Dementia with Lewy Bodies

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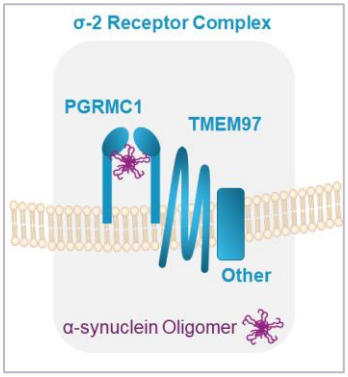
Dementia with Lewy bodies and related “synucleinopathies” (diseases characterized by a build-up and abnormal accumulation of α-synuclein aggregates) such as Parkinson’s disease and multiple system atrophy (MSA) are neurodegenerative disorders involving motor and cognitive dysfunction. Motor symptoms and anxiety associated with these diseases are addressed by currently available medications, but no disease-modifying treatments exist to address the cognitive deficits.



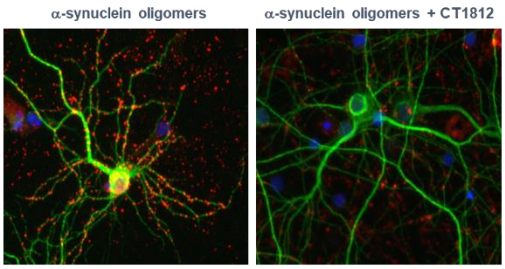
Synucleinopathies are characterized by an age-related build-up of α-synuclein oligomers and other stressors in the brain, which disrupt key cellular damage response processes, including autophagy, trafficking and lipid synthesis.[2,3,6,11] The sigma-2 (σ-2) receptor components, PGRMC1 and TMEM97, regulate these processes. Further, α-synuclein oligomers have been shown to bind directly to PGRMC1[1]. Compounds that bind to the σ-2 receptors and block α-synuclein binding / internalization therefore are expected to be disease-modifying.

Preclinical and Biomarker

Substantial cellular and clinical biomarker evidence demonstrate that Cognition’s σ-2 antagonists, including clinical drug candidate CT1812, have a beneficial impact on the pathways impaired in synucleinopathies:

1) Cognition antagonists block the binding / internalization of α-synuclein oligomers at synapses. See Figure 1 (right).
2) α-synuclein oligomers cause a reduction in membrane trafficking rate. This activity is normalized by Cognition’s antagonists.[9] See Figure 2 A (below).
3) α-synuclein oligomers cause upregulation of autophagy receptor, LAMP2a[5]. This upregulation is blocked by Cognition’s antagonists.[9] See Figure 2 B (below).
4) In a Phase 2 study of a σ-2 candidate in Alzheimer’s disease patients, several biomarkers that are implicated in α-synuclein pathology in Parkinson’s and related diseases moved in a therapeutic direction.

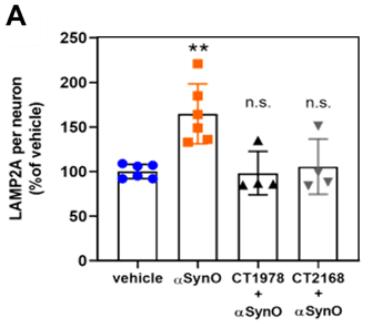
Figure 1



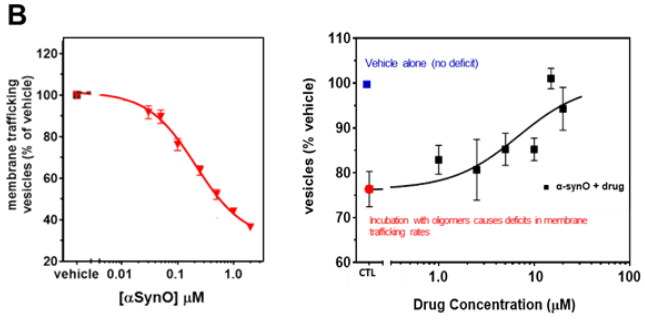
α-Synuclein oligomers in red

Cognition compounds block α-synuclein oligomer binding / internalization

Figure 2



Cognition compounds (black and gray) reverse the effect of α-synuclein oligomers on LAMP2a (orange)



α-synuclein oligomer-induced trafficking deficits (red) are reversed by Cognition drug (black)

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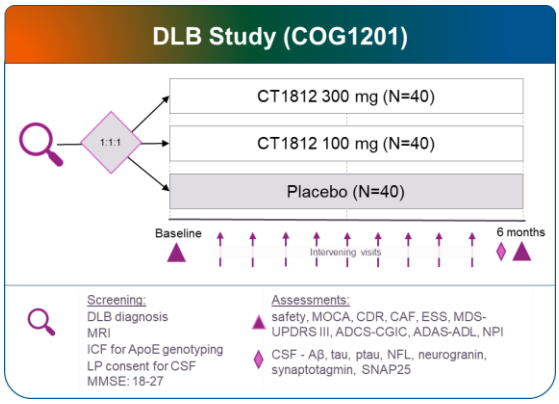
Next Steps

Cognition plans to initiate a Phase 2 clinical trial evaluating the use of CT1812, the company's selective σ-2 modulator, to treat patients diagnosed with DLB. Subject to discussion with the FDA, this study is expected to commence in 2H 2021.

The design of this study is anticipated to be a double-blind, randomized trial involving three dose groups, two active treatment cohorts and a placebo group. We expect to enroll 120 patients in a six-month study, with equal participant numbers in each of the three dose groups, with daily (QD) dosing.



Eligibility requirements will include individuals between 50 and 80 years of age that have received a diagnosis of DLB and have a mini-mental state exam, or MMSE, score of between 18 and 27. Proposed clinical endpoints of the trial include safety and physical activity measurements, cognitive assessments, and PK and pharmacodynamic biomarker analyses compared to baseline measurements recorded at the beginning of the trial. In addition, CSF will be collected and analyzed for α-synuclein content and established patterns of differential protein expression.

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