AWARD NUMBER: W81XWH-20-1-0213

TITLE: Genetic Mechanisms of Neurofibromatosis-Related Arteriopathy and Renovascular Hypertension

PRINCIPAL INVESTIGATOR: Dr. Santhi Ganesh

CONTRACTING ORGANIZATION: REGENTS OF THE UNIVERSITY OF MICHIGAN
ANN ARBOR, MI

REPORT DATE: May 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21701- 5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
May 2021	Annual	01Apr2020-31Mar2021

4. TITLE AND SUBTITLE
Genetic Mechanisms of Neurofibromatosis-Related Arteriopathy and Renovascular Hypertension

5a. CONTRACT NUMBER
W81XWH-20-1-0213

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
0011446118

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study will identify genetic associations underlying pediatric renovascular hypertension, specifically as it relates to variants in the NF1 gene. Analysis of germline and somatic/tissue genetic variation will provide insights into the mechanisms of vascular disease in NF1. Initial studies are identifying early genotype-phenotype associations, human tissue signaling pathway alterations, and the initial stages of the somatic variant detection study are completed, with sequencing of tissue and vascular cell-derived DNA to occur in Year 2 of this grant.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	18	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Renovascular hypertension (HTN) resulting from renal artery and abdominal aortic narrowing is due to a process known as arterial dysplasia (AD) and is an important cause of high blood pressure in children that may lead to heart failure, stroke and early death. Neurofibromatosis type 1 (NF-1) is a common cause of pediatric renovascular HTN. A third of pediatric AD patients in the University of Michigan experience carry a diagnosis of NF-1 and others have described vascular involvement in nearly 20% of individuals with NF-1. It remains unclear why some children with NF-1 develop AD. The relationship of specific gene mutation in the NF1 gene to the severity of disease has not been previously reported. The possibility of mutations in tissues that were not present in the original fertilized egg ("somatic mutations") has not been previously explored as a cause or pediatric AD. NF-1 is characterized by variable symptoms and disease presentation. The protein product of the neurofibromin gene (NF1), is involved in regulating the growth of several cell types including those that make up the arterial wall, in particular, vascular smooth muscle cells (VSMCs). Neurofibromin regulates a cell-signaling pathway (Ras-Erk) and it is speculated that vascular cells that have lost neurofibomin will develop excessive tissue on the inside of the artery resulting in narrowing. If these same vascular cells are removed from mouse models of NF-1, the cells grow more rapidly in culture than expected. Research Questions and/or Concepts: The overall goal of our proposed study is to identify the underlying causes of arterial disease in NF-1. We are conducting unbiased genetic analyses of pediatric patients with AD by examining the subset of DNA (genetic 'code') that encodes proteins (exons) across the entire human genome. Thus far, our preliminary data has confirmed damaging NF1 mutations in approximately 25% of cases pediatric renovascular hypertension cases. Our overall goal is to identify why only a subset of patients with NF-1 develop AD. We hypothesize that specific mutations in the fertilized egg ("germline mutations", such as those that can be inherited) and/or mutations in tissues after the egg is fertilized ("somatic mutations") may underlie developmental AD. The information we gain in the proposed studies will improve our understanding of how genetic changes influence vascular disease in NF-1 patients and may identify novel targets for treatment of AD.

2. KEYWORDS:

Genetics, neurofibromatosis, hypertension, vascular disease, aortic coarctation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Characterize spectrum of mutations in the NF1 gene and other genes that may contribute to arterial disease in NF-1 using a whole exome sequencing approach integrated with RNASeq to identify mutations that alter proper RNA expression.

Specific Aim 2: Sequence DNA from arterial tissue, to determine whether mutations have occurred in the tissue itself, which could contribute to abnormal growth of the artery or AD. We will look in patients with known NF-1 to see if there is additional loss of genes in the arterial tissue and cells, and we will look in patients without a diagnosis of NF-1 but who may have a loss of NF-1 expression or function due to somatic mutation arising in the arterial tissue itself.

What was accomplished under these goals?

1. We have completed an analysis of 13 individuals with NF-1, specifically examining genotype-phenotype correlations of DNA sequence variants in the NF1 gene. We identified an enrichment of variants in a particular domain of the NF1 gene, the SEC domain, and truncating variants were associated with a more severe phenotype. We validated through RNASeq analysis over-activation of the MAPK/Erk pathway that has been shown to have increased activity in a mouse model of NF-1.
2. We have conducted integrative analysis of RNASeq data and exome sequencing data of genomic (germline) DNA from patients with PRVH, to enhance the yield of DNA variants affecting RNA splicing.
3. We have designed the MIPS sequencing panel that will be used for detection of somatic DNA variants.
4. We have derived primary vascular cells from patient tissue samples for the somatic MIPS sequencing analysis.

Abbreviations: NF-1, Neurofibromatosis type 1; NF1, Neurofibromin gene; PRVH, pediatric renovascular hypertension; MIPS, molecular inversion probe sequencing.

What opportunities for training and professional development has the project provided?

Postdoctoral research fellow Yu Wang, PhD has conducted studies of genotype-phenotype analysis and thus trained in the molecular genetic considerations of NF-1 as well as how to handle not only genetic data, but clinical patient data as well. He is learning the relevant signaling pathways and considerations for somatic genetic variant detection. A graduate student, Shirley Liu, conducted the analyses to detect splice variants, and gained bioinformatics and genetics training.

How were the results disseminated to communities of interest?

We have presented the data at institutional meetings, and we have submitted a manuscript to a journal for genotype-phenotype correlations described.

What do you plan to do during the next reporting period to accomplish the goals?

We will generate and test the MIPS probe pool for efficacy of obtaining deep sequencing for the designed targets. Following these validation steps, we will conduct the MIPS sequencing in patient samples. We will analyze these and the exome sequencing data.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The identification of an early genotype-phenotype correlation of specific regions of the NF1 gene and pediatric renovascular hypertension provides an important clue for clinicians caring for NF1 patients to consider; this may assist with early detection of hypertension and prevention of some of the more severe cardiovascular complications that can occur as a result of untreated vascular disease and hypertension.

What was the impact on other disciplines?

Our findings regarding an early genotype-phenotype correlation will be potentially useful to individuals caring for patients with NF-1, especially medical genetics specialists.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

All work in the laboratory was on hold during the COVID-19 pandemic and related stay-home orders at our location. We are currently up to 75% occupancy of the laboratory, and we are resuming work as capacity allows, according to the guidance of state, local, and institutional authorities.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subject

Nothing to report

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Ganeshlab.org Our lab website maintains a list of publications and periodically provides updates on the lab's research progress and findings.

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

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Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Title	Effort
Santhi Ganesh, MD	PI	1.2 CM
Kristina Hunker	Lab Specialist	1.2 CM
Yu Wang	Research Fellow	3.0 CM
Jacob Kitzman, MD	Co-I	0.3 CM
Dawn Coleman, MD	Co-I	0.5 CM

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Please see attachments

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

QUAD CHARTS

9. APPENDICES

OTHER SUPPORT

GANESH, SANTHI

Changes since last RPPR:
CIHR/University of British Columbia 20R21713 ended
PCORI Engagement Award was awarded

CURRENT SUPPORT

Title: Genetic Mechanisms of Neurofibromatosis-related Arteriopathy and Renovascular Hypertension
Time Commitments: 1.2 CM
Supporting Agency: DOD
Grants Contact: Jason Kuhns Jason.d.kuhns.civ@mail.mil
Performance Period: 4/01/2020-3/31/2023
Level of Funding/Total Award:
Goals/Specific Aims: The major goals are to: Specific Aim 1: Characterize spectrum of mutations in the NF1 gene and other genes that may contribute to arterial disease in NF-1 using a whole exome sequencing approach integrated with RNASeq to identify mutations that alter proper RNA expression. Specific Aim 2: Sequence DNA from arterial tissue, to determine whether mutations have occurred in the tissue itself, which could contribute to abnormal growth of the artery or AD. We will look in patients with known NF-1 to see if there is additional loss of genes in the arterial tissue and cells, and we will look in patients without a diagnosis of NF-1 but who may have a loss of NF-1 expression or function due to somatic mutation arising in the arterial tissue itself.
Role: PI
Overlap: None

Title: Genetic Studies of the Impact of Hematologic Traits on Cardiovascular Disease
Time commitment: 2.4 CM
Supporting Agency: NIH R01-HL122684
Grants contact: Youngsuk Oh, yoh@mail.nih.gov,
Performance Period: 8/10/2015-4/30/2021 (NCTX)
Level of Funding:
Brief description of project goal/specific aim: To test the overall hypothesis that genetic determinants of RBC traits influence BP and that through statistical analyses of pleiotropy, we may more precisely define the contributions of RBC traits to BP, which are relevant for the outcomes of HTN and CHD. We will conduct statistical analyses in population cohorts as well as functional experiments to evaluate target identified in the statistical analyses.
Role: PI
Project overlap with other existing/pending projects: None

Title: From GWAS Loci to Blood Pressure Genes, Variants & Mechanisms (FEHGAS3)
Time commitment: 1.2 CM
Supporting Agency: NIH/New York University R01-HL086694
Grants contact: Dallas, dallas@jhmi.edu,
Performance Period: 8/3/2018-1/31/2022
Level of Funding:
Brief description of project goal/specific aim: We will analyze the impact of genetic loci associated with blood pressure on gene regulation in tissues, to identify mechanisms of blood pressure regulation and hypertension.
Role: Co-Investigator (Aravinda Chakravarti, PI)
Project overlap with other existing/pending projects: None

Title: Genetic and Genomic Analysis of Arterial Dysplasia
Time commitment: 2.64 CM
Supporting Agency: NIH R01-HL139672
Grants contact: Youngsuk Oh, yoh@mail.nih.gov, (301)435-0560
Performance Period: 1/1/2018-12/31/2021
Level of Funding:
Brief description of project goal/specific aim: To determine that this spectrum of FMD implicates a limited number of genes and pathways, and a combined analysis of many cases, covering familial, sporadic, pediatric and adult cases, using both genetic and gene expression data, is the best way to uncover recurrently affected genes or convergent pathways.
Role: PI
Project overlap with other existing/pending projects: None

Title: Canadian Spontaneous Coronary Artery Dissection Genetics Study
Time commitment: 0.6 CM
Supporting Agency: Heart & Stroke Foundation/ University of British Columbia
Grants contact: Melissa Pak, mpak@icvhealth.ubc.ca
Performance Period: 7/1/2018-07/11/2021 (NCTX)
Level of Funding:
Brief description of project goal/specific aim: Genotyping for the GWAS analysis and whole exome sequencing will be coordinated by the Ganesh Lab at the University of Michigan.
Role: Co-Investigator
Project overlap with other existing/pending projects: None

Title: Lysyl oxidase activities in arterial development and arterial remodeling in aneurysms
Time commitment: 0.12 CM
Supporting Agency: University of Michigan – Israel Partnership for Research Education
Grants contact: Jennifer Frick, frick@umich.edu,
Performance Period: 9/1/2018-8/31/2020
Level of Funding:
Brief description of project goal/specific aim: To determine that by analyzing the roles of a key enzyme such as LOX, we will generate for the first time a temporal sequence of events leading to adverse remodeling culminating in TAA/D and ruptures.
Role: PI (Ganesh/Hasson, MPI)
Project overlap with other existing/pending projects: None

Title: Michigan Medicine Dysplasia-Associated Arterial Disease Precision Medicine Network
Time commitment: 1.2 CM
Supporting Agency: Taubman Institute (University of Michigan)
Grants contact: Grace Wu, glwu@umich.edu,
Performance Period: 3/1/2019-2/29/2029
Level of Funding:
Brief description of project goal/specific aim: To establish a one of a kind patient resource to facilitate research and clinical care of patients afflicted with non-atherosclerotic vascular diseases, defined as arterial dysplasia.
Role: PI
Project overlap with other existing/pending projects: None

Title: Pediatric Renovascular Hypertension: A pRVH PCOR Collaborative
Time Commitment: 0.12 CM
Supporting Agency: PCORI Engagement Award
Grants contact: fundedea@pcori.org
Performance Period: 12/01/2020-11/30/2022
Level of Funding:
Brief description of project goal/specific aim: The goals of this project are: 1) Create a pRVH PCOR collaborative; 2) Prioritize PCOR and comparative effectiveness research around critical diagnostic and treatment decisions; 3) Conduct a pRVH symposium in 2022.
Role: (Coleman, PI and Ganesh/Parekh, Co-Leads)
Project overlap with other existing/pending projects: None

OTHER SUPPORT

COLEMAN, DAWN M.

Changes since Last RPPR:
IRWG Michigan Women's Surgical Collaborative Project ended 06/30/20
Medtronic Endurant Evo US Clinical Trial ended 12/30/20
Pediatric Renovascular Hypertension: A pRVH PCOR Collaborative began 12/01/20

CURRENT SUPPORT

Project Title: Michigan Medicine Dysplasia-Associated Arterial Disease (DAAD) Precision Medicine Network
Time Commitments: 1.2 CM
Supporting Agency: Taubman Research Institute (Internal-UM)
Grants Officer & Contact Information: Grace Wu, Managing Dir., Taubman Research Institute;
Performance Period: 03/01/2019 – 02/29/2029
Level of Funding: Total Award:
Goals/Specific Aims: Establish a multidisciplinary Michigan Medicine DAAD cohort to facilitate clinical, genomic and cellular studies of pediatric and adult DADD.
Role: Co-PI
Overlap: none

Project Title: Genetic and Genomic Analysis of Arterial Dysplasia
Time Commitments: 0.60 CM
Supporting Agency: NIH/NHLBI
Grants Officer & Contact Information: Chantal D. Falade, Chantal.falade@nih.gov;
Program **Official:** Charyl McDonald, mcdonalc@mail.nih.gov
Performance Period: 01/01/2018 - 12/31/2021
Level of Funding: Total Award
Goals/Specific Aims: Specific Aim 1: We will conduct gene discovery analyses of FMD in a large clinical resource of diverse demographic and phenotypic characteristics, in adult and pediatric cases of FMD, using both case-control approaches as well as family-based analyses. Specific Aim 2: We will conduct follow-up studies of genes associated with FMD, including studies of RNA expression in FMD and control arterial tissues and replication experiments in additional, independent samples. Specific Aim 3: Using functional laboratory approaches, we will test the cellular and arterial function of identified genes and variants relevant for arterial remodeling and dysplasia. The analyses and experiments proposed in these Specific Aims will allow us to systematically uncover causal DNA variants underlying FMD and to expand our knowledge of molecular defects driving arterial dysplasia.
Role: Co-I (UM Ref#: AWD004639)
Overlap: none

Project Title: Genetic Mechanisms of Neurofibromatosis-related Arteriopathy and Renovascular Hypertension
Time Commitments: 0.60 CM
Supporting Agency: Department of Defense (DoD)
Grants Officer & Contact Information: Jason Kuhns, Contracting Officer, Jason.d.kuhns.civ@mail.mil
Performance Period: 04/01/2020 – 03/31/2023
Level of Funding/Total Award:
Goals/Specific Aims: The major goals are to: Specific Aim 1: Characterize spectrum of mutations in the NF1 gene and other genes that may contribute to arterial disease in NF-1 using a whole exome sequencing approach integrated with RNASeq to identify mutations that alter proper RNA expression. Specific Aim 2: Sequence DNA from arterial tissue, to determine whether mutations have occurred in the tissue itself, which could contribute to abnormal growth of the artery or AD. We will look in patients with known NF-1 to see if there is additional loss of genes in the arterial tissue and cells, and we will look in patients without a diagnosis of NF-1 but who may have a loss of NF-1 expression or function due to somatic mutation arising in the arterial tissue itself.
Role: Co-I (UM Ref#: AWD014756)
Overlap: none

Project Title: Assessment of GORE EXCLUDER Conformable AAA Endoprosthesis in the Treatment of Abdominal Aortic Aneurysms
Time Commitments: 0.12 CM
Supporting Agency: W.L. Gore & Associates
Grants Officer & Contact Information: Clinical Contracts Administration c/o Kyle Lathrop,
Performance Period: 02/21/2017 – 12/31/2022
Level of Funding/Total Award:
Goals/Specific Aims: Evaluate the safety and effectiveness of the GORE EXCLUDER conformable AAA endoprosthesis in the treatment of abdominal aortic aneurysm specifically those with high neck angulation. **Role:** Co-I (UM Ref#: AWD002895)
Overlap: none

Project Title: The Natural History and Genetics of Renal Artery Aneurysm Through a Prospective Multi-Institutional Registry
Time Commitments: 0.12 CM
Supporting Agency: Society for Vascular Surgery
Grants Officer & Contact Information: Raul Guzman, Chair, Clinical Research Committee; Sarah Murphy, Dir. Of Research, smurphy@vascularsociety.org;
Performance Period: 07/01/2017 - 06/30/2021
Level of Funding/Total Award:
Goals/Specific Aims: The major goals of this project are: 1. Determine the natural history of renal artery aneurysm through a multi-institutional prospective registry by phenotype emphasizing young women with underlying fibromuscular dysplasia (FMD) that may benefit from tailored screening, surveillance and even treatment indications and 2. Expand a genetic biobank for patients with renal artery aneurysm for further sequencing efforts that are already in place at the University of Michigan.
Role: PI (UM Ref#: AWD005957)
Overlap: none

Project Title: Predicting the Safety and Effectiveness of Inferior Vena Cava filters (PRESERVE)
Time Commitments: 0.12 CM
Supporting Agency: IVC Filter Study Group Foundation to New England Research Institute (NERI)
Grants Officer & Contact Information: Julie Miller, VP Research Operations or Flora Sandra Siami, VP Clinical & Reg. Affairs; ssiami@neriscience.com; (fax)
Performance Period: 02/18/2016 - 09/30/2021

Level of Funding/Total Award:
Goals/Specific Aims: Evaluate the safety and effectiveness of participating inferior vena cava filters in subjects with clinical need for mechanical prophylaxis of PE.
Role: PI (UM Ref# AWD002622)
Overlap: none

Project Title: Pediatric Renovascular Hypertension: A pRVH PCOR Collaborative
Time Commitments: 0.6 CM
Supporting Agency: Patient-Centered Outcomes Res. Inst. (PCORI)
Grants Officer & Contact Information: Laura Lyman Rodriguez, Interim Chief Program Support Officer (Signing Authority); tbn, Director of Engagement Awards, fundedea@pcori.org
Performance Period: 12/01/2020 – 11/30/2022
Level of Funding/Total Award:
Goals/Specific Aims: The goals of this project are: 1) Create a pRVH PCOR collaborative; 2) Prioritize PCOR and comparative effectiveness research around critical diagnostic and tretament decisions; 3) Conduct a pRVH symposium in 2022.
Role: PI/Project Lead (UM Ref#: AWD016910)
Overlap: none

OTHER SUPPORT

Kitzman, Jacob O.

Changes since Last RPPR:
W81XWH-20-1-0213 began 04/01/2020
SubK to Brigham & Women's Hospital began 08/01/2020
R01 HL148565 01S1 began on 08/05/2020
R01 GM024872 43 began on 09/01/2020 CRFF-2018-005 ended on 01/31/2021
R01 GM118647 ended on 08/31/2020

CURRENT SUPPORT

Title: Massively parallel experimental measurement of variant functional impacts
Time commitment: 3.0 CM
Supporting Agency: NIH R01-GM129123
Grants Contact: Veerasamy Ravichandran, veerasamy.ravichandra@nih.gov
Performance Period: 8/6/2018-5/31/2023
Level of Funding:
Brief description of project goal/specific plan: Variants of uncertain significance are a barrier to the actionability and utility of genetic testing. This proposal aims to develop methodologies for functional studies of human genetic variants in a high-throughput fashion, to support the prospective classification of risk alleles before they are observed in patients.
Role: PI
Project overlap with other existing/pending projects: None

Title: Role of histone ubiquitination in neurodevelopment and disease
Time commitment: 0.6 CM
Supporting Agency: NIH R01-NS101597
Grants Contact: Robert Riddle, riddler@ninds.nih.gov
Performance Period: 12/15/17-11/30/2022
Level of Funding:

Brief description of project goal/specific aim: The goals are to establish the epigenetic underpinning of cortical development, identify generalizable paradigms for how the fate of cortical neurons is established in NPCs and deregulation leads to ASD pathology.
Role: Co-Investigator (PI: Stephanie Bielas)
Project overlap with other existing/pending projects: None

Title: Genetic and Genomic Analysis of Arterial Dysplasia
Time commitment: 0.6 CM
Supporting Agency: NIH R01-HL139672
Grants contact: Youngsuk Oh, yoh@mail.nih.gov,
Performance Period: 1/1/2018-12/31/2021
Level of Funding:
Brief description of project goal/specific aim: To determine that this spectrum of FMD implicates a limited number of genes and pathways, and a combined analysis of many cases, covering familial, sporadic, pediatric and adult cases, using both genetic and gene expression data, is the best way to uncover recurrently affected genes or convergent pathways.
Role: Co-Investigator (PI: Santhi Ganesh)
Project overlap with other existing/pending projects: None

Title: Context-specific and Combinatorial Genetic Regulatory Grammars in Diabetes
Time commitment: 0.6 CM
Supporting Agency: NIH R01-DK117960
Grants Contact: Olivier Blondel, blondelol@niddk.nih.gov
Performance Period: 9/1/2018 – 6/30/2023
Level of Funding:
Brief description of project goal/specific aim: This project aims to uncover contributions of regulatory variation to the genetic risk for type 2 diabetes (T2D). My group is contributing to this study by assisting with genetic knock-out and knock-in models of selected T2D enhancers.
Role: Co-Investigator (PI: Stephen Parker)
Project overlap with other existing/pending projects: None

Title: Molecular and evolutionary mechanisms of poxviral cross-species transmission
Time commitment: 0.6 CM
Supporting Agency: NIH R21-AI135257-A1
Grants Contact: Ramya Natarajan, natarajanr@mail.nih.gov
Level of Funding: (subcontract to UC Davis)
Performance Period: 01/22/2019-12/30/2020
Brief description of project goal/specific plan: Animal poxviruses pose a threat to human health, yet we know very little about how these viruses may adapt to productively infect humans. This project will **I)** determine how distinct mutations in the catalytic subunit of the poxviral RNA polymerase inhibit different host immune proteins, and **II)** define how gene amplification impacts the ability of poxviruses to infect new species.
Role: MPI with Dr. Greg Brennan, UC-Davis
Project overlap with other existing/pending projects: None

Title: Clonal Hematopoesis in the Women's Health Initiative
Time commitment: 0.9 CM
Supporting Agency: NIH R01-HL148565
Grants Contact: N/A
Performance Period: 7/15/19-05/31/2023
Level of Funding: (Subcontract to Fred Hutchinson)
Brief description of project goal/specific aim: Clonal hematopoiesis is a common, age-related condition in which hematopoietic stem cells in the bone marrow undergo somatic mutations that lead to overgrowth (?clones?) of a genetically distinct subpopulation of blood cells. We will use deep sequencing and somatic mutation detection

measure clonal hematopoiesis of indeterminate potential (CHIP), in a diverse lognitudinal cohort provided by the Women's Health Initiative.
Role: Co- Investigator (MPI: Alex Reiner and Eric Whitsel)
Project overlap with other existing/pending projects: None

Title: Clonal Hematopoesis in the Women's Health Initiative
Time commitment: 0.24 CM
Supporting Agency: NIH R01-HL148565
Grants Contact: N/A
Performance Period: 08/05/2020 - 05/31/2021
Level of Funding: (Supplement)
Brief description of project goal/specific aim: Clonal hematopoiesis is a common, age-related condition in which hematopoietic stem cells in the bone marrow undergo somatic mutations that lead to overgrowth (?clones?) of a genetically distinct subpopulation of blood cells. We will use deep sequencing and somatic mutation detection measure clonal hematopoiesis of indeterminate potential (CHIP), in a diverse lognitudinal cohort provided by the Women's Health Initiative.
Role: Co- Investigator (Prime) Fred Hutch (Direct) (PI Reiner)
Project overlap with other existing/pending projects: None

Title: Using genetics to discover mechanisms of myocardial infarction – HUNTing renewal resub
Time commitment: 0.6 CM
Supporting Agency: NIH R01-HL10994606-A1
Grants Contact: Shelia Ortiz; ortizs@nhlbi.gov
Performance Period: 9/1/2019 – 7/31/2023
Level of Funding:
Brief description of project goal/specific aim: This renewal aims to identify significant genetic factors underlying variation in blood lipid levels, and their causal relationship to heart disease. My part of this collaboration is to apply targeted sequencing (MIPS) to profile rare variants in previously implicated risk genes.
Role: Co- Investigator (PI: Eugene Chen)
Project overlap with other existing/pending projects: None

Title: Genetic Mechanisms of Neurofibromatosis-related Arteriopathy and Renovascular Hypertension
Time Commitments: 0.3 CM
Supporting Agency: DOD
Grants Contact: Jason Kuhns Jason.d.kuhns.civ@mail.mil
Performance Period: 4/01/2020-3/31/2023
Level of Funding/Total Award:
Goals/Specific Aims: The major goals are to: Specific Aim 1: Characterize spectrum of mutations in the NF1 gene and other genes that may contribute to arterial disease in NF-1 using a whole exome sequencing approach integrated with RNASeq to identify mutations that alter proper RNA expression. Specific Aim 2: Sequence DNA from arterial tissue, to determine whether mutations have occurred in the tissue itself, which could contribute to abnormal growth of the artery or AD. We will look in patients with known NF-1 to see if there is additional loss of genes in the arterial tissue and cells, and we will look in patients without a diagnosis of NF-1 but who may have a loss of NF-1 expression or function due to somatic mutation arising in the arterial tissue itself.
Role: Co-I
Overlap: None

Title: Clonal Hematopoesis-associated Somatic Mutation and COVID-19 Clinical Outcomes
Time Commitments: 0.3 CM
Supporting Agency: Brigham and Women's Hospital
Grants Contact: N/A
Performance Period: 08/01/2020 - 07/31/2021
Level of Funding/Total Award:

Goals/Specific Aims: This subcontract is to support a collaboration examining whether somatic mutations associated with CHIP (clonal hematopoesis of indeterminate potential) may contribute to the clinical course of SARS-CoV-2 infection.
Role: Co-I
Overlap: None

Title: Gene Interaction in Development and Disease
Time Commitments: 0.6 CM
Supporting Agency: NIH/NIGMS
Grants Contact:
Performance Period: 09/01/2020 - 07/31/2024
Level of Funding/Total Award:
Goals/Specific Aims: This project is focused on characterization of genes involved in lysosome regulation that interact with the PI(3,5)P2 biosynthesis pathway. We will functionally characterize a set of genes that were identified during the current funding period by genome-wide screens in cultured cells. We will also carry out a drug screen for compounds that reverse the enlarged vacuoles in FIG4 and VAC14 deficient cells.
Role: Co-I
Overlap: None