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Gapmer Oligonucleotides: Sugar-Modified Wings to Antisense Therapeutics

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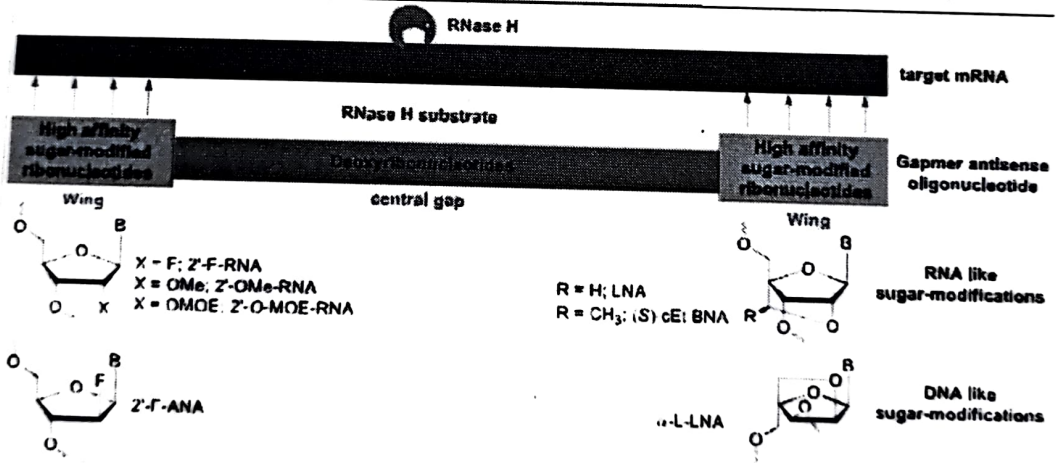
Abstract

Antisense oligonucleotides (AONs) have demonstrated a great therapeutic potential towards sequence-specific silencing of selected gene. Over the last two decades, inclusion of chemical modifications has imbued AONs with essential drug-like properties. Gapmers are beautifully designed AONs that contain a central 'gap' of deoxyribonucleotides which are flanked by 'wings' of sugar-modified nucleotides. Central gap is responsible for recruitment of RNase H cleavage; whereas, sugar-modified terminal 'wings' ensure high affinity for its complementary target and also shield the central gap from nuclease degradation. Gapmer design has embarked new directions to antisense therapeutics as evident from the recent approval of Kynamro comprising sugar-modified wings. With gapmer design, it is now possible to achieve high potency with shorter AONs that can avoid 'irrelevant cleavage' and have significantly reduced toxicities. Interestingly, gapmer AONs have been delivered naked without any transfection assistance, called gymnosis. The present review article aims at providing an insight into pharmacodynamic and pharmacokinetic properties of gapmer AONs as compared to the most successful phosphorothioate backbone-modification.

Gapmer antisense oligonucleotides have demonstrated high potency and specificity towards



sequence specific gene silencing. Central gap is responsible for recruitment of RNase H cleavage; whereas, sugar-modified terminal 'wings' ensure high affinity for its complementary target and also shield the central gap from nuclease degradation.

Keywords: Vitravene, Kynamro, sugar-modified oligonucleotides, gapmer oligonucleotides.

Introduction

The therapeutic potential of synthetic oligonucleotides (ONs) was realised after the seminal experiment carried out by Zamecnik and Stephenson in 1978. It was found that an antisense oligonucleotide (AON) complementary to a specific mRNA of Rous sarcoma virus (RSV) could inhibit the viral replication.[1,2] They also realised the necessity to chemically modify natural ONs that are likely to be degraded by ubiquitous nucleases.[3] Subsequent extensive efforts got delighted

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