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Autologous non-genetically modified NK Cells (troculeucel) shows high expression of receptors involved in modulating neuroinflammation and cell migration, shows increased cytotoxicity against activated T cells, migrates towards CSF, and degrades A $\beta$  and  $\alpha$ -synuclein aggregates *in vitro*, and after 3 months treatment of AD patients shows stable or improved ADCOMS scores in 92% of subjects, with improved levels of CSF AD biomarkers for neuroinflammation and protein aggregates.

## PURPOSE & OBJECTIVE

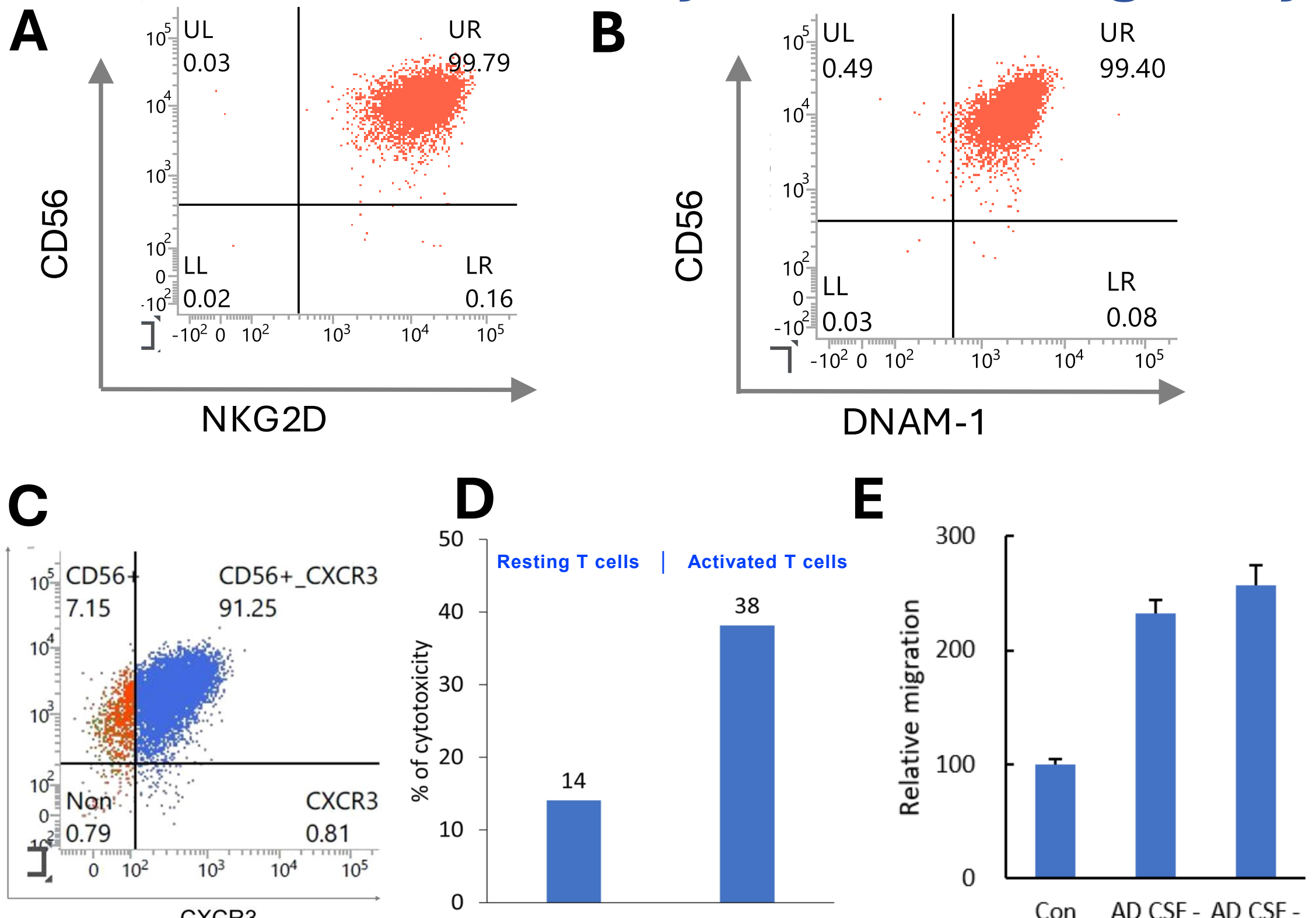
- In AD, chronic deposition of misfolded products such as amyloid- $\beta$  (A $\beta$ ) and  $\alpha$ -synuclein contributes to an **autoinflammatory cascade** involving pathogenic activation of autoreactive T cells which cross the blood-brain-barrier via CXCR3 expression.
- Natural Killer (NK) cells**, members of the innate immune system, have been described to efficiently internalize and **degrade  $\alpha$ -synuclein aggregates** and to selectively **eliminate autoreactive T cells and damaged neurons** via **NKG2D** and **DNAM-1** expression.
- We have developed an **autologous non-genetically modified NK cell product (troculeucel)** with enhanced cytotoxic activity and over 90% activating receptor expression.
- We hypothesize that troculeucel is safe and can impact protein accumulation and neuroinflammation in AD patients, hence improving cognition.

## METHODS

In vitro studies were performed to evaluate troculeucel's receptor expression profile, cytotoxicity against activated T cells, migratory potential towards CSF, and capacity to eliminate amyloid and  $\alpha$ -synuclein aggregates. Additionally, troculeucel was administered to 13 patients in two Phase I trials (NCT04678453 and NCT06189963). The primary endpoint was safety while secondary endpoints included changes in cognitive assessment and CSF biomarkers.

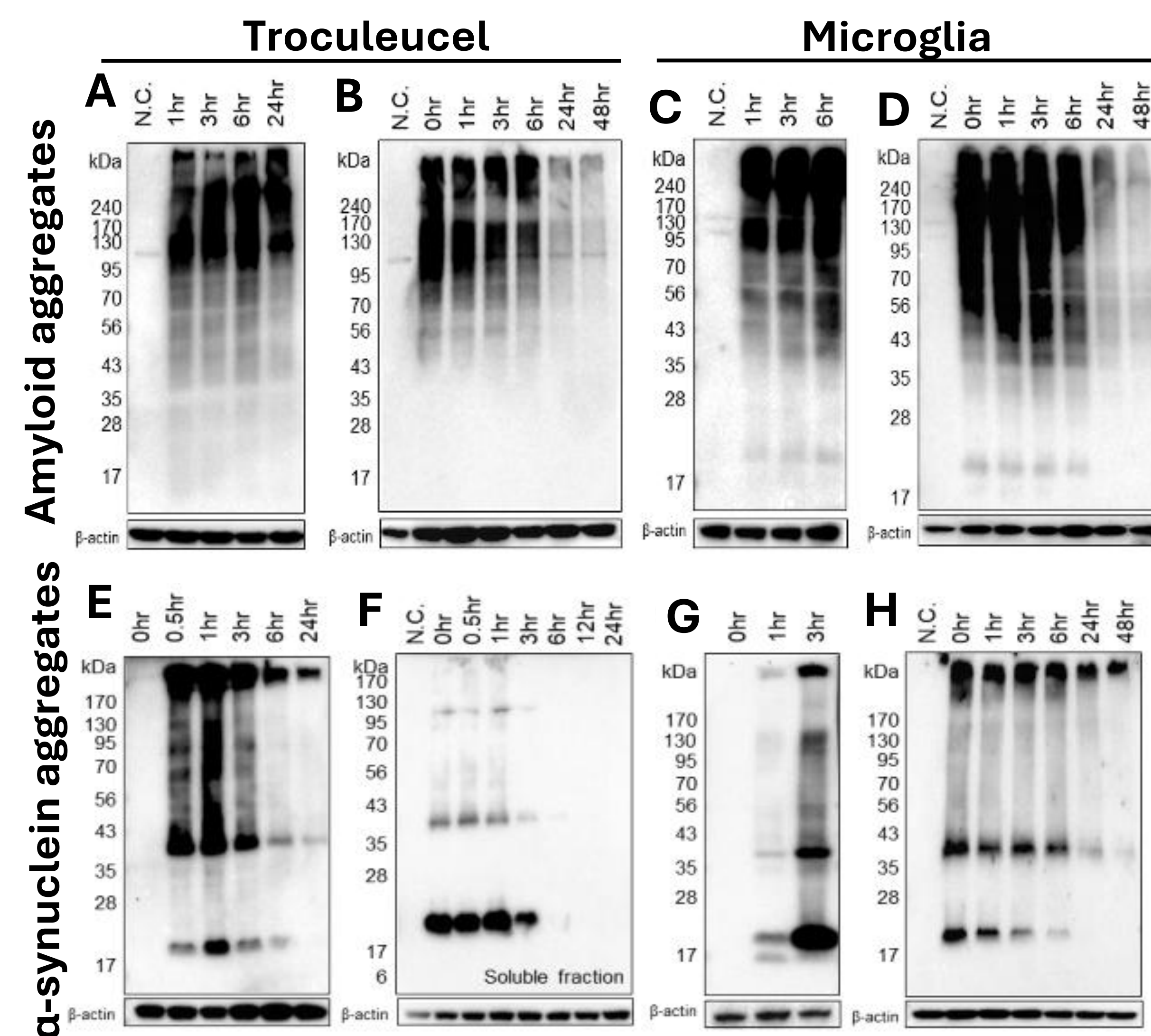
## PRE-CLINICAL RESULTS

### Troculeucel is active, cytotoxic and migratory



**Fig. 1:** Troculeucel exhibited high NKG2D (A), DNAM-1 (B) and CXCR3 expression (C), showed increased cytotoxicity in the presence of activated T-cells as compared to resting T cells (D), and showed increased migration towards CSF of AD patients (E).

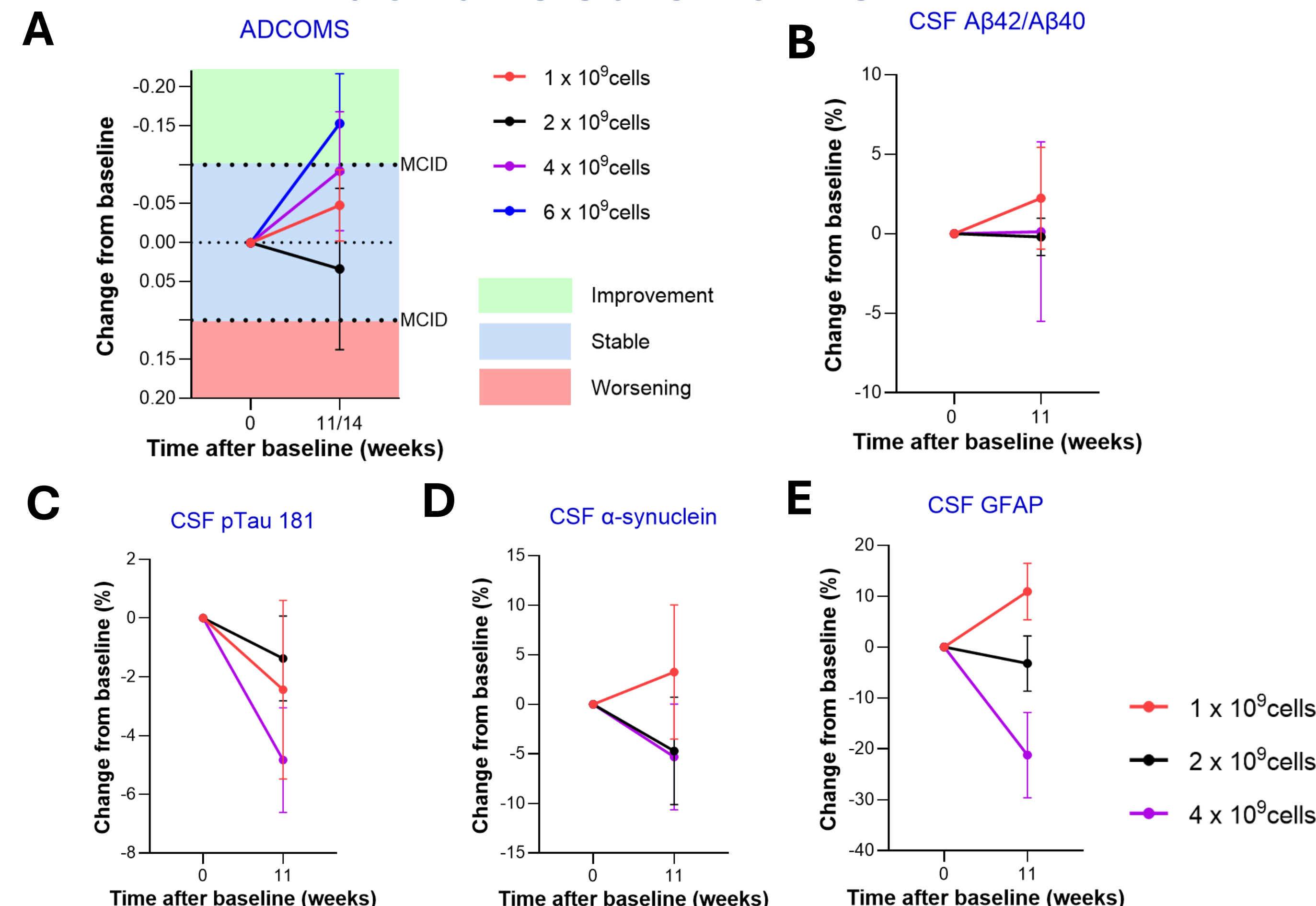
## Troculeucel degrades A $\beta$ and $\alpha$ -synuclein



**Fig. 2:** Troculeucel internalizes (A) and degrades (B) A $\beta$  as well as  $\alpha$ -syn (E, F) aggregates similarly to brain microglial cell line HMC3 (C, D for A $\beta$  and G, H for  $\alpha$ -syn).

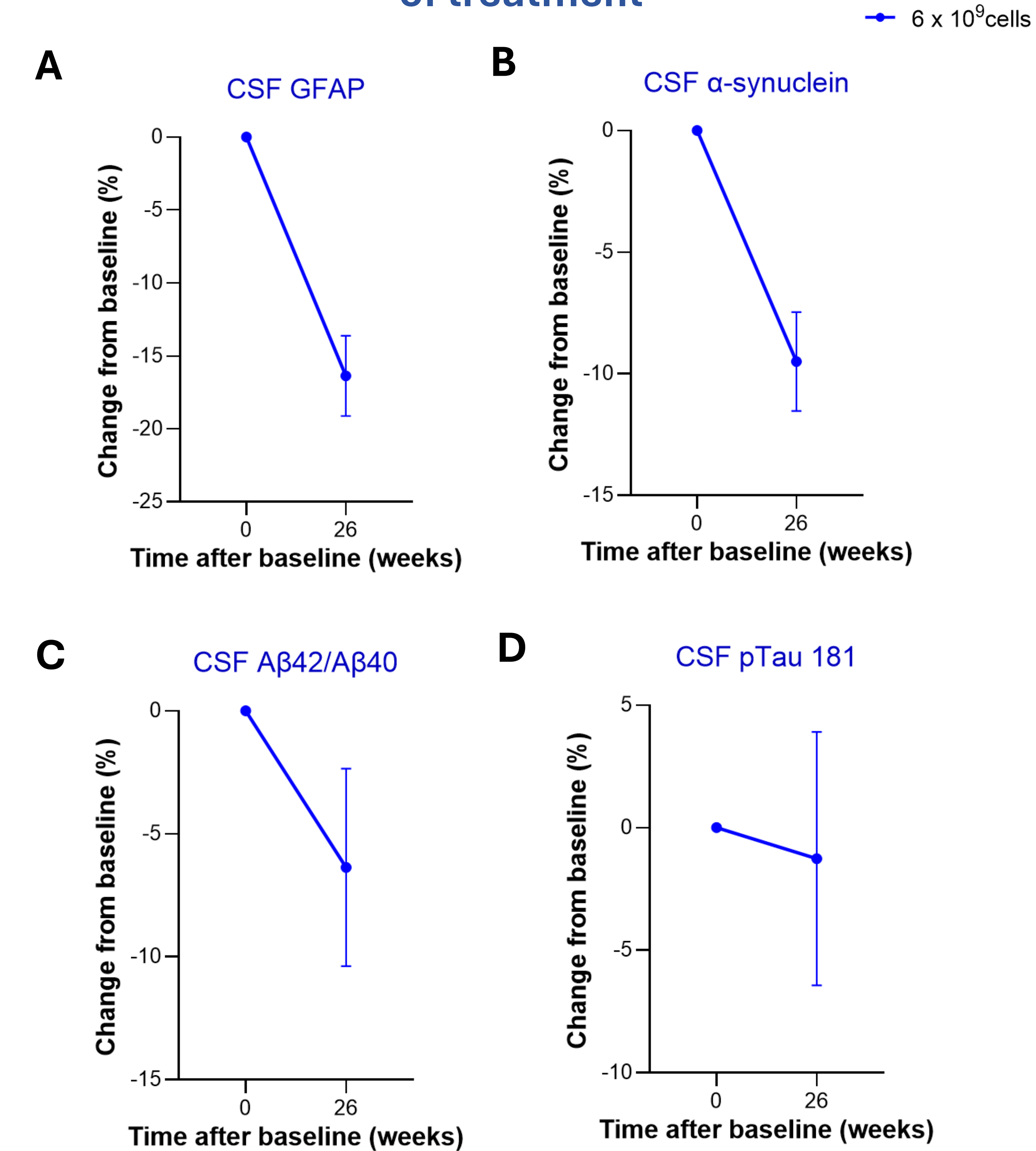
## CLINICAL RESULTS

### Troculeucel stabilizes/improves cognition as well as CSF biomarkers at 3 months



**Fig. 3:** Despite 60% of subjects being treated at relatively low doses of troculeucel, 92% of all evaluable subjects (12/13) had either stable or improved ADCOMS scores at 3 months (A). In patients treated for 3 months only (n=10), tested CSF biomarkers were stabilized or improved: A $\beta$ 42/40 in 60% of patients (B), pTau181 in 90% (C),  $\alpha$ -synuclein in 70% (D), and GFAP in 60% (E). MCID: Minimal Clinically Important Difference

## Troculeucel improves CSF biomarkers after 6 months of treatment



**Fig. 4:** After 6 months of treatment, CSF GFAP and  $\alpha$ -syn levels are decreased in all patients (n=3) treated with the highest dose (A, B). Effects on A $\beta$ 42/40 and pTau 181 are more mitigated and warrant further exploration to confirm mechanism of action (C, D).

## CONCLUSIONS

- Troculeucel shows high expression of receptors involved in modulating neuroinflammation and cell migration, shows increased cytotoxicity against activated T cells, migrates towards the CSF, and degrades A $\beta$  and  $\alpha$ -synuclein aggregates *in vitro*.
- Troculeucel therapy for 3 months in AD patients is safe and stabilizes or improves cognition in most patients.
- We propose that troculeucel crosses the blood-brain-barrier via CXCR3 expression and modulates inflammation as well as protein aggregation in patients. This is supported by high NKG2D, DNAM-1 and CXCR3 expression, and consistently decreased CSF GFAP and  $\alpha$ -synuclein levels at 3 and 6 months of treatment

## CONTACT

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