

# MODULATION OF CSF miRNAs IN ALS PHASE 2 STUDY PARTICIPANTS TREATED WITH MSC-NTF CELLS (NUROWN®)

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# Objective

**To measure cell-secreted and ALS-related miRNA expression in the CSF pre- and post- single intrathecal MSC-NTF cell transplantation in a randomized phase 2 ALS study and to evaluate their correlation with treatment outcomes.**

# Background

- 48 study participants were randomly allocated (3:1) to receive a single dose of combined intrathecal and intramuscular autologous MSC-NTF cells (NurOwn<sup>®</sup>) or placebo
- A three month run-in period was followed by a single transplantation and participants were then followed for 6 months
- CSF was collected prior to, and two weeks after intrathecal MSC-NTF cells transplantation.
- CSF miRNAs in ALS rapid progressors were analyzed in pools of three homogeneous groups: responders (n=6, )\*; non-responders (n=9); and placebo (n=6) using the Exiqon platform.

\* $\geq 1.5$  point/month improvement ALSFRS-R slope

# **MSC-NTF cells express miRNA relevant to ALS**

- MicroRNAs (miRNAs) are short (20-24 nt) non-coding RNA sequences that regulate a wide variety of biological processes via RNA-dependent post-transcriptional silencing mechanisms**
- The miRNA profile of MSC-NTF cells is modified by the differentiation process**
- miRNAs such as miR-132 and miR-146, involved in immunomodulation and neuroprotection, are expressed by MSC-NTF cells**

# MSC-NTF cells have a unique miRNA signature

Gothelf *et al. Stem Cell Research & Therapy* \_#####\_  
DOI 10.1186/s13287-017-0692-1

Stem Cell Research & Therapy

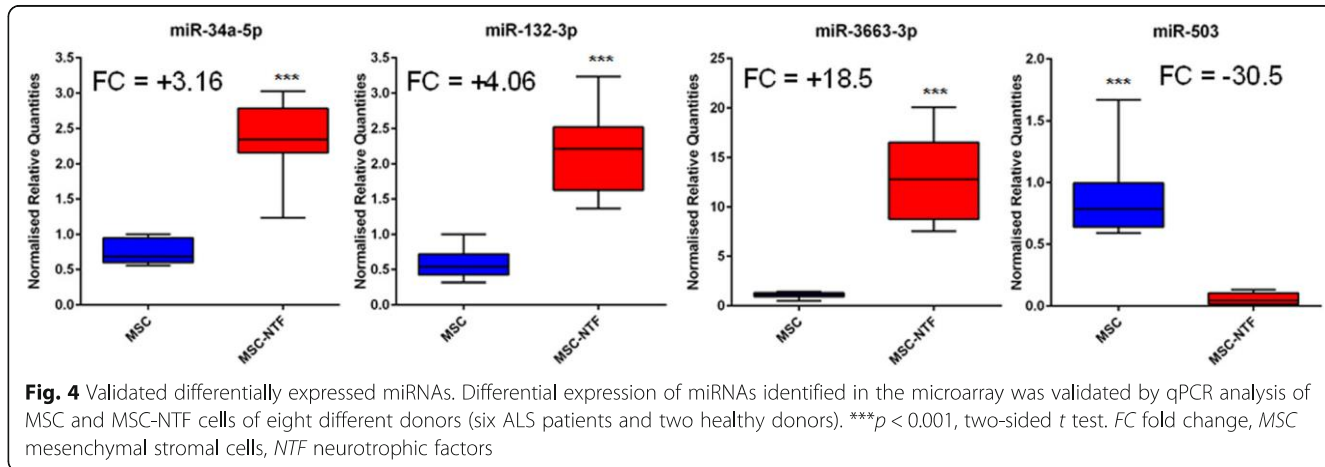
RESEARCH

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## miRNA profiling of NurOwn®: mesenchymal stem cells secreting neurotrophic factors



Yael Gothelf<sup>\*</sup>, Haggai Kaspi, Natalie Abramov and Revital Aricha



miR expressed by  
MSC-NTF cells

miR-19

miR-34a

miR-132

miR-146a-5p

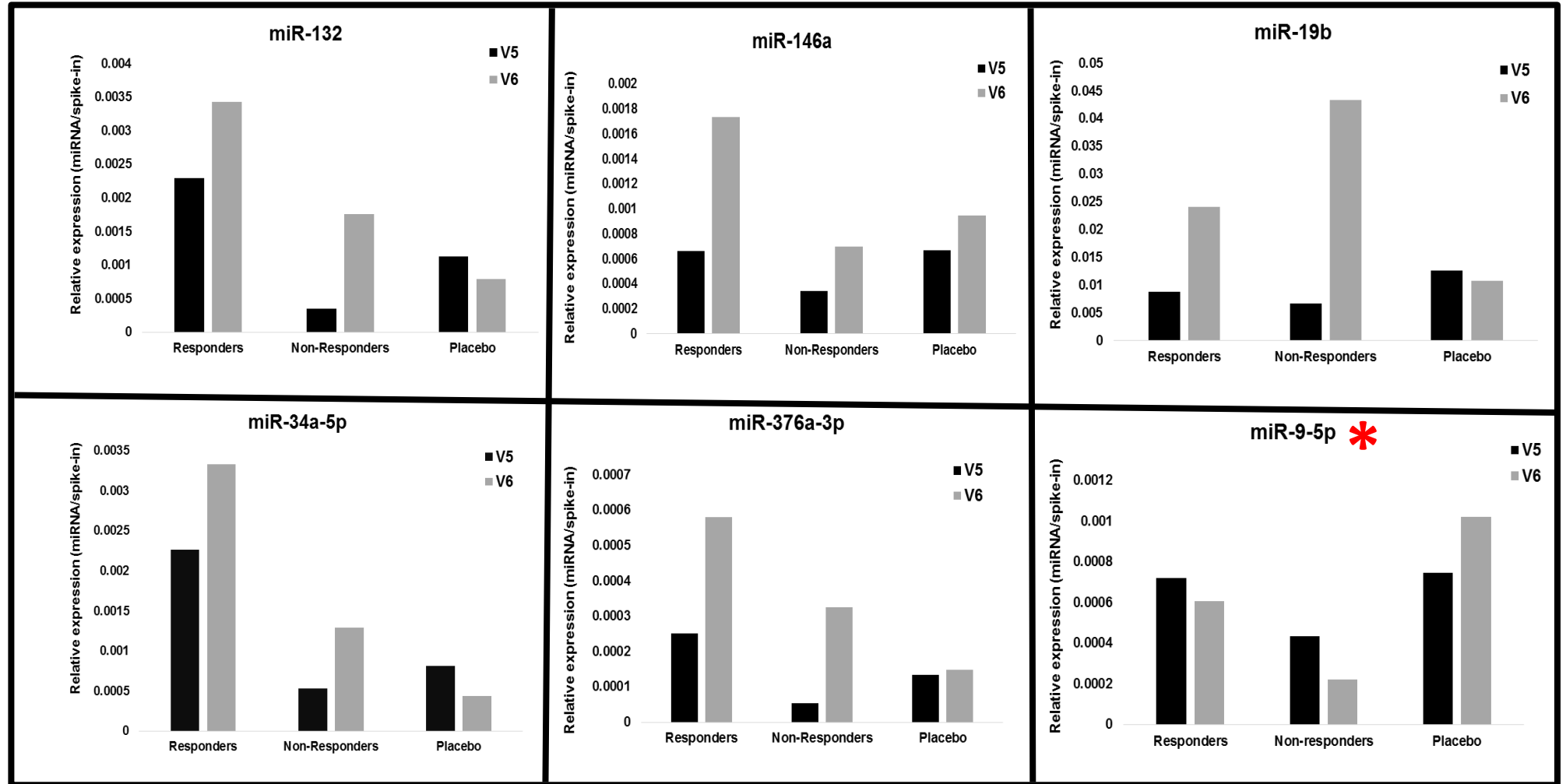
miR-376

# Post transplantation: MSC-NTF secreted miRNAs are elevated in treated but not placebo patients

Pre-transplant



Post-transplant



miR-9 is not expressed by MSC-NTF cells

# CSF miR responder analysis

Baseline miRNA lower in  
non-responders



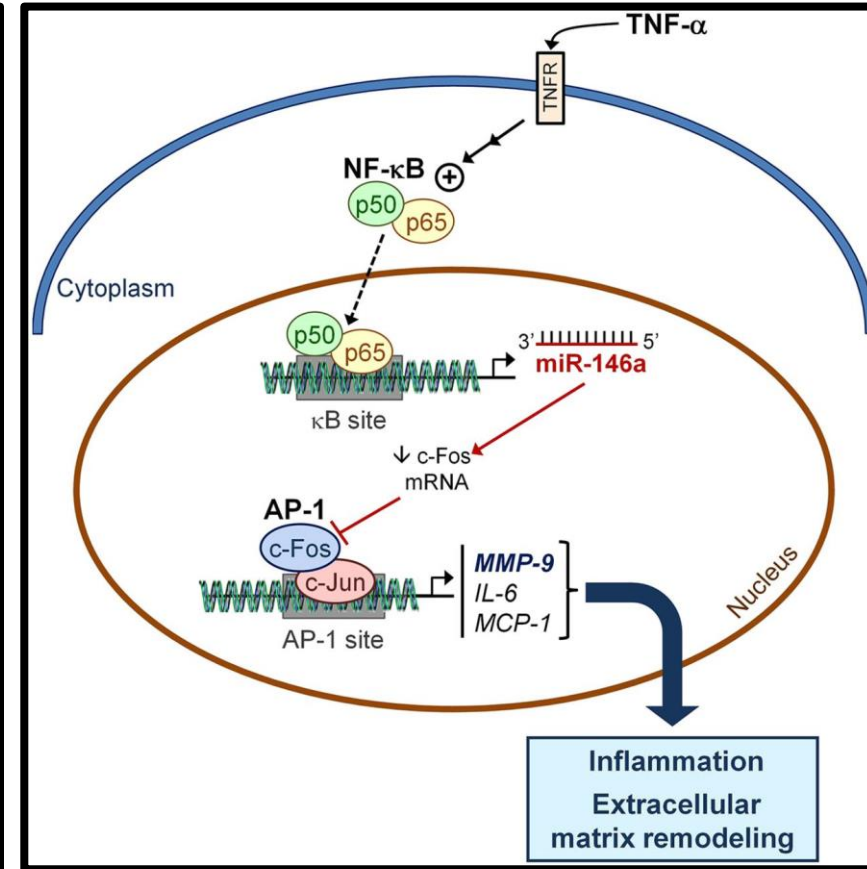
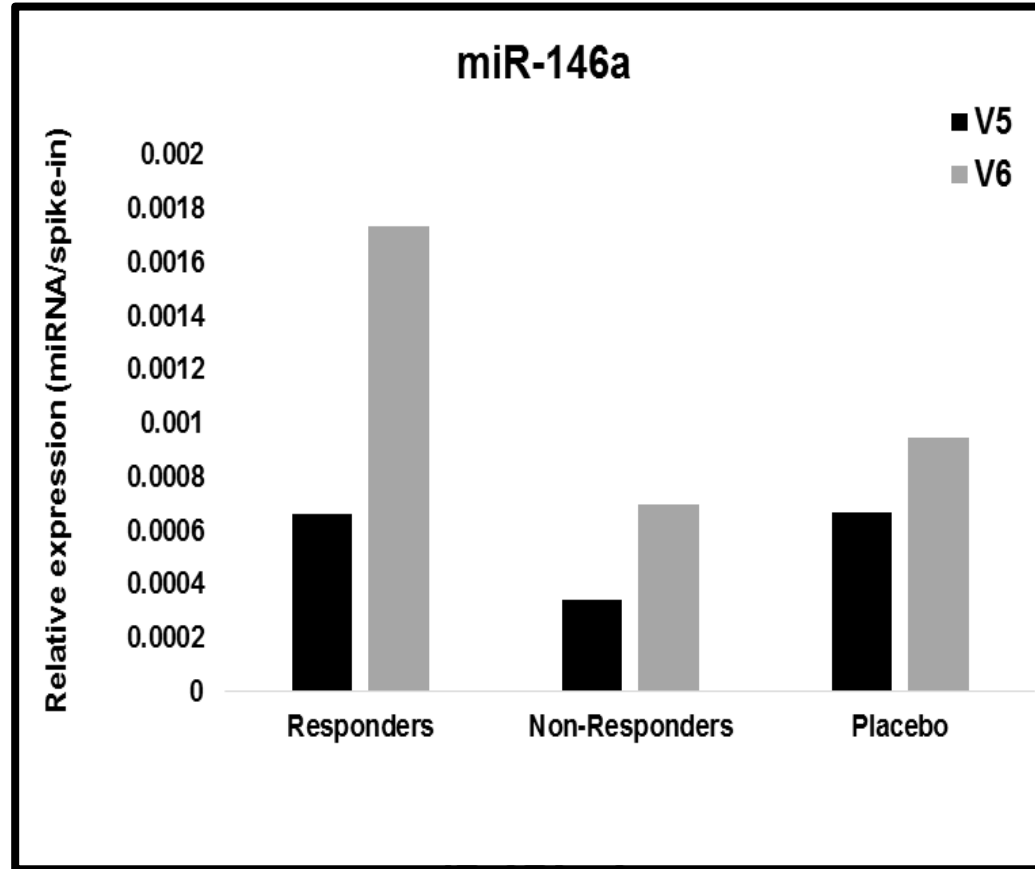
miR-34a  
miR-132  
miR-376a

Post-treatment miR higher in  
responders



miR-34a  
miR-146a  
miR-132  
miR-376a

# miR-146a: negative regulator of the innate immune response is significantly increased in responders



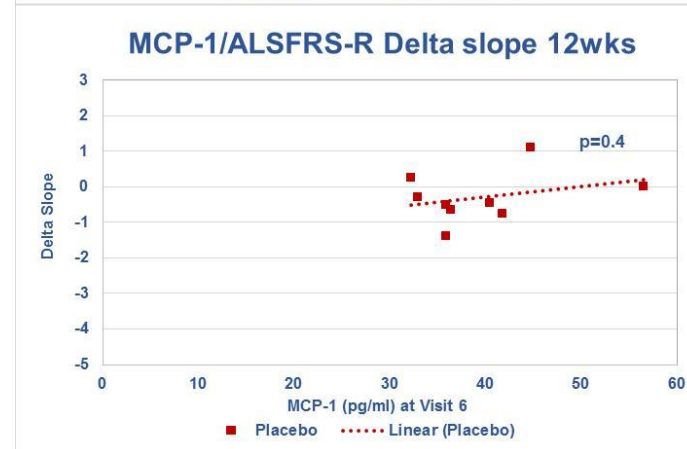
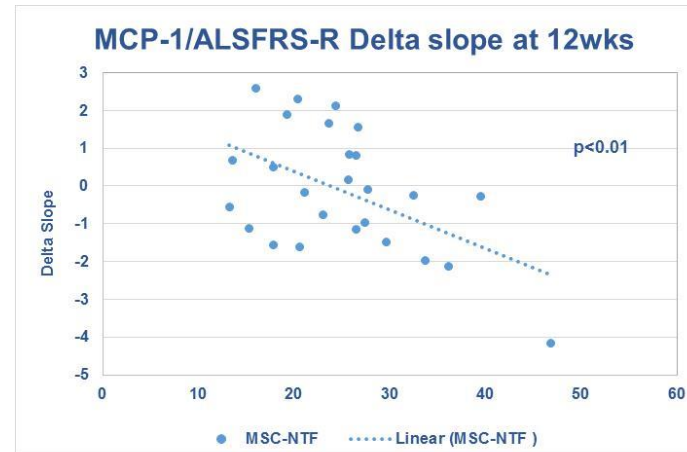
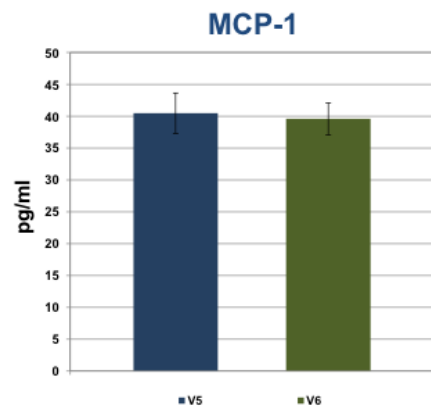
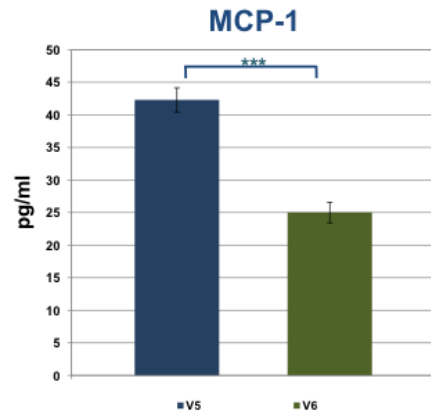


# miR-146-5p findings are consistent with MSC-NTF effects on CSF MCP-1 (CCL2)

Pre-transplant



Post-transplant



MSC-NTF  
N=26

Placebo  
N=9

Mean  $\pm$  SEM \*\*  $p < 0.01$  \*\*\*  $p < 0.001$

# CSF miR responder analysis

Baseline miRNA lower in  
non-responders

miR-34a

miR-132

miR-376a

miR-34a

miR-146a

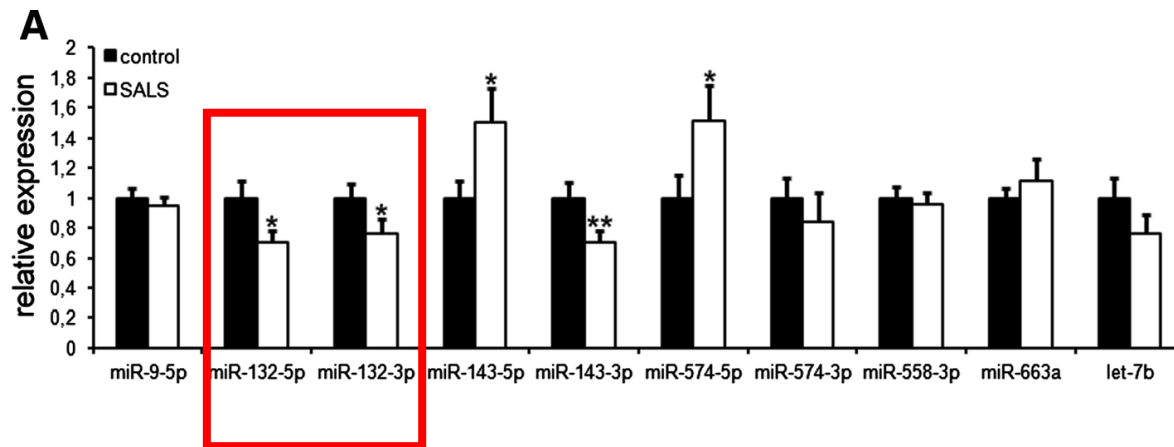
miR-132

miR-376a

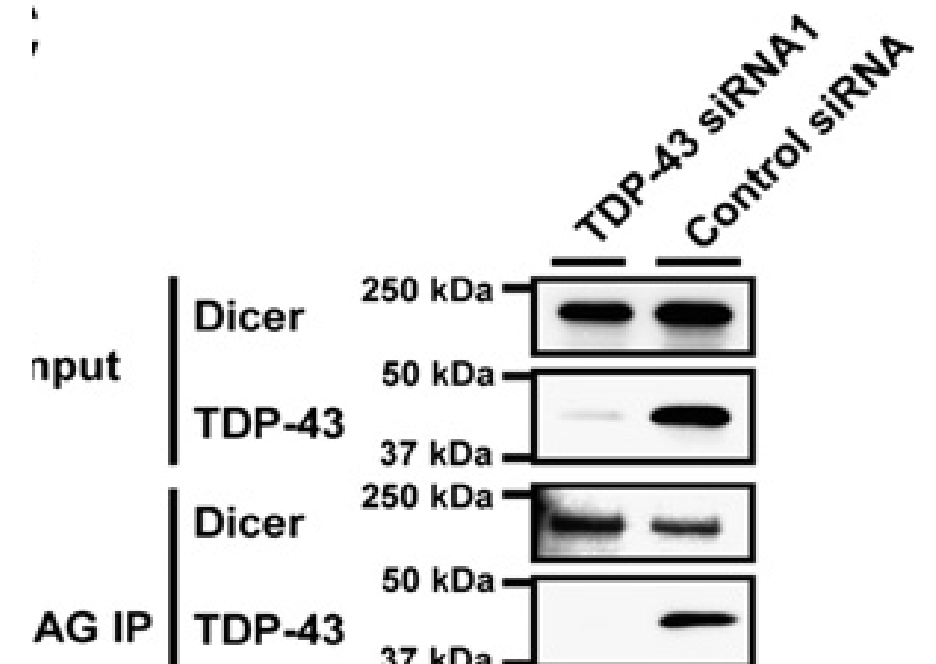
Post-treatment miR higher in  
responders

# CSF miR-132 is reduced in sporadic ALS

# TDP-43 is required for miR-132 biogenesis



Freischmidt et al. Acta Neuropathologica Communications 2013, 1:42



Kawahara PNAS | February 28, 2012 | vol. 109 | no. 9 | 3347–3352

# Conclusions

- **Baseline CSF miR-34a, miR-376a and miR-132 levels were lower in non-responders and might serve as prognostic biomarkers**
- **miR-146-5p and miR-132 are negative regulators of the immune response and are increased following MSC-NTF cell transplantation**
- **Post-treatment CSF miR-146-5p was higher in responders, consistent with the observed decrease in CSF MCP-1 (CCL2)**
- **The results are consistent with the proposed immunomodulatory and neurotrophic mechanism of action of NurOwn® in ALS**
- **CSF miR is being further evaluated in the ongoing phase 3 ALS study\***

\* [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) identifier NCT03280056

# Thank you