UK Dementia Research Institute

A novel C9FTD/ALS therapy

Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are intrinsically related and C9orf72-mediated ALS and FTD (C9FTD/ALS) is the most common hereditary cause. Whereas FTD is a cognitive and behavioural disorder characterized by changes to personality and language skills, ALS is a neuromuscular disease, which leads to paralysis and movement disorders to eventually respiratory failure.

FTD is the 2nd most common cause of dementia in patients < 65yo

Mutations in C9orf72 account for:

- **40% of familial ALS**
- **8-10% of sporadic ALS**
- **25-30% of familial FTD**
- **10% of sporadic FTD**

The onset age of C9FTD/ALS ranges from 27 to 83 years of age

It can progress as rapidly as one year to a progressive deterioration of over 20 years

The target: C9orf72 gene

- Abundant in neurons in the cerebral cortex and in motor neurons
- MoA: loss of function, toxic gain of function and toxic dipeptide repeats proteins (DRP) from GGGGCC hexanucleotide repeats
- Unclear threshold of number of repeats to cause FTD/ALS
- Antisense and sense transcripts lead to five different types of DRPs, all of them related to pathology
- Unclear whether pathology is only related to the final toxic repeats and/or to the transcripts themselves

Therapeutic approaches and limitations

antisense therapy	gene editing	gene therapy	immuno-therapy	small molecules
recent ASOs efficacy failures in Ph1/2a in other CNS disorder	CRISPR approaches targeting the repeat transcript	DNA-targeting and increased risk of off-target effects	protein-level approach, missing RNA toxicity	tracking downstream defects, chronic medication

Our approach: An effective RNA targeting therapy based on CasRx (Cas13d - RNA binding) and gRNAs for both sense and antisense C9orf72 hexanucleotide repeat transcripts

Stage of development

patient-derived iPSC neurons and C9orf72 BAC mouse model - reduction of hexanucleotide repeats

Upcoming data

Further studies in C9orf72 BAC transgenic mice, delivery and AAV construct optimisation

IP position

UK priority filed on 16 April 2021

Team: Prof. Adrian M Isaacs and Liam Kempthorne
http://adrianisaacslab.com/
https://ukdri.ac.uk/team/adrian-isaacs

Founding funders: UKRI Medical Research Council, Alzheimer's Society, Alzheimer's Research UK