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RESEARCH NEWS

MARCH 11, 1999

Scientists Link Body Weight Regulation and Immune System Control

A newly discovered gene that governs a mouse's weight and the color of its coat may also help orchestrate the immune system, say researchers from the Howard Hughes Medical Institute (HHMI) at Stanford University.

In the March 11, 1999, issue of the *Nature,* Gregory Barsh, an HHMI investigator at Stanford University, and colleagues detail the discovery of *mahogany,* a gene that codes for a protein that suppresses obesity in mice. A team from Millennium Pharmaceuticals reported similar findings in the same issue of *Nature.*

"It's extremely interesting that the *mahogany* gene should turn out to have a function in the immune system," said Barsh. "This implies that this molecule could provide a functional link between regulation of energy and the immune system."

"The mahogany mouse (left) is darker and usually more active than its "wild-type" cousin (right)."
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Barsh's team, working in collaboration with Jonathan S. Duke-Cohan of the Dana-Farber Cancer Institute, showed that the mahogany protein is made inside the cell and is quite large consisting of 1,428 amino acids. Despite its size, however, mahogany passes partway through the cell's outer membrane, where most of the protein hangs on the outer surface of the cell. The part of mahogany that sticks outside the cell most likely helps to detect the presence of passing hormones or other signaling molecules.

"Our research suggests that mahogany is possibly a receptor, something that sticks out and grabs other molecules passing by," Barsh said. Two such molecules that may bind to the mahogany "receptor" are agouti and

agouti-related protein, which regulate hair color and body weight in mice respectively.

The researchers also showed that a large fragment of the human mahogany protein is released into the bloodstream where it goes by a different name, attractin. This circulating form of attractin was only recently discovered in humans and was shown to mediate communication among T cells and other white blood cells that form part of the immune system.

Pinpointing the *mahogany* gene and showing its relationship to attractin is important, says Barsh, "because it suggests an additional molecular pathway that could affect immune function."

Although the circulating form of the mahogany protein has not yet been found in mice, the implications are that the system is the same in mice and humans. "If that turns out to be the case, a new window to the intricate communication grid of the immune system is now opened through a powerful mouse model," says Barsh.

The discovery also poses an intriguing question of basic biology. "Why should immune function be connected to regulation of body weight?" asks Barsh. That remains an open question, but the new research may hold some long-term prospects for the treatment of obesity. "This will obviously require further study, but one might imagine that a subclass of obese patients will be found to have alterations in mahogany-attractin, and that drugs might be developed that affect how mahogany protein functions."