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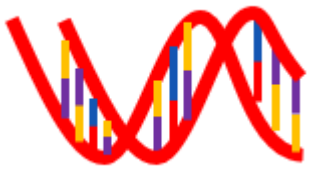
Oligonucleotides can be used to control gene expression and this makes them of increasing interest in the move to control disease. Oligonucleotides have very different chemical properties to typical small molecule drugs, which makes them an interesting drug candidate. Oligotherapeutics target mRNA, not proteins, and therefore interfere with the transmission of disease making them a unique prospect in the fight against many illnesses.

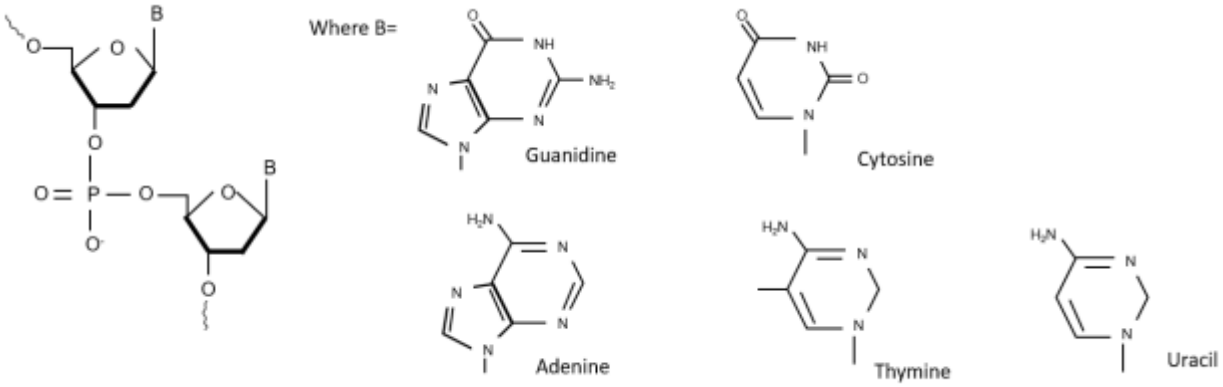
In this four-part series we will look at the synthetic make up of oligonucleotides, their structure and how it is important in their function. The clinical significance of oligonucleotides, their analysis and the future of these interesting molecules as a therapeutic agent.

What is an Oligonucleotide?



An oligonucleotide is a short chain of genetic information built from single nucleotide units. These building blocks comprise of a five-carbon sugar unit, a nitrogenous base such as

adenine, cytosine, guanidine, thymine or uracil and a phosphate group which is consistent in all nucleotides.



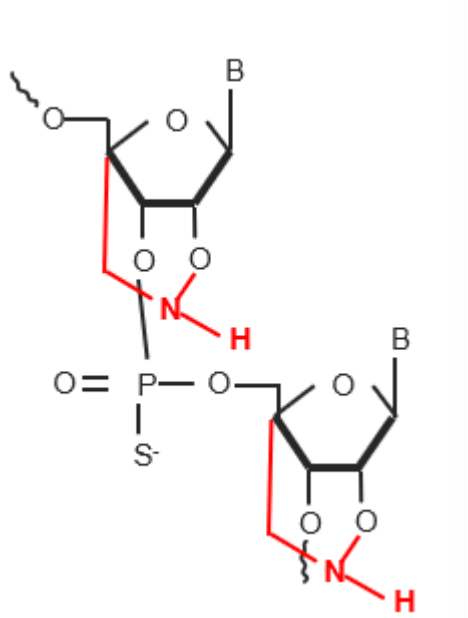
Oligonucleotides are short DNA or RNA oligomers between 20 and 60 units in length; They can be synthesized or found naturally as single stranded (ss) or double stranded (ds) oligomers. Together with ssDNA/RNA and dsDNA/RNA oligonucleotides also exist as short interfering RNA and larger oligo's known as aptamers which have 40-60 base pairs. These oligonucleotide aptamers can bind to a target molecule and generally have a high affinity to proteins making them highly site specific.

Synthetic oligonucleotides are most reliably produced using a solid synthesis approach. It allows oligonucleotides to be custom designed to produce specific genetic sequences. To obtain the desired oligonucleotide each building block, comprising on a nucleic acid is coupled sequentially to the growing chain until the desired product is achieved. Once complete the oligonucleotide chain is released from the solid support used for synthesis,

deprotected and the final product purified.

Synthetic oligonucleotides can be modified to counteract the effect of nucleases increasing their stability and making them less susceptible to metabolism. RNA oligonucleotides are more prone to this effect so are often modified at the 2 position on the ribose sugar and with groups such as Omethyl (OMe) O-(2-methoxy)ethyl (MOE) or 2-fluoro.

It is also common to see oligonucleotides modified at the ribose sugar to form bridged nucleic acids or linked nucleic acids which is promising for antisense and silencing RNA applications ; the process by which gene expression is negatively affected leading to sequence specific gene silencing. These bridged nucleic acids lead to the formation of constrained or inaccessible oligonucleotides which introduces additional stability to the molecule. The conformational inflexibility bridging the sugar moiety brings results in a gain in binding affinity of the oligonucleotide to complementary strands of RNA and DNA.



These different forms of oligonucleotides discussed in this article have a variety of applications in all areas of molecular biology and the treatment of disease. In the next blog we will discuss the therapeutic significance of oligonucleotides and how they are used to treat some of the more complex diseases in humans including neuromuscular disorders and other infectious diseases.

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