BIOGRAPHICAL SKETCH

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NAME: Molly Martorella

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

POSITION TITLE: MD/PhD 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	Start Date	Completion Date	FIELD OF STUDY
Oberlin College, Oberlin, OH	B.A.	09/2010	05/2014	Biochemistry & Neuroscience
Columbia University, New York, NY	Ph.D.	09/2018	05/2023 (expected)	Integrated Program in Cellular, Molecular, and Biomedical Studies
Columbia University, New York, NY	M.D.	09/2016	05/2024 (expected)	Medicine

A. Personal Statement

My long term career goals are to become a physician scientist leading an academic lab that develops novel diagnostic, screening, and treatment strategies in addition to investigating underlying genetic and environmental mechanisms of disease risk. When I began my MD/PhD, I envisioned myself studying molecular mechanisms of neuropsychiatric illness that would elucidate novel treatment targets, diagnostic biomarkers, or patient subtypes. However, during my medical training I realized many diseases share the same limitations and complications as neuropsychiatric disease - they are extremely heterogeneous in their presentation, our diagnostic tools may be limited in their accurate characterization or ability to predict future outcomes, and our treatments are not one size fits all and often come with debilitating side effects that can limit their efficacy and use. I decided my interests lie more broadly in understanding causative mechanisms of common, complex disease, and that studying the genetic effects of gene regulation suited my future goals of influencing clinical approaches to patient care.

Thus far my research experience has been diverse, but working across many different levels of scientific inquiry has given me perspective and direction regarding my future research goals. During the summer after my sophomore year of college, I worked on developing polymer platforms for drug delivery, and this experience taught me how to leverage biological characteristics of disease and of the body to develop improved therapeutics. My research experiences during my junior and senior year summers, my senior year, and my post-collegiate years focused on understanding neurobiology and behavior. Combined, these projects provided me with fundamental experimental tools for investigating cellular pathways and phenotypes and how these translate to behavioral observations in rodent models. My post-baccalaureate research experience at the University of Virginia was particularly formative for my future, and the skills I learned prepared me for the many aspects of a PhD and of running an academic research laboratory: scientific writing, mentoring, seeking out collaborators, and pushing experimental findings forward.

I joined Tuuli Lappalainen's laboratory because my medical training revealed to me that I was interested in understanding the underlying mechanisms of disease etiology outside the realm of neuroscience, and that I wanted my future work to have potentially more immediate clinical implications. The research I propose here will first leverage my expertise in developing and optimizing novel wet lab methodologies, and during that part of the project I will learn programming skills central to computational genomics (R, unix, and python). My final aim will

develop new ways of measuring disease risk in patient populations, and it will give insight as to the genetic regulatory architecture involved in determining risk. All of these aims combined will give me a complete toolkit for pursuing my future research endeavors – to develop methods of monitoring disease onset, progression, and treatment response, and to understand the genetic regulatory mechanisms underlying these traits. My medical training will give me perspective of the most clinically pressing questions and problems faced in improving medical care, and the extensive training I received prior to my PhD will enable me to run and collaborate with experimental wet labs in addition to spearheading a computational genomics laboratory. Receiving the NRSA fellowship would contribute greatly to my training and development as a future clinician scientist.

B. Positions and Honors

Positions:

2011-2013	Introductory Chemistry lab TA – Oberlin College
2012	Material Research Science and Engineering Center REU – Dr. Todd Emrick, UMass Amherst
2013	Undergraduate Research – Dr. Michael Nee, Oberlin College
2013	HHMI Exceptional Research Opportunities Program – Dr. Richard Huganir, Johns Hopkins
2013-2014	Undergraduate Research – Dr. Jan Thornton, Oberlin College
2014	HHMI Exceptional Research Opportunities Program – Dr. Richard Huganir, Johns Hopkins
2014-2015	Academic Tutor for Math and Science – Varsity Tutors
2015-2016	Post-baccalaureate Research Fellow – Dr. Chistopher Deppmann, University of Virginia
2016-2017	Junior Clinician – Auduban UrgiCare Center in Manhattan

Honors:

2010-2014	John F. Oberlin Scholarship – Academic achievement
2011	CRC Press Chemistry Achievement Award – First years with high achievement in chemistry
2012	Frank Fanning Jewett Award in Chemistry – Second years with unusual promise in chemistry
2013	Harrol and Virginia Baker Scholarship – Exceptional chemistry/biochemistry major
2014	Merck Index Award – Outstanding senior biochemistry major with interests in medicine
2010-2013	Cross Country Academic All-American – National competitor with >3.30 GPA
2012-2014	Track and Field Academic All-American – National competitor with >3.30 GPA
2014	Nu Rho Psi Honor Society – By invitation and with GPA >3.50 in neuroscience major

C. Contributions to Science

1. Developed polymer platform for targeting treatments to cancerous tissues

In the summer of 2012 I was accepted into the Materials Research Science and Engineering Center REU at UMass Amherst and I worked in Dr. Todd Emrick's laboratory designing polymers for use as cancer drug delivery platforms. The majority of drugs are water-insoluble small molecules that if given directly would either be renally cleared before exerting their effect, or, would accumulate in off-target tissues and result in unwanted side effects. Conjugating drugs to polymer platforms slows renal clearance and allows for triggered drug release in response to certain biological microenvironment niches. Cancer forms disorganized vasculature and has poor lymphatic drainage, resulting in an enhanced permeation and retention effect (EPR) of drugs within the diseased tissue. Many cancers also exhibit a local reducing environment. For these reasons, I worked in coordination with a graduate student, Dr. Samantha McRae Page, to develop a polymer platform with improved drug carrying capacity and that released the drug in response to reducing agents. Our final construct formed stable 15-30nm micelles in water, attached the drug using a disulfide linker, and showed less cellular toxicity at higher drug concentrations compared to the drug alone due to the environmentally-triggered drug release.

Publication: McRae Page, S., Martorella, M., Parelkar, S., Kosif, I., and Emrick, T., (2013). "Disulfide Cross-Linked Phosphorylcholine Micelles for Triggered Release of Camptothecin" Molecular Pharmaceuticals. 10 (7): 2684-2692. DOI: 10.1021/mp400114n

2. Showed KCTD1 interacts with key proteins involved in AMPA receptor recycling and memory formation

For the summers of 2013 and 2014 I worked in Dr. Richard Huganir's lab at Johns Hopkins studying long term potentiation of synapses. Strong signaling between pre and post-synaptic neurons leads to long term potentiation of that connection, and these connections are considered to be the substrate for memories. Retention of AMPA receptors at the post-synaptic surface is important for initializing and maintaining excitatory synaptic connections. Many of the proteins involved in localizing receptors to cell surfaces contain PDZ binding domains. The protein KCTD1 contains PDZ binding domains, and I conducted experiments to investigate whether KCTD1 was part of the AMPA receptor recycling complex. I was able to show KCTD1 co-immunoprecipitated with GRIP1 and PICK1, proteins previously identified as part of the AMPA receptor recycling complex. However, co-immunoprecipitation experiments showed KCTD1 did not directly bind KIBRA, a protein shown by the lab to bind PICK1 and GRIP1 as well as play a central role in contextual fear learning and memory. I further investigated the binding of KCTD1 to GRIP1 and PICK1 by performing yeast-two hybrid assays and was able to narrow down the domains involved in the interaction.

Poster: Martorella M, Lala T, Johnson R, and Richard Huganir R. The Role of KCTD1 in AMPA Receptor Recycling and Memory Formation. Poster presented at: Johns Hopkins Summer Research Symposium; 2013 Aug. 2; Baltimore, MD.

3. Demonstrated LRRTM4 increases localization of AMPA receptors at hippocampal post-synaptic densities

For the summer of 2014 I returned to Dr. Richard Huganir's lab at Johns Hopkins to do a capstone project through the HHMI EXROP Scholars Program. Previously, LRRTM proteins 2 and 4 had been shown to have synaptogenic activity in adult mice and to localize with glutamatergic receptors in a heparan sulfate-dependent manner. However, LRRTM proteins are primarily implicated in neurodevelopmental disorders, namely, autism and intellectual disability. For this reason I investigated the effect of LRRTM4 on AMPA receptor surface localization and synaptogenesis using hippocampal neurons isolated from mice at E18 and P0. To do so, I used splicing by overlap extension PCR to generate LRRTM4 tagged with GFP on its N-terminus. I used this method in order to preserve the N-terminal signal peptide and to leave the C-terminal protein-binding domain intact. I transfected and imaged my neuron samples using confocal microscopy, and I was able to determine that LRRTM4 enhanced AMPA receptor surface expression and increased the number of synapses at a developmental stage.

Poster: Martorella M, Johnson R, and Huganir R. Localization of Leucine-rich transmembrane proteins (LRRTMs) at Excitatory Synapses and Implications in Neurodevelopmental Disease. Poster presented at: Johns Hopkins Summer Research Symposium; 2012 Aug. 1; Baltimore, MD.

4. Elucidated exosomes as a potential novel signaling mechanism during sympathetic neurodevelopment

After college I joined Dr. Christopher Deppmann's lab at the University of Virginia to study signaling mechanisms involved in sympathetic neurodevelopment. Neurotrophic signaling is an essential process by which sympathetic neurons are directed towards and innervate their target. Neuronal survival and growth are determined by NT3 signaling along the vasculature, and by NGF release at the target organ. Neurodevelopment begins as a process of overproduction, and neurons are pruned in order to establish the appropriate amount of neuronal innervation, however, a neurotrophin signaling gradient is not sufficient to establish the differential survival of neurons, thus indicating a potential alternative signaling mechanism. I investigated exosomal signaling by developing methods to isolate exosomes from neuronally differentiated PC12 cells and by generating exosome-conditioned media from mouse sympathetic neurons. Collected exosomes were characterized via density gradients, western blot and TEM, and I discovered TrkA, the NGF receptor, to be present in exosomes. To determine the functional consequences of exosomal signaling, I conducted neuronal survival and branching assays. From these experiments, I observed maintenance of neuronal branching in the absence of NGF and enhanced branching when exosomes and NGF were both present.

Publication: Martorella, M., Barford, K., Winckler, B., & Deppmann, C. D. (2017). Emergent Role of Coronin-1a in Neuronal Signaling. Vitamins and Hormones, 104, 113–131. http://doi.org/10.1016/bs.vh.2016.10.002

D. Additional Information: Research Support and/or Scholastic Performance

Oberlin College, 2010-2014
Majors: Biochemistry & Neuroscience
GPA = 3.86

YEAR	COURSE TITLE	GRADE
2010	Structure and Reactivity	A
2010	Calculus II	A
2010	Cats, Cattle, & Corn	A
2011	Chemical Principles	A
2011	Stat Methods for Biological Sciences	A-
2011	The Brain: Intro to Neuroscience	A
2011	Neuroscience Laboratory	P
2011	Writing: Motives and Methods	A
2011	Organismal Biology Lecture	A
2011	Organismal Biology Laboratory	A
2011	Principles of Organic Chemistry (with Lab)	A
2011	Elementary Latin	P
2011	Practicum in Journalism	P
2012	Inorganic Chemistry (with Lab)	A
2012	Bioorganic Chemistry (with Lab)	A
2012	American Constitional Law	B+
2012	Philosophy and Morality	P
2012	Cellular and Molecular Biology Lecture	A-
2012	Cellular and Molecular Biology Laboratory	A
2012	Hormones, Brain and Behavior	A
2012	Philosophy of Science	B
2012	Mechanics and Relativity	B+
2013	Quantum Chemistry and Kinetics (with Lab)	A-
2013	Self-Defense and Community Healing	P
2013	Neuroanatomy	A+
2013	Laboratory in Neuroanatomy	P
2013	Elementary Physics II	A+
2013	Analytical Chemistry (with Lab)	A
2013	Biochemistry (with Lab)	A+
2013	Chinese Thought & Religion	A-
2014	Neuropharmacology	A
2014	Neuropharmacology Lab	P
2014	Senior Seminar - Neuroscience	A-
2014	Independent Research	A-
2014	Abnormal Psychology	A-

Oberlin College Grading System:
Letter Grades - The grades recorded and their equivalents in quality points (used in computing grade-point averages) are as follows:

A+	A	A-	B+	B	B-	C+	C	C-	D	F	W
4.33	4.00	3.67	3.33	3.00	2.67	2.33	2.00	1.67	1.00	0.0	0.0

Pass/No Pass - All passing work (A+ to C-) is given the uniform grade of Pass (P). Work below C- is considered not passing and is given a grade of No Pass (NP). Laboratory courses within the Neuroscience major and single credit electives are graded P/NP.

Columbia University College of Physicians and Surgeons, 2016-Present
GPA = 4.0 (& P/NP)*

YEAR	COURSE TITLE	GRADE
2016	Foundations of Clinical Medicine I	P
2016	Molecular Mechanisms of Health & Disease	P
2016	Clinical Gross Anatomy	P
2016	Biochemistry & Molecular Cell Biology	P
2017	Foundations of Clinical Medicine II	P
2017	The Body in Health & Disease I	P
2017	Foundations of Clinical Medicine Tutorials I	P
2017	Psychiatric Medicine	P
2017	The Body in Health & Disease II	P
2017	Foundations of Clinical Medicine III	P
2017	Foundations of Clinical Medicine Tutorials II	P
2018	Surgery Clerkship	HP
2018	Obstetrics & Gynecology Clerkship	HP
2018	Deep Sequencing	A
2018	Responsible Conduct of Research	P
2018	Seminars in CBMS I	P
2019	Seminars in CBMS II	P
2019	Readings in Human Genetics	Audit

Columbia University College of Physicians and Surgeons grading system is as follows: P indicates pass under pass/fail grading (all courses completed as part of the preclinical curriculum are graded Pass (P) or No Pass (NP)). Courses in the clinical curriculum are graded for the University transcript using grades of honors, high pass, pass, and fail, except for one-week clerkships, selectives, Major Clinical Year Foundations, Mechanisms and Practice, Scholarly Project, and Ready 4 Residency, which are graded pass and fail.

Columbia University Graduate School's grading system is as follows: A, excellent; B, good; C, fair; D, passing but poor; F, failure. +/- are used, from A+ to D-. P indicates pass under pass/fail grading.