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New Mouse Model in Rett Syndrome Reveals Promise

(Cincinnati, OH) In an article released today from Jeannie T. Lee, MD PhD of Massachusetts General Hospital (MGH), there is hope on the horizon for future research specific to Rett syndrome, a rare childhood neurodevelopmental disorder.

Dr. Lee, a Translational HeArt Award recipient from Rettsyndrome.org, developed a new female mouse model called "Tsix-Mecp2" that shows great promise in inactive X-chromosome (Xi) research for Rett syndrome.

The results prove the newly developed female mouse model produces more Rett-like symptoms (i.e., repetitive behaviors, motor weakness, tremors, and gait disturbance) — an improvement over previous mice with a mixed expression pattern for the *Mecp2* mutation. The MGH team introduced an X-inactivation mutation (*Tsix*) into the mouse strain to increase the disease penetrance in a female model. For this reason, the team was able to observe that expression of 5-10% normal MeCP2 protein in the brain resulted in improved motor skill and extended lifespan 5-8 fold. Thus, the study indicates possible therapeutic benefit even when MeCP2 protein levels do not reach 100% in every brain cell.

Rett syndrome is caused by mutations in the *MECP2* gene located on the X chromosome. Females carry two X chromosomes, but with Rett syndrome, one X chromosome is inactivated randomly – through a process called X-inactivation silencing the whole chromosome. The *Tsix* gene helps regulate the process of X chromosome inactivation. It is widely thought that one potential curative treatment for Rett syndrome is to activate a normal copy of the *MECP2* gene found on this silenced X chromosome.

"We are excited there's a new mouse model to study Xi reactivation for preclinical studies," shares Rettsyndrome.org's Chief Science Officer, Steven Kaminsky, PhD. "Female mice have largely been neglected in preclinical studies because their Rett-like symptoms have not been as strong as in male mice lacking *Mecp2*. This new female model exhibits symptoms closer to what we see in the human condition, and it is well suited for drug studies to activate the normal MECP2 gene.

Dr. Lee, the senior author of the study, added, "We are very grateful to Rettsyndrome.org for

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providing critical funding to spearhead this work. A most exciting finding to arise from the mouse model which has not been so easy to recapitulate in other systems is the repetitive and self-injurious behaviors that typify Rett Syndrome. Our female mouse model now sets the stage for us to test candidate drugs for the X-reactivation approach that we have been building towards for the past several years."

Dr. Lee's new research provides additional evidence that restoring *MECP2* will alleviate symptoms of Rett syndrome "Which we hope," says Dr. Kaminsky of Rettsyndrome.org, "will translate to an improved quality of life to those individuals affected by this disorder. Rettsyndrome.org is very proud of her work."

About Rettsyndrome.org

As a major private funder of Rett syndrome research, Rettsyndrome.org has funded over $44M in high-quality, peer-reviewed research grants and programs to date. The organization hosts the largest global gathering of Rett researchers and clinicians to establish research direction for the future. Rettsyndrome.org, a 501(c) 3 organization, has earned Charity Navigator's prestigious 3 star rating year after year. To learn more about our work and Rett syndrome, visit www.rettsyndrome.org or call (513) 874-3020.

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