PRINCIPE FELIPE
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Seminario CIPF

Towards the Design of Personalised Polymer-based Combination Conjugates for Advanced Stage Breast Cancer Patients

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Date: 16/03/2018 – 13h
Place: Salón de Actos CIPF

Abstract: Breast cancer (BC) accounts for 21% of all female cancer deaths in Europe, with a mortality rate of ~31 per 100,000. It is considered the main cause of death for women aged 35-64 years [1]. Overall survival rate has vastly improved over recent decades due to early detection and improved therapies, but metastatic disease is largely incurable [2]. Anti-cancer therapeutics research has provided little progress towards improved survival rates for patients with metastatic disease due in part to the complex and heterogeneous nature of the disease. However, the intrinsic advantages of polymer conjugates can be optimised to rationally design targeted combination therapies that would permit enhanced therapeutic efficiency [3]. Early clinical trials involving anti-cancer polymer conjugates have shown activity in chemotherapy refractory patients and significantly reduced drug-related toxicity [4].

Our objective is to engineer tumour-targeted polymer-based combination therapies specifically designed to treat metastatic breast cancer in a personalised manner. To achieve this goal, we plan to developed novel multicomponent polymer conjugates with precise control over size, shape, solution conformation, multifunctionality, and bioresponsiveness and assess structure activity relationships clinically relevant models to understand mechanisms of action. In particular, our recent studies using NCA polymerization techniques have allowed us to precisely control the synthesis of well-defined star-based and linear polypeptidic architectures [5, 6] that are capable to undergo a self-assembly process according to a structure/conformation-concentration dependency. Based on this behaviour, we described for the first time, a bottom-up methodology for the stabilization of soft-assembled star-shaped polyglutamates by crosslinking. Covalent capture of these labile assemblies provides access to unprecedented architectures as potential nanocarriers [7]

In parallel, we have performed a High Throughput Screening (HTS) to select synergistic drug combinations to be used in polymer-based combination approaches through rationally designed linkers that confer adequate drug release kinetics. To perform this approach we selected four metastatic human BC cell lines representing the four clinical BC subtypes. Prior to HTS, all cell models have been fully characterized regarding their Cathepsin B activity, intracellular pH, as well as oestrogen, progesterone, Her2 receptors, GSH and exosomes levels; all representing patient-specific biomarkers. Cell viability and exosomes release modulation have been studied following treatments and several drug combinations have been selected for each specific BC subtype.

With selected drug combinations different linking chemistry has been explored (carbamates, hydrazones, disulphides, etc.) yielding different drug(s) release kinetics. This provided different therapeutic outputs in cells and in a orthotopic breast cancer model, not only for the primary tumor but also for metastasis progression in lungs as well as lymph nodes.

The strategy proposed and the results obtained so far open up a wide range of opportunities for the currently unsuccessful clinical approaches to target lymph node metastasis and cancer immunotherapy.

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Acknowledgments: The authors acknowledge MINECO (grants SAF2013-44848-R, SAF2016-80427-R) and the European Research Council (grant ERC-CoG-2014- 648831 MyNano) for financial support.

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