Arizona Department of Health Services

Arizona Biomedical Research Commission

Annual Report 2013–2014

Accelerating Biomedical Research and Innovation in Arizona

Front Cover and Section Photographs

Arizona Public Cord Blood Program Artwork

Permission granted by Yovannah Diovanti of Diovanti Designs to use program artwork for the annual report only. Artwork may not be copied, duplicated, or used in any other publications, brochures, or designs without the expressed written consent of Yovannah Diovanti

http://fineartamerica.com/art/all/Yovannah+diovanti/all

Notice

The Arizona Department of Health Services does not discriminate on the basis of disability in the administration of its programs and services as prescribed by Title II of the Americans with Disabilities Act of 1990 and Section 504 of the Rehabilitation Act of 1973.

If you need this publication in an alternative format, please contact:

Arizona Biomedical Research Commission

150 N. 18th Avenue, Suite 550, Phoenix, Arizona 85007

(602) 364-0157

Biomedical@azdhs.gov

Arizona Biomedical Research Commission

Annual Report: 2013–2014

Douglas A. Ducey
Governor, State of Arizona

Will Humble
Director, Arizona Department of Health Services

Commissioners

General Public

Toni J. Eberhardt, M.B.A.

Jeanette K. Shea, M.S.W., L.C.S.W.

Medical Community

Peter C. Kelly, M.D.

Howard C. Pitluk, M.D., M.P.H., F.A.C.S.

Mitchell Shub, M.D.

Scientific Community

Kasey L. Benson, Ph.D.

Iman A. Hakim, M.B.B.Ch., Ph.D., M.P.H.

Thomas Lon Owen, Ph.D.

Commission Staff

Tracey E. Sotelo, M.B.A.
Executive Director

Theresa Napoleon
Commission Coordinator

Daniel Powell
Administrative Services Officer II

ADHS Support Staff

David Havrilla
Program & Project Specialist II

Marianne Morrow
Finance Lead

Table of Contents

Executive Summary 1

About ABRC 2
- Our Mission 2
- Strategic Map 2

The Commissioners 3
- Commissioner's Role 3
- Commissioner's Bio 3
- Commission Meetings 7

Financial Summary 8
- Fiscal Year 2014 Revenue 8
- Fiscal Year 2014 Expenditures 9

Program Activities 10
- Program Activities 11
- Research Grants 12
- Arizona Biospecimen Locator 70
- Research Education 72
- Arizona Public Cord Blood Program 75
- Other Research 78
  - Arizona Alzheimer's Consortium 78
  - Translational Research Facility 80

Executive Summary

It's been a remarkable year at the Arizona Biomedical Research Commission (ABRC), full of exciting changes and progress. As we strive to fulfill our mission of "Identifying and supporting innovative biomedical research to improve the health of all Arizonans", we recognize that none of these achievements would be possible without the unwavering support of our valued community partners, Agency leadership, the Governor's Office, and Legislators.

In fact, community support has become an integral part of our successes. Our partners worked tirelessly to discuss ways in which existing programs could be leveraged, collaborated on campaigns to increase program awareness, and generously gave of their time and resources. Together, we've achieved many program milestones.

Key Highlights for 2014:

- Awarded 29 new grants
- Initiated two conferences
  - From Research to Practice: Funding For A Healthier Arizona
  - Institutional Review Board Educational and Networking Event
- Partnered with Tucson Medical Center to expand umbilical cord blood collections in Southern Arizona
- Revised and reissued umbilical cord blood patient information pamphlet in accordance with §32-3212

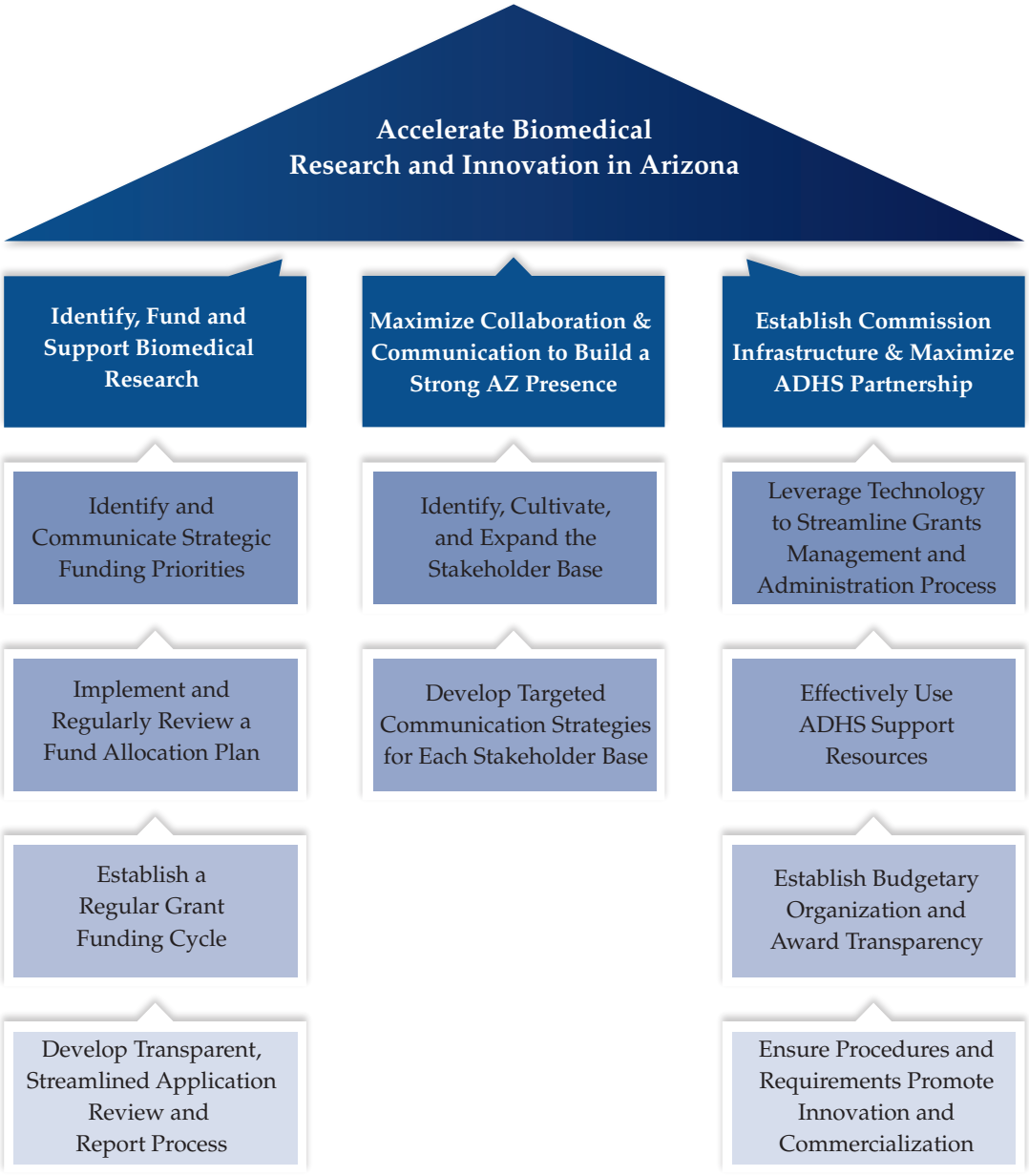
We look forward to serving Arizona in the years to come and will continue to work towards supporting research, by stewarding the funds wisely, and continuing to leverage community partnerships productively.

Our Mission

Identify and support innovative biomedical research to improve the health of all Arizonans.

Strategic Map

The ABRC Strategic Map outlines the renewed commitment to identify and support innovative biomedical research in Arizona. Carefully constructed, the map is focused on leveraging existing resources, maximizing partnerships, cultivating communication, and promoting innovation.



The Commissioners

The Commissioners' Role

The Commission has nine members appointed by the Governor and confirmed by the Senate. The Commission is an integration of three communities: General Public, Medical, and Scientific Research. Each community is represented by three Commissioners appointed for three-year terms.

In accordance with A.R.S. §36-272, the Commission shall advise the department regarding ways to advance research relating to:

1. The causes, epidemiology, and diagnosis of diseases.
2. The formulation of cures for diseases.
3. The development of medically accepted treatment and prevention of diseases, including the discovery and development of new drugs.

The Commissioners guide the work of ABRC by establishing research priorities and identifying key challenges and potential solutions to biomedical research in Arizona. Priorities could range from regional diseases (such as valley fever) to ubiquitous conditions (such as targeted diagnosis or treatment for cancer). Challenges to research may range from increasing availability and access of biospecimens to increasing communication between researchers within fields.

Commissioner Bios—General Public

Toni J. Eberhardt, M.B.A.
Public Relations Director
Banner Medical Group

Commissioner Toni J. Eberhardt is the Director of Public Relations for Banner Medical Group (BMG), Banner Health's employed physician group. In this role, she manages the public relations, marketing, and internal and executive communications for BMG which includes over 1,000 employed physicians across seven states.

Commissioner Eberhardt began her career in the healthcare industry with McKesson, the largest healthcare solutions company in North America. At McKesson, she was the Director of Marketing Communications for McKesson Specialty. As part of her responsibilities, she developed and executed the communications strategies for the Centers for Disease Control and Prevention's (CDC) Vaccines for Children and H1N1 national distributions. In addition, Commissioner Eberhardt worked with bio-tech manufacturers of specialty pharmaceuticals in oncology, rheumatology and other complex disease states to develop patient education and adherence programs.

Commissioner Eberhardt is a fellow from Class IV of the Flinn-Brown Arizona Center for Civic Leadership. She received her Bachelor of Science in Marketing from Arizona State University and also earned her Master of Business Administration.

Jeanette K. Shea, M.S.W., L.C.S.W.
Chief Executive Officer
Jeanette Shea & Associates, L.L.C.

Commissioner Jeanette Shea is the owner and Chief Executive Officer for Jeanette Shea & Associates, L.L.C., a full service consultation and training firm. As the former Assistant Director for the Arizona Department of Health Services, Public Health Prevention Services, Commissioner Shea was responsible for providing leadership in public health prevention services, overseeing the bureaus of Women's and Children's Health, Nutrition and Physical Activity, Health Systems Development and Tobacco and Chronic Disease. Trained as a Social Worker, specializing in planning, administration, and community development, she has worked in healthcare for more than 30 years. Commissioner Shea has also served as a liaison with federal, state, and local health agencies.

Commissioner Bios—Medical Community

Peter C. Kelly, M.D., F.A.C.P.
Infectious Diseases Consultant
Arizona Department of Health Services
Bureau of Public Health Emergency Preparedness

Commissioner Peter Kelly is an infectious disease physician. Dr. Kelly was educated at Providence College and Boston University School of Medicine. He completed an Internal Medicine residency and an Infectious Diseases fellowship at the State University of New York at Buffalo. He is a diplomat of the American Board of Internal Medicine and Infectious Diseases.

Commissioner Kelly maintains professional affiliations with the American College of Physicians, the American Society for Microbiology, the Infectious Diseases Society of America and the Arizona Medical Association. Commissioner Kelly is a past president of the Arizona Infectious Diseases Society.

Early in his career, Commissioner Kelly joined the medical staff at Maricopa Medical Center as Chief of Infectious Diseases in the Department of Internal Medicine and later served as President of the Medical Staff. He was active in the Internal Medicine Residency Program and was Program Director for a portion of his time there. He was also Chairman of the Infection Control Committee for many years. He has a career long interest in Coccidioidomycosis and has published in this field.

Currently, Commissioner Kelly is an infectious disease consultant to the Arizona Department of Health Services in the Bureau of Public Health Emergency Preparedness.

Howard C. Pitluk, M.D., M.P.H., F.A.C.S.
Vice President for Medical Affairs and Chief Medical Officer
Health Services Advisory Group (HSAG)

Commissioner Pitluk, HSAG's Vice President for Medical Affairs and Chief Medical Officer, works closely with healthcare providers and stakeholders to furnish information and guidance on the public reporting of clinical data, development of quality improvement plans, and incorporation of evidenced-based quality improvement clinical measures into all aspects of patient care. His special interest in health information technology is focused on the use of electronic health records (EHRs) to advance patient care, enhance quality measurement and outcomes, and facilitate transitions of care between clinical settings.

Commissioner Pitluk has more than 35 years of experience in healthcare. From 1979 through 1998, he practiced general and vascular surgery in Cleveland, Ohio and was an Associate Clinical Professor of Surgery at Case-Western Reserve University College of Medicine. He has held Board Certification from the American Board of Surgery and remains a Fellow of the American College of Surgeons. Upon completion of his Master's Degree in Public Health in 2001, he led the formation of the Institute for Consumer Empowerment, a consortium of healthcare professionals dedicated to the education and self-activation of patients and providers in a holistic approach to wellness and disease prevention.

Commissioner Pitluk joined Health Services Advisory Group in 2001 as a Physician Advisor and has been continuously engaged in the promotion of a multidisciplinary approach to patient centered care leading to his present position.

Mitchell Dennis Shub, M.D.
Division of Gastroenterology, Co-Chair, IRB, Phoenix Children's Hospital
Professor and Vice-Chair, Department of Child Health
University of Arizona College of Medicine-Phoenix

Commissioner Mitchell Shub is a Pediatric Gastroenterologist and received his M.D. from the University of Vermont. He completed a residency in Pediatrics at Duke University Medical Center and a fellowship in Pediatric Gastroenterology at Massachusetts General Hospital and Harvard Medical School. 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). He previously served as Co-director of the Pediatric Residency Program and as Division Chief of Gastroenterology. Commissioner Shub was elected President of the Medical Staff and served a 2 year term and was appointed as the first Medical Director of Research at PCH.

Commissioner Shub is Vice-chair and Professor, Department of Child Health for the University of Arizona College of Medicine, Phoenix. 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, Commissioner Shub has been appointed to various leadership positions in the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. He also served as 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 Bios—Scientific Community

Kasey L. Benson, Ph.D.

Commissioner Kasey Benson earned her Ph.D. in Biochemistry and Molecular Biology from Colorado State University (Fort Collins, CO), and a B.S. in Biology from Rocky Mountain College (Billings, MT). She is a Good Laboratory Practices (GLP)-trained biochemist with research experience for Covance, Amgen and the Mayo Clinic, among others.

As part of Commissioner Benson's most recent work with the Mayo Clinic, she focused on identifying ways to improve treatment of myeloproliferative neoplasms via the screening of drugs in leukemic cell lines and primary patient samples. Earlier, with Covance, Commissioner Benson was the scientific lead for the immunogenicity program, which included design and conduct of immuno- and bio-assays.

Iman A. Hakim, M.B.B.Ch., Ph.D., M.P.H.
Dean, Mel & Enid Zuckerman College of Public Health
University of Arizona

Commissioner Iman Hakim is the Dean of the University of Arizona Mel and Enid Zuckerman College of Public Health (MEZCOPH). She is the Mel and Enid Zuckerman Endowed Chair in Public Health and the founding director of the Global Health Institute at MEZCOPH. She is internationally known for her translational research and work on the role of phytochemicals such as green tea and limonene in modulation of oxidative damage and prevention of chronic diseases such as cancer and cardiovascular diseases. Her research focuses on health promotion, dietary interventions, and the role of gene-environment and gene-nutrition interactions in chronic disease prevention. She has been the principal investigator of several large-scale, behavioral change interventions and clinical trials focused on nutrition and cancer prevention; tea consumption and coronary heart disease; nutrition and tobacco; chemoprevention of lung carcinogenesis using green tea; dietary interventions to study the effects of tea consumption on smoking-related oxidative stress; and role of citrus-cancer association in Mediterranean diet.

Commissioner Hakim earned her medical degree from Cairo University in Egypt where she completed her Pediatric residency. She received her Ph.D. in childhood studies from Ain Shams University in Cairo and her MPH from the University of Arizona. Commissioner Hakim worked as a researcher and as an assistant and associate professor at the National Research Center in Egypt. She is a tenured Professor at the University of Arizona. Her current other academic appointments at the University of Arizona include the Arizona Cancer Center, the Sarver Heart Center, the College of Medicine and the Department of Nutritional Sciences at the College of Agriculture and Life Sciences.

Thomas Lon Owen, Ph.D.
Professor Emeritus of Biological Sciences
Northern Arizona University

Commissioner T. Lon 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 University of California-Davis. He was a National Institutes of Health Postdoctoral Fellow at Michigan State University and visiting associate professor in the Pharmacology Department of the University of Arizona College of Medicine.

Commissioner Owen has chaired the Research Committees of the American Heart Association at both the Arizona affiliate and Southwestern Regional levels. He has been published in the areas of cardiovascular, aging, and environmental physiology. He is Professor Emeritus at Northern Arizona University.

Commission Meetings

A.R.S. §36-272(E) states that the Commission shall meet at least quarterly at the call of the chairperson. During 2014, the Commission met five (5) times to evaluate processes, identify a marketing and communications campaign strategy, and review proposed research projects.

For the upcoming year, the Commissioners will be focused on determining funding categories, streamlining the application process, and establishing a regular funding cycle.

Meeting Date	Meeting Highlights
March 28, 2014	ADHS Production Studio Tour Introduction of Constant Contact for ABRC Newsletters and Updates
June 19, 2014	BioAccel and TGen Guest Presentation
September 12, 2014	RFGA Evaluation Committee met to Review and Discuss 213 Applications
September 26, 2014	RFGA Evaluation Committee met to Review and Discuss 213 Applications
October 5, 2014	Recommendation to Fund 30 Research Projects totaling $3,775,000 for FY 2015

*Agendas and meeting minutes can be viewed at http://azdhs.gov/biomedical/meetings/index.htm.

Financial Summary

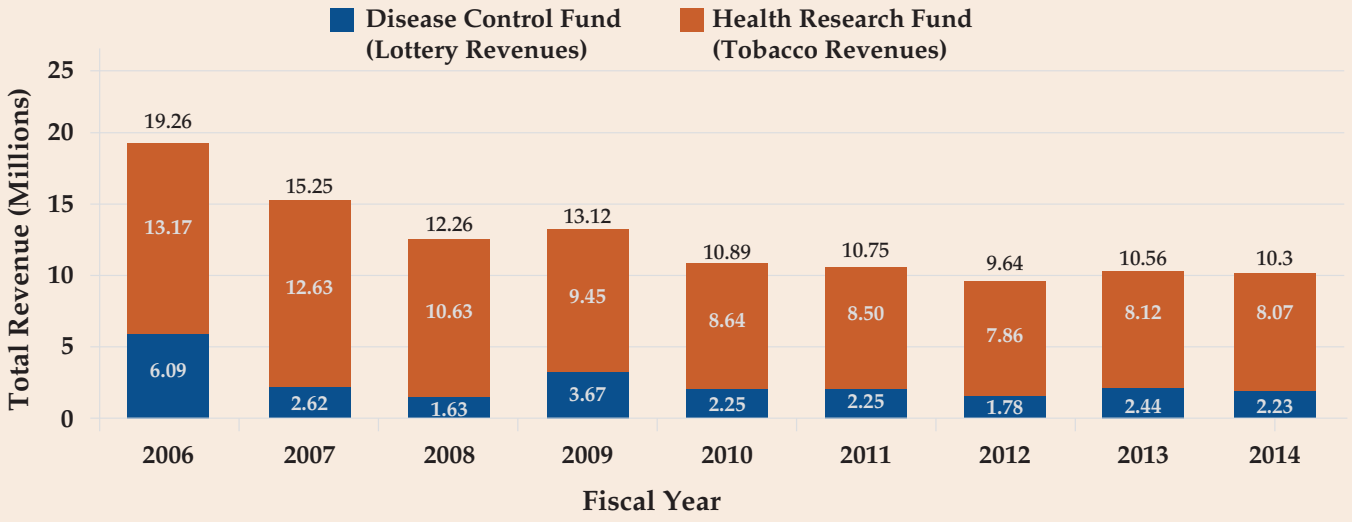
The purpose of the Commission, envisioned by its founders, was to provide competitively awarded funding for research in Arizona. The original funding source was tax penalties and interest from delinquent sales tax collections. Today, ABRC receives its funding from two sources: the Disease Control Research Fund (ARS §36-274) and the Health Research Fund (ARS §36-275).

The Disease Control Research Fund consists of monies received from the Arizona lottery which have been allocated under the Lottery's Health and Welfare programs. The Health Research Fund consists of monies received from the tobacco tax; ABRC receives 5 cents of each dollar deposited into the Tobacco Products Tax Fund and the Tobacco Tax and Health Care Fund. Both the Disease Control Research Fund and the Health Research Fund are non-lapsing, non-appropriated fund sources. In addition to the revenue received from the Arizona lottery and the state's tobacco tax, both funds earn interest on the balances invested with the State Treasurer.

Revenue

For Fiscal Year 2014, ABRC's total combined revenue was $10.3 million. The distribution of all the revenue sources, seen in the below chart, breaks out as follows: the Disease Control Research Fund equated to $2.23 million or 21.7% of ABRC's total revenue and the Health Research Fund revenue makes up 78.3% or $8.07 million.

Historic ABRC Revenue Distribution

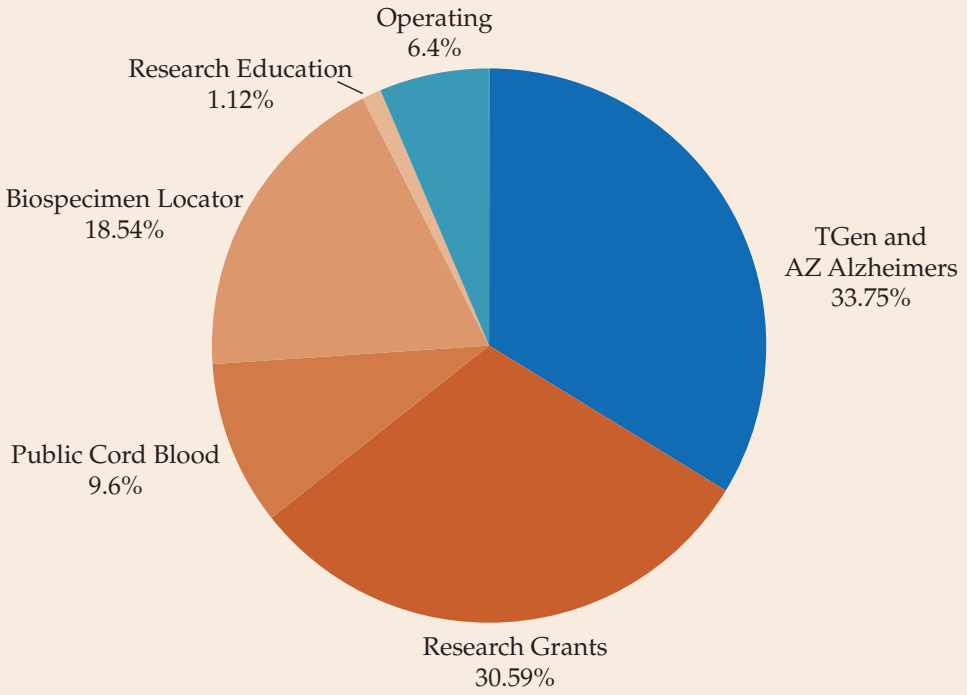


Expenditures

In FY 2014, ABRC expended $8.89 million. This included $5.72 million in research grants, 64.34% of all expenditures; a 20% drop compared to FY 2013. Of the research funding, $3 million went towards non-competitive research awards, which included the Translational Genomic Research Institute—TGen ($2.00M) and the Arizona Alzheimer's Consortium ($1.00M). The remainder of the research funding, $2.72 million, was awarded to competitively selected research projects in the final year of funding.

To meet the needs of ABRC's core programs (Biospecimen Program, Research Education, and Arizona Public Cord Blood Program), a combined total of $2.6 million was expended; these three areas constituted 29.26% of ABRC's total expenditures. Only $0.57 million, 6.4% of expenditures, was used to cover program operations. The pie chart provides a breakout of ABRC's FY 2014 expenditures.

ABRC FY 2014 Expenditures



Program Activities

Program Activities

ABRC is more widely known for its grant funding to the Arizona community. In addition to providing competitively awarded funding for research in Arizona, ABRC recognized its role to help advance Arizona as a bioscience leader. To do this, multiple initiatives were launch guided by input from leaders and professionals from Arizona's universities, nonprofit research institutions, hospitals, medical centers, and patient advocacy groups. Many of those initiatives have evolved into distinct programs: Research Grants, Arizona Public Cord Blood Program, Arizona Biospecimen Locator, and Research Education.

As a result of funding, these programs have created the following positive impacts for Arizona:

- A focus on special Arizona population needs—Projects funded include Valley Fever, rabies transmission models, cures using desert plants, scorpion anti-venom, sun-induced skin cancer, and targeted health promotion and prevention strategies for the Hopi tribe.
- Additional research dollars brought into Arizona—Researchers use the projects funded by ABRC to generate the preliminary data needed to apply for larger grants. An additional $1,481,000 in outside funding was secured to continue and further advance their projects.
- Jobs funded—ABRC funded research grants resulted in the employment of 57 Arizonans (percentage basis at either full or part-time). Under the Biospecimen Locator and Cord Blood Programs, ABRC funds a total of 26 positions—15 are full time employees of the program partners.
- Publications and presentations—In Fiscal Year 2014, ABRC funded research grants resulted in 13 articles submitted for publication and 55 invited papers, panels, and presentations.

Research Grants

At-A-Glance

RESEARCH GRANTS

Funding Source Used

Health Research Fund

Disease Control Research Fund

About the Program

Funding is provided through a competitive grant process to accelerate promising research toward clinical testing and breakthroughs designed to improve the health of all Arizonans. While our strong emphasis is on funding basic and translational research projects to generate preliminary data, we continue to seek innovative projects that leverage all of Arizona's resources and strengthen collaboration.

Research Projects supported include those that may advance the prevention and treatment of tobacco related disease and addiction, and research that is aimed at the causes, epidemiology, and diagnosis of diseases, the formulation of cures, the medically accepted treatment, or the prevention of diseases, including new drug discovery and development; and that may include behavioral studies and attitude assessments.

Program Highlights

23 Ongoing Research Projects

29 New Research Projects Awarded

Ongoing Research Projects

In the past, the Commission has awarded funding based on three distinct request types.

Category I

- Individual principal investigator award
- Aimed at testing basic research hypotheses
- Project collects data to support request for additional funding from other sources
- Amount awarded is limited to $50,000 per year
- Three-year grant award

Category II

- Collaborative approach
- Aimed at basic research or translational research
- Goal for investigators is to seek larger funding from other sources
- Amount awarded is up to $150,000 per year
- Three-year grant award

Category III

- Limited to senior researchers
- Conducts on-going basic or translational research
- Work product goal is to seek larger federal grant funding, move into clinical trials/device studies, or commercialize the invention.
- Amount awarded varies
- One to three-year grant award

23 awards expired June 30, 2014. Research Project Abstracts and related information begin on the next page.

David Adelson, M.D.

Phoenix Children's Hospital

Annual Award Amount

$149,946

Project End Date

June 30, 2014

Rapid Cycle Outcomes Research to Improve Clinical and Operational Outcomes

The project aims are directed toward a main goal of enhancing the continuous improvement of clinical outcomes. We will develop working templates for expansion of outcome research (OR). OR focuses primarily on the end results of medical care episodes to help determine if they are efficacious, are clinically effective, are of high quality, improve quality of life, improve patient satisfaction, and are cost-effective. Therefore, OR presents itself as a natural way to approach the existing problem of medical errors and health care efficiency. Specifically, care that has poorer outcomes than anticipated could be due to errors, ineffective care prescriptions, and/or ineffective delivery systems. Care that is better than expected may be due to fewer errors, effective care prescriptions, and/or effective delivery systems. The study will use a 3-fold methodology which divides the studied time period between pre-intervention, intervention implementation, and post-intervention periods.

Trent Anderson, Ph.D.

University of Arizona

Annual Award Amount

$49,995

Project End Date

June 30, 2014

Sex Hormones and Neurosteroids as Triggers of Migraine Headache

Cortical spreading depression {CSD) is a profound depolarization of neurons and glia that migrates across the cortex and is known to lead to migraine pain. The incidence and severity of migraine is linked to hormonal changes and in this proposal we are specifically investigating the influence of brain derived hormones known as neurosteroids on cortical excitability and CSD. Over the last year we have been focusing on Aim 2 examining exposure of neurosteroids on CSD. Outside of the initial scope of the project, we have developed an innovative new imaging and electrophysiology modality that takes advantage of new optogenetic approaches. This cutting edge approach has refined the experimental approach and has been successfully used to complete and reach beyond our initial experimental expectations. We have discovered that neurosteroids paradoxically increase cortical excitability and decrease the threshold for CSD. Using our optogenetic approach we have discovered key neuronal cell types, specifically cortical pyramidal neurons, to be a site of neurosteroid action and specifically have shown that inhibition of pyramidal neurons directly can prevent propagation of CSD. The altered cortical excitability, and actions of pyramidal neurons on CSD may pay important roles of the influence of hormones on migraines. The work through funding from the ADHS has been instrumental in developing our research program and has lead to the successful awarding of a 1.65 million dollar National institute of Health—ROI grant award.

Publications

Venugopal S, Konowalik A, Anderson Tr. Select action of neurosteroids on phasic and tonic GABAergic neurotransmission in layer V cortical neurons. (In preparation, anticipated submission fall 2014 to Journal of Physiology) (Impact Factor: 4.834).

Goddeyne C, Anderson Tr. Neurosteroids act through GABA-A receptors to enhance cortical spreading depression (In preparation, anticipated submission fall 2014). Journal of Neuroscience. (Impact Factor: Impact Factor: 7.87).

Leslie Boyer, M.D.

University of Arizona

Annual Award Amount

$183,170

Project End Date

June 30, 2014

Remote Entry Global Information System for Translational Envenomation Research (REGISTER)

The purpose of this project is to establish a registry for rare and unusual envenomation cases and to use this registry in retrospective and prospective clinical and translational research protocols. During this reporting period: we finalized the REDCap registry and starting populating it with existing cases; we programmed, tested and activated the web interface; we met three times with the Board of Advisors; we appealed to VIPER member professionals regarding submission of research proposals; the Board of Advisors assisted in the selection of 2 proposals; both pilot studies were initiated and data collection was completed; and we developed a draft online envenomation patient questionnaire.

Publications

Boyer, LV; Degan, J; Ruha, A-M; Mallie, J; Mangin, E; Alagón, A. "Safety of Intravenous Equine F(ab')$_2$: Insights Following Clinical Trials Involving 1534 Recipients of Scorpion Antivenom." Toxicon. http://dx.doi.org/10.1016/j.toxicon.2013.07.017.

Boyer, LV; Theodorou, AT; Chase, PB; Osnaya, N; Berg, M; Mallie, J; Carbajal, Y; de Jesus-Hernandez, T; Olvera, F; Alagón, A. "Effectiveness of Centruroides Scorpion Antivenom Compared to Historical Controls." Toxicon. 2013. http://dx.doi.org/10.1016/j.toxicon.2013.07.014.

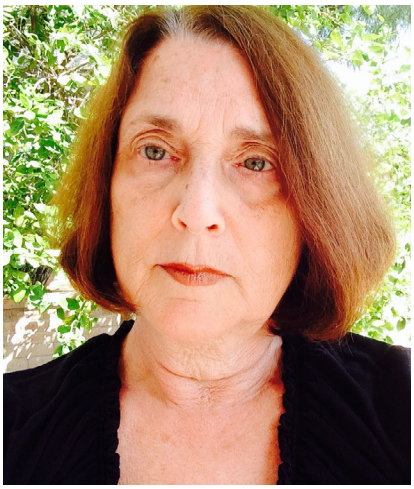
Boyer, LV; Chase, PB; Degan, JA; Figge, G; Buelna-Romero, A; Luchetti, C; Alagón, A. "Subacute Coagulopathy in a Randomized, Comparative Trial of Fab and F(ab')$_2$ Antivenoms." Toxicon. 2013. In press.

Invited Papers, Panels, Presentations

Sinha, M, Quan D, McDonald FM, Valdez A. Cost minimization analysis of different strategies of management of clinically significant scorpion envenomation among pediatric patients. Presented at 2014 ACMT Midyear Meeting, Phoenix, Arizona. (Abstract 72, attached)

O'Connor, A. Severe bark scorpion envenomation in adults. Presented at 2014 ACMT Midyear Meeting, Phoenix, Arizona. (Abstract 61, attached)

Mangin E, Boyer L, Garcia R. Venomous creatures survey: household and occupational risks – preliminary results at the Arizona-Sonora Desert Museum. Presented to staff of ASDM, 2014.



Sylvia Brown, Ph.D.

University of Arizona

Annual Award Amount

$99,993

Project End Date

June 30, 2014

Chronic Disease in an Arizona Native American Community

Due to a lack of population based tribal-specific health information and the need by the Hopi Tribe for an assessment of its health, a team of university researchers and Hopi tribal members developed, implemented, analyzed and reported on three health surveys of Hopi tribal enrollees The first survey was an in-person survey of 500 randomly-selected Hopi enrollees (248 men/252 women) who lived on the Hopi reservation at the time of recruitment. The second was a mail survey of 144 (85 women/59 men) randomly selected Hopi men and women who lived off the reservation (520 surveys mailed/144 returned). The third was a convenience survey of any willing participant (n=151) visiting the Hopi Health Center or attending a Hopi community health event in October 2013. With these surveys, we quantified thel level of chronic disease in the community and identified targeted health promotion and prevention strategies for the Hopi tribe.

Invited Papers, Panels, Presentations

Sylvia R. Brown, PhD, MPH, Lorencita Joshweseoma, MPH, Priscilla Sanderson, PhD, Delores Ami, Joyce Hamilton, Eldon Kalemsa, Jason Roberge, PhD, MS, Erelda Gene, Rebecca Scranton, Kwaayesnom Onsae, Robin Harris PhD, MPH, Identifying Cancer Risk Factors in A Native American Tribe: The 2012 Hopi Survey of Cancer and Chronic Disease, ORAL presentation, Changing Patterns of Cancer in Native Communities: Strength through Tradition and Science, October 26 2013, Albuquerque, New Mexico.

Sylvia R. Brown, PhD, MPH, Lorencita Joshweseoma, MPH, Delores Ami, Kathylynn Saboda, MS, Robin Harris PhD, MPH, Cancer Screening on Hopi: A Model for Success in a Native Community, ORAL presentation, Changing Patterns of Cancer in Native Communities: Strength through Tradition and Science, October 26 2013, Albuquerque, New Mexico

Sanderson, PR, Joshweseoma, L., Scranton, R., & Onsae, K. (July 2013). Exploring Perceptions of Cancer and Tobacco Use: Focus Group Discussions with a Southwest Tribe. Intertribal Council of Arizona, Phoenix, AZ

Scranton R., Gene E., Sanderson PR, & Joshweseoma L. (July 2013). Understanding the attitude and perspectives of tobacco use and cancer amongst the rural Hopi population through focus groups. 2013 American Indian Research Center for Health (AIRCH) Conference "Addressing Tribal Health Priorities through a Community-Based Translational Research Framework." Wild Horse Pass Casino and Hotel, Chandler, Arizona.

Community Presentations: July 2013, August 2013, October 2013, Second Mesa, Arizona

Yin Chen, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2014

Susceptibility to Respiratory Infections in Smokers

The objective is to test the hypothesis that cigarette smoke (CS) exposure causes the impairment of innate epithelial antiviral response against rhinovirus infection. This defect will lead to enhanced viral production, which will exacerbate the symptoms of smoke induced diseases such as COPD. In the past grant period, autophagy has been found to be the key event leading to the defect of innate defense. In this grant period, we have made two significant progresses to elucidate this process. First, we have completed the study about the negative regulation of autophagy by Nrf2 activation. These data have been published. Second, we have found highly elevated autophagic activities in three in vivo or ex vivo models, which supports the significant translational value of our study. These findings, for the first time, demonstrate the molecular mechanism of CS-induced defect in airway defense against viral infection.

Publications

Zhu, L; Barret, EC; Xu, Y; Liu, Z; Chen, Y. "Regulation of Cigarette Smoke (CS)-Induced Autophagy by Nrf2." PLOS ONE. 2013. In Press.

Gerardo Chowell-Puente, Ph.D.

Arizona State University

Annual Award Amount

$52,622

Project End Date

June 30, 2014

Predicting Viral Emergence: A Host Shift of Rabies Virus from Bats to Carnivores In Arizona

Extensive field work in Flagstaff, Arizona generated the following field-based demographic parameters for striped skunks: population size, annual survival, reproductive potential and fall/winter contact rate. Moreover, data on population dynamics of Big Brown Bats were collected and preliminary results are provided in the publications listed below. Based on these and prior field work results, Dr. Chowell and his doctoral student Hans Nesse are parameterizing mathematical rabies transmission models for the setting of Flagstaff, Arizona. This work will be the focus for the last year of the grant. A major research article is being prepared for publication.

Publications

Theimer, T.C., A. Clayton, D. Peterson, and D. L. Bergman. In review. Cat food increases contacts among skunks visiting bird feeders. Urban Ecology

Maestas, Jesse. Seasonal Contact Rates Among Striped Skunks in Flagstaff, Arizona and Implications for Rabies Modeling, MS thesis, NAU

Chowell G, Chambers C, Theimer T. Modeling the transmission dynamics and control of Rabies in Flagstaff, Arizona. To be submitted to PLOS.

Invited Papers, Panels, Presentations

G. Chowell. Stochastic models of Rabies transmission tailored to Flagstaff, Arizona. Applied Mathematics Seminar. Arizona State University. November 18, 2013.

T. Halvorsen (undergraduate), J. Busch and T.C. Theimer. Den sharing and relatedness in striped skunks (Mephitis mephitis) and implications for rabies management. 2014 Undergraduate Symposium, Northern Arizona University April 2014

T. Halvorsen (undergraduate), J. Busch and T.C. Theimer. Den sharing and relatedness in striped skunks (Mephitis mephitis) and implications for rabies management. 2014 Undergraduate Symposium, Northern Arizona University (April), Poster AZ BIO Expo, Scottsdale AZ June 2014

D. Bergman, C. L. Chambers, and T. Theimer. Rabies in Arizona, 2014 Arizona Vector Control Workshop (May 2014), Presentation

Gerardo Chowell-Puente, Ph.D. (cont.)

C. E. Platts (undergraduate), F. M. Walker, C. L. Chambers, and B. Keeley. Absence of Genetic Relatedness within Maternity Colonies of Big Brown Bats in Flagstaff: Implications for Rabies Transmission, 2014 Undergraduate Symposium, Northern Arizona University (April), Poster

C. E. Platts (undergraduate), F. M. Walker, C. L. Chambers, and B. Keeley. Genetic Relatedness among Maternity Colonies of Big Brown Bats (Eptesicus fuscus) in Flagstaff: Implications for Disease Transmission, National Conference on Undergraduate Research (April), Poster

C. E. Platts (undergraduate), F. M. Walker, C. L. Chambers, and B. Keeley. Genetic Relatedness among Maternity Colonies of Big brown Bats (Eptesicus fuscus) in Flagstaff: Implications for Disease Transmission, Arizona/New Mexico Chapters of The Wildlife Society 45th Joint Annual Meeting (February), Poster (Won Best Student Wildlife Poster Award)

"Urban Ecology of Striped Skunks and Implications for Rabies Transmission", Invited speaker, Beijing Forestry University, Beijing China, August 2014 (Theimer)

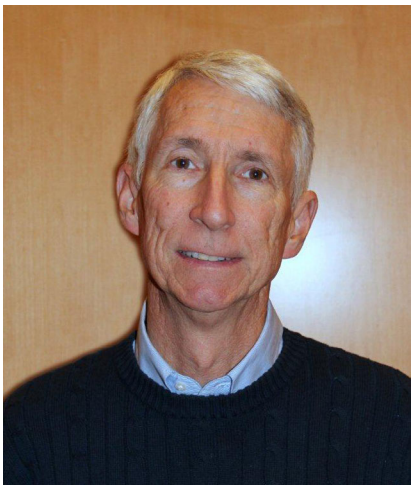
"Differences in visitation and behavior of striped skunks at two anthropogenic food sources and potential for disease transfer" Joint Annual Meeting of the Az-NM Chapters of The Wildlife Society, Phoenix, AZ Feb 2014 (Theimer)

"Spatial and temporal patterns of Wildlife rabies in Flagstaff, Arizona and implications for other cities on the Colorado Plateau". 12th Biennial Conference of Research on the Colorado Plateau. Oct 2013 (Maestas and Theimer)

"Skunk use of spilled bird seed and implications for rabies", Northern Arizona Audubon Society, October 17 and 18 2012, Flagstaff and Sedona AZ (Theimer)

"Urban ecology of striped skunks in Flagstaff, Az" School of Forestry Invited Seminar Series, NAU, Feb 13, Flagstaff AZ (Theimer)

"Striped skunks in Flagstaff: challenges of studying urban ecology of an unpopular mammal" US Forest Service Interpreter Workshop, 15 July, Hart Prairie, AZ (Theimer)



Timothy Flood, M.D.

Arizona Department of Health Services

Annual Award Amount

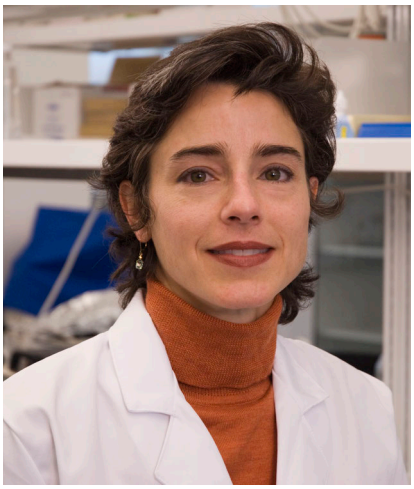
$125,000

Project End Date

March 31, 2014

Improving the Medical Certification of Cause of Death on Arizona Certificates

The Bureau of Public Health Statistics has completed the development of the module concerning certification of the cause of death on a death certificate. This on-line module allows doctors and nurse practitioners who certify the cause of a patient's death to take a one-hour course and receive 1 hour of CME credit. The site also is open to use by medical students. The training covers the basic steps in death registration and emphasizes the importance of accurately recording the immediate and underlying cause of death on the death certificate. ADHS charges no fee to persons who take the on-line course and the CME credit also is offered free. However, utilization of the site by physicians has been rather disappointing. We learned that the marketing of the site remains a big challenge.



Amelia Gallitano, Ph.D., M.D.

University of Arizona

Annual Award Amount

$49,995

Project End Date

June 30, 2014

Deciphering the Neurobiological Function of Schizophrenia Candidate Gene Egr3 and its Role in the Response to Antipsychotic Medications

We have hypothesized that risk for schizophrenia results from dysfunction in molecular genetic pathways that consist of numerous genes, which act in a cascade to enact critical neural processes. Egr3 is a key regulatory gene activated in the brain in response to environmental events that, in turn, regulates downstream target genes that dictate long-term changes in the brain. The EGR3 gene is associated with schizophrenia risk in humans, but few downstream targets are known. The long-term goal of our laboratory is to identify mechanisms by which Egr3 may influence schizophrenia susceptibility. The hypothesis we were testing with the funded ABRC grant was that the transcription factor Egr3 is required to regulate expression of the serotonin 2A receptor, a gene which itself has been linked with risk for schizophrenia, in the mouse cortex.

Publications

Williams AA, Ingram WM, Levine S, Resnik J, Kamel CM, Lish J, Elizalde D, Janowski SA, Kozlenkov A, Gonzalez-Maeso J, Gallitano AL: Reduced levels of serotonin 2A receptors underlie resistance of Egr3-deficient mice to locomotor suppression by clozapine. Neuropsychopharmacology 2012; 37(10):2285-98.

Invited Papers, Panels, Presentations

1. Williams A, Ingram WM, Kozlenkov A, Gonzalez-Maeso J, Gallitano AL: Resistance of Egr3-deficient mice to sedation by clozapine is mediated by the 5HT2A receptor. Program No. 368.15/ll24, 2011 Abstract Viewer/Itinerary Planner. Washington D.C.: Soc. for Neuroscience 2011.

Williams A, Ingram WM, Levine S, Resnik J, Janowski S, Kamel C, Lish J, Elizalde D, Kozlenkov A, Gonzalez-Maeso J, Gallitano AL: Resistance of Egr3-deficient mice to sedation by clozapine is mediated by the 5HT2A receptor. Neuropsychopharmacology 36; S183-184, 2011.

Williams AA, Ingram WM, Levine S, Resnik J, Kamel CM, Lish J, Elizalde D, Janowski SA, Kozlenkov A, Gonzalez-Maeso J, Gallitano AL: Reduced levels of serotonin 2A receptors underlie resistance of Egr3-deficient mice to locomotor suppression by clozapine. Serotonin Club 25th Anniversary Meeting, Montpellier, France, July 10–12, 2012.

Gallitano AL, Muppana L, Corneveaux J, Monib A, Huentelman M: Case-control and family association study of early growth response gene 3 with schizophrenia. Society for Neuroscience Annual Meeting, San Diego, CA Nov. 9–13, 2013.

Maple AM, Zhao X, Elizalde DI, Gallitano AL: Htr2a expression responds rapidly to environmental stimuli in an Egr3-dependent manner. 11th Congress of the International Society for Serotonin Research, Hermanus, South Africa, July 9–12, 2014. Invited Talk and Poster Presentation.

Robert Garfield, Ph.D.

St. Joseph's Hospital and Medical Center

Annual Award Amount

$125,000

Project End Date

June 30, 2014

Uterine Electrical Stimulation to Treat PPH

Uterine atony causing post-partum hemorrhage (PPH), is one of the greatest health problems, resulting in deaths of large numbers of women worldwide, due to a lack of uterine contractile activity after delivery. We propose to use simple electrical stimulation to treat this uterine contractility disorder. Worldwide more than 500,000 pregnancy related deaths occur each year with about 160,000 due to PPH. Maternal death follows quickly after birth if the uterus does not contract to stop bleeding. Third world countries without adequate medical facilities report very high maternal deaths due to PPH. Women everywhere must have access to prevention and emergency treatment for PPH. Oxytocin and misoprostol are used to contract the uterus and arrest PPH but these are not always effective or not available in poor countries. Removal of the uterus is often used to stop PPH but this surgical procedure cannot be used in countries without facilities and this course renders the patient sterile. The object of these studies is to develop a safe, effective and inexpensive treatment of PPH that can be used anywhere employing a hand-held device to electrically stimulate the uterus to contract and stop bleeding.

Karen Hastings, M.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2014

Regulation of Immune Tolerance to Melanoma

Regulating the balance between T cell activation and tolerance is essential for stimulating an anti-tumor immune response and in controlling autoimmunity. The contribution of particular antigen processing components, such as gamma-interferon-inducible lysosomal thiolreductase (GILT), in maintaining tolerance is unknown. We have shown that GILT is required for efficient MHC class II-restricted processing of melanoma antigen tyrosinase related protein 1 (TRP1). Our preliminary data demonstrate that GILT is required for thymic deletion of TRP1-specific CD4 T cells, and that TRP1-specific CD4 T cells that develop in the absence of GILT are tolerant to TRP1 and do not induce autoimmune vitiligo. We will test the hypothesis that GILT is critical for shaping the T cell repertoire. We will define the role of GILT in central and peripheral tolerance to melanoma using TRP1-specific TCR transgenic mice together with new and existing genetic tools.

Publications

Rausch MP, Hastings KT; Multiple peripheral tolerance mechanisms constrain the activity of CD4+ T cells specific for the melanocyte differentiation antigen tyrosinase-related protein 1, submitted.

Rausch MP, Metzger TC, Anderson MS, Hastings KT; GILT expression in medullary thymic epithelial cells is required for presentation of tissue-specific self antigens and deletion of autoreactive T cells, in preparation.

Invited Papers, Panels, Presentations

Rausch MP, Metzger TC, Anderson MS, Hastings KT. (2014) GILT expression in medullary thymic epithelial cells is required for presentation of tissue-specific self antigens and deletion of autoreactive T cells. 8th International Antigen Processing and Presentation Workshop, Philadelphia, PA (oral presentation).

Rausch MP, Hastings KT. (2014) Multiple peripheral tolerance mechanisms constrain the activity of CD4+ T cells specific for the melanocyte differentiation antigen tyrosinase-related protein 1. 9th Annual Frontiers in Immunobiology and Immunopathogenesis Symposium, Tucson, AZ.

GILT-mediated antigen presentation shapes T cell responses against melanoma, Dermatology Grand Rounds, University of Texas Southwestern Medical Center, Dallas, TX, July 2014.

GILT-mediated antigen presentation shapes T cell responses against melanoma, Huntsman Cancer Institute Special Seminar, University of Utah, Salt Lake City, UT, July 2014.

Yao (Joyce) Huang, Ph.D.

St. Joseph's Hospital and Medical Center

Annual Award Amount

$100,000

Project End Date

June 30, 2014

Signal Pathway Underlies GABAA Receptor-Mediated Excitation in Human Hypothalamic Hamartomas

In Year 3, we aimed to complete the experimental phase of this project, to analyze our results, and to publish our most important findings. We have made significant progress towards these goals (detailed in separated summary of results). (1) Signaling pathways: We continued to profile the three major BDNF-TrkB signaling pathways in human hypothalamic hamartoma (HH) versus normal hypothalamic control tissue. Our experimental data and statistical analysis results demonstrate that compared to control tissue, in HH tissue: a) Activation of TrkB and expression of mature BDNF are elevated; b) MAPKs (including ERK1/2, p38, and JNK), Akt, and PLCγ1 are highly activated; and c) KCC2 expression is downregulated. (2) Electrophysiology: We continued to test the effects of pharmacological manipulation of BDNF-TrkB signaling on HH neuronal action potential (AP) firing rate. In freshly prepared HH slices, patch-clamp recordings were made on multiple large and small HH neurons, respectively. Our results show that a) BDNF increases neuronal firing rate in large sized HH neurons ($P<0.01$); and b) the specific TrkB kinase inhibitor, K252a, reduces AP firing rate in large but not in small HH neurons ($P<0.01$).

Publications

Semaan S., Wu J., Gan Y., Jin Y., Li G., Kerrigan J. F., Chang Y., and Huang Y.* (2014) Hyperactivation of BDNF-TrkB signaling cascades in human hypothalamic hamartoma (HH): a potential mechanism contributing to epileptogenesis. CNS Neuroscience & Therapeutics.

Invited Papers, Panels, Presentations

Semaan S., Wu J., Chang Y., and Huang Y.* (2013) Profiles of BDNF/TrkB signaling pathways in human hypothalamic hamartoma tissues. The Society for Neuroscience Annual Meeting, Nov 9–13, 2013, San Diego, California.

Huang Y.*, Semaan S., Liu Q., Chang Y., and Wu J. (2014) The role of BDNF-TrkB signaling in epileptogenesis in human hypothalamic hamartoma. The Society for Neuroscience Annual Meeting, Nov 15–19, 2014, Washington, DC. (Accepted for poster presentation)

William G. Johnson, Ph.D.

Arizona State University

Annual Award Amount

$89,178

Project End Date

June 30, 2014

CHIR Trauma Registry

We released a de-identified dataset, removing the 18 identifiers to the research team at JCL containing data points from the Trauma1 system for each of the four Trauma centers involved in the study (JCL, Dignity Health, MIHS, and Scottsdale), co-morbidity and severity scores from aggregated ADHS discharge data, and mortality information from the state death certificates. We helped the research team analyze and interpret the data in addition to developing graphs and tables summarizing descriptive and inferential statistics. We designed the outline of a report summarizing the findings from the project and began work on completing the report. Apparently as a result of the merger between JCL and Scottsdale Healthcare, one member of the JCL research team has left the organization and we have not received a date on which they will complete the publication from the remaining member, Dr. Dzandu.

Two data sets have been created for Phoenix Childrens' Hospital. The ADHS IRB ask for some additional information before granting final approval for the release of the ADHS section of the data and we are awaiting that approval before releasing the data to PCH. We have identified and matched cases and controls for both the NICU and PEDUS (Previous ED Use Study) projects. Both projects will be completed by PCH after the end of this contract but full recognition will be given to ABRC sponsorship.

John Kerrigan, M.D.

St. Joseph's Hospital and Medical Center

Annual Award Amount

$100,000

Project End Date

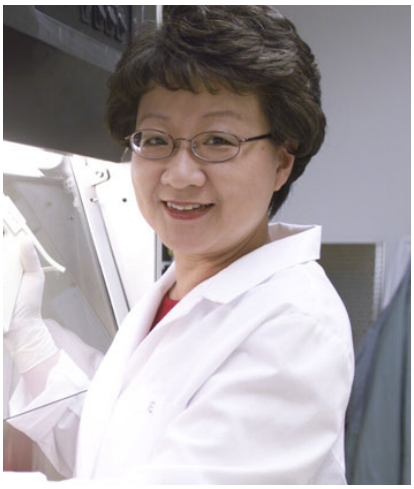
June 30, 2014

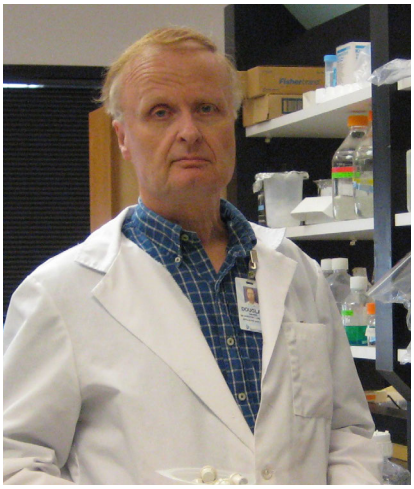
Cellular Mechanisms of Epileptogenesis in Human Hypothalamic Hamartoma Tissue

Role of Gap Junctions: Data collection is complete for the cellular neurophysiology and neuropharmacology studies in freshly-resected HH tissue slices (Wu laboratory) and immunohistochemistry and Western blot analysis (Kerrigan laboratory) for gap junction (connexin protein) expression in HH tissue. This work was presented in abstract form at the 2012 Meeting of the American Epilepsy Society. The manuscript is currently in preparation for peer review and publication.

Role of HCN Channels: Data collection is continuing for this project, consisting of pharmacological h-current blocking studies during microelectrode patch-clamp recordings in freshly resected HH tissue slices (Wu laboratory) and immunohistochemistry and Western blot analysis of HCN subunit expression in HH tissue and normal human autopsy control material (Kerrigan laboratory).

Microanatomy of HH neurons: Data collection is continuing, though nearing completion, for this project, which consists of single cell microinjection and imaging of HH neurons after patch-clamp microelectrode recordings in freshly-resected, perfused HH tissue slices.





Lih-Fen Lue, Ph.D.
Douglas Walker, Ph.D.

Banner Sun Health Research Institute

Annual Award Amount

$199,329

Project End Date

March 31, 2014

Longitudinal Change in Circulating Tau Levels Associated with Changing Cognitive Performance

The goals of this project were to validate different assay methods for measuring levels of plasma tau protein in samples derived from human non-demented, mild cognitive impairment and Alzheimer's disease (AD) patients. Initial studies detecting values in the 520–819 pg/ml range in plasma samples along with a disease difference in levels were shown to be dependent on the assay method. This assay method was no longer available and we attempted to measure free tau levels with a current standard tau ELISA kit and three high sensitivity methods. Our results demonstrated values of tau using the high sensitivity assays in the range of 1–15 pg/ml. We also demonstrated that methods of sample collection and processing were critical to the successful detection of plasma tau. Longitudinal studies using a high sensitivity digital ELISA method in a select group of subjects showed relatively small changes over a 2–3 year period.

Sarada Panchanathan, M.D.

Maricopa Integrated Health System

Annual Award Amount

$16,339

Project End Date

June 30, 2014

Ascertaining Optimum Public Health Interventions to Control The Spread of Methicillin Resistant Staphylococcus Aureus Infections in the Pediatric Population

We have created and validated an agent based model in an iterative process with existing epidemiological data. We have validated it against data in the Medicaid population and are currently adjusting the validation for a more general population. We are studying this infection in the pediatric population, which spends most of its time at home or school, with a limited number of contacts. The transmission rate in both settings, homes and schools, have been calculated to determine the relative contribution of the two settings to the overall spread within the community. We have ascertained that control measures targeted at only the infected individuals in a community can decrease recurrent infections but colonized individuals remain a reservoir for first infections in the community.

The model will be used to examine the impact of specific, targeted interventions to the spread of the infections throughout the community.

Publications

Wang X, Panchanathan S, Chowell G (2013) A Data-Driven Mathematical Model of CA-MRSA Transmission among Age Groups: Evaluating the Effect of Control Interventions. PLoS Comput Biol 2013; 9(11): e1003328. doi:10.1371/journal.pcbi.1003328 PMID 24277998. Epub 2013 Nov 21.

Wang X, Towers S, Panchanathan S, Chowell G (2013) A Population Based Study of Seasonality of Skin and Soft Tissue Infections: Implications for the Spread of CA-MRSA. PLoS ONE 2013; 8(4): e60872. doi:10.1371/journal.pone.0060872 PMID 23565281. Epub 2013 Apr 2.

George Pettit, Ph.D.

Arizona State University

Annual Award Amount

$125,000

Project End Date

June 30, 2014

Expansion of New Approaches to Treatment of Brain (gliomas), Colon, and Prostate Cancer by Molecular Targeting

Because of the exceptional financial assistance from past ABRC awards including the past year we have made extraordinary advances in the discovery and development of new anti-cancer drugs and potentially a new drug Bryostatin 1 for greatly improving the reversal of lethal and other brain diseases. Also, our discovery of the drug component of ADCETRIS has resulted in a quantum leap in human cancer treatments. As of a month ago, ADCETRIS has been approved for use in 40 countries with more in progress. In the brain disease area our discovery and development of Bryostatin 1 has led to its recent entry into what may be the first successful reversal of Alzheimer's Disease which represents another pending quantum leap in such brain diseases. Other achievements in the past year included the first total synthesis of Dolastatin 16 that now allows further development., and significant advances in the development of specific synthetic linkers to ADC's. We have also made considerable progress in expanding the chemistry and cancer biology of the pancratistatin family of anti-cancer drug candidates potentially useful for future treatments needed for colon and brain gliomas.

Publications

Pettit, George; Melody, Noeleen; Hempenstall, Frank; Chapuis, Jean-Charles; Groy, Thomas; Williams, Lee "Antineoplastic Agents. 595. Structural Modifications of Betulin and the X-ray Crystal Structure of an Unusual Betulin Amine Dimer.[1a], "Journal of Natural Products , 77,(4), 863-872, (2014).

Hadimani, Mallinath; MacDonough, Matthew; Strecker, Tracy; Lopez, Ramona; Sriram, Madhavi; Nguyen, Benson; Kessler, Raymond; Ghatak, Anjan; Shirali, Anupama; Liu, Li; Garner, Charles; Pettit, George; Hamel, Ernest; Chaplin, David; Mason, Ralph; Trawick, Mary Lynn; Pinney, Kevin "Synthesis of a 2-Aryl-3-Aroyl-lndole Salt (OXi8007\)} Resembling Combretastatin A-4 with Application as a Vascular Disrupting Agent", Journal of Natural Products., 76,(9), 1668-1678, (2013)

Invited Papers, Panels, Presentations

Keynote Lecture: World ADC 2013 Conference, October 14–17 in San Francisco, CA. Lecture Title: "From Africa: The Quest to Discover New ADC Anti-Cancer Candidates"

Gregory Rogers, Ph.D.

University of Arizona

Annual Award Amount

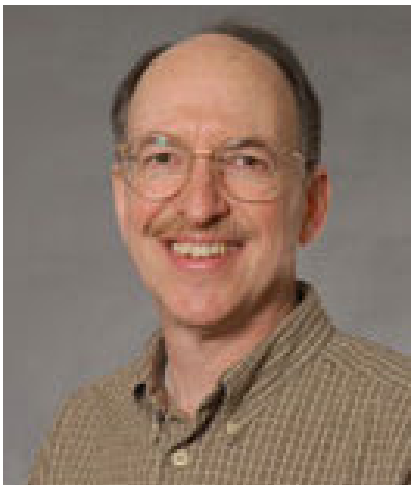
$50,000

Project End Date

June 30, 2014

Molecular Mechanisms of Centrosome Amplification in Cancer Cells

Carcinogenesis involves errors in mitosis that select for altered genomes imparting growth and survival advantages. During mitosis, bipolar spindle assembly is vital to properly segregate chromosomes. Spindle assembly is influenced by centrosomes, organelles that organize spindle shape. Excess centrosomes (amplification) however promote multipolar spindle formation and chromosomal instability—a hallmark of cancer. Presently it is unclear how cells prevent centrosome amplification and how this regulation goes awry in cancer. Our proposal entails a multidisciplinary approach to dissect mechanisms of centrosome amplification in cancer cells and identify compounds that block this process. We hypothesize that cancer cells utilize a unique set of genes to promote centrosome amplification. Compounds that block the activity of these genes offer a viable clinical treatment to prevent centrosome amplification. Our approach combines high-throughput functional-genomics and drug screening with mechanistic cell biological studies in cancer cells: a translational approach with the potential to generate mechanism-targeted anticancer treatments.



Seth Rose, Ph.D.

Arizona State University

Annual Award Amount

$125,000

Project End Date

June 30, 2014

Electrophilic Chalcones for Treatment of Paclitaxel-Resistant Cancer

The general goal of this work is to design, prepare, and test new compounds with anticancer activity. In FY2012-FY2013 we found compounds that showed the desired anticancer activity against cancer cells grown in culture. In addition, we identified the molecular structural features required for retention of activity of the compound in the biological milieu (e.g., resistance to plasma esterases) and in FY2014 explored possible improvements.

The leading compound to emerge from this work was synthesized on a large scale for use in xenograft studies of human cancers. The compound administered alone exhibited statistically significant but only marginal activity against pancreatic cancer and triple negative breast cancer. When applied in combination with paclitaxel, the compound showed statistically significant enhancement of tumor growth inhibition relative to paclitaxel alone. Thus, the combination of an electrophilic chalcone with paclitaxel is more effective than paclitaxel alone in the treatment of a human breast cancer model.

Nader Sanai, M.D

St. Joseph's Hospital and Medical Center

Annual Award Amount

$175,000

Project End Date

June 30, 2014

Spectral Tracking of Human Glioblastoma Stem Cells

The cellular heterogeneity of glioblastomas is a devastating biological feature. The inefficacy of therapeutic strategies may be attributed to the persistence of a comparatively small proportion of glioblastoma cells that survive microsurgical resection, radiation therapy, and chemotherapy, only to repopulate and disseminate the disease. The recent discovery of tumor-initiating stem cells, coupled with evidence that these brain tumor stem cells are uniquely resistant to radiation and chemotherapy, raise the possibility that glioblastoma stem cells are a central cause for treatment failure. To date, no specific marker can identify this potent population, although the capacity to localize human glioblastoma stem cells in vivo would enable their selective targeting and allow for their monitoring in response to therapy. In recent years, magnetic resonance spectroscopy has been successfully used to detect trace quantities of known and unknown metabolites in human tissue. The development of ultrahigh field strength magnets (>7-Tesla) now enables cellular resolution in vitro and in vivo. Both adult neural stem cells and glioblastoma stem cells are functionally defined by their self-renewal and multipotency, suggesting a shared metabolic profile and spectral signature. During Year 2, we have used in vitro NMR spectroscopy, in collaboration with Dr. Jeffrey Yarger at Arizona State University, to identify putative spectral signatures specific to normal and abnormal CNS progenitor populations. These signatures have since been validated in larger animal studies using in vivo spectroscopy techniques. We are now working on transitioning these results to humans.

Marshall Smith, Ph.D., M.D.

Banner Health

Annual Award Amount

$70,752

Project End Date

June 30, 2014

Safety and Efficacy of a Virtual Reality Approach to Neurorehabilitation for Traumatic Brain Injury

Identification of factors that impact clinical outcomes is imperative for hospital-based clinicians. Integration of information related to pre-, peri-, and post-hospitalization is essential for individualized patient care. Aggregate data on specific conditions can inform interventions. Subgroup analyses can indicate that different approaches be utilized. Comparative effectiveness and modeling of outcomes requires access to complex information that allows for systematic examination of factors. Examination of the cause(s) of readmissions and complications can support development of education and prevention programs and frank referral when indicated. Observed trends can reveal gaps to fill and allocation of resources. This grant provided funding for the creation of a complex database for the purpose of addressing issues listed above as well developing a smaller database supporting an applied project. Another purpose was to promote interaction between several departments through the pooling and interpretation of these data. The intent was that database user groups encourage communication across disciplines and can facilitate the exchange of information and innovative approaches could evolve from these data-driven discussions. An applied project that directly impacts patient care was developed. The focus of the project was to address the challenges associated with the implementation of efficacious and low-cost treatments for the rehabilitation of individuals who had incurred traumatic brain injury. A goal was to identify and provide therapeutic interventions that targeted specific areas of physical and cognitive need as well as provide options and recommendations for continuance of outpatient progress. Given short-term hospital stays and financial restraints, therapeutic impact must be rapidly delivered and assessed. With this in mind, the project was designed to implement a novel therapeutic intervention to meet the needs of patients with Traumatic Brain Injury (TBI). The impact of virtual technology training on short-term and potential for long-term rehabilitation outcomes was the focus of this study. Virtual Reality (VR) methodology and the use of 'video games' for rehabilitation as emerging technologies seems to be an appropriate venue for delivery and maintenance of therapeutic interventions. Observed success of this technology can likely be attributed to the multi-modal nature of delivery, active over passive participation, social interactive nature, and observation of 'real life' responses by patients that inform therapists.

Clarisse Tsang

Arizona Department of Health Services

Annual Award Amount

$100,000

Project End Date

March 31, 2014

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

Arizona accounts for two-thirds of all reported coccidioidomycosis cases in the United States. Coccidioidomycosis is the second most commonly reported infectious disease in the state. Between 2009 and 2013, there were significant changes in the number of cases reported annually to the Arizona Department of Health Services (ADHS). In 2009, a major commercial laboratory, Lab A, altered its reporting practices by beginning to report positive coccidioidomycosis enzyme immunoassay (EIA) results without confirmation by immunodiffusion assay, thereby increasing the number of reported coccidioidomycosis cases from about 4,000–5,000 cases annually to 12,000–17,000 cases. In 2012, Lab A changed its EIA testing method, leading to a decrease to 5,861 reported cases in 2013. We investigated the impact of laboratory reporting and testing practices on the epidemiology of reported coccidioidomycosis in Arizona.

The proportion of cases reported by Lab A increased from 28.7% in 2008 to a peak of 75.8% in 2011, followed by a decline to 45.8% in 2013. There were corresponding changes in the age and gender distribution of reported cases. In 2008, 48% of reported cases in Arizona were female. From 2009–2012, 56.5% of reported cases were female while in 2013, 49.1% of reported cases were female. Cases reported by Lab A had a median age of 46.7 years while cases reported by other labs and healthcare providers had a median age of 51.8 years. However, the age distribution of cases reported by Lab A in 2013 changed significantly with the median age of reported cases increasing from 44 years in 2012 to 50 years in 2013. Laboratory reporting and testing practices contributed significantly to the observed changes in the epidemiology of coccidioidomycosis from 2008 to 2013. ADHS continues to monitor changes in epidemiology of coccidioidomycosis to guide in making recommendations for this disease.

Due to the changes in laboratory reporting and testing practices over recent years, ADHS conducted enhanced surveillance of coccidioidomycosis cases amongst a 15% random sample of reported cases in 2012 to assess the impact of coccidioidomycosis on Arizonans. At this time, 566 cases have been interviewed and preliminary analysis is pending. Furthermore, ADHS conducted a physician knowledge, attitudes and practices assessment of coccidioidomycosis in 2013 to compare with a similar survey that was conducted in 2007. ADHS emailed out 3,083 surveys and mailed out 8,819 surveys to Arizona physicians and received a total of 1,001 responses. We are currently cleaning the data and conducting preliminary analyses.

Publications

Tsang CA, Tabnak F, Vugia DJ, Benedict K, Chiller T, and Park BJ, Increase in Reported Coccidioidomycosis—United States, 1998–2011, Arizona Department of Health Services, California Department of Public Health and the Center for Disease Control and Prevention, MMWR 2013; 62(12);217-221.

Clarisse Tsang (cont.)

Hector RF, Rutherford GW, Tsang CA, Erhart LM, McCotter O, Anderson SM, Komatsu K, Tabnak F, Vugia DJ, Yang Y, Galgiani JN. The Public Health Impact of Coccidioidomycosis in California and Arizona. International Journal of Environmental Research and Public Health 2011; 8(4):1150-1173

Tsang CA, Anderson SM, Imholte SB, Erhart LM, Chen S, Park BJ, Christ C, Komatsu K, Chiller T, Sunenshine RH. Enhanced Surveillance of Coccidioidomycosis, Arizona, USA, 2007–2008. Emerging Infectious Diseases 2010; 16(11):1738-44.

Chen S, Erhart LM, Anderson S, Komatsu K, Park B, Chiller T, Sunenshine R. Coccidioidomycosis: knowledge, attitudes, and practices among healthcare providers—Arizona, 2007. Medical Mycology 2011; Early Online 1-8.

Invited Papers, Panels, Presentations

Khan M and Tsang CA, The Impact of Changing Laboratory Reporting and Testing Practices on the Epidemiology of Coccidioidomycosis in Arizona, 2008–2013. Abstract at 58th Annual Coccidioidomycosis Study Group Meeting, Phoenix, AZ, April 5, 2014.

Tsang CA, McDougall S, and Anderson SM, Coccidioidomycosis in Younger Populations, Arizona, 2011. Abstract at 57th Annual Coccidioidomycosis Study Group Meeting, Pasadena, CA, April 6, 2013 and Abstract at IDWeek 2013, San Francisco, CA, Oct 2–6, 2013.

Lusk R and Erhart L, Comparison of Enzyme Immunoassay (EIA) to Immunodiffusion & Complement Fixation for Coccidioidomycosis Diagnosis & Surveillance, Arizona Department of Health Services, Abstract at the Arizona Infectious Disease Conference, Tempe, AZ, Jul 31-Aug 2, 2012.

Benedum C and Tsang CA, Coccidioidomycosis Surveillance in Arizona: Comparison of 2007 and 2011 Data, Arizona Department of Health Services, Abstract at 56th Annual Coccidioidomycosis Study Group Meeting, Tucson, AZ, March 24, 2012 and Abstract at the Border Binational Infectious Disease Conference, Austin, TX, May 22–24, 2012 and Abstract at the Arizona Infectious Disease Conference, Tempe, AZ, Jul 31-Aug 2, 2012.

Foley C, Tsang CA, Christ C, Anderson SM. Impact of Disseminated Coccidioidomycosis in Arizona, 2007–2008. Arizona Department of Health Services, Abstract at the 55th Annual Coccidioidomycosis Study Group Meeting, Davis, CA, April 2, 2011.

Petein N, Erhart LM, Ryan F, Tsang CA, Sunenshine RH. Specificity of Enzyme Immunoassay for Serologic Coccidioidomycosis Diagnosis Compared to Immunodiffusion with Subsequent Medical Record Review of "False Positive" Results. Arizona Department of Health Services, Maricopa County Department of Public Health, Abstract at the 55th Annual Coccidioidomycosis Study Group Meeting, Davis, CA, April 2, 2011.

Victor Waddell, Ph.D.

Arizona Department of Health Services

Annual Award Amount

$175,000

Project End Date

March 31, 2014

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

The Arizona State Public Health Laboratory (ASPHL) completed the development and implementation of a procedure for the detection of resistance to antiviral medications used in the treatment of the 2009 pandemic Influenza A H1N1 virus and other Influenza A viruses. Upon completion of the verification study for the new assay in the fall of 2013, the ASPHL conducted testing throughout the 2012–13 influenza season using the newly developed assay. All influenza A viruses identified at the ASPHL during the influenza season were analyzed for resistance markers associated with antiviral resistance.

Frederic Zenhausern, Ph.D.

University of Arizona

Annual Award Amount

$125,000

Project End Date

June 30, 2014

A Rapid Viscosity-Based Method to Characterize Biological Fluids

During FY 2014, we have started to use the automated splash system to tackle systems where viscosity changes can be monitored using this new technique. The use of the system enabled researchers to observe and measure rheological changes in liquid sample states and could in turn monitor specific biomolecular interactions such as the one in a peptide selfassembly reaction in real time. There is no report in the literature of such measurement of self assembly in real-time so this technique will open new paths for molecular discovery. A series of 2 mm glass beads were dropped into an Fmoc-L3-OMe peptide sample mixed with Alcalase 2.4 L enzyme and resulting splashes were observed via images recorded from a high speed camera. The results demonstrate that the viscosity of the peptide sample changes during the peptide self-assembly reaction and affects the profile and timing of the splashing event. The increasing viscosity of the sample during the reaction decreased the size of the splash and the amount of time for the splash to reach maximum extension from the moment for the beads to impact the sample. The ability to observe rheological changes of sample state presents the opportunity to monitor the real time dynamics of the peptide self-assembly.

Publications

C. Hurth, D. Whitfield, B. Duane, S. Smith, A. Nordquist and F. Zenhausern, "Automation of a high-speed imaging setup for differential viscosity measurements", Journal of Applied Physics, 114, 244701 (2013) (incl. front cover).

Dynamic measurement of biomolecular interactions in molecular self-assemblies by high speed imaging Analytical Methods (Royal Society of Chemistry): In Preparation

Invited Papers, Panels, Presentations

Applications and Challenges in Biometrology, AMFA 2013, August 4th, Indiana Convention Center, Indianapolis, IN

New Research Projects Awarded

The following New Research Projects were awarded under the Request For Grant Applications for Arizona Department of Health Services, Arizona Biomedical Research Commission—Research to Improve the Health of all Arizonans.

A. Arizona Biomedical Early Stage Investigator Award ("AZ ESI"):
The Arizona Biomedical Early Stage Investigator Award was established to help a new investigator generate the preliminary data necessary to apply for a larger federal grant.

Project End Date: October 22, 2017

B. Arizona Biomedical Catalyst Award ("ABC"):
The ABC Award is designed to support investigators whose projects were favorably reviewed by a federal granting agency (i.e. NIH, National Science Foundation ("NSF"), or Department of Defense ("DOD")) but were just outside the respective funding score. The goal of this Grant is to provide funding for the investigator to generate additional needed data, with the intent to resubmit the Application to the respective federal granting agency within twelve (12) to eighteen (18) months of receiving the ABC Award.

Project End Date: October 22, 2015

C. Arizona Biomedical Investigator Grant ("AZ BIG"): The AZ BIG is a competitive research grant requiring a rigorous scientific and collaborative approach. Collaboration among investigators could include: within an institution, across institutions, or across disciplines.

Project End Date: October 22, 2017

Bridget Barker, Ph.D.

Northern Arizona University

Annual Award Amount

$74,969

Project End Date

October 22, 2017

Understanding Early Innate Immune Responses to Infection with Coccidiodes, Causal Agent of Valley Fever

Coccidioidomycosis, or Valley Fever, is caused by soil-dwelling dimorphic fungi endemic to Arizona. Inhaling Coccidioides' arthroconidia from the environment often leads to an asymptomatic infection. However, symptomatic coccidioidomycosis causes pneumonia and flu-like illness, which is misdiagnosed as other pneumonias in 30% of patients. If an acute infection does not resolve, it can progress to chronic or disseminated disease, and the factors influencing this outcome are unknown. The knowledge gained from this project will lead to a better understanding of the events that occur at the onset of disease, which may lead to the treatments targeting acute coccidioidomycosis. We hypothesize that initial interactions with macrophages are important for the activation and continuation of the parasitic cycle of Coccidioides and outcomes of coccidioidomycosis. The approach in this proposal will determine if Coccidioides can proliferate in the phagosome. Future treatment may focus on blocking Coccidioides' interactions with host macrophages and arresting the parasitic life cycle within the phagosome of macrophages. Our analysis of interactions between host and pathogen using new technology of multifactorial cytokine screening was not possible until recently. Previous work has laid a foundation; the work proposed here will expand our knowledge, and potentially change management and treatment of disease.

Christian Bime, M.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Effects of Aerobic Exercise on Asthmatic Responses in Obese Adults

The incidence, prevalence, and severity of asthma have increased in the last four decades. African Americans and Latinos living in poverty are disproportionately affected. Possible explanations for these changes include allergen exposure, hygiene, and lifestyle changes. Obesity, a product of dietary changes and physical inactivity is a well-established risk factor for incident asthma and has also increased during this period. The mechanisms that underlie these associations are complex and poorly understood. It has been suggested that obesity leads to an increased expression of pro-inflammatory cytokines such as interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α), that worsen asthma. Previous research has shown significant improvement in asthma control, T-cell function, and cytokine production among severely obese asthmatics after bariatric surgery. In animal studies, aerobic exercise at a moderate intensity level ameliorates asthmatic responses. Few studies have assessed the effects of aerobic exercise on pro-inflammatory markers and other asthmatic responses in obese patients. We propose to conduct a feasibility/proof of concept study to recruit and retain obese adult asthma patients for a protocol that involves 12-weeks of moderate intensity aerobic exercise. We will assess the effect of exercise on markers of eosinophilic inflammation, markers of obesity, and overall asthma control.

Timothy Bolger, Ph.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Modulation of RNA dynamics in Medulloblastoma by DDX3/Ded1

Cancer afflicts tens of thousands in Arizona each year. In medulloblastoma, the most common malignant brain tumor in children, even survivors often suffer reduced quality of life with current treatments, arguing for further research. Recently, frequent mutations were reported in the gene DDX3 in medulloblastoma. DDX3 is an enzyme that affects RNA and protein interactions, and it is required for protein synthesis during gene expression. However, it is not understood how DDX3 influences cancer progression, and the effects of the identified mutations in DDX3 are not known. Here we propose to make equivalent mutations in DED1, the yeast version of DDX3, and examine the cellular effects. Ded1 and DDX3 are highly similar, as is the gene expression machinery in humans and yeast; thus our results should be directly applicable to human biology. Furthermore, the DDX3 mutations in medulloblastoma frequently correlated with mutations in ®-catenin, an important signaling molecule. DDX3 was also recently shown to interact with casein kinase-1, a regulator of ®-catenin signaling. Therefore we will examine this interaction to determine whether DDX3/Ded1 regulates casein kinase-1 or vice versa. The results from these studies will lead to future proposals to further elucidate the role of DDX3 in cancer.

Elena DeFilippis, M.D., Ph.D.

Mayo Clinic

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Response Immunomodulatory Role of Eosinophils in Determining Inflammation and Insulin Sensitivity in Human Adipose Tissue

Obesity affects over 60% of the population in Arizona and is characterized by low-grade, chronic inflammation of adipose tissue (AT). In human AT, the relation between inflammation and insulin resistance is not clear. This project aims to investigate how eosinophils modulate the immune environment in AT and reduce inflammation and insulin resistance in human fat. We will test the hypothesis that eosinophils promote insulin sensitivity in human AT in two ways: first by releasing cytokines to sustain alternatively activated M2 macrophages, and second by increasing generation of small anti-inflammatory, immunoregulatory lipid molecules like protectins and resolvins. We will first evaluate whether differences in eosinophil content between subcutaneous and omental fat of lean, insulin sensitive and obese, insulin resistant subjects and determine the correlation with insulin sensitivity assessed by euglycemic-hyperinsulinemic clamp. Next, we will collect subcutaneous fat from obese, insulin resistance subjects before and after 3 months of fish oil supplementation to investigate whether ω-3 PUFA supplementation improves adipose metabolism and inflammation via changes in eosinophil content, cytokine levels and/or generation of protectins and resolvins. This study will define whether, like in mice, eosinophils play a crucial role in human fat metabolism and inflammation and potentially highlight new therapeutic targets.

Brittany Dugger, Ph.D.

Banner Health

Annual Award Amount

$74,832

Project End Date

October 22, 2017

The Effects of APOE Genotype on APP/AB Levels in Human Liver and Brain

In Arizona, it is projected by the year 2025 that 130,000 people will be affected by Alzheimer's disease (AD). This is nearly the entire population of Peoria, Arizona. With an average annual expense for AD of $20,638/person, this would equate to 2.7 billion dollars each year for Arizonans. To alleviate this financial burden and emotional toll it takes on family and friends, methods are needed for better diagnostic accuracy and treatment. There are many factors implicated in AD, two of which are amyloid-beta (Aβ) and Apolipoprotein E (APOE) genotype, but much of the understanding of these proteins are based on brain research. Relatively few studies have examined other organs. This is surprising since the liver is major source of APOE and major clearing point for Aβ. We propose to determine the relationship of Aβ levels within human liver and brain and if these levels are dependent on APOE genotype. These experiments will aid in understanding if APOE acts solely on the brain or if there is a peripheral contribution. If successful, this highrisk high-reward approach could provide an initial foundation for the discovery of peripheral biomarkers that could help in the understanding, early detection, and diagnosis of AD.

Andrew George, Ph.D.

St. Joseph's Hospital and Medical Center

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Amyloid Beta-Induced Homeostatic Neuronal Instability in Basal Forebrain Cholinergic Neurons

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is one of the most common causes of mental deterioration in the elderly. Brain regions associated with higher cognitive functions, particularly the neocortex, are affected by the characteristic pathology of AD. Several studies have correlated the cognitive severity associated with early-onset AD with a loss of basal forebrain cholinergic neurons. However, the precise mechanisms underlying cholinergic neurodegeneration and subsequent memory impairments remain unknown. Recently, a unique nicotinic acetylcholine receptor (nAChR), containing only α7 and β2 subunits, has been identified on basal forebrain cholinergic neurons, is highly sensitive to functional blockade by amyloid-beta (Aβ). As demonstrated in hippocampal pyramidal neurons, Aβ/α7β2-nAChR interactions lead to neuronal homeostatic instability and subsequent hyperexcitation. If successful, this proposal will delineate the relationship between Aβ/α7β2-nAChR interactions, forebrain neuronal homeostatic stability, and mammalian cognitive function. Through a combination of neuropharmacology, in vitro electrophysiology and rigorous animal behavior testing this proposal seeks to achieve a "behavior to molecules to behavior" account of cognitive decline associated with early-onset AD. This research is relevant to prevention or treatment of AD since it would provide a set of novel therapeutic targets (e.g. disruption of the critical Aβ/α7β2-nAChR interaction, or suppression of neuronal hyperexcitation directly).

Kamella Haynes, Ph.D.

Arizona State University

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Synthetic Biology for Cancer Research

This is an application for an AZ ESI award to support Dr. Karmella Haynes, assistant professor in Biomedical Engineering at Arizona State University, in gaining computational biology expertise, establishing translational cancer research collaborations with scientists at the Mayo Clinic, and in developing an independent research career. Dr. Haynes' mentoring team includes Professor Mark Spano, an expert in nonlinear dynamics of biological systems, and Professor Joshua LaBaer, Director of the ASU Biodesign Institute's Center for Personalized Medicine. Disease states such as cancer arise from the disruption of chromatin, the central DNA-protein structures that package human genetic material. Cancer has led to over 10,000 deaths for Arizonans each year. The resistance of cancer to conventional treatment is a tenacious problem. Dr. Haynes has developed novel synthetic chromatin proteins that interfere with cancer-associated histone methylation signals. The innovation of the proposed project lies in a new methodology to halt cancer with engineered chromatin instead of small molecule-based drugs that cause undesirable pleiotropic effects. The outcome will be a cure for cancer that activates anti-cancer genes within cancer cells. If awarded, support from the AZ ESI will be used to generate preliminary data for a highly competitive NIH R01 grant application.

Jesse Hunter, Ph.D.

Translational Genomics Research Institute

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Identification and Functional Characterization of Novel Neuromuscular Disease-Causing Variants in Arizona Infants and Children

Neuromuscular disease (NMD) accounts for a significant proportion of infant and childhood mortality and devastating chronic disease in Arizona. NMDs result in muscle weakness and muscle deterioration. NMDs are caused by defects in muscle development and structure, or when the wires connecting the brain to muscles (motor neurons) don't form or function properly. Our joints also depend on muscle movement and lack of muscle function can result in stiff or even immobile joints and disfigurement. There are hundreds of different NMDs. Many of the symptoms of these diseases are very similar, even though the underlying cause of disease is different. NMDs are usually genetic, meaning that the underlying cause of disease is a mistake in the DNA code. One of the first steps to helping a child with NMD is to find the mistake in the DNA code. Each of us has a unique genetic DNA code made up of over 3 billion letters. Our DNA contains about ~25,000 genes that code for proteins, the building blocks of our bodies. A single wrong letter in one gene can result in devastating disease. Finding the one wrong letter in a child's DNA is literally like finding a needle in a haystack. For most infants and children with NMD, the mistake in their DNA causing their disease is found in them alone or in a few other people around the world, making their disease virtually unique. Since there are many thousands of unique DNA mistakes in many hundreds of genes that can cause NMD, all with similar clinical symptoms, this makes it difficult for physicians to choose which gene to look in for mistakes and to determine exactly what disease the child has. Without knowing exactly what the problem is, it is also difficult for the physician to provide the best treatment for the child. That is where our project comes in. New technologies called "Next-generation sequencing" make it possible to look at the DNA code for all 25,000 genes all at once instead of one gene at a time. In fact we can look at each letter in each gene a hundred or a thousand times over all at once. As one can imagine, this creates a mountain of data. We use a supercomputer to help us organize and sort through this mountain of data to find the unique DNA mistake causing disease. Usually this all takes several months from when the physician sees the child to when we identify the DNA mistake, but in an emergency, this can be done in as little as a week. While it is essential to find the DNA mistake, this is only the beginning. Unfortunately, we don't know enough about most NMDs yet to treat them effectively and no helpful medications are available. This is where the second part of our project comes in to play. In order to develop a treatment for disease, we have to make a model of the disease. We do this by replicating the DNA mistake in cells and in animals. Another new technology called "CRISPR/CAS" can find a specific letter in the DNA code of a normal cell and change it to cause disease in the cell. We grow these cells in petri dishes and can study what happens to the cell when it has the DNA mistake. We can do similar things in mice to make mice with disease. We can then study the mice to further understand the disease and test medications in the mice that we think might help treat the disease. If the treatment works, we can eventually adapt that treatment to help the child with disease. This is our primary goal; to find the cause of disease and then start the research that will hopefully lead to a treatment for infants and children in Arizona suffering from NMD.

Anita Koshy, M.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Harnessing Evolution: Defining the Neuroprotective Effects of Chronic Toxoplasmosis

As we naturally age, our thinking abilities wane. We have very little understanding of the mechanisms that cause this decline, but, recently, age-associated increases in brain inflammation have been implicated in playing a role in this decline. Thus, the goal of this study is to try to understand how to limit age-associated brain inflammation in the hopes of developing new treatments to slow or reverse age-associated cognitive decline. Our approach is to study the brain-parasite interaction of a common brain parasite (Toxoplasma gondii) which naturally and silently infects the brain of up to a third of the world's population. Toxoplasma's ability to remain quietly in the brain suggests that the parasite decreases the brain's immune response, a capability with therapeutic potential, an idea that is supported by recent laboratory studies showing that chronic toxoplasmosis can be neuro-protective in models of stroke and Alzheimer's disease. By defining how Toxoplasma and the mammalian brain have evolved to tolerate each other, we will identify new therapeutic targets for manipulating the brain's immune response to preserve our cognitive capacity even in the late-stages of life.

Lalitha Madhaven, Ph.D.

University of Arizona

Annual Award Amount

$74,184

Project End Date

October 22, 2017

Rejuvenating the Aging Brain by Improving Stem Cell Function

Due to their unique ability to induce cellular plasticity and repair in the brain, neural stem cells (NSCs) are therapeutic candidates to treat age-related neurodegenerative disorders such as Alzheimer's and Parkinson's Disease, which are increasingly prevalent in Arizona. However, to exert their therapeutic effects, NSCs need to survive and function efficiently in an aging brain milieu. Part of the challenge is that aging tissue is ridden with stressors such as high oxidative stress, inflammation, and diminishing trophic molecules, creating roadblocks toward optimal performance of NSCs. In fact, it is known that aging depletes stem cell niches in the brain and negatively impacts their function. In this proposal, for the first time, we examine how NSCs can respond to such environmental demands in the aging brain while still providing significant structural and functional benefits. In particular, we focus on a target molecule, Nfe2l2, which increases cellular stress resistance. More specifically, we investigate whether interventional strategies utilizing high Nfe2l2 expression, before a certain critical time period during aging, can augment NSC effectiveness and rejuvenate the microenvironment of the aging brain ultimately to enhance neural function. These studies establish a concrete framework toward potential stem cell therapies for aging and related neurodegenerative diseases.

Diego Mastroeni, Ph.D.

Banner Health

Annual Award Amount

$74,984

Project End Date

October 22, 2017

A Novel Compound to Protect Mitochondria against Oligomeric Abeta Toxicity: Implications for the Synapse

In this proposal we aim to test a model of Alzheimer pathophysiology that would establish relationships among Abeta oligomers, mitochondrial function, epigenetic mechanisms and expression of genes related to the synapse. Thus, this proposal aims to consolidate the established amyloid and mitochondrial hypotheses and synaptic phenomena with the newly developing field of epigenetics. In addition, we propose to test the ability of a newly synthesized coenzyme Q10 analogue to mitigate the effects of oligomeric Abeta in vitro. Besides the potential therapeutic promise held in this application, the work proposed here would broaden understanding of the fundamental underlying mechanisms regulating altered gene expression in AD. This, then, could lead to new molecular targets for therapeutic intervention, and pave the way for future work into animal models and eventually into clinical trials.

Chinh Nguyen, M.D.

Southern Arizona VA Health Care System (SAVAHCS)

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Use of Whole Blood Immune Assay to Determine the Prognosis of Non-menigeal Coccidioidomycosis

Coccidioidomycosis is a major health problem in Arizona. A problematic area of management is determining the prognosis of disease and the need for antifungal therapy. Current laboratory tests, particularly the serologic titer for complement fixation, while helpful in determining severity of disease and response to antifungal therapy, do not predict the risk of recurrence, relapse or dissemination. However, there is evidence that measurements of cellular immune response during coccidioidal infection do predict these outcomes. Our research laboratory has developed a whole blood assay that measures the release of interferon-γ (IFN-γ), a key cytokine that reflects a protective cellular immune response, after incubation with the coccidioidal antigen preparation T27K. We have previously demonstrated that this assay correlates with the coccidioidin skin test, which is no longer available. We propose to perform a three-year prospective observational cohort study to assess the usefulness of applying the results of this assay to the clinical outcome of patients with various types of non-meningeal coccidioidomycosis. The results should establish if the release of IFN-γ from whole blood incubated with a coccidioidal antigen preparation predicts the prognosis of coccidioidal disease. If so, it would improve outcomes and reduce the costs of managing this coccidioidomycosis in Arizona.

Benjamin Renquist, Ph.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Targeting the Hepatocyte/Vagal Nerve Communication to Develop Therapeutics for Type 2 Diabetes

The incidence of Type 2 diabetes in Arizona has more than doubled since 1990. Liver fat accumulation, a hallmark of insulin resistance, is a co-morbidity common in 60–80% of Type 2 diabetics. In fact, the severity of liver fat accumulation is directly related to the severity of insulin resistance. We propose that liver fat accumulation induces hyperinsulinemia and insulin resistance by communicating nutritional status to the peripheral nervous system. Preliminary data from our lab shows that pharmacologically mimicking the effects of lipid accumulation in hepatocytes inhibits activity of the hepatic afferent nerve and increases serum insulin. Studies proposed in this grant aim to understand the mechanism by which hepatocytes communicate to the vagal afferent nerve. The Renquist laboratory is uniquely suited to perform these studies, as we have developed an electrophysiology technique that allows for simultaneous measurement of liver cell membrane potential and hepatic vagal afferent nerve activity, while using a virus to specifically manipulate liver cell neurotransmitter release. Studies proposed in this grant will justify development of pharmacological agents that aim to treat type 2 diabetes by governing hepatocyte communication to the peripheral nervous system.

Dominik Schenten, Ph.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Innate Control Mechanisms of Adaptive Immunity to Live Infections

Innate immune recognition is an important regulatory checkpoint in the initiation of adaptive immune responses. The activation of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) by microbial ligands leads to release of proinflammatory cytokines that are essential for the T cell response. In previous work, I have shown that TLR-induced IL-1 and IL-6 play a critical role in this process as these cytokines help CD4+ T cells to overcome the suppressive effects of regulatory T cells (Tregs). However, IL-1 and IL-6 are only important in the context of immunizations using TLR ligands or dead microbes as adjuvants whereas these cytokines are dispensable in the context of live infections with a variety of bacteria and viruses. The overall goal of this proposal is therefore the identification and characterization of the innate immune signals that distinguish adaptive immune responses to infections from responses to immunizations. Despite considerable interest in vaccine design, these signals are currently poorly understood. The identification of such signals will be critical for understanding of the parameters that define protective immune responses and will allow the development of novel vaccine strategies and therapies for autoimmune diseases including colitis and its associated cancers.

Sarah Stabenfeldt, Ph.D.

Arizona State University

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Redecorating the Neural Injury Landscape to Promote Regeneration

Traumatic brain injury (TBI) is the leading cause of injury related death in America. However, current clinical treatment modalities for TBI focus on minimizing the secondary symptoms and complications associated with TBI; however, no clinical treatments currently exist to address the underlying neuropathology for any level of TBI severity ranging from mild to severe. The long-term goal of the proposed research is to develop novel intervention strategies that directly tackle neurodegenerative cues and promote regeneration. This proposal is the first step in achieving our longterm goal whereby our primary objective is to mask and "redecorate" the neurodegenerative cues in the injury extracellular microenvironment by employing novel targeting probes generated from single-chain antibody fragments (nanobodies). Ultimately, our approach will contribute significant advances to improved understanding of how the extracellular microenvironment impacts neural regeneration after brain injury.

Theresa Thomas, Ph.D.

Arizona State University

Annual Award Amount

$75,000

Project End Date

October 22, 2017

Experimental TBI-Induced Endocrine Dysfunction: Timing, Mechanisms and Treatment

The occurrence of endocrine dysfunction occurs in as many as 20–30% of patients with a history of TBI. Endocrine dysfunction significantly impairs health and quality of life, impedes rehabilitation efforts and lowers life expectancy. The full understanding of endocrine dysfunction can be advanced by translational work in rodents, with cost-effective and rapid assessment of the pathological events associated with endocrine dysfunction and validation of the efficacy of various treatment strategies. We hypothesize that endocrine dysfunction in the wake of diffuse TBI involves specific pathology in the hypothalamic-pituitary-adrenal (HPA) axis, which is amenable to hormone replacement therapy (HRT) and/or rehabilitation intervention. We propose a temporal evaluation of neuroendocrine dysfunction after diffuse TBI in a rodent model of diffuse TBI to determine the onset and extent of endocrine dysfunction and associated pathology. Knowledge gained from these studies will guide clinical investigations to advance diagnosis and develop novel therapeutic approaches that can improve the lives of Veterans and civilians living with TBI.

Mingwu Wang, M.D., Ph.D.

University of Arizona

Annual Award Amount

$74,999

Project End Date

October 22, 2017

NHE8 and the Ocular Surface Homeostasis

Dry eye disease (DED) is very common in Arizona due to low average annual humidity and high temperature. We recently discovered that mice deficient of Sodium/Hydrogen exchanger (NHE)8 in the conjunctiva have dry eyes. By studying how lack of NHE8 in conjunctiva causes DED, we can further understand the pathogenesis of this disease, and hope to unravel new treatment strategies.

Christopher Buneo, Ph.D.

Arizona State University

Annual Award Amount

$100,000

Project End Date

October 22, 2015

Neural Correlates of Cooperative Manipulative Actions

Cooperative or 'joint' actions involve two or more agents coordinating their behavior in space and time to perform a particular task. Joint actions are an important component of interaction and cooperation in both the social and motor domains however surprisingly little is known about the planning and control of these actions, particularly their neural correlates. The work proposed here is aimed at providing preliminary data for a federal grant application focused on characterizing the neural correlates of one of the most fundamental and commonly performed joint actions, object handovers, in the sensorimotor cortices of awake, behaving monkeys. In addition to expanding our knowledge of joint actions and the sensorimotor systems of the brain, the proposed research has significant potential to impact state and national needs in the consumer, healthcare, military, and industrial settings by advancing the fundamental engineering and neuroscience knowledge necessary to create the next generation of neural prosthetic and rehabilitative systems, specifically those employing robots as cooperating agents. In the healthcare domain, such systems are expected to be in widespread usage in the next few decades, and will be critical for improving the quality of life of Arizonans with disabilities resulting from stroke, Parkinson's disease and other conditions.

David W. Galbraith, Ph.D.

University of Arizona

Annual Award Amount

$100,000

Project End Date

October 22, 2015

Identification of Changes in Gene Expression at the Earliest Stages of Prostate Oncogenesis

Solving human health problems requires a detailed comprehension of the functions of organs and tissues within the body, and an ability to pinpoint those differences distinguishing normal and disease states. Organs and tissues comprise mixtures of cell types, and unraveling the individual functions and contributions of these different cell types is impeded by their complex interspersion. The goal of this project is identify and thoroughly characterize the earliest changes in gene expression that occur within prostate cells as they initiate tumorigenesis. Early identification is crucial, since prostate cancer (PC) initiation occurs long before the cancer is symptomatic. Identifying the different manners in which PC can initiate and progress should also provide a means to distinguish indolent from aggressive forms of the disease, since this is also of great clinical significance. Our approach is designed to provide novel biomarkers for early detection and treatment of prostate cancer. The main technical issue is to accurately identify early neoplastic cells and characterize their transcriptional states, within the very large background of normal prostate cells. We have devised a novel mouse PC genetic model to provide this information. This model combines, through directed breeding, a drug (tamoxifen) inducible form of the Cre recombinase (Cre), two tumor suppressor coding sequences (PTEN and p53), a nuclear-targeted version of the Green Fluorescent Protein (H2B-GFP), and the genetic background carrying a common prostate cancer translocation between TMPRSS2 and the ETS transcription genes.

Kaushal Rege, Ph.D.

Arizona State University

Annual Award Amount

$100,000

Project End Date

October 22, 2015

Nanoassemblies for Gene Silencing

Hyperthermia (elevated temperatures) is a promising therapeutic approach for cancer, particularly where localized administration is possible. However, cancer cells overexpress heat shock proteins (HSPs) that enable survival at elevated temperatures. We propose a nanoassembly platform that can simultaneously deliver nucleic acids for silencing (knocking down) HSPs, as well as near infrared (NIR) light-triggered hyperthermia to cancer cells. This 1–2 punch is anticipated to enhance the ablation of malignant cells due to synergy between the two treatments; silencing of HSPs sensitizes cancer cells to nanoparticle-induced hyperthermia. Gold nanorods (GNRs) are coated with polymers (polyaminoethers or PAEs), unique to the PI's laboratory, resulting in the formation of PAE-GNR nanoassemblies. Plasmid shRNA and siRNA targeting HSPs (e.g. 90, 72 or 27) will be loaded on PAE-GNR nanoassemblies and delivered to cancer cells. HSP knockdown kinetics will be studied in order to appropriately time the second (hyperthermia) hit using NIR lasers. The proposed research is anticipated to result in novel combination treatments for cancer cell ablation, non-viral methods for gene silencing, and fundamental advancements in nanoscale and molecular therapeutics. Existing and proposed outreach activities from the Rege lab will enhance STEM engagement of high-and middle-school students in Arizona.

Donato F. Romagnolo, Ph.D.

University of Arizona

Annual Award Amount

$100,000

Project End Date

October 22, 2015

Early-life Exposure and Risk of Breast Cancer

This project focuses on the impact of exposure to environmental agents on the development of breast cancer. Information from animal models and population studies suggest that mammary tumor promotion in adult life is influenced by exposure to carcinogens in early-life (5,6). Specifically, we wish to target the mechanisms that are responsible for the loss of expression of the breast cancer susceptibility gene, BRCA-1, and how reduced BRCA-1 expression impacts the development of mammary tumors in adult life. The BRCA-1 protein participates in DNA repair and transcriptional control (7). In women who carry a mutated BRCA-1 gene (BRCA-1+/-), the silencing of the wild-type (WT) copy creates a BRCA-1-/--like phenotype with a high probability (~60–80%) of developing breast cancer (8–11). On the other hand, sporadic breast cancers, which represent the vast majority (~90%) of breast tumor cases, do not have mutations in the BRCA-1 gene (BRCA-1+/+), but have absent or markedly reduced levels of BRCA-1 protein (12–18). Therefore, understanding the mechanisms that contribute to silencing of BRCA-1 has important implications for the prevention of both hereditary and sporadic breast tumors.

Nafees Ahmad, Ph.D.

University of Arizona

Annual Award Amount

$250,000

Project End Date

October 22, 2017

Viral, Immunological and Clinical Factors in HIV-1 Aging Patients

Recent clinical evidence suggests that older individuals infected with HIV (the virus that causes AIDS) present with a more severe form of AIDS disease. In addition, HIV infected individuals who have aged with HIV infection while on anti-HIV drugs as well as normal elderly population experience an accelerated aging of the immune system. These age-related changes may result in altered functions of the major cells of the immune system (T and B cells) and reduced response against other infections. We propose to determine the specific features of HIV that influence AIDS progression and alter the functions of the immune system in HIV aging patients. We will compare these aging related immune system markers between HIV infected older individuals and normal older individuals. We will enroll 50 recently HIV-infected older patients, 50 HIV-infected patients aged with HIV treatment, 50 older HIV long-term non-progressors, and 50 uninfected older individuals (all aged >50 years). These patients will be clinically evaluated and blood samples will be collected every 4 months for 3 years to determine the specific properties of HIV that alter the functions of the immune system. Results from this study may provide new information to develop strategies for prevention and treatment of HIV infection in these aging patients, including improving the process of aging of the immune system in elderly population.

Yin Chen, Ph.D.

University of Arizona

Annual Award Amount

$250,000

Project End Date

October 22, 2017

A Microfuidic Ex Vivo Lung Model (MEVL) for Studying Pulmonary Diseases

The main goal of the present project is to develop a novel system that can mimic the physiological condition of the human lung and can respond to environmental stimuli similarly to the human lung. The current cell model has been proven to yield poor results for predicting physiological or toxicological responses; and the major reason for this failure is the lack of communication between different cell types in the body. The alternative is to use animal model. However, the high cost and the potential ethical consideration have always been controversial and unavoidable issues for such studies. Furthermore, the physiological responses in an animal model may not be identical to what actually occurs in humans. Thus, a new model is urgently needed for bridging this gap. In this proposal, we plan to construct a miniature lung on a microchip-like device, which is able to "breathe" and to respond to the external stimuli similarly to the actual lung. We will further test this "lung" by letting it "breathe" in different environmental insults such as pollutants (e.g. nanoparticles) and pathogens (e.g. bacteria) to examine and record the responses. Then, these data will be compared with the data recorded from the real lung under similar challenges. The results from this comparison will be further used to fine-tune the artificial lung to its perfection. This system ("MEVL") will be extremely useful for a number of applications such as drug testing, toxicant screening, anti-terrorism etc.

Robert Handa, Ph.D.

University of Arizona

Annual Award Amount

$250,000

Project End Date

October 22, 2017

Fetal Risk factors for Obesity and Comorbid Depression

Obesity is a major health issue and often co-occurs with psychiatric illnesses such as depression. Importantly, some Arizona populations (low-income Hispanic females; Pima Indians) are at very high risk for obesity. Moreover, Arizona now has the 7th-highest rate of childhood obesity. Since the origins of obesity and depression can begin during fetal development, we hypothesize that enhanced risk for adult obesity and comorbid depression are long-term consequences of in utero stress. Our studies take advantage of a unique community population of women whose pregnancies and offspring were followed from 1959–1966. From their offspring (now ~50 years old) we identified a unique cohort exposed to prenatal stress and with comorbid depression and obesity. In this application, we will determine risk biomarkers from fetal development and early childhood predicting human adult comorbidity. In analogous animal studies, rats exposed in utero to excessive glucocorticoids to mimic prenatal stress have comorbid metabolic disturbances and depressive-like behaviors in adulthood. Endocrine and genomic biomarkers will be identified and compared in human and animal cohorts. This translational approach to elucidating factors involved in the etiology of disease comorbidity will allow identification of therapeutic targets and biomarkers in humans and may identify early periods for intervention and prevention.

Karl Kern, M.D.

University of Arizona

Annual Award Amount

$250,000

Project End Date

October 22, 2017

A Pilot Randomized Clinical Trial of Early Coronary Angiography versus No Early Coronary Angiography for Post-Cardiac Arrest Patients without ECG ST Segment Elevation

Cardiac arrest is a major public health issue. Arizona has been a leader in improving long-term survival by introducing new and innovative resuscitation approaches including "Chest Compression-Only CPR" and "Cardiocerebral Resuscitation." Post-resuscitation care is the next great opportunity for further improvements. Early coronary angiography (early CAG) combined with therapeutic hypothermia has become the recommended standard of care for post-cardiac arrest patients manifesting ST segment elevation on their electrocardiogram (ECG). However, the majority of cardiac arrest victims do not have ST segment elevation. There is clinical equipoise as to whether these patients will benefit from early CAG. This proposal is for a pilot randomized, clinical trial to evaluate the safety and efficacy of performing early CAG versus no early CAG in post-cardiac arrest patients without ST segment elevation. Safety will be assessed by the lack of association between early CAG and major adverse events (rearrest, bleeding, pulmonary edema, hypotension, acute renal insufficiency, and pneumonia), while efficacy will be evaluated using a composite endpoint of improved left ventricular regional and global function, survival to discharge, and good functional status after discharge. A three year, multi-centered, prospective, randomized study of 240 cardiac arrest patients is proposed.

Diego Martin, M.D., Ph.D.

University of Arizona

Annual Award Amount

$249,960

Project End Date

October 22, 2017

MRI of Non-Alcoholic Steatohepatitis (NASH) Biomarkers

Our goal is to improve the health of over 20% of Arizonans with fatty liver disease. Our objective is to improve diagnosis, therapy and outcomes related to Non-Alcoholic Fatty Liver Disease (NAFLD) and Steatohepatitis (NASH) by developing new magnetic resonance imaging (MRI) liver disease biomarkers that will provide measures of disease risk and progression not currently available . NAFLD/NASH is associated with diabetes and obesity and affects ~2 million Arizonans; Native and Mexican-Americans have higher risk. A subset of NAFLD develops NASH with hepatic fibrosis and risk of hepatocellular carcinoma (HCC). We rely on biopsies to diagnose NAFLD/NASH. Biopsies are limited and many patients present with later stage disease and HCC, increasing cost of care and with worse outcomes. Non-invasive disease stratification biomarkers will improve our understanding of NAFLD/NASH and facilitate development of therapy. We have assembled a coalition of researchers who are leaders in the fields of adult/pediatric NAFLD/NASH. This unique group of investigators bridges the basic and clinical sciences; we will be able to examine the roots of the NAFLD/NASH epidemic. Our proposal will establish the tools and framework for a definitive prospective study of the prevalence and onset of NAFLD/NASH, identifying disease biomarkers to facilitate prevention and therapy.

George Pettit, Ph.D.

Arizona State University

Annual Award Amount

$250,000

Project End Date

October 22, 2017

Discovery of Powerful Anticancer Drugs for Monoclonal Anticancer Drugs (ADC) Development Capable of Improving Cancer Treatments

The human population of Arizona and worldwide is rapidly expanding and in concert the urgent need for new and more effective drugs. The traditional/alternative medicine applications of the Amaryllidaceae species has remained one of the most prominent in folk medical applications for some 2400 years of human history back to the records of Hippocrates of Cos (circa 460–377 B.C., the "Father of Medicine") who treated breast and uterine cancer patients with an Amaryllidaceae species now known to contain important anticancer drugs. A goal of the proposed research is the discovery and development of novel small molecule anticancer and anti-infective drugs from Amaryllidaceae species. A top specific aim of the proposed research will be the discovery of powerful (low nanomolar activity) anticancer drugs that can be linked to monoclonal antibodies for direct transport to cancer cells or antibody drug conjugates (ADC). The general pathway for development of new and robust ADC's for cancer treatment will follow the very productive course that led to our anticancer drug discovery Auristatin E becoming the first successful ADC now known as ADCETRIS. Over the past two years ADCETRIS has entered clinical use for cancer in 36 countries.

Kaushal Rege, Ph.D.

Arizona State University

Annual Award Amount

$250,000

Project End Date

October 22, 2017

Targeted Therapeutics for Triple Negative Breast Cancer Disease

More than two women die of breast cancer every day in Arizona, and over 4600 women are diagnosed with the disease. Triple-negative breast cancer (TNBC), which occurs in approximately 15–30% breast cancer patients, is associated with poor prognosis, limited therapeutic options, and no targeted therapies. Our recent discovery indicated that mitoxantrone, a clinically relevant drug in advanced breast cancer, sensitized several cancer cell lines (including breast cancer) to TRAIL-induced death in a synergistic manner. The proposed research will focus on targeting mitoxantrone to folate-overexpressing TNBC cells. We will investigate novel folate-targeted mitoxantrone conjugates, in addition to mitoxantrone encapsulated in biocompatible nanoparticles as to strategies for targeted delivery to TNBC cells. This treatment will by synergized with TRAIL, which selectively induces death in cancer cells, leading to a powerful, targeted approach for TNBC. We will extensively evaluate efficacy in cell culture, and carry out pre-clinical investigation of effective combinations using an orthotopic ('at the site') tumor model of TNBC tumors. Our research is anticipated to result in exhaustive preclinical evaluation of a novel combination treatment, and novel routes for selective delivery of these. Successful completion of this work will set the stage for future clinical trials for this disease.

Marwan Sabbagh, M.D.

Banner Health

Annual Award Amount

$246,198

Project End Date

October 22, 2017

Longitudinal Assessment of Florbetapir PET, FDG PET, and MRI in Down Syndrome Individuals with and without Alzheimer's Dementia

Down syndrome (DS) is associated with increased risk of Alzheimer's dementia due to amyloid precursor protein gene overexpression, and fibrillar amyloid-β (Aβ) deposition by age 30. Studies using florbetapir positron emission tomography (FBP-PET), fluorodeoxyglucose (FDG) PET and magnetic resonance imaging (MRI) found increased fibrillar Aβ binding, reduced cerebral metabolic rate for glucose (CMRgl) and gray matter volume (GMV) in subjects with late-onset AD. In our pilot study, we compared fibrillar Aβ binding, CMRgl and GMV in 5 DS with AD (DS/AD+), 12 older and younger non-dementia DS (DS/AD-), and 9 normal controls (NC). Fibrillar Aβ measures in predefined regions were associated with disease severity, with age in DS, and spatial pattern similar in late-onset AD. DS had lower CMRgl than NC and DS/AD+ had lower GMV than DS/AD-in AD regions. Here, we propose longitudinal follow-up of 15 DS/AD+; 15 DS/AD-subjects; and 15 age-matched NC individuals. Cognitive exams, MRI, FDG-and FBP-PET will be performed at baseline/followup visits. We will (a) characterize the longitudinal fibrillar amyloid, CMRgl and GMV changes within/between groups; (b) describe the linkage among them and their relationship to cognitive measures; and (c) provide foundation for interventions in preclinical AD stage of DS patients.

Biospecimen Locator

At-A-Glance

BIOSPECIMEN LOCATOR

Funding Source Used

Disease Control Research Fund

About the Program

Acquiring quality biospecimens is one of the largest obstacles researchers face as they strive to advance medical science and improve patient care. The Arizona Biospecimen Locator (ABL) was designed to provide researchers with specimens needed to advance their research studies. The ABL is a web-based biospecimen database of both diseased and normal solid tissues, cells, fluids and molecular samples stored at participating Arizona hospitals and tissue banks. Researchers can use the ABL to search and request biospecimens which are organized by disease, type of specimen, preservation type, anatomic source and demographics of participants to use in their qualified research studies. Using ABL encourages research collaboration that may lead to more effective treatments and potential cures.

The Arizona hospitals that participate in the program and currently link to the ABL include St. Joseph's Hospital and Medical Center, Maricopa Integrated Health System, and Phoenix Children's Hospital.

Program Highlights

Business/Strategic Long-Term Bio-repository Funding Plan submitted by participating hospitals

Research Education

At-A-Glance

RESEARCH EDUCATION

Funding Source Used

Disease Control Research Fund

About the Program

In working with Arizona researchers and through its commitment to the Arizona Biosciences Roadmap, ABRC identified a need to make high quality educational resources available. The Research Education Program seeks to create a shared sense of community by bringing national and local experts together to engage Arizona researchers and clinical professionals in emerging topics at little or no cost to the research community.

Program Highlights

2014 ABRC Workshops and Conferences Included:

May 7, 2014—Institutional Review Board Educational and Networking Event. This one-day workshop covered topics related to human research protection and practical strategies to enhance hospitals and other institutions' review board operations.

May 8–9, 2014—From Research to Practice: Funding For a Healthier Arizona.
This two-day conference covered topics for pursuing funding opportunities and writing a successful grant proposal for all types of funding, including federal, local government, tribal, private, and academic.

A Special Thank You to the Sponsors of the 2014 ABRC Conference

1. Arizona State Credit Union:
   www.azstcu.org
2. Save the Cord Foundation:
   www.savethecordfoundation.org
3. LeCroy & Milligan Associates, Inc.:
   www.lecroymilligan.com
4. Association of Clinical Research Professionals (ACRP) Phoenix Chapter:
   www.acrpnet.org
5. Arizona Governor's Office of Highway Safety:
   www.azgohs.gov

Public Cord Blood

At-A-Glance

PUBLIC CORD BLOOD

Funding Source Used

Disease Control Research Fund

About the Program

The Arizona Public Cord Blood Program was created to advance the collection of and increase the number of cord blood units available for transplantation. Umbilical cord blood is blood that remains in the blood vessels of the placenta and the umbilical cord after the baby is born and the cord has been clamped and cut. It contains hematopoietic stem cells or blood-forming cells (cells that can form other blood cells). These blood-forming cells are also found in bone marrow. In the past, the placenta and umbilical cord were thrown away. Today, the blood can be collected, stored, and made available for transplant to children and adults that have certain genetic or life-threating diseases such as leukemia or lymphoma.

Currently, seven out of ten people will not have a suitable matched donor in their family and will depend on the National Marrow Donor Program (NMDP) registry to find a match. Adding diverse units to the registry increases the likelihood that all patients will find a match.

Participating hospitals include Maricopa Medical Center, Phoenix Baptist Hospital, St. Joseph's Hospital and Medical Center in Phoenix, and Tucson Medical Center. This program officially began collection in late 2011. Since the program's inception, the participating hospitals have collected over 3,737 cord blood units. Of those, 553 have been banked and listed on the registry for potential transplantation.

Program Highlights

14 Arizona cord blood units selected and transplanted in patients

Tucson Medical added as a collection site in Southern Arizona for donated umbilical cord blood

Umbilical cord blood; patient information pamphlet revised and distributed in accordance with A.R.S. §32-3212

Arizona Public Cord Blood Program

Artist: Yovannah Diovanti

EDUCATION

DONATION

RESEARCH

Arizona Alzheimer's Consortium

Arizona Alzheimer's Consortium

The Arizona Alzheimer's Consortium is the nation's leading state-wide collaboration in Alzheimer's disease research, and its core mission is to find a way to end Alzheimer's disease as quickly as possible. Established in 1998, the Consortium is comprised of about 150 researchers and colleagues from seven principal institutions: Arizona State University, Banner Alzheimer's Institute, Barrow Neurological Institute, Mayo Clinic Arizona, Banner Sun Health Research Institute, Translational Genomics Research Institute (TGen), and University of Arizona. It also seeks to educate Arizona's residents about the disease, research progress in the state and the resources needed to help patients, families and professionals manage the disease.

Under an Appropriation, the Consortium receives $2,375,000 for Alzheimer Disease research. Of that amount, the Consortium is required to match $1,000,000.

A complete guide to all of the Consortium's research summaries, key personnel, project progress reports, publications, manuscripts, poster abstracts and grants can be found at http://azalz.org/about-us/2014-aac-annual-report/.

Translational Research Facility

Translational Research Facility

In 2002, Arizona identified the need for "a nonprofit medical research foundation in Arizona that specializes in biotechnology and that collaborates with universities, hospitals, biotechnology and health science research centers and other public and private biotechnology businesses in Arizona." Seeking to fulfill this need, ABRC contracted with the Translational Genomics Research Institute (TGen). The contract, established in December 2002 through June 30, 2013 in accordance with Laws 2002, Chapter 320, Section 1 and A.R.S. §36-276, sought to provide funding to support the basic operational infrastructure of a Translational Genomics Research Facility. For the period of July 1, 2013 through June 30, 2014, in accordance with A.R.S. §41-2702, a grant was issued to maintain continuity of the translational work being conducted in Arizona.

In years one through nine of the contract, ABRC provided $5,500,000 annually to TGen. In Fiscal Years 2012 and 2013, a total of $7,854,661 was issued. This past fiscal year, TGen received a grant of $2,000,000. Funds are used for genomic based research and clinical work aimed at discovering the underlying causes of disease progression and fostering collaboration-based projects.

Summary of FY 2014 TGen Activities:

Enterprise Efforts

During FY14, TGen formed and secured investment for three companies.

Invention Disclosures

TGen filed 20 invention disclosures in FY14 based on discoveries stemming from TGen-led research, and 20 provisional patent applications.

Contracts and Collaborations

TGen signed a total of 436 contracts in FY14, broken down as follows:

103	CDAs
66	MTAs
69	Research Collaborations
30	Consulting Agreements
61	Professional Service Agreements
4	Commercialization Licenses
103	Agreements Covering Miscellaneous Activities

Job Creation

Eighteen new full-time equivalent positions were created in 2014 with salaries and benefits totaling $1,531,245. Salaries for temporary positions (those positions created for a finite period of time) totaled $205,700, which includes temporary TGen staff and temporary service fees. Student salaries were just over $439,000, bringing the overall FY14 total to $2,175,944.

Additional information on TGen's Key personnel, research areas, and publications can be found at https://www.tgen.org/news/publications.aspx.

Arizona Department of Health Services

Arizona Biomedical Research Commission

Grants • Biospecimen Locator • Education • Public Cord Blood

Arizona Department of Health Services | 150 North 18th Avenue | Phoenix, Arizona 85007 | 602.364.0157