Chemical Knockdown of Phosphorylated p38 MAPK as a Novel Platform for the Treatment of Alzheimer's Disease

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P38 MAPK (Mitogen-Activated Protein Kinase) has been known as an impotnar target for various chronic inflammatory diseases for past decades. However, drugging the kinase has not been successful. Alzheimer's disease (AD) is characterized by the presence of amyloid-β plaques and tau-aggregated neurofibrillary tangles in the brain, as well as neurodegeneration, and there is no known cure. Recent studies on the underlying biology of AD in cellular and animal models have suggested that phosphorylation of p38 MAPK would lead to orchestrating diverse events related to AD, such as tau phosphorylation, neurotoxicity, neuroinflammation and synaptic dysfunction. Recently, we developed a series of p38 MAPK degraders. In particular, p-p38 MAPK, causing downstream activation as well as aggravating its pathology in the chronic inflammation, is selectively degraded by our approach. In addition, we confirmed that this novel approach is working well in the AD transgenic mouse model.

References

[1] Son, S.-H.; Lee, N.-R.; Gee, M. S.; Song, C W.; Lee, S. J.; Lee, S.-K.; Lee, Y.; Kim, H.; Lee, J.-K.*; Inn, K.-S.*; **Kim, N.-J.*** Chemical Knockdown of Phosphorylated p38 Mitogen-Activated Protein Kinase (MAPK) as a Novel Approach for the Treatment of Alzheimer's Disease, *ACS Cent. Sci.,* **2023**, *9(3)*, 417-426.

[2] Gee, M. S.; Son, S.-H.; Jeon, S. H.; Do, J.; Kim, N.; Ju, Y.-J.; Lee, S. J.; Inn, K.-S.*; **Kim, N.-J.***; Lee, J.-K.* A selective p38α/β MAPK inhibitor alleviates neuropathology and cognitive impairment, and modulates microglia function in 5XFAD mouse. *Alzheimers Res. Ther.,* **2020**, *12*, 45.

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