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ABSTRACT:

Translating dosage compensation to trisomy 21

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Down syndrome is the leading genetic cause of intellectual disabilities, occurring in 1 out of 700 live births. Given that Down syndrome is caused by an extra copy of chromosome 21 that involves over-expression of 400 genes across a whole chromosome, it precludes any possibility of a genetic therapy. Our lab has long studied the natural dosage compensation mechanism for X chromosome inactivation. To “dosage compensate” X-linked genes between females and males, the X-linked XIST gene produces a large non-coding RNA that silences one of the two X chromosomes in female cells. The initial motivation of this study was to translate the natural mechanisms of X chromosome inactivation into chromosome therapy for Down syndrome. Using genome editing with zinc finger nucleases, we have successfully inserted a large XIST transgene into Chromosome 21 in Down syndrome iPS cells, which results in chromosome-wide transcriptional silencing of the extra Chromosome 21. Remarkably, deficits in proliferation and neural growth are rapidly reversed upon silencing one chromosome 21. Successful trisomy silencing in vitro surmounts the major first step towards potential development of “chromosome therapy” for Down syndrome. The human iPSC-based trisomy correction system we established opens a unique opportunity to identify therapeutic targets and study transplantation therapies for Down syndrome.

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