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Research Report

# Oligonucleotide-based therapy for neurodegenerative diseases

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ABSTRACT

Molecular genetics insight into the pathogenesis of several neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, encourages direct interference with the activity of neurotoxic genes or the molecular activation of neuroprotective pathways. Oligonucleotide-based therapies are recently emerging as an efficient strategy for drug development and these can be employed as new treatments of neurodegenerative states. Here we review advances in this field in recent years which suggest an encouraging assessment that oligonucleotide technologies for targeting of RNAs will enable the development of new therapies and will contribute to preservation of brain integrity.

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## 1. Introduction

Oligonucleotide-based therapy covers a range of methods for modifying gene expression, which have the potential to revolutionize the development of therapeutics and biomedical practice. The uniting idea underlying oligonucleotide-based therapies is to interfere with gene expression at the post-transcriptional RNA level through Watson–Crick base pairing. In this review, we describe ways to change the molecular genetics status of the nervous system, and discuss the approaches by which synthetic oligonucleotides may be employed for brain and spinal cord therapy. We describe the specific challenges associated with RNA delivery into the central nervous system (CNS) by referring to strategies that are under investigation for a number of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS).

In many neurodegenerative diseases, the expression of some proteins is up-regulated as primary or secondary event in the molecular pathogenesis and often abnormal proteins possess aggregation tendency that is thought to play a pivotal role in the pathogenesis. Thus, mutated proteins or even accumulation and aggregation of wild-type proteins may be toxic and can contribute to disease onset or progression. In other cases RNA-based intervention can rescue the expression of a protein that is not well spliced or translated. Many of the strategies to manipulate the expression of specific genes at the RNA level have proven very promising in animal preclinical models and in the most advanced examples initial evidence for

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the relevance of oligonucleotide-based approaches already exist from clinical trials in human patients.

## 2. Biochemical properties of different types of therapeutic oligonucleotides

The biochemical properties of oligonucleotide-based technologies divide the many chemical variants that can be generated through synthetic production into two primary categories: double stranded RNA (dsRNA) that generates RNAi activity through RISC-dependent silencing and single-stranded antisense oligonucleotides (ASOs). These two primary types of nucleic-acid molecule affect downstream targets by different mechanisms that are described in the following reviews (Bennett and Swayze, 2010; Davidson and McCray, 2011; Goodchild, 2011; Kole et al., 2012) and in the text below.

### 2.1. *Single stranded—antisense oligonucleotides*

Antisense oligonucleotides, ASOs, is the more established family that is utilized for RNA-based therapy. These single-stranded oligos are able to either knockdown RNA expression or to modify splicing. Hence, ASOs can reduce or increase the expression of specific proteins, depending on context and biochemistry. ASOs mechanism of action depends on steric blocking of translation, inhibition of splicing or recruitment of RNase H, and in this sense is essentially different from dsRNAs that impart RISC-dependent silencing.

The phosphodiester bonds at the backbone of ribonucleic acid can be modified in order to change the chain biochemical properties. For example, in phosphorothioate nucleotides (PS), one oxygen atom is substituted by sulfur, thus conferring nuclease resistance. PS nucleotides also contribute to the pharmacokinetic profile by improving serum binding and enable RNase H digestion of target RNA. Thiophosphoramidate modifications or isosteres are also used as means for further improving ASOs nuclease resistance. Other non-natural backbones may be used to replace the ribose nucleic acid backbone with peptide nucleic acids (PNAs) or phosphorodiamidate morpholino oligonucleotides (PMOs). "Locked-nucleic acids" (LNAs), are bicyclic nucleic acids that tether the 2′-O to the 4′-C via a methylene bridge. LNAs inhibit nuclease activity and offer a superior binding affinity (Lennox and Behlke, 2011; Petersen et al., 2002; Petersen and Wengel, 2003). Additional insight into the therapeutic use and chemistry of oligonucleotides is reviewed in (Bennett and Swayze, 2010; Lennox and Behlke, 2011).

**Table 1 – Selected clinical trials with RNA-based therapy in neurodegenerative diseases.**

| Disease (alphabetical) | Target | Delivery system | Company (drug name) | ClinicalTrials.gov identifier (s) |
|---|---|---|---|---|
| Age-related macular degeneration (AMD) | DNA damage-inducible transcript 4 | Naked siRNA | Quark Pharmaceuticals (PF-04523655) | NCT00725686<br>NCT01445899<br>NCT00713518<br>NCT00701181 |
| Amyotrophic lateral sclerosis (ALS) | SOD1 | Naked ASO | Isis Pharmaceuticals (SOD1Rx) | NCT01041222<br>Miller et al. (2013) |
| | Dystrophin, exon 51 | Naked ASO (morpholino) | Sarepta therapeutics (AVI-4658/PMO) | NCT00159250<br>Cirak et al. (2012)<br>NCT00844597<br>NCT01396239<br>NCT01540409 |
| Duchenne muscular dystrophy (DMD) | Dystrophin, exon 51 | Naked ASO | GlaxoSmithKline (PRO051/GSK2402968) | NCT01128855<br>NCT01910649<br>NCT01254019<br>NCT01153932<br>NCT01480245<br>NCT01462292 |
| | Dystrophin, exons 44, 45, 53 | Naked ASO | Prosensa therapeutics (PRO044, PRO045, PRO053) | NCT01037309<br>NCT01826474<br>NCT01957059 |
| Familial amyloid polyneuropathy | TTR | Naked ASO | Isis Pharmaceuticals (ISIS-TTRRx) | NCT01737398 |
| | TTR | LNP-formulated GalNac-conjugated siRNA | Alnylam Pharmaceuticals (Patisaran ALN-TTR02) | NCT01960348 |
| Multiple sclerosis | Integrin alpha (4) beta1 | Naked ASO | Isis Pharmaceuticals (ATL/TV-1102) | – |
| Optic atrophy, non-arteritic anterior ischaemic optic neuropathy | CASP2 | Naked siRNA | Quark Pharmaceuticals (QPI-1007) | NCT01064505 |
| Spinal muscular atrophy (SMA) | SMN2 | Naked ASO | Isis Pharmaceuticals (ISIS-$SMN_{Rx}$) | NCT01839656<br>NCT01780246<br>NCT02052791<br>NCT01703988<br>NCT01494701 |