2016

# ANNUAL REPORT

## Arizona Biomedical Research Commission

www.azdhs.gov/abrc

Research Grants • Research Education
Arizona Public Cord Blood Program • Arizona Biospecimen Locator Program

ARIZONA DEPARTMENT
OF HEALTH SERVICES

# ABRC MISSION & VISION

## Mission

+ To identify and support innovative biomedical research to improve the health of all Arizonans

## Vision

+ Accelerating Biomedical Research and Innovation in Arizona


Prepared by:

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Douglas A. Ducey
*Governor, State of Arizona*

Cara M. Christ, M.D., M.S.
*Director, Arizona Department of Health Services*

# WHO WE ARE

The Arizona Biomedical Research Commission's (ABRC) mission is "Identifying and supporting innovative biomedical research to improve the health of all Arizonans." In FY 2016, the four core programs accomplished great achievements in working to meet the mission of the ABRC. None of these achievements would be possible without the unwavering support of our valued community partners, Agency leadership, the Governor's Office, and Legislators.

Community support is 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 their time and resources. Together, we've achieved many program milestones.

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.

ARIZONA DEPARTMENT
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH COMMISSION

# OUR COMMISSIONERS

The ABRC is made up of nine commissioners: three public members, three medical community members, and three scientific community members. Commissioners are appointed by the Governor, take an oath of office, and are confirmed by the senate. Terms are for three years. Click to read the commissioners' bios.

## 3 Public Members


Brandy Wells


Cosmo Magliozzi


John Ragan

## 3 Medical Community Members


John Cover


Mitchell Shub, MD


Hugo Vargas, MD

## 3 Scientific Community Members


Howard Eng


Mary Kay Turner


Vacant

# OUR STAFF

| | |
|---|---|
| Executive Director | Victor Waddell, Ph.D. |
| Program Manager | Jennifer Botsford, M.S.PH. |
| Program Coordinator | Theresa Napoleon, B.S. |

Click to read the staff's bios.

## WITH SUPPORT FROM:

- Yesenia Sandoval, Procurement Specialist
- Nicki Strattard, Finance Manager
- Michelle Cardenas, Procurement Tech

# OUR CORE PROGRAMS

# WE ALSO SUPPORT

| | |
|---|---|
| Alzheimer's Research | Arizona Alzheimer's Consortium |
| Translational Genomics Research | TGen |



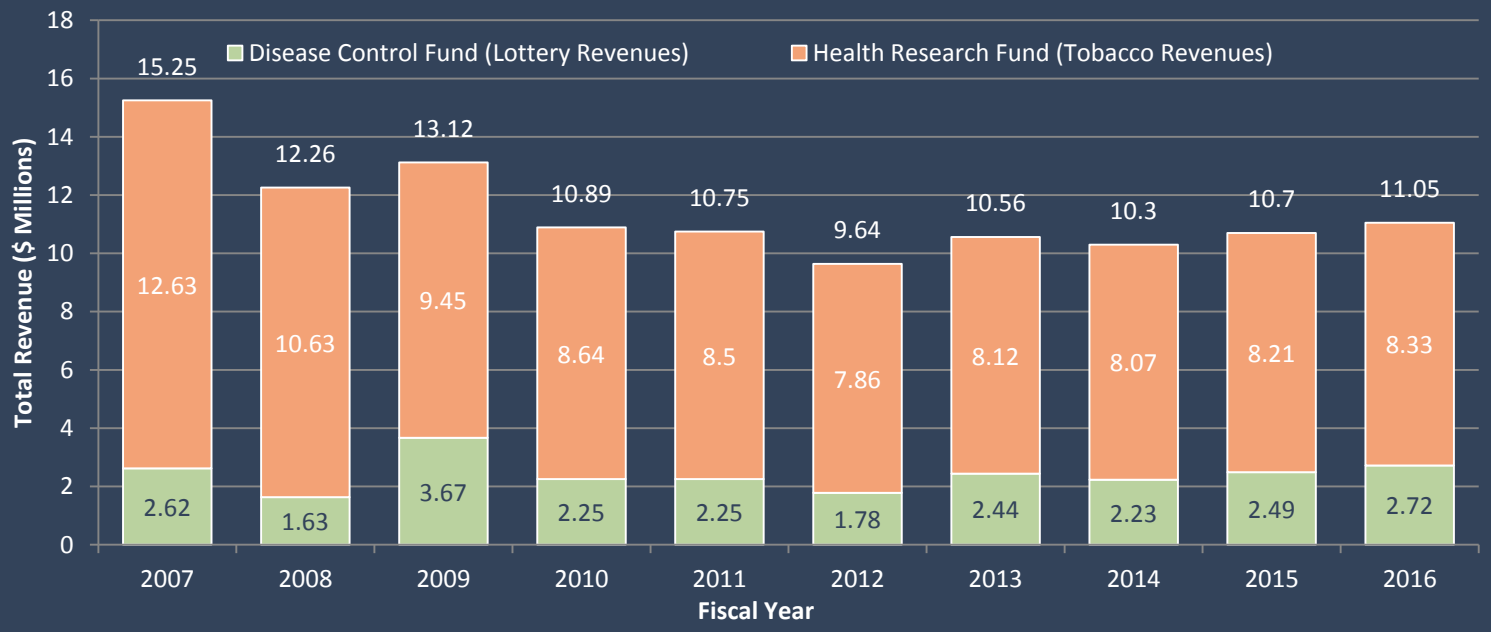
To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#about-collaboration

# FINANCIAL SUMMARY

## Funding Sources

+ Disease Control Research Fund ARS §36-274
+ Health Research Fund ARS §36-275

## Revenue

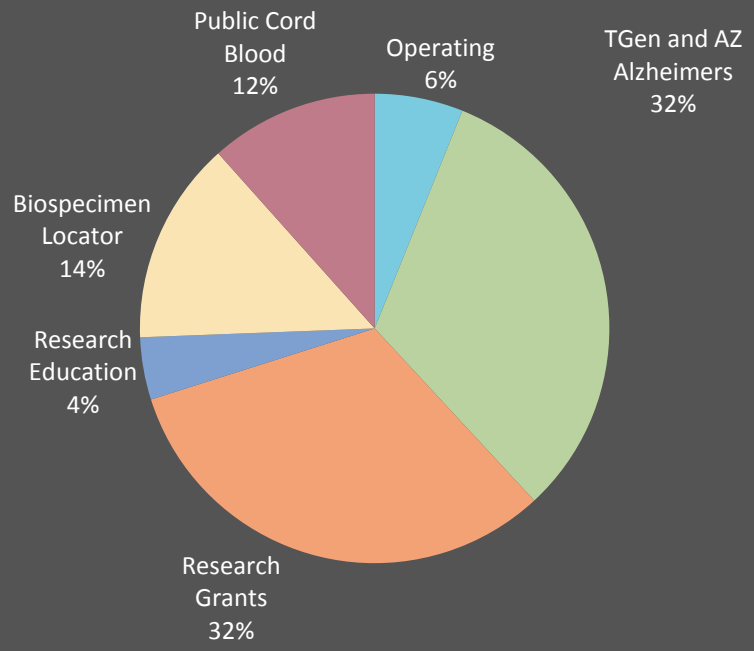


# FINANCIAL SUMMARY

## Expenditures

+ Disease Control Research Fund ARS §36-274 $ 2,608,278
+ Health Research Fund ARS §36-275 $ 6,764,565

| Category | Total |
|---|---|
| **Research Grants** | $ 2,999,088 |
| **Research Education** | $ 402,500 |
| **Biospecimen Locator** | $ 1,312,103 |
| **AZ Public Cord Blood Program** | $ 1,087,641 |
| **TGen** | $ 2,000,000 |
| **AZ Alzheimer's Consortium** | $ 1,000,000 |
| **Operating** | $ 571,511 |






To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#reports

# COMMISSION MEETINGS

+ Commissioners should meet quarterly ARS §36-272(E)
+ The commission could not meet from January to June 2016 due to lack of quorum

| Meeting Dates | Meeting Highlights |
|---|---|
| **July 30, 2015** | Overview of ABRC, Strategic Plan, Strategic Map, Grant Application & Review Process |
| **September 9, 2015** | Letters of Intent Process for Grant Application |
| **October 9, 2015** | Review RFGA language |
| **October 16, 2015** | Review Process for Letters of Intent, Presentation by Arizona Alzheimer's Consortium |

# ARIZONA PUBLIC CORD BLOOD PROGRAM

**6,000+** cord blood units collected

**600+** cord blood units banked

**38** cord blood units transplanted

+ 100% of providers delivering at partner hospitals were trained in cord blood collection protocol

+ Multiple speaking engagements across the state to educate providers, students, parents, and the public

+ 1st Annual Arizona Cord Blood Conference

**PARTNER HOSPITALS**

+ Dignity Health - St. Joseph's Hospital and Medical Center
+ Maricopa Integrated Health System
+ Abrazo Central Campus
+ Tucson Medical Center

**35,000** Cord blood transplants worldwide to date

**850** Cord blood transplants in the US annually

Every year **3,000 Americans die** because they cannot find a matching donor

African-American patients find a donor 25% of the time

Asian patients find a donor about 40% of the time

Hispanic patients find a donor about 45% of the time

Caucasian patients find a donor about 75% of the time

Multi-racial people face the worst odds

Umbilical cord blood is blood that remains in the blood vessels of the placenta and the umbilical cord, and is collected after the baby is born and the cord has been clamped and cut. Cord blood can be used much the same way that bone marrow stem cells are used for a life-saving transplant. For many patients in need, a cord blood transplant is the best or only hope for a cure. Donating umbilical cord blood is free, painless and neither mother nor child is harmed in the collection.

References:
http://www.aabb.org/aabbcct/Documents/NMDP-Cord-Blood-Advisory-Group-Organization-and-Highlights.pdff
http://bloodcell.transplant.hrsa.gov/research/transplant_data/registry_tx_data/longdesc/index.html#Fig6
http://ij.org/bonemarrowstatistics/
http://bloodcell.transplant.hrsa.gov/about/general_faqs/



To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#cord-blood-home

# ARIZONA BIOSPECIMEN LOCATOR (ABL)

**6,782+** specimens collected

**446** specimens distributed for research

**25** studies supported

**16** resulting publications and presentations

**PARTNER HOSPITALS**

+ Dignity Health - St. Joseph's Hospital and Medical Center
+ Maricopa Integrated Health System
+ Phoenix Children's Hospital

Acquiring quality biospecimens is one of the largest obstacles researchers face as they strive to advance medical science and improve patient care. The ABL will be 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 will 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.



To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#biospecimen-locator

# RESEARCH EDUCATION PROGRAM

+ General Research Funding and Management Workshops
+ Clinical Trial Management and Compliance Workshop
+ Research Conference – ABRC award recipients showcased research
+ Cord Blood Conference
+ IRB workshop & 3 other workshops
+ Sources of Funding for Health Research – Search Engines Workshop
+ Developing a Research Concept and a Research Team Workshop
+ Designing Community-Based Participatory Research Projects Workshop
+ IRB Issues for Health Disparities Research in Northern Arizona Workshop Series

**PARTNER UNIVERSITIES**

+ University of Arizona, Tucson
+ University of Arizona, Phoenix
+ Northern Arizona University

**ATTENDEE COMMENTS**

"[The presenter] energetically and articulately presented this informative workshop. The workshop was impressively up-to-date in the coverage of the latest NIH guidelines."

"[The presenter] was very knowledgeable and presented thoroughly all aspects and sections of the grant writing workshop. She was particularly attentive to the questions asked by the audience. Sincerely one of the best workshops I have ever attended."

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 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. ABRC is partnering with local universities.



To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#research-education-program

# RESEARCH GRANTS

+ Continued Support for 30 ongoing research projects
  + 18 Early Stage Investigator Awards (ESI) | $ 75,000 per year / 3 years
  + 3 Catalyst Awards (CA) | $ 100,000 for 1 year
  + 8 Arizona Biomedical Investigator Grants (BIG) | $ 250,000 per year / 3 years

## tangible IMPACT in Arizona

"...this award has definitely strengthened the enthusiasm among clinicians and researchers to find new collaborations, creating team based projects to answer key questions for the mechanism(s) involved in the genesis of this disease and create potential opportunities for new therapeutic approaches."

"...findings from [this funding] allowed me to present data at the National Institute on Aging. 50 were selected out of ten thousand applicants. Needless to say, it was quite an honor to spend a week at NIA."

"This project has led to strengthening of research collaboration between [institutions]. This will be critical for long-term success of this biomedical interaction and environment."

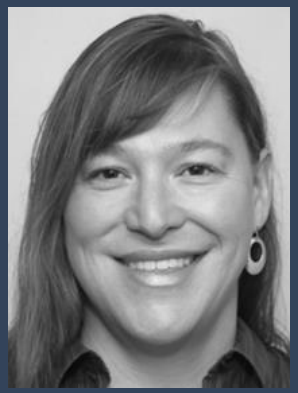
"This research would not have been possible without funding from ABRC. We are on course to generate sufficient data to make significant impact on novel targeted therapeutics..."

"...In summary such exciting advances in anti cancer drug discoveries were and will continue to be made possible by our ABRC financial assistance."

~ as stated by ABRC awardees



To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#research-grants



# Bridget Marie Barker, Ph.D.

Northern Arizona University

Annual Award Amount

$74,999

Project End Date

October 22, 2017

ESI

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

In the second year of this grant, we have expanded on the preliminary data using a BSL2 (lower biosafety level) strain of C. posadasii and have replicated these experiments with wild type Coccidioides strains that must be handled within strict biosafety containment (BSL3). Our early data suggests that host alveolar macrophages (an immune cell type that is found in lungs of healthy people) engulf the fungal conidia (spores that are inhaled from the environment), and that the conidia start to turn into the parasitic form inside macrophages. Because the strain we were working with at the lower safety level does not complete this part of the life cycle, we transferred all work to the BSL3. We have also begun working on creating a gene deletion of the SREBP gene described in our Aim 3 and this will be the focus of the third and final stage for the grant. This gene in other fungal pathogens is critical for pathogenicity. Based on our growth experiments, it appears that lower oxygen favors the development of the parasitic phase, and thus we expect that this gene deletion strain will be attenuated and be able to be handled in a BSL2 setting. This gene deletion and other information regarding host-interactions during infection will be useful in our exploration for potential drug targets and vaccines for Valley Fever.

## PUBLICATIONS & PRESENTATIONS

Teixeira, M.d.M., J.S.L. Patané, M.L. Taylor, E. Castañeda, S. de Hoog, D.M. Engelthaler, R.M. Zancopé-Oliveira, M.S.S. Felipe, B.M. **Barker**. 2016. Worldwide phylogenetic distribution and population dynamics of *Histoplasma capsulatum*. PLoS Neglected Tropical Diseases. 10(6): e0004732. PMID 27248851.

Chow, N.A., D. W. Griffin, B.M. **Barker**, A.P. Litvintseva. 2016. Molecular detection of airborne *Coccidioides* in Tucson, Arizona. Medical Mycology. 54(6): 584-92. PMID 27143633.

Engelthaler, D.M., C.C Roe, C.M. Hepp, M.M. Teixeira, E.M. Driebe, J.M. Schupp, L. Gade, V. Waddell, K. Komatsu, E. Arathoon, H. Longemann, G.R. Thomson, T. Chiller, B.M. **Barker**, P. Keim, A.P. Litvintseva. 2016. Local population structure and patterns of Western Hemisphere dispersal for *Coccidioides spp*., the fungal cause of Valley Fever. MBio. 26;7(2). pii: e00550-16. PMID 27118594.

{CONTINUED ON FOLLOWING PAGE}

# Bridget Marie Barker, Ph.D.

Northern Arizona University

## ... CONTINUED

## PUBLICATIONS & PRESENTATIONS

Teixeira, M.d.M, B.M. **Barker**. Use of population genetics to assess the ecology, evolution, and population structure of Coccidioides. 2016. Emerging Infectious Diseases. 22(6):1022-30. PMID 27191589.

Momany, M., A. Di Pietro, W.G. Alexander, B.M. **Barker**, O.S. Harb, S. Kamoun, F. Martin, J.C. Pires, J.E. Stajich, B.P.H.J. Thomma, S. Unruh. 2015. Fungal Genomics Meets Social Media: Highlights of the 28th Fungal Genetics Conference at Asilomar. G3. 5(12):2523-2525.

Lee, M. J., H. Liu, B.M. **Barker**, B.D. Snarr, F.N. Gravelat, Q. Al Abdallah, T. Xiao, N.V. Solis, M. Lehoux, S.D. Baptista, R.P. Cerone, S.G.W. Kaminskyj, D.C. Vinh, M.-C. Guiot, J.-P. Latgé, T. Fontaine, R.A. Cramer, S.G. Filler, D.C. Sheppard. 2015. The Fungal Exopolysaccharide Galactosaminogalactan Mediates Virulence by Enhancing Resistance to Neutrophil Extracellular Traps. PLoS Pathogens. 11(10):e1005187. doi: 10.1371/journal.ppat.1005187. PMID 26492565.

Shubitz, L.F., H.T. Trinh, J.N. Galgiani, M.L. Lewis, A.W. Fothergill, N.P. Wiederhold, B.M. **Barker**, E.R.G. Lewis, A.L. Doyle, W.J. Hoekstra, R.J. Schotzinger, and E.P. Garvey. 2015. Evaluation of VT-1161 for treatment of coccidioidomycosis in murine infection models. Antimicrobial Agents and Chemotherapy. 2015 Sep 14. pii: AAC.00593-15. [Epub ahead of print] PMID 26369964.

Vogler, A.J., R. Nottingham, K.L. Parise, P. Keim, B.M. **Barker**. 2015. Effective Disinfectants for Coccidioides immitis and C. posadasii. Applied BioSafety Journal. 20(3): 154-158.

Lewis, E. R. G., V. R. David, A. L. Doyle, K. Rajabi, J. A. Kiefer, P. Pirrotte, and B. M. **Barker**. 2015. Differences in host innate response among isolates of Coccidioides in a murine model of pulmonary coccidioidomycosis. Eukaryotic Cell. 14(10):1043-53. doi: 10.1128/EC.00122-15. PMID 26275879.

Rosen S., B. **Barker**, B. Larsen, I. Poojary. 2015. Medical image of the week: fungus ball. Southwest Journal of Pulmonary Critical Care. 10(4):182-3. doi: http://dx.doi.org/10.13175/swjpcc025-15.

Lewis, E.R.G., J.R. Bowers, B.M. **Barker**. 2015. Dust Devil: The Life and Times of the Fungus That Causes Valley Fever. PLoS Pearls invited review. PLoS Pathogens. 11(5): e1004762. doi: 10.1371/journal.ppat.1004762. PMID: 25973899.

Litvintseva, A.P. N. Marsden-Haug, S. Hurst, H. Hill, L. Gade, E.M. Driebe, C. Ralston, C. Roe, B.M. **Barker**, M. Goldoft, P. Keim, R. Wohrle, G.R. Thompson III, D.M. Engelthaler, M.E. Brandt, T. Chiller. 2015. Valley Fever: An old disease finding its way to new places: Coccidioides immitis found in Washington State from soil associated with recent human infection. Clinical Infectious Dis. 60(1):e1-3. PMID: 25165087.

Caffrey, A.K., M.M. Lehmann, J.M. Zickovich, V. Espinosa, K.M. Shepardson, C.P. Watschke, K.M. Hilmer, B.M. **Barker**, A. Rivera, R.A. Cramer, J.J. Obar. 2015. IL-1□□signaling is critical for leukocyte recruitment after pulmonary Aspergillus fumigatus challenge. PLoS Pathogens. DOI:10.1371/journal.ppat.1004625. PMID: 25629406.

H.L. Mead, E.R.G. Lewis, A.L. Doyle, M.M. Teixeira, P.S. Keim, B.M. **Barker**. Fighting Valley Fever: Developing Tools to Investigate a Deadly Human Pathogen. Oral presentation at the Helios Symposiu, Phoenix, AZ, July 2015.

# Christian Bime, M.D.

University of Arizona

Annual Award Amount

$75,000 ( YR 1) , $ 48,125 (YR 2)

Project End Date

October 22, 2017

## Effects of Aerobic Exercise on Asthmatic Responses in Obese Adults

Over the past two decades, there has been a significant increase in the number of asthma patients with poorly controlled disease. This increase in rate of poorly controlled asthma disproportionately affects African Americans and Hispanics living in poverty. Some possible explanations for this observation include increased allergen exposure, poor hygiene, or obesity. The observed increase in rate of obesity parallels the rate of poorly controlled asthma. We believe that there is an association between obesity and rate of asthma, especially poorly controlled asthma.

Our goal is to elucidate the mechanisms that underlie this association. To achieve this goal, we pursue the following specific aims: Recruit and retain obese adults with asthma for a protocol that includes 12 weeks of moderate intensity aerobic exercise. In a randomized controlled manner, we are measuring changes in obesity-related markers, markers of inflammation, and overall asthma control between those participants randomized to moderate intensity aerobic exercise versus those randomized to no exercise.

The intervention is a community-based exercise prescription. Information about asthma control, exercise fitness level, lung function, blood samples for markers of inflammation are collected at baseline and at the end of 12 weeks for all patients enrolled in the study.

Enrollment is progressing well and information obtained from this pilot study will be the bases for submission of a large, multicenter and multi-investigator NIH grant through the American Lung Association Airway Clinical Research Centers (ALA-ACRC).

# 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

In Arizona, cancer afflicts tens of thousands of people of all ages, including children, each year. The most common brain cancer in children is called medulloblastoma, and even survivors suffer from developmental defects from current treatments. Therefore, more research into the causes of medulloblastoma is needed in order to design more targeted therapies. Recently, a particular gene (called DDX3) was found to be frequently mutated in medulloblastoma, although it had not previously been linked to this disease. Our study is examining how the mutations in the DDX3 gene cause problems in cells that lead to medulloblastoma. Thus far, we have found that while the mutations cause significant effects on cells, they are not equivalent to simple non-functioning versions of the gene. Instead, the effects of the different mutations are complex and somewhat variable. Recently, however, we have identified a defect on the cellular level that appears to be shared by all of the mutations, and we hypothesize that this defect may be critical in promoting the development of medulloblastoma. In addition, we are also examining other cellular molecules that may interact with DDX3 in cancer. This research has led to new discoveries in how DDX3 and its equivalents in other organisms help to mediate responses to changes in the extracellular environment. In the coming year, we anticipate making further progress, including the submission of manuscripts, in both of these research areas with the eventual goal of providing the biological framework for designing new treatments for medulloblastoma and other cancers.

## PUBLICATIONS & PRESENTATIONS

Aryanpur, PP. Working Under Stress: Insights into the Regulation of the DEAD-Box Protein Ded1. Joint Biology Research Retreat, Oracle, AZ. Oct 2015.

# Elena De Filippis, Ph.D.

Mayo Clinic

Annual Award Amount

$75,000

Project End Date

October 22, 2017

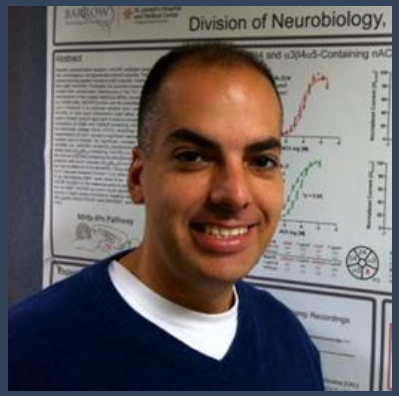
## Response Immunomodulatory Role of Eosinophils in Determining Inflammation and Insulin Sensitivity in Human Adipose Tissue

Obesity affects over 60% of the population in Arizona and is characterized by a state of low-grade, chronic **inflammation** of adipose tissue (AT), the scientific term for fat. In presence of obesity several metabolic dearrangements lead to development of mild to severe elevation of blood glucose (sugar) up to development of frank diabetes (uncontrolled blood sugar levels). Prior to the diagnosis of diabetes, obese people can be found to have mild elevation of fasting blood sugar levels together with elevation of insulin levels, a hormone normally produced by our pancreas in response to food intake. This state is called **insulin resistance**. In human fat, the relation between inflammation and insulin resistance is not clear. This project aims to gain more information on the role of a cell component of the inflammatory system, the eosinophils in modulation of the immune environment in human fat. In addition we wanted to evaluate whether the eosinophils may 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 some mediators to sustain an anti-inflammatory environment by acting on promotion of other cell populations (alternatively activated M2 macrophages), and second by increasing generation of small anti-inflammatory molecules called protectins and resolvins.

In our first aim we proposed to evaluate whether differences in eosinophil content between different fat depots of lean and obese subjects and determine the correlation with insulin sensitivity assessed by euglycemic-hyperinsulinemic clamp. Currently, we have recruited half of the obese group, while we have not enrolled any of the lean subjects. Because of the nature of this aim, we cannot begin analysis of the collected samples unless we have a small number of "control" subjects. We are considering opening recruitment in local surgical clinic outside Mayo Clinic to increase our pool of potential volunteers.

In our aim 2, we sought to collect subcutaneous fat from obese, subjects before and after 3 months of fish oil supplementation to investigate whether supplementation of healthy fat improves adipose (fat) metabolism and inflammation via changes in eosinophil content, levels and/or generation of specific mediators. In the next few weeks we will complete the first 3 subjects (afetr 3 months of fish oil supplementation) and will begin analysis of data. Recruitment is still ongoing for this aim.

Altogether 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.




# Andrew George, Ph.D.

Dignity Health - St. Joseph's Hospital and Medical Center

Annual Award Amount

$75,000

Project End Date

October 22, 2017

ESI

## 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 and 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. The focus of this work is to delineate the relationship between Aβ/α7β2-nAChR interactions, forebrain neuronal excitability, and mammalian cognitive function. Through a combination of neuropharmacology, in vitro electrophysiology and rigorous animal behavior testing we seek to achieve a "molecules to behavior" account of cognitive decline associated with early-onset AD.

## PUBLICATIONS & PRESENTATIONS

**George** AA, Bloy A, Miwa JM, Lindstrom JM, Lukas RJ and Whiteaker P.Isoform-Specific Mechanisms of α3β4*-Nicotinic Acetylcholine Receptor Modulation by the Prototoxin lynx1. 2016. FASEB J. Under review.

# Karmella Haynes, Ph.D.

Arizona State University

Annual Award Amount

$75,000

Project End Date

October 22, 2017

## Synthetic Biology for Cancer Research

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. Solving this public health challenge is impeded by the tenacious barrier of cancer's resistance to conventional treatments. Dr. Haynes has developed novel synthetic chromatin proteins that interfere with cancer-associated histone methylation signals. The innovation of the project lies in a new methodology to halt cancer with engineered chromatin instead of conventional small molecule-based drugs that cause undesirable pleiotropic effects. The Haynes lab identifies effective engineered proteins by measuring gene expression in cultured breast cancer-derived cells. Her group's efforts will lead to a cure for cancer where anti-cancer genes become activated within cells.

## PUBLICATIONS & PRESENTATIONS

**Haynes**, KA. Epigenetic Engineering of Human Cells with Fusion Proteins. Gordon Research Conference. Waltham, MA. Aug 2015.

**Haynes**, KA. Teaching Synthetic Transcription Factors to Read the Histone Code. Monsanto Science Fellows Symposium. St. Louis, MO. Invited talk. April 2016.

## Jesse Hunter, Ph.D. (Until January 2016)

TGen

## Lisa Baumbach-Reardon, Ph.D. (as of January 2016)

TGen

ESI

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. Diagnosis of the underlying genetic cause of a child's NMD is challenging, as there are many thousands of unique or rare genetic mutations that can result in overlapping NMD symptoms. Physicians face these challenges with limited resources, testing for mutations one at a time, rarely resulting in confirmation of the causal genetic aberration. Furthermore, there are no effective therapies for most NMDs. Without a genetic diagnosis, patients are left without answers, physicians cannot provide optimal treatment, and researchers cannot develop effective therapeutics. Whole exome sequencing (WES) is a contemporary and powerful technique that can overcome genetic diagnostic limitations by sequencing all genes simultaneously. Our primary goals are to use WES to identify disease causing mutations in Arizona infants and children with NMD and to study these new mutations to lead to development of effective therapeutic strategies. In doing so, we can aid physicians in genetic diagnosis and provide answers and hope to Arizona children and families with NMD.

### PUBLICATIONS & PRESENTATIONS

**Hunter** JM, Balak C, Ahearn ME, Legendre C, Liang W, Kurdoglu A, Corneveaux J, Russell M, Huentelman M, Craig D, Carpten J, Bernes SM, B**aumbach-Reardon** L. Identification of New Genes and Pathways for Rare Infantile Forms of Myopathies and Neuromuscular Disorders. ASHG (Baltimore, MD), 5-6pm, Oct. 7, 2015, Poster 2885W.

# 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. 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 and supported by recent laboratory studies showing that chronic toxoplasmosis can be neuro-protective in models of stroke and Alzheimer's disease. The goals of our study are to: 1) profile the distinct brain immune responses elicited by the genetically divergent type II and type III *Toxoplasma* strains, 2) identify the brain regions that different strains of *Toxoplasma* hone to, and 3) determine if brain functions served by parasite-enriched regions are protected against age-associated cognitive decline. To date, we have established that Type II parasites cause a less pro-inflammatory immune response than Type III parasites. This difference appears to be secondary to Type II-infected mice having an increase in anti-inflammatory T cells and macrophages compared to Type III-infected mice. In addition, we have established that the inflammatory response in the brain is reflective of the inflammatory response in the rest of the body (as judged by evaluation of immune cells in the spleen). Currently we are working on establishing how this immune response changes later in infection. Our semi-automated system for detecting brain regions enriched for parasites interactions is working, and the first preliminary data suggest that certain parts of the brain are more susceptible to infection than other parts. Currently, our aged mice (18 months of age), which have been infected for 15 months, show no difference in cognitive testing, which may be secondary to the early time point we used for cognitive testing. We will continue this study to see if we find protection by 20-22 months of age. The completion of these studies will establish a global and comprehensive program in which to identify the cellular and molecular mechanisms that underlie *Toxoplasma*'s neuroprotective effects. The identified mechanisms will offer new therapeutic targets for preserving our cognitive capacity even in the late-stages of life.

# Lalitha Madhaven, M.D., Ph.D.

University of Arizona

Annual Award Amount

$74,943

Project End Date

October 22, 2017

ESI

## Rejuvenating the Aging Brain by Improving Stem Cell Function

Due to their regenerative ability, stem cells can mediate the replacement and repair of dysfunctional or dying brain cells making them promising candidates to develop therapeutic approaches for age-related neurological disorders such as Parkinson's and Alzheimer's disease. However, in order to exert such beneficial effects, stem cells need to survive and function efficiently in an aged brain environment. A significant challenge is that aging retards the regenerative capacity of brain stem cells (referred to as neural stem cells) creating roadblocks towards developing effective stem cell therapies. In this context, our lab has discovered the progressive reduction of a specific molecule called Nrf2, within neural stem cells, as a mechanism contributing to their regenerative decline with advancing age. Given this, the current ABRC funded research project focuses on increasing Nrf2 within neural stem cells to investigate the potential utility of this approach to counteract the decline in stem cell regeneration during aging. The experimental plan involves aging animals which will (a) directly receive Nrf2 into existing brain stem cells via a cutting-edge gene transfer technology, or (b) alternatively receive transplants of externally grown 'young' stem cells that have high Nrf2. To date the first phase of our studies have determined that increased Nrf2 can indeed boost neural stem cell regeneration and promote behavioral improvement in aging animals, thus identifying it as a potential therapeutic target to improve brain stem cell function with age. Presently, we are in the second phase of the studies, which examine the ability of Nrf2 to augment the function of neural stem cells implanted into aging animals.

Overall, this work will generate fundamental information on the role of Nrf2 in brain stem cell function during aging, and provide a robust foundation for future endeavors geared towards building clinically effective stem cell-based approaches to support healthy aging and treat age-related neurodegenerative disorders - which is our ultimate goal.

## PUBLICATIONS & PRESENTATIONS

MJ Corenblum, S Ray, Remley QW, Long M, B Harder, DD Zhang, CA Barnes, and **Madhavan**. Abstract Title: A role for Nrf2 in neural stem cell function during aging. Society for Neuroscience annual meeting, Chicago, IL, October 17-21, 2015.

MJ Corenblum, S Ray, Long M, B Harder, DD Zhang, CA Barnes, and L **Madhavan**. "A critical middle-age period and a role for Nrf2 in the decline in neural stem cell function with age," American Society for Neural Therapy and Repair conference, Clearwater, FL, April 28-30, 2016.

# Diego Mastroeni, Ph.D.

Arizona State University

Annual Award Amount

$74,782

Project End Date

October 22, 2017

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

Synaptic dysfunction, or the loss of connections between neighboring nerve cells is one the earliest known problems in Alzheimer's disease (AD). Recent studies have suggested that oligomeric amyloid beta, a protein that is found in the Alzheimer's brain is responsible for the synaptic dysfunction. How exactly this occurs and what exactly are the main targets are yet to be fully understood. This proposal aims to look at the underlying targets which oligomeric abeta can affect the synapse, and offer a therapeutic approach to treating this problem.

There are huge numbers of variables that are affected by Abeta oligomers in AD, and in this proposal we focus on selected aspects of four: energy, epigenetics, chromatin structure and expression of synaptic genes. Aim 1) treat nerve cells with Abeta oligomers, and determine the effects of selected aspects of mitochondrial, epigenetic, chromatin structure and expression of synaptic genes; 2) obtain the same data as in (Aim 1) from identified neurons by laser capture from AD and non-diseased brains; 3) obtain the same data as in (Aim 1) and (Aim 2) from identified neurons by laser capture from the Osaka mouse model of AD; 4) compare data from (Aim1) (Aim 2) and (Aim 3); and 4) quantify same dependent variables in Abeta treated SY5Y cells that have had a)prior treatment with a novel coenzyme Q10 analog or b) treatment with a novel coenzyme Q10 analog following exposure to oligomeric Abeta at doses and times selected on the basis of Specific Aim 1.

Thus far the project has yielded little as far as challenges, but some important accomplishments have been made: 1) starting a neuronal cell line 2) synthesizing the oligomeric amyloid beta 3) synthesizing co-enzyme Q10 analogue 4) differentiating the sy5y's 5) treating and testing the cell model with select mitochondrial assays 5) isolating RNA, DNA and Protein from treated cells 6) prepared samples for RNA sequencing, chromatin analysis and western blotting 7) determined protein, RNA and DNA quality 8) selecting cases for Aim 2, and 9) secured brain tissue from the Mori mice (Aim 3) 10) Started cutting the Mori mice (Aim 2) 11) all the tissue from the brain bank has been secured (Aim 3), and most recently the samples from (Aim 1) have been sent to the translational genomics institute for RNA sequencing and analysis.

## PUBLICATIONS & PRESENTATIONS

Lecturer, Arizona State University Feb 19th, 2016, Arizona State University

Neuroscience Seminar Series, March 23rd, 2016, Arizona State University

Presentation ASU School of Life Sciences seminar series, April 10th, 2016

Arizona Alzheimer's Consortium Poster Presentation, May 19th, 2016

Butler Williams Scholar recipient, July, 22-27, 2016

# Chinh Nguyen, M.D.

Biomedical Research and Education Foundation of Southern Arizona

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

Valley fever, or coccidioidomycosis, is a major health problem in Arizona. It is an infection caused by the soil-dwelling fungi Coccidiodes immitis and C. posadasii. The main site of infection is the lungs. Infection causes the body's inflammatory cells to release certain inflammatory markers, called cytokines. Some of these are associated with improved outcome. We are particularly interested in the inflammatory marker, interferon-gamma (IFN-γ) as well as others. We have proposed a three-year observational cohort study to establish if there is a correlation between inflammatory markers and clinical outcomes in patients with infection from coccidioidomycosis at sites other than the nervous system.

The aim of this proposal is to determine the utility of measuring cytokines released by whole blood incubated with portions of the Valley fever fungus, called antigens, among patients with coccidioidomycosis and determine if there is a correlation between these cytokine concentrations and clinical outcome

Adults with a new diagnosis of Valley fever other than involving the nervous system who are attending the Valley Fever Clinic at the Southern Arizona Veterans Affairs Health Care System (SAVAHCS) will be enrolled. A small amount (about a teaspoonful) of blood will be drawn from them and this will be incubated overnight with a mixture of Valley fever fungus antigens. Levels of cytokines will be measured in the blood sample and correlated with the outcome of the Valley fever.

## PUBLICATIONS & PRESENTATIONS

Roller B, Robey I, Ampel NM, **Nguyen** CT, Pappagianis D. Whole blood analysis in patients with newly diagnosed coccidioidomycosis. Submitted as an abstract to IDWeek 2016.

# Benjamin Renquist, Ph.D.

University of Arizona

Annual Award Amount

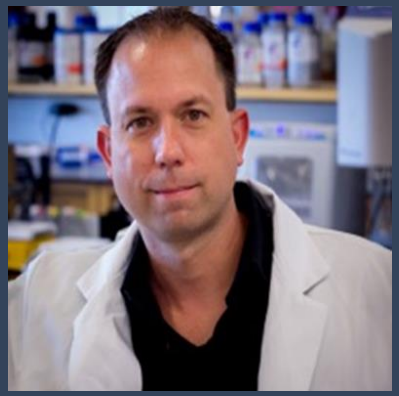
$74,867

Project End Date

October 22, 2017

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

The incidence of insulin resistance and Type II diabetes mellitus has risen 4 fold in the past 20 years. The severity of insulin resistance is directly associated with the degree of hepatic (liver) lipid accumulation. Our ABRC funded research project aims to understand the mechanism linking hepatic lipid accumulation to hyperinsulinemia and insulin resistance. We propose that hepatic lipid accumulation alters the hepatocyte to affect communication from the hepatocyte to the nerve that runs from the liver to the brain. Our data confirms that diet-induced obesity does alter the release of neurotransmitters from liver slices. We have further established the mechanism by which lipid accumulation changes hepatic neurotransmitter release. In fact, we have mouse models with severe hepatic lipid accumulation that are normoinsulinemic and insulin sensitive. We have further developed hepatic specific mouse models that are hyperinsulinemic and insulin resistant in the absence of liver lipid accumulation. Future studies are aimed at strengthening our model that aims to mechanistically understand the causative link between hepatic lipid accumulation and type II diabetes. We expect that the improved understanding developed through this funding will allow for development of therapeutics that inhibit the causative signals rather than treating the symptoms of Type II diabetes.



# Dominik Schenten, M.D.

University of Arizona

Annual Award Amount

$75,000

Project End Date

October 22, 2017

## Innate Control Mechanisms of Adaptive Immunity to Live Infections

The detection of microbes such as bacteria, viruses, and fungi by the immune system induces many molecular signals that collectively control the activation and outcome of immune responses. However, the signals necessary to induce protective immunity against future infections are currently poorly understood. Our preliminary work indicates that the immune response to immunizations with dead microbes depends on specific signals that are dispensable for immune responses to live infections. This observation suggests a fundamental difference between the regulation of immune responses to immunizations and to infections. We are currently analyzing the immune response in mice infected with the model pathogen Listeria monocytogenes in order to compare this response to immunizations with heat-killed Listeria. Specifically, we are investigating the role of two signaling molecules, namely IL-1 and IL-6, in the regulation of the immune response to live and dead Listeria. This work will help us to determine which immune signals distinguish the immune responses to live and dead microbes. The identification of such signals will be critical for understanding of the parameters that define protective immune responses and is essential for the development of new vaccine strategies.


## Brittany Duggar, Ph.D. (Until Nov. 2015)

Banner Health

## Geidy Serrano, Ph.D. (as of Nov. 2015)

Banner Health


ESI

Annual Award Amount

$74,800

Project End Date

October 22, 2017

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

It has been established for nearly 30 years that Apolipoprotein E (APOE) genotype alters the risk of developing Alzheimer's disease (AD). Although great advances have been made in understanding these alterations in the brain, little is known of how this genotype may alter peripheral tissues in AD. This is especially critical since genotypes are present in all cells and understanding if a genotype known to alter the brain can also alter peripheral organs. This study utilizes an innovative approach by examining the liver, which is known to synthesize ApoE and is the major clearing point for one of the main protein aggregates in AD, amyloid-β (Aβ). Our goal is to investigate whether Aβ levels are dependent on APOE genotype in normal controls (NC) and AD and how these proteins in the liver relate to brain. Over the last year we analyzed post-mortem human liver and brain tissue from the Brain and Body Donation Program (BBDP) located at the Banner Sun Health Research Institute in Sun City, Arizona. The BBDP is an autopsy-based, research-devoted brain bank, where consented elderly volunteers living in Maricopa county and metropolitan Phoenix, Arizona can leave a legacy through donating their time during life through clinical evaluations and then their tissues after death. If successful, this we could provide an initial foundation for the discovery of peripheral biomarkers that could help in the understanding, early detection, and diagnosis of AD utilizing the legacy left by Arizonians who donated their tissues to the BBDP.

# Sarah Stabenfeldt, Ph.D.

University of Arizona

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 long-term goal whereby our primary objective is to mask and “redecorate” the neurodegenerative cues in injured neural tissue. The proposed work will employ a molecular biology screening technique to identify molecules that bind to markers that are more abundant in injured neural tissue versus healthy neural tissue. These targeting molecules will then be investigated to mask and "redecorate" the injured tissue with regenerative cues. Ultimately, this approach will contribute significant advances to improved understanding of how the extracellular microenvironment impacts neural regeneration after brain injury.

## PUBLICATIONS & PRESENTATIONS

Song, S, Marsh, W, **Stabenfeldt**, SE*. “Exploiting astrocytic phenotypic alterations to augment the neural injury microenvironment.” Gordon Research Conference – 2015 Biomaterials & Tissue Engineering, Girona, Spain, July 2015. *Award for Outstanding Junior Faculty Poster Presentation.

Arens, D, Witten, A, Song, S, Marsh, W and **Stabenfeldt**, SE. “Targeting the neural injury microenvironment after traumatic brain injury.” Submitted to the World Congress of Biomaterials (May 2016).

# Theresa Thomas, Ph.D.

Arizona State University

Annual Award Amount

$75,000

Project End Date

October 22, 2017

ESI

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

As many as 20-55% of patients with a history of traumatic brain injury (TBI) experience chronic endocrine dysfunction, leading to impaired quality of life, impaired rehabilitation efforts, and lowered life expectancy. Endocrine dysfunction after TBI is thought to result from acceleration-deceleration forces to the brain within the skull, creating enduring hypothalamic and pituitary neuropathology, and subsequent hypothalamic-pituitary endocrine (HPE) dysfunction. These experiments were designed to test the hypothesis that a single diffuse TBI results in chronic dysfunction of corticosterone (CORT), a glucocorticoid released in response to stress, and testosterone. We used a rodent model of diffuse TBI induced by midline fluid percussion (mFP). At 2 months post-injury compared to uninjured control animals, circulating levels of CORT were evaluated at rest, under restraint stress and in response to dexamethasone, a synthetic glucocorticoid commonly used to test HPE axis regulation. Testosterone was evaluated at rest. Further, we assessed changes in injury-induced neuron morphology (Golgi stain), neuropathology (silver stain) and activated astrocytes (GFAP) in the paraventricular nucleus (PVN) of the hypothalamus and in a amygdala, a structure that contributes to the regulation of circulating CORT levels. Resting plasma CORT levels were decreased at 2 months post-injury and there was a blunted CORT increase in response to restraint induced stress. No changes in testosterone were measured. These changes in CORT were observed concomitantly with altered complexity of neuron processes in the PVN over time. In the amygdala, TBI resulted in early and persistent dendritic hypertrophy in the absence of neuropathology, but in the presence of activated astrocytes. Results provide evidence that a single moderate diffuse TBI leads to changes in CORT function, which can contribute to the persistence of symptoms related to endocrine dysfunction.

## PUBLICATIONS & PRESENTATIONS

R.K. Rowe, B.M. Rumney, H.G. May, P.D. Adelson, S.M. Harman, P. Permana, L. Lifshitz, T.C. **Thomas**. Diffuse traumatic brain injury affects chronic corticosterone function in the rat. Endocrine Connections. 2016 Jun 17 [Epub ahead of print] PMID: 27317610.

A.N. Hoffman, P.R. Paode, H.G. May, J.B. Ortiz, S. Kemmou, J. Lifshitz, C.D. Conrad, T.C. **Thomas**. Early and Persistent Dendritic Hypertrophy in the Basolateral Amygdala Following a Single Diffuse Traumatic Brain Injury. J Neurotrauma 2016 Jun 15. [Epub ahead of print] PMID: 27306143.


## Mingwu Wang, MD, Ph.D. (Until April. 2015)

University of Arizona

## Mohammad Shahidulla, Ph.D. (as of April. 2015)

University of Arizona


ESI

Annual Award Amount

$74,999

Project End Date

October 22, 2017

### NHE8 and the Ocular Surface Homeostasis

Arizona typically has the lowest annual average relative humidity (in US) resulting in a desert type climatic conditions. This dry weather results in the widespread dry eye disease which deeply impacts the living quality of people. Dry eye disease (DED) is a disorder of tears (inadequate tear secretion and/or augmented tear evaporation) and ocular surface resulting in ocular discomfort, visual disturbances, and in severity, may lead to loss of vision. The proposed study focuses on understanding triggers of dry eye phenotype detected in the mice deficient of a sodium/hydrogen exchanger, NHE8. The conjunctiva regulates the tear film by maintaining an optimal balance of water and electrolytes to protect the ocular surface. Therefore, understanding such mechanisms might potentially leads to novel therapeutic intervention for DED. Our discovery that NHE8 knockout mice have dry eyes phenotype suggests that NHE8 plays a crucial role in the maintaining ocular surface homeostasis. The aim was to investigate the exact role played by NHE8 in this process.

## PUBLICATIONS & PRESENTATIONS


Bhattacharya D, **Wang** M. The Conjunctiva Plays an Important Role in Modulating Ocular Surface Tear. Open Acc. J of Opt 2016; 1(1): OAJO-MS-ID-000102.

H. Xu, Y. Zhao, J. Li, M. **Wang**, F. Lian, M. Gao, F. Ghishan: Loss of NHE8 Expression Impairs Ocular Surface Function in Mice. American Journal of Physiology – Cell Physiology. 2015;308(1):79-87.

# Christopher Buneo, Ph.D.

Arizona State University

Award Amount

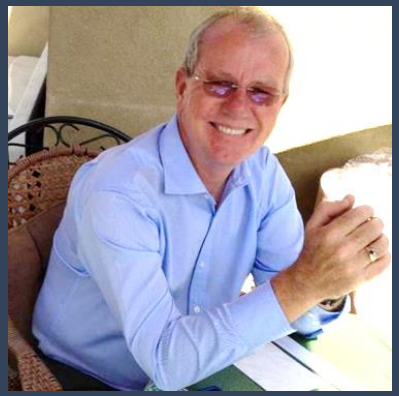
$100,000

Project End Date

April 22, 2016

## Neural Correlates of Cooperative Manipulative Actions

Cooperative or 'joint' actions involve two or more agents (e.g. humans or robots) 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 how they are reflected in the activity of cells in the brain. The work proposed here is aimed at providing preliminary data for a federal grant application focused on characterizing this activity during one of the most fundamental and commonly performed joint actions, object handovers. This will be accomplished by training animals to perform handovers first with humans then with robots and recording and analyzing the resulting brain activity. In addition to expanding our knowledge of joint actions and brain activity, the proposed research has significant potential to impact state and national needs in the consumer, healthcare, military, and industrial settings by providing the fundamental knowledge necessary to create the next generation of 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 Galbraith, Ph.D.

University of Arizona

Award Amount

$100,000

Project End Date

October 22, 2016

CA

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

Dysfunction of organs in disease states, particularly cancer, involve an alteration in state of a minor,and sometimes very minor subset of cells. It therefore is hard to detect early indicators of disease states within the overwhelming background of normal cells. The current screening tests to detect early prostate cancer are not very accurate, and cannot assure men that there is no risk of cancer. The objective of this proposal is to use a novel approach that we have devised to identify potential biochemical markers for early cancer detection. Our aim is to use these for the discovery of new drugs to stop prostate cancer. The approach for this research will use genetically-engineered mice that have tumor-suppressor genes which, when switched off, cause prostate cancer. We have developed a Genetically-Engineered Mouse Model (GEMM) specifically to analyze the initial stages of oncogenesis within single cells. The GEMM comprises a floxed-stop cassette separating the constitutive CAGGS promoter from a histone 2B-EGFP fusion protein (H2B-EGFP). Expression of Cre recombinase within cells carrying this integrated transgene results in the appearance of greenfluorescent nuclei. These nuclei are then individually isolated from tissue homogenates via fluorescence-activated sorting. We have devised RNA-seq methods to characterize the transcriptional activities of the individual sorted nuclei. We describe the characterization of these lines using a combination of microscopic imaging and flow cytometry, and describe strategies for employing these lines in the study of oncogenesis. We propose to collect just the green nuclei from the mouse prostate at different ages. These nuclei, on isolation, are in the process of making messenger RNA which contains the coding information for all the proteins in the cancer-initiated prostate cells. Individual green nuclei will be isolated and the messenger RNA from each single nucleus will be sequenced to identify what prostate genes have become active in the cancer-initiated cells but not in normal cells. This approach will allow us to identify those gene changes that occur in the human prostate long before tumors develop.

## PUBLICATIONS & PRESENTATIONS

Samadder, P., Weng, N., Doetschman, T.C., Heimark, R., and **Galbraith**, D.W. (2016). Flow cytometry and single nucleus sorting for Cre-based analysis of changes in transcriptional states. *Cytometry* 89A:430-442.

**Galbraith**, D.W., Sliwinska, E., and Samadder, P. (2016). Nuclear Cytometry: Analysis of the patterns of DNA synthesis and transcription using flow cytometry, confocal microscopy, and RNA sequencing. Flow Cytometry Protocols, 4th edition (Hawley and Hawley, eds.). *Methods in Molecular Biology*: In Press.

# Kaushal Rege, Ph.D.

Arizona State University

Award Amount

$100,000

Project End Date

October 22, 2016

## Nanoassemblies for Gene Silencing

Cancer is the second leading cause of death in the United States. The estimated number of new cancer cases within the US for 2015 is 1,658,370 with 589,430 deaths projected during the same year. Urinary bladder cancer is the fourth most common type of cancer in men with 74,000 new cases and 16,000 deaths expected for both men and women in 2015. The current work focusses on knockdown of genes that enable survival of bladder cancer cells. Of particular importance are Heat Shock Proteins (HSPs); these are present at low levels under normal conditions. However, these proteins are overexpressed in cancer cells, and are responsible for resistance against chemotherapy and radiation treatment. Hence, HSPs are potential diagnostic, prognostic, as well as therapeutic targets for cancer therapy. Thus, inhibiting HSPs using small molecules and / or knocking down their expression in cells using short interfering RNA (siRNA) - either alone or in combination with chemo / radiation therapy - are attractive potential treatment strategies for cancer diseases. In our present research, HSP90 knockdown was achieved by delivering small interfering RNA (siRNA) to UMUC3 bladder cancer cells using novel lipopolymer nanoparticles. Briefly, cells were plated in 6-well plates (100,000 cells/well) overnight and treated with Hsp90 or the scrambled non-targeting siRNA (25 nM) the following day. Cells were then harvested 96 h following treatment and HSP90 protein levels were analyzed using Western blots. Actin, a cytoskeletal protein, was used as the loading control. Lipopolymers that resulted in the highest levels of HSP90 knockdown in cancer cells were identified; HSP90 knockdown levels as high as 64% were obtained. These results suggest that lipopolymer nanoparticles can be successfully used for knocking down Hsp90 levels and possibly other HSPs. This can help sensitize cancer cells to other treatments including anticancer drugs and nanoparticle-induced heat treatment. Further validation of these studies is currently in progress, and other combination strategies (e.g. including nanoparticle mediated heat treatment), will be explored together with Hsp silencing for effective destruction of bladder cancer.

# Donato Romagnolo, Ph.D.

University of Arizona

Award Amount

$99,740

Project End Date

October 22, 2015

CA

## Early-life Exposure and Risk of Breast Cancer

Sporadic breast cancers, which represent the vast majority (~90%) of breast tumor cases, do not have mutations in the BRCA-1 gene, but have absent or markedly reduced levels of BRCA-1 protein. The main objective of this project is to explore the mechanisms that contribute to silencing of BRCA-1. Aims: This project deals with mechanisms that go under the definition of epigenetics, i.e. changes in gene expression that do not involve modifications of the DNA sequence. Because epigenetic changes are reversible, they represent a potential target in breast cancer prevention and treatment.

Information from animal models and population studies indicate that mammary tumor promotion in adult life may be influenced by prior exposure to epigenetic modifiers. The central hypothesis of this project is that early-life exposure to agents that bind a nuclear receptor termed aromatic hydrocarbon receptor (AhR) silences the BRCA-1 gene, and that this event predisposes to the epigenetic development of triple-negative breast cancers in adult life. The rationale for this project stems from evidence women are exposed to many agents that activate the AhR and are known carcinogens. These include dietary compounds, metabolites of dietary fatty acids, environmental contaminants, and photoproducts generated in the skin from ultraviolet radiation, (i.e. sun exposure). Therefore, this project integrates etiological and lifestyle factors with broad implications for breast cancer therapy.

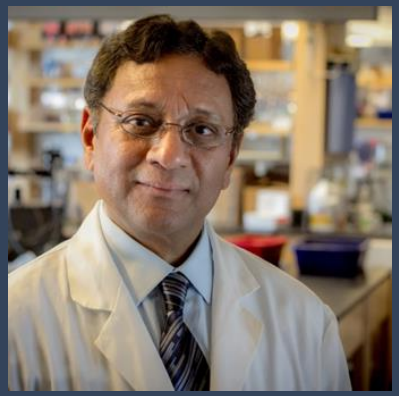
## PUBLICATIONS & PRESENTATIONS

**Romagnolo** DF, Selmin OI. Development of Endocrine Tumors in Women and Dietary Prevention. Preventive Nutrition: The Comprehensive Guide for Health Professionals, 5th Edition. Adrianne Bendich, Ph.D., FASN, FACN and Richard J. Deckelbaum, M.D., FRCP(C) (In Press, 2015).

**Romagnolo** DF, Andreas J. Papoutsis and Ornella I. Selmin. Increased BRCA-1 promoter hypermethylation as biomarker of mammary tumorigenesis associated with increased expression and activation of AhR. BMC Cancer.

Selmin OI, Papoutsis JA, and **Romagnolo** DF. BRCA-1 promoter CpG hypermethylation as biomarker of mammary tumorigenesis associated with increased expression and activation of AhR. BMC Cancer, 2015 (submitted August 12, 2015, under review).

**Romagnolo** DF, Selmin OI. Repression of BRCA-1 expression in AhR-activated breast cancer cells and reversal with dietary antagonists of the AhR. In preparation (Breast Cancer Research).



# 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

As we age, our immune system that controls infections and cancers also deteriorates. In addition, HIV infection may influence the aging process of the immune system in HIV-infected individuals and those infected individuals who have aged with HIV infection while being treated with anti-HIV drugs. Furthermore, the elderly population (a significant number in Arizona) also experiences an accelerated aging of the immune system. These age-related changes may result in altered functions of the immune system and reduced response against other infections. We have been investigating the role of HIV in older HIV-infected individuals, especially the specific properties of HIV that may alter the functions of the immune system in HIV aging patients and compare with aging uninfected individuals. We have created a cohort of HIV-infected who are receiving medical care at the University of Arizona and uninfected individuals (all aged >50 years). These patients are clinically evaluated and blood samples are collected every 4 months followed by isolation peripheral blood mononuclear cells (PBMC). We amplified HIV envelope gene by polymerase chain reaction (PCR) from patients PBMC DNA followed by cloning and characterization of correct size recombinants. The correct size recombinants were sequenced to determine the specific features of HIV that persist in these older infected individuals. We found that HIV envelope gene sequences were very homogenous, suggesting that anti-HIV drugs are suppressing viral replication. In addition, we have optimized two panels consisting of 12 antibodies for markers of CD4 and CD8 T cells that are associated with the aging of the T cells. These two panels are being used to determine the function of T cells in HIV-infected older individuals and uninfected older individuals. Data analysis continues on these T cell panels. This study may provide new and novel information that may help researchers to develop new strategies for prevention and treatment of HIV infection in older infected patients, including improving the aging of the immune system in older population to prevent new infections.


# Yin Chen, Ph.D. & Yitshak Zohar 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 construct a miniature lung on a microchip-like device (microfluidic ex vivo lung, or MEVL), which is able to respond to the external stimuli similarly to the actual lung. In this second grant period, we have made an improved version of MEVL. In this MEVL, airway epithelial cells are able to routinely grow and differentiate to different cell types such as mucous, ciliated and basal cells. Mucus secretion and cilia beating have been observed indicating the epithelium in MEVL is live and functional. We have also introduced air flow onto epithelial surface mimicking "breathing." Now, we have MEVL that can "breathe." In order to obtain output from MEVL, we have reinvented several macromolecular methods for this microscale operation. To date, we have successfully introduced exogenous genes into these cells, and detected protein expression by fluorescence microscope. These applications are first-of-its-kind and specifically developed for this microdevice. In the meantime, we are starting the experiments testing various toxic compounds (e.g. ambient particulates, metals, pathogens) using MEVL. For the next step, we are planning to formalize the design, manufacture and operating protocols so that the single-chip MEVL can be used for routine testing. Then, we will use a range of model toxicants and pathogens to optimize the system and also develop specific applications for toxicological or medical use.

# 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

These studies represent a collaboration between scientists at the University of Arizona College of Medicine- Phoenix and at Brigham and Women's Hospital, Harvard Medical School. Our studies investigate potential common developmental origins of adult diseases such as major depressive disorder (MDD) and cardiometabolic disease using both a human cohort and animal models. Of importance, these studies will identify sex-specific developmental changes in gene expression that might underlie the sex-selectivity of adult risk for these diseases. The Boston team has been examining a cohort of patients that participated in the National Collaborative Perinatal Project (NCPP) which followed individuals in utero (born from 1959-1966) through adulthood (ages 49-57 yrs of age). Current analyses are underway that evaluate relationships between gene biomarkers associated with prenatal stress and the risk for MDD and cardiometabolic diseases in adulthood. The Phoenix team is using preclinical approaches to identify new risk biomarkers in animal models of prenatal stress and glucocorticoid exposure. Recent studies have identified several cytokines/chemokines that may correspond to alterations in adult function and changes in gene expression during development that may give rise to physiological changes in adulthood.

## PUBLICATIONS & PRESENTATIONS

Goldstein JM, Holsen L, Huang G, Hammond BD, James-Todd, T, Hale TM, **Handa** RJ. Prenatal stress-immune programming of sex differences in comorbidity of depression and obesity/metabolic syndrome. Dialogues in Clin Neurosci, Special edition Sex Differences 71 (vol.18 no.4) 2016, in press.

# Karl Kern, M.D.

University of Arizona

Annual Award Amount

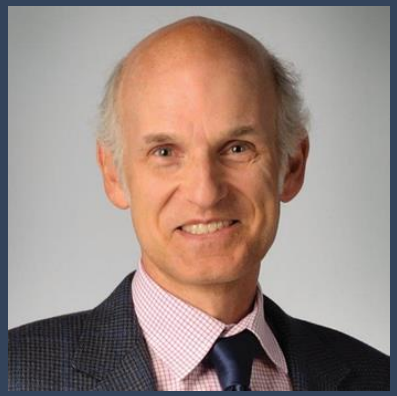
$249,383

Project End Date

October 22, 2017

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

This is a randomized clinical trial (RCT) to evaluate the value of early coronary angiography after cardiac arrest in patients without ST segment elevation on their ECG. This pilot clinical trial will evaluate this question. The potential impact is large since approximately three-fourths of all resuscitated cardiac arrest patients DO NOT have ST segment elevation on their post arrest ECG. If such a strategy benefits this subgroup of patients as it does those patients with ST segment elevation, many additional lives will be benefited and long-term outcomes improved. Due to the emergent nature of cardiac arrest and the importance of rapid and timely treatment of this condition, this research must be performed under the strict Federal regulations for "Exception for Informed Consent." To date we have screened 82 successfully resuscitated cardiac arrest patients, identifying 20 who have met the inclusion/exclusion criteria and have been enrolled.



# Diego Martin, Ph.D.

University of Arizona

Annual Award Amount

$249,963

Project End Date

October 22, 2017

## MRI of Non-Alcoholic Steatohepatitis (NADH) Biomarkers

The goal of the research project that is supported by the ABRC is to improve diagnosis, therapy and outcomes related to Non-Alcoholic Fatty Liver Disease (NAFLD) and Steatohepatitis (NASH). The main objective of the project is to developing new magnetic resonance imaging (MRI) biomarkers that can be used to diagnose and follow progression of these liver conditions. NAFLD/NASH is associated with diabetes and obesity and affects ~2 million Arizonans; Native and Mexican-Americans have higher risk. A subset of NAFLD patients will develop NASH with hepatic fibrosis and a risk to develop liver cancer. Currently, we rely on biopsies to diagnose NAFLD/NASH which is an invasive procedure and limited to a handful of subjects. As a consequence many patients will not be diagnosed early on and present symptoms associated with advanced liver disease including cirrhosis liver cancer. The proposed non-invasive imaging biomarkers will allow diagnosing NAFL/NASH at earlier stages and facilitate development of therapy. The first step of the project is to use liver samples obtained at autopsy to develop a diagnostic system based on MRI to characterize NAFLD and NASH. The next step is to test the diagnostic system in a set of patients with biopsy-proven fatty liver disease. During the first year of the grant we have worked in developing the MRI-based diagnostic system and started initial testing in humans.

## PUBLICATIONS & PRESENTATIONS

Brand JF, Furenlid LR, Altbach MI, Galons JP, Bhattacharyya A, Sharma P, Bhattacharyya T, Bilgin A, **Martin** DR, "Task-based optimization of flip angle for fibrosis detection in T1-weighted MRI of liver" *J. Med. Imag.* 3(3), 035502 (2016).

Li Z, Berman BP, Galons JP, Bilgin A, Altbach MI, **Martin** DR, Rapid High-resolution T1 mapping using highly accelerated radial steady-state free-precession acquisition, Proceedings of Annual Meeting of the ISMRM, 24: 4196, 2016.

Brand JF, Furenlid LR, Altbach MI, Galons JP, Bhattacharyya T, Bhattacharyya A, Bilgin A, Li Z, **Martin** DR, Autocorrelation Analysis of Hepatic Fibrosis on MRI, Proceedings of the International Society for Magnetic Resonance in Medicine, 23, 4136, 2015.

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# Diego Martin, Ph.D.

University of Arizona

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## PUBLICATIONS & PRESENTATIONS


Jonathan Brand, “Staging Liver Fibrosis with Statistical Observers,” PhD Dissertation in Optical Sciences, University of Arizona, April 2016.

Brand JF, Furenlid LR, Altbach MI, Galons JP, Bhattacharyya A, Sharma P, Bhattacharyya T, Bilgin A, **Martin** DR, "Task-based optimization of flip angle for texture analysis in MRI" Proc. of SPIE Vol. 9787 97870B-1, presentation, SPIE Medical Imaging Conference, Feb 2016

# 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

Worldwide the population of humans is rapidly growing far beyond six billion and the global incidents of cancer is rapidly increasing. That acceleration is increased owing to steadily aging populations and the globalization of destructive life styles. Currently there are some ten million new cancer patients with six million deaths per year. By the year 2020 with a population of eight billion there will be twenty million new cancer patients and twelve million deaths per year. At that time 70% of these deaths will be in developing countries. Now the rate is 50%. In the coming year 600,000 people in the United States will die from devastating attacks by one or more types of human cancer. Although a relatively small number of anti-cancer drugs are now available that have greatly improved cancer treatment and provided various levels of curative treatments for some 20-25 types of human cancer 12 of the major types of human cancer are usually refractory to current anti-cancer drugs and urgently require discovery and development of curative anti-cancer drug treatments. The continuation of these tragic death rates of the more than 200 types of human cancer makes it abundantly clear that a great acceleration in the discovery and development of new anti-cancer drugs is vitally important and urgently needed.

The goal of our vitally important research continues to be the discovery and development of most promising and new anti-cancer drugs from leads obtained from marine organisms, microorganisms and plants with highly effective anti-cancer components that offer the potential for ultimate clinical activity against human cancer. By the ABRC financial support of this long term and highly productive new anti cancer drug discovery research it will certainly add to our 12 such drugs we discovered now in human cancer clinical trials and 2 that have already received worldwide approval for human cancer treatment in the past two years. A very exciting illustration using one of the worldwide approved drugs now follows.

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## PUBLICATIONS & PRESENTATIONS

George R. **Pettit**, Qinghua Ye, Delbert L. Herald, John C. Knight, Fiona Hogan, Noeleen Melody, Venugopal J.R.V. Mukku, Dennis L. Doubek, and Jean-Charles Chapuis. "Isolation and Structure of Cancer Cell Growth Inhibitory Tetracyclic Triterpenes from the Zimbabwean Monadenium lugardae" Journal of Natural Products; 2016.

# George Pettit, Ph.D.

Arizona State University

## ... CONTINUED

With very significant and critically important financial support from various periods of ABRC assistance in the past we discovered the exceptionally powerful anti-cancer drug Dolastatin 10 from the Indian Ocean Sea Hare Dolabel/a auriculaira and that opened a new frontier needed for improving human cancer treatments. Subsequently we structurally modified Dolastatin 10 to provide Auristatin E. Next the anti-cancer equivalent Desmethyl Auristatin E was linked to a CD30 monoclonal antibody provided the very successful anticancer drug ADCETRIS now approved for use in 65 countries. Recently I learned from an officer of the ASU licensee that in the last two years worldwide 26,000 patients that would have died from Hodgkin's Lymphoma with stage 4 (terminal) 40% (10,400) have received complete remissions. Furthermore even a higher percentage with Large Cell Lymphoma have also received complete remission. Indeed ADCETRIS became the first really successful anti-body drug conjugate and has led to current excitement in that new area. Presently our ABRC support is allowing us to advance several other discoveries of anti-cancer drugs with remarkable potency and candidates for attachment to appropriate monoclonal antibodies used for transport to the cancer. In summary such exciting advances in anti cancer drug discoveries were and will continue to be made possible by our ABRC financial assistance.

# 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

The estimated number of new cases of breast cancer in the United States is over 200,000, which leads to death of approximately 40,000 women. In the state of Arizona, two deaths occur due to breast cancer and more than 4,600 cases are diagnosed every year (American Cancer Society). Triple-negative breast cancer (TNBC) is diagnosed in 15-30% of all breast cancer cases, and represents an aggressive form of the disease. The lack of estrogen, progesterone, and HER2 receptors in this disease type makes discovery of effective targeted therapies further challenging. We have shown that mitoxantrone, a DNA damaging drug, can sensitize triple-negative breast cancer cells to TRAIL, which is a protein that can selectively kill cancer cells. In this one-year period, we formulated nanoparticles (liposomes; 110-160 nm in diameter) for encapsulation and delivery of mitoxantrone to cancer cells. Five different liposomes, consisting of lipid-containing polymers (lipopolymers) synthesized in our laboratory, were formulated and characterized for their size, surface charge, and stability. The efficacy of mitoxantrone-encaspulated liposomes for ablation of TNBC (and other) cancer cells was evaluated both as a single-agent treatment and in combination with TRAIL. Treatment with liposomal mitoxantrone and TRAIL resulted in synergistic death of cancer cells, indicating the promise of this approach. Cell-based studies with liposomal mitoxantrone together with other chemotherapeutic drugs indicated high efficacy albeit in an additive manner. We have also generated lipopolymers conjugated with folic acid in order to facilitate the targeting of TNBC cells which overexpress the folate receptor. We are currently formulating these folic acid conjugated lipids into liposomes to enable targeted drug delivery. Finally, we are initiating studies for evaluating the pre-clinical efficacy of these approaches using mouse models of TNBC disease.

# Marwan Sabbagh, M.D.

Banner Health

Annual Award Amount

$248,629

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

Changes in the brain can happen long before Alzheimer's disease is noticed by a patient or by a patient's family. People with Down syndrome are much more likely to develop Alzheimer's disease. This makes people with Down syndrome a good population for the investigators to work with during this study. This study aims to track the development of Alzheimer's disease by using multiple methods to examine changes in the brain before and after a patient develops Alzheimer's disease. Methods include (a) cognitive status tests (which determine mental ability) and (b) brain scans (which show brain images). The imaging scans include Magnetic Resonance Imaging (MRIs), FDG-PET, Florbetapir PET, and tau-PET scans, all of which provide different kinds of pictures of the brain. Tests and brain scans will be performed at different times over several years, which will allow the investigators to begin a long-term analysis of the study participants. To date, the study has recruited 15 participants. Of the 15 participants:

- 6 received all baseline assessments (MRI, PET FDG, PET FBP), excluding tau.
  - 3 of the original participants are in the process of completing their year 2 assessments, including tau.
- 4 received all baselines including tau.
- 3 are in the process of completing their baseline assessments (MRI, PET FDG, PET FBP, PET TAU).
- 1 received baseline PET FBP but dropped out because of medical issues (since deceased).
- 1 was recruited but dropped because of medical issues (since deceased).

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# Marwan Sabbagh, M.D.

Banner Health

## ... CONTINUED

The study has successfully transitioned from Banner Health to Barrow Neurological Institute and we are once again enrolling new participants as well as continuing the collection of additional tests and brain scans over time for those participants already enrolled. Preliminary analysis of the images collected has led two published papers. Additionally, Dr. Sabbagh is working to involve the participants of this study in two additional research grants. The first, Dr. Sabbagh, in collaboration with Dr. Matt Huentelman of the Translation Genomics Research Institute (TGen), has been awarded an Alzheimer's Association Investigator Initiated Research Grant to collect a small amount of blood monthly from the patients participating in this study in the hopes of developing a risk assessment tool which will eventually assist in identifying those patients that may benefit from Alzheimer's prevention approaches. For the second grant, Dr. Sabbagh will be leading the Barrow Neurological Institute as a site on the Biomarkers of Alzheimer's Disease in Down Syndrome initiative. It is hoped this study, combined with data gained on the same population through the additional grants, will provide the foundation to guide future Alzheimer's disease treatment and prevention trials.

# ARIZONA ALZHEIMER'S CONSORTIUM

**Primary goal: to find effective treatments to stop and end Alzheimer's Disease as quickly as possible**

- $1 million in support from ABRC, $125,000 from ADHS General Fund
- 18th Annual Conference, May 19, 2016
  - 101 supported projects presented
- 150 researchers, 7 principal organizations, several affiliated organizations
- Conducted annual site visits and reviewed progress and productivity
- Generated over 4,000 publications, 1,000 research grants and contracts, and $1 billion in new investments (1/2 in the last year) since 1998

The Arizona Alzheimer's Consortium is a statewide collaboration that was established in 1998 whose intention is "to make a major difference in the scientific fight against AD, to engage Arizona's underserved and understudied Native American and Latino communities, and to help address the unmet needs of patients and family caregivers. ...major themes are early detection and prevention..." Collaborating institutions excel in brain imaging, computer science, genomics, the basic and cognitive neurosciences, and clinical and neuropathology research.

**PRINCIPAL INSTITUTIONS**

- Arizona State University
- Banner Alzheimer's Institute
- Banner Sun Health Research Institute
- Barrow Neurological Institute
- Mayo Clinic Arizona
- Translational Genomics Research Institute
- University of Arizona

**AFFILIATED INSTITUTIONS**

- Banner Good Samaritan Medical Center
- Southern Arizona Veterans Administration Health Care System
- University Physician's Hospital at Kino



To Learn More, visit: http://www.azdhs.gov/biomedical/index.php#about-collaboration

# TGen

- $2 million in support from ABRC
- According to an independent auditing firm,
  - TGen's total annual economic impact was $174 million
  - TGen created more than 1,400 jobs
  - TGen's direct economic impact rate of return was $46.50 for every $1 invested by the State
- Helios Scholars at Tgen celebrated 10 years with 45 students graduating in July 2015
- MRSA detection technology developed by TGen-NAU is granted first patent
- Deputy Director presented "A Visit to the Brain" at TEDx Talk in Arizona
- TGen & Mayo Clinic scientists issue a report in the journal *Cell* on advances in basal cell carcinoma treatment
- Received the 2015 Regents' Award for Outstanding Service to Higher Education from Arizona Board of Regents

"Translational Genomics Research Institute (TGen) is a Phoenix, Arizona-based non-profit organization dedicated to conducting groundbreaking research with life changing results. TGen is focused on helping patients with neurological disorders, cancer, and diabetes, through cutting edge translational research (the process of rapidly moving research towards patient benefit). TGen physicians and scientists work to unravel the genetic components of both common and rare complex diseases in adults and children. Working with collaborators in the scientific and medical communities literally worldwide, TGen makes a substantial contribution to help our patients through efficiency and effectiveness of the translational process. For more information, visit: www.tgen.org."

ARIZONA DEPARTMENT
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH COMMISSION

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