# Mary E. Hatten, Ph.D.

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**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 discovered the cellular and molecular mechanisms of glial-guided CNS migration.

To analyze how epigenetic mechanisms regulate CNS development, the Hatten lab recently studied patterns of histone methylation in developing cerebellar granule cells (GCs). Their studies showed that in proliferating GC progenitors, H3K4me3/H3K27me3 bivalency is common at neuronal genes and undergoes dynamic changes that correlate with gene expression during migration and circuit formation. Blocking histone bivalency in ex vivo cultures of cerebellum inhibited glial-guided migration and accelerated terminal differentiation. Thus, histone bivalency regulates the timing of the progression of CNS progenitor cells to mature neurons. The discovery that histone bivalency controls the timing of cerebellar GC differentiation revealed a critical, novel feature of CNS development.

The Hatten lab previously discovered and studied the neuron-glial adhesion protein astrotactin (ASTN1), a receptor critical for glial-guided migration. The lab also discovered the gene *Astn2*, which has been identified as a risk factor in ASDs, attention deficit hyperactivity disorder, and other neurodevelopmental disorders. Experiments showed that ASTN2 localizes to synapses, binds to the synaptic protein neuroligin, and functions in synaptic protein trafficking. More recent work revealed that a mouse with a loss-of-function mutation in *Astn2* is an important model for the role of the cerebellum in ASDs. *Astn2* knockout (KO) mice exhibit strong ASD-related behavioral phenotypes, and *Astn2* KO Purkinje cells (PCs) have region-specific changes in dendritic spine density and filopodia numbers. Electrophysiological experiments indicated a reduced frequency of spontaneous excitatory postsynaptic currents (EPSCs), as well as increased amplitudes of both spontaneous EPSCs and inhibitory postsynaptic currents (IPSCs) in the *Astn2* KO animals, suggesting that pre- and postsynaptic components of synaptic transmission are altered. Thus, ASTN2 regulates ASD-like behaviors and cerebellar circuit properties.

To study cerebellar neurodevelopmental and neurodegenerative diseases in human neurons, the Hatten lab developed protocols to generate human pluripotent stem cell (hPSC)-derived GCs and PCs. To mimic native brain lamination thought that underlies CNS circuit properties, they designed a novel 3D microfluidic culture system. The lab is currently using electrophysiology and calcium imaging, combined with gene and proteomic expression studies, to study human cerebellar neurons from patients with cerebellar disorders. This system provides a novel stem cell model for analyzing molecular properties underlying circuit properties of human cerebellar neurons in development and disease.

## 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

American Academy of Arts and Sciences

Fellow, American Association for the Advancement of Science

## SELECTED PUBLICATIONS


Hanzel, M. et al. Mice lacking Astn2 have ASD-like behaviors and altered cerebellar circuit properties. *Proc. Natl. Acad. Sci. U.S.A.* (2024).

Matlik, K. et al. Histone bivalency regulates the timing of cerebellar granule cell development. *Genes Dev.* 37, 570–589 (2023).

Behesti, H. et al. Altered temporal sequence of transcriptional regulators in the generation of human cerebellar granule cells. *Elife* 10, e67074 (2021).

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).

Hatten, M.E. Adding cognitive connections to the cerebellum. *Science* 370, 1411–1412 (2020).