AAN 2019 Emerging Science Data Blitz

MODULATION OF CSF CASPASE-3 IN MSC-NTF CELLS (NUROWN®) IN A PHASE 2 ALS STUDY: CORRELATIONS WITH CSF BIOMARKERS AND CLINICAL RESPONSE

Revital Aricha[1], Haggai Kaspi[1], Merit Cudkowicz[2], James Berry[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]**

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Dr. Ralph Kern is an employee of Brainstorm Cell Therapeutics

Phase 2 Study: CSF Biomarkers and Responder Analysis

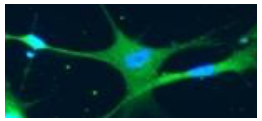
Study Design n=48 (3:1 randomization)

-12 to -16 weeks — Screening

~3-4 months

-3 to -5 weeks — BMA

CSF Collection (V5 and V6) — Week 0, Week 2 — IT/IM Transplantation

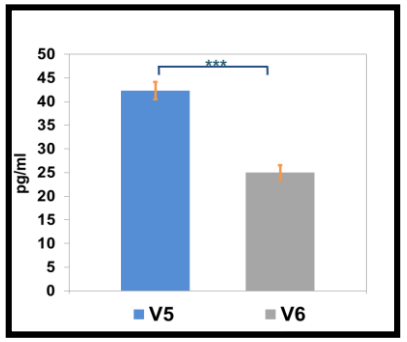


~ 6 months

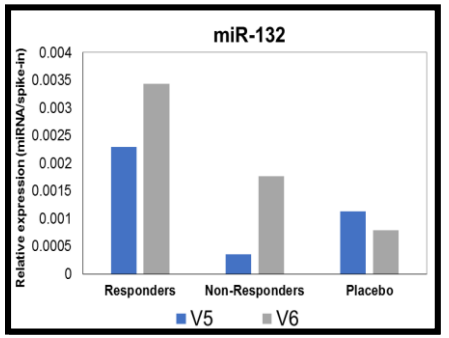
12 weeks

24 weeks — End of Study

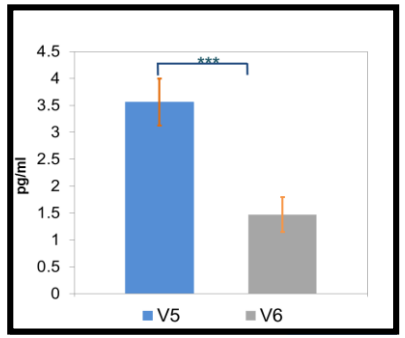
↓MCP-1



↑miR-132

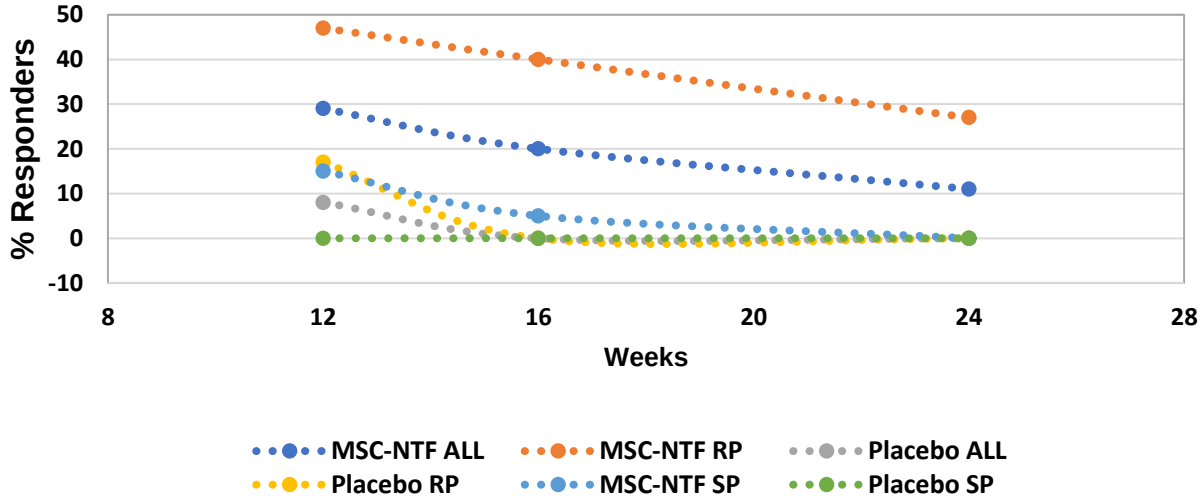


↓Caspase 3

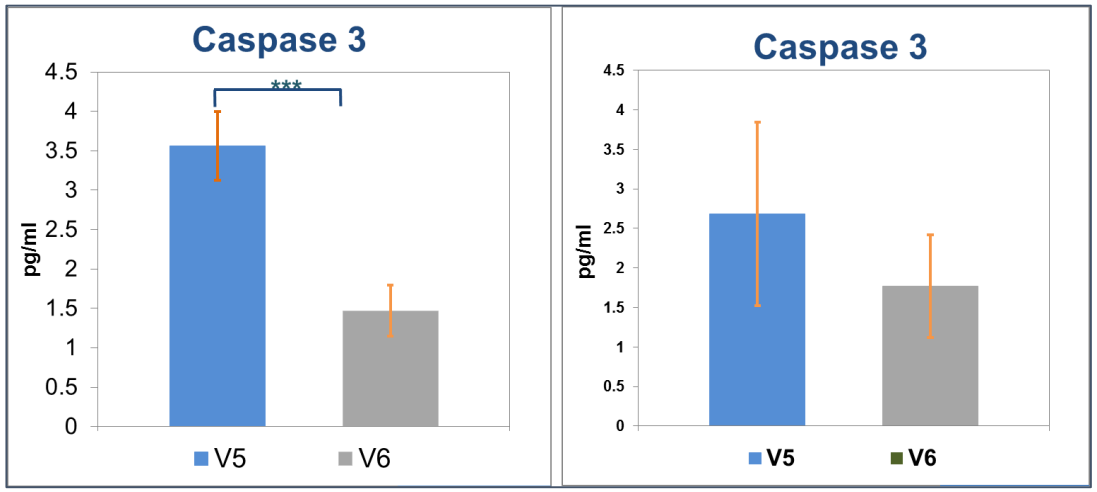


*** p< 0.001

Responder analysis: 100% ALSFRS-R slope improvement



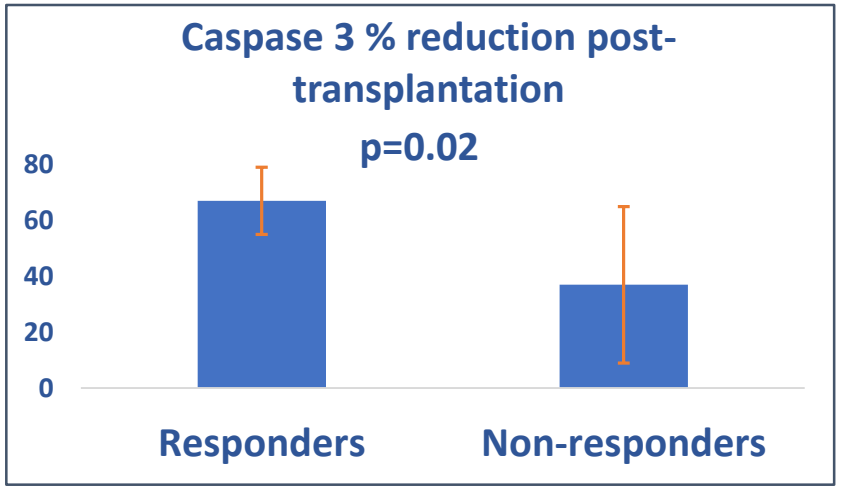
2X Greater CSF Caspase 3 % reduction in responders compared to non-responders at 12 weeks post-transplantation*



MSC-NTF cells

Placebo

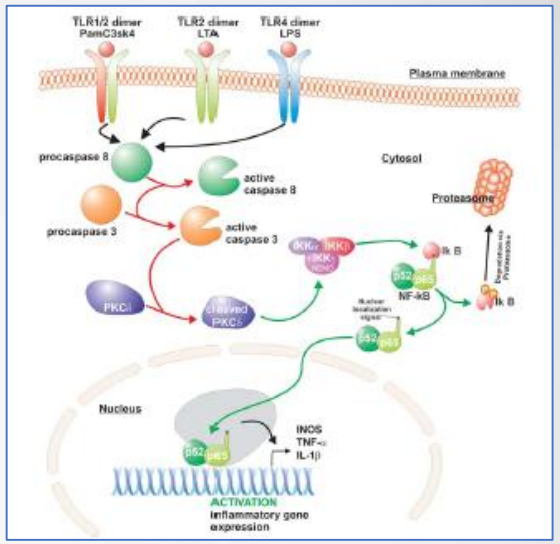
*** p< 0.001



*Responder defined as ≥100% ALSFRS-R slope improvement at 12 weeks

NurOwn® (MSC-NTF cells) may tip the balance linking neuronal cell death and neuroinflammation

Neuronal apoptosis activates neuroinflammation via NFκ-B



Cell Death and Differentiation (2011) 18, 1679–1691
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www.nature.com/cdd

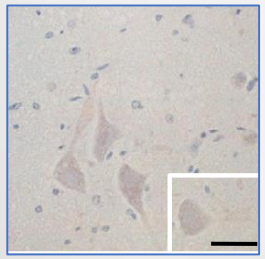
Review

The executioners sing a new song: killer caspases activate microglia

JL Venero[1], MA Burguillos[2,3], P Brundin[3] and B Joseph[*,2]

MSC-NTF Cell Neuroprotection

MSC-NTF Cell Immunomodulation



Functional Role of Caspase-1 and Caspase-3 in an ALS Transgenic Mouse Model

Mingwei Li,[1] Victor O. Ona,[1] Christelle Guégan,[2] Minghua Chen,[1] Vernice Jackson-Lewis,[2] L. John Andrews,[1] Adam J. Olszewski,[1] Philip E. Stieg,[1] Jean-Pyo. Lee,[4] Serge Przedborski,[2,3] Robert M. Friedlander[1]*

Cell Death and Differentiation 2011

Dahlke *et al. Journal of Neuroinflammation* (2015) 12:215

MODULATION OF CSF CASPASE-3 IN MSC-NTF CELLS (NUROWN®) IN A PHASE 2 ALS STUDY: CORRELATIONS WITH CSF BIOMARKERS AND CLINICAL RESPONSE

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1. BrainStorm Cell Therapeutics, Petach Tikva, Israel and New York, NY, United States 2. Massachusetts General Hospital, Boston, MA, United States 3. Mayo Clinic, Rochester, MN, United States 4. UMass Medical School, Worcester, MA, United States

brainstorm cell therapeutics

Background

MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) that secrete high levels of neurotrophic factors (NTFs) and immunomodulatory cytokines having a signature miRNAs profile. MSC-NTF cells were administered by the intrathecal (IT) route of administration to participants in a US Phase 2 ALS multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT02017912).

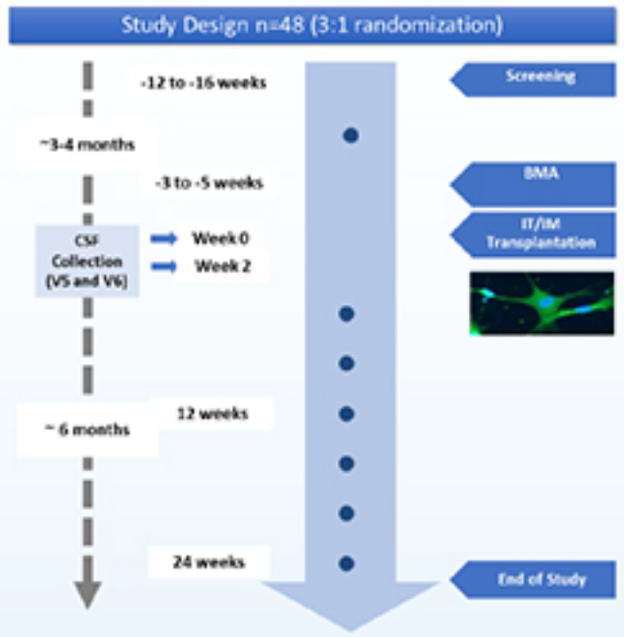
Objective

To measure CSF Caspase 3 levels pre- and post-single IT MSC-NTF cell transplantation and to correlate with clinical response and other CSF biomarkers.

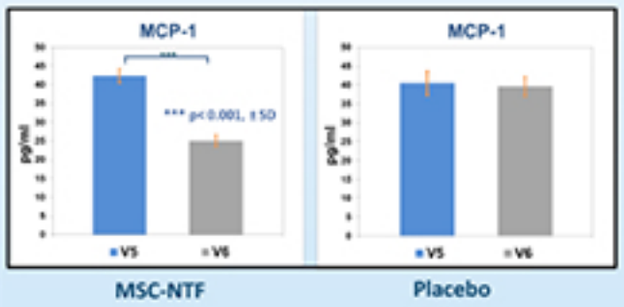
Methods

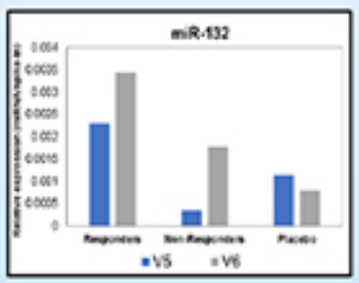
CSF was collected prior to, and two weeks post-IT MSC-NTF cell transplantation. CSF Caspase-3, NTFs, cytokines and miRNAs were analyzed. Caspase-3 reduction was evaluated in responders (≥100% improvement in ALSFRS-R slope 12-weeks post transplantation) and non-responders. miR were analyzed in pooled CSF samples from responders, non-responders and placebo.

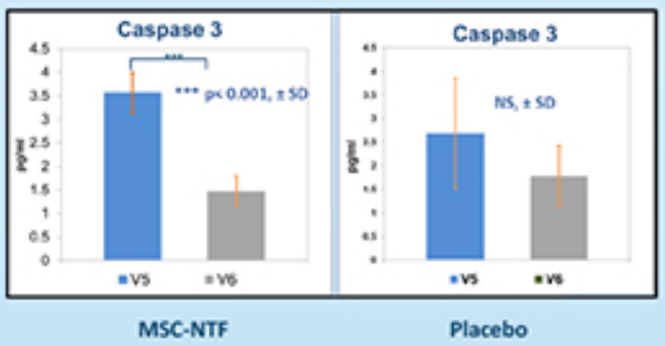
Results



CSF analysis pre-transplantation (V5) and two weeks post-transplantation (V6)

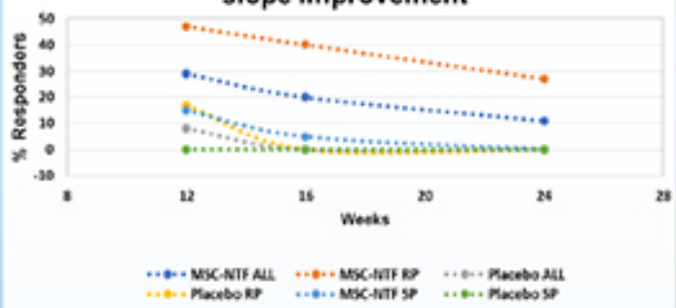






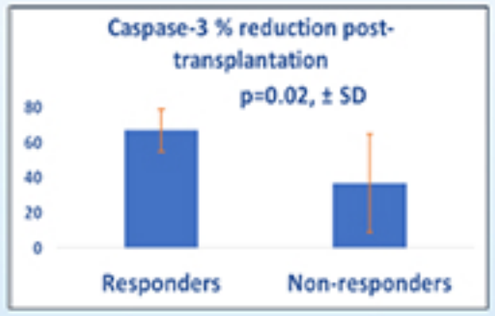
MCP-1 and Caspase 3 were significantly reduced post-transplantation in MSC-NTF treated participants and not in the placebo group. Expression of miR-132 was increased post - transplantation in MSC-NTF treated but not placebo participants.

Responder analysis: 100% ALSFRS-R slope improvement



The percentage of participants with a 100% improvement in their ALSFRS-R at the indicated time points in the treated (MSC-NTF) and the Placebo group total population (ALL), rapid progressors (RP) and slow progressors (SP).

Caspase-3 reduction was greater in responders compared to non-responders



Discussion

Decreased CSF Caspase-3 may reflect reduced neuronal apoptosis and serve as a biomarker for neuroprotection. While MSC-NTF cells may have anti-apoptotic effects through direct paracrine NTF mechanisms such as VEGF, it is possible that indirect effects may be mediated via immunomodulation and miR-132 secretion. Caspases are known to activate microglia via NF-kB signaling and miR-132 may regulate apoptotic genes. miR-132 appears to be lower in the CSF of sporadic ALS patients and TDP-43 is required for the biogenesis of miR-132. These findings support the combined immunomodulatory and neuroprotective mechanism of action of MSC-NTF cells through NTF, immunomodulatory and miRNA pathways.