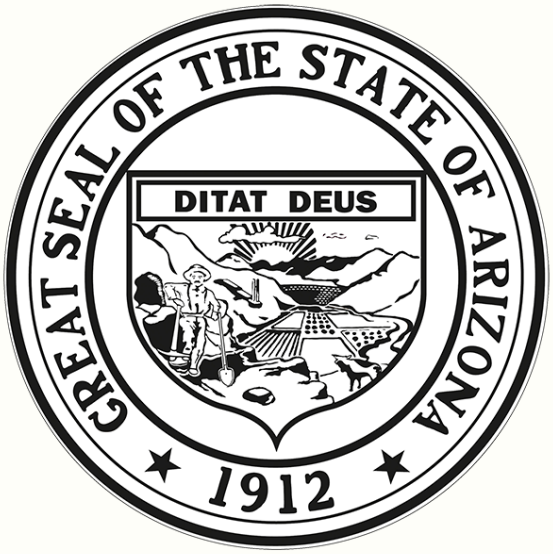
# Annual Report

## 2016 - 2017

## Arizona Biomedical Research Centre

ARIZONA DEPARTMENT
OF HEALTH SERVICES




Douglas A. Ducey, Governor
*State of Arizona*

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

## Arizona Biomedical Research Centre

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## Mission

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

## Vision

Accelerating Biomedical research and innovation in Arizona

# Table of Contents

# Executive Summary

The Arizona Biomedical Research Centre's (ABRC) mission is "Identifying and supporting innovative biomedical research to improve the health of all Arizonans." In FY 2017, the four core programs (Arizona Public Cord Blood Program, Research Grants, Arizona Biospecimen Locator, and Research Education) accomplished great achievements in working to meet the mission of the ABRC.

Community support is an integral part of our successes. Together, we've achieved many program milestones. None of these achievements would be possible without the unwavering support of our valued community partners, agency leadership, the Governor's office, and legislators.

A few highlights from ABRC (FY 2017) are listed below.

**43rd** cord blood unit from the **Arizona Public Cord Blood Program** was used in a life-saving transplant for a patient with ALL (Acute Lymphoblastic Leukemia, which is a blood cancer).


**877** biospecimens collected by the **Arizona Biospecimen Locator Program** were used in research

**18** workshops, trainings, and symposiums were supported by ABRC's **Research Education Program**

**55** research projects currently funded by ABRC's **Research Grants Program** (including 30 new grants!)

# COMMISSION

The ABRC was made up of nine commissioners: three public members, three medical community members, and three scientific community members. Commissioners were appointed by the Governor and confirmed by the senate to three year terms. Appointments to fill vacant positions in the middle of a term needed to be reappointed at the end of the partial term. Commissioners provided expert advise to the department, helped review grant applications, and recommend applications to fund.

## COMMISSION MEETINGS

Commission meetings were held quarterly in compliance with **ARS §36-272(E).** Below is a list of the meetings for FY 2017 and the topics that were covered. To review meeting minutes, visit www.azdhs.gov/biomedical/#commission-meetings

| | |
|---|---|
| **April 28, 2017** | Presentation from the AZ Biospecimen Locator Program partners; program updates |
| **February 3, 2017** | Signed evaluation committee signature pages; program updates; presentation from TGen |
| **November 4, 2016** | Executive Session: discussion of grant applications; vote to fund grant applications; next grant application cycle |
| **August 1, 2016** | Presentation from the ABRC Executive Director to welcome and onboard new commissioners; program updates; presentation from AZ Public Cord Blood Partners; overview of AZ open meeting law; selection of chair and co-chair |

# FY 2017 Commissioners

## Public Members

Brandy Wells, M.S.

Commissioner Brandy Wells is the Director of Public Affairs and Education at the non-profit Translational Genomics Research Institute (TGen) in Phoenix, Arizona. In this role, she interacts with the science, business and lay communities to interpret the scientific research of the Institute, increase public knowledge of translational medicine and its relevance to healthcare delivery and economic competitiveness. She also directs TGen's science education initiatives including training programs and scientific conferences.

A native Floridian, Commissioner Wells moved to Phoenix from Washington, D.C. in 2009. She earned a BS in Biology and Secondary Education from American University in Washington, DC and MS in Biotechnology from Johns Hopkins University in Baltimore, MD. She previously taught secondary-level science at public schools in Washington, D.C. and Phoenix.

Commissioner Wells is a fellow of the Flinn-Brown Civic Leadership Academy in the Arizona Center for Civic Leadership, sits on the Board of Directors as Treasurer for the Women's Metropolitan Arts Council and volunteers with Hospice of the Valley at the St. Joseph's Hospital and Medical Center Palliative Care Unit.

Cosmo Magliozzi

Commissioner Cosmo Magliozzi is the Vice President for the largest family controlled bank in the US. He works from the Chandler, Arizona office. His role is to provide banking services to the local medical community. His job is to recognize cash flow improvements, streamline billing and provide a strategic plan by helping doctors expand their practices. He enjoys learning and researching the medical field, primarily in the Biomedical Innovation sector. After his older son was diagnosed with autism, he became more involved in medical research and the care provided to his son.

Commissioner Magliozzi found his passion in helping the community find resources needed to live better and productive lives. He does this by sponsoring the Science Expo each year for the Mesa public schools. He helps honor over 300 students by presenting each with a Certificate of Achievement for their projects. He helped cultivate the program with 160 students 5 years ago. Furthermore, he is also in the process of publishing his first book.

Commissioner Magliozzi migrated to the US from Italy and was the first member of his family to earn an associate degree from El Camino College in Torrance, CA and a bachelor's degree in business finance with a minor in manufacturing from DeVry University in Long Beach, CA. He is fluent in both English and Italian.

John Ragan

Commissioner John Ragan is Chief Operating Officer for the Arizona Chamber, where he provides invaluable and extensive experience in both the business and political arenas, and charts the course to continue to grow the Arizona Chamber's influence and membership development. John spent a number of years on Capitol Hill, working on the staffs of U.S. Senator Jon Kyl and U.S. Congressman Matt Salmon. Under Senator Kyl, he served as Legislative Assistant for three years. In this capacity, John managed budget, technology, transportation, and healthcare policy projects for the senator. John was then appointed as U.S. Congressman Matt Salmon's Co-Chief of Staff.

John was also Vice President of Business Development, Government Affairs, and Communications for TPI Composites, one of the world's largest manufacturers of composite wind blades and military vehicle applications. Additionally, he is a founding partner of both The Symington Group and Health Care Futures, LLC (HCF). He is currently HCF's Managing Director of Liability Exchange and Denial Management and acted as managing partner of The Symington Group's private equity interests. John has also served on a number of boards including St. Thomas The Apostle School and Certive Solutions.

# FY 2017 Commissioners

## Medical Community

John Cover

Commissioner John is the Chief Executive Officer at Transplant For Life and Chief Operating Officer at Research For Life. Currently John oversees all aspects of tissue donation for transplant and medical education as well as overseeing the biorepository for disease research. John has almost 20 years in blood and tissue banking in both quality assurance and technical operations. Previously, John was the Director of Quality Assurance and Regulatory Affairs at TissueNet and the Executive Director and Chairman for the American Medical Education and Research Association. John's prior roles were as the principle quality management consultant at Verus Quality Consulting, LLC., Director of Quality Assurance/Regulatory Affairs at Science Care, leadership positions in technical operations at both the American Red Cross national testing laboratory in San Diego, CA and the American Red Cross Blood Component Manufacturing operations in Boise, ID. John began his career in quality management and technical operations at Blood Systems Laboratories, where he was assigned to two of the nation's largest CLIA blood screening & high complexity testing laboratories.

John has a BS in Biology/Chemistry from Northern Arizona University and secondary education from California State University – Dominguez Hills in Quality Assurance. He is a Certified Tissue Banking Specialist by the American Association of Tissue Banks and was a Certified Quality Auditor by the American Society for Quality for many years. He is a past member of the American Association of Tissue Banks Quality Assurance Task Force and Education Committee as well as the National Quality Control Standing Committee at the American Red Cross. John has presented for the American Association of Tissue Banks, the American Medical Education and Research Association, the American Association of Blood Banks, California Blood Bank Society, University of Texas Southwestern and the American College of Sports Medicine.

Mitchel Shub, MD

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 has previously served as Co-director of the Pediatric Residency Program and as Division Chief of Gastroenterology at PCH. 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 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 was part of a team that identified the gene mutation for a rare digestive disorder, microvillus 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."

Hugo Vargas, MD

Commissioner Hugo E. Vargas is a Transplantation Hepatologist at the Mayo Clinic Arizona. He is a graduate of UC Davis and the Hahnemann Medical College (now Drexel University College of Medicine). He completed a residency in Internal Medicine at the University of Utah Medical Center and a fellowship in Gastroenterology and Hepatology at the University of Pittsburgh Medical Center. He served in the faculty at the University of Pittsburgh as the director of Hepatology and Medical Director of Liver Transplantation. In 2000 he joined the staff of the Mayo Clinic in Arizona as part of the multidisciplinary team in adult liver transplantation. He has served as chair of the Division of Hepatology and currently is the Vice Chair of the Division of Gastroenterology and Hepatology.

Commissioner Vargas' research interests include Hepatitis C viral infection, particularly in the setting of cirrhosis and liver transplantation. Currently he is the Director of the Office of Clinical Research in Mayo Clinic Arizona and the site representative for the Mayo Clinic CTSA. He has kept a leadership profile in national and international societies including the American Association for the Study of Liver Diseases, American Gastroenterological Association, American College of Gastroenterology and the American College of Physicians.

# FY 2017 Commissioners

## Scientific Community

Howard Eng, Ph.D.

Commissioner Howard J. Eng has more than 40 years of working experience in health care and has conducted health -related research for more than 30 years. He has been a researcher at University of Florida College of Pharmacy, University of Arizona College of Medicine, and University of Arizona Mel and Enid Zuckerman College of Public Health. Dr. Eng was the Director of the Southwest Border Rural Health Research Center at the Center for Rural Health, Mel and Enid Zuckerman College of Public Health, University of Arizona.

Commissioner Eng earned his Bachelor of Science degrees in Zoology and Pharmacy, and Master of Pharmaceutical Sciences degree from the University of Arizona and his Doctor of Public Health (Community Health) degree from the University of Texas. His research expertise and training include: pharmacy, public health, health services/health policy research, health economics, epidemiology, and rural/border health research. He was selected the White House "Champions of Changed," and honored by the White House and U.S. Department of Health and Human Services in April 2014

Mary Kay Turner

Commissioner Mary Kay Turner is currently the head of Public Affairs for Mitsubishi Tanabe Pharma America leading the commercialization of a compound for ALS (Amyotrophic Lateral Sclerosis). Prior to this role, Mary Kay spent 28 years with Bristol Myers Squibb Company where she held various positions of increasing responsibility. Her most recent position at BMS was the head of State Government Affairs. She is a government affairs executive with political action and legislative/advocacy /regulatory expertise.

Mary Kay is recognized as a leader within the Biopharma industry for developing advocacy and public affairs strategies and national initiatives. She has built strategic alliances and partnerships with third party allies who share common agendas of maintaining and improving access to treatment and care for patients living with chronic diseases and healthcare disparities.

Mary Kay has a Bachelor of Arts degree in Political Science and History from the University of Oregon.

| | |
|---|---|
| 3rd Member | Vacant |

# 2017 Updates

## HB 2205

In 2011, the Arizona Biomedical Research Commission (ABRC) transitioned from an independent commission to an advisory commission when it moved under the Arizona Department of Health Services. In the fifty-third legislative session (2017), the Arizona State Legislature passed House Bill 2205. The bill was signed into law by Governor Doug Ducey on April 4, 2017 and became effective in August 2017. HB 2205 further transitioned ABRC from a commission to a program without commissioners within the Arizona Department of Health Services in an effort to streamline the functions of the ABRC. The ABRC mission, vision, goals, and funding remain the same.

## Name Change

After HB 2205 came into effect, the Arizona Biomedical Research Commission changed its name to the **Arizona Biomedical Research Centre**.

# Program Staff

| | |
|---|---|
| **Executive Director** | Victor Waddell, Ph.D. |
| **Program Director** | Jennifer Botsford, MSPH |
| **Program Coordinator** | Theresa Napoleon, BS |
| **Science Advisor** | Hsini Lin, Sc.D. |

# 4 Core programs

Arizona Public Cord Blood Program

Arizona Biospecimen Locator

Research Education

Research Grants

# We also support

Arizona Alzheimer's Consortium

Translational Genomics Research Institute

**PANS / PANDAS**

(Pediatric Acute-onset Neuropsychiatric Syndrome ) / (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections)

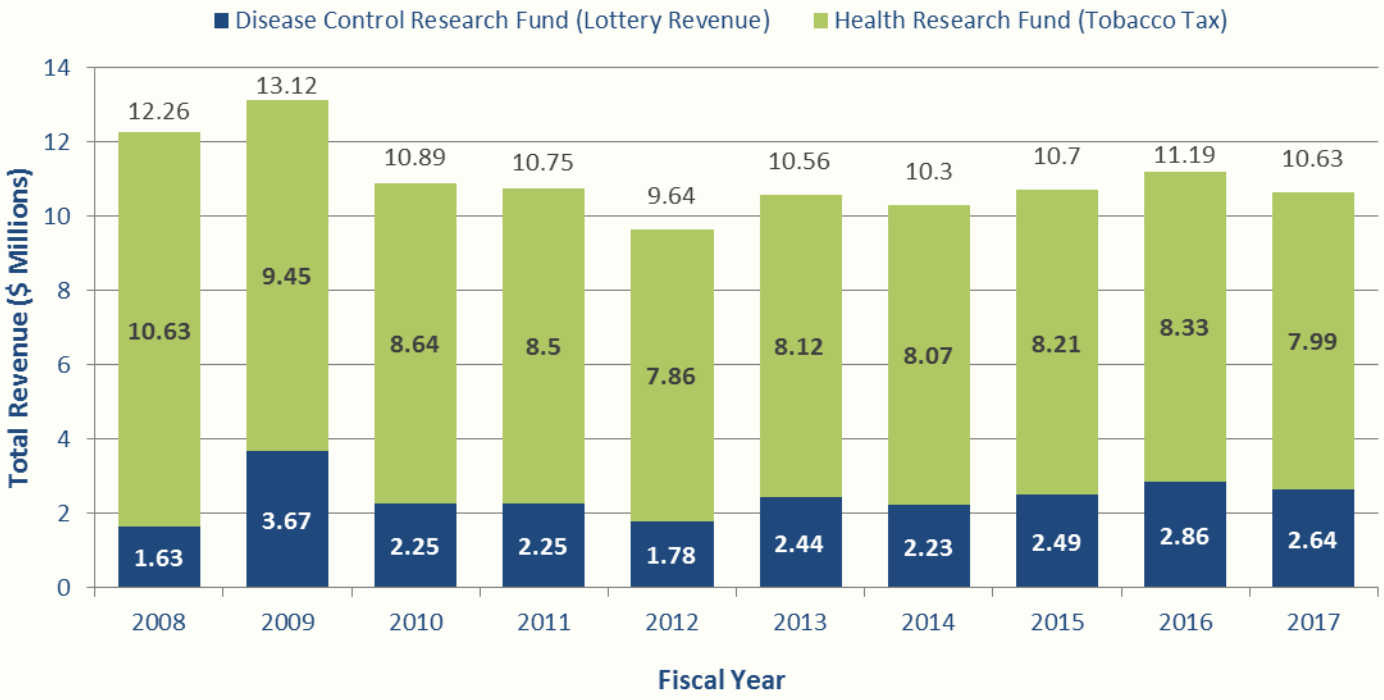
# Financial Summary

## Revenue

ABRC'S revenue in FY 2017 was $ 10,630, 677

→ Disease Control Research Fund ARS §36-274 (Lottery Revenue) $ 2,640,234

→ Health Research Fund ARS §36-275 (Tobacco Tax) $ 7,990,443



# Financial Summary (Cont.)

## Expenditures

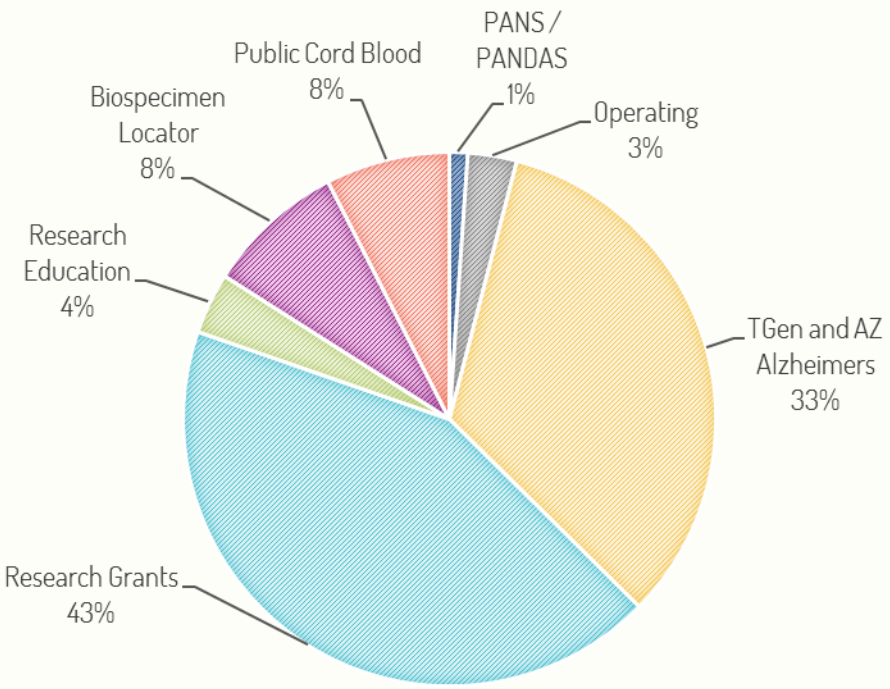
ABRC's expenditures in FY 2017 were $ 11,996,097

→ Disease Control Research Fund ARS §36-274 $ 2,227,105

→ Health Research Fund ARS §36-275 $ 9,768,992

| Category | Expenditure |
|---|---|
| Research Grants | $ 5,148,669 |
| Research Education | $ 443,004 |
| Biospecimen Locator | $ 1,013,843 |
| AZ Public Cord Blood Program | $ 903,047 |
| Translational Genomics Research Institute (TGen) | $ 2,000,000 |
| AZ Alzheimer's Consortium | $ 2,000,000 |
| PANS/PANDAS* | $ 132,000 |
| Operating | $ 355,534 |
| **Total** | **$ 11,996,097** |

* PANS / PANDAS: Pediatric Acute-onset Neuropsychiatric Syndrome / Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections



# Arizona Public Cord Blood Program

## Overview

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. Donating umbilical cord blood is free, painless and neither mother nor child is harmed in the collection.

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. Cord blood can be used to treat or cure over 80 diseases, such as blood cancers (e.g. leukemia) and bone marrow disorders (e.g. aplastic anemia.

## FY 17 Highlights

**1844** cord blood units were collected at 4 AZ hospitals.

**723** met the criteria to send to the cord blood bank.

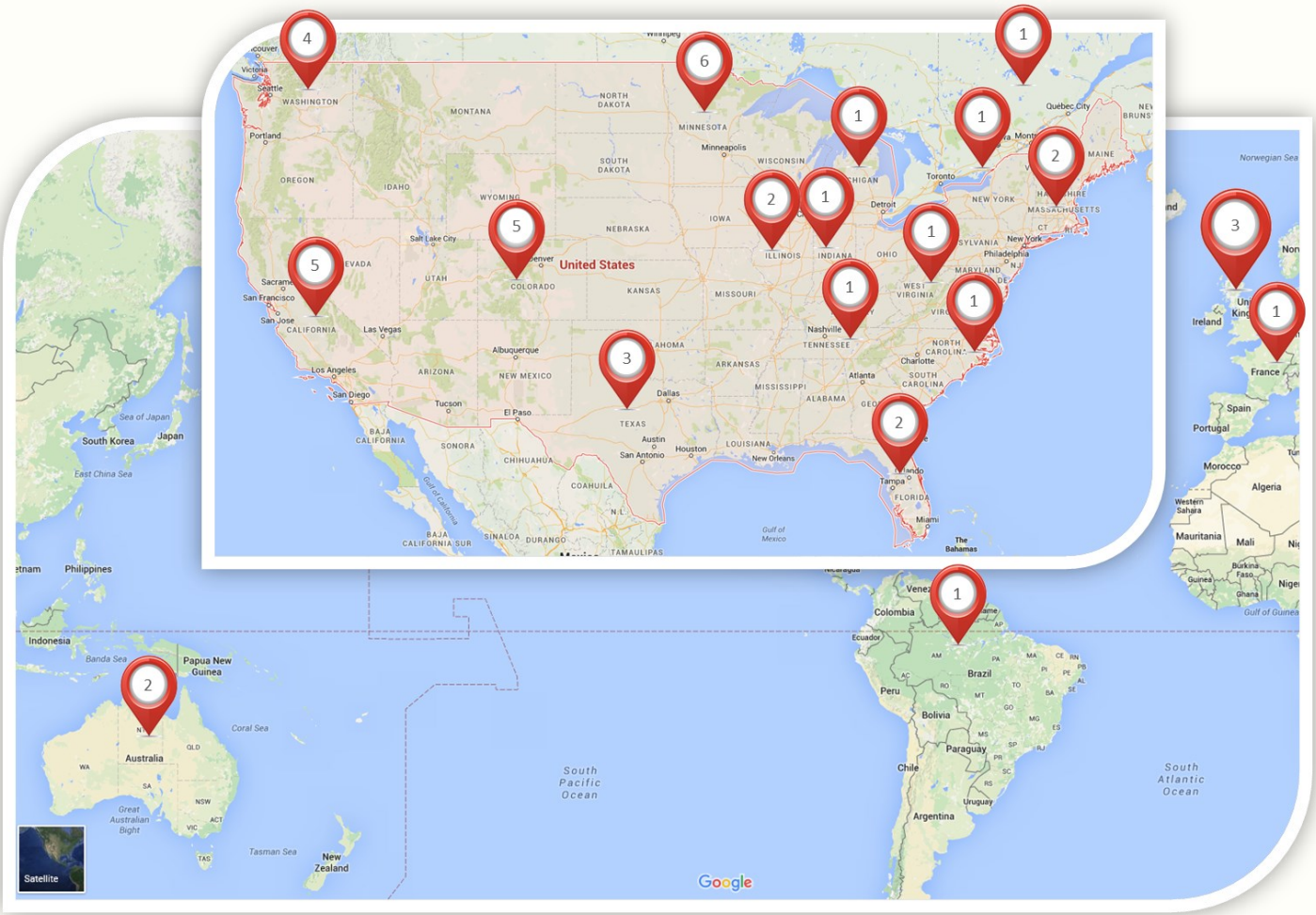
**112** units were used by AZ researchers with the mother's consent.

**2nd Annual AZ Cord Blood Conference** was held in Phoenix, AZ on April 13, 2017.

# Arizona Public Cord Blood Program

## Transplants

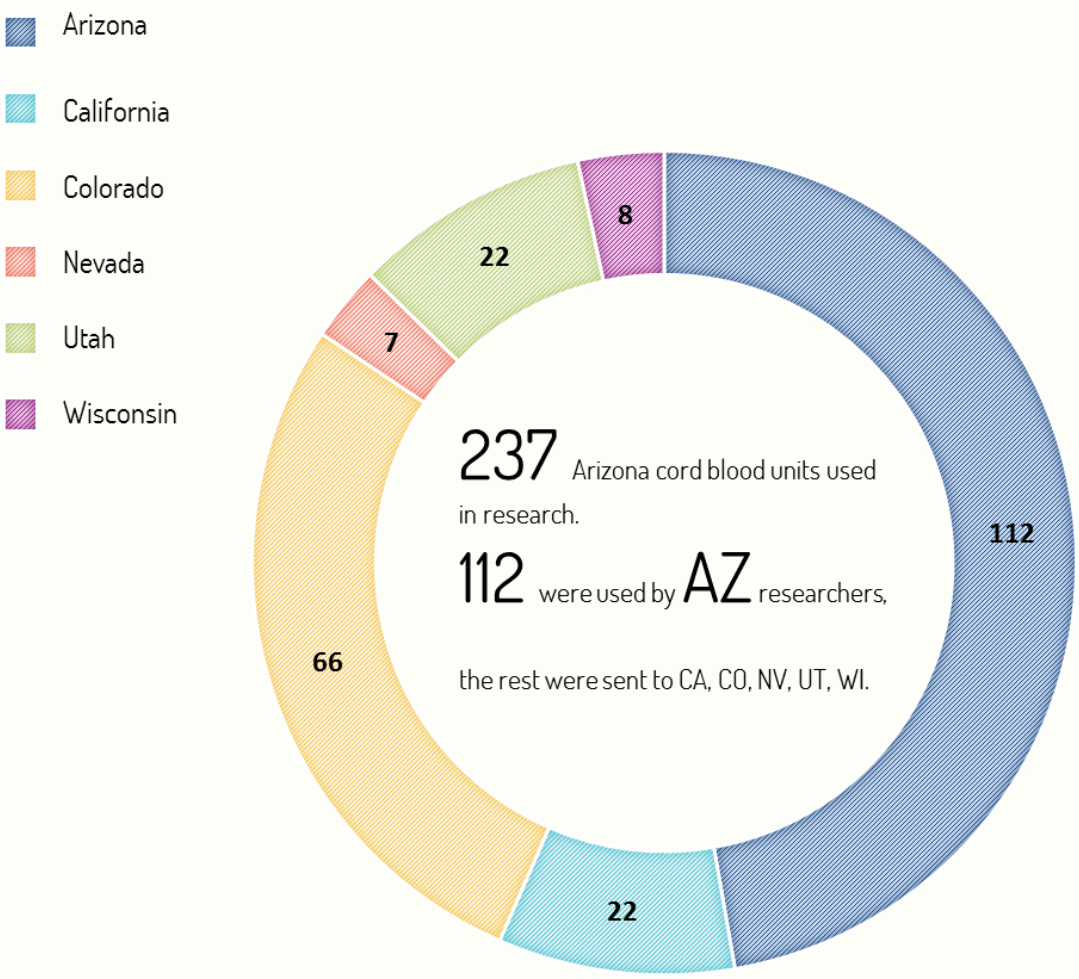
Cord blood that is donated to the AZ Public Cord Blood Program and meets the banking requirements are listed on national and international registries. The National Marrow Donor Program (NMDP), Be the Match is the national registry that lists bone marrow donors as well as available cord blood units. The NMDP has noted that many patients, particularly non-white patients, have a harder time finding a suitable match. The AZ Public Cord Blood Program is a highly effective collection program that adds large, high-quality, genetically diverse units to the registries. As of June 30, 2017 forty-three (43) of our cord blood units have been sent for life-saving transplants throughout the US and around the world. The map below shows where our cords have been used.



# Arizona Public Cord Blood Program

## Research Cord Blood

Mothers can elect to donate their cord blood unit to research if it doesn't qualify for banking for transplant. Cord blood used in transplant needs to meet strict criteria, such as a minimum dose of stem cells. If the unit does not meet these criteria, it may still be valuable for researchers, who can request units directly from the cord blood bank. In 2017, 237 cords collected by the Arizona Public Cord Blood Program were used in research.



# Arizona Public Cord Blood Program

## Partner Hospitals

Abrazo Central Campus

Dignity Health, Chandler Regional Medical Center

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

Maricopa Integrated Health System

Tucson Medical Center

## Educational Partner

Save the Cord Foundation, Tucson

## Partner Cord Blood Banks

Celebration Stem Cell Centre

University of Colorado

# Arizona Biospecimen Locator

## Overview

Acquiring quality biospecimens is one of the obstacles researchers face as they strive to advance medical science and improve patient care. The Arizona Biospecimen Locator (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 can currently request biospecimens on the website, and when the database is live, researchers will be able to search for biospecimens based on disease, type of specimen, preservation type, anatomic source and demographics of participants to use in their qualified research studies.

## Contracted Hospitals

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

## FY 2017 Highlights

**3242+** biospecimens **collected** this year

**877+** biospecimens **distributed** to researchers this year

**35+** research studies **supported** by contracted hospitals this year

New **website is live**: www.arizonabiospecimenlocator.com

# Research Education Program

## Overview

ABRC identified a need to make high quality educational resources available to Arizona researchers to help develop them into successful, nationally competitive researchers. ABRC developed the Research Education Program through partnering with local universities and listening to AZ researchers . This initiative is also in line with the Arizona Biosciences Roadmap and shows ABRC's commitment to advance research in Arizona. The Research Education Program supports local researchers and clinical professionals by bringing national and local experts together to cover emerging topics at little or no cost to the Arizona research community.

## Contracted Universities

- → Arizona State University
- → Northern Arizona University
- → University of Arizona, College of Medicine, Phoenix
- → University of Arizona, Tucson

# Research Education Program

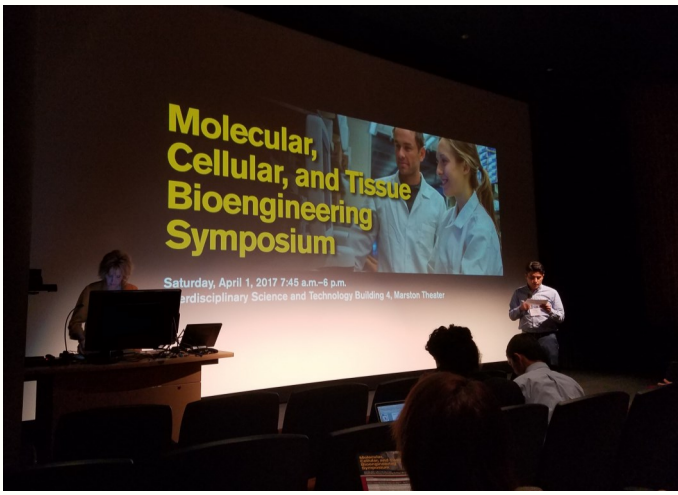
## FY 2017 Highlights

### Workshops and Trainings

ABRC supported 4 local universities with resources to host workshops, trainings, and symposiums tailored to local researchers' needs. This year, the universities held 18 events, listed below.

#### Arizona State University

→ Second Annual Molecular, Cellular, and Tissue Bioengineering (MCTB) Symposium




#### Northern Arizona University

→ THRIVE Workshop Series 4: Getting the Word Out: Translating and Disseminating Research Results

→ Transforming Patient Care: The Cutting Edge of Stroke Rehabilitation Research

→ Developing Health Research Capacity along the Yuma County/SLRC Sonora Border Region

→ Yavapai Apache Health Disparities Grant Writing Workshop

#### University of Arizona, Tucson

→ FDA Clinical Trial Audits and Clinical Trial Billing Compliance

→ Building Community-Engaged Health Research

→ Careers in Translational Research

→ Write Winning NIH Grant Proposals

→ Improving Healthcare with Precision Medicine & Big Data

→ Biobanking and Informed Consent

# Research Education Program

## Highlights (Cont.)

### Workshops and Trainings

#### University of Arizona, Phoenix

- → Research Conference
- → 2nd Annual Arizona Cord Blood Conference
- → Grant Writing Workshop
- → Basic Medical Sciences Seminar Series
- → Technology Conference
- → ALS Symposium
- → RNA Salon

# Research Grants Program

## Overview

ABRC funding opportunities aim to accelerate promising research toward clinical testing and breakthroughs designed to improve the health of Arizonans. While ABRC's strong emphasis is on funding basic and translational research projects to generate preliminary data, ABRC continues to seek innovative projects that leverage Arizona's resources and strengthen collaboration. The Arizona New Investigator Award (AZ NIA) helps new investigators conduct research aimed at testing basic hypotheses to generate preliminary data necessary to apply for larger funding opportunities. The Arizona Investigator Grant (AZ IG) funds more senior researchers who conduct on-going basic or translational research with a goal of seeking larger federal grant funding, moving into clinical trials/device studies, or commercializing their research.

ABRC funds research projects that are aimed at the causes, epidemiology, and diagnosis of human diseases; public health and community-based participatory research; the formulation of cures and medically accepted treatments; prevention of human diseases, including new drug discovery and development; advancing the prevention and treatment of tobacco-related disease and addiction; and/or behavioral studies and attitude assessments.

## Highlights

- **30 new awards in FY 2017**
  - 10 Investigator Grants ($250,000 per year for 3 years)
  - 20 New Investigator Awards ($75,000 per year for 3 years)
- **25 continued projects** (which includes carryforward funds)
  - 8 Investigator Grants ($250,000 per year for 3 years)
  - 17 New Investigator Awards ($75,000 per year for 3 years)
- **Abstracts of the funded projects are provided** in Appendix A (2015 cohort) and Appendix B (2017 cohort)

# Research Grants Program

## Funded Projects

### 2015 Cohort

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| **Early Stage Investigator (ESI) Awards (up to $75,000 / year for 3 years)** | | |
| Bridget Marie Barker | Northern Arizona University (Flagstaff) | Therapeutic: identify potential drug target and vaccine for Valley Fever. |
| Lisa Baumbach-Reardon | Translational Genomics Research Institute (Phoenix) | Diagnostic and therapeutic: use whole exome sequencing (WES) to identify disease causing mutations in children with neuromuscular disease, and to study these new mutations to lead to development of effective therapeutic strategies. |
| Timothy Bolger | University of Arizona (Tucson) | Therapeutic: providing the biological framework for designing new treatments for medulloblastoma and other cancers. |
| Christian Bime | University of Arizona (Tucson) | Intervention: a community based exercise prescription to understand the mechanism underlying the association between aerobic and asthmatic responses in obese adults. |
| Elena DeFilippis | Mayo Clinic (Scottsdale) | Therapeutic: define whether eosinophils play a crucial role in human fat metabolism and inflammation and highlight new therapeutic targets. |
| Andrew George | St. Joseph's Hospital and Medical Center (Phoenix) | Diagnostic: seek to achieve a "molecules to behavior" account of cognitive decline associated with early-onset Alzheimer's Disease (AD). |
| Karmella Haynes | Arizona State University (Phoenix) | Therapeutic: use a new methodology to halt cancer with engineered chromatin instead of conventional small molecule-based drugs that cause undesirable pleiotropic effects. |
| Anita Koshy | University of Arizona (Tucson) | Therapeutic: identify the cellular and molecular mechanisms that underlie *Toxoplasma*'s neuroprotective effects to offer new therapeutic targets for preserving our cognitive capacity. |
| Lalitha Madhavan | University of Arizona (Tucson) | Therapeutic: understand the role of Nrf2 molecule in brain stem cell function during aging for building clinically effectiveness to treat age-related neurodegenerative disorders. |
| Diego Mastroeni | Arizona State University (Phoenix) | Therapeutic: look at the underlying targets which oligomeric a-beta can affect the synapse, and offer a therapeutic approach to treating this problem. |
| Chinh Nguyen | Biomedical Research and Education Foundation of Southern Arizona | Diagnostic: determine the utility of cytokines released by whole blood among patients with coccidioidomycosis in prediction of clinical outcome. |
| Benjamin Renquist | University of Arizona (Tucson) | Therapeutic: further understanding of hepatic lipid accumulation and type II diabetes to assist the development of therapeutics that target the causative signals rather than treating the symptoms of type II diabetes. |
| Dominik Schenten | University of Arizona (Tucson) | Therapeutic: identify and understand the immune signals that are critical for protective immune responses, which are essential for the development of new vaccine strategies. |

# Research Grants Program

## Funded Projects

### 2015 Cohort (Cont.)

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| Geidy Serrano | Banner Health (Sun City) | Diagnostic: provide a foundation for the discovery of peripheral biomarkers that could help in the understanding, early detection, and diagnosis of Alzheimer's disease. |
| Mohammad Shahidullah | University of Arizona (Tucson) | Therapeutic: understand the mechanisms of triggers of dried eye disease (DED) to lead to novel therapeutic intervention for DED. |
| Sarah Stabenfeldt | Arizona State University (Phoenix) | Therapeutic: develop novel intervention strategies that directly tackle neurodegenerative cues and promote regeneration. |
| Theresa Thomas | Arizona State University (Phoenix) | Therapeutic: gain understanding of the structural, functional and hormonal mechanisms involved with the genesis and persistence of endocrine dysfunction and associated pathology for future therapeutic development. |
| **Biomedical Investigator Grants (BIG) (up to $250,000 / year for 3 years)** | | |
| Nafees Ahmad | University of Arizona (Tucson) | Therapeutic: provide novel information that may help 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 | University of Arizona (Tucson) | Device: 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. |
| Robert Handa | University of Arizona (Tucson) | Diagnostic: identify sex-specific developmental changes in gene expression that might underlie the sex-selectivity of adult risk for the developing of depressive disorder and cardiometabolic diseases. |
| Karl Kern | University of Arizona (Tucson) | Therapeutic: evaluate the value of early coronary angiography after cardiac arrest in patients without ST segment elevation on their ECG. |
| Diego Martin | University of Arizona (Tucson) | Diagnostic and Therapeutic: develop new magnetic resonance imaging (MRI) biomarkers to improve diagnosis, therapy and outcomes related to Non-Alcoholic Fatty Liver Disease (NAFLD) and Steatohepatitis (NASH). |
| George Pettit | Arizona State University (Phoenix) | Therapeutic: develop anti-cancer drugs from marine organisms, microorganisms and plants with highly effective anti-cancer components that offer the potential for ultimate clinical activity against human cancer. |
| Kaushal Rege | Arizona State University (Phoenix) | Therapeutic: formulate the folic acid conjugated lipids into liposomes to enable targeted drug delivery to triple-negative breast cancer cells. |
| Marwan Sabbagh | St. Joseph's Hospital and Medical Center (Phoenix) | Therapeutic: Track the development of Alzheimer's disease by using: (a) cognitive status tests (which determine mental ability) and (b) brain scans (which show brain images) to examine changes in the brain before and after a patient develops Alzheimer's disease. The results will guide future treatments. |

# Research Grants Program

## Funded Projects

### 2017 Cohort

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| **New Investigator Awards (up to $75,000 / year for 3 years)** | | |
| Smita Bailey | Phoenix Children's Hospital (Phoenix) | Diagnostic and Intervention: utilize non-invasive imaging techniques such as ultrasound and magnetic resonance imaging (MRI) to identify changes on liver, cardiovascular, and metabolic health following an intensive 6-month lifestyle intervention program among obese Latino adolescents with prediabetes in prediabetes Arizona Latinos. |
| Nadine Bakkar | St. Joseph's Hospital and Medical Center (Phoenix) | Therapeutic: characterize amyotrophic lateral sclerosis (ALS) choroid plexus (CP) morphology and structural integrity, and correlate them to immune infiltration into the cerebrospinal fluid (CSF), as well as clinical parameters of disease onset and progression. In addition, identify overall molecular changes in the CP in ALS using a transcriptomic approach to potential new targets for ALS therapy development. |
| Bridget Barker | Northern Arizona University (Flagstaff) | Diagnostic: improve our knowledge of the ecological niche of C. posadasii in soil, further develop molecular techniques for detection, and validate the ability to predict the presence of Coccidioides in soil and dust. |
| Blair Braden | Arizona State University (Phoenix) | Therapeutic: investigate and characterize cognitive and brain aging in older women and men with autism spectrum disorder (ASD) to shed light on vulnerabilities and resilience in age-related decline to be targeted in future interventions. |
| David Brafman | Arizona State University (Phoenix) | Therapeutic: Utilize two transformative technologies—human induced pluripotent stem cells (hiPSCs) and CRISPR/Cas9—to elucidate the genetic, molecular, and cellular mechanisms of Alzheimer's disease onset and age-related disease progression to assist the design of molecularly targeted therapies. |
| Adam Buntzman | University of Arizona (Tucson) | Therapeutic: identify multi-gene network for Severe Respiratory Syncytial Virus (RSV) induced asthma, and measure the genetic contributions to identify genetic markers for therapeutic development. |
| Mohammad Ebrahimkhani | Arizona State University (Phoenix) | Therapeutic: use mouse livers and human stem cells to modulate liver tissue regeneration and repair and to identify important cellular subpopulations for regeneration that could be used for human therapeutics. |
| Deveroux Ferguson | University of Arizona (Tucson) | Therapeutic: determining the role of SIRT1 in mediating cocaine reward to help develop targeted therapeutics for addiction, and gain a more comprehensive understanding of the molecular-neurobiology of addiction. |
| Viacheslav Fofanov | Northern Arizona University (Flagstaff) | Diagnostic and Health Disparities: Characterize and quantify Early Childhood Caries causing bacteria strains in Native American and Hispanic children. Help predict child's caries outcomes on the basis of biological indicators. |

# Research Grants Program

## Funded Projects

### 2017 Cohort (Cont.)

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| Sheba Goklany | Arizona State University (Phoenix) | Therapeutic: develop novel strategies for ablation of dormant and proliferating breast cancer cells by using nucleic acids to knock down cellular resistances to ER stress in combination with chemotherapeutic drugs to cause cancer cell death. |
| Alexander Green | Arizona State University (Phoenix) | Diagnostic: develop a low-cost diagnostic for rapid and highly accurate detection of Valley fever from serum samples. This Valley fever test will combine the capabilities of cell-free systems with the ease-of-use of paper-based diagnostics to enable detection of nucleic acids associated with infection in a few hours at a cost of $1 per test with results that can be read out by eye. |
| May Khanna | University of Arizona (Tucson) | Therapeutic: identify small molecules to modulate interactions between TDP-43 (TAR DNA Binding Protein, a hallmark feature for Amyotrophic Lateral Sclerosis, ALS) and its partners, and emulate FMRP (Fragile X Mental Retardation protein) overexpression, thereby decreasing toxicity. |
| Shyamal Mehta | Mayo Clinic (Scottsdale) | Diagnostic: perform clinical pathologic correlation using clinically detectable differences in autonomic nervous system (ANS) function and histopathological survey of biopsy-accessible peripheral nervous system sites and ANS innervation of peripheral organs to indicate whether there is an anatomical substrate that would account for differential ANS clinical symptoms in Progressive supranuclear palsy (PSP) and Parkinson's disease (PD). |
| Shenfeng Qiu | University of Arizona (Tucson) | Therapeutic: test whether enhancing neuronal autophagy rescues synaptic and circuit abnormality and restores the protein homeostasis in Angelman syndrome mice. |
| Patrick Ronaldson | University of Arizona (Tucson) | Therapeutic and health disparities: development of novel approaches for treating diseases with a hypoxia/reoxygenation component by targeting of endogenous blood-brain barrier transporters. |
| Jason Sahl | Northern Arizona University (Flagstaff) | Therapeutic: Using a single informative marker and high throughput sequencing method to identify transmission networks of urinary tract infections associated with E. coli to help develop appropriate interventions. |
| Barbara Smith | Arizona State University (Phoenix) | Diagnostic: utilizes a gas chromatograph/mass spectrometer to identify volatile organic compounds known to correlate with psychological reasoning and mental health stability to forge an entirely new path in monitoring human health in real time. |
| Ashley Stokes | St. Joseph's Hospital and Medical Center (Phoenix) | Therapeutic: identify advanced imaging signatures that are indicative of high tumor cellularity for biopsy guidance and that are able to reliably assess treatment response. |

# Research Grants Program

## Funded Projects

### 2017 Cohort (Cont.)

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| Kyle Winfree | Northern Arizona University (Flagstaff) | Device: design, prototype, and test a harness support system that can be installed inside an existing home. This system will build on the designs of the robotic exoskeletons, and the harness systems. |
| Jin Zhou | University of Arizona (Tucson) | Therapeutic: develop a data-driven paradigm to understand the heterogeneity of medication treatment effects in type 2 diabetes and to provide an evidence-based treatment guidance that is tailored to subgroups of patients sharing similar characteristics (precision medicine). |
| **Investigator Grants (up to $250,000 / year for 3 years)** | | |
| Heddwen Brooks | University of Arizona (Tucson) | Therapeutic: develop a novel therapeutic product for polycystic kidney disease that can be used in vivo, to reduce proliferation and cyst formation. This is done by producing a bivalent ligand that will bind with high specificity to principal cells in the collecting duct of the kidney which will reduce cAMP formation, renal cell proliferation and reduce cyst formation and cyst volume. |
| Steven Goldman | University of Arizona (Tucson) | Therapeutic: create a tissue engineered cardiac patch embedded with human neonatal fibroblasts and seeded with human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) as a new treatment for congestive heart failure. |
| Leslie Gunatilaka | University of Arizona (Tucson) | Therapeutic: evaluate the therapeutic efficiency of 17-beta-hydroxywithanolides (17-BHWs) in combination with various immunotherapeutic regimens to treat melanomas. 17-BHWs, natural products from a plant collected in Arizona, were highly effective in sensitizing melanoma cells to undergo apoptosis. |
| Eric Kostelich and Kristin Swanson | Arizona State University (Phoenix) | Therapeutic: create a "tumor forecast system" to make short-term (2-4 months) predictions of tumor progression in individual patients with glioblastoma multiforme brain tumors. The prediction can be used for the planning of radiotherapy and other treatment, by indicating where in the brain a particular tumor may be likely to invade. |
| Monica Kraft | University of Arizona (Tucson) | Therapeutic: determine the effect of genetic variation in surfactant protein A2 in the development and exacerbations of human asthma, and use a mouse model to test the effectiveness of surfactant protein A replacement therapy for asthma. |
| Douglas Lake | Arizona State University (Phoenix) | Diagnostic: develop a diagnostic test for valley fever using an antigen detection assay that will capture the antigens with monocloncal antibodies and detect them with certain carbohydrate-binding proteins in a sandwich-based enzyme immunoassay. |
| Wei Liu | Mayo Clinic (Scottsdale) | Therapeutic: improve intensity-modulated proton therapy for lung cancer by accounting for intrafractional irregular respiratory motion and interfractional anatomical changes. |

# Research Grants Program

## Funded Projects

### 2017 Cohort (Cont.)

| Grantee | Grantee Organization | Technology and Significance |
|---|---|---|
| Lois Loescher | University of Arizona (Tucson) | Awareness and Prevention: train massage therapists in Arizona on how to deliver sun safety and early detection education, effectively communicate with their clients about these behaviors, and provide resources for further evaluation by a physician. |
| Myra Muramoto | University of Arizona (Tucson) | Intervention: adapt the existing Helpers tobacco cessation training program to prepare behavioral health professionals and peer mental health mentors to motivate their clients to engage in evidence-based tobacco cessation treatment and implement clinical practice changes to support cessation. |
| Michael Sierks | Arizona State University (Phoenix) | Therapeutic: use antibody based reagents that selectively target toxic alpha-synuclein based on the hypothesis that alpha-synuclein are responsible for neuron degeneration and spread of toxicity in Parkinson's diseases. |

# Additional Support

## AZ Alzheimer's Consortium

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 [Alzheimer's Disease (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. (azalz.org)

### FY 2017 Highlights

→ A legislative initiative directs ABRC funds to support the Arizona Alzheimer's Consortium

→ $2 million from ABRC supported **150** researchers and staff

→ Consortium members matched an additional **$1.536 million**, see the table below

| Consortium Member | Match Provided |
|---|---|
| Arizona State University | $ 200,000 |
| Banner Neurological Institute | $ 213,881 |
| Banner Alzheimer's Institute | $ 205,304 |
| Mayo Clinic | $ 200,000 |
| Banner Sun Health Research Institute | $ 210,499 |
| Translational Genomics Research Institute (TGen) | $ 200,000 |
| University of Arizona | $ 200,000 |
| University of Arizona, Phoenix | $ 35,000 |
| Critical Path Institute (C-Path) | $ 37,030 |
| Midwestern University | $ 35,000 |
| **Total** | **$ 1,536,714** |

# Additional Support

## TGen

"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." (www.tgen.org)

### FY 2017 Highlights

- → A legislative initiative directs ABRC funds to support TGen
- → $2 million from ABRC supported
  - → 49 research projects
  - → Personnel (0.7 FTE)
  - → Other associated costs related to Collaborative Project Support, Proteomics, Next-Generation Sequencing, Tissue Processing, Researcher Start-Up, Informatics, High-Performance Computing, and Technical Maintenance and Support as outlined in the contract agreement.

# Additional Support

## PANS / PANDAS

In FY 2017, ABRC was directed by legislature to set aside a one-year award of $250,000 through a competitive grant process to conduct research and provide community resources for PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) and PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection). The University of Arizona's Children's Post-infectious Autoimmune Encephalopathy (CPAE) Center of Excellence at the UA Steele Center won the award.

CPAE, "developed in partnership with Banner-University Medicine and in cooperation with the NIH/NIMH (National Institutes of Health / National Institute of Mental Health), is the first in the U.S. to implement an integrated model of basic science and clinical research, clinical care and teaching to address a spectrum of neuropsychiatric disorders that are often misdiagnosed, underdiagnosed or undiagnosed in children." (peds.arizona.edu/cpae)

The CPAE Center of Excellence has three goals:

1. To deliver multidisciplinary, state-of-the-art care to children who experience behavioral and neurological changes after an infection.
2. To investigate the causes of Post-infectious Autoimmune Encephalopathy (PAE).
3. To find new treatments to improve outcomes and eventually cure children with Post-infectious Autoimmune Encephalopathy (PAE).

## Appendix A

# 2015 Cohort Research Abstracts

| | | |
|---|---|---|
| Early Stage Investigator (ESI) Awards | I | $ 75,000 / year for 3 years |
| Biomedical Investigator Grant (BIG) Awards | I | $ 250,000 / year for 3 years |

**Bridget Barker, Ph.D.**

Northern Arizona University

**Project Title: Understanding Early Innate Immune Responses to Infection with Coccidioides, Causal Agent of Valley Fever**

Valley Fever is caused by two fungal species within the *Coccidioides* genus. These species, *Coccidioides immitis* and *C. posadasii,* are normally soil dwelling dimorphic fungi that are endemic to arid regions of both North and South America. The most common route of infection is inhaling airborne fungal arthroconidia that are present in the environment. Being exposed to environmental *Coccidioides* arthroconidia often leads to an asymptomatic infection. In many cases, pulmonary coccidioidomycosis can lead to the development of asymptomatic benign nodules. It has been estimated that at least 30% of lung nodules biopsied in the endemic region are caused by coccidioidomycosis. When pulmonary coccidioidomycosis is symptomatic in a host, the clinical presentation mimics pneumonia or other flu-like illness. Even in endemic regions, it is estimated that misdiagnosis of coccidioidomycosis as viral or bacterial pneumonia occurs in 30% of patients. If the acute infection does not resolve, it can progress to chronic and/or disseminated disease, and the specific factors influencing this outcome are unknown. We predict that interaction with innate immune cells involved in host defense is critical for the development of *Coccidioides* switching from an environmental form to a parasitic form, known as a spherule. Using standard cell culture methods, we will determine if engulfment or co-cultivation initiates spherule development of *Coccidioides*. We further predict that certain proteins (produced by the fungus or the host) are signals for this development. Many host cell lines are available that have defects in production of specific cell factors. We will use this information to assess which are required for the transition. For other pathogenic fungi, it has been shown that adaptation to hypoxia (low oxygen) is critical for causing disease. We propose to test this for *Coccidioides*.

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**Lisa Baumbach-Reardon, Ph.D.**

TGen

**Project Title: 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.

## ESI AWARDS

$75,000 per year for three years

**Timothy Bolger, Ph.D.**

University of Arizona

**Project Title: 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. This study is examining how the mutations in the DDX3 gene cause problems in cells that lead to medulloblastoma. From this work, future researchers may be able to design new treatments for medulloblastoma and other brain cancers.

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**Christian Bime**

University of Arizona

**Project Title: 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 will measure 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 methods used for this project will be a randomized controlled experiment. The intervention will be a community-based exercise prescription. Information about asthma control, exercise fitness level, lung function, blood samples for inflammatory markers will be collected at baseline and at the end of 12 weeks for all patients enrolled for the study.

To date, few studies have determined the effects of aerobic exercise on pro-inflammatory markers on asthma. Information obtained from this pilot study will be the bases for submission of a large, multi-center and multi-investigator NIH grant.

$75,000 per year for three years

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

Mayo Clinic

**Project Title: Immunomodulatory Role of Eosinophil's 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 enviroment 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 will 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. This technique is the gold standard research technique to assess insulin actions in humans. Fat will be collected during pre-planned surgery and the sample obtained will also undergo a series of investigation to look at protein and gene expression changes between lean and obese people.

In our aim 2, we will 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.

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.

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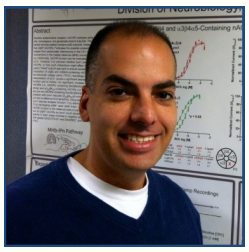

**Andrew George, Ph.D.**

St. Joseph's Hospital and Medical Center

**Project Title: 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. 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).

Specific Aim 1 will address whether the chronic administration of Aβ induces similar hyperexcitability in basal forebrain organotypic in vitro slice preparations to that seen in the hippocampal preparations. This aim will test the hypothesis that chronic inhibition of α7β2 nAChRs by Aβ leads to homomeric α7 nAChR homeostatic upregulation and enhancement of neuronal output. Specific aim 2 seeks to identify specific α7β2 subunit stoichiometries that confer high sensitivity to Aβ inhibition. This aim will test the hypothesis that nAChR sensitivity to Aβ is dependent upon the stoichiometry of β2 subunits within α7-containing nAChRs. Specific aim 3 will investigate whether memory deficits, and basal forebrain and hippocampal neurodegeneration observed in a mouse AD model, are ameliorated by disrupting Aβ/α7β2-nAChR interactions. This aim will test the hypothesis that the high affinity Aβ/α7β2 nAChR interaction is a critical trigger for basal forebrain and hippocampal degeneration early in AD.

## ESI AWARDS

$75,000 per year for three years

**Karmella Haynes, Ph.D.**

Arizona State University

**Project Title: 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 group combines molecular biology, protein engineering, and bioinformatics to test novel therapies in cultured breast cancer-derived cells. Her group's efforts will lead to a new type of treatment where anti-cancer genes become activated within cancer cells.

**Anita Koshy, M.D.**

University of Arizona

**Project Title: 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) that 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. In this study, we will determine how different strains of Toxoplasma provoke different brain immune responses and characterize these immune both in terms of the type of immune cells responding as well as the type of brain cytokines/chemokines being produced. Using a technology pioneered by our lab that allows us to track which areas of the brain interact the most with parasites, we will determine if different strains hone to different brain regions. Finally, we will determine if aged mice chronically infected with different strains of Toxoplasma show a strain-specific protective effect on brain functions, and if the brain functions served by brain areas enriched for Toxoplasma interaction are specifically protected. 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.

## ESI AWARDS

$75,000 per year for three years

**Lalitha Madhaven, Ph.D.**

University of Arizona

**Project Title: Rejuvenating the Aging Brain by Improving Stem Cell Function**

Aging is a phenomenon that carries an increased risk of a number of diseases including neurodegenerative conditions such as Alzheimer's and Parkinson's disease. This creates an enormous socioeconomic impact since the aging population is rapidly growing worldwide, and particularly in Arizona. Our studies are motivated by this important concern and develop a novel stem cell strategy that may help tackle detrimental age-related changes in the brain and to promote healthy aging.

Due to their regenerative ability, stem cells can promote the replacement and repair of dead or dysfunctional brain cells and are promising candidates to foster therapeutic approaches to promote healthy aging and treat neurodegenerative diseases. 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 creating roadblocks towards developing effective stem cell therapies. In this context, our lab has identified the progressive reduction of a specific molecule, called Nfe2l2 or Nrf2, in stem cells as a mechanism contributing to their regenerative decline with advancing age. Given this, the current project aims to increase Nrf2 within brain stem cells to investigate its potential utility to counteract the decline in stem cell regeneration during aging. These experiments will be carried out in aging rats, which will directly receive Nrf2 into existing stem cells in the brain via a gene transfer technology, or alternatively be implanted with externally grown young stem cells that have high Nrf2. These studies will provide a foundation for future endeavors geared towards building clinically effective stem cell based approaches to support healthy aging and prevent age-related neurodegeneration.

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**Diego Mastroeni, Ph.D.**

Arizona State University

**Project Title: 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 cells with Abeta oligomers, determine effects of selected aspects of mitochondrial, epigenetic, chromatin structure and expression of synaptic genes; 2)obtain the same data as in (1) from identified neurons by laser capture from AD and non-diseased brains; 3) obtain the same data as in (1) and (2) from identified neurons by laser capture from the Osaka mouse model of AD; 4)compare data from(1) (2) and (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.

**Chinh Nguyen, M.D.**

Biomedical Research and Educational Foundation of Southern Arizona

**Project Title: Use of a Whole Blood Immune Assay to Determine the Prognosis of Non-meningeal 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.

**Objectives:** 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

**Methods:** 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.

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**Benjamin Renquist, Ph.D.**

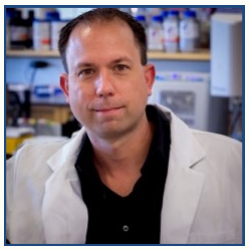
University of Arizona

**Project Title: Targeting the Hepatocyte/Vagal Nerve Communication to Develop Therapeutics for Type 2 Diabetes**

In this project we aimed to understand how liver fat induces insulin resistance and hyperinsulinemia in obesity. All cells maintain an electrochemical gradient across their cellular membrane, which acts as an energy storage method that cells use to transport nutrients into and out of the cell. Hepatic lipid accumulation decreases the charge gradient (depolarizes) across the cellular membrane. We showed that by depolarizing the hepatocyte we could induce hyperinsulinemia. Moreover, we showed that 2 models that prevented hepatocyte depolarization (Uncoupling protein 2 knockout and viral induced Kir2.1 channel expression) prevented the hyperinsulinemia and insulin resistance in obesity. We wanted to understand how these changes in the liver could affect insulin sensitivity at skeletal muscle and insulin release at the pancreas. We had previously shown that hepatocyte depolarization decreased activity of the hepatic vagal afferent nerve. Thus, we aimed to understand if hepatic lipid accumulation affected a change in neurotransmitter release from the liver. We showed that livers from obese mice released more GABA (inhibitory neurotransmitter) and less Aspartate (excitatory neurotransmitter). We subsequently identified the enzyme (GABA transaminase) responsible for hepatic GABA production and aspartate depletion in obese, gluconeogenic mice. Expression of this enzyme is increased in the livers of obese mice. Finally, we pharmacologically inhibited GABA-transaminase in obese mice and showed that within 3 days hyperglycemia, hyperinsulinemia, insulin resistance and glucose intolerance were abrogated by inhibition of GABA-transaminase. This research has identified a previously unknown pathway linking hepatic lipid accumulation to type II diabetes, while identifying an extremely promising therapy to treat diabetes.

## ESI AWARDS

$75,000 per year for three years



**Dominik Schenten, Ph.D.**

University of Arizona

**Project Title: 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. The overall goal of this proposal is therefore the identification and characterization of the specific signals that distinguish these types of immune responses. 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.

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**Geidy Serrano, Ph.D.**

Banner Sun Health

**Project Title: The Effects of APOE Genotype on APP/Aβ Levels in Human Liver and Brain**

The brain is connected to the body, yet many studies on Alzheimer's disease (AD) focus solely on the brain. 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 high-risk 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.

**Mohammad Shahidullah, Ph.D.**

University of Arizona

**Project Title: NHE8 and the Ocular Surface Homeostasis**

Arizona 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 initially focused 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. Previous discovery that NHE8 knockout mice have dry eyes phenotype suggested NHE8 might play a crucial role in maintaining ocular surface homeostasis. The 3 aims were:

1. To define the physiologic role of NHE8 in the conjunctiva and determine how deficiency of this molecule causes cell dysfunction and DED.
2. To study the regulation of NHE8 expression in the conjunctiva by associated DED factors, specifically testosterone, osmolarity and pro-inflammatory cytokines.
3. To verify if NHE8 expression is down regulated in the conjunctiva with a dry eye mouse model and in patients with DED

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**Sarah Stabenfeldt, Ph.D.**

Arizona State University

**Project Title: 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.

## ESI AWARDS

$75,000 per year for three years

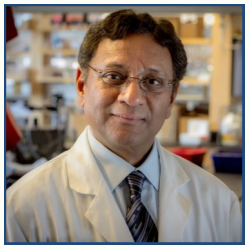
**Theresa Thomas, Ph.D.**

University of Arizona

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

Endocrine dysfunction occurs in as many as 20-50% of patients with a history of traumatic brain injury (TBI), which can impair health and quality of life, impede rehabilitation efforts and lower life expectancy. Veterans living with brain injury are equally susceptible to endocrine dysfunction and its health consequences, but sparse few clinical processes or research investigations tackle this area. The full understanding of endocrine dysfunction after TBI can be advanced by translational work in rodents, with cost-effective and rapid assessment of the pathology and validation of therapeutic efficacy. We hypothesize that endocrine dysfunction in the wake of diffuse TBI involves specific pathology in the hypothalamic-pituitary-adrenal (HPA) axis. We propose a temporal evaluation of endocrine dysfunction after mild and moderate diffuse TBI in a rodent model of midline fluid percussion TBI to determine the onset and extent of endocrine dysfunction and associated pathology. We will implement mild restraint stress to activate the endocrine system in Aim 1 and pharmacological provocation of the endocrine system in Aim 2. The brains from subsets of animals will be processed for histology to assess pathology over time, elucidate the structural deficits and identify loci for injury-induced endocrine dysfunction. These data will provide insight into the structural, functional and hormonal mechanisms involved with the genesis and persistence of endocrine dysfunction in Veterans and other diffuse TBI patients.

$250,000 per year for three years



**Nafees Ahmad, Ph.D.**

University of Arizona

**Project Title: 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.**

University of Arizona

**Project Title:**

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.

$250,000 per year for three years

**Robert Handa, Ph.D.**

University of Arizona

**Project Title: Fetal Risk Factors for Obesity and Comorbid Depression**

The overarching goal of this project is to investigate the fetal changes which might underlie and be common to the shared risk of cardiometabolic diseases and Major Depressive Disorder in adults. The specific aims are to:

1. Determine if risk biomarkers identified in preliminary animal studies are altered in a similar fashion in the human cohort.
2. To identify new biomarkers in the prenatally-stressed animal model for follow-up testing in the human cohort.
3. Validate findings in Aims 1 and 2 with animal studies in attempt to reverse the effects of prenatal GC treatment by targeting specific genes identified as risk biomarkers in Aims 1 and 2.

The team at Harvard Medical School will utilize a prospective cohort, the National Collaborative Perinatal Project (NCPP), which has followed individuals in utero (born from 1959-1966) through adulthood (ages 49-57 years), to address Aim 1. Current analyses underway are evaluating relationships between biomarkers associated with prenatal stress and inflammation with the incidence of obesity and Major Depressive Disorders in adults. The team at UACOM-Phoenix are using protein arrays from plasma, and tissues from animal studies and identifying autonomic changes using radiotelemetry, to identify genes and biomarkers that may be altered in offspring of rat dams that were exposed to glucocorticoids in utero.

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**Karl Kern, M.D.**

University of Arizona

**Project Title: A Pilot Randomized Clinical Trial of Early Coronary Angiography versus No Early Coronary Angiography for Post-Cardiac Arrest Patients without ECG 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 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"

$250,000 per year for three years

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

University of Arizona

**Project Title: 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) 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 aims of the project are: (1) Optimize a new MRI technique, refer to as 3D MRWave, to extract features from the images that are related to liver fibrosis. (2) Validate the radGRASE MRI method, developed at the University of Arizona, for imaging liver inflammation as an early indication of NASH. (3) Use 3D MRWave and radGRASE to study 200 subjects using liver biopsy as a reference standard for NAFLD/NASH diagnosis. Our methods include the use of liver samples obtained at autopsy, novel MRI techniques, and a sophisticated statistical approach to develop a model of disease. The model will be used to characterize NAFLD/NASH in patients.

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**George Pettit, Ph.D.**

Arizona State University

**Project Title: Discovery of Powerful Anticancer Drugs for Monoclonal Anticancer Drugs (ADC) Development Capable of Improving Cancer Treatments**

In the coming year about 600,000 people will die of cancer in the United States and approximately 10,000 in Arizona so the discovery and development of more effective and curative anticancer drugs is a Vital component in the global effort to address this devastating health problem. The objective of this research proposal is the discovery and development of promising new anticancer drugs with highly efficacious anticancer properties that offer the potential for ultimate clinical activity against human cancer. The discovery of new anticancer drugs with greatly increased selectivity and curative potential is urgently needed. Fortunately an exceptional recent advance in human cancer treatment has been achieved with our anticancer drug discovery necessary to development of the first successful antibody drug conjugate (ADCETRIS) for cancer treatment. The drug component of this ADC is desmethyl Auristatin E from our discovery of Auristatin E. The sharply focused objective of the proposed research will continue to be the discovery and preclinical development of new and structurally unique anticancer drugs. Special emphasis will be placed on discovery of such new drugs powerful enough to be the ADC drug candidates for linkage to a broad variety of monoclonal antibodies representing a spectrum of human cancer types.

## BIG AWARDS

$250,000 per year for three years

**Kaushal Rege, Ph.D.**

Arizona State University

**Project Title: Targeted Therapeutics for Triplenegative Breast Cancer Disease**

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that leads to significant mortality in patients. This research project involves the design, synthesis, characterization and evaluation of targeted therapeutics for TNBC disease. The goal of this project is to deliver chemotherapeutic drugs selectively to triple negative breast cancer cells by either conjugating them to molecules that can target cancer cells, or by encapsulating them in nanoparticles that can target TNBC tumors.

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**Marwan Sabbagh, M.D.**

Banner Sun Health

**Project Title: 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. With the right tests, scientists are able to view images of the brain to see physical problems that may lead to Alzheimer's disease. 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 examining brain changes, over time, in three groups of people:

Group 1: People with Downs syndrome and with Alzheimer's disease
Group 2: People with Downs syndrome and without Alzheimer's disease
Group 3: People without Downs syndrome and without Alzheimer's disease (normal controls)

Various methods will be used to measure the brain changes that happen 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 we are now adding 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 .

## Appendix B

# 2017 Cohort Research Abstracts

| | | |
|---|---|---|
| New Investigator Awards (NIA) | I | $ 75,000 / year for 3 years |
| Investigator Grant (IG) Awards | I | $ 250,000 / year for 3 years |

**Smita Bailey, M.D.**

Phoenix Children's Hospital

**Project Title: Assessment of Liver and Metabolic Disease Risks in Overweight and Obese Youths by Advanced Ultrasound and MRI Techniques**

Childhood obesity represents a significant health and socioeconomic challenge in Arizona. In particular, obese Latino adolescents are disproportionately impacted by an increased risk for type 2 diabetes, liver, metabolic, and cardiovascular diseases. This proposal's will establish advanced non-invasive imaging techniques including ultrasound (US) and magnetic resonance (MR) imaging to understand obesity-related liver disease phenotypes in Arizona Latinos. There are three aims. First, we will cross-validate US and MR elastography techniques for assessing liver stiffness, a measure of tissue scarring and fibrosis, in a cohort of normal-weight, overweight, and obese children. Second, we will measure abdominal adipose tissue volumes, organ fat content, and liver tissue stiffness in a cohort of obese Latino adolescents. The associations between these parameters with other markers of cardiovascular, metabolic, and diabetes risk, such as blood pressure, fasting glucose and triglyceride levels, and insulin resistance, will be examined. Lastly, we will utilize US and MR modalities to examine the positive changes in liver, cardiovascular, and metabolic health following an intensive 6 -month lifestyle intervention program among obese Latino adolescents with prediabetes. The successful results from these studies will lead to advances in the early diagnosis and management of liver and metabolic diseases in Arizona children.

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**Nadine Bakkar, Ph.D.**

St. Joseph's Hospital and Medical Center

**Project Title: Disrupted Blood-CSF Barrier Integrity in ALS**

The choroid plexus (CP) is an epithelial cell layer that forms the blood-CSF barrier (BCSFB) and separates the blood from the cerebrospinal fluid (CSF) bathing neurons. Besides its role as a physical barrier, the CP functions in CSF secretion and the selective transport of nutrients into the brain and CSF, and harmful metabolites out of the CSF. Under inflammatory conditions, the CP also serves as a gated point of entry of circulating immune cells into the brain. Our group and others have shown increased levels of inflammatory proteins and metabolites in CSF from ALS patients, strongly suggesting impaired function and permeability of the BCSFB. To date there have been very few studies investigating changes in CP and the BCSFB integrity in ALS. We propose that the BCSFB is disrupted in ALS, altering the normal influx/efflux of immune cells into the CSF and the brain. This study will characterize ALS CP morphology and structural integrity, and correlate them to immune infiltration into the CSF, as well as clinical parameters of disease onset and progression. We will also identify overall molecular changes in the CP in ALS using a transcriptomic approach, thus identifying potentially new targets for ALS therapy development.

**Bridget Barker, Ph.D.**

Northern Arizona University

**Project Title: Using Molecular Tools to Understand the Ecological Niche of Coccidioides Posadasii, the Causative Agent of Valley Fever**

The scope of the proposed work will improve our knowledge of the ecological niche of C. posadasii in soil, further develop technologies for detection, and validate the ability to predict the presence of Coccidioides in soil and dust. The proposed work will improve epidemiological models to reduce the disease impact on Arizonans. Previous efforts to understand and map the ecological niche of Coccidioides have had limited success. Applying molecular techniques to identify the fungus in the soil is a breakthrough that allows for large scale mapping of the organism in the environment, providing data for geospatial and temporal mapping of the pathogen. Solving the question of where and when the organism is at highest prevalence will help to protect the health of Arizonans. Recent work from our group has shown that the real-time qPCR technique developed at TGen-North is successful at detecting soils positive for Coccidioides. We anticipate that mapping the prevalence of other organisms in the Coccidioides positive and negative soils will improve our understanding of the ecological niche of this vastly understudied fungal pathogen. A method to predict the distribution of Coccidioides in soil would be a public health benefit to all Arizona citizens.

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**Blair Braden, Ph.D.**

Arizona State University

**Project Title: Longitudinal Cognitive and Brain Aging in Autism Spectrum Disorder: Interactions with Gender**

As the first children diagnosed with autism spectrum disorder (ASD) reach old age, it is imperative to understand the impact of aging on their cognitive and brain functioning. We developed a model of hypothesized accelerated aging in ASD based on striking parallels of cognitive challenges between young men with ASD, and neurotypical (NT) older adults. Studies describing cognitive challenges in ASD primarily include men due to the large male-female disparity in diagnosis (~5:1) and identify deficits in executive functioning, which is largely subserved by the frontal lobe. The frontal lobe is also susceptible to normal age-related changes. Therefore, weaknesses in older men with ASD may be exacerbated beyond normal aging. Importantly, women with ASD perform better than men on certain aspects of executive functioning, thus they may be protected from exacerbated cognitive aging hypothesized in men with ASD. Thus, we will characterize cognitive and brain aging in older women with ASD, compared to NT older women. We will also directly investigate sex differences by combining the dataset generated from this funding with our ongoing study in older men with and without ASD. Sex differences will shed light on vulnerabilities and resilience in age-related decline to be targeted in future interventions.

## NEW INVESTIGATOR AWARDS

$75,000 per year for three years

**David Brafman, Ph.D.**

Arizona State University

**Project Title: Using Human Induced Pluripotent Stem Cells to Investigate the Contribution of Risk Variants and Aging to the Onset and Progression of Alzheimer's Disease**

Alzheimer's disease (AD) affects over 120,000 individuals in Arizona and has a direct cost to Arizona that is estimated in excess of $5 billion/year. Developing therapies for the treatment of AD requires an understanding of the mechanisms that cause the disease. Animal models that overexpress specific AD-related proteins or have familial AD-related mutations introduced into the genome have provided important insights. Nonetheless, these animal models do not display important AD-related pathologies and have not been useful in modeling the complex genetics associated with "sporadic" AD. In this proposal, we will use two transformative technologies—human induced pluripotent stem cells (hiPSCs) and CRISPR/Cas9—to elucidate the genetic, molecular, and cellular mechanisms of AD onset and age-related disease progression. The data obtained as part of this proposal will have a significant translational impact on the design of molecularly targeted therapies to treat the many patients in Arizona suffering from AD. Finally, the disease models developed in this proposal will be an attractive platform for large pharmaceutical companies to develop and screen potential therapeutic compounds, thereby benefiting the Arizona economy.

**Adam Buntzman, Ph.D.**

University of Arizona

**Project Title: Investigating the Genetics of Asthma with the Collaborative Cross**

Asthma affects over 6.7 million Arizonans and costs the state of Arizona billions of dollars in health costs and lost school/work productivity. Severe Respiratory Syncytial Virus (RSV) infections within the first two years of life are associated with the development of asthma. RSV induced asthma is a complex disease governed by multi-gene networks, but the complex genetic determinants that contribute to RSV induced asthma are not well studied by classical genetic techniques (e.g. GWAS analysis). In this study, we will utilize the revolutionary Collaborative Cross (CC) Complex Trait Consortium's mouse panel to map multi-genic asthma phenotypes to find gene networks that are not identifiable by classical genetic techniques. We will measure 12 additional RSV induced asthma quantitative traits in the CC founder strains, including Type 2 inflammation, mucus and IgE production, and airway hyper-responsiveness. These quantitative traits will be used to map the genetic contribution to RSV induced asthma. In doing so we will identify novel genetic markers to identify patients at risk, identify novel biological targets that can be leveraged for pharmaceutical intervention, and will recruit grant funding to the state of Arizona.

**Mohammad Ebrahimkhani, M.D.**

Arizona State University,

**Project Title: Understanding and Modulating Tissue Regeneration and Repair Using Mouse Liver and Human Stem Cells**

The number of patients waiting for liver transplantation is expected to increase 23% over 20 years while the donor pool will become smaller in the U.S. In the state of Arizona, liver disease is among the top 4 causes of death between the active age groups of 35 to 64, with Liver transplantation being the only curative treatment in end-stage liver disease. Therefore, novel molecular targets and cell sources to enhance liver regeneration and reduce disease burden are in high demand. During my past studies, I extensively investigated cellular cross-talk in liver following tissue injury in rodent models. Recently, we generated vascularized liver organoids from human induced pluripotent stem cells that include several subsets of cells present in human liver such as unique progenitor cells, hepatocyte and stellate-like cells. In this proposal, I combine my expertise in mouse models of liver injury and human stem cells to systematically study tissue genetic signatures in vivo, validate therapeutic potential of generated human liver cells, and advance our organoid technology with a micro-perfusion device. Our study has the potential to reveal cellular subpopulations important for regeneration, generate valuable cell sources for human therapeutics and a platform for future liver disease modeling.

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**Deveroux Ferguson, Ph.D.**

University of Arizona

**Project Title: Cell-Type Specific Role for Sirtuin Signaling in Cocaine Addiction**

In the United States, everyday approximately 8,000 individuals consume drugs of abuse for the first time, adding to the expanding population of drug-users (20 million Americans). Drugs of abuse exert a substantial public health and financial costs to society and currently, there are few treatments for addiction; thus there is a significant need to discover and develop innovative and novel therapeutics to treat addiction to psychostimulants. My group recently demonstrated that chronic cocaine administration induces SIRT1, a Class III histone deacetylase, in the nucleus accumbens (NAc), a brain region that regulates reward, and that such induction influences the rewarding effects of cocaine. The NAc is primarily composed of two medium spiny neuronal (MSN) subtypes, namely gaberic MSNs enriched with dopamine D1 or D2 receptors. What is not understood is how SIRT1 influences cocaine reward in a cell and circuit- specific manner in the NAc. Determining the role of SIRT1 in mediating cocaine reward in these distinct cell-types, will significantly propel the field forward towards developing targeted therapeutics for addiction and build a more comprehensive understanding of the molecular-neurobiology of addiction.

**Viacheslav Fofanov, Ph.D.**

Northern Arizona University

**Project Title: Quantifying the Biological Component of Early Childhood Caries Health Disparities in Preschool Children of Northern Arizona**

Dental caries is the most prevalent chronic disease in children, occurring 5 times as frequently as asthma, and Arizona has one of the highest rates of Early Childhood Caries (ECC) in the US. Caries experience in Arizona's children is a staggering 52% by age 4, with kindergarten through third grade children averaging 5 affected teeth – 3 times the national average. The impact of ECC is unequal among ethnic groups, with Native American and Hispanic children exhibiting disproportionately high incidence and caries severity.

Recent research indicates that infection by bacteria from mutans streptococci group (S. mutans and S. sobrinus species) is the most common cause of dental caries. As part of proposed work, we seek to characterize the ECC causing S. mutans and S. sobrinus bacterial strains in preschool-aged children of Northern Arizona, and to quantify the effect their bacterial load and virulence has on caries progression and outcomes. This research will (1) help describe the biological component of why ECC rates are so high in Arizona, (2) quantify the degree to which strain identity drives the health disparities observed in Native American and Hispanic children, and (3) help predict child's caries outcomes on the basis of biological indicators.

**Sheba Goklany, Ph.D.**

Arizona State University

**Project Title: New Therapeutic Approaches for Elimination of Tumor Dormancy and Relapse in Breast Cancer**

Breast cancer is the most common type of cancer diagnosed in women and the 2nd leading cause of cancer related deaths in the US. The estimated number of new breast cancer cases in the US for 2016 is approximately 250,000 with 41,000 projected deaths. Breast cancer affects 4900 women every year and claims 2 lives every day in the state of Arizona. Despite early diagnosis, recurrence occurs in 25-30% of cases even after 10-15 years, indicating a role of tumor dormancy in cancer relapse. Cancer cell dormancy is characterized by growth arrest in the G0/G1 phase of the cell cycle and resistance to conventional chemotherapeutic drugs that target actively proliferating cells. The overall goal of this proposal is to develop novel strategies for ablation of dormant and proliferating breast cancer cells. We will focus on using nucleic acids to knock down cellular resistances to ER stress in combination with chemotherapeutic drugs to cause cancer cell death. Novel aminoglycoside-derived hydrogels called "Amikagels" developed in my senior mentor's lab facilitate the growth of 3D tumor microenvironment (3DTM) for breast cancer and will be used to develop dormant breast cancer platforms and determine treatment efficacies. The most effective treatments will be tested in vivo.

**Alexander Green, Ph.D.**

Arizona State University

**Project Title: Rapid Low-Cost Detection of Valley Fever via Paper-Based Cell-Free Systems**

Valley fever is a fungal infection that is becoming increasingly common in Arizona with over 62,000 cases reported from 2008-2013. Those affected can suffer from flu-like symptoms through to chronic and disseminated forms of infection requiring life-long therapy. Although early detection of Valley fever substantially improves health outcomes, current tests for Valley fever take days or even weeks. We propose to develop a low-cost diagnostic for rapid and highly accurate detection of Valley fever from serum samples. This Valley fever test will combine the capabilities of cell-free systems with the ease-of-use of paper-based diagnostics to enable detection of nucleic acids associated with infection in a few hours at a cost of $1 per test with results that can be read out by eye. To develop this diagnostic, we will use computer-based design to generate nucleic acid sensing systems targeted to genetic sequences of the Coccidioides fungi responsible for the infection. These sensors will be incorporated into our paperbased cell-free diagnostics and validated using patient serum samples provided by the Valley Fever Center for Excellence. These specific and low-cost diagnostics will enable early detection of Valley fever so that Arizonans can receive the best possible treatment for this increasingly common illness.

**May Khanna, Ph.D.**

University of Arizona

**Project Title: Small Molecule Restoration of Translation Dysregulation in ALS**

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease, leading to death within 2-5 years of diagnosis. Currently there is no cure for ALS. Over 5,600 people/year are diagnosed with ALS in the U.S., with those over 65 and veterans being at higher risk. Identifying therapeutic strategies for ALS is expected to have a high impact on the health of Arizonans. A hallmark feature of ALS is the presence of TAR DNA Binding Protein (TDP-43) aggregates in >95% of post-mortem samples isolated from ALS and >20% from fronto-temporal dementia (FTD) and Alzheimer's disease patients. TDP-43 mutations have also been identified in patients with familial and sporadic ALS/FTD, highlighting the significance of TDP-43 in the pathophysiology of neurodegeneration. Significant efforts in the field have focused on the disruption of aggregates, which is not sufficient to mitigate cytotoxicity. Interestingly, TDP-43 binds to nucleic acids and has various roles in RNA processing. TDP-43 also exhibits interactions with Fragile X Mental Retardation protein (FMRP), a regulator of translation. FMRP overexpression is neuroprotective and improves several aspects of TDP-43 toxicity. The goal of this grant is to identify small molecules to modulate interactions between TDP-43 and its partners, and emulate FMRP overexpression, thereby decreasing toxicity.

**Shyamal Mehta, Ph.D.**

Mayo Clinic

**Project Title: A Clinico-Pathologic Study of Autonomic Dysfunction in Patients with Progressive Supranuclear Palsy**

Progressive supranuclear palsy (PSP) is a rapidly progressive neurodegenerative disorder characterized by parkinsonism, falls, and eye movement abnormalities. However, due to significant phenotypic variability, the diagnosis is often confused with Parkinson's disease (PD). This has a major impact on clinical treatment, prognosis and clinical research. While there is a lot of literature on autonomic dysfunction in PD, there is relatively little known in PSP. Besides conflicting reports in PSP, the gold-standard clinico-pathologic correlation is lacking. In this research project, we aim to perform clinico-pathologic correlation using clinically detectable differences in autonomic nervous system (ANS) function and histopathological survey of biopsy-accessible peripheral nervous system sites and ANS innervation of peripheral organs to indicate whether there is an anatomical substrate that would account for differential ANS clinical symptoms in PSP vs PD. Tissues from sites such as skin, sigmoid colon, submandibular gland and heart will be immunohistochemically stained for pathological tau (PSP) and alpha-synuclein (PD). Results of this project will serve as preliminary data for a NIH grant for prospective clinicopathological studies of PSP and PD subjects and include EKG and/or cardiac MIBG studies. This may lead to the development of diagnostic autonomic test criteria to distinguish PSP from PD during life.

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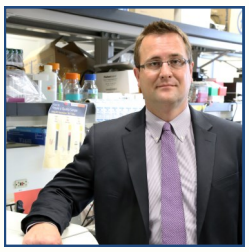
**Shenfeng Qiu, M.D., Ph.D.**

University of Arizona

**Project Title: A Translational Research Program on Neurodevelopmental Disorders in Arizona**

Neurodevelopmental disorders, such as autism spectrum disorders (ASD), constitute an overwhelming disease burden for Arizona and the United States. Many human genetic variations or mutations predispose a child to autism diagnosis, but the exact mechanism(s) is poorly understood. To gain mechanistic understanding on how brain development is affected by risk genes likely offer novel insights on devising effective behavioral interventions. Angelman syndrome (AS), a severe, debilitating neurodevelopmental disorder, is caused by mutation of the UBE3A gene and shares strong phenotypic and genetic underpinnings with ASD. Our preliminary studies utilizing genetic mouse models for AS (Ube3a maternal deficient mice) revealed that impaired excitatory synapse maturation, pruning, and disrupted neuronal autophagy and protein metabolism likely play a role in AS pathogenesis. We hypothesize that enhancing the protein autophagy pathway in neurons lacking Ube3a may rescue the neurodevelopmental deficits. To test this hypothesis, we will create controllable transgenic mice lines (Atg5, P62/SQSTM1) with enhanced neuronal autophagy function, and test whether enhancing neuronal autophagy rescues and synaptic and circuit abnormality and restores the protein homeostasis in AS mice. Our work may reveal a paradigm-shifting practice in AS therapeutics aimed at restoring cellular protein homeostasis by enhancing neuronal autophagy at a critical brain development period.



**Patrick Ronaldson, Ph.D.**

University of Arizona

**Project Tile: Effect of Aging on Transporter Functional Expression at the Blood-brain Barrier: Relevance to the Treatment of Hypoxia/ Reoxygenation Stress**

Individuals over the age of 65 are a growing component of the Arizona population. Therefore, the burden of many diseases (i.e., diseases with a hypoxia/reoxygenation (H/R) component) disproportionately affects Arizonans. Development of new approaches to treat diseases with an H/R component will address this health disparity. In this grant, we will test the hypothesis that endogenous blood-brain barrier (BBB) transporters (i.e., organic anion transporting polypeptides (Oatps), organic cation transporters (Octs)) can be targeted for H/R treatment. We propose two specific aims. In aim 1, we will investigate, in vivo, localization and molecular expression of Oatps and/or Octs at the BBB in young adult Sprague Dawley rats, in "middle aged" Sprague-Dawley rats, and in old adult Sprague-Dawley rats. In aim 2, we will examine, in vivo, Oatp mediated transport of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (i.e., statins) and Oct-mediated transport of N-methyl-D-aspartate (NMDA) receptor antagonists in young adult, middle aged, and old adult rats. We will correlate changes in brain drug uptake with indices of neuroprotection. Our goal is to facilitate development of novel approaches for treating diseases with an H/R component by therapeutic targeting of endogenous BBB transporters, discoveries that will greatly benefit Arizonans and health care institutions.

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**Jason Sahl, Ph.D.**

Northern Arizona University

**Project Title: Tracking Pathogenic Escherichia Coli in Meat Food Products in Flagstaff, Arizona**

Escherichia coli is an important human pathogen that can cause severe disease in Arizona, including urinary tract infections (UTIs). The source of UTI associated E. coli is often unknown due to limitations in surveillance methods. Recent work in our laboratory has suggested a link between UTIs and the ingestion of contaminated meat products in Arizona. However, limitations currently exist in the approach of linking genotypes between environmental and clinical sources; these limitations are primarily associated with labor and materials involved in high throughput sequencing (HTS) methods. Our approach proposes using a single informative marker (SIM) in order to track E. coli genotypes between diverse sample types. The SIM will be combined with other markers associated with pathogenesis in E. coli. We will screen this multiplexed amplicon sequencing (AmpSeq) assay across environmental, clinical, and food sources. Associations will be further investigated using HTS, but will be performed in a targeted way based on AmpSeq data. The results are expected to identify transmission networks of UTI associated E. coli, which can help in the development of appropriate interventions that will improve patient outcomes in Arizona.

## NEW INVESTIGATOR AWARDS

$75,000 per year for three years

**Barbara Smith, Ph.D.**

Arizona State University

**Project Title: Olfactory Identification of Biological Signatures of Mental Illness**

Suicide is the 10th leading cause of death in the United States, resulting in an estimated $44 billion annual cost, in terms of combined medical and work loss. Mental illness accounts for 90% of suicides. The suicide rate in Arizona is 39% higher than the national average, accounting for 17.1 suicides per 100,000 people. If accurately diagnosed, treated and monitored, suicide can be prevented. Current medical diagnostic measures and continued care require the patient to be proactive in seeking medical help, therefore, failing to provide sufficient support in addressing the needs of the individual with mental health issues, i.e., real time monitoring, feedback, and response. Despite advancements throughout the field, no method currently exists for monitoring suicidal intent, in real-time. To address the above gaps in mental health diagnostics, our research is designed to present a unique approach towards significantly impacting the complex problem of suicide prevention. Heightened stress levels, as indicated by shifts in hormone levels, correlate strongly with mental illness and the risk of suicide. Our previous studies laid the groundwork for novel discoveries of relevant volatile organic compounds (VOC) expressed from hormones; thus, providing a successful model for measuring suicidal intent by olfaction. Through the proposed work, we will expand preliminary data into a full study to identify VOC signatures of specific chemicals, known to correlate with psychological reasoning and mental health stability. By identifying hormone and stress-related physiologic cues, we will forge an entirely new path in monitoring human health in real time, correlating specific VOC hormone signatures to mental illness. Our approach utilizes extremely sensitive equipment, a gas chromatograph/mass spectrometer, designed for chemical analysis to identify VOCs, on the order of parts-per-billion, from non-invasive biological samples (i.e., sweat, saliva, urine, breath, blood). Through this work lives may be saved; Arizonians under duress may get access to mental health services in a more-timely fashion.

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**Ashley Stokes , Ph.D.**

St. Joseph's Hospital and Medical Center

**Project Title: Multi-parametric MR Imaging Signatures of Brain Tumor Burden**

The goal of this project is to improve brain cancer patient care by developing and validating advanced magnetic resonance imaging (MRI) methods for tumor characterization and therapeutic response assessment. Conventional imaging methods suffer from limited specificity to tumor-rich cell populations and confounding factors following treatment. Advanced imaging is more sensitive to the underlying tumor biology, including cellularity, vasculature, and metabolism, and may be able to overcome the challenges associated with conventional MRI. The goals of this proposal are to discover advanced imaging signatures that are indicative of high tumor cellularity for biopsy guidance and that are able to reliably assess treatment response. Our first aim is to validate the sensitivity of our advanced MRI metrics to histologic tumor content to determine whether these metrics enable the identification of tumor-rich biopsy sampling sites. Our second Aim is to establish threshold values for our advanced MRI parameters that accurately differentiate high-grade glioma recurrence from treatment effect and validate by direct correlation to image-guided tissue histopathology. The ability to probe pathologically relevant tumor characteristics, including cellularity, vasculature, and metabolism, could improve tumor localization and offer more specific indicators of treatment response.

**Kyle Winfree, Ph.D.**

Northern Arizona University

**Project Title: Living "At My Home," not in "A Home"**

The overall goal of this project is to develop the high impact technology to allow individuals with significant mobility impairments to remain happy and healthy within their own home. In the U.S., there are over 5 million stroke survivors - the majority of which are left with physical or cognitive impairments. When the burden of care from physical impairments are too great, the survivors often must sell their family home and relocate to an assisted living or nursing care provided facility. Most survivors prefer to continue living at their own home. At Northern Arizona University, we will design, prototype, and test a harness support system that can be installed inside an existing home. Existing harness systems have failed, as they are often unable to track from one room to another and rely on counter weights that create a large inertia. This system will build on the designs of the robotic exoskeletons developed by Drs. Winfree and Agrawal, and the harness systems developed by Dr. Galloway. The prototype system will be configured with motion sensors, allowing us to record multiple measures of system use and identify what aspects are most important to provide the greatest impact to physically impaired stroke survivors.

**Jin Zhou, Ph.D.**

University of Arizona

**Project Title: Development of a Data-Driven Precision T2D Treatment Regimen using the Veteran Healthcare Database**

Currently 1 in 9 Arizonans has T2D. African-Americans, Hispanics, American Indians and Asian-Americans account for 40% of Arizona residents, and are nearly twice as likely to have T2D as are Whites. In 2008, 9,883 hospitalizations in Arizona were due to diabetes that make diabetes one of most costly diseases. Treatment regime for T2D is rather complex. After failure of diet and lifestyle efforts, step-wise addition of glucose-lowering medications is the usual course of T2D therapy. The decision to prescribe subsequent medications in the best sequence after initiation of the generally agreed upon initial oral medication (metformin) is strikingly challenging due to the unclear advantages of 2, 3, 4 and 5 drug regimens and the increased potential for adverse effects. Right now, most T2D treatments guidance are designed for the average patient. But one size doesn't fit all, and treatments that are very successful for some patients don't work for others. In addition, there are also new uncertainties regarding the benefits of intensive glycemic control on macrovascular complications and the ideal target goals for therapy. Comparative effectiveness studies are the traditional tools to preform comparisons. However, this approach is impractical with multiple medication combinations due to the complexity, cost and length of the required study. In this proposal, we focus on developing a data-driven paradigm to understand the heterogeneity of medication treatment effects in T2D and to provide an evidence-based treatment guidance that is tailored to subgroups of patients sharing similar characteristics (precision medicine). Our data-driven approach will be based on the study of the US Veteran Healthcare Database, using the VA Informatics and Computing Infrastructure (VINCI). The clinical data includes the longitudinal data profiles starting from the year 2000.

**Heddwen Brooks, Ph.D.**

University of Arizona

**Project Title: Targeted Therapeutics for Polycystic Kidney Disease**

The primary limitation of all therapies shown effective for reducing PKD in animal models 24,45,67, is their non-specific delivery to organs other than the kidneys, which in humans has lead to deleterious systemic side effects, obviating their use for treating PKD at current effective doses. Our work has demonstrated that targeting therapeutic agents in a cell-specific manner, reduces the therapeutic concentration. This is achieved by linking together the binding elements for two different receptors into a bivalent ligand. We have shown that only cells expressing both receptors bind the bivalent ligand (cell specific targeting), and bind with a higher affinity and lower Kd. We have also demonstrated that our targeting strategy works in vivo.

Studies proposed here will build on our previous expertise. Here, we propose to develop a novel therapeutic product for polycystic kidney disease that can be used in vivo, to reduce proliferation and cyst formation. By linking the binding domains of the V2R antagonist (Tolvaptan), specific for collecting duct cells, and a somatostatin receptor (SST2R) agonist (Lanreotide), also expressed in collecting duct cells, we will produce a bivalent ligand that will bind with high specificity to principal cells in the collecting duct of the kidney. In polycystic kidneys this will reduce cAMP formation, renal cell proliferation and reduce cyst formation and cyst volume. Moreover, our bivalent ligand will be used to deliver anti-proliferative payloads to the cells of interest, payloads previously shown to be therapeutically active in PKD, the bioactive mTOR inhibitors (rapamycin, metformin).

We hypothesize that a bivalent approach will increase drug specificity for renal cells, thus lowering the effective concentration needed, will enhance cell uptake and processing, and increase therapeutic efficacy. We can achieve this goal due to our experience in using chemical scaffolds to produce bivalent agents, with attached payload31. Our goal is to provide a much needed PKD therapeutic whilst limiting the deleterious off target effects of these bioactive agents.

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**Steven Goldman, M.D.**

University of Arizona

**Project Title: New Treatment for Heart Failure: Human Induced Pluripotent Stem Cells on a Matrix Patch**

Cardiovascular disease is the leading cause of death both nationally and in Arizona. Current therapies for CHF rely heavily on drug/device management that aims to prevent further cardiac deterioration and improve quality of life. None of the current treatments address the pathology of CHF, loss of functioning cardiomyocytes, except for cardiac transplantation. Simply put, there is a need for the development of novel therapeutics to treat CHF patients with an emphasis on restoring cardiac function through regenerative approaches. We propose a tissue engineered cardiac patch embedded with human neonatal fibroblasts and seeded with human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) as a new treatment for CHF.

We have shown efficacy with this patch in the rat coronary ligation model of CHF and feasibility of implantation and assessment in a swine model. Now we propose testing its long term safety and efficacy in a swine model of CHF. Our aims are: 1) Evaluate long term (6 months) left ventricular functional improvements after implantation of the patch in a swine coronary artery occlusion model of CHF, 2) Evaluate quality of life and functional capacity improvements of swine treated with the patch, and 3) Evaluate long term safety of the patch.

**Leslie Gunatilaka, Ph.D.**

University of Arizona

**Project Title:**

**Natural Product-Based Induction of Cancer Cell Death Combined with Immunotherapy for Melanoma Treatment**

Skin cancer, consisting of melanoma and non-melanoma, is the most common form of cancer in the US. Over 90% of melanomas develop as a result of skin-cell damage from UV exposure most of which comes from the sun making Arizonans more susceptible to melanoma. We recently discovered that 17-beta-hydroxywithanolides (17-BHWs), natural products from a plant collected in Arizona, were highly effective in sensitizing melanoma cells to undergo apoptosis leading to the hypothesis that 17-BHWs when combined with immunotherapeutic regimens will increase cancer cell death and amplify anti-cancer immune responses – an approach valuable in treating currently untreatable forms of melanoma. Guided by strong preliminary data, this hypothesis will be tested by: (i) exploring structure-activity relationships to identify 17-BHWs with potent activity for TRAIL and poly (I:C) induced apoptosis sensitization of melanomas (Aim 1); (ii) identifying molecular target(s) of promising 17-BHWs (Aim 2); (iii) preparing these on large-scale (Aim 3): and (iv) evaluating in mouse models for their toxicity and therapeutic efficacy in combination with various immunotherapeutic regimens (Aim 4). Clearly, development of a promising 17-BHW in collaboration with NCI to treat drug resistant melanomas has the potential for translating the proposed research into applications that will benefit the health of Arizonans.

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**Kristin Swanson, Ph.D.**

and **Eric Kostelich, Ph.D.** (not pictured)

Arizona State University

**Project Title: Patient-Specific Neuro-Oncology: Forecasting Tumor Growth and Recurrence in Individual Patients**

This proposed work seeks to test the feasibility of a "tumor forecast system" to make short-term (2--4 month), clinically useful predictions of tumor progression in individual patients who have been diagnosed with glioblastoma multiforme brain tumors, the most common, aggressive, and lethal type of primary brain cancer in adults. If successful, our prototype could in the future become a useful clinical tool for the planning of radiotherapy and other treatment, by indicating where in the brain a particular tumor may be likely to invade. The project will apply partial differential equation models successfully used in previous studies with synthetic data and in a laboratory experiment with murine glioma.

This project is a collaboration between the School of Mathematical and Statistical Sciences at Arizona State University and the neurosurgical services at the Barrow Neurological Institute in Phoenix and the Mayo Clinic Arizona. The goals of the project are to create computational domains that approximate each individual patient's brain and tumor at initial diagnosis, and to run ensembles of mathematical models of tumor growth as the patient undergoes treatment to determine prospectively whether and how accurately the simulated tumors approximate the actual ones as observed under magnetic resonance imaging.

**Monica Kraft, M.D.**

University of Arizona

**Project Title: Surfactant Protein A as an Innate Immune Modulator in Asthma**

Asthma affects 5-10% of the population nationally but 14% of Arizonans and is characterized by persistent symptoms, reduced lung function and frequent exacerbations. Interleukin-13 (IL-13) is central to the allergic phenotype of asthma and Mycoplasma pneumoniae is a common cause of asthma exacerbations. Surfactant Protein A (SP-A) is a member of the collectin family that binds to specific receptors within its collagen and lectin domains and regulates key inflammatory pathways. Our preliminary data support the hypothesis that SP-A significantly suppresses airway inflammation in asthma through disruption of IL-13 and M. pneumoniae-dependent pathways but that crucial anti-inflammatory properties of SP-A are rendered ineffective in asthmatic subjects as a consequence of SP-A genotype and cytokine milieu. Specific SP-A peptides can rescue this dysfunction, offering a novel therapeutic alternative for asthma. To test this hypothesis, we will determine the effect of genetic variation in SP-A2 in the development and exacerbations of human asthma (Aim 1). Next, we will determine the effect of genetic variation in SP-A2 in mouse models of asthma and the effectiveness of SP-A replacement therapy (Aim 2). We propose that SP-A is a complex functional protein that regulates innate immunity of asthma and exacerbations, and offers a novel alternative treatment.

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**Douglas Lake, Ph.D.**

Arizona State University

**Project Title: Development of an Antigen-Based Diagnostic Test for Valley Fever**

We are developing a new diagnostic test for Coccidioidomycosis (Valley Fever, VF), a fungal infection endemic in major population centers in Arizona. Sixty percent of VF cases reported nationally occur in Arizona. Unlike community acquired pneumonia (CAP) caused by bacteria or viruses, diagnosis of pneumonia caused by VF often takes >2 months. One reason for this delayed diagnosis is that serologic (antibody) responses against this fungus are slow to develop and even absent in some patients. Instead of depending on the antibody response of the patient, an antigen detection assay would allow clinicians to provide an accurate and timely diagnosis of VF. Furthermore, detecting antigen in blood plasma would differentiate exposure from infection, thus yielding more information than the current test. We have begun to identify Coccidioides antigens from plasma in patients using mass spectrometry. These antigens will be validated in a prospective collection of ~200 patients with CAP in which 20-30% of patients will have VF while 70-80% will have a viral or bacterial CAP. The end-goal is to develop an antigen detection assay that will capture the antigens with monocloncal antibodies and detect them with certain lectins (carbohydrate-binding proteins) in a sandwich-based enzyme immunoassay.

**Wei Liu, Ph.D.**

Mayo Clinic

**Project Title:**

**Towards Precise Intensity-Modulated Proton Therapy for Lung Cancer**

Intensity-modulated proton therapy (IMPT) has great potential to provide highly conformal tumor coverage while sparing adjacent healthy organs. However, IMPT is highly sensitive to uncertainties such as those due to range or patient setup, respiratory motion, and anatomic changes. These uncertainties can cause under-treatment of tumors or overexposure of surrounding normal tissue. Some research has attempted to account for uncertainties due to patient setup/range and regular respiratory motion. However, efficient planning approaches to render IMPT plans robust to intrafractional irregular respiratory motion and interfractional anatomical changes are lacking, especially in lung cancer.

We hypothesize that the therapeutic ratio of IMPT can be significantly improved for lung cancer through our novel informatics solutions to 1) control plan robustness by accounting for intrafractional irregular respiratory motion and 2) enhance plan robustness by accounting for interfractional anatomical changes. We will develop innovative methods to achieve robustness quantification (quantifying the sensitivity of IMPT plans to uncertainties) and robust optimization (delivering precise and predictable IMPT plans to ensure the highest clinical benefit). Our aim is to overcome the major limitations of IMPT and achieve precise and robust proton therapy for lung cancer. Furthermore, we expect our research to be applicable to many other cancers.

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**Lois Loescher, Ph.D., RN, FAAN**

University of Arizona

**Project Title: Massage Therapists Skin Health Awareness, Referral, and Education (MTsSHARE) to Reduce Cancer Risks in Arizonans**

Skin cancer in Arizona adds to the public health burden of our state. Skin cancer is common, expensive, and may cause death or disfigurement. Engaging in sun safe behaviors prevents most skin cancers; survival increases with early detection. Massage therapists (MTs) have unique access to nearly all of a client's skin. They see clients more frequently and for longer appointments than do physicians, leading to established and trusted relationships with clients. The 10,045 MTs practicing in Arizona are an innovative resource for reducing skin cancer risk in our state. This project proposes to develop and evaluate training tailored for MTs to promote skin cancer risk reduction. Our long-term goal is to reduce the morbidity, mortality, and cost of skin cancer in Arizona. Our objective is to train MTs in Arizona how to deliver sun safety and early detection education, effectively communicate with their clients about these behaviors, and provide resources for further evaluation by a physician. We know that MTs are willing to engage in behavioral brief interventions for health promotion to encourage healthy behavior change in their clients. This training creates a source for skin surveillance that has been overlooked in skin cancer prevention public health efforts in Arizona.

**Myra Muramoto, M.D. Ph.D.**

University of Arizona

**Project Title: Tobacco Cessation Brief Intervention Training for Behavioral Health**

Persons with serious mental illness (SMI) treated in public systems die approximately 25 years earlier than the general US population, and 30 years earlier in Arizona. Causes of this premature mortality are the same chronic diseases affecting the general adult population, e.g. heart disease, lung disease, and diabetes. Smoking is closely linked with these chronic diseases and related health care costs. Smoking prevalence among Arizona adults is 15% - for those with SMI and other behavioral health disorders, smoking prevalence is estimated at 30-50%. Peer mental health mentors have a unique role in behavioral health care: increasing client engagement, helping clients navigate health systems, offering a bridge between clients and their medical and behavioral treatment teams. They may be an untapped resource for increasing smoking cessation in behavioral health clients. Our project goals are to adapt our existing Helpers tobacco cessation training program to prepare behavioral health professionals and peer mental health mentors to motivate their clients to engage in evidence-based tobacco cessation treatment and implement clinical practice changes to support cessation. We will conduct a pilot study to evaluate the feasibility and acceptability the training and practice changes, and evaluate the program's impact with surveys and insurance claims data.

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**Michael Sierks, Ph.D.**

Arizona State University

**Project Title: Treatment of Parkinson's Disease with Enhanced Delivery of Antibody Therapy Selectively Targeting Toxic Protein Variants**

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease following Alzheimer's disease, affecting around 2% of people over the age of 65. PD results in disturbances in motor function characterized by tremor, rigidity and bradykinesia. A 50 to 70% loss of dopaminergic neurons in the substantia nigra, neuronal loss in other regions of the nervous system and the presence of Lewy bodies and Lewy neurites are all hallmarks of PD. Lewy bodies are intracellular protein inclusions composed of a dense core of filamentous and granular material coated with radially oriented filaments. Lewy neurites contain filaments that are structurally and immunologically similar to those found in Lewy bodies. Lewy body and neurites are present in both peripheral and central neurons in PD and seem to progress in a defined pattern throughout the brain. While fibrillar aggregates of alpha-synuclein (a-syn) are the primary constituents of the hallmark Lewy bodies and neurites numerous studies indicate that various soluble oligomeric forms of a-syn are responsible for neuron degeneration and spread of toxicity. PD has recently been characterized as an infectious disease because of the potential for oligomeric a-syn aggregates to induce toxicity in healthy cells. Because of the critically important role of oligomeric a-syn variants in the onset and spread of PD, selectively targeting and clearing toxic variants of a-syn is a promising therapeutic approach for treating PD and other related diseases. Animal models that reproduce a-syn pathology have been developed and are suitable hosts to study how selectively targeting toxic a-syn variants affects neuronal function in vivo. Our laboratory has generated antibody based reagents that selectively target toxic a-syn variants and have shown that they have potential therapeutic value. Our hypothesis is that toxic variants of a-syn are involved in the onset and progression of neurodegeneration in PD, and that selectively targeting toxic a-syn variants with passively administered antibodies is a very safe and effective therapeutic approach.

ARIZONA DEPARTMENT
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH CENTRE

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