Proyecto PID2020-119368RB-I00 financiado por:

"siRNA-based combined nano-immunotherapies applied to the treatment of lung cancer" (ONCO-SIRNA).

Despite notable advances in cancer treatment, specific types of tumors, i.e. Non-small cell lung (NSCL) carcinoma, still represent a leading cause of death worldwide. A promising strategy to advance further in the fight against cancer is to target Tumor Associated Macrophages (TAM). TAMs, which may represent up to 50% of the tumor mass. TAMs favor the proliferation of tumor cells and promote angiogenesis, invasion and metastasis. Unfortunately, the pharmacological agents intended to act on TAMs, including immunostimulatory agents and inhibitors of transcription factors, have shown significant toxicity due to their systemic biodistribution and limited access to the target cells. Another limiting barrier for the efficient treatment of cancer is the difficult access to specific oncoproteins localized at the intracellular level in cancer cells. Attempts to reach these oncoprotein targets using small molecules have been quite unsuccessful and as a consequence, these targets have been named as undruggable.

Genetic analysis of tumors from patients have made it possible to identify the key oncoproteins which control the tumoral progression inside cancer cells and also inside TAMs (i.e. KRAS or STAT3), which are particularly relevant in lung cancer. To address these targets, we envisage the use of nanotechnology as an exceptional opportunity, to develop nanocarriers with the capacity to deliver siRNA molecules to prevent the production of these oncoproteins inside cancer cells and TAMs. The design of a siRNA synthetic nanocarrier implies the consideration of a series of biological barriers, such as: i) Protection of siRNA from degradation and premature release in the bloodstream; ii) Tissue targeting; iii) Diffusion through the tumor stroma; iv) Cell internalization (cancer and immune cells). In this framework, the studies carried out in our research group have opened the doors to intra- and extra-cellular targets related to cancer cells and TAMs.

With these premises, the ultimate objective of this project is the development of new personalized therapies based on nanotechnology for the treatment of lung cancer. This will be addressed through the rational design and optimization of multifunctional polymeric nanocarriers, some of which have already been developed and patented at USC, called LPN, to achieve the intracellular release of different types of siRNA (anti-KRAS and anti-STAT3) to different cell populations. More specifically, in the tumor tissue, LPNs will be designed to act at the level of cancer cells and TAMs, while in the lymphatic system the objective is to reach metastatic cells and immunosuppressive myeloid cells. This global aim involves specific objectives, namely: 1) Intracellular release of anti-KRAS siRNA in cancer cells (tumor and metastatic cells present in lymph); 2) Intracellular release of anti-STAT3 siRNA in tumor-associated macrophages (tumor and lymphatic system); 3) Combination treatment consisting of STAT3 plus anti-KRAS to both targets.

To accomplish these objectives, we have a research team with three PIs, two of them highly specialized in drug delivery and one of them in nano-immunotherapies. The work team counts on 3 PhD students and a tech transfer manager. Additionally, the project counts with the ongoing collaboration of the applicant with outstanding internal and external collaborators. Special attention will be paid to the impact in terms of training, international dissemination and technology transfer.