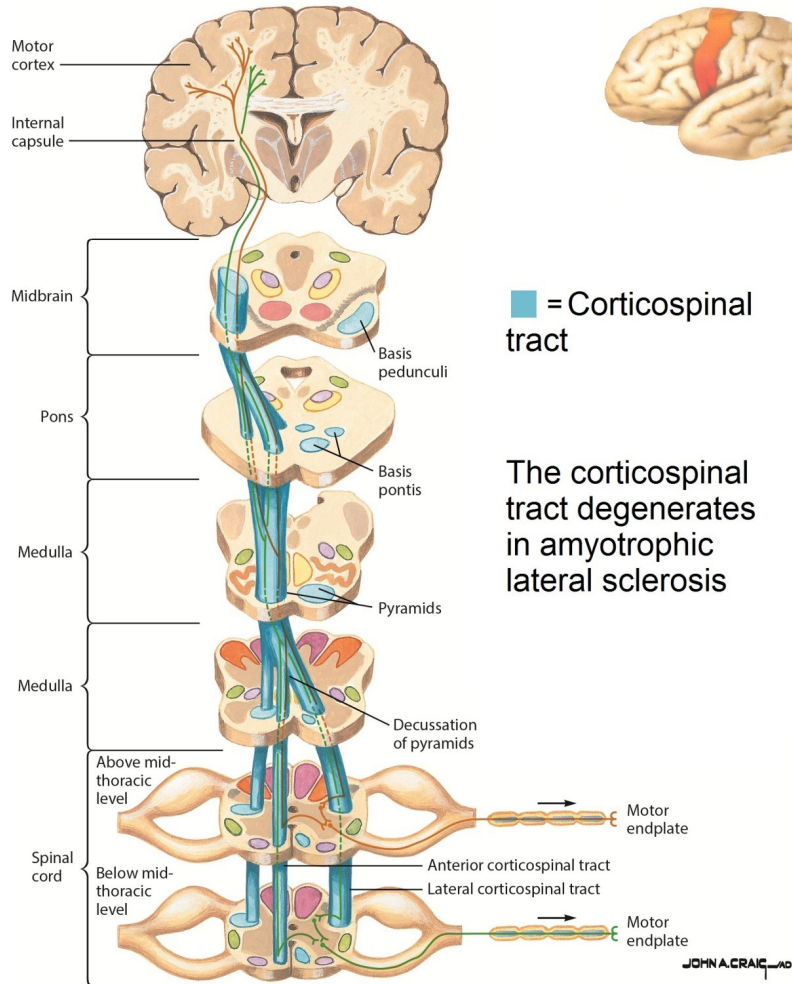


Updates in preclinical ALS research – globally and at KI

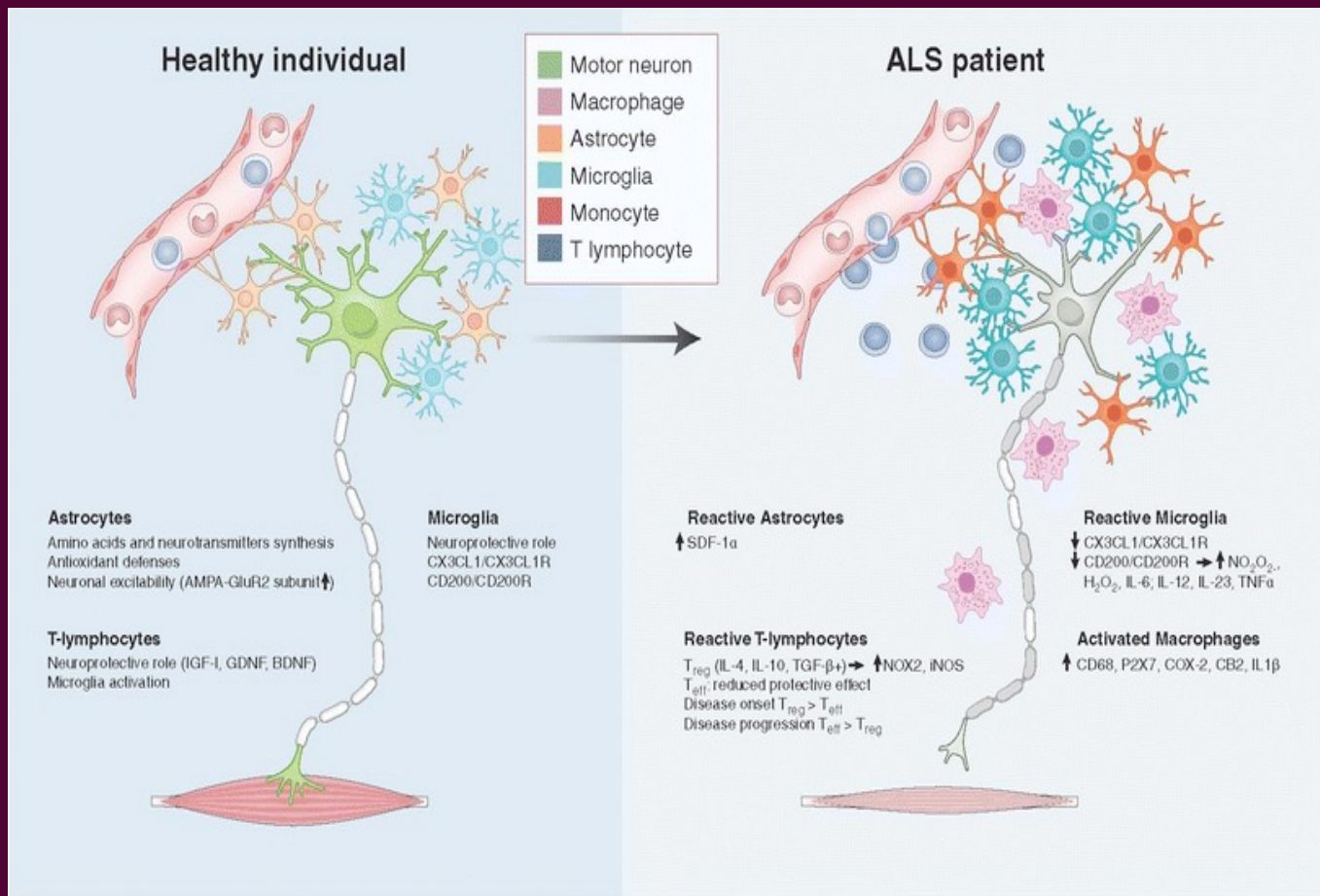
Prof Bob Harris

Applied Immunology & Immunotherapy

ALS



Different pathologies
and cells in different
regions of the spinal cord?



Activated immune cells negatively affect motoneurons so that they lose contact with the muscle

RESEARCH QUESTIONS

Why does ALS occur?

What are the disease mechanisms?

How can we slow or stop them?

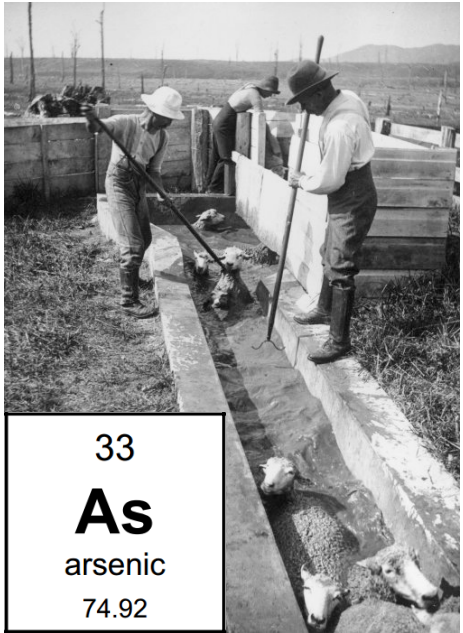
RESEARCH QUESTIONS

Why does ALS occur?

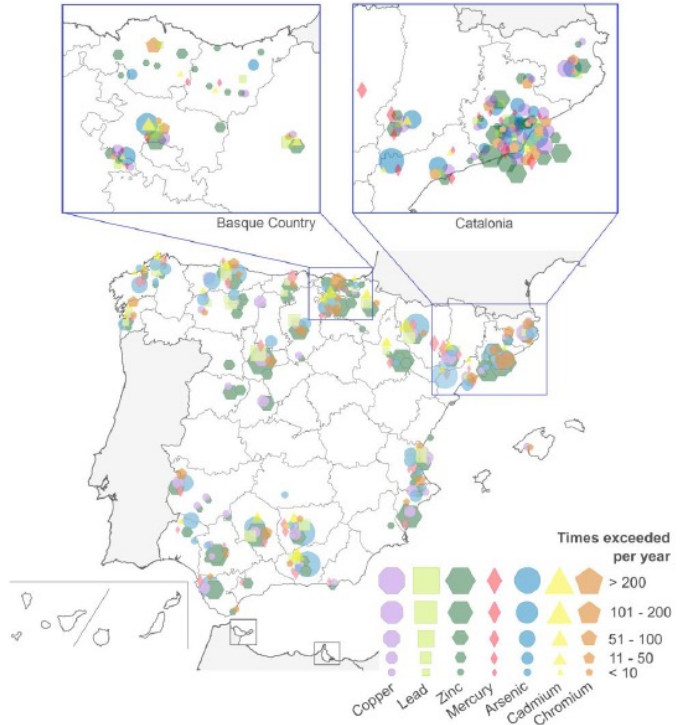
What are the disease mechanisms?

How can we slow or stop them?

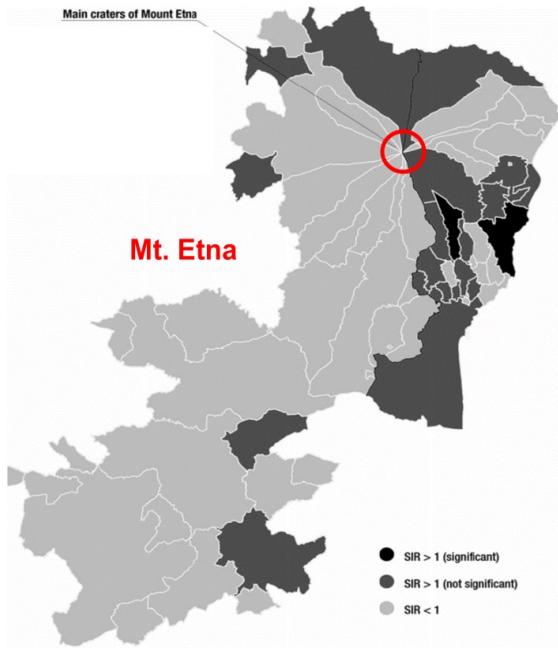
Does metal exposure cause ALS?



Sheep workers
New Zealand



Metal factories
Spain



Mount Etna volcano
Italy

Exposure to metals in the environment is associated with higher ALS incidence

Exposure to metals

- Respiratory Mount Etna; Mn, As, V, U
- Orally Water, Food
- Skin Makeup, Skin cream
- Dental Amalgam fillings; Cu, Hg
- IUD Copper spiral; Cu
- Medical Surgical Bone pins; Fe, Co, Mn, As
Hip replacement; Cr, Co, Ni, Ti, Mo

* Tracy L. Peters, Caroline E. Weibull et al. *Association of Fractures with the Incidence of Amyotrophic Lateral Sclerosis*. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017 August ; 18(5-6): 419–425.

Identity	Element								
	Al	V	Mn	Co	Cu	Zn	Cd	Pb	U
ALS 173									
ALS 200	▼		▼	◦			▼	▼	▼
ALS 202									
ALS 204									
ALS 208	▼								
ALS 209									▼
ALS 386	▼				◦				▼
ALS 422	▼	◦	▼	◦	◦	◦	▼	▼	▼
ALS 485								▼	
ALS 554									
ALS 644									▼
ALS 648								▼	▼
ALS 649					◦	◦	▼	▼	▼
ALS 734	▼	◦	▼	◦	◦	◦	▼		
ALS 871			▼			◦	▼		▼
ALS 926			▼		◦		▼		
ALS 977									
Ctrl 233									
Ctrl 242									
Ctrl 407									
Ctrl 504									
Ctrl 603									
Ctrl 661									
Ctrl 792									
Ctrl 793									
Ctrl 852						◦		▼	
Ctrl 948									

Neurotoxic metals are significantly elevated in ALS CSF, but not in ALS blood plasma

Clinical correlates of neurotoxicity

Aluminium	Injected mice show motor neuron degeneration.
Vanadium	Intoxication causes death preceded by hind limb paralysis.
Manganese	Elevated concentrations in ALS spinal cord sections.
Cobalt	Neuron death in cell cultures.
Copper	Case report of ALS with elevated Cu plasma concentrations.
Zinc	No association to ALS described.
Cadmium	Guam ALS elevated Cd. Case report of ALS after Cd exposure.
Lead	Several studies show elevated Pb in ALS. Several case reports.
Uranium	No connection to ALS previously reported.

Roos Per M et al. *Metal concentrations in cerebrospinal fluid and blood plasma from patients with amyotrophic lateral sclerosis*. *Biological Trace Element Research*. 2013. Feb;151(2):159-170.



Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Copper delivery to the CNS by CuATSM effectively treats motor neuron disease in SOD^{G93A} mice co-expressing the Copper-Chaperone-for-SOD



Jared R. Williams^a, Emiliano Trias^{b,c}, Pamela R. Beilby^a, Nathan I. Lopez^a, Edwin M. Labut^a, C. Samuel Bradford^a, Blaine R. Roberts^d, Erin J. McAllum^{d,e}, Peter J. Crouch^{d,e}, Timothy W. Rhoads^{a,1}, Cliff Pereira^f, Marjatta Son^g, Jeffrey L. Elliott^g, Maria Clara Franco^h, Alvaro G. Estévez^h, Luis Barbeito^c, Joseph S. Beckman^{a,*}

> [Neuropathol Appl Neurobiol.](#) 2023 Aug;49(4):e12919. doi: 10.1111/nan.12919.

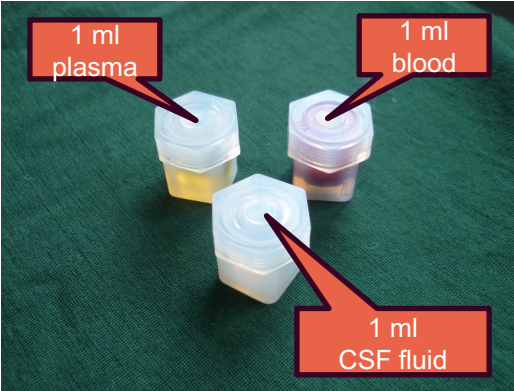
Treatment with the copper compound CuATSM has no significant effect on motor neuronal pathology in patients with ALS

Yue Yang^{1 2}, Dominic Rowe³, Heather McCann⁴, Claire E Shepherd⁴, Jillian J Kril^{2 5}, Matthew C Kiernan^{1 6}, Glenda M Halliday^{1 2}, Rachel H Tan^{1 2}

While copper treatment was beneficial in ALS mice, it was not in ALS patients



Measuring metals and altering metal balance



Blood & CSF



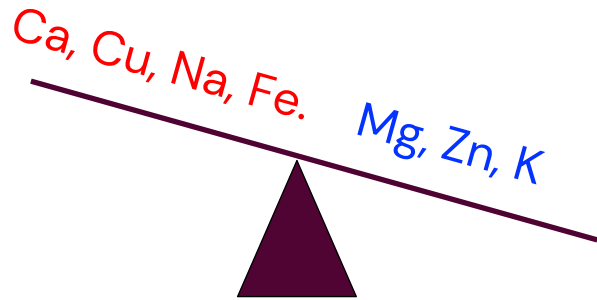
Hair sample



Bone biopsy



X-ray fluorescence



RESEARCH QUESTIONS

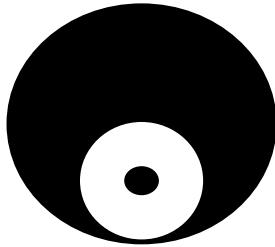
Why does ALS occur?

What are the disease mechanisms?

How can we slow or stop them?

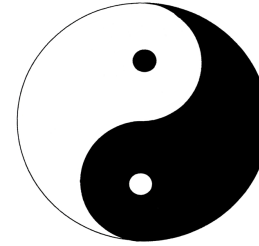
Genetic difference in immune cell activation states

PROINFLAMMATORY



ANTI-INFLAMMATORY

PROINFLAMMATORY



ANTI-INFLAMMATORY

GENETICALLY SUSCEPTIBLE



GENETICALLY RESISTANT



Inbalance in proinflammatory/anti-inflammatory immune reactions (left panel) occurs in ALS

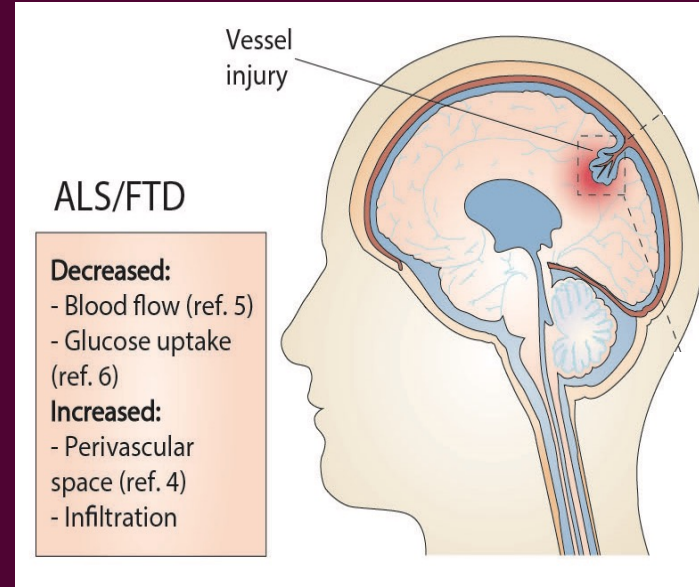
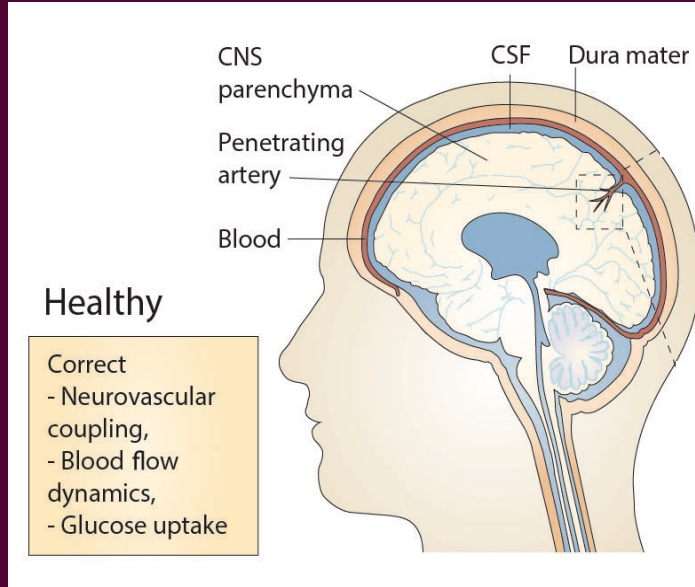


Altered perivascular fibroblast activity precedes ALS disease onset

Anna Månberg ^{1,21}, Nathan Skene^{2,3,4,21}, Folkert Sanders⁵, Marta Trusohamn ², Julia Remnestål¹, Anna Szczepińska⁵, Inci Sevval Aksoylu⁵, Peter Lönnerberg², Lwaki Ebarasi⁶, Stefan Wouters ⁵, Manuela Lehmann⁷, Jennie Olofsson ¹, Inti von Gohren Antequera⁵, Aylin Domaniku ⁵, Maxim De Schaepdryver ⁸, Joke De Vocht⁹, Koen Poesen^{8,10}, Mathias Uhlén ^{11,12}, Jasper Anink¹³, Caroline Mijnsbergen¹³, Hermieneke Vergunst-Bosch¹⁴, Annemarie Hübers^{15,20}, Ulf Kläppe ¹⁶, Elena Rodriguez-Vieitez¹⁷, Jonathan D. Gilthorpe ⁷, Eva Hedlund ¹², Robert A. Harris ⁵, Eleonora Aronica¹³, Philip Van Damme ⁹, Albert Ludolph^{15,18}, Jan Veldink ¹⁴, Caroline Ingre^{16,19}, Peter Nilsson ¹ and Sebastian A. Lewandowski ^{1,5} ✉

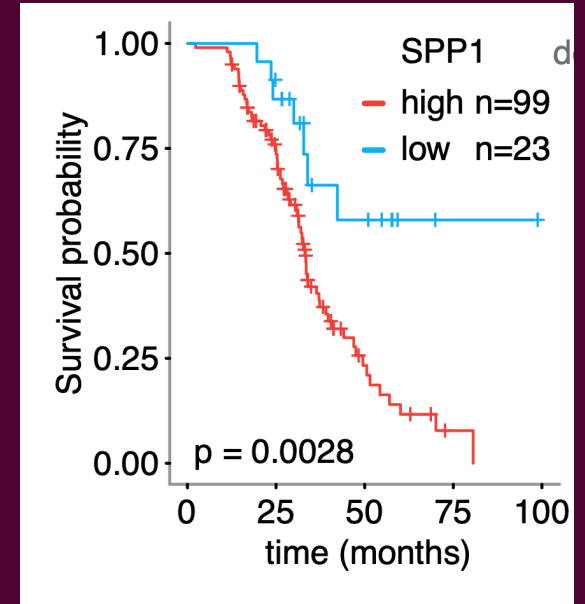
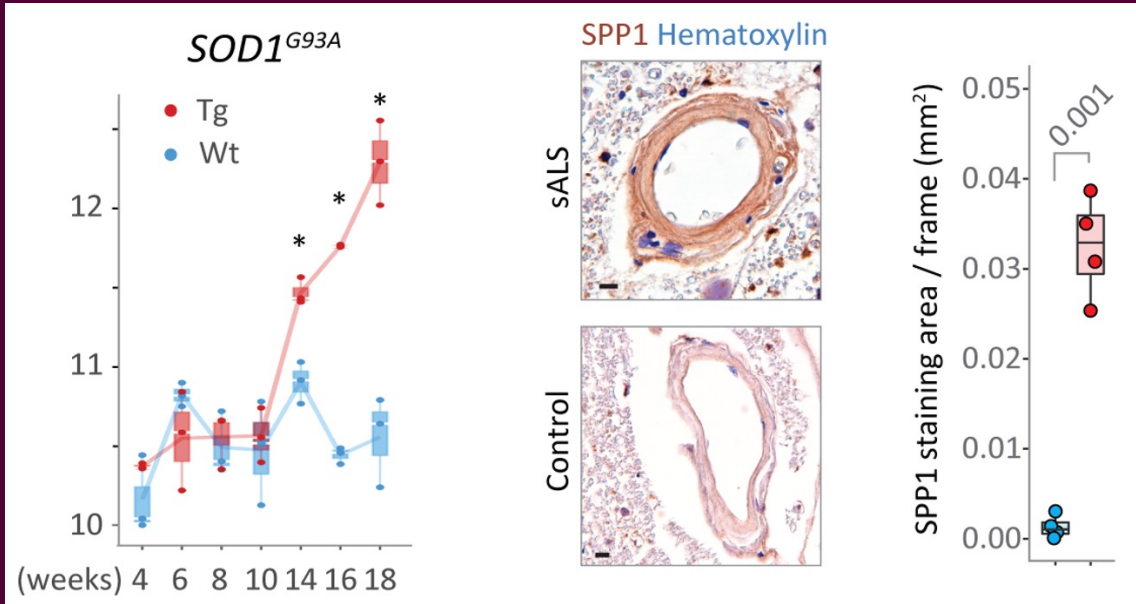
We have demonstrated the role of fibroblasts as the earliest biomarker for ALS disease onset

Vascular injury symptoms in ALS-FTD



Vascular alterations are the first physiological changes in ALS

Vascular injury symptoms in ALS-FTD

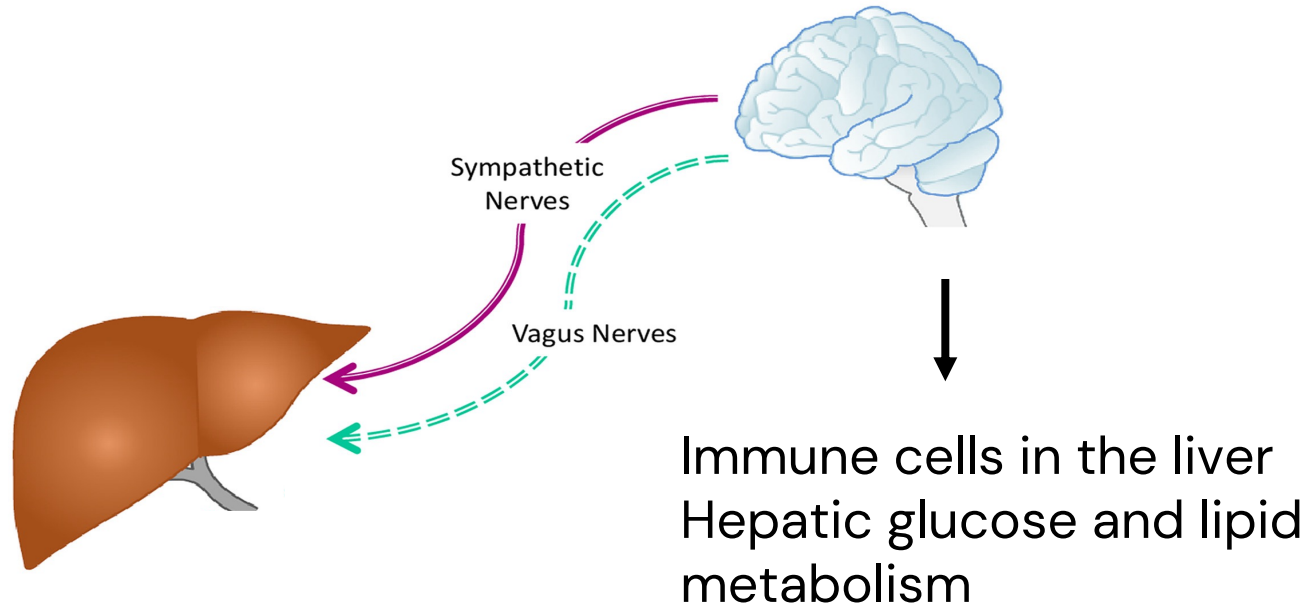


SPP1 is the first blood biomarker to predict ALS progression

Brain – Liver Axis – is there a link in ALS?

Changes in the liver in ALS

- Liver atrophy
- Ultrastructural, inflammatory and metabolic changes occur in liver



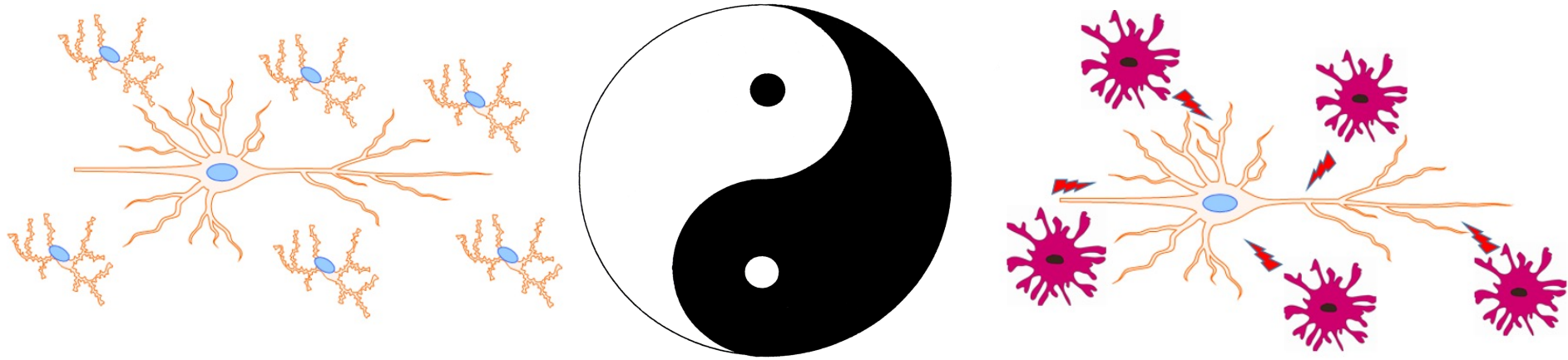
RESEARCH QUESTIONS

Why does ALS occur?

What are the disease mechanisms?
















How can we slow or stop them?

Harmful & Helpful cells



Proinflammatory microglia/macrophages (red cells on right) attack motor neurons

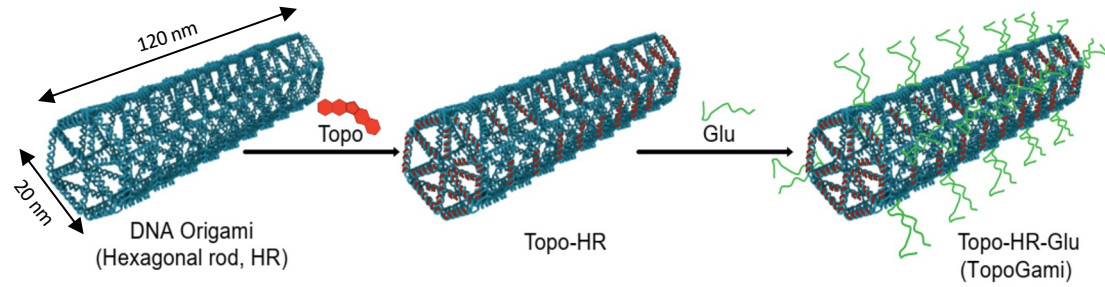
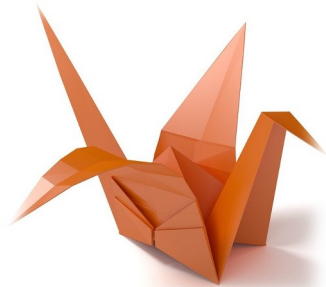
Myeloid cell-specific topoisomerase 1 inhibition using DNA origami mitigates neuroinflammation

Keying Zhu^{1,*} , Yang Wang^{2,†} , Heela Sarlus^{1,†} , Keyi Geng^{3,†} , Erik Nutma⁴, Jingxian Sun^{5,6,7}, Shin-Yu Kung¹ , Cindy Bay¹ , Jinming Han¹ , Jin-Hong Min¹, Irene Benito-Cuesta¹, Harald Lund⁸ , Sandra Amor⁴ , Jun Wang^{5,6,7} , Xing-Mei Zhang¹ , Claudia Kutter³ , André Ortlieb Guerreiro-Cacais¹ , Björn Högberg²  & Robert A Harris^{1,**} 



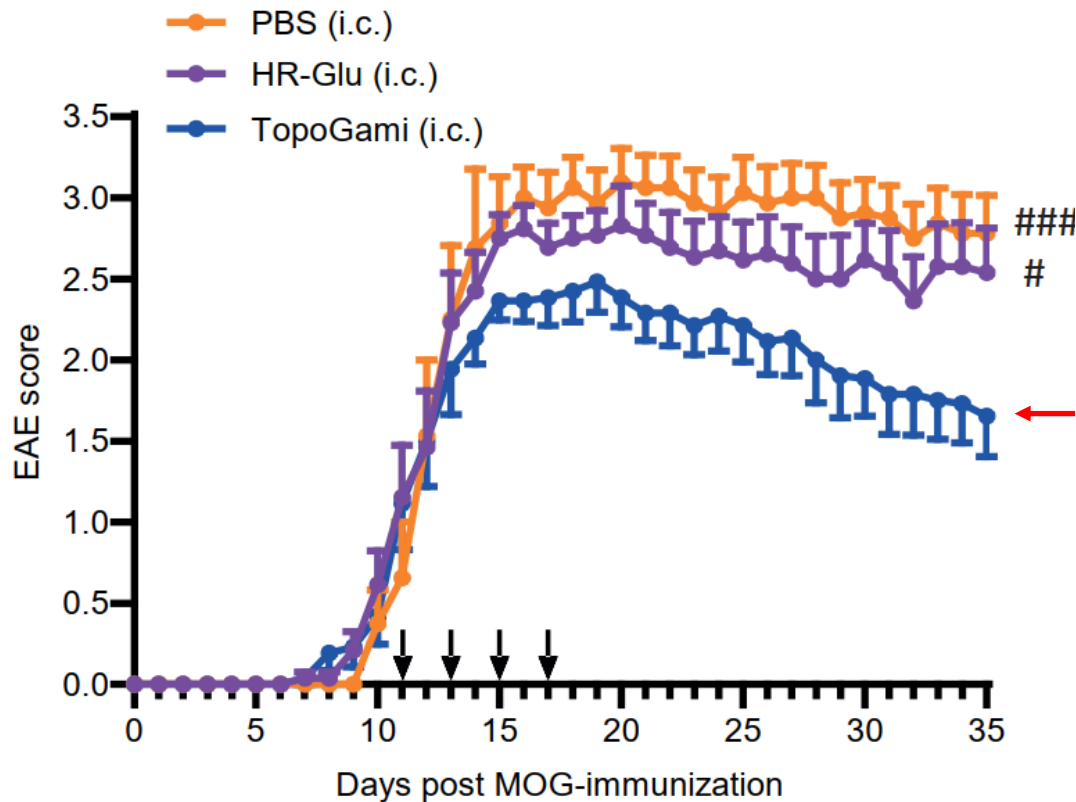
Keying
Zhu

Encapsulating topotecan in glucan- DNA-origami



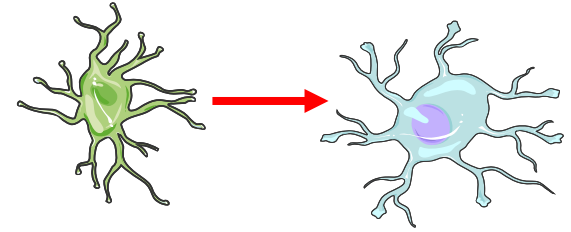
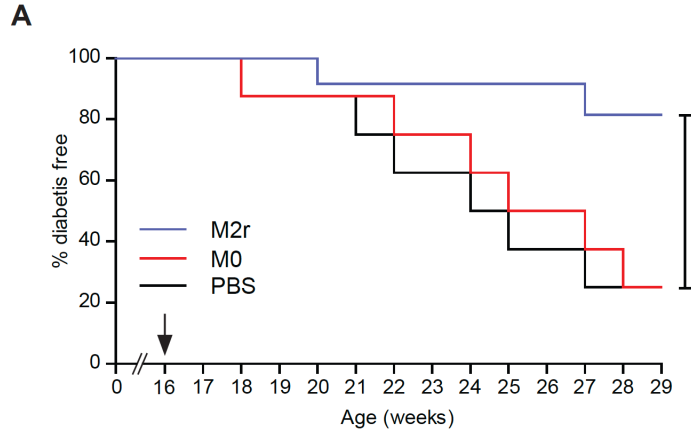
Drug delivery system
specific for microglia

TopoGami mitigates EAE disease severity



Reduced Multiple Sclerosis disease in mice when treated with our drug delivery system

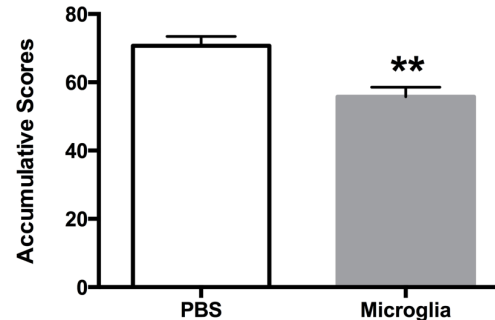
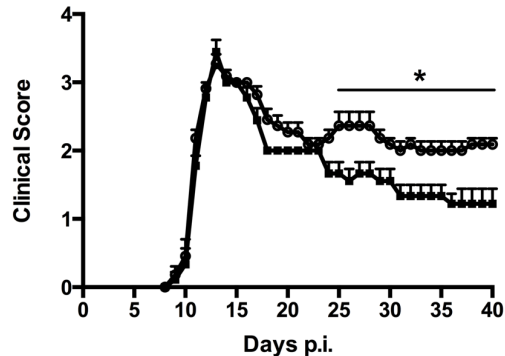
Cell therapy with IL-4/IL-10/TGF β -activated immunoregulatory macrophages prevents autoimmune disease



Type 1 diabetes

Parsa *et al* Diabetes 2012 61:2881-92

D. M2 microglia transfer on day 15 p.i.



MOG-EAE

Zhang *et al* Glia 2014 62:804-17.

RESEARCH

Open Access

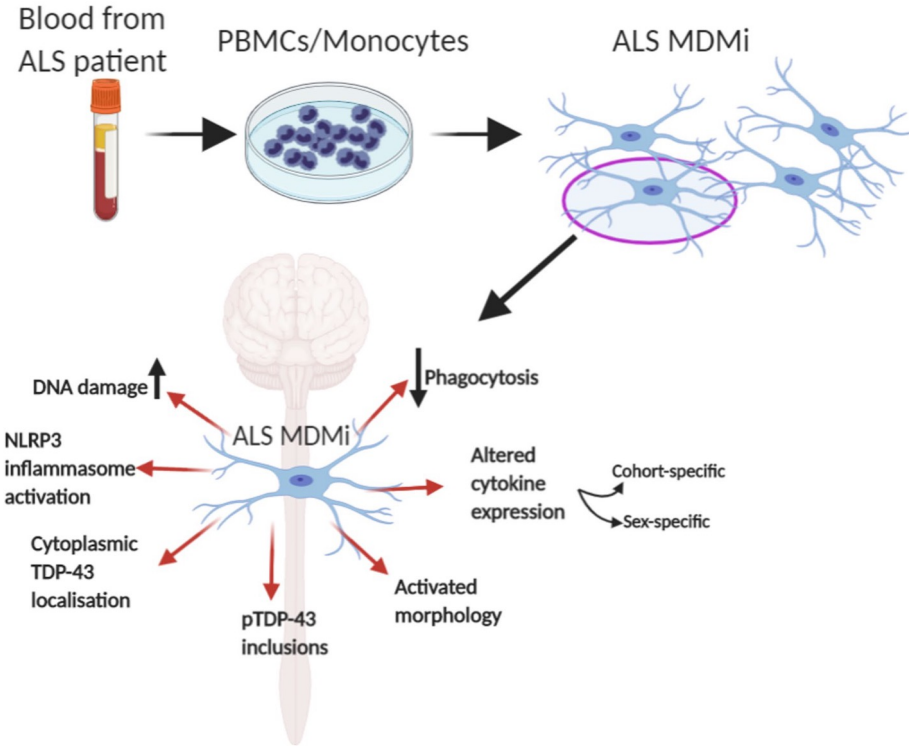


ALS monocyte-derived microglia-like cells reveal cytoplasmic TDP-43 accumulation, DNA damage, and cell-specific impairment of phagocytosis associated with disease progression

Hazel Quek^{1*}, Carla Cuní-López¹, Romal Stewart¹, Tiziana Colletti², Antonietta Notaro², Tam Hong Nguyen¹, Yifan Sun¹, Christine C. Guo¹, Michelle K. Lupton¹, Tara L. Roberts³, Yi Chieh Lim⁴, Lotta E. Oikari¹, Vincenzo La Bella² and Anthony R. White^{1*}

Dysfunctional cells in ALS patients.

Differences in cell functions depending on speed of disease course (slow, medium, fast).



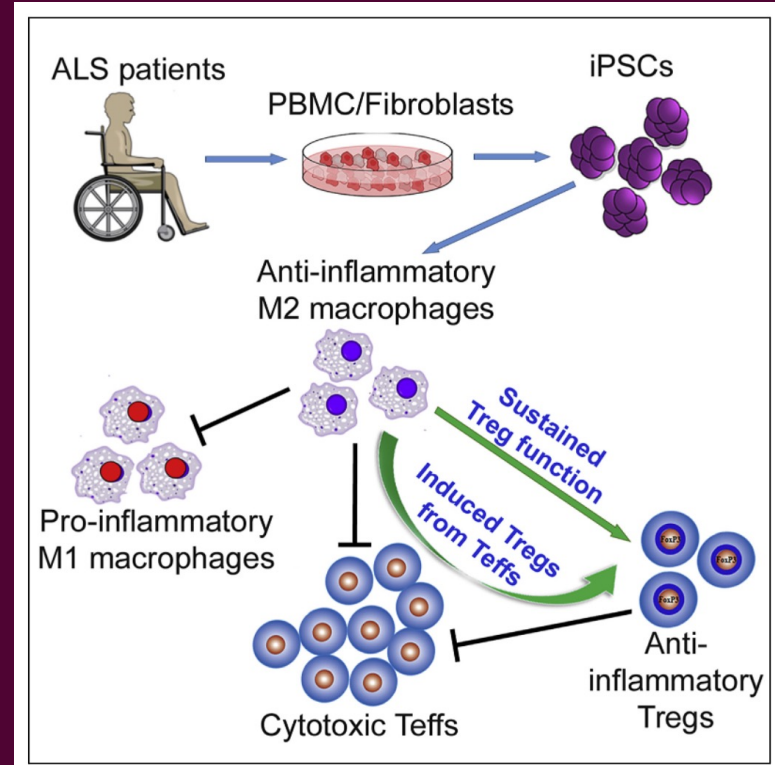
iScience

CellPress
OPEN ACCESS

Article

Immunosuppressive Functions of M2 Macrophages Derived from iPSCs of Patients with ALS and Healthy Controls

Macrophages from the blood of ALS patients can be activated to be immunoregulatory





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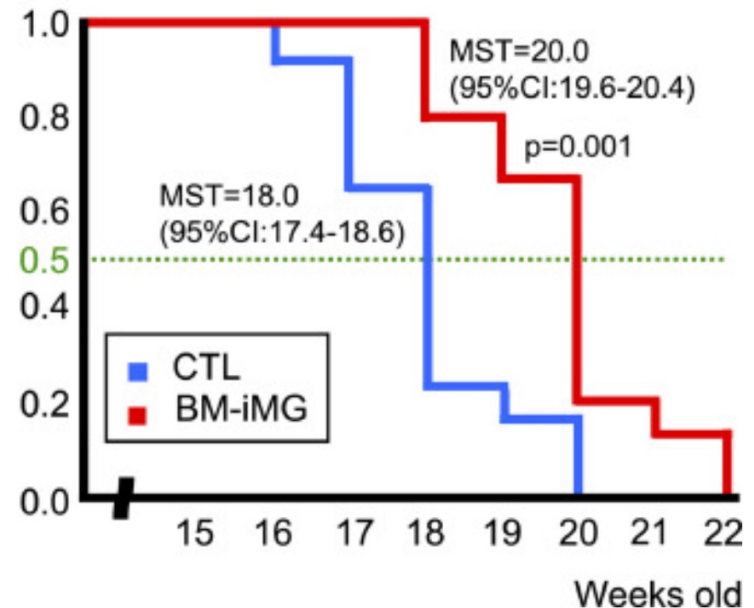
Basic Research

Bone marrow-derived inducible microglia-like cells ameliorate motor function and survival in a mouse model of amyotrophic lateral sclerosis

Shuhei Kobashi^{1,2}, Tomoya Terashima^{1,*}, Miwako Katagi¹, Makoto Urushitani², Hideto Kojima¹

Limited clinical improvement with this cell therapy– we think because of suboptimal protocol for cell stimulation

Survival to endpoint





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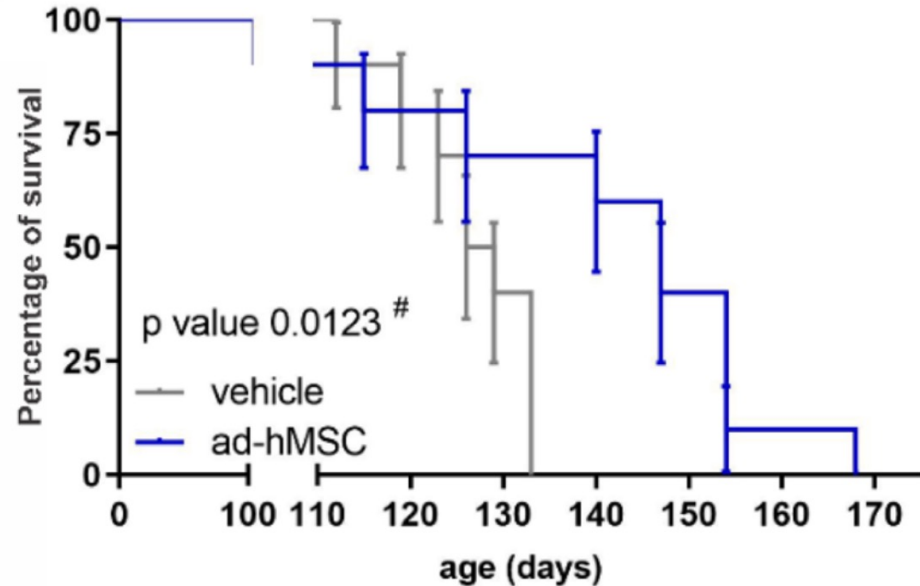
Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

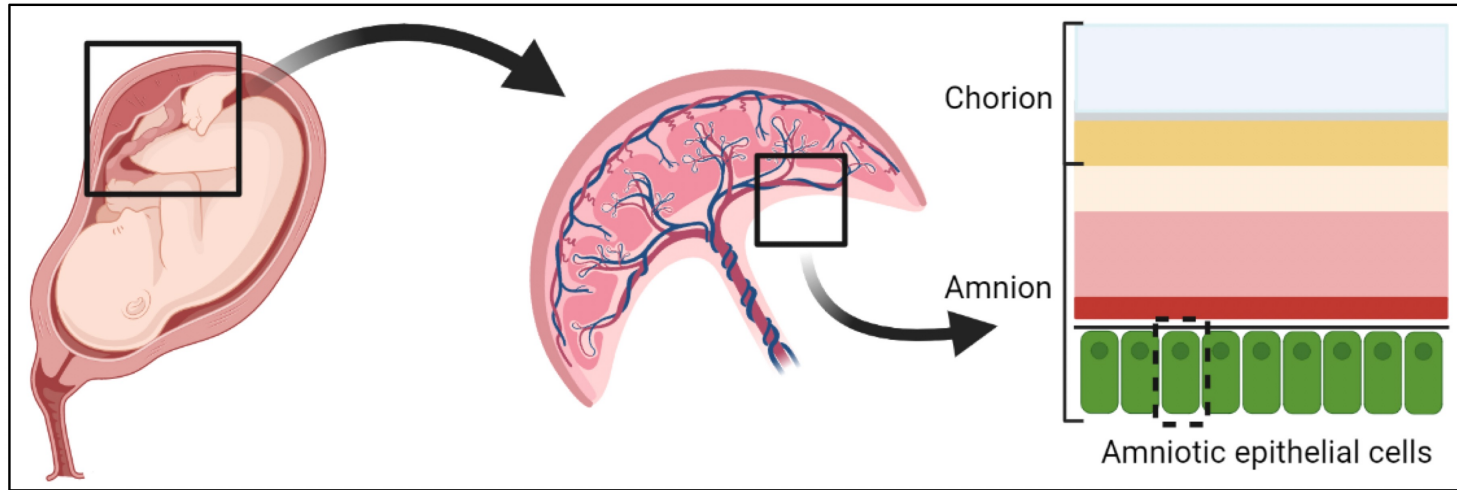
Delayed onset, immunomodulation, and lifespan improvement of SOD1^{G93A} mice after intravenous injection of human mesenchymal stem cells derived from adipose tissue

Gabriela Bortolança Chiarotto^a, Luciana Politti Cartarozzi^a, Matheus Perez^{a,b}, Ana Laura Midori Rossi Tomiyama^a, Mateus Vidigal de Castro^a, Adriana S.S. Duarte^c, Ângela Cristina Malheiros Luzo^c, Alexandre Leite Rodrigues de Oliveira^{a,*}

Some therapeutic effect of stem cell therapy



Human amniotic epithelial cells (AECs)



Amniotic sacs were used to treat damaged skin 120 years ago

AECs in disease models of neurodegeneration

↑ Cognitive deficits ↓ inflammation, plaques in Alzheimers Disease

↓ Inflammation in ischemic stroke, migrated to the brain

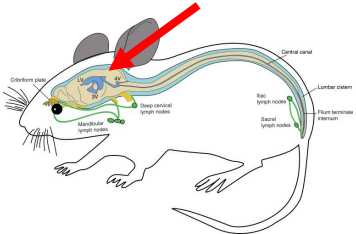
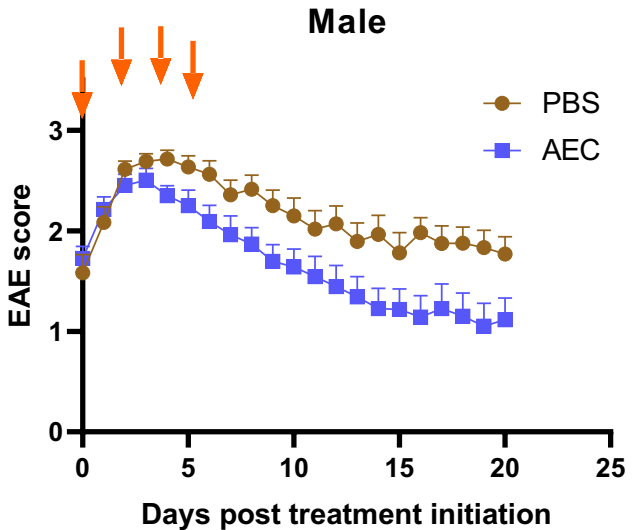
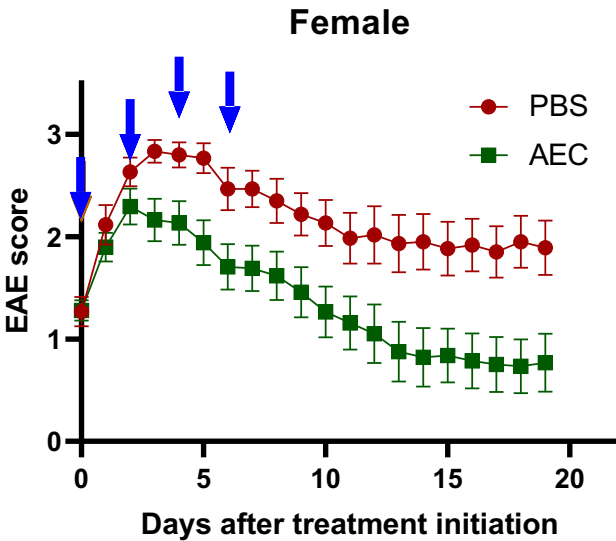
↓ Macrophage and T cell infiltration in the spinal cord in Multiple Sclerosis

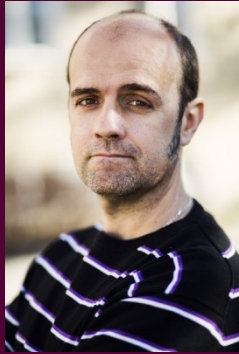
2 ongoing clinical trials in humans:

Parkinson's Disease – NCT04414813

Ischemic stroke –ACTRN12618000076279p

AEC treatment reduced EAE disease progression





ALSKI



T
E
C
H

Together
Everything
Can
Happen

Thankyou to everyone involved at
Alltid Litt Sterkere
for being such valuable members of
my research team

TECH