# ORGTHERAPY

**Multicellular organoids: modelling, mechanisms and therapy development for C9ORF72-associated neurodegeneration**

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are devastating disorders. The most common genetic form of ALS and FTD is caused by mutations in C9ORF72 gene. While significant discoveries have recently been made in the genetics of ALS/FTD, patients still have no real therapeutic treatments. The lack of any cure for ALS-linked C9ORF72 is attributable primarily to:

(i) Poor understanding of the molecular pathogenesis of neurodegeneration;
(ii) Lack of reliable animal models mimicking the multicellular and multi-mechanism complexity of the human disease;
(iii) Delivery of therapeutically attractive molecules has been hampered by inefficient delivery methods including factors like the blood-brain barrier;
(iv) Ineffective targeting of therapeutic agents specifically to the diseased sites of the brain and spinal cord.

Research efforts aimed at understanding how mutations in ALS causative genes leads to motor neuron injury are of the utmost importance to enable therapeutic development for these disorders. The limitations associated with existing C9orf72 models can be overcome by using specific patient cells - derived 3D models named organoids. Thus, organoids provide unique opportunities as a system for the development of pharmacological or tailored gene therapies for C9ORF72-linked neuronal injury. Here, we assembled a multidisciplinary research team with complimentary expertise to examine strategies to overcome some of these challenges.

The overall aims of our research programme are:

1) Generate 3D in vitro multicellular organoids models from iPSCs derived from healthy and patients with C9ORF72 ALS/FTD;
2) Fully characterise the newly generated models using established assays in the consortium (e.g. molecular markers and electrophysiology);
3) Explore how neuronal injury happen in ALS;
4) Develop treatment for C9orf72 linked ALS.

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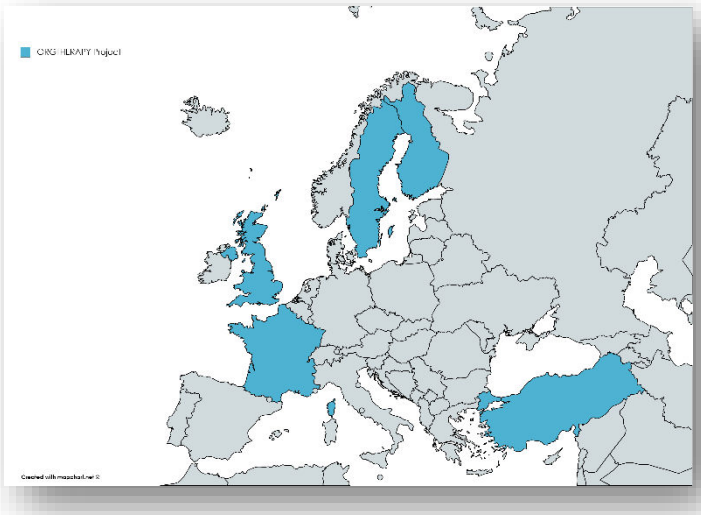

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