

AWARD NUMBER: W81XWH-17-1-0662

TITLE: Targeting Histone Deacetylase in Focal Segmental Glomerulosclerosis- From Mice to Patients

PRINCIPAL INVESTIGATORS: Shuta Ishibe

CONTRACTING ORGANIZATION: Yale University, New Haven, CT

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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1. REPORT DATE October 2020		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2019-29Sep2020	
4. TITLE AND SUBTITLE Targeting Histone Deacetylase in Focal Segmental Glomerulosclerosis- From Mice to Patients				5a. CONTRACT NUMBER W81XWH-17-1-0662	
				5b. GRANT NUMBER 0011018130-0001	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Shuta Ishibe, Francis P. Wilson shuta.ishibe@yale.edu , francis.p.wilson@yale.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Yale University Office of Sponsored Projects P.O. Box 1873 New Haven, CT 06508-1873				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel 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 Glomerular diseases account for approximately 80% of end stage kidney disease (ESKD). Nearly 600,000 US residents have end-stage kidney disease (ESKD) at an annual Medicare expenditure of 28 billion dollars. Through RNA profiling in our models of FSGS, we have found that HDAC activity is increased in the glomerulus and blocking with HDAC inhibitor, valproic acid or suberanilohydroxamic acid mitigates progression of kidney disease. During the last funding period, we have generated podocyte specific knockout mice for HDAC1 and 2, which also appears protective against glomerular injury in toxin mediated and genetic mouse models. In parallel, the co-PI of this study, F. Perry Wilson has continued to examine the Veterans Affairs Cohort and added multiple other cohorts to examine the stability of preliminary results that suggested a protective role of VPA in proteinuric kidney disease.					
15. SUBJECT TERMS Proteinuria, Chronic kidney disease, focal segmental glomerulosclerosis, nephrotic syndrome, Veterans Affairs, Valproic acid, Valproic Acid, Longitudinal					
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	13	19b. TELEPHONE NUMBER (include area code)

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Introduction

The fundamental goal of this proposal is to integrate cellular, animal models, and human databases to examine how inhibition of histone deacetylase (HDAC) activity may alter progression of proteinuric kidney disease through the Co-PI, Francis Perry Wilson, at Yale School of Medicine. We are examining the role of different HDAC inhibitor, namely suberanilohydroxamic acid (SAHA), a FDA approved drug for Cutaneous T-Cell Lymphoma, in our mouse models of focal segmental glomerulosclerosis (FSGS). Further aims were to focus on genetically deleting HDAC specifically in the podocytes to determine whether podocyte specific HDAC activation is what is responsible to drive disease progression in FSGS and to identify and characterize novel pathways downstream of HDAC. The other major focus of this grant is to determine the impact of valproic acid (VPA) exposure on the incidence and progression of CKD in humans by using several large national databases.

During the last funding period, we have examined how HDAC inhibition shows great promise for inhibiting progression of mice proteinuric disease. We had successfully generated and phenotyped a podocyte specific HDAC 1 and 2 knockout mouse and retrospective cohort data on VA patients with proteinuria receiving valproic acid had reduced loss of kidney function which was most profound in the patients with proteinuria. These findings were published in *The Journal of Clinical Investigation*, Inoue et al. in March 2019 in a collaborative work from both our groups.

Keywords

Focal segmental glomerulosclerosis, proteinuria, chronic kidney disease, end stage kidney disease, histone deacetylase inhibitor, valproic acid

Accomplishments

What are the major goals of the project?

1. Elucidate HDAC1 and 2's role in proteinuric kidney disease following podocyte injury by performing hypothesis driven experiments, which investigate the likely site of action of VPA in the kidney **80% complete**
2. Determine the critical pathways regulated by the HDAC1 and 2. **80% complete**
3. Assess not only if such an effect of VPA treatment is observed in FSGS patients but also if these findings extend beyond this disease by examining its effects on other causes of nephrotic syndrome such as diabetic nephropathy examining the VA cohort study, Veterans Aging Birth Cohort, and Geisinger **80% complete**

What was accomplished under these goals?

During the past year, we have examined the downstream mechanism after revealing the salutary effects of VPA in mitigating the progression of proteinuric kidney disease in the Pod-rtTA *Tln1* KO mice. In the last update we had performed RNA profiling revealing increased *EGR1* expression in the glomeruli isolated from the Pod-rtTA *Tln1* KO mice upon development of proteinuria which was reduced following VPA treatment. Although we have performed a microarray on the entire glomeruli from *Tln1^{fl/fl}* Pod-rtTA TetO-Cre mice, and identified *Egr1* as a potential candidate, simultaneous knockout of this gene with *Tln1^{fl/fl}* Pod-rtTA TetO-Cre mice resulted in a partial rescue of the phenotype suggesting that other genes may also play a critical role. Previous studies have suggested that mRNA profile of the entire glomerulus in mouse models do not always reflect those observed in isolated podocytes (1). Therefore, we will now examine differentially expressed genes directly reflected at the level of the podocytes and compare this in the *Tln1^{fl/fl}* *Hdac*, *Hdac2^{fl/fl}* Pod-rtTA TetO-Cre mice and *Tln1^{fl/fl}* Pod-rtTA TetO-Cre mice treated with VPA. We have shown that reduction of HDAC1 and HDAC2 activity resulted in a striking improvement in proteinuria,

kidney failure and podocyte loss. Leveraging use of TRAP technology to isolate podocyte specific RNA in vivo will allow us to attain a highly selective, cell-specific in vivo transcriptomic evaluation, to isolate purely podocytes to perform RNA-Seq (2,3) We have pursued this unbiased method so as to elucidate novel, in vivo mechanisms of podocyte loss in our animal model. In this method, the L10a ribosomal protein is fused with eGFP and inserted into the ROSA26 locus with a flox-STOP cassette (R26 Rpl10a-, JAX #024750). When Cre is activated, it deletes both *Tln1* and flox STOP cassette, allowing expression of L10a-eGFP. Anti-GFP pulldown purifies ribosomes that have incorporated L10a-eGFP and with them, the actively translating mRNA from only Cre -active cells. We currently have developed the *Tln1^{fl/fl} Hdac1, Hdac2^{fl/fl} Pod-rtTA TetO-Cre* L10a-eGFP and *Tln1^{fl/fl} Hdac1, Hdac2^{fl/fl} Pod-rtTA TetO-Cre* L10a-eGFP mice, which display perinuclear expression of GFP in the podocytes (Figure 1).

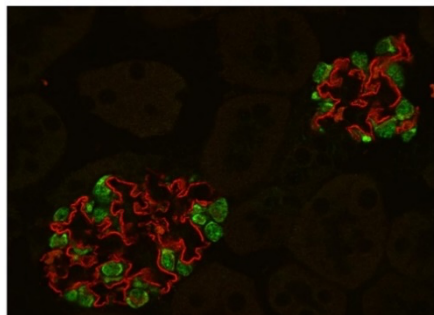


Figure 1 Immunofluorescence of *Tln1^{fl/fl} Pod-rtTA TetO-Cre* L10a-eGFP with nephrin (1) and GFP(green)

In the previous report in 2019, we showed the importance of EGR1 in-vivo, downstream of HDAC1 and 2 activation through the generation of the *Egr1^{-/-} Tln1^{fl/fl} Pod-rtTA TetO-Cre* mice which reduced albuminuria, kidney failure, glomerulosclerosis, and interstitial fibrosis, (data not shown as published), similar to what was observed following VPA treatment.

We have also determined that EGR1 has been highly expressed in podocytes in mouse models of FSGS which is mitigated following treatment with VPA. Next, we asked whether there was a EGR1 expression patterns were also association in human glomerular diseases by interrogating the Nephroseq v5 database. We observed that EGR1 expression in micro dissected glomeruli obtained from patients with FSGS and diabetic kidney disease

(DKD) positively correlated with increasing serum creatinine (Figure 2A and Figure 2B). Moreover, preliminary data from 4 DM patients' kidney biopsy samples appeared to corroborate increased EGR1 expression in the podocytes, colocalizing with WT1, a podocyte specific marker, when compared to control samples from normal kidney sections from post nephrectomy renal cell carcinoma patients (Figure 2C and quantified in Figure 2D). Thus, further clarification and validation as to whether EGR1 expression would be suppressed in VPA treated proteinuric patients is of extreme interest.

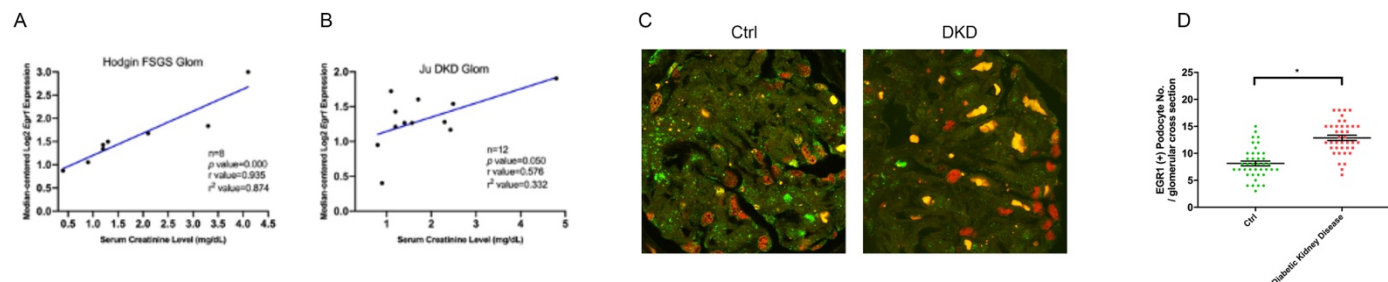


Figure 2 EGR1 expression is positively correlated with biochemical evidence of kidney failure measured by serum creatinine in A) FSGS and B) DKD, p value as noted. C) Representative image of glomeruli stained with WT1 (1) and EGR1 (Green) in healthy control and DKD patient kidney section. D) Quantification of C, *p<0.05, n=4

Human Cohort Studies using VA Cohort Study and Veterans Birth Cohort

Results from the Veterans Birth Cohort

We further examined the incidence of CKD and the progression of CKD using time-varying Cox proportional hazards modeling in two Veterans Affairs datasets – VACS (as discussed above) and the Veterans Birth Cohort which comprises data on all veterans born between 1945 and 1965 in the VA system (4) We first defined a

time-varying propensity score predicting the probability of an individual receiving VPA based on a variety of characteristics including comorbidities such as depression, bipolar disorder, post-traumatic stress disorder (PTSD), and seizure disorder as well as demographic and laboratory information. We then used a 2:1 propensity-matched approach (identifying individuals with similar time in the cohort who had not received VPA to those who initiated VPA) to analyze the effect of VPA use independent of these factors, mimicking what might be found in a randomized trial of VPA in a Veterans population. We found similar results in our two cohorts, the smaller Veterans Aging Cohort Study (VACS, N=122,870) and the larger Veterans Birth Cohort (N=206,616). Of note, the rate of progression to dialysis and end-stage kidney disease was reduced by approximately 30% among those receiving VPA compared to propensity-matched controls (Figure 3).

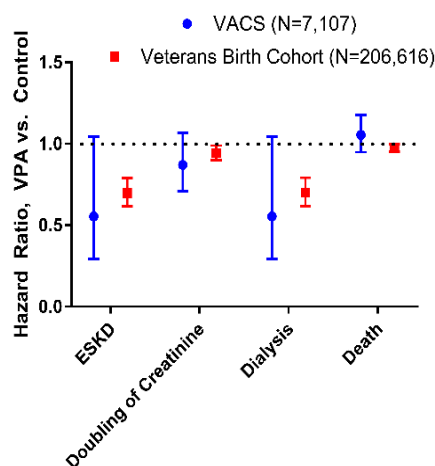


Figure 3: VPA usage associates with a delay to ESKD and dialysis Hazard ratios for clinically important outcomes among VPA-exposed versus non-exposed individuals in two VA cohorts.

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

Dr. Kazunori Inoue, who conducted research on this project is now an Assistant Professor at Osaka University School of Medicine, Japan. He was selected to present these findings at a Japan Society of Nephrology Young Investigator Symposium in August 2019.

Elizabeth Cross conducted research on this project from her NIH funded summer fellowship, and now matriculated Medical School as of August 2019.

How were the results disseminated to communities of interest?

Results from this project has been published in the Journal of Clinical Investigation. An accompanying editorial was published in Kidney International. An invited American Society of Nephrology lecture on Oct 22, 2020 on this topic in the session Preserving the Tuft: New Concepts in Glomerular Disease Therapeutics. The titles of the talk/abstracts/oral presentation and manuscript are included in Section 6. Data were also presented in Nephrology Renal conferences at Yale and Veterans Affairs research in progress conferences. The HDAC 1 and 2 floxed mice were distributed to Jianning Tao PhD, at the University of South Dakota following completion of a MTA

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

We have performed IF analyses of podocytes co-stained for nephrin and TRAP (by eGFP) specificities to confirm the fidelity of simultaneous transgene expression (Figure 7). Next, podocyte-specific RNA will be isolated by TRAP technology. Briefly, the *Pod-rtTA TetO-Cre L10a-eGFP* and *Tln1^{fl/fl} Pod-rtTA TetO-Cre L10a-eGFP +/- valproic acid* (administered for 3 weeks after completion of doxycycline), *Tln1^{fl/fl} Hdac1, Hdac2^{fl/fl} Pod-rtTA TetO-Cre L10a-eGFP* mice, 3 weeks after the completion of doxycycline induction, will be perfused with cold PBS through the left ventricle. Kidneys will be immediately harvested and homogenized. Immunoprecipitation for streptavidin using Dynabeads (Invitrogen) will purify for the podocyte specific ribosomes. RNA purification will be performed by using the standard Qiagen RNeasy MinElute protocol. RNA quantification and quality control will be analyzed using Agilent Bioanalyzer 2100 using RNA pico chip. Library construction and sequencing will be performed by the Yale Center for Genome Analysis Facility. Briefly, library construction will be carried out using Illumina Truseq RNA sample Prep kit v2 through poly A selection. Manufacturer's instructions will be followed. The library will be quantified using both Bioanalyzer (as above) and the Kapa Biosystems Library Quantification kit. Libraries will be applied to an Illumina flow cell and run on the Illumina HiSeq 4000 using single-end 100bp reads. Illumina's

pipeline software package will be utilized for analysis using Firecrest for image analysis, Bustard for base calling and Gerald for sequence analysis. Fastq files will be provided by Core facility and input into the RNA-seq analysis pipeline on the Yale High Performance Computing cluster in collaboration with Dr. Hongyu Zhao. Briefly, data will be aligned to the mouse genome via Bowtie2. Data will be quantified to an annotation model by RNA-Seq by Expectation-Maximization (RSEM), low quality and low count data will be filtered out and normalized gene counts will be determined using Bioconductor package EdgeR. Benjamini–Hochberg procedure will be used for multiple test adjustment and $FDR < 0.05$ will be used as the statistical significance threshold. No fold-change threshold will be applied. We will generate output files with fold changes (in log 2 scale), p-values, and gene- and transcript-related attributes. As part of this bioinformatics pipeline, a heat map, volcano plot, hierarchical clustering, gene ontology annotations and KEGG pathway analysis will also be performed. Quality control will be performed at each step in this bioinformatic pathway. To further validate the pathways altered in our gene set, we will utilize two software: Ingenuity Pathway Analysis (IPA) by Qiagen and Transfac by Gene Xplain. These softwares are available to the Yale community through a university license. IPA software will be utilized to perform data interpretation by pathway analysis. Transfac allows for the entry of RNA-seq data to identify upstream transcription factors that regulate your data set and downstream transcription factors that may be enriched in the data set. We make extensive use of animal models with multiple combined alleles. Unless otherwise noted, all strains have been backcrossed onto the C57BL/6 congenic background and male and female mice are used in equal numbers.

With regard to our pharmacoepidemiologic studies, we will validate the above results in the Veterans Birth Cohort with data from the Geisinger Health System, which, as it is not a VA site, has more representation of women. Additionally, there is a lower burden of PTSD (a potential confounding variable in our analyses) in this cohort. We also have begun to design a phase 1/2 trial to prospectively assess the effect of valproic acid on patients with proteinuric kidney disease, although this effort will not be supported by the current grant.

4. Impact: Describe distinctive contributions, major accomplishments, innovations, successes or any change in practice or behavior that has come about as a result of the project relative to:

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

This project has potential to make impact in the therapy of FSGS and proteinuric diseases, which often progress to ESKD where there is a current lack of treatment short of blocking angiotensin. We have not only shown the effectiveness of HDAC inhibitors in mouse glomerular diseases but also retrospectively in humans with proteinuric diseases, this motivates further studies examining whether this class of drug can be tested prospectively in humans with FSGS suggesting of repurposing of a drug for broader use and have now applied for grant support to initiate a phase 1 and phase 2 trial.

What was the impact on technology transfer?

These findings have the possibility to qualify for use patents for proteinuric patients with FSGS and glomerular diseases as an adjuvant therapy.

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report

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

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report"

Publications, conference papers, and presentations

Journal Publications.

Podocyte histone deacetylase activity regulates murine and human glomerular diseases
Kazunori Inoue,¹ Geliang Gan,² Maria Ciarleglio,² Yan Zhang,^{4,5,6} Xuefei Tian,¹ Christopher E. Pedigo,¹ Corey Cavanaugh,^{1,3} Janet Tate,³ Ying Wang,¹ Elizabeth Cross,¹ Marwin Groener,¹ Nathan Chai,¹ Zhen Wang,¹ Amy Justice,^{1,7} Zhenhai Zhang,^{4,5,6} Chirag R. Parikh,^{1,3} Francis P. Wilson,^{1,3} and Shuta Ishibe,¹
Journal of Clinical Investigation. 2019, 129:1295-1313. Federal Support Acknowledged.

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

Nothing to report.

Other publications, conference papers, and presentations

American Society of Nephrology- 2018 abstract for oral presentation
The role of HDAC activation in proteinuric kidney disease progression in Mice and Humans
Kazunori Inoue, Chirag E. Parikh, Francis P. Wilson, and Shuta Ishibe

Japan Society of Nephrology Young Investigator Symposium 2019 for Kazunori Inoue

Invited Lecture during the 2020 Virtual American Society of Nephrology Revisited Meeting live streamed titled "Targeting Podocyte Histone Deacetylases.- Shuta Ishibe

Website(s) or other Internet site(s)

We have published the following website to allow the public to keep track of papers, presentations, and new data that has resulted from this study:

<https://medicine.yale.edu/intmed/ctra/projects/deacetylase/>

Technologies or techniques

We developed and validated an operation definition of proteinuria based on clinically-collected urinalysis results within a large VA cohort. This is notable in that the values are inconsistently coded across various VA centers. We have shared this code with the VACS executive committee and will make it available to anyone who wishes to assess for clinically-detected proteinuria in a Veterans Affairs dataset.

Inventions, patent applications, and/or licenses

A provisional patent application, Composition and Method for Treating Kidney Disease has been accorded U.S. Application Serial No. 62/717,024 for use of HDAC inhibitors for treatment of kidney disease has been filed by Drs'. Kazunori Inoue, Shuta Ishibe, Chirag Parikh, and Francis Perry Wilson.

Other products

Nothing to report.

7. PARTICIPANTS and OTHER COLLABORATING ORGANIZATIONS

Name:	Ishibe, Shuta
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest Person Month Worked:	3.6
Contribution to Project:	Overall supervisory responsibility for the Yale site providing oversight of the project progress for the basic science arm of the grant along with collaboration with Dr. Francis Perry Wilson, who directs the clinical arm of the grant. Reviewing results, experimental design and quality control weekly and discussion of results on toxin and mouse models of glomerular disease
Funding Support:	

Name:	Anupama Priyadarshini
Project Role:	Post doctoral associate
Researcher Identifier (e.g. ORCID ID):	
Nearest Person Month Worked:	3
Contribution to Project:	Performs experiments in-vitro (podocyte cell culture) and in-vivo (mice) examining HDAC activation in glomerular disease.
Funding Support:	

Name:	Geliang Gan
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest Person Month Worked:	6

Contribution to Project:	Longitudinal analysis of cohort data
Funding Support:	

Name:	Maria Ciarleglio
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest Person Month Worked:	3
Contribution to Project:	Longitudinal analysis of cohort data
Funding Support:	

Name:	Morgan Grams
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest Person Month Worked:	1
Contribution to Project:	Study design / implementation at Geisinger
Funding Support:	

Name:	Alex Chang
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	

Nearest Person Month Worked:	1
Contribution to Project:	Study design / implementation at Geisinger
Funding Support:	

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

Updated Other Support Pages are included in Appendix 1.

What other organizations were involved as partners?

Geisinger Health in Danville, PA is collaborating on this project by evaluating their clinical database to validate the findings from VACS and the Veterans Birth Cohort.

This is a COLLABORATIVE AWARD. Our collaboration partner is Dr. Francis Perry Wilson. Details are below:

Organization Name: Yale School of Medicine

Location of Organization: New Haven, CT, USA.

Partner's contribution to the project clinical arm of the grant

Financial support: None

In-kind support: Analysis of human cohorts

Facilities: None

Collaboration: Examines the role of valproic acid in large cohorts of patients with kidney disease and proteinuria

Personnel exchanges: None

Other: None

8. SPECIAL REPORTING REQUIREMENTS

This is a COLLABORATIVE AWARD. This represents a joint report from the Initiating PI (Shuta Ishibe) and collaborating PI (F. Perry Wilson). The reports are therefore very similar. Throughout the report, the responsible PI is shown.

9. APPENDICES

Appendix 1: Shuta Ishibe Updated Other Support Pages

2R01 DK083294-08 (PI: Ishibe) 07/01/2015 – 06/30/2020 3.60 calendar months
NIH/NIDDK
Role of Calpain in Podocyte Injury
The major focus of this grant is to investigate the role of focal adhesion proteins and the activation of calpain induced ER stress.
Overlap-None

No Cost extension

R25-DK101408-01 (PI: Ishibe) 04/01/2019 – 03/31/2024 0.3 calendar months
NIH/NIDDK
KUH Undergraduate Summer Research Program at Yale University
The major goal of this grant is to provide undergraduate students an opportunity to perform kidney, urology, and hematology research during the summer months.

Overlap-None

2R01 DK093629-05A1 (PI: Ishibe) 09/01/2017 – 08/31/2022 2.40 calendar months
NIH/NIDDK
Role of Clathrin Mediated Endocytosis in Podocyte
The major goal of this grant is to examine the role of endocytic process in podocyte biology.

Overlap-None

Appendix 2: F. Perry Wilson Updated Other Support Pages

R01 DK113191-01A1
WILSON, FRANCIS PERRY (PI)
02/01/18-01/31/23
Optimizing Electronic Alerts for Acute Kidney Injury
Role: PI

Overlap: None

K23 DK097201-06
WILSON, FRANCIS PERRY (PI)
07/15/13-04/30/20
Mediators & prognostic value of muscle mass & function in chronic kidney disease
Role: PI

Overlap: None

2P30DK079310-11, NIH/NIDDK
WILSON, FRANCIS PERRY (PI)
08/01/18-07/31/23
George M. O'Brien Kidney Center at Yale
This Kidney Center provides an administrative core and three research cores whose specific objectives are to provide small animal physiology services to allow detailed characterization of renal function at the level of the tubule, the kidney, and the intact organism; provide mouse genetics and cell line services to develop new animal models and kidney cell lines to elucidate the molecular mechanisms underlying the pathophysiology of kidney diseases; and provide human genetics and clinical research services to apply genetic and genomic

technologies to the study of human kidney diseases. There is also a pilot and feasibility program of small grants

Role: Co-Investigator

Overlap: None

1UG3DK114866-01 , John Hopkins University

Parikh (PI)

07/01/18-06/30/20

AKI Matched Phenotype Linked Evaluation with Tissue (AMPLE-Tissue)

The major goal is to obtain biopsies from 90-100 participants and closely monitor patient safety.

Role: Co-Investigator

Overlap: None

Bibilography

1. Fu J, Wei C, Lee K, Zhang W, He W, Chuang P, et al. Comparison of Glomerular and Podocyte mRNA Profiles in Streptozotocin-Induced Diabetes. *J Am Soc Nephrol*. 2016;27(4):1006-14.
2. Liu J, Krautzberger AM, Sui SH, Hofmann OM, Chen Y, Baetscher M, et al. Cell-specific translational profiling in acute kidney injury. *J Clin Invest*. 2014;124(3):1242-54.
3. Grgic I, Krautzberger AM, Hofmeister A, Lalli M, DiRocco DP, Fleig SV, et al. Translational profiles of medullary myofibroblasts during kidney fibrosis. *J Am Soc Nephrol*. 2014;25(9):1979-90.
4. Njei B, Esserman D, Krishnan S, Ohl M, Tate JP, Hauser RG, et al. Regional and Rural-Urban Differences in the Use of Direct-acting Antiviral Agents for Hepatitis C Virus: The Veteran Birth Cohort. *Med Care*. 2019;57(4):279-85.