DESIGNING A NEW SIALIDASE-ANTIBODY CONJUGATE FOR CANCER: LOOKING FOR NEW THERAPEUTIC STRATEGY

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Despite advances in cancer immunotherapies, many patients remain unresponsive, highlighting the need for new therapeutic targets. Aberrant glycosylation in cancer has emerged as a key mediator of immune evasion, with the overexpression of sialic acid-capped glycans being a common cancer associated alteration. These tumor-associated sialoglycans can engage sialic-acid-binding Ig-like lectin (Siglec) receptors on immune cells, triggering inhibitory pathways that suppress antitumor immunity. In human breast cancer (HBC), multiple Siglec receptors have been implicated in its ability to evade immune surveillance. Given the similarities between HBC and feline mammary carcinoma (FMC), cats serve as a valuable model for developing immunotherapeutic strategies. As such, we sought to develop a new therapeutic approach for FMC with potential translation to HBC, based on the design of a sialidase – single chain fragment variable (scFv) antibody conjugate with the ability to promote a targeted tumour cell desialylation, blocking Siglec activation and promoting cell mediated tumour clearance.

A panel of putative neuraminidases was designed and expressed in *E. coli*. Sialidase activity was assessed using a fluorometric assay, while flow cytometry was used to evaluate the capacity of the sialidases to remove cell surface sialic acids from tumour cells. The most promising sialidase, a feline neuraminidase, was conjugated to an anti-Trop2 scFv antibody. The resulting conjugate (fNeu-scFv) was characterized for its ability to desialylate tumour cells and bind Trop2 using flow cytometry, fluorescence microscopy, and western blot. fNeu-scFv retained sialolytic activity comparable to the isolated neuraminidase while exhibiting specific Trop2 binding in both HBC and FMC cell lines.

These findings suggest that targeted tumor desialylation via a sialidase-antibody conjugate represents a promising immunotherapeutic strategy for FMC, with potential translational applications in HBC. This approach aligns with the “One Health” concept, emphasizing its translational potential. Future studies will assess the conjugate’s ability to promote anti-tumoral FMC clearance by PBMCs and macrophage *in vitro*, as well as its capacity to reduce disease progression in mouse models of FMC.

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