Use of an antisense-mediated exon skipping approach as a therapeutic option for a common Mucolipidosis type II causing mutation

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Lysosomal Storage Disorders (LSDs) are a group of rare inherited diseases caused by the malfunction of the lysosomal system, resulting in the accumulation of undegraded substrates inside the lysosomes and leading to severe and progressive pathology. Among them is ML II, one of most severe LSDs, which is caused by the total or near total deficiency of the GlcNAc-phosphotransferase, a key in enzyme for the correct trafficking of lysosomal hydrolases to the lysosome. GlcNAc-phosphotransferase is a multimeric enzyme and is encoded by two genes: *GNPTAB* and *GNPTG*. One of the most frequent ML II causal mutations is a dinucleotide deletion on exon 19 of the *GNPTAB* gene that disrupts the reading frame and prevents the production of an active GlcNAc-phosphotransferase, which in turn impairs the proper targeting of lysosomal enzymes. Despite broad understanding of the molecular causes behind this and other LSDs, the same progress has not been observed in the development of new therapies, with current treatments still mostly symptomatic and presenting several limitations. Therefore, alternative options should be investigated in order to provide patients and families with better healthcare and more promising therapies. One possibility is the modulation of splicing by antisense oligonucleotides with the purpose of altering the splicing pattern, the mature mRNA and ultimately the final protein product. Acknowledging this, the present study intends to design and develop a RNA-based therapeutic agent through the use of antisense oligonucleotides capable of inducing the skipping of exon 19 of the *GNPTAB* gene and consequently circumvent the effects the most common ML II causal mutation. The approach is presently ongoing and different 2'O-Methyl AOs were designed and synthesized to target the *GNPTAB* exon 19 and promote its skipping. We have already succeed in inducing the skipping of exon 19 in control and ML II patient cell lines and we are now evaluating the effects of this therapeutic approach at biochemical levels.

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