NEWS

Study questions promise of bone marrow transplant for Rett

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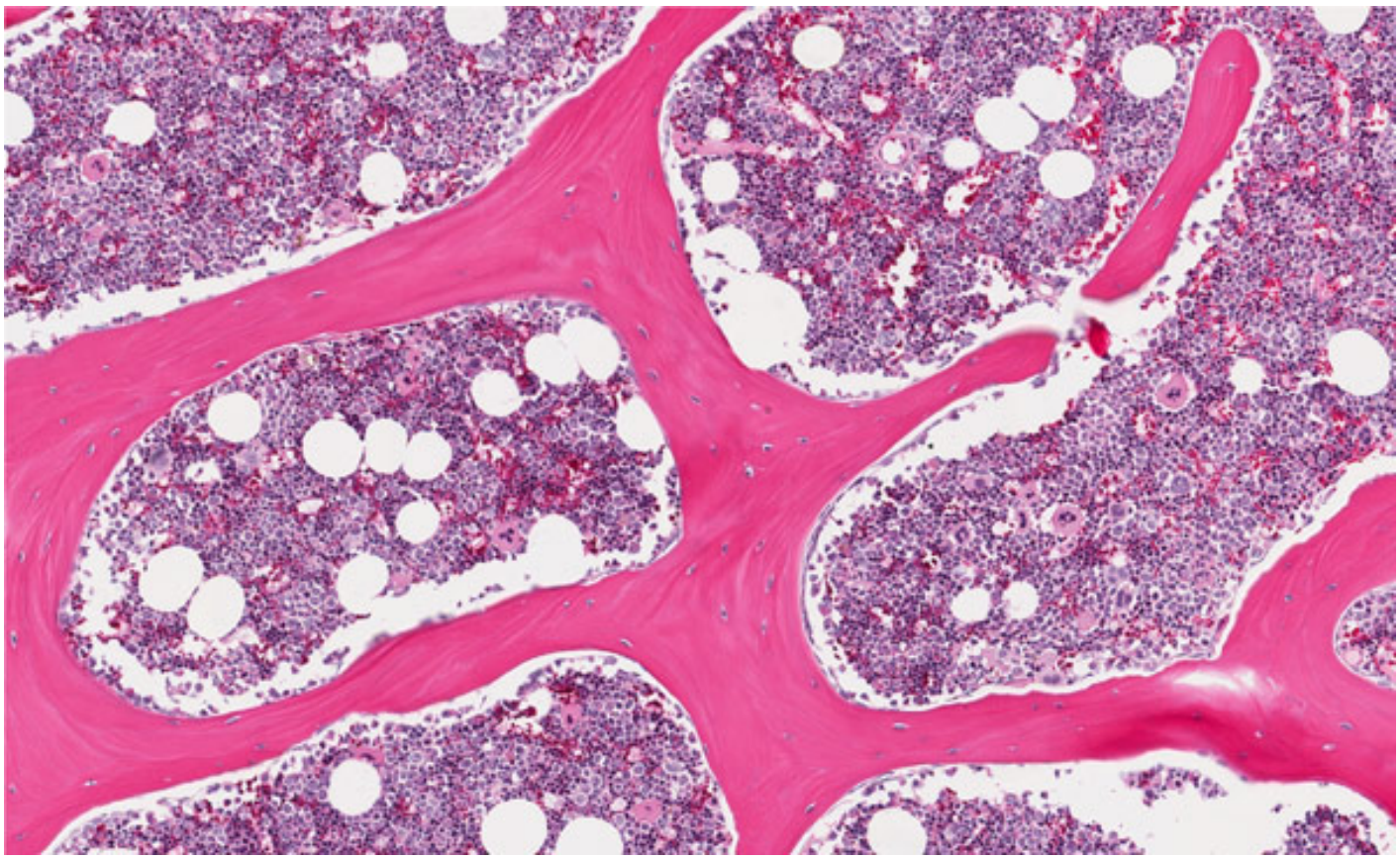

Researchers from four labs were unable to reproduce the findings from a high-profile 2012 study in which bone marrow transplants dramatically extended the lives of mice with features of Rett syndrome. Their findings were published yesterday in *Nature*, but the original team is disputing the results[1].

Scientists familiar with both studies say that the new findings raise serious concerns about

translating this approach to people.

“At the very least, one has to say that this is not easy to reproduce, even in mice, let alone translate into a human clinical situation,” says **Adrian Bird**, professor of genetics at the University of Edinburgh in the U.K., who was not involved in either study.

It’s been three years since the original study, also published in *Nature*, claimed that a bone marrow transplant eases the breathing and motor problems associated with Rett syndrome and **dramatically extends the lifespan** of a mouse model of Rett[2]. Parents of children with the syndrome immediately began asking about the treatment, and one transplant clinic even took steps toward testing bone marrow transplants in boys with the syndrome.

Because of these high stakes, scientists set out to first reproduce the finding. But from the start, there were hints that **this would not be straightforward**. Four teams that independently could not verify the work agreed to publish their concerns together.

Questioning the results of a prominent paper carries a high burden of proof, and publication took the researchers nearly a year.

With these results in hand, any clinical tests of bone marrow transplants for children with the syndrome are premature, says **Jeffrey Neul**, chief of child neurology at the University of California, San Diego, who is one of the four researchers. “I think you’d be subjecting people to undue risk.”

Based on the new findings, the clinic has canceled its trial of bone marrow transplants in children with Rett syndrome.

Jonathan Kipnis, lead researcher on the 2012 study, disputes the new study’s conclusion. He says the discrepancies are due to differences in experimental protocol, but agrees that there is much to resolve before the transplants should be attempted on people. “We were not there yet,” he says. But, he adds, “I worry now that clinical trials will never start and this could potentially have been a real treatment for kids."

Early promise:

Rett syndrome primarily affects girls, who begin to show language deficits, intellectual disability, breathing problems and seizures around age 1. Boys with the syndrome are typically more severely affected, and die early in childhood.

To study the syndrome, researchers routinely turn to male mice missing **MeCP2**. The mice show breathing and motor difficulties — symptoms reminiscent of Rett syndrome — and have shortened lifespans (the exact length varies depending on the strain).

Transplanting bone marrow from healthy mice into the Rett model mice alleviates the breathing and motor problems, according to the 2012 study. It also dramatically extends the lifespan of the mice from 8 or 9 weeks to as long as a year. Kipnis suggested that the transplant works by replacing defective immune cells in the brain, called microglia, with healthier stand-ins.

Based on the promising results, the Masonic Cancer Center at the University of Minnesota in Minneapolis **began recruiting boys with Rett** for a compassionate trial of bone marrow transplants. The announcement of the trial raised alarms for **Antonio Bedalov**, transplant specialist at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

Bone marrow transplants are complicated procedures requiring harsh drugs to ward off rejection and carry a sizable risk of death — but the parents had no other options.

“There was tremendous pressure from patients’ families to act on these findings and act early,” says Bedalov. He says he, too, was hoping to test the procedure in children with Rett syndrome, but needed more evidence to go on. “Because these findings are so unusual and extraordinary, I really wanted to see in my own hands if I could really replicate this before I did anything.”

Bedalov tested the transplants on a different mouse model of Rett syndrome. These mice also lack the MeCP2 protein, but through a different genetic mechanism. This was an important test to see whether the approach could be broadly used to help any child with the syndrome, Bedalov says.

“If it’s something that’s really specific to one [mouse] model in one lab, it would really be a stretch to think we could use that to help people,” Bedalov says. The transplant did not extend the mice’s lifespan.

Meanwhile, **Peter Huppke** at the University Medical Center in Göttingen, Germany, tried the transplants in a third mouse strain, this one with one of the most common MeCP2 mutations seen in people. He also found that the transplant did not allow the mice to live longer.

Finally, **Andrew Pieper** at the University of Iowa was trying the procedure on mice from the same colony used in the 2012 study. In fact, the mice Kipnis used originally came from Pieper. But Pieper, too, was unable to reproduce the 2012 results.

Trial and error:

Interestingly, Pieper’s team saw that any bone marrow transplant — whether one from a healthy donor or from another mouse model of Rett — extends the recipient’s life. He credits this improvement to the extra care and antibiotics that the mice receive after the transplant.

Kipnis has another explanation: the genetic background of these mice, which has become a point of contention between the teams.

Kipnis says Pieper's mice may have become genetically impure since the 2012 study was published. Despite being from the same colony, Pieper's mice in the new study are twice as big and live almost twice as long as the mice in the 2012 study, Kipnis says.

If that's true, Kipnis adds, Pieper might have been transplanting mice with a mismatched marrow. This sort of mismatch can trigger graft-versus-host disease — an immune reaction that destroys the transplanted cells and negates any potential benefits.

"On the one hand you're helping them with Rett syndrome, but on the other hand you're killing them with graft-versus-host. So they're canceling each other out," says Kipnis, professor of neuroscience at the University of Virginia in Charlottesville.

Pieper maintains that his mice are genetically pure. He has provided the sequencing data as supplementary information with the new study so that others can verify this for themselves.

Third-party researchers say each side has a valid argument. It's possible that natural variations among genetically identical mice bred and housed in different labs can lead to differences in lifespan and weight, says **Huda Zoghbi**, professor of pediatrics at Baylor College of Medicine in Houston, Texas.

"It is well known that phenotypes can vary widely between animal facilities, and the weight and survival of MeCP2-null mice are no exception," says Zoghbi.

The new study also calls into question the mechanism proposed in the 2012 study.

Kipnis' team showed that restoring MeCP2 expression in microglia using a genetic approach alleviates Rett symptoms in mice. Neul says that approach also turns the gene on in neurons. Activating MeCP2 in neurons is **known to ease Rett symptoms**.

In a follow-up study published earlier this month, Kipnis' team showed more modest improvements in the lifespan of Rett mice using another technique to turn on MeCP2 only in **microglia and other immune cells**, called macrophages.

However, in the new study, Neul used yet another genetic tool that restores MeCP2 only in immune cells, including microglia. This method has no effect on the mice's symptoms. Kipnis counters that this tool is notoriously unreliable.

This sort of disagreement and inconsistency among different labs is not at all unusual, says **Ben Barres**, professor of neurobiology at Stanford University in California.

"As far as I know, this is science as usual," Barres says. "There are two different results now, and so others will have to figure out which group is correct — in a peer-reviewed publication — and get to

the bottom of whether experimental differences can explain the different outcomes.”

References:

1: Wang J. *et al. Nature* **521**, E1-E4 (2015) **Abstract**

2: Derecki N.C. *et al. Nature* **484**, 105-109 (2012) **PubMed**