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A Versatile Immune-Stimulatory Actinium-225 Complex for Combination Radiotherapy and Antibody Recruiting Therapy

Antibody recruiting small molecules (ARMs) are a unique class of immune-stimulatory agents that contain two key regions: the antibody-binding terminus (ABT), which recruits endogenous antibodies, and the target-binding terminus (TBT), which interacts with the site of interest.(1,2) When bound to a cell, the endogenous antibodies can promote antibody-dependent cellular cytotoxicity (ADCC) resulting in clearance of the antibody-labelled cells. There is an opportunity to enhance the immune response caused by ARMs through the addition of a radionuclide that delivers cytotoxic radiation directly to the site of interest.(3) Evidence suggests that for cancerous lesions combination therapy of immune stimulation and cytotoxic radiation can lead to regression of not only primary tumours, but also simultaneous regression and control of distant metastases.(3)

Rather than develop a specific targeted radiolabelled ARM for each biomarker, a platform was established with three functional regions, a tetrazine, a DOTA chelate and a 2,4-dinitrophenyl moiety. The tetrazine was introduced in place of the TBT, permitting a bioorthogonal reaction with a trans-cyclooctene (TCO)-labelled ligand to be employed for targeting a choice tumour marker. The chelate, DOTA, was chosen due to the wide range of radiometals it can bind, including alpha emitters such as actinium-225. The target trifunctional ligand was synthesized and radiolabelled with lutetium-177 and actinium-225 in high yield and both compounds were found to be stable in formulation over 24 hours. A proof of concept study has been performed by reacting the lutetium-177 ligand with TCO functionalized bovine serum albumin (BSA) aggregates, which act as a protein "anchor". The radiolabelled aggregates were injected intratumourally in a 4T1 breast cancer model which showed high retention over 24 hours. As a result of the high tumour retention, we will proceed with a therapy study comparing the individual monotherapies, targeted alpha and antibody recruiting, to the combination therapy to determine if this platform can generate an antitumour response.

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