

From Marshmallows to Missiles

KNOCKOUT YIELDS NEW CLUES TO HOW SPERM ARE PERFECTED FOR PENETRATION.

Examining mouse testes under a microscope, Yi Zhang couldn't find any mature sperm. But that was a good thing. It meant that knocking out a single gene, called *Jhdm2a*, in mice wrecked their ability to produce mature sperm.

The knockout had blocked "chromatin condensation," a process critical for sperm maturation. Chromatin condensation entails replacing the protein packing material around the genes in a sperm's head with basic proteins—specifically, transition proteins and protamines—transforming maturing sperm from marsh-



The round, dense head of a mature sperm allows it to penetrate the outer layer of an egg.

mallows into missiles. The resulting denser heads can slam into an egg with enough force to penetrate its outer layer, enabling fusion and fertilization.

HHMI investigator Zhang and his colleagues at the University of North Carolina at Chapel Hill published their

findings online in *Nature* on October 18, 2007.

By showing that the *Jhdm2a* gene is necessary for DNA condensation in sperm, Zhang shed light on an important gene regulatory mechanism, called epigenetic control. Epigenetic modification alters histone proteins—the "smart stuffing" that DNA coils around within chromosomes. This alteration switches genes on or off. Genetic regulation, in contrast, depends on control sequences integral to the DNA molecule.

The Zhang group demonstrated that the *Jhdm2a* gene encodes an enzyme that removes methyl groups from histones and switches on associated genes. *Jhdm2a* activates genes that encode the transition proteins and protamines needed for condensation of sperm DNA. According to Zhang, the finding could have implications for treating infertility and for birth control.

"Many cases of human infertility arise from defects in sperm production," he says. "While we have yet to demonstrate that this gene is important in human spermatogenesis, our findings raise the possibility that it might be. If so, remedying this defect could treat such infertility.

"On the other hand," he adds, "because this gene is very specific to spermatogenesis, a drug that inhibits the enzyme could provide highly targeted male birth control." ■ —DENNIS MEREDITH

IN BRIEF

crystals for x-ray crystallography studies.

"This new approach gave us dramatic new insight, because we could actually see the lipid molecules gathered around the protein, and see them form the characteristic leaflets of the bilayer biological membrane," says MacKinnon. "With an earlier structure that we published in 2005 we could only speculate why the use of lipids was important, but now we can see it very clearly."

ANTIDEPRESSANT EXTENDS LIFE SPAN IN WORM

A drug used to treat depression can extend the life span of adult roundworms, according to a team of scientists led by HHMI investigator Linda B. Buck.

The antidepressant drug mianserin can extend the life span of the worm *Caenorhabditis elegans* by about 30 percent, Buck and colleagues Michael Petrascheck and Xiaolan Ye report in the November 22, 2007, issue of *Nature*.

The researchers don't understand exactly how mianserin staves off the effects of aging. Buck says it was a surprise to find that a drug used to treat depression in humans could extend life span in worms. The drug appears to act the same way in both *C. elegans* and humans: by blocking certain receptors for the neurotransmitter serotonin.

Serotonin, a chemical cells use to communicate, helps regulate many functions, including mood, appetite, and sensory perception. But the group found that, in addition to inhibiting certain serotonin receptors in the worm, the drug also blocked receptors for another neurotransmitter, octopamine.

A number of observations suggest that serotonin and octopamine may complement one another, with serotonin signaling the presence of food and octopamine signaling its absence or a state of starvation.

Buck says that her lab has yet to identify what kinds of cells the drug affects, because while the serotonin receptors involved are found only on neurons, many types of cells—not just cells of the nervous system—have receptors for octopamine.

THE AGING BRAIN: FAILURE TO COMMUNICATE

Using advanced imaging techniques, a team of HHMI researchers has shown that normal aging disrupts communication across the brain. The research shows that this decline happens even in the absence of serious pathologies like Alzheimer's disease.

Researchers have known for some time that normal aging degrades bundles of axons in the central nervous system

that transmit critical signals. "Our study now shows that cognitive decline in aging may be linked to disruption of communication between different regions of the brain," says Randy L. Buckner, an HHMI investigator at Harvard University. The work was published December 6, 2007, in *Neuron*.

Buckner's group explored whether aging in a group of adults caused a loss of correlation between the regions of the brain that—at least in young adults—engage in robust neural crosstalk.

They focused on the links within two critical networks, one responsible for processing information from the outside world and one, known as the default network, that is more internal and kicks in when we muse to ourselves. The default network, for example, is presumed to depend on two regions of the brain linked by long-range white matter pathways. The new study revealed a dramatic difference in these regions in young and old subjects.

"We found that in young adults, the front of the brain was pretty well in sync with the back of the brain," says Jessica Andrews-Hanna, a graduate student in Buckner's lab and lead author of the study. "In older adults this was not the case. The regions became out of sync and were less correlated with each other."