BIOGRAPHICAL SKETCH

NAME: Mollie Woodworth

eRA COMMONS USER NAME: woodworth

POSITION TITLE: Postdoctoral fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	S.B.	06/2006	Biology
Massachusetts Institute of Technology, Cambridge, MA	S.B.	06/2006	Brain and Cognitive Sciences
Harvard University, Cambridge, MA	Ph.D.	05/2013	Cell and Developmental Biology (J. Macklis)
Children's Hospital Boston	postdoctoral	08/2016	Neurogenetics (C. Walsh)
Stanford University School of Medicine	postdoctoral	ongoing	Ophthalmology (J. Goldberg)

A. Personal Statement

The goals of the proposed research are to identify genetic controls over retinal ganglion cell development, and to use this knowledge to motivate regenerative strategies for retinal ganglion cell replacement. My experience and qualifications make me particularly well-suited to undertake this project. I have a broad background in neuroscience, beginning from my undergraduate studies in both biology broadly and in molecular and cellular neuroscience specifically. As a Ph.D. student in Jeffrey Macklis' laboratory at Harvard, my major focus was on the developmental specification and differentiation of cerebral cortical neuron subtypes; as a postdoctoral researcher in Christopher Walsh's laboratory at Children's Hospital Boston, I investigated lineage relationships between neurons in the human cortex. This proposed work, therefore, utilizes my previous experience in subtype specification and lineage commitment, while providing me the opportunity to undertake training in the retina, and carry that work with me when I begin my independent career.

My long-term career goal is to direct a research laboratory investigating how neuronal diversity arises during nervous system development and applying these insights to regenerative strategies. Although my previous work has focused on the cerebral cortex, I have realized that the retina will provide a more tractable system for exploring the scientific questions that I plan to take on as I begin my independent research career. In particular, the retina has been extensively characterized in terms of its cellular diversity, but many open questions remain regarding cell-type-specific developmental programs. The retina is also more easily accessible to labeling and surgery than the cerebral cortex, which, in combination with new genetic tools, will enable me to address these important scientific questions as an independent early-career investigator. My sponsor, Jeffrey Goldberg, and our close collaborator, Sui Wang, are recognized leaders in retinal biology, and their training will be invaluable as I learn this new system.

During the time between my first and second postdoctoral research positions, I have been away from laboratory work due to the birth and care of a child. During this period, I have continued to develop my teaching skills for a future faculty job by working as an adjunct lecturer, teaching human physiology, human biology, and developmental biology at several institutions in the San Francisco Bay area, but have not pursued laboratory work. This teaching experience has been extremely valuable, but has not advanced my research training.

B. Positions and Honors

Positions and Employment

06/2003-08/2003 NIH Intramural Research Training program, laboratory of David Goldman, NIH/NIAAA
08/2003-08/2006 Undergraduate research student, laboratory of Morgan Sheng, MIT
09/2006-05/2013 Graduate student, laboratory of Jeffrey Macklis, Harvard University
09/2010-12/2010 Teaching fellow, Harvard University (Professors: Jeffrey Macklis and Paola Arlotta)
09/2011-12/2011 Teaching fellow, Harvard University (Professor: Jeffrey Macklis)
07/2013-08/2016 Postdoctoral research fellow, laboratory of Christopher Walsh, Children's Hospital Boston
01/2016-05/2016 Teaching fellow, Harvard University (Professor: Steven Hyman)
09/2016-01/2019 Adjunct lecturer: Santa Clara University, Cañada College, San Francisco State University
02/2019-present Postdoctoral fellow, laboratory of Jeffrey Goldberg, Stanford University

Honors

2016 Invited nanosymposium speaker, somatic mutation in neurons, Society for Neuroscience meeting
2016 Harvard Certificate of Distinction in Teaching (student evaluation score 4.7/5.0)
2015 Leonard and Isabelle Goldenson Research Fellowship, Harvard Medical School (Competitive renewal)
2014 Leonard and Isabelle Goldenson Research Fellowship, Harvard Medical School
2012 DEARS Foundation research fellowship
2011 Harvard Certificate of Distinction in Teaching (student evaluation score 4.7/5.0)
2011 Hoopes Prize for Undergraduate Research and Mentoring, Harvard University
2010 NIH Predoctoral NRSA
2010 Harvard Certificate of Distinction in Teaching (student evaluation score 4.5/5.0)
2010 Speaker, Christopher Reeve Hot Topics in Stem Cell Biology, Society for Neuroscience conference

C. Contributions to Science

Subtype and areal specification of neocortical projection neurons. The complex neocortical circuits that mediate higher-order brain functions are assembled from an extraordinary variety of neuronal subtypes, which are further specialized across different cortical areas. These two tiers of organization are established under precise molecular regulation during neocortical development. In recent years, several key transcriptional controls over specification of projection neuron subtype and area identity have been identified. However, less is known about how subtype and area development are linked, so that distinct areas can establish specific input/output connectivity and gene expression, and also produce specific ratios of neuronal subtypes. In my doctoral research, I identified that the transcription factor *Ctip1* functions in primary sensory areas to repress motor and activate sensory programs of gene expression, while also regulating the precise ratios of subcerebral and corticothalamic projection neurons in deep cortical layers. In *Ctip1* mutants, abnormal gene expression leads to aberrantly motorized corticocortical and corticofugal output connectivity. These findings bridge an important gap in understanding of how progenitor-level fate maps are ultimately impressed upon the postmitotic cortex.

1. Woodworth MB*, Greig LC*, Liu KX, Ippolito GC, Tucker HO, Macklis JD. (2016) "Ctip1 regulates the balance of projection neuron subtype specification in deep cortical layers." Cell Reports 15(5): 999-1012. PMID: 27117402. With cover. *equal contribution
2. Greig LC*, Woodworth MB*, Greppi C, Macklis JD. (2016) "Ctip1 controls acquisition of sensory area identity and establishment of sensory input fields in the developing neocortex." Neuron 90(2):261-277. PMID: 27100196. *equal contribution
3. Woodworth MB*, Greig LC*, Kriegstein AR, Macklis JD. (2012) "Snapshot: Cortical development." Cell 151(4): 918-918.e.1. PMID: 23141546. *equal contribution
4. Greig LC*, Woodworth MB*, Galazo MJ, Padmanabhan H, Macklis JD. (2013) "Molecular logic of neocortical projection neuron specification, development, and diversity." Nature Reviews Neuroscience 14(11): 755-69. PMID: 24105342. *equal contribution

Single-neuron genome sequencing, somatic mutation, and lineage mapping. The genome is under constant pressure from environmental and endogenous mutagens, and many human diseases are caused by somatic mutations, or those that occur in the body after birth. Somatic mutation is an inevitable consequence of cellular metabolism, so understanding the rate, mechanisms, causes, and consequences of this process is of critical importance. As a postdoctoral fellow, I performed whole genome sequencing on individual neurons isolated from postmortem human brain to quantify and characterize somatic single-nucleotide variants (SNVs). I found that normal human neurons harbored ~1,700 SNVs per cell, with a signature of transcriptional damage, suggesting gene expression was driving the mutation rate in these cells. This was the first study to use whole genome sequencing to identify mutations in individual cells. I further used these endogenously occurring somatic mutations as tools to investigate a fundamental question of human brain development. The organization of the human central nervous system, including the pattern of folding of the cortex, the organization into distinct cytoarchitectural layers, the arealization of function, and the diversity of cell types, is central to the function of the brain, so developmental perturbations in this organization lead to neurodevelopmental disorders. While brain development has been studied in many mammalian and non-mammalian systems, these models have limited utility in understanding the human brain, since the developmental expansion of the human neocortex is one of the distinct anatomical attributes of our species. Using somatic mutations discovered by single-neuron sequencing, I defined clones and subclones of related neurons in the human brain, using the variants as endogenous lineage tracers. I found that the human brain is profoundly polyclonal, and that neurons in close physical proximity in the brain may have a most recent common cellular ancestor that was a pluripotent cell in the pre-gastrulation embryo.

1. Lodato MA*, Woodworth MB*, Lee S*, Evrony GD, Mehta BK, Karger A, Lee S, Chittenden TW, D'Gama AM, Cai X, Luquette LJ, Lee E, Park PJ, Walsh CA. (2015) "Somatic mutation in single human neurons tracks developmental and transcriptional history." Science 350(6256):94-8. PMID: 26430121. With cover. *equal contribution
2. Lodato MA, Rodin RE, Bohrson CL, Coulter ME, Barton AR, Kwon M, Sherman MA, Vitzhum CM, Luquette LJ, Yandava CN, Yang P, Chittenden TW, Hatem NE, Ryu SC, Woodworth MB, Park PJ, Walsh CA. (2018) "Aging and neurodegeneration are associated with increased mutations in single human neurons." Science 359(6375): 555-9. PMID: 29217584.
3. Woodworth MB, Girskis K, Walsh CA. (2017) "Building a lineage from single cells: Genetic techniques for cell lineage tracking." Nature Reviews Genetics 18(4): 230-244. PMID: 28111472. With cover.

Human neurogenetics. Human genetics is a powerful source of information about important genes and pathways in nervous system development, and, conversely, understanding nervous system development can lead to potential treatments or cures for human neurodevelopmental disease. As a postdoctoral fellow, I investigated genetic causes of microcephaly, focal cortical dysplasia, and hemimegalencephaly. My primary contribution to these studies was through my expertise in surgery and histology at critical developmental timepoints in genetically modified mouse lines. I found that somatic mutations activating the mammalian target of rapamycin (mTOR) pathway, derived from studies of human patients, lead to focal cortical dysplasia in mice when the pathway is activated by *in utero* electroporation late in cortical development, and hemimegalencephaly or megalencephaly when the pathway is activated early in cortical development. In a separate study, I investigated the function of the gene *Katnb1*, which causes severe microcephaly and lissencephaly in human patients, and found that mice carrying a *Katnb1* null allele demonstrate severely reduced cortical neurogenesis, likely due to mislocalization of the KATNB1 protein away from the centrosome.

1. D'Gama AM, Woodworth MB, Hossain AA, Bizzotto S, Hatem NE, LaCoursiere CM, Najm I, Ying Z, Yang E, Barkovich AJ, Kwiatkowski DJ, Vinters HV, Madsen JR, Mathern GW, Blümcke I, Poduri A, Walsh CA. "Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias." Cell Reports 21(13): 3754-66. PMID: 29281825.
2. Hu WF, Pomp O, Ben-Omran T, Kodani A, Henke K, Mochida GH, Yu TW, Woodworth MB, Bonnard C, Raj GS, Tan TT, Hamamy H, Masri A, Shboul M, Al Saffar M, Partlow JN, Al-Dosari M, Alazami A, Alowain M, Alkuraya FS, Reiter JF, Harris MP, Reversade B, Walsh CA. (2014) "Katanin p80 regulates human cortical development by limiting centriole and cilia number." Neuron 84(6): 1240-1257. PMID: 25521379

Complete list of publications: https://orcid.org/0000-0003-2130-2289

D. Additional Information: Research Support

Completed Research Support

Leonard and Isabelle Goldenson Research Fellowship 01/01/16-08/31/16
Genetic lineage mapping in human brain (Competitive renewal)
The goal of this project was to use somatic mutations in the genome to perform lineage tracing in human brain.
Role: PI

Leonard and Isabelle Goldenson Research Fellowship 08/01/14-07/31/15
Single-cell genetic lineage mapping in human brain
The goal of this project was to use somatic mutations in the genome to perform lineage tracing in human brain.
Role: PI

NIH Predoctoral NRSA F31NS647302 02/01/10-11/30/12
Ctip2 function in corticospinal motor neuron development
The goal of this project was to explore functions of the transcription factors CTIP2 and CTIP1 in the development of projection neuron subtypes in the mouse brain.
Role: PI