PERSONAL STATEMENT EXAMPLE

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PERSONAL STATEMENT OF TEACHING

Teaching Philosophy.

Learning is an active process by the student, facilitated by the teacher. As a faculty member at the University of lowa one of my goals has been to facilitate the process by which students learn. This entails delivering clear lectures and inspiring students to take responsibility for their own learning. One way to inspire students is to develop interesting and pertinent coursework. While a faculty member I have developed lectures for three distinct courses. In two advanced courses (Biophysical Chemistry and Experimental Biochemistry) I incorporated the didactic material with experimental research to show how the two can be integrated to create new knowledge. In contrast, my approach to developing the lower level Biochemistry course has been to emphasize the more practical, daily usefulness of the course material.

My major contributions to the University's teaching mission are described below and include didactic course-work for undergraduate and graduate students, "guest" lectures, establishing a Structural Biology Interest Group seminar series, and mentoring laboratory personnel. In addition, yearly student evaluations of my teaching performance and representative teaching materials are included in Appendices I and II, respectively.

Biophysical Chemistry II (99:242; 3 semester hours; Spring 2007-2013).

This course is taught by three faculty members and designed to introduce blophysics to senior undergraduate and first-year graduate students. I developed and delivered 15 lectures on the fundamentals of nuclear magnetic resonance (NMR). This module, entitled "NMR of Biological Macromolecules", is the only bimolecular NMR course available on campus, and attracts ~20-25 students per year from across campus. The course begins with the basic principles of NMR and eventually covers more complex theoretical concepts. The practical uses of NMR for addressing research questions in structural biology are highlighted throughout the course using examples taken from the literature and from my own research. Weekly problem sets are assigned to reinforce the lecture material. The major challenge in teaching this course is that the material in inherently difficult and the students have little background in the subject. Thus, problem sets are designed to help the students build confidence in the material. Overwhelmingly, students put the concepts together at the end of the course and realize that they have obtained a solid understanding for how NMR-based methods can be used to solve structural problems. It has been very satisfying to know that several former students have continued graduate studies in biophysics, particularly in laboratories that use NMR as a primary research technique. My teaching evaluations have been positive with evaluations (based on scale from 1 to 5, where 1 is the best score) ranging from 1.44 to 2.48 with an average of 1.91.

Experimental Biochemistry (99:140; 4 semester hours; Spring 2009 and 2010).

This course is a requirement for all undergraduate biochemistry majors and covers topics in experimental biochemistry and molecular biology. The course is divided into four sections, each designed and administered by a different faculty member. In my section, I developed a series of biophysical experiments that were performed on the enzyme lysozyme. The goal of these experiments is to highlight how biophysical methods can be used to understand the underlying cause of disease. The students were introduced to the protein lysozyme and its connection to amyloidosis disease. They used the program GeneCard to identify disease-related mutations in lysozyme and the ExPASy bioinformatics portal to determine the physical properties (isoelectric point, molecular weight, extinction coefficient, etc.) of the enzyme. The students learned to use the molecular graphics program PyMol and mapped the disease-causing amino acids onto a crystal structure of lysozyme. Because these mutations are known to destabilize lysozyme, the students performed several biophysical experiments such as chemical denaturation and isothermal titration calorimetry (ITC) to highlight quantitative techniques capable of measuring thermodynamic parameters associated with protein stability and substrate binding. In addition, the students learned about the principles behind protein purification and applied them to the isolation of lysozyme from chicken eggs. They also performed enzymatic activity assays. The students used their purified lysozyme to grow protein crystals and then exposed the crystals to an X-ray source to obtain a protein diffraction pattern. At the end of the section, the students wrote a laboratory report in the style of a journal article. Through this module, the students gained valuable insight and experience into how biophysical methods can be used in biomedical research to understand mechanisms of disease. It is worth noting that historically, this course has not incorporated biophysical techniques. One of the key innovations and challenges of this course was organizing the logistics of using state-of-the-art Core Facility instrumentation and teaching how to analyze the data. However, the students seemed to enjoy this challenge and the diversity of techniques covered. The average evaluation was 2.2/5.0 (based on scale from 1 to 5, where 1 is the best score).

Biochemistry (99:110; 3 semester hours; Fall 2012 and 2013, web course Spring 2012).

I was among a group of faculty members who developed and taught a one semester biochemistry course for non-biochemistry majors. I developed and delivered 6 lectures on anzyme structure and function. These lectures have been videotaped and offered online. This course accounts for 9 contact hours of teaching including lecturing, administering exams and responding to student questions in the in the classroom and online versions. This course reaches an audience of ~200 students per semester, and is of great importance for building molecular literacy at our institution. The main challenge in teaching this course is connecting the biochemistry concepts to everyday life. However, I have been able to overcome this challenge by using clinical examples and interesting scientific anecdotes to relate the biochemical concepts to real-world experiences. The students enjoyed the course and my evaluation for the Fall 2012 received a 4.41/5.00 (note that the scale used in this course is 1 to 5, where 5 is the best score; the College of Liberal Arts uses a different scoring system then the College of Medicine).

Guest Lectures.

During my first summer (2006) at the University of Iowa, I developed and presented 5 lectures to the Carver College of Medicine (CCOM) on the fundamentals of NMR. These lectures were widely attended by students and faculty and served to acquaint the College to the use and practice of NMR. In the Fall 2006 and 2007, I participated in the *Principles in Molecular & Cell Biology* course as a small group facilitator. Here, I was responsible for directing the discussion of several papers by a group ~5-8 graduate students. During the Fall 2007, I designed and presented a lecture for the *Advanced Problem Solving in Pharmacological Sciences* course for students associated with the Pharmacological Sciences Training Grant. This lecture was entitled "NMR in Pharmacological Research" and detailed how NMR can aid the drug discovery process. Subsequently, the students wrote an NIH-style proposal that included the use of NMR in drug discovery.

Structural Biology Interest Group Seminar Series.

I have been very active in organizing and promoting opportunities for students to obtain specialized training in structural biology. One venue has been the bi-weekly "Structural Biology Interest Group Meetings" seminar that Pro and I established in the Fall 2007. This group has participants from several laboratories across the campus and meets throughout year. The aim is to foster training in structural biology for undergraduate students, graduate students, and postdoctoral fellows by having them present their on-going research. Occasionally, faculty and CCOM facility staff (X-ray Crystallography, NMR, Proteomics and Microscopy Cores) present seminars. This series is ongoing and continues to have a wide-based audience.

Teaching in the Laboratory.

In addition to lecture-based courses, a significant amount of time is dedicated to teaching students with a wide variety of educational backgrounds - ranging from high school students to postdoctoral fellows. This involves weekly one-on-one meetings and group meetings, which not only allow the flow of information from the student to Pi, but also from peer to peer. My philosophy to mentoring in the laboratory is to pair new members with established personnel, usually a graduate student or postdoctoral fellow. This approach has worked very well because both the mentor and mentee have a stake in the outcome of the research. In the case of my first graduate student. 1, I served as his direct mentor and teacher. Mentoring ed to harnessing his enthusiasm and focusing his efforts on completing papers. Ultimately, he published 3 firstauthored papers and contributed to several other manuscripts.d is currently a postdoctoral fellow at Uppsala University in the laboratory of Prof. . This same approach has worked with Ms. , an undergraduate student who has been working with . T (5th-year graduate student) for the past two years. n has made exceptional progress on her research, in part, because of dedication to mentorship. It is noteworthy that received a 2013 Sandra H. Barkan Graduate Student Mentorship Award for mentoring Ms n. This basic approach is now the paradigm in my laboratory.

PERSONAL STATEMENT OF SCHOLARSHIP

Research in my laboratory focuses on important problems in signal transduction pertinent to human health. We are interested in both eukaryotic and prokaryotic systems and the major goal is to elucidate the molecular mechanisms that regulate signal transduction. Below is a description of our major accomplishments and future directions.

(1) Tiam1 GEF. Our recent work has focused on guanine nucleotide exchange factors (GEFs) that catalyze the exchange of GDP for GTP in Rho-family GTPases. Both GEFs and GTPases are critical for the coordination of gene expression and remodeling of the actin cytoskeleton and have been associated with developmental abnormalities, mental retardation, and human diseases.

We have focused our studies on the T-lymphoma invasion and metastasis 1 (Tiam1) GEF, which regulates several essential biological processes including cell-matrix and cell-cell adhesion, cell migration and cell polarity. Importantly, aberrant function of Tiam1 contributes to cancer and neurodegeneration. Tiam1 contains five defined protein domains (PHnCCEx-RBD-PDZ-DH-PHc) whose catalytic GEF activity is normally auto-inhibited. Relief of this inhibition is critical for its full activation and biological function and occurs by protein-protein interactions and phosphorylation. Deregulation of auto-inhibition leads to constitutive activity and contributes to disease. The long-term goal of our research is to understand the detailed mechanism(s) by which Tiam1 is regulated. Knowledge of Tiam1 regulation will be critical for understanding its biological function and may lead to new strategies to inhibit its function in cancer.

Our general approach is interdisciplinary and consists of using biochemistry and structural biology to gain atomic level insights into how individual protein domains regulate Tiam1 function. This information is complemented by biological studies to help integrate the mechanistic details into a working model in the context of the cell

Studies of the Tiam1 and Tiam2 PDZ domains. Upon starting my faculty position, essentially nothing was known about the function of Tiam1 (or its closely related homolog, Tiam2) PDZ domain. We were interested in (i) determining the structures and specificity of the Tiam1 and Tiam2 PDZ domains and (ii) establishing the physiological role of these domains in vivo. Our first major accomplishment was identifying that the adhesion receptor syndecan1 binds to the Tiam1 PDZ domain and determining that this interaction is critical for coordinating Tlam1-dependent cell migration and cell-matrix adhesion (publication #17). A second major accomplishment was determining the crystal structures of the Tiam1 PDZ domain bound to peptides derived from syndecan1. This study included the first structure of a PDZ domain bound to a phosphorylated ligand (phosphorylated syndecan1) and revealed a unique phosphoryl binding pocket. In addition, NMR relaxation experiments indicated that protein interactions with the phosphate dampen the dynamics in distal regions of the PDZ domain, decoupling them from the ligand-binding. Together, the data suggest that phosphorylation might allosterically regulate the binding of ligands. These observations were published as the cover article in the March 2013 issue of Structure (publication #22) and highlighted in the Faculty of 1000. A third major accomplishment was establishing that the Tiam1 and Tiam2 PDZ domains have distinct ligand specificities. This observation suggests that there is a fundamental divergence in biological function between Tiarn1 and Tiam2 that is PDZdependent (publications #20 and #21). This work also identified several novel Tiam1- and Tiam2-interacting proteins.

The work described above has evolved into several ongoing projects. First, our ligand specificity studies with the Tiam1 and Tiam2 PDZ domains identified a mutant of the Tiam1 PDZ domain whose specificity is changed to that of the Tiam2 PDZ domain (publications #20 and #21). Using solution NMR and X-ray crystallography, we have determined that both structural rearrangements and protein dynamics contribute to the observed change. These studies are being prepared for publication and should result in an interesting manuscript describing the relationship between protein flexibility and protein binding specificity in this system. A second project is based on the observation that disrupting the Tiam1-syndecan1 interaction significantly affects cell migration and cell-matrix adhesion (publication #17), which suggests that this interaction might be a novel target for treating cancer. Using *in silico* docking and high-throughput screening methods, we have identified six compounds that bind to the Tiam1 (or Tiam2) PDZ domain and disrupt PDZ-ligand interactions *in vitro*. Our ongoing studies are aimed at developing and optimizing additional small-molecule inhibitors and testing their efficacy in inhibiting invasion and metastasis in a cell culture model. A third ongoing project involves determining the

solution structure of the Tiam2 PDZ domain bound to a peptide from a neuronal adhesion receptor. These studies will provide new insights into Tiam2 biology because there is no structure of this PDZ domain and the functional consequence of this interaction is completely uncharacterized. Together, these studies will be the subject of a new NIH proposal to be submitted in the near future.

Studies of the Tiam1 PH_n-CC-Ex domain. The PH_n-CC-Ex domain of Tiam1 is critical for sub-cellular localization through interactions with phospholnositides and with over eight known scaffold proteins. These interactions ultimately help dictate the particular protein complex that Tiam1 is associated with, and hence physiological function. The long-term goal of this project is to determine the structure of the Tiam1 PH_n-CC-Ex domain bound to various protein partners to gain an understanding of the structural origin of PH_n-CC-Ex/protein interactions. We established conditions that yield high-quality crystals of the Tiam1 PH_n-CC-Ex domain and determined the structure of the Tiam1 PH_n-CC-Ex region in the absence of protein partners (publication #24). In addition, in collaboration with (University of North Carolina), we identified that the p67 subunit of NADPH oxidase (p67phox) interacts with Tiam1 through the PH_n-CC-Ex domain (publication #23). Both Tiam1 and p67phox are part of a novel polarity complex that provides the positional cues to direct spatially localized reactive oxygen species signaling. Ongoing studies in my laboratory are focused on determining complexes of the PH_n-CC-Ex domain bound to partner proteins to elucidate the structural basis for signaling specificity. These studies are funded by a National Science Foundation CAREER Award.

Studies of Tiam1 regulation and structure. Although the studies described above have provided a wealth of information on the structure and function of isolated Tiam1 domains, knowledge of how these domains are integrated to regulate the GEF activity of Tiam1 is lacking. We are interested in (i) elucidating the role of intramolecular Tiam1 interactions in the regulation of auto-inhibition and (ii) determining how intermolecular protein-protein interactions and phosphorylation relieve this inhibition to activate Tiam1. To address these experimental problems, we have created several protein fragments that contain different combinations of the five domains in Tiam1. The goal is to use biochemical and structural approaches to identify the Intermolecular mechanisms that regulate GEF activity. Our preliminary data have revealed that the N-terminal PH-CC-Ex domain is critical for Tiam1 auto-inhibition. Moreover, we have determined low resolution structural models for several of the Tiam1 fragments using small angle x-ray scattering (SAXS). Together, these data are beginning to define the mechanisms for how auto-inhibition is relieved by protein-protein interactions. Ongoing work will strive to elucidate the atomic structures of the activated and inhibited states of Tiam1 in an effort to reveal the mechanisms of regulation. Because Tiam1 is associated with the regulation of cell polarity and neuronal processes, understanding the regulatory mechanisms may provide novel insights into how deregulation leads to disease. These studies are funded by a CAREER Award from the National Science Foundation.

This first project involves the soil bacterium Myxococcus xanthus, a model organism for studying chemosensory signal transduction systems that regulate developmental gene expression, motility, and biofilm formation. Analysis of the M. xanthus signaling systems is expected to improve our understanding of chemosensory systems in bacteria and provide new insights into the regulation of biofilm formation and surface gliding motility. The primary focus of this project is to profile the specificity of two-component systems (TCS) in M. xanthus. Two-component systems are comprised of a histidine kinase (HK) and a response regulator (RR) and are known to regulate the M. xanthus developmental program. Previous work by the ratory revealed that the Che3 chemosensory pathway is cross-regulated by the CrdS/A two-component system. In addition to CrdA, M. xanthus contains 26 other NtrC-like RR protein homologs that are phosphorylated (and dephosphorylated) by their cognate HKs. Although it is generally presumed that HK/RR pairs are specific, the extent of cross-talk (unwanted interactions) versus cross-regulation between HKs and RRs in M. xanthus was not known. Iv a graduate student in laboratory, took a systems approach to this problem and his results indicated that both the kinase and phosphatase activities had essentially no cross-talk on a physiological time scale. Because both HKs and RRs have a high degree of amino acid identity, we sought to understand the physical basis for HK/RR specificity. N (an RA in my laboratory), in collaboration used isothermal titration calorimetry to determine the affinities of cognate and non-cognate with N HK/RR Interactions. The results showed that cognate HK/RR pairs had similar dissociation constants (~1μΜ),

while non-cognate HK/RR had little to no affinity. Moreover, using mutagenesis we created a CrdS mutant whose RR specificity was switched to a non-cognate RR. This mutant no longer bound CrdA, but had an affinity of ~1µM for its new RR. These are the first quantitaive data to show that binding affinity is a critical parameter in defining HK/RR specificity. These data have been submitted for publication (publication #25).

t (Chair of Microbiology, The second project is in collaboration with and involves structural studies of the Staphylococcus aureus SrrB/A two-component system. The SrrB/A TCS is a key regulator of S. aureus virulence factors and directly regulates the production of the toxic shock syndrome toxin-1 (TSST-1). As the name suggests, this toxin is the causative agent of toxic shock syndrome but it also contributes to methicillin-resistant (MRSA) infections and their complications. The laboratory identified that treatment of S. aureus cultures (or infected rabbits) with coenzyme Q (CoQ1) or glycerol monolaurate (GML) results in downregulation of TSST-1 and prevents infection in low oxygen environments. These and other studies suggest that the direct target of CoQ1 is the SrrB/A TCS. The SrrA protein contains a RR and DNA-binding domain that regulates expression of various genes including TSST-1. SrrA activity is regulated by SmB, a HK that contains a PAS domain. The PAS domain is hypothesized to bind heme and regulate HK activity in a redox-dependent manner. The goals of this project are to elucidate the structural basis for SrrA and SrrB regulation. We have expressed several SrrA and SrrB expression constructs and begun biophysical characterization. We now have evidence that the PAS domain binds home, reinforcing our working hypothesis. Recently, we obtained SAXS data of the entire cytoplasmic domain of SrrB. This model suggests that direct PASkinase domain interactions might regulate SrrB function. Future studies will combine NMR and X-ray crystallography to elucidate the structures of both SrrA and SrrB to provide insights into their regulation. We will leverage the cell biological expertise of (to validate in vivo the structural principles uncovered in our studies. These studies are the subject or perioring proposal submitted to the Burroughs Welcome Fund.

(3) Other collaborations on campus. My laboratory has had several collaborations at the University of Iowa. In collaboration with I (Med. Chemistry), we determined a model of the asialoglycoprotein receptor (ASGP-R) bound to an oligosaccharide (publication #18). We collaborated with (Internal Medicine) on a project concerning SKP Cullin F-Box protein ligases, which led to a manuscript (publication #19). We are collaborating with Chemistry) on a project concerning the structural mechanism for the allosteric regulation of an RGS domain protein by a small-molecule inhibitor (manuscript in preparation). In addition, in collaboration with L (Biochemistry), we performed preliminary NMR studies on the protein BAF. Finally, we have supported the research of Dr. Pharmacology) by helping with the biophysical characterization of the mitochondrial fusion protein Mff. In several of these collaborations we have written sections that were included in grant proposals.

Intramural Awards. I was supported by two intramural grants during the first two years of my appointment in Biochemistry. The first grant was awarded by the American Cancer Society through the Holden Cancer Center. I also received an award from the Carver Charitable Trust. Both of these grants funded preliminary studies on Tiam1 that were critical for obtaining an American Heart Association grant.

PERSONAL STATEMENT OF SERVICE

Since joining the faculty! have been involved in serving the Department of Biochemistry, the Carver College of Medicine (CCOM), and various national (and international) organizations. Overall, my efforts have been largely in the recruitment of students and supporting structural biology initiatives. Below! outline the major service contributions to the University of lowa over the past several years.

Departmental Service.

I have served on various committees as a member of the Department of Biochemistry. Perhaps the most noteworthy has been my participation in the Biochemistry Graduate Student Admissions Committee, which I chaired during the last year of service. While Chair, I led an effort to add a vigorous component of recruitment to the committee. The committee implemented an "open house" for local colleges and universities that has grown in scale, and is currently under the auspices of the Biosciences Program and CCOM. Under my guidance, the admissions committee redesigned the Departmental web page and a new postcard mailer used for recruitment. Although it is difficult to assess the impact of these changes on recruitment in the short term, it is clear that these efforts have increased the Department's visibility state-wide and regionally.

I also served as the Director of the Biochemistry Summer Undergraduate Research Fellowship (BSURF) program. BSURF is the Department's summer research program for students from outside the University of Iowa. As the director, I updated the application process and extended the program from 8 to 10 weeks to be more competitive with other national research summer programs. In 2012, the Department initiated a program to included students from India in BSURF. These students are formally Khorana Scholars, a program established by the University of Wisconsin-Madison (http://www.biochem.wisc.edu/faculty/ansari/khorana_program/). As a BSURF I also revamped the student summer enrichment events. This included designing a weekly departmental lecture series, coordinating a visit to Genencor (a subsidiary of DuPont that produces proteins commercially), and various social events. During the weekly lectures, the students were exposed to different aspects of biochemistry (microscopy, structural biology, bioinformatics) and received training on writing job resumes and giving presentations (oral and poster). Overwhelmingly, the students were very pleased with the BSURF program.

College of Medicine Service.

As member of the Carver College of Medicine I have served on numerous Graduate and Medical School admissions and recruiting committees. In particular, I have served on the Biosciences Admissions Committee and the MSTP Admissions and Recruitment Committees. Both committees evaluate and Interview a large number of candidates yearly. I have also represented the CCOM at the Annual Biomedical Research Conference for Minority Students (ABRCMS) multiple times. At the 2009 ABRCMS meeting, I was fortunate to meet several students and faculty from Morehouse and Spelman Colleges, two historically African American liberal arts colleges. This interaction catalyzed an unprecedented event that should have a lasting impact on diversity at the University of Iowa. Namely, this initial contact led to several visits by Morehouse and Spelman faculty and students that I helped organize. These visits were intended to acquaint their faculty and students with the various graduate programs and program directors across all University of lowe Colleges. In October 2010 I was invited to a recruiting event at Morehouse College that included a scientific lecture to Department of Chemistry. Importantly, the CCOM has continued to visit Morehouse College on a consistent basis. Since the initial contact, several students from Morehouse and Spelman Colleges have enrolled in summer research and graduate programs at the University of Iowa. Continued strengthening of the interactions between Morehouse College and the University of lowe should be a major step in increasing the diversity at the University of lowe and recruiting top minority students into Ph.D. and Medical School programs.

As faculty member at CCOM I have also participated in the management and oversight of Core Facilities. During the Summer of 2007 I was the "de facto" NMR F. while the position was vacant. I also served on the search committees that hired the current directors of the CCOM Nuclear Magnetic Resonance and Crystallography Facilities. Currently I am an active member of Structural Biology Advisory Committee, which provides oversight to the Protein Crystallography and Nuclear Magnetic Resonance Facilities. I have contributed to new instrumentation grants and the renewal of training grants throughout campus. In particular, I have

contributed to the acquisition of a new 600 MHz instrument in the Department of Chemistry and high-throughput screening robot in Medicinal Chemistry.

National Service.

As a faculty member at the University of Iowa, I have taken an active role in service at the national level. I have chaired sessions at the Annual Biophysical Society Meeting and served on the organizing committee for the Great Plains Regional Annual Symposium (GRASP) on Protein and Bimolecular NMR Meeting held at the University of Kansas. I was recently appointed as an Associate Editor to BMC Biochemistry and have been a peer reviewer for numerous scientific journals. In addition, I have served on the review panels of federal (NSF and NIH), private (AHA) and international granting agencies.

As part of an NSF Career Award, I established a yearly "lowa Biochemistry Workshop" to create research and education partnerships with faculty from primarily undergraduate institutions (PUIs) throughout lowa. These workshops are also intended to familiarize PUI faculty and students with new experimental biochemical and biophysical methods that might be incorporated into didactic courses and/or lead to future collaborative projects. The first lowa Biochemistry Workshop was held in the Summer of 2011 and focused on biological NMR spectroscopy. I have organized two other workshops – one on macromolecular crystallography and small angle X-ray scattering techniques (Summer 2012) and another on single-molecule biophysics (Summer 2013). Over the last three years the workshops have attracted ~50 faculty and undergraduate students from nearly 14 distinct lowa colleges. In addition, nearly 50 faculty and students from the University of lowa routinely participate yearly. By all accounts the workshops have been very successful and participants have been very pleased with the organization and content (advertisement flyers and reviews are Included in Appendix I).

The workshops have also had farther-reaching outcomes. Specifically, as a result of the initial workshop, Professor From Loras College in Dubuque, IA spent a summer and a sabbatical in my laboratory working on an NMR-based structural project. His sabbatical was funded through a supplemental awarded to my original NSF Career Award. This project is now nearly complete and will be a contributing author on a manuscript. Moreover, as a direct result of his experience in my laboratory, initiated an NMR-based laboratory course at Loras College which continue to support.