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Translating dosage compensation to trisomy 21

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Et al.

ABSTRACT:

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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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