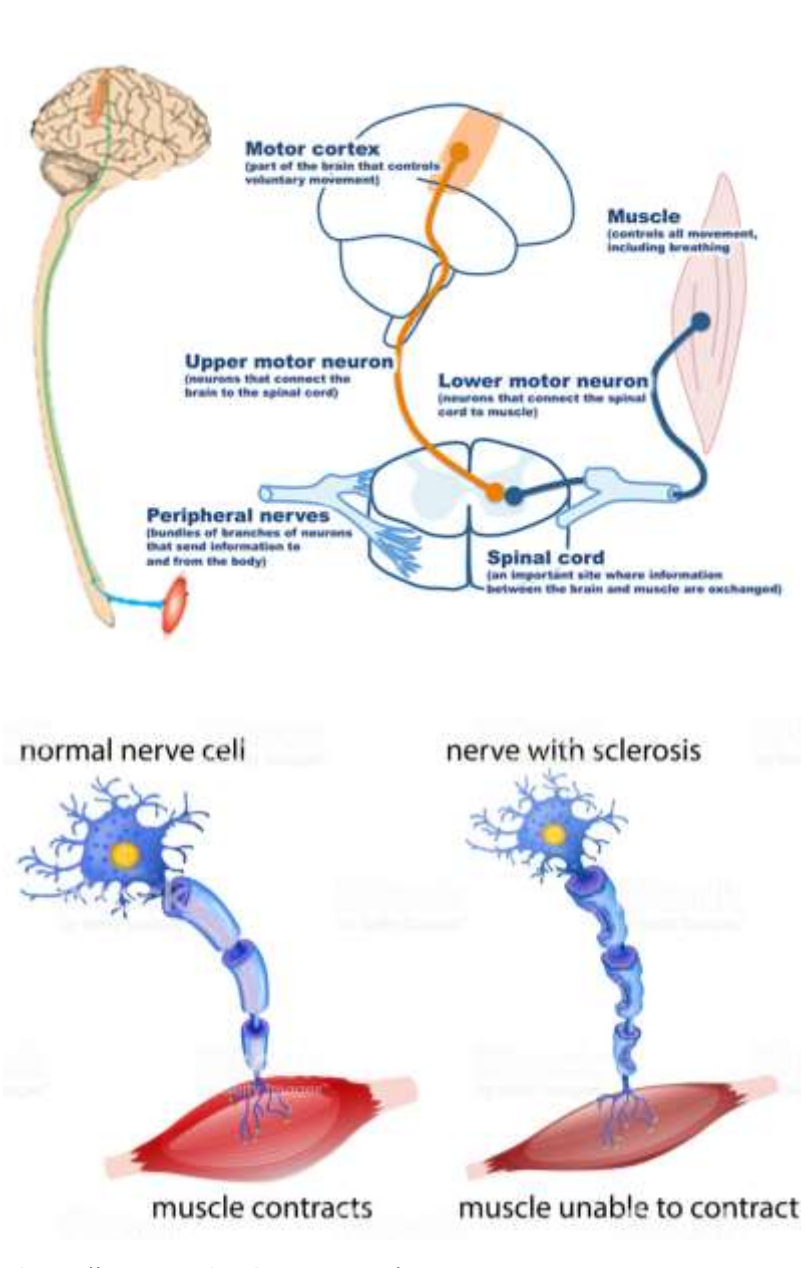


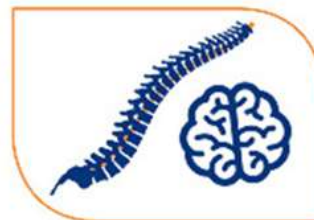
Enhancing the delivery of gene therapy for Motor Neuron Disease using focused ultrasound assisted nanoparticles

Dr Amal Jayakumar Sivaram



Motor neurone disease kills a third of people within a year and more than half within two years of diagnosis.

MND is a fatal, rapidly progressing disease that affects the brain and spinal cord.



MND attacks the nerves that control movement so muscles no longer work. It does not usually affect the senses such as sight, sound, feeling etc.



MND can leave people locked in a failing body, unable to move, talk, swallow and eventually breathe.

Around 35% experience mild cognitive change causing difficulties with planning, decision-making and language.

A further 15% of people show signs of a form of dementia resulting in more pronounced behavioural change.

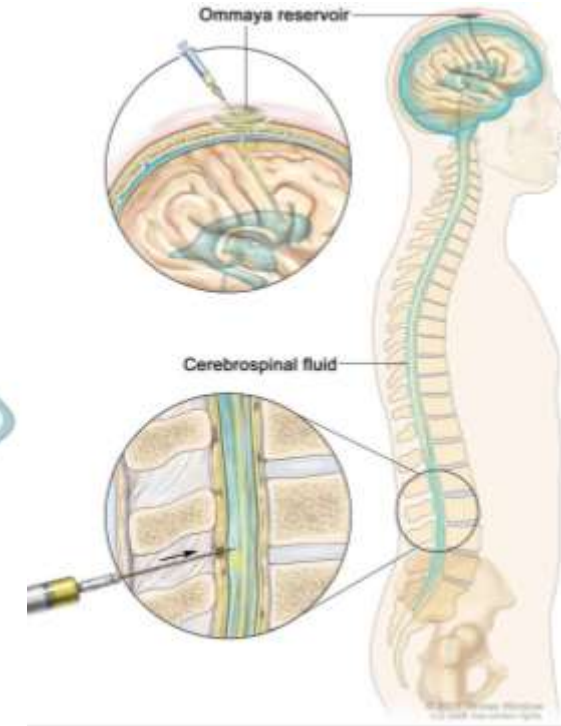
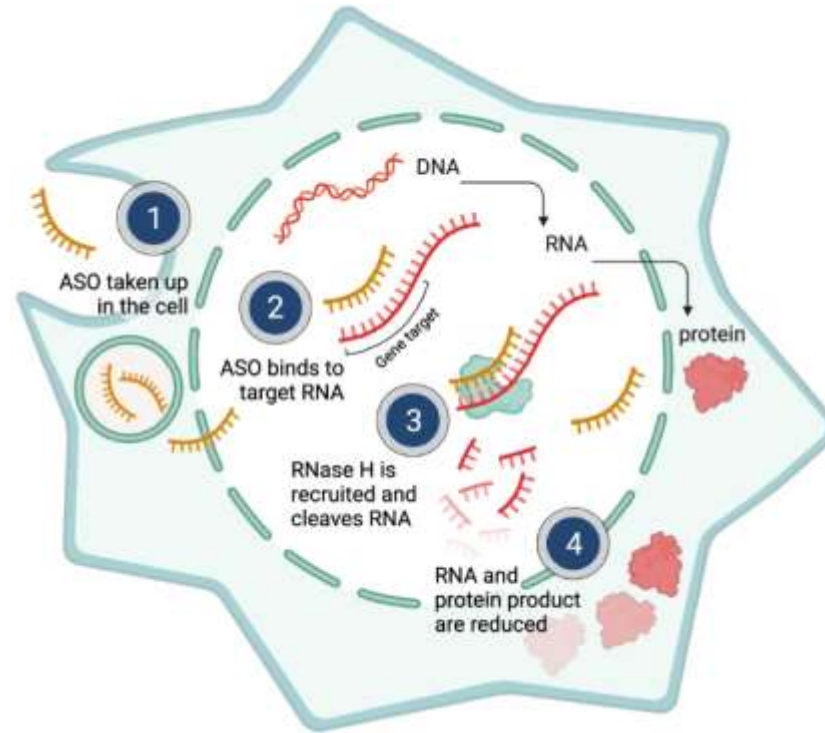
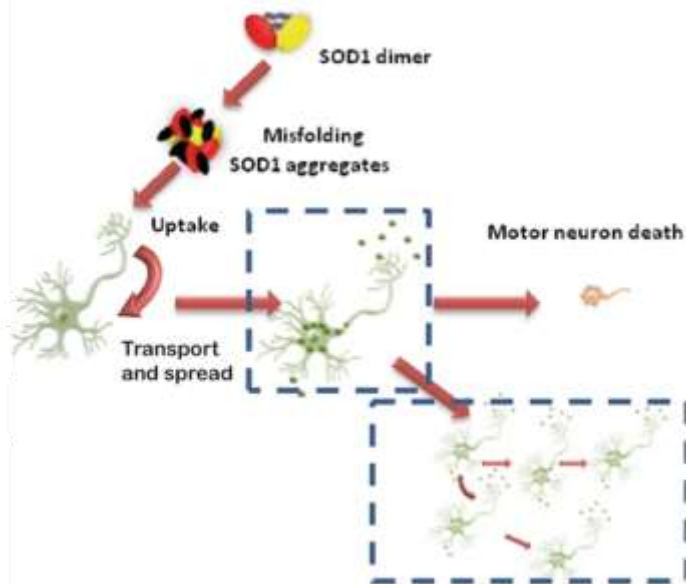
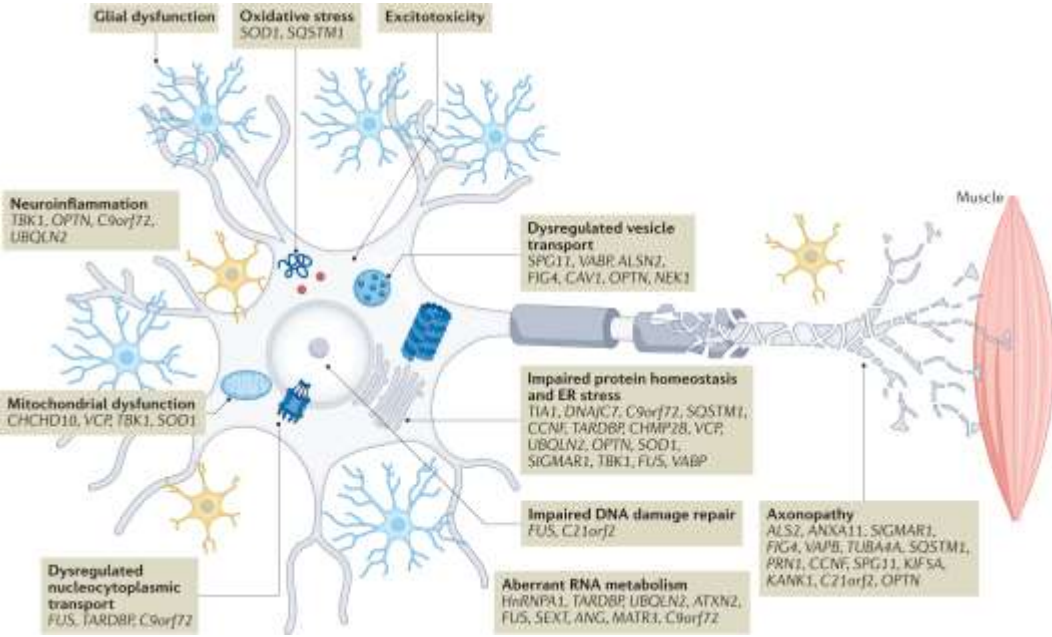
MND affects people from all communities.



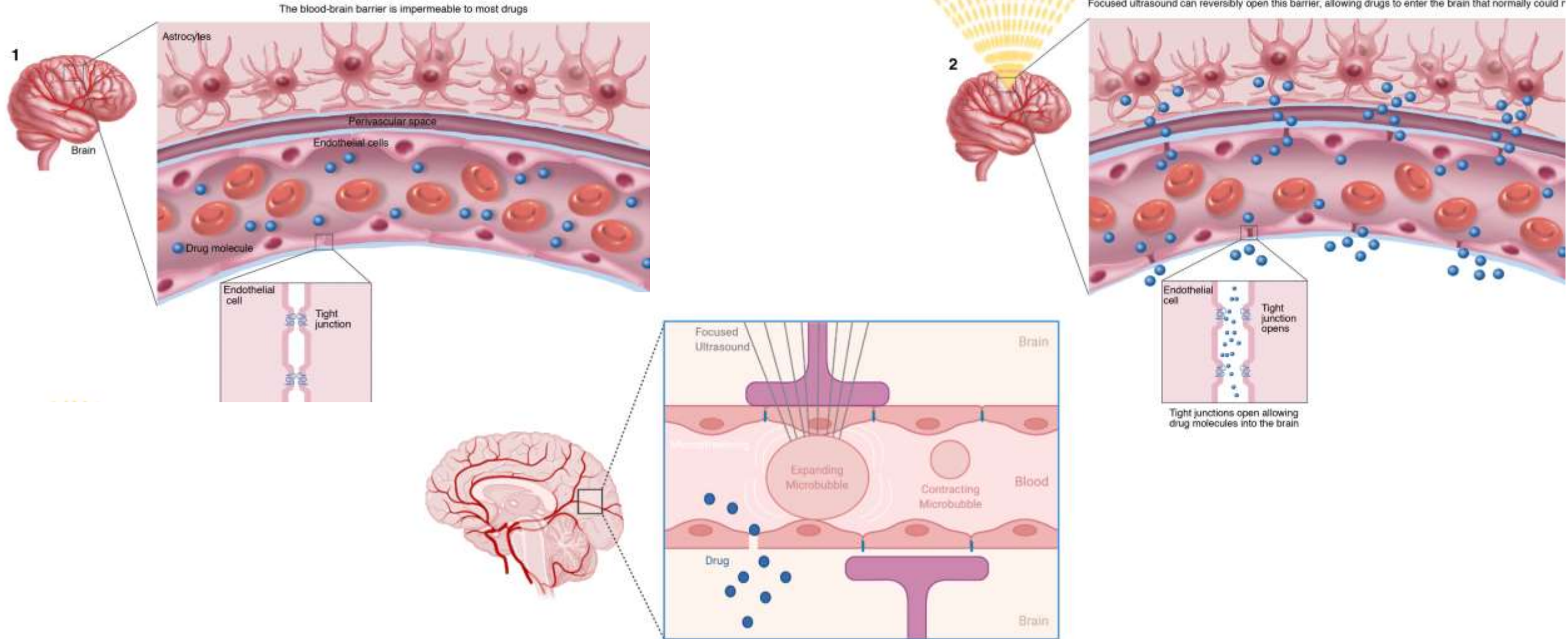
Therapy	Administration method	Mechanism of action
Riluzole formulations	Oral (tablets, liquid suspension, and film)	Reduce signals that overstimulate and damage nerve cells
Edaravone formulations	Intravenous (liquid suspension)	Reduce a type of cell damage called oxidative stress
Relyvrio (sodium phenylbutyrate and taurursodiol)	Oral (packets dissolved in water)	Blocks stress signals in specific cellular compartments
Qalsody (tofersen)	Intrathecal injection	Reduces the amount of toxic SOD1 protein in people with SOD1 mutations

There's no cure for MND. Treatment is to increase survival.

MND and Gene therapy



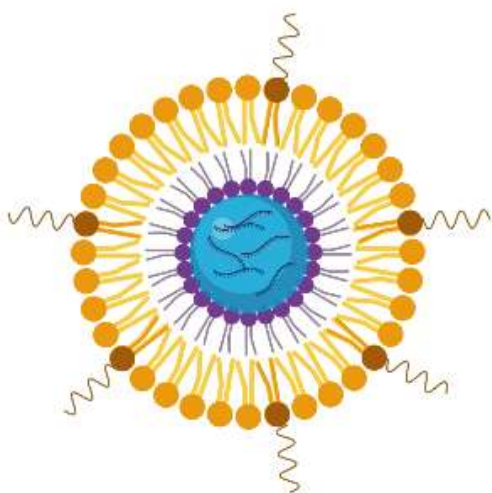
Opening up the Blood-Brain Barrier to Deliver Drugs








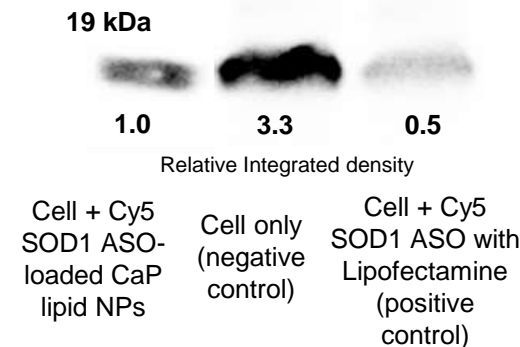
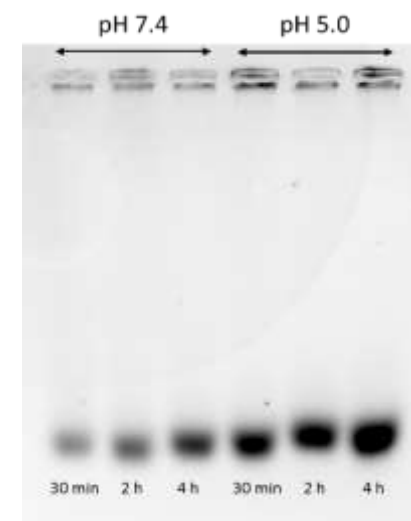
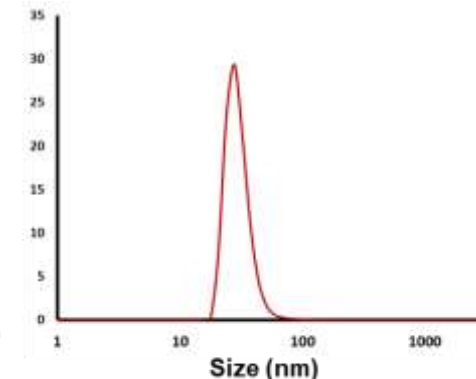
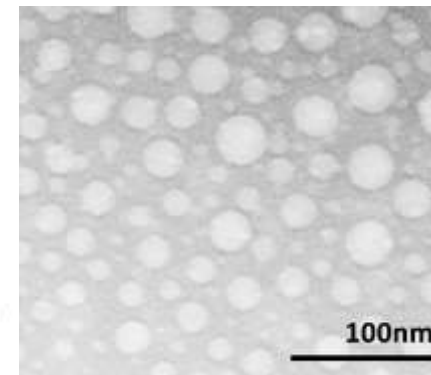
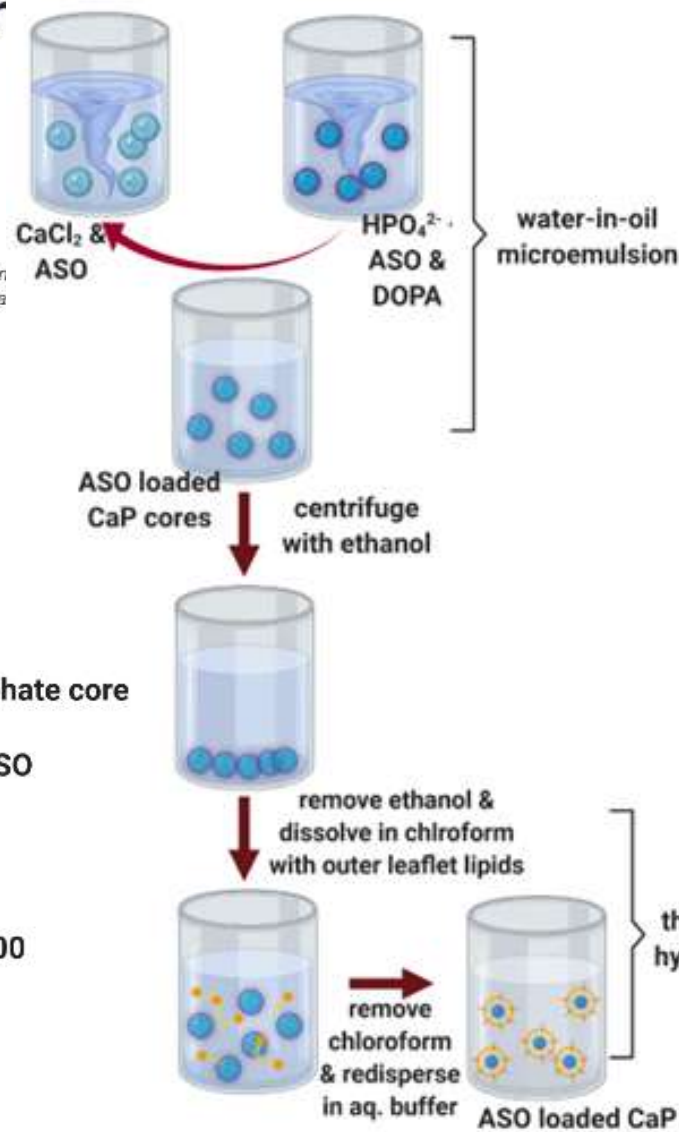
Improving the Delivery of SOD1 Antisense Oligonucleotides to Motor Neurons Using Calcium Phosphate-Lipid Nanoparticles

Liyu Chen^{1,2*}, Clare Watson^{1,2†}, Marco Morsch³, Nicholas J. Cole³, Roger S. Chung³, Darren N. Saunders⁴, Justin J. Yerbury² and Kara L. Vine^{1,2*}

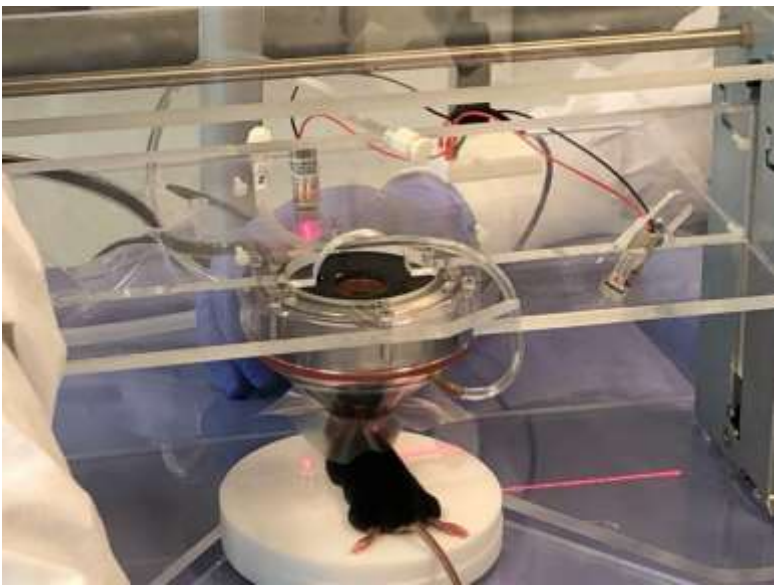
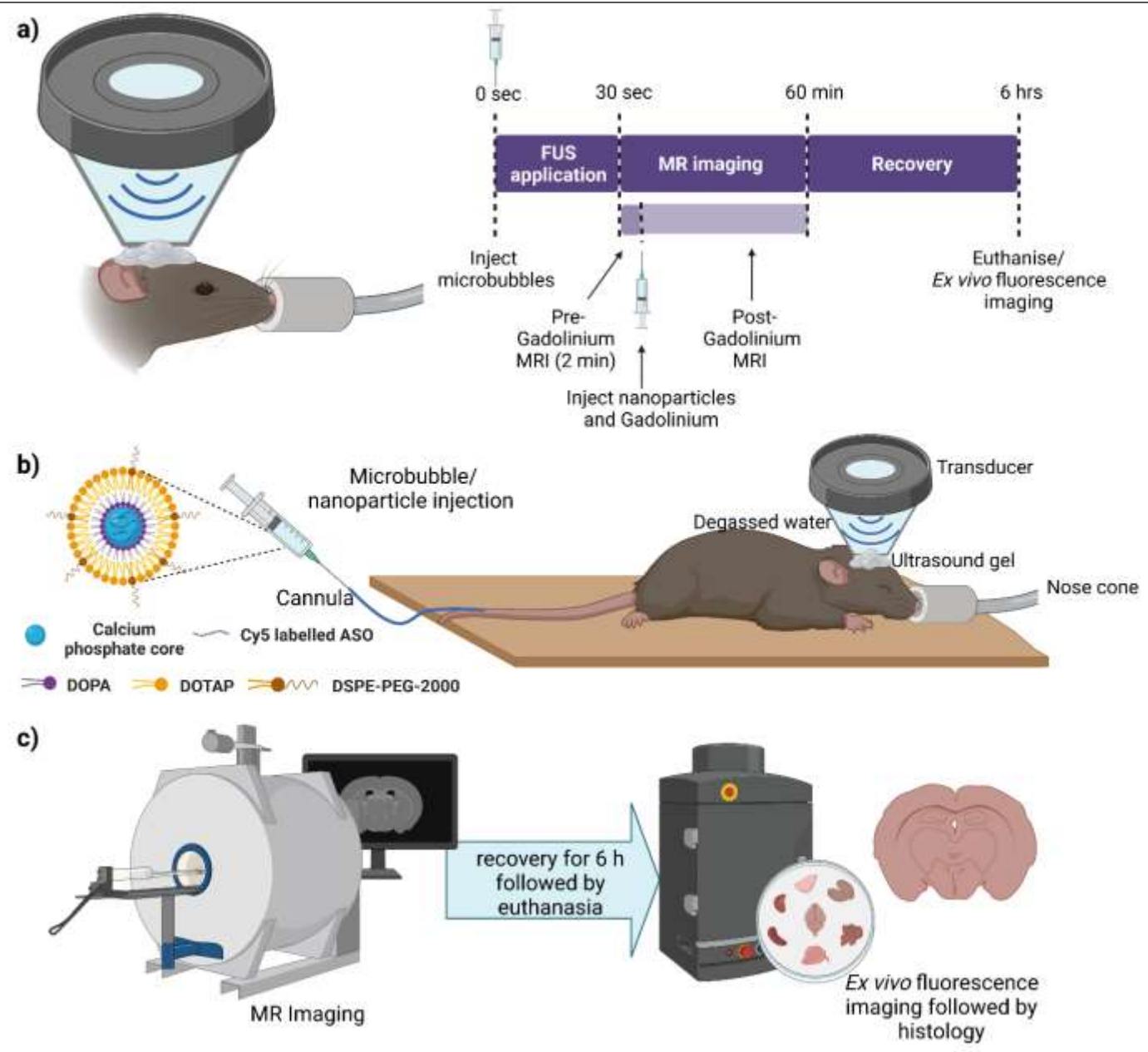
¹ Illawarra Health and Medical Research Institute, Wollongong, NSW, Australia, ² Science Medicine and Health Faculty, Centre for Medical and Molecular Bioscience, School of Biological Sciences, University of Wollongong, Wollongong, NSW, Australia, ³ Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia, ⁴ School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia



-  Calcium phosphate core
-  Cy5 labelled ASO
-  DOPA
-  DOTAP
-  DSPE-PEG-2000



Project Overview



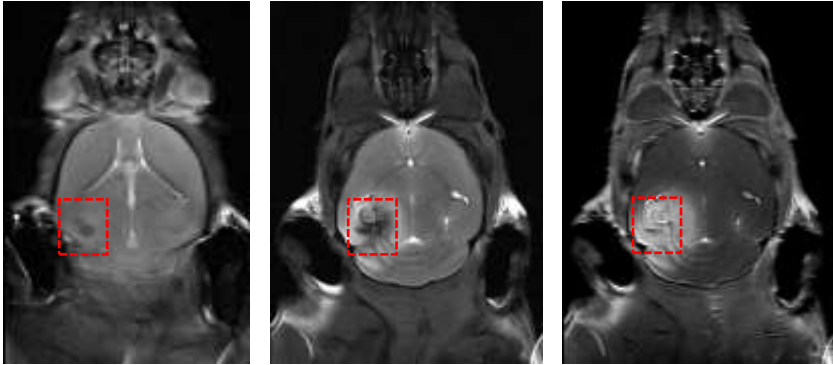
0.33 MI/120 sec/high MB dose

0.33 MI/120 sec/low MB dose

Pre-Gd T2

Post-Gd T2

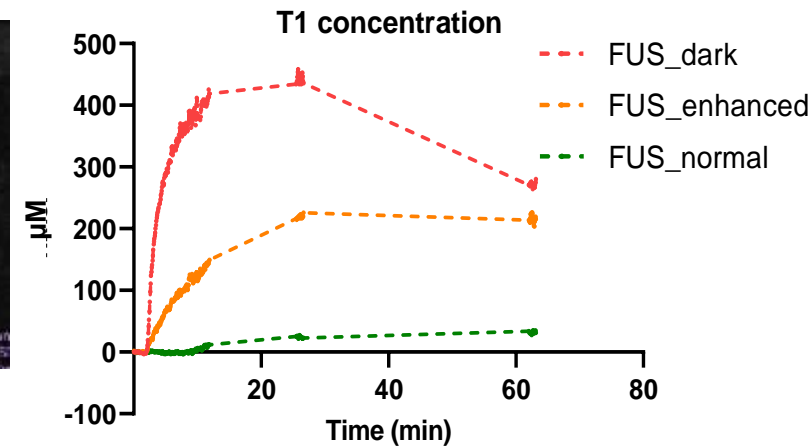
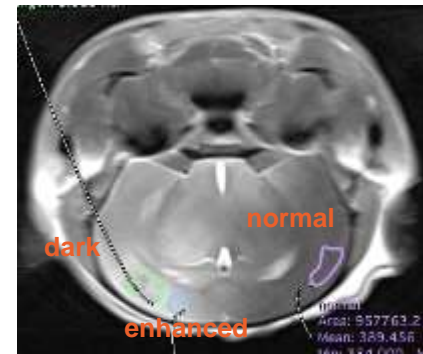
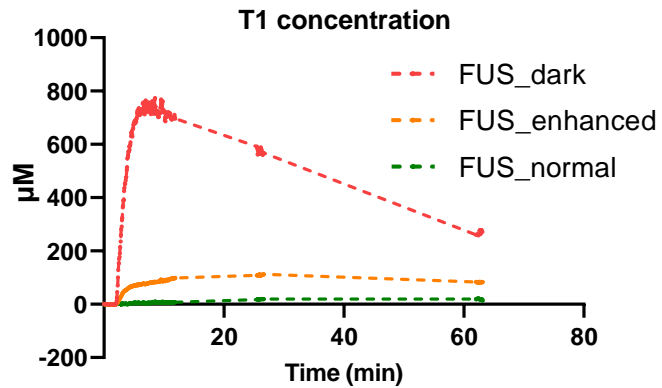
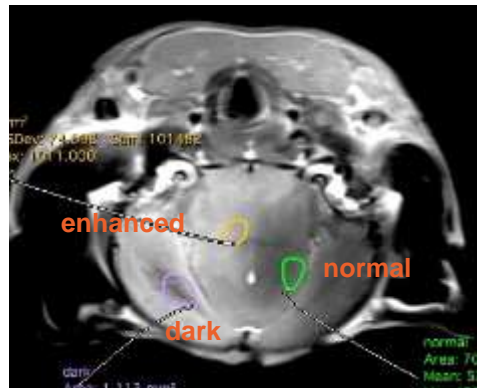
Post-Gd T1



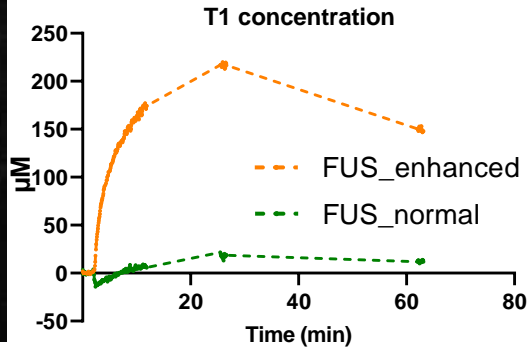
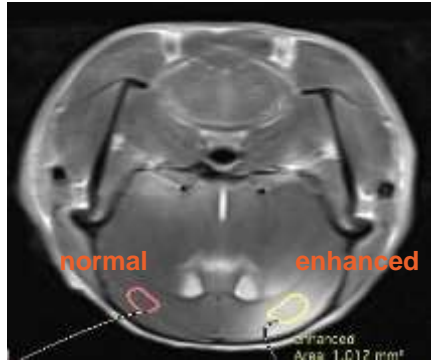
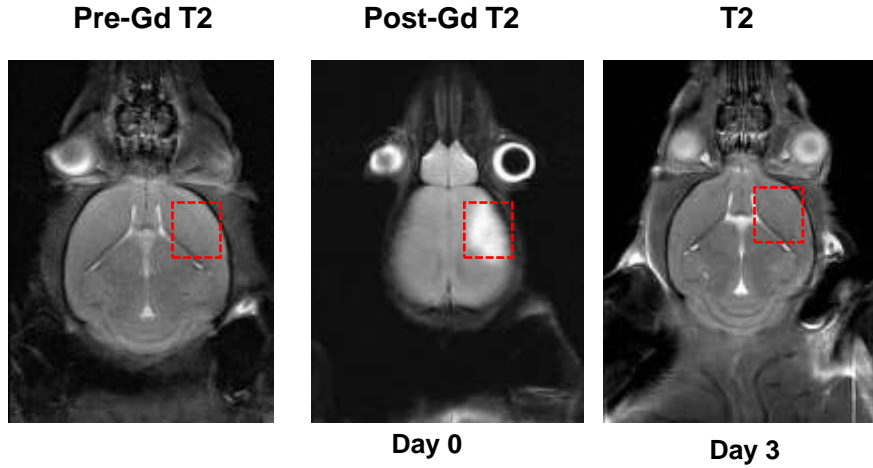
Pre-Gd T2

Post-Gd T2

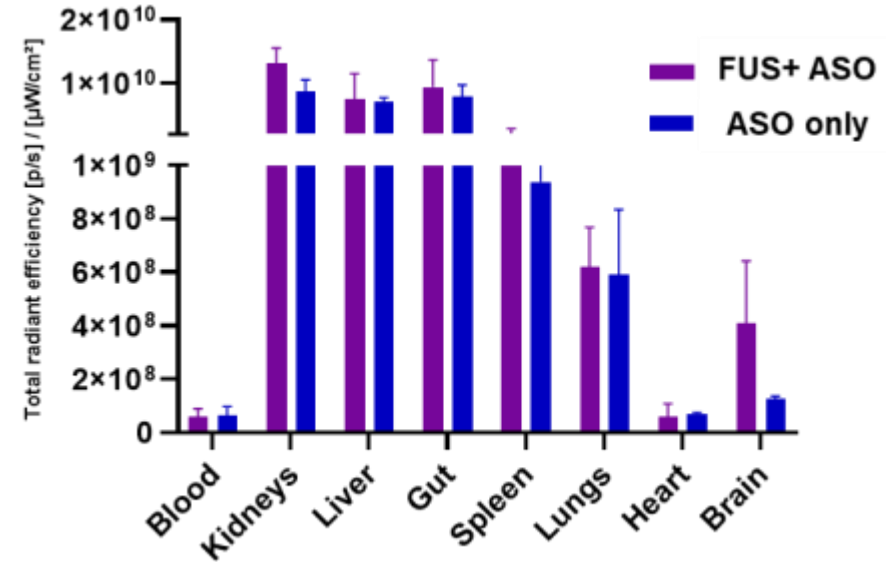
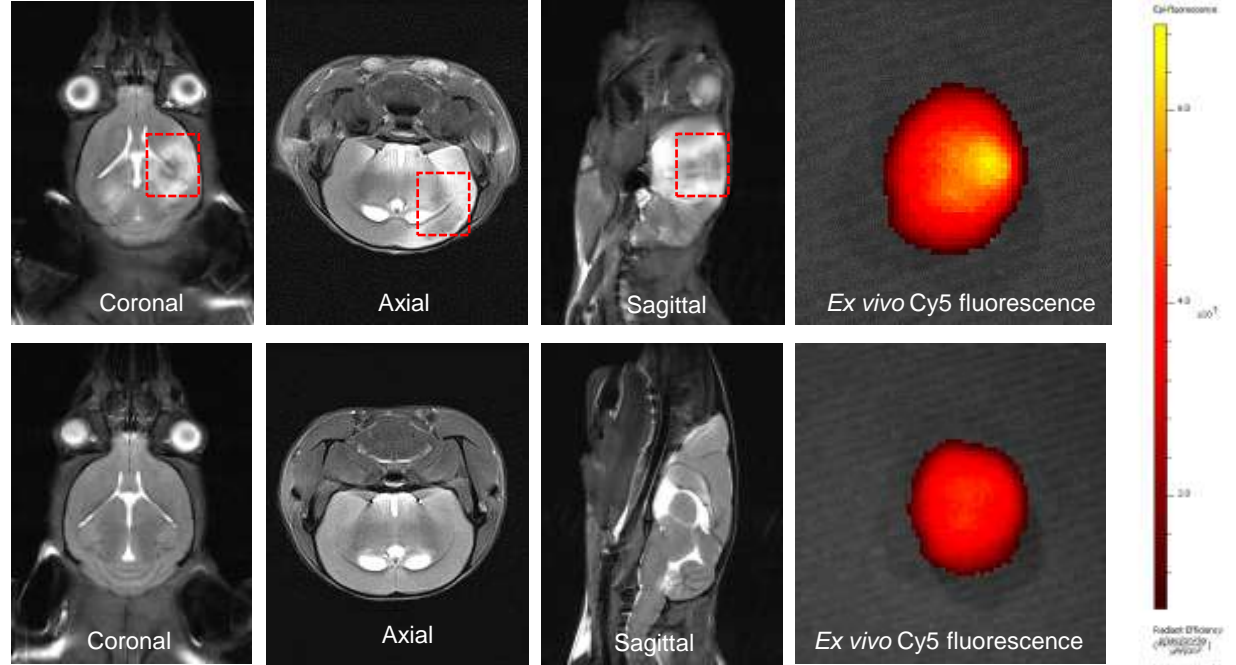
Post-Gd T1



0.33 MI/30 sec/low MB dose



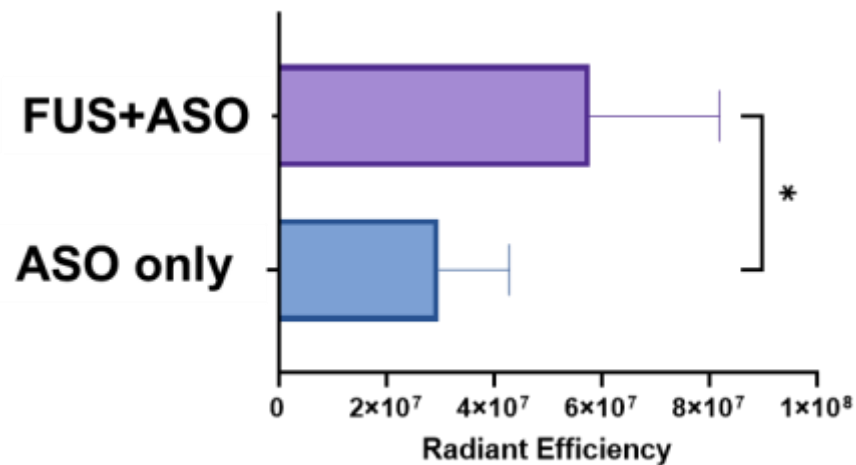
FUS+ ASO



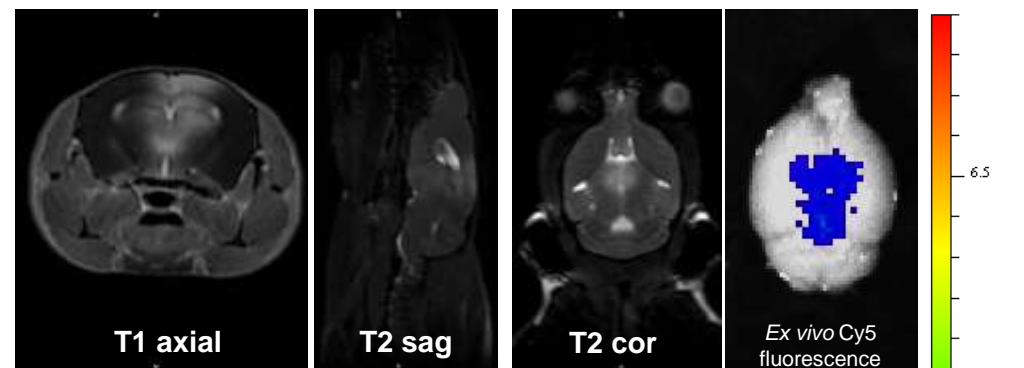
Therapeutic study



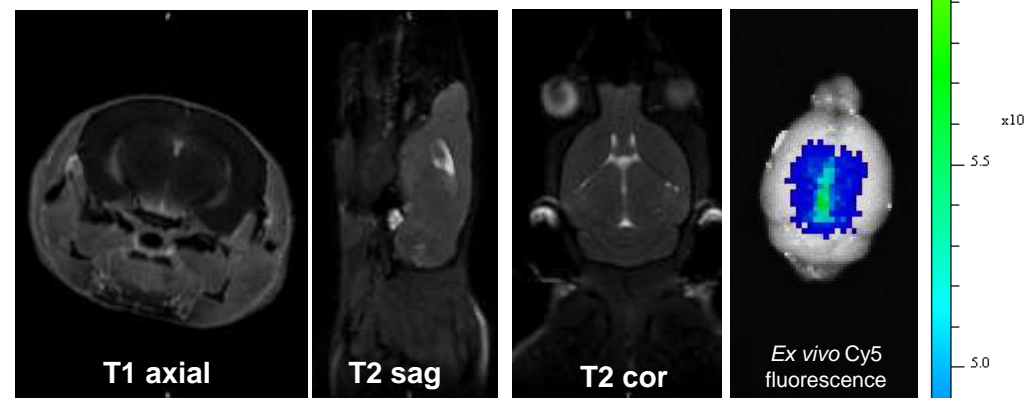
Group	Microbubble dose	FUS exposure	No of mice
FUS only	Yes	Yes	6
ASO only	Yes	No	6
FUS +ASO	Yes	Yes	6



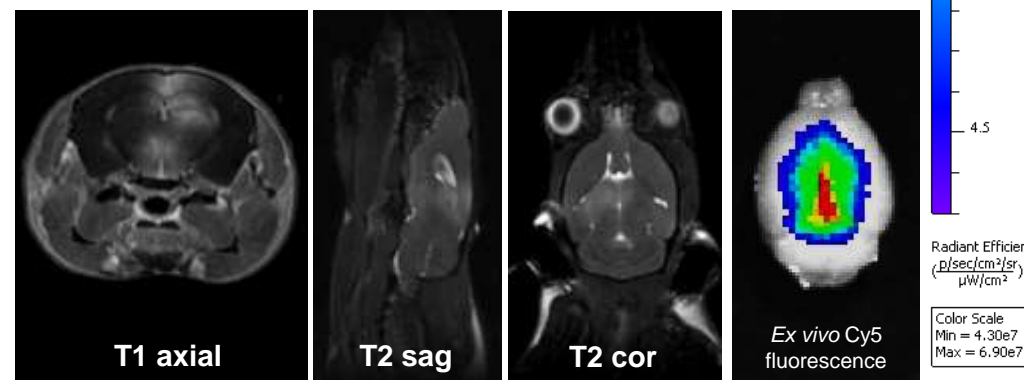
FUS only

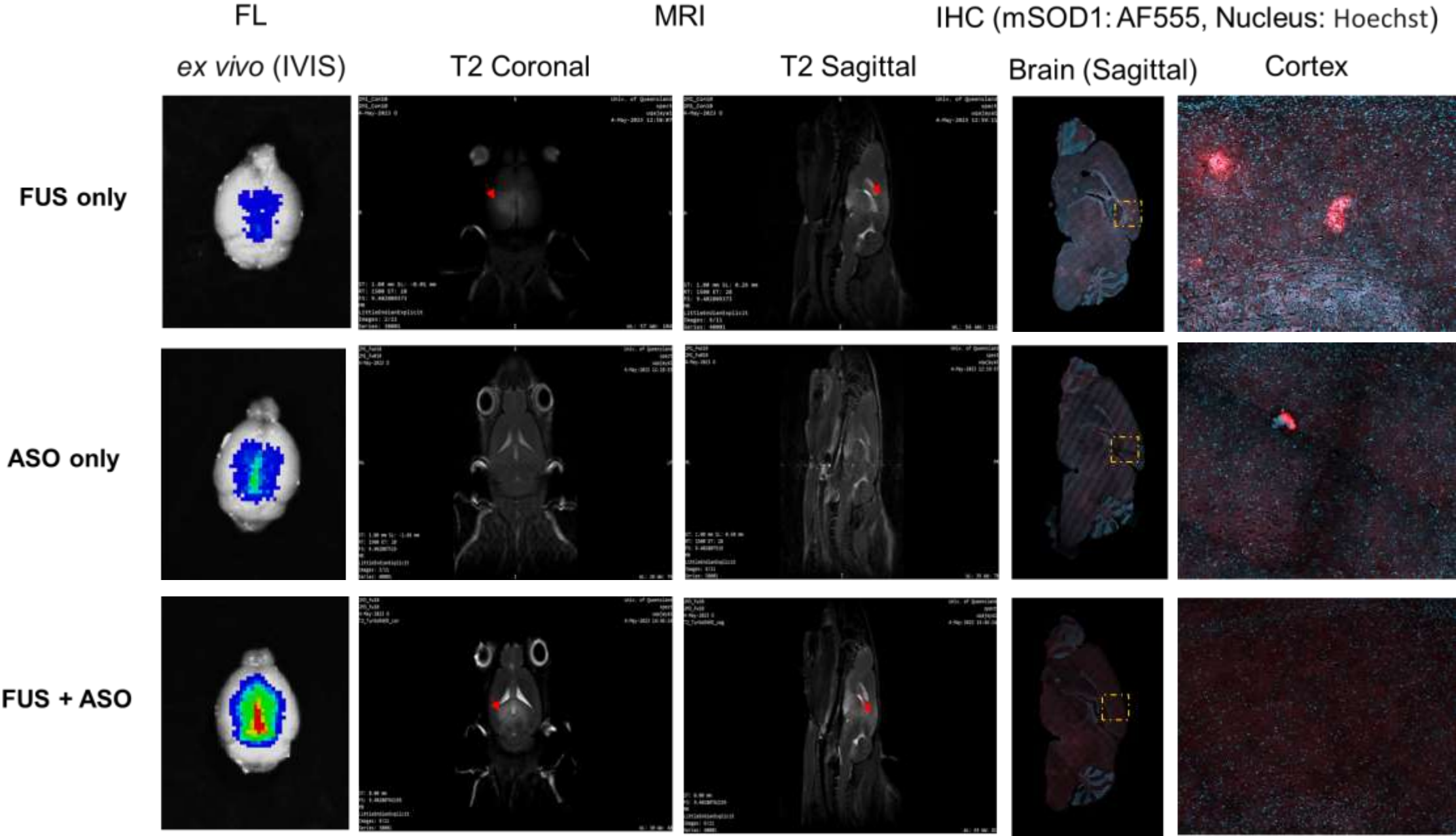


ASO only



FUS + ASO





- Motor Neuron Disease (MND) is a **severe neurodegenerative disorder** leading to muscle weakness and respiratory failure.
- Antisense oligonucleotides (**ASOs**) target genes in MND but face **delivery challenges** like low BBB penetrability.
- We have **developed** a **FUS-assisted PEGylated lipid nanoparticle**-based system for efficient ASO delivery into the CNS.
- Focused ultrasound parameters has been **optimized for the transient opening** the blood brain barrier.
- SOD1 ASO-loaded NPs successfully shown **enhanced delivery** into the CNS in the transgenic mice.
- Further studies needs to be carried out related to the long-term therapeutic effect of these nanoparticles on the transgenic mice

Acknowledgement

- Prof. Kristofer Thurecht
- Assoc. Prof. Kara Vine Perrow
- Vale Prof. Justin Yerbury
- Dr. Jeremy Lum
- Mikayla Brown
- Dr. Gayathri Ediriweera
- Dr. Gary Cowin
- Dr. Nyoman Kurniawan
- Dr. Liyu Chen
- Dr. Joanna Wasielewska
- Dr. Claire Stevens
- Thurecht group members
- Perrow group members





Thank you.....