UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers use novel sperm stem-cell technique to produce genetically modified rats

DALLAS – May 27, 2010 – For two decades, the laboratory mouse has been the workhorse of biomedical studies and the only mammal whose genes scientists could effectively and reliably manipulate to study human diseases and conditions.

Now researchers at UT Southwestern Medical Center have added another experimental research animal to the scientific stable: the rat.

In a new study appearing online and in an upcoming issue of *Nature Methods*, UT Southwestern researchers detail how they created 35 new rat "lines," with each type of animal harboring mutations in specific genes. More than half of these mutated genes are associated with biological processes linked to human diseases, including cancer, diabetes, Alzheimer's disease, aberrant circadian rhythms and mental illness.

Dr. Kent Hamra, assistant professor of pharmacology and lead author of the study, said the ability to easily, reliably and inexpensively produce genetically modified rats offers tremendous potential for biomedical research for even small laboratories with limited resources. For example, compared to the mouse, the rat is a larger, more intelligent animal; it is often better for biochemistry, pharmacology and physiology studies; and its behavior often is more in tune with that of humans.

"Our studies are focused on sperm-cell biology and fertility genes, but ultimately, we think other scientists will utilize these relatively simple, cost-effective techniques to generate genetically altered rats for use in experiments related to human disease," Dr. Hamra said.

One of the keys to producing the mutated rats was a novel technique Dr. Hamra and his colleagues in the Cecil H. and Ida Green Center for Reproductive Biology Sciences at UT Southwestern developed five years ago to prevent rat sperm stem cells – sperm precursor cells – from differentiating, or changing, permanently into sperm.

"Getting sperm stem cells to grow in culture was a huge step," Dr. Hamra said. "In these new experiments, we took the next step and genetically modified these precursor cells in culture, selected them for mutations and introduced the cells into the testes of a sterile male rat."

The animal produces genetically altered sperm, resulting in mutant offspring that can be used for biomedical research.

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Other methods have been used in limited ways to produce altered rats, but those methods do not involve manipulating stem cells in culture. In addition, genetic methods typically used to modify mice employ the use of the rodents' embryonic stem cells, and these methods have not worked well in other mammals, including the rat, Dr. Hamra said.

The latest work, he said, is proof-of-principle that genetic mutations introduced into mammalian stem cells from species other than mice can indeed be preselected for in culture and passed on to offspring.

Another key to Dr. Hamra's success in producing genetically altered rats came from two co-authors on the study, Drs. Zsuzsanna Izsvák and Zoltán Ivics of the Max-Delbruck Center for Molecular Medicine in Berlin. They developed a method to trigger mutations in specific areas of mammalian DNA. The method relies on deploying a segment of DNA called a transposon, which, when introduced into an organism's DNA, "jumps" randomly around the genome, creating mutations along the way.

"A transposon is nature's simplified way of cutting and pasting DNA in and out of the genome," Dr. Hamra said.

The researchers in Germany developed ways to harness the power of transposons for mammalian species and to control precisely where and how in a given genome they do their mutagenic "hopping." For example, a transposon can be limited to producing mutations only in an area of the genome where scientists think a disease-related gene resides.

In addition to producing actual animals, Dr. Hamra and his colleagues also are now using the transposon method to generate complex libraries of sperm stem cells harboring various genetic mutations. To date, they have about 100 cell lines with different mutations stored frozen in their labs.

"Because testes of a single rat can support sperm production from thousands of individual stem cells and because rats are so prolific, these libraries open the door to an economic strategy for high-throughput mutagenesis screens in the rat," Dr. Hamra said.

Other UT Southwestern pharmacology researchers involved in the work are research intern James Shirley, research assistant Heather Powell and research scientist Karen Chapman.

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