Projekt 1 (P1): Development of an experimentally based diagnostic tool to predict consequences of silent mutations affecting HIV-1 replication fitness

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Project Background

Occurring HIV-drug resistances are often explained by causal research by nucleotide changes resulting in amino acid changes. However, the evaluation of so called silent mutations, nucleotide changes that do not lead to a different protein product, is currently rather difficult. Especially in terms of viruses that carry a small genome such as HIV-1, the RNA contains numerous cis-acting regulatory elements which are crucial for various processes such as the packaging signal of genomic RNA, the pre-mRNA processing, the polyadenylation or the export of nucleic RNA, hence for the overall replication capacity (fitness) of the virus. Most regulatory elements and especially splicing regulatory elements can be found in the coding sequence, which means that silent mutations altering cis-acting elements can impair viral fitness just as mutations changing the resulting protein. Consequently, drug resistance associated mutations only found by sequencing parts of the viral genome can not only influence the activity of proteins but also cis-acting regulatory elements. In this context, basic experimental methods should be elaborated in order to promote the development of an algorithm that confidently evaluates splicing relevant nucleotide changes that impact the fitness and pathogenicity of HIV-1.