CT1812 preserves neurons and decreases levels of neurodegeneration biomarker NfL in disease-relevant neuronal model

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INTRODUCTION

The sigma-2 receptor (S2R) modulator CT1812 (zervimesine) is an investigational oral oligomer antagonist currently in clinical development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). In preclinical studies, CT1812 displaces amyloid-beta (Aβ) and alpha-synuclein oligomers bound to synapses, resulting in a neuroprotective effect by preventing synaptotoxicity and restoring neuronal function (Figure 1) (1, 2). In the SHINE Ph2 clinical study (COG0201, NCT03507790) in patients with mild to moderate AD, participants treated for six months with CT1812 had lower levels of the neurodegenerative biomarker neurofilament light (NfL) in the CSF compared to placebo-treated participants. In neurodegenerative diseases like AD and DLB, oxidative stress is a key contributing factor. Previously, CT1812 has been demonstrated to normalize functions disrupted by oxidative stress in non-neuronal cells (3). To investigate the neuroprotective effect of S2R-modulator CT1812 on neurons, we assessed its ability to rescue cell death elicited by oxidative stress.

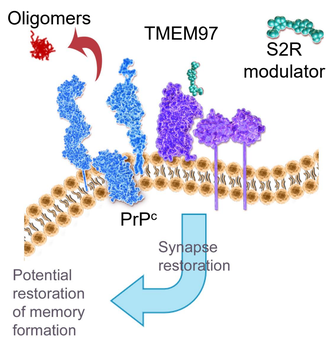


Figure 1. Representation of S2R (TMEM97) and oligomer receptor, prion protein (PrPc).

METHODS

SH-SY5Y cells were differentiated into neurons and characterized by RT-qPCR and immunofluorescence. Differentiated SH-SY5Y cells were treated with oxidative stressor 4-Hydroxynonenal (4-HNE), a byproduct of lipid peroxidation elevated in patients with AD, at multiple concentrations in the presence or absence of CT1812. Cell viability was assessed by measurement of lactate dehydrogenase (LDH) release into the medium using LDH-Glo assay and nuclear count by DAPI staining. Cell morphology was analyzed by imaging after immunostaining with neuronal marker MAP2.

Markers used to characterize differentiated SH-SY5Y

- MAP2: Microtubule-Associated Protein 2
- SYP: Synaptophysin
- ID1: Inhibitor of DNA binding 1

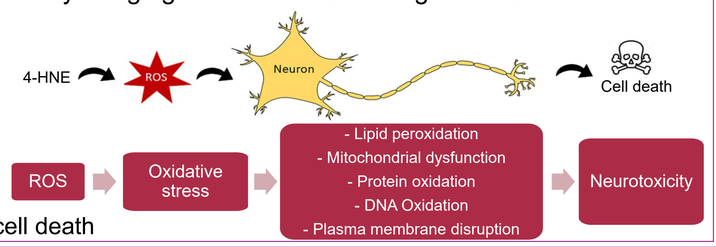


Figure 2. Role of oxidative stress in neuronal cell death

RESULTS

Characterization of SH-SY5Y cells

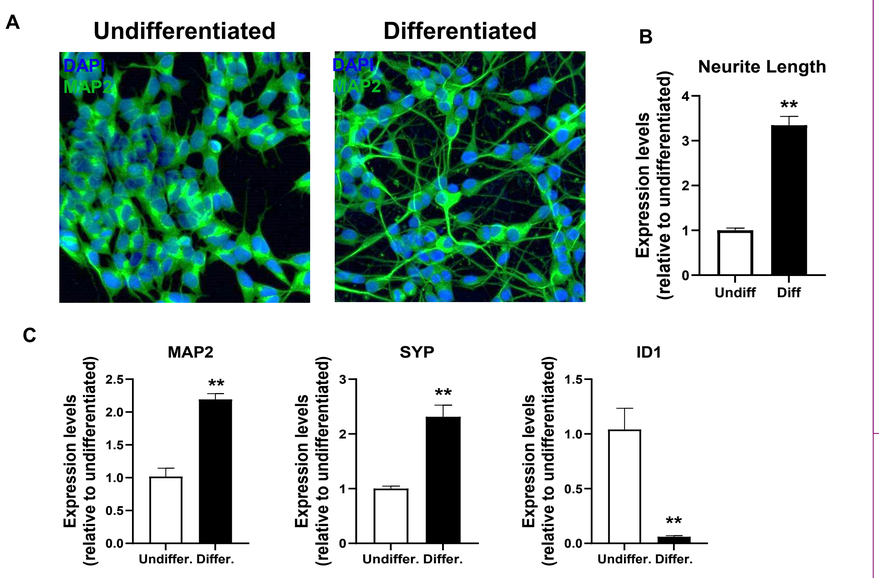


Figure 3. Characterization of SH-SY5Y cells after differentiation (A) Representative images of nuclear (DAPI, blue) and neuron (MAP2) stains via immunofluorescence (B) neurite length of cells (MAP2+) quantified after imaging and (C) mRNA levels of differentiation (SYP, ID1) and neuronal (MAP2) markers. N=3; Data shown as mean ± SEM, significance determined by one-way ANOVA ** p≤0.01.

The S2R modulator CT1812 protects against cell death but not PRE084, a S1R-selective modulator

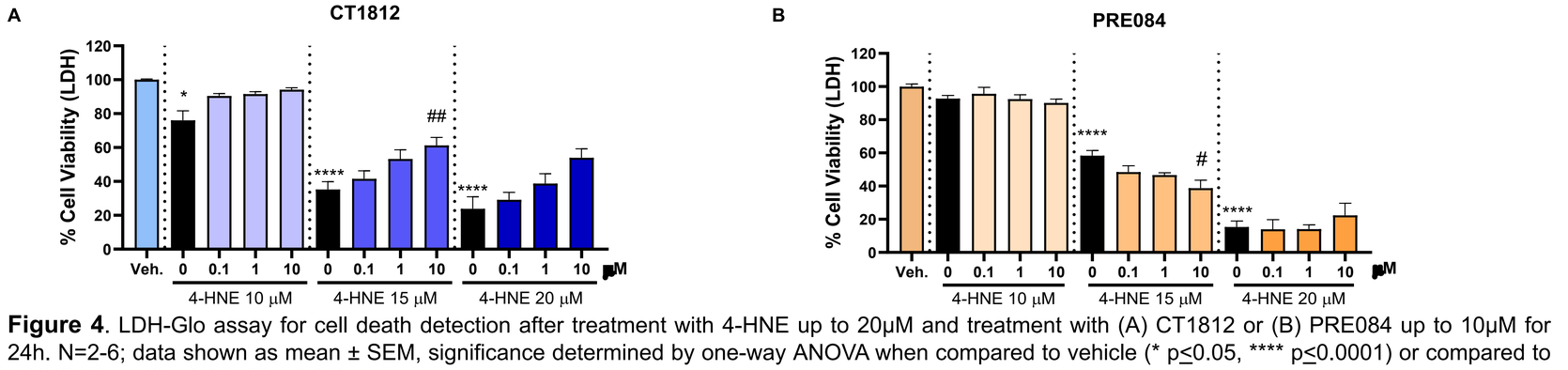


Figure 4. LDH-Glo assay for cell death detection after treatment with 4-HNE up to 20μM and treatment with (A) CT1812 or (B) PRE084 up to 10μM for 24h. N=2-6; data shown as mean ± SEM, significance determined by one-way ANOVA when compared to vehicle (* p≤0.05, **** p≤0.0001) or compared to 4-HNE alone (#p≤0.05, ##p≤0.01).

CT1812 preserves neurite length after oxidative stress

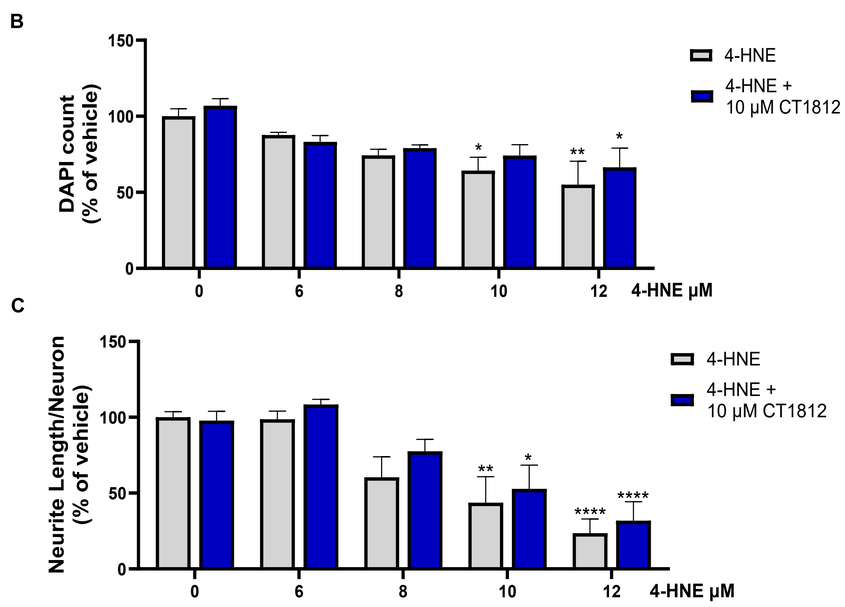


Figure 5. 8h treatment with 4-HNE shows greatest change in morphology with recovery of neurite lengths with CT1812 treatment (A) Representative images of nuclear (DAPI, blue) and neuron (MAP2, green) stains via immunofluorescence after treatment with 4-HNE +/- 10μM CT1812. Red arrows indicate loss of neurites; green arrows indicate presence of healthy neurites. (B) Nuclear count (DAPI+) and (C) neurite length per neuron (MAP2+) quantified after imaging, with IC50=7.6μM 4-HNE and IC50=8.6μM 4-HNE + CT1812. N=2; Data shown as mean ± SEM, significance determined by two-way ANOVA compared to vehicle * p≤0.05, ** p≤0.01, **** p≤0.0001.

NfL levels preserved by CT1812

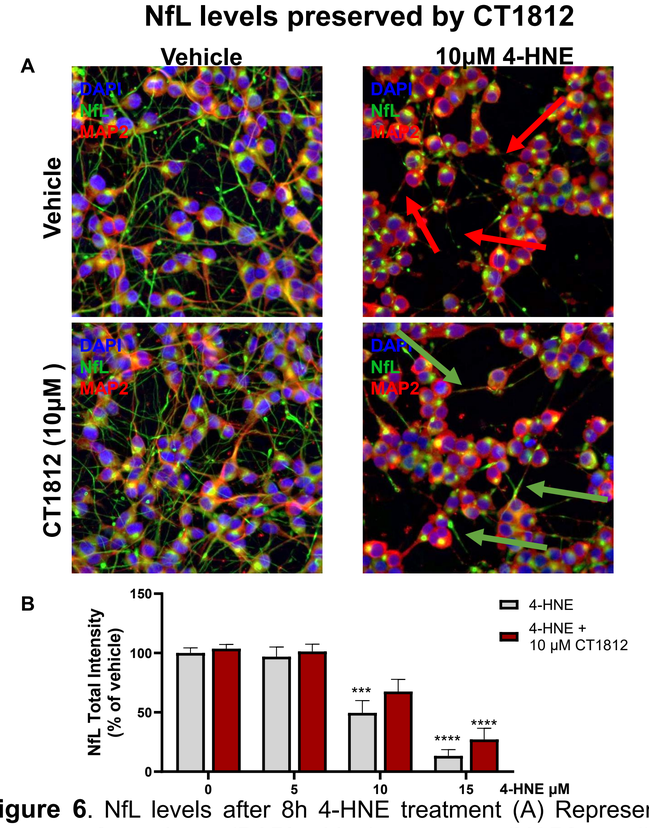
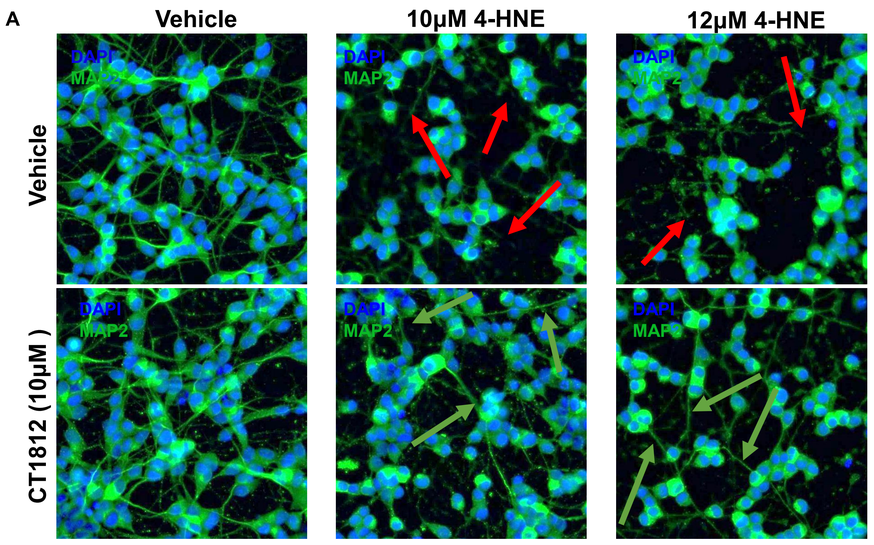


Figure 6. NfL levels after 8h 4-HNE treatment (A) Representative images of nuclear (DAPI, blue), neuron (MAP2, red) and neurofilament light (NfL, green) via immunofluorescence. Red arrows indicate loss of NfL, green arrows indicate presence of NfL (B) Quantification of intensity of NfL with IC50=10.1μM 4-HNE and IC50=13.1μM 4-HNE + CT1812. N=3; Data shown as mean ± SEM, significance determined by two-way ANOVA compared to vehicle *** p<0.001, **** p<0.0001.



CONCLUSIONS

- **CT1812 is neuroprotective as assessed by cell viability and morphology in disease-relevant conditions where oxidative stress is present**
- **The S2R modulator CT1812, but not a S1R modulator, preserves cell viability, supporting S2R-pathway as a promising therapeutic target for AD and DLB**
- **Preliminary data show that CT1812 preserves NfL levels, supporting clinical biomarker data that CT1812 plays a protective role in preventing neurodegeneration.**
- **In addition to protecting neurons from the toxicity of oligomers, these data demonstrate that CT1812 can also protect neurons from oxidative damage and support its continued clinical development for AD and DLB.**

Other Posters on CT1812 by Cognition Therapeutics

Poster 2550: The sigma-2 receptor modulator and investigational therapeutic CT1812 is neuroprotective against 4-HNE-induced cell death in a disease-relevant neuronal model. Eunah Cho, PhD, Jill K Thiel, Anthony O Caggiano, MD, PhD, Valentina Di Caro, PhD, Mary E Hamby, PhD

Poster 1507: Sigma-2 receptor modulators including CT1812 modulate low-density lipoprotein uptake in primary rat neurons. Nicole Knezovich, Jill K Thiel, Britney N Lizama, PhD, Aidan Reaver, Anthony O Caggiano, MD, PhD, Valentina Di Caro, PhD, Mary E Hamby, PhD

References:
1. Izzo et al. (2014) Alzheimer's therapeutics targeting Amyloid Beta 1–42 oligomers I: Abeta 42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits (doi:10.1371/journal.pone.0111898)
2. Izzo et al. (2014) Alzheimer's therapeutics targeting Amyloid Beta 1–42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity (doi:10.1371/journal.pone.0111899)
3. Lizama et al., (2025) Sigma-2 receptor modulator CT1812 alters key pathways and rescues retinal pigment epithelium (RPE) functional deficits associated with dry age-related macular degeneration (AMD) (doi: 10.1038/s41598-025-87921-9)

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