Formulaire de stage
Parcours M2 GGBS 2019-2020

**Laboratoire :** INSERM UMR 1089, Nantes
Thérapie génique translationnelle des maladies génétiques

**N° d'équipe** : Groupe « Innovation Vectorology »

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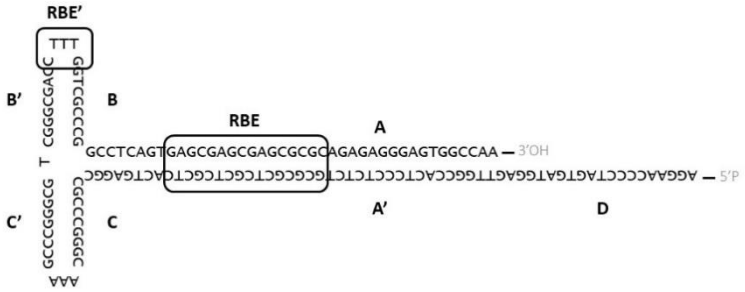
**Titre du stage: Prediction and design of new AAV genome extremities in order to improve gene transfer efficiency**

Adeno-Associated Viral Virus (AAV) are one of the most suitable viral vectors for gene delivery *in vivo*. Encouraging preclinical data using AAV vectors have been followed by several successful gene therapy clinical trials and by the marketing authorization of two AAV-based products, Glybera® and Luxturna®. The scientific community is now facing news issues addressing systemic diseases. Indeed, injecting a high dose of AAV vectors may trigger unwanted side effects such as an immune response against the viral capsids. AAV particle and genome can also be sensed by the targeted cells and lead to a decrease in the expression of the gene of interest. The strategy developed in our lab to improve the efficiency of these vectors is the optimization of the recombinant AAV genome. The AAV genome is a single-stranded DNA of ≈ 4.7 kb composed of three open reading frames, *rep*, *cap* and AAP. To generate a recombinant AAV vector, these ORFs are replaced by the therapeutic gene. The only viral sequences that remain in the vector genome are the ITR (inverted terminal repeats). ITR are 145 base-sequences comprising palindromic regions that can form a T-shaped structure (Figure). These sequences can be recognized by the cellular sensing pathways after transduction.




The M2 student will analyze and compare *in silico* the DNA/RNA secondary structures of the ITR of several AAV serotypes. The project also includes the prediction of DNA/RNA motifs that can be involved in transcription and translation. The candidate will finally test new ITR mutants for the generation of AAV vectors. The candidate must have knowledge in molecular biology and particular in DNA/RNA structure, and skills in bioinformatics for the prediction of nucleic acid motifs. Finally, he will participate to plasmid cloning, generation of viral vectors, quality control assays (ELISA, qPCR) and *in vitro* experiments. Qualities such a rigor, organization and motivation will be appreciated.

**Mots-clés:** adeno-associated virus, viral vectors, DNA/RNA motif prediction, DNA structure, gene regulation