NINDS for Martin's laboratory and five collaborating laboratories.

Refai obtained blood samples from healthy human donors who had been injected with a factor that helps enrich their blood supply of CD34-positive stem cells. He then fished out that scant supply (only 1 percent) of candidate cells with the help of a magnetic tag and grew the cells in petri dishes. As with most first-time investigators, Refai's early months were slow going. He lost all the stem cells on the first try because of a fluke in the isolation procedure, but by the second try, he was up and running. He can now get the cells to stay in culture for up to a week and is tinkering with conditions to see whether he can trick the cells into maturing into neural stem cells, which the team eventually hopes to inject into the central nervous systems of mice.

Refai resumes his medical training in June, but he is so taken with the project that he wants to return to it periodically over the next eight years as he completes neurosurgery training. That plan pleases Martin, who characterizes his protégé as the kind of young physician who is much needed in the research community. "It is actually a sad development," Martin says, "that fewer and fewer students who have chosen M.D. paths are eager to venture into the very difficult but very rewarding career of physician-scientist." **—TRISHA GURA**

Gene Prevents Excessive "Grooming"—at Least in Mice

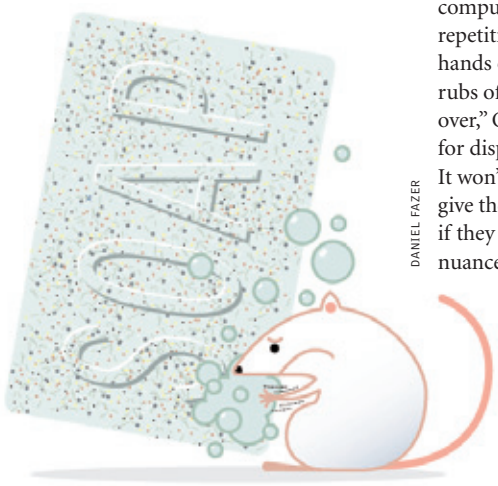
Talk about compulsive behavior. This group of mice didn't just lick themselves clean, as normal creatures do, but licked and bit themselves so continuously and vigorously that they became bald in some places and even developed open wounds. Joy Greer, a graduate student in Mario Capecchi's lab at the University of Utah, reported that the mice had body hair trapped between their teeth and gums, suggesting they had torn it off.

Why were these mice, all of whom lacked a gene called *Hoxb8*, so driven to groom themselves? "We initially thought they may have an itch," says Capecchi, an HHMI investigator who studied these animals with Greer. "We looked very carefully at their skin and all sensory inputs to the skin—sensitivity to pressure, temperature, pain, etc. Was there an irritation? An allergic response? We even gave them grafts of normal skin, but that didn't reduce the obsessive grooming. The skin appeared perfectly normal."

The researchers then set up infrared cameras to record what the mice did by night, when they are most active, as well as by day. Each mouse cage held a normal and a mutant mouse. After analyzing 24 hours of videotape, the researchers concluded that the mutant mice acted normally in almost every way. They ate, drank, climbed, hung upside down from the roof of the cage and built nests at the same rate as their normal counterparts. However, they spent nearly twice as much time licking and biting their bodies. They also groomed their cage mates. All this activity kept them so busy that they slept about one hour less each day than the normal mice.

Intrigued, the researchers wondered whether the missing *Hoxb8* gene—one of 39 homeobox-containing (*Hox*) genes that play major roles in the early development of the body and brain—is normally expressed in the central nervous system of adult mice. They found that it is, and apparently, the protein produced by this single gene is required to prevent mice from compulsively grooming their bodies.

Because mouse genes are nearly identical to ours, Capecchi points out, this research very likely applies to humans as well. Thus his lab has become interested in people who suffer from trichotillomania—a condition in which people cannot stop pulling their hair out. As one patient reported to the Trichotillomania Learning Center, in Santa Cruz, California, "Talking on the phone for more than five minutes usually means that I won't have eyebrows or lashes when I hang up."



DANIEL FAZER

About 6 million Americans are estimated to have trichotillomania. What especially interests Capecchi is that identical twins share this trait 95 percent of the time and that it runs in families, suggesting some sort of genetic component. Could these people be suffering from a defect in *Hoxb8*?

Capecchi is determined to find out. He is collecting blood samples from approximately 150 patients in Utah and is planning to collect more samples nationwide. "We'll sequence the *Hox* genes from each patient," he says. "Besides *Hoxb8*, two other *Hox* genes may be involved. Obviously, if these genes are mutated in patients, we may find new targets for therapy."

If this project works out, other kinds of obsessive-compulsive disorders may benefit from studies of mouse genes. "Obsessive-compulsive disorders are associated with repetitive functions, such as washing one's hands over and over again until the skin rubs off, or lining up one's shoes over and over," Capecchi says. "We're going to look for displays of repetitive behavior in mice." It won't be easy, he admits. "Perhaps we'll give them some things to play with and see if they line them up. There are lots of subtle nuances to mouse behavior, and we'll have to keep our minds open. We're just beginning our analysis of what the *Hox* genes are doing in the adult brain." **—MAYA PINES**

» For movies of the mice grooming themselves, see: *www.hhmi.org/bulletin*