CUTTING EDGE PRECISION MEDICINE: ANTISENSE OLIGONUCLEOTIDES AS SPLICING SOLUTIONS

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INTRODUCTION

Recently, the power of RNA as a therapeutic agent has been studied to challenge some of the most persistent problems in medicine. Thus, personalized and genome-specific approaches are now being used to treat several diseases including those considered rare and neglected. In the past year, two successful RNA drug applications have been carried through clinical trials which utilize antisense oligonucleotides (ASO), or short complementary sequences, as a therapeutic RNA approach. With this new class of orphan drugs, it appears researchers have broken ground on a widely applicable field. They feature splice modulating mechanisms, where the binding of the ASO to mRNA results in decreased splicing defects and translation of functional proteins. The lessons learned along with new technologies can be applied not only to other neuromuscular diseases, including Huntington's, ALS, and myotonic dystrophy, but also those amenable to alternative splicing or RNA degradation such as various cancers. The number of pending FDA clinical trials for ASOs and plans to enter clinical trials for a wide range of diseases shows that this approach may greatly impact the future of personalized medicine.

RECENT CLINICAL TRIALS

Spinal Muscular Atrophy (SMA) is the leading cause of childhood death associated with a genetic dysfunction with an incidence in 1:10,000 live births. In December of 2016, Spinraza was approved by the FDA through an accelerated process, and utilizes an 18-nucleotide 2'-O-methoxyethyl phosphorothioate (2'MOE PS) ASO that causes exon 7 to be included by sterically blocking an intron splicing silencer (N1) thus restoring a functional protein (SMN) which SMA patients lack.[1] During two independent late-stage clinical trials, the studies were halted to allow the placebo group access to the life-saving drug. In another study for the treatment of Duchenne Muscular Dystrophy (DMD), a 30-nucleotide phosphorodiamidate morpholino oligomer (PMO), Exondys 51, was

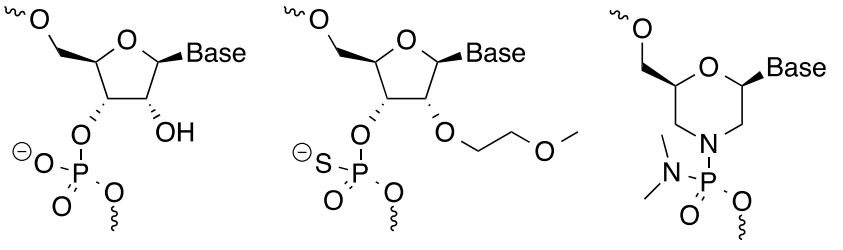

Figure 1. Oligonucleotide modifications.

approved to restore the reading frame by skipping exon 51 to form a truncated version of the protein, dystrophin, which is partially functional. The ASO masks key splicing sites ahead of exon 51 on the pre-mRNA. This treatment is applicable to the largest group of DMD patients, but there are still several limitations to the functionality.[2]

LIMITATIONS AND IMPROVEMENTS

The current approach to ASO is limited by rapid degradation, cell penetration and target delivery. In addition, repeated injections open the door for questions of long-term toxicity. Spinraza (for SMA) is by far the best of the drug candidates to date, but it is no way perfect; the drug cannot cross the blood-brain barrier, requiring repeated intrathecal injections. Though Exondys 51 showed improvement of the DMD disease phenotype, there was only a limited increase in the levels of dystrophin likely due to poor cell penetration and tissue distribution. New technologies[3] are emerging to address delivery and potency issues including: viral vectors, nanoparticles, cell-penetrating peptides, and the incorporation of tricyclo-DNA. In DMD, the use of cell-penetrating peptides conjugated to PMO antisense oligonucleotides show efficacy in preventing cardiomyopathy. The use of tricyclo-DNA oligomers has also been reported to show increased efficacy in the heart and central nervous system. Tricyclo-DNA oligomers are readily soluble in aqueous solution where they form nanoparticles, increasing cellular uptake following IV administration. Viral vector-mediated antisense therapy, such as small nuclear RNA shuttling, address several issues, including extra-nuclear instability and poor cellular uptake. Antisense oligonucleotides could also benefit from nanoparticle delivery systems which can be engineered to be tissue-specific.

CONCLUSION

To propel the field forward, researchers must first study the recent and past clinical trials to better understand the successes and limitations. With this information, informed decisions can be made to create better oligonucleotides which show increased penetration and potency. Among the best of the new technologies are cell-penetrating peptides and tricyclo-DNAs. With increased delivery profile, nuclease resistance, and binding affinity, these modifications show better potential than those in the clinic today. If these technologies prove effective in human patients, they could change the future of the field.

REFERENCES

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