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Therapeutic GST enzymes targeting cancer via epitope-binding fusion proteins

Abstract: The directed delivery of a drug-activating enzyme to a tumor is an emerging clinical treatment modality with a potential to significantly improve drug efficacy and concomitantly reduce adverse side effects. We are designing combinations of drug-activating enzymes and a prodrug with tumor-targeting antibodies, which is expected to give synergy and enhanced therapeutic efficacy in the treatment of leukemia and other malignancies. Antibodies, or alternative specific binding proteins, will target selected epitopes of cancer cells in which the accompanying enzyme will exert its drug-activating function. We have engineered human glutathione transferase (GST) enzymes for increased catalytic activity with the alkylating prodrug Telcyta with the aim of delivering the enzyme selectively to tumors. The approach is generic and can be implemented with alternative binding proteins and GSTs with different functionalities. Our prototypes for recombinant GST-antibody proteins are based on tumor-homing antibodies for use against leukemias featuring CD123 or CD22 epitopes. Recombinant GSTs are covalently linked to antibodies, which direct the GST to the tumor prior to administration of the prodrug. The enzyme-catalyzed activation of the prodrug will locally induce a cytotoxic effect to the tumor. Anti-CD22 and anti-CD123 antibodies by themselves have tumor-killing properties, and the simultaneous prodrug activation is expected to offer synergy and enhanced tumor cell death. Our novel approach of GST-mediated toxicity directed to CD22- or CD123-expressing cancer cells is expected to synergistically combine the effects of conventional chemotherapy with those of immunotherapy, reducing the likelihood of relapse of disease as well as counteracting the induction of secondary malignancies due to off-target effects.

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Keywords: Prodrug activation, Glutathione transferase (GST), Antibody-directed enzyme prodrug treatement (ADEPT), Leukemia, Therapeutic fusion protein

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