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Our previous study has established that Glypican-3 (GPC3) is a promising target for immunotoxin therapy in hepatocellular carcinoma (HCC). GPC3 targeting immunotoxins can inhibit HCC cell proliferation by blocking Wnt binding and through the elimination of cellular protein synthesis. While immunotoxins have shown great success in the clinical for treating blood cancers, in particular hairy cell leukemia, the same clinical success has not been demonstrated in treating solid tumors. We believe that modification of the Pseudomonas toxin domain may help to overcome clinical limitations associated with the treatment of solid tumors. Clinical limitations include off-target toxicity associated with the development of vascular leak syndrome, a short serum half-life and the development of a neutralizing antibody responses. To understand the effect of deimmunization on the immunotoxins' cytotoxic function, in the present study we constructed a panel of anti-GPC3 immunotoxins with point mutations to remove antigen residues predicted to be involved in B cell, T cell, or a combination of both responses. The deimmunizied immunotoxins exhibited similar levels of cytotoxic function in cell proliferation assays. All of the deimmunized versions showed a significant increase in overall survival as determined by Hep3B subcutaneous and HuH-7 intraperitoneal mouse models. The new deimmunized immunotoxins appear to be well tolerated in mice. To improve their serum half-life, we are further engineering the immunotoxins by incorporating albumin binding domains. The optimized immunotoxin will be clinically developed for the treatment of liver cancer.