JAN 10th 2023 | 4PM CET VIRTUAL

iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

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DRUG SCREEN IN iPSC-NEURONS IDENTIFIES NUCLEOSIDEANALOGS 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.