

University of Arizona Research Symposium: Biomarkers: From Specimen to Clinical Impact

Keynote Speaker:

John D. Halamka, MD

International Healthcare Innovation Professor, Harvard Medical School
Chief Information Officer, Beth Israel Deaconess Health System

*The Next Great
Informatics Challenges in Healthcare*



December 6, 2018 8:30 AM - 6:00 PM

University of Arizona College of Medicine - Phoenix

Biomedical Sciences Partnership Building - 475 N. 5th Street, Phoenix, AZ 85004



ARIZONA DEPARTMENT
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH CENTRE



THE UNIVERSITY OF ARIZONA
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8:00 – 9:00 a.m.

Breakfast and Registration

9:00 – 9:15 a.m.

Welcome and Opening Remarks

Paul E. Boehmer, PhD

Interim Associate Dean for Research,
Chair, Department of Basic Medical Sciences,
University of Arizona College of Medicine-Phoenix

Michael D. Dake, MD

Senior Vice President, University of Arizona Health Sciences

9:15 – 10:25 a.m.

Biomarker Research & Development

Biomarkers: An Evolving Story of Possibilities vs. Challenges

Anna D. Barker, PhD

Director, Transformative Healthcare Knowledge Networks,
Co-Director, Complex Adaptive Systems Initiative,
Arizona State University

Developing Biomarkers Associated with Internalized Isotope Treatment for Refractory and Relapsed Neuroblastoma

Matthew Coleman, PhD

Senior Scientist, Biosciences and Biotechnology Division,
Lawrence Livermore National Laboratory

10:25 - 10:40 a.m.

Break

10:40 – 11:15 a.m.

Identifying Systems Biology-Level Biomarkers Using Network Science and Machine Learning

Yves A. Lussier, MD, ACMI

Associate Vice President for Health Sciences & Chief Knowledge Officer
Executive Director, Center for Biomedical Informatics and Biostatistics
University of Arizona Health Sciences

11:15 – 12:15 p.m.

Panel Discussion

Analysis of Large Scale Multi-Omics Data: Trends & Data Collection

Moderator:

Jonathan Lifshitz, PhD

Director, Translational Neurotrauma Research Program,
University of Arizona College of Medicine – Phoenix

Panelists:

Suwon Kim, PhD

Associate Professor, Department of Basic Medical Sciences,
University of Arizona College of Medicine – Phoenix
Associate Professor, Cancer and Cell Biology Division,
Translational Genomics Research Institute

Yves A. Lussier, MD, ACMI

Associate Vice President for Health Sciences & Chief Knowledge Officer
Executive Director, Center for Biomedical Informatics and Biostatistics
University of Arizona Health Sciences

Eric M. Reiman, MD

Executive Director, Banner Alzheimer's Institute,
Chief Executive Officer, Banner Research

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- 12:15 – 1:30 p.m.** **Lunch**
- 1:30 – 1:35 p.m.** **Introduction to Keynote Speaker**
Guy Reed, MD, MS
Dean, University of Arizona College of Medicine – Phoenix
- 1:35 – 2:35 p.m.** **Keynote Presentation**
The Next Great Informatics Challenges in Healthcare
John D. Halamka MD, MS
Chief Information Officer, Beth Israel Deaconess Health System
International Healthcare Innovation Professor, Harvard Medical School
- 2:35 – 2:50 p.m.** **Break**
- 2:50 – 3:25 p.m.** **New Classes of Clinical Trial Design**
Donald A. Berry, PhD
Professor, Department of Biostatistics
University of Texas MD Anderson Cancer Center
- 3:25 – 4:25 p.m.** **Panel Discussion**
Large Research Cohorts for Real World Evidence
Moderator:
Akinlolu Ojo, MD, MPH, PhD, MBA
Associate Vice President for Clinical Research and Global Health Initiatives,
University of Arizona Health Sciences
Panelists:
Michael Fallon, MD, FACP
Executive Director, Clinical Research
Chair, Department of Medicine
University of Arizona College of Medicine-Phoenix
Titilayo Ilori, MD, MSCR
Associate Director, Global Health Institute, University of Arizona
Medical Director, All of Us Research Program Phoenix
Timothy K. McDaniel PhD
Senior Vice President of Emerging Opportunities,
Translational Genomics Research Institute & City of Hope
Andreas Theodorou, MD, FCCM, FAAP
Chief Clinical Education Officer, Banner University Medical Group
Vice Chair, Department of Pediatrics,
University of Arizona College of Medicine – Tucson
- 4:25 – 4:30 p.m.** **Closing Remarks**
Paul E. Boehmer, PhD
Interim Associate Dean for Research,
Chair, Department of Basic Medical Sciences,
University of Arizona College of Medicine-Phoenix
- 4:30 – 6:00 p.m.** **Poster Session, Happy Hour, and Networking**
Drinks and hors d'oeuvres served in the Grand Canyon Patio



Anna D. Barker, PhD

Director, Transformative Healthcare Knowledge Networks

Co-Director, Complex Adaptive Systems Initiative

Professor, School of Life Sciences

Arizona State University

CAS at ASU creates knowledge networks to solve complex systems problems in biomedicine. Examples of current programs include the NBDA, a non-profit think tank that addresses major barriers in biomarker discovery and development, and the first global adaptive clinical trial for glioblastoma (GBM AGILE). Prior to ASU, Dr. Barker served as the deputy director of the National Cancer Institute (NCI) where she planned and implemented the: Nanotechnology Alliance for Cancer; The Cancer Genome Atlas (TCGA) with NHGRI; Clinical Proteomics Technologies Initiative for Cancer; Physical Sciences-Oncology Centers; and national programs in biospecimens and bioinformatics. Prior to NCI, Dr. Barker served as a research scientist and subsequently senior executive at Battelle Memorial Institute and as the co-founder and CEO of a public biotechnology company. She has received a number of awards for her work and service in cancer research. Her research interests include CAS, biomarker discovery and development, innovative clinical trials and free-radical biochemistry. She completed her Ph.D. degree at The Ohio State University.



Donald A. Berry, PhD

Professor, Department of Biostatistics

University of Texas MD Anderson Cancer Center

Donald Berry is professor in the Department of Biostatistics of the University of Texas MD Anderson Cancer Center. He received his doctorate in statistics from Yale University and has held endowed faculty positions at Duke University and MD Anderson. He has designed and supervised the conduct of many innovative clinical trials, including adaptive Bayesian trials, in cancer and other diseases. A principal focus of his research is the use of biomarkers for learning which patients benefit from which therapies, based on genomics and phenotype. In particular, he designed and is a co-PI of I-SPY 2 and GBM-AGILE, Bayesian adaptive platform clinical trials in high-risk early breast cancer and glioblastoma, respectively. He has authored many books on biostatistics and more than 400 peer-reviewed articles. He is a Thomson Reuters Highly Cited Researcher in recognition of ranking among the top 1 percent of most cited researchers in clinical medicine. He has received numerous research grants from the NIH and NSF and is fellow of the American Statistical Association and of the Institute of Mathematical Statistics. He is founder and co-owner of Berry Consultants, a company that designs innovative clinical trials for industry, cooperative groups, international consortia, and patient advocacy groups.



Paul E. Boehmer, PhD

Interim Associate Dean for Research

Chair and Professor, Department of Basic Medical Sciences

University of Arizona College of Medicine-Phoenix

Dr. Paul Boehmer is a founding faculty member at the University of Arizona College of Medicine-Phoenix, joining the college in July of 2006. He currently serves as the interim Associate Dean for Research and as Chair of the Department of Basic Medical Sciences. Dr. Boehmer received his undergraduate and doctoral degrees in Biochemistry from the University of Newcastle upon Tyne in the UK. Thereafter, Dr. Boehmer pursued post-doctoral training at Stanford University. Prior to his tenure at the University of Arizona, Dr. Boehmer held faculty positions at the University of Medicine and Dentistry of New Jersey-New Jersey Medical School, and the University of Miami-Miller School of Medicine. Dr. Boehmer is interested in elucidating the molecular mechanisms underlying genome integrity. Specifically, his research focuses on mechanisms of DNA replication, recombination and repair in herpes simplex virus, leading to the identification of novel anti-viral drug targets.



Matthew Coleman, PhD

Senior Scientist, Biosciences and Biotechnology Division

Lawrence Livermore National Laboratory

Dr. Matthew Coleman is currently an Adjunct Professor at the University of California, Davis in the Department of Radiation Oncology and a member of the NIH funded Cancer Center. Dr. Coleman also holds a scientific appointment as a Senior Scientist at the Lawrence Livermore National Laboratory in Livermore, California. Dr. Coleman's research focuses on understanding the processes involved in genome instability following genotoxic stresses such as ionizing radiation. Dr. Coleman's research also uses novel approaches in nanotechnology using nanolipoproteins to help characterize biological components involved in cell signaling. Dr. Coleman's training is in molecular biology where he received his B.A. from the University of Massachusetts, and his Ph.D. in biophysical studies of membrane proteins from Boston University. He has authored over 100 publications in peer-reviewed journals, published proceedings and book chapters covering a diverse breadth of molecular biology and biochemistry. Dr. Coleman has 7 patents related to biomarker discovery and biotechnology.



Michael D. Dake, MD

Senior Vice President, University of Arizona Health Sciences

**Professor, Department of Medical Imaging, Department of Surgery, Department of Medicine
University of Arizona**

Michael D. Dake, MD, directs strategic integration of undergraduate and graduate education, research, service and clinical activities in the UA Health Sciences colleges, centers and clinical affiliates.

Dr. Dake is a leading researcher, clinician, teacher, and administrator. He is internationally known for pioneering image-guided therapies and novel approaches in interventional therapy in the fields of vascular imaging, venous thromboembolic disease, aortic aneurysms, and dissection. Dr. Dake made medical history with the implantation of the world's first thoracic stent-graft in 1992 and his groundbreaking research with CT angiography and stent-grafts has re-written medical and surgery textbooks.

Prior to joining the UA, he served at Stanford University as Professor of Cardiothoracic Surgery and Director of the Catheterization and Angiography Laboratories at Stanford Medical Center. Previously, he served as Chairman of the Department of Radiology in the Virginia Health System.

He is a graduate of Harvard College and Baylor College of Medicine, where he completed an internship, residency and chief residency in internal medicine. He pursued fellowship training in pulmonary diseases followed by a residency and chief residency in radiology at the University of California San Francisco. As a member of the UA's senior executive team, Dr. Dake works collaboratively with teams throughout the UA and with Banner Health to build the UA's competitiveness in education, clinical care and biomedical research.



Michael B. Fallon, MD

Professor of Medicine

Chair, Department of Internal Medicine

Executive Director, Clinical Research

University of Arizona College of Medicine—Phoenix

Dr. Fallon's experience in Gastroenterology and Hepatology has been broad, spanning from developing a translational research program in complications of cirrhosis, to implementing clinical care and research programs, to integrating an academic focus into a well-established and productive community based clinical system. These experiences include initiating an externally funded research program as a junior faculty at Yale, building and growing the University of Alabama at Birmingham Liver Center, serving as Chief of Gastroenterology at the Birmingham VA Medical Center, and developing a broad clinical and investigative program as Chief of Gastroenterology at the University of Texas Health Science Center Houston. He is currently the Chair of Internal Medicine at the University of Arizona College of Medicine – Phoenix integrated with Banner University Medical Center.



John D. Halamka, MD

**Chief Information Officer, Beth Israel Deaconess Health System
International Healthcare Innovation Professor, Harvard Medical School**

John D. Halamka, M.D., is the chief information officer (CIO) at Beth Israel Deaconess System, chairman of the New England Healthcare Exchange Network (NEHEN), and a practicing emergency physician. He is also the International Healthcare Innovation professor at Harvard Medical School.

Dr. Halamka completed his undergraduate studies at Stanford University, where he received a degree in medical microbiology and a degree in public policy with a focus on technology issues. He entered medical school at the University of California, San Francisco and simultaneously pursued graduate work in bioengineering at the University of California, Berkeley focusing on technology issues in medicine. He completed his residency at Harbor –UCLA Medical Center in the Department of Emergency Medicine.

In his role at BIDMC, Dr. Halamka is responsible for all clinical, financial, administrative, and academic information technology, serving 3,000 doctors, 12,000 employees, and 1,000,000 patients. As chairman of NEHEN, Dr. Halamka oversees clinical and administrative data exchange among the payers, providers, and patients in Massachusetts.

As a Harvard professor, he has served the George W. Bush administration, the Obama administration, and national governments throughout the world planning their healthcare IT strategy. Dr. Halamka has authored five books on technology-related issues, hundreds of articles and thousands of posts on the popular Geekdoctor blog. He runs Unity Farm in Sherborn, MA and serves as caretaker for 150 animals, 30 acres of agricultural production and a cidery/winery.



Titilayo Ilori, MD, MSCR

**Assistant Professor of Medicine
Associate Director, Global Health Institute
University of Arizona Health Sciences
Medical Director All of Us Research Program Phoenix**

Dr. Ilori is an Assistant Professor of Medicine and the Associate Director for the Center of Clinical Research and Global Health Initiatives at the University of Arizona. She completed medical school at the University of Lagos and internal medicine residency training at Morehouse School of Medicine. She completed a research fellowship at Emory University School of Medicine and Master of Science in Clinical Research degree at Emory University in 2015. Her research interest focuses on health disparities in CKD and the Role of Dietary Sodium and Potassium in Apolipoprotein L1 Nephropathy. She is a co-investigator in the Human Hereditary and Health in Kidney Disease Research Network, which has enrolled over 10,000 individuals in sub-Saharan Africa. She also has an interest in the role of lifestyle, genes and environment in chronic diseases and is a co-investigator in a the All of Us Research Program, a part of the Precision Medicine Initiative funded by the National Institute of Health.



Suwon Kim, PhD

**Associate Professor, Department of Basic Medical Sciences
University of Arizona College of Medicine—Phoenix
Associate Professor, Cancer and Cell Biology Division
Translational Genomics Research Institute**

Suwon Kim, Ph.D. is an Associate Professor in the department of Basic Medical Sciences. Dr. Kim's research focuses on deciphering the molecular mechanisms of cancer in order to develop better therapy and prevention strategies.

Dr. Kim's lab is located in Translational Genomics Research Institute (TGen) where she employs leading-edge technology including whole genome/RNA sequencing and single cell analysis. Dr. Kim is currently the lead principal investigator on several multi-institutional grants addressing precision medicine initiatives, for which she works closely with the clinician at the University of Arizona Cancer Center, Dignity Health, and Baylor Scott & White Research Institute in Texas.

Dr. Kim obtained her undergraduate degree from University of California Berkeley and her PhD from Yale University School of Medicine. She developed her research program as a postdoctoral fellow in the laboratory of Nobel Laureate Dr. J. Michael Bishop at University of California San Francisco.

Dr. Kim joined the UACOM-P founding faculty in 2007 and installed the inaugurating Hematology/Oncology Block in 2008 as a co-block director. She launched the new Personalize Active Learning (PAL) block in 2014. Dr. Kim currently serves as the PAL block director, teaches the subjects of cancer in the preclinical curriculum, and participates in the K-12 education outreach activities each year. She received the Educator of the Year award in 2013.



Jonathan Lifshitz, PhD

**Director, Translational Neurotrauma Research Program
Associate Professor, Department of Child Health
University of Arizona College of Medicine – Phoenix**

Jonathan Lifshitz, PhD, serves as the Director of the Translational Neurotrauma Research Program, which is a joint venture through BARROW Neurological Institute at Phoenix Children's Hospital, the Department of Child Health at the U of A College of Medicine – Phoenix and the Phoenix Veterans Affairs Health Care System.

In 2007, he joined the Spinal Cord and Brain Injury Research Center at the University of Kentucky as faculty. In 2012, he was recruited to direct Translational Neurotrauma Research in Phoenix with the vision to improve quality of life for those with acquired neurological injury.

His research questions primarily investigate traumatic brain injury as a disease process that dismantles, repairs and regenerates circuits in the brain. The underlying principle is that adaptive repair and regeneration fail, leaving a miswired brain and neurological impairments that decrease quality of life.

The Translational Neurotrauma Research Program is supported by Federal extramural grants, institutional funds and philanthropic donations. He has won five national or international awards for his research on traumatic brain injury and an NCAA/DOD Mind Matters Challenge for Concussion Education. He has more than 60 peer-reviewed publications, in addition to other monographs and book chapters. He serves on the Arizona Governor's Council on Spinal and Head Injury and is the Lead Scientist and Director of Research and Development for the CACTIS Foundation.



Yves A. Lussier, MD, ACMI

**Associate Vice President for Health Sciences & Chief Knowledge Officer
Executive Director, Center for Biomedical Informatics and Biostatistics
University of Arizona Health Sciences**

Dr. Lussier is the Associate Vice President for Information Science and Chief Knowledge Officer of the UA Arizona Health Sciences (UAHS), Founding Director of the Center for Biomedical Informatics and Biostatistics, and Professor of Medicine. He received a bachelor of engineering and his medical degree from the University of Sherbrooke, Quebec, Canada. He performed predoctoral research in the Departments of Medicine and Human Physiology at the University of Sherbrooke and then completed an internship in ophthalmology at Laval University Hospital in Quebec City, and a residency in family medicine at the University of Sherbrooke Medical Center. He was a post-doctoral residential fellow in the Department of Biomedical Informatics in the College of Surgeons & Physicians at Columbia University. Dr. Lussier's research group conducts pioneering hypothesis-driven computational modeling predictions in precision medicine that are then validated *in vitro*, *in vivo* and in clinical trials. As a leader of the fields of translational bioinformatics and of Data Science-augmented precision medicine, he has launched successful companies and international conferences, authored 185 publications, and delivered more than 100 invited presentations in precision medicine, systems medicine, and translational bioinformatics, including 21 opening keynotes at international conferences. He has been awarded \$190,000,000 in grants as principal, core leader, or co-investigator, and mentored 53 graduate and postgraduate students as well as 40 junior faculty members. Dr. Lussier's honors include three IBM Faculty Awards, inducted Fellow of the American College of Medical Informatics (ACMI), 1st recipient of the Columbia University Faculty Mentoring Award, "Ambassador for Health Sciences" at the University of Sherbrooke (Canada), and 16 outstanding publication awards from the American Medical Informatics Association (AMIA), the International Society for Computational Biology (ISCB), and the Translational Bioinformatics Conference (TBC). In 2016, Dr. Lussier was invited among ten USA academic leaders invited by the White House for its Precision Medicine Summit, where the University of Arizona Center for Biomedical Informatics and Biostatistics that he directs has committed \$20M of R&D in bringing precision medicine to practice.



Timothy McDaniel, PhD,

**Senior Vice President of Emerging Opportunities
Professor of Integrative Cancer Genomics
Translational Genomics Research Institute**

Timothy McDaniel, Ph.D. is Sr. Vice President of Emerging Opportunities and Professor of Integrated Cancer Genomics at TGen, a non-profit medical research institute located in Phoenix. In this role, Dr. McDaniel has responsibility for the strategy of TGen's clinical genomics laboratory, Ashion Analytics, and for creating research programs and alliances that can advance TGen's mission of deploying genomics to serve patients. Prior to joining TGen and Ashion, Dr. McDaniel worked at Illumina, Inc., in San Diego, where he served in a variety of roles in R&D, quality, product development, and clinical laboratory development. In over 14 years with Illumina, he helped grow the company from a privately held startup with no products to a leader in the biotechnology industry whose technology has been used to produce more than 90% of all DNA sequencing data ever generated.

Dr. McDaniel received a B.A. in Biological Sciences from U.C. Santa Barbara, a Ph.D. In Molecular and Cell Biology from the University of Maryland, Baltimore, and was a Damon Runyon Cancer Research Foundation postdoctoral fellow at Stanford Medical School. In his personal life, Tim led a genome sequencing project for a close family member, which led to the identification of a new treatment for a rare cancer.



Akinlolu Ojo, MD, PhD, MBA

**Associate Vice President for Clinical Research and Global Health Initiatives
Professor of Medicine & Health Promotion Sciences
University of Arizona Health Sciences**

Dr. Akinlolu (“Ojo”) Ojo is the Associate Vice President for Clinical Research and Global Health Initiatives at the University of Arizona Health Sciences. Dr. Ojo clinical and translational research interests are in precision medicine, chronic kidney disease, kidney and kidney-pancreas transplantation and global health. Dr. Ojo is the Principal Investigator of the *All of Us Research Program (AoU RP)* at the University of Arizona – Banner Health. The *AoU RP* is a 1 million-person cohort that constitutes the *centerpiece of the federal Precision Medicine Initiative*. Dr. Ojo also serves as the U.S. Principal Investigator of the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network – which develops research capacity and conduct clinical and translational research in kidney disease in sub-Saharan Africa (SSA) and currently has >14,000 research participants at 19 academic medical centers in seven SSA countries. Dr. Ojo received his medical education from the University of Lagos, Nigeria and completed residency training in internal medicine at the University of Kentucky, Lexington. He earned a Master of Public Health (MPH) degree in Global Health from the University of Alabama in Birmingham and completed nephrology fellowship, a PhD in Epidemiology and a Master of Business Administration at the University of Michigan. Dr. Ojo has over 200 peer-reviewed publications. Dr. Ojo currently serves on the Board of Directors of the United Network for Organ Sharing (UNOS) and on editorial boards, Data and Safety Monitoring Boards (DSMBs), FDA Advisory Committees and NIH study sections. Dr. Ojo has mentored >20 research scientists and physician scientists and has been elected into the American Clinical and Climatological Association (ACCA), American Society of Clinical Investigation, and the Association of American Physicians.



Guy Reed, MD, MS

**Dean
University of Arizona College of Medicine—Phoenix
Valley of the Sun Professor**

Dean of the University of Arizona College of Medicine – Phoenix, Guy Reed, MD, MS, is an internationally recognized and renowned cardiologist, physician-scientist and health administrator. As dean, he spearheads the college’s proud tradition of excellence in advancing medical education in the state of Arizona and beyond.

Prior to joining the college, Dr. Reed was the Lemuel Diggs Professor of Medicine and chair of the Department of Medicine at the University of Tennessee Health Science Center, as well as interim executive vice president for Methodist Le Bonheur HealthCare.

Dr. Reed is known for his research on the mechanism of blood clots and vascular disease. Through grant support from the National Institutes of Health, he translated his laboratory research findings into an innovative, clot-dissolving therapy to treat patients with strokes and heart attacks, which is now in clinical trials.

Dr. Reed graduated from Columbia University in New York City, where he received his bachelor’s degree in English literature and pre-medical studies. He received a master’s degree in mathematical statistics and a medical degree from Stanford University. He completed his internship, residency and chief residency in internal medicine at Yale University. Dr. Reed completed a fellowship in cardiovascular disease at Massachusetts General Hospital and a post-doctoral research fellowship in biochemistry and molecular biology at Harvard Medical School.



Eric M. Reiman, MD

**Executive Director, Banner Alzheimer's Institute
Chief Executive Officer, Banner Research**

Dr. Reiman is Executive Director of the Banner Alzheimer's Institute, Chief Executive Officer of Banner Research, Professor of Psychiatry at the University of Arizona, University Professor of Neuroscience at Arizona State University, Clinical Director of Neurogenomics at the Translational Genomics Research Institute, and Director of the Arizona Alzheimer's Consortium. His research interests include brain imaging, genomics, the unusually early detection and tracking of Alzheimer's disease, and the accelerated evaluation of Alzheimer's prevention therapies. He is also interested in new models of research collaboration and dementia care. He and his Banner Alzheimer's Institute colleagues lead the Alzheimer's Prevention Initiative (API), including prevention trials in cognitively unimpaired persons who, based on their genetic background and age, are at high risk for Alzheimer's disease, biomarker development and data and sample sharing agreements, unusually large registries to support enrollment in prevention trials, and other efforts to help accelerate the evaluation, approval and availability of prevention therapies. Dr. Reiman is an author of more than 400 publications, a principal investigator of several NIH grants, and a recipient of the Potamkin Prize.



Andreas Theodorou, MD, FCCM, FAAP

**Chief Clinical Education Officer, Banner University Medical Group
Vice Chair, Department of Pediatrics
University of Arizona College of Medicine – Tucson**

Andreas Theodorou, MD, FCCM, FAAP completed medical school (1983), pediatric residency, and pediatric critical care fellowship at Wayne State University, School of Medicine in Detroit MI. He is the Chief Clinical Education Officer for Banner Health working in partnership with University of Arizona (UA) Colleges of Medicine (Phoenix and Tucson) to ensure medical students, Residents, and Fellows are integrated throughout Banner's clinical sites. In addition, he oversees Banner Health's Clinical Education and Simulation for the entire health system.

Dr. Theodorou was Chief Medical Officer for The University of Arizona Medical Center (UAMC) in Tucson (2008-2016) and remains Professor and Vice Chair of the Department of Pediatrics at the University of Arizona College of Medicine-Tucson. Dr. Theodorou's research interests include interprofessional education, medical error reduction, medication error and adverse drug event detection and was a Co-PI in the UA VIPER Institute's clinical trials network for antivenom studies, that resulted in the only FDA-approved scorpion antivenom in the United States. He was the Site Co-PI for the multi-center NIH-funded clinical trial, Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA), and is co-investigator in several other pediatric critical care studies. He is currently part of the UA-Banner Health All of Us Research Program.

POSTERS

1. A matrix trifactorization algorithm to identify patient similarities and subgroups in acute myeloid leukemia
2. Allopregnanolone as a Regenerative Therapeutic for Alzheimer's Disease: Phase 1 Clinical Trial Biomarker Analysis of Responders
3. Cervicovaginal Metabolome Associated with HPV, Vaginal Microbiota, and Inflammation in Cervical Carcinogenesis
4. Clinical Utility of Comprehensive Genomic Profiling for Advanced Prostate Cancer
5. Developing Breath Biomarkers for Diagnosing Lung Infection Etiology in Persons with Cystic Fibrosis
6. Does Vaginal Microbiome Composition Alter Local Cancer Biomarker Expression in Cervical Dysplasia and Cancer?
7. Electroencephalography as a Measure of Cerebral Autoregulation in Pediatric Acute Brain Injury
8. Emergence of pathway-level composite biomarkers from converging gene set signals of heterogeneous transcriptomic responses
9. High GILT expression and an active and functional MHC class II antigen presentation pathway are associated with improved survival in melanoma
10. Paired Associates Performance is Altered by a First-Degree Family History of Alzheimer's Disease: An Effect Modified by Apolipoprotein E Genotype, Diabetes, and Heart Disease
11. Identification of Endometrial Cancer Specific miRNA Biomarkers in Endometrial Fluid Collected Using Saline Infusion Sonohysterography Techniques
12. Phage Display as a Biomarker Discovery Tool for Neural Injury
13. Precision drug repurposing via convergent eQTL-based molecules and pathway targeting independent disease-associated polymorphisms
14. Tumor Molecular Profiling in Advanced Pediatric Solid Tumors

1 - A matrix trfactorization algorithm to identify patient similarities and subgroups in acute myeloid leukemia

Francesca Vitali^{†,1,2}, Simone Marini^{†,3}, Daniele Pala⁴, Andrea Demartini^{4,5}, Stefano Montoli⁴, Alberto Zambelli⁶, Riccardo Bellazzi^{*,4,5,7}
1Center for Biomedical Informatics and Biostatistics (CB2), 2Department of Medicine COM-T, The University of Arizona, Tucson, AZ, USA,
3Department of Computational Biology and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA, 4Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, PV, Italy, 5Centre for Health Technologies, University of Pavia, PV, Italy, 6Oncology Unit, ASST Papa Giovanni XXIII, Bergamo, BG, Italy, 7IRCCS Istituti Clinici Scientifici Maugeri, Pavia, PV, Italy

[†] authors contributed equally to this work ^{*}corresponding author

Computing patients' similarity is of great interest in precision oncology supporting clustering and subgroup identification, eventually leading to tailored therapies. The availability of large amounts of biomedical data, characterized by large feature sets and sparse content, motivates the development of new methods to compute patient similarities by fusing heterogeneous data sources with the available knowledge. In this context, we developed a data integration approach based on matrix trfactorization to compute patient similarities through the integration of several data and knowledge sources, including patient data, biological processes, gene interaction and disease ontologies [1]. We assess the accuracy of the proposed method: (1) on several synthetic data sets which similarity structures are affected by increasing levels of noise and data sparsity, and (2) on a real data set coming from an acute myeloid leukemia (AML) study. In the analysis of the synthetic data set, where the ground truth is known, we measured the capability of reconstructing the correct patient clusters, while in the AML study we evaluated the Kaplan-Meier curves obtained with the different clusters and measured their statistical difference by means of the log-rank test.

We further validate our approach by comparing it with traditional similarity calculation methods. In presence of noise and sparse data, our data integration method outperforms other techniques, both in the synthetic and in the AML data.

We demonstrated how a matrix trfactorization technique can successfully fuse all the information in a joint model and how this approach can be efficiently applied to discover meaningful patient similarities. The better performance of the proposed approach presents an advantage over previous methods to compute accurate patient similarities supporting precision medicine and providing a reliable data driven strategy for the definition of new research hypothesis for precision oncology.

1. Vitali F, Marini S, Pala D, Demartini A, Montoli S, Zambelli A, Bellazzi R: Patient similarity by joint matrix trfactorization to identify subgroups in acute myeloid leukemia. JAMIA Open 2018.

Funding: 3 project grant no. 2015-0042 "Genomic profiling of rare hematologic malignancies, development of personalized medicine strategies, and their implementation into the Rete Ematologica Lombarda (REL) clinical network."

2 - Allopregnanolone as a Regenerative Therapeutic for Alzheimer's Disease: Phase 1 Clinical Trial Biomarker Analysis of Responders

G. D. HERNANDEZ¹, Y. WANG^{1,2}, A. MISHRA^{1,2}, C. M. LOPEZ¹, C. M. SOLINSKY², N. KONO³, R. W. IRWIN⁶, K. E. RODGERS¹, Y. SHI⁷, M. LAW⁷, W. MACK³, L. SCHNEIDER⁸, R. D. BRINTON¹

¹Center for Innovation in Brain Science, University of Arizona, Tucson, AZ; ²Clinical Pharmacy and Pharmaceutical Economics & Policy, ³Preventive Medicine, ⁶Pharmacology and Pharmaceutical Science, ⁷Radiology, ⁸Psychiatry, USC, Los Angeles, CA

Background: Targeting the regenerative system of the brain while simultaneously activating systems to reduce burden of Alzheimer's disease (AD) pathology is a novel and innovative therapeutic approach. Allopregnanolone (Allo) is a first in class regenerative therapeutic for delaying progression and treating AD with a strong foundation of human safety exposure. AD failed clinical trials are, in part, due to the heterogeneity across AD and within study cohorts. Variability in therapeutic response could be reduced by development of predictive biomarkers to identify therapeutic responders.

Methods: A phase 1 randomized controlled trial was conducted in participants age ≥ 55 years with early AD. Participant blood derived peripheral mononuclear cells (PBMCs) were collected prior to randomized treatment of Allo or placebo. Lymphocyte derived iPSCs differentiated to neural stem cells (NSCs) were used to develop biomarker strategy to detect therapeutic response. To identify responders to allopregnanolone treatment, we measured mitochondrial respiratory and regenerative capacity by metabolic analyzer and flow cytometry respectively. We also conducted plasma cytokine analysis to identify blood biomarkers indicative of structural grey matter changes.

Results: Proliferation of NSCs in culture, as an indicator of regeneration, was highly variable. Analysis of Allo-induced mitochondrial respiration in NSCs indicated a correlation between Allo-induced mitochondrial respiration and Allo-induced change in left hippocampal volume ($r^2=0.61$ $p<0.06$). In APOE e3 participants the correlation was $r^2=0.71$ $p<0.05$. Further analysis revealed that three AD risk genetic markers – APOE genotype, mitochondrial haplogroups, and sex can differentiate responders from non-responders to allopregnanolone treatment. Plasma cytokine profile revealed that sex and APOE genotype significantly impacted outcome analysis and biomarker assessment.

Conclusion: These data suggest that Allo promotes regeneration and mitochondrial function of iPSC-derived NSCs in a subset of the participants, and supports further development of blood-based predictive biomarkers to identify therapeutic responders and non-responders.

3 - Cervicovaginal Metabolome Associated with HPV, Vaginal Microbiota, and Inflammation in Cervical Carcinogenesis

Zehra Esra Ilhan¹, Pawel Laniewski², Dana Chase³, Melissa Herbst-Kralovetz^{1,2}

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Presenting Author: Zehra Esra Ilhan, Postdoctoral Research Associate

Invasive cervical cancer (ICC), caused by human papillomavirus (HPV) infections, is a deadly malignancy among females, especially in developing countries. Recent studies have demonstrated that patients with ICC harbor dysbiotic cervicovaginal microbiota that is associated with inflammation and the progression of cancer. Metabolites produced by the host and the microbiota have been widely used in characterization of cancer metabolism and biomarker identification. However, to the best of our knowledge, to date cervicovaginal metabolites have not been characterized in ICC patients. Hence, we hypothesize that ICC patients have a diverse cervicovaginal metabolome that is distinct from healthy individuals. We characterized the cervicovaginal metabolome in HPV negative (-) and positive (+) controls compared to patients with low grade dysplasia (LGD), high grade dysplasia (HGD), and ICC using gas chromatography – mass spectrometry performed by Metabolon, Inc. Based on 475 metabolites detected, ICC patient metabolomes formed a distinct cluster on principal component analysis plots mainly due to enrichment of lipids derived from the host and microbial products of xenobiotic degradation and polyamines. The majority of the metabolites (40%) were highly correlated with genital inflammation. Changes in oxidative stress and glycolysis metabolites in HPV (+), LGD, HGD, and CC in comparison to HPV (-) was associated with cell proliferation. Hierarchical clustering of metabolites has shown that a diverse microbial community state in comparison to *Lactobacillus* dominated state increased the microbial products in ICC patients. In summary, our findings indicate that there are host and microbiota-derived metabolites in the cervicovaginal microenvironment that can serve as biomarkers of HPV infection and CC. Identification of metabolic biomarkers will enhance the stratification of patients to high and low risk groups and advance the development of non-invasive ICC detection technologies. Funding: This research was supported by Flinn Foundation (#1974) and Banner Foundation in Obstetrics and Gynecology Research.

4 - Clinical Utility of Comprehensive Genomic Profiling for Advanced Prostate Cancer

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Background: Tumor molecular profiling by targeted next generation sequencing (NGS) is increasingly used in oncology, but have yet to be widely used for prostate cancer. Clinicians are often unfamiliar with interpretation and incorporation of the information into practice. At University of Arizona Cancer Center (UACC) at Dignity Health St. Joseph's Hospital and Medical Center, we developed Prostate Molecular Tumor Board (PMTB) to track, and interpret clinical genomic profiling and potential targeted therapeutic recommendations. This retrospective case series includes patients reviewed by the UACC MTB from October 2015 to October 2018.

Methods: Comprehensive genomic profiling (CGP) was performed in Clinical Laboratory Improvement Amendments (CLIA)-certified, CAP-accredited laboratories. Results of tumor molecular profiling were discussed at PMTB. Recommendations on genomically targeted therapies, and outcomes were assessed.

Results : Sixty prostate cancer patients had 67 reportable results with alteration(s) identified in 54 (90%) patients. The median number of genes altered per tumor was 2 (range 0-20). The most common recurrent somatic mutations were P53 (41%). Significant portion of patients had alterations in DNA repair genes, including BRCA1/2(24%). There was significant difference ($p < 0.001$) in median and frequency of alterations between hormone sensitive and metastatic castration resistant prostate cancer (mCRPC). In addition to mutations in genes frequently observed in prostate cancer such as AR (36%), APC (25%), MYC (17%), CDK6 (14%), RB (14%), BRAF (14%), EGFR (11%), PTEN (7%); we also identified several alterations in genes previously have not reported in prostate cancer, such as ALK (7%), IDH2 (7%), FH (3%), PDK1(3%), WT1 (3%). Based on the molecular profiling findings of DNA repair defects, five refractory mCRPC patients were enrolled into ongoing clinical trial; three heavily pretreated patients found eligible and treated with PARP inhibitor olaparib: one patient with BRCA 2 deletion who had partial response last eight months; another patient with TMPRSS2-ERG fusion and PTEN loss had complete pathological response. One patient with microsatellite instability (MSI) had complete remission with checkpoint inhibitor pembrolizumab.

Conclusions : Targeted molecular profiling may enhance clinical trial enrollment and help guide the target treatment options for men with refractory mCRPC. The major barriers to implementation of molecularly guided therapy in clinic were poor performance status of the elderly patients (likely reflect the delay in getting tumor profiling) and access of target drugs. Earlier tumor profiling and facilitating availability of targeted drugs through "umbrella clinical trials" may expand patients' access to innovative therapies and precision cancer care.

5 - Developing Breath Biomarkers for Diagnosing Lung Infection Etiology in Persons with Cystic Fibrosis

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Chronic respiratory infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the leading cause of morbidity and mortality in persons with cystic fibrosis (CF). Accurate microbiological profiling of the lower airways and prompt antibiotic treatment are crucial for delaying chronic infection onset and preserving lung function. Our long-term goal is to substantially shorten the time-to-diagnosis for common CF lung pathogens through the development of sensitive and specific breath-based diagnostics for infection etiology in the polymicrobial CF lung milieu. In a preliminary study we aimed to identify volatile organic compound (VOC) biomarkers from bronchoalveolar lavage (BAL) samples that can guide breath biomarker development for pathogen identification. BAL samples (n = 154) from CF patients were analyzed using two-dimensional gas chromatography time-of-flight mass spectrometry (GC×GC-TOFMS). Random Forest was used to select and validate suites of VOCs for identifying *P. aeruginosa*-positive and *S. aureus*-positive samples. Using nine VOCs, we differentiated *P. aeruginosa*-positive (n = 7) from *P. aeruginosa*-negative (n = 53) samples with an area under the receiver operating characteristic curve (AUROC) of 0.86 and with positive and negative predictive values of 0.67 and 0.92, respectively. We were also able to discriminate *S. aureus*-positive (n = 15) from *S. aureus*-negative (n = 45) samples with an AUROC of 0.88 using eight VOCs and with PPV and NPV of 0.86 and 0.70, respectively. With these results we are initiating a multi-site clinical study to validate the *P. aeruginosa* volatile biomarkers in the breath of adult and pediatric CF patients. The IMproving *P. Aeruginosa* de C Tion via Breath (IMPACT-Breath) study will collect breath samples and sputum microbiome data from 288 subjects with CF, half who are *P. aeruginosa*-positive, to validate the sensitivity and specificity of breath biomarkers for diagnosing *P. aeruginosa* infection.

Funding: Cystic Fibrosis Foundation Therapeutics, Cystic Fibrosis Foundation, Burroughs Wellcome Fund, National Institutes of Health

6 - Does Vaginal Microbiome Composition Alter Local Cancer Biomarker Expression in Cervical Dysplasia and Cancer?

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Funding: The Flinn Foundation (#1974)

The microbiome has been shown to be a vital modifier of the immune system and to impact immunotherapy efficacy. *Lactobacillus*-depleted dysbiotic vaginal microbiota (VMB) is associated with cervical carcinogenesis. Our objective is to study the association of cancer biomarkers and VMB composition in the local microenvironment, as a potential link to therapeutic outcomes. In a multicenter study, we enrolled 78 premenopausal, non-pregnant women with low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL), invasive cervical cancer (ICC), or healthy controls. Twenty-four circulating cancer biomarkers were quantified in cervicovaginal lavages using multiplex analysis. VMB composition was determined by 16S rRNA sequencing using vaginal swabs. The statistical differences were tested using ANOVA or a mixed linear model. VMB beta diversity varied significantly based on vaginal pH, age (38 ± 8) and ethnicity (47% Hispanic), but not BMI (68% had a BMI >25). Abnormal vaginal pH was significantly higher in the ICC group ($P < 0.003$). Cancer biomarker analysis revealed significantly increased levels of IL-6, TNF, sFas, sFasL, TRAIL, VEGF, leptin, prolactin, HGF, SCF, AFP, OPN and CYFRA 21-1 in CVLs in ICC compared to other groups. After adjustment for covariates, 13 cancer biomarkers were positively associated with ICC in patients with dysbiotic VMB, whereas only 3 biomarkers were associated with patients with lactobacilli dominant VMB. The majority of cancer biomarkers were also highly correlated to other biomarkers and linked to genital inflammation and VMB composition. Our study revealed that circulating biomarkers are present in the local microenvironment and specifically elevated in ICC patients. Moreover, the cancer biomarkers are associated with vaginal microbiome composition. Finally, a hierarchical clustering analysis of cancer biomarkers and immune mediators revealed a group of patients that may be at increased risk of progressing to dysplasia and ICC.

7 - Electroencephalography as a Measure of Cerebral Autoregulation in Pediatric Acute Brain Injury

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Funding: Moberg ICU Solutions, Inc & Phoenix Children's Hospital

Given limited high-level evidence to guide care after pediatric acute brain (ABI) injury, physiologic dynamics must be explored to understand the circumstances in which cerebral autoregulation is intact and secondary injury is minimized. Promising research has brought forward validated model-based indices of cerebral autoregulation using intracranial pressure monitoring and near infrared spectroscopy. These include the pressure reactivity index (PRx) and cerebral oximetry index (COx), which are moving-average cross correlation coefficients of high-frequency, time-aligned physiological measurements of intracranial pressure (ICP) and cerebral oximetry saturation (rSO₂-C) to mean arterial blood pressure (MAP), respectively. Such techniques lack sufficient spatial resolution to describe regional differences in cerebral autoregulation after heterogeneous injuries. Continuous electroencephalography (cEEG) represents a commonly utilized non-invasive technique that provides both high temporal and spatial resolution data. cEEG has been established as not only useful for seizure detection, but as a sensitive biomarker for changes in cerebral blood flow. We aim to explore whether the development of EEG-derived model-based indices for cerebral autoregulation is feasible and can be utilized to determine the optimal physiologic parameters to minimize secondary brain injury in children. Some of our current research questions are to investigate the correlation between these indices. Analyzing this type of big data presents challenges including the lack of a traditional methodology to analyze panel time series, and the computational burden when the estimation is based on maximum likelihood. In order to address this, we use dynamic structural equations modeling (DSEM) which relies on the Bayesian methodology and structural equations modeling in the context of time series.

8 - Emergence of pathway-level composite biomarkers from converging gene set signals of heterogeneous transcriptomic responses

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Recent precision medicine initiatives have led to the expectation of improved clinical decision-making anchored in genomic data science. However, over the last decade, only a handful of new single-gene product biomarkers have been translated to clinical practice (FDA approved) in spite of considerable discovery efforts deployed and a plethora of transcriptomes available in the Gene Expression Omnibus. With this modest outcome of current approaches in mind, we developed a pilot simulation study to demonstrate the untapped benefits of developing disease detection methods for cases where the true signal lies at the pathway level, even if the pathway's gene expression alterations may be heterogeneous across patients. In other words, we relaxed the cross-patient homogeneity assumption from the transcript level (cohort assumptions of deregulated gene expression) to the pathway level (assumptions of deregulated pathway expression). Furthermore, we have expanded previous single-subject (SS) methods into cohort analyses to illustrate the benefit of accounting for an individual's variability in cohort scenarios. We compare SS and cohort-based (CB) techniques under 54 distinct scenarios, each with 1,000 simulations, to demonstrate that the emergence of a pathway-level signal occurs through the summative effect of its altered gene expression, heterogeneous across patients. Studied variables include pathway gene set size, fraction of expressed gene responsive within gene set, fraction of expressed gene responsive up- vs down-regulated, and cohort size. We demonstrated that our SS approach was uniquely suited to detect signals in heterogeneous populations in which individuals have varying levels of baseline risks that are simultaneously confounded by patient-specific "genome -by- environment" interactions (G×E). Area under the precision-recall curve of the SS approach far surpassed that of the CB (1st quartile, median, 3rd quartile: SS = 0.94, 0.96, 0.99; CB = 0.50, 0.52, 0.65). We conclude that single-subject pathway detection methods are uniquely suited for consistently detecting pathway dysregulation by the inclusion of a patient's individual variability.

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9 - High GILT expression and an active and functional MHC class II antigen presentation pathway are associated with improved survival in melanoma

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Anti-tumor immune responses depend on T cell recognition of tumor antigens in the context of major histocompatibility complex (MHC) proteins to destroy tumors. While defects in the MHC class I antigen presentation pathway in melanoma cells have been well established as a mechanism of immune evasion, the clinical significance of the MHC class II antigen presentation pathway in melanoma cells is less well understood. In antigen presenting cells, gamma-interferon-inducible lysosomal thiol reductase (GILT) is critical for MHC class II-restricted presentation of multiple melanoma antigens to CD4 T cells. While not expressed in benign melanocytes in nevi specimens, expression of GILT and MHC class II proteins is induced in malignant melanocytes in a portion of melanoma specimens. This variation in expression led us to investigate the clinical significance of GILT and the MHC class II antigen presentation pathway in melanoma. Our analysis of The Cancer Genome Atlas (TCGA) cutaneous melanoma dataset showed that high GILT mRNA expression was associated with improved overall survival (logrank $p = 0.0071$; Cox proportional hazards model $p = 0.0038$). Expression of cytokines IFN- γ , TNF, and IL-1 β was positively associated with GILT expression in the TCGA melanoma specimens. IFN- γ , TNF, and IL-1 β were capable of inducing GILT expression in melanoma cells in vitro. GILT protein expression in melanocytes was induced in halo nevi, which are nevi undergoing immune-mediated regression, and is consistent with the association of GILT expression with improved survival in melanoma. To explore possible mechanisms of GILT's association with patient outcome, we analyzed the activity and consistency of the MHC class II antigen presentation pathway in melanoma. In contrast to normal skin in which the activity and consistency of the MHC class II pathway was nearly uniformly equal to one, there was substantial variation in the MHC class II pathway in the TCGA melanoma dataset, suggesting that the MHC class II pathway is altered in melanoma. Both high activity and consistency scores in the MHC class II antigen presentation pathway were associated with improved overall survival in melanoma (logrank $p = 6.9 \times 10^{-4}$ and 5.4×10^{-4} , respectively). These studies support a role for GILT and the MHC class II antigen presentation pathway in melanoma outcome.

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10 - Paired Associates Performance is Altered by a First-Degree Family History of Alzheimer's Disease: An Effect Modified by Apolipoprotein E Genotype, Diabetes, and Heart Disease

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Background: A first-degree family history Alzheimer's disease (FH) is a leading risk for dementia. However, the exact influence of FH on cognition across the lifespan is poorly understood. Further, whether the cognitive effects of FH are modified by lifestyle choices, medical conditions, and genetics remains unexplored. We examined the effect of FH on paired associate learning (PAL) and if this effect was altered by demographic, health, lifestyle, and genetic factors.

Methods: We developed a web-based PAL task (at www.mindcrowd.org), which included 22 demographic, health, and lifestyle questions, and tested over 75,000 individuals between the ages of 18-85. In addition, we examined the well-known Alzheimer's disease genetic risk factor, the apolipoprotein E (APOE) E4 allele, in over 600 FH participants via self-collected dried blood spots.

Results: FH impaired PAL with larger effect sizes found in participants under 65 years old. Next, we found that heart disease and diabetes interacted with FH to modify PAL. Interestingly, heart disease enhanced PAL only in FH men. Lastly, FH carriers of the APOE E4 allele had impaired PAL.

Conclusions: This study suggests that FH, APOE genotype, heart disease, and diabetes are important factors that modify the trajectory of an individual's cognitive performance across their lifespan.

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11 - Identification of Endometrial Cancer Specific miRNA Biomarkers in Endometrial Fluid Collected Using Saline Infusion Sonohysterography Techniques

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Presenting Author: Jianing Yang, MD, PhD. Senior Research Scientist, Center for Applied Nanobiosciences and Medicine, U of A COM-P

Background: Abnormal uterine bleeding is a common benign gynecologic complaint around the time of menopause, and is also the most common symptom of cancer of the lining of the uterus (endometrial cancer). This complaint prompts in-office endometrial biopsy to exclude malignancy. Unfortunately, because only a limited portion of the lining tissue is sampled, the endometrial biopsy is not always accurate which can lead to delays in diagnosis and the potential for worsening of the disease and prognosis. Biomolecules have proven to be useful tools in cancer screening and diagnosis. These are usually detected by sampling the patient's blood for circulating cancer-related markers or by biopsy with tissue analysis using special stains to detect the presence of cancer-specific biomolecules. No such circulating biomarkers have been identified in endometrial cancer, and as stated direct sampling of the endometrium has limitations. MicroRNA are a class of small molecules related to cell protein production. They have also shown promise in cancer detection. MicroRNAs may be detected by testing tissue or by testing the fluid that cells secrete. Endometrial tissue is inherently difficult to sample in the office, but the cell fluid can be easily sampled using a technique adapted from an in-office procedure known as a sonohysterography. This procedure is used in the evaluation of abnormal uterine bleeding by introducing saline solution into the endometrial cavity as a contrast material during transvaginal ultrasound. The infused saline is normally discarded, but can be collected for microRNA analysis. This project is the first stage in developing a method to improve the detection and diagnosis of endometrial cancer in women.

Methods: Patients were recruited who planned to undergo hysterectomy for either benign indication or for a known endometrial cancer diagnosis. We collected endometrial fluid prior to surgery using a technique similar to that used in sonohysterography. The miRNA was extracted and purified. The product was used to amplify and quantify miRNA candidate markers using RT-PCR. Patient demographic and health information was collected to be used in the final analysis along with the final pathology results of their surgery.

Results and Discussion: In total, 60 patient samples have been collected and processed to date (30 cancer and 30 controls). Significant variations in expression were identified in several miRNA markers. Markers with at least a two-fold increase or decrease in expression were considered candidates for validation. We chose to narrow this field to the twelve markers with the greatest variation in expression. These markers will be used on an additional set of patients to further validate the results.

Support: Valley Research Partnership P2 grant (\$80,000), University of Arizona College of Medicine, Phoenix

12 - Phage Display as a Biomarker Discovery Tool for Neural Injury

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Traumatic brain injury affects over 1.7 million US citizens annually. The initial trauma sustained by the brain kicks off a degenerative signaling cascade that may include excessive release of chemotactic factors, inflammation, blood-brain barrier breakdown, edema, and gliosis. Clinical diagnosis of brain injury commonly relies on subjective measurements whereby objective biomarker markers may provide a more accurate diagnosis. Phage display is a unique biochemical tool that enables unbiased discovery of ligand-antigen pairs ideal for biomarker development. Here, we present a pipeline of phage display for a known upregulated chondroitin sulfate proteoglycan (neurocan) in many neural injury sequelae. The goal of this project was to utilize phage display to identify single-domain antibodies (DAB) that bind preferentially and specifically to neurocan to serve as a platform for many diagnostic and therapeutic intervention strategies. Phage display biopanning was conducted using the highly diverse human DAB phagemid library (Source BioScience). Each biopanning round consisted of a sequence of both negative and human recombinant neurocan exposures to ensure maximal selectivity to neurocan. After three biopanning rounds, a high-throughput ELISA was conducted to identify clones with preference to neurocan. A subsequent concentration dependent ELISA was then conducted with the top clones to further characterize affinity parameters. Further binding assays identified a unique DAB that exhibited preferential binding to neurocan with minimal non-specific binding to negative controls. The final phase of this project focuses on employing unique bacterial systems to produce high yields of the recombinant DABs for assessment in pre-clinical in vivo models. Ultimately, we have established we pipeline for identifying and producing antibody fragment-antigen pairs for neural injury biomarker discovery.

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13 - Precision drug repurposing via convergent eQTL-based molecules and pathway targeting independent disease-associated polymorphisms

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Repurposing existing drugs for new therapeutic indications can improve success rates and streamline development. Use of large-scale biomedical data repositories, including eQTL regulatory relationships and genome-wide disease risk associations, offers opportunities to propose novel indications for drugs targeting common or convergent molecular candidates associated to two or more diseases. This proposed novel computational approach scales across 262 complex diseases, building a multi-partite hierarchical network integrating (i) GWAS-derived SNP-to-disease associations, (ii) eQTL-derived SNP-to-eGene associations incorporating both cis- and trans- relationships from 19 tissues, (iii) protein target-to-drug, and (iv) drug-to-disease indications with (iv) Gene Ontology-based information theoretic semantic (ITS) similarity calculated between protein target functions. Our hypothesis is that if two diseases are associated to a common or functionally similar eGene - and a drug targeting that eGene/protein in one disease exists - the second disease becomes a potential repurposing indication. To explore this, all possible pairs of independently segregating GWAS-derived SNPs were generated, and a statistical network of similarity within each SNP-SNP pair was calculated according to scale-free overrepresentation of convergent biological processes activity in regulated eGenes (ITSeGENE-eGENE) and scale-free overrepresentation of common eGene targets between the two SNPs (ITSSNP-SNP). Significance of ITSSNP-SNP was conservatively estimated using empirical scale-free permutation resampling keeping the node-degree constant for each molecule in each permutation. We identified 26 new drug repurposing indication candidates spanning 89 GWAS diseases, including a potential repurposing of the calcium-channel blocker Verapamil from coronary disease to gout. Predictions from our approach are compared to known drug indications using DrugBank as a gold standard (odds ratio=13.1, p-value=2.49x10⁻⁸). Because of specific disease-SNPs associations to candidate drug targets, the proposed method provides evidence for future precision drug repositioning to a patient's specific polymorphisms.

Supplementary material: http://lussiergroup.org/publications/drug_repurposing_by_eQTL

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14 - Tumor Molecular Profiling in Advanced Pediatric Solid Tumors

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Introduction: Outcome of pediatric cancer patients have improved in recent times due to enhanced understanding of tumor biology and application of novel discoveries in the clinic. However, survival for many pediatric oncology patients remains dismal. The identification of targetable genomic alterations has the potential to offer diagnostic, prognostic and predictive information for better disease management.

Methods: Next Generation Sequencing of tumor/normal exome and tumor RNA Seq assay was performed which enabled the detection of SNVs, indels, copy number events, and fusions. Clinically, actionable alterations were identified which could be targeted with FDA approved or clinical trials. Sequencing was done on 6 pediatric cancer samples (age range 5 months-14 years).

Results: Data analysis of all 6 patient samples identified at least one targetable alteration in each sample. BRAF was the gene most frequently altered in our study. A constitutively active KIAA1549-BRAF fusion was identified both in the DNA and RNA in a 1 yr old pilomyxoid astrocytoma patient. A BRAF V600E mutation was identified in a 14 yr old patient with recurrent anaplastic ganglioglioma. BRAF (N486_P490del) and MAP2K1 (K57_G61del) mutations, predicted to be activating were identified in a 14 yr old and a 5-month-old infant with Langerhans Cell Histiocytosis (LCH) respectively. In tumors with RAS/RAF/MEK pathway alterations, inhibitors of MAPK pathway have been considered as a potential targeted therapy. In a 12-year-old patient with GBM, loss of function mutations were identified in NBN, ATRX, SETD2 and TP53, which may be sensitive to PARP inhibitors and WEE1 inhibitors. A breakpoint translocation concurrent with LOH of PTCH1 locus was noted in a 1 yr old medulloblastoma patient. PTCH1 loss resulting in constitutively active hedgehog signaling (Hh) has been reported in Shh-Medulloblastoma subtype and may provide a therapeutic option with SMO inhibitors.

Conclusions: Our results underline the importance of next generation sequencing in identifying targetable markers in a diverse population of pediatric solid tumors. Although our study is limited by small sample size, the impact of identifying even one clinically actionable genomic alteration provides a valuable therapeutic option in tumors where no standard of care options is available.

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