

First in vivo proof-of-concept in Steinert's myotonic dystrophy

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Ana Buj Bello's team, a researcher in an Inserm unit at Genethon, the AFM-Telethon laboratory, has made the proof-of-concept of a CRISPR-Cas9 approach in a mouse model of Steinert's myotonic dystrophy, the most common neuromuscular disease in adults. Indeed, thanks to this genome editing approach, the expanded CTG triplet repeat in the DMPK

gene, which is responsible for the disease, was "cut" and removed from the gene, and the number of toxic RNA aggregates was decreased in the muscle cells of the tested models. Based on these encouraging results, published in the June 5 issue of *Molecular Therapy*, the researchers are currently investigating whole body treatment.

Steinert's myotonic dystrophy (DM1) is the most common form of adult muscular dystrophies. With a genetic origin, its prevalence is estimated at 1 in 8,000 persons, and is mainly characterized by difficulties in relaxing after contraction (myotonia) and a progressive muscle weakness. The disease is due to mutations in the DMPK gene, in particular, to an increase in the number of repeats of a small 3-nucleotide DNA sequence, a CTG triplet, located in the DMPK gene. This results in the accumulation of mutated DMPK RNA in the [cell nucleus](#), leading to alterations in cellular functions. There is currently no cure for this neuromuscular disease.

In this study, Ana Buj Bello's team, in collaboration with Denis Furling's team at the Institute of Myology and Genevieve Gourdon's team at the Imagine Institute, have developed and evaluated a gene therapy approach using the CRISPR-Cas9 molecular scissors in cellular and in vivo mouse (DMSXL) models of the disease:

In the cellular model : The team has identified guide RNAs that target DNA sequences around the CTG triplet region of the DMPK gene, and demonstrated that the Cas9 protein removes this part of the genome, resulting in the disappearance of nuclear toxic RNA aggregates in treated cells.

In the mouse model : The team has used the same technology in vivo and administrated intramuscularly gene therapy vectors (AAV9) that carry Cas9 and guide RNAs targeting the DMPK gene. Few weeks after injection, a decrease in toxic RNA aggregates was observed in the nuclei

of [muscle cells](#) of diseased mice.

"After several years of work, we have been able to demonstrate that the CRISPR-Cas9 system works in skeletal muscle for Steinert's disease. These results represent a very encouraging first step, and we now plan to optimize this approach to correct the entire musculature and other tissues affected by the [disease](#)," highlights Ana Buj-Bello, lead author of the work.

More information: Mirella Lo Scudato et al. Genome Editing of Expanded CTG Repeats within the Human DMPK Gene Reduces Nuclear RNA Foci in the Muscle of DM1 Mice, *Molecular Therapy* (2019). [DOI: 10.1016/j.ymthe.2019.05.021](https://doi.org/10.1016/j.ymthe.2019.05.021)

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