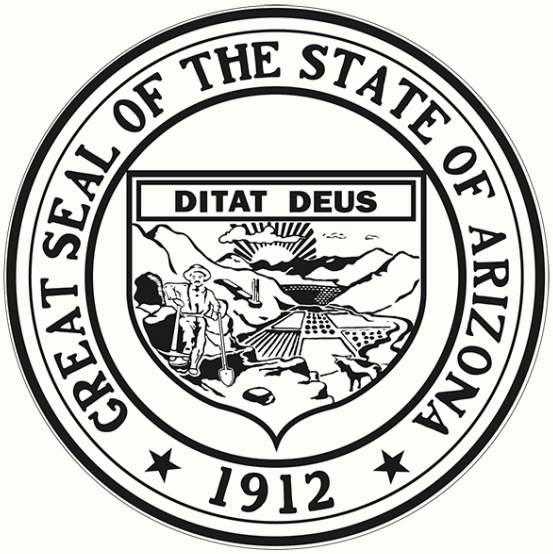
Annual Report

2017 - 2018

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

Accelerating biomedical research, education, and innovation to benefit Arizonans

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Executive Summary

The Arizona Biomedical Research Centre's (ABRC) mission is "accelerating biomedical research, education, and innovation to benefit Arizonans." In FY 2018, the four core programs (Arizona Public Cord Blood Program, Research Grants, Arizona Biospecimen Locator, and Research Education) celebrated many achievements in working towards the mission of the ABRC.

Community support is integral to the ABRC core programs' 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.

FY 2018 Highlights

48th cord blood unit from the Arizona Public Cord Blood Program was used in a life-saving transplant for a patient with Acute Lymphoblastic Leukemia

1,260 Arizona biospecimens collected by the Arizona Biospecimen Locator Program were provided to researchers

22 workshops, trainings, symposiums and other educational events were supported by ABRC's Research Education Program.

31 research projects awarded by ABRC's Research Grants Program

105 manuscripts published by 22 ABRC funded research projects

$10,196,000 in additional funds leveraged by researchers funded by ABRC in FY 2015 used to support 23 new projects.

4 Core programs

Arizona Public Cord Blood Program

Arizona Biospecimen Locator

Research Education

Research Grants

We also support

Arizona Alzheimer's Consortium

TGen

Program Staff

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

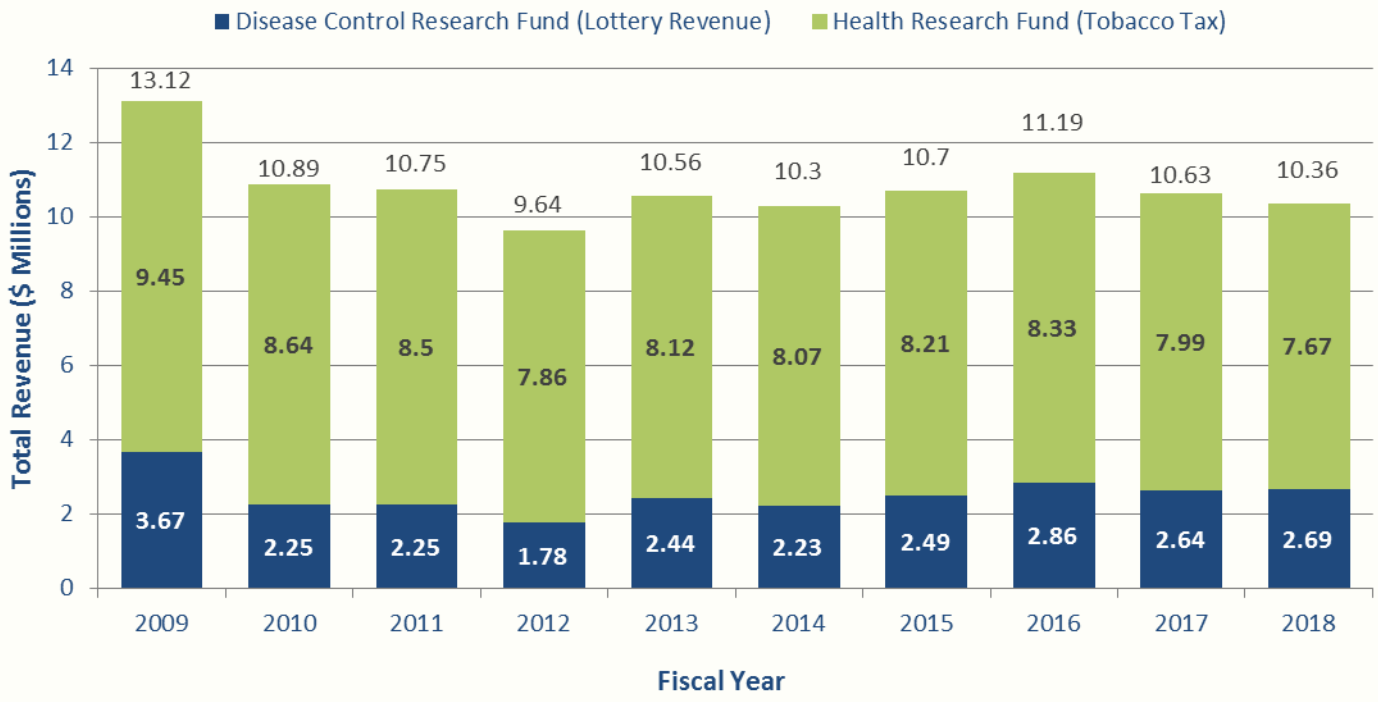
Financial Summary

Revenue

ABRC'S revenue in FY 2018 was $ 10,360,809

→ Disease Control Research Fund ARS §36-274 (Lottery Revenue) $ 2,688,509

→ Health Research Fund ARS §36-275 (Tobacco Tax) $ 7,672,300



Financial Summary (Cont.)

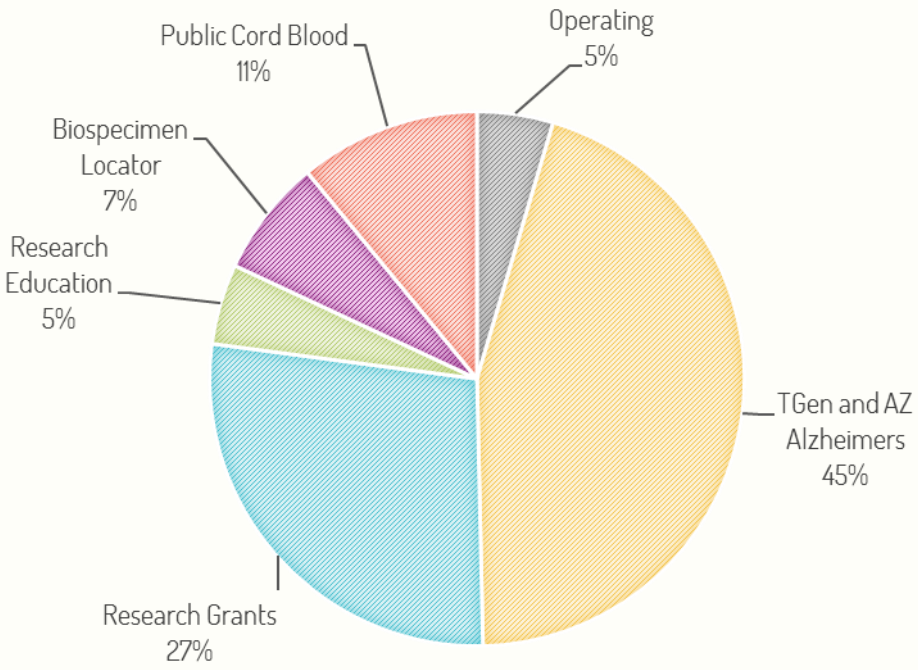
Expenditures

ABRC's expenditures in FY 2018 were $ 8,880,830

→ Disease Control Research Fund ARS §36-274 $ 1,793,923

→ Health Research Fund ARS §36-275 $ 7,086,907

Category	Expenditure
Research Grants	$ 2,438,148
Research Education	$ 431,767
Biospecimen Locator	$ 630,000
AZ Public Cord Blood Program	$ 972,211
Translational Genomics Research Institute (TGen)	$ 2,000,000
AZ Alzheimer's Consortium	$ 2,000,000
Operating	$ 408,704
Total	**$ 8,880,830**



Arizona Public Cord Blood Program

FY 2018 Highlights

3rd AZ Cord Blood Conference was held in Tempe, AZ on April 13, 2018

1,929 cord blood units were **collected** at 5 AZ hospitals

576 were **processed** by the cord blood banks

139 units were used by **researchers** with the mother's consent

320 mL was the **largest** cord blood unit collected

5 cord blood units were used in **transplants**

Overview

Arizona PUBLIC CORD BLOOD PROGRAM

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.

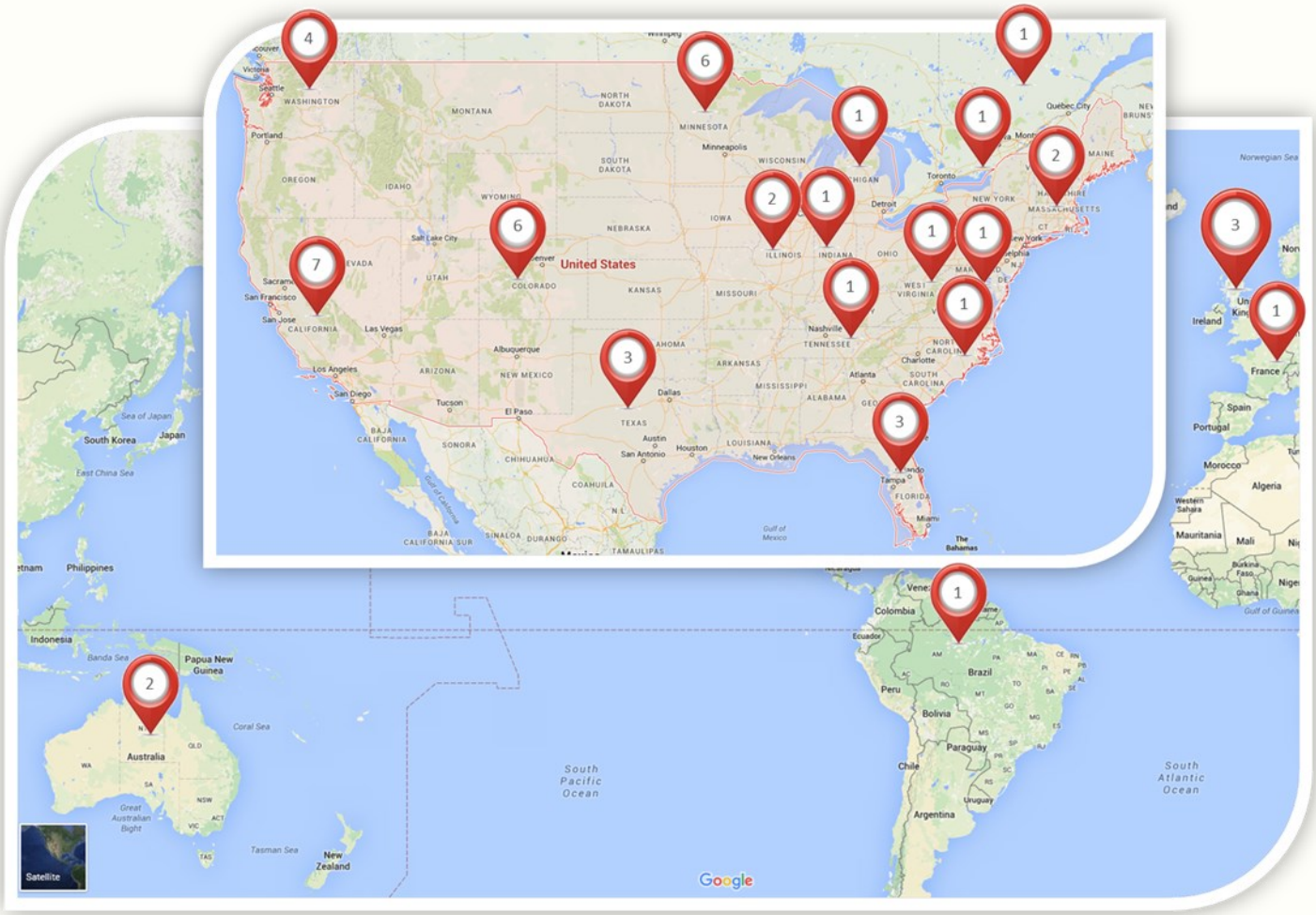
Cord blood can be used much the same way that bone marrow stem cells are used for a life-saving transplant. For many patients in need, a cord blood transplant is the best or only hope for a cure. Cord blood can be used to treat or cure over 80 diseases, such as blood cancers (e.g. leukemia) and bone marrow disorders, e.g. aplastic anemia.

Cord blood used in transplants must have a high Total Nucleated Cell count (TNC). In order to ensure a collected unit has enough cells, the provider collects as much cord blood as possible. Cord blood units over 90 mL are sent to the cord blood bank for processing. Most cord blood units used in transplant have more than 1.75×10^9 TNC. The unit collected with 320 mL had a post-cryopreserved TNC of 3.79×10^9.

Arizona Public Cord Blood Program

Transplants

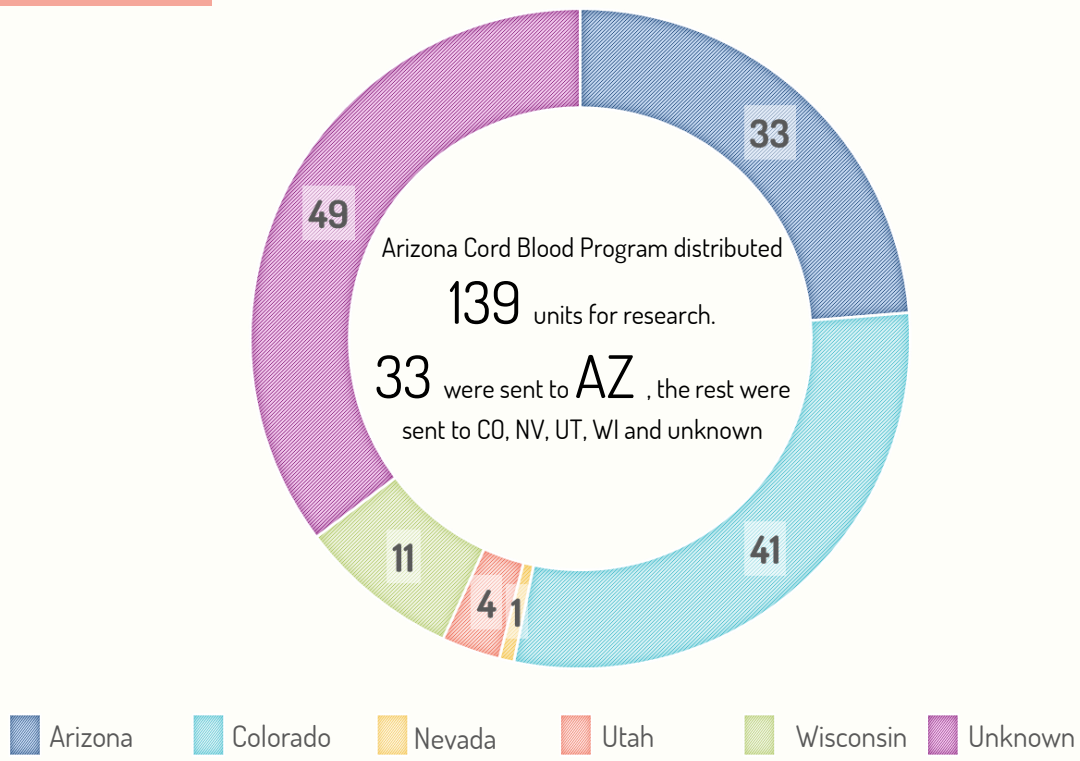
48 cord blood units collected by the Arizona Public Cord Blood Program used in transplants around the world.



Cord blood units donated to the AZ Public Cord Blood Program that meet 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, 2018 forty-eight (48) of our cord blood units have been sent for life-saving transplants throughout the US and around the world. The map above shows where our cords have been used.

Arizona Public Cord Blood Program

Research



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 2018, 139 cords collected by the Arizona Public Cord Blood Program were used in research.

Contracted Partners

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

Education

- Save the Cord Foundation, Tucson

Cord Blood Banks

- Celebration Stem Cell Centre
- University of Colorado

Arizona Public Cord Blood Program

Collection Highlights

The Arizona Public Cord Blood Program could not accomplish its mission or goals without the dedication from individuals around the state. ABRC would like to highlight some of the collection successes the program has experienced at each hospital in FY 2018.

Dignity Health, Chandler Regional Medical Center

- ★ Largest cord blood unit collected by Gerald Pass, DO (188.7 mL)
- ★ Most cord blood units collected by Heather Andrews, MD (23)
- ★ Successfully completed the first year of collections and now we will strengthen our program and increase quality and quantity of collections.

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

- ★ Largest cord blood unit collected by Michael Medchill, MD; Kathryn Reise; Carmela Fernandez, RN; and Wendy Barrett, RN (320 mL)
- ★ Most cord blood units collected by Michael Medchill, MD (53)
- ★ 33rd cord blood unit was shipped for transplant

Maricopa Integrated Health System

- ★ Largest cord blood unit collected by Caitlin Robison and Lori Vega, RN (204 mL)
- ★ Most cord blood units collected by Stephanie Chalifour, MD resident (13)
- ★ 5th cord blood unit shipped for transplant

Tucson Medical Center

- ★ Largest cord blood unit collected by Erica Heitmann, MD, Erica B, Ali Baker (225 mL)
- ★ Most cord blood units collected by Gayle Dean, MD (46)
- ★ 4th cord blood unit shipped to treat a patient with AML. Collected by Dr. Hernandez, Katia Meyer, RN, and our consenter, Katie Frey.

A special thanks goes to...

Monte Swarup, MD for his outstanding work with staff, collaboration with the cord blood bank and the startup challenges, and **Amber Vegh** who collected the most cords over 100 mL (5). (Dignity Health, Chandler Regional Medical Center)

Michael Medchill, MD for providing the most cord blood units to the national registry and responsible for most transplanted units (13/48 so far) and is an outstanding advocate for cord blood collection. (Dignity Health, St. Joseph's Hospital and Medical Center)

Lucy Hofmer, CNM. She is always supportive and involved in collections; she talks to her patients about donation; and she gets involved and is eager to learn. (Maricopa Integrated Health System)

Ali Baker and Katie Frey. They are both 100% committed to the APCBP and saving lives. Day after day they show up excited to talk to patients about donating their cord blood. They are enthusiastic when working with nurses and providers, as well. Our program wouldn't be nearly as successful without their dedication. (Tucson Medical Center)

Arizona Biospecimen Locator

FY 2018 Highlights

2608+ biospecimens **collected**

1260+ biospecimens **distributed** to researchers

37+ research studies **supported** by contracted hospitals

Overview

ARIZONA BIOSPECIMEN LOCATOR

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) is a web-based biospecimen database of both diseased and normal solid tissues, cells, fluids and molecular samples stored at participating Arizona hospitals and tissue banks. Researchers can 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.

Visit www.arizonabiospecimenlocator.com

Contracted Hospitals

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

→ Maricopa Integrated Health System

→ Phoenix Children's Hospital

Research Education Program

FY 2018 Highlights

1,000+ Arizonans participated

22+ free events such as workshops, conferences, webinars, series, etc.

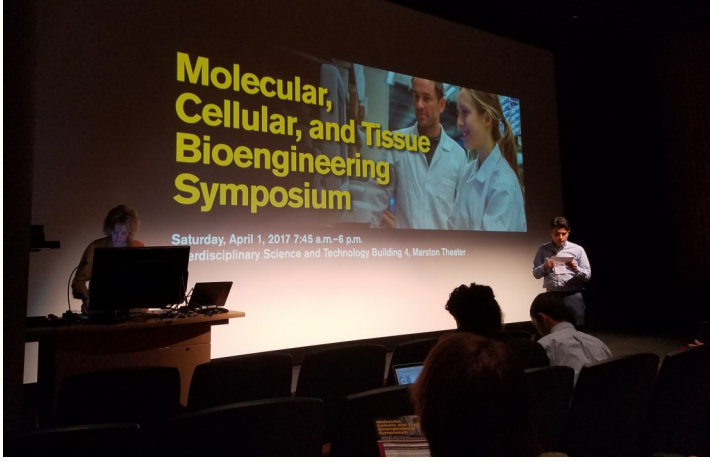
Overview

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 2018 Highlights

Workshops and Trainings

Arizona State University

- → Third Annual Molecular, Cellular, and Tissue Bioengineering (MCTB) Symposium
- → Doing Research in Indian Country
- → Translating Translational Biomedical Research to Market

Northern Arizona University

- → Community Health Representatives Summit III
- → Developing Health Research Capacity along the Yuma County/SLRC Sonora Border Region
- → Transforming Patient Care: The Cutting Edge of Stroke Rehabilitation Research
- → IRB Workshop
- → Basic Medical Sciences Seminar Series
- → Technology Conference
- → ALS Symposium
- → REDCap Workshop
- → Planning and Writing Successful Grant Proposals

University of Arizona, Tucson

- → Surviving FDA Clinical Trial Audits Symposium
- → Clinical Trial Billing Compliance
- → NIH Grant Writing
- → Precision Medicine and Big Data
- → Biobanking and Informed Consent
- → Translational Research Career Panel
- → Building Community Research Partnerships

University of Arizona, College of Medicine, Phoenix

- → Third Annual ABRC Research Conference with Flinn and VRP
- → Third Annual Arizona Cord Blood Conference
- → RNA Salon

Research Grants Program

FY 2018 Highlights

31 new awards

- → 11 Investigator Grants ($250,000 / year X 3 years)
- → 20 New Investigator Awards ($75,000 / year X 3 years)

43 continued projects (which includes carryforward funds)

- → 16 Investigator Grants ($250,000 / year X 3 years)
- → 27 New Investigator Awards ($75,000 / year X 3 years)

105 Publications from 22 funded projects

* Abstracts of the funded projects are provided in Appendices A, B, and C.

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.

Research Grants Program

Survey of 2015 Cohort

$10,101,511 was awarded in FY 2015 to 28 researchers from 8 Arizona Institutions.

63% of researchers used work from ABRC awards to leverage $10,196,000 in additional funds and 23 additional projects.

88% of researchers gave at least one poster or oral presentation of their work.

297 oral or poster presentations have been presented.

447 manuscripts have been published.

35% of researchers were awarded 54 patents with another 55 pending.

Overview

In FY 2018, ABRC surveyed researchers who were awarded an ABRC grant in FY 2015 to better understand the impact that ABRC funding has on Arizona researchers. Some researchers have been funded multiple times by ABRC, and answers include the impact from all current and prior ABRC support.

Respondents were asked to share any other way ABRC has impacted them. The following responses were provided at least once.

- → Provided means to attract or retain key scientists
- → Provided path to pursue additional opportunities
- → Provided means to continue research during critical point
- → Research results used in further development of drugs/products by others
- → Attracted or retained quality students
- → Contributed to national guidelines or regulations
- → Became a recognized leader or improved reputation among peers
- → Developed a research agenda
- → Improved collaboration
- → Provided means to mentor student researchers

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).
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.
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).
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.

* Early Stage Investigator (ESI) is later named "New Investigator Award" (NIA) and Biomedical Investigator Grants (BIG) is later named "Investigator Grant" (IG) in FY 2017

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.
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.
Sydney Rice	University of Arizona (Tucson)	Intervention: increase access to care for families in Arizona, increase support services available to families to families in Arizona, increase the number of projects involving PANS/PANDAS research, increase medical professional awareness and knowledge, create and maintain collaborations to expand awareness and research for PANS/PANDAS [Awarded $250,000 total]
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.

Research Grants Program

Funded Projects

2018 Cohort

Grantee	Grantee Organization	Technology and Significance
New Investigator Awards (up to $75,000 / year for 3 years)		
Jennifer Andrews	University of Arizona (Tucson)	Intervention: use a systematic approach to identify children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) who could benefit from simple antibiotic and anti-inflammatory treatments. The finding would shorten recovery time, increase the future health and productivity of children affected with PANS, and decrease the overall health care costs.
Heather Bean	Arizona State University (Phoenix)	Diagnostic: identify and validate putative volatile biomarkers of *Coccidioides* infections via metabolomics analyses of *in vitro* cultures, mouse model lung infections, and lung specimens from humans with Valley Fever. A panel of 10-15 volatile biomarkers for the sensitive and specific detection of Valley Fever in lung specimens is expected at the completion of the project.
Frank Duca	University of Arizona (Tucson)	Therapeutic: determine the role of small intestinal nutrient sensing in mediating the beneficial effects of prebiotics, demonstrate the impact of altered small intestinal microbiota in this effect, and identify unique changes in the small intestinal microbiota and metabolites following prebiotics. A better knowledge of prebiotic-induced changes in microbe-host crosstalk could uncover novel, gut-targeted therapeutics to better treat obesity.
Delrae Eckman	Midwestern University	Diagnostic: use a mouse model with human Apolipoprotein E (APOE) variants in place of the murine APOE to determine if cognitive and cerebrovascular dysfunction are linked to attenuated CA blood flow in aging APOE4 vs age-matched APOE2 and APOE3 mice.
Rizal Hariadi	Arizona State University (Phoenix)	Diagnostic: develop a digital nucleic acid test for Valley Fever that is accurate, specific, inexpensive, easy to use and can be administered with minimal infrastructural requirements using DNA nanoarrays and enzyme-free reactions to target the pathogen's RNA and systemically exploring the probe sequence space and tune the reaction conditions
Crystal Hepp	Northern Arizona University (Flagstaff)	Prevention and Intervention: determine 1) how different strains of West Nile Virus (WNV) and St. Luis Encephalitis Virus (SLEV) are entering and circulating throughout Maricopa County, and 2) if additional pathogens are also circulating within the same vector populations. The findings will allow for development of additional intervention strategies prospectively targeting source populations, as well as new surveillance strategies that will target any additional pathogens circulating in Maricopa County.
Ye Hu	Arizona State University (Phoenix)	Diagnostic: develop and validate an automated nanoplasmon-enhanced scattering for pancreatic cancer diagnosis in clinical cohorts, as well as develop and validate a quantitative prediction model for treatment outcomes.

Research Grants Program

Funded Projects

2018 Cohort (Cont.)

Grantee	Grantee Organization	Technology and Significance
Tally Largent-Milnes	University of Arizona (Tucson)	Therapeutic: determine the expression of NHE1 in brain endothelial cells, neurons, and astrocytes in an in vivo model of migraine using KCl, measure the function of NHE1 in brain endothelial cells, neurons, and astrocytes after KCl exposure in vitro and ex vivo, and determine the role of NHE1 in migraine pathophysiology and therapeutic effect in vivo by measuring sumatriptan CNS uptake in our model of migraine in the presence and absence of an NHE1 inhibitor.
Zachary Lerner	Northern Arizona University (Flagstaff)	Device: determine how repeated training with knee and ankle assistance from a wearable exoskeleton affects walking economy, neuromuscular control, and gait mechanics in children with cerebral palsy, and evaluate the mobility-related benefit of battery-powered knee and ankle assistance on walking speed and metabolic cost of transport for children with CP in real-world settings
Mary Lind	St. Joseph's Hospital and Medical Center (Phoenix)	Device and Diagnostic: create and test a catheter connection to enable the patent pending colorimetric optoelectronic dynamics analyzer, which continuously measures urine NH4+ levels non-invasively, to automatically sample urine from a catheter. It is expected that changes in urine NH4+ will precede standard markers of acute kidney injury in patients based on previous study results.
Qiang Liu	St. Joseph's Hospital and Medical Center (Phoenix)	Therapeutic: determine the efficacy of selective sphingosine 1-phosphate receptor (S1PR1) modulation in experimental intracerebral hemorrhage (ICH); assess novel S1PR1 modulators with superior cardiac safety; and investigate the mechanisms underlying the benefit of S1PR1 modulation after ICH. The outcome will improve the understanding of ICH immunology and pave the way for advanced ICH trials using S1PR modulators.
Mehdi Nikkhah	Arizona State University (Phoenix)	Therapeutic: develop a next generation state-of-the-art MRT that involves nanoengineering of electrically conductive and scaffold-free cardiac micro-tissues to replenish injured myocardium. This project is representing a conceptual and technological leap in innovation from currently available MRT strategies, with significant potential to disrupt existing paradigms in the treatment of MI and heart failure.
George Noutsios	Arizona State University (Phoenix)	Therapeutic: determine the effects of exogenous surfactant protein A (SP-A) in chronic rhinosinusitis (CRS) and whether it helps resolve sinusitis using 598 tissues from healthy and CRS patients, SP-A humanized transgenic mice and recombinant SP-A to conduct the proposed *in vitro* and *in vivo* studies.
Panagiotis Polygerinos	Arizona State University (Phoenix)	Device and Therapeutic: develop a novel, soft robotic exosuit to provide advanced rehabilitation therapy to lower-limb impaired patients. Compared to rigid rehabilitation exoskeletons, which are bulky, heavy, and difficult to align with joints, the proposed undergarment design will enable synergetic biomechanical assistance with a number of active components that can be disengaged to ensure that the system is functionally transparent to the wearer when needed.

Research Grants Program

Funded Projects

2018 Cohort (Cont.)

Grantee	Grantee Organization	Technology and Significance
John Purdy	University of Arizona (Tucson)	Therapeutic: understand how viruses hijack lipid metabolism to aid development of therapies for enveloped viruses. This is done by studying two unrelated enveloped viruses—human cytomegalovirus (HCMV) and Zika virus (ZIKV) to broadly identify potential antiviral targets.
Barbara Smith	Arizona State University (Phoenix)	Diagnostic: develop a physiologically-relevant three-dimensional ovarian tissue model (organoid) within a contained system, and identify molecular expression representative of early stage ovarian cancer through volatile signatures.
John Streicher	University of Arizona (Tucson)	Therapeutic: prove that Hsp90 inhibitor therapy could be used to reduce the dose of opioid needed to manage pain, while also reducing side effects like addiction. This is done by measuring the equi-efficacious doses of morphine in acute, post-surgical, and HIV neuropathic pain with and without spinal Hsp90 inhibitor, then using this dose of morphine combined with spinal inhibitor in side effect assays of dependence, constipation, and addiction risk, and testing the effects of Hsp90 inhibitor infusion into the spinal cord on toxicity and neuroinflammation, which will begin to establish a safety profile for Hsp90 inhibitor therapy.
Rebecca Vanderpool	University of Arizona (Tucson)	Diagnostic: investigate the role of prolyl hydroxylase domain protein 2 (PHD2) and hypoxia -inducible factor 2α(HIF-2α) in right ventricular failure and develop progressive markers of right ventricular failure in patients with pulmonary arterial hypertension, especially Hispanics.
Jun Wang	University of Arizona (Tucson)	Therapeutic: develop a new and effective influenza antiviral by targeting the viral polymerase subunit PA–PB1 interactions. This research will (1) optimize the antiviral potency, selectivity index, and *in vitro* pharmacokinetic properties of PA-PB1 inhibitors, and (2) test the *in vivo* antiviral efficacy of PA–PB1 inhibitors in influenza-infected mouse model studies.
Benjamin Wright	Mayo Clinic (Scottsdale)	Therapeutic: understand if IgG4 actively contributes to Eosinophilic esophagitis (EoE) pathogenesis and identify if it serves as a useful diagnostic marker of disease activity and antigenic food triggers. This research provides mechanistic insights into the interface between EoE and IgE-mediated food allergy and paves the way for the development of novel treatment strategies.
Investigator Grants (up to $250,000 / year for 3 years)		
Katherine Ellingson	University of Arizona (Tucson)	Prevention: expand and rigorously evaluate implementation of an antibiotic stewardship (ASP) protocol in 16 Arizona skilled nursing facilities (SNFs) –including four facilities in rural or border regions of Arizona – by determining intervention-attributable decreases in antibiotic use, C. difficile and cost. Findings will contribute to an emerging body of ASP implementation research and guide future expansion of ASPs to SNFs statewide. The ASP showed >50% reductions in antibiotic use and adverse events.

Research Grants Program

Funded Projects

2018 Cohort

Grantee	Grantee Organization	Technology and Significance
David Engelthaler	Translational Genomics Research Institute (Phoenix)	Diagnostic: conduct translational research on invasive Group A Streptococcus (GAS) in Arizona through a study of epidemiologic, genomic, and clinical factors that lead to the establishment and spread of new virulent subtypes of GAS in the region. The research findings provide: 1) an evolutionary and epidemiologic understanding of GAS in Arizona populations; 2) a model system to rapidly detect and respond to GAS outbreaks; and 3) new laboratory tools (e.g. genotyping and virulence assays) for local invasive GAS characterization.
Paul Keim	Northern Arizona University (Flagstaff)	Diagnostic: develop a T cell diagnostic ELISPOT assay using a novel liquid multiplexed peptide array technology (PepSeq). These diagnostic assays can indirectly detect both tuberculosis and Lyme disease with a higher sensitivity and specificity than serological assays.
Kenneth Knox	University of Arizona (Tucson)	Device: use the structure of a decellularized leaf to recapitulate the lung endothelial-epithelial micro- environment. The "Lung on a Leaf" model will provide a platform to study cell-cell interactions in a 3-D context and granulomatous immunological responses. The model will be widely applicable to other diseases and has the capacity to accelerate testing of therapeutic molecules in a more biologically relevant system.
Carlo Maley	Arizona State University (Phoenix)	Therapeutic: develop "adaptive therapy", based on pest management principles from agriculture, to adjust the dose of a cancer drug in order to keep some sensitive cells that can outcompete resistant cells. The goal is to keep the tumor a stable size and transform cancer from an acute lethal disease to a chronic disease we can live with.
C. Chad Quarles	St. Joseph's Hospital and Medical Center (Phoenix)	Diagnostic: the findings will provide the validation of fluciclovine PET imaging as a biomarker of glioma cell burden, the identification of robust image analysis techniques, and the biological characterization of fluciclovine uptake that can inform future clinical interpretation.
Benjamin Renquist	University of Arizona (Tucson)	Therapeutic: test the effect of GABA-T inhibition on glucose tolerance and insulin sensitivity in obese, hyperglycemic, hyperinsulinemic patients, and identify the tissue specific response to eliminating GABA-T expression in hepatocytes or pancreatic β-cells. These studies test a novel therapy designed to block the cause of T2DM, a predominant health concern for Arizonans.
Sidney Rice	University of Arizona (Tucson)	Health Promotion and Prevention: document symptom remission, health improvement, and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) exacerbations using immune regulation therapies among PANS patients; demonstrate the role for the microbiome as an environmental factor contributing the autoimmune neuropsychiatric symptoms; and educate Arizona professionals about the PANS condition and support primary care providers to treat these conditions in a timely manner.

Research Grants Program

Funded Projects

2018 Cohort (Cont.)

Grantee	Grantee Organization	Technology and Significance
Scott Sherman	University of Arizona (Tucson)	Therapeutic: conduct a Phase I open-label, dose-finding clinical trial and a placebo controlled Phase II clinical trial to establish ketamine's potential to reduce L-DOPA-induced dyskinesia (LID) in Parkinson's disease patients. This is based on preclinical evidence that low-dose sub-anesthetic ketamine infusion reduces and limits the development of LID.
Sarah Stabenfeldt	Arizona State University (Phoenix)	Therapeutic and Intervention: exploit the attributes of neural tissue engineering and rehabilitation therapy by prompting enhanced directed neuroplasticity. This is done by establishing synergistic effect of rehabilitation and neural tissue engineering on cortical plasticity following traumatic brain injury, and examining the influence of regenerative rehabilitation on host neural circuits and networks.
Todd Vanderah	University of Arizona (Tucson)	Therapeutic: investigate the efficacy of Angiotensin(1-7) in clinically relevant preclinical pain models, or after extended exposure to determine retained efficacy. Angiotensin(1-7) is biologically active in the CNS and shows high selectivity to the Mas receptor (MasR). Competed studies will offer a novel drug class.

Additional Support

AZ Alzheimer's Consortium

FY 2018 Highlights

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

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

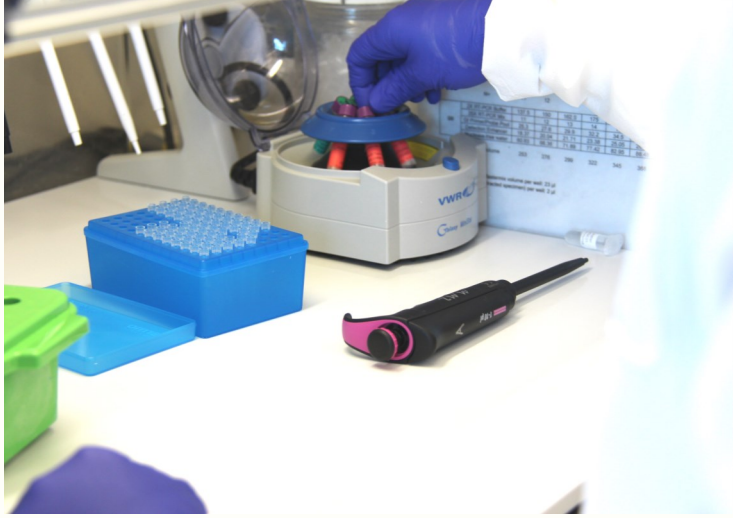
→ Consortium members matched an additional **$1.72 million**, see the table below

Overview

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)

Consortium Member	Match Provided
Arizona State University	$ 219,934
Banner Neurological Institute	$ 219,944
Banner Alzheimer's Institute	$ 248,999
Mayo Clinic	$ 219,934
Banner Sun Health Research Institute	$ 258,155
Translational Genomics Research Institute (TGen)	$ 219,934
University of Arizona	$ 219,934
University of Arizona, Phoenix	$ 38,487
Critical Path Institute (C-Path)	$ 38,488
Midwestern University	$ 38,488
Total	**$ 1,722,297**

Additional Support



TGen

FY 2018 Highlights

→ A legislative initiative directs ABRC funds to support TGen

→ $2 million from ABRC supported:

  → 59 research projects

  → Personnel (0.55 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.

Overview

"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)

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

*Abstracts are included as submitted by the research team

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*.

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. Genomic sequencing of medulloblastoma patients revealed that a particular gene (called DDX3) was frequently mutated, although it had not previously been linked to this disease. Our study has examined how the mutations in the DDX3 gene cause problems in cells that lead to medulloblastoma. We have found that while the mutations cause significant effects on cells, they are not equivalent to simple non-functioning versions of the gene. Instead, the effects of the different mutations are complex and somewhat variable. However, we have identified a defect on the cellular level that appears to be shared by all of the mutations, and we hypothesize that this defect may be critical in promoting the development of medulloblastoma. In addition, we are also examining other cellular molecules that may interact with DDX3 in cancer. This portion of the study has led us to new discoveries in how DDX3 and its equivalents in other organisms help to mediate the response to cellular stresses such as low nutrient availability. Overall, we have revealed important mechanisms for understanding DDX3 function and regulation in normal cells and how these functions are altered in medulloblastoma.

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

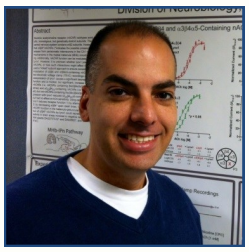
Project Title: Immunomodulatory Role of Eosinophils in Determining Inflammation and Insulin Sensitivity in Human Adipose Tissue

Obesity affects over 60% of the population in Arizona and is characterized by a state of low-grade, chronic inflammation of adipose tissue (AT), the scientific term for fat. In presence of obesity several metabolic dearrangements lead to development of mild to severe elevation of blood glucose (sugar) up to development of frank diabetes (uncontrolled blood sugar levels). Prior to the diagnosis of diabetes, obese people can be found to have mild elevation of fasting blood sugar levels together with elevation of insulin levels, a hormone normally produced by our pancreas in response to food intake. This state is called insulin resistance. In human fat, the relation between inflammation and insulin resistance is not clear. This project aims to gain more information on the role of a cell component of the inflammatory system, the eosinophils in modulation of the immune environment in human fat. In addition we wanted to evaluate whether the eosinophils may reduce inflammation and insulin resistance in human fat. We will test the hypothesis that eosinophils promote insulin sensitivity in human AT in two ways: first by releasing some mediators to sustain an anti-inflammatory 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.



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.

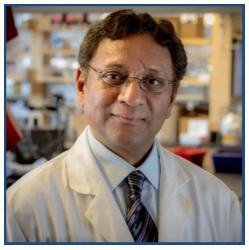
$75,000 per year for three years

Mohammad Shahidullah, Ph.D.

University of Arizona

Project Title: NHE8 and the Ocular Surface Homeostasis

In a healthy eye, tears lubricate and protect the ocular surface. Persons with dry eye disease experience pain and ocular surface inflammation caused by defective tear film. Arizona's dry weather acts as a promoting factor for this disease because of excessive tear evaporation. In other tissues it is known that thicker fluid (technically called hyperosmotic solution) can activate a sensor protein on the cell surface, called TRPV1 and that TRPV1 activation leads to production of endogenous chemicals that produce inflammation and pain. With ADHS funding we studied TRPV1 in the conjunctiva, an ocular surface tissue that influence tear film composition. We discovered that hyperosmotic solution indeed activates TRPV1 in human conjunctival epithelium and this causes an increase in production of inflammatory mediators TNFα, IL-1β, IL-6 and IL-8. We have shown that production of these inflammatory mediators can be blunted by using a TRPV1 blocker. Furthermore, production of the inflammatory mediators can be mimicked by treating the conjunctival epithelium with capsaicin, a proven activator of TRPV1. To show the clinical relevance of our finding, we collected tear samples from normal human and dry eye patients and determined that tears from dry eye patients have increased inflammatory mediators. Our study presents strong evidence that hyperosmotic tears can activate TRPV1 on the conjunctival epithelium and triggers production of inflammatory mediators. We propose that hyperosmotic tear-mediated TRPV1 activation acts as the trigger for dry dye disease and that a TRPV1 antagonist might be used to prevent or treat this condition. The data are being prepared for publication.



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

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

$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.

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.

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.

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

*Abstracts are included as submitted by the research team

NEW INVESTIGATOR AWARDS

$75,000 per year for three 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 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.

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.

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 find preliminary evidence of accelerated cognitive and brain aging in adults with ASD, presumably due to the vulnerability of individuals with ASD to the normal aging process. Studies describing cognitive aging in ASD primarily include men due to the large male-female disparity in diagnosis (~3:1) and identify deficits in executive functioning and frontal lobe connectivity. How cognitive and brain aging may effect women with ASD differently is unknown. In one of the first investigations of sex differences in older adults with ASD, this study shows a tendency toward greater executive function difficulties in females with ASD, compared to males with ASD and neurotypical controls. Identifying brain mechanisms underlying the female difficulties in executive function is in progress, as well as longitudinal follow-up in both men and women with ASD and neurotypical controls. Further describing sex differences will shed light on vulnerabilities in age-related decline of older adults with ASD 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. Although the pathological hallmarks of AD, such as axonal transport defects, synaptic loss, and selective neuronal death, are well-characterized, the underlying mechanisms that cause AD onset and age-related progression are largely unknown, thereby making it difficult to design effective therapies. Rodent models have provided valuable information in understanding AD but these models do not recapitulate all aspects of the human disease. To date, studies of AD with human neuronal cells have been restricted to experiments with cadaveric tissue samples which are limited in supply and only provide an end-stage view of the disease. With hiPSC technology it is possible to obtain a fully differentiated cell type (such as a skin cell) from an AD patient and reprogram it back into a cell type that is capable of differentiating into all of the cell types of the mature, adult body (such as cortical neurons). Therefore, with hiPSC-based technologies we have the potential to probe AD disease mechanisms and design molecularly targeted therapies. Although we and others have used AD hiPSC-derived neurons to study this disease in a simplified and accessible system, these models have been limited by the (i) absence of phenotypes and pathological hallmarks associated with later stages of the disease in aging humans and (ii) inability to consistently model the sporadic form of AD. Based on extensive characterization of hiPSC-derived neurons, we contend that these cells are too immature to accurately mimic the degenerative phase of AD that is observed in aging adults. To that end, we are using our collective experience in stem cell bioengineering, neurodegenerative disease modeling, and computation modeling to develop an inducible model of cortical aging that allows for the real-time tracking of AD phenotypes in an age-dependent manner. Ongoing detailed phenotypic analysis of control and AD-cortical neuronal cultures of various 'ages' has revealed genetic, biochemical, and signaling pathways that are independently influenced by age and disease status. Overall, the new insights gained from this project will have significant impact on our understanding of the genetic, biochemical, and cellular events that lead to AD onset and age-related progression.

Adam Buntzman, Ph.D.

University of Arizona

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

Viral respiratory infections have a profound influence on the severity of underlying respiratory diseases including asthma. The patient's underlying genetics also contribute to both the severity of the infectious outcomes as well as infection-induced exacerbations of asthma. Respiratory Syncytial Virus (RSV) infections in early life are mild in most individuals, however some individuals have severe responses to RSV infection that lead to increased risk of developing asthma. These patients' genetics contribute to this severe response in a complex way. Variations in many genes collaborate to contribute to the development of asthma in these patients that is costly to map with traditional GWAS techniques. We utilize the Collaborative Cross (CC) Complex Trait Consortium's mouse panel to identify the genes that alter the severity of RSV induced asthma to find new asthma-risk biomarkers and find new pharmaceutical targets for treating this infection and the asthma risks associated with it.

Appendix B: **2017 Cohort Research Abstracts**

New Investigator Awards

$75,000 per year for three years

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.

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 2018 is approximately 270,000 with over 41,000 projected deaths. Breast cancer affects 5700 women every year and claims over 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 project is to develop novel strategies for ablation of dormant and proliferating breast cancer cells. We are focusing on using nucleic acids to knock down cellular resistances to Endoplasmic Reticulum (ER) stress in combination with chemotherapeutic drugs to cause cancer cell death. We have successfully established platforms for developing 3D dormant and proliferative breast cancer tumor microenvironments on "Amikagels". Amikagels are novel hydrogels developed in our lab using Amikacin hydrate and polyethylene glycol diglycidyl ether (PEGDE). We can modulate the Amikacin hydrate: PEGDE ratio to change the cell cycle profiles of different breast cancer cell lines. We have shown that these 3D tumor microenvironments (3DTMs) provide a physiologically relevant system compared to 2D cell culture systems; cells in these 3DTMs demonstrate cell-cell interaction, cell-extracellular matrix (ECM) interaction, are resistant to chemotherapeutic agents despite drug penetration, and demonstrate hypoxia. The most effective treatments will be tested in vivo.

Appendix B: 2017 Cohort Research Abstracts

New Investigator Awards

$75,000 per year for three years

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.

NEW INVESTIGATOR AWARDS

$75,000 per year for three years

Shyamal Mehta, Ph.D.

Mayo Clinic

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

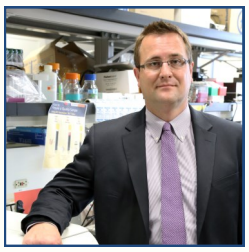
Progressive supranuclear palsy (PSP) is a rapidly progressive neurodegenerative disorder characterized by parkinsonism, falls, and eye movement abnormalities. However, due to significant phenotypic variability, the diagnosis is often confused with Parkinson's disease (PD). This has a major impact on 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.

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, 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 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 Title: 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.

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 genetic types (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 locus molecular (SLIM) marker in order to track E. coli genotypes between diverse sample types. The SLIM will be combined with other markers associated with pathogenesis and antimicrobial resistance in E. coli into an amplicon assay. 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.

Appendix B: 2017 Cohort Research Abstracts

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

Globally, more than 800,000 people die annually due to suicide, amounting to 1 death every 40 seconds. Mental illness accounts for 90% of suicides, 50% of which are caused by depression. The suicide rate in Arizona is 39% higher than the national average. Current surveillance measures are all based on human interaction, requiring the patient to seek out medical help. Recent studies have shown that 30% of people seek help within 60 days of their suicide. Despite efforts, no method currently exists for either accurately diagnosing or monitoring mental health. To address the above gaps in suicide prevention, our research is designed to identify chemical signatures, completely non-invasively, through the detection of low molecular weight volatile organic compounds. This work employs a unique combination of biological characterization, chemical analysis, and a clinical study to confirm findings of identified biomarkers associated with mental health. The goal of this project is to identify volatile signatures 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 , 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.

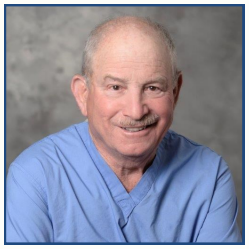
University of Arizona

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.



Steven Goldman, M.D.

University of Arizona

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

This grant is a long-term (6 month) evaluation of a biologically active cardiac cell patch as a new treatment for chronic heart failure (CHF). We examine changes in left ventricular (LV) systolic/diastolic function, electrophysiology and quality of life after implantation of the patch in a swine coronary artery occlusion model of CHF. This study also includes long-term safety of the patch by examining transplanted cell survival, potential humoral/cellular immune responses and possible teratoma formation after implantation.

The patch is composed of a bioabsorbable mesh embedded with human neonatal fibroblasts, and co-cultured with human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs). The mesh is robust and resilient, permitting easy handling and manipulation, as needed during surgical implantation and provides structural support for the cells. Fibroblasts secrete angiogenic growth factors that increase microvascular formation and myocardial blood flow in the infarcted heart, they also produce fibronectin and collagen extracellular matrix deposits to which hiPSC-CM can attach. The patch spontaneously beats in a synchronized fashion, can be paced to physiological heart rates, generates force and enhances electrical activity in the native myocardium. When implanted in-vivo, activates endogenous growth factor secretion and improves LV function in rats with CHF.

The study is progressing as planned. In brief, we have developed all the techniques required including: upscaling the patch to a size that we can implant in swine and humans, creating a myocardial infarction in the mini swine with ischemia/ reperfusion balloon occlusion of the left anterior descending (LAD) coronary artery and surgical implantation of the patch via a minimal median sternotomy. To evaluate the effects of the patch, we obtain pressure tipped catheter hemodynamic evaluations, perform serial Magnetic Resonance Imaging (MRI) studies, perform exercise testing and activity monitoring as well as perform electrophysiologic testing including programmed electrical stimulation (PES) to induce ventricular tachycardia

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.

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

Skin cancer, consisting of melanoma and non-melanoma, is the most common form of cancer in the U.S. 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 yellow nightshade ground cherry, a plant belonging to the nightshade family collected in Arizona, were effective in sensitizing melanoma cells to undergo death by apoptosis. This led us to hypothesize 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. Additional 17-BHWs were obtained by the application of an innovative aeroponic technique for the cultivation of several plant species of the nightshade family known to produce 17-BHWs. These 17-BHWs and their semi-synthetic structural analogues were then evaluated for their cytotoxic activity and the ability to induce melanoma cells to undergo TRAIL (TNF-alpha-Related Apoptosis Inducing Ligand)- and TLR3 (Toll Like Receptor 3)-ligand, poly I:C-mediated apoptosis providing valuable information on their structure-activity relationships. These studies led to the identification of a promising 17-BHW, preliminary molecular studies of which suggested that its mechanism of action is due to a dramatic reduction in the levels of anti-apoptotic proteins in melanoma cells. Intra-tumor administration of this 17-BHW combined with the immune adjuvant, poly I:C, in a xenograft M14 melanoma mouse model provided therapeutic benefit resulting in complete tumor regression in about 90% of the mice compared to untreated mice.

$250,000 per year for three years

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.

Douglas Lake, Ph.D.

Arizona State University

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

Coccidioidomycosis (Valley Fever; VF) is a debilitating respiratory disease common to the Southwestern USA and northern Mexico. It is caused by fungi from the genus Coccidioides. Diagnosing VF can be difficult due to similarities among the symptoms associated with pneumonia caused by viral and bacterial organisms or even cancer. The median time from symptom onset to diagnosis is 100 days due to lack of an accurate and sensitive diagnostic test. Current tests detect patient antibody response to infection, whereas an antigen-based diagnostic test could detect infection more accurately and earlier. We hypothesized that because fungal carbohydrates differ from that of human carbohydrates, identification of unique VF carbohydrates can be exploited as biomarkers of infection. Urine specimens from 22 patients with VF and 55 healthy controls were collected from excess clinical specimens from the Mayo Clinic Arizona Microbiology Department, in accordance with Investigational Review Board guidelines. Samples of each urine (1 mL) were enriched for free carbohydrates using a specialized enrichment and fractionation method and analyzed on a mass spectrometer instrument that identifies carbohydrates and protein molecules. Specialized software was used to search for carbohydrates present in urine from VF patients and not present in non-VF urine. 1,321 carbohydrates were identified in patient urine that were not found in any of the normal controls ($p<0.05$) or other related fungi. 380 of these carbohydrates were determined to be statistically significant. Ultimately, a set of six biomarkers provides 100% sensitivity for all 22 patients with VF and 100% specificity among 55 healthy control patients. Four of the carbohydrate structures were previously known but two were not.

The identification of unique VF carbohydrates excreted into urine from VF patients that are not present in urine from control donor urine supports our hypothesis that carbohydrates might be useful for the accurate diagnosis of Valley Fever from acutely ill patients. These results provide proof of principle for the development of an antigen-based test to detect components of the fungus itself in an easily collected specimen. We have begun generating antibodies against these Coccidioidal carbohydrates for development of a point-of-care diagnostic test for Valley Fever.

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.

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.

INVESTIGATOR GRANTS

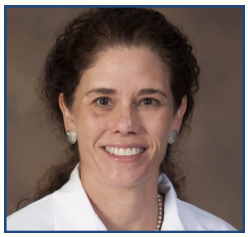
$250,000 per year for three years

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.



Sidney Rice, MD

University of Arizona

Project Title: Pediatric Acute-onset Neuropsychiatry Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)

The overarching ADHS and ABRC goal for this project is to accelerate promising research and improve the health of patients with PANS/PANDAS. The University of Arizona, Department of Pediatrics' Dr. Sydney Rice (Developmental and Behavioral Pediatrics) and Dr. Michael Daines (Allergy/Immunology and Rheumatology) are the lead investigators for the Arizona partner site of the PANS/PANDAS national collaboration under the direction of Dr. Sue Swedo at the National Institute of Mental Health (NIMH), Pediatrics and Developmental Neuroscience Branch. The group is developing national data collection standards for identifying, tracking, and treating individuals with PANS/PANDAS and UA Pediatrics is one of the designated sites. The overarching goals of this project are:

1) increase access to care for families in Arizona.
2) Increase support services available to families to families in Arizona.
3) Increase the number of projects involving PANS/PANDAS research.
4) Increase medical professional awareness and knowledge of PANS/PANDAS. 5) Create and maintain collaborations to expand awareness and research for PANS/PANDAS

INVESTIGATOR GRANTS

$250,000 per year for three years

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.

Appendix C

2018 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

*Abstracts are included as submitted by the research team

Jennifer Andrews, Ph.D.

University of Arizona

Project Title: Retrospective Assessment of PANS Incidence

The overall aim of this project is to improve the health of all Arizonans by determining a systematic approach to identifying children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) who could benefit from simple antibiotic and anti-inflammatory treatments. The future impact on this identification process would shorten recovery time through appropriate interventions, increase the future health and productivity of children affected with PANS, and decrease the overall health care costs through elimination of psychiatric admissions and reduction for the need of long-term cognitive and behavioral interventions. Completion of this aim will also provide evidence in the literature of the ability to implement the current diagnostic criteria for PANS to identify children using medical records including a comparison with the ability to differentiate with those children who meet criteria for differential diagnoses. Data from this study will provide an approximate incidence of PANS and the scope of the condition in Arizona.

Heather Bean, Ph.D.

Arizona State University

Project Title: Volatile Biomarkers for a Valley Fever Breath Test

Coccidioidomycosis, or Valley Fever, is highly prevalent in Arizona, with more than 12,000 new human infections diagnosed every year. In Phoenix and Tucson, up to 30% of community-acquired pneumonias may be caused by Valley Fever, and with growing populations in Arizona, Valley Fever cases are expected to climb. The current diagnostics for Valley Fever are severely lacking due to poor sensitivity (serology) and invasiveness (biopsy). The lack of a suitable diagnostic strongly contributes to an unacceptable 23 day median time-to-diagnosis. There is a critical need for sensitive and non-invasive diagnostics for detecting and identifying Valley Fever lung infections. Our long-term goal is to substantially shorten the time -to-diagnosis for Valley Fever through the development of a breath test. In this project, we are working to identify and validate putative volatile biomarkers of Valley Fever infections via metabolomics analyses of lab-grown cultures, mouse model lung infections, and lung specimens from humans with Valley Fever. After completing this study, our next step will be to validate the volatile biomarkers in the breath of humans with Valley Fever.

Frank Duca, Ph.D.

University of Arizona

Project Title: Role of the Small Intestine in the Prebiotic Treatment for Obesity

Obesity has reached epidemic levels, with Arizona exhibiting the largest increase in the amount of overweight or obese people over the past 20 years. Obesity is associated with an aberrant gut microbiota, defined as all the microorganisms, mainly bacteria, residing in the gut. Therefore, targeting this microbial dysbiosis could prove an efficacious treatment for obesity. One of the more promising dietary interventions to normalize gut microbiota is the consumption of non-digestible carbohydrates called prebiotics, which reduces body weight, food intake and hunger. Despite the therapeutic potential, the precise mechanisms upon which prebiotics contribute to a reduction in food intake and body weight remains poorly understood. We hypothesize that prebiotics alter small intestinal nutrient-sensing pathways controlling food intake via beneficial alterations in the small intestinal microbiota. Herein we propose 3 Aims focused on determining the role of small intestinal nutrient sensing in mediating the beneficial effects of prebiotics, demonstrating the impact of altered small intestinal microbiota in this effect, and identifying unique changes in the small intestinal microbiota and metabolites following prebiotics. A better knowledge of prebiotic-induced changes in microbe-host crosstalk could uncover novel, gut-targeted therapeutics to better treat obesity.

Delrae Eckman, Ph.D.

Northern Arizona University

Project Title: Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice

The number of Alzheimer's disease (AD) patients continues to grow and this number is predicted to climb by greater than 50% by the year 2025. A better understanding of the risk factors and pathogenesis of this devastating disease would provide the potential to greatly impact the health of many people. AD is well known to be associated with accumulation of amyloid plaques and neurofibrillary tangles, but the greatest genetic risk factor for the development of non-familial AD is carrying a variant of apolipoprotein E (APOE). Three isoforms of APOE have been identified in humans: ε2, ε3, and ε4 (APOE2, APOE3, and APOE4). Epidemiological studies have demonstrated that human carriers of APOE4 alleles are at increased risk for AD. Individuals with AD have an APOE4 prevalence of 40% (compared to the 14% in the overall population) and APOE4 prevalence is about four times higher in individuals with mild cognitive impairment (MCI). Based on these findings, a mouse model using targeted-replacement (TR) of the murine APOE with human APOE3 or APOE4 was developed providing an excellent model system for exploring the role of APOE4 in the pathogenesis of AD. The development of AD has been linked to vascular dysfunction in several clinical studies, and in humans APOE4 is associated with increased plasma cholesterol and a greater risk of coronary artery disease. However, the interaction of APOE4 and vascular dysfunction in the pathogenesis of AD has not yet been explored. Thus in our project, we will assess the relationship between cardiovascular function, cerebrovascular function, and cognitive status throughout the lifespan of APOE2, APOE3 and APOE4 targeted replacement mice. To address the aims of this study we have established a multidisciplinary team consisting of research and clinical faculty from Biomedical Sciences, Clinical Psychology, Anatomy, and Physiology. We feel this multidisciplinary approach will provide novel insights into early pathogenic processes underlying the increased AD risk of APOE4 carriers. Ultimately, it is our hope that these rodent studies will help to identify novel clinical metrics, biomarkers, and therapeutic approaches for early detection and effective treatment of AD in humans.

NEW INVESTIGATOR AWARDS

$75,000 per year for three years

Rizal Hariadi, Ph.D.

Arizona State University

Project Title: An Ultra-sensitive and Low-cost Diagnostic for Valley Fever

Valley Fever (VF) is a disease caused by a fungal infection that occurs mainly in dry desert areas of Arizona and Central California. In 2015, nearly two-thirds of the Valley Fever cases nationwide originated in Arizona, and upwards of $50 million dollars in hospitalization charges were reportedly spent by Arizona residents. Its vague symptoms, high time-to-diagnosis of five months, and empirically expensive diagnosis/treatment make access to a reliable and cheap early-detection platform paramount.

In this proposal, we aim to employ our patent-pending biomarker detection array as a low-cost digital diagnostic technology for Valley Fever without complex microfluidic devices, bulky microscopes, or PCR machines. The proposed diagnostic tool is expected to rival the sensitivity of droplet digital PCR (1 molecule in 10 μL of sample). Digital diagnostics, such as the one proposed here, measure biomarker concentration by counting individual molecules instead of merely monitoring bulk changes in colorimetric and fluorescence intensity. At single (biomarker) molecule resolution, the proposed assay will be 100–1000 times more sensitive than traditional antibody assays. We have calculated that our biomarker nanoarray can be made at below $1 per chip and expect our on-chip digital assay for VF with sub-femtoMolar sensitivity to be priced at <$10/ test.

Crystal Hepp, Ph.D.

Northern Arizona University

Project Title: Deciphering the Establishment and Circulation of West Nile Virus and Other Arboviruses of Maricopa County

West Nile Virus is the most important arbovirus circulating in the United States, causing 95% of all arbovirus infections. The virus has reliably been detected in Maricopa County each year since 2003 when it was first detected in a sparrow. From 1999-2016, there have been 1,617 infections throughout the state of Arizona, and of these, 963 cases have resulted in severe neuroinvasive disease. A second virus, which only impacted Arizonans in 2015, is St. Louis Encephalitis Virus. The CDC reports that from 2007-2016, Arizona has had the highest number of cases (n=24) and neuroinvasive disease cases (n=19) in the United States. Despite the resurgence of both of these viruses, and the potential for other pathogens circulating in the same vectors, little is known about how the viruses are being imported into Maricopa County or how they are circulating. The overarching goals of this proposal are to determine 1) how different strains of WNV and SLEV are entering and circulating throughout Maricopa County, and 2) if additional pathogens are also circulating within the same vector populations. Achieving these goals will allow for development of additional intervention strategies prospectively targeting source populations, as well as new surveillance strategies that will target any additional pathogens circulating in Maricopa County.

Ye Hu, Ph.D.

Arizona State University

Project Title: Early Diagnosis of Pancreatic Cancer by Nanoplasmonic Detection of Tumor-derived Extracellular Vesicles

Extracellular vesicles (EVs) are of great interest as diagnostic biomarkers, as they are enriched in factors that may indicate disease stage and treatment response, but most current EV assays are impractical for clinical use. We have developed

a rapid, sensitive and inexpensive nanoplasmon-enhanced scattering (nPES) assay that can directly quantify disease-specific EVs in ≥1 μL of plasma. In this assay, dual binding of antigen-conjugated gold nanospheres (disease-specific)

and nanorods (EV-specific) to serum EVs produces a nanoplasmon that permits sensitive and specific detection of disease-specific EVs. An nPES assay performed with the tumor marker EphA2 distinguished pancreatic cancer (PC) patients from pancreatitis patients with high specificity and sensitivity, and was informative in staging tumor progression and detecting early response to neoadjuvant therapy, markedly outperforming the alternate assay. We propose that our nPES assay represents a sensitive and minimally invasive diagnostic for early PC cases. We thus plan to optimize this assay for rapid, accurate and highthroughput early PC diagnosis. In the proposed study, we aim to: 1) Develop and validate an automated nPES assay for PC diagnosis; 2) conduct extensive clinical validation of this assay in well-characterized cohorts; and 3) develop and validate a quantitative prediction model for treatment outcomes.

Tally Largent-Milnes, Ph.D.

University of Arizona

Project Title: NHE1 at the Blood Brain Barrier: Implications for Anti-Migraine Therapy

Migraine is one of the most common neurological disorders affecting 14.2% of US adults; in Arizona that accounts for nearly 955,000 patients across racial, economic, and educational divides. Overall, migraine is an~ 10-billion-dollar burden for Arizonans. Overcoming the blood brain barrier BBB and the neurovascular unit (NVU) is a major obstacle in the development of drugs that target the CNS. Our pilot studies utilizing an *in vivo* animal behavioral model of migraine showed periorbital tactile sensitivity, a clinical symptom of migraine, was significantly increased in female versus male subjects. BBB paracellular transport of antimigraine drugs was transiently enhanced in these animals.

Recently, the Na^+/H^+ exchangers (NHEs) membrane solute carriers that regulate intracellular pH/Na^+ homeostasis were implicated in migraine pathophysiology. The dominant isoforms on cells comprising the NVU are NHE1 and NHE2. Our preliminary data suggest that dysregulation of NHE (NHE1) expression and function at the BBB/NVU significantly changes active blood-to-CNS uptake of the anti-migraine agent, sumatriptan. Moreover, we found that loss of NHE1 inhibits paracellular permeability to the marker sucrose. Together these data suggest that NHE1 on cells of the NVU regulate transport of both drugs and nutrients to the brain during migrainous events. Cells of the CNS/NVU differentially contributes to BBB integrity in response to cortical spreading depression and sex steroid treatment. We continue to investigate the underlying sex differences and implications for NHE dysregulation at the BBB/NVU in the pathophysiology of migraine.

8 publications

NEW INVESTIGATOR AWARDS

$75,000 per year for three years

Zachary Lerner, Ph.D.

Northern Arizona University

Project Title: Wearable Robotic Assistance to Improve Walking Economy and Mobility for Arizona's Children with Cerebral Palsy

Cerebral palsy (CP) is the most common cause of pediatric physical disability in Arizona and the U.S., affecting ~4 per 1000 children. CP results in pathological gait patterns that lead to severely reduced levels of physical activity and many secondary health issues. Sadly, children with CP in Arizona's rural and urban areas alike lack the basic treatment needed to prevent the ambulatory decline that results in the inability to walk in adulthood. Through research on wearable devices that can provide home-based gait training and mobility assistance, this proposal aims to lessen the life-long suffering and economic burden placed on many families.

The overarching goal of our research is to improve the ability of children with gait disorders to walk independently and accumulate adequate levels of daily physical activity. To meet this goal, our proposal seeks to evaluate the benefits of powered lower-extremity assistance on rehabilitation (Aim 1) and mobility (Aim 2) related outcomes. Our central hypothesis is that repeated walking with powered knee and ankle assistance will help re-train the neuromuscular system to achieve a more efficient gait pattern, and that battery-powered exoskeleton assistance can improve walking performance in real-world settings. We have two aims:

Aim 1: To determine how repeated training with knee and ankle assistance from a wearable exoskeleton affects walking economy, neuromuscular control, and gait mechanics in children with CP.

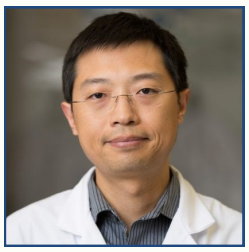
Aim 2: To evaluate the mobility-related benefit of battery-powered knee and ankle assistance on walking speed and metabolic cost of transport for children with CP in real-world settings.

Mary Lind, Ph.D.

St. Joseph's Hospital and Medical Center

Project Title: Rapid Detection of Acute Kidney Injury (AKI) in Hospitalized Patients

Truly early diagnosis of acute kidney injury (AKI) in a hospitalized patient, an event without symptoms or signs, is impossible with current medical technology. AKI results in poor long term health outcomes, increases mortality, and annually impacts ~167,000 patients in Arizona. Our team is performing studies to validate a new urine biomarker of AKI as well as develop a non-invasive diagnostic device for recognition of acute kidney distress prior to permanent kidney injury or damage. Our goal is ambitious. If successful, implementation of our device will change a prevailing clinical practice paradigm for kidney monitoring.



Qiang Liu, MD, Ph.D.

St. Joseph's Hospital and Medical Center

Project Title: Selective S1PR Modulation in Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is the most severe type of stroke without effective treatment. The inflammatory response following ICH amplifies blood-brain barrier (BBB) disruption and brain edema by secreting proteases and reactive oxygen species from brain-infiltrating lymphocytes. Therefore, reducing brain inflammation would be a promising remedy for ICH. Sphingosine 1-phosphate receptor (S1PR) modulators can prevent the egress of lymphocytes from lymphoid organs and reduce the infiltration of lymphocytes into ICH brain. However, the use of S1PR modulators is associated with bradycardia induced by activating S1PR3, limiting its use in ICH patients that often carry cardiac comorbidities. In this study, we will use a new S1PR1 modulator RP101075 with reduced bradycardia effect to test the effect of selective S1PR1 modulation on hemorrhagic brain edema and neurological outcome following experimental ICH in mice. The outcome of this project will be crucial to understand whether and how immune modulation could benefit ICH victims.

Mehdi Nikkhah, Ph.D.

Arizona State University

Project Title: Next Generation of Scaffold-Free, Electrically Conductive, Vasculogenic Micro-Tissues for Myocardial Replacement Therapy

Cardiovascular diseases, including myocardial infarction (MI), remain the leading cause of mortality worldwide. About 5 million people in the U.S. are diagnosed with heart failure, and almost half of them will die within 5 years of diagnosis. Each year, about 3,000 patients are on a wait list to receive a heart transplant. Cell-based myocardial replacement therapies (MRT) and scaffold-based tissue engineering have been promising alternatives for regeneration of infarcted myocardium. However, their clinical use has been hampered by poor cellular survival and retention, inefficient cell-cell coupling and lack of vascularization to from new blood vessel. To address these critical limitations, in this project we aim to leverage our expertise in regenerative medicine and biomaterials to develop a next generation state-of-the-art microengineered cardiac tissues to replenish injured myocardium upon MI. Our research design is founded on a novel multi-fold strategy utilizing human induced pluripotent stem cell derived cardiomyocytes, Microscale tissue engineering as well as Mechanistic in vitro studies paired with in vivo functional assessments. The proposed study is a key step toward the development of personalized MRT, potentially improving the care of thousands of critically ill patients who are suffering from HF in the US and specifically in the state of Arizona.

George Noutsios, Ph.D.

Arizona State University

Project Title: Surfactant Protein A as a New Therapeutic in Cinusitis

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease of the sinus mucosa affecting Arizonans of all ages with staggering health costs. The sinonasal epithelium (SNE) is the physical barrier between the environmental insults and the respiratory system and has immunological functions. Therefore, it is the frontline defense mechanism of the whole respiratory system. Surfactant protein A (SP-A) is a critical innate immune molecule secreted by the airway epithelia and can directly eliminate bacteria. Our data show that SP-A is expressed in the SNE and its levels are significantly changed in bacterial infections, suggesting a role in sinus innate immunity. We hypothesize that SP-A plays a role in susceptibility to CRS and its exogenous administration positively affects CRS. We are using experimental plans that include definition of SP-A role in CRS, identification of endogenous and exogenous factors which come together in a different extent and determine CRS. We will determine the effects of exogenous SP-A in CRS and whether it helps resolve sinusitis. We have tissues from healthy and CRS patients, SP-A humanized transgenic mice and recombinant SP-A to conduct the proposed in vitro and in vivo studies. The use of SP-A as an agent to ameliorate the innate immune responses in the CRS is a new concept and is likely to lead to new horizons in CRS therapeutic regimens.

Panagiotis Polygerninos, Ph.D.

Arizona State University

Project Title: Improving Lower-limb Rehabilitation and Assistance with a Soft Robotic Exosuit

For this award, we will develop a novel, soft robotic exosuit to provide advanced rehabilitation therapy to lower-limb impaired Arizonans. Utilizing the advantages of soft robotics, such as compliance, high power-to-weight ratios, and low fabrication costs, pneumatically driven soft actuators will be employed to provide lower-limb joint support. Compared to rigid rehabilitation exoskeletons, which are bulky, heavy, and difficult to align with joints, the proposed undergarment design will enable synergetic biomechanical assistance with a number of active components that can be disengaged to ensure that the system is functionally transparent to the wearer when needed. In its active state, the soft suit can alter its stiffness to provide joint support, enabling gait training, and strengthening exercises. Such design

will also allow the therapist to control the level of assistance utilizing wearable sensors that measure and record the interactions between the patient and the environment. Through this study we aim to provide preliminary evidence to support our hypothesis that soft robotic technology can be used in wearables to offer improved rehabilitation exercises and assistance in activities of daily living. Feasibility will be demonstrated through the enhancement of collaborations, the recruitment of impaired participants in a pilot study, and by dissemination of our findings.

NEW INVESTIGATOR AWARDS

$75,000 per year for three years

John Purdy, Ph.D.

University of Arizona

Project Title: Targeting Host Metabolism during Infection of Two Diverse Viruses

Enveloped viruses are responsible for devastating acute (e.g. Ebola, Zika), sustained (e.g. influenza, Dengue) and chronic (e.g. herpesviruses, HIV) infections. Although they are diverse, all enveloped viruses 'steal' host lipids to make their envelope, providing a unifying weakness we can target. Blocking these viruses from hijacking lipid metabolism and stealing lipids will stop infection. First, however, we must understand how infection alters lipid metabolism. Unfortunately, little is known how viruses hijack lipid metabolism. Our long×term goal is to fill this knowledge gap to aid developing therapies for enveloped viruses by targeting metabolic pathways. We study two unrelated enveloped viruses—human cytomegalovirus (HCMV) and Zika virus (ZIKV) to broadly identify potential antiviral targets. HCMV infects most people and can cause life×threatening diseases in some, including newborns. ZIKV also causes birth defects. To accomplish our objective, we will test the central hypothesis that that enzymes in lipid metabolism are required for HCMV and ZIKV infection, providing targets for broad antiviral treatments. Our work will address the urgent need to limit the negative impact on human health from emerging and established viruses.

Barbara Smith, Ph.D.

Arizona Sate University

Project Title: Early Detection of Ovarian Cancer by Olfactory Biomarkers

Ovarian cancer is a highly aggressive disease and the deadliest of all gynecologic cancers that leads to death in approximately 60% of the affected women. This silent disease has a rapid progression, resulting in the advanced stage diagnosis for over 70% of patients. Early stage diagnosis of ovarian cancer is directly associated with drastically improved prognosis (stage I: 90%, stage IV: 17%). Despite efforts, no method currently exists for accurately diagnosing ovarian cancer in the early stages of the disease. As the impact of this disease becomes more imminent within Arizona, better diagnostic tools are required to identify biomarkers to screen individuals for early stage ovarian cancer. This research project involves monitoring the growth of ovarian cancer within a 3D tissue model, to enable real time measurement of volatile signatures as they relate to early stage ovarian cancer. The goal of this project is to develop a system for the identification of volatile biomarkers to develop a real-time screening tool for ovarian cancer.

NEW INVESTIGATOR AWARDS

$75,000 per year for three years

John Streicher, Ph.D.

University of Arizona

Project Title: Spinal Cord Heat Shock Protein 90: A New Target for Opioid Dose-Reduction

Prescription opioids used to manage pain are a significant source of addiction and overdose, which has increased 74% since 2012 in Arizona. In our work, we've shown that Heat shock protein 90 (Hsp90) regulates opioid signaling differently in the brain vs. spinal cord, and that Hsp90 inhibitor applied to the spinal cord strongly promotes analgesia. We further show that low dose morphine combined with spinal Hsp90 inhibitor produces analgesia equal to a high dose of morphine, without increased side effects. Our data thus suggests that Hsp90 inhibitor therapy could be used to reduce the dose of opioid needed to manage pain, while also reducing side effects like addiction. We will test this hypothesis by measuring the equi-efficacious doses of morphine in acute, post-surgical, and HIV neuropathic pain with and without spinal Hsp90 inhibitor. We will then use this dose of morphine combined with spinal inhibitor in side effect assays of dependence, constipation, and addiction risk, which we expect to be reduced. Lastly, we will test the effects of Hsp90 inhibitor infusion into the spinal cord on toxicity and neuroinflammation, which will begin to establish a safety profile for Hsp90 inhibitor therapy. These results may provide the basis for Hsp90 inhibitor therapy in patients to reduce opioid dosing, side effects, and addiction, leading to long term health benefits for Arizonans.

Rebecca Vanderpool, Ph.D.

University of Arizona

Project Title: Diagnostic and Progressive Markers of RV Failure in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a fatal and progressive disease with no cure. Right ventricular (RV) failure is the main cause of mortality but specific approaches quantifying RV function are needed. RV function in Hispanics in the US is largely unknown; however, at the University of Arizona (UA), a major regional referral center for treatment of PAH, Hispanics constitute 25-50% of patients whose severity is greater than non-Hispanics. By leveraging the UA PH Registry of >400 patients, we will systematically characterize hemodynamic and molecular markers of RV failure and use those markers to identify PAH patients, especially Hispanics (18%), in need of more effective therapies. 1.

Goals and Objectives: The goal of this study is to investigate the role of prolyl hydroxylase domain protein 2 (PHD2) and Hypoxia-inducible factor 2α (HIF-2α) in RV failure and develop progressive markers of RV failure in patients with PH. We hypothesize that the level of endothelial HIF-2α determines hemodynamic severity of PH and associates with RV failure.

Aim 1: To examine whether EC-specific knockdown of PHD2 promotes RV failure in mice with experimental PH. We will determine whether endothelial HIF-2α plays a critical pathogenic role in the development of RV failure.

Aim 2: To identify a novel progressive marker of RV failure in patients with PAH. Predicting progression from RV dysfunction to failure remains challenging but RV diastolic stiffness is a potential novel hemodynamic marker.

Jun Wang, Ph.D.

University of Arizona

Project Title: Discovery of Broad-spectrum Influenza Antivirals to Combat Influenza Epidemics and Pandemics

Influenza viruses pose a persistent threat to global public health. Despite the existence of influenza vaccines and antiviral drugs, each seasonal influenza epidemic claims an estimated 250,000–500,000 lives worldwide. Oseltamivir (Tamiflu®) is currently the only FDA-approved oral influenza drug, but it has a narrow therapeutic window and needs to be taken within 48 h after the onset of symptoms. Moreover, the number of oseltamivir-resistant influenza strains continues to increase. Accordingly, a continuing and urgent need for the development of new therapeutic agents exists. The current proposal aims to develop a new and effective influenza antiviral by targeting the viral polymerase subunit PA–PB1 interactions. The influenza polymerase is essential for viral replication and is highly conserved among influenza A and B viruses. Using structure-based drug design, we have identified several PA-PB1 inhibitors with broad-spectrum antiviral activity. Furthermore, viruses could not easily mutate to develop resistance to PA-PB1 inhibitors. Following this discovery, we propose to: (1) optimize the antiviral potency, selectivity index, and in vitro pharmacokinetic properties of PA-PB1 inhibitors, and (2) test the in vivo antiviral efficacy of PA–PB1 inhibitors in influenza-infected mouse model studies. Successful execution of this project will lead to a preclinical antiviral candidate that is ready for comprehensive pharmacokinetic and pharmacological studies before filing an investigational new drug application.

Benjamin Wright, Ph.D.

Mayo Clinic

Project Title: Linking Food Allergy and Eosinophilic Esophagitis: The Role of IgG4 in EoE Pathogenesis

Eosinophilic esophagitis (EoE) is a chronic allergic condition of the esophagus characterized by eosinophilic inflammation. For unclear reasons, it has increased over 20-fold in recent decades. Treatments include high dose antacids, swallowed steroids and extensive elimination diets. Moreover, it can only be diagnosed by an invasive procedure – endoscopic biopsy. In healthy individuals, the squamous epithelium forms a physical barrier to food and microbes; however, in EoE, this barrier is disrupted allowing penetration of food proteins. In the susceptible allergic host, this provokes an immunologic response associated with Type 2 inflammation including marked eosinophilia. Left unchecked, eosinophils eventually promote tissue remodeling and fibrosis, which accounts for clinical symptoms of dysphagia and food impaction. Recent evidence suggests that unlike food allergy, EoE is not IgE-mediated, but is associated with IgG4. Staining for IgG4 in EoE biopsies suggest it is produced by IgG4 secreting plasma cells within the submucosa and deposits of IgG4 layer across the surface of the epithelium. This observation has led us to investigate the role of IgG4 in a biochemical barrier that until now has been almost totally neglected in EoE research – the esophageal mucin layer.

Our *central hypothesis* is that persistent food antigen-exposure in EoE drives muco-protective responses resulting in the production of food-specific IgG4 (FS-IgG4). The *rationale* for the proposed research is that FS-IgG4 production in EoE may be a protective response to food antigen exposure that represents an attempt to restore epithelial barrier integrity in EoE. The objectives of this proposal will test our central hypothesis by the completion of the following *specific aims*: **1. To characterize the esophageal mucin layer in EoE subjects vs. controls. 2. To compare FS-IgG4 levels to common EoE food triggers (milk, wheat and egg) in saliva, throat swabs and esophageal homogenates from EoE subjects and controls. 3. To determine the muco-protective effects of IgG4 *ex vivo*.** This research may have a dramatic and *positive impact* on the care of patients with EoE, as disruption of the esophageal mucin layer may be amenable to targeted therapies.

Katherine Ellingson, Ph.D.

University of Arizona

Project Title: Antibiotic Stewardship in Arizona Skilled Nursing Facilities

Despite evidence that antibiotic resistance is reaching crisis levels, inappropriate antibiotic prescribing persists across a range of healthcare settings, including Arizona's 146 skilled nursing facilities (SNFs). Overconsumption of antibiotics by SNF residents diminishes quality of life by increasing the risks of Clostridium difficile infection, acquisition of antibiotic-resistant bacteria, and adverse drug reactions. Yet up to 75% of antibiotic prescriptions in SNFs are unnecessary. New federal regulations require SNFs to have an antibiotic stewardship program (ASP) in place by November of 2017, but in a recent survey, only a quarter of Arizona SNFs reported any preparation for ASP implementation. We piloted an ASP protocol in two Arizona LTCFs that included technical assistance with data collection, use of standardized infection definitions to guide prescribing, administrative engagement, education and quarterly feedback of ASP metrics – we found >50% reductions in antibiotic use and adverse events. We aim to expand and rigorously evaluate implementation of this protocol in 16 Arizona SNFs – including four facilities in rural or border regions of Arizona – by determining intervention-attributable decreases in antibiotic use, C. difficile and cost. Findings will contribute to an emerging body of ASP implementation research and guide future expansion of ASPs to SNFs statewide.

David Engelthaller, Ph.D.

Translational Genomics Research Institute

Project Title: Understanding Invasive Group A Strep in Arizona

Group A Streptococcus (GAS), or Streptococcus pyogenes, may result in invasive, sometimes fatal, illnesses, including necrotizing fasciitis (otherwise knows as flesh-eating bacteria). GAS strains vary and can cause low level background disease or local and even nationwide outbreaks, and some strain types are more virulent than others. Invasive GAS (iGAS) is an increasing health threat in Arizona, in particular to high-risk populations (e.g., Native Americans). Through a multi-disciplinary collaboration of public health, clinical, and infectious disease scientists, we have previously shown that the use of applied genomics can substantially increase the ability to detect and characterize iGAS clusters in hospitals and the emergence of new strains in the community. For example, the GAS strain known as emm59 is highly virulent and recently emerged in Arizona, causing a significant outbreak of iGAS in Northern Arizona, predominantly within Native America populations. The detection and characterization of the emerging emm59 strain in Arizona was only possible through the use of whole genome sequencing and phylogenetic analyses. This ABRC-funded project allows us to advance the concept of next generation public health science (including genomic epidemiology and novel virulence surveillance) to affect the growing impact of iGAS on high-risk populations and on overall health care costs. Our primary goal here is to conduct translational research on iGAS in Arizona through a study of epidemiologic, genomic, and clinical factors that lead to the establishment and spread of new virulent subtypes of GAS in the region. The outcomes of this study will include: 1) an evolutionary and epidemiologic understanding of GAS in Arizona populations; 2) a model genomic surveillance system to rapidly detect and respond to GAS outbreaks; and 3) new laboratory tools (e.g. genotyping and virulence assays) for local iGAS characterization. Beyond these specific outcomes, this project is providing a foundation for statewide genomic surveillance for all pathogens of interest to public health and clinical medicine.

Paul Keim, M.D. Ph.D.

Northern Arizona University

Project Title: Discovery of Coccidioides Epitopes that Stimulate Adaptive T-cell Responses for Diagnostic Assay Development

There is a lack of robust diagnostic assays to monitor the adaptive cellular immune response (e.g., activated T cells) against Coccidioides infection. In addition, we lack understanding of specific protective T cell responses that occur during coccidioidomycosis (CM). To address these important questions, we will identify the Coccidioides proteomic peptide epitopes that are recognized by specific T-cells during infection and vaccination. We will use these epitopes to develop a T cell diagnostic ELISPOT assay, similar to the FDA-approved tuberculosis ELISPOT assays and the recently developed Lyme ELISPOT assay (1). These diagnostic assays can indirectly detect both tuberculosis and Lyme disease with a higher sensitivity and specificity than serological assays. The discovery of T cell epitopes for the assay will be accomplished using a novel liquid multiplexed peptide array technology (PepSeq). PepSeq arrays couple tens of thousands of peptides to unique DNA tags that are then read and counted using Next-Gen DNA sequencing. A single PepSeq assay can evaluate thousands of potential Coccidioides T cell epitopes per major histocompatibility (MHC) class II allotype in a single screen. In comparison, previous approaches only evaluate a single MHC bound peptide at a time. A large PepSeq array representing the Coccidioides proteome will be used to identify sequences that bind across a panel of mouse and human HLA proteins and so have the potential for immunogenicity. The resulting shortlist of peptides will then be used to design a focused panel of ELISPOT assays to identify T cell responses that arise during murine Coccidioides vaccination and challenge. Finally, the most promising assays will be combined and evaluated for diagnostic performance (sensitivity and specificity). This work will improve ability to diagnose infection, evaluate current proposed and future potential vaccines, and aid in quicker treatment for CM patients in the Arizona community.

Kenneth Knox, Ph.D.

University of Arizona

Project Title: A Novel Ex-Vivo Leaf-Lung Model to Study Pulmonary Diseases

The lung is a highly sophisticated organ responsible for protection against airborne toxins, immunity against pulmonary pathogens and efficient gas exchange. Because of this complexity, lungs are the most difficult to transplant with the worst prognosis compared to other organs. As such, there is a desperate need for more sophisticated ex-vivo models of lung diseases to advance our knowledge. We are now using a decellularized spinach leaf to simulate the lung micro-environment. Human lung epithelial cells and vascular endothelial cells are cultured on and within the leaf scaffolding to make the lining of an air sac. The proposed "Lung on a Leaf" model will provide a platform to study cell-cell interactions in a 3-D context, will be widely applicable to the study of inflammatory and fibrotic lung diseases (sarcoidosis, pulmonary fibrosis, Valley Fever) and has the capacity to accelerate testing of therapeutic molecules in a biologically relevant system.

Carlo Maley, M.D. Ph.D.

Arizona State University

Project Title: Pilot Trial of Adaptive Therapy for Late Stage Breast Cancer

Most therapies for metastatic cancer fail because some mutant cells in the tumors are resistant to the therapy. Based on pest management principles from agriculture, we have developed "adaptive therapy" in which we adjust the dose of a cancer drug in order to keep some sensitive cells that can outcompete resistant cells. The goal is to keep the tumor a stable size and transform cancer from an acute lethal disease to a chronic disease we can live with. In three mouse models and a pilot clinical trial in prostate cancer, we have shown that adaptive therapy can keep control of tumors for much longer than the standard high dose therapy, and requires a lower dose of toxic cancer drugs. In a multi-disciplinary collaboration with ASU, the Mayo Clinic and TGen, we propose the test adaptive therapy for the first time in a pilot clinical trial on metastatic breast cancer. We will also test if circulating tumor DNA can be used to frequently and cheaply monitor the tumor. If we are successful, we will open a larger clinical trial that could have a rapid impact on breast cancer clinical management and mortality, as well as establish Arizona as a leader in this new form of cancer therapy. Adaptive therapy is particularly exciting because it can be used with any drug, on any type of cancer, and so could rapidly change clinical practice without the delays of drug development and FDA approval.

Chad Quarles, Ph.D.

St. Joseph's Hospital and Medical Center

Project Title: Improving Brain Tumor Delineation with Molecular PET Imaging

Conventional MRI methods underestimate brain tumor margins and fail to detect invading tumor cells. Consequently, MRI-guided surgical resections and radiosurgeries fail to target disseminated tumor cells, leading to increased rates of tumor recurrence and poor patient survival. This proposal seeks to overcome this limitation through the use of the PET radiotracer 18F-fluciclovine, which enables the detection of glioma cells that overexpress amino acid transporters. Preliminary studies demonstrate that fluciclovine exhibits high uptake in gliomas and, importantly, in tumor cells found outside contrast enhancing regions on MRI. The goals of our study are to systematically validate the sensitivity of fluciclovine to histologic tumor content in patient derived xenograft models and to compare its uptake to advanced bioimaging MR data in high grade glioma patients. The outcomes of this project are the validation of fluciclovine PET imaging as a biomarker of glioma cell burden, the identification of robust image analysis techniques and the biological characterization of fluciclovine uptake that can inform future clinical interpretation. This study will provide the basis for future clinical trials focused on further validating the ability of fluciclovine to detect whole brain tumor burden, its use to guide and improve response to image-guided neurosurgery and radiotherapy and use a new outcome measure in clinical trials.

Menjamin Renquist, M.D. Ph.D.

University of Arizona

Project Title: Targeting the Cause of Type 2 Diabetes

50% of Arizonans are diabetic or pre-diabetic resulting in $6.4 billion in health care and productivity costs. The severity and incidence of Type 2 Diabetes Mellitus (T2DM) is directly related to the hepatic lipid concentration. The degree of hepatic lipid accumulation is communicated by the hepatic vagal afferent nerve (HVAN) to regulate pancreatic insulin secretion and whole body insulin sensitivity. We have shown that obesity enhances expression of GABA-Transaminase (GABA-T) decreasing hepatic release of the excitatory neurotransmitter, aspartate, and increasing release of the inhibitor neurotransmitter, GABA. This enhanced inhibitory tone decreases hepatic vagal afferent nerve activity, increasing pancreatic insulin release and decreasing skeletal muscle glucose clearance/insulin sensitivity. Pharmacological inhibition of GABA-T robustly improves glucose homeostasis in diet induced obese mice. Two clinical objectives that will test the effect of GABA-T inhibition on glucose tolerance and insulin sensitivity in obese, hyperglycemic, hyperinsulinemic patients, while a basic science objective will focus on identifying the tissue specific response to eliminating GABA-T expression in hepatocytes or pancreatic β-cells. Initial work using an anti-sense oligonucleotide to eliminate GABA-T expression in the liver has established that the improvements in hyperinsulinemia and insulin sensitivity are dependent on hepatic GABA production. These studies test a novel therapy designed to block the cause of T2DM, a predominant health concern for Arizonans.

Sidney Rice, MD

University of Arizona

Project Title: Assessing the Causes, Epidemiology and Under-Diagnosis of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) in Arizonans

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a post-infectious autoimmune disorder resulting from bacterial or viral infections that attack the brain, specifically, the basal ganglia. PANS is characterized by abrupt-onset clinically significant obsessive-compulsive behaviors, food avoidance, and restrictive eating. Children who have untreated PANS experience ongoing brain injury due to untreated brain inflammation and these children are more likely to have ongoing neuropsychiatric symptoms. In contrast, children treated in a timely fashion with low-risk inexpensive interventions return to their previous level of functioning. Children with PANS present with acute onset psychiatric symptoms. However, the medical association of these symptoms with an infection can be overlooked when caring for a child with severe mental illness.

The following project AIMS will be achieved through our Center of Excellence for Post-Infectious Autoimmune Encephalopathy:

1) Prospectively follow diagnosed PANS patients to document symptom remission, health improvement, and PANS exacerbations using immune regulation therapies;
2) Demonstrate the role for the microbiome as an environmental factor contributing the autoimmune neuropsychiatric symptoms; and
3) Educate professionals in Arizona about the PANS condition and support primary care providers to treat these conditions in a timely manner.

Scott Sherman, M.D. Ph.D.

University of Arizona

Project Title: Ketamine, a New Symptomatic Treatment for Parkinson's Disease

Parkinson's disease (PD) is the 2nd most common neurodegenerative disorder. PD treatments are based largely on administration of dopamine replacement drugs such as L-DOPA; however, these treatments have side effects. The most severe side effect is L-DOPA-induced dyskinesia (LID) which, after ~5 years, results in debilitating involuntary movements. The only effective LID treatment is deep-brain stimulation (DBS) surgery. Therefore, non-surgical treatments to limit LID are needed. We have substantial preclinical evidence that low-dose sub-anesthetic ketamine infusion reduces and limits the development of LID, and this evidence is further supported by case studies from PD patients. Since ketamine is a multifunctional ligand and the specific mechanism underlying its therapeutic efficacy in PD is unknown, filling gaps in knowledge of understanding these mechanisms in preclinical studies will be important for further clinical development, and may also facilitate identification of novel improved drug candidates. We hypothesize that ketamine has neuroplastic effects mediated by BDNF (AIM 1). Given the long-established excellent safety profile of ketamine, we also plan a Phase I open-label, dose-finding clinical trial and a placebo controlled Phase II clinical trial to establish ketamine's potential to reduce LID in PD patients (AIM 2), facilitating fast bench-to-bedside translation.

Sarah Stabenfeldt, Ph.D.

Arizona State University

Project Title: Regenerative Rehabilitation for Traumatic Brain Injury

Despite the numerous obstacles that restrict recovery after traumatic brain injury (TBI), many patients can regain motor and cognitive function following injury. This functional recovery is largely attributed to the brain's capacity for compensatory reorganization of residual neural circuits. As such, therapies and intervention strategies that harness neuroplasticity may provide viable and clinically translatable treatments. Our primary objective is to exploit the attributes of neural tissue engineering and rehabilitation therapy by prompting enhanced directed neuroplasticity. Our preliminary studies supported the notion that neural stem cell transplants in combination with motor rehabilitation training, promote functional reorganization of forelimb motor cortex. Therefore, we postulate that coupling neural tissue engineering with rehabilitation therapy (regenerative rehabilitation) will further enhance and direct neuroplasticity toward more significant functional gains following TBI. Our specific aims are to, 1. establish synergistic effect of rehabilitation and neural tissue engineering on cortical plasticity following TBI, and 2. examine the influence of regenerative rehabilitation on host neural circuits and networks. We expect that this study will provide unprecedented insight into regenerative rehabilitation and advance this combination therapy to the clinic.

Todd Vanderah, Ph.D.

University of Arizona

Project Title: Novel Derivatives of Ang-(1 - 7) for the Treatment of Neuropathic and Cancer Pain

There are 100 million chronic pain patients in the US, with estimates for the State of AZ at 2.1 million. For Arizonans, the cost of chronic pain reaches nearly $12.7 billion/year. More than 431 million opioid pills were prescribed in AZ last year to treat pain; that is more than 60 pills for every man, woman and child. Extended opioid use has led to enhanced FDA regulations, and patients resorting to finding opioids on the street giving way to overdose and death. Drug abuse is a leading cause of death in AZ. Two Arizonans died/day from opioid overdoses in 2016.

Opioids have limited efficacy for long-term treatment of chronic pain due to analgesic tolerance/hyperalgesia leading to inadequate pain relief, over-prescription, and addiction.

Angiotensin(1-7) is biologically active in the CNS and shows high selectivity to the Mas receptor (MasR). We have preliminary data that suggest Ang(1-7)/MasR acts on the pain pathways to significantly inhibit chronic pain while not producing unwanted side effects including no addiction and no cardiovascular events. We believe that an alternative strategy to opioid therapy is targeting the MasR. Yet, few reports have investigated the efficacy of Ang(1-7) in clinically relevant preclinical pain models, or after extended exposure to determine retained efficacy. Competed studies will offer a novel drug class with patents rights by the UofA.

ARIZONA DEPARTMENT
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH CENTRE

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