RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine

September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Oligonucleotide therapy for rare genetic diseases

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Antisense oligonucleotides (ASOs) have been developed for Duchenne muscular dystrophy (DMD). Splice modulating ASOs can induce exon skipping to restore the reading frame, allowing production of shorter but partially functional dystrophin proteins, as found in the less severely progressive Becker muscular dystrophy. Currently, 4 exon skipping ASOs are approved by the USA Food and Drug Administration.

We know delivery of ASOs to skeletal muscles is challenging. Delivery to the central nervous system, however, is relatively straightforward using intrathecal injections, which leads to uptake of ASOs throughout the central nervous system. The advantages of local delivery are that a low dose can be used with low systemic exposure and that treatment frequency is low (3-6 times per year). This is exemplified in nusinersen, an ASO for the treatment of spinal muscular dystrophy that is approved since 2016.

Tim Yu (Boston Children Hospital) showed it is possible to develop an **individualized** ASO for a Batten disease patient with a cryptic splicing variant (milasen). Inspired by this, in the Netherlands we established the Dutch Center for RNA Therapeutics, a collaboration of different academic medical centers with ASO development expertise, where the goal is to develop individualized ASOs for eligible patients with genetic brain or eye diseases within an academic setting and to provide them to patients without a profit. Developing ASOs for single patients is a challenge as the normal drug development routes are not fit for purpose. As such new routes and tools need to be developed. To align and streamline efforts and provide guidance the European 1 Mutation 1 Medicine and global N-of-1 Collaborative were established as European and global umbrella organisations. So far, guidance on selecting which patients and genetic variants are eligible for personalized ASO treatment has been produced, as well as guidance on preclinical assessment of ASO efficiency.