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Research in the Heintz laboratory aims to identify the genes, circuits, cells, macromolecular assemblies, and individual molecules that contribute to the function of the mammalian brain and to its dysfunction in disease. Understanding the distinct classes of neurons and the circuits that control specific aspects of cognition and behavior can lead to more targeted treatments for central nervous system disorders.

Cognition and behavior emerge from hundreds of different classes of cells in the mammalian brain, arranged into specific circuits that control various functions of the nervous system. Heintz has developed a suite of tools to investigate the molecular mechanisms that contribute complexities of the mammalian brain, enabling the characterization of different cell types and furthering our understanding of the biochemical basis behind this diversity.

As a first step in identifying the mechanisms that are essential for normal brain functioning and those that go awry in disease, the Heintz laboratory invented a method to reproducibly target defined central nervous system (CNS) cell types using genetics. The system is based on manipulating bacterial artificial chromosomes (BACs) to engineer DNA by homologous recombination in *E. coli*, a process now known as "recombineering."

Working with Mary E. Hatten, Heintz launched the NINDS Gene Expression Nervous System Atlas project (www.gensat.org), a large-scale screen using BAC transgenic mice to create an atlas of cellular CNS gene expression. It includes detailed anatomical data on cell types targeted in over 1,500 BAC transgenic mouse lines and a library of verified BAC vectors and transgenic mouse lines, offering the scientific community experimental access to CNS regions, cell classes, and pathways. The information gleaned from this project serves as the foundation for many of the studies currently pursued in the Heintz lab.

Many of the genes involved in neurological and psychiatric disorders are ubiquitously expressed throughout the brain, but Heintz proposes that disease-linked genes differentially impact finely-tuned biochemical pathways controlling specific neurons and circuits. To shed light on the elements that are most affected in a given disorder, the laboratory, in collaboration with Paul Greengard, developed the translating ribosome affinity purification (TRAP) technique. By fusing an affinity tag to a ribosomal protein, TRAP enables the isolation of bound messenger RNAs from a targeted cell type without requiring isolation of that cell type from tissue.

The laboratory employs TRAP to determine molecular constitutions of a wide variety of cell types in the mouse brain and the molecular phenotypes of select cell types in mouse models of common disorders. TRAP profiling has led to the definition of biochemical pathways whose altered activity contributes to the pathophysiology of CNS disorders, including autism-spectrum disorders, obsessive-compulsive disorder, Parkinson's disease, addiction, anxiety, and depression. Recent studies have also revealed that the circuits involved in these disorders work differently in male and female mice.

Another focus of Heintz's work centers on an epigenetic modifier discovered by the lab, called 5-hydroxymethylcytosine (5hmC), which is present in the mammalian genome and specifically enriched in neurons. The researchers are currently addressing the potential significance of 5hmC, a novel epigenetic mark not previously observed in metazoans, on epigenetic mechanisms of neurological and psychiatric disease.

EDUCATION

B.A. in biology, 1974
Williams College

Ph.D. in biological sciences, 1979
University at Albany, State University of New York

POSTDOC

Washington University, 1979–1982

POSITIONS

Assistant Professor, 1983–1987
Associate Professor, 1987–1992
Professor, 1992–
Director, Fisher Center for Alzheimer's Disease Research, 2022–
The Rockefeller University

Assistant Investigator, 1987–1988
Associate Investigator, 1988–1992
Investigator, 1992–
Howard Hughes Medical Institute

AWARDS

Pew Biomedical Scholar, 1985

Junior Faculty Research Award, American Cancer Society, 1986

HONORARY SOCIETIES

National Academy of Sciences

Fellow, American Association for the Advancement of Science

SELECTED PUBLICATIONS

Nakajima, M. et al. Oxytocin modulates female sociosexual behavior through a specific class of prefrontal cortical interneurons. *Cell* 159, 295–305 (2014).

Mellén, M. et al. MeCP2 binds to 5hmC enriched within active genes and accessible chromatin in the nervous system. *Cell* 151, 1417–1430 (2012).

Schmidt, E.F. et al. Identification of the cortical neurons that mediate antidepressant responses. *Cell* 149, 1152–1163 (2012).

Kriaucionis, S. and Heintz, N. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. *Science* 324, 929–930 (2009).

Heiman, M. et al. A translational profiling approach for the molecular characterizan of CNS cell types. *Cell* 135, 738–748 (2008).