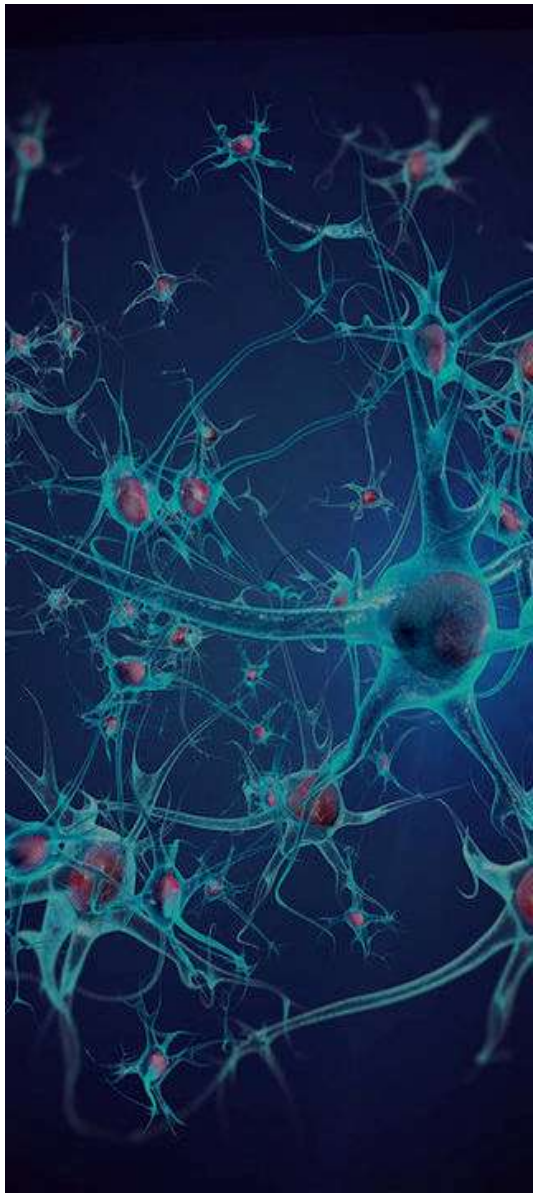
NestaCell®: A Breakthrough Therapy Offering Hope for ALS Patients

CELLAVITA™
EXPANDING CELLS FOR LIFE



Pioneering Over a Decade of Innovation in Treatment Approaches

NestaCell®: Over 5 Years of Human Studies with excellent efficacy and safety profile

- **Extensive Clinical Research:**
  - NestaCell has been studied in Huntington's Disease through Phase I (6 patients) and Phase II (35 patients) clinical trials.
- **Long-Term Benefits in Huntington's Disease:**
  - All patients from previous studies were enrolled in an Extension Study, with some receiving treatment for over 5 years. Continuous therapeutic benefits have been observed in Total Motor, Total Function, and Chorea scores.
- **Broader Applications:**
  - NestaCell was also investigated in a Phase II study for COVID-19, where 45 patients received injections due to its anti-inflammatory effects.
- **Excellent Safety Profile:**
  - The product has demonstrated immune-evasive capabilities over 5 years of study, requiring no immunosuppression.
  - Across all studies, adverse effects were minimal, with no serious or significant negative events reported.
- **Phase III Trial Authorization:**
  - NestaCell has received approval to recruit over 100 patients for a Phase III clinical trial.

NestaCell®, human Immature Dental Pulp Stem Cells (hIDPSCs), represent a distinct type of mesenchymal stem cell (MSC)

- Mesenchymal stem cells (MSCs) can be isolated from various tissues, including amniotic fluid, umbilical cord, Wharton's jelly, bone marrow, adipose tissue, menstrual blood, and others.
- Studies have demonstrated that these cells exhibit transcriptional signatures that are closely aligned with their tissue of origin.
- The hIDPSCs exhibit a distinctive transcriptional signature when compared to other MSCs. This unique profile underscores their specialized properties and potential therapeutic applications.
- **Due to their ectomesenchymal origin (neural crest), NestaCell® expresses 375 unique genes not found in other MSCs, conferring them with distinctive neuroprotective and neuroregenerative properties.** Additionally, these cells exhibit a significantly higher immunomodulatory potential compared to typical MSCs.
- NestaCell®, show great promise as candidates for cell therapy, particularly in the treatment of neurological diseases.

Unique Transcriptional Signatures Observed in Stem Cells from the Dental Pulp of Deciduous Teeth Produced on a Large Scale

Rodrigo Pinheiro Araldi, Mariana Viana, Gabriel Avelar Colozza-Gama, João Rafael Dias Pinto, Lior Ankol, Cristiane Wenceslau Valverde, Eran Perlson and Irina Kerkis

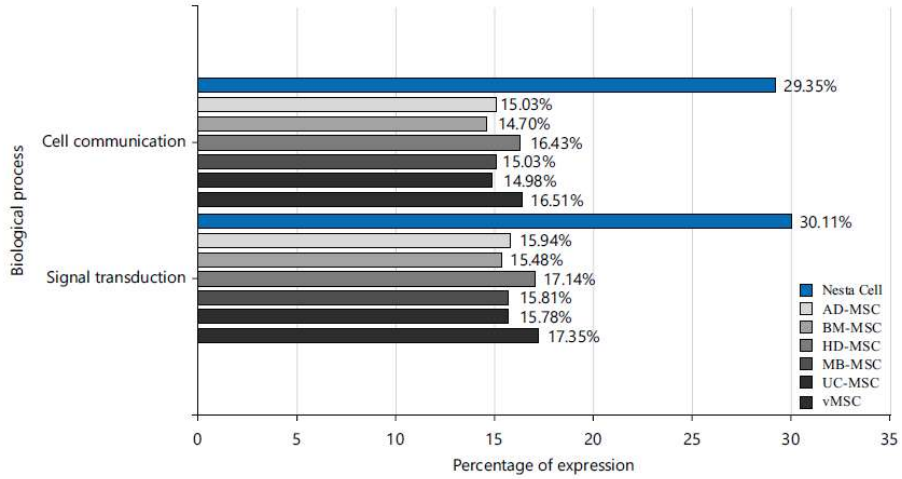


Figure: *Functional enrichment analysis based on the biological process showing the active component of the NestaCell® product (hIDPSCs) naturally express about 2-fold more transcripts involved in cell communication and signal transduction in relation to other MSCs. Analysis was performed using the FunRich software*

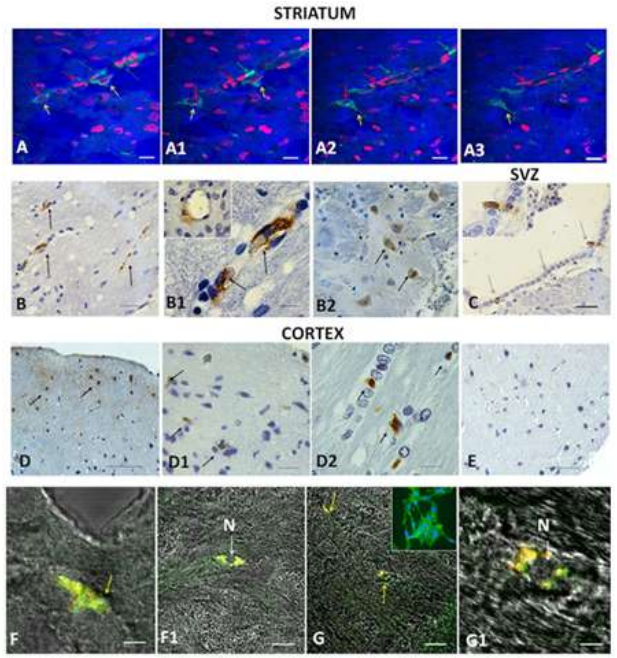
NestaCell®: A Promising Therapy for the Prevention and Treatment of Neurodegenerative Diseases

- NestaCell® naturally overcomes the challenge of crossing the blood-brain barrier, enabling direct intervention to prevent neuronal apoptosis in regions of progressive degeneration, particularly in the brain's vulnerable areas. In the context of neurodegeneration, the anti-apoptotic properties of NestaCell® suggest significant therapeutic potential for Amyotrophic Lateral Sclerosis (ALS), offering a promising approach to slowing or halting disease progression.

Mechanism of Action of NestaCell®

- NestaCell® exerts its effects through the secretion of neurotrophins, such as brain-derived neurotrophic factor (BDNF), nestin, and various cytokines, including interleukin-6 (IL-6).
- Additionally, it demonstrates potential anti-inflammatory action, characterized by elevated levels of IL-10 and reduced tumor necrosis factor (TNF).

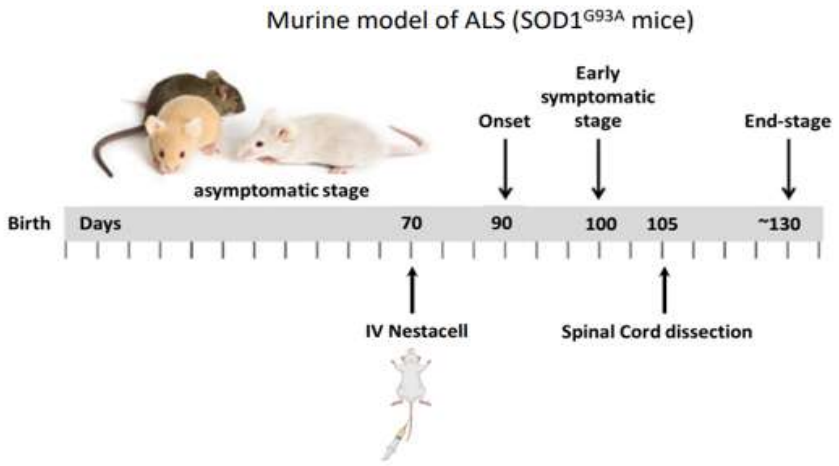
NestaCell® is able to migrate and stay into brain areas
Specific staining (fluorescence) in rodent brain areas



Wenceslau et al.. Cells. 2022 17. 1664.

NestaCell® is currently being investigated for its therapeutic potential in ALS using the SOD1G93A murine model

- **NestaCell®** was studied in an Amyotrophic Lateral Sclerosis (ALS) animal model:
  - Motoneuron Survival.
  - Glial Reactivity.
  - Synaptic Coverage Evaluation.
  - Clinical Evaluation of Disease (behavioral tests).
  - Probability of Survival.
- A single intravenous dose of NestaCell® was administered at a concentration of 1×10^6 cells per kilogram.

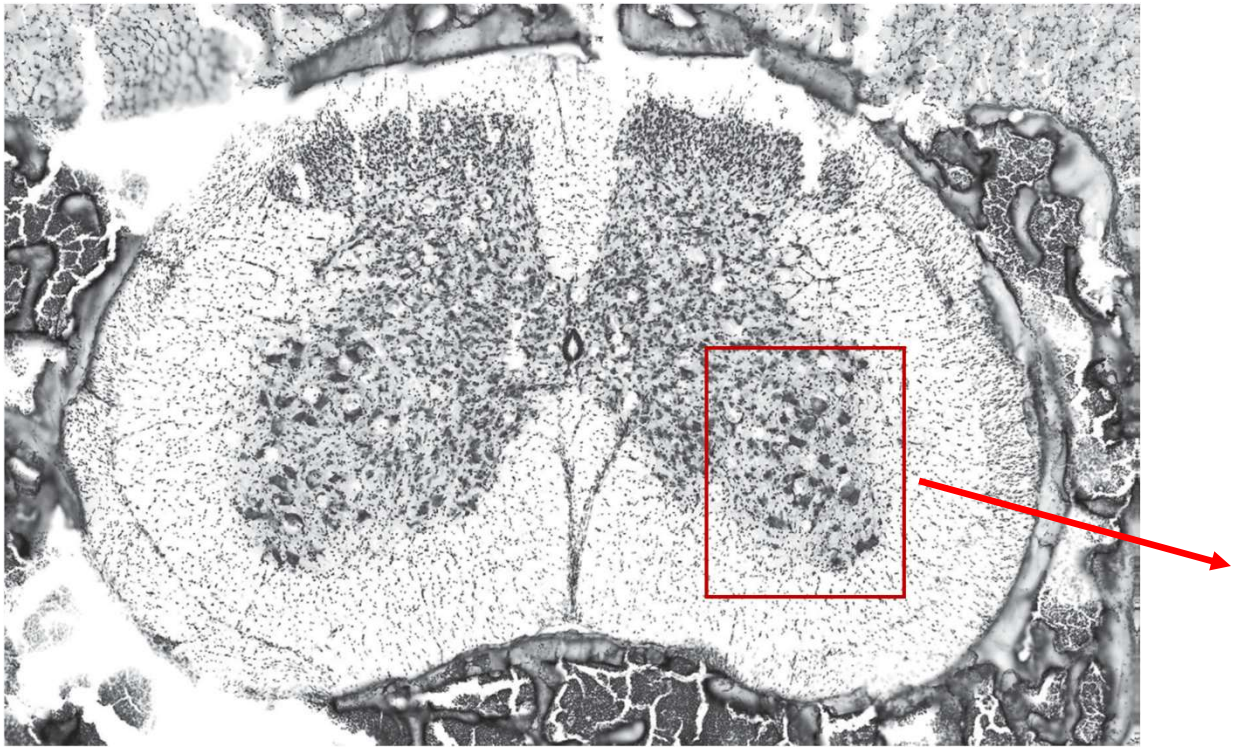


Experimental Techniques	Timepoint	No Transgenic Group (NTG)	SOD Vehicle (Placebo)	SOD NestaCell®
Behavioral tests - Motoneuron survival Immunofluorescence	15 Weeks	5	5	7
Behavioral tests - Probability of Survival	End-stage	5	5	4*

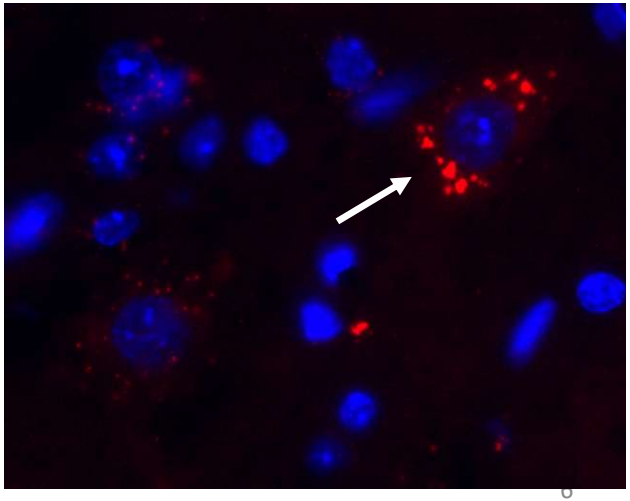
* One individual has not reached end-stage yet

Targeted Delivery of NestaCell®: Evidence of hIDPSC Localization in the Lumbar Spinal Cord

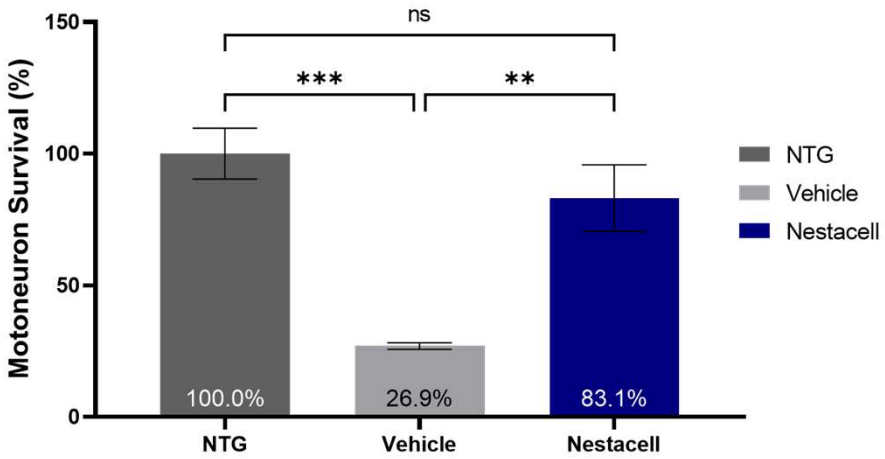
Atlas of the Mouse Spinal Cord



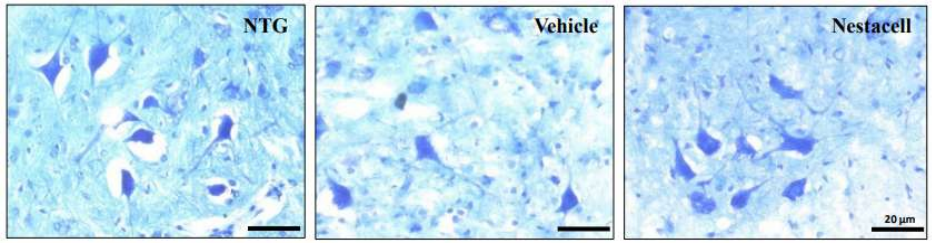
Twenty-four hours following intravenous injection, transplanted human immature dental pulp stem cells (NestaCell®) were detected throughout the lumbar spinal cord, predominantly localized within the gray matter of Rexed lamina IX, thereby indicating successful target delivery.



After 15 weeks of DPSC transplantation, treatment led to enhanced neuronal survival



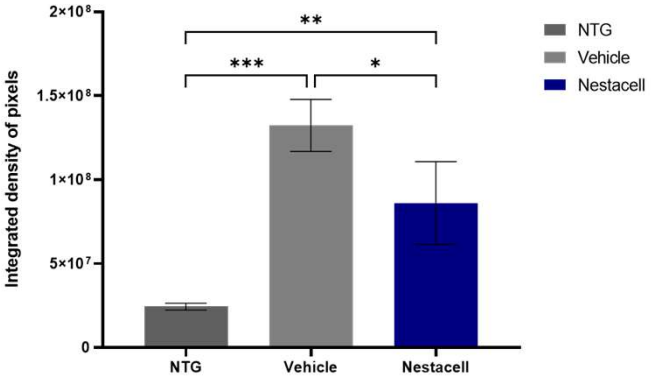
Motoneuron survival



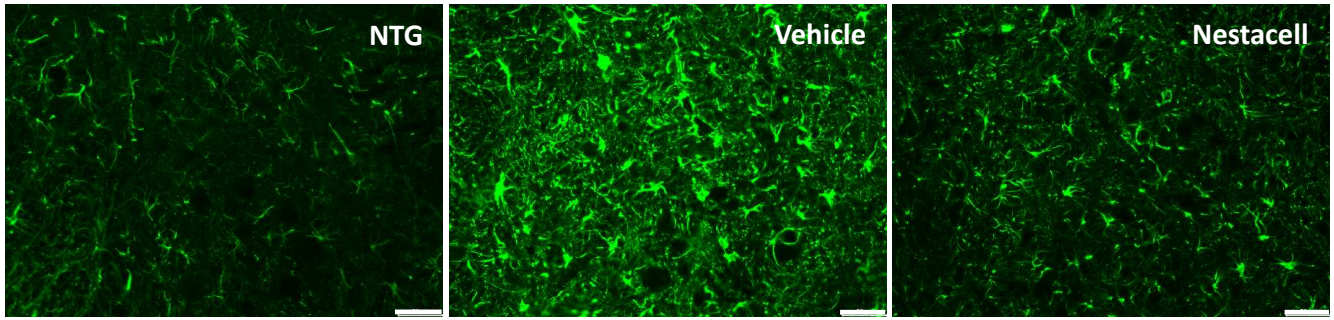
The treatment resulted in significantly greater neuronal survival, with rates of 83% compared to 27%

NestaCell® has exhibited notable improvements in additional neurological indicators (1/3)

Astrocytosis reaction (anti-GFAP)

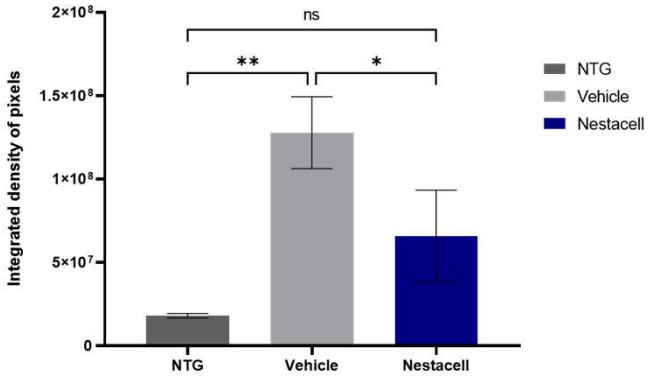


Astrogliosis reactivity were significantly reduced in the treated group

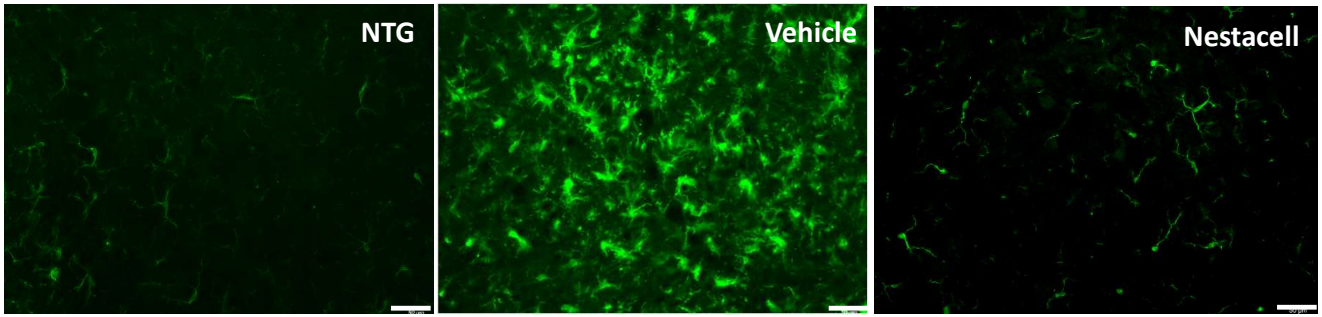


NestaCell® has exhibited notable improvements in additional neurological indicators (2/3)

Microglia Reaction (anti-IBA1)

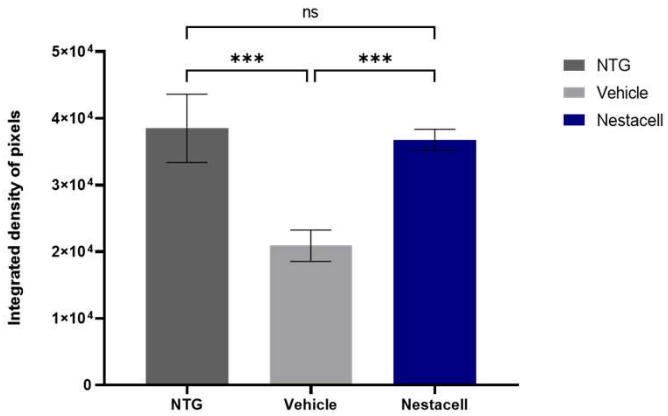


Microglial reactivity were significantly reduced in the treated group

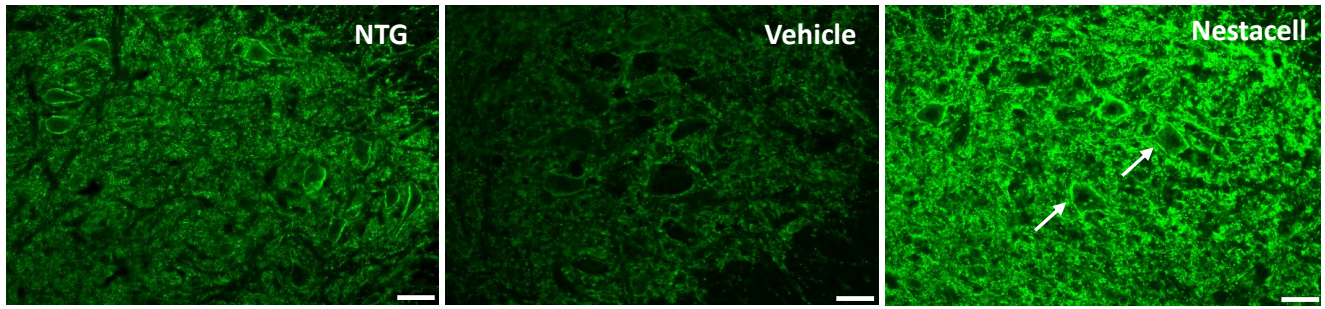


NestaCell® has exhibited notable improvements in additional neurological indicators (3/3)

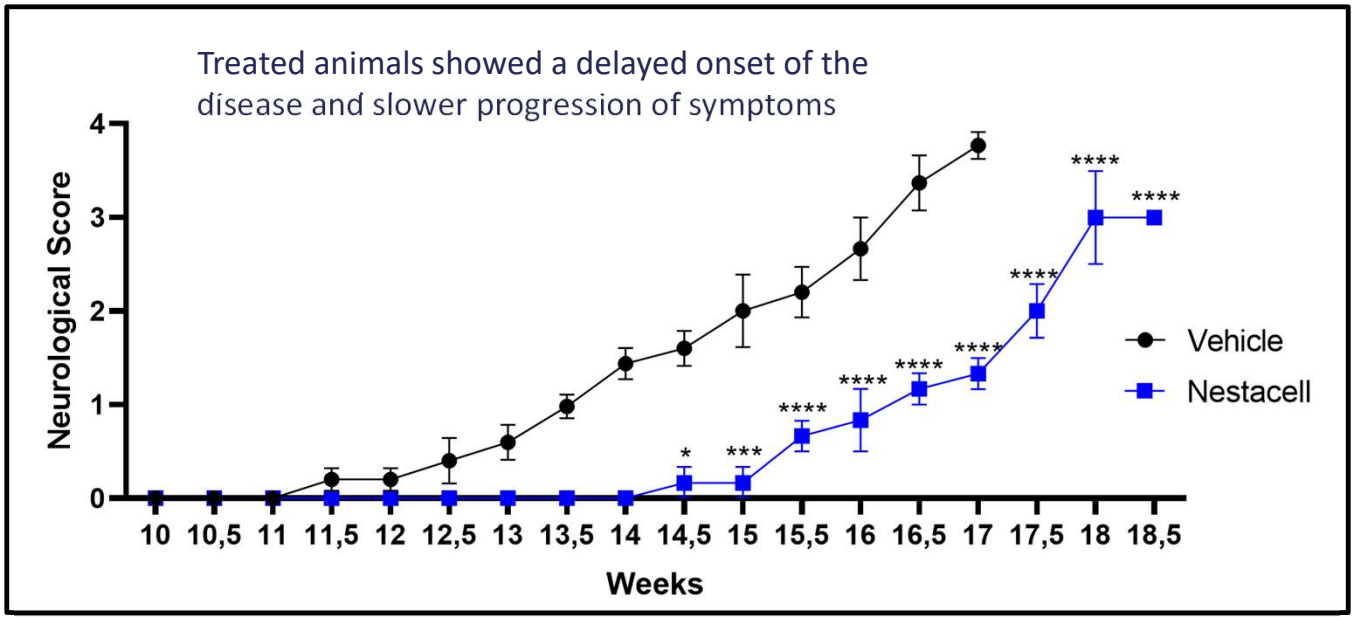
Synaptic Coverage Evaluation
(anti-synaptophysin)

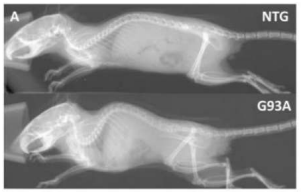


The white arrow indicates that NestaCell® was effective in preserving synapses



Treatment led to slower progression of symptoms

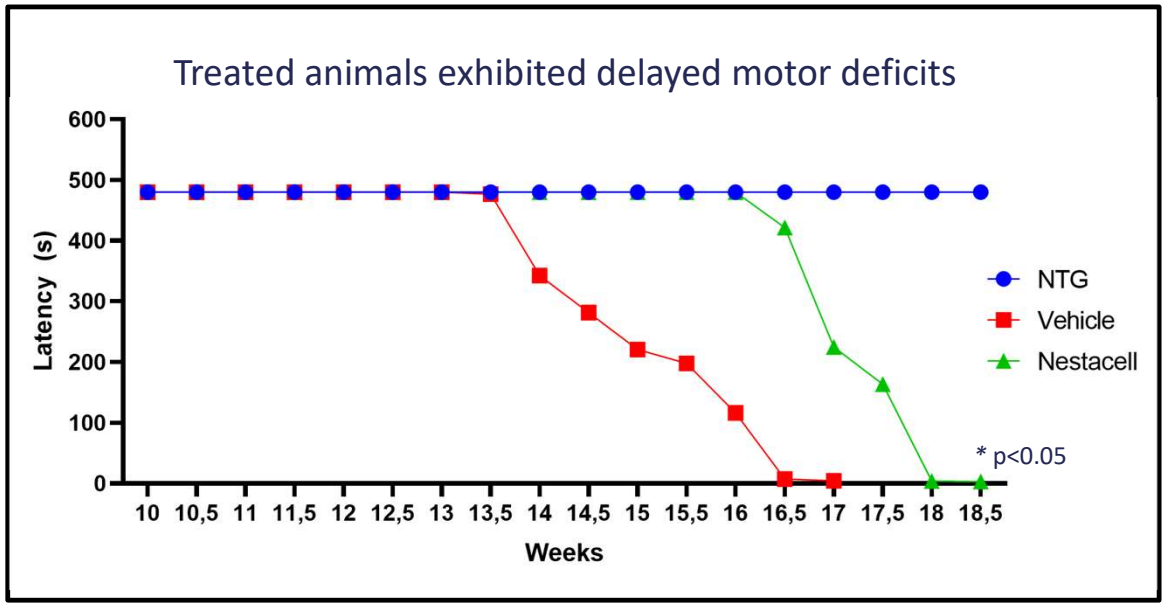




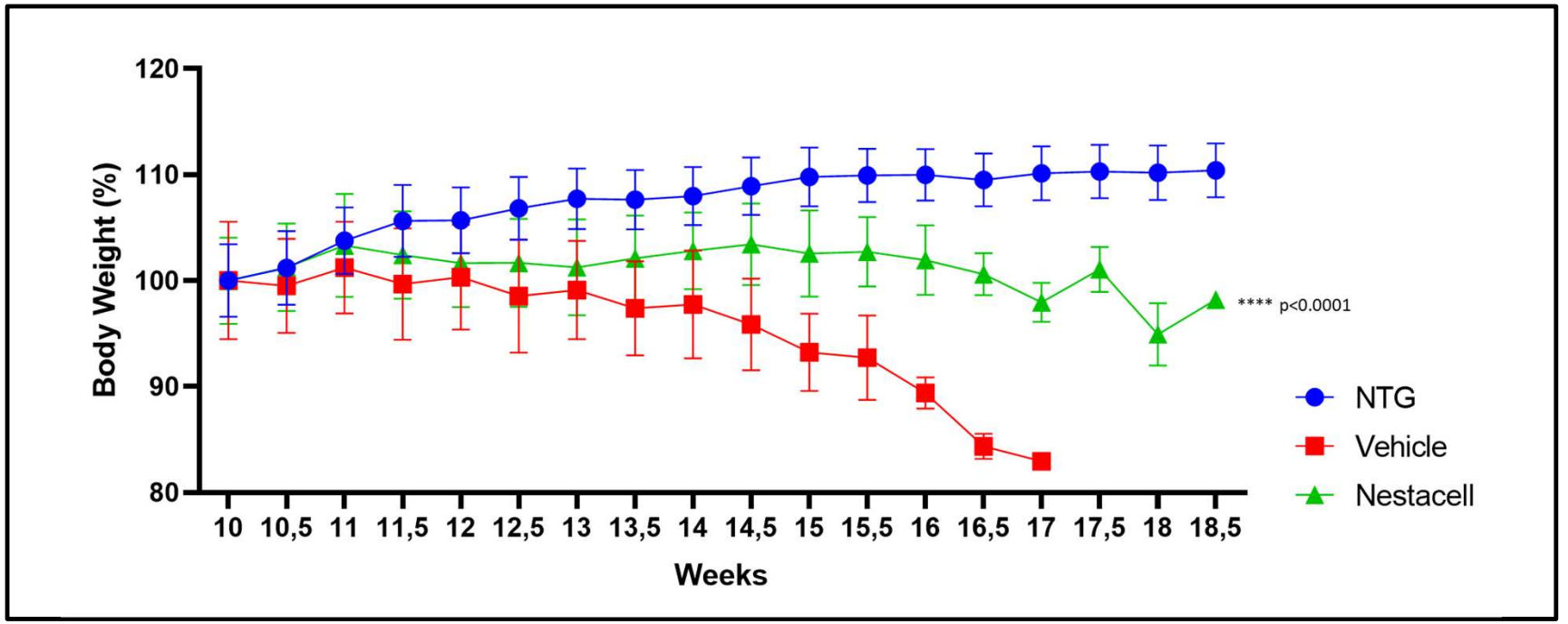
Neurological Score

- **Score of 0: Full extension of hind legs away from lateral midline when mouse is suspended by its tail, and mouse can hold this for two seconds, suspended two to three times.**
- **Score of 1: Collapse or partial collapse of leg extension towards lateral midline (weakness) or trembling of hind legs during tail suspension.**
- **Score of 2: Toes curl under at least twice during walking of 12 inches, or any part of foot is dragging along cage bottom/table.**
- **Score of 3: Rigid paralysis or minimal joint movement, foot not being used for generating forward motion.**
- **Score of 4: Mouse cannot right itself within 30 seconds after being placed on either side.**

Treated animals exhibited delayed motor deficits and prolonged survival, demonstrating the potential of the treatment following a single dose of 1 × 10^6 cells/kg

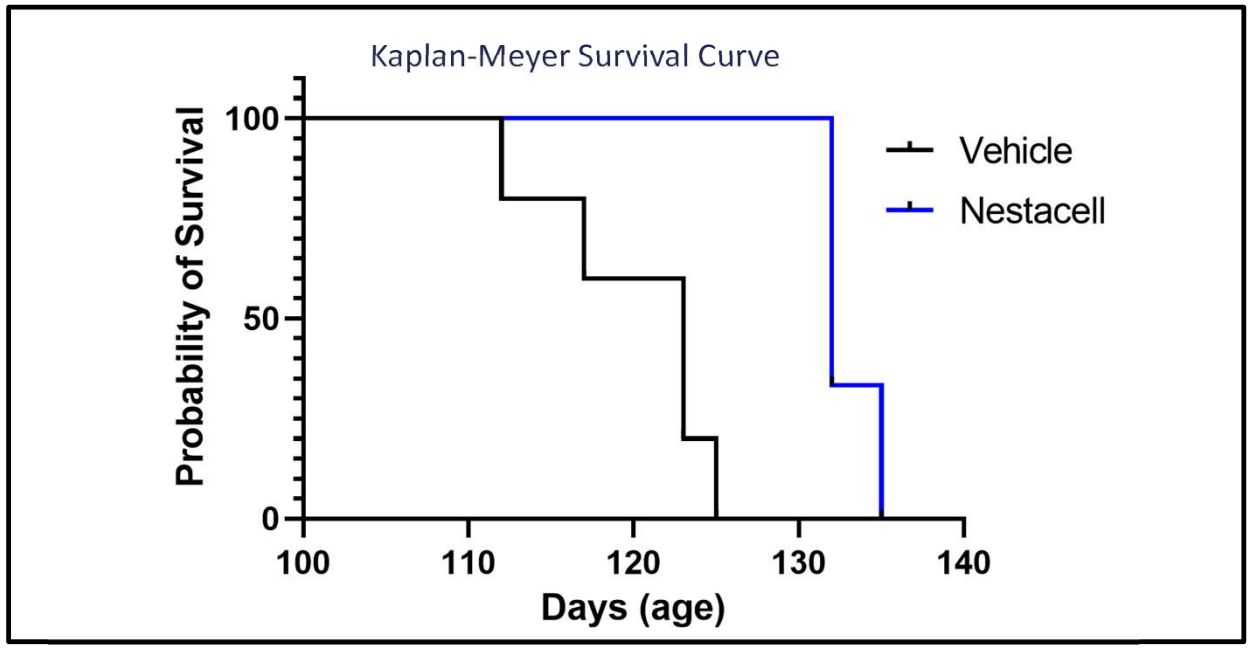


NestaCell® may contribute to the attenuation of weight loss



ALS is a neurodegenerative disease that affects motor neurons, resulting in muscle weakness and atrophy. The treatment effectively attenuated body weight loss during the advanced symptomatic stage of the disease.

Treated animals exhibited delayed motor deficits and extended survival, highlighting the potential of the treatment, even following a single dose



NestaCell® extended the survival of animals by approximately 10 days.

Outcomes Highlighting the Therapeutic Potential of NestaCell® in Amyotrophic Lateral Sclerosis

- Therapeutic potential of hIDPSCs demonstrated in a murine ALS model:
  - Enhanced neuronal survival.
  - Reduced gliosis.
  - Preserved synapses.
  - Improved structural preservation of the ventral horn.

- Clinical effects:
  - Delayed disease progression.
  - Attenuated motor deficits.
  - Reduced weight loss.
  - Later onset of disease symptoms.

- Preclinical findings suggest that DPSC represent a promising therapeutic strategy for ALS.

NestaCell®: A Promising Therapy for Neurodegenerative Diseases

- The unique transcriptional signature of NestaCell® demonstrates its neuroregenerative and neuroprotective properties, which justify the therapeutic effects observed in both preclinical and clinical studies for neurodegenerative disorders.
- NestaCell® has the capacity to modulate multiple disease pathways simultaneously, reducing inflammatory response and exerting anti-aging effects through the reduction of oxidative stress, ultimately leading to decreased neuronal death.
- Clinical development for Huntington's disease and COVID-19 has indicated the safety of NestaCell® in humans.
- Moreover, NestaCell® treatment may provide sustained benefits for individuals with Amyotrophic Lateral Sclerosis (ALS); however, further studies are required to optimize dosage, posology, and treatment duration.

Study NestaCell® in ALS - Researcher

- **Alexandre Hilário Berenguer de Matos**
  - PhD in Neuroscience, is a postdoctoral fellow at the School of Medical Sciences, UNICAMP. He has extensive expertise in Human and Medical Genetics, Molecular Biology, Neurobiology, and Physiology. His experience includes gene expression studies in epilepsy models, and he is currently focused on preclinical trials using human immature dental pulp stem cells (hIDPSC) for Amyotrophic Lateral Sclerosis (ALS), aiming to contribute to the understanding and treatment of these conditions.

- **João Pedro Nunes Gonçalves**
  - PhD student at the School of Medical Sciences, UNICAMP. His research focuses on preclinical trials using exosomes from human immature dental pulp stem cells (hIDPSC) for ALS, aiming to explore their therapeutic potential in the disease.

Study NestaCell® in ALS - Supervisor

- **Marcondes Cavalcante França Jr., MD, PhD**
  - Is an Associate Professor in the Department of Neurology at the School of Medical Sciences, UNICAMP. He specializes in neuromuscular diseases, clinical neurophysiology, and neurogenetics, with significant expertise in Amyotrophic Lateral Sclerosis (ALS). His research focuses on advancing the understanding and treatment of neuromuscular disorders and genetic neurological conditions, particularly ALS, integrating clinical, neuroimaging, and molecular approaches to improve patient outcomes.

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- **Irina Kerkis, PhD**
  - Is a full professor and the Director of the Laboratory of Genetics at the Butantan Institute in São Paulo, Brazil, with extensive expertise in Genetics, Cell Biology, and Biotechnology. Her research focuses on the isolation and characterization of human dental pulp stem cells. Dr. Kerkis has made significant contributions through her pre-clinical studies, exploring the potential of these cells in therapeutic strategies for treating neurodegenerative diseases using various animal models. With a strong commitment to bridging the gap between basic research and clinical applications, she is at the forefront of advancing regenerative medicine.

INSTITUTO BUTANTAN

- **Rodrigo Araldi, PhD**
  - Graduated in Biological Sciences (Bachelor's and Teaching Degree) from UNESP, with a specialization in Genetics (Viral Oncogenesis) from the Butantan Institute, and both a master's and doctorate in Biotechnology from USP. He completed a postdoctoral fellowship in Cancer Molecular Biology at EPM-UNIFESP. With extensive experience in mutagenesis, cancer molecular biology, CRISPR-Cas9 gene editing, oncogenesis, and biotechnology, his research focuses on molecular mechanisms of epithelial-mesenchymal transition and aims to identify biomarkers for diagnostics, immunotherapies, and exosome-based therapies. Currently, he is a professor in Molecular Biology and Business Management in various graduate programs at UNIFESP and serves as co-founder and CEO of BioDecision Analytics Ltda

BioDecision Analytics

Cellavita® Scientific Advisory Board

- **Joyce Macedo, MD**
  - Graduated in Medicine from the Faculty of Medicine at the Federal University of Bahia (UFBA), with a specialization in Epilepsy and Electroencephalogram from UNIFESP (2009-2011). Currently serves as a faculty member in the Health Sciences Education program at Hospital Alemão, focusing on Clinical Research. Professionally, held the position of National Medical Manager of Clinical Research at Aché Laboratories from 2011 to 2014 and then as Senior National Medical Manager of Clinical Research at EMS Laboratories from 2014 to 2017. In 2017, became the Director of the Medical Writing Department at Azidus Brazil CRO. Has extensive experience as a Principal Investigator in Phase 1, 2, and 3 clinical studies. Presently pursuing a PhD at UNICAMP, researching magnetic resonance imaging in patients with Spinocerebellar Ataxia Type 3 (SCA3).

- **Francisco Rotta, MD**
  - Graduated in Medicine from the Federal University of Rio Grande do Sul (UFRGS), with specialized training in Neurology and Neuromuscular Medicine at the University of Miami, FL. Board Certified in Neurology by the American Board of Psychiatry and Neurology (ABPN). Currently engaged in clinical research at Intercoastal Medical Group in Sarasota, FL, and serving as Medical Coordinator at the Paulo Gontijo Institute in São Paulo, Brazil.

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- **Eduardo Pagani, MD**
  - Has over 20 years of professional experience in drug discovery and development across small molecules, biologics, herbal medicines, and cell therapy. A graduate of FMUSP (1986) with further training in Pharmaceutical Medicine at UNIFESP (1995), he also holds a master's in Molecular Biology (1995) and a Ph.D. in Pathophysiology (1999) from the same institutions. Dr. Pagani has honed his skills in Good Clinical Practices at the Schering Plough Research Institute in the USA (2002). Currently, he is the Medical Writing Director at Azidus Brasil, Medical Director at Cellavita, and a Scientific Consultant at ATME, where he evaluates projects for FDA and EMA submissions. His previous roles include managing interactions between academia and pharmaceutical companies at LNBio/CNPEM, focusing on small molecules, monoclonal antibodies, and microfluidic devices for biomedical testing. Additionally, he served as Medical Manager at Cristália and the Schering-Plough Research Institute, overseeing both pre-clinical and clinical trials


Thank you !