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Drug Discovery for Genetic Diseases Caused by Aberrant mRNA Splicing

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Patients of congenital diseases have abnormalities in their chromosomes and/or genes. Therefore, it has been considered that drug treatments can serve to do little for these patients more than to patch over each symptom temporarily when it arises. Although we cannot normalize their chromosomes and genes with chemical drugs, we may be able to manipulate the amounts and patterns of mRNAs transcribed from patients DNAs with small chemicals. Based on this simple idea, we have looked for chemical compounds which can be applicable for human diseases targeting kinase families of CDKs, CLKs and DYRKs which are involved in the regulation of gene expression, and eventually succeeded to find FIT039 (1), TG003 (2), and ALGERNON (3) as potential therapeutic drugs to cure diseases such as viral infections, Duchenne muscular dystrophy, and Down syndrome, respectively. In addition, we established splicing reporter assay with dual color (SPREADD) using a segment of pathogenic genes, and found a splicing modulator, RECTAS (4), which can rectify the aberrant IKBKAP splicing in patient iPS cells of Familial dysautonomia. EDA-ID (anhidrotic ectodermal dysplasia with immunodeficiency), cardiac Fabry diseas**,** and type V cystic fibrosis are often induced by pseudo-exon recognition, and our chemical therapeutics can normalize the splicing patterns (5).

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