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 EXTERNAL FUNDING

ONGOING

OnCOVac.PT- ***Evaluation of the Immunologic Response to COVID-19 Vaccination in Oncological Patients*** **Funded** by AstraZeneca; Budget: 460 000.00€ **PI and Co-PI:** Júlio Oliveira | Rui Medeiros

The Portuguese Health Authorities declared the existence of active community transmission of COVID-19 virus since 26 of March 2020 and state of emergency was declared in order to combat the coronavirus pandemic. Reported illnesses have ranged from very mild to severe, including illness resulting in death. Cancer patients are more susceptible to infection compared to healthy people and noncancer patients. That predisposition has been historically related to the systemic malignancy-related immunosuppressive state and to active disease-oriented treatments, such as chemotherapy, radiotherapy and surgery. Despite the limited data, medical organizations and cancer experts indicate for vaccination most cancer patients. However, more data are needed on the safety and efficacy of COVID-19 vaccines, as well as the effect of vaccine booster doses, in people with compromised immune systems. Therefore, it is expected that cancer patients would be more prone to have a weaker response to vaccination. In addition, the non-responders to the vaccine will be at greater risk of developing COVID-19 infection, and subsequent complications. The importance of this issue is growing in the scientific community since there are new anti-COVID-19 therapies emerging that could benefit the non-responders and prevent them from developing aggressive forms of infection. Therefore, it is imperative to study the immunological response of cancer patients to booster doses of COVID-19 vaccination to get more insight on the percentage of non-responders and to study new molecular, genetic and epigenetic biomarkers that enable the distinction between responders and non-responders.

Publications

Almeida B, Dias TR, Teixeira AL, Dias F, Medeiros R. ***MicroRNAs Derived from Extracellular Vesicles: Keys to Understanding SARS-CoV-2 Vaccination Response in Cancer Patients?*** *Cancers (Basel). 2023 Aug 8;15(16):4017. doi: 10.3390/cancers15164017*

Dias TR, Dias F, Teixeira AL, Sousa H, Oliveira J, Medeiros R. ***MicroRNAs as Potential Tools for Predicting Cancer Patients' Susceptibility to SARS-CoV-2 Infection and Vaccination Response.*** *Cells. 2022;11(15), doi:* 10.3390/cells11152279

PAINLESS – Pain relief in palliative care of cancer using home-based neuromodulation and predictive biomarkers **Funded by** *European Union, Horizon Europe Initiative HORIZON-HLTH-2021-DISEASE-04 (2022-2027)* **Ref.:** 101057243; **Budget:** 5 952 245.00 € (IPO Porto 342 250.00 €) **PI@IPO Porto:** Rui Medeiros
Project Team: Universidade de Santiago de Compostela, **IPO Porto**, Servizo Galego de Saude, Universitaets medizing Goettingen, Aalborg Universitet, Hospice Casa Sperantei, Technion -Israel Institute of Technology, Institutul Oncologic Prof. Dr. Alexandru Trestioreanu Bucuresti, European Association of Palliative Care, European Cancer Patient Coalition, Neuroconn Gmbh, Betthera S.r.o., Software Imagination &Vision Srl, Qst.lab, Mentalab Gmbh, Association Europeenne des Ligues Contre Le Cancer Asbl

More than 50% of cancer patients develop pain before death: 80% can be treated with drugs, but 20% show a low response or have serious adverse effects. Although non-pharmacological interventions such as neurosurgical procedures have been tested, these alternatives are not a preferred option to treat cancer pain due to their high cost, risk, invasiveness and not always proven efficacy. PAINLESS addresses a core component of pain relief, by using an innovative, evidence-based approach. The objective is to adapt and implement a novel, cost-effective, home-based intervention based on neuromodulation to reduce pain and improve quality of life of cancer patients with chronic pain. On the assumption that treatment of chronic pain can benefit from research on the brain mechanisms of pain, we will first attempt to improve our understanding of the role of central pain modulation. The project will be organized in 3 studies: 1) A cohort, longitudinal study to explore whether the biomarkers of central pain modulation mechanisms can be predictive of the future occurrence of chronic pain in cancer patients; 2) A cross-sectional study to characterize and stratify cancer patients with vs. without chronic pain; 3) A pilot study to assess the feasibility an efficacy of at-home delivery of transcranial low intensity electric stimulation (tES) for the palliative care of cancer patients suffering from pain PAINLESS will develop a customized web portal to share knowledge and to improve management of the patients; perform technoeconomic analyses and Health Technology Assessment of the solution; analyze the possibilities of implementation in different European healthcare systems and results exploitation; and undertake an ambitious dissemination and communication strategy. We will also propose a wide range of measures to ensure compliance with the highest ethical standards.

Publications

Carrillo-de-la-Peña, M. T., **Fernandes, C., Castro, C.,** PAINLESS Consortium, & **Medeiros, R.** (2024). Validity of central pain processing biomarkers for predicting the occurrence of oncological chronic pain: a study protocol. *BMC cancer*, *24*(1), 705. https://doi.org/10.1186/s12885-024-12455-8

EVmiRs4PC – microRNAs derivados de vesículas extracelulares como mediadores da resistência ao tratamento em modelos in vitro 3D esferoides de cancro da próstata **Funded by** LPCC-NRN **REF.:** CI-IPOP 13-2022; **Budget** 5 000 €
PI: Ana Luísa Teixeira

Prostate Cancer (PCa) is the second most frequent neoplasia in men, worldwide, representing 6.8% of deaths by this disease. Androgen Deprivation Therapy (ADT) is frequently applied in the treatment of advanced and metastatic PCa, since prostatic tumors are highly dependent on the androgen pathway to proliferate and progress. ADT presents high efficiency in an early stage of treatment but, on average, patients develop resistance in 2-3 years, progressing to Castration Resistant PCa (CRPC). Enzalutamide (ENZ) is a second-generation antiandrogen developed to treat CRPC. However, 15-20% of patients present primary resistance and a high percentage of patients end up developing resistance to this new agent. In the last years, microRNAs (miRNAs) arose as potential biomarkers in several tumor models. Due to their important role in gene expression regulation, their deregulation has been frequently associated with the acquisition of resistance phenotypes and to the metastatic forms of the disease. Besides their potential as prognosis and therapy monitorization biomarkers, miRNAs present a high potential as therapeutic agents through the usage of miRNAs mimics and anti-miRNAs. Therefore, this study intends to define an EVs-miRNA profile associated to ENZ resistance and to analyze their dynamics of expression during the process of resistance acquisition in in vitro 3D spheroids. The identification of these miRNAs, along with the identification of their targeted genes and the signalling pathways in which they are involved, will allow the clarification of the molecular mechanisms behind ENZ resistance. In a clinical context, this resistance miRNAs-profile may, in the future, be applied, through a liquid biopsy approach, not only in the follow-up of patients submitted to ENZ treatment to predict resistance, but also reveal new therapeutic targets. Thus, the identification of

this miRNAs-profile may potentiate the development of an anti-miRNAs therapy, useful in the restoring of tumor cells sensitivity to ADT.

Publications

Tavares I, Morais M, Dias F, Medeiros R, Teixeira AL. ***Deregulated miRNAs in enzalutamide resistant prostate cancer: A comprehensive review of key molecular alterations and clinical outcomes***. *Biochim Biophys Acta Rev Cancer. 2024 Mar;1879(2):189067, doi: 10.1016/j.bbcan.2023.189067.*

Neurodevice - The Challenge in the Diagnostic Assessment of Neurodevelopmental Disorders: Innovative Neurochemical Tools **Funded by:** COMPETE2030-FEDER **REF.:** COMPETE2030-FEDER-00699000 |Project 15875
Budget: 52 509.60€ **PI:** Ana Luísa Teixeira

The NeuroDevice project aims to address the current gap in the prognosis and diagnosis of neurodevelopmental disorders by developing bioanalytical tests capable of detecting specific microRNA biomarkers associated with these types of conditions. This bioanalytical test is based on the development of disposable paper-based biosensors.

CONCLUDED

Nanowar2UrCancer – *Sensitization of Urologic Tumors Therapy Driven by Nanotechnology;* Funded by Fundação Para a Ciência e a Tecnologia **REF.:** PTDC/MED-QUI/29800/2017; **Budget:** 239.937,55 € **August 2018 - January 2022**
PI and Co-PI: Rui Medeiros | João Prior (FFUP| REQUIMTE)

Cancer remains one of the main problems of public health worldwide. In fact, in Portugal it has been observed a significant increase of new diagnosed cancers over the last years. Moreover, the lack of response or resistance to cancer treatments represents the major issue in the oncology field. The increase of new cancer cases walks side by side with the increase of patient care costs, and the associated social and economic burden. However, despite the investment in innovative therapies, they become totally ineffective as a consequence of the early resistance development by the tumor cells. This originates a total loss of all financial investment made since the beginning of treatment and, unfortunately with no benefit for the patients. Other treatment options, such as radiotherapy, also present resistance problems despite the large investment made in equipment and infrastructures in the last few years. Therefore, there is an urgent need to optimize the effectiveness of cancer therapies in order to improve the quality of patient care. The approach proposed to solve this problem, is to combine the cytotoxic power of silver nanoparticles (AgNPs) with chemotherapy and radiotherapy, in order to maximize the effect of these standard treatments. It is important to note that with the increasing costs of new therapies, the older ones are now cheaper.
AgNPs are easy to synthetize using "green synthesis? approach, present a low production cost and can be design to act on specific target, such as a cell membrane receptor. The potential application of AgNPs in cancer treatment is related to the fact that, on the one hand they can be directed to cancer cells and on the other hand their cytotoxic power is able to weaken cancer cells. With weaker cells, the anti-neoplasic treatments will have greater effects in lower doses.

The main goal is to determine the sensitization power of AgNPs in order to maximize chemotherapy and/or radiotherapy response. This new approach will allow the reduction of patient care costs and the treatment side-effects and will also be easy to implement in clinical practice in a near future.

Publications

Morais M, Machado V, Dias F, Figueiredo P, Dias F, Craveiro R, Lencart J, Palmeira C, Mikkonen KS, Teixeira AL, Medeiros R. ***Silver Nanoparticles (AgNPs) as Enhancers of Everolimus and Radiotherapy Sensitivity on Clear Cell Renal Cell Carcinoma.*** *Antioxidants (Basel). 2023 Nov 28;12(12):2051. doi: 10.3390/antiox12122051.*

Morais M, Machado V, Dias F, Figueiredo P, Palmeira C, Martins G, Fernandes R, Malheiro AR, Mikkonen KS, Teixeira AL, Medeiros R. ***Glucose-Functionalized Silver Nanoparticles as a Potential New Therapy Agent Targeting Hormone-Resistant Prostate Cancer cells.*** *Int J Nanomedicine 2022 17: 4321-4337, doi: 10.2147/IJN.S364862. eCollection 2022.*

Morais M, Machado V, Dias F, Palmeira C, Martins G, Fonseca M, Martins CSM, Teixeira AL, Prior JAV, Medeiros R. ***Starch-Capped AgNPs' as Potential Cytotoxic Agents against Prostate Cancer Cells****, Nanomaterials 2021 11(2): 256, doi*: 10.3390/nano11020256

Morais M, Teixeira AL, Dias F, Machado V, Medeiros R, Prior JAV. ***Cytotoxic Effect of Silver Nanoparticles Synthesized by Green Methods in Cancer****. Journal of Medicinal Chemistry 2020 63(23): 14308-14335*, doi: 10.1021/acs.jmedchem.0c01055

SIRNAC - *Novel Therapies Against Metastatic Colorectal Cancer* Funded by Agência de Inovação/ FEDER **REF.:** NORTE-01-0247-FEDER-033399; **Budget** 758 401. 000 €(IPO 169 378,34€) **June 2018- January 2022 Project Team:** Phyzat, IPO Porto, INEB **PI@ IPO Porto:** Rui Medeiros

This project refers to a new therapy against colorectal cancer metastatic to the liver and aims at reducing significantly the impacts of a disease with an extremely heavy human and economic burden. This project covers the development phase of a new medicine, following the phase of discovery, successfully finished by the consortium leader, with proof of efficacy in vitro and in vivo of the elected molecules. It comprises the development of the elected molecules, the development of the delivery system and the validation of the clinical and therapeutical relevance, either isolated or sinergistically of the two new targets.This project will allow to finish the development phase and outlicense the program for initiation of the regulatory trials leading to market approval.

Publications

Almeida C, Teixeira AL, Dias F, Morais M, Medeiros R. ***Extracellular Vesicles as Potential Therapeutic Messengers in Cancer Management.*** *Biology (Basel). 2023 Apr 27;12(5):665. doi: 10.3390/biology12050665.*

Almeida C, Teixeira AL, Dias F, Machado V, Morais M, Martins G, Palmeira C, Sousa ME, Godinho I, Batista S, Costa-Silva B, Medeiros R. ***Extracellular Vesicles Derived-LAT1 mRNA as a Powerful Inducer of Colorectal Cancer Aggressive Phenotype****. Biology (Basel), 2022. 11(1), doi*: 10.3390/biology11010145

Dias F, Almeida C, Teixeira AL, Morais M, Medeiros R. ***LAT1 and ASCT2 Related microRNAs as Potential New Therapeutic Agents against Colorectal Cancer Progression****. Biomedicines. 2021 16;9(2):195, doi*: 10.3390/biomedicines9020195

Lopes C, Pereira C, Medeiros R. ***ASCT2 and LAT1 Contribution to the Hallmarks of Cancer: From a Molecular Perspective to Clinical Translation***. *Cancers (Basel). 2021 Jan 8;13(2):203, doi*: 10.3390/cancers13020203