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BRINGING OUT THE BEST IN CHROMOSOMES

FOCUS: Developing a novel therapeutic for Rett syndrome.

Rett syndrome is a rare chromosomal disorder that occurs almost exclusively in girls, usually recognized at 6 to 18 months, when symptoms arise that include motor abnormalities, severe seizures, absent speech, and autism. Individuals typically live wheelchair-bound for 40 years or more and require full-time care. There is no disease-specific treatment or cure.

Rett is caused by mutations on the X chromosome, specifically on the MECP2 gene that is crucial for neuronal development. Females have two X

chromosomes, but only one is expressed in any cell, and the other is inactive.

In Rett girls, every affected cell harbors a normal but dormant copy of MECP2 on the inactive X chromosome. Dr. Lee's aim is to alleviate disease by reactivating that dormant chromosome to restore MECP2 protein to the brain.

"There's a central molecule, Xist RNA, that orchestrates the X chromosome shutdown," Dr. Lee says. "Then DNA methylation (a process that plays a crucial

role in regulation of gene expression) cements that shutdown. After years of trial and error, I had an epiphany: because no single compound can reactivate the X chromosome sufficiently, why not combine two modalities in such a way that the whole is greater than the sum of the parts? So we used drugs to target both of them—lo and behold, we got reactivation."

Dr. Lee claims that this approach can potentially be applied to other diseases caused by mutations on the X chromosome.

"The Harrington Therapeutic Development team has made a huge difference to our drug discovery efforts, bringing logistical support not typically found in academia."

Harrington Discovery Institute

