Prion-like Mechanisms of Disease Progression in Alzheimer's Disease: New Therapeutic Opportunities

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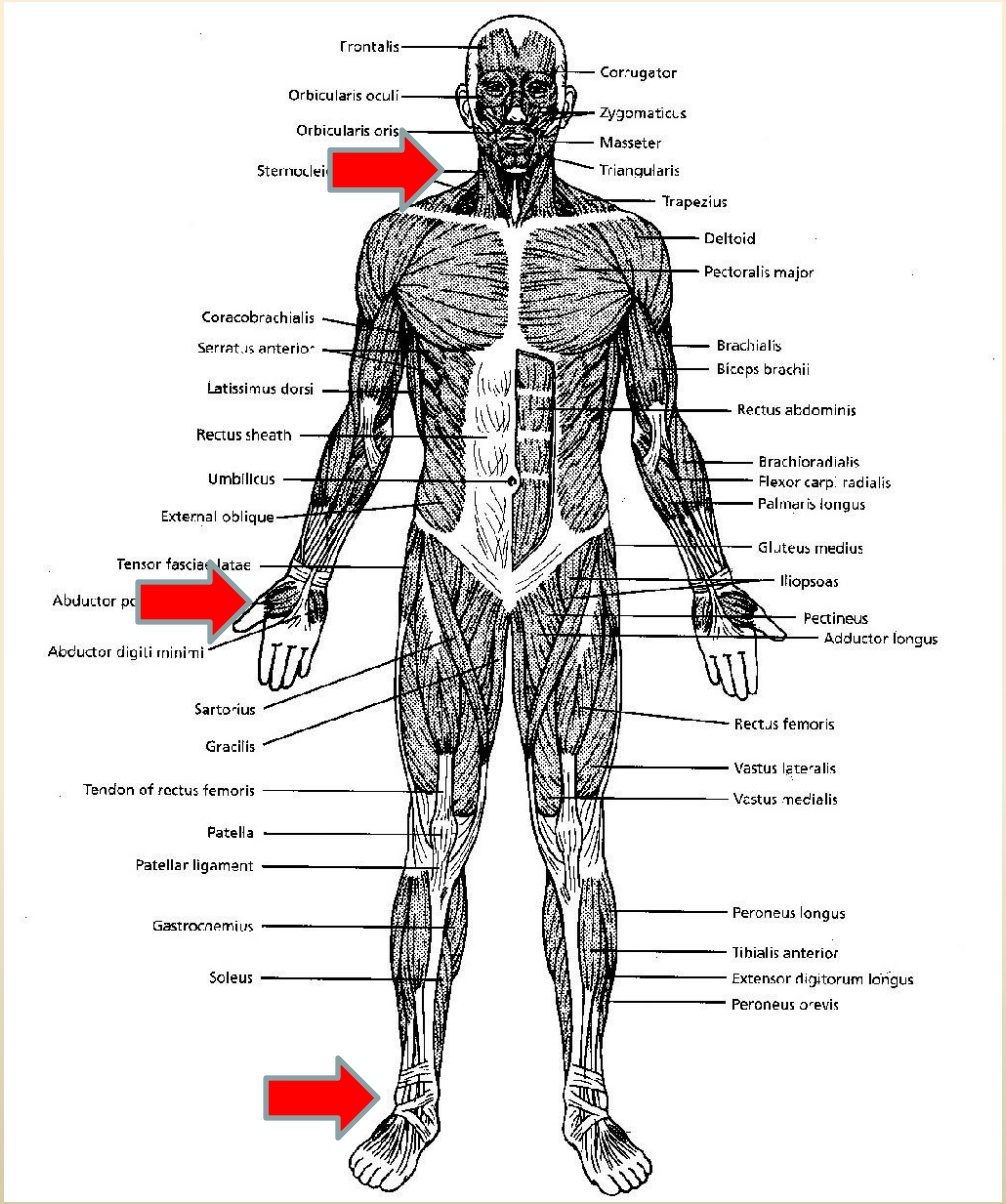
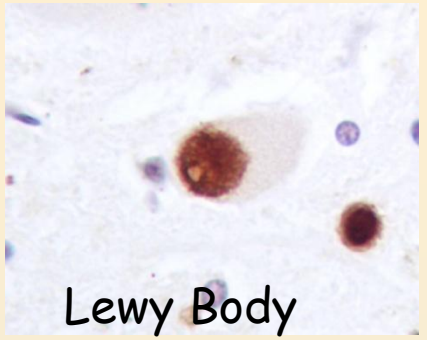
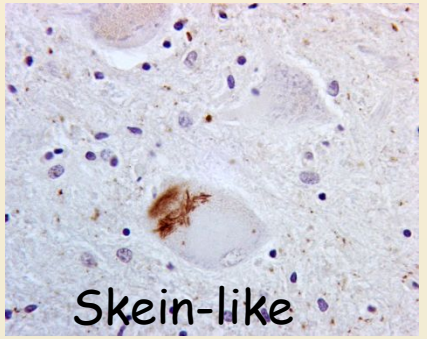
ALS

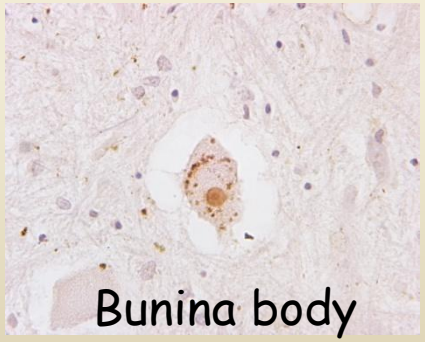


The duration of disease is at least partially a function of the speed with which muscle groups throughout the body weaken – end stage is reached when a ventilator is required to sustain life.

Perhaps the opportunity to determine whether a therapy can stop prion-like spreading.

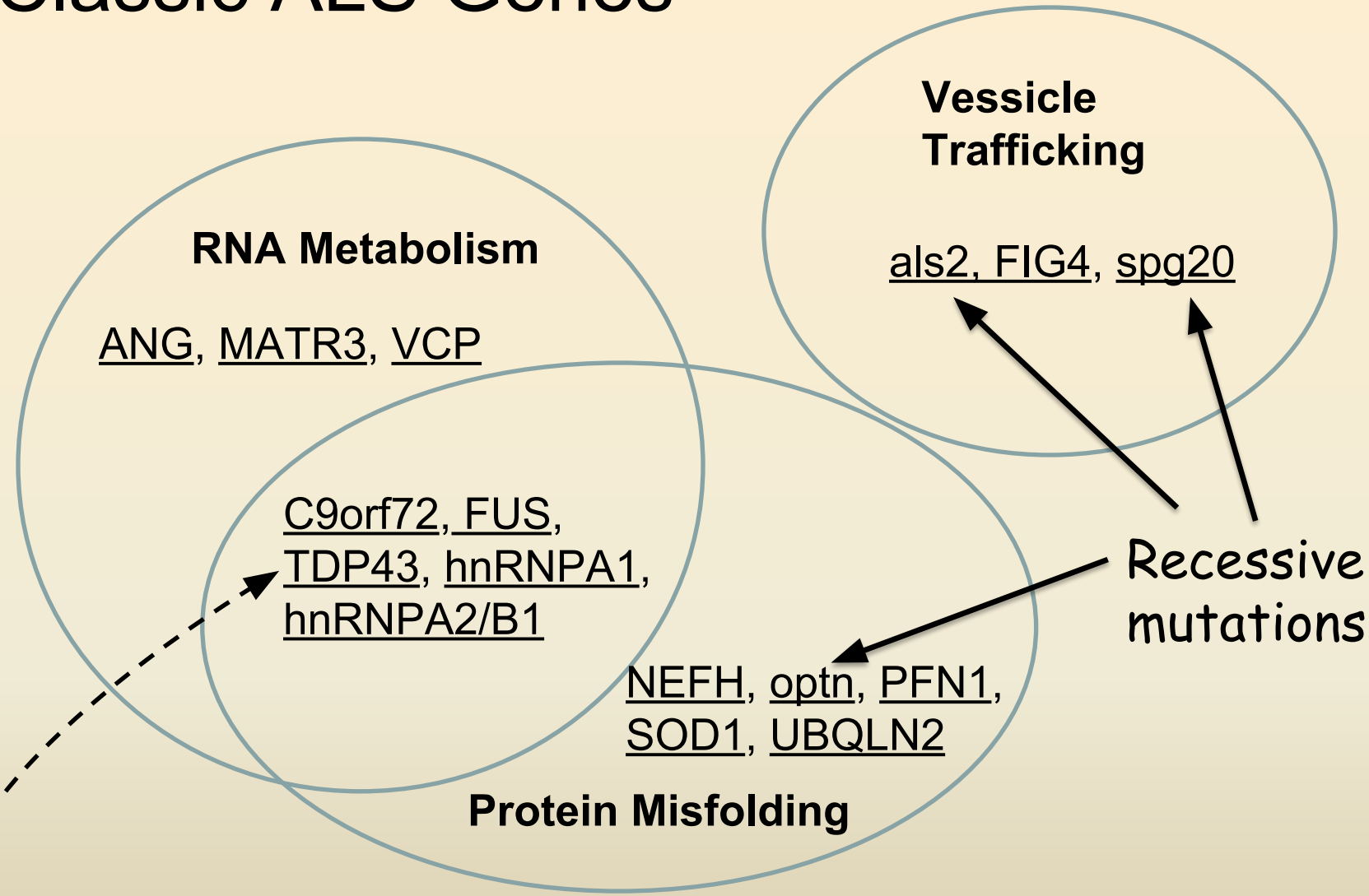

Lewy Body


Skein-like


Bunina body

Ubiquitin, neurofilament, TDP-43, Peripherin, Cystatin C, ubiquilin 2 SOD1 – (antibody-dependent)

Classic ALS Genes



80% of ALS – no identifiable mutation

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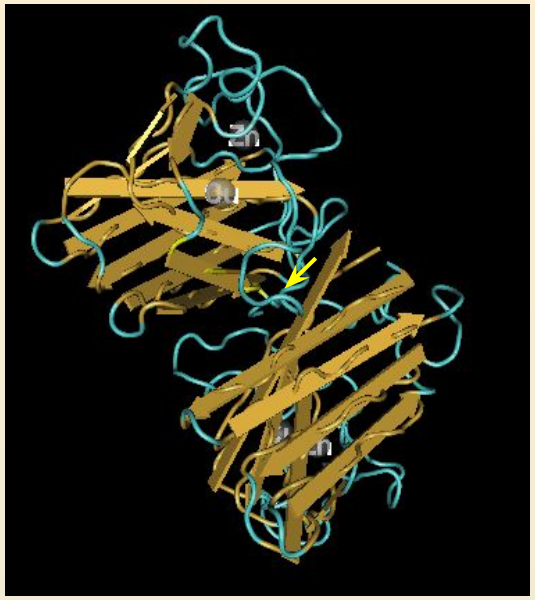
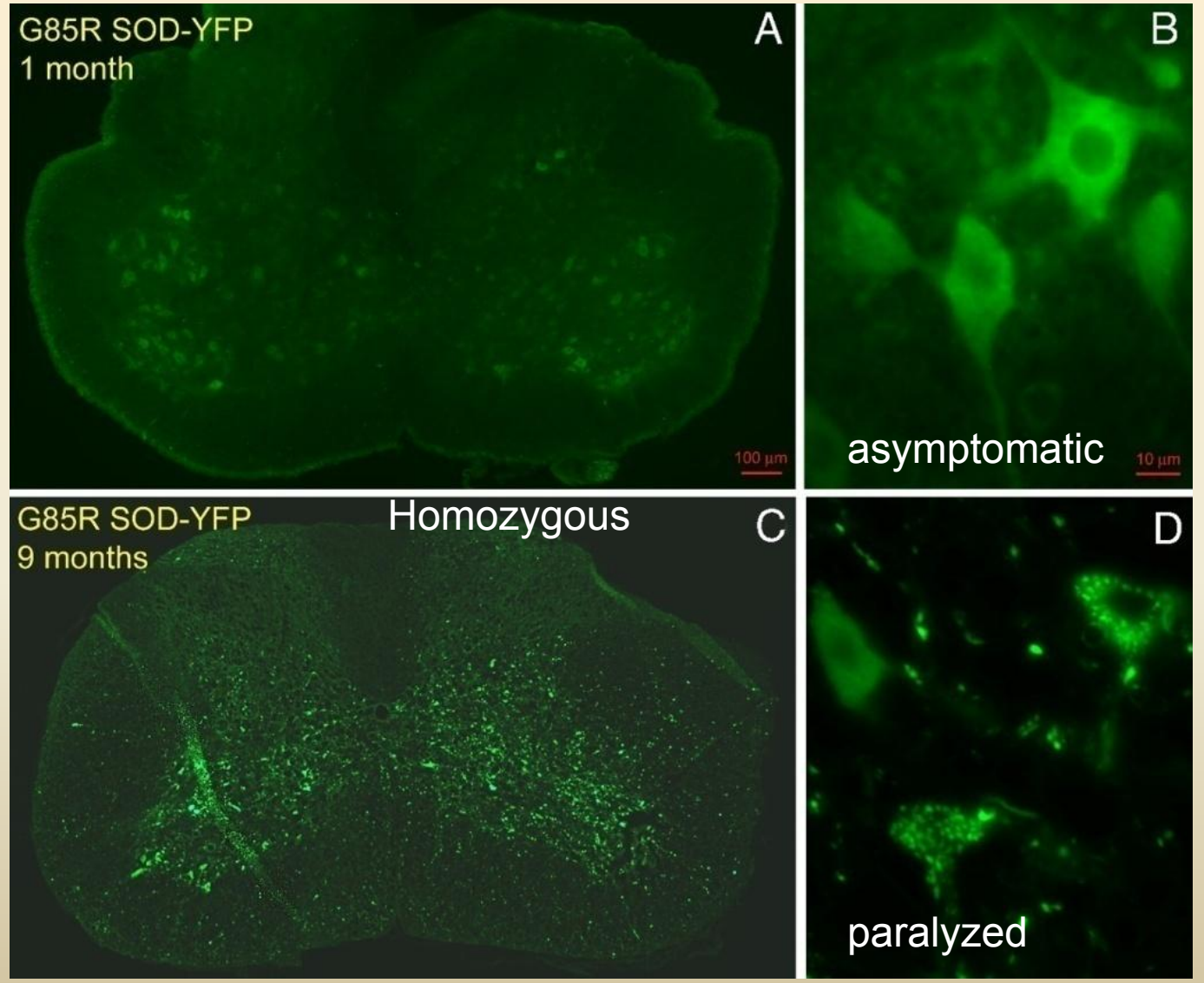
www.alsod.iop.kcl.ac.uk
www.genecards.org

Aggregation of mutant superoxide dismutase 1 mediates the symptoms of familial amyotrophic lateral sclerosis.



Homodimeric highly stable and soluble enzyme. Ubiquitously expressed.

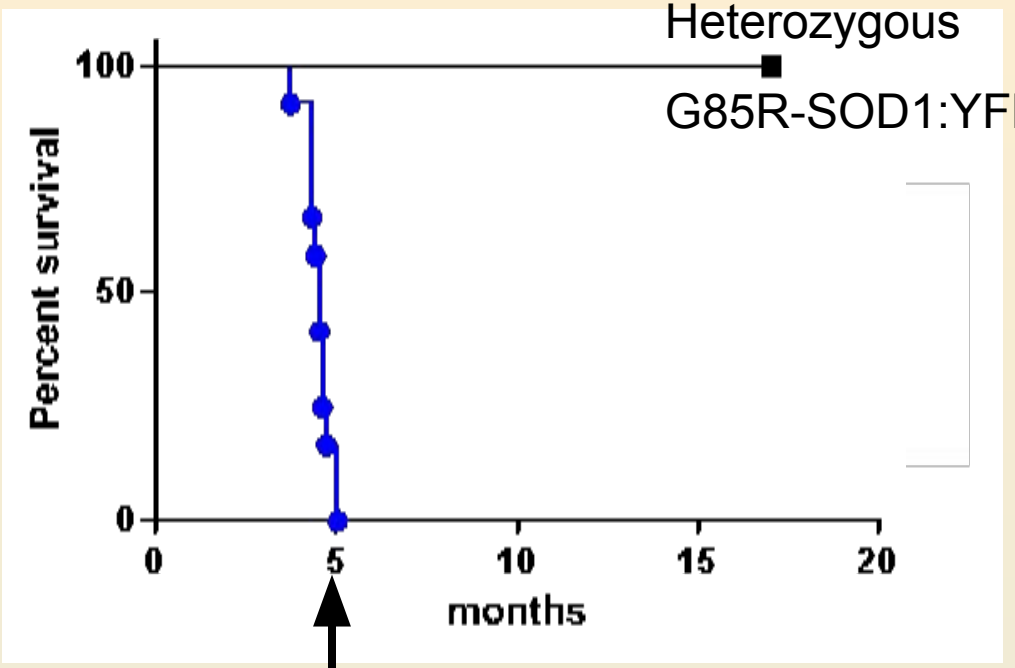
Transgenic mice that express human SOD1 fused to Yellow fluorescent protein

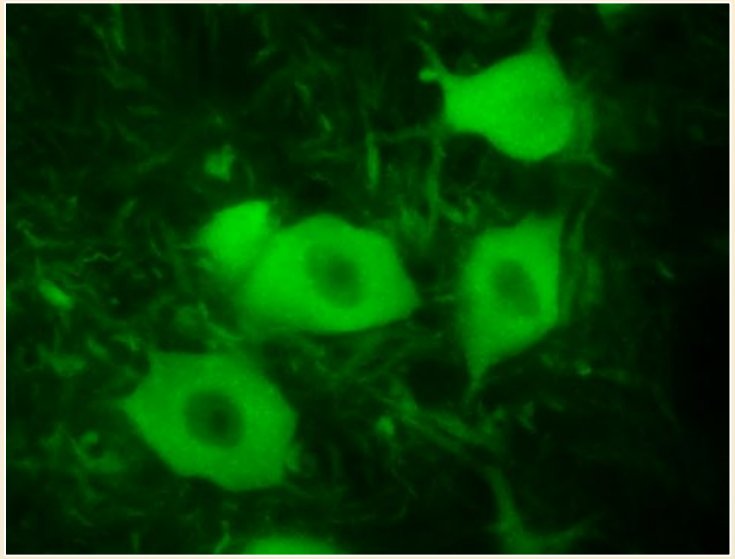


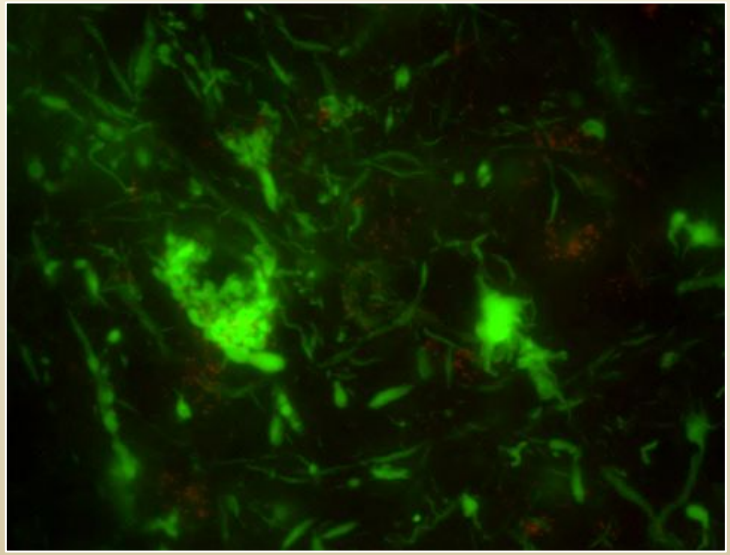
Detergent-insoluble

Wang et al, PNAS 2009

Crossing mice expressing G93A SOD1 to G85R-SOD1:YFP mice accelerates disease onset and pathology







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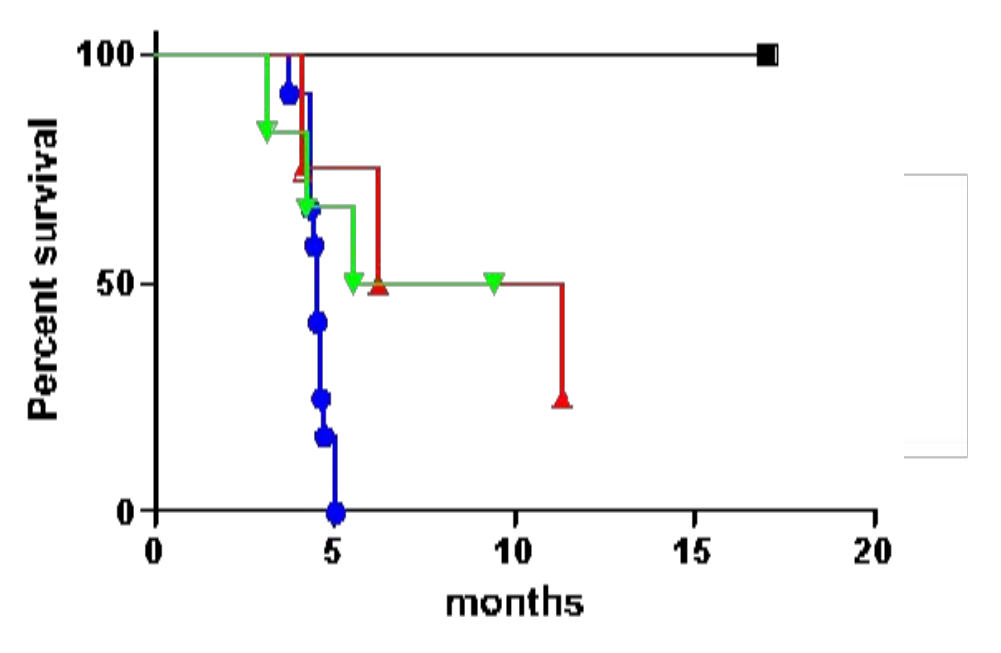
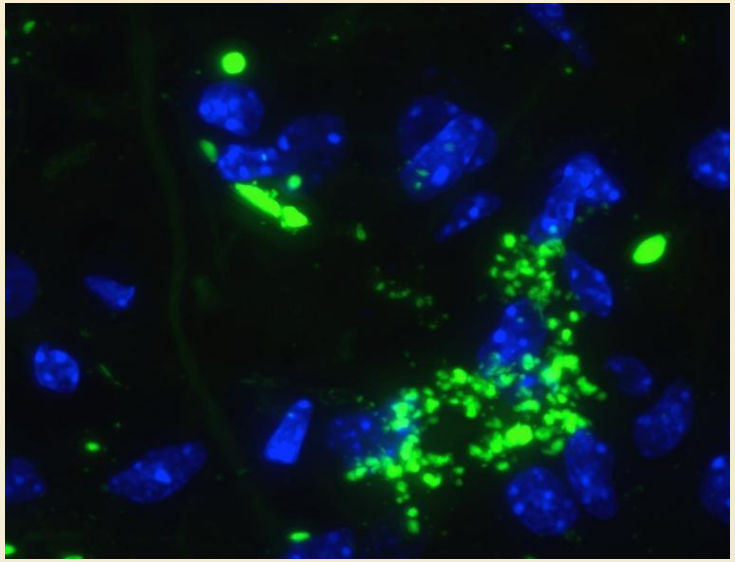
Transmissibility of MND in G85R-YFP mice



Pathology induced by tissue homogenate from paralyzed G93A mouse



A large number of non-Tg mice have been injected as littermate controls – none have ever shown any symptoms

Accelerated MND in 2 of 15 mice injected with tissue homogenates from paralyzed G37R mice, and in 2 of 4 mice injected with tissue homogenates from paralyzed L126Z mice.

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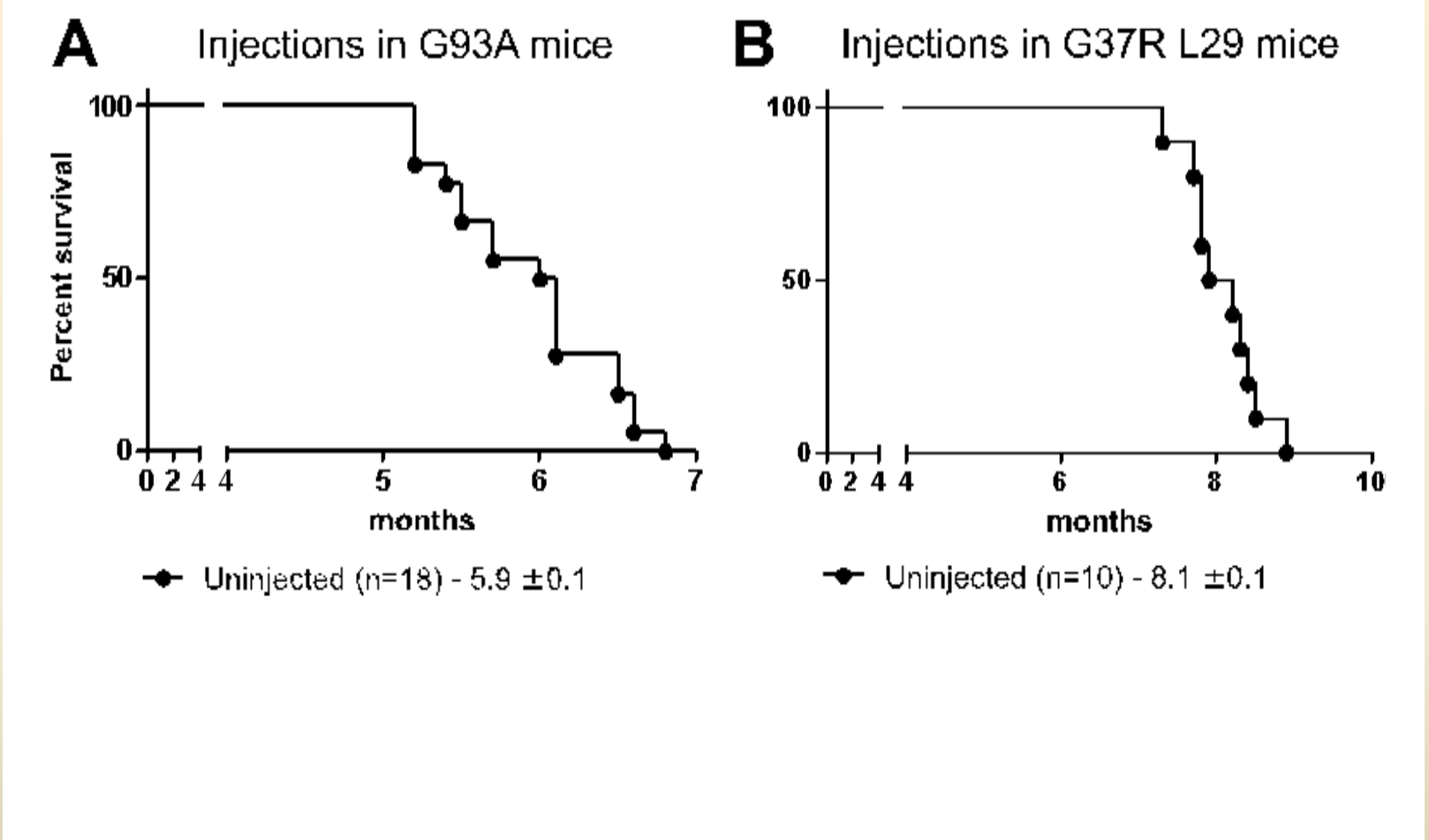
The onset of MND in mice expressing G93A or G37R human SOD1 is not accelerated by autologous seeding.



Intraspinal injection of newborn mice.

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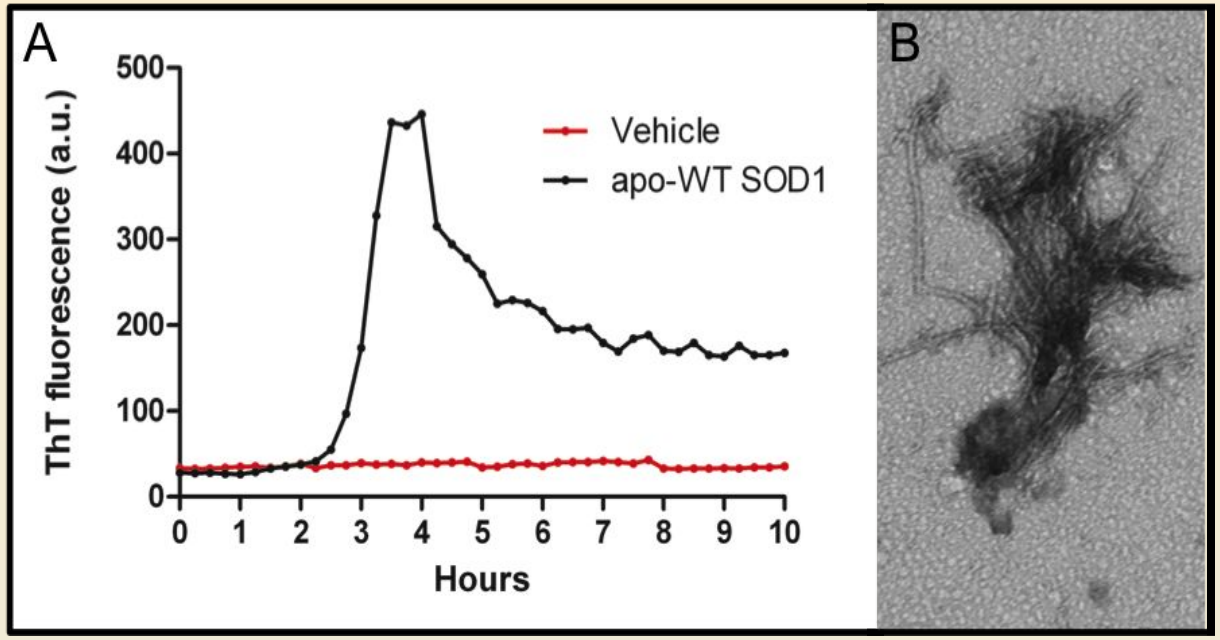
Transmission of MND by recombinant apoWT fibrils



- De-metallated WT SOD1 isolated from human erythrocytes fibrillized *in vitro* – injected into spinal cords of new born G85R-SOD1:YFP mice.

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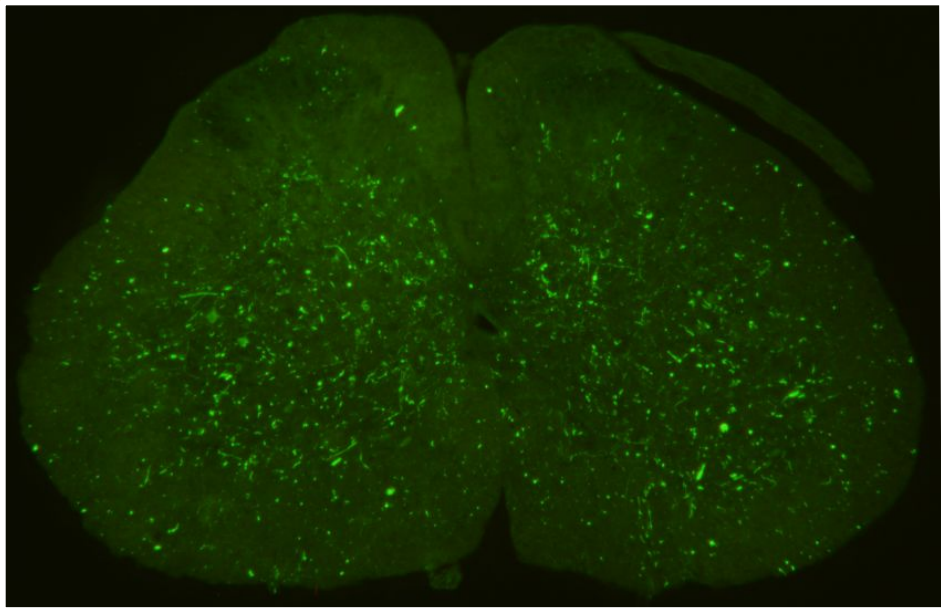
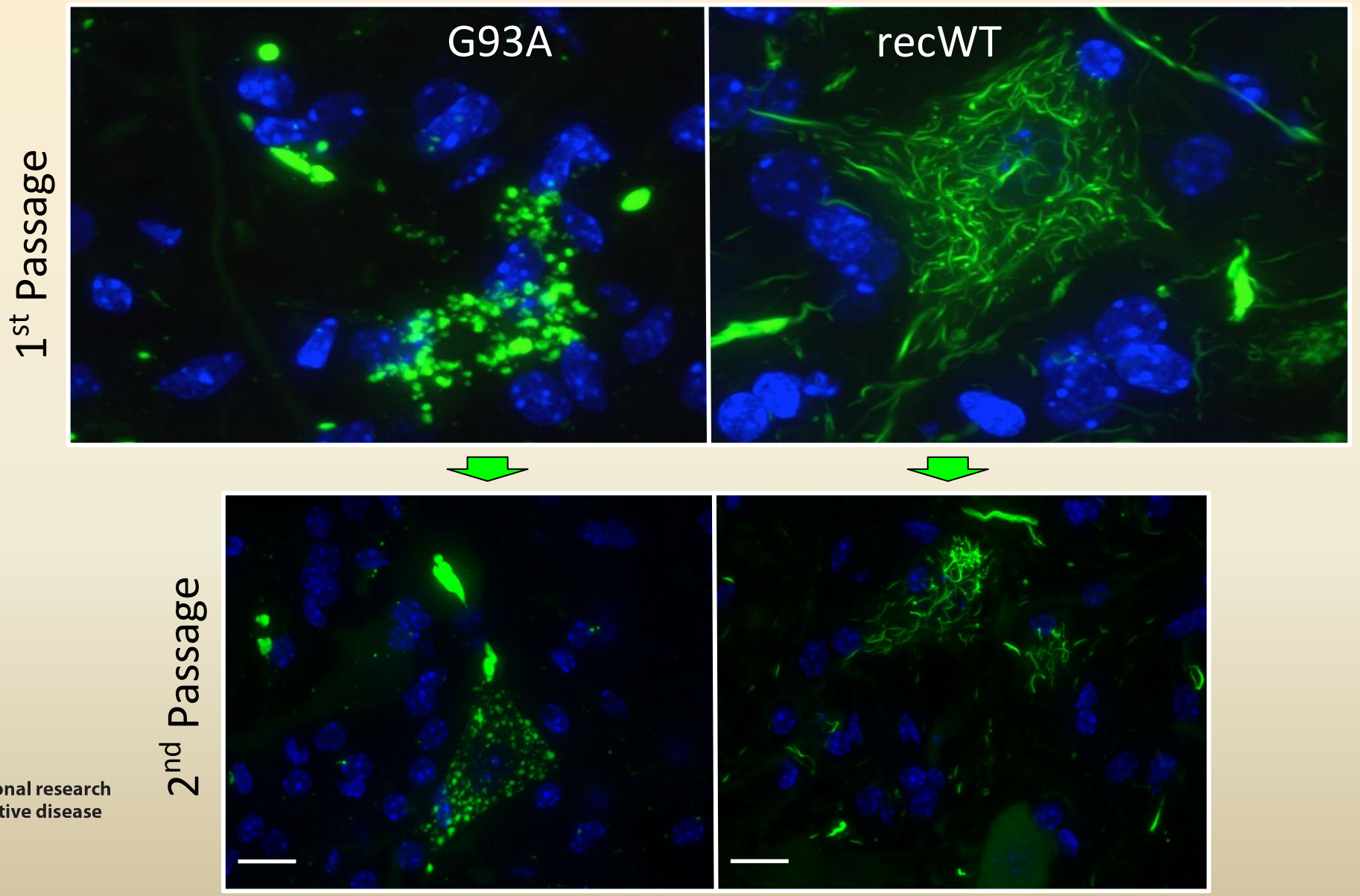
Transmission of MND by recombinant apoWT fibrils



Inoculum	No. disease/no. inoculated	Age at paralysis (months)	Age of oldest disease-free mice (months)
Recomb. apoWT fibrils	5/6	5, 8.6, 9.8, 11, 11.5, 15	20
apoWT→G85R-YFP	10/10	3.3-4.2	n.a.
Non-injected G85R-YFP	0/5	n.a.	10.2

Distinct pathologic strains of misfolded SOD1 maintain distinctive features in successive transmission experiments.



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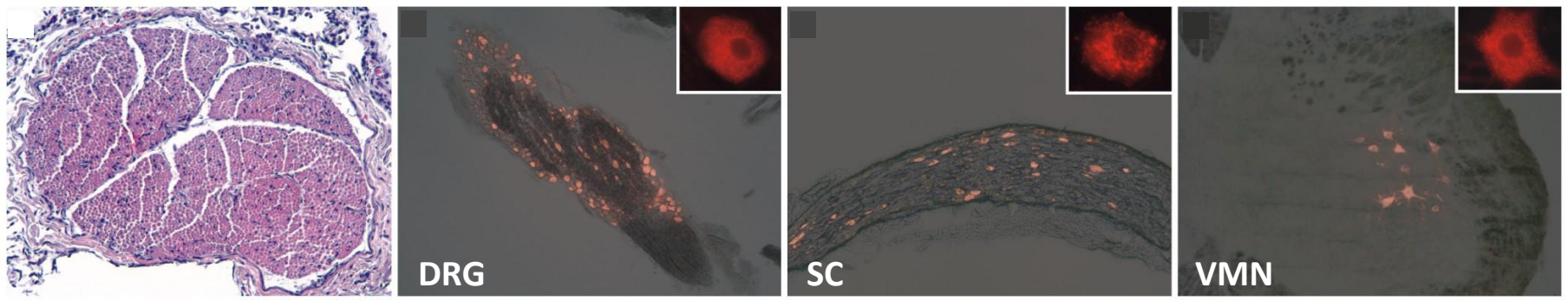
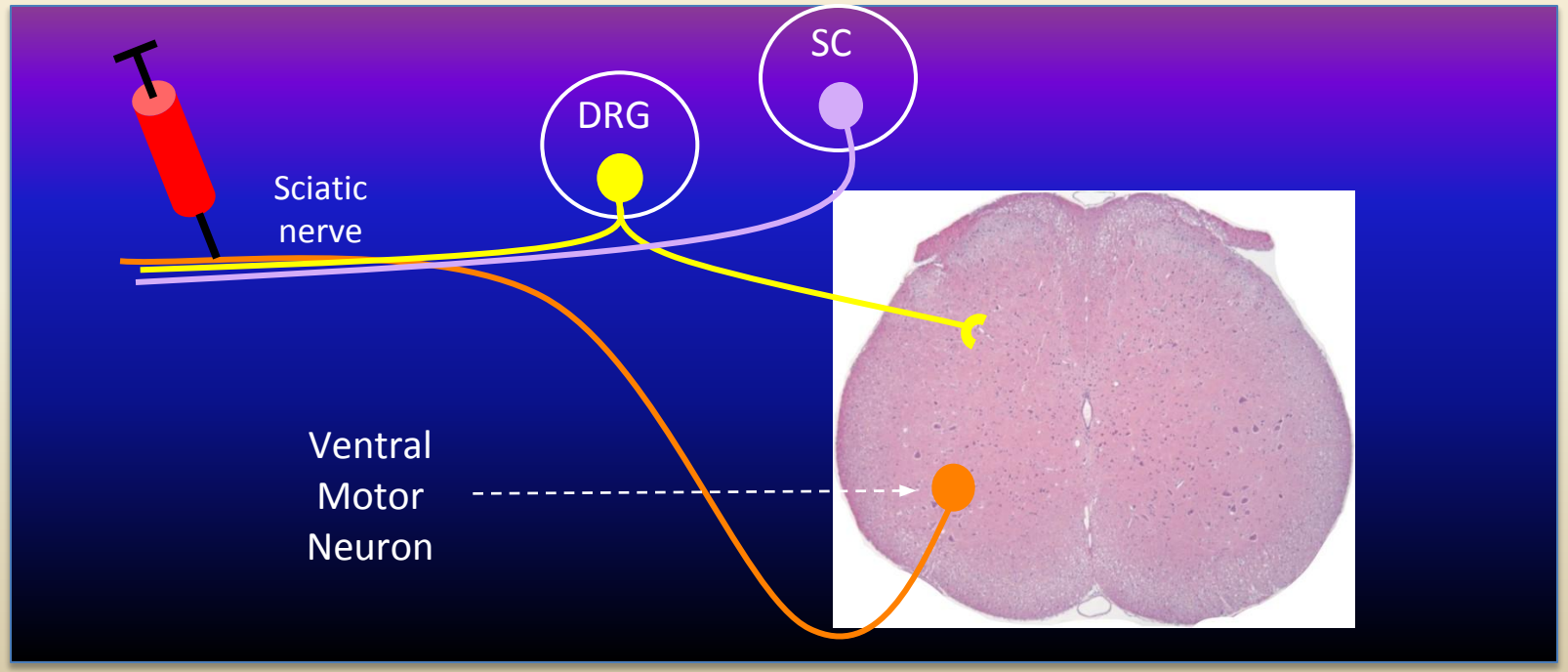
Prion infection from sciatic nerve inoculation





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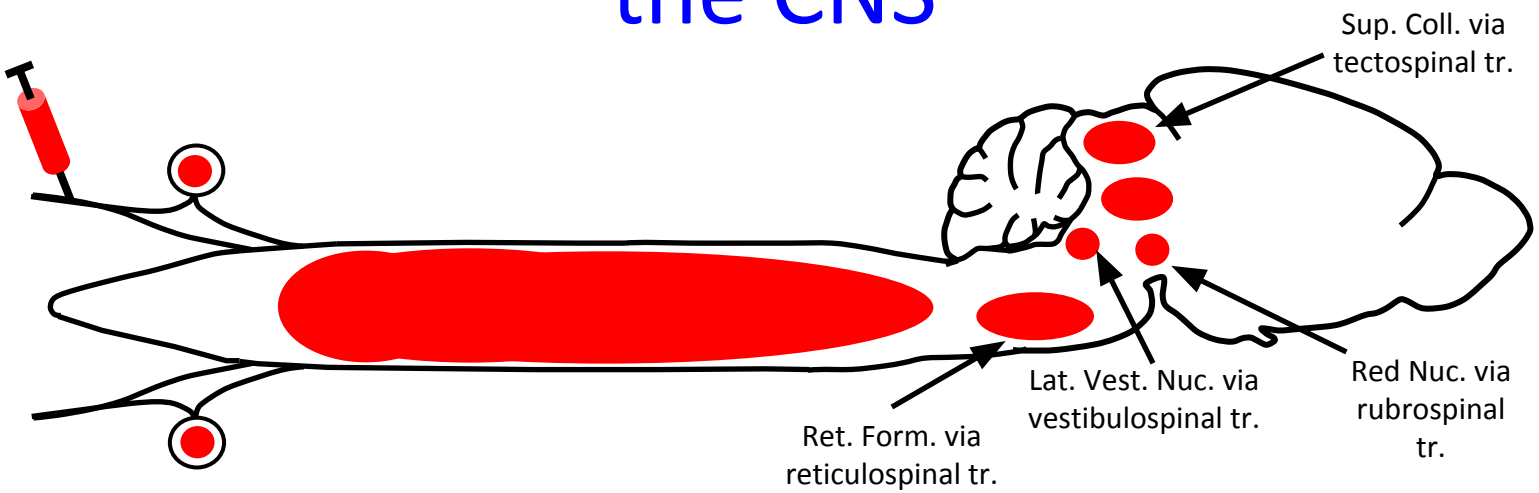
Propagation of G85R-YFP aggregation in the CNS



	1 month	2 month-asym	2 month-sym	End-stage
Spinal Cord				
Lumbar	-	++	+++	+++
Thoracic	-	+	++	+++
Cervical	-	+	+	+++
Brain				
Ret. Form.	-	+	++	+++
Lat. Vest. Nuc.	-	+	+	++
Red Nuc.	-	+	+	++
Periaq. gray	-	-	+	++
Sup. Coll.	-	-	+	++

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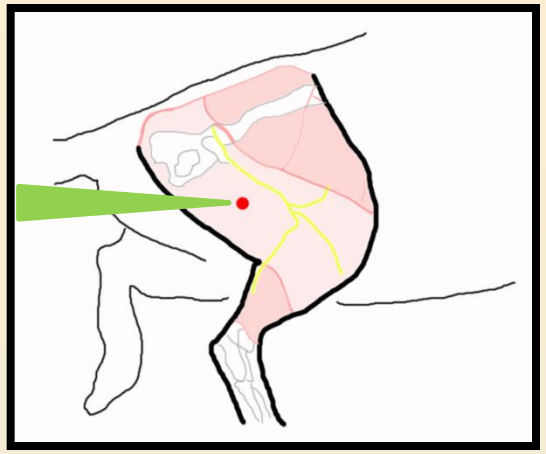
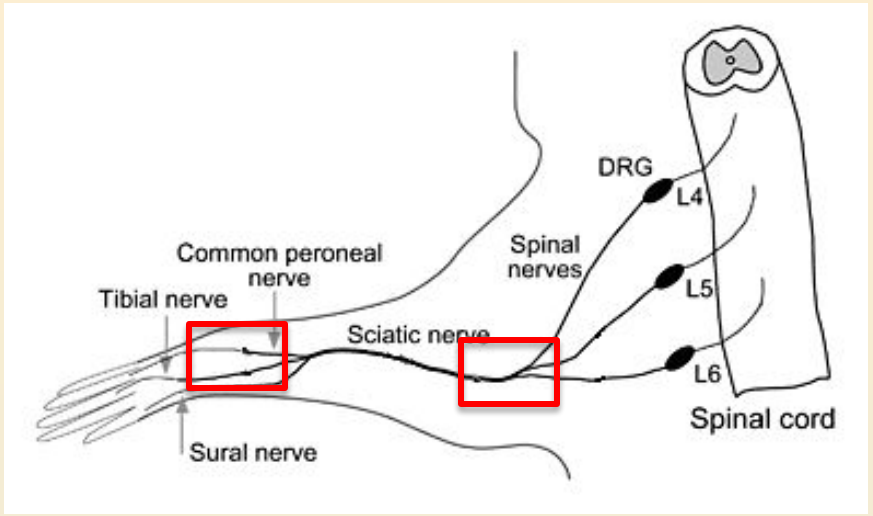
Peripheral Induction/Transmission of α-Synuclein Pathology in α-Synuclein Transgenic Mice

Injection site

Biceps femoris muscle
Gastrocnemius muscle

Unilateral
Bilateral





Inoculum prepared from purified aSyn expressed in E. coli

Mouse lines	Seeded Path
nTg	NO
αS-KO	NO
WT- M20	YES
A53T- M83	YES
E46K- M47	YES

Inoculum	Seeded Path
LPS	NO
Δ71-82	partial
FL WT αS mfib	YES
21-140 WT αS hfib	YES

Sacino et al, PNAS 2014

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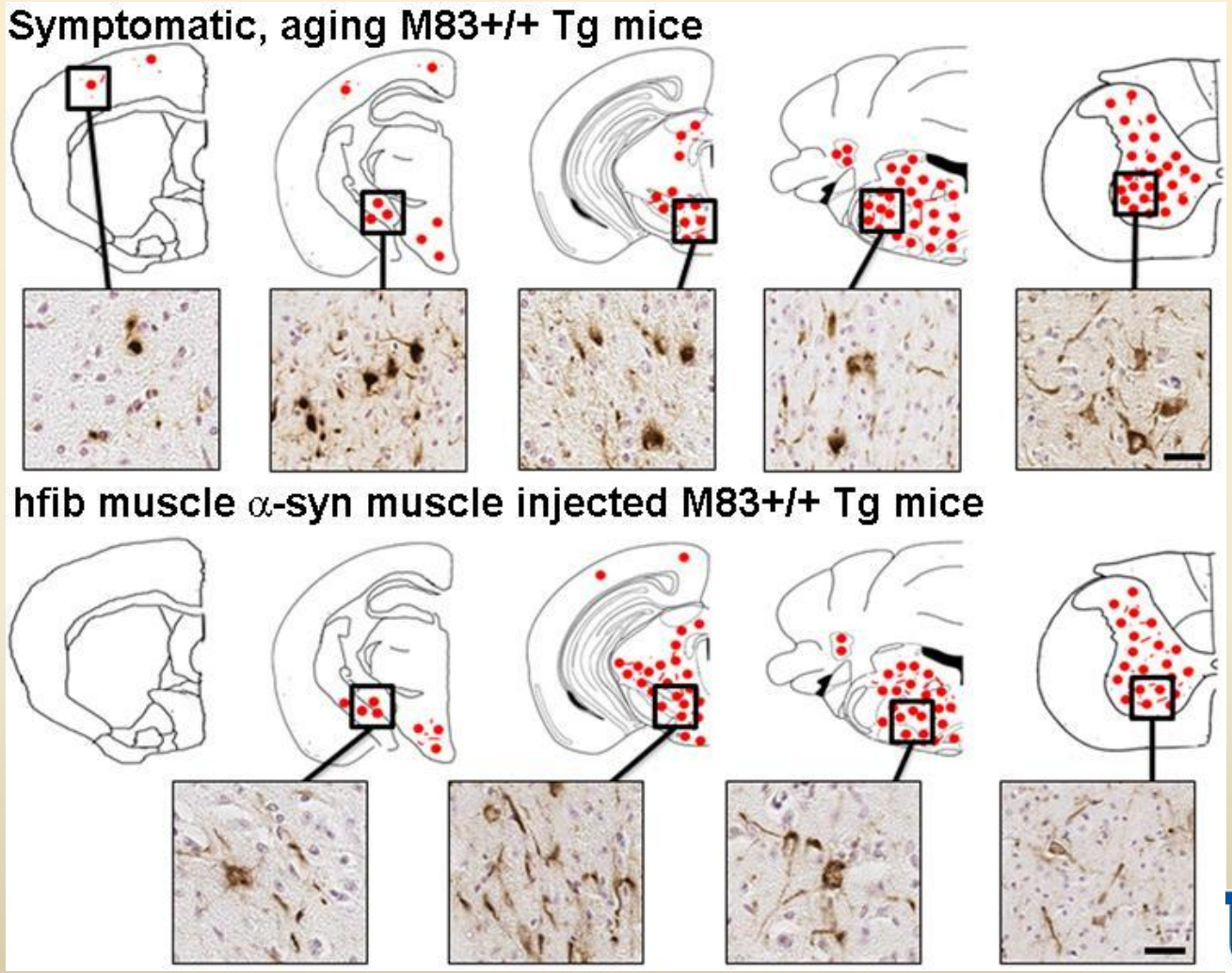
aSyn pathology in “induced” mice is similar to what naturally occurs in aged homozygous mice.



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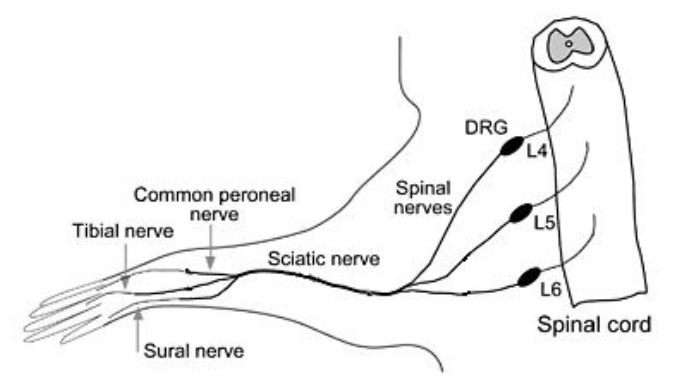
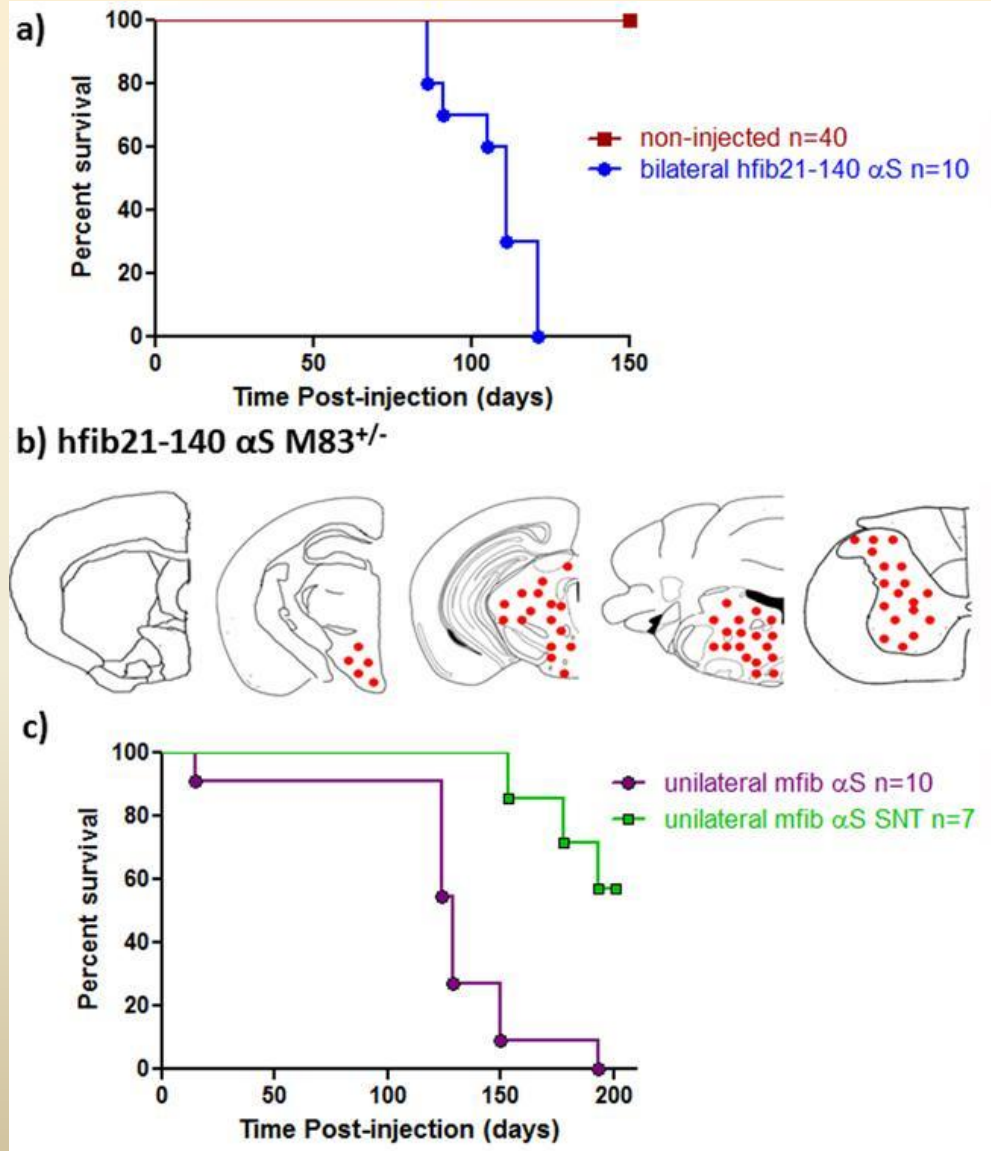
Significant Delay of Motor Phenotype and Inclusion Pathology Induced by Intramuscular α-Synuclein Injection Following Sciatic Nerve Transection of M83 (+/-) Transgenic Mice





Sacino et al, PNAS 2014

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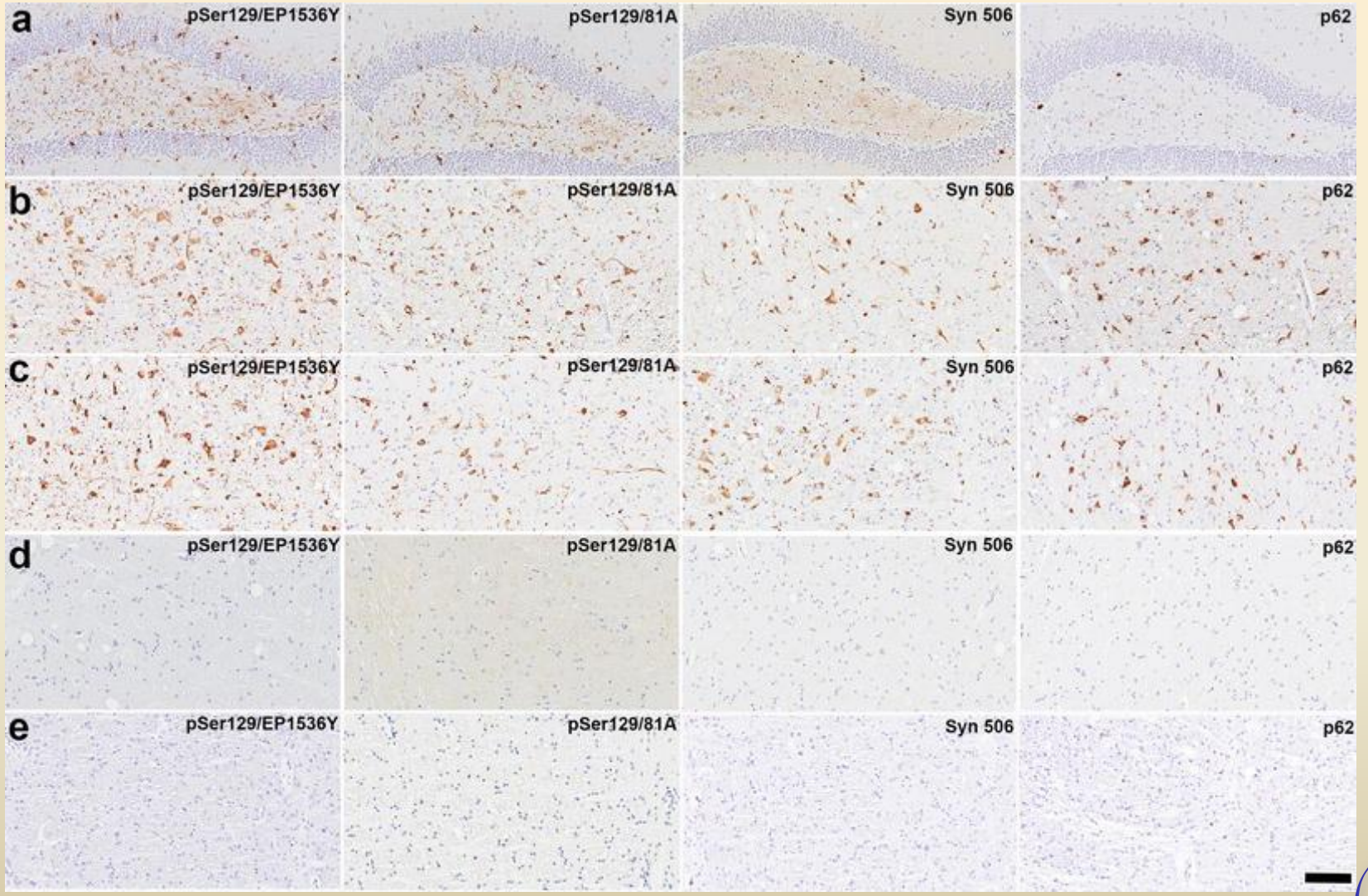
Controls are critical when tissue homogenates are used to seed pathology in A53T aSyn mice.

Non-prion-type induction of a-Syn pathology in A53T mice.



G93A SOD1 Sc

G93A SOD1 Sc

NTg Sc

NTg Cortex

Sham

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Prion-like transmission of misfolded and aggregated tau along interconnected neural circuits

Synthetic Tau Fibrils Mediate Transmission of Neurofibrillary Tangles in a Transgenic Mouse Model of Alzheimer's-Like Tauopathy

Michiyo Iba, Jing L. Guo, Jennifer D. McBride, Bin Zhang, John Q. Trojanowski, and Virginia M.-Y. Lee

The Journal of Neuroscience, January 16, 2013 • 33(3):1024–1037

Brain homogenates from human tauopathies induce tau inclusions in mouse brain

Florence Clavaguera[a], Hiroyasu Akatsu[b], Graham Fraser[c], R. Anthony Crowther[c], Stephan Frank[a], Jürgen Hench[a], Alphonse Probst[a], David T. Winkler[a,d], Julia Reichwald[e], Matthias Staufenbiel[e], Bernardino Ghetti[f], Michel Goedert[f], and Markus Tolnay[a,1,2]

PNAS | June 4, 2013 | vol. 110 | no. 23 |

Transmission and spreading of tauopathy in transgenic mouse brain

[illegible]ristan Bolmont[2], R. Anthony Crowther[3], Dorothee Abramowski[4], Stephan Frank[1], [illegible]am Fraser[3], Anna K. Stalder[5], Martin Beibel[4], Matthias Staufenbiel[4], Mathias Jucker[2] Michel Goedert[3,6,7] and Markus Tolnay[1,6,7]

NATURE CELL BIOLOGY VOLUME 11 | NUMBER 7 | JULY 2009

A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity

Zeshan Ahmed · Jane Cooper · Tracey K. Murray · Katya Garn · Emily McNaughton · Hannah Clarke · Samira Parhizkar · Mark A. Ward · Annalisa Cavallini · Samuel Jackson · Suchira Bose · Florence Clavaguera · Markus Tolnay · Isabelle Lavenir · Michel Goedert · Michael L. Hutton · Michael J. O'Neill

Acta Neuropathol (2014) 127:667–683

Peripheral administration of tau aggregates triggers intracerebral tauopathy in transgenic mice

Florence Clavaguera · Jürgen Hench · Isabelle Lavenir · Gabriel Schweighauser · Stephan Frank · Michel Goedert · Markus Tolnay

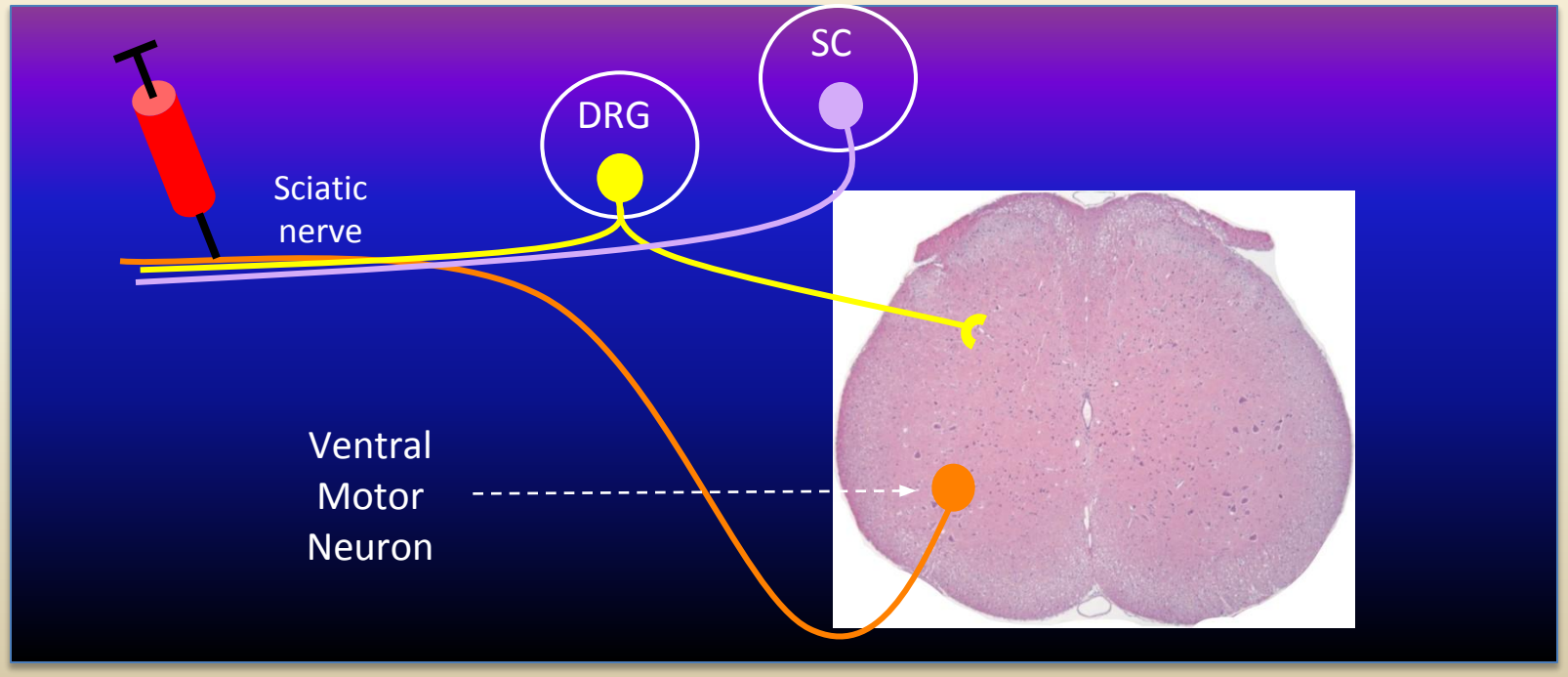
Acta Neuropathol (2014) 127:299–301

Distinct Tau Prion Strains Propagate in Cells and Mice and Define Different Tauopathies

David W. Sanders,[1,4] Sarah K. Kaufman,[1,4] Sarah L. DeVos,[1] Apurwa M. Sharma,[1] Hilda Mirbaha,[1] Aimin Li,[1] Scarlett J. Barker,[1] Alex C. Foley,[3] Julian R. Thorpe,[3] Louise C. Serpell,[3] Timothy M. Miller,[1] Lea T. Grinberg,[2] William W. Seeley,[2] and Marc I. Diamond[1,*]

Neuron 82, 1271–1288, June 18, 2014

Ayers and Giasson labs are working to establish the sciatic nerve transmission model in P301S mice.



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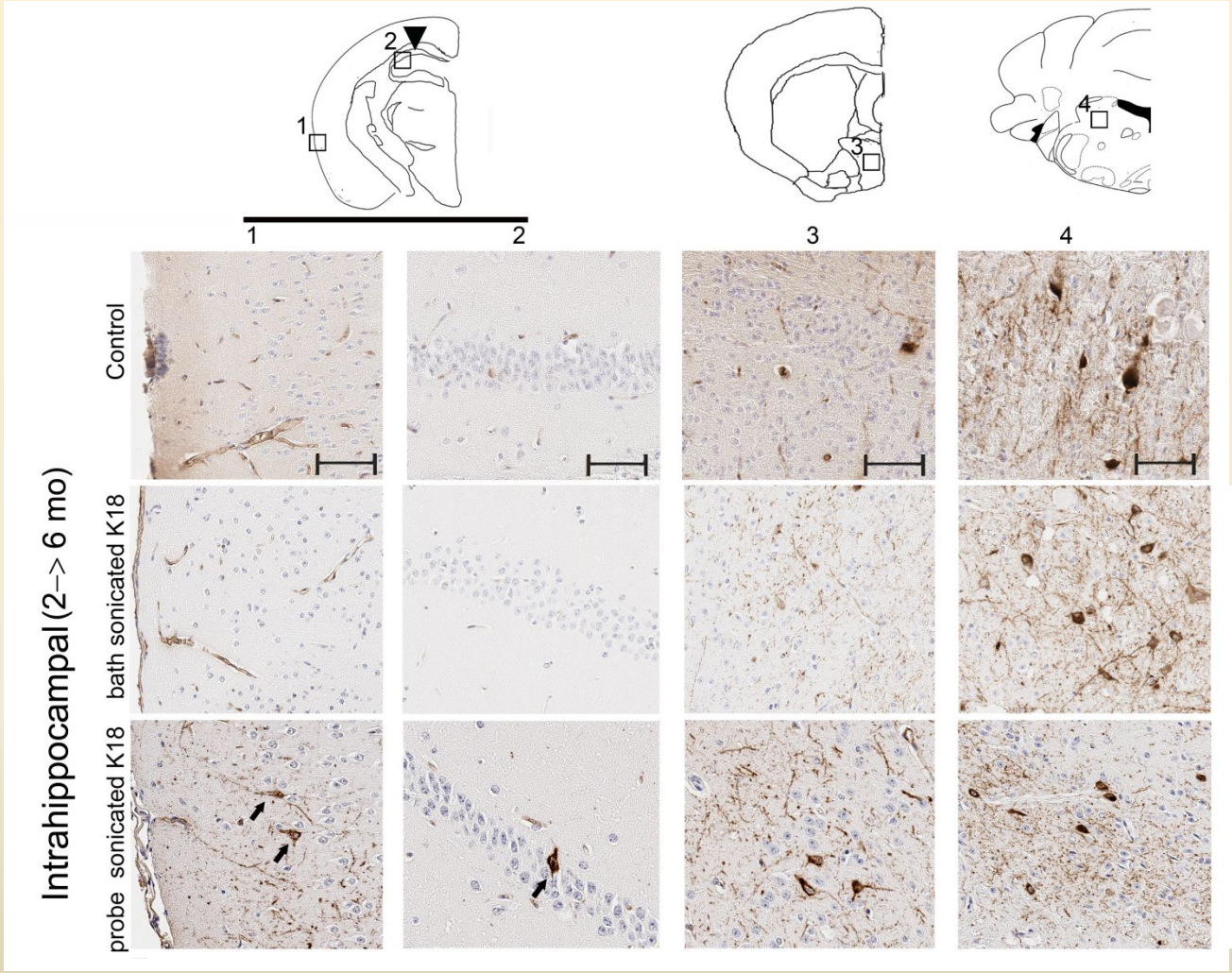
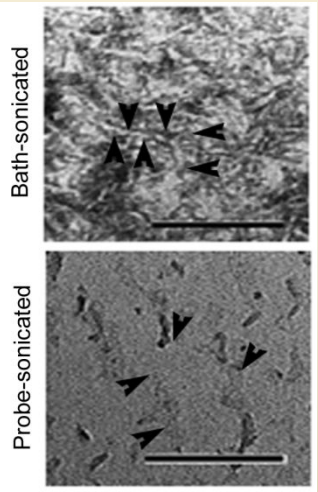
Hippocampal injection of probe-sonicated K18/WT induces limited tauopathy in hP301L mice (PrP vector JNPL3)



K18 – all 4 repeats of 4R human tau – expressed and purified from E. coli.

EM analysis of sonicated K18 fibrils



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Chakrabarty et al. (2015). Inefficient induction and spread of seeded tau pathology in P3 suggests inherent barriers to transmission. Acta Neuropathologica

Comparison of seeding by amyloid in non-demented and Alzheimer brain: Is there a distinct strain of amyloid in non-demented cases?

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The ability to inject aggregated SOD1, aSyn, or tau in a peripheral nerve location and induce the spread of pathology to the brain is consistent with prionic mechanisms of spread.

These new models enable rigorous testing of therapeutic strategies (such as immunotherapy) that are designed to slow the progression of neurodegenerative disease. With a known point of attack, timing of onset, and route of transmission, it should be possible to determine whether a therapeutic can effectively slow the spread of pathology and progression of disease.

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- Yona Levites
- Brenda Moore
- Todd Golde
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National Institutes on Aging

National Institute of Neurological Disease and Stroke

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