

LESS IS MORE:

AN OVERVIEW ON THE USE OF RNAI AS A TOOL TO ACHIEVE SUBSTRATE REDUCTION  
IN MUCOPOLYSACCHARIDOSES

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Lysosomal storage diseases (LSDs) are a group of genetic disorders caused by dysfunction in enzymes responsible for the intralysosomal degradation of particular compounds. 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 viewing to improve the clinical outcome of LSD patients. We consider that treatment strategies relying on RNA interference (RNAi), as well as in other RNA-based methodologies, may be feasible and particularly promising if designed in the context of a synergistic combinatorial therapeutic approach. We are currently evaluating an RNAi-dependent strategy based upon the selective downregulation of genes involved in the biosynthesis of glycosaminoglycans (GAGs), the major substrates that accumulate in patients suffering from a subset of LSDs called mucopolysaccharidoses (MPSs). Although enzyme replacement therapy is already available for some MPSs, it has some serious drawbacks, justifying the challenge of developing additional therapies targeting this group of disorders. Our goal is to promote an effective reduction of the accumulating substrate, ultimately decreasing or delaying MPSs' symptoms.

It should be noticed that, even though some substrate reduction therapy (SRT) drugs have already been approved (miglustat for GD) or are undergoing clinical trial (genistein and/or rhodamine B for MPSs), clinical evaluation of those same drugs has unveiled a few side effects, the most well-known being those observed for miglustat, which included osmotic diarrhea and weight loss. Nevertheless, chemical drugs aren't the only way to achieve substrate reduction. Ours is fully molecular, *drug-free* approach, whose major focus relies on the biosynthetic pathways giving origin to each one of the GAGs whose degradation is impaired in MPS. 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. 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.