THEMATIC

HEALTHCARE

Regenerative Medicine – Stem Cells

Neurodegeneratives – Motor Neuron Disease

Regenerative medicine remains an extremely exciting area of healthcare with vast investment potential. In spite of the usual setbacks in valuation and strategy, the sub-sector has pivoted and the market remains innovative and attracts investment capital. Rather than replace entire tissues, which is a complex activity, we believe the immediate future for stem cells is more likely to be in the successful stimulation of the bodies on repair mechanisms. Within regenerative medicine we believe there is significant potential for stem cell therapies for neurodegenerative diseases. To illustrate we look at Motor Neuron Disease (MND) also called ALS or Lou Gehrig's disease. Lou Gehrig was a baseball player, thought to be the first formally recognized sufferer of MND. We examine results from BCLI's recent biomarker peer reviewed research in relation to the treatment of MND using a stem cell MSC-NTF proprietary platform called NurOwn (debamestrocel, MSC-NTF).

Monday, 10 June 2024

- Biotech global market value forecast 2031E USD 5.11trn, CAGR 16%;
- Biotech global market 2023 estimate US $1.55trn;
- NDD market 2031E USD 50bn, CAGR 4.5% and rising;
- NDD market 2021A USD 40bn, absolute number of patients rising;
- MND (ALS), fatal, currently no cures or reversal therapies.

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Global Biotechnology Market - An Overview

Biotechnology impacts an array of sectors – medical, agricultural, industrial and environmental. Its diverse applications have led to the development of life-saving drugs, genetically modified crops, biofuels, biodegradable plastics and the use of microorganisms to clean up contamination and significant returns for investors.

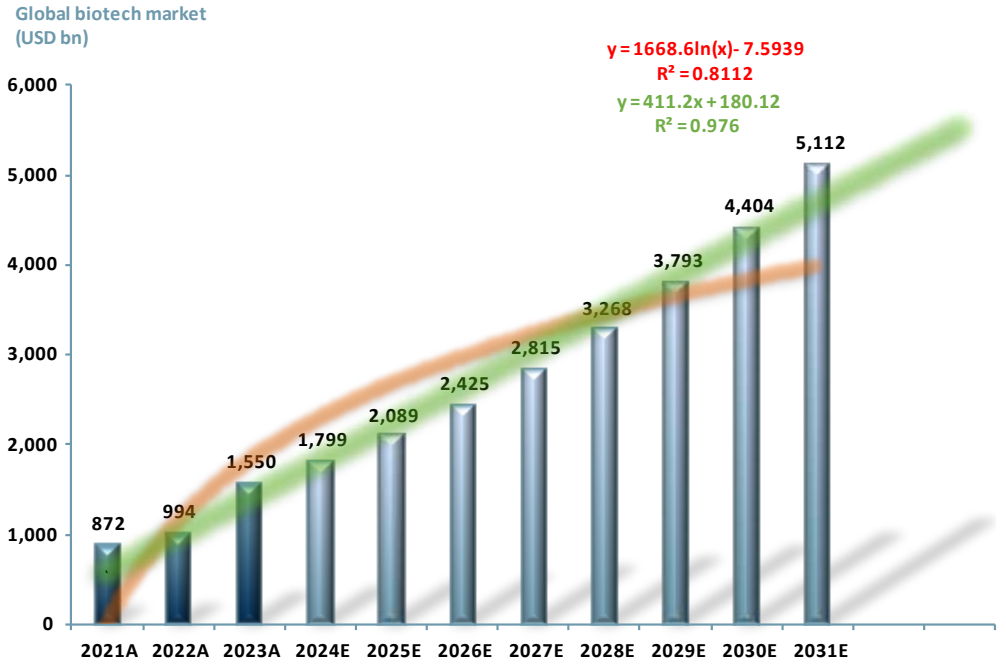
Biotechnology is a multidisciplinary field - the integration of natural sciences and engineering sciences. It involves the use of biology to solve problems and create useful products, via genetic engineering (the manipulation and modification of an organism's genes using technology). These organisms include bacteria, yeast, plants, and human cells. According to some authors the market can be segmented by bio-pharmacy (~42% by market value (bMV), bio-industries (~24% bMV), bio agriculture (~21% bMV), bio-services (~7% bMV), and bio-informatics (~6% bMV)), see exhibit below. Technologies include tissue engineering and regeneration (stem cells, part of bio-pharmacy), PCR, nanobiotech, DNA sequencing, cell-based assay and chromatography.

ACF has taken an industry forecast average to achieve the value in 2031E (10-year forecast) from various verified sources.

Though there is a relatively wide spread of estimates, the global biotechnology market is estimated to grow at least with a CAGR >10% out to 2030E. Some market value estimates are significantly higher. Our mid-range estimate suggests a biotech global market value of US $5.11trn by 2031E up from US $1.55trn in 2023A, a CAGR of 16% (Grand View Research, Reports and Data, Expert Market Research). This is driven primarily by improved government support that has led to initiatives and modernization of the regulatory framework. As a result, the approval, reimbursement, and standardization of clinical studies has significantly improved in terms of efficiency.

Exhibit 1: **Global biotechnology market 2021A-2031E**

The green linear forecast best fit line, $R^2$0.976, could lead investors to conclude that we expect a constant growth rate beyond 2031E. A safer interpretation would be to assess the logarithmic trend line which reveals our view that the rate of growth will inevitably decline, even though the value of the market will continue to increase. Investors could, for example, think about this in terms of the interplay between innovation/value add, deteriorating environmental conditions and inflation driving values up vs. policy changes, competition and knowledge democratization leading to behavior change, all usually serving to drive values down.



Sources: ACF Equity Research Estimates & Graphics; Grand View Research; Reports and Data; Expert Market Research; Econ Market Research.

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Market growth and demand - The Covid-19 pandemic propelled advancements in drug development vaccine manufacture. The success of mRNA vaccines during Covid helped accelerate the drug approval process and increased vaccine revenues. In 2021A, 11bn+ doses of the C19 vaccine were produced globally and revenues generated by Pfizer (NYSE : PFE), Moderna (Nasdaq : MRNA) and Johnson & Johnson (NYSE : JNJ) reached USD 31bn (Grand View Research).

Agricultural applications increased demand for biotechnology - genetically modified crops, herbicide-tolerant, and insect resistant seeds contributed to market growth.

Clinical trial success in cell and gene therapy and tissue regeneration attracted growth in global investment for companies reaching USD 23.1bn in 2021A, up 16% vs. 19.9bn y/y (Alliance for Regenerative Medicine). In addition, increased demand for neurodegenerative and chronic disease treatments is driving clinical solution demand.

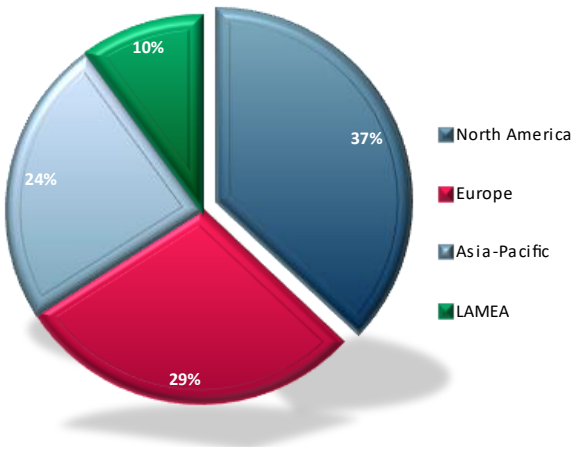
Key market players include:

Abbott Laboratories
Amgen
AstraZeneca
Biogen
Bristol-Myers Squib
F. Hoffman-La Roche
Gilead Sciences
Johnson & Jonson
Lonza Sanofi
Merck
Novartis
Novo Nordisk
Pfizer
Sanofi

Celgene

Regional insights - North America accounts for the largest geographical proportion of market share with estimates ranging between 37.8% and 41.4% in 2023 (Grand View Research et al). **North American dominance** comes from the presence of leading industry players (as we saw during the pandemic), extensive Research & Development, high healthcare expenditure, and investor culture (willingness to invest in and support high risk high reward projects). North America also has effective processes for the identification and diagnosis of chronic disease (relatively reliable data for investors) combined with the adoption and interest in personalized medication. Chronic disease diagnostics and cultural expectations have become significant drivers for North American market growth.

Exhibit 2: **Biotech market value share by region 2023A**



Sources: ACF Equity Research Estimates & Graphics; Precedence Research.

The fastest growing regions in the biotechnology market are Asia Pacific and India. Our low-end estimate for Asia Pacific biotechnology market growth is a CAGR ~7% from 2024-2030, market consensus estimates suggest a CAGR range between 11% and 13%, with China as the major growth contributor to the region. The drivers for market growth are increased investments and improved health care infrastructure, government support and expansion from key market players (e.g., Moderna indicated in 2022 that it plans to expand into Asia and open subsidiaries in Malaysia, Singapore, Hong Kong, and Taiwan). Although estimates are sparse, India's biotechnology market CAGR to 2030 is expected by financial markets to be ~17%. India has recently established a potentially leading presence in recombinant therapeutics and vaccines. India was a key player in vaccine distribution during Covid, providing 150 countries with medical supplies and equipment.

Market characteristics and applications

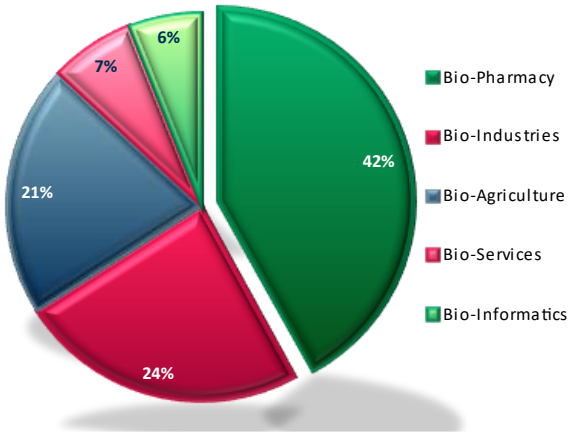
- **Medical** – biotechnology is used in drug discovery, gene testing, and gene therapy.

- **Agriculture** – biotechnology is used in the development of genetically modified crops, herbicide-tolerant, insect resistant seeds, and tissue culture technology that can produce new plant variants.

- **Industrial** – biotechnology is used to produce biofuels, bioplastics, and other bio-based products.

- **Environmental** – biotechnology is used for environmental cleanup, e.g., bioremediation.

Exhibit 3: **Biotechnology applications 2023A**



Sources: ACF Equity Research Estimates & Graphics; Grand View Research, Precedence Research.

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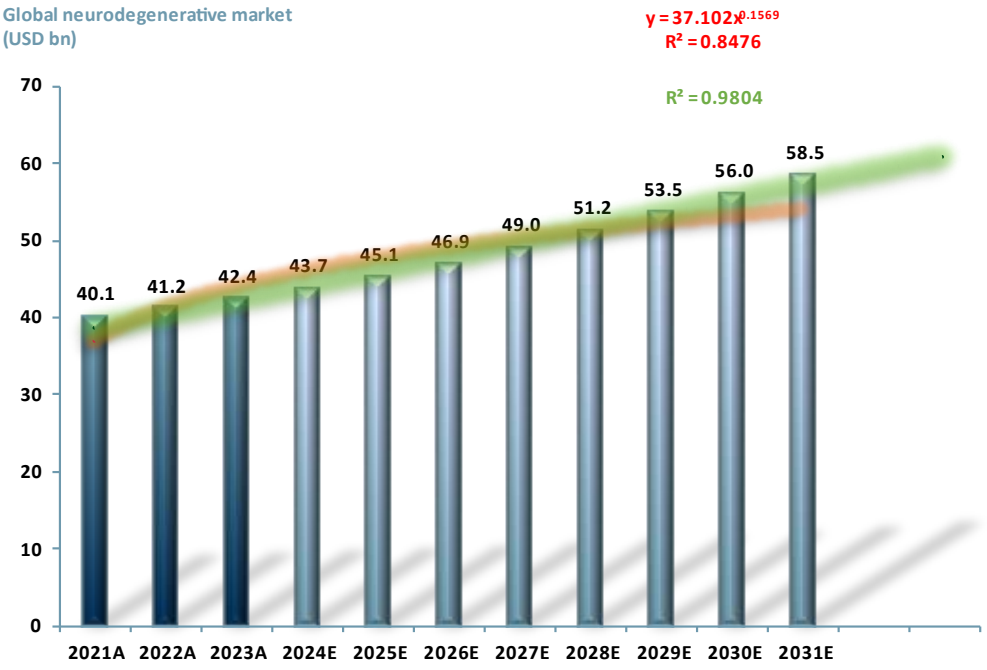
Neurodegenerative Disease Market

Neurodegenerative diseases (NDDs) are characterized by the progressive loss of the structure or function of neurons (nerve cells that enable functions such as breathing, talking, eating, walking and thinking). Neuronal damage can ultimately lead to cell death.

The types of neurodegenerative diseases include amyotrophic lateral sclerosis (ALS), Alzheimer's Disease, Parkinson's, Huntington's, multiple sclerosis, multiple system atrophy, tauopathies, and prion disease. Symptoms can include impaired mental function, loss of muscle control, memory loss, disorientation, emotional blunting, social withdrawal, hallucinations, delusions, and depression.

Based on our market consensus research, we assess that the neurodegenerative disease market may reach USD 50bn by 2031E, up from USD 40bn in 2021A, with an average CAGR of 4.5% (sources Mordor Intelligence, Straits Research, GlobeNewswire, Research and Markets, ACF Estimates). Growth is driven primarily by the rising occurrence of neurological diseases, increased awareness of these diseases and a strong and viable product pipeline for disease treatment.

Exhibit 4: **Global neurodegenerative market 2021A-2031E**



The green line is the CAGR linear (best fit) forecast line indicating a direction and 'rate of travel' beyond the end of the forecast period 2031E, with an R^2 value of 0.9892. The red line is the power trend line, R^2 0.9892 and indicates in this case that our expectation for the rate of acceleration is that it will decline. We describe our forecast as an interplay between better diagnosis and deteriorating environmental factors accelerating the rate of growth vs. knowledge, driving behavior changes that moderate this acceleration rate over time. It is not that we expect our forecast numbers to be explicitly met it is more that we want to help investors think about our forecasting approach over prolonged periods.

Sources: ACF Equity Research Estimates & Graphics; Mordor Intelligence; Straits Research; GlobeNewswire; Research and Markets.

Market growth and demand

Market growth has been temporarily held back by a Covid enforced delay in product approvals.

The Covid-19 pandemic, much like the biotechnology market, has significantly impacted the neurodegenerative disease market. The pandemic disrupted workflows of clinical trials, R&D, and the development of therapies for these diseases. We assess there is likely to be a spate of new therapy approval applications as the industry catches up on delivery timelines.

Global population demographics are leading to an increase in the absolute number of neurodegenerative disease patients. The National Institute of Environmental Health Sciences (NIEHS – US based) reported that in the US in 2022, ~62m people had Alzheimer's and ~1m had Parkinson's (out of a population of ~332m). In Europe, the total number of disability-adjusted like-years (DALYs) attributed to neurological disorders in 2020 was 21m and in the WHO-EU region it was 41.1m (Lancet Journal).

~6.5m Americans aged 65+ were living with Alzheimer dementia in 2022A. This number is expected to increase ~2x to 12.7m by 2050E (Alzheimer's Association).

The US FDA launched and action plan in 2022 for the manufacturing of safe and effective drugs to treat rare neurodegenerative diseases, including ALS.

Regional insights - The neurodegenerative disease (NDD) market is distributed across North America, Europe, Asia-Pacific, South America, the Middle East, and Africa. North American expected market revenues 2023E of USD ~18bn (Straits Research) by 2023E up from USD ~17bn in 2021A, a CAGR of 2.5% (Straits Research). The US population is growing at 0.6% or ~1.8m p.a.. NDDs occur relatively rarely in the general population. Market value forecasts may be reliant on both a growth in incidence and a growth in diagnosis effectiveness.

By 2021, the National Institute of Health (NIH) had allocated USD 4.1m to neurodegenerative diseases hoping to attract larger market players. The US also dominates NDD R&D spend/investment. NDD R&D is sponsored/funded by academic and R&D institutions as well as public (and private) pharma and biotech companies.

Key market players:

AbbVie (ABBV, MCAP ~$300bn)
Amneal Pharmaceuticals (AMRX, MCAP ~$2bn)
Boehringer Ingelheim International (private)
F. Hoffman-La Roche (ROG.SW, MCAP ~$215bn)
Merck (MRK, MCAP ~$330bn)
Pfizer (PFE, MCAP ~$160bn)
Teva Pharmaceuticals (TEVA, MCAP ~$19bn)
Novartis (NVS, MCAP ~$220bn)

Europe is the second largest NDD market with revenues 2023E are expected to have reached USD 12.3bn up from USD 11.5bn 2021A, a CAGR of 3.5% (Straits Research). Germany dominates the European region, providing a base for global companies to develop neurodegenerative drugs. Our consensus market forecasts suggest that major pharma companies In Germany will deliver an increase in drug launches driven by the increasing prevalence (and or detection) of NDDs. Some sources suggest that the number of people with dementia in Germany is expected to increase to 2.8m by 2050E up from 1.6m in 2018A.

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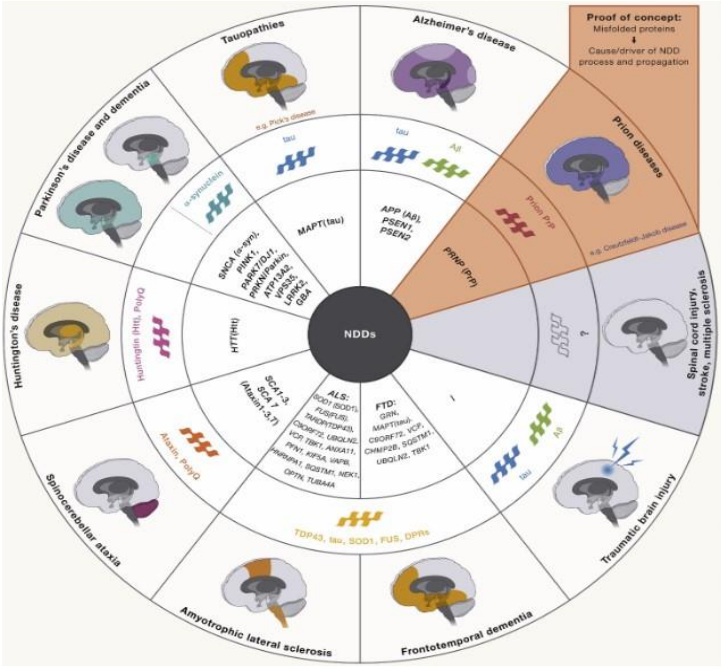
Market segmentation - Amyotrophic Lateral Sclerosis (ALS) forms part of the neurodegenerative disease (NDD) market. See top level segmentation below.

Exhibit 5: **Market segments – neurodegenerative diseases (NDDs)**

NDD Market Top Level Segments by Indidcation	Description
MND/ALS/Lou Gehrig's	Progressive loss of biochemical functionality in both upper motor neurons (UMNs) and lower motor neurons (LMNs) that normally control voluntary muscle contractions.
Parkinson's	Progressive brain damage from nerve cell loss, primarily the dopamine producing neurons.
Alzheimer's	Progressive starting with mild memory loss and moving to dementia.
Multiple Sclerosis (MS)	Brain and spinal cord; the immune system attacks [mistakenly] the CNS.
Huntington's	Brain, inherited/genetic, damages nerve cells degrading their function.

NDD Market by Therapy	Description
Receptor Antagonists	E.g. N-methyl-D-aspartate (NMDA) – are commonly used to treat Alzheimer's (as well as having anesthetic indications).
Cholinesterase Inhibitors	Break down acetylcholine a (neurotransmitter that serves memory, learning, attention, arousal, and muscle movement), treats Alzheimer's.
Dopamine Agonists	Activate brain/dopamine receptors, key for treating coordination disorders, e.g., Parkinson's.
Immunology Therapies	Includes stem cells, gene editing and drugs – modify the immune response, enhances/suppresses the immune system, used to treat MS.



Sources: Hallmarks of neurodegenerative diseases, 16 Feb 2023, sciencedirect.com.

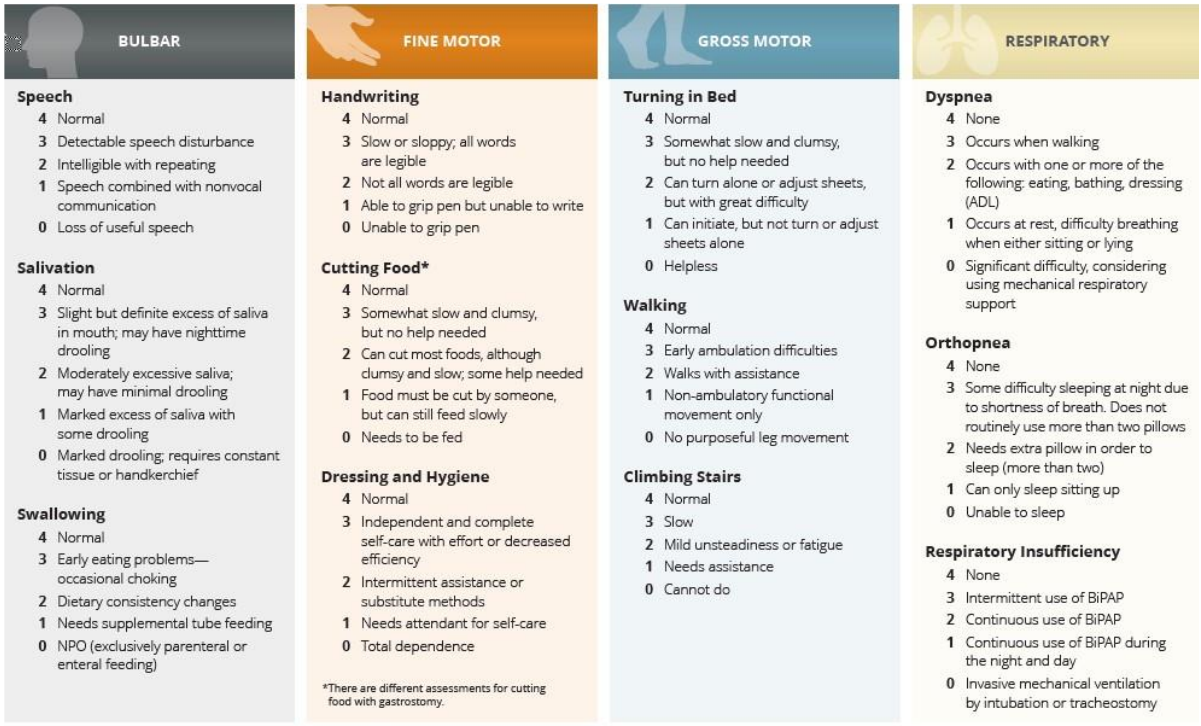
ALS – Amyotrophic lateral sclerosis

What is ALS? Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND) in the UK or Lou Gehrig's disease in the United States, is, arguably, the most common form of a complex condition - motor neuron disease. Death typically occurs within 2-5 years. **There is currently no cure**.

ALS describes the progressive loss of biochemical functionality in both upper motor neurons (UMNs) and lower motor neurons (LMNs) that normally control voluntary muscle contractions. Other cell types in the central nervous system that support motor neurons, called glia, including astrocytes and oligodendrocytes, are also affected in ALS. Genetic variations, in e.g., alleles of gene UNC13A C, may also influence ALS progression and survival and serve as pharmacogenomic biomarkers.

ALS disease progression is evaluated using the ALS Functional Rating Scale-Revised (ALSFRS-R). ALSFRS-R is a clinician assessed (subjective) set of 12 characteristics scored from 4 to 0 (see exhibit below), totaling 48 points, where the higher the score the less affected the patient is by ALS. A baseline degradation progression of the loss of 1 point per month is cited in some sources as a reasonable median rate of progression when guiding patients on their likely rate of physical decline.

Exhibit 6: Evaluating the progression of ALS using ALSFRS-R



Sources: alspathways.com; Mitsubishi Tanabe Pharma America.

ALS is a terminal complex multifactorial neurodegenerative disease. ALS's occurrence in the general population is rare and there is neither a current cure nor effective therapy to extend life substantively.

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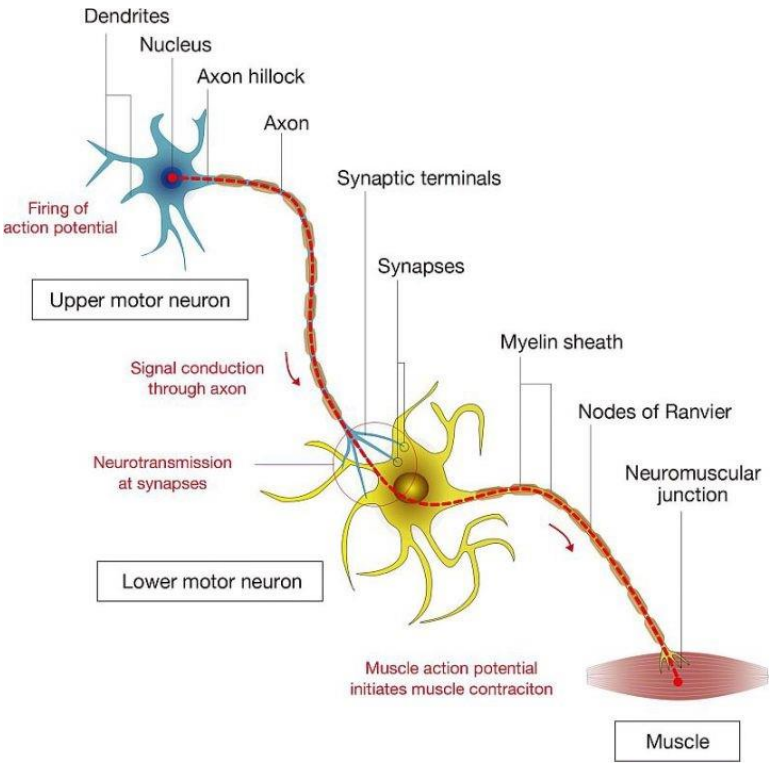
Although the etiology (causes) of ALS is complex and thought to be multifactorial and are incompletely understood, ALS is associated with both genetic defects (10%-15% of cases, according to the MSD Manual professional version) and environmental causes.

Antibody biomarkers (vs. protein biomarkers) - Although antibody biomarkers are a relatively high-profile area of interest, there are, as far as we are aware, no established antibody biomarkers or strong candidates for ALS.

Current biomarker candidates are largely protein based. Biomarker relationships are complex and as far as we are aware there are currently no established biomarkers that could be used to detect the very early stages of ALS before symptoms manifest. Only one protein biomarker – Neurofilament light – has been used in a regulatory approval at the date of this note, to the best of our knowledge.

The exhibit below shows where ALS damage occurs i.e., in upper and lower motor neurons. Upper motor neurons are cells that have a point of origin in the cerebral cortex and terminate within the spinal cord (or brainstem). Lower motor neurons are connected via synapses to the spinal cord (or brainstem) and terminate in muscles.

Exhibit 7: **Motor Neurons upper (cerebral cortex) lower (muscle)**



Sources: Frontiers in Cellular Neuroscience; techitonics.com

Ordinarily, a sense organ such as the skin sends touch or heat detection along sensory neurons to the spinal cord and then along spinal cord neurons to the thalamus (cortex processing area for sensory information).

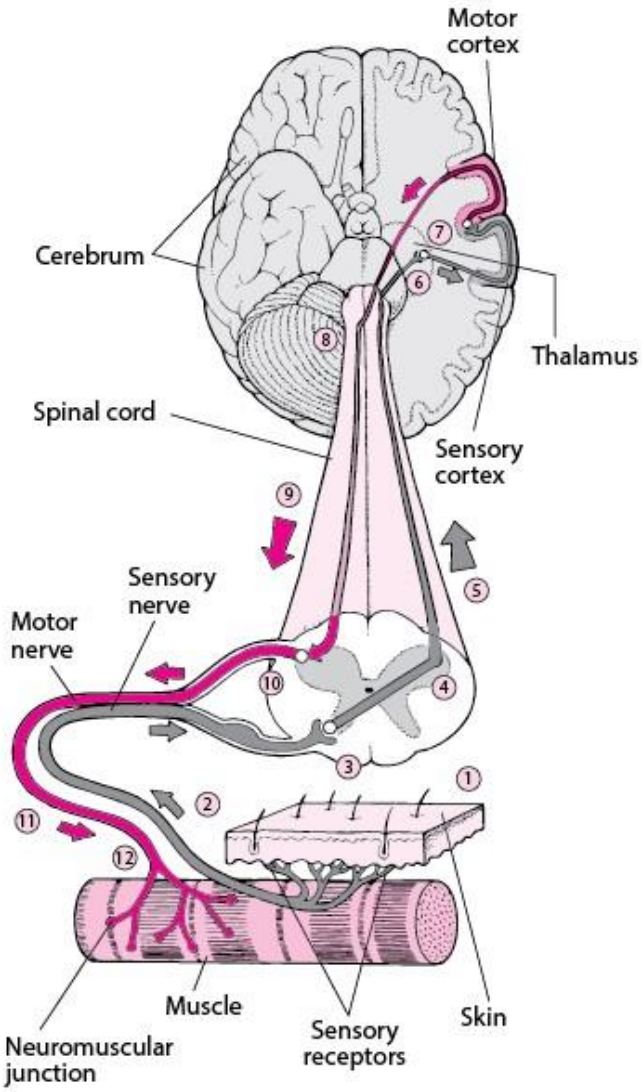
The information crosses from the thalamus via a synapse to the sensory cortex, a different structure in the brain. The sensory cortex interprets sensory information.

The brain then makes a decision about response. If this response decision is to move, this information is passed to the motor cortex (a cerebral cortex structure that plans, controls, and executes voluntary movement) that in turn generates an electrochemical signal that, ordinarily, causes muscles to move.

A return electrochemical response is sent to the relevant muscles via an upper motor neuron from the cortex and along the spinal cord, where it connects via a synapse to a lower motor neuron that innovates the muscle, which then contracts to do work.

Broadly, in other motor neuron diseases either the lower or upper neurons are affected. **In ALS both upper and lower motor neurons deteriorate**.

Exhibit 8: **Nervous relay system affected by ALS**



Sources: https://msdmanuals.com/images/using the brain to move a muscle.

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Amyotrophic lateral sclerosis (ALS) disease progression - most patients with ALS present with random, asymmetric symptoms, consisting of cramps, weakness, and muscle atrophy of the hands (most commonly) or feet. Weakness progresses to the forearms, shoulders, and lower limbs.

Rapid development - fasciculations, spasticity, hyperactive deep tendon reflexes, extensor plantar reflexes, clumsiness, stiffness of movement, weight loss, fatigue, and difficulty controlling facial expression and tongue movements soon follow.

Other symptoms - include hoarseness, dysphagia, and slurred and often nasal speech. Because swallowing is difficult, salivation appears to increase, and patients tend to choke on liquids.

Late stage - in the ALS disorder, a pseudobulbar affect occurs, with inappropriate, involuntary, and uncontrollable excesses of laughter or crying in later stages of the conditions.

Death – respiratory failure is the usual cause of death due to the failure of the respiratory muscles; 50% of patients die within 3 years of ALS onset, 20% of patients survive 5 years, 10% of sufferers live 10 years. Survival for > 30 years is unlikely.

(Unaffected - Sensory systems, consciousness, cognition, voluntary eye movements, sexual function, and urinary and anal sphincters are, typically, unaffected).

Incomplete knowledge - understanding of the biochemical pathways degraded by ALS remains incomplete. The exhibit below helps elucidate the multifactorial nature of ALS and hints at its etiological complexity. In spite of these challenges, BCLI has made extraordinary progress in identifying 45 potential biomarkers.

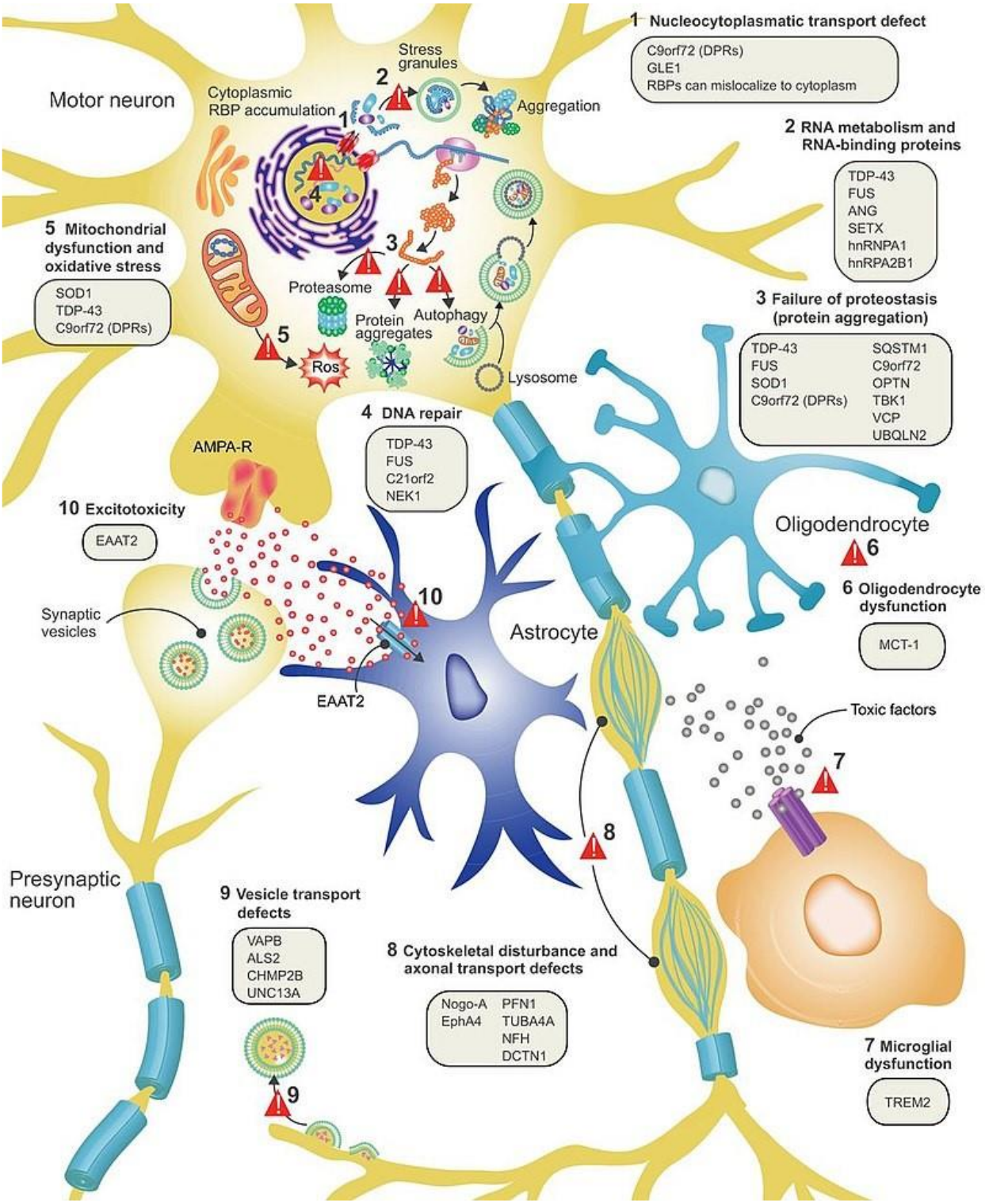
Exhibit 9: **UMN and LMN biochemical pathway degradation in ALS**

UM and LM neuron location	Pathway	Impairment/activation of	Outcome
Cell body, axons	Protein Misfolding and Aggregation	SOD1, TDP-43, FUS proteins	disrupted cellular function
Cell body, axons, synaptic terminals	Mitochondrial Dysfunction	energy production	neuronal degeneration
Synaptic termains and dendrites	Excitotoxicity	glutamate receptors	neuronal degeneration
Axons	Axonal Transport Defects	nutrient delivery	neuronal dysfunction
CNS (inc. spinal cord and brain	Neuroinflammation	activation of microglia, astrocytes, pro-inflamatory cytokines	Chronic neuroinflamation and damage

Sources: ACF Equity Research Graphics; MDPI; BMC; Springer Nature.

Biochemical Pathways to ALS

Exhibit 10: 10 proposed disease mechanisms for ALS



Sources: https://en.wikipedia.org/wiki/ALS#.

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Biochemical paths in the Upper Motor Neurons (UMNs) and Lower Motor Neurons (LMNs) that are thought to be degraded by ALS:

Protein Misfolding and Aggregation:

Location: Cell body and axons of motor neurons.
Pathway: Protein misfolding and aggregation, involving proteins including superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43), and fused in sarcoma (FUS). Misfolded proteins can form aggregates disrupting cell function leading to neuronal death.

Mitochondrial Dysfunction:

Location: Cell body, axons, and synaptic terminals.
Pathway: Mitochondrial dysfunction, impaired energy production, oxidative stress, defects in mitochondrial dynamics, and quality control mechanisms. Dysfunction in mitochondria can compromise the energy supply to motor neurons leading to neuronal degeneration.

Excitotoxicity:

Location: Synaptic terminals and dendrites of motor neurons.
Pathway: Excitotoxicity when over activation of glutamate receptors leads to calcium influx and neuronal damage. Dysregulation of glutamate homeostasis and excitotoxicity have been implicated in ALS, contributing to motor neuron degeneration.

Axonal Transport Defects:

Location: Axons of motor neurons.
Pathway: Axonal transport is essential to nutrient delivery to vesicles, organelles and distal parts of the neuron. Defects in axonal transport, including abnormalities in microtubule dynamics and motor protein function, can impair the delivery of essential cargoes to axonal terminals, contributing to neuronal dysfunction and degeneration.

Neuroinflammation:

Location: Central nervous system (CNS), including the spinal cord and brain.
Pathway: Neuroinflammation, characterized by activation of microglia and astrocytes, release of pro-inflammatory cytokines and infiltration of immune cells, is a prominent feature of ALS pathology. Chronic neuroinflammation can exacerbate neuronal damage contributing to disease progression.

Part of the challenge of identifying the etiology, biomarkers (protein, antibody, and other) and treatments for ALS is related to the presence of numerous possible variants. Questions arise as to whether ALS comes with many sub-types or whether similar symptoms are produced by significantly different etiologies.

Throughout this note to help reader recall we use three interchangeable terms for BCLI's ALS therapy/platform – these are NurOwn®, NurOwn and MSC-NTF. Increasingly in publicly available sources the noun of choice is NurOwn, reflecting BCLI's closeness to commercialization of its ALS therapy.

Is ALS one condition with many sub-types that are patient specific or is it a family of diseases that present with conditions and outcomes currently referred to as ALS? This conundrum suggests to us that drug specific approaches to treatment come with particularly high medical and investment risk.

In contrast, the nature of stem cells, as for example in BCLI's NurOwn (debamestrocel, MSC-NTF) therapeutic approach, may have the best and safest chance of capturing a family of different diseases with ALS symptoms, given that the damage caused by all sub-types of ALS appears to be both to the U and L Motor Neuron cells. Treatment with NurOwn (debamestrocel, MSC-NTF) suggested its potential ability to reduce inflammation, neuronal protection, nerve cell damage and disease progression. NurOwn (debamestrocel, MSC-NTF) multimodal effects on biomarker pathways in amyotrophic lateral sclerosis are linked to clinical outcomes, Muscle & Nerve, 09 Apr 24).

Exhibit 11: **Selection of ALS variants and sub-types**

Selected ALS variants and sub-types	Apperance in ALS population	Genetic / Environmental
Sporadic ALS	90-95%	No clear genetic pattern
Familiar ALS (FALS)	5-10%	Genetic mutations associated
ALS-FTD	rare	Uncertain
Progressive Muscular Atrophy (PMA)	rare	Unknown
Primary Lateral Scleroris (PLS)	rare	Unknown
Respiratory-Onset ALS	rare	Unknown
Guamanian ALS	region of Guam	Uncertain genetic/ environmental
Juvenile ALS	rare	Unknown
ALS-PDC (Parkinsonism Dementia Complex)	rare	Unknown
ALS Cognitive (C) Impairment	rare	Unknown
ALS Behavioural (B) Impairment	rare	Unknown
ALS Combined C & B impairment	rare	Unknown
Comorbid ALS & AD (Alzheimer's Disease)	rare	Possible combination genetic/environmental

Sources: ACF Equity Resaerch Estimates.

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ALS Therapy Landscape

We estimate that there are currently 4 unique ALS therapies with FDA approval for marketing. One of these, riluzole is now a generic with various reformulations. With the possible exception of tofersen all current FDA licensed ALS therapies could be characterized better as alleviating symptoms and improving quality of life, rather than making a meaningful extension to life expectancy. None of the current therapies represent a cure for ALS.

Exhibit 12: **Current ALS FDA approved treatments**

FDA Approved ALS/MND Therapies	Description	Marketed by	Brand name	FDA licence year	US$ launch price per annum	Qualifying ALS patients estimated
tofersen	Developed to treat ALS associated with the superoxide dismutase 1 (SOD1) gene mutuation	Biogen	Qalsody	2023	172,120	2%
edavarone	The first new treatment specifically for ALS in 22 years. Oral formulation approved 2022	Mitsubishi Pharma	Radicava™	2017	145,000	5%
riluzole (generic)	Inhibits glutamate release - prolongs life by appox three months. Riluzole is the generic name of Rilutek.	Sanofi et al	Rilutek	1995	8,000	NA
riluzole oral film	Riluzole re-formulation for ALS sufferers with severe swallowing difficulties. The oral film is placed on top of the person's tongue and dissolves, where swallow pills or liquids would be difficult	Sanofi	Exservan	2019		NA
riluzole thickened	Riluzole re-formulation designed to avoid potential cahllenges involved in the crushing of tablets	Sanofi	Tiglutik	2018		NA

Sources: ACF Equity Research Estimates.

We estimate that globally there are currently at least 27 ALS potential therapies under development, of which 16 are funded by listed companies ranging from large cap to nano cap. We estimate that 2 of these are stem cell therapies (one of which is BCLI's). As far as we are aware US listed BCLI's NurOwn (debamestrocel, MSC-NTF) is the only US, Canadian, UK, European, South African or Australian ALS stem cell therapy (private or public) under development. We also estimate that since 2020, one therapy with FDA approval has been voluntarily withdrawn (Amylx's Relyvrio) and 8 investigations have been stopped because of lack of clinical effect, a stop rate of 25% (9/36).

Exhibit 13: **Current ALS treatments and therapies under investigation**

Sponsor / Funding	Tkr	Therapeutic investigations ALS	Pathway/Approach	Phase
Brainstorm Therapeutics	BCLI	NurOwn (NCT04681118)	Stem cells	Phase IIIb
Corestemchemom	166480.KQ	Lenzumestrocel (NCT04745299)	Stem cells	Phase III
Gold Coast Hospital & Health Service	Private	CBD oil (NCT03690791)	Excitotoxicity	Phase III
Peking University Third Hospital	Private	Huolingshengji granules (NCT04950933)	Oxidative stress	Phase III
Macquarie University, Australia	Private	Triumeq (NCT05193994)	Neuroinflammation	Phase III
AB Science SA	AB.PA	Masitinib (NCT03127267)	Neuroinflammation	Phase III
Eisai Co., Ltd	4523.T	Methylcobalamin (NCT03548311)	Reduces denervation and muscle weakness	Phase III
Eisai Co., Ltd	4523.T	Insulin-like growth factor (NCT00035815)	Blockage of cell death pathways	Phase III
Ionis Pharmaceuticals, Inc.	IONS	Jacifusen/ION363 (NCT04768972)	Gene specific–ASO, FUS-mutations	Phase III
Prilenia Therapeutics	Private	Pridopidine (NCT04615923)	Oxidative stress	Phase II/III
LifeArc	Private	Deferiprone (NCT03293069)	Oxidative stress	Phase II/III
MedicNova, Inc	MNOV	MN-166/Ibudilast (NCT04057898)	Neuroinflammation	Phase II/III
Biohaven Pharmaceutical	BHVN	Verdiperstat (NCT04436510)	Neuroinflammation	Phase II/III
Seelos Therapeutics	SEEL	Trehalose (NCT05136885)	Enhances autophagy, decreases SOD1 aggregates	Phase II/III
Clene Inc.	CLNN	CNM-Au8 (NCT04615923)	Energy Metabolism	Phase II/III
University Medical Centre Goetingen	Private	Fasudil (NCT03792490)	rho Kinase inhibitor - Post-translational modifications	Phase IIa
Alector, Inc.	ALEC	AL001 (NCT05053035)	Monoclonal AB, C9orf72	Phase II
AL-S Pharma	Private	AP-101 (NCT05039099)	Monoclonal AB, SOD1	Phase II
Annexon, Inc.	ANNX	ANX-005 (NCT04569435)	Monoclonal AB	Phase II
Anelixis Therapeutics	Private	AT-1501 (NCT04322149)	Monoclonal AB	Phase II
Genentech	Private	Tocilizumab (NCT02469896)	Monoclonal AB	Phase II
Wave Life Sciences	WVE	WVE-004 (NCT04931862)	Gene specific–ASO, mutant C9orf72	Phase I/II
Uniqure N.V.	QURE	APB-102	SOD1 microRNA	Phase I/II
Biogen Inc.	BIIB	BIIB105 (NCT04494256)	Gene specific–ASO, ATXN2	Phase I
Uniqure N.V.	QURE	AMT-161	C9orf72 microRNA	Substance in developmen
Uniqure N.V.	QURE	AAV-miQURE	Mutant C9orf72 microRNA	Substance in developmen
InSightec	Private	Blood-Brain Barrier Opening Using MR-Guided Focused Ultrasound (NCT03321487)	Blood-Brain Barrier Opening	NA

Sources: ACF Equity Research Graphics; https://www.ncbi.nlm.nih.gov.

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BCLI's Stem Cell Therapy Approach

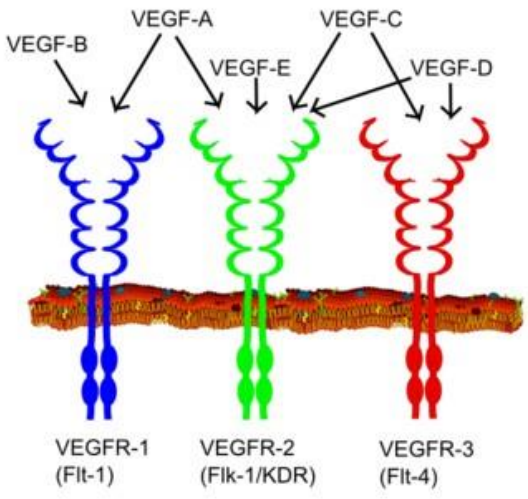
Throughout this note to help reader recall we use three interchangeable terms for BCLI's ALS therapy/platform – these are NurOwn®, debamestrocel and MSC-NTF. Increasingly in publicly available sources the noun of choice is NurOwn, reflecting BCLI's closeness to commercialization of its ALS therapy.

Brainstorm Therapeutics (Nasdaq : BCLI) has secured FDA commitment to a Phase IIIb trial for the use of **autologous mesenchymal stem cells (MSCs)** for the treatment of the fatal neurodegenerative disease **ALS (MND/Lou Gehrig's)**. BCLI's proprietary technology platform NurOwn® is deployed to produce NurOwn (debamestrocel), a mesenchymal stem cell engineered in-vitro that emits enhanced neurotrophic factors (MSC-NTF). Neurotrophic factors (NTFs) are peptides (usually) that promote the growth, immune protection, and the differentiation of mature neurons – their trophic effects on neurons are mediated via receptor tyrosine kinases (RTKs). BCLI has received FDA approval for NurOwn use in a Phase IIIb clinical trial for early-stage ALS patients to determine NurOwn's ability to improve the survival of neurons in ALS patients and so deliver a therapy for early-stage sufferers. Debamestrocel is injected intrathecally (into the spinal cord).

BCLI's research approach is to measure NurOwn's ability to increase or reduce the cerebral spinal fluid (CSF) concentrations of a range of biomarkers associated with ALS and to show a relationship between biomarker concentration changes with changes in disease progression. BCLI's panel of biomarkers are associated with neuroinflammation (MCP-1, LAP, SDF-1a) neurodegeneration (**NfL**, **pNfH**, DR6) and neuroprotection (**VEGF-A**, G-CSF, Galectin-1). Other more exploratory BCLI markers include Follistatin, has-miR-132-3p and has-miR-124-3p.

Exhibit 14: **Receptor tyrosine kinase (RTKs)**

Receptor tyrosine kinases (RTKs) are high binding affinity cell surface receptors associated with a range of polypeptide growth factors and cytokines (as well as hormones). RTKs are most commonly activated by dimerization (a process in which a signal molecule causes two receptor molecules to move toward one another and then associate).



Sources: https://en.wikipedia.org/wiki/Receptor_tyrosine_kinase#/media/File:VEGF_receptors.png.

Stem cells and MSCs – an introduction - Stem cells are undifferentiated progenitor cells – broadly, stem cells can change to become any of the body's tissues or cell types. As a result of this fundamental property, stem cells are of great interest to the

healthcare industry because of their potential use for the regeneration of damaged tissues and cell types. Mesenchymal stem cells (MSCs) are a type of stem cell. (It should be noted that not all stem cells are MSCs.)

MSCs were first described ~30 years ago and by 2019 there were over 950 FDA registered clinical trials involving MSC medical applications. Entirely separately, many unregulated and medical tourism clinics have sprung up offering untested, unproven, and largely unmonitored 'stem cell' regenerative therapies. These **stem cell private clinic and medical tourism product offerings are in no way comparable to FDA/EMA registered and monitored research and related phase trial tested therapies, such as those in development by BCLI and other companies.** Clinical MSC trials have accumulated longitudinal data over the last 25 years that suggests an excellent safety record (npj Nature Regenerative Medicine, 2019).

MSCs were initially considered as a source cell for tissue replacement therapies. However, tissue replacement is a complex process. Over the past ~15 years MSC derived therapies have focused on MSCs' immune modulation and anti-inflammation characteristics through production of cytokines and factors and the associated paracrine activity (localized, short duration intercellular signaling) leading to innate tissue repair in vivo (in patients).

Initially therapy strategies envisioned the use of autologous (derived from the individual to be treated) MSCs. However, MSCs do not immediately trigger a T cell immune response. This reduced or non-immunogenic characteristic is further emphasized in MSC exosomes, which are associated with the MSC paracrine signaling function. BCLI is also examining the therapeutic development of exosomes.

(MSC immune system tolerance has led to a redirection of a proportion of research dollars into allogeneic MSC strategies designed to deliver multiple therapies).

MSCs produce over 10 factors known to interact with immune cells leading to a reduction in inflammation. For example, when MSCs interact with dendritic cells (see exhibit below, pathways 2, 3 and 4) proinflammatory mature DC1, TNF-α and IL-12 are reduced. MSCs modulate macrophage production (see exhibit below pathway 7) to decrease the proinflammatory M1 phenotype and to increase the anti-inflammatory M2 phenotype. MSCs are also understood to reduce B cell antibody production (see exhibit below pathway 8).

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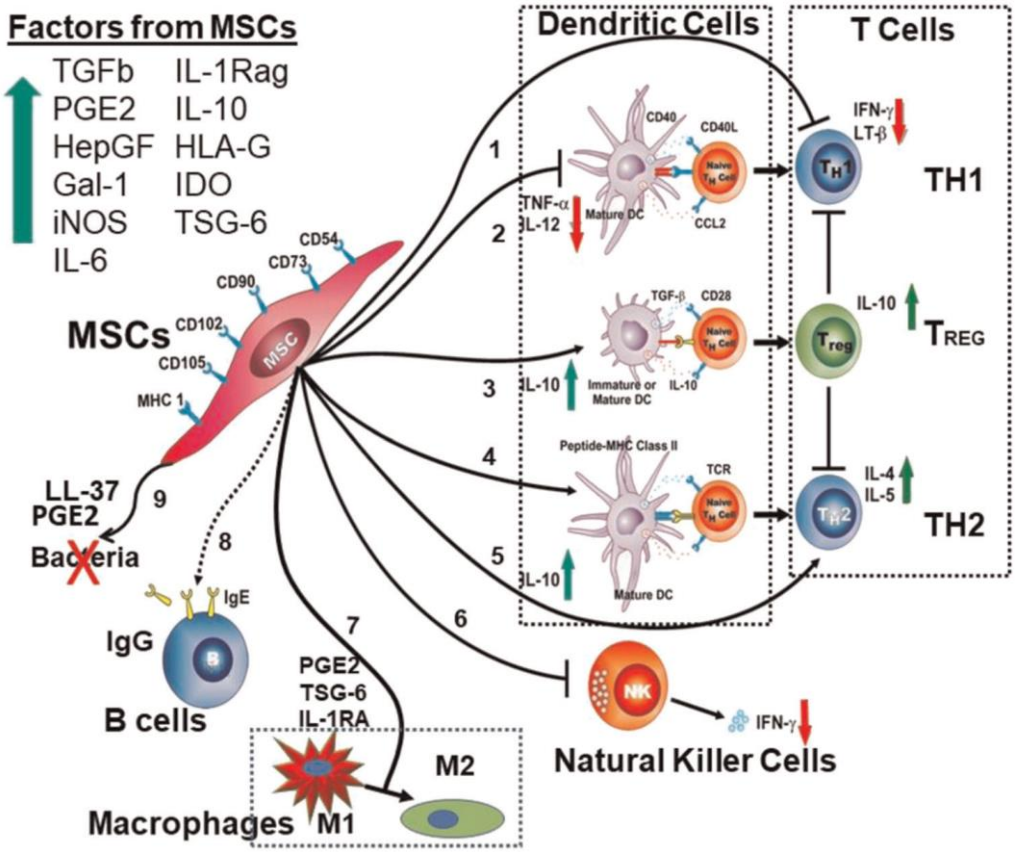
Exhibit 15: **Neurotrophic factors secreted by MSCs**

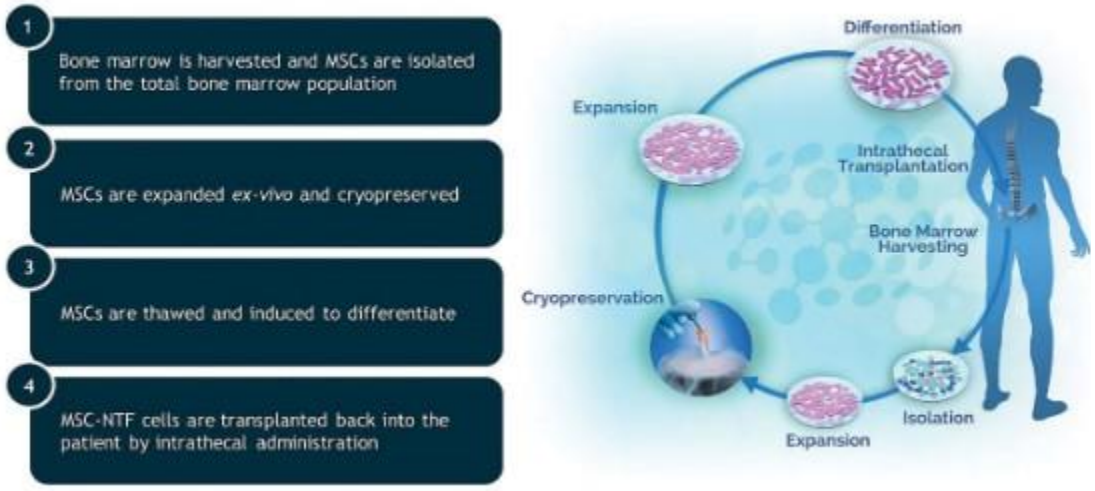
Trophic capabilities in MSC-NTF cells refer to their ability to secrete neurotrophic factors (NTFs) for neuronal growth and survival (repairing and regenerating). MSC-NTF cells combine the immunomodulatory benefits of mesenchymal stem cells (MSCs) with enhanced neurotrophic factor secretion. Trophic activities can be enhanced via implant material modifications.



Sources: nature.com after Blood/Agrawaal; Pittenger et al.

NurOwn® (debamestrocel) derived from adult bone marrow, are MSC-NTF cells with inherent immunomodulatory functions and trophic (neurotrophic factors help repair and regenerate neurons) capabilities. MSC-NTF cells can be engineered to enhance their immunomodulatory characteristics.

Exhibit 16: **MSC-NTF propagation generalized schema**



Sources: https://www.diwou.com/2020/01/17/neurodegenerative-treatments-build-to-a-tipping-point/.

The paracrine effect in MSC-NTFs (a form of stem cell) is where specialized 'donor cells' (BCLI's MSC-NTF cells, it is hoped) stimulate the patient's cells to repair diseased tissue without directly contributing to the new tissue.

Effector molecules selectively bind to proteins, regulating activity. They act as ligands - either increasing or decreasing enzyme activity, gene expression, or mediating cell signaling.

BCLI's autologous (derived from tissues for the individual subject to the treatment) MSC-NTF cells after bone marrow extraction are propagated and induced under proprietary ex vivo conditions to secrete high levels of neurotrophic factors. BCLI's ALS/MND therapy hopes to achieve neuroprotection and immune modulation by leveraging the paracrine signaling (signals or 'factors' that induce changes in nearby cells over a short time duration) that MSC-NTFs can deliver to targeted tissues and indirectly via the induction of effector molecules (regulate biochemical activity) in the target cellular microenvironment.

BCLI identified a panel of 45 cerebral spinal fluid (CSF) biomarkers (a record number of biomarkers for ALS). **Neurofilament light chain (NfL) biomarker** - Current research papers and the FDA accelerated approval of tofersen (licensed to and co-developed by Biogen) for the treatment of ALS, suggest CFS biomarker NfL is of particular interest. In BCT-002, 20 weeks after treatment there was an average 11% concentration reduction from the NfL baseline concentration in patients treated with debamestrocel ($p < 0.05$ compared to patients on a placebo).

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Exhibit 17: **Non-exhaustive list biomarkers assoc. w/ ALS pathways.**

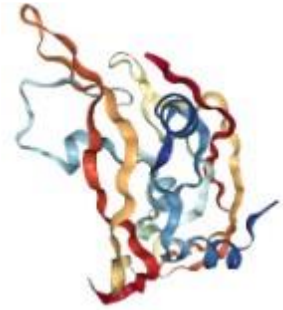
BCLI ALS biomarkers	Description & action
NfL - Neurofilament light chain	Biomarker polypeptide protein for neuronal damage in the CSF. Member of the type IV intermediate filaments found in the cytoplasm of neurons. They are protein polymers measuring 10 nm in diameter and many micrometers in length. They contribute to forming the neruonal cytoskeleton. Recognised biomarker for ALS/MND, MS, Alzheimer's and Huntingdons. EnCor Biotechnology and the University of Florida showed that the NfL antibodies used in the commonest NfL assays are specific for cleaved forms of NfL generated by proteolysis induced by cell death.
VEGF-A – Vascular endothelial growth factor	Dimeric glycoprotein playing signficant role in neurons in respect of vascular supply. Stimulates formation of blood vessels. Coded for by gene VEGFA - abolishing VEGFA expression from neural progenitors results in brain vascularisation defects and neuronal apoptosis.
MCP-1 – Mononcyte chemotactic factor-1	Chemokine (a small signalling protein from the CC Chemokine family), important role in inflammation - attracts or enhances the expression of other inflammatory factors/cells. Infiltrates inflammatory cells, e.g. monocytes/macrophages.
Galectin-1	Beta-galactoside-binding protein - possible immunosuppression and inflammatory process mediation via T and T helper cells and differentiation of dendtric cells (highly conserved across species).
TGF-β1 – Latency-associated peptide of transforming growth factor beta1.	Cytokine protein - controls proliferation, differentiation, apoptosis, important immune system role in T cells, B cells and Myeloid cells. Most leucocytes secrete TGF-β1. Down regulates activity of immune cells by reducing expression of cytokine receptors e.g. IL-2 receptor (interlukin-2).

Sources: ACF Equity Research; multiple public sources.

Experimental approach – BCLI's NurOwn® (debamestrocel, MSC-NTF) is injected into the CSF intrathecally (directly via the spinal canal) as the most efficacious way to reach the central nervous system (CNS). BCLI monitored the reduction or increase of the biomarkers and compared these changes to changes in ALS disease progression in the trial patient cohort as measured using the ALSFRS-R assessment system. The hypothesis is that changes in biomarker concentrations as a result of NurOwn (debamestrocel, MSC-NTF) treatment (via a multi-modal simultaneous positive effect on inflammation, neurodegeneration, and neuroprotection) drives either reversals or reductions in the rate of ALS disease progression in the patient cohort as assessed using the ALSFRS-R test.

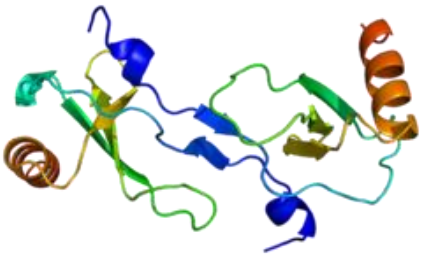
Exhibit 18: **Biomarker structures for VEGF-A, MCP-1, Gal-1, TGF-β1**

VEGF-A protein structure



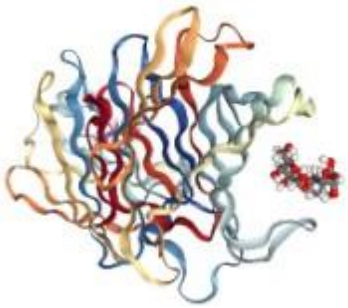
Sources: Sino Biological.com.

MCP-1 (CCL2) protein structure



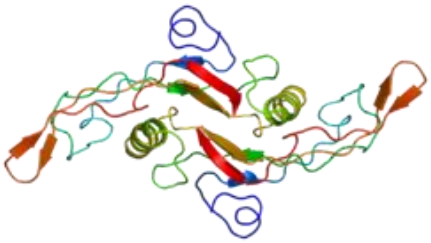
Sources PMC (nih.gov).

Galectin-1 protein structure



Sources: Sino Biological.com.

TGF-β1 protein structure



Sources: Wikipedia wikidata commons.

Exhibit 19: **NfL Neurofilament light chains**

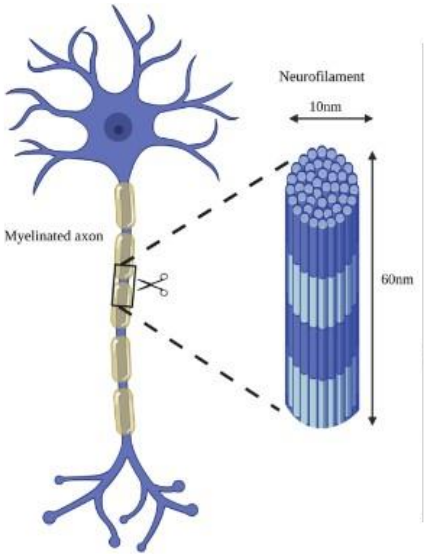
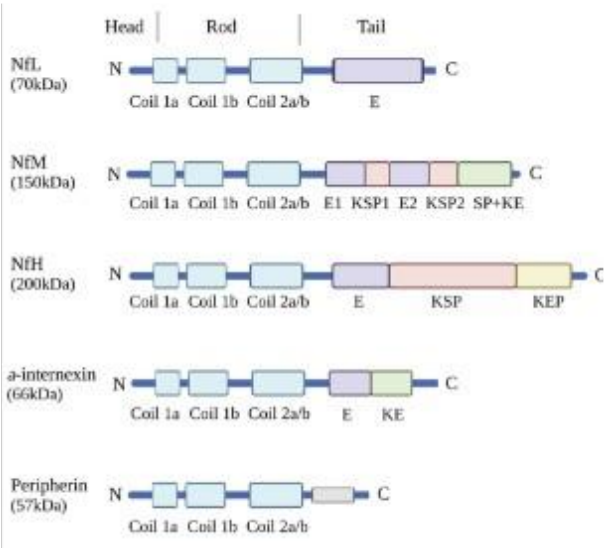


Exhibit 20: **NfL Neurofilament subunits**



Sources: J cachexia sarcopenia muscle; Volume: 13, Issue: 3, Pages: 1811-1820, First published: 13 April 2022, DOI: (10.1002/jcsm.12979; https://onlinelibrary.wiley.com/doi/10.1002/jcsm.12979.

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PIII Biomarker Data – Supports Clinical Effect

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Experimental PIII design summary and biomarker aims – The primary goal was to identify and select ALS biomarkers that are most important in terms of their relationship with NurOwn and with its impact on clinical outcomes via the ALS Function Rating Scale-Revised (ALSFRS-R).

The PIII design leveraged current biomarker scientific literature linked to ALS disease progression, with the aim of moving closer to identification of reliable ALS cerebral spinal fluid (CSF) biomarkers. In addition, the PIII was designed to evaluate the effect of debamestrocel on CSF biomarker concentrations and the concentration relationship with ALS disease progression via ALSFRS-R.

The PIII trial used a double blind (neither patient nor physician is given confirmation as to whether placebo or therapy is used), 1:1 debamestrocel : placebo split over 28 weeks. Debamasctrocel was injected three [3] times over 28 weeks and seven [7] CSF samples were collected from the trial patients.

- 196 original participants, 189 received at least one treatment with NurOwn or the placebo. 144 patients completed the study;
- 45 associated biomarker concentrations were analyzed - **33** were CSF ALS pathway specific;
- 7 CSF samples were collected;
- Clinical responses were assessed using ALSFRS-R.

Stepwise regression models and causal inference were used to identify the presence of clinical outcomes in debamestrocel treated patients.

Biomarker classifications - BCLI grouped its chosen CSF biomarkers linked to key cellular changes within ALS disease patients into four [4] categories. These categories are: **Neuroinflammatory** (pro inflammatory expected to decrease in response to treatment, anti-inflammatory expected to increase), **Neurodegenerative** (expected to decrease in response to treatment), **Neuroprotective** (expected to increase in response to treatment), Other (belong to other pathways, may increase/decrease in response to treatment).

Some samples could not be collected because of Covid-19 restrictions.

Results summary PIII trial – treatment with BCLI's NurOwn reduced NfL concentrations, which is predictive of positive clinical outcomes.

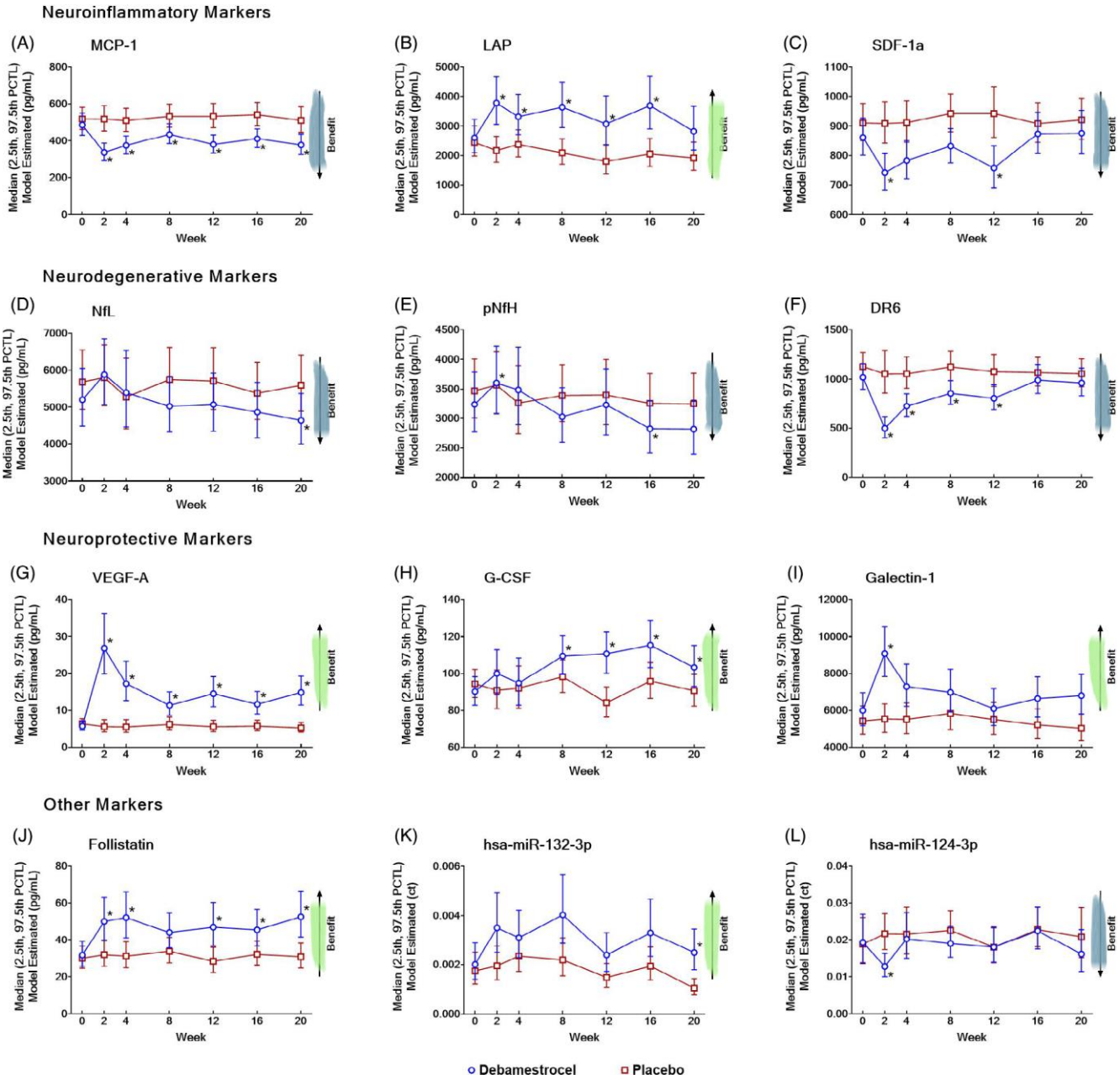
Biomarker results summary for PIII trial lend support to NurOwn PIII positive clinical outcomes – Treatment with NurOwn (debamestrocel, MSC-NTF) led to significant CSF biomarker concentration changes spanning pathways involved in ALS pathology. Certain biomarkers, specifically NfL, LAP and Galectin-1 were found to be predictive of positive clinical outcomes in NurOwn-treated participants.

- 64% of ALS pathway biomarkers changed CSF concentration as a result of treatment with NurOwn (debamestrocel, MSC-NTF), compared with a placebo, indicating a possible reduction in disease activity and nerve cell damage.

Though not a pre-requisite, all trial participants were permitted to enter the BCLI PII trial on a stable dose of riluzole (considered the standard of care at that time). As a result riluzole use was relatively balanced across the two treatment groups. Riluzole was not observed to influence treatment outcomes.

In the exhibit below data indicates that the effect of BCLI's NurOwn therapy was fast in terms of reducing concentrations of proinflammatory and increasing concentrations of anti-inflammatory biomarkers. The greatest magnitude of change relative to the control group who were administered the placebo occurred at the first post treatment CSF sample measurement, i.e., two weeks after first treatment.

Exhibit 21: **CSF biomarker concentrations & treatment effect (time)**



Sources: ACF Equity Research Graphics, Muscle&Nerve (Wiley) accepted 19 March 2024 – Debamestrocel multimodal effects on biomarker pathways in amyotrophic lateral sclerosis are linked to clinical outcomes.

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The results were presented in a peer reviewed academic research paper published in Muscle&Nerve (Wiley) accepted 19 March 2024 – Debamestrocel multimodal effects on biomarker pathways in amyotrophic lateral sclerosis are linked to clinical outcomes.

In the exhibit above, by way of example, the MCP-1 biomarker in patients treated with BCLI's NurOwn (augmented MSC-NTF cell therapy) reduced 155x or -31% vs. -0.2% for MCP-1 placebo patients, according to week 2 CSF data. By week 20 MCP-1 remained significantly lower in NurOwn treated patients at -22.6% vs. -1.6% for the placebo group. In terms of changes from the baseline biomarkers NfL and pNfH showed the greatest decrease by week 20 vs. the placebo group, (NfL -11% vs. -1.6%; pNfH -13.1% vs. -6.4%). The implication is that some biomarkers respond positively and substantively to treatment with BCLI's NurOwn.

It should be noted that patients with baseline ALSFRS-R scores <=25 (higher is better) had biomarker results that suggest NurOwn (debamestrocel, MSC-NTF) is biologically active irrespective of clinical progression, which means it could have potentially had positive clinical effects (obscured by the floor effect) for later stage sufferers.

Exhibit 22: **Debamestrocel treated**

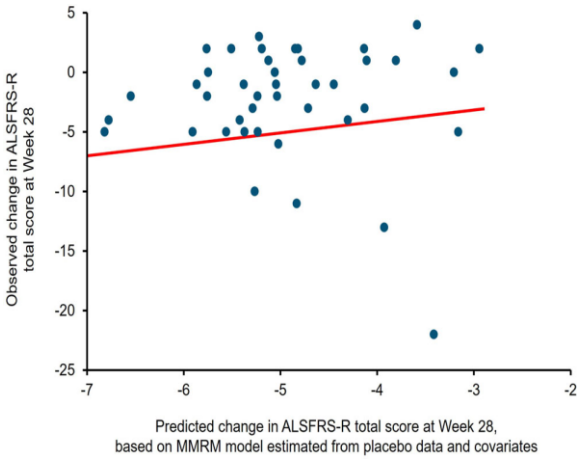
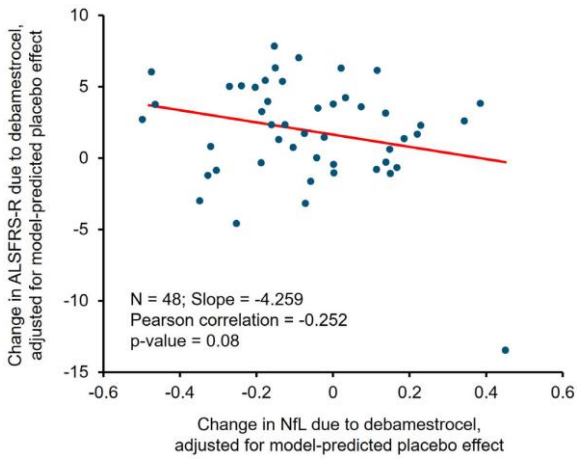


Exhibit 23: **Debamestrocel's NfL impact**



Sources: Muscle and Nerve 2024 - Debamestrocel multimodal effects on biomarker pathways in ALS

Sanofi markets riluzole. There are several brand names including Rilutek and Exservan.

Participants (patients with ALS), some of whom were using riluzole, marketed by Sanofi NasdaqGS : SNY), MCAP ~USD 125bn, who were administered NurOwn had better ALSFRS-R scores at week 28 than patients that were administered a placebo. **Exhibit 22**, above, **shows 86% of patients treated with NurOwn have better ALSFRS-R scores than the expected ALSFRS-R scores for untreated patients (red line, where being above the red line is better)**. Exhibit 23 , which uses NfL biomarker and ALS disease covariates, shows that participants with larger NurOwn-driven reductions in NfL lost less function in the trial, as measured by ALSFRS-R scores (higher scores in the ALSFRS-R test are better i.e., healthier patients). The data indicates that treatment with NurOwn impacts CSF biomarker concentrations for the better – increasing anti-inflammatory and neuroprotective biomarkers and reducing

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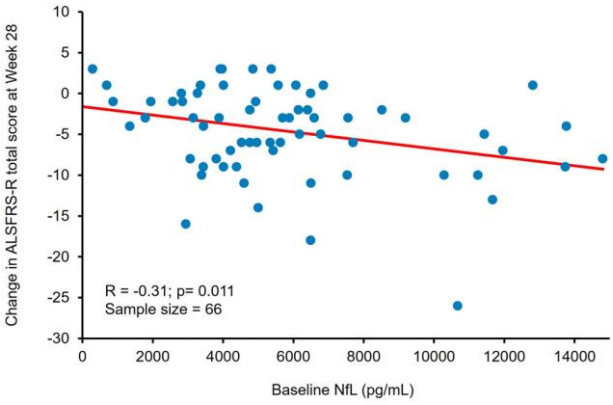
inflammatory or neurodegenerative biomarkers. In turn, this data suggests a possible beneficial clinical (treatment) effect. The NfL biomarker data suggests that NurOwn has a broad impact fast and has delayed positive effects across multiple biochemical pathways. Note that across the relevant biomarkers in the panel, NurOwn had sustained positive impacts on some biomarkers, whereas impacts appeared more transient on other biomarkers.

The effects of BCLI's MSC-NTFs may be attributable to their 'hit and run' mechanism that serves to activate repair mechanisms associated with immune function. The reduction effects on neurodegeneration of BCLI's NurOwn on the NfL biomarker were similar in magnitude (though lower in correlation) to Biogen's (NasdaqGS : BIIB), MCAP ~USD 35bn) co-developed, and FDA accelerated, licensed ALS drug - Tofersen (marketed as Qalsody). In addition, the PIII BCLI funded study 'observed [that] larger reductions in NfL were associated smaller changes in ALSFRS' – which in turn implies the progression of ALS was slowed in BCLI's NurOwn treated patients.

Additional background observations:

Exhibit 24: **Lower NfL equals better functionality as per prior research**

Past research has indicated that lower NfL levels (less neurodegeneration) at baseline are associated with patient higher functionality.



Sources: Muscle and Nerve 2024 - Debamestrocel multimodal effects on biomarker pathways in ALS.

Genetic variant implications for NurOwn efficacity - In the BCLI PIII trial, it should be noted that of the 189 trial participants 124 participants agreed to undergo genetic 'profiling' for ALS gene pathogenic alleles. 62% of these participants (77/124) had a gene UNC13A C risk allele (genotypes AC 47% and CC 15%) the remainder, 33%, had the AA wildtype. UNC13A genotypes AC and CC participants treated with NurOwn in the PIII study were associated with a slower rate of functional decline as assessed by clinicians using the ALSFRS-R tests (which are nevertheless unavoidably subjective). The inference is that NurOwn may be particularly helpful for patients with ALS/MND pathogenic genotypes AC and CC.

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Whilst there is a statistical risk of false positives due to multiple testing runs, NurOwn trial data showed positive impacts on the levels of both inflammatory and degenerative process biomarkers and that this was sustained over the trial period – longer courses of treatment might deliver greater positive effects, which, if demonstrated, would be a positive for BCLI and for ALS patients.

Exhibit 25: **El Escorial Criteria (revised)**

Diagnostic category	Inclusion criteria
Definite ALS	Presence of upper motor neuron and lower motor neuron signs in three anatomical regions
Probable ALS	Presence of upper motor neuron and lower motor neuron signs in at least two regions with upper motor neuron sign rostral to lower motor neuron signs
Probable ALS, laboratory results supported	Presence of upper motor neuron and lower motor neuron signs in one region with evidence by EMG of lower motor neuron involvement in another region
Possible ALS	Presence of upper motor neuron and lower motor neuron signs in one region or upper motor neuron signs in two or three regions, such as monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis

Sources: ACF Equity Research Graphics; Revised El Escorial classification of ALS (). Four anatomical regions, bulbar, cervical, thoracic, and lumbar are included for disease stratification - Amyotrophic Lateral Sclerosis - NCBI Bookshelf (nih.gov).

Glossary

(p< .005)	p-value - A probability value that measures how statistically significant outcome or observation is. P-values are a measure of how likely data would occur if no real (clinical) effect were present, i.e., if the null hypothesis were true. The lower the p-value the less likely the observed data is generated by chance alone. A p-value of p<.005 suggests that the probability of the data occurring by chance is less than 0.5% i.e., strong evidence against the H_0 hypothesis (the H_0 would typically be - our drug or therapy has no clinical effect).
ALS	Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease (NDD) also known as motor neuron disease (MND) and Lou Gehrig's disease.
ALSFRS-R	ALS Functional Rating Scale-Revised (ALSFRS-R) is a subjective (clinician's judgement) test used to define or describe the degree for functional decline in patients with ALS/MDN/Lou Gehrig's.
Biomarker	Biomarkers are measurable indicators of biological condition. They come in several broad types – molecular (e.g., DNA, RNA, proteins), physiologic (e.g., heart rate, glucose levels), histologic (e.g., cell and tissue characteristics observable under a microscope) and radiographic (e.g., anatomical changes detected by MRI or PET scans). Clinical biomarker applications can be divided into predictive (predict clinical outcomes), prognostic (disease progression), diagnostic (narrowing/filtering diagnoses), response (treatment response) and surrogate (indirect indicators e.g., cholesterol levels to assess cardiovascular risk).
CAGR	Compound Annual Growth Rate – Average annual growth rate over a period longer than one year.
Cargo	Cargo refers to molecules and substances transported within the cell often via small, membrane bound, structures called vesicles. They are often considered to be two categories of cargo – soluble proteins and transmembrane proteins. The process of moving cargo in cells is crucial to cell functioning.

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Causal inference	Casual inference in biochemical research is the process of determining if a causal relationship exists between specific variables. There are two flavors – 1. The causal relationship investigating a direct relationship between one variable and another (genotype causes a phenotype). 2. The quantitative causal effect in which the aim is to establish not only if there is a direct relationship between the variables but also the quantity of that effect (1g of drug has Y effect, 2g has 2Y effect).
Cellular microenvironments	The cellular microenvironment is the local environment surrounding a cell. It contains physical and chemical signals that influence cell behavior and it includes the extracellular matrix. It is very dynamic in space and time and is bidirectional in terms of communications pathways and mechanisms.
CSF	Cerebrospinal fluid (CSF) is a clear fluid in all vertebrates found in the brain and spinal cord. CSF is produced by the ependymal cells in the choroid plexus in the brain's ventricles where it circulates. CSF acts as a shock absorber, immunological protection, cerebral autoregulator and a distribution mechanism for nutrients etc.. CSF is obtained or accessed by lumbar puncture.
CSF biomarkers	Biomarkers (see glossary) found in the CSF.
Debamestrocel	Debamestrocel / MSC-NTF also known as NurOwn® (Brainstorm Therapeutics, Nasdaq : BCLI) is made up of autologous mesenchymal stem cells (MSC) that secrete neurotrophic factors. Debamestrocel's upcoming phase IIIb trial is designed to investigate the therapy as a treatment for ALS/MND.
El Escorial criteria	The El Escorial criteria are a set of guidelines for diagnosing ALS, a neurodegenerative disease that affects the motor neurons. The criteria require the presence of signs of upper and lower motor neuron degeneration in different regions of the body, such as the bulbar region and spinal regions. The criteria also categorize ALS patients into four levels of diagnostic certainty, from clinically definite to possible ALS.

Glial cells	Glial cells or neuroglia are a class of non-neuronal cells that supply metabolites and physical support to neurons in the central and peripheral nervous systems. They facilitate inter-neuronal communication and regulate inflammation amongst other functions.
Intrathecal	Intrathecal means directly into the spinal canal. Intrathecally injected compounds reach the central nervous system (CNS) effectively.
miR	MicroRNA (miR) biomarkers. MicroRNA are single stranded non-coding RNA of 21-23 nucleotides that are involved in gene regulation (RNA silencing), differentiation, cellular proliferation, apoptosis. Aberrant miR expression is linked to disease states. (15 biomarkers in BCLI's trial were excluded from multivariate analysis but included in univariate analysis. 13 of these multivariate analyses excluded biomarkers were miR biomarkers. These 13 miR biomarkers were excluded due to administrative censoring).
MSC	Mesenchymal stem cells (MSCs) are cells capable of differentiating into other cells. MSCs are present in bone marrow, umbilical cord, adipose tissue, adult muscle, corneal stroma or dental pulp of deciduous teeth (baby) teeth. In adults MSCs are most commonly obtained from bone marrow.
MSC-NTF	MSC-Neurotrophic Factor (MSC-NTF) are stem cells that are able to secrete neurotrophic factors that stimulate the body's own mechanism to engage in neuronal repair and maintenance.
Multimodal	Multimodal mechanism of action is when a drug or therapy affects biological systems via multiple distinct pathways.

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Neurotrophic Factor (NTF)	Neurotrophic factors (NTFs) are biomolecules, the majority of which are peptides (2-50 aminos acids held together by peptide bonds) or small proteins (not all peptides are proteins due to their simpler structure and smaller size). NTFs support the growth, survival, and differentiation of developing and mature neurons. The mechanism of action is via signaling through tyrosine kinases. NTFs are capable of stimulating the regrowth of damaged neurons in-vitro and in animal models. NTFs come in three families – Neurotrophins, Glial cell-line derived neurotrophic factor family ligands (GFLs) and Neuropoietic cytokines.
NfL	Neurofilament light chain (NfL) is a protein that when elevated in cerebrospinal fluid (CSF) or blood is assessed to be indicative of neuronal damage or degeneration. NfL is used as a biomarker for NDDs such as ALS/MND, Alzheimer's, Parkinson's and MS.
Paracrine signaling	Paracrine signaling refers to a type of intercellular communication characterized by close physical proximity (very localized) and short duration.
Placebo	Placebo – is an inert dosage that closely resembles the active substance or treatment in order that the patient (and usually in research, the physician too) are unable to tell the difference between the placebo and the active substance. Therefore, attention must be paid to the appearance, color and flavor, etc., of the placebo. Patients receiving the placebo in clinical trials are referred to as the control group, whilst the experimental group receives the active substance or therapy. This is the central pillar of in-vivo clinical trials to determine if an active substance or therapy has a clinical effect when compared to non-treatment.

Tofersen

Tofersen, marketed under the brand name Qalsody, developed by Ionis Pharmaceuticals and subsequently licensed to and co-developed by Biogen, is a medication specifically designed for the treatment of amyotrophic lateral sclerosis (ALS). **Mechanism of Action:** Tofersen is an antisense oligonucleotide (ASO). ASOs are small strings of DNA letters that bind to specific RNA molecules. Tofersen targets the RNA produced from mutated SOD1 genes. By doing so, it prevents the production of toxic SOD1 proteins associated with ALS.

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