Press Release:
Rett Syndrome Research Trust Awards $5.8 Million to Advance the Development of Treatments and Cures for Rett Syndrome and MECP2 Disorders

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Rett Syndrome Research Trust Awards $5.8 Million to Advance the Development of Treatments and Cures for Rett Syndrome and MECP2 Disorders

Today the Rett Syndrome Research Trust (RSRT) announced research investments of **$5.8 million** awarded in 2014. RSRT's sole and urgent goal is to abolish Rett Syndrome and related disorders. To that end, RSRT has awarded **$25 million** to research since its launch in 2008.

Rett Syndrome is caused by mutations in a gene called MECP2 that result in a cascade of devastating symptoms that worsen over time. These symptoms begin to manifest in early childhood and leave Rett sufferers dependent on 24-hour-a-day care for the rest of their lives.

The 2014 awards support projects ranging from basic science to drug development and clinical trials. Each project was selected via a rigorous peer review process that assures the highest scientific integrity. To receive funding, every project was required to demonstrate that it has the potential to advance the development of treatments and cures.

Highlights of RSRT's 2014 awards:

- Funding of **$1.3 million** was awarded to Case Western Reserve University and the Cleveland Clinic for a Phase 2 dose escalating, placebo controlled clinical trial of low-dose ketamine for the treatment of Rett Syndrome. The study is being led by David Katz, Ph.D., Professor of Neurosciences and Psychiatry at Case Western Reserve University School of Medicine and Daniel I. Sessler, M.D., Michael Cudahy Professor and Chair, Department of Outcomes Research at the Cleveland Clinic. Studies undertaken by Dr. Katz showed that low-dose ketamine can reverse deficits in brain activity in mouse models of Rett Syndrome in conjunction with significant improvements in neurological function, including breathing. Ketamine, a drug that has historically been used for sedation and anesthesia, has recently generated much enthusiasm for its ability to rapidly reverse major depression at low, sub-anesthetic, doses. This trial will determine the effect of single doses of ketamine on breathing abnormalities and overall clinical severity, as well as EEG abnormalities, visually evoked potentials, and repetitive behaviors.

  According to Drs. Katz and Sessler, "This trial evolved as a dynamic collaboration among basic scientists, clinicians, and clinical trialists including expert advisers recruited by RSRT. We are grateful to RSRT for fostering this collaborative spirit and providing the support necessary to make this trial a reality." Co-investigators include Tom Frazier, Ph.D, Director of the Cleveland Clinic Center for Autism; Sumit Parikh, M.D., Director of the Cleveland Clinic Neurogenetics, Metabolic & Mitochondrial Disease Program; and Edward J. Mascha, Ph.D., Senior Biostatistician in the Department of Outcomes Research at the Cleveland Clinic.

- Aleksandra Djukic, M.D., Ph.D., medical director of the Tri-State Rett Syndrome Center at the Children's Hospital at Montefiore was awarded $403,000 to conduct a Phase 2 dose escalating open label clinical trial of lovastatin, a cholesterol lowering medication. The scientific basis for this trial stems from experiments conducted in the lab of mouse geneticist, Monica Justice, Ph.D., who identified the cholesterol pathway as a potential avenue to improve Rett symptoms. The trial will determine the effect of lovastatin on gait, respiratory function, cognition, EEG and severity of the disease.

  "Cholesterol is vitally important for brain function. In fact, although the brain is only 2-3% of total body weight, it contains and makes 25% of the body's cholesterol. Dr. Justice's work suggests that elevated cholesterol levels in the brain may play a role in Rett symptoms. Our trial will test the hypothesis that reducing cholesterol in the brain will lead to symptom improvement," stated Dr. Djukic.

- (cont.) Dr. Djukic recently concluded an open label Phase 2 trial testing safety and efficacy of copaxone in Rett Syndrome. The data is currently being analyzed.

The ketamine and lovastatin trials will begin recruitment shortly. Information will be available on the RSRT website.

- Individuals with Rett display a broad spectrum of symptom severity. Some girls can run, have a degree of hand use and can speak in short sentences while others cannot even sit or hold their head up. One reason for this variation is the child's own unique genetic makeup – in other words, variations in other genes that impact the severity of the Rett mutation. Monica Justice, Head and Senior Scientist in the Genetics & Genome Biology program at The Hospital for Sick Children in Toronto, has undertaken a mutagenesis screen to identify these modifying genes with a focus on suppressors of symptoms, hoping that they might suggest a therapeutic pathway. The first suppressor she identified, squalene epoxidase, led to the lovastatin trial described above. The screen is currently at the halfway point with 12 modifiers identified. RSRT has awarded Dr. Justice $716,000 in additional funding to complete the screen. This brings RSRT's total commitment to the project to $2.3 million.

  "Monica Coenraads approached me a number of years ago asking how I would identify modifiers. I thought that an unbiased suppressor screen using a mouse supermutagen would be the most effective approach, and was timely with the advent of new genome sequencing technologies. Such an approach was considered very risky, requiring funding through a forward-looking organization such as the RSRT. It has been extremely rewarding to move from the development of a concept…to isolating modifiers that were unexpected…to a clinical trial. Our ongoing screen is much easier and quicker now as technologies advance. My hope is that many more trials will come from the continuing screen," says Dr. Justice.

- Two additional projects are aimed at awakening a healthy but silenced back-up copy of the mutated Rett gene. If the flawed gene could be replaced by reawakening its silenced counterpart we could conceivably reverse Rett symptoms. Currently pursuing this approach with RSRT funding are labs at the University of North Carolina at Chapel Hill, the University of Massachusetts, Harvard University, and Fred Hutchinson Cancer Research Center. RSRT's strong belief in collaborative research models has facilitated the sharing of data, cell lines and compounds amongst these labs that are now in regular communication. RSRT has awarded additional funding totaling $755,000 to two projects ongoing in the labs of Jeannie Lee, Ph.D., of Harvard and Antonio Bedalov, M.D., Ph.D., of Fred Hutchinson to aggressively pursue this work.

- RSRT funding will allow David Katz to generate a robust preclinical package for the drug, LM22A-4, which will include pharmacokinetic/pharmacodynamic, efficacy and safety data. Encouraging data will support a subsequent application to the FDA for an IND (Investigational New Drug).

- Successful fundraising on the part of the MECP2 Duplication Syndrome community facilitated two awards to Huda Zoghbi, M.D., Professor in the Departments of Pediatrics, Molecular and Human Genetics, Neurology and Neuroscience at Baylor College of Medicine and director of the Jan and Dan Duncan Neurological Research Institute, totaling $644,065. The funds will support two strategic approaches to treating the disorder.

  "We are very excited to receive support for exploring two different strategies to reduce MeCP2 levels. The two strategies are complementary, one involving genetic screens in human cells to find potential targets that can be druggable with a pharmaceutical agent, while the other employs antisense oligonucleotides developed by Isis pharmaceuticals and designed to reduce MeCP2 levels directly," said Dr. Zoghbi.

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"Every dollar donated to RSRT can be tracked back to a family of an affected child and this family's network of relatives, friends and colleagues. Our supporters around the world make our work possible and they have my immense appreciation. We are especially grateful to Reverse Rett (UK), Rett Syndrome Research & Treatment Foundation (Israel), and Girl Power 2 Cure. If you love a child with Rett or MECP2 Duplication Syndrome and find their current status quo unacceptable then I invite you to join us in our effort to end their immense suffering," says Monica Coenraads, RSRT Executive Director and mother of an 18 year-old daughter with Rett Syndrome.

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.

List of 2014 Awards

Clinical Trials

Low-dose Ketamine for the Treatment of Rett Syndrome
David Katz, Daniel Sessler, Tom Frazier, Sumit Parikh (Cleveland Clinic)
$1,295,131 / 2 years

Pharmacological Treatment of Rett Syndrome with 3-Hydroxy-3 methylglutaril-coenzyme A reductase Inhibitor-Lovastatin (Mevacor)
Aleksandra Djukic (Children's Hospital at Montefiore)
$403,000 / 18 months

Supplement for Copaxone Clinical Trial
Aleksandra Djukic (Children's Hospital at Montefiore)
$47,000

Awards

Identifying Genetic Modifiers of MECP2 in the Mouse
Monica Justice (Hospital for Sick Children, Toronto)
$715,680 / 2 years

Identification of Genetic Modifiers in Rett Syndrome
Jeffrey Neul (Baylor College of Medicine)
$314,456 / 2 years

Re-awakening the Silenced Normal MECP2 Allele with Small Molecules to Treat Rett Syndrome
Jeannie Lee (MGH/Harvard)
$465,000 / 3 years

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Reactivation of Mecp2 on the Silent X
Antonio Bedalov (Fred Hutchinson Cancer Research Institute)
$290,000 / 1 year

Preclinical Studies of LM22A-4 in Mouse Models of Rett Syndrome
David Katz (Case Western)
$272,000 / 2 years

Testing Whether LM22A-4 Improves Hippocampal Function in Female MECP2 heterozygous mice
Lucas Pozzo-Miller (University of Alabama Birmingham)
$110,000 / 1 year

Exploring the Link between MeCP2 and Gut Physiology to Test a Novel Probiotic Therapy for Rett Syndrome
Ali Khoshnan, Sarkis Mazmanian (California Institute of Technology)
$200,000 / 2 years

NLX-101 as a Treatment for Breathing Disorders in Rett Syndrome
Neurolixis
$54,945 / 6 months

Outlining the Autonomic Signature of Rett Syndrome
Michael Carroll and Debra Weese-Mayer (Lurie Children's Hospital of Chicago)
$157,300 / 2 years

Systems Genetics Approach toward Understanding Regulation of MECP2 Expression
Terry Magnuson (University of North Carolina at Chapel Hill)
$200,000 / 1 year

High Content Phenotypic Screening of Existing Drugs for the Treatment of Rett Syndrome
Recursion Pharmaceuticals
$50,000 / 1 year

MECP2 Consortium Supplement
Gail Mandel, Michael Greenberg, Adrian Bird (OHSU, Harvard, University of Edinburgh)
$250,000

Supplement for Gene Therapy Consortium
Steven Gray (UNC Chapel Hill)
$67,401 / 2 years

Life Sciences Research Foundation Fellow
$91,500

Tri-State Rett Syndrome at Montefiore
Aleksandra Djukic
$67,500

Miscellaneous Pilot Studies
$100,000

MECP2 Duplication Syndrome
Antisense Oligonulcleotide Therapy for the Treatment of MECP2 Duplication
Huda Zoghbi (Baylor College of Medicine)
$230,000 / 2 years

A Forward Genetic Screen to Identify Druggable Modulators of MECP2 Levels
Huda Zoghbi (Baylor College of Medicine)
$414,065 / 2 years

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.