Mary E. Hatten, Ph.D.

FREDERICK P. ROSE PROFESSOR, LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY

Hatten studies the development of the complex cellular architecture of the mammalian brain. Her research on how neurons migrate and differentiate has implications for the genetics of brain disease, as well as conditions that are partially due to developmental abnormalities, such as autism spectrum disorders (ASDs), attention deficit disorder, and childhood epilepsy. Her work has also provided insights into medulloblastoma, a prevalent childhood metastatic brain tumor.

Using the mouse cerebellar cortex as a model, Hatten studies the mechanisms of cerebellar neurogenesis and migration during central nervous system (CNS) development. Her lab pioneered the development of video imaging methods to view the dynamics of CNS neuronal migration along glial fibers. Using these methods, Hatten has discovered the cellular and molecular mechanisms of glial-guided CNS migration.

To analyze global changes in gene expression in postmigratory neurons, Hatten has used a method called translating ribosome affinity purification (TRAP) to reveal dramatic changes in multiple chromatin remodeling reactomes of postmigratory neurons during the formation of cerebellar circuitry. Notably, the Tet genes and a DNA demethylation product, 5-hydroxymethylcytosine (5hmC), are upregulated. The activation of Tet enzymes elevated 5hmC levels in axon guidance and ion channel genes, and knockdown of Tet1 and Tet3 by RNA interference markedly inhibited circuit formation in the developing cerebellum by blocking dendritic arborization. Work is ongoing, in collaboration with the Allis Lab, to analyze how histone modifications, in particular histone methylation, regulate changes in transcription during CNS circuit formation. For these experiments, she is using both molecular and imaging approaches.

The Hatten lab discovered and studied the neuron-glial adhesion protein astrotactin (ASTN1), a receptor critical for glial-guided migration. The lab has also discovered Astn2, which has been identified as a risk factor in ASDs, attention deficit hyperactivity disorder, and other neurodevelopmental disorders. Recent experiments show that ASTN2 localizes to synapses, binds to the synaptic protein neuroligin, and functions in synaptic protein trafficking. New work shows that a mouse with a loss-of-function mutation in Astn2 is an important model for the role of the cerebellum in ASDs, because Purkinje neurons—the cerebellum's primary output cell—in the Astn2 mutant have a decrease in evoked excitation relative to inhibition and a decrease in dendritic spines. The mutant also has ASD-like behaviors, including a decrease in ultrasonic vocalizations and deficits in open field tests.

To study neurons with Astn2 lesions from autism patients, as well as other neurogenetic defects that affect cerebellar development, Hatten has developed protocols to differentiate induced pluripotent stem cells (iPSCs) into cerebellar neurons. Importantly, she is currently using bio-engineering to develop 3D layered cultures to study circuit formation by human cerebellar neurons.

EDUCATION

A.B. in chemistry, 1971
Hollins College

Ph.D. in biochemical sciences, 1975
Princeton University

POSTDOC

Harvard Medical School, 1975–1978

POSITIONS

Assistant Professor, 1978–1982
Associate Professor, 1982–1986
New York University School of Medicine

Associate Professor, 1986–1988
Professor, 1988–1992
Columbia University College of Physicians and Surgeons

Professor, 1992–
Co-director, Shelby White and Leon Levy Center for Mind, Brain and Behavior, 2016–
Senior Advisor, Kavli Neural Systems Institute, 2016–2023
Associate Director, Kavli Neural Systems Institute, 2023–
The Rockefeller University

AWARDS

Irma T. Hirschl/Monique Weill-Caulier Trust Research Award, 1980

Pew Neuroscience Award, 1988

McKnight Endowment Fund for Neuroscience Investigator Award, 1991

NIH Javits Neuroscience Investigator Award, 1991

NSF Faculty Award for Women Scientists and Engineers, 1991

Weil Award, American Association of Neuropathologists, 1996

Cowan-Cajal Award for Developmental Neuroscience, 2015

The Rockefeller University Distinguished Teaching Award, 2016

Ralph W. Gerard Prize in Neuroscience, 2017

HONORARY SOCIETIES

National Academy of Sciences

National Academy of Medicine

Fellow, American Association for the Advancement of Science

American Academy of Arts and Sciences

SELECTED PUBLICATIONS

Buchholz, D.E. et al. Novel genetic features of human and mouse Purkinje cell differentiation defined by comparative transcriptomics. *Proc. Natl. Acad. Sci. U.S.A.* in press (2020).

Behesti, H. et al. ASTN2 modulates synaptic strength by trafficking and degradation of surface proteins. *Proc. Natl. Acad. Sci. U.S.A.* 115, E9717–E9726 (2018)

Horn, Z. et al. N-cadherin provides a cis and trans ligand for astrotactin that functions in glial-guided neuronal migration. *Proc. Natl. Acad. Sci. U.S.A.* 115, 10556–10563 (2018)

Zhu, X. et al. Role of Tet1/3 genes and chromatin remodeling genes in cerebellar circuit formation. *Neuron* 89, 100–112 (2016).