Dia do Jovem Investigador do Instituto Ricardo Jorge 2017

Lisboa, 8 de maio de 2017

Área(s) temática(s): Assinalar a(s) que se aplica(m)

[X] Doenças crónico degenerativas e genéticas
[ ] Doenças infeciosas
[ ] Epidemiologia, biostatística e bioinformática
[ ] Imunologia
[ ] Promoção da saúde
[ ] Saúde ambiental e da alimentação
[ ] Serviços de saúde

Title: Splicing therapeutics for patients affected by lysosomal storage disorders

Author(s), Affiliation(s):

Liliana Matos[1], Vânia Gonçalves[2], Isaac Canals[3,4,5], Peter Jordan[2], Daniel Grinberg[3,4,5], Belén Pérez[4,6], Maria João Prata[7,8], Sandra Alves[1]

1 *Department of Human Genetics, Research and Development unit, INSA, Porto, Portugal;* ***2*** *Department of Human Genetics, Research and Development Unit, INSA, Lisbon, Portugal;* ***3*** *Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain;* ***4*** *CIBER de Enfermedades Raras (CIBERER), Madrid, Spain;* ***5*** *Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain;* ***6*** *Centro de Diagnóstico de Enfermedades Moleculares, Centro de Biología Molecular Severo Ochoa, UAM-CSIC, Universidad Autónoma de Madrid, Madrid, Spain;* ***7*** *Department of Biology, Faculty of Sciences, Porto, Portugal;* ***8*** *i3S - Instituto de Investigação e Inovação em Saúde/IPATIMUP - Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal*

Abstract

Splicing defects are among the most frequent pathogenic mechanisms underlying genetic diseases. Thus, the development of therapeutic strategies targeting RNA represents an important opportunity to correct faulty splicing, opening the prospects of treatment for numerous genetic disorders. The vast majority of RNA-based approaches have exploited, *in vitro* and *in vivo*, the use of antisense oligonucleotides or modified U1 snRNAs to overcome different splicing mutations.
Lysosomal storage disorders (LSDs) are a group of inherited diseases that can result in severe and progressive pathology due to a specific lysosomal dysfunction. In several patients, splicing mutations have been identified and are frequently associated with particular types of LSDs worldwide. Some treatment strategies are already available for conventional LSDs, but yet with some limitations. Therefore, for splicing mutations, splicing therapeutics might represent a crucial option or an important adjunct of other treatments.
In this study, we have used a modified U1 snRNA that completely matches the splice donor site of *HGSNAT* gene exon 2, which corrected the effect of the common 5'

splice site mutation c.234+1G>A in Mucopolysaccharidosis IIIC (1). In another approach using an antisense oligonucleotide (AO) we have succeeded in the correction of the c.66G>A splicing mutation in *CSTB* gene (Unverricht–Lundborg disease). Besides that, we have performed the functional analysis of some *IDS* gene splicing mutations (Mucopolysaccharidosis II) and used AOs to exploit an alternative therapy for one of those mutations (c.1122C>T on exon 8) (2).

1. Matos et al. Orphanet J Rare Dis. 2014; 9:180.
2. Matos et al. Biochim Biophys Acta. 2015; 1852:2712-21.

Acknowledgements

Liliana Matos FCT grant (SFRH/BD/64592/2009)