Arizona Department of Health Services

Arizona Biomedical Research Commission



Annual Report 2012–2013

Accelerating Biomedical Research and Innovation in Arizona

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Arizona Biomedical Research Commission

Annual Report: 2012–2013

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Director, Arizona Department of Health Services

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General Public

Kasey L. Benson, Ph.D.

Toni J. Eberhardt, MBA

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

Medical Community

Wade Kartchner, MD

Peter C. Kelly, MD

Mitchell Shub, MD

Scientific Community

David M. Engelthaler, MS

Iman A. Hakim, MBBCh, PhD, MPH

Thomas Lon Owen, PhD

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Executive Summary

Fiscal Year 2013 marks the second year that the Arizona Biomedical Research Commission (ABRC) operated under the Arizona Department of Health Services (ADHS). As a public health entity, ABRC works in conjunction with ADHS to fulfill the "10 Essential Public Health Services." The "10 Essential Public Health Services" provide public health entities a framework of core services when serving their communities. ABRC's mission, "Identify and support innovative biomedical research to improve the health of all Arizonans," falls into one of the core services: "Research for new insights and innovative solutions to health problems." The continued emphasis of supporting research, facilitating policy and building collaboration capacity are paramount in fulfilling ABRC's mission and branding Arizona as a bioscience hub.

Key Highlights for this Year:



We are pleased with the progress made and look toward 2014 in contributing to future successes for Arizona. Everything that the Arizona Biomedical Research Commission has accomplished this year was made possible by the continued support of Agency leadership, the Governor's Office, Legislators, and community partners. This report is prepared and submitted to the Governor, the President of the Senate and the Speaker of the House of Representatives.

Our Mission

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

History

For more than 29 years, the Arizona Biomedical Research Commission (ABRC) has been an integral part in furthering biosciences within Arizona.

ABRC, originally known as the Arizona Disease Control Research Commission, was established in 1984 through the combined efforts of Governor Bruce Babbitt; House Majority Leader Burton Barr; Representative Jack B. Jewett; the director of the University of Arizona Cancer Research Center, Sydney Salmon M.D.; and the director of the Arizona State University Cancer Research Institute, G. Robert Pettit. ABRC was founded to provide funding to Arizonans to conduct research on the causes and cures, medically accepted treatments, and prevention of diseases, including new drug discovery and development.

In 2002 the Flinn Foundation, Arizona's largest foundation supporting medical research, commissioned Battelle to develop the "Arizona's Bioscience Roadmap." In June 2004, the Commission hired Battelle to continue analysis of translational research development work needed in Arizona and to assist the Arizona's Bioscience Roadmap Steering Committee in furthering the goals and recommendations included in the 2002 report.

An outgrowth of that effort has been the Arizona Translational Resource Network (AzTransNet). AzTransNet is an ongoing ABRC initiative to increase Arizona's capacity to facilitate and coordinate translational and clinical research. AzTransNet activities include maintaining a customer relationship database of Arizona researchers, developing and managing technical policy retreats; and addressing critical issues, including Institutional Review Board education, tissue banking, grant writing workshops, and research proposal education. Other continuing activities include community based participatory research, policy analysis and fact sheets on a variety of issues, the establishment of the Arizona Biospecimen Consortium, the Arizona Biospecimen Locator, and the Arizona Public Cord Blood Program.

In 2005, the Arizona Disease Control Research Commission changed its name to the Arizona Biomedical Research Commission. In 2011, under Senate Bill 1615, ABRC was placed under the direction of the Arizona Department of Health Services.

Today, on the eve of its 30th year in service to Arizona, ABRC remains committed to accelerating innovative biomedical research to improve the health of all Arizonans.

The Commissioners

The Commissioners' Role

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

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

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

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

Commissioner Bios—General Public



Kasey L. Benson, Ph.D.

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

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



Toni J. Eberhardt, MBA

Public Relations Director
Banner Medical Group

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

Commissioner Eberhardt began her career in the healthcare industry with McKesson, the largest

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

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



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

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

Commissioner Bios—Medical Community



Wade Kartchner, M.D., M.P.H.
Direct, Navajo County Public Health Services District

Commissioner Wade Kartchner has served as the director of the Navajo County Public Health Services District in Arizona for the past eight years. Prior to that role, he practiced pediatrics in New Mexico and Arizona for thirteen years. He is a graduate of the University of Arizona College of Medicine and trained in pediatrics at the University of California, San Diego. He earned his Master of Public Health degree from the University of Massachusetts, Amherst. He is an adjunct instructor for the Master of Public Health program at Grand Canyon University in Phoenix. He previously served on the Arizona Area Health Education Center State Advisory Board and as a member of the National Association of County and City Health Officials Global Health Workgroup. Aside from the Biomedical Research Commission, Commissioner Kartchner currently sits as a member of the Arizona Child Fatality Review Team. He has been a volunteer Newborn Resuscitation Program instructor in Latin America. His professional interests include the epidemiology of pediatric injury in rural Arizona, public health emergency preparedness issues, and global and travel medicine.



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

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

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

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

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



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

Commissioner Mitchell Shub is a Pediatric Gastroenterologist and received his M.D. from the University of Vermont. He completed a residency in Pediatrics at Duke University Medical Center and a fellowship in Pediatric Gastroenterology at Massachusetts General Hospital and Harvard Medical School. After serving on the faculty at the University of North Carolina, Chapel Hill, he joined the full time faculty at Phoenix Children's Hospital (PCH). He previously served as Co-director of the Pediatric Residency Program and as Division Chief of Gastroenterology. Commissioner Shub was elected President of the Medical Staff and served a 2 year term and was appointed as the first Medical Director of Research at PCH.

Commissioner Shub is Vice-chair and Professor, Department of Child Health for the University of Arizona College of Medicine, Phoenix. He has been actively engaged in research throughout his career and recently was part of a team that identified the gene mutation for a rare digestive disorder, microvillous inclusion disease. On a national level, Commissioner Shub has been appointed to various leadership positions in the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. He also served as the Chairman of the Medical Advisory Committee for the Southwest Chapter of the Crohn and Colitis Foundation of America and was honored with the Chapter's "Physician of the Year Award".

Commissioner Bios—Scientific Community



David M. Engelthaler, M.S.
Director of Programs and Operations
TGen North

Commissioner David Engelthaler is the Director of Programs and Operations at TGen North in Flagstaff, AZ, part of the non-profit Translational Genomics Research Institute. Besides directing the day-to-day operations at TGen North, Commissioner Engelthaler oversees a number of research groups working on developing tools to detect and analyze infectious diseases such as influenza, valley fever, MRSA, cholera, plague, anthrax and others. He is also the co-founder of PathoGene LLC, a for-profit company, developed to transform mid-to-late stage diagnostic intellectual property into market-ready assays.

Commissioner Engelthaler was previously the Arizona State Epidemiologist and the Arizona Biodefense Coordinator. He has over twenty years' experience in public health related research, including ten years with the Arizona Department of Health Services and three years with the Centers for Disease Control and Prevention working with such diseases as plague and tularemia.

Commissioner Engelthaler earned his undergraduate in Biology at Northern Arizona University and has a Master's Degree in Microbiology from Colorado State University. He currently teaches classes on infectious diseases and epidemiology at NAU, where he holds a research faculty position. In addition to the Arizona Biomedical Research Commission, Commissioner Engelthaler sits on a number of non-profit boards and committees in Arizona.



Iman A. Hakim, MBBCh, Ph.D., MPH
Dean, Mel & Enid Zuckerman College of Public Health
University of Arizona

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

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



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

Commissioner T. Lon Owen received his B.A. in Zoology from the University of California, a Master's Degree in Biology from California State University at Sacramento, and his Ph.D. in Physiology from University of California-Davis. He was a National Institutes of Health Postdoctoral Fellow at Michigan State University and visiting associate professor in the Pharmacology Department of the University of Arizona College of Medicine.

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

Commission Meetings

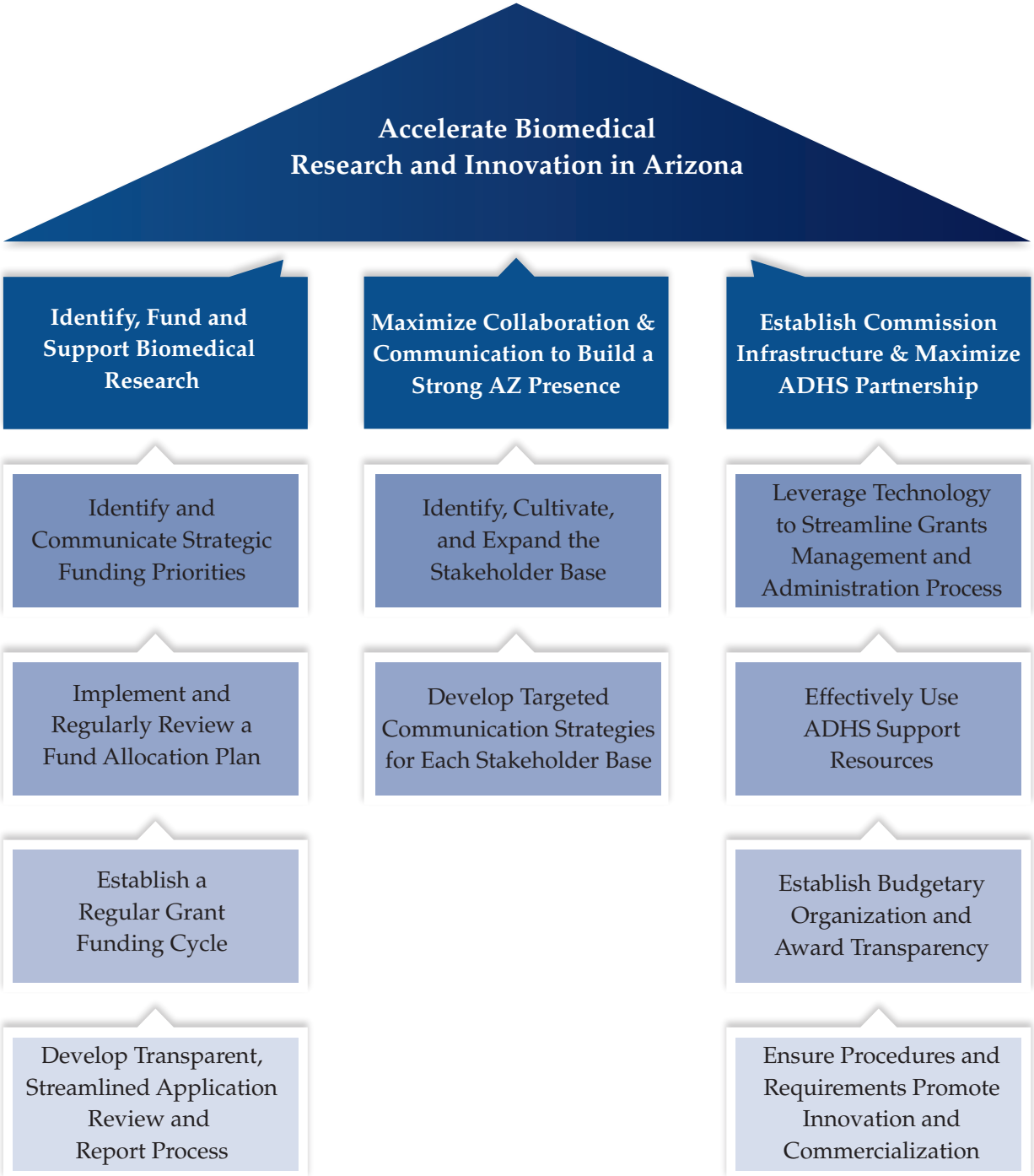
A.R.S. §36-272(E) states that the Commission shall meet at least quarterly at the call of the chairperson. Since July 1, 2012, the Commission met a total of ten (10) times to elect the Commission Chair and Co-Chair, review existing projects, assess the Commission's strengths, review areas for improvement, and identify critical public health issues that may impact basic, translational, and clinical research. Equipped with this information, the Commissioners focused 2012–2013 on setting the Commission's future direction. Activities included drafting and finalizing ABRC's Mission Statement and Strategic Map; developing key strategic priorities; and determining funding categories as well as application format and timetables.

Meeting Date	Meeting Highlights
July 12, 2012	Chair & Vice Chair Elected Open Meeting Law Training
December 5, 2012	Introduction of Executive Director Development of Strategic Planning
February 12, 2013	Letter of Support Issued by Commissioners on Behalf of the Biospecimen Locator to Pursue NIH Grant Application for Tissue Bank
February 21, 2013	ABRC Strategic Map Approved
April 12, 2013	April Guest Presentation—Arizona Alzheimer's Consortium
May 10, 2013	Commissioner Appointment to the Biospecimen Advisory Board
August 15, 2013	Patent Portfolio Transfer Begins Recommendation to Extend Biospecimen Locator Program, Cord Blood Program, and Education Program
September 10, 2013	Funding Categories Established
December 12, 2013	Introduction of Two Newly Appointed Public Member Commissioners 2014 Regular-Quarterly Meeting Schedule Established

Strategic Map

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

Arizona Biomedical Research Commission (ABRC) Strategic Map: 2013–2016



ABRC Funding Categories

The Commissioners established three new categories for funding. These categories help ABRC identify innovative biomedical research designed to improve the health of all Arizonans. They are specifically designed to prepare awardees for an improved likelihood of success in achieving continued funding from a larger national source such as National Institutes of Health or the American Heart Association.

The Three New Categories Are:

Arizona Biomedical Early Stage Investigator Award ("AZ ESI")

Designed with the Arizona Biosciences Roadmap in mind, the Arizona Biomedical Early Stage Investigator Award is established to help a new investigator generate the preliminary data necessary to apply for a larger national grant. The investigator should be within ten years of their terminal degree or residency, shall not have received a prior ABRC Basic Science Award, and shall collaborate with a senior mentor who is able to demonstrate the ability to receive past national funding success. Collaboration with a senior mentor will help support early investigators and will incentivize them to establish their careers in Arizona.

Arizona Biomedical Catalyst Award ("ABC")

The ABC Award is designed to support investigators whose projects were favorably reviewed by a federal granting agency but were just outside the respective funding score. The goal of this grant is to provide funding for the investigator to generate additional, needed data, with the intent to resubmit the application to the respective federal granting agency within twelve (12) to eighteen (18) months of receiving the ABC Award.

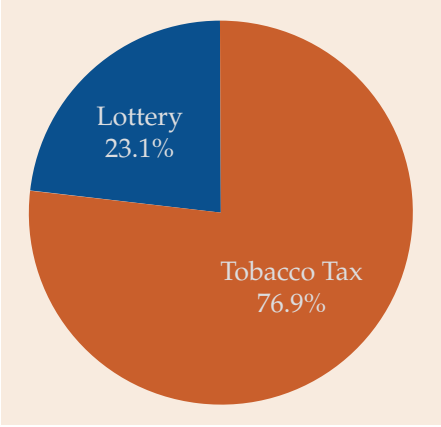
Arizona Biomedical Investigator Grant ("AZ BIG")

The AZ BIG is a competitive research grant requiring a rigorous scientific and collaborative approach. Collaboration among investigators will open funding doors through strategic, synergistic partnerships within an institution, across institutions, or across disciplines.

Financial Summary

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

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

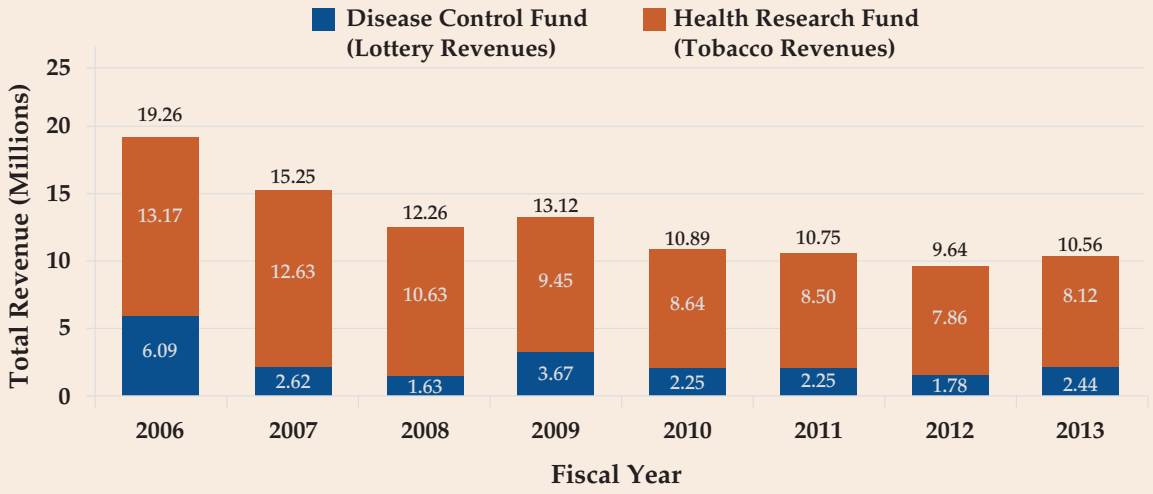


Revenue

For Fiscal Year 2013, ABRC's total combined revenue was $10.56 million. The distribution of all the revenue sources breaks out as follows: the Disease Control Research Fund equated to $2.44 million or 23.1% of ABRC's total revenue and the Health Research Fund revenue makes up 76.9% or $8.12 million.

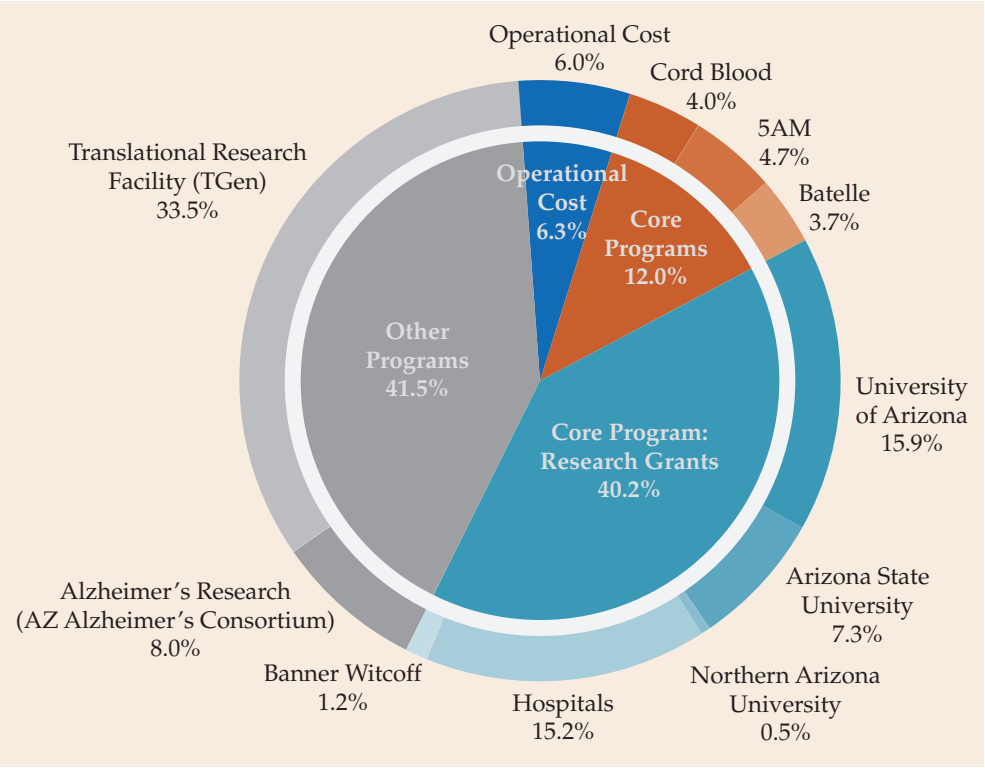
An analysis of ABRC's revenue demonstrates that it has been steadily declining for the last decade. Financial data from the State of Arizona Audited Financial Statements shows that the Disease Control Research Fund revenue (lottery) declined by more than 60% from 2006 to 2011 while in the same time period the Health Research Fund (tobacco tax) revenue declined by $4.6 million or 35%. Combined revenue of both funds fell by $8.5 million in the same time frame. Although it is anticipated that revenues will begin to plateau, the funding available for ABRC to continue its mission, is significantly less than it was just a few years ago.

Historic ABRC Revenue Distribution



Expenditures

In FY 2013, ABRC expended $12.41 million. These expenditures included $9.98 million in research grants, 80% of all expenditures. Of the research funding, $5.16 million, went towards non-competitive research awards, which included TGEN ($4.16M) and the Arizona Alzheimer's Consortium. The remainder of the research funding, $4.82 million, was awarded to competitively selected research grants. ABRC also hired the law firm Banner & Witcoff, which specializes in patent law, to provide legal support regarding patent issues that arose from research. ABRC spent $150,000, slightly more than 1% of total expenditures, on providing patent support for its research grants.



Furthermore, to fulfill the robust mission of ABRC, $490,000 was expended on the cord blood program and $1.04 million in consulting services to meet the needs of the core programs; these two areas constituted 12.4% of ABRC's total expenditures. Operational costs for ABRC were $740,000, only about 6% of the total budget.

Program Activities



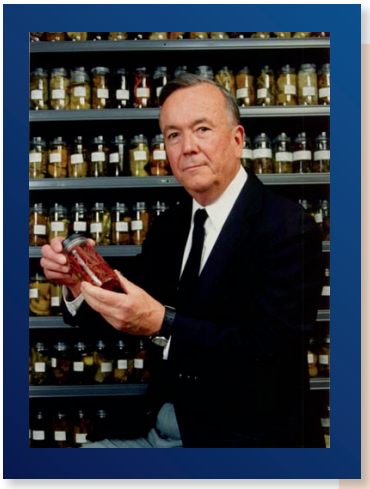
Program Activities

"The information, the techniques, and the research experience developed by the Office of Scientific Research and Development and by the thousands of scientists in the universities and in private industry, should be used in the days of peace ahead for the improvement of the national health, the creation of new enterprises bringing new jobs, and the betterment of the national standard of living."

FRANKLIN D. ROOSEVELT
November 17, 1944

This call to action by then President Roosevelt has resulted in remarkable strides in the knowledge gained on the war on disease and, in turn, has ushered in many positive benefits for Arizona. Through the pioneering vision of the Commission creators, the research funding issued to pursue the betterment of health has created the following positive impacts for Arizona:

- A focus on special Arizona population needs—Projects funded include Valley Fever, rabies transmission models, cures using desert plants, scorpion anti-venom, sun-induced skin cancer, and targeted health promotion and prevention strategies for the Hopi tribe.
- Additional research dollars brought into Arizona—Researchers use the projects funded by ABRC to generate the preliminary data needed to apply for larger grants. Sponsored Project Summary Reports show that St. Joseph's Hospital & Medical Center received an additional $602,000 in outside funding to continue and further advance their projects. The University of Arizona generated $1,011,658.
- Jobs funded—ABRC-funded research grants resulted in the employment of 99 Arizonans (percentage basis at either full-time or part-time). Under the Biospecimen Locator and Cord Blood Programs, ABRC funds a total of 22 positions—11 are full-time employees.
- Publications and presentations—In Fiscal Year 2013, ABRC-funded research grants resulted in 21 articles submitted for publication and 52 invited papers, panels, and/or presentations. Arizona State University's Cris Wells, and Svetlana Mihaylova-Todorova, of Maricopa Integrated Health System, submitted and received the "Best Poster of the Year Award" from the Society of Research Administrators (SRA) for their poster, "The Building Blocks of a Successful Biospecimen Repository."
- Patents—University of Arizona researcher Dr. Joyce Schroeder, supported by ABRC, received a $300,000 award from the National Institutes of Health (NIH) in the category of Small Business Technology Transfer (STTR). Additionally, the results of supporting and encouraging research in Arizona's patent portfolio has long-lasting benefits for Arizona. See the below Sponsored Project Summary Reports excerpt from Dr. George Pettit, Regents Professor, Department Chemistry and Biochemistry at Arizona State University with regard to anti-cancer drugs developed through ABRC supported research:



George Pettit, Ph.D.
Regents Professor
Arizona State University

"In Summary, the worldwide distribution of Adcetris, (now in 36 countries) where the drug is for greatly improving the treatment of certain refractory Lymphomas, is our Auristatin E discovery, where the ABRC financial support was very essential. So this seemed like an appropriate time to send you a special year end report with other advances from our anticancer drug discovery research involving past ABRC support. Another drug where we made the initial discoveries is HALAVEN and like Adcetris approved for essentially worldwide marketing over the past two years.

In short to my knowledge no other single group in Arizona has made such progress in improving human cancer treatment by discovery of completely new anticancer drugs.

The ABRC research funding has, as always, led to our outstanding research progress. Among the most exceptional research achievements over multiyear of ABRC research support has been our discovery and development of the dolastatin/auristatin series of remarkable anticancer drugs based on the original lead structure we isolated from an Indian Ocean Sea Hare. Currently the structural modification Auristatin E is the powerful anticancer drug component of the first successful antibody conjugate (ADC), Adcetris, first to be approved by the U.S. FDA nearly some two years ago. Adcetris is now in cancer clinics essentially world-wide for sending otherwise terminal cancer patients with one of two types of refractory lymphomas into extended complete remission: 57% for large cell lymphoma and 37% with Hodgkins lymphoma. That's just the beginning of a wonderful series of successes for the ABRC research investment, Arizona and public support of our research. In parallel over the past year of ABRC contract support we have markedly advanced our total synthesis of dolastatin 16 another excellent candidate for ADC construction as well as other objectives in our ABRC Contract.

Another serious plus impact is occurring on the ASU license with about $150 million Adcetris sales received in the first year and over $2 billion in sublicense contracts which is expected to be over $3.5 billion in future milestone and royalty payments.

Please refer to our recent research publications for details of recent advances that received financial support from our on-going ABRC support. In addition and very importantly, the first 3rd stage salvage drug for breast cancer, HALAVEN, is presently in essentially global use! The structure of Halaven arose from our discovery of the halistatins from a Western Pacific marine sponge. In turn the halistatins and our co-discovery of halichondrin B received early and consistent research financial assistance from the ABRC.

In summary, all past and present personnel, and a great number of supporting public of the ADCRC-ABRC should be greatly commended for all their vital contributions to our past and present research achievements. Here the PI and his ASU Cancer Research Institute (now cancer research group) research groups discoveries leading to Adcetris and Halaven advancing to global cancer clinics along with another twelve of our anticancer drug discoveries now in phase I to III cancer clinical trials is markedly illustrative of the vital importance of the ABRC and public need for its urgent continuation and funding."

ABRC Programs Redefined

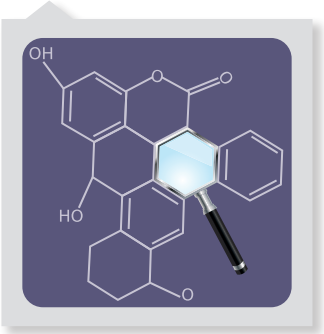
In addition to providing competitively awarded funding for research in Arizona, ABRC recognized its role to help advance Arizona as a bioscience leader. In 2004, ABRC partnered with the Flinn Foundation and Battelle to establish the Arizona Translational Research Pathway. The Pathway work group focused on harmonizing business practices, streamlining IRB and HIPAA process, and collaborating with diverse populations. The result of the Pathway's workgroups gave rise to ABRC's Arizona Translational Resource Network (AZTransNet).

AZTransNet focused on areas that would advance the sciences while supporting innovation and research. To this, multiple initiatives were launch guided by input from leaders and professionals from Arizona's universities, nonprofit research institutions, hospitals, medical centers, and patient advocacy groups. Many of those initiatives have evolved into distinct programs or can be categorized under as a service provided by ABRC through one of its four Core Programs.

Research Grants



Arizona Biospecimen Locator



Research Education



Arizona Public Cord Blood Program



4 Core Programs

Research Grants



At-A-Glance

RESEARCH GRANTS



Funding Source Used

Health Research Fund

Disease Control Research Fund

Program Highlights

41 Ongoing Research Projects

3 New Funding Categories Established

A Request For Grant Applications (RFGA) issued through ProcureAZ

All Program Agreements Uploaded for Public Viewing in ProcureAZ

Patent Portfolio Transferred to Arizona Cancer Therapeutics, Investigator Dr. Joyce Schroeder

2014 Program Goals

Streamline Contract Administration Process & Reporting through an electronic and automated program.

Promote Investigator's Research Project Advancements Using Video Series Issued With Social Media

Provide Investigator Annual Update Seminar to Commissioners, Public, and Research Community

Publish Arizona's Catalog of Research to promote Arizona's Capacity and Quality

2014 Performance Metrics

Measure 1: 90% of all Contract Reports received within 7 days after reporting requirement deadline

Measure 2: 95% of all Contracts administratively closed out within 30 days of end of award

Research Grants

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

Category I

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

Category II

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

Category III

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

41 active awards are all set to expire by June 30, 2014. Research Project Abstracts and related information begin on the next page.

No new awards were made in Fiscal Year 2013.



David Adelson, M.D.

Phoenix Children's Hospital

Annual Award Amount

$156,814

Project End Date

December 31, 2013

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

Brain-computer interface (BCI) technology aims to establish a direct link between the brain and external devices, enabling faster and more intuitive communication and control for those patients with severe neurological disorders such as spinal cord injury, amyotrophic leukodystrophy (ALS), stroke, etc. Our goal is to translate knowledge and experience gained from previous animal and human BCI research into a clinical BCI device and technologic advancement with micro-ECoG technology. Data will be collected from ECoG electrodes that are surgically implanted in the normal course of diagnosis and treatment of intractable epilepsy in 10 pediatric subjects. Cortical organization, movement direction and brain control data will be captured using a neural signal recording system. The ultimate goal is to create a seamless interface between the human brain and prosthetic and communicative devices for patients that have lost that ability through improved software and hardware applications. The proposed work is an integral and critical part for developing a fully-implantable, minimally-invasive BCI device that can be used in clinical practice.

Invited Papers, Panels, Presentations

"Evaluation of the Performance of a Brain-Computer Interface Under Two Biofeedback Paradigms." American Academy of Neurology 66th Annual Meeting. Pennsylvania Convention Center, Philadelphia, PA. April 28, 2014. Poster Presentation.



David Adelson, M.D.

Phoenix Children's Hospital

Annual Award Amount

$148,518

Project End Date

June 30, 2014

Rapid Cycle Outcomes Research to Improve Clinical and Operational Outcomes

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

Invited Papers, Panels, Presentations

"Development of a Prospective Clinical Quality Initiative in Pediatric Neurosurgery." Congress of Neurological Surgeons, 2013 Annual Meeting. San Francisco, CA. October 19–23, 2013.



Trent Anderson, Ph.D.

University of Arizona

Annual Award Amount

$49,995

Project End Date

June 30, 2014

Sex Hormones and Neurosteroids as Triggers of Migraine Headache

Cortical spreading depression (CSD) is a profound transient depolarization of neurons and glia that migrates across the cortex and is known to lead to migraine pain. The incidence and severity of migraine is linked to hormonal changes and in this proposal we are specifically investigating the influence of brain derived hormones known as neurosteroids on cortical excitability and CSD. Over the last year and as planned we have completed Aim 1.3 examining the effects of neurosteroids on tonic neurotransmission and begun work on Aim 2 examining acute and chronic exposure of neurosteroids on CSD. We have discovered that neurosteroids paradoxically increase cortical excitability and decrease the threshold for CSD. Altered cortical excitability is a key feature of migraine patients and this action of neurosteroids may play an important role in understanding the influence of hormones on migraines. In the upcoming year we will complete Aim 2 and examine if blockade of the synthesis of neurosteroids of their action(s) may be beneficial in preventing hormone related CSD.

Publications

Venugopal, S; Konowalik, A; Anderson, TR. "Neurosteroid Modulation of Synaptic and Extrasynaptic GABA-A Activity in Cortical Neurons." In Preparation.

Goddeyne, C; Anderson, TR. "Neurosteroids Act Through GABA-A Receptors to Enhance Cortical Spreading Depression." In Preparation.



Kevin Bennett, Ph.D.

Arizona State University

Annual Award Amount

$50,000

Project End Date

June 30, 2013

Implantable, MRI-detectable Hydrogel Sensors with Picomolar Sensitivity

We have developed a technique to detect the structure of synthetic and biological, implantable biomaterials with MRI. The basis of the technique is to embed functionalized magnetic nanoparticles in the material and detect the aggregation state of the particle. We have demonstrated this effect in subcutaneous injections and in bulk gels degraded by cells. We have demonstrated good toxicity and efficacy of various nanoparticles for this purpose, and discovered a new technique to detect tissue microstructure with targeted nanoparticles.

Publications

Hann, BL; Bennett, KM "Tracking the Dynamic Ultrastructure of Implantable Hyaluronic Acid/Collagen Hydrogels with MRI." Magnetic Resonance in Medicine. In revision.

Beeman, SC; Georges, JF; Bennett, KM "Toxicity, Biodistribution, and Ex Vivo MRI of Cationic Ferritin." Magnetic Resonance in Medicine, 2013. 69(3):853–861.

Clavijo-Jordon, V+; Kodibagkar, V; Beeman, SC+; Hann, B+; Bennett, KM*. "Nanomagnetic Properties of Biomaterials: Fundamental Physics and Applications in Medicine." Wire's Nanomedicine and Nanobiotechnology, 2012. 4(4):345–65.

Invited Papers, Panels, Presentations

Clavijo-Jordan, V+; Bennett, KM. "Strategic Doping in an Iron Oxide Nanoparticle to Form a Contrast Agent with High r1 and Low r2." International Society for Magnetic Resonance in Medicine. Salt Lake City, UT. 2013.

Erickson, IE; Hann, BD+; Doty, NJ; Bennett, KM; Zarembinski, T. "Polymerization and Degradation Kinetics of Hydrogel for Flexor Tendon Repair. Society for Biomaterials." New Orleans, LA. 2012. Poster Presentation.

Hann, BD+; Bennett, KM. "T2 Tracks Microstructural Changes in Implantable, Iron Oxide-Doped Hyaluronic Acid/Collagen Hydrogels for Preclinical and Regenerative Medicine." International Society for Magnetic Resonance in Medicine. Melbourne, Victoria, Australia. 2012. Oral Presentation.



Leslie Boyer, M.D.

University of Arizona

Annual Award Amount

$149,656

Project End Date

June 30, 2014

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

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

Publications

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

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

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

Invited Papers, Panels, Presentations

"Translational Medicine and International Cooperation." 2nd Ibero-American Meeting on Toxicology and Environmental Health (IBAMTOX). Ribeirão Preto, Brazil. June 2013.

Leslie Boyer, M.D. (cont.)



"It is an honor to be part of the REGISTER project and to be able to implement a tool that is unique and valuable to translational research and clinical care of patients who suffered an envenomation."

—Emmanuelle Mangin, Pharm.D



"The REGISTER project has allowed VIPER to put our extensive database of venomous bite and sting information to greater scientific use, and to extend its scope so that what we learn can be shared better with people in Arizona.

—Leslie Boyer, MD



Sylvia Brown, Ph.D.

University of Arizona

Annual Award Amount

$100,000

Project End Date

June 30, 2014

Chronic Disease in an Arizona Native American Community

There is a dearth of information on the health of specific tribal communities. Consequently, university researchers and Hopi tribal members jointly developed and are now implementing a culturally appropriate population based survey (248men / 252 women) among Hopi tribal members living on the reservation. A mail in survey of randomly selected Hopi men and women living off the reservation is currently underway. A convenience survey will be held at various locations on the reservation upon UA IRB approval. Together, these efforts will fulfill our objectives to ascertain the prevalence of cancer, other chronic diseases and various risk factors and behaviors among adults enrolled in the Hopi tribe, regardless of residence, to help identify targeted health promotion and prevention strategies for the Hopi tribe, to provide a model of a tribal specific health survey for Arizona tribes/nations and to identify optimal methods for implementing on-reservation tribal health surveys.

Invited Papers, Panels, Presentations

"Improving Hopi Communities through Research." 2013 Hopi Research Conference: Hopi Health Survey, Research to Reality. Kykotsmovi, Arizona. April 4, 2013. Oral Presentation.

"Understanding Hopi Perspectives on Tobacco Use and Cancer in Both the Urban and Reservation Populations Through Conducting Focus Group Sessions." 2013 Hopi Research Conference: Research to Reality, Improving Hopi Communities through Research. Kykotsmovi, Arizona. April 4, 2013. Poster Presentation.
(Also Presented at Northern Arizona University and University of Arizona student forums.)



Yin Chen, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

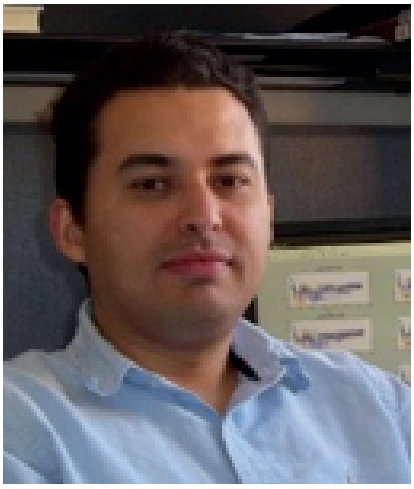
June 30, 2014

Susceptibility to Respiratory Infections in Smokers

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

Publications

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



Gerardo Chowell-Puente, Ph.D.

Arizona State University

Annual Award Amount

$109,079

Project End Date

June 30, 2014

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

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

Publications

Theimer, TC; Clayton, A; Peterson, D; Bergman, DL. "Cat Food Increases Contacts Among Skunks Visiting Bird Feeders." Journal of Wildlife Management. In review.

Invited Papers, Panels, Presentations

"Skunk Use of Spilled Bird Seed and Implications for Rabies." Northern Arizona Audubon Society. Flagstaff and Sedona, AZ. October 17–18 2012.

"Urban Ecology of Striped Skunks in Flagstaff, AZ." School of Forestry Invited Seminar Series, NAU. Flagstaff AZ. February 13, 2013.

"Striped Skunks in Flagstaff: Challenges of Studying Urban Ecology of an Unpopular Mammal." US Forest Service Interpreter Workshop. Hart Prairie, AZ. July 15.







Michael O. Daines, M.D.

University of Arizona

Annual Award Amount

$112,500

Project End Date

June 30, 2013

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

Allergic asthma is a disease that impacts the lives of millions in the US and across the world. Many clinical, environmental, biologic, and genetic factors intersect to create this disease. Asthma in Arizona is strongly associated with sensitization to *Alternaria*, a common mold. Critical features of *Alternaria* differentiating it from more benign allergens are chitin and proteases. Chitins are protective components of fungal cell walls, are pro-inflammatory, and may contribute to alternative macrophage activation, lung inflammation, and asthma. Allergen proteases provide mechanisms for increased allergen biological activity such as disrupting epithelial barrier function. The Central Hypothesis of this application is that *Alternaria* is an allergic pathogen because of chitin and proteases. We will determine impacts of *Alternaria* chitin and proteases of *Alternaria* on lung development and the development of asthma in novel murine models. Strategies to mitigate chitins and proteases may lead to prevention or treatment of asthma.

Publications

Boitano, S; Flynn, AN; Sherwood, CL; Schulz, SM; Hoffman, J; Gruzinova, I; Daines, MO. "Alternaria Alternata Serine Proteases Induce Lung Inflammation and Airway Epithelial Cell Activation Via PAR2." American Journal of Physiology—Lung Cellular and Molecular Physiology. April 2011. 300(4):L605-14. doi:10.1152/ajplung.00359.2010. Epub February 4, 2011.

Invited Papers, Panels, Presentations

Polley, D[1]; Mihara, K[1]; Ramachandran, R[1]; Vliagoftis, H[2]; Boitano, S[3]; Hollenberg, MD[1]; Daines, M[3]. "Cockroach Allergen Proteinases Regulate Proteinase-ActivatedReceptor-1 (PAR1) Signalling."

1. Physiology & Pharmacology, University of Calgary. Calgary, AB, Canada;
2. Pulmonary Research Group, Department of Medicine, University of Alberta. Edmonton, AB, Canada;
3. Bi05 Institute, University of Arizona. Tucson, AZ;
4. Experimental Biology Meeting. Boston, MA. April 2013. Submitted.

Rothers, J PhD[1]; Stern, DA, MS; Halonen, M, PhD; Wright, AL, PhD; Daines, M, MD. "Environmental Tobacco Smoke Exposure is Associated with Increased IL-13/IFN-y Ratio in Infancy."

1. University of Arizona. Tucson, Arizona;
2. American Thoracic Society Meeting. Philadelphia, PA. May 2013. Submitted, accepted for oral presentation.

Michael O. Daines, M.D. Invited Papers, Panels, Presentations (cont.)

Cunningham, A; Pereira, R; Daines, M. "Differential Immune Responses to Alternaria alternata Components."

1. Arizona Respiratory Center, University of Arizona. Tucson, AZ;
2. American Thoracic Society Meeting. San Francisco, CA. May 2012.

Pereira, R; Cunningham, A; Daines, M. "Impact of Early Postnatal Exposure to Alternaria on Mouse Lung Development."

1. Arizona Respiratory Center, University of Arizona. Tucson, AZ;
2. American Thoracic Society Meeting. San Francisco, CA. May 2012.



Hermann Fasel, M.D.

University of Arizona

Annual Award Amount

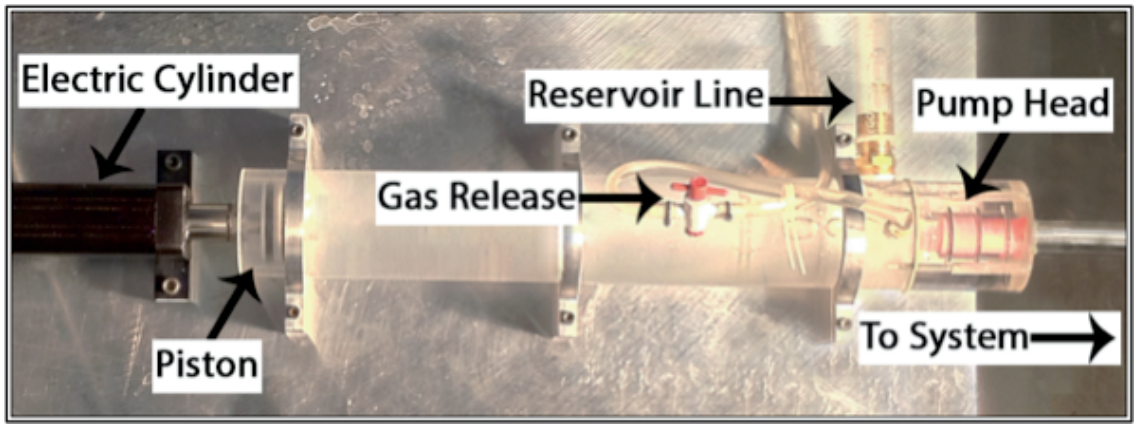
$131,734

Project End Date

June 30, 2013

Numerical Simulation of Arterial Blood Flow in Vivo

The research focus of the last year was to implement and modify the computer simulation code by taking a more generic approach, i.e. cut-cell strategy for the immersed boundary, allowing for simulation of much larger variety of geometrics of stenosis. It also enables Flow Structure Interactions, such as between the arterial walls and the arterial blood flow. The three-dimensional code has been verified by comparison with results from generic geometries. Efficient implementation of key computational modules allows for faster and more robust simulations of the highly unsteady flows. In parallel to the simulation code development at CFD Laboratory at the University of Arizona, construction and testing of the proposed experimental apparatus has been completed at the Energetic Flow and Turbulence Laboratory at Arizona State University. Detailed PIV measurements have been obtained for pipe flow for Reynolds numbers between 1,000 and 10,000, which demonstrated full functionality for providing reference data for CFD simulations.



Apparatus for pulsating blood flow experiments used for validation of Direct Numerical Simulations



Timothy Flood, M.D.

Arizona Department of Health Services

Annual Award Amount

$119,094

Project End Date

March 31, 2014

Improving the Medical Certification of Cause of Death on Arizona Certificates

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



Randall Friese, MD

University of Arizona

Annual Award Amount

$125,000

Project End Date

June 30, 2013

Sleep Promotion in Critically Ill and Injured Patients Cared for in the Intensive Care Unit

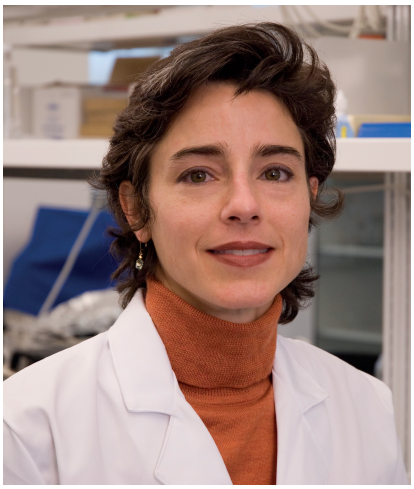
Sleep is highly abnormal during recovery from illness in the intensive care unit and providing protected time for sleep is overlooked and underemphasized by healthcare providers. Our study highlights several important issues:

1. Sleep architecture during recovery from illness/injury in the intensive care unit is abnormal. Most sleep time is spent in superficial stages of sleep (N1 and N2} with minimal to no time in deep sleep (N3 and REM). Additionally, this sleep is fragmented. These findings replicate those of other studies of sleep in this patient population.
2. Healthcare provider attitudes toward sleep promotion in the intensive care unit can be changed by a dedicated staff education/training experience.

These findings are important because they emphasize the need for more research in sleep promotion in this patient population and indicate that healthcare workers will change their behavior once they recognize the importance of sleep in recovery from illness.

Invited Papers, Panels, Presentations

"SLEEP IN THE INTENSIVE CARE UNIT: IS THERE TIME FOR IT?" 2012 Annual Meeting, Southwestern Surgical Congress. March 27, 2012.



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

University of Arizona

Annual Award Amount

$49,995

Project End Date

June 30, 2014

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

To establish whether *Egr3* regulates expression of the 5-HT_{2A}R we will examine the level and localization of 5-HT_{2A}Rs in brains of *Egr3-/-* and WT mice using Western Blot analyses. We will compare levels of 5-HT_{2A}R under basal conditions, and following induction of *Egr3* in WT mice, to levels in *Egr3-/-* mice under these conditions. We predict that these studies will identify the brain sites where 5-HT_{2A}R is regulated by *Egr3* and indicate whether the loss of 5-HT_{2A}R binding we have previously identified is due to decreased overall levels of receptor protein, or may instead result from mis-localization or other dysfunction of the receptor protein.



Robert Garfield, Ph.D.

St. Joseph's Hospital

Annual Award Amount

$125,000

Project End Date

June 30, 2014

Uterine Electrical Stimulation to Treat PPH

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

Publications

Carp, H; Maner, W; Garfield, R; Winkler, C; Coleman, F; Slayton-Milam, S; Buckmaster, J. "Potential New Treatment for Post-Partum Hemorrhage: A Pilot Study Testing the Ability of an Electric Stimulator to Increase Uterine Tone During Cesarean Delivery." Submitted for publication.

Miller, S; Towe, B; Garfield, R. "Optimal Electrical Stimulation Parameters to Contract the Post-partum Rat and Human Uterus of Rats." Submitted for publication.

Invited Papers, Panels, Presentations

Carp, H; Maner, W; Garfield, R; Winkler, C; Coleman, F; Slayton-Milam, S; Buckmaster, J. "Potential New Treatment for Post-Partum Hemorrhage: A Pilot Study Testing the Ability of an Electric Stimulator to Increase Uterine Tone During Cesarean Delivery." SOAP (Society for Obstetric Anesthesia and Perinatology), ATWI. 2012.

Miller, S; Carr, G; Garfield, R. "Optimal Electrical Stimulation Parameters to Contract the Post-Partum Uterus." Society for Gynecological Investigation, Supplement to Reproductive Sciences. March 2013. Abstract T-208.



Vince Guerriero, Ph.D.

Annual Award Amount

$50,000

Project End Date

June 30, 2013

Inhibition of Melanoma Growth by HspBP1

The use of proteins as drugs is increasing and has become established for cancer treatment with the development of monoclonal antibodies that are engineered to bind to select sites on the exterior of a cancer cell. These antibodies are not normally found in patients and therefore can have negative side effects. We have characterized a novel protein called HspBP1 that binds to cancer cells, and is present in human serum and have shown that exogenous delivery of HspBP1 into B16F10 melanoma tumor bearing mice reduces tumor growth. Additional experiments have shown that the amnia terminal region of HspBP1 is required for this activity and for *in vitro* activity.



Karen Hastings, M.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2014

Regulation of Immune Tolerance to Melanoma

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

Publications

Phipps-Yonas, H; Semik, V; Hastings, KT**. "GILT Expression in B Cells Diminishes Cathepsin S Steady-State Protein Expression and Activity." European Journal of Immunology. 2013. 43(1): 65–74.

Invited Papers, Panels, Presentations

Rausch, MP; Metzger, TC; Anderson, MS; Hastings, KT. "GILT Expression in Medullary Thymic Epithelial Cells is Required for Presentation of Tissue-Specific Self-Antigens and Deletion of Autoreactive T Cells." 100th Annual Meeting of the American Association of Immunologists. Honolulu, HI. 2013. Oral Presentation.

Phipps-Yonas, H; Cui, H; Haddock, E; Deymier, MJ; Lybarger, L; Roe, DJ; Hastings, KT. "Low GILT Expression is Associated with Poor Survival in Diffuse Large B-cell Lymphoma." 100th Annual Meeting of the American Association of Immunologists. Honolulu, HI. 2013.

Rausch, MP; Metzger, TC; Anderson, MS; Hastings, KT. "GILT Expression in Medullary Thymic Epithelial Cells is Required for Presentation of Tissue-Specific Self-Antigens and Deletion of Autoreactive T Cells." International Investigative Dermatology Meeting. Edinburgh, Scotland. 2013. Oral Presentation.



Yao (Joyce) Huang, Ph.D.

St. Joseph's Hospital

Annual Award Amount

$100,000

Project End Date

June 30, 2014

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

In Year 2, we have obtained significant progress. First, in molecular and cellular biology. We profiled the major BDNF-TrkB signaling pathways in human hypothalamic hamartoma (HH) and normal hypothalamic control tissues. We found that in HH group: a) phosphorylation of TrkB at Tyr816 was enhanced; b) activation of three subfamilies of MAPKs (ERKs, p38, and JNK) was elevated; c) both activation of Akt and expression of PTEN were increased; d) both PLC phosphorylation and CaMKII expression levels were higher. In contrast, KCC2 expression was down-regulated in HH group. Also in electrophysiology, we have tested effects of BDNF-TrkB pathway blocker (K252a) and enhancer (BDNF) on human HH neuronal firing under patch-clamp recording conditions (current-clamp mode). Results showed that bath-application of 100 nM K252a remarkably reduced HH neuron action potential firing, while bath-application of 10 nM BDNF enhanced firing rate. These results suggest the importance of BDNF-TrkB pathway-associated CaMK and phosphorylase kinase in controlling H neuronal function.

Publications

"Profiling BDNF-TrkB Signaling Pathways in Human Hypothalamic Hamartoma." Manuscript in Preparation.

Invited Papers, Panels, Presentations

Semaan, S; Wu, J; Chang, Y; Huang, Y. "Profiles of BDNF/TrkB Signaling Pathways in Human Hypothalamic Hamartoma Tissues." The Society for Neuroscience Annual Meeting. San Diego, California. November 9–13, 2013. Poster Presentation.



Randa Jarrar, M.D.

Phoenix Children's Hospital

Annual Award Amount

$100,000

Project End Date

December 31, 2013

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

Aggregated, disease-specific clinical data is a valuable resource for researchers and clinicians to determine research study feasibility, assess patient care quality, and when linked to patient-specific data, aid in clinical trial recruitment. In this proposal, we will adapt, implement and evaluate the i2b2 Workbench, developed at Harvard-Partners National Center for Biomedical Computing, to create a pediatric research patient data repository (RPDR) at Phoenix Children's hospital. We will formally assess the quality of the data found in the RPDR by comparing the RPDR data to a manual review of medical charts for two neurologic diseases—anti-epileptic drug therapy and intractable seizures. If the pilot implementation is successful, the modular nature of the i2b2 framework will allow rapid extension of the tool to other disease-specific data at PCH and serve as a model for other patient data repository initiatives.



William G. Johnson, Ph.D.

Arizona State University

Annual Award Amount

$100,000

Project End Date

June 30, 2014

CHIR Trauma Registry

The project will organize and maintain a centralized repository linking the eight Level 1 Trauma Centers and the Arizona Burn Center by standardizing the trauma data collected from each Center. The trauma data will be merged with existing hospital claims data for inpatient and emergency department visits from all Arizona acute care hospitals to create patient level records. The combined data will serve as an aggregated reference and research repository and will assist the Centers in performing the scholarly research required for certification as Level 1 Trauma Centers.



John Kerrigan, M.D.

St. Joseph's Hospital

Annual Award Amount

$100,000

Project End Date

June 30, 2014

Cellular Mechanisms of Epileptogenesis in Human Hypothalamic Hamartoma Tissue

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

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

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

Publications

Kerrigan, JF; Strobel, A; Rice, G; Simeone, K; Shetter, A; Abla, A; Prenger, E; Coons, S. "Hypothalamic Hamartomas: Neuropathological Features With and Without Prior Gamma Knife Radiosurgery." Stereotactic and Functional Neurosurgery. 2013. 91:45-55.

Steinmetz, PN; Lekovic, GP; Wait, S; Rekate, HL; Kerrigan, JF. "Firing Behavior and Network Activity of Single Neurons in Human Epileptic Hypothalamic Hamartoma." Submitted for Publication.

Kerrigan, JF; Parsons, A; Simeone, K; Beggs, J; Coons, S; Wu, J. "Golgi-Cox Staining Identifies at least Two Neuron Phenotypes in Human Epileptic Hypothalamic Hamartoma." In preparation.

Invited Papers, Panels, Presentations

Wu, J; Rice, SG; Beggs, J; Kerrigan, JF. "Gap-Junction is a Potential Target for Epileptic Therapy in Human Gelastic Seizures with Hypothalamic Hamartoma." 2012 Annual Meeting of the American Epilepsy Society.

Steinmetz, PN; Lekovic, GP; Wait, S; Rekate, HL; Kerrigan, JF. "Firing Behavior and Network Activity of Single Neurons in Human Epileptic Hypothalamic Hamartoma." 2012 Annual Meeting of the American Epilepsy Society.

John Kerrigan, M.D.: Invited Papers, Panels, Presentations (cont.)

Beggs, J; Wu, J; Coons, S; Kerrigan, JF. "Abnormal Subsurface Cisterns in Small Neurons in Human Epileptic Hypothalamic Hamartoma: An Ultrastructural Study." 2012 Annual Meeting of the American Epilepsy Society.

Kerrigan, JF; Parsons, AS; Simeone, K; Wu, J; Beggs, J; Coons, S. "Small and Large Neurons from Human Epileptic Hypothalamic Hamartoma: Golgi Analysis of Surgically-Resected Tissue." 2012 Annual Meeting of the American Epilepsy Society.

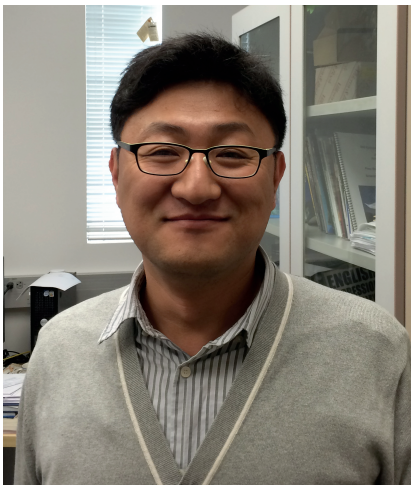
"Hypothalamic Hamartoma: Disease Model and Cellular Mechanisms of Epileptogenesis." Pediatric Neurosciences Conference, Nationwide Children's Hospital. Columbus, OH. May 3, 2012.

"Hypothalamic Hamartoma 2012: Bench and Bedside." Neurology/Neurosurgery Grand Rounds, Barrow Neurological Institute. Phoenix, AZ. August 24, 2012.

"Hypothalamic Hamartoma: Cellular Model for Epileptogenesis." Neuroscience Graduate Degree Course MCB/NEU 555, Arizona State University. Tempe, AZ. October 30, 2012. Invited Speaker.

"Hypothalamic Hamartoma and Epilepsy: Basic Cellular Mechanisms." Department of Neurology Grand Rounds, Mayo Clinic. Rochester, MN. April 22, 2013.

"HH: Neuropathology and Mechanisms for Seizure Genesis." Second International Conference on Hypothalamic Hamartoma. Marseilles, France. September 20, 2013.



Do Young Kim, DVM, Ph.D.

St. Joseph's Hospital

Annual Award Amount

$49,509

Project End Date

June 30, 2013

Multiple Sclerosis-Induced Impairment of Learning and Memory

Metabolic alteration has been considered a promising target for intervening in pathological conditions, as prototypically illustrated by the ketogenic diet (KD) and its metabolic substrate, ketones. Little is known about the underlying mechanisms of the diet therapy, but the possibility of the therapeutic relevance of the KD in models of multiple sclerosis (MS) has been raised. In this context, this work has provided that the KD down-regulates the activation of astrocytes following autoimmune responses, and additional data supporting the notion that ketones may be a pivotal role for ameliorating pro-inflammatory mediation in microglia cell lines. Given that metabolic changes induced by the KD or ketones are increasingly being implicated in diverse beneficial actions associated with oxidative stress and neuroinflammation, the progress made through this project suggests that metabolism-based treatments and/or metabolic substrates might represent a worthy paradigm for therapeutic development in MS.

Invited Papers, Panels, Presentations

Lee, SH; Abdelwahab, M; Kim, DY. Administration of Ketones "Attenuate Against Lipopolysaccharide-Induced Microgilal Inflammatory Responses and Oxidative Stress-Evoked Neuronal Death." Society for Neuroscience. San Diego, California. November 2013.



Walter Klimecki, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2013

The Unfolded Protein Response: Mechanism of Inorganic Arsenic Resistance

In the second year of the project we focused on the myeloma cell line 8226, including its response to arsenic trioxide (ATO) and to a prototypical inducer of the unfolded protein response (UPR), tunicamycin. Our work included generating several genetically manipulated derived cell lines of 8226, and its arsenic-resistant counterpart K-562. Results from this project suggest that the UPR exhibited by 8226 in response to both tunicamycin and to ATO is atypical, and may not confer resistance to ATO. We are currently testing K-562 cells to determine if the UPR functions in a similar role. Several exciting leads have emerged from the project, including the sensitivity of the 8226 myeloma cell line to a hypoxia inducible factor inhibitor, 2-methoxyestradiol, as well as the potential for chronic low-dose exposure to arsenic compounds to induce a global resistance to xenobiotic-induced cytotoxicity. The latter phenomenon is clinically relevant, given the ubiquitous human exposure to arsenic in the environment.



Kenro Kusumi, Ph.D.

Arizona State University

Annual Award Amount

$112,500

Project End Date

June 30, 2013

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

While mammals have only limited ability for regeneration, lizards can regrow their entire tail after loss, including their spinal cord. Lizards and mammals are both amniote vertebrates, and we hypothesize that spinal cord regeneration involves activation of conserved genetic pathways that could potentially be activated to stimulate human axonal outgrowth. With the recent release of genome sequence for the lizard, *Anolis carolinensis*, RNA-Seq cutting-edge technology is ideally suited for identifying all genes in spinal cord regeneration. We have carried out RNA Seq and functional anatomical analysis of the regenerating tail of *Anolis carolinensis*, in comparison with spinal cord and brain tissue We have shared these data with the research community through publications and release of data to the NIH and other public databases. These studies have identified a unique pattern of gene expression in regeneration with direct applicability to future regenerative medical therapies for spinal cord injury.

Publications

Ritzman, TB; Stroik, LK; Julik, E; Hutchins, ED; Lasku, E; DeNardo, DF; Wilson-Rawls, J; Rawls, JA; Kusumi, K; Fisher, RE. "The Gross Anatomy of the Original and Regenerated Tail in the Green Anole (*Anolis carolinensis*)." Anatomical Record (Hoboken). July 2, 2012. 295(10):1596–1608. doi:10.1002/ar.22524.

Kusumi, K; Fisher, RE. "Studying Mechanisms of Regeneration in Amphibian and Reptilian Vertebrate Models." Anatomical Record. August 29, 2012. 295(10):1529–1531. doi:10.1002/ar.22541.

Fisher, RE; Geiger, LA; Stroik, LK; Hutchins, ED; George, RM; DeNardo, DF; Kusumi, K; Rawls, JA; Wilson-Rawls, J. "A Histological Comparison of the Original and Regenerated Tail in the Green Anole, (*Anolis carolinensis*)." Anatomical Record. August 29, 2012. 295(10):1609–1619. doi:10.1002/ar.22537.

Eckalbar, WL; Hutchins, ED; Markov, GJ; Allen, AN; Corneveaux, JJ; Lindblad-Toh, K; Di Palma, F; Alföldi, J; Huentelman, MJ; Kusumi, K. "Genome Reannotation of the Lizard *Anolis carolinensis* Based on 14 Adult and Embryonic Deep Transcriptomes." BMC Genomics. January 23, 2013. 14:49. doi:10.1186/1471-2164-14-49.

Invited Papers, Panels, Presentations

Hutchins, ED; George, RM; Markov, GJ; Eckalbar, WL; Geiger, L; DeNardo, DF; Fisher, RE; Rawls, JA; Huentelman, MJ; Wilson-Rawls, J; Kusumi, K. "Coordinated Programs of Cell Growth and Transcriptional Regulation in Lizard Tail Regeneration." Society for Developmental Biology 71st Annual Meeting. Montreal, QC, Canada. July 19–23, 2012. Published in Developmental Biology. 368(1):146.



Liwen Lai, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2013

Improving Recovery from Acute Kidney Injury by Enhancing Tubular Regeneration

Acute kidney injury (AKI) caused by trauma and various toxins is a major health care problem in Arizona. About one half of patients with AKI will die and survivors are likely to develop chronic kidney failure requiring dialysis and transplantation. IQGAP1 is a scaffold protein that plays a critical role in regulating actin cytoskeleton. Since actin cytoskeleton remodeling plays an important role in the repair of acute kidney injury (AKI), we investigated the role of IQGAP1 in tubular regeneration after AKI. Using IQGAP1 knock out (KO) mice, we have demonstrated that KO mice failed to regenerate the renal epithelial tubules after AKI, thus establish IQGAP1 as a key player for tubular regeneration A pharmacological approach was developed to activate IQGAP1 signaling to improve recovery from AKI by facilitating tubular regeneration. Our data suggest that EGF/EGFR signaling may not play a major role in IQGAP1 mediated renal tubular regeneration. Further pharmacological studies would provide the foundation for developing therapeutic agents targeting at tubular regeneration for AKI.

Publications

Lai, L; Yong, KC; Lien, YH. "IQGAP1 is Critical for Recovery from AKI by Enhancing Tubular Cytoskeleton Regeneration." Journal of the American Society of Nephrology. 2011. Vol. 22: 40A.

Lai, L; Yong, KC; Lien, YH. "IQGAP1 is Critical for Recovery from AKI by Enhancing Tubular Cytoskeleton Regeneration." In Preparation.

Invited Papers, Panels, Presentations

Lai, L, PhD.; Yong, KC, PhD., Lien, YH, MD., PhD. "IQGAP1 is Critical for Recovery from AKI by Enhancing Tubular Cytoskeleton Regeneration." American Society of Nephrology Annual Meeting. Philadelphia, PA. November 12, 2011.



Serrine Lau, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2013

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

Diabetes is a disease that has been diagnosed in 7.1% of the adult population in Arizona, greater than the U.S. average (5.5%) [kaiserhealthnews.org]. Diabetes is known to be associated with numerous cardiovascular complications. Fibrinogen is a protein that is directly tied to blood clotting, which was found to be modified in diabetic patients. To better understand how these modifications may play a role in type-2 diabetic cardiovascular complications, we studied key blood clotting proteins modified with reactive sugars that are present in diabetic patients. We found that heavily modified fibrinogen and plasminogen led to disruption of fibrinolysis cascade. While this indicates an overall cardiovascular effect, precise link of structure and function changes of these proteins remain unclear. The current focus of this study is to determine the functional changes of the modified fibrinogen and plasminogen, which may have an overall deleterious effect on the cardiovascular system seen in type-2 diabetes.

Publications

Kinsky, OR; Kimzey, MJ; Monks, TJ; Lau, SS. "Disruption of the Fibrinolysis Cascade Via Dicarbonyl Adduction of Plasminogen." Manuscript in Preparation.

Kimzey, MJ; Kinsky, OR; Yassine, HN; Allred S; Tsaprailis, G; Billheimer, D; Stump, C; Monks, TJ; Lau, SS. Site-Specific Arginine Dicarbonyl Modiciations of Serum Albumin are Reduced in Metformin-Controlled T2DM Patients. Manuscript in Preparation.

Kimzey, MJ; Yassine, HN; Tsaprailis, G; Monks, TJ; Lau, SS. "Identification of Methylglyoxal Sites in the Plasma Proteome." Manuscript submitted.

Invited Papers, Panels, Presentations

Kinsky, OR; Kimzey, MJ; Allred, SF; Anumol, T; Yassine, HN; Stump, C; Tsaprailis, G; Snyder, S; Billheimer, D; Monks, TJ; Lau, SS. "Metformin Decreases Glyco-oxidation Markers: A Study Utilizing Multiple Reaction Monitoring." American Society for Mass Spectrometry. Minneapolis, MN.

Kinsky, OR; Kimzey, MJ; Tsaprailis, G; Monks, TJ; Lau, SS. "Modifications of Plasminogen by Methylglyoxal Disrupts Normal Zymogen Activation." XIVth International Workshop—Molecular and Cellular Biology of Plasminogen Activation, University of Notre Dame. South Bend, IN.

Serrine Lau, Ph.D.: Invited Papers, Panels, Presentations (cont.)

Kinsky, OR; Kimzey, MJ; Tsaprailis, G; Monks, TJ; Lau, SS. "*In Vitro* Modification of Plasminogen by Methylglyoxal Disrupts Normal Zymogen Activation." Society of Toxicology National Conference. San Antonio, TX.

Kinsky, OR; Kimzey, MJ; Tsaprailis, G; Monks, TJ; Lau, SS. "Dicarbonyl Adduction of Plasminogen: Possible Role in Diabetic Cardiovascular Complications." Frontiers in Biomedical Research. Tucson, AZ.



Alexander McLaren, M.D.

Banner Good Samaritan

Annual Award Amount

$102,091

Project End Date

June 30, 2013

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

The work this year focused on the understanding how the distribution of antimicrobial surrogate around a local depot changed over time as wound healing occurred. Understanding how the dynamics of wound healing affect kinetics of local delivery will allow for a much greater understanding of how this technology improves patient care and infection management. The results showed that dose was the most important factor affecting tissue coverage, and while fibrosis did occur around the implant, it did not seem to greatly affect the drug distribution independent of the dosage placed in the depot. By modeling these results using a finite element simulation, we are able to understand how the antimicrobials are distributing, and observe that they are not crossing intact fascial planes in concentrations sufficient to manage prosthetic joint infections. These results provide an excellent basic science foundation which has greatly improved understanding of the kinetics and dynamics of local delivery.

Publications

"Spatiotemporal Qualification of Local Drug Delivery Using MRI." Computational and Mathematical Methods in Medicine. PMID: 23710248.

"Distribution of Molecules Locally Delivered from Bone Cement." JBMR. Submitted.

"Local Antimicrobial Coverage from Bone Cement Depends on Dose: A Pilot Study with MRI." CORR. In Preparation.

"Tissue Architecture Predicts Local Delivery Patterns." In Preparation.

Invited Papers, Panels, Presentations

"Controlled Release of Antimicrobials from Bone Cement in Vivo." Banner Orthopaedic Research Symposium. Scottsdale, Arizona. June, 2013. Paper Presentation.

"Controlled Release of Antimicrobials Surrogate from Bone Cement in Vivo." Arizona Orthopaedic Society Annual Meeting. Scottsdale, Arizona. June, 2013. Paper Presentation.

"Controlled Release of Antimicrobials Surrogate from Bone Cement in Vivo." Academic Excellence Day. Phoenix, Arizona. May, 2013. Paper Presentation.

"MRI Can Be Used to Detect Antimicrobials Delivered from Polymeric Biomaterials." American Chemical Society Annual Meeting. New Orleans, Louisiana. April, 2013. Paper Presentation.

Alexander McLaren, M.D.: Invited Papers, Panels, Presentations (cont.)

"Controlled Release of Antimicrobial Surrogate Can be Imaged Over 7 Days in Vivo." Society for Biomaterials Annual Meeting. Boston, Massachusetts. April, 2013. Paper Presentation.

"MRI Visualization of Local Drug Delivery in Orthopaedic Wounds." Research Society Annual Meeting. San Antonio, Texas. January, 2013.

"Monitoring the Delivery of Therapeutic Agents from Antibiotic Loaded Bone Cement with Contrast-Enhanced MRI." International Society for Magnetic Resonance in Medicine Annual Meeting. Melbourne, Australia. May, 2012. Paper Presentation.



Sarada Panchanathan, M.D.

Maricopa Integrated Health Service

Annual Award Amount

$99,773

Project End Date

June 30, 2014

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

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

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

Publications

Chowell , G; Panchanathan, S; Wang, X. "A Data-Driven Mathematical Model of CA-MRSA Transmission among Age Groups: Evaluating the Effect of Control Interventions." PLOS Computational Biology. 2013. 9(11): e1003328. doi:10.1371/journal.pcbi.1003328.

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



George Pettit, Ph.D.

Arizona State University

Annual Award Amount

$125,000

Project End Date

June 30, 2014

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

The second year of ABRC research funding has as always led to outstanding research progress. Among the most exceptional research achievements over multiyear of ABRC research support has been our discovery and development of the dolastatin/auristatin series of remarkable anticancer drugs based on the original lead structures we isolated from an Indian Ocean Sea Hare. Currently the structural modification Auristatin E is the powerful anticancer drug component of the first successful antibody drug conjugate (ADC), Adcetris, first to be approved by the U.S. FDA nearly some two years ago. Adcedtris is now in cancer clinics essentially world-wide for sending otherwise terminal cancer patients with one of two types of refractory lymphomas into extended complete remission; 57% for large cell lymphoma and 37% with Hodgkins lymphoma. That's just the beginning of a wonderful series of successes for the ABRC research investment, Arizona and public support of our research. In parallel over the past year of ABRC contract support we have markedly advanced our total synthesis of dolastatin 16 another excellent candidate for ADC construction as well as other objectives in our ABRC contract. In addition the six research publications that received ABRC financial support have been attached. We hope a new ABRC Request for Proposal will soon be issued that will allow this PI to compete for support beyond this 3rd and terminal year.

Publications

Pinney, KG; Pettit, GR; Trawick, ML; Jelinek, C; Chaplin, DJ. "The Discovery and Development of the Combretastatins." (Citation Information Anticancer Agents from Natural Products, Second Edition. Cragg, DJ; Kingston, GM; Newman, DGI. CRC Press. 2011. Pp. 27–64.

Pettit, GR; Tang, Y; Zhang, Q; Bourne, GT; Hogan, F; Arm, C; Knight, JC; Pettit, RK; Chapuis, JC; Doubek, D; Ward, F.; Hooper, JNA. "Isolation and Structure of Axistatins 1–3 from the Republic of Palau Marine Sponge *Agelas axifera*." Journal of Natural Products. 2013. 76(3), 420–424.

Pettit, GR; Moser, BR; Mendonca, RF. "The Cephalostatins 22. Synthesis of Bis-steroidal Pyrazine Pyrones." Journal of Natural Products. 2012. 75 (6):1063–1069

Pettit, GR; Rosenberg, HJ; Dixon, R; Knight, JC; Hamel, E; Chapuis, J-C; Pettit, RK; Hogan, F; Sumner, B; Ain, KB; Trickey-Platt, BB. "Antineoplastic Agents 548. Synthesis of Iodo- and Di-iodocomstatin Phosphate Prodrugs." Journal of Natural Products. 2012. 75, 385–393.

Pettit, GR; Bao, GH; Melody, N; Tan, R; Doubek, DL; Gao, S; Williams, L. "Antineoplastic Agents 587. Isolation and Structure of 3-Epipancratistatin from *Narcissus v. Ice Follies*." Journal of Natural Products. 2012. 75, 771–773

George Pettit, Ph.D. (cont.)

Park, JS; Asuncion, MM; Aspe, JR; Pettit, GR; Wall, NR. "Auristatin Drugs Decrease Long-Term Surviving Levels and Induce Apoptosis in Human Pancreatic Cancer (Panc-1) Cells." Journal of Investigative Medicine. 2012. 60 148–149.

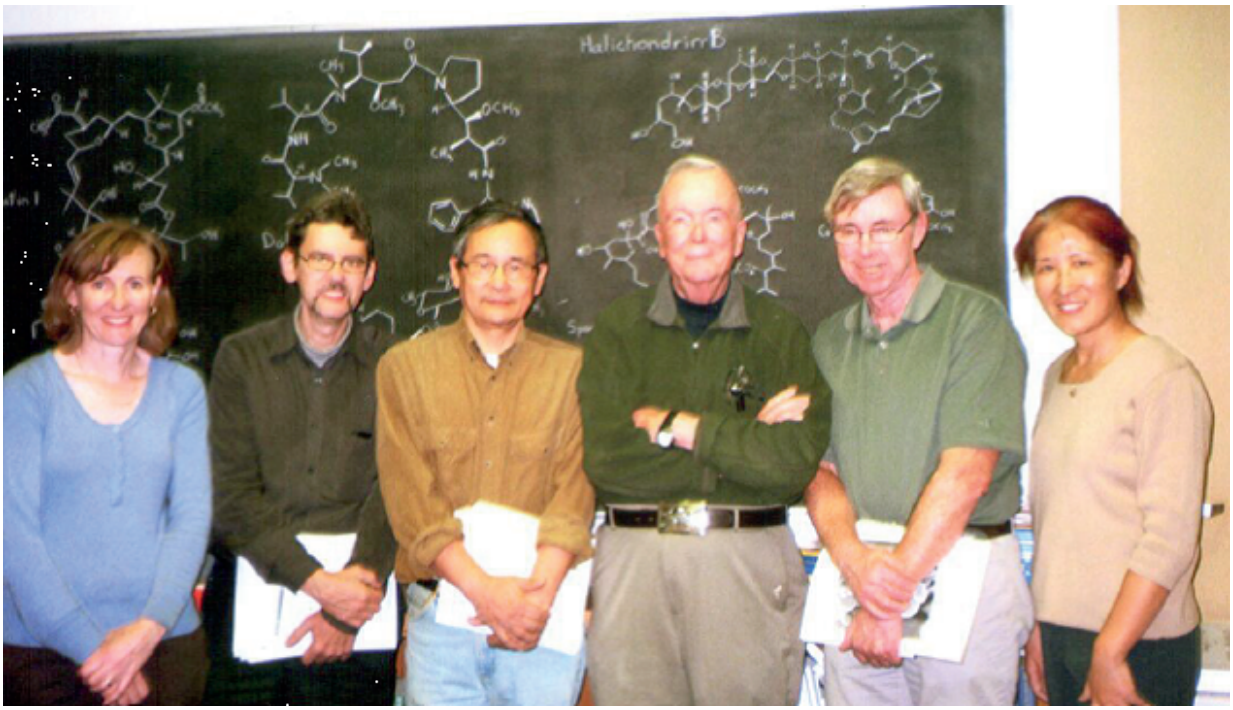
Lubahn, C; Schaller, JA; Shewmacker, E; Wood, C; Bellinger, DL; Byron, D; Melody, N; Pettit, GR; Lorton, D. "Preclinical Efficacy of Sodium Narcistatin to Reduce Inflammation and Joint Destruction in Rats With Adjuvant-Induced Arthritis." Rheumataology International. 2012. 32 (12), 3751–3760

Invited Papers, Panels, Presentations

"From a Marine Mollusc to the Clinic: The Discovery of ADCETRIS and other ADC Frontiers." World ADC Conference. San Francisco, CA. October, 2012. Keynote Lecture.

"From the Indian Ocean to Global Clinics: Discovering New Paths to Improve Cancer Treatment." Regents Distinguished Alumnus Award, WSU. Pullman, WA. September 2012. Award Lecture.

"From a Sea Hare to Global Clinics." The International Congress of Natural Products Research. New York, New York. July 28–August 1, 2012. Plenary Lecture.



From left: Noeleen Melody, Ph.D. Professor Chemistry Research Jean-Charles Chapuis, Ph.D. Sr. Research Scientist Jun-Ping Xu, Ph.D. Professor Chemistry Research Dr. Pettit Thomas Smith, Ph.D. Professor Chemistry Research Rui Tan, Ph.D. Professor Chemistry Research



Linda Powers, Ph.D.

University of Arizona

Annual Award Amount

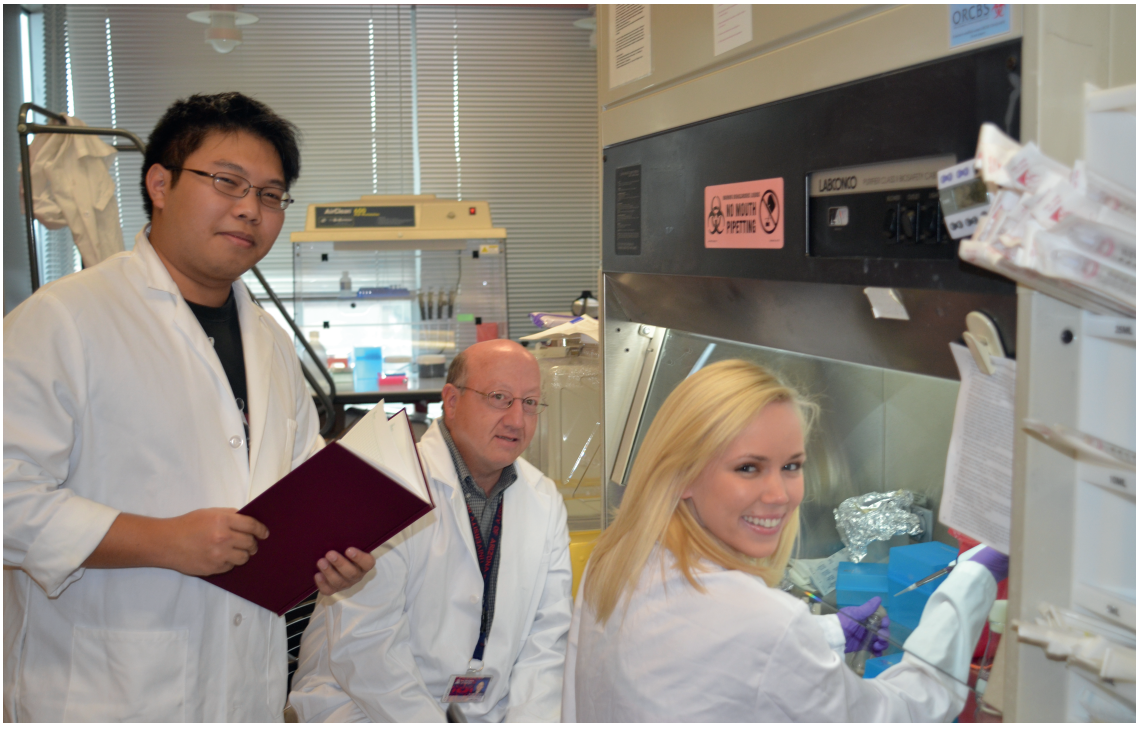
$49,999

Project End Date

June 30, 2013

Attenuating Yersinia Pestis Growth by Iron Withholding

One alternative to the development of new antibiotics is the development of strategies to 'withhold' critical nutrients, particularly iron cations that any infecting bacterium must obtain from its host. Interfering with these events would induce severe iron starvation, which would compromise the ability of the bacterium to reproduce after initially infecting a host. This would give the host's immune system more time to recognize and kill the bacterial cells. *Yersinia pestis*, the causative agent of plague, is being used as a model pathogen in carrying out our work. This project involves identifying siderocalins and peptides that might be useful in blocking bacterial uptake of ferric yersiniabactin and block the action of a secreted protein ($HasA_{YP}$) that is used to strip the heme cofactor from host hemoglobin. In this project year, we report tests results for the efficacies of these molecules in attenuating the growth of *Y. pestis* in liquid cultures



Jonathan Wan, Dr. Walther Ellis, and Hannah Curtis



Gregory Rogers, Ph.D.

University of Arizona

Annual Award Amount

$50,000

Project End Date

June 30, 2014

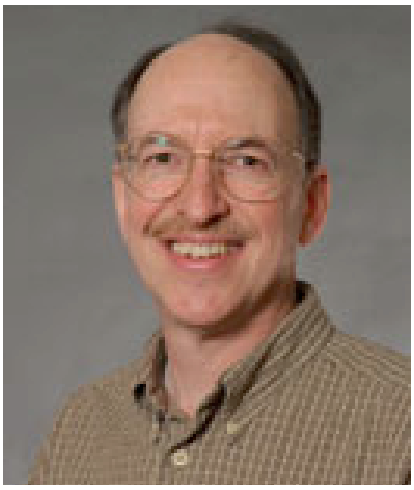
Molecular Mechanisms of Centrosome Amplification in Cancer Cells

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

Publications

Slevin, LK; Nye, J; Pinkerton, DC; Buster, DW; Rogers, GC*; Slep, KC*. "The Structure of the Plk4 Cryptic Polo Box Reveals Tandem Polo Boxes Required for Centriole Assembly." *Co-corresponding Author. Structure. July 28–August 1, 2012. 20, 1905–1917. **Received a Commentary in this issue.

Klebba, JE; Buster, DW; Nguyen, AL; Swatkoski, S; Gucek, M; Rusan, NM; Rogers, GC. "Polo-like Kinase 4 Autodestructs by Generating its Slimb-binding Phosphodegron." Resubmitted to Current Biology.



Seth Rose, Ph.D.

Arizona State University

Annual Award Amount

$125,000

Project End Date

June 30, 2014

Electrophilic Chalcones for Treatment of Paclitaxel-Resistant Cancer

The general goal of this work is to design, prepare, and test new compounds with anticancer activity. Previously we found compounds that showed the desired anticancer activity against cancer cells grown in culture, but pharmacological studies revealed that blood plasma degraded the compounds, which interferes with potential use as a drug. Consequently we set about designing modified structures that would survive in plasma.

More than a dozen new compounds were designed, prepared, analyzed for purity, and found to be active against many different types of cancer cells in culture, including drug-resistant cells. Several compounds were not degraded by blood plasma, and the compound with the best overall properties was used in a xenograft study (in progress) to assess its potential to inhibit tumor growth. The results of that study will be used for the development of compounds with improved efficacy and reduced toxicity for possible eventual use as anticancer drugs.



We are grateful to the ABRC for support of our effort to find new drugs to treat cancer. This funding has been instrumental in both the discovery and translational phases of our work. We are now attempting to advance one of our new cytotoxic agents through preclinical testing. Any success will ultimately be to the credit of the Commission for their commitment to improving the health of Arizonans through research.

—Seth Rose



Nader Sanai, M.D

St. Joseph's Hospital

Annual Award Amount

$175,000

Project End Date

June 30, 2014

Spectral Tracking of Human Glioblastoma Stem Cells

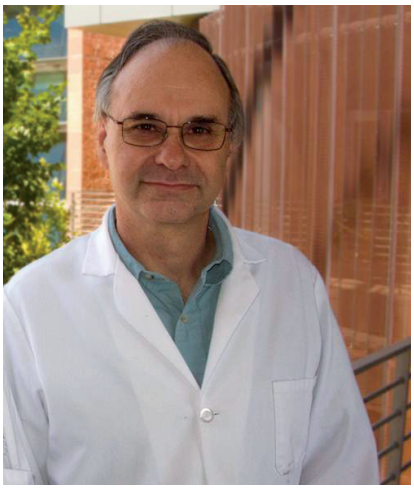
The cellular heterogeneity of glioblastomas is a devastating biological feature. The inefficacy of therapeutic strategies may be attributed to the persistence of a comparatively small proportion of glioblastoma cells that survive microsurgical resection, radiation therapy, and chemotherapy, only to repopulate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

Invited Papers, Panels, Presentations

Sanai, N. "Under the Radar: Human Glioma Dissemination through Stem Cell Corridors." 62nd Annual Meeting of the Congress of Neurological Surgeons. Chicago, IL. October, 2012.

Sanai, N. "Human Glioma Dissemination through Stem Cell Corridors." World Academy of Neurological Surgeons Annual Meeting. October, 2012.

Sanai, N. "Human Glioma Dissemination through Stem Cell Corridors." Swedish Neuroscience Institute Grand Rounds. Seattle, WA. March, 2013.



Samuel Schluter, Ph.D.

University of Arizona

Annual Award Amount

$112,500

Project End Date

June 30, 2013

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

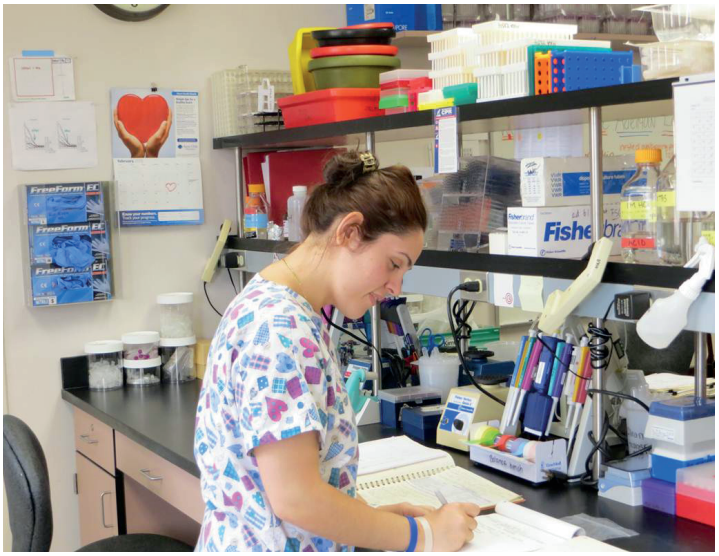
The immune system of healthy individuals produces specific autoantibodies against opioid receptors that initiate cell-signaling events similar to those associated with pain control. Utilizing this natural pool of autoantibodies, we have generated human monoclonal autoantibodies reactive against the drug-binding site of opioid receptors that bind either to 1) mu opioid receptors; 2) delta opioid receptors; or 3) both mu and delta opioid receptors. We developed an ELISA protocol to optimally discern the differential binding activities of these three classes of mAbs. We now have a panel of mAbs with fully defined binding specificity. We were unable to show binding to cell surface receptors using flow cytometer, and are now moving to more sensitive assays. Our overall goal is to test whether antibody "large protein molecules" might be advantageous over the "small peptide molecules" currently used as pain medications.

Invited Papers, Panels, Presentations

"Isolation of Human Monoclonal Antibodies to Pioid Receptors." College of Medicine, University of Arizona. March 2013.

Samuel Schluter, Ph.D. (cont.)







Innovative research is, by definition, risky. Thus, providing preliminary results showing the feasibility of these ideas is a fundamental component of federal grant applications. I am very grateful to the members of the Research Council for being receptive to new concepts and agreeing with me on the potential of my ideas. In this way, funding by ABRC is vitally important in maintaining the competitiveness of researchers in Arizona's Universities for federally funded grants. Funding by ABRC helped maintain the vitality of my lab and allowed me to continue mentoring senior high school and undergraduate students. This type of experience has been valuable to many students who have gone on to careers in science and medicine.

—Samuel Schluter, Ph.D.



Joyce Schroeder, Ph.D.

University of Arizona

Annual Award Amount

$112,500

Project End Date

June 30, 2013

Theranostic Development for the Treatment of Metastatic Breast Cancer

Our proposal is to develop a peptide-based theranostic, which is a peptide-based therapy that combines treatment with imaging, allowing clinicians to effectively monitor tumor-response. The objectives for the current year of the contract were to finalize our work on the efficacy and mechanism of action of the EJ1 peptide. Experiments into the mechanism of action revealed that EJ1 functions in two key ways. The first is through eliciting mitochondrial damage and reactive oxygen species. This appears to be one of the primary functions in vivo as well. The second is through the inactivation of the erbB receptors, by inducing the formation of inactive receptor multimers. Upon finalizing our in vivo studies, we found that EJ1 had a limited half-life and was undetectable shortly after injection, indicating further work must be done to stabilize the peptide in vivo.

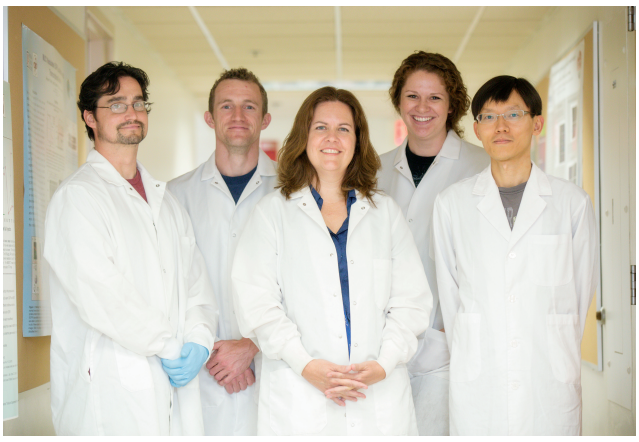
Publications

Hart, MR[1,2]; Su, HY[1,3]; Broka, D[4]; Goverdhan, A[4]; Schroeder, JA[2,3,4,5,6]. "Inactive ERBB Receptors Cooperate with Reactive Oxygen Species to Suppress Cancer Progression." Submitted.

Invited Papers, Panels, Presentations

Hart, M. "Understanding EGFR Modification, Trafficking and the Importance of its Juxtamembrane Domain in Cancer." April 12, 2013.

Su, HY. "Therapeutic Potential of EGFR-Derived Peptides in Breast Cancer." April 3, 2013.



In 2003, I had submitted a grant proposal to the NCI that included a lot of basic science, but also an aim to develop a breast cancer drug. The reviews came back from the NCI that they liked the science (they eventually funded the grant), but that the drug development was 'too risky', and they wouldn't fund the grant if that aim was included. I subsequently turned that drug development aim into a grant that was submitted to the ABRC, who funded the project. As the project progressed, ABRC continued to fund the project, including paying to patent the discoveries as they were made. Fast-forward to 2013: we have now created a biotech startup to take this very promising drug into clinical trials. Now that we have proved the drugs effectiveness in pre-clinical trials, the NCI has agreed to fund the work (via an STTR award). None of it would have been possible if the ABRC hadn't been there to fund what the NCI wouldn't.

—Joyce Schroeder, Ph.D.



Michael Sierks, Ph.D.

Arizona State University

Annual Award Amount

$157,500

Project End Date

December 31, 2013

Intracellular Targeting and Clearance of Toxic Synuclein Aggregates

The protein, α-synuclein (a-syn) is a major component of the hallmark Lewy Bodies indicative of Parkinson's Disease (PD). While specific aggregated forms of a-syn are likely to be a causative factor in PD, several studies have indicated that a-syn has protective functions in neurons. An effective therapeutic for PD should thus target only the toxic forms of a-syn without affecting other forms. Using a novel biopanning protocol developed in our lab, we have isolated recombinant antibody fragments that specifically recognize different forms of a-syn. Since a-syn aggregation occurs inside cells, the morphology specific antibody fragments when expressed intracellularly as an intrabody provide a means to test whether targeting specific forms of a-syn intracellularly represents an effective therapeutic strategy for treating PD. Here we will demonstrate that this therapeutic approach works in animal models of PD by intracellularly expressing a antibody fragment that selectively targets a toxic variant of a-syn.



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

Banner Health

Annual Award Amount

$74,810

Project End Date

June 30, 2014

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

Implementation of efficacious and low-cost rehabilitation for individuals who have incurred Traumatic Brain Injury (TBI) is a challenge. The goal of hospital-based clinicians is to identify and provide therapeutic interventions that target specific areas of physical/cognitive need as well as provide options and recommendations for continuance of outpatient programs. Given short-term hospital stays and financial constraints, therapeutic impact must be rapidly delivered and assessed. Arizona is impacted by the financial environment of dwindling resources and insurance coverage. This project addresses the challenge by examining the effects of a relatively novel therapeutic intervention that meets the needs of patients with TBI. Specifically, this program will study virtual technology training on short-term outcome and long-term rehabilitation potential. Virtual Reality (VR) methodology is an emerging technology. Success of this technology can likely be attributed to the multimodal nature of delivery, active over passive participation, social interactive nature and observation of 'real life' responses by patients. Communication among clinicians for TBI is essential. Understanding the impact of clinical factors on outcome is critical. Primary objectives of this project are:

1. To compare the safety and efficacy of a VR approach to neurorehabilitation for individuals who have incurred TBI;
2. Create a database and diverse database user group with representation from Trauma, Neurorehabilitation, Toxicology and Simulation to inform clinical decisions for inpatient therapeutic interventions with implications for out-patient treatment, and;
3. Examine significant differences between VR-based and standard therapeutic intervention groups on outcome measures for TBI.



Larry Sparks, Ph.D.

Sun Health Research Institute

Annual Award Amount

$199,456

Project End Date

March 31, 2014

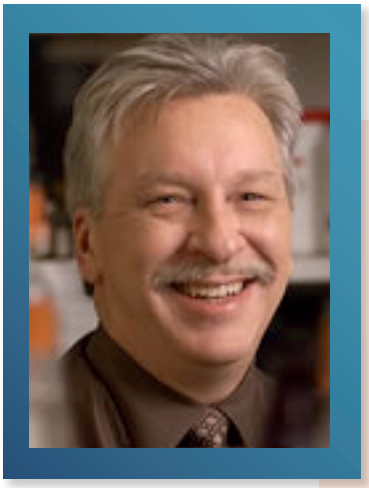
Longitudinal Change in Circulating Tau Levels Associated with Changing Cognitive Performance

The objective of this study is to establish an easily accessible biomarker in order to follow changing cognitive performance among those with or destined to develop Alzheimer's disease (AD). Our initial publication (see below) details a significant difference in plasma tau levels between normal controls and AD patients and between controls and individuals with mild cognitive impairment (MCI; considered by most to be the precursor to AD). To validate this biomarker as a surrogate to follow ongoing cognitive deterioration or possibly predict AD we have initiated a blinded longitudinal study assessing plasma tau levels in controls, individuals with MCI, and AD patients over a three year period. We have begun to collect year two samples from 389 individuals collected in year one each being yearly assessed clinically for cognitive performance during the study. We have also obtained 126 year one samples from individuals yearly assessed clinically at the University of Kentucky—year two samples will be available later this year. As a result we are currently following 515 study participants, and in the process of recruiting young controls in order to determine any age-related changes in plasma tau levels in normal controls. As a blinded study we measure tau levels without knowledge of an individual's diagnosis, or performance on standardized clinical instruments of cognition; such clinical data are directly transmitted to the data coordinating/statistical analysis unit at the University of Kentucky as are plasma tau level data and will not be available until the end of the study.

Publications

Sparks, DL[1]; Kryscio, RJ[2]; Sabbagh, MN[3]; Ziolkowski, C[1]; Lin, Y[2]; Sparks, LM[1]; Liebsack, C[3]; Johnson-Traver, S[1]

1. Roberts Laboratory for Neurodegenerative Disease Research, Banner Sun Health Research Institute. Sun City, AZ;
2. Department of Statistics, University of Kentucky. Lexington, KY;
3. Cleo Roberts Clinical Research Center, Banner Sun Health Research Institute. Sun City, AZ. May 30, 2012



In Memoriam

Dr. Larry Sparks, senior scientist at the Banner Sun Health Research Institute (BSHRI), passed away on May 12, 2013, following a brainstem hemorrhage.

After earning his Ph.D. in Biochemistry at the Medical University of South Carolina, Larry became a faculty member in the Departments of Pathology, Pharmacology and Experimental Therapeutics and a Chief Biochemical Consultant with the Kentucky Medical Examiner's Program. He joined the Sun Health Research Institute in 1997.

During his career, Larry made a number of important contributions to the understanding of the human brain, and during his 16 years at BSHRI, his research has made an indelible impact on Alzheimer's research. In addition to his other contributions, Larry was the first to demonstrate an association between cholesterol and amyloid plaque deposition; the first to show that this association is mediated by copper metabolism; and in conjunction with BSHRI and industry colleagues, the first to test the efficacy of a cholesterol-lowering agent in the treatment of Alzheimer's disease. He was the author of more than a 100 research articles, some of which were published in the most prestigious scientific and neurology journals, and his seminal contributions to the relationship between heart and Alzheimer's disease were described in numerous national and scientific news outlets, including a cover article in *Newsweek*.

Larry loved his research. He treasured the idea of taking out-of-the-box approaches to helping address important problems in the most impactful way, and he cherished the time he got to spend with his wife, Lisa, fishing in their vacation home in the Florida Keys. Dr. Sparks was a respected member of the research community and a valued member of the Arizona Alzheimer's Consortium.



David Treiman, M.D.

St. Joseph's Hospital

Annual Award Amount

$300,000

Project End Date

June 30, 2013

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

Post-traumatic epilepsy (PTE) as a result of traumatic brain injury (TBI) is a growing problem. Five to 50% of individuals who suffer TBI will eventually develop epilepsy as the result of the injury. However, which patients will develop post-traumatic epilepsy cannot be predicted currently. There exists a need for the development of novel algorithms that can reliably characterize EEG signals that may be a marker of epileptogenesis, and thus predictive of the development of PTE. The intent of this study has been to develop such an algorithm by identifying patients with moderate and severe TBI during their initial acute hospitalization and then following them with serial EEG to predict which patients will develop epilepsy. The human study has been complemented by use of a rat model of TBI, the controlled cortical impact model, with 16 weeks of continuous EEG recordings obtained from each rat. We have preliminary evidence for an algorithm that will predict PTE after TBI, which is more fully described in the report summary.

Publications

Faith, A; Lasemidis, LD; Marsh, S; Treiman, DM; Tsakalis, K; Vlachos, L; White-James, J. "Brain Network Characteristics in Status Epilepticus." Optimization in Science and Engineering.

Invited Papers, Panels, Presentations

Krishnan, B; Lasemidis, L; Tobin, E; Treiman, D; Venkataraman, V; Vlachos, L; White-James, J. "Long-term EEG Dynamics following TBI in a Rat Model of PTE." Neurotrauma Society 2012 Symposium. Phoenix, AZ. July 22–25, 2012. Poster Presentation.

Tobin, E. "Long-term EEG Dynamics following TBI in a Rat Model of PTE." Degree Master of Science. Arizona State University. Approved 2012. Thesis.

Al-Omaishi, L; Theodore, N; Treiman, DM; Treiman, LJ. "Difficulties with Recruitment of Traumatically Brain Injured Patients for a Prospective Post-Traumatic Epilepsy Study." American Epilepsy Society Annual Meeting. San Diego, CA. December 2012. Poster Presentation.

Krishnan, B; Lasemidis, L; Tobin, E; Treiman, D; Vlachos, L; White-James, J. "Dynamics of EEG in a Longitudinal Study of Post-Traumatic Epilepsy after TBI." American Epilepsy Society Annual Meeting. San Diego, CA. December 2012. Poster Presentation.



Clarisse Tsang

Arizona Department of Health Services

Annual Award Amount

$100,000

Project End Date

March 31, 2014

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

Coccidioidomycosis is a fungal disease endemic to the southwestern United States. In June 2009, a major commercial laboratory changed its reporting practice by beginning to report positive coccidioidomycosis enzyme immunoassay (EIA) results without confirmation by immunodiffusion assay, thereby increasing the number of reported coccidioidomycosis cases from about 4,000–5,000 cases annually to 12,000–17,000 cases. To evaluate the effect of EIA laboratory results in diagnosing coccidioidomycosis, ADHS reviewed all coccidioidomycosis results from two major laboratories. The enzyme immunoassay (EIA) was calculated to have 83.8% and 97.4% sensitivity and 92.6% and 27.5% specificity, respectively. To evaluate the impact that the change in EIA reporting has on coccidioidomycosis surveillance in Arizona, 2011 data was compared to 2007 data. Results from this investigation suggested that reporting of positives identified only by EIA significantly altered the 2011 data by shifting the demographics of coccidioidomycosis in Arizona to be mostly in females and in a younger population than what was previously reported. Further investigations will be done on 2012 coccidioidomycosis cases to assess whether positive EIA results should be confirmed as coccidioidomycosis cases.

ADHS interviewed and reviewed medical records of disseminated coccidioidomycosis cases to identify risk factors to improve physician diagnosis and treatment of this disease. Disseminated coccidioidomycosis cases were significantly more likely to be hospitalized and treated with antibiotics for a longer period of time than those without disseminated disease. Further study of risk factors associated with disseminated disease is being done to improve diagnosis and clinical management of coccidioidomycosis. In addition, ADHS conducted interviews on patients that were 25 or younger. A preliminary analysis determined that asthma (17%) was the most common comorbidity among younger coccidioidomycosis cases whereas diabetes was only 2%. The most common symptoms presented were fatigue (77%), fever (60%), cough (58%), headache (52%), shortness of breath (49%) and sore throat (44%).

A subset of samples on cases with severe coccidioidomycosis will be collected for genetic sequencing. This data will be used to identify risk factors and characteristics associated with coccidioidomycosis, evaluate the state's surveillance program and target clinical recommendations for improved management and outcomes for cases of coccidioidomycosis.

Publications

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

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

Clarisse Tsang (cont.)

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

Chen, S; Erhart, LM; Anderson, S; Komatsu, K; Park, B; Chiller, T; Sunenshine, R. "Coccidioidomycosis: Knowledge, Attitudes, and Practices Among Healthcare Providers—Arizona, 2007." Medical Mycology. 2011. Early Online 1–8.

Invited Papers, Panels, Presentations

Tsang, CA; McDougall, S; Anderson, SM. "Coccidioidomycosis in Younger Populations, Arizona, 2011."

1. 57th Annual Coccidioidomycosis Study Group Meeting. Pasadena, CA. April 6, 2013. Abstract;
2. IDWeek 2013. San Francisco, CA. October 2–6, 2013. Abstract.

Lusk, R; Erhart, L. "Comparison of Enzyme Immunoassay (EIA) to Immunodiffusion & Complement Fixation for Coccidioidomycosis Diagnosis & Surveillance." Arizona Infectious Disease Conference, Arizona Department of Health Services. Tempe, AZ. July 31–August 2, 2012. Abstract.

Benedum, C; Tsang, CA. "Coccidioidomycosis Surveillance in Arizona: Comparison of 2007 and 2011 Data."

1. 56th Annual Coccidioidomycosis Study Group Meeting, Arizona Department of Health Services. Tucson, AZ. March 24, 2012. Abstract;
2. Border Binational Infectious Disease Conference. Austin, TX. May 22–24, 2012. Abstract;
3. Arizona Infectious Disease Conference. Tempe, AZ. July 31–August 2, 2012. Abstract.

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

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



Victor Waddell, Ph.D.

Arizona Department of Health Services

Annual Award Amount

$175,000

Project End Date

March 31, 2014

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

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

Invited Papers, Panels, Presentations

Forbes, L. "Detection of Influenza Antiviral Resistance by Pyrosequencing." ASCLS Symposium. Mesa, AZ. March 6, 2013.



Frederic Zenhausern, Ph.D.

University of Arizona

Annual Award Amount

$125,000

Project End Date

June 30, 2014

A Rapid Viscosity-Based Method to Characterize Biological Fluids

During FY 2013, we have finalized the automation of the setup used to drop milimetric glass beads into liquids and study their splashing behavior and have started to use it to tackle systems where viscosity changes can be monitored using this new technique. For instance, we are able to use a series of water-glycerol dilutions as viscosity standards and use the calibration curve to extract an interpolated value of the viscosity of an "unknown" cellulose solution. In addition, we are able to use the glass beads as both actuators and sensors to induce, and then probe the evolution of acrylamide polarization by dipping them in the tetraethylenediamine initiator and dropping them in the solution. This step is important towards the monitoring of a self-assembly reaction such as the fibril assembling of Fmoc-L3-OMe by demethylation using subtilisin, for which all reagents have now been obtained.

Publications

"Review of Scientific Instruments." American Institute of Physics. June 2013. Reviewed and Declined.

"Measurement Science and Technology." Institute of Physics. July 2013. Under Review.

Invited Papers, Panels, Presentations

The work has been often presented in part of other larger lectures given by the PI at various internal seminars, for example at an invited seminar on biosensors organized by the Chemical Engineering Department at UA Tucson (May 2013). More recently, the work was presented by Dr. C. Hurth at the Departmental Scientific Retreat, Basic Medical Science Department, College of Medicine Phoenix, June 28–29, Cave Creek, AZ.

4 Core Programs

Biospecimen Locator



At-A-Glance

BIOSPECIMEN LOCATOR



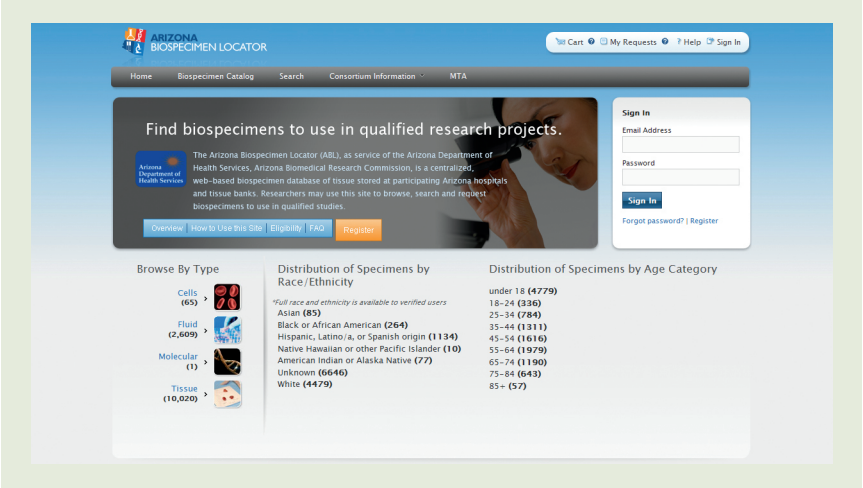
Funding Source Used

Disease Control Research Fund

Program Highlights

Collaborated on and submitted two federal grant applications.

Biospecimen Locator



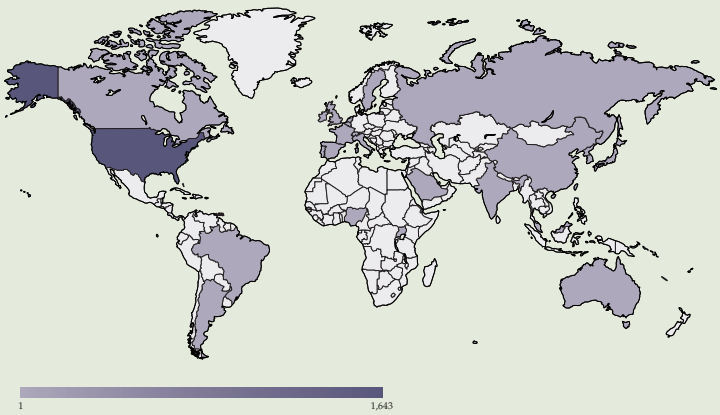
Acquiring quality biospecimens is one of the largest obstacles researchers face as they strive to advance medical science and improve patient care. The Arizona Biospecimen Locator (ABL) was designed to provide researchers with specimens needed to advance their research studies. The ABL is a web-based biospecimen database of both diseased and normal solid tissues, cells, fluids and molecular samples stored at participating Arizona hospitals and tissue banks.

Researchers can use the ABL to search and request biospecimens which are organized by disease, type of specimen, preservation type, anatomic source and demographics of participants to use in their qualified research studies. Using ABL encourages research collaboration that may lead to more effective treatments and potential cures.

To guide the work of the ABL, ABRC facilitated the creation of the Arizona Biospecimen Consortium. The Consortium is comprised of scientific, legal and research representatives from Arizona healthcare institutions and university professionals that take an active role in the development of the website and implementing best practices. This service is a novel approach to address specific infrastructure and staffing needs of hospitals, allowing for a unique blend of collaboration while retaining individual identity, ownership, and business models. All participating sites agree to use one Material Transfer Agreement to govern the terms and conditions of specimen transfer and use.

The Arizona hospitals that participate in the program and currently link to the ABL include St. Joseph's Hospital and Medical Center, Maricopa Integrated Health System, and Phoenix Children's Hospital. ABRC is in the process of on-boarding additional organizations. ABRC also partners with 5AM Solutions to develop and maintain the website. Battelle assists in project coordination. Additionally, members from the Arizona State University, University of Arizona-College of Medicine, Barrows Neurological Institute, Children's Hospital of Los Angeles, and patient advocacy groups, Kay Kayes and Arizona Myeloma Network sit on the Arizona Biospecimen Locator Advisory Board.

ABL Website Activity



Country/Territory	Acquisition		
	Visits	% New Visits	New Visits
	1,803 % of Total 100.00% (1,803)	**36.16%** Site Avg: 36.11% (0.15%)	**652** % of Total 100.15% (651)
1. United States	1,643	32.01%	526
2. Australia	38	76.32%	29
3. United Kingdom	18	72.22%	13
4. China	16	87.50%	14
5. India	16	87.50%	14
6. Canada	12	83.33%	10
7. Taiwan	10	50.00%	5
8. South Korea	9	66.67%	6
9. Japan	6	83.33%	5
10. France	5	80.00%	4

As of December 2013, the ABL has had over 1800 visits from over 600 unique individuals/ organizations with over 70 researchers signing on as a registered user. The ABL visitors and registered users are from sites throughout the world:

Average visit durations on the site were more than eight minutes indicating that the website is "sticky" and researchers were searching through an inventory of over 12,000 diverse samples. In addition, the ABL website has attracted new traffic through the addition of back links from relevant sites including ABRC, Phoenix Children's Hospital, University of Arizona College of Medicine, Neurolex and One Mind for Research. Researchers have submitted requests for biospecimens needed for their research and the current participating sites have been working with these researchers to find the specific types of samples they are seeking, including requests for prospective collections. The goal is to add additional partner sites to be able to increase the biospecimen inventory through the ABL and meet the needs of researchers.

ABL Value to Arizona Entities.

The dollars spent to provide a program do not always directly translate to dollar-for-dollar ratio. Although specimens are available online, the indirect value brought to an organization through this program is immeasurable. Identifying successes must be thought of in a distinct way. As a needed, yet supportive function in research, the following questions are provided to the facilities for the Year End Summary Reports.

1. What has ABRC's funding allowed your Tissue Repository to do?
2. How has it directly benefited the State of Arizona?
3. Were there any resulting publications, abstracts, presentations from internal or external investigator using the tissue collected through this program?
4. How many of your existing contracts and investigators use the tissue for their projects?
5. Have there been any resulting collaborations between the tissue bank and other organizations as a result that were not previously formed or could not have been formed without the financial assistance of ABRC?

St. Joseph's Hospital and Medical Center reported:

Q1: What has ABRC's Funding allowed SJHMC and the SJHMC Tissue Repository to do?

ABRC's funding has allowed St. SJHMC (HSPS) to expand collections beyond neurosurgical specimens to include endoscopic procedures and general surgical specimens, including gynecological tumor specimens. In addition, HSPS is now providing progenitor cell lines isolated from glioma tissue specimens. These cell lines are being offered with matched banked tissue, which is a valuable resource for researchers. HSPS has been able to coordinate with the neurosurgeons and neurosurgical operating staff the collection of tissue intraoperatively, allowing for better preservation and integrity of tissue specimens.

Q2: How has it directly helped the State of Arizona?

HSPS has provided tissue for local researchers within Arizona, which has been a vital component to securing grants. It brings together separate institutions who might not otherwise collaborate on issues relating to bioscience research.

Q3: Were there any resulting publications, abstracts, presentations from internal or external investigator using the tissue collected through this program? If yes, how many and could you provide a list?

Not available at this time

Q4: How many of your existing contracts and SJHMC investigators use the tissue for their projects?

We have numerous contracts to provide tissue for many investigators, including NIH (TCGA project—glioma tissue specimens and general surgical tumor types), NCI, Angioma Alliance, Chordoma Foundation, and many local or internal investigators. Because of ABL funding, we have formed relationships with Mayo Clinic in Scottsdale, TGEN, and Stanford University.

Q5: Are there any resulting collaborations between SJHMC and other organization as a result that were not previously formed or could not have been formed? If yes, how many and could you provide additional details?

HSPS is in the process of working on a biospecimen related research project in collaboration with TGEN. HSPS through ABL support has been able to significantly contribute and collaborate with NIH on the TCGA project. HSPS has also been able to participate in a research project providing 100 low grade gliomas to NCI for the evaluation of the IDH1 mutation and a possible targeted treatment. Through the TCGA project, Dr. Eschbacher has played a role as a member of reviewing committee of pathology tissue integrity, in conjunction with other neuropathologists from renowned institutions, including Stanford, Emory, and Mayo. In addition, HSPS has forged relationships with external organizations, such as the Chordoma Foundation and the Angioma Alliance. HSPS has provided tissue for a collaborative project between Stanford and BNI. HSPS has forged a collaboration with Mayo Clinic in Scottsdale and more recently Mayo Clinic in Rochester in providing tissue for project investigating perfusion MRI imaging and correlation with molecular tumor markers. HSPS is currently working with the neurosurgery department and Zeiss Optics to investigate novel ways of tissue assessment to better predict and collect tissues of adequate celluarity for research and patient molecular studies. To this end, Zeiss has provided the department of pathology and ns with a state of art confocal microscope. HSPS has supported numerous internal investigators in their pursuance of publications and grants, including NIH and local ABL and BNF funded grants.

Maricopa Integrated Health Services reported:

Q1: What has ABRC's Funding allowed MIHS and the MIHS Tissue Repository to do?

The Creation of a Bio Bank at the only Public Hospital and Health Care System. Prior to MIHS obtaining the award for the Bio-specimen Locator Project, the ability to bank tissues that were of interest to the scientific community did not exist. There are cases where MIHS has individual agreements and approvals in place to provide tissues to a limited number of researchers, but with very limited preservation or storage capabilities. The ABRC grant has allowed for the development of the space, equipment, standard operations, Institutional Review Board approvals, and the foundation for the infrastructure to create a modern Bio-bank.

Q2: How has it directly helped the State of Arizona?

Research that promotes health equities. The patient population at MIHS is a racially diverse group which is best suited for research that recognizes and aims to prevent health disparities. A Bio-Repository consisting of tissues from this population is an ideal opportunity to help address the scientific questions that come with the most cutting-edge research of individualized medicine.

International Presence. MIHS was able to send the Bio-repository's clinical research coordinator, Svetlana Mihaylova-Todorova to the global conference for the International Society for Biological and Environmental Repositories (ISBER) to be able to learn from the experts leading Bio-repositories globally. As the Bio-Repository at MIHS is only now getting established, this information is critical for ensuring long-term success from the start. Collaborations with ISBER has also allowed for the exploration of marketing opportunities to make Arizona's tissues available to scientists anywhere.

Q3: Were there any resulting publications, abstracts, presentations from internal or external investigator using the tissue collected through this program? If yes, how many and could you provide a list?

Society of Research Administrators Award: Cris Wells, director of Arizona State University's Clinical Research Management graduate program and co-author Svetlana Mihaylova-Todorova, of MIHS, received the "Best Poster of the Year Award" from the Society of Research Administrators (SRA). Their poster, "The Building Blocks of a Successful Bio-specimen Repository," discussed the four essential elements of a successful bio-specimen repository, including ethics, management, science and technology. The poster was exhibited and judged at SRA's annual meeting in October, and the winner was announced in December.

Q4: How many of your existing contracts and MIHS investigators use the tissue for their projects?

MIHS has recently started "making deposits" into the bank with post-retention paraffin blocks of tumor tissues. These tissues can benefit certain scientific endeavors. MIHS had been providing these types of tissues to local scientists for the study of genomic structures found in tumors over the past few years. With the grant, these tissues have become much more widely available. The benefit of having the grant available to pay for personnel to begin the cataloging of these tumor tissues has had the immediate benefit of helping the MIHS pathology department with quality analysis. Archived tissues that were all but impossible to locate after a few years previously are now very easily located. The MIHS pathologists have been the first of what we plan to be many physicians to find the new Bio-repository helpful. This is an indirect benefit to the citizens of Arizona in need of crucial diagnoses at Maricopa Medical Center.

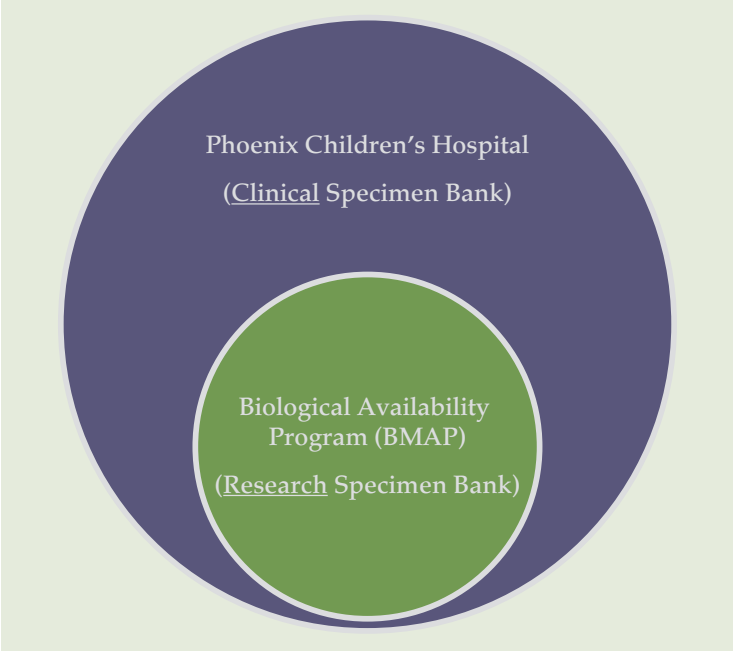
Q5: Are there any resulting collaborations between MIHS and other organization as a result that were not previously formed or could not have been formed? If yes, how many and could you provide additional details?

Pursing College of American Pathologist Certification. MIHS Bio-repository personnel were able to meet with representatives of the regulatory institution College of American Pathologists (CAP) to look into the steps that will need to be taken to obtain certification. Certification, although not required, will add credibility and position MIHS's new Bio-Repository alongside the county's top intuitions.

Future Opportunities for Collaborations: As MIHS moves forward in establishing a Bio-repository from the ground up, the team is planning to establish an advisory board to ensure that the project remains on course for many years to come. MIHS is currently considering what the most important and useful tissues would be to the scientific community and to the specific patient population that is served here. There have been preliminary meetings with researchers from some of Arizona's universities to look into the possibility of collaborations for collecting saliva samples, blood samples, and other tissues in addition to tumor tissue. MIHS is also exploring which tissues would most benefit the patients that we treat such as pediatrics, HIV positive patients, and trauma and burn victims. Once a strategic business plan is established, the tissues that will be stored will be preserved utilizing the latest methods to ensure that the highest quality of samples are available to researchers world-wide for many years.

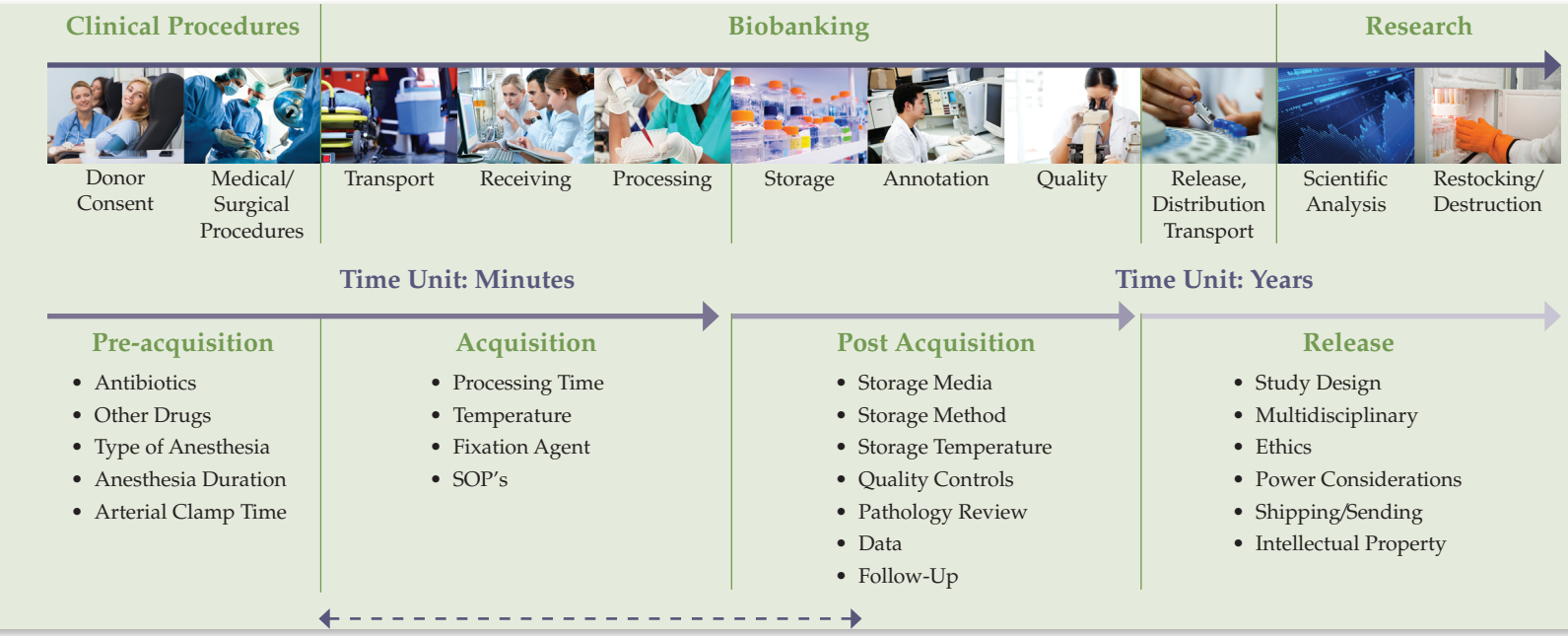
Phoenix Children's Hospital reported:

Current research to unlock the mysteries of pediatric diseases is largely left for laboratory scientists in conjunction with clinicians and is the main drive for the future of personalized medicine. The availability of de-identified, well annotated high quality patient specimens for research is crucial for the advancement of any translational research program like companion diagnostics and clinical trials.



At PCH, the pathology department has been saving tissue specimens which were no longer needed for patient care ("surplus" specimens) since 2002. Over the last 10 years, this practice has accrued over 30,000 specimens saved as paraffin blocks and approximately 2,000 frozen tissue specimens in the "Pathology Tissue Bank." However, the availability of these specimens for research requires additional levels of security and processing beyond the routine protocol performed in the pathology department. For this purpose, the "Research Specimen Bank" also called BMAP was proposed as a sub-set from the existing tissue bank and the project was approved by the PCH institutional review board (IRB) in 2009 (see right).

The initial three-year funding from ABRC allowed us to hire a coordinator and assistants, and purchase start-up software, equipment and supplies. The following illustration exemplifies the activities currently performed by the BMAP personnel in order to have high quality specimens available for research while preserving patient's confidentiality and without detrimental impact on his/her care.



At this point, PCH currently hold approximately 4,000 patients in the database, with over 200 consented cases associated with 1,400 specimen aliquots. More importantly, the database has also created the background for matching HIPAA compliant data from existing PCH clinical research registries to the aliquots. The service is currently utilized by neuroscience and oncology investigators and is expanding to include the endocrinology and dermatology divisions.

OUTCOMES and IMPACT:

The BMAP offers translational researchers the availability of consented and properly processed "surplus" specimens for projects with outside investigators like Translational Genomics (TGen), Arizona State University (ASU) and University of Arizona among many others who don't have access to patient specimens and data. The biorepository aims at building a bridge between bench discovery and the patient's bedside in a cost-effective way.

BMAP is necessary for PCH to become an active participant in the fight against pediatric diseases, and it is anticipated that the BMAP could even become a national/international resource for pediatric samples associated with de-identified data, especially rare diseases. Research advanced by the PCH Biorepository is likely to contribute to discoveries on the role of genetic alterations in cancer initiation, progression and metastasis and may lead to improvements in the diagnosis, classification and therapy of tumors and non-oncologic diseases. In addition to enabling the development of new diagnostic and therapeutic options for children, this core service supports the research of PCH investigators and promotes collaboration with other institutions which have a well-established research infrastructure but lack the critical clinical component (consented human specimens with associated clinical data) to make their research directly relevant to the treatment of children. In other words, the availability of this program allows Phoenix Children's Hospital to become more actively involved with pediatric research at national and international levels.

The following list illustrates some of the publications that originated from collaborative efforts in recent years utilizing BMAP specimens:

1. Bristol RE, Rennert J, Beaudry C, Coons S, Carpentieri D, Berens ME. Gene expression profiling of pediatric brainstem gliomas. Congress of Neurological Surgeons Annual Meeting, October 2005.

2. Fortin SP, Ennis MJ, Savitch BA, Carpentieri D, McDonough WS, Winkles JA, Loftus JC, Kingsley C, Hostetter G, Tran NL. Tumor necrosis factor-like weak inducer of apoptosis stimulation of glioma cell survival is dependent on Akt2 function. Mol Cancer Res. 2009 Nov;7(11):1871–81.
3. Carpentieri D, Adelson P, Etzl M, Rosenfeld A, Kaplan A, Coons S, Eschbacher J, Kiefer J,Polpitiya A Petritis K. Therapeutic Drug Target Interactions by Mass Spectrometry Proteomic Analysis of Formalin Fixed Paraffin Embedded Pediatric Brain Tumors. TGen-VARI retreat. November 2011, Phoenix, AZ; ISBER annual meeting, May 2012, Vancouver, BC.
4. Chakravadhanula M, Tembe W, Legendre C, Carpentieri D, Liang WS, Bussey KJ, Carpten J, Berens ME, Bhardwaj RD. Detection of an Atypical Teratoid Rhabdoid Brain Tumor Gene Deletion in Circulating Blood Using Next-Generation Sequencing. J Child Neurol. 2013 Oct 17.

Recently, internal investigators have also utilized our specimens and services to support collaborative projects with several outside institutions:

1. **PCH Investigator**
   Bhardwaj R et al
   Collaborator
   The Scripps Institute
   Title
   The Role of Lysophosphatidic Acid (LPA) in Human Hydrocephalus
2. **PCH Investigator**
   Bhardwaj R et al
   Collaborator
   TGen
   Title
   Genomics of Pediatric Brain Tumors
3. **PCH Investigator**
   Hingorani P et al.
   Collaborator
   Internal
   Title
   Disialoganglioside (GD2) Expression in Pediatric Rhabdomyosarcoma
4. **PCH Investigator**
   Rosenfeld A et al
   Collaborator
   Denver Children's Hospital
   Title
   Craniopharyngiomas
5. **PCH Investigator**
   Eshun F. et al
   Collaborator
   Arizona State University
   Title
   Analysis of the phosphorylation sites and kinases implicated in the phosphorylation of ShcC, a scaffold protein over-expressed in high-risk neuroblastoma, and their implication in tumorigenicity.

4 Core Programs

Research Education



At-A-Glance

RESEARCH EDUCATION



Funding Source Used

Disease Control Research Fund

Program Highlights

Sponsored Clinical Research Conference—Embracing Change: Clinical Research in the 21st Century

Sponsored Arizona's Clinical Research Workforce Survey

Updated and published IRB Statewide Directory

Research Education

In working with Arizona researchers and through its commitment to the Arizona Biosciences Roadmap, ABRC identified a need to make high quality educational resources available. The ABRC Educational Initiative sought to create a shared sense of community by bringing national and local experts together to engage Arizona researchers and clinical professionals in emerging topics.

Past Educational Workshops included:

- 2007—The Tissue Issue Retreat
- 2008—The Patient Registry Symposium
- 2008—Arizona IRB Directory Launched
- 2008—IRB At Your Doorstep 250 Workshop
- 2009—Grant Writing Workshop
- 2010—Clinical Research Compliance Workshop Series:
  - Clinical Trials Reimbursement and Payment
  - Clinical Trials Contracting
  - CHTN Grant Application
  - Conflict of Interest in Clinical Research
  - Clinical Research Privacy and Security
  - Biospecimens in Clinical Research
- 2011—Grant Writing and Clinical Research Skills Development Symposium

Other Educational Projects included:

Developing resource materials to support the conduct of research

Includes template informed consent documents, HIPAA authorization forms, clinical trial agreements and other resources

Developing Community-based participation guides

Advance research collaborations with Native American and Hispanic/Latino Population Groups

Supporting collaborative IRB resources

Provide support for networking and information sharing, including the Arizona IRB Directory which is updated annually and shared with the Arizona research community

Education Endeavors Today:

A 2013 survey reported the Mountain state region, which includes Arizona, had the most reliance on grant funding as a percentage of their annual budgets.

Funding from Grants (% of Budget)	All Respondents	New England	Mid-Atlantic	East North Central	West North Central
Under 25%	58.4%	62.2%	60.8%	58.9%	59.0%
Over 25%	42.4%	37.9%	40.2%	41.1%	41.1%
Funding from Grants (% of Budget)	**All Respondents**	**South Atlantic**	**South Central**	**Mountain**	**Pacific**
Under 25%	58.4%	54.0%	57.6%	55.9%	62.2%
Over 25%	42.4%	47.0%	42.4%	45.5%	39.0%

http://www.grantstation.com/sog_main.asp

Currently, ABRC offers on-line access to the CITI Program at no cost for those working in research. The CITI Program is an educational training tool with a comprehensive suite of courses to enable those engaged in performing and overseeing human subjects clinical research with the training required by the U.S. Department of Health and Human Services.

Providing workshops and developing templates for institutional policy, procedures, and practices is key for the sustainability of many of Arizona's research and public health programs. Hosting an affordable IRB networking event and Grant Writing Workshop during May of 2014 is one such way to assist the Arizona community in searching for and pursuing collaborative funding opportunities while staying abreast on emerging trends.

4 Core Programs

Public Cord Blood



At-A-Glance

PUBLIC CORD BLOOD



Funding Source Used

Disease Control Research Fund

Program Highlights

Student Ambassador Program

10 Arizona Cord Blood Units Selected and Transplanted into Patients

Sponsored Education Tables:

- Northern Arizona AWHONN Conference
- Phoenix AWHONN Conference
- Northern Arizona American Indian Maternal Child Wellness Forum
- Arizona SciTech Festival
- Arizona Public Health Association Fall Conference

Arizona Public Cord Blood Program



Artist: Yovannah Diovanti

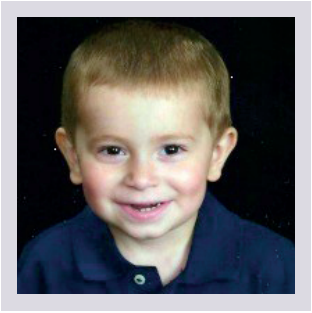
EDUCATION

DONATION

RESEARCH

Public Cord Blood

Why is PUBLIC DONATION of Cord Blood important?



If you ever doubted if cord blood was really used or that it could really change someone's life, look no further… meet Noah Swanson. Here is his story:

Noah is the son of Scott and Nancy Swanson. Born on September 18, 2009, Noah was diagnosed with severe Neutropenia and Myelodysplastic Syndrome. He had been classified as having Refractory Cytopenia of Childhood (RCC) MDS. Noah was on the bone marrow registry since December 2011. After 1 1/2 years of searching for a bone marrow match with no success, the transplant team at Phoenix Children's Hospital (PCH) decided on a cord blood transplant for Noah. Noah was admitted to PCH on June 27th, 2013 to begin his transplant journey. Noah received his publicly donated cord blood stem cell transplant on July 5, 2013. Noah stayed in-patient for 12 weeks. He was released on September 17, 2013 to begin his outpatient journey. Learn more about Noah on his website: http://cota.donorpages.com/PatientOnlineDonation/COTAforNoahRDS

The Arizona Public Cord Blood Program was created to advance the collection of and increase the number of cord blood units available for transplantation. Currently, seven out of ten people will not have a suitable matched donor in their family and will depend on the National Marrow Donor Program (NMDP) registry to find a match. Adding diverse units to the registry increases the likelihood that all patients will find a match.

In the past when a baby was born, the umbilical cord was thrown away. But today, blood from the umbilical cord can be collected for children and adults with certain genetic or life-threatening diseases such as leukemia or lymphoma. More than 22,000 patients around the world have received transplants from donations to the public cord blood banks.

The current participating collection sites include:

- St. Joseph's Hospital and Medical Center
- Maricopa Integrated Health System
- Phoenix Baptist Hospital

Tucson Medical Center is in the process of rolling out the donation program as part of the Arizona Public Cord Blood Program. A separate contract was entered into with the University of Colorado—ClinImmune Labs as Arizona's Cord Blood Bank authorized by NMDP to upload into the registry. ABRC has also partnered with Save The Cord Foundation to help educate others on the importance of public donation and what the Arizona Public Cord Blood Program is all about.

Public Cord Blood (cont.)

This program officially began collections in late 2011. Since the program inception, the participating sites have collected over 2,524 Cord Blood Units. Of those, 479 Cord Blood Units have been banked and listed on the registry for potential transplantation. To date, 10 Arizona Cord Blood Units have been selected through the registry and transplanted into those with Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), or Non-Hodgkin's Lymphoma.

	Overall Summary	St. Joseph's Hospital and Medical Center	Phoenix Baptist Hospital	Maricopa Integrated Health Care System
Total # of Births	19,777	8,788	6,450	4,539
Total # of Cord Blood Units Collected	2,524	1,381	743	400
Total Banked Cord Blood Units	479	302	107	70

Other Research

Arizona Alzheimer's Consortium



Arizona Alzheimer's Consortium



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

Under an Appropriation, the Consortium receives $1,125,000 for Alzheimer Disease research. Of that amount, the Consortium is required to match $1,000,000. This year, the match contributed by the Consortium was $1,070,107.

Since the Consortium's inception, its researchers have generated more than 3,000 publications and 800 research grants and contracts. In addition to major scientific contributions, its researchers have generated more than a half billion dollars in new research investments, new research facilities and numerous jobs. The Consortium has played leadership roles in helping to uncover Alzheimer's disease mechanisms, genetic and non-genetic risk factors, characterize the earliest brain changes associated with the predisposition to Alzheimer's disease and the brain changes associated with normal aging, develop new scientific and clinical procedures, and establish a new era in Alzheimer's disease prevention research.

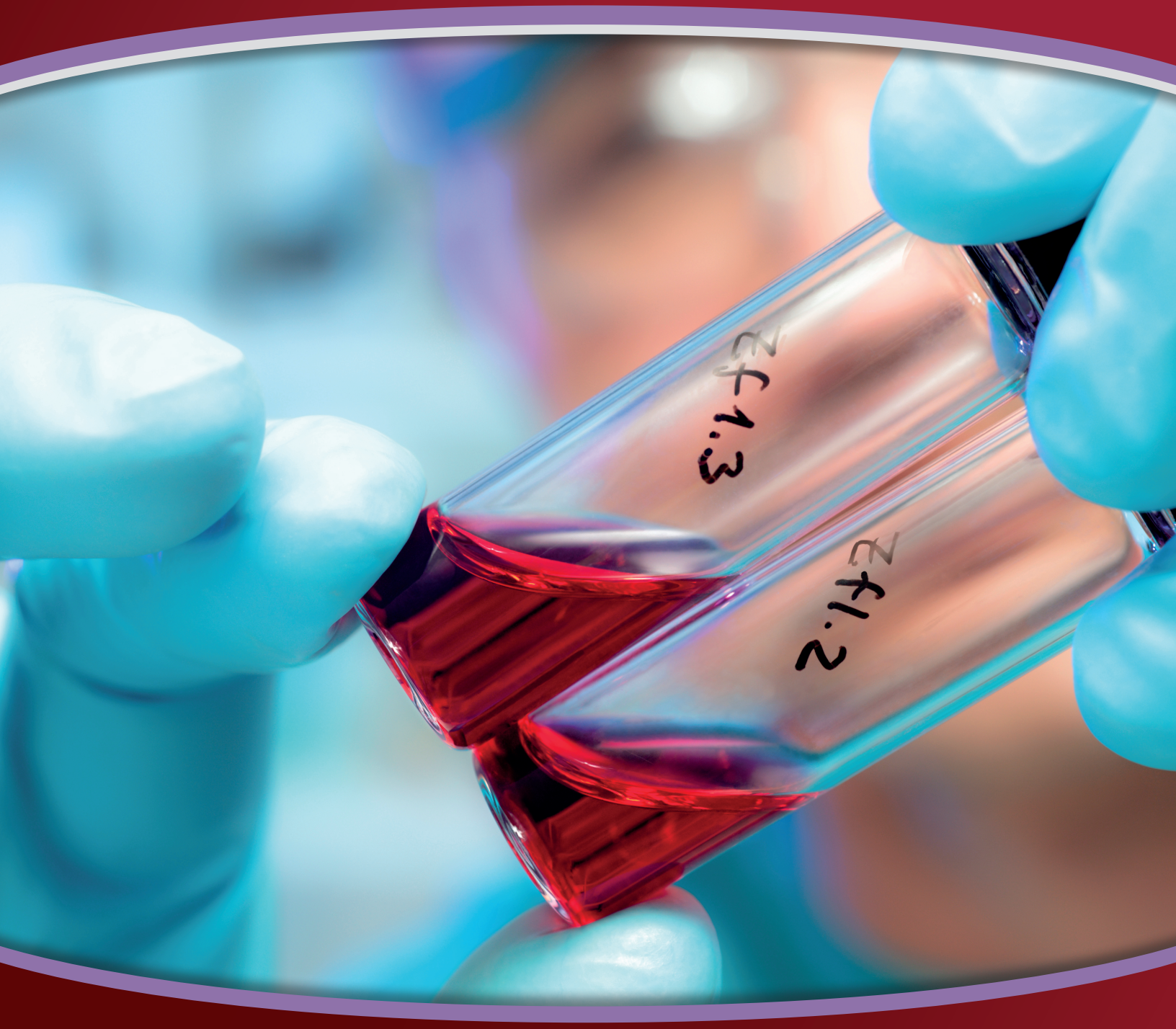
To highlight the advancements made, provide an overview of the research being conducted, and offer educational opportunities to scientific colleagues, corporate leaders, the community, public officials, and other interested parties, the Consortium hosts an annual conference. This event is comprised of two tracks – a public conference and a scientific one. This past year the scientific conference event was held at the University of Arizona, College of Medicine in Phoenix and the public conference event was held at the Rio Vista Center in Peoria, AZ. The annual conference is a unique way to foster interaction with the public, patients' families and caregivers, professional colleagues, and other stakeholders.

A complete guide to all of the Consortium's research summaries, key personnel, project progress reports, publications, manuscripts, poster abstracts and grants can be found at http://azalz.org/about-us/2013-aac-annual-report/.



Other Research

Translational Research Facility



Translational Research Facility

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



In years one through nine of the contract, ABRC provided $5,500,000 annually to TGen. In Fiscal Year 2012, $3,754,661 was issued and this past fiscal year, TGen received $4,100,000. Funds are used for genomic based research and clinical work aimed at discovering the underlying causes of disease progression and fostering collaboration-based projects.



Fiscal Year 2013 Activities include (as directly reported from TGen' Summary of FY 2013 TGen Activities):

Peer-Reviewed Laboratory Research Publications and Presentations

TGen researchers published their research results in numerous scholarly peer-reviewed academic journals and through presentations at leading national and international conferences. These include publication in leading scientific journals such as *Nature, Nature Genetics, Cancer, Genome Medicine, PLos One, Human Genetics, Blood, Science Translational Medicine*, and a host of other disease-associated publications.

FY13 Select Highlights

1. Isolation and characterization of muscle fatigue substance with anti-tumor activities.
   Munoz RM, Han H, Tegeler T, Petritis K, Von Hoff DD, Hoffman SA. J Cancer. 2013 May 9;4(4):343-9. Print 2013.
2. Cancer of the ampulla of Vater: analysis of the whole genome sequence exposes a potential therapeutic vulnerability.
   Demeure MJ, Craig DW, Sinari S, Moses TM, Christoforides A, Dinh J, Izatt T, Aldrich J, Decker A, Baker A, Cherni I, Watanabe A, Koep L, Lake D, Hostetter G, Trent JM, Von Hoff DD, Carpten JD. Genome Med. 2012 Jul 4;4(7):56. [Epub ahead of print].
3. Reciprocal Activation of Transcription Factors Underlies the Dichotomy between Proliferation and Invasion of Glioma Cells.
   Dhruv HD, McDonough Winslow WS, Armstrong B, Tuncali S, Eschbacher J, Kislin K, Loftus JC, Tran NL, Berens ME. PLoS One. 2013;8(8):e72134.
4. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG).
   Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, Cannon-Albright LA, Teerlink CC, Camp NJ, Johnson AM, Zuhlke KA, Stanford JL, Ostrander EA, Wiley KE, Isaacs SD, Walsh PC, Maier C, Luedeke M, Vogel W, Schleutker J, Wahlfors T, Tammela T, Schaid D, McDonnell SK, DeRycke MS, Cancel- Tassin G, Cussenot O, Wiklund F, Grönberg H, Eeles R, Easton D, Kote-Jarai Z, Whittemore AS, Hsieh CL, Giles GG, Hopper JL, Severi G, Catalona WJ, Mandal D, Ledet E, Foulkes WD, Hamel N, Mahle L, Moller P, Powell I, Bailey-Wilson JE, Carpten JD, Seminara D, Cooney KA, Isaacs WB; International Consortium for Prostate Cancer Genetics. Hum Genet. 2013 Jan;132(1):5-14. Epub 2012 Oct 12.
5. Detection of chromosomal alterations in the circulation of cancer patients with whole-genome sequencing.
   Leary RJ, Sausen M, Kinde I, Papadopoulos N, Carpten JD, Craig D, O'Shaughnessy J, Kinzler KW, Parmigiani G, Vogelstein B, Diaz LA Jr, Velculescu VE. Sci Transl Med. 2012 Nov 28;4(162):162ra154.
6. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs.
   Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, et. al. Nat Genet. 2013 Aug 28;45(9):984-94. Epub 2013 Aug 11.
7. An integrated map of genetic variation from 1,092 human genomes.
   1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. Nature. 2012 Nov 1;491(7422):56-65.
8. Multicenter phase I trial of the mitogen-activated protein kinase 1/2 inhibitor BAY 86-9766 in patients with advanced cancer.
   Weekes CD, Von Hoff DD, Adjei AA, Leffingwell DP, Eckhardt SG, Gore L, Lewis KD, Weiss GJ, Ramanathan RK, Dy GK, Ma WW, Sheedy B, Iverson C, Miner JN, Shen Z, Yeh LT, Dubowy RL, Jeffers M, Rajagopalan P, Clendeninn NJ. Clin Cancer Res. 2013 Mar 1;19(5):1232-43. Epub 2013 Feb 22.

Clinical Research/Clinical Trials

Established in 2006, The Virginia G. Piper Cancer Center (VGPCC) Clinical Trials Program at Scottsdale Healthcare, a strategic alliance between TGen and Scottsdale Healthcare (SHC), provides a direct clinical research site for TGen: Dr. Daniel Von Hoff, TGen's Physician-in-Chief, serves as Chief Scientific Officer.

Program clinicians' focus on clinical trials with targeted agents and genomics-based individualized therapy. The VGPCC Clinical Trials Program allows the unique opportunity for TGen to transition its laboratory-based research to patient care centered on individualized therapy. In FY13, program staff managed nearly 50 Phase I–III clinical trials for advanced or rare cancers.

Patient participation in clinical trials include:

- Over 300 visits per month
- Nearly 40 new patients per month
- Over 400 patient samples collected per month.

FY13 Select Highlights

1. In August 2012, a Phase I/II, multi-center trial designed to test the safety and preliminary efficacy of a first in class cancer treatment opened worldwide at the Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare. PR610 is designed to activate in tissues with low levels of oxygen, which is characteristic of many cancers. This "targeted" approach should deliver more active drug to cancer tissue and less active drug to normal tissue. The two-part trial, would first determine acceptable dose levels of PR610 in patients with various types of advanced cancer. After determining acceptable dose levels, the study would then evaluate the safety and efficacy of PR610 when given to patients with non-small cell lung cancer whose tumors contain a certain genetic mutation.
2. In November 2012, a new cancer drug combination demonstrated significant improvement in overall survival of late-stage pancreatic cancer patients compared to those receiving standard treatment, according to results of a Phase III clinical trial. SHC/TGen Physicians were first to design a clinical trial to determine the safety, tolerability and effectiveness of nab-paclitaxel (Abraxane) in combination with the standard drug gemcitabine in patients with advanced pancreatic cancer. Results of that multicenter study chaired by Dr. Daniel Von Hoff were encouraging enough that it led to one of the largest international studies ever done in pancreatic cancer, with 861 patients.
3. In March 2013, The FDA has approved a thyroid cancer drug successfully tested at Virginia G. Piper Cancer Center Clinical Trials, a partnership of Scottsdale Healthcare and the Translational Genomics Research Institute (TGen). The U.S. Food and Drug Administration approved Cabozantinib for the treatment of progressive, metastatic medullary thyroid cancer (MTC), a rare endocrine gland cancer affecting the thyroid. Previously, MTC patients had limited treatment options.
4. In April 2013, TGen and SHC reported the safety and preliminary efficacy of a new class of tumor fighting drugs. Early results from the phase I, first in-human study of an RNA interference (RNAi) drug were announced during the American Association for Cancer Research (AACR) Annual Meeting 2013, April 6–10, in Washington, D.C. Tekmira Pharmaceuticals developed TKM-080301 (also known as TKM-PLK1). The study was conducted at Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare, a partnership with TGen. It found that the RNAi drug acts by silencing the PLK1 gene involved in tumor growth and can be safely administered in humans. Most patients tolerated the drug well; some showed therapeutic benefit.

Grant Support

FY13 Select Highlights

1. Three-year grant from the National Institutes of Health (NIH) totaling $1,207,367 to Dr. Nhan Tran to develop small molecule chemical probes against the TWEAK-Fn14 signaling pathway to treat glioma invasion.
2. Five-year grant from the National Institutes of Health (NIH) totaling $1,515,154 to Drs. Haiyong Han and Daniel Von Hoff to study targeted stromal collagen in pancreatic cancer.
3. Four-year grant from the National Institutes of Health (NIH) totaling $1,800,094 to Dr. Lance Price to study the rapid emergence of Livestock-associated methicillin-resistant Staphylococcus aureus (MRSA) ST398.
4. Five-year subcontracted grant to MRIGlobal from the Virginia Contracting Agency totaling $757,834 to Dr. Paul Keim to provide microbial forensics support.
5. Two-year grant under subcontract with the Barrow Neurological Institute/St. Joseph's Hospital and Medical Center from the National Institutes of Health (NIH) totaling $202,880 to Dr. Holly Yin for the development of high-throughput assays for testing non-nicotine components in tobacco products.
6. Two-year grant from National Institutes of Health totaling $472,035 to Drs. Matthew Huentelman and Kendall Jensen to identify a biomarker to predict complications of brain injury under the NIH Common Fund Extracellular RNA Communication Consortium.
7. One-year grant from the Adenoid Cystic Carcinoma Foundation totaling $106,066 to Dr. Michael Barrett to study the determinants of therapeutic benefit for adenoid cystic carcinomas (ACC) patients.
8. Eighteen-month fellowship from the NCF/Merck Science Initiative totaling $92,000 to Dr. Troy McEachron to investigate the molecular and cellular biology that underlies chemo-resistance in pediatric cancer patients.
9. Under subcontract from Arizona Alzheimer's Consortium, a one-year grant totaling $165,000 to Dr. Matthew Huentelman to study novel biomarker and genetic risk factor identification in Alzheimer's disease.
10. Under subcontract from the University of Maryland, a two-year grant from the National Institutes of Health (NIH) totaling $54,172 to Dr. Jason Sahl to identify Cloud- enabled genomics resources for automated pathogen diagnostics in the field.

Enterprise Efforts, Collaboration, Spin offs & Job Creation

In FY13, TGen launched 2 initiatives to leverage internal discoveries and developments in genomics research and informatics tools. These are:

1. TGen Animal Health: A research and development project with a local Arizona firm to evaluate the portability of human diagnostic tools in the treatment of canine cancer. TGen is one of the early adopters of the canine model as a vehicle to accelerate human research.
2. Translational Systems, LLC: Translational Systems, LLC was created to facilitate the commercialization of a suite of informatics tools used in the creation, analysis and interaction of data from a variety of sources including patient samples, genomic data.

Invention Disclosures

TGen filed 28 invention disclosures in FY13 based on discoveries stemming from TGen-led research, and 26 provisional patent applications.

Contracts and Collaborations

TGen signed a total of 440 contracts in FY13, broken down as follows:

113	CDAs
70	MTAs
40	Research Collaborations
38	Consulting Agreements
79	Professional Service Agreements
4	Commercialization Licenses
96	Agreements Covering Miscellaneous Activities

A sample of the universities, institutes, medical centers and corporations that TGen worked with include: Veterinary Neurological Center; Texas Engineering Experiment Station (TEES); Hills Pet Nutrition; Mayo Clinic; Illumina; Pathogene; Phoenix Children's Hospital; Spectrum Health Hospitals; Geisinger Clinic; Michigan State University; AztraZeneca Pharmaceuticals; Onyx Pharmaceuticals; Novartis Horsham Research Centre; Dignity Health; MMRC; Hoffmann-LaRoche; FDA/AZ Dept of Health Services; and Ventana Medical Systems.

Job Creation

Sixteen new full-time equivalent positions were created in 2013 with salaries and benefits totaling $1,213,836. Salaries for temporary positions (those positions created for a finite period of time) totaled $93,600 and student salaries were just over $340,000, bringing the overall total to $1,647,436. Eighty-eight percent of full-time TGen staff holds a college degree and fifty percent holds an advanced degree.

FY13 full-time positions filled (new and replacements) included:

- Accountant II
- Assistant Professor
- Bioinformatician, Associate
- Business Analyst
- Chief Financial Officer
- Clinical Research Coordinator
- Sr. Engineer, High-Performance Computing
- Histotechnologist
- IT Administrator
- Manager, Physician In Chief's Office
- Post-Doc Fellow
- Research Associate
- Research Associate II
- Research Associate III
- SharePoint Developer
- Education and Outreach Specialist
- Sr. Data Base Administrator
- Staff Scientist
- Vice President, Corporate Development

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

Arizona Department of Health Services

Arizona Biomedical Research Commission

Grants • Biospecimen Locator • Education • Public Cord Blood

Arizona Department of Health Services | 150 North 18th Avenue | Phoenix, Arizona 85007 | 602.542.1025