GROUP'S NAME: (sugere-se que o nome fique a 2 linhas, no máximo 3 linhas – 57 caracteres, sem espaços)

Molecular Oncology & Viral Pathology Group

PROJECTS WITH INTERNAL FUNDING

EXOmiRs4RCC - *Renal cell carcinoma-derived exosome: the microRNA content as a new disease predictive biomarker and an opportunity to invasive/metastatic disease management under the genetic background* REF: CI-IPOP-21-2015; 02/01/2019 - 30/12/2026 **Budget:** 7500€ **PI and Co-PI:** Ana Luísa Teixeira | Rui Medeiros

One of the biggest paradigms in oncobiology is the lack of evidence regarding what causes a tumor to metastasize. Thus, understanding the mechanisms of the metastatic process will significantly improve the clinical management of the disease. The analysis of circulating miRNAs may provide an opportunity for the definition of new and more accessible molecular biomarkers, useful for renal cell carcinoma progression motoring, opening new possibilities for the development of new targeted therapies. Extracellular vesicles-related miRNAs (EVs-miRNAs) may be useful to characterize the disease progression, allowing therapeutic adjustment before the development of metastases, improving patient survival. The analysis of an EVs-miRNAs profile, which could be analyzed in blood samples, may be a more accurate and less invasive strategy, with the capacity to predict disease progression.
Additionally, the identification of functional genetic polymorphisms in genes encoding proteins involved in the biogenesis of miRNAs could be a useful and complementary approach in understanding their regulation.

Publications

*Teixeira AL, Patrão AS, Dias F, Silva C, Vieira I, Silva JF, Ferreira M, Morais A, Maurício J and Medeiros R. **AGO2 expression levels and related genetic polymorphisms: influence in renal cell progression and aggressive phenotypes**. Pharmacogenomics 2021. 22(16):1069-1079, doi: 10.2217/pgs-2021-0072*

*Dias F; Teixeira AL; Nogueira I; Morais M; Maia J; Bodo C; Ferreira M; Silva A; Vilhena M; Lobo, J; et al. **Extracellular Vesicles Enriched in hsa-miR-301a-3p and hsa-miR-1293 Dynamics in Clear Cell Renal Cell Carcinoma Patients: Potential Biomarkers of Metastatic Disease**. Cancers (Basel) 2020, 12, doi:10.3390/cancers12061450*

*Dias F.; Teixeira AL; Nogueira I; Morais M; Maia J; Bodo C; Ferreira M; Vieira I; Silva J; Lobo J; et al. **Plasma Extracellular Vesicle-Derived TIMP-1 mRNA as a Prognostic Biomarker in Clear Cell Renal Cell Carcinoma: A Pilot Study**. Int J MolSci 2020, 21, doi:10.3390/ijms21134624*

EUPICPHARMADCP - *Pharmacogenomic determinants of therapeutic response of urogynecological cancer* REF.: CI-IPOP-22-2015 01/01/2016 - 30/12/2026 **Budget:** 7500€ **PI:** Rui Medeiros

This line of research aims the characterization of the molecular mechanisms associated with the cancer onset and with therapeutic outcome, through the identification of molecular biomarkers. Within the framework of Precision Medicine, the aim is especially focused on the study and validation of circulating cancer biomarkers with clinical relevance. Patients' stratification and optimization of current therapy approaches are important outcomes (Pharmacogenomics and Molecular Epidemiology) from this knowledge. Since the beginning, Molecular Oncology and Viral Pathology Group research on Pharmacogenomics and Comparative Personalized Medicine or Precision Medicine incorporated individualized genetic

information to understand how this individuality may influence therapeutic responses, drug efficacy, drug side effects, and adverse events related to drug therapy.

Publicações:

Neto BV, Tavares V, da Silva JB, Liz-Pimenta J, Marques IS, Carvalho L, Salgado L, Pereira D, Medeiros R. ***Thrombogenesis-associated genetic determinants as predictors of thromboembolism and prognosis in cervical cancer***. *Sci Rep. 2023, 13 1: 9519-9519. doi.org/10.1038/s41598-023-36161-w.*

Silva J, Tavares V, Afonso A, Garcia J, Cerqueira F, Medeiros R. ***Plasmatic MicroRNAs and Treatment Outcomes of Patients with Metastatic Castration-Resistant Prostate Cancer: A Hospital-Based Cohort Study and In Silico Analysis.*** *Int J Mol Sci. 2023, 24 10: 9101-9101. doi.org/10.3390/ijms24109101*

Abreu, SC, Tavares, V, Carneiro, F and Medeiros, R. ***Venous thromboembolism and prostate cancer: what about genetic markers?*** *Pharmacogenomics. 2021, 22, doi: https://doi.org/10.2217/pgs-2020-0094*

Afonso, A.; Silva, J.; Lopes, A.R.; Coelho, S.; Patrão, A.S.; Rosinha, A.; Carneiro, F.; Pinto, A.R.; Maurício, M.J.; Medeiros, R. ***YB-1 variant and androgen receptor axis-targeted agents in metastatic castration-resistant prostate cancer patients****. Pharmacogenomics 2020, 21, 919-928, doi:10.2217/pgs-2020-0008*

Tavares, V, Pinto, R, Assis, J, Coelho, S, Brandão, M, Alves, S, Pereira, D and Medeiros, ***Implications of venous thromboembolism GWAS reported genetic makeup in the clinical outcome of ovarian cancer patients****. The pharmacogenomics journal. 2021, 21) DOI: https://doi.org/10.1038/s41397-020-00201-9*

Cardoso J, Medeiros R, Dias F, Costa I, Ferrari R, Berardo P and Perini J. ***DROSHA rs10719 and DICER rs3742330 polymorphisms in endometriosis and different diseases: Case-control and review studies****. Exp Mol Pathol 2021, 119:104616. Doi: 10.1016/j.yexmp.2021.104616*

Brausi, M.; Hoskin, P.; Andritsch, E.; Banks, I.; Beishon, M.; Boyle, H.; Colecchia, M.; Delgado-Bolton, R.; Höckel, M.; Leonard, K.; et al. ***ECCO Essential Requirements for Quality Cancer Care: Prostate cancer****. Crit Rev Oncol Hematol 2020, 148, 102861, doi:10.1016/j.critrevonc.2019.102861.*

Morais, M.; Dias, F.; Resende, T.; Nogueira, I.; Oliveira, J.; Maurício, J.; Teixeira, A.L.; Medeiros, R. ***Leukocytetelomerelength and hTERT genetic polymorphism rs2735940 influence the renal cell carcinoma clinical outcome****. Future Oncol 2020, 16, 1245-1255, doi:10.2217/fon-2019-0795*

Morais, M.; Dias, F.; Teixeira, A.L.; Medeiros, R. ***Telomere Length in Renal Cell Carcinoma: The Jekyll and Hyde Biomarker of Ageing of the Kidney****. Cancer Manag Res 2020, 12, 1669-1679, doi:10.2147/cmar.S211225*

MIRNAVIRAL - *microRNA-mediated viral regulation of the tumor microenvironment* **REF.:** CI-IPOP-66-2017 01/01/2018 - 30/12/2026 **Budget:** 7500€

PI: Rui Medeiros

High-risk human papillomavirus (HPV) is the etiologic agent of several types of cancer. Tissue Microenvironment role as either a driving or opposing force for cancer progression remains controversial. MicroRNAs/LncRNAs are proposed to be dysregulated in several HPV-induced cancers, and can influence cell biology. This

study/line of research aims to evaluate MicroRNAs/LncRNAs potentially regulating this process.

Publications:

Costa AC, Santos JMO, Medeiros-Fonseca B, Oliveira PA, Bastos MMSM, Brito HO, Gil da Costa RM, Medeiros R. ***Characterizing the Inflammatory Microenvironment in K14-HPV16 Transgenic Mice: Mast Cell Infiltration and MicroRNA Expression****. Cancers (Basel). 2022 Apr 28;14(9):2216, doi: 10.3390/cancers14092216*

Dias TR, Santos JMO, Estêvão D, Costa NR, Mestre VF, Medeiros-Fonseca B, Bastos MMSM, Oliveira PA, Gil DA Costa RM, Medeiros R. ***Expression of LncRNAs in HPV-induced Carcinogenesis and Cancer Cachexia: A Study in K14-HPV16 Mice.*** *Anticancer Res. 2022 May;42(5):2443-2460, doi: 10.21873/anticanres.15723*

Brito HO, Calixto JRR, Medeiros R, da Costa RMG. ***Comment on DKK1 inhibits canonical Wnt signaling in human papillomavirus-positive penile cancer cells.*** *Transl Oncol. 2022 Feb;16:101326, doi: 10.1016/j.tranon.2021.101326*

Dias, T.R., Santos, J.M.O.,Gil da Costa, R.M.,Medeiros, R., ***Long non-coding RNAs regulate the hallmarks of cancer in HPV-induced malignancies****, Crit Rev Oncol Hematol, 161 (2021) 103310, doi: 10.1016/j.critrevonc.2021.103310*

Costa, A.C., Santos, J.M.O., Gil da Costa, R.M.,Medeiros, R., ***Impact of immune cells on the hallmarks of cancer: A literature review.*** *Crit Rev Oncol Hematol, 168 (2021) 103541 DOIhttps://doi.org/10.1016/j.critrevonc.2021.103541*

Mestre, V.F.; Medeiros-Fonseca, B.; Estêvão, D.; Casaca, F.; Silva, S.; Félix, A.; Silva, F.; Colaço, B.; Seixas, F.; Bastos, M.M.; Medeiros R et al. ***HPV16 is sufficient to induce squamous cell carcinoma specifically in the tongue base in transgenic mice****. The Journal of Pathology 2020, 251, 4-11, doi:10.1002/path.5387*

Peixoto da Silva S, Santos JMO, Mestre VF, Medeiros-Fonseca B, Oliveira PA, M MSMB, Gil da Costa RM, Medeiros R: ***Human papillomavirus 16-transgenic mice as a model to study cancer-associated cachexia****. Internationaljournal of molecular sciences 2020, 21(14).*

NeutroSAC – Cachexia Anorexia Syndrome and its Clinical, Pharmacogenomic and Biochemistry (**REF.:** CI-IPOP-118-2019) 01/01/2020-31/12/2025 **Budget:** 7500€
PI: Rui Medeiros

A syndrome known as cachexia is frequently present in cancer patients, increasing morbidity and mortality. Inflammatory cytokines are known to play a key role in the development of this syndrome. In addition, microRNAs have also emerged as important molecules in cachexia. Our hypothesis is that microRNAs may act as mediators in inflammation-induced cachexia.

Publications:

Mota INR, Satari S, Marques IS, Santos JMO, Medeiros R. ***Adipose tissue rearrangement in cancer cachexia: The involvement of β3-adrenergic receptor associated pathways****. Biochim Biophys Acta Rev Cancer. 2024 May;1879(3):189103. doi: 10.1016/j.bbcan.2024.189103*

Liz-Pimenta J, Tavares V, Neto BV, Santos JMO, Guedes CB, Araújo A, Khorana AA, Medeiros R. ***Thrombosis and cachexia in cancer: Two partners in crime?*** *Crit Rev Oncol Hematol. 2023 Jun;186:103989. doi: 10.1016/j.critrevonc.2023.103989.*

Dias TR, Santos JMO, Estêvão D, Costa NR, Mestre VF, Medeiros-Fonseca B, Bastos MMSM, Oliveira PA, Gil DA Costa RM, Medeiros R. ***Expression of LncRNAs in HPV-induced Carcinogenesis and Cancer Cachexia: A Study in K14-HPV16 Mice.*** *Anticancer Res. 2022 May;42(5):2443-2460. doi: 10.21873/anticanres.15723. doi: 10.21873/anticanres.15723.*

Santos JMO, Peixoto da Silva S, Bastos MMSM, Oliveira PA, Gil da Costa RM, Medeiros R. **Decoding the role of inflammation-related microRNAs in cancer cachexia: a study using HPV16-transgenic mice and in silico approaches**. J Physiol Biochem. 2022 May;78(2):439-455. doi: 10.1007/s13105-021-00866-1.

Santos JMO, Costa AC, Dias TR, Satari S, Costa E Silva MP, da Costa RMG, Medeiros R. **Towards Drug Repurposing in Cancer Cachexia: Potential Targets and Candidates**. Pharmaceuticals (Basel). 2021 Oct 26;14(11):1084. doi:10.3390/ph14111084.

GWASPHARMAGEN – GWAS and Data Science as putative approaches for identifying pharmacogemomics determinants of response to therapy (**REF.:** CI-IPOP-91-2018) 01/01/2019-31/12/2026 **Budget:** 55000€ **PI:** Rui Medeiros

The goal of this project is to use GWAS data and international databases to identify pharmacogenomic determinants that could potentially be used to assess response to therapy

CANONIC – Assessment of Response to Medicinal Cannabis in Patients with Chronic Cancer Pain: A Pharmacogenomic Profile (**REF.:** CI-IPOP-99-2025) 01/01/2026-31/12/2027 **Budget:** 7500€ **Co-PI:** Rui Medeiros

The CANONIC project aims to evaluate the efficacy and safety of medical cannabis in adult patients with chronic cancer pain with neuropathic characteristics that is refractory to conventional treatments. The study will follow, over a six-month period, patients at the IPO Porto who begin treatment with medical cannabis, analyzing the impact of the therapy on pain intensity, functionality, and quality of life using validated questionnaires. At the same time, biological samples will be collected to study the participants' pharmacogenomic profile, with the aim of identifying genetic variants associated with therapeutic response and the occurrence of adverse effects. The goal is to contribute to a more effective, safe, and personalized use of medical cannabis, enabling a better understanding of which patients are most likely to benefit from this therapeutic approach and reducing variability in treatment response.