

Title: Understanding the impact of BRCA mutations on breast cancer

Synopsis:

We are investigating how heterozygous mutations in BRCA1 and BRCA2 genes alter gene expression in mammary cell progenitors. Ultimately, we aim to identify new targets for prevention strategies for BRCA mutation carriers.

Required skills:

Cell culture (human stem cells); molecular biology

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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 fibroblasts and safeguards 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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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*