Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Understanding the impact of disease-causing mutations on neuronal and cardiac gene expression

Synopsis:
We are investigating global transcriptomic profiles in cardiomyocytes and neurons differentiated from patient-derived iPSC that contain disease-causing mutations. Ultimately, we aim to develop new treatment strategies based on interfering with the expression of specifically altered genes.

Required skills:
Bioinformatics tools for transcriptomic analysis, with particular focus on splicing analysis

Supervisor: *Maria Carmo-Fonseca, MCFonseca Lab, carmo.fonseca@medicina.ulisboa.pt*
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Webpage of the group

Bibliography:
Nojima T, Rebelo K, Gomes T, Grosso AR, Proudfoot NJ, Carmo-Fonseca M (2018) RNA Polymerase II phosphorylated on CTD Serine 5 interacts with the spliceosome during co-transcriptional splicing. Mol Cell 72(2):369-379. doi: 10.1016/j.molcel.2018.09.004. *Genome-wide analysis of nascent RNA complexes using NET-seq revealed unanticipated dynamic links between Pol II and the spliceosome*.

Bernardes de Jesus B, Matinho SP, Barros S, Sousa-Franco A, Alves-Vale C, Carvalho T, Carmo-Fonseca M (2018) Silencing of the lncRNA Zeb2-NAT facilitates reprogramming of aged fibroblastos and safegards stem cell pluripotency. Nat Commun. 9(1):94. doi: 10.1038/s41467-017-01921-6. *This study highlights the physiological importance of antisense transcription in fine tuning the expression of a protein coding gene. We identified the transcription factor Zeb2 as a novel age-associated barrier to reprogramming. We show that forcing Zeb2 downregulation may help improve reprogramming efficiency, and we uncovered a long non-coding RNA that is overlapping and antisense to the Zeb2 locus as a target to achieve robust Zeb2 downregulation.*

Mendes de Almeida R, Tavares J, Martins S, Carvalho T, Enguita FJ, Brito D, Carmo-Fonseca M, Lopes LR. (2017) Whole gene sequencing identifies deep-intronic variants with potential functional impact in patients with hypertrophic cardiomyopathy. Plos One 12(8):e0182946. *In this pioneer study we identified genetic variants located deep within introns of sarcomeric genes that may be important for the development of hypertrophic cardiomyopathy.*

Carvalho T, Martins S, Rino J, Marinho S, Carmo-Fonseca M. (2017) Pharmacological inhibition of the spliceosome subunit SF3b triggers EJC-independent NMD. J Cell Sci. 130 (9): 1519-1531. *This study not only shows that cytoplasmic pre-mRNAs evoke an EJC-independent NMD pathway response when splicing is blocked, but also provides insights into the effects of a set of potential anti-cancer drugs on the stability and transport of mRNAs.*

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Nojima T, Gomes T, Grosso AR, Kimura H, Dye MJ, Dhir S, Carmo-Fonseca M, and Proudfoot N. (2015) Mammalian NET-seq reveals genome-wide nascent transcription coupled to RNA processing. Cell 161(3): 526-540. *This study provides the first genome-wide analysis of co-transcriptional RNA splicing at single-nucleotide resolution.*

Vaz-Drago R, Pinheiro MT, Martins S, Enguita FJ, Carmo-Fonseca M, Custódio N (2015) Transcription-coupled RNA surveillance in human genetic diseases caused by splice site mutations. Hum Mol Genet. 24(10): 2784-95. *We analyzed the consequences of splice site mutations in biogenesis of mRNAs using patient-derived lymphoblastoid cell lines and found a subset of genes with reduced transcriptional activity.*

Remunerated or volunteer training: *volunteer*