

Press Release:
First Pre-Clinical Gene Therapy Study to
Reverse Rett Symptoms

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The concept behind gene therapy is simple: deliver a healthy gene to compensate for one that is mutated. New research published today in the *Journal of Neuroscience* suggests this approach may eventually be a feasible option to treat Rett Syndrome, the most disabling of the autism spectrum disorders. Gail Mandel, Ph.D., a Howard Hughes Investigator at Oregon Health and Sciences University, led the study. The Rett Syndrome Research Trust, with generous support from the Rett Syndrome Research Trust UK and Rett Syndrome Research & Treatment Foundation, funded this work through the MECP2 Consortium.

In 2007, co-author Adrian Bird, Ph.D., at the University of Edinburgh astonished the scientific community with proof-of-concept that Rett is curable, by reversing symptoms in adult mice. His unexpected results catalyzed labs around the world to pursue a multitude of strategies to extend the pre-clinical findings to people.

Today's study is the first to show reversal of symptoms in fully symptomatic mice using techniques of gene therapy that have potential for clinical application.

Rett Syndrome is an X-linked neurological disorder primarily affecting girls; in the US, about 1 in 10,000 children a year are born with Rett. In most cases symptoms begin to manifest between 6 and 18 months of age, as developmental milestones are missed or lost. The regression that follows is characterized by loss of speech, mobility, and functional hand use, which is often replaced by Rett's signature gesture: hand-wringing, sometimes so intense that it is a constant during every waking hour. Other symptoms include seizures, tremors, orthopedic and digestive problems, disordered breathing and other autonomic impairments, sensory issues and anxiety. Most children live into adulthood and require round-the-clock care.

The cause of Rett Syndrome's terrible constellation of symptoms lies in mutations of an X-linked gene called MECP2 (methyl CpG-binding protein). MECP2 is a master gene that regulates the activity of many other genes, switching them on or off.

"Gene therapy is well suited for this disorder," Dr. Mandel explains. "Because MECP2 binds to DNA throughout the genome, there is no single gene currently that we can point to and target with a drug. Therefore the best chance of having a major impact on the disorder is to correct the underlying defect in as many cells throughout the body as possible. Gene therapy allows us to do that."

Healthy genes can be delivered into cells aboard a virus, which acts as a Trojan horse. Many different types of these Trojan horses exist. Dr. Mandel used adeno-associated virus serotype 9 (AAV9), which has the unusual and attractive ability to cross the blood-brain barrier. This allows the virus and its cargo to be administered intravenously, instead of employing more invasive direct brain delivery systems that require drilling burr holes into the skull.

Because the virus has limited cargo space, it cannot carry the entire MECP2 gene. Co-author Brian Kaspar of Nationwide Children's Hospital collaborated with the Mandel lab to package only the gene's most critical segments. After being injected into the Rett mice, the virus made its way to cells throughout the body and brain, distributing the modified gene, which then started to produce the MeCP2 protein.

As in human females with Rett Syndrome, only approximately 50% of the mouse cells have a healthy copy of MECP2. After the gene therapy treatment 65% of cells now had a functioning MECP2 gene.

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The treated mice showed profound improvements in motor function, tremors, seizures and hind limb claspings. At the cellular level the smaller body size of neurons seen in mutant cells was restored to normal. Biochemical experiments proved that the gene had found its way into the nuclei of cells and was functioning as expected, binding to DNA.

One Rett symptom that was not ameliorated was abnormal respiration. Researchers hypothesize that correcting this may require targeting a greater number of cells than the 15% that had been achieved in the brainstem.

“We learned a critical and encouraging point with these experiments – that we don’t have to correct every cell in order to reverse symptoms. Going from 50% to 65% of the cells having a functioning gene resulted in significant improvements,” said co-author Saurabh Garg.

One of the potential challenges of gene therapy in Rett is the possibility of delivering multiple copies of the gene to a cell. We know from the MECP2 Duplication Syndrome that too much of this protein is detrimental. “Our results show that after gene therapy treatment the correct amount of MeCP2 protein was being expressed. At least in our hands, with these methods, overexpression of MeCP2 was not an issue,” said co-author Daniel Liroy.

Dr. Mandel cautioned that key steps remain before clinical trials can begin. “Our study is an important first step in highlighting the potential for AAV9 to treating the neurological symptoms in Rett. We are now working on improving the packaging of MeCP2 in the virus to see if we can target a larger percentage of cells and therefore improve symptoms even further,” said Mandel. Collaborators H el ene Cheval and Adrian Bird see this as a promising follow up to the 2007 work showing symptom reversal in Rett mice. “That study used genetic tricks that could not be directly applicable to humans, but the AAV9 vector used here could in principle deliver a gene therapeutically. This is an important step forward, but there is a way to go yet.”

“Gene therapy has had a tumultuous road in the past few decades but is undergoing a renaissance due to recent technological advances. Europe and Asia have gene therapy treatments already in the clinic and it’s likely that the US will follow suit. Our goal now is to prioritize the next key experiments and facilitate their execution as quickly as possible. Gene therapy, especially to the brain, is a tricky undertaking but I’m cautiously optimistic that with the right team we can lay out a plan for clinical development. I congratulate the Mandel and Bird labs on today’s publication, which is the third to be generated from the MECP2 Consortium in a short period of time,” said Monica Coenraads, Executive Director of the Rett Syndrome Research Trust and mother of a teenaged daughter with the disorder.

Citation: Systemic delivery of MeCP2 rescues behavioral and cellular deficits in female mouse models of Rett syndrome. The Journal of Neuroscience.

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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.

About the MECP2 Consortium

The MECP2 Consortium, launched by the Rett Syndrome Research Trust in 2011, fosters novel alliances among leading scientists to interrogate the molecules at the root of Rett Syndrome and apply these discoveries to treatments. Consortium members include Adrian Bird of the University of Edinburgh, Michael Greenberg of Harvard University and Gail Mandel of Oregon Health and Sciences University.

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.