FVSP Faculty Application Checklist-DUE 1/19/2024 5PM EST

X Completed cover page with prior mentorship history

X Training/Registration requirements needed

X Abstract of proposed work

X NIH-format biosketch

Submission Instructions

Convert the application to ***one .pdf document.*** Name the file using your last name, followed by an underscore, and your first initial. For example: Martyniuk_C.pdf

Submit the following pages, via email attachment, to Dr. Chris Martyniuk (cmartyn@ufl.edu). The subject line should read "FVSP Faculty Application".

The FVSP Research Program runs 5/27/2024 to 8/07/2024 with final research presentations prior to the national symposium.

2024 Linda F. Hayward Florida Veterinary Scholars Program Faculty Application

Name	Chris Vulpe
Email address	cvulpe@ufl.edu
Proposed project title	Rodent Model of Chronic Kidney Disease of Unknown Etiology
Will you provide matching student stipend funding ($3250)?	yes
Source of project/research funding	NIOSH grant

Prior student research mentees (last 5 years, if applicable):

CLASS	STUDENT	PROJECT TITLE	STATUS
2025	Nirali Pathak	Optimizing CRISPR/Cas9 Gene Editing in Canine Cells for Pyruvate Dehydrogenase Kinase 4	in progress
2025	Sasha Spada O'Neill	CRISPR-Mediated Gene Editing in Canine Cells for Pyruvate Dehydrogenase Kinase 4 to Treat Dilated Cardiomyopathy	in progress
2025	Arielle Admonius	CRISPR Gene Editing in Feline Cells for Alstrom Syndrome Protein 1 Associated Hypertrophic Cardiomyopathy	in progress

If project qualifies for Morris Animal Foundation Student Scholarship Funding and you have identified a specific interested student, please provide their name and email address

LAST NAME	FIRST NAME	EMAIL ADDRESS

I agree to obtaining all necessary approvals (e.g. IACUC/IRB/EH&S/VHRRC – see below for specifics) to conduct the project with the student PRIOR to the commencement of the summer program, as well as submitting documentation of these approvals to the FVSP board by 5/11/2024

YES

I agree to assisting my student prepare for the summer program during the Spring semester, which will include preparation of a study outline, and training in relevant laboratory techniques

YES

I agree to plan for commencing the experiment/data collection by the beginning of the summer program (5/22/24)

YES

I agree to be available to the student throughout the summer to assist with the experiment/data collection, preparation of the manuscript and poster.

YES

	Needed (Yes/No)	Approval by 5/11/24 (Yes/No)?
IACUC Approval and Training	Yes	Yes
IRB Registration and Training	No	
Biological Agent Registration	No	
Biopath Registration	No	
Veterinary Hospital Research	No	
FERPA Training	No	
Biohazardous Waste Training	Yes	Yes
Laboratory Safety Training	Yes	Yes

Abstract of proposed student project (1 page limit. This should mirror the aims page of a grant and CLEARLY indicate the student's role.)

Development and Characterization of a Rodent Model of CKDu

Agricultural workers are subjected to a unique combination of occupational stressors that may impact health. Across the globe, there has been a growing realization of an increase in chronic kidney disease (CKD) and renal failure, primarily among agricultural workers in hot and humid climates, of unknown etiology (CKDu). Increased CKD in the US have been identified in agricultural communities in the South of the United States. In contrast to other forms of kidney disease, CKDu disproportionately affects young men (< 40 years of age) with little evidence of diabetes or hypertension, and current evidence indicates interstitial, as well as glomerular damage in the kidney. While epidemiological studies note an association with heat exposure and agricultural chemical use, and exposure to several common agricultural chemicals in animal models can result in kidney toxicity, the cause(s) of CKDu remain controversial. Importantly, no biomarkers have been identified, so far, which can predict the development of CKDu, detect pre-symptomatic CKDu, or assess disease severity. Previously, in NIOSH funded work, we assessed the impact of acute exposures to agricultural chemicals and/or heat on the development of kidney toxicity in a rat model. In this work, we will extend these efforts to assess the relationship between chronic and repeated heat stress and agricultural chemical exposure in the development of kidney disease in both human and animal studies. Our central hypothesis is that urinary, exosome based, biomarkers of CKDu (UEBs) could identify those individuals at most risk, enable pre- symptomatic intervention and prevent development of renal failure.

Relevant Aim from NIOSH grant

Aim: Characterize urinary exosome biomarkers (UEBs) of heat and agricultural chemical stressors. Hypothesis: Nephrotoxic agents affecting different parts of the kidney will produce distinct urinary exosomes with characteristic biomarkers. CKDu manifests with a unique renal tubulo-interstitial disease, and we will use our established rat model and well characterized renal toxicants to identify region-specific UEBs of glomerular injury, tubular necrosis, and interstitial nephritis confirmed by histopathology. We will subsequently evaluate these UEB in rats in response to acute and intermittent chronic exposure to agricultural chemicals and/or environmental stressors (heat, dehydration) for their capability to identify region specific renal damage associated with these stressors. We will compare region/stressor specific UEBs defined in this rat study to the human equivalent UEBs indicative of kidney disease in farmworkers to identify candidate stressors/region specific toxicity contributing to the renal effects in CKDu. We expect to identify UEBs indicative of acute and chronic toxicity associated with CKDu relevant stressors in years 1-3 which overlap with UEBs identified in farmworkers with acute and chronic renal disease.

FVSP student role: The student would work with Post-doctoral fellow and research scientist as part of the team working on the rat model of CKDu. The specific project would be dependent on the interests and skills of the student. The rat model requires survival surgery for temperature probe placement, gavage treatments, metabolic cage collection of urine samples, and collection of tissue samples for analysis. Urine samples will be processed for exosomes and biomarker discovery. The kidneys will be analyzed using histopathology in collaboration with Dr. John Roberts and AI based histopathology software.

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: Chris Vulpe

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

POSITION TITLE: Professor

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.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology	S.B.	09/1986	Biology
University of California, San Francisco	Ph.D.	06/1994	Biochemistry, Genetics
University of California, San Francisco	M.D.	06/1996	Medicine

A. Personal Statement

I am a molecular toxicologist with broad experience both in model systems and human studies. I have worked extensively in the development of genomic approaches to probe the effects of toxicants. I have both a medical and science background so I can bridge between the basic science and applied aspects of this proposal. I have coordinated several multi-PI proposals and have assembled a multi-disciplinary team with all of the requisite skills in animal studies, heat stress, pesticide exposure, and molecular assessment of tissue injury in order to carry out the work.

Ongoing and recently completed projects that I would like to highlight include

NIOSH
Vulpe (PI)
9/30/2019 - 8/31/2022
Heat and Pesticide stress in the kidney

Consumer Protection Safety Commission
Vulpe (PI)
9/13/2016 - 8/15/2020
NanoWIR2ES -NanoWire Intelligent Re-design and Recycling for Environmental Safety

NIEHS
Vulpe (PI)
CRISPR screens of population relevant genes governing toxicant resilience
12/01/21-11/30/26

1. Fuqua BK, Lu Y, Frazer DM, Darshan D, Wilkins SJ, Dunn L, Loguinov AV, Kogan SC, Matak P, Chen H, Dunaief JL, Vulpe CD, Anderson GJ. Severe Iron Metabolism Defects in Mice With Double Knockout of the Multicopper Ferroxidases Hephaestin and Ceruloplasmin. Cellular and Molecular Gastroenterology and Hepatology. 2018;6(4):405-27. doi: https://doi.org/10.1016/j.jcmgh.2018.06.006.
2. McLachlan S, Page KE, Lee SM, Loguinov A, Valore E, Hui ST, Jung G, Zhou J, Lusis AJ, Fuqua B, Ganz T, Nemeth E, Vulpe CD. Hamp1 mRNA and plasma hepcidin levels are influenced by sex and strain but do not predict tissue iron levels in inbred mice. Am J Physiol Gastrointest Liver Physiol.

2017;313(5):G511-G23. doi: 10.1152/ajpgi.00307.2016. PubMed PMID: 28798083; PubMed Central PMCID: PMCPMC5792216.
3. Silva RM, Xu J, Saiki C, Anderson DS, Franzi LM, Vulpe CD, Gilbert B, Van Winkle LS, Pinkerton KE. Short versus long silver nanowires: a comparison of in vivo pulmonary effects post instillation. Part Fibre Toxicol. 2014;11:52. doi: 10.1186/s12989-014-0052-6. PubMed PMID: 25292367; PubMed Central PMCID: PMCPMC4198797
4. North M, Shuga J, Fromowitz M, Loguinov A, Shannon K, Zhang L, Smith MT, Vulpe CD. Modulation of Ras signaling alters the toxicity of hydroquinone, a benzene metabolite and component of cigarette smoke. BMC Cancer. 2014;14(1):6. Epub 2014/01/07. doi: 10.1186/1471-2407-14-6. PubMed PMID: 24386979; PubMed Central PMCID: PMC3898384

B. Positions, Scientific Appointments, and Honors

1989-1994 Graduate student, Dr. Seymour Packman & Dr. Jane Gitschier, Univ. of California, San Francisco
1996-1998 Post-doctoral fellow, Dr. Jane Gitschier, University of California, San Francisco
1997-1998 Clinical Molecular Genetics Fellow, University of California, San Francisco.
1998-2004 Assistant Professor, Nutritional Sciences and Toxicology, University of California, Berkeley
2004-2012 Associate Professor, Nutritional Sciences and Toxicology, University of California, Berkeley
2010-2014 Associate Director of Toxicology, Berkeley Center for Green Chemistry
2012-2014 Professor, Nutritional Sciences and Toxicology, University of California, Berkeley
2015-present Professor, Physiological Sciences, University of Florida, Gainesville

C. Contributions to Science

A complete list of publications can be found at http://www.ncbi.nlm.nih.gov/sites/myncbi/1XmgXX3u2qmkO/bibliography/47990729/public/?sort=date&direction=ascending

Functional Toxicology

The number of manmade chemicals continues to grow yet we have a limited understand of the biological effects of the vast majority. Our group has pioneered the use of a functional approach to comprehensively assess and identify key genes, processes and pathways underlying the eukaryotic cellular response to chemical toxicity. Other genomic approaches do not functionally assess the role of each gene/protein/metabolite in response but only identify a correlation with environmental stressors. As such, these observations do not identify a causal link between exposure, gene/protein/metabolite level, and phenotypic outcome. In contrast, functional approaches directly identify the genes necessary for cellular survival in a toxicant exposure. We have used this approach to develop a better understand the mechanism of action of multiple chemical contaminants including arsenicals, benzene metabolites, TCE metabolites. Most recently we have developed similar approaches in mammalian cells using CRISPR based approaches.

Pallares RM, Faulkner D, An DD, Hebert S, Loguinov A, Proctor M, Villalobos JA, Bjornstad KA, Rosen CJ, Vulpe C, Abergel RJ. Genome-wide toxicogenomic study of the lanthanides sheds light on the selective toxicity mechanisms associated with critical materials. Proc Natl Acad Sci U S A. 2021;118(18). Epub 2021/04/28. doi: 10.1073/pnas.2025952118. PubMed PMID: 33903247; PubMed Central PMCID: PMCPMC8106350.

Russo M, Sobh A, Zhang P, Loguinov A, Tagmount A, Vulpe CD, Liu B. Functional Pathway Identification With CRISPR/Cas9 Genome-wide Gene Disruption in Human Dopaminergic Neuronal Cells Following Chronic Treatment With Dieldrin. Toxicol Sci. 2020;176(2):366-81. Epub 2020/05/19. doi: 10.1093/toxsci/kfaa071. PubMed PMID: 32421776.

Sobh A, Loguinov A, Yazici GN, Zeidan RS, Tagmount A, Hejazi NS, Hubbard AE, Zhang L, Vulpe CD. Functional Profiling Identifies Determinants of Arsenic Trioxide Cellular Toxicity. Toxicol Sci. 2019;169(1):108-21. doi: 10.1093/toxsci/kfz024. PubMed PMID: 30815697; PubMed Central PMCID: PMCPMC6484884.

De La Rosa VY, Asfaha J, Fasullo M, Loguinov A, Li P, Moore LE, Rothman N, Nakamura J, Swenberg J, Scelo G, Zhang L, Smith MT, Vulpe CD. High throughput functional genomics identifies modulators of TCE metabolite genotoxicity and candidate susceptibility genes. Toxicol Sci. 2017. doi: 10.1093/toxsci/kfx159. PubMed PMID: 28973557.

Ecotoxicogenomics

In order to implement the most advanced practices for ensuring water quality, rapid and accurate screens are necessary to identify water bodies and additionally the design and production of new chemicals for manufacturing or agriculture require effective methods to predict their environmental toxicity. We have been a leader in the utilization of genomic approaches to identify and understand the toxicity of xenobiotics in aquatic ecosystems.

Poynton HC, Varshavsky JR, Chang B, Cavigiolio G, Chan S, Holman PS, Loguinov AV, Bauer DJ, Komachi K, Theil EC, Perkins EJ, Hughes O, Vulpe CD. Daphnia magna ecotoxicogenomics provides mechanistic insights into metal toxicity. Environ Sci Technol. 2007;41(3):1044-50. Epub 2007/03/03. PubMed PMID: 17328222.

Poynton HC, Zuzow R, Loguinov AV, Perkins EJ, Vulpe CD. Gene expression profiling in Daphnia magna, part II: validation of a copper specific gene expression signature with effluent from two copper mines in California. Environ Sci Technol. 2008;42(16):6257-63. Epub 2008/09/05. PubMed PMID: 18767696.

Garcia-Reyero N, Poynton HC, Kennedy AJ, Guan X, Escalon BL, Chang B, Varshavsky J, Loguinov AV, Vulpe CD, Perkins EJ. Biomarker discovery and transcriptomic responses in Daphnia magna exposed to munitions constituents. Environ Sci Technol. 2009;43(11):4188-93. Epub 2009/07/03. PubMed PMID: 19569350.

Antczak P, Jo HJ, Woo S, Scanlan L, Poynton H, Loguinov A, Chan S, Falciani F, Vulpe C. Molecular toxicity identification evaluation (mTIE) approach predicts chemical exposure in Daphnia magna. Environ Sci Technol. 2013;47(20):11747-56. Epub 2013/07/24. doi: 10.1021/es402819c. PubMed PMID: 23875995.

Genetic Modifiers of Iron Homeostasis

Genetic variants influence iron homeostasis in mammals. My group has utilized genome wide approaches to identify genetic factors that influence iron status in mammals. In mice, we performed an “in silico” QTL analysis of inbred strains of mice. In humans, we were the molecular genotyping site in two large multi-center studies to identify genetic determinants influencing iron overload and deficiency. While considerable work remains to be done to transition from these GWAS studies to a molecular and functional understanding of the effect of these genetic determinants on iron metabolism, these two complementary approaches in mice and man provide a novel approach to understand vertebrate iron metabolism which my group continues to actively pursue. We recently utilized genome CRISPR screens to identify genetic factors modulating iron homeostasis in red blood cells.

Sobh A, Loguinov A, Zhou J, Jenkitkasemwong S, Zeidan R, El Ahmadie N, Tagmount A, Knutson M, Fraenkel PG, Vulpe CD. Genetic screens reveal CCDC115 as a modulator of erythroid iron and heme trafficking. Am J Hematol. 2020 Sep;95(9):1085-1098. doi: 10.1002/ajh.25899. Epub 2020 Jul 9. PubMed PMID: 32510613.

Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, McLaren CE, Bahlo M, Nisselle AE, Vulpe CD, Anderson GJ, Southey MC, Giles GG, English DR, Hopper JL, Olynyk JK, Powell LW, Gertig DM. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med. 2008;358(3):221-30. Epub 2008/01/18. doi: 10.1056/NEJMoa073286. PubMed PMID: 18199861.

Constantine CC, Anderson GJ, Vulpe CD, McLaren CE, Bahlo M, Yeap HL, Gertig DM, Osborne NJ, Bertalli NA, Beckman KB, Chen V, Matak P, McKie AT, Delatycki MB, Olynyk JK, English DR, Southey MC, Giles GG, Hopper JL, Allen KJ, Gurrin LC. A novel association between a SNP in CYBRD1 and serum ferritin levels in a cohort study of HFE hereditary haemochromatosis. Br J Haematol. 2009;147(1):140-9. Epub 2009/08/14. doi: 10.1111/j.1365-2141.2009.07843.x. PubMed PMID: 19673882; PubMed Central PMCID: PMC2767327.

McLachlan S, Lee SM, Steele TM, Hawthorne PL, Zapala MA, Eskin E, Schork NJ, Anderson GJ, Vulpe CD. In silico QTL mapping of basal liver iron levels in inbred mouse strains. Physiol Genomics. 2011;43(3):136-47. Epub 2010/11/11. doi: 10.1152/physiolgenomics.00025.2010. PubMed PMID: 21062905; PubMed Central PMCID: PMC3055709.

Mammalian ferroxidases - Hephaestin

Intestinal iron absorption is remarkably balanced to provide adequate iron to meet the body's iron needs while preventing toxic excess. In a collaboration which continues to this day, Greg Anderson from QIMR, Brisbane Australia and I identified and extensively characterized the gene that is mutant in mice with sex linked anemia. Hephaestin (Hp) was identified to be a membrane-bound copper containing ferrroxidase required for export of iron from the intestinal enterocyte into the circulation. Most recently, we have utilized floxed Hephaestin (Heph) to generate both complete and tissue specific knockouts confirming that global and intestinal specific knockouts result in systemic iron deficiency. Furthermore, we have developed mice which lack both Hephaestin and Ceruloplasmin, the circulating ferroxidase, which develop a much more severe phenotype of iron deficiency than either alone and provide compelling evidence for complementary and partially compensatory functions. Most recently, we have demonstrated increased iron levels in many regions of the brain in mice lacking the Heph gene.

Vulpe CD, Kuo YM, Murphy TL, Cowley L, Askwith C, Libina N, Gitschier J, Anderson GJ. Hephaestin, a ceruloplasmin homologue implicated in intestinal iron transport, is defective in the sla mouse. Nat Genet. 1999;21(2):195-9. Epub 1999/02/13. doi: 10.1038/5979. PubMed PMID: 9988272

Chen H, Attieh ZK, Su T, Syed BA, Gao H, Alaeddine RM, Fox TC, Usta J, Naylor CE, Evans RW, McKie AT, Anderson GJ, Vulpe CD. Hephaestin is a ferroxidase that maintains partial activity in sex-linked anemia mice. Blood. 2004;103(10):3933-9. Epub 2004/01/31. doi: 10.1182/blood-2003-09-3139. PubMed PMID: 14751926.

Jiang R, Hua C, Wan Y, Jiang B, Hu H, Zheng J, Fuqua BK, Dunaief JL, Anderson GJ, David S, Vulpe CD, Chen H. Hephaestin and Ceruloplasmin Play Distinct but Interrelated Roles in Iron Homeostasis in Mouse Brain. J Nutr. 2015. doi: 10.3945/jn.114.207316. PubMed PMID: 25788583.

Fuqua BK, Lu Y, Frazer DM, Darshan D, Wilkins SJ, Dunn L, Loguinov AV, Kogan SC, Matak P, Chen H. Severe iron metabolism defects in mice with double knockout of the multicopper ferroxidases hephaestin and ceruloplasmin. Cellular and molecular gastroenterology and hepatology. 2018;6(4):405-27.

Copper transporting ATP7A – Menkes disease

Copper is an essential metal that can lead to toxicity in excess. Menkes disease is an X-linked inherited disorder resulting in severe copper deficiency and consequent defects in copper containing enzymes and proteins. As a graduate student in Seymour Packman's and Jane Gitschier's laboratory, I carried out a positional cloning effort which identified the gene defective in Menkes disease as a copper transporting ATPase. Subsequently, we identified that the mottled mouse, a model of Menkes disease, resulted from defects in the homologous gene.

Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. Nat Genet. 1993;3(1):7-13. Epub 1993/01/01. doi: 10.1038/ng0193-7. PubMed PMID: 8490659.

Levinson B, Vulpe C, Elder B, Martin C, Verley F, Packman S, Gitschier J. The mottled gene is the mouse homologue of the Menkes disease gene. Nat Genet. 1994;6(4):369-73. Epub 1994/04/01. doi: 10.1038/ng0494-369. PubMed PMID: 8054976.