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Título	Substrate reduction therapy for mucopolysaccharidosis using the CRISPRi system
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Introduction: Substrate Reduction Therapy (SRT) is a treatment option to reduce the production of substrates in certain metabolic disorders. This work suggests that gene editing-mediated inhibition (CRISPRi) of genes involved in heparan, and dermatan sulfate (HS and DS) synthesis could be used as SRT in Mucopolysaccharidosis I and II. To negatively regulate the biosynthesis of DS and HS, critical genes involved in this process must be targeted. : *CHST15*, a sulfotransferase, and *FAM20B*, a phosphokinase **Objective:** To develop an alternative method to treat MPS type I and II through SRT by CRISPRi to reduce glycosaminoglycans (GAGs) biosynthesis. **Methodology**: We designed sgRNAs for the promoter regions of these genes using CHOPCHOP program version 3 based on the reference genome (hg38/GRCh38). Minimum efficiency of 40%, GC content between 40 and 80%, and the lowest possible number of mismatches up to 3 were considered. Besides, the sgRNAs for the 1st exon were designed based on the same gene strand for disturbing transcription elongation. Additional selection criteria were based on the repression of different gene transcripts. A total of 15 sgRNAs were found for *CHST15* and 15 for *FAM20B.* For the *CHST15* gene, at least one sgRNA without predicted off-targets was found either for the 1st exon or the promoter region. For the *FAM20B* gene, the best results in terms of off-targets were sgRNAs without predicted off-targets in coding regions, both for the 1st exon and the promoter region. **Conclusion:** The repression of *FAM20B* and *CHST15* is crucial to influencing the GAGs biosynthesis. Thus, it reduces the amount of glycosaminoglycans accumulation into lysosomes, which triggers the MPSs patient's multi-systemic symptoms. These results suggest a new therapeutic option to treat MPS diseases using CRISPRi, that must be corroborated by experimental validation.