A DRUG REPURPOSING STRATEGY FOR IDENTIFYING NOVEL PHARMACOLOGICAL TARGETS IN A MURINE MODEL OF DOWN SYNDROME

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Down syndrome (DS) is a neurodevelopmental disorder caused by the triplication of chromosome 21and the most common genetic cause of intellectual disability. Decreased proliferation of neural progenitor cells (NPC), widespread neurogenesis impairment and increased astrogliogenesis are considered major determinants of brain atrophy and mental retardation in DS. A well-studied preclinical model for DS is the Ts65Dn mouse line that recapitulates several features of the human disorder, including cognitive impairment. Recent findings in Ts65Dn mice suggest that an early pharmacological treatment may correct NPC proliferation, neurogenesis and, in parallel, also cognitive performance. Unfortunately none of the drugs effective in the animal model, i.e lithium chloride, appear suitable for clinical applications. Drug repurposing, the process of discovering new indications for clinically approved drugs, is an attractive drug development strategy for several disorders with high medical need. The obvious advantage of this approach is that for those compounds pharmacokinetic and pharmacodynamic features as well as safety/tolerability are already characterized so to allow, in principle, a rapid progression from preclinical to clinical studies. Based on these premises, the goal of this study was to develop in vitro cell-based assays to identify, among clinically approved drugs, compounds able to correct proliferative and/or differentiative deficits of Ts65Dn neonatal NPC.
To this aim we screened 1,887FDA/EMA approved drugs from two distinct chemical libraries in a proliferation assay based on Ts65Dn-derived trisomic NPC, using LiCl (2mM) as a positive control. As result of this effort, we identified 27compounds more effective than lithium ($p<0.001$) in promoting Ts65Dn NPC proliferation. Among the most potent hits we identified the immunosuppressant cyclosporin A (CSA) which was effective at nM concentrations. In secondary assays the drug not only promoted NPC proliferation, but also remarkably stimulated their neuronal differentiation and neurite outgrowth, and in parallel reduced astrogliogenesis. At present, CSA treatment is under evaluation in neonatal Ts65Dn mice to assess its ability to correct DS-associated neuropathology and, hopefully, to improve cognitive performance.

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