Functional and biological characterization of VB6-845, a recombinant Ep-CAM-specific Fab antibody genetically-linked with de-immunized Bouganin (de-bouganin)

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ABSTRACT

Chemotherapeutics are highly cytotoxic agents that often represent the standard of care in the treatment of many of the solid tumor cancers. The cytotoxic action of these drugs targets rapidly dividing cells, both normal and tumor, thus creating a variety of adverse clinical side-effects. VB6-845 is a Fab antibody linked to a de-immunized form of the plant-derived toxin bouganin. Unlike chemotherapeutics which lack defined tumor-target specificity, VB6-845 restricts its cytolytic effect to Ep-CAM-positive tumor targets alone. In this study, flow cytometry analysis and cytotoxicity were measured to assess the potency and selectivity of VB6-845. Flow cytometry with VB6-845 against a large panel of tumor cells lines showed strong binding by the Fab to cell lines representative of a wide variety of cancer indications. In contrast, VB6-845 exhibited only limited cell surface binding to normal epithelial cell lines. The level of killing for VB6-845 was comparable to another Fab VB6-845 variant containing a different plant-derived toxin, gelonin. When assayed for cytotoxicity against OVCAR-3, an Ep-CAM positive ovarian carcinoma, using a panel of standard chemotherapeutic agents, VB6-845 was shown to be more potent than 12 of the 17 drugs tested. Though 5 chemotherapeutics were more cytotoxic, they were also shown to be far more toxic in that they lacked any cell-specific killing. Of the five recommended chemotherapeutic agents for the treatment of ovarian cancer (Paclitaxel, Carboplatin, Cisplatin, Doxorubicin and Topotecan), only two (Paclitaxel and Topotecan) were more cytotoxic. While VB6-845 demonstrated highly potent cytolytic activity with an IC 50 of 1 to 2 nM, the potent killing was restricted exclusively to the Ep-CAM-positive tumor cell line OVCAR-3. Although some Ep-CAM negative cell lines exhibited some level of killing, the cytotoxic effect was at least 220-fold and at most >1000-fold less toxic. VB6-845 thus represents a potent antibody-directed treatment alternative to chemotherapeutics that when combined with the lower toxicity profile, holds much promise in the treatment of many different types of solid tumors.