

Press Release:
Statins Suppress Rett Syndrome
Symptoms in Mice

July 28, 2013

Media Contact:
Monica Coenraads
Executive Director, RSRT
monica@rsrt.org
203.445.0041

Statins, a class of cholesterol-lowering drugs found in millions of medicine cabinets, may help treat Rett Syndrome, according to a study published today in *Nature Genetics*. The Rett Syndrome Research Trust (RSRT) funded this work with generous support from the Rett Syndrome Research Trust UK and Rett Syndrome Research & Treatment Foundation.

Rett Syndrome is a neurological disorder that affects girls. A seemingly typical toddler begins to miss developmental milestones. A regression follows as young girls lose speech, mobility, and hand use. Many girls have seizures, orthopedic and severe digestive problems, as well as breathing and other autonomic impairments. Most live into adulthood and require total, round-the-clock care. Rett Syndrome affects about 1 in 10,000 girls born in the U.S. each year.

The new study screened for randomly induced mutations in genes that modify the effect of the Rett gene, MECP2 (methyl-CpG-binding protein 2), in a mouse model. MECP2 turns other genes on or off by disrupting chromatin, the DNA-protein mix that makes up chromosomes.

The challenge of treating Rett Syndrome is what drove senior author Monica Justice, Ph.D., Professor in the Departments of Molecular and Human Genetics and Molecular Physiology and Biophysics at the Baylor College of Medicine, to look beyond MECP2, hoping to find new drug targets that might improve symptoms or even reverse the course of the disease. In 2007, Adrian Bird, Ph.D., Buchanan Professor of Genetics at the Wellcome Trust Centre for Cell Biology at the University of Edinburgh, showed that symptoms in mice are reversible regardless of the age of the animal.

Exploring cholesterol metabolism in neurological diseases is an emerging area, with statin drugs being tested in fragile X syndrome, neurofibromatosis, amyotrophic lateral sclerosis, and other conditions. But it hadn't been on the radar for Rett Syndrome. "Our screen was to see if we could suppress the symptoms to reveal alternative pathways to treatment. The cholesterol hit was a big one," Dr. Justice said. The screen was unbiased – the researchers were looking for any gene that would interact with MECP2 in a useful way, rather than employing a candidate gene approach based on hypotheses.

Dr. Justice and her team injected healthy male mice with a chemical called ENU (a form of nitrosourea) that mutates sperm stem cells randomly, then mated the males to Rett females. The researchers then looked for offspring that should have developed the syndrome (according to their genes), but didn't (according to their good health).

Key to the investigation was being able to tell sick mice from healthy ones. Fortunately this turned out to be easy. The rescued mice didn't develop the characteristic tremor, trouble breathing, poor limb-clasping, and general scruffiness of their affected cage-mates. They moved around more, performed better on mobility tests and lived longer.

Once the rescued mice had been identified the random gene mutations from the 24,000 genes that make up the mouse genome had to be pinpointed. "With next generation DNA sequencing, we are finding mutations so easily and quickly. It's amazing," said Dr. Justice, compared to the old days of setting up many more generations of crosses to narrow down a part of the genome harboring a gene of interest.

"We are only 15% of the way through the screen, and so far we have identified 5 modifiers. The most drug-targetable is a gene called squalene epoxidase (Sqle), which encodes a rate-limiting enzyme in the cholesterol biosynthetic pathway. Frankly, this discovery was a surprise," Dr. Justice said. It's important to note that this enzyme is different from the rate-limiting enzyme (HMG CoA reductase) influenced by statin drugs.

Cholesterol is of course best known for its negative effects on the cardiovascular system, but the lipid has multiple roles in the brain: it helps to form the myelin insulation on neurons and takes part in membrane trafficking, dendrite remodeling, synapse formation, signal transduction, and neuropeptide synthesis.

The next step was to test several statins (fluvastatin and lovastatin) on Rett mice. Like the *Sqle* mutation, the drugs improved symptoms. Treated mice performed well on mobility and gross motor tests, had better overall health scores and lived longer. The drugs didn't, however, improve breathing.

"When we saw the mutation in a cholesterol pathway enzyme, we immediately thought of statin drugs. Now that our eyes have opened to what is going on, we have a multitude of drugs that modulate lipid metabolism that we can try in addition to statins," said first author Christie Buchovecky, graduate student in the Justice lab.

With additional RSRT funding, pediatric neurologist and Director of the Tri-State Rett Syndrome Center in the Bronx Dr. Sasha Djukic undertook a detailed review of lipid data in girls with Rett Syndrome. She found that a subset have elevated cholesterol levels which normalize as they age. These data are not included in the Nature Genetics publication but will be part of a subsequent paper. Dr. Djukic is now planning a clinical trial.

Drs. Justice and Djukic caution that carefully designed and rigorously executed clinical trials are essential to test whether what works in mice will also work in girls with Rett Syndrome. Clinical trials should also determine the most effective timeframe for treatment, ways to identify which girls are most likely to respond, (for example, will statins help girls with Rett who do not have elevated cholesterol?), which drugs to trial and what dosages are effective but not toxic.

"Although statins are blockbuster drugs taken by a large percentage of the population they are not without risks and side-effects, and data on statins in the general pediatric population are quite limited. One of the key objectives of the clinical trial will be to determine correct dosages for Rett symptoms. It's important to note that the mice in Dr. Justice's study received very low doses of statins. I urge parents to resist any temptation to medicate their children with off-label statins," cautions Dr. Djukic. "The only way to know if this class of drugs will be efficacious in Rett is through controlled trials. Working with Dr. Justice and RSRT we will be bringing families additional information as soon as possible."

"The biggest finding is the discovery that this pathway is so important to the pathology of the disorder; it suggests new directions for trying to learn more about Rett Syndrome," Dr. Justice explains. "Emerging evidence from both mice and humans suggest that Rett Syndrome may have a component of disease that is metabolic. Certainly, this study will further clarify our data, and may suggest avenues for treatment that were previously unexplored."

Monica Coenraads, Executive Director of RSRT and mother of a teenaged daughter with Rett Syndrome, says, "I have a special affinity for this project because it's one that I've followed closely from the very beginning. The concept for the modifier screen came from an early morning brainstorming session at a science meeting I organized in 2006. After discussing the feasibility of the project with various investigators, I invited Dr. Justice to submit a proposal. It's been a rewarding experience to follow the science from the kernel of an idea to the discovery of the first handful of modifiers, one of which, *Sqle*, is leading to a clinical trial. RSRT is committed to seeing the screen through to completion. Having a comprehensive list of modifiers will likely open more doors to novel treatments. I congratulate Dr. Justice and her colleagues on the publication and thank all of our donors who make this work possible."

Citation "A suppressor screen in *Mecp2* mutant mice implicates cholesterol metabolism in Rett syndrome" Nature Genetics, Published online July 28, 2013 DOI 10.1038/ng.2714

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 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.