TDP-43 MODULATION BY CDC7 INHIBITORS AS A THERAPEUTIC STRATEGY FOR AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of motor neurons, leading to muscle wasting and early death due to respiratory failure. Listed as a “rare disease”, ALS affects 2 to 3 people of every 100.000 citizens in Europe and North America. However, the etiology remains unknown and no effective treatment exists to date, thus the search for new drugs able to modulate this neurodegeneration is needed. Approximately, between 5 to 10% of ALS cases have a genetic link, while the sporadic ones represent 90% of all cases [1].

TDP-43 has been recognized to play a key role in the disease, in both familiar and sporadic cases. In normal conditions, TDP-43 is a nuclear protein and regulates the expression of many genes, but it’s hyperphosphorylated, ubiquitinated and N-terminally truncated in the cytoplasm of motor neurons in ALS patients [2].

Protein kinases are important targets for several neurodegenerative disorders, as well as inflammatory diseases, diabetes and cancer. The reason is that aberrant protein kinase signaling is implicated in many of these human diseases [3]. In this context, it has been recently discovered that cell division cycle kinase 7 (CDC7) is responsible for pathological TDP-43 phosphorylation [4]. So that, CDC7 inhibition by brain permeable small molecules will be a good strategy for the treatment of ALS, as they could strongly reduce TDP-43 phosphorylation, preventing TDP-43-dependent neurodegeneration.

In our laboratory, CDC7 inhibitors have been designed and synthesized showing a low micromolar activity against this kinase. Furthermore, these compounds were predicted as able to cross the blood brain barrier based on PAMPA assays and selective against other kinases. Here, we present the ability of these compounds to reduce TDP-43 phosphorylation both in vitro and in vivo in ALS models as well as restore its nuclear location. Additionally, this same behavior is observed when FTLD patient´s lymphoblasts are treated [5][6].

References

1) Zarei, S.; Carr, K.; Reiley, L.; Diaz, K.; Guerra, O.; Altamirano, P.F.; Pagani, W.; Lodin, D.; Orozco, G.; Chinea, A., A comprehensive review of amyotrophic lateral sclerosis. Surg. Neurol. Int. 2015; 6: 171.
2) Neumann, M.; Sampathu, D.M.; Kwong, L.K.; et al., Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006; 314: 130-133.
3) Cohen, P.; Alessi, D.R., Kinase Drug Discovery – What’s Next in the Field? ACS Chem. Biol. 2013; 8 (1): 96-104.
4) Liachko, N.F.; McMillan, P.J.; Guthrie, C.R.; Bird, T.D.; Leverenz, J.B.; Kraemer, B.C., CDC7 Inhibition Blocks Pathological TDP-43 Phosphorylation and Neurodegeneration. Ann. Neurol. 2013; 74 (1): 39-52.
5) Martinez, A.; Perez, D.I.; Gil, C.; Martin-Requero, A.; Rojas-Prats, E.; Martinez-Gonzalez, L.; Perez, C., CDC-7 inhibitor compounds and use thereof for the treatment of neurological conditions, 2018, WO 2018172587 A1 20180927.
6) Martinez, A.; Gil, C.; Martin-Requero, A.; Rojas-Prats, E.; Martinez-Gonzalez, L., Derivados de purina inhibidores de CDC7 y su uso para el tratamiento de patologías neurológicas, P201830914.