Press Release:
Rett Syndrome Research Trust Awards $9 Million to Accelerate Translation of Lab Discoveries to the Clinic

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Today the Rett Syndrome Research Trust (RSRT) announced research awards totaling nearly **$9 million in 2015**. This is the most research ever awarded in a given year by any Rett Syndrome organization.

This significant influx of funding was made possible by the generosity and commitment of donors, partner organizations, and the critically important effort of families that hold events and raise funds. RSRT's low overhead costs (an average of **96% of every dollar** raised is spent on our research program), rigorous scientific standards, and fierce motivation of our trustees and staff assure that these contributors' funds have maximum impact on RSRT's ultimate goal—eradicating Rett Syndrome and related disorders.

> *"We are in a new era of genetics and neurobiology, which suggests that some disorders, including Rett Syndrome, need not equate to permanent disability. The **$34 million awarded by RSRT since 2008** has enabled researchers to leverage decades of scientific progress toward the study of MECP2 with unwavering focus on the most important deliverable – the development of novel disease-altering therapeutics. The 2015 awards are more clinically focused than ever, a sure sign that we are getting closer to advancing the first therapeutics developed from the bottom up, from gene identification to pathophysiology in animals to human trials. Families who have helped to fund this research have a lot to be proud of. I am excited to be joining this effort as together we move the research forward with urgency."*
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> **DR. RANDALL CARPENTER**
> ***Chief Scientific Officer, RSRT***

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Highlights of RSRT's 2015 Awards

OUTCOME MEASURES AND BIOMARKER DEVELOPMENT:

Funding of **$4.5 million** was awarded to the ***Outcome Measures and Biomarker Development Consortium*** **(OMBD)**, a collaboration among four Rett Syndrome clinicians - **Alan Percy** (University of Alabama at Birmingham), **Aleksandra Djukic** (Montefiore Medical Center, Bronx), **Daniel Tarquinio** (Children's Healthcare of Atlanta), and **Timothy Benke** (Children's Hospital Colorado)—to advance clinical trial methodology for the disease. The clinicians will design a number of Rett specific scales as well as test wearable devices and novel technology to yield objective, simple and reproducible read-outs for clinical trials.

The goal of the OMBD is to help define the regulatory pathway to drug approval. Funding will also support the infrastructure to curate this project including a cutting edge data management system. This ambitious project will be managed by ***Randall Carpenter*** who has decades of experience in clinical research.

FROM SENSORY-PERCEPTUAL REPRESENTATIONS TO COGNITIVE PROCESSING IN RETT SYNDROME:

A complementary project under the direction of **John Foxe** at the University of Rochester and **Sophie Molholm** at Albert Einstein College of Medicine was awarded **$533,607**. They will characterize the processing capabilities of individuals with Rett using a variety of auditory electroencephalogram (EEG) and event-related potentials (ERP). These brain-mapping techniques should improve our understanding of the fundamental auditory processing abilities of individuals with Rett syndrome and establish a set of biomarkers that will have potential utility as outcome measures in clinical trials.

CLINICAL DEVELOPMENT OF NLX-101:

An award of **$530,000** was made to **Neurolixis**, a company developing a drug, NLX-101, to treat breathing abnormalities in Rett Syndrome. The drug targets a specific serotonin receptor (5-HT1A) located in regions of the brain that affect respiration, mood and cognition. It's possible that, beyond breathing, the drug may also improve other core symptoms such as anxiety and movement disorders. Neurolixis has already obtained Orphan Drug status for NLX-101 in both the US and in Europe.

LONG GENE EXPRESSION | MECP2 CONSORTIUM:

Michael Greenberg, a member of the ***MECP2 Consortium***, reported that Rett mice and patients have abnormally high levels of genes that are physically long. An award of **$400,000** to **Mark Zylka** (University of North Carolina Chapel Hill) will support research to screen for compounds that can bring the expression levels of long genes back to normal. The Zylka lab has expertise in the study of long gene expression and chemical screening.

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REACTIVATING MECP2 CONSORTIUM:

Jeannie Lee (Harvard Medical School/Massachusetts General Hospital), **Antonio Bedalov** (Fred Hutchinson Cancer Research Center) and **Joost Gribnau** (Erasmus MC), part of the ***Reactivating MECP2 Consortium***, were awarded a total of **$1.8 million** to further their efforts aimed at waking up the silent *MECP2* gene on the inactive X chromosome. Successful reactivation of the gene addresses the underlying root cause of the disease that could profoundly improve Rett symptoms. Reactivation of *MECP2* is a therapeutic strategy identified and aggressively pursued by RSRT. The first award was made to Antonio Bedalov in 2008. Currently there are seven laboratories working collaboratively on this approach that has recently garnered considerable interest from the pharmaceutical industry.

DISCOVERY OF COMPOUNDS PROMOTING MECP2 READ-THROUGH:

Many of the most severely afflicted children with Rett have nonsense mutations in MeCP2 caused by a premature stop codon that shortens the protein. Read-through drugs have the ability to splice out the stop codon thereby restoring the full-length protein. To date, aminoglycoside antibiotics have shown the most promise, but their use is limited by significant systemic toxicity. Conversely, the compound ataluren (PTC Therapeutics) is structurally different from the aminoglycosides and is much less toxic; unfortunately, it is also less potent and has limited brain penetrability. An award of **$268,452** was made to **Andrew Napper** of duPont Hospital for Children who will screen for novel "read-through" compounds.

> *"What RSRT does best is identify and fill knowledge gaps, often by catalyzing teams of scientists and clinicians working together. We've done that with the MECP2 Consortium, the Gene Therapy Consortium, the Reactivating MECP2 Consortium. Today we launch the OMBD Consortium. With every conversation I had with pharmaceutical executives and investors it became more and more apparent that the lack of objective and sensitive read-outs for trials was impeding companies from entering the Rett drug development space. I am confident that the thoughtful and creative work of Doctors Benke, Djukic, Percy and Tarquinio and the financial resources and infrastructure provided by RSRT will solve this problem. I thank every donor who supports us for making this critical work possible."*
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> **MONICA COENRAADS**
> ***Executive Director, RSRT***

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List of 2015 Awards

CLINICAL RESEARCH:

Outcome Measures and Biomarkers Development
Alan Percy, Aleksandra Djukic, Daniel Tarquinio, and Timothy Benke | *University of Alabama at Birmingham, Montefiore Medical Center, Children's Healthcare of Atlanta, Children's Hospital Colorado*
$4.5 million / 3 years

From Sensory-Perceptual Representations to Cognitive Processing in Rett Syndrome
John Foxe and Sophie Molholm | *University of Rochester, Albert Einstein College of Medicine*
$533,607 / 3 years

Tri-State Rett Syndrome Center at Montefiore
Aleksandra Djukic
$88,000

ATTACKING THE ROOT OF RETT SYNDROME:

Genetic and pharmacologic reactivation of Mecp2 on the silent X-chromosome as a therapeutic approach to Rett Syndrome
Antonio Bedalov | *Fred Hutchinson Cancer Research Center*
$533,607 / 3 years

Treating Rett Syndrome by Targeting the Xist Interactome
Jeannie Lee | *Harvard University*
$766,854 / 3 years

In vivo and in vitro models for X chromosome reactivation
Joost Gribnau | *Erasmus MC (The Netherlands)*
$177,900 / 2 ½ years

ATTACKING THE ROOT OF RETT SYNDROME (CONT.) :

Spliceosome-Mediated RNA Trans-Splicing Therapy in Rett Syndrome
Stuart Cobb | *University of Glasgow*
$86,208 / 1 year

DRUG DEVELOPMENT AND SCREENING:

Clinical Development of NLX-101 in Rett Syndrome
Neurolixis
$533,607 / 3 years

Testing NR2A and NR2B NAMs in mouse models of Rett Syndrome
Michela Fagiolini | *Boston Children's Hospital*
$337,336 / 2 years

Exploration of the impact of 2-hydroxypropyl-B-cyclodextrin treatment on lifespan and brain cholesterol metabolism in male mecp2 deficient mice
Stephen Turley/Adam Lopez | *University of Texas Southwestern Medical Center*
$156,180 / 1 year

High Throughput screen to identify drugs that normalize long gene expression in Rett Syndrome model neurons
Mark Zylka | *UNC School of Medicine*
$156,180 / 1 year

Discovery and In Vivo Characterization of Compounds Promoting MECP2 Read-Through
Andrew Napper | *Nemours/A.I. duPont Hospital for Children*
$268,452 / 1 ½ years

Miscellaneous Pilot Studies
$111,021

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Our Partners

Our partners in supporting this work are parents' organizations worldwide including **Reverse Rett** (UK), **Rett Syndrome Research & Treatment Foundation** (Israel), **Rett Syndrome Ireland**, **Rett Syndrom Deutschland**. 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**, **New Jersey Rett Syndrome Association**, and **Rett Syndrome Association of Massachusetts**.

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 gastrointestinal 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

The Rett Syndrome Research Trust (RSRT) is a non-profit organization with a highly personal and urgent mission: a cure for Rett Syndrome and related *MECP2* disorders. In search of a cure and effective treatment options, RSRT operates at the nexus of global scientific activity. We enable advances in knowledge and drive innovative research through constant engagement with academic scientists, clinicians, industry, investors and affected families. These relationships catalyze the development and execution of a research agenda that neither academia nor industry could achieve alone. 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. Since 2008, RSRT has awarded $34 million to research projects. To learn more about the Trust, please visit ***www.ReverseRett.org***.