BIOGRAPHICAL SKETCH

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NAME: Helen S. Bateup

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

POSITION TITLE: Associate Professor of Neurobiology

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
Pennsylvania State University, Schreyer Honors College, University Park, PA	B.S.	05/2000	Biobehavioral Health, minor in Neuroscience
Rockefeller University, New York, NY	Ph.D.	09/2007	Cellular and Molecular Neuroscience
Harvard Medical School, Boston, MA	Postdoctoral	05/2013	Neurobiology

A. Personal Statement

Research in my lab broadly aims to understand the cellular and molecular basis of neurological and psychiatric disease. We have a particular interest in "mTORopathies", which are developmental brain disorders caused by mutations in the mTOR signaling pathway that lead to epilepsy, intellectual disability, and autism. To elucidate disease mechanisms for these and related disorders, we use genetic mouse models in combination with a variety of techniques spanning molecular profiling, electrophysiology, and behavior. Our goal is to generate a mechanistic understanding of how disease-associated mutations affect the cell biology and physiology of specific types of neurons, and how altered neuronal activity impacts circuit function and behavior. In addition, we are investigating the early developmental alterations that may contribute to neurodevelopmental disorders using genetically engineered human brain organoids.

Recent publications:

1) Karalis, V., Caval-Holme, F., and **Bateup, H.S.** (2022) Raptor downregulation rescues neuronal phenotypes in mouse models of Tuberous Sclerosis Complex. Nature Communications. Aug 9,13(1):4655. PMID: 35945201.
2) Kosillo, P., Ahmed, K.M., Aisenberg, E.E., Karalis, V., Roberts, B.M., Cragg, S.J., and **Bateup, H.S.** (2022) Dopamine neuron morphology and output are differentially controlled by mTORC1 and mTORC2. eLife. Jul 26;11:e75398. PMID: 35881440.
3) Benthall, K.N., Cording, K.R., Agopyan-Miu, A.H.C.W., Wong, C.D., Chen, E.Y., and **Bateup, H.S.** (2021) Loss of Tsc1 from striatal direct pathway neurons impairs endocannabinoid-LTD and enhances motor routine learning. Cell Reports. Aug 10;36(6):109511. PMID: 34380034.
4) Kosillo, P., Doig, N.M., Ahmed, K., Agopyan-Miu, A.H.C.W., Wong, C.D., Conyers, L., Threlfell, S., Magill, P.J. and **Bateup, H.S.** (2019) Tsc1-mTORC1 signaling controls striatal dopamine release and cognitive flexibility. Nature Communications. 10(1):5426. PMID: 31780742.

B. Positions, Scientific Appointments, and Honors

Research Positions

2020-present	Associate Professor, Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute, University of California, Berkeley, CA
2019-present	Investigator, Chan Zuckerberg Biohub, San Francisco, CA
2013-2020	Assistant Professor, Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute, University of California, Berkeley, CA
2008-2013	Postdoctoral Fellow, Laboratory of Bernardo Sabatini, Department of Neurobiology, Harvard Medical School, Boston, MA
2001-2007	Ph.D. student, Laboratory of Paul Greengard, Rockefeller University, NY, NY
2000-2001	Postbaccalaureate research fellow, Behavioral Endocrinology Branch, National Institute of Mental Health, Bethesda, MD

Professional activities

2021-2023	Reviewer for Simons Foundation Autism Research Initiative (SFARI) research grants
2021	Member of the Science and Medical Committee at the Tuberous Sclerosis Alliance and International Conference co-organizer
2021	Ad hoc member of NIH ETTN-J (02) M study section (Member Conflict: Bioengineering, Cellular and Circuit Neuroscience)
2020	Reviewer for CZI Neurodegeneration Challenge Network research grants
2018-2022	Ad hoc member of NIH ZRG1 MDCN-P(57) study section (Cellular and Molecular Biology of Complex Brain Disorders)
2018	Reviewer for DoD CDMRP Tuberous Sclerosis Complex Research Program
2018	Reviewer for American Epilepsy Society grant program
2017	Ad hoc member of NIH SYN study section (Synapses, Cytoskeleton, and Trafficking)
2017-2018	Reviewer for NJ Governor's Council on Autism grant program
2016-2019	Reviewer for Tuberous Sclerosis Alliance grant program
2013-present	Manuscript reviewer for: *Nature, Cell, Nature Medicine, Neuron, Nature Neuroscience, Cell Stem Cell, Nature Methods, Nature Communications, eLife, Science Advances, Cell Reports, Cell Chemical Biology, Molecular Psychiatry, Cerebral Cortex, Neuropsychopharmacology, Journal of Neuroscience, Developmental Neuroscience, Scientific Reports, PLOS Genetics, Trends in Neurosciences, Frontiers in Neuroanatomy, Frontiers in Neural Circuits* and others

Honors

2021	Weill Neurohub Investigator
2019	Chan Zuckerberg Biohub Investigator
2018	NINDS Travel Award, International SYNGAP1 Conference
2018	C.J. Herrick Award in Neuroanatomy from the American Association of Anatomists
2017	Janett Rosenberg Trubatch Career Development Award from the Society for Neuroscience
2016	NARSAD Young Investigator Award from the Brain & Behavior Research Foundation
2016	Hellman Family Faculty Fellow Award
2015	Alfred P. Sloan Research Fellow in Neuroscience
2014	Regents' Junior Faculty Fellowship, University of California, Berkeley
2011	International Society for Neurochemistry, Travel Award
2011	Vicky H. Whittemore Travel Award, International TSC Research Conference
2010	Nancy Lurie Marks Postdoctoral Research Fellowship in Autism, Harvard Medical School
2000	Postbaccalaureate Intramural Research Training Award, NIMH, Bethesda, MD
2000	First place, Pennsylvania State University Senior Honors Thesis competition
1999	Pennsylvania State University Undergraduate Research Award

C. Contributions to Science

1. Elucidated cell type-specific signaling mechanisms in striatal neurons and defined their roles in motor behaviors.

As a graduate student in Dr. Paul Greengard's lab, I developed novel genetic mouse models that allowed, for the first time, quantitative analysis of biochemical signaling in specific cell populations in the brain. With this approach I resolved a long-standing paradox in the field, namely how psychostimulant and antipsychotic drugs could produce the same biochemical changes in the striatum but exert opposing behavioral and clinical effects. I demonstrated that these drugs act selectively on distinct populations of striatal neurons that differentially control behavior, thus explaining their opposing effects. In addition, working with researchers at GENSAT, I was at the forefront of using striatal cell type-specific Cre mice to delete genes of interest. Using these genetic mouse models, we revealed the differential behavioral contribution of the two classes of striatal projection neurons to normal and pathological motor behaviors relevant for Parkinson's disease and schizophrenia.

1. **Bateup, H.S.**, Santini E., Shen, W., Birnbaum, S., Valjent, E., Surmeier, D.J., Fisone, G., Nestler, E.J., and Greengard, P. (2010) Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. PNAS, 107(33), 14845-50. PMID: 20682746
2. **Bateup, H.S.**, Svenningsson, P., Kuroiwa, M., Gong, S., Nishi, A., Heintz, N., and Greengard, P. (2008) Cell type-specific regulation of DARPP-32 phosphorylation by psychostimulant and antipsychotic drugs. Nature Neuroscience*,* 11(8), 932-9*.* PMID: 18622401

2. Identified mechanisms of synapse and circuit dysfunction in mouse models of TSC

In my post-doctoral work in Dr. Bernardo Sabatini's lab, I determined how the TSC-mTOR signaling pathway regulates synaptic transmission and network activity and how these functions become disrupted in disease states. Specifically, I discovered that the TSC-mTOR pathway is both a regulator of excitatory synapses, via the control of protein translation-dependent long-term plasticity, and an activity-sensing pathway that influences hippocampal activity by modulating levels of inhibition. Mutations in *TSC1* or *TSC2* cause hyperactivation of mTORC1 signaling and lead to the neurodevelopmental disorder Tuberous Sclerosis Complex (TSC). The neuropsychiatric presentations of TSC include early onset epilepsy, intellectual disability, and a high prevalence of autism spectrum disorder and other behavioral conditions. I showed that disruption of the *Tsc1* gene in mice results in a cell autonomous weakening of inhibitory inputs onto pyramidal neurons leading to excitatory/inhibitory (E/I) synaptic imbalance, network hyperactivity, and seizures. Importantly, I demonstrated that correcting the biochemical perturbation caused by loss of Tsc1 could not only normalize network activity and restore E/I balance, but also reverse many of the compensatory changes resulting from chronically high activity. These findings advanced our understanding of the pathogenesis of seizures in TSC and identified a novel target for modulating E/I balance that may be broadly applicable to epilepsy. Moreover, this work showed that by reversing the underlying molecular perturbation, it may be possible to successfully treat neurodevelopmental disorders in adults even after dysfunction has already occurred.

1. **Bateup, H.S.**, Johnson, C.A., Denefrio, C.L., Saulnier, J.L., Kornacker, K., and Sabatini, B.L. (2013) Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis. Neuron, 78(3), 510-22. PMID: 23664616
2. **Bateup, H.S.**, Denefrio, C.L., Johnson, C.A., Saulnier, J.L. and Sabatini, B.L. (2013) Temporal dynamics of a homeostatic pathway controlling neural network activity. Frontiers in Molecular Neuroscience, 6**:**28. doi: 10.3389/fnmol.2013.00028. PMID: 24065881
3. **Bateup, H.S.**, Takasaki, K.T., Saulnier, J.L., Denefrio, C.L., and Sabatini, B.L. (2011) Loss of Tsc1 *in vivo* impairs hippocampal mGluR-LTD and increases excitatory synaptic function. Journal of Neuroscience, 31(24), 8862-9. PMID: 21677170

3. Defined the cell type-specific consequences of Tsc1 loss in the basal ganglia

As an independent investigator, my lab has been identifying the cellular, synaptic, and behavioral phenotypes caused by Tsc1/2 loss from major basal ganglia projection neurons. Our goal is to elucidate the cellular basis of TSC-associated neuropsychiatric disorders (TAND) including autism spectrum disorder. We have found that

deletion of *Tsc1* has cell type-specific consequences on synaptic and intrinsic physiology, resulting in distinct behavioral endophenotypes. Specifically, loss of Tsc1 from direct (but not indirect) pathway striatal neurons leads to synaptic E/I imbalance via potentiation of corticostriatal excitatory inputs, which drives alterations in motor routine learning. In addition, deletion of *Tsc1* from dopamine neurons profoundly changes their structure and function, leading to impaired striatal dopamine release and cognitive inflexibility. Together this work provided the first evidence that disruption of TSC-mTOR signaling in basal ganglia circuits alters cellular and synaptic physiology and is sufficient to induce disease-relevant behavioral alterations.

1. Kosillo, P., Ahmed, K.M., Aisenberg, E.E., Karalis, V., Roberts, B.M., Cragg, S.J., and **Bateup, H.S.** (2022) Dopamine neuron morphology and output are differentially controlled by mTORC1 and mTORC2. eLife. Jul 26;11:e75398. PMID: 35881440.
2. Benthall, K.N., Cording, K.R., Agopyan-Miu, A.H.C.W., Wong, C.D., Chen, E.Y., and **Bateup, H.S.** (2021) Loss of Tsc1 from striatal direct pathway neurons impairs endocannabinoid-LTD and enhances motor routine learning. Cell Reports. Aug 10;36(6):109511. PMID: 34380034
3. Kosillo, P., Doig, N., Ahmed, K.M., Agopyan-Miu, A., Wong, C., Conyers, L., Threlfell, S., Magill, P.J., and **Bateup, H.S.** (2019) Tsc1-mTOR signaling controls striatal dopamine release and cognitive flexibility. Nature Communications. Nov 28;10(1):5426. PMID: 31780742
3. Benthall, K.N., Ong, S.L., and **Bateup, H.S**. (2018) Corticostriatal transmission is selectively enhanced in striatonigral neurons with postnatal loss of Tsc1. Cell Reports. Jun 12;23(11):3197-3208. PMID: 29898392

4. Utilized genetic approaches to catalog cell type diversity in the brain

Determining the cellular “parts list” and connectivity diagram of the brain are key first steps towards building a complete understanding of brain development and function in both normal and disease states. Our lab has been part of the BRAIN Initiative Cell Census Network (BICCN), which seeks to define and catalog all cell types in the mammalian brain. As part of this network, we participated in a large-scale multi-lab effort to derive a consensus taxonomy for cell types in the motor cortex. Our role in this project was to characterize novel transgenic mouse lines that target reporters to specific cortical neuron populations. In my lab, we received a BRAIN Initiative grant supplement to use single cell-RNA sequencing (scRNAseq) to dissect the genetic heterogeneity of dopamine neurons. We identified dopaminergic sub-populations based on their gene expression patterns and used detailed anatomical analyses, circuit tracing, and electrophysiology to determine the functional properties of these genetically-defined cell types. In addition, we showed that the marker genes identified by scRNAseq could be used to label dopamine neuron types with differentially susceptibility to degeneration in the 6-OHDA model of Parkinson’s disease. Most recently, we generated a novel DAT-Flp knock-in mouse line to allow intersectional Cre/Flp-dependent targeting of dopamine neuron sub-populations, which we anticipate will become a valuable resource for the field.

1. BRAIN Initiative Cell Census Network (BICCN). (2021) A multimodal cell census and atlas of the mammalian primary motor cortex. Nature. Oct;598(7879):86-102. PMID: 34616075
2. Kramer, D.J., Aisenberg, E.E., Kosillo, P., Friedmann, D., Stafford, D.A., Lee, A.Y., Luo, L., Hockemeyer, D., Ngai, J., and **Bateup, H.S.** (2021) Generation of a DAT-P2A-Flpo mouse line for intersectional genetic targeting of dopamine neuron subpopulations. Cell Reports. May 11;35(6):109123. PMID: 33979604
3. Kramer, D.J., Risso, D., Kosillo, P., Ngai, J., and **Bateup, H.S.** (2018) Combinatorial expression of *Grp* and *Neurod6* defines dopamine neuron populations with distinct projection patterns and disease vulnerability. eNeuro. Jun 13;5(3). PMID: 30135866

5. Established genetically-engineered human cellular models for neurodevelopmental disorders

My lab has been at the forefront of combining CRISPR/Cas9 gene-editing technology with disease modeling using human stem cell-derived neurons and brain organoids. This approach allows genetic, cellular and molecular investigations into human brain development and function, which have previously not been possible. Using this state-of-the-art system, we established the first human brain organoid models for TSC. We used these models to define the genetic requirements for the formation of cortical tuber cells, which comprise focal

cortical malformations that are a hallmark pathology of TSC. We showed that tuber cells likely form due to biallelic inactivation of *TSC1* or *TSC2*. In addition, we showed that mTORC1 signaling is dynamically regulated during human corticogenesis and that deregulation of mTORC1 signaling during critical developmental periods strongly affects the balance of neurogenesis and gliogenesis.

1. Blair, J.D. and **Bateup, H.S.** (2020) New frontiers in modeling tuberous sclerosis with human stem cell-derived neurons and brain organoids. Developmental Dynamics. Jan;249(1):46-55.
2. Blair, J.D., Hockemeyer, D., and **Bateup, H.S.** (2018) Genetically engineered human cortical spheroid models of tuberous sclerosis. Nature Medicine. Oct;24(1):1568-1578.
3. Blair, J.D., Hockemeyer, D., Doudna, J.A., **Bateup. H.S.***, and Floor, S.N.* (2017) Widespread translational remodeling during human neuronal differentiation. Cell Reports. Nov 14;21(7):2005-2016. *Co-corresponding authors
4. Li, Y., Wang, H., Muffat, J., Cheng, A.W., Orlando, D.A., Loven, J., Kwok, S., Feldman, D.A., **Bateup, H.S.**, Gao, Q., Hockemeyer, D., Mitalipova, M., Lewis, C.A., Vander Heiden, M.G., Sur, M., Young, R.A., and Jaenisch, R. (2013) Global Transcriptional and Translational Repression in Human embryonic-Stem-Cell-Derived Rett Syndrome Neurons. Cell Stem Cell, 13(4), 446-458.

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