

Recombinant engineering of an Ep-CAM-specific Fab antibody (VB6-845) with de-immunized bouganin

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ABSTRACT

Antibodies carrying a cytotoxic payload offer an alternative mechanism of action to conventional anti-cancer agents; however, immunogenicity remains a limitation to therapeutic success. A Fab version of an anti-Ep- CAM scFv antibody, was genetically-linked to a de-immunized form of bouganin, a type I RIP, to create VB6-845. Unlike other members of this toxin group, bouganin is one of the least toxic thus the de-immunized form is eminently suitable for systemic delivery. The optimal antibody de-bouganin orientation was identified from several forms of a dicistronic expression unit. The optimal configuration comprised a PelB leader sequence adjacent to a V -C domain linked to de-bouganin by a protease-sensitive linker for the first unit. Immediately following is a second unit comprised of a PelB-V -C domain with an N-terminal histidine affinity tag. Flow cytometry and cytotoxicity were measured to assess the selectivity and potency of VB6-845. VB6-845 was more potent than most of the chemotherapeutic agents tested against OVCAR-3, an Ep-CAM-positive ovarian carcinoma. While some chemotherapeutics were more cytotoxic, they were also more toxic as they lacked any cell-specific killing. VB6-845 with its lower toxicity profile represents a potent antibody-directed treatment alternative to chemotherapeutics for the treatment of solid tumors.