

Press Release:
RSRT Advisor Makes Significant
Discovery with Potential for Novel
Therapeutic Approaches

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A paper published online today in *Nature Neuroscience* reveals the presence of methyl CpG binding protein 2 (MeCP2) in glia. MeCP2 is a protein associated with a variety of neurological disorders, including Rett Syndrome, the most physically disabling of the autism spectrum disorders. The researchers show that MeCP2-deficient astrocytes (a subset of glia) stunt the growth of neighboring neurons. Remarkably, these neurons can recover when exposed to normal glia in culture.

The discovery was made by Gail Mandel, Ph.D. of the Vollum Institute at Oregon Health and Science University and a Howard Hughes Medical Institute investigator and Nurit Ballas, Ph.D., a research associate, at the time, in the Mandel lab at the State University of New York at Stony Brook. Dr. Mandel is a scientific advisor of the Rett Syndrome Research Trust (RSRT) a recently formed nonprofit organization intensively focused on the development of treatments and cures for Rett Syndrome and related MECP2 disorders.

Rett Syndrome strikes little girls almost exclusively, with first symptoms usually appearing before the age of 18 months. These children lose speech, motor control and functional hand use, and many suffer from seizures, orthopedic and severe digestive problems, breathing and other autonomic impairments. Most live into adulthood, and require total, round the clock care. Individuals with Rett and their families suffer the emotional and financial cost of the wide range of symptoms and the ongoing struggles to address them.

Glial cells, which reside throughout the nervous system, comprise the vast majority (90%) of cells in the brain. Glia support and interact with neurons in innumerable ways, from providing the structural underpinnings and guidance of axons and dendrites (the neuronal processes that carry information), to creating protective insulation for axons. These and other glial functions are essential to the health of neurons.

Since MECP2 is located on the X chromosome, girls with Rett Syndrome are mosaic: cells with a healthy copy of the gene lie side by side with cells that have the mutated version. Mandel and colleagues found that MECP2-deficient astrocytes could not sustain normal neuronal growth. In fact, their experiments suggest that MeCP2-deficient astrocytes secrete a toxic factor that impacts the entire neighborhood of neurons, including neurons with wildtype (normal) MECP2.

Conversely, they found that wildtype astrocytes could restore the stunted growth of MeCP2-deficient neurons. This finding supports the 2007 *Science* publication by Professor Adrian Bird showing reversal of Rett symptoms in adult mouse models of the disorder. Results from ongoing in vivo mouse studies deleting MeCP2 in glia are promising in terms of supporting the culture studies.

“This new study adds to the growing body of evidence that glial cells are critically important contributors to neurological diseases and therefore attractive targets for drug development,” said Ben Barres, Professor and Chair of the Department of Neurobiology at Stanford University and a glial cell expert.

Recent studies from multiple groups, including the lab of Dr. Tom Maniatis, a neurodegenerative disease researcher at Harvard University, have implicated glia in Lou Gehrig’s disease (Amyotrophic Lateral Sclerosis – ALS), a devastating neurodegenerative disorder that leads to the death of motor neurons and total paralysis. “In Rett Syndrome, faulty glia seem to poison neurons, inhibiting growth; in ALS glia appear to release a toxic factor that kills motor neurons.” Maniatis stated that “studies of the role of glia in a broad spectrum of neuronal diseases should lead to exciting advances in understanding disease mechanisms.”

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“Dr. Mandel’s sharp insights have given the scientific community an entirely new way to think about treating Rett Syndrome. One could envision a scenario where halting the secretion of this potential toxic factor could restore health, in particular to the MECP2 positive neurons, which could bring about amelioration of symptoms. I look forward to her lab’s continued contributions as we explore the therapeutic implications of her research,” comments Monica Coenraads, Executive Director of RSRT and parent of a child with the disorder.

Other people who worked on the project include Daniel T. Lioy of the Vollum Institute and Christopher Grunseich, M.D. while at the State University of New York at Stony Brook. Nurit Ballas is now a Research Associate Professor in the Department of Biochemistry and Cell Biology at Stony Brook.

For more information on Rett Syndrome and MECP2 spectrum disorders please visit the website of the Rett Syndrome Research Trust at www.ReverseRett.org.

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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 OHSU

Oregon Health & Science University is the state’s only health and research university, and Oregon’s only academic health center. OHSU is Portland’s largest employer and the fourth largest in Oregon (excluding government), with 12,400 employees. OHSU’s size contributes to its ability to provide many services and community support activities not found anywhere else in the state. It serves patients from every corner of the state, and is a conduit for learning for more than 3,400 students and trainees. OHSU is the source of more than 200 community outreach programs that bring health and education services to every county in the state.

About Stony Brook University

Part of the State University of New York system, Stony Brook University encompasses 200 buildings on 1,600 acres. In the 50 years since its founding, the University has grown tremendously, now with nearly 24,000 students and 2,100 faculty, and is recognized as one of the nation’s important centers of learning and scholarship. It is a member of the prestigious Association of American Universities, and ranks among the top 100 national universities in America and among the top 50 public national universities in the country according to the 2008 U.S. News & World Report survey. Considered one of the “flagship” campuses in the SUNY system, Stony Brook University is a driving force of the Long Island economy, with an annual economic impact of \$4.65 billion, generating nearly 60,000 jobs. Stony Brook accounts for nearly 4% of all economic activity in Nassau and Suffolk counties, and roughly 7.5 percent of total jobs in Suffolk County.