Project 1 (P1): **Characterization of the mode of action of splicing regulatory proteins: determining selection and usage of HIV-1 splice sites**

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Summary:

HIV-1 is a member of the lentivirus genus of the Retroviridae family. HIV contains two identical copies of single-stranded RNA, which have positive polarity. Contrary to RNA viruses with a genome of (+)-polarity, e.g., Polio virus, HIV genomic RNA is not directly available for translation after cell entry, but is first reverse transcribed into double-stranded linear DNA, which is actively imported into the nucleus and then integrated into the host DNA. As a provirus its gene expression is subjected to host cellular gene expression mechanisms. Nevertheless, there are virus-specific peculiarities which can be attributed to the compactness of the viral genome, in some cases protein translation may use all three reading frames. Due to the cap-dependent translational mechanism of the host cell the viral primary transcript has to be extensively spliced in order to generate mRNAs carrying one of each of the eight open reading frames on one hand, and on the other hand, unspliced RNA has to be exported into the cytoplasma to serve as both, a translatable gag-pol mRNA and as genomic RNA to be packaged into new virions.
The balance between these two opposing processes, extensive splicing and no splicing, and thus the use and non-use of one and the same splice site sequence respectively, is maintained by several cellular splicing regulatory proteins. We have focussed our attention on these proteins and are interested in their mode of action and how they regulate the selective HIV-1 splice site use.