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New studies contradict earlier findings on Rett syndrome

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Independent reproduction of other scientists' results is a cornerstone of solid research, but scientists are rarely recognized for successfully reproducing published findings, much less for demonstrating that scientific findings cannot be reproduced. However, failure to reproduce a finding may suggest doubt about the robustness of the original work, which carries implications for anyone looking to build on those findings.

University of Iowa neuroscientist Andrew Pieper unexpectedly found himself in the position of contradicting seemingly promising results published in 2012 in the journal *Nature* that prompted a clinical trial for human patients.

The original study from the laboratory of Jonathan Kipnis at the University of Virginia School of Medicine, conducted in mice, suggested that a bone marrow transplant from a healthy mouse could prevent the development of Rett syndrome—a severe neurodevelopmental disorder on the autism spectrum—and prolong the lifespan of the treated mice. The study also suggested that the bone marrow transplant arrested the disease because it restored normal microglia cells to the affected animals' brains.

The finding was exciting because it suggested that an approach already used in medicine might provide a treatment for a devastating and incurable disease that strikes very young children. On the basis of this work, a clinical trial for bone marrow transplantation in patients with Rett syndrome was initiated at the University of Minnesota.

Rett syndrome is caused by mutations in the X-linked MECP2 gene and affects about 1 in every 10,000 girls (it is most often fatal in boys at or near birth). Rett syndrome causes many disabilities, both intellectual and physical. Because many different MECP2 mutations can cause Rett syndrome, a wide range of disability, from mild to severe, can result from the disorder.

Pieper was asked by the Rett Syndrome Research Trust to confirm the results from the Kipnis laboratory. Pieper's group used the same mice and bone marrow transplantation methods as the original study, as well as the same outcome measures, but conducted a more highly-powered experiment on a larger number of animals. Pieper also randomized the treatment and used blinded methods to analyze the results. His team found no benefit to the bone marrow transplant.

Moreover, three other groups—the laboratory of Jeffrey Neul at Baylor College of Medicine in Houston, Texas; the laboratory of Antonio Bedalov at Fred Hutchinson Cancer Research Center in Seattle, Wash.; and the laboratory of Peter Huppke at the University Medical Center Gottingen, in Germany—also were unable to reproduce the original findings.

The four independent research groups decided to pool their findings into a single manuscript, which they submitted to *Nature*, the same journal where the original study was published. The new studies found that bone marrow transplant provided no benefit in terms of alleviating symptoms or extending lifespan in three separate mouse models of Rett syndrome. In addition, they showed that even early, targeted rescue of MECP2 expression specifically in microglia cells did not rescue the animals from disease.

"In group discussions about the data with Dr. Kipnis, we were unable to determine why bone marrow transplantation worked so well in his

laboratory and not our laboratories," says Pieper, associate professor of psychiatry in the UI Carver College of Medicine.

The new work was published as a "Brief Communication Arising" in the journal *Nature* on May 20. According to the journal, this new form of peer-reviewed article provides a mechanism to publish exceptionally interesting or important scientific comments and clarifications on original research papers or other peer-reviewed material published in *Nature*. Specifically, Brief Communications Arising are manuscripts that challenge the main conclusions of a previously published *Nature* paper and contain new, unpublished data to support the arguments. A unique aspect of this format is that Brief Communications Arising are linked bidirectionally with the original published paper, facilitating dissemination of the full body of work to all readers.

Success rates for turning promising preclinical results into human therapies is generally low. Increasing the rigor and reliability of preclinical trials should help improve that success rate.

"It's important for families of children with Rett syndrome, as well as clinicians and researchers, to be aware of the full body of work that has been conducted in this area," Pieper says. "This new publication format by *Nature* perfectly facilitates this goal."

Provided by University of Iowa