Projet 4: Flavin-oligonucleotide and Flavin-PNA conjugates as selective DNA cleaving agents
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Inhibition of gene expression is of great interest to explore gene function or for therapeutic applications. Oligonucleotides that interact with a specific RNA (antisense strategy) or DNA (antigene strategy) sequence are very attractive to disrupt gene expression. Structural modifications brought to the last generation of oligonucleotides like PNAs (peptide nucleic acids) have led to molecules with high affinities for their targets and high resistance to nucleases and peptidases. However, the poor cellular uptake of these compounds is a limitation for therapeutic applications.

A study carried on vitamin B2 initiated at the CEA (Grenoble) has shown that a covalently linked flavin increases the cellular uptake of the PNA moiety without impairing its biological activity.

The goal of this project is to study and modify the flavin properties to induce cellular uptake of oligonucleotides with various chemical structure (morpholino, siRNA,...) but also nanoparticles loaded with different types of molecules such as oligonucleotides, peptides or enzymes (collaboration with Clément Sanchez laboratory at the Collège de France).

Additionally PNA-flavin conjugates have been shown to be able to induce in vitro oxidative lesions and DNA cleavage after reduction of the flavin moiety by a flavin reductase, an ubiquitous enzyme.
Until now, DNA double-stranded cleavage within cells has only been achieved using enzymatic systems which are difficult to implement. We aim at developing a simple DNA cleaving system based on three components: a specific sequence targeting PNA, a flavin, and the flavin reductase available in the cellular medium.

References


Targeting DNA with triplex-forming oligonucleotides to modify gene sequence. Simon P., Cannata F., Concordet, J-P., Giovannangeli C. Biochimie 2008, 90 (8), 1109-1116.