Update on ALS and Related Neurodegenerative Disorders

Brent T Harris, MD, PhD, FCAP
Associate Prof of Neurology and Pathology
Director of Neuropathology and the Georgetown Brain Bank
Georgetown University Medical Center/MedStar Health
Washington, DC USA
Brent.Harris@Georgetown.edu

AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures (No conflicts for this talk)

FUNDING FOR THE SOME PROJECTS I'LL DISCUSS TODAY:

- NIH, ALSA, AND TARGET ALS

- Neuropathology Consults, LLC
  - For consult work I do for the Dept of Justice/HHS and for the Office of the Chief Medical Examiner of DC

Learning Objectives

At the end of this activity learners should be able to:

- Define the evidence that ALS and some FTLD diseases lie on a disease spectrum
- Describe the histopathological findings that define ALS and FTLD-MND
- Describe the genetic alterations found in familial and sporadic forms of ALS and FTLD-MND

TOPICS

- ALS REVIEW
- COLLABORATIVE SCIENCE TO STUDY PATHOGENESIS/PATHOPHYSIOLOGY OF ALS/FTLD
- BIOBANKING IN THE 21ST CENTURY AND ALS/FTLD BIOBANKING INITIATIVES

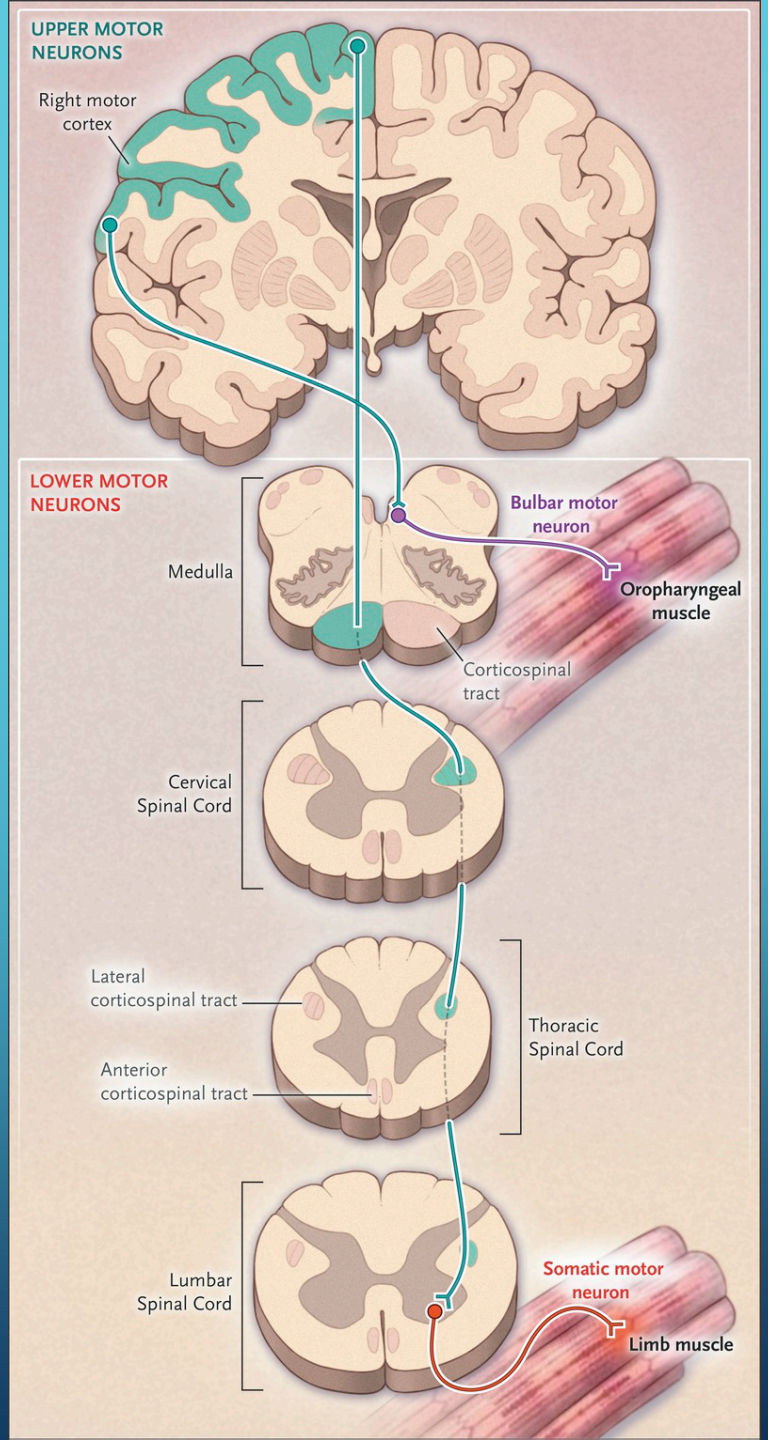
AMYOTROPHIC LATERAL SCLEROSIS FACTS

- ALS is a neurodegenerative disease causing progressive paralysis leading to death within 2-5 years in the majority of patients.
- ALS is highly variable in terms of early symptoms and patterns of progression.
- Most cases of ALS are sporadic with perhaps 20% familial.
- Only two FDA approved medications (Riluzole and Edavarone) exist which may provide a minimal therapeutic benefit of several months extended survival.

Other common names for this disease:

- Motor neuron disease (England and Australia)
- Charcot's disease (French, 1869)
- Lou Gehrig's disease (base ball player, Yankees)

THE MOTOR PATHWAY



Amyotrophic lateral sclerosis: a clinical review

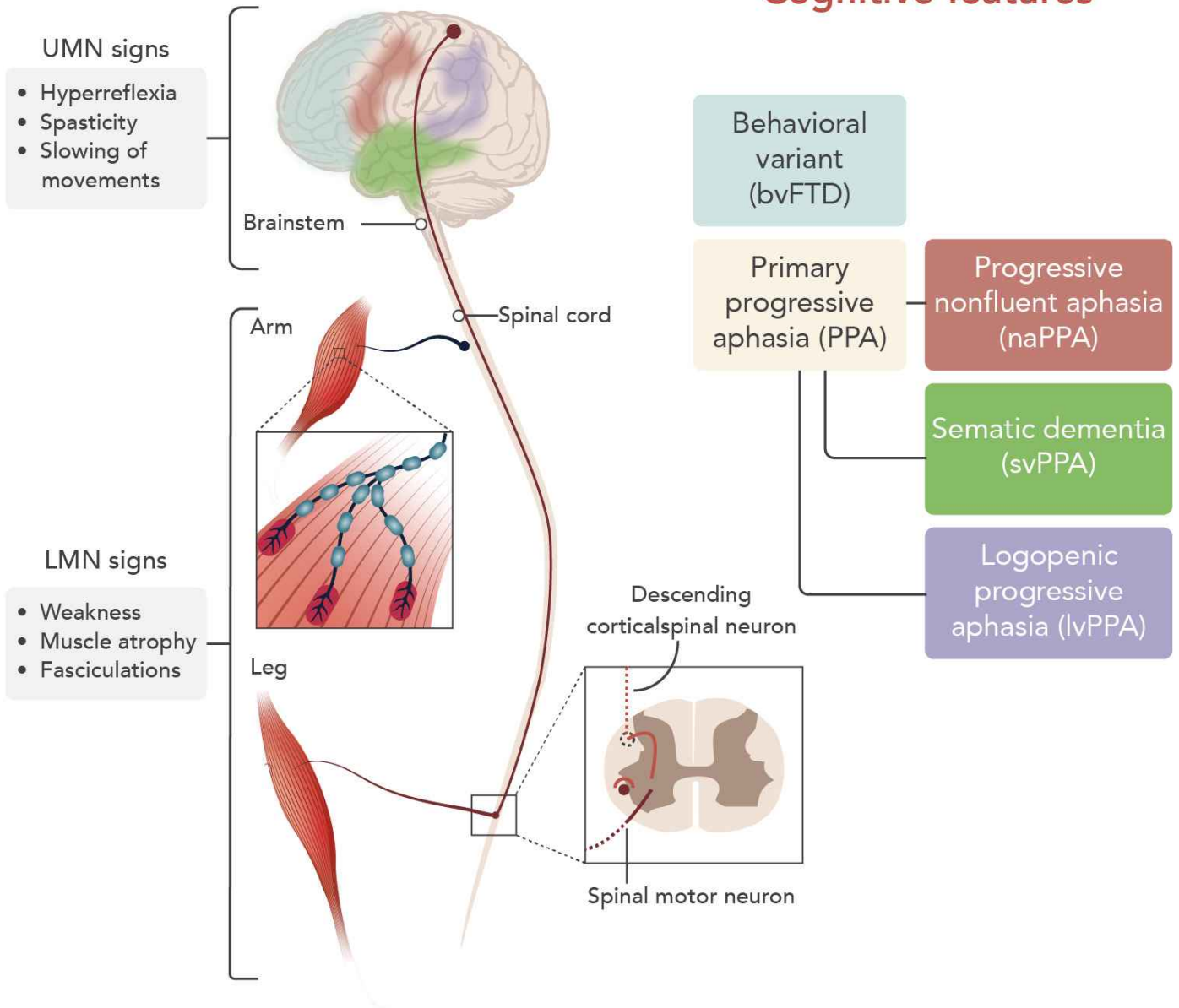
Motor features

Subtypes by regional onset

Classic ALS
- Bulbar ALS
- Spinal ALS

Specific subtypes
- Pseudobulbar palsy
- Progressive bulbar palsy
- Mill's syndrome (hemiplegic)
- Respiratory ALS
- Axial ALS
- Flail arm syndrome
- Flail leg syndrome
- Pseudopolyneuritic ALS

Subtypes by UMN vs LMN involvement
- Primary lateral sclerosis (PLS)
- UMN predominant ALS
- ALS
- LMN predominant ALS
- Progressive muscular atrophy (PMA)

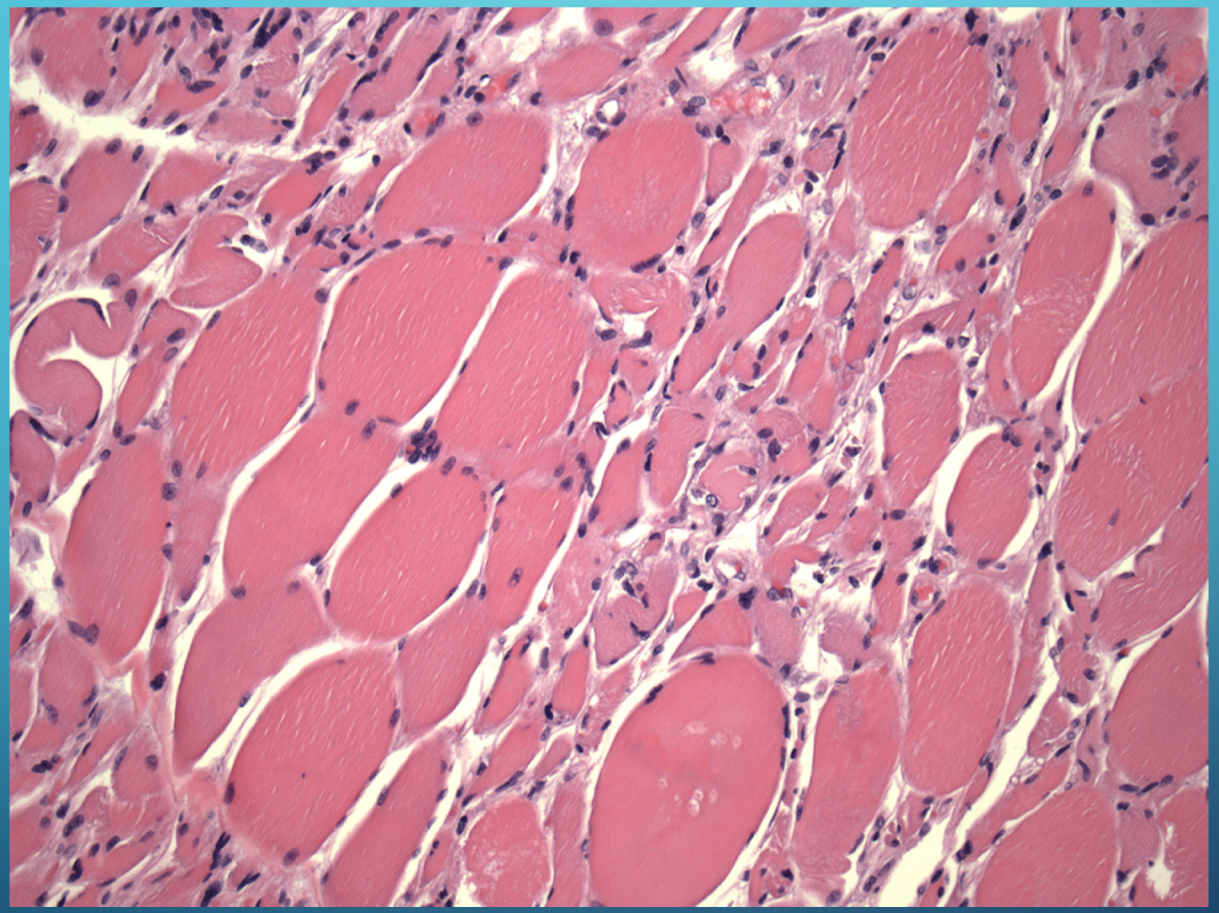


Cognitive features

- Behavioral variant (bvFTD)
- Primary progressive aphasia (PPA)
  - Progressive nonfluent aphasia (naPPA)
  - Sematic dementia (svPPA)
  - Logopenic progressive aphasia (lvPPA)

European Journal of Neurology, Volume: 27, Issue: 10, Pages: 1918-1929, First published: 11 June 2020, DOI: (10.1111/ene.14393)

"AMYOTROPHIC"



Harris B.T. (2014) Amyotrophic Lateral Sclerosis. In: Linda M. McManus, Richard N. Mitchell, editors. *Pathobiology of Human Disease*. San Diego: Elsevier; p. 2036-2044.

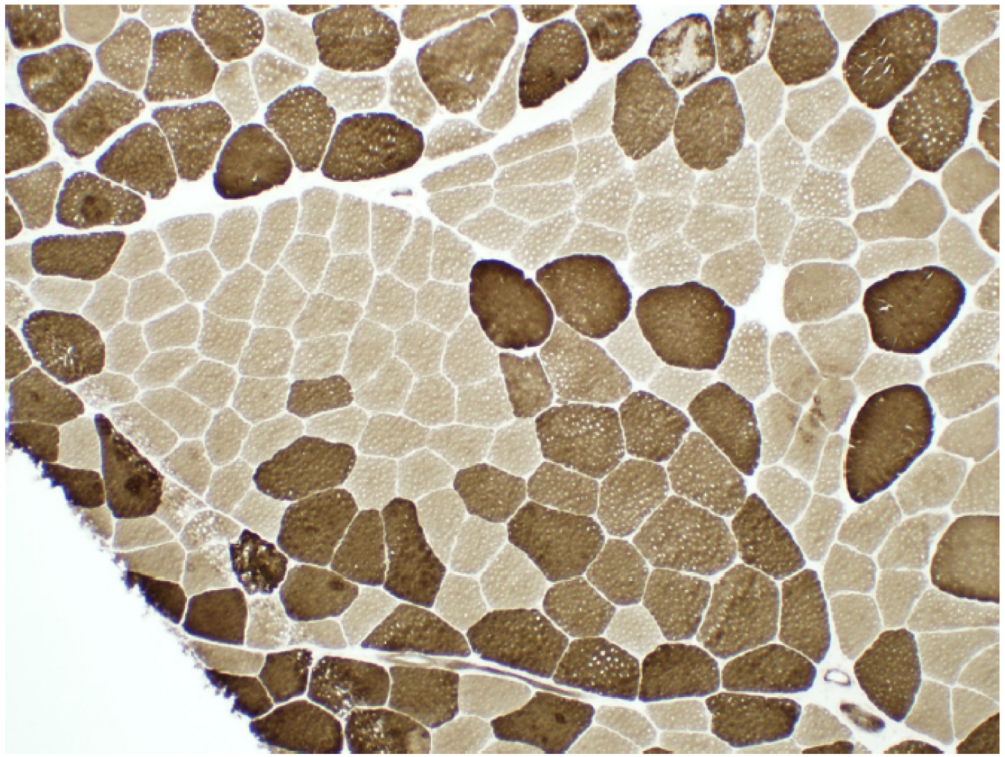


Figure 4 Muscle fiber type grouping in ALS. Skeletal muscle histochemically stained for ATPase activity (ATPase pH 9.4) shows groupings of type I (light fibers) and type II (dark fibers).

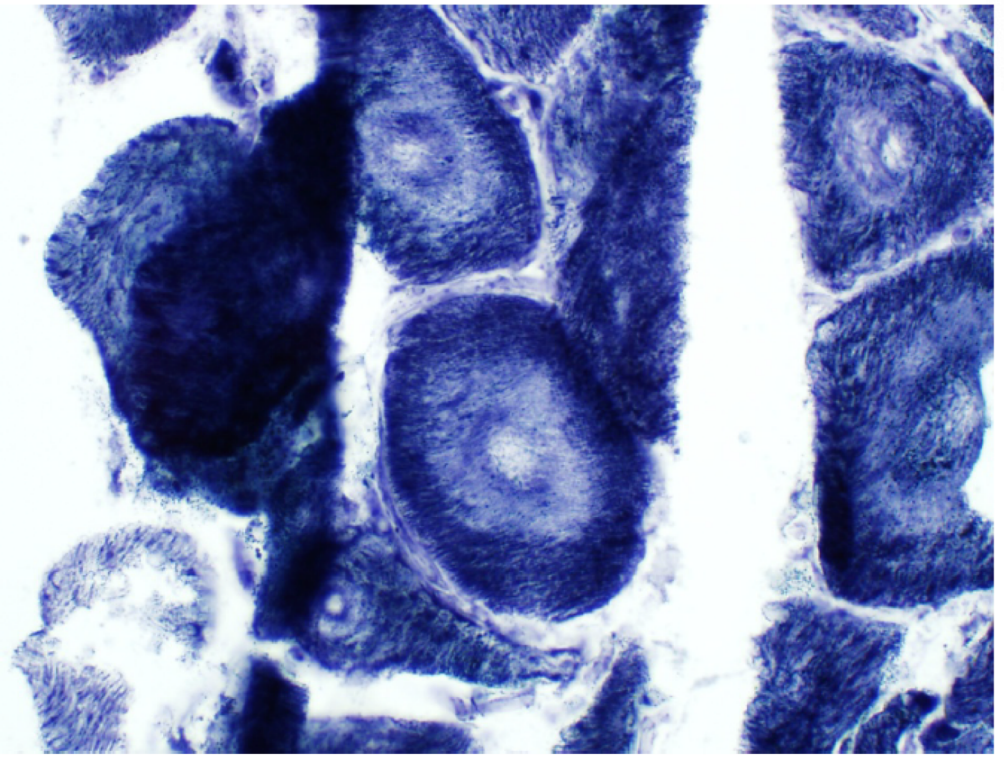
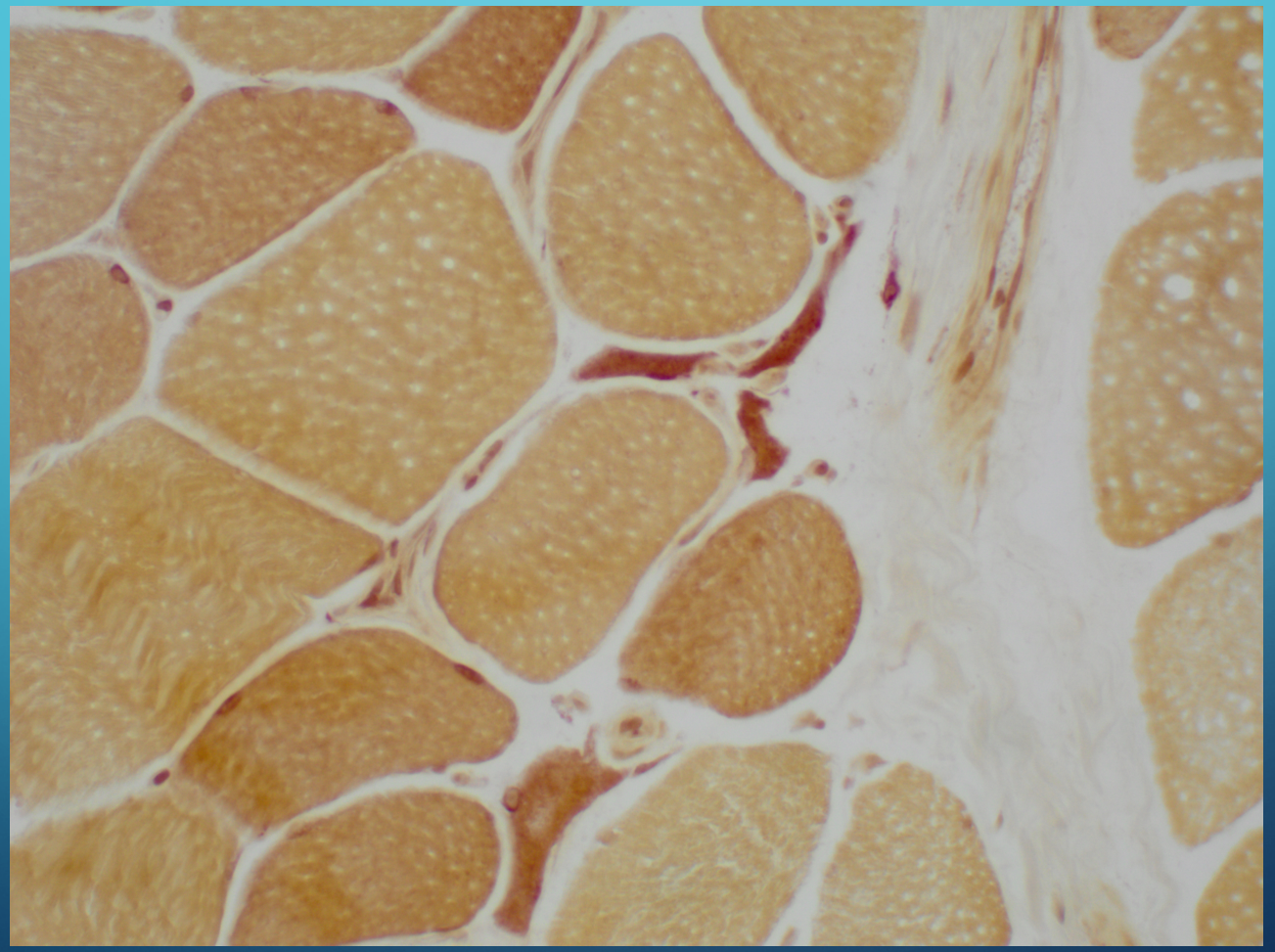
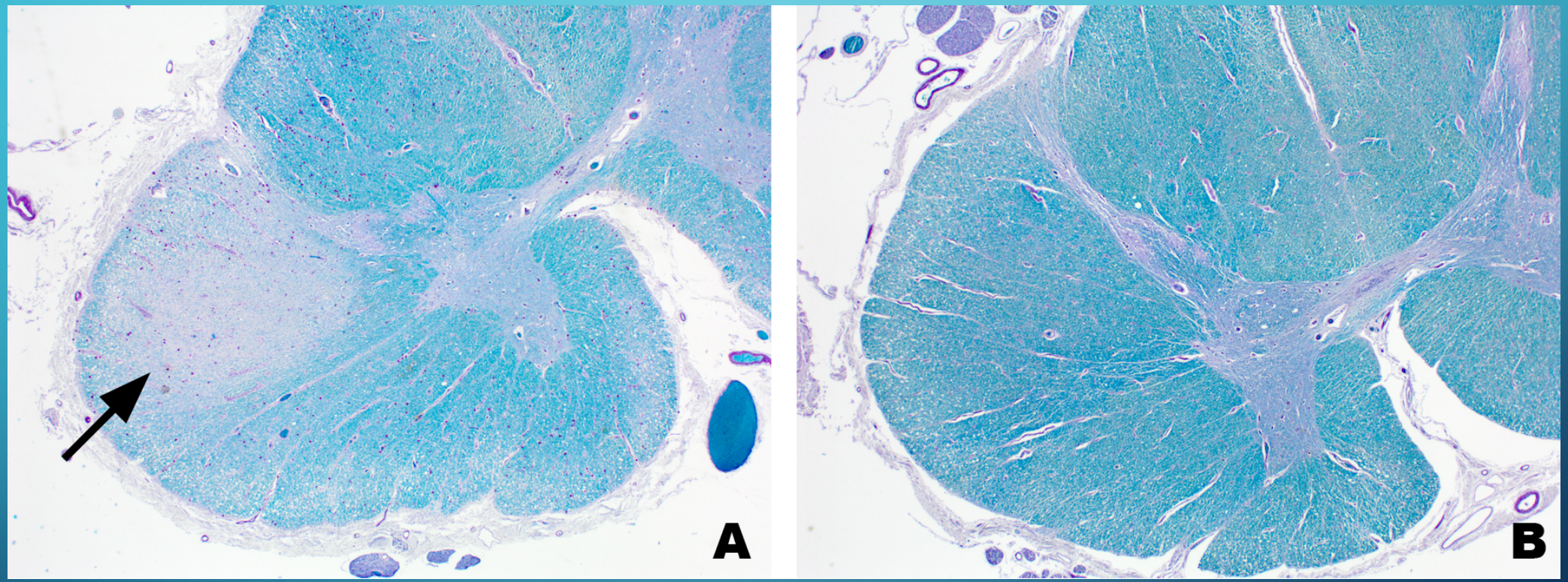


Figure 5 Target muscle fibers in ALS. Skeletal muscle histochemically stained for NADH shows central clearing of mitochondria conveying a 'shooting target' appearance.

ANGULATED, ATROPHIED ESTERASE POSITIVE MYOFIBERS



“LATERAL SCLEROSIS”



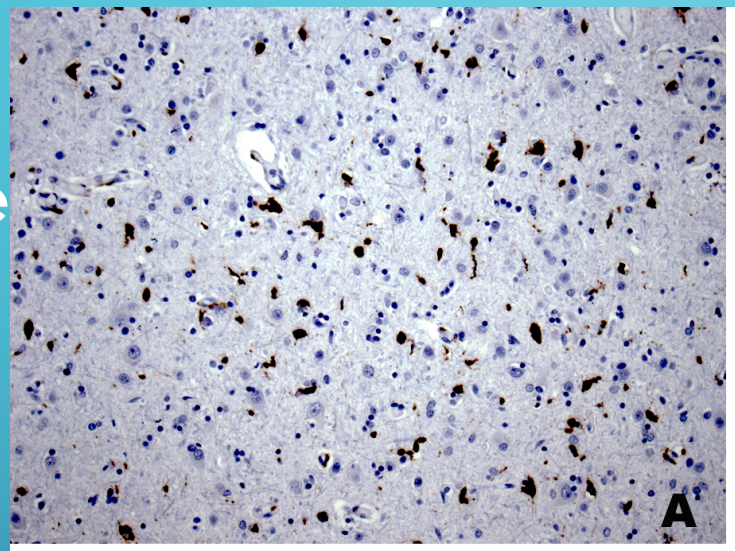
ALS PATIENT FROM TALS PM CORE

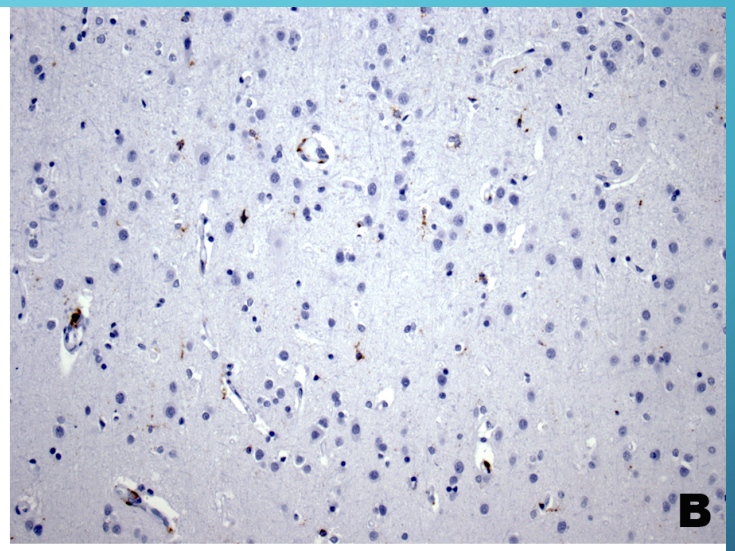
MOTOR CORTEX

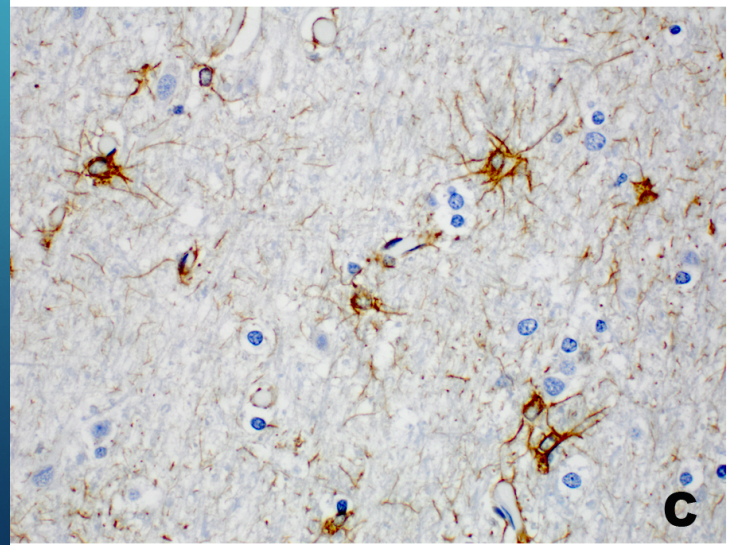
SENSORY CORTEX

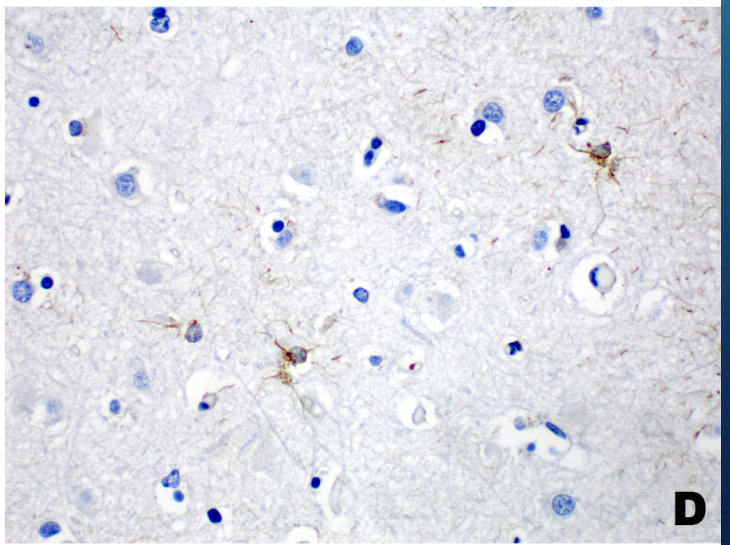
CD68 positive microglia

GFAP positive astrocytes

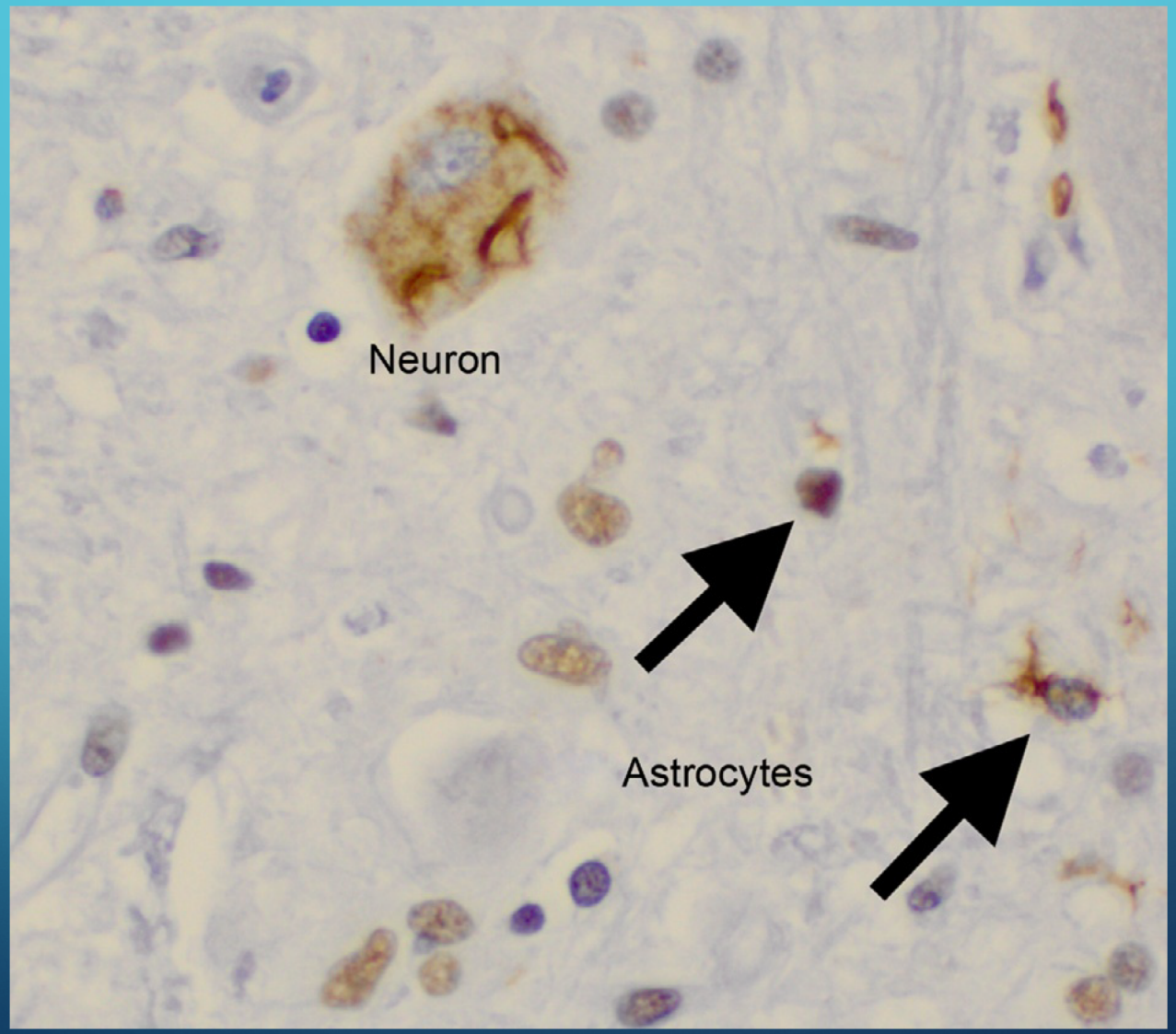




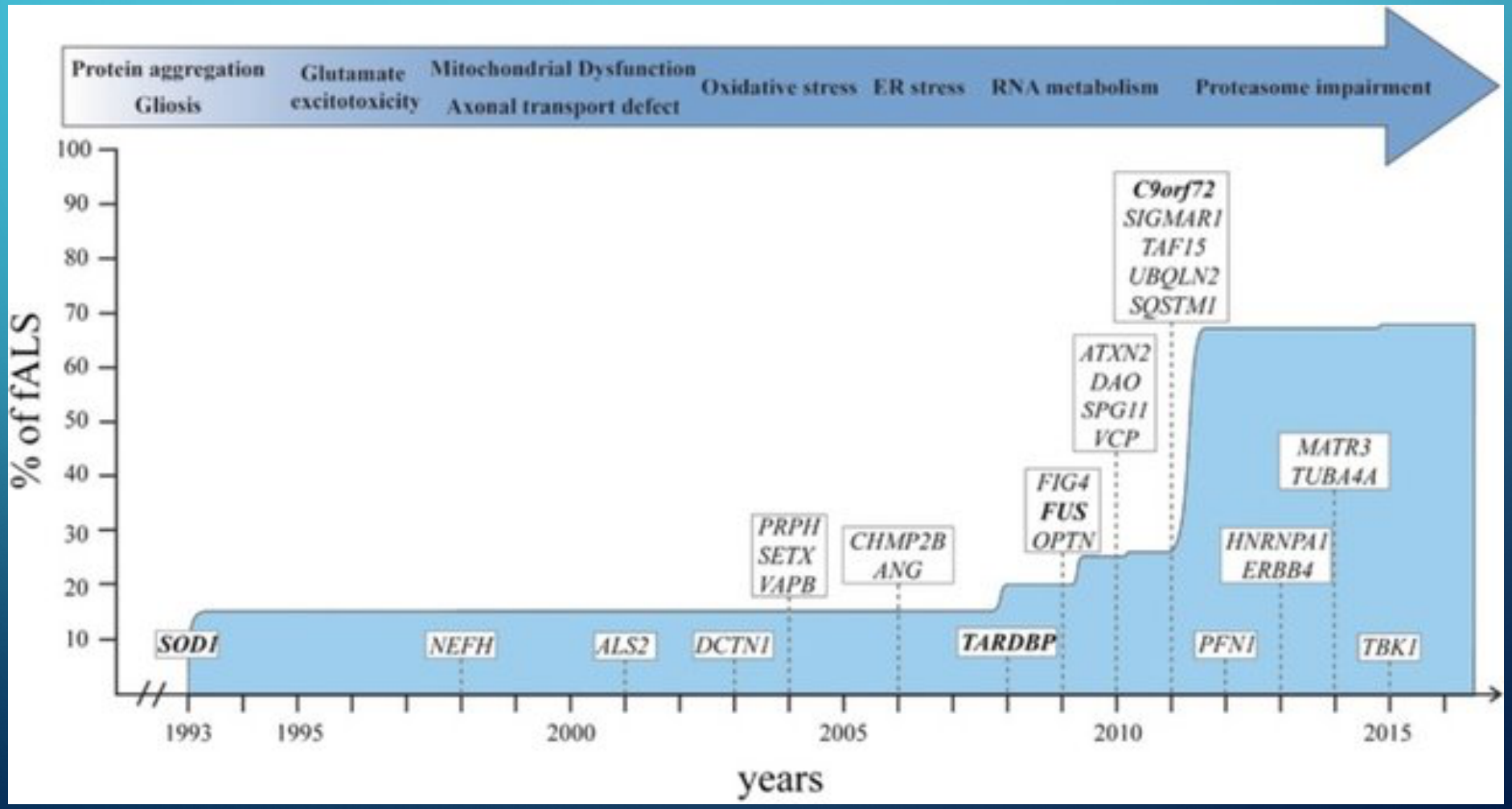




TRANSACTIVE RESPONSE DNA-BINDING PROTEIN 43 (TDP43) AGGREGATES IN NEURONS AND GLIA



GENETICS OF ALS TIMELINE



C9ORF72

A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD.

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita VM, Kaivorinne AL, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wuu J, Chiò A, Restagno G, Borghero G, Sabatelli M, ITALSGEN Consortium., Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ

Neuron. 2011 Oct 20; 72(2):257-68.

Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS.

DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R

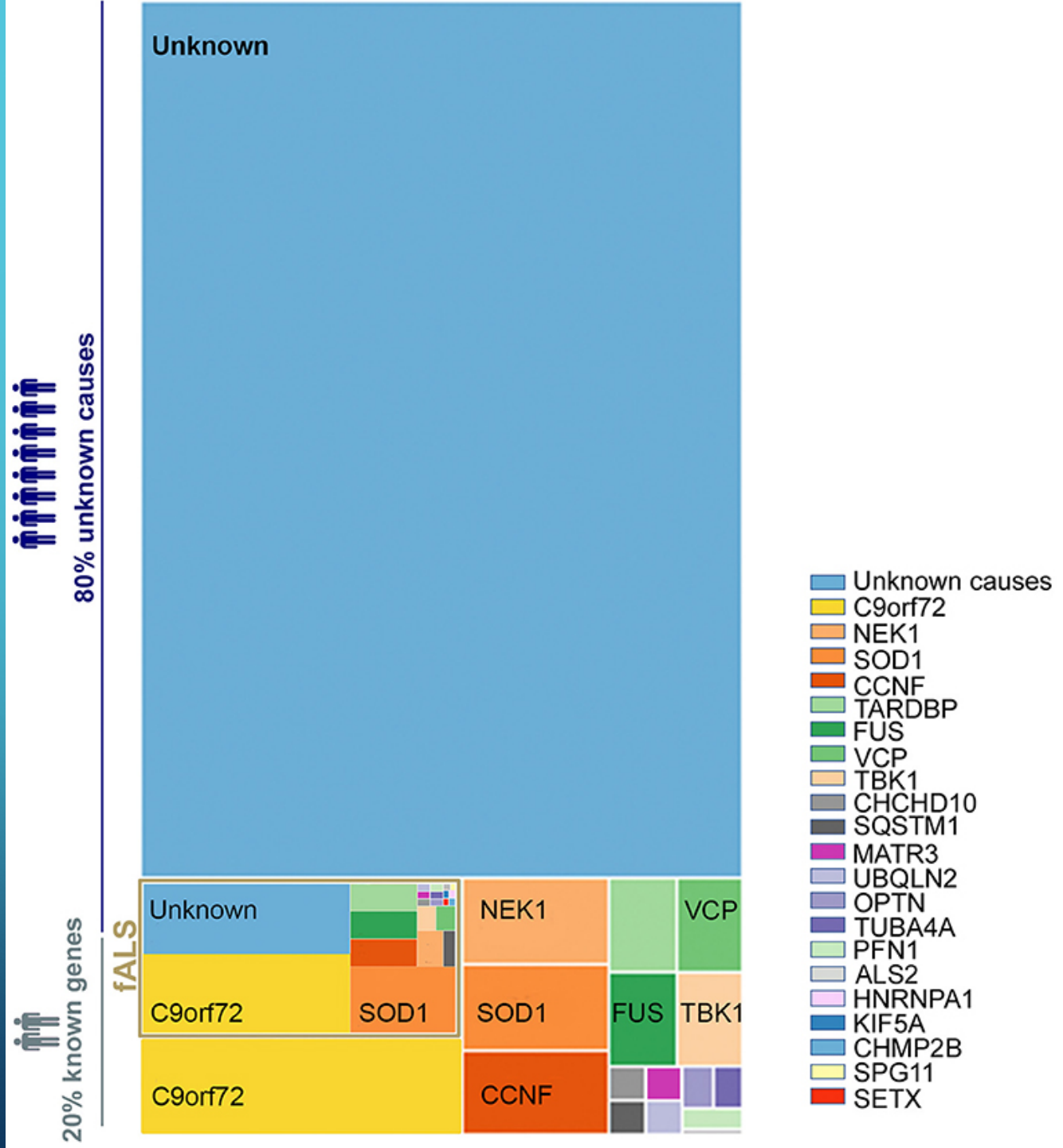
Neuron. 2011 Oct 20; 72(2):245-56.

Table 1 | **Genes known to be associated with ALS**

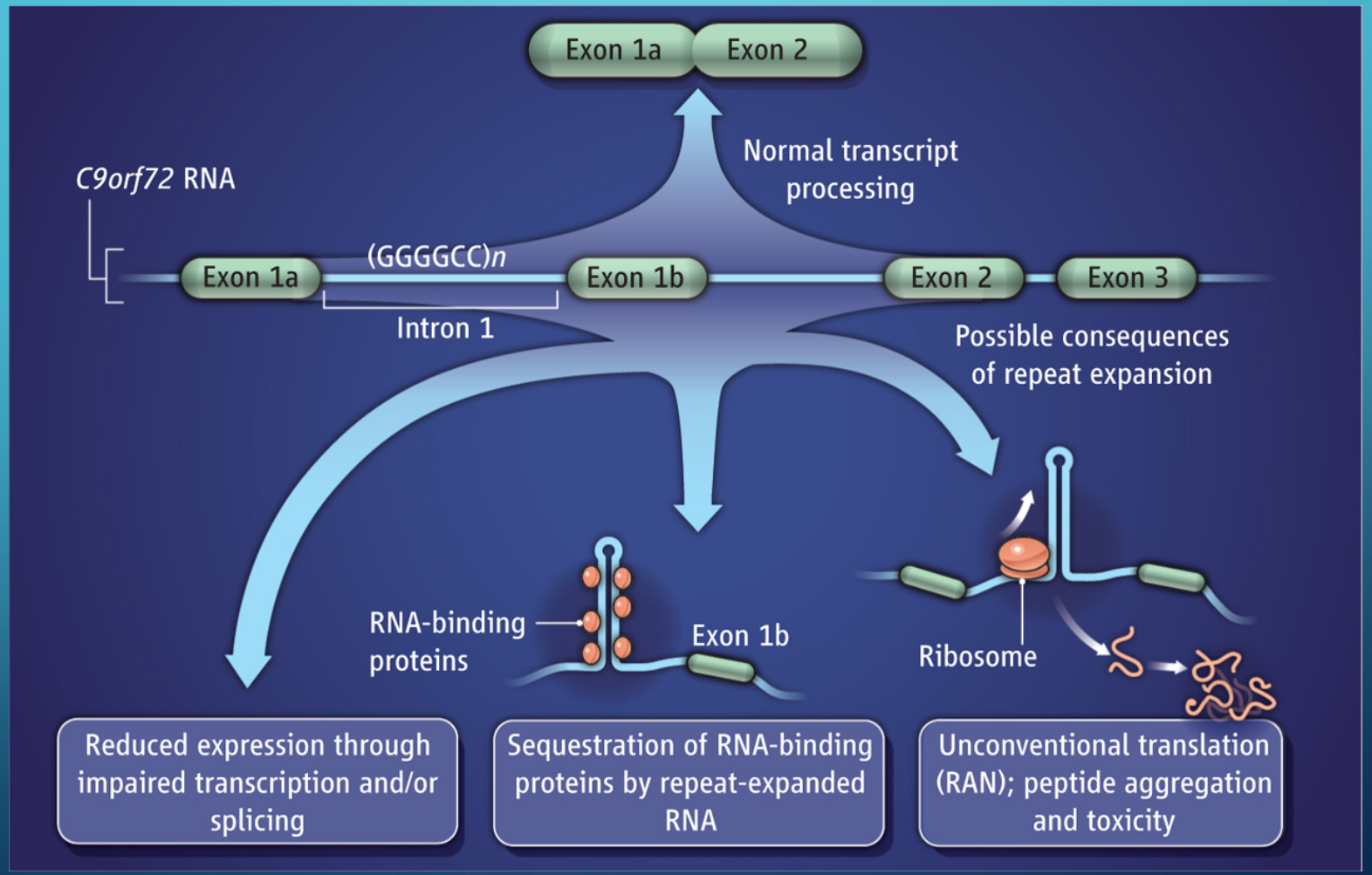
Gene	Protein product	Protein function	Locus	Proportion of cases associated with gene[a]	
				Familial ALS	Sporadic ALS
C9orf72	Chromosome 9 open reading frame 72	Nucleotide factor	9p21–22	20–50%	10%
SOD1	Superoxide dismutase 1	Superoxide dismutase	21q22.1	10–20%	2%
TARDBP	TDP43	RNA-binding protein	q36	5%	<1%
FUS	Fused in sarcoma protein	RNA-binding protein	16p11.2	5%	<1%
MAT3	Matrin 3	RNA-binding protein	5q31.2	<1%	<1%
HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1	RNA-binding protein	12q13.1	<1%	<1%
OPTN	Optineurin	Mediator of apoptosis, inflammation and vasoconstriction, cellular morphogenesis, membrane trafficking, vesicle trafficking, transcription activation	10p15–p14	4%	<1%
UBQLN2	Ubiquilin 2	Ubiquitination and protein degradation	Xp11.23–Xp13.1	<1%	<1%
SQSTM1	Sequestosome 1	Autophagosome cargo protein, targets proteins for autophagy	5q35.3	<1%	<1%
TBK1	Serine/threonine-protein kinase TBK1	Phosphorylation of nuclear factor-κB, regulation of cell proliferation, apoptosis and glucose metabolism, promotion of autophagy via the ubiquitylation pathway	12q14.2	<1%	<1%
VCP	Transitional endoplasmic reticulum ATPase	Ubiquitin segregase	9p13.3	2%	<1%
DCTN1	Dynactin subunit 1	Mediator of organelle transport, spindle formation and axonogenesis	2p13	1%	<1%
ANG	Angiogenin	Ribonuclease	14q11	<1%	<1%
PFN1	Profilin 1	Actin-binding protein	17p13.2	<1%	<1%
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	Maintenance of cristae morphology in mitochondria, oxidative phosphorylation	22q11.23	<1%	<1%
TUBA4A	Tubulin α4A chain	Microtubule formation, maintenance of cytoskeleton and structure of cells	2q36.1	<1%	<1%

ALS, amyotrophic lateral sclerosis; TDP43, TAR DNA-binding protein 43. [a]The proportion of ALS cases associated with each genetic mutation varies depending on the population studied[13,18–22].

Nature Reviews Neurology **17**, 104–118 (2021)


80% unknown causes
20% known genes
fALS
Unknown
Unknown
C9orf72
SOD1
C9orf72
NEK1
SOD1
CCNF
VCP
FUS
TBK1
Unknown causes
C9orf72
NEK1
SOD1
CCNF
TARDBP
FUS
VCP
TBK1
CHCHD10
SQSTM1
MATR3
UBQLN2
OPTN
TUBA4A
PFN1
ALS2
HNRNPA1
KIF5A
CHMP2B
SPG11
SETX

C9ORF72


Exon 1a
Exon 2
Normal transcript processing
C9orf72 RNA
(GGGGCC)n
Exon 1a
Exon 1b
Exon 2
Exon 3
Intron 1
Possible consequences of repeat expansion
RNA-binding proteins
Exon 1b
Ribosome
Reduced expression through impaired transcription and/or splicing
Sequestration of RNA-binding proteins by repeat-expanded RNA
Unconventional translation (RAN); peptide aggregation and toxicity

EXPERIMENTAL MODEL

Modeling ALS/FTD in mice: Updates on the *C9orf72* BAC transgenic mice

Mordes, D.A. et al *Neuron* **108**, 775–783.e4 (2020)
Nguyen, L. et al. *Neuron* **108**, 784–796.e3 (2020)

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a progressive loss of motor neurons, which leads to muscle weakness and eventual paralysis and respiratory failure. Mutations in the *C9orf72* gene have been identified as the major cause of ALS, accounting for 40–50% of familial ALS cases and ~7% of sporadic cases. The mutations, which consist of hexanucleotide repeat expansions (GGGGCC) have also been linked to frontotemporal dementia (FTD).

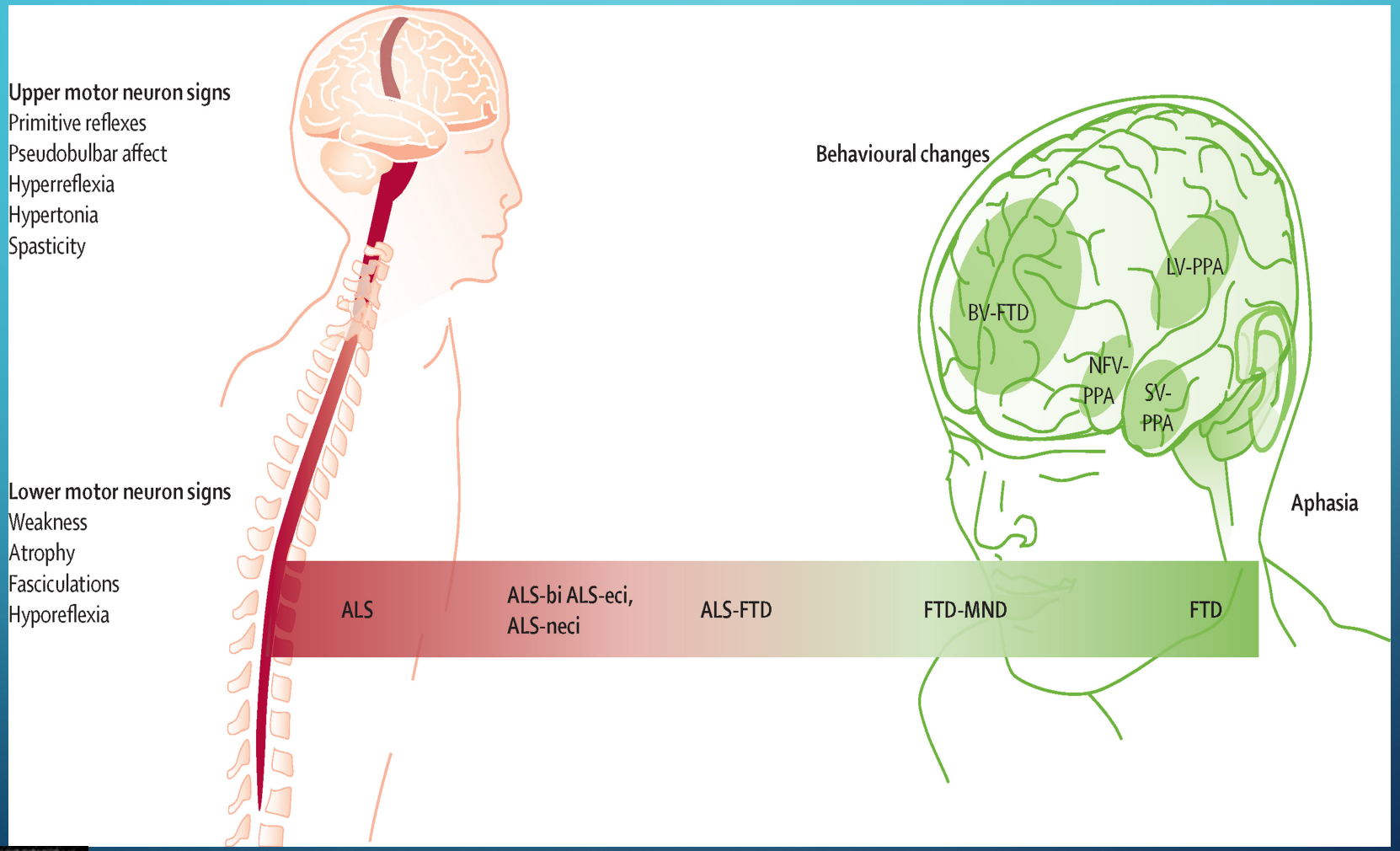
The high prevalence of these mutations in ALS and FTD has led to the development of several mouse models, including several bacterial artificial chromosome (BAC) transgenic mice, harboring GGGGCC

Credit: Marina Spence/ Springer Nature

shown by Liu et al. could be reproduced in four different cohorts of FVB C9-500 BAC transgenic mice, including two new studies performed independently at the University of Bern and the University of Rochester Medical Center. In a previous report, Nguyen et al. had also shown that the phenotype of C9-500 mice including decreased survival, DigiGait abnormalities, open field abnormalities, motor neuron loss, RNA foci and RAN protein accumulation could be improved by targeting GA RAN proteins with a-GA1 antibody, which would further support that the FVB C9-500 phenotype is caused by RAN protein pathology and not a FVB-strain phenotype.

"Although occasional seizures occurred

ALS AND FTLD AS A SPECTRUM OF DISEASES



The Lancet 2017 3902084-2098DOI: (10.1016/S0140-6736(17)31287-4)

	Predominant pathology	Associated genes
Classic ALS	TDP-43	*ALS2, SETX, TARDBP, VAPB,CHMP2b, ANG, UBQLN2, OPTN, PFN1, TUBA4a, UNC13a, FIG4, ELP3, NEK1, C21orf2, SIGMAR1, DCTN1, MATR3, CHCHD10, VCP, hnRNPA1, hnRNPA2b1, NIPA1, SMN1, TBK1, ATXN2, MOBP, SARM1, UBQLN2, SQSTM1*
Classic ALS	SOD1	*SOD1*
Classic ALS	FUS	*FUS*
ALS with cognitive or behavioural impairment or comorbid FTD	TDP-43	*TARDBP, CHMP2b, TBK1, UBQLN2, SQSTM1, DCTN1, UNC13a*
Classic ALS, ALS-FTD, FTD	TDP-43, p62, dipeptide repeats, RNA foci	*C9orf72*
Multi-system proteinopathy*	TDP-43	*VCP, hnRNPA1, hnRNPA2b1, SQSTM1*
Behavioural variant FTD	TDP-43	*CHMP2, GRN*
Behavioural variant FTD	FUS	-
Behavioural variant FTD	Tau	*MAPT*
Semantic variant primary progressive aphasia	TDP-43	*GRN, C9orf72*
Semantic variant primary progressive aphasia	Tau	*MAPT*
Logopenic and non-fluent variant primary progressive aphasia	Tau	*MAPT*

ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia. *A familial disorder in which patients present with ALS, FTD, inclusion body myositis, Paget's disease of the bone, or combinations thereof.

***Table 3*: The complex correlations between genes, pathology, and phenotypes**

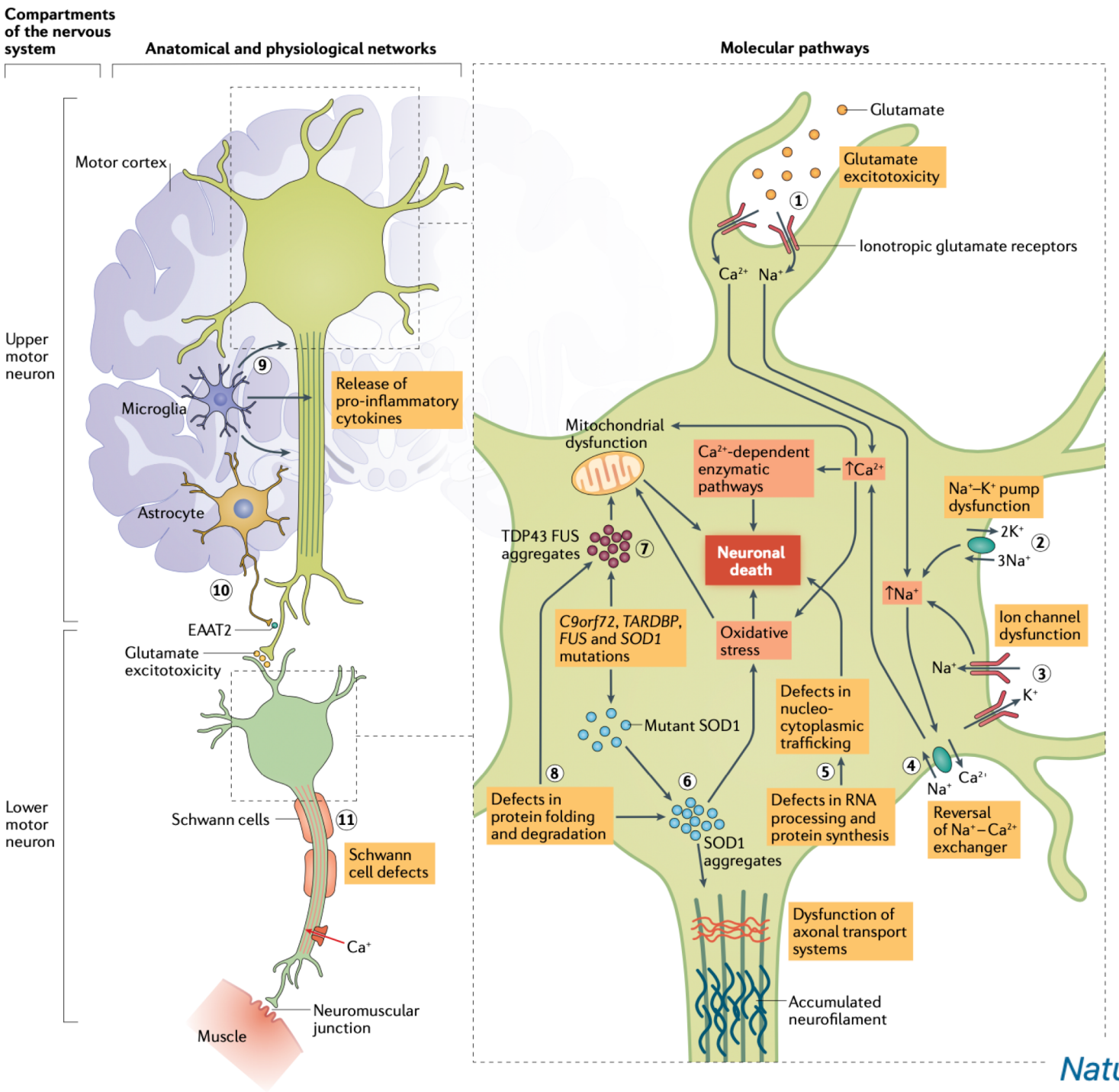
WHY DO THIS PHENOTYPIC/GENOTYPIC CHARACTERIZATION?

	Associated with long survival	Associated with short survival
Clinical features	Flail arm variant; lower motor neuron-predominant disease; upper motor neuron-predominant disease; long time to diagnosis; young age at diagnosis	Bulbar-onset ALS; respiratory onset; executive dysfunction and comorbid FTD; poor nutritional status; neck flexor weakness; old age at diagnosis
Genetic factors	*SOD1* mutations: Glu22Gly, Gly38Arg, Asp91Ala, Gly94Cys, and Ile114Thr; reduced *EPHA4* expression	Ala5Val mutation in *SOD1*; repeat expansions in *C9orf72* or *ATXN2*; mutations in *FUS* (also associated with early onset); homozygosity for the C allele of rs12608932 in *UNC13a*
Environmental and life style factors	None	Low socioeconomic status; smoking
Treatments	Riluzole treatment; non-invasive ventilation; enteral feeding; moderate exercise; multidisciplinary clinic care	Carbamazepine; minocycline; diaphragm pacing

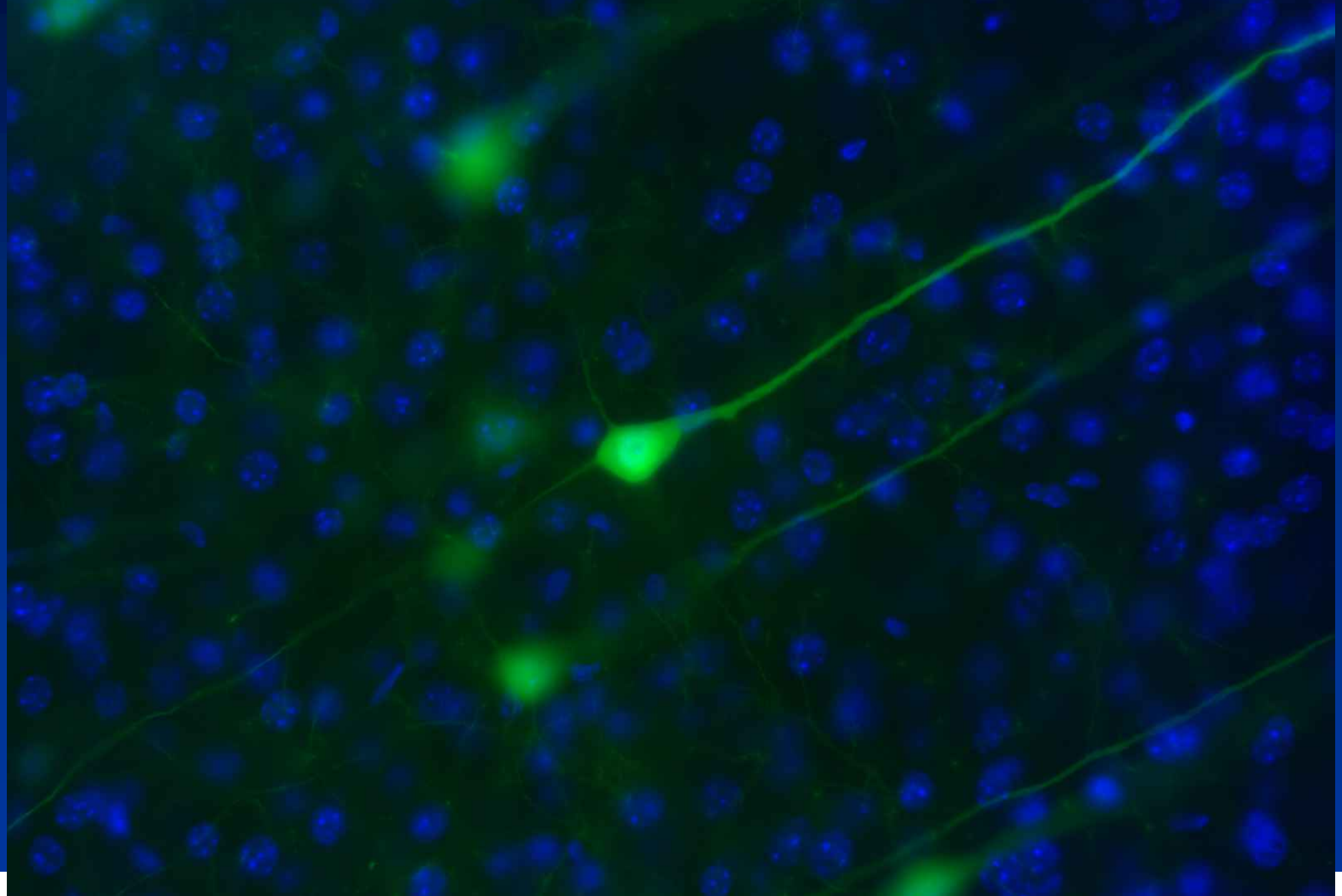
ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia.

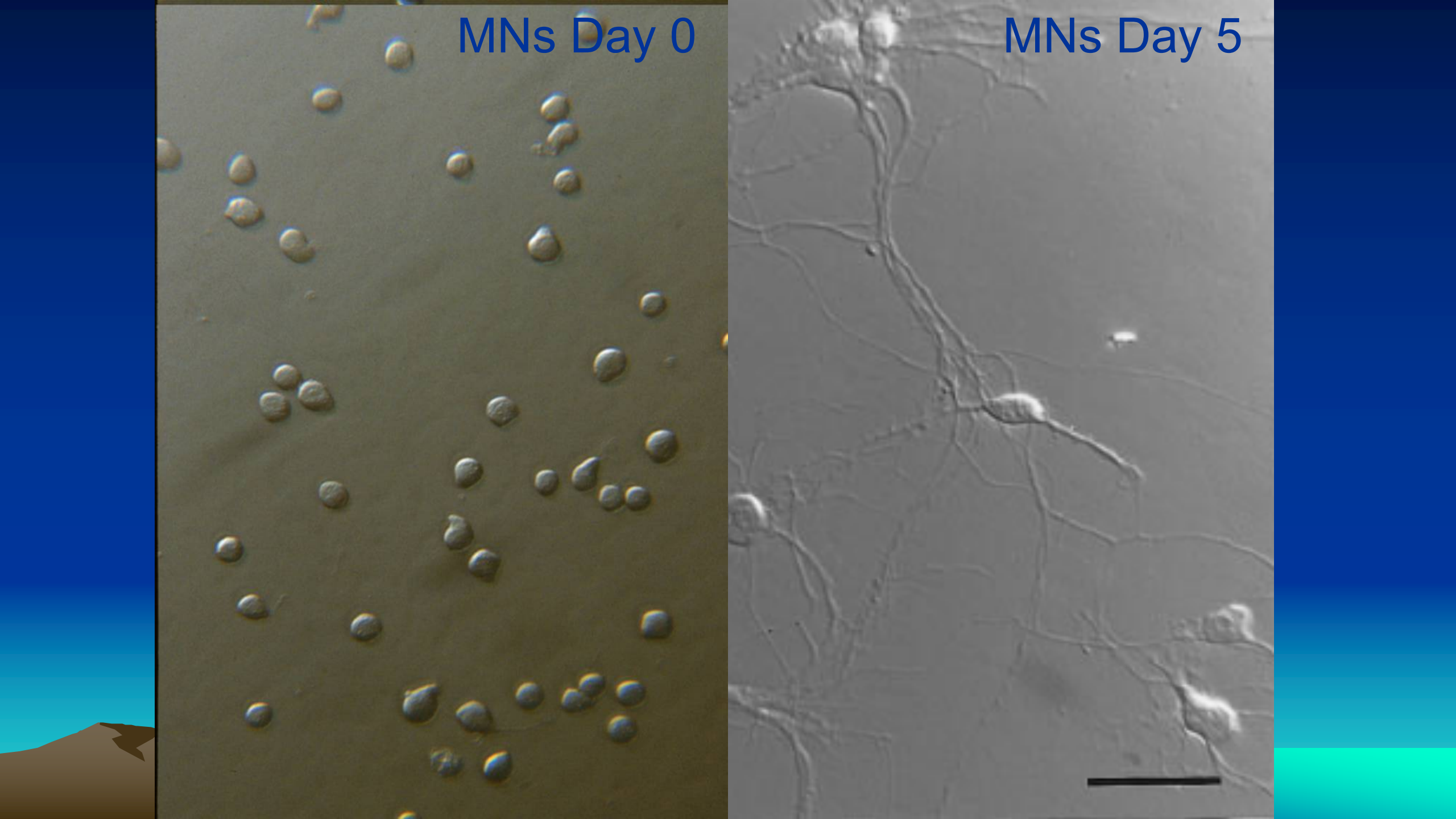
***Table 2*: Prognostic factors in amyotrophic lateral sclerosis**

Ideas about the Pathogenesis and Pathophysiology of ALS



Nature Reviews Neurology **17**, 104–118 (2021)




MNs Day 0
MNs Day 5

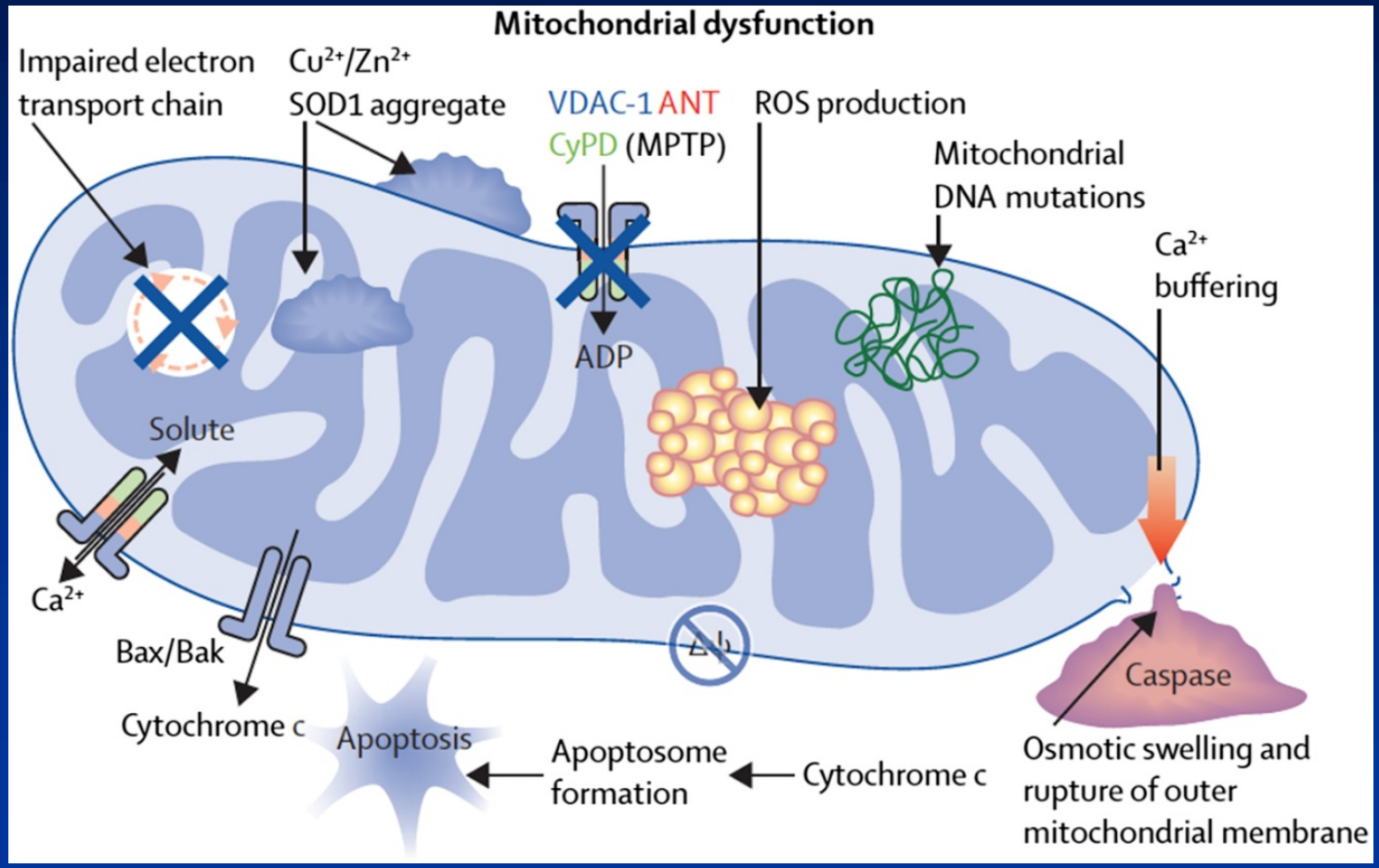
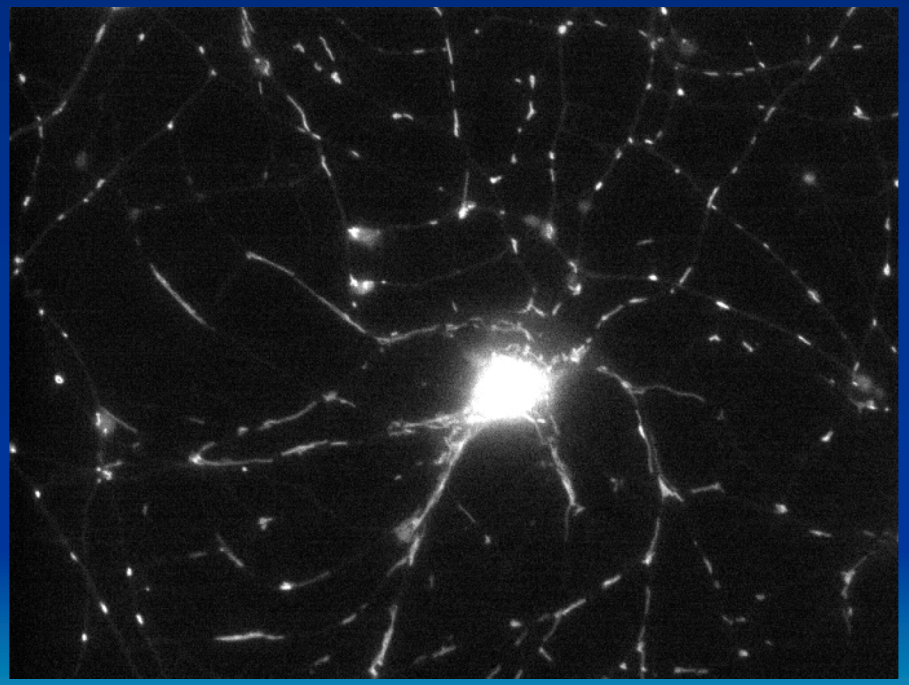
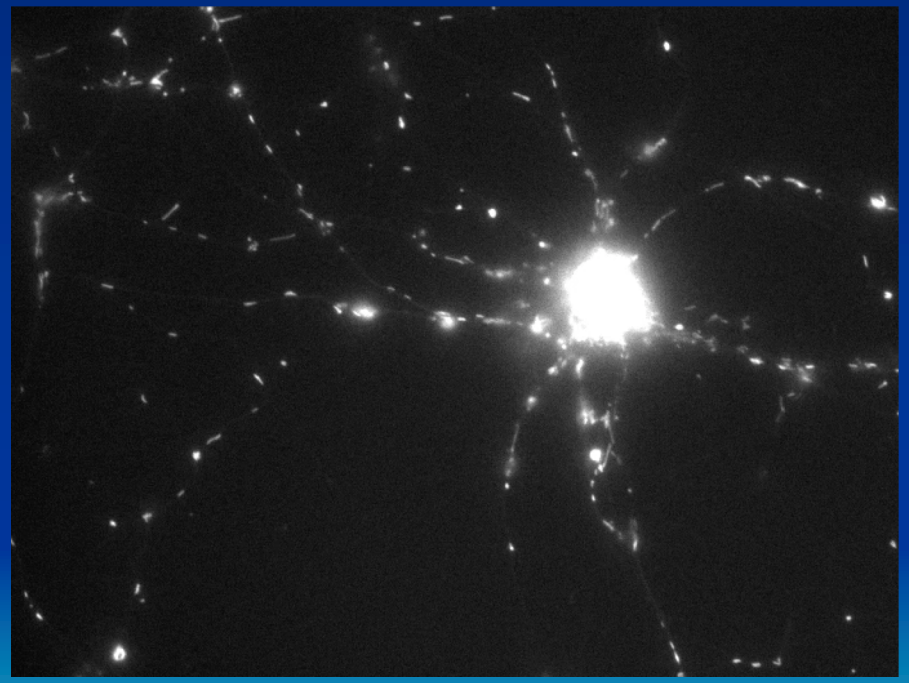


Figure 12 Mitochondrial dysfunction in amyotrophic lateral sclerosis. The aggregation of mutant *SOD1* causes a failure in energy production, a breakdown of the mitochondrial membrane potential, and a loss in Ca^{2+} buffering by mitochondria. The release of cytochrome c initiates apoptotic death in the affected neuron. ADP, adenosine diphosphate; ROS, reactive oxygen species.

Reproduced with permission from Ref. 20.

TNFa affects mitochondrial transport



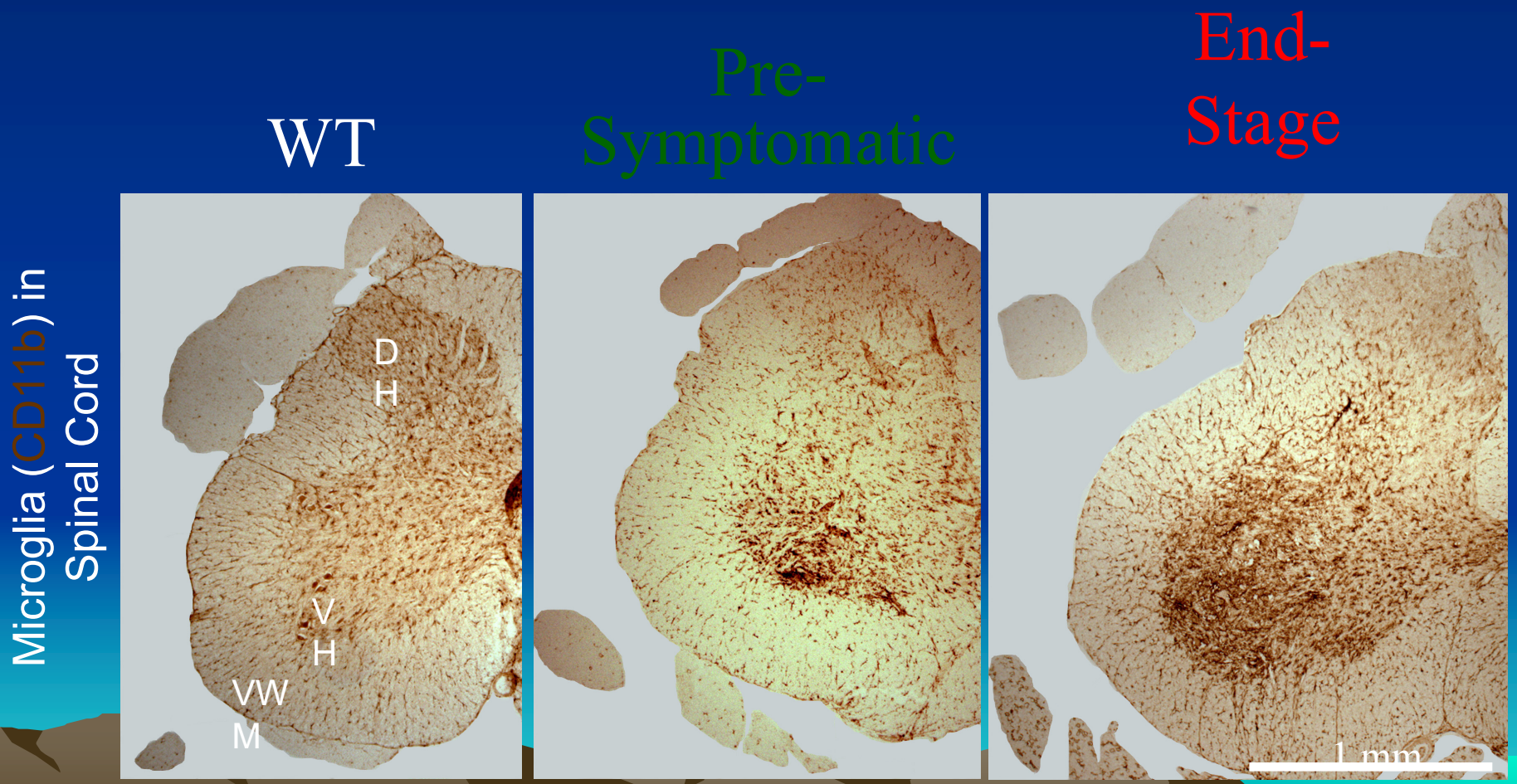


Neuroscience 146 (2007) 1013–1019

hmSOD1 G93A transgenic rat

Howland, et al. PNAS 2002

Increased Microglia in Ventral Horn and White Matter Before and After Symptom Onset



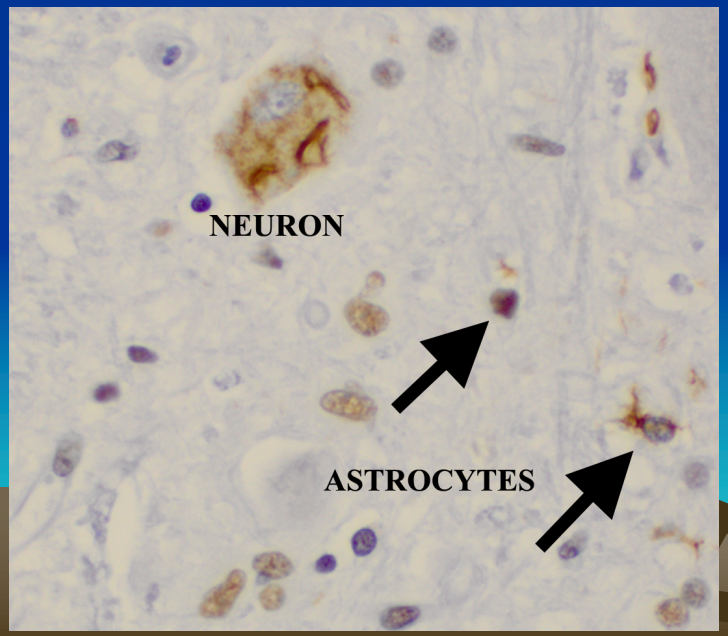
Graber et al. Journal of Neuroinflammation 2010, 7:8

TDP-43

- TDP-43 is a DNA/RNA binding protein with a number of different splice forms.
- It binds to a variety of RNA and DNA sequences, particularly to poly UG RNA sequences, as well as other proteins.
- It can shuttle back and forth from the cytoplasm. In FTD and ALS cases, affected neuron and glial cells show a variety of different TDP-43 forms that accumulate in inclusion bodies in the cytoplasm and/or nucleus with loss of normal diffuse nuclear distribution.

TDP-43 Pathology

- Formation of intranuclear and cytoplasmic inclusions
- Hyperphosphorylation
- Cleavage generates C-terminal fragments of approximately 24–26 kDa
- Dramatic translocation from nucleus to cytoplasm



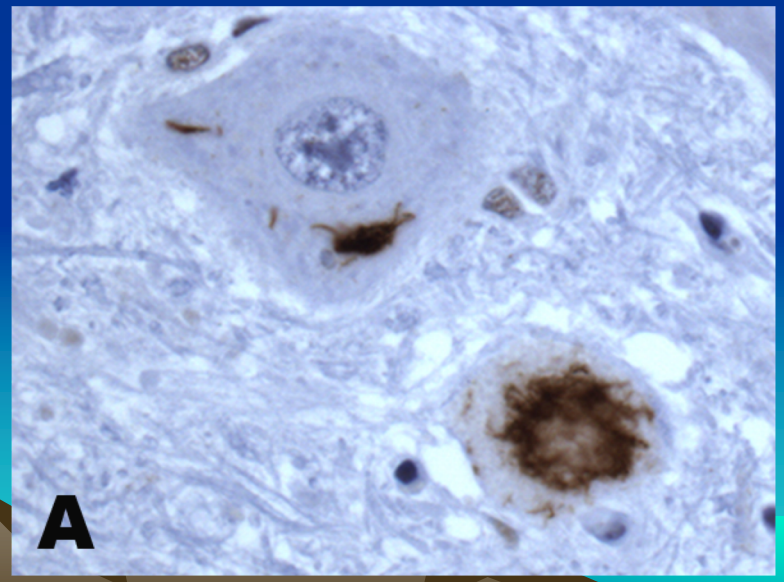
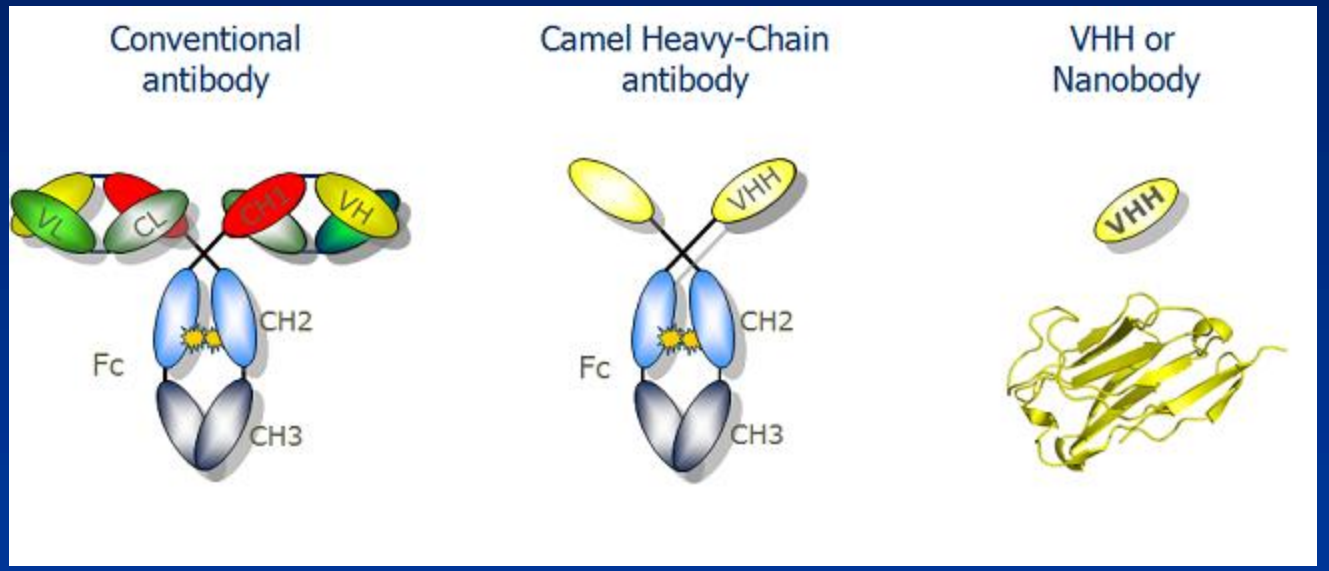


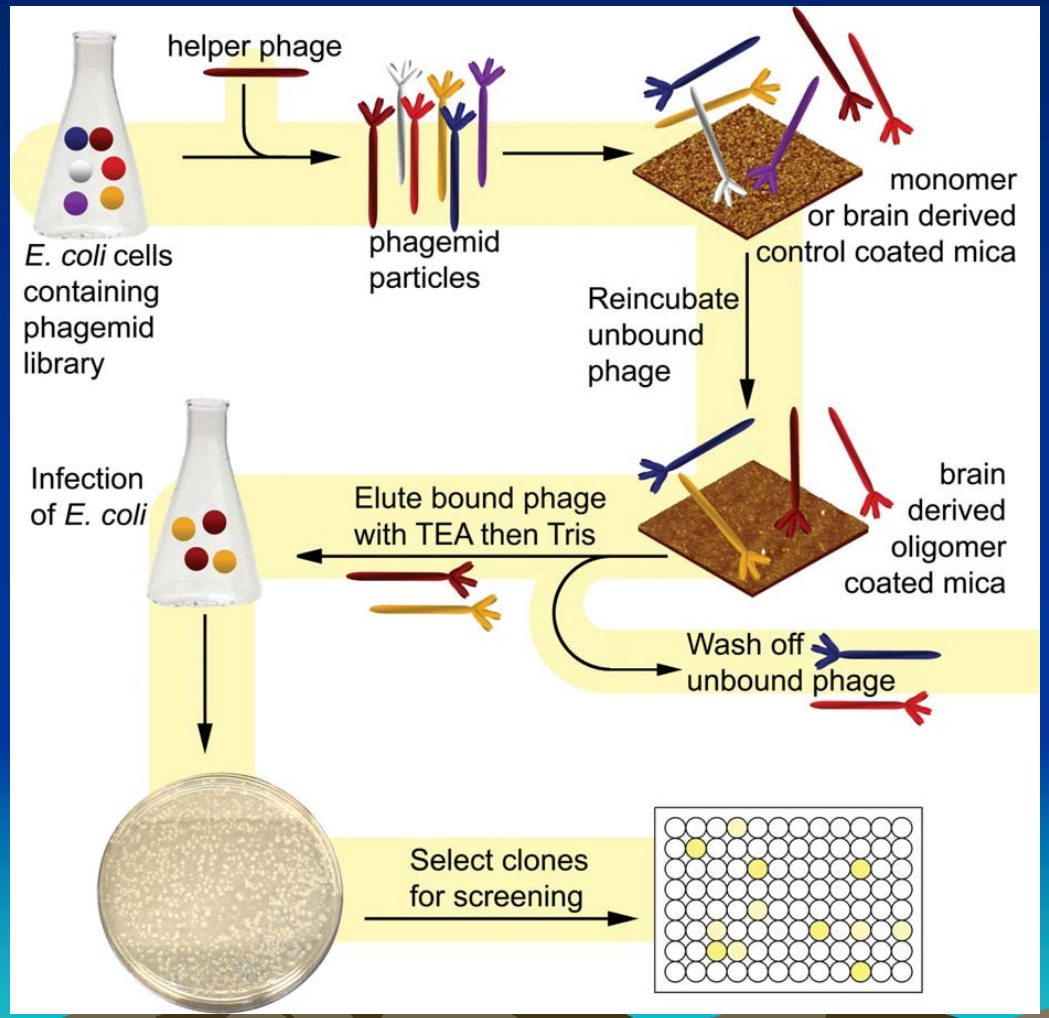
Diagram of Nanobody

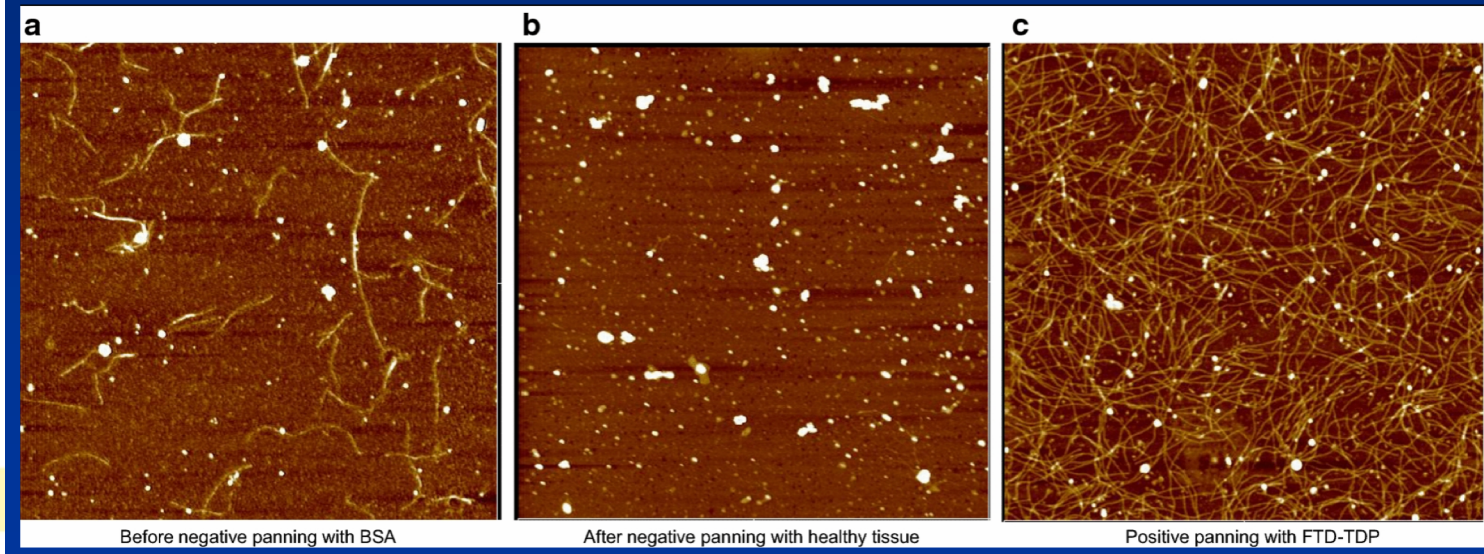


a) Single domain nature
b) Small size
c) Increased hydrophilicity
d) High sequence stability
e) Extended CDR3 loop
f) Variable N terminal of CDR1

Potentially useful for diagnostics and Therapeutics

Cloning and nanobody production (collaboration with Sierks lab at ASU)





Isolation and characterization of antibody fragments selective for human FTD brain derived TDP-43 variants.

Venkataraman L, He P, Khan G, Harris BT, Sierks MR.

BMC Neurosci. 2020 Sep 4;21(1):36. doi: 10.1186/s12868-020-00586-0.

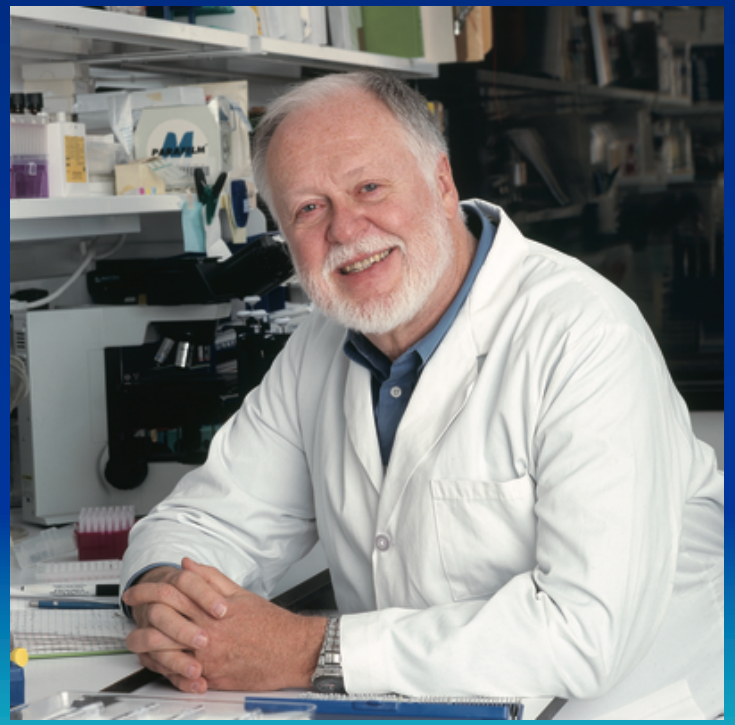
Novel atomic force microscopy based biopanning for isolation of morphology specific reagents against TDP-43 variants in amyotrophic lateral sclerosis.

Williams SM, Venkataraman L, Tian H, Khan G, Harris BT, Sierks MR.

J Vis Exp. 2015 Feb 12;(96):52584. doi: 10.3791/52584.

New collaboration with NCI, NIH

Curt Harris, Chief Lab of Human Carcinogenesis and Casmir Turnquist, PhD



Investigating the role of p53 isoforms in brain aging, senescence, and neurodegeneration

Harris Lab, Georgetown University

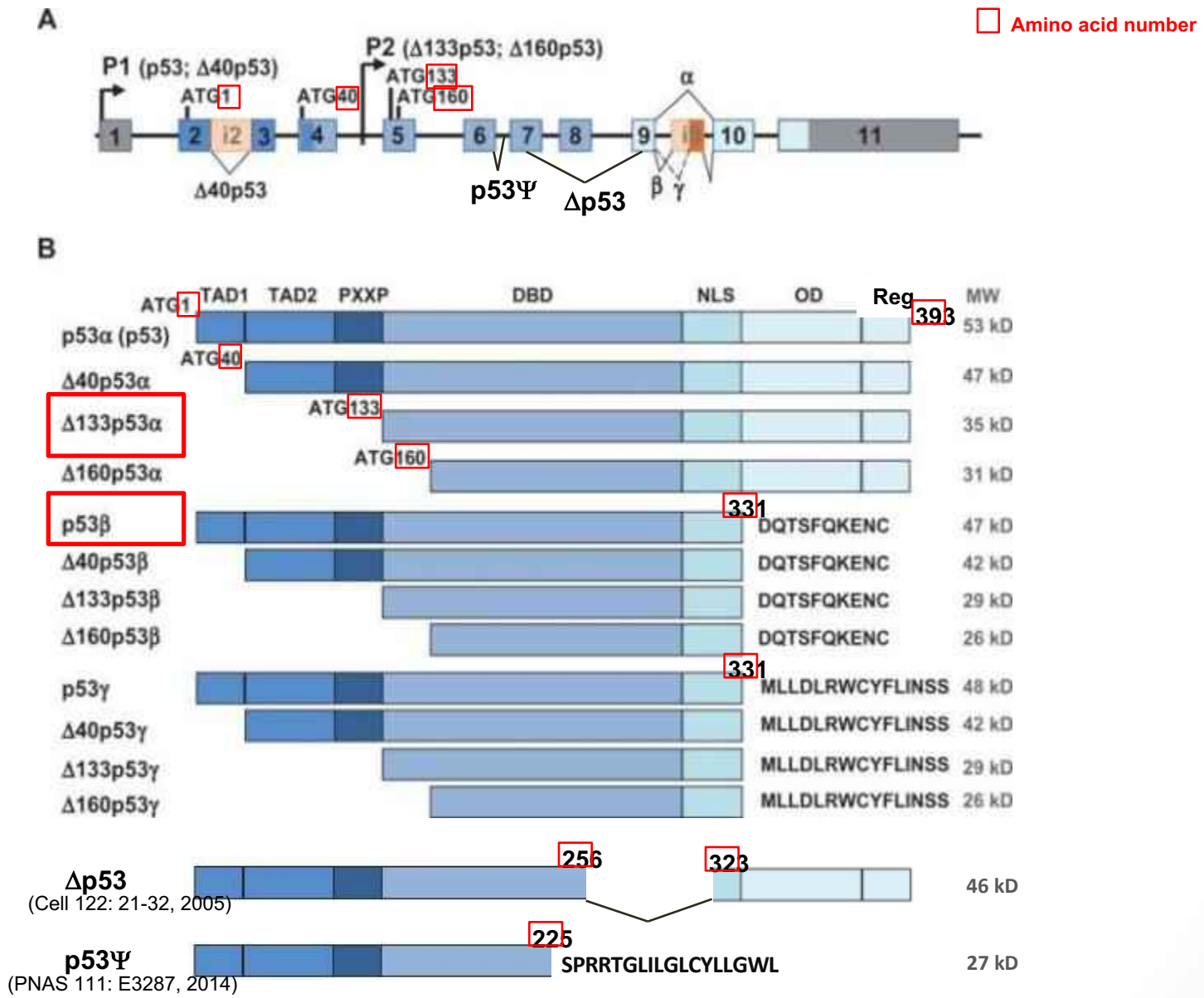
Harris Lab, Laboratory of Human Carcinogenesis, NCI/NIH

What is senescence?

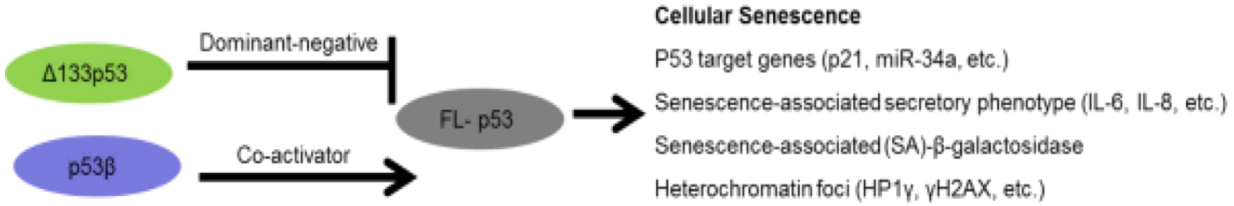
- Biological aging
- Gradual deterioration of functional characteristics
- Loss of a cell's power of division and growth (cellular senescence)
- Inevitable

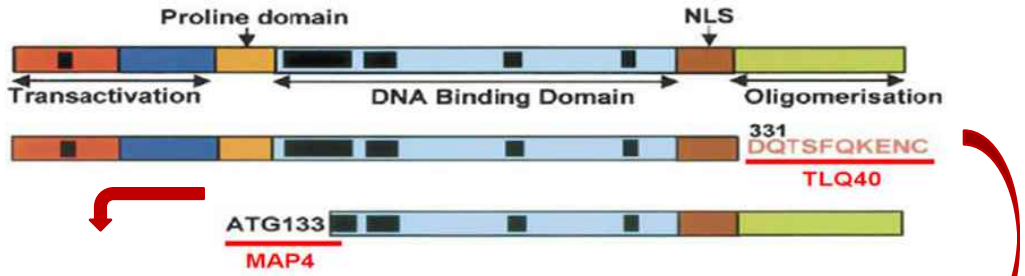
- Can be also accelerated via: stress, disease, genetic mutations, chromosomal abnormality (Progeria, Down's syndrome), UV radiation, DNA or cellular damage, etc.
- May be delayed – Drugs? Caloric restriction?

13 p53 isoforms



Δ133p53 and p53β Regulate Cellular Senescence





Δ133p53α

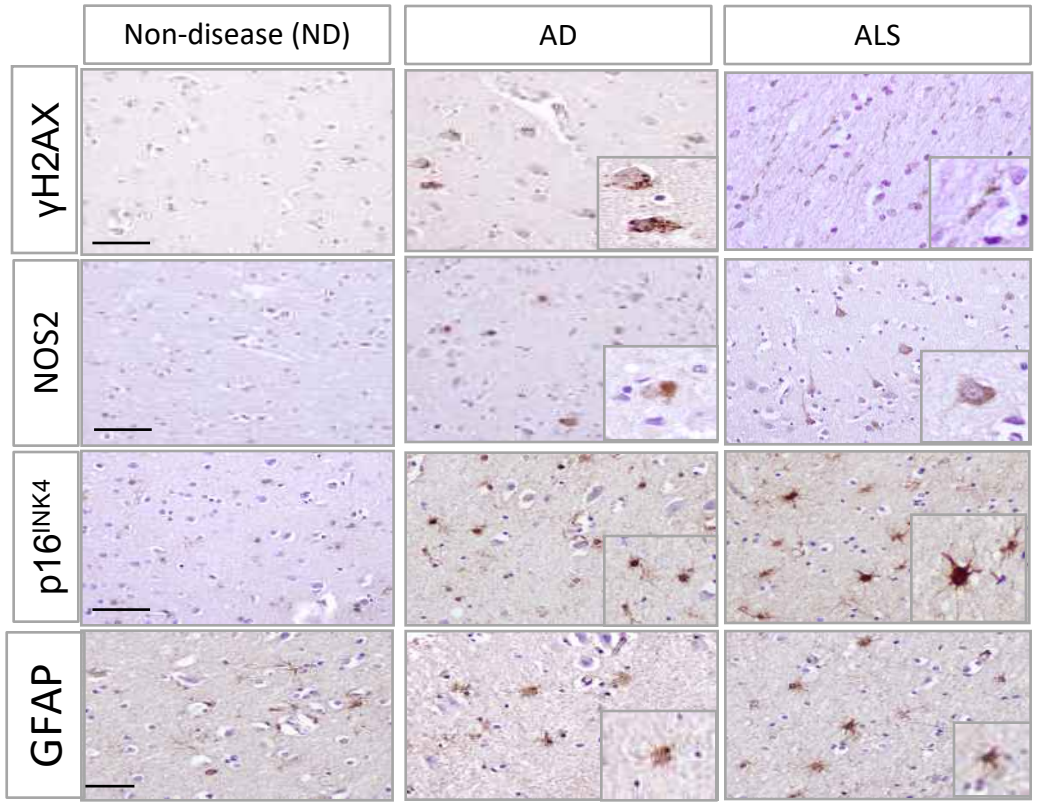
- ✓ **Downregulated at replicative senescence**
- ✓ **Inhibits full-length p53**
- ✓ **Degraded via selective autophagy**

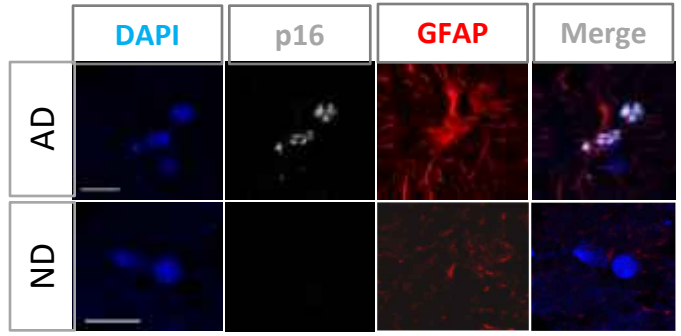
p53β

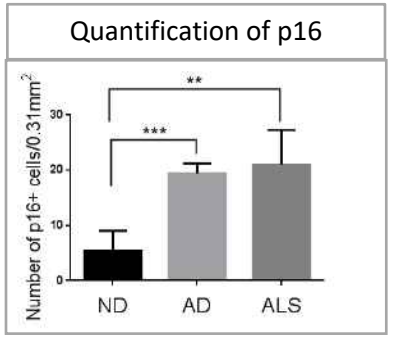
- ✓ **Upregulated at replicative senescence**
- ✓ **Cooperates with full-length p53**
- ✓ **Regulated by alternative RNA splicing**

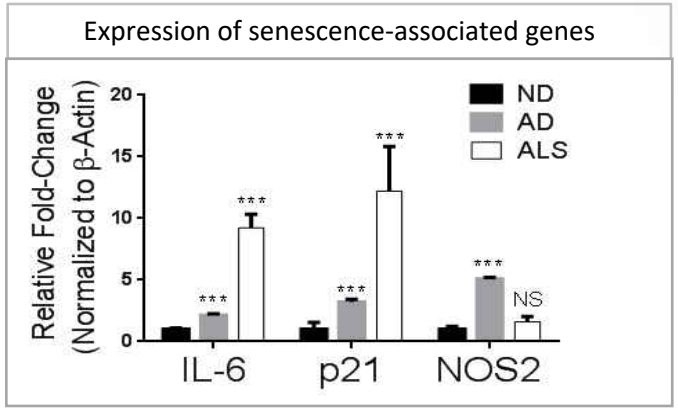
Horikawa et al. *Nat Commun* 2014
Tang et al. *Oncogene* 2013
Marcel et al. *Cell Death Differ* 2014
Fujita et al. *Nat. Cell Biology* 2009

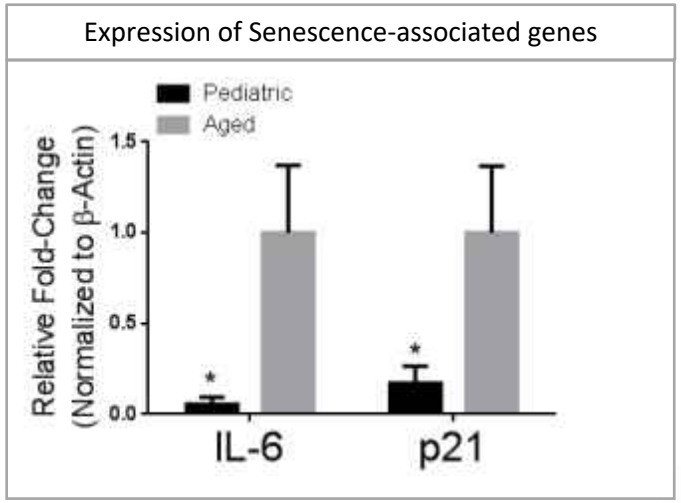
Cellular Senescence of Astrocytes in Brain Tissues from Neurodegenerative Disease Patients







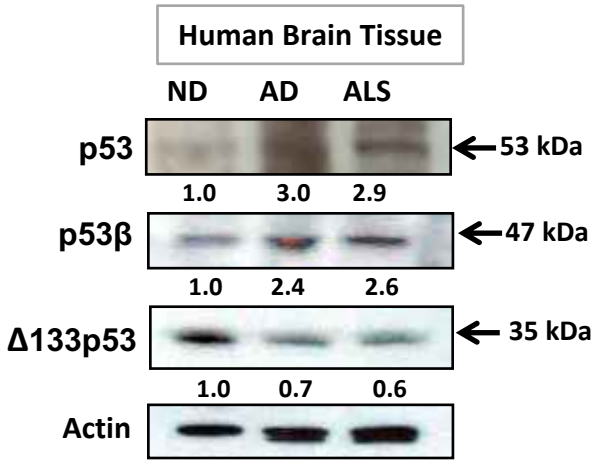


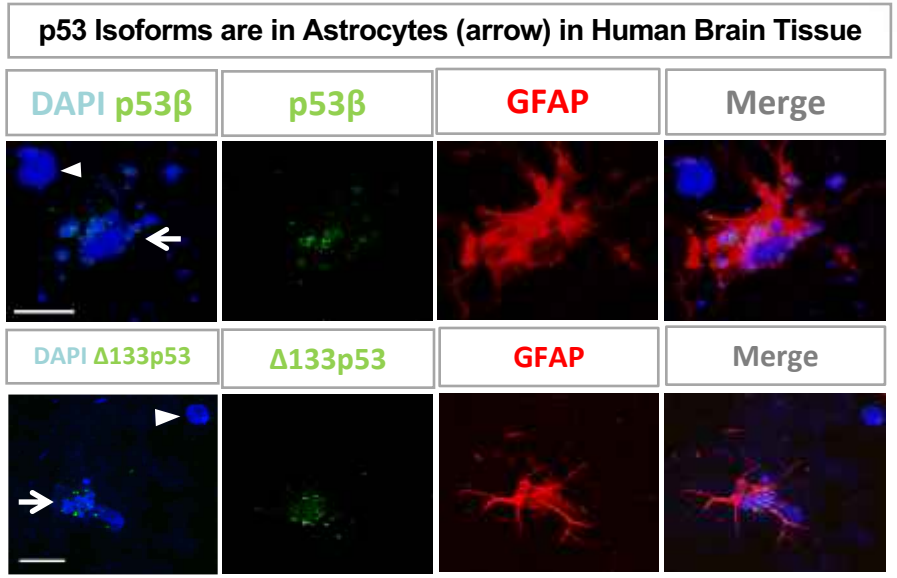


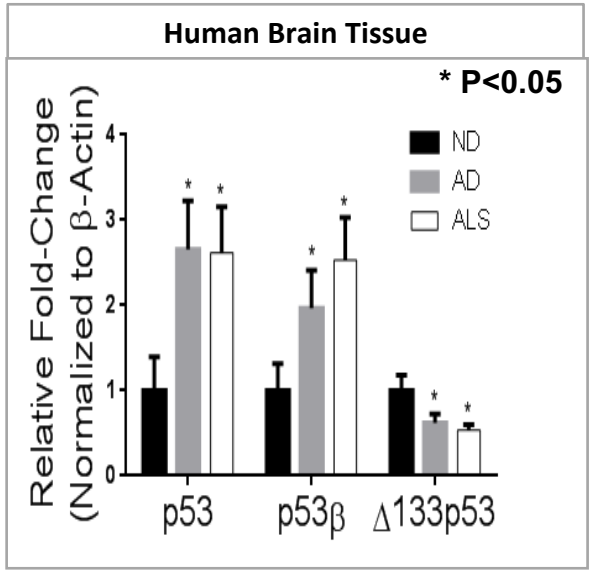
*** P<0.05 ** P<0.01 *** P<0.001**

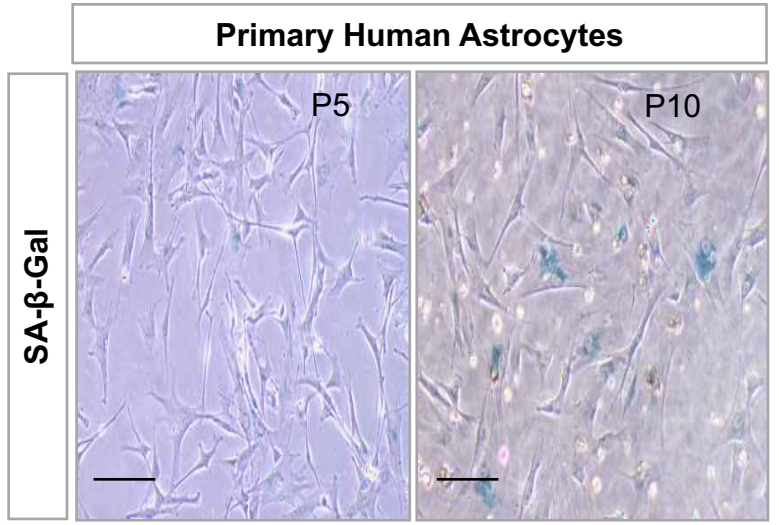
Turnquist et al., *CDD*, 2016

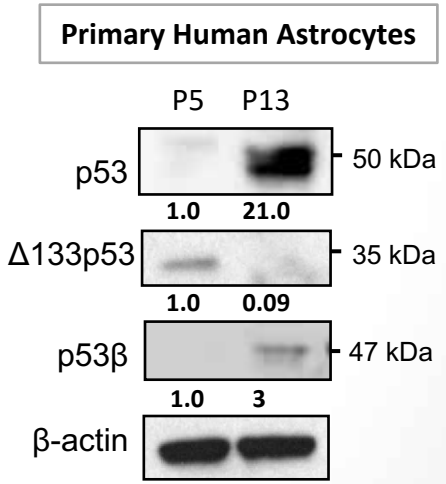
p53β is Upregulated and Δ133p53 is Downregulated in Neurodegeneration and in Aged Astrocytes *in vitro*





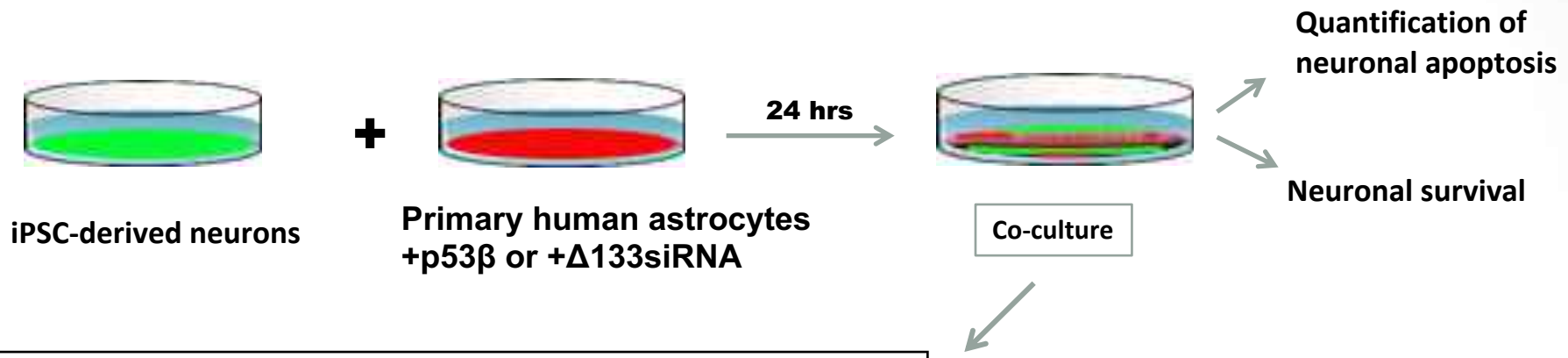




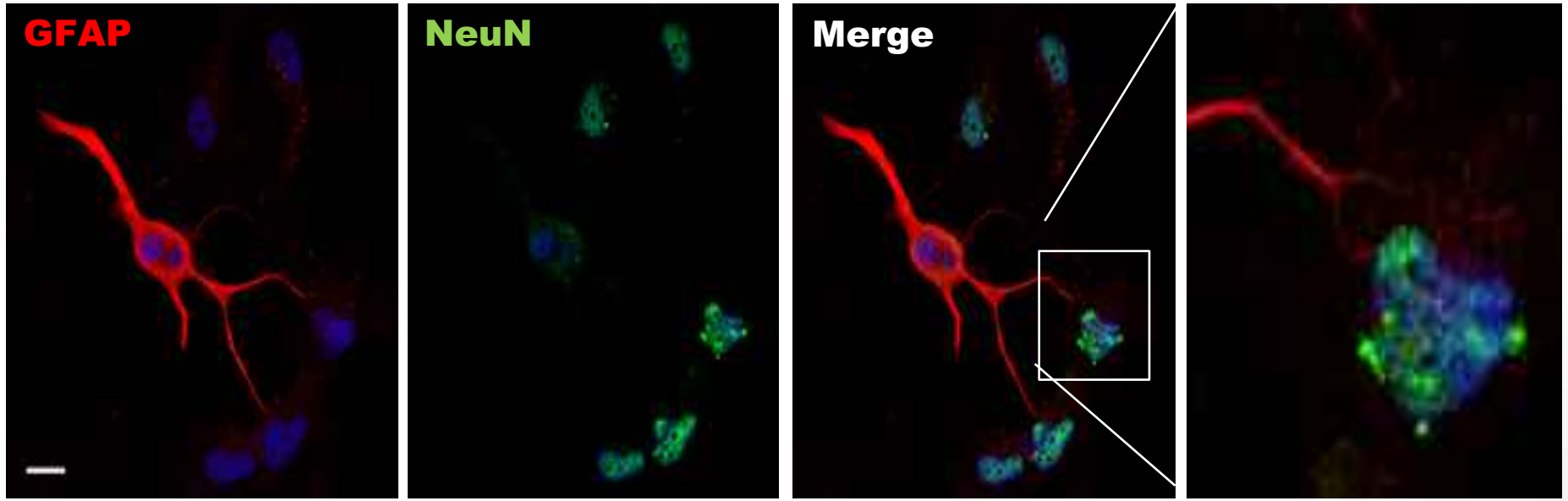


Turnquist et al., *CDD*

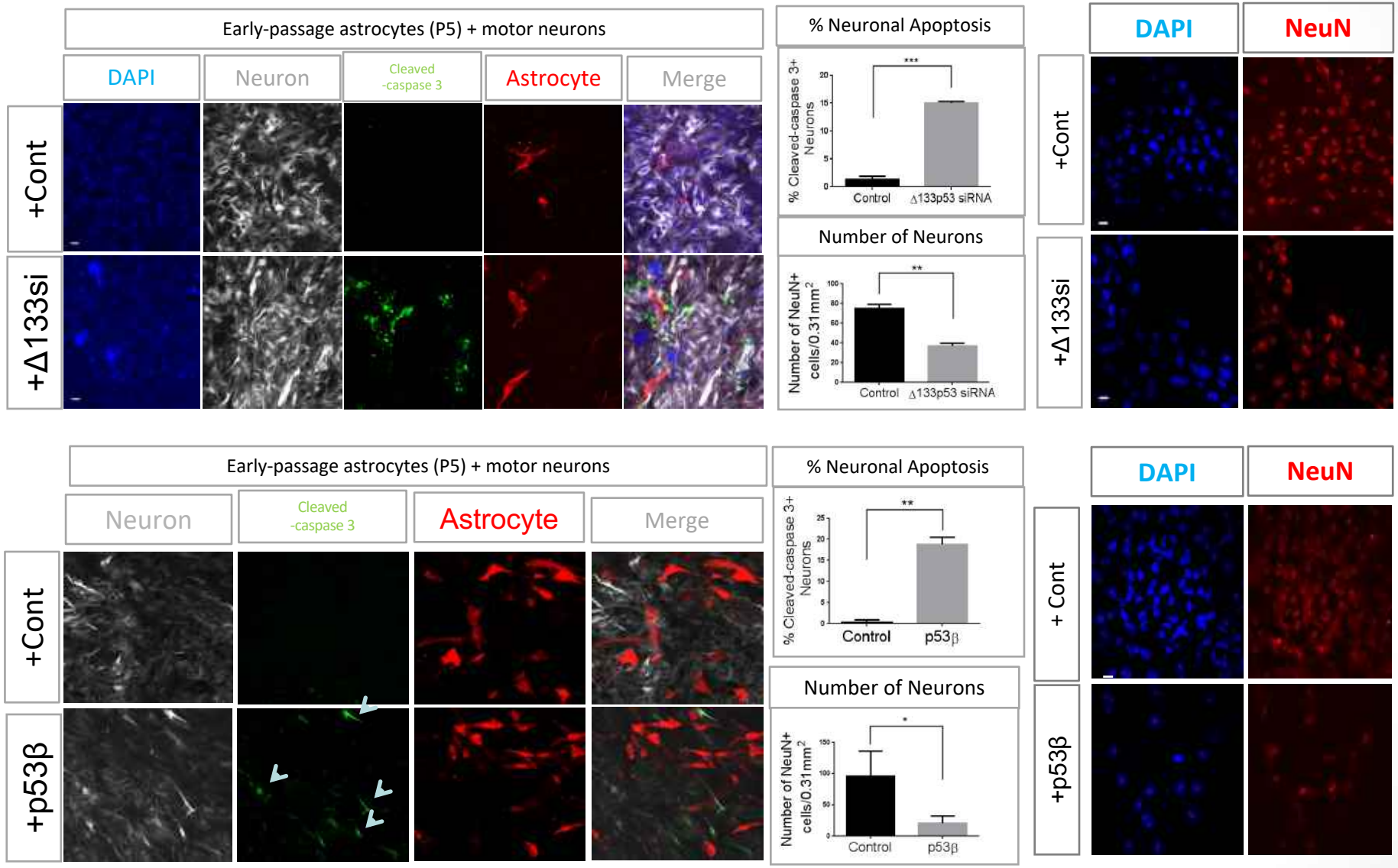
Co-Culture of Human Astrocytes and Neurons



Astrocyte and Neuron co-culture

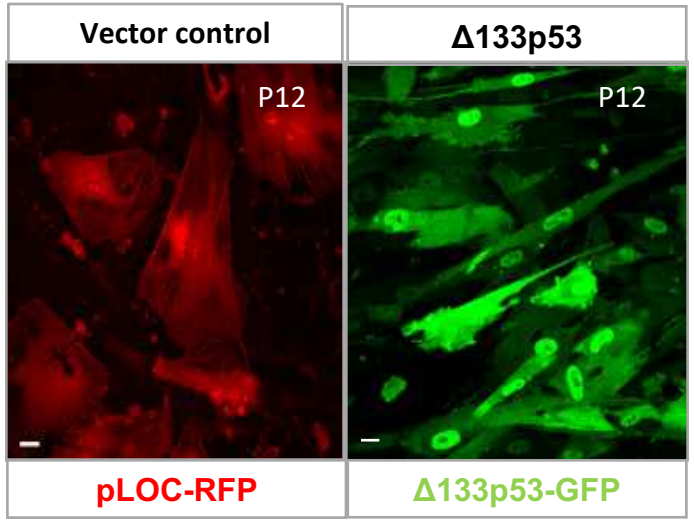


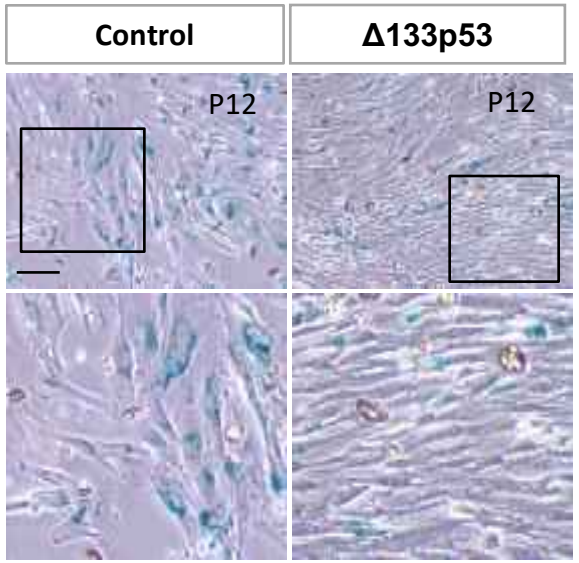
Increased Neuronal Death upon Co-culture with Δ133p53-knocked-down or p53β-overexpressing Astrocytes

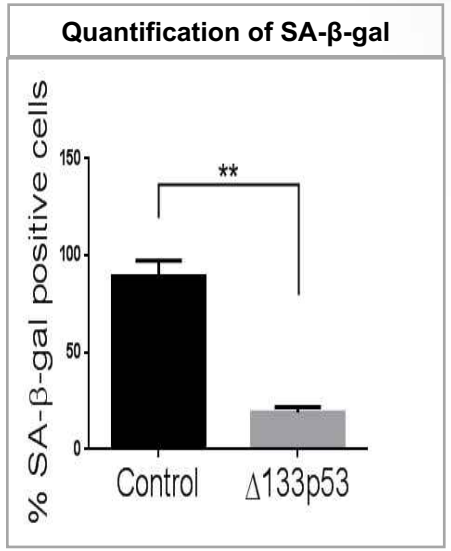


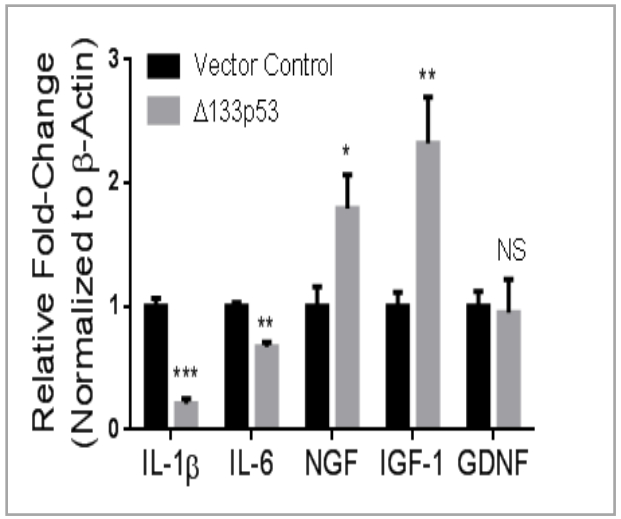
* P<0.05 ** P<0.01 *** P<0.001

Δ133p53 Overexpression Rescues Human Astrocyte SASP and Enhances Neurotrophic Factor Expression

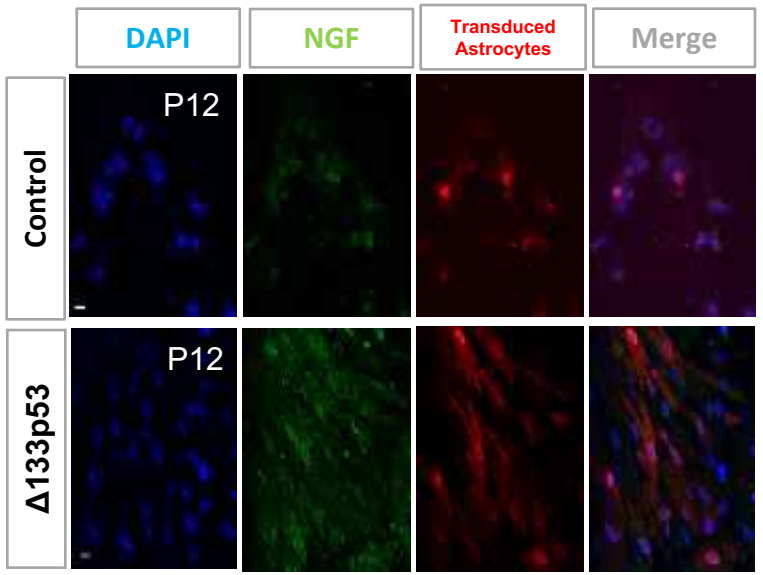


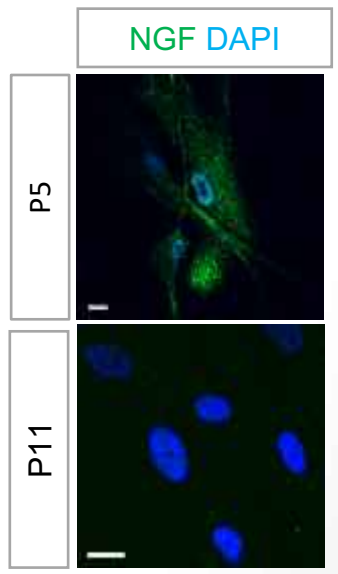




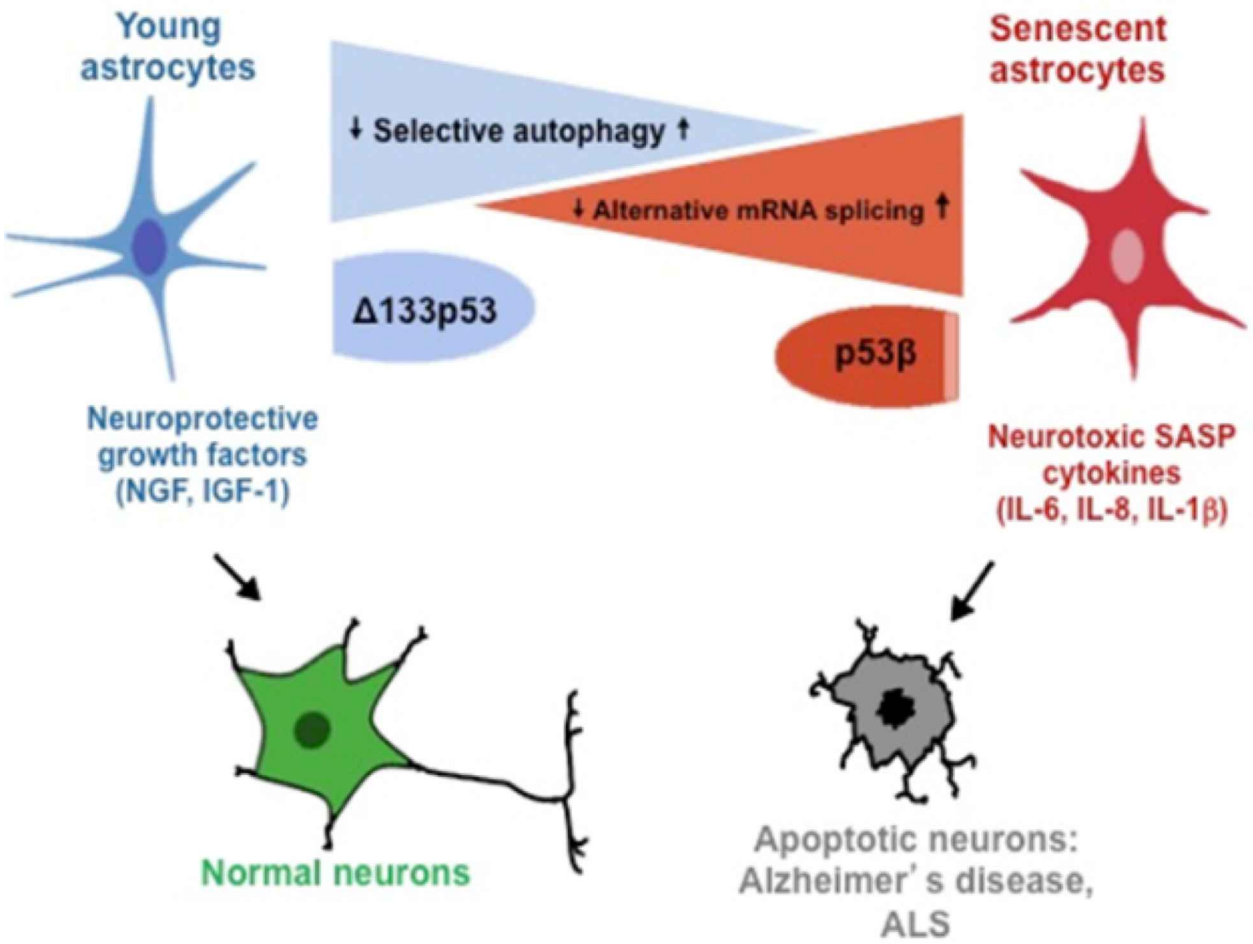


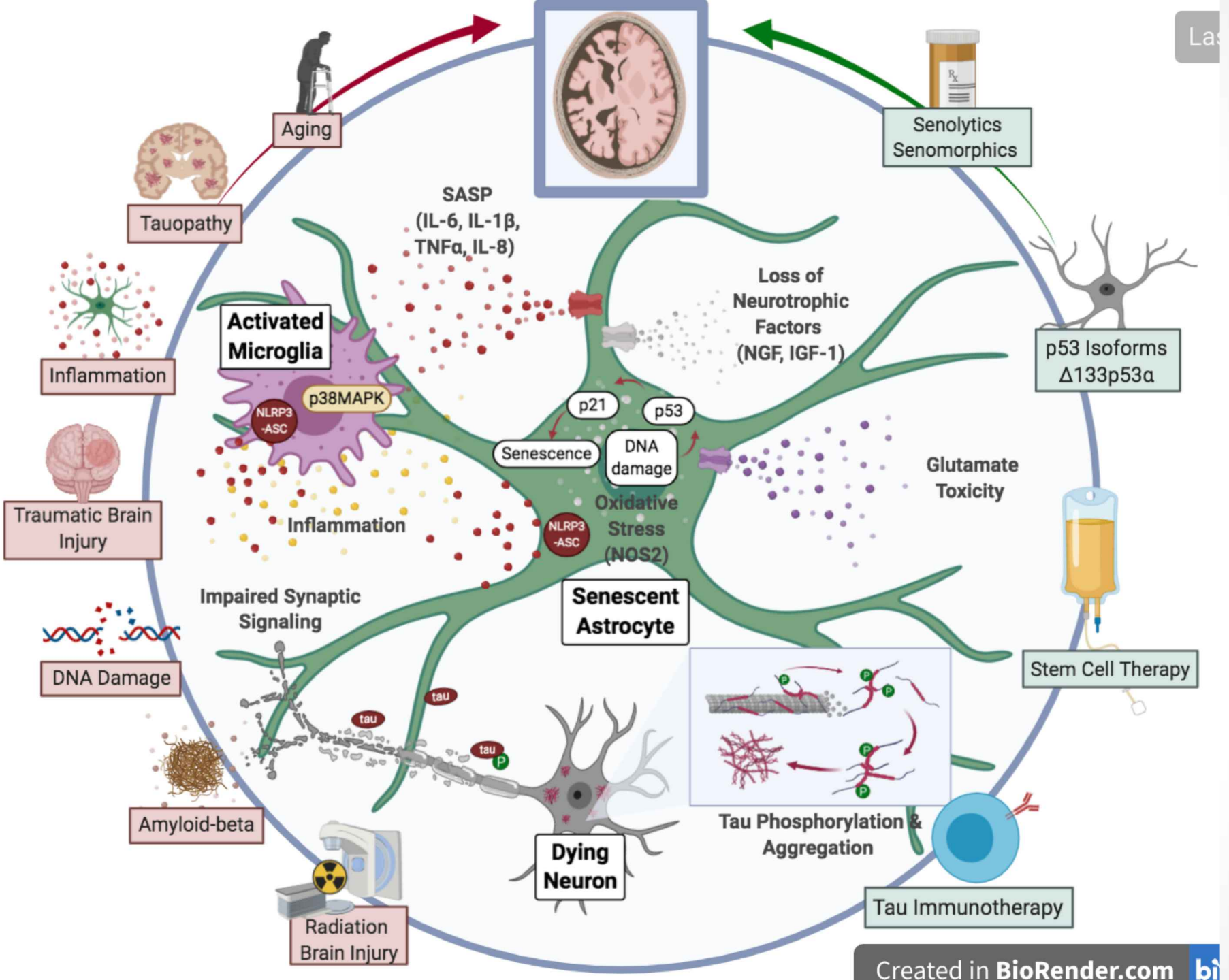
* P<0.05 ** P<0.01 *** P<0.001





Model of p53 Isoform Regulation of Astrocyte-mediated Neuroprotection and Neurodegeneration

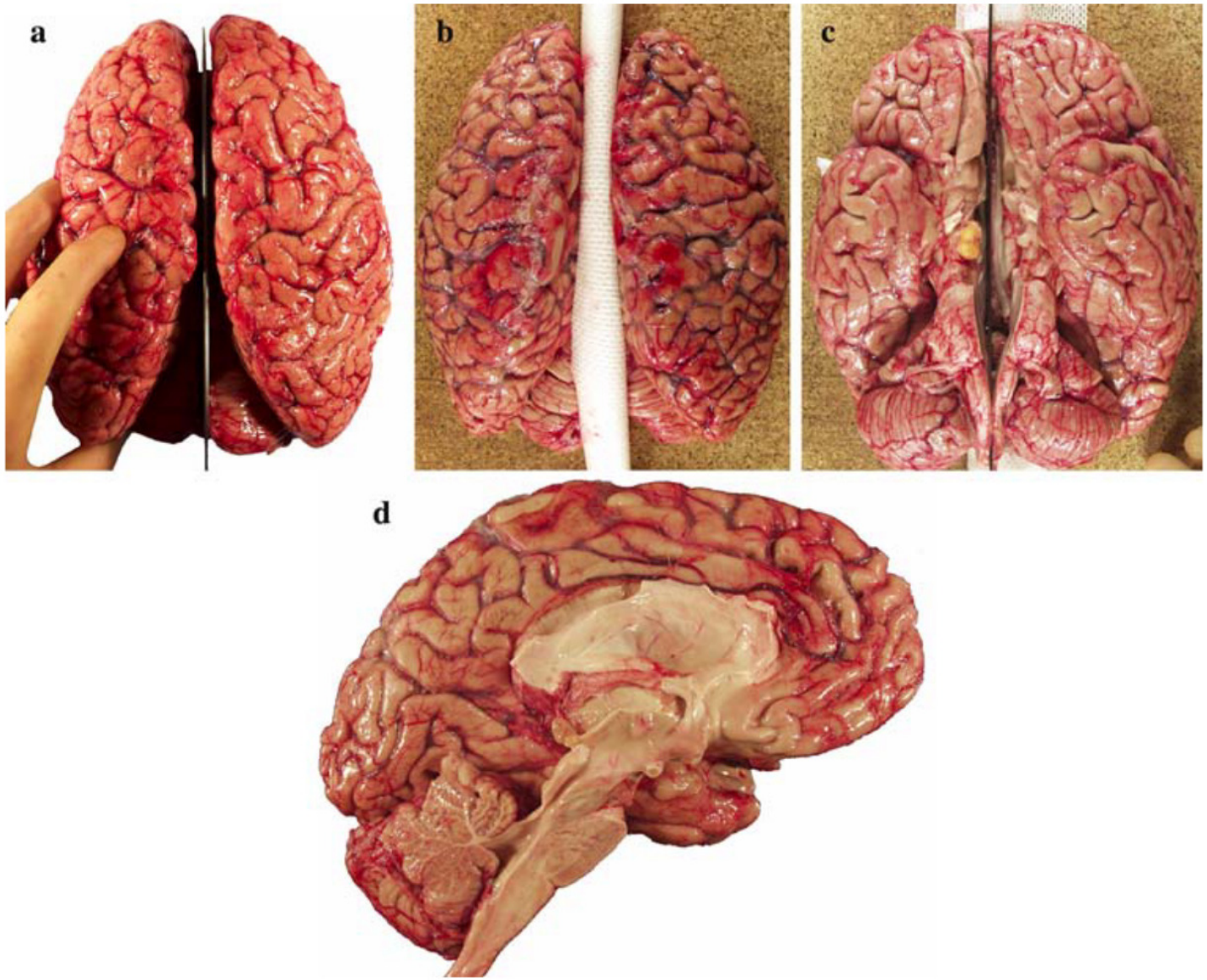



Aging
Tauopathy
Inflammation
Traumatic Brain Injury
DNA Damage
Amyloid-beta
Radiation Brain Injury
Senolytics
Senomorphics
p53 Isoforms
Δ133p53α
Stem Cell Therapy
Tau Immunotherapy
SASP
(IL-6, IL-1β, TNFα, IL-8)
Activated Microglia
p38MAPK
NLRP3 -ASC
Inflammation
Loss of Neurotrophic Factors (NGF, IGF-1)
p21
p53
Senescence
DNA damage
Oxidative Stress (NOS2)
NLRP3 -ASC
Glutamate Toxicity
Impaired Synaptic Signaling
Senescent Astrocyte
tau
tau
tau
Dying Neuron
Tau Phosphorylation & Aggregation
Created in BioRender.com

MY INSPIRATION TO BECOME A BRAIN BANKER…

YOUNG FRANKENSTEIN (1974)
YES, IT'S ON NETFLIX

21st Century Brain banking

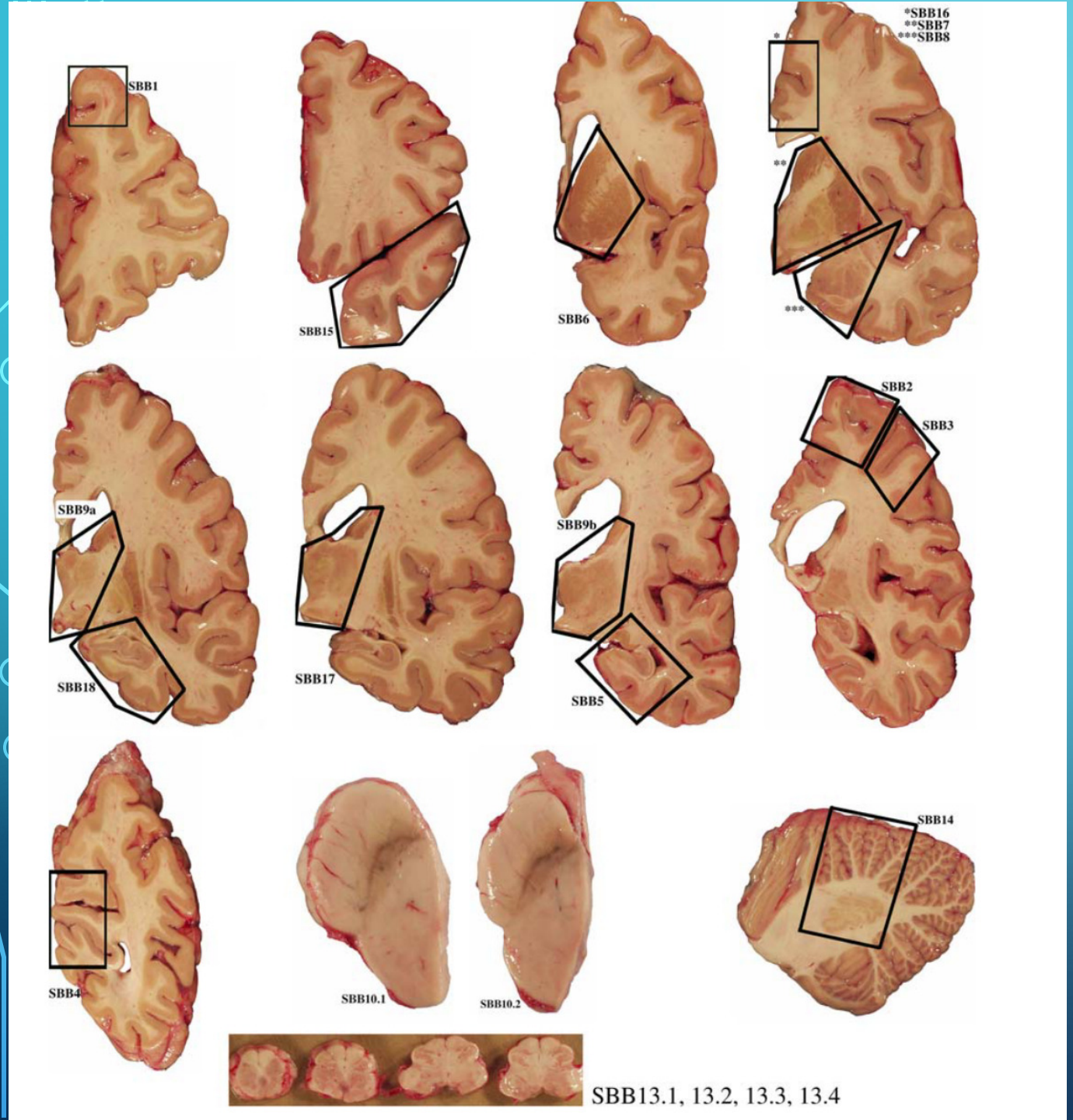


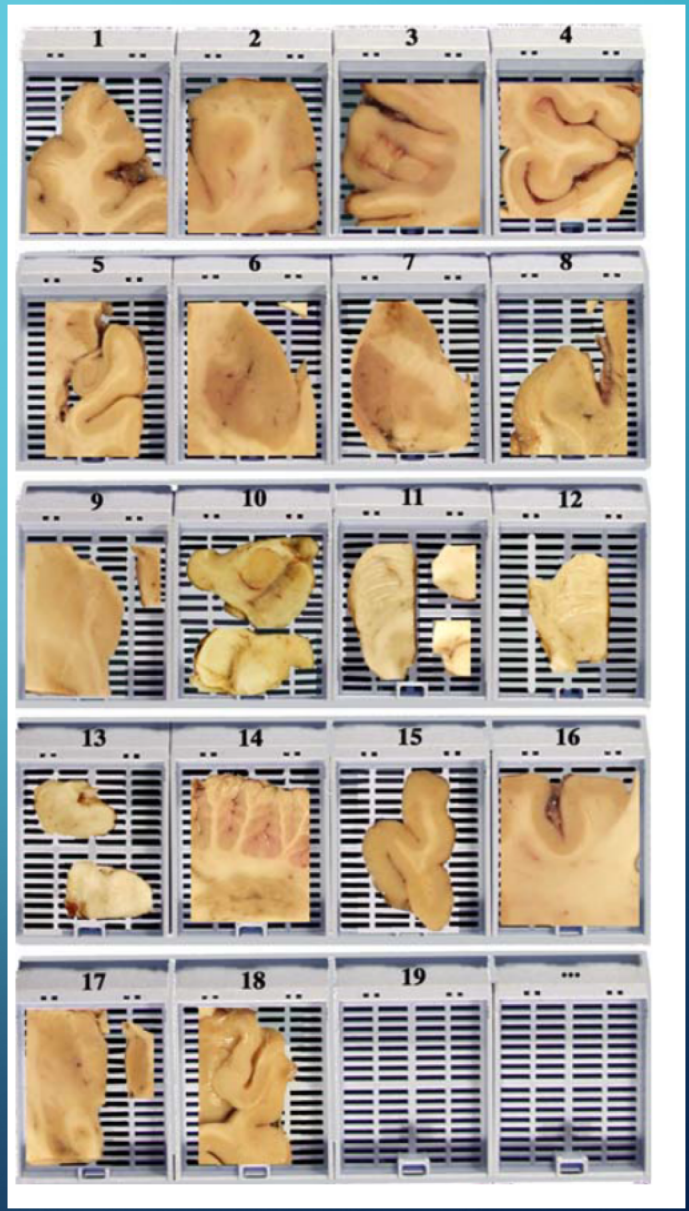
Acta Neuropathol (2008) 115:509–532
DOI 10.1007/s00401-007-0311-9

METHODS REPORT

Twenty-first century brain banking. Processing brains for research: the Columbia University methods

Jean Paul G. Vonsattel · Maria Pilar del Amaya · Christian E. Keller


SBB1
SBB15
SBB6
*SBB16
**SBB7
***SBB8
SBB9a
SBB18
SBB17
SBB9b
SBB5
SBB2
SBB3
SBB4
SBB10.1
SBB10.2
SBB14
SBB13.1, 13.2, 13.3, 13.4


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

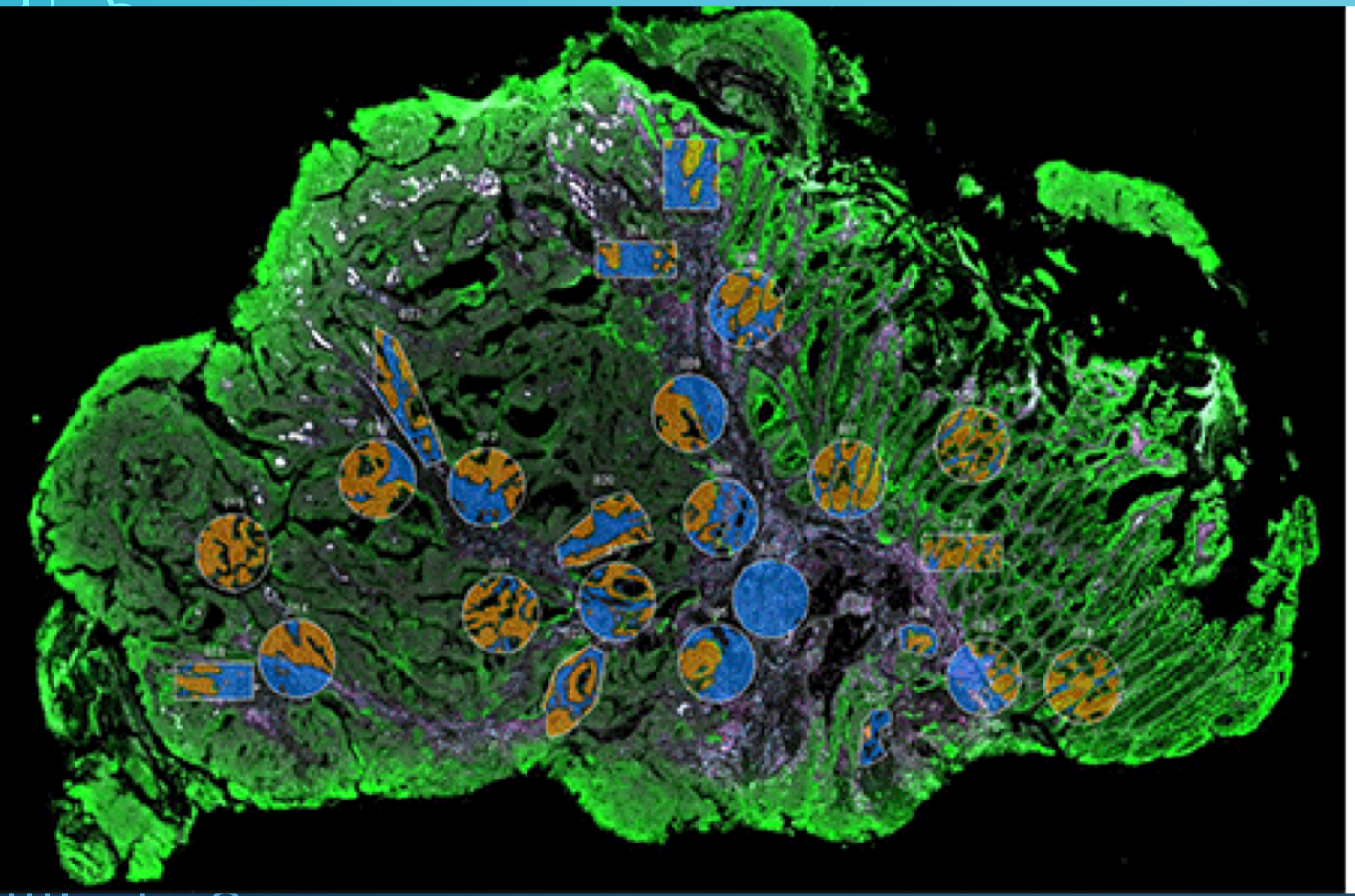
STORAGE OF TISSUES IN FIXATIVE AND BLOCKS

STORAGE OF TISSUES

FROZEN TISSUES AND MORE RECENTLY FFPE TISSUES

- Genomics
- Proteomics
- Transcriptomics
- Metabolomics
- Any ”omics” you can think of

COMBINING OMICS WITH SPATIAL/HISTOPATHOLOGY:



Target ALS Resources

- Biofluids, Tissues, Sequencing

Robert Bowser, PhD
Brent Harris, MD, PhD
Hemali Phatnani, PhD

Overall Goals

- Create Repositories of samples (longitudinal biofluids, post-mortem tissues) linked to sequencing information (WGS, RNA-seq), clinical information and at-home measures that capture the disease from diagnosis to end-stage.

- Includes ALS, healthy controls, and disease controls

- All coded samples, data and clinical information immediately available to the research community

Goal and Sites

- **Collect, process, bank, analyze, and distribute postmortem CNS tissues and skeletal muscle from ALS and neurological disease-free controls**
- **Sites and PIs:**
  - **Barrow Neurological Institute – Robert Bowser, PhD**
  - **Columbia University – Neil Shneider, MD, PhD and Matt Harms, MD**
  - **UCSD – John Ravits, MD**
  - **Georgetown University – Brent Harris, MD, PhD**
  - **Washington University – Cindy Ly, MD, PhD and and Timothy Miller, M.D., Ph.D.**

Core co-Directors: Drs. Bowser and Harris

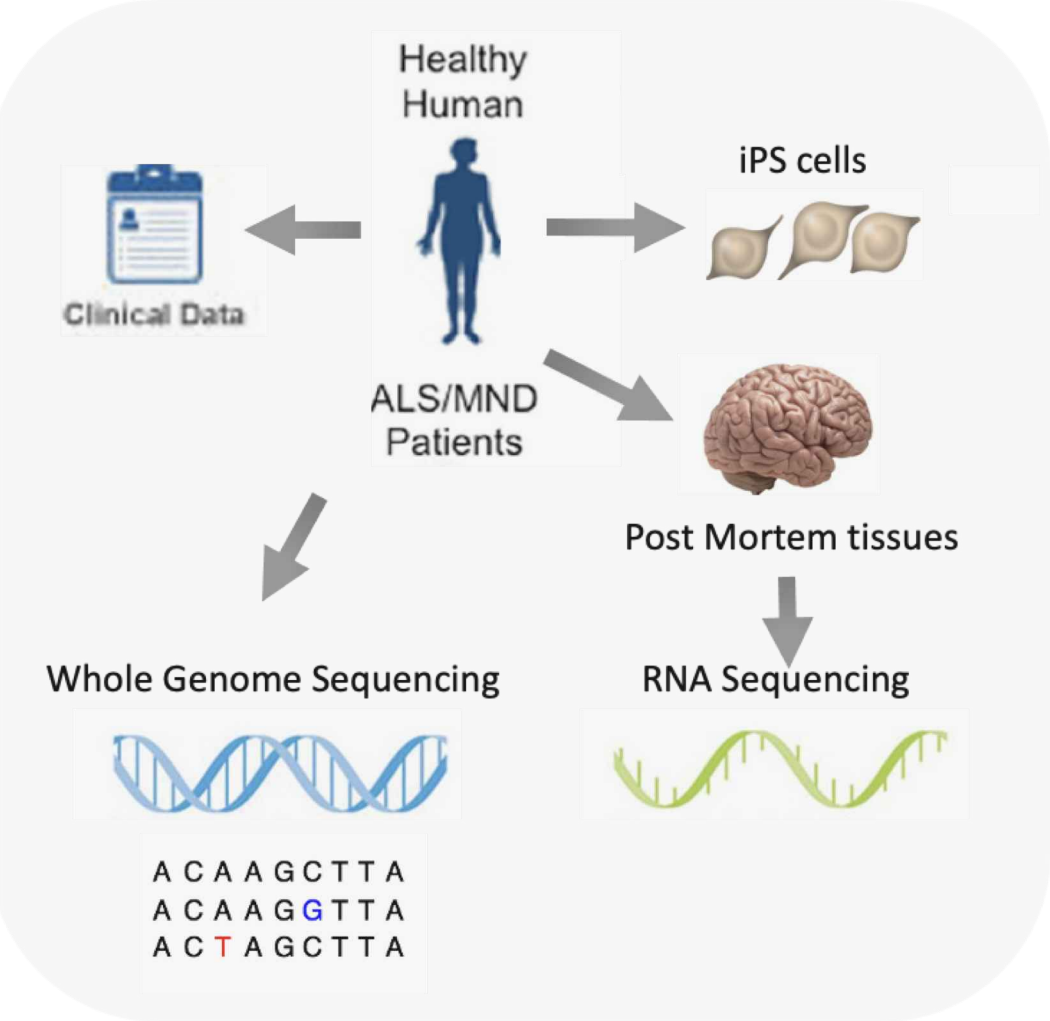
Core Neuropath Director: Dr. Harris

TALS PM CORE

Approximately 250 ALS Cases and 30 Control Cases

Now starting premortem longitudinal Biofluid collections to bank and match with clinical progression.

Genomics Data Overview

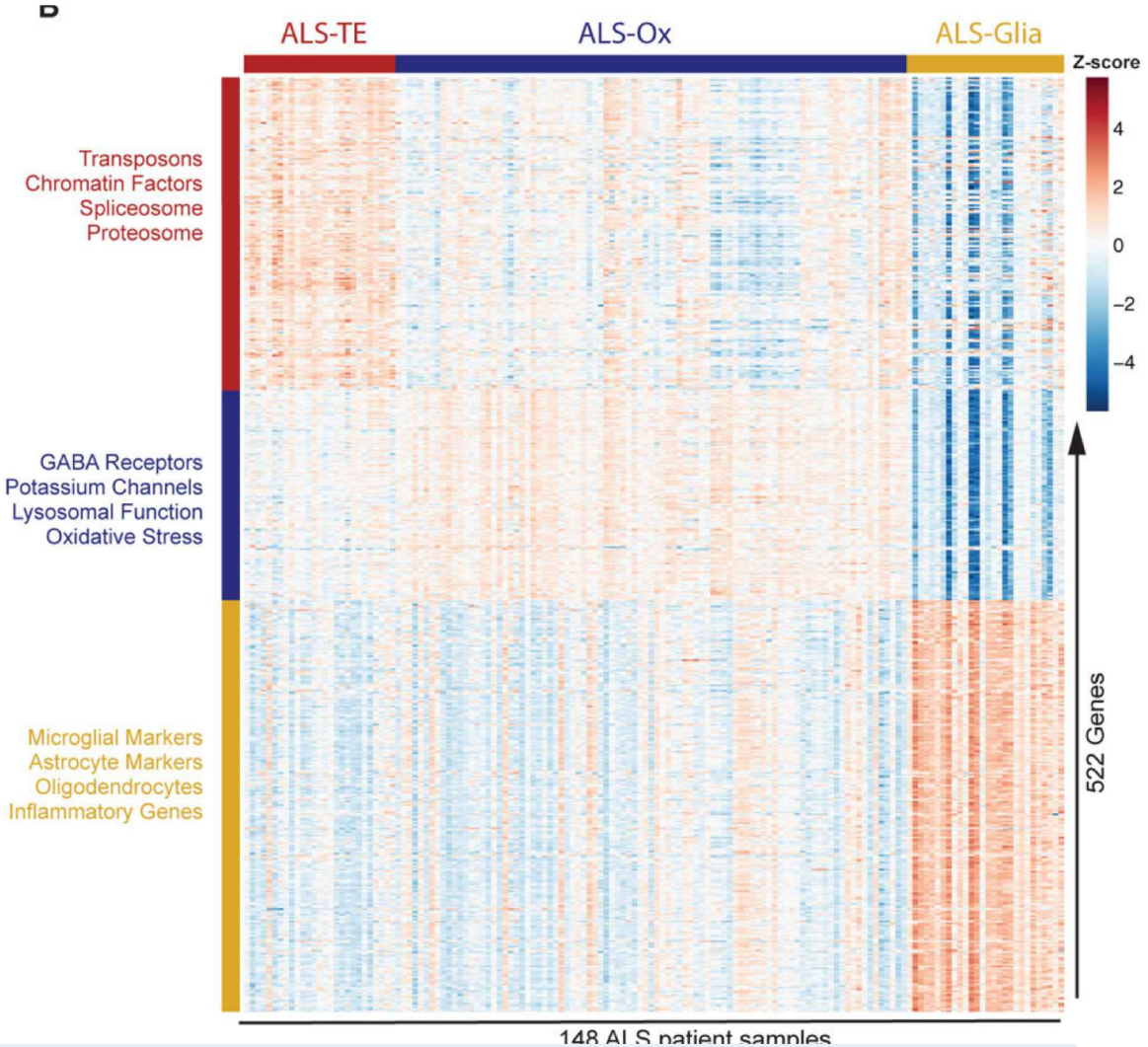


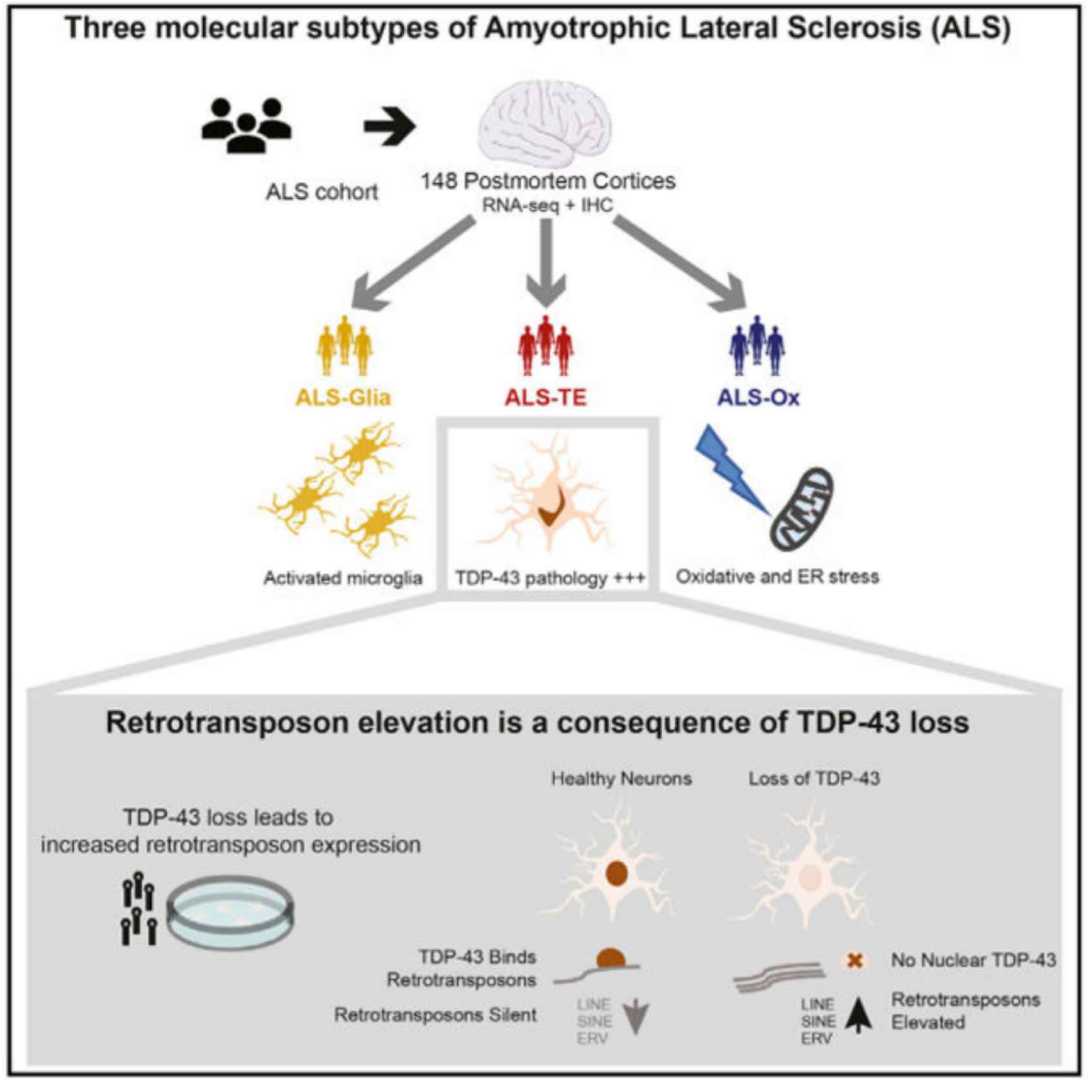
Cell Rep. 2019 October 29; 29(5): 1164–1177.e5. doi:10.1016/j.celrep.2019.09.066.

Postmortem Cortex Samples Identify Distinct Molecular Subtypes of ALS: Retrotransposon Activation, Oxidative Stress, and Activated Glia

Oliver H. Tam[1,9], Nikolay V. Rozhkov[1,9], Regina Shaw[1,9], Duyang Kim[2], Isabel Hubbard[2,10], Samantha Fennessey[2], Nadia Propp[2], The NYGC ALS Consortium, Delphine Fagegaltier[2], Brent T. Harris[3,4], Lyle W. Ostrow[3,5], Hemali Phatnani[2,3], John Ravits[3,6], Josh Dubnau[3,7,8], Molly Gale Hammell[1,3,11,*]

Graphical Abstract





Summary

- ALS and FTLD sit on a spectrum of neurodegenerative diseases characterized by variable clinical, genetic, and cellular/molecular changes.
- Familial and sporadic forms exist and we can learn a lot from studying the genetic changes.
- Collaboration and biofluid/tissue banking are the only way we are going to make headway on this devastating group of diseases.

ACKNOWLEDGEMENTS

Special thank you to all the patients and families that volunteer for clinical trials and biobanking in order to help others with these devastating diseases.

ACKNOWLEDGEMENTS

LHC/NCI/NIH
Curt Harris
Izumi Horikawa
Casmir Turnquist
Jessica Beck
Kyra Ungerleider

NINDS/NIH
Eugene Major
Kenneth Fischbeck
Douglas Fields

Harris Lab/GBB
Galam Khan
Carolyn Ward
Andrew Wodrich
Karli Gilbert
Ashwini Gadalay

Target ALS Consortium
Bob Bowser
Manish Raisinghani
Hemali Phatnani

Sierks Lab/ASU
Michael Sierks

THANKS FOR YOUR ATTENTION!

QUESTIONS??

References

1. Harris B.T. Amyotrophic Lateral Sclerosis. In: Linda M. McManus, Richard N. Mitchell, editors. Chapter in *Pathobiology of Human Disease*. 2014; San Diego: Elsevier; p. 2036-2044.
2. Michael A van Es, Orla Hardiman, Adriano Chio, Ammar Al-Chalabi, R Jeroen Pasterkamp, Jan H Veldink, Leonard H van den Berg. Amyotrophic Lateral Sclerosis. Lancet 2017; 390: 2084–98.
3. Ito Kawakami, I, Arai, T, and Hasegawa, M. The basis of clinicopathological heterogeneity in TDP-43 proteinopathy. Acta Neuropathologica 2019;138:751–770.
4. Vahsen, BF et al. Non- neuronal cells in amyotrophic lateral sclerosis — from pathogenesis to biomarkers. Nature Reviews Neurology, 2021; 17:333–348.