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# "Repurposing cytotoxic compounds from sea organisms for intratumoral cancer immunotherapy"
RECYTSEA

Marine organisms constitute a source of compounds with pharmacological potential. The Spanish pharmaceutical company PharmaMar has screened and selected over the years a great number of compounds which exert potent cytotoxic activities on malignant cells but which were discarded when found to be excessively toxic upon systemic administration to rodents, even though through upon adequate refinements they bear potential for repurposing leading to intellectual property protection and clinical applicability. Local intratumoral administration is gaining momentum as an immunotherapy approach based on the induction of immunogenic cell death (ICD) in malignant cells and proinflammatory changes in the treated tumor lesions. Discarded agents with cytotoxic activity will be screened in mouse models and human carcinoma cell lines to study if they experiencethe biochemical hallmarks of immunogenic cell death and if tumor cells killed with such compounds are able to immunize immunocompetent mice against re-challenges by the same viable syngeneic tumor cell line in an antigen-specific fashion. Those agents attaining such an immunizing activity will be tested for tolerability and therapeutic activity following intratumoral delivery in various regimens. Incisive state-of-the-art cell biology, proteomics and metabolomics experiments will be performed to characterize the mechanistic links of the compounds to the immunogenic cell death process, as well as the potential deleterious effects on immune cells seating in the tumor microenvironment, in tumor-draining lymph nodes or elsewhere in the mouse. Selected compounds achieving local and systemic signs of efficacy will be studied in their immunological requirements using gene-modified mouse strains and selective depletions of immune cell subpopulations. The potential combinatorial synergy for efficacy of the novel intratumoral compounds with systemic anti-PD(L)1 and CTLA-4 checkpoint inhibitors will also be pre-clinically explored. Several parameters of adaptive T-cell immune activation towards model tumor antigens will be comparatively monitored. Innovatively, intratumoral release of the selected compounds will be performed in experimental fluorescent tumors engrafted under glass chambers or in the livers of CD2-RFP transgenic mice, whose T and NK lymphocytes can be visualized and followed in their time-lapse behavior by intravital multiphoton confocal microscopy. Moreover, the best candidate compounds will be optimized for local intratumoral delivery by formulation in polymers and nanoparticles to optimize local tumor control and immunogenicity, while minimizing systemic toxicity at workable doses. Such clinical candidate agents and formulations will be intratumorally tested in a collection of immunodeficient mice xenografted with human tumors and autologous T lymphocytes to measure T-cell activation and therapeutic control of the injected and non-injected distant tumors. The capabilities for pharmaceutical development of PharmaMar join efforts with two prestigious teams of immunologists led by Professors Sanchez-Madrid and Melero. The contributions of excellent pharmaceutical technology expertise (Prof Alonso's team) and proteomics and metabolomics expertise (Prof. Vazquez's team) build a consortium able to deliver feasible and innovative cancer therapies.