MicroRNA Changes in the NurOwn® Phase 2 ALS Randomized Clinical Trial: Relationship to Neuroprotection and Innate Immunity

James Berry[2], Revital Aricha[1], Haggai Kaspi[1], Merit Cudkowicz[2], Anthony Windebank[3], Nathan Staff[3], Margaret Ayo Owegi[4], Yossef S. Levy[1], Chaim Lebovits[1], Robert Brown[4], Yael Gothelf[1], Ralph Kern[1]

1. BrainStorm Cell Therapeutics, Petach Tikva, Israel. 2. Massachusetts General Hospital , Boston, MA, USA. 3. Mayo Clinic, Rochester, MN, USA. 4. UMass Medical School, Worcester, MA, USA

Background

MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) induced to secrete high levels of neurotrophic factors (NTFs). miRNAs are small non-coding RNAs that regulate a wide variety of biological processes via RNA-dependent post-transcriptional silencing mechanisms. MSC-NTF cells were administered by a single intrathecal injection to ALS patients in a US Phase 2 multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT02017912).

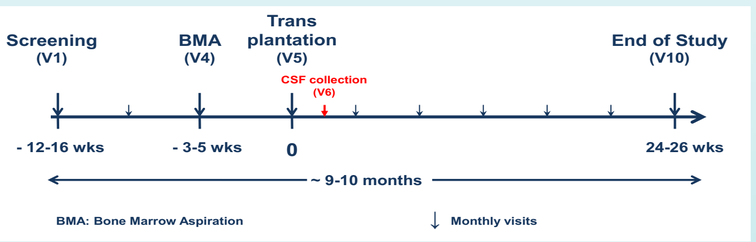
Objective

To relate CSF miRNA changes to CSF biomarkers of apoptosis and innate immunity pre- and 2 weeks post-intrathecal transplantation of NurOwn® in the Phase 2 placebo-controlled trial.

Design/Methods

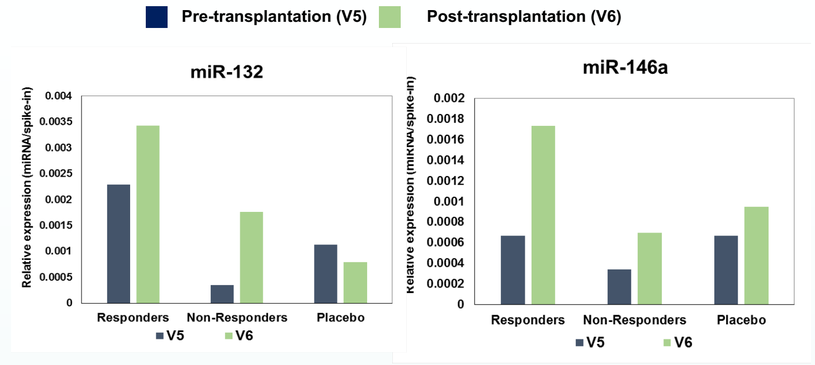
CSF was collected prior to, and two weeks after intrathecal MSC-NTF cells transplantation. miRNAs were analyzed in CSF pools of three homogeneous groups: a) responders; b) non-responders as determined by the ALSFRS-R score and c) placebo patients. Levels of Caspase 3, MCP-1, SDF-1 and Chitotriosidase (CHIT)-1 in CSF from each patient was measured using the Exiqon platform.

Study Schematic

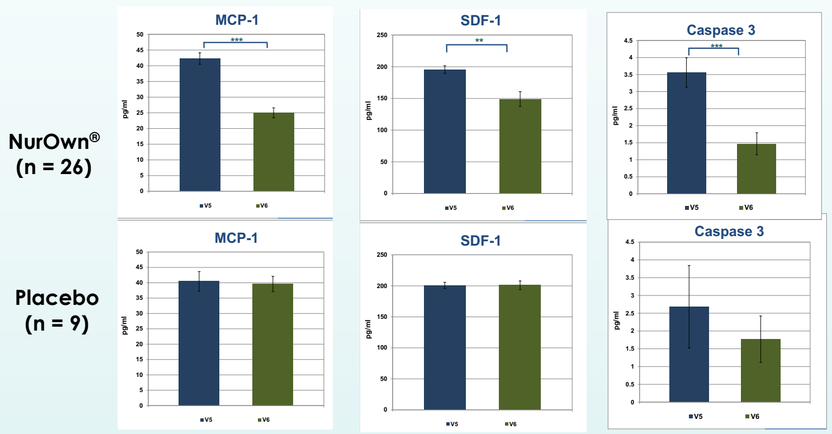


Results

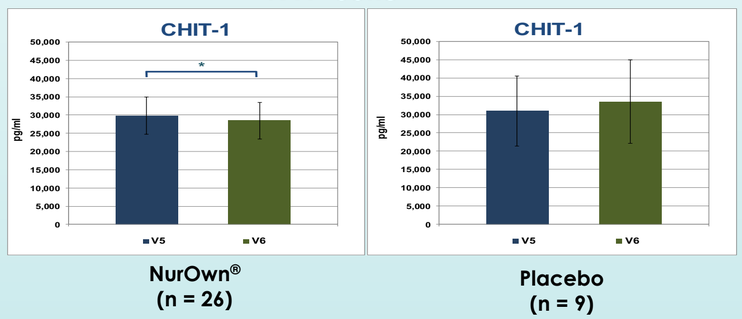
Increased CSF miR-132 and miR-146a after treatment with MSC-NTF cells



Decreased CSF inflammatory markers and Caspase-3 after treatment with MSC-NTF cells



Decreased CSF CHIT-1 after treatment with MSC-NTF cells



Mean ± SEM * p<0.03 ** p<0.01 *** p< 0.001

Pre-transplantation Post-transplantation

Discussion

- **miR-132** is known to positively modulate axon and dendrite development and maturation in response to various signals and may provide neuroprotection in tauopathies, through modulation of **caspase 3** activation[1].
- **miR-132** is downregulated in the CSF of sporadic, TARDBP, FUS and C9ORF72 ALS patients[2].
- **miR-146** is known to modulate innate immunity under neuroinflammatory conditions through effects on microglia[3], astrocytes[4], and Tregs[5].
- **miR-146** negatively regulates innate immunity and signal transduction linked to NF-kB activation[3].

Conclusions

- The biomarker data demonstrates **increases** in CSF miR-132 and miR-146a and statistically significant **decreases** in MCP-1, SDF-1, CHIT-1 and Caspase 3 in ALS phase 2 study participants 2 weeks following a single MSC-NTF cell transplantation.
- The observed miR modifications and corresponding CSF biomarker changes suggest that miR secreted by MSC-NTF cells may contribute to neuroprotection and immunomodulation.
- Additional miRNA and biomarker correlations will be examined in the ongoing NurOwn® Phase 3 ALS trial (NCT03280056).

1. Fatimy et al. Acta Neuropathologica, 2018.
2. Freischmidt et al. Acta Neurpathologica, 2013.
3. Saba et al. Front Immunology, 2014.
4. Iyer et al. PlosONE, 2012.
5. Li-Fan et al. Cell 2010.

Sponsored by BrainStorm Cell Therapeutics