EGFR/SHP2-targeted medicines for colorectal cancer theranostics

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Colorectal cancer (CRC) is the second leading cause of cancer-related death worldwide. Cancer mortality is associated with the metastatic spreading of this disease, due to the lack of effective treatment options for this setting. Cetuximab is an Epidermal Growth Factor Receptor (EGFR)-targeted therapy approved for treatment of patients with metastatic colorectal cancer (mCRC) [1]. However, in many cases patients develop resistance to anti-EGFR targeted therapies [2]. Therefore, it is crucial to successfully identify responder patients, as well as to develop new therapeutic strategies to overcome cetuximab resistance. Recently, it was demonstrated that the inhibition of SH2-containing protein tyrosine phosphatase 2 (SHP2) is able to sensitize cetuximab-resistant cells, with combined treatments being beneficial to overcome resistance [3]. With that in mind, our major goal is to build targeted drug delivery platforms for combined EGFR/SHP2-targeted therapy to improve the therapeutic efficacy and overcome resistance in the treatment of mCRC, reducing systemic toxicity. Moreover, our strategy may assist in the selection of patients who are expected to benefit from this combined EGFR/SHP2-targeted therapy and to monitor response for personalized cancer treatment.

To achieve this goal, we aim to develop strategies that can combine in the same platform: i) an anti-EGFR antibody (cetuximab) to confer specificity and therapeutic effect; ii) a specific SHP2-inhibitor (SHP099); iii) a bifunctional chelating agent to stabilize a radionuclide (^{67}Ga) for imaging. Within this work, two distinct platforms will be considered to deliver both drugs to the EGFR(+) tumors and their metastases: antibody drug conjugates (ADCs) and polymeric micelles (PMs). ADCs enable the conjugation of a tumor targeting monoclonal antibody (mAb) to a payload through a chemical linker, allowing the delivery of the payload to a specific target. On the other hand, PMs have demonstrated unique advantages for encapsulating a wide range of bioactive molecules and are highly versatile to be functionalized with targeting ligands to specific receptors.

The synthesis and characterization of different ADCs carrying cetuximab and SHP099 will be reported, including the optimization of the reaction conditions for the conjugation of the antibody to the SHP2 inhibitor *via* maleimide chemistry, with drug-to-antibody ratios in the range of 0.8 - 3.9. Preliminary biological studies in both cetuximab-sensitive and cetuximab-resistant colorectal cancer cell lines will be presented, in order to evaluate the ability of the ADCs in overcoming drug resistance. The optimization of the conditions for the preparation of PMs loaded with SHP099 will also be reported, as well as their characterization in terms of hydrodynamic diameter, polydispersity index and zeta potential values.

Using these strategies, we anticipate a synergistic effect for this dual targeting approach, overcoming resistance to cetuximab therapy. All in all, we expect to obtain two differentiated platforms with improved biological properties for cancer treatment and radiotools to assess EGFR level and heterogeneity in tumors.

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References:

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