Discovery of proteolysis targeting chimeras for leucine-rich repeat kinase 2 (LRRK2)

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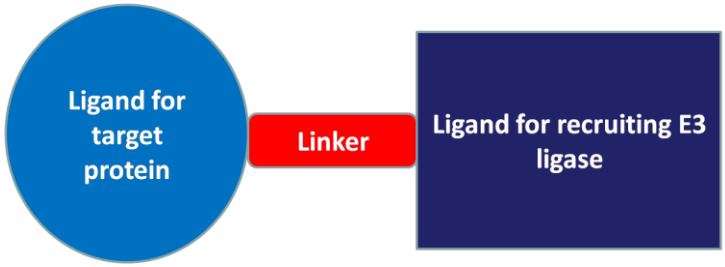
Proteolysis targeting chimeras are hetero-bifunctional molecules, consisting of a ligand that recruits an E3 ligase and a ligand interacting with the protein of interest. The two ligands are connected via a linker. The recognition of the ligand by the E3 ligase initiates the ubiquitination process that eventually leads to the degradation of the complex. Thus, the protein of interest is not inhibited, but degraded and this has certain advantages.[1,2]



Our protein of interest is the leucine-rich repeat kinase 2 (LRRK2), which has drawn considerable attention regarding its role in the pathogenesis of Parkinson's disease.[3] We have chosen two low nanomolar, highly selective and brain-penetrating known inhibitors of LRRK2 and modified them in order to attach the linkers and the ligand for recruiting the E3 ligase, which in this case is Cereblon. A small library of LRRK2 – PROTAC was synthesized and their ability to act as degraders was evaluated by Western blots showing clear dose-dependent POI degredation.

References

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3. Chan SL, Tan EK. *Expert Opinion Ther. Targets* **2017**, *21*, 601-610

Acknowledgement: This project has received funding from the European Union's Framework Programme for Research and Innovation Horizon 2020 (2014 – 2020) under the Marie Skłodowska – Curie Grant Agreement No. 675555, Accelerated Early staGe Drug Discovery (AEGIS).