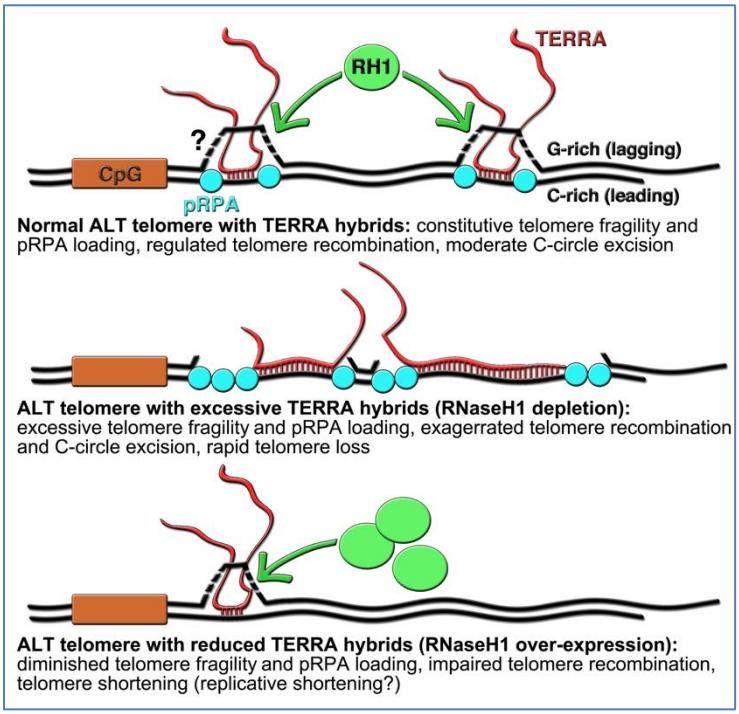
Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Understanding the roles of the long noncoding RNA TERRA in telomerase-independent telomere elongation in ALT cancer cells

Synopsis:

Cancer cells need to maintain the ends of their chromosomes, the telomeres, in order to achieve immortality and thus propagate indefinitely. While the majority of human cancers maintain telomeres through reactivation of the specialized reverse transcriptase telomerase, approximately 15% of them are telomerase-negative and are collectively known as ALT (Alternative Lengthening of Telomeres) cancers. The ALT pathway is found to be active in particularly aggressive tumors often developed during childhood, such as juvenile osteosarcomas and glioblastomas. While it is well established that ALT relies on interchromosomal homologous recombination, it remains to be established what molecular triggers render ALT telomeres recombinogenic. We previously reported that ALT telomeres are heavily transcribed by RNA polymerase II into the long noncoding RNA TERRA, which engages in DNA:RNA hybrids with the telomeric DNA duplex (telomeric R-loops or telR-loops). Alteration of telR-loop levels, through overexpression or depletion of the human endoribonuclease RNaseH1, compromises telomere maintenance specifically in ALT cells. Analysis of RNAseq data from ALT cells overexpressing or downregulating TERRA levels by the *in vivo* expression of transcription activator like effectors (TALEs), revealed changes in genes associated with cell cycle regulation, DNA replication, chromatin remodeling and inflammatory response pathways. The aim of this project is to validate RNAseq data, to unveil how TERRA modulates gene expression and, finally, to understand how it translates into telomere maintenance and proliferation of ALT cells. To this goal, we will apply molecular biology, cell biology and high-end microscopy of both live and fixed cells to different human cultured ALT cancer cells where transcription of specific telomeres will be modulated through the TALEs system. This research project should not only contribute to expand our understanding of ALT but also to expose novel potential targets for the design of therapeutic strategies against these aggressive forms of cancer.



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Bibliography:

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Remunerated or volunteer training: *volunteer*