Efficacy of targeted nanoparticles coated with hybrid cell membranes against pancreatic cancer heterogeneity

Pancreatic cancer (PC) presents formidable challenges due to its aggressive nature, poor prognosis, and limited treatment options. Conventional anticancer therapies struggle against its heterogeneity and the protective tumor microenvironment (TME), including tumor cells (TCs), cancer stem cells (CSCs), and cancer-associated fibroblasts (CAFs). Enrichment in CSCs subpopulations contributes to aggressiveness and treatment resistance, highlighting the potential of CSCs targeting. The dynamic interplay of tumor and immune cells, notably tumor-infiltrating lymphocytes (TILs), is pivotal in cancer progression. TILs, having recognize multiple cancer cell targets, ideal for targeted therapy. Moreover, platelets, typically involved in hemostasis, adjust their function in response to tumor signals, becoming tumor-educated platelets (TEP), thus offering a promising intervention target

The main objective of this project is the development of complex new biomimetic hybrid cell membrane (CM)-based nanoparticles (NPs) loaded with anticancer therapeutic agents (drugs and miRNAs) to target proliferative TCs, CSCs and the TME of PC in two *in vitro* (based on 3D bioprinted biomimetic hydrogels) and *in vivo* (patient-derived xenograft organoids) models. This general objective will be achieved through the development of the following specific objectives: Objective 1. Synthesis, physico-chemical, colloidal and ultrastructural (cryoEM) of MA-SLNPs and SFNPs with the chemotherapeutics encapsulated. Isolation, characterization (flow cytometry, and CM extraction of CSCs, CAFs (primary cell cultures from surgical samples), Platelet and TILs (tumor tissue) from PC patients (male and female) and/or established cell lines. Phenotypic, metabolomics and proteomics characterization of the hybrid CM will be done in accordance with methodologies developed by the research group and using bioinformatics. Also, NPs will be functionalized with 4 miRNA mimics and their correct incorporation will be evaluated. Objective 2. *In vitro* targeting effects of NPs and hybrid CM-based NPs loaded with therapeutic agents on 2D and 3D-bioprinted hydrogels that mimic TME and based on natural biomaterials such as decellularized extracellular matrices (dECMs) obtained from tumor stromal cells (CAFs), fibrinogen and thrombin, and including 3D patient-derived organoids (PDO) and patient-derived xenograft organoids (PDXOs) (male and female). The hydrogels will be physicochemical and mechanical characterized to analyse changes in the viscoelastic properties. Objective 3. *In vivo* systemic toxicity, bioavailability, biodistribution and targeted anti-tumor effectiveness of biomimetic CM-based NPs in humanized PDX (male and female mice) to simulate patient immune-tumor interactions realistically.

This multidisciplinary approach, leveraging nanomedicine, omics and biofabrication methods, holds significant potential in enhancing outcomes for PC patients with poor prognosis. Collaborations with internationally recognized centers of excellence will contribute to the advancement of knowledge in this critical area and will improve translational research and personalized oncology.

Supervisor(s) name(s), Affiliation(s), eMail address(es) for contact:
Prof. Juan Antonio Marchal
BioFab i3D Lab- Biofabrication and 3D (bio)printing Singular Laboratory
Faculty of Medicine
Centre for Biomedical Research (CIBM)
Instituto de Investigación Biosanitaria de Granada (ibs. GRANADA
University of Granada
email: jmarchal@go.ugr.es

Proposed list of secondments (not mandatory, but recommended if known already):

- University of Munich
- University of Padua
- University of Claude Bernard Lyon

Main ArchiFun theme involved:

- ☐ Host-pathogen interactions;
- ☐ Mechanisms of bacterial resistance and cancer onsets;
- ☐ Neurodegenerative and autoimmune diseases;
- ☑ **Translational research in prevalent diseases**;
- ☐ Physiology and ecology;
- ☐ Neurosciences and cognition.