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## Application Summary

### Competition Details

| Competition Title: | 2021 Vice President's Clinical and Translational (VPCAT) Research Scholars Program Application |

### Application Information

<table>
<thead>
<tr>
<th>Submitted By:</th>
<th>Sabrina Malone Jenkins</th>
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</thead>
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<tr>
<td>Application ID:</td>
<td>2658</td>
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<tr>
<td>Application Title:</td>
<td>Next Generation Genetic Sequencing in the NICU: Improving Healthcare Through Precision Medicine</td>
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<tr>
<td>Date Submitted:</td>
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### Personal Details

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<tr>
<th>uNID (U of U ID number/u00000000):</th>
<th>u0969254</th>
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<tbody>
<tr>
<td>Applicant First Name:</td>
<td>Sabrina</td>
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<tr>
<td>Applicant Middle Initial:</td>
<td></td>
</tr>
<tr>
<td>Applicant Last Name:</td>
<td>Malone Jenkins</td>
</tr>
<tr>
<td>Applicant Alias (i.e., Name Applicant Prefers to Go By):</td>
<td></td>
</tr>
<tr>
<td>Applicant Degree(s):</td>
<td>MD</td>
</tr>
<tr>
<td>Academic Rank (i.e., Primary Appointment Title):</td>
<td>Assistant Professor</td>
</tr>
<tr>
<td>Secondary Appointment Title (i.e., clinic director, chair, chief, etc.):</td>
<td></td>
</tr>
<tr>
<td>Academic Track:</td>
<td>Career-Line: Clinical Track</td>
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<tr>
<td>College or School:</td>
<td>Medicine</td>
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<tr>
<td>Department:</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Division:</td>
<td>Neonatology</td>
</tr>
<tr>
<td>Work Address:</td>
<td>295 Chipeta Way Salt Lake City, UT 84108</td>
</tr>
<tr>
<td>Email Address:</td>
<td><a href="mailto:sabrina.malonejenkins@hsc.utah.edu">sabrina.malonejenkins@hsc.utah.edu</a></td>
</tr>
<tr>
<td>Work Phone Number:</td>
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<td>Cell Phone Number:</td>
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<td>Month of Birth:</td>
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<td><strong>ORCID Identifier # (if applicant does not have an ORCID, please register for a unique ID via <a href="http://www.orcid.org">www.orcid.org</a>):</strong></td>
<td>0000-0001-8810-7619</td>
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<tr>
<td><strong>Twitter Handle (if applicant does not have one, list &quot;none&quot;):</strong></td>
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<td><strong>Race:</strong></td>
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<td><strong>Do you have a disability? (NIH defines individuals with disabilities as those with a physical or mental impairment that substantially limits one or more major life activities.):</strong></td>
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<td><strong>Are you from a disadvantaged background? (see NIH NOT-OD-20-051 for definition):</strong></td>
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<tr>
<td><strong>Separating each with a semicolon, list up to 5 key SCIENTIFIC TERMS aligned to your research interests that we could use to search for funding opportunities via online systems (i.e., Grants.gov, NIH, Pivot, etc.).:</strong></td>
<td>neonatal;genomics;sequencing;prenatal</td>
</tr>
<tr>
<td><strong>Separating each with a semicolon, list up to 5 FUNDING AGENCIES you are interested in submitting an application for funding considerations. NOTE: if you are interested in the National Institute of Health (NIH), provide the name of the specific institute.:</strong></td>
<td>NIH K23</td>
</tr>
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<td><strong>Are you a Scholar in one of the following programs?:</strong></td>
<td>None of the Above</td>
</tr>
<tr>
<td><strong>Administrative Assistant First Name:</strong></td>
<td>Kathy</td>
</tr>
<tr>
<td><strong>Administrative Assistant Last Name:</strong></td>
<td>Aller</td>
</tr>
<tr>
<td><strong>Administrative Assistant Email:</strong></td>
<td><a href="mailto:Kathy.Aller@hsc.utah.edu">Kathy.Aller@hsc.utah.edu</a></td>
</tr>
<tr>
<td><strong>Administrative Assistant Phone #:</strong></td>
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</table>
Application Details

Proposal Title
Next Generation Genetic Sequencing in the NICU: Improving Healthcare Through Precision Medicine

Scientific Mentor Unid (U of U ID number/u0000000. If none, list "Not Applicable")
u0029928

Scientific Mentor First Name
Martin

Scientific Mentor Middle Initial

Scientific Mentor Last Name
Tristani-Firouzi

Scientific Mentor Alias (i.e., Name Mentor Prefers to Go By)

Scientific Mentor Degree(s)
MD

Scientific Mentor Academic Rank (i.e., Primary Appointment Title)
Professor

If selected "Other Title," please designate Mentor's Primary Appointment Title

Scientific Mentor Secondary Appointment Title (i.e., clinic director, chair, chief, etc.)

Scientific Mentor College or School
Malone Jenkins, Sabrina - #2658

Pre-Award Support Staff
First Name (This person should be the individual in your division/department that supports you with the submission of grants. If unknown, state 'Unknown'):
Joy
Last Name:
Blatchford
Email:
Joy.Blatchford@hsc.utah.edu

Post-Award Support Staff
First Name (This person should be the individual in your division/department that supports you with accounting/payroll. If unknown, state 'Unknown'):
Jared
Last Name:
Olney
Email:
Jared.Olney@hsc.utah.edu
Malone Jenkins, Sabrina - #2658
September 3, 2020

Michael A. Rubin, MD, PhD, MS
Director, VPCAT Program
University of Utah Health, SVPHS Education Office
EHSEB 5515

Dr. Dr. Rubin,

I write to express my sincere interest in the Vice President’s Clinical and Translational (VPCAT) Research Scholars Program. I have served as an Assistant Professor in the Department of Pediatrics, Division of Neonatology, following completion of my fellowship at the University of Utah in 2017. As I begin my research career, I plan to pursue studies aimed at improving care for newborn infants, born either at term or prematurely, by integrating the use of genomics in the NICU to provide personalized medicine to critically ill neonates. This is my passion within Neonatology and represents a significant knowledge deficit with the field pertinent to an extremely vulnerable and understudied population – newborn infants. As a clinician in the NICU, I provide care for critically ill newborn infants and understand the importance of personalized clinical care in improving outcomes. My long-term goal is to become an independent clinical researcher who improves care for newborn infants by integrating the use of genomic testing in the NICU to provide personalized medicine and focused clinical care. My participation in the VPCAT Scholars Program will provide the intensive mentorship required to become an accomplished and funded principal investigator.

Each step of my research career has prepared me for the role of physician-scientist. During the first years of my fellowship, I initiated and conducted a clinical research study focused on nephrocalcinosis and bone metabolism in preterm infants. This work led to five abstracts, which I presented at regional and national conferences. For these abstracts, I received a Western Section Scholar Award from the American Federation for Medical Research and the Best Clinical Research Abstract Award from the AAP District VIII Section on Neonatal-Perinatal Medicine. In the second half of my fellowship, and now as a junior faculty, I have led the application of next generation sequencing (NGS) in the NICU. A critical turning point in my development as a physician-scientist occurred during my fellowship when I participated in the development, initiation, and implementation of a rapid turn-around, targeted gene panel (RapSeq) for care of critically ill infants in the NICU. We showed reduction in the number of invasive procedures, diagnostic clinical testing, and decreased lengths of stay for select infants undergoing RapSeq testing. In 2018, under the mentorship of Luca Brunelli, we published a letter describing our clinical inclusion criteria and initial cases using RapSeq in the *American Journal of Medical Genetics*. We published our second manuscript evaluating clinical utility and cost effectiveness of our first 20 cases using RapSeq in the NICU in *Molecular Genetics & Genomic Medicine*, and I served as co-first author. I presented our results at the Pediatric Academic Societies meeting in 2018. Our results demonstrate that NGS represents the next step towards providing personalized, precision medicine to critically ill neonates. I have also learned first-hand of the challenges involved in addressing testing issues and ethical concerns associated with NGS studies. I now serve as the NICU Physician Lead for the Pediatric Personalized Medicine Program. Through this program, we now offer rapid whole genome sequencing (rWGS) on critically ill infants in the PCH NICU, CICU, and PICU; both at the University of Utah, and at Primary Children’s Hospital. With the mentorship of Josh Bonkowski, Martin Tristani, and Luca Brunelli, I was selected to serve as PI on the NeoSeq project, in which I have led development of a research pipeline for rapid whole genome sequencing for acutely ill infants in the University of Utah NICU.
In my current faculty position, I have 65% protected research time for investigation that is funded by the Department of Pediatrics (see table, and Letter of Support from my Division Chair). I have a guarantee of 75% protected research time when awarded an NIH K23 award. Currently, I am Principal Investigator on a Primary Children’s Hospital Foundation Early Career Development Award “Next Generation Sequencing in the NICU: Improving Healthcare Through Precision Medicine”. I am testing whether rWGS will increase the diagnostic yield in select NICU patients suffering from arthrogryposis, non-immune hydrops fetalis, or skeletal dysplasia. I also serve as the Principal Investigator for the Utah NeoSeq project studying the implementation of rapid whole genome sequencing in the University of Utah NICU using a research pipeline with ARUP and the Utah Center for Genetic Discovery. This project is funded by the Margolis Foundation, the Utah Center for Genomic Medicine, and the University of Utah. The NeoSeq project provides the opportunity to facilitate follow up collaborative studies not only for myself but for my colleagues for years to come. We have parental consent and provider satisfaction surveys to assess how this new technology not only affects parents but providers as well using novel and validated methods. I am the principal investigator on Optimizing Identification of Fetal-Derived Monogenic Variants in Circulation Cell-Free DNA by Next Generation Sequencing, funded by a grant from the Primary Children’s Center for Personalized Medicine.

My primary research mentor is Dr. Martin Tristani-Firouzi, an expert in the field of personalized medicine. His research focuses on the genomic determinants of susceptibility to cardiac arrhythmia disorders and congenital heart disease. He has successfully used NGS to guide clinical management, stratify risk, and improve clinical outcomes in patients with cardiac disease. The NGS techniques, including rWGS are directly applicable to critically ill neonates. Dr. Tristani will provide the hands-on mentorship I require during this program as I establish myself as an independent researcher. We recently had two abstracts accepted and have one manuscript in preparation and an additional four planned.

In an environment that fosters accountability, communication, and skills development, I have the potential to develop into a successful independent investigator. I have a promising research focus, and established research mentors who are NIH funded, and I have established a track record of success by obtaining local grants to generate pilot data. I plan to apply for an NIH K23 grant award within the next two years. I have a passion for research and a plan to improve the care of newborn infants.

Sincerely,

[Signature]

Sabrina Malone Jenkins, MD
Assistant Professor, Pediatrics
Division of Neonatology
Curriculum Vitae

PERSONAL DATA
Name: Sabrina Malone-Jenkins, M.D.

EDUCATION
<table>
<thead>
<tr>
<th>Years</th>
<th>Degree</th>
<th>Institution (Area of Study)</th>
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<tbody>
<tr>
<td>2014 - 2017</td>
<td>Fellow</td>
<td>University of Utah (Neonatal-Perinatal Medicine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt Lake City, UT</td>
</tr>
<tr>
<td>2011 - 2014</td>
<td>Resident</td>
<td>University of Nebraska Medical Center/Creighton University Medical Center (Pediatrics)</td>
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<tr>
<td></td>
<td></td>
<td>Omaha, NE</td>
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<tr>
<td>2007 - 2011</td>
<td>M.D.</td>
<td>Ross University School of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portsmouth, Dominica</td>
</tr>
<tr>
<td>2002 - 2006</td>
<td>B.S.</td>
<td>University of Florida (Nutritional Sciences)</td>
</tr>
<tr>
<td></td>
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<td>Gainesville, FL</td>
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</tbody>
</table>

BOARD CERTIFICATIONS
10/09/2014 - Present  American Board of Pediatrics (Pediatrics), Certified
08/03/2020 - Present  American Board of Pediatrics (Sub: Neonatal-Perinatal Medicine), Eligible

CURRENT LICENSES/CERTIFICATIONS
2016 - Present  United States Department of Justice Drug Enforcement Administration: Controlled Substance (UT) - Physician (MD)
2014 - Present  State of Utah: State License (UT) - Physician (MD)
2011 - Present  America Heart Association: Pediatric Advanced Life Support (UT) - Physician (MD)
2011 - Present  American Academy of Pediatrics: Neonatal Resuscitation Program (UT) - Physician (MD)

TRAINING
2016 - Present  Utah Certificate of Palliative Education, Salt Lake City, UT

UNIVERSITY OF UTAH ACADEMIC HISTORY
Pediatrics (Neonatology), 07/01/2017 - Present
07/01/2017  Assistant Professor (Clinical)

PROFESSIONAL EXPERIENCE
Full-Time Positions
2019 - Present  Faculty Member, Utah Center for Genomic Medicine, Salt Lake City, UT
2017 - Present  Assistant Professor, University of Utah, Salt Lake City, UT
Reviewer Experience
Reviewer for *Journal of Perinatology*

**SCHOLASTIC HONORS**

- **2019 - Present**
  Gary M. Chan Endowed Chair in Pediatrics, University of Utah, Department of Pediatrics
- **2017**
  Travel Award, AAP District VIII Sectional on Neonatal-Perinatal Pediatrics 41st Annual Conference, Seattle, WA
- **2017**
  Best Clinical Research Abstract, AAP District VIII Sectional on Neonatal-Perinatal Pediatrics 41st Annual Conference, Seattle, WA
- **2016**
  Travel Award, AAP District VIII Section on Neonatal-Perinatal Pediatrics 40th Annual Conference, Honolulu, Hawaii
- **2015**
  Western Region Scholar, American Federation for Medical Research, Western Society for Pediatric Research Conference, Carmel, CA
- **2004 - 2006**
  Golden Key National Honor Society
- **2002 - 2006**
  Bright Futures Scholarship Award

**ADMINISTRATIVE EXPERIENCE**

*Administrative Duties*

- **2019 - Present**
  NICU Physician Lead, Primary Children's Center for Pediatric Personalized Medicine
- **2018**
  Session Moderator, AAP District VIII Section on Neonatal-Perinatal Pediatrics 42nd Conference, Midway, UT
- **2018 - Present**
  Membership Chair, AAP District VIII Section on Neonatal-Perinatal Pediatrics Council

*Grant Review Committee/Study Section*

- **2020**
  Reviewer, Grant for Pediatric Personalized Medicine Program

**UNIVERSITY COMMUNITY ACTIVITIES**

*University of Utah Health*

- **2018 - Present**
  Moderator, University of Utah Health, University Advanced Communication Training

*Division Level*

- **2018 - Present**
  Physician Scheduler, Neonatology, Scheduling committee
- **2015 - 2016**
  Coordinator, Neonatology, Fellow Lecture Series

**SERVICE AT AFFILIATED INSTITUTIONS**

- **2018 - Present**
  Advisory Board Member, Primary Children's Hospital, Primary Children's Center for Personalize Medicine
- **2018 - Present**
  Committee Member, Intermountain Medical Center, Extremely Low Birth Weight (ELBW) Committee. Improving outcomes in extremely low birth weight infants during resuscitation and admission to IMC NICU.

Malone Jenkins, Page 2
2015 - 2017 Committee Member, Intermountain Healthcare, Intermountain Healthcare Nutrition Feeding Progression Guidelines. Developed guidelines to standardize initiation and progression of enteral feedings for infants of various weights and gestations

SERVICE AT PREVIOUS INSTITUTIONS
2012 - 2014 Pediatric Representative, University of Nebraska Medical Center, Creighton University Medical Center, Children’s Hospital & Medical Center, ResQ
2012 Member, University of Nebraska Medical Center, Creighton University Medical Center, Children’s Hospital & Medical Center, Curriculum Committee
2011 - 2014 Member, University of Nebraska Medical Center, Creighton University Medical Center, Children’s Hospital & Medical Center, NICU Quality Improvement Committee

CURRENT MEMBERSHIPS IN PROFESSIONAL SOCIETIES
American Academy of Pediatrics
American Academy of Pediatrics - District VIII Section on Neonatal-Perinatal Medicine
American Society of Human Genetics
Society for Pediatric Research
Western Society for Pediatric Research

FUNDING
Active Grants
04/27/20 - Present Optimizing Identification of Fetal-Derived Monogenic Variants in Circulating Cell-Free DNA by Next Generation Sequencing
Principal Investigator(s): Sabrina Malone-Jenkins
Role: Principal Investigator
01/01/20 - Present Next Generation Genetic Sequencing in the NICU: Improving Healthcare Through Precision Medicine
Principal Investigator(s): Sabrina Malone-Jenkins
Primary Children's Hospital Foundation
Role: Principal Investigator
07/01/19 - Present Implementation of Rapid Whole Genome Sequencing (rWGS) in the Newborn Intensive Care Unit (NICU) to Diagnose and Treat Critically Ill Infants
Principal Investigator(s): Sabrina Malone-Jenkins
Ben B. and Iris M. Margolis Foundation
Role: Principal Investigator
07/01/19 - Present Utah NeoSeq
Principal Investigator(s): Sabrina Malone-Jenkins
Role: Principal Investigator

Pending Grants
07/01/20 - Present  
Next-Generation Sequencing for the Diagnosis and Treatment of Critically Ill Neonates  
Principal Investigator(s): Joshua Leitch Bonkowsky  
Thrasher Research Fund  
Role: Co-Investigator

Past Grants

01/01/14 - 06/30/17  
Preterm Infants and Nephrocalcinosis: Diagnosis and Pathogenesis  
Principal Investigator(s): Sabrina Malone-Jenkins; Gary M. Chan  
Intermountain Research and Medical Foundation  
Role: Co-Principal Investigator

Clinical Studies

2020 - Present  
SafeBoosC-III: Safeguarding the brain of our smallest children—an investigator-initiated, pragmatic, open label, multinational randomized phase III clinical trial evaluating treatment based on near-infrared spectroscopy monitoring versus treatment as usual in premature infants, Study Team Member

2020 - Present  
Assessing the Impact of Whole Genome Sequencing (WGS) at Primary Children’s Hospital, Principal Investigator

2020 - Present  
Assessing Providers Confidence in Performing Tasks Common to Genomic Medicine, Principal Investigator

2020 - Present  
Utah NeoSeq Project, Implementing rapid whole genome sequencing into the Newborn ICU, Principal Investigator

2019 - Present  
Next Generation Genetic Sequencing in the NICU: Increasing Healthcare Value Through Precision Medicine, Principal Investigator

2018 - Present  
CIRB Randomized Controlled Trial of Home Therapy with Caffeine Citrate in Moderately Preterm Infants with Apnea of Prematurity (MoCHA Trial), Study Team Member

2018 - Present  
Management of the Patent Ductus Arteriosus in Preterm Infants Trial (PDA Trial), Study Team Member

2017 - Present  
A Prospective, Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare Safety and Efficacy of Smoflipid 20% to Intralipid 20% in Hospitalized Neonates and Infants Requiring 28 Days of Parenteral Nutrition, Study Team Member

2017 - Present  
Enteral zinc to improve growth in infants at risk for bronchopulmonary dysplasia, Co-Investigator

2017 - Present  
Darbepoetin Trial to Improve Red Cell Mass and Neuroprotection in Preterm Infants, Study Team Member

2017 - Present  
Mild Encephalopathy in the Neonate treated with Darbepoetin (MEND), Study Team Member

2017 - Present  
Milrinone in Congenital Diaphragmatic Hernia, Study Team Member

2017 - Present  
A randomized trial of targeted temperature management with whole body hypothermia for moderate and severe neonatal encephalopathy in premature infants 33-35 weeks gestational age- A Bayesian Study, Study Team Member

2017 - Present  
Rapid Sequencing in Acutely Ill Infants in the NICU, Principal Investigator
2014 - Present  Preterm Infants and Nephrocalcinosis: Diagnosis and Pathogenesis, Principal Investigator

TEACHING RESPONSIBILITIES/ASSIGNMENTS

Clinical Teaching
2017 - Present  Attending, Primary Children's Hospital, 4-6 weeks per year, 2-3 residents, 1-3 neonatal fellows, and neonatal nurse practitioner students
2017 - Present  Attending, Intermountain Medical Center, 4-6 weeks per year, 1 resident on procedural elective per year and neonatal nurse practitioner students
2017 - Present  Attending, University of Utah Hospital, 2-4 weeks per year, 2-3 residents, 1-2 neonatal fellows, and neonatal nurse practitioner students

Trainee Supervision
Fellow
2017 - 2019  Mentor, Methab Sekhon, University of Utah, Advised and supervised neonatal fellow on assessing bone status with tibial bone ultrasound as part of her enteral zinc study.

Medical Student
2019 - Present  Mentor, Danielle Bonser, University of Utah

Didactic Lectures
2020  Malone Jenkins S. Rapid Sequencing in the NICU, University of Utah School of Medicine, Foundations in Personalized Healthcare Course, Salt Lake City, UT
2019  Malone Jenkins S. rWGS in the NICU, University of Utah School of Medicine, Foundations in Personalized Healthcare Course, Salt Lake City, UT
2019  Malone Jenkins S. Clinical Approach to Metabolic Bone Disease. University of Utah College of Nursing, Doctor of Nursing Practice, Neonatal Program, Salt Lake City, UT

Internal Teaching Experience
2020  Utah NeoSeq, University Health Sciences Research Forum, University of Utah
2020  Hydrops fetalis: Diagnosis, Management, & Outcomes. Maternal Fetal Medicine Division, University of Utah
2017  Nephrocalcinosis in Preterm Infants, Pediatric Research in Progress, University of Utah School of Medicine
2016  Nephrocalcinosis in Preterm Infants, Pediatric Research in Progress, University of Utah School of Medicine
2016  Cloacal Malformations, Neonatal-Surgery Conference, University of Utah School of Medicine
2015  Fetal-Maternal Hemorrhage, Neonatology Morbidity and Mortality Conference, Primary Children’s Hospital
2015  Duodenal Atresia, Neonatal-Surgery Conference, University of Utah School of Medicine
Continuing Education

**PEER-REVIEWED JOURNAL ARTICLES**


**ADDITIONAL PUBLICATIONS**

**Letters**


**POSTER PRESENTATIONS**


2020 Malone Jenkins S, Palmquist R, Fishler K, Torr C, Brunelli L. Assessing provider interest is essential to developing genomic education activities. Center for Genomic Medicine Symposium, Salt Lake City, UT

2018 Malone Jenkins S, Gudgeon J, Rong M, Ostrander B, Flores J, Brunelli L. Rapid Targeted Gene Sequencing in the NICU Helps Focus Clinical Care and Decreases Costs. Pediatric Academic Society, Toronto, Canada


2016  **Malone Jenkins S, Grinsell M, Weaver Lewis K, Felix J, Chan G. Preterm Infants with Nephrocalcinosis Have Lower Bone Mineralization.** Pediatric Academic Societies Conference, Baltimore, MD

2015  **Malone Jenkins S, Chan G. Differences in pH and Potential Renal Solute Load Among Infant Enteral Feeds.** Pediatric Academic Societies Conference, San Diego, CA

2015  **Malone Jenkins S, Grinsell M, Rau C, Chan G. Neonatal Nephrocalcinosis in Preterm Infants.** Pediatric Academic Societies Conference, San Diego, CA

2012  Roberts H, Needelman H, Jackson B, McMorris C, **Malone Jenkins S. An Examination of the disparities in the long term follow up of neonatal intensive care unit graduates.** National Rural Health Association's Rural Multiracial and Multicultural Health Conference, Asheville, NC

2012  **Malone Jenkins S, Llamas C, Rathore G, Fernandez C. Floppy Baby: A Case of Congenital Hypotonia.** University of Nebraska Medical Center/Creighton University Medical Center/Children's Hospital & Medical Center Research Forum, Omaha, NE

**ORAL PRESENTATIONS**

**Meeting Presentations**

**National**


**Local/Regional**

2017  **Malone Jenkins S, Grinsell M, Weaver Lewis K, Felix J, Chan G. Elevated Serum Vitamin D levels associated with Nephrocalcinosis in Preterm Infants.** Western Society for Pediatric Research, Carmel, CA

2016  **Malone Jenkins S, Chan G, Grinsell M, Weaver Lewis K. Effects of Prematurity, Birth weight and Postnatal age on Preterm Infants’ Hypercalciuria.** Western Society for Pediatric Research, Carmel, CA

2016  **Malone Jenkins S, Chan G, Grinsell M, Weaver Lewis K. Lower Bone Mineralization in Preterm Infants with Nephrocalcinosis.** Western Society for Pediatric Research, Carmel, CA
2015  Malone Jenkins S, Chan G. pH and Potential Renal Solute Load Vary Among Infant Enteral Feeds. Western Society for Pediatric Research, Carmel, CA

Grand Rounds Presentations

2020  Hydrops Fetalis: Diagnosis, Management, & Outcomes. Neonatal Grand Rounds, University of Utah School of Medicine, Salt Lake City, UT

2019  rWGS in the NICU. Neonatal Grand Rounds, University of Utah School of Medicine, Salt Lake City, UT

2016  Iron Supplementation After Blood Transfusions. Neonatal Grand Rounds, University of Utah School of Medicine, Salt Lake City, UT

2015  Clinical Approach to Neonatal Metabolic Bone Disease. Neonatal Grand Rounds, University of Utah School of Medicine, Salt Lake City, UT

2014  Antenatal Hydronephrosis. Neonatal Grand Rounds, University of Utah School of Medicine, Salt Lake City, UT

2014  Caring for the NICU baby after the NICU. Pediatric Grand Rounds, University of Nebraska Medical Center/ Creighton University Medical Center/ Children’s Hospital & Medical Center, Omaha, NE

OTHER SCHOLARLY ACTIVITIES

Quality & Value Improvement Projects

2018 - Present  Team Member, Neurodevelopmentally Sensitive Intubations, University of Utah Hospital & Intermountain Medical Center
1. Career Plan
   a. Career Statement: I will become an expert in the clinical application of next generation sequencing (NGS) in the critical care setting. I plan to become a physician-scientist and principle investigator for translational studies evaluating the meaningful use of NGS in clinical neonatal-perinatal medicine.

   b. Career Goals and Objectives:
      Short term career goals:
      1. Collect and analyze retrospective cases of critically ill neonates with arthrogryposis, non-immune hydrops fetalis (NIHF), and skeletal dysplasia
      2. Evaluate the prospective use of NGS molecular diagnosis for critically ill neonates with arthrogryposis, NIHF, and skeletal dysplasia
      3. Determine the clinical utility and feasibility of neonatal NGS for these pathologies

      Long term career goals:
      1. Leverage this pilot data to compete for a Mentored Patient-Oriented Career Development Award (K23) through the NIH
      2. Become an expert in the clinical application of NGS in the critical care setting
      3. Become an independent investigator with the ability to meaningfully contribute to the field of NGS in the NICU through translational research evaluating the application of NGS in clinical care

   Training Aim 1: Understand the technology of NGS and its limitations. By understanding the scientific foundations of NGS and its limitations, I will gain the experience necessary to accomplish Specific Aim 2.
   Didactic: PED 575 Genomic Analysis I: I will get the hands-on training necessary to analyze NGS DNA data from start to finish through completion of this introduction to genomic technologies, NGS study design, biostatistics, genome biology, and Linux script writing. I complete an entire NGS analysis project on WGS data and learn to identify and assess risk variants, mutations, and copy number aberrations.
   Mentor: Dr. Gabor Marth, a collaborating investigator on this grant, will also provide expertise for analyzing the large datasets and provide additional training in data analysis.

   Training Aim 2: Implementing rWGS in the NICU. I will identify challenges and best practices in relation to workflow, consent, and results reporting allowing me to successfully accomplish Specific Aims 1 and 2.
   Didactic: MDCRC 6370 Ethical, Legal and Social Issues in Genomic Medicine: I will be immersed in cultural and ethical issues facing the use and practice of NGS in medicine. The course offers a mix of didactic content, case studies, and class discussion.
   Didactic: MDCRC 6150 Foundations in Personalized Health: I will discuss fundamental elements of personalized healthcare, consider case studies of preventive and therapeutic applications, anticipate future developments in NGS, and propose methods for advancing personalized healthcare locally, nationally, and globally.

   Training Aim 3: Improve my manuscript and grant writing skills. I am planning to submit four first author/co first author manuscripts over the next year. My mentors will work with me on these publications and freely give feedback and constructive criticism with the goal of improving my writing skills. I will participate in the University of Utah Grant Writing Workshop at Deer Valley Fall 2021 while preparing my NIH K award application. My attendance to this workshop will be supported by the Division of Neonatology. My Division will also support my attendance at the Best Practices for Competitive Grant Applications: NIH Funding for Research & Career Development Activities offered through Columbia Medicine.

   Training Aim 4: Improve my presentation skills and establish myself in the field of neonatal genomics. I plan to present my research findings annually at the Pediatric Academic Society (PAS) meetings, and will also attend the annual meeting of the American Society of Human Genetics (ASHG). I will also attend the weekly medical genetics meetings to further my clinical genetic knowledge and ability to recognize which patient phenotypes will benefit from genomic testing.

   Summary: My career development plan outlines a step-by-step path for career enhancement as a physician-scientist and builds on my prior experiences with clinical research and targeted gene panels for a more rigorous and in depth use of NGS to provide personalized, precision care for critically ill neonates born with complex genetic syndromes.
2. Scientific Mentoring Plan: I have the availability of the necessary resources, mentorship, and facilities to complete this and future projects. My mentors are experts in their fields and their complementary skills will provide me the support I require to become a successful independent investigator. My team has agreed to meet as a group four times a year to guarantee my career and research development is progressing.

Primary Research Mentor: Dr. Martin Tristani-Firouzi is an expert in the field of personalized medicine. His research focuses on the genomic determinants of susceptibility to cardiac arrhythmia disorders and congenital heart disease. He has successfully used NGS to guide clinical management, stratify risk, and improve clinical outcomes in patients with cardiac disease. The NGS techniques, including rapid whole genome sequencing (WGS), that he employs are directly applicable to critically ill neonates in the NICU. Dr. Tristani will provide the hands-on mentorship I require. He is my primary mentor on my PCHF Early Career Development award. The practical aspects of clinical study design and data analysis will be modeled during planned twice monthly meetings for 1 hour during the first year. Dr. Tristani will also provide ongoing insight into NGS research techniques and the mechanisms underlying the data analysis utilizing large dataset analytic strategies. Dr. Tristani will assist in manuscript preparation and data reporting as the project begins to yield results. We have had two abstracts accepted, one manuscript in preparation, and three additional manuscripts planned. I also look to him as a career mentor given his success in obtaining extramural research funding and I anticipate his guidance.

Co-Mentor: Dr. Josh Bonkowsky is a collaborating investigator on this project and Director of the Primary Children’s Center for Personalized Medicine Program. His expertise is clinical rWGS and academic professional development. I am currently working with Dr. Bonkowsky on rapid WGS at the University of Utah and Primary Children’s Hospital. Dr. Bonkowsky is a well-established researcher with NIH-funding. We will meet monthly to discuss progress, manuscript preparation, and plan future directions with intra- and extra-mural funding opportunities.

Co-Mentor: Dr. Gabor Marth is a collaborating investigator on this project and will assist Dr. Tristani in my mentorship. Dr. Marth is an expert in the field of human genetic analysis and bioinformatics, with over 100 peer-reviewed publications and significant extramural funding. He will provide additional expertise for analyzing the large datasets generated by NGS and will provide additional hands-on training in the data analysis after WGS. We will meet monthly during this project.

Co-Mentor: Dr. Christian Con Yost is a collaborating investigator and Professor in the Division of Neonatology. He conducts NIH-funded basic and translational research. He will assist in correlating clinical conditions with the genetic data provided by NGS. We will meet 2x/month to discuss progress, work on manuscript preparation, and plan future directions with intra- and extra-mural funding opportunities.

Professional Development Milestones: My mentorship team and I have developed a detailed timeline, research plan, and career course that I will achieve during the next two years (see above). The measurable outcomes of my VPCAT mentoring plan will be a successful submission of an NIH K23 application, submission of four manuscripts (Ethical and Laboratory Challenges for Initiation of a NICU rWGS Program, RapSeq verse rWGS, Change in management and cost effectiveness of rWGS, NGS in the NICU), and abstract submission at national meetings.

A. Specific Aims

Infants with the clinical phenotype of arthrogryposis, non-immune hydrops fetalis (NIHF), or skeletal dysplasia often experience a prolonged diagnostic odyssey during their NICU stay. Each of these three complex neonatal conditions is identifiable prenatally, and each arises from a myriad of molecular etiologies leading to a similar phenotype. Identification of the molecular etiology allows clinical care teams to deliver precision medicine in an expeditious manner to improve outcomes. Next generation sequencing (NGS) is under-utilized in critically ill newborns affected by these types of morbid and sometimes lethal congenital syndromes. Over the past 3 years, we implemented a rapid targeted diagnostic gene panel of 4,503 established disease-causing genes (RapSeq) in the NICU and showed a reduction in the number of invasive procedures, diagnostic clinical testing, and lengths of stay among all tested critically ill neonates 1. However, RapSeq only queries a portion of the coding sequence, thus interrogating only a small fraction of the entire genome. Consequently, we discovered causative genetic variants in only about 50% of all patients tested with RapSeq. The other 50% of potential causative variants may lie outside the coding regions, or be a result of a complex genomic structural variant. Our goal is to widen the scope of discovery to include the patient’s entire genome.

This proposal tests the overall hypothesis that rapid whole-genome sequencing (WGS) will increase the diagnostic yield in select NICU patients suffering from arthrogryposis, NIHF, or skeletal dysplasia. Our goal is to reduce the diagnostic odyssey of these patients and facilitate more targeted medical tests and therapies. For this project, we will use both retrospective and prospective cohorts to accomplish the following aims:

**Specific Aim 1: Define the clinical course and healthcare utilization of retrospective cases of arthrogryposis, NIHF, or skeletal dysplasia, with or without an existing molecular genetic diagnosis.** We will establish a database of all previous cases of arthrogryposis, NIHF, or skeletal dysplasia from 2008-2018 at the University of Utah and across the Intermountain Healthcare system to compare the clinical trajectories and healthcare utilization of these patients. We identified 235 retrospective patients for this Aim that will also serve as our historical control group in Aim 2.

**Specific Aim 2: Conduct a pilot study evaluating rapid WGS as a diagnostic tool in the NICU.** This pilot study of approximately 30 patients will determine the feasibility and utility of rapid WGS for molecular diagnosis of prospective cases of prenatally diagnosed arthrogryposis, NIHF, or skeletal dysplasia. Recruitment will begin in the prenatal period, with a DNA sample obtained from the affected child (proband) at the time of delivery (cord blood). WGS will be used for the proband-parent trio and analyzed using a rapid analysis approach. A panel of Utah genomic experts will adjudicate the pathogenicity of identified genetic variants in the context of the clinical phenotype. Rates of prenatal identification of cases and successful recruitment, turn-around time of testing, sequencing and analysis, and successful genetic diagnoses will be measured to define feasibility aspects of the pilot study. We will determine the utility of rapid WGS by comparing the diagnostic yield and effect on clinical management against the historical control cohort (Aim 1).

Results of this pilot study will determine the ability of rapid WGS to increase the diagnostic yield in critically ill patients in the NICU. My proposal addresses a significant deficit in current approaches to rapidly diagnose and treat critically ill newborns with complex clinical phenotypes. This proposal is innovative because it applies rapid WGS to these three clinical phenotypes with multiple etiologies and outcomes. My primary mentor, Dr. Martin Tristani-Firouzi, an expert in the field of precision medicine, has trained multiple physician-scientists. Successful completion of this study will support an NIH (K23) grant to further define the application of rapid WGS in the NICU and its impact on patients and families. It will also establish me as a physician-scientist at the intersection of precision medicine and clinical care. The impact of this project will increase the diagnostic yield in select NICU patients, which has the potential to advance precision medicine, translating to improved outcomes for infants with arthrogryposis, NIHF, and skeletal dysplasia.
B. Significance & Rigor of Prior Research

The significance of our proposal lies in the rapid diagnosis of critically ill newborns with complex clinical phenotypes, allowing for more rapid treatment and more efficient utilization of medical resources. Specifically, arthrogryposis, non-immune hydrops fetalis (NIHF), and skeletal dysplasia are prenatally diagnosed neonatal conditions with high morbidity and mortality that often have a delayed diagnosis or lack a unifying molecular diagnosis. We hypothesize that the use of WGS will increase the diagnostic yield and decrease the time to diagnosis, with the goal of reducing the slow diagnostic odyssey that is the current standard of care.

Background and Rigor of Prior Research: Genetic disorders with pathologic mutations lead to significant morbidity and mortality in critically ill newborn infants. These genetic pathologies vary from larger scale chromosomal abnormalities and copy number variations (CNVs) to smaller scale insertion/deletions (indels) and single nucleotide variants (SNVs) including autosomal and X-linked mutations. Such genetic mutations represent the leading cause of neonatal mortality in the NICU. The rapid clinical progression of many gene disorders necessitates a path to quickly identify the underlying genetic mutations and facilitate early, personalized treatment plans. Previous studies show that NGS, including WGS, leads to earlier diagnosis and improved outcomes due to rapid, more precise intervention in neonates. Furthermore, the steady decrease in the overall cost of using NGS methods has prompted its integration into numerous fields of medicine including neonatology.

Decisions regarding the clinical care of critically ill neonates can be difficult to make. WGS provides the comprehensive, detailed, and affordable genetic information required for personalized, precision medicine. Currently, this cutting-edge technology is a hot topic in the care of critically ill newborns affected by a variety of morbid and sometimes lethal congenital syndromes. A recent study using rapid WGS demonstrated its ability to rapidly diagnose pathogenic genetic conditions, decrease the morbidity and mortality of critically ill infants, facilitate end-of-life care decisions, and decrease costs of care in the NICU. This proposal focuses on three life-threatening pathologies affecting neonates. These pathologies are arthrogryposis, NIHF, and skeletal dysplasia. Each syndrome has a high morbidity and mortality in the perinatal period, with the genetic etiology commonly unidentified despite a long and slow diagnostic odyssey using older and inferior biochemical-based techniques.

Arthrogryposis multiplex congenita (AMC) consists of numerous conditions, which are characterized by multiple congenital contractures, many of which arise from genetic mutations. Collective studies have identified over 300 genes associated with AMC phenotypes; however, only half of AMC diagnosed patients test positive for at least one of these associated genes. This suggests at least some cases are due to yet unidentified mutations. Currently, 38 centers worldwide offer some form of genetic testing for AMC often limited to only sequencing of the TPM2 gene or MYBPC1 gene. Other centers using NGS methodologies are limited to WES panels averaging around 100 genes and include many other arthrogryposis-like syndromes. No current test utilizes WGS to identify new or known mutations for AMC.

NIHF represents cases of severe, global edema of the fetus and neonate and can be sub-categorized into three main groups: congenital anemias, congenital metabolic disorders, and idiopathic hydrops fetalis. Most genetic testing for conditions associated with NIHF include single gene sequencing, small gene panels, or are microarray based. One center is currently offering an 87 gene WES panel for NIHF. No current test utilizes WGS to identify new or known mutations for NIHF.

Skeletal dysplasias are heritable diseases with generalized abnormalities in cartilage and bone. The estimated incidence of disorders of skeletal development manifesting in the neonatal period is 15.7 per 100,000 births. Long-term prognosis ranges from inevitable death shortly after birth to survival into adulthood with normal intellectual development. In the neonatal period, respiratory compromise is the leading cause of morbidity and mortality. Many of the genetic disorders of skeletal development lead to significant morbidity and mortality in utero or in the early neonatal period. Due to the large number and heterogeneous nature of these disorders, their diagnosis and management can be overwhelming. Understanding the genetic alterations that produce these disorders will allow us to delineate the spectrum of disease associated with a particular disorder, provide diagnostic service for families at risk for recurrence based on mode of inheritance, and further our
understanding of pathways involved in the development and maintenance of the skeleton. Multiple centers are offering NGS panels of up to 111 genes and one center offers a prenatal panel (ARUP Skeletal Dysplasia Panel) (CTGT Skeletal dysplasia core & extended NGS panel) (Blueprint Genetics Skeletal Dysplasias Core Panel) (Gene Dx Prenatal Skeletal Dysplasia Panel). No current test utilizes WGS to identify new or known mutations for skeletal dysplasia.

This proposal, thus, fills an important gap in the diagnosis of arthrogryposis, NIHF, and skeletal dysplasia in the NICU. Rapid WGS may allow for an improved and more timely diagnostic yield, and the ability to focus targeted therapies and interventions, thereby improving the efficiency of medical care for vulnerable infants with these complex disorders.

C. Prior Research Efforts:
To date, I have participated in a variety of research studies, all of which fueled my passion and commitment to investigating the application of next generation sequencing (NGS) in the neonatal intensive care unit (NICU). In 2015, I participated in the development, initiation, and implementation of a rapid turn-around, targeted gene panel (RapSeq) for care of critically ill infants in the NICU. We showed reduction in the number of invasive procedures, diagnostic clinical testing, and decreased lengths of stay. In 2018, under the mentorship of Luca Brunelli, we published a letter discussing our clinical inclusion criteria and initial cases using RapSeq in the American Journal of Medical Genetics. Our second manuscript evaluating clinical utility and cost effectiveness of our first 20 cases using RapSeq in the NICU was published in Molecular Genetics & Genomic Medicine, for which I served as co-first author. We found causative genetic variants in at least 50% of the cases. This allowed us to inform parents in a timely manner of a unifying diagnosis for their acutely ill infants and to provide personalized, precision care to these patients. After testing 19 trios and one patient-parent pair, we showed that this precision medicine approach in NICU limits the number of invasive procedures and diagnostic tests performed on these patients. The results from RapSeq provided information regarding prognosis, disease management, and recurrence risks. The rapid turn-around time (average preliminary result 9.6 days) impacted the ongoing management of patients in the NICU. Further analysis of our RapSeq cohort identified seven cases of NIHF. Of these seven cases, only four cases (57%) had a genetic diagnosis identified by the targeted gene panel.

I have learned first-hand of the challenges involved in addressing testing issues and ethical concerns associated with NGS studies. I now serve as the NICU Physician Lead for the Primary Children’s Center for Personalized Medicine Program. Through this program, and under the leadership of Josh Bonkowski and Martin Tristani, we have started doing rapid whole genome sequencing (rWGS) on critically ill infants in the PCH NICU, CICU, and PICU. I also serve as the principle investigator for the Utah NeoSeq Project, where in collaboration with ARUP and the Utah Center for Genetic Discovery, we do rapid WGS on acutely ill infants in the UU NICU. The Utah NeoSeq Project is funded by the Utah Center for Genomic Medicine and the Margolis Foundation. The project presented in this application is funded by the PCHF Early Career Development Grant. I also have funding through the Primary Children’s Center for Personalized Medicine for a project titled Optimizing Identification of Fetal-Derived Monogenic Variants in Circulating Cell-Free DNA by Next-Generation Sequencing.

D. Future Research Plan:
My clinical and research experience has prepared me to study the application of NGS in the NICU. The impact of this project will increase the diagnostic yield in select NICU patients, which has the potential to advance precision medicine, translating to improved outcomes for infants with arthrogryposis, NIHF, and skeletal dysplasia. The data generated from this pilot study in combination with the mentorship and training provided by the VPCAT program will enable me to apply for an NIH K23 grant. This will allow me to further define the application of NGS in the NICU and its impact on patients and families. In summary, I have a track record of early career research success and a proven and excellent mentorship milieu in support of several projects that I’m currently working on. I have been privileged to secure multiple local grants to obtain pilot data to use for applications for extramural funding. I am excited to use the additional mentorship resources of the VPCAT program to become an independent and funded researcher in the application of NGS in clinical care.
References

Plan for Transition into an Independent Investigator

My leadership team and I have developed a detailed career plan that ensures resources, mentorship, and facilities to complete this project and facilitate my transition into an independent investigator. Our division prioritizes research and currently I have 65% protected research time. Currently, I do not hold any divisional administrative responsibilities further protecting my research time. My educational time is included with my clinical service time. Currently, I do 13 weeks of clinical service and 40 night-calls per year. With acceptance into the VPCAT Research Scholars Program, my clinical service time will be reduced to 10 weeks and 30 night-calls per year starting July 2021. I will have 75% protected research time for an NIH K23 award. This time commitment should be adequate to achieve research independence.

The division also contributes financially to my research endeavors. I was awarded the Gary M. Chan Endowed Chair of Pediatrics which provides additional funding to my research efforts and further demonstrates my department’s confidence in my research career. The division also supports registration and transportation to academic conferences throughout the year. I also have access to a research nurse to aid in my neonatal genomic projects.

I thoroughly enjoy my job as a neonatologist and my clinical practice overlaps nicely with my investigative goals. I have been able to apply my investigative knowledge to my clinical care practice by integrating next generation sequencing to provide a genetic diagnosis in critically ill infants and personalizing their care. I will balance the rigor and time requirements needed to be a good clinician and an independent investigator as I advance in my career.

Sabrina Malone Jenkins, MD

Bradley Yoder, MD
Chair of the Division of Neonatology
September 10, 2020

RE: Letter of support for Sabrina Malone Jenkins, MD
VPCAT Research Scholars Program Application

Dear Members of the Review Committee:

It is a great pleasure to write this letter of support on behalf of Dr. Sabrina Malone Jenkins’ Vice President’s Clinical and Translational (VPCAT) Research Scholars application to deploy rapid whole-genome sequencing (WGS) to increase the diagnostic yield of critically ill neonates with select disorders. Her goals of reducing the diagnostic odyssey suffered by these families while facilitating more targeted evaluation and therapies align perfectly with my personal research interests and expertise. I am excited and enthusiastic to continue to serve as the primary research mentor for Sabrina’s research and career.

In my role as VPCAT mentor for 2 junior faculty (Dr. Omar Wever-Pinzon, Internal Medicine/Cardiology and Dr. Jason Glotzbach, Cardiothoracic Surgery), I understand and I am willing to commit to the required responsibilities, as outlined in the Scientific Mentor Requirements and Expectations. I can ensure Dr. Malone Jenkins’ commitment to devote 30% FTE to the development of her career and research program. While she currently has 65% protected research time, she has the support her Division Chair to increase to 70% upon acceptance to the VPCAT program. I am dedicated to help Sabrina achieve her research objectives within the context of this study and crucially, to help guide her longer term with her career development decisions and goals. I will assist in this endeavor by meeting with her on a twice monthly basis to discuss progress, obstacles, pitfalls, and future directions and to provide insight, guidance and support as she embarks on her research journey. Specifically, I will help Sabrina integrate into the world of genomic medicine by bringing her in contact with my research infrastructure and colleagues in the field of precision genomic medicine. I will help her navigate issues related to time management and resources and importantly, help her to build her research team.

My role as mentor and collaborator for Dr. Malone Jenkins will include advice on building teams of collaborative investigators in the disciplines of precision medicine, genomic bioinformatics, and human genetics. As we all recognize, team-based science is clearly the future of translational science, as the days of the exclusive investigator-initiated R01 funding are waning. It is crucial that junior clinician-scientists, such as Dr. Malone Jenkins, receive the appropriate training and mentorship in these new mechanisms of team-based science. My experience as PI for 3 major research consortia (Bridging the Gap between Genomics and Clinical Outcomes in Congenital Heart Disease, UM1HL128711;
Integrating Genomic and Clinical Approaches to Sudden Death in the Young, U01HL131698; and Leveraging Big Data Science to Link Genomics, Epigenetics and the Family to Improve the Health of Children with CHD, SFRN33630041) will be invaluable to Dr. Malone Jenkins as she embarks on her path toward a successful career as a future leader of neonatal genomic medicine in this new era of team-based science.

As a Medical Center, we are not yet prepared for a future that is crashing down upon us; that is, the impending advance of precision medicine. Rapid NICU WGS, upon which Dr. Malone Jenkins’ proposal is based, is poised to become the standard of care within the next few years and yet, most hospitals/medical institution are ill equipped for this reality, as they lack dedicated clinicians with crucial expertise in this domain. Together with my colleagues, Drs. Mark Yandell, Gabor Marth and Joe Yost, we have built a sustainable program in Cardiovascular Precision Medicine, securing upwards of $25 million in research funding. Crucial to our endeavors to translate this research program into point-of-care precision medicine, is the availability of motivated, genomically-savy clinicians. Dr. Malone Jenkins fits this mold perfectly and is ideally suited to usher in precision medicine principles at the point of care. As a Fellow in Neonatology, she was perceived by most faculty as the point person for NICU genomics, given her role in promoting the application of rapid gene panel sequencing in the NICU. She is now the champion of rapid WGS in the NICU and has been at the forefront of the rapid NICU sequencing programs at Primary Children’s Hospital and University of Utah NICUs. She is well recognized and supported for her research/clinical efforts in the Division of Neonatology and her receipt of an Endowed Chair is one such example. Along these lines, the VPCAT proposal is perfectly in sync with Dr. Malone Jenkins’ clinical, research and career goals. And I am whole-heartedly committed to assuring that her goals are indeed realized.

Over the past several years, mentoring undergraduates, post-doctoral fellows and junior faculty has become an important component of my research endeavors. A primary motivation is the paucity of residents/fellows who have an interest in the clinician-scientist model. Two of my funded research programs include infrastructure for fellow education and incorporation into the research aims. Together with Dr. Andy Weyrich, I submitted an NHBLI T35 Medical Student Mentor program proposal that recently received a perfect score of 1.0 and is awaiting Council Mentor review. Below is a list of post-doctoral trainees and junior faculty that I previously and currently mentor.

I have an established mentorship relationship with Dr. Malone Jenkins, serving as her mentor for her PCHF Early Career Development Grant and all of her current sequencing studies. Based on her initiatives, we have four manuscripts in progress that I anticipate will be published during the two-year program. Dr. Malone Jenkins and I have extensively discussed her career plan, scientific mentoring plan, and research plan. Sabrina and I will meet 2x/month for at least one hour to discuss her progress on this project and assess her career advancement. She will update our shared outline of topics discussed and action items. We have outlined a schedule for manuscript preparation, additional educational classes/workshops, and an application timeline for her K23. Myself, and Sabrina’s other mentors, Joshua Bonkowsky, Gabor Marth, and Con Yost have agreed to meet quarterly to discuss Sabrina’s evolution and advancement as a strong
independent investigator. Her co-mentors are my research and clinical colleagues, and we have great working relationships built upon years of working together.

I am confident that Dr. Malone Jenkins will be successful with the proposed research plan for this award and will establish herself as a leader in the field of NICU genomic medicine. She is poised to offer meaningful contributions to the field of neonatology and I expect her to thrive as a productive academic clinician throughout her career.

With best regards,

Professor of Pediatrics, Pediatric Cardiology
Edward B. Clark Endowed Chair in Pediatrics
Deputy Director, Nora Eccles Harrison CVRTI
University of Utah School of Medicine
Martin.Tristani@utah.edu
September 21, 2020

Michael A. Rubin, MD, PhD, MS  
Director, VPCAT Program  
University of Utah Health, SVPHS Education Office  
EHSEB 5515

RE: Sabrina Malone Jenkins, MD; Letter of Support;  
Vice President’s Clinical and Translational (VPCAT) Research Scholars Program

Dear Committee

It is with great pleasure that I write this letter of support as a co-mentor for Dr. Sabrina Malone Jenkins (“Sabrina”) for the VPCAT Research Scholars Program. Sabrina completed her neonatal-perinatal fellowship in 2017 and joined the faculty at the University of Utah the same year. She is a dedicated neonatologist with a passion for research. Sabrina’s investigative focus is the application of genomics and personalized medicine to impact the care of infants in the neonatal intensive care unit (NICU). Her contributions to this area began as a fellow when she was involved with the development and implementation of a rapid turn-around target gene panel called RapSeq. Dr. Jenkins is co-first author on the manuscript describing this study. Involvement in the RapSeq study sparked a passion in Dr. Jenkins. This led her to her current study “Next Generation Sequencing in the NICU: Improving Healthcare Through Precision Medicine”. Dr. Jenkins is evaluating whether rapid whole-genome sequencing (WGS) will increase the diagnostic yield in select NICU patients suffering from arthrogryposis, non-immune hydrops fetalis, or skeletal dysplasia.

I have had the opportunity to work with Sabrina in the PCH Center for Pediatric Personalized Medicine doing clinical and research rapid whole genome sequencing. We have submitted two abstracts together, an article in preparation, and an additional three planned manuscripts over the next 6 months. As her co-mentor I can provide the expertise in rapid whole genome sequencing and academic professional development. I have read, understand, and can meet the required responsibilities outlined in the Scientific Mentor Requirements and Expectations. I will meet with Sabrina monthly and with the mentoring team 4x/year to make sure she has the necessary time, resources, and mentorship to become an independent investigator. We have developed a timeline of education, publications, and presentations for her to accomplish in the next two years. I will help guide her in preparation of an NIH K23 application.
As an academic physician-scientist, I have an appreciation of the challenges in this career path, as well as productive manners to tackle these challenges. I currently run a bench lab as well as oversee clinical and translational research efforts, and have over 96 peer-reviewed publications. I have a long record of extramural funding: I have been continuously funded by NIH since 2006, and currently am PI on an R21/R33 grant, as well as serving as a co-investigator on several other NIH grants. I serve as the Director of the Primary Children’s Center for Personalized Medicine, where I am ideally situated to work closely with Sabrina on her projects. I have worked with over 65 mentees, more than half of whom are woman. My mentees have gone on to independent faculty positions; or, as faculty, have obtained their own R01-level NIH funding. My mentees have ranged from high school students to faculty, and they have published and presented on the work we have done together; or the work that I assisted with as their coach and mentor.

In summary, Dr. Malone Jenkins has the potential to be a successful independent investigator in the field of neonatal genomic medicine. Her career trajectory is on a rapid upwards slope, and her scientific and clinical work interfaces in an ideal fashion. I am enthusiastic to mentor her as she advances in her career and hope you seriously consider her application to your program. Please do not hesitate to contact me if more information would be helpful.

Please feel free to contact me if I can provide any further information.

Sincerely yours,

Josh Bonkowsky, MD, PhD
Professor
Chief, Division of Pediatric Neurology
Bray Presidential Chair
Department of Pediatrics
University of Utah School of Medicine
email: joshua.bonkowsky@hsc.utah.edu
September 21, 2020

RE: Letter of support for Dr. Sabrina Malone Jenkins

Dear Members of the VPCAT Program Selection Committee:

I am writing this letter is to express my enthusiastic support for Dr. Sabrina Malone Jenkins’ application to the Vice President’s Clinical and Translational (VPCAT) Research Scholars Program. Furthermore, I am pleased to serve as a co-mentor on Sabrina’s career proposal. I have already witnessed Sabrina’s commitment and dedication to her research as a co-investigator on her PCHF Early Career Development Grant entitled “Next Generation Genetic Sequencing in the NICU: Improving Healthcare Through Precision Medicine.” This project represents the natural progression of her scientific interests, first developed during her neonatal fellowship. As a fellow, she was involved with next generation genetic sequencing and the application of this technology to the critically ill neonatal population. She was involved with the development and implementation of a rapid turn-around targeted gene panel called RapSeq. This clinical test has proven to be invaluable in the Neonatal Intensive Care Units. A letter discussing the clinical inclusion criteria and initial cases was published in the American Journal of Medical Genetics in 2018. She also presented the first 20 cases as a poster presentation at Pediatric Academic Societies national meeting in the Spring of 2018. Her manuscript is published in Molecular Genetics & Genomic Medicine.

Her passion for neonatal genetic research has begun as she takes her first steps towards a research career aimed at optimizing NGS studies for the NICU population. She is committed to her career goal of becoming an independent physician-scientist. Sabrina has selected an extremely well-qualified mentor, Dr. Martin Tristani-Firouzi, to guide her career development and this proposal. Dr. Tristani-Firouzi and I are co-Principal Investigators, and work closely together on an R01 project aimed at developing new web tools to allow subspecialty clinicians to carry out diagnostic analysis of their patients’ genomic data fully independently, and without bioinformatician support. My role as Sabrina’s co-mentor will be to provide her with the expertise of analyzing DNA sequences in a similar manner. We will meet monthly to discuss obstacles she is encountering and strategically plan to prevent other issues in the analysis process. I look forward to meeting quarterly with her entire mentoring team to assess her overall progress. I have read, understand, and can enthusiastically meet the required responsibilities outlined in the Scientific Mentor Requirements and Expectations.

Over the past 15 years, my group has developed software to aid genome sequence assembly, single-nucleotide polymorphism discovery, and population genetic analysis of genomic variation data. More recently, my laboratory has been playing an increasing role in developing tools for precision genomics, both in the context of inherited disease and cancer. Research in my laboratory has led to well over 100 publications with over 70,000 total citations. Our work is currently supported by three R01s, two U01s, and a U24 award, on which I serve as Principal Investigator; as well as a number of foundation and academic/small business grants. I have mentored 15 graduate students, and over 20 postdocs, and have served as a mentor for numerous junior faculty members.

Sabrina is a strong junior faculty member with a promising career ahead of her. Successful completion of the aims set forth in this proposal will put her in a solid position to competitively apply for an NIH K23 in the next two years. I will be delighted to help her work in any way I can. I urge you to consider Sabrina’s application. Please do not hesitate to contact me for further information.

Sincerely,
Gabor Marth, D.Sc.
Professor of Human Genetics
Director, USTAR Center for Genetic Discovery
Eccles Institute of Human Genetics
University of Utah School of Medicine
15 North 2030 East, Room 7410B
Salt Lake City, UT 84112-5330
Phone: (801) 581-6158
Email: gmarth@genetics.utah.edu
September 22nd, 2020

Re: VPCAT Research Scholars Program Application for Sabrina Malone Jenkins, MD

Dear Members of the Review Committee:

I greatly appreciate the opportunity to recommend Dr. Sabrina Malone Jenkins to you as an applicant for the VPCAT Research Scholars Program. I look forward to serving as a Co-mentor for her during her participation in this Program. I currently serve as a tenured Professor of Pediatrics in the Division of Neonatology where I care for critically ill newborns and conduct NIH-funded basic and translational research. I am the recipient of extramural funding from the National Institutes of Health. My research focus includes exploration of the regulatory mechanisms governing the acute inflammatory response in syndromes of dysregulated inflammation in patients of all ages, with a particular interest in the role of neutrophil extracellular trap (NET) formation in health and disease.

As a Co-mentor, I am deeply committed to helping Sabrina achieve the objectives of this ambitious application. I have read, understand, and can meet the required responsibilities outlined in the Scientific Mentor Requirements and Expectations. I know Sabrina very well as her Program Director during her fellowship training in Neonatal-Perinatal Medicine at the University of Utah. Sabrina’s research experience began early in residency with two abstracts accepted for presentation and one co-authored manuscript published during that time. Her passion for neonatal research intensified during her fellowship. She now serves as an Assistant Professor of Pediatrics in the Division of Pediatrics here at the University of Utah. She clearly exhibits all of the determination, curiosity, and critical thinking necessary to succeed as an academic neonatologist conducting clinical and translational research. As a fellow, she has been recognized as a Western Section AFMR Scholar and has received an award for her clinical research from the AAP District VIII Section on Neonatal-Perinatal Medicine. In 2018, Sabrina published a letter in the American Journal of Medical Genetics discussing the clinical inclusion criteria and initial cases using a rapid gene sequencing panel (RapSeq) in the NICU. She presented the results at the national Pediatric Academic Societies meeting in 2018. Her second manuscript evaluating clinical utility and cost effectiveness of the first 20 cases using RapSeq in the NICU was published in Molecular Genetics & Genomic Medicine, in which she was a co-first author. Her results demonstrate that NGS represents the next step towards providing personalized, precision medicine to critically ill neonates. She has proved to be productive with several abstracts accepted regionally and nationally. I feel this is indicative of her passion and commitment to research in neonatology.

Sabrina’s proposal entitled “Next Generation Genetic Sequencing in the NICU: Improving Healthcare Through Precision Medicine” aims to improve our clinical ability to diagnose genetic causes for arthrogryposis, non-immune hydrops fetalis, and skeletal dysplasia using next-generation sequencing. These three common prenatal diagnoses are associated with significant morbidity and mortality after birth and can lead to long diagnostic odysseys that often fail to yield a unifying molecular diagnosis. Sabrina’s recent work detailing the clinical use of a ≈ 4500 gene rapid sequencing panel in the NICU has uniquely prepared her to take this next step with whole
genome sequencing to aid in the rapid and precise diagnosis of critically ill NICU patients with these challenging clinical syndromes. Furthermore, in the past year, she has also led the Neonatology group at PCH and the University of Utah to implement next-generation sequencing in the NICU.

The proposed studies will contribute significantly to advancements in the fields of neonatal medicine and precision medicine for these critically ill infants and, most importantly, potentially lay the foundation for prenatal genetic testing in these three patient populations. As a research mentor in the Division of Neonatology, I commit to assisting Sabrina by meeting every two weeks to discuss progress, help plan future directions, and correlate clinical conditions with the genetic data provided by next-generation sequencing. I will further assist in manuscript preparation while actively fostering her career as a physician-scientist by assisting with future intra- and extra-mural funding opportunities. As a mentoring team, Martin Tristani-Firouzi, Josh Bonkowsky, Gabor Marth, and myself will meet as necessary but at least four times a year to assess overall progress.

Sabrina has the support of our Division of Neonatology to devote at a minimum 30% FTE to the development of her career, research, and this Program. With acceptance to the VPCAT Program, her protected research time will increase to 65% FTE.

In summary, I relish the opportunity to collaborate with Dr. Malone Jenkins. As a neonatologist practicing in the tertiary care NICU at Primary Children’s Hospital, I care for neonates with these three disorders frequently, and, as such, can guide Sabrina in clinical aspects of this much needed research. As an experienced and established investigator, I can offer guidance for Sabrina’s scientific career and provide specific mentoring for this project. I am confident that Dr. Malone Jenkins will be successful in her research objectives. Acceptance to this Program will serve to further support and motivate her to achieve her ambitious goals in academic neonatology.

Sincerely,

Christian Con Yost, MD
Professor, Pediatrics/Neonatology
Program Director, Neonatal-Perinatal Medicine Fellowship Training Program
Program Director, Neonatal ECMO Therapy Program
295 Chipeta Way
Salt Lake City, UT 84108
Phone: 801.662.4180 / 801.581.7052
Email: christian.yost@u2m2.utah.edu

HEALTH
UNIVERSITY OF UTAH
September 20, 2020

VPCAT Program Committee
Office of Academic Affairs and Faculty Development
HSEB 5515, University of Utah

Re: Sabrina Malone-Jenkins, MD, VPCAT Research Scholars Program Application

Dear Members of the Review Committee:

We are delighted to provide a letter of support for Sabrina Malone-Jenkins, MD application for the VPCAT Research Scholars Program. Dr. Malone-Jenkins is an Assistant Professor in the Division of Neonatology. As her Division Chief (BAY), I have gotten to know Sabrina well over the course of her fellowship and early career as a physician scientist. During fellowship, Sabrina became involved with next generation genetic sequencing and the application of this technology to the critically ill neonatal population. She has been instrumental in the development and implementation of a rapid turn-around target gene panel called RapSeq. A letter discussing the clinical inclusion criteria and initial cases was published in the American Journal of Medical Genetics in 2018. The manuscript evaluating clinical utility and cost effectiveness of the first 20 cases using the rapid sequencing gene panel in the NICU was published in Molecular Genetics & Genomic Medicine in 2020. This has led to Sabrina’s on-going passion of providing personalized, precision medicine to critically ill neonates. She has been an active participant in the newly formed Pediatric Precision Medicine Program, a component of the Primary Children’s Center for Pediatric Personalized Medicine. She is the physician lead for the rapid Whole Genome Sequencing (rWGS) project. Because of her hard work and dedication, we have been able to do rWGS clinically at PCH. Dr. Malone-Jenkins is also the principal investigator for NeoSeq, a research rWGS study at the University of Utah NICU. She has proven successful in obtaining grant funding and is currently the principal investigator on four active grants.

Dr. Malone-Jenkins has the full support of the Division of Neonatology and the Department of Pediatrics to participate in this program. We prioritize her research and recently awarded her the Gary M. Chan Endowed Chair of Pediatrics to further support here research efforts. With a reduction in her clinical service weeks to 13 per year, Dr Malone-Jenkins currently has more than 60% protected research time. The minimal allowed clinical time for funded research faculty in the Division of Neonatology is 10 weeks. The Division also supports Sabrina’s availability to participate in professional development activities and associated costs.

If selected for the VPCAT program, the Division can ensure her attendance at the VPCAT orientation, the twice monthly curricular sessions, the three-day Leadership Seminar
Series, and all of her VPCAT mentor meetings. We also support her attendance at grant writing workshops and other planned career development activities.

To further protect Sabrina’s research time, she does not have any divisional administrative responsibilities. Specific educational activities are integrated into her clinical service time. Dr. Malone-Jenkins currently has a 20% reduction in FTE for her role as the physician lead in the Primary Children’s Center for Personalized Medicine. She does use her dedicated research time as part of her PCHF Early Career Development Grant.

As the Division Chief, I meet with Sabrina at least twice per year to ensure she has all of the equipment, personnel, finances, and resources she may need to be successful in her research. If selected, Dr. Malone-Jenkins clinical service time will be reduced to 10 clinical weeks per year. She will continue to provide in-house call and weekend duties at the level of all faculty in our Division. The remainder of her time will be allotted to participation in the VPCAT research program and her other research activities. We are anticipating hiring additional neonatology faculty for 2021, which will provide us the flexibility to further protect Dr. Malone-Jenkins’s time. We agree to protect her research time at this level (approximately 75%) when she obtains an NIH K Award. She will also have continuing protection from administrative responsibilities for at least the next 5 years. This is further described in the Transition to Independence Plan.

Dr. Malone-Jenkins has a passion for neonatal genomic research and exhibits all the determination, curiosity, and critical thinking necessary to succeed as an academic neonatologist conducting clinical and translational research as an independent investigator. This prestigious research program will serve to further support and motivate her to achieve her ambitious goals. Our Division and Department prioritizes research and are committed to her success and development. We are willing to address any issues that might prevent her the time or resources to accomplish her career goals.

Thank you for considering Sabrina’s application. We give her our strongest recommendation.

Sincerely yours,

August L. (Larry) Jhung MD
President and Chair
Professor of Pediatrics
Chief, Division of Neonatology

Angelo P. Giardino, MD, PhD
Wilma T Gibson Presidential Professor
Chair, Department of Pediatrics
University of Utah School of Medicine
Chief Medical Officer
Intermountain Primary Children’s Hospital
BIOGRAPHICAL SKETCH
Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Tristani-Firouzi, Martin

eRA COMMONS USER NAME: mtristanifirouzi

POSITION TITLE: Professor

EDUCATION/TRAINING

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<td>1983</td>
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<td>University of Minnesota, Minneapolis, MN</td>
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<tr>
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<td>Fellow</td>
<td>1992-1995</td>
<td>Pediatric Cardiology</td>
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A. Personal Statement
I am highly qualified to serve as a Mentor for Dr. Sabrina Malone Jenkins’ VPCAT application. I am a board-certified pediatric cardiologist and clinician-scientist with over 22 years of continuous federal and foundational extramural funding.

Over the past several years, I have served as an active mentor for the Cardiovascular T32 and Genomic Medicine T32 Training Programs at the University of Utah and have had the privilege of shepherding post-doctoral fellows and junior investigators into faculty and industry positions. More recently, I have expanded training components into my funded research in Precision Cardiovascular Medicine for post-doctoral fellows and junior faculty, with formalized and peer-reviewed training programs (Bridging the Gap between Genomics and Clinical Outcomes in Congenital Heart Disease [UM1HL128711] and Leveraging Big Data Science to Link Genomics, Epigenetics and the Family to Improve the Health of Children with CHD [SFRN33630041]). In addition, I am Co-PI for the University of Utah T35 Medical Student Summer Research Program that recently received a perfect score at peer review. My motivation for mentoring Dr. Malone Jenkins is my personal observation of the paucity of clinician-scientists in biomedical sciences, and pediatric medicine in particular. The VPCAT program will provide Dr. Malone Jenkins a structured and productive environment to further her training, expertise and knowledge in the field of genomic medicine. By building upon her current clinical and research expertise, the VPCAT award will uniquely position Dr. Malone Jenkins to lead the next round of innovation in genomic medicine.

My lab is dedicated to the study of Precision Cardiovascular Medicine using a multi-disciplinary approach coupled with cutting-edge research techniques. I focus on the genomic basis of inherited arrhythmia syndromes and congenital heart disease (CHD); the functional characterization of putative CHD and arrhythmia disease causing genetic variants; the mechanisms controlling heart development and cardiac excitability; and functional properties of voltage-sensitive cardiac proteins. My lab strives to build the infrastructure supporting personalized medicine by connecting disciplines that excel in genomic analysis, functional analyses, and health care information technology, while leveraging the unique local resources such as the Utah Population Database. Our goal is to understand the genomic determinants of disease susceptibility in order to improve clinical management, risk stratification and clinical outcomes.

I serve as Contact PI for the NHLBI Bench to Bassinet (B2B) Pediatric Cardiovascular Genomics Consortium (PCGC) project, Bridging the Gap between Genomics and Clinical Outcomes in Congenital Heart Disease (UM1HL128711), with the goal of defining the genomic basis for susceptibility to and outcomes in CHD. I am also Contact PI for the NHLBI Sudden Death in the Young (SDY) consortium project, Integrating Genomic and Clinical Approaches to Sudden Death in the Young (U01HL131698) that focuses on the molecular epidemiology of SDY, characterization of disease mechanisms and prevention of sudden cardiac death. I serve as Center Director for the AHA Children's Strategically Focused Research Network (SFRN33630041) Leveraging Big Data Science to Link Genomics, Epigenetics and the Family to Improve the Health of Children with CHD. I am Co-PI for an NIH Clinical Sequencing Evidence-Generating Research (CSER) Program grant, (Web Tools for Physician-Driven Diagnostic Interpretation of Genomic Patient Data, R01HG009712), with the goal of integrating genome sequencing into clinical care. These projects are built upon an integrated team of expert bioinformaticians, developmental biologists and translational and clinical researchers that is dedicated to
interpreting structural variants, coding variants and non-coding regulatory variants from personal genomes in the context of disease causation and heterogeneity in clinical outcomes.

My experience as a Principal Investigator for several prestigious consortia, leading multiple projects and NIH-funded Core Facilities, and translating basic science discoveries into clinical practice underscores my leadership capacity, productivity, and ability to interact in a collaborative fashion. I am committed to the mission of promoting team science, creating expert multi-disciplinary research and mentoring teams, and fostering a collaborative approach to multicenter research. In this context, I remain highly committed to mentoring the next generation of clinician scientists, including Dr. Malone Jenkins as an ideal candidate.

B. Positions and Honors

Positions and Employment
1995-1996 AHA Research Fellow, Pediatric Cardiology, University of Minnesota, Minneapolis, MN
1996-1998 Research Instructor, Pediatric Cardiology, University of Utah, Salt Lake City, UT
1998-2003 Assistant Professor, Pediatric Cardiology, University of Utah, Salt Lake City, UT
2004-2011 Associate Professor, Pediatric Cardiology, University of Utah, Salt Lake City, UT
2005- Investigator, Nora Eccles Harrison Cardiovascular Research Training Institute (CVRTI), University of Utah, Salt Lake City, UT
2011- Professor, Pediatric Cardiology, University of Utah, Salt Lake City, UT
2016- Associate Director, Nora Eccles Harrison CVRTI, University of Utah, Salt Lake City, UT

Professional Activities
2003- present University of Utah Human Subjects Institutional Review Board
2004-2010 AHA, Western Consortium Research Committee 2a
2006-2007 Co-Chair, AHA Western Consortium Research Committee 2a
2006-2010 Chair, AHA Western Consortium Research Committee 2a
2006-2011 Editorial Board, Heart Rhythm
2006-2014 Scientific Advisory Board, SADS Foundation
2006-2016 Scientific Advisory Board, Children’s Heart Network
2007-2011 AHA, Western States Affiliate Research Steering Committee
2011-2014 AHA Unified Peer Review Research Committee
2011-present Scientific Advisory Board, Intl Periodic Paralysis Foundation
2012-2014 Chair, AHA Unified Peer Review Electrophysiology Committee
2013-2014 Vice-Chair, University of Utah IRB
2015- present Director, Pediatric Cardiology Genotype-Phenotype Core
2017- present Member, Oversight Advisory Board, AHA Obesity Strategic Focused Research Network
2018- present Editorial Board, Heart Rhythm Case Reports

C. Contributions to Science
1. My lab contributed to the initial characterization of the genetic and molecular basis for arrhythmia susceptibility in various forms of LQTS. We defined the molecular mechanisms of ion channel dysfunction in LQT1, LQT2, LQT5, and LQT7. We were the first group to design an effective trial of gene-specific therapy for the treatment of LQTS. Some of these papers serve as landmark studies in the field of LQTS research.
2. My lab was instrumental in defining the fundamental biophysical properties of the HERG (KCNH2) potassium channel; properties that are crucial for maintaining normal electrical stability in the heart. We are one of a handful of labs in the world that is capable of measuring gating currents, the intramembrane charge displacement associated with re-arrangements of the voltage-sensing domain. We defined the molecular steps that couple movement of the voltage sensor to channel opening and inactivation in the HERG channel.

   
   
   

3. Building upon our experience in measuring gating currents in voltage-gated ion channels, we demonstrated that the cardiac M2R muscarinic receptor “senses” transmembrane voltage and undergoes distinct conformational changes in response to membrane depolarization and ligand binding. This novel feature of muscarinic receptors has important implications for physiological modulation of the cardiac action potential by vagal stimulation, as well as implications for the design of pharmacological agents that target the M2R.

   
   
   

4. My lab has played in integral role in promoting the zebrafish as model organism for study of human arrhythmia. We designed, tested, and validated a high throughput in vivo cardiac assay to distinguish benign from pathogenic variants associated with LQTS and Sick Sinus Syndrome. This cost-efficient assay is easily adaptable to characterization of other arrhythmia-associated genetic variants and thus will accelerate the translation and interpretation of genomic findings to the clinic.

   
   
   
5. My lab is actively focused on the application of functional genomics for novel cardiovascular gene discovery and disease mechanisms. We currently utilize the Utah Population Database to identify high-risk pedigrees amenable to Next Gen sequencing for disease discovery in inherited arrhythmias and congenital heart disease. We established a robust human iPSC-CM model system for the study of arrhythmia disorders. We were the first to characterize the electrophysiological and pharmacological properties of CMs using human peripheral blood mononuclear cell as a somatic cell source for IPSCs. Moreover, we designed a system for moderate-throughput characterization of the electrophysiological properties of patient- and disease-specific iPSC-CM.


Complete List of Published Work: https://www.ncbi.nlm.nih.gov/pubmed/?term=tristani-firouzi+m+or+tristani+and+bache

D. Research Support

Ongoing Research Support

R01HL153025-01 Tristani-Firouzi (PI) 07/01/2020-06/30/2024
A Novel Role for NFATC1 in Modulating Cardiac Excitability
The overall goal of this proposal is to explore the molecular and electrophysiological role of NFATC1 as a novel atrial fibrillation susceptibility gene and to define the previously unknown contribution of NFATC1 to atrial excitability, using patient-specific iPSC-CMs and zebrafish models.
Role: Principal Investigator

2 U01 HL128711-06 Tristani-Firouzi/Yandell/Yost (MPI) 07/01/2020-06/30/2025
Bridging the Gap between Genomics and Clinical Outcomes in Congenital Heart Disease
The overall goal of this project is to apply genomic discoveries toward prediction of clinical outcomes in congenital heart disease. We propose to leverage existing data infrastructure to obtain Electronic Health Records and other clinical variables at scale and deploy a platform of AI-based predictors for CHD outcomes research, with the goal of translating genomic discoveries into improved management and therapeutic strategies for CHD.
Role: Contact Principal Investigator

1 U01 HL153007-01 Tristani-Firouzi/Marth/Yost (MPI) 07/01/2020-06/30/2025
Cardiovascular Development Data Resource Center
The goal of this project is to provide an innovative cloud-based platform to facilitate the analysis, visualization and sharing of genomic data from research in heart development across several species. Our project will bring together researchers with a diverse range of expertise, with the goal of understanding the causes of congenital heart disease in children.

R01HG009712 Tristani-Firouzi/Marth (MPI) 07/01/2017-06/30/2021
NIH / NHGRI
Web Tools for Physician-Driven Diagnostic Interpretation of Genomic Patient Data
The aim of this proposal is to design web-based tools for identification of disease-causing variants in exomes/genomes for use by physicians at the point of care to advance the goals of Precision Medicine.

Role: Principal Investigator

17SFRN33630041  Tristani-Firouzi (PI)  07/01/2017-06/30/2021
American Heart Association
Leveraging Big Data Science to Link Genomics, Epigenetics and the Family to Improve the Health of Children with CHD

Our program focuses on engaging the family to improve the quality of care and outcomes for children with CHD by understanding the root causes of CHD and by delivering family-centered health care. First, we apply novel data-science algorithms to assemble cohorts enriched for a genetic or environmental cause for CHD. Second, we test the novel hypothesis that abnormal placenta function plays a crucial role in the development of CHD. And finally, we move from “big data” to the bedside, by using the data-science algorithms to transform how medical decisions are made by the family.

Role: Center Director

U01HL131698  Tristani-Firouzi/Yandell (MPI)  04/01/2016-03/31/2021
NIH / NHLBI
Integrating Genomic and Clinical Approaches to Sudden Death in the Young

The goal of the Utah Center is to use innovative concepts and collaborative methodologies to define the genomic basis for autopsy-negative SDY; functionally characterize candidate disease-causing variants; and facilitate evaluation of relatives of SDY victims.

Role: Contact Principal Investigator

Nora Eccles Treadwell Foundation Grant  Tristani-Firouzi (PI)  07/01/2018-06/30/2022
Improving Induced Pluripotent Stem Cell-Derived Cardiomyocyte Models for the study of Arrhythmia Disorders

The overall goal of this proposal is to overcome the maturational hurdles in order to design a valid iPSC-CM model system for the study human arrhythmia disorders.

Role: Principal Investigator

Pending Research Support

T35HL007744  Tristani-Firouzi/Weyrich (MPI)  04/01/2021- 03/31/2026
NIH / NHGRI
Short-term Training: Students in Health Professional Schools

The main focus of this proposal is to introduce medical students to basic and clinical research, with the goal of encouraging and facilitating their futures in academic medicine.

Role: Principal Investigator

1 U24 HG000000  Marth/Tristani (MPI)  04/01/2021-03/31/2026
NIH / NHGRI
A diagnostic analysis system to enable community-wide adoption of longitudinal genomic medicine

We propose to develop a cloud-based diagnostic analysis system to enable real-world practitioners to deliver genomic medicine even in the most challenging and resource-limited settings e.g. supporting rapid genomics-based decision-making in a NICU, or outside of a well-resourced academic research center. This system will serve as a community resource to accelerate nationwide adoption of genome-based precision medicine.

Role: Principal Investigator

1 U01 HG000000  Quinlan/Hobbs/Brunelli/Botto/Martha/Murtaugh/Yandell/Tristani (MPI)  12/2020-11/2025
NIH / NHGRI
Utah Center for Mendelian Genomics

The primary objective of our proposal is to establish the Utah Center for Mendelian Genomics with the goal of increasing the proportion of genetically solved Mendelian conditions by (1) identifying novel cohorts enriched for Mendelian conditions and (2) developing and applying novel approaches to genomic discovery.

Role: Principal Investigator
NAME: Bonkowsky, Joshua Leitch

eRA COMMONS USER NAME: JOSHUABONKOWSKY

POSITION TITLE: Professor

EDUCATION/TRAINING: (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<td>BA</td>
<td>1991</td>
<td>Biochemistry</td>
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<td>University of California, San Diego, La Jolla, CA</td>
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<tr>
<td>University of California, San Diego, La Jolla, CA</td>
<td>PhD</td>
<td>2000</td>
<td>Biomedical Sciences</td>
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<td>University of Utah/Primary Children’s Hospital, Salt Lake</td>
<td>Residency</td>
<td>2000-2003</td>
<td>Pediatrics</td>
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<td>City, UT</td>
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<tr>
<td>Boston Children’s Hospital, Boston, MA</td>
<td>Residency</td>
<td>2003-2004</td>
<td>Child Neurology</td>
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<tr>
<td>University of Utah/Primary Children’s Hospital, Salt Lake</td>
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<tr>
<td>University of Utah David Eccles School of Business, Salt</td>
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<td>2012</td>
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<tr>
<td>Lake City, UT</td>
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A. Personal Statement

I am well qualified to serve as a mentor for Dr. Malone-Jenkins and her training as a VPCAT scholar. I am a tenured Professor in Pediatric Neurology, Bray Presidential Chair, and Director of the Center for Personalized Medicine, in the Department of Pediatrics. I perform clinical, translational, and bench research, in addition to my patient care responsibilities. My scientific and clinical training has been augmented by experience in administration, including didactic (Certification in Leadership Development Course at the School of Business) and on-the-job experience (program director of the University of Utah Child Neurology Residency Training Program; Director of Research for the Division of Pediatric Neurology; Chief, Division of Pediatric Neurology). The goal of my own research is the characterization of fundamental mechanisms that mediate development and disease. I was one of the first investigators to use zebrafish for the study of human disease, particularly neurological diseases, with studies on the foxP2 gene; and also one of the first to demonstrate the utility of zebrafish for testing the pathogenicity of identified mutations from whole exome sequencing in a collaborative project on the LAS1L gene. My lab has been on the forefront of new technology development in zebrafish mutagenesis; including identification of morpholino limitations and the use of zinc-finger nuclease mutagenesis (Xing et al., 2012); the development of rapid PCR based screening (Xing et al., 2012; 2014); and use of microfluidics for zebrafish (Samuel et al., 2015). Since 2006, I have personally mentored >60 individuals, more than half of whom are women or minorities; and I have helped faculty obtain their first NIH grants. These trainees have included high school students, undergraduates, medical students, graduate students, residents, fellows, and junior faculty. My first graduate student trainee is now a faculty member at Nantong University; and my first post-doctoral fellow is now a faculty member at the University of Scranton. My mentees have gone on to present at national meetings including the Child Neurology Society, Pediatric Academic Societies, and International Zebrafish Meetings; and to publish their work (Nelson et al., 2012; Brimley et al., 2013; Anderson et al., 2014).

B. Positions and Honors

Positions and Employment

2000-2003 Pediatrics Residency, University of Utah, Salt Lake City, UT
2003-2004 Child Neurology Residency, Boston Children’s Hospital, Boston, MA
2004-2006 Child Neurology Residency, University of Utah, Salt Lake City, UT
2006-2008 Instructor, Pediatric Neurology, Department of Pediatrics, University of Utah, Salt Lake City, UT
2008-2013 Adjunct Assistant Professor, Department Neurobiology and Anatomy, University of Utah, Salt Lake City, UT
2008-2013 Assistant Professor, Pediatric Neurology, Department of Pediatrics, University of Utah, Salt Lake City, UT
2010-present  Assistant Professor, Department of Neurology, University of Utah, Salt Lake City, UT
2013-present  Adjunct Associate Professor, Department Neurobiology and Anatomy, University of Utah, Salt Lake City, UT
2013-2019  Associate Professor, Pediatric Neurology, Department of Pediatrics, University of Utah, Salt Lake City, UT
2019-present  Professor, Pediatric Neurology, Department of Pediatrics, University of Utah, Salt Lake City, UT

Honors
1987  National Merit Scholar
1991-1992  Fulbright Fellowship
1994-1998  Markey Fellow in Biomedical Sciences
2004-2007  Primary Children's Medical Center Foundation Scholar
2004  American Neurological Association Travel Fellowship Award
2005  Child Neurology Society Junior Member Award
2010  Fellow, Society for Pediatric Research
2016  Visiting Fellow, Clare Hall, University of Cambridge
2016  Parke Davis Fellowship, School of the Biological Sciences, University of Cambridge

Certifications
2003  American Board of Pediatrics
2007  American Board of Neurology

Professional Memberships
2000-present  Member, American Association of Pediatrics
2003-present  Member, Child Neurology Society
2006-present  Member, Society for Neurosciences

C. Contributions to Science

1) In my PhD I worked on Drosophila axon guidance. My work was among the first to recognize the relevance of inhibitory midline axon guidance cues for “channeling” midline crossing. We published our description of this in Nature, and this work has led to the increased understanding of the importance of midline crossing commissures such as the corpus callosum.

2) After my PhD I returned to my training in clinical medicine for the next 8 years (1998-2006). During that time I established two large-scale clinical projects, and began to study neurogenetic conditions.


3) A major focus of my mentored research when I returned to bench science was the development of tools to study CNS development in the zebrafish, which I continued in my own lab. I pioneered the use of targeted enhancers for visualization of axon pathways in zebrafish, I brought the use of intersectional mapping using Gal4 and Gal80 to zebrafish, applied microfluidics and advanced PCR techniques to genotyping, and applied novel tools for labeling synapses.


4) A major thrust of my lab’s efforts has been to define the genetic regulation of normal and abnormal development of the brain. We were one of the first groups to demonstrate the utility of zebrafish for studying neurodevelopmental disorders and for testing next-generation sequencing results.


5) My lab’s recent work has been to understand and to approach therapeutics for leukodystrophies. This started with work in the clinical arena, which we have translated into collaborative work in Drosophila, and a zebrafish model for understanding disease pathology and for small molecule discovery.


D. Research Support

**Ongoing Research Support**

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<td>The Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN)</td>
<td>The GLIA-CTN is a Rare Disease Clinical Research Network project to develop tools and databases to study leukodystrophies, and bring therapies to clinical trial trials and accelerate readiness.</td>
<td>Role: Co-Investigator</td>
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<table>
<thead>
<tr>
<th>Grant ID</th>
<th>Principal Investigator(s)</th>
<th>Start Date</th>
<th>End Date</th>
<th>Duration</th>
<th>Sponsor</th>
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<td>R21(R33)NS109441</td>
<td>Bonkowsky (PI)</td>
<td>12/15/2018-11/30/2021</td>
<td>1.2 Cal Mos</td>
<td>NIH/NINDS</td>
<td>$246,922</td>
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<tr>
<td>Development and Validation of a Zebrafish Model for Vanishing White Matter Disease</td>
<td>This study generates a new model for VWMD and validates its parameters to use for compound screening.</td>
<td>Role: Principal Investigator</td>
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<tr>
<td>U24NS107156</td>
<td>Singleton (PI)</td>
<td>07/01/2018-06/30/2023</td>
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<td>NIH/NINDS</td>
<td>$200,000</td>
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<tr>
<td>The Utah Regional Network for Excellence in Neuroscience Clinical Trials</td>
<td>The UR-NEXT will strengthen the overall NEXT network by providing leadership and clinical trial expertise for both pediatric and adult neurologic disorders In addition, the UR-NEXT will provide an ideal venue for access to NEXT studies for patients living in the 5 state Intermountain West.</td>
<td>Role: Co-Investigator</td>
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<td>Marth/Tristani-Firouzi (MPI)</td>
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<td>NIH/NHGR</td>
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<td>Web Tools for Physician-Driven Diagnostic Interpretation of Genomic Patient Data</td>
<td>The overall goal is to build a set of web tools that offer novel functionality for deeper, systematic reexamination of the data for disease-causing variants, but are also intuitive and easy to use so clinicians can themselves analyze their patients’ genomic datasets.</td>
<td>Role: Co-Investigator</td>
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**Completed Research Support (past 3 years)**

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<tr>
<td>U54UL1TR002538 (Administrative Supplement)Dere/Hess (MPI)</td>
<td>07/01/2018-03/31/2019</td>
<td>2.0 Cal Mos</td>
<td>NIH/NCATS</td>
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<tr>
<td>University of Utah Center for Clinical and Translational Science (Utah CCTS)</td>
<td>The Utah CCTS serves as the major infrastructure and home for clinical and translational research in the state of Utah. The proposed administrative supplement develops and uses novel bioinformatics tools (PheWAS, PHIS), to analyze leukodystrophy disease prevalence and disparities in diagnosis.</td>
<td>Role: Co-Investigator</td>
<td></td>
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<th>Duration</th>
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<tr>
<td>1R21 MH107039</td>
<td>Bonkowsky (PI)</td>
<td>08/15/2015-07/31/2018</td>
<td>NIH / NIMH</td>
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<td>Mechanisms of Serotonergic Regulation for Connectivity Development</td>
<td>The goal of this work is to understand how serotonin regulates early axon pathfinding.</td>
<td>Role: PI</td>
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<table>
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<tr>
<td>U10NS077305</td>
<td>Smith (PI)</td>
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<tr>
<td>The Utah Regional Network for Excellence in Neuroscience Clinical Trials</td>
<td>The UR-NEXT will strengthen the overall NEXT network by providing leadership and clinical trial expertise for both pediatric and adult neurologic disorders In addition, the UR-NEXT will provide an ideal venue for access to NEXT studies for patients living in the 5 state Intermountain West.</td>
<td>Role: Co-Investigator</td>
<td></td>
<td></td>
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</tbody>
</table>
European Leukodystrophy Association
Screenable Zebrafish Models for Leukodystrophy Therapeutics
This project develops zebrafish models for adrenoleukodystrophy and uses pharmacological screening to restore myelin growth.
Role: PI

1 R43 OD023027 Bonkowsky (co-PI) 08/01/2016-02/28/2018
NIH/NCATS
Microfluidic devices for early (less than 48 hpf), non-destructive zebrafish genotyping
This SBIR grant develops a novel microfluidic device to use for the embryonic genotyping of live zebrafish in collaboration with a company (Nanonc, Inc.).
Role: co-PI

DP2 MH100008/New Innovator Bonkowsky (PI) 09/31/2012-09/30/2017
NIH / NIMH
Trans-cellular Activation of Transcription to Analyze Dopaminergic Axon Reorganization
This work develops a novel genetic method for labeling and manipulating neural circuits.
Role: PI
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Marth, Gabor Tamas

eRA COMMONS USER NAME (credential, e.g., agency login): GMARTH

POSITION TITLE: Professor, Human Genetics

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>Completion Date MM/YYYY</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Technical University of Budapest, Budapest, Hungary</td>
<td>B.S.-M.S.</td>
<td>1983 - 1987</td>
<td>Electrical Engineering</td>
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<tr>
<td>Washington University, St. Louis MO</td>
<td>D.Sc.</td>
<td>1988 - 1994</td>
<td>Systems Science and Math</td>
</tr>
<tr>
<td>Washington University, St. Louis MO</td>
<td>Post-doc</td>
<td>1994 - 2000</td>
<td>Genome Informatics</td>
</tr>
<tr>
<td>National Center for Biotechnology Information, NLM, NIH, DHHS</td>
<td>Staff scientist</td>
<td>2000 - 2003</td>
<td>Genome variation research</td>
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</table>

A. Personal statement

I am a computational biologist with a long history of algorithm development for genomic data analysis, starting with the first whole-genome sequencing projects (C. elegans, human). The research areas of my laboratory encompass human variation discovery and analysis, genomic data standards development, the analysis of tumor cellular heterogeneity and subclonal structure, computational method development for analyzing single-cell genomic data, functional precision oncology, and the development of intuitive web tools for genomic and clinical data analysis (http://iobio.io). I have served as a mentor for many graduate students, postdocs, and junior faculty. I will be delighted to serve as a mentor for Dr. Sabrina Malone-Jenkins.

B. Positions and Honors

Positions and Employment

1987      Internship - Institute for Heavy Ions Research, Darmstadt, Germany
1994 - 2000 Post-Doctoral Research Associate, Genome Sequencing Center, Dept. of Genetics, Washington University School of Medicine, St. Louis MO
1999 - 2008 Instructor, Cold Spring Harbor Lab Genome Informatics
2000 - 2003 Staff Scientist, Computational Biology Branch, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda MD (position ends August 31, 2003)
2000 - present Instructor, Canadian Genetic Diseases Network Genome Informatics Course
2003 - 2014 Assistant/Associate Professor, Department of Biology, Boston College, Chestnut Hill MA
2008 – present Course organizer and instructor, Cold Spring Harbor Lab High-throughput Sequencing
2014 – present Professor, Department of Human Genetics, University of Utah School of Medicine
2014 – present Director, USTAR Center for Genetic Discovery, University of Utah School of Medicine

Other Experience and Professional Memberships

2001 – present Member, Scientific Advisory Board, Marshfield Clinic Research Foundation Personalized Medicine Program
2003 – NCI Review Panel: Mammalian Gene Collection
2004 – NHI Review Panel: Genome Study Section (ad hoc reviewer)
2008 – NIMH Review Panel: Methods of Statistical Analysis of DNA Sequence Data
Genome-wide Resequencing in Well-Phenotyped Populations

2008 – present Chair, Scientific Advisory Council, Computational Biology Program, Ontario Institute for
Cancer Research

2009 – NCI Review: Cancer Genome Centers (ad hoc reviewer)

2009 – 2014 Member, Scientific Advisory Board, EdgeBio Systems

2010 – NHGRI Review Panel: Centers of Excellence in Genome Sciences (ad hoc reviewer)

2010 – present Editorial Board Member, Genome Research

2012 – present Member, External Evaluation Committee, T2D-GENES Project, NIDDK/NIH

2014 – present Chair, Scientific Advisory Board, Computational Biology Program, Ontario Institute for
Cancer Research (OICR)

2015 Reviewer, NHGRI Genome Science and Genomic Medicine training programs

2003 – present Reviewer, ad hoc, BDMA and GCAT study sections

2017 – present Member, Scientific Advisory Board, Canada’s Genomic Enterprise

2017 – present Member, Scientific Advisory Board, Adaptive Oncology Program, OICR

C. Contribution to Science

1. **Software algorithms for genetic variant identification.** Genetic variations underlie heritable traits
including human diseases. Identification of genetic variants is necessary to find disease-causing variants in
patient genomes. Early in my career, I developed the first statistically rigorous algorithm (POLYBAYES) for
the detection of single-nucleotide polymorphisms (SNPs) that utilized the then-emerging human genome
reference sequence for mapping fragmentary DNA sequences from multiple samples, and a Bayesian
statistical framework that used the read base quality values to calculate the probability that sequence
mismatches are the result of true polymorphism, as opposed to sequencing errors. This software was used
in a number of polymorphism discovery projects, including The SNP Consortium, to construct early genome-
wide maps of human genetic variation. More recently, I played a central role in the development of methods
supporting the use of high-throughput sequencing technologies to study DNA variation on a large scale: base
calling programs (PYROBAYES), read mappers (MOSAIK), SNP and INDEL variant calling programs
(FREEBAYES), structural variant (SV) detection programs (SPANNER, TANRAM), and the first next-
generation alignment viewer (EAGLEVIEW). These tools were used from the earliest days of organismal
genome resequencing, establishing the fundamental analytical procedures used by the community today.
We utilized these tools extensively in the 1000 Genomes Project for the discovery of diverse types of
sequence variations, including larger, structural variants. My laboratory led the construction of the first,
genome-wide map of mobile element insertion polymorphisms (MEIs), essential types of structural genetic
variation. I served as principal investigator for software development, and as co-Chair of various 1000
Genomes Project working groups, in these projects.

   a. A general approach to single-nucleotide polymorphism discovery. **Marth GT**, Korf I, Yandell MD, Yeh RT,

   b. A comprehensive map of mobile element insertion polymorphisms in humans. Stewart C, Kural D,
   Strömberg MP, Walker JA, Konkel MK, Stütz AM, Urban AE, Grubert F, Lam HY, Lee WP, Busby M,
   Indap AR, Garrison E, Huff C, Xing J, Snyder MP, Jorde LB, Batzer MA, Korbel JO, **Marth GT**; 1000

   c. The functional spectrum of low-frequency coding variation. **Marth GT**, Yu F, Indap AR, Garimella K,
   Gravel S, Leong WF, Tyler-Smith C, Bainbridge M, Blackwell T, Zheng-Bradley X, Chen Y, Challis D,
   Clarke L, Ball EV, Cibulskis K, Cooper DN, Fulton B, Hartl C, Koboldt D, Muzny D, Smith R, Sougnez C,
   Stewart C, Ward A, Yu J, Xue Y, Altschuler D, Bustamante CD, Clark AG, Daly M, Depristo M, Flicek P,

   d. 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**,

2. **Standard genomic data formats.** Standard data formats promote data sharing and analysis tool
interoperability. As part of the 1000 Genomes Project effort to develop community standards for high-
throughput sequence analysis, I designed the first versions of file formats that are the de facto data standards
today in genetic analysis: the SAM/BAM sequence alignment format, the VCF and GVF variant reporting
formats. These formats have been widely adopted by the biomedical research community and are the de
The prevailing view is that cancer evolution occurs through a series of clonal expansions and subclonal genetic diversification. This diversification is driven by both somatic and germline mutations, as well as by selective pressures that favor particular genetic configurations. The ability to reconstruct the evolutionary history of tumor subclones is therefore critical for understanding the mechanisms of tumorigenesis, drug response, relapse, and metastasis.

3. Population genetic methods for studying early human demographic history. Genetic polymorphisms are features within a population that allow us to study population structure and demographic history. I utilized the data, from early genome-scale human polymorphism maps I helped create, for population genetic analyses. Fitting these data to demographic models my colleagues and I developed, we were among the first to show that the demographic histories of European and Asian populations are characterized by genetic bottlenecks, resulting in reduced diversity, as compared to African populations. These results have since been confirmed, and greatly refined, by many population genetics studies using high-density genomic polymorphism data from many human populations. I acted as the primary developer of our early population genetic data analysis methods, and a co-PI on our more recent analyses.


4. Algorithms for the analysis of tumor cellular substructure and subclone evolution. Many tumors are composed of genetically divergent subpopulations of cells. The ability to delineate each such clonal subpopulation, determine its frequency within the tumor mass, and to infer the evolutionary relationships among subclones allows one to determine the order in which the mutation events occurred, and identify the mutations most likely to play a part in tumorigenesis, drug response, relapse, and metastasis. We have recently developed a computational method, SUBCLONESEEKER, to reconstruct tumor subclones, and their evolution from normal cell to primary tumor, and to relapse or metastasis. We are currently extending this method for longitudinal monitoring of the tumor subclones in metastatic tumor patients across multiple courses of chemotherapy. I act as the PI for subclone reconstruction method development.


Ongoing clonal evolution in chronic myelomonocytic leukemia on hypomethylating agents: a computational perspective. Than H, Qiao Y, Huang X, Yan D, Khorashad JS, Pomicter AD, Kovacsovics TJ, Marth GT, O'Hare T, Deininger MW. *Leukemia*. 2018 Sep;32(9):2049-2054.

Web-based software for visually driven, real-time interactive analysis of genome-scale data. Rapidly decreasing sequencing costs allow even small laboratories to carry out experiments at the scale of an entire genome or exome, but because current genomic analysis systems have been designed and optimized for analyses at a large scale, e.g. end-to-end processing of a whole genome or exome, they are time consuming, unintuitive for novice users, and require hardware resources, technical IT expertise, and bioinformatics skills that makes them inaccessible for many bench scientists today. We are developing a new, web-based analysis system, IOBIO, to address rapid, focused, low-cost analyses within vast genomic datasets, e.g. in the region of a single gene, and to quickly provide intuitive, visual overviews of large genomic datasets, which is what many biomedical researchers need. Instead of end-to-end analysis that lasts hours, days, or even weeks, IOBIO “apps” can access, transmit, analyze, and display all data within the region of a gene in seconds, or randomly sample a genome-scale dataset to estimate and display its statistical properties, also in seconds. This results in a highly interactive user experience, allowing scientists to quickly explore their data, visualize their results, refine and repeat their analyses in real time, and develop an intuitive understanding of their datasets, results, and the analyses they perform. IOBIO apps can access remote data (e.g. on cloud storage), and use back-end analysis servers to carry out data analysis, obviating tool installation, local storage and computing hardware: researchers can analyze their data in a web browser on a laptop. IOBIO based analysis is also interactive for more advanced users, who can use IOBIO apps to carry out many types of analysis rapidly, interactively, and in combination with end-to-end genomic analyses. IOBIO is a functioning and rapidly expanding system, currently offering four distinct, fully featured web apps (see http://iobio.io), including genomic data inspector as well as more complex genomic analysis apps, with new apps being developed at a rapid pace. Our tools are already being utilized by thousands of users, many of them returning “customers” who have incorporated our tools into their analysis routine. I act as the PI for this development.


D. Research Support

**Current Research Support**

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<td>Marth (PI)/Quinlan (MPI)</td>
<td>09/01/2016-08/31/2021</td>
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<tr>
<td>R01HG009000-A101</td>
<td>Marth (PI)</td>
<td>08/01/2017-05/31/2021</td>
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</tbody>
</table>

Monitoring tumor subclonal heterogeneity over time and space

Goal: We are developing computer software to discover and interpret genetic differences between individual human genomes from DNA sequencing data.

Role: Project Director/Principal Investigator (contact)

IOBIO: Web-based, interactive tools for real-time analysis in genomic big data
Goal: We are developing web-accessible software that will allow biomedical scientists to analyze genetic data more easily, intuitively, and without huge computer resources. These tools will accelerate genetic discovery by enabling all researchers to access and analyze vast biological datasets.

Role: Principal Investigator

1R01HG009712-01  Marth (PI)/Tristani-Firouzi (MPI)  09/01/2017-06/30/2021
Web tools for physician-driven diagnostic interpretation of genomic patient data

Goal: We will develop highly visual web software tools to enhance the identification of disease causing genetic variants for physicians and diagnostic pathologists at the point of care. These tools will facilitate rapid, effective, highly visual data quality control, and the rapid interrogation of inherited, potentially disease-causing variants.

Role: Principal Investigator/Project Director

Simons Foundation  Coon/Marth/Quinlan/Docherty (MPI)  07/01/2017-06/30/2020
Interaction of WGS Variation and Polygenic Risk

Role: Co-Principal Investigator

2R44HG009096  Ward/Marth/Miller (MPI)  04/01/2018-03/31/2020
IOBIO based, distributed genomic data access, management, visualization and analysis

Goal: This project will democratize genomic analysis by providing intuitive data management, organization, data analytics, and integrated visually driven analysis in a single application that can be used by experts across the bioinformatics research and healthcare disciplines. By simplifying organization and improving collaboration, this project will reduce the costs associated with genomic analysis, while simultaneously improving research results and diagnostic outcomes.

Role: Co-Principal Investigator

1U01CA217617-01A1  Welm/Varley/Marth (MPI)  09/06/2018-08/31/2023
Longitudinal models of breast cancer for studying mechanisms of therapy response and resistance

Goal: The goal of this proposal is to establish three types of patient-derived breast cancer models from patients at multiple longitudinal time points during treatment and directly test the fidelity of each model with regard to genomic and epigenetic aberrations, clonal heterogeneity and evolution, and treatment response/resistance.

Role: Co-Principal Investigator

1U01HG010217-01  Botto (PI)  09/20/2018-06/30/2022
Intermountain West Clinical Site for the Undiagnosed Disease Network (UDN), Phase 2

Goal: The proposed Intermountain West Clinical Site of the Undiagnosed Disease Network will help adults and children with undiagnosed diseases spread across ~10% of the Continental US get access to unprecedented diagnostic and care resources. The Clinical Site combines the cognitive expertise of teams of master clinicians in multiple specialties with innovative genetic tools to solve medical mysteries that have eluded diagnosis, sometimes for many years. The overall goal is to help families get better care through a precise diagnosis, and in doing so discover new genetic causes, disease pathways, and treatments that will help many more families in future.

Role: Co-Investigator

Completed Research Support (recent)

1R43HG009868-01  Ward/Marth/Miller (MPI)  09/01/2017-03/14/2019
Novel iobio analysis supporting genome scale data quality control.

Goal: We will develop commercial software for genomic data quality control.

Role: Co-Principal Investigator

1R01HG008628-01  Eilbeck (PI)/Marth (MPI)  09/01/2015-06/30/2019
A community-driven framework for genome-based clinical diagnostics

Goals: To produce and distribute VCFclin, a clinical grade variant file type that incorporates variant graph methods for unambiguous variant annotation.

Role: Co-Principal Investigator
NAME: Christian Con Yost

eRA COMMONS USER NAME (credential, e.g., agency login): CHRISYOST

POSITION TITLE: Associate Professor of Pediatrics, University of Utah School of Medicine

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>University of Utah, Salt Lake City, UT</td>
<td>B.S.</td>
<td>05/1993</td>
<td>Biology</td>
</tr>
<tr>
<td>University of Utah Hospital School of Medicine, Salt Lake City, UT</td>
<td>M.D.</td>
<td>05/1997</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of Vermont College of Medicine, Burlington, VT</td>
<td>Intern</td>
<td>06/1998</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>University of Vermont College of Medicine, Burlington, VT</td>
<td>Resident</td>
<td>06/2000</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>University of Utah School of Medicine, Salt Lake City, UT</td>
<td>Fellow</td>
<td>06/2003</td>
<td>Neonatology</td>
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</tbody>
</table>

A. Personal Statement

I am a physician-investigator and neonatologist focused on understanding regulatory mechanisms governing acute inflammatory responses in neonates, born at term or prematurely. I aim to determine how sepsis and other inflammatory syndromes such as necrotizing enterocolitis and bronchopulmonary dysplasia (BPD) alter these regulatory mechanisms and how to ameliorate the ongoing pathologic inflammatory tissue damage that results in the inflammatory tissue damage that leads to significant morbidity and mortality in newborn infants. Since 2004, I have studied the neonatal neutrophil in newborn infants, focusing on the perinatal period and transition to extrauterine life. Using this “model,” my laboratory has defined a previously undescribed immune deficit of newborn infants – impaired neutrophil extracellular trap (NET) formation – and discovered a family of NET-Inhibitory Peptides (NIPs), which are novel endogenous modulators of NET formation.

For Dr. Malone Jenkins’s VPCAT Program application, I commit fully to the role of co-mentor. I have a track record of successful mentorship for > 12 mentees with resulting mentee first author publications and national presentations. Although this will be my first VPCAT mentorship experience, I have mentored junior faculty members, neonatology fellows, pediatric residents, medical students, and undergraduate students successfully, both in research and in career development. 4 mentee first author (in italics) publications are listed as representative of my success and productivity as a research mentor. I also serve as the Program Director for the Fellowship Training Program in Neonatal-Perinatal Medicine at the University of Utah. This also gives me the opportunity to mentor fellows in career development and success in academic medicine. With Dr. Malone Jenkins, I very much relish the opportunity to serve as a co-mentor and to help guide her and her mentorship team in support of her career development. I anticipate that my experience with neutrophil biology, molecular biology, and translational studies elucidating alterations in chromatin access and gene expression will greatly benefit Dr. Malone Jenkins and her team. Indeed, I have collaborated successfully with Dr. Malone Jenkins in the past and look forward to working with her mentorship team during her VPCAT Program participation. All members of Dr. Malone Jenkin’s VPCAT mentorship team will offer career development advice and mentoring.

References Related to this Proposal

2. BC MacQueen, RD Christensen, CC Yost, DK Lambert, VL Baer, MJ Sheffield, PV Gordon, MJ Cody, E Gerday, R Schlaberg, J Lowe, JG Shepherd. Elevated fecal calprotectin levels during necrotizing


**B. Positions and Honors**

**Positions and Employment**

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Position and Institution</th>
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<tr>
<td>2003 - 2006</td>
<td>Instructor (Clinical) in Pediatrics, University of Utah Medical Center, Salt Lake City, UT</td>
</tr>
<tr>
<td>2006 - 2013</td>
<td>Assistant Professor in Pediatrics, University of Utah Medical Center, Salt Lake City, UT</td>
</tr>
<tr>
<td>2013 – Present</td>
<td>Associate Professor in Pediatrics, University of Utah Medical Center, Salt Lake City, UT</td>
</tr>
</tbody>
</table>

**Honors**

- **1998** Dean’s Excellence in Teaching Award: Pediatrics, University of Vermont School of Medicine
- **2003 - 2009** Primary Children’s Medical Foundation Scholar
- **2003 - 2004** Fellowship-to-Faculty Transition Program, University of Utah
- **2003** David W. Smith Pediatric Trainee Research Award, Western Society for Pediatric Research
- **2004 - 2005** Program Scholar, Children’s Health Research Career Development Award, University of Utah
- **2010** Nominee, Physician of the Year, Primary Children’s Medical Center
- **2011** Abbott Nutrition Young Investigator Award, Western Society for Pediatric Research
- **2017** Nominee, Physician of the Year, Primary Children’s Hospital
- **2019** Nominee, Physician of the Year, Primary Children’s Hospital

**Other Experience and Professional Memberships**

<table>
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<th>Year Range</th>
<th>Position and Institution</th>
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<tbody>
<tr>
<td>2007 – Present</td>
<td>Member, Western Society for Pediatric Research</td>
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<tr>
<td>2010 – Present</td>
<td>Member, Society for Pediatric Research</td>
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<tr>
<td>2013 – 2015</td>
<td>Council Member, Western Society for Pediatric Research</td>
</tr>
<tr>
<td>2015 – 2019</td>
<td>Secretary-Treasurer, Western Society for Pediatric Research</td>
</tr>
</tbody>
</table>

**C. Contribution to Science**

I have a record of inquiry as a physician investigator that is consistent, thematic, and has led to important discoveries in the cell biology of inflammation, platelet neutrophil interactions, and neonatal medicine by primarily investigating inflammation in human neonates, an understudied, unique, and challenging population. In recognition of my contributions to the field, I received the Abbot Nutrition Western Society for Pediatric Research (WSPR) Young Investigator Award for 2011, and gave an invited plenary presentation on some of my published and unpublished studies at the annual WSPR meetings (January, 2011). I also presented as an invited speaker at the Neutrophil 2014 international conference (July 2014 – Montreal, CAN) where I addressed the topic of regulatory mechanisms governing NET formation. More recent invited lectures include a seminar for the Pediatric Hematology/Oncology Division at Boston Children’s Hospital/Harvard Medical School (September 2017), a presentation at the National Meeting for the Association of American Blood Banks in San Diego, CA (October 2017), and an Educational Spotlight presentation at the National Meeting for the American Society for Hematology in Atlanta, GA (December 2017). For these recent invited lectures, I addressed the topic of dysregulated NET formation and lessons learned from translational studies using...
Infection (cited here). In the neonatal NET laboratory, we demonstrated decreased NET formation in patients undergoing bone marrow transplantation with polymicrobial sepsis induced via cecal ligation and puncture (directly examined). As a co-author, my laboratory designed and carried out all of the NET-related experiments demonstrating for the first time dysregulated NET formation in NEC (not cited here). Recently, I also co-authored a report which directly examined the role of NET formation and its induction by a PPARγ agonist used in an in vivo model of polymicrobial sepsis induced via cecal ligation and puncture (publication A). My laboratory has also studied NET formation in cancer patients. We demonstrated decreased NET formation in patients undergoing bone marrow transplantation with some of the study participants having cancer (not cited here). Finally, my laboratory has identified a novel inhibitor of NET formation by human PMNs which circulates in cord blood: Neonatal NET-Inhibitory Factor (nNIF). These experiments suggest nNIF and additional NET-inhibitory peptides (NIPs) as key regulatory molecules governing NET formation and as focused and powerful tools to examine the question of whether NETs “heal or harm” in various inflammatory syndromes including cancer (publication C). Patent protection for this technology is awarded in the US and pending internationally (not cited here). My laboratory has also demonstrated a role for NET-triggered immunothrombosis in SARS-CoV-2 infection (publication D).


2. Epigenetic Regulation of Gene Expression in Translational Models.

I have co-authored two reports examining the effects of nucleosome positioning and epigenetic regulation on IGF-1 gene expression (publication A) and eukaryotic elongation factor 2 kinase expression (publication D).
B) in a murine model of intrauterine growth restriction (IUGR). These studies are laying the ground work for studies elucidating alterations in gene expression in human neonates born with IUGR.


Translational Regulation of Gene Expression in Adult and Neonatal PMNs.

I demonstrated that human PMNs respond to pro-inflammatory stimuli with rapid, *de novo* protein expression regulated at the translational level by the mammalian Target of Rapamycin (mTOR) pathway (publication A), building on earlier collaborative studies (publication B) completed during my neonatology fellowship. These reports documented for the first time that the mTOR regulatory machinery functions not only as an integrator of signals and cellular energy status in growing and dividing cells, but also has novel activities as a rapid response regulator in myeloid leukocytes, controlling amplification and modulation of the acute inflammatory response. My findings indicated that rapid translational regulation of protein expression is a previously-unrecognized mechanism by which human PMNs alter their phenotype and function in acute inflammation and suggested the mTOR pathway as a potential site of dysregulation in inflammatory syndromes such as sepsis and NEC. I have subsequently examined mTOR activity and translational regulation in neonatal and adult PMNs and have identified significant differences in PMNs from healthy and diseased infants compared to those from adults (publication D). I contributed as a co-author to additional studies in a murine model of ALI/ARDS to demonstrate that decreased expression of TLT-1 may predict acute lung injury. I contributed the neutrophil transcriptome studies which we accomplished using next generation RNA sequencing (publication C).


3. Novel Activities of Platelets

I co-authored a report documenting for the first time that anucleate platelets splice pre-messenger RNAs (pre-mRNAs) into mature mRNA transcripts, leading to translation of new, biologically-active protein products (publication A). This is a novel mechanism of “signal-dependent protein synthesis” in this unique myeloid cell type. This study demonstrated that pre-mRNA splicing in the cytoplasm of activated platelets is a key regulatory event in the expression of IL-1β, a potent pro-inflammatory cytokine, and provided the first evidence for extranuclear splicing in mammalian cells. These observations have subsequently been confirmed by other laboratories, and by ongoing studies by other members of our group. These ongoing collaborative studies have also allowed qualitative and quantitative comparison of the transcriptomes of human and murine platelets and PMNs using next generation paired end RNA sequencing (RNA-seq), and demonstrate the potential for discovery using this cutting edge technique (publication B). Collaborative studies also led to elucidation of one novel mechanism by which stimulated platelets can induce NET formation by human PMNs – the secretion of β-defensin 1 (publication C).


Complete List of Published Work in My Bibliography: https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41141705/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

1 R01 HD093826 (NICHD)  Yost  07/20/2018 – 04/30/2023
NETs: Protection or Harm in Neonatal Inflammation and Infection
The goal of this study is to elucidate the regulatory mechanisms governing NET-Inhibitory Peptide generation in vivo, determine their mechanism(s) of action, and use the NIPs in a pre-clinical model of neonatal sepsis to determine whether NET formation ameliorates or exacerbates inflammatory tissue damage in neonatal sepsis.
Direct Costs: $1,220,000
Role: Principle Investigator

Completed Research Support

UTAG 18065 (USTAR)  Yost  06/01/18 – 12/31/19
NET-Inhibitory Peptides (NIPs): New Treatment for Sepsis and Inflammatory Bowel Disease
This project will explore therapeutic possibilities for NIPs in sepsis and inflammatory bowel disease by performing NIP pharmacokinetic properties in vivo, assessing nanoparticle encapsulation as an optimized peptide delivery system, and determining efficacy of treatment of NET-mediated tissue damage in a pre-clinical model of inflammatory bowel disease.
Direct Costs: $300,000
Role: Principle Investigator

1 R21 HD088907 (NICHD)  McKnight, Albertine Yost (Co-PIs)  07/01/2017- 06/30/2019
Predicting Lung Chromatin Access Profiling in Preterm Mechanically Ventilated Lambs
The goal of this study is to characterize lung, brain, and CD4+ lymphocyte chromatin access in prematurely born and mechanically ventilated lambs that serve as the best model for bronchopulmonary dysplasia. Comparison of the chromatin access profiles for lung, brain, and lymphocytes will lay the foundation for further studies aimed at determining the epigenetic effects of mechanical ventilation that is commonly required for prematurely born infants.
Direct Costs: $275,000
Role: Co-Principal Investigator

1 K08 HD049699 (NICHD)  Yost (PI)  04/01/2006 – 03/03/2011
Translational regulation of gene expression in neonatal PMNs
The goal of this study is to characterize the role of translational regulation of gene expression in neonatal PMNs by interrogating signaling through the mTOR pathway and its differential activity in neonatal PMNs as it relates to pro-inflammatory syndromes of prematurity such as NEC.
Role: PI