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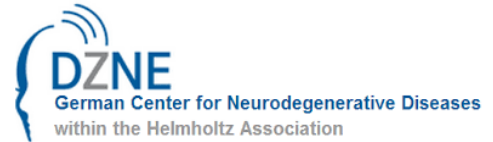
iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells



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DRUG SCREEN IN iPSC-NEURONS IDENTIFIES NUCLEOSIDE ANALOGS AS INHIBITORS OF (G4C2)_n EXPRESSION IN c9orf72 ALS/FTD

In the talk, I will highlight a scalable protocol for human neuronal differentiation from hiPS cells that allows the generation of ~ 1 billion neurons in a dish in a short period and how we used the protocol in a phenotypic screen of 1430 FDA-approved compounds. We identified three nucleoside analogs as inhibitors of (G4C2)_n expression in the C9orf72 gene linked to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The clinically used guanosine/cytidine analogs decitabine, entecavir, and nelarabine reduce poly-GA/GP expression, with decitabine being the most potent. Hit compounds nearly abolish sense and antisense RNA foci and reduce expression of the repeat-containing nascent C9orf72 RNA transcript and its mature mRNA with minimal effects on global gene expression, suggesting that they specifically act on repeat transcription. Importantly, decitabine treatment reduces (G4C2)_n foci and DPRs in C9orf72 BAC transgenic mice. Our findings suggest that nucleoside analogs are a promising compound class for therapeutic development in C9orf72 repeat-expansion-associated disorders.

The neuronal differentiation protocol we developed can be easily applied for disease modeling and therapeutic discovery screens for other neurodegenerative diseases.



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