

ALS Research Forum January 24, 2019

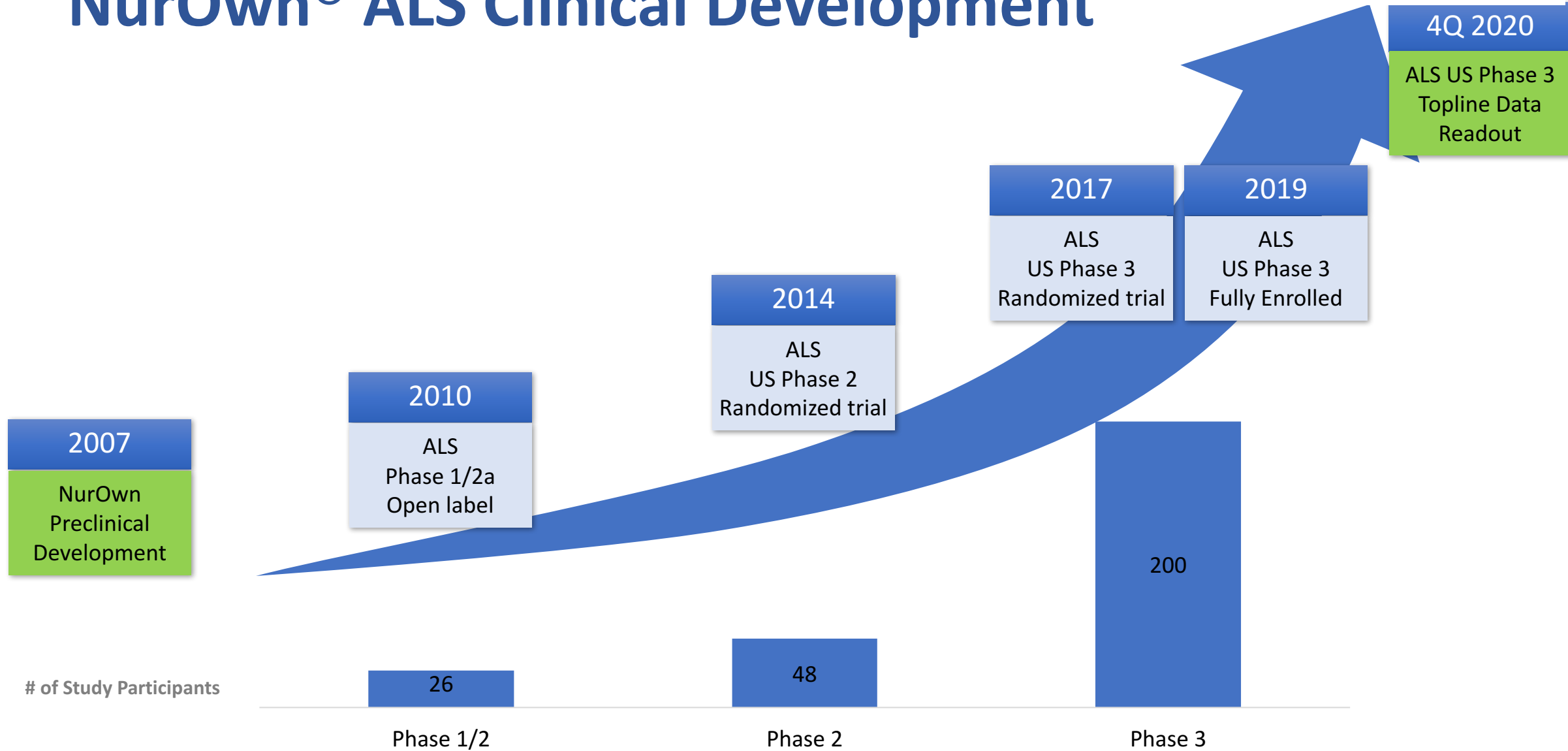
NurOwn Phase 3 Clinical Trial Update

Ralph Kern MD MHSc

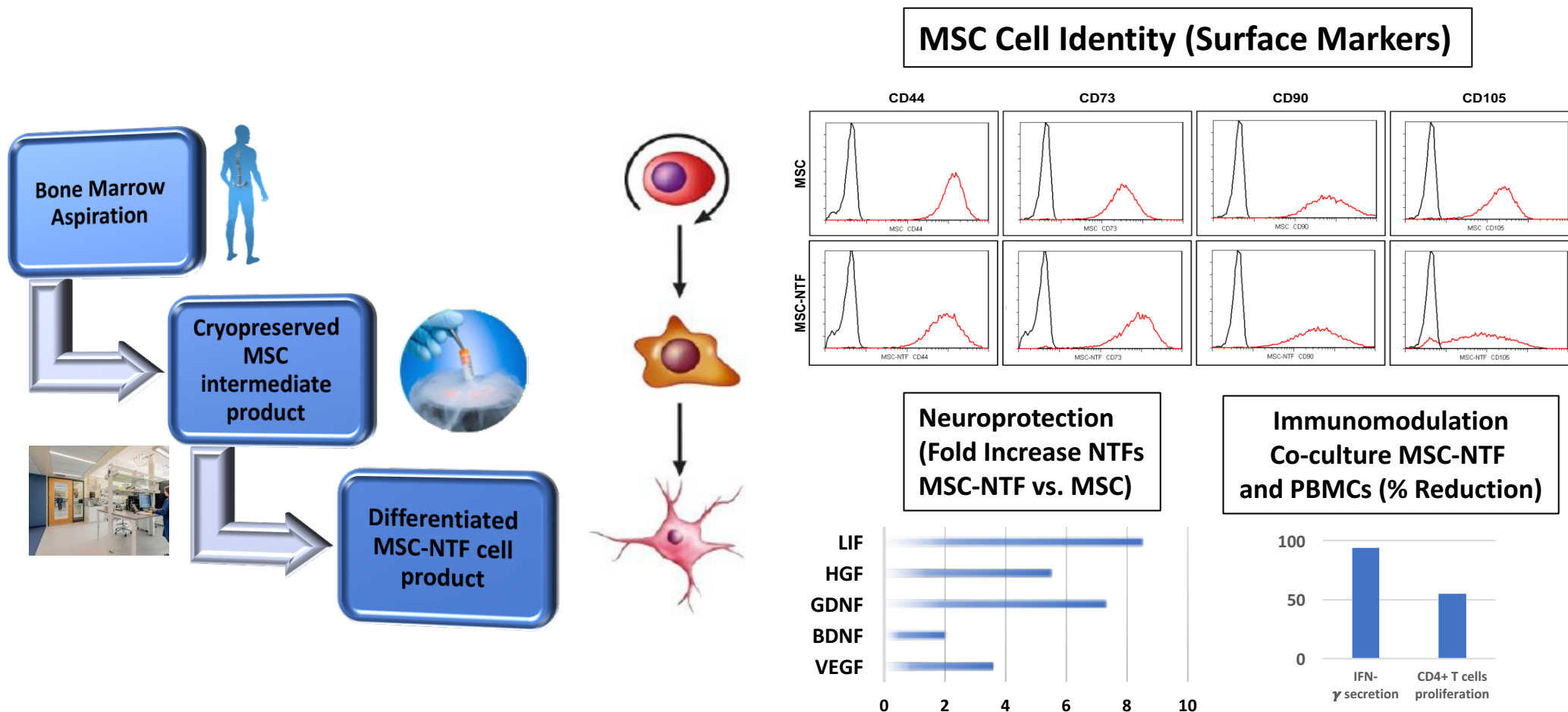
Chief Operating Officer and Chief Medical Officer

Brainstorm Cell Therapeutics

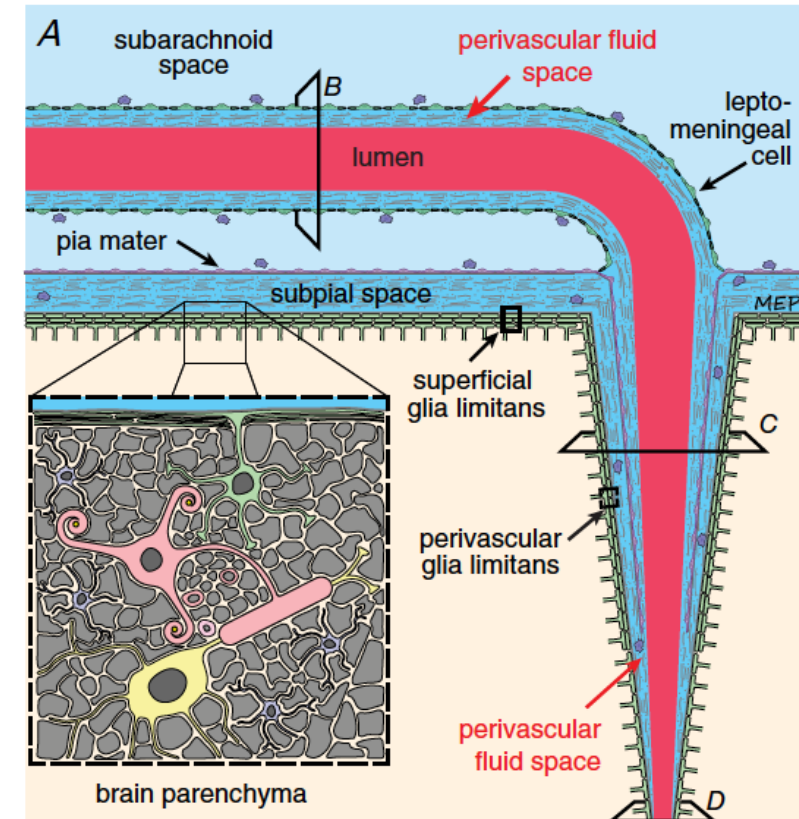
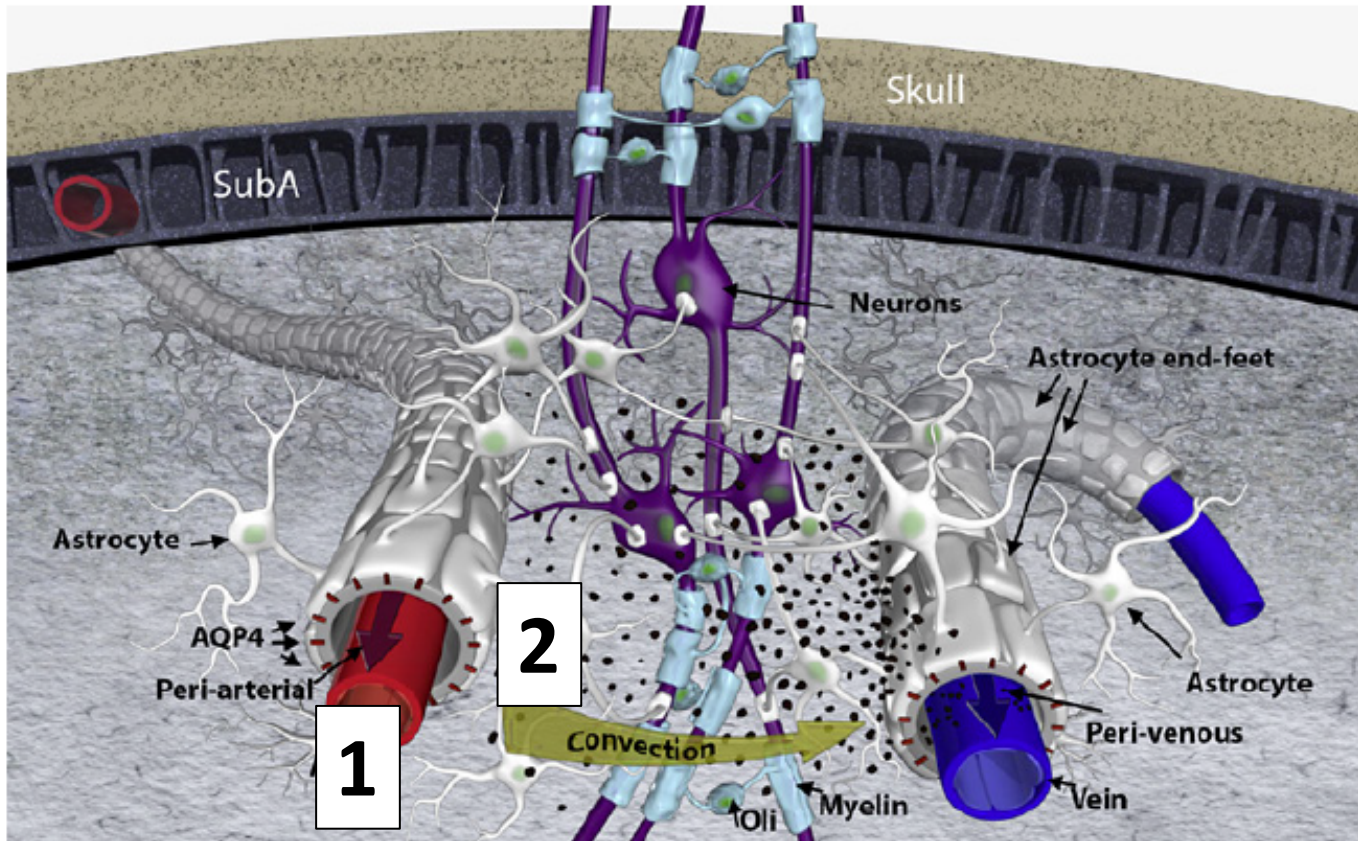
NurOwn® ALS Clinical Development



NurOwn® (MSC-NTF Cells) Technology Platform

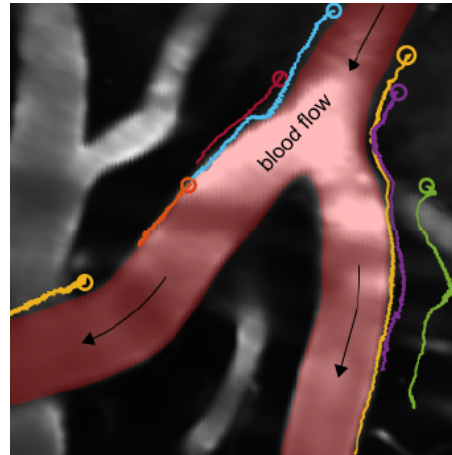


CSF cell and molecular delivery system: 2 step process

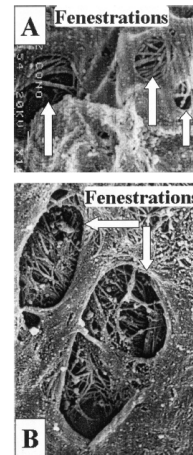


- (1) CSF enters the periarterial spaces driven by arterial pulsation
- (2) CSF moves from the periarterial compartment into the ISF space facilitated by aquaporin 4 (AQP4) water channels on astroglia end-feet, a process enabling CSF-ISF mixing

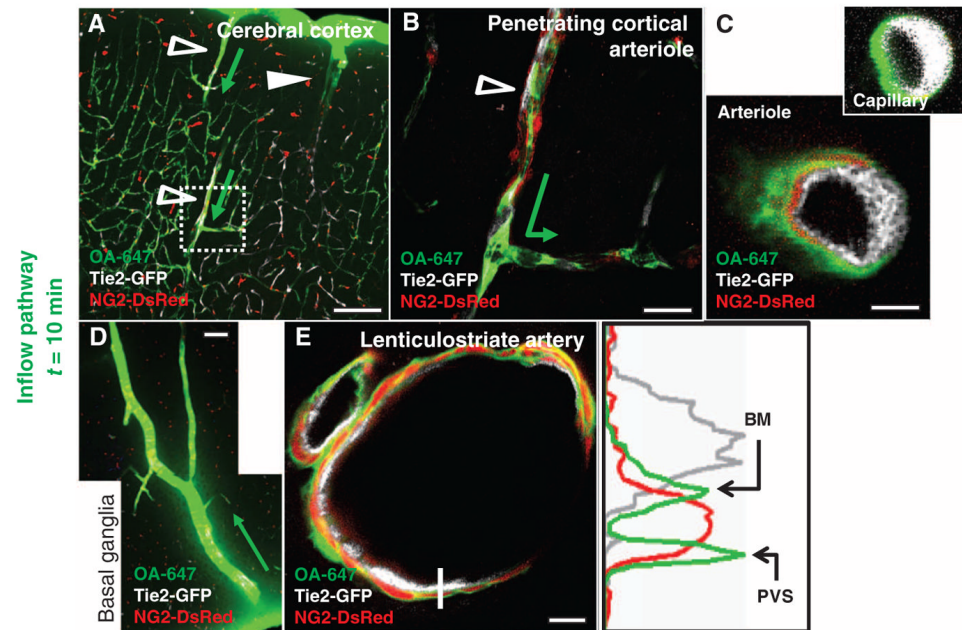
CSF cell and molecular delivery system: mechanisms



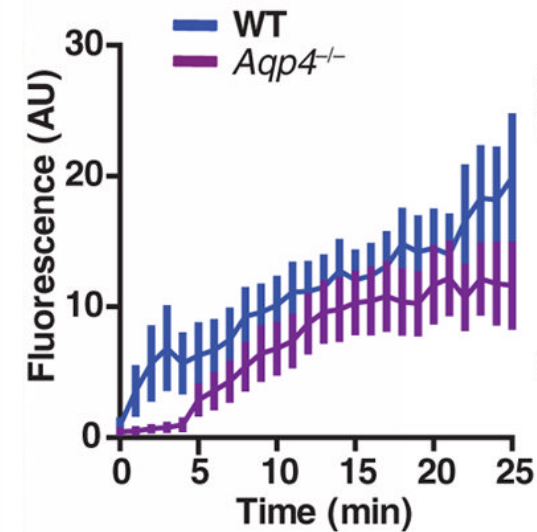
Courtesy of Iben Lundgaard



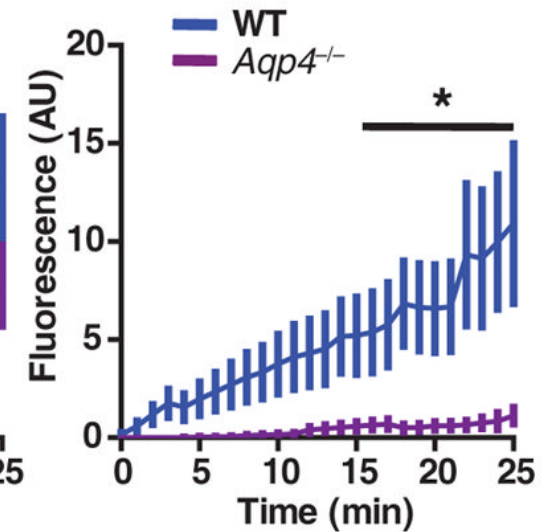
Anesth Analg 2004



H Paravascular tracer



I Interstitial tracer



BCT-001-US Phase 2 ALS Study

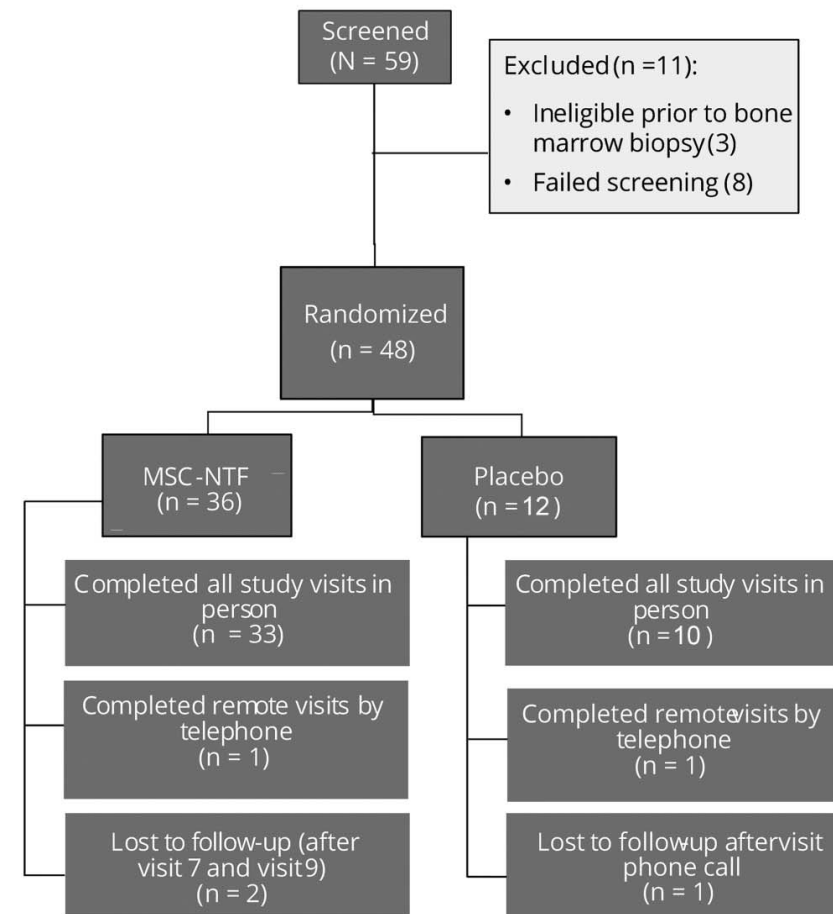
NurOwn, phase 2, randomized, clinical trial in patients with ALS

Safety, clinical, and biomarker results

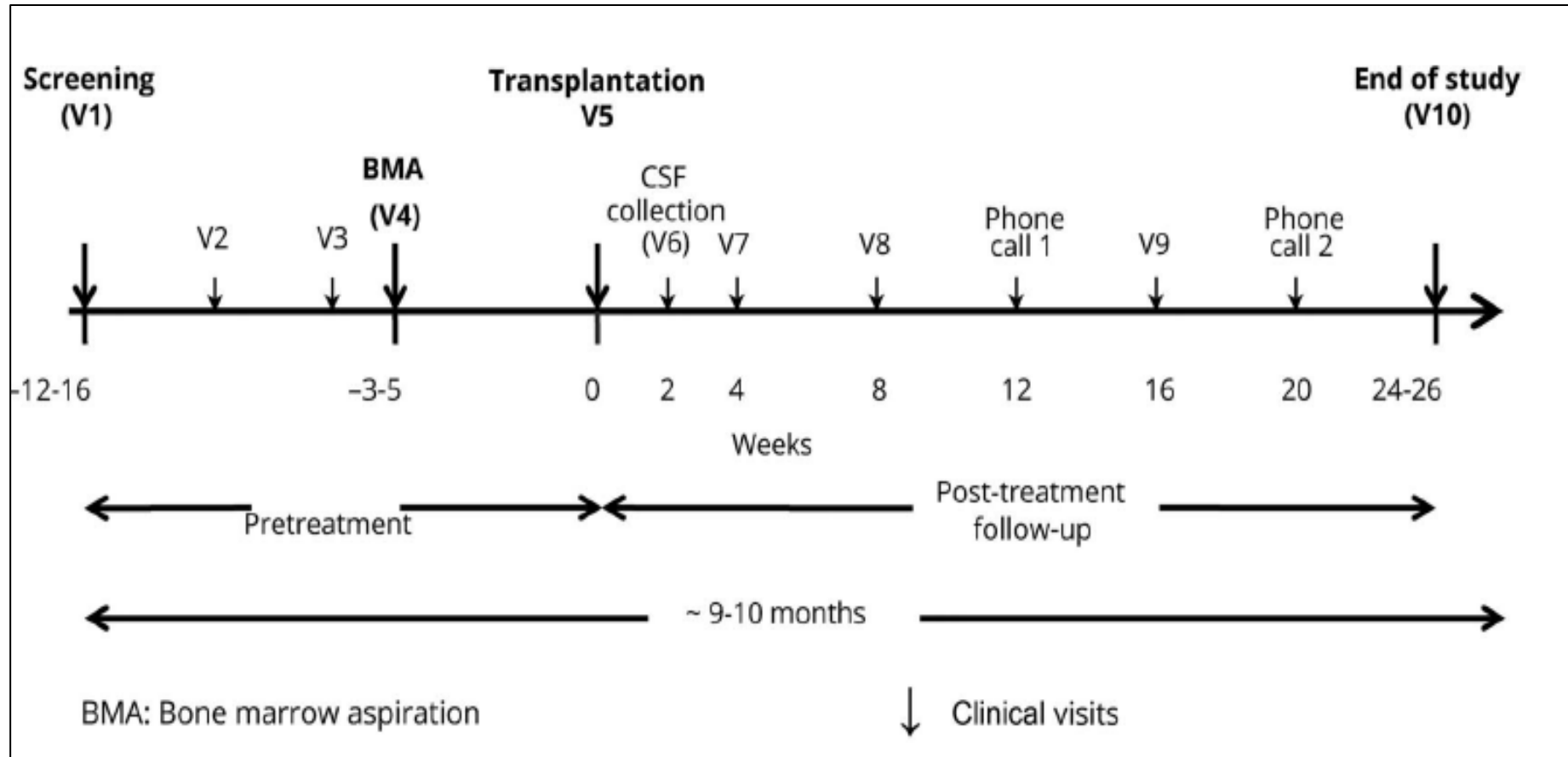
James D. Berry, MD, Merit E. Cudkowicz, MD, Anthony J. Windebank, MD, Nathan P. Staff, MD, Margaret Owegi, MD, Katherine Nicholson, MD, Diane McKenna-Yasek, Yossef S. Levy, PhD, Natalie Abramov, MSc, Haggai Kaspi, PhD, Munish Mehra, PhD, Revital Aricha, PhD, Yael Gothelf, PhD, and Robert H. Brown, DPhil, MD

Neurology® 2019;93:e1-e12. doi:10.1212/WNL.00000000000008620

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Phase 2 ALS Study Design



Phase 2 ALS Clinical Trial Demographics: Baseline Characteristics Balanced

Table 1 Demographics and baseline characteristics by treatment group

	MSC-NTF (n = 36)	Placebo (n = 12)	All participants (n = 48)
Sex			
Male	25 (69.4)	10 (83.3)	35 (72.9)
Female	11 (30.6)	2 (16.7)	13 (27.1)
Age, y	50.3 (11.90)	53.5 (9.11)	51.1 (11.27)
El Escorial criteria			
Possible	3 (8.3)	1 (8.3)	4 (8.3)
Laboratory-supported probable	5 (13.9)	1 (8.3)	6 (12.5)
Probable	16 (44.4)	7 (58.3)	23 (47.9)
Definite	12 (33.3)	3 (25.0)	15 (31.3)
ALS medical history, months since diagnosis	9.00 (5.57)	9.01 (4.63)	9.00 (5.31)
ALS medical history, months since first symptom ^a	17.62 (3.79)	16.75 (3.10)	17.40 (3.62)

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Revised ALS Functional Rating Scale; MSC = mesenchymal stem cell; NTF = neurotrophic factor. Data are presented as n (%) or mean ($\pm$ SD). Percentages are based on the number of participants in a given treatment group for the population being analyzed.

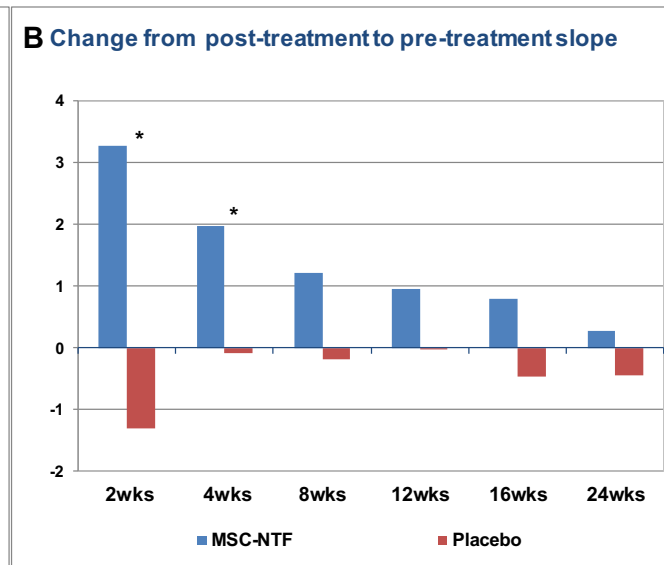
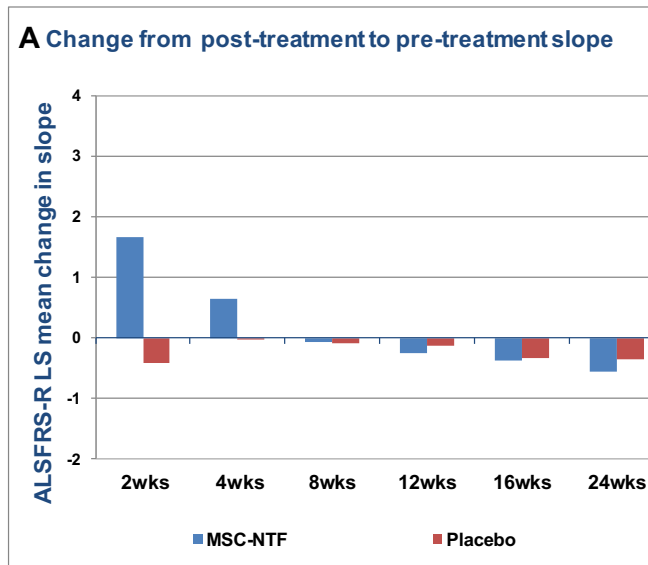
^a The site of ALS onset was not tracked in the course of the study.

ALSFRS-R Efficacy Outcomes

All n=46

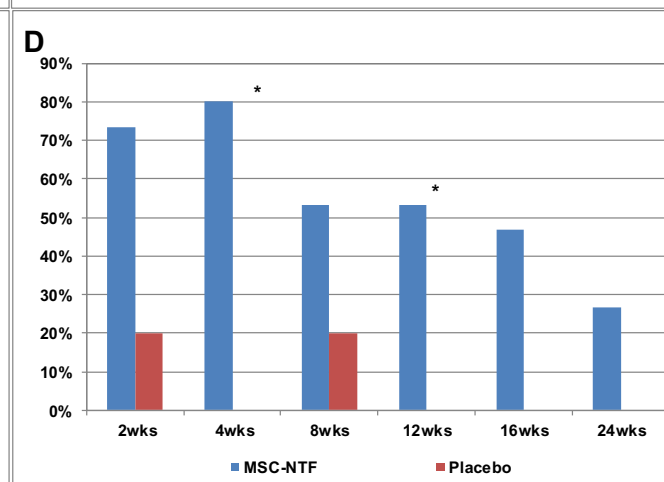
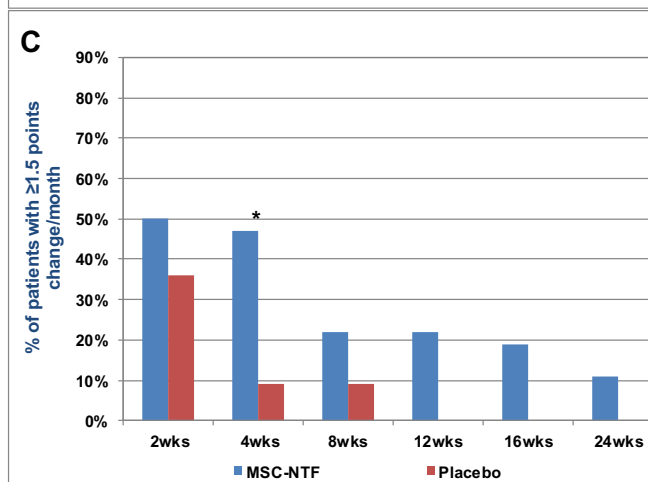
Rapid Progressors n=21

Mean ALSFRS-R
Post-pre slope change



MSC-NTF
Placebo

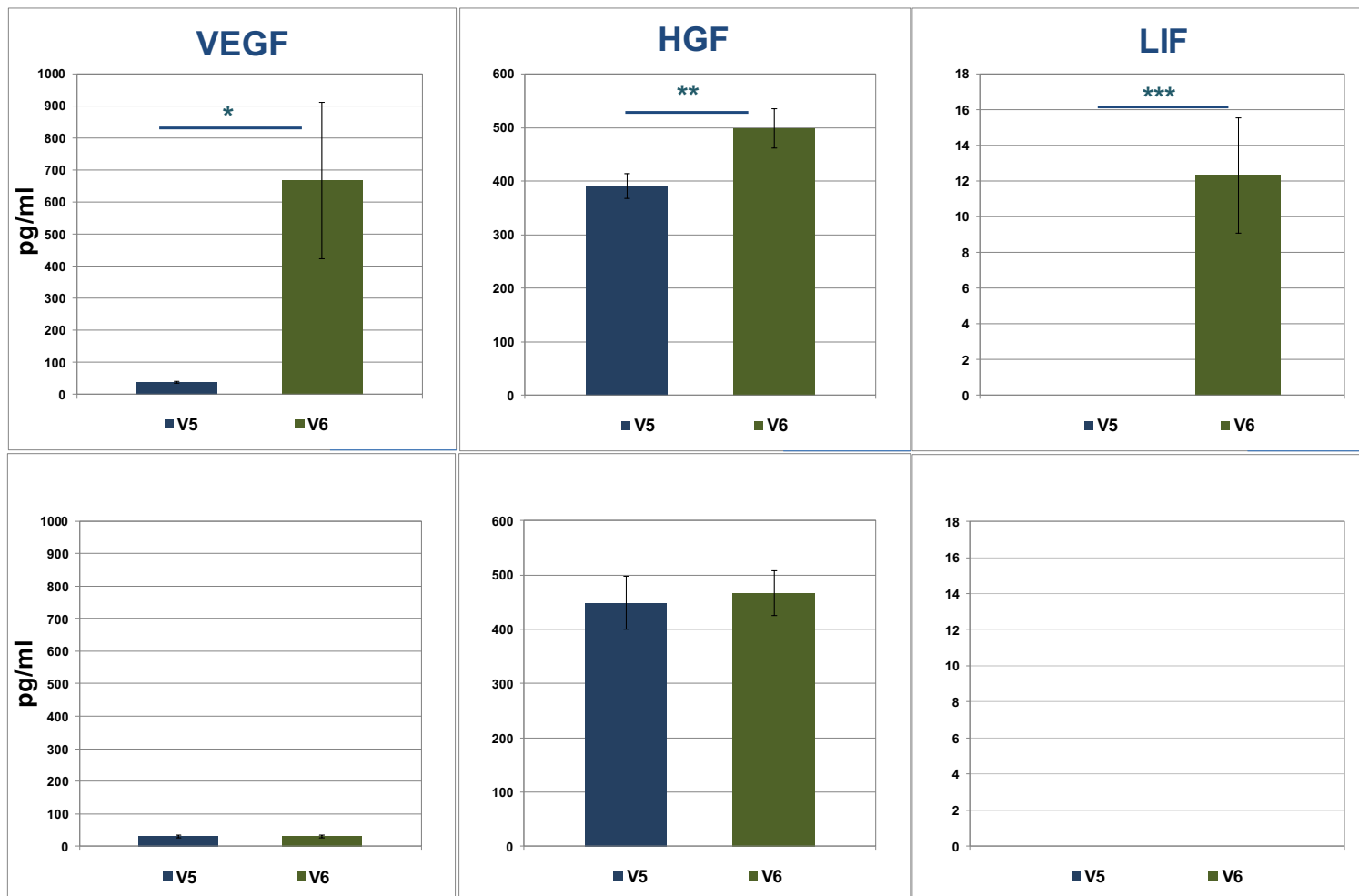
Proportion of
Responders showing
≥1.5 points/month
ALSFRS-R slope
improvement



*p<0.05

CSF Neurotrophic Factors Increased Post-Treatment

NurOwn®
(n = 26)



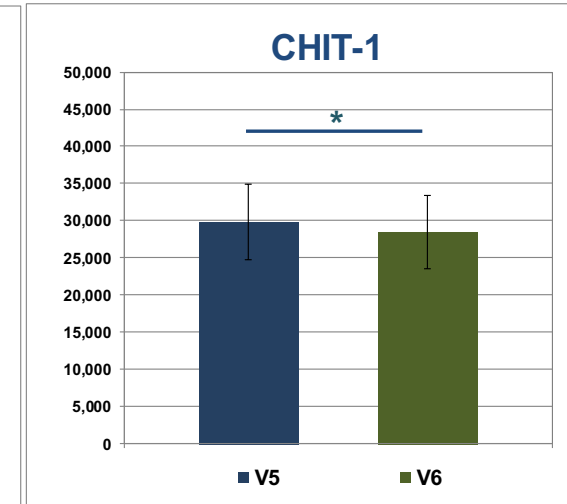
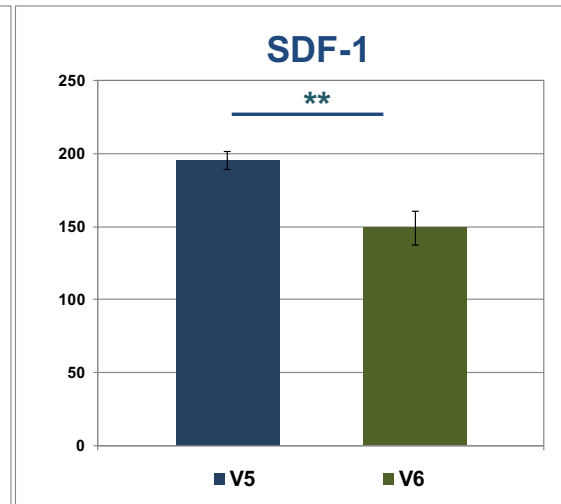
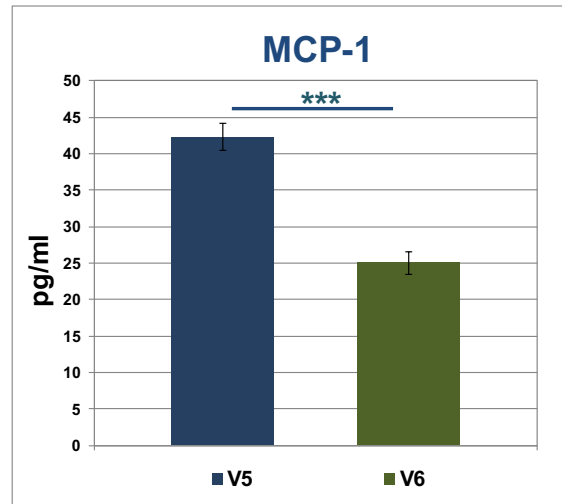
■ V5 -Pre transplantation
■ V6 - Post transplantation

*p<0.05, **p<0.01, ***p<0.001

Berry et al Neurology 2019

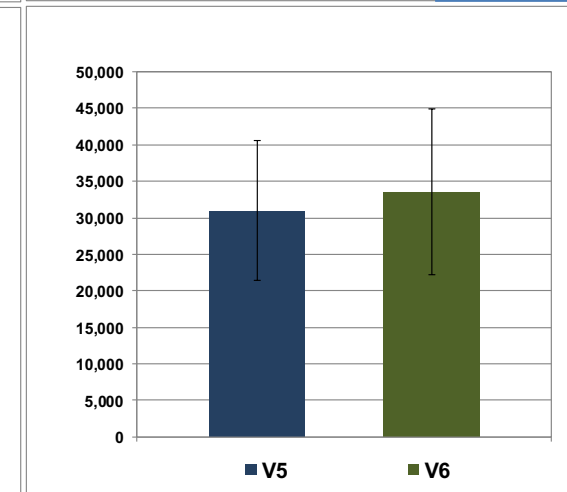
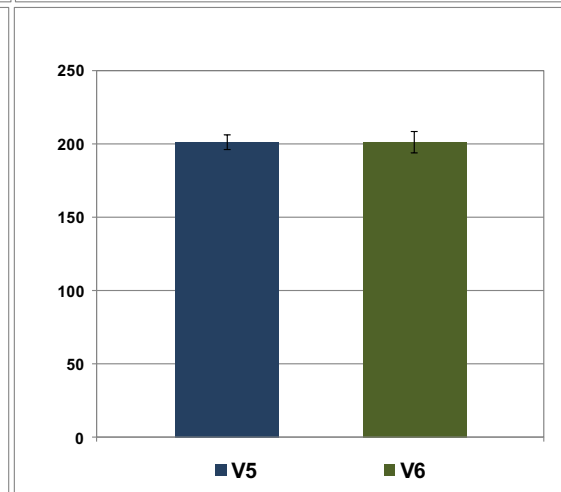
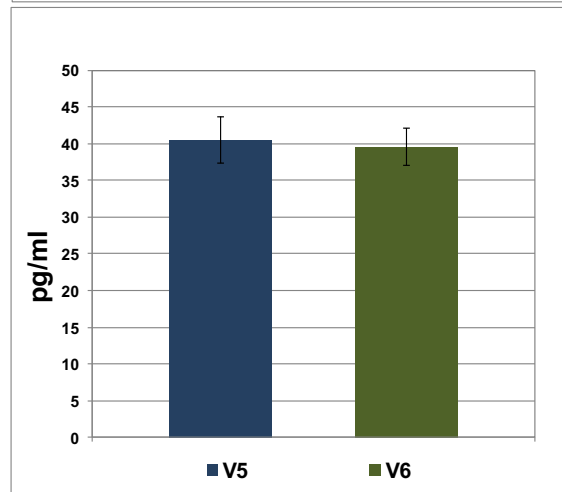
CSF Inflammatory Biomarkers Reduced Post-Treatment

NurOwn®
(n = 26)



■ V5 -Pre transplantation
■ V6 - Post transplantation

Placebo
(n = 9)



*p<0.05, **p<0.01, ***p<0.001

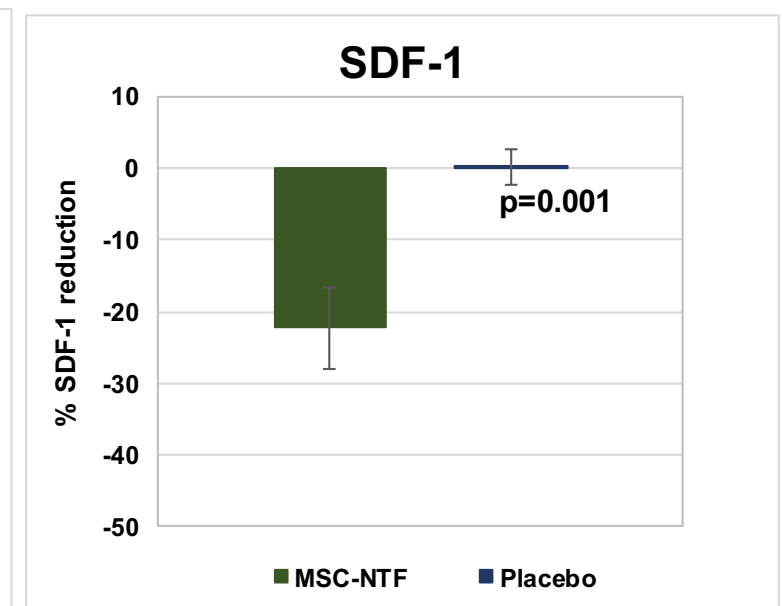
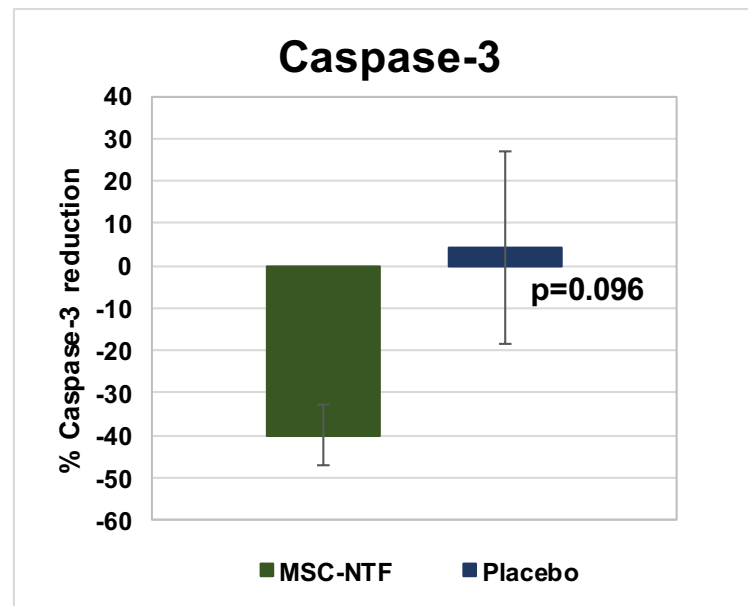
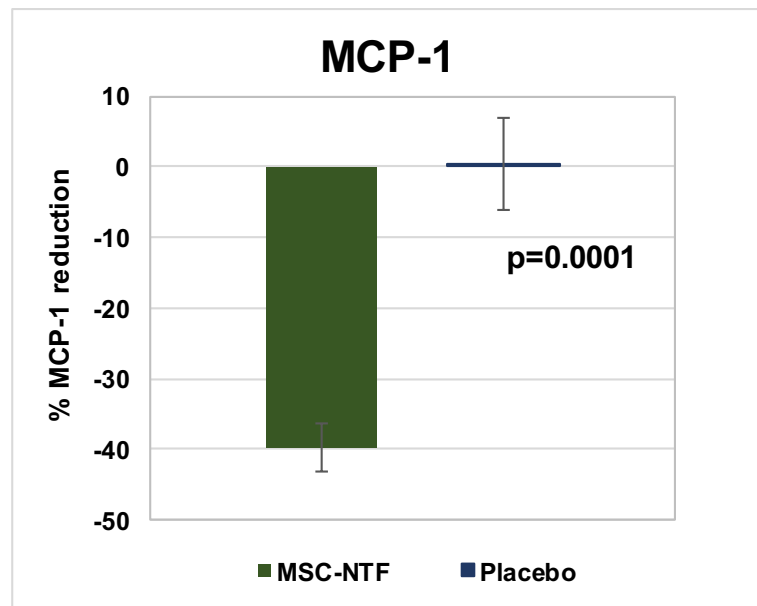
Berry et al Neurology 2019

Post-treatment % reduction CSF MCP-1, Caspase-3 and SDF-1

MCP-1 (40%)

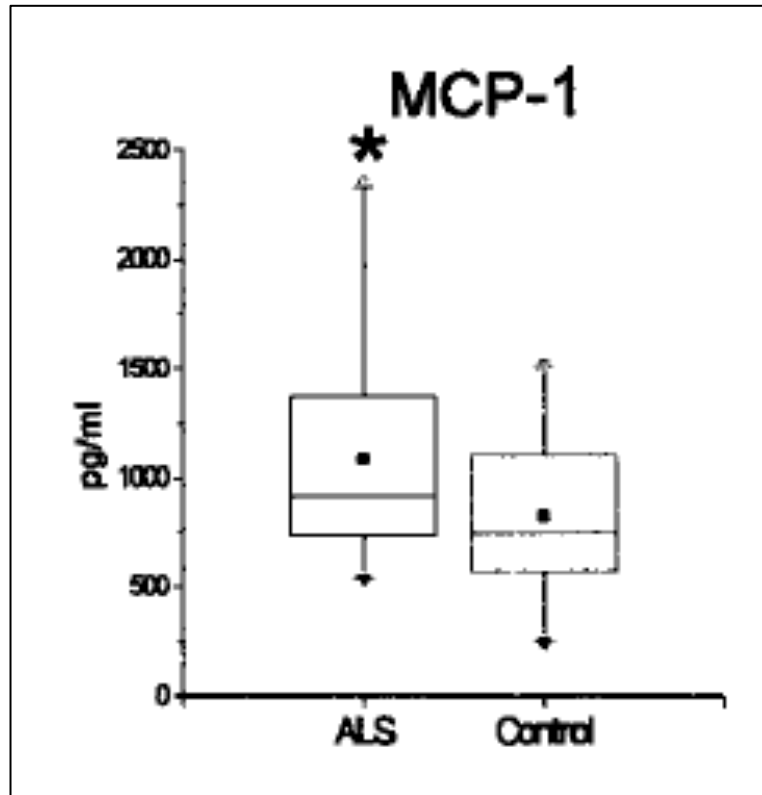
Caspase-3 (40%)

SDF-1 (22%)



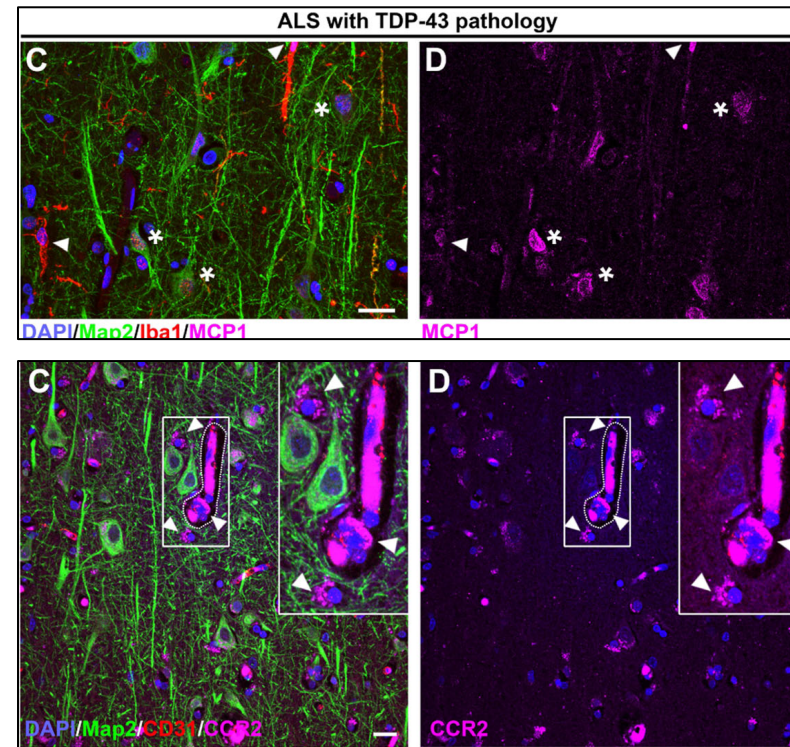
MCP-1 expression is increased in the spinal cord and motor cortex of ALS patients

Spinal Cord



Henkel Ann Neurol 2004

Brain



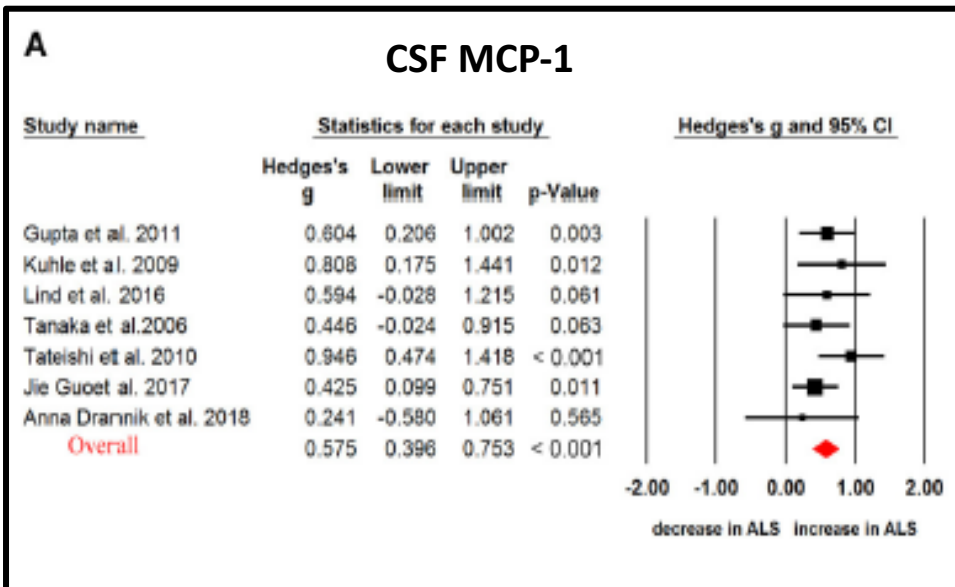
Degenerating Betz cells express MCP-1

Betz cells surrounded by CCR2+ invading monocytes

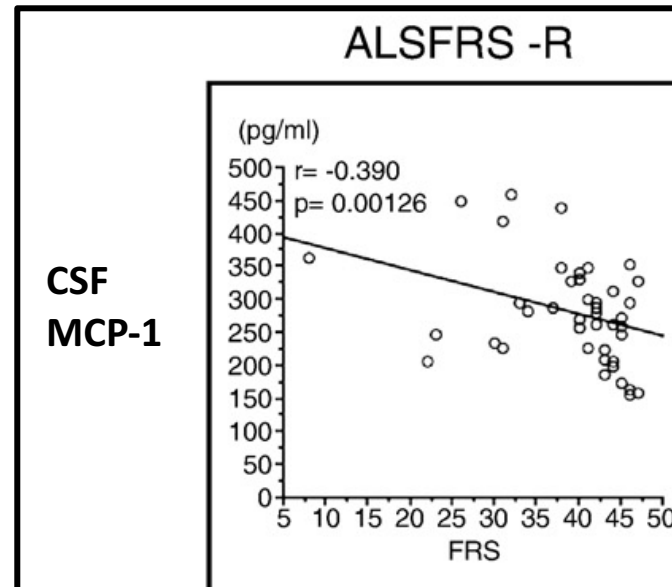
Jara et al J Neuroinflamm 2019

CSF MCP-1 is increased in ALS and correlates with function and survival

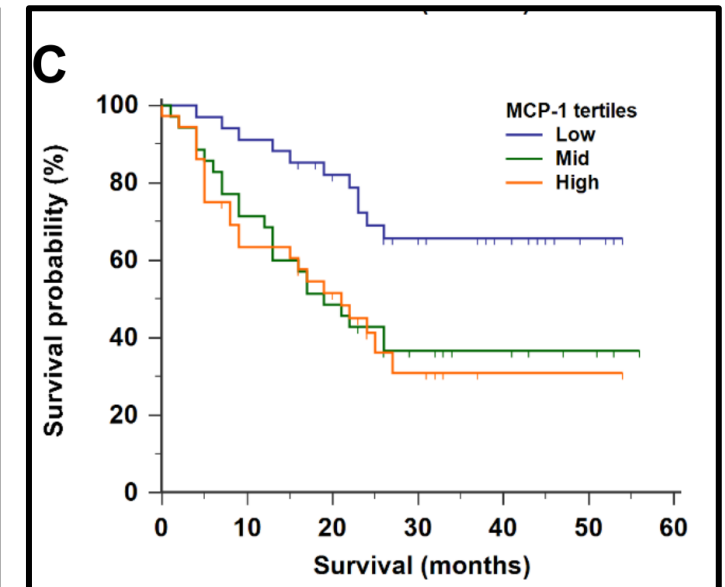
MCP-1 meta-analysis (n=7)



MCP-1:ALSFRS-R Correlation

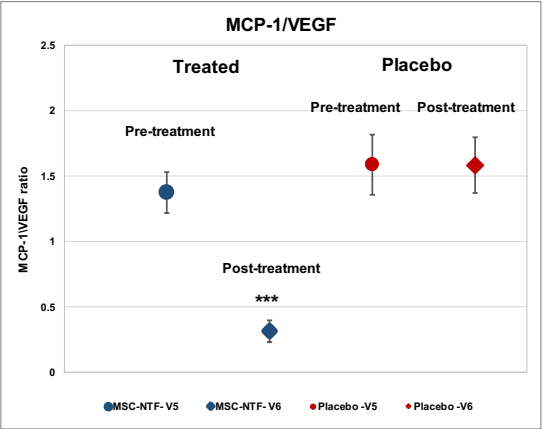
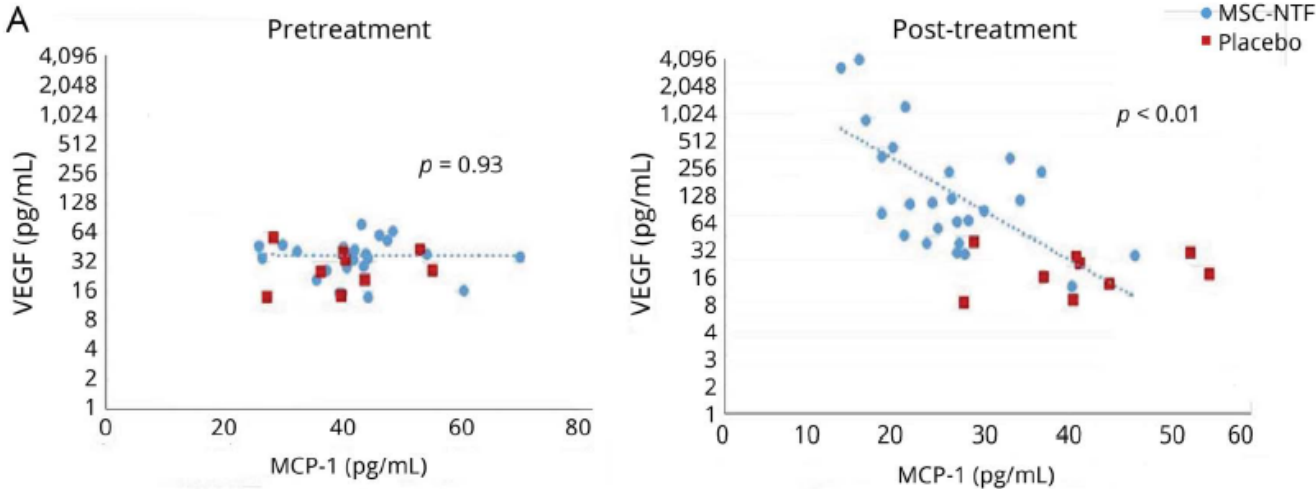


MCP-1:Survival Correlation

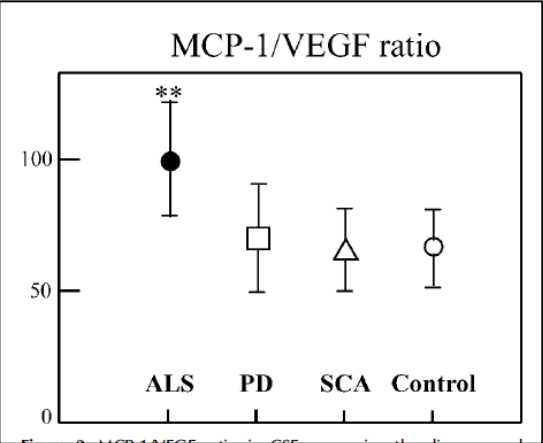
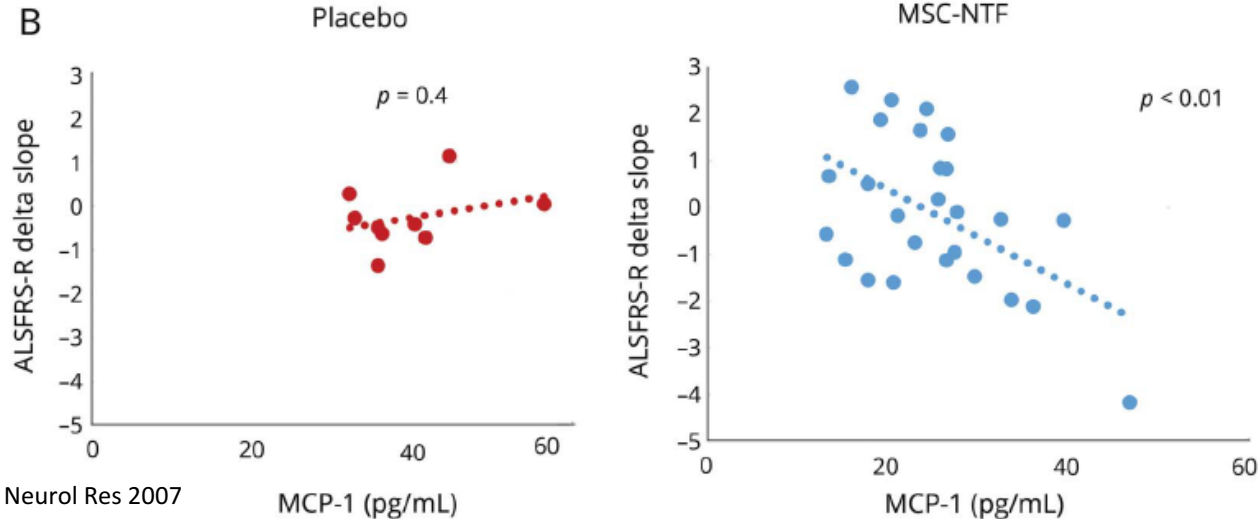


Phase 2 ALS Clinical Trial: Biomarker Correlations

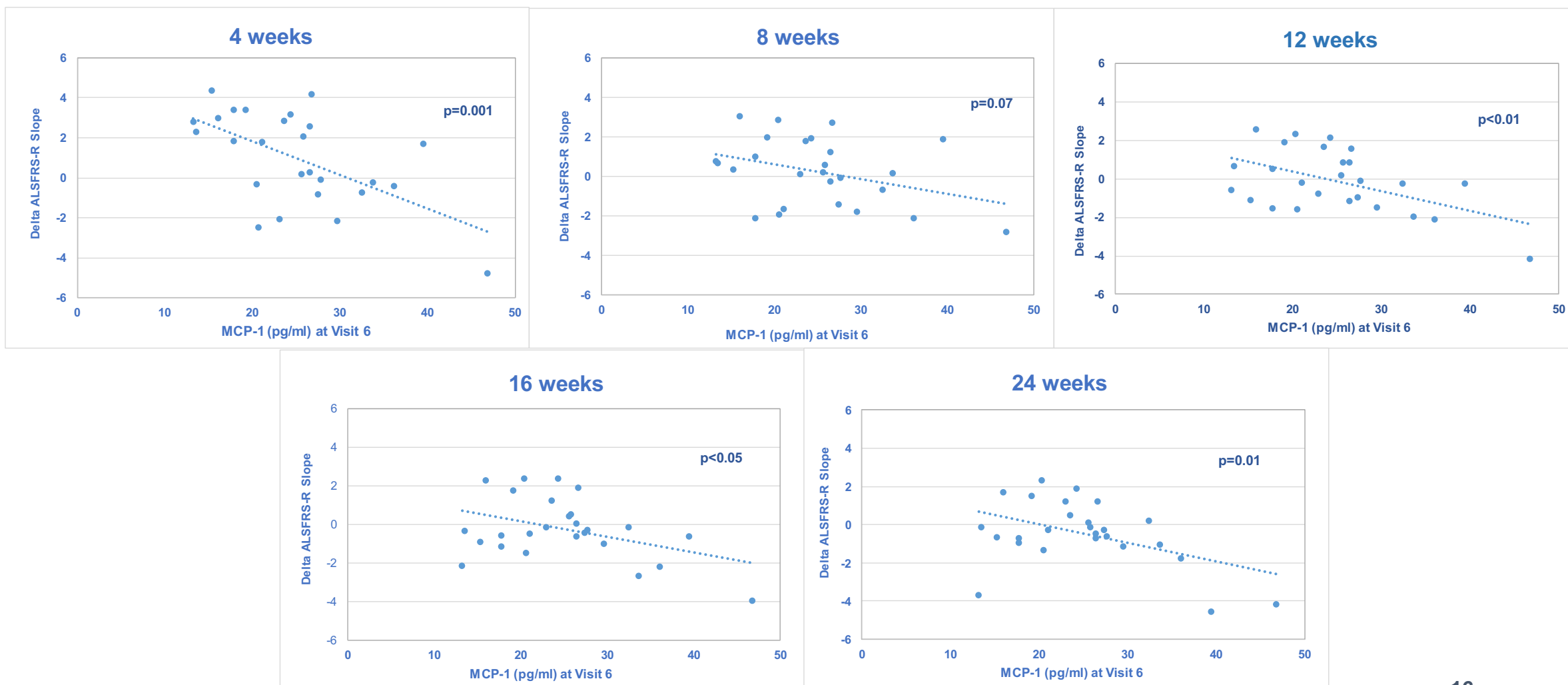
CSF MCP-1 inverse correlation with VEGF



CSF MCP-1 inverse correlation with ALSFRS-R

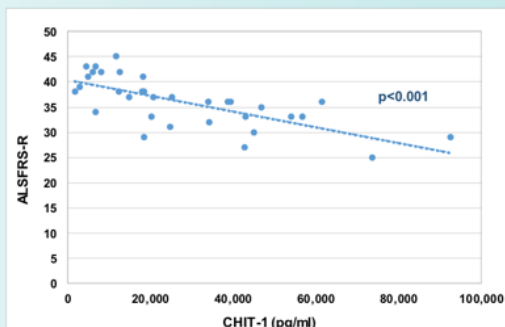


Strong correlation between CSF MCP-1 (2 weeks) and improvement in disease progression in treated patients at all time points

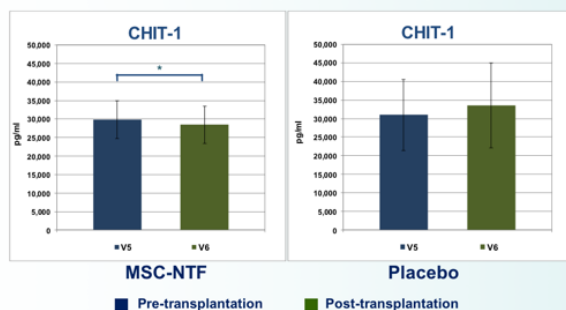


CSF Chitotriosidase correlates with ALS function and survival and is higher in ALS rapid progressors

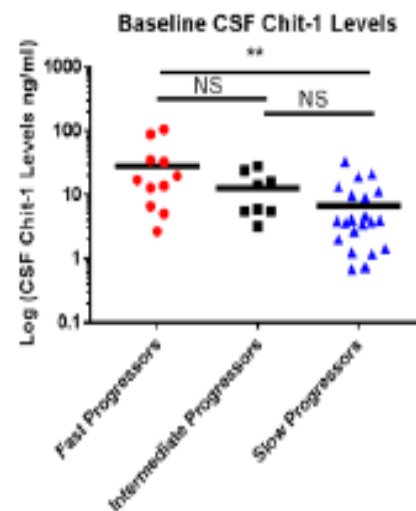
Baseline CSF CHIT-1 correlates with baseline ALSFRS-R score



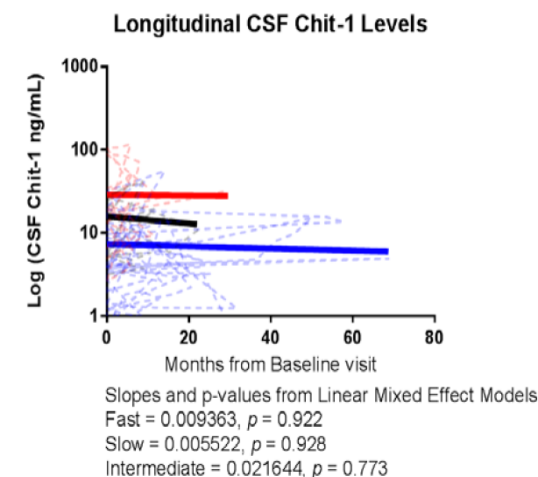
NurOwn® (MSC-NTF cells) decreases CHIT-1 in the CSF 2 weeks post-transplantation



A



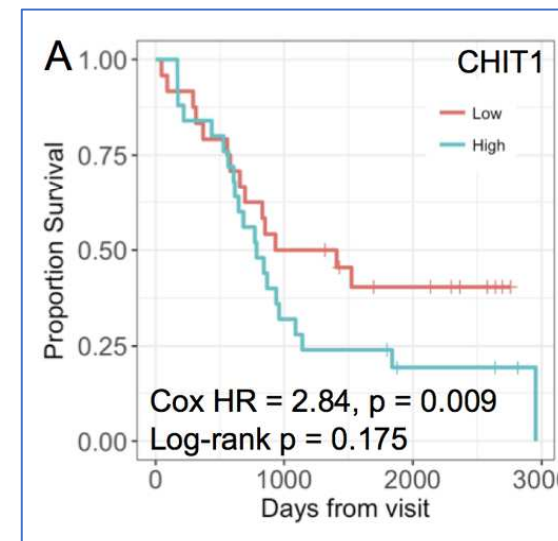
C



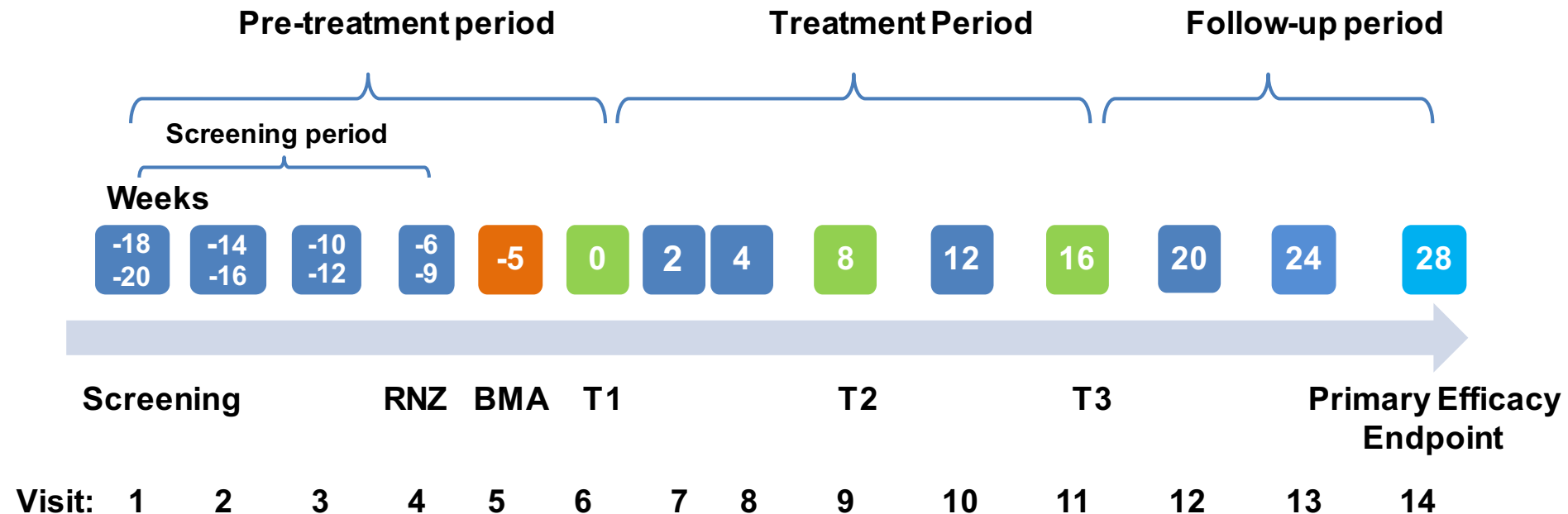
ORIGINAL RESEARCH

Cross-sectional and longitudinal measures of chitinase proteins in amyotrophic lateral sclerosis and expression of CHI3L1 in activated astrocytes

Lucas Vu ,¹ Jiyan An,¹ Tina Kovalik,¹ Tania Gendron,² Leonard Petrucelli,² Robert Bowser^{1,3}



Phase 3 BCT-002-US ALS Clinical Trial Design



BMA: Bone Marrow Aspiration

RNZ: Randomization

T1, T2, T3: Treatments 1, 2 and 3, respectively

ALSFRS-R: Revised amyotrophic lateral sclerosis functional rating scale will be assessed at all time points except at Week -5

7 CSF collections

10 serum collections (Serum samples are also collected 20 hours post each transplantation).

Phase 3 Update

- **Enrollment**
 - Phase 3 Study is fully enrolled as of October 2017
 - Top line data Q4 2020
- **Biomarkers/Genetic testing**
 - Genetic testing for a panel of ALS genetic mutations or gene variants
 - Testing for T regulatory cells pre- and post-transplant included in a recent protocol amendment
- **Data and Safety Monitoring Board (DSMB)- October 2019**
 - After completing an interim safety analysis the study independent DSMB recommended the trial should continue as planned without any protocol changes.

Phase 3 Biomarkers

Biomarker Type	CSF	Serum
MSC-NTF derived Neurotropic Factors and Neuronal Biomarkers	BDNF, GDNF, HGF, LIF, VEGF, TSG-6 and a panel of markers related to neurobiological processes, cell death, neuropathology and neurodegeneration	BDNF, GDNF, HGF, LIF, VEGF, TSG-6 and a panel of markers related to neurobiological processes, cell death, neuropathology and neurodegeneration
Inflammatory Biomarkers	MCP-1, SDF-1, CHIT-1, and a panel of cytokines, chemokines and proteins associated with inflammation and related biological processes	Panel of cytokines, chemokines and proteins associated with inflammation and related biological processes
miRNA	miRNA panel	miRNA panel

Thank you

Massachusetts General Hospital

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James Berry MD

University of Massachusetts

Robert Brown DPhil MD

Margaret Owegi MD

Mayo Clinic Rochester Minnesota

Anthony Windebank MD

Nathan Staff MD

UCI

Namita Goyal MD

Cedars Sinai

Robert Baloh MD

CPMC

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BrainStorm Cell Therapeutics

Yossef Levy PhD

Yael Gothelf PhD

Revital Aricha PhD

Chaim Lebovits

Haggai Kaspi PhD

Jonathan Semo PhD

Natalie Abramov MSc

Manufacturing sites

City of Hope

Dana Farber Cancer Institute

California Institute for Regenerative Medicine

Abla Creasey PhD

Maria Millan MD