ATTEC: A new potential strategy of drug discovery for Huntington's disease and similar diseases

With the support by the National Natural Science Foundation of China, the research team led by Prof. Lu BoXun (鲁伯埙) with his collaborators Prof. Fei YiYan (费义艳) and Prof. Ding Yu (丁澦) at Fudan University, demonstrated the concept of using Autophagosome Tethering Compounds (ATTEC) as an innovated approach to discover treatment drugs for Huntington's disease and similar diseases. The research was recently published in *Nature* (2019, 575(7781): 203—209).

Huntington's disease (HD) is an incurable devastating neurodegenerative disorder. Since the biochemical activity of the mutant huntingtin protein (mHTT) that causes the disease is uncharacterized, the conventional drug discovery approach relying on inhibitors that block the bioactivity of the pathogenic proteins is inapplicable. The team came up with a fundamentally new idea for HD discovery: harnessing the autophagy, an intracellular protein degradation machinery, to degrade mHTT. During autophagy, the key protein LC3 is lipidated and expanded to form a double-membrane structure, which then engulfs degradation cargoes for degradation. The team envisioned a "small molecule glue" function as Autophagosome Tethering Compounds (ATTEC), which can interact with LC3 and mHTT to tether them together so that mHTT is engulfed into autophagosomes for degradation. Meanwhile, the ATTEC does not interact with the wild-type HTT protein, leaving it unaffected. Through screening, the team identified four compounds that have the desired properties above.

The team further demonstrated that these four compounds significantly reduced mHTT levels in HD mouse neurons, HD patient cells, and HD *Drosophila* models at nanomolar concentrations, with little effect on wild-type HTT levels. Excitingly, at least two out of these four compounds are able to cross the blood-brain barrier, and the low dose by intraperitoneal administration significantly reduced mHTT levels in brain tissue disease in the cortex and striatum of HD mice, without affecting wild-type HTT levels. They also significantly improved disease-related phenotypes, providing an entry point for the development of oral or injectable drugs for HD.

The team further revealed that the compounds can selectively bind to the excessively long polyQ stretch to distinguish mHTT from wtHTT, and demonstrated that these compounds can effectively reduce the level of the mutant ATXN3 protein with an expanded polyQ, which causes another polyQ disease called SCA3, without affecting the wild-type ATXN3. Thus, these compounds may not only be effective in the treatment of Huntington's disease, but may also be applied to other polyQ diseases. The new concept of drug development using ATTEC may also be applied to other pathogenic proteins that are undruggable, or even to pathogenic substances that are not proteins, such as organelles or lipids, although further studies are required.

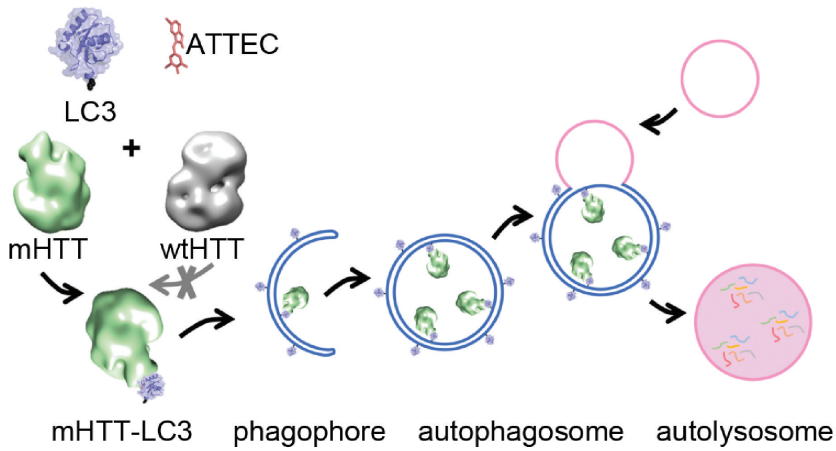

Figure A schematic picture showing the mechanism of actions of the ATTEC targeting mHTT.