

2019-10-30

Allele-selective lowering of mutant HTT protein by HTTLC3 linker compounds

Li, Z

<http://hdl.handle.net/10026.1/15145>

10.1038/s41586-019-1722-1

Nature

Springer Science and Business Media LLC

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

Model and treatment	Readout and figures	Compound effects
cultured primary cortical neurons, from mice (Hdh ^{Q7/Q140})	the mHTT level by Western-blot (Fig. 2a&d)	10O5: 26.0±3.3% lowering
		8F20: 40.1±12.6% lowering
		AN1: 35.7±2.8% lowering
		AN2: 34.0±6.2% lowering
primary human HD patient fibroblasts (Q49)	the mHTT level by HTRF (Fig. 3a)	10O5: 45.1±4.0% lowering
		8F20: 44.8±4.9 lowering
		AN1: 46.1±6.2% lowering
		AN2: 54.8±7.5% lowering
primary human HD patient fibroblasts (Q55)	the mHTT level by HTRF (Fig. 3a)	10O5: 34.3±5.4% lowering
		8F20: 28.7±3.6% lowering
		AN1: 26.5±7.0% lowering
		AN2: 39.3±4.8% lowering
primary human HD patient fibroblasts (Q68)	the mHTT level by HTRF (Fig. 3a)	10O5: 20.9±2.7% lowering
		8F20: 22.9±5.3% lowering
		AN1: 26.4±2.8% lowering
		AN2: 18.1±5.1% lowering
HD patient iPSC-derived neurons (Q47)	the mHTT level by HTRF (Ext. Data. Fig. 5c)	10O5: 31.4±3.2% lowering
		8F20: 28.9±3.7% lowering
		AN1: 39.3±3.2% lowering
		AN2: 40.5±2.8% lowering
	surface area of each neuron by Tuj1 staining (Fig. 5a)	10O5: 69.5±1.6% rescue
		8F20: 51.6±3.1% rescue
		AN1: 58.8±4.9% rescue
		AN2: 64.4±2.7% rescue
immortalized human HD patient fibroblasts (Q47)	the mHTT level by HTRF (Fig. 3b)	10O5: 30.2±4.5% lowering
		8F20: 22±4.8% lowering
		AN1: 42.0±3.9% lowering
		AN2: 41.4±5.1% lowering
icv-injected mice (Hdh ^{Q7/Q140})	the mHTT level by Western-blot (Ext. Data Fig. 9a)	10O5: 43.3±2.2% lowering
		8F20: 9.1±5.3% lowering (n.s.)
		AN1: 29.9±2.9% lowering
		AN2: 30.3±7.4% lowering
ip-injected mice (Hdh ^{Q7/Q140})	the cortical mHTT by Western-blot (Ext. Data Fig. 9b)	10O5: 24.8±4.2% lowering
		AN2: 36.6±7.4% lowering
	the striatal mHTT by Western-blot (Ext. Data Fig. 9c)	10O5: 22.9±2.3% lowering
		AN2: 26.3±5.5% lowering
	the cortical HTT by MASS-SPEC (Ext. Data Fig. 11b)	10O5: 18.1±2.4% lowering
		AN2: 25.2±3.2% lowering
	latency to fall by rotarod tests (Fig. 5d)	10O5: (60.8% averaged rescue)
		AN2: (64.3% averaged rescue)
	passing time by balance beam tests (Fig. 5e)	10O5: (77.2% averaged rescue)
		AN2: (92.8% averaged rescue)
	10O5: (43.6% averaged rescue)	
	AN2: (52.4% averaged rescue)	