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## **UT Southwestern researchers discover how brain's memory center repairs damage from head injury**

DALLAS – March 30, 2011 – Researchers from UT Southwestern Medical Center have described for the first time how the brain's memory center repairs itself following severe trauma – a process that may explain why it is harder to bounce back after multiple head injuries.

The study, published in *The Journal of Neuroscience*, reports significant learning and memory problems in mice who were unable to create new nerve cells in the brain's memory area, the hippocampus, following brain trauma. The study's senior author, Dr. Steven G. Kernie, associate professor of pediatrics and developmental biology at UT Southwestern, said the hippocampus contains a well of neural stem cells that become neurons in response to injury; those stem cells must grow into functioning nerve cells to mend the damage.

"Traumatic brain injury (TBI) has received a lot of attention recently because of the recognition that both military personnel and football players suffer from debilitating brain injuries," Dr. Kernie said, adding that memory and learning problems are common after repeated severe head injuries.

"We have discovered that neural stem cells in the brain's memory area become activated by injury and remodel the area with newly generated nerve cells," Dr. Kernie said. "We also found that the activation of these stem cells is required for recovery."

The scientists developed unique transgenic mice that were unable to create hippocampal neurons when exposed to a usually harmless chemical called ganciclovir soon after brain injury. Four groups of these transgenic mice received either sham surgery or a controlled cortical injury (CCI) to mimic the diffuse damage of a moderate to severe head injury, and two of the groups were exposed to ganciclovir, Dr. Kernie said.

After a month – the time earlier experiments indicated it takes for neural stem cells to mature and integrate as neurons into the hippocampus – the researchers gave the mice a learning task called the Morris water maze in which the mice had to find a white platform hidden in a white pool of water. On the first day of learning the task, there were no group-noteworthy differences in swim speed, indicating no motor impairment in the test mice. During the next 10 days, however, the test group spent more time swimming along the edges of the tank, and they travelled longer distances to reach the platform.

"This suggests that injured mice who lack new nerve cells fail to progress to a more efficient

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spatial strategy to find the hidden platform. We interpret this result as a mild but statistically significant learning deficit,” he said.

The UT Southwestern scientists then let the mice rest a day, removed the platform and retested them to see how well they remembered where the platform’s location.

Compared to controls, CCI mice showed no preference for the platform’s previous location or even for the target quadrant of the pool where the platform had been, Dr. Kernie said.

In comparison, CCI mice with intact nerve cell generation had an intermediate response to the water maze and non-CCI mice with intact nerve cell generation had the best response. Dr. Kernie said those findings suggest that neurogenesis is necessary for learning after TBI, and they raise the question of whether the neural stem cell pool is limited.

“The ability to self-repair may be limited,” he said.

Since there are already Food and Drug Administration-approved medications available to increase neurogenesis, the next steps are to determine if these can be used to improve outcomes after traumatic brain injuries. In addition, Dr. Kernie and colleagues are determining what molecules direct this process and how the stem cell pool might be preserved in order to enhance the ability to recover from recurrent injury.

Other UT Southwestern researchers involved in the study were lead author Dr. Cory Blaiss, a former postdoctoral researcher who now is an assistant research scientist at the Ernest Gallo Clinic and Research Center at the University of California, San Francisco; Dr. Tzong-Shiue Yu, former graduate student who now is a postdoctoral researcher at Toronto Hospital for Sick Children; Gui Zhang, research assistant in pediatrics; Georgi Dimchev, former graduate student presently enrolled at Manchester Metropolitan University in England; Dr. Luis Parada, chairman of developmental biology; and Dr. Craig Powell, assistant professor of neurology and neurotherapeutics and psychiatry.

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