PhD position in organic chemistry/biology at Nantes (France)

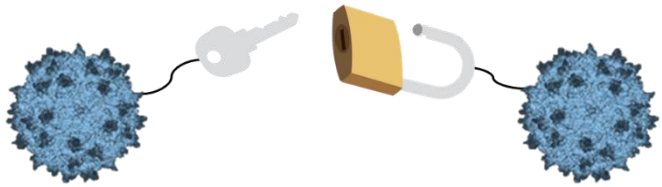
Dimère AAV : a new tool for the vectorization of large-size genes

Background:

Stargardt's disease, which is caused by mutations in the ABCA4 gene, is the most common monogenic inherited retinal disease and leads to vision loss. Currently, unfortunately, there is no treatment, which is why the use of adeno-associated viruses (AAVs) to deliver this healthy gene into retinal cells could provide a solution. However, one of the main limitations is the size of the ABCA4 gene, which cannot be encapsulated in a single AAV. It has been proposed to "split" the ABCA4 gene into two fragments and integrate them into two AAVs. After injection into the retina, recombination at the DNA or protein level allows the full-length protein to be generated. Nevertheless, the main limitation of this strategy, called "dual-vector," lies in its random encounter process.

Hypotheses and research program:

The molecular assembly of two AAV vectors, either by covalent coupling or by supramolecular interaction, each carrying a part of the gene of interest, could allow them to be simultaneously transported to the nucleus of retinal cells. This would enable optimal, rather than random, recombination of the two DNA fragments to form the healthy ABCA4 gene. The objective of this thesis, at the interface between vectorology (UMR INSERM 1089, Mathieu Mével) and organic chemistry (UMR CNRS 6230, David Deniaud), will be to chemically associate two AAV carriers, each carrying a fragment of the ABCA4 gene. To achieve this, we will utilize an organic connector based on various AAV bioconjugation techniques developed in both laboratories. During this thesis, the recruited student will be responsible for synthesizing the molecular assemblies capable of connecting two different AAVs. To create covalent AAV dimers, we will use an alkyne-azide cycloaddition reaction (SPAAC) linking a first AAV functionalized with an azide (AAV-N_3) to a second AAV functionalized with a dibenzocyclooctyne group (AAV-DBCO). For supramolecular assembly, we will employ the adamantane/β-cyclodextrin pair, a well-established supramolecular system known to form highly stable inclusion complexes ($K_a \approx 10^4$ M^{-1}). The AAVs will be pre-functionalized with the different partners through bioconjugation reactions. During this thesis, the student will focus on synthesizing the molecules of interest, modifying the AAVs through bioconjugation (lysine, tyrosine, cysteine), validating the covalent coupling of AAVs using molecular biology techniques, and finally assessing the efficiency of these vectors in vitro.



Candidate profile:

The successful candidate will have a Master degree with honors in organic chemistry and should have a solid background in molecular biology. He/she must speak English fluently and must be motivated to learn French.

Application:

Candidates will send a cover letter, a detailed CV (indicating marks or ranks of Master 1 and Master 2), as well as the names of two referees to mathieu.mevel@univ-nantes.fr or david.deniaud@univ-nantes.fr