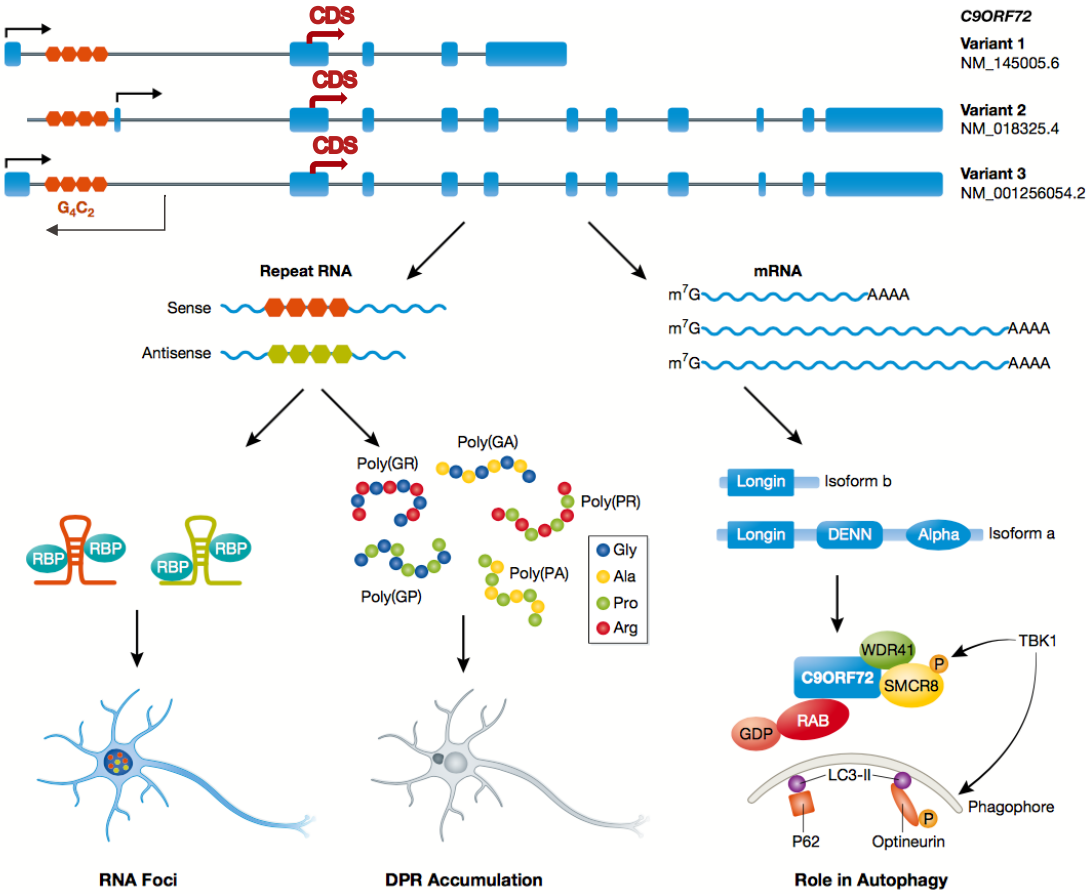
Main pathogenic pathways

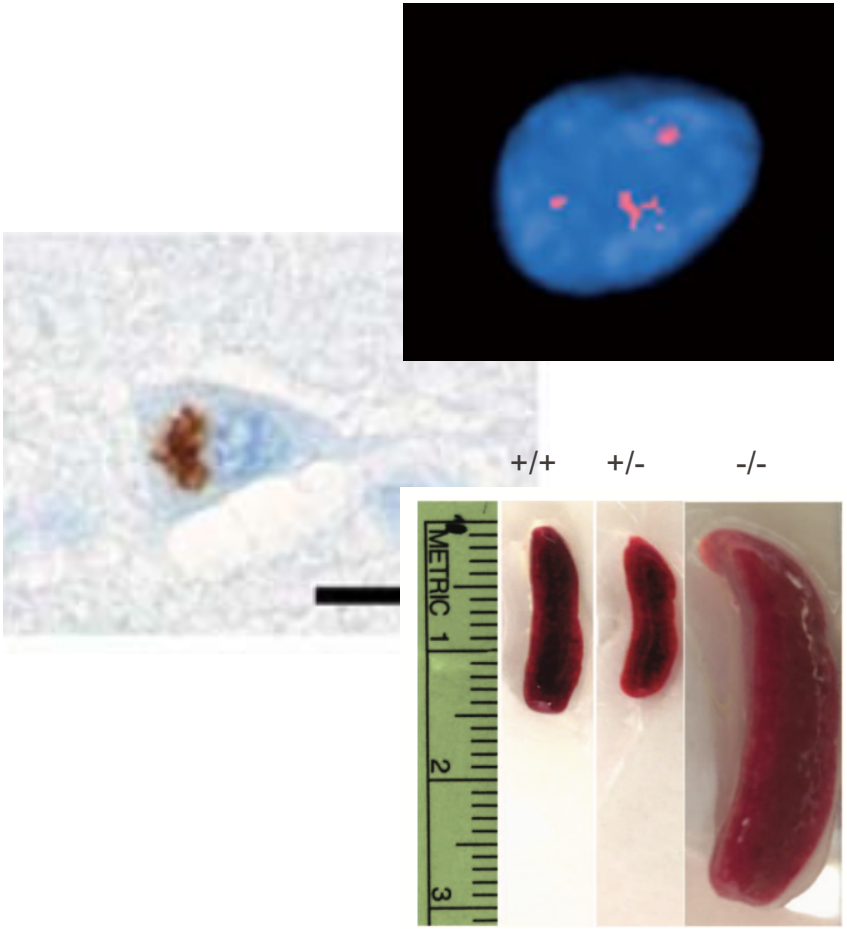


C9orf72 pathology

ALS: C9orf72

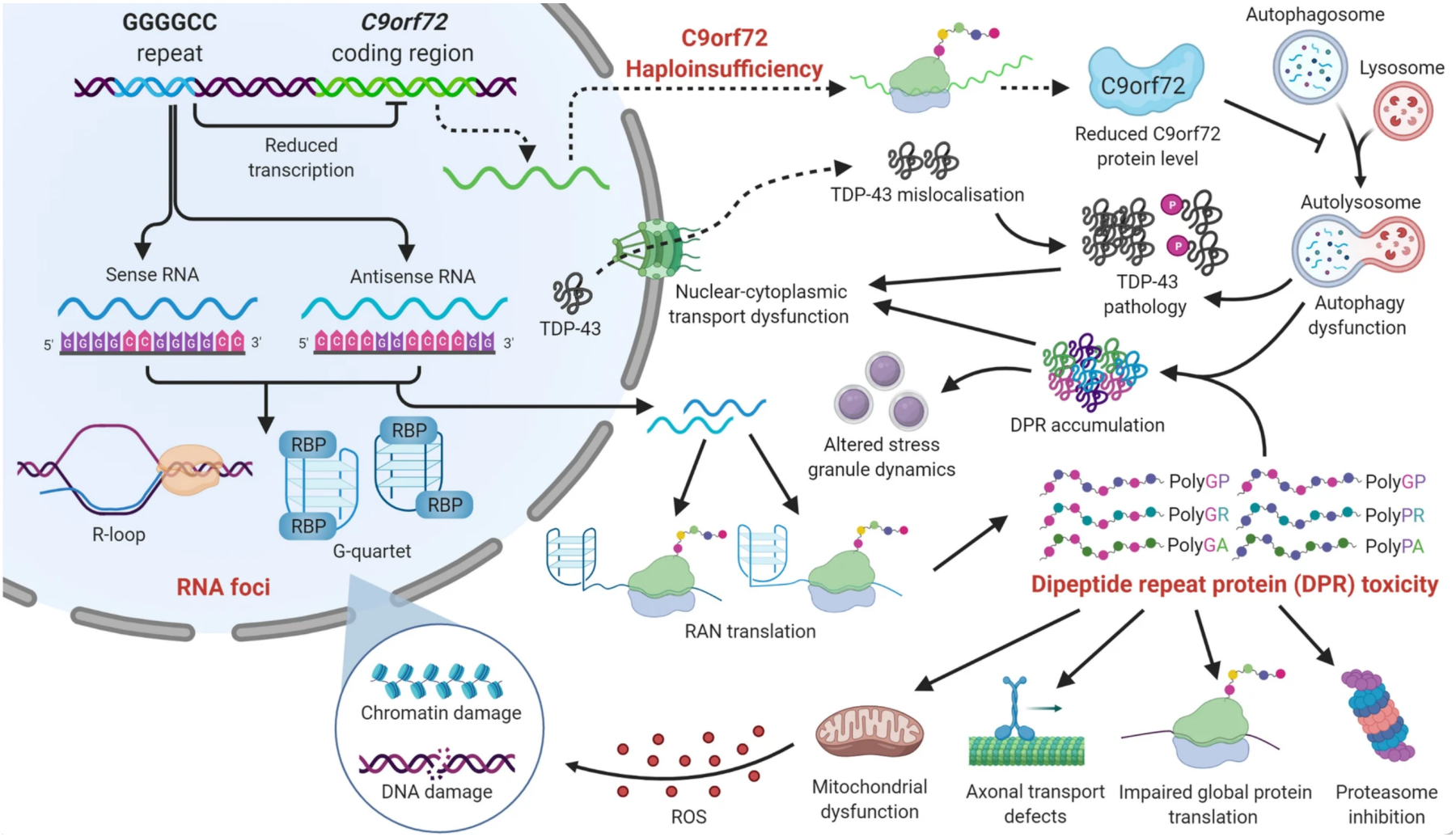
The following mechanisms have been proposed to explain the C9orf72 pathology:

- 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)

ALS: C9orf72



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ALS: C9orf72

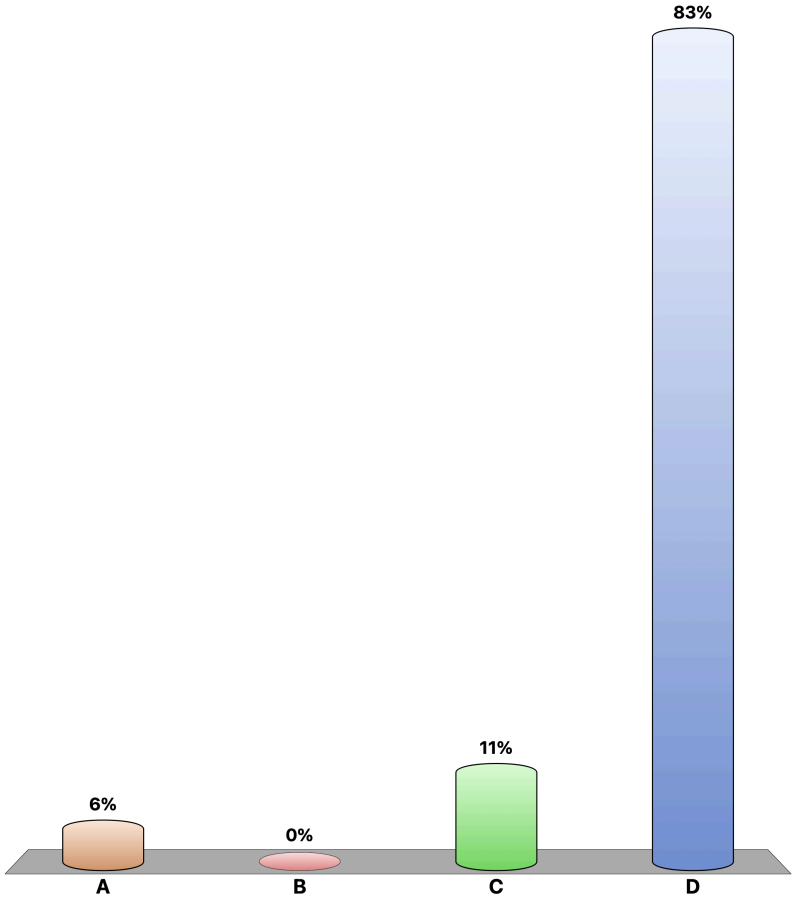
In your opinion, which approach has the best chance to provide therapeutic efficacy ?

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**



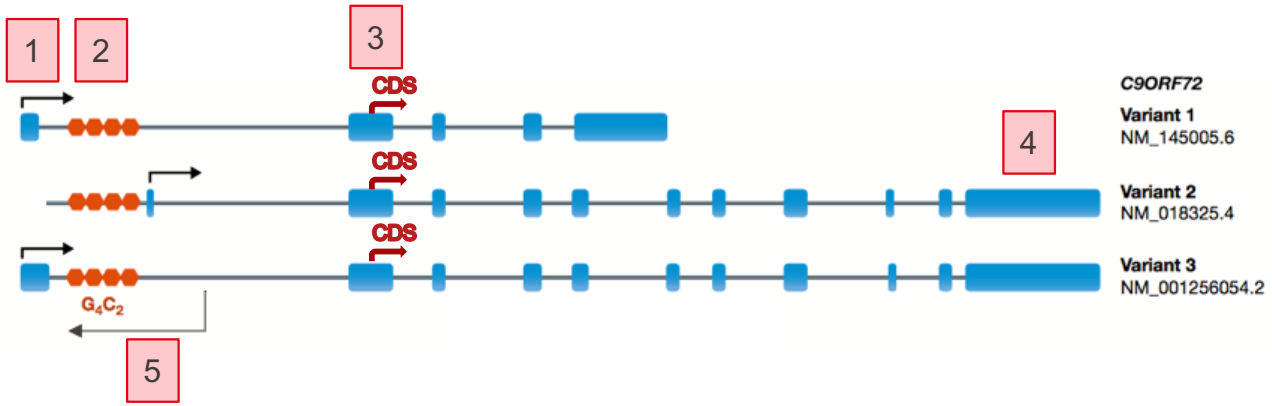
Complete the following table, indicating the suitable treatment(s) for each toxic activity of C9orf72:

	Cause of toxicity:	RNA foci	Dipeptide expression	Loss of C9orf72 activity
Treatments	Small RNA for RNA interference	✓	✓	May worsen
	Compound inducing autophagy		(✓)	✓
	Antibody		(✓)	
	Gene editing to eliminate the GGGGCC repeats	✓	✓	✓
	Small RNA for exon skipping (splicing modifier)		(✓)	May worsen

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) ?



- **A. 1**
- **B. 2**
- C. 3
- D. 4
- **E. 5**