DEVELOPMENT OF USP30 INHIBITORS AS DISEASE MODIFYING THERAPEUTIC FOR PARKINSON'S DISEASE

Bahareh (Spring) Behrouz[1], Donna Romero[1], Edward L Fritzen Jr[1], Mingchong Yang[3], Nuo Sun[3], Jeremy Yu[2], Andy D. Lee[1]

1- Vincere Biosciences Inc, Cambridge, MA, USA
2- Division of Endocrinology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA
3 -Departments of Physiology and Cell Biology, The Ohio State University Wexner Medical Center, Columbus, OH, USA.

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Introduction

- No disease modifying therapeutics currently exist for Parkinson's disease (PD).
- Several lines of evidence suggest that deficits in mitophagy are a shared feature of genetic and idiopathic forms of PD
- Despite strong genetic evidence from monogenic mutations in PINK1, parkin, and FBXO7, as well as risk factors for idiopathic PD, no clinical trials to enhance mitophagy have been initiated.
- USP30 has emerged as a key regulator of mitochondrial clearance in opposition to the actions of parkin to drive ubiquitination and clearance of depolarized mitochondria.
- We have developed potent selective USP30 inhibitors useful for preclinical studies and proof of concept studies.

Vincere USP30 Inhibitors are Potent *in vitro*

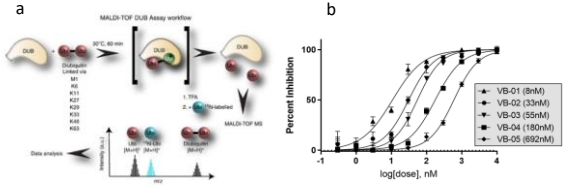

Figure 1. (a) Describes a previously published MALTI-ToF MS based assay used to determined IC50 values[1]. Concentration response curves of exemplar compounds with varying potencies lead to insight of structure activity relationships (SAR), IC50s in parentheses. Single digit nanomolar potencies can be attained.

Vincere Inhibitors are Highly Selective

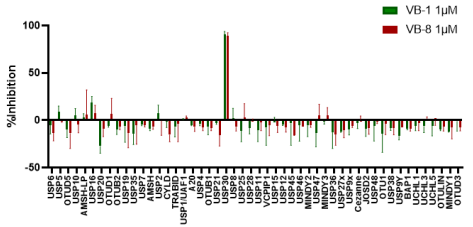

Figure 2. Two representative compounds which display >80x selectivity for USP30 inhibition over other a panel of 39 other tested de-ubiquitinating enzymes (DUBS) in a MS-based assay.

Vincere Inhibitors Increase Mitophagy in Neural Cells

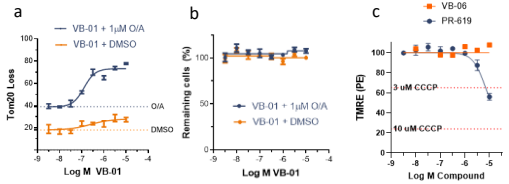

Figure 3. (a) Compounds induce mitophagy in a dose-dependent manner when mitochondria are damaged and to a lesser degree under basal conditions in differentiated ReNcell VM[2]. Dotted line represents treatment with oligomycin/antimycin (O/A) or DMSO alone. (b) Tested compounds did not cause cell loss as measured by nuclei count. (c) Tested compounds did not cause depolarization of mitochondria (3 & 10 uM CCCP, and PR-619 were positive controls).

Inhibitors Increase Brain Mitophagy *In Vivo* (Pilot)

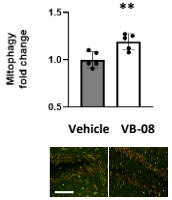

Figure 4. Pilot experiment showing increased mitophagy in the brain (hippocampus) of Mt-Keima[3] mice following 5 daily treatments (30 mg/kg IP) of VB-08. No adverse events were reported with 5 days of treatment. N=5 mice/grp, 1 section/mouse, Bar graph depicts mean ± SD, ** = P <0.01, Image scale bar at 100 um.

Discussion

Vincere's potent and selective USP30 inhibitors increase mitophagy in human neural cells and in the brain of mice in vivo. These compounds have potential as disease modifying therapeutics for PD.

References

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2. VERKAAR et al; 470.12 / M3 - Development and validation of a high content-based assay to measure Tom20 loss in dopaminergic human neurons differentiated in vitro; Society for Neuroscience 2018
3. Sun N et al, A fluorescence-based imaging method to measure in vitro and in vivo mitophagy using mt-Keima. Nat Protoc. 2017 Aug;12(8):1576-1587. doi: 10.1038/nprot.2017.060. Epub 2017 Jul 13.

Acknowledgements

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