# Brain transcriptomic and proteomic analyses in an *in vivo* AD model further elucidate the role of the sigma-2 receptor modulator CT1812 in Alzheimer's disease

#P1-1008

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CT1812 is a first in class small molecule sigma-2 receptor (S2R) modulator, currently in Phase II clinical trials[1] for Alzheimer's disease (AD), that selectively displaces Aβ oligomers from synapses[2]. CT1812 prevents synaptotoxicity and restores cognitive performance in a transgenic mouse model of AD[3]. To better understand and identify the biological process that S2R modulators can impact, we performed transcriptomic and proteomic analysis in brain from an *in vivo* mouse model of AD treated with our leading investigational therapeutic CT1812.

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## ACKNOWLEDGE

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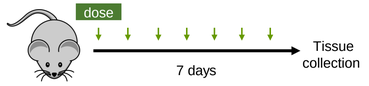
## REFERENCES

1. Clinical trials NCT04735536, NCT03507790, NCT05531656
2. Izzo NJ et al., Alzheimer's Dement. 2021 Aug;17(8):1365-1382;
3. Izzo NJ et al., PLoS One. 2014 Nov 12;9(11):e111898

Five-month-old non-transgenic mice (nTg) were treated with vehicle and transgenic hAPPsl mice were dosed with vehicle and/or CT1812 (10 mg/kg) given orally, once daily for 7 days. Animals were sacrificed 24 hr after last dose, and hippocampi collected.

## Study design:




| Group | Genotype | Test Article | Dose (mg/kg) | Schedule | Route | Number animals |
|---|---|---|---|---|---|---|
| A | nTg | Vehicle | NA | Once daily for 7 days | Oral | 10 (m) |
| B | hAPPsl (Tg) | Vehicle | NA | Once daily for 7 days | Oral | 10 (m) |
| C | hAPPsl (Tg) | CT1812 | 10 | Once daily for 7 days | Oral | 10 (m) |

Unbiased RNA-Sequencing and tandem-mass tag mass spectrometry proteomic measurements and analyses were performed of mouse hippocampus to evaluate differential expression between transgenic (Tg) and non-transgenic (nTg) mice, and to assess effect of CT1812 compared to vehicle. STRING and MetaCore pathway analyses were performed on both RNA-Seq and proteomics analysis using gene lists of p≤0.05.

## Total Differentially Expressed Genes in Proteomics and Transcriptomics Analyses

A Transcriptomics

| Condition | # DEGs (p≤0.05) | # DEGs up regulated | # DEGs down regulated |
|---|---|---|---|
| Tg vs nTg | **909** | 368 | 541 |
| CT1812 vs vehicle | **2031** | 1101 | 930 |

B Proteomics

| Condition | # DEGs (p≤0.05) | # DEGs up regulated | # DEGs down regulated |
|---|---|---|---|
| Tg vs nTg | **1715** | 859 | 856 |
| CT1812 vs vehicle | **219** | 105 | 114 |

**Table 1**: Summary of differentially expressed genes (DEGs) in each treatment conditions in A) transcriptomics and B) proteomics analyses.

## CT1812 Treatment Impacts the Transcriptomic and Proteomic Profiles of Treated Animals

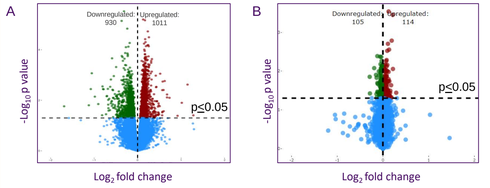



**Figure 1**: Volcano plots to visualize the global A) transcriptomic and B) proteomic change after treatment with CT1812. Each data point in the scatter plot represents a gene. Green dots and red dots represent down- and upregulated protein, respectively; p≤0.05.

## S2R Modulator CT1812 Alters Pathways Related to AD Pathology

A

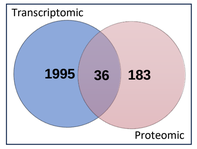
| # | Top Transcriptomic Pathways (CT1812 vs vehicle; p≤0.05) | p-value |
|---|---|---|
| 1 | Transport Clathrin-coated vesicle cycle | 1.42E-09 |
| 2 | Cell cycle Influence of Ras and Rho proteins on G1/S Transition | 9.43E-08 |
| 3 | Cytoskeleton remodeling CDC42 in cellular processes | 5.30E-07 |
| 4 | Transport_RAB1A regulation pathway | 4.22E-05 |
| 5 | Neurophysiological process _Visual perception | 4.98E-05 |

B

| # | Top Proteomic Pathways (CT1812 vs vehicle; p≤0.05) | p-value |
|---|---|---|
| 1 | Development Negative regulation of WNT/Beta-catenin signaling in the cytoplasm | 5.10E-03 |
| 2 | DNA damage ATR activation by DNA damage | 1.05E-02 |
| 4 | Transport Clathrin-coated vesicle cycle | 2.29E-02 |
| 5 | Putative pathways of activation of classical complement system in major depressive disorder | 2.37E-02 |
| 9 | Cytoskeleton remodeling RalA regulation pathway | 2.70E-02 |

**Table 2**: Metacore pathway analysis (v. 23.1.71200) of transcriptomic (A) and proteomic (B) data. Pathways identified in non-relevant disease pathologies/organs were excluded from Top 5 pathways.

## CT1812 Alters the Expression of 36 Genes at both mRNA and Protein Level




| Common Gene list | | | |
|---|---|---|---|
| Zfp91 | Lrrc40 | Naa15 | Dld |
| Ints12 | **Lamtor3** | Lmtk3 | Gdpd1 |
| Trmt61a | Zfand6 | Tfe3 | Rap1b |
| Impact | Ppp4r3b | Tada1 | **Opa1** |
| Hsd17b12 | Glt1d1 | Pex6 | Ipo7 |
| Ociad1 | Adck5 | Mical2 | Hnrnpa0 |
| Ccdc47 | Fscn1 | Git2 | Ndufb7 |
| **Rab8b** | Clcn2 | Ercc2 | Cdc42bpb |
| Nr1d1 | Rai1 | Incenp | Ddx39b |

**Figure 2**: Common proteins differentially expressed (p≤0.05) at the transcript and protein level include **Rab8b, Lamtor3**, and **Opa1** in response to CT1812 treatment, all of which are associated with **AD phenotype**.

## Proteins Showing a Normalization Towards Healthy nTg Control

| Comparison between groups | | |
|---|---|---|
| Gene name | Tg vs nTg | CT1812 vs vehicle |
| Rai1 | ↓ | ↑ |
| Mical2 | ↓ | ↑ |
| Ccdc47 | ↑ | ↓ |
| Dld | ↑ | ↓ |
| Gdpd1 | ↑ | ↓ |
| Naa15 | ↑ | ↓ |
| Ociad1 | ↑ | ↓ |
| Opa1 | ↑ | ↓ |

↓ Protein down regulated
↑ Protein up regulated

**Table 3:** Proteins showing an aberrant expression in the Tg vs nTg that are regulated in the opposing direction by CT1812 may underling a possible regulatory activity of CT1812 (red, increased log2 fold change; blue, decreased log2 fold change; p≤0.05) .

## CONCLUSION

- Collectively, findings in this mouse model show that S2R modulator CT1812 regulates key mRNA transcripts and proteins relevant in AD;
- Biological pathways, including membrane trafficking, autophagy, inflammation, and WNT/β-catenin signaling are impacted by CT1812;
- A better understanding of modulated pathways will help us to further elucidate CT1812 mechanism of action in AD.

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