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AUTOTAC is a novel Parkinson's disease therapeutic agent targeting alpha-synuclein aggregates to autophagic-lysosomal degradation

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Currently, there is no disease-modifying therapeutics for treating Parkinson's disease (PD). Though many efforts were undertaken to develop therapeutic approaches aiming to lead to transient symptomatic relief of PD, the presence of untreated α-synuclein aggregates stimulate recurrence of symptoms and even further progression of PD. Here, we propose a promising disease-modifying therapeutic agent targeting PD, Autophagy Targeting Chimera (AUTOTAC), which is comprised of its α-syn aggregate-binding ligand (TBL) linked to autophagy targeting ligand (ATL) that binds to ZZ domain of autophagy receptor p62/SQSTM1. This chemical platform provides a basis for targeting α-syn aggregates for autophagic-lysosomal degradation. We employed α-syn implicated PD experimental models using α-syn preformed fibrils (PFFs) in order to explicitly study α-syn aggregate-induced PD pathology. We witnessed that PD-AUTOTAC selectively targets α-syn aggregates through its TBL and sequestration mediated through p62 oligomerization, and this enables activation of downstream autophagic machinery for further lysosomal degradation in concentration-dependent manner (Fig. 1A). We also show that PD-AUTOTAC induces alleviation of synucleopathy-associated genotoxicity and mitotoxicity (Fig. 2A and B). The degradation of α-syn aggregates is expected to fundamentally suppress the progression of PD by attenuating α-syn aggregate-induced cytotoxicity, as the PO administration of PD-AUTOTAC into PFF-stereotaxic surgery mouse model mitigated progression of behavioral deficits (Fig 3A and B). As there has been little to no efforts in developing therapeutics degrading the fundamental causative agents of PD, PD-AUTOTAC will provide a distinct paradigm of therapeutic strategy for targeting PD.

A

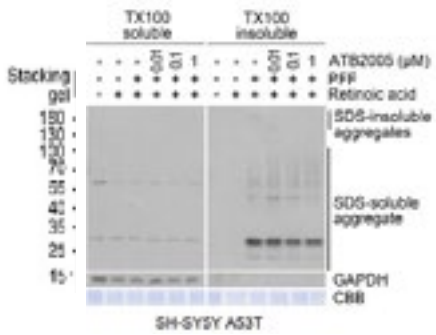
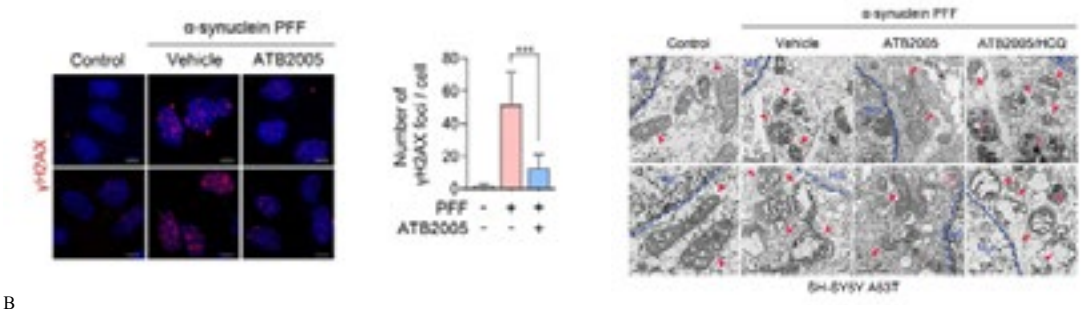


Figure 1: A, SH-SY5Y cells overexpressing A53T mutant α-syn were subjected to retinoic acid differentiation and subsequently transduced with α-syn PFFs for 48 h for α-syn aggregate generation. ATB2005 was then treated for 24 h, and the cell lysates were fractionated with triton x-100 for western blot analysis.



B

Figure 2: A, transmission electron microscopy analysis. α-Syn PFFs were transduced into SH-SY5Y A53T mutant cells, and the cells were administrated with PD-AUTOTAC (1 uM, 24 h) or HCQ (an autophagy inhibitor, 25 uM, 24 h). B, immunocytochemistry analysis and its quantification in HEK293A cells transduced with α-syn PFFs. PD-AUTOTAC was treated at 0.1 uM for 48 h (24 h * 2).

A B

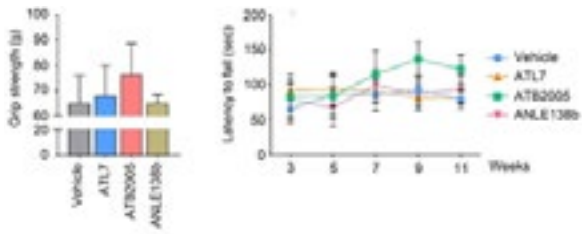


Figure 3: A, 6-week-old C57BL6/J male mice were subjected to stereotaxic surgery with α-syn PFFs into brain striata, and after 12 weeks, grip strength was measured. B, the mice were subjected to rotarod test

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Biography

Jihoon Lee studied human biology and cell and molecular biology at the University of Toronto. After finishing his study in Canada, he moved to Korea and joined the research team in Cellular Degradation Biology Center, College of Medicine, Seoul National University. He is also co-affiliated with AUTOTAC Bio Inc., Seoul, South Korea, and has been participating as a researcher to study the utilization of AUTOTAC compounds in proteinopathies for targeted degradation. Collaborating with researchers at Seoul National University and research team members at AUTOTAC Bio Inc., he is now focusing his project on targeting α-syn aggregates as a therapeutic approach to treat Parkinson's disease.

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