SONATA BIS 12

ABSTRACT FOR THE GENERAL PUBLIC (File format: 1 page, A4)

In English:

The project goal

In this proposed work we aim to understand how HIV (causing AIDS disease) antisense transcripts interfere with its sense RNA transcription driven by the HIV 5' long terminal repeat, subsequently promoting the establishment of HIV latency.

Description of research

"How HIV latency is established?" is one of the long-standing questions that has been addressed by the HIV-1 research community for many years. Viruses evolved various strategies to establish a latent state to ensure their persistence in the host. For instance, Herpes viruses encode latency proteins which are responsible for switching the viral cycle from a lytic to latent state. Retroviruses, like HIV, in contrast, known to persist through transcriptional silencing, do not encode latency proteins. To date, the mechanisms leading to HIV latency are still not fully understood. HIV latency is presently seen as a passive outcome led by the consequence of cell quiescence; whereas, lines of evidence suggest that HIV may somehow actively program the establishment of latency, strongly implying an additional intrinsic determinant awaits further investigation. For this reason, in this proposed work, we will employ barcoded wildtype HIV, with which we will be able to unveil both sense- and antisense RNA transcriptional landscapes in a quantitative manner and closely dissect their molecular basis and mutual interactions associated with the three-dimensional organization of the human genome.

Reasons for attempting a particular research topic

In physiological HIV-1 infection conditions HIV latent infection can be established in the early stage of infection, indicating that an additional molecular determinant that functions as an antagonist to its sense RNA transcripts when sense RNA transcription is initiated. However, at present none of experimental evidence has shown the presence of such molecular determinant throughout disease progression of HIV-1. Although the importance of HIV antisense transcripts for its pathogenesis based on experimental research and clinical observations has been highlighted, the fundamental mechanisms behind HIV antisense transcripts is currently not fully understood. One of the major obstacles that impedes the progress of studying HIV antisense transcripts is due to the fact that the abundance of HIV antisense transcripts is much lower than that of the sense RNA transcripts, rendering quantitative investigation difficult. In this work, we thus propose to verify our hypothesis that HIV latency may be a pathological process actively programmed by HIV itself through the function of HIV antisense transcripts rather than a consequence of cell quiescence by employing barcoded wildtype HIV.

Substantial results expected

This proposed work will be expected to publish in high impact, broad readership peer-reviewed journals and will have a high technological and scientific impact. In spite of the study of HIV gene expression has been well characterized, the scientific community has not yet come up with any technology to map insert-specific HIV antisense transcription over chromosomes. In this respect, the B-HIVE technology with barcoded wildtype HIV will mark a paradigm shift. We expect that our results will be the first time to visualize HIV antisense RNA transcriptional landscape in a quantitative manner. Beyond the technology itself, we also expect that the results of our work will have a strong influence in the field of HIV research. Since we attempt to show evidence that HIV itself is capable of governing the establishment of latency through the function of HIV antisense transcripts, if successful, we will reveal an unprecedented mechanism used by HIV-1 to establish a persistent infection. In the meanwhile, our results will also reinforce our knowledge of antisense RNA transcription and gene expression. Essentially, this work will mark a significant conceptual advance in translational research with commercial values to evaluate the potential of *ectopic overexpression* of HIV antisense transcripts that can serve as a therapeutic target to achieve a functional cure for HIV-1 infection.