BIOGRAPHICAL SKETCH

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NAME: **Singh, Balvindar**

eRA COMMONS USER NAME (credential, e.g., agency login): **singh308**

POSITION TITLE: Graduate Research Assistant, 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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, San Diego, La Jolla, CA	BS	09/2011	Microbiology
University of Minnesota, Minneapolis, MN	PhD	06/2019	Neuroscience
University of Minnesota, Minneapolis, MN	MD, *expected*	05/2021	Medicine

A. Personal Statement

My long-term career plan is to take a systems level approach to investigating neurodegenerative diseases, aiming to understand how neural networks communicate and degenerate in various disease states. Ultimately, I aspire to establish a collaborative and integrated research program, as well as a clinical practice at an academic institution. To achieve such a demanding goal, I am utilizing my time in the lab of Michael Lee PhD to build a foundation of skills and experience essential in this pursuit. Specifically, my current research with Dr. Lee, studying the mechanisms underlying neuronal dysfunction and behavioral changes in Parkinson's disease, supports this goal, allowing me to develop and hone the scientific acumen in order to become successful and independent investigator. Dr. Lee is a role model scientist and demonstrates how to effectively establish and run a strong research laboratory, traits I hope to adopt and nurture during my time in his lab as a graduate student. Improving how scientific discovery translates into improved clinical practice relies on the ability to couple the exponential development of laboratory research with evolving bedside medicine. Given the intricacy and necessity of such a relationship, building a strong foundation in neuroscience and training as a physician-scientist to prepare for a career that communicates across lab and clinic are fundamental goals of my education, learning how to identify gaps in knowledge and ask questions that advance both disciplines. My undergraduate career at UC San Diego was instrumental in helping me forge the intellectual skills and scientific curiosity essential to being successful in the next phase of my training as a dual medical and graduate student. It additionally served to help me refine my career interests and goals. I forayed into basic research, working in the lab of Dr. Stuart Lipton MD, PhD, when he was at the Sanford-Burnham-Prebys Medical Research Institute, studying neurodegenerative diseases. The ability to ask a cohesive scientific question utilizing different experimental approaches expanded my basic research skills from technical and critical thinking perspectives. Dr. Lipton served both as scientific mentor and physician-scientist role model, demonstrating how to structure one's career and research to be successful in both lab and clinic.

To gain exposure into different academic environments, research interests, and careers, I spent a summer at Stanford University as an Amgen Scholar in the lab of Dr. Olivia Martinez PhD, studying microRNAs in malignancies, two interests of mine outside of neuroscience the time. The program and research pushed me to become more autonomous in the laboratory setting, and showed me the uniqueness of integrated medical and research training and careers. While this was productive and informative, I discovered that neuroscience remained my calling. During my senior year at UC San Diego, and the year following, I joined the lab of Dr. Jonathan Sebat PhD, whose lab brings a genomics approach to the study of psychiatric disorders. My tenure with Jonathan illustrated one exciting area and methodology of disease research with translational promise. This cemented a desire to bridge the gulf between increases in scientific knowledge and improved clinical care for individuals suffering from neurological disorders, a gulf where the physician-scientist holds great potential.

I aim to use my MD/PhD training at the University of Minnesota to hone my skills as a scientist in technique, methodology, and thinking, and further refine my career direction for research and clinical specialty. It did take an increased amount of time for me find a thesis advisor and lab that fit my training goals, scientific interest, and professional aspirations. With the support of the MSTP and Graduate Program in Neuroscience, I was fortunate

to identify Dr. Michael Lee as my advisor. He has an extensive record of training successful academic scientists and performs intellectually stimulating research with strong connections to human disease, a key factor in choosing him and his lab. My decision to join the lab of Dr. Michael Lee is additionally due to his strength as a mentor, our ability to work well together, and the potential to gain expertise in a breadth of skills, approaches, and knowledge pertaining to basic neuroscience and neurodegeneration research. I am committed to rigorous graduate training that prepares me for success as an independent and competitive investigator. I am confident that this proposal and training plan will facilitate my career and professional goals. I believe neurodegeneration research suits the unique physician-scientist skillset and is of great interest to me. With aging being the greatest risk factor for developing a majority of neurodegenerative disorders, and current medical treatments improving management of chronic conditions, the need to better understand nervous system dysfunction and degeneration is of huge clinical and scientific relevance. The ability to learn how to think, become expert in a specific field, develop a varied skillset, and train towards becoming an independent investigator are goals of mine that are incredibly well matched by Dr. Lee. When I return to medical school to complete my clinical clerkships, I will use this time to identify a specialty that complements my neuroscience discipline, graduate training, and career goals. While this picture is evolving, it is a tremendous privilege, motivating me to be a curious, driven, and dedicated individual who contributes to the advancement of our body of scientific knowledge, clinical practice, and care of patients and community.

B. Positions and Honors

ACTIVITY/OCCUPATION	START DATE (mm/yy)	END DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Undergraduate Research Assistant	01/09	03/11	Neurological disorders	SBP Medical Research Institute	Stuart Lipton MD, PhD
Amgen Scholar	06/10	09/10	Immunology	Stanford University, Dept. of Surgery	Olivia Martinez PhD
Staff Research Associate	06/11	06/12	Psychiatry	UC San Diego, Dept. of Psychiatry	Jonathan Sebat PhD
Volunteer Medical Student Clinician	01/13	Present	Medicine	Phillips Neighborhood Clinic, UMN	Brian Sick MD
GPN Student Board	07/14	07/15	Neuroscience	University of Minnesota GPN	David Redish PhD (DGS)
MSTP Retreat Planning Committee	07/13	07/15	MD/PhD leadership	University of Minnesota MSTP	Jenny Zick (MSTP Student Advisory Committee Chair)
MSTP Student Advisory Committee, Chair	07/15	07/16	MD/PhD leadership	University of Minnesota MSTP	Yoji Shimizu PhD (MSTP Director)

2018 *Roth-Steer Award for Research in Alzheimer's Disease.* Awarded by the University of Minnesota Medical School.

2017 *3rd Place: Walling Neuroscience Discovery Day, Poster Session*. Annual University of Minnesota neuroscience-based research symposium.

2015 *1st Place: Emory University Virtual International Global Health Case Competition*, Emory University, Global Health Initiative. As winners of the UMN Global Health Case Competition, my team participated in the international version of this competition, hosted by Emory University. We competed against schools from across the nation, Africa, Europe, and Central America. The prompt for this competition was how to address gun violence in Honduras.

2015 *1st Place: University of Minnesota Global Health Case Competition*, UMN Center for Global Health and Social Responsibility. The competition is an opportunity for interdisciplinary teams to analyze real-world global health challenge with the goal of providing strategic recommendations and proposals to address these challenges efficiently and effectively. My team was made up of two MD/PhD students (including myself), one dual MHA/MBA student, one MBA student, and one PharmD student. We had one week to

address the prompt and create a 15-minute presentation presenting our recommendations on where to hold the 2020 Olympic Games and how to use the Games as a venue for improvements in public health worldwide. Judges, including engineers, epidemiologists and physicians, graded presentations.

2014 *Most Clinically Applicable Proposal,* Essentials of Clinical Medicine, Quality Improvement Project, UMN Medical School. ECM is a three-part course in the medical school curriculum. Students are organized into groups and are tasked to identify a clinically-relevant issue and propose a solution via poster. The "Most Clinically Applicable Proposal" was awarded to the group presenting an intervention that did the best job of addressing a problem and providing a solution with great potential for implementation. This award was chosen by UMN faculty, leadership, and Medical School Dean Brooks Jackson MD, MBA.
Singh B, Chamberland C, Thompson D, Gursahaney D, & Donaldson, M*. Assessing Mental Health in Caretakers of Children with Down Syndrome*

2011 *Provost Honors*, Revelle College, UC, San Diego. 2009-11 quarters. Provost Honors is a quarterly award for students achieving 3.5 GPA or higher in at least 12 graded units for that quarter.

2010 *Amgen Scholar,* Stanford University School of Medicine. The Amgen Scholars Program provides hundreds of selected undergraduates with the opportunity to engage in hands-on research at many of leading educational institutions.

C. Contributions to Science

I. *In vitro* system to examine cellular responses to environmental risk factors for Parkinson's disease
I began my scientific career working with Dr. Stuart Lipton and the Sanford-Burnham-Prebys Medical Research Institute (now at the Scintillon Institute). At this time, Dr. Simone Engelender was working in the lab on sabbatical from the Rappaport Institute in Israel and was my mentor on a day-to-day basis within the Lipton lab. My project was to develop an *in vitro* model for neurodegeneration. More specifically, our model system was the human neuroblastoma SH-SY5Y cell line, utilizing these cells as a platform for creating a model for understanding the neuronal responses to the pesticide paraquat. Paraquat is an environmental toxin that has a very similar structure to MPTP, an agent that is sufficient to cause human Parkinsonism. While increasing evidence emerges implicating gene mutations in the onset of Parkinson's disease (PD), the role of environmental chemicals in the pathogenesis of the disease is debated, but certain pesticides, like paraquat, are linked to PD by epidemiological studies. Thus, my project was to characterize neuronal responses to chronic paraquat exposure *in vitro*. My metric for identifying an appropriate dose was at least 50% survival at 5 days of exposure, achieved via a dose-response curve. With this concentration established, we then moved onto the experimental phase of our study, using biochemical techniques to analyze cellular responses pesticide exposure. Since neurons have elaborate cytoskeletal structures, we were interested in paraquat-induced changes in the cytoskeleton, examining expression levels of key proteins such as spectrin, ankyrin, actin, and tubulin.
[Poster] **Singh B**, Engelender SE, & Lipton SA. *Establishing a model for chronic paraquat exposure-mediated neurodegeneration in SH-SY5Y neurons.* UC San Diego Undergraduate Research Conference, June 2010

II. B cell transformation by modification of post-transcriptional regulation
Epstein-Barr Virus (EBV) is one of the most common human viruses and is implicated in the development of post-transplant lymphoproliferative disorder (PTLD), a recognized complication of solid organ transplantation. To further examine the link between EBV and malignancy, my project focused on understanding how expression of latent membrane protein 1 (LMP1), a viral protein that regulates EBV expression, can modulation B cell signaling and post-transcriptional regulation to promote cell survival, proliferation, and ultimately transformation. Through the use of patient-derived B cells, we created a stable cell line expressing an inducible version of LMP1. Following induction of LMP1 signaling, we would assay cells via biochemistry at various time-points post induction to see how various oncogenic pathways and proteins change, such as the p38/MAP kinase and mTOR cascades. Additionally, we isolated RNA from these cells to examine and demonstrate that how LMP1 activation alters microRNA profiles, implicating changes in post-transcriptional regulation and cell signaling as mechanisms for mediating these changes in B cells to produce malignancy. This work ultimately aims to provide areas for therapeutic intervention in cases of EBV-mediated malignancies such as PTLD, through microRNA-based therapies, anti-sense oligonucleotides, or modulators of cell signaling proteins.
[Talk] **Singh B**, Harris A, Krams S, & Martinez OM. *Modulation of host cellular microRNA by Epstein-Barr Virus Latent Membrane Protein 1 in B lymphocytes.* Amgen Scholar Symposium, August 2010

[Poster] **Singh B**, Harris A, Krams, S, & Martinez OM. *Characterization of major signaling domains in Epstein-Barr Virus Latent Membrane Protein 1 in B lymphocytes.* Amgen Scholar Symposium, August 2010

III. Computational approaches to understanding genomic mutations in psychiatric disorders

During my tenure as a staff research associate with Dr. Jonathan Sebat at UC San Diego, one of my projects involved genomic analysis of identical twins with autism spectrum disorder (ASD). ASD is a neurodevelopmental disability that can manifest as deficits in socialization, various behaviors, and communication, affecting approximately 1-2% of individuals in North America. Our goal of using affected twins and their parents for genomic analysis was to understand how de novo mutations in genomes contribute to disease pathogenesis. My initial efforts in the project focused on handling of patient samples, preparing DNA for whole-genome sequencing by our collaborators. During the second phase of the study, I worked with a postdoctoral fellow, Dr. Jacob Michaelson, to learn how develop and apply computational tools to genetic information, and also interpret large datasets. Importantly, we wrote software in R that allowed us to analyze compare sequences between individuals and identify single base pare changes. Another layer to this was identifying the number of mutations per individual and how often those sites were found to be mutated in healthy individuals or those diagnosed with ASD. We then added in tools to examine the loci and genomic regions of these mutations and found that some of genomic regions are more likely to mutate than others, and that mutations in these regions are located in genes linked to ASD and other psychiatric disorders.

[Publication] Michaelson JJ, Shi Y, Gujral M, Zheng H, Malhotra D, Jin X, Jian M, Liu G, Greer D, Bhandari A, Wu W, Corominas R, Peoples A, Koren A, Gore A, Kang S, Lin GN, Estabillo J, Gadomski T, **Singh B**, Zhang K, Akshoomoff N, Corsello C, McCarroll S, Iakoucheva LM, Li Y, Wang J, Sebat J. *Whole-genome sequencing in autism identifies hot spots for de novo germline mutation.* Cell*. 2012; **151**:1431-1442. PMCID: PMC3712641.*

IV. Characterizing a population of spinal interneurons *in vivo*

During my tenure as a student in the laboratory of Mark Masino PhD at the University of Minnesota, I investigated the spinal circuits involved in vertebrate locomotion through the use of zebrafish (Danio rerio). The vertebrate spinal cord contains a central pattern generator (CPG) capable of producing coordinated locomotion (e.g., walking, swimming, flying), even in isolation from the brain. However, the neuronal populations that generate the locomotor rhythm are unknown. In particular, my project was to characterize one population of spinal neurons, the ventrally-located and excitatory V3 interneurons, in the production of motor activity. I employed electrophysiological and imaging techniques, and behavioral analysis, to parse out V3 neuron function in the zebrafish. Complementing these experiments, I worked with Dr. Masino and another graduate student in the lab to develop the MATLAB software that allowed us to analyze fine motor behaviors, swimming characteristics, and neuronal function data obtained. Laser-ablation of V3 neurons in zebrafish spinal cord served as a comparative model to understand how V3s influence locomotion. In comparing ablated versus intact animals, I discovered that gross motor (swimming) behaviors remain intact even in animals lacking V3 interneurons, and also that these animals are capable of producing coordinated movements. However, in these studies, I did reveal that removal of V3 interneurons impairs the ability of zebrafish activate certain motor neuron populations, impairing its ability to swim a faster speeds.

[Talk] *Investigating a promising population of spinal cord interneurons in the production and regulation of coordinated locomotor activity*. University of Minnesota MSTP Annual Retreat, July 2015

[Talk] *Applying genetic and functional techniques in zebrafish research to studying neuronal function and locomotor activity in vivo.* University of Minnesota Zebrafish Core Facility Users Meeting, October 2015

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

YEAR	**GRADUATE SCHOOL, UMN-** COURSE	GRADE	YEAR	**GRADUATE SCHOOL, UMN** - COURSE	GRADE
2014	Cellular and Molecular Neuroscience	A-	2015	Neuroscience Career Skills	S
2014	Systems Neuroscience	V	2015	Neurostatistics	A-
2014	Itasca Neurobiology Lab	S	2015	Readings in Neurobiology	*S*
2014	Laboratory Neuroscience	S	2015	Developmental Neurobiology	A
2014	Neuroscience Career Skills	S	2016	Neurodegenerative Diseases	A
2015	Behavioral Neuroscience	B			

*University of Minnesota Pass/Fail courses for the Graduate School are graded as S (Satisfactory) / N (Not satisfactory). V denotes “Visitor” for auditing a class that was satisfied via previous medical school coursework

YEAR	**MEDICAL SCHOOL UMN** - COURSE	GRADE	YEAR	**MEDICAL SCHOOL, UMN –** COURSE	GRADE
2012	Science of Medical Practice (M1)	P	2013	Principles of Pharmacology (M1)	P
2012	Human Structure and Function (M1)	P	2013	Human Disease 1 (M2)	P
2013	Microbiology and Immunology (M1)	P	2013	Human Disease 2 (M2)	P
2013	Physiology (M1)	P	2014	Human Disease 3 (M2)	P
2013	Neuroscience (M1)	P	2014	Human Disease 4 (M2)	P
2013	Human Sexuality (M1)	H	2014	Human Disease 5 (M2)	P
2013	Human Behavior (M1)	H	2014	Human Disease 4 (M2)	P
2013	Principles of Pathology (M1)	P	2014	Human Disease 5 (M2)	P

*University of Minnesota Medical School courses (M1-M4) are on an honors (H), pass (P), fail (F) system

YEAR	**UNDERGRAD, UCSD** - COURSE	GRADE	YEAR	**UNDERGRAD, UCSD** - COURSE	GRADE
2007	Calculus/Science & Engineering I	B	2009	Genetics	A
2007	General Chemistry I	B	2009	Metabolic Biochemistry	A+
2007	Intro to C/C++	A-	2009	Biochemical Techniques	A+
2008	Calculus/Science & Engineering II	B	2009	Structural Biochemistry	A
2008	Calculus & Analytical Geometry III	A+	2009	Human Physiology	B
2008	Intro to Differential Equations	A	2010	Humanities: Renaissance/Reform	A-
2008	Linear Algebra	B+	2010	Humanities: Enlightenment/Romanticism/Revolt	A
2008	General Chemistry II	A-	2010	Humanities: Modern Culture	A
2008	General Chemistry Lab	A	2010	Immunology	A+
2008	General Chemistry III	A	2010	Molecular Biology	A
2008	Humanities: Foundations of Western Civilization: Israel/Greece	B+	2010	Microbiology Lab	A
2008	Humanities: Rome/Christianity/Middle Ages	B	2010	Medical Microbiology	A
2009	Vector Calculus	B	2010	Cell Biology	A
2009	Physics– Mechanics	A	2010	Introductory Pharmacology	A+
2009	Physics– Electricity and Magnetism	B-	2010	Molecular Basis of Human Disease	A+
2009	Physics Lab– Mechanics/Electrostatics	B+	2011	Eukaryotic Gene Expression	A+
2009	Physics- Fluid/Waves/Thermo/Optics	C	2011	Virology	A
2009	Organic Chemistry I	A-	2011	Bacteriology	A
2009	Organic Chemistry II	A+	2011	Quantitative Biology	A
2009	Organic Chemistry IIII	A+	2011	Medical Microbiology TAship	--
2009	Organic Chemistry Lab	A	2011	Organism & Evolutionary Biology	A-