Robert B. Darnell, M.D., Ph.D.

INVESTIGATOR, HOWARD HUGHES MEDICAL INSTITUTE • SENIOR ATTENDING PHYSICIAN •
ROBERT AND HARRIET HEILBRUNN PROFESSOR, LABORATORY OF MOLECULAR NEURO-ONCOLOGY

RNA is the driving force of biological complexity, determining which genes any given cell expresses at specific times and under specific circumstances. Darnell developed high-throughput sequencing and crosslinking methods to investigate how RNA binding proteins (RBPs) modulate gene expression. He discovered neuron-specific RNA-binding proteins in the mammalian brain, and studies their link to intellectual function and human disease.

Darnell's interest in RNA and RNA-binding proteins arose from studies of paraneoplastic neurologic disorders (PNDs), a group of rare conditions that affect the nervous system in people with certain tumors. These disorders are thought to arise when tumors make proteins normally unique to the brain, triggering an immune response that thwarts the cancer but also causes collateral damage to the nervous system.

Darnell's lab discovered that neuron-specific proteins are targeted by the immune system in PNDs. The team found that the immune systems of PND patients kill tumor cells with what is essentially an antiviral response: CD8+ killer T cells that recognize the neuron-specific proteins. The lab also found that dying apoptotic tumor cells instigate this anti-tumor response and has worked on developing cancer vaccines that mimic this effect.

Subsequent studies in the Darnell lab explored why tumors induce the expression of neuron-specific proteins, and these proteins' normal roles in neurons. This work led the lab to discover and explore the function of neuron-specific RNA-binding proteins in the mammalian brain, including the Nova and Hu (nElavl) PND targets. Additional studies led to the discovery of the function of the Nova-related RNA-binding protein FMRP, whose function is lost in fragile X syndrome, the most common inherited form of intellectual disability. The lab further expanded these investigations to include other RNA-binding proteins, such as Argonaute (Ago, which works with microRNAs to regulate messenger RNA), as well as Ptbp2, Mbln2, and Rbfox. Finally, the lab has expanded their work to consider RNA regulation over time, and apply this to the study of autoimmune disease (rheumatoid arthritis) and infectious disease (including COVID-19).

To understand these proteins' functions in the brain, the lab developed a general and powerful method called cross-linking immunoprecipitation (CLIP), which allowed the team to create precise, genome-wide maps of protein binding sites on RNAs in living tissue. They used CLIP, together with the analysis of knockout mice and bioinformatic approaches, to discover that where a protein binds influences how messenger RNAs are altered through processes called alternative splicing and polyadenylation. Recent computational improvements in the analysis of CLIP maps have allowed single-nucleotide and single cell-type resolution of RNA regulatory sites in different neurons, and robust genome-wide predictions of combinatorial RNA regulation in the non-coding genome.

The lab has revealed how disruptions in RNA-protein interactions contribute to common neurologic disorders, such as that mediated by FMRP in autism spectrum disorders, by Ago in stroke and hepatitis infection, by nElavl in Alzheimer's disease, and by Nova in axonal guidance and brain development. Studies with Nova and FMRP have led to insight into the balance of neuronal inhibition, excitation, and control of gene expression, leading to new approaches to study protein-synthesis dependent synaptic plasticity during neuronal excitation, and to apply these findings to the study of neurodegenerative disorders such as Parkinson's disease, epilepsy, and autism.

EDUCATION

B.A. in biology and chemistry, 1979
Columbia University

M.D., 1985
Ph.D. in molecular biology, 1985
Washington University School of Medicine

MEDICAL TRAINING

Internship and residency in internal medicine, 1985–1987
Mt. Sinai Hospital

Resident in neurology, 1987–1989
Chief Resident 1989–1990
New York Hospital

POSITIONS

Assistant Professor, 1992–1997
Associate Professor, 1997–2000
Professor, 2000–
The Rockefeller University

Associate Physician, 1993–1998
Physician, 1998–2000
Senior Physician, 2000–
Associate Medical Director, 1996–2006
Associate Program Director, General Clinical Research Center, 1996–2006
Director for Science Programs, Center for Clinical and Translational Research, 2006–2013; 2020–
The Rockefeller University Hospital

Founding Director, 2012
President and CEO, 2012–2016
The New York Genome Center

Investigator, 2002–
Howard Hughes Medical Institute

AWARDS

Irma T. Hirschl/Monique Weill-Caulier Trust Research Award, 1996

Derek Denny-Brown Young Neurological Scholar Award, 1998

Burroughs Wellcome Fund Award, 2000

NIH Director's Transformative Research Award, 2012

Columbia University Medical Center Distinguished Service Award, 2015

NINDS Outstanding Investigator Award, 2016

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

Hacisuleyman, E. et al. Neuronal activity rapidly reprograms dendritic translation via eIF4G2:uORF binding. *Nat. Neurosci.* 27, 822 –835 (2024).

Tajima, Y. et al. NOVA1 acts on Impact to regulate hypothalamic function and translation in inhibitory neurons. *Cell Rep.* 42, 112050 (2023).

Hale, C.R., et al. FMRP regulates mRNAs encoding distinct functions in the cell body and dendrites of CA1 pyramidal neurons. *ELife* 10, e71892 (2021).

Orange, D., et al. RNA identification of PRIME cells predicting rheumatoid arthritis flares. *NEJM* 383, 218–228 (2020).

Saito, Y., et al. Differential NOVA2-mediated splicing in excitatory and inhibitory neurons regulates cortical development and cerebellar function. *Neuron* 101, 707–720 (2019).