RESEARCH TOPIC PRIME2

Novel Cancer Therapy: Inducing Double-strand DNA Breaks to Foster Tumour Cell Death, Antigenicity and Immunotherapy Response in New Personalized Models

Thematic field of the project

Organ-on-chip

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Main field of interest

Organs-on-chip

Abstract

Background and Rationale. Cancer remains a leading cause of mortality worldwide, with the WHO reporting 10 million deaths in 2022. Projections indicate a 77% increase in new cancer cases by 2050, driven by population aging, socioeconomic changes, and environmental factors. Platinum (Pt)-based chemotherapeutic agents are fundamental for treating multiple solid cancers and have significantly improved patient survival rates.

However, drug resistance develops in up to 70% of patients, limiting their effectiveness.

Current Pt-based drugs, like Cisplatin (CisPt), primarily cause single-strand DNA breaks, enabling cancer cells to activate DNA repair mechanisms and develop resistance.

Hypothesis. We hypothesize that novel chemotherapeutic agents designed to induce a high-frequency of double-strand DNA breaks can prevent the activation of DNA repair mechanisms in cancer cells. This approach aims to enhance cancer cell death and stimulate a tumour immunogenic response, potentially improving the efficacy of immunotherapy. A recent collaboration between BHRI and UPV/EHU groups led to the design, synthesis, and patenting (PCT/EP2023/083500) of a novel family of chemotherapeutic agents with unique polyelectrophilic features against DNA specifically in cancer cells, named "Aurkine".

Aims. The primary aim of this project is to assess the therapeutic potential of Aurkine, both alone and in combination with immune checkpoint inhibitors (ICIs), using mouse and novel

patient-derived models developed by our consortium. This initiative will include various cancer types as a proof of concept, with a focused investigation into biliary cancer, also known as cholangiocarcinoma (CCA). Specific aims include: 1) Developing innovative, translational, and personalized cancer models, including 2D and 3D in vitro and ex vivo models, as well as diverse in vivo cancer models; 2) Evaluating the antitumour effects and molecular mechanisms of Aurkines, both alone and in combination with ICIs, in cutting-edge in vitro, ex vivo, and in vivo experimental models; 3) Profiling of tumour mutational burden, molecular characteristics, and neoantigens in vitro, ex vivo, and in vivo with or without exposure to Aurkine (+/- ICIs).
Methods. We will employ pioneering 2D and 3D human in vitro and ex vivo cancer models, including Patient-Derived Organoids (PDOs), human Precision-Cut Tissue Slices (PCTS), and a human Cancer-on-CHIP platform. Additionally, various cancer animal models with different etiological backgrounds will be employed.
Expected Results and Potential Impact. In TITAN, our goal is to develop next-generation targeted therapies for both treatment-naïve and CisPt-resistant cancers, leveraging innovative personalized models. The consortium's outcomes have the potential to transform drug design, personalized cancer modelling, and clinical practices, ultimately advancing research and improving treatment management and outcomes for patients with cancer.

Main technical approaches
Drug tesing and personalised medicine in patient derived organ-on-chip

Scientific references

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Type of contract

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