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.

* [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) identifier NCT02017912
Background

- 48 study participants were randomly allocated (3:1) to receive a single dose of combined intrathecal and intramuscular autologous MSC-NTF cells (NurOwn®) 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.

*>=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

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

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Fig. 4 Validated differentially expressed miRNAs. Differential expression of miRNAs identified in the microarray was validated by qPCR analysis of MSC and MSC-NTF cells of eight different donors (six ALS patients and two healthy donors). ***p < 0.001, two-sided t test, FC fold change, MSC mesenchymal stromal cells, NTF neurotrophic factors
Post transplantation: MSC-NTF secreted miRNAs are elevated in treated but not placebo patients

*miR-9 is not expressed by MSC-NTF cells*
CSF miR responder analysis

Baseline miRNA lower in non-responders

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

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

MSC-NTF
N=26

Placebo
N=9

Pre-transplant
Post-transplant

Mean ± SEM  ** p<0.01 *** p< 0.001
CSF miR responder analysis

Baseline miRNA lower in non-responders

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 identifier NCT03280056
Thank you