GSK3-beta inhibitors: a promising strategy for the CDKL5 variant of Rett Syndrome

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Mutations in the *CDKL5* gene have been described in patients diagnosed with an atypical variant of Rett Syndrome. CDKL5 is highly expressed in the developing brain, suggesting its importance for correct brain maturation. However, very little is known on the role of CDKL5 in brain development and no therapeutic approaches are available so far.

Brain phenotype characterization of a *Cdkl5* KO mouse model has shown that CDKL5 plays a fundamental role on dendritic development [1]. Looking at the molecular mechanisms underlying this neurodevelopmental defect, we found an increased activity of GSK3β, a crucial inhibitory regulator of many brain functions.

We recently found that treatment with the ATP-competitive GSK3β inhibitor, SB216763, recovers hippocampal defects in *Cdkl5* KO mice [2], suggesting that GSK3β inhibitors may be an excellent choice for the improvement of neurodevelopmental alterations due to CDKL5 loss-of-function. However, compounds that inhibit GSK3β kinase activity in an ATP-competitive manner may also affect other kinases, with harmful effects, while ATP-noncompetitive GSK3β inhibitors, such as NP-12 are more selective. Moreover, NP-12 is already approved for use in humans and is under test in Phase II clinical trials for other pathologies.

By exploiting hippocampal neuronal cultures from *Cdkl5* KO mice, we found that reinstatement of GSK3β activity with NP-12 resulted in the recovery of neuronal maturation. Importantly, we found that treatment with NP-12 restored dendritic hypotrophy in the hippocampus of *Cdkl5* KO mice. Given these premises, NP-12 treatment may offer an attractive therapy for the CDKL5 disorder, rapidly translatable into clinical trials.

1. Fuchs, C., et al., *Loss of CDKL5 impairs survival and dendritic growth of newborn neurons by altering AKT/GSK-3beta signaling*. Neurobiol Dis, 2014. 70C: p. 53-68.
2. Fuchs, C., et al., *Inhibition of GSK3β rescues hippocampal development and learning in a mouse model of CDKL5 disorder. Neurobiol Dis*, in press.