

Research directions at Cold Spring Harbor Laboratory Cold Spring Harbor Laboratory follow an ever-changing landscape that is influenced by the intellect of our scientists, by the evolution of scientific problems that can be addressed by current or newly developed technologies, and by a dynamic institutional view that promotes collaborative research and a focus on specific problems that are of collective interest.

future. Massachusetts Institute of Technology (MIT) president Susan Hockfield. Their collaborations soon generated insights into the development and organization of the mammalian nervous system. But, alas, these forays into the emerging field of what the 1983 CSHL Symposium called "Molecular Neurobiology" were not sustained because the Laboratory lacked year-round space for neuroscience experimentation. It was a missed opportunity, but one decisively addressed by Jim Watson and an ad hoc committee of the Board of Trustees. In 1983, they set the Laboratory on a course that would result in a full and lasting commitment to neuroscience and in the construction of a major state-of-the-art laboratory. Named for Arnold and Abel DeCman, it would enable CSHL to initiate year-round neuroscience research in the Laboratory's centennial year, 1997.

The current era of neuroscience investigation at Cold Spring Harbor dates from this time, over 20 years ago. An early focus on the molecular basis of learning and memory led, in time, to studies pertaining to neural dysfunction in people — to memory loss and, separately, to neurofibromatosis 1, an inherited illness in which tumors form in nerve tissue. These studies, initially focusing on the fruit fly *Drosophila*, enabled our new neuroscientists to include a genetic approach to under-

olfactory receptors to the brain's olfactory cortex, where decisions are made based on processed signals. Some decisions, it is believed, are innate, whereas others, such as these, are forged in response to experience or environmental cues. Tonyodor, who heads our Swarthmore Center for Computational Neu-

their life span. Whether stem cells that have been expended can be enticed to revert to their former identity and be recruited back into the stem cell pool is a question that Enikolopov's team is now pursuing. Hiro Furukawa's research concerns another aspect of nerve cell biology, that of proteins that lie on the surface of individual nerve cells. He studies the structure of the immense multiunit protein that forms NMDARs (*N*-methyl-D-aspartate receptors) that control the strength of connections between neurons and thereby have a central role in learning and memory. Membrane receptors, the place where neurotransmitter molecules "dock" with nerve cells, are at the "front end" of cell-signaling networks and are of great interest as targets for drug discovery in diseases such as Alzheimer's and in cognitive disorders such as autism and depression. This year, Hiro's team discovered and mapped a new regulatory site in a class of NMDARs, progress that now opens the way to the development of a potentially new class of drugs to modulate the receptor.



igler pursued an inspired hunch that some common genetic disorders — such as autism and schizophrenia — might be traceable to CNVs that occurred spontaneously, that is, not present in either parent of an affected individual. In subsequent work, this hypothesis was confirmed for both disorders. In autism especially, it became clear that spontaneous CNVs accounted for a large fraction of cases. With generous support from the Simons Foundation, a large sample of families with an autistic child was assembled. Analysis of the genomes of the affected child compared with that of the parents and sometimes an unaffected sibling enabled the identification of hundreds of regions in the human genome associated with autism. The surprising fact that we all have CNVs, coupled with the igler lab's invention of the technological means to identify them across the genome, was a major step along the path toward understanding the cause of the disorder and toward the eventual use of chromosome engineering to create a mouse model of autism.

igler continues to explore the genetics of neuro-psychiatric disorders in humans. He and collaborators have also made a major contribution to describing the role of both spontaneous and inherited CNVs in schizophrenia. Another of our senior scientists, Dr. Richard McCombie, shares this interest in the human genetics of brain disorders. He heads the Laboratory's Stanley Institute for Cognitive Genomics and is sequencing patients with schizophrenia, bipolar disorder, and depression. The collaboration between igler and McCombie has enabled the genetic analysis of autism to proceed to identifying rare single-gene mutations.

The three paths of research in neuroscience — human genetics, connectivity, and the study of cognition — are rapidly converging. Furthermore, the Laboratory's recent investment in building a quanti-