ARIZONA BIOMEDICAL RESEARCH COMMISSION ANNUAL REPORT 2009–2010

Janice K. Brewer, Governor

David Landrith, M.P.A., Chairman

COMMISSION MEMBERS

General Public
David Landrith, M.P.A.
Gregorio M. Garcia, J.D.
Kenneth Lewis, M.P.A.

Medical Community
Mitchell Shub, M.D.
Robert Cannell, M.D.

Scientific Community
Thomas "Lon" Owen, Ph.D.
Joan Rankin Shapiro, M.D., Ph.D.
Ranu Jung, Ph.D.

Staff
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Message from the Chairman

The Arizona Biomedical Research Commission is not immune from the same economic forces facing the nation. As detailed in this report, Commission revenue continues a decline first experienced two years ago. The Commission has taken steps to preserve its mission of fostering and supporting Arizona researchers and clinicians in making Arizona a world class biomedical leader.

The total dollar value of the Commission investment in research reflects the amount of available revenue. The number of research contracts has declined from a high of 73 in 2009 to 56 in both 2010 and 2011. An emphasis is placed on supporting Category I or individual investigator awards. By supporting researchers new to the field, we hope to encourage the development of researchers armed with exploratory data to seek out and receive additional funding from other sources, in particular the National Institutes of Health.

The Commission's interest in translational research continues. Two projects stand out. The Commission has developed a web based biospecimen repository. Participants in the virtual repository include St. Joseph's Hospital, Phoenix Children's Hospital, Maricopa Integrated Health System, and Banner Sun Health Research Institute. The project has gathered attention from the National Cancer Institute Bioinformatics Grid as well as others around the country. The second project begun in FY2010 and coming on line in FY2011 is the Arizona Cord Blood Bank. There is a great need for public cord blood banking especially for Arizona ethnic minorities. Cord blood provides pluripotent non-embryonic stem cells for therapeutic transplant. In addition, the non-transplant quality cells are highly valuable for research. The Commission has created a regional bank in cooperation with the University of Colorado Clinimmune Labs. Cords collected at St. Joseph's Hospital, Baptist Hospital, Chandler Regional Hospital, and Maricopa Integrated Health System will be transported to Denver, Colorado for storage. The cords will then be available for transplant or research. The Health Resource and Service Administration is excited by the regional approach and is providing additional financial support. These projects are just two examples of the innovative ways the Commission and the state of Arizona are addressing the challenges of moving biomedical science from the laboratory to the clinic and patients.

Opportunities abound. The Commission has encouraged the research community to bring forward new ideas. Unfortunately, the lack of revenue has resulted in many intriguing ideas and proven methods going unfunded. We all hope that the future will be brighter. In the meantime, the Commission continues to support its basic research program and its translational research program.

The citizens of Arizona are indeed blessed to have the services of the members of the Commission. I consider it a privilege to serve with the three research scientists, two medical doctors and the other two members of the general public. They have a dedication to do the time consuming analysis of the proposed research, applying scientific knowledge and common sense, in order to make the difficult decisions concerning the awarding of successful projects.

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

The Commission Members

Nine Commissioners guide the work of the Arizona Biomedical Research Commission. They are appointed by the Governor and confirmed by the Senate. The Commission is divided into three communities—General Public, Medical, and Scientific Research. Each community is represented by three Commissioners appointed for three-year terms. Generally, the terms of three members expire each year; Commissioners may be reappointed. The Chairman and Commissioners who served during 2009-2010 are presented below.

Medical Community Commissioners:

Dr. Robert Cannell, M.D.

Medical Director

Yuma Regional Medical Center School Health Program

Dr. Robert Cannell is a pediatrician who has lived in Yuma, Arizona since 1969. He came to Yuma as a Navy General Medical Officer serving at the Marine Corps Air Station Dispensary. After completing his pediatric residency in Tucson, he returned to Yuma in 1972 and started Yuma Pediatrics, Ltd, a general pediatric group practice which is still caring for patients.

Dr. Cannell became medical director of the Yuma Regional Medical Center School Health Program in 1996. He also spent several years as Medical Director of Yuma Children's Rehabilitative Services. Dr. Cannell took a break from the School Health Program to serve in the Arizona State House of Representative and State Senate from 2000 to 2006. While there he served as co-chairman of the Children's Caucus, a group of state legislators advocating for children during legislative and budget negotiations. He served on the Health Committees as the ranking minority member of the House Health Committee. He was chosen to be a member of a group of Arizonans who accompanied Governor Jane Hull to Washington, D.C. to recruit the Translational Genomics Research Institute to Arizona.

Dr. Cannell continues to serve as medical director of the Yuma Regional Medical Center School Health Program which provides medical care to elementary school children and their younger siblings. Care is provided at three elementary schools in Yuma and San Luis and through a mobile van serving three elementary schools in East Yuma County. Dr. Cannell and his wife, Leslie, have been married for 46 years, live in the Yuma Foothills, and have three married children and eight grandchildren.
Dr. Cannell was appointed by Governor Jan Brewer. His term expires in 2011.

Dr. Mitchell Shub, M.D.

Medical Director of Research

Phoenix Children's Hospital

Commissioner Mitchell Shub is a Pediatric Gastroenterologist and received his M.D. from the University of Vermont in 1976. He completed a residency in Pediatrics at Duke University Medical Center in 1979 and a fellowship in Pediatric Gastroenterology at Massachusetts General Hospital and Harvard Medical School in 1982. After serving on the faculty at the University of North Carolina, Chapel Hill, he joined the full time faculty at Phoenix Children's Hospital (PCH) in 1985. He served as Co-director of the Pediatric Residency Program from 1986 to1999 and as Division Chief of Gastroenterology from 1992 to 2003. In 2004 he was elected President of the Medical Staff and served a 2-year term. He was appointed the first Director of Research at PCH in 2008. Dr. Shub is Professor of Clinical Pediatrics and Associate Head, Department of Pediatrics for the University of Arizona College of Medicine, Phoenix Campus. He has been actively engaged in research throughout his career and recently was part of a team that identified the gene mutation for a rare digestive disorder, microvillous inclusion disease. On a national level, Dr. Shub has been appointed to various leadership positions in the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. He is also the Chairman of the Medical Advisory Committee for the Southwest Chapter of the Crohn and Colitis Foundation of America and was honored with the Chapter's "Physician of the Year Award." Commissioner Shub was appointed to the Commission by Governor Brewer in 2009. His term expires in 2012.

Scientific Community Commissioners:

T. Lon Owen, Ph.D.

Professor of Medical Anatomy and Physiology

Northern Arizona University

Commissioner Owen received his B.A. in Zoology from the University of California, a Master's Degree in Biology from California State University at Sacramento, and his Ph.D. in Physiology from U.C. Davis in 1972. He was an NIH Postdoctoral Fellow at Michigan State University and Visiting Associate Professor in the Pharmacology Department of the University Of Arizona College Of Medicine. He is a member of the American Physiological Society and has chaired the Research Committees of the American Heart Association at both the Arizona Affiliate and Southwestern Regional levels. His publications are in the areas of cardiovascular, aging, and environmental physiology. He has taught physiology and pathology at Northern Arizona University since 1974. Commissioner Owen was appointed to the Commission by Governor Hull in 1998 and 2001. His term expired in 2004, and he was reappointed by Governor Brewer for a term set to expire in 2012.

Joan Shapiro, M.D. Ph.D.

Human Geneticist & Neuro-Oncologist

Associate Dean for Research

University of Arizona College of Medicine Phoenix

Commissioner Shapiro is a human geneticist receiving her M.D. and Ph.D. from Cornell University Medical College in 1979. Her initial research was in human birth defects at Rockefeller University. She began her cancer research career at Memorial Sloan-Kettering Cancer Center, New York where she resided for twelve years. In September 1989, she relocated to the Barrow Neurological Institute (BNI) of St. Joseph's Hospital and Medical Center, Phoenix, Arizona as the Director of Neuro-Oncology Research. Her research involved the characterization of genetic abnormalities associated with central

nervous system malignancies. Since 1979 her grant awards have totaled more than fourteen million dollars. She is among an elite group of scientists that have received National Institutes of Health funding for more than 26 years on a single grant application. In 2001, Dr. Shapiro retired from the laboratory and assumed the role of V.P. of Clinical and Translational Research at St. Joseph's Hospital and Medical Center until 2010 when she joined the University of Arizona College of Medicine Phoenix as the Associate Dean of Research. She is the past president of the national organization Women in Cancer Research. Dr. Shapiro has also retained a strong commitment to community education. She has developed and continues to teach numerous school enrichment programs. In conjunction with the American Academy of Neurology, she conducted K-12th grade neuroscience enrichment workshops for physicians and scientists. She is the past Chairperson of the National Neuroscience Prize for high school students. In November of 2007 she received the Life Time Achievement Awards from the Society of Neuro-Oncology for her contributions to the field of neuro-oncology. In February 2008, she was awarded the YWCA award for Health and Science Leadership. In 2009 she received the Hon Kachina Volunteer award and the John Theobald Award from the Arizona Alzheimer's Consortium. Commissioner Shapiro was appointed by Governor Napolitano. Her term expired in 2010.

Ranu Jung, Ph.D.

Professor Bioengineering and Electrical Engineering

Arizona State University

Ranu Jung is Co-Director of the Center for Adaptive Neural Systems and Professor of Bioengineering and Electrical Engineering at Arizona State University. She received her B.Tech with Distinction in Electronics and Communication Engineering from the National Institute of Technology, Warangal, India and her M.S. and Ph.D. degrees in the field of Biomedical Engineering from Case Western Reserve University. Ranu's honors include a National Research Service Award from the National Institutes of Health, the 2002 Science and Engineering Award, and the Governor's Certificate of Recognition Commonwealth of Kentucky. She is a Senior Member IEEE, the Society of Women Engineers, and past-president of the Organization for Computational Neurosciences. She has served on scientific review panels for the National Science Foundation, the National Institutes of Health, and advisory committees for international universities as well as associate editor for several professional journals. Her research includes projects focused on understanding neuromotor organization after spinal neurotrauma, developing biomimetic and biohybrid living-hardware systems for sensorimotor control, and exploring the use of biohybrid neurotechnology for promoting neuroplasticity. With a two decade record of competitive federal funding, she has been a leader in establishing academic-clinical-industrial partnerships. She is actively engaged in the development of neurotechnology that is inspired by biology, is adaptive, and could be used to promote adaptation in the nervous system to overcome neurological disability or trauma. Commissioner Jung was appointed by Governor Brewer. Her term expires in 2011.

General Public Commissioners:

David Landrith, M.P.A.

Vice President for Policy and Political Affairs

Arizona Medical Association

Commissioner Landrith received his undergraduate degree in philosophy and history from Arizona State University. He received a Masters of Public Administration from Harvard University John F. Kennedy School of Government. He was a Dougherty Foundation Fellow. Commissioner Landrith is co-chairman of the ASU Dean's Advisory Council, a member of the Arizona Town Hall Board of Directors, member of the St. Vincent De Paul Free Medical and Dental Clinic Endowment Committee, Director of the Arizona Bioethics Network, and past chairman and executive secretary of the Arizona Council of Governments Directors' Association. He has received the Partnership Award from the Arizona Chapter of the American Academy of Pediatrics and the Presidential Award for the Arizona State Association of Physician's Assistants. Commissioner Landrith was appointed by Governor Napolitano in 2004. His term expired in 2010.

Gregorio Garcia, Esq.

Attorney

Polsinelli Shughart P.C.

Commissioner Garcia received his undergraduate and graduate degrees from Arizona State University. He holds a Juris Doctorate and Master of Business Administration. He is currently pursuing a Master of Laws (LL.M.) in Biotechnology and Genomics. Commissioner Garcia is an attorney and practices with the firm of Shughart, Thomson & Kilroy, P.C. He sits on the board of directors for Arizona's largest legal aid law firm, Community Legal Services, and has held other leadership positions within the State Bar of Arizona and other legal organizations. Commissioner Garcia was appointed by Governor Napolitano in 2006 and reappointed by Governor Brewer. His term expires in May 2012.

Kenneth Lewis, M.P.A.

Principal Planning Analyst

Salt River Project

Commissioner Lewis received his undergraduate degree in Industrial Technology from East Texas State University and a Masters of Public Administration from the University of Nevada, Reno. Commissioner Lewis' first career was in fire service. He worked as a firefighter, paramedic, and hazardous materials technician. He rose through the ranks to serve as the Fire Chief in Pinewood/Munds Park, Arizona and Tahoe City, California. He is past president of the Arizona Fire Chief's Association.
Commissioner Lewis now serves as a Principal Planning Analyst in the Business Continuity and Emergency Management department for Salt River Project. He was appointed by Governor Brewer and his term expires April 2011.

Commission Staff:

Dawn C. Schroeder, D.D.S., MA Executive Director
James Matthews, M.P.A., HR-CP Deputy Director
Daniel Powell, Program Specialist II
Ismene Quintanilla, Fiscal Service Specialist I
Michelle Anderson, Administrative Assistant

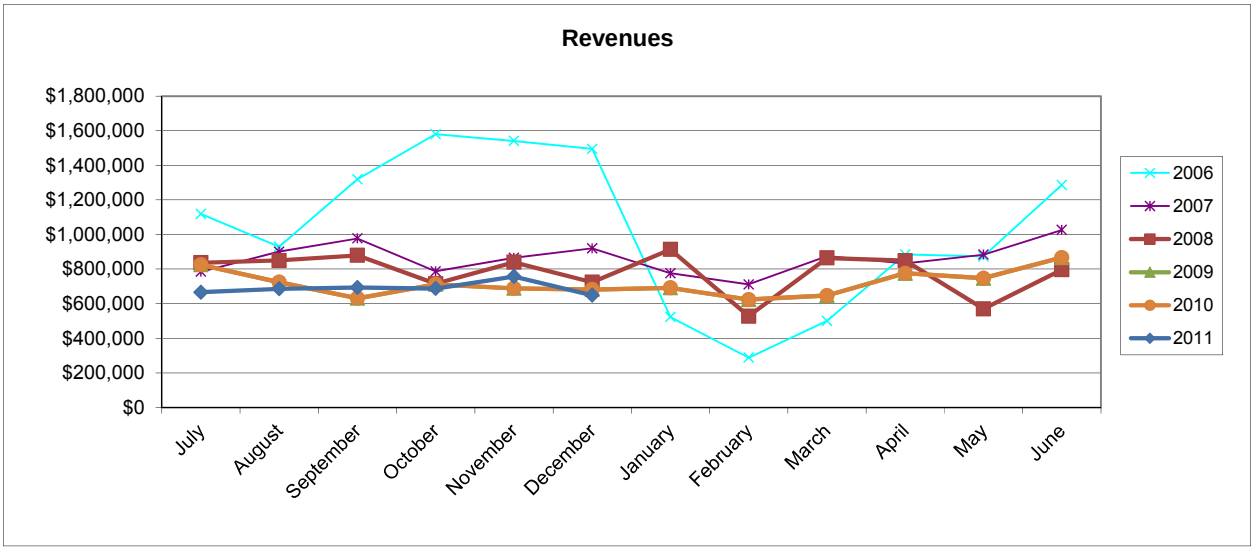
Summary of 2009–2010 Commission Activities

In the fiscal year 2009–2010, Arizona biomedical researchers received more than $3,956,000 in research contracts administered by the Commission. In the FY2010 request for proposals and awards cycle 150 project proposals were received and twelve new contracts for approximately $1.2 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. The number of projects and funding amounts are a sharp decline from previous years reflecting the impact of the economic recession and declining Commission revenues.

Section headings in this report list the projects supported by the Commission basic research program. Projects are listed according to 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 140 scientific publications, abstracts, and presentations arising out of the research by 27 different projects are also listed. Section D provides information on new contracts awarded beginning July 1, 2010 (FY2011).

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 2010 was $2.4 million.

RFP Review Process and Selection for Award

In response to the RFP, the Commission received 150 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 continued to experience some difficulty in obtaining timely reviews. In the spring of 2009 the Commission evaluated all proposals and selected 11 for funding.

ABRC Projects Submitted/AwardedFY2010

Institution	Submitted	Accepted	$ Amount Awarded	Percent of Total $
ASU	23	1	50,000	4
Mayo	3	2	355,000	30
NAU	1	1	103,000	9
St. Josephs	26	3	225,000	17
UA	79	5	475,000	40
All Others	18	0		
Total	150	12	1,208,000	100

During 2009–2010 the ABRC managed a total of 84 translational and biomedical research projects representing eleven research institutions.

ABRC Total New and Continuing Project Contracts FY2010

Institution	Projects	% of Total Awarded
Arizona State University	13	16
St Joseph/Barrow	14	17
Northern Arizona University	3	4
University of Arizona	47	56
Mayo Clinic Scottsdale	2	2
Banner Health System	0	0
Maricopa Integrated Health	0	0
Phoenix Children's Hospital	0	0
Sun Health Research Institute	2	2
TGen	2	2
Southern Arizona VA	1	1
Total	84	100

FY2011 Project Awards

In June of 2010 the Commission awarded 21 new research contracts for a total of approximately $2.0 million from all sources. The contracts were effective on July 1, 2010. Summaries of the projects are contained in Section D. Progress on these projects will be reported in the next Commission Annual Report.

ABRC Total New and Continuing Project Contracts FY2011

Institution	Number of Projects	Percent Awarded
Arizona Department of Health Services	3	5
Arizona State University	10	18
Banner Health System	1	2
Mayo Clinic -Scottsdale	2	4
Northern Arizona University	1	2
Phoenix Children's Hospital	3	5
Southern Arizona Veterans Affairs	1	2
St. Joseph's Hospital Barrow's Neurological Institute	10	18
University of Arizona	25	44
Total	**56**	**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 eighteen 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 five workshops on Compliance Challenges for Clinical Research Sites. The workshops were conducted both in conference style and as webinars.

Arizona Biospecimen Consortium and Arizona Biospecimen Locator

The Commission sponsored virtual biospecimen repository project continued to develop during 2010. Consortium members St. Joseph's Hospital, Phoenix Children's Hospital, Maricopa Integrated Health System, and Banner Sun Health Research Institute resolved issues related to system features as well as governing principles. St. Joseph's and Phoenix Children's entered into

agreements with the ABRC to enable them to establish the necessary infrastructure to support their participation in the Biospecimen Locator. Maricopa will also receive support in early 2011. The system is operational with limited data sets. Full operation of the web based virtual tissue repository is expected in early 2011. Commission representatives made presentations about the projects at the National Cancer Institute and at the annual Pharma iQ biospecimen banking conference. The Arizona Biospecimen Consortium and Locator are unique in the United States and worldwide.

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 2009–2010, 734 full-time and part-time jobs were supported as a result of Commission sponsorship. An additional 284 jobs were supported in full or in part at TGen.

Arizona Specific Populations and Needs Projects

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

Researcher	Institution	Project	Type
Anderson	ADHS	Understanding the Risk Factors for Valley Fever to Improve Prevention, Diagnosis, Reporting and Treatment	Infectious Disease
Goldman	SAVA	Seeding Fibroblast Patch for Chronic Heart Failure	Cardiovascular
Helms-Tillery	ASU	Role of the Basal Ganglia in Learning to Control Neuroprosthetics	Trauma/Bioengineering
Lewis	ITCA	Promoting Tribal Community Participation in Biomedical Research	Health Promotion and Disease Prevention
Schroeder	UA	Theranostic Development for the Treatment of Metastatic Breast Cancer	Cancer
Waddell	ADHS	Development of Antiviral Susceptibility Test Methods for the 2009 Pandemic and Seasonal Influenza Viruses for State and Local Public Health Interventions	Health Promotion, Disease Prevention, and Infectious Disease
Sparks	BSHRI	CSF Copper and Cognitive Performance	Neuroscience

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. The research and clinical work of TGen is focused on discovering the underlying causes of disease progression and improving the lives of those afflicted with disease.

Some TGen activities include:

- TGen is a "Center of Excellence" with Affymetrix, Agilent, and Life Technologies providing high throughput genomic sequencing. The long-term hope is that doctors will leverage genomic data to inform decisions about patient care.
- TGen and University of California Berkeley researchers identified a gene variant that carries nearly twice the risk of developing a common type of blood cancer, follicular lymphoma.
- TGen Clinical Research Services have demonstrated a new potential therapy that appears to shrink basil cell carcinoma tumors. Basil cell carcinoma is the most common cancer in the United States, and Arizona has one of the highest incidence rates in the world.
- TGen as part of a national consortium conducted the largest genome-wide association study in Alzheimer's disease to date, identifying two new genetic variants and confirming two others.
- TGen scientists identified five genetic biomarkers that could lead to improved treatments for patients with diabetes.

TGen researchers:

- Patient participation in clinical trials expanded to 125 visits per month, 35 to 45 new patients per month, and 400 to 600 patient samples collected per month.
- TGen researchers submitted 149 grant proposals in FY2010 totaling $160,926,066. TGen was awarded 15 grants totaling $9,256,581. An additional 64 grant applications are either in review or pending. $29,844,531 was received from previous fiscal year grants bringing the awarded total for FY2010 to $39,101,112.
- The TGen grant award success rate is 26 percent nearly six percent higher than the overall national average (National Institutes of Health success rate).

Some TGen research projects:

- A two year National Institutes of Health (NIH) grant to TGen North in Flagstaff for genomics-based diagnostics of *Coccidioides* Valley Fever.
- A two year grant from the Melanoma Research Alliance to identify novel melanoma risk genes.
- A five year NIH grant for a genome-wide association study of radiation exposure and bilateral breast cancer.
- A two year NIH grant to conduct follow-up studies about genetically determined risk factors for hip fractures.

- A two year NIH grant to conduct a genome-wide association study to help identify the genetic origins of arthritis of the knee.
- A three year grant from the American Association for Cancer Research to develop revolutionary treatments for pancreatic cancer.

TGen enterprise and collaborative efforts:

- 26 invention disclosures were filed in FY2010. (Disclosure is the first step toward protecting intellectual property via the patent process.)
- 87 confidential disclosure agreements were signed in FY2010. (Confidential disclosure agreements are one measure of collaboration between TGen and the research community.)
- 102 material transfer agreements between TGen researchers and other collaborators were signed in FY2010.
- TGen entered into 85 research collaborations including agreements to further research into brain cancer, melanoma, Alzheimer's disease, and autism.
- TGen signed 18 consulting agreements, 69 professional services agreements, and 9 commercialization licenses.

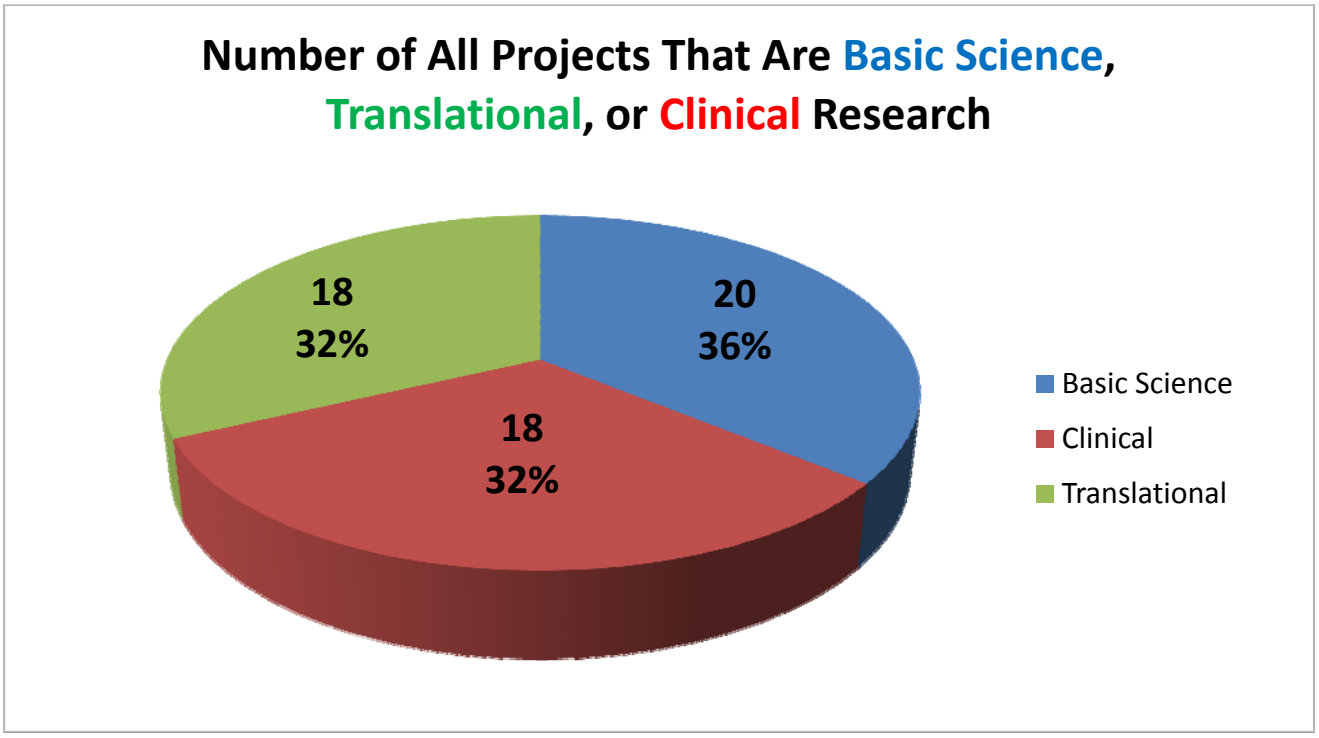
TGen job creation:

- There are 284 full-time TGen employees with 83 percent holding a college degree.
- 36 new full-time equivalent positions were created in FY2010 with salaries and benefits totaling approximately $2,550,475.
- Salaries for temporary positions totaled $160,000 and student salaries were just over $390,000, bringing the overall total for all new FY2010 TGen employees to $3,100,475.

TGen education and outreach:

- 67 bioscience students participated in scientific and administrative internships at TGen.
- 16 of the internships went to outstanding high school students.
- 10 of the internships went to graduate medical school students.
- New in FY2010 was a cooperative internship program between TGen and the Phoenix Bioscience High School placing students in a research lab environment.
- TGen continued its summer genomics workshops for teachers program in collaboration with Northern Arizona University. The workshops are designed to enhance science teaching in grades 5, 7, and 9.
- TGen websites saw more than 1.2 million page views in FY2010.

Types of ABRC Supported Projects in FY2011



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

Setsuko Chambers, M.D. **University of Arizona**
Award Amount FY10: $50,000

Regulation of c-fms Proto Oncogene Related Breast Cancer Risk

Breast cancer, a common malignancy in women in this country, often spreads beyond the breast. Patients with a cancer that has invaded normal breast tissue and has spread to other organs have only at 25 percent chance of surviving 10 years. In Arizona, the incident rate of breast cancer is second only to prostate cancer; however, the mortality rate is higher. At the Arizona Cancer Center, breast cancer is the most common (non skin) cancer seen. Our research has discovered that silencing 2 proteins, HuR and/or vigilin, results in decreased invasiveness and motility of human breast cancer cells. Further, we have discovered that effecting change in these proteins has a greater impact on cancer behavior than simply targeting c-fms, a gene that allows cancer spread, directly. We are now applying and expanding these findings specifically to metastasis to the bone, a condition affecting over 7 percent of patients with breast cancer spread.

Abstracts

Lamb T, Woo HH, Baker T, Chambers SK. The Effects of c-fms 3'UTR Binding Proteins HuR and Vigilin on Cellular Motility and Invasion in a Breast Cancer Cell Line. **Fourth International Meeting on Epithelial-mesenchymal Transition**, Tucson, Arizona. September 2009.

Lamb, T, Woo HH, Baker T, Chambers SK. The Effects of c-fms 3'UTR Binding Proteins HuR and Vigilin on Cellular Motility and Invasion in a Breast Cancer Cell Line. **Arizona Health Sciences Poster Forum.** Tucson, Arizona. October 2009.

Presentation

RNA Binding Proteins in Regulation of c-fms Proto-Oncogene Related Breast Cancer Metastasis. **Society for Gynecologic Investigation.** Orlando, Florida. March 2010.

Harinder Garewal, Ph.D. **University of Arizona**
Award Amount FY10: $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. A high fat diet doubles the level of bile acids (which help digest fat) to be deposited in the digestive tract. We found such increased levels of bile acids cause chromosome abnormalities in cells in culture. Adding this “double” level of a bile acid to a mouse diet for 10 months caused 10 out of 18 mice to have colon cancers, but also adding chlorogenic acid (comparable to the amount in three cups of coffee a day for humans) prevented the majority of these colon cancers in the bile acid-supplemented mice. We also found that tissues surrounding human colon cancers (fields of cancerization) were frequently deficient in one or more of 3 DNA repair proteins, allowing DNA damages to be converted to mutations, and thus these deficiencies are likely early steps in progression to cancer.

Pawel Kiela, DVM, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Modulation of Neutrophil Function by Curcumin in Inflammatory Bowel Disease

Neutrophils (PMN) are the first cells recruited at the site of inflammation. Although they are beneficial in the initial stages of inflammation, in inflammatory bowel disease (IBD) their perpetual infiltration within the gut wall leads to further damage of the mucosal lining and exacerbates the inflammation. Curcumin (diferulolymethane) displays a protective role in mouse models of IBD and in human ulcerative colitis, a phenomenon consistently accompanied by a reduced mucosal neutrophil infiltration. We have demonstrated that curcumin interferes with colonic inflammation partly through inhibition of the chemokine expression and through direct inhibition of neutrophil chemotaxis and chemokinesis (cell motility) (Larmonier et al. Modulation of Neutrophil Motility by Curcumin: Implications for Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2010, Jul 13. [Epub ahead of print]). Preliminary data generated with the ABRC funding were also instrumental in securing additional extramural funding to continue the project (NIH R01 grant for $1.3 million).

George Pettit, Ph.D. **Arizona State University**
Award Amount FY10: $150,000

Molecular Targeting of Prostate Cancer Vasculature: New Approach to Treatment

The vitally important challenge of discovering new drugs to improve the treatment of prostate cancer continues where 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 (2005) statistics indicate some 240,000 new cases diagnosed and 30,000 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 or radiotherapy requires the disease to be confined to the prostate. Metastatic prostate cancer is usually incurable and most men diagnosed with metastatic disease die over a period of months to years. To further complicate the treatment problem, prostate cancer is not a homogenous disease at the molecular level. In addition, no treatment regimen has been proved to provide a substantial improvement in survival time and many are quite detrimental to the quality of life. 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.

Publications

Prokopiou EM, Cooper A, Pettit GR, Bibby MC, Shnyder SD. Potentiation of the Activity of Cisplatin in a Human Colon Tumor Xenograft Model by Auristatin PYE, a Structural Modification of Dolastatin 10. **Mol. Med. Rep.** 3:309-13. 2010.

Pettit GR, Ducki S, Eastham A, Melody N. Antineoplastic Agents 454: Synthesis of the Strong Cancer Cell Growth Inhibitor *trans*-Dihydronarciclasine and 7-Deoxy-*trans*-dihydronarciclasine. **J. Nat. Prod.** 72:1279-82. 2009.

Pettit GR, Minardi MD, Hogan F, Price PM. An Efficient Synthetic Strategy for Obtaining 4-Methoxy Carbon Isotope Labeled Combretastatin A-4 Phosphate and Other Z-Combretastatins. **J. Nat. Prod.** 73:399-403. 2010.

Pettit GR, Meng Y, Pettit RK, Herald DL, Cichacz SA, Doubek DL, Richert L. Antineoplastic Agents 556: Isolation and Structure of Coprinastatin 1 from *Coprinus cinereus*. **J. Nat. Prod.** 73: 388-92. 2010.

Pettit GR, Ye Q, Herald DL, Hogan F, Pettit RK. Antineoplastic Agents 573: Isolation and Structure of Papilistatin from the Papilionid Butterfly *Byasa polyeuctas Termessa*. **J. Nat. Prod.** 73:164-6. 2010.

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Pettit GR. Dolastatins. In: **Marine Anticancer Compounds in the Era of Targeted Therapies.** Chabner B, Cores-Funes (Eds.), Permanyer SL, Barcelona,19-49. 2009.

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Pettit GR, Thornhill A, Melody N, Knight JC. Antineoplastic Agents 578: Synthesis of Stilstatins 1 and 2 and their Water-soluble Prodrugs. **J. Nat. Prod.** 72:380-8. 2009.

Donato Romagnolo, Ph.D. **University of Arizona**
Award Amount FY10: $49,445

Epigenetics of Breast Cancer 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 and develop dietary strategies. The BRCA-1 protein is involved in repair of DNA damage, and loss of BRCA-1 confers a high risk of developing breast cancer. The primary objective of this project is to understand how the BRCA-1 gene is silenced in breast tissue. During the period covered by this progress report, we have investigated the mechanisms responsible for silencing of the BRCA-1 gene in breast epithelial cells. We also investigated how food compounds normally present in the human diet may be useful in preventing loss of BRCA-1 expression. The progress made through this project will help in understanding how to prevent the onset of this malignancy, which in 2010 afflicted 39,500 women in the State of Arizona (source: American Cancer Society, 2010).

Publications

Papoutsis AJ, Lamore SD, Wondrak GT, Selmin OI, Romagnolo DF. Epigentic Regulation of BRCA 1 by AhR Agonists and Preventative Effects of Resveratrol in Breast Cancer Cells. **J Nutr.**140(9):1607-14. 2010.

Book Chapter

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Romagnolo DF, Degner SC, Selmin O. Aryl Hydrocarbon Receptor-mediated Carcinogenesis and Modulation by Dietary Xenobiotic and Natural Ligands. In: **Bioactive Food Components and Cancer.** Milner and Romagnolo (Ed.). Humanna Press/Springer. 2010.

Abstract

Papoutsis AJ, Lamore SD, Wondrak GT, Selmin IO, Romagnolo DF. Epigenetic Regulation of BRCA-1 by AhR Agonists and Preventative Effects of Resveratrol in Breast Cancer Cells. **Annual Meetings of FASEB/ASN**. Anaheim, California. 2010.

Ornella Selmin, Ph.D. **University of Arizona**
Award Amount FY10: $44,998

Folate as a Nutrient Competitor Against Environmental Exposure to Trichloroethylene

During the past year we documented that low, environmentally significant doses of TCE exposure (10 parts per billion) affect the expression and function of proteins essential for physiological cardiac function in embryos. Folic acid supplementation in the maternal diet was not able to counteract the effects of low dose TCE exposure on gene expression; therefore, analysis of embryonic phenotypic changes due to maternal TCE exposure in the presence of folate supplementation was not pursued. However, analysis of DNA methylation alterations induced by TCE exposure on the promoter region of the calcium pump Serca2a led to the finding that TCE may exert its cardiotoxicity by inducing epigenetic changes (which are reversible) on the regulatory regions of target genes. This result is important because it opens a new field of research looking at molecules involved in chromatin remodeling, which may be used to counteract TCE effects on both embryos and adult organisms.

Publications

Makawana O, King NM, Ahles L, Selmin O, Granzier HL, Runyan RB. Exposure to Low-dose Trichloroethylene Alters Shear Stress Gene Expression and Function in the Developing Chick Heart. **Cardiovasc Toxicol**. 10:100-7. 2010.

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Larry Sparks, Ph.D. **Sun Health Research Institute**
Award Amount FY10: $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. 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 a gradual reduction of copper levels in the cerebro-spinal fluid (CSF) as an individual makes the transition 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 in this three-year longitudinal investigation.

Danzhou Yang, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Novel AP-1 Inhibition of a 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. In our last funding period, we found that the AP-1 inhibitory concentration of XR5944 in the UVB-treated HCL14 cells was significantly increased from the previous number. In addition, we found that the exact 100 percent inhibitory concentration of XR5944 for UVB induced transcriptional AP-1 activity could not be accurately determined in mouse keratinocytes cells. In this funding period, XR5944 was shown to have to clear induction of AP-1 activity at higher concentrations. Rather than purely inhibiting the AP-1 activity, XR5944 also appears to induce the AP-1 activity at lower dose levels. While the effect of XR5944 on the AP-1 transcriptional activity was shown to be related with the DNA sequence of the AP-1 binding site, this complicated mechanism of action of XR5944 on the AP-1 activity suggests that using XR5944 as a drug prototype to inhibit AP-activity may need further consideration and examination.

Daniela Zarnescu, Ph.D. **University of Arizona**
Award Amount FY10: $49,999

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

Fragile X Syndrome (FXS) is the most common form of inherited mental retardation and effects 250,000 males worldwide. The disease is caused by the loss of function for the RNA-binding protein, FMRP. Using the genetically tractable fruit fly as a model, we discovered that FMRP is required in neural stem cells before neurons are born. Studies of mutant brains revealed that FMRP controls the timing of neural stem cell proliferation and the overall number of neurons in the developing brain. Our results indicate that loss of FMRP in neutral stem cells leads to the formation of approximately16-20 percent more neurons. With similar size increases in the brains of autistic children, our results could provide an explanation for the autistic component of FXS. Currently, we are using molecular and genetic approaches to test the possibility that FMRP controls neural stem cell proliferation by controlling the expression of cyclin E, a critical component of the cell cycle machinery. Our work is the first demonstration of FMRP being required at this early stage in brain development. We propose that the supranumerary neurons produced in the absence of FMRP contribute to abnormal circuits and behaviors in FXS.

Publications

Callan MC, Cabernard C, Heck J, Luois S, Doe CQ, Zarnescu DC. Fragile X Protein Controls Neural Stem Cell Proliferation in the *Drosophila* Brain. **Hum Mol Genet.** 19(15):3068-79. 2010.

Presentations

Fragile X Protein Controls the Proliferation and Differentiation of Neural Stem Cells. **Model Organisms to Human Biology Meeting.** Boston, MA.

Fragile X Protein Controls the Proliferation and Differentiation of Neural Stem Cells. **EMBO Workshop, Molecular and Developmental Biology of *Drosophila*.** Greece.

2nd Year Contracts

Mohamad Azhar, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Role of TGFbeta Ligands in Aortic Aneurysm

The hypothesis is that Transforming Growth Factor beta2 & 3 (TGFβ2 & TGFβ3) genes are required for protection against aortic aneurysm. Our data indicated that a complete absence of TGFβ2 TGFβ3 genes caused death during embryonic development due to aortic aneurysm, aneurysm and localized dilation of the right ventricle, and cardiomyopathy (which resembles Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D or ARVD)). The data also revealed that the adult mice with just one copy of both TGFβ2 and TGFβ3 genes were highly susceptible to aortopathy and cardiomyopathy. Molecular studies found decreased levels of the activated SMAD2 protein were involved in the pathogenesis in mutant mice. Overall, these data indicate that TGFβ2 and TGFβ3 are required for development and maintenance of cardiovascular systems and protection against aortic aneurysm and cardiomyopathy. These studies are highly significant to the biomedical issues facing Arizona because adult or fetal cardiovascular diseases remain the leading cause of death of Arizonans.

Publications

Azhar M, Wang PY, Frugier T, Koishi K, Deng CX, Noakes PG, McLennan IS. Muscle-specific Deletion of Smad4 Causes Cardiac Outflow Tract Alignment and Septation Defects in Mice. **International Journal of Biological Sciences.** In Press. 2010.

Keys JT, Borowicz S, Rader J, Utizinger U, Azhar M, Vande Geest JP. Design and Demonstration of a Microbiaxial Optomechanical Device for Multi-scale Characterization of Soft Biological Tissues. **Microscopy and Microanalysis.** In Press. 2010.

Presentations

Azhar M, Nusayr E, Haskett D, Utizinger U, Vande Geest JP. Postnatal Function of Transforming Growth Factor beta2 in Cardiovascular Disease. **8th International Research Symposium on Marfan Syndrome.** Warrenton, VA. 2010.

Azhar M. Analysis of TGFbeta Function in Aortic Aneurysms. **Aortic Disease Summit.** Baltimore, MD. 2009.

Poster Abstracts

Azhar M, Nusayr E, Gard C. Role of TGFbeta3 in Arrythmogenic Right Ventricular Cardiomyopathy/Dysplasia Type 1 (AVRD1). **8th International Research Symposium on Marfan Syndrome.** Warrenton, VA. 2010.

Azhar M, Keyes J, Haskett D, Gard C, Vande Geest JP, Utzinger U, Doetschman T. Prognostic Utility of Physiologic Assessment of Extracellular Matrix Fiber Alignment and Tissue Biomechanics in Detection of Latent Aortic. **Weinstein Cardiovascular Development Conference.** Amsterdam, Netherlands. 2010.

Azhar M, Conway SJ, Doetschman T. Transforming Growth Factor Beta Ligands Play Essential Roles in Epicardium and Epicardial Cardiac Progenitor Cells During Heart Development. **Weinstein Cardiovascular Development Conference.** Amsterdam, Netherlands. 2010.

Azhar M, Kim N, Gard C, Runyan R, Conway SJ, Doetschman T. Periostin Mediates Transforming Growth Factor beta2 Function in Valve Development. **Weinstein Cardiovascular Development Conference.** Amsterdam, Netherlands. 2010.

Azhar M, Conway SJ, Doetschman T. Transforming Growth Factor beta2 Is Expressed in the Second Heart Field and Is Required for Outflow Tract and Right Ventricular Development. **Weinstein Cardiovascular Development Conference.** Amsterdam, Netherlands. 2010.

Vande Geest JP, Keyes J, Borowicz S, Utzinger U, Azhar M. Quantification of Biomechanical Differences in Wild-type and Heterozygous *Tgfb2* Knockout Mice. **Summer Bioengineering Conference.** Naples, FL. 2010.

Vande Geest JP, Utzinger U, Azhar M, Haskett D, Fouts M, Larson D. The Effects of Angiotensin II on the Mechanical Response and Microstructural Organization of Mouse Aorta. **Summer Bioengineering Conference.** Naples, FL. 2010.

Azhar M, Pawloski S, Martin J, Runyan RB. TGFβ2 Is Required for Mouse Epicardial EMT and Adherence of the Epicardial Cells Over the Myocardial Surface During Heart Development. **The 4th EMT International Association Meeting.** Tucson, AZ. 2009.

Michael Caplan, Ph.D. **Arizona State University**
Award Amount FY10: $50,000

Reverse Engineering the Basement Membrane

Caplan's project seeks to improve blood-contacting materials (for use in medical devices such as stents, vascular grafts, and heart valves) by understanding how normal human blood vessels prevent blood clotting. Blood vessels are lined by living cells that prevent blood clotting; but, when those cells are grown on man-made materials, blood clots. Therefore, blood vessels must send some cue to the cells that man-made materials do not. Caplan's lab tested different types of cues (chemical composition and stiffness of the material) and determined that cells distinguish to which material they are attached by the pattern of signals generated inside the cell. Caplan's lab has shown that these patterns of signals cause different levels of factors that prevent blood clotting and inflammation. This information may allow engineers to make man-made materials that recreate a pattern of signals that optimizes production of factors preventing clotting and inflammation thus preventing blood clotting clinically.

Publications

Shankarraman V, Shah MM, Caplan MR. Substrates Elicit Different Patterns of Intracellular Signaling Which in Turn Cause Differences in Cell Adhesion. **Cellular and Molecular Engineering.** 3(3):229-46. 2010.

Caplan MR, Shah MM. Translating Biomaterial Properties to Intracellular Signaling. **Cell Biochemistry and Biophysics.** 54(1-3):1-10. 2009.

Shankarraman V, Davis-Gorman G, Copeland JG, Caplan MR, McDonagh PF. Standardized Methods to Quantify Thrombogenicity of Blood-contacting Materials via Thromboelastography. In Press. 2010.

Presentations

Caplan MR, Shankarraman V, Shah MM. Intracellular Signaling: The Key to Understanding Why Cells Behave Differently on Different Materials. **Society for Biomaterials.** Seattle, WA. April 2010.

Caplan MR, McLamore R. Statistics in the Design of Experiments. **Society for Biomaterials.** Seattle, WA. April 2010.

Posters

Caplan MR, Shankarraman V, Kelso BG, Gorman G, McDonagh PF. How Do Cells Know What Biomaterial They Are On? **Gordon Research Conference: Signal Transduction from Engineered Extracellular Matrices.** Biddeford, ME. 2010.

Shankarraman V, Gorman G, McDonagh PF, Caplan MR. ERK Signaling Mediates Variation in Endothelial Recruitment of Thrombosis in Response to Varied Matrix Composition. **Biomedical Engineering Society Annual Meeting.** Pittsburgh, PA. 2009.

Kelso BG, Caplan MR. Intracellular Signaling Varies with Mechanical Properties of Cell Substrate. **Biomedical Engineering Society Annual Meeting.** Pittsburgh, PA. 2009.

Cheryl Conrad, Ph.D. **Arizona State University**
Award Amount FY10: $49,977

Stress and Estrogen Actions in the Female Hippocampus

Projections for the year 2020 indicate that major effective disorder (MDD) will be the leading cause of disability and disease burden throughout the world, which is relevant to Arizona as its population and retirement communities continue to grow. Neurobiological substrates contributing to MDD, as well as other psychiatric conditions such as Alzheimer's disease (AD) and schizophrenia, include the hippocampus, important in learning and memory, prefrontal cortex (PFC), critical for planning and attention, and the amygdala, essential for emotional arousal. Women exhibit nearly two-fold increase in susceptibility to MDD than do men, and so, understanding the underpinnings of MDD in women and how these changes differ than in men is paramount to successfully treat and provide intervention for both genders.

The long-term objective of this proposal is to understand the mechanisms contributing to neuropsychiatric disorders. Damage to the hippocampus is a common feature in Alzheimer's disease (AD), Schizophrenia and major depressive disorder (MDD), and all show symptoms of cognitive decline. Women are at higher risk than men for developing AD and MDD, with ovarian hormones being important factors in disease development and exacerbation of symptoms. However, the controversy over hormone therapy in the Women's Health Initiative for increasing the risk for dementia emphasizes that more studies are needed to fully understand the mechanisms.

The short-term objectives of this proposal are to use a rat model to investigate mechanisms underlying MDD. Rats that are chronically stressed show neuromorphological, neurochemical and behavioral changes that have face and predictive validity with MDD. Specifically, we are determining the neurobiological contributions of critical limbic structures such as the hippocampus, PFC and amygdala in producing cognitive and depressive-like behavior in males and females and the role of estrogen in mediating these effects.

Publications

McLaughin 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 Females: Possible Correspondence Between CA1 Spine Properties and Spatial Acquisition. **Hippocampus.** 20:768-86. 2010.

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

Conrad CD. A Critical Review of Chronic Stress Effects on Spatial Learning and Memory. **Progress in Neuro-Psychopharmacology and Biological Psychiatry.** 34:742-55. 2010.

Baran SE, Armstrong CE, Niren DC, Conrad CD. Prefrontal Cortex Lesions and Sex Differences in Fear Extinction and Perseveration. **Learning and Memory.** 17:27-278. 2010.

Abstracts

Hoffman A, Anouti D, Hutchinson K, Krigbaum A, Ortiz J, Mika A, Hanna JJ, Bimonte-Nelson HA, Conrad CD. Recovery of Hippocampal CA3 Dendritic Retraction and Correspondence to Spatial Learning and Memory After Chronic Stress in Mature Adult Male Rats. **Society for Neuroscience Abstracts.** 36. 2010.

Hutchinson KM, McLaughlin KJ, Wright RL, Anouti DP, Ortiz JB, Mika A, Huynh TN, Hanna JJ, Diamond DM, Conrad CD. Protective Effects of Environmental Enrichment, Initiated Before and During Chronic Stress, on Cognitive and Morphological Measures of Hippocampal Integrity. **Society for Neuroscience Abstracts.** 36. 2010.

Huynh TN, Krigbaum AM, Hanna JJ, Mika A, Hoffman AN, Ortiz JB, Conboy NS, Conrad CD. The Effects of Chronic Stress, Sex Differences and Light Phase on Anxiety and Depressive-like Behaviors. **Society for Neuroscience Abstracts.** 36. 2010.

McLaughlin KL, Sparks M, El-Ashmawy M, Huynh TN, Hanna JJ, Conrad CD. Effects of Cyclic 17β-estradiol Injections on Chronic Stress-induced CA3 Dendritic Retraction and CA1 Dendritic Spines in Ovariectomized Female Rats. **Society for Neuroscience Abstracts.** 36. 2010.

Torsten Falk, Ph.D. **University of Arizona**
Award Amount FY10: $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% 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 a 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.

Publications

Falk T, Zhang SL, Sherman SJ. Vascular Endothelial Growth Factor B Is Up-regulated and Exogenous VEGF-B Is Neuroprotective in a Culture Model of Parkinson's Disease. **Molecular Neurodegeneration.** 4:49. 2009.

Falk T, Gonzales RT, Sherman SJ. The Yin and Yang of VEGF and PEDF: Multifaceted Neurotrophic Factors and Their Potential in the Treatment of Parkinson's Disease. **International Journal of Molecular Sciences.** 11:2857-900. 2010.

Falk T, Yue X, Zhang SL, McCourt AD, Yee BJ, Gonzales RT, Sherman SJ. Vascular Endothelial Growth Factor B Is Neuroprotective in an *in vivo* Model of Parkinson's Disease. **Experimental Neurology.** In Press. 2010.

Presentations

Yue X, Falk T, Zhang SL, Sherman SJ. Vascular Endothelial Growth Factor B_{186} Improves Motor Behavior *in vivo* in a Rat Model of Parkinson's Disease. **Movement Disorders Society Meeting.** Buenos Aires, Argentina. 2010.

Falk T, Yue X, Zhang SL, Sherman SJ. Evidence for Neuroprotection After Treatment with Vascular Endothelial Growth Factor B *in Vivo* in the 6-hydroxydopamine Rat Model of Parkinson's Disease. **Society for Neuroscience Meeting.** San Diego, CA. 2010.

Abstracts

Falk T, Zhang SL, Sherman SJ. Vascular Endothelial Growth Factor B Is Upregulated and Neuroprotective in a Culture Model of Parkinson's Disease. **Society for Neuroscience Abstracts.** 6932**.** 2009.

Hanna Fares, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Deciphering Endocytosis in Multicellular Eukaryotes

We identified several new regulations of lysosomal transport in eukaryotic cells. Lysosomes are dynamic organelles that participate in many functions in eukaryotic cells. Our results impact all aspects of lysosome-related research. For example, lysosomal dysfunction is a hallmark of many neurodegenerative diseases collectively referred to as lysosomal storage disorders. In addition, since lysosomes are involved in cell death pathways in normal cells, they are being investigated as targets for cancer therapy. Our studies will provide a crucial, more detailed understanding of the molecular machineries that control lysosomal transport that will allow for more thorough investigations of lysosomal dysfunction in disease states.

Publications

Van der Bliek A, Fares H. Analysis of Organelles. **Methods in Cell Biology.** In Press. 2010.

Sourav Ghosh, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Cell Polarity Regulation during Differentiation of Embryonic Stem Cells

"Polarity" or internal asymmetry within the cells of our body allows for their normal physiological function. We propose that altered polarity is responsible for disease including cancer. The aPKC enzyme is essential for polarity. We have discovered a strong association between increased aPKC and glioblastoma, a brain tumor where astrocyte-like (a type of brain cell) tumor cells exhibit pathological migration and invasion into surrounding normal brain. Glioblastoma is uniformly lethal to patients because of the highly invasive behavior of tumor cells. We have identified aPKC as part of the molecular circuitry that is abnormally activated in glioblastoma cells. We have also learned how aPKC contributes to the invasiveness of these cells. Finally, we have demonstrated that reducing aPKC levels arrests glioblastoma cell migration and invasion. Since aPKC belongs to the protein kinase class of enzymes, it represents a tractable and attractive pharmacological target for future drug development and discovery.

Presentations

Ghosh S. Regulation of Apical-basal Polarity During Neural Development. **Department of Molecular and Cellular Biology Seminar Series.** Tucson, AZ. 2008.

Ghosh S. To Prevent and to Cure: Intracellular Signal Pathways as Potential Therapeutic Targets. **Basic Medical Sciences Seminar Series.** Phoenix, AZ. 2008

Ghosh S. Regulation of Apical-basal Polarity During Neural Development and CNS Tumorigenesis. **Midwestern University Seminar Series.** Phoenix, AZ. 2008.

Ghosh S. Regulation of Apical-basal Polarity During Neural Development and in CNS Tumorigenesis. **Barrow Neurologic Institute.** Phoenix, AZ. 2009.

Ghosh S. Regulation of Apical-basal Polarity During Neural Development and in CNS Tumorigenesis. **IIT-Bombay School of Biological Sciences and Bioengineering.** Mumbai, India. 2009.

Ghosh S. Functional Characterization of the Apical-basal Polarity Signaling Pathway in CNS Development and in GBM. **Mayo Clinic.** Scottsdale. AZ. 2009

Ghosh S. Functional Characterization of the Apical-basal Polarity Signaling Pathway in CNS Development and in Brain Tumors. **Ege University.** Izmir, Turkey. 2010.

Ghosh S. Deciphering CNS Tumorigenesis: Taking Cues from Embryonic Development. **Frontiers in Medical Research.** Tucson, AZ. 2008

Ghosh S. TAMing Inflammation. **4th Annual Frontiers in Immunobiology and Immunopathogenesis Symposium.** Tucson, AZ. 2009.

Ghosh S. Regulation of Apical-basal Polarity During Neural Development and in CNS Tumorigenesis. **2nd Annual BITS World Cancer Congress.** Beijing, China. 2009.

Ghosh S. Apical-basal Polarity in Glioblastoma. **Mechanisms and Models of Cancer Meeting.** La Jolla, CA. 2009

Ghosh S. Functional Characterization of the Polarity Signaling Pathway in CNS Development in GBM. **West Coast Salt and Water Club 29th Annual Meeting.** Morrow Bay, CA. 2010.

Ghosh S. Polarity Signaling in GBM. **FASEB Summer Meeting.** Carefree, AZ. 2010.

Ghosh S. Polarity Signaling in Glioblastoma. **16th Meeting on Protein Phosphorylation and Cell Signaling: Thirty years of Tyrosine Phosphorylation.** La Jolla, CA. 2010.

Steven Goldman, M.D. **Southern Arizona VA**
Award Amount FY10: $50,000

Seeding Fibroblast Patch for Chronic Heart Failure

This proposal develops a new approach to cell-based therapy for heart failure using a bioengineered scaffold implanted on the damaged heart. Our goal is to develop a new cell-based treatment for patients in heart failure after a heart attack. Because the scaffold provides support for the heart cells and increases blood flow for the heart, we will use it as a delivery system unto which we can seed cardiac stem cells. The idea is to treat heart failure by putting new heart cells into patients with heart failure. We have shown that you can take early heart cells and put them on our scaffold and improve heart function in animal models of heart failure. Before proceeding to patients we need to do more basic scientific work on the mechanism of action of this scaffold. Our work provides the foundation for future stem cell treatment of heart failure.

Publications

Thai HM, Juneman E, Lancaster JJ, Hagerty T, Do R, Castellano L, Kellar R, Williams S, Sethi G, Schmelz M, Gaballa MA, Goldman S. Implantation of a 3 Dimensional Fibroblast Matrix Improves Left Ventricular Function and Blood Flow After Acute Myocardial Infarction. **Cell Transplantation.** 18 (3):283-95. 2009.

Lancaster JJ, Juneman E, Hagerty T, Do R, Hicks M, Meltzer K, Standley P, Gaballa MA, Kellar R, Goldman S, Thai HM. Viable Fibroblast Matrix Patch Induces Angiogenesis and Increases Myocardial Blood Flow in Health Failure After Myocardial Infarction. **Tissue Engineering.** In Press. 2010.

Abstracts

Lancaster JJ, Johnson NM, Juneman E, Thai HM, Bahl J, Goldman S. Construction of a Spontaneously Contracting Biologically Active Cardiomyocyte Scaffold. **J. Cardiac Failure.** 15(1):S45. 2009.

Lancaster JJ, Johnson NM, Thai HM, Juneman E, Bahl J, Goldman S. Construction of a Spontaneously Contracting Biologically Active Cardiomyocyte Scaffold. **Circulation Research.** 105:10-53e. 2009.

Lancaster JJ, Arnce S, Johnson NM, Juneman E, Thai HM, Kellar R, Vitorin J, Burt J, Bahl J, Goldman S. *In Vivo* Evaluation of a Biologically Active Cardiomyocyte Seeded Scaffold. **American Heart Association Basic Cardiovascular Sciences 2010 Scientific Sessions.** Rancho Mirage, CA. 2010.

Website References

Lancaster J, Goldman S. Three-dimensional Scaffold of Beating Heart Cells. **National Public Radio Science Friday.** 2009. www.theregen.com/heartbeat-popup.html

Lancaster J, Goldman S. VA Study: Heart-healing Patch. 2009. www.azstarnet.com/sn/byauthor/303476

Lancaster J, Goldman S. Researchers Design Patches of Cells to Repair Damaged Hearts. 2009. www.scientificamerican.com/article.cfm?id=patches-repair-damaged-hearts&SID=mail&sc=emailfriend

Jui-Cheng Hsieh, Ph.D. **University of Arizona**
Award Amount FY10: $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 major progresses in second year are: 1) we discovered that the purified hairless protein can bind to the p53 DNA-binding motifs, two copies of GGGCWWGYYY (G=purine bases, W=A or T, Y=pyridine bases); and 2) the phosphorylation site(s) of hairless protein may locate at the 324-364 and 492-514 regions. 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 the Hr-related diseases.

Publications

Hsieh JC, Slater SA, Whitfield GK, Dawson JL, Hsieh G, Sheedy C, Haussler CA, Haussler MR. Analysis of Hairless Corepressor Mutants to Characterize Molecular Cooperation with the Vitamin D Receptor in Promoting the Mammalian Hair Cycle. **J. Cell Biochem.** 110(3):671-86. June 2010.

Kathryn Lemmery-Chalfant, Ph.D. **Arizona State University**
Award Amount FY10: $48,386

Molecular and Quantitative Genetic Approaches to Understanding Child Psychopathy

During our second year of funding, we accomplished many of our key aims and have begun to incorporate genetic data into our process twin models of the development of child psychopathology. We identified 17 promising candidate genes for behavior and typed within these genes 67 short variants and five longer variants that were likely (based on previous literature and gene function) to influence child psychopathology.

This research has resulted in novel and exciting results elucidating the importance of gene-environment interplay on temperament and child psychopathology (depression, anxiety, ADHD, conduct disorder) in children. These findings are being disseminated at a variety of professional conferences. This work contributes to the growing literature reframing “genetic risk” as “genetic sensitivity,” such that some individuals are more sensitive to environments in general than other individuals. It is important for both researchers and policy makers to understand that genetic variants may not put children at greater risk for negative outcomes, but may instead make them more sensitive to their environment—for better and for worse.

Lonnie Lybarger, Ph.D. **University of Arizona**
Award Amount FY10: $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. In the past year we have made substantial progress on this project describing how MARCH1 expression and function are regulated in APC. Indeed, we recently published a manuscript detailing our findings. Ultimately, a full understanding of the pathways we are studying will result in better treatments for diseases of immune dysregulation.

Publications

Jabbour M, McCarthy-Campbell E, Fares H, Lybarger L. Discrete Domains of MARCH1 Mediate Its Localization, Functional Interactions, and Post-transcriptional Control of Expression. **Journal of Immunology.** 183:6500-12. 2009.

Presentations

Lybarger L. Substrate Selection Mechanisms Used by E3 Ligases that Affect Antigen Presentation. **6th International Antigen Processing and Presentation Workshop.** Cargese, Corsica, France. 2010.

Leslie Ritter, Ph.D. **University of Arizona**
Award Amount FY10: $49,999

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 the three year project. During this first year we verified that, indeed, turmeric treatment significantly reduced the amount of brain cell death after a 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. Therefore, in the upcoming year we will determine if the reduction in brain cell death that we observed is, in fact, due to inflammation within the brain blood vessels. We believe that turmeric will reduce both blood cell and blood vessel inflammation. If this is true, it may be the reason why brain cell death is decreased with turmeric treatment. As brain damage after stroke is (otherwise the safe effect of turmeric) 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 stroke could have a major impact on the health and health care costs of our state. This 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.

Presentations

Funk JL, Beischeil-Frye J, Morrison H, Ritter L. Botanicals and Stroke: A Novel Therapeutic Approach. **American Society of Pharmacognosy Annual Meeting.** Honolulu, HI. 2009.

Poster Abstracts

Ritter L, Funk J, McDonagh P, Spera A, Gorman G, Beischeil J. Turmeric Targets Neutrophil-endothelial Interactions During Reperfusion After Ischemic Stroke. **International Microcirculatory Society Meeting.** Missouri. 2009.

Ritter L, Funk J, McDonagh P, Spera A, Gorman G, Beischeil J. Novel Neuroprotection After Stroke: Effects of Turmeric. **Western Institute of Nursing.** Phoenix, AZ. 2010.

Website Reference

www.opa.ahsc.arizona.edu/newsroom/news/2010/panacea-spice-rack

Marek Romanowski, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Contrast Agent for Colonoscopy

The overall goal of this project is to develop a contrast agent that will enhance standard colonoscopy by marketing areas of precancerous changes, or adenomas, with highly visible and stable luminescent nanoparticles. Experiments conducted in the second year of this project focused on characterization of luminescent nanoparticles, development of the imaging system, and development of appropriate biological assays *in vitro*. We obtained highly efficient luminescence upconversion in these contrast agents, a process in which bright colors are generated by illumination with invisible near-infrared radiation for improved contrast in diagnostic imaging. We demonstrated an augmented microscope; a new type of diagnostic and surgical microscope in which electronically generated diagnostic image is merged with optical image in real time.

Presentations

Gainer CF, de Silva C, Romanowski M. Augmented Microscopy-simultaneous Acquisition of Bright Field and Luminescence Lifetime Images. **30th Annual Meeting of the American Society for Laser Surgery and Medicine.** Phoenix, AZ. 2010.

Gainer CF, Romanowski M. Diffusion Enhanced FRET Assay Using Lanthanide Nanoparticles. **54th Annual Meeting of the Biophysical Society.** San Francisco, CA. 2010.

Jiong Shi **Barrow Neurological Institute**
Award Amount FY10: $50,000

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

Multiple sclerosis (MS) is a devastating disease that causes not only motor but cognitive deficits as well. MS is a leading cause of disability in young adults, with most people experiencing their first symptoms between the ages of 20 and 40. Cognitive symptoms of MS are considered the most debilitating and have the heaviest impact economically and socially. Studies indicate and our research confirms that 40-70 percent of patients with MS exhibit significant cognitive impairment. Our studies found a strong association between the development of cognitive problems and a gene for apolipoprotein E4 (APOE 4). Our studies further indicated that a markedly disproportionate percentage of the young patients with cognitive deficits have the APOE4 gene.

Our goal is to establish an animal model to study the underlying mechanism of the above clinical observation and then to find a treatment and translate it back to patient care. Our first objective is to use transgenic mice which have no APOE (APOE knockout, KO) and have APOE 4 (APOE 4 knock-in, E4) and compare their cognitive function to mice with normal APOE after inducing them with experimental autoimmune encephalomyelitis (EAE), the animal version of MS. We have tested them early in the course of the disease as our MS studies indicate that cognitive symptoms precede motor and may be the first indication of disease. We have tested their cognitive function using a water maze and examined their brain using special stains for chemical and cellular changes seen the hippocampus, the memory region of the brain. We have successfully induced EAE in KO and E4 mice to study the interaction of APOE and neuroinflammation on cognition. After EAE induction, KO and E4 showed significant deficits in spatial learning and recall. Regional decreases in choline acetyltransferase localized to the hippocampus. We, therefore, have an animal model that provides a template from which we can decipher the role APOE has on cognition in the context of neuroinflammation.

Our second objective is to use an APOE peptide mimetic, a peptide – small protein fragment—which mimics the therapeutic effect of APOE to determine if it can overcome the detrimental effects of the absent (knockout) and less efficient APOE 4. We are currently working on this phase.

Publications

Shi J, Zhao CB, Vollmer TL, Tyry TM, Kuniyoshi SM. APOE Epsilon4 Allele Is Associated with Cognitive Impairment in Patients with Multiple Sclerosis. **Neurology.** 70:185-90. 2008.

Tu JL, Zhao CB, Vollmer TL. APOE 4 Polymorphism Results in Early Cognitive Deficits in an EAE Model. **Biochem Biophys Res Commun.** 384:466-70. 2009.

Caselli RJ, Dueck AC, Osborne D. Longitudinal Modeling of Age Related Memory Decline and the APOE Epsilon4 Effect. **N Engl J Med.** 361:255-63. 2009.

Abstracts

Junxiang Y, Lin H, Shi F, Shi J. Neuro-inflammation Induced Cognitive Impairment in APOE Transgenic Mice. **Society for Neuroscience.** Chicago, IL. 2009.

Turner GH, Yin J, Shi J. Characterization of Age Related Structural Change in a Human APOE E4 Knock-in Mouse Model of Alzheimer's Disease. **International Society for Magnetic Resonance in Medicine 18th Scientific Meeting and Exhibition.** Stockholm, Sweden. 2010.

Shi J. Age Related Decline in Visual-spatial Memory Performance in an APOE-4 Transgenic Mouse Model. **Preclinical Imaging in Biomedical Research Symposium.** Tempe, AZ. 2010.

Catharine Smith, Ph.D. **University of Arizona**
Award Amount FY10: $49,999

Identification of the Acetylated Transcriptional Proteome in Leukemia and Lymphoma

Lymphoma ranks among the top 10 causes of cancer death in Arizonans. A new class of anticancer drugs, histone deacetylase inhibitors, has shown promise in treating lymphoma but lack of knowledge about how they work has limited our ability to target them to patients in whom they will be effective. Our goal is to determine how these drugs impair survival of the most common non-Hodgkin's lymphoma, diffuse large B cell lymphoma (DLBCL), taking a comprehensive approach. To date we have determined how cell lines representing DLBCL respond to HDAC inhibitors in terms of cell growth and survival. We have identified genes activated and repressed by the drugs in these cell lines, and we are poised to begin mass spectrometry techniques to identify transcriptional proteins that are acetylated in response to drug treatment. Our accomplishments are consistent with our suggested timeline, and we look forward to continuing progress in the final year.

Abstracts

Tula-Sanchez AA, An L, Klein ME, Rimsza LM, Smith CL. The Cellular and Genomic Response to Histone Deacetylase Inhibitors in Diffuse Large B-Cell Lymphoma. **American Society of Hematology Annual Meeting.** 2010.

Peter Steinmetz, Ph.D., M.D. **St. Joseph's Hospital**
Award Amount FY10: $49,920

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

This project's goal is to understand how memory of words is represented by the firing of neurons in the human hippocampus, a part of the brain critical for memory. To date we have recorded the responses of 1282 single neurons in the brains of 7 epilepsy patients as they performed a continuous recognition memory experiment; seeing word twice, with random numbers of intervening words. Analysis of these recordings has shown that neurons within the hippocampus have a higher firing rate when a word is presented a second time in a different font than when presented in the same font. This is when subjects have more difficulty recalling and may correspond to single neuron correlates of trying harder to remember. This provides a new understanding of how single neurons implement memory for language, an important step in treating disorders of memory such as those produced by Alzheimer's disease and stroke.

Presentations

Steinmetz PN, Goldinger S, Papesh M, Treiman DM. Repetition Enhances Single Neuron Response to Word Recognition in Human Anterior Cingulate Cortex. **Society for Neuroscience.** 2010.

Steinmetz PN, Goldinger S, Papesh M, Treiman DM. Single-neuron Responses in Continuous Recognition Memory for Printed Words. **Psychonomics Society.** 2010.

Raoul Tibes, M.D., Ph.D.

Translational Genomics Research Institute

Award Amount FY10: $50,000

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

Acute leukemias are often incurable with current therapies and better therapies need to be developed. In this grant we pursued a novel approach called RNA interference (RNAi). Using this new technology we were able to identify genes that when inhibited strongly enhanced the anti-leukemic activity of the most commonly used acute leukemia drug called cytarabine. For one gene in particular we were able to find a new drug that is in early clinical studies. When this drug was combined with cytarabine, most leukemia cells, including samples taken from leukemia patients, died in experiments in the lab. Now we are planning a clinical study of these two drugs together for patients with leukemia here in Arizona. Additional grants to national funding organizations have been submitted to continue our research that was started with help from ABRC!! If we are also awarded the clinical study that was proposed based on the ABRC work, this would bring a major patient and research program to Arizona.

Abstracts

Tibes R, Bogenberger J, Hagelstrom T, Buechel ME, Bhagavatula K, Choudhary A, Azorsa DO. Synthetic Lethal RNAi Screen of the Human Kinome with Cytarabine in Myeloid Leukemias. **Blood (ASH Annual Meeting).** 114:590. 2009.

Tibes R, Bogenberger J, Hagelstrom T, Buechel M, Azorsa DO. RNAi as a Tool to Identify Novel Molecular Vulnerabilities in Myeloid Leukemias. **Mol CancerTher.** 8(12):A202. 2009.

Hagelstrom RT, Bogenberger JM, Bhagavatula K, Buechel M, Azorsa DO, Tibes R. Synthetic Lethal RNAi Screen of the Human Kinome with Cytarabine (AraC) in Leukemia Cells. **Late Breaking Abstract LB-202 AACR Annual Meeting.** Washington, DC. 2010.

Tibes R, Hagelstrom T, Bogenberger J, Arora S, Azorsa DO, Mesa R. RNAi Lethality Screening in Acute Leukemias Identifies Wee1 Inhibition as Potent Sensitizer to Cytarabine and Uncovers a Genomic Context in Lymphoid Malignancies. **AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.** 2010.

Theodore Trouard, Ph.D. **University of Arizona**
Award Amount FY10: $50,000

MRI, MRS and Molecular Modeling of Three Dimensional Cell Cultures

Although clinically useful, interpretation of diffusion-weighted MRI (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. One paper has been published on the mathematical modeling of water movement in tissue, and another paper describing experimental results in the model cell cultures has been accepted with minor revisions. We also submitted a grant to the NIH that received a good priority score but will not likely be funded this round. A resubmission of this grant is planned for November, 2010.

Publications

Harkins KD, Galons JP, Secomb TW, Trouard TP. Assessment of the Effects of Cellular Tissue Properties on ADC Measurements by Numerical Simulation of Water Diffusion. **Magn. Reason. Med.** 62:1414-21. 2009.

Harkins KD, Galons JP, Divijak J, Trouard TP. Determining the Biophysical Mechanisms of Intracellular Water Diffusion and Its Response to Ischemia in Perfused Cell Cultures. **Magn. Reason**. **Med.** Submitted and in revision.

Abstract

Harkins KD, Galons JP, Secomb TW, Trouard TP. Determining the Biophysical Mechanisms of Intracellular Water Diffusion and Its Response to Ischemia in Perfused Cell Cultures. **Proc. Intel. Soc. Magn. Reason.** 18:295. 2010.

Pak Kin Wong, Ph.D. **University of Arizona**
Award Amount FY10: $49,999

Molecular Probe Biosensors for Rapid Screening of Photoprotective Compounds

The overall goal of the project is to establish a novel biosensor platform for screening compounds that protect against skin cancer. In this funding period, all the technical milestones have been successfully achieved. In addition to detection in cell lysates, we have discovered new opportunities that will dramatically enhance the progress of the overall goal. We identified immobilization of the molecular probe biosensors on micron-sized or sub-micron-sized particles offer a unique approach for enhancing the performance of the sensor for detecting chemopreventive compounds. The ability to rapidly identify agents that can prevent the occurrence and reduce the severity of UV-induced skin cancer is one of the most critical steps toward the development of novel therapeutics and prevention approaches for skin cancer protection. This is particularly essential in southern Arizona, which ranks near the top in skin cancer incidence rates worldwide.

Publications

Li N, Wong PK. Transfection of Molecular Beacons in Microchannels for Single Cell Gene Expression Analysis. **Bioanalysis.** In Press. 2010.

Gidwani V, Riahi R, Zhang DD, Wong PK. Hybridization Kinetics of Double-stranded DNA Probes for Rapid Molecular Analysis. **Analyst.** 134:1675-81. 2009.

1st Year Contracts

Charles Adler, M.D., Ph.D. **Mayo Clinic**
Award Amount FY10: $230,000

Arizona Parkinson Disease Consortium: Mechanisms and Predictors of Parkinson's Disease and Parkinson's Disease with Dementia

This proposal is organized into two cores (Clinical and Neuropathology) and two projects. The Clinical Core provides recruitment and longitudinal evaluation of subjects enrolled in the Banner Sun Health Research Institute Brain and Body Donation Program and administrative support for the entire ABRC grant. One of the major functions of the Clinical Core is to provide detailed, prospective, standardized clinical evaluation and quantitative biomarker testing on all subjects that come to autopsy. Upon death the Clinical Core provides a consensus final clinical diagnosis for the movement disorder and cognitive status of the subject. Upon death the Neuropathology Core provides the autopsy services needed for rapid brain autopsy and then neuropathologic assessments to determine the causes for the clinical findings. The Clinical and Neuropathology Cores also provide the clinical information and the CSF and brain tissue samples needed for all the projects. The two projects can be divided into 1) identification of differences in CSF protein levels between PD, preclinical PD (incidental Lewy body disease), and PD with dementia, and 2) identification of protein and neurotrophic factor differences at different stages of PD.

Publications

Papers published under this and previously funded projects.

McKinnon J, Evidente VGH, Driver-Dunkley E, Premkumar A, Hentz JG, Shill H, Sabbagh MN, Caviness JN, Connor DJ, Adler CH. Olfaction in the Elderly: A Cross-sectional Analysis Comparing Parkinson's Disease with Controls and Other Disorders. **Int. J. Neurosci.** 120:36-9. 2010.

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.** 25:642-6. 2010.

Choi SA, Evidente VG, Caviness J, Shill H, Sabbagh MN, Connor D, Hentz JG. Adler C, Beach TG. Are There Differences in Cerebral White Matter Lesion Burdens Between Parkinson's Disease Patients With and Without Dementia? **Acta Neuropathologica.** 119:147-9. 2010.

Beach TG, Adler CH, Sue LI, Lue LF, Bachalukuri J, Henry-Watson J, Boyer S, Shirohi S, Brooks R, White CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG, (the Arizona Parkinson's Disease Consortium). Multi-organ Distribution of

Phosphorylated Alpha-Synuclein Histopathology in Subjects with Lewy Body Disorders. **Acta Neuropathologica.** 119:689-702. 2010.

Dodiya HB, Chu Y, Beach TG, Adler CH, Olanow CW, Bartus RT, Korodower JH. Striatal Dopamine Innervation with Nigra Neurons in Parkinson Patients as a Function of Disease Duration: Relevance to Trophic Factor Therapy. **Cell Transplant**. 19:336-7. 2010.

Adler CH, Caviness JN, Sabbagh MN, Shill HA, Connor DJ, Sue L, Evidente VGH, Driver-Dunkley E, Beach TG. Hetrogeneous Neuropathological Findings in Parkinson's Disease with Mild Cognitive Impairment. **Acta Neuropathol.** 120:827-8. 2010.

Adler CH, Beach TG. Variability of Diffuse Plaques and Amyloid Angiopathy in Parkinson's Disease with Mild Cognitive Impairment. **Acta Neuropathol.** 120:831. 2010.

Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, Eklund AC, Zhang-James Y, Kim PD, Hauser MA, Grunblatt E, Moran LB, Rieder P, Miller RM, Federoff HJ, Wullner U, Papapetropoulos S, Youdim MB, Canturi-Castelvetri I, Young AB, Vance JM, Davis RL, Hedreen JC, Adler CH, Beach TG, Graeber MB, Middleton FA, Rocket JC, Scherzer CR. Pathway Analysis of Parkinson's Reveals PGC-1ά as Therapeutic Target for Early Intervention. **Science Translational Medicine.** 2:52-73. 2010.

Abstracts

Abstracts published or presented under this and previously funded projects.

Dodiya HB, Chu Y, Beach TG, Adler CH, Olanow CW, Bartus RT, Kordower JH. The Status Dopaminergic Putamenal Innervation in Parkinson's Disease as a Function of Disease Duration: Relevance to Trophic Factor Therapy. **Society for Neuroscience.** 2009.

Adler CH, Hentz JG, Shill HA, Sabbagh MN, Connor DJ, Evidente VGH, Driver-Dunkley E, Tanner C, Kukull W, Vedders L, Jacobson S. Caviness JN, Beach TG. Parkinson's Disease (PD) Increases Risk for Mild Cognitive Impairment (MCI). **Neurology.** 74(Suppl. 2):A74. 2010.

Adler CH. Mild Cognitive Impairment in Parkinson's Disease. **Parkinsonism Relat. Disord.** 15(Suppl. 3):S81-2. 2009.

Driver-Dunkley E, Hentz J, Shill HA, Caviness J, Sabbagh MN, Vedders L, Adler CH. Longitudinal Changes in UPSIT Scores. **Neurology.** 74(Suppl. 2):A61. 2010.

Damian A, Jacobson S, Belden C, Shill HA, Sabbagh MN, Vedders L, Adler CH. Comparison of the Montreal Cognitive Assessment (MoCA) with the Mini-Mental State Examination in Cognitively Impaired and Cognitively Normal Subjects as Assessed by Neuropsychological Testing. **Neurology.** 74(Suppl. 2):A137. 2010.

Beach TG, Adler CH, Sue LI, Lue LF, Bachalukuri J, Henry-Watson J, Boyer S, Shirohi S, Brooks R, White CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG, (the Arizona Parkinson's Disease Consortium). Multi-Organ Distribution of Phosphorylated Alpha-Synuclein Histopathology in Subjects with Lewy Body Disorders. **American Association of Neuropathologists.** 2010.

Klassen B, Hentz J, Adler CH, Shill HA, Driver-Dunkley E, Evidente VGH, Sabbagh MN, Caviness Jn. Quantitative Electroencephalography as a Predictor for Parkinson's Disease Dementia. **Mov Disorders.** 25(Suppl. 2). 2010.

Damian A, Jacobson S, Belden C, Shill HA, Sabbagh MN, Vedders L, Hentz JG, Caviness JN, Adler CH. Analysis of the Montreal Cognitive Assessment (MoCa) and Its Individual Domains Versus the Mini-Mental State Examination in Cognitively Impaired and Cognitively Normal Subjects as Assessed by Neuropsychological Testing. **Arizona Alzheimer's Consortium Annual Meeting.** 2010.

Beach TG, Adler CH, Sue LI, Vedders L, Lue LF, White CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG, (the Arizona Parkinson's Disease Consortium). Multi-Organ Distribution of Phosphorylated Alpha-Synuclein Histopathology in Subjects with Lewy Body Disorders. **Arizona Alzheimer's Consortium Annual Meeting.** 2010.

Salvatore Albani, M.D., Ph.D. **University of Arizona**
Award Amount FY10: $50,000

Immune Tolerance In The Therapy of Rheumatoid Arthritis

Blood samples from patients with Rheumatoid Arthritis treated with novel therapy to reduce their level of inflammation were studied. We separated the various immune cells and discovered that the mechanism of action of the drug and the basis of its clinical efficacy are related to the restoration of an otherwise impaired immune function. This mechanism ensures physiologic control of inflammation and its efficacy is recovered in treated patients. These findings are of fundamental importance for the development of novel, less toxic therapies for rheumatoid arthritis, and other autoimmune diseases. There is no specific benefit exclusive to the citizens of Arizona as the significance of this work transcends the boundaries of the state. Of note, this work amply satisfies the objectives stated in the first year of the project.

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

Multi-Modality Imaging of Window Chamber

A platform apparatus for multi-modality optical, MRI, and nuclear imaging of dorsal skin-fold window chambers implanted in mice was constructed. This platform allows detailed studies of basic tumor biology and cancer treatment strategies in this animal model. Imaging of pH and vascular permeability by optical and MRI methods has been demonstrated with continuing work focused on evaluating the precision and accuracy of these measurements. Additional work is planned to make dual optical and nuclear contrast agents to demonstrate the potential for imaging of molecular targets in window chambers with these two methods.

Publications

Lin Y, Gmitro AF. Errors in Confocal Fluorescence Ratiometric Imaging. **Applied Optics.** In Press. 2010.

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

Glioblastoma (GBM) is the most aggressive and deadly primary brain tumor with approximately 15-month median survival. As drug discovery programs search for GBM treatment strategies that build upon the modest survival benefit from combined temozolomide (TMZ) and radiation therapy (RT), the need for an efficient endpoint to predict outcome has never been greater. Current imaging techniques can not accurately assess treatment response or predict survival. A primary aim of the first year of this ABRC-funded project was to develop and validate a Perfusion MRI (pMRI) method to detect, localize, and quantify tumor progression relative to treatment-induced reactive changes, known as Post-treatment Radiation Effect (PTRE). This pMRI method will not only serve as a new endpoint to assess treatment response and predict survival in clinical trials but can also be incorporated into various image-guided procedures. In fact, a secondary aim during this first year was to incorporate pMRI maps to guide surgical biopsy of lesions that are suspicious for tumor progression following multimodality therapy. The overarching goal is to develop safer, more efficient, and more accurate diagnosis and treatment of glioma patients.

Abstracts

Hu L. Perfusion MRI Estimation of Glioma Microvascular Density to Predict Tumor Recurrence and Treatment Response: Validation Study Through Stereotactic Tissue Analysis. **101st AACR Annual Meeting.** Washington, DC. 2010.

Hu L. Image-guided Tissue Validation of Combined Preload Dosing and Mathematical Modeling Correction of Perfusion MRI Measures. **ISMRM-ESMRMB Joint Annual Meeting.** Stockholm, Sweden. 2010.

Hu L. Perfusion MRI Fractional Tumor Bulk Mapping: Correlation with Multiple Stereotactic Biopsies in Recurrent GBM. **ISMRM-ESMRMB Joint Annual Meeting.** Stockholm, Sweden. 2010.

Hu L. Accuracy of a Modeling Algorithm to Optimize Perfusion MRI Detection of Glioma Recurrence. **American Society of Clinical Oncology (ASCO) Annual Meeting.** Chicago, IL. 2010.

Richard Lane, M.D. **University of Arizona**

Award Amount FY10: $150,000

Neural Basis of Vagal Tone Dysregulation in Depression

Depression is a major public health problem in Arizona. Major depressive disorder (MDD) is common and disabling condition for which treatment exists; however, many patients do not respond and most do not recover fully. The purpose of the research is to examine how patterns of brain activity interact with physiological responses (particularly heart rate variability [HRV]) in patients with MDD as compared to healthy volunteers. If HRV is an indicator of brain activity, clinicians could use HRV to help diagnose and treat depression, which would ultimately lead to reductions in the prevalence of depression in Arizona. Sixteen depressed patients and ten controls have completed the protocol. Analysis of imaging, HRV and clinical data is ongoing.

Sean Limesand, Ph.D. **University of Arizona**
Award Amount FY10: $125,000

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

Loss of pancreatic insulin-producing β-cells is a primary cause of diabetes. The ability to monitor declines in β-cell mass (BCM) is critical for pathology and treatment evaluation, but all attempts have been limited by an inability to discriminate β-cells from their surroundings. We propose that targeting a combination of surface epitopes, unique to the β-cell, with one molecule will provide adequate specificity for imaging BCM in humans. Several accomplishments have been made during the first year of this proposal: two heterobivalent ligands consisting of GLP-1 and glibenclamide and GLP1- and serotonin (5-HT_{1F}) were synthesized; these heterobivalent ligands have improved affinities for β-cells compared to monomers; and positive results were obtained with *in vivo* β-cell labeling. However, *in vivo* studies also reveal a need for greater specificity. As originally planned, we will incorporate the K14D10 antibody, which is β-cell specific, with the constructs above to improve its specificity.

Publications

De Silva CR, Vagner J, Lynch RM, Gillies RJ, Hruby VJ. Optimization of Time-resolved Fluorescence Assay for Detection of Europium-tetraazacyclododecyltetraacetic Acid-labeled Ligand-receptor Interactions. **Analytical Biochemistry.** 398:15-23. 2010.

Xu L, Vagner J, Alleti R, Rao V, Jagadish B, Morse DL, Hruby VJ, Gillies RJ, Mash EA. Synthesis and Characterization of a Eu-DTPA-PEGO-MSH(4) Derivative for Evaluation of Binding of Multivalent Molecules to Melanocortin Receptors. **Bioorg. Med. Chem. Lett.** 20:2489-92. 2010.

Xu L, Vagner J, Josan JS, Lynch RM, Morse DL, Baggett B, Han H, Mash EA, Hruby VJ, Gillies RJ. Enhanced Targeting with Hetrobivalent Ligands. **J. Hol. Cancer Ther.** 8:2356-65. 2009.

Josan JS, De Silva CR, Yoo B, Lynch RM, Pagel MP, Vagner J. Hruby VJ. Fluorescent and Lanthanide Labeling for Ligand Screens, Assays, and Imaging. **Methods in Molecular Biology PMC Journal.** In press. 2010.

Chung W, Weber CS, Hart NJ, Gilles RJ, Limesand SW, Vagner J, Lynch R<. Heterobivalent Ligands Targeting of the Pancreatic β-cells. **Chem Bio Chem.** Accepted for publication. 2010.

Abstract

Limesand SW, Hart N, Vagner J, Anderson MJ, Chung WJ, Weber CS, Lynch RM. Specific Targeting of Pancreatic β-cells with a Heterobivalent GLP-1/glibenclamide Ligand. **Diabetes 70th Scientific Session Abstract Book.** Abstract 2514-PO. 2010.

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

The Use of Ketones as an Adjuvant Therapy for Malignant Gliomas

We and others have observed that the metabolic changes induced by a ketogenic diet, a diet currently used for the treatment of refractory epilepsy in children, can prolong survival in mouse models of brain tumors. We now report that there is also a significant increase in survival when the ketogenic diet is used with radiation, chemotherapy, or radiation and chemotherapy combined, compared to these same treatments given to animals fed a standard diet. This makes it even more attractive for clinical use since it can be added to treatments that are the current standard of care for brain tumor patients. The mechanism(s) of action of the ketogenic diet for the treatment of brain tumors is not known. Our results suggest that the ketogenic diet reduces the activity of a number of growth factors known to promote brain tumor growth and may be inhibiting tumor growth through these pathways.

Abstacts

Scheck AC, Abdelwahab MG, Stafford P, Kim DY, Fenton K, Kushchayev SV, Preul MC, Rho JM. The Ketogenic Diet as as Adjuvant Therapy for Malignant Gliomas. **Neuro-Oncology.** 11(5): 601. 2009.

New Projects

David P. Adelson, M.D. **Phoenix Children=s Hospital**
Award Amount FY11: $156,057

A Practical Brain-Computer Interface Based on Micro-ECoG Technology

Arizona is the 2nd fastest growing state in the nation, and the number of people with brain disorders is estimated to increase considerably in years to come. People with severe brain disorders who lack the capacity to communicate as a result of diseases like stroke, amyotrophic lateral sclerosis (also known as “Lou Gehrig’s Disease”), or spinal cord injury (as occurred with Christopher Reeve), lose the motor ability and movement to participate in daily activities most take for granted. The goal of the project is to expand upon previous research to refine a method of communication that will provide people suffering from these severe disorders a means to communicate either with a computer interface or prosthetic devices.

Electrocorticography (EcoG) is a technology that is normally used in the diagnosis of patients with intractable seizures ultimately to identify the location of the seizure focus and remove it to cure their epilepsy or chronic seizure disorder. In EcoG, small electrodes are surgically placed directly on the brain to record seizures and find the location to cure them. Brain-computer interface (BCI) uses these same electrodes to transmit brain signals to a computer during different activities or thoughts. The computer will then learn to convert brain signals into simple commands that will control communication aids such as a pointer on a computer screen, voice sounds, or robotic or artificial limbs. Ultimately, completion of the proposed project will provide an important step towards the creation of a device that will provide patients with brain or spinal cord disorders a means to communicate and better interact with their environment through computers or controlling/moving artificial limbs or robots.

Shoana M. Anderson, MPH **AZ Dept. Of Health Services**
Award Amount FY11: $100,000

Understanding the Risk Factors for Valley Fever to Improve Prevention, Diagnosis, Reporting, and Treatment

Valley Fever (VF or coccidioidomycosis) is one of the most important infections in Arizona resulting in estimated 90,000 infections and over 1,700 hospitalizations each year. Although most cases are mild, infection can cause severe disease resulting in an average of 1 month of missed work and an average of $54,000 in charges for each hospitalization. People become infected with VF by inhaling the spores from soil that is disrupted by either human- or weather- related activities. Since the fungus that causes valley fever is found in soil throughout Arizona, VF is difficult to prevent. Initial evaluations by ADHS indicate that one of the key factors to reducing the impact and complications of infection is to ensure people are diagnosed and treated as soon as possible.

We will work with the Translational Genomics Research Institute to determine whether human and microbial genetic factors are associated with severe VF outcomes and we will compare the sensitivity and specificity of serologic tests to DNA based tests in the diagnosis of VF. We hope that understanding the epidemiology related to microbial and human genetic factors of VF will provide better guidelines in prevention of VF. Further, determining the sensitivity and specificity of laboratory tests will optimize diagnosis of VF for future patient care.

Kevin Bennett, Ph.D. **Arizona State University**
Award Amount FY11: $50,000

Implantable, MRI-Detectable Hydrogel Sensors with Picomolar Sensitivity

Artificial tissues in the form of gels have been made that can be implanted into the body to deliver drugs, promote wound healing, and potentially deliver cell therapy. These tissues are being used to treat many diseases facing Arizona including puncture and infected fracture wounds, tumors, and skin cancer. While still exploratory, artificial gels may enable precise, controlled delivery of therapy to many diseases. A major problem with implantable gels is that their structure cannot be monitored without cutting them out of the tissue. Here we have invented “MRI reporter gels” made of gels with small magnetic nanoparticles that can be monitored by MRI, so that the action of the gels can be studied inside the body without biopsy. We will create natural and synthetic reporter gels and test them to see if they can be used to detect molecules, cells, and degradation outside and inside the body. The focus of this project is to develop and test these gels in an animal model. In biological reporter gels, we will test the hypotheses that aggregation of the functionalized nanoparticles, bound to insoluble macromolecules, can be controlled in a determined MRI relaxivity; the relaxivity of the gel should depend on the distribution of its structural molecules before and after enzymatic degradation; and the rate and sensitivity of reporter gel degradation can be enhanced through and enzymatic cascade. In synthetic reporter gels, we will test the hypotheses that the macromolecular structure of synthetic reporter gels can be detected with MRI; that enzymatic and cellular degradation will modulate the synthetic reporter gel relaxivity by changing the aggregation state of nanoparticles in gel, and synthetic reporter gels can be used to detect cells invading into a hydrogel matrix *in vivo*.

Jeffrey R. Buchhalter, M.D., Ph.D. **Phoenix Children=s Hospital**
Award Amount FY11: $100,000

Implementation of a Research Patient Data Repository at Phoenix Children=s Hospital

Research is traditionally done in one of two ways. One method involves designing a research study, then asking patients to participate when they appear in the clinic or hospital. The other way is to think of an important question and review the medical records of patients who have already been seen. This second method exposes protected health information that is not relevant to the question, and it is very time consuming and labor intensive. After reviewing a lot of charts one may discover that there are not enough patients to answer the study question. Also, if there are enough patients found, every piece of information regarding the diagnoses, age, gender, medications and chemistry, radiology, surgery, pathology results needs to be recorded for each person. Although expensive and time consuming, this method of data collection can be done for tens or hundreds of people over months to years depending on the number of patients. However, it is not feasible when thousands of patient records are involved. This proposal will create a computer-based, automated means of searching various electronic records for data and placing those pieces of information in a Research Patient Data Repository (RPDR). Using this technology, it is possible to find, compile and categorize thousands of pieces of information on each of thousands of patients. Of note, no individual patients will be identified, thereby maintaining confidentiality. The many pieces of information that will allow an investigator to know if a project is feasible will be obtained. At that point, the investigator can apply to the Institutional Review Board for permission to review actual records with the important data elements already extracted. The two goals of this study are to install the necessary hardware and software at PCH to create a RPDR, and then use it to determine the number of children with difficult to control seizures at PCH and study the outcome of children with continuous uncontrolled seizures. The RPDR will eventually be a resource for every investigator at PCH to pursue clinical research of various diseases that will enhance the lives of our patients.

Michael O. Daines, M.D. **University or Arizona**
Award Amount FY11: $112,500

Alternaria Chitin and Proteases Impact Alternative Macrophage Activation, Lung Development, and Asthma

Allergic asthma is a disease of lung remolding that often begins in childhood and can be difficult to treat. The direct costs of asthma management total billions of dollars in the United States alone, and the incidence of asthma is increasing, especially in the industrialized world. Critical to the pathogenesis of allergic asthma is allergen exposure, but allergens are not equal in their ability to act as allergic pathogens, creating asthma. In Arizona it has been shown the most important allergic pathogens causing allergic asthma is the mold *Alternaria*. *Alternaria* shares features with allergic pathogens important in other regions such as house dust mite allergens and cockroach allergens, including the presence of chitin and protease activity. Chitins and proteases may both contribute to the development of asthma. Chitin can activate inflammatory pathways that lead directly to allergic inflammation, and proteases can damage airway defenses leading to increased susceptibility to allergic pathogens. The goal of this application is to use a novel mouse model of *Alternaria* induced lung inflammation to study the effects of *Alternaria* and *Alternaria* without chitin, protease, or chitin and protease combined. The objectives are to determine the contributions of chitin and proteases to *Alternaria* as an allergic pathogen. This may lead to new techniques of treating or preventing asthma in the children of Arizona.

Hermann F. Fasel **University of Arizona**
Award Amount FY11: $133,956

Numerical Simulation of Arterial Blood Flow *in Vivo*

The treatment of cardiovascular disease (disease that includes the heart and the blood vessels) are costing the public health system billions of dollars each year. A condition that involves clogging of the oxygen rich blood vessels (the arteries), known as atherosclerosis, can lead to heart attacks and strokes. The outcome of medical procedures that open up such clogged arteries with mechanical devises (stents) or that "bypass" completely blocked arteries is often uncertain. A tool that would allow for a pre-surgery evaluation of a medical procedure is highly desirable, would reduce the number of required surgeries, and could dramatically increase their success rate. The success of surgery is determined by its ability to restore flow and/or reduce blood flow losses. The main requirement for the pre-surgery tool is, therefore, the ability to allow for realistic blood flow simulations. Computational Fluid Dynamics (CFD) has been established as the leading instrument for the analysis of flows in aerospace and mechanical engineering applications. Because of the complexity of the cardiovascular system (blood vessels are branching out into an immeasurable number of capillaries with almost fractal geometric complexity) current commercial CFD methods are not suitable for simulating such flows. We have decades of experience in the development of CFD methods and are networking with other researchers that are active in the development of problem-adapted special-purpose CFD codes. Our proposed research will result in CFD methods that are tailored for easy-to-use and cost-effective simulations of blood flow in human tissue *(in vivo*). The simulation methods will be validated by comparison with flow data obtained from in vitro measurements using a generic laboratory model. The final validation will be conducted by in vivo measurements using a generic laboratory model. The final validation will be conducted by *in vivo* measurements obtained at the University Medical Center. By forming a team of researchers from UA medical center and the UA and ASU engineering departments we will ensure that the proposed research is closely aligned with the immediate needs of the medical community.

The burden put on society in general and on the Arizona health system in particular by the increasing rate of cardiovascular disease gives reason for concern. The proposed research will result in computer methods that eventually will dramatically increase the success rate of cardiovascular surgery and care. This will bring new life and new hope to patients suffering from cardiovascular disease and ease the related financial stain put on the nation's health system. The proposed research will lay the foundation for enabling realistic blood flow simulations of increasingly larger parts of the cardiovascular system as computing power of supercomputers increase in coming years. We believe that in the not-so-distant future such computer simulations will guide procedure planning prior to surgery and improve the safety of anesthesiology in patients with cardiovascular disease.

We are not alone in this belief. In fact, two teams have already embarked along that road: The University of Chicago together with the University of Illinois and Stanford University have already started similar research. With the proposed funding we will be in a very good position to successfully compete with these two teams (or compliment their work, as this field is wide open and the rewards are enormous). Other teams will likely follow as the potential of CFD in this field becomes more obvious. There is no doubt that CFD will become a major tool for medical research and clinical care. The question is if the State of Arizona and its two major universities will be at the forefront of this development and implementation.

Timothy J. Flood, M.D.

AZ Dept. of Health Services
Award Amount FY11: $119,100

Improving the Certification of Cause of Death on Arizona Death Certificates

The State death certificate provides important personal information about the decedent and about the circumstances and cause of death. In addition, aggregated information from death certificates serves as the basis of nearly all public health programs. Having accurate cause of death information is crucial to determining the state's health priorities and measuring the success of state health programs. However, the community doctors who list the cause(s) of death on certificates receive little or no formal training on how to do this correctly. This lack of training is leading to reluctance or even refusal on of the part of physicians to perform their duty, and it may affect the quality of death information.

The research goal is to determine whether physicians and nurse practitioners (who now have authority to medically certify the cause of death) will utilize ADHS-developed training about their role in signing death certificates of persons who die of natural causes. This training will consist of a short (approximately 40-minute) on-line course that physicians can complete at their own pace. The training will explain how providers are expected to sequentially list the conditions that have led to, or contributed to, the training program (E-Learning); obtain feedback from the county medical examiners on inappropriately referred cases; determine from the participants what specific aspects of the training are helpful and that will draw colleagues to take the training; determine whether offering free credits for continuing medical education provides incentive for their participation in the training; and measure changes in the quality of the listed causes of death for certain deaths.

The project=s hypothesis is that community doctors will take advantage of the training. This will be measured in several ways: the number of doctors and nurses who complete the training; changes in proportion of natural deaths that are inappropriately referred to the medical examiner (we expect the proportion to decrease); and the proportion of medically certified cases that have more detailed causes of death rather than a generic cause such as heart disease.

Vince Guerriero, Ph.D. **University of Arizona**
Award Amount FY11: $50,000

Inhibition of Melanoma Growth by HspBP1

Melanoma accounts for approximately four percent of skin cancers but causes approximately 80% of skin cancer deaths. Skin melanoma is, therefore, one of the most aggressive tumors in humans, and a hundred thousand new melanoma cases are reported every year in western countries. Factors influencing melanoma development include excessive exposure to sun light, skin type, and genetic predisposition. Arizona residents must be extra vigilant because the state ranks No. 2 in the world in skin cancer incidence rates and Arizonans develop melanomas twice as often as residents of other states. The sole effective cure is surgical resection of the primary tumor before it achieves substantial invasion. Currently, the outlook for patients with late stage diagnosis of this type of cancer is poor.

The long term goal of this project is to explore the development of a new treatment for primary and metastatic melanoma tumors. The basis for this therapy is focused on a protein, HspBP1, that is an interaction partner to one of the molecular chaperones, HSPA1A (Hsp70). Both HSPA1A and HspBP1 are found inside the cell but are also extracellular and can interact with the outside of cancer cells. Preliminary data has shown that over expression of HspBP1 dramatically inhibits melanoma tumor growth in mice. The hypothesis to be tested is that extracellular HspBP1 can inhibit the growth of melanoma tumors. The goals are to determine if tumor growth inhibition is due to intracellular or extracellular activity of HspBP1, determine if delivery of exogenous HspBP1 will reduce melanoma tumor growth in mice, and determine if growth inhibition in the whole animal involves the immune system. New therapies are needed for the treatment of melanoma, and this project will provide new information about the mechanism by which HspBP1 inhibits melanoma growth and, therefore, potentially lead to new treatments.

William G. Johnson, Ph.D. **Arizona State University**
Award Amount FY11: $100,000

CHIR Trauma Registry

Eight hospital systems in Arizona operate centers (Level 1 Trauma Centers) that specialize in the treatment of serious injuries, and one system operates a regional center for the treatment of serious burns. These hospital systems are cooperating with ASU=s Center for Health Information and Research to create a data center that gathers and combines health care data from each system to permit a better understanding of the ways in which care is provided and, by so doing, to identify methods of improving the care of injuries and burns. The cooperative will also work to reduce errors and omissions in the data by improving the methods used to collect and enter data. The cleaned and merged data will form a research repository that can be used by the participating centers to compare performance to other centers, establish benchmarks for effective care and improve on current methods of treatment.

Do Young Kim, DVM, Ph.D. **St. Joseph=s Hospital**
Award Amount FY11: $49,509

Multiple Sclerosis-Induced Impairment of Learning and Memory

Multiple Sclerosis (MS) is a progressive disease of the central nervous system (CNS)-characterized by broad lesions in the brain and spinal cord- and affects over two million people. A prominent clinical symptom in MS is memory dysfunction. Although recent emerging findings have suggested that either dysregulated cytokines expression or oxidative stress may play a critical pathogenic role in MS, the pathological basis for MS-mediated memory dysfunction, has not been fully elucidated. Given the wide prevalence of memory dysfunction in MS patients, understanding the underlying mechanisms of MS-induced memory dysfunction is a critical key to approach therapy. While either dietary antioxidant therapy or immunotherapy is emerging as a therapeutic approach against MS following the encouraging findings in EAE model, MS remains without an effective treatment. Thus, FDA approved therapy to MS patients is not still addressed.

The principal goal of the proposed studies is to determine whether autoimmune disease induces cognitive and memory impairment using EAE model and to identify the functional correlation of either oxidative stress or cytokine expression with MS-induced cognitive impairment. This study comprises three specific aims. In the first aim, we will determine whether impairment of long-term potentiation (LTP), which is considered one of the major cellular mechanisms that underlies learning and memory, in CA1 hippocampus of EAE mice is correlated with the deficiency of spatial learning and memory. We hypothesize that EAE mice impair LTP induction and maintenance accompanied with the onset of severe disability and the pathological changes may induce a detrimental effect on synaptic integrity. Consequently, the changed synaptic arrangement may remain after a partial recovery of motor disability. In the second specific aim, we will determine whether cognitive deficiency in EAE mice is associated with the expression of oxidative stress and cytokines. We hypothesize that EAE mice may exhibit enhanced reactive oxygen species production and cytokines expression related to synaptic suppression, and that the antioxidant activity may also decrease in the hippocampus of EAE mice. In the third specific aim, we will ask whether ketogenic diet treatment induces a therapeutic effect against EAE and whether the effect is related to a regulation of cytokine expression or oxidative stress.

Kenro Kusumi, Ph.D. **Arizona State University**
Award Amount FY11: $112,500

Transcriptome Analysis and Functional Anatomy of Spinal Cord Regeneration in the Anolis Lizard

One of the most striking examples of regeneration is the ability of lizards to regrow their tails after loss. In addition to growing new muscle and cartilage, lizards are also able to regenerate the core of their spinal cord to help establish spinal nerve proliferation. Humans are not able to regenerate this core of the spinal cord like lizards. Among animals, lizards still share most of the same genetic blueprint as humans, and there is great potential for lizard studies that would advance medical therapies for spinal cord injuries. The ability to study regeneration in lizards has been limited by the lack of information about its genome, but the release this year of the draft genome sequence of the first reptile, the green anole lizard, gives us a unique opportunity to begin molecular studies.

We are currently studying spinal cord regeneration in the green anole lizard, and we propose to use a cutting-edge molecular tool, RNA-Seq, which would allow us to examine all the genes activated in spinal cord repair. We hypothesize that the shared genetic blueprint between lizards and humans will allow us to activate genes to stimulate growth of the spinal cord core. In addition, we are examining the anatomy of the spinal cord and the nerves serving regenerated muscle, which has not been well studied. Altogether, we now have a unique opportunity to learn from one of nature=s greatest examples of spinal cord regeneration and work to apply those findings to improve medical therapies for the future.

Liwen Lai, Ph.D. **University of Arizona**
Award Amount FY11: $50,000

Improving Recovery from Acute Kidney Injury by Enhancing Tubular Regeneration

Acute kidney injury (AKI) caused by trauma and various toxins is a major health care problem in Arizona. About on half of patients with AKI will die and survivors are likely to develop chronic kidney failure requiring dialysis and transplantation. The goal of this project is to develop therapeutic agents targeting the regeneration process after AKI. The approach is particularly useful because AKI is frequently diagnosed after damage has already occurred. In addition to evaluating the efficacy of potential agents, mechanisms underlying kidney regeneration will be studied to facilitate new drug development and improve clinical outcome of AKI.

Serrine S. Lau, Ph.D. **University of Arizona**
Award Amount FY11: $50,000

The Effect of Glyco-oxidative Modifications on Plasma Fibrinogen Function in Diabetes

It is estimated that diabetes afflicts nearly 24 million Americans, with nearly one third of these individuals unaware that they are actually affected by the disease. Of these diabetic individuals, approximately 95 percent of the cases represent Type 2 Diabetes Mellitus (T2DM). Complications of diabetes are conservatively estimated to be the sixth leading cause of death in the U.S., and occur disproportionately in minority populations. In 2007, the estimated total national cost of diabetes was $174 billion, the majority of which is spent solely on medical expenditures. Diabetes is a significant contributing factor to atherosclerosis and its contribution to other adverse cardiovascular diseases are not well defined. Fibrinogen is a critical plasma protein involved in the formation of blood clots. This process of blood clot formation is altered in the setting of diabetes. The mechanism by which the diabetic disease process affects fibrinogen=s structure and function is not well known. The increased blood sugar in diabetes is associated with increased information of toxic products such as methylglyoxal (MG) which is formed from broken sugar molecules. We have shown that MG is very reactive and can bind to proteins, subsequently altering their function. However, MG-mediated damage to proteins is difficult to measure and has been elusive to conventional analytical approaches. The University of Arizona has developed world-renowned proteomic technology to study damaged proteins at the molecular level. The application of this technology to a complex disease such as diabetes can not only advance our understanding of the precise mechanism by which patients develop complications but also permit a determination (prediction) of which patients are at the highest risk. After initial pilot funding we discovered that fibrinogen, isolated from plasma of two diabetic subjects, was damaged by MG. To understand whether this damage affects fibrinogen function, we added MG to blood samples in the laboratory, and indeed, fibrinogen=s ability to develop clots was impaired. In this proposal, we plan to extend our initial findings to carefully select plasma from subjects with and without diabetes and cardiovascular disease. Our aims are to continue to uncover all possible sites within fibrinogen that are modified by MG and to measure the extent to which this damage adversely influences fibrinogen function. The discovery of damaged fibrinogen is novel. The studies described in this proposal will assist in identifying subjects at risk of diabetic complications, and an understanding of how fibrinogen is affected at the molecular level may also provide drug development strategies designed to minimize the complications from T2DM.

Alexander C. McLaren **Banner Good Samaritan**
Award Amount FY11: $108,662

Understanding Antimicrobial Dynamics and Fluid Distribution in Orthopaedic Wounds for the Management of Infection and Trauma

Locally delivered antibiotics are frequently used to treat or prevent orthopaedic infections. Within hours to a few days, essentially all organisms that cause infection of bone and implants adhere to the surfaces, surrounding themselves in sugar-protein slime. This layer of glycoprotein and bacteria, called biofilm, provides an environment for the bacteria that is highly resistant to antibiotics and immune defenses. The antibiotic levels necessary to kill bacteria living in biofilm can be 100-1000 times higher than the levels necessary to kill the same bacteria living free in fluid or tissues. Because oral or intravenous delivery of such high levels would be toxic or lethal to the patient, delivery of the antibiotics must be done locally. The challenge with local delivery is to ensure that enough antibiotics reach all the areas that are infected for long enough to kill all of the bacteria. Current clinical practice involves mixing antibiotics into the cement that is usually used to attach artificial joints, and placing this antibiotic cement in the surgery site after the irretrievably infected tissue is removed. The antibiotic is released into the wound over time. The problem is that there is no way to know whether the released antibiotic reaches all the places in the wound in levels high enough and for long enough to kill the bacteria that remain after surgery. Past studies have measured antibiotic levels in fluids and tissues at specific places and at specific times. Although some antibiotic levels are measured, even when the findings from all these studies are combined there is not enough information to know if the antibiotics maintain effective levels where they are needed. These studies are not enough to understand how antibiotics spread in the surrounding tissues or how to improve that.

By delivering a MRI-detectable “drug equivalent” tracer to experimental wounds in the same way an antibiotic would be delivered locally to an orthopaedic infection, MRI can be used to map the “drug” level everywhere in the wound as time progresses. A mathematical model developed by Dr. Caplan is capable of calculating antibiotic penetration in surgical wounds and the surrounding tissues based on our understanding of tissue structure and fluid flow. This mathematical model will be used to predict antibiotic levels everywhere in the wound and the surrounding tissues as time progresses following local antibiotic delivery. It will be used to predict how different sizes and locations of wounds change the antibiotic levels and how changing the way antibiotics are locally delivered changes the antibiotic levels. The mathematical model design will be updated as new MRI measurements show how the “drug” levels change in experimental wounds. When the predictions from the model match the observed “drug” levels in the experimental wounds, the way in which tissue structure and fluid flow effect local drug delivery will be better understood.

When successful, the mathematical model will provide a predictive tool that will guide efforts to better deliver antibiotics from antibiotic cement, or other controlled release devices, to orthopaedic infections. Understanding antibiotic levels from local delivery is also important to guide locally delivered antibiotics used to prevent surgical infections. This will have a significant impact on the health of Arizonans by reducing the infection rates after routine surgery. Better treatment of infections would reduce pain and disability, and improve patient quality of life. Prevention would save an estimated $50,000 per case of infection.

Linda S. Powers, Ph.D. **University of Arizona**
Award Amount FY11: $49,999

Attenuating *Yersinia pestis* Growth by Iron Withholding

Many different strains of bacteria pathogenic to humans are acquiring new virulence strains, particularly resistance to many antibiotics. One attractive alternative to the development of new antibiotics is the development of strategies to “withhold” critical nutrients, particularly iron, that any infecting bacterium must obtain from its host. Once a pathogenic bacterium has colonized a host, it experiences a state of iron starvation that induces it to secrete a variety of molecules that strip iron ions from a variety of host sources (including hemoglobin). Interfering with these events would induce severe iron deprivation, compromising the ability of the bacterium to reproduce after initially infecting a host, thereby giving the host=s immune system more time to recognize and kill the infecting bacteria. This approach to managing a bacterial infection would circumvent critical problems with antibiotics. *Yersinia pestis*, the causative agent of plague, will be used as a model pathogen in carrying out the experimental work because of its presence in wild animal populations in Arizona (particularly rodents), our prior experience with this organism (in classified Department of Defense contracts), and a substantial body of published work to rely on. We will target two kinds of molecules that are secreted by infecting *Y. pestis*. We will then demonstrate that adding our new blocker molecules indeed prevents iron uptake by the bacterial cells and renders them incapable of rapid growth. Successful demonstration of this iron-withholding strategy would provide a proof of concept that could then be extended to *in vivo* studies, as well as other virulent bacterial pathogens.

Amy Rosenfeld, M.D. **Phoenix Children=s Hospital**
Award Amount FY11: $110,000

A Phase I Study Submyeloablative Dosing of Intravenous Busulfan (Busulfex7) for Refractory Brain Tumors

The second most common type of cancer in children is brain tumors. Treatment for this disease, which consists of a combination of surgery, chemotherapy, and radiation, can be unsuccessful. Several treatment strategies have been attempted for use when initial treatment has failed and the tumor has come back. Using a very high dose of chemotherapy has been one such attempt, but this also typically has failed. In addition, high dose chemotherapy is very toxic and results in the patient needing a bone marrow transplant.

Busulfan is a chemotherapy drug historically used at high doses for transplant. Busulfan is a unique chemotherapy agent because it crosses the barrier separating the brain from the rest of the body more easily than other chemotherapy drugs. Thus, it may be very useful in treating brain tumors in children at a lower, less toxic dose. If this is in fact the case, then children might not have to go through a bone marrow transplant procedure which can have a lot of side effects.

Samuel F. Schluter, Ph.D. **University of Arizona**
Award Amount FY11: $112,500

Characterization of the Signaling and Immunomodulatory Activities of Human Autoantibodies to the Delta and Mu Opioid Receptors

Opioid receptors are cell surface proteins expressed on neurons throughout the nervous system. The biological activity of opioid neuropeptides ligands (the molecules in the body that bind to opioid receptors) are mediated by three classes of opioid receptors; mu, delta and kappa. The interaction of these receptors with specific ligands control pain pathways and exert significant influences on emotional responses. Ligands that bind the mu receptor are the drugs of choice (e.g., morphine) for treatment of pain; however, these have numerous adverse side effects including suppression of respiration, constipation and in some cases addiction. The control of pain is a significant problem in health care, and considerable research is being done to find effective drugs that are not associated with adverse side effects. There is evidence that drugs targeted to the delta receptor are very effective analgesics and have significantly less adverse side effects. For reasons that are not fully understood, the same opioid receptors found on nerve cells are also widely expressed on many immune system cells types. This may explain why pain drugs not only induce analgesic responses but also significantly effect and suppress immune responses. Conversely, the immune system of healthy individuals produces specific autoantibodies against the opioid receptors, which have ligand activity and can initiate cell signaling events triggered by opioid receptors. Thus, there appears to be a bidirectional communication network between the neuroendocrine and immune systems. Normally, cells of the immune system are educated to recognize non-self from self during development, and this is a critical checkpoint since reactivity to self can cause tissue damage leading to autoimmune diseases. The earlier dogma of horror autotoxicus, according to which all autoantibodies were considered to contribute to autoimmune disease, has been replaced by the knowledge that the presence of a low level of circulating serum autoantibodies is a hallmark of a healthy immune system.

While the exact function of this subset of antibodies remains to be clearly elucidated, it is believed that autoantibodies contribute to the maintenance of immune homeostasis. A major goal of our laboratory research activities is the characterization of the activities and functions of natural autoantibodies. We hypothesize that these natural autoantibodies are not deleted during development and are part of a normal immune system since their actions have been selected for their favorable positive effects. Furthermore, we propose that this pool of natural autoantibodies may be a source for the isolation of monoclonal antibodies with significant therapeutic potential. In other words, nature may have already provided solutions for targeting and controlling autoimmune and other diseases. Under previous ABRC support, we have developed efficient methods to isolate autoantibodies as monoclonal preparations (i.e., homogenous preparations produced from a single cell population, rather than the extremely heterogeneous population found in blood) that allow precise evaluation of the activities and functions of these molecules.

The goal of this proposal is to characterize the activity and function of human autoantibodies specific for opioid receptors. In this proposal, our focus is on autoantibody activity against the delta opioid receptor, a receptor shown to be present on immune cells such as lymphocytes and monocytes. We propose to generate human monoclonal antibodies against the parts of the delta opioid receptors exposed on the cell surface that form the ligand binding receptor regions. We will investigate the ability of these antibodies to activate the signaling pathway associated with opioid receptors as the first step in characterizing the biological activity of the autoantibodies. Secondly, the effects on the immune system will be assessed by the ability to modulate several immune activities of immune cells isolated from human blood. It has been shown that morphine increases susceptibility to HIV infection. Therefore, we will also test the ability of these autoantibodies to modulate the expression levels of cell surface chemokine receptors since these are the co-receptors on cells necessary for HIV-1 infection.

The work proposed here will provide analytical reagents for specifically imaging opioid proteins, and for investigating the specific roles of the different surface regions in ligand binding and initiation of signaling pathways. Although we intend to perform *in vitro* assays in this proposal, the results will provide a rational basis for future translational work to test the potential of anti-opioid monoclonal antibodies as therapeutic reagents, either for analgesia or manipulation of immune response.

Joyce A. Schroeder, Ph.D. **University of Arizona**
Award Amount FY11: $112,500

Theranostic Development for the Treatment of Metastatic Breast Cancer

Breast cancer is the third leading cause of cancer-related deaths in Arizona. The majority of these patients die when breast cancer spreads from the breast to distant sites in the body (metastasis). While current chemotherapeutic treatments are making small gains against this devastating disease, the need for a treatment that targets a larger number of patients is needed.

Metastatic breast cancers typically express and are driven by a particular class of proteins known as the erbB receptors. This category of breast cancer is also highly metastatic and deadly as it is unresponsive to most standard therapies. By identifying molecular interactions specific to this breast cancer subtype, we have identified targets that may allow us to develop a novel and nontoxic therapy.

Our proposal is to develop an erbB3-specific theranostic, which is a peptide-based therapy that combines treatment with imaging, allowing clinicians to effectively monitor tumor-response. Our current proposal would allow us to take this goal to preclinical completion, including *in vivo* testing of efficacy in cell lines, preclinical testing on animal models and evaluation of *in vivo* imaging.

Michael Sierks, Ph.D. **Arizona State University**
Award Amount FY11: $157,500

Intracellular Targeting and Clearance of Toxic Synuclein Aggregates

The protein, *a*-synuclein, is strongly correlated with Parkinson=s Disease (PD) and other related neurodegenerative disorders and is a major component of the hallmark Lewy Bodies indicative of PD. The a-synuclein (a-syn) protein can adopt a number of different aggregated morphologies including various oligomeric species which are increasingly implicated in disease progression. While specific aggregated forms of a-syn are likely to be a causative factor in PD, several studies have indicated that a-syn has protective functions in neurons. An effective therapeutic for PD should thus target only the toxic forms of a-syn without affecting other forms.

Using a novel biopanning protocol developed in our lab, we have isolated recombinant antibody fragments that specifically recognize different forms of a-syn. The antibody fragments can block aggregation and toxicity of a-syn *in vivo* and also in cell models of PD. Since a-syn aggregation occurs inside cells, the morphology specific antibody fragments when expressed intracellularly as an intra-body provide a means to test whether targeting specific forms of a-syn intracellularly represents an effective therapeutic strategy for treating PD. Studies in cell models of PD show that targeting and clearing toxic oligomeric a-syn aggregates with intracellularly expressed recombinant antibodies can provide complete protection against toxicity. These very promising studies demonstrate that targeting and clearing specific toxic aggregate species has tremendous potential for treating PD by reducing a source of neurotoxicity. Here we propose to demonstrate that this therapeutic approach works in animal models of PD. Since some forms of a-syn have protective effects for cells, an effective therapeutic would target only toxic forms of a-syn leaving other beneficial forms untouched. The therapeutic approach proposed here will not alterthe a-syn function, but will only target toxic aggregated forms offering important benefits over other approaches including minimizing side effects that could result from reducing monomeric a-syn function, targeting a potential cause of the disease rather than treating symptoms resulting from neurotoxicity, and establishing a paradigm for treating other protein misfolding diseases.

David M. Treiman, M.D. **St. Joseph=s Hospital**
Award Amount FY11: $100,000

A Bench-to-Bed-Side Approach to Prediction of Post-Traumatic Epilepsy after Traumatic Brain Injury in Head Trauma Patients Using Quantitative Analysis of EEG

Traumatic brain injury (TBI) from injuries to the head is a major public health problem in the United States. There are about 1.5 million cases of TBI in the civilian population each year. Head trauma is also common in wartime. This is especially true in the current Iraq and Afghanistan conflicts where TBI has been called “signature wound” because it is more common than in any other war, mostly due to a higher rate of survival and the frequency of blast injuries. Head trauma is a common cause of epilepsy, which is the second most common neurological disorder after headache. Uncontrolled epilepsy is acquired in a previously healthy person as the result of brain trauma. Anywhere from 5 percent to 50 percent of people who suffer TBI will develop post traumatic epilepsy (PTE), usually within the first two years after TBI. The percent of people who develop PTE is determined by a number of factors, the most important of which is the severity of the brain injury.

A critical problem for neurologists who care for patients with TBI is to be able to predict which patients will develop post traumatic epilepsy. Up to now there has been no reliable method to make such a prediction. However, if it could be determined with a high degree of accuracy which TBI patients will develop PTE, this would have at least two major benefits. The first is that antiepileptic drugs could be started shortly before PTE is predicted to develop and thus prevent the devastating effects of epileptic seizures. The second is that when effective antiepileptogenic drugs (drugs that prevent the development of epilepsy after some sort of insult to the brain, including TBI) are developed, as is highly likely in the near future, administration of such drugs could be limited to only those individuals with a high probability of developing PTE, without subjecting the other 50 percent to 95 percent of TBI patients who are unlikely to ever develop PTE to the potentially toxic effects of such drugs and the necessity of daily drug administration. A further benefit would be that a highly accurate PTE prediction procedure should also lead to greater understanding of the reasons that PTE develops. This in turn may lead to the development of more effective antiepileptogenic drugs. Only through understanding the mechanisms by which epilepsy actually develops can we start to investigate therapies that directly intervene in that process, thereby preventing epilepsy from occurring in the first place.

This project proposes to use computerized analysis of EEG (brain waves) to predict which individuals will develop PTE after TBI and which will not. We have very exciting but very preliminary data that suggest that we can differentiate between these two groups using a refined EEG analysis procedure. We will get further data from a rat model of PTE and refine our EEG analysis procedure in the first year of the study. We

will then apply the procedure to human patients who have suffered TBI to translate our results to human patients.

This project is of direct relevance to the people of Arizona. It will mean better and more timely care for people in Arizona who suffer TBI and are likely to develop PTE, a number that is expected to grow dramatically with the return of combat troops who have suffered from head injuries incurred in the current wars in Iraq and Afghanistan. Furthermore, the intellectual property that will be generated through this project should lead to investment opportunities and commercial development of the procedure and associated hardware within the state of Arizona.

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Development of Antiviral Susceptibility Test Methods for the 2009 Pandemic and Seasonal Influenza Viruses for State and Local Public Health Interventions

Influenza is a rapidly progressing and fatal infection particularly in people who are subjected to certain risk factors such as pregnancy, those who are immunocompromised, or those with chronic underlying disease. People in these high risk categories who are treated with inappropriate antiviral medication are more likely to succumb to the disease. There are four subtypes of influenza A virus currently circulating among people worldwide: seasonal H1N1, 2009 H1N1 (aka: the Swine flu virus and novel H1N1 virus), H1N2, and H3N2. However, during the 2009-2010 influenza season, over 99 percent of all subtyped influenza A viruses in the United States have been 2009 H1N1 viruses. Influenza antiviral resistance testing for the currently available antiviral drugs (adamantanes and neuraminidase inhibitors) is currently performed using conventional DNA sequencing or pyrosequencing method, to look for specific genetic mutations. This sequencing typically is limited to large reference or research laboratories. These methods are labor intensive, require highly skilled technicians, are relatively expensive, and have been used more for surveillance rather than diagnostic purposes. Development of rapid antiviral resistance tests for the purposes of statewide influenza surveillance activities and patient treatment can lower the risk for an adverse outcome for patients. The Arizona State Public Health Laboratory (ASPHL) proposes to work with the Translational Genomics Research for the detection and characterization of antiviral resistance in influenza viruses in Arizona. The ASPHL will work with TGen North to build a repository of samples containing both novel and seasonal strains of circulating influenza viruses collected throughout the influenza seasons. TGen will use these viruses for development of a new assay capable of detecting antiviral resistance in influenza samples and to rapidly provide physicians with more information ultimately leading to more effective patient treatment.