

# A Brief Discussion of Genomic Therapeutics



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## Mini Review

Purines and pyrimidines are nitrogenous bases that make up the nucleotide base molecular structure of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The two carbon nitrogen ring bases are purines while the one carbon ring bases are pyrimidines. These aromatic molecules form the code for protein manufacturing in all living organisms on earth. A nucleoside is a purine or pyrimidine base attached to a sugar moiety; a nucleotide is a nucleoside which has been phosphorylated at the sugar alcohol group forming a pentose sugar. The base chemical structures are: adenine, cytosine, guanine, and thymine for DNA. RNA substitutes thymine with uracil.

DNA is first copied into RNA through a process called transcription by RNA polymerase. The RNA is then converted by reading three nucleotide sequences along the string to form proteins. The process by which RNA is converted to protein is termed translation and requires one or more of: mRNA, tRNA, and intracellular structures termed ribosomes. Proteins are long chains of amino acids that function as biomolecules and structural components of cells.

Oligonucleotides are polynucleotides or oligomers of DNA or RNA used in genetic testing, research, forensics, and most recently therapeutic medicine. Oligonucleotides are produced using several methods and are then used to modify expression of key genes in a disease pathway. DNA and RNA strings are oriented in 5 prime to 3 prime directions referring to the sugar carbon number which attaches the terminal molecule. The orientation gives a direction from the 5 prime ends to the 3 prime ends also termed "sense" and "antisense" respectively. Antisense oligonucleotides are emerging as an important therapeutic tool in medicine.

In gene therapy, oligonucleotides are used to inactivate genes involved in a disease process. Antisense oligonucleotides are used to target a specific gene sequence to disrupt (and correct) transcription. In 2005, researchers at Albert Einstein College of Medicine of Yeshiva University, New York, USA, evaluated antisense oligonucleotide strategies for oncogene inactivation [1]. In this study, they discussed the mechanism of the antisense effect and its dependence on cellular internalization

of nucleotides and the activity of RNase H. The data from early phase I and II trials were examined. Chan et al. [2], later examined antisense oligonucleotides in terms of protein target identification, therapeutic strategy, delivery systems, and toxicology. Various antisense oligonucleotide drugs in clinical studies were surveyed.

Delivery of antisense oligonucleotides was initially seen as a challenge. Traversing the blood-brain barrier and cellular membrane needed to be overcome as oligonucleotides tend to be polyanions. Therefore, a delivery system must take the molecular limitations such as lipophilicity and ionic interactions into account. Researchers at Columbia University, New York, USA reviewed the use of cationic lipids, protein and peptide agents, and novel chemical and viral molecules as delivery methods for oligonucleotides [3].

Effective oral delivery of antisense oligonucleotides was first demonstrated in 2008 after efficacy was demonstrated for local and parenteral routes. Tillman, et.al, report the effective oral delivery of a second generation oligonucleotide whereby significant milligram amounts of intact drug were absorbed by human subjects. The study evaluated a variety of solid oral dosage formulations. The average performance achieved in the study was 12.0% bioavailability suggesting that formulations can be devised that allows oral administration of oligonucleotides that maintain systemic concentrations associated with inhibition of targeted human mRNA [4].

A multicenter trial of a phase I study of ISIS-SMNRx in children with spinal muscular atrophy (SMA) was completed in 2016. This study examined the safety, tolerability, pharmacokinetics and preliminary clinical efficacy of intrathecal nusinersen, an antisense oligonucleotide designed to alter splicing of SMN2 mRNA in patients with childhood spinal muscular atrophy. This study provides class IV evidence that in children with SMA, intrathecal nusinersen is not associated with safety or tolerability concerns [5]. The American Academy of Neurology (AAN) established a classification scheme for therapeutic studies: Class IV studies do not meet rigid criteria in terms of controlled trials or trials for equivalence, and as such, generally establish safety and tolerability of agents under study [6].

Amino acids linked in a chain, carbonyl to amino group, are termed a peptide. Larger peptides cause three dimensional complex structures termed proteins. Protein structures can be secondary, tertiary, and even quaternary in structural complexity. Proteins and peptides are bioactive molecules that form the structure of cellular organelles, membrane channels, receptors, and even neurotransmitters and hormones. Therapeutic use of proteins and peptides may exploit several advantages for maximal efficacy. Firstly, proteins may be used to substitute or mimic naturally occurring proteins present in vivo to compensate for endogenous deficiencies.

Secondly, proteins may be used to provide substrates for the maintenance of more complex bioactive molecules for normal biological pathways disturbed by a disease process. Lastly, proteins may be supplied to provide an excess of substrates necessary for cellular repair from damage caused by chronic pathological destruction which alters the repair/destruction ratio normally present in cellular systems to tilt the ratio in favour of repair overwhelming the destructive pathological process. It is this last phenomenon that is the most potentially useful therapeutically in the chronic neurodegenerative process. This

phenomenon, if successfully altered, offers the best therapeutic chance in neurodegenerative disorders by supplementing the vitamins, amino acids, proteins, and fatty acids necessary for repair of neural structures such as the neuron.

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