Press Release:
MECP2 Duplication Syndrome is Reversible

November 25, 2015

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

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The methyl CpG binding protein 2 gene (*MECP2*) produces a protein of the same name, the level of which is critical for normal brain function. Mutations leading to protein under-expression cause Rett Syndrome while gene duplication causing over-expression lead to *MECP2* Duplication Syndrome. Both disorders are severely debilitating childhood neurological diseases.

In 2007 symptoms of Rett in a disease mouse model were shown to be reversible. Research led by Huda Zoghbi, M.D., at Baylor College of Medicine and HHMI and published today in the journal Nature reveals that the *MECP2* Duplication Syndrome is also reversible. Importantly the study paves the way for treating duplication patients with an antisense oligonucleotide strategy.

The research, funded in part by the *MECP2* Duplication Syndrome Fund at the Rett Syndrome Research Trust (RSRT), was made possible through the global fundraising efforts of families affected by the duplication syndrome.

In 1999 Dr. Zoghbi identified mutations in *MECP2* as the cause of Rett Syndrome. In 2004 she developed a mouse model for the duplication syndrome and hypothesized that overexpression of *MECP2* could cause neurological disease in people. A year later the first individuals with duplication syndrome were diagnosed.

The *MECP2* Duplication Syndrome is seen more frequently in males and is characterized by developmental delay, motor dysfunction, epilepsy, anxiety, frequent respiratory infections and early death. The absence of neurodegeneration in the duplication mouse model raised the important question of potential symptom reversibility. Dr. Yehezkel Sztainberg, a post-doctoral fellow in Zoghbi's laboratory and first author of the paper designed mice with an extra copy of the *MECP2* gene that could be deleted at will. As the gene was silenced and protein level normalized the symptoms of hypoactivity, anxiety, motor abnormalities and social behavior deficits disappeared.

The *MECP2* gene regulates thousands of downstream genes. Mutations in or duplication of *MECP2* causes expression changes in these downstream genes. Upon deletion of the extra copy of *MECP2* these gene expression changes also normalized.

Armed with the proof of concept that normalizing *MECP2* levels in adult duplication mice reversed symptoms, the Zoghbi lab set out to test a gene silencing strategy that could be employed to treat people: antisense oligonucleotide therapy (ASO).

There are two steps to protein production, transcription and translation. During transcription the DNA strand is used as a template for making an RNA molecule. In the translation step the RNA molecule travels to the ribosome where the protein is assembled.

Antisense technology interrupts translation through synthetic nucleic acids that bind to the RNA molecule and prevent it from reaching the ribosome.

The ASO therapy was delivered directly to the brain via tiny osmotic pumps over a 4-week period. Ten weeks after treatment began the symptoms were gone. When treatment stopped and *MECP2* protein levels rose, the symptoms returned.

"We are very encouraged by these findings but before we move this into clinical trials we must establish how to fine tune the amount of the ASOs so that we decrease *MECP2* precisely to the expected normal levels and not below that to avoid the potential of Rett-like symptoms due to under-expression," said Zoghbi who is also the Director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital.

"Today's announcement should bring great hope to families around the world whose children are battling this devastating disorder. Antisense therapy holds great promise. In the US there are two approved antisense drugs on the market and many more being tested in clinical trials. I congratulate Dr. Zoghbi on this exciting progress and applaud the families whose fundraising efforts made this research possible," said Monica Coenraads, Executive Director of RSRT.

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 Duplication Syndrome Fund at RSRT

In an effort to leverage RSRT's deep knowledge base and well-established global scientific networks the *MECP2* Duplication Syndrome Fund at RSRT was created in late 2010. The Fund exclusively supports projects devoted to the study and means of treatment of *MECP2* Duplication Syndrome. 100% of every dollar contributed is invested in research – not a single penny goes to overhead.