Title: **Synthesis of oligonucleotide-lipid conjugates.**
Student: Marc Guasch Albanieve
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Supervisor/s: Dr. Jordi Robles i Brau
Departament of Inorganic and Organic Chemistry, UB
Dr. Ramon Eritja Casadellà
Dra. M. Carme Fàbrega Claveria
Group of Nucleic Acids Chemistry, IQAC-CSIC

SUMMARY

In the last years, the use of oligonucleotides to treat different diseases has growth enormously. As the number of oligonucleotides approved to clinical practice is increasing, the search for more efficient oligonucleotide derivatives is one of the major interests in this area. One common problem of the oligonucleotides is the low cellular uptake of the target tissues. Recently, lipid-oligonucleotide conjugates have attracted a large interest as they have been described to facilitate cellular uptake of therapeutic oligonucleotides in several tissues such as liver, kidney and muscle.

The present project addresses the study and optimization of the synthesis of several lipid-oligonucleotide conjugates. In particular, it addresses the preparation of oligonucleotides carrying amide derivatives of fatty acids. To this end, solution and solid-phase couplings methods between amino-oligonucleotides and fatty acid ester derivatives are assayed. Careful analysis of some protocols described in the bibliography demonstrates that these conjugations can undergo dramatic differences in yields. In this work, the optimal conditions for the preparation of these compounds are described. In addition, the biophysical properties of some of the products synthetized are also studied.

Keywords: Oligonucleotide-lipid conjugates, oligonucleotide synthesis, therapeutic oligonucleotides, cellular uptake, fatty acids, protecting group.