

# Building a Better Mouse Transposon

*A breakthrough in mouse molecular genetics may mark a significant research advance.*

**BY INACTIVATING EACH MOUSE GENE** one by one and assessing the biological consequences, geneticists can deduce a gene's functions. HHMI investigator Mario R. Capecchi of the University of Utah in Salt Lake City pioneered targeted mouse gene knockout technologies some two decades ago, unleashing a flood of knowledge about mammalian biology. Despite such successes, progress toward being able to delete all the mouse's 30,000 or so genes has been slow. The method is technically challenging, expensive, and time-consuming—it can take more than a year of full-time work to generate a single knockout mouse. So far, researchers have managed to inactivate only about 10 percent of mouse genes.

Tian Xu, an HHMI investigator at Yale University School of Medicine, has been searching for a faster and easier approach for the past 7 years. In the August 12, 2005, issue of *Cell*, Xu and collaborators—HHMI investigator Min Han of the University of Colorado at Boulder, Yuan Zhuang at Duke University Medical Center, and colleagues at China's Fudan University—reported they had finally succeeded.

The new method takes advantage of a transposon—a short segment of DNA that can “hop” to another position of an organism's genome and that is capable of landing squarely inside a gene and inactivating it. For decades, geneticists had exploited transposons to disrupt genes in plants, worms, and fruit flies, among other models, but they hadn't worked very well in mammals. “About 40 percent of the sequences in our genome, and in the mouse genome, are actually transposon sequences,” Xu says. Those transposons are no longer active, however, but are the molecular relics of an era when transposons ran rampant through mammalian genomes. “Evolution managed to make all these transposons inactive, probably so that they wouldn't destroy our genomes,” Xu says.

Xu's lab tried to modify several of the standard transposons used in other organisms to prod them to hop to mammals, but the researchers' efforts were unsuccessful. Then they tried an unusu-

al transposon called piggyBac, discovered a decade ago by University of Notre Dame professor Malcolm J. Fraser, Jr. PiggyBac appears to be evolutionarily distant from other known transposons and has properties that make it unique. “I thought maybe it's

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“You just look at the mice in the next generation, and if they're red you know you have your transposon” without the need for further testing, Xu says. Another advantage is that, like a normal gene, the transposon carries just one copy of the transferred gene into the chromosome, in contrast to traditional transgenic methods that result in multiple copies being inserted. “These features make piggyBac a dream tool for mutating genes,” Xu says. He predicts that this new technique will become the method of choice for creating mouse knockouts.

Notre Dame's Fraser, who maintains a Web site for disseminating information about piggyBac to the scientific commu-



ABOVE \_ AFTER SEARCHING FOR 7 YEARS FOR A BETTER WAY TO INACTIVATE MOUSE GENES, TIAN XU AND COLLEAGUES HAVE SOME GOOD NEWS TO REPORT.

so strange it will work,” Xu says. And when Fudan graduate student Sheng Ding introduced piggyBac into mouse and human cells, it did work. In one pilot experiment, Ding and fellow researcher Xiaohui Wu, each working only half-time in their Shanghai research laboratory, generated 75 different knockout mouse mutants in just 3 months.

Besides the agility with which piggyBac lodges itself in mammalian genes, one of its most practical properties is that it can carry additional genes within it, without losing its ability to hop. Xu's team inserted a marker gene that encodes a red fluorescent protein into piggyBac.

nity, appreciates witnessing the fruits of his discovery: “I congratulate [Xu and colleagues] on the thoroughness of their analysis. It's gratifying to have been involved with finding something that other people can use for such great advantage. That's why you get into science.”

For his part, Xu intends to continue Fraser's spirit of scientific openness. “We plan to inactivate the majority of the mouse genes in the next 5 years,” he says. “We're going to make those mutant mouse strains available to the scientific community, and I believe this will significantly advance science.” ■

-Paul Muhlrads