UNIVERSITY OF CALIFORNIA, LOS ANGELES UCLA

BERKELEY • DAVIS • FRESNO • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Dear Search Committee,

I write to express my enthusiastic interest in the professorship position in Computational Medicine.

I am a systems biologist with extensive training in genomics, heart biology and DNA methylation and with experience developing and improving tools to identify genes associated with heart failure and related cardiac diseases. I earned my PhD from the University of California, Los Angeles and have five years of experience as a postdoctoral fellow applying systems biology methods to the study of heart failure. I have published extensively on genetics, genomics and systems biology, producing 33 publications to date, including nine as first author. In addition, I am supported by a K99/R00 from NHLBI.

My dissertation research under the supervision of Dr. Aldons Lusis focused on using the Hybrid Mouse Diversity Panel (HMDP) to study the genetic underpinnings of cardiac dysfunction using GWAS and novel co-expression network analysis approaches to identify key genes and pathways which contributed to heart disease. As a postdoctoral fellow with Dr. Yibin Wang, my interests have expanded to the study of DNA methylation in cardiac dysfunction as well as the study of heart failure using next generation sequencing techniques in multiple model systems as well as human populations.

I am passionate about the potential for bioinformatic approaches blended with high quality bench research to make a lasting contribution to our understanding and treatment of complex diseases. It is my belief that many great discoveries are waiting to be found in the data we already possess and that by looking at these data in a comprehensive, biologically intuitive way we will be able to uncover novel, fruitful hypotheses to improve our understanding of disease. To me, there is nothing more exciting than seeing new insights emerge from the dovetailing of computational and bench science approaches. My work is by its nature highly collaborative: I have a history of working with biologists, mathematicians and computer scientists to identify candidate genes and drivers of disease. I am drawn to UNC due to its history as a pioneer in the field of mouse genomics, its interests in merging *in silico* and *in vivo* research, its collaborative research environment and its focus on both teaching and research.

In the future, my goal is to explore heart failure in a unified way from DNA variation through epigenetic modifications, transcriptome perturbations and beyond using sophisticated wet and dry-lab approaches and leveraging data generated from my previous research.

I am also passionate about educating the next generation of scientists, having mentored 18 undergraduate, masters and doctoral students in laboratory techniques, mouse genetics and bioinformatic approaches. Additionally, I have taught several multi-part seminars on computational biology and programming to my colleagues, grant writing strategies to a class of graduate students, and designed lectures and led discussion on cutting-edge scientific papers as a teaching assistant for an upper-division genetics course. I look forward to applying my teaching skills to teaching the University of North Carolina's graduate and undergraduate student populations as a professor.

Thank you very much for your consideration.

Sincerely,

Christoph D. Rau, Ph.D.

Christoph D. Rau, Ph.D.

11760 National Blvd #10, Los Angeles, CA, 90064
Tel: 425-753-7048
Email: chrau@ucla.edu

EDUCATION AND TRAINING

Harvey Mudd College, Claremont, California
B.S. (with honors), Mathematical Biology, **2003-2007**

University of California, Los Angeles, Los Angeles, California
PhD, Molecular Biology, Immunology and Molecular Genetics, **2007-2013**
Advisor: Aldons J. Lusis

University of California, Los Angeles, Los Angeles, California
Postdoctoral Training, Department of Anesthesiology, **2013-2019**
Mentor: Yibin Wang

University of California, San Francisco, San Francisco, California
Visiting Scholar, Department of Medicine, **2017**
Mentor: Noah Zaitlen

RESEARCH EXPERIENCE

University of California, Santa Cruz, *Dept. of Biomolecular Engineering* Santa Cruz, California
Advisor: Todd Lowe **Summer 2006**
Designed tools for the UCSC Genome Browser to identify and characterize snoRNAs.

Harvey Mudd College, *Dept. of Biology* Claremont, California
Advisor: Robert Drewell **2006-2007**
Senior Thesis research on regulation of HOX gene expression by poorly conserved enhancer elements. Used bioinformatic tools to identify preserved 2' lncRNA structures in enhancers

University of California, Los Angeles, *Dept. of Microbiology, Immunology and Molecular Genetics*
Advisor: Aldons J. Lusis **2007-2013**
Ph.D Dissertation: A Systems Genetics Approach For The Identification of Causal Genes In Heart Failure Using A Large Mouse Panel.

University of California, Los Angeles, *Dept. of Anesthesiology* Los Angeles, California
Advisor: Yibin Wang **2013-2019**
Postdoctoral Research into the epigenetics underlying heart failure and numerous collaborations in and beyond UCLA.

University of California, San Francisco, *Dept. of Medicine* San Francisco, California
Advisor: Noah Zaitlen **2017**
Visiting Scholar exploring the role of individual ancestry on SNP effect sizes in mice and humans.

ACADEMIC AND PROFESSIONAL HONORS

Harvey S. Mudd Scholarship (2003-2007)
Cell and Molecular Biology Training Grant (Ruth L. Kirchstein Predoctoral NRSA) (2008-2011)
Vascular Biology Training Grant (Ruth L. Kirshstein Predoctoral NRSA) (2011-2013)
Early Career Investigator Award of Excellence, Kern Lipid Conference (2012)
Basic Cardiovascular Sciences Conference Travel Award, American Heart Association (2014)
Postdoctoral Leadership Program Award (2015)
Best of AHA Specialty Session Poster Award (2014, 2017)

PROFESSIONAL SOCIETIES

American Heart Association, Basic Cardiovascular Sciences Council (2010-)
International Society for Heart Research (2014-)

GRANT SUPPORT

NIH 1K99 HL138301 Program Title: *Discovery of Novel Epigenetic Regulators of Heart Failure in a Panel of Mice*. 5/1/2018-4/30/2023
This grant is concerned with the identification and characterization of epigenetic factors and associated genes which regulate the progression of cardiac hypertrophy and failure by integration of novel DNA methylome data with other available 'omics from the same cohort of animals

AHA 15POST25310006 Program Title: *A Systems Approach to Dissect the Epigenetic Regulation of Heart Failure*. 07/01/15-06/30/2017
The goal of this grant was to isolate DNA from the Hybrid Mouse Diversity Panel and perform Reduced Representation Bisulfite Sequencing to identify possible drivers of heart failure.

TEACHING AND MENTORSHIP

Student Tutor, *Harvey Mudd College*, Fall 2004, Fall 2005, Spring 2006
Mentored and graded students in introductory (2004,2005) and upper division (2006) programming courses

Teaching Assistant, *University of California--Los Angeles*, Fall 2008, Winter 2010,2011
Teaching assistant for an upper division/graduate level course on human genetics. Developed course materials, led 3 discussion sections (20-30 students each) teaching critical manuscript analysis and topics related to candidate gene identification and modes of inheritance

Undergraduate Mentor, *University of California--Los Angeles*, 2008-present
Mentored 15 undergraduate students in lab. Taught basic lab techniques, developed and guided them in independent projects.

Graduate Student Mentor, *University of California--Los Angeles*, 2013-present
Mentored 2 doctoral and 2 masters student in mouse genetics and bioinformatic techniques

Postdoctoral Leadership Program, *University of California--Los Angeles,* Fall 2015
Guided first year graduate students through the process of writing NSF-style pre-doctoral training grants.

PUBLICATIONS

An up-to-date list of my publications may be found at https://tinyurl.com/RauPubs

Rau CD, Tzimas C, Jean-Louis G, Lee K, Chukwuneke J, Dun W, Wang Y, Tsai EJ. Wipi1 is a Genetic Hub That Mediates Right Ventricular Failure in Humans and Mice. *Science Translational Medicine* In review.

Wong E, Tan WLW, Tan HS, Li Y, Ng SH, Tejo E, Vondriska, TM, Wang Y, Foo R, **Rau CD**. Differential DNA Methylation Co-segregates with Severity of Heart Failure. *Cardiovascular Research*. In review.

Lin L, Chun-Chang S, O'Hearn J, Hui ST, Seldin M, Gupta P, Bondar G, Deng M, Jauhiainen R, Kuusisto J, Laakso M, Sinsheimer JS, Deb A, **Rau C**, Ren S, Wang Y, Lusis AJ, Wang JJ, Huertas-Vazquez A. Systems Genetics Approach to Biomarker Discovery: GPNMB and Heart Failure. *G3* pii*: g3.200655.2018* (2018)

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Chang SC, Ren S, **Rau CD,** Wang JJ. Isoproterenol-Induced Heart Failure Mouse Model Using Osmotic Pump Implantation. *Methods in Molecular Biology* 1816:207-220 (2018)

Rau CD, Vonriska TM. DNA Methylation and Human Heart Failure: Mechanisms or Prognostics. *Circulation* 136(16):1545-1547 (2017)

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Gao C, Howard-Quijano K, **Rau CD**, Takamiya T, Song Y, Shivkumar K, Wang Y, Mahajan A. Inflammatory and Apoptotic Remodeling in Autonomic Nervous System Following Myocardial Infarction. *PloS one*. 12(5):e0177750 (2017)

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Ho MCW, Johnsen H, Goetz SE, Schiller BJ, Bae E, Tran D a, Shur AS, Allen JM, **Rau C**, Bender W, Fisher WW, Celniker SE, & Drewell R a. Functional evolution of cis-regulatory modules at a homeotic gene in Drosophila. *PLoS Genet.* **5,** e1000709 (2009).

INVITED TALKS

A Systems Approach to Unraveling the Genetic Basis of Heart Failure. Presented at the NHLBI Systems Biology Meeting 10/16

A Network-based Approach to Identify Novel Regulators of Heart Failure. Presented at the International Society of Heart Researchers Conference 6/15

Application of Systems Genetics Tools for the Discovery of Genes Contributing to Complex Diseases. Presented at the Singapore Heart Failure Conference 11/14

The Genetic Basis of Isoproterenol-induced Cardiac Fibrosis. Presented at the American Heart Association Basic Cardiovascular Sciences Conference 7/17/14

A Primer on Systems Genetics. Presented at Cedars Sinai Hospital 10/29/12

INTRODUCTION

I am a systems biologist who studies complex diseases--particularly cardiovascular diseases--using mouse models and computational algorithms. My research explores the complicated interactions that lie between genomic variation and phenotypic expression. Because of my strong background in both genetics and computer science, I am able to effectively collaborate with biologists, mathematicians, and computer scientists alike, and often serve as bridge between collaborators with different backgrounds.

My research explores biological relationships in high-dimensional data, including relationships between SNPs and phenotypes and relationships between a set of genes within a cell. More broadly, my research explores the web of connections that link DNA to disease through the epigenome, transcriptome, proteome and beyond. I elucidate these complex interactions through a combination of biology-grounded bioinformatics and *in vitro* and *in vivo* validations of candidate genes, gene modules and other putative drivers of disease.

My graduate and doctoral work focuses primarily on the study of cardiovascular diseases, especially heart failure. Over the course of my training, I have utilized the Hybrid Mouse Diversity Panel (HMDP) to explore genetic, transcriptomic and, most recently, epigenomic factors underlying cardiac dysfunction. I have treated over 100 strains of mice from the HMDP with the chronic adrenergic agonist isoproterenol to induce cardiac hypertrophy, dysfunction and fibrosis. I have gathered over 90 phenotypes, 30,000 probesets and profiled the methylation status of over 1.4 million CpGs in these mice. These data have been a rich source of results and an ideal testbed for my computational methods.

UTILIZING SYSTEMS GENETICS TO UNDERSTAND CARDIAC FAILURE

Heart disease remains the primary cause of mortality and morbidity in the United States and the world[1–4]. The highly heterogeneous presentation of cardiovascular disease, combined with the difficulty in obtaining detailed, comprehensive phenotyping and tissue samples from human populations, has confounded efforts to identify significant candidate genes and pathways using currently available systems genetics tools[5–8]. Mouse model research, by contrast, allows for greater control over environmental conditions and easier tissue and data collection, making it an ideal resource for systems biology exploration[9,10]. My research focuses on the identification and validation of candidate genes, the exploration of the epigenome, and the development novel bioinformatic tools. My work is, by its nature, highly collaborative and I look forward to the opportunity to collaborate with the faculty at UNC in the development of new model systems and deepening the understanding of cardiac disease and other phenotypes of mutual interest.

PROJECT 1: ELUCIDATE THE ROLE OF DNA METHYLATION IN HEART FAILURE AND ASSOCIATED TRAITS

There has been a recent explosion of interest in the epigenome, changes to DNA or chromatin structures which do not affect the underlying sequence. Studies have shown that this previously poorly-explored biological layer can be altered by environmental factors and DNA variation and possesses a degree of inheritability independent of DNA itself[11,12]. Research has also demonstrated that epigenomic changes may contribute to changes in phenotype, including dilated cardiomyopathies and other cardiovascular disorders[13,14].

As part of my postdoctoral training I have generated Reduced Representational Bisulfite Sequencing libraries from 85 strains of my HMDP Heart Failure study in both healthy and failing hearts. Supported by a K99/R00 mechanism from NHLBI, I envision two complementary sub-projects arising from these novel data.

The first sub-project is exploring how **DNA Variation Affects DNA Methylation in the Heart.** The genetic factors that control DNA methylation differences between individuals are currently largely unknown, especially in the heart, the accessibility of which is highly limited in human studies. Previous work done in the HMDP on liver samples revealed that individual polymorphisms play a strong role in the regulation of both individual CpG methylation sites and numerous CpGs simulaneously[15]. My research shows that the heart and liver methylomes differ significantly, suggesting that it is highly likely that an examination of the cardiac methylomes will reveal novel and distinct regulators of global DNA methylation unique to cardiac tissue. I will perform GWAS on each variable methylation site across the genome to identify methylation QTL hotspots.

The accepted paradigm of DNA methylation suggests that DNA methylation and gene expression

are anticorrelated to one another. Recent data, however, suggests this relationship may not be as universal as expected[16]. I will use previously generated gene expression data from this HMDP[17] to test this hypothesis in two ways. First, I will directly associate DNA methylation with the expression of its nearest gene to obtain a rough estimate across the HMDP of the correlation strength and direction of DNA methylation and gene expression. Second, if DNA methylation and Gene expression are truly closely related, then methylation QTL hotspots should be significantly enriched for expression QTL hotspots as well. Sites of significant overlap will be fruitful regions for the identification candidate 'master regulator' genes with high potential for strong effects on cardiac phenotypes.

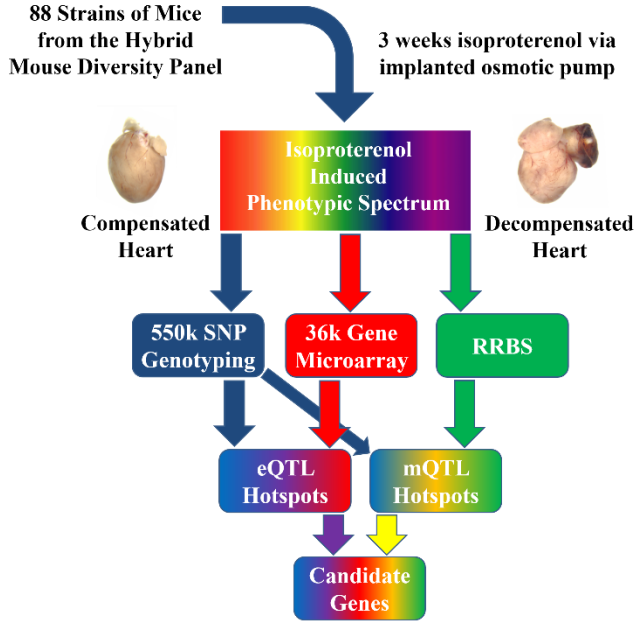

Figure 1. An example systems genetics approach integrating methylomics and transcriptomics to uncover regulatory genes that control heart-associated traits

The second sub-project will center on **Understanding the Role of DNA Methylation on Heart Failure-Related Phenotypes.** In my graduate research, individual strains of mice in the HMDP developed a spectrum of cardiac pathologies in response to chronic adrenergic stimulation.[18,19] Many of these phenotypes were linked to individual polymorphisms using GWAS, however much of the total phenotypic variance expected to be explained by genetics remains unrecovered. Non-genetic inheritance, such as epigenetic profiles, can partially explain this missing variance. My goal is to use the DNA methylomes to further reveal mechanisms by which genetics and epigenetics drive disease by linking specific CpG fingerprints to pathological features in the heart via epigenome-wide association studies (EWAS). Preliminary EWAS on a subset of phenotypes have already identified several interesting candidate genes, which form the basis for the next major part of my work as a PI.

PROJECT 2: VALIDATION AND MECHANISTIC STUDIES OF HEART FAILURE ASSOCIATED GENES

Over the course of my research, I have identified over three dozen possible candidate genes, a number of which have been validated in published[17,18] and soon-to-be-published work, including the coexpression network identified hypertrophy-driver *Adamts2* and the GWAS identified protector against cardiac fibrosis *Abcc6*, the lncRNA *Miat* and the adrenal gland regulator *Eprs*. Many candidate genes remain to be validated in the future using *in vitro* cell models and *in vivo* CRISPR/*Cas9*-mediated knockouts for phenotypic observation and analysis.

I have been given permission to pursue any of these genes in my independent career, however I currently have K99/R00 support to pursue two genes in particular. The first is a gene which is located on a locus for right ventricular weight on chromosome 5 which replicated both in GWAS and EWAS studies. This gene, ***Mospd3***, is under genetic control at this same locus by a strong *cis*-interacting SNP, and its significance is further underscored by a report of an not fully penetrant developmental defect in right ventricular wall formation[20] whose mechanism was not explored. The second is ***Serpina3n*****,** a gene on chromosome 12 which lies in the middle of an eQTL hotspot that significantly regulates the response of over 5% of the expressed genes in the heart to catecholamine challenge. Although *Serpina3n* is a poorly described member of the serine protease inhibitor family, which as a whole has been linked to improved wound healing and attenuation of muscular dystrophy symptoms[21], its exact mechanism in cardiac tissue is unknown, but preliminary qPCR performed on *in vitro* siRNA-mediated knockdown cells demonstrates that *Serpina3n* is significantly associated with the expression of 8 of the top 10 genes associated with the locus by eQTL analyses.

I have established *in vitro* assays for each of these genes and will shortly have knockout mice on

hand to pursue questions into the mechanism of each gene.

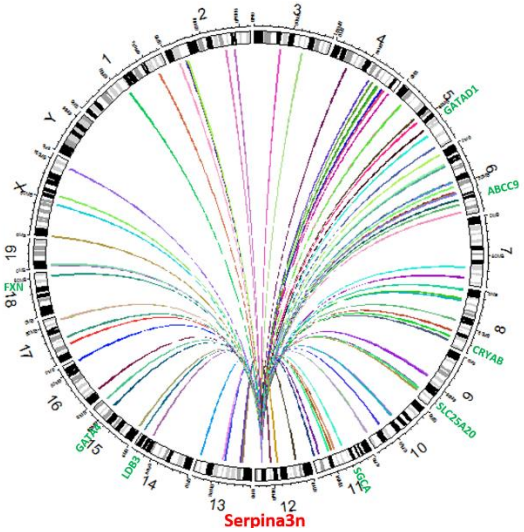

Figure 2. Interaction of the *Serpina3n* locus with other genes across the genome in cardiac tissue

PROJECT 3: BIOINFORMATIC APPROACHES

Genetics research is rapidly changing, and a vital and important portion of any laboratory should be the identification, implementation and, when necessary creation of bioinformatic tools to aid in research. Throughout my academic career, beginning as a summer researcher at UC Santa Cruz through my postdoctoral visiting scholarship at UC San Francisco, I have created or modified a number of bioinformatic tools to answer questions that I was working to solve. There are currently two bioinformatic projects which I am actively working on and anticipate continuing to focus on as I transition to an independent position.

The first tool is an expansion and refinement of a network analysis approach which I developed and used to analyze my heart failure data during my postdoctoral fellowship called **weighted Maximal Information Component Analysis** (wMICA)**.**[17] We demonstrated that this method, in conjunction with causal equation modeling, can create testable hypotheses about gene network connectivity and validated the predicted transcriptional effects of an important driver of cardiac hypertrophy. wMICA also identifies and prioritizes SNPs which are located near causal mutations for that drive phenotypes. I am currently working to expand wMICA to incorporate multiple sources of data simultaneously, especially the epigenetic data generated as part of my K99/R00 projects. Additionally, I am working on an improved version of causality modeling in wMICA which allows for feedback loops in the data and which will allow for more nuanced analyses of information flow in the networks.

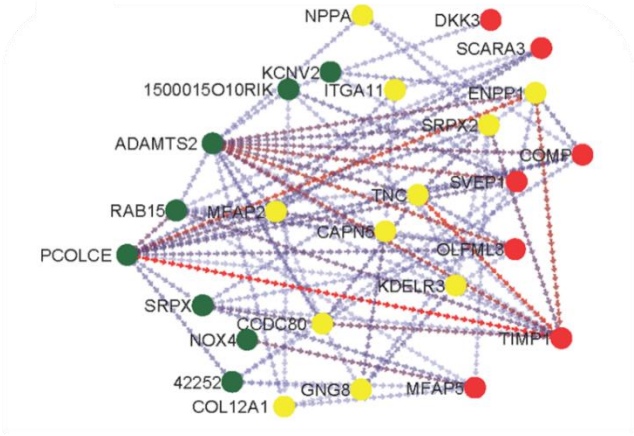

Figure 3. Directed gene network created using the wMICA/NEO algorithm. Adapted from Rau 2017[17]

The second tool is designed to aid in the study of how individual SNPs can have wildly different effect sizes on phenotypic variation based on genetic context. This tool, which explores **Gene by Ancestry Associations** in admixed populations is capable of drawing out novel SNPs whose effect size varies across a population based on the percentage of SNPs in the genome of an individual that come from a particular genetic background. We use this approach in both the HMDP and another large mouse population to identify loci affecting heart weights, glucose levels, body weights, and overall organismal fitness. I am preparing to submit an R03 or R21 grant to validate some of our findings using focused CRISPR/*Cas9*-mediate base editing to demonstrate the effects of these context-dependent SNPs in different genetic backgrounds.

CONCLUSION

The long-term goals of my research program will be to identify novel genes which underlie cardiac dysfunction and identify the functional mechanisms by which they act through a combination of molecular and bioinformatic approaches. I will aim for a highly interdisciplinary research group as I believe the best research is done when many perspectives are brought to bear on a problem. As I have done in the past, I will collaborate extensively with other research groups in an effort to tackle significant problems in cardiac pathology and other phenotypes of shared interest.

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Teaching is a highly rewarding part of academia. My favorite topic to teach has always been genetics. Genetics, and biology more generally, is a rapidly evolving field filled with unanswered questions, unexpected exceptions and a constantly moving horizon. Since what is the cutting edge today might be obsolete in a decade, I strongly believe that teaching must be skills-centered, focused on helping each student learn the techniques needed to understand and digest new information in our rapidly evolving field. As a teacher, I strive to cultivate scientific curiosity, analytical thinking and technical communication in my students. I follow this philosophy regardless of whether I am teaching a class, helping a student at office hours or mentoring undergraduates in the laboratory.

As a graduate student, I was a TA for the same upper division Human Genetics class for three years (CM156), where I was responsible for teaching three 20+ person discussion sections a week. My goal in the discussion sections was to reinforce and enhance what the students were learning using cutting-edge scientific articles to demonstrate how the field is developing *today* in the topics they had covered in the larger lectures. The students, many who had never read a scientific paper before, were challenged to apply their knowledge to understanding brand new research, and I would help guide them through their analyses by asking them focused, direct questions: Why did the authors want to write this paper? What question are they asking? What steps did they take to find the answer? Each week, one question would be a graded written prompt to assess their development and understanding and their participation in discussion would form the other portion of their grade. One week, we might use a paper on Genghis Khan's Y-chromosomal haplotype to discuss many examples of how genetics can be used to solve historical mysteries. The next, I might bring in some of my own data and walk them through a simple GWAS calculation.

I find that unexpected, seeming exceptions to scientific rules, the 'rough edges' of real science are like intellectual Velcro, grabbing learner's attentions and helping to solidify understanding. In my classes, I made a point to expose my students to these sorts of unexpected exceptions. For example, when we discussed sex determination and the X and Y chromosomes, I would ask them questions about why XY in humans are male, but ZW in birds are female, or how it might come about that there would be a temperature-dependent sex determination in some reptiles, or even the multiple sex chromosomes observed in monotremes. In doing this, I saw them truly come to understand how sex was determined. Nearly every paper we discussed had something unexpected or something that, at first glance, didn't quite seem to match up with what they had learned in lecture or in an earlier class. Near the end of each year I taught, I would devote one of my office hours to answering any questions they might have on papers they had found themselves that interested them and those office hours were frequently better attended than any other office hour I gave, with many students attending and asking careful, insightful questions about what they had read, or, sometimes, just eager to share what they had learned.

Refining my teaching design to better reach my students was one of the benefits of teaching the same course for three years. I was able to help select the next set of manuscripts we would discuss in the coming year, rework my presentations to better explain the topics that students had struggled with in the past year and refine my question prompts. Between my first and second year, I overhauled how I began class, telling the students to break apart into small groups of 4 or 5 at the start of class and discuss the paper between themselves for five minutes before starting to ask questions and I saw my students become more participatory and their answers to my prompts improve as they helped answer each other's questions about the material. Seeing my students curious about science and able to engage with scientific research was deeply rewarding. I am especially proud that one of my former students who went on to graduate school herself let me know that she uses the exact same approach to teach her students with similar positive results.

I take a similar approach to one-on-one mentoring of undergraduate research assistants or graduate students. My goal is, ultimately, to provide them with the support and training they need to work through a novel scientific problem on their own. First, we review the literature. Why is it that we are doing this experiment? What question are we asking? What steps have others taken when doing similar projects? Next, I help them see the differences between prior experiments and their own, whether those differences are small (querying gene A versus gene B) or large (synthesizing two *in vitro* methods together into a new protocol). Then, I employ a three-step process to equip my students with a solid grounding of laboratory techniques and confidence in their abilities. First, I will perform the experiment for them as they watch me do it. The next time, we will work side-by-side, with the student following my lead on each step as I give them advice and pointers as they proceed with the experiment. Then, I will observe them as they work, stepping back and letting them take the lead. Invariably, this leads to discussions of alternate techniques or approaches which help my students develop the critical thinking skills they

need to approach a novel scientific problem and claim it as their own and, ultimately, to become responsible and dedicated scientists. I strive to help my students find their own niche in the projects I am working on so that they will have the opportunity to tackle and troubleshoot their own scientific questions. I have trained 15 undergraduates and 3 graduate students using this approach and have been consistently rewarded with high-quality research and analysis. I have co-authored publications with each of my mentored graduate students, and two of my undergraduate students are second authors on my published papers, with several other manuscripts in preparation which feature the work of other undergraduates.

I am eager to have teaching opportunities in my new faculty position where I can utilize my expertise in the fields of bioinformatics, genetics and cardiac biology. Whether I am challenging students to read about exciting new research in journal articles in a classroom or encouraging them to troubleshoot an unexpected result in the laboratory, my ultimate goal and desire is to instill in my students, both in the classroom and those that I mentor directly, the same excitement and passion which I feel about biology and the skills to identify and engage with whatever problem most intrigues them.