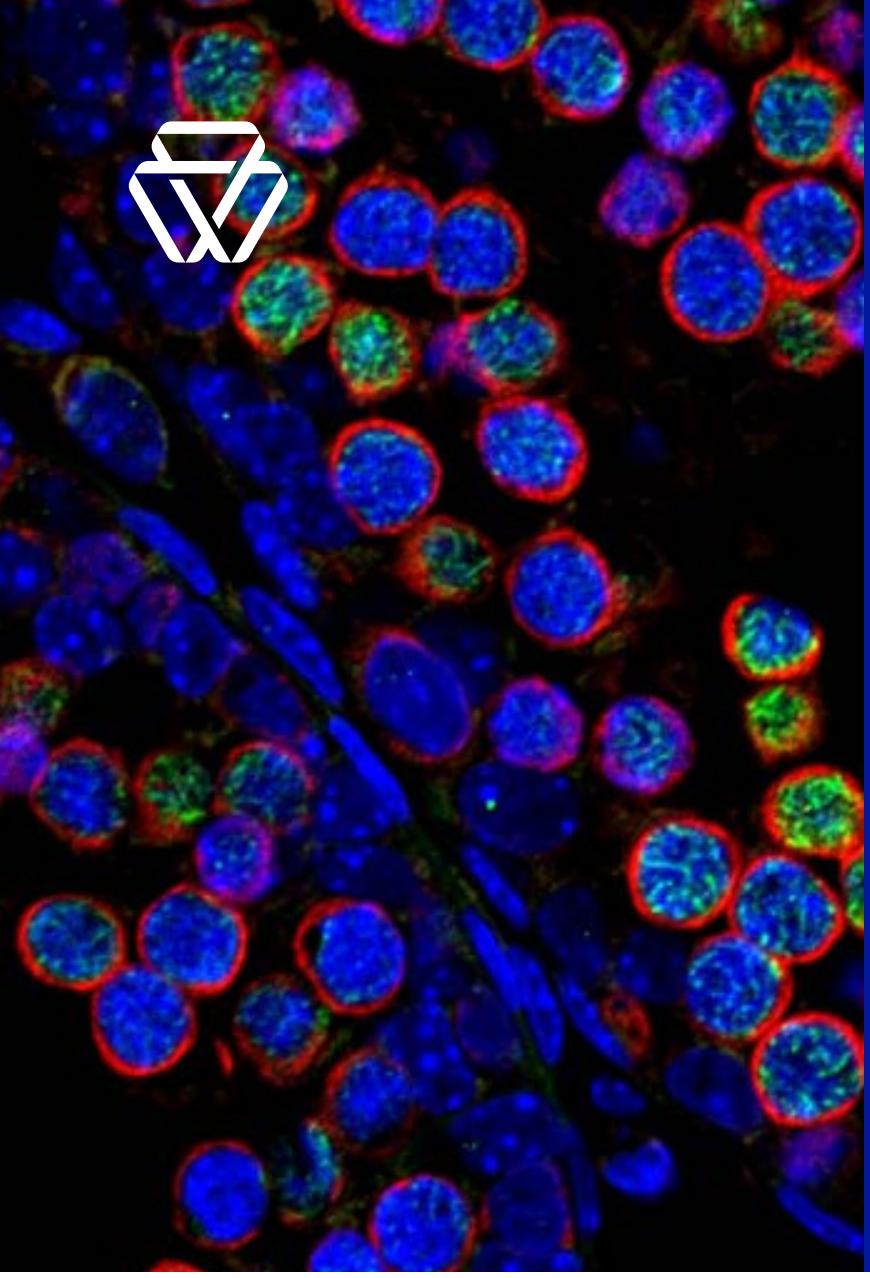

The biology of the brain and neurodegenerative disease

Discovering the fundamental biology underlying how the brain and nervous system develop and function is critical for understanding how the systems deviate in developmental disorders, neurodegenerative diseases, mental health disorders, and infectious diseases that affect the nervous system. Whitehead Institute researchers are creating innovative models, tools, and strategies with which to study the brain. Their insights could lead to new diagnostic tools, disease risk assessments, and therapies.

Member **Olivia Corradin** has developed an innovative approach to look at genetic alterations linked to disease and determine how these DNA sequences regulate gene activity and alter disease progression. She first used this approach to provide new insights into multiple sclerosis. Corradin has also identified likely genetic risk factors for opioid use disorder, a complex disorder with many possible contributing factors that are difficult to tease out of genomic data using previous approaches. Corradin's ongoing work to understand the disorder could lead to better prevention and treatment strategies that could reduce opioid overdose deaths.

Valhalla Fellow **Allison Hamilos** studies the neural circuits disrupted in neurological and psychiatric disease. Inspired by clinical observations, she is testing a unifying theory for how dopamine may interact with these circuits to cause symptoms across a spectrum of diseases,

including Parkinson's, Huntington's, Tourette's, Bipolar Disorder, Schizophrenia, and delirium. Leveraging an innovative toolkit, including complex behavior in humans and animals, optogenetics and artificial intelligence, this work aims to inform novel, precision treatments for these conditions, for which effective therapies do not exist or remain limited.

Member **Siniša Hrvatin** studies how during periods of food scarcity or difficult environmental conditions, many mammals enter dormant states called torpor and hibernation, in which their body temperatures drop and their metabolisms slow, reducing their need for energy and food. Hrvatin previously identified the region of the brain that regulates torpor in mice. At Whitehead Institute, he continues to study how the brain regulates torpor and hibernation in different animals. Torpor and hibernation may have long-term effects such as slowing disease progression, tissue damage, and the process of aging, and Hrvatin wants to understand whether the mechanisms underlying these states could be induced in humans to yield these health benefits.

Founding Member **Rudolf Jaenisch** has pioneered the creation and use of various innovative models to study neurological diseases in conditions mimicking cells' natural environment. His methods are leading to a deeper understanding of conditions ranging from Fragile X and Rett syndromes to Parkinson's disease to Zika-caused microcephaly—and to new strategies for prevention and treatment. Additionally, Jaenisch studies the effects of SARS-CoV-2, the virus that causes Covid-19, on nervous system cells. His group found that the virus can infect sensory neurons, which could help to explain certain Covid symptoms such as loss of smell.

Member **Ankur Jain** studies how dysfunctional RNA molecules that clump together into large droplets or gels can build up in brain cells. This disrupts normal processes and may contribute to cell death in neurological disorders such as amyotrophic lateral sclerosis (ALS) and Huntington's disease. Jain lab researchers found that the RNA clumps become most harmful to cells when they leave the nucleus and enter the main body of the cell. Jain is looking into drugs that could target disease-causing RNA clumps and either dissolve them or corral them in the nucleus.

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