BIOGRAPHICAL SKETCH

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NAME: Zimmet, Austin

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

POSITION TITLE: Graduate Student

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)	END DATE MM/YYYY	FIELD OF STUDY
Franklin and Marshall College, Lancaster, PA	BA	05/2014	Chemistry
University of Pennsylvania, Philadelphia, PA	PHD	03/2021	Biochemistry and Molecular Biophysics

A. Personal Statement

My research focuses on the molecular basis of cytoskeletal regulation and its role in human disease. I have been involved in multiple research projects, spanning fields from chemistry to biophysics. These training settings have been instrumental in my development as a technically skilled researcher formulating hypothesis driven research. In my sophomore and junior years at Franklin and Marshall College, I worked with Dr. Christine Phillips-Piro, using a structure-guided approach to study heme distortion in the nitric oxide sensor protein, HNOX. I created a series of mutants to determine which residues were essential for heme bending. I did my senior year thesis project with Dr. Scott Van Arman studying NADH/FADH2 synthetic analogs and their viability as hydride donors. I published work showing that a Hantzsch amide could be used as a safe, synthetic reagent for transfer hydrogenation reactions. Moreover, throughout college I presented both of my projects at multiple poster sessions. I also had a recurring internship in industrial chemistry at Stoner Inc. Here, I worked on an R&D team to formulate various glass treatments and aerosol products. I learned how to troubleshoot production issues and design new assays to test merchandise. As a post-bac at the NIH, in Dr. Mayer's lab I studied the structural and biochemical properties of post synaptic ionotropic glutamate receptors (iGluRs). Seeking to gain structural and biochemical understanding of an evolutionarily important iGluR from primitive metazoans, I found that these species' iGluRs were not glutamate receptors at all, but instead bound to and activated exclusively by glycine. This was fascinating insight into the evolutionary biology of iGluRs and synapses as a whole. This work resulted in two publications. As a Ph.D. student in the lab of Professor Roberto Dominguez, a world-leader in actin cytoskeleton regulation and structural biology, I have pursued my interest in mechanistic biochemistry and biophysics. My proposed research will address the molecular mechanism by which actin nucleation by Arp2/3 complex is regulated and Arp2/3 complex's role in focal adhesion formation; processes that are linked to muscular dystrophy, cardiomyopathies, platelet dysfunction and many other diseases. I will be using *in vitro* biochemical and structural techniques to determine the mechanisms that facilitate these processes. In future work, I hope to understand how actin structures form, change and disassemble in a cancer specific context, and ultimately discover novel therapeutic approaches that target actin cytoskeleton rearrangements in cancer metastasis. The proposed work here will allow me to further my training in biochemical and biophysical approaches towards this goal. This experience will also allow me to pursue my goals as a scientific mentor which I have continued to develop as a student. I have already taught in several high school and middle school settings, as well as supervised the work of a high school intern in our lab. Taken together, these experiences will provide me with a solid foundation for a career as an independent researcher and mentor to future generations of scientists.

B. Positions and Honors

Positions and Employment

2012 - 2014 Research and Development Intern, Stoner Inc., Quarryville, PA
2014 - 2015 Postbaccalaureate IRTA, NICHD, Bethesda, MD

Honors

2009	F&M Dean's Scholarship, Franklin and Marshall College
2012	F&M Organic Chemistry Award, Franklin and Marshall College
2012	F&M COG Grant, Franklin and Marshall College
2013	F&M COG Grant, Franklin and Marshall College
2014	Southeastern Pennsylvania Section of the American Chemical Society Award, American Chemical Society
2017 - 2018	NIH T32 Structural and Molecular Biology training grant, University of Pennsylvania

C. Contribution to Science

1. Single celled organisms need to quickly adapt to their surrounds. Bacteria use a variety of 'sensor' proteins to monitor their environment. In Dr. Piro's lab I studied a nitric oxide binding protein that anaerobes used to monitor the composition of their environment. We used a mutagenic approach to study how the protein, HNOX, bent its heme cofactor to specifically coordinate nitric oxide at sub-nanomolar affinity. By understanding how bacteria sense their environment, we could tap into a novel antibiotic chemical space.

Poster:

   a. **Zimmet AJ**, Piro, C., A mutagenic approach to understanding NO binding coordination in *tt*HNOX. Franklin and Marshal summer research poster session. 2012

2. Ruthenium catalysts are currently the industrial standard for hydrogenation reactions. These reactions occur under dangerously high pressure and temperature and create many toxic side products. I was able to show that a Hantzsch amide could be used as a safe, synthetic reagent for transfer hydrogenations of α, β unsaturated ketones and aldehydes with almost 100% conversion.

Posters and Citation(s):

   a. Van Arman SA, **Zimmet AJ**, Murray IE. A Hantzsch Amido Dihydropyridine as a Transfer Hydrogenation Reagent for α,β-Unsaturated Ketones. J Org Chem. 2016 May 6;81(9):3528-32. PubMed PMID: 27083498.
   b. **Zimmet AJ**, Van Arman SA. A Hantzsch Amido Dihydropyridine as a Transfer Hydrogenation Reagent for α,β-Unsaturated Ketones Franklin and Marshal summer research poster session. 2013

3. Ionotropic glutamate receptors (iGluR) are ligand-gated, nonspecific cation channels that mediate excitatory signals in postsynaptic cells. iGluRs are important in memory development and have been linked to various neurological disorders including, but not limited to, Alzheimer's, Parkinson's, and schizophrenia. The focus of my research was to gain structural and biochemical understanding of an evolutionarily important iGluR from the comb jellies, *M. leidyi* and *P. bache*. Recent work has shown these species are a key pit-stop on the metazoan phylogenetic roadmap and are the first species to develop a neural network. The comb jelly's primitive neural network also has synapses that utilize iGluRs. These iGluRs are likely the first of the diverse family that higher metazoans utilized. Therefore, our goal was to understand the mechanism of ligand binding and activation in these channels. Towards this end, the members of the lab and I used various ligand binding assays, structural analysis and electrophysiology. Interestingly, we found that the iGluRs we studied were not glutamate receptors at all but bound to and were activated by glycine exclusively. The NMDA family of iGluRs are known to be co-activated by glycine and therefore we hypnotized that these proteins may be NMDA precursors.

Citation(s):

   a. Alberstein R, Grey R, **Zimmet A**, Simmons DK, Mayer ML. Glycine activated ion channel subunits encoded by ctenophore glutamate receptor genes. Proc Natl Acad Sci U S A. 2015 Nov 3;112(44):E6048-57. PubMed PMID: 26460032.

4. Following up our work elucidating novel NMDA-like receptors in primitive metazoans, I sought to understand the biochemical basis of their activation and ligand binding. Towards this end, through

biochemical assays and MD simulations we found a 'molecular-lock', consisting of an inter-domain salt bridge, that pinched the ligand binding domain closed. It is likely this molecular lock generates the free energy for the conformational change required to open the channel. This work showed how these receptors are regulated at a mechanistic level and lent insight into how NMDA receptors may work.

a. Yu A, Alberstein R, Thomas A, **Zimmet A**, Grey R, Mayer ML, Lau AY. Molecular lock regulates binding of glycine to a primitive NMDA receptor. Proc Natl Acad Sci U S A. 2016 Nov 1;113(44):E6786-E6795. PubMed PMID: 27791085.

D. Research Support

Ongoing Research Support

F31-HL146077 NIH/NHLBI Zimmet, A (PI) 01/01/19 – 12/31/21 $40,600
"Structure-function study of Arp2/3 complex and a novel role for actin branching"

E. Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE
	FRANKLIN AND MARSHALL COLLEGE	
2009	HUMAN GENETICS	B
2009	GENERAL CHEMISTRY 1	B
2009	CALCULUS 1	A
2010	EVOL, ECOL, HEREDITY	B
2010	GENERAL CHEMISTRY 2	B+
2010	CALCULUS 2	A-
2011	PRINCIPLES OF PHYSIOLOGY AND DEVELOPMENT	A
2011	ORGANIC CHEMISTRY 1	A
2011	HISTORY OF SPACE AND TIME	A
2012	CELL BIOLOGY	A
2012	ORGANIC CHEMISTRY 2	A
2012	CALCULUS 3	PASS*
2012	FUNDEMENTALS OF PHYSICS 1	A
2012	FUNDEMENTALS OF PHYSICS 2	A
2012	KINETICS & THERMODYNAMICS	B+
2012	INTRODUCTORY BIOCHEMISTRY	B+
2012	DIRECTED STUDY IN CHEMISTRY	A
2013	INORGANIC CHEMISTRY	B
2013	STRUCTURE AND BONDING	A-
2013	MEDICINAL CHEMISTRY	A-
2013	CHEMISTRY OF SOLAR ENERGY CONVERSION	PASS*
2013	CHEMICAL ANALYSIS	B+
2013	INDEPENDENT STUDY IN CHEMISTRY	A
2014	SCIENCE TEACHING INTERNSHIP	A-
2014	ADVANCED BIOCHEMISTRY	A-
2014	INDEPENDENT STUDY IN CHEMISTRY	A
	UNIVERSITY OF PENNSYLVANIA	
2015	CELL BIOLOGY	A-
2015	MACROMOLECULAR BIOPHYSICS: PRINCIPLES AND METHODS	A
2015	MACROMOLECULAR CRYSALLOGRAPHY: METHODS AND APPLICATIONS	A-
2015	NMR IN STRUCTURAL BIOLOGY	A
2015	LAB ROTATION	A

YEAR	SCIENCE COURSE TITLE	GRADE
2016	BIOLOGICAL DATA ANALYSIS	A
2016	STRUCTURAL AND MECHANISTRIC BIOCHEMISTRY	A
2016	PRINCIPLES OF MECHANO-ENZYMES	A
2016	COMPUTATION PROGRAMING IN BIOCHEMISTRY AND BIOPHYSICS	A
2016	LAB ROTATION	A
2016	SELECTED TOPICS IN CHEMISTRY	A
2016	INDEPENDENT STUDY	A
2016	LAB ROTATION	A
2013	GRE GENERAL TEST	
	Verbal Reasoning: 157/170	(76%)
	Quantitative Reasoning: 159/170	(73%)
	Analytical Writing: 4.0/6.0	(60%)

*CLASS TAKEN FOR CREDIT ONLY. NO GRADE GIVEN.