208 YM201636, a PIKFYVE kinase inhibitor for ALS treatment

Asset Overview

Product Type	Small molecule
Indication	CNS diseases
Current Stage	Lead Identification/optimization
Target(MoA)	Replacing C9ORF72 function with chemical compound
Brief Description	USC researchers have identified a method of treating ALS by restoring the levels of the C9ORF72 protein. Additional studies have shown that inhibiting the PIKFYVE kinase with inhibitors prevent the degeneration of neurons derived from ALS patients and rescues neurodegeneration in cell models of sporadic ALS. These results demonstrate how stem cell and reprogramming-based approaches can help to identify new therapeutic targets to treat ALS and other neurological diseases.
Organization	University of Southern California

Differentiation

□ **No cure for ALS is known**

- Amyotrophic lateral sclerosis (ALS) is a rare neurological disease that affects approximately 30,000 people in the United States (Roughly 5,000 new cases each year)
- **Riluzole** may extend life by about two to three months. (Its MOA is poorly understood). In clinical trials, 14% (n = 141) of 982 patients discontinued medication as a side effect

□ **A Repeat expansion in C9ORF72 is the most common cause of ALS**

- An intronic GGGGCC repeat expansion in C9ORF72 is the most common cause of ALS, but its pathogenic mechanism remains unclear
- C9ORF72 patient induced motor neurons (iMNs) undergo rapid neurodegeneration. C9ORF72 interacts with endosomes and is required for normal vesicle trafficking and lysosomal biogenesis in motor neurons (Nature Medicine, 2018)

□ **YM201636 significantly increased C9ORF72 patient iMN survival by increasing PI3P levels**

- They identified a PIKFYVE kinase inhibitor (YM201636) that significantly increased C9ORF72 patient iMN survival (screened 800 bioannotated compounds targeting cellular processes)
- Inhibition of PIKFYVE increases autophagosome-lysosome fusion and may compensate for reduced C9ORF72 activity by increasing PI3P levels to facilitate removal of glutamate receptors

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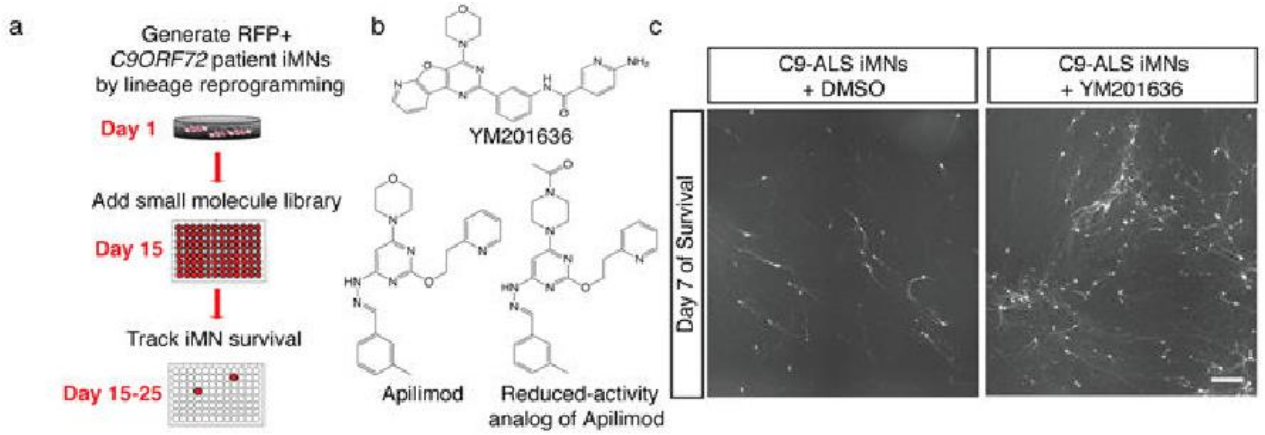
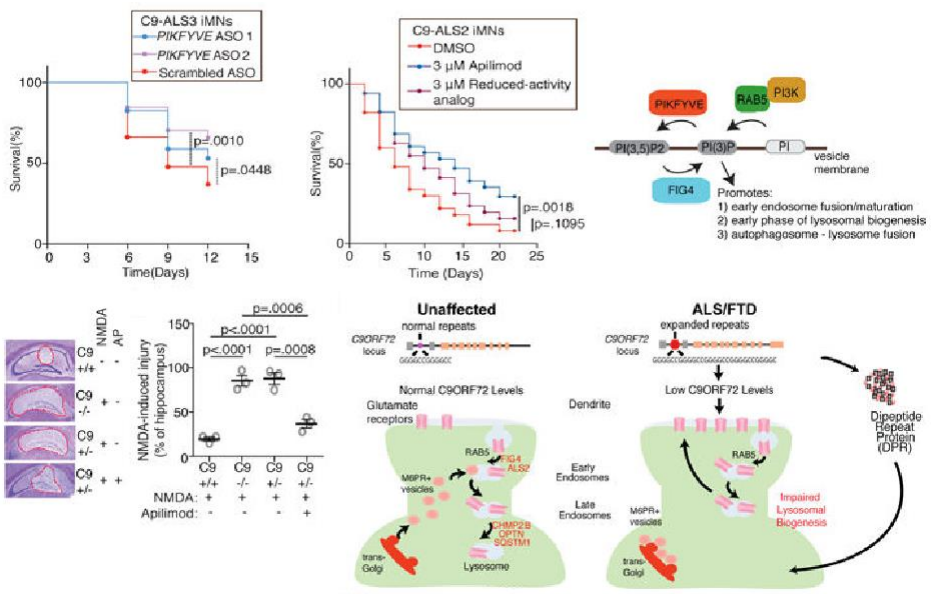
Key Data

Small molecule modulators of vesicle trafficking rescue neurodegeneration



(a) Phenotypic screening for small molecules that enhance the survival of C9-ALS iMNs. (b) Chemical structure of the PIKFYVE inhibitors YM201636 and Apilimod, and a reduced-activity analog of Apilimod. (c) Live cell images of iMNs at day 7 of treatment with DMSO or YM201636

Model for the mechanisms that cooperate to cause neurodegeneration in C9ORF72 ALS



Survival effect of scrambled or PIFKVYE ASOs on C9-ALS iMNs in excess glutamate. A Model for the mechanisms that cooperate to cause neurodegeneration in C9ORF72 ALS/FTD. Proteins in red are known to be mutated in ALS.

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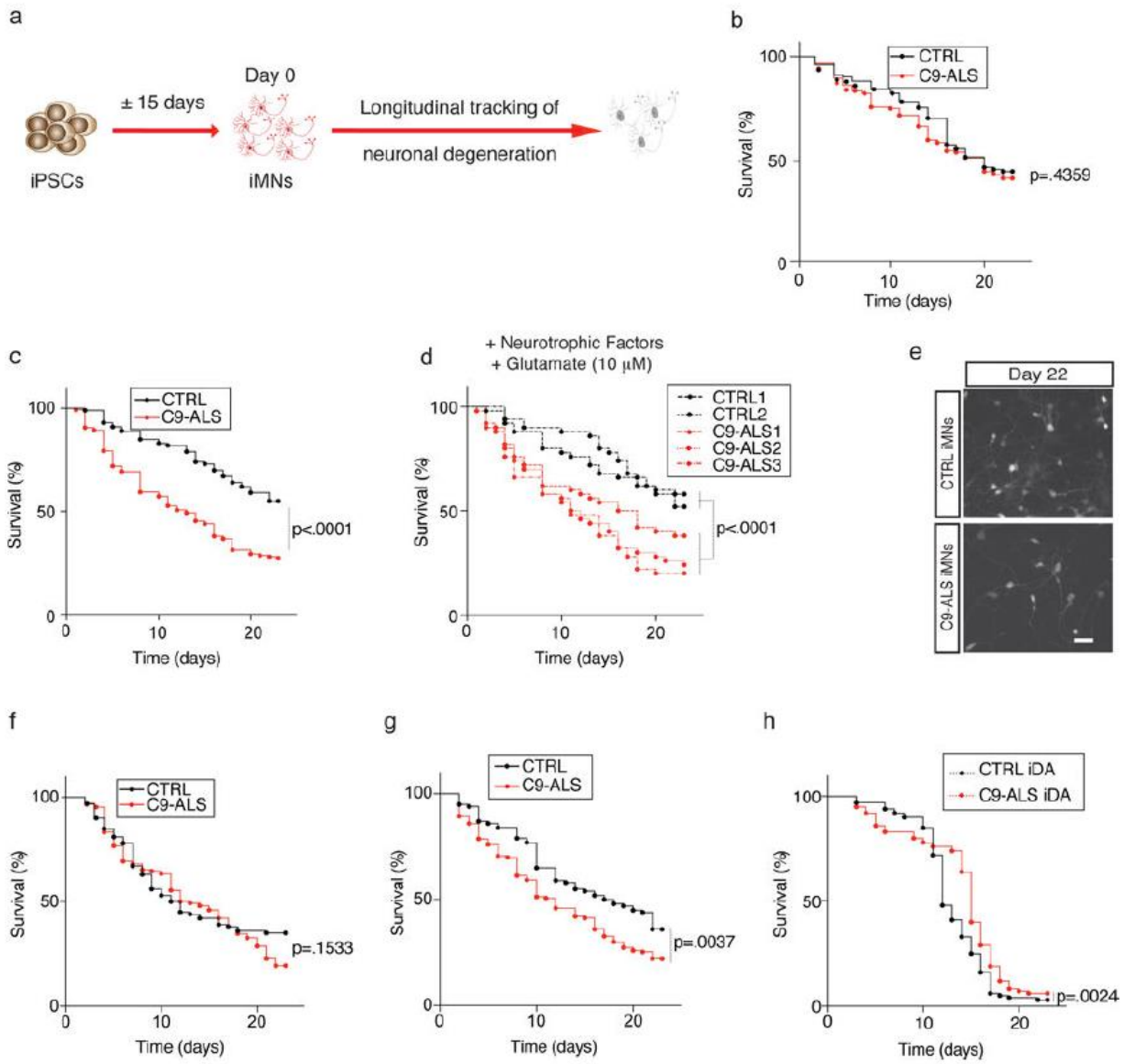
C9ORF72 patient iMNs undergo rapid neurodegeneration



(a) Production of Hb9::RFP+ iMNs and survival tracking by time-lapse microscopy. (b-d) Survival of control (CTRL) and C9ORF72 patient (C9-ALS) iMNs with neurotrophic factors (b) or in excess glutamate. (e) iMNs at day 22 in excess glutamate. This experiment was repeated three times with similar results. (f-g) Survival of control and C9-ALS iMNs in excess glutamate with glutamate receptor antagonists (f) or without neurotrophic factors (g). (h) Survival of induced dopaminergic (iDA) neurons in excess glutamate.

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Intellectual Property

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