florida Department of Financial Services' requirements for grant/contract management and oversight, regularly reviewing and evaluating the performance of all King Program grantees.

The Department also provides oversight through site visits and annual progress reports, which are peer-reviewed and provide valuable feedback to grantees. Such practices exceed the national standard for grant management set by the National Institutes of Health (NIH). See "Program Operations" for a detailed description of grant management practices that ensure research and financial accountability.

*Luisana Austudillo, laboratory member on Jaroslava Miksovska's grant, 2010 NIR, Florida International University*

## Program Leadership and Partners Span Florida's Research and Health Care Communities

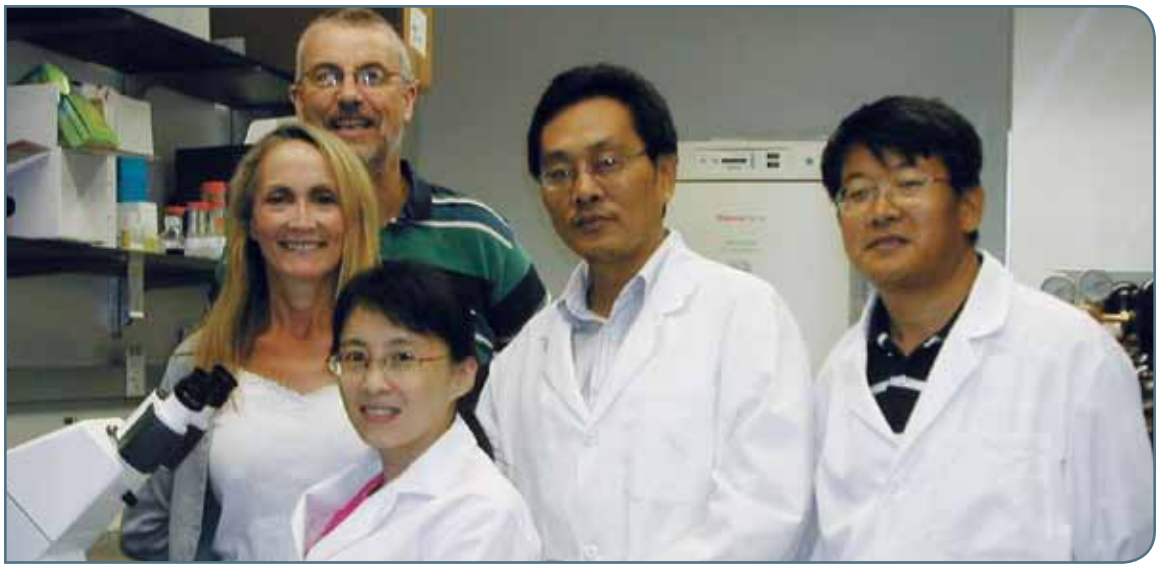
The Advisory Council is an 11-member group of Floridians that includes biomedical research experts, behavioral or social researchers that represent cancer programs, members from voluntary health and professional medical organizations, and the general public. The Advisory Council guides the Department in managing the King Program and builds appropriate bridges to the Program's external partners. See "The Biomedical Research Advisory Council" for more detail.

Key King Program community strategic partnerships include the American Heart Association, American Cancer Society, American Lung Association, Florida Center for Universal Research to Eradicate Disease (FL CURED), university technology transfer directors, the Florida Department of Health Office of Minority Health, and BioFlorida.

> "King Program [technology transfer] grants fill a critical gap in the growth of Florida's economy by assisting in late-stage technology development and early-stage new company formation. The Program is important in the creation of new medicines and the formation of companies in Florida."
>
> **David Day, Director of Office of Technology Licensing, University of Florida**

## Grant Types Strategically Chosen to Leverage Funds and Address Florida's Greatest Needs

On an annual basis, the Advisory Council deliberately designs the King Program's annual grant types to address high priority needs within Florida's biomedical research community and to maximize the impact of Florida's investment. In doing so, they take into account King Program goals (listed on the inside cover), current federal funding priorities and trends, and an awareness of the needs of Florida's researchers. A major objective of every grant is to assist or better position Florida researchers to compete for federal research dollars and to continue research in diseases related to tobacco use. Appendix B contains brief descriptions of all grant types that have been offered by the King Program.



*Research team members (front) Zhijuan Chen; (middle row left to right); Maria Grant, Jun Cai, Li Liu; and (back) Principal Investigator, Michael Boulton, 2009 RC1, University of Florida*

# 2010 COMPETITION FOR GRANT AWARDS

This year the Program awarded 42 grants totaling $19.05 million from FY 2010-2011 funds. Grant offerings included a broad range of types that appealed to both new and experienced investigators and a new award to facilitate technology commercialization.

## Inviting Broader Participation for Florida Investigators in 2010

With more funding, the King Program was able to offer more grant types than in previous competitions, targeting diverse approaches to research of diseases related to tobacco use. The offerings extended greater opportunities for more experienced investigators and specifically encouraged translational and health disparities research. See "Choosing to Study Health Disparities" in the section "King Goal: Researching Better Prevention, Diagnosis, Treatment, and Cures" for more information.

The King Program released four 2010 Calls for Applications on December 4, 2009, inviting proposals by February 12th for the following types of grants:[9]

- **Research Project Grant (RPG):** Supports investigators focused on bringing research discoveries to patient care and/or seeking to reduce health disparities.
- **New Investigator Research (NIR) Grant:** Seeks to fund new investigators so they can establish independent research careers and be competitive for national funding.
- **Team Science Program (TSP) Grant:** Supports a collaborative, multidisciplinary research program with a well-defined theme that results in a national application to continue the research.
- **Postdoctoral Research Fellowship (PRF):** Attracts postdoctoral scientists into tobacco-related research careers.

Even though the Advisory Council defined research emphases in order to avoid an oversupply of applications, researchers submitted a record number of proposals, reflecting the high demand in Florida's biomedical research community for funding to conduct research in diseases related to tobacco use.

## Quick Facts about the 2010 Competition

- The King Program received 156 applications requesting a total of $121.8 million, the largest proposal response since the inaugural competition.
- The King Program awarded 42 grants totaling $19.05 million for projects beginning July 1, 2010.
- As anticipated, the King Program received only a small number of TSP applications due to the Program's limits on the number of applications per institution as well as the magnitude of the work and the high degree of collaboration and interdisciplinary research involved.
- At press time, the King Program received four TTCP and six TTF applications requesting a total of $999,850. Two awards were pending and more applications were expected before the March 31, 2011 deadline, with final funding decisions taking place in May 2011.

## Grants Offered to Support Technology Transfer

To facilitate commercialization of research results, the King Program processes applications on an ongoing basis for two types of technology transfer grants:

- **Technology Transfer Feasibility (TTF) Grant:** Offers early stage funding to develop intellectual property and improve commercial potential and competitiveness for further development.

- **Technology Transfer/Commercialization Partnership (TTCP) Grant:** Encourages the collaboration of investigators and small businesses to stimulate technology transfer activities for promising research discoveries.

Starting June 15, 2010, and continuing through March 31, 2011, the King Program has an ongoing or Open Call for Applications for these grants in order to be more responsive to commercial opportunities as they arise, returning award notifications to applicants within 60 days of application submission.

Refer to Appendix B for more information about current and previous grant types offered by the King Program. This background can aid in understanding the wide range of grant types mentioned in the profiles featured in the Accomplishments section.

Table 1 contains a breakdown of requests and awards by grant type.

**Table 1 – 2010 Grant Applications Received and Awarded as of 12/15/2010**

**2010-2011 Grant Applications Received/Awarded in Annual Call**

| Grant Mechanism | Applications Received | Applications Awarded | Percent of Applications Awarded | Awarded Funding Amounts |
|---|---|---|---|---|
| New Investigator Research (NIR) Grant | 52 | 15 | 29% | $5,899,349 |
| Team Science Program (TSP) Grant | 7 | 1 | 14% | $1,335,420 |
| Research Project (RPG) Grant * | 63 | 14 | 22% | $10,180,757 |
| Postdoctoral Research Fellowship (PRF) | 24 | 12 | 50% | $1,635,400 |
| Technology Transfer Feasibility (TTF) Grant ** | 6 | 0 | 0% | – |
| Technology Transfer/Commercialization Partnership (TTCP) Grant ** | 4 | 0 | 0% | – |
| **Total:** | **156** | **42** | **27%** | **$19,050,926** |

* Value of RPG grants does not include requested funding for years 4 and 5, which will be allocated from FY 2013-2014 funds, subject to the availability of funds and scientific progress.

**Numbers are current at press time; applications will be accepted through March 2011, and awards are possible through May 2011 from FY 2010-2011 funding.

For more information about each awarded grant, see Appendix C or visit the Florida Biomedical Research Program website, www.floridabiomed.com and select the menu option "Funded Projects."

## Final Outcome of the 2009 TTCP Open Competition

On March 31, 2010, the King Program concluded its first trial of the open call concept with the close of the 2009 TTCP Open Call for Applications. As hoped, the total number of these applications increased significantly compared to the response to a single annual deadline.

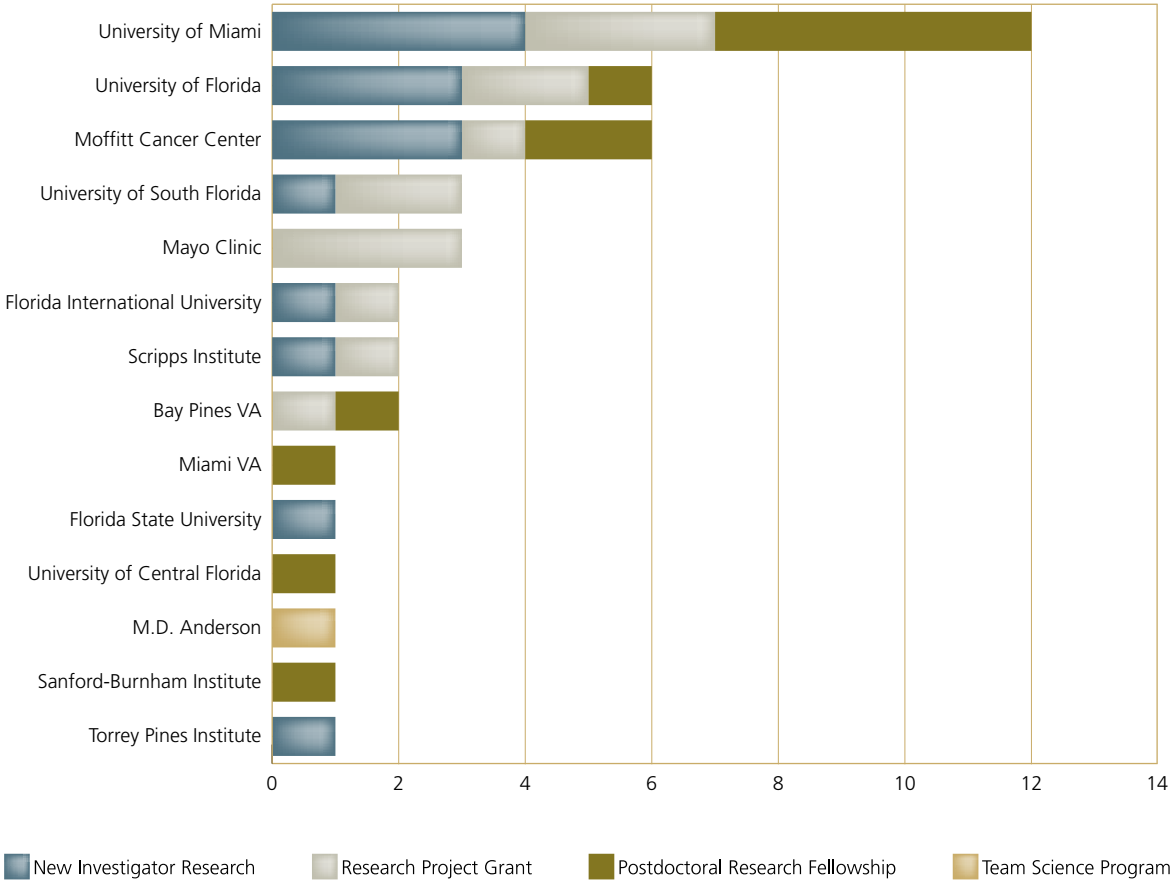
- Applicants submitted ten proposals compared to five for the 2008 Call for Technology Transfer applications, which was only open for 60 days.
- The King Program awarded six TTCP grants valued at $599,853 compared to an average of two per year previously.
- The TTCP grants brought the total value of all FY 2009-2010 King Program awards to $20.9 million.

Appendix C includes information about the three 2009 TTCP awards that were made after the 2009 Annual Report went to press.

## Awards Distributed throughout Florida

As illustrated in Figure 1, 14 public and private research organizations throughout Florida benefited from 2010 grant awards.

**Figure 1 - 2010 Number of Grants Awarded by Institution**

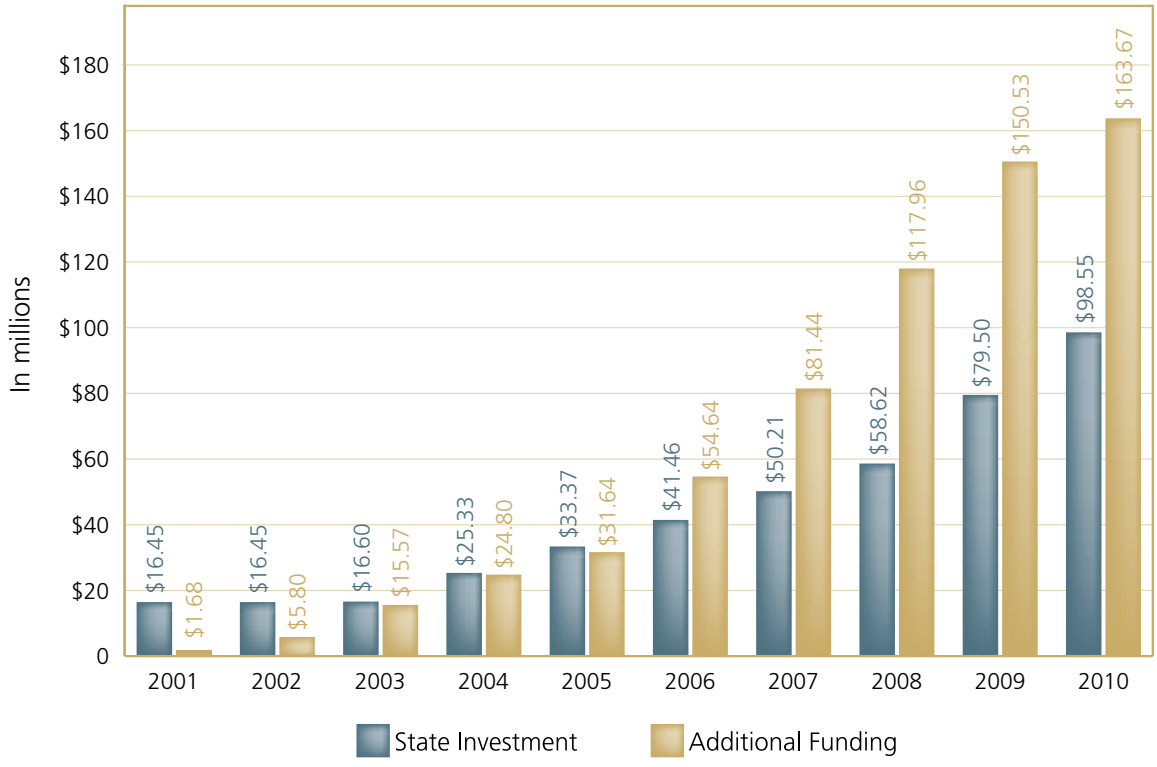


# PROGRESS TOWARDS GOAL: Increasing Florida's Per Capita Research Funding

For all completed grants, 73 percent of grantees report receiving additional funding, averaging more than $976,000 each. Total amount of additional funding is nearly $164 million.

Based on the outcome of their grants, King Program grantees are consistently obtaining additional funding, 97 percent of which is from outside Florida. Figure 2 reflects the combined cumulative value of King Program grants and additional funding earned by King grantees by year of award. As of October 2010, this amounted to nearly $164 million, increasing the King Program's effect in statewide high-technology employment and economic stimulus. With a typical lag of at least 1½ years for grants to generate external funding,[10] this amount represents a return of 2.8 times on Florida's first eight years of the King Program investment. Appendix D contains a list of additional funding reported by grantees in 2010.

**Figure 2 - Cumulative State Investment and Additional Funding by Year**



## Grantee Receives $8 Million in Additional Research Funding

Dr. Matthias Salathe, 2005 TSP grantee at the University of Miami, attributes his grant with generating important ideas and a number of follow-on grants. "Five researchers on this TSP led projects and collected data for federal funding, winning $8 million in NIH and private foundation funding. This was a tight, integrated, multidisciplinary collaboration, and all the researchers on this team are still here and still collaborating," he noted. The TSP led to discoveries about how tobacco smoke changes the airways of smokers resulting in chronic bronchitis and why the disease does not disappear in all ex-smokers. "We touched upon ideas not studied by others and developed new techniques. Since then, some ideas have been confirmed by others and led to new investigations."

*(From left to right) Principal Investigator Dr. Matthias Salathe and Advisory Committee member Nevis Fregien, 2005 TSP and 2009 SIG, University of Miami*

"State funding encourages established investigators not to give up and helps young investigators compete for federal funding. It allows people to come to the state, stay, and work to get NIH funding. I use it as a recruiting tool, telling scientists that the Program is a unique opportunity that does not exist everywhere. My colleagues in other states are jealous of this funding. The state of Florida benefits from federal grant dollars coming into the state, allowing researchers to hire staff and directing federal dollars to state institutions," explained Dr. Salathe.

## Leveraging State Funding

New and seasoned investigators alike are quick to point out how their King Program grant has helped them generate data for competitive national applications. For new investigators, it is virtually impossible to get federal funding without seed money to conduct research. Even for seasoned investigators, applicants often have a good percentage of the work already done and the hypothesis partially proven at grant submission time.

One way to view how grantees are leveraging state funding is an analysis by grant type. Of all completed TSP's, 100 percent have acquired additional funding, and 78 percent of completed NIR's received grants from national or private foundations. The King Program's success in helping new investigators launch productive research careers is evidenced in the average $1.3 million in additional funding earned by each completed NIR grantee.

## Multidisciplinary Approach Leads to Additional Funding

Dr. Keith Brew, 2008 TSP grantee at the Florida Atlantic University, leads this multidisciplinary project seeking to understand neurobiological differences in nicotine use, addiction, and immune response. The data generated from this grant has led to $3 million in additional funding from the NIH, and the team is currently preparing a multi-project federal grant application. "The TSP has encouraged collaboration across disciplines [neurobiology, immunology, and biochemistry] to open up new research areas and to combine approaches resulting in a model that is a predictor of risk. Collaborative, neuro-immune interaction studies are being encouraged by the NIH because of the need and current lack of programs like this," explained Dr. Brew. "Such research activities are a critical component of being a medical school, and contribute to our accreditation process," added Dr. Brew.

# Increasing Florida's Per Capita Research Funding

## Providing Key State-of-the-Art Research Equipment

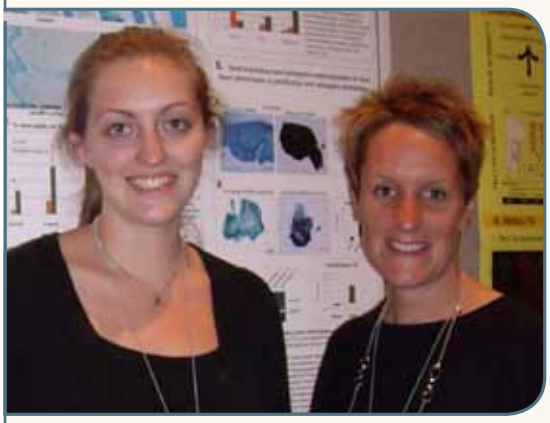
The Program provides funds through the Shared Instrument Grant (SIG) to purchase state-of-the art equipment, which enables the research and data collection required to prepare competitive applications and win grant awards that otherwise would remain out of reach. King Program grantees purchased seven major instruments during the last 12 months, an investment of $2.6 million, with each piece of equipment totaling less than $500,000. Awards were made on the basis of merit through a competitive, peer-reviewed process. Already these instruments have a full schedule of use by many investigators. The recipient institutions provide support for service contracts, salaries for skilled staff to manage the equipment, and in some cases, supplement the funding needed for equipment purchase. The benefits of access to these instruments will continue to accrue over the next several years as studies begin to produce results that enable researchers to acquire additional grant funding from outside the state.

The instruments listed in Table 2 are just beginning to pay dividends in expanded research capacity and capability.

> "This instrument is already very heavily used with a waiting list. There are two main groups comprised of 14 researchers using it now, and three more groups are scheduled to start. We have already seen it strengthen our collaborations here and expect it to support good grant applications and facilitate industrial collaborations."
>
> ***Dr. Alfred Lewin, 2009 SIG grantee, University of Florida***

## Both Grantee and Her Graduate Student Receive Additional Funding

Dr. Joy Lincoln, 2007 NIR grantee at the University of Miami, has received $2.2 million in two NIH grants and is planning to submit a third based on her King Program grant. "This grant, my first, was an excellent opportunity to develop a project that was not yet competitive and establish myself as an independent investigator. It gave me the resources to hire people, generate data, publish papers, and establish my niche in the field. One NIH reviewer commented that, 'Dr. Lincoln has already secured funding from somewhere else and is obviously competitive.'"



*(From left to right) Laboratory member Jacqueline Peacock and Principal Investigator Joy Lincoln, 2007 NIR, University of Miami*

"Also, my graduate student, Jacqueline Peacock, received all her training on this grant, and the preliminary data she generated resulted in her own fellowship from the American Heart Association in addition to two publications and an invited seminar in Europe this year. We were the first group to show a genetic basis for aortic valve calcification in a mouse model. Our overall goal is to find a way to manipulate the function of this gene to prevent or treat valve disease. Our studies in mouse models have led to an informal collaboration with the Division Chief of Cardiology at the University of Miami Hospital to study diseased human valve tissue."

**Table 2 - Type and Location of Shared Instruments Provided through King Grants**

| Instrument | Purpose | Institution |
|---|---|---|
| Biplane Cardiac Angiography System | Study therapies for cardiovascular damage | University of Miami |
| Computer-Controlled Tobacco Smoke Delivery System | Mimic the tobacco smoke exposure of human airways of smokers | University of Miami |
| Confocal Laser Microscope | Capture high-quality images of cells and molecular events at high speed and enhanced sensitivity | University of Miami |
| 4-D Live Cell Imaging System | Look inside cells and see which proteins and enzymes are being made | University of South Florida |
| Fluorescence-Activated Cell Sorter | Study individual live cells in large numbers and analyze characteristics of individual cells | University of Florida |
| High-throughput Nuclear Magnetic Resonance Instrument | Enable structural analysis of molecules at high speeds to accelerate progress in finding drug candidates to treat disease | University of South Florida |
| Spectral Domain Optical Coherence Tomography Instrument | Produce high-resolution, 3-dimensional images from within tissues and cross-sectional analysis with high resolution | University of Florida |

## Grantee Research Results Lead to Additional Funding

Dr. David Lee, 2006 TSP grantee at the University of Miami, led this team in the creation of innovative methodologies and the study of tobacco use in medically underserved areas. The result is $6.2 million in additional grant awards, with several applications pending. These newly funded projects reflect the breadth and reach of this TSP: a Florida smoking cessation program, a Florida secondhand smoke study, testing a novel saliva marker for cancer detection, and identifying breast cancer disparities outcomes. The TSP's goal was to analyze tobacco-related cancers and tobacco use in Florida in order to: (1) reduce tobacco use, (2) increase early cancer detection, and (3) ensure access to state-of-the-art treatment.

"The results of our TSP really pushed us in the direction of disparities. Our research interests are now more targeted because we saw that the burden of tobacco-associated diseases was not randomly distributed across communities. We have to focus limited resources in areas that suffer disproportionately."

"This Program is essential in building research infrastructure that is focused on the problems and health issues that directly impact Floridians. Program grants will help us prepare competitive grant applications and receive additional funding in a time when federal grant budgets are constricting," explained Dr. Lee.

## NIR Grantee Acquires National Funding

Dr. Hengli Tang, 2006 NIR grantee at the Florida State University, received $1.3 million in NIH funding using data generated by his NIR Grant. Other outcomes that will support his future grant applications include a consulting partnership with a pharmaceutical company, one patent issued and another patent application filed, and collaborations throughout the world.

Dr. Tang described how the NIR serves as a catalyst for federal funding. "For several of us at Florida State University, the NIR did exactly what it was supposed to do. It boosted our research programs, gave us confidence that we could pursue our ideas, enhanced our reputations, and we went on to win federal funding. Many of us are now very successful. This beginning certainly helped." Dr. Tang's team studies tobacco smoking, alcohol use, and the hepatitis C virus in order to guide drug development efforts for a form of liver cancer.

"Beyond the value for individual grantees, the Program has brought a lot to our institution. The NIR is a very strong selling point in terms of FSU's ability to attract high-quality people. Having this Program in place helps the recruiting efforts of most Florida institutions and makes us more competitive for national research talent. Very few states have this mechanism," explained Dr. Tang.

# PROGRESS TOWARDS GOAL: Stimulating Economic Activity in Florida

Florida's investment in the King Program is helping build the state's technology-based economy by attracting highly skilled workers, developing new intellectual property, and facilitating new commercial ventures that partner academic researchers with Florida-based small businesses. King grants have provided employment in partial or full salary support for an estimated 1,100 skilled workers.

Research stimulates job growth in the pharmaceutical and biotechnology industries and small businesses. According to Dr. E. Albert Reece, Chairman for the Council of Deans of the American Association of Medical Colleges, academic centers are increasingly being stymied in their ability to create high-paying, sustainable jobs and provide economic opportunities because of tight federal research funding.[11] ***State funding becomes even more critical in such times and captures the attention of researchers across the country.***

The King Program provides necessary support for grantees to develop innovative technologies and form new commercial partnerships, stimulates technology transfer activities, and strengthens the economic feasibility of projects. As a result, the state's universities and biotechnology clusters gain increased visibility in the marketplace among pharmaceutical companies and potential commercialization collaborators.

## Grantee Established New Company in Florida

Dr. Shyam Mohapatra, 2003 SBTT (now called TTCP) and 2007 TSP grantee, at the University of South Florida, founded Transgenex Nanobiotech, Inc., in Tampa with the intent of commercializing technologies he developed from his 2003 SBTT funding. "It grew with funds from NIH and survives today as an innovative R&D company with six employees. The Company is still selling custom nanoparticle formations to diagnose and treat acute and chronic pulmonary inflammatory diseases, such as cancer and asthma," Dr. Mohapatra explained.

"With the 2007 TSP, we were able to establish the Nanomedicine Research Center at University of South Florida and received a Nanomedicine Research Core grant from NIH. This grant allowed us to hire new faculty focused on nanomedicine. We hired three faculty, and all have received NIH R01 grant funding. We are developing a cluster of great scientists using the platform of translational research with a clinical component."

"Without the support of the James & Esther King Program, it would have been impossible for us to get the success in federal support we have achieved today. We would not have been able to establish the Nanomedicine Research Center at USF. Our success exemplifies what the state support can do to bring in outside dollars. The history of Florida's biomedical research programs has clearly illustrated how research funds increase federal funding for Florida science and increase manpower training," explained Dr. Mohapatra.

## Creating Intellectual Property

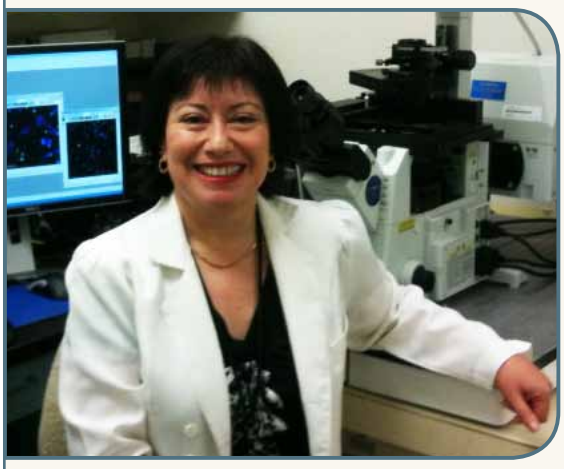
As of October 2010, King Program grantees have filed 33 patent requests,[13] and nine patents have been issued. In addition, there have been five invention disclosures, which represent the first step in the process of intellectual property protection. New inventions and patents are critical because of the vital role intellectual property plays in today's knowledge-based economy and the growth of new businesses. Many of these discoveries are forming the basis for early commercial partnerships with biotechnology or pharmaceutical companies.

"The Program provides incubator funds to enable high-risk, high-reward biomedical research so that excellent Florida investigators can take a chance on new ideas. Additionally, this grant was responsible for joint research with a small Florida biotech business that would not otherwise have occurred. If it is a Florida priority to develop a biotech industry by strengthening existing biomedical research institutions and attracting complimentary industries to the state, these programs are essential."

***Dr. Melvyn Tockman, 2009 TTCP grantee, Moffitt Cancer Center & Research Institute***

## International Patent Granted, Commercial Partnership Pending

Dr. Valentina Echeverria-Moran, 2007 NIR grantee at the Bay Pines VA Healthcare System, has filed four provisional patents for her work with cotinine (a nicotine byproduct) and its effect on the nervous system. One patent is an international patent, which means the discovery is expected to have global impact. She has six grants and is currently pursuing drug development.



*Principal Investigator Valentina Echeverria-Moran, 2007 NIR, Bay Pines VA Healthcare System*

"People may smoke for the effects of cotinine. We are exploring it as a way to prevent tobacco addiction in the first place. Cotinine, unlike nicotine, has a good safety profile in humans." In addition, her grant collaborations led to a new experimental psychology department at Bay Pines, and she said that the "Program has had an incredible effect on our institution."

"Before coming from Columbia University in New York, my professor told me about the King Program and the NIR grant. The Program made Florida more attractive, and other states did not have a program like this. Here I knew I would have the opportunity to develop my own ideas and start as an independent scientist. It's made an enormous difference. Nine people have been trained [in my lab] thanks to the Program. The support of serious and unbiased programs like the King Program can make the difference to advance preventive and curative health programs," explained Dr. Echeverria-Moran.

# Stimulating Economic Activity in Florida

## Moving Technology to the Marketplace

The King Program has awarded $1.54 million for 17 Technology Transfer/Commercialization Partnership (TTCP) grants since 2003. Of the 11 completed grants, 5 have been successful in moving technology into the commercial marketplace, a remarkable outcome given the high-risk nature of this effort. These grants have contributed to 5 active, new companies in Florida that have created at least 45 industry jobs, including research and development, engineering, scientific management, and assembly.

TTCP application numbers tend to be low because scientific research skills and product commercialization skills are so divergent. Moreover, it is difficult for scientists to find and connect with small business partners that have appropriate capabilities and resources.

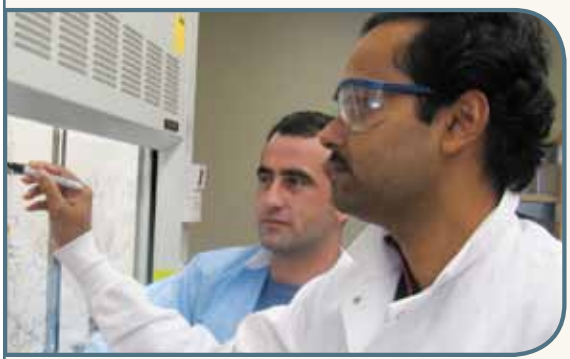
In order to improve the commercialization of research discoveries, the King Program collaborated with a network of university-based technology transfer directors in 2010 and adopted the following two new strategies in an effort to increase the volume of high-potential technology transfer projects:

- The creation of the Technology Transfer Feasibility (TTF) Grant to provide support for early-stage projects with commercial potential. The TTF is designed to stimulate technology transfer activities and to strengthen the project's economic feasibility and commercial prospects.
- The adoption of an "open call" and 60-day funding response for both the TTF and TTCP grants. This move is intended to allow researchers to capitalize on time-sensitive commercial opportunities.

### Working with a Florida Business to More Selectively Target Cancer

Dr. Igor Alabugin, 2009 TTCP grantee at Florida State University, has developed a molecule to target cancer cells selectively. He is working with Florida Custom Synthesis to make the compound and has received one patent already with two more pending. This approach targets melanoma and cancers of the lung, esophagus, throat, and mouth.

Proximity to DNA and light activates the molecule resulting in the cleavage of both strands of a cell's DNA, which is difficult for the cell to repair. Dr. Alabugin is now adding a third level of selectivity – acidity. Tumor environments are more acidic, so he is making the molecule more reactive in acidic environments. "The next step is animal testing then licensing the technology to a pharmaceutical company or creating a start-up company," he explained. "This program is developing a new approach for selective, efficient programmed death of cancer cells and new approaches to cancer therapy."



*(From left to right) Kemal Kaya and Saumya Roy, laboratory members on Igor Alabugin's grant, 2009 TTCP, Florida State University*

"Through the TTCP, we formed new collaborations at the Mayo Clinic and at Albert Einstein College of Medicine, New York, and established a commercial partnership with Florida Custom Synthesis, Inc., in Tallahassee that allows for more efficient creation of the molecules. They make a part, then we make another part and put them together. The TTCP has provided additional training opportunities as well–seven students are involved," explained Dr. Alabugin.

## Increasing Florida's High-Tech Job Opportunities

With approximately 64 percent of the total funds awarded by the King Program dedicated to salaries, the Program has made its largest investment in Florida's human capital. At 20 different research institutions across the state, 234 grants have provided employment and partial or full salary support for an estimated 1,100[12] skilled workers; when factoring in the employment effect of the additional funding King grants have acquired, this employment number is much greater.

Including the principal investigators leading the research, there has been an average of 4.8 people compensated to some degree by each grant, including collaborating scientists and clinicians, graduate students, postdoctoral researchers, research associates, laboratory technicians, nurses, and biostatisticians. In addition to paying salaries, the King Program has also accelerated the growth of skills by providing mentored research experiences to new investigators and postdoctoral fellows. A strong research base draws companies as supported by the following quote.

"Two major companies have just come down to University of South Florida wanting to have an affiliation with the research programs here. Bringing a company here and employing people is a win-win. That's what comes out of this Program," explained Dr. Duane Eichler, Professor & Vice Chair of Education, Department of Molecular Medicine, College of Medicine, University of South Florida, in a recent interview.

## Developing Commercial Partners to Improve Survival for Females Undergoing Lung Cancer Surgery

Dr. Tatyana Zhukov, 2007 NIR grantee at the Moffitt Cancer Center & Research Institute, has made important discoveries about female survival following lung cancer surgery resulting in two patents. Both discoveries are in the beginning stages of commercial development.

The research started with a troubling trend based on 25 years of lung cancer data from the Florida Cancer Data System. Females with lung cancer consistently experienced shorter survival times after lung cancer surgery than males. Why? Dr. Zhukov used King Program funding and a collaboration with scientists at University of South Florida and University of Central Florida as well as a Florida-based imaging company, IntelliSense Design, Inc., to find the answer. The team is in the process of licensing their findings to a pharmaceutical company.

## Collaborating with Florida Business to Develop Instrument for Early Cancer Diagnosis

Dr. Melvyn Tockman, 2009 TTCP grantee at the Moffitt Cancer Center & Research Institute, is laying the scientific groundwork to prepare for the design of a potential diagnostic instrument to identify the presence of cancer. Dr. Tockman is collaborating with a Florida small business, IntelliSense Design, Inc. "Together, we will automate image acquisition, analysis, and enhance instrument design [while] considering factors for commercialization. In a subsequent federal grant, we intend to build and validate the instrument. We are currently pursuing protection for intellectual property."

"During the course of Dr. Zhukov's research we began to ask questions about centrosomes and how they relate to the diagnosis and prognosis of cancer. That work led to the questions we are exploring."

Dr. Tockman is looking at changes in the number and structure of centrosomes, which cause irregular chromosomal separation into daughter cells, indicating cancer. "By measuring the centrosomes, we may be able to predict treatment response and survival. Although our focus is lung cancer, these changes may apply to other cancers as well," explained Dr. Tockman.

# PROGRESS TOWARDS GOAL: Researching Better Prevention, Diagnoses, Treatments, and Cures

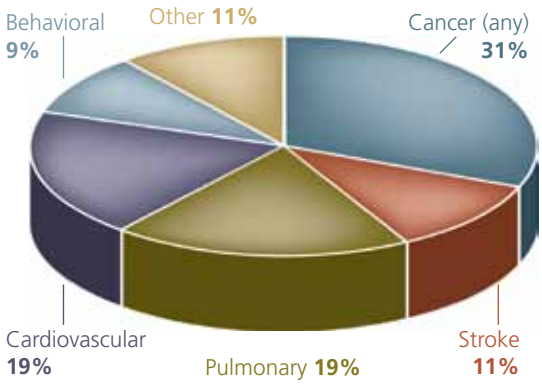
The King Program supports research at all stages and with various approaches in addressing diseases related to tobacco use, primarily cancer, cardiovascular disease, pulmonary disease, and stroke. In the fundamental design of certain grant types, the King Program has specifically encouraged multidisciplinary research, the application of findings to human populations, and studies aimed at reducing health disparities.

King Program grants have intensified the research effort in Florida aimed at improving our capability to prevent, diagnose, treat, and cure diseases related to tobacco use. Of all King Program grants, 71 percent focus on treatment/cure; 17 percent on prevention, and 12 percent on diagnosis. In addition to research goals, grants vary widely in disease focus and stage of research. As a result, grants can be characterized in a number of ways as shown below.

## Building a Diverse Portfolio of Tobacco-Related Research

Figure 3 depicts the allocation of the King Program's cumulative grant portfolio by research focus. Behavioral research projects seek a better understanding of the environmental, psychological, and physiological factors that lead people to use tobacco and/or improved intervention strategies for tobacco use prevention and cessation. Grants grouped into the "Other" category represent crosscutting projects with the potential to address multiple diseases, such as research in basic science, health disparities, imaging, or the purchase of a major state-of-the-art research instrument.

**Figure 3 – Grants by Research Focus**




Projects with more than one emphasis are counted more than once.

## Long-Term Smokers Quit through Grantee's New Treatment Plan

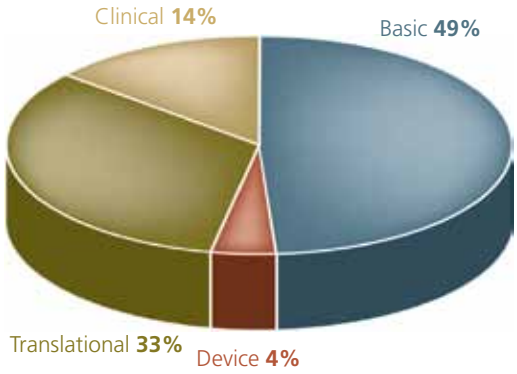
The purpose of Dr. Mary Gerend's study, 2007 NIR grantee from Florida State University, is to develop a novel approach to smoking cessation treatment for smokers with elevated levels of anxiety. One month after completion of the program, 61 percent have successfully quit smoking. The following testimonial is from a smoking cessation therapist, Chris Blagg, who works with Dr. Gerend:

"I met with an elderly female participant for her one year follow-up visit to the smoking cessation intervention. She was pleased to report that in the past year she had been able to remain smoke-free. I'll never forget how her face lit up as she told me that after struggling with COPD for many years, her doctor had been able to take her off breathing treatments because her health had improved so drastically. She was overjoyed because she had been able to quit smoking after having smoked for close to six decades. She told me that she never thought she would be able to quit."

## Supporting Every Stage of Research

Another way to look at King Program grants is along the research continuum from discovery in the lab to testing in human subjects. Basic research is the foundation of all new discoveries and builds understanding about how things operate at a molecular level. Basic research often leads to intermediate applications (translational research) involving testing in animals and human-derived tissue. These studies, in turn, may enable testing in clinical studies and human use. Figure 4 illustrates a percentage breakdown of grants by research stage.

**Figure 4 – Grants by Research Stage**




## Testing a New Cessation Treatment for Young Adult Smokers

Dr. Steven Ames, 2009 RC1 grantee at the Mayo Clinic, is researching a treatment strategy as the first step in developing a standard of care for young adults who are established smokers and binge drinkers. Based on his 2001 King Program NIR grant, he found that binge drinking combined with smoking is extraordinarily common in young adults. "The King New Investigator Research grant I received in 2001 was instrumental in getting me to Florida. That study led to an NIH grant, which helped us learn how to design intervention treatments for young adults. I'm using information from both grants for the current study," explained Dr. Ames.

"Young adults (ages 18-30) have the highest rate of smoking, and half of them also binge drink.[16] Yet only a handful of studies have been done with this group. The other thing that is overlooked is that tobacco and alcohol create a synergistic risk factor for cancer," he explained. "Young adults have different needs, motivations, and risk behaviors, and traditional treatment strategies are aimed at older adults." Dr. Ames, in collaboration with the Alachua County Department of Health, has recruited 170 young adults. The 12-week treatment includes a nicotine patch with follow-up at six months.

*(From left to right) Laboratory members Edgar Covil and Andrea Tavlarides with Principal Investigator Steven Ames, 2009 RC1, Mayo Clinic*

## Choosing to Study Health Disparities

During the last two years, the King Program has encouraged grantees to study the perplexing problem of health disparities. Health disparities are differences in the incidence, prevalence, mortality, burden of diseases, and other adverse health conditions or outcomes that exist among specific population groups. Health inequality describes instances where the health outcomes among specific population groups differ despite comparative access to health care services.[14] Smoking is increasing among minorities, and the tobacco industry has aggressively increased its advertising campaigns targeted at minorities.[15] Increased tobacco use leads to increases in the tobacco-related disease burden in affected populations. Additionally, for reasons still not completely understood, for many conditions, minority populations experience poorer health outcomes compared to the majority population. Some of the populations King grantees are researching include African Americans, Hispanics, Native Americans, Asian Americans, women, and low-socioeconomic status groups.

## Identifying Differences in Immune System Function that May Indicate Risk for Diseases Related to Tobacco Use

Dr. Marie Jose Miguez, 2010 RPG grantee at the Florida International University, is examining biological and behavioral, rather than socioeconomic reasons, behind health disparities in tobacco-related diseases. "Our data suggests that differences may be the result of unique patterns of cytokine production among racial ethnic groups. We have found differences in at least two patterns, and we suspect that there may be more. If cytokines are too high or too low, they may cause certain diseases. If we identify the sources of the problem, there are many pathways to try to resolve them." The team hopes to provide information to reduce health disparities, enhance treatment protocols, and guide policymakers and health care providers in prevention efforts to reduce health disparities and health care costs for the state.

*Principal investigator Claudia Rodrigues, 2009 NIR, University of Miami*

## Researching A Treatment Where None Exists for a Smoking-Related Eye Disease

Dr. Alfred Lewin, 2009 SIG grantee at the University of Florida, purchased a spectral domain instrument for age-related macular degeneration (AMD) research. Smoking is a risk factor for AMD, a disease associated with aging that gradually destroys vision. The team is using the instrument to test new drug and gene therapies using high-resolution images of the retina. No treatment exists for the dry form of AMD that the team is investigating.

"The Program has been fantastic in that it allows people to bring new ideas to the forefront, to develop external funding, and to produce experimental results more effectively. It provides seed money that gets things started and that's what it's done for us," explained Dr. Lewin.

"The support of the James & Esther King Program has been huge for our research program getting off the ground. The Program has made possible our lab's initial growth and development in our efforts to bridge the gap between the bedside and the bench. Our mission in translational research, to better understand the obstacles we face in treating patients with cancer, testing our hypotheses in the research lab, and bringing real solutions back to our patients, would not be possible without the dedication of the James & Esther King Program."

***Dr. Thomas Shellenberger, 2008 NIR grantee, M.D. Anderson Cancer Center***

## Detecting Cancer Earlier at the Nanoparticle Level Using New Technique

Dr. Ming Su, 2007 NIR grantee at the University of Central Florida, has created a new technique for detecting indicators of cancer (called biomarkers) at the nanoparticle level. The ability to detect such small biomarker quantities enables earlier detection of cancer and treatment before cancer spreads. Dr. Su has tested the technique in blood and will test it in tissue samples through a collaboration with M.D. Anderson Cancer Center.

"Without the support from the King grant, I could not have reached this level of discovery. This grant built the foundation of this group so we could start to work. It gave me time to learn cancer issues, train my students, and collect preliminary data to compete at a national level." Dr. Su has a patent for his work, a Department of Defense grant, and has submitted applications for additional national grants. His research has been highlighted on the website of the Lung Cancer Research Program of the Department of Defense Congressionally Directed Medical Research Programs.

*(From front to back): Research team members Lauren Bello, Angie Fink, and Riddhi Patel navigate through the College Student Smoking Intervention designed by Principal Investigator, Vani Simmons, (on right) 2008 NIR, Moffitt Cancer Center & Research Institute*

"The college years represent an important window of opportunity to intervene with regards to smoking cessation. This is the youngest legal population the tobacco industry can target, making them more vulnerable for nicotine dependence. It is easier to intervene now than as an older adult because they're at a lower level of nicotine dependence, yet this age group has received very little attention in the smoking cessation literature."

***Dr. Vani Simmons, 2008 NIR grantee, Moffitt Cancer Center & Research Institute***

# PROGRESS TOWARDS GOAL: Delivering Research Advances to Florida's Academic Health Centers and Health Care Providers

The King Program has awarded grants to 53 researchers who are also medical doctors. This represents nearly one-fourth of all grant awards. The involvement of physician scientists is a key factor in enabling the translation of basic research into clinical practice.

Research advances stemming from basic science must be carried through to medical practice to fulfill the overarching King Program goal of improving the health of Floridians. Physician scientists can facilitate clinical testing, direct basic research to pertinent questions based on patient experience, and immediately transmit research findings into the training of physicians and medical personnel. Finally, they can open the doors of Florida's health centers, hospitals, and clinics to new methods of diagnosis, treatment, and prevention.

## Physician Gains Experience Conducting Asthma Clinical Trials

Dr. Jason Lang, 2009 NIR grantee and pediatrician at the Nemours Children's Clinic, is gaining invaluable research skills and experience through his grant. "Through a fantastic mentor, Dr. John Lima, I am learning all the critical pieces of conducting clinical trials. This experience will definitely impact the clinical teaching I do for medical students and residents at University of Florida."

Due to their patient contact, physicians raise important questions for research and can facilitate the translation of findings from the bench to the bedside. "In my case, we're using 300 kids from the American Lung Association's Asthma Clinical Research Centers to determine the role of secondhand smoke (SHS) in asthma. If we can explain why SHS is so damaging to the lungs of asthmatic kids, we can really push zero tolerance for SHS exposure and develop better-focused treatments."

*(From left to right) Mentor John Lima with Principal Investigator Jason Lang, 2009 NIR, Nemours Children's Clinic*

"Since receiving the James & Esther King Grant I have had the opportunity to learn and apply cutting-edge techniques to the science of childhood asthma, including analyzing DNA sequences and the measurement of secondhand tobacco exposure in children. This knowledge has allowed me to apply for and receive a 5-year Patient Oriented Research Career Enhancement Award from the NIH."

***Dr. Jason Lang, 2009 NIR grantee, Nemours Children's Clinic***

## Training the Next Generation of Health Care Providers

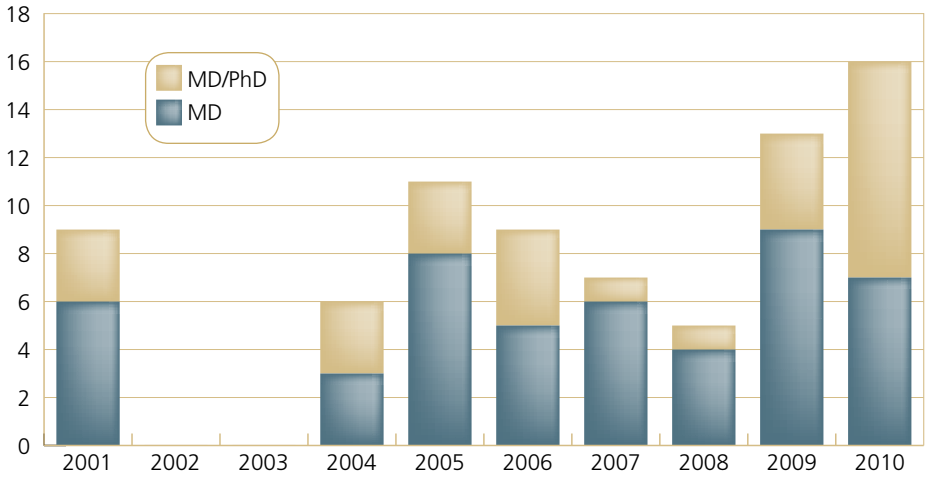
A recent article in the journal *Medical Education* recommended that clinical teachers should attempt to make explicit connections between biomedical knowledge and clinical facts during training.[17] Several King Program grantees interviewed for this report say they are stressing research in their curriculum from the first year all the way through medical school. They are integrating their research experience into their lectures, mentoring, and clinical instruction. Students–from medical students and residents to postdoctoral and graduate students–are responding with interest and enthusiasm to this firsthand exposure to research.

## Promoting Research among Florida's Physician-Scientists

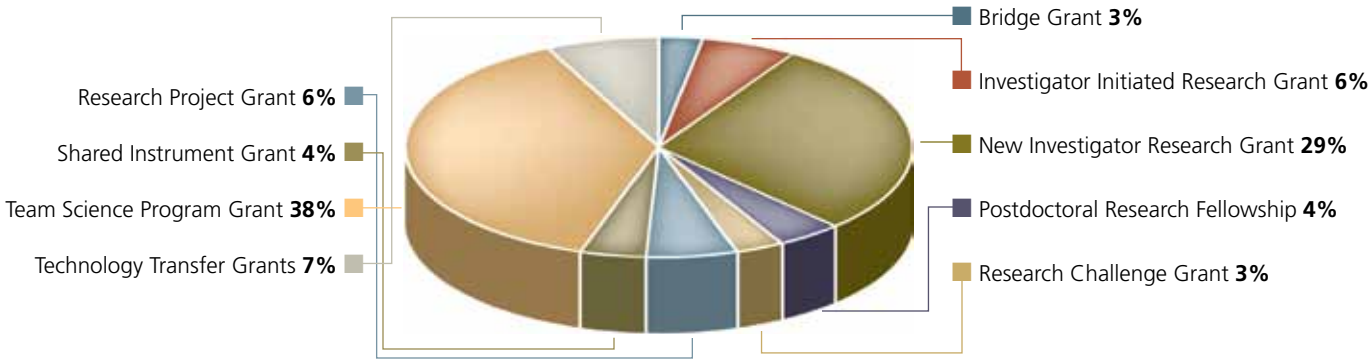
As illustrated in Figure 5, the number of physician scientists receiving King grants has grown in the last two years.

Physician scientists have received all types of grants, but are especially active in Team Science Program grants, which are collaborative in nature. See Figure 6 below for a percentage breakout of types of grants awarded to this group. See Appendix B for a description of each grant type.

### Figure 5 – Physician Scientists Awarded King Program Grants by Year




### Figure 6 – Grants Awarded to Physician Scientists by Grant Type



# Delivering Research Advances to Florida's Academic Health Centers and Health Care Providers

## Bringing Innovative, Effective Radiotherapy Methods to the Clinic

Dr. Sanford Meeks, 2008 TSP grantee at the M.D. Anderson Cancer Center, leads an inter-institutional team of three interrelated projects that has developed improved techniques for radiotherapy, including a way to more accurately target tumors, predict and optimize doses, and reduce healthy tissue damage.

"We have validated our method in 18 patients; our goal is 24. We are extending our work to head and neck cancer, and may expand to the entire body. Also, we formed a strong collaboration between M.D. Anderson and University of Central Florida (UCF) at a clinical level; medical institution collaborations are a new focus for UCF," explained Dr. Anand Santhananm, a Project Leader.

"We now have the ability to predict tumor motion in real time (the fastest known system) at any instant of the breathing cycle. We can also reconstruct patient lung geometry more accurately, reducing this step from 2-3 days to 2-3 hours," explained Dr. Segun Ilegbusi, a Project Leader. The team holds three patents on this work and seven copyrights for intellectual property, indicating good commercial potential.

"Based on this research, we are offering a new course and have introduced clinicians and students to biomechanical modeling and its clinical relevance. Faculty and students alike have received background training in radiotherapy techniques. Nearly 200 undergraduate and graduate students have been exposed to the research. Many are considering a career in cancer research."

***Dr. Segun Ilegbusi, 2008 TSP Project Leader, University of Central Florida***

*Principal Investigator Jon Alexander, 2010 PRF, University of Florida, performing surgery*

## Strengthening Existing and Establishing New Clinically Oriented Laboratories

Dr. Keith Webster, 2007 TSP grantee at the University of Miami, attributes his grant with creating new relationships between basic researchers and medical personnel that have strengthened Miami's Vascular Biology Institute (VBI) and resulted in a new direction to study cardiovascular disease and type 2 diabetes, both exacerbated by tobacco use. The team is now at an advanced stage in the process of translating a treatment that combines gene and stem cell therapies to treat cardiovascular disease.

"The VBI at University of Miami is functioning at a higher and more interactive level since getting this TSP grant. The King funding cemented the relationships between clinical and basic scientists into [long-term] collaborations, which has streamlined a large portion of our research for rapid translation to the clinic. We also have been able to create a critical mass of researchers. Finally, in a brand new program for the University of Miami, we have established a molecular diabetes core laboratory that includes new facilities and expertise to integrate studies on exercise, obesity, type 2 diabetes, and cardiovascular disease. This was initiated by the King Program funding," explained Dr. Webster.

## Incorporating Heart Surgery Research in Medical School Instruction

Dr. Thomas Beaver, 2009 RC1 grantee at the University of Florida and heart surgeon, explained that "everyday we're working with medical students and residents, and they are able to see us working on the project and have joined us as part of our research program. When they see a physician scientist, I think it motivates them to take the next step themselves."

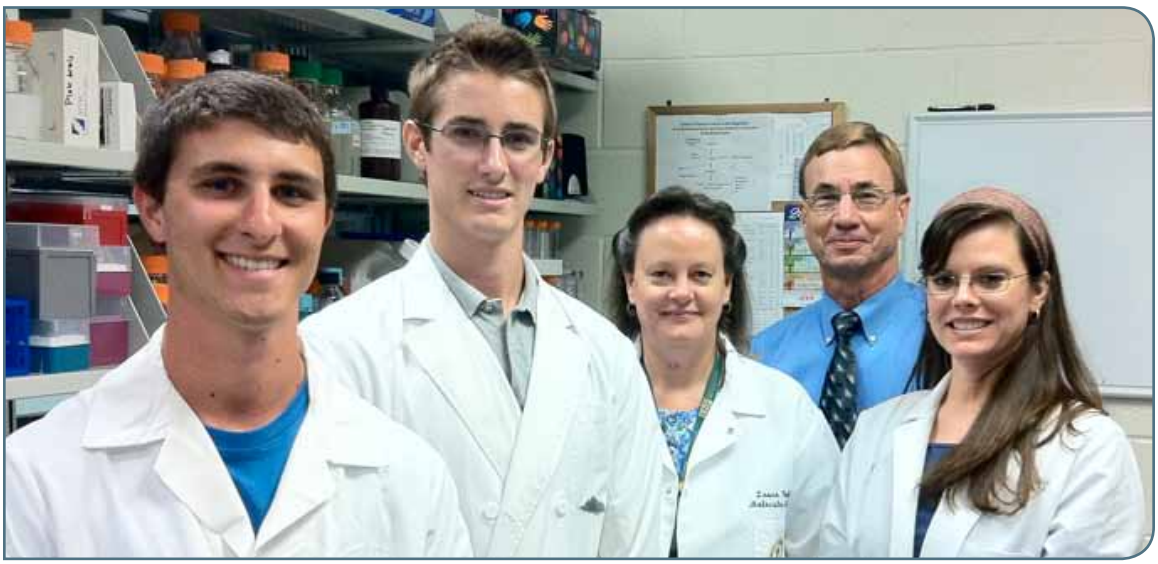
Dr. Beaver developed this project based on his experience with patients. "This is a pilot study by a multi-disciplinary team to see if the drug nesiritide can prevent kidney injury that sometimes occurs as a result of heart surgery. We are studying how this drug works and which patients may benefit. As a physician, we're taking care of these patients everyday so we are able to translate that directly into our bench research and back into the patient world."

"This research is working towards making heart surgery safer for Florida residents, and this drug may have a benefit in preventing lung transplant injury. The NIH recognizes the value of researchers who have patient contact." Dr. Thomas Beaver, 2009 RC1 grantee, University of Florida

## Using Research to Strengthen Medical Instruction

Dr. Duane Eichler, 2008 Bridge grantee at the University of South Florida, is researching the mechanisms by which physiologic and disease-causing agents such as tobacco affect blood vessel wall health. Results from his research will be used to develop new therapeutic approaches to protect the cardiovascular system. Dr. Eichler, Professor of Molecular Medicine, teaches medical students and graduate students at the University of South Florida College of Medicine, as well as Continuing Medical Education (CME) courses, which physicians take to maintain their licenses. Dr. Eichler explained the positive effect of the King Program and other funded research at University of South Florida. "We provide research exposure and experience to medical students and residents through our funded research. A direct relationship between teaching and research provides students with the best of both worlds."

"There is a constant exchange between cutting-edge research and the topics we teach. Being personally involved in medically related research gives me a much better perspective on how to address the science that underlies the disease process. The questions we ask in research can be used as tools to help students understand the significance of the science that supports the practice of medicine," explained Dr. Eichler.



*(From left to right) Laboratory team members Geoffrey Ciarlone, Robert Boudreaux, Laura Pendleton, Principal Investigator Duane Eichler, and Ricci Haines, 2008 Bridge, University of South Florida*

# PROGRESS TOWARDS GOAL: Expanding Biomedical Knowledge Regarding Diseases Related to Tobacco Use

King Program grantees are disseminating research findings from their sponsored projects, on average publishing more than three papers in peer-reviewed journals and delivering five invited presentations at scientific meetings.

Much of biomedical research is dedicated to identifying the mechanisms of disease – how it develops and why. This knowledge then becomes the basis for identifying new interventions to diagnose, treat, prevent, and cure disease. Before interventions can move to the clinic, several questions must be answered: Which molecules are causing the problem, and which ones can be blocked with good results? What is the best way to block a disease-causing molecule? Will blocking it be harmful or beneficial?[18] This section illustrates King Program accomplishments in increasing disease understanding and building a solid knowledge foundation.

## Researching Nicotine's Effects in the Brain

According to Dr. Roger Papke, 2010 RPG grantee at the University of Florida, people affected with mental illness smoke at rates four times higher than the general population.[19] "How the receptors in the brain change due to depression or nicotine is not well understood. Nor do we understand the biological underpinnings of current smoking cessation therapies. The Food and Drug Administration has issued a black box warning for one of the three primary treatments, varenicline, because its use has resulted in increased suicide risk."

"Our goal is to extend current therapies in new ways that will help the population of nicotine-dependent individuals who suffer from mental illness, where they are most seriously needed," explained Dr. Papke. Based on their understanding of how nicotine affects the brain, they plan to test a new drug combination to alleviate the negative side effects of current treatments.

## Building Florida's Reputation for Excellence in Disease Research Related to Tobacco Use

Publications in peer-reviewed journals and presentations at scientific meetings are the means for expanding biomedical knowledge within the scientific community and are viewed as an important measure of research success. King Program research findings are stimulating dialogue among Florida's own research community and helping to earn increasing national and global recognition for the quality of research conducted in Florida. This is evidenced by the growth in the number of publications (Figure 7) and the proportion of presentations at national and international scientific meetings (Figure 8). Appendix E contains the list of this year's publications, as reported by King Program awardees.

**Figure 7 – Publications in Peer Reviewed Journals by Year**

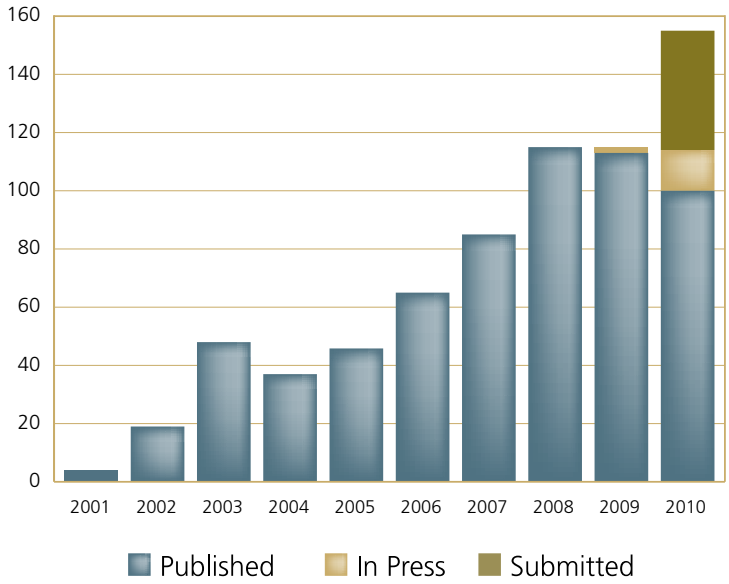
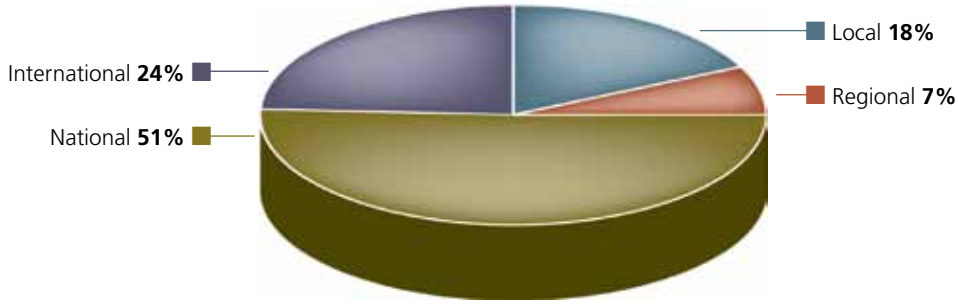


**Figure 8 – Proportion of Scientific Presentations based on King Grants as of October 2010**




## Instrument Enables the Study of Multiple Tobacco-Related Diseases

Dr. Vincent Moy, 2009 SIG grantee at the University of Miami, purchased a confocal laser microscope and is using the microscope in combination with an existing Atomic Force Microscope. Already, more than 25 investigators, including one from Florida Atlantic University, and ten labs use the confocal laser microscope to study tumor cells, skin cancer, stroke, and atherosclerosis. The combined equipment results in a versatile instrument that allows viewing of cells at a nanometer scale and enables mechanical manipulation of them. "Cells undergo all kinds of physical changes when they become cancerous. We can study the biochemical and physical changes with this machine and manipulate them in real time. Understanding why they undergo such changes will help us analyze the basic progression of tumor development and how cells become metastatic," he explained.

## Adding a New Dimension to the Study of Stroke

Dr. Alison Willing, 2007 Bridge grantee at the University of South Florida, has made some startling discoveries about stroke and its treatment. Through her King Program research, Dr. Willing established that the spleen and adrenal system play a major role in stroke.

"These findings surprised us and have the potential to change the way we look at and treat stroke. Perhaps stroke is not just a brain injury, but has a whole body component. It could mean that treatment is most effective 24-48 hours after stroke, and we could treat or rescue injury to a significant portion of the brain. Clinicians and researchers alike have found our research fascinating, and some research groups are now exploring this treatment direction."

"Money to do good research is absolutely critical at times when funding pay lines at the NIH will not get any more liberal. These grants are helping the Florida university system, and we are starting to be recognized nationally as top-notch research institutions. Program funding is helping us get there," explained Dr. Willing.

# Expanding Biomedical Knowledge Regarding Diseases Related to Tobacco Use

"The Program helps to bring in more scientists and has helped to expand our graduate school. Program grants also help to build strong preliminary results, which is the central issue in obtaining national grant funding."

***Dr. Norito Takenaka, 2007 NIR grantee, University of Miami***

## Bringing New Understanding to the Role of Smoking in Chronic Obstructive Pulmonary Disease (COPD)

Dr. Marina Casalino-Matsuda, 2007 NIR grantee at the University of Miami, studies how smoking produces chronic obstructive pulmonary disease (COPD). "We have described how smoking changes the cells of the trachea to produce more mucous. Eventually, this progresses until a person cannot breathe. If we understand how it develops, then we can create an effective medicine." Dr. Casalino-Matsuda has formed collaborations with a pharmaceutical company and researchers in England to develop new therapeutic strategies for COPD based on her grant findings. "Unfortunately, we can't [currently] reverse COPD or treat advanced disease. We need to continue to investigate COPD and improve the quality of life for these patients."

"Basic researchers have to pay their salaries and conduct research with grant funds. Research does not happen without grant funding–that's why the Program is so important. When recruiting people here at University of Miami, the Program and university grants are mentioned. Most states do not have a Program like this," explained Dr. Casalino-Matsuda.

*(From left to right) Instrument Advisory Committee member Nevis Fregien and Principal Investigator Marina Casalino-Matsuda, 2007 NIR, University of Miami*

## Increasing Knowledge about the Heart's Electrical Signals and Rhythm

Dr. Eric Bennett, 2007 Bridge grantee at the University of South Florida, studies cardiac arrhythmias or irregularities in heart rhythms. The use of tobacco exacerbates arrhythmias significantly. "We study function of the proteins responsible for the heart's electrical signals and rhythm. We showed that by changing the number or type of sugars attached to these proteins, we can alter electrical signaling and thereby affect cardiac rhythm. This provides another consideration in evaluating new treatments for cardiac arrhythmias," explained Dr. Bennett. Project results include a provisional patent, two National Science Foundation grant submissions, and multiple publications. "These findings have led us to ask new questions in cardiovascular research: How does attaching sugar to proteins change with disease and how do such changes contribute to disease symptoms?"

"The Program is invaluable to the citizens of Florida for health and economic reasons. The Program provided resources and support for our lab to make significant contributions to the field. With approximately one million Floridians suffering from heart rhythm disorders, this is one small example of the Program's importance and relevance to the health and economic welfare of our state," explained Dr. Bennett.

"When I arrived at the University of Miami, I knew that I had to try applying for grants, but my choices were somewhat limited. The James & Esther King award was an option for me that was not available in other places where I had worked, and I jumped at it the first time I saw the announcement. My first try was not successful, but with the help of tough but great [peer reviewers], I decided to work on a research idea that I had been thinking about for several years. The second time, I got an award. This Program helped me establish my independence, develop new ideas for future work, start collaborations, and furthered my career. Now I am in a place where I can make my basic research more translational as I am very close to medical doctors in different areas of expertise. I hope my findings can be used in the near future for the development of new therapies to treat patients."

*Nithya Bagavatula, Laboratory member on Claudia Rodrigues' grant, 2009 NIR, University of Miami*

***Claudia Rodrigues, 2009 NIR grantee, University of Miami***

## Identifying Underlying Causes of Non-Melanoma Skin Cancer

Dr. Dana Rollison, 2006 NIR grantee at the Moffitt Cancer Center & Research Institute, studied the associations between smoking, antibodies to skin types of human papillomavirus (HPV), and non-melanoma skin cancer (NMSC). "We recruited 700 patients with and without NMSC and observed a statistically significant association between smoking and NMSC. We also found an increased risk for skin cancer associated with antibodies to certain HPV types among non-smokers, but not among smokers. Our results suggest that there may be two pathways to skin cancer, one involving smoking and one involving HPV," explained Dr. Rollison. "Beyond my research findings, I've gained broad experience in the field of viruses and cancer and learned how to conduct large-scale research studies."

"I came to Moffitt from Johns Hopkins. In my interview, they mentioned the NIR grant as a way to generate data for federal applications. I now use the state money as a selling point when recruiting faculty. Several of us at Moffitt have received these awards, and they have been instrumental in our success and form the basis of public health interventions. The Program is not only impacting Florida's science, but also our rankings in the U.S.," explained Dr. Rollison.

## Defining Bold Priorities and Strategies with Increased Funding

In light of the increase in the Program's appropriation in 2009, the Advisory Council began a strategic visioning process that took into account the possibility of stable funding in the $20–25 million per year range. On November 16-17, 2009, the Biomedical Research Advisory Council held a strategic planning retreat. Leading up to the retreat, a series of three informational conference calls took place. The calls covered four themes: early translational science (basic science to pre-clinical), translation to the clinic and beyond (dissemination of research findings), health disparities, and best practices from like models of research funding. The specific goals of the retreat were to:

- Set a new course for a relatively stable increased funding base
- Thoughtfully reconsider King Program statutory goals
- Analyze how the Program has performed to date
- Sharpen the Program's focus
- Define metrics that demonstrate the King Program's commitment to the research enterprise, to state lawmakers, and to the people of Florida

In the past, with less funding to work with, the Advisory Council prioritized Program goals and made tough choices in the face of high demand in Florida for research grants. Each year, requests for funding greatly exceed the funds available. With additional funding, goals can be pursued in a more comprehensive fashion, for instance by offering a greater variety of grant types and expanding eligibility criteria.

The Advisory Council continued deliberations on strategic planning at the January and March 2010 meetings. In March, the Advisory Council settled **on the following top priorities:**

### PRIORITY 1. Target the training of new scientists and support successful ongoing research efforts

**STRATEGY:** Continue Bridge grant support for Florida tobacco-related disease research projects with high potential for federal funding. See "Selecting Grant Offerings for 2011" for steps taken to implement this grant type. A funding crisis looms in 2011-2012 after American Recovery and Reinvestment Act (ARRA) funds are depleted, and Florida researchers and their institutions may be hard pressed to maintain momentum.

**STRATEGY:** Sponsor cluster hires to quickly build capacity in new areas of research and attract follow-on funding. One possible target, highly relevant to Florida's need, is health disparities research. An institutional grant, which is authorized under statute, might be considered.

**STRATEGY:** Offer high-performing King Program grantees additional awards as incentives to continue their work in Florida.

Advisory Council members emphasized the need to recruit and retain high-quality researchers and a skilled research workforce in order to obtain the highest quality science, citing examples of recent talent losses due to recruitment by other states. Different strategies are required to recruit new talent versus retain Florida's best research personnel.

## PRIORITY 2. Provide equipment and core resources to support research discovery and emerging technologies

**STRATEGY:** Help establish core resources to support research programs that require access to tools and collaboration with experts beyond the independent investigator's normal means through large institutional grants in addition to smaller investigator-initiated grants.

Possible core resources include bioinformatics, high-throughput genome studies with broad sequencing, statistical sensors, innovative technologies for collecting outcome data, data management, and a center to assist with clinical trial recruitment and retention of diverse populations. Such an approach builds research capacity. It also serves a dual purpose of supporting talent recruitment and retention, particularly of translational researchers, due to access to resources not available elsewhere.

## PRIORITY 3. Increase investment in clinical, translational, and health disparities research

**STRATEGY:** Provide funding for tools to increase patients' and community practitioners' awareness of existing clinical trials, to match patients to existing trials, and to help users navigate the enrollment process.

**STRATEGY:** Invest in a statewide framework to support collaboration between academic health centers and community practitioners to conduct new clinical trials.

**STRATEGY:** Convene a statewide work group to define a research agenda for Florida in health disparities as well as to identify core resources needed by Florida researchers for health disparities research. See "Health Disparities Summit" inset box.

As is the case with Priorities 1 and 2, institutional grants may be the vehicle to accomplish this priority.

### Health Disparities Summit

The Advisory Council and staff collaborated with FL CURED and the Department's Office of Minority Health in hosting a number of activities in conjunction with the BioFlorida 13th Annual Conference in October. Dr. Louis H. Sullivan, former Secretary of Health and Human Services and President Emeritus of the Morehouse College of Medicine, delivered the closing keynote address. According to Dr. Sullivan, "Between 2003 and 2006, the combined direct and indirect costs of health disparities in the United States were $1.24 trillion." Immediately following the close of the BioFlorida conference, a first-of-its-kind invitational summit on health disparities research was convened by FL CURED. A major goal of the summit was to begin defining a health disparities research agenda for Florida to guide future King Program grant offerings designed to address the problem of health disparities. Follow-up activities are being planned as this report goes to press. One clear consensus emerged from the gathering: To optimize health disparities research, there needs to be efforts to recruit representatives of affected minority populations into the health professions in general, and specifically into research careers.

*Delegates to the first-ever Florida Health Disparities Research Invitational Summit, October 2010, work to develop recommendations to shape a Florida research agenda on health disparities.*

# Strategic Planning for the Near and Long Term

## PRIORITY 4. Accelerate technology transfer

**STRATEGY:** Increase support for promising early stage projects through a new feasibility grant type in addition to the existing commercialization partnership grant to help fill the pipeline of projects moving toward commercialization. See "Pioneering Improvements in the Annual Funding Cycle" in the Program Operations section for details.

*Computer-Controlled Tobacco Smoke Delivery System for Cell Cultures, Principal Investigator, Matthias Salathe, 2009 SIG, University of Miami*

## PRIORITY 5. Improve key processes

**STRATEGY:** Enhance the peer review process by introducing a means for resolving differences in reviewer opinions on the scientific merit of individual proposals. See "Advisory Council Recommendations to Further the King Program's Purpose."

**STRATEGY:** Develop a standardized project classification system to characterize the portfolio of funded research more completely. At press time, the Department was in the process of implementing a classification system.

**STRATEGY:** Increase Program communication, public relations, and outreach efforts; solicit feedback from stakeholders in crafting grant types and refining business processes; and educate Florida's biomedical research community, its lawmakers, and the public regarding the Program's strengths, achievements, and vision for the future. See "Demonstrating Accountability" in Program Operations for details.

## Selecting Grant Offerings for 2011

In May and July 2010, the Advisory Council began to determine grant types for 2011[20] based on strategic planning discussions, and staff began implementing short-range initiatives recommended by the Advisory Council.

In preparing for the FY 2011-2012 competition, the Advisory Council and staff were very concerned that the NIH will fund significantly fewer applications as the ARRA funds are depleted, therefore raising the importance of King Program Bridge grants. The Advisory Council recommended a conservative approach utilizing proven grant types in order to create a balance between researcher needs in Florida and Program goals.

In anticipation of available funding, the Program released Calls for Applications for New Investigator Research Grants and Team Science Program Grants as this report was going to press for awards to begin on July 1, 2011. Additionally, the Program will continue to offer Technology Transfer Feasibility and Technology Transfer/ Commercialization Partnership grants as open calls for applications.

New for 2011, the Program will offer Bridge Grants in three rounds (March, July, and November) in alignment with the award announcement schedule of the NIH. By doing so, Florida applicants to the NIH with highly rated proposals, who are not funded at the federal level due to budget shortfalls have three opportunities to submit applications to the King Program as opposed to only one yearly submission in the past. King Program research can be used to strengthen federal applications as Bridge grantees wait for the next opportunity to resubmit to the NIH. This is an example of the Program's responsiveness and adaptability to the needs of Florida's research community.

## Advisory Council Recommendations to Further the King Program's Purpose

*To further the King Program's ability to pursue its goals, priorities, and strategies, the Biomedical Research Advisory Council makes the following set of recommendations:*

### 1. Provide stable state funding.

The demand for King Program funding is very high, as evidenced by record-setting applications requesting $121.8 million in 2010; however, even this level of demand was constrained by the Program's limitations on research project emphases and applicant eligibility. Consistent investment is necessary to maintain the momentum built over the last ten years.

### 2. Provide authority to carry forward funds for up to five years.

The King Program is currently authorized to carry obligated funds forward for three years; however, certain types of grants (such as for clinical trials) would benefit from a longer period of support.

### 3. Remove the requirement that peer review panels be subject to Florida's open meeting law.

The industry norm for scientific peer review, as practiced by the NIH, is that peer review panel communications are confidential. There is compelling evidence that allowing peer reviewers to interact with each other in their determination of scientific merit improves inter-reviewer understanding of the project and therefore reliability of merit scores. However, the King Program implementing statute requires all peer reviewer interactions be conducted in the sunshine, which would inhibit frank discussion. Peer reviewers are reluctant to candidly discuss scientific merit or render opinions publicly due to concerns of professional repercussions. In addition, proposals may contain confidential information important to judging merit that would have to be adapted, further hampering the evaluation process. Consequently, the King Program uses a highly regarded, but completely independent peer review process (no reviewer interaction), which could be made stronger if non-public interaction were authorized.

### 4. Maintain an adequate allowance for administrative expenses.

Administrative expenses are driven not only by the volume of grant applications processed and new grants awarded (a function of the annual appropriated budget), but also by the number of active grants being managed. With an active portfolio of 121 multi-year grants valued at $58.6 million, contract oversight responsibilities are substantial.

### 5. Expand authority to issue grants for core resources.

The methods for achieving the King Program goals can be enhanced by offering grants for not only research, but also for core resources. In the case of the latter, such project grant proposals would not be required to pose a research question in order to qualify for an award. This would require thoughtful legislative change that includes parameters for the basis of awards since traditional peer review and the determination of scientific merit may not be appropriate.

# BIOMEDICAL RESEARCH ADVISORY COUNCIL

The Advisory Council, per s. 215.5602, *F.S.*, advises the Department regarding the direction and scope of the King Program and assists in developing guidelines to ensure fairness, neutrality, and adherence to the principles of merit and quality in the conduct of the Program. The Advisory Council also functions in the same role for the Bankhead-Coley Cancer Research Program.

Among the significant contributions of the Advisory Council are the recommendations of specific grant types and eligibility requirements to achieve the statutory goals of the King Program. The Advisory Council employs strict measures to avoid conflicts-of-interest in making funding recommendations to the Department of Health, relying primarily upon the outcome of the scientific peer review process.

## 2010 Membership Changes

Three notable changes occurred in 2010 to the Advisory Council membership. The designated American Cancer Society representative and founding member Sigurd Normann, M.D., Ph.D., retired and was replaced by Daniel Armstrong, Ph.D. Claes Wahlestedt, M.D., Ph.D., filled the Biomedical Research appointment vacated in 2009 by Dr. Nikolaus Gravenstein, M.D. The American Lung Association representative Veena Antony, M.D., was recruited out of state and was replaced by Mark Brantly, M.D.

*(From left to right) Laboratory member Zita Burkhalter, Mentor Jay Patel, Co-Investigator Kamal Mohammed, Principal Investigator Nasreen Najmunnisa, and Laboratory member Nazli Khodayari, 2009 NIR, University of Florida*

## Dr. Normann Recognized for Pioneering Efforts

In January 2010, Dr. Sigurd Normann announced his retirement from the Advisory Council after more than ten years of service. As a founding member of the Advisory Council, Dr. Normann represented the American Cancer Society. He was instrumental in crafting the original legislation creating Florida's first competitive, peer-reviewed biomedical research program following the historic 1997 tobacco settlement. At the January 2010 Advisory Council meeting, Dr. Bookman, Advisory Council Chair, Mr. Paul Hull, Vice-President of Advocacy and Public Policy of the American Cancer Society, Florida Division, and Dr. Susan Phillips, Director of the Office of Public Health Research, Florida Department of Health, all spoke of the many contributions made by Dr. Normann over the years. Dr. Normann reminded the Advisory Council of the five pillars on which the Program was built:

*(From left to right) Paul Hull, American Cancer Society (ACS) Vice President for Advocacy and Public Policy; Dr. Sig Normann, and Dr. Danny Armstrong, the new ACS designee to the Advisory Council.*

1. To be an annual and perpetual source of funding on which researchers could rely
2. To be a competitive program open to all qualified investigators regardless of institutional affiliation
3. To base awards on scientific merit, through a non-conflicted peer review process
4. To restrict administrative costs to a reasonable level (15 percent), thereby preserving the majority of funds for research
5. To provide professional, administrative, and scientific oversight by housing the program at the Department of Health, while requiring at least one advisory council representative from the research community

# 2010 ADVISORY COUNCIL MEMBERSHIP

## Veena Antony, M.D.

Professor of Medicine, Molecular Genetics, and Microbiology

Division of Pulmonary Critical Care and Sleep Medicine

Vice Chair for Research, Department of Medicine

University of Florida

**Seat:** **American Lung Association**
**Appointed:** **July 2007**

## Randal Henderson, M.D.

Associate Medical Director, Proton Therapy Institute

Professor of Radiation Oncology

University of Florida, Jacksonville

**Seat:** **House – Cancer Program (ACoS)**
**Appointed:** **April 2007**

## Daniel Armstrong, Ph.D.

Professor and Associate Chair, Pediatrics

Director, Mailman Center for Child Development

University of Miami Miller School of Medicine

*(Replaces Dr. Normann)*

**Seat:** **American Cancer Society**
**Appointed:** **January 2010**

## Myra Hurt, Ph.D.

Senior Dean, Research, Graduate, and Undergraduate Programs

Florida State University College of Medicine

**Seat:** **Governor - Research University**
**Appointed:** **February 2006**

## Richard J. Bookman, Ph.D.

Advisory Council Chair

Vice Provost for Research

Executive Dean for Research & Research Training

University of Miami Miller School of Medicine

**Seat:** **American Heart Association**
**Appointed:** **July 2000**

## Albert Latimer, B.B.A.

Senior Vice President

External Affairs & Investor Relations

Enterprise Florida, Inc.

**Seat:** **General Public**
**Appointed:** **February 2006**

## Mark Brantly, M.D.

Chief, Division of Pulmonary and Critical Care Medicine

University of Florida College of Medicine

*(Replaces Dr. Antony)*

**Seat:** **American Lung Association**
**Appointed:** **October 2010**

## Sigurd Normann, M.D., Ph.D.

Professor

College of Medicine

Department of Pathology, Immunology, and Laboratory Medicine

University of Florida

**Seat:** **American Cancer Society**
**Appointed:** **July 2000, retired January 2010**

### Edith Perez, M.D.

Professor of Medicine
Hematology/Oncology
Mayo Clinic, Jacksonville

**Seat:** Senate - Cancer Program (ACoS)
**Appointed:** August 2009

### Penny Ralston, Ph.D.

Director, Dean Emeritus and Professor
Center on Better Health & Life for Underserved Populations
Institute of Science & Public Affairs
Florida State University

**Seat:** Senate - Behavioral/Social Research
**Appointed:** July 2006

### Mary Lou Sole, R.N., Ph.D., CCNS, FAAN

College of Nursing Professor
College of Health & Public Affairs
University of Central Florida

**Seat:** House – Professional Medical Organization
**Appointed:** April 2007

### Claes Wahlestedt, M.D., Ph.D.

Professor
Neuroscience and Molecular Therapeutics
The Scripps Research Institute

**Seat:** Governor - Biomedical Research
**Appointed:** April 2010

### Herbert Weissbach, Ph.D.

Advisory Council Vice Chair
Distinguished Research Professor and Director
Center for Molecular Biology and Biotechnology
Florida Atlantic University

**Seat:** Governor - Biomedical Research
**Appointed:** February 2006

## Composition of the Advisory Council

**The 11 appointees to the Biomedical Research Advisory Council include:**

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

The Advisory Council has responded to increasing competition for national funds and end of ARRA funding by offering a Bridge grant for highly rated but unfunded federal applications.

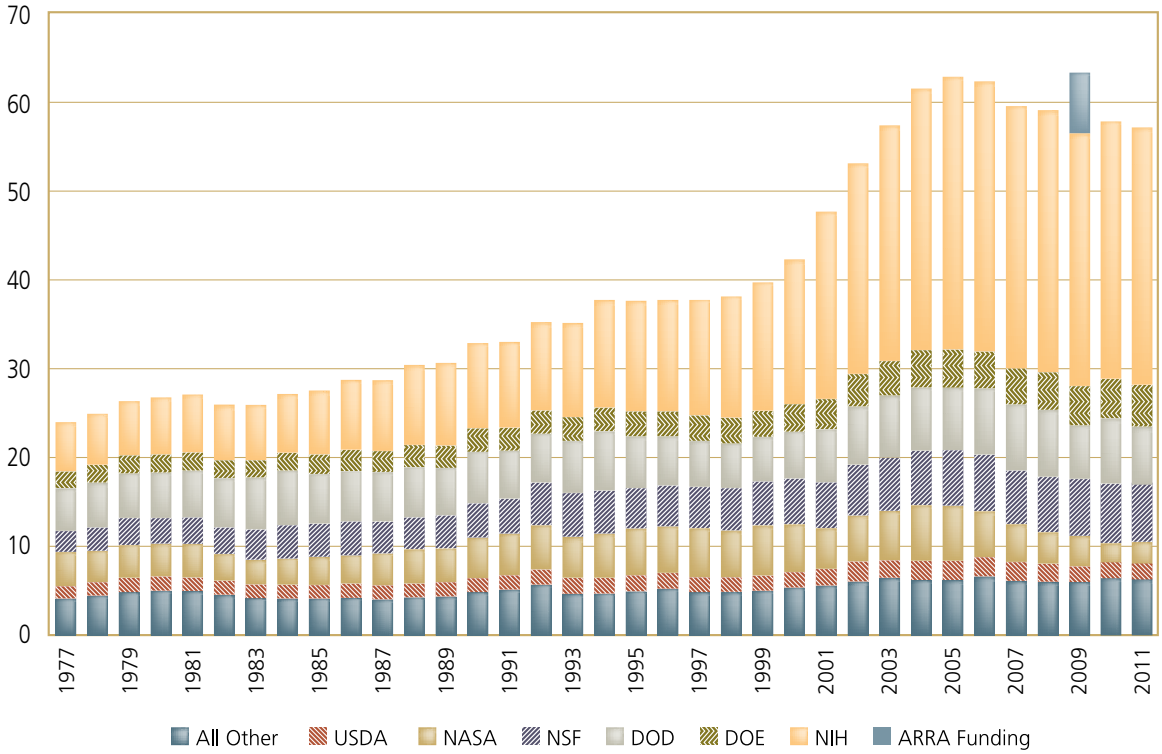
## National Funding Perspective and 2011 Projections

National biomedical research funding and funding trends provide a context in which to assess Florida's biomedical research funding priorities. Trend information also provides insight into the challenges and opportunities that Florida faces as the state seeks to attract biomedical research and industry jobs, at a time when other states are making similar efforts.

From 1976 to 1998, the combined budgets for federal research agencies remained relatively steady (see Figure 9). Between 1998 and 2003, however, a campaign to double the NIH budget led to a rapid expansion of funding for biomedical research. In 2004, as domestic spending was curtailed in response to growing federal deficits, the NIH and other federal agencies experienced a slowing and then a contraction of their budgets.[21]

**Figure 9 – Trends in Research Dollars by Federal Agency, in billions***

*Reprinted with permission from American Association for the Advancement of Science (AAAS).

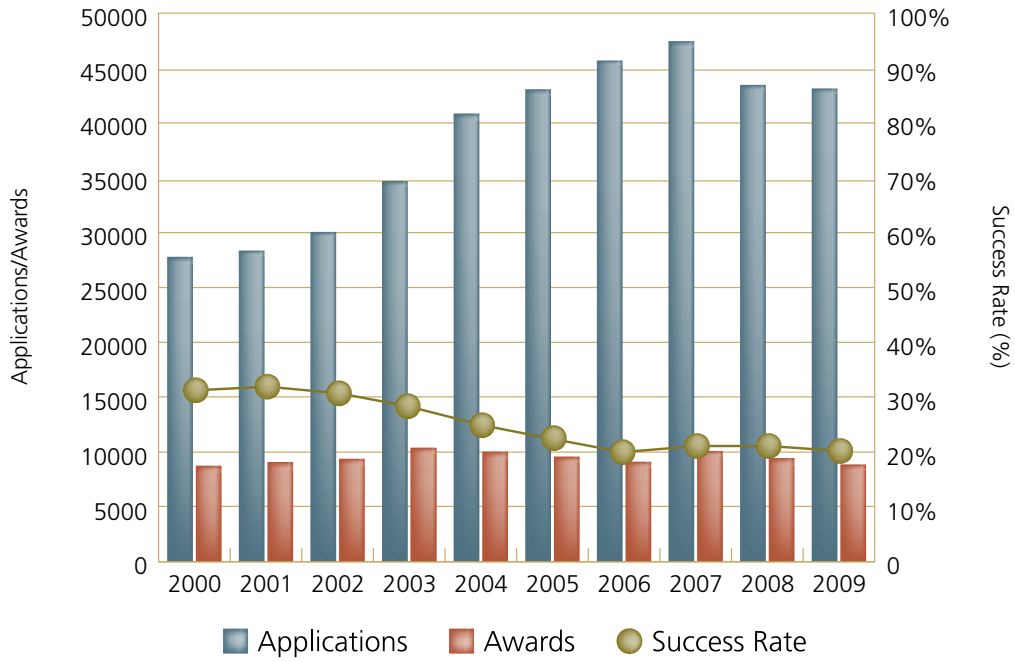



Source: AAAS Report: Research & Development series. FY 2010 and FY 2011 figures are latest estimates. Research includes basic research and applied research. 1976-1994 figures are NSF data on obligations in the Federal Funds survey.

## Competition for Federal Dollars Expected to Increase

Important points to note about the 2011 projections are: 1) Because of an emphasis on centers and contract awards, NIH expects to fund 199 fewer Research Project Grants, which are the mainstay of investigator-initiated grants and basic research labs.[22] 2) ARRA funding in 2009 and 2010 provided an additional source of funds for two years that will not be available in the future. NIH forecasts a high volume of submissions for unfunded ARRA applications. As a result, the agency is estimating a declining success rate for grant applications from 20 percent to 15 percent in 2011.[23] Figure 10 illustrates this trend in success rate as well as a decline and leveling off of grant awards.

**Figure 10 - National Institutes of Health Trends in Grant Awards and Success Rates**




## Florida's Rank in National Funding and the Critical Role of State Funding

As of October 2010, more than 1,000 researchers at 53 Florida organizations classified as domestic higher education, research institutes, independent hospitals, and industry received new NIH awards totaling $374 million.[24] This places Florida 18th among the 50 states as a percent of total NIH funding – up from 21st over the last 10 years[25] – and 43rd on a per capita basis. See Appendix F for a table of NIH funding by state.

Direct investment by the state of Florida will continue to play a critical role in maintaining the health of the state's biomedical research community and its related economy. Similarly, continued funding by the Program is essential if Florida is to retain and advance its leadership in disease research related to tobacco use.

The King Program currently oversees 121 active grants. Sixty-six of these grants were either awarded or began research in 2010.

## Maintaining Administrative Costs and King Program Quality

The King Program by statute can use up to 15 percent of the appropriated funds for administrative expenses. As shown in Table 3 below, King Program staff has held administrative costs below this legislative limit. Funds not used for administrative expenses are awarded as grants.

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

**Table 3- King Program Expenditures (Millions)**

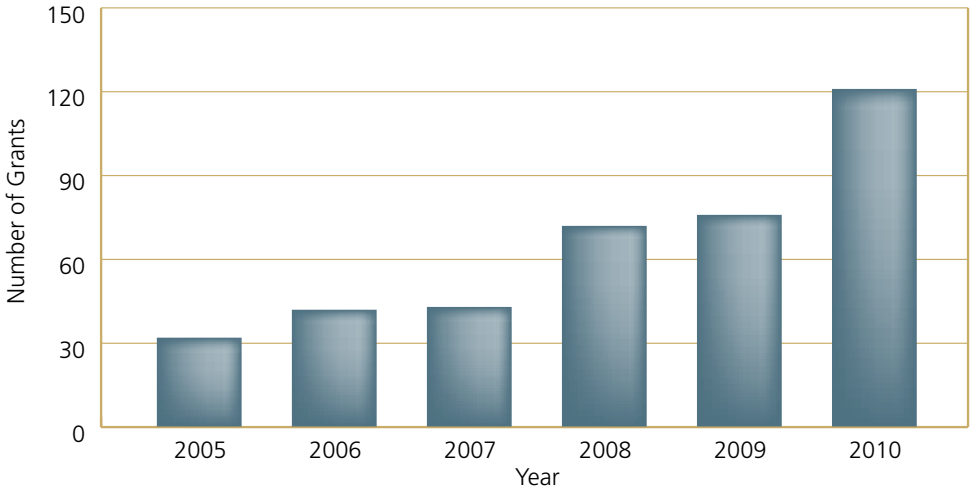
| Fiscal Year | Appropriation | Grant Awards | Percent | Administrative Expenses | Percent |
|---|---|---|---|---|---|
| FY 10-11[a] | 22.20 | 19.05 | 86% | 1.93 | 9% |
| FY 09-10 | 25.57 | 20.90 | 82% | 1.75 | 7% |
| FY 08-09[b] | 8.40 | 7.32 | 87% | 1.05 | 13% |
| FY 08-09[c] | 9.90 | 8.41 | 85% | 1.25 | 13% |
| FY 07-08 | 9.90 | 8.75 | 88% | 1.13 | 11% |
| FY 06-07 | 9.50 | 8.09 | 85% | 0.88 | 9% |
| FY 05-06 | 9.37 | 8.04 | 86% | 0.80 | 9% |
| FY 04-05 | 9.40 | 8.73 | 93% | 0.68 | 7% |
| FY 01-04 | 17.64 | 16.60 | 94% | 0.87 | 5% |
| **Total (excluding FY2010-11)** | **89.78** | **78.43** | **87%** | **7.16** | **8%** |

a Projected awards and expenses (includes $250,000 for the Center for Universal Research to Eradicate Disease pursuant to s. 215.5602(12), *F.S.*)
b Mid-year revision due to budget reduction.
c Original grant awards and projected expenses prior to mid-year budget reduction.

Florida's Chief Financial Officer requires that state agencies perform contract monitoring. Each grant awarded through the King Program has both standard and unique terms and conditions that the Program must monitor for compliance.

The state of Florida has invested nearly $40 million in the last two years in the King Program and there is now an active portfolio of 121 grants.[26] Figure 11 illustrates the growing number of active grants requiring ongoing management. This investment in active projects requires continued administrative oversight of financial and scientific progress through grant completion as detailed in the next section.

### Figure 11 - Number of Active Grants Requiring Administrative Oversight




## Incorporating Best Practices in Grant and King Program Management

Grant management involves active monitoring and includes review of a number of grantee deliverables including quarterly financial reports, yearly scientific progress reports, mechanism-specific deliverables, annual budgets, no-cost extension requests, and a site visit during multi-year grants to evaluate the scientific and financial health of the project.

The King Program uses industry best practices to ensure financial and research accountability, to support grantees, and to maintain compliance with grant terms and conditions, as illustrated in Table 4. Reporting requirements are intended to ensure progress rather than add administrative burden. Annual continuation of multi-year grants is dependent on satisfactory performance as well as the availability of funds.

### Table 4 - Grant Management Processes and Tools

| Process or Tool | | Value |
|---|---|---|
| **Internal Controls** | Signed terms and conditions (contract) with schedule of deliverables | ■ Defines expectations |
| | Grant Administration Manual | ■ Clarifies policies and procedures<br>■ Helps grantees comply with requirements |
| | Web-based system | ■ Provides grantees with convenient report submission<br>■ Serves as central data center<br>■ Provides efficient review of post-award deliverables |
| **Financial Management** | Regular review of budgets, financial reports, and expenditure changes | ■ Assures fiscal accountability |
| | Analysis of spending patterns | ■ Identifies potential accounting problems or project delays |
| **Performance Management** | Project progress reports and research milestone charts | ■ Provides measurement framework |
| | Peer review of annual progress reports for multi-year grants | ■ Obtains informed progress assessment<br>■ Provides additional mentoring to grantees |
| | Periodic site visits | ■ Validates project progress and reviews project expenses<br>■ Checks institutional controls<br>■ Solicits stakeholder feedback<br>■ Promotes the Program to increase applicant pool |

# King Program Operations

## Delivering King Program Support

At a program level, a number of planning, development, analysis, and evaluation activities are required to inform the decision-making and strategic planning activities of the Advisory Council. In 2010, the King Program successfully managed an annual competition for grants that produced 2.5 times the number of applications customarily received in any previous round. Staff completed application processing, peer review, and award announcements within the normal funding schedule.

The processes in Table 5 support the smooth implementation of King Program planning efforts and coincide with the yearly grant funding cycle.

**Table 5 - Key King Program Operation Activities**

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

## Using a Partnership to Support Applicants, Grantees, and Advisory Council

The Office of Public Health Research, within the Department of Health, manages the King Program. In addition to support from the Advisory Council, the Department of Health obtains services from a contracting partner to assist in Program oversight and administration.

From 2004 through 2010, Lytmos Group, Inc., has filled the contracting role. In preparation for the expiration of the original contract at the end of 2010, the Department conducted a competitive procurement for these services. After negotiating with the top two vendors submitting proposals, the Department awarded a new contract to Lytmos Group, Inc.

Jointly, the Office of Public Health Research and the Lytmos Group fulfill a number of behind-the-scenes responsibilities, providing a seamless interface to support applicants, grantees, and the Advisory Council.

### All of the following quotes are from the February 2010, Grantee Satisfaction Survey:

"The support by this program is strong, which makes it easier for us to make substantial progress on our projects. We will be more competitive when applying for national funds."
***Respondent 59750956***

"This is an excellent organization that does its job so well. The executives are very friendly, helpful, and knowledgeable. The program itself is an outstanding success for Florida researchers."
***Respondent 61196304***

"I cannot see any other way for new Florida researchers to get their first experience with major peer-reviewed funding. It is the most logical step to establish a research career."
***Respondent 59782986***

## Demonstrating Accountability

The King Program employs a number of strategies to communicate clearly and openly regarding all aspects of its operations and to proactively seek feedback from stakeholders in order to continuously improve the effectiveness of its strategies and tactics.

- Comprehensive and timely information is maintained on the King Program's website, including funding opportunities and outcomes, detailed minutes for all Advisory Council meetings, and a Grant Administration Manual to help grantees manage their awards.
- Progress is measured and reported against metrics developed from the King Program's statutory goals.
- Feedback is solicited in surveys of applicants, current and past grantees, the Advisory Council, and technology transfer directors, among many others. Survey topics have encompassed grant management and design as well as application and procedural questions to gather comprehensive feedback. As a result, surveys are planned on a regular basis and viewed as a valuable part of process improvement and program evaluation. Program changes made based on surveys include extending the length of the application period for grant types, providing improved question and answer processes and better instructions with each Call for Application, improved communication to all grantees at an institution regarding site visits, and offering flexible application schedules for others, providing more information on the website regarding competition results, and decreasing reporting requirements for minor grant changes.

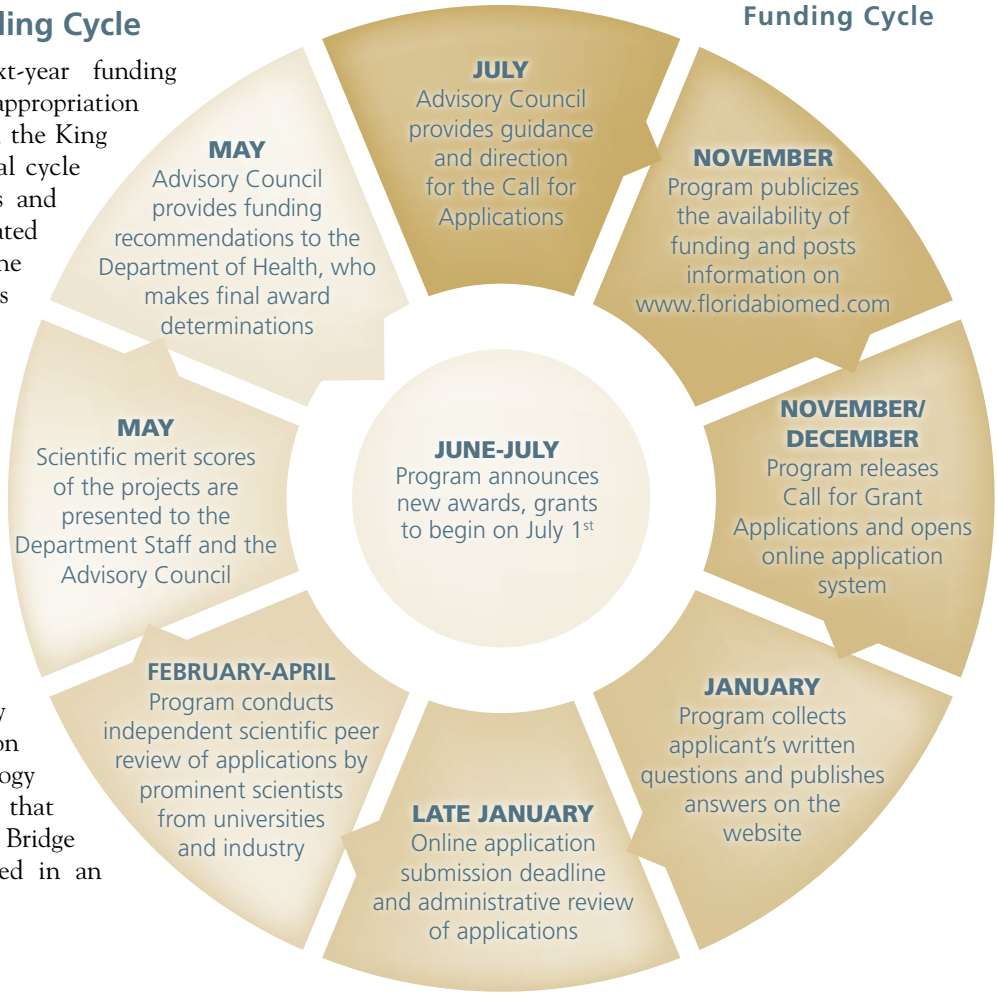
# King Program Operations

## Pioneering Improvements in the Annual Funding Cycle

In anticipation of next-year funding through the annual appropriation process of the Legislature, the King Program follows an annual cycle for soliciting applications and making awards, as illustrated in Figure 12. This year the competition for grants began in mid-November with the release of Calls for Applications and the announcement of a deadline in late January to eliminate overlap with the NIH grant cycle.

In 2010, the King Program pioneered an open-ended application deadline for Technology Transfer/Commercialization Partnership and Technology Transfer Feasibility grants that will continue into 2011. Bridge grants will also be offered in an Open Call in 2011.

Figure 12 - The Annual Funding Cycle




## Employing Innovative Peer Review to Ensure Merit-Based Awards

In evaluating proposals, the King Program drew on the expertise of approximately 450 independent subject matter experts from outside Florida. These peer reviewers evaluate grant applications that match their specific expertise, rating scientific and technical merit and project fit with King Program goals. Unlike other peer review processes in which reviewers consult with each other, these reviews are performed independently and scores are averaged.

While the King Program is meeting high standards for peer review, the Program is seeking an adjustment in the process through an exemption from Florida open meeting law for scientific peer review of grant proposals. See "Advisory Council Recommendations to Further the King Program's Purpose" in Strategic Planning for more information. This will align the Program with best practices and enable open discussion regarding scoring variations.

In making funding recommendations, the Advisory Council considers a number of factors about each application without knowing the names of the researchers, their institutions, or the proposal titles in order to avoid conflicts-of-interest. They consider the peer review scores for scientific merit and tobacco-relatedness to develop a funding plan across all grant types, within budget constraints. After awards are announced, the King Program obtains signed contracts, final budgets, and human subject and animal study approvals from grantees.

## 2010 Grantee Satisfaction Survey Results

When asked to rate responsiveness of their grant manager, 96 percent of respondents were very satisfied or satisfied (3 percent selected NA). All of the following quotes were gathered from the February 2010, Grantee Satisfaction Survey.

"The King Program has been instrumental in helping me to further develop my program of research. I received very helpful feedback from the site visit team and progress report reviewers." ***Respondent 60662583***

"The King Program has significantly helped in funding of the project and served as a good starting point for my academic career." ***Respondent 61656754***

"This is an outstanding Program that the Government of Florida has to retain its rich source of biomedical researchers." ***Respondent 61196304***

"The Florida Biomedical Research Program has been incredible for Florida science and scientists, our research growth, and reputation." ***Respondent 59804764***

"I found many of the reviewers' comments very helpful, and it was even more satisfying and unique to receive comments for the progress report." ***Respondent 61658548***

"I think the review process of grants is very professional." ***Respondent 59753005***

"Excellent review system, outstanding grant management system, extremely competent grant manager/personnel, and timely report feedback." ***Respondent 60145391***

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

(1) There is established within the Department of Health the James and Esther King Biomedical Research Program funded by the proceeds of the Lawton Chiles Endowment Fund pursuant to s. 215.5601. The purpose of the James and Esther King Biomedical Research Program is to provide an annual and perpetual source of funding in order to support research initiatives that address the health care problems of Floridians in the areas of tobacco-related cancer, cardiovascular disease, stroke, and pulmonary disease. The long-term goals of the program are to:

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

(b) Expand the foundation of biomedical knowledge relating to the prevention, diagnosis, treatment, and cure of diseases related to tobacco use, including cancer, cardiovascular disease, stroke, and pulmonary disease.

(c) Improve the quality of the state's academic health centers by bringing the advances of biomedical research into the training of physicians and other health care providers.

(d) Increase the state's per capita funding for research by undertaking new initiatives in public health and biomedical research that will attract additional funding from outside the state.

(e) Stimulate economic activity in the state in areas related to biomedical research, such as the research and production of pharmaceuticals, biotechnology, and medical devices.

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

(3) There is created within the Department of Health the Biomedical Research Advisory Council.

(a) The council shall consist of 11 members, including: the chief executive officer of the Florida Division of the American Cancer Society, or a designee; the chief executive officer of the Florida/Puerto Rico Affiliate of the American Heart Association, or a designee; and the chief executive officer of the American Lung Association of Florida, or a designee. The remaining 8 members of the council shall be appointed as follows:

1. The Governor shall appoint four members, two members with expertise in the field of biomedical research, one member from a research university in the state, and one member representing the general population of the state.
2. The President of the Senate shall appoint two members, one member with expertise in the field of behavioral or social research and one representative from a cancer program approved by the American College of Surgeons.
3. The Speaker of the House of Representatives shall appoint two members, one member from a professional medical organization and one representative from a cancer program approved by the American College of Surgeons.

In making these appointments, the Governor, the President of the Senate, and the Speaker of the House of Representatives shall select primarily, but not exclusively, Floridians with biomedical and lay expertise in the general areas of cancer, cardiovascular disease, stroke, and pulmonary disease. The appointments shall be for a 3-year term and shall reflect the diversity of the state's population. An appointed member may not serve more than two consecutive terms.

(b) The council shall adopt internal organizational procedures as necessary for its efficient organization.

(c) The department shall provide such staff, information, and other assistance as is reasonably necessary to assist the council in carrying out its responsibilities.

(d) Members of the council shall serve without compensation, but may receive reimbursement as provided in s. 112.061 for travel and other necessary expenses incurred in the performance of their official duties.

(4) The council shall advise the State Surgeon General as to the direction and scope of the biomedical research program. The responsibilities of the council may include, but are not limited to:

(a) Providing advice on program priorities and emphases.

(b) Providing advice on the overall program budget.

(c) Participating in periodic program evaluation.

(d) Assisting in the development of guidelines to ensure fairness, neutrality, and adherence to the principles of merit and quality in the conduct of the program.

(e) Assisting in the development of appropriate linkages to nonacademic entities, such as voluntary organizations, health care delivery institutions, industry, government agencies, and public officials.

(f) Developing criteria and standards for the award of research grants.

(g) Developing administrative procedures relating to solicitation, review, and award of research grants and fellowships, to ensure an impartial, high-quality peer review system.

(h) Developing and supervising research peer review panels.

(i) Reviewing reports of peer review panels and making recommendations for research grants and fellowships.

(j) Developing and providing oversight regarding mechanisms for the dissemination of research results.

(5) (a) Applications for biomedical research funding under the program may be submitted from any university or established research institute in the state. All qualified investigators in the state, regardless of institution affiliation, shall have equal access and opportunity to compete for the research funding.

(b) Grants and fellowships shall be awarded by the State Surgeon General, after consultation with the council, on the basis of scientific merit, as determined by an open competitive peer review process that ensures objectivity, consistency, and high quality. The following types of applications shall be considered for funding:

1. Investigator-initiated research grants.

2. Institutional research grants.

3. Predoctoral and postdoctoral research fellowships.

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

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

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

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

(10) The council shall submit an annual progress report on the state of biomedical research in this state to the Florida Center for Universal Research to Eradicate Disease and to the Governor, the State Surgeon General, the President of the Senate, and the Speaker of the House of Representatives by February 1. The report must include:

(a) A list of research projects supported by grants or fellowships awarded under the program.

(b) A list of recipients of program grants or fellowships.

(c) A list of publications in peer reviewed journals involving research supported by grants or fellowships awarded under the program.

(d) The total amount of biomedical research funding currently flowing into the state.

(e) New grants for biomedical research which were funded based on research supported by grants or fellowships awarded under the program.

(f) Progress in the prevention, diagnosis, treatment, and cure of diseases related to tobacco use, including cancer, cardiovascular disease, stroke, and pulmonary disease.

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

(12) From funds appropriated to accomplish the goals of this section, up to $250,000 shall be available for the operating costs of the Florida Center for Universal Research to Eradicate Disease. Beginning in the 2010-2011 fiscal year and thereafter, $50 million from the revenue deposited into the Health Care Trust Fund pursuant to ss. 210.011(9) and 210.276(7) shall be reserved for research of tobacco-related or cancer-related illnesses. Of the revenue deposited in the Health Care Trust Fund pursuant to this section, $50 million shall be transferred to the Biomedical Research Trust Fund within the Department of Health. Subject to annual appropriations in the General Appropriations Act, $20 million shall be appropriated to the James and Esther king Biomedical Research Program, $20 million shall be appropriated to the William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program created under s. 381.922, and $10 million shall be appropriated to the H. Lee Moffitt Cancer Center and Research Institute established under s. 1004.43.

**History** – s. 2, ch. 99-167; s. 4, ch. 2000-159; s. 2, ch. 2000-255; s. 5, ch. 2000-367; s. 4, ch. 2001-73; s. 1, ch. 2003-414; s. 8, ch. 2004-2; s. 3, ch. 2006-182; s. 14, ch. 2008-6; s. 1, ch. 2009-5; s. 2, ch. 2009-58; s. 13, ch. 2010-161.

# APPENDIX B. Grant Types Designed to Achieve Program Goals

The Advisory Council recommends various types of grant offerings in order to meet the specific needs of Florida's tobacco-related disease research community, to capitalize on federal funding opportunities, and to maintain a balanced research portfolio over multiple-year grants. Selection is always directed by King Program statutory goals.

Table B-1 briefly describes each of the grant types the Program has awarded to Florida investigators since 2001.* **Use it as a reference tool and foundation for understanding the results reported throughout the report, particularly in Program Accomplishments.**

**Table B-1 Grant Types Offered Throughout the Program's History**

| Grant Type | Purpose | Maximum Amount & Duration |
|---|---|---|
| **Bridge Grant** | Provide one year of interim support for tobacco-related research projects receiving high scores in federal competitions that were not funded due to Federal budget constraints. (Offered 2008, 2009, 2011) | Up to $200,000 for one year |
| **Florida Research Challenge (RC1) Grant** | Provide support for high-risk, high-reward tobacco-related research proposals submitted by Florida researchers in response to NIH's 2009 Challenge Grant competition and not funded due to Federal budget constraints. (Offered 2009) | Up to $1,000,000 over two years |
| **Historically Black Colleges and Universities (HBCU) Grant** | Provide support for tobacco-related research proposals submitted by Florida researchers located at Historically Black Colleges and Universities | Up to $50,000 for one year |
| **Investigator Initiated Research (IIR) Grant** | Fund research for Florida investigators at all experience levels on a wide variety of tobacco-related research topics. (Offered 2001) | $400,000 for 25 months |
| **New Investigator Research (NIR) Grant** | Provide support to Florida-based investigators starting independent research careers in tobacco-related projects, completed under the guidance of an experienced Florida mentor. (Offered 2001, 2004-2011) | Up to $425,000 over three years |
| **Postdoctoral Research Fellowship (PRF)** | Attract scientists into careers addressing important tobacco-related research questions and to provide support to promising postdoctoral researchers who have the potential to become productive and independent researchers. (Offered 2010) | Up to $58,350 per year for one to three years |
| **Research Project Grant (RPG)** | Support experienced investigators who are conducting tobacco-related research in translational and/or health disparities and who will submit a national application to continue the research. (Offered 2010) | Up to $1.5 million over five years *(including contract renewal)* |
| **Shared Instrument Grant (SIG)** | Improve access to state-of-the-art research instruments that can only be justified on a shared-use basis. (Offered 2009) | Up to $500,000 for a single instrument |
| **Team Science Program (TSP) Grant** | Foster collaboration among three to five Florida researchers, supporting complex projects with the potential to secure large external grants. (Offered 2004-2011) | Up to $1,500,000 over three years |
| **Small Business Technology Transfer Grant (SBTT) and Technology Transfer/ Commercialization Partnership (TTCP) Grant** | Fund collaborations between academic researchers and small, Florida-based biomedical businesses to translate discoveries into new products and therapies. (Offered 2004-2007 and 2009-2011) | Up to $100,000 for one year |
| **Technology Transfer Feasibility (TTF) Grant** | Offer early stage funding in order to develop intellectual property and improve a project's commercial potential and competitiveness for further development activities. (Offered 2010-2011) | Up to $100,00 for one year |

* When referring to a grant within this report, the year indicates the fiscal year in which the grant begins. For example, a 2010 grant begins July 1, 2010, and ends June 30 of the year of completion.

# APPENDIX C. Abbreviated Abstracts of 2010 Grant Awards

The following is a list of grants awarded in 2010. The grants are listed in alphabetical order by Principal Investigator's name.

## Alexander, Jon

2010 PRF University of Florida

## $159,750

### Investigation of the Role of Corticotropin-Releasing Factor in the Basolateral Amygdala During Nicotine Withdrawal and Stress-Induced Reinstatement

The overall idea of this project is that the negative feelings or emotions experienced as a result of quitting smoking and the tendency to start smoking again during stressful times are in part, a result of altered functioning of the signaling protein known as corticotropin-releasing factor within the basolateral amygdala, a brain area that plays a critical role in regulating emotional states. We will conduct experiments in the basolateral amygdala (BLA) area to determine if blockade of corticotropin-releasing factor 1 (CRF1) receptors and stimulation or blockade of corticotropin-releasing factor 2 (CRF2) receptors reverse these negative emotions. First, we will examine the role of CRF1 and CRF2 receptors within the BLA in the negative feelings or emotions experienced due to quitting smoking. Next, we will examine the role of CRF1 and CRF2 receptors within the BLA in the tendency to start smoking again due to stress. The experimental approach is based on the idea that long-term smoking induces changes in CRF signaling within the BLA and that these changes are associated with the negative feelings or emotions experienced from stress or tobacco cessation. Understanding the role of CRF within the BLA may help in the development of improved treatments for tobacco addiction.

## Angiolillo, Dominick

2010 NIR University of Florida

## $377,628

### Effects of Cigarette Smoking on Clopidogrel-Induced Antiplatelet Effects in Patients with Coronary Artery Disease

Cardiovascular disease affects over 80 million people in the U.S. and is the most important cause of mortality. Smoking is a strong risk factor for cardiovascular disease as it has a number of adverse effects, including increasing platelet activation, which in turn increases blood clots. The P2Y12 receptor is a key platelet receptor that influences blood clots as shown by studies in high-risk patients with coronary artery disease (CAD). Thus, there is a clinical benefit associated with antiplatelet agents that block this receptor as it plays a pivotal role in patients with CAD. Importantly, smoking affects the response to inhibitors of P2Y12 receptor. This project will use comprehensive and innovative functional assessments to better elucidate how smoking affects P2Y12 response. The project will test the central hypothesis that cigarette smoking enhances chemical alterations of clopidogrel (medication to prevent blood clots) and that the inhibition of platelet P2Y12 effects is greater in smokers compared to non-smokers. The studies are clinically significant since they advance our knowledge of how smoking influences P2Y12, a key therapeutic target for the treatment of CAD patients. These investigations are part of our long-term goal of defining the best antiplatelet treatment strategy in high-risk patients with CAD.

## Armishaw, Christopher

2010 NIR Torrey Pines Institute

## $400,000

### Alpha-Conotoxins as Subtype-specific Nicotinic Acetylcholine Receptor Antagonists for Studying Tobacco Addiction

Tobacco addiction and nicotine dependence are major health issues that can lead to many associated illnesses. While there are several options available to treat tobacco addiction, a more thorough understanding of the mechanisms of nicotine dependence in the brain is required to develop more effective, safer smoking cessation treatments with fewer side effects. Nicotine acts on the nervous system by activating nicotinic acetylcholine receptors, which leads to a release of dopamine that causes the pleasurable effects of smoking. There are many different types of nicotinic acetylcholine receptors, and each one plays a different role in nicotine addiction. As such, blocking certain types of these receptors may help reduce cravings in smokers. However, a major problem for researchers lies in identifying the specific role for each type of nicotinic acetylcholine receptor in the nervous system. Toxins that originate from venomous marine cone snails may hold the key for discovering new research tools to better understand tobacco addiction. One class of cone snail toxins, the a-conotoxins, can distinguish between different types of nicotinic acetylcholine receptors. Our goal is to use a-conotoxins to develop potent compounds that block specific types of nicotinic acetylcholine receptors involved in tobacco addiction. An important outcome will be the development of new research tools and drug leads for treating nicotine dependence.

# Abbreviated Abstracts of 2010 Grant Awards

## Borlongan, Cesar

2010 RPG University of South Florida

## $1,196,000

### Blood Brain Repair in Cell Therapy for Stroke

Smoking can cause lung and other cancers, coronary heart disease, chronic respiratory disease, and other diseases, including stroke. This project advances the motto "you break it, we repair it." Blood-brain barrier (BBB) breakdown negatively influences central nervous system (CNS) regenerative processes after brain injury. Intravenous administration of a heterogenous cell population containing stem or progenitor cells shows benefit in animal models of stroke. We recently ascribed this functional recovery in transplanted stroke animals to the presence of endothelial progenitor cells in the grafted cell population. Whereas cell-based technologies are largely designed to break the BBB for delivery of therapeutics into the brain, we are taking a novel approach of repairing the BBB damage in stroke. The treatment of ischemic stroke is limited to tissue plasminogen activator (tPA), which only benefits less than 3 percent of stroke patients due to the drug's narrow 3-hour therapeutic window and its detrimental side effects related to BBB damage. That 1) stroke is accompanied by BBB damage, 2) tPA adversely contributes to this BBB damage, and 3) cell therapy can afford BBB repair, form the basis of our overarching hypothesis. Our aim is to show that a treatment regimen directed at BBB repair will restore CNS homeostasis and enhance neuronal regeneration in stroke. Our long-term goal is to advance clinical application cell therapy for stroke.

## Chang, Jessica

2010 PRF Bay Pines VA Healthcare System

## $159,750

### Antioxidant Transcription Factor Regulation and Alzheimer's Disease

In response to cigarette smoking, the human body produces detoxifying antioxidants to combat carcinogens. While these antioxidants are beneficial, sometimes they are not sufficient to prevent disease. Recent studies show that in addition to cancer, smoking may also increase a person's risk for Alzheimer's disease (AD). Alzheimer's is a progressive disease characterized by cognitive and memory loss, affecting almost 500,000 people in Florida and 25 million people worldwide. The reasons for the increased risk are not yet understood. One commonality between smoking and Alzheimer's disease is that the same antioxidant is affected. In moderate smokers, this factor is increased as a protective mechanism, but this protection is lost and a decrease in antioxidants is observed in heavy smokers. This same antioxidant is reduced in Alzheimer's patients, suggesting that the detoxifying enzymes may be the link between smoking and AD. This grant aims to further investigate which detoxifying enzymes are altered in AD, and whether increasing a specific factor will improve the prognosis of AD in a mouse model.

## Cheng, Jin

2010 RPG Moffitt Cancer Center & Research Institute

## $1,200,000

### Targeting AKT Pathway in Lung Cancer

Lung cancer is the leading cause of cancer-related death in the U.S.; 85-90 percent of such cases are associated with tobacco use. Current lung cancer non-surgical treatment is based on chemotherapy and radiation, and improvement in survival and quality of life has been observed. However, the disease is eventually refractory to these treatments. Therefore, there is a need to develop new therapies. Hyperactivation of Akt, an enzyme causing tumor development, is detected in more than 50 percent of lung cancer cases and is closely associated with chemo- and radio-resistance as well as EGFR and mTOR (key proteins involved in cancer cell growth) inhibitor resistance. Tobacco activates Akt, which is believed to mediate tobacco-induced lung cancer. We have identified two AKT inhibitors. API-2 is currently in clinical trial, and API-1 is a new small molecule inhibitor of Akt. These two inhibitors significantly decrease tumor growth and induce cancer cell death. Therefore, the goal of this project is to determine whether AKT inhibitors can be used as potential therapeutic and chemoprevention agents to inhibit AKT-dependant lung cancer cell growth, and as chemo- and radio-sensitizers to overcome the resistance of chemo-radiotherapy, EGFR inhibitors, and ineffectiveness of mTOR inhibitors. These investigations will provide important information on Akt inhibitor use for combinational clinical trials and chemoprevention of lung cancer.

## Del Valle, Juan

2010 NIR Moffitt Cancer Center & Research Institute

## $399,999

### Chemical and Biological Studies of Marine-Derived Non-Ribosomal Peptides

Despite great strides in our understanding of cancer, the development of targeted therapies remains a slow and arduous process. Many cells that proliferate in an uncontrolled manner avoid death due to an overabundance of protective, or pro-survival, proteins. Once proteins such as these are identified, chemists are charged with the task of developing molecules that can modulate or block their function. Unfortunately, many protein interactions are difficult to target with small molecules, and chemical efforts represent a significant bottleneck. In order to accelerate this process, researchers have increasingly looked to nature for new leads. Natural products offer a wealth of structural diversity and often exhibit potent anticancer activity. The development of efficient synthetic strategies to access structurally complex analogues is critical to the discovery of new anticancer agents. The goals of this project are to synthesize natural product-inspired compound libraries and to evaluate their ability to modulate Mcl-1, a protein that contributes to uncontrolled cell proliferation and drug resistance. The long-term objective is to discover structurally novel Mcl-1 inhibitors that will aid in our understanding of cancer signaling and may ultimately be used as anticancer therapeutics.

## Dezfulian, Cameron

2010 NIR University of Miami

## $345,000

### Nitrite-Mediated Neuroprotection After Cardiac Arrest

Cardiac arrest results in over 300,000 deaths annually in the U.S. Smokers are at significantly higher risk of cardiac arrest primarily due to a condition often resulting from heart and lung disease. Smoking results in endothelial dysfunction and diminished nitric oxide and nitrite availability, which is believed to contribute to worsening brain injury after lack of blood flow (ischemia). This project investigates nitrite therapy. Nitrite is emerging as a source of nitric oxide after ischemia that can protect organs such as the brain and heart from injury. Based on preliminary evidence that nitrite protects the brain from injury after cardiac arrest, this project seeks to optimize this therapy as its first aim and to study a promising and novel pathway whereby protection occurs as its second aim. The information gained from this research should provide needed information for bench to bedside translation of a novel therapy for a highly lethal tobacco-linked disease (cardiac arrest) where therapies are badly lacking. By targeting ischemia and tobacco-related endothelial dysfunction and nitrite/nitric oxide depletion, this therapy will potentially identify new pathways where additional ischemic brain injury therapies may be developed.

## Dweck, David

2010 PRF University of Miami

## $107,900

### High Throughput Screening to Discover New Compounds that Modulate Cardiac Muscle Contractility

In pathological hypertrophy (increase in the volume of an organ), the heart abnormally increases in size and mass in efforts to compensate for higher demands in workload, such as in hypertension due to smoking. Since smoking promotes hypertrophy and its many unwanted side effects, e.g., fibrosis, arrhythmia, and sudden cardiac death; there is an urgent need to improve the treatments of cardiovascular diseases. Current drug treatments focus on altering the force of muscle contraction in order to strengthen the failing heart or to slow the fast-paced hypertrophic heart. Typically these drugs alter the cellular calcium levels, which have desirable and undesirable side effects. Therefore, the discovery of new compounds that specifically interact with the contractile proteins of the muscle, rather than altering the cellular calcium level, could potentially improve contraction and become therapeutic. The goal of this project is to test ~ 250,000 compounds for the ability to modulate contractile protein activity using the resources of fully integrated and automated screening/testing centers. Using these approaches, we aim to uncover new compounds that can be studied in molecular detail and eventually in physiological systems for the investigation and treatment of hypertrophy, heart failure, and other cardiovascular diseases exacerbated by tobacco use.

# Abbreviated Abstracts of 2010 Grant Awards

## Echeverria-Moran, Valentina

2010 RPG Bay Pines VA Healthcare System

## $583,023

### Investigating Cotinine to Improve Memory and Prevent Tobacco Abuse in Subjects with Cognitive Impairment Due to Psychiatric Disorders

Attention and memory are affected in conditions such as schizophrenia, Alzheimer's disease (AD), posttraumatic stress disorder (PTSD), and depression. In the U.S., more than 25 million individuals are affected by these conditions, and cognitive deficits greatly diminish their ability to work and socialize. Currently available medications do not target this problem. These mental health conditions are associated with higher tobacco consumption and a deficiency in the nicotinic acetylcholine receptors. It is believed that tobacco use is related to the self-administration of nicotine to reduce symptoms such as anxiety and feelings of depression, and to stimulate the nicotinic receptors to improve memory and attention. Cotinine, the main metabolite of nicotine, stimulates these receptors, improves memory in AD mice, reduces anxiety, and presents a good safety profile in humans. At the preclinical level, this project will investigate the use of cotinine on memory impairment induced by PTSD and schizophrenia using three mouse models of stress/PTSD and a drug-induced model of schizophrenia. This research will permit us to predict the utility of cotinine in reducing cognitive impairment and anxiety present in individuals with these mental conditions. This is intended to be a first step toward the investigation of cotinine in preventing or reducing smoking behavior in individuals with psychiatric conditions.

## Fields, Alan

2010 RPG Mayo Clinic

## $1,200,000

### Combined PKCiota and mTOR Inhibition for Treatment of Advanced Non-small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and the leading cause of cancer death in the United States. Ninety percent of NSCLC cases are linked to tobacco smoking, the major cause of this disease. Despite the best available treatments, the five-year survival rate for NSCLC patients is only 15 percent. The dismal outlook for NSCLC patients has prompted a search for more effective strategies to treat this deadly smoking-related disease. We recently identified a new lung cancer-causing gene termed PKC iota. PKC iota is activated in the majority of NSCLC tumors. We have also discovered a small molecule PKC iota inhibitor, aurothiomalate (ATM), which shows potent activity against NSCLC tumors in pre-clinical studies. ATM has synergistic activity when combined with a second drug that inhibits a second cancer-related gene, mTOR. In this project, we will conduct a Phase I/II clinical study to determine the safety and efficacy of ATM when combined with an mTOR inhibitor, temsirolimus, in patients with NSCLC. We will also develop tumor biomarkers of PKC iota and mTOR activity as predictors of response to therapy, and identify biomarkers of PKC iota and mTOR activity in circulating lymphocytes. These studies aim to develop a novel therapy to better treat NSCLC as well as develop tests to monitor and predict how patients respond to this therapy.

## Fields, Alan

2010 RPG Mayo Clinic

## $1,200,000

### Atypical PKC Signaling in Lung Cancer Stem Cells

Lung cancer is the number one cause of cancer death in the U.S. with a five-year survival rate of only 15 percent. Cigarette smoking, the major cause of lung cancer, is responsible for 90 percent of lung cancer cases. Our long-term goal is to better understand what drives lung tumor formation and progression, and translate this knowledge into better treatment strategies. Human lung tumors contain cells termed lung cancer stem cells that are necessary for lung tumor maintenance and progression. Given their critical role in lung cancer, lung cancer stem cells must be eliminated to treat lung cancer effectively. However, these cells are highly resistant to current cancer drugs. We have identified a gene, PRKCI, which is necessary for lung tumor formation. We hypothesize that PRKCI controls the ability of lung cancer stem cells to form lung tumors and that PRKCI is an attractive therapeutic target. In this project, we will determine how PRKCI causes lung cancer stem cells to form tumors. Completion of these studies will enhance our understanding of lung tumor formation and progression, and identify novel treatment strategies that target deadly lung cancer stem cells. These studies are a critical step in the development of new, more effective therapeutic approaches for the treatment of smoking-related lung cancer.

## Gopalan, Priya

2010 NIR University of Florida

## $400,000

### A Phase II Clinical Trial of the CDK 4/6 Inhibitor, PD 0332991, in Previously-Treated, Advanced NSCLC Patients with Wildtype RB and Inactivated CDKN2a

Lung cancer is the leading cause of cancer death worldwide. Smoking is the predominant risk factor. Despite the use of newer drugs, survival rates are poor. To improve survival while minimizing side effects, treatments need to be tailored to a patient's genetic profile. In this project, we aim to treat patients with a specific abnormality in their Retinoblastoma (RB) gene pathway. Abnormalities in the RB pathway are found in all patients with non-small cell lung cancer, the most prevalent type of lung cancer. We will conduct a clinical trial and laboratory experiments to study the efficacy of PD 0332991, a drug that blocks a specific protein in the RB pathway that is abnormally turned on, in combination with decitabine, an FDA-approved drug that targets this pathway by a separate mechanism. By including only patients with a specific tumor genetic profile, we anticipate a good response. Importantly, using genetic markers to define the patients that are likely to respond to therapy will also allow us to identify other genetic markers for potential resistance to therapy and allow for optimal planning for future studies. Benefits of the study include: 1) the evaluation of a novel drug combination in patients with specific tumor characteristics; and 2) laboratory studies evaluating other drugs to prevent the potential development of resistance. The project may thus significantly advance the personalized treatment of lung cancer.

## Gray, Jhanelle

2010 NIR Moffitt Cancer Center & Research Institute

## $399,962

### Combination Immunotherapy for Lung Cancer

Despite chemotherapy, patients with metastatic adenocarcinoma of the lung have poor prognosis; therefore, novel modalities such as immunotherapy are being developed for this disease. A new lung cancer vaccine, GM.CD40L, has been developed at the Moffitt Cancer Center. This vaccine contains GM-CSF and expresses CD40L. These proteins work together to activate immune cells to migrate to the regional lymph nodes where an amplified immune response can occur, leading to tumor cell killing. In early-stage human clinical trial testing, the GM.CD40L vaccine was found to be a safe method to deliver anti-tumor cell immune responses and to diminish disease burden in a variety of solid tumors. CCL21 is a protein that may amplify the T cell responses to this vaccine. Based on this information, a Phase II randomized study is planned to evaluate two vaccine formulations (allogeneic tumor cells plus GM.CD40L bystander cells plus or minus CCL21L) in patients with adenocarcinoma who have failed first-line therapy. Specific aims are to evaluate: (1) clinical efficacy, and (2) the development of specific anti-tumor immune responses. The information obtained from this project will serve as the basis for a more expansive project where vaccine therapy is compared with standard therapies. The long-term goals are to develop a safe, feasible, and effective therapy to improve the outcomes of individuals with adenocarcinoma of the lung.

## Guan, Jingjiao

2010 NIR Florida State University

## $391,496

### Array-Based Fiber FISH for Genetic Analysis of Lung Cancer

Lung cancer is the leading cause of all cancer deaths, and tobacco smoking is responsible for the prevalence of this disease. Although tremendous efforts have been devoted to the treatment of lung cancer, conventional therapies have been ineffective to increase the survival rate over the past decade. However, an emerging treatment strategy based on the detection and characterization of genetic mutations underlying this disease has shown great potential to improve the situation significantly. Fiber fluorescence in situ hybridization (fiber FISH) is a powerful assay (or analysis) for confirming, identifying, and quantifying cancer-relevant mutations, but the conventional fiber FISH suffers from various drawbacks. The purpose of this project is to develop a novel array-based fiber FISH that can allow more reliable identification and more accurate quantification of mutations in lung cancer. Successful development and application of this technique will deepen our understanding of lung cancer genetics and lay a solid foundation for developing more effective therapies against this devastating disease.

# Abbreviated Abstracts of 2010 Grant Awards

## Guo, Jianping

2010 PRF Moffitt Cancer Center & Research Institute

## $111,300

### IKBKE Oncogene in Lung Cancer

A previous study verified that IKBKE is a breast cancer oncogene (a gene when mutated or expressed at high levels contributes to converting a normal cell into a cancer cell). We have recently shown high IKBKE expression in lung cancer. Further, overexpression (excessive expression of) IKBKE induces lung epithelial cell transformation and tumor formation. Decreased expression of IKBKE sensitizes lung cancer cells to apoptosis (programmed cell death) by chemotherapeutic agents. Based on these findings, we hypothesize that IKBKE plays an important role in lung carcinogenesis and could be a critical target for therapeutic intervention of lung cancer. We have identified a small molecule inhibitor of IKBKE. Therefore, the objectives of this project are to: 1) Examine the clinical pathological significance of IKBKE overexpression in lung cancer. We will evaluate if IKBKE is a valuable tumor marker for prognosis, diagnosis, and treatment response of lung cancer by examining a large series of tumor specimens. 2) Determine the role of IKBKE in lung tumorigenesis in vivo using mice with specific genetic characteristics. 3) Examine the role of IKBKE in chemoresistance and as a target for lung cancer intervention by evaluating the effect of our IKBKE inhibitor on lung cancer growth in cell culture and a mouse animal model.

## Kim, Donghwa

2010 NIR Moffitt Cancer Center & Research Institute

## $399,999

### Determine Clinic Pathological Significance of Alteration of NGB and Regulation by AKT2 in Lung Cancer

Lung cancer is the leading cause of cancer-related death in the world. The risk of developing lung cancer is directly related to smoking because patients eventually resist chemotherapeutic drugs and radiotherapy. Therefore, there is a need to understand the molecular mechanism of this resistance. Activation of the AKT(one of the oncogenic protein families that plays an important role in cell signaling for tumor development) pathway by tobacco components increases lung epithelial cell proliferation and survival, and inhibits apoptosis (programmed cell death) in response to DNA damage. Similarly to AKT, mTOR regulates cellular processes critical to tumorigenesis such as cell growth, proliferation, and metabolism, and many cancers are characterized by aberrant activation of mTOR, including lung cancer. Recently, we identified a tumor suppressor protein, NGB, which is associated with AKT and mTOR and is frequently altered in various human tumors include lung cancer. Overexpression of NGB significantly reduced lung cancer cell growth, proliferation, and metastasis. Therefore, compelling evidence may be implicating NGB as a bona fide tumor suppressor. However, this hypothesis has not yet been tested in vivo. We plan to address this question using a novel mouse model with NGB loss of function. This study will provide important insights to the research community to guide potential strategies to inhibit cancer progression.

## Kojetin, Douglas

2010 NIR Scripps Research Institute

## $400,000

### Dynamic Regulation of Allosteric Communication Networks in PPARgamma Pharmacology

Our long-term goal is to understand how nuclear receptor (NR) transcription factors (proteins that bind DNA at specific sites to regulate copying) function and contribute to disease development and progression for purposes of preventative and therapeutic control. Tobacco smoke contributes to numerous health issues; in heart disease patients, tobacco smoke significantly affects the expression of a particular NR protein, PPARg. As an obligate heterodimer (protein partner) with the NR protein RXRa, PPARg regulates the expression of genes involved in cellular metabolism, growth, differentiation, and inflammation. Recent emphasis has been placed on a new class of selective PPARg drugs that preserve beneficial properties and decrease side effects of current PPARg drugs. Understanding how existing PPARg drugs work will aid the development of next-generation PPARg drugs. To accomplish this, we will test the hypothesis that pharmacologically distinct PPARg ligands (drugs) modulate (1) the surface used for interacting with other proteins and the ability to preferentially recognize one protein over another of RXRa/PPARg; (2) the function of RXRa/PPARg via unique allosteric (change in shape and activity) changes in dynamics. We predict these studies will provide new insight into how ligands control PPARg function and may provide the basis for the development of novel therapeutics for disease treatment.

## Koniaris, Leonidas

2010 RPG University of Miami

## $1,200,000

### Identifying and Addressing Cancer Outcome Disparities in Breast and Lung Cancer

Many minority and poor communities exhibit increased cancer risk and higher rates of cancer death. While higher smoking rates are partly to blame, other factors are also responsible. Our long-term goal is to identify and eradicate disparities and provide optimal treatment for all cancer patients. In this project, we will determine whether and where disparities exist for two of the most common tobacco-associated cancers, lung and breast, then communicate that knowledge to Florida communities. The interdisciplinary team consists of cancer surgeons, oncologists, statisticians, epidemiologists, and community educators. A very detailed database will be made by linking the Florida Cancer Data System, which collects diagnosis and treatment data for every Florida cancer patient, to the Agency for Health Care Administration database, which collects extensive inpatient and outpatient data for individual patients. The resulting dataset will cover the treatment, health, and outcomes status of ~500,000 cancer patients. Subsequent analysis of this dataset will be powerful enough to detect disparities in diagnosis, treatment, and outcomes for patient groups representing even a small fraction of the population. Next, we will identify causes of the disparities. Finally, we will present our findings in culturally appropriate ways to patients, health-care providers, and at-risk communities in order to improve cancer care.

## Kusmartsev, Sergei

2010 NIR University of Florida

## $400,000

### Tumor-infiltrated Myeloid Cells and Prostaglandin Catabolism in Human Bladder Cancer

Bladder cancer (BC) is common urologic cancer. Smoking causes about 50 percent of all BC. Existing therapies require a strong immune response. However, expressions of immunosuppressive factors by cancers lead to the formation of an immunosuppressive environment that protects cancer from immune system surveillance. A significant portion of tumor is represented by tumor-infiltrated inflammatory CD11b cells. These cells are recruited by the tumor from bone marrow and play a major supportive role in bladder cancer progression by inhibiting immune response. The most evident immunosuppressive factor in BC is prostaglandin E2 (PGE2). PGE2 is synthesized by cycolooxygenase-2 (COX-2), and biologically degraded by 15-PGDH. Our preliminary results show that CD11b cells isolated from tumor tissue produce large amounts of PGE2 but show reduced ability to inactivate it because of low expression of 15-PGDH. The major goal of this research is to establish whether correction of PGE2 imbalance in the BC microenvironment can reverse the immunosuppressive function of tumor-infiltrated CD11b cells and lead to the inhibition of tumor growth. We will explore the mechanisms underlying the association between imbalance of PGE2 and the immunosuppressive behavior of CD11b cells within the BC. Obtained results may directly lead to development of new therapeutic interventions for treatment of BC.

## Lee, David

2010 RPG University of Miami

## $716,672

### A Community-Focused Smoking Cessation Intervention

Research indicates that friends and close family members of people who smoke cigarettes are themselves more likely to smoke, forming a type of social network (e.g., "birds of a feather flock together"). It is possible that smokers in these networks who quit smoking will also be successful in helping their friends and family members to quit smoking as well, particularly if they receive training in how to provide assistance and support. However, this approach has yet to be tested. Our research group at the University of Miami has developed a partnership with community groups in a neighborhood that we have identified as having higher-than-expected rates of tobacco-associated cancers, including lung and oral cancers. Together with our community partners, we have completed a pilot study that documented smoking rates that are more than two times higher than the rates in the greater Miami metropolitan area. This study will develop a unique smoking cessation program that will involve training former smokers living in this community to help current smokers interested in quitting. We will monitor the success of the program and conduct interviews with both smokers and their smoking cessation counselors to identify ways we can improve upon the success of this unique way to help smokers quit smoking.

# Abbreviated Abstracts of 2010 Grant Awards

## Lewin, Alfred
2010 RPG University of Florida

## $720,000

### Developing Gene Therapy for Age-Related Macular Degeneration

Age-Related Macular Degeneration (AMD) is a blinding disease affecting as many as 1 in 3 people over 70. Smoking is a major risk factor for developing this disease. This is a project to develop a mouse model of early AMD and to test two novel approaches to gene therapy in that model. Our goals are to better understand the cause of AMD and to develop a treatment for early stages of the disease. We have created a genetically modified mouse strain in which a protective enzyme is missing from one layer of the retina, the part of the eye that absorbs light. In our previous experiments, we observed that reducing levels of the enzyme caused serious structural damage similar to that occurring in early ("dry") AMD. In this project, we will determine the time course of these retinal changes and see if they progress to the "wet" form of AMD, in which leaky blood vessels sprout into the retina causing loss of central vision. We will also attempt to use gene transfer methods to arrest the progression of AMD-like changes. First, we will use a non-harmful virus to deliver genes that prevent the generation of reactive oxygen molecules by an enzyme called NOX. Blocking NOX in patients could slow the progression of AMD. Our second approach will be to restrain the release of a molecular signal that stimulates inflammation in the retina. We believe that blocking inflammation will prevent the damage to the retina seen in AMD.

## Li, Qiongzhen
2010 PRF University of Miami

## $56,550

### Tobacco Smoke, Stem Cells and Impaired Lung Repair: An Emerging Paradigm in COPD

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. Currently, there is no effective cure for the disease. Tobacco smoke is the greatest risk factor for COPD. It is estimated 80-90 percent of COPD patients are current or past smokers. Recent evidence suggests that tobacco smoke not only causes lung injury, but also harms stem cells thereby hindering lung repair. Our preliminary data suggest that the inflammatory mediator interleukin-1 (IL1) may mediate the effects of the tobacco smoke on lung tissues and stem cells. To better understand how the IL1 pathway may impact lung injury and repair after tobacco smoke, we will use specially developed mice that are genetically deficient in IL1 receptor antagonist (IL1RA) that protects against the inflammatory and scarring actions of IL1; have additional IL1RA, or are deficient in IL1 productions. We will expose these mice to chronic tobacco smoke to quantify the effects on lung injury and stem cells' responses. At the end of this one-year Project, we will have determined the relationship between the IL1 pathway, stem cell functions, and the promotion of lung disease by tobacco smoke. In summary, this project will deepen our understanding of how cigarette smoking may hamper the repair process associated with lung disease leading to new therapeutic approaches for tobacco-related lung disease.

## Li, Xiao
2010 NIR University of South Florida

## $398,944

### A Rapid and Sensitive Optical Spectroscopic Method for Simultaneous Determination of Cotinine, Trans-3'-hydroxycotinine and Thiocyanate In Vitro

This research intends to develop a rapid, robust, and simple method based on optical spectroscopy to determine the concentration of three tobacco-related biomarkers simultaneously: cotinine, trans-3'-hydroxycotinine, and thiocyanate. Compared with conventional methods, the technique offers several advantages: little sample preparation; simple, fast, wide concentration range; and direct detection in blood, urine, or plasma. Preliminary data showed that the method is sensitive enough for the detection of nicotine and thiocyanate in both non-smokers and smokers, but not for trans-3'-hydroxycotinine in non-smokers yet. Therefore, the aims are: 1. improve its sensitivity through the use of nanoparticles with special structures; 2. optimize it in terms of stability, reproducibility, and selectivity; 3. validate the method by investigating the effect of cotinine, trans-3'-hydroxycotinine, and thiocyanate on the survival of neuronal cells in vitro and explore their relationship with the decreased incidence of Parkinson's disease in smokers. The long-term goal of the research is to develop a multipurpose and clinically applicable tool that is useful in both molecular diagnosis and scientific research. Information obtained from such methods will shine light on the interplay between tobacco-related chemicals and many diseases including various cancers and lead to a possible therapeutic approach for such diseases.

## Lin, Hung Wen

2010 PRF University of Miami

## $111,300

### Nicotine Exacerbates Post-ischemic Cerebral Blood Flow Derangements After Cardiac Arrest

Tobacco smoke is responsible for increased risk for cardio- and cerebrovascular diseases. Nicotine, the addictive component of tobacco smoke, is responsible for cardiovascular deficits such as heart rate and blood pressure. Enhanced nicotine levels can cause cardiac arrhythmias, contributing to cardiac-related sudden death. Thus, cardiopulmonary arrest remains one of the leading causes of death and disability in the U.S. Survival rates following cardiac arrest (CA) are poor, despite prompt emergency treatment and better resuscitation techniques. Of 70,000 patients per year that are resuscitated after CA, 60 percent die from extensive brain injury and only 3–10 percent are able to resume their former lifestyles. Most neuroprotective trials for cerebral ischemia (restriction in blood supply) have been unsuccessful; therefore, new drug interventions are greatly needed. Our goal in this project is to further our understanding of nicotine's involvement in brain circulation after CA in order to lay the foundation for a common therapy and greatly improve the outcome from nicotine-enhanced CA. Utilizing in vivo and in vitro cerebral blood flow (CBF) detection techniques, we plan to: define the role of nicotine as it relates to CBF after CA and determine the specific factors involved in promoting CBF derangement after CA.

## Micalizio, Glenn

2010 RPG Scripps Research Institute

## $1,199,600

### A Future for Natural Product-Inspired Hsp90 Inhibitors in the Search for Clinically Relevant Chemotherapeutic Agents

This project is a collaborative effort to enable the discovery of therapeutically relevant anticancer compounds. Hsp90 is a validated, therapeutic target that has been recognized as the most novel and broadly applicable anticancer target being explored today. That said, no Hsp90 inhibitors have made it to the market. While the search for clinically relevant Hsp90 inhibitors is a focus of numerous pharmaceutical and academic laboratories, the project described here defines an innovative and powerful pathway to the discovery of natural product-inspired Hsp90 inhibitors. The expertise of organic chemists will provide a means to design and prepare natural product-inspired Hsp90 inhibitors that will avoid the well-understood limitations of derivatives in clinical trials through the application of state-of-the-art chemical methods. Thorough biochemical analysis will guide the search for a collection of the most potent and selective Hsp90 inhibitors. The significance of the project is in the ability to open a pathway to chemotherapeutic discovery that is not currently available. As such, the efforts described define an innovative entry to the discovery of new therapeutically relevant anticancer agents.

## Miguez, Maria Jose

2010 RPG Florida International University

## $1,199,788

### Cytokines: An Underlying Cause of Health Disparities in Tobacco-Related Diseases

The biological mechanisms whereby tobacco use may influence the development of tobacco-related diseases (TRD), particularly among certain racial ethnic groups, are incompletely defined. Nonetheless, our preliminary data indicated that there are some differences in the production of cytokines, thus raising the question of whether differences on other key cytokines may exist, and if they contribute to the observed differences in TRD. Therefore, one of the goals of this project is to consider the profile of cytokine production among different groups (people living with or without HIV, Black and whites who are or are not smokers), so that any disparities in the TRD burden are appropriately attributed. Considering the burden of tobacco-related diseases in our society, early detection of those at risk will be of paramount importance. So, to be pro-active, our second goal is to identify the potential usefulness of cytokines in recognizing specific segments of the population bearing a greater risk of developing TRD.

# Abbreviated Abstracts of 2010 Grant Awards

## Miksovska, Jaroslava

2010 NIR Florida International University

## $387,063

### Conformational Dynamics in Vertebrate Hexacoordinate Hemoglobins

Two hexacoordinate heme proteins have recently been discovered in humans and other vertebrates. (Hexacoordinate heme means that there are six ligands in this pocket-shaped protein that hold a heme ion or iron atom in place). Neuroglobin (Ngb) has been found predominantly in brain tissue where it plays an important role in the protection of neuronal tissue under conditions of hypoxia (deprived of adequate oxygen) and ischemic (lack of blood supply) stress. Cytoglobin (Cygb) is found in connective tissue of body organs including lung, heart and brain. The physiological role of this protein has not been fully established; however, evidence points to its role in protecting cells against oxidative stress. Cygb was also associated with several types of cancer including sporadic non-small cell lung cancer, and head and neck cancer. Our long-term goal is to determine the physiological function of Ngb and Cygb and to understand the structure-function relationship in the family of hexacoordinate globins. Our goal in this study is to provide detailed information about ligand-induced changes in the structure of vertebrate hexacoordinated heme proteins and thus provide important insight into the mechanism of ligand interactions with Ngb and Cygb, which will lead to a clearer understanding of the role of these proteins in brain injuries and cancer and ultimately to novel therapeutic targets for the treatment of stroke.

## Palacio, Ana

2010 RPG University of Miami

## $1,199,757

### Improving Adherence to Cholesterol Lowering Medications among Minority Populations in Florida: A Randomized Trial

Coronary heart disease is a leading cause of morbidity and mortality in the U.S. There is significant evidence that taking a cholesterol-lowering medication known as a "statin" for more than 1-2 years significantly reduces the risk of serious cardiovascular outcomes, even among people with no known heart disease. Yet adherence to statin therapy is suboptimal, particularly among minority populations. Studies have consistently found that at one year, only half of the subjects that started a statin continue to take it. Many other health disparities in cardiovascular care and outcomes have also been reported. We plan to compare the effectiveness of a phone-based behavior modification program that uses motivational interviewing (MINT) to usual care, using a randomized design. MINT has shown good results at improving health behaviors and smoking quitting rates. We will recruit 1200 subjects from a large health benefits carrier who received a new statin prescription and who are either African American or Hispanic, and will randomize them to either group. We will administer a telephonic survey assessing barriers to adherence, self-reported adherence, and a smoking history questionnaire at baseline and at 24 months to evaluate the impact of the intervention. Also, we will use claims data to objectively determine if the intervention increases by at least 15 percent the proportion of subjects who refill their statin adequately at 2 years.

## Papke, Roger

2010 RPG University of Florida

## $1,200,000

### Therapies to Improve Smoking Cessation in Neuropsychiatric and Depressed Patients

Smoking is more common in people with depression and other neuropsychiatric conditions than in the general population. It is believed that for these individuals, smoking is driven by a desire to self-medicate by stimulation of alpha7 type of nicotine receptor, which is decreased under stressful conditions and in neuropsychiatric populations. Varenicline, a drug developed to help people quit smoking, is a weak stimulator of the alpha7 beta2* receptors associated with addiction. It is believed to partially replace and suppress the rewarding effects of nicotine. However, our data show that varenicline also further decreases the function of alpha7 receptors. Reports of suicide and worsened depression in patients taking varenicline have led the FDA to issue a black box warning on the drug. We have shown that GTS-21, an approved drug for human studies, currently in clinical trials for schizophrenia, is a selective partial activator of alpha7 receptors. Our data indicates that GTS-21 should reverse the negative effects of varenicline on the alpha7 receptors of the brain, and propose that if GTS-21 were given as an adjunct therapy to varenicline, it would lessen depression and improve successful smoking cessation in a patient population at high risk for depression or other neuropsychiatric disorders. We will test this idea with humans at high risk for mental illness and conduct pre-clinical studies to validate and advance this approach.

## Parker, Alexander

2010 RPG Mayo Clinic

# $1,161,771

### The Molecular Epidemiology of Renal Cell Carcinoma

Renal cell carcinoma (RCC) is by far the most common form of kidney cancer. Of interest, the number of people diagnosed each year with RCC, as well as those who eventually die from this cancer, has been steadily increasing in the U.S. (and Florida) for more than three decades. Despite this, the underlying causes of RCC remain poorly understood. The goal of this project is to conduct a large case control study of RCC in order to improve our understanding of the causes of RCC. This project will be the result of a combined effort by investigators at two Florida academic medical institutions (Mayo Clinic and Moffitt Cancer Center) and will involve recruitment of 1,400 individuals with RCC and 1,400 controls with no history of cancer. Using data and tissue samples collected from these individuals, we will build on the current knowledge that smokers, obese individuals, and those with a history of urinary tract infections are at increased risk of developing RCC. We will test specific hypotheses regarding exactly how these factors work at the cellular level in the kidney to cause RCC. By doing so, we have the potential to enhance our understanding of how these common exposures increase a person's risk of RCC. As such, our findings could translate into new intervention strategies (i.e., better risk stratification, early detection, and/or chemoprevention) that would ultimately reduce the burden this cancer places on individuals and society.

## Pinto, Jose

2010 NIR University of Miami

# $399,258

### Understanding the Molecular Mechanisms of Troponin Mutations in Cardiac Muscle Dysfunction

Long-term tobacco use induces a ventricular hypertrophic response (increase in size) that compensates for damage to the myocardium (heart muscle) and can eventually result in heart failure. Hypertrophic cardiomyopathy (HCM) and Restrictive cardiomyopathy (RCM) are cardiovascular diseases that cause severe cardiac disability and heart failure. These diseases possess a genetic component that is an inherent risk factor for familial heart disease and are greatly affected by tobacco use. An urgent need exists for the development of therapeutic approaches that can tailor the myofilaments' (single functional unit that is responsible for the muscle contraction) contractile response. HCM is a common cardiac disorder and main cause of sudden death in the young. RCM is not well understood; however, it results in abnormal diastolic function and impaired ventricular filling. Mutations in Troponin, the protein that binds Ca2+ and regulates cardiac muscle contraction, have been linked to HCM and RCM, and both mutations induce sensitization of the myofilament to calcium. Calcium sensitization may contribute to the development of many overlapping features of both diseases. However, the clinical aspects of each disease are distinct. This project will explore the molecular mechanisms that underlie HCM and RCM mutations and will delineate specific in vitro and in situ observable differences in characteristics that arise from these inherited mutations.

## Rangel, Erika

2010 PRF University of Miami

# $111,300

### Isolation, Characterization, and Differentiation of c-kit Positive Cells from Neonatal Rat Kidneys

Tobacco smoking is a renal risk factor in the general population and also in patients with primary and secondary kidney disease, such as glomerulonephritis, hypertension, and diabetes. At present, dialysis and transplantation remain the only treatment options for chronic kidney disease. However, there is hope that stem cell therapy may provide an additional regenerative approach for kidney disease. In this study, we are planning to isolate and expand stem cells from neonatal rat kidneys. To test their potential to differentiate to kidney structures, such as endothelial and epithelial cells, we are going to culture the cells in differentiation media and analyze specific markers both before and after differentiation. Further, the cells will be injected into mice to assess their regenerative potential in a model of ischemia-reperfusion injury. (Ischemia is an inadequate blood supply; reperfusion is restoration of blood flow to an area that has previously experienced deficient blood flow).

# Abbreviated Abstracts of 2010 Grant Awards

## Rosser, Charles

2010 TSP M.D. Anderson Cancer Center

## $1,335,420

### A Multidisciplinary Approach to Improve Patient Outcome in Bladder Cancer- A Tobacco-Related Disease

Bladder cancer (BCa) is among the five most common malignancies worldwide. The major risk factor associated with the development of BCa is tobacco smoke. BCa cases for 2010 are estimated at 60,000, with estimated deaths at 12,700. Despite these figures, BCa remains a cancer that is poorly understood. There are currently several pressing issues regarding (1) how and why BCa develops, (2) what factors in the urine can be used to diagnose or monitor BCa, and (3) what novel therapies could be used alone or in combination to improve patient outcomes. We have assembled a collaborative team from a variety of medical and research fields in order to harness the incredible resources in Florida for the express purpose of addressing these issues. Our intention is to conduct five projects: one focused on a new therapeutic agent for BCa, one focused on new targets for drug development, one focused on determining new markers for early BCa detection, one focused on how smoking increases the risk of developing BCa, and one focused on the effects of cigarette smoke extract on tumor growth. At the participating institutions, M.D. Anderson Cancer Center, Moffitt Cancer Center & Research Institute, University of Miami School of Medicine, Mayo Clinic, and University of Central Florida, we have the resources, study personnel, and patient populations to complete the necessary tasks in a timely and successful manner.

## Salihu, Hamisu

2010 RPG University of South Florida

## $1,197,479

### Preventing Fetal Body and Brain Size Reduction in Low-income Smoking Mothers: A Randomized Clinical Trial

Since smoking cessation programs during pregnancy have been only partially successful, especially in low-income subpopulations, it is important to develop interventions that include a strategy to reduce the undesirable impact of smoking during pregnancy. Current low-strength folic acid prescribed to pregnant women is insufficient to compensate for depleted blood folate levels among smokers. This project seeks to assess the value of higher-strength folic acid (in comparison to standard of care) combined with a smoking cessation program in reducing the negative effects of tobacco smoke on the fetal body and brain. In three follow-up visits, participating pregnant women will be administered questionnaires and will undergo ultrasound examinations. Maternal blood will also be collected for the testing of folic acid levels and other related substances. All participants will be followed until delivery when umbilical cord blood will be collected for assessment of brain growth and development. At birth, the infant's body and brain growth limits will also be measured. The two groups will then be compared to determine the effectiveness of higher-strength folic acid supplementation in improving fetal body and brain growth among smokers. This study will provide important information for subsequent follow-up of these infants to determine whether the intervention improves future intellectual, behavioral, and physical development.

## Wang, Liyong

2010 NIR University of Miami

## $400,000

### Understanding the Mechanisms of Smoking on Complex Diseases from NOS2A-Smoking Interaction

Cigarette smoking (CS) is a strong environmental factor for many complex diseases, including Parkinson's disease (PD) and age-related macular degeneration (AMD). Prevention and treatment of CS-related diseases requires knowledge of the underlying molecular mechanisms of CS, which remain elusive. The genetic revolutions of the past decade have provided substantial insights into the etiology of complex diseases. Statistical evidence for interaction between CS and genes has been reported in many cases. For example, genetic variants in the inducible nitric oxide synthase (NOS2A) gene have been associated with increased disease risk and significantly interacted with CS in PD and AMD. Understanding the mechanisms for these statistical interactions has great potential to make novel findings on CS's biological effects as the genetic approach tackles the question from an unconventional angle. As the first step to illustrate the CS-NOS2A interaction, this study will map all CS-interacting variants in NOS2A using cutting-edge genomic technologies and evaluate them in well-powered datasets using PD and AMD as primary disease models. NOS2A has been associated with other CS-related diseases, such as cancer and stroke. Therefore, knowledge gained from this study will be a valuable resource for studies focusing on other CS-related diseases.

## Wangpaichitr, Medhi

2010 PRF Miami VA Healthcare System

## $164,450

### Targeting ROS and Tumor Metabolism to Selectively Kill Cisplatin Resistant Lung Cancer

Lung cancer is one of the leading causes of death in the United States and the most common cancer found in South Florida. While early stage lung cancer can be treated by surgical resection, chemotherapy remains the mainstay for treatment for locally advanced and metastatic disease. Cisplatin, a platinum-based chemotherapy drug, or its analog carboplatin is one of the main drugs that has been utilized for the treatment of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Development of platinum resistance is inevitable, hinders the likelihood of achieving remission, and hence leads to poor survival. We have found that all Cisplatin-resistant lung cancer cells express higher baseline levels of oxidative stress. Moreover, these resistant cells appear to change their metabolic pathway in order to adapt to survive under high oxidative stress conditions. By identifying and targeting this pathway, Cisplatin-resistant cells can be selectively killed. We predict the knowledge gained from this work will contribute to improved treatment outcome and survival in these patients. Furthermore, identifying which patients will respond to treatment helps reduce costs and hospitalizations of cancer patients. Thus, the project not only represents a new avenue for overcoming Cisplatin-resistance but will also assist in future selection of patients who will benefit from this treatment.

## Wen, Yuhui

2010 PRF University Of Miami

## $164,450

### Mechanisms of Hypoxia-Induced Dendrite Degeneration

Low oxygen level (hypoxia) caused by tobacco smoking is a risk factor for stroke. Once the brain has been traumatized by hypoxia, a flurry of molecular signals encourages healthy neurons to kill themselves. The degeneration (beading and fragmentation) of dendrites, which play an important role in the integration of information flow from one neuron to another, is tightly associated with loss of key brain function. Previous studies have shown that Drosophila melanogaster (a species of fruit fly) exhibits remarkable resistance to lack of oxygen. In preliminary studies, we found that wild-type flies under anoxia (extreme condition of hypoxia, 0.1 percent O2) did not exhibit any beading or fragmentation of dendrites. However, flies heterozygous nmnat (total protein level is reduced), showed severe dendrite beading and fragmentation under the same anoxic conditions. These results suggest that normal levels of NMNAT offer protection for dendrites under anoxia. For the next three years, we will further dissect the underlying mechanism and role of chaperone NMNAT in hypoxia-induced dendrite degeneration. We will start a genetic screen to find new dendrite protective factors. These studies will shed light on hypoxia-induced brain injury and are important to develop effective stroke treatment.

## Xie, Xiangyang

2010 PRF Sanford-Burnham Medical Research Institute

## $164,450

### Functional Analysis of Novel Akt Substrate ASC2D in Glucose Transport System and Its Role in Insulin Resistance

Smoking – long known to increase the risk of cardiovascular disease – is also associated with an increased risk of developing type 2 diabetes. It has been found that smokers are more than twice as likely to develop the condition of insulin resistance and type 2 diabetes as non-smokers. Impaired sugar glucose transport into the cells for metabolism is the hallmark of type 2 diabetes. Insulin regulates glucose metabolism primarily through the activation of glucose transport system that is impaired under insulin resistant state in humans. We discovered an unknown protein molecule ASC2D, which is essential for insulin-stimulated glucose transport in the fat cells. In this project, we plan to further investigate the molecular mechanisms whereby ASC2D regulates glucose transport and the movement of glucose transporter GLUT4 inside the cells. In addition, we will also investigate how ASC2D is regulated in normal control mice and mice treated with nicotine and high-fat diet. This project will lead to uncovering a novel signal pathway involved in the regulation of glucose metabolism, and provide new insight for potential therapeutic targets for smoking- and high-fat diet-induced diabetes.

# Abbreviated Abstracts of 2010 Grant Awards

## Yanez, Ciceron

2010 PRF University of Central Florida

## $159,750

### Synthesis and Evaluation of Small Molecule Photoactive Bcl-2 and Bcl-XL Inhibitors for Pro-apoptotic Photodynamic Lung Cancer Therapy

In the U.S., one in five deaths is tobacco related. There are at least 15 kinds of cancers associated with tobacco, with lung cancer accounting for the highest rate of mortality of tobacco-related deaths. Resistance of certain cancers to current treatments, even to emerging treatments such as tyrosine kinase inhibitor (TKI) drugs, has been a recent problem in cancer therapy. This project aims to aid in solving drug resistance in tobacco-related cancer treatment. We propose to make and use small-molecules that will react with light once they reach malignant tissue. The affected tissue should undergo apoptosis, a selective and organized type of cell death, more efficiently in the presence of these new drugs because once the affected tissue is exposed to light, the signaling pathways that avoid apoptosis within the cell will be blocked. Traditional photodynamic therapy reagents absorb light linearly, so they absorb throughout the light path, translating to poor penetration. The molecules that we propose are designed to absorb two-photons very efficiently, restricting absorption of light to the point where it is being focused, enabling better tissue penetration and increased 3D control of the photochemical reaction that blocks the anti-apoptotic routes in the malignant tissue. This will make treatment much more selective, minimizing collateral damage.

## Young, Karen

2010 NIR University of Miami

## $400,000

### Importance of c-kit in Neonatal Lung Development and Disease

Cigarette smoking is the most preventable cause of prematurity, low birth weight, and infant death. According to the Center for Disease Control, approximately 10 percent of mothers in the U.S. smoke during pregnancy, and smoking attributable neonatal expenditures are more than $150 million. One of the leading reasons for this economic burden is prematurity and the lung disease that results from early birth. This lung disease, so called chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD) occurs in 30-50 percent of preterm infants with birth weights <1000 grams and is characterized by an arrest of normal lung development. This 'arrest' in lung development results in alveolar simplification (larger but fewer alveoli) and abnormal blood vessel growth. Whilst the mechanisms that lead to this arrested lung development are unclear, recent studies suggest that preterm birth may lead to abnormal lung vascular growth and this will impair alveolar growth. The goals of this project are to unravel the mechanisms that impair lung vascular growth when an infant is born preterm and to generate new therapeutic interventions to prevent chronic lung disease of prematurity or BPD.

## Zheng, Hong

2010 PRF Moffitt Cancer Center & Research Institute

## $164,450

### Regulation of SirT1 Activity by Extra-cellular pH in Lung Cancer

Tobacco is one of the strongest cancer-causing agents. Tobacco use is associated with a number of different cancers, including lung cancer, chronic lung diseases, and other diseases. According to recent research, tobacco smoke maintains an acidic systemic environment that may facilitate the development of lung cancer. Previous studies have shown that lung cancer cells overexpress SirT1, but its role or mechanism of pathogenesis is unknown. SirT1 is an important regulator of energy metabolism and stress resistance while DBC1 (a gene) has emerged as a novel regulator of SirT1 and a potential signaling mediator in the SirT1 pathway. This study addresses the regulation of SirT1 activity by extra-cellular pH in lung cancer. We plan to characterize the structure of acidosis-induced (abnormally high acidity) DBC1 fragment and to identify how it is generated, testing the significance of DBC1S production on SirT1 activity and tumor cell response to chemotherapy. As a result, we will be able to determine how SirT1 contributes to tumor progression and treatment resistance, and whether SirT1 inhibitor can be used in the treatment of lung cancer.

# 2009 PROGRAM (Unpublished abstracts)

The following 2009 awards resulted from the Open Call for Applications and were made after the 2009 Annual Report had gone to press.

## Alabugin, Igor

2009 TTCP Florida State University

## $100,000

### Tunable Light-Activated Agents for Double-Stranded DNA-Cleavage

Lung cancer is the leading cause of cancer death among both men and women in the U.S. Of that, 90 percent of lung cancer deaths among men and approximately 80 percent of lung cancer deaths among women are attributed to smoking. According to the American Cancer Society, tobacco consumption is linked to at least 15 different cancers, and accounts for ~30 percent of all cancer deaths. Smoking also increases the risk of many other types of cancer, such as cancers of the throat, mouth, and esophagus. We have developed a new family of light-activated molecules combining unprecedented efficiency of double-stranded DNA cleavage with built-in selectivity for cancer cells. Spatial and temporal selectivity for the activation stems from the use of light, which can activate the prodrugs accumulated in the cancer cells. Importantly, the delivery of light via fiber optics is effective for the types of cancer that are commonly associated with smoking (lungs, mouth, throat, and esophagus). In this project, we will join efforts with Florida Custom Synthesis, Inc., for the development of a library of hybrid molecules needed to find the optimal combination of photochemical warheads with functional parts capable of selective delivery of the warheads to their target in the cancer cells.

## Arlen, Philip

2009 TTCP M.D. Anderson Cancer Center

## $99,854

### A Novel Biomarker for the Detection of Lung Cancer

Lung cancer is the leading cause of cancer-related death in the USA. The American Cancer Society estimates that nearly 160,000 lung cancer deaths occur each year due to tobacco use. For a variety of reasons, tobacco use continues to be widespread, and early cancer detection is a pressing need. When a diagnosis of lung cancer is made, patients receive treatment and wait to see if the cancer returns. At the early stages of recurrence, however, the symptoms of most lung tumors may be vague. Once symptoms develop, the cancer is usually advanced and opportunities for successful treatment decrease. X-rays, CT scans, and molecular markers can help detect cancer at earlier stages, when cancer survival is more promising. However, these tests are not always precise. We have preliminary results that suggest a simple blood test may have the ability to accurately detect cancer. The question we want to address with this research is: can this blood test be used to detect lung cancer? The long-term goal of this study is to establish a commercially available diagnostic laboratory test to aid existing methods for the detection of lung cancer. Specific goals for this study are: 1. To evaluate a newly identified cancer protein as a marker for lung cancer. 2. To monitor the effectiveness of lung cancer treatment.

## Kuzmin-Nichols, Nicole

2009 TTCP Saneron CCEK Therapeutics, Inc.

## $100,000

### Novel Autologous Stem Cell Source for Transplant Therapy in Stroke

Smoking can cause lung and other cancers, coronary heart disease, chronic respiratory disease, and other diseases, including stroke. The role of stem cells in brain injury has been recently recognized. In this project, we are examining stem cell therapy for stroke. Recent studies show that transplantation of menstrual blood-derived stem cells ameliorates stroke-induced behavioral and histological deficits, but the mechanisms of action remain poorly understood. The goal of this project is to test the hypothesis that transplantation of menstrual blood-derived stem cells promotes angiogenesis and neurogenesis as mechanisms of action for brain repair after stroke. Our long-term goal is to advance clinical application autologous cell therapy for stroke.

## Mandal, Prabir

2009 HBCU Edward Waters College

## $50,000

### Molecular Analysis of Cardiac Modulatory Neurotransmitters and Study of Their Association with Smoking

The overall idea of this project is that the negative feelings or emotions experienced as a result of quitting smoking and the tendency to start smoking again during stressful times are in part, a result of altered functioning of the signaling protein known as corticotropin-releasing factor within the basolateral amygdala, a brain area that plays a critical role in regulating emotional states. We are conducting experiments in the basolateral amygdala (BLA) area to determine if blockade of corticotropin-releasing factor 1 (CRF1) receptors and stimulation or blockade of corticotropin-releasing factor 2 (CRF2) receptors reverse these negative emotions. First, we are examining the role of CRF1 and CRF2 receptors within the BLA in the negative feelings or emotions experienced due to quitting smoking. Next, we are examining the role of CRF1 and CRF2 receptors within the BLA in the tendency to start smoking again due to stress. Understanding the role of CRF within the BLA may help in the development of improved treatments for tobacco addiction.

# APPENDIX D. Related Awards Reported by Grantees

The following list represents $11.0 million in additional single and multi-year research awards reported since October 2009 by current and past grantees that are based directly on research findings from projects funded by the King Biomedical Research Program. Grants are presented in alphabetic order by last name of the principal investigator, with the award year and grant type listed in parentheses.

Bolaños, C. (2007 NIR), "Ontogeny of Drug Exposure and Mood Dysregulation." National Institute on Drug Abuse, $1,125,000.

Brew, K. (2008 TSP), "Individual Differences in Relapse of Nicotine." National Institute on Drug Abuse, $213,750.

Davenport, P. (2006 TSP), "Neurogenesis of Coughing." National Institutes of Health, $2,386,641.

Davenport, P. (2009 TSP), "Undergraduate Summer Research Fellowship Program." American Physiological Society, $4,000.

Davies, L. (2001 IIR), "Cognitive Function after Coronary Artery Bypass Graft Surgery with or without Cardiopulmonary Bypass." Medtronic, $30,000.

Dempsey. J. (2004 NIR), "Experimental Analysis of Advanced Radiotherapy Dosimetry." National Cancer Institute, $235,799.

Dempsey, J. (2004 NIR), "MicroRT." National Cancer Institute, $420,750.

Dempsey, J. (2004 NIR), "Efficient Global Fluence-Map Optimization." Varian Medical Corporation, $139,107.

Fletcher, B. (2006 NIR), "Baculoviral Expression and Purification of Single Chain Antibodies." University of Florida Gatorade Fund, $60,000.

Fletcher, T. (2004 NIR), "DNA Contributions to Telomere Assembly." Stanley J. Glaser Foundation, $30,000.

Fletcher, T. (2004 NIR), "TRF2 Function in Telomere Assembly and Maintenance." American Heart Association, $42,000.

Fontoura, B. (2001 NIR), "Nucleoporins in Cardiomyocyte Hypertrophy." American Heart Association Fellowship, $38,000.

Grobmyer, S. (2006 NIR), "Monovalent Targeting of Nanoparticles for Imaging Metastatic Breast Cancer." University of Florida/Moffitt Collaboration Grant Mechanism, $100,000.

Jent, J. (2009 NIR), "Healthy Steps for Young Children." The Children's Trust, $272,785.

Kenny, P. (2007 NIR), "Mechanisms on Nicotine Reinforcement in Mice." National Institute on Drug Abuse, $196,000.

Lee, D. (2006 TSP), "Secondhand Smoke: Prevalence, Validation, and Effects." Flight Attendant Medical Research Institute, $325,000.

Li, J. (2004 NIR), "Laminin-8 and Laminin-10 in Squamous Cell Carcinomas." National Cancer Institute, $130,249.

Li, J. (2004 NIR), "Targeting Laminin-511 Matrix Protein in Melanoma Therapy." Women's Cancer Association, $50,000.

Luesch, H. (2006 NIR), "In Vivo Target Identification and Antitumor Efficacy of Novel Anticancer Agents." University of Florida Opportunity Fund, $100,000.

Podack, E. (2009 TTCP), "Development of Anti-Human TL1A Monclonal Antibody for the Treatment of Human Asthma." National Institute of Allergy and Infectious Diseases, $300,000.

Rodrigues, C. (2009 NIR), "Molecular Mechanisms of Stem Cell Engraftment." National Heart, Lung, and Blood Institute, $664,215.

Rose, D. (2009 NIR), "Combining Neural and Behavioral Therapies to Enhance Stroke Recovery." Department of Veterans' Affairs, $141,200.

Rosser, C. (2005 NIR), "Bladder Cancer Associated Gene Expression Signatures Identified by Profiling of Exfoliated Urothelia." Flight Attendant Medical Research Institute, $350,000.

Salathe, M. (2005 TSP), "Therapeutic Development Center Miami." Cystic Fibrosis Foundation, $70,000.

Siegel, E. (2005 NIR), "Defining Epigenetic Alterations in Cervical Neoplasia as Novel Diagnostic and Prognostic Biomarkers." University of Florida, $50,000.

Su, M. (2007 NIR), "Encapsulated Solid-Liquid Phase Change Nanoparticles as Thermal Barcodes for Highly Sensitive Detections of Multiple Lung Cancer Biomarkers." Department of Defense, $100,641.

Tang, H. (2006 NIR), "Cyclosporine, Cyclophilins and HCV Replication." American Cancer Society, $720,000. Relinquished for NIH award.

Tang, H. (2006 NIR), "Cyclosporine, Cyclophilins and HCV Replication." National Institute of Allergy and Infectious Diseases, $1,298,172.

Visner, G. (2001 IIR), "Pirfenidone as a Therapeutic Agent for Transplant Obliterative Bronchiolitis." American Lung Association of Florida, $75,000.

Zhang, X. (2009 NIR), "Role of Histone Deacetylase 6 and p53 in Cisplatin-Resistance of Lung Cancer." Moffitt Lung Cancer SPORE Program, $100,000.

Zhu, L. (2008 NIR), "Development of Sensitive Fluorescent Probes for Physiological Zinc Over Large Concentration Ranges." National Institutes of Health, $1,311,564.

# Related Awards Reported by Grantees

Since October 2009, current and past grantees reported $35.8 million in awards that are indirectly related to research findings from projects funded by the King Program. However, the King award enhanced their competitiveness in earning this additional funding. Grants are presented in alphabetical order by last name of the principal investigator, with the King award year and type listed in parentheses.

Alexandrow, M. (2006 NIR), "Chromatin Remodeling by Cdt1: Role in DNA Replication and Tumorogensis." National Cancer Institute, $1,559,365.

Brew, K. (2008 TSP), "Interfering with CCL2 and CCR2 to Inhibit Tumor Growth." National Cancer Institute, $213,750.

Brew, K. (2008 TSP), "Structure, Function, and Application of Metalloproteinase Inhibitors in Osteoarthritis." National Institute of Arthritis and Musculoskeletal and Skin, $2,623,959.

Briegel, K. (2005 NIR), "Role of Transcription Co-factor LBH (Limb-Bud and Heart) - A Novel Target of the Oncogenic Wnt Signaling Pathway in Breast Cancer." University of Miami Sylvester Cancer Center, $50,000.

Casalino-Matsuda, S. (2007 NIR), "Role of Epithelium-Derived Monocyte Chemotactic Protein-1 (MCP-1) in Airway Smooth Muscle Hyperplasia in Asthma." University of Miami Sylvester Cancer Center, $40,000.

Cogle, C. (2005 NIR), "UFCC for Cardiovascular Cell Therapy Research Network." National Institutes of Health, $2,766,826.

Cogle, C. (2005 NIR), "Translational Research Program in Blood Stem Cell Disorders." University of Florida, $52,762.

Dietz, N. (2005 NIR), "Second Hand Tobacco Smoke and Worker Health." Flight Attendant Medical Research Institute, $300,000.

Fletcher, T. (2004 NIR), " SWI/SNF Chromatin Remodeling in Nucleotide Excision Repair." National Institute of Environmental Health Services, $1,687,210.

Johnson, K. (2008 NIR), "Evaluation of Dual Energy Computed Tomography for Detection of Iron Deposition." University of Florida, $10,000.

Lang, J. (2009 NIR), "Obesity and Asthma: Genetics and Nutrigentic Response to Omega-3 Fatty Acids." National Heart, Lung, and Blood Institute, $796,500.

Lee, D. (2006 TSP), "A Pilot Study Examining a Relationship-Based Smoking Cessation Smoking Program." American Cancer Society, $45,000.

Lee, D. (2006 TSP), "2007 Tobacco Control Media Evaluations." Florida Department of Health, $2,394,394.

Lee, D. (2006 TSP), "University of Miami Vision Loss Prevention Translational Research Center (TRC)." National Center for Chronic Disease Prevention and Health Promotion, $1,247,025.

Melker, R. (2004 SBTT), "Detection of Ethanol and Interferents in Breath: Validation of a Novel Technology." National Institute on Alcohol Abuse and Alcoholism, $910,853.

Miksovska, J. (2010 NIR), "Conformational Dynamics Associated with Ca2+ Binding to DREAM Protein." National Science Foundation, $523,223.

Mohapatra, S. (2007 TSP), "Targeting of Curcumin-Genistein Nanocomplexes for Treatment of Prostate Cancer." National Institutes of Health, $158,829.

Mohapatra, S. (2007 TSP), "Micro-RNA Directed Generation of Blood Cells from Cord Blood Stem Cells on Integrated Nano-scale Surface Patterns." Office of Naval Research, $396,937.

Mohapatra, S. (2007 TSP), "Differentiation of Stem Cells to Blood Cells Using Nanomatrix Scaffolds." Office of Naval Research, $387,388.

Mohapatra, S. (2007 TSP), "Production of Platelets from Hematopoetic Stem Cells Using 3-D Smart Scaffolds to Examine the Possibility of Producing Blood Cells from Embryonic and/or Adult Stem Cells using 3-D Scaffolds." Office of Naval Research, $480,236.

Salathe, M. (2005 TSP), "Mechanisms of Oxidant-Induced Chronic Bronchitis." National Heart, Lung, and Blood Institute, $1,530,000.

Salathe, M. (2005 TSP), "Hispanic Community Health Study – Miami." National Institutes of Health, $13,156,167.

Schabath, M. (2009 NIR), "Developing Information Infrastructure Focused on Cancer Comparative Effectiveness." National Cancer Institute, $1,657,980.

Schabath, M. (2009 NIR), "Radiomics of NSCLC." National Cancer Institute, $2,282,832.

Simmons, V. (2008 NIR), "A Brief DVD-based Smoking Education Intervention for Cancer Outpatients: A Feasibility Study." University of South Florida Area Health Education Center, $33,883.

Su, M. (2007 NIR), "Encapsulated Phase Change Nanoparticles for Heat Transfer." National Science Foundation, $300,000.

Zhai, R. (2007 NIR), "Class of 2009 Pew Scholars in the Biomedical Sciences Program." The Pew Charitable Trusts, $240,000.

# APPENDIX E. Grantee Publications

The following list represents new publications in peer-reviewed journals and books reported from October 2009 through October 2010 based on funded research from current King Program grantees. This list does not include works submitted or in preparation. Publications are presented in alphabetical order by last name of the principal investigator, shown in **bold** type.


Yang WY, Cao Q, Callahan C, Galvis C, Sang QX, and **Alabugin IV.** Intracellular DNA damage by lysine-acetylene conjugates. *J Nucleic Acids*, 2010;pii:931394.

Mukherjee P, Winter SL, and **Alexandrow MG.** Cell cycle arrest by transforming growth factor beta1 near G1/S is mediated by acute abrogation of prereplication complex activation involving an Rb-MCM interaction. *Mol Cell Biol*, 2010;30(3):845-56.

**Aponick A,** Biannic B, and Jong MR. A highly adaptable catalyst/substrate system for the synthesis of substituted chromenes. *Chem Commun (Camb)*, 2010;46(36):6849-51.

Schwetz TA, Norring SA, and **Bennett ES.** N-glycans modulate K(v)1.5 gating but have no effect on K(v)1.4 gating. *Biochim Biophys Acta*, 2010;1798(3):367-75.

Iñiguez SD, Vialou V, Warren BL, Cao JL, Alcantara LF, Davis LC, Manojlovic Z, Neve RL, Russo SJ, Han MH, Nestler EJ, and **Bolaños-Guzmán CA.** Extracellular signal-regulated kinase-2 within the ventral tegmental area regulates responses to stress. *J Neurosci*, 2010;30(22):7652-63.

Iñiguez SD, Warren BL, Neve RL, Russo SJ, Nestler EJ, and **Bolaños-Guzmán CA.** Viral-mediated expression of extracellular signal-regulated kinase-2 in the ventral tegmental area modulates behavioral responses to cocaine. *Behav Brain Res*, 2010;214(2):460-4.

Sanbert PR and **Borlongan CV.** The proliferation and differentiation of stem cell journals. *Stem Cell Rev*, 2010;[Epub ahead of print].

**Brew K** and Nagase H. The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity. *Biochim Biophys Acta*, 2010;1803(1):55-71.

Lim NH, Kashiwagi M, Visse R, Jones J, Enghild JJ, **Brew K,** and Nagase H. Reactive-site mutants of N-TIMP-3 that selectively inhibit ADAMTS-4 and ADAMTS-5: biological and structural implications. *Biochem J*, 2010;431(1):113-22.

Lindley LE and **Briegel KJ.** Molecular characterization of TGFbeta-induced epithelial-mesenchymal transition in normal finite lifespan human mammary epithelial cells. *Biochem Biophys Res Commun*, 2010;399(4):659-64.

Rieger ME, Sims AH, Coats ER, Clarke RB, and **Briegel KJ.** The embryonic transcription cofactor LBH is a direct target of the Wnt signaling pathway in epithelial development and in aggressive basal subtype breast cancers. *Mol Cell Biol*, 2010;30(17):4267-79.

Al-Ali H, Rieger ME, Seldeen KL, Harris TK, Farooq A, and **Briegel KJ.** Biophysical characterization reveals structural disorder in the developmental transcriptional regulator LBH. *Biochem Biophys Res Commun*, 2010;391(1):1104-9.

**Cappendijk SL,** Pirvan DF, Miller GL, Rodriguez MI, Chalise P, Halquist MS, and James JR. In vivo nicotine exposure in the zebra finch: a promising innovative animal model to use in neurodegenerative disorders related research. *Pharmacol Biochem Behav*, 2010;96(2):152-9.

Monzon ME, Fregien N, Schmid N, Santos-Falcon N, Campos M, **Casalino-Matsuda SM,** and Malbran Forteza R. Reactive oxygen species and hyaluronidase 2 regulate airway epithelial hyaluronan fragmentation. *J Biol Chem*, 2010;M110.135194.

Chigurupati S, Venkataraman R, Barrera D, Naganathan A, Madan M, Paul L, Pattisapu JV, Kyriazis GA, Sugaya K, Bushnev S, Lathia JD, Rich JN, and **Chan SL.** Receptor channel TRPC6 is a key mediator of Notch-driven glioblastoma growth and invasiveness. *Cancer Res*, 2010;70(1):418-27.

Chen M, **Chen LM,** Lin CY, and Chai KX. Hepsin activates prostasin and cleaves the extracellular domain of the epidermal growth factor receptor. *Mol Cell Biochem*, 2010;377(1-2):259-66.

**Chen LM,** Verity NJ, and Chai KX. Prostasin protects lung epithelial cell integrity from cigarette smoke induced stress. *BMC Cancer*, 2009;9:377.

Fu YY, Wang WL, Chen M, Chai KX, and **Chen LM.** Prostasin regulates human placental trophoblast cell proliferation via the epidermal growth factor receptor-signaling pathway. *Hum Reprod*, 2010;25(3):623-32.

Chen YW, Wang JK, Chou FP, Chen CY, Rorke EA, **Chen LM,** Chai KX, Eckert RL, Johnson MD, and Lin CY. Regulation of the matriptase-prostasin cell surface proteolytic cascade by hepatocyte growth factor activator inhibitor-1 (HAI-1) during epidermal differentiation. *J Biol Chem*, 2010;[Epub ahead of print].

Madlambayan GJ, Butler JM, Hosaka K, Jorgensen M, Fu D, Guthrie SM, Shenoy AK, Brank A, Russell KJ, Otero J, Siemann DW, Scott EW, and **Cogle CR.** Bone marrow stem and progenitor cell contribution to neovasculogenesis is dependent on model system with SDF-1 as a permissive trigger. *Blood*, 2009;114(19):4310-9.

Madlambayan GJ, Meacham A, Hosaka K, Mir S, Jorgensen M, Scott EW, Siemann DW, and **Cogle CR.** Leukemia regression by vascular disruption and anti-angiogenic therapy. *Blood*, 2010;[Epub ahead of print].

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Kim M, Madlambayan GJ, Rahman MM, Smallwood SE, Meacham AM, Hosaka K, Scott EW, **Cogle CR,** and McFadden G. Myxoma virus targets primary human leukemic stem and progenitor cells while sparing normal hematopoietic stem and progenitor cells. *Leukemia,* 2009;23(12):2313-7.

Cooper SJ, Zou H, Legrand SN, Marlow LA, von Roemeling CA, Radisky DC, Wu KJ, Hempel N, Margulis V, Tun HW, Blobe GC, Wood CG, and **Copland JA.** Loss of type III transforming growth factor-beta receptor expression is due to methylation silencing of the transcription factor GATA3 in renal cell carcinoma. *Oncogene,* 2010;29(20):2905-15.

Tun HW, Marlow LA, von Roemeling CA, Cooper SJ, Kreinest P, Wu K, Luxon BA, Sinha M, Anastasiadis PZ, and **Copland JA.** Pathway signature and cellular differentiation in clear cell renal cell carcinoma. *PLoS One,* 2010;5(5):e10696.

Chan PY and **Davenport PW.** The role of nicotine on respiratory sensory gating measured by respiratory-related evoked potentials. *J Appl Physiol,* 2010;108(3):662-9.

Vargas C, Saito AI, Hsi WC, Indelicato D, Falchook A, Zengm Q, Oliver K, Keole S, and **Dempsey J.** Cine-magnetic resonance imaging assessment of intrafraction motion for prostate cancer patients supine or prone with and without a rectal balloon. *Am J Clin Oncol,* 2010;33(1):11-6.

**Diaz F.** Cytochrome c oxidase deficiency: patients and animal models. *Biochim Biophys Acta,* 2010;1802(1):100-10.

Barrientos A, Fontanesi F, and **Diaz F.** Evaluation of the mitochondrial respiratory chain and oxidative phosphorylation system using polarography and spectrophotometric enzyme assays. *Curr Protoc Hum Genet,* 2009;19.3.

**Diaz F,** Barrientos A, and Fontanesi F. Evaluation of mitochondrial respiratory chain and oxidative phosphorylation system using blue native gel electrophoresis. *Curr Protoc Hum Genet,* 2009;19.4.

Fontanesi F, **Diaz F,** and Barrientos A. Evaluation of the mitochondrial respiratory chain and oxidative phosphorylation system using yeast models of OXPHOS deficiencies. *Curr Protoc Hum Genet,* 2009;19.5.

**Dietz NA,** Westphal L, Arheart KL, Lee DJ, Huang Y, Sly DF, and Davila E. Changes in youth cigarette use following the dismantling of an anti-tobacco media campaign in Florida. *Prev Chronic Dis,* 2010;7(3):A65.

Bianchi L and **Díez-Sampedro A.** A single amino acid change converts the sugar sensor SGLT3 into a sugar transporter. *PLoS ONE,* 2010;5(4):e10241.

Aljure O and **Díez-Sampedro A.** A functional characterization of mouse sodium/glucose transporter type 3b. *Am J Physiol Cell Physiol,* 2010;299(1):C58-65.

Burgess S and **Echeverria V.** Raf inhibitors as therapeutic agents against neurodegenerative diseases. *CNS Neurol Disord Drug Targets,* 2010;9(1):120-7.

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Qi Y, Liang J, She ZG, Cai Y, Wang J, Lei T, Stallcup WB, and **Fu M.** MCP-induced protein 1 suppresses TNFalpha-induced VCAM-1 expression in human endothelial cells. *FEBS Lett,* 2010;584(14):3065-72.

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Sharma P, Brown S, Singh A, Pyrgiotakis G, Krishna V, Knapik J, Barr K, Iwakuma N, Moudgil B, and **Grobmyer SR.** Near infrared absorbing and luminescent gold speckled silica nanoparticles for photothermal therapy. *J Mater Chem,* 2010;205182-5.

**Grobmyer SR** and Moudail BM (eds). *Cancer Nanotechnology: Methods and Protocols (Methods in Molecular Biology)*, New York, New York: Humana Press, 2010.

Snead DR, Inagaki S, Abboud KA, and **Hong S.** Bis(2-Alkylpyrrolidin-1-yl) methylidenes as chiral acyclic diaminocarbene ligands. *Organometallics,* 2010;29(7):1729-39.

**Ibrahim el-SH,** Johnson KR, Miller AB, Shaffer JM, and White RD. Measuring aortic pulse wave velocity using high-field cardiovascular magnetic resonance: comparison of techniques. *J Cardiovasc Magn Resona,* 2010;12(1):26.

**Jiang Z,** Tao M, Omalley KA, Wang D, Ozaki CK, and Bercelia SA. Established neointimal hyperplasia in vein grafts expands via TGF-beta-mediated progressive fibrosis. *Am J Physiol Heart Circ Physiol,* 2009;297(4):H1200-7.

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# APPENDIX F. National Institutes of Health, Funding by State

## Table F-1 2010-2011 Funding by State[27]

| Rank | State | 2009 Population Estimate | Population Rank | $ Per Capita | Per Capita Rank | Funding 2010 | % of Total Funding | $ Per Capita | Per Capita Rank |
|---|---|---|---|---|---|---|---|---|---|
| 1 | California | 36,961,664 | 1 | 89.10 | 11 | 3,293,408,442 | 15.32% | 104.81 | 11 |
| 2 | Massachusetts | 6,593,587 | 15 | 366.58 | 1 | 2,417,110,060 | 11.25% | 436.09 | 1 |
| 3 | New York | 19,541,453 | 3 | 101.11 | 8 | 1,975,831,794 | 9.19% | 118.97 | 9 |
| 4 | Pennsylvania | 12,604,767 | 6 | 107.11 | 7 | 1,350,082,189 | 6.28% | 133.27 | 7 |
| 5 | Texas | 24,782,302 | 2 | 43.45 | 30 | 1,076,725,788 | 5.01% | 52.77 | 29 |
| 6 | Maryland | 5,699,478 | 19 | 174.72 | 3 | 995,826,877 | 4.63% | 209.66 | 3 |
| 7 | North Carolina | 9,380,884 | 10 | 93.26 | 10 | 874,878,421 | 4.07% | 123.74 | 8 |
| 8 | Washington | 6,664,195 | 13 | 127.00 | 6 | 846,358,652 | 3.94% | 145.62 | 6 |
| 9 | Illinois | 12,901,409 | 5 | 56.41 | 21 | 727,771,400 | 3.39% | 68.54 | 21 |
| 10 | Ohio | 11,542,645 | 7 | 56.06 | 22 | 647,060,378 | 3.01% | 66.94 | 22 |
| 11 | Michigan | 9,969,727 | 8 | 59.40 | 20 | 592,221,830 | 2.76% | 72.32 | 20 |
| 12 | Missouri | 5,987,580 | 18 | 79.72 | 13 | 477,300,978 | 2.22% | 95.86 | 13 |
| 13 | Tennessee | 6,296,254 | 17 | 74.59 | 15 | 469,607,265 | 2.18% | 87.69 | 15 |
| 14 | Connecticut | 3,518,288 | 29 | 133.36 | 5 | 469,195,050 | 2.18% | 155.98 | 5 |
| 15 | Minnesota | 5,266,214 | 21 | 85.81 | 12 | 451,906,147 | 2.10% | 97.82 | 12 |
| 16 | Georgia | 9,829,211 | 9 | 44.05 | 29 | 433,017,347 | 2.01% | 52.06 | 30 |
| 17 | Wisconsin | 5,654,774 | 20 | 68.51 | 16 | 387,396,202 | 1.80% | 78.28 | 17 |
| **18** | **Florida** | **18,537,969** | **4** | **20.19** | **43** | **374,326,240** | **1.74%** | **25.40** | **42** |
| 19 | Colorado | 5,024,748 | 22 | 60.79 | 19 | 305,451,067 | 1.42% | 75.88 | 19 |
| 20 | Oregon | 3,825,657 | 27 | 76.02 | 14 | 290,825,955 | 1.35% | 88.75 | 14 |
| 21 | Virginia | 7,882,590 | 12 | 32.25 | 34 | 254,239,005 | 1.18% | 48.95 | 32 |
| 22 | Alabama | 4,708,708 | 23 | 51.36 | 25 | 241,858,336 | 1.13% | 62.25 | 26 |
| 23 | New Jersey | 8,707,739 | 11 | 25.71 | 39 | 223,890,793 | 1.04% | 34.17 | 39 |
| 24 | Iowa | 3,007,856 | 30 | 64.45 | 18 | 193,854,339 | 0.90% | 76.68 | 18 |
| 25 | Indiana | 6,423,113 | 16 | 30.15 | 37 | 193,660,766 | 0.90% | 40.72 | 37 |
| 26 | District of Columbia | 599,657 | 50 | 295.49 | 2 | 177,190,125 | 0.82% | 378.50 | 2 |
| 27 | Arizona | 6,595,778 | 14 | 23.55 | 40 | 155,349,397 | 0.72% | 29.39 | 40 |
| 28 | Utah | 2,784,572 | 34 | 54.05 | 24 | 150,495,161 | 0.70% | 64.44 | 25 |
| 29 | Rhode Island | 1,053,209 | 43 | 142.24 | 4 | 149,805,210 | 0.70% | 167.90 | 4 |
| 30 | Kentucky | 4,314,113 | 26 | 32.44 | 33 | 139,957,946 | 0.65% | 44.47 | 34 |
| 31 | South Carolina | 4,561,242 | 24 | 30.47 | 36 | 138,988,586 | 0.65% | 41.03 | 36 |
| 32 | Louisiana | 4,492,076 | 25 | 28.83 | 38 | 129,487,948 | 0.60% | 34.43 | 38 |
| 33 | New Mexico | 2,009,671 | 36 | 54.06 | 23 | 108,642,182 | 0.51% | 66.36 | 23 |
| 34 | Kansas | 2,818,747 | 33 | 33.73 | 32 | 95,082,570 | 0.44% | 41.42 | 35 |
| 35 | New Hampshire | 1,324,575 | 40 | 67.70 | 17 | 89,671,848 | 0.42% | 86.45 | 16 |
| 36 | Nebraska | 1,796,619 | 38 | 49.28 | 26 | 88,533,190 | 0.41% | 60.96 | 27 |
| 37 | Oklahoma | 3,687,050 | 28 | 19.13 | 45 | 70,521,757 | 0.33% | 17.58 | 48 |
| 38 | Arkansas | 2,889,450 | 32 | 22.27 | 41 | 64,359,150 | 0.30% | 27.46 | 41 |
| 39 | Maine | 1,318,301 | 41 | 48.61 | 27 | 64,083,879 | 0.30% | 64.78 | 24 |
| 40 | Hawaii | 1,295,178 | 42 | 46.58 | 28 | 60,332,163 | 0.28% | 52.99 | 28 |
| 41 | Vermont | 621,760 | 49 | 96.74 | 9 | 60,147,608 | 0.28% | 118.57 | 10 |
| 42 | Delaware | 885,122 | 45 | 35.35 | 31 | 31,292,964 | 0.15% | 44.86 | 33 |
| 43 | Montana | 974,989 | 44 | 32.08 | 35 | 31,282,385 | 0.15% | 49.70 | 31 |
| 44 | Mississippi | 2,951,966 | 31 | 10.12 | 49 | 29,874,665 | 0.14% | 10.91 | 49 |
| 45 | West Virginia | 1,819,777 | 37 | 11.27 | 48 | 20,508,455 | 0.10% | 17.77 | 47 |
| 46 | Nevada | 2,643,085 | 35 | 6.77 | 50 | 17,895,511 | 0.08% | 9.43 | 51 |
| 47 | South Dakota | 812,383 | 46 | 19.22 | 44 | 15,614,034 | 0.07% | 23.56 | 44 |
| 48 | North Dakota | 646,844 | 48 | 21.70 | 42 | 14,035,496 | 0.07% | 23.42 | 45 |
| 49 | Alaska | 698,473 | 47 | 15.79 | 46 | 11,027,353 | 0.05% | 23.73 | 43 |
| 50 | Idaho | 1,545,801 | 39 | 5.22 | 51 | 8,065,296 | 0.04% | 9.70 | 50 |
| 51 | Wyoming | 544,270 | 51 | 14.11 | 47 | 7,680,276 | 0.04% | 18.08 | 46 |
| | **Total** | **306,997,520** | | | | **21,493,730,476** | | **80.02** | |

# ENDNOTES


[1] The number of jobs is cumulative since 2001 and is a conservative estimate.

[2] Florida: Burden of Chronic Diseases. Center for Disease Control, 2008. Available at http://www.cdc.gov/chronicdisease/states/pdf/florida.pdf. Accessed November 3, 2010.

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[8] The Florida Senate, Interim Report 2010-219, September 2009.

[9] When referring to a grant within this report, the year refers to the fiscal year in which the grant begins. For example, a 2010 grant generally begins July 1, 2010, and ends June 30 of the year of completion.

[10] It can take up to 1½ years for grants to generate significant research findings and obtain additional funding: one year of research with King Program funding and at least six months for a standard federal grant application review cycle.

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[12] The number of jobs is cumulative since 2001 and is a conservative estimate.

[13] This is the number of patents reported by grantees that have been filed with institutional, U.S., or international patent offices.

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[19] Available at www.statehealthfacts.org. Accessed October 22, 2010.

[20] When referring to a grant within this report, the year refers to the fiscal year in which the grant begins. For example, a 2010 grant generally begins July 1, 2010, and ends June 30 of the year of completion.

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[25] NIH Funding Data referenced in the 2002 Florida Biomedical Research Advisory Council Annual Report.

[26] The number of active grants is dynamic since grants are in the process of completing.

[27] NIH Funding Data-http://report.nih.gov/award/State/state10.cfm, accessed November 16, 2010.


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