

ington, D.C.

"This is obviously a very serious matter," the university said in a brief statement. "We know that Dr. Wilson understands its importance, is reviewing the letter carefully and intends to respond in a timely way." Wilson has 30 days to reply to the FDA's letter. After reviewing Wilson's response, FDA administrators will make a final decision.

This is a "drastic" step, says Inder Verma of the Salk Institute for Biological Studies in La Jolla, California, who headed a special working group at the National Institutes of Health that investigated the Gelsinger trial. But Savio Woo, a gene therapy researcher at Mount Sinai School of Medicine in New York City and past president of the American Society of Gene Therapy, says that vigorous FDA oversight will strengthen gene therapy research.

—GRETCHEN VOGEL

NEUROSCIENCE

Immune Molecules Prune Neural Links

The developing brain starts off as a tangle of neuronal connections, then activity reinforces some of these connections and causes others to atrophy. Over the past few years, neurobiologists have been on the prowl for molecules that help the nervous system make and break these connections, and they've come up with a few contenders. But now Carla Shatz's team at Harvard Medical School in Boston is proposing an unlikely new candidate: a type of protein previously known for its role in helping the immune system fend off viruses and other foreign invaders.

In work described on page 2155, Shatz and her colleagues suggest that the class I major histocompatibility complex (MHC) proteins are necessary for the formation of normal neuronal connections in a visual area of the brain during development. Later in life, they're called into play in the hippocampus, a brain area involved in memory and learning. The work shows "a completely unexpected function for the molecules," says neurobiologist Marc Tessier-Lavigne of the University of California, San Francisco.

The current results are an outgrowth of observations that Shatz's team, then at the University of California, Berkeley, reported 2 years ago. While examining how gene expression patterns in the brain react to changes in retinal activity, the researchers found, to their surprise, that the genes encoding class I MHC proteins are active in the developing brain. To explore what these seemingly alien molecules were doing there, Gene Huh, a postdoc in the Shatz lab, turned to three strains of mice that had been genetically altered. Two of these strains lacked the ability to display class I MHC proteins in their nor-

mal location on the cell surface; the third lacked part of a receptor that T cells use to respond to class I MHC proteins. In the first phase of their work, Huh and his colleagues tested how these gene knockouts affected the development of the animals' visual systems.

Like many animals, mice aren't born with the ability to see. The visual system matures only when neural signals, originating either from spontaneous neural firing in the retina before the eyes open or from looking around afterward, help organize the parts of the brain that receive and process visual information. Huh found that this process, which involves both strengthening frequently used connections and pruning useless ones, is disrupted in all three knockout mice.

The visual signal's first stop after the eye is the lateral geniculate nucleus (LGN). There, neuronal projections from the retina normally form what Huh describes as a "big misshapen doughnut." The doughnut itself, occupying most of the LGN, receives input from the eye on the opposite side of the body, while a small "doughnut hole" in the middle of the LGN gets projections from the same-side eye. But in the knockout mice the doughnut hole is much larger, implying that the inputs from the two eyes overlap. The finding suggests that in the absence of functioning class I MHC proteins, the normal pruning of connections that should have occurred in the LGN is defective.

Similar strengthening and weakening of neuronal connections is thought to occur during memory formation in the adult hippocampus. So Shatz and her colleagues next looked at synapses in that brain region, where their earlier work had shown that the class I MHC genes are also active.

When postdoc Lisa Boulanger stimulated the hippocampal neurons, she found that neurons in the knockout mice reacted strangely. Long-term potentiation (LTP), the strengthening of signals with stimulation, was enhanced: Hippocampal neurons in the knockout mice responded more dramatically than did those in normal mice to a high-frequency stimulus that can evoke LTP. And when she applied low-frequency stimulation, which causes the synapse weakening known as long-term depression, neurons in the knockout mice failed to rein in their signals as they should have. "To us," says

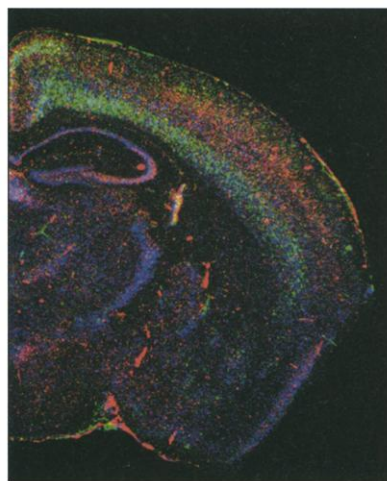
Shatz, "the results imply that there may be a commonality of cellular and molecular mechanisms" in how neurons in the hippocampus and the developing nervous system respond to activity.

Huh and Shatz suspect that the class I MHC proteins also help neurons tune their connections in other areas of the brain. The mouse carries about 30 different varieties of the protein. When Huh tested where four of the genes are expressed, he found that different ones are active in different places in the brain (see figure), possibly tailoring nearby neurons to fit into the correct neural pathways.

Despite the evidence indicating that the class I MHC proteins are somehow involved in refining neuronal connections in the brain, researchers don't yet know how the mole-

cules are acting. Immunologist Hidde Ploegh of Harvard says he's "intrigued by the possible role of [these molecules] in something that appears to have no immunological correlate." But he awaits the details of how they might be helping the nervous system figure out which connections should atrophy.

—LAURA HELMUTH



Sort it out. As indicated by the colored staining patterns, different class I MHC genes are expressed in different brain areas.

NEUROPSYCHOLOGY

Language Affects Sound Perception

NEWPORT BEACH, CALIFORNIA—Neuropsychologists may owe a debt to the devil. At the 140th meeting of the Acoustical Society of America here last week, University of California, San Diego, psychologist Diana Deutsch demonstrated that an auditory illusion based on the tritone—also known as the "devil in music"—is perceived differently by listeners with different linguistic histories. And those perceptions might help psychologists understand how the brain rewires itself during childhood.

Played together, two notes a half-octave apart (such as C and F sharp) sound jarring; medieval musicians considered this combination, a tritone, so discordant that they dubbed it the "diabolus in musica." But a tritone is music to Deutsch's ears. For more than a decade, she has been studying an auditory illusion—the acoustical equivalent of an optical illusion—based upon the tritone.

With a computer, Deutsch created am-