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21.ª Reunião Anual da Sociedade Portuguesa de Genética Humana

Development of RNA based approaches to exploit alternative therapies for Lysosomal Storage Diseases.

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Lysosomal Storage Disorders (LSDs) are a group of rare inherited metabolic 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.
Treatment strategies such as substrate reduction and enzyme-replacement therapy, among others, are available for some LSDs, yet still with some limitations.
In recent years, the RNA molecule became one of the most promising targets for therapeutic intervention and currently, a large number of RNA-based therapies are being investigated at the basic research level and in late-stage clinical trials, as also some of them are already approved for treatment (e.g. Duchenne muscular dystrophy; Familial hypercholesterolemia).
RNA-based approaches constitute a potential alternative or an adjuvant therapeutic strategy for many diseases; either acting at pre-mRNA levels (by splicing modulation/correction using antisense oligonucleotides or U1snRNAs vectors) or at mRNA levels (e.g. using small interfering RNA (siRNA) and antisense oligonucleotides).
Currently we are developing some of these therapeutic approaches for LSDs. Two main research lines are ongoing; one involves the use of antisense U1 snRNAs and antisense oligonucleotides to overcome the effect of the LSDs causing mutations c.234+1G>A in Mucopolysaccharidosis type IIIC and c.3503_3504delTC in Mucolipidosis type II respectively, and the other is based on the use of RNA interference (RNAi) technology to promote efficient substrate reduction therapy for a subset of LSDs called Mucopolysaccharidoses.