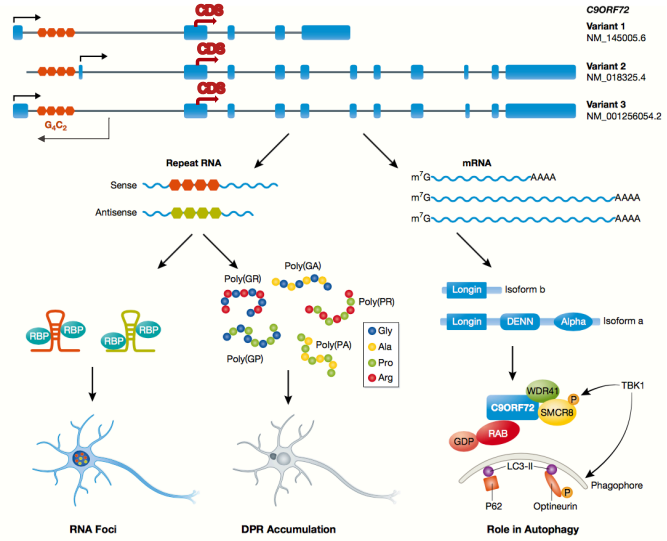
Main pathogenic pathways



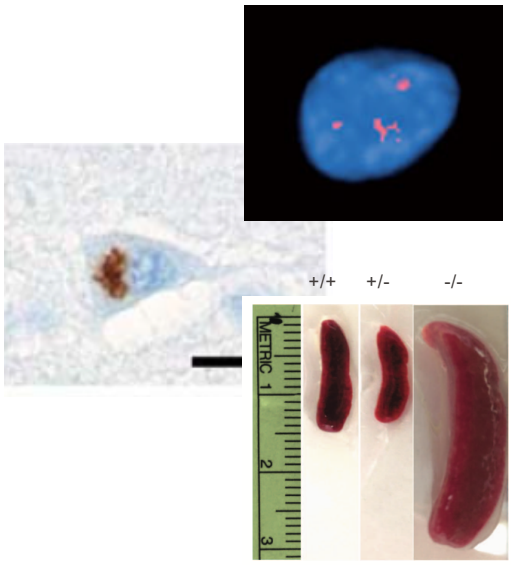
C9orf72 pathology

1

EPFL ALS: C9orf72

The following mechanisms have been proposed to explain the C9orf72 pathology:

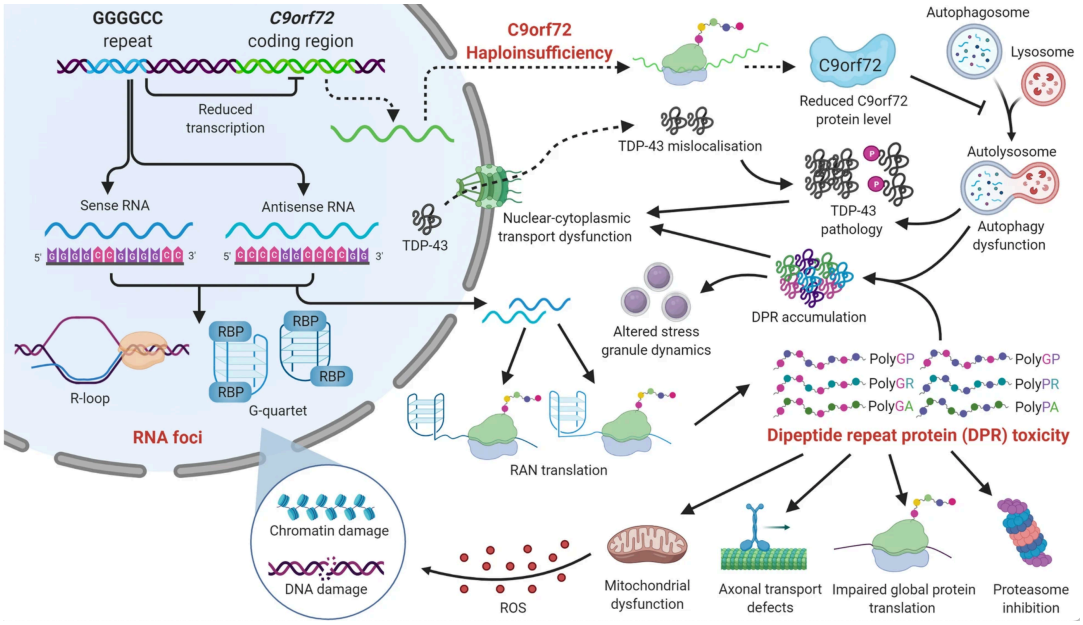
- r(GGGGCC) RNA is toxic (RNA foci).
- RAN translation of poly[PR], poly[GR], poly[GP] or poly[GA] dipeptides leads to expression of toxic species in neurons.
- The presence of r(GGGGCC) in the C9orf72 gene reduces expression and activity of the C9orf72 protein (loss of function). C9orf72 appears to upregulate cell autophagy and control inflammation.



EMBO J. 2020;39(4):e100574.
Nature 585, pp. 96–101 (2020)

2

ALS: C9orf72



Molecular Neurodegeneration volume 17, Article number: 22 (2022)

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ALS: C9orf72

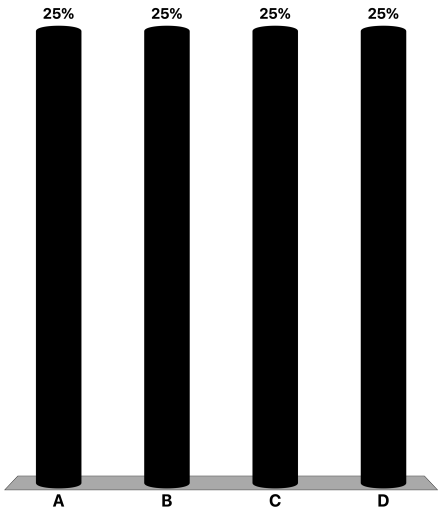
In your opinion, which approach has the best chance to provide therapeutic efficacy ?

A. Suppress toxic RNA

B. Silence the toxic dipeptides

C. Restore physiological C9orf72 expression

D. A combination of two or more of the treatments above



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Complete the following table, indicating the suitable treatment(s) for each toxic activity of C9orf72:

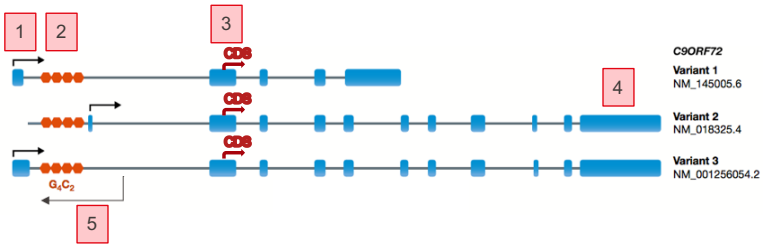
	Cause of toxicity:	RNA foci	Dipeptide accumulation	Loss of C9orf72 activity
Treatments	Small RNA for RNAi			
	Compound inducing autophagy			
	Antibody			
	Gene editing to reduce the number of GGGGCC repeats			
	Small RNA for exon skipping (splicing modifier)			

5

C9orf72 pathology: exercise

You plan to design a small RNA to oppose C9orf72 toxicity.

Where in the precursor mRNA do you think that the small RNA should bind (multiple options are possible) ?



0% A. 1

0% B. 2

0% C. 3

0% D. 4

0% E. 5

6

Biogen

BIOGEN.COM INFORMATION REQUEST SIGN UP FOR ALERTS SEARCH

OVERVIEW NEWSROOM EVENTS & PRESENTATIONS FINANCIALS STOCK INFORMATION CORPORATE GOVERNANCE

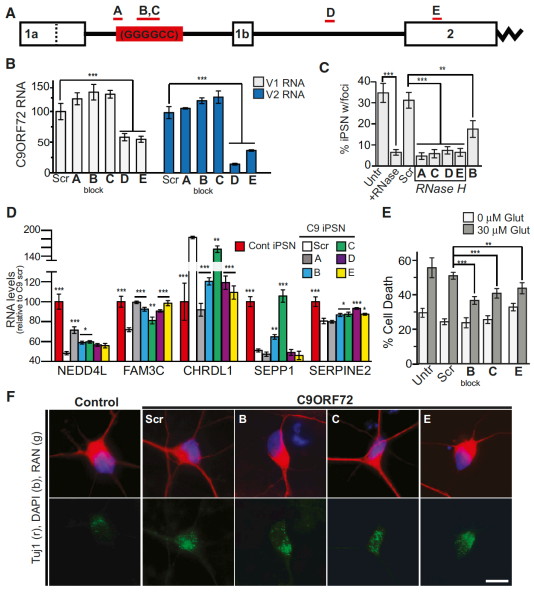
Biogen and Ionis Announce Topline Phase 1 Study Results of Investigational Drug in C9orf72 Amyotrophic Lateral Sclerosis

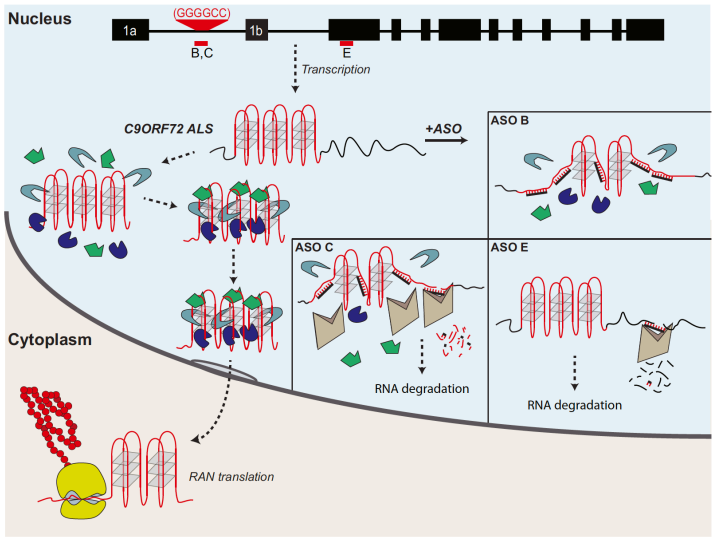
MARCH 28, 2022 • COLLABORATIONS

BIIB078 did not meet any secondary efficacy endpoints and it did not demonstrate clinical benefit. In the dose cohorts up to 60 mg there were no consistent differences between the BIIB078 group and the placebo group. Participants in the BIIB078 90 mg dose cohort trended toward a greater decline than those in the placebo group across secondary endpoints. Based on these results, the BIIB078 clinical development program will be discontinued, including its ongoing open-label extension study.

7

ASO C9orf72 in iPS cell model





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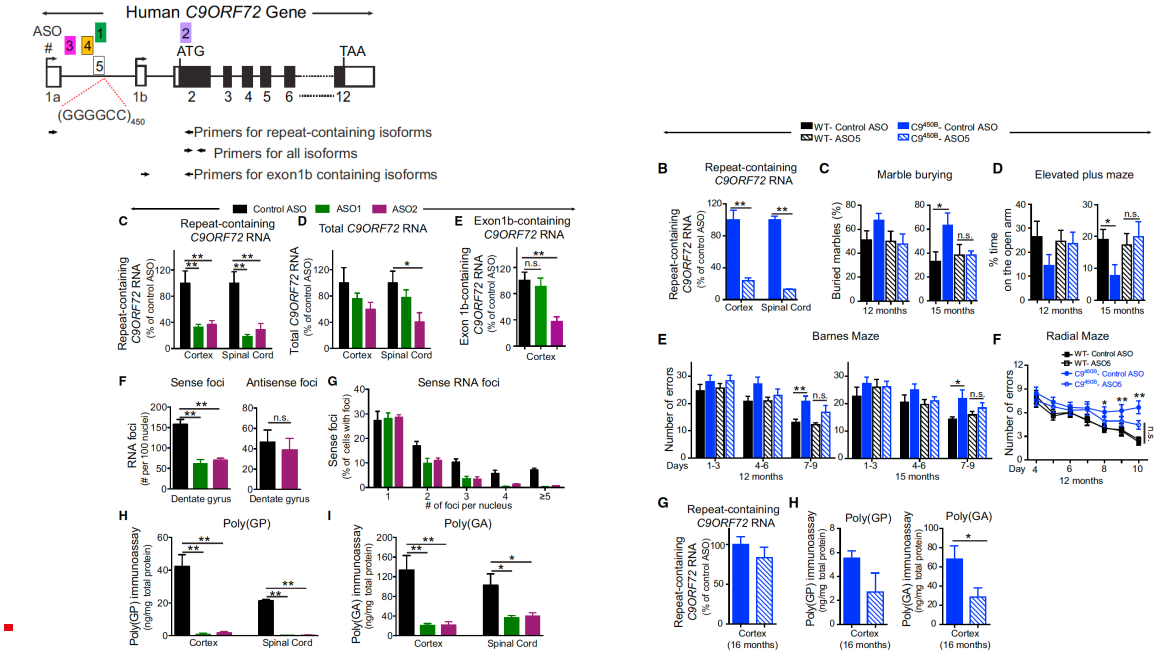
C9orf72 BAC mice



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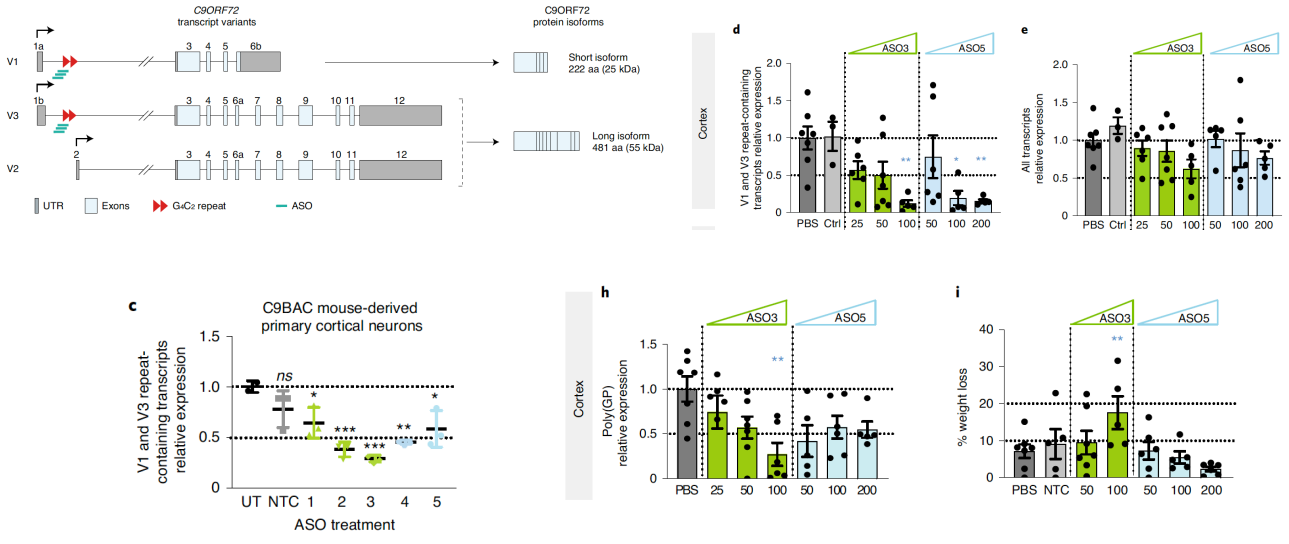
C9orf72 BAC mice



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