ProRegeM 2017 – Research Proposal

Title: Unveiling the epigenetic signatures that control carcinogenesis.

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Cancer is controlled by genetic and epigenetic events that tightly regulate tumor initiation and progression. Although extensive studies have dissected the effects of genetic changes in cancer, little is still known about the epigenetic alterations that occur throughout carcinogenesis. Some examples are the "switch-on" and "switch-off" of oncogenes and tumor repressors where our group contributed to better understand the impact of DNA methylation on such genes. This project aims to dissect the signatures of DNA methylation in key cancer genes, towards controlling cancer development/progression by gene-specific epigenetic silencing or activation.

The project will focus on genes differentially methylated in tumor *vs*. normal tissues and explore co-relations with gene expression, tumor progression and patient survival. Methylation of specific DNA sequences will be first identified through available databases baring patient data and, genes/pathways selected as key players in cancer will be further validated in patient cohorts. Then, we will identify methylation signatures and characterize patterns that could direct methylation and demethylation enzymes to target specific sites of the genome by analyzing DNA sequence, chromatin conformation and histone marks.

PI's Short Biography: Pedro Castelo-Branco worked abroad for 14 years and during this time he read for a PhD at Oxford University and completed two postdoctoral fellowships in oncology and cancer therapeutics (Harvard University) and cancer stem cell therapies/cancer biomarker development (University of Toronto). In 2015 he joined the Department of Biomedical Sciences and Medicine at the University of Algarve as an Assistant Professor. He also joined the Center for Biomedical Research as the Leader of the Epigenetics and Human disease Group.

Selected publications:

1) Castelo-Branco, P., et al. (2010). An Oncolytic virus armed with a Xenogeneic homolog of Prostatic Acid Phosphatase enhances anti-tumor efficacy in Prostate Cancer. ***Gene Ther***.
2) Castelo-Branco, P**.**, et al (2011). Neural Tumor Initiating Cells have distinct telomere maintenance and can be safely targeted for telomerase inhibition. ***Clinical Cancer Res***.
3) Schwartzentruber J,et al (2012). Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. ***Nature***.
4) Castelo-Branco, P. et al (2012).Promises and challenges of exhausting pediatric neural cancer stem cells. (2012). ***Pediatric Research***.
5) Castelo-Branco, P., et al.(2013). Differentially methylated region of the hTERT promoter and risk stratification of childhood brain tumors: An integrative genomic and molecular study ***The Lancet Oncol.***
6) Nataliya Zhukova, et al (2013). Subgroup Specific Prognostic Implications of TP53 Mutation in Medulloblastoma. ***Journal of Clinical Oncology,***
7) Mack SC,et al. (2014). Epigenomic alterations define lethal CIMP-positive ependymomas of infancy (2014). ***Nature***.
8) Pawel Buczkowicz, et al. (2014). Comprehensive genomic analysis of diffuse intrinsic pontine gliomas unravels three molecular subgroups and a novel cancer driver. ***Nature Genetics***.
9) Matthew Mistry, et al. BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high grade glioma (2015). ***Journal of Clinical Oncology,*** 2015 Mar 20;33(9):1015-22. doi: 10.1200/JCO.2014.58.3922.
10) Ernst A, et al (2016). Telomere dysfunction and chromothripsis. ***International Journal of Cancer.***
11) Pedro Castelo-Branco**,** et al. (2016). A cancer specific hypermethylation signature of the TERT promoter predicts biochemical relapse in prostate cancer (2016). ***Oncotarget (under second review).***