

Press Release:
Bone Marrow Transplant arrests symptoms
in model of Rett Syndrome
Results Emphasize Immune Component of Autism Spectrum Disorder

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A [paper](#) published online today in Nature describes the results of using a bone marrow transplant (BMT) to replace faulty immune system cells in models of Rett Syndrome. The procedure arrested many severe symptoms of the childhood disorder, including abnormal breathing and movement, and significantly extended the lifespan of Rett mouse models. Exploring the function of microglia deficient in methyl-CpG binding protein 2 (Mecp2), the protein encoded by the “Rett gene,” principal investigator Jonathan Kipnis, Ph.D. and his team at the University of Virginia School of Medicine uncovered a completely novel approach to this devastating neurological syndrome. The work was funded by the Rett Syndrome Research Trust and the Rett Syndrome Research Trust UK.

Rett Syndrome, the most physically disabling of the autism spectrum disorders, is caused by random mutations in the gene MECP2. Predominantly affecting girls, symptoms usually manifest between 6 and 18 months of age, when a frightening regression begins. Children lose acquired language skills and functional hand use; movement deteriorates as other Rett symptoms appear. These may include disordered breathing, Parkinsonian tremors, severe anxiety, seizures, digestive and circulatory problems and a range of autonomic nervous system and orthopedic abnormalities. Although most children survive to adulthood, many are wheelchair-bound, rely on feeding tubes, are unable to communicate and require total, lifelong care.

Kipnis was drawn to Rett Syndrome from his perspective as a neuroimmunologist. “What began as intellectual curiosity,” he explains, “has become an intense personal commitment to studying the correlation between neurological function and the immune system in Rett Syndrome. The impact of BMT on so many different symptoms has triggered a flood of experiments we are now pursuing at full speed.”

The brain is largely comprised of several types of glial cells, which have diverse and complex functions that include sustaining a healthy environment for neuronal growth and maintenance. Microglia are small glial cells that participate in the brain’s immune response. One of their roles is to clean up normal cellular debris in the brain through the process of phagocytosis. Kipnis and his team discovered that when microglia lack properly functioning Mecp2, they are unable to perform this crucial duty efficiently. Because microglia are derived from immune progenitor cells, it is possible to replace them via a bone marrow transplant.

First author Noël Derecki and his colleagues began their work with male Rett mouse models, which lack any Mecp2. These Mecp2-null mice mimic the human disorder, with neurological symptoms beginning to appear at about 4 weeks of age and an approximate life expectancy of only 8 weeks. Radiation treatment was administered at 4 weeks, followed by a bone marrow transplant from normal (wild-type) mice. As engraftment – the migration and repopulation of new microglia – took place, the Rett mice began to grow instead of fail. Body and brain sizes approached those of wild-type mice, gait improved and mobility increased significantly. There were no signs of the severe tremors seen in untreated mice. Apneas and other breathing irregularities were markedly diminished. The oldest of these mice is now almost a year. Work with female Rett mouse models at more advanced stages of disease is currently underway.

Gail Mandel, Ph.D., whose Rett research focuses on astrocytes, another type of glial cell impaired by mutations in MECP2, comments, “A fascinating aspect of these findings is the data suggesting that deficits in the engulfing properties of microglia are a crucial aspect of Rett neuropathology. It will now be necessary to develop cellular assays to determine all the ways these immune cells are bolstering neuronal functions and whether they can be therapeutically harnessed.” Dr. Mandel is a Senior Scientist at the Vollum Institute and a Professor in the Department of Biochemistry and Molecular Biology in the School of Medicine at Oregon Health & Science University and an Investigator of the Howard Hughes Medical Institute.

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Monica Coenraads, Executive Director of the Rett Syndrome Research Trust added, “I’ve been in almost daily contact with Dr. Kipnis since he brought his very original proposal to RSRT, and have been amazed to see the development of this brutal disease stopped in its tracks. A question that arises, of course, is whether replacing faulty immune cells with healthy microglia through bone marrow transplant would arrest or ameliorate already existing symptoms in humans. We do know of a case in which a girl with Rett Syndrome who was treated for leukemia gained considerable communication skills after a bone marrow transplant, and was able to converse with her mother for the first time in their lives. RSRT is in the process of exploring bone marrow transplant as a treatment modality, with full awareness of the serious nature of such a trial. In research, we are risk-takers. In clinical application, we are conservative and will be examining this carefully as more information emerges.”

Adds Noël Derecki, “Our encouraging results point to how surprisingly tractable this severe disorder proves to be, at least in the lab. We are currently exploring how bone marrow transplantation might affect Rett symptoms once they have become more advanced, and whether there are other effective ways of modulating immune responses and subsequent effects in the central nervous system.”

The paper, authored by Noël C. Derecki, James C. Cronk, Zhenjie Lu, Eric Xu, Stephen B.G. Abbott, Patrice G. Guyenet and Jonathan Kipnis, is entitled Wild type microglia arrest pathology in a mouse model of Rett Syndrome. doi:10.1038/nature10907

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About Rett Syndrome

Rett Syndrome is a genetic neurological disorder that almost exclusively affects girls. It strikes randomly, typically at the age of 12 to 18 months, and is caused by random mutations of the MECP2 gene on the X chromosome. Rett Syndrome is devastating as it deprives young girls of speech, hand use, normal movement often including the ability to walk. As the girls enter childhood the disorder brings anxiety, seizures, tremors, breathing difficulties, severe GI issues. While their bodies suffer, it is believed that their cognitive abilities remain largely intact. Although most children survive to adulthood, they require total round-the-clock care.

About the Rett Syndrome Research Trust

RSRT is a non-profit organization with a highly focused and urgent mission: eradicate Rett Syndrome and related MECP2 disorders. In search of a cure and effective treatment options, RSRT operates at the center of global scientific activity, funding bold projects that are unlikely to be supported by the NIH or other more traditional funding agencies. RSRT refutes the conventional practice of labs working in isolation, instead seeking out, promoting and funding collaborations and consortia in which scientists work across multiple disciplines. These relationships enable the development and execution of a research agenda that neither academia nor industry could achieve alone. Since 2008, RSRT has provided \$25 million of financial support to: 4 clinical trials testing 3 compounds, 33 scientists in 27 academic institutions and 3 biotech firms. To learn more about the Trust, please visit www.ReverseRett.org.

Our Partners

Our partners in supporting this work are parents' organizations worldwide including [Reverse Rett \(UK\)](#), [Rett Syndrome Research & Treatment Foundation \(Israel\)](#), [Skye Wellesley Foundation \(UK\)](#), [Rett Syndrome & CDKL5 Ireland](#), [Rett Syndrom Deutschland](#), [Stichting Rett Syndrome \(Holland\)](#).

Our U.S. partners that helped make this research possible include [Girl Power 2 Cure](#), [Eva Fini Fund at RSRT](#), [Kate Foundation for Rett Syndrome Research](#), [Rocky Mountain Rett Association](#), [Anastasi Fund](#), [Claire's Crusade](#), [New Jersey Rett Syndrome Association](#), [Rett Syndrome Association of Massachusetts](#), and the [MECP2 Duplication Syndrome Fund](#) at RSRT.