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"Nanovectors for directed, loco-regional and controlled intravenous administration of antitumor drugs. Strategies to minimize adverse effects and maximize therapeutic response" ONCOLIBERYX

Nowadays, cancer is the second leading cause of death in developed western countries.

Despite notable advances clarifying the biological mechanisms underlying this disease and the new therapeutic approaches, the concerns regarding the side effects caused by these drugs are prompting the investigation of more selective and effective, and less toxic therapeutic regimens and formulations. In the last 20 years, drug nanocarriers -liposomes, nanoparticles (NPs), nanocapsules (NCs), antibody drug conjugates, etc.- have demonstrated remarkable advantages to address some of these challenges.

PharmaMar is a key company in the research for new chemical structures for cancer treatment. Its portfolio includes new molecules, isolated from marine macro and microorganisms, with potent cytotoxic activity and new mechanisms of action. A considerable amount of these active cytotoxic drugs cannot demonstrate their full potential against cancer due to its very low solubility, short half-life or toxicological profiles.

ONCOLIBERYX focuses on finding and preclinically testing new drug administration strategies in order to increase the specificity of the oncological active compounds, decreasing their toxicity and side effects, while maintaining or even increasing their therapeutic effects.

ONCOLIBERYX proposes to seek solutions to correct the pharmacokinetic and biopharmaceutical limitations derived from the solubility profile of the **selected active molecules**, reducing their toxic side effects and concentrating the drug in the tumour or tissues surrounding tumor lesions.

Two main approaches will be intensively tested:

A. **Directed intravenous administration** of drug-loaded nanosystems.
B. **Loco-regional and controlled administration** of the drug directly into the tumour in order to achieve immunogenic cell death sustained over time, in a fashion to be combined with currently used immunotherapies based on checkpoint-inhibitors.

The following formulations will be administered intravenously and, when considered suitable (especially when high loading efficiency is achieved), also via loco-regional administration:

A. **Targeted polymeric NCs** composed of a lipid core and covered by a hydrophilic polymeric capsule of hyaluronic or a polyacid (i.e. hyaluronic or polysialic acid) and membrane tLyp-1 peptide-recognition ligands, with the ability to promote penetration into the tumor stroma and interaction with cancer cells.
B. **Functional lipid based nanosystems**, manufactured by microfluidic techniques, including new synthetic bioinspired exosome-like nanoparticles.
C. **Solid lipid nanoparticles**, suitable for the encapsulation of lipophilic molecules, and **PLGA polymeric nanoparticles**, for the administration of hydrophilic active compounds, designed for preferential accumulation in tumour or immediately surrounding tissues.

Seven (7) new active molecule families with different structures, physicochemical, biopharmaceutical and toxicological properties will be encapsulated in the suitable drug

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carrier and they will be tested for PK, biodistribution, antitumor efficacy, tumor concentration and toxicological profile in the suitable animal models.

ONCOLIBERYX counts on the outstanding experience and knowledge of three key research groups in the field of new drug delivery systems: the teams of Prof. María José Alonso from the University of Santiago de Compostela (USC), Prof. José Luis Pedraz from the University of the Basque Country (UPV/EHU) and Prof. María Blanco from the University of Navarra (UNAV).

The study of antitumoral activity and the involvement of the immune system in the specific fight against the tumour after a locoregional administration by intratumoral injection of cytotoxic compounds will be carried out by the team of Dr. Ignacio Melero at the Center for Applied Medical Research (CIMA) who brings expertise in cancer immunotherapy to the ONCOLIBERYX consortium.