ARIZONA BIOMEDICAL RESEARCH COMMISSION ANNUAL REPORT 2008–2009

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David Landrith, M.P.A., Chairman

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Message from the Chairman

Medical care and the provision of medical care are front and center in the national public policy debate. Seldom mentioned in the debate is the role that basic scientific research plays in making discoveries with the promise of improving the health status of all Americans. The Arizona Biomedical Research Commission has a long history of supporting and promoting biomedical research in the state of Arizona. The 2008-2009 Commission Annual Report provides insight into the efforts of the ABRC to foster and support Arizona researchers and clinicians in making Arizona a world class biomedical leader.

Of particular interest during the last year are eight Arizona specific projects listed in the Summary section of the report. The projects address Alzheimer's disease, skin cancer and melanomas, prostate cancer, exposure to TCE, therapy for acute strokes, and the risk from "kissing bugs". Each of these projects as well as all others sponsored by the Commission are innovative and novel approaches that continue to advance scientific discovery in Arizona.

The Commission awarded twenty-eight new scientific research contracts this past year with a particular emphasis on new investigators. There were a total of seventy-three research projects under contract with the Commission during fiscal year 2008-2009. The Annual Report contains abstracts of all the projects along with information on funding levels and institutional involvement. The abstracts demonstrate the wide breadth of inquiry being undertaken by Arizona investigators. Commission contract awards enabled many Arizona researchers to prove their investigative concepts and go on to obtain additional funding at the national level. The Commission through its statutory authority continues its technology transfer efforts.

The Commission continued to work in cooperation with the Flinn Foundation to move the recommendations of the Arizona Bioscience Roadmap forward. The Commission has taken the lead in accomplishing the translational research goals. The Arizona Translational Resource Network (AzTransNet) continues its outreach efforts to remove institutional barriers to research, promote clinical research, and develop collaborative projects. AzTransNet is pursuing a joint effort with the InterTribal Council of Arizona to increase tribal research capacity.

The Commission completed its ten-year sunset audit review. The Auditor General found that the Commission is having positive impacts. The Auditor General recommended that the Commission improve its communication of the results of sponsored research and the impact on Arizona. This Annual Report contains some of the improvements and others will be in place for the 2010 Annual Report. The Commission thanks the Auditor General for the time and effort they gave the Commission. In June 2009 the Legislature approved continuation of the Commission for another ten years.

Commissioners Wuebbels, Jerman, and Modiano have left the Commission. We thank them for their tireless efforts in the work of the Commission and wish them well in the future.

The Annual Report is prepared and submitted each year to the Governor, the President of the Senate, and the Speaker of the House of Representatives. The Annual Report is also posted on the Commission website. It is the hope of all of the members of the Arizona Biomedical Research Commission that encouraging both new researchers and large scale multi-institutional/multidisciplinary investigations will advance scientific discovery in the search for better health and lives of all Arizonans.

David Landrith, Chair

Summary of 2008 – 2009 Commission Activities

In the fiscal year 2008-2009, Arizona biomedical researchers received more than $5.8 million in contracts administered by the Commission. In the face of the overall economic recession and declining Commission revenues, the Commission continued its commitment to individual investigators, investigator collaborations, and furthering translational research. 28 new contracts and approximately $1.3 million from the Health Research Fund and the Disease Control Research Fund were directed toward assisting individual investigators in developing proof of their research concepts, collecting preliminary data, and in continued support of translational research.

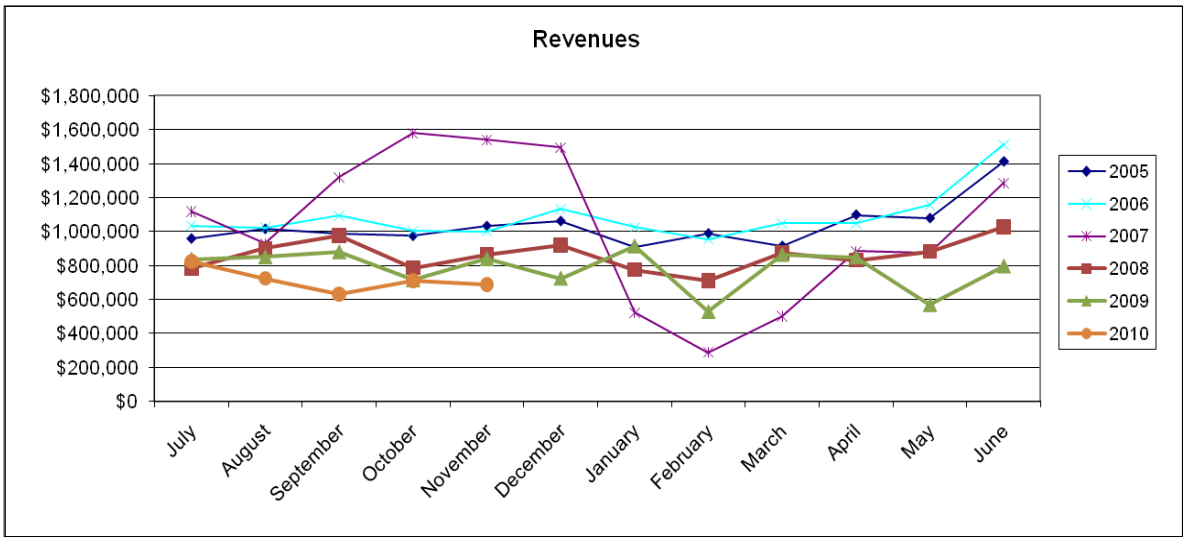
Section headings in this report list the projects supported by the Commission basic research program. Projects are listed according whether the project is in its first, second, or third year of funding. Research abstracts outlining the progress made during the year are contained in Sections A-C. Citations for 65 scientific publications, abstracts, and presentations arising out of the research by eleven different projects are also listed. Section D provides information on new contracts awarded beginning July 1, 2009 (FY2010).

Revised Request for Proposal Process

FY2009 marked the move from hard copy based Request for Proposals (RFP) process to an electronic process. The RFP was posted on the Commission website and over 1,000 postcards were mailed to potential applicants notifying them of the announcement. 115 proposals were received, 105 of those were electronic. Researchers reported their preference for the electronic RFP and filing process.

Commission Revenue

Beginning in January 2007 the Commission has seen a steady revenue decline in proceeds from the sale of tobacco products which in turn decreases the amount of funding for new biomedical research.



While revenue from the tax on tobacco sales has fallen, revenue from the proceeds of the State Lottery remained consistent with the previous fiscal years. Lottery revenue in fiscal year 2007 was $2.4 million, $2.5 million in fiscal year 2008, and in fiscal year 2009 it was $2.4 million.

RFP Review Process and Selection for Award

In response to the RFP, the Commission received 124 unrestricted biomedical research proposals. In November and December the research proposals were sent to a panel of national and international scientific and medical experts for peer review and evaluation. The Commission received the proposal evaluations prepared by more than 100 out-of-state peer reviewers. Three reviews were sought for each proposal. The Commission is experiencing some difficulty in obtaining timely reviews and is undertaking to improve the review process. In the spring of 2008 the Commission evaluated all proposals and selected 28 for funding.

ABRC Projects Submitted/Awarded FY2009

Institution	# Submitted	# Awarded	% Awarded	$ Amount Awarded	% of Total $
Arizona State University	22	6	21	297,705	23
St Joseph/Barrow	21	7	25	347,572	25
Northern Arizona University	2	0	0	0	0
University of Arizona	70	14	50	648,801	49
Sun Health Research Institute	3	0	0	0	0
TGen	2	1	4	50,000	3
All Others	4	0	0	0	0
Total	124	28	100	1,344,078	100

During 2008 -2009 the ABRC managed a total of 73 translational and biomedical research projects representing eight research institutions.

ABRC Total New and Continuing Project Contracts FY2009

Institution	# of Contracts	% Contracts
Arizona State University	12	16
St Joseph/Barrow	11	15
Northern Arizona University	2	3
University of Arizona	42	58
Mayo Clinic Scottsdale	1	1
Sun Health Research Institute	2	3
TGen	2	3
Southern Arizona VA	1	1
Total	73	100

FY2010 Project Awards

In June of 2009 the Commission awarded 11 new research contracts for a total of approximately $1 million from all sources. The contracts were effective on July 1, 2009. Progress on these projects will be reported in the next Commission Annual Report.

ABRC Total New and Continuing Project Contracts FY2010

Institution	Projects	% of Total Awarded
Arizona State University	9	17
St Joseph/Barrow	11	19
Northern Arizona University	2	4
University of Arizona	28	52
Mayo Clinic Scottsdale	1	2
Sun Health Research Institute	1	2
TGen	1	2
Southern Arizona VA	1	2
Total	54	100

Arizona Translational Resource Network (AzTransNet)

The Commission remains committed to making the results of scientific discovery more readily available to health care providers and then to patients. The Commission currently has seventeen translational projects underway. The Commission sponsored Arizona Translational Resource Network (AzTransNet) has been in the forefront in conducting workshops, developing model documents, and providing consulting services related to Institutional Review Boards, collaborative agreements, intellectual property contracts, clinical trial networks, and community based research. AzTransNet conducted a well received workshop on grantsmanship and clinical research skills attended by over 140 researchers and coordinators.

Arizona Biospecimen Consortium and Arizona Biospecimen Locator

Starting in fiscal year 2009 and continuing through the calendar year and into 2010 is the Commission's virtual biospecimen repository project, the Arizona Biospecimen Locator (ABL). ABL is a centralized, web-based biological specimen tracking database system and associated software, supporting a single view of the bio specimens (fresh and frozen tissue, paraffin blocks, cell lines, blood, serum, sputum DNA, RNA and etc.) and, potentially, related data (clinical, genomic, proteomic and etc.) which are stored in repositories at a number of Arizona hospitals and research facilities and available for acquisition and use by researchers at participating institutions. The Commission formed the Arizona Biospecimen Consortium composed of the participating institutions St. Joseph's Hospital, Phoenix Children's Hospital, Maricopa Integrated Health System, Sun Health Research Institute, and Banner Health System. The Consortium has provided guidance to the Commission's project implementer 5AM Solutions on design and policy issues. The Consortium will continue as the governance mechanism for ABL. ABL has gained considerable international attention. Announcement of the project was carried as a news item in over 75 publications. Inquiries have been received

from several other states concerning the project. The Commission Deputy Director made a presentation on ABL at the National Cancer Institute caBIG annual meeting.

Commission Performance Audit

During the reporting year the Commission undertook its statutorily required decennial audit. The State of Arizona Office of the Auditor General conducted a performance audit of the Commission. The audit conducted over a span of nine months found that the Commission has a positive impact and is beneficial to the state. The audit recommended that the Commission improve the reporting of Commission impacts. The legislature subsequently approved renewal of the Commission for another 10 years. The Commission welcomed the audit recommended improvements and has undertaken to implement them. This annual report and subsequent annual reports will reflect those improvements.

Arizona Specific Population and Needs Projects

All Commission sponsored projects are conducted for the benefit of Arizona citizens as well as advancing scientific discovery. There were eight projects during the fiscal year that have particular relevance to Arizona citizens. For a more complete description of the project refer to the appropriate section in the full annual report.

Researcher	Institution	Project	Type
Coleman	SHRI	Development and Validation of a Blood Diagnostic for Alzheimer's Disease	Neuroscience
Dixon	UA	Imaging of Markers for Skin Cancer	Cancer
Hildebrand	UA	Kissing Bugs in Southern Arizona: Potential Risks for Human Health and Development of Tools for Monitoring and Control	Neuroscience
Pettit	ASU	Molecular Targeting of Prostate Cancer Vasculature: A New Approach to Treatment	Cancer
Ritter	UA	Novel Use of a Natural Product for Acute Stroke Therapy	Cardiovascular
Selmin	UA	Folate as a Nutrient Competitor Against Environmental Exposure to Trichloroethylene	Health Effects
Sparks	SHRI	CSF Copper and Cognitive Performance	Neuroscience
Wondrak	UA	Melanoma Cell Survival Signaling by Glycolytic Intermediates	Cancer

ABRC Patented Discoveries

If a scientific discovery has the potential for commercial application, it is important that the rights to that discovery be protected. The Commission on behalf of the citizens of Arizona holds seven patents on biomedical compounds with potential commercial value. The number is unchanged from fiscal year 2008.

Five Rose et al patents are focused on technologies that will increase the effectiveness of cancer chemotherapy drugs by reducing the ability of cancer cells to expel the drugs from the host cell.

Two Gervay-Hague patents are for drugs that block the incorporation of tumor cell markers into cancer cells. These drugs may help stop the spread of cancer in the human body.

One Schroeder patent relates to methods of inhibiting, retarding, and reducing metastatic cancer growth.

Arizona Jobs
Scientific discovery relies upon the ingenuity, persistence, and knowledge of the project principle investigator and project laboratory and support personnel. During the Annual Report period fiscal year 2008-2009, 134 full-time and part-time jobs were created as a result of Commission sponsorship.

Translational Genomics Research Institute (TGen)
The ABRC through a contract provides funding to support the basic operational infrastructure of TGen, the Translational Genomics Research Institute. TGen is on the cutting edge of translational research where investigators are able to unravel the genetic components of common and complex diseases.

TGen is pursuing research on oncology, diabetes and heart disease, and neurological disease. All of these disease areas are of extreme importance to Arizona citizens.

Some TGen activities include:

- The national *Stand Up to Cancer* initiative awarded a total of $74 million for five major cancer research projects. The TGen/University of Pennsylvania proposal to launch new techniques in the fight against pancreatic cancer received the largest amount — $18 million. TGen Physician-In-Chief Dr. Daniel Von Hoff will co-direct the project.
- The National Institutes of Health (NIH) through its National Center for Research Resources awarded a one-year grant totaling $1,996,810 to Dr. Ed Suh, a senior investigator and TGen's Chief Information Officer, which will allow TGen to work with Arizona State University in doubling our supercomputing capabilities.
- NIH's National Institute of Allergy and Infectious Diseases awarded a four-year subcontracted grant, totaling $674,304 to Dr. Paul Keim, director of TGen's Pathogen Genomics Division. Keim is conducting a three-part study involving flu clones and drug resistance, optimal dosages of drugs to suppress viruses and minimize drug resistance, and optimizing drug combinations aimed at helping avoid flu pandemic.
- NIH's National Cancer Institute awarded a nearly four-year subcontracted grant, totaling $615,824 to TGen, which is assisting Wake Forest University's School of Medicine in Winston-Salem, N.C., with genomic analysis in the study of prostate cancer.
- The Arizona Biomedical Research Commission awarded a three-year grant totaling $75,000 to Dr. Nhan Tran, an Associate Investigator in TGen's Tumor Research Lab.

- $2.4 million over four years was awarded from the NIH to work with Seattle's Fred Hutchinson Cancer Research Center for the Women's Health Initiative, which will involve the genotyping of 72,000 participants for about 50 putative disease-specific genetic variants and 50 inherited genetic markers.

TGen researchers:

- Have published more than 100 scholarly articles in peer-reviewed academic journals
- Are conducting nearly 30 clinical trials for advanced and/or rare cancers, averaging 125 visits per month, 35–45 new patients per month with 400-600 samples collected per month.
- TGen researchers submitted 210 grants in FY009 totaling $158,050,724 — a 65 percent increase over FY08 in terms of submission and an 82 percent increase in terms of total dollar value. TGen was awarded 14 grants totaling $1,207,081 with an additional 135 grants pending and in reviews totaling $125,806,587. Additionally, TGen received $17,722,428 from FY08 pending grants, bringing the awarded total for FY09 to $18,929, 509. TGen's success rate currently rests at 27 percent of total grants submitted, placing the Institute nearly eight percent higher than the national average.

TGen enterprise and collaborative efforts:

- 48 invention disclosures have been filed in FY09. (Disclosure is the first step toward protecting intellectual property via the patent process.)
- 101 confidential disclosure agreements have been signed in FY09. (Confidential disclosure agreements are one measure of collaboration between TGen and the research community.)
- 70 material transfer agreements between TGen researchers and other collaborators have been signed in FY09.
- 55 research collaborations have been signed in FY09 including agreements with research institutes and hospitals around the world, and agreements that further research into a host of diseases including brain cancer, melanoma, Alzheimer's and autism.

TGen job creation:

- There are 287 full-time TGen employees with 83 percent holding a college degree
- 38 new full-time equivalent positions were created in FY09 with pay and benefits totaling approximately $2,638,000.
- Salaries for temporary positions (those positions created for a finite period of time) totaled $350,000 and student salaries were just over $300,000, bringing the overall total for all new FY09 TGen employees to $3,288.000.

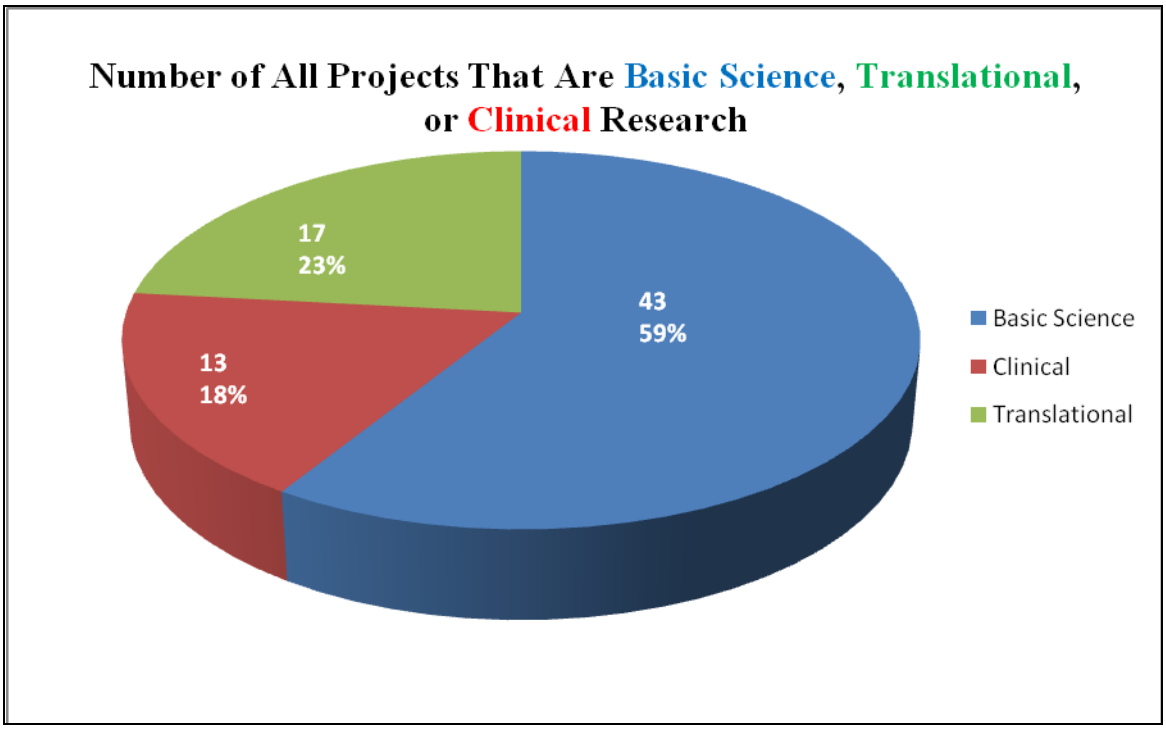
Teacher Training Programs:

- In FY09, TGen completed a three-year grant funded by the Arizona Board of Regents (ABOR) in partnership with NAU that provided biotech programming for Arizona's top high school science teachers. Teachers gained new content knowledge, become aware of rapid advances in biotechnology, current and future uses of biotechnology, and

learned hands-on laboratory skills. Most importantly, teachers learned how to transfer the content learned into curriculum and activities for their classrooms. As part of the final phase of the program, teachers learned how to research, write and successfully compete for grants for their classrooms.

- TGen also received (2009-2012) a new subcontract with NAU — a 3-year GK-12 National Science Foundation (NSF) grant providing content for teachers paired with graduate student mentors. As part of this grant, TGen will provide summer workshops in genomics for the teachers and graduate students.

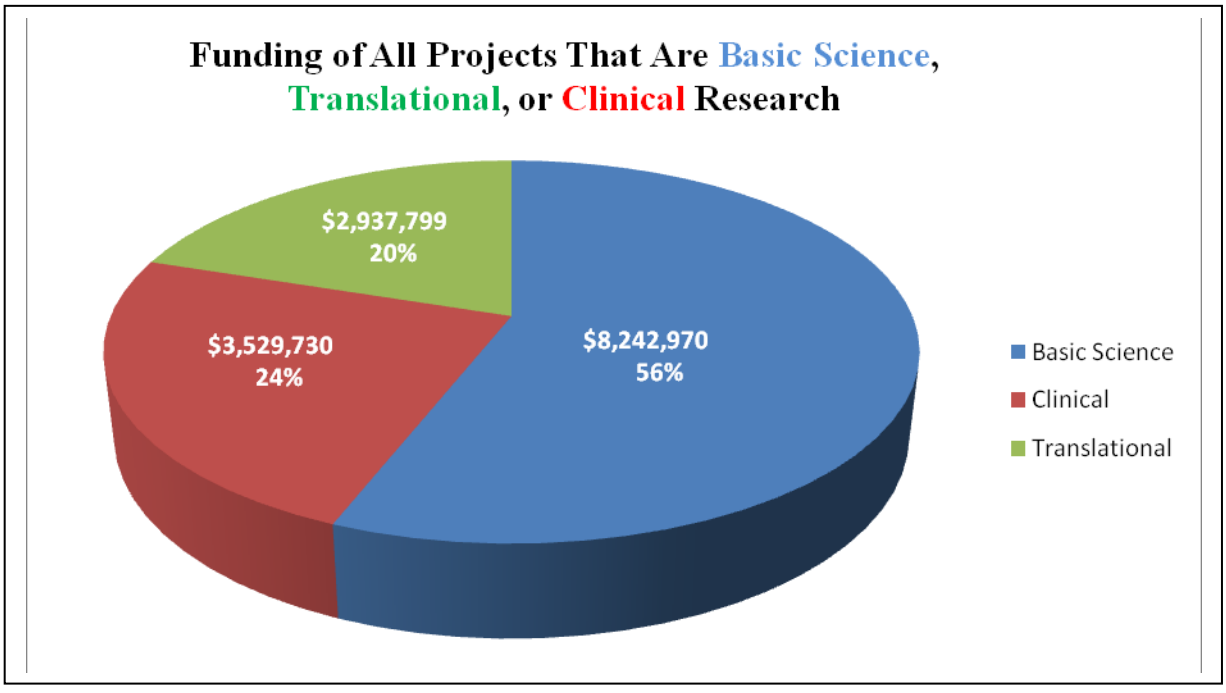
The energy and focus of TGen researchers is rapidly advancing collaborative, multi-institutional, interdisciplinary research in Arizona. The financial infrastructure support provided by the Arizona Biomedical Research Commission makes these things possible. The Commission is encouraged by the efforts of TGen and hearten by the impact that TGen research is making in biomedical research.



Basic Science Research: Scientific studies that increase knowledge of basic life processes.

Translational Research: Medical research that attempts to more directly connect basic research to patient care.

Clinical Research: The study of drugs, biologics, or devices in human subjects with intent to discover potential effects and/or determine safety or usefulness.



3rd Year Contracts

Charles H. Adler, M.D., Ph.D. **Mayo Clinic**
CID: 0011 **Award Amount FY09: $250,000**

Arizona Parkinson's Disease Center: Prevention of Progression to Parkinson's Disease and Parkinson's Disease with Dementia: Development of Biomarkers and Novel Treatment Strategies

The Arizona Parkinson's Disease Center is working on clinical biomarkers and novel treatment strategies for Parkinson's disease (PD) and PD with dementia (PDD). There is clinical core, which prospectively examines PD and control subjects enrolled in the brain and body donation program, and neuropathology core that performs the autopsies and provides cerebrospinal fluid (CSF) and brain tissue to the laboratory scientists. To date >5,000 clinical evaluations of >1,000 subjects have occurred. To date there have been 70 Control and 77 PD subjects autopsied with antemortem clinical data. Projects 1 and 2 have found changes in BDNF, α-synuclein, and DJ-1 proteins in PD. Project 3 found dysregulation of multiple sets of genes in PD and PDD while project 4 has investigated differences in cerebrospinal fluid proteins in PD. Stated goals have been met. In the past year 12 papers were published and 9 presentations were made. Funding from multiple foundations was received.

Papers Published

Beach TG, White CL, Hladik CL, Sabbagh MN, Connor DJ, Caviness JN, Sue LI, Sasse J, Bachalakuri J, Akiyama H, Adler CH. High Secificity and Sensitivity of Olfactory Bulb Synucleinopathy for Lewy Body Disorders. **J Neuropathol Exp Neurol**.67:489. 2008.

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Zhong Z, Nural H, He P, Civarella G, Beach T, Sue L, Adler C, Shill H, Caviness J, Xia W, Shen Y. Dissembled DJ-1 High Molecular Weight Complex in Cortex Mitochondria from Parkinson's Disease Patients. **Molecular Neurodegeneration.** 4:23. 2009.

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Sabbagh MN, Adler CH, Lahti TJ, Connor DJ, Peterson LK, Caviness JN, Shill HA, Sue LI, Ziabreva I, Perry E, Ballard CG, Aarsland D, Walker DG, Beach TG. Parkinson's Disease with Dementia: Comparing Patients with and without Alzheimer's Disease Pathology. **Alz Dis Assoc Disord**. 23:295-97. 2009.

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Beach TG, Adler CH, Lue LF, Sue LI, Bachalakuri J, Sasse J, Henry-Watson J, Boyer S, Shirohi S, Brooks R, Eschbacher J, White CL, Akiyama H, Caviness J, Shill HA, Connor DJ, Sabbagh MN, Walker DG. Unified Staging System for Lewy Body Disorders: Correlation with Nigrostriatal Degeneration,Cognitive Impairment and Motor Dysfunction. **Acta Neuropathol**. 117:613-34. 2009.

Driver-Dunckley E, Connor D, Hentz J, Sabbagh M, Silverberg N, Hernandez J, Vedders L, Evidente VG, Shill H, Caviness JN, Adler CH. No Evidence for Cognitive Dysfunction or Depression in Patients with Mild Restless Legs Syndrome. **Mov Disorders**. Epub 16 July 2009, **Mov Disorders.** 24:1840-42. 2009.

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Adler CH, Connor DJ, Hentz JG, Sabbagh MN, Caviness JN, Shill HA, Noble B, Beach TG. Incidental Lewy Body Disease: Clinical Comparison to a Control Cohort. **Mov Disorders**, *in press*.

Choi SA, Evidente VG, Caviness J, Shill H, Sabbagh M, Connor D, Hentz J, Adler C, Beach TG. Are There Differences in Cerebral White Matter Lesion Burdens Between Parkinson's Disease Patients with and without Dementia? **Acta Neuropathologica**, *in press*.

Abstracts

Adler CH, Caviness JN, Shill HA, Sabbagh MN, Connor DJ, Walker D, Lue LF, Sue L, Vedders L, Hentz JG, Beach TG. New Unified Staging System for Lewy Body Disorders. **Mov Disorders**. 2009.

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Choi SA, Evidente VG, Caviness J, Shill H, Sabbagh M, Connor D, Hentz J, Adler C, Beach TG. Are There Differences in Cerebral White Matter Lesion Burdens Between Parkinson's Disease Patients with and without Dementia? **Asian Society Against Dementia**. 2009.

Craig A. Aspinwall, Ph.D. **University of Arizona**
Award Amount FY09: $48,323

Stabilized Polymer Phospholoid Imaging Probes

The primary goal of this research was to develop a new class of high sensitivity fluorescence imaging probes that would be applicable for studying a number of biological problems, e.g. small changes in cellular mass associated with disease, i.e. Type I diabetes, cancer, etc. We successfully developed a series of modular, extremely bright, biomimetic imaging probes that provide large amplification compared to existing probes and provide reduced non-specific adsorption (false positives). The realization of these research goals will have impact on the residents of Arizona and beyond for potentially detecting life threatening disease at an earlier state, and thus may provide much earlier treatment and diagnosis. Further, this project provided the basis for collection of preliminary data for submission of a number of research proposals that, when funded, will benefit the economy of Arizona as well.

Papers Published

Senarath-Yapa MD, Phimphivong S, Coym JW, Wirth MJ, Aspinwall CA, Saavedra SS. Preparation and Characterization of Poly(lipid)-Coated Fluorophore-Doped Silica Nanoparticles for Biolabeling and Cellular Imaging. **American Chemical Society**. Novemer2007.

Roberts DL, Ma, Y, Bowles SE, Janczak CM, Pyun J, Saavedra SS, Aspinwall CA. Polymer-Stabilized Phospholipid Vesicles with a Controllable, pH-Dependent Disassembly Mechanism. **American Chemical Society**. January 2009.

Yongchang Chang, M.D., Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $49,973

Mechanisms of p1 $GABA_c$ Receptor Activation and Antagonism

This project helped us to better understand structural basis for GABA receptor function. It will help in the future to design new GABA receptor subtype specific compounds to treat neurological and psychiatric disorders such as sleep disorders, seizures, depression, and schizophrenia, which affect many Arizonians. In addition, we have also started applying the gained knowledge of mechanism of this receptor function to nicotinic receptor research to expand our research to other members of the cys-loop receptor family. An abstract was submitted to the 2009 Annual Neuroscience Meeting. With the support of ABRC last year, we submitted a NSF proposal and resubmitted an NIH R01 grant proposal. The NIH R01 proposal received 23 percentile ranking and "just in time" notice. We also published one research paper in ***Molecular Pharmacology***, one research paper in ***Journal of Physiology***, and one review article in ***Acta Pharmacologica Sinica***.

John K. DiBaise, M.D. **Mayo Clinic**

Award Amount FY09: $145,561

Transmucosal Delivery of Erythromycin to Treat Gastroparesis

Gastroparesis, a condition in which a slowing of stomach emptying occurs, results in numerous gastrointestinal (GI) symptoms and inconsistent delivery of medications. The short-term goal of this research study was to develop a sublingual drug delivery system that would bypass the GI tract but still be able to deliver therapeutic levels of erythromycin, a potent stimulant of stomach emptying, with the ultimate goal of improving gastroparetic symptoms. During the first 2 years of this study, we demonstrated the release of erythromycin from Carbopol, developed a reliable test to measure erythromycin blood levels, and showed successful buccal absorption in animals. During the final year, we refined the Carbopol-erythromycin formulation to optimize its sublingual penetration. A small study in humans demonstrated its successful sublingual absorption, albeit at a level too low to be useful clinically. An alternative method will be required to improve the sublingual delivery of medications to treat gastroparesis.

Johanna K. DiStefano, Ph.D. **Translational Genomics Research Institute**
Award Amount FY09: $50,000

Diabetic Kidney Disease in American Indians

Diabetes is the leading cause of end-stage renal disease (ESRD) in developed countries. In this study, we sought to identify the genetic determinants of diabetic ESRD in Native Americans. We originally found a region on chromosome 3 increase linked to susceptibility to diabetic ESRD in Pima Indians. We initiated investigations of genes mapping to this region and found evidence for association between variants in the succinate receptor gene (SUCNR1) and ESRD. We found that SUCNR1 is differentially expressed in kidney cells and is upregulated by hyperglycemia. These findings suggests that glucose output from the kidney is regulated at the level of the SUCNR1, which implies a key role for this gene in the regulation of normal kidney function in the face of persistent hyperglycemia. These accomplishments are a major step in identifying and characterizing genes with significant effects on the development of diabetic ESRD in Pima Indians.

Kathleen Dixon, Ph.D. **University of Arizona**
Award Amount FY09: $148,147

Imaging of Markers for Skin Cancer Risk

Arizona has one of the highest rates of skin cancer in the world. Exposure to UV radiation in sunlight is a major risk factor for skin cancer development. We have established a multidisciplinary collaboration for the image analysis of cellular response to UV radiation. This work focuses on the identification of signatures of skin cancer susceptibility and the development of chemopreventive agents. We have made significant progress in the development of the methodology for detecting and analyzing a specific marker for UV exposure of the skin. This marker was first developed in cultural human and mouse cells and then further characterized in a mouse model; currently it is being validated in human skin. The ultimate goal of this work is to provide tools that can be used in a clinical setting to monitor skin cancer susceptibility, progression, and responses to prevention/intervention strategies.

Robert J. Gillies, Ph.D. **University of Arizona**
Award Amount FY09: $250,000

Multimeric Ligands for Targeting Cancer for Imaging and Therapy

Diagnoses and treatment of cancer by targeting diagnostic imaging or therapeutic agents directly to the tissue or cell of interest, without cross-reacting with other cells or tissues is the goal of this project. Cell surface receptors are attractive as targets since they express selective binding for ligands and are accessible from outside. This proposal sought to develop agents that can discriminate these target cells from normal cells using a multimeric ligand approach. A multimeric ligand is a molecule that contains more than one ligand binding motif attached to a backbone linker, a nanoparticle.

This is important to Arizonans since the proposal is focused on pancreatic adenocarcinoma and Arizona has leading edge research into this disease, with Specialized Programs in Research Excellence at the Mayo-Scottsdale and at UA-Tucson, and a pancreatic cancer program project at TGen. This technology was invented at the UA and remains a leader in the discovery and design of these complexes.

John G. Hildebrand, Ph.D. **University of Arizona**
Award Amount FY09: $49,999

Kissing Bugs in Southern Arizona Potential Risks for Human Health and Development of Tools for Monitoring and Control

We continued our studies of the species distribution of kissing bugs in the vicinity of Tucson. We launched an extensive collection campaign with public participation that has yielded more that 600 bugs since March 2009. We finalized a study on the rates of infection of collected kissing bugs by *Trypanosoma cruzi*, the causative agent of Chagas Disease. We found that 41.5 percent of collected bugs (n=164) were infected with *T. cruzi,* and that 63 percent of the collection sites (n=22) yield at least one infected specimen. Although many factors might contribute to the lack of reported cases of human disease in Arizona, these results indicate that the risk of infection in this region may be greater than previously thought. We completed a comprehensive study demonstrating that only adult females of the principal local species of kissing bugs, *Triatoma rubida*, likely could be efficient transmitters of the Chagas parasite. Our outreach activities successfully increased public awareness of the risks attributable to kissing bugs.

Kobus Barnard, Ph.D. **University of Arizona**
Award Amount: FY09: $50,000

Genetic Diagnostics of Angiogenesis

The overall goal of this project is to identify genes that are indicators of small blood vessel (microvessel) health and potential targets for new therapies. Previous ABRC supported work has shown that microvessels can exist in three distinct health conditions, and that there are significant differences in gene expression profiles associated with these conditions. Recent work has focused on developing Bayesian statistical models to model the gene expression level statistics over time for microvessel repair and development. This has led to new methods for predicting phenotype which both serves the overall goal and provides for principled evaluation of the models. Particularly promising are models for the joint statistics of gene expression levels and gene ontology (GO) tags. This novel multimodal approach allows principled incorporation of what is already known about genes and what is measured in experiments examining specific processes such as microvessel development in implanted tissue. We have found that models that incorporate the GO tag data outperform those that do not by 7-12 percent on the microvessel data set as measured by prediction of condition on data help out from model training in cross-validation evaluation.

Papers Published

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Richard D. Lane, M.D., Ph.D. **University of Arizona**
Award Amount FY09: $150,000

Neural Basis of Vagal Tone Dysregulation in Depression

This project has faced significant recruitment challenges. Through maximized spending on advertisement we have significantly increased enrollment numbers (32 of targeted 39, up to 82 percent enrollment this quarter from 62 percent last quarter). We have reached our target enrollment in our study arm of subjects with major depressive disorder (MDD) receiving medication; we have 6 completed subjects with MDD in the study group receiving Cognitive Behavioral Therapy (CBT); and we anticipate reaching our target enrollment of healthy control subjects (5 have completed, 5 are currently active, and we have screened a sufficient number of potential subjects to match the remaining controls to MDDs).

Note when we speak of *enrollment* numbers the targeted total is 39, whereas when we speak of *completed* subjects, the targeted total is 36. In our proposal we projected *enrolling* 39 subjects (13 per group in each of the three groups), allowing for an attrition rate of 1 subject per group, for a total *completion* number of 36 subjects.

Our best guess is that by the time the study is completed, we will reach 83 percent of the original target number of completed subjects (12 medication group, 12 control group and 6 CBT group completed or 30/36).

To date (September 30, 2009) 32 subjects have been enrolled, 18 subjects have completed the protocol and 8 subjects are currently active (5 controls, 3 with MDD receiving medication). Therefore 82 percent of targeted enrollment is completed (32 of 39) and 50 percent of targeted subjects completing the protocol has been achieved (18 of 36), with 22 percent still active (8 of 36).

Data collection for the 18 completed subjects represents 50 percent completing (18/36), not including data already collected on the 8 active subjects.

As data collection has increased, likewise processing and analysis of the structural imaging data has increased significantly during this quarter at our subcontract site, Banner Health, Phoenix. To date approximately 45 percent of this data processing and analysis is complete, and we anticipate completion of the remainder in the 4^{th} quarter.

John Lewis **InterTribal Council of Arizona**
Award Amount FY09: $150,000

Promoting Tribal Community Participation in Biomedical Research

This project is designed to promote tribal participation in health research. Goals were achieved through three phases: 1) research review process assessment, 2) research agenda setting, and 3) development of a regional tribal institutional review board (IRB) and technical assistance program. 18 of Arizona's 21 tribes participated in the project.

PHASE I: Key informant interviews were conducted and all participating tribes have a research review protocol and at least 6 have a formal policy in place.

PHASE II: Technical assistance needs identified through group interviews include policy development, research and methodology training, and data management.

PHASE III: Interviewees responded favorably to the concept of InterTribal Council of Arizona's development of a Regional Tribal IRB. Focus groups are scheduled to inform development.

A final document entitled *Tribal Research Review Processes in the State of Arizona* is forthcoming for statewide dissemination. Concepts for a Technical Assistance Program and Regional Tribal IRB are being developed.

Ana Maria Lopez, M.D., M.P.H., F.A.C.P **University of Arizona**
Award Amount FY09: $150,000

Expedited Breast Care: A New Model in Breast Health

Patients requiring breast biopsy were approached sequentially for participation at a community hospital and a mammography center. Following biopsy, tissue underwent ultra-rapid processing. Slides were reviewed by telepathology. Time assessments were collected. For the first year of the study, patients from the mammography center received their results as per usual care and patients from the surgical clinic received their results via videoconference by a teleoncologist. The second and third years of the study, recruitment continued only at the mammography center. During the second and third years, patients had the option to receive results per usual care or via video – or teleconference by a teleoncologist. 100 percent of patients opted to receive results via teleconference by a teleoncologist where they also completed a satisfaction survey.

This data indicate that expedited breast care (EBC) can reduce the wait for breast biopsy results for patients. EBC may help ameliorate health care disparities in many regions of Arizona.

Raymond B. Nagle, M.D., Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Translational Regulation of Protein Expression in Prostate Cancer Progression

Mortality from prostate cancer is primarily due to metastasis to distant sites. Each year in Arizona approximately 4300 new cases of prostate cancer are diagnosed and 500 men die due to prostate cancer. Therefore, understanding the molecular mechanisms of prostate cancer metastasis could provide great therapeutic potential. Laminin-332 provides stable adhesion structures in normal prostate and prevents cellular invasion and metastasis. Its expression is lost in prostate cancer progression and we have been working on determining the cause of this loss. We have previously demonstrated that LM-332 loss in prostate cancer is not due to alterations in translational regulation, nor transcriptional regulation. We have now shown evidence that the loss may be through targeted protein degradation. We are also currently investigating the significance of the increase of 4EBP1 in prostate cancer tissue using the prostate tissue bank that was created with the support of a previous ABRC award (Establishment of cancer tissue and serum bank in Arizona for the purpose of improving life for men with prostate cancer).

Naomi E. Rance, M.D., Ph.D. **University of Arizona**
Award Amount FY09: $49,644

Effects of Estrogen Withdrawal of Hypothalamic Thermoregulation

Despite the extraordinary number of individuals affected by hot flushes, the mechanism of flushes remains an enigma and the basic biological effects of estrogen on thermoregulation are not understood. This ABRC project was designed to initiate a programmatic effort to characterize the thermoregulatory responses to estrogen in laboratory rodents. We have made great progress. We have set up a thermoregulatory laboratory and our first manuscript on the effects of estrogen on the thermoneutral zone has recently been accepted for publication. Moreover, we are currently writing a manuscript on the effects of estrogen on the activation of thermoregulatory pathways in response to changes in ambient temperature. Finally, we have initiated experiments to determine if the neuropeptide that changes profoundly in the hypothalamus of postmenopausal women could influence temperature regulation. Our goal is to provide new information related to etiology of menopausal flushes.

Seth Rose, Ph.D. **Arizona State University**
Award Amount FY09: $50,000

Sulfonium-Salt Suicide Inhibition (SSSi) of Cancer Cell Division

We are developing compounds that activate the process by which cancer cells undergo self-destruction instead of growing and spreading. Our goal is also to prevent the cell from pumping the drug out and becoming resistant. The strategy is to attach the compound to an essential cellular biomolecule in the cancer cell by covalent bonding. We devised and made a dozen new compounds, to test efficacy against cancer cell growth and to test the mode of action of the compounds. We demonstrated that one class of compounds under development did indeed covalently bond to its target, a protein required for cancer cell division. We also carried out structural and mechanistic studies on another class of compounds. These studies further the development of anticancer drugs for the benefit of Arizona cancer patients.

Philip M. Service, Ph.D. **Northern Arizona University**
Award Amount FY09: $49,916

Genetics of Aging: Fine-Scale Mapping of Life Span Genes in Drosophila

During the final project year we achieved two objectives. First, we completed the laboratory molecular genetic work for mapping genes that control natural variation in life span in fruit flies. We also completed an initial analysis of this genetic data, which localized 9–13 such "life span genes". We expect that a similar analysis of human populations would yield comparable results: variation in life span is controlled by several to many genes, as well as being strongly influenced by environment. Second, we completed a large-scale simulation study designed to determine the best strategy for analysis of our actual data. As a result of these simulations, we developed a strategy that improves our power to detect life span genes while at the same time reducing the likelihood that we will "identify" non-existent genes. This strategy for analysis of genetic data and gene discovery should be broadly applicable.

Marlys H. Witte, M.D. **University of Arizona**
Award Amount FY09: $49,962

Massage Therapy in Childhood Lymphedema

Swollen or asymmetric limbs of children are most commonly due to birth defects of lymphatic drainage ("congenital lymphedema (LE)") or complications of cancer treatment ("acquired LE"), which slow down removal of excess tissue fluid (lymph). These children often suffer severe physical and psychological disabilities. At least several hundred Arizona children, occasionally with other family members, suffer from childhood LE (CLE). During this project's third year, we continued testing a simplified CLE management protocol of specialized massage therapy (manual lymph drainage – MLD), without the compressive bandaging usually applied to these growing children, to determine short-term and long-term responsiveness and compliance to intensive and home maintenance MLD monotherapy. We screened, enrolled, and followed up subjects ranging from young children to adolescents with moderate to severe congenital and acquired LE of arms, legs, pelvis, and face, including one with intestinal lymph reflux. In each instance, MLD monotherapy alone substantially and visibly reduced volume of swollen limbs, face, and/or other body parts during the acute intensive treatment phase, and, with (but not without) compliance, reduction was sustained during long-term home maintenance MLD. This beneficial limb volume reduction effect of intensive MLD monotherapy in CLE was replicated in a pilot study by our lymphologist colleagues at the University of Genoa following a similar protocol.

Georg Thomas Wondrak, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Melanoma Cell Survival Signaling by Glycolytic Intermediates

The rising incidence of skin cancers in the State of Arizona is a public health problem of increasing concern. In the State of Arizona, melanoma accounts for only 5 percent of all skin cancers, but causes almost 80 percent of all skin cancer deaths. Metastatic melanoma is a particularly aggressive tumor that originates from pigment producing cells in human skin. In this ABRC-sponsored research period my laboratory has examined a novel molecular mechanism that regulates melanoma cell survival and progression. Based on our identification of a gene that regulates melanoma cell drug sensitivity (GL01), a novel prototype drug (DCPIP) that effectively kills melanoma cells without harming normal cells has been identified and tested successfully in animal models of human melanoma. Further research will define the role of the GLO1 gene as a potential biomarker and therapeutic target in human malignant melanoma skin cancer.

Yitshak Zohar, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Novel Applications of Nanotechnology: Microdevices for Capture and Analysis of Circulating Tumor Cells

The goal of this project is to use bio-technology to create microdevices for capturing specific populations of cells from complex suspensions, such as blood, for further analysis. In the previous two years, we have developed the technology and demonstrated the highly specific capture of target cancer cells in antibody-functionalized microchannels. In the last year, the kinematics of capturing target cells under flow conditions has been studied utilizing both the functionalized particles mimicking cells and the biological target cells. A critical flow rate beyond which no cells can be captured has been identified, and the spatial distribution of captured cells along the microchannel follows a log-normal statistical model. Mathematical models for both phenomena are proposed. As for the particles, they tend to aggregate into clusters under shear flow in a microchannel. The cluster growth rate follows a power law depending on the shear rate, particle concentration and particle size, and the exponents in the power law have been determined empirically.

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Cheung, LSL, Zheng XJ, Stopa A, Schroeder JA, Heimark RL, Baygents JC, Guzman R, Zohar Y. Detachment of Captured Cancer Cells Under Flow Acceleration in a Bio-functionalized Microchannel. **Lab Chip**. 9:1721-31. March 2009.

2nd Year Contracts

Setsuko K. Chambers, M.D. **Arizona Cancer Center**

Award Amount FY09: $50,000

Regulation of c-fms Proto Oncogene Related Breast Cancer Risk

We show that vigilin, by binding to the same tail end sequences of the RNA for the c-fms oncogene (c-fms binding element) as does the HuR protein, decreases the levels of this oncogene. Thus, the action of vigilin opposes that of HuR, which is tumor-promoting and elevates the level of this oncogene. In breast cancer cells, we show that vigilin and HuR competitively bind the c-fms binding element only when the sequence is correct, but not when it is mutated. This suggests that a dynamic ratio of vigilin and HuR association with this c-fms binding element could regulate cellular c-fms levels. This is important because elevated c-fms levels lead to enhanced invasiveness of breast cancer cells through normal tissues and spread of breast cancer, ultimately leading to poor survival of breast cancer patients.

Harinder Garewal, Ph.D. **University of Arizona**
Award Amount FY09: $150,000

Hypothesis-Driven Biomarkers of Colon Cancer Risk

Arizona has 6.5 million residents of whom 360,000 will likely develop a colorectal cancer. Current test indicating colon cancer risks are only 20-50 percent accurate.

We obtained 6 colon biopsies from each of 155 female and 142 male patients undergoing colonoscopies and evaluated the biopsies for deficiency of Cytochrome c Oxidase I (CcOI). Our early results indicate that CcOI deficiency may be a good predictor of colon cancer risk.

We found that most colon cancers and large colon polyps are surrounded by tissue (>20 centimeters in extent) that is deficient in two DNA repair proteins. This double deficiency, causing many mutations, is a newly found likely major early cause of progression to cancer.

We evaluated two potential cancer therapeutic drugs, phenstatin and pancratistatin, for their mechanism of killing cancer cells, finding that phenstatin causes “mitotic catastrophe” (the chromosomes get mixed up and don’t divide properly) while pancratistatin causes cell suicide.

Leslie Gunatilaka, Ph.D. **University of Arizona**
Award Amount FY09: $150,000

Withaferin A Analogs Targeting Annexin II as Novel Drugs for Pancreatic Cancer

The overall goal of this multi-institutional and interdisciplinary project is to define the molecular mechanisms of the small-molecule natural product, withaferin A (WA), and to evaluate its potential to treat pancreatic cancer. During the course of the second year of this project, eleven analogs of withaferin A selected on the basis of the bioassay results obtained during the previous year were evaluated in three pancreatic cancer cell lines, Panc-1 (poorly-differentiated), MiaPaCa-2 (moderately-differentiated), and BxPC-3 (well-differentiated). Based on cytotoxicity data two analogs, 4-*epi*-withaferin A and 4-*epi*-withaferin A diacetate, were selected for further evaluation. Apoptosis was analyzed by morphology, flow cytometry, and PARP cleavage. The data showed that apoptosis was induced both in MiaPaCa-2 and BxPC-3 cells in a dose-dependent manner. In BxPC-3 cells apoptosis was induced as early as 6 hours after treatment with 1.5 uM 4-*epi*-withaferin A diacetate proving this to be the most promising analog. Thus, 4-*epi*-withaferin A diacetate was subject to gene expression analysis and the results suggested that it inhibits pancreatic cancer cell proliferation and induces apoptosis by activating the MAP kinase and glutathione (stress) pathways. Sufficient amounts of 4-*epi*-withaferin A diacetate will be synthesized for *in vivo* animal studies planned for the year three of this project. We are hopeful that this project would provide a lead compound that can be further studied and developed into a natural product-based non-toxic drug that can be used to treat pancreatic cancer.

Melissa D. Halpern, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Enterohepatic Circulation of Bile Acids in Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a life-threatening gastrointestinal emergency of premature infants. In Arizona, approximately 500 prematurely born infants will develop NEC each year; 20 – 50 percent will die. Using a neonatal rat model of NEC, our laboratory was the first to show that elevated levels of bile acids in the ileum (the site of NEC injury) contribute to intestinal damage. The goals of this proposal are to systematically examine the mechanisms involved in bile acid induced injury during the development of NEC using neonatal rat and mouse intestinal tissue cultured with bile acids and the inflammatory components of the NEC intestine. The newborn intestine is less able to protect itself against bile acid induced injury than older intestine and specific inflammatory mediators found in excess during NE development are capable of up-regulating ileal bile acid transporters. These data suggest mechanisms by which premature infants may be at risk for this devastating disease.

Ronald P. Hammer, Ph.D. **University of Arizona**
Award Amount FY09: $49,995

Brain Dopamine, Glutamate and Cortical Activity: A Rodent Model of Schizophrenia

The broad, long-term objective of the project is to determine the cellular and molecular brain mechanisms underlying symptoms of schizophrenia using an experimental animal model. During this project year we have accomplished the major aims of the project by examining the effect of excess neurotransmitter within corticostriatal brain circuits. We obtained preliminary results suggesting that excess dopamine can cause selective cortical activation in a pattern that resembles that in schizophrenia. We also studied the effect of chronic phencyclidine treatment which causes specific behavioral symptoms in schizophrenia and examined subsequent cortical and subcortical activities. The resulting data are still being analyzed completely, but our goal remains to submit project data for presentation, publication and federal research support in 2010.

Pawel R. Kiela, DVM, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Modulation of Neutroophil Function by Curcumin in Inflammatory Bowel Disease

Neurtophils play a key role in the immune response by eliminating pathogens. However, inflammatory bowel diseases causes disproportionate and persistent inflammatory process mediated by the transepithelial neutrophil migration and also leads to reduction of epithelial barrier function, perpetuation of inflammatory processes and tissue destruction via oxidative damage and the release of proteases. Our central hypothesis is that curcumin affects the recruitment and function of neutrophils at multiple levels to reduce the extent of mucosal damage in colitis. In the past reporting period, we have prepared and submitted a manuscript largely composed of data acquired during the first 1.5 years of the project. The article was submitted to “Inflammatory Bowel Diseases”, a journal with wide recognition in the field of IBD. The reviewers requested minor experimental additions, and the paper will be resubmitted by mid-January 2010. Based on the acquired preliminary data, we have submitted an R01 grant application to the NIH. The proposal ranked in the top 25 percent and will be resubmitted early 2010. We have made additional novel observations on the mechanisms of the protective role of curcumin, particularly in the area of neutrophil-epithelial cell interactions summarized in the report.

George R. Pettit, Ph.D. **Arizona State University**
Award Amount FY09: $150,000

Molecular Targeting of Prostate Cancer Vasculature: A New Approach to Treatment

The vitally important challenge of discovering new drugs to improve the treatment of prostate cancer continues. Both the need and our research focus will be summarized as follows. Over one million American families are vitally affected and impacted by prostate cancer. One in six men in the United States will be diagnosed with prostate cancer in their lifetime. In Arizona in 2004, some 4,000 new cases of prostate cancer were detected and about 600 men died from the disease. Prostate cancer is the most commonly diagnosed non-skin cancer and the second most common cancer killer of American men. Recent (2007) statistics indicate some 218,890 new cases diagnosed and 27,050 deaths. The generally tragic and all-too-frequently lethal outcome for prostate cancer victims will not be alleviated until treatment approaches are greatly improved by introduction of new and more generally curative anticancer drugs for controlling prostate cancer. Unfortunately, curative therapy in the form of radical surgery of radiotherapy requires most men diagnosed with metastatic disease die over a period of months to years. Our research group has pioneered the discovery and development of new cancer vascular targeting drugs/prodrugs and we are extending this very successful research focus to making improvements in the treatment of human prostate cancer.

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Richard D. Posner, Ph.D. **Northern Arizona University**
Award Amount FY09: $133,416

Modeling Vulnerability of Cancer

This project develops and experimentally verifies computational models of signaling networks to guide and identify new treatment protocols for cancer. Molecular changes in cellular signaling pathways are the underlying basis for many diseases including cancer. Due to the complexity of these networks, it is not possible to use intuition alone to guide targeted drug discovery, hence the need for computer modeling. We have developed a new approach for modeling complex systems in which mechanistic facts about molecular interactions are represented using formal rules. A rule defines the properties of reactants in a class of reactions, the products of the reaction as well as its rate law. By only stipulating the context necessary for specific interactions to occur, a set of rules typically implies a much larger set of reactions which allows for compact model specification. As part of this project t we developed Dynstoc, a software package that simulates the dynamics of comprehensive signaling networks.

Donato Romagnolo, Ph.D. **University of Arizona**
Award Amount FY09: $49,445

Epigenetics of Breast Cancer and Chromatin Remodeling of the BRCA-1 gene

The long-range goal of this project is to identify the factors that increase the risk of sporadic breast cancer through epigenetic regulation and to develop dietary strategies that prevent this event. The BRCA-1 protein is involved in repair of DNA damage and mutations of the BRCA-1 gene confer a high risk of developing breast cancer. Interestingly, mutations of BRCA-1 account for only 5-10 percent of breast cancer cases, whereas sporadic breast tumors represent the remaining 90-95 percent. In sporadic breast cancers there is silencing of BRCA-1 in the absence of mutations. The primary objective of this project is to understand how the BRCA-1 gene is silenced. Once these mechanisms are understood, preventive strategies may be developed based on dietary interventions. Because the vast majority of breast cancers are sporadic, i.e. are not linked to family history but result from changes that occur during life, the proposed experiments may help in understanding how to prevent the onset of this malignancy which afflicted 3,220 women in the State of Arizona in 2008 (source: American Cancer Society, 2008).

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Joyce A. Schroeder, Ph.D. **University of Arizona**
Award Amount FY09: $49,999

Mechanism of CD44-HA Mediated Inhibition of Breast Cancer Metastasis

The majority of breast cancer patients die when the cancer spreads from the breast to distant sites in the body (metastasis). CD44 is a protein on cells that controls how cells migrate through tissue (the extracellular matrix, ECM). We hypothesized that CD44 engagement of the ECM is a response of the body to prevent metastasis, and we propose to determine how this occurs.

During year two of this project we sought to determine how ligand activation affects CD44-dependent cell behavior; determine if CD44 is affecting known mediators of metastasis, such as EGFR; and complete the generation of mouse models to investigate these findings.

The primary ligand for CD44, hyaluronan (HA), can be supplied to the cells in two ways: soluble (made by the epithelial cells, sHA) or embedded in the tissue extracellular matrix (made by tissue fibroblasts, eHA). This difference markedly affects the response of CD44 expressing cells in that they are metastatic with sHA but normal behaving with eHA. We have found that this is due to altered activity of a primary oncogene, the Epidermal Growth Factor Receptor (EGFR). We have been able to show that CD44 effects are mediated by EGFR. Animal studies to demonstrate this *in vivo* are progressing.

Ornella Selmin, Ph.D. **University of Arizona**
Award Amount FY09: $49,954

Foliate as a Nutrient Competitor Against Environmental Exposure to Trichloroethylene

The objective of this study is to assess the effects of folic acid deficiency and supplementation, created by diet, on alteration of phenotype and gene expression induced by maternal exposure to trichloroethylene (TCE).

The results of this past year indicate that folic acid supplementation in the maternal diet may be able to counteract the negative effects of TCE on expression of marker genes, and possibly prevent the development of heart defects in rats exposed to TCE through maternal drinking water. These findings are important because they may help in designing strategies to protect TCE exposed groups of populations from increased risk of congenital heart disease.

D. Larry Sparks, Ph.D. **Banner Sun Health Research Institute**
Award Amount FY09: $ 150,000

CSF Copper and Cognitive Performance

Alzheimer's disease (AD) affects nearly 5 million Americans and 125,000 Arizonans, as a progressive dementing disorder gradually ending in a total loss of self. The financial and emotional burden on the caregiver (normally the spouse) of an AD patient can be staggering. Cognitive dysfunction (dementia) is one of the most devastating possibilities facing Arizona's aging population. Identifying a method of predicting which individuals might develop AD could reveal a method of treating and hopefully delaying progression or onset of the disorder. In an autopsy study we found that there is gradual reduction of copper levels in the cerebrospinal fluid (CSF) as an individual courses from normal cognitive performance to dementia of AD. We have shown that we can quantify copper levels in human saliva, but have yet to show that they co-vary with CSF levels. We are testing the hypothesis that reduced copper levels in CSF/saliva are predictive of future cognitive impairment by yearly assessment to this three-year longitudinal investigation.

Discovering a biomarker predictive of impending cognitive dysfunction would also aid in developing better medications to treat and medically follow disorders causing dementia such as Alzheimer's disease (AD) and Parkinson's disease (PD). In an autopsy study very low levels of brain and CSF copper levels were identified in demented AD and PD patients, while intermediate brain and CSF copper levels were found in patients with mild cognitive impairment (no longer considered control, but not sufficiently severe to be diagnosed as dementia). This 3-year longitudinal assessment, with CSF collection and neurologic evaluation at 1-year intervals, is ongoing in order to test the hypothesis that CSF concentrations of copper are significantly associated with and/or predict cognitive decline in living individuals with dementia or mild cognitive impairment as well as in normal elderly subjects.

As recruitment for the ongoing trial assessing copper levels in CSF was not as robust as anticipated coupled with advent of predictive CSF biomarkers amyloid-beta and tau, we have modified the protocol and informed consent for the investigation. The changes include additional assessments of CSF for levels of amyloid-beta and tau and the inclusion of private practice patients in addition to those individuals participating in the Sun Health Research Institute Brain Bank program as candidates for participating in the ongoing CSF biomarker study.

Brent L. Vernon, Ph.D. **Arizona State University**
Award Amount FY09: $150,000

Improved Materials for Endovascular Embolization

For treatment of aneurysms and arteriovenous malformations, an efficient material is needed to block blood flow to the site. Due to its temperature-sensitive properties and wide use in the biomedical field, NIPAAm is suitable for such applications. The structural, thermal and mechanical properties of the NIPAAm-based copolymers were analyzed using various techniques and demonstrated promising characteristics for embolization. Due to the simultaneous chemical cross-linking which occurs through a chemical reaction and the physical gelling undertaken at higher temperatures with phase transition, the polymer has shown its ability to endure stress and strain experienced in the endovascular system. Cytotoxicity studies have also demonstrated its non-toxic effects on cells. *In vivo* tests performed on swine models were done to analyze the performance of the polymer network at physiological conditions. This work is being conducted in collaboration with an internationally-renowned neurological institution located in Phoenix, Arizona to develop a non-invasive method of treating patients suffering from endovascular malfunctions.

Danzhou Yang, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Novel AP-1 Inhibition of Highly Potent Anticancer Drug XR5944

XR5944 is a novel cytotoxic agent with exceptional anti-tumor activity against a range of human tumor models both *in vitro* and *in vivo*. The objective of this project is to characterize the AP-1 inhibition of XR5944. We have shown previously that XR5944 is capable of inhibiting UVB induced transcriptional activity of AP-1 in mouse keratinocytes cells; however, the exact 100 percent inhibitory concentration of XR5944 cannot be accurately determined. Further experiments showed that XR5944 inhibits the AP-1 transactivation in MCF-7 cells that have high AP-1 transcriptional activity, but it has reduced effect in HeLa cells that have low AP-1 activity. However, we found that the AP-1 inhibitory concentration of XR5944 in the UVB-treated HCL14 cells was significantly increased from the previous numbers. In addition, XR5944 was shown to have a clear induction of AP-1 activity at higher concentrations.

Christopher Buneo, Ph.D. **Arizona State University**
Award Amount FY09: $50,000

Contribution of Parietal Areas to State Estimation

This project is aimed at understanding how the brain combines sensory information from various sources and uses it to guide our limb movements. Such basic sensorimotor functions can be altered by strokes and traumatic brain injuries, as well as by the normal aging process and developmental abnormalities. We have been studying these functions by monitoring the activity of cells in a brain region known to be involved in sensorimotor control, the posterior parietal cortex (PPC). We have found that in one part of the PPC cells appear to signal the position of the arm solely by using information obtained from the muscles, i.e. they do not appear to use visual information when it is available, suggesting visual and muscular information are integrated in another area. We hope that a more complete understanding of this important function will benefit the citizens of Arizona through improved rehabilitation protocols and assistive technologies.

Papers Published

Shi Y, Buneo C. Exploring the Role of Sensor Noise in Movement Variability. **Annual International Conference of the IEEE Engineering in Medicine and Biology Society**. 2009.

Daniela C. Zarnescu, Ph.D. **University of Arizona**
Award Amount FY09: $49,999

Mechanisms for Local Translational Control in Drosophila Neural and Germ Stems Cells Gene

Fragile X Syndrome (FraX) is the most common form of inherited mental retardation and affects approximately 14,000 males. Patients exhibit reduced cognitive function, attention deficit and hyperactivity as well as autistic behaviors. The disease is caused by the loss of function for the RNA-binding protein, FMRP. Currently, FMRP is thought to play a role in learning and memory by regulating the expression of specific mRNAs at synapses. Using the genetically tractable fruit fly as a model, we discovered that FMRP is required in neural stem cells, before neurons form. Studies of mutant brains revealed a novel FMRP function: controlling neural stem cell proliferation. Recent results suggest that loss of FMRP in these neural stem cells leads to an overproduction of neurons in the brain, which may explain the autistic behaviors in FraX patients. Future studies will use molecular genetic approaches to identify the mechanisms of FraX in the developing brain.

Joyce A. Schroeder, Ph.D. **University of Arizona**
Award Amount FY09: $70,000

Therapeutic Peptides for the Treatment of Metastatic Cancer

Breast cancer is the third leading cause of cancer related deaths in Arizona. The oncogene MUC1 is made in excess in greater than 90 percent of breast cancer patients. We have previously developed a therapeutic drug (PMIP) that blocks the action of MUC1, thereby stopping breast cancer growth and spread. We hypothesize that the PMIP is acting through a second oncogene, EGFR and may work well in combination with established therapies that target EGFR.

This project investigated how PMIP works and determined if EGFR activity is required for PMIP activity. We were unable to detect any synergy between EGFR targeted drugs and PMIP. In side-by-side comparisons, we found that PMIP worked as well as, if not better than, current FDA approved anti-EGFR therapeutics. We have also begun to develop a second-generation class of peptide based therapeutics to target MUC1-dependent EGFR biology in breast cancer.

1st Year Contracts

Mohamad Azhar, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Role of TGFbeta Ligands in Aortic Aneurysm

The hypothesis is that Transforming Growth Factor (TGF)-beta2 and –beta3 proteins are required for protection against aortic aneurysm. We have produced genetically engineered mice in which TGFbeta2 and TGFbeta3 genes are completely deleted. These TGFbeta2/TGFbeta3-doubly-deficient (DKO) mice die during embryonic development at E15.5 day of gestation. Histological analysis of E14.5 day old DKO embryos revealed severe aneurysm in aortic arteries. The data also identified a constellation of cardiovascular anomalies: malformed aortic arch arteries, abnormal septation and alignment of the developing heart, impaired myocardial and coronary artery development. Overall, these data indicate that TGFbeta2 and TGFbeta3 are required for protection against widespread arterial aneurysm and congenital heart disease. These studies are highly significant to the biomedical issues facing Arizona because environmental agents (e.g., tobacco, trichloroethylene) caused adult or fetal cardiovascular diseases remain the leading cause of death of Arizonans.

Papers Published

Azhar M, Runyan RB, Gard C, Sanford LP, Miller ML, Andringa A, Pawlowski S, Rajan S, Doetschman T. Ligand-Specific Function of Transforming Growth Factor *Beta* in Epithelial-Mesenchymal Transition in Heart Development. **Developmental Dynamics**. 238:431-42. 2009.

Azhar M, Yin M, Bommireddy R, Duffy JJ, Yang J, Pawlowski SA, Boivin GP, Engle SJ, Sanford LP, Grisham C, Singh RR, Babcock GF, Doetschman T. Generation of Mice with a Conditional Allele for Transforming Growth Factor *beta* 1 Gene. **Genesis**. 00:1-9. 2009.

Azhar M, Yin M, Zhou M, Li H, Mustafa M, Nusayr E, Keenan JB, Chen H, Pawloski S, Gard C, Grisham C, Sanford LP, Doetschman T. Gene Targeted Ablation of High Molecular Weight Fibroblast Growth Factor-2. **Developmental Dynamics**. 238:351-7. 2009.

Ross M. Bremner, Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $50,000

Predictors of Therapy Response in Adenocarcinoma of the Lung

Non-small cell lung cancer remains the leading cause of cancer death in industrialized countries. In Arizona, there are 2,760 new cases of lung cancer each year, of which many will die. Novel small molecule biologic therapies have demonstrated promising activity against cancer. Our goal is to establish a pre-clinical xenograph model for lung adenocarcinoma and determine whether molecular profiling can identify predictors of tumor response or non-response to conventional chemotherapeutic agents. To this end, we have accrued 16 primary adenocarcinoma tumors and propagated 4 of these tumors in mice (i.e. xenograph). Genomic profiling of half of the primary tumors is complete and statistical analysis of this dataset is forthcoming. The genomic profiling of the remaining primary tumors and xenographs is expected to be completed by the end of October and the calendar year, respectively, with publication of the initial results expected by the end of the fiscal year.

Michael R. Caplan, Ph.D. **Arizona State University**
Award Amount FY09: $50,000

Reverse Engineering the Basement Membrane

Interactions between cells and materials have been studied by measuring the activation of signals inside the cells when they contact different materials. Ten materials (9 proteins and uncoated tissue culture plastic) each elicited a unique pattern of signal activation showing that cells can use these signals to convey differences in materials to the cell's nucleus. Several cell behaviors have been studied on these different materials. Cell adhesion and expression of an adhesive protein was shown to be strong when two signals were highly activated. Cell prevention of blood clotting has also been studied. Blocking these signals decreased cell adhesion and increased blood clotting providing additional evidence that the links between these signals and behaviors are causal. Variation of substrate stiffness has been shown to be primarily linked to two other signals. Understanding these responses can help engineers design better materials for medical implants.

Qin M. Chen **University of Arizona**
Award Amount FY09: $50,000

Oxidant Induced c-Fos Phosphorylation

Arizona is among the states that have the highest population of tobacco smokers. Smoking produces oxidants. While oxidants can damage macromolecules or cells, our body has evolved defense mechanisms against oxidants. Oxidants cause rapid activation of AP-1 transcription factor, which contains c-Fos protein. We found that c-Fos protein is phosphorylated at the amino acid Serine residues. To study the biological significance of such an event, we have made mutant c-Fos either mimicking or deleting phosphorylation. We found that Serine located at 374^{th} amino acid of c-Fos protein sequence regulates the stability of c-Fos protein and AP-1 activity under oxidative stress. This study focuses on one molecule, e.g. c-Fos, at a time to identify important signaling events controlling certain type of diseases associated with oxidant overexposure such as in the case of tobacco smoking.

Cheryl Conrad, Ph.D. **Arizona State University**
Award Amount FY09: $49,940

Stress and Estrogen Actions in the Female Hippocampus

We made substantial progress: two publications and five abstracts. We show that estrogen protects females against stress-induced damage in the hippocampus, important for memory (Hippocampus). We discuss the implications of these findings for mental health in a review describing how estrogen influences neuron communication among the hippocampus, prefrontal cortex (PFC) and amygdale, brain regions involved in cognition and mood (Molecular Neurobiology). In our abstracts, lesions to the PFC, involved in planning, produces sex differences in fear learning (Baran et al.), which is not influenced by estrogen (Hoffman et al.). However, estrogen influences the hippocampus by altering strategy use, which is modulated by chronic stress (McLaughlin et al.). We also show that sex differences influence how chronic stress alters anxiety (Huynh et al.). Finally, we report that young rats improve from their stress-induced cognitive deficit when allowed several weeks to recover from the end of chronic stress.

Papers Published

McLaughlin KJ, Wilson JO, Harman J, Wright RL, Wieczorek LA, Gomez J, Korol DL, Conrad CD. Chronic 17β-Estradiol or Cholesterol Prevents Stress-Induced Hippocampal CA3 Dendritic Retraction in Ovariectomized Female Rats: Possible Correspondence Between CA1 Spine Properties and Spatial Acquisition. **Hippocampus**. July 2009.

McLaughlin KJ, Baran SE, Conrad CD. Chronic Stress and Sex- Specific Neuromorphological and Functional Changes in Limbic Structures. **Journal of Molecular Neurobiology**. 40(2):166-82. October 2009.

Abstracts

Baran SE, Armstrong CE, Niren DC, Hanna JJ, Hamilton GF, Wright RL, Conrad CD. Sex Differences and the Role of the Prefrontal Cortex in Fear Conditioning and Delayed Recall of Fear Extinction. **Neuroscience**. May 2009.

Hoffman AN, Armstrong CE, Dille R, Hanna JJ, Nelson C, Huynh TN, Conrad CD. Chronic Stress Facilitates Acquisition of Fear Conditioning in Ovariectomized Female Rats, Regardless of 17β-estradiol Treatment. **Neuroscience**. May 2009.

Mclaughlin KJ, Paine T, Hamilton G, Baran SE, Wright RL, Conrad CD. Chronic Stress Facilitates Spatial Memory, Which is Prevented with Cyclic 17β estradiol in Ovariectomized Female Rats. **Neuroscience**. May 2009.

Huynh TN, Nelson C, Schilling A, Dille R, Armstrong CE, Hanna JJ, Anouti D, Dorathy K, Hoffman, AN, Coombs KM, Conrad CD. The Effects of Chronic Stress and Sex Differences on Several Measures of Anxiety and Depressive-like Behaviors. **Neuroscience**. May 2009.

Coombs KM, Nelson C, Schilling A, Hoffman AN, Anouti D, Dille R, Armstrong CE, Hanna JJ Bimonte-Nelson HA, Conrad CD. Recovery of Spatial Working and Reference Memory After Chronic Stress in Mature Adult Male Rats. **Neuroscience**. May 2009.

Keith D. Coon, Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $47,749

Perioperative Strategies to Improve Outcomes in Patients with CCLC

Non-small cell lung cancer is the most common cause of cancer death in the western world. Surgery can increase patient's long-term survival, but many will still recur with distant metastases. The severity of surgery can impact the incidence and magnitude of recurrence. It has been suggested that perioperative treatment with an anti-cancer agent might reduce these complications. The COX-2 inhibitor, celecoxib, has been shown to have significant anti-cancer properties with few side effects. This study will use celecoxib in human subjects to minimize surgery-induced metastases and subsequently assess the induced molecular changes via gene expression analyses. Little progress has been made on this project to date due to poorer than expected patient accrual; however, we expect the addition of a dedicated research nurse coordinator in the coming months to bolster enrollment and permit us to attain our Year 1 objective of gene expression profiling on 9 patients (45 blood samples).

Torsten Falk, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Transplantation of Adult RPE Cells as a Treatment for Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting the senior population in Arizona (2 percent of the population over 65 years of age). At the present time treatment of this movement disorder is inadequate. Developing new treatments for this disorder has been identified as a major focus area defined by the Arizona Bioscience Roadmap report commissioned by the Flinn Foundation. This research project is testing a novel cell therapy approach that has the potential to become neuroprotective therapy for patients with PD, an essential advance. In our research we show that the cells we study for transplantation (RPE cells), in addition to producing levodopa (the gold standard symptomatic treatment drug), also make a cocktail of growth factors (PEDF, VEGF-A, VEGF-B) that we and others have shown in animal model systems to have the potential to be protective for the brain cells that degenerate in PD.

Papers Published

Falk T, Zhang S, Sherman SJ. Pigment Epithelium Derived Factor (PEDF) is Neuroprotective in two *in vitro* Models of Parkinson's Disease. **Neuroscience Letters**. 458:49-52. 2009.

Hanna F. Fares, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Deciphering Endocytosis in Multicellular Eukaryotes

We identified a novel plasma membrane quality control system that recognizes misfolded proteins at the surfaces of cells and targets them for degradation. This novel quality control mechanism at the plasma membrane would be crucial to remove stable proteins at the plasma membrane that are misfolded. The accumulation of these misfolded proteins would alter the properties of the plasma membrane leading to cell death. This quality control mechanism may also be used for the removal of stable integral membrane protein during the remodeling of membranes. One example is the clearing of junctional proteins, a necessary step for epithelial mesenchymal transition during normal development and a necessary step for the metastasis of tumors. This system also has profound implications on other biological systems, for example, the mechanisms used by some plant and bacterial toxins to kill cells.

Sourav Ghosh, Ph.D. **University of Arizona**
Award Amount FY09: $ 50,000

Cell Polarity Regulation During Differentiation of Embryonic Stem Cells

A fundamental feature of the three-dimensional architecture of diverse cell types is “apical-basal polarity” or internal asymmetry along an apical-basal axis. This defines the front-to-end orientation of cells allowing for their structural organization and physiological function in the context of tissues. We propose that altered apical-basal polarity is causal for metabolic disease, developmental abnormalities, as well as aberrant cell migration and invasion in cancer and metastasis. The aPKC gene codes for an enzyme that is essential for apical-basal polarity. We have discovered a strong association between increased aPKC protein and high-grade glioblastoma. We have also demonstrated that reducing aPKC level arrests cell migration. Currently, we are defining the molecular circuitry that leads to aPKC activity and increased cell migration to better understand its role in glioblastoma. Since aPKC belongs to the protein kinase class of enzymes, it represents a tractable and attractive pharmacological target for future drug development and discovery.

Steven Goldman, M.D. **Southern Arizona VA**
Award Amount FY09: $50,000

Seeding Fibroblast Patch for Chronic Heart Failure

This project is designed to develop a new treatment for patients with heart failure after a heart attack. There is current enthusiasm to use “cell-based” therapy by injecting stem cells into patients after a heart attack to improve heart function. The results from clinical trials have been disappointing mainly because when you inject new cells into a damage heart, they do not survive. Our thought is that these cells do not survive because they are injected directly into the injured heart muscle without any support structure and without adequate blood supply. We are developing a new approach to cell-based therapy for heart failure using a viable 3-dimensional fibroblast construct (3DFC) matrix patch. We propose that implanting 3DFC on the damaged heart after a heart attack will improve heart functional blood flow. We also propose to add heart cells to this 3DFC to deliver new heart cells to the heart.

Stephen I. Helms-Tillery **Arizona State University**
Award Amount FY09: $50,000

Role of the Basal Ganglia in Learning to Control Neuroprosthetics

This project researches the use of neuroprosthetic systems to learn how the brain learns to perform complex tasks. Prior research has established that the basal ganglia are an important part of the brain's learning systems. Our project forces learning in neuroprosthetic systems as a way to study how the basal ganglia contribute to that process. So far the necessary hardware has been implanted to create a neuroprosthetic and we have begun training the implanted animal in the general outlines of neuroprosthetic control. Once the animal has adequately learned the task (2-4 months), we will begin recording signals from the basal ganglia. The results will provide important insights into learning and how that might be compromised in diseases of the basal ganglia such as Parkinson's Disease.

Jui-Cheng Hsieh, Ph.D. **University of Arizona**
Award Amount FY09: $49,999

Functional Analyses of the Mammalian Hairless Protein

The goal of this proposal is to probe the molecular details of the mammalian hairless (Hr) protein, an important regulator of human skin and hair growth. Particular emphasis will be placed on two aspects of Hr structure/function that have great potential for explaining how Hr carries out its molecular functions, but which have received scant attention in the research community. The specific aims are to optimize a system for over expression and purification of Hr; to study potential Hr DNA binding, and to identify Hr phosphorylation sites. The *E. coli*-expressed rat Hr has been fine purified and confirmed by a western blot. Its initial DNA-binding capacity has also been examined. These results will allow us to better understand the final common pathway involved in hair growth and brain development, possibly resulting in better therapeutic interventions targeting this pathway to help treat or cure patients with alopecia.

Leland S. Hu, M.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $49,500

Distinguishing Post-Treatment Radiation Effects from Glioma Recurrence Using Dynamic Susceptibility Contrast (DSC) MRI

Many new and existing therapies for brain tumor patients can help maximize survival following initial treatment. Applying appropriate treatment plans relies on accurate distinction between tumor regrowth and non-tumor post-treatment changes. Accurate diagnosis currently requires surgery and tissue analysis since conventional imaging tests are not sufficient. However, development of specialized imaging tests can vastly improve accuracy and may help forgo the need for invasive procedures. Dynamic susceptibility contrast (DSC)-MRI is a specialized imaging test which provides information about tissue blood flow and can improve non-invasive detection of tumor growth. DSC can track the effectiveness of new anti-tumor therapies and distinguish tumor regrowth from non-tumor inflammatory changes. Our Arizona-based collaborative consortium has optimized the DSC method and validated measures with image-guided tissue analysis to establish clinically reliable values that non-invasively diagnose tissue with over 95 percent accuracy. Our goal is to provide more accurate, non-invasive brain tumor diagnosis and treatment planning.

Mrinalini Kala, Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $50,000

Role of B Cells in Glatiramer Acetate Mediated Suppression of Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS). The CNS consists of the brain, spinal cord, and the optic nerves. A fatty tissue called myelin protects nerve fibers and helps conduct electrical impulses. Myelin is attacked in MS with loss in multiple areas, leaving scar tissue in the brain or spinal cord and producing various symptoms. MS is leading cause of disability among young adults in North America and Europe. One immunotherapy for MS is Glatiramer Acetate (GA). GA is a randomized copolymer of 4 amino acids (L-alanine,L-lysine, L-glutamic acid and L-tyrosine) and slows the progression of disability with few side effects. Understanding GA's mechanism will be a major advance towards developing an effective therapy for multiple sclerosis.

B-cells are present in meningis of MS patients and regulate MS. On stimulation with antigen, B-cell secrete a panel of stimulatory and inhibitory proteins called cytokines, which can influence the outcome of the immune responses. B-cells secreting inhibitory cytokines are called regulatory B-cells or Bregs. B- cells can also present antigen to T-cells. We hypothesized that GA suppresses MS by: changing the antigen presenting property of B-cells, and by acting on B-cells to differentiate into regulatory B-(Breg) cells. These Breg cells secrete a panel of cytokines e.g. IL-4, IL-10 and TGF-B that can regulate immune response, directly or indirectly via T-cells.

Based on this hypothesis our study showed that B-cells from GA-treated mice did not present the MS causing neuroantigen effectively to T-cells and this could be one of the reasons for reduced systems of MS. In addition, we also showed that GA acted on B-cells to differentiate into regulatory B-cells that make more IL-10. These IL-10 producing regulatory B-cells from GA-treated mice protected recipient mice both before and after induction of MC. When GA was used in mice with no B cell we did not see any protection. These data indicate that B-cell have important role in suppression of MC by GA. Moreover, we showed that transfer of B-cells from GA-treated mice reduced the expansion of harmful autoreactive T cells as well as the development of Th1 and Th17 cells but promoted the production of immunoprotective cytokine IL-10 in recipient mice. Another lymphocyte called macrophage, that promotes MC was reduced in mice receiving the B-cells from GA-treated mice. Although more work need to be done before these GA-treated Breg cells becomes reality for MS treatment, nevertheless our results suggest that B-cells are important to the protective effects of GA in EAE.

Annual economic cost of MS in the United States is approximately $28 billion. In Arizona alone, there are at least 6000 people suffering from MS and developing this regulatory B cell therapy will be an immediate benefit for them and their family.

Kathryn Lemery-Chalfant, Ph.D. **Arizona State University**
Award Amount FY09: $47,438

Molecular and Quantitative Genetic Approaches to Understanding Child Psychopathy

During our first year of funding, we accomplished many of our key aims and are well positioned to incorporate genetic data into our process twin models of the development of child psychopathology. Variants within 10 promising candidate genes have been targeted that are most likely to have a key influence on child psychopathology.

The DNA has been extracted from cheek cells and the genotyping is largely completed. We are poised to begin to test our novel developmental models that challenge the current field standard of testing each genetic variant independently. Understanding genes in their context will provide an ability to better understand the development and interplay of genetic influences on child psychopathology.

Papers Published

Lemery-Chalfant K, Doelger L, Goldsmith HH. Genetic Relations between Effortful and Attentional Control and Symptoms of Psychopathology in Middle Childhood. **Infant and Child Development**. 17:365-85. 2008.

Wagner AI, Schmidt NL, Lemery-Chalfant K, Leavitt LA, Goldsmith HH. The Limited Effects of Obstetrical and Neonatal Complications on Conduct and Attention-Deficit Hyperactivity Disorder Symptoms in Middle Childhood. **Journal of Developmental Behavior Pediatrics**. 30(3):217-25. June 2009.

Lemery-Chalfant K, Doelger L, Goldsmith HH. Difficult and Unadaptable Temperament in Infants, Toddlers, and Preschoolers: Genetic Analyses and Predicting Symptoms of Psychopathology. **Child Development**. Accepted for publication 2009.

Lemery-Chalfant K, Turner PA, O'Brien TC, Van Hulle C, Goldsmith HH. (in press). Mother and Father Depression and Child Psychopathology: Moderation by Child Effortful Control. **Journal of Child Psychology and Psychiatry.**

Abstracts

Lemery-Chalfant K. Genetic Risk or Resilience? Elucidating the Role of Context. **Behavior Genetics.** Presented at the Behavior Genetics Association Meetings in Minneapolis, Minnesota. 2009.

O'Brien TC, Lemery-Chalfant K, Goldsmith HH. A Monozygotic Twin Difference Score Approach to Parenting as a Nonshared Environmental Influence on Behavior Problem Symptoms. **Behavior Genetics**. Presented at the Behavior Genetics Association Meetings in Minneapolis, Minnesota. 2009.

Lonnie Lybarger, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Regulation of Immune Activation by Ubiquitination

Activation of the immune system is a tightly controlled process, with dysregulation resulting in serious health consequences such as arthritis and asthma diseases which are especially prevalent in Arizona. Cells of the immune system, known as antigen presenting cells (APC), represent key regulators of the process of immune system activation. Recently, the protein MARCH1 was reported to influence APC function and our lab has studied the molecular mechanisms by which this occurs. We have made significant progress in the past year to understanding how MARCH1 affects pathways in immune cells that control the extent of activation of the immune system. In fact, we have submitted a research paper for publication describing our findings. Ultimately, a full understanding of the pathways we are studying will result in better treatments for diseases of immune dysregulation.

Anjan Misra, Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $50,000

Exploiting Receptor Tyrosine Phosphatases for Diagnosis and Treatment of Malignant Astrocytoma

Malignant astrocytoma (MA) account for >50 percent of all brain tumors, and come in two grades, Anaplastic Astrocytoma (AA, grade 3) and Glioblastoma Multiform (GBM, grade 4). GBM has a median survival of about one year and AA and 3.5 years. Protein Tyrosine Phosphatase Receptor D (PTPRD) gene is frequently lost in MA and is associated with poor survival, suggesting loss of PTPRD helps malignant astrocytomas. We are investigating how frequently PTPRD is lost in malignant brain tumors at protein level and how loss of PTPRD affects MA initiation, progression and behavior. Our data show that PTPRD is lost at the protein level in every GBM tested and its restoration in GBM cells reduce their growth and kills them. PTPRD can be used as a marker for screening patients, and as a therapeutic target for treatment of brain tumor patients not only in Arizona, but rest of the world.

Jong Min Rho, M.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $49,819

Epilepsy-Induced Impairment of Circadian Rhythms

Epileptic seizures occur commonly during sleep, but it is unclear whether the epileptic brain causes dysfunction of circadian rhythms normally controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus. Our principal goal is to study the development of circadian rhythm disturbances in a developmental rodent model of epilepsy and to examine the role of the SCN in these mice using electrophysiological and immunocytochemical techniques. We hypothesize that normal circadian function is impaired after the development of seizures, and that this is due to altered neuronal activity and/or phase shifts associated with differential expression of clock genes within the SCN. SCN dysfunction may impact genesis, sleep disorders, obesity, and neurocognitive functioning. Given the epidemic of sleep problems and obesity in the general population, the results of the proposed studies may help shed further light on the relevance of SCN function to a wide range of physiological and neuroendocrine functions.

Leslie Ritter, Ph.D., R.N. **University of Arizona**
Award Amount FY09: $47,608

Novel Use of a Natural Product for Acute Stroke Therapy

The overall goal of this research is to test if a natural product, turmeric, will reduce brain damage after stroke. We have completed our second year of a three year project. The first year we verified that turmeric treatment significantly reduced the amount of brain cell death after a stroke. During this past year, we conducted experiments to determine how turmeric protected the brain after stroke. It is well known that turmeric, from the root of the curcumin plant, is an ancient spice that is thought to have beneficial health effects due to its anti-inflammatory properties. Inflammation is known to result in worse outcomes after stroke. Indeed, the results of the experiments conducted this year reveal that this natural product reduces the molecular signals that promote inflammation after stroke. If so, then we can look toward the possible use of turmeric not only as a treatment when stroke occurs, but as a chronic dietary supplement that could reduce the damaging effects of inflammation before stroke occurs. As the third leading cause of death and major cause of disability, identification of a safe and beneficial effect of turmeric that could act in a novel way to limit brain injury in stoke could have a major impact on the health and health care costs of our state. This is particularly true at a time when baby boomers approach retirement and the percentage of our population over the age of 65, i.e. those individuals at greatest risk of stroke, is projected to double.

Marek Romanowski, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

Contrast Agent for Colonoscopy

The overall goal of this project is to develop a contrast agent that will enhance standard colonoscopy by marking areas of precancerous changes, or adenomas, with highly visible and stable luminescent nanoparticles. Experiments conducted over the first year of this project focused on preparation and characterization of luminescent nanoparticles. Doped nanoparticles of lanthanum fluoride were prepared using several methods. The initially tested low temperature process has been replaced by a high temperature protocol in order to improve the yield of luminescence upconversion, as appropriate for *in vivo* imaging applications. Nanoparticles have been prepared for surface modifications to improve their water solubility and to perform ligand attachment for disease-targeted imaging. In the meantime, an imaging system was assembled and tested for capturing wide-field images of luminescent nanoparticles with high temporal resolution.

Jiong Shi, M.D., Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY09: $50,000

APOE Mimic Peptide as a Novel Therapy on Cognition in a Transgenic Mouse Model

Multiple sclerosis (MS) is a devastating neurological disease that impairs not only motor but also cognitive abilities of young people. Since MS patients tend to develop cognitive deficits at an earlier age, to help them at an early stage before full-blown dementia will dramatically reduce the social and economic burdens of caregivers and the healthcare system.

Our goal is to establish an animal model to study the underlying mechanism, find a treatment, and translate it back to patient care. We have successfully induced an animal version of MC in transgenic mice. As a result, we have found a significant impairment in their learning skills which is caused by a reduction in choline acetyltransferase, a chemical that is believed to play a critical role in learning. We therefore have an animal model that provides a template from which we can test a treatment to reverse it.

Papers Published

Tu JL, Zhao CB, Vollmer T, Coons S, Lin HJ, Marsh S, Treiman DM, Shi J. APOE 4 Polymorphism Results in Early Cognitive Deficits in an EAE Model. **Biochemical and Biophysical Research Communications**. 384:466-70. 2009.

Catharine L. Smith, Ph.D. **University of Arizona**
Award Amount FY00: $49,999

Identification of the Acetylated Transcriptional Proteome in Leukemia and Lymphoma

Leukemia and lymphoma rank among the top 10 causes of cancer death in Arizonans. A new class of anticancer drugs has shown promise in treating these cancers. Histone deacetylase inhibitors inhibit enzymes that remove acetyl groups from proteins. Our goal is to identify acetylated proteins critical for mediating the death of cancer cells through regulation of gene expression. In the past year we have obtained cell lines representing different leukemias and lymphomas, identified the dose of these drugs that stops growth within 48 hours, and determined which genes are repressed and activated. We have also worked out a method to purify cellular proteins directly involved in regulation of gene expression. Such protein extracts will be used to identify acetylated proteins. Our accomplishments over the first year of the project are consistent with our suggested timeline and we look forward to continuing progress in the coming year.

Peter N. Steinmetz, Ph.D. **Arizona State University**
Award Amount FY 09: $44,311

Representation of Memory for Spoken Words and Voice Detail by Single Neurons in the Human Hippocampus

The main goal of this project is to understand how memory of words is represented by the firing of neurons in the human hippocampus. Prior behavioral experiments have shown that apparently incidental details of word presentation, such as the font or voice, influence how well words can be recalled upon a second presentation. Our working hypothesis is that words presented and later repeated in the same voice or font should evoke stronger responses in hippocampal neurons than when the voice or font is changed. We record the responses of single neurons in the hippocampus of epilepsy patients as they perform a continuous recognition memory experiment seeing or hearing words twice in the experiment, with random numbers or other words intervening. By studying how neural firing rates change as a function of both the number of intervening words and change or lack of change of font or voice, we can better understand the neural representation of memory for linguistic forms.

Overall project progress has been good in obtaining pilot data in normal subjects, recording from human epilepsy patients, and staffing to assist in testing patients. An NIH grant supplements the research and we have applied for NSF support as well.

Raoul Tibes, M.D., Ph.D. **Translational Genomics Research Institute**
Award Amount FY09: $50,000

RNAi Kinome Screening to Identify Rational Combinations with Cytarabine in Acute Myeloid Leukemia

Acute myeloid leukemias (AML) are often incurable with currently available therapies. New, completely different, research approaches are needed to develop better therapies in AML. We are pursuing an approach called RNA interference (RNAi). This technology allows to individually "shut down" (inhibit) activity of several hundred (~572) genes/kinases and to assess which gene(s) need to be inhibited to reduce growth of leukemia cells. We performed such an RNAi screen with Cytarabine (AraC), the most active drug in AML and found several genes that when inhibited led to increased death of leukemia cells in combination with AraC. Novel inhibitors (drugs) were identified that target the identified genes/kinases. When these drugs are now combined with AraC, increased leukemia cell death over AraC alone is seen. Based on our results we are conceptualizing clinical trials in collaboration with other Arizona health care systems to offer to leukemia patients in Arizona.

Theodore P. Trouard, Ph.D. **University of Arizona**
Award Amount FY09: $50,000

MRI, MRS and Molecular Modeling of Three Dimensional Cell Cultures

Diffusion-weighted MRI (DWMRI) is a technique that allows measurement of the microscopic motion of water in living tissue. DWMRI is being used to study a variety of diseases including stroke and cancer. Although clinically useful, interpretation of DWMRI results is limited by a lack of fundamental knowledge of how water moves within tissue and how that affects MRI results. To overcome this, MRI experiments are being carried out in novel cell culture systems, developed at the University of Arizona, that mimic biological tissue. Mathematical models are also being utilized to describe water motion in simple cell systems and predict the results of DWMRI experiments. The more we know about how water moves within tissue, the better physicians will be able to interpret results from studies of stroke and cancer. One paper has been published this year on the mathematical modeling and another has been submitted for publication.

Pak Kin Wong, Ph.D. **University of Arizona**
Award Amount FY09: $49,999

Molecular Probe Biosensors for Rapid Screening of Photoprotective Compounds

The long-term goal of the project is to develop an automated high-throughput screening (HTS) system for photoprotective compounds. During the year we have successfully achieved all the technical milestones including characterization and optimization of the molecular probe designs for screening photoprotective compounds and demonstrating the sensor for detection of purified targets. These probe designs will form the foundation for a large scale screening of photoprotective compounds toward skin cancer prevention. The ability to rapidly identify agents that can prevent the occurrence and reduce the severity of UV-induced skin cancer is of great importance in the area of photoprotection and chemoprevention. It is especially important in Arizona, which ranks one of the highest in skin cancer incidence rates in the world.

New Projects 2010

Charles Adler, M.D., Ph.D. **Mayo Clinic**

Award Amount FY10: $250,000

Arizona Parkinson Disease Consortium: Mechanisms and Predictors of PD and PDD

Description of the Research Problem

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by slowness of movement, rest tremor, and rigidity that requires an autopsy to make a definitive diagnosis. PD is estimated to affect 1.5 million people is the U.S., increases with age, and as the older population in Arizona continues to grow PD could be a major economic burden as signs of PD have been found in up to 40 percent of people over age 80. While predominantly considered a motor disorder, 30-90 percent of PD patients develop dementia. The motor symptoms can be disabling and the development of dementia leads to higher rates of nursing home placement and death. Medical and surgical treatment may improve motor symptoms but no treatment slows or stops disease progression nor adequately improves dementia in PD. This project is designed to include cores and projects that build on our previous ABRC research whose theme is the development of biomarkers and novel treatments for preventing the development of PD and progression of PD to PD with dementia (PDD). The work will be performed by the Arizona Parkinson Disease Consortium (APDC) with investigators at multiple institutions in the Phoenix area: Sun Health Research Institute, Mayo Clinic Arizona, and Banner Good Samaritan.

Goals and Objectives of the Research:

The project will build and expand on previous ABRC research by the APDC to develop clinical and cerebrospinal fluid (CSF) biomarkers that have high predictive values for the development of both PD and PDD. The clinical data collected will be validated by autopsy confirmation, the "gold standard" for diagnosing PD. Additionally, projects are proposed that also build on previous ABRC sponsored work investigating causes for PD and PDD with the goal of finding novel targets for treatment to prevent or slow disease progression.

The clinical core will enroll and longitudinally evaluate subjects in the Sun Health Research Institute Brain and Body Donation Program categorizing them as being controls or PD and documenting motor and cognitive decline in these cases. The role of the Clinical Core will be to recruit subjects with PD into the research program and to determine if clinical examination biomarkers can be used to predict who will develop PD and PDD. These biomarkers would then be used to identify individuals at-risk for developing PD or PDD so they could be entered into clinical trials of new treatments that would potentially prevent or stop progression to PD and PDD. Additionally, the Clinical Core will provide the Neuropathology Core and the projects with extensive clinical data obtained during the life of the autopsied subjects. The Neuropathology Core will perform all autopsies, provide data on Lewy bodies and other pathological markers to correlate with clinical data, and provide brain tissue and CSF for the projects.

One project will investigate potential biomarkers in CSF from PD, PDD, and autopsy identified preclinical PD cases (incidental Lewy body disease). As no test for PD currently exists, this CSF project will build on previous work in our laboratory which identified CSF markers for Alzheimer's disease with high sensitivity and specificity. A second project will investigate different protein (α-synuclein, β-amyloid, and tau) and neurotrophic factor (BDNF and its receptor, TrkB) levels in brain tissue from subjects at various stages of PD and PDD.

The goal will be to determine if, as the disease progresses, these levels change and whether there may be a sequence of changes and interactions/synergistic effects that may indicate a therapeutic target for disease modifying treatments. The final project will not use humane tissue but, using transgenic mice, will build on the question as to whether mutations in α-synuclein and tau synergistically lead to neurodegeneration and thus provide therapeutic targets for disease modifying treatments.

We have leveraged previous funding from the ABRC to obtain a $2.7 million, three year grant from the Michael J. Fox Foundation for Parkinson's Disease Research that expanded the scope of activity in the Clinical and Neuropathology Cores. The funding did not provide support for the laboratory projects and with this project, however, we will be in a better position to request additional Fox Foundation funding. We will also apply for at least two federally funded grants, including a program project or Udall Center. If appropriate targets are found with the laboratory study data then we will propose clinical trials of novel treatments designed to prevent or slow the progression to PD and PDD. Given the size of the Arizona Parkinson Disease Consortium clinical population, the treatment trials could be performed here in Arizona by the consortium.

Salvatore Albani, M.D., Ph.D **University of Arizona**
Award Amount FY10: $125,000

Immune Tolerance in the Therapy of Rheumatoid Arthritis

According to the CDC, nearly 21 percent of Arizonans suffer from some form of arthritis, including rheumatoid arthritis (RA). Prevalence is anticipated to increase as Arizona's population ages. In RA, the immune system is no longer able to distinguish some of the body's own cells from a viral or bacterial infection. As a result, the body essentially attacks itself on a perpetual basis via a process of inflammation, which can cause extensive structural damage as a result of this misguided response.

Current therapies may in many cases induce disease control but cannot maintain it in a medication free status unless therapy is continued indefinitely, with associated costs and risks. Hence, there is a need for a novel category of drugs which can restore the naturally occurring mechanisms of immune regulation which are impaired in arthritis. Our program is focused on the development of a novel class of drugs, called tolerogens, which can indeed re-establish in a physiologic fashion immune regulation. The initial clinical studies are encouraging insofar as they suggest clinical efficacy and safety. Our project aims at using samples obtained from the clinical studies to understand how tolerance can be induced to treat arthritis.

There is little published data concerning the induction and maintenance of immune tolerance based on concurrent clinical and mechanistic studies in rheumatoid arthritis (RA). It is of critical importance to understand the mechanisms of the induction of tolerance because the approach may be effective in maintaining disease control once the initial, symptomatic immune activation has been controlled by currently used immunosuppressants.

End objectives of this study are: to demonstrate that a tolerogenic therapy prepares the body, through engaging specific immune components such as T-cells and dendritic cells (APC) changing (i.e. deviate from) its destructive response to "self"; to characterize the basic features of therapy-induced immune deviation from pro-inflammatory to more tolerogenic; and to characterize the "adjuvant" role that hydroxychloroquinine (HCQ), a common drug used in the early treatment of RA, has on the mechanism of tolerization.

James C. Baldi, Ph.D. **Northern Arizona University**
Award Amount FY10: $125,000

Effect of Diabetes on Pulmonary Vascular Control at Increased Altitude

An increasing number of people with type 1 diabetes (sometimes called juvenile onset diabetes) are participating in adventure activities at moderate or high altitude. This is particularly true for people living in Arizona, where adventure attractions like hiking in the Grand Canyon or White Mountains and skiing the Arizona Snow Bowl occur at altitudes about 7000 feet. In addition, each year an American Diabetes Association-sponsored 'diabetes camp' attracts hundreds of type 1 diabetic Arizona youth to participate in adventure activities in Prescott, altitude 5400 feet. New data suggest that some type 1 diabetic patients may find the combination of exercise and high altitude unusually difficult due to impaired lung function, which often goes unnoticed at sea level. The cause of diabetic lung dysfunction is unclear, and may involve a deficit in oxygen transfer from lung air sacs into the blood (alveolar membrane diffusing capacity; D_M) or a reduced ability of the vascular supply to the lung to expand during exercise (increased pulmonary capillary blood volume; Vc). When presented with the combination of exercise and increased altitude, diabetic patients may experience abnormally low levels of oxygen in arterial blood, which lowers their work capacity and may increase the prevalence of altitude illness. This proposal will combine the expertise of faculty in the departments of Biological Sciences at Northern Arizona University and Endocrinology and Pharmacology at the University of Arizona to examine the limitations to physical work imposed by the diabetic lung during acute altitude exposure. Identical laboratories at the University of Arizona (2500 feet) and Northern Arizona University (7000 feet) will be developed to measure the responses of the lung to exercise when subjects are transported to increased altitude. Both labs will use a mass spectrometer to separate the influence of D_M and Vc, and thus determine which of these factors affects lung function during exercise. The proposal will also determine whether type 1 diabetics who carefully control their blood sugar respond better to high altitude exercise than those who do not. If so, this would mean that the problems experienced by type 1 diabetic patients during acute altitude exposure could be reduced or prevented by short-term, inexpensive "pre-treatment" with careful blood sugar control.

Randall S. Friese, Ph.D. **University of Arizona**
Award Amount FY10: $125,000

Sleep Promotion in Critically III and Injured Patients Cared for in the Intensive Care Unit

Sleep, a complex process involving a variety of physiologic and behavioral components, is divided into two district states: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. REM sleep normally accounts or about 25 percent of sleep time during an episode of restful sleep. Several researchers have described highly abnormal sleep patterns and architecture in patients cared for in the intensive care unit (ICU) setting. These patients do not achieve restful sleep and spend only a fleeting portion (1-3 percent) of sleep time in REM sleep. Prior research has established that sleep deprivation has a profound suppressive effect on immune function within normal subjects. However, there is a distinct lack of research describing the effects of sleep deprivation coupled with acute or chronic illnesses. In fact, the critically ill patient may be more vulnerable to the deleterious effects of sleep deprivation and poor sleep quality may adversely impact outcome in this patient population.

The overall goal of this project is to demonstrate whether a strategy to promote sleep in patients cared for in an intensive care setting, during recovery from critical illness or injury, results in improved sleep patterns and sleep architecture. We will approach this goal in three phases. Phase I (Development and Training): Develop an intervention manual for sleep promotion, the Sleep Enhancement Program (SEP), and train intensive care unit staff. Phase II (Validation and Safety): Implement the SEP and test for protocol fidelity and safety. Phase III (Efficacy): Conduct a pilot trial to determine efficacy of the SEP to improve sleep patterns and architecture in intensive care unit patients.

This proposal focuses on the impact of sleep promotion during recovery from acute illness or injury while receiving care in an intensive care unit environment. The University Medical Center is the only Level One Trauma Center in Southern Arizona, serving the citizens of Tucson and Pima county (approximately 1,000,000). Being the only Level One center in the entire region puts us in a singularly distinct position to promote the advancement of the care of the acutely ill and injured patient. If successful this project would be the first to demonstrate that sleep promotion is possible in the ICU and hospital setting. A positive result could potentially change the way care in the ICU is delivered, highlighting a focus on sleep promotion. Further studies could then be undertaken to evaluate the potential benefits of sleep promotion during recovery from illness and injury such as, decreased length of hospital stay, decreased complications, and improved survival

Arthur F. Gmitro, Ph.D. **University of Arizona**
Award Amount FY10: $125,000

Multi-Modality Imaging of Window Chambers

New medical imaging techniques are being developed to improve cancer diagnosis as well as to assist in the development and testing of new cancer treatments. Moreover, imaging methods promise to help with the implementation of treatment strategies tailored to an individual's disease. Imaging is also being used increasingly to monitor therapy to assess whether a treatment strategy is working at the earliest possible stage and to redirect that therapy in case the patient is not responding to the treatment. Although many of these imaging methods appear to be very promising and are currently being translated into the clinic, a major issue is proving or validating that they work effectively for their intended purpose. For example, measurement of the acidity in a tumor can provide important information on whether a particular cancer treatment will work or not. Imaging the acidity in a tumor is possible, but it is important to know just how accurately this can be done. Testing in laboratory animals can be done, but it is still difficult to show that one achieving accurate measurement because there is no proven way to measure the local acidity in a live animal and acidity changes rapidly when tissue is removed from a living system. The solution is to use a well controlled test system and multiple approaches to measurement of the same quantity so that results can be compared and accuracy assessed. This project is about development and demonstration of a window chamber testing system that will allow this type of comparison.

A primary goal of the work is to build a flexible platform system that will allow multiple types of imaging techniques to be used on the same tumor model. Specifically, the platform will allow optical microscopic imaging, magnetic resonance imaging (MRI) and nuclear imaging of the same tumor. This platform technology will be used to show that we can validate imaging measurements of three important biological properties: tumor pH (acidity); the permeability (leakiness) of vessels in a tumor; and the presence of particular molecular signatures known to be present on certain types of disease, such as breast cancer. We will compare the accuracy and precision of the measurements made by the different imaging methods (modalities). The fundamental hypothesis is that this unique multi-modality imaging capability will allow the validation of imaging methods that are being developed to improve cancer diagnosis, test new cancer treatments, and allow earlier assessment of treatment effectiveness in an individual patient. Ultimately, we believe this will lead to better and more cost-effective health care.

Leland Hu, M.D. **Mayo Clinic**

Award Amount FY10: $125,000

Clinical Applications of MR Perfusion to Characterize Histologic Heterogeneity in the Post-Treatment Glioma Bed: Developing Safe and Accurate Methods for Image-Guided Therapy and Diagnosis

Improving post-treatment diagnosis and management of high-grade glioma patients often relies on technical advancements in MR Imaging. Unfortunately, many novel technologies do not reach the routine clinical setting. MR perfusion has long been studied and offers the potential to solve common clinical problems by distinguishing tumor re-growth from non-tumor therapy-related inflammatory reactions based on differences in blood flow. However, this technique has historically been under-utilized in post-treatment tumor surveillance because of specific technical limitations, including lack of standardized methods and absent validation of quantitative measurements.

Our work to this point, supported by ABRC, has significantly improved test accuracy and measurement validation. Clinical radiologists can now use our MR Perfusion methods to routinely diagnose and localize subregions of tumor or non-tumor reactions with over 95 percent accuracy. The technique can potentially improve the standard of care for glioma patients; however, diagnostic information must be made routinely available to treating physicians, such as radiation oncologists and neurosurgeons, in order to realize the full clinical benefits.

The aims of this project will incorporate MR Perfusion information into several image-guided clinical applications that may lead to safer, more efficient, and more accurate diagnosis and treatment of glioma patients. We will use MR Perfusion maps to guide surgical biopsy of tumor and non-tumor regions to improve procedural accuracy and efficiency. We will also use these maps to more accurately guide focused re-radiation therapy with the intent of reducing toxic effects on adjacent normal brain and improving overall quality of life. We will also validate technical improvements in the MR Perfusion method that can evaluate current and future novel anti-cancer drug therapies. This MR Perfusion information can potentially identify which patients will best respond to treatment and help improve the efficiency of medical care.

Sean W. Limesand **University of Arizona**
Award Amount FY10: $124,993

Development of Multimeric Ligands for Specific Analysis of Beta Cell Mass and Activity

Dysfunction and loss of β-cells of the pancreas, and thereby loss of insulin secretion, is the ultimate cause of diabetes, a disease that is rapidly rising across all age groups. The ability to monitor changes in the number of β-cells and/or their function is critical to analyzing the developing disease state, but also for following the response to treatments whose goal is to retard β-cell loss. Imaging technologies have been applied to monitor β-cell mass, but have not been useful to date because all the methods tested are limited by an inability to completely discriminate the small number of β-cells from the large amount of other cell types within the imaging field. The products of our research are intended to overcome this problem.

We have proposed that imaging agents can be targeted specifically to pancreatic β-cells, and not other cell types, by identifying a pattern of surface proteins on β-cells and building molecule that bind only to that specific pattern. As an example, an antibody called K14D10 is known to bind tightly to β-cells, but also binds to cells in the liver, while the hormone GLP-1 binds b-cells as well, but also is found to bind cells in the intestine. Therefore, if we put an imaging probe onto either of these molecules, not only will the β-cells be targeted for imaging, but so too will the other cell types. This has been the primary problem for imaging, inability to adequately differentiate β-cells from other cell types. However, if a targeting molecule is made that has both K14D10 and GLP-1 domains, then only the β-cell will bind this tightly; we have proven this concept for detection of cancer cells independent of other “normal” cell types, and with this research we will attempt to extend this technology for use in the analysis of β-cell mass.

As a combination, the K14D10 antibody, GLP-1 and another receptor called the sulfonylurea receptor (SUR-1) have been identified as potentially unique to the β-cell. In the proposed work, we will design and synthesize what are termed “multivalent ligands” which will be made from the binding domains of three different molecules that bind to these three β-cell targets. These multivalent ligands will crosslind the combination of surface receptors on β-cells, but not tightly to cells that express only one of these receptors. Therefore we predict that these multivalent ligands will specifically identify β-cells. If successful, these ‘super’-ligands will allow for analysis of changes in β-cell mass that occur during the development and treatment of Diabetes, using standard clinically proven imaging technologies.

The research from this project will extend our studies *in vitro* to an *in vivo* model system (rats), to fully test the potential of this strategy for pre-clinical and ultimately clinical β-cell mass analysis.

Vinodh Narayanan **St. Joseph's Hospital and Medical Center**
Award Amount FY10: $125,000

Characterization of the MeCP2 A140V Mutant Mouse Model of Rett Syndrome / X-linked Mental Retardation

The pathogenesis of the neurological phenotype in Rett syndrome and related mental retardation syndromes remains unknown and continued study of animal models will improve our understanding. Although much has been learned about RTT through the study of existing mouse models, the model we have created (MeCP2 A140V mutation) has several advantages. First, it reproduces a recurring mis-sense mutation seen in humans. Second, it results in an X-linked mental retardation phenotype (rather than classical RTT). Third, the transmission in mice mimics the inheritance pattern in humans. We expect that by a careful analysis of the A140V mouse, we will better understand the important roles that MeCP2 plays in dendrite/synapse development and maintenance and in the pathogenesis of developmental brain disorders that result in mental retardation or autism.

In this research, our goal is to define the neurological phenotype of this mouse, and develop this into a good model for pre-clinical therapeutic trials. This characterization includes the following: motor coordination studies, behavioral studies, and studies of spatial learning and memory – as a function of age; correlation between deficits in neurological function, and fine structure of the brain (dendrite and spine development); and correlation between deficits in neurological function, and cellular defects in synaptic plasticity (electrophysiology).

Preliminary studies with the MeCP2 A140V mouse have already suggested that the male mutant mice develop motor coordination by around 4 months of age, and they have definite abnormalities of brain fine structure. These abnormalities need to be quantified so that we may use this mouse model in our search for novel compounds that might cure this disease.

Disorders such as Rett syndrome, Fragile X syndrome, and other X-linked mental retardation syndromes, account for a large fraction of disabled children all over the world, including the state of Arizona. Understanding how MeCP2 mutation leads to mental retardation may allow us to design better treatments for these disorders.

Kaushal Rege **Arizona State University**
Award Amount FY10: $50,000

Ablation of Advanced Prostate Cancer Disease using Targeted Non Viral Gene Delivery

The overall goal of this project is to identify novel biocompatible polymers for targeted prostate cancer gene therapy. Nucleic acids, including genes (plasmid DNA), hold tremendous promise in cancer therapy since they can encode for toxic proteins resulting in cancer cell ablation. Viral vectors have been traditionally employed in gene therapy due to their high transduction efficacies. However, concerns relating to safety, selectivity, and production costs have necessitated the discovery of non-viral gene transfer agents that possess high efficacies and biocompatibilities either by themselves or in combination with existing viral systems. Currently available non-viral delivery vectors do not match the efficiency of viral vectors and as a result, there is a pressing need for discovering efficient non-viral gene delivery vectors and non viral-viral hybrid systems as safer alternatives to virus-based delivery systems.

Our project is at the interface of molecular engineering, molecular and cellular biology, and cancer research, addresses two critical areas: bioengineering highly effective and safe vectors for gene delivery; and novel therapeutics for advanced (i.e. metastatic and drug resistant) prostate cancer disease.

The research is aligned with the strategic interests of the State of Arizona in the areas of cancer research, basic molecular and cellular sciences, and bioengineering. Based on the roadmap outlined in the 2006 Arizona's Bioscience Roadmap Progress Report, while cancer research is a broad competency in the state of Arizona, there is, at best, only moderate presence in research merging this with engineering and technology (bioengineering); this project is therefore well suited in two of the three signature development opportunities namely, molecular therapeutics and advanced medical technologies. Furthermore, the current research focuses on novel therapeutics for advanced prostate cancer disease. Nationally, and in the state of Arizona, prostate cancer is the most diagnosed cancer in men and the second leading cause of cancer death after skin cancer. In Arizona, 4,290 new cases and 500 deaths (greater than one individual / day) of prostate cancer were reported in 2006 by the American Cancer Society. Our focus on the identification of novel gene-based therapeutics, safer and efficient gene delivery vehicles, and combination gene therapies, addresses a critical need in prostate cancer research in the state of Arizona, and in the Phoenix metropolitan area in particular, by accelerating the identification of clinically relevant therapeutic strategies. It is anticipated that the current research will lay the foundation for further pre-clinical studies leading to successful federal funding in the future. This will have further significant positive impact on cancer therapeutics research in Arizona.

Adrienne C. Scheck, Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY10: $50,000

The Use of Ketones as an Adjuvant Therapy for Malignant Gliomas

This year, approximately 21,810 people will be diagnosed with a primary brain or spinal tumor in the US, and ~13,070 people will die of this disease. Approximately 750 of these cases will be from Arizona, and over 240 people will die of their disease this year. This figure is likely to worsen in Arizona, as the incidence of gliomas (the most common form of brain tumor) in people over the age of 65 has increased at a rate substantially higher than that of the general population. Furthermore, brain tumors are a leading cause of cancer death in children and young adults. New treatment modalities are of critical importance in this disease. Treatment currently includes surgery, radiation and chemotherapy; however, these tumors typically recur within a year and are often then resistant to further chemotherapy. Improvement in the survival of these patients requires novel approaches to treatment which can include the design of new therapies, or the identification of adjuvant therapies that enhance the efficacy of currently available therapies.

A hallmark of cancer is the unregulated growth of cells accompanied by changes in cellular metabolism that probably contributes to this phenomenon. Altered cellular metabolism has been shown in human malignant brain tumors, suggesting that treatments that alter cellular metabolism may be effective in the therapy of these tumors. To this end we propose to determine if altering cellular metabolism through the use of dietary intervention (ketogenic diet) can potentiate currently used therapies. The ketogenic diet is a high fat, low carbohydrate diet currently used for the treatment of refractory epilepsy in children. We and others have observed that the metabolic changes induced by a ketogenic diet, can prolong survival in a mouse model following intracranial brain tumor cell implantation. Furthermore, there is a case report in the literature suggesting that this diet may also be effective in people. Despite this, it is unlikely that clinical trials would be proposed in the absence of radiation and temozolomide (TMZ), the current standard of care for patients with malignant brain tumors. Our preliminary data suggests that in addition to slowing the growth of tumors, the ketogenic diet may, in fact, potentiate the effects of current therapies without an increase in side effects. This has led us to hypothesize that the use of ketogenic diet in addition to current standard therapies including chemotherapy and radiation therapy may prolong survival in patients with malignant brain tumors. The objective of the work our project is to definitively demonstrate the utility of the ketogenic diet when used in combination with standard therapies, thus opening the door for the design of clinical trials. We will also begin the studies necessary to understand the mechanism of action of this diet alone and in combination with temozolomide and/or radiation. This information will promote its use as an adjuvant therapy for the newer markers specific treatments.

Fu-Dong Shi, M.D., Ph.D. **St. Joseph's Hospital and Medical Center**
Award Amount FY10: $50,000

NK Cells Control Microglial During CNS Inflammation

Multiple sclerosis (MS) is an autoimmune condition wherein the body's defense attacks the central nervous system (CNS), particularly the brain and spinal cord, leading to demyelization. MS onset usually occurs in young adulthood and affects more women than men. About 7,000 Arizonans are affected by this dreadful disease. Without immune therapies, MS often progresses rapidly and imposes profound social and economic impacts. For several decades, studies on MS and other autoimmune diseases have focused on antigen-specific T-cells and B-cells. Unfortunately, the target antigens differ from patient to patient and the reactivation of autoreactive T-cells and B-cells correlate poorly with disease status, as measured by clinical and imaging parameters. Furthermore, the majority of the FDA approved MS therapies (e.g. IFNs), as well as therapies that are being evaluated in clinical trials (e.g. Tarsabri) act in an antigen-independent manner. Therefore, the question arises as to whether we are examining all the relevant cell populations (in this case NK cells) and compartments to probe the immune system to monitor disease course and therapies. Thus, completion of this project will establish theoretical and practical strategies for NK-cell-based therapy in MS and other neuroinflammatory disorders.

Natural killer (NK) cells are a type of cytotoxic lymphocyte that comprise a major component of the innate immune system and play a critical role in autoimmune disorders. Research has shown that the functions of NK cells are defective in patients with MS. Enrichment of NK cells can reduce the relapse rate and improve the symptoms of MS patients. However, the underlying mechanisms in which these NK cells affect MS are still not clear. The current protocol to expand NK cells is available for clinical use in anti-tumor therapy, but remains suboptimal. In the animal model representing human MS, experimental autoimmune encephalomyelitis (EAE), our lab has found that NK cell depletion leads to severe demyelization, CNS inflammation and neurological deficit, whereas NK cell expansion attenuated EAE. Moreover, we have demonstrated that NK cells reside in close proximity to microglia, the main form of active immune defense in the CNS and observed an inverse correlation between NK cells and microglia. Thus, one aim of this project is to test whether NK cells can control microglia to attenuate the development of EAE and elucidate the mechanism to halt the progression of this disease. Another goal of this proposal is to identify the specific genes and/or receptors that govern the inhibitory effects of NK cells on microglial cells, and to optimize the protocol to expand NK cells for clinical application for patient infusion.

Colin L. Willis, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Hypoxia Induces Regional Loss of Blood-Brain Barrier Integrity Through Activated Protein Kinase C Signaling Mechanism

Stroke is a major cause of death, second only to heart disease and causes 9 percent of all deaths worldwide. There are two types of stroke: those caused by blood clots in the brain and those that occur when blood vessels burst. In both cases, the brain is starved of oxygen, damaging or killing cells. Sufferers are often left with difficulty talking, walking and performing other basic tasks. Age is one of the most significant stroke risk factors. 95 percent of strokes occur in people age 45 and older. During stroke, and subsequent reperfusion, studies have shown that the integrity of the vasculature within the brain is compromised allowing potentially harmful substances to leave the blood and enter the brain. Why the integrity of the vasculature is lost, is presently unknown. The aim of this project is to determine the role protein kinase-C plays in modifying the integrity of the vasculature during periods of oxygen deprivation (hypoxia) and subsequent re-oxygenation (post-hypoxic re-oxygenation) and explain why certain regions of the brain are more vulnerable to reduced oxygen than others. Our hypothesis is that: functional changes at the blood brain barrier occur due to alterations in the endothelial cell tight junction proteins as a result of intracellular signaling mechanisms/mediators stimulated by hypoxia and/or re-oxygenation HR insult.

The research in our project is critical to biomedical issues facing Arizona, now and in the future. The Arizona population is increasing in age. The proportion of Arizona's population classified as elderly is expected to increase from 13.3 percent in 1995 to 21.3 percent in 2025. The Report of the Eighty-second Arizona Town Hall on the subject "Health Care options: Healthy Aging-Later Life Decisions" states "Some of the toughest questions involving health care in Arizona in the next twenty years relate to how we as individuals, as communities and as a state can deal with the health care challenges presented by the approaching surge in Arizona's elderly population". Age is one of the most significant stroke risk factors. The risk of stroke doubles with each decade after the age of 55. Rehabilitation is crucial for people who have suffered stroke leaving them without the powers of movement, speech and thought they had previously. Studies aimed at reducing the vascular and subsequent neuronal damage from stroke will be of great benefit to Arizona and the USA.