NEWS

Study spells caution for bone marrow transplants for Rett

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Sowing seeds: After a bone marrow transplant, healthy immune cells (red) populate the brains of mice that model Rett syndrome.

Bone marrow transplants, which have been shown to arrest symptoms of Rett syndrome in young mice, have little effect on older mice, according to preliminary results presented Monday at the **2013 Society for Neuroscience annual meeting** in San Diego. The findings suggest that this approach may not be a viable treatment for those who already have symptoms of the disorder.

Rett syndrome is a developmental disorder caused by mutations in **MeCP2**, which is on the X chromosome. Girls with the disorder have a number of symptoms — including seizures, language problems and breathing difficulties — that emerge around 2 years of age. The few boys born with the disorder are severely affected and die in infancy.

Mouse studies in the past few years have shown that MeCP2 is expressed not only in neurons, but in **the brain's support cells**, called glia. Restoring MeCP2 expression in a subtype of these cells **prevents symptoms** in Rett syndrome mice. This type of genetic engineering is not possible in people, however.

Last year, **Jonathan Kipnis** and his colleagues **replaced the bone marrow** of 4-week-old male mice lacking MeCP2 with marrow from their healthy peers. This transplant is thought to repopulate the mice with healthy **microglia** — scavenger cells that protect the brain from pathogens and prune

connections between neurons.

Kipnis and his team found that mice given the transplant live longer, gain weight and recover from some of their breathing difficulties. This created a stir in the community because it suggested a potential treatment for children with the syndrome.

However, the researchers performed the transplant before the onset of most symptoms. That means the treatment arrested the symptoms, but did not reverse the disorder, notes Kipnis, professor of neuroscience at the University of Virginia.

That caveat limits the treatment's promise for children older than 2, notes **Jeffrey Neul**, associate professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas, who presented the new work at the conference. What's more, the children would need to have a full sibling to serve as a bone marrow donor. This makes the pool of potential clinical trial participants impossibly small, Neul says.

"It would be the symptomatic people who are going to want to be transplanted, and we wanted to see if it would help them," Neul says.

Hail Mary:

To see whether Kipnis' results hold up in older mice, Neul designed what he calls a "Hail Mary experiment," using 18-month-old female Rett syndrome mice.

These mice are near the end of the lifespan for Rett mutants, middle-aged by control-mouse standards and, in Kipnis' words, "crazy old."

Rett syndrome progressively worsens throughout an individual's lifespan, and 18-month-old mice show severe symptoms — including repeatedly clasping their hind limbs and struggling with motor activity.

The researchers examined the mice before and four months after bone marrow transplantation. As in the juvenile mice, the transplants successfully repopulate microglia in the adult female mice.

However, the symptoms in these mice do not improve. Across a range of tests for anxiety, motor coordination and breathing, they scored essentially the same as before the transplant. (One mouse dramatically improved in its ability to balance on a rod after the test, but this result is an outlier, the researchers say.)

The researchers did not compare these mice with other Rett syndrome mice of the same age, or control for the effect of the transplant. This lack of controls is significant, notes Kipnis, because untreated mice might have continued to deteriorate during those four months. He says Neul may in

fact be underestimating the benefits he sees.

“You take a mouse that is very sick, put it through severe radiation, wipe out its entire bone marrow, and then you compare it to before and say that it’s not getting better,” Kipnis says. “But the mouse is very sick and it’s supposed to get worse. The fact that it stays at the same level is very exciting.”

Neul plans to repeat the experiment with controls and to try to replicate Kipnis’ results in young mice. A clinical trial of the approach may still be possible, but the risk-benefit ratio needs to be considered carefully, Neul says.

“There is a mortality and morbidity associated with bone marrow transplant,” he says. Parents of boys with the syndrome are particularly interested in trying the treatment, which for them may even be “compassionate use,” says Neul. Still, boys with Rett syndrome are typically so sick that they are unlikely to survive a transplant procedure.

For more reports from the 2013 Society for Neuroscience annual meeting, please ***click here****.*