Title: **A bibliographic review of oligonucleotide therapeutics.**
Student: Mireia Tomàs Sanz
Date: June,2019
Supervisor/s: Dra. Núria Escaja Sánchez
Department of Inorganic and Organic Chemistry. Organic Chemistry Section.

The use of oligonucleotides-based therapies began approximately 40 years ago with the birth of antisense concept. These therapies are divided according to the action mechanism and basically there are three different classes of therapies: antisense therapy, anti-gene therapy and the use of oligonucleotides as aptamers, in which the therapeutic targets are the mRNA, the double stranded or the proteins, respectively. Within antisense therapies there are the siRNAs, the gapmers and oligonucleotides that modulate the splicing of pre-mRNAs. It took some years that oligonucleotides were considered as possible therapeutic agents. This has been due to an oligonucleotide needs to have some properties to be an effective drug, as having enough stability inside the organism and a high specificity for the target. Chemical modifications of oligonucleotides are thus necessary. The most common modifications used in oligonucleotides drugs are found in the backbone and in the sugar ring. The development of these therapies has been accompanied by the improvement of the oligonucleotides synthesis methods.

Until now there are in the market a total of eight oligonucleotide drugs approved by the FDA, being the Vitravene the first approved, in 1998. Out of the eight drugs that are in the market, two of them are aptamers whereas the other six correspond to antisense therapeutic approaches. It should be noted that the last five were approved during the last four years, meaning that in this moment these type of therapies are finding now more applications. It should also be considered that many clinical trials are being carried out, and there are a few new oligonucleotide drugs that may be in the final stages, as the Fitusiran, Givosiran or Inclusiran.

Within the last oligonucleotide drugs approved by the FDA, two of them, Eteplirsen and Nusinersen, are designed, respectively, against two diseases that will be described in more detail: the Duchenne muscular dystrophy and the spinal muscular atrophy. Both diseases consist in genetic mutations, and both drugs have the same action mechanism, they are antisense oligonucleotides capable of modulating splicing process.

Keywords: oligonucleotides, antisense therapy, anti-gene therapy, aptamer, drug, chemical modifications, Duchenne muscular dystrophy, spinal muscular atrophy.