



This is a repository copy of *Gene Therapy for Familial ALS Using AAV9 Mediated Silencing of Mutant SOD1*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/106640/>

Version: Accepted Version

Proceedings Paper:

Iannitti, T., Scarrot, J.M., Coldicott, I.R.P. et al. (4 more authors) (2016) Gene Therapy for Familial ALS Using AAV9 Mediated Silencing of Mutant SOD1. In: Human Gene Therapy. British Society for Gene and Cell Therapy Annual Conference, 15th April 2016, University College London Institute of Child Health. Mary Ann Liebert Inc , A12-A12.

<https://doi.org/10.1089/hum.2016.29027.abstracts>

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Gene Therapy for Familial ALS Using AAV9 Mediated Silencing of Mutant SOD1

Iannitti T¹, Scarrott JM¹, Coldicott IRP¹, Kaspar BK², Ferraiuolo L¹, Shaw PJ^{1*}, Azzouz M^{1*}
(*Joint senior authors)

¹University of Sheffield, Sheffield Institute for Translational Neuroscience (SITraN), 385 Glossop Road, Sheffield, S10 2HQ, UK.

²The Research Institute at Nationwide Children's Hospital, Department of Neuroscience, The Ohio State University, Columbus, OH 43205

Background. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder resulting in death of brain and spinal cord motor neurons. Some familial cases are caused by missense mutations in the gene encoding the Cu/Zn superoxide dismutase 1 (SOD1) conferring a toxic gain of function to this protein. We hypothesised that specifically silencing expression of the mutant form of the human SOD1 gene would alleviate SOD1-linked ALS symptoms.

Objectives. Evaluate the therapeutic efficacy of AAV9-shRNA mediated SOD1 silencing in the SOD1G93A mouse model.

Methods. Animals were treated either at postnatal day 1 (P1, pre-onset) or P40 (onset). scAAV9-hSOD1si or scrambled control scAAV9-hSOD1ssi were delivered using 2 routes of delivery, facial vein or cisterna magna. Mice were then tested using behavioural tests including weekly rotarod runs, neurological scoring and CatWalk gait analysis. Weekly body weight was also collected.

Results. We observed an improvement in rotarod performance in mice treated with scAAV9-hSOD1si vs. scAAV9-hSOD1ssi and untreated controls in all studies. Survival analysis revealed that scAAV9-hSOD1si delivery via cisterna magna at P1 and P40 extended SOD1G93A mouse life span by 67 days and 16 days, respectively. The P1 cisterna magna study is still ongoing. **So far the longest survival has been 241 days.** SOD1 silencing at P40 also improved motor function as revealed by CatWalk gait analysis.

Conclusions. AAV9-shRNA mediated SOD1 silencing through cisterna magna improved motor performance and led to remarkable life span extension in the SOD1G93A mouse model. Our gene therapy approach offers promising strategy for clinical application in SOD1-linked familial ALS.