WORLD ALS DAY

NEW ADVANCES AND FUTURE THERAPIES FOR ALS

SUNDAY, 21ST JUNE, 2020

Asha Ek Hope
Foundation for MND/ALS, INDIA

Dr. Hemangi Sane

Founder, Asha Ek Hope Foundation

Deputy Director and Head of research and development department,
NeuroGen Brain and Spine Institute


"SOMEWHERE, SOMETHING INCREDIBLE IS
WAITING TO BE KNOWN."
- CARL SAGAN
PICTUREQUOTES.ME

Overview of the talk

Recent Advances in potential treatment options

Medicines

Cell therapy

Gene therapy

Adjuvant therapy

- Hormone therapy
- Hyperbaric Oxygen Therapy
- Ozone Therapy
- Chelation Therapy
- IV vitamin Therapy

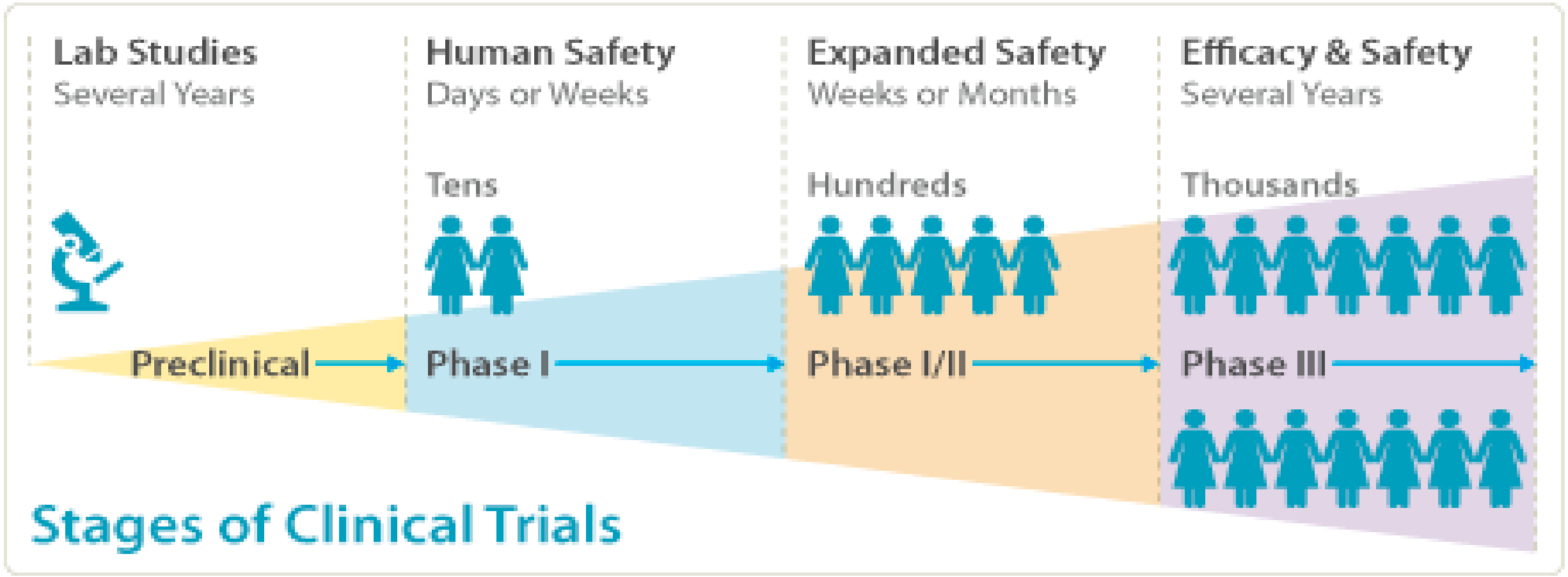
Technology

- Assistive devices
- My voice

Single arm studies

Randomized Placebo controlled studies, with blinding

Multicenter Randomized Placebo controlled studies, with blinding



ALS Platform Trial

HEALEY ALS Platform Trial

This is the first ALS platform trial, accelerating the path to new ALS therapies

- test multiple treatments at once,
- reduce the cost of research by 30%,
- decrease the trial time by 50%,
- increase patient participation by 67%

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Medicines

Immune Modulation Pathway	• DNL747, Ibudilast MN 166, Masitinib, Trametinib, RNS60, Clenbuterol
Complement Pathway	• Zilucoplan, Ravulizumab
Oxidative stress pathway	• Verdiperstat
Heat Shock Proteins	• Colchicine, Arimoclomal
Cell energy pathway	• Nanocrystalline gold
Antibody to misfolded protein	• AP101
Cell survival pathway	• AMX0035
Regulatory pathway	• GM640
Neuroprotection	• Recombinant Human Erythropoeitin,Izogabin, Rasigiline, Biotin, Sinemet, Primozide
Anti-retroviral pathway	• Darunavir, Ritonavir, dolutegravir, Tenofovir alafenamide

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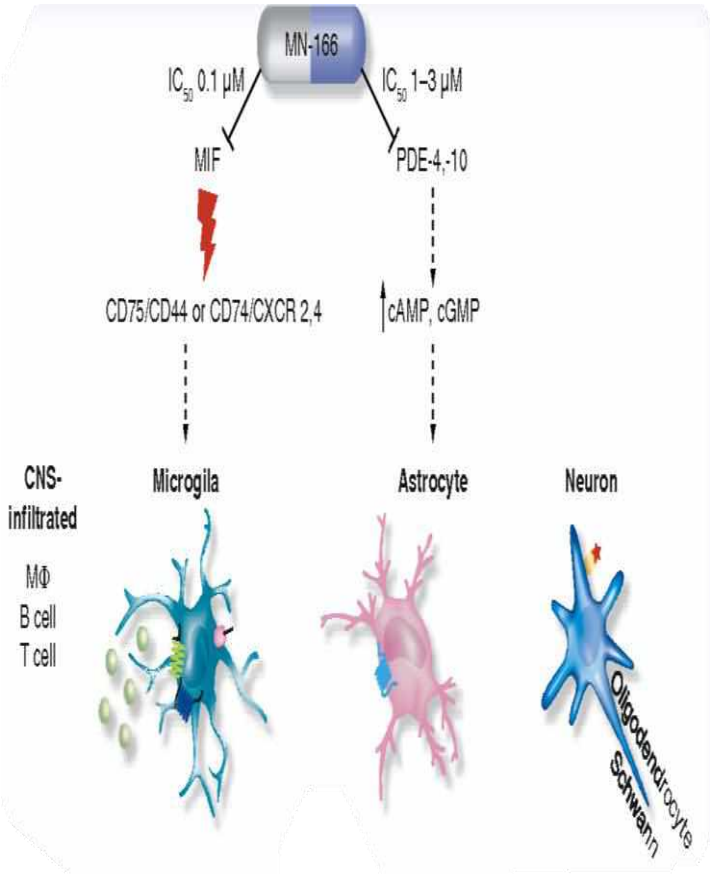
Ibudilast (MN-166)

Currently in Phase 2b/3

- A phosphodiesterase inhibitor
- Has anti-inflammatory and neurotrophic effect
- Phase 1b/2a trial - MN-166 in combination with riluzole more effective than riluzole alone.
- In phase 2 trial the primary goal was to test safety
- average change in ALSFRS-R scores to six months of treatment was not significantly different in Ibudilast and placebo treated patients
- **Reanalysis of the data suggested that the efficacy of MN-166 is expected to be effective in patients with a short ALS history**



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Masitinib

Currently in Phase 3

- Tyrosine-kinase inhibitor
- Phase 2 results show that Masitinib showed a significant benefit with acceptable safety in ALS patients with a baseline ALSFRS-R progression rate of 1.1 points/month.
- Progression slowed down in treatment group

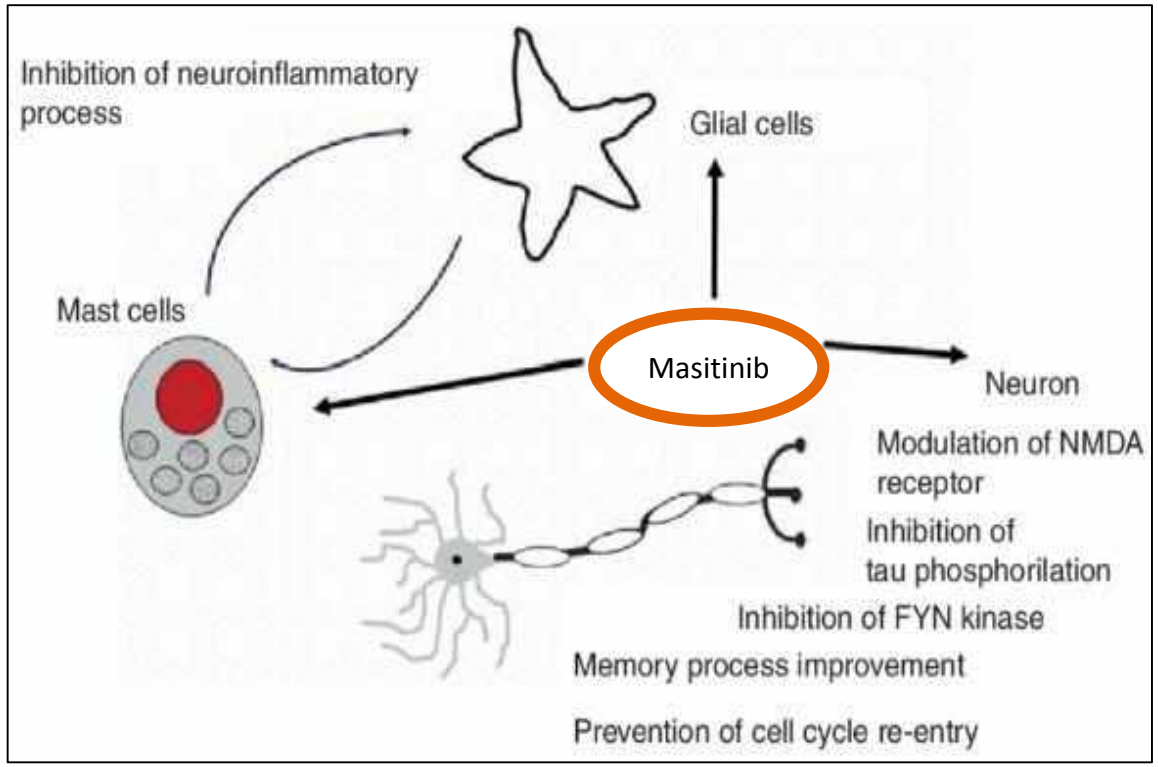

Image courtesy J Folch, D Petrov, M Ettcheto,et al. (2015) Masitinib for the treatment of mild to moderate Alzheimer's disease, Expert Review of Neurotherapeutics, 15:6, 587-596,

AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEGENERATION2020, VOL. 21, NO. 1-2, 5-14
https://doi.org/10.1080/21678421.2019.1632346

ABSTRACT

Objective: To assess masitinib in the treatment of ALS. *Methods:* Double-blind study, randomly assigning 394 patients (1:1:1) to receive riluzole (100 mg/d) plus placebo or masitinib at 4.5 or 3.0 mg/kg/d. Following a blinded transition from phase 2 to phase 2/3, a prospectively defined two-tiered design was implemented based on ALSFRS-R progression rate from disease-onset to baseline (ΔFS). This approach selects a more homogeneous primary efficacy population ("Normal Progressors", ΔFS < 1.1 points/month) while concurrently permitting secondary assessment of the broader population. Primary endpoint was decline in ALSFRS-R at week-48 (ΔALSFRS-R), with the high-dose "Normal Progressor" cohort being the prospectively declared primary efficacy population. Missing data were imputed *via* last observation carried forward (LOCF) methodology with sensitivity analyses performed to test robustness. *Results:* For the primary efficacy population, masitinib ($n = 99$) showed significant benefit over placebo ($n = 102$) with a ΔALSFRS-R between-group difference (ΔLSM) of 3.4 (95% CI 0.65–6.13; $p = 0.016$), corresponding to a 27% slowing in rate of functional decline (LOCF methodology). Sensitivity analyses were all convergent, including the conservative multiple imputation technique of FCS-REGPMM with a ΔLSM of 3.4 (95% CI 0.53–6.33; $p = 0.020$). Secondary endpoints (ALSAQ-40, FVC, and time-to-event analysis) were also significant. Conversely, no significant treatment-effect according to ΔALSFRS-R was seen for the broader "Normal and Fast Progressor" masitinib 4.5 mg/kg/d cohort, or either of the low-dose (masitinib 3.0 mg/kg/d) cohorts. Rates of treatment-emergent adverse events (AEs) (regardless of causality or post-onset ΔFS) were 88% with masitinib 4.5 mg/kg/d, 85% with 3.0 mg/kg/d, and 79% with placebo. Likewise, rates of serious AE were 31, 23, and 18%, respectively. No distinct event contributed to the higher rate observed for masitinib and no deaths were related to masitinib. *Conclusions:* Results show that masitinib at 4.5 mg/kg/d can benefit patients with ALS. A confirmatory phase 3 study will be initiated to substantiate these data.

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Trametinib (SNR 1611)
Completed Phase 1/2 trial

- **Trametinib** (SNR1611) is a MEK inhibitor that downregulates the MAPK/ERK pathway'
- These signaling pathway regulate a variety of cellular activities including proliferation, differentiation, survival, and death.
- Can help in preventing TDP43 accumulation
- First in human Phase 1/2 trial has been initiated

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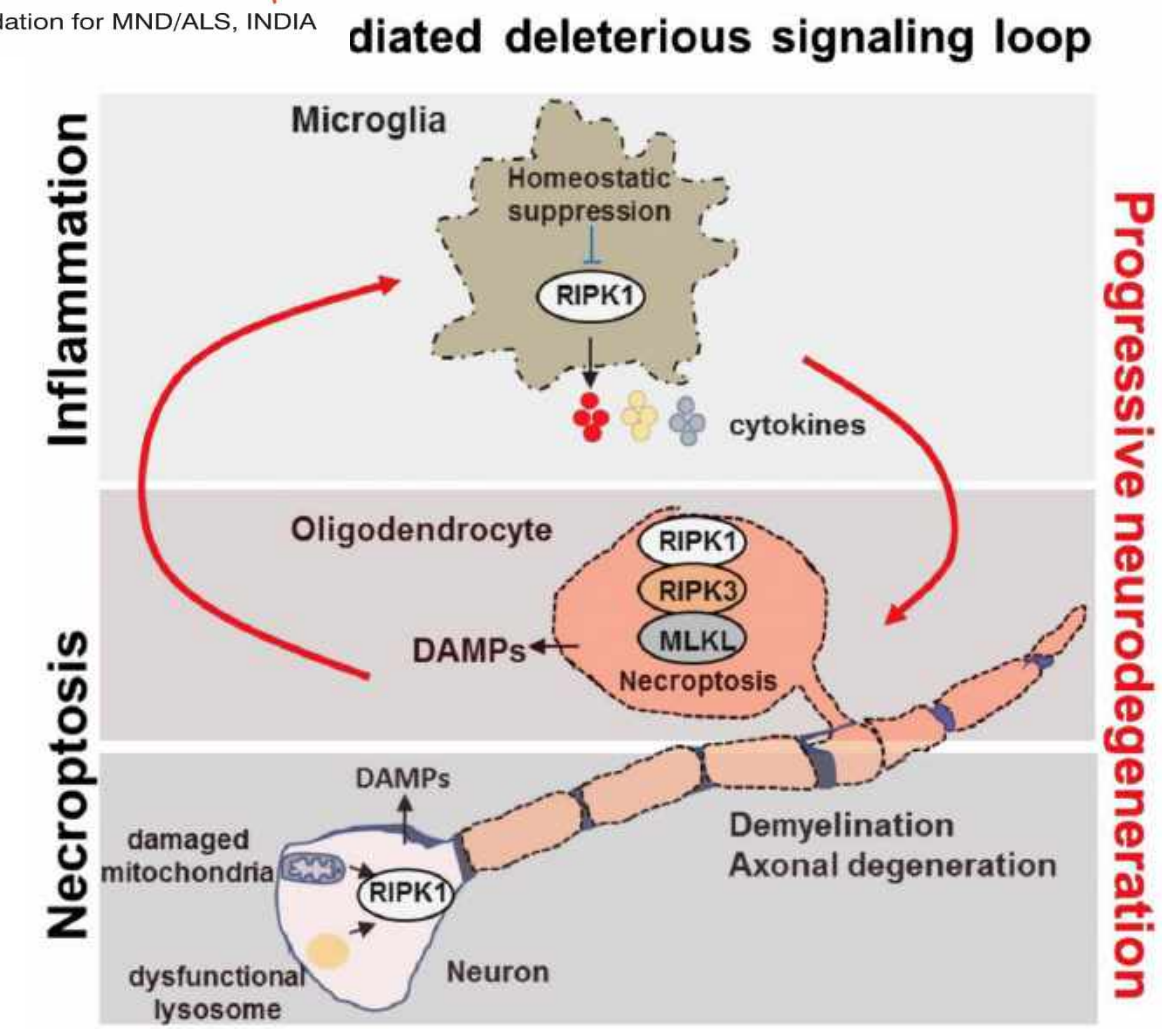
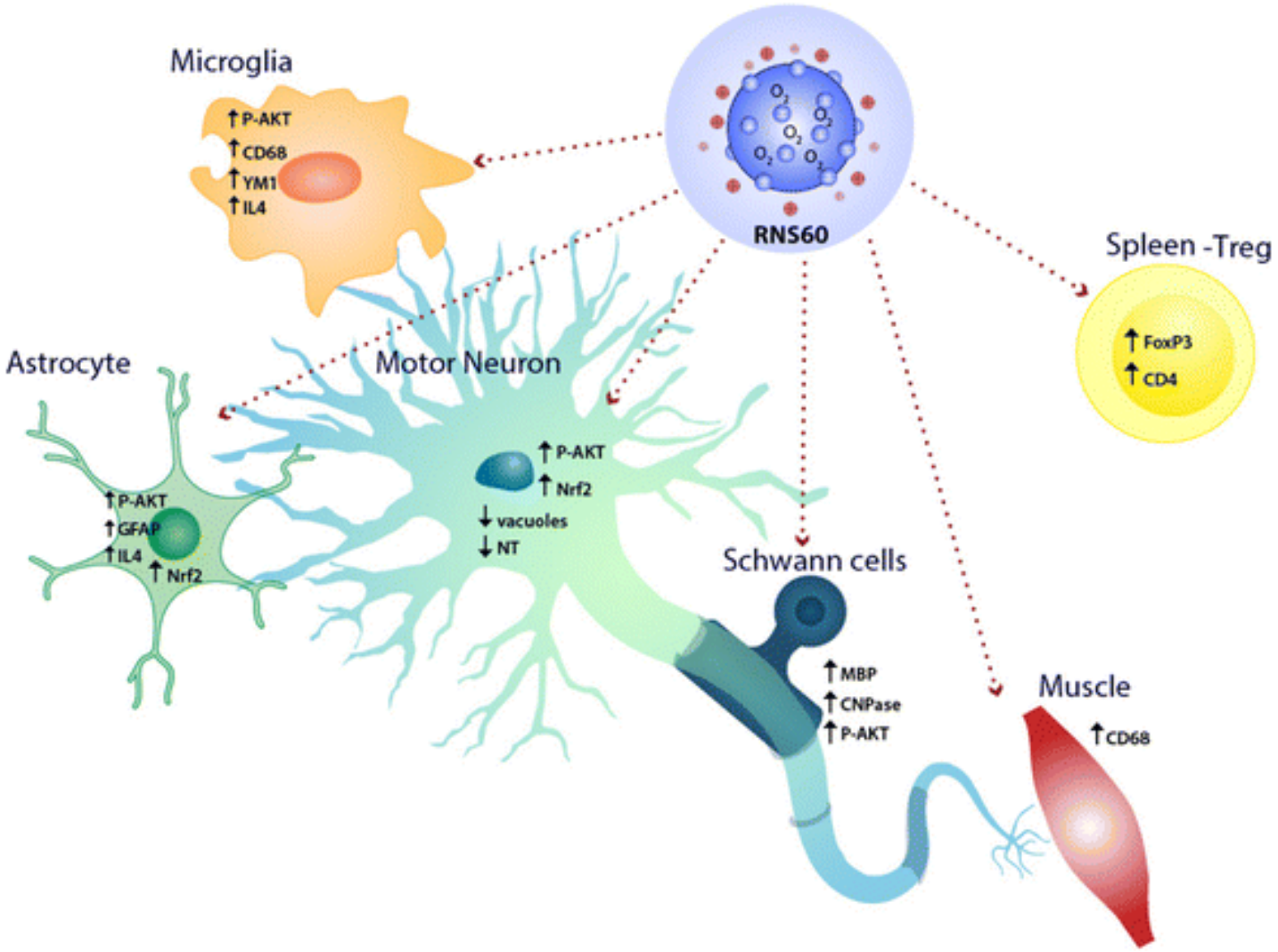


DNL747
Started Phase 2 trial

- Overactive RIPK1 protein is involved in excess inflammation and cell death in the brain, contributing to neurodegeneration in diseases that include ALS.
- DNL747 inhibits RIPK1 protein

RNS60 Currently in Phase 2 trial

- RNS60 is an electrokinetically altered aqueous fluid. Chemically, RNS60 is composed of saline and oxygen
- Acts on the immune and inflammatory mechanisms implicated in ALS.
- thus preventing cell damage or death.



Clenbuterol

Currently in Phase 2

- ✓ It is a beta2 adrenergic agonist.
- ✓ It has an anabolic effect on skeletal muscles mediated by beta 2 adrenergic receptors on the cell membrane
- ✓ It also stimulates the beta adrenoreceptors in the CNS leading to increase Neurotrophic Growth Factor (NGF).
- ✓ It has shown neuroprotective effect on animal models

Open label pilot trial in which 25 people with ALS will take clenbuterol orally at 40-80 micrograms twice daily for 24 weeks.

The critical test of treatment efficacy will be the comparison of the ALSFRS-R slope during treatment to the estimated pre-treatment slope.

NCT04245709

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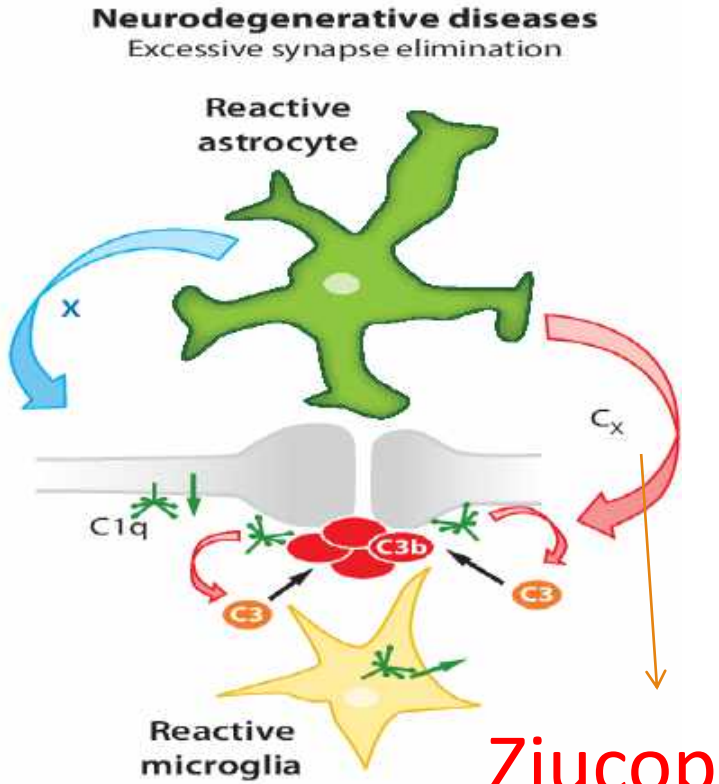
ZILUCOPLAN

Currently in Phase 2

- a small peptide that binds to key players of the complement cascade with high affinity and specificity (C5 and C5b).
- Complement inhibition represents a targeted approach toward addressing the main mechanism of tissue damage in generalized myasthenia gravis.



Ziucoplan

JAMA Neurology | Original Investigation

Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients With Moderate to Severe Generalized Myasthenia Gravis

Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial

IMPORTANCE Many patients with generalized myasthenia gravis (gMG) have substantial clinical disability, persistent disease burden, and adverse effects attributable to chronic

Significance testing was prespecified at a 1-sided α of .10. Safety and tolerability were also assessed.

Zilucoplan yielded rapid, meaningful, and sustained improvements over 12 weeks in a broad population of patients with moderate to severe AChR-Ab–positive gMG. Near-complete complement inhibition appeared superior to submaximal inhibition. The observed safety and tolerability profile of zilucoplan was favorable.

INTERVENTIONS Patients were randomized 1:1:1 to a daily SC self-injection of placebo, 0.1-mg/kg zilucoplan, or 0.3-mg/kg zilucoplan for 12 weeks.

MAIN OUTCOMES AND MEASURES The primary and key secondary end points were the change from baseline to week 12 in QMG and MG Activities of Daily Living scores, respectively.

CONCLUSIONS AND RELEVANCE Zilucoplan yielded rapid, meaningful, and sustained improvements over 12 weeks in a broad population of patients with moderate to severe AChR-Ab–positive gMG. Near-complete complement inhibition appeared superior to submaximal inhibition. The observed safety and tolerability profile of zilucoplan was favorable.

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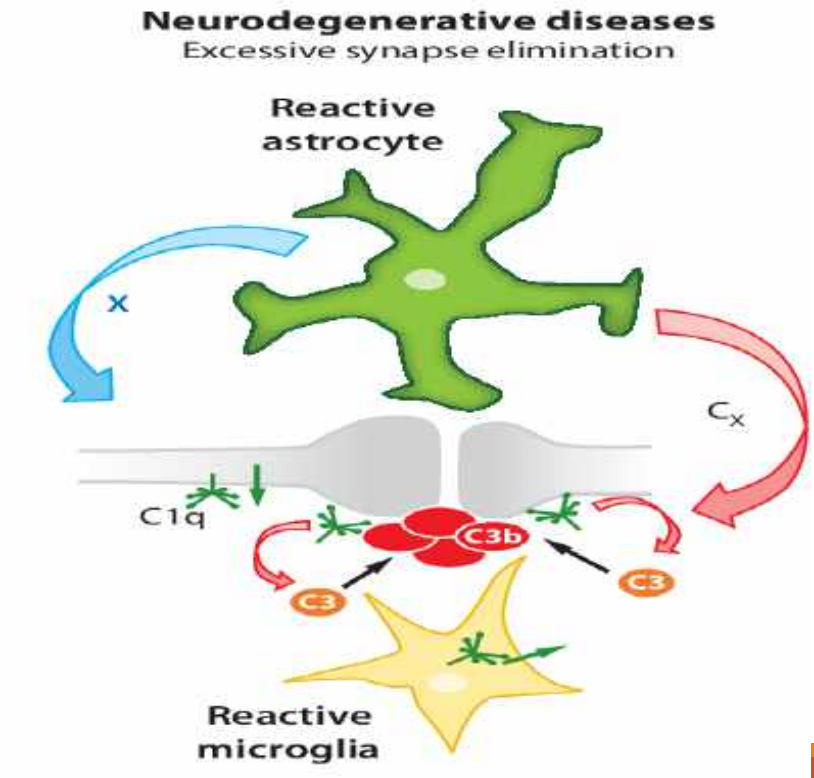
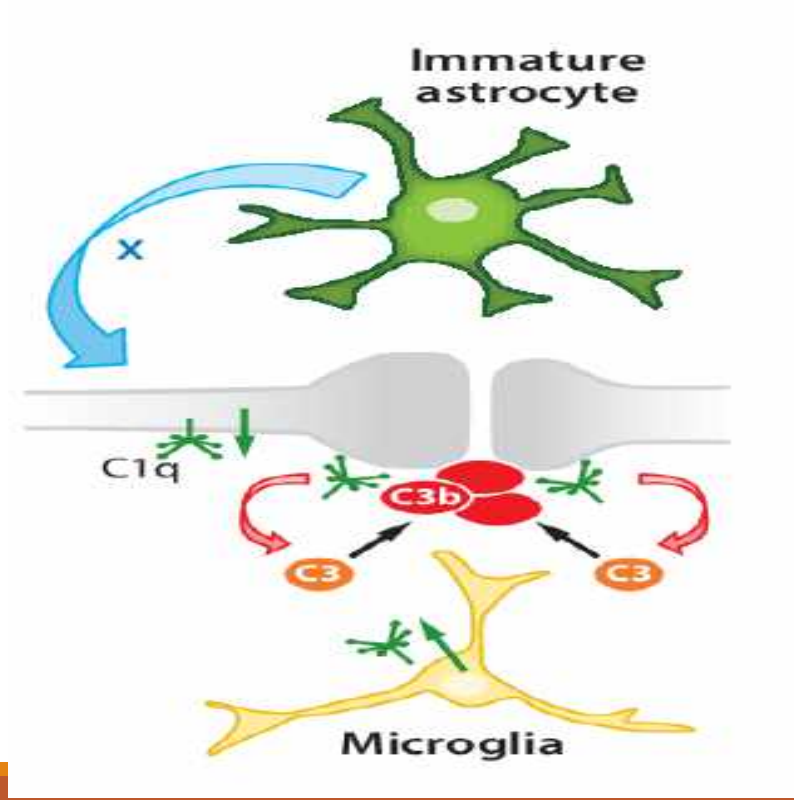
Ravulizumab

Currently in Phase 3

- Excessive or deregulated complement activation can cause ALS
- **Ravulizumab** is a long acting C5 complement system inhibitor
- It can help to slow down disease progression



Ravuliumab reduces synaptic elimination by inhibiting complement system



Clinical Study Identifier: NCT02605993

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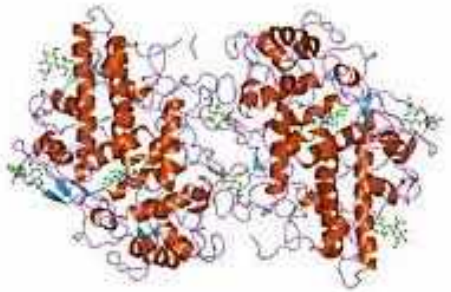
VERDIPERSTAT (AZD3241)

Currently in Phase 2/3



- Irreversible myeloperoxidase (MPO) inhibi
- Reduces oxidative stress and neuro-inflam
- Consistently shown neuroprotective efficacy in MPTP-lesioned mice model
- Demonstrated significant neuroprotection, with preservation of neurons at the level of substantia nigra pars compacta, striatum, cerebellar cortex, pontine nuclei, and inferior olivary complex, as well as functional recovery

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Effect of the Myeloperoxidase Inhibitor AZD3241 on Microglia: A PET Study in Parkinson's Disease

Aurelija Jucaite [1], Per Svenningsson [2], Juha O Rinne [3], Zsolt Cselényi [4], Katarina Varnäs [5], Peter Johnström [4], Nahid Amini [5], Anna Kirjavainen [3], Semi Helin [3], Margaret Minkwitz [6], Alan R Kugler [6], Joel A Posener [6], Samantha Budd [6], Christer Halldin [5], Andrea Varrone [5], Lars Farde [4]

Affiliations + expand

PMID: 26137956 DOI: 10.1093/brain/awv184

NeuroGen
Brain and Spine Institute
Centre for Stem Cell Therapy and Neurorehabilitation
ISO 9001:2008 Certified

Myeloperoxidase is a reactive oxygen generating enzyme and is expressed by microglia. The novel compound AZD3241 is a selective and irreversible inhibitor of myeloperoxidase. The hypothesized mechanism of action of AZD3241 involves reduction of oxidative stress leading to reduction of sustained neuroinflammation. AZD3241 was safe and well tolerated. The reduction of (11)C-PBR28 binding to translocator protein in the brain of patients with Parkinson's disease after treatment with AZD3241 supports the hypothesis that inhibition of myeloperoxidase has an effect on microglia. The results of the present study provide support for proof of mechanism of AZD3241.

equal to 0.5–0.6. There was no overall change in total distribution volume in the placebo group (n = 6). AZD3241 was safe and well tolerated. The reduction of (11)C-PBR28 binding to translocator protein in the brain of patients with Parkinson's disease after treatment with AZD3241 supports the hypothesis that inhibition of myeloperoxidase has an effect on microglia. The results of the present study provide support for proof of mechanism of AZD3241 and warrant extended studies on the efficacy of AZD3241 in neurodegenerative disorders.

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Arimoclomal
In Phase III as of 2020

- Arimoclomol increases expression of a number of Heat Shock Proteins (HSPs)
- HSPs can bind to misfolded or faulty proteins and help to remove it from the cells
- HSP70 is found to bind with the faulty SOD1 protein and remove it
- Arimoclomol also acts on the muscle resulting in better preservation of muscle innervation.

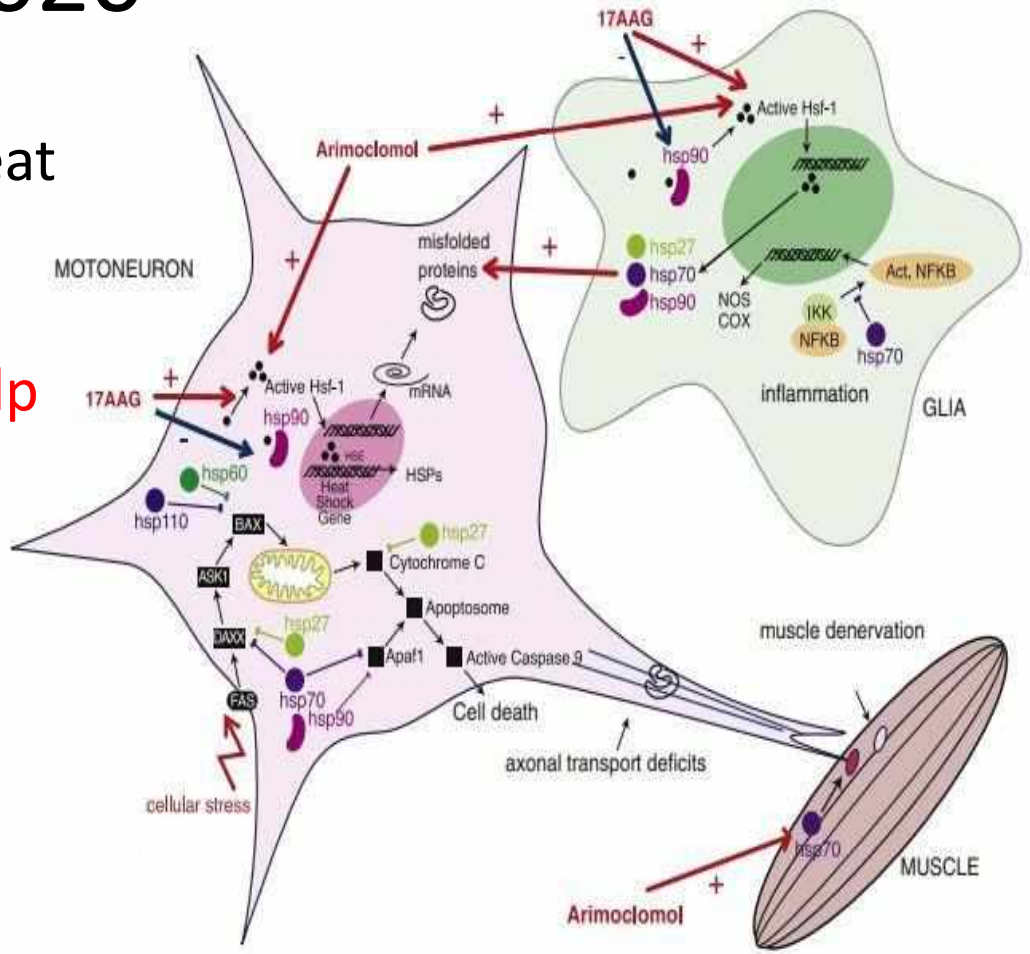

Image adapted from Kalmar, B., et al., The role of heat shock proteins in Amyotrophic Lateral Sclerosis: The therapeutic potential of Arimoclomol, Pharmacol. Ther. (2013), http://dx.doi.org/10.1016/j.pharmthera.2013.08.003

Previously published results

Arimoclomol at Dosages Up to 300 mg/day Is Well Tolerated and Safe in Amyotrophic Lateral Sclerosis

Merit E Cudkowicz [1], Jeremy M Shefner, Elizabeth Simpson, Daniela Grasso, Hong Yu, Hui Zhang, Amy Shui, David Schoenfeld, Robert H Brown, Scott Wieland, Jack R Barber, Northeast ALS Consortium

Collaborators, Affiliations + expand

PMID: 18551622 DOI: 10.1002/mus.21059

Abstract

Arimoclomol is an investigational drug for amyotrophic lateral sclerosis (ALS) that amplifies heat shock protein gene expression during cell stress. The objectives of the present study were to assess the safety, tolerability, and pharmacokinetics of arimoclomol in ALS. Eighty-four participants with ALS received arimoclomol at one of three oral doses (25, 50, or 100 mg three times daily) or placebo. The primary outcome measure was safety and tolerability. A subset of 44 participants provided serum and cerebrospinal fluid (CSF) samples for pharmacokinetic analysis. Participants who completed 12 weeks of treatment could enroll in a 6-month open-label study. Arimoclomol at doses up to 300 mg/day was well tolerated and safe. Arimoclomol resulted in dose-linear pharmacologic exposures and the half-life did not change with continued treatment. Arimoclomol CSF levels increased with dose. Arimoclomol was shown to be safe, and it crosses the blood-brain barrier. Serum pharmacokinetic profiles support dosing of three times per day. An efficacy study in ALS is planned.

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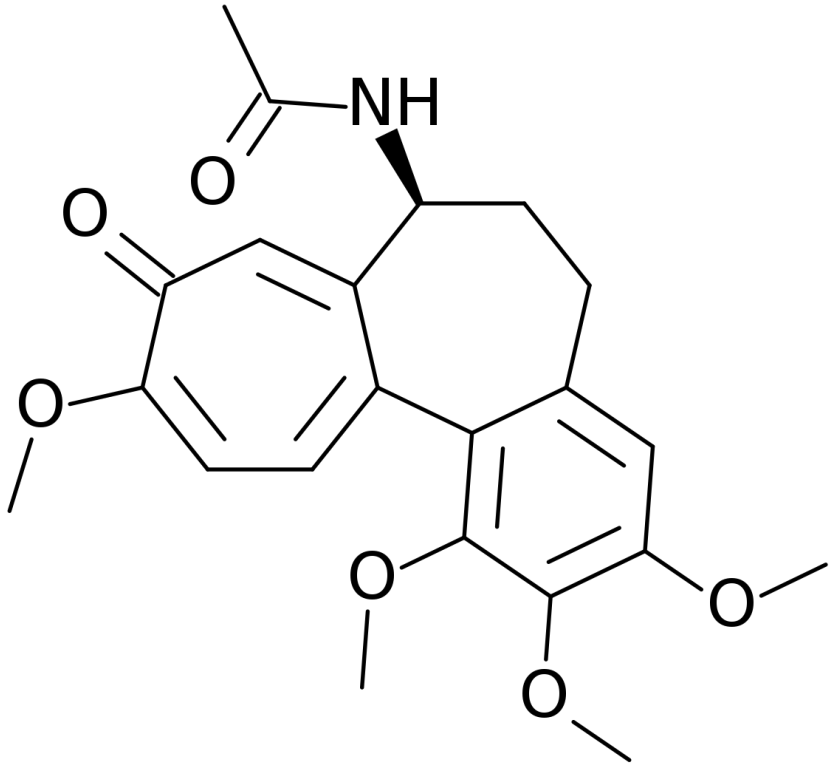
Colchicine

Started Phase 2 trial

- Enhances the expression of HSPB8 and of several autophagy players
- Blocks TDP-43 accumulation in neurons
- Has an anti-inflammatory effect



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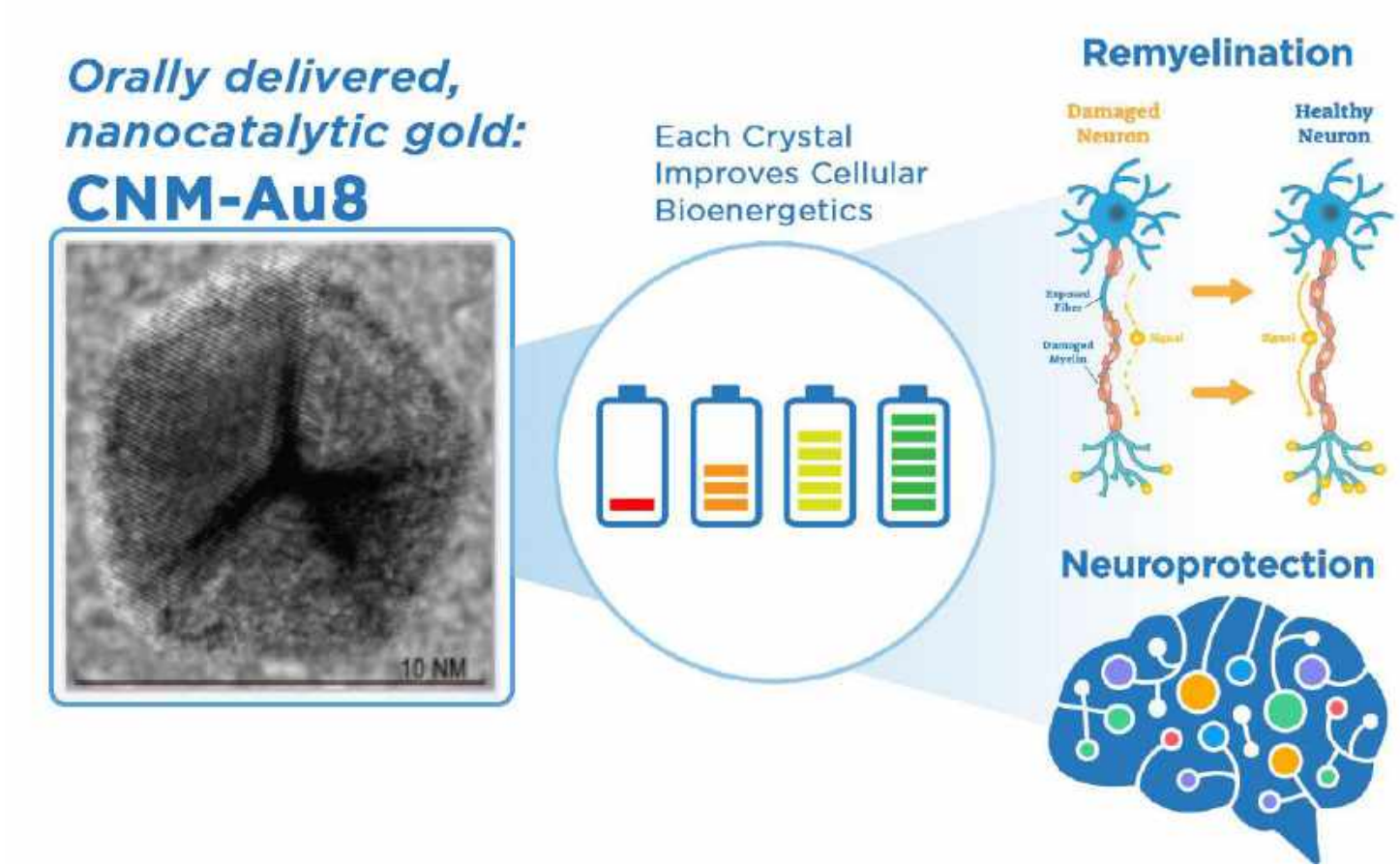
CNM-Au8



- CNM-Au8 is being explored for ALS,PD and MS
- Suspension of Nanocrystalline gold
- Support biological reactions within cells and cellular reactions that generate energy,
- Remove the destructive by-products of cellular metabolism
- Preclinical studies have demonstrated that CNM-Au8 is able to protect motor neurons
- 2 Phase 2 trials currently underway: RESCUE-ALS (Australia), recruiting patients; and REPAIR-ALS (USA), not yet recruiting

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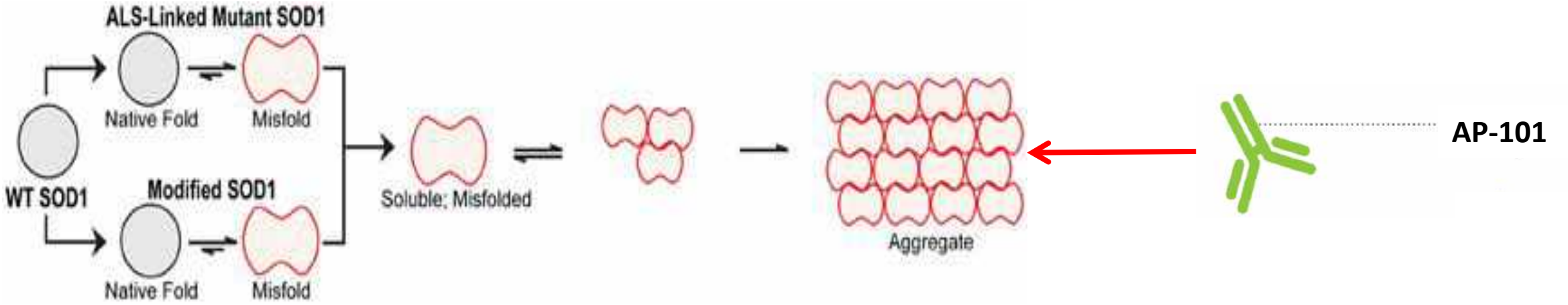
AP-101

Enrolling in Phase 1 trial

- AP-101 is a human monoclonal antibody that targets, and therefore reduces or eliminates, misfolded superoxide dismutase-1 (SOD1)



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NeuroGen
Brain and Spine Institute

02.28.20

Nanocatalytic Gold Therapy Well Tolerated in Clinical Trial for Multiple Sclerosis

MS & Immune Disorders

Preliminary data from the randomized placebo-controlled phase 2 VISIONARY-MS trial (NCT03536559) of nanocatalytic gold therapy (CNM-Au8; Clene Nanomedicine, Salt Lake City, UT) suggest the drug is well tolerated. Preliminary blinded data also suggest that treatment with nanocrystalline gold improves disability measures for people with multiple sclerosis (MS).

For the first 34 enrolled participants, median improvements were seen in low contrast letter acuity (LCLA) and the Multiple Sclerosis Functional Composite (MSFC) subscales (Symbol Digit Modalities Test, 9-Hole Peg Test, and Timed 25-foot Walk (gait). Physiologic measures are also being studied, including retinal cell ganglion layer thickness on optical coherence tomography (OCT) and visual evoked potential latency.

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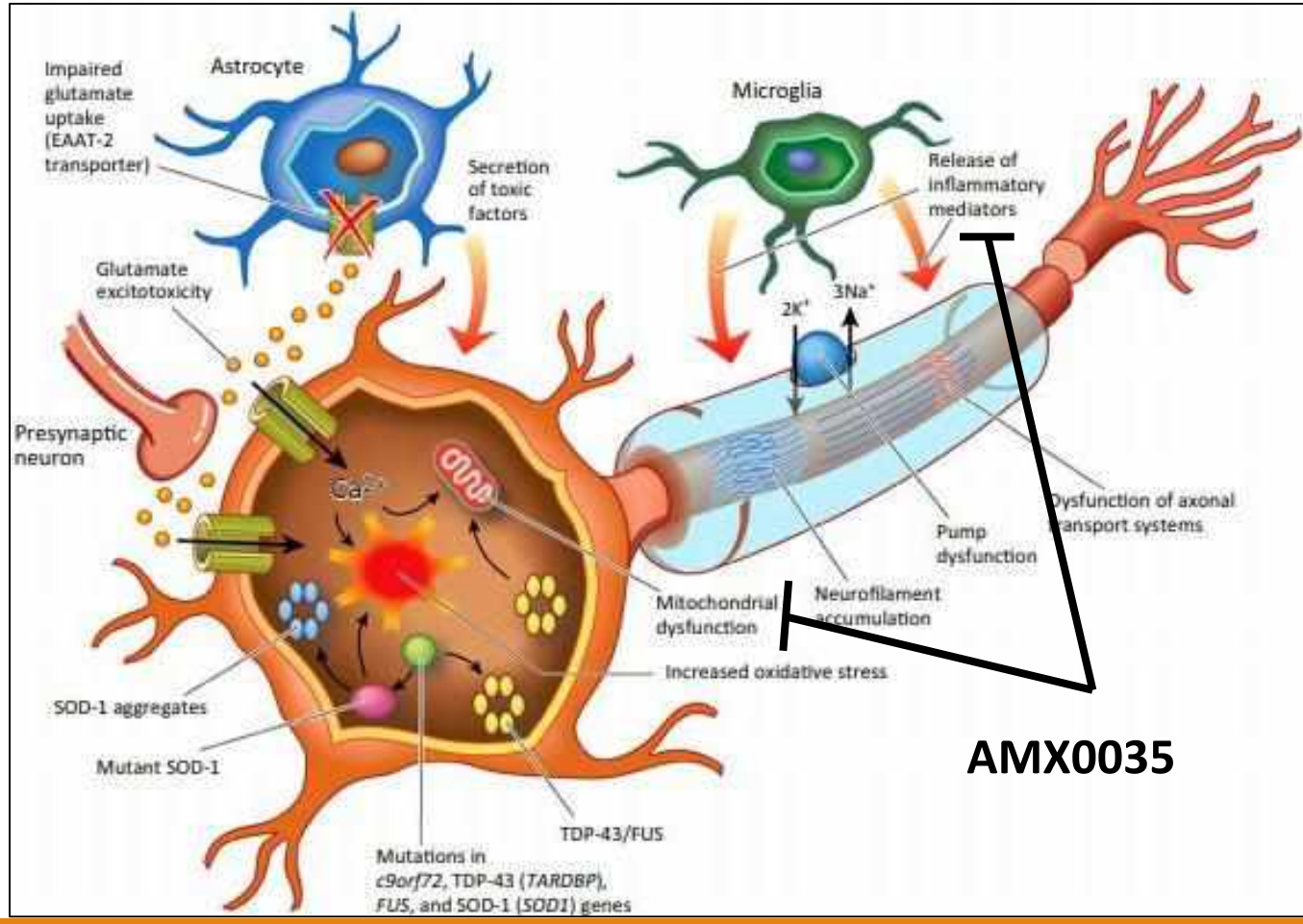
AMX0035
Enrolling in Phase 2 trial

- Combination of two compounds — sodium phenylbutyrate (PB) and tauroursodeoxycholic acid (TUDCA)

- Minimizes cellular mechanisms linked to cell death



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GM604

Currently in Phase 2b/3

- GM604 affects multiple pathways to treat ALS and promote motor neuron survival by slowing degeneration

Phase 2 A trial results

- ✓ Respiratory symptoms significantly better
- ✓ Decreased ALS biomarkers (TDP, Tau and SOD1)
- ✓ Slower funtional decline in ALS-FRSr
- ✓ Symptomatic improvement

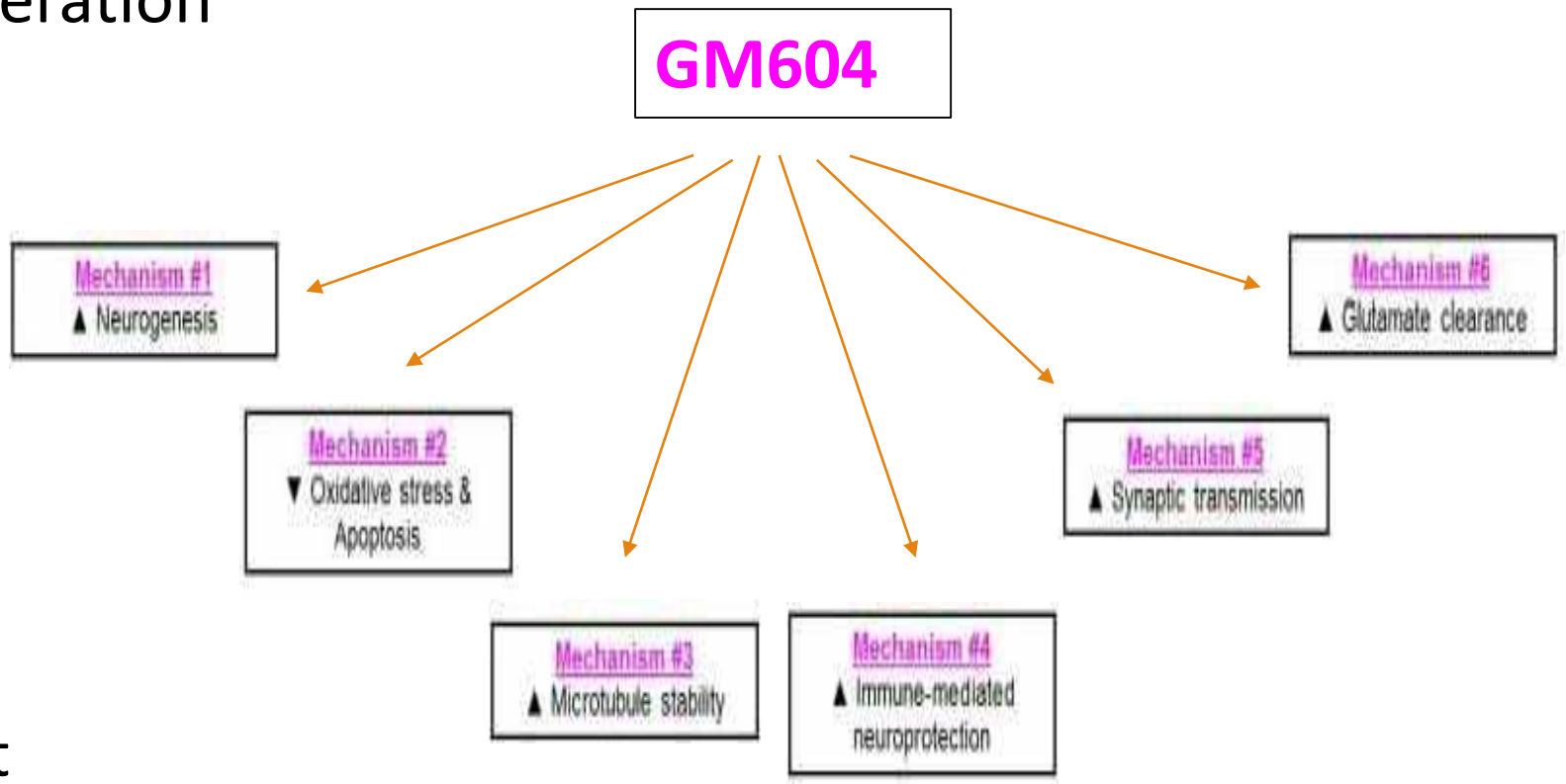

Figure adapted from Partnership Presentation by Winston Ko CEO, Genervon Biopharmaceuticals 2018 BIO CEO & Investor Conference, New York

RECOMBINANT HUMAN ERYTHROPOIETIN

Currently in Phase 1/2

Recombinant Human Erythropoietin in Amyotrophic Lateral Sclerosis: A Pilot Study of Safety and Feasibility

Abstract

Objective: The primary objective of the study is to evaluate the efficacy of MN-166 on patient's functional activity

There were no serious adverse events in the first study. In the second study, the mean rate of decline in ALSFRS-R score was significantly lower in the rhEPO group than in the control group (during months 0-3, 1.8±1.7 vs. 3.1±2.3, *p*=0.03; during months 4-6, 2.1±2.2 vs. 3.5±2.3, *p*=0.02).
Intravenous high-dose rhEPO is both safe and feasible for the treatment of ALS.

Riluzole is believed to delay disease progression and prolong survival by a few months. Edaravone has shown benefit in slowing disease progression, but its effect for survival is uncertain. There is a great need for safe, effective conventionally administered therapy for this fatal disease.

MN-166 is an orally available small molecule that penetrates the central nervous system well. It inhibits macrophage migration inhibitory factor and phosphodiesterases 3,4, and 10 with demonstrated neuroprotective action and glial cell attenuation in multiple in vitro and in vivo models. Based on findings from a completed Phase 1b/2a trial in ALS subjects, we hypothesize MN-166 in combination with riluzole can slow disease progression more effectively than riluzole alone.

RECOMBINANT HUMAN ERYTHROPOIETIN

Currently in Phase 1/2

- ✓ Inflammatory cytokine levels have important roles in both toxic and protective functions depending on the stage of disease progression in ALS patients.
- ✓ Erythropoietin (EPO) has been shown to be neuroprotective in animal models of neurodegenerative diseases including ALS.
- ✓ Also, reduction of inflammation
- ✓ enhancement of survival signals
- ✓ prevention of neuronal cell death.
- ✓ Ongoing Phase 1/2 Randomized, Double-blind, Safety and Efficacy of Recombinant Human Erythropoietin in Amyotrophic Lateral Sclerosis (NCT03835507).

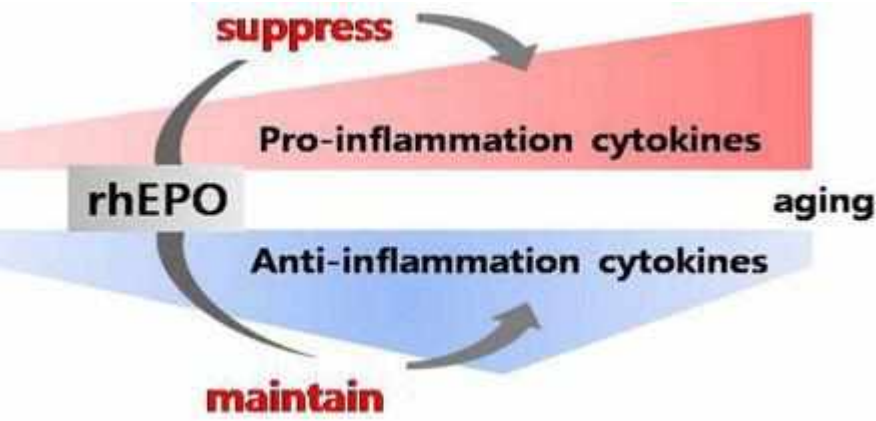

Image: Noh MY, Cho KA, Kim H, Kim SM, Kim SH. Erythropoietin modulates the immune-inflammatory response of a SOD1G93A transgenic mouse model of amyotrophic lateral sclerosis (ALS). Neuroscience letters. 2014 Jun 27;574:53-8.

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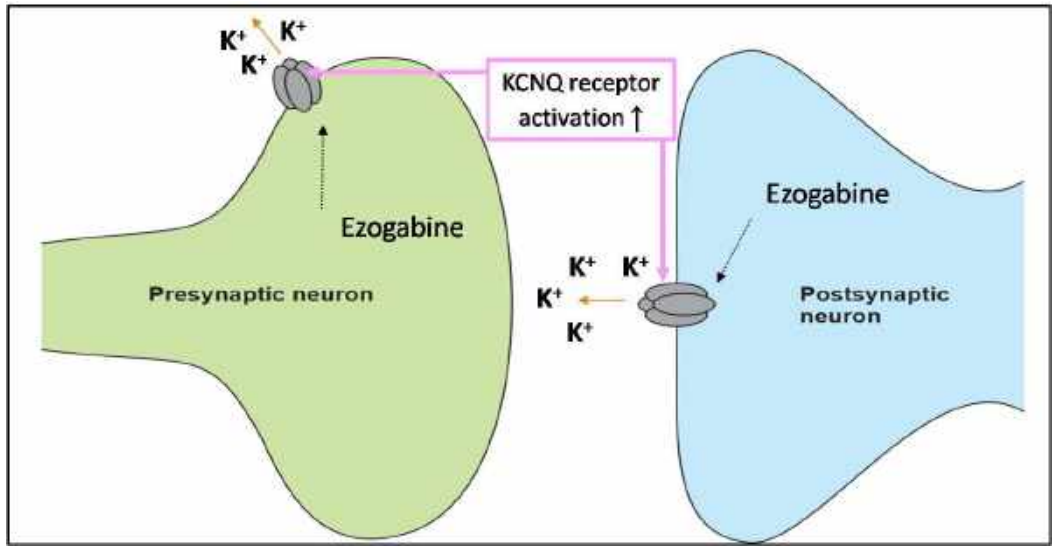
Ezogabine

Completed Phase 2 as of September 2018

- Activates the KCNQ family of voltage-gated potassium channels in neuronal membranes in resting states and calms the excitability that cause seizures
- Results of Phase 2 trial shows that it lessens abnormal motor neuron excitability, or responsiveness
- **There is no further development of trial initiated do you still want to keep this slide?**



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Rasagiline

Completed Phase 2

- Monoamine oxidase B inhibitor, mitochondrial stabilizer already approved for the treatment of Parkinson's Disease.

Abstract

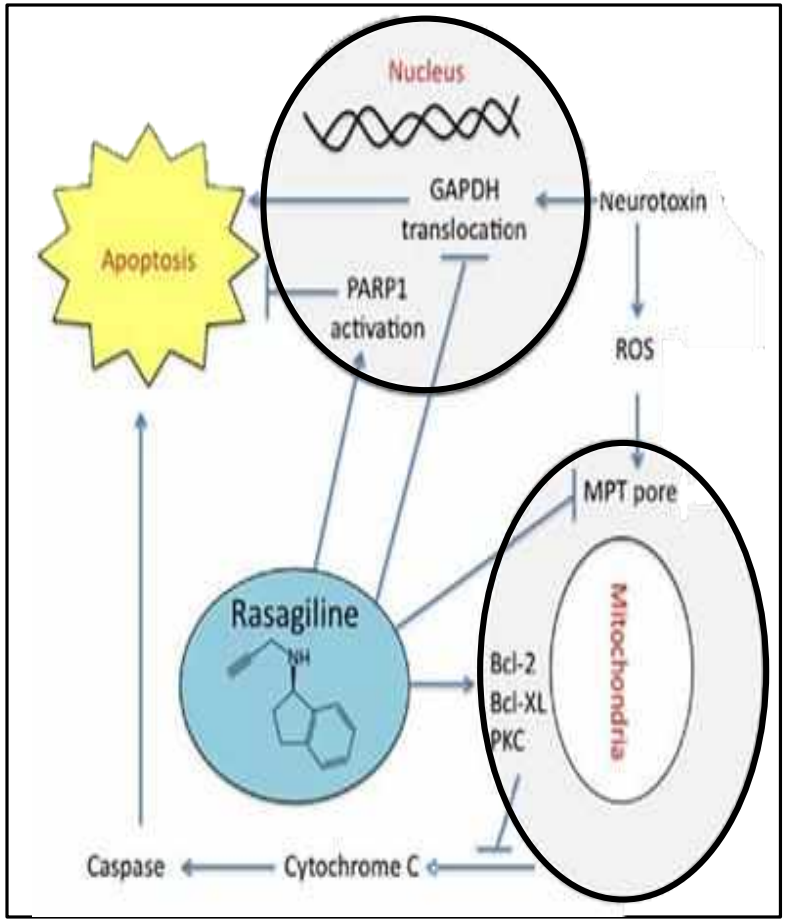
Introduction: Rasagiline is an MAO-B inhibitor with possible neuroprotective effects in patients with amyotrophic lateral sclerosis (ALS).

Methods: We performed a randomized, double-blind, placebo-controlled trial of 80 ALS participants with enrichment of the placebo group with historical controls (n=177) at 10 centers in the United States. Participants were randomized in a 3:1 ratio to 2 mg rasagiline daily or placebo. The primary outcome was the average slope of decline of the ALS Functional Rating Scale-Revised (ALSFRS-R). Secondary measures included slow vital capacity, survival, mitochondrial and molecular biomarkers, and adverse event reporting.

Results: There was no difference in the average 12 months ALSFRS-R slope between rasagiline and the mixed placebo and historical control cohorts. Rasagiline did not show signs of drug-target engagement in urine and blood biomarkers. Rasagiline was well tolerated with no serious adverse events.

Discussion: Rasagiline did not alter disease progression compared to controls over 12 months of treatment.

Clinicaltrials.gov identifier: NCT01786603.



Adapted from Seidl SE, Potashkin JA. The promise of neuroprotective agents in Parkinson's disease [published correction appears in Front Neurol. 2013;7:69]. *Front Neurol*. 2011;2:68. Published 2011 Nov 21.

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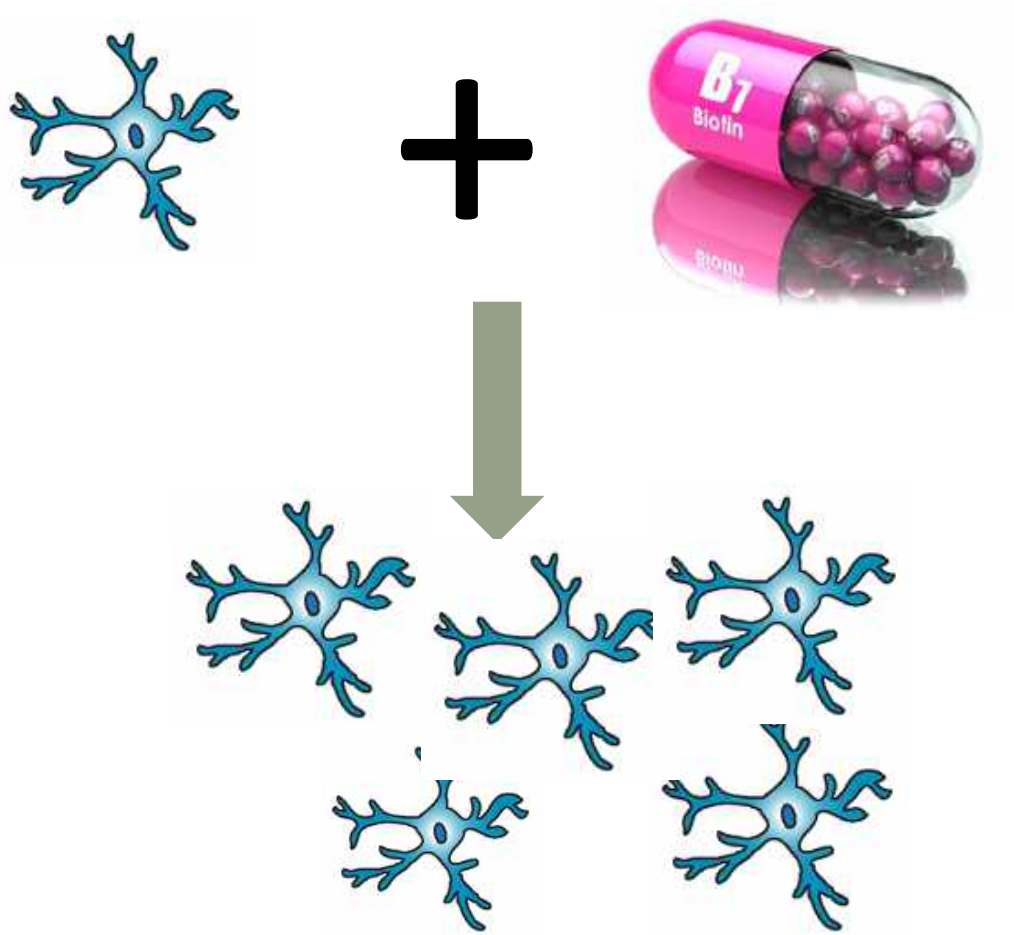
Biotin

Enrolling in Phase 2 trial

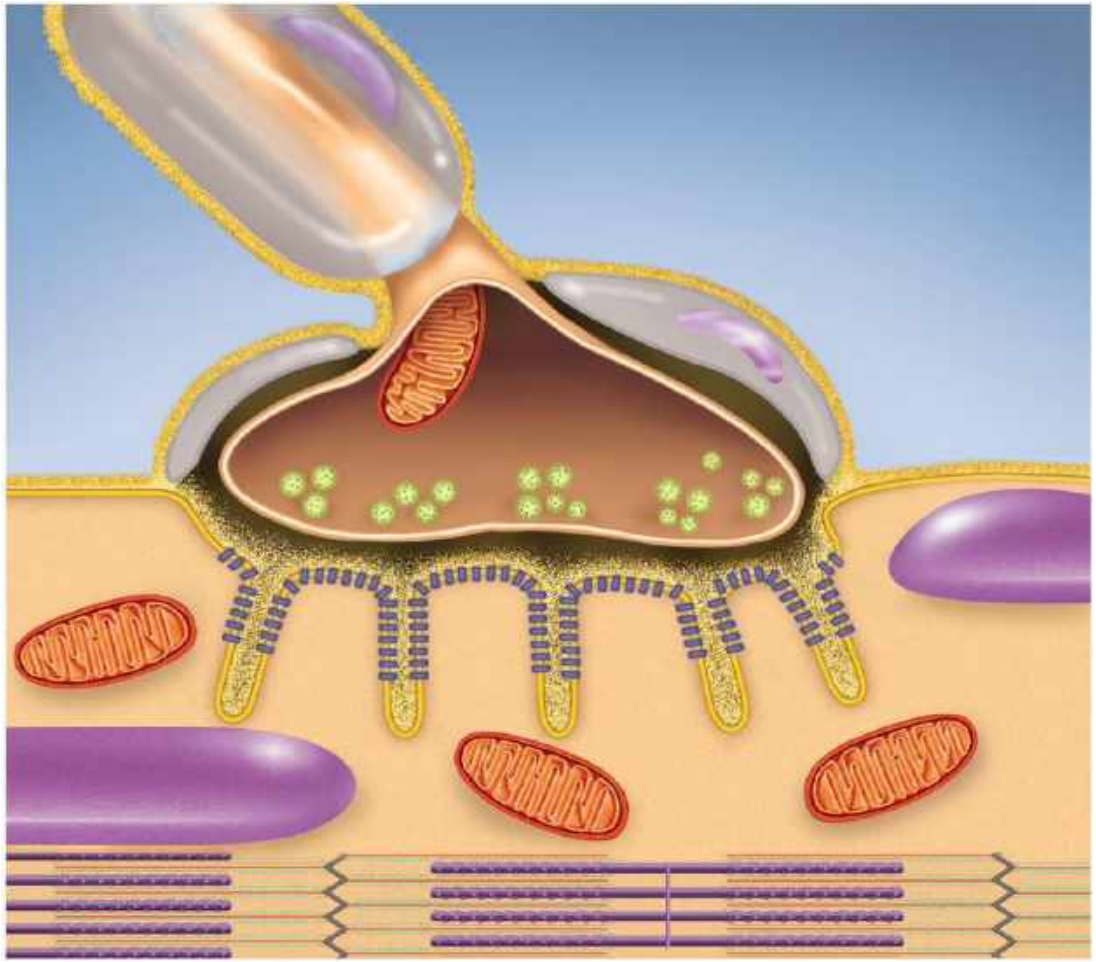
- Low biotin levels cause oligodendrocyte and axonal degeneration
- Treatment with Biotin prevents motor neuron degeneration by preserving oligodendrocytes
- Pilot study results show that Biotin is a safe



Pimozide

Currently in Phase 2

- Pimozide is a FDA approved neuroleptic drug used to treat psychosis, Tourette syndrome, and resistant tics.
- Enhances communication in NMJ
- Phase I study showed that after only six weeks of treatment with, patients were able to retain the control of the thenar muscles



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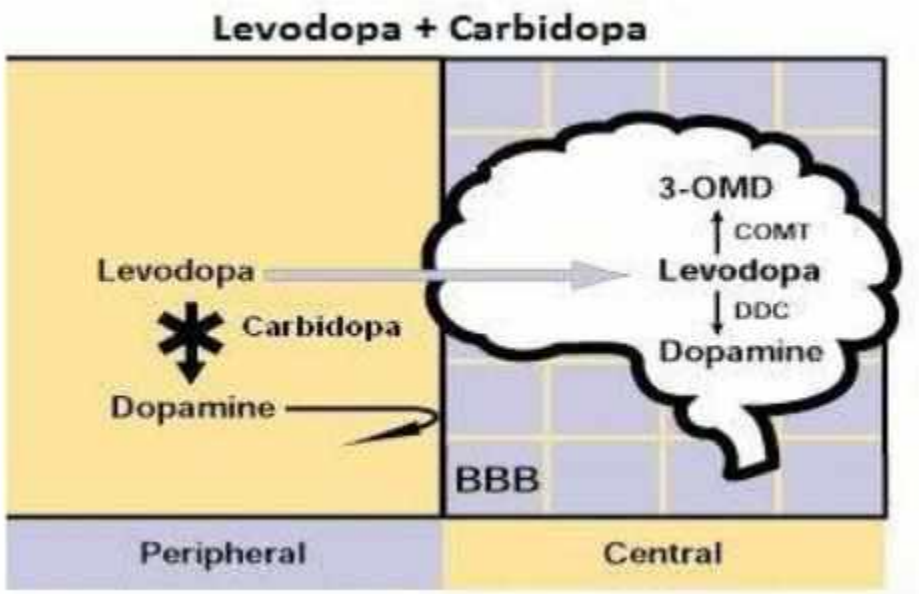
Sinemet (Carbidopa-levodopa)

Currently in Phase 1

- ✓ It is a combination medication that improves the efficacy of levodopa.
- ✓ It is the mainstay of treatment of Parkinson's disease and might have an effect in ALS and PLS patients.
- ✓ In Parkinson's disease pa improved patients' rigidity.



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CuATSM

Currently in Phase 2/3 study

- It is a low-toxicity PET-imaging agent, with excellent ALS patient blood-brain barrier penetration
- It selectively releases of copper in cells with damaged mitochondria
- **Previous results –**

  When compared to the historical cohort over a six-month period
  - ✓Lung function improved
  - ✓Cognitive ability improved
  - ✓Rate of disease progression reduced

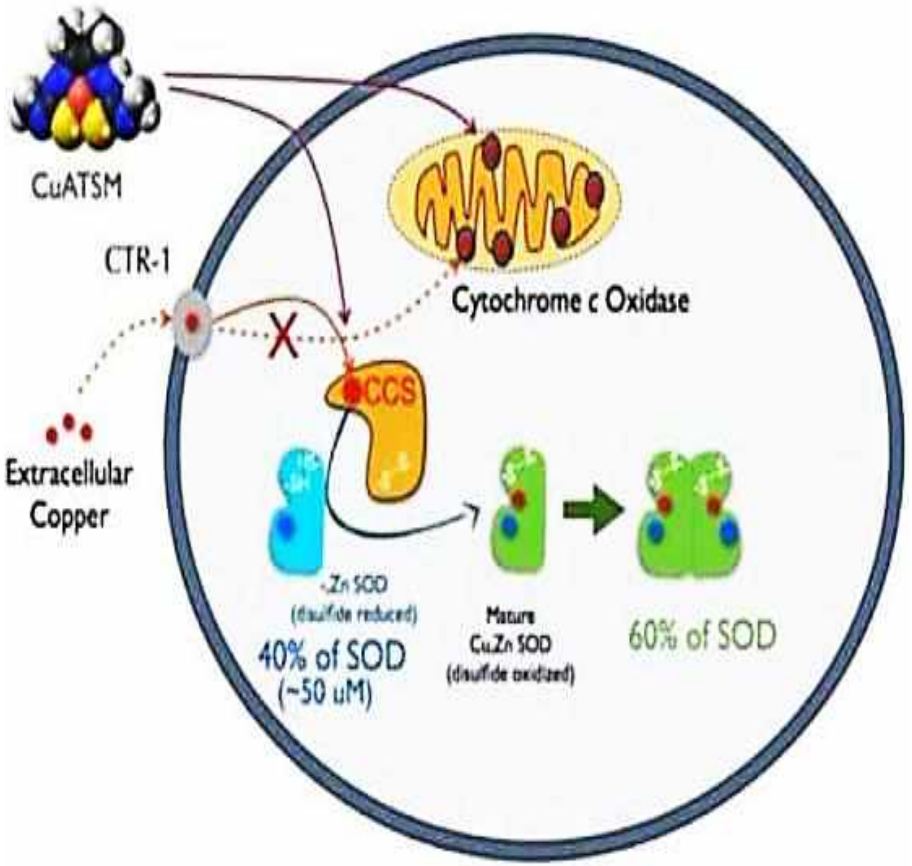
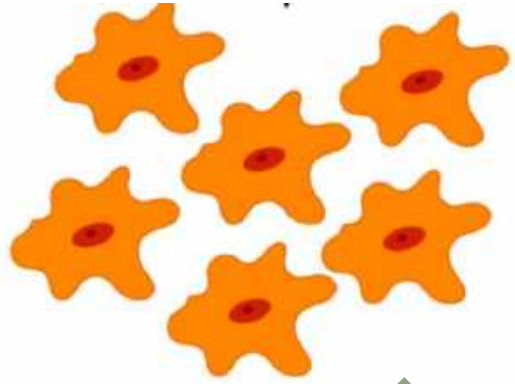


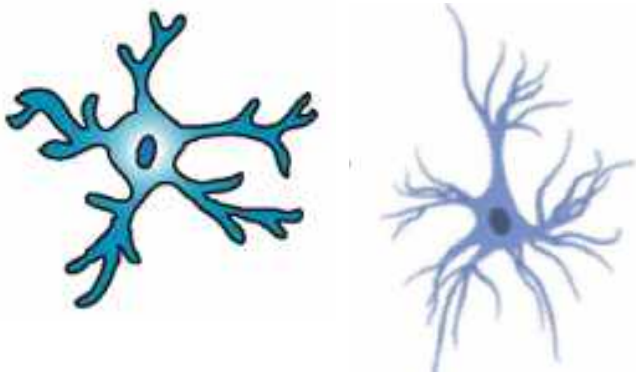
Image courtesy Williams JR, Trias E, Beilby PR, et al. Copper delivery to the CNS by CuATSM effectively treats motor neuron disease in SOD(G93A) mice co-expressing the Copper-Chaperone-for-SOD. *Neurobiol Dis*. 2016;89:1–9. doi:10.1016/j.nbd.2016.01.020

BLZ945

Currently in Phase 2

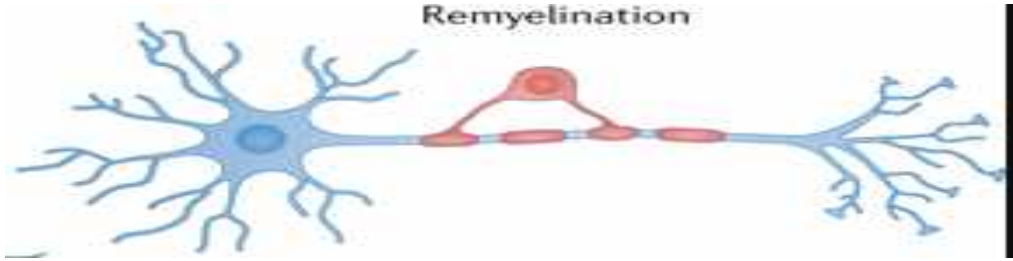


- Induces reduction of microglia



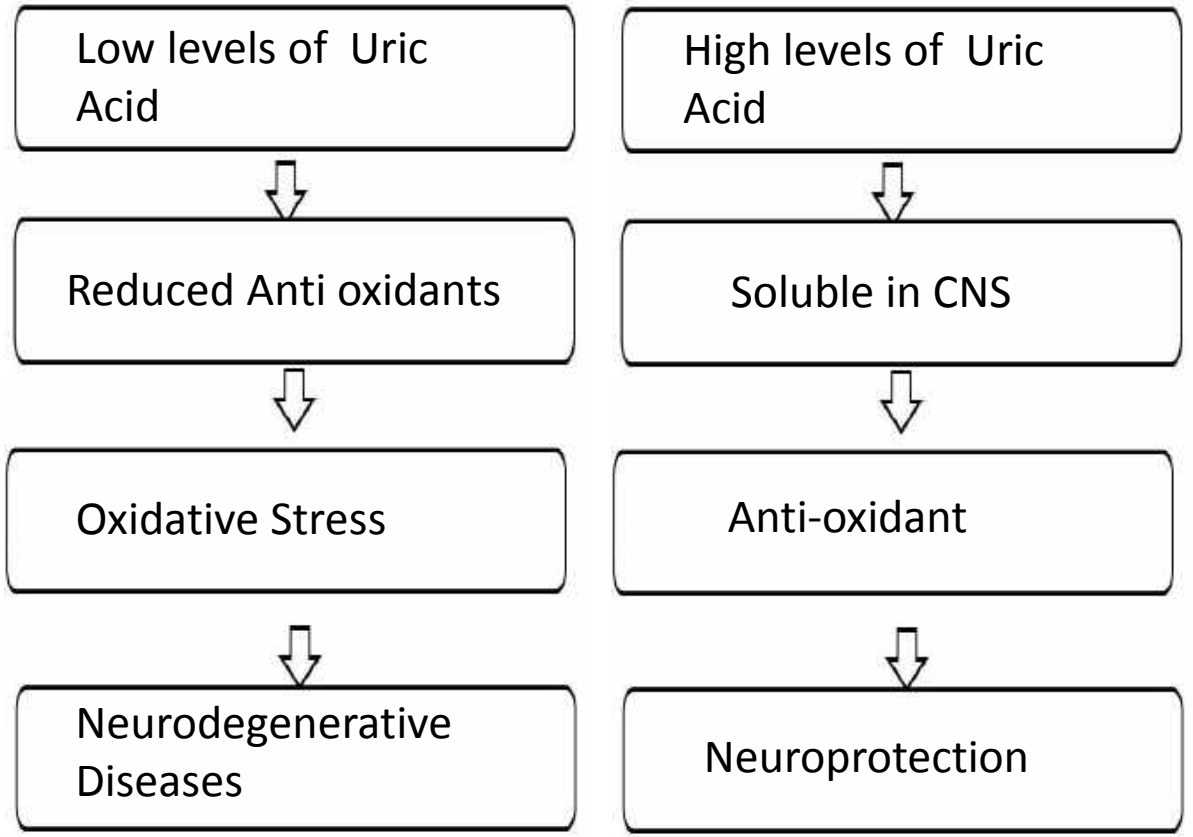
- increased oligodendrocytes and astroglias

- Induces brain region specific enhancement of remyelination



Inosine
In Phase II as of May 2020

- Urates are endogenous anti oxidants and offer neuroprotection
- Rationale of use is to increase urate levels by administering precursor inosine
- A small pilot study with 25 ALS patients over 12 weeks of follow up reported that Inosine is safe.
- Several markers of oxidative stress favourably changed from baseline levels.
- An ongoing Phase 2 trial to test its efficacy (NCT03168711).



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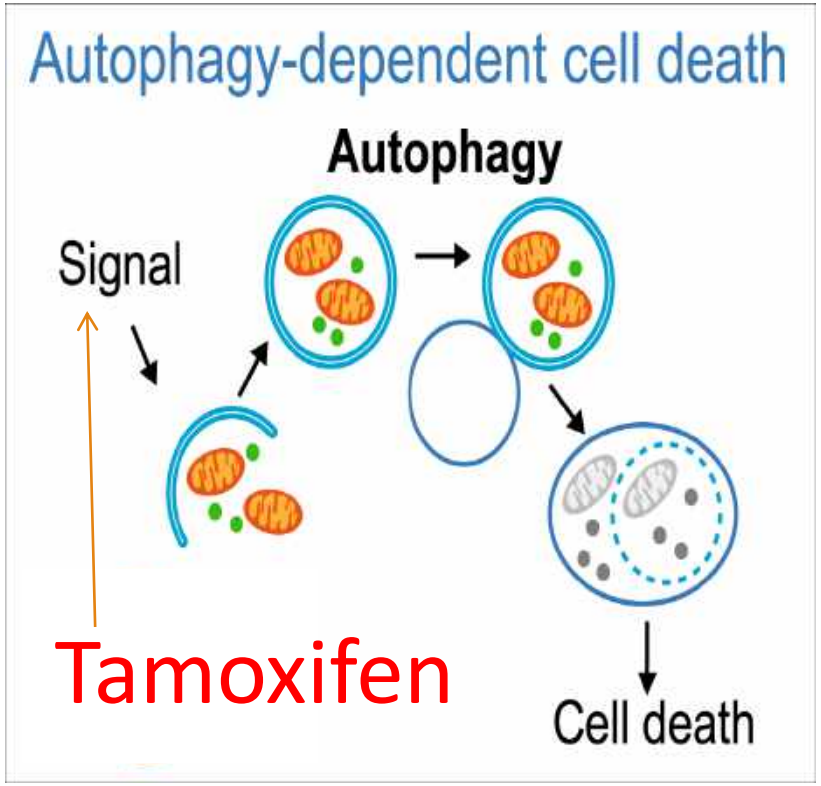
Tamoxifen
Completed Phase 1/2 trial

- Neuroprotective effect
- Regulates autophagy,
- Helps to eliminate toxin protein aggregates and cell components
- Helps to slow down the disease progression
- Phase 1/2 trial results –
  - ✓ The decline in ALSFRS-R scores was lower among those on tamoxifen in the initial period but at 1 year follow up there was not difference
- Tamoxifen given when neuronal loss is minimal may have better effect

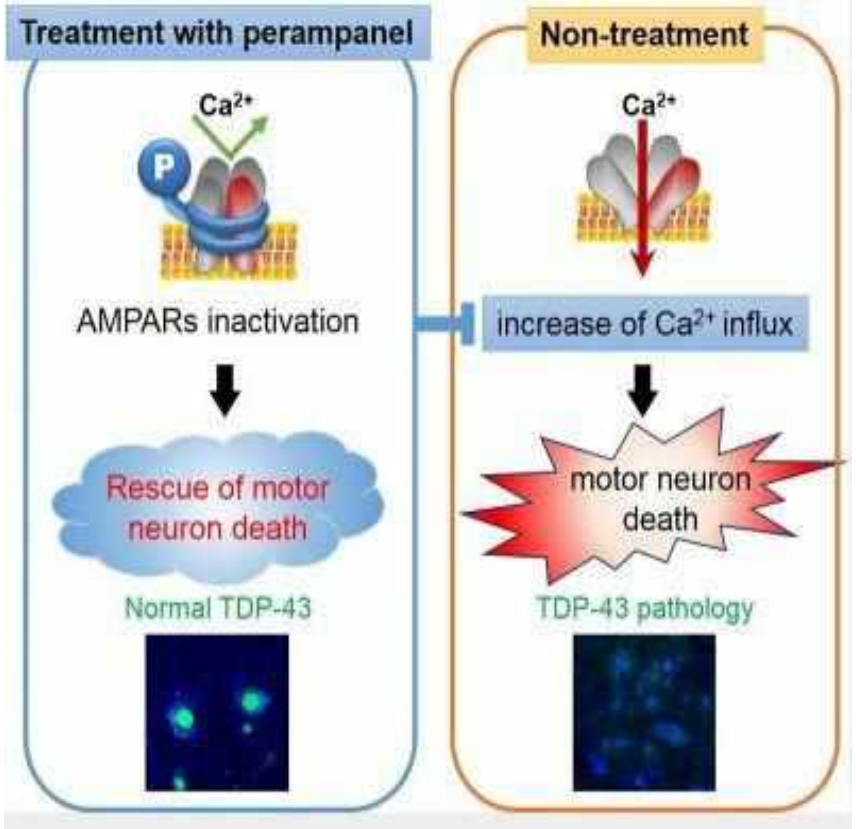


Perampanel (Fycompa)

Currently in Phase 1/2

- It is effective in restricting the inflow of calcium ions into cells.
- Perampanel is approved by the FDA for treatment of seizures in patients with epilepsy.
- a randomised, pilot trial to test perampanel (Fycompa; Eisai, Inc.) in ALS patients.

(NCT03020797).



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Anti retroviral
Started Phase 1 trial

- Some forms of amyotrophic lateral sclerosis (ALS) could actually be caused by an infectious virus, with scientists reporting that human endogenous retrovirus-K (HERV-K), normally dormant, has been found in an active form in the postmortem brain cells of certain individuals with ALS.
- Anti-retroviral drugs like darunavir, Ritonavir, dolutegravir, Tenofovir alafenamide are being tested

Tenofir Alafenamide (TAF)

Currently in Phase 1

- ✓ Antiretroviral therapy for **HERV-K Suppression**
- ✓ Some people with Amyotrophic Lateral Sclerosis (ALS) have a high level of the virus Human Endogenous Retrovirus-K (HERV-K) in their blood.
- ✓ Although Researchers do not think this virus causes ALS but why some people with ALS have a high level is not known.
- ✓ Pilot study demonstrated that the drug was well tolerated.
- ✓ Phase I study aims to determine whether the drug, approved to treat HIV infection would also suppress levels of HERV-K in a subset of patients with ALS (NCT02437110).

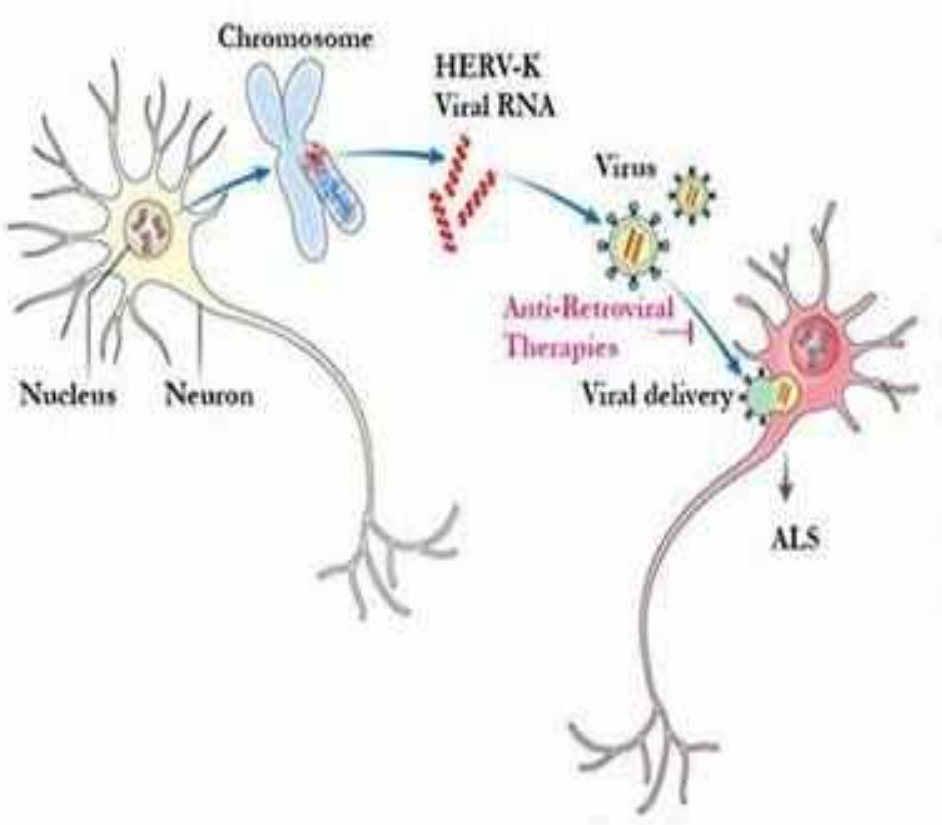

Image: ALZFORUM

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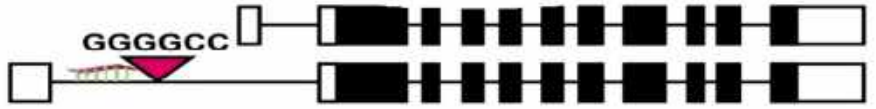
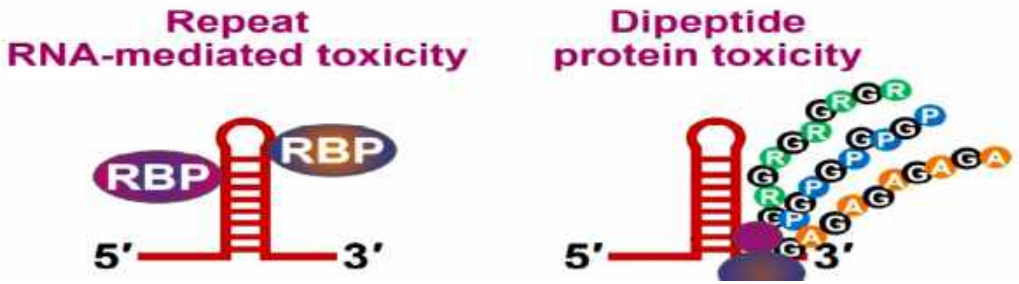
Gene therapy

BIIB067 Tofersen

Currently In Phase III

- ✓ BIIB067, an antisense oligonucleotide, inhibitis the SOD1mRNA and aims at reducing production of the toxic protein.
- ✓ Has the potential to slow disease progression and support rapid path to patients.
- ✓ On ALS FRS-R scale there was an average decline of 1.1 points compared to an average decline of 5.3 points in the placebo group



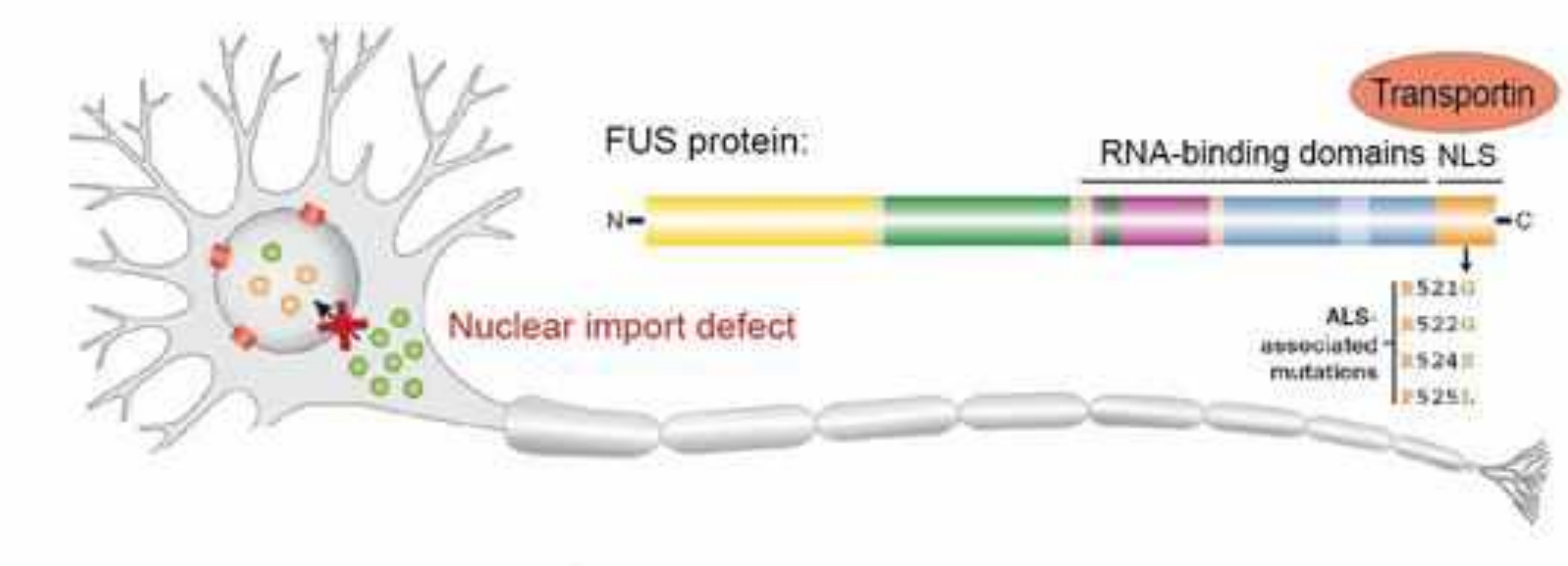


RBP-RNA Binding Protein

Gene therapy for C9ORF mutation

Currently In Phase I

- ✓ A gene therapy candidate targeting a key amyotrophic lateral sclerosis (ALS) mutation in the C9orf72 gene is able to lower the accumulation of toxic RNA clumps and reduce the activity of this mutated gene, in cells collected from a patient with frontotemporal dementia (FTD) and in a mouse model of ALS, according to two preclinical studies.


Transportin
FUS protein:
RNA-binding domains
NLS
N
C
Nuclear import defect
ALS-associated mutations
521
522
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Jacifusen

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Cell therapy for ALS

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Literature Review: 2009-2019

- 39 pre-clinical studies using multiple cell types show that stem cells migrate, engraft and differentiate into target cell types to restore lost tissue function in ALS/MND
- They improve motor performance as measured on rotarod (test measuring rodent balance, grip strength, endurance, and motor coordination), decelerate disease pathology and safely extend survival in rodent models
- 27 clinical studies using 21 different cell types show that a robust safety profile and efficacy in mitigating the hostility of a degenerating prognosis
- A systematic review and meta-analysis of clinical studies by Moura *et al.,* 2016 highlights the benefits of stem cell therapy in humans
- Stem cells also bring about paracrine effects by directly or indirectly modulating the local secretome and regulating neurotrophic factors such as GDNF, BDNF, vascular endothelial growth factor (VEGF), Insulin-like growth factor (IGF)-1, NGF and Neurotrophin (NT)-3

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e-ISSN :2348-991X, p-ISSN: 2454-9576

Case Report

Neuroregenerative Rehabilitation Therapy with long-term Lithium in a Male Amyotrophic Lateral Sclerosis Patient: A Case Report.

Alok Sharma[1], Hemangi Sane[2], Radhika Pradhan[3], Amruta Paranjape[4], Nandini Gokulchandran[5], Jasbinder Kaur[6], Rohit Das[7], Prerna Badhe[8]

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[8]Department of Regenerative Laboratory Services, NeuroGen Brain and Spine Institute

Abstract: Various cellular therapies are being increasingly investigated for the treatment of Amyotrophic Lateral Sclerosis, a progressive neurodegenerative disease with selective loss of anterior horn cells. Lithium is known to enhance the potency of transplanted cells, while being well tolerated by ALS patients. Additionally, rehabilitation significantly improves outcomes in various neurodegenerative disorders. We present a 47-year-old male patient suffering from ALS for 2 years, whose treatment involved intrathecal transplantation of autologous Bone Marrow-Derived Mononuclear Cells and long-term Lithium, followed by multidisciplinary neurorehabilitation, and standard Riluzole treatment. ALSFRSr score improved from 39 to 41; FIM remained stable at 101; 6MWT distance improved from 396 m to 480 m and Berg Balance score remained stable at 56 over a span of 18 months. Symptomatic improvements were seen in speech, swallow, stamina, walking and muscle strength; fasciculations and cramps reduced drastically. The highlight of this case is the maintenance of the patient's condition in view of a degenerative prognosis. Cellular therapy along with long-term Lithium and holistic rehabilitation, in addition to standard Riluzole treatment—together termed as Neuroregenerative Rehabilitation Therapy—is a novel approach for halting disease progression and qualitatively improving living conditions, for ALS patients and caregivers alike.

Figure 1 charts these outcome measures depicting his stability over time.

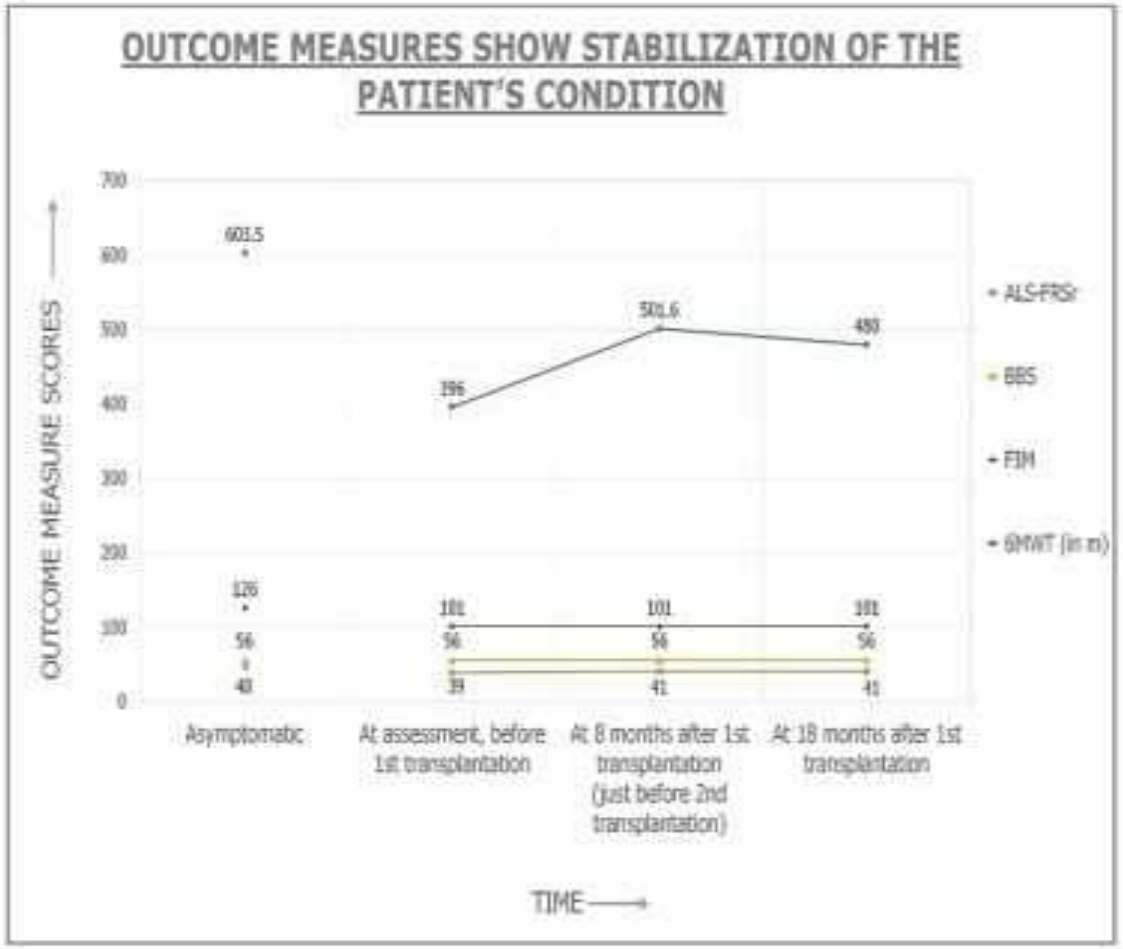


Figure 1: Various outcome measures over time.

Data points show score values measured at different intervals. Initial points indicate asymptomatic scores for each outcome, i.e. the highest possible score; these denote complete functionality. Amyotrophic Lateral Sclerosis Functional

Outcome Measures	At Assessment, Before 1st Transplantation	At 8 Months After1st Transplantation (Just Before 2nd Transplantation)	At 18 Months After 1st Transplantation
ALSF RSr	39	41	41
BBS	56	56	56
FIM	101	101	101
6MWT (in m)	396	501.6	480

Table 1: Changes in outcome measures over a period of 18 months.

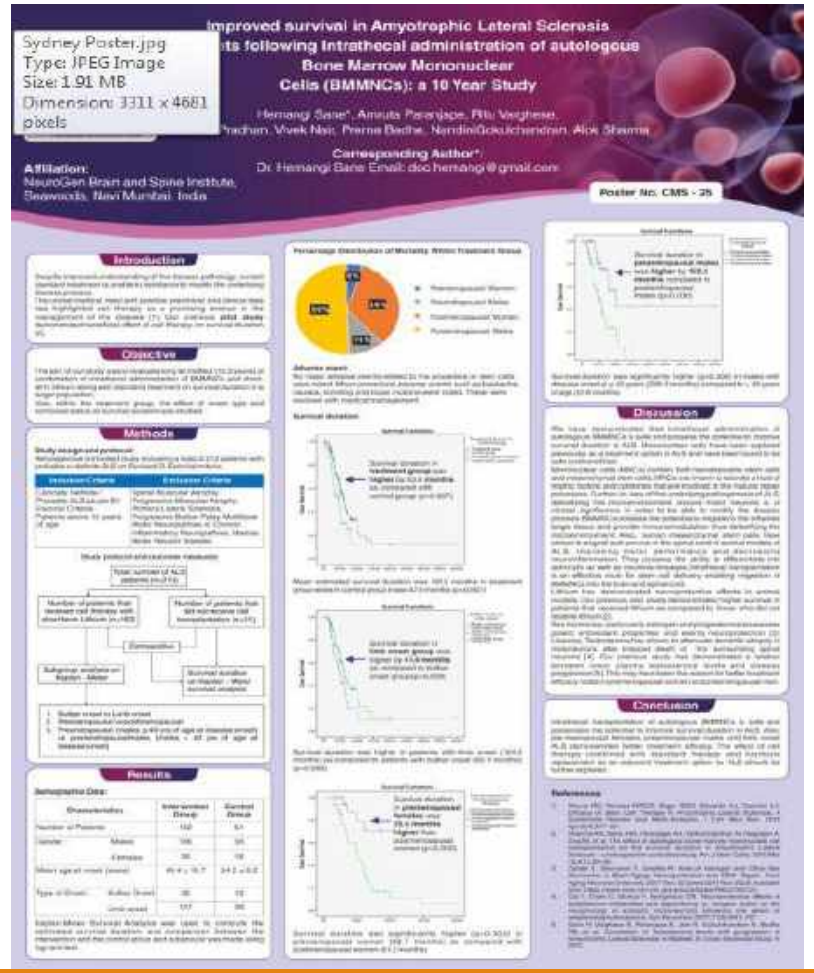
TITLE: multiple doses of cell therapy and neurorehabilitation in amyotrophic lateral sclerosis: a case report.

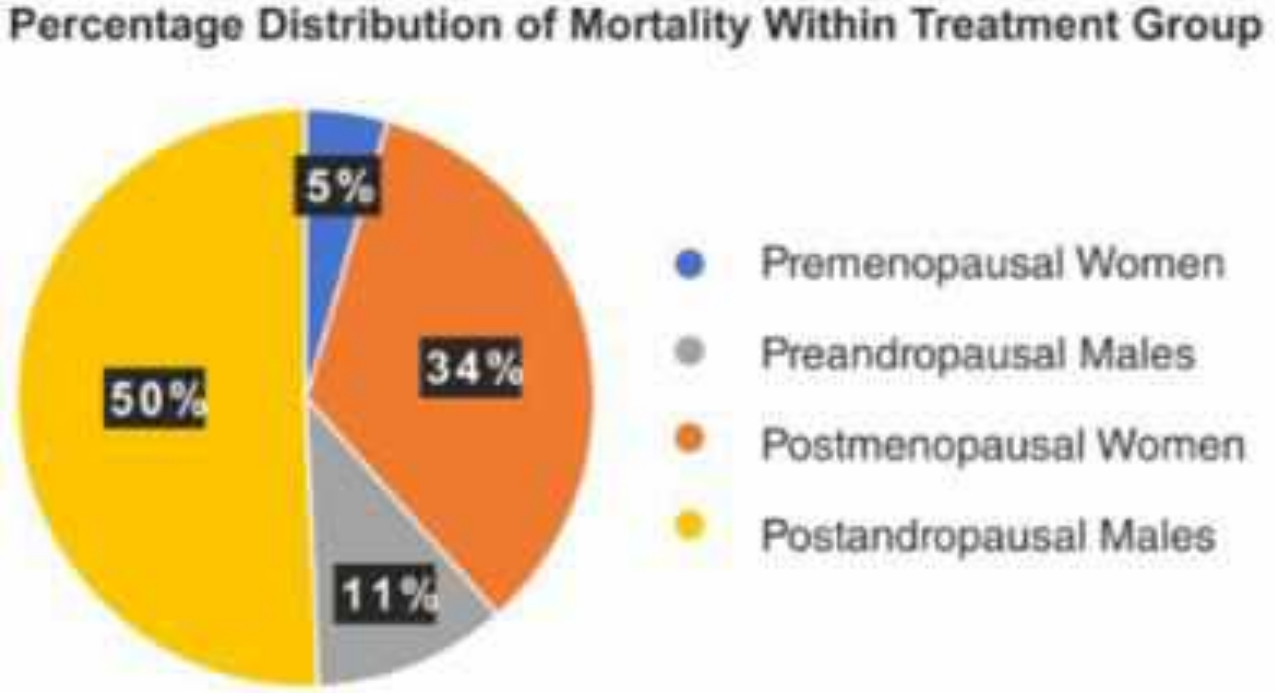
Abstract

Cell therapy, along with intensive rehabilitation has been shown to significantly improve outcomes in Amyotrophic Lateral Sclerosis, in addition to standard therapy. We present a 40-year-old male ALS patient, suffering for the past four years, who underwent multiple doses of cell therapy at our institution. Along with Riluzole treatment and Lithium co-administration, his treatment involved multiple intrathecal transplants of autologous bone marrow-derived mononuclear cells, followed by multidisciplinary neurorehabilitation. The outcome measures of Amyotrophic Lateral Sclerosis-Functional Rating Scale Revised score remained stable, and importantly, Six Minute Walk Test distance improved from 475.2 m to 580.8 m, over a span of 16 months. Improved outcomes are indicative of slowing down of disease progression. Multiple doses of intrathecal autologous cell therapy along with rehabilitation and Lithium, in addition to standard Riluzole treatment is a novel approach for decelerating disease progression and qualitatively improving living conditions for ALS patients and their caregivers.

Accepted for publication in clinics and practice journal

Improved survival in Amyotrophic Lateral Sclerosis patients following Intrathecal administration of autologous Bone Marrow Mononuclear Cells (BMMNCs): a 10 Year Study





✓ Survival duration in cell therapy group was higher than control group by 54 months.

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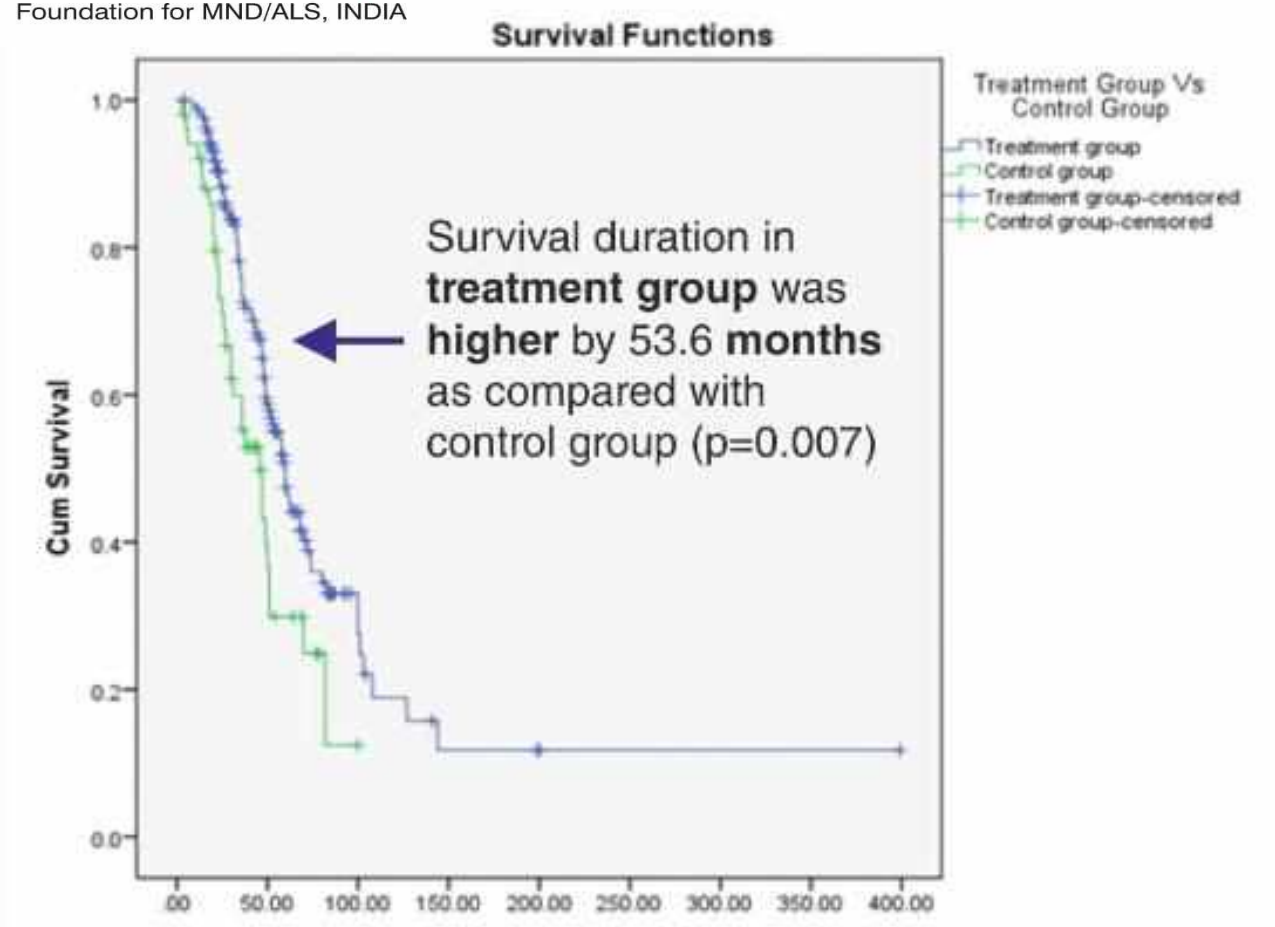
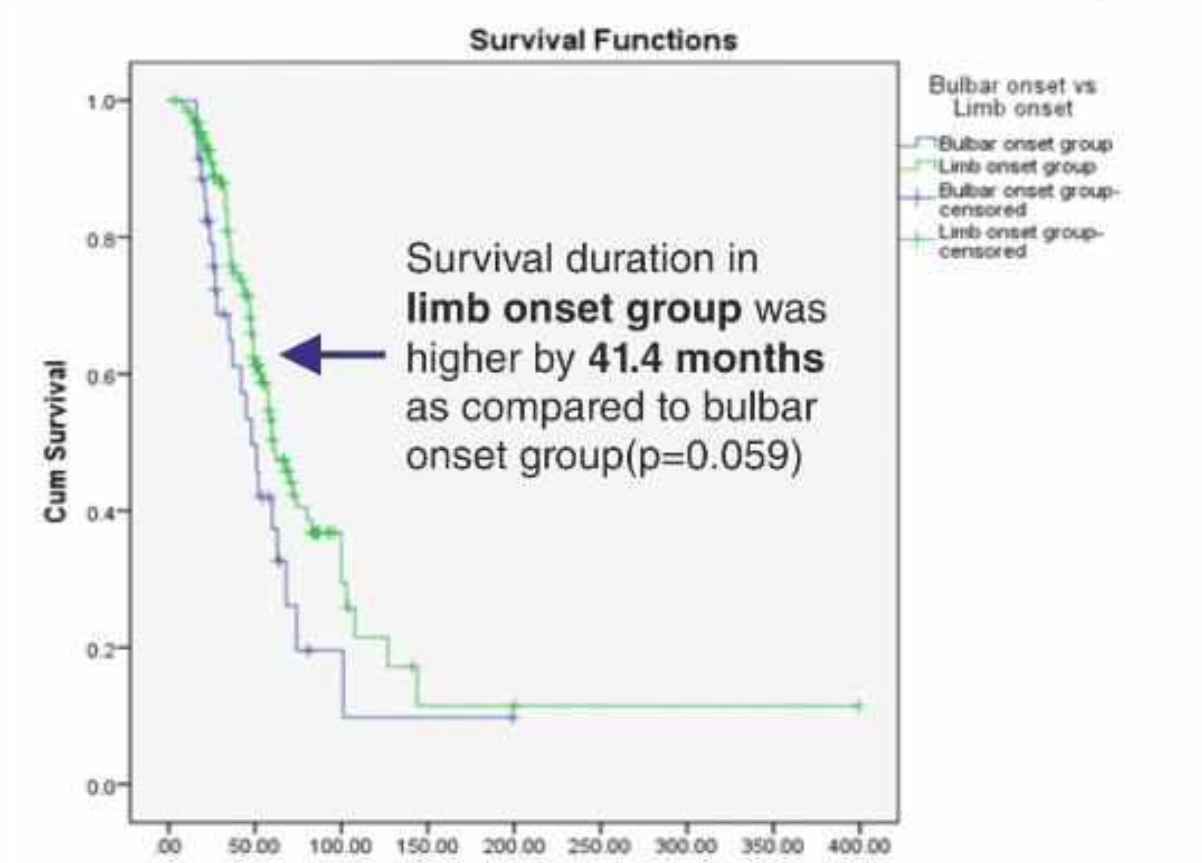


Mean estimated survival duration was 101.5 months in treatment group while in control group it was 47.9 months (p=0.007)



Survival duration was higher in patients with limb onset (104.5 months) as compared to patients with bulbar onset (63.1 months) (p=0.059)

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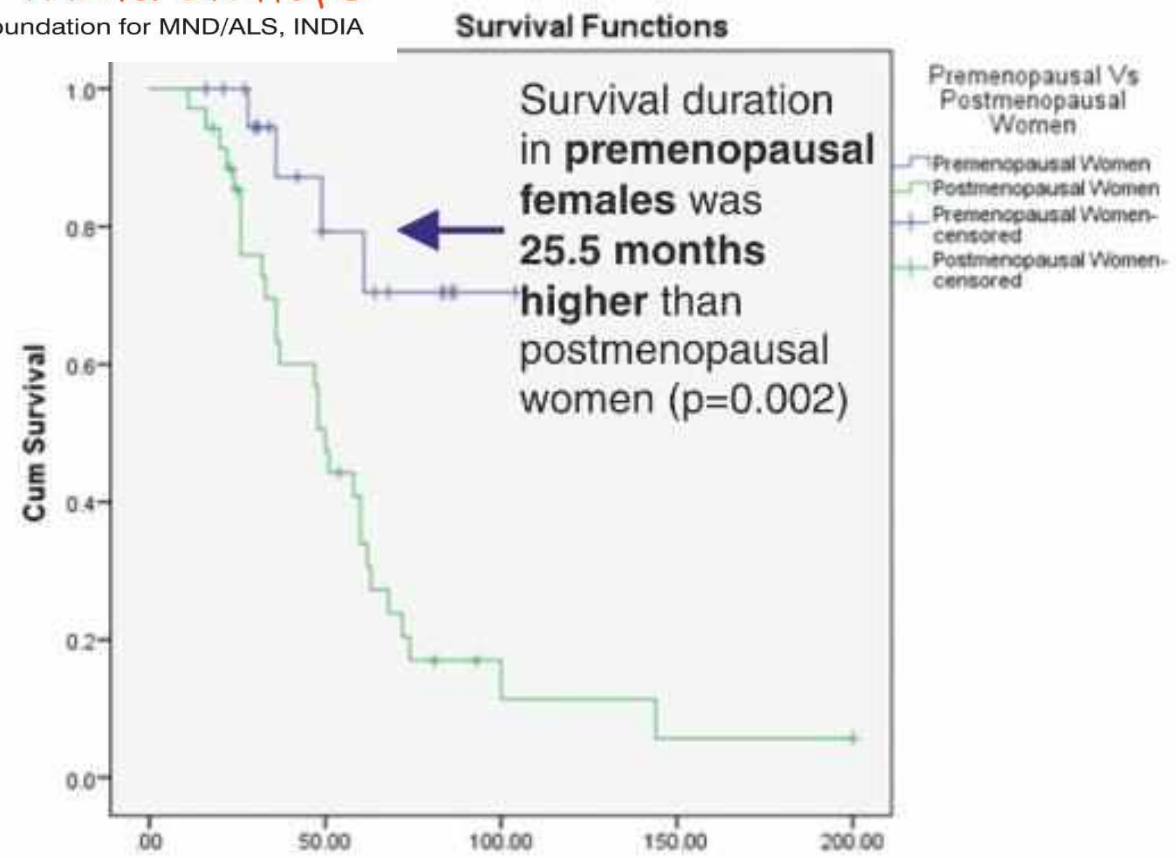
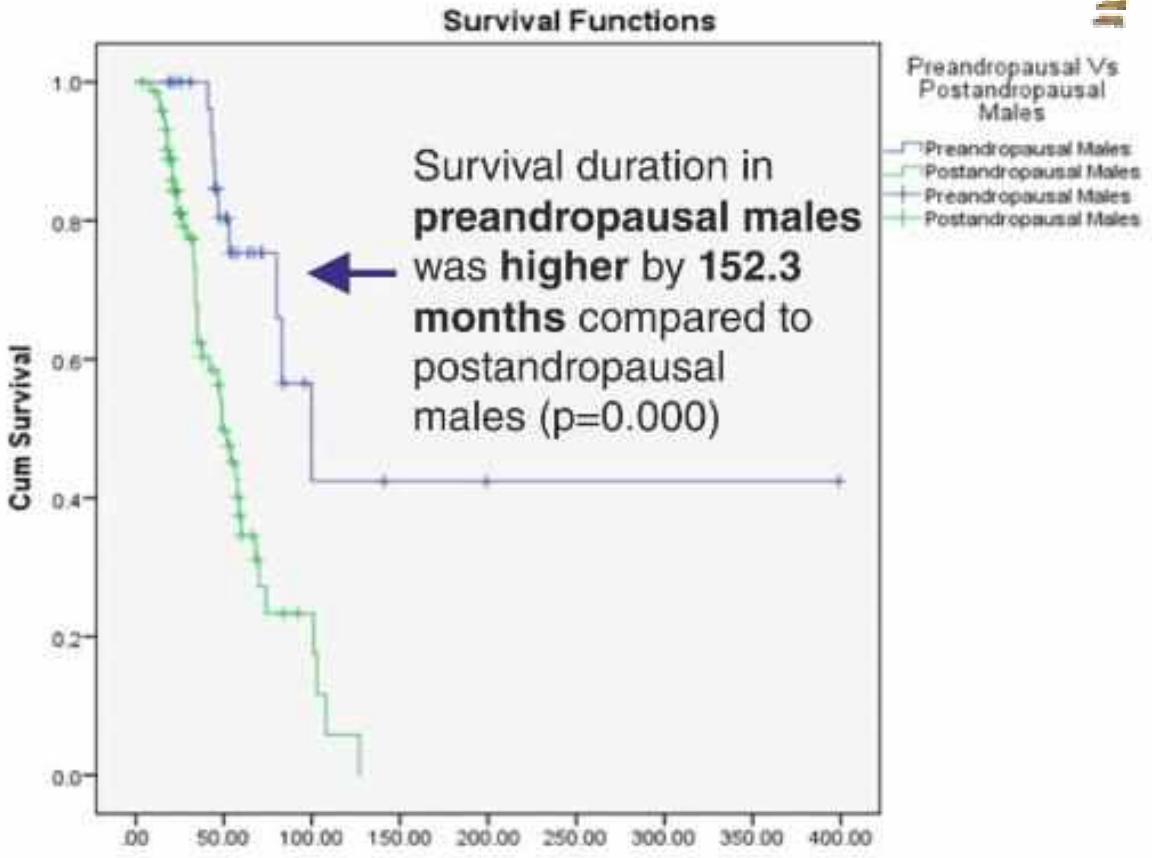


Survival duration was significantly higher (p=0.002) in premenopausal women (86.7 months) as compared with postmenopausal women (61.2 months)



Survival duration was significantly higher (p=0.000) in males with disease onset at ≤ 40 years (209.9 months) compared to > 40 years of age (57.6 months)

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NurOwn® (MSC-NTF cells)
Currently in Phase 3

1. Bone marrow is harvested and MSCs are isolated from the total bone marrow population
2. MSCs are expanded *ex-vivo* and cryopreserved
3. MSCs are thawed and induced to differentiate
4. MSC-NTF cells are injected back into the patient by intrathecal administration

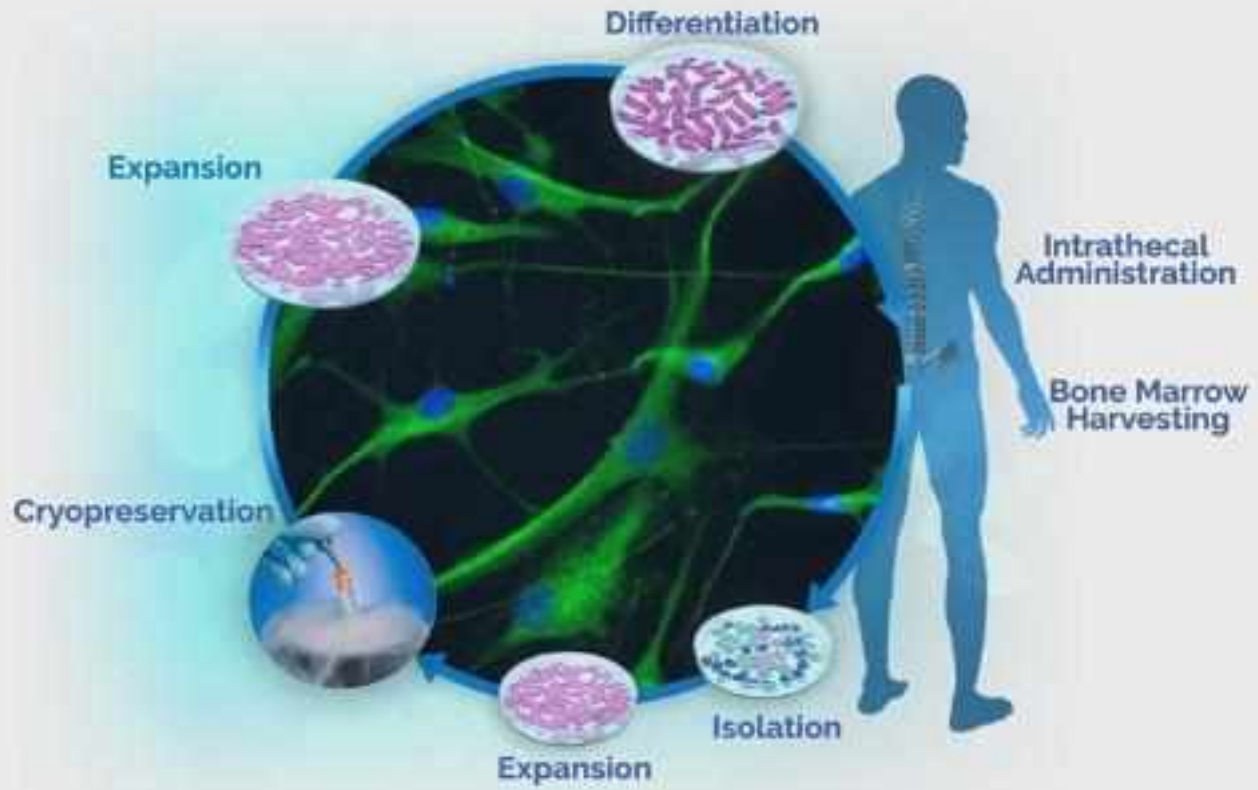

Image Courtesy Brainstorm Therapeutics. https://vimeo.com/330511539

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NurOwn® (MSC-NTF cells) Phase 2 RCT Results published in December 2019

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

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

Correspondence
Dr. Brown
robert.brown@umassmed.edu

Neurology® 2019;93:e2294-e2305. doi:10.1212/WNL.0000000000008620

Abstract

Objective
To determine the safety and efficacy of mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells (NurOwn®, autologous bone marrow-derived MSCs, induced to secrete NTFs) delivered by combined intrathecal and intramuscular administration to participants with amyotrophic lateral sclerosis (ALS) in a phase 2 randomized controlled trial.

Methods
The study enrolled 48 participants randomized 3:1 (treatment: placebo). After a 3-month pretransplant period, participants received 1 dose of MSC-NTF cells (n = 36) or placebo (n = 12) and were followed for 6 months. CSF was collected before and 2 weeks after transplantation.

Results
The study met its primary safety endpoint. The rate of disease progression (Revised ALS Functional Rating Scale [ALSFRS-R] slope change) in the overall study population was similar in treated and placebo participants. In a prespecified rapid progressor subgroup (n = 21), rate of disease progression was improved at early time points ($p < 0.05$). To address heterogeneity, a responder analysis showed that a higher proportion of treated participants experienced ≥1.5 points/month ALSFRS-R slope improvement compared to placebo at all time points, and was significant in rapid progressors at 4 and 12 weeks ($p = 0.004$ and 0.046, respectively). CSF neurotrophic factors increased and CSF inflammatory biomarkers decreased in treated participants ($p < 0.05$) post-transplantation. CSF monocyte chemoattractant protein-1 levels correlated with ALSFRS-R slope improvement up to 24 weeks ($p < 0.05$).

Conclusion
A single-dose transplantation of MSC-NTF cells is safe and demonstrated early promising signs of efficacy. This establishes a clear path forward for a multidose randomized clinical trial of intrathecal autologous MSC-NTF cell transplantation in ALS.

RELATED ARTICLE
Editorial
Stem cells in amyotrophic lateral sclerosis: Hype or hope?
Page 1028

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Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

- ✓ A higher proportion of treated participants experienced ≥1.5 points/month ALSFRS-R slope improvement compared to placebo at all time points and was significant in rapid progressors at 4 and 12 weeks (p = 0.004 and 0.046, respectively).
- ✓ CSF neurotrophic factors increased and CSF inflammatory biomarkers decreased in treated participants ($p < 0.05$) post-transplantation.
- ✓ A single-dose transplantation of MSC-NTF cells is safe and demonstrated early promising signs of efficacy.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Safety of intrathecal injection of Wharton's jelly-derived mesenchymal stem cells in amyotrophic lateral sclerosis therapy
Neural Regen Res. 2019 Feb; 14(2): 313–318.

Neural Regeneration Research
Wolters Kluwer -- Medknow Publications

Safety of intrathecal injection of Wharton's jelly-derived mesenchymal stem cells in amyotrophic lateral sclerosis therapy

Monika Barczewska, Mariusz Grudniak, [...], and Wojciech Maksymowicz

Abstract

Animal experiments have confirmed that mesenchymal stem cells can inhibit motor neuron apoptosis and inflammatory factor expression and increase neurotrophic factor expression. Therefore, mesenchymal stem cells have been shown to exhibit prospects in the treatment of amyotrophic lateral sclerosis. However, the safety of their clinical application needs to be validated. To investigate the safety of intrathecal injection of Wharton's jelly-derived mesenchymal stem cells in amyotrophic lateral sclerosis therapy, 43 patients (16 females and 27 males, mean age of 57.3 years) received an average dose of 0.42 $\times 10^6$ cells/kg through intrathecal administration at the cervical, thoracic or lumbar region depending on the clinical symptoms. There was a 2 month interval between two injections. The adverse events occurring during a 6-month treatment period were evaluated. No adverse events occurred. Headache occurred in one case only after first injection of stem cells. This suggests that intrathecal injection of Wharton's Jelly-derived mesenchymal stem cells is well tolerated in patients with amyotrophic lateral sclerosis. This study was approved

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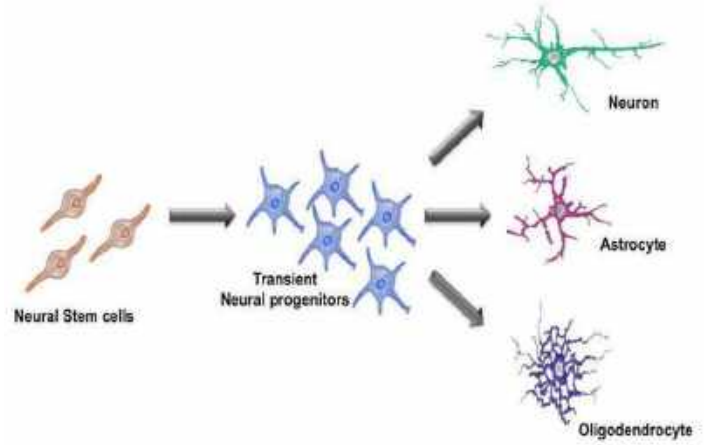
NSI-566 HSSC Transplantation

Currently in Phase 3

Human spinal cord-derived neural stem cell line (HSSC),
Treated patients had a median survival of 4.7 years, versus control (2.3 years median survival)

Mean ALSFRS-R at 24 months **significantly differed** between treated vs. control cohorts

- Treated 30.1 ± 8.6 vs. PRO-ACT database 24.0 ± 10.2, p=0.048;
- Treated 30.7 ± 8.8 vs. Ceftriaxone treatment 19.2 ± 9.5, p=0.0023



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PUBLISHER : INTERNATIONAL JOURNAL FOUNDATION (IJF)

Correlation of Testosterone levels with progression of Amyotrophic Lateral Sclerosis in Males: A Cross-Sectional Study

*** Hemangi Sane[1], Ritu Varghese[2,*], Amruta Paranjape[3], Reena Jain[4], Nandini Gokulchandran[5], Prerna Badhe[6], Alok Sharma[7]**

[1,4,5,7] *Department of Medical Services and Clinical Research, Neuro Gen Brain & Spine Institute, India.*
[2,3] *Department of Research & Development, Neuro Gen Brain & Spine Institute, India.*
[6] *Department of Regenerative Laboratory Services, NeuroGen Brain & Spine Institute, India.*

ABSTRACT

The known higher incidence of Amyotrophic Lateral Sclerosis (ALS) in men and older age suggests a role of sex steroidal hormones in the disease process. Animal models of ALS have shown lower levels of plasma testosterone. Testosterone is known to exert neuroprotective and neurotrophic actions on neurons. Our objective was to study the association of total testosterone (TT) levels with disease severity on ALS Functional Rating Scale-Revised (ALS FRS-R) scale and King's Staging. This cross-sectional study included 64 males with definite/probable ALS. Patients' morning plasma TT levels were tested, and ALS FRS-R and King's Staging was marked. Standard score was used to compare the deviation of patients' TT levels from average TT levels of age matched healthy males. A scatter plot was constructed, and correlation analysis was performed using Spearman's Rank Correlation. 39/64 patients (60.9 %) had TT levels that were lower by 1/more standard deviation, than age matched average levels in healthy men. There was a statistically significant positive correlation of TT levels with ALS FRS-R (r=.326, p=0.009) and negative correlation with King's Staging (r=-.312, p=0.012). Thus, with declining function and disease progression, standard scores of TT levels decreased. Maintaining plasma TT levels, as close to age matched average levels, may be explored as an adjuvant therapy in ALS.

Keywords: Amyotrophic Lateral Sclerosis, King's Staging, Testosterone, Amyotrophic Lateral Sclerosis Functional Rating-Revised.

Figure 3: There was a statistically significant positive monotonic correlation between ALS FRS-R score of the patients and standard scores of plasma TT levels; r=0.326, p=0.009

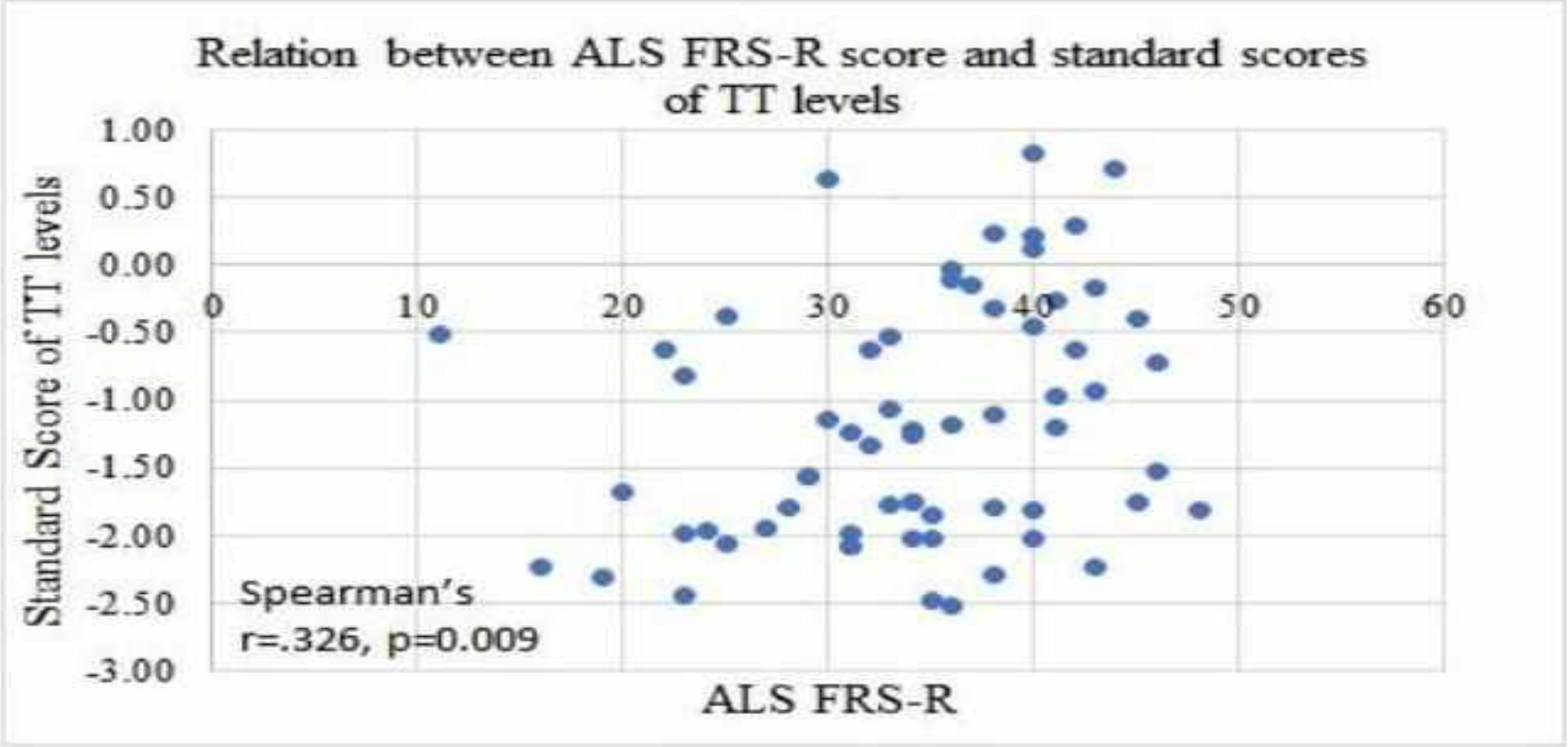
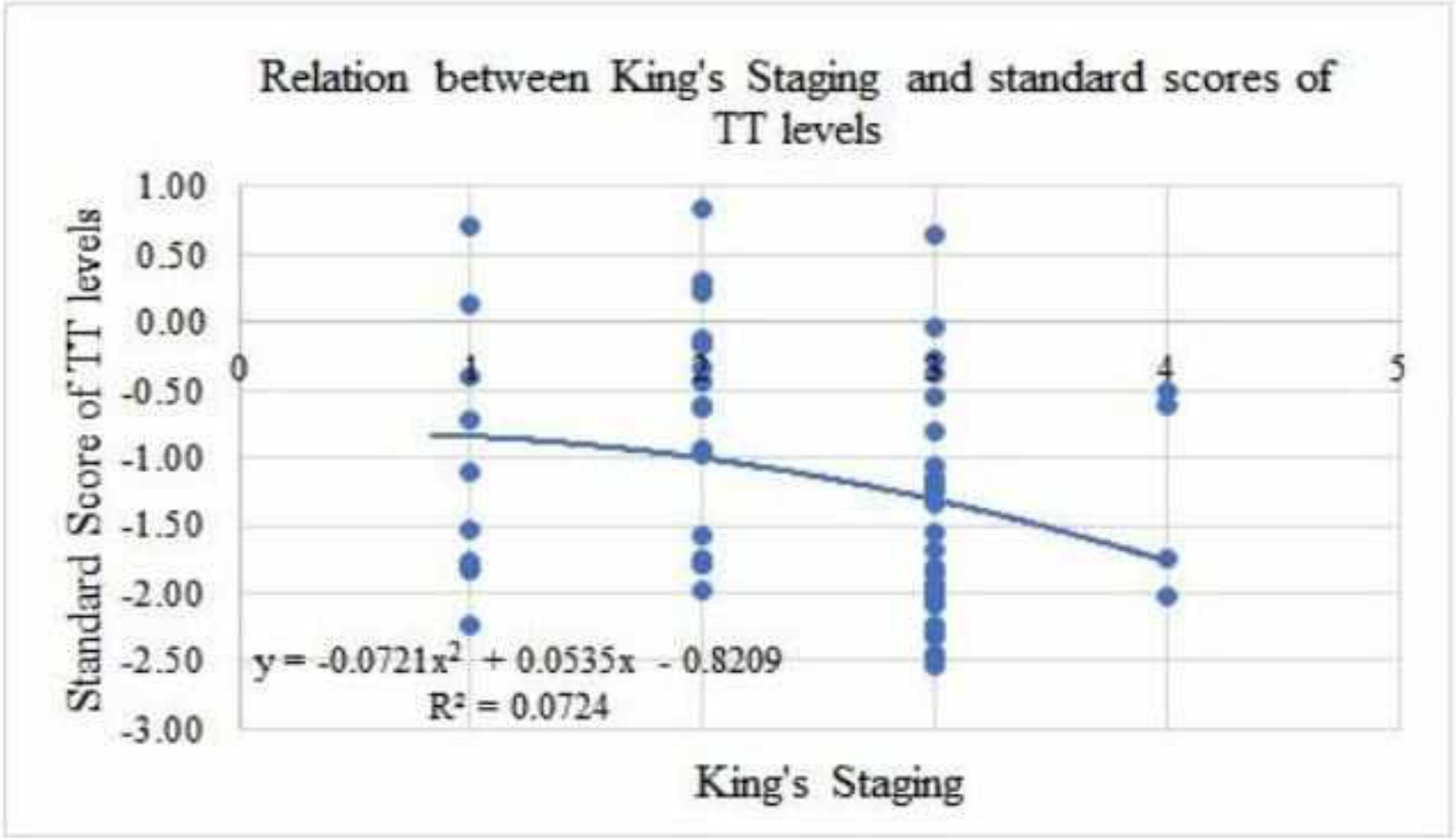


Figure 4: There was a statistically significant negative monotonic correlation between King's staging and standard score of TT levels, r=-0.312, p=0.012.



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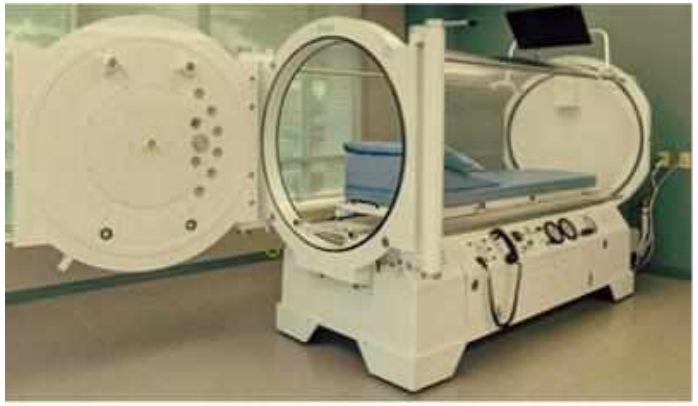
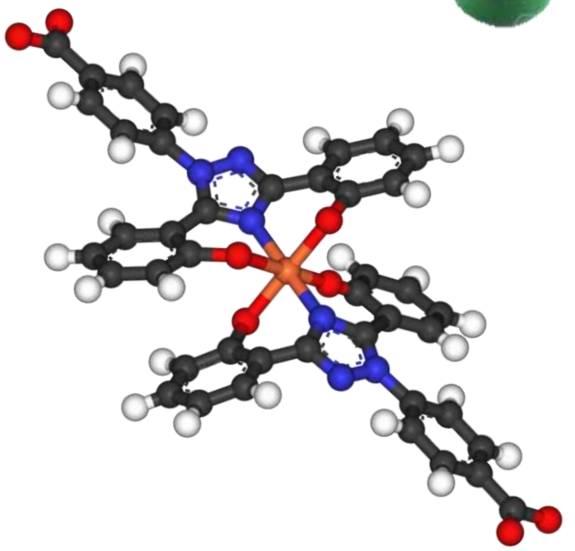
Adjuvant therapies being explored to improve Quality of Life in ALS

- Hormone therapy
- Hyperbaric Oxygen Therapy
- Ozone Therapy
- Chelation Therapy
- IV vitamin Therapy
  - ✓ Glutathione
  - ✓ N-acetyl cysteine
  - ✓ Vitamin C
  - ✓ Myers' cocktail
  - ✓ L-Carnitine
  - ✓ Alpha-Lipoic acid



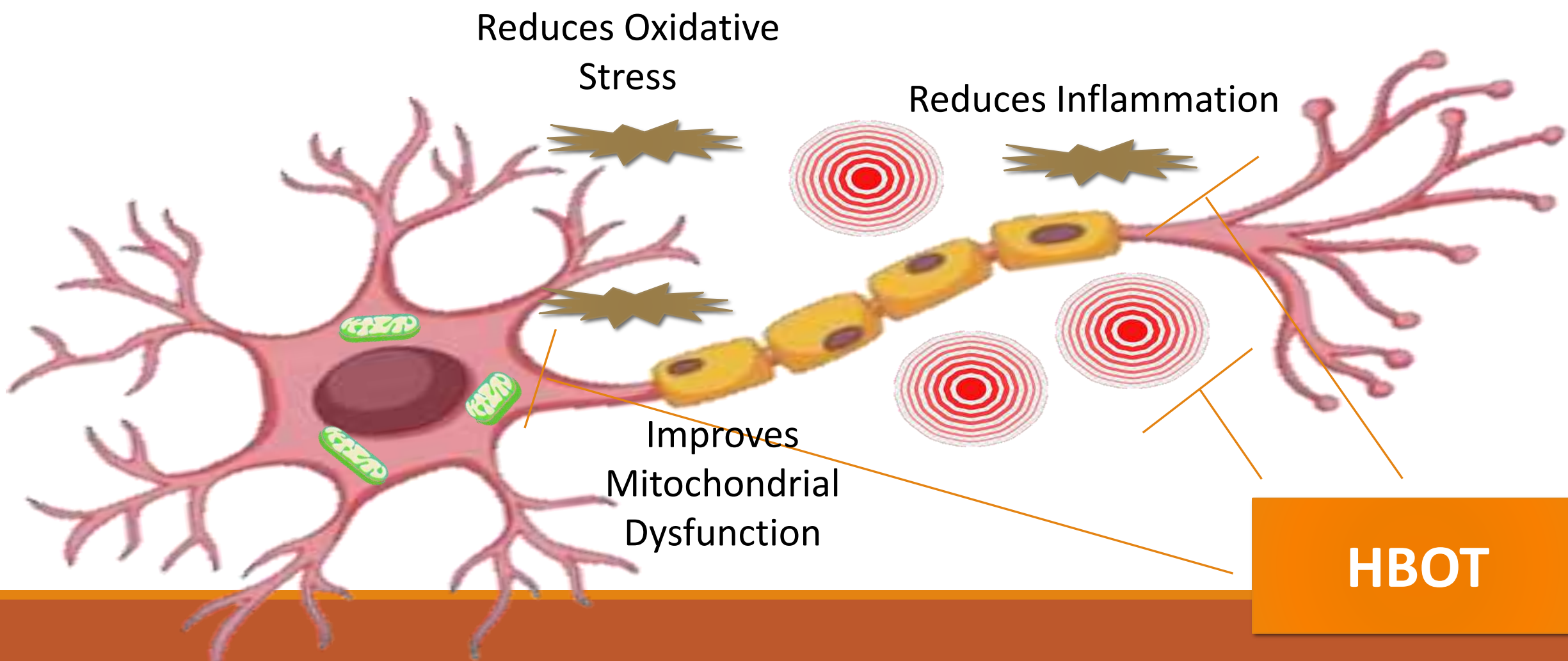


Hyperbaric Oxygen Therapy (HBOT)

What is Hyperbaric Oxygen Therapy (HBOT)?

- 100% oxygen is given to the patient in a special enclosed chamber at higher pressure
- It increases the concentrations of oxygen in the blood, which is forced deep into the tissues due to increased pressure

How would HBOT help for ALS?



How is HBOT done?

- It is a non-invasive procedure: patient is in a transparent chamber for around 1 hour, under constant supervision.
- The patient may watch his favourite serial, web series, film, songs, etc. as per their wish on the monitor which will be placed outside, on the top of the chamber. After the pressurisation is done and the pressure is stable in the chamber, they may relax or even go to sleep.

Referemces

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Ozone Therapy

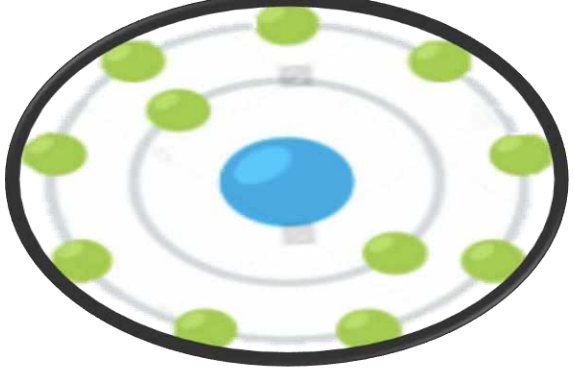
What is Ozone Therapy?

Ozone therapy involves administration of Medical Ozone gas via various routes

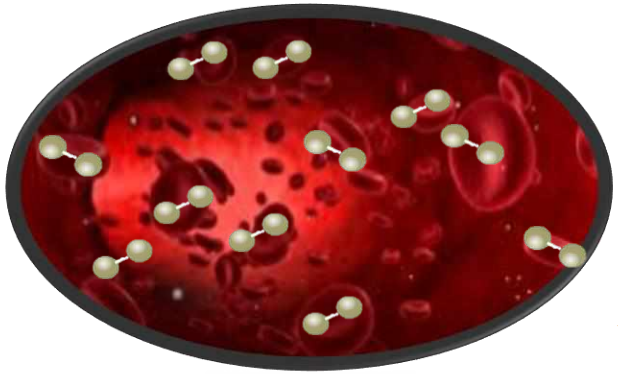
Medical Ozone is a mixture of 95-99.5% of oxygen with 0.5 to 5% ozone

It is made from pure oxygen by an “ozonator” machine and administered to the patient right away

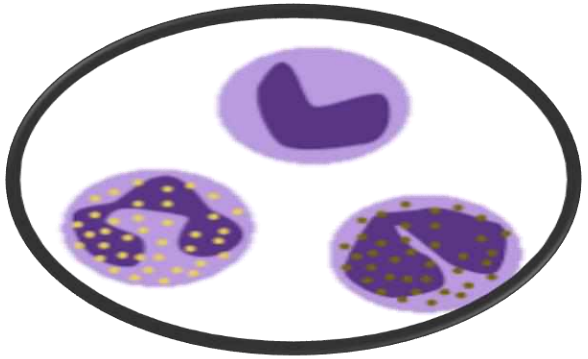
How would Ozone Therapy work for ALS?



Triggers cellular antioxidant enzymes

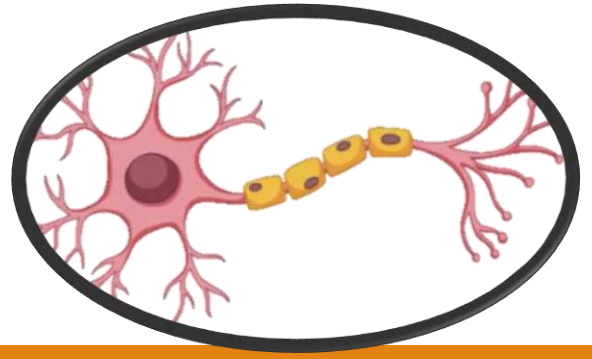


Improves blood circulation and oxygen delivery

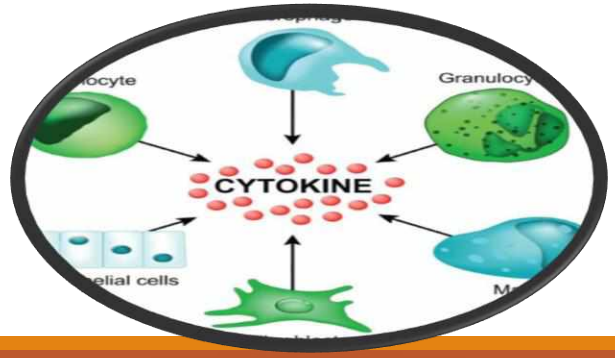


Activates the immune system

Ozone Therapy

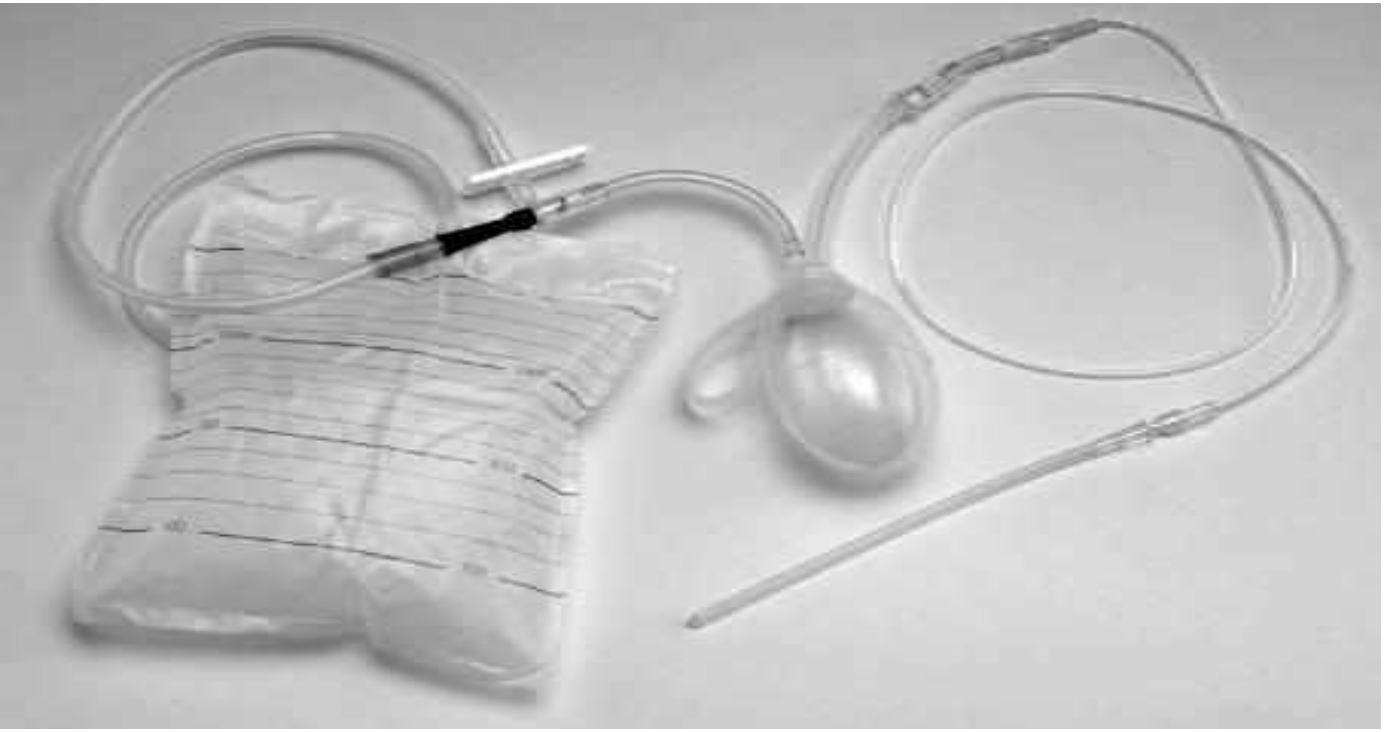


Activates neuroprotective systems



Enhances cytokine release

How is Ozone Therapy done?



- *Rectal Insufflation*
  - Ozone gas is passed in rectum painlessly through a small tube attached to a rectal bag in 10 mins with the patient lying on one side
  - Tube is then removed, patient lies down for another 5 mins, then can be sent back

How is Ozone Therapy done?

Ear Insufflation

- The ear piece of the Stethoscope is put in the patient's ear, ozone gas is passed painlessly via the other end of the stethoscope

How is Ozone Therapy done?

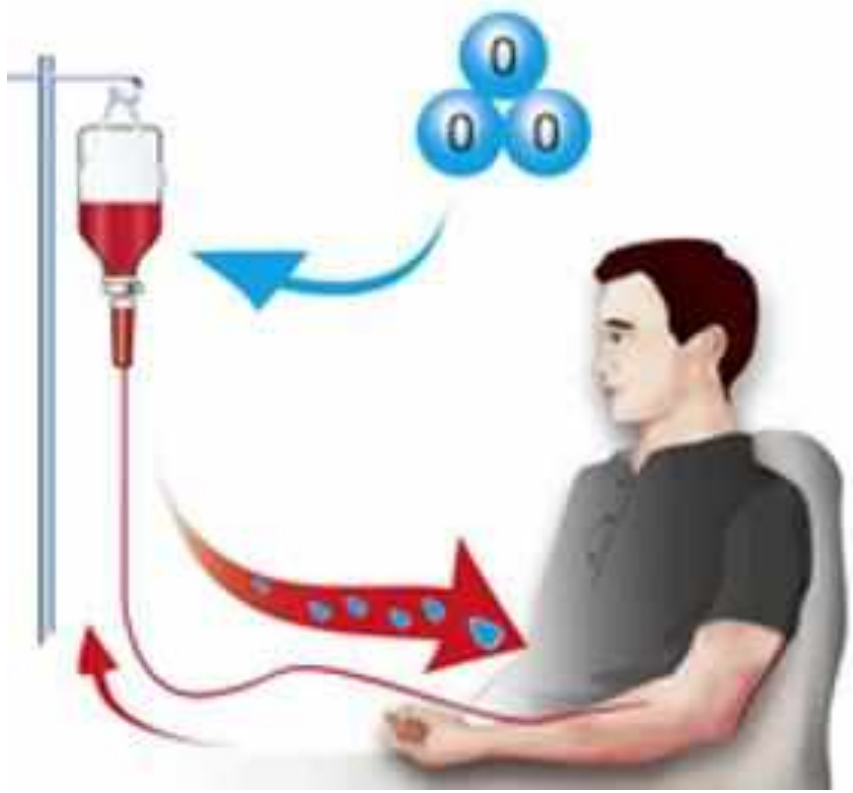
Ozone steam bath

- Ozone is introduced into a special steam sauna cabinet, where it is absorbed across the skin. The result on the patient is a combination of the beneficial oxygenation and detoxification effects of both **Ozone and Sauna Therapy**.

How is Ozone Therapy done?

Major Auto-hemotherapy

- Major Auto-hemotherapy (MAH) involves the injection of medical grade ozone gas into blood drawn from a person. The ozone is allowed to mix with the blood for a period of time. The ozonated blood is then intravenously infused back into the same person.



How is Ozone Therapy done?

Ozonized saline

- This method is based on much longer and gentle contact of ozone dissolved in physiological sodium chloride solution with the internal environment of the patient when ozone drop by drop, molecule by molecule is put into blood circulation and immediately reacts with blood components, so the whole blood quantity being in circulation comes in contact with ozone therefore producing much better and prolonged therapeutic effects.

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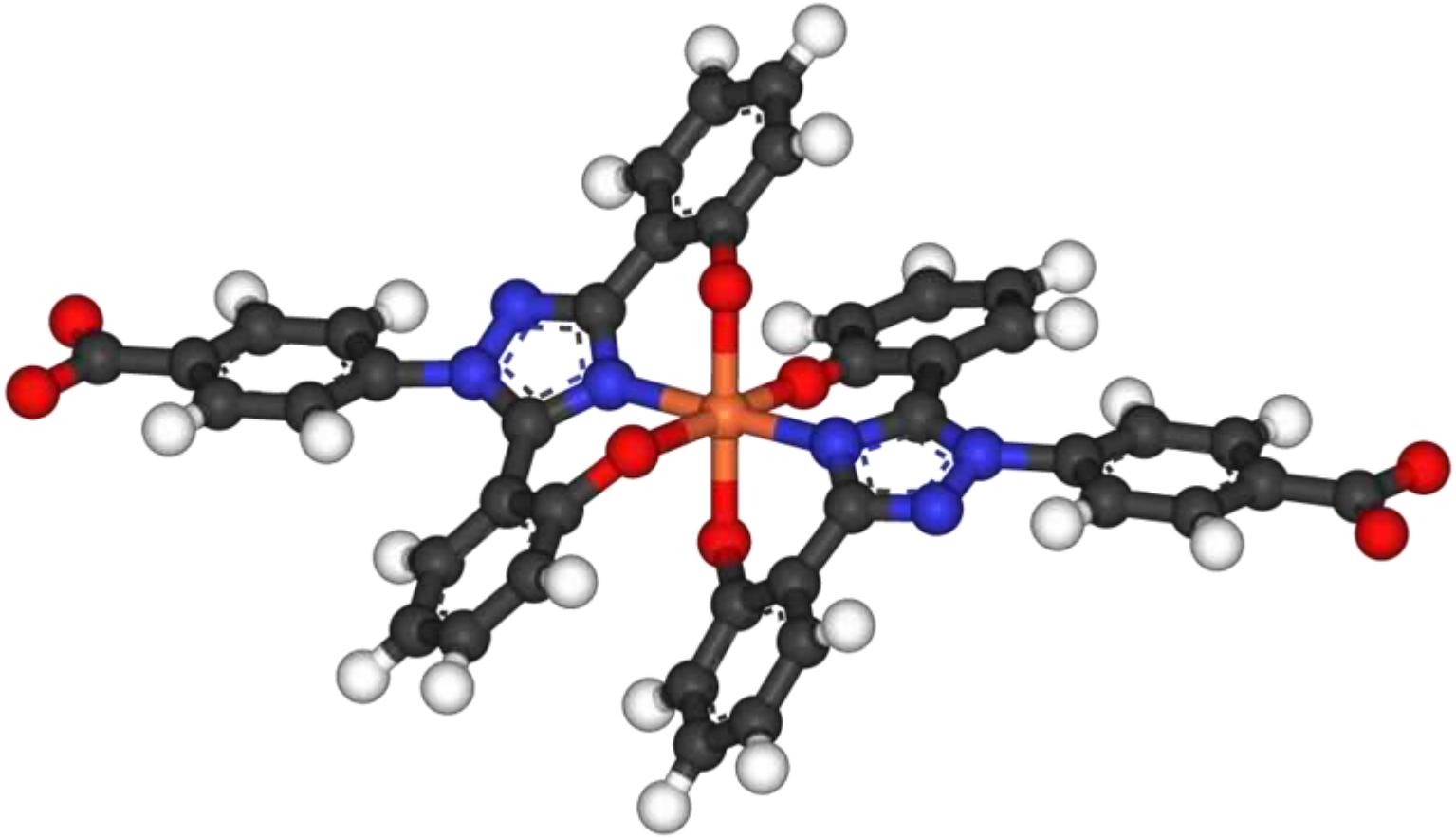
Chelation Therapy

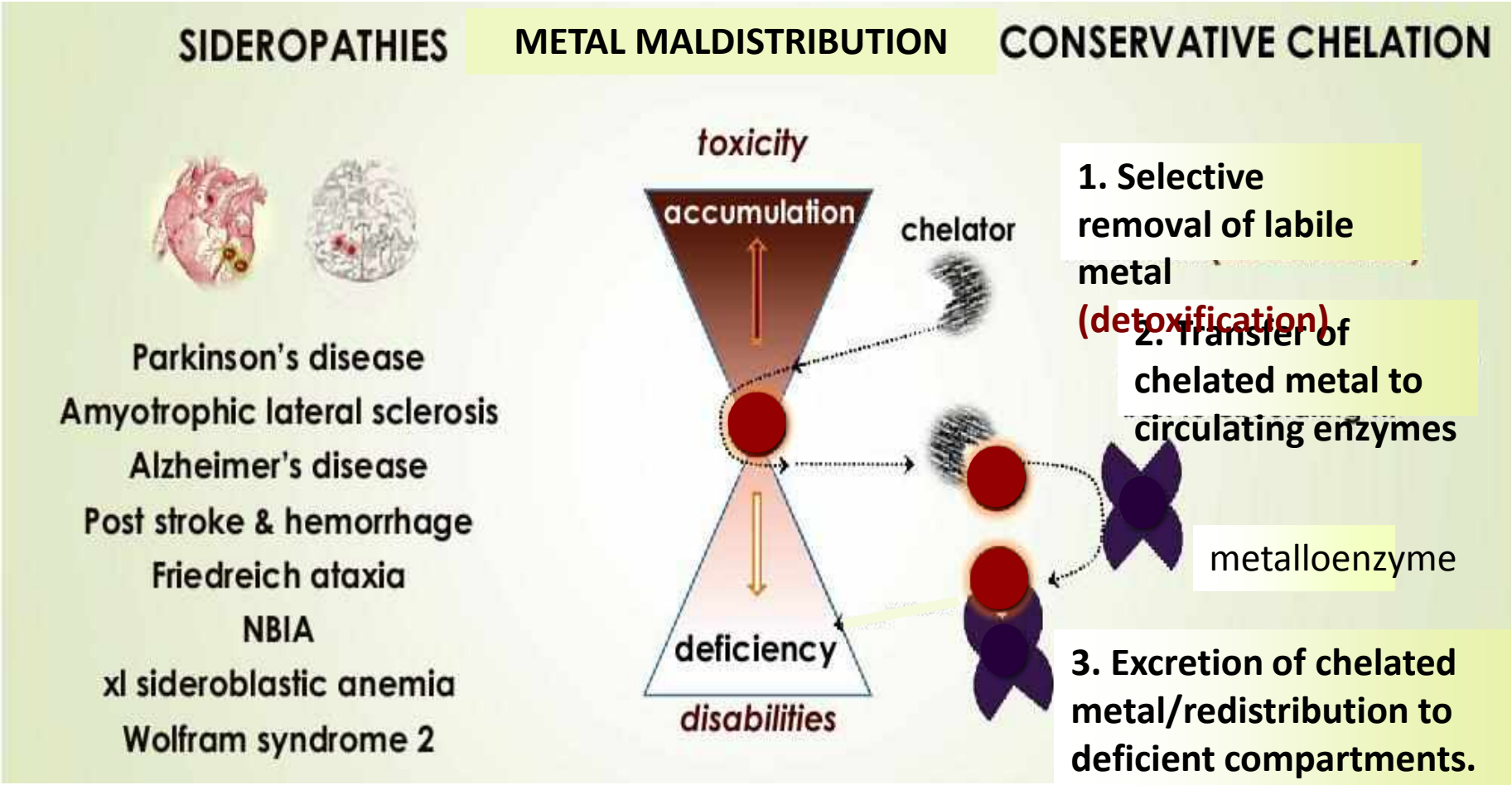


What is Chelation Therapy?

Chelation is a way to detoxify the body

A “chelator” binds to the toxins in the blood, and is excreted out of the body

How would Chelation Therapy work for ALS?



- ✓ Reduces arterial plaques and decreases thickening of the membrane
- ✓ Improves capillary blood-tissues perfusion and blood circulation

Adapted from Devos et al., 2020.

How is Chelation Therapy done?

Chelation therapy is administered over a few hours via an intravenous drip and is strictly monitored by your physician

References:

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Hormone Therapy

What is Hormone Therapy?

Hormone therapy involves the replacement of deficient hormone levels within the body

These may include:

- **DHEAS**
- **Serum testosterone**
- **Serum estradiol**
- **Serum progesterone**
- **Growth hormones**
- **Thyroid hormones**
- **Insulin**
- **Serum cortisol**

Hormonal imbalance findings in ALS?

- DHEAS – Reduced
- Serum testosterone – Reduced
- Serum estradiol – Reduced
- Serum progesterone – Reduced
- Thyroid hormones – Reduced
- Growth hormones – Reduced
- Insulin – Reduced
- Serum cortisol – Increased

How is Hormone Therapy done?

Blood tests determine the levels of the following hormones:

- DHEAS
- Serum testosterone
- Serum estradiol
- Serum progesterone
- Thyroid hormones
- Growth hormones
- Insulin
- Serum cortisol

An experienced physician administers hormones as required intravenously

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IV Vitamin Therapy

What is IV Vitamin Therapy?

- IV Vitamin Therapy replenishes essential nutrients ***rapidly*** in the body intravenously

- Some of these nutrients are:
  - Glutathione,
  - N-acetyl cysteine,
  - Vitamin C,
  - Myers' cocktail,
  - L-carnitine,
  - α-Lipoic acid

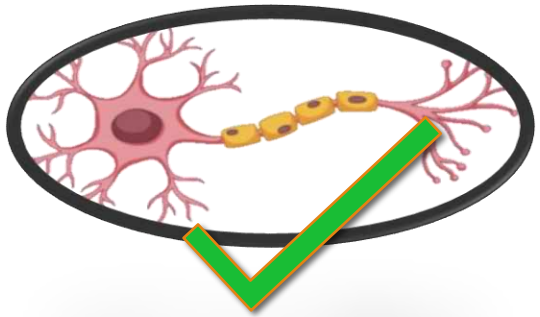
IV Vitamin Therapy: How is it done?

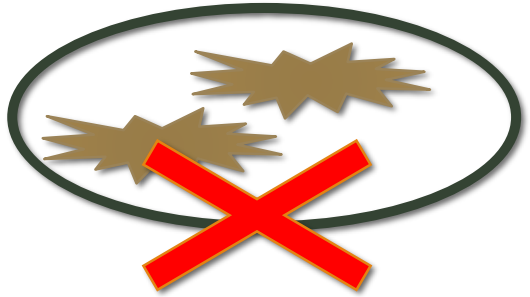
Quite simply: it is administered via an intravenous drip personalized by your physician, over a few hours.

IV Vitamin: Glutathione

- ✓ Glutathione is a powerful antioxidant present naturally in the cells, but is depleted in ALS
- ✓ It is neuroprotective in nature
- ✓ Reduces oxidative stress
- ✓ Delayed disease onset and slowed loss of grip strength in ALS mice

- Andreassen et al., 2000; Ross et al., 2014





Glutathione and mitochondria

Vicent Ribas[1,2], Carmen García-Ruiz[1,2,3] and José C. Fernández-Checa[1,2,3]*

[1]Department of Cell Death and Proliferation, Institute of Biomedical Research of Barcelona, Consejo Superior de Investigaciones Científicas (IIBB-CSIC), Barcelona, Spain

[2]Liver Unit, Hospital Clínic, Centre Esther Koplowitz, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)–Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain

[Glutathione] plays a key role in defense against respiration-induced reactive oxygen species and in the detoxification of lipid hydroperoxides and electrophiles. Moreover, as mitochondria play a central strategic role in the activation and mode of cell death, mitochondrial GSH has been shown to critically regulate the level of sensitization to secondary hits that induce mitochondrial membrane permeabilization and release of proteins confined in the intermembrane space that once in the cytosol engage the molecular machinery of cell death.

the intermembrane space that once in the cytosol engage the molecular machinery of cell death. In this review, we summarize recent data on the regulation of mitochondrial GSH and its role in cell death and prevalent human diseases, such as cancer, fatty liver disease, and Alzheimer's disease.

Immunocal® and Preservation of Glutathione as a Novel Neuroprotective Strategy for Degenerative Disorders of the Nervous System

Erika K Ross [1], Josie J Gray, Aimee N Winter, Daniel A Linseman

In particular, mitochondrial dysfunction leads to the aberrant production and accumulation of reactive oxygen species (ROS), which are capable of oxidizing key cellular proteins, lipids, and DNA, ultimately triggering cell death. In addition to other roles that it plays in the cell, GSH functions as a critical scavenger of these ROS. Therefore, GSH depletion exacerbates cell damage due to free radical generation. Strategies that increase or preserve the levels of intracellular GSH have been shown to act in a neuroprotective manner, suggesting that augmentation of the available GSH pool may be a promising therapeutic target for neurodegeneration.

supplement (Immunocal®) to enhance the de novo synthesis of GSH in neurons, and highlights its potential as a novel therapeutic approach to mitigate the oxidative damage that underlies the pathogenesis of various neurodegenerative diseases. Additionally, this review discusses various patents from 1993 to 2012 both with Immunocal® and other methods that modulate GSH in neurodegeneration.

IV Vitamin: N-acetyl cysteine

Reduces motor neuron loss and improves neuronal calibre

Increases Glutathione levels

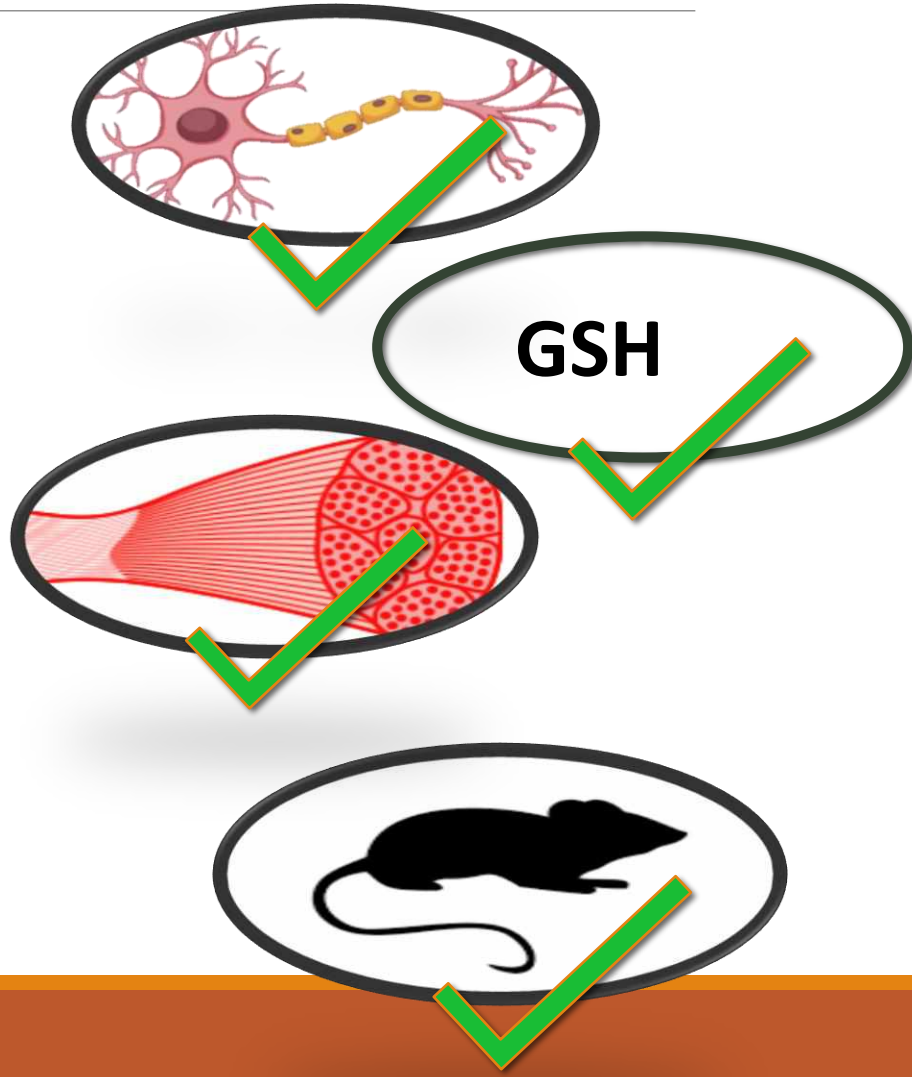
Increases muscle mass and fibre

Increases forelimb function

- Hendersen et al., 1998

Improves survival and preserves motor function in ALS animal model

- Andreassen et al., 2000



Evaluation of the Neuroprotective Potential of N-Acetylcysteine for Prevention and Treatment of

Based on the available literature, a nutraceutical formulation containing N-acetylcysteine among other compounds has shown some pro-cognitive benefits in Alzheimer's patients and older adults, but the evidence for N-acetylcysteine alone is less robust. Although N-acetylcysteine crosses the blood-brain-barrier, low bioavailability is an obstacle. One promising avenue of research may be to explore derivatives of N-acetylcysteine such as N-acetylcysteine amide, which has been reported in preclinical studies to have higher permeability through cellular and mitochondrial membranes with increased central nervous system bioavailability compared to N-acetylcysteine.

decline associated with dementia. Discussion will also include possible mechanisms of action of N-acetylcysteine, its effects on aging biology, and safety of long-term use. Based on the available literature, a nutraceutical formulation containing N-acetylcysteine among other compounds has shown some pro-cognitive benefits in Alzheimer's patients and older adults, but the evidence for N-acetylcysteine alone is less robust. Although N-acetylcysteine crosses the blood-brain-barrier, low bioavailability is an obstacle. One promising avenue of research may be to explore derivatives of N-acetylcysteine such as N-acetylcysteine amide, which has been reported in preclinical studies to have higher permeability through cellular and mitochondrial membranes with increased central nervous system bioavailability compared to N-acetylcysteine.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Overview on the Effects of *N*-Acetylcysteine in Neurodegenerative Diseases

Giuseppe Tardiolo [1] Placido Bramanti [2] Emanuela Mazzon [3]

N-acetylcysteine (NAC) is a glutathione precursor and shows antioxidant and anti-inflammatory activities. In addition to the uses quoted in the literature, NAC may be considered helpful in therapies to counteract neurodegenerative and mental health diseases. Furthermore, this compound has been evaluated for its neuroprotective potential in the prevention of cognitive aging dementia. NAC is inexpensive, commercially available and no relevant side effects were observed after its administration.

inflammatory activities. In addition to the uses quoted in the literature, NAC may be considered helpful in therapies to counteract neurodegenerative and mental health diseases. Furthermore, this compound has been evaluated for its neuroprotective potential in the prevention of cognitive aging dementia. NAC is inexpensive, commercially available and no relevant side effects were observed after its administration. The purpose of this paper is to give an overview on the effects and applications of NAC in Parkinson's and Alzheimer's disorders and in neuropathic pain and stroke.

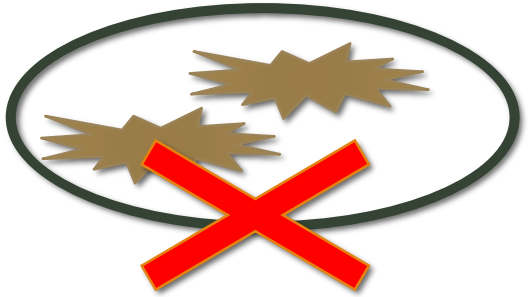
IV Vitamin: Vitamin C

Vitamin C slows progression in mouse models of ALS

- Padayatty et al., 2003

It is also a powerful antioxidant, and may scavenge molecules that cause oxidative stress in ALS

- Orrell et al., 2004



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2. Monacelli F, Acquarone E, Giannotti C, Borghi R, Nencioni A. Vitamin C, aging and Alzheimer's disease. Nutrients. 2017 Jul;9(7):670.
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IV Vitamin: Myers' cocktail

Myers cocktail was first developed by John Myers, MD Baltimore, Maryland

It is used widely and is safe for a variety of conditions, most notably Fibromyalgia, migraines, and muscle spasms

- Gaby A, 2002

It is completely safe for patients suffering from musculoskeletal conditions like fibromyalgia

- Ali et al., 2009

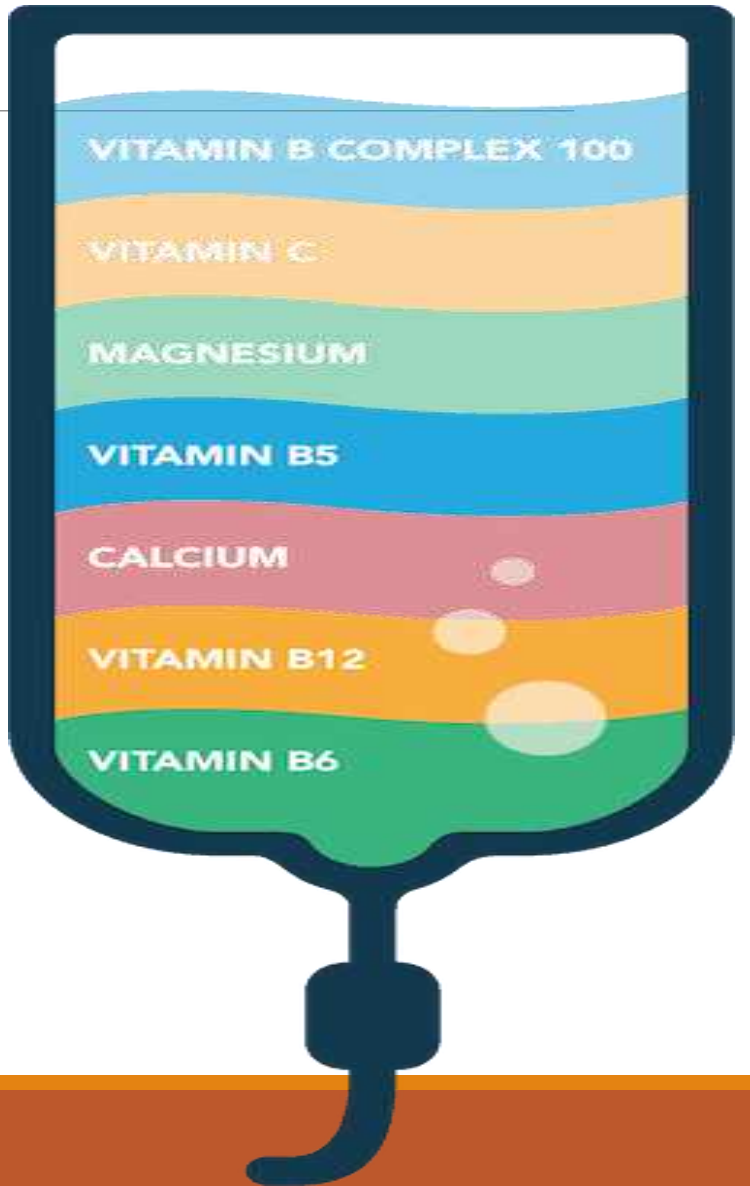

Figure courtesy: Duke City Health

Intravenous Micronutrient Therapy (Myers' Cocktail) for Fibromyalgia: A Placebo-Controlled Pilot Study

Results: Clinically significant improvements were noted (of a magnitude similar to other effective interventions). However, in part because of the high placebo response and the small sample size, no statistically significant differences were seen between groups, in any outcome measure, at 8 and 16 weeks. Statistically significant within-group differences were seen in both the intervention and placebo groups, demonstrating a treatment effect for both IVMT and placebo. At 8 weeks, the IVMT group experienced significantly improved tender points, pain, depression, and quality of life directly following treatment (all p≤0.02), while the placebo group experienced significantly improved tender points only (p 0.05). The treatment effects of IVMT persisted at 4 weeks post intervention for tender points, pain, and quality of life, while placebo effects persisted only for tender points. A single minor adverse event was noted in one subject in the intervention group.

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Conclusions: This first controlled pilot study established the safety and feasibility of treating FMS with IVMT. Most subjects experienced relief as compared to baseline, but no statistically significant differences were seen between IVMT and placebo. The efficacy of IVMT for fibromyalgia, relative to placebo, is as yet uncertain.

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Foundation for MND/ALS, INDIA

NeuroGen
Brain and Spine Institute

Intravenous Nutrient Therapy: the "Myers' Cocktail"

Alan R. Gaby, MD

Abstract

Building on the work of the late John Myers, MD, the author has used an intravenous vitamin-and-mineral formula for the treatment

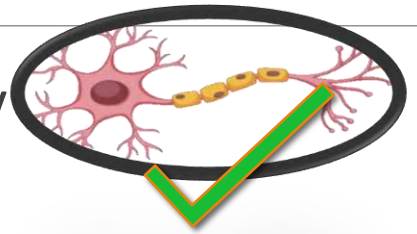
The modified "Myers' cocktail," which consists of magnesium, calcium, B vitamins, and vitamin C, has been found to be effective against acute asthma attacks, migraines, fatigue (including chronic fatigue syndrome), fibromyalgia, acute muscle spasm, upper respiratory tract infections, chronic sinusitis, seasonal allergic rhinitis, cardiovascular disease, and other disorders.

infections, chronic sinusitis, seasonal allergic rhinitis, cardiovascular disease, and other disorders. This paper presents a rationale for the therapeutic use of intravenous nutrients, reviews the relevant published clinical research, describes the author's clinical experiences, and discusses potential side effects and precautions.

(Altern Med Rev 2002;7(5):389-403)

IV Vitamin: L-Carnitine

Reduces neuronal excitotoxicity and increases motor neuron activity

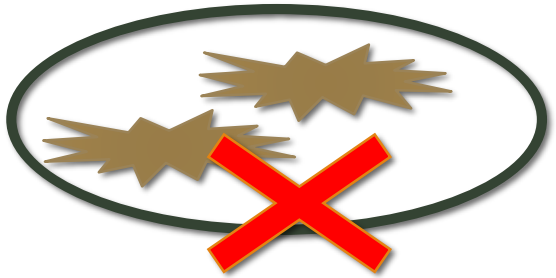


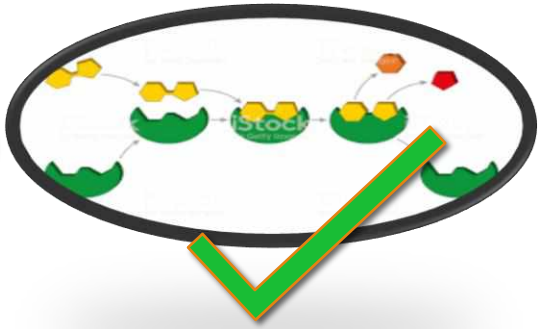
- *Bigini et al., 2002*

Suppresses onset of neuromuscular degeneration and increases lifespan of ALS mice

- *Kira et al., 2006*

- Ameliorates oxidative damage, enzyme activity, and mitochondrial dysfunction
  - *Liu et al., 2002*





IV Vitamin Therapy: L-Carnitine

Clinical Trials

Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS

Ettore Beghi, Elisabetta Pupillo, Virginio Bonito, Paolo Buzzi, Claudia Caponnetto, Adriano Chiò, ...show all

Pages 397-405 | Received 06 Nov 2012, Accepted 03 Jan 2013, Published online: 19 Feb 2013

Abstract

Our objective was to assess the effects of acetyl-L-carnitine (ALC) with riluzole on disability and mortality of amyotrophic lateral sclerosis (ALS). Definite/probable ALS patients, 40-70 years of age, duration 6-24 months, self-sufficient (i.e. able to swallow, cut food/handle utensils, and walk), and with forced vital capacity (FVC) > 80% entered a pilot double-blind, placebo-controlled, pa[illegible] nu[illegible] (C[illegible] co[illegible] (8[illegible] percentages were 84.4 and 100.0% (p = 0.0538), respectively. Mean ALSFRS-R scores at 48 weeks were 33.6 (SD 10.4) and 27.6 (9.9) (p = 0.0388), respectively, and mean FVC scores 90.3 (32.6) and 58.6 (31.2) (p = 0.0158), respectively. Median survival was 45 months (ALC) and 22 months (placebo) (p = 0.0176). MRC, QoL and adverse events were similar. In conclusion, ALC may be effective, well-tolerated and safe in ALS. A pivotal phase III trial is needed.

Acetyl-L-carnitine may be effective, well-tolerated and safe in ALS.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients

NeuroGen
Brain and Spine Institute

M. Rossini[1], O. Di Munno[2], G. Valentini[3], G. Bianchi[4], G. Biasi[5], E. Cacace[6], D. Malesci[3], G. La Montagna[3], O. Viapiana[1], S. Adami[1]

[1]Rheumatology Unit, University of Verona; [2]Rheumatology Unit, University of Pisa;

Results: The "total myalgic score" and the number of positive tender points declined significantly and equally in both groups until the 6th week of treatment. At the 10th week both parameters remained unchanged in the placebo group but they continued to improve in the LAC group with a statistically significant between-group difference. Most VAS scores significantly improved in both groups. A statistically significant between-group difference was observed for depression and musculo-skeletal pain. Significantly larger improvements in SF36 questionnaire were observed in LAC than in placebo group for most parameters. Treatment was well-tolerated.

Conclusion: Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients.

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Conclusion

Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Randomized Double-Blind Placebo-Controlled Trial of acetyl-L-carnitine for ALS

NeuroGen
Brain and Spine Institute
Centre for Stem Cell Therapy and Neurorehabilitation
ISO 9001:2008 Certified

Ettore Beghi [1], Elisabetta Pupillo, Virginio Bonito, Paolo Buzzi, Claudia Caponnetto, Adriano Chiò, Massimo Corbo, Fabio Giannini, Maurizio Inghilleri, Vincenzo La Bella, Giancarlo Logroscino, Lorenzo Lorusso, Christian Lunetta, Letizia Mazzini, Paolo Messina, Gabriele Mora, Michele Perini, Maria Lidia Quadrelli, Vincenzo Silani, Isabella L Simone, Lucio Tremolizzo, Italian ALS Study Group

Collaborators, Affiliations + expand

PMID: 23421600 DOI: 10.3109/21678421.2013.764568

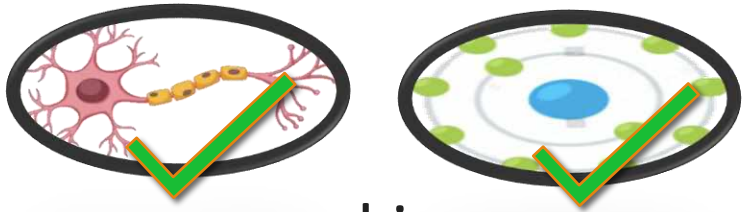
In conclusion, acetyl-L-carnitine (ALC) may be effective, well-tolerated and safe in ALS.

utensils, and walk), and with forced vital capacity (FVC) > 80% entered a pilot double-blind, placebo-controlled, parallel group trial and were followed for 48 weeks. ALC or placebo 3 g/day was added to riluzole 100 mg/day. Primary endpoint: number of patients no longer self-sufficient. Secondary endpoints: changes in ALSFRS-R, MRC, FVC and McGill Quality of Life (QoL) scores. Analysis was made in the intention-to-treat (ITT) and per-protocol (PP) population, completers and completers/compliers (i.e. taking > 75% of study drug). Forty-two patients received ALC and 40 placebo. In the ITT population, 34 (80.9%) patients receiving ALC and 39 (97.5%) receiving placebo became non-self-sufficient (p = 0.0296). In the PP analysis, percentages were 84.4 and 100.0% (p = 0.0538), respectively. Mean ALSFRS-R scores at 48 weeks were 33.6 (SD 10.4) and 27.6 (9.9) (p = 0.0388), respectively, and mean FVC scores 90.3 (32.6) and 58.6 (31.2) (p = 0.0158), respectively. Median survival was 45 months (ALC) and 22 months (placebo) (p = 0.0176). MRC, QoL and adverse events were similar. In conclusion, ALC may be effective, well-tolerated and safe in ALS. A pivotal phase III trial is needed.

IV Vitamin Therapy: α-Lipoic Acid

- "Exerts strong and positive antioxidant and neuroprotective effects in ALS models"

  - Wang et al., 2018



- Improves mitochondrial health, reduces oxidative damage, and improves enzyme function

  - Liu J., 2019

- Improves lifespan of ALS mouse model

  -Andreassen et al., 2001

- Isn't available in India yet, but has been used abroad

Lipoic Acid as an Anti-Inflammatory and Neuroprotective Treatment for Alzheimer's Disease

Annette Maczurek [1], Klaus Hager, Marlene Kenklies, Matt Sharman, Ralph Martins, Jürgen Engel, David A Carlson, Gerald Münch

Affiliations + expand

PMID: 18655815 DOI: 10.1016/j.addr.2008.04.015

Lipoic acid (LA) has been shown to have a variety of properties which can interfere with the pathogenesis or progression of AD. For example, LA increases acetylcholine (ACh) production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh. LA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione. In addition, LA down-regulates the expression of redox-sensitive pro-inflammatory proteins including TNF and inducible nitric oxide synthase. Furthermore, LA can scavenge lipid peroxidation products such as hydroxynonenal and acrolein.

release" LA) will be beneficial for delivery of LA to the brain. Evidence for a clinical benefit for LA in dementia is yet limited. There are only two published studies, in which 600 mg LA was given daily to 43 patients with AD (receiving a standard treatment with choline-esterase inhibitors) in an open-label study over an observation period of up to 48 months. Whereas the improvement in patients with moderate dementia was not significant, the disease progressed extremely slowly (change in ADAScog: 1.2 points=year, MMSE: -0.6 points=year) in patients with mild dementia (ADAScog<15). Data from cell culture and animal models suggest that LA could be combined with nutraceuticals such as curcumin, (-)-epigallocatechin gallate (from green tea) and docosahexaenoic acid (from fish oil) to synergistically decrease oxidative stress, inflammation, Abeta levels and Abeta plaque load and thus provide a combined benefit in the treatment of AD.

Asha Ek Hope
Foundation for MND/ALS, INDIA

α-Lipoic Acid, Functional Fatty Acid, as a Novel Therapeutic Alternative for Central Nervous System Diseases: A Review

Fatemeh Seifar [1], Mohammad Khalili [1 2], Habib Khaledyan [3], Shirin Amiri Moghadam [4]

α-lipoic acid (ALA) is a natural antioxidant which acts as a cofactor of bioenergetic mitochondrial enzymes. Along with its mitochondrial action, ALA and its reduced form have many biological functions resulting in a wide variety of actions such as anti-inflammation and antioxidant protection, scavenging reactive oxygen species, regenerating other antioxidant agents, such as vitamins C and E, and cytosolic glutathione, chelating the transitional metal ions (e.g. iron and copper), and modulating the signal transduction of nuclear factor.

Results: ALA as an antioxidant and anti-inflammation agent has therapeutical effects on central nervous system diseases, especially multiple sclerosis and PD.

Discussion: ALA can be considered as a potentially useful treatment in central nervous disorders.

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Discussion: ALA can be considered as a potentially useful treatment in central nervous disorders.

Alpha-lipoic Acid Supplement in Obesity Treatment: A Systematic Review and Meta-Analysis of Clinical Trials

Nazli Namazi [1], Bagher Larijani [2], Leila Azadbakht [3]

Affiliations + expand

PMID: 28629898 DOI: 10.1016/j.clnu.2017.06.002

Abstract

Background & aims: Previous studies have supported positive roles of antioxidant

Conclusions: The present study revealed that supplementation with ALA slightly but significantly decreased body weight and BMI. Safe dosage for ALA is up to 1200 mg/day.

Methods: We searched five electronic databases till September 2016. Placebo-controlled clinical trials were included. Weighted Mean Difference (WMD) was pooled using a random-effects model.

Results: Findings of 12 included trials indicated that ALA supplement reduced body weight (WMD: -0.69 kg; 95% CI: -1.27, -0.10; I^2 = 0%) and BMI (WMD: -0.38 kg/m^2; 95% CI: -0.53, -0.24; I^2 = 0%) significantly compared to the placebo group. However, its effects on Waist Circumference (WC) was not significant (WMD: -0.30 cm; 95% CI: -1.18, 0.58; I^2 = 17.8%). Stratification by health status indicated that ALA decreased WC in unhealthy subjects (WMD: -2.00 cm; 95% CI: -4.19, 0.19; I^2 = 1.3%) more than healthy individuals (0.03 cm; 95% CI: -0.69, 0.75; I^2 = 0%).

Conclusions: The present study revealed that supplementation with ALA slightly but significantly decreased body weight and BMI. Safe dosage for ALA is up to 1200 mg/day. However, it seems that ALA cannot be cost-effective. Further studies are needed to clarify the effects of ALA on metabolic parameter in unhealthy obese individuals.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Technology

21st June 2019 – 21st June 2020

Asha Ek Hope
Foundation for MND/ALS, INDIA

First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound

NeuroGen
Brain and Spine Institute
Centre for Stem Cell Therapy and Neurorehabilitation
ISO 9001:2008 Certified

- Here, we show successful BBB opening using MRgFUS as demonstrated by gadolinium leakage at the target site immediately after sonication in all subjects, which normalized 24 hours later.
- The procedure was well-tolerated with no serious clinical, radiologic or electroencephalographic adverse events. This study demonstrates that non-invasive BBB permeabilization over the motor cortex using MRgFUS is safe, feasible, and reversible in ALS subjects.
- In future, MRgFUS can be coupled with promising therapeutics providing a targeted delivery platform in ALS.

demonstrates that non-invasive BBB permeabilization over the motor cortex using MRgFUS is safe, feasible, and reversible in ALS subjects. In future, MRgFUS can be coupled with promising therapeutics providing a targeted delivery platform in ALS.

Asha Ek Hope
Foundation for MND/ALS, INDIA

Asha Ek Hope Collaborations for Technology

21st June 2019 – 21st June 2020

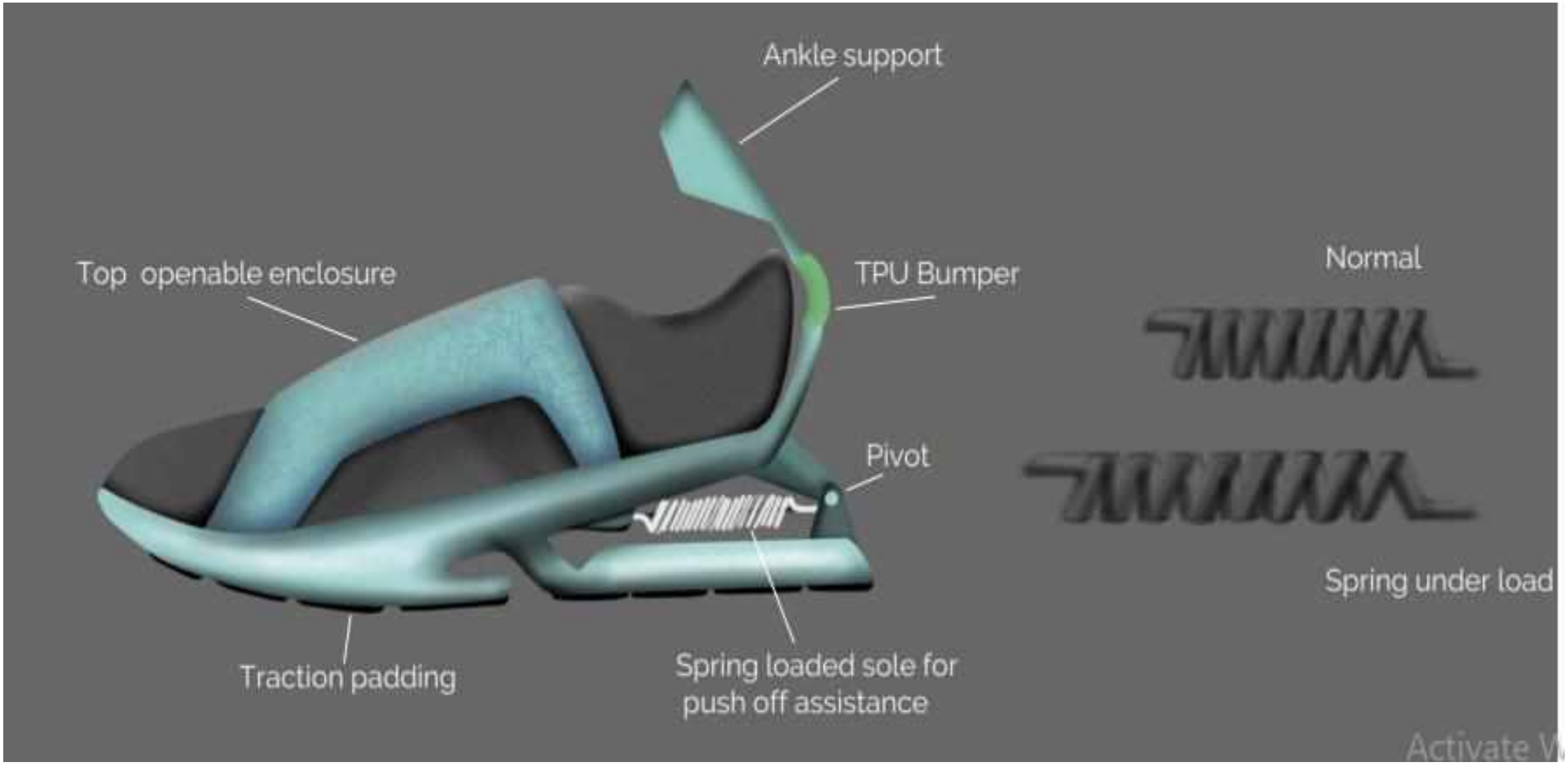
Asha Ek Hope foundation collaborated with IIT Mumbai and two of the students completed their projects in assistive devices for PALS

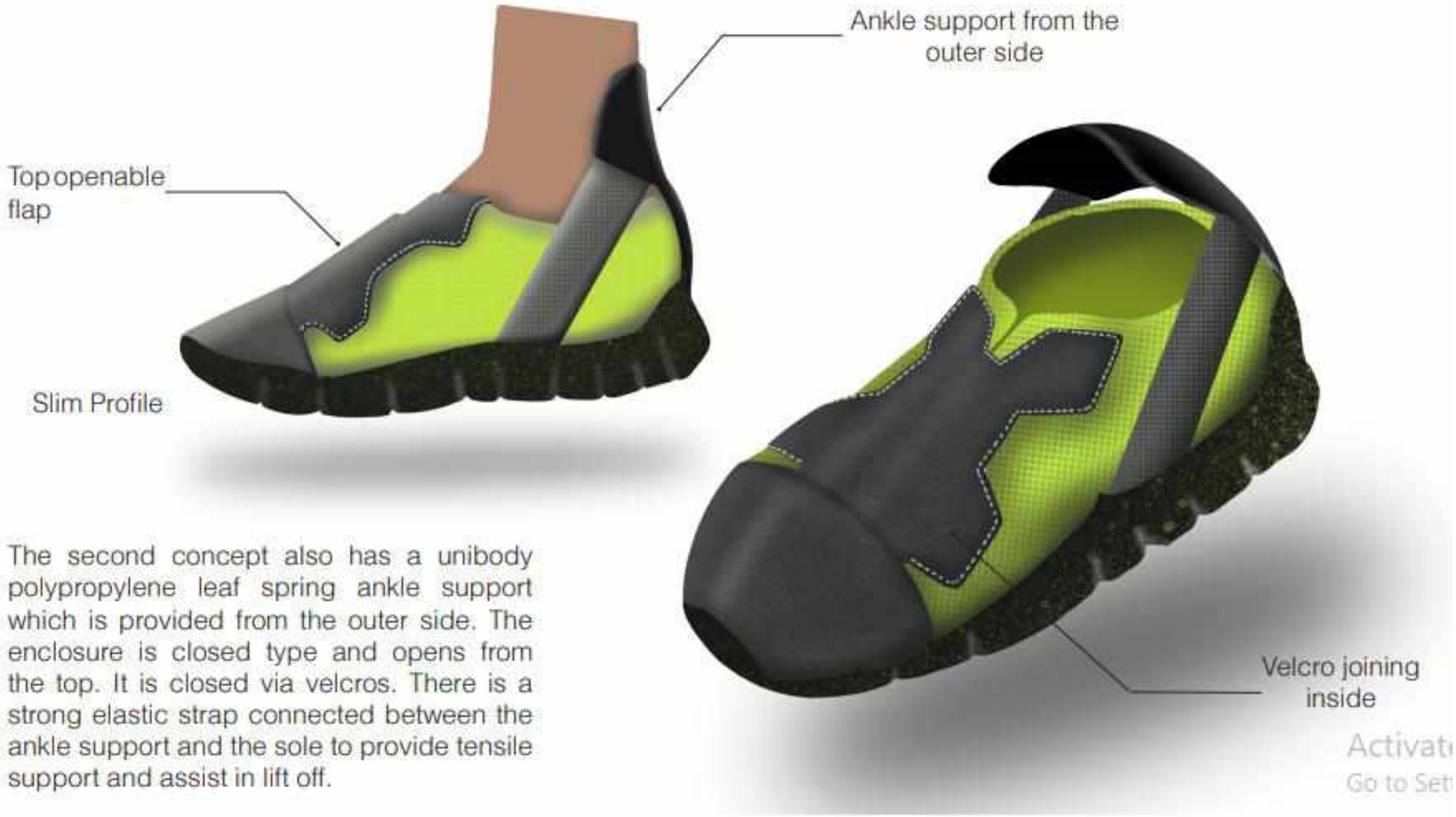
Redesign of Footwear for Motor Neuron Disease Patients

M.Des Industrial Design Project II

Gaurav Nandan
186130001
Guide : **Prof. Purba Joshi**

IDC School of Design
Indian Institute of Technology, Bombay
2018-2020


Ankle support
Top openable enclosure
TPU Bumper
Pivot
Traction padding
Spring loaded sole for
push off assistance
Normal
Spring under load



The second concept also has a unibody polypropylene leaf spring ankle support which is provided from the outer side. The enclosure is closed type and opens from the top. It is closed via velcros. There is a strong elastic strap connected between the ankle support and the sole to provide tensile support and assist in lift off.

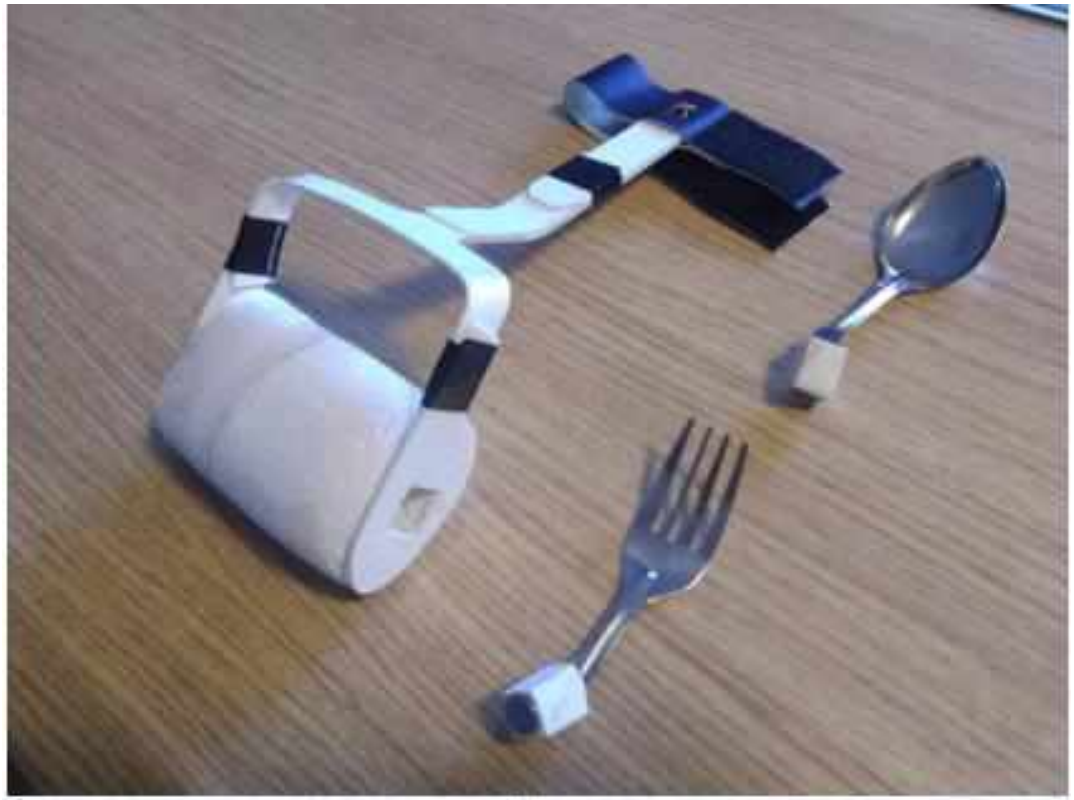
Final Design

Project II

Designing an assistive device for eating purpose for MND patients with wrist drop situation

Nikhil Dhamnaskar
186130012 (2018-2020)
Guid - Prof. Purba Joshi

IDC School of Design
Indian Institute of Technology, Mumbai



Recognition

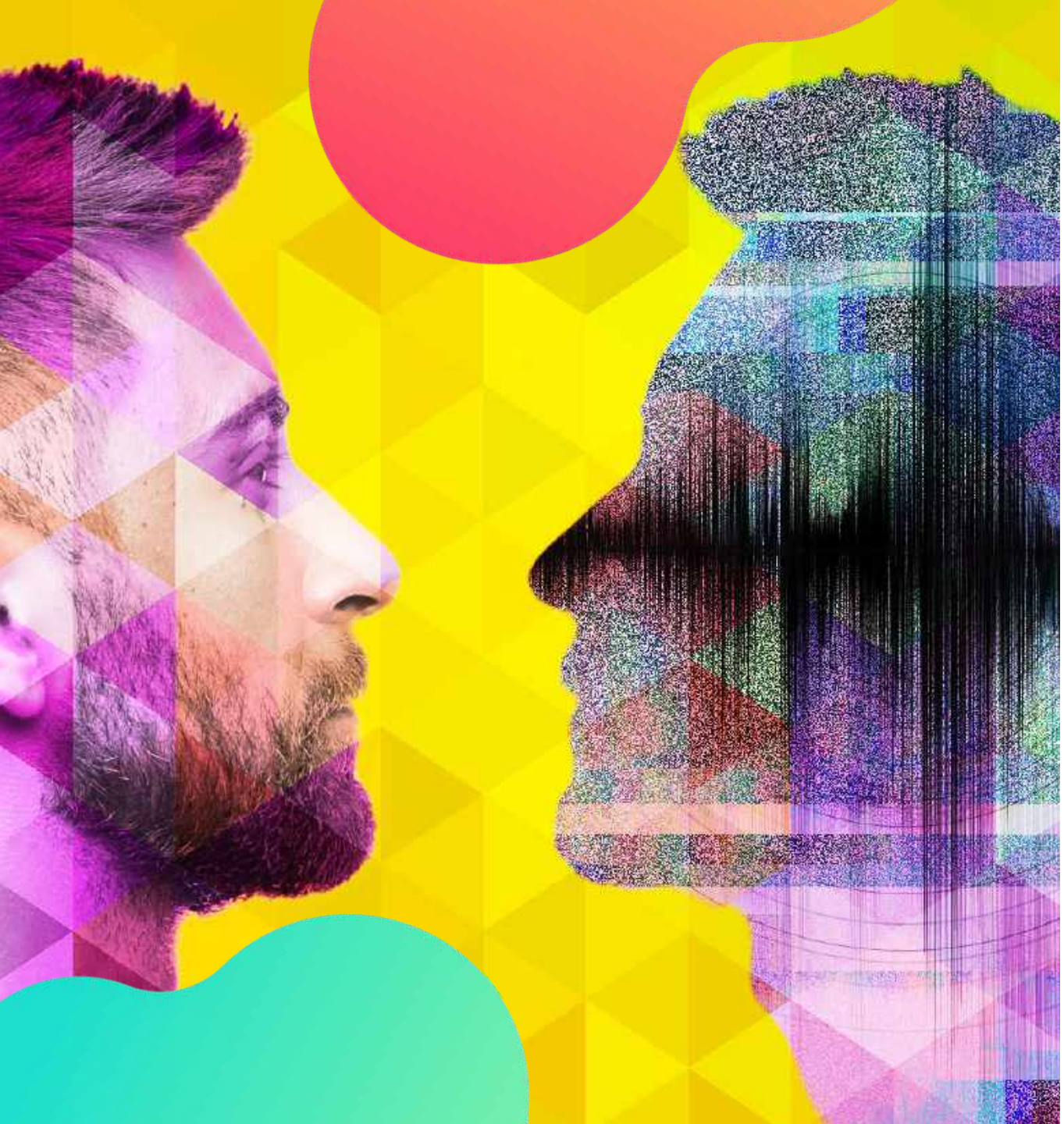
Nikhil Dhamnaskar received the 2nd Prize in "battle of projects" competition in the industrial design category

DECIMAL SPACE VENTURES AND ASHA EK HOPE FOUNDATION

MY VOICE

AN INITIATIVE TO BRING BACK & PRESERVE VOCAL INDIVIDUALITY

Asha Ek Hope
Foundation for MND/ALS, INDIA



VOICE CLONING

THE TECHNOLOGY

Decimal Space's Voice Cloning AI technology allows anyone to digitize , store and use their voice forever

INDIVIDUALITY

VOICE CLONING

GET A DIGITAL COPY OF YOUR VOICE FOR LIFE

VOICE BANKING

PRESERVE A VOICE FOR ETERNITY AND GET A MESSAGE BEYONG THE BIOLOGICAL CLOCK OF A VOICE

COMMUNICATE

USE YOUR VOICE WITH AN AFFORDABLE COMMUNICATION AID AND TALK IN YOUR VOICE

HOW IT WORKS

Voice Recording

We take a 10-15 min sample of your voice

AI Cloning

Our AI clones your voice and preserves it in a digital format forever

Voice Usage

We offer you a pay-as-you-talk service to use your voice supplemented with multiple communication aids

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