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Title

Less is More: an overview on the use of RNAi as a tool to achieve Substrate Reduction in Mucopolysaccharidoses

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Abstract

Mucopolysaccharidoses (MPSs) are a subgroup of Lysosomal Storage Diseases (LSDs) caused by dysfunction in enzymes responsible for the intralysosomal degradation of glycosaminoglycans (GAGs). Given their complex nature and the limitations of available therapies, the shift towards the development of combination treatments to counteract more effectively the pathological burden of these disorders is in the agenda of current research.

We consider that treatment strategies relying on RNA interference (RNAi), as well as in other RNA-based methodologies, may be feasible and particularly promising in the context of a synergistic combinatorial therapeutic approach. Therefore, we have designed an RNAi-dependent strategy based upon the selective downregulation of genes involved in the biosynthesis of GAGs, which is currently under evaluation. Our goal is to promote an effective reduction of the accumulating substrate, ultimately decreasing or delaying MPSs' symptoms. Taking advantage of the RNAi technology potential, we have designed and assayed specific siRNAs targeting genes on those biosynthetic cascades to decrease the levels of production of each one of the four substrates: dermatan sulphate (DS), heparan sulphate (HS), keratan sulphate (KS), and chondroitin sulphate (CS). Their efficiency is currently being evaluated in vitro.

Here we present an overview of the preliminary results of this project and unveil its next steps towards a full characterization/evaluation of its potential therapeutic effect.

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